Tetrahedron 74 (2018) 3624–3633

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Bifunctional metal-free photo-organocatalysts for enantioselective aerobic oxidation of β-dicarbonyl compounds

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ARTICLE INFO

*Article history:*
Received 16 March 2018
Received in revised form
4 May 2018
Accepted 8 May 2018
Available online 11 May 2018

*Keywords:*
Photo-organocatalyst
Bifunctional
Visible-light
Metal-free
Oxidation

ABSTRACT

A series of bifunctional metal-free photo-organocatalysts have been developed by grafting the photosensitizer to cinchona-derived phase-transfer catalysts. Using air as a green oxidant and visible light as the driving force, these catalysts are applied to the oxidation of a range of β-dicarbonyl compounds in good yields (up to 97%) and enantioselectivities (up to 93:7 er).



## 1. Introduction

As an environmentally friendly and sustainable source of energy, visible light has been used to drive catalytic asymmetric photoredox chemistry in recent years.[1,2] In 2004, Córdova first reported the amino acid-catalysed asymmetric photoredox incorporation of singlet molecular oxygen into the α-position of aldehydes with UV light in moderate yields and enantioselectivities.[3] The conventional strategy for asymmetric visible light photocatalysis[4] employs a photoredox catalyst to furnish reactive radical species in visible light and a chiral catalyst to control the stereoselectivity of the ground state process. In 2014, Meggers reported a chiral iridium complex as a bifunctional photoredox catalyst,[5] in which the metal center simultaneously serves as the chiral center and photoredox center. Recently, the Xiao group developed a bifunctional photoredox catalyst that combined a photosensitizer with a metal-organic catalyst.[6] However, compared with metal-organic catalysts, organic catalysts have the advantages of being low cost and not leaving metal residue in the product.[7] Therefore, the use of metal-free photo-organocatalysts to activate molecular oxygen in visible light is still a novel and valuable method in asymmetric photoredox catalysis.[8]

Cinchona alkaloids serve as excellent chiral organic catalysts, with many functional groups that can be modified, and have been applied in many fields of asymmetric catalysis.[9] Cinchona-derived phase-transfer catalysts were used to catalyse asymmetric perfluoroalkylation of cyclic β-keto esters under visible light.[10] These catalysts don't contain any photosensitive units, and rely on the formation of photoactive electron donor–acceptor complexes.[10c] As a new strategy in asymmetric catalysis, bifunctional catalysts have been used to emulate enzymes to some extent and have been shown to have high activity and selectivity.[11] Therefore, in accordance with our previous research,[12] novel bifunctional photo-organocatalysts were synthesized by combining photosensitizers with a cinchona-derived phase-transfer catalyst and applied to the activation of molecular oxygen in visible light for asymmetric C–O bond formation.

## 2. Results and discussion

At first, we wanted to find the most effective organic photosensitizer to promote this reaction. In line with our previous research,[12b] we used 1a as the phase-transfer catalyst. Compared to rose bengal, eosin Y, eosin B, phthalocyanine and methylene blue,

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https://doi.org/10.1016/j.tet.2018.05.023
0040-4020/

tetraphenylporphyrin (**TPP**) had higher enantioselectivity (90.5:9.5 er) and faster reaction rate (Table 1).

After **TPP** was identified as a suitable photosensitizer, we considered how to graft **TPP** to chiral organic catalyst **1a**. Structural modification of **TPP** was mostly focused on the **R[1]** position (Fig. 1). Correspondingly, structural modification of cinchonine was mostly focused on the **C-2′**, **C-9**, **C-3** and **N-1** positions. Using this strategy, we designed and synthesized the bifunctional photo-organocatalysts **1b**-**1f** (Scheme 1).

As shown in Schemes 1 and 2, a series of bifunctional photo-organocatalysts **1b**-**1f** and tetraphenylporphyrin derivatives[13] were synthesized. To connect to the **C-9** position of **1a**, we synthesized **TPP-3**, and then synthesized the catalyst **1c**.[14] Next, we synthesized two catalysts (**1c** and **1d**) by connecting **TPP** to the **N-1** position of **1a**. In accordance with Itsuno's method,[15] we synthesized bifunctional photo-organocatalyst **1c** through an ion exchange reaction with **TPP-4**. **TPP-3** was linked to the **N-1** position by synthesis of a chiral quaternary ammonium salt (**1d**). According to our previous research,[12b] stereocontrol is sensitive to structural modifications at the **C-2′** position of the quinoline ring. We designed and synthesized the bifunctional photo-organocatalyst **1e** (Scheme 2).[16] Using a Suzuki-Miyaura coupling reaction, we synthesized a bifunctional photo-organocatalyst (**1e**) from **TPP-8,** which connected with **TPP** at the **C-2′** position. In addition, finally, we synthesized bifunctional photo-organocatalyst **1f,** which was modified at the **C-3** position through a Mizoroki-Heck reaction with **TPP-7** (Scheme 2).[17]

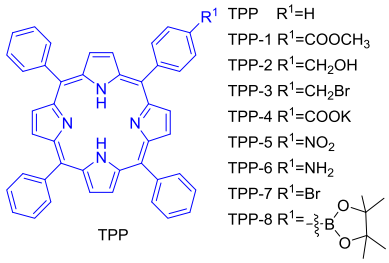
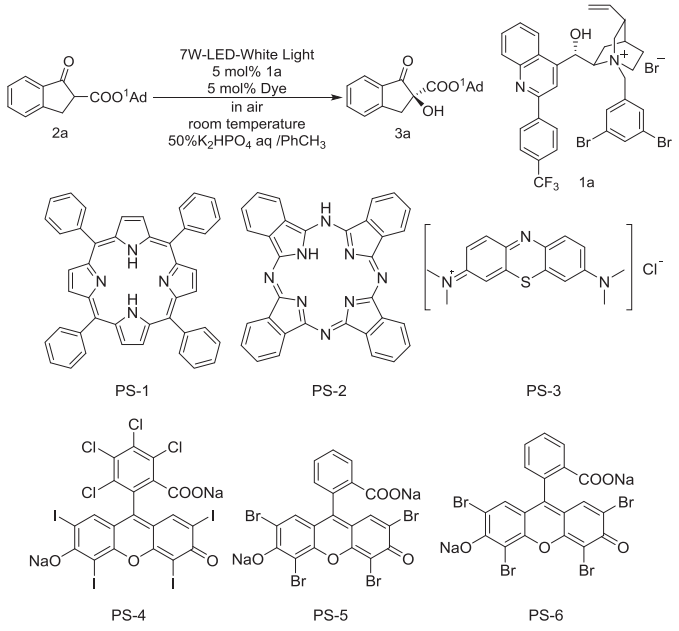



**Fig. 1.** TPP and its derivatives.

**Table 1**
Screening of Photosensitizer for α-Hydroxylation of β-Keto Ester 2a[a].



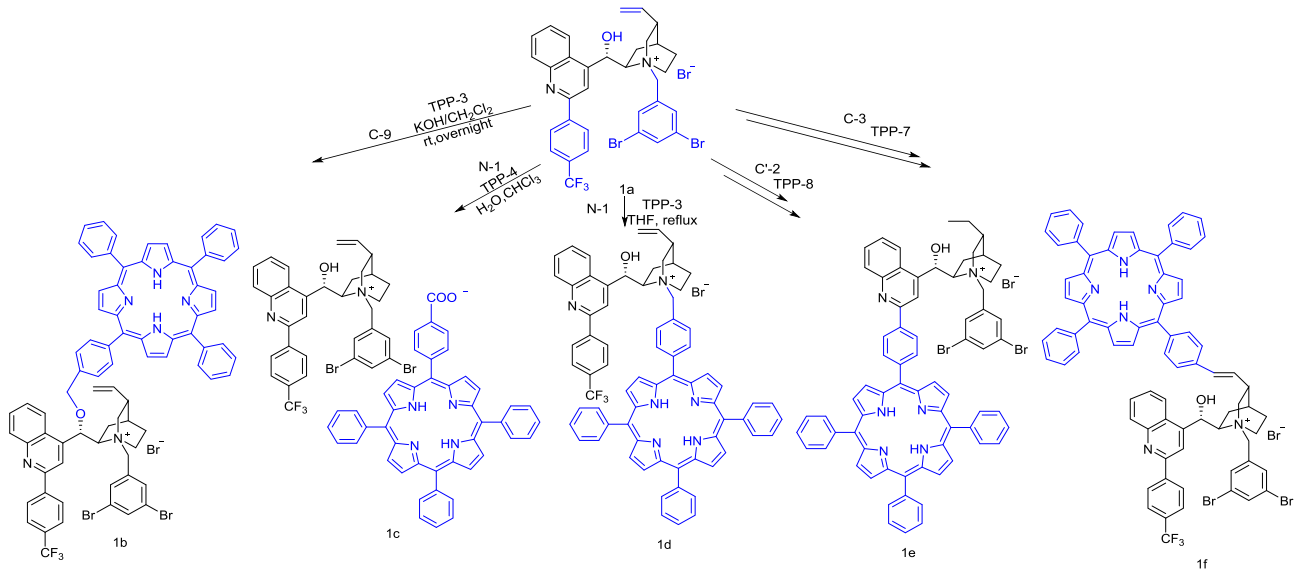

| Entry | Dye | t(min) | Conv.(%)[b] | er(%)[c] |
|---|---|---|---|---|
| 1 | PS-1 | 20 | >95 | 90.5:9.5 |
| 2 | PS-2 | 120 | >95 | 90.5:9.5 |
| 3 | PS-3 | 150 | >95 | 90.5:9.5 |
| 4 | PS-4 | 20 | >95 | 89.5:10.5 |
| 5 | PS-5 | 20 | >95 | 89:11 |
| 6 | PS-6 | 20 | >95 | 90:10 |

[a] β-Keto Ester 2a (31 mg, 0.1 mmol) and catalyst (5 mol%) were added to a test tube equipped with stirring bar and dissolved in 10 mL $PhCH_3$, then, 50% $K_2HPO_4$ (4 mL) was added. The mixture was stirred in air with exposure to a 7 W LED white light at room temperature until the reaction was completed.
[b] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Kromasil, $SiO_2$, 5 mm).
[c] Determined by HPLC analysis (Chiralcel AD-H) with hexane/2-propanol (80:20) as the eluent.

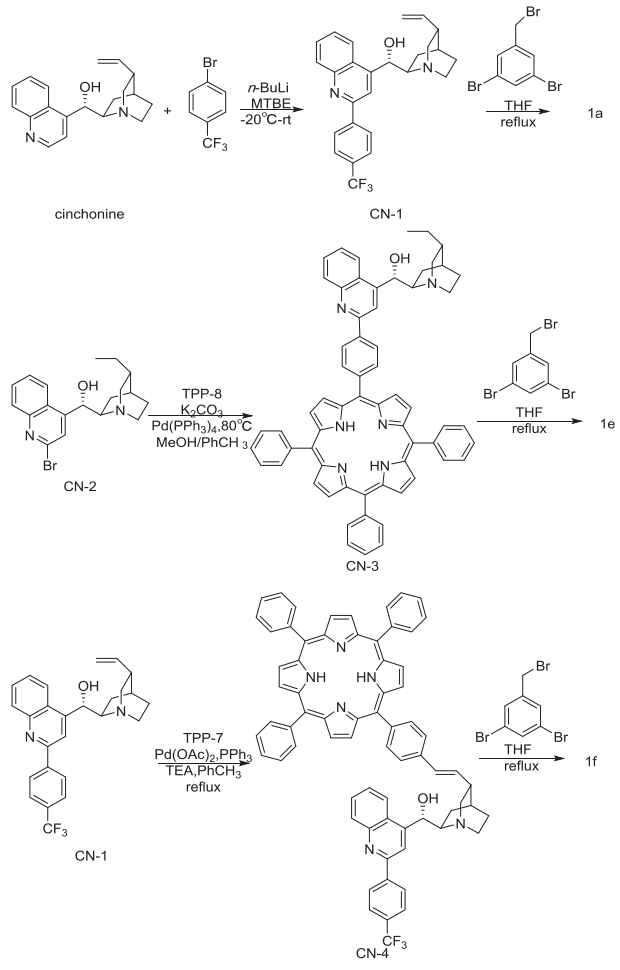
To our disappointment, **1b** showed poor results for a reaction time of 30 min, giving 60:40 er (Table 2, **entry 1**). This result points to the importance of the **C-9** hydroxyl group in this reaction. We were pleased to see that the enantiomeric ratio was increased to 86.5:13.5 with **1e** as the catalyst (Table 2, **entry 4**). In addition, to our delight, catalyst **1f** afforded the desired product **3a** with 90:10 er and almost quantitative conversion in 20 min (Table 2, **entry 5**). From there, further reaction optimization was undertaken. First, the base was investigated (Table 2, **entries 6**–**8**). When the amount of base was reduced to 2 equivalents, $Cs_2CO_3$ attained a higher enantioselectivity (91:9 er). Without base, nearly no reaction occurred (Table 2, **entries 8**). We considered that the reaction activity was possibly due to the wattage of the light source. To our delight, the enantioselectivity was improved to 93:7 when using a 25W white LED lamp (Table 2, **entries 9**). When the light was too weak or too strong, enantioselectivity suffered. It is worth mentioning that the reaction also proceeded well in the sunlight and gave the corresponding product **3a** in almost quantitative yield and 91:9 er after approximately 20 min (Table 2, **entry 11**). Conversely, nearly no reaction occurred in the dark (Table 2, **entry 12**).

Once optimized conditions were established, the scope of substrates was examined, and the results are summarized in Scheme 3. At first, a series of 1-indanone-derived adamantyl β-keto esters were investigated. Esters with a variety of substituents on the aromatic ring, such as methyl, methoxy, chloro, and bromo groups, were nicely converted into the corresponding products **3a**-**3g** in good yields (88–97%) and 90:10-93:7 er. However, a lower enantiomeric ratio was acquired for the 4-methoxy-substituted substrate (87:13 er, **3h**). We then investigated the effect of the ester group on 1-indanone derivatives. We observed that enantioselectivities were influenced by the size of substitution in the ester group. The substrates with larger ester groups worked better than those with smaller ones, and the enantiomeric ratio gradually decreased from 83:17 to 72.5:27.5 (**3i**-**3l**). Next, we explored the α-hydroxylation of 1-tetralone-derived adamantyl β-keto esters (**3m**-**3p**). Compared to 1-indanone-derived adamantyl β-keto esters, the yields and enantiomeric ratios of the corresponding products were slightly decreased (63–95% yield, 85.5:14.5–81:19 er). After investigation of β-keto esters, the scope of the β-keto amides was examined (**3q**-**3s**). To our delight, **3q** was obtained after 12 h in 64% yield and 88.5:11.5 er.

To demonstrate the utility of this reaction, a catalyst recirculation experiment was performed. The catalyst **1f** was recycled after separation of the product by column chromatography. After three rounds of recycling catalyst **1f** achieved a similar yield and enantioselectivity (95% yield, 92:8 er, Table 3).



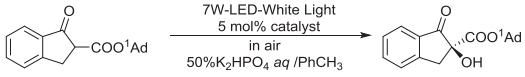

**Scheme 1.** Preparation of Bifunctional Metal-Free Photo-Organocatalysts.




**Scheme 2.** Preparation of Bifunctional Metal-Free Photo-Organocatalysts.

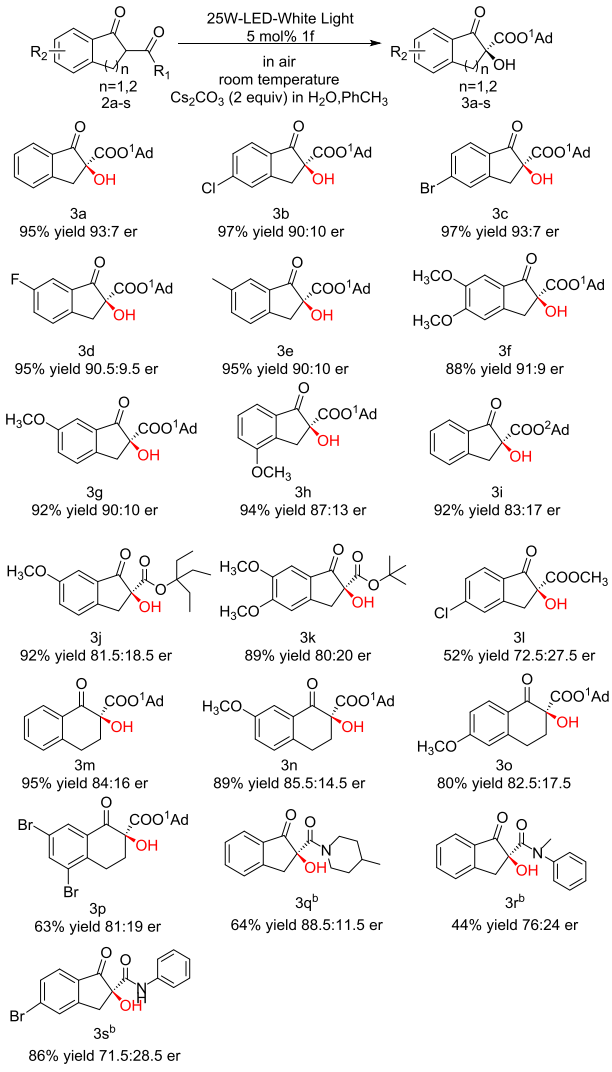
Finally, to better understand this reaction by bifunctional photo-organocatalysts, we proposed a plausible mechanism for this photo-organocatalytic α-hydroxylation of β-dicarbonyl compounds. Addition of **TEMPO** into the reaction system still produced **3a** with 94% yield and 93:7 er, and no α-oxyamination products **8** were detected from the reaction mixture (Scheme 4).[6,18] However, when a singlet oxygen quencher (**DABCO**)[19] was added to the reaction, the reaction time was increased to 30 min, and the mass spectrum of the reaction solution certified the existence of the N-

**Table 2**
Optimization of the Reaction Conditions for the α-Hydroxylation of β-Keto Ester 2a with Bifunctional Metal-Free Photo-Organocatalysts[a].



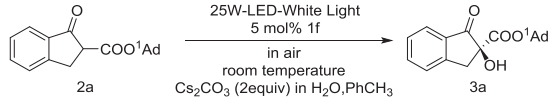

| Entry | Cat. | base | t (min) | T (°C) | Conv. (%)[b] | er (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 1b | $K_2HPO_4$ | 30 | 20 | >95 | 60:40 |
| 2 | 1c | $K_2HPO_4$ | 360 | 20 | >90 | 76:24 |
| 3 | 1d | $K_2HPO_4$ | 20 | 20 | >95 | 80:20 |
| 4 | 1f | $K_2HPO_4$ | 20 | 20 | >99 | 86.5:13.5 |
| 5 | 1f | $K_2HPO_4$ | 20 | 20 | >99 | 90:10 |
| 6[d] | 1f | $K_2HPO_4$ | 20 | 20 | >99 | 90.5:9.5 |
| 7[d] | 1f | $Cs_2CO_3$ | 20 | 20 | >99 | 91:9 |
| 8[d,e] | 1f | no | 20 | 20 | trace | nd |
| 9[d,f] | 1f | $Cs_2CO_3$ | 20 | 20 | >99 | 93:7 |
| 10[d,g] | 1f | $Cs_2CO_3$ | 20 | 20 | >99 | 90.5:9.5 |
| 11[d,h] | 1f | $Cs_2CO_3$ | 20 | 20 | >99 | 91:9 |
| 12[d,e,i] | 1f | $Cs_2CO_3$ | 20 | 20 | trace | nd |
| 13[d] | 1f | $Cs_2CO_3$ | 20 | −10 | >99 | 88:12 |
| 14[d] | 1f | $Cs_2CO_3$ | 20 | 10 | >99 | 93:7 |
| 15[d] | 1f | $Cs_2CO_3$ | 20 | 30 | >99 | 90.5:9.5 |

[a] Unless otherwise specified, reactions were performed with 0.1 mmol of 1a using the conditions described in Table 1.
[b] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Kromasil, $SiO_2$, 5 mm).
[c] Determined by HPLC analysis ( Chiralcel AD-H ) with hexane/2-propanol (80:20) as the eluent.
[d] 2eq. base in 4 mL $H_2O$.
[e] Reaction time 12 h.
[f] 25 W LED white light.
[g] 100 W LED white light.
[h] Sunlight.
[i] In the dark.




**Scheme 3.** Substrate Scope in the Asymmetric α-Hydroxylation of β-dicarbonyl compounds.[a].

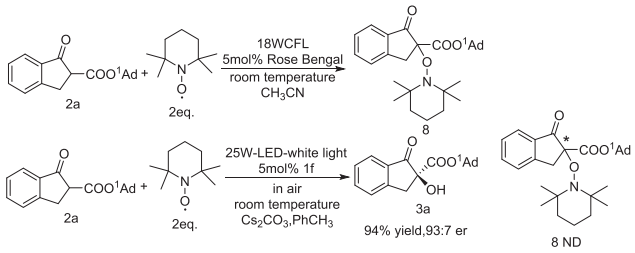
**Table 3**
Reusability of **1f** for the asymmetricα-hydroxylation of **2a**[a].




| run | t (min) | Yield (%) | er |
|---|---|---|---|
| 1 | 20 | 95 | 93:7 |
| 2 | 20 | 95 | 93:7 |
| 3 | 20 | 95 | 92:8 |

[a] Unless otherwise specified, the reaction was performed with 0.1 mmol of 1a using the conditions described in Scheme 3.

oxide of **DABCO**. Therefore, we proposed that the enol of the β-keto ester could react with active singlet molecular oxygen ($^1\mathbf{O_2}$) to afford the photo-oxygenation product. With further research, we could clearly observe the existence of active intermediate **7** by TLC when the reaction temperature was dropped to −20 °C. Due to its instability, we could not separate pure intermediate **7**. However, the mass spectrum of the reaction solutions certify the existence of




**Scheme 4.** Intermediate -Trapping Experiments.

intermediate **7**. Therefore, we propose a plausible mechanism in Scheme 5. The bifunctional photo-organocatalysts have two parts, a photosensitization part and an organic phase-transfer catalyst part. First, molecular oxygen is activated from the non-excited triplet state ($^3\mathbf{O_2}$) to the reactive singlet state ($^1\mathbf{O_2}$) with light by the photosensitization part of the catalyst. In the presence of base, deprotonation of **2** occurs to form enolate **5**. Then, the chiral enolate complex **6** can form using the organic phase-transfer part of the catalyst[10c] and react with the active singlet molecular oxygen ($^1\mathbf{O_2}$). As a result, active α-hydroperoxide intermediate **7** is formed. Finally, the active intermediate **7** can be rapidly converted into the final α-hydroxylation product **3** (Scheme 5).

## 3. Conclusions

A series of bifunctional metal-free photo-organocatalysts have been developed by grafting photosensitizers to a cinchona-derived phase-transfer catalyst. These catalysts have the following two functions: activation of oxygen with visible light or sunlight by the photoredox center and control of stereoselectivity during the chemical bond formation by the chiral center. A wide range of α-hydroxy β-dicarbonyl compounds can be obtained in short time under mild conditions with excellent yields and enantiopurity. A mechanism for this asymmetric photoredox α-hydroxylation of β-dicarbonyl compounds was proposed. Further research on extending these novel bifunctional photo-organocatalysts to other visible-light-driven asymmetric photochemical syntheses is currently underway.

## 4. Experimental section

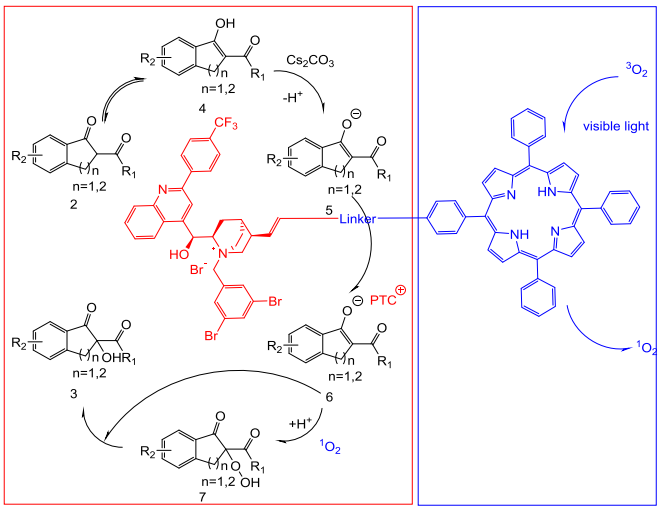
### 4.1. General

$^1$H NMR (400 MHz) or (500 MHz) spectra was obtained at 25 °C; $^{13}$C NMR (126 MHz) were recorded on a VARIAN INOVA-400 M and AVANCE II 400 spectrometer at 25 °C. Chemical shifts are reported as $\delta$ (ppm) values relative to TMS as internal standard and coupling constants (J) in Hz. UV–Vis was performed with a UV–Vis spectrophotometer. The enantiomeric ratio (er) were determined by HPLC. HPLC analyses were performed on equipped with Diacel Chiralpak AD-H, OD-H and AS-H chiral column (0.46 cm × 25 cm), using mixtures of n-hexane/isopropyl alcohol as mobile phase, at 25 °C. Mass spectra are reported by using electron ionization and electrospray ionization techniques. Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at 25 °C.

### 4.2. General procedure for the synthesis of TPP and its derivatives

#### 4.2.1. 5,10,15,20-Tetraphenylporphyrin (*TPP*)

TPP was prepared partly according to Longo's method.[13a] To a solution of propionic acid (200 mL) and Nitrobenzene (50 mL) was




**Scheme 5.** Proposed Mechanism for the Photo-Oxygenation of β-Dicarbonyl Compounds.

added benzaldehyde (10 g, 94.34 mmol) and pyrrole (6.33 g, 94.34 mmol) and re-fluxed for 3 h. Then poured into iced water (200 mL). The aqueous solution was neutralised with aqueous ammonium hydroxide until pH = 8, then extracted with $CH_2Cl_2$ until colourless. The organic layer was reduced of volume under reduced pressure. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:3) as eluent to afford TPP as a purple solid (4.03 g, 28% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.84 (s, 8H), 8.24–8.19 (m, 8H), 7.81–7.70 (m, 12H), −2.76 (s, 2H).

#### 4.2.2. Methyl 4-(10,15,20-triphenylporphyrin-5-yl)benzoate (***TPP-1***)

TPP-1 was prepared partly according to Souza's method.[13b] To a solution of propionic acid (90 mL) containing methyl-4-formyl benzoate (2.57 g 15.63 mmol) was added benzaldehyde (3.98 g 37.50 mmol) and pyrrole (3.35 g, 50 mmol) and refluxed for 2 h, then poured into iced water (200 mL). The aqueous solution was neutralised with aqueous ammonium hydroxide until pH = 8, then extracted with $CH_2Cl_2$ until colourless. The organic layer was reduced of volume under reduced pressure. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:1) as eluent to afford TPP-1 as a purple solid (0.57 g, 7% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.85 (m, 6H), 8.78 (d, $J$ = 4.8 Hz, 2H), 8.43 (d, $J$ = 8.2 Hz, 2H), 8.30 (d, $J$ = 8.1 Hz, 2H), 8.21 (m, 6H), 7.83–7.69 (m, 9H), 4.10 (s, 3H), −2.77 (s, 2H).

#### 4.2.3. (4-(10,15,20-triphenylporphyrin-5-yl)phenyl)methanol (***TPP-2***)

TPP-2 was prepared partly according to Bonifazi' method.[13c] A solution of TPP-1 (87 mg, 0.13 mmol) in dry THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.39 mL, 1 M) in dry THF at 0 °C under $N_2$. The reaction was left to stir for 30 min at room temperature before being quenched with 1% HCl (15 mL). Then extracted with $CH_2Cl_2$ until colourless. The organic layer was neutralised with aqueous ammonium hydroxide until pH = 8, then reduced of volume under reduced pressure. The crude product was purified by column chromatography using $CH_2Cl_2$/PE (1:1) as eluent to afford TPP-2 as a purple solid (71 mg, 85% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.84 (s, 8H), 8.27–8.15 (m, 8H), 7.75 (m, 11H), 5.05 (s, 2H), −2.77 (s, 2H).

#### 4.2.4. 5-(4-(bromomethyl)phenyl)-10,15,20-triphenylporphyrin (***TPP-3***)

To dried flask equipped with a magnetic stirring bar, $PBr_3$ (49 mg, 0.18 mmol) was added to a 30 mL $CH_2Cl_2$ solution of TPP-2 (77 mg, 0.12 mmol). The reaction cooled to 0 °C for 1 h. Then the mixture was warmed to ambient temperature for 2 h. Then poured into saturated sodium bicarbonate (30 mL), extracted with $CH_2Cl_2$ until colourless and reduced of volume under reduced pressure. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:1) as eluent to afford TPP-3 as a purple solid (42 mg, 49% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.84 (s, 8H), 8.30–8.12 (m, 8H), 7.76 (m, 11H), 4.83 (s, 2H), −2.78 (s, 2H).

#### 4.2.5. Potassium 4-(10,15,20-triphenylporphyrin-5-yl)benzoate (***TPP-4***)

TPP-4 was prepared partly according to Borhan's method.[13d] TPP-1 (0.071 g, 0.105 mmol) were dissolved in THF (8 mL), and 2 M KOH (2 mL) was added. The solution was refluxed for 16 h and cooled to room temperature. The mixture was extracted with water (3 × 5 mL). The water layers were collected and used in the next step without further purification.

#### 4.2.6. 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (***TPP-5***)

TPP-5 and TPP-6 were prepared partly according to Smith's method.[13e] To a solution of TPP (1.84 g, 3 mmol) in trifluoracetic acid (TFA) (25 mL), a crop of sodium nitrite (0.29 g, 4.2 mmol) was added. After 3 min stirring at ambient temperature, the reaction mixture was quenched with water (100 mL) and the mix-ture extracted with $CH_2Cl_2$ (4 × 50 mL). The organic layers were collected and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), and finally with water (3 × 100 mL). The solution was finally dried over anhydrous $Na_2SO_4$, and the solvent evaporated under reduced pressure. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:2) as eluent to afford TPP-5 as a purple solid (2.36 g, 64% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.97–8.86 (m, 6H), 8.77 (d, $J$ = 4.8 Hz, 2H), 8.66 (d, $J$ = 8.6 Hz, 2H), 8.43 (d, $J$ = 8.7 Hz, 2H), 8.30–8.20 (m, 6H), 7.86–7.75 (m, 9H), −2.74 (s, 2H).

#### 4.2.7. 4-(10,15,20-Triphenylporphyrin-5-yl)aniline (***TPP-6***)

TPP-5 (2.31 g, 3.5 mmol) was dissolved in concentrated HCl (175 mL) and solid $SnCl_2$ (3.16 g, 14 mmol) was carefully added under stirring. The reaction mixture was heated to 65 °C for 4 h under $N_2$ before poured into iced water (100 mL). The aqueous solution was neutralised with aqueous ammonium hydroxide until pH = 8. The aqueous solution was extracted with $CH_2Cl_2$ until colourless. The organic layer was evaporated under reduced pressure. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:1) as eluent to afford TPP-6 as a purple solid (1.98 g, 90% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.93 (d, $J$ = 4.7 Hz, 2H), 8.83 (d, $J$ = 2.6 Hz, 6H), 8.21 (m, 6H), 7.98 (d, $J$ = 8.3 Hz, 2H), 7.77–7.73 (m, 9H), 7.03 (d, 2H), 3.98 (s, 2H), −2.75 (s, 2H).

#### 4.2.8. 5-(4-bromophenyl)-10,15,20-triphenylporphyrin (***TPP-7***)

TPP-7 was prepared partly according to Lin's method.[13f] TPP-6 (3.15 g, 5 mmol) was dissolved in 600 mL 50% $H_2SO_4$ aq. and the mixture was stirring in cryohydrate bath. Sodium nitrite solution consisted of $NaNO_2$ (6.90 g, 100 mmol) and $H_2O$ (200 mL) was slowly added into the porphyrin solution. The reaction was stirring for 10 min below 0 °C. Then urea (69.37 g, 1.16 mol) was added and the mixture was stirring for additional 10 min. After that, CuBr (7.17 g, 50 mmol) in cold hydrobromic acid (300 mL, ≥40.0%) was poured into the above reaction mixture and the reaction mixture was stirred for additional 2 h with the ice melting. Then the reaction mixture was diluted with water and the solution was adjusted to pH = 10 with 3 M NaOH. The aqueous phase was extracted with

chloroform and the obtained organic phase was dried over $Na_2SO_4$. The residue was purified over silica gel column using $CH_2Cl_2$/PE (1:3) as eluent to afford TPP-7 as a purple solid (2.75 g, 79% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.92–8.79 (m, 8H), 8.25–8.19 (m, 6H), 8.12–8.06 (m, 2H), 7.93–7.87 (m, 2H), 7.83–7.72 (m, 9H), −2.79 (s, 2H).

#### 4.2.9. 5,10,15-Triphenyl-20-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)porphyrin (*TPP-8*)

TPP-8 was prepared partly according to Vinogradov's method.[13g] TPP-7 (416 mg, 0.6 mmol), bis(pinacolato)diboron (381 mg, 1.5 mmol), and NaOAc (0.49 g, 6 mmol) were dissolved in DMF (6 mL) under $N_2$. $PdCl_2(dppf)_2$ (88 mg, 0.12 mmol, 20%), used as a catalyst in this Miyaura coupling reaction, was dissolved separately in DMF (1 mL). The solution of the catalyst was added to the mixture of the reactants, and it was stirred vigorously at 80 °C for 12 h. The mixture was cooled, $CH_2Cl_2$ (50 mL) was added, and the resulting solution was washed with water (3 × 50 mL) in a separatory funnel. The organic phase was collected, dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to dryness. The remaining solid was purified by column chromatography on silica gel ($CH_2Cl_2$/PE = 1:1) to afford the target TPP-8 as a purple solid after removing the solvent and drying the product in vacuum (0.28 g, 63%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.84 (d, $J$ = 2.1 Hz, 8H), 8.25–8.19 (m, 10H), 7.80–7.73 (m, 9H), 1.50 (s, 12H), −2.78 (s, 2H).

### 4.3. Preparation of Bifunctional Metal-free photo-organocatalysts

#### 4.3.1. (1S,2R,4S,5R)-1-(3,5-dibromobenzyl)-2-((S)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (*1a*)

According to Melchiorre's and Meng's method, the intermediate CN-1 and catalysts 1a was prepared according to the reported procedures.[10c,12b] 1a as white solid, m. p. 235–237 °C, $[\alpha]_D^{25} = +110$ (c 0.1, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.56–8.22 (m, 4H), 7.82 (s, 3H), 7.67 (t, $J$ = 1.6 Hz, 2H), 7.02 (d, $J$ = 29.1 Hz, 3H), 6.56–6.32 (m, 2H), 5.85 (m, 1H), 5.44 (d, $J$ = 12.0 Hz, 1H), 5.32–5.20 (m, 1H), 4.53 (t, $J$ = 10.8 Hz, 2H), 4.24 (s, 1H), 4.09 (s, 1H), 3.48 (q, $J$ = 7.0 Hz, 1H), 3.22 (t, $J$ = 11.5 Hz, 1H), 2.72 (d, $J$ = 10.8 Hz, 1H), 2.36 (d, $J$ = 8.8 Hz, 1H), 2.13 (m 1H), 1.81 (s, 1H), 1.76 (s, 1H), 1.21 (t, $J$ = 7.0 Hz, 1H).

#### 4.3.2. (1S,2R,4S,5R)-1-(3,5-dibromobenzyl)-2-((S)-(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl) ((4-(10,15,20-triphenylporphyrin-5-yl)benzyl)oxy)methyl)-5-vinylquinuclidin-1-ium bromide (*1b*)

1b was prepared partly according to Huffman's method.[14a] To a flame-dried flask equipped with a magnetic stirring bar was added 1a (0.0767 g, 0.1 mmol), $CH_2Cl_2$ (5 mL), and TPP-3 (0.212 g, 0.3 mmol). The mixture was added 50% KOH (0.1 mL) under $N_2$ for 10 h at room temperature until judged to be complete by TLC. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (3 × 5 mL). The organic layers were collected and washed with water (3 × 10 mL). The solution was finally dried over anhydrous $Na_2SO_4$, and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (MeOH/EA/PE/$Et_3N$ = 5/30/63/2) to give the reaction product 1b as a purple solid (0.0524 g, 38% yield). m. p. 190–191 °C.$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 8.84 (s, 4H), 8.72 (d, $J$ = 4.7 Hz, 2H), 8.62 (s, 2H), 8.58–8.46 (m, 4H), 8.29 (m, 3H), 8.21 (m, 6H), 8.04 (d, $J$ = 7.7 Hz, 2H), 8.01–7.94 (m, 4H), 7.87 (m, 9H), 7.74–7.67 (m, 1H), 7.59 (t, $J$ = 7.4 Hz, 1H), 7.49 (t, $J$ = 7.7 Hz, 1H), 6.65 (s, 1H), 6.19 (d, $J$ = 8.5 Hz, 1H), 5.33 (d, $J$ = 14.3 Hz, 2H), 5.26–5.17 (m, 1H), 5.09 (d, $J$ = 11.9 Hz, 1H), 4.67 (d, $J$ = 12.1 Hz, 1H), 4.37 (s, 1H), 4.02 (d, $J$ = 15.0 Hz, 1H), 3.77–3.70 (m, 1H), 3.38 (s, 2H), 3.13–2.98 (m, 3H), 2.79–2.65 (m, 2H), 1.96 (s, 1H), 1.81 (s, 1H), −2.94 (s, 2H). $^{13}$C NMR (126 MHz, $CHCl_3$) $\delta$ 154.51, 147.37, 145.83, 144.76, 142.85, 142.03, 142.01, 141.10, 136.35, 135.82, 135.00, 134.71, 134.50, 130.79, 130.08, 129.84, 128.58, 127.89, 127.74, 127.39, 126.68, 126.66, 125.71, 123.53, 123.29, 122.39, 120.43, 120.30, 118.46, 118.31, 117.07, 67.48, 59.68, 56.48, 54.12, 37.90, 26.94, 23.62, 21.76, 12.90, 11.98. IR (KBr) $cm^{-1}$ 3405, 3318, 3054, 2955, 1595, 1555, 1472, 1427, 1403, 1350, 1324, 1216, 1165, 1126, 1072, 1018, 1000, 983, 966, 851, 801, 746, 703; HRMS calculated for $C_{78}H_{60}Br_3F_3N_6O$ [$(M-Br)^+$]: 1311.3142, found $m/z$ 1311.3164. UV/Vis (toluene): $\lambda_{max}$ = 420 nm.

#### 4.3.3. (1S,2R,4S,5R)-1-(3,5-dibromobenzyl)-2-((S)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium 4-(10,15,20-triphenylporphyrin-5-yl)benzoate (*1c*)

1c was prepared partly according to Itsuno's method.[15a] To the solution of TPP-4 in water (100 mL) was added 1a (0.077 g, 0.1 mmol) and $CHCl_3$ (20 mL). The reaction was left to stir for 1 h at room temperature. The organic layers were collected and washed with water (3 × 10 mL). The solution was finally dried over anhydrous $Na_2SO_4$, and the solvent evaporated under reduced pressure. The solution was filtered and concentrated in vacuum to give a purple solid of 1c (0.131 g, 97% yield). m. p. 195–198 °C. $^1$H NMR (500 MHz, DMSO-d6) $\delta$ 8.83 (s, 8H), 8.53 (d, $J$ = 8.1 Hz, 2H), 8.47 (s, 1H), 8.39 (d, $J$ = 8.4 Hz, 1H), 8.34 (d, $J$ = 7.4 Hz, 2H), 8.25–8.19 (m, 7H), 8.19–8.15 (m, 4H), 8.09 (d, $J$ = 1.7 Hz, 1H), 7.98 (d, $J$ = 8.2 Hz, 2H), 7.91 (t, $J$ = 7.6 Hz, 1H), 7.88–7.77 (m, 10H), 6.67 (s, 1H), 6.64 (d, $J$ = 8.7 Hz, 1H), 6.51 (d, $J$ = 8.6 Hz, 1H), 6.19–6.11 (m, 1H), 5.33 (d, $J$ = 12.4 Hz, 1H), 5.27–5.24 (m, 1H), 5.11 (d, $J$ = 12.3 Hz, 1H), 4.44 (t, $J$ = 10.3 Hz, 1H), 3.91 (d, $J$ = 10.2 Hz, 2H), 3.54 (t, $J$ = 11.5 Hz, 1H), 3.11 (d, $J$ = 10.5 Hz, 1H), 2.68 (d, $J$ = 8.9 Hz, 2H), 1.87 (s, 1H), 1.78 (s, 2H), −2.91 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.14, 154.66, 152.91, 147.57, 145.64, 144.47, 143.08, 142.18, 139.43, 136.75, 136.25, 135.29, 135.09, 134.60, 134.55, 131.74, 131.12, 130.86, 130.14, 128.92, 128.02, 127.89, 127.77, 127.59, 126.74, 125.75, 125.37, 123.70, 123.25, 120.33, 120.27, 119.91, 118.45, 117.40, 116.47, 114.73, 68.16, 60.24, 56.45, 55.74, 54.29, 38.37, 29.71, 27.29, 24.02, 21.75. IR (KBr) $cm^{-1}$ 3402, 3319, 3059, 2970, 2926, 1700, 1595, 1555, 1472, 1378, 1325, 1218, 1166, 1126, 1075, 1049, 1017, 1001, 983, 966, 871, 849, 801, 732, 703; HRMS calculated for $C_{78}H_{59}Br_2F_3N_6O_3$ [$(C_{33}H_{30}Br_2F_3N_2O)^+$]: 685.0671, found $m/z$ 685.0683; [$(C_{45}H_{29}N_4O_2)^-$]: 657.2296, found $m/z$ 657.2309. UV/Vis (toluene): $\lambda_{max}$ = 420 nm.

#### 4.3.4. (1S,2R,4S,5R)-2-((S)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-1-(4-(10,15,20-triphenylporphyrin-5-yl)benzyl)-5-vinylquinuclidin-1-ium bromide (*1d*)

1d was synthesized by the same procedure as mentioned above for 1a from CN-1 and TPP-3(1.1 equiv) as a purple solid (91% yield). m. p. 248–251 °C. $^1$H NMR (500 MHz, DMSO-d6) $\delta$ 8.98 (d, $J$ = 4.8 Hz, 2H), 8.88 (d, $J$ = 17.6 Hz, 6H), 8.56 (t, $J$ = 9.7 Hz, 3H), 8.49 (s, 1H), 8.45 (d, $J$ = 7.5 Hz, 2H), 8.30–8.20 (m, 8H), 8.02 (d, $J$ = 8.2 Hz, 2H), 7.97 (t, $J$ = 7.6 Hz, 1H), 7.91–7.79 (m, 10H), 7.71 (d, $J$ = 5.2 Hz, 1H), 7.08 (d, $J$ = 3.6 Hz, 1H), 6.79 (s, 1H), 6.37–6.11 (m, 1H), 5.45 (d, $J$ = 11.9 Hz, 1H), 5.36 (d, $J$ = 18.3 Hz, 1H), 5.33–5.27 (m, 1H), 4.72 (d, $J$ = 39.6 Hz, 1H), 4.45 (s, 1H), 4.23 (s, 1H), 4.14 (t, $J$ = 9.4 Hz, 1H), 3.98 (t, $J$ = 12.0 Hz, 1H), 2.90 (d, $J$ = 8.7 Hz, 1H), 2.03 (s, 1H), 1.99–1.94 (m, 1H), −2.88 (s, 2H). $^{13}$C NMR (126 MHz, $CHCl_3$) $\delta$ 154.71, 147.80, 145.16, 144.46, 142.77, 142.35, 142.11, 141.41, 137.31, 135.53, 135.38, 134.92, 134.60, 134.03, 132.62, 131.13, 130.40, 129.28, 128.00, 127.82, 127.52, 127.45, 127.33, 126.85, 126.79, 126.76, 126.18, 125.72, 123.76, 123.39, 120.42, 120.34, 119.83, 119.25, 118.30, 117.92, 117.22, 67.43, 66.22, 62.15, 56.84, 54.22, 38.23, 33.50, 27.29, 24.00, 21.88. IR (KBr) $cm^{-1}$ 3419, 2970, 1598, 1555, 1507, 1473, 1442, 1402, 1349, 1325, 1218, 1167, 1126, 1076, 1048, 1017, 1000, 983, 966, 934, 878, 850, 801, 752, 729, 703; HRMS calculated for $C_{71}H_{56}BrF_3N_6O$ [$(M-Br)^+$]: 1065.4462, found $m/z$ 1065.4477. UV/Vis (toluene): $\lambda_{max}$ = 419 nm.

#### 4.3.5. (1S,2R,4S,5R)-1-(3,5-dibromobenzyl)-5-ethyl-2-((S)-hydroxy(2-(4-(10,15,20-triphenylporphyrin-5-yl)phenyl)quinolin-4-yl)methyl)quinuclidin-1-ium bromide (**1e**)

1e was prepared partly according to Deng's method.[9g] Cinchonine could be easily reduced to hydrocinchonine. Hydrocinchonine was oxidized by *m*-CPBA to form N,N′-dioxide, and the N-oxide can be obtained through a reduction reaction of $NaHSO_3$ and HCl. The N-oxide was brominated by $PBr_3$ to obtain the catalyst precursor (CN-2) with Br in the C-2′ position. CN-2 was afford as a white solid (55% yield). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 8.5 Hz, 1H), 7.84 (d, $J$ = 8.4 Hz, 1H), 7.75 (s, 1H), 7.68–7.60 (m, 1H), 7.40–7.32 (m, 1H), 5.67 (d, $J$ = 3.4 Hz, 1H), 3.01 (m, 2H), 2.93–2.82 (m, 2H), 2.73 (m, 1H), 1.97–1.87 (m, 1H), 1.71 (s, 1H), 1.53–1.38 (m, 5H), 1.25 (s, 1H), 1.18–1.08 (m, 1H), 0.88 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, DMSO-d6) $\delta$ 154.99, 148.22, 141.35, 130.21, 128.58, 126.77, 125.27, 124.80, 123.06, 70.66, 61.01, 49.79, 49.18, 37.02, 26.95, 25.83, 24.87, 23.61, 11.95; HRMS calculated for $C_{19}H_{23}BrN_2O$ [(M+H)$^+$]: 375.1067, found *m*/*z* 375.1071.

CN-2 (75 mg, 0.2 mmol), TPP-8 (178 mg, 0.24 mmol), $K_2CO_3$ (55 mg, 0.4 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) were dissolved in MeOH(10 mL) and $PhCH_3$(15 mL) nuder $N_2$. The solution was stirred vigorously at 80 °C for 12 h. The mixture was cooled, $CH_2Cl_2$ (50 mL) was added, and the resulting solution was washed with 10% $Na_2CO_3$ (20 mL) and water (3 × 50 mL) in a separatory funnel. The organic phase was collected, and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to dryness. This crude product CN-3 was used in the next step without further purification.

1e was synthesized by the same procedure as mentioned above for 1a from CN-3 and 1,3-dibromo-benzyl bromide (1.2 equiv) as a purple solid (50% yield). m. p. 245–249 °C. $^1$H NMR (400 MHz, DMSO-d6) $\delta$ 8.99 (s, 2H), 8.88 (d, $J$ = 12.8 Hz, 6H), 8.79 (d, $J$ = 7.7 Hz, 2H), 8.69 (s, 1H), 8.49 (d, $J$ = 7.8 Hz, 2H), 8.40 (d, $J$ = 8.6 Hz, 1H), 8.33 (d, $J$ = 8.4 Hz, 1H), 8.28–8.22 (m, 6H), 8.13 (s, 3H), 8.00–7.92 (m, 2H), 7.86 (d, $J$ = 6.1 Hz, 9H), 6.91 (s, 1H), 6.60 (s, 1H), 5.12 (d, $J$ = 12.3 Hz, 1H), 4.04 (s, 1H), 3.94 (s, 2H), 3.63–3.58 (m, 3H), 3.05 (d, $J$ = 10.0 Hz, 1H), 1.93 (s, 1H), 1.83 (s, 2H), 1.62 (s, 2H), −2.87 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 156.52, 147.72, 145.09, 143.40, 142.22, 139.51, 136.34, 135.38, 135.11, 134.63, 131.17, 130.36, 129.70, 128.86, 127.79, 127.36, 126.77, 126.27, 123.58, 122.81, 120.33, 119.74, 117.77, 67.96, 65.98, 59.95, 56.77, 56.30, 36.19, 25.62, 24.70, 24.43, 24.11, 21.80, 11.50. IR (KBr) cm$^{-1}$ 3410, 2970, 2926, 2606, 1599, 1557, 1472, 1442, 1401, 1384, 1348, 1220, 1181, 1156, 1085, 1049, 1001, 983, 966, 879, 802, 731, 703, 562, 517, 425; HRMS calculated for $C_{70}H_{57}Br_3N_6O$ [(M−Br)$^+$]: 1155.2955, found *m*/*z* 1155.2961. UV/Vis (toluene): $\lambda_{max}$ = 421 nm.

#### 4.3.6. (1S,2R,4S,5S)-1-(3,5-dibromobenzyl)-2-((S)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-5-((E)-4-(10,15,20-triphenylporphyrin-5-yl)styryl)quinuclidin-1-ium bromide (**1f**)

1f was prepared partly according to Manna's method.[17b] In an oven dried round-bottom flask, cooled under air, was taken CN-2 (0.392 g, 0.81 mmol, 1.0 equiv.) with 50 mL of absolute toluene. To this was added $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.1 equiv.), $PPh_3$ (43 mg, 0.16 mmol, 0.2 equiv.) and TPP-4 (3.38 g, 4.87 mmol, 6.0 equiv.), followed by $Et_3N$ (0.493 g, 4.87 mmol, 6.0 equiv.). The resulting mixture was stirred at 110 °C. After 72 h, reaction mixture was cooled to r.t., filtered through a plug of cotton, washed with 10% $Na_2CO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic phase was collected, and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to dryness. The remaining solid was purified by column chromatography on silica gel (MeOH/$CH_2Cl_2$ = 1/20) to afford CN-4 as a purple solid after removing the solvent and drying the product in vacuum (0.346 g, 40% yield). m. p. 200–203 °C.$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 8.91 (s, 2H), 8.84 (s, 6H), 8.54–8.48 (m, 4H), 8.23 (d, $J$ = 10.4 Hz, 8H), 8.11 (s, 1H), 8.03 (d, $J$ = 8.0 Hz, 1H), 7.97–7.92 (m, 4H), 7.85 (d, $J$ = 12.2 Hz, 7H), 7.74 (s, 1H), 7.51 (d, $J$ = 7.9 Hz, 1H), 7.37 (t, $J$ = 7.5 Hz, 1H), 6.97 (d, $J$ = 9.7 Hz, 2H), 4.54 (s, 1H), 3.82 (s, 3H), 3.68 (s, 1H), 2.98 (s, 1H), 2.13 (s, 3H), 1.61 (s, 2H), −2.90 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.25, 147.94, 147.04, 143.07, 142.12, 135.95, 135.02, 134.59, 132.94, 131.24, 130.46, 129.36, 128.54, 128.11, 127.81, 127.37, 126.77, 125.78, 125.02, 123.63, 122.60, 120.31, 119.71, 117.11, 116.48, 114.79, 66.82, 55.73, 49.46, 45.79, 37.65, 28.29, 23.61, 18.05, 8.50. HRMS calculated for $C_{70}H_{53}F_3N_6O$ [(M+H)$^+$]: 1051.4306, found *m*/*z* 1051.4314.

1f was synthesized by the same procedure as mentioned above for 1a from CN-4 and 1,3-dibromo-benzyl bromide (1.3 equiv) as a purple solid (78% yield). m. p. 246–249 °C.$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 8.88 (d, $J$ = 18.7 Hz, 8H), 8.57 (d, $J$ = 7.6 Hz, 3H), 8.43 (s, 2H), 8.29–8.11 (m, 11H), 7.98 (d, 5H), 7.85 (s, 10H), 6.99 (s, 1H), 6.95 (s, 2H), 6.64 (s, 1H), 5.20 (s, 1H), 5.01 (d, $J$ = 11.8 Hz, 1H), 4.45 (d, $J$ = 11.0 Hz, 1H), 4.02 (d, $J$ = 13.0 Hz, 2H), 3.76 (s, 1H), 3.22 (s, 1H), 3.04 (s, 1H), 2.75 (s, 1H), 2.10 (s, 1H), 1.91 (s, 2H), −2.87 (s, 2H). $^{13}$C NMR (126 MHz, $CHCl_3$) $\delta$ 154.62, 147.51, 144.78, 142.82, 142.26, 142.09, 136.48, 135.35, 135.17, 135.00, 134.54, 133.44, 131.12, 130.90, 130.21, 128.75, 127.92, 127.76, 127.59, 126.71, 126.61, 125.72, 124.83, 123.69, 123.41, 120.32, 119.35, 117.18, 67.75, 59.94, 56.57, 54.64, 52.98, 37.96, 27.62, 23.83, 22.07, 8.17. IR (KBr) cm$^{-1}$ 3386, 3057, 2972, 2926, 1597, 1556, 1472, 1427, 1403, 1378, 1350, 1324, 1217, 1166, 1126, 1077, 1049, 1016, 982, 966, 880, 807, 745, 703; HRMS calculated for $C_{77}H_{58}Br_3F_3N_6O$ [(M−Br)$^+$]: 1297.2985, found *m*/*z* 1297.3010. UV/Vis (toluene): $\lambda_{max}$ = 420 nm.

### 4.4. General produce for the asymmetric α-hydroxylation of β-keto esters and β-keto amides

The reaction was conducted with substrate 2a-2s (0.1 mmol) in the presence of PTC 1f (5 mol%) in $PhCH_3$ (10 mL) and $Cs_2CO_3$ (2equiv.) in $PhCH_3$ (10 mL) and $H_2O$ (4 mL) at room temperature with exposure to a 25W LED white lamp. After completion of the reaction (confirmed by TLC analysis), the mixture was diluted with EtOAc (50 mL), washed with water (3 × 20 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuum. The residue was purified by flash chromatography to give 3a-3s. The er of the product was determined by chiral HPLC.

#### 4.4.1. 1-Adamantyl 2-hydroxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3a**)

White solid; (32.6 mg, 95% yield, 93:7 er), m. p. 87–89 °C, $[\alpha]_D^{25}$ = +30.0 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$ = 7.7 Hz, 1H), 7.66 (t, $J$ = 7.4 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.44 (d, $J$ = 7.4 Hz, 1H), 4.03 (s, 1H), 3.68 (d, $J$ = 17.1 Hz, 1H), 3.24 (d, $J$ = 17.0 Hz, 1H), 2.14 (s, 3H), 1.98 (d, $J$ = 2.9 Hz, 7H), 1.62 (d, $J$ = 2.9 Hz, 7H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 10.6 min, $t_R$ (minor) = 16.5min.

#### 4.4.2. 1-Adamantyl 2-hydroxy-5-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3b**)

White solid; (36.1 mg, 97% yield, 90:10 er). m. p. 182–185 °C, $[\alpha]_D^{25}$ = +58.8 (c 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.2 Hz, 1H), 7.50 (d, $J$ = 1.6 Hz, 1H), 7.41 (d, $J$ = 8.2 Hz, 1H), 4.05 (s, 1H), 3.64 (d, $J$ = 17.3 Hz, 1H), 3.21 (d, $J$ = 17.3 Hz, 1H), 2.15 (s, $J$ = 3.4 Hz, 4H), 1.99 (d, $J$ = 3.0 Hz, 6H), 1.62 (s, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 11.4 min, $t_R$ (minor) = 18.4 min.

*4.4.3. 1-Adamantanyl 2-hydroxy-5-bromo-1-oxo-2,3-dihydro-1H-ndene-carboxylate (**3c**)*

White solid; (40.5 mg, 97% yield, 93:7er). m. p. 194–196 °C, $[\alpha]_D^{25}$ = +71.8 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 11.3 Hz, 2H), 7.57 (d, $J$ = 8.8 Hz, 1H), 4.05 (d, $J$ = 3.0 Hz, 1H), 3.64 (d, $J$ = 17.3 Hz, 1H), 3.21 (d, $J$ = 17.3 Hz, 1H), 2.15 (s, 3H), 1.99 (s, 6H), 1.62 (s, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 10.4 min, $t_R$ (minor) = 16.1 min.

*4.4.4. 1-Adamantanyl 2-hydroxy-6-fluoro-1-oxo-2,3-dihydro-1H-ndene2-carboxylate (**3d**)*

White solid; (34.4 mg, 95% yield, 90.5:9.5 er). m. p. 58–60 °C, $[\alpha]_D^{25}$ = +20.0 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58–7.43 (m, 2H), 7.42–7.32 (m, 1H), 4.06 (s, 1H), 3.63 (d, $J$ = 17.0 Hz, 1H), 3.20 (d, $J$ = 16.8 Hz, 1H), 2.15 (s, 3H), 1.98 (s, 6H), 1.62 (s, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 8.9 min, $t_R$ (minor) = 15.8 min.

*4.4.5. 1-Adamantyl 2-hydroxy-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3e**)*

White solid; (34.0 mg, 95% yield, 90:10 er). m. p. 113–115 °C, $[\alpha]_D^{25}$ = +37.5 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (s, 1H), 7.48 (d, $J$ = 7.9 Hz, 1H), 7.37 (d, $J$ = 7.8 Hz, 1H), 4.01 (s, 1H), 3.63 (d, $J$ = 17.0 Hz, 1H), 3.17 (d, $J$ = 17.0 Hz, 1H), 2.43 (s, 3H), 2.18–2.11 (m, 3H), 1.99 (d, $J$ = 3.0 Hz, 6H), 1.62 (t, $J$ = 3.1 Hz, 7H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 9.7 min, $t_R$ (minor) = 17.1 min.

*4.4.6. 1-Adamantyl 2-hydroxy-5,6-di-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3f**)*

Yellow solid; (38.6 mg, 88% yield, 91:9 er). m. p. 145–148 °C, $[\alpha]_D^{25}$ = +73.0 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.21 (s, 1H), 6.90 (s, 1H), 4.01 (d, $J$ = 1.4 Hz, 4H), 3.94 (s, 3H), 3.59 (d, $J$ = 16.8 Hz, 1H), 3.13 (d, $J$ = 16.9 Hz, 1H), 2.17–2.12 (m, 3H), 2.02 (d, $J$ = 3.0 Hz, 6H), 1.63 (m, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 17.8 min, $t_R$ (minor) = 28.2 min.

*4.4.7. 1-Adamantyl 2-hydroxy-6-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3g**)*

Colorless oil; (35.6 mg, 92% yield, 90:10 er). $[\alpha]_D^{25}$ = +20.3 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (d, $J$ = 8.2 Hz, 1H), 7.27–7.21 (m, 2H), 4.04 (s, 1H), 3.87 (s, 3H), 3.59 (d, $J$ = 16.8 Hz, 1H), 3.15 (d, $J$ = 16.7 Hz, 1H), 2.19–2.08 (m, 3H), 1.99 (d, $J$ = 3.1 Hz, 6H), 1.62 (t, $J$ = 3.1 Hz, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 12.3 min, $t_R$ (minor) = 20.2 min.

*4.4.8. 1-Adamantyl 2-hydroxy-4-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3h**)*

White solid; (35.6 mg, 94% yield, 87:13 er). m. p. 115–118 °C, $[\alpha]_D^{25}$ = +38 (c 0.1, $CHCl_3$). 1H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35 (d, $J$ = 8.3 Hz, 1H), 7.25–7.20 (m, 2H), 3.85 (s, 3H), 3.57 (d, $J$ = 16.7 Hz, 1H), 3.13 (d, $J$ = 16.8 Hz, 1H), 2.12 (s, 3H), 1.98 (d, $J$ = 2.9 Hz, 6H), 1.63–1.57 (m, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 23.6 min, $t_R$ (minor) = 32.4 min.

*4.4.9. 2-Adamantyl 2-hydroxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3i**)*

White solid; (32.6 mg, 92% yield, 83:17 er). m. p. 56–59 °C, $[\alpha]_D^{25}$ = +14.3 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 7.7 Hz, 1H), 7.68 (d, $J$ = 7.4 Hz, 1H), 7.52 (d, $J$ = 7.7 Hz, 1H), 7.44 (t, $J$ = 7.5 Hz, 1H), 4.98 (d, $J$ = 3.6 Hz, 1H), 4.07 (s, 1H), 3.73 (d, $J$ = 16.8 Hz, 1H), 3.32 (d, $J$ = 16.8 Hz, 1H), 1.96–1.57 (m, 10H), 1.36–1.23 (m, 4H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 95/5, 1 mL/min, 254 nm, $t_R$ (major) = 28.8 min, $t_R$ (minor) = 37.8 min.

*4.4.10. 3-Ethyl amyl 2-hydroxy-6- methoxyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3j**)*

Yellow oil, (32.0 mg, 92% yield, 81.5:18.5 er). $[\alpha]_D^{25}$ = +21.4 (c 0.25, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (d, $J$ = 8.3 Hz, 1H), 7.27–7.20 (m, 2H), 4.07 (s, 1H), 3.86 (s, 3H), 3.58 (d, $J$ = 16.7 Hz, 1H), 3.18 (d, $J$ = 16.7 Hz, 1H), 1.78–1.68 (m, 6H), 0.69 (t, $J$ = 7.5 Hz, 9H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 95/5, 1 mL/min, 254 nm, $t_R$ (major) = 18.1 min, $t_R$ (minor) = 15.7 min.

*4.4.11. t-butyl 2-hydroxy-5,6-di-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3k**)*

White solid; (30.8 mg, 89% yield, 80:20 er). m. p. 113–116 °C, $[\alpha]_D^{25}$ = +60.5 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.21 (s, 1H), 6.90 (s, 1H), 3.97 (d, $J$ = 30.0 Hz, 6H), 3.58 (d, $J$ = 16.9 Hz, 1H), 3.13 (d, $J$ = 16.9 Hz, 1H), 1.40 (s, 9H). HPLC conditions: Chiralcel AS-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 35.2 min, $t_R$ (minor) = 24.1 min.

*4.4.12. Methyl 2-hydroxy-5-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3l**)*

White solid; (24.0 mg, 52% yield, 72.5:27.5 er). m. p. 113–116 °C, $[\alpha]_D^{25}$ = +44.7 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.2 Hz, 1H), 7.52 (s, 1H), 7.47–7.40 (m, 1H), 4.03 (s, 1H), 3.77 (s, 3H), 3.26 (d, $J$ = 17.4 Hz, 1H). HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 13.0 min, $t_R$ (minor) = 15.8 min.

*4.4.13. 1-Adamantyl 2-hydroxy-1-oxo-1,2,3,4-tetra- hydronaphthalene-2-carboxylate (**3m**)*

White solid; (34.0 mg, 95% yield, 84:16 er). m. p. 79–81 °C, $[\alpha]_D^{25}$ = −9.0 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 7.9 Hz, 1H), 7.54 (t, $J$ = 7.5 Hz, 1H), 7.36 (t, $J$ = 7.6 Hz, 1H), 7.29 (s, 1H), 4.26 (s, 1H), 3.18–3.10 (m, 2H), 2.67 (m, 1H), 2.24 (m, 1H), 2.17–2.12 (m, 3H), 2.03 (d, $J$ = 3.0 Hz, 6H), 1.63 (d, $J$ = 3.0 Hz, 7H). HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 9.3 min, $t_R$ (minor) = 7.1 min.

*4.4.14. 1-Adamantyl 2-hydroxy-7-methoxyl-1-oxo-1,2,3,4-tetra-hydronaphthalene-2-carboxylate (**3n**)*

Colorless oil; (37.0 mg, 89% yield, 85.5:14.5 er). $[\alpha]_D^{25}$ = −26.9 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 2.8 Hz, 1H), 7.19 (d, $J$ = 8.4 Hz, 1H), 7.12 (dd, $J$ = 8.4, 2.8 Hz, 1H), 4.24 (s, 1H), 3.86 (s, 3H), 3.06 (dd, $J$ = 7.4, 5.2 Hz, 2H), 2.64 (m, 1H), 2.27–2.20 (m, 1H), 2.15 (t, $J$ = 3.2 Hz, 3H), 2.07–2.03 (m, 6H), 1.63 (t, $J$ = 3.0 Hz, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 10.8 min, $t_R$ (minor) = 17.1 min.

*4.4.15. 1-Adamantyl 2-hydroxy-6-methoxyl-1-oxo-1,2,3,4-tetra-hydronaphthalene-2-carboxylate (**3o**)*

White solid; (34.0 mg, 80% yield, 82.5:17.5 er). m. p. 77–79 °C, $[\alpha]_D^{25}$ = 12.0 (c 0.1, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 8.8 Hz, 1H), 6.88 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.72 (d, $J$ = 2.5 Hz, 1H), 4.28 (s, 1H), 3.89 (s, 3H), 3.10 (d, $J$ = 5.5 Hz, 2H), 2.64 (m, 1H), 2.25–2.18 (m, 1H), 2.17–2.13 (m, 3H), 2.05 (d, $J$ = 3.0 Hz, 6H), 1.64 (t, $J$ = 3.1 Hz, 6H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$

(major) = 15.0 min, $t_R$ (minor) = 20.8 min.

#### 4.4.16. 1-Adamantyl 2-hydroxy-5,7-di-bromine-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**3p**)

White solid; (49.8 mg, 63% yield, 81:19 er). m. p. 116–118 °C, $[\alpha]_D^{25} = -2$ (c 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J = 2.1$ Hz, 1H), 7.96 (d, $J = 2.1$ Hz, 1H), 4.14 (s, 1H), 3.19–2.95 (m, 2H), 2.66 (m, 1H), 2.30–2.21 (m, 1H), 2.20–2.15 (m, 3H), 2.03 (d, $J = 3.0$ Hz, 6H), 1.65 (t, $J = 3.1$ Hz, 7H). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/i-PrOH = 80/20, 1 mL/min, 254 nm, $t_R$ (major) = 9.2 min, $t_R$ (minor) = 14.8 min.

#### 4.4.17. 2-Hydroxy-1-oxo-N-phenyl-N-4-methylpiperidine-2,3-dihydro-1H-indene-2-carboxamide (**3q**)

Colorless oil; (39.1 mg, 64% yield, 88.5:11.5 er). $[\alpha]_D^{25} = -17.7$ (c 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 7.4$ Hz, 1H), 7.50–7.41 (m, 2H), 4.61 (s, 1H), 3.45 (d, $J = 17.8$ Hz, 1H), 3.30 (d, $J = 17.9$ Hz, 1H), 3.04 (d, $J = 39.5$ Hz, 1H), 2.77 (d, $J = 39.8$ Hz, 2H), 1.77–1.41 (m, 3H), 1.09 (d, $J = 35.5$ Hz, 1H), 0.90 (d, $J = 6.4$ Hz, 4H). HPLC conditions: Chiralcel AS-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 28.5 min, $t_R$ (minor) = 36.3 min.

#### 4.4.18. 2-Hydroxy-1-oxo-N-phenyl-N-methyl-2,3-dihydro-1H-indene-2-carboxamide (**3r**)

White solid; (38.1 mg, 44% yield, 76:24 er). m. p. 92–94 °C, $[\alpha]_D^{25} = -19.0$ (c 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.63–7.33 (m, 3H), 7.20 (d, $J = 7.5$ Hz, 1H), 7.12–6.87 (m, 5H), 3.57 (d, $J = 18.1$ Hz, 1H), 3.36 (s,3H), 3.14 (d, $J = 18.1$ Hz, 1H). HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/i-PrOH = 95/5, 1 mL/min, 254 nm, $t_R$ (major) = 41.0 min, $t_R$ (minor) = 35.7 min.

#### 4.4.19. 2-Hydroxy-1-oxo-5-bromine-N-phenyl-2,3-dihydro-1H-indene-2-carboxamide (**3s**)

White solid; (34.6 mg, 86% yield, 71.5:28.5 er). m. p. 177–180 °C, $[\alpha]_D^{25} = 18.7$ (c 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, Methanol) $\delta$ 7.74 (d, $J = 1.5$ Hz, 1H), 7.69–7.50 (m, 4H), 7.43–7.24 (m, 2H), 7.22–7.06 (m, 1H), 3.87 (d, $J = 17.2$ Hz, 1H), 3.33 (p, $J = 1.7$ Hz, 1H), 3.16 (d, $J = 17.2$ Hz, 1H). HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/i-PrOH = 90/10, 1 mL/min, 254 nm, $t_R$ (major) = 24.8 min, $t_R$ (minor) = 33.2 min.

### 4.5. Intermediates -Trapping Experiments

#### 4.5.1. 1-Adamantanyl-1-oxo-2-((2,2,6,6-tetramethylpiperidin-1-yl) oxy)-2,3-dihydro-1Hindene-2-carboxylate (**8**)

$^1H$ NMR (400 MHz, $CHCl_3$) $\delta$ 7.72 (d, $J = 7.7$ Hz, 1H), 7.57 (t, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 4.55 (d, $J = 17.5$ Hz, 1H), 3.31 (d, $J = 17.5$ Hz, 1H), 2.11–2.06 (m, 4H), 2.00 (d, $J = 3.0$ Hz, 6H), 1.58 (d, $J = 3.0$ Hz, 7H), 1.52 (d, $J = 2.9$ Hz, 0H), 1.44 (s, 0H), 1.33 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H), 0.55 (s, 3H). HRMS calculated for $C_{29}H_{39}NO_4$ $[(M+H)^+]$: 466.2952, found: 466.2951.

## Acknowledgments

We would like to thank the National Natural Science Foundation of China (no. 21176041, 21476041, U1608224) and the State Key Laboratory of Fine Chemicals for their support.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.023.

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