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# Chemistry A European Journal



# **Accepted Article**

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.202001032

Link to VoR: https://doi.org/10.1002/chem.202001032

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# Metal-free, Visible Light-induced Selective C-C Bond Cleavage of Cycloalkanones with Molecular Oxygen

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Dedicated to Professor Rof Huisgen on the occasion of his 100th birthday

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**Abstract:** A metal-free, visible light-induced oxidative C-C bond cleavage of cycloketones with molecular oxygen is described. Cooperative Brønsted-acid catalysis and photocatalysis enabled selectively C-C bond cleavage of cycloketones to generate an array of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -keto esters under very mild conditions. The mechanistic studies indicate that singlet molecular oxygen (<sup>1</sup>O<sub>2</sub>) is responsible for this transformation.

## Introduction

In recent years, selectively catalytic C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond activation has emerged as an attractive and alternative strategy for new chemical bonds formations.<sup>[1]</sup> For instance, the C-C bond cleavage of cycloalkanones has been developed to construct new C-C and C-heteroatom bonds.<sup>[2]</sup> However, due to the inherent lack of ring strain tension, the unstrained C-C bond cleavage is relatively challenging. Taking advantage of some unique synergistic catalytic activity of transition metals and ligands, the group of Jun and Dong disclosed several elegant metal-catalyzed C-C bond transition activation of cycloalkanones through the formation of ketamine intermediates to afford linear ketones or ring-expanded ketones, respectively.<sup>[3]</sup> On the other hand, radical strategy has also displayed vast potential in this area. For example, through modification cycloalkanones to the tertiary alcohols, the alkoxyl radicaltriggered C-C bond cleavage has been extensively investigated to obtain versatile functionalized linear carbonyl compounds.<sup>[4]</sup> Very recently, Zuo and co-workers reported an intriguing example of C-C bond cleavage of ketones.<sup>[5]</sup> Therein the ketones underwent a sequential nucleophilic addition and alkoxyl radical-mediated C-C bond scission via combined Lewis-acid catalysis with LMCT catalysis, offering a potential opportunity for diverse transformations of the cleaved C-C bond. Although direct photolysis of ketones was discovered more than 80 years ago, however, the further applications remains undeveloped due to its harsh reaction conditions (high-energy UV light) and complex conversions.<sup>[6]</sup> Given that cycloalkanones are commonly occurring functionalities in organic synthons, pharmaceuticals and natural products, the catalytic, selective C-C bond cleavage in cycloalkanones remains highly demanding and desirable.

Oxidation of cycloalkanones belongs to an important reaction in organic synthesis and industrial applications, which could provide a straightforward access to the dicarboxylic esters and the keto esters via C(CO)-C bond cleavage.<sup>[7]</sup> Among them, the molecular oxygen (O<sub>2</sub>) is undoubtedly the ideal oxidant, owing to its abundant, natural, and environmental friendly merits.<sup>[8]</sup> However, molecular oxygen (O2) is sometimes limited by its reaction efficiency. As we know, singlet molecular oxygen  $({}^{1}O_{2})$ is a more reactive oxygen species, which is probably responsible for most of the oxidation reactions. To activate the molecular oxygen, photocatalytic energy transfer was recognized as an attractive and sustainable method.<sup>[9]</sup> As a part of our interest in C-C bond cleavage,<sup>[10]</sup> we set out to explore the oxidation of unstrained cycloalkanones with O2 by means of visible-light driven photocatalysis. Herein, we report a metal-free, visible-light induced selective C-C bond cleavage of cycloalkanones with O<sub>2</sub>, which offers an environmental friendly and sustainable approach to the keto esters. For this reaction, the low-cost and easily available Rosolic acid was utilized as the photosensitizer.

## **Results and Discussion**

Initially, we examined the reaction of 2-phenylcyclohexan-1-one **1a** in the presence of 1 mol% of *fac*-lr(ppy)<sub>3</sub> as the photocatalyst, 8 mol% of AlCl<sub>3</sub> as the co-catalyst in EtOH at room temperature under irradiation of blue LEDs (10 W). To our delight, the desired  $\varepsilon$ -keto ester **3a** was obtained in 60% yield (Table 1, entry 1). The screening of photocatalysts revealed that using Mes-Acr-Me<sup>+</sup>ClO<sub>4</sub> – instead of the expensive *fac*-lr(ppy)<sub>3</sub> also furnished a comparable yield (Table 1, entries 2-6). Thus, we evaluated the co-catalysts using Mes-Acr-Me<sup>+</sup> ClO<sub>4</sub> – as the photocatalyst. Other Lewis acids such as VO(OEt)Cl<sub>2</sub>, FeCl<sub>3</sub>, TiCl<sub>4</sub> and Brønsted acid H<sub>2</sub>SO<sub>4</sub> were also effective (Table 1, entries 7-10). Among them, H<sub>2</sub>SO<sub>4</sub> gave a slight higher yield than AlCl<sub>3</sub>. The photocatalyst loading was also adjusted. However, increasing the photocatalyst loading to 2 mol% or 5 mol% didn't further improve the reaction efficiency (Table 1,

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desired products 4k and 4l in 50% and 40% yields, respectively. It was found that the sterically hindered tertiary alcohols gave poor yields of the esters (4m and 4n), which was attributed to the formation of by-product 4q and the incomplete conversion of 1a. Furthermore, the phenols were also applicable, delivering the phenolic esters 4o and 4p, albeit with somewhat low yields. However, thiols and thiophenols failed to give the expected

Rosolic Acid (8 mol%)

H<sub>2</sub>SO<sub>4</sub> (8 mol%)

toluene, O<sub>2</sub> (balloon Blue LEDs (10 W)

Scheme 1. The Scope of alcohols.<sup>[a]</sup>

**3i**. 85%

3n, 72%

3o. 43%

3s. 68%

3u 50%

**3w**, 80%

alcohols

**4a**, n = 0, 70%<sup>[b]</sup>

**4b**, n = 1, 49%<sup>[b]</sup> 4c n = 5 45% ဂူ

**4h**, n = 0, 45%

4i, n = 2, 63%

4k 50%

4m, 28% (32%)<sup>[c]</sup>

40 R = H 40%

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Tertiary alcohols С

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Phenols

Scondary

0

Ö 3q, 24% (54% brsm

ROF

performed well under air atmosphere to give the product 3a in 67% yield (Table 1, entry 12). Finally, control experiments revealed that visible light, photocatalyst and co-catalyst were all essential for the success of this reaction (Table 1, entries 13-15). It is worth mentioning that when we performed the reaction under Matsumoto's condition,<sup>[7d]</sup> only 51% yield of 3a was obtained (for details, see supporting information). Table 1. Optimization of the reaction conditions.[a] Primary alcohols PC (x mol%) co-catalyst (8 mol%) EtOH, O<sub>2</sub> (balloon) 3b, n = 0, 74%<sup>[b</sup> 3c, n = 2, 81%<sup>[b]</sup> 3d, n = 3, 71%<sup>[b]</sup> 3e, n = 4, 87%<sup>[b]</sup> Blue LEDs (10 W)

3a

entries 3 and 10). Interestingly, it was found that using 8 mol%

of low-cost Rosolic acid as the photocatalyst and 8 mol% of

H<sub>2</sub>SO<sub>4</sub> as the co-catalyst raised the yield of 3a up to 76 %. As

we know, the Rosolic acid was commonly used as an acid-base

indicator, which was rarely applied as a photosensitizer in the

photocatalyzed reaction.<sup>[11]</sup> Remarkably, the reaction also

Entry	Photocatalyst	Co-catalyst	Yield (%)
1	<i>fac</i> -Ir(ppy)₃ (1 mol%)	AICI <sub>3</sub>	60
2	[Ru(bpy) <sub>3</sub> ](PF <sub>6</sub> ) <sub>2</sub> (1 mol%)	AICI <sub>3</sub>	49
3	Mes-Acr-Me <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> (1 mol%)	AICI <sub>3</sub>	57 (56) <sup>[b]</sup>
4	Methylene Blue (1 mol%)	AICI <sub>3</sub>	30
5	Eosin Y (1 mol%)	AICI <sub>3</sub>	52
6	Rosolic Acid (1 mol%)	AICI <sub>3</sub>	28
7	Mes-Acr-Me <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> (1 mol%)	VO(OEt)Cl <sub>2</sub>	39
8	Mes-Acr-Me <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> (1 mol%)	FeCl <sub>3</sub>	24
9	Mes-Acr-Me <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> (1 mol%)	TiCl <sub>4</sub>	23
10	Mes-Acr-Me <sup>+</sup> ClO <sub>4</sub> <sup>-</sup> (1 mol%)	$H_2SO_4$	62 (48) <sup>[b]</sup>
11	Rosolic Acid (8 mol%)	AICI3 or $H_2SO_4$	72, 76 (78) <sup>[c]</sup>
12 <sup>[d]</sup>	Rosolic Acid (8 mol%)	H <sub>2</sub> SO <sub>4</sub>	67
13	-	H <sub>2</sub> SO <sub>4</sub>	n.r.
14	Rosolic Acid (8 mol%)	-	n.r.
15 <sup>[e]</sup>	Rosolic Acid (8 mol%)	H <sub>2</sub> SO <sub>4</sub>	n.r.

[a] Reaction conditions: 1a (0.2 mmol, 1.0 equiv), photocatalyst (1 mol%), cocatalyst (8 mol%), EtOH (2.0 mL), Blue LEDs(10 W), r.t., for 24 h, under O2. Yields of isolated product were given. [b] 5 mol% photocatalyst. [c] Using 2.0 equiv of EtOH as nucleophiles in toluene (2.0 mL). [d] Under air atmosphere. [e] In the dark.

With the optimal conditions in hand, the scope of alcohols 2 was evaluated with 1a. Satisfactorily, a range of structurally diverse alcohols engaged in this reaction smoothly to give the corresponding  $\varepsilon$ -keto esters **3** and **4**. A variety of primary alcohols delivered the  $\varepsilon$ -keto esters **3a-3x** with yields ranging from 24 to 95%. Functional groups such as unsaturated C-C bonds (3n-3q), ethers (3r-3u) and halogens (3w and 3x) survived well in this reaction. Both acyclic and cyclic secondary alcohols gave the desired products 4a-4j in moderate yields. The cholesterol and menthol were also amenable, providing the

**4q**, 13%

10.1002/chem.202001032

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3 or 4

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products due to the formation of disulphides under the standard conditions.<sup>[11c]</sup> In addition, using benzylamine as the nucleophile also could not give the corresponding amide, along with the formation of benzaldehyde<sup>[14]</sup>. However, other alkyl amines such as *n*-amylamine and piperidine were used as substrates, none of them gave the desired products under the standard conditions, along with 83% and 89% of **1a** were recovered, respectively (not shown). Finally, it is worth mentioning that the 6-oxo-6-phenylhexanoic acid (**4q**) was isolated as the major by-product sometimes (**3v**, **4m** and **4n**). Surprisingly, using 2.0 equiv of water instead of alcohol furnished only 13% yield of **4q** with 83% of **1a** recovered. Notably, the esterification reaction of the 6-oxo-6-phenylvaleric acid (**4q**) and phenylethyl alcohol also worked under the standard conditions, giving the ester **3k** in 60% isolated yield (for details, see SI).

#### Scheme 2. The Scope of cycloalkanones.[a]



[a] Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2j (0.4 mmol, 2.0 equiv), 8 mol% of Rosolic Acid, 8 mol% of  $H_2SO_4$ , toluene (2.0 mL), Blue LEDs (10 W), r.t., for 24 h, under O<sub>2</sub>. Yields of isolated product were given. [b] 5.0 equiv of BnOH was used.

Subsequently, we examined the scope of this visible lightinduced oxidative C-C bond cleavage with various cycloalkanones. A wide range of 2-aryl cyclohexanones reacted regioselectively to afford the  $\varepsilon$ -keto esters **5a-51** in moderate to good yields, except for 2-(2-methoxyphenyl) cyclohexanone (**5f**). 2-(2,6-Dimethylphenyl)cyclohexan-1-one also failed to give the target product, probably due to the large steric effect. Not only 2aryl cyclohexanones but also 2-alkyl substituted cyclohexanones were compatible under the standard conditions. The 2-methyl cyclohexanone reacted smoothly to give the product 5m in 45% yield. When the menthone was used, relatively lower 33% yield of the target 5n was isolated due to low conversion. Unfortunately, the unsubstituted cyclohexanone only resulted in trace amount of the anticipated product, which instead provided 25% yield of the ketal 5o'. We speculated that the existence of substituent on the  $\alpha$  position is probably beneficial to enhance the stability of intermediates in this reaction. However, the steric hindrance of the a-substituent could also be an unfavourable factor, because it might prevent or slow down the formation of the hemiacetal. 2-Tetralone participated in this reaction to give the desired product 5p in 43% yield, along with 16% yield of the diester 5p' as by-product. In addition, cycloalkanones with different ring sizes were also investigated. 2-Substituted cyclopentanones underwent this reaction to afford the  $\delta$ -keto esters 5q-5s in 47-60% yields. The more strained 2phenylcyclobutan-1-one also worked, producing the y-keto ester 5t in 54% yield. A comparison of the yield of 3j (90%), 5g (60%) and 5t (54%) showed that there is not a positive correlation between the yields and the strain force, implying that the ring strain was not a crucial factor in this C-C bond cleavage reaction. Furthermore, the acetophenone was also subjected to the reaction system. However, no reaction occurred (not shown).

#### Scheme 3. Control experiments



To shed light on the mechanism of this reaction, a series of experiments were performed carefully. When 2.0 equiv of TEMPO, well-known radical scavenger, was subjected into the reaction of 1a with ethanol, no product 3a was observed. Meanwhile, 15% yield of the TEMPO-adduct 6a was isolated and 78% of 1a was recovered. These results suggests that a radical process might be involved in this reaction (Scheme 3, Eq.1).<sup>[12]</sup> Additionally, using meso-tetraphenylporphyrin (TPP) instead of Rosolic Acid, which was reported to be a singlet oxygen generator<sup>[9][13]</sup> also led to the product **3a** in 73% yield (Scheme 3, Eq.2). Furthermore, the  $^{1}O_{2}$  generated from the evidenced catalvtic svstem was bv usina 1.3diphenylisobenzofuran (DPBF) as a trapping reagent (for details, see SI). This result is consistent with the performance of the reaction with TPP. Furthermore, the reaction could completely shut down in the absence of oxygen or photocatalyst as well as without irradiation (Table 1, entries 13-15). These results implied that <sup>1</sup>O<sub>2</sub> was the reactive oxygen species in this oxidative C-C

bond cleavage reaction. Moreover, the results of light on-off experiments and relative low quantum yield ( $\Phi = 0.12$ ) indicated that the reaction proceeded through a catalytic process rather than a radical chain process (for details, see SI). Finally, to verify the reaction intermediates the enol ester **7a** and peroxy alcohol **8a** were synthesized respectively. Both of them gave the desired products under the standard reaction conditions (Scheme 3, Eq. 3 and Eq. 4), implying that they are the possible intermediates in this reaction.

#### Scheme 4. Proposed two mechanistic pathways



On the basis of these results mentioned above and literature.<sup>[2b, 9e-g]</sup> two possible reaction pathways were proposed in Scheme 4. In pathway a: hemiketalization of ketone 1 in the presence of sulfuric acid and alcohol delivers intermediate A, which further undergoes dehydration to afford vinyl ether B. Meanwhile, the visible light irradiation to RA gives rise to excited RA\* species, which activates <sup>3</sup>O<sub>2</sub> to provide the active singlet <sup>1</sup>O<sub>2</sub> through an energy transfer process. Subsequently, the reaction of singlet <sup>1</sup>O<sub>2</sub> with vinyl ether **B** leads to the formation of dioxetane intermediate C. Finally, the fragmentation of the C-C bond and O-O bond of dioxetane C produces the target keto esters 3-5. Another plausible mechanistic pathway was showcased in pathway b: enolization of 1 forms the enol D, which reacts with singlet <sup>1</sup>O<sub>2</sub> to give the hydroperoxide E. Then, peroxide E undergoes homolytic O-O bond scission, followed by C-C bond fragmentation to afford the acetyl radical intermediate G. The radical G rapidly converts to the keto esters 3-5 or acid 4q via an oxidation/nucleophilic attack cascade. Based on the fact that poor yield of the 4q was obtained when water was employed as the nucleophile and the results of 7a and 8a, we speculated that the reaction is probably in favor of the pathway a in the presence of alcohols.

### Conclusion

In conclusion, we have developed a visible light-induced C-C bond cleavage of cycloketones with  $O_2$ . This protocol features low-cost catalytic systems, mild conditions (metal free, room temperature) and operational simplicity, thus providing an environmentally benign and sustainable method to achieve the C-C bond cleavage of cycloketones for the distal keto ester synthesis. The mechanistic studies suggest that the  ${}^1O_2$  would be the real reactive oxygen species in this transformation. Further mechanism investigation and possible application of this method are ongoing in our laboratory.

### Acknowledgements

Financial support from the National Natural Science Foundation of China (21971201), Natural Science Basic Research Plan in Shaanxi Province of China (No. 2019JM-299), Key Laboratory Construction Program of Xi'an Municipal Bureau of Science and Technology (No. 201805056ZD7CG40) is greatly appreciated. We also thank Mr Chang and Miss Lu at Instrument Analysis Center of Xi'an Jiaotong University for their assistance with NMR and HRMS analysis.

**Keywords:** visible-light catalysis • metal-free • C-C bond cleavage • singlet molecular oxygen • cycloalkanone

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# **RESEARCH ARTICLE**

## **Entry for the Table of Contents**



A metal-free, visible light-induced selective C-C bond cleavage of cycloketones with molecular oxygen is achieved through merging Brønsted-acid catalysis and photocatalysis. This protocol features low–cost catalytic systems, mild conditions and operational simplicity, thus providing an environmentally benign and sustainable approach to an array of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -keto esters. The mechanistic studies indicate that singlet molecular oxygen (<sup>1</sup>O<sub>2</sub>) is responsible for this reaction.

Institute and/or researcher Twitter usernames: ((optional))