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Visible light-induced oxidative α -hydroxylation of β -dicarbonyl compounds catalyzed by ethylenediamine–copper(II)[†]

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We have developed an efficient oxidative α -hydroxylation of β -keto esters with firstly using the structurally simple ethylenediamine–copper(II) as a catalyst for β -keto esters activation and using visible light as the driving force for generating more active singlet oxygen ($^1\text{O}_2$) from triplet state oxygen ($^3\text{O}_2$) in the air, providing a series of α -hydroxy β -keto esters in excellent yields (up to 99%) under extremely low photosensitizer loading (0.01 mol%) and catalyst loading (1 mol%) within a short time. Moreover, the gram-scale synthesis showed the practical utility of this protocol.

Introduction

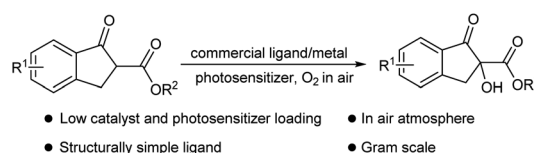
The α -hydroxy β -dicarbonyl moiety is a functional and structural motif in numerous natural products and pharmaceuticals such as hamigeran A,¹ vindoline analogue,² Y224A,³ kjellmanianone,⁴ and pramanicin.⁵ Furthermore, the intact α -hydroxy β -dicarbonyl compound is the key intermediate in synthetic transformations, as represented by the manufacture of the insecticide indoxacarb.⁶ The oxidative α -hydroxylation of dicarbonyl compounds, providing a direct access to such a skeleton, have therefore been extensively studied over the past years. In this respect, the extensive investigation revealed that most of these works often rely on using strong oxidants such as organic peroxide,⁷ oxaziridine,⁸ dimethyldioxirane⁹ or nitrosobenzene.¹⁰ From economic as well as environmental viewpoints, visible light has been recognized as a type of environmentally-friendly sustainable energy and molecular oxygen is considered a green oxidant, so visible light-induced aerobic oxidation is undoubtedly a more appealing strategy for the α -hydroxylation of β -dicarbonyl compounds. At present, considerable achievements have been made in this promising project by Meng's groups using the salan-copper(II) and cinchona alkaloid derivatives as a catalyst for activating the β -keto esters and tetraphenyl-porphyrin (TPP) or phthalocyanine (PC) as the optimal photosensitizer.¹¹ Meanwhile, the combination of bis(oxazoline)–Ni(II) complexes and a visible light photosensitizer in grafting or physically mixed way, reported by Xiao's group¹² and our group,¹³ respectively, providing

alternative catalysis systems to realize this transformation. Despite these important advances, when we consider the long-standing challenges that lowering catalyst and photosensitizer loading, using structurally simple catalyst and achieving excellent catalyst performance and practicable reaction scale-up in such light-mediated oxidative α -hydroxylation of β -dicarbonyl compounds, developing new competent catalytic system to be compatible with photooxidation remain highly desirable (Scheme 1 and Fig. 1).

In our previous works, the chiral bisoxazolines have been demonstrated as a type of competent N-donor ligands in the asymmetric α -functionalization of dicarbonyl compounds, such as the electrophilic fluorination and Michael addition reactions of β -keto esters and the brominative dearomatization of naphthol derivatives.¹⁴ Basing on the recognition of the activating nature of bisoxazoline–metal complexes, we turn our attention to developing structurally simple N-donor ligands, particularly some commercial organic molecule, to coordinate with metal salts and realize the α -functionalization of dicarbonyl compounds in enantioselective or nonenantioselective manner.

Results and discussion

The β -amino alcohol, being the starting material of bisoxazoline ligands to provide nitrogen coordination center to metal ion, was chosen as the ligand in our initial study. We employed 1-



Scheme 1 The visible-light induced oxidative α -hydroxylation of β -keto esters catalyzed by structurally simple ligand/metal complexes.

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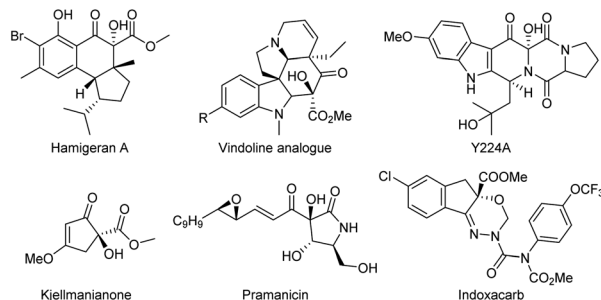


Fig. 1 The natural products and pharmaceuticals containing α -hydroxy β -dicarbonyl moiety.

methyl indanone carboxylate **1a** as a model substrate and O_2 in the air as an oxidant for the α -hydroxylation reaction under the green light of 525 nm, the desired product **2a** was obtained in 86% yield in one hour with using benzylethanolamine **L₁** as ligand and $Cu(OAc)_2$ as metal salt (Table 1, entry 1). Encouraged by this result, the other β -amino alcohols **L₂**–**L₄** were investigated, the α -hydroxylation product would be provided in an excellent yield of 99% within one hour when using

Table 1 The catalyst and photosensitizer screening^a

Entry	Ligand	Lewis acid	Time/h	Yield ^b /%
1	L₁	$Cu(OAc)_2$	1	86
2	L₂	$Cu(OAc)_2$	1	99
3	L₃	$Cu(OAc)_2$	2	95
4	L₄	$Cu(OAc)_2$	2	83
5	L₅	$Cu(OAc)_2$	1	99
6	L₆	$Cu(OAc)_2$	1	95
7	L₇	$Cu(OAc)_2$	2	50
8	L₅	$Zn(OAc)_2 \cdot 2H_2O$	1	95
9	L₅	$Ni(OAc)_2 \cdot 4H_2O$	1	89
10	L₅	$CuSO_4$	1	91
11	L₅	$CuCl_2$	1	83
12	L₅	$Cu(OTf)_2$	1	86
13 ^c	L₅	$Cu(OAc)_2$	1	40
14 ^d	L₅	$Cu(OAc)_2$	1	82
15	—	$Cu(OAc)_2$	1	28
16	L₅	—	1	Trace
17 ^e	L₅	$Cu(OAc)_2$	1	Trace

^a Reactions were performed with **1a** (0.1 mmol), TPP (1 mol%) and 10 mol% of ligand and Lewis acid in PhMe (2.0 mL) under an air atmosphere. ^b Isolated yields. ^c Thioxanthone was used as photosensitizer. ^d Rose Bengal was used as photosensitizer. ^e No photosensitizer.

phenylglycinol **L₂** as ligand (entry 2 vs. entry 1), and the ligands **L₃** and **L₄** led to comparable results in longer time (entries 3 and 4 vs. entry 1). The no-substituted ethylenediamine **L₅** and cyclohexane diamine **L₆** which were generally used to construct salen ligands were then tested, it was shown that better catalyst performance was observed with using ethylenediamine **L₅** as ligand, affording the α -hydroxylation product in 99% yield (entry 5 vs. entry 6). We continued the investigation by using 1,10-phenanthroline **L₇** as the ligand, providing an eroded result (entry 7). From the viewpoint of economy and accessibility, the ethylenediamine **L₅** was identified as the optimal ligand. Next, various metal salts complexing with ethylenediamine **L₅** were investigated. When using $Zn(OAc)_2 \cdot 2H_2O$, $Ni(OAc)_2 \cdot 4H_2O$ instead of $Cu(OAc)_2$, the yield of reaction would be slightly decreased (entries 8 and 9 vs. entry 5). Considering the influence of counterions, different copper(II) salts were then assessed, and the results showed that the coordination of **L₅** with $Cu(OAc)_2$ gave better yield (entries 10–12). Subsequently, other photosensitizers such as rose Bengal and thioxanthone were tested, while the isolated yield of desire products were obviously decreased (entries 13 and 14 vs. entry 5). The indispensability of the ligand, metal salts and visible light in this reaction was demonstrated by single factor test (entries 15–17).

With the optimum catalyst and photosensitizer identified, other parameters such as solvent and catalyst loading were investigated. As shown in Table 2, the screening of organic solvent revealed that an excellent yield could be obtained when using toluene, MTBE or THF as the solvent (entries 1–7). To further explore the efficiency of this catalytic system, the lower catalyst loadings were tested (entries 8–10). In detail, the

Table 2 Optimization of reaction conditions^a

Entry	Solvent	$Cu(OAc)_2/L_5$ (mol%)	Time/h	Yield ^b /%
1	Toluene	10	1	99
2	DCE	10	1	58
3	MeOH	10	1	91
4	DMF	10	1	41
5	EtOAc	10	1	94
6	MTBE	10	1	99
7	THF	10	1	99
8	Toluene	1	12	82
9	MTBE	1	12	67
10	THF	1	2	99
11	THF	0.5	12	35
12 ^c	THF	1	4	99
13 ^d	THF	1	7	99
14 ^e	THF	1	12	42

^a Reactions were performed with **1a** (0.1 mmol), TPP (1 mol%) in solvent (2.0 mL) under an air atmosphere. ^b Isolated yields. ^c With 0.1 mol% TPP loading. ^d With 0.01 mol% TPP loading. ^e With 0.005 mol% TPP loading.



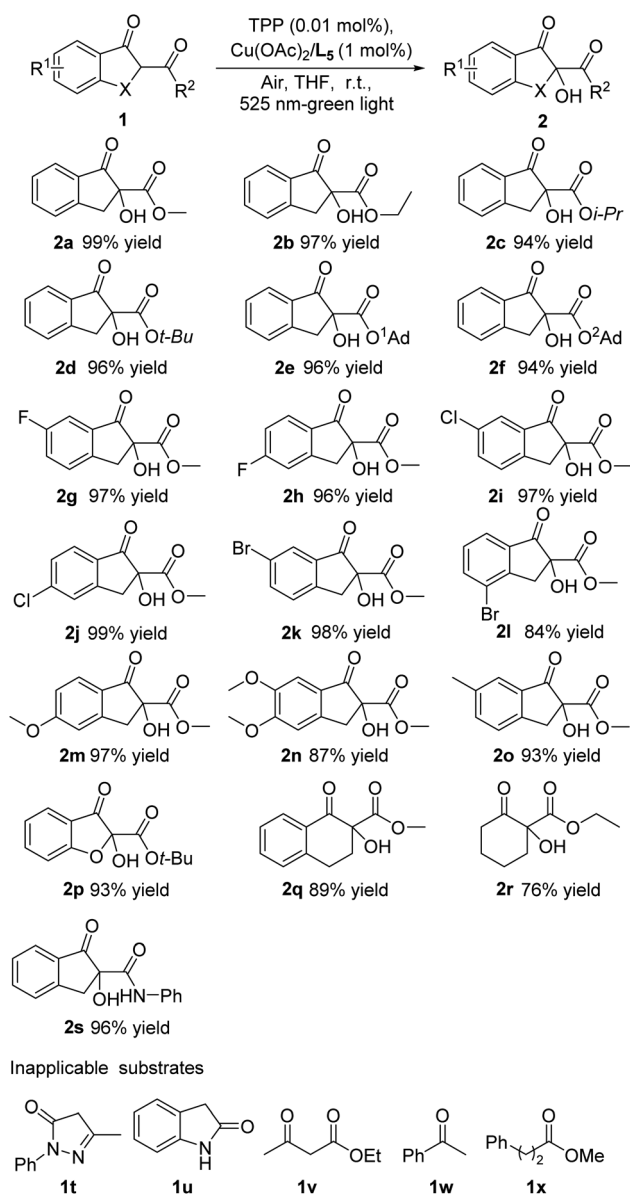
decrease to 1 mol% metallic catalyst loading still enabled the transformation to work well when using THF solvent, providing the product **2a** in the maintained yield (99% yield) within two hours (entries 8 and 9 vs. entry 10). With further decrease in catalyst loading, the much-diminished yield would be observed albeit in longer reaction time (entry 11). The next study shown that the TPP loading could be reduced to as low as 0.01 mol%, providing same perfect reaction outcome (99% yield) *via* prolonging the reaction time to 7 h (entry 13), and the lower TPP loading of 0.005 mol% would result in observably eroded catalytic performance (entry 14).

Under the above optimized conditions, we initially assessed the generality of the α -hydroxylation reaction for different β -

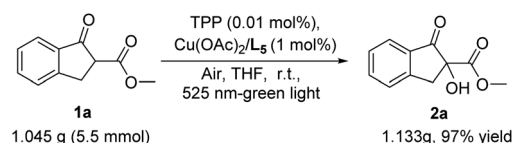
keto esters. As shown in Scheme 2, in most cases, the α -hydroxylation reaction of various β -keto esters proceeded efficiently with high yields. In detail, the ester functionality with different steric hindrance (**1a–1f**) was well tolerated and the corresponding products were afforded with excellent yields (94–99% yields). The β -keto esters with the aromatic ring bearing electron-withdrawing halogen groups at different positions (**1g–1l**) underwent the reaction smoothly, give the desired products in comparable yields (up to 84–99% yields). Besides, when the electron-donating groups such as MeO and Me were tethered to the aromatic ring, a maintained reaction outcome could be obtained (**1m–1o**). Next, benzofuranone, tetralone and cyclohexanone-derived β -keto esters (**1p–1r**) were demonstrated to be amenable to the reaction protocol, furnishing the desired products in satisfactory yields (76–93% yields). In order to investigate the possible extension of this reaction, the β -keto amide **1s** were chose as substrates, allowing the reaction to provide α -hydroxylation products in still high yields (96% yield). Meanwhile, the substrates with no α -substituent such as pyrazolin-5-ones, oxindole, acetoacetic ether, acetophenone and 3-phenylpropionic acid esters have been tested under the optimized reaction conditions, while these transformations did not proceed smoothly and no desired products were isolated, presumably because the C–H bond enthalpy or dissociation energy of primary carbon and secondary carbon was higher than tertiary carbon, making it hard for above substrates to be oxidized in present catalytic system.

To demonstrate the synthetic potential of this aerobic hydroxylation of β -keto esters, the scale-up of this reaction was performed. The result shown that the reaction of β -keto esters **1a** at 5.5 mmol proceeded well under the standard conditions to generate the corresponding adduct **2a** in 97% yield, suggesting that this aerobic α -hydroxylation has the potential for a large-scale production without a decrease in chemical yield (Scheme 3).

Some control experiments have also been conducted to better understand the reaction mechanism. The hydroperoxide **2A** was prepared *in situ* at lower temperature of 0 °C, and the high-resolution mass spectrum of the reaction mixture could certify the generation of intermediate **2A**.¹⁵ While because of the high reactivity and the instability of **2A**, we could not isolate such intermediate product. Moreover, tertiary butyl indanone carboxylate **1d** was added to above reaction solution (Scheme 4a), the α -hydroxylation product **2d** could be obtained with no light irradiation, revealing that the hydroperoxide **2A** may also as oxidizing agent in this photooxygenation. Comparing with the result of the entry 11 in Table 2, the control experiment using 0.5 mol% of Cu/ethylenediamine 1 : 2 mixture as catalyst

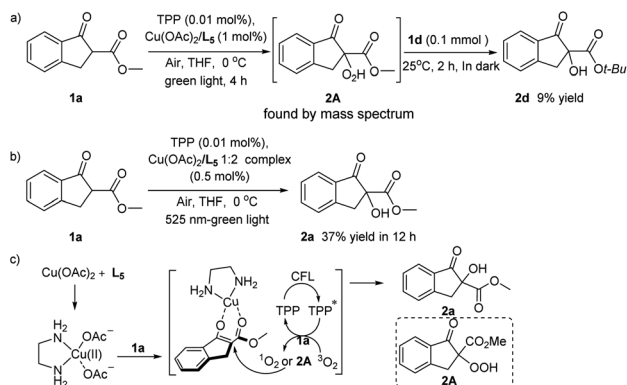


Scheme 2 The evaluation of substrate scope. All yields are of isolated products. Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), TPP (0.01 mol%), 1 mol% of Cu(OAc)₂ and L₅ in THF (2.0 mL) under air atmosphere.



Scheme 3 Synthetic potential.





Scheme 4 The control experiments (a and b) and the proposed mechanism (c).

shown almost same catalysis performance (Scheme 4b). That is, only increasing the amount of ligand didn't improve the transformation efficiency, indicating that the molar ratio of Cu(II) ion and ethylenediamine ligand in the transition state of this reaction might be 1:1, even though the bis(ethylenediamine)copper complex could also be formed in literature precedents.¹⁶

Based on the experimental results and the previous studies,^{11–14,17} a plausible reaction pathway was suggested. As shown in Scheme 4c, the pre-synthetic ethylenediamine-copper(II) complex acting as a Lewis acid catalyst to form the copper enolate species bearing increased nucleophilicity. Under the visible light, molecular oxygen was activated from the triplet state ($^3\text{O}_2$) to the singlet state ($^1\text{O}_2$) with the photosensitizer by energy transfer, and the hydroperoxide intermediate **2A** would be simultaneously yielded in this transformation. The subsequent attack of $^1\text{O}_2$ or hydroperoxide intermediate **2A** to the activated **1a** afforded the α -hydroperoxide product **2a**.

Conclusions

In summary, with firstly using structurally simple ethylenediamine-copper(II) catalyst for β -keto esters activation and TPP photosensitizer for generating highly active singlet oxygen ($^1\text{O}_2$) in the air atmosphere, an oxidative α -hydroxylation reaction of β -keto esters was developed under visible light, allowing an high-efficient access to various α -hydroxy β -keto esters with a wide substrate scope. Moreover, the low catalyst and photosensitizer loading, structurally simple ligand, easy scalability also demonstrated the fascination of this reaction protocol.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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