

A Novel Intermolecular Synthesis of γ -Lactones via Visible-Light Photoredox Catalysis

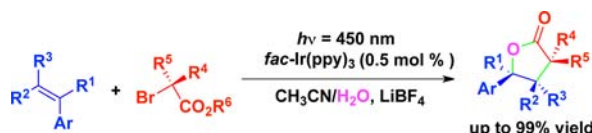
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ABSTRACT



Direct γ -lactone formation via visible-light photoredox catalysis has been achieved efficiently including hydroxylalkylation of aromatic alkenes and transesterification. The present photocatalytic protocol has good regioselectivity and substrate compatibility, affording a novel way to intermolecular γ -lactone synthesis by the reaction of styrenes with α -bromo esters in the absence of any external oxidants.

γ -Lactones are basic structural elements in many natural products and are prevalently used building blocks in agrichemicals, pharmaceuticals and organic materials.¹ A tremendous amount of effort has been devoted and much progress has been made to introduce the γ -lactone moiety into organic molecules,² among which the intra- or intermolecular reactions of alkenes with nucleophiles³ or radical precursors⁴ are most common approaches to construct the skeletons. However, stoichiometric oxidants and harsh reaction conditions are always employed to activate alkenyl moieties or produce radicals in the transformations.

Moreover, the addition of oxidant tends to cause a crisis of undesired side reactions and may lead to pollution of the environment. As a result, an efficient and environmentally friendly method should be developed.

As an efficient and sustainable method to perform organic reactions, visible-light photoredox catalysis has attracted widespread research interest owing to its attractive features such as mild and green conditions, excellent functional group tolerance, and high reactivity.⁵ In addition, as the main wave band of solar energy, visible light is generally readily available and can easily be used without the need of a special instrument or apparatus. Moreover, compared to ultraviolet irradiation, the transparent properties of most organic substrates for visible light minimize the side reactions.

Over these years, a variety of elegant chemical transformations via visible-light photoredox have been developed.⁶ Seminal works by MacMillan,^{7a,b} Stephenson,^{7c,d} and Gagné^{7e} et al. have demonstrated that activated haloalkanes such as carbonyl, benzyl, alkenyl, aryl, and heteroatom

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Table 1. Screening of Reaction Conditions^a

entry	conditions	yield (%) ^b
1	(CH ₃) ₂ CO:H ₂ O = 9:1	28
2	DMF:H ₂ O = 9:1	74
3	CH ₃ CN:H ₂ O = 9:1	80
4	CH ₃ CN:H ₂ O = 4:1	82
5	CH ₃ CN:H ₂ O = 4:1; LiBr (1.2 equiv)	79
6	CH ₃ CN:H ₂ O = 4:1; LiCl (1.2 equiv)	84
7	CH ₃ CN:H ₂ O = 4:1; LiBF ₄ (1.2 equiv)	93
8	CH ₃ CN:H ₂ O = 4:1; LiBF ₄ (0.5 equiv)	87
9 ^e	CH ₃ CN, LiBF ₄ (1.2 equiv) (no H ₂ O)	N.D.
10 ^{e,f}	CH ₃ CN:H ₂ O = 4:1, LiBF ₄ (1.2 equiv)	N.R.
11 ^{d,f}	CH ₃ CN:H ₂ O = 4:1, LiBF ₄ (1.2 equiv)	N.R.

^a Reaction conditions: a mixture of **1a** (0.20 mmol), **2a** (0.24 mmol) and photocatalyst *fac*-Ir(ppy)₃ (0.5 mol %) in solvent was irradiated with a 3 W blue LEDs at room temperature for 24 h. ^b Isolated yield. ^c Irradiated without *fac*-Ir(ppy)₃. ^d The reaction was conducted in the dark. ^e N.D. = not detected. ^f N.R. = no reaction.

halides are efficient precursors for the generation of carbon-centered radicals under photoredox catalytic conditions. In some of these reactions both the quenching and the regeneration of the photocatalyst are promoted by the substrates or intermediates of the catalyzed reaction; therefore, external reductants or oxidants are no longer needed.⁷

With this in mind, we initiated the study by using 1,1-diphenylethylene **1a** and α -bromo diethyl malonate **2a** with catalytic amount of *fac*-Ir(ppy)₃. It was encouraging to see that the aimed product **3a** was obtained in 28% yield after 24 h of irradiation (blue LEDs, λ = 450 nm) at room temperature when the reaction was performed in a mixture of acetone and water (9:1 v/v) (Table 1, entry 1). The replacement of acetone by *N,N*-dimethylformamide (DMF) or acetonitrile resulted in a significant improvement of the yield (Table 1, entries 2 and 3), and acetonitrile was chosen as the ideal organic solvent for the reaction. Next, we investigated the amount of water for the transformation; the result proved that acetonitrile/water (4:1) gained a better result (Table 1, entry 4). Considering the activation

Table 2. Scope of Visible-Light-Induced γ -Lactones Synthesis with α -Bromo Esters **2**^a

entry	α -bromo esters	product	yield (%) ^b
1	2a	3a	93
2	2b	3b	95
3	2c	3c	98
4	2d	3d	94
5	2e	3e	94
6	2f	3f	92
7	2g	3g	60
8	2h	3h	99

^a Reaction conditions: a mixture of **1** (0.20 mmol), **2** (0.24 mmol), LiBF₄ (0.24 mmol) and photocatalyst *fac*-Ir(ppy)₃ (0.5 mol %) in CH₃CN/H₂O (4:1 v/v) was irradiated with a 3 W blue LEDs at room temperature for 24 h. ^b Isolated yield.

of carbonyl moiety may be beneficial for the production of γ -lactones, a brief screen of lithium salts additives was performed (Table 1, entries 5–7). The best result was achieved when 1.2 equiv of LiBF₄ was introduced to the system. In this case we obtained the desired γ -lactone **3a** in 93% isolated yield. In addition, the attempt to reduce the amount of LiBF₄ slightly decreased the yield (Table 1, entry 8). It was worth noting that no product was detected when the reaction was carried out in dry acetonitrile (Table 1, entry 9). Moreover, when the reaction was carried out in the absence of *fac*-Ir(ppy)₃ (Table 1, entry 10) or in the dark (Table 1, entry 11), no conversion could be observed, which indicated that the reaction was indeed a visible-light-driven photoredox process.

On submission to the optimized conditions, we next investigated the scope of α -bromo esters **2** for the reaction. α -Bromo dimethyl malonate **2b** can also react with **1a** to produce **3b** in excellent yield (Table 2, entry 2). Moreover, this kind of reaction was successfully applied to ethyl

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Table 3. Reaction of **1a** with Various Alkyl Bromoacetates^a

entry	bromoacetate	yield (%) ^b
1	2i (R = Et)	99
2	2j (R = Me)	99
3	2k (R = ^t Bu)	29 (67) ^c
4	2l (R = TMS)	70
5	2m (R = Ph)	75
6	2n (R = <i>p</i> -NO ₂ Ph)	23

^a The reaction conditions as described in Table 2. ^b Isolated yields.^c Yield in bracket performed with 2.0 equiv of 2,6-lutidine.

bromoacetate with substituted groups such as methyl and phenyl group. The corresponding γ -lactone products **3c–3e** were obtained in excellent yields (98–94%). Reaction of **2f** and **2g** proceed effectively, and lactones with fluorine group such as **3f**, **3g** might be helpful in the pharmaceutical and agrochemical fields (Table 2, entries 6 and 7). Ethyl 2-bromo-2-methylpropanoate **2h** was also smoothly transformed to corresponding lactone with excellent yield (Table 2, entry 8).

We next studied the reactivities of bromoacetates with various alkoxyl groups⁸ in the visible-light-promoted γ -lactone synthesis. The results showed that methyl and ethyl 2-bromoacetate were completely converted into γ -lactones, respectively (Table 3, entries 1 and 2). Trimethylsilyl and phenyl 2-bromoacetate could also produce the same product **3i**, even though the reaction proceeded less efficiently than the former cases (Table 3, entries 4 and 5). Finally, we found the *tert*-butyl and *p*-nitrophenyl just could afford small amount of target compound (Table 3, entries 3 and 6), but in the case of *tert*-butyl 2-bromoacetate the yield could be improved to 67% by addition of a base 2,6-lutidine.

Having found a broad range of α -carbonyl alkyl bromides, the substrate scope with regard to substituted styrene was examined. As shown in Table 4, both styrene and *p*-methoxy-substituted styrene could obtain the γ -lactones with good yields (Table 4, entries 1 and 2). Not surprisingly, the α and β methyl substituted styrene yielded the aimed products with good to excellent yields (Table 4, entries 3 and 4). Biaryl lactone **3n** was obtained in similar way (Table 4, entry 5). It is noteworthy that when conjugated benzyl diene (*E*)-buta-1,3-dien-1-ylbenzene **1g** was used, the desired product **3o** was isolated in 78% yield with exclusive regioselectivity toward the terminal olefin (Table 4, entry 6). At the same time, benzocycloalkene (Table 4, entries 7 and 8) gave

Table 4. Scope of Visible-Light-Induced γ -Lactones Synthesis with Styrenes **1**^a

entry	alkene	2	product	yield (%) ^b
1	1b (styrene)	2a (EtO ₂ C-CH ₂ -Br)	3j	70 (1:1.5) ^c
2	1c (<i>p</i> -MeO-C ₆ H ₄ -CH=CH ₂)	2a	3k	72 (1:1)
3	1d (2-methylstyrene)	2a	3l	80 (1:1.6)
4	1e (2-phenyl-2-butene)	2a	3m	99 (1:6.4)
5	1f (1,1-diphenylethylene)	2a	3n	85
6	1g (<i>E</i> -buta-1,3-dien-1-ylbenzene)	2i (EtO ₂ C-CH ₂ -Br)	3o	78 (1:1.9)
7	1h (benzocyclopentadiene)	2i	3p	83
8	1i (benzocyclohexadiene)	2i	3q	56

^a The reaction conditions as described in Table 2. ^b Isolated yield. ^c dr and *E/Z* were determined by ¹H NMR spectrum.

the tricyclic γ -lactones with moderate to good yields, which had been employed as starting materials for the synthesis of strigolactone analogues.^{1a}

Since both bromoacetates and styrenes are transparent to 450-nm photons (see the Supporting Information), only the photocatalyst *fac*-Ir(ppy)₃ can be excited under the

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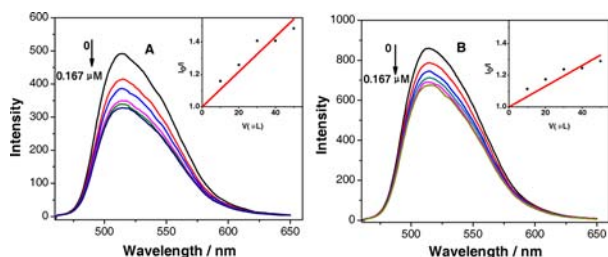
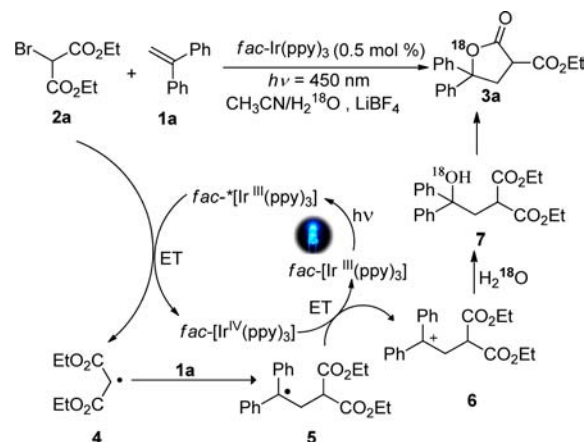


Figure 1. Photoluminescence quenching experiments. (A) Luminescence quenching of *fac*-Ir(ppy)₃ (2.00×10^{-4} M) with progressive addition of bromoacetate **2a**. (B) Luminescence quenching of *fac*-Ir(ppy)₃ (2.00×10^{-4} M) with progressive addition of styrene **1a**.

irradiation of blue LEDs (blue LEDs, $\lambda = 450$ nm). As shown in Figure 1, excitation of the characteristic absorption of *fac*-Ir(ppy)₃ resulted in a maximal photoluminescence at 513 nm in acetonitrile/water (4:1, v/v) solution, which was quenched by bromoacetate **2a** with a rate constant of 6.00×10^4 L mol⁻¹. Although the luminescence of *fac*-Ir(ppy)₃ can also be quenched by styrene **1a**, the rate was smaller (2.90×10^4 L mol⁻¹). As the spectral overlap of absorption of bromoacetate **2a** and photoluminescence of *fac*-Ir(ppy)₃ is rather small, the energy transfer from the excited *fac*-Ir(ppy)₃ to **2a** would be negligible. The photoluminescence quenching is therefore attributed to the electron transfer from the excited *fac*-Ir(ppy)₃ to bromoacetate **2a**. The ET procedure generates electron-deficient radical **4** along with *fac*-Ir^{IV}(ppy)₃. Then intermolecular π -addition of the radical **4** to styrene **1a** produces a benzylic radical **5**. Further ET from radical **5** to *fac*-Ir^{IV}(ppy)₃ affords carbocation **6** and regenerates the photocatalyst. The nucleophilic attack of the carbocation **6** by water results in the hydroxyalkylation of styrene, which was proved by H₂¹⁸O labeling experiment (see the Supporting Information). Finally, a spontaneous intramolecular transesterification promoted by LiBF₄ provided the desired γ -lactone **3a** (Scheme 1).⁹

Scheme 1. Proposed Mechanism Cycle



In summary, we have developed a catalytic, external-oxidant-free method for the construction of aryl-substituted γ -lactone via photoredox catalysis for the first time. The highlight of this operationally simple reaction is the avoidance of stoichiometric oxidants, low catalyst loading, and the generation of γ -lactone in high yields under mild conditions. Moreover, the photocatalytic transformation is also a beneficial supplement for alkene difunctionalization with photoredox catalysis.¹⁰ Further explorations on the method to build δ -lactone mediated by visible light is under investigation in our laboratory.

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Supporting Information Available. Experimental procedure, characterization data for the products and UV/vis absorption spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.