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Visible-Light-Driven Enantioselective Aerobic Oxidation of β-Dicarbonyl Compounds Catalyzed by Cinchona-Derived Phase Transfer Catalysts in Batch and Semi-Flow

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Abstract: The direct asymmetric α-hydroxylation of β-dicarbonyl compounds has been developed using cinchona-derived phase-transfer catalysts in batch and semi-flow processes. Using visible light as the driving force and air as oxidant, the corresponding products were obtained in excellent yields (up to 96%) and good enantioselectivities (up to 90% ee). The catalyst acts as a chiral center and a catalytic center and forms a chiral enolate complex with the substrate to act as a photosensitive center in the reaction. The use of semi-flow photochemical processes allowed a reduction in reaction time (24 h to 0.89 h) and good yields (up to 93%) and enantioselectivities (up to 88% ee) were obtained.

Keywords: aerobic oxidation; asymmetric catalysis; phase-transfer catalyst; semi-flow; visible light catalysis

Over recent years, as visible light has been increasingly used in organic synthesis as a wide-ranging, green and sustainable resource, interest in enantioselective photochemical reactions has significantly grown.[1,2] In 2005, T. Bach embedded photochemical substrates into a rigid chiral catalyst to enable a catalytic enantioselective cyclization driven by photoinduced electron transfer ($\lambda > 300$ nm).[3] This strategy was not explored further until the use of a chiral thioxanthene catalyst was extended to a visible light-induced asymmetric cycloaddition in 2014.[4] The same year, Eric Meggers reported the use of a chiral ruthenium complex as a catalyst to catalyze the asymmetric alkylation of 2-acylhydrazine.[5] The chiral iridium(III) or rhodium(III) complex in the reaction simultaneously acted as the catalytic center, chiral center and photoredox center.[6] This type of bifunctional or multifunctional catalyst that enables photoreactions with both high yields and enantioselectivities has attracted considerable attention.[7]

Oxygen is regarded as a widely accessible and environmentally benign sustainable oxidant in nature. The best way of efficiently using photoactivated oxygen to achieve asymmetric oxidations has become a research hotspot.[8] To obtain bifunctional chiral catalysts that can activate oxygen, the Xiao group (Scheme 1a) and the Meng group (Scheme 1b) independently carried out research, mainly involving combination of chiral catalysts with a photosensitizer.[9,10] However, the preparation of these catalysts increases the number of synthetic steps, especially the modification of tetraphenylporphyrin (TPP) in our work, making the catalyst synthesis more difficult. This prompted us to develop a new method to use a cinchona-derived phase-transfer catalyst (PTC) for the direct asymmetric α-hydroxylation of β-dicarbonyl compounds by visible-light irradiation.

Microreactors have been widely used in the synthesis of fine chemicals and pharmaceuticals due to advantages in improving safety, efficient heat and mass transfer, and automation.[11] Photomicroreactors have been used to achieve various photocatalytic reactions.[12] In 2012, Kirsten Zeitler reported a photoredox asymmetric α-alkylation of aldehydes, performed in a microreactor.[13] However, most reported reactions using photomicroreactors have been synthesized of achiral compounds,[14] especially, aerobic oxidations.[15] Herein, we report a visible-light driven heterogeneous gas-liquid-liquid asymmetric aerobic

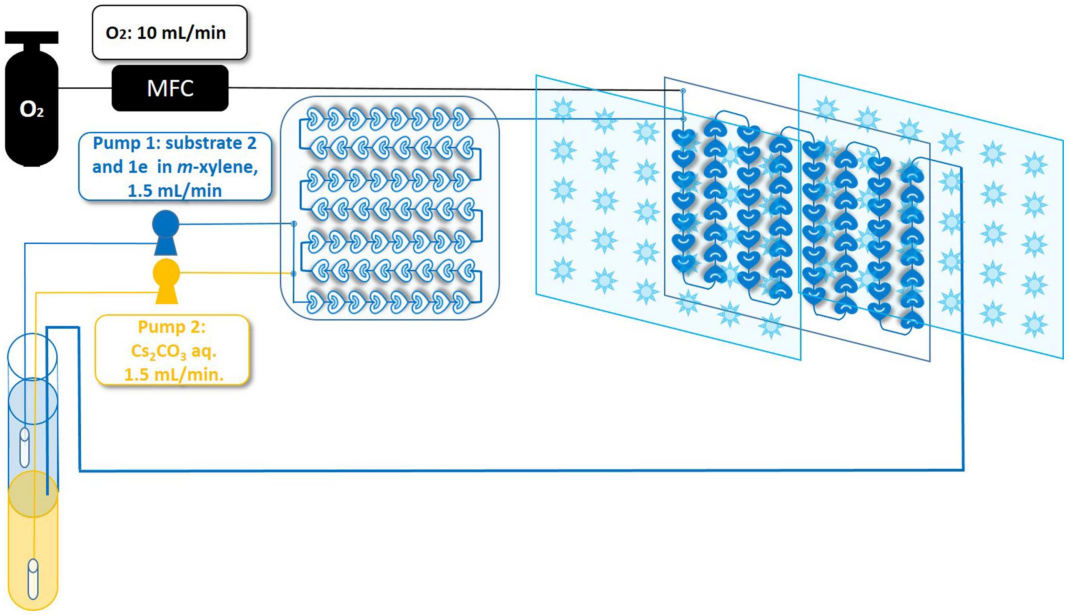
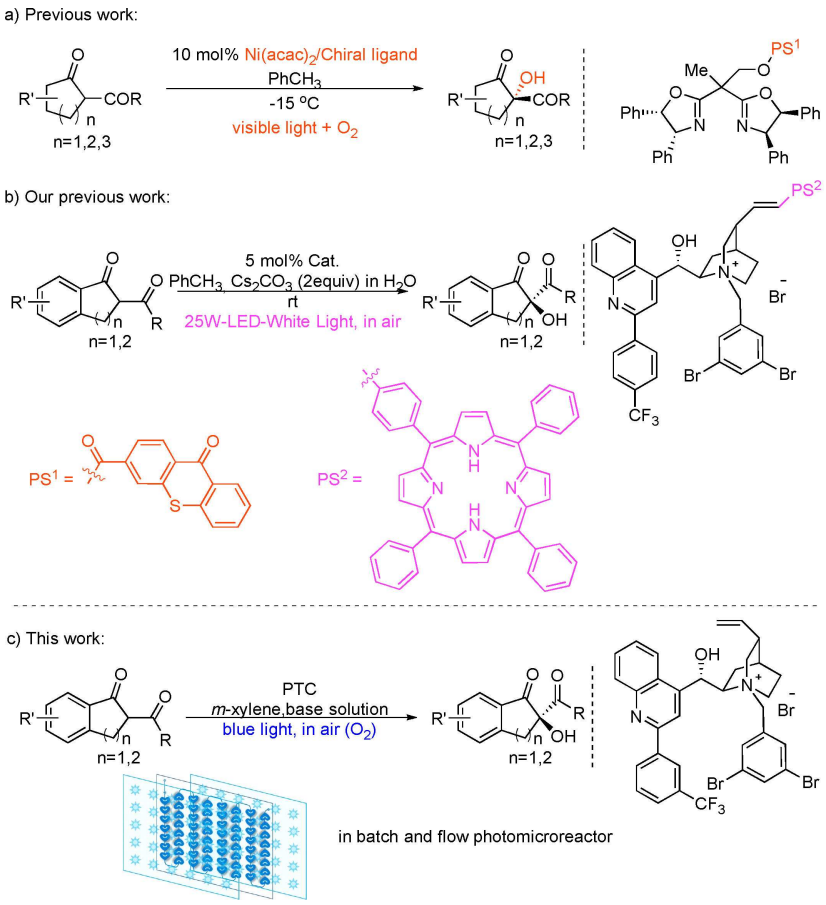
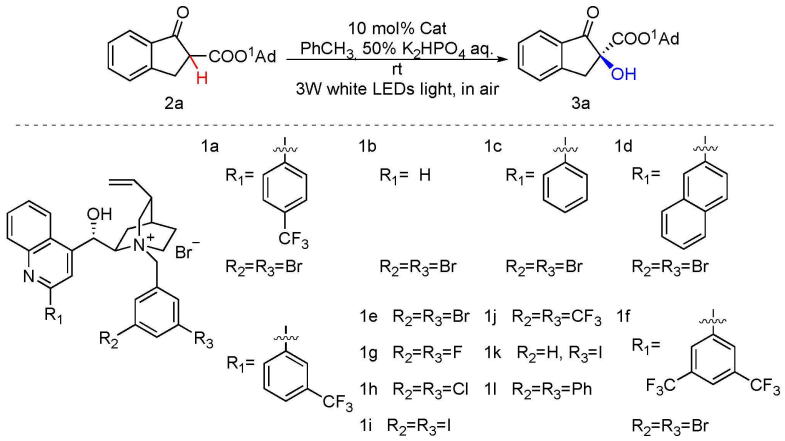


Figure 1. Schematic Representation of a Flow Photomicroreactor for the Asymmetric Photocatalytic Oxidation of β-Dicarbonyl Compounds.



Scheme 1. Bifunctional Photocatalysts for Enantioselective Aerobic Oxidation of β-Dicarbonyl Compounds.

Table 1. Screening of PTCs of the α-Hydroxylation of β-Keto Ester 1a[a]



Entry	Cat.	Light	Solvent	Yield[b] (%)	ee[c] (%)
1	1a	white	toluene	75	70
2	1a	Darkness	toluene	NR	ND
3	1b	white	toluene	27	74
4	1c	white	toluene	91	76
5	1d	white	toluene	94	58
6	1e	white	toluene	91	77
7	1f	white	toluene	92	74
8	1 g	white	toluene	55	62
9	1 h	white	toluene	66	64
10	1i	white	toluene	54	67
11	1j	white	toluene	71	59
12	1k	white	toluene	47	50
13	1 l	white	toluene	63	51
14[d]	1e	blue	toluene	95	77
15[d]	1e	blue	*m*-xylene	96	80
16[d]	1e	blue	*p*-xylene	95	70
17[d,e]	1e	blue	*m*-xylene	96	82
18[d,e,f]	1e	blue	*m*-xylene	96	85
19[d,e,f,g]	1e	blue	*m*-xylene	96	90

[a] Unless otherwise specified, the reaction was performed with β-keto ester **2a** (31 mg, 0.1 mmol), 10 mol% catalyst, 4 mL solvent and 2 mL 50% K_2HPO_4. The reaction was covered by a 3 W LEDs light at rt for 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Chiralcel AD–H).
[d] Reaction time 24 h.
[e] 2 equiv. Cs_2CO_3 in 2 mL H_2O as a basic solution.
[f] **2a** (31 mg, 0.1 mmol) in 16 mL *m*-xylene.
[g] Reaction performed at −5 °C. NR = No reaction, ND = Not determined

oxidation catalyzed by cinchona-derived phase-transfer catalysts in both batch and semi-flow processes (Scheme 1c).

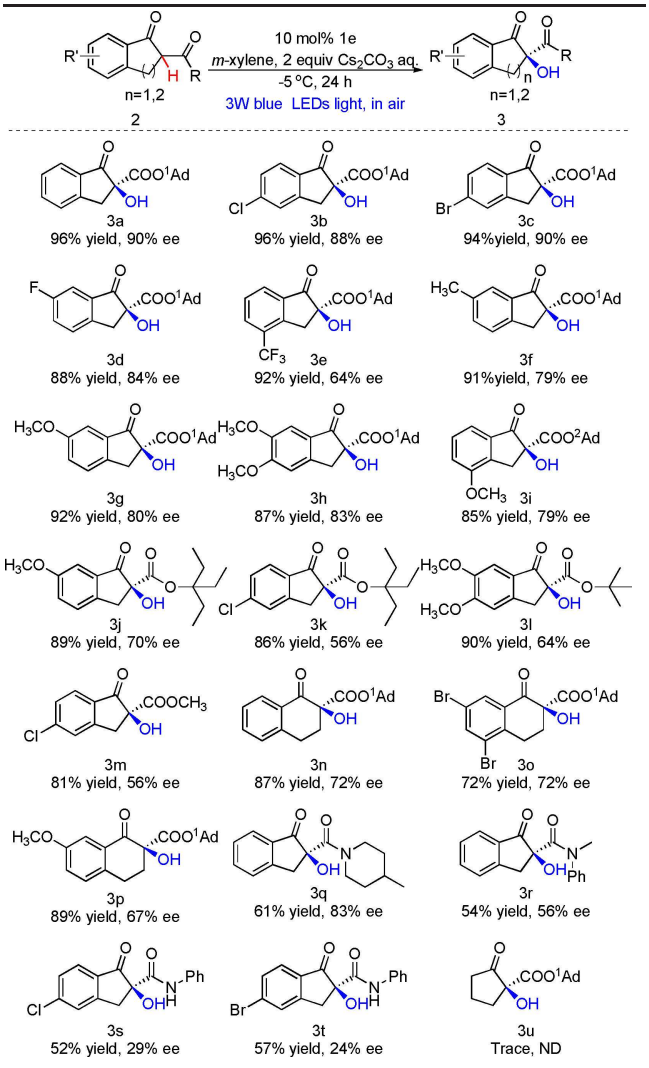
Inspired by Melchiorre's work, we wondered whether the cinchonine-derived PTCs or the complex formed by the PTCs and a β-keto ester could act as a photosensitive center to activate oxygen under visible light.[7c] When we tried to use PTC **1a** to catalyze the enantioselective α-hydroxylation of β-keto ester **2a** with air under 3 W white LEDs light without a photosensitizer, we were surprised to find that product **3a** was obtained in 75% yield with 70% ee after 48 h (Table 1, entry 1). However, when the reaction was conducted in darkness, **3a** was not detected (Table 1, entry 2). The C-2′ unmodified catalyst **1b** was found to give product **3a** in only 27% yield and 74% ee (Table 1, entry 3). Furthermore, other C-2′ modified catalysts were screened (Table 1, entries 4–7, **1c**–**1f**).[7c,16] The phenyl-substituted catalyst **1c** and 2-naphthalene-substituted catalyst **1d** afforded product **3a** with high yields and moderate enantioselectivities, and catalyst **1e** achieved a better enantioselectivity

than the others (91% yield, 77% ee). A benzyl substituent was then examined; 3,5-fluoro, 3,5-chloro and 3,5-iodo groups in the benzylic position resulted in an obvious decrease of enantioselectivity (Table 1, entries 8–13, **1j**–**1l**). The other reaction conditions were then screened further. When the light source was changed to blue light, the reaction time was shortened to 24 h, and **3a** was obtained in 95% yield with 77% ee (Table 1, entry 14). When the solvent was changed to *m*-xylene, **3a** was obtained in 80% ee (Table 1, entry 15). When the base solution was replaced with 2 equiv. Cs_2CO_3 in water, the enantioselectivity was improved (Table 1, entry 17). Reducing the substrate concentration to 6.25 mM resulted in a significant increase of enantioselectivity (Table 1, entry 18). Finally, the enantioselectivity could be further improved to 90% ee by lowering the temperature (−5 °C, Table 1, entry 19).

Once the optimized conditions had been established, the scope of substrates was examined. 1-Indanone-derived 1-adamantyl β-keto esters substrates were investigated initially (Table 2, **2b**–**2h**). The 5- or 6-position halogen-substituted substrates (Table 2, **2b**–**2d**) were well tolerated in the reaction and the corresponding products **3b**–**3d** were obtained in excellent yields (88–96%) with good enantioselectivities (84–90% ee). However, the enantioselectivity of the 4-trifluoromethyl-substituted product **3e** decreased to 64% ee. Introducing electron-donating groups (–CH_3, –OCH_3) into the 5- and 6-substituted of indanone provided the corresponding products **3f**–**3h** in 87–92% yields and 79–83% ee. Next, the ester groups of the substrates (Table 2, **2i**–**2m**) were investigated. It was found that the enantioselectivity decreased with a decrease of steric hindrance in the ester substituents. The 2-adamantyl ester product **3i** was obtained in 85% yield and 79% ee. Products **3j**–**3m** (Table 2) were produced in good yields (81–90%) and moderate enantioselectivities (56–70% ee). Then, the tetralone substrates (Table 2, **2n**–**2p**) were also examined, and were smoothly transformed into the desired products **3n**–**3p** in 72–89% yields and 67–72% ee. Finally, the reaction was further extended to β-ketone amide substrates (Table 2, **2q**–**2t**) and provided products **3q**–**3t** in acceptable yields. Of note, the product **3q** achieved an impressive 83% ee. Products **3r**–**3t** were obtained in 52–57% yield and only 24–56% ee, probably due to steric hindrance. The steric hindrance effect was similar to that of the ester substrates, where the enantioselectivity decreased with decreasing steric hindrance in the ester substituents. In addition, the reaction failed to occur for cyclopentanone-derived β-keto ester substrate **2u**.

Next, we attempted to transfer the photocatalytic asymmetric oxidation reaction from a batch to a continuous flow reactor. As the low temperature causes solidification and expansion of water, and the strong

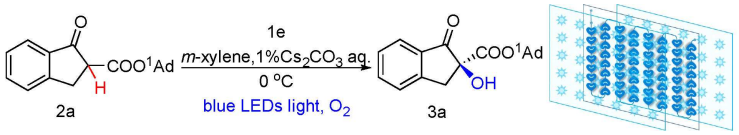
Table 2. Substrate Scope[a]



[a] General conditions: substrate **2** (0.1 mmol), **1e** (10 mol%), *m*-xylene (16 mL) and 2 equiv. Cs_2CO_3 in 2 mL H_2O at −5 °C. The reaction was covered by a 3 W blue LEDs light for 24 h. All yields are isolated yields and enantiomeric ratios were determined by chiral HPLC.

basic solution damages the glass, the reaction conditions in the flow photomicroreactor were not exactly the same as those for the batch reactor. The residence time was shortened from 24 h in the batch reactor to 0.89 h in the flow photomicroreactor, and **3a** was obtained in 95% yield and 87% ee (Table 3, entry 1). Then, different light sources were investigated (Table 3, entries 2–4). It was found that violet light could further shorten the residence time to 0.14 h, but gave the product **3a** with only 84% ee (Table 3, entry 2). The yield of **3a** decreased significantly with red light and white light (Table 3, entries 3–4). The enantioselectivity decreased slightly with higher reaction pressure and temperature (Table 3, entries 5–6). The

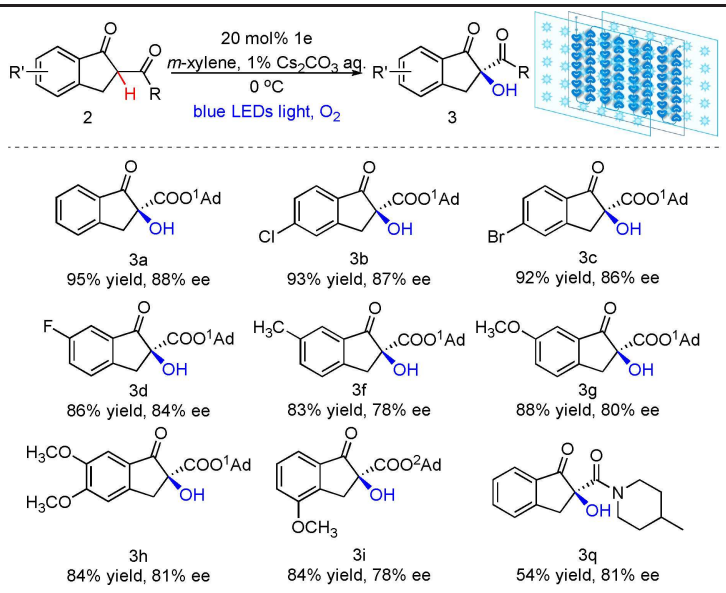
Table 3. Optimization of the Reaction Conditions for α-Hydroxylation of β-Keto Ester 1a in Semi-flow[a]



Entry	Light	Pressure (bar)	Residence time (h)	Yield[b] (%)	ee[c] (%)
1	blue	3	0.89	95	87
2	violet	3	0.14	96	84
3	red	3	0.89	< 10	ND
4	white	3	0.89	47	86
5	blue	5	1.12	96	85
6[d]	blue	3	0.86	95	85
7[e]	blue	3	0.89	95	88

[a] General conditions: pump 1: substrate **2a** (0.1 mmol), 10 mol% **1e** in 16 mL *m*-xylene, 1.5 mL/min; pump 2: 1% Cs_2CO_3 aq. 1.5 mL/min. O_2:10 mL/min. The reaction was covered by LEDs light. The reaction pressure was 3 bar and the reaction temperature was 0 °C in the flow photomicroreactor as shown in Figure 1.
[b] All Isolated yields.
[c] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Chiralcel AD–H).
[d] Reaction temperature 20 °C.
[e] 20 mol% **1e**.

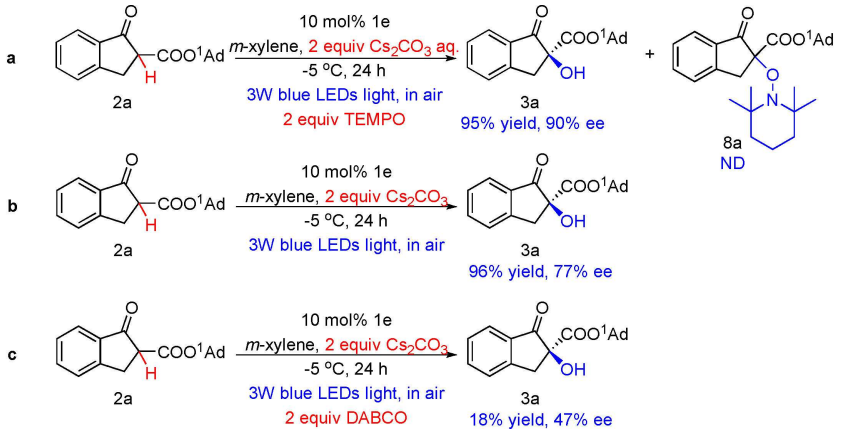
Table 4. Substrate Scope in the Photomicroreactor[a]



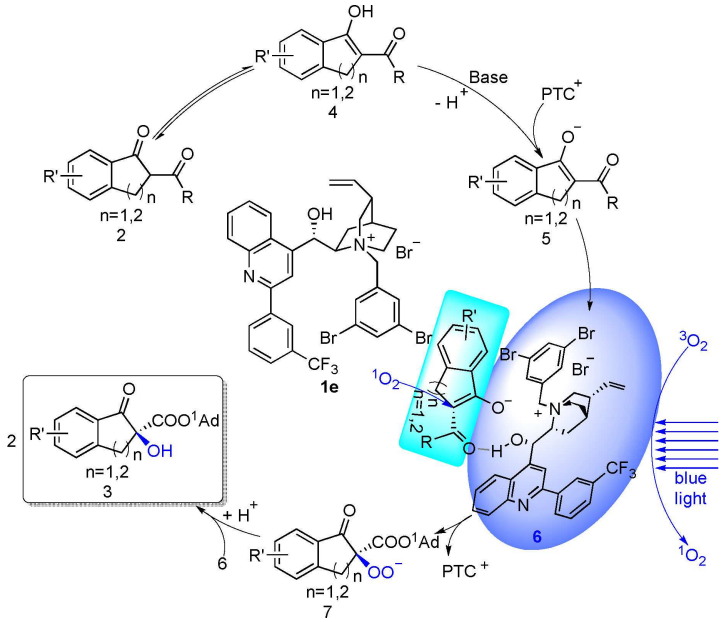
[a] General conditions: pump 1: substrate **2** (0.1 mmol), **1e** (20 mol%) in *m*-xylene (16 mL), 1.5 mL/min; pump 2: 1% Cs_2CO_3 aq. 1.5 mL/min. O_2:10 mL/min. The reaction was covered by blue LEDs light. The reaction temperature was 0 °C, and reaction pressure was 3 bar. All yields are isolated yields and enantiomeric ratios were determined by chiral HPLC.

enantioselectivity could be improved to 88% ee by increasing the catalyst **1e** loading to 20 mol% (Table 3, entry 7). The substrate scope was then expanded. Substrates (**2a–2d**, **2f–2i** and **2q**) could be transformed into the corresponding products (**3a–3d, 3f–3i** and **3q**) in good yields (54–95%) and enantioselectivities (78–88% ee).

To better understand the mechanism of the reaction, control experiments were performed. When the radical quencher 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction,[5] product **3a** was obtained in 95% yield with 90% ee and no α-oxyamination products **8a** were detected from the reaction mixture (Scheme 2a). As 1,4-diazabicyclo-



Scheme 2. Control Experiments.



Scheme 3. Postulated Mechanism.

[2,2,2]octane (DABCO) has good solubility in water, a control experiment without water was carried out. As a result, the product **3 a** was obtained in 96% yield with 77% ee (Scheme 2b). The $^1O_2$ inhibitor (DABCO) was added to the reaction (Scheme 2c), and it was found that the reaction rate decreased significantly. After 48 h of reaction, only 18% yield and 47% ee were achieved. Therefore, it was confirmed that $^1O_2$ is present in the oxidation reaction. The product **3 a** was obtained in higher yields with C-2′ modified catalysts (**1 a**, **1 c**–**1 f**) than with unmodified catalyst **1 b** (Table 1, entries 1 and 3–7). The reaction also failed to occur for aliphatic cyclic β-keto ester substrate **2 u**. PTC **1 e** did not completely dissolve in *m*-xylene and formed a turbid solution. However, when substrate **2 a**, PTC **1 e** and Cs_2CO_3 were added to *m*-xylene and H_2O, a clear solution formed after 10 min (See Supporting Information Figure S4). We also performed UV-vis and fluorescence spectroscopy. The absorption of a solution of substrate **2 a**, PTC **1 e** and Cs_2CO_3 was higher than a solution of substrate **2 a** and PTC **1 e**, or a solution of PTC **1 e** at 330–365 nm, exhibiting an obvious bathochromic shift (See Supporting Information Figure S5 and S6). With the addition of PTC **1 e**, the emission intensity of substrate **2 a** dramatically decreased (See Supporting Information Figure S7). Therefore, we believe that substrate **2 a** and PTC **1 e** form a chiral enolate complex under basic conditions, and that the complex acted as a photosensitive center in the reaction. According to these results and previous studies,[9,10,17] we proposed a plausible mechanism (Scheme 3). The enol anion **5** forms from substrate **2**

under the action of base, and forms chiral enolate complex **6** with PTC **1e**. Under visible light, the complex **6** acts as a photosensitizer to activate $^3O_2$ into $^1O_2$. The *Re*-face of complex **6** is shielded by the ^{1}Ad group, so the $^1O_2$ or hydroperoxide **7** can only attack the complex **6** from the *Si*-face, affording α-hydroxylation product **3** with the *S*-configuration. Therefore, the cinchona-derived phase-transfer catalyst simultaneously acts as a chiral center and a phase-transfer catalytic center and forms a chiral enolate complex with substrate to act as a photosensitive center in the reaction.

In conclusion, a visible light-driven enantioselective aerobic oxidation of β-dicarbonyl compounds catalyzed by cinchona-derived PTCs in batch and semi-flow is reported. The easily modified cinchona-derived PTCs act as a chiral center and a phase-transfer catalytic center and form a chiral enolate complex with substrates to act as a photosensitive center in the reaction. A flow photomicroreactor was used to achieve a visible light-driven heterogeneous gas-liquid-liquid asymmetric aerobic oxidation reaction. Good yields and enantioselectivities were obtained and the reaction residence time could be substantially shortened by semi-flow processes. Further research on extending the cinchona-derived PTCs to other asymmetric reactions are currently underway in our laboratory.

Experimental Section

General Produce for Synthesis of 3 in the Batch

Substrate **2** (0.1 mmol) and **1e** (10 mol%) in *m*-xylene (16 mL), and 2 equiv. Cs_2CO_3 aq (in 2 mL H_2O) were added to a test tube equipped with a stirring bar. The reaction was covered by a 3 W LED blue light at −5 °C for 24 h. After completion of the reaction (confirmed by TLC), the mixture was diluted with EtOAc (50 mL), washed with water (3×20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, 5/1) to afford the product **3**. The ee of the product was determined by chiral HPLC.

General Produce for Synthesis of 3 in the flow Photomicroreactor

The organic phase was prepared by dissolving substrates **2** (0.1 mmol) and **1e** (20 mol%) in *m*-xylene (16 mL). The aqueous phase was a Cs_2CO_3 solution (1% Cs_2CO_3). The organic phase and aqueous phase were introduced through pump 1 and pump 2 at a flow rate of 1.5 mL/min. Oxygen was introduced through a mass flowmeter at a flow rate of 10 mL/min. The reaction pressure was 3 bar and the reaction temperature was 0 °C in the flow photomicroreactor. The outlet of the back pressure regulator was directly attached to the original reaction tube (the reaction tube was connected to air with a pipe to release the excess O_2 and relieve pressure quickly), and the reaction mixture was circulated. O_2 was continuously inlet to the microreactors in the full process (without reuse). After completion of the reaction (confirmed by TLC), the mixture was diluted with EtOAc (50 mL), washed with water (3×20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, 5/1) to afford the product **3**. The ee of the product was determined by chiral HPLC.

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