

Visible Light-Induced Salan-Copper(II)-Catalyzed Enantioselective Aerobic α -Hydroxylation of β -Keto Esters

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Abstract: A strategy of visible light-induced salan-copper(II)-catalyzed asymmetric α -hydroxylation of β -keto ester with utilization of sustainable air as the oxidant was developed. This protocol allows convenient access to a number of enantioenriched α -hydroxyl β -keto esters (up to 95% yield, 96% ee), especially for β -keto methyl esters that are valuable architectures in pharmaceuticals, including the key intermediate of the sodium-channel blocker (*S*)-indoxacarb. Experimental studies suggest that reactive singlet oxygen may participate in this reaction.

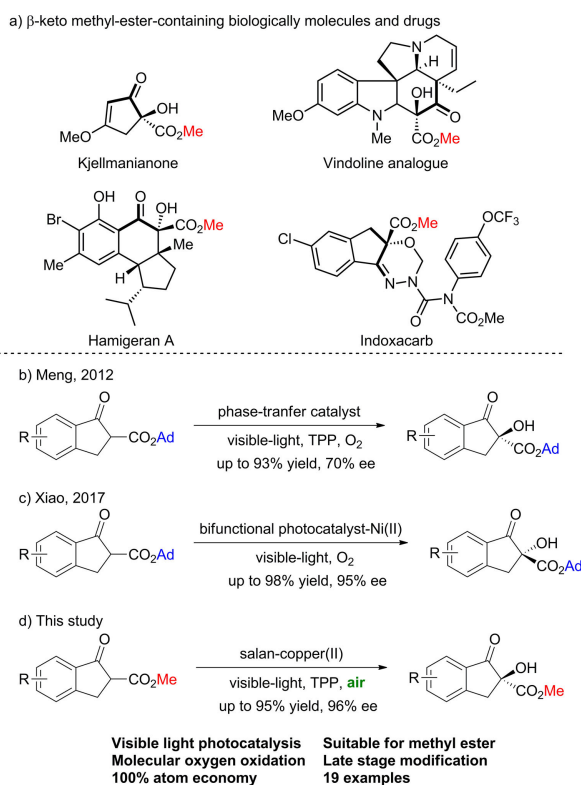
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Recently, visible light photocatalysis has offered a technically attractive and energy-saving platform for aerobic oxidation.^[1] In particular, the reactivity of singlet oxygen ($^1\text{O}_2$) has been applied to visible light activated asymmetric catalysis in recent years.^[2] However, the stereoselectivity control of the enantioselective hydroxylation reaction using photogenerated $^1\text{O}_2$ as the terminal oxidant still remains a challenge, and work in this field has rarely been reported.^[3] Specifically, our group first reported on the chiral phase-transfer catalyzed aerobic transformation using tetraphenylporphyrin (TPP) as the photosensitizer (Scheme 1b),^[3a] while Xiao et al. reported the asymmetric aerobic oxidation reaction by bifunctional photocatalyst-Ni(II) catalysis (Scheme 1c).^[3c] However, current methods are limited in application due to their dependence on the use of either structurally complex

catalysts or the steric induction of substrate itself to generate the requisite chiral environment.

Enantioenriched α -hydroxy β -keto esters, and particularly the those containing methyl ester compounds, are prevalent in a wide range of bioactive natural products and pharmaceuticals,^[4] including Kjellmanianone,^[5] Vindoline,^[6] Hamigeran A,^[7] and Indoxacarb (Scheme 1a).^[8] However, in previous studies, consistently high yields and enantioselectivities were achieved only for the β -keto esters bearing bulky ester groups,^[3,9] and an additional transesterification step is required for synthesis of the abovementioned biological molecules. Given these important advances, the direct enantioselective hydroxylation of valuable β -keto esters from sustainable, environmentally benign molecular oxygen remains an important yet elusive goal. Within this field, we sought to develop a new approach based on asymmetric photocatalysis to provide highly enantioselective access toward a broad range of α -hydroxy β -keto ester bearing smaller ester groups; such esters are highly valuable architectures but are challenging and difficult to achieve directly.

We started our study of this topic by investigating the asymmetric α -hydroxylation of 5-chloro indanone carboxylic methyl ester **1a** that served as the model reaction. In previous work, we demonstrated that using cumene hydro peroxide as the oxidant, the salan-Zr complex^[10] can catalyze the α -hydroxylation of β -keto methyl esters with excellent yields and enantioselectivities. Inspired by this result, we became interested in further exploring the potential of the easily prepared salan-metal complex-catalyzed asymmetric α -hydroxylation of β -keto esters **1a** under visible light and aerobic conditions (Scheme 1d). We initially investigated a series of metal salts such as Zr, Ti, Mn, and Cu chelated with the bionic salan ligand **L1** to catalyze the α -hydroxylation reaction (Table 1,



Scheme 1. Importance of α -hydroxylation of β -keto esters and approaches for their formation.

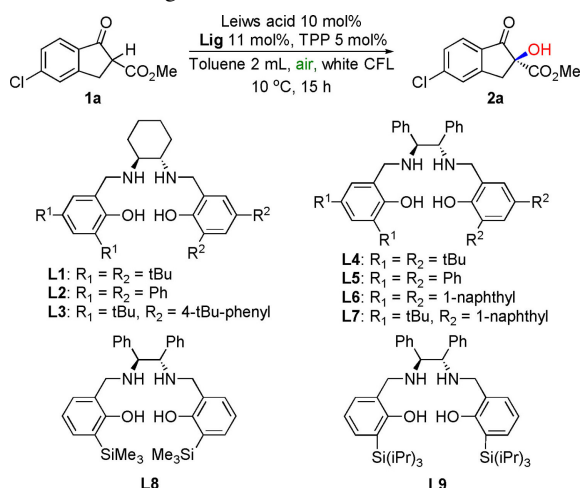
entries 1–4) in the presence of accessible TPP as the photosensitizer to produce $^1\text{O}_2$ from air under white compact fluorescent lamp (CFL) irradiation conditions. Gratifyingly, the desired product **2a** was obtained in 28% yield with 46% ee by using copper as the central metal. Then, we modified the catalysts with different copper salts (Table 1, entries 5–7) and found that the counterions had a crucial influence in the reaction. To our delight, the combination of $\text{Cu}(\text{OTf})_2$ with **L1** afforded the desired product **2a** in excellent yield and moderate enantioselectivity (Table 1, entry 7). When the phenyls (**L2**) were used instead of *tert*-butyls (**L1**), the enantioselectivity clearly decreased (Table 1, entry 8). The use of the ligand with C_1 -symmetry (**L3**) led to the decreased yield and enantioselectivity of product **2a** (Table 1, entry 9). Nevertheless, when (*1S*, *2S*)-diphenyldiamine provided the chiral source of the ligand (**L4**), excellent yield and good enantioselectivity were observed (Table 1, entry 10). The yields and enantioselectivities decreased rapidly when *tert*-butyls of **L4** were replaced by different aromatic rings (Table 1, entries 11, 12). Although the excellent yield can be obtained by the combination of $\text{Cu}(\text{OTf})_2$ and **L7**, only moderate enantioselectivity was obtained (Table 1, entry 13). According to the results of entries 10–13, it was revealed that the *tert*-butyls on the both

ortho- and *para*-positions of the hydroxyl groups in the ligands had a significant impact on the enantioselectivities of the α -hydroxylation because of their steric hindrance and electron donation effect. When different sterically hindering groups such as trimethylsilyl **L8** and triisopropylsilyl **L9** were used instead of *tert*-butyls, good to excellent yields and only moderate enantioselectivities were obtained (Table 1, entries 14, 15). When the $\text{Cu}(\text{OTf})_2$ was activated by vacuum drying, the better enantioselectivity 84% ee can be observed (Table, entry 16). In order to prevent the in-situ generation of the salen-copper(II) from being affected by the water vapor, the air dried by 4 Å molecular sieves was slowly injected via an air pump into the reaction flask, the enantioselectivity was improved to 90% ee (Table 1, entry 17). Lower reaction temperatures and the loading of TPP were beneficial for the ee value of α -hydroxy- β -keto ester product (Table 1, entries 18, 19), and the (Not segmented here)

enantioselectivity increased to 96% ee. The enantioselectivities decreased dramatically when other aromatic solvents were used (Table 1, entries 20, 21). Control experiments indicated that visible light, copper salt, chiral ligand, photosensitizer, and air were essential for this transformation (Table S3). After further screening of additional solvents, temperatures, and photosensitizers, the best conditions for α -hydroxylation were as follows: **L4** with $\text{Cu}(\text{OTf})_2$ as the catalyst and TPP as the photosensitizer in toluene at -15°C under white CFL irradiation.

Experiments were conducted under the optimized conditions to probe the substrates of this visible light-induced asymmetric α -hydroxylation reactions. As shown in Table 2, a wide range of β -keto esters can effectively participate in the reaction to create the desired products. The unsubstituted indanone carboxylic methyl ester **2b** gave slightly worse results than those obtained for **2a** (89% yield and 89% ee). There were some slight fluctuations in the enantioselectivities of the 5- or 6-position halogen-substituted substrates (84%–93% ee, **2d–2g**). However, a much lower ee value was obtained by the 4-bromo-substituted substrate (58% ee, **2c**). When electron-donating methoxyl groups were introduced to the meta-positions of the carbonyl in the aromatic ring, good yields and ee values were observed (up to 96% ee, **2h**, **2i**, and **2k**). Unexpectedly, the enantioselectivity declined to 73% ee when the methoxyl group was on the para-position of the carbonyl (**2j**). The substrates with more hindered substituents replacing methoxyl of **1k** were also examined and were successfully transformed into α -hydroxylation products with satisfactory yields and enantioselectivities (71%–90% yields, 78%–86% ee, **2l–2n**). In addition to investigating the effects of the substituents of the aromatic ring, various ester groups were also examined. To our delight, most ester

Table 1. Screening of Reaction Conditions.^[a]



Entry	Lewis acid	Lig	Solvent	Yield ^[b] (%)	ee ^[c] (%)
1	Zr(acac) ₄	L1	toluene	72	18
2	Ti(O- <i>i</i> Pr) ₄	L1	toluene	89	0
3	Mn(OAc) ₂	L1	toluene	27	7
4	CuCl ₂	L1	toluene	28	46
5	Cu(ClO ₄) ₂	L1	toluene	44	48
6	Cu(acac) ₂	L1	toluene	52	34
7	Cu(OTf) ₂	L1	toluene	92	51
8	Cu(OTf) ₂	L2	toluene	86	24
9	Cu(OTf) ₂	L3	toluene	73	42
10	Cu(OTf) ₂	L4	toluene	93	67
11	Cu(OTf) ₂	L5	toluene	76	31
12	Cu(OTf) ₂	L6	toluene	84	49
13	Cu(OTf) ₂	L7	toluene	92	49
14	Cu(OTf) ₂	L8	toluene	47	50
15	Cu(OTf) ₂	L9	toluene	93	20
16 ^[d]	Cu(OTf) ₂	L4	toluene	92	84
17 ^[d,e]	Cu(OTf) ₂	L4	toluene	93	90
18 ^[d,f]	Cu(OTf) ₂	L4	toluene	94	96
19 ^[d,e,g]	Cu(OTf) ₂	L4	toluene	92	89
20 ^[d,e,g]	Cu(OTf) ₂	L4	<i>o</i> -xylene	91	77
21 ^[d,e,g]	Cu(OTf) ₂	L4	mesitylene	90	84

^[a] Unless otherwise noted, reactions are conducted with **1a** (0.2 mmol), 5 mol % photosensitizer under visible light and air for 15 h.

^[b] Isolated yields.

^[c] Determined by HPLC on chiral stationary.

^[d] Activation of Cu(OTf)₂ in a vacuum oven at 110 °C.

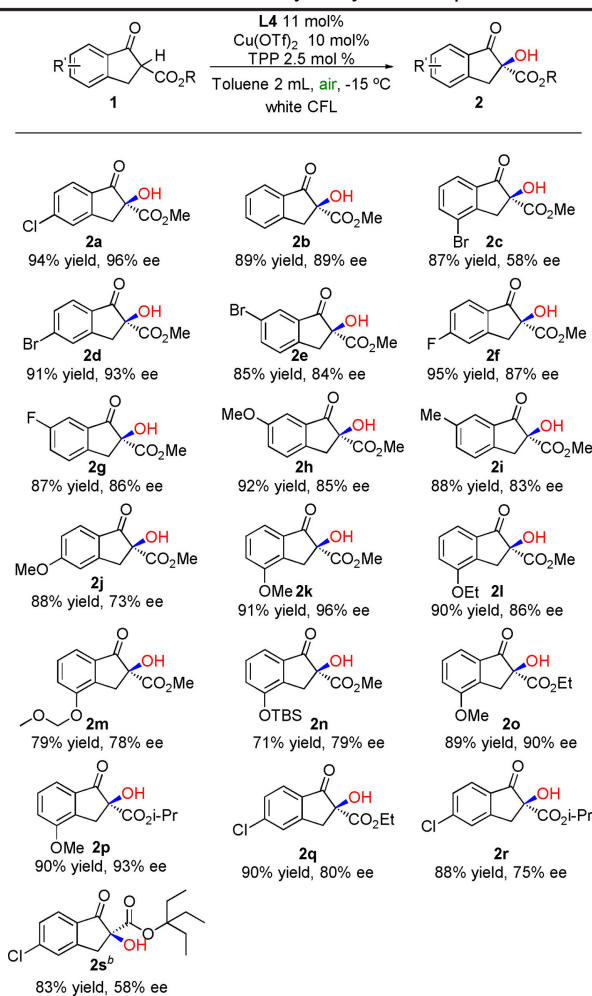
^[e] Dried air by 4 Å MS.

^[f] Reaction performed at −15 °C, TPP 2.5 mol %.

^[g] Reaction performed at −20 °C, TPP 2.5 mol %.

groups were tolerated in this transformation. Interestingly, the yields and ee values of the corresponding products decreased for more hindered substituents on the ester side of the substrates (83%–90% yields, 58%–93% ee, **2o–2s**). Better results were obtained for the substrates with smaller ester groups than for the substrates with the larger ester groups, which is very different from the results of the previous studies.^[3,9]

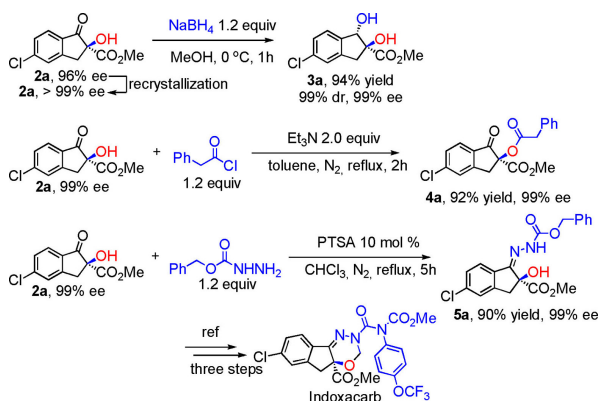
Table 2. Enantioselective α -Hydroxylation of β -Keto esters.^[a]



^{a)} Unless otherwise noted, the reactions were performed under the optimal conditions as indicated in Table 1, entry 15. All yields are isolated yields, and ee values were determined by chiral HPLC.

^{b)} The reaction was performed for 24 h.

To highlight the utility of this enantioselective α -hydroxylation, we carried out further transformations of the obtained α -hydroxyl products (Scheme 2). The enantioenriched **2a** was improved to >99% ee (**S**) after the recrystallization. The product **2a** was smoothly converted into chiral pinacol **3a** by NaBH₄ reduction, providing a useful method for the synthesis of highly substituted α,β -dihydroxyl esters. Moreover, the catalytic product **2a** can be easily protected by acylation to afford **4a** without a decrease in the enantioselectivity. Significantly, the triethylamine catalyzed ketone-hydrazine condensation reaction was used to transform product **2a** into α -hydroxyl hydrazone **5a** with high yield and 99% ee, and then **5a** could be further modified to afford the sodium-channel blocker pesticide (*S*)-indoxacarb.^[8]



Scheme 2. Further transformations of the α -hydroxyl- β -keto ester compounds.

Table 3. Control Experiments.

standard conditions			
Entry	Variation of standard conditions	yield ^[a] (%)	ee ^[b] (%)
1	1,1-diphenylethylene	93	93
2	TEMPO	94	96
3	DABCO	34	N.D.
4	D8-toluene	97	N.D.

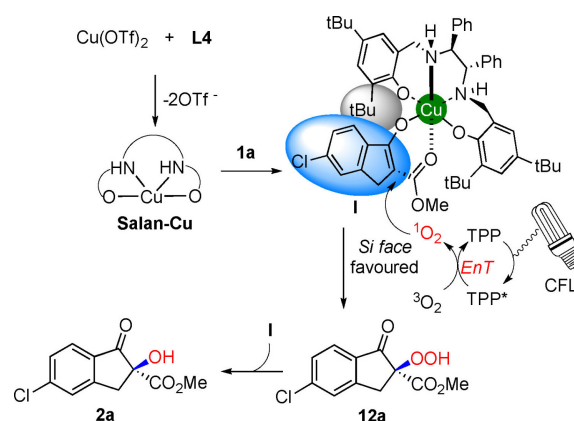
^[a] isolated yields.

^[b] Determined by chiral HPLC analysis. N.D., not determined.

To gain an understanding of the mechanism of the reaction, we performed some control experiments. The reaction proceeded well in the presence of the 1,1-diphenylethylene or the radical trap 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to produce the desired chiral product **2a** in 93% yield and 93% ee or 94% yield and 96% ee, respectively (Table 3, entries 1, 2).^[11] Thus, the visible light-induced reactions indicated that a radical process may not be involved in the present transformation. By contrast, when the $^1\text{O}_2$ inhibitor 1,4-diazabicyclo-[2,2,2]octane (DABCO)^[12] was added to the model reaction, a greatly reduced product yield was observed (Table 3, entry 3, 15 h,

34% yield). Furthermore, replacing toluene with D₈-toluene resulted in an accelerated reaction (toluene, 15 h, 97% yield; D₈-toluene, 10 h, 97% yield, see SI 6.2). The lifetimes of $^1\text{O}_2$ were found to be strongly dependent on the solvents; for example, comparison of D₈-toluene ($\tau\Delta=280\ \mu\text{s}$) and toluene ($\tau\Delta=29\ \mu\text{s}$) showed that the rate of $^1\text{O}_2$ reactions was higher in deuterated solvents.^[13] These results suggested the presence of photoexcited $^1\text{O}_2$ in this reaction system. Therefore, the detection of the intermediate formed by reactive $^1\text{O}_2$ with substrate **1a** was carried out, and the intermediate α -hydroperoxide β -keto ester **12a** was observed though HRMS. Notably, α -hydroperoxide **12a** was the major product when the photo-oxygenation reaction was carried out under 10 bar of O_2 in a flow photoreactor. Then, substrate **1a** was added into the reaction mixture, and the intermediate **12a** smoothly reacted with the substrate resulting in the formation of the α -hydroxylation product **2a** under dark and airtight conditions (see SI 6.3).^[14] This suggests that the α -hydroperoxide **12a** is a strong oxidant with high reactivity.

Based on these results and the results obtained in previous studies,^[10,15] a plausible induction model is proposed in Scheme 3. It is assumed that the aromatic ring of **1a** was located away from the chiral ligand to avoid possible stereo-selection. The *Re*-face of the enolate intermediate was effectively shielded by the back *t*-Bu group. Thus, the oxidants, $^1\text{O}_2$ or α -hydroperoxide **12a**, could only attack the enolate from the *Si*-face, resulting in the α -hydroxylation product **2a** with the *S*-configuration. We proposed that a methyl group in this process is more conducive to approach the chiral catalyst center, which explained the reason why methyl-substituted group in this work can achieve better results in opposite to previous works, in which only substrates with large steric hindrance group, such as adamantyl group, gave good results.



Scheme 3. Plausible salan-copper(II)-catalyzed route of α -hydroxylation.

In conclusion, using the easily prepared salan ligand as a stereoselective controller and green sustainable air as the oxidant, we have developed a practical, efficient, and safe protocol for visible light-induced salan-copper(II)-catalyzed asymmetric α -hydroxylation of β -keto esters. Cyclic substrates were converted to the corresponding α -hydroxyl products with good to excellent yields and enantioselectivities (up to 95% yield, 96% ee), particularly for the substrates with smaller ester groups which until now were difficult to achieve. Tetraphenylporphyrin was introduced as the photosensitizer to produce singlet oxygen from unreactive triplet oxygen under visible light irradiation to participate in the reactions. The importance of this transformation was highlighted through the synthesis of the key intermediate of (S)-indoxcarb. Further investigations of the synthetic application of this transformation and the exploration of the scope of α -hydroxylation are underway in our laboratory.

Experimental Section

A dried 10 mL Schlenk tube equipped with a magnetic stir bar was charged with $\text{Cu}(\text{OTf})_2$ (7.2 mg, 0.02 mmol), salan ligand **L4** (14.24 mg, 0.022 mmol) and toluene 2 mL. The mixture was stirred at 50 °C for 30 min in the dark and N_2 atmosphere. Then, the mixture was cooled to -15 °C. Then, the methyl 5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (44.9 mg, 0.2 mmol), and TPP (3.1 mg, 0.005 mmol) were added while air (dried by 4 Å MS) was slowly injected via air pump into the reaction flask and the reaction mixture was stirred under irradiation of a 25 W white compact fluorescent lamp (distance 3 cm). The resulting solution was stirred at -15 °C for 15 h. After the reaction was completed the solution of the crude product was concentrated in vacuo, and the residue was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 5/1) to afford the product **2a** (45.2 mg, 94% yield, 96% ee) as a white solid.

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