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Communication

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Bifunctional Photocatalysts for Enantioselective Aerobic Oxidation of β–Ketoesters

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Supporting Information Placeholder

ABSTRACT: A novel visible light-responsive chiral ligand has been developed by grafting a triplet state photosensitizer to chiral bisoxazoline ligands. Complexation of this ligand with $Ni(acac)_2$ results in a powerful catalyst for the asymmetric oxidation reaction of β-ketoesters, which uses oxygen or air as the green oxidant and visible light or sunlight as the ideal driving force. Using this protocol, products containing the α-hydroxy-β-dicarbonyl motif are produced in high yields and with excellent enantiopurities.

New strategies in asymmetric catalysis hold the potential to revolutionize the production of chiral materials, pharmaceuticals, agro-, and fine chemicals. For this reason, seeking efficient catalysts to promote stereoselective chemical transformations is a fundamentally important task in contemporary chemical synthesis.[1] Over the past decade, asymmetric photocatalysis induced by visible light has flourished as a powerful tool for the sustainable, highly efficient and selective production of enantioenriched compounds.[2,3] However, asymmetric visible light photocatalysis has mainly relied on the use of two separate catalysts, an achiral photocatalyst and a chiral co-catalyst, in a single organic transformation.[4,5] A single chiral photocatalyst that is able to induce a stereoselective photochemical reaction would be advantageous but is challenging,[6-8] because it must possess the following two functions: harvest visible light or sunlight to activate the reagents and control the stereoselectivity during the chemical bond formation. In this area, Bach demonstrated the first example of highly enantioselective photochemical reactions where a chiral hydrogen bonding-based thioxanthone was used as a bifunctional visible light photosensitizer to promote an intramolecular asymmetric [2+2] cycloaddition.[6b] Soon after, Meggers elegantly developed a chiral iridium complex as bifunctional photocatalysts to achieve asymmetric transformations of 2-acyl imidazoles with excellent enantiocontrol.[7a] Despite these pioneering work, the design and invention of new bifunctional chiral photocatalysts bearing cheap metals for efficient asymmetric photochemical transformations is highly desirable to enable new reactivity.[8e,f]

Given that bisoxazolines (BOXs) are privileged ligands in asymmetric catalysis[9] and that diarylketones (e.g., xanthone, thioxanthone and 9-fluorenone) can activate many functional groups or reagents under irradiation with ultraviolet (UV)/visible light,[6,10] we considered whether new visible light-responsive ligands could be invented by grafting a thioxanthone motif onto chiral BOX ligands (Figure 1). Tang and Gade have elegantly demonstrated that the introduction of an additional group in the bridge carbon would improve the stereo-control capacities of chiral BOX ligands in the asymmetric catalysis. Thus, as a critical element of this design, we recognized that the BOX component in this ligand/photosensitizer hybrid would efficiently coordinate the various metals and that a library of chiral bifunctional photocatalysts could be established for asymmetric visible light photocatalysis.

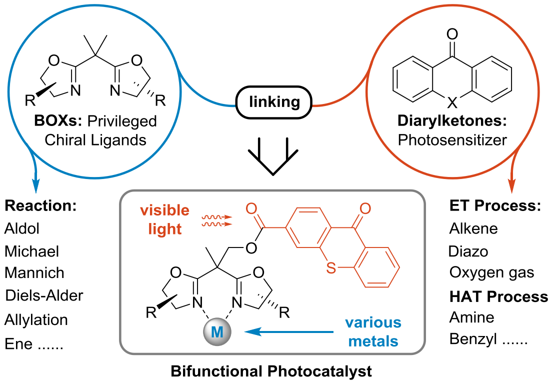


Figure 1. Blueprint for bifunctional photocatalysts. ET: energy transfer. HAT: hydrogen abstraction transfer. X: O, S…

Oxidative hydroxylation is an important process in Nature. For example, Cytochrome P-450, an important monooxygenase, can activate dioxygen under mild conditions and allow the living cells to introduce the hydroxyl group with high efficiencies and perfect selectivities.[12] In contrast to Nature's biosynthesis, the chemical synthesis most often relies on the use of strong oxidants. In this field, given many bioactive molecules containing the α-hydroxy-β-dicarbonyl motif (e.g., natural product Hamigeran A and insecticide Indoxacarb),[13] ongoing efforts have been dedicated to the direct asymmetric oxidative hydroxylation of β-keto esters.[14] The use of oxygen gas as a green oxidant to perform this transformation under mild conditions would be ideal. In this work, we chose the visible light-induced asymmetric aerobic photooxygenation of β-keto esters to assess our approach for bifunctional photocatalyst development and applications. As illustrated in Figure 2, we

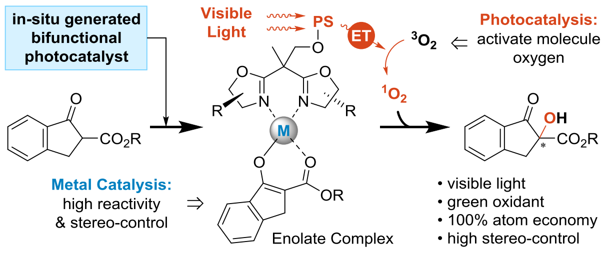
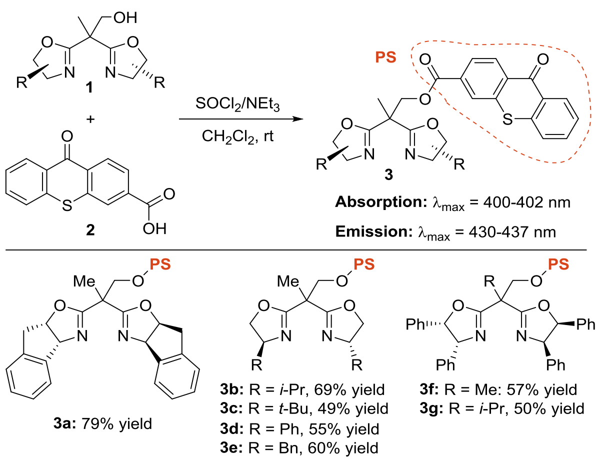


Figure 2. Work hypothesis: application of bifunctional photocatalysts in asymmetric photooxygenation of β-keto esters.

speculated that the thioxanthone component could function as an efficient energy-transfer photocatalyst,[15] with its ground state absorbing visible light and its triplet state then sensitizing the unreactive triplet state of molecule oxygen ($^3O_2$) to generate the reactive singlet state of molecular oxygen ($^1O_2$).[16] The chiral metal complex derived from the BOX component can serve as an efficient catalyst to activate β-keto carbonyls and then control the enantioselectivity of the C-O bond-formation step of the reaction.

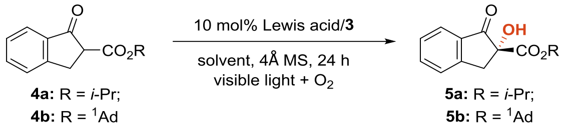
To start this research, as shown in Scheme 1, chiral ligands **3** were synthesized from readily available reagents **1** and **2** through an esterification operation. The UV/Vis spectra (Figure S1) revealed that chiral ligands **3** have a maximum absorb of visible light at ca. 400 nm wavelengths. Then, the aerobic photooxygenation of isopropyl ester **4a** was investigated with a series of bifunctional chiral photocatalysts which were in situ generated from **3a** and various metal precursors (Table 1, entries 1-6). Preliminary studies revealed that the use of $Ni(acac)_2$ gave the hydroxylation product **5a** in high yield and with modest enantioselectivity (entry 6, 88% yield and 33% ee) under irradiation with visible light. Surveying the reaction media for this photoreaction indicated that toluene substantially improved the stereochemical control (entries 7-8). Chiral ligands **3a-g** were examined in the presence of $Ni(acac)_2$ (entries 8-14), and gratifyingly, biphenyl-substituted ligand **3f** was determined to be the optimal ligand choice for enantiocontrol (entry 13, 80% yield and 73% ee). The substituents on the spacer, such as Me or *i*-Pr, show only minimal impact on the reaction efficiency (entry 13 vs 14). Varying the ester moiety in the substrate from isopropyl to adamantyl groups gave superior levels of enantioselectivity and reaction efficiency (entry 16, 97% yield and 95% ee). Control experiments indicated that visible light, Lewis acid, chiral ligand and oxygen gas were essential for this transformation (Table S3).[17]

Scheme 1. Synthesis of New Chiral Ligands



Experiments were conducted under the optimized conditions to probe the substrate scope of this asymmetric photooxygenation reaction. As summarized in Table 2, a wide range of β-keto esters were tolerated, and generally, high levels of stereoselectivity and reaction efficiency were observed. In the case of 1-indanone-derived substrates, incorporation of either electron-donating or electron-accepting substituent on the benzene ring had little impact on the reaction, and the corresponding products were obtained in 78-97% yields and 90-95% ee (**5b-f**). The steric modification of the benzene ring could be accomplished with little influence on the reaction outcomes, affording hydroxylation products in 82-98% yields and 90-94% ee (**5g-l**). Some functional groups, e.g., alkynyl, vinyl and heteroaryl motif, such as pyridine and thiophene, that are prone to oxidation were inert under the reaction conditions; thus, the reaction displayed excellent chemoselectivity (**5m-p**, 90-96% yields and 90-92% ee). Substrates with other steric ester groups and amide groups were also examined and could be successfully transformed into hydroxylation products with satisfactory yields and enantioselectivities (**5q-s**, 82-95% yields and 88-90% ee). Six- and seven-membered bicyclic β-keto esters and the aliphatic cyclic β-keto esters could be effectively employed as substrates for this transformation, producing the hydroxylation products **5t-v** in 85-95% yields and 85-93% ee. In contrast, when cyclic 1,3-diketones and acyclic β-keto esters were examined with this asymmetric photooxygenation reaction, no conversion was observed at this stage.

Table 1. Optimization of Reaction Condition[a]

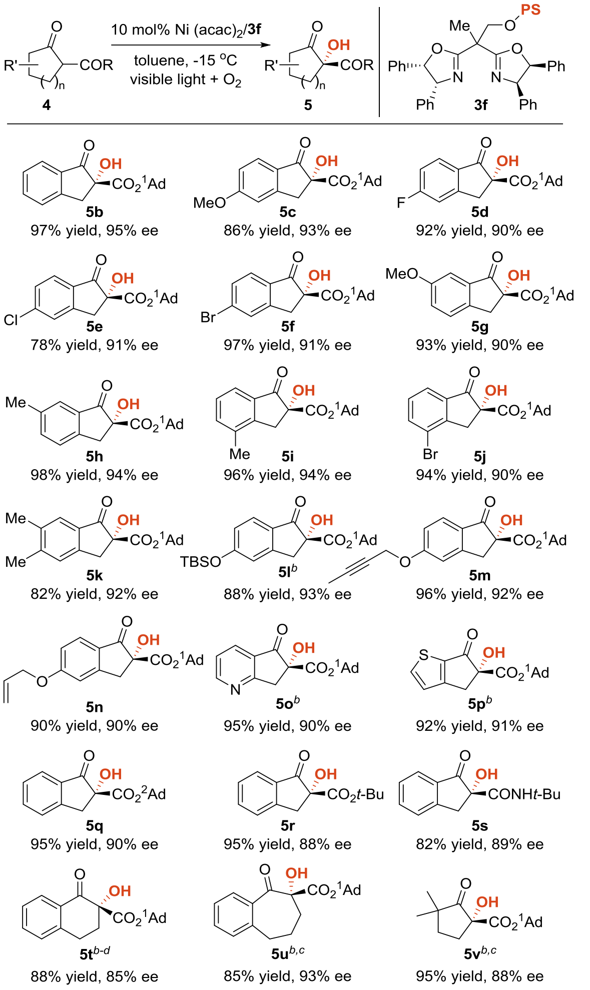


entry	Lewis acid	3	solvent	*T* (°C)	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	**3a**	DCM	-20	32	13
2	$Zn(OTf)_2$	**3a**	DCM	-20	29	10
3	$Mg(OTf)_2$	**3a**	DCM	-20	42	0
4	$Ni(OTf)_2$	**3a**	DCM	-20	57	20
5	$Sc(OTf)_3$	**3a**	DCM	-20	41	0
6	$Ni(acac)_2$	**3a**	DCM	-20	88	33
7	$Ni(acac)_2$	**3a**	toluene	-20	88	62
8	$Ni(acac)_2$	**3a**	toluene	-10	92	64
9	$Ni(acac)_2$	**3b**	toluene	-10	73	-70
10	$Ni(acac)_2$	**3c**	toluene	-10	51	-27
11	$Ni(acac)_2$	**3d**	toluene	-10	89	-68
12	$Ni(acac)_2$	**3e**	toluene	-10	83	-64
13	$Ni(acac)_2$	**3f**	toluene	-10	80	73
14	$Ni(acac)_2$	**3g**	toluene	-10	84	71
15[d]	$Ni(acac)_2$	**3f**	toluene	-15	80	75
16[d,e]	$Ni(acac)_2$	**3f**	toluene	-15	97	95

[a] Unless otherwise noted, reactions are conducted with **4a** (0.1 mmol), Lewis acid/**3** (10 mol%) and 4Å MS (20 mg) in 2 mL of solvent under visible light at O_2 for 24 h. [b] All yields are isolated yields [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Without 4Å MS. [e] Substrate **4b** was used.

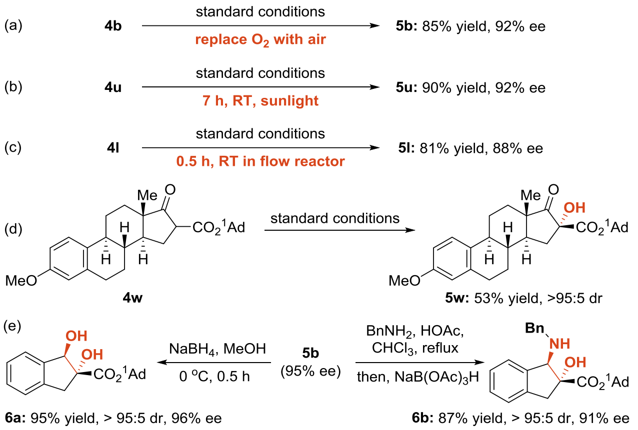
Further experiments were conducted to demonstrate the utility of this bifunctional catalyst system. For example, the photooxygenation reaction of β-keto ester **4b** proceeded well when air was directly used as the oxidant (Scheme 2a, **5b**, 85% yield and 92% ee). Notably, a shorter reaction time was observed by directly applying sunlight as the light source (Scheme 2b, **5u**, 90% yield and 92% ee). Also, we were gratified to find that the reaction efficiency could be further improved by using a continuous-flow reactor, achieving the photooxygenation reaction of substrate **4l** in 30 min (Scheme 2c, **5l**, 81% yield and 88% ee). Moreover, a structurally complex β-keto ester derived from the pharmaceutical agent, estrone 3-methyl ether,[18] was subjected to our standard conditions. In this case, the hydroxyl functional group was readily incorporated with excellent stereocontrol albeit in moderate yield (Scheme 2d, **5w**, 53% yield, >95:5 dr), providing a new protocol for the late-stage modification of complex molecules.[19] Furthermore, synthetic transformations of chiral hydroxylation products are presented in Scheme 2e. As expected, reduction or reductive amination of **5b** gives *anti*-1,2-diol **6a** or 1,2-amino alcohol **6b** with excellent stereoselectivities, which are useful synthetic blocks in asymmetric synthesis.[20]

Table 2. Substrate Scope[a]



[a]Unless otherwise noted, reactions were performed under the standard condition as indicated in Table 1, entry 16. All yields are isolated yields and ee values were determined by chiral HPLC. [b]Reaction conducted at 25 °C. [c]Toluene/n-hexane (1:3) used as solvent. [d]**3a** used as the chiral ligand.

Scheme 2. Demonstration of Synthetic Utility



To better understand this photochemical oxidation reaction, the basic properties of the bifunctional photocatalysts were initially probed. Comparison of the UV-Vis absorption and fluorescence emission spectra of photocatalyst **3f-Ni** complex with those of ligand and **3f** showed that no variation of the maximum absorption and emission wavelengths was observed. This result indicated that the coordination of $Ni(acac)_2$ with the **3f** did not change photochemical behaviour of the thioxanthone moiety in **3f** (Figure S1). The fluorescence quenching experiments of photocatalyst **3f-Ni** were performed with the addition of substrate **4b**,[21] and the results showed that substrate **4b** itself cannot quench the fluorescence of photosensitizer, even at the concentration of 1 mol/L. Thus, the energy or electron transfer between photocatalyst **3f-Ni*** and substrate **4b** might be ruled out in our cases (Figure S3d). In addition, the results of cyclic voltammetry (CV) measurements and the radical control experiments (see section 7.3 and 7.4 in SI) suggested that the radical pathway might not be dominant in the current reaction.[22] By contrast, when the singlet oxygen quencher[23] (DABCO) was added to the reaction of **4b**, a greatly reduced product yield was observed. Additionally, replacing toluene with D_8-toluene resulted in an accelerated reaction (toluene, 12 h, 97% yield; D_8-toluene, 7 h, 95% yield) because of the significantly longer lifetime of singlet oxygen in deuterated solvents.[24] These results suggested the presence of photoexcited singlet oxygen in this reaction system (See section 7.5 in SI). Thus, the thioxanthone component in **3f-Ni** most likely functions as a triple-state sensitizer for the activation of molecular oxygen, although the indirect way involving the triplet–triplet energy transfer between the Ni(II) and the excited state of the photosensitizer cannot be ruled out at the current stage (Figure S1 and Section 7.3 in SI).[25] Note that both the isolated yield and the ee of the product decreased significantly when the photooxygenation reaction was performed with chiral BOX ligand **3h** and photosensitizer **Me-PS** separately (Section 7.6 in SI). This result indicated that the introduction of a thioxanthone not only provides a visible light photosensitizer, but also improves the stereo-controlling capacity of chiral BOX component through dynamic steric effect.[11] Furthermore, a linear relationship between the enantiopurity of chiral ligand **3f** and product **5b** suggested that the 1:1 complex of ligand **3f** and $Ni(acac)_2$ is the catalytically active species. Control experiments reveal that the acac anion is important for the high reaction efficiency and enantioselectivity (Section 7.9 in SI). According to these results and previous studies,[26] a possible stereo-induction model is proposed in Figure 3 based on the assumption that the ^{1}Ad group was located away from the chiral ligand to avoid possible steric constraints. The *Si*-face of enol-formed *β*-keto ester **4b** was blocked by the back phenyl groups. Therefore, the attack of oxidants, activated $^1O_2$ or peroxide **7b**,[14c,g] from the *Re*-face of **4b** seems relatively favourable, resulting in the hydroxylation product **5b** with the *R*-configuration.

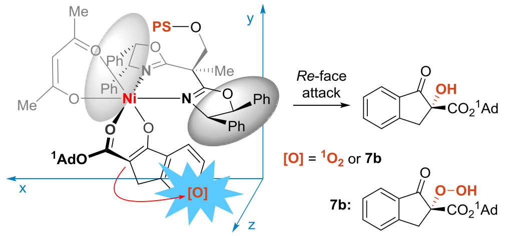


Figure 3. Proposed asymmetric induction model.

In conclusion, we have successfully developed a novel family of visible light-responsive chiral ligands for asymmetric photocatalysis. Complexation of these ligands in situ with different metal catalyst precursors will result in a broad spectrum of chiral bifunctional photocatalysts. Moreover, the application of these catalysts accomplished a visible light-induced metal-photocatalytic asymmetric aerobic oxidation reaction of *β*-ketoesters and *β*-ketoamides, affording *α*-hydroxy-*β*-dicarbonyl products in high yields and enantioselectivities. We believe that this novel bifunctional photocatalyst will be transferable to other transformations, providing new opportunities for visible light-driven asymmetric photochemical synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, and characterization data for all the products. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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(21) See the details and discussion of the fluorescence quenching experiments of photosensitizer with the addition of Ni(II) complex and substrate **4b** in Section 7.2 in SI.

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Graphic Abstract: