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Cooperative iodine and photoredox catalysis for direct oxidative lactonization of carboxylic acids†

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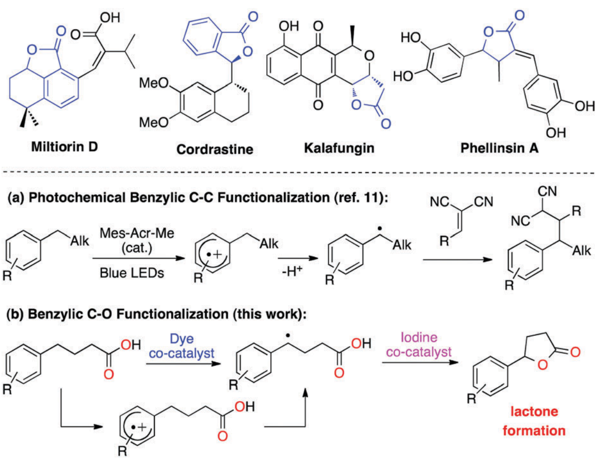
A new method for the formation of γ- and δ-lactones from carboxylic acids through direct conversion of benzylic C–H to C–O bonds is described. The reaction is conveniently induced by visible light and relies on a mild cooperative catalysis by the combination of molecular iodine and an organic dye.

Lactones are abundant structural units in natural products and important building blocks in the pharmaceutical sciences.[1] In particular, significant biological activities have been reported for certain benzylic γ-lactone derivatives.[2] Four representative examples are depicted in Scheme 1. There exist various synthetic approaches for the formation of lactones. Among the diverse methodologies, recent work in the area has dealt with the development of economic lactonization reactions combining the concept of direct C–H oxygenation[3] with free carboxylic acids. Examples to this end involve oxidative C–H functionalization concepts such as 1,5-hydrogen atom transfer (HAT) within the Hofmann–Löffler manifold,[4] by copper single electron transfer or by the use of stoichiometric amounts of iodine(III) reagents.[5]

Visible light-mediated photoredox catalysis has attracted more and more attention over the last few years because it renders new transformations accessible *via* single electron transfer (SET) processes.[6,7] However, so far, photoredox catalysts have been used in association with carboxylic acids only to promote visible light-mediated decarboxylation at the outset of arylation or alkylation reactions.[8,9] To the best of our knowledge, no metal-free direct oxidative cyclisation of carboxylic acids under the conceptual control of photocatalysis has been reported to date. In previous work, Nicewicz explored the decarboxylation of free carboxylic acids through organic photoredox catalysis.[10] As an interesting starting point, work by Wu has demonstrated that photoredox catalysis with organic dyes enables an efficient pathway to benzylic radicals *via* initial oxidation of the phenyl ring (Scheme 1a).[11] Consequently, our strategy was to develop a new route that would allow selective visible light-initiated benzylic oxidation and provide conditions under iodine co-catalysis to subsequently intercept the benzylic radical, thereby promoting a unique pathway to lactonization from the corresponding benzyl iodide intermediate (Scheme 1b).[12]

Here, we present the development of a mild, metal-free cooperative catalysis for the synthesis of such γ- and δ-lactones starting from the corresponding free carboxylic acids under mild conditions using an organic dye as the photoredox catalyst.

As a conceptual approach, the modular combination of distinct organocatalysts enabling consecutive reactions to be performed in one pot has become a powerful tool in organic synthesis.[13] Previously, we developed a new cooperative light-activated catalysis based on molecular iodine and TPT (2,4,6-triphenylpyrylium tetrafluoroborate) to perform the intramolecular amination of C_{sp^3}–H bonds.[14,15] In this process, hypoiodite was generated as the



Scheme 1 Representative lactone-containing natural products and the design of a strategy for oxidative cyclisation.

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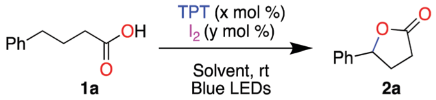
Table 1 Optimisation of the reaction conditions for the cooperative catalysis



Entry[a]	x	y	Solvent	Time [h]	Conversion [%]
1	2	—	DCE/HFIP	18	21
2	—	5	DCE/HFIP	18	nr[b]
3	—	10	DCE/HFIP	18	nr[b]
4	1	5	DCE/HFIP	18	70
5	2	5	DCE/HFIP	18	95 [94][c]
6	2.5	5	DCE/HFIP	18	64
7	2	7.5	DCE/HFIP	18	53
8	2	5	DCE/HFIP	24	77
9	2	5	DCE	18	56
10	2	5	HFIP	18	44
11	2	5	C_6H_5Cl/HFIP	18	52
12	2	5	ACN/HFIP	18	25
13	2	5	DCE dried	18	30
14	2	5	DCE/HFIP dried	18	60
15	2	5	DCE/HFIP	18	nr[b,d]
16	2	5	DCE/HFIP	18	[80][c,e]

[a] Reaction conditions: 0.3 mmol **1a** in 3 mL of solvent under blue light irradiation. [b] nr = no reaction. [c] The number in brackets refers to the isolated yield after purification by column chromatography. [d] Reaction performed in the absence of light. [e] Reaction performed with 1 mmol **1a**.

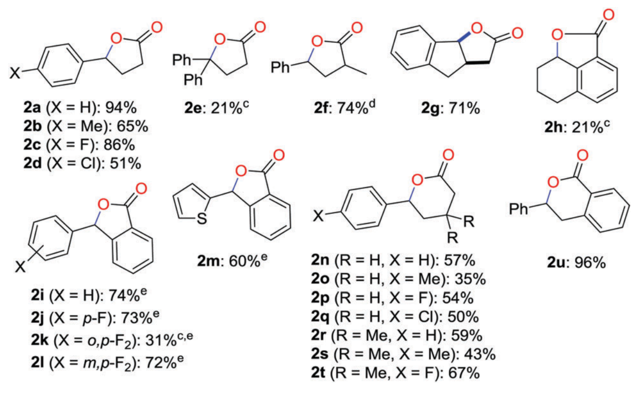
active species, which promoted the prerequisite *N*-iodination of the sulphonamide as the key step of this catalytic Hofmann–Löffler variant.

We decided to extend the study of such a cooperative catalysis to the case of carboxylic acids for the realisation of the corresponding C–H oxidation reaction using both TPT and molecular iodine. Gratifyingly, the initial experiment using only 2 mol% TPT and the carboxylic acid **1a** in a mixture of DCE/HFIP (1,2-dichloroethane/hexafluoropropan-2-ol, 1/1, v/v) already yielded 21% conversion (Table 1, entry 1) without any observable side products.[16] Under the conditions of cooperative catalysis starting from 1 mol% photoredox catalyst and 5 mol% molecular iodine, 70% conversion was obtained (entry 4). An increase in the amount of the photoredox catalyst to 2 mol% led to an increased 94% of isolated **2a** (entry 5). In the absence of the photoredox catalyst, the reaction does not proceed (isolated starting material only, entries 2 and 3). This observation suggests that TPT in the photocatalysis not only acts as the terminal oxidant for the regeneration of the molecular iodine, but plays a more direct role in the functionalization of the substrate. It is important to note that an adequate ratio of the two catalysts is decisive for the effectiveness of the cooperative catalysis as a whole. A relative increase of TPT or molecular iodine results in a significant decrease of the conversion (entries 6 and 7). In particular, the latter causes undesirable absorption of visible light and prevents the photochemical activation of the dye. It is also crucial to control the reaction time to avoid product decomposition, which was noticed when the mixture remained for an extended period of 24 h (entry 8). Solvent investigations were performed to finally conclude that the use of a 1/1-mixture of DCE/HFIP provides the best conditions (entries 9–12). The transformation still occurs with dry solvents, although with a decrease in the yield (entries 13 and 14). Here, the working hypothesis suggests that the presence of water is increasing the yield due to the formation of hypoiodite in wet medium,[17,18] which is an important acceleration factor of the overall reaction (*vide supra*). As expected, the reaction is not working in the absence of light irradiation (entry 15). On a preparative 1 mmol scale, 80% isolated yield is obtained (entry 16).

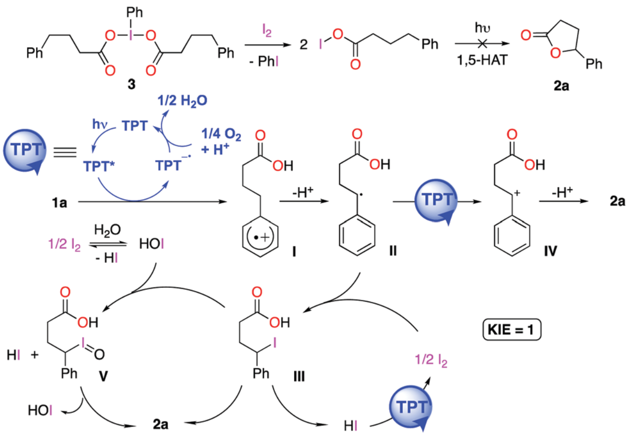
With the optimised conditions in hand, we then investigated the scope of the reaction to produce structurally diversified γ-lactone derivatives (Table 2).

As a starting point, we focused on the oxidative cyclisation of aliphatic carboxylic acids (**2a–g**, 21–94%). Different substituents in the *para*-position are well tolerated (**2a–d**, 51–94%). As the only example, *para*-chlorinated **1d** showed a decreased yield (**2d**, 51%) due to the quenching of the photoredox catalyst. We also noticed that the *para*-methyl derivative **1b** provided a comparably lower yield due to the potential competition between the formation of the two possible benzylic radicals (**2b**, 65%). As a result of the radical conditions, no acyclic stereocontrol was observed in the formation of **2f**, while cyclic stereocontrol was indeed possible, providing **2g** as a single diastereoisomer. Heteroatoms are well tolerated in this process as observed from the oxidation-labile thiophene derivative **2m** (60% yield). The γ,γ-diphenylated derivative **1e** provided a reduced yield of 21% for **2e**, which is a consequence of the slow lactone formation. The product **2h** is particularly interesting as it proves that it is possible to cyclise benzoic acid derivatives onto a fused aliphatic chain. Moreover, the γ-lactone **2h** constitutes the major structural unit of the natural product miltiorin D.[1b] We were also able to access isobenzofurane derivatives in moderate to excellent yields (**2i–l**, 31–74%). Due to the higher stability of the double benzylic radical intermediate, the process is faster and the reaction time can be reduced from 18 h to 12 h. The substituents in the *meta* or *para* position do not affect the cyclisation process to the final lactones, although an *ortho*-substituent led to a decrease

Table 2 Oxidative cyclisation of carboxylic acids **1a–u** for the formation of lactones **2a–u**[a,b]



[a] Reaction conditions: 0.3 mmol substrate in 3 mL of DCE/HFIP (1 : 1) for 18 h at room temperature under blue LED irradiation. [b] Isolated yields after purification by column chromatography. [c] >95% based on the recovered starting material. [d] Product obtained as a 1 : 1 mixture of diastereoisomers. [e] 12 h reaction time.



Scheme 2 Control experiment and proposed mechanism for the iodine–photoredox cooperative catalysis.

in the yield (**2k**, 31%, >95% based on the recovered material), which may be due to steric hindrance. Using this process, we are also able to achieve decorated δ-lactones (**2n–u**, 35–96%). Interestingly, 2-phenethylbenzoic acid **1u** exclusively yields the 6-membered ring isochromanone **2u**.

Regarding the reaction mechanism (Scheme 2), the most noteworthy detail of the present transformation is the marked absence of the decarboxylation pathway, particularly in the presence of molecular iodine. As a general possibility at the outset, one should consider the formation of an intermediary acyl hypoiodide RCO_2I from iodine and the substrate. Under irradiation, such a compound should be prone to undergo the corresponding homolytic O–I cleavage followed by a Hunsdiecker decarboxylation.[19] The absence of decarboxylation products suggests that such a pathway is not operative, however, the initial formation of a carboxylate radical remains a possibility. Such an intermediary species would then need to be involved in a 1,5-hydrogen atom abstraction, in a step that would be analogous of related 1,5-HAT with amide-based radicals. To rule out such a possibility, we investigated the reactivity of [bis(4-phenylbutanoxy)iodo]benzene **3** in the presence of molecular iodine. Upon *in situ* formation of the *O*-iodinated intermediate, irradiation does not provide the desired product **2a**.[5c,20] Only traces of the decarboxylation side-product and free carboxylic acid **1a** were observed after 18 h at rt.[21] This outcome provides strong evidence that the phenyl oxidation occurs selectively at the outset and is not due to a putative carboxylate radical. The formation of product **2a** from a reaction with involvement of only TPT (Table 1, entry 1) can be rationalised as follows: TPT in its excited state, TPT*, can only be oxidised by the SET mechanism. Substrate **1a** contains two oxidation labile sites, which are the carboxylic acid and the phenyl substituent. In previous work on photoredox-based decarboxylation,[8,10] it has been predicted that initial oxidation of the carboxylic acid by the dye should generate an alkane. Since no traces of decarboxylation side-products were observed in any of the investigated cases and no reactivity was obtained for molecular iodine without TPT, we conclude that no carbonyloxy radical is involved.[23] Instead, the benzylic radical **II** should be formed from arene oxidation with a cyclohexadienyl radical cation **I**.[11,22] To further advocate for the arene oxidation, we carried out cyclic voltammetry (Fig. 1). We observed that both butylbenzene **4** and substrate **1a** have the same oxidation potential (1.8 V *vs.* Ag/AgNO$_3$), which is lower than that of cyclohexylbutanoic acid **5** (2.2 V *vs.* Ag/AgNO$_3$). Therefore, the aromatic core should be oxidised first. TPT, in its triplet exited state TPT*, has an oxidation potential E^t(TPT*/TPT$^{\bullet-}$) of 2.3 V. Hence, TPT* can oxidise the aromatic core by a single electron transfer to form the π-C–H radical cation **I**.[3d] At this stage, the acidity of the benzylic proton is dramatically increased; the estimated pK_a of a toluene radical-cation in acetonitrile is between −9 and −13, thus making it an extremely strong acid that deprotonates readily, even in moderately acidic media.[24] Moreover, we determined a KIE of 1 for a competition experiment between **1a** and its mono-deuterated benzylic derivative, which is in perfect agreement with an initial arene oxidation. A subsequent additional TPT oxidation to **IV** may be contributing to the product formation, but it is not the major pathway. In the presence of molecular iodine, the process needs to proceed through interplay between photoredox and iodine catalysis. Following the formation of the benzylic radical **II**, interception of the benzyl radical by molecular iodine generates the benzylic iodide **III**. Formation of product **2a** can occur directly by nucleophilic substitution liberating HI, which is then re-oxidised by the photoredox system.

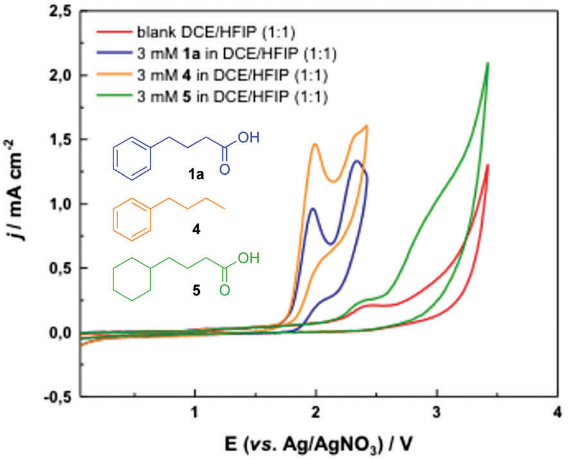


Fig. 1 Cyclic voltammetry of **1a** (3 mM, blue line), **4** (3 mM, yellow line) and **5** (3 mM, green line). The voltammogram for the blank electrolyte is shown for comparison (red line). Working electrode: glassy carbon; counter electrode: platinum wire; reference electrode: Ag/0.01 M AgNO$_3$ in 0.1 M Bu$_4$NClO$_4$; and scan rate: 50 mV s^{-1}.

An alternative mechanism is based on the observation that water traces are a requirement in the present catalysis. In agreement with our earlier work,[15] this points to an involvement of hypoiodite. We used Raman spectroscopy to clearly identify the rapid formation of hypoiodite in the wet medium by disproportionation of the molecular iodine.[21,25] Hypoiodide should then be involved in the formation of the corresponding iodoso benzyl derivative **V**, which provides sufficient leaving group ability to foster rapid reductive C–O bond formation.[26] This sequence to **2a** releases HOI, which is thus a steady component under these conditions. While we are currently unable to differentiate the individual cycles, the observed selectivity of the overall transformation proves the superior performance (synthetic potential) of dual iodine/photoredox catalysis. As a mechanistic consequence, all oxidation is exclusively promoted by the dye within multiple events. These include initial oxidation of the organic substrate and the regeneration of the molecular iodine. In addition, a competing, albeit kinetically less competent pathway based on photoredox catalysis alone may be involved.

We have discovered a new oxidative process for the lactonization of benzylic C–H bonds. The reaction combines catalytic amounts of molecular iodine and a dye and relies on photoredox catalysis as the terminal oxidation. The present protocol broadens molecular iodine catalysis and should be instructive for the development of related C–H oxidation reactions.

Conflicts of interest

There are no conflicts to declare.

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