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

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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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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]

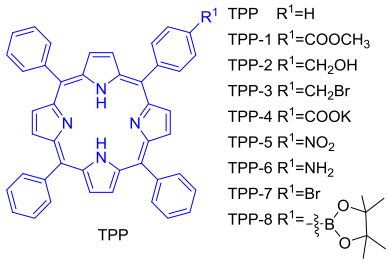
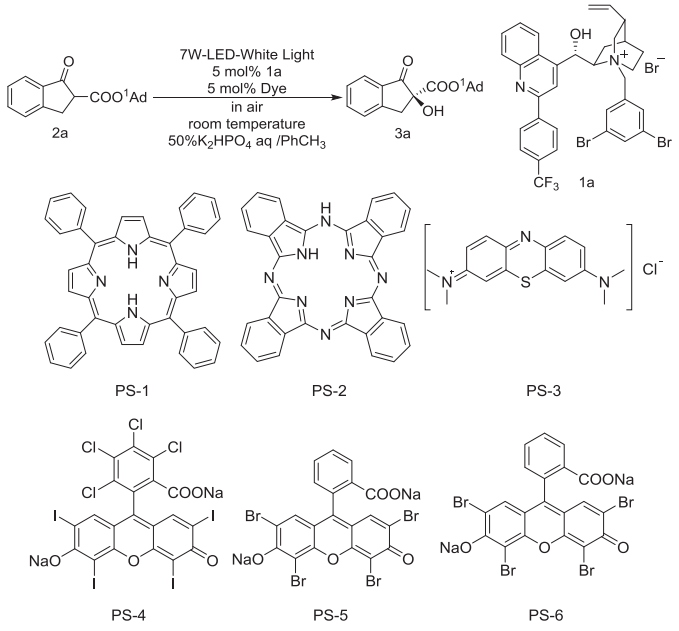


Fig. 1. TPP and its derivatives.

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).