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Photo-organocatalytic enantioselective α-hydroxylation of β-keto esters and β-keto amides with oxygen under phase transfer catalysis

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An efficient and enantioselective photo-organocatalytic α-hydroxylation of β-dicarbonyl compounds using molecular oxygen was extended. This simple catalytic procedure is applicable to a range of β-keto esters and β-keto amides (30 examples) with a new series of C-2′-substituted phase transfer catalysts in good enantiopurity (up to 90% ee) and yield (up to 99%). Moreover, the reaction was successfully scaled up to gram quantity without any loss of enantioselectivity.

Introduction

Over the past several decades, visible light has been recognized as a type of environmentally friendly and sustainable energy.[1] Moreover, enormous research interest in visible-light-driven catalytic asymmetric chemistry has been shown in recent years.[2-4] Among the photo-chemical reactions, photo-oxygenation is a novel oxidation method. Furthermore, molecular oxygen in air is considered a green oxidant, but it is usually torpid. However, molecular oxygen can be transferred from its non-excited triplet state ($^3O_2$) to its more reactive singlet state ($^1O_2$) by photosensitization. The application for visible-light-activated asymmetric catalysis with oxygen is a challenge. In 2004, Córdova and his co-workers first reported enantioselective photo-oxygenation of aldehydes and ketones using singlet molecular oxygen as the oxidant and amino acids as chiral organocatalysts.[5] Our group independently reported an enantioselective α-hydroxylation of β-keto esters with molecular oxygen by a chiral phase transfer catalyst.[6] The limited success in photo-oxygenation urges us to extend its use in oxidation reactions.

The optically active α-hydroxy β-dicarbonyl compounds represent a functional and common structural motif in a variety of natural products and pharmaceuticals.[7] These compounds have been used for the synthesis of bioactive products, such as Ginkgolide B,[8] Kjellmanianone,[9] Hamigeran A[10] and Doxycycline.[11] Furthermore, they have been used as an important intermediate in the synthesis of the insecticide indoxacarb.[12] Therefore, asymmetric α-hydroxylation of β-dicarbonyl compounds is a significant transformation. Davis first reported the enantioselective α-hydroxylation of β-keto esters using stoichiometric amounts of chiral oxaziridine in 1981.[13] Asymmetric catalysis by chiral metal complexes and organocatalysts were then developed rapidly.[14-15] In regard to organocatalytic approaches, chiral phosphoric acids,[15b] lappaconitine[15c] and S-timolol analogues,[15d] chiral guanidines[15h, i] and cinchona alkaloids[15a, o] have been reported as efficient catalysts. However, most of these reactions require oxidants such as organic peroxide, oxaziridine, dimethyldioxirane or nitrosobenzene. Considering economical as well as environmental viewpoints, the use of molecular oxygen as the oxidant would undoubtedly make it an ideal candidate in organic synthesis,[16] especially in the field of asymmetric catalysis.[17]

Results and Discussion

Currently, phase-transfer catalysis has been recognized as an effective and sustainable method for organic synthesis. The enantioselective phase-transfer reactions have been developed rapidly, and the research area has become attractive in the pursuit of green and sustainable chemistry.[18] Based on our previous research, an efficient and enantioselective phase-transfer catalyzed photo-oxygenation of β-keto esters has been developed under mild conditions, but the enantioselectivity is moderate and the substrate scope is limited to the β-keto esters derived from indanone[6]. Here, we have developed a series of new phase-transfer catalysts (PTC's) derived from cinchona alkaloids and attempted the reaction of 1-indanone-derived β-keto ester **1a** (0.1 mmol) in toluene, treated with a PTC (10 mol%, 0.01 mmol), tetraphenylporphine (TPP, 1 mol%, 0.001 mmol), and K_2HPO_4 (50% aq.) in air for enantioselective α-hydroxylation. First, the use of the simplest PTC **3a** provided **2a** with 38% ee after two hours (Table 1, entry 1). Next, we prepared a series of phase-transfer catalysts via modification of the C-9 and C-6′ group. PTC **3b** with a methoxyl group at C-6′ position led to lower

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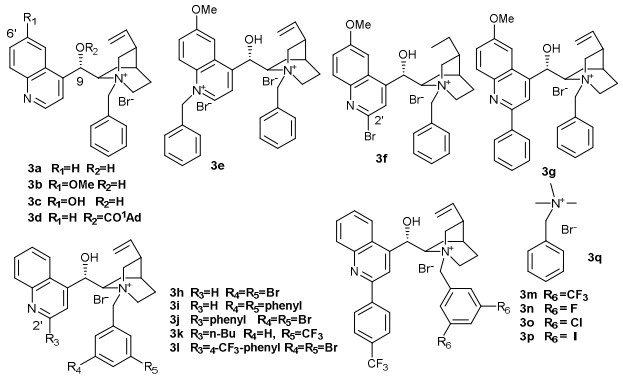
enantioselectivity and conversion (Table 1, entry 2). To our disappointment, PTC **3c**, which has two hydroxy groups at C-9 and C-6' positions, showed poor results (Table 1, entry 3). PTC **3d** was then introduced with a bulky 1-adamantyl group at C-9 position, but the ee value was slightly lower than that of **3a**, which supported the assumption that the free hydroxy group at the C-9 position was responsible for inducing high enantioselctivity in the reaction process (Table 1, entry 4).

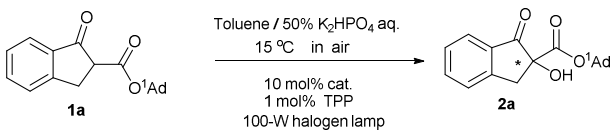
Recently, doubly quaternized cinchona-alkaloid based phase-transfer catalysts were developed.[18] We obtained the PTC **3e** using the method mentioned above. Although the reaction time was shortened, the enantioselectivity of **2a** was poor (Table 1, entry 5). We were therefore interested in the structural modification at C-2' position,[19] and **3f** and **3g** were synthesized. They had been modified with a bromo atom and phenyl at C-2' position, respectively. We were pleased to see that their respective values of enantiomeric excess were increased to 43% and 51% (Table 1, entries 6,7). These results revealed that the stereocontrol was sensitive to structural modifications at the C-2' position of the quinoline ring. Next, **3h** and **3i** were introduced. Interestingly, **3h** containing 3,5-bromo groups in the benzyl position, worked well and gave enantioselectivity of 68% ee. Nevertheless, **3i** containing

Scheme 1. Cinchona alkaloid derivatives employed for the α-hydroxylation reaction.



3,5-phenyl groups gave **2a** in only 32% ee (Table 1, entries 8, 9). These examples indicated that the enantioselective control in the benzyl position was possibly due to the electronic tuning. Addition of large steric hindrance groups, such as phenyl in the benzyl position, seems to have little influence on the enantioselectivity. We next examined catalyst **3j**, which was designed to have not only a phenyl group at C-2' position but also 3,5-bromo groups in the benzyl position. Gratifyingly, **3j** afforded **2a** with 85% ee and almost quantitative conversion in 30 min (Table 1, entry 10).

Table 1. Screening of cinchona alkaloid derivatives for α-hydroxylation of β-keto ester.[a]



Entry	Cat.	t [h]	Con [%][b]	*ee* [%][c]
1	**3a**	2	90	38
2	**3b**	3	80	31
3	**3c**	6	40	20
4	**3d**	2	>95	35
5	**3e**	1	>95	21
6	**3f**	1	>95	43
7	**3g**	1	>99	51
8	**3h**	1	>95	68
9	**3i**	2	81	32
10	**3j**	0.5	>99	85
11	**3k**	1	>99	58
12	**3l**	0.3	>99	86
13	**3m**	0.5	95	78
14	**3n**	0.5	>99	80
15	**3o**	0.5	>99	84
16	**3p**	0.5	>99	80
17	**3q**	4	Trace	-

[a] Unless otherwise specified, β-keto ester **1a** (31.0 mg, 0.1 mmol), catalyst (0.01 mmol, 10 mol%), and TPP (0.6 mg, 0.001 mmol) were added to a test tube equipped with a stirring bar and dissolved in toluene (10 mL). Then, 50% K_2HPO_4 (4 mL) was added. The mixture was stirred in air with exposure to a 100-W halogen lamp at 15 °C until the reaction was completed. [b] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Kromasil, SiO2, 5 m). [c] Determined by HPLC analysis (Chiralcel AD-H) with hexane/2-propanol (80:20) as the eluent.

An n-Bu group at C-2' position was also introduced: **3k** provided **2a** with only 58% ee (Table 1, entry 11). Importantly, **3l** which has a 4-CF_3-C_6H_4 group, afforded even higher activity and enantioselectivity (>99% conversion, 86% ee) (Table 1, entry 12). We next focused on the substituent group in the benzyl position. Unfortunately, 3,5-trifluoromethyl, 3,5-fluoro, 3,5-chloro, and 3,5-iodo groups in the benzyl position showed slightly lower ee values compared with the 3,5-bromo groups (Table 1, entries 13-16). Only a trace of **2a** was formed using benzyltrimethylammonium bromide (BTMAB) (**3q**) as the quaternary ammonium salt (Table 1, entry 17), which confirmed that the structural characteristics of the phase-transfer catalysts were responsible for both the catalytic activity and the enantioselectivity observed for the α-hydroxylation.

After a suitable catalyst **3l** had been identified, further reaction optimization was undertaken. Table 2 summarizes the effect of several parameters on this reaction. First, we found that the enantioselectivity of the reaction could be increased from 81% to 86% ee when the substrate concentration was reduced from 0.02 M to 0.01 M (Table 2, entries 1, 2). However, further reduction in the reactant concentration (0.01 M to 0.005 M) resulted in no significant improvement for the

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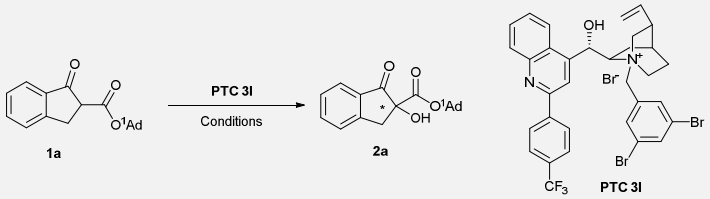
ee value (Table 2, entry 3). The effect of using different light sources was evaluated. Similar enantioselectivities with

Table 2. Optimization of the reaction conditions for α-hydroxylation of β-keto ester with catalyst **3I.**[a]



Entry	Sub (mmol)	Light source	Solvent	PTC 3I (mol%)	base	Sensitizer	T [°C]	Reaction time	Con [%][b]	ee [%][c]
1	0.1	100-W halogen lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	20 min	97[d]	86
2	0.2	100-W halogen lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	15 min	98[d]	81
3	0.05	100-W halogen lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	40 min	93[d]	85
4	0.1	7-W LED blue lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	40 min	>99	83
5	0.1	3-W LED blue lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	30 min	>99	83
6	0.1	3-W LED red lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	10 min	>99	85
7	0.1	3-W LED yellow lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	10 min	>99	86
8	0.1	3-W LED purple lamp	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	30 min	>99	77
9	0.1	Sunlight	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	10 min	>99	86
10	0.1	Darkness	PhMe	5	50%K_2HPO_4	TPP (1 mol%)	15	360 min	Trace	Nd
11	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	50%K_2HPO_4	TPP (1 mol%)	15	10 min	>99	89
12	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	50%K_2HPO_4	Rose bengal (1 mol%)	15	20 min	>99	87
13	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	50%K_2HPO_4	$[Ru(bpy)_3]Cl_2$ (1 mol%)	15	60 min	Trace	Nd
14	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	50%K_2HPO_4	I_2 (1 mol%)	15	360 min	15	41
15	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	50%K_2HPO_4	TPP (0.05 mol%)	15	30 min	>99	90
16	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	25%K_2HPO_4	TPP (0.05 mol%)	15	60 min	>99	89
17	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	5	30%K_2CO_3	TPP (0.05 mol%)	15	10 min	>99	84
18[e]	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	2.5	50%K_2HPO_4	TPP (0.05 mol%)	15	30 min (15 min)[e]	>99 (>99)[e]	90 (87)[e]
19	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	0.5	50%K_2HPO_4	TPP (0.05 mol%)	15	360 min	80	85
20	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	2.5	50%K_2HPO_4	TPP (0.05 mol%)	0	60 min	>99	88
21	0.1	3-W LED yellow lamp	PhMe/$CHCl_3$ =8:2	2.5	50%K_2HPO_4	TPP (0.05 mol%)	35	30 min	>99	89

[a] Unless otherwise specified, the reaction was performed with 0.1 mmol **1a** by using the same conditions described in Table 1. [b] Determined by HPLC analysis with hexane/2-propanol (80:20) as the eluent (Kromasil, SiO_2). [c] Determined by HPLC analysis (Chiralcel AD-H) with hexane/2-propanol (80:20) as the eluent. [d] Isolated yield [e]Using pure oxygen gas as the oxidant.

complete conversion in a short time (40 min) were obtained when a 7-W LED blue lamp was used (Table 2, entry 4). **We think the reaction activity was possibly due to the wavelength of the light rather than the wattage**. Next, we tested 3-W LED lamps of different wavelength, such as blue, red, yellow and purple. To our delight, the yellow lamp and red lamp showed high activity for the α-hydroxylation, and the reaction was completed in only 10 minutes without evident loss of enantioselectivity (Table 2, entries 6, 7). However, the purple and blue lamps showed obviously poor results (Table 2, entries 5, 8). It is worth mentioning that the reaction also proceeded well in the sunlight and gave the corresponding product **2a** in almost quantitative yield (without any impurities by HPLC) with 86% ee after approximately 10 min (Table 2, entry 9).

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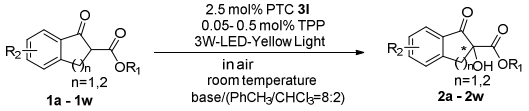
Conversely，nearly no reaction happened in the darkness (Table 2, entry 10). The ee value was improved to 89% when we used PhMe/$CHCl_3$ =8:2 as the component solvent (Table 2, entry 11). Other sensitizers such as Rose Bengal, $[Ru(bpy)_3]Cl_2$ and I_2 were also tested. It was found that rose bengal showed considerable reactivity, whereas $[Ru(bpy)_3]Cl_2$ and I_2 showed poor results. The reason for the significant differences in reactivity among these sensitizers may have been that the two different photo-oxygenation reaction mechanisms. In this reaction system, singlet oxygen ($^1O_2$), activated by energy-transfer sensitization, is more suitable than electron-transfer (ET) sensitization. Thus, TPP (tetraphenylporphine) was selected as the best sensitizer for this reaction (Table 2, entries 12-14). Further study showed that the sensitizer (TPP) loading could be decreased to as low as 0.05 mol%, while maintaining a comparable reaction conversion and achieving a higher ee value (90%) (Table 2, entry 15). We also tested other bases. The use of 25% K_2HPO_4 led to a slightly long reaction time compared with 50% K_2HPO_4. The 30% K_2CO_3 was also tested and led to lower ee, although the reaction time was shortened (Table 2, entries 16, 17). The use of pure oxygen will obviously lead to a faster reaction rate. Under the standard conditions, **1a** was nicely converted into **2a** in 15 minutes, but the ee value was decreased to 87% accordingly (Table 2, entry 18). Considering economy, practicability and enantioselectivity, we still choose air as the most suitable oxidant. As a testament to the remarkable reactivity of this new class of catalysts, the loading of catalyst **3l** in this α-hydroxylation was reduced to as low as 0.5 mol% while still achieving 80% conversion in 6 h at 15 °C, with no apparent decrease in enantioselectivity (85% ee) (Table 2, entry 19). Finally we investigate the effect of temperature on reaction. Whether at 0 °C or 35 °C, the enantioselectivity of **2a** was maintained (Table 2, entries 20, 21).

Table 3. Substrate scope in the asymmetric α-hydroxylation of β-keto esters.[a]



Entry	Sub	n	R_1	R_2	t [h]	Yield (%)[b]	ee (%)[c]
1	1a	1	^{1}Ad	H	0.5	98	90
2	1b	1	^{1}Ad	5-Cl	0.5	97	87
3	1c	1	^{1}Ad	5-Br	0.5	96	83
4	1d	1	^{1}Ad	4-Br	0.5	88	89
5	1e	1	^{1}Ad	6-Br	0.5	92	85
6	1f	1	^{1}Ad	6-F	0.5	89	85
7	1g	1	^{1}Ad	6-Me	0.5	97	82
8	1h	1	^{1}Ad	4-OMe	1	93	84
9	1i	1	^{1}Ad	6-OMe	0.5	98	85
10	1j	1	^{1}Ad	5,6-di-OMe	1	97	88
11	1k	1	^{2}Ad	H	0.5	97	81
12	1l	1	tert-amyl	H	0.5	96	78
13	1m	1	3-ethyl amyl	H	0.5	99	70
14	1n	1	3-ethyl amyl	5-Cl	0.5	97	69
15	1o	1	t-Bu	H	0.5	97	76
16	1p	1	t-Bu	5,6-di-OMe	1	92	72
17	1q	1	i-Pr	H	0.5	96	65
18	1r	1	Me	H	0.5	98	62
19	1s	2	^{1}Ad	H	6	85	67
					(1)[d]	(92)[d]	(74)[d]
20[d]	1t	2	^{1}Ad	7-Br	1	89	68
21[d]	1u	2	^{1}Ad	5,7-di-Br	1	70	71
22[d]	1v	2	^{1}Ad	7-OMe	1	93	80
23[d]	1w	2	^{1}Ad	6-OMe	1	87	74

[a] The reaction was conducted with substrate (0.1 mmol) in the presence of PTC **3l** (2.5 mol%) and TPP (0.05 mol%) in a mixture containing $PhCH_3/CHCl_3$=8:2 (10 mL) and K_2HPO_4 (4 mL, 50% aq.) at room temperature, with exposure to a 3-W LED yellow lamp for the given reaction period. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis of the product using a chiral column (DAICEL Chiralcel OD-H, AD-H, or AS-H) with n-hexane/2-propanol as the eluent (see the supporting information for details). [d] Using K_2CO_3 (4 mL, 30% aq.) as an inorganic base, TPP: 0.5 mol% .

With the optimized conditions in hand, we explored the substrate scope of the α-hydroxylation reaction shown in Table 3. A series of 1-indanone-derived adamantly β-keto esters were first investigated. Esters with a variety of substituents on the aromatic rings, such as methyl, methoxy, chloro, and bromo groups, were nicely converted into the corresponding products **2a** - **2j** in good yields (88–98%) with 82–90% ee (Table 3, entries 1-10). Then, we investigated the effect of the ester group on the 1-indanone derivatives. We observed that the enantioselectivities were influenced by the size of substitution in the ester group. For example, **1o**, which contains a bulky tert-butyl ester group, provided the α-hydroxylation product with 76% ee (Table 3, entry 15), whereas the β-indanone methyl ester **1r** afforded the corresponding product with 62% ee (Table 3, entry 18). Next, we explored the α-hydroxylation of 1-tetralone-derived adamantly β-keto ester **1s.** The reaction with 50% K_2HPO_4 led to a long reaction time (6 hours), producing **2s** in 85% yield with 67% ee. We then used a stronger inorganic base: 30% K_2CO_3 instead of 50%K_2HPO_4. We can clearly see that the reaction time was shortened to 1 hour and that the ee value was improved to 74%. In consideration of the enantioselectivity and the reactivity, we chose 30% K_2CO_3 as the inorganic base (Table 3, entry 19). Different substituents such as methoxy and bromo groups were investigated.

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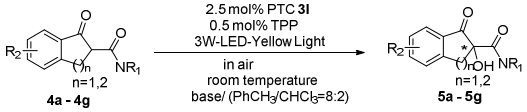
Under mild conditions, **2t–2w** were all easily obtained with up to 80% ee (Table 3, entries 20-23).

Table 4. Substrate scope in the asymmetric α-hydroxylation of β-keto amides.[a]



Entry	Sub	n	NR_1	R_2	t [h]	Yield (%)[b]	ee (%)[c]
1	4a	1		H	0.5	92	39
2	4b	1		H	0.5	99	5
3	4c	1		5-Br	0.5	94	52
4[d]	4d	1		H	4	73	66
5[d]	4e	1		H	4	71	63
6[d]	4f	2		H	1	84	25
7[e]	4g	2		H	4	Trace	Nd

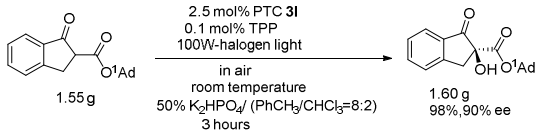
[a] The reaction was conducted with substrate (0.1 mmol) in the presence of PTC **3l** (2.5 mol%) and TPP (0.5 mol%) in a mixture containing $PhCH_3/CHCl_3$=8:2 (10 mL) and K_2HPO_4 (4 mL, 50% aq.) at room temperature, with exposure to a 3-W LED yellow lamp for the given reaction period. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis of the product using a chiral column (DAICEL Chiralcel OD-H or AD-H or AS-H) with n-hexane/2-propanol as the eluent (see the supporting information for details). [d] Using K_2CO_3 (4 mL, 30% aq.) as an inorganic base. [e] Using NaOH (30% aq.) as an inorganic base, TPP:1 mol%.

Compared with the β-keto esters, the α-hydroxylation of β-keto amides has been much less explored,[14h,15k,15o] even though the amido groups are useful for their easy manipulation[20]. Thus, after investigation of the β-keto esters, the scope of β-keto amides was examined. Under the standard conditions, we found that **4a** was nicely converted into **5a** in 92% yield with moderate enantioselectivity (Table 4, entry 1). Compounds **4b**, with H and isopropyl in N-position, afforded **5b** in near racemisation(Table 4, entry 2). **4c**, which bears a Br-atom at 5-position, afforded **5c** with 52% ee (Table 4, entry 3). Next we found the enantioselectivity of β-keto amides was related to the N-substituent group. **4d** with methyl and phenyl in N-position afforded **5d** with 66% ee, though with the reaction time extended to 4 hours (Table 4, entry 4). **5e** was obtained in 71% yield with 63% ee (Table 4, entry 5). The 1-tetralone-derived β-keto amide **4f** provided **5f** with 25% ee (Table 4, entry 6). Unfortunately, the β-keto amide **4g** showed low reaction activity even though 30% NaOH was used (Table 4, entry 7). Overall, this method showed good substrate suitability of β-keto esters and β-keto amides using an operationally simple and economical method.

The absolute configurations of α-hydroxy β-keto esters **2a**, **2o**, and **2r** were determined to be *S*, by comparison of their optical rotations with literature data.[15o,15l]

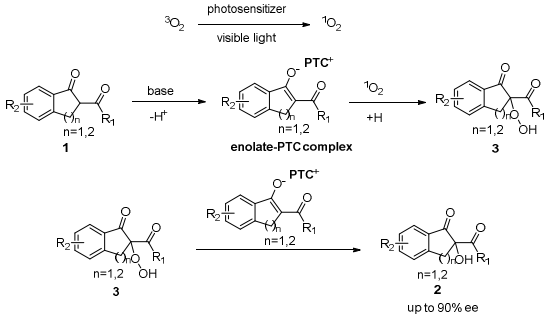
To test the scale-up potential of our methodology, a 1.55 g sample (50 mmol) of 1-adamantyl (1-Ad) indanone carboxylate **1a** was treated with PTC **3l** (2.5 mol%) and tetraphenylporphine (TPP, 0.1 mol%) on a gram-quantity scale in toluene (500 mL) and an aqueous solution containing 50% K_2HPO_4 (200 mL) under mild conditions. The reactor was exposed to a 100-W halogen lamp in air room temperature. After 3 hours, the reaction was completed and the α-hydroxylation product was obtained by chromatography in 98% yield and 90% ee (Scheme 2). It is worth mentioning that the catalyst **3l** can be recovered by chromatography in 85% yield. The recovered catalyst was reused in the model reaction (Table 3, entry 1), giving almost identical yields and enantioselectivities.

Scheme 2. Scaled-up version of the reaction



Next, we proposed a plausible mechanism for this photo-organocatalytic α-hydroxylation of β-dicarbonyl compounds. The molecular oxygen in air was easily transferred from its non-excited triplet state ($^3O2$) to its more reactive singlet state ($^1O2$) by photosensitization with light. Then, deprotonation of **1** quickly occurred in the presence of base. The **enolate-PTC complex** could have formed and reacted with the active singlet molecular oxygen ($^1O2$), thereby resulting in the formation of α-hydroperoxide intermediate **3**. Bruice have indicated that the relative reaction rates of ROOHs correlate satisfactorily with the pKa values of the corresponding ROHs[21]. The α-hydroperoxide intermediate 3 which contains two electron-withdrawing carbonyl groups at the α-position seemed to be a stronger oxidant than traditional hydrogen peroxide. The very active hydroperoxide intermediate could be rapidly converted into the final α-hydroxylation product **2** in the second step.

Scheme 3. Plausible mechanism



A plausible transition state, depicted in Scheme 4, was proposed. Three different types of interactions could exist: 1) an ion-pair interaction between the substrate and the PTC; 2) hydrogen bonding between the C-9 hydroxy group and the ester group; and 3) two π-π stacking interactions between the PTC and the substrate. This activation model may explain the structure-function relationship between the PTC and the substrate, as mentioned above. For example, when PTC **3h** was used, the reaction was completed in 60 min and the ee value of 2a was 68% (Table 1, entry

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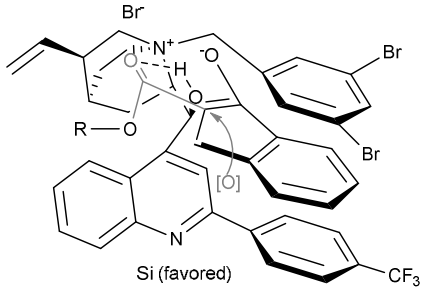
8). However, when PTC **3l** was introduced, the ee value of 2a was improved to 86% and the reaction time was shortened to 20 min (Table 1, entry 12). These results indicated that adding another π-π stacking interaction between the benzene ring of the substrate and the phenyl group in the C-2′ position was important for the higher activity and enantioselectivity of the α-hydroxylation.

Scheme 4. Plausible transition state



Conclusions

An efficient and enantioselective phase-transfer catalyzed photo-oxygenation of β-keto esters and β-keto amides was extended under mild conditions. A series of new C-2′-substituted phase transfer catalysts were identified and demonstrated to be effective catalysts for α-hydroxylation. A wide range of α-hydroxy β-keto esters and β-keto amides can be obtained with excellent yields and enantiopurity under mild conditions with relatively low catalyst and photosensitizer loadings. Further research of expanding the applications of C-2′-substituted phase transfer catalysts and other asymmetric photo-oxygenation reactions are currently underway.

Experimental Section

Preparation of PTC 3l

To a flame-dried flask equipped with a magnetic stirring bar and a reflux condenser was added **Cn-3'** (0.44 g, 1 mmol), THF (20 mL), and 1,3-dibromo-benzyl bromide (0.43 g, 1.3 mmol). The mixture was heated to reflux under N_2 for 12 hours until the reaction was judged to be complete by TLC analysis (CH_2Cl_2/MeOH=15:1). The mixture was then cooled to room temperature and poured into Et_2O (50 mL) under stirring. The resulting suspension was stirred for1 h, and the precipitated solids were isolated by filtration. The solids were recrystallized from MeOH/Et_2O to afford the product **3l** as a light yellow solid (0.68 g, 89% yield). m. p. 230-233 °C, $[\alpha]_D^{25}$ +113.0 (*c* 0.1, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, *J* = 8.1 Hz, 2H), 8.39 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.12 (dd, *J* = 15.1, 1.8 Hz, 3H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 3.8 Hz, 1H), 6.54 (t, *J* = 3.0 Hz, 1H), 6.21 – 6.05 (m, 1H), 5.34 – 5.22 (m, 2H), 5.14 (d, *J* = 12.3 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.24 (m, 1H), 4.04 – 3.84 (m, 2H), 3.55 (t, *J* = 11.4 Hz, 1H), 3.16 – 3.01 (m, 1H), 2.76 – 2.65 (m, 1H), 2.42 (t, *J* = 11.7 Hz, 1H), 1.99 – 1.70 (m, 3H), 1.16 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 154.11, 147.64, 146.61, 142.38, 137.22, 135.48, 135.07, 132.41, 130.15, 129.85, 129.60, 128.05, 127.69, 125.87, 125.84, 125.81, 125.31, 123.84, 123.79, 123.15, 122.78, 67.79, 65.08, 60.46, 55.97, 54.31, 37.03, 26.34, 23.06, 20.47. HRMS calcd. for $[C_{33}H_{30}F_3N_2OBr_3\text{-}Br]^+$ requires m/z 685.0677, found m/z 685.0655.

General procedure for α-hydroxylation of β-keto esters and β-keto amides

The reaction was conducted with substrate (0.1 mmol) in the presence of PTC **3 l** (2.5 mol%) and tetraphenylporphine (TPP) (0.05 mol% or 0.5 mol%) in a mixture containing $PhCH_3/CHCl_3$=8:2 (10 mL) and 50% K_2HPO_4 (4 mL) or 30% K_2CO_3 (4 mL) at room temperature, with exposure to a 3-W LED yellow lamp for the given reaction period. After the reaction was completed (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 vacuo. The residue was purified by flash chromatography to give the desired product. The ee of the product was determined by chiral HPLC.

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Notes and references

1 K. L. Skubi and T. P. Yoon, *Nature*, 2014, **515**, 45-46.
2 J. M. Narayanam and C. R. Stephenson, *Chemical Society Reviews*, 2011, **40**, 102-113.
3 R. Brimioulle, D. Lenhart, M. M. Maturi and T. Bach, *Angewandte Chemie International Edition*, 2015, **54**, 3872-3890.
4 E. Meggers, *Chemical Communications*, 2015, **51**, 3290-3301.
5 a) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem and J. Casas, *Journal of the American Chemical Society*, 2004, **126**, 8914-8915.; b) I. Ibrahem, G.-L. Zhao, H. Sundén and A. Córdova, *Tetrahedron letters*, 2006, **47**, 4659-4663; c) H. Sunden, M. Engqvist, J. Casas, I. Ibrahem and A. Córdova, *Angewandte Chemie*, 2004, **116**, 6694-6697
6 M. Lian, Z. Li, Y. Cai, Q. Meng and Z. Gao, *Chemistry–An Asian Journal*, 2012, **7**, 2019-2023.
7 J. Christoffers, A. Baro and T. Werner, *Advanced Synthesis & Catalysis*, 2004, **346**, 143-151.
8 M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson and A. S. Wagman, *Journal of the American Chemical Society*, 2000, **122**, 8453-8463.
9 M. Nakayama, Y. Fukuoka, H. Nozaki, A. Matsuo and S. Hayashi, *Chemistry Letters*, 1980, **9**, 1243-1246.
10 K. D. Wellington, R. C. Cambie, P. S. Rutledge and P. R. Bergquist, *Journal of natural products*, 2000, **63**, 79-85.
11 G. Olack and H. Morrison, *The Journal of Organic Chemistry*, 1991, **56**, 4969-4971.
12 McCann, S. F.; Annis, G. D.; Shapiro, R.; Piotrowski, D. W.; Lahm, G. P.; Long, J. K.; Lee, K. C.; Hughes, M. M.; Myers, B. J.; Griswold, S. M.; Reeves, B. M.; March, R. W.; Sharpe, P. L.; Lowder, P.; Barnette, W. E.; Wing, K. D. *Pest. Manages. Sci*. 2001, **57**, 153–164.
13 a) D. Boschelli, A. B. Smith, O. D. Stringer, R. H. Jenkins and F. A. Davis, *Tetrahedron Letters*, 1981, **22**, 4385-4388.; b) F. A. Davis and B. C. Chen, *Chemical reviews*, 1992, **92**, 919-934.
14 a) A. L. Casalnuovo, WO Patent WO/03/002255, **2003**;b) P. Y. Toullec, C. Bonaccorsi, A. Mezzetti and A. Togni, *Proceedings of the National Academy of Sciences of the United States of*

View Article Online
DOI: 10.1039/C6GC01245K

America, 2004, **101**, 5810-5814.; c) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *Journal of the American Chemical Society*, 2006, **128**, 16488-16489.; d) A. M. Smith, D. Billen and K. K. M. Hii, *Chemical Communications*, 2009, 3925-3927.; e) A. M. Smith, H. S. Rzepa, A. J. White, D. Billen and K. K. Hii, *The Journal of organic chemistry*, 2010, **75**, 3085-3096.; f) J. Li, G. Chen, Z. Wang, R. Zhang, X. Zhang and K. Ding, *Chemical Science*, 2011, **2**, 1141-1144.; g) J. J. Jiang, D. Wang, M. X. Zhao and M. Shi, *Tetrahedron: Asymmetry*. 2010, **21**, 794–799; h) C. Yin, W. Cao, L. Lin, X. Liu and X. Feng, *Advanced Synthesis & Catalysis*, 2013, **355**, 1924-1930.; i) X. Gu, Y. Zhang, Z.-J. Xu and C.-M. Che, *Chemical Communications*, 2014, **50**, 7870-7873.

15 a) M. R. Acocella, O. G. Mancheño, M. Bella and K. A. Jørgensen, *The Journal of organic chemistry*, 2004, **69**, 8165-8167.; b) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu and G. Zhong, *Journal of the American Chemical Society*, 2009, **131**, 4562-4563.; c) B. Gong, Q. Meng, T. Su, M. Lian, Q. Wang and Z. Gao, *Synlett*, 2009, 2659-2662.; d) Y. Cai, M. Lian, Z. Li and Q. Meng, *Tetrahedron*, 2012, **68**, 7973-7977; e) M. Lian, Z. Li, J. Du, Q. Meng and Z. Gao, *European Journal of Organic Chemistry*, 2010, **2010**, 6525-6530. f) H. Yao, M. Lian, Z. Li, Y. Wang and Q. Meng, *The Journal of organic chemistry*, 2012, **77**, 9601-9608.; g) M. Lian, Z. Li, Y. Cai, Q. Meng and Z. Gao, *Chemistry–An Asian Journal*, 2012, **7**, 2019-2023.; h) L. Zou, B. Wang, H. Mu, H. Zhang, Y. Song and J. Qu, *Organic letters*, 2013, **15**, 3106-3109.; i) M. Odagi, K. Furukori, T. Watanabe and K. Nagasawa, *Chemistry–A European Journal*, 2013, **19**, 16740-16745.; j) M. Odagi, K. Takayama, K. Furukori, T. Watanabe and K. Nagasawa, *Australian Journal of Chemistry*, 2014, **67**, 1017-1020.; k) C. De Fusco, S. Meninno, C. Tedesco and A. Lattanzi, *Organic & biomolecular chemistry*, 2013, **11**, 896-899.; l) Z. Li, M. Lian, F. Yang, Q. Meng and Z. Gao, *European Journal of Organic Chemistry*, 2014, **16**, 3491-3495.; m) Y. Wang, Z. Li, T. Xiong, J. Zhao and Q. Meng, *Synlett*, 2014, **25**, 2155-2160.; o) Y. Wang, H. Yin, H. Qing, J. Zhao, Y. Wu and Q. Meng, *Advanced Synthesis & Catalysis*, 2016, **358**, 737-745.

16 For some reviews on reactions using molecular oxygen as an oxidant, see: a) S. S. Stahl, *Science*, 2005, **309**, 1824-1826. b) S. S. Stahl, *Angewandte Chemie International Edition*, 2004, **43**, 3400-3420. c) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chemical reviews*, 2005, **105**, 2329-2364.d) J. Piera and J. E. Bäckvall, *Angewandte Chemie International Edition*, 2008, **47**, 3506-3523; e) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chemical Society Reviews*, 2012, **41**, 3381-3430.

17 There are some examples concerning the catalytic enantioselective hydroxylation using molecular oxygen, see: a) M. Masui, A. Ando and T. Shioiri, *Tetrahedron letters*, 1988, **29**, 2835-2838. b) E. F. de Vries, L. Ploeg, M. Colao, J. Brussee and A. van der Gen, *Tetrahedron: Asymmetry*, 1995, **6**, 1123-1132. c) D. Sano, K. Nagata and T. Itoh, *Organic letters*, 2008, **10**, 1593-1595.d)Y. Wang, T. Xiong and Q. Meng, *Tetrahedron*, 2015, **71**, 85-90.e) S.-B. D. Sim, M. Wang and Y. Zhao, *ACS Catalysis*, 2015, **5**, 3609-3612.

18 For recent reviews on asymmetric phase-transfer catalysis, see: a) K. Maruoka and T. Ooi, *Chemical reviews*, 2003, **103**, 3013-3028.b) M. J. O'Donnell, *Accounts of chemical research*, 2004, **37**, 506-517.c) B. Lygo and B. I. Andrews, *Accounts of chemical research*, 2004, **37**, 518-525.d) T. Ooi and K. Maruoka, *Angewandte Chemie International Edition*, 2007, **46**, 4222-4266.e) T. Hashimoto and K. Maruoka, *Chemical reviews*, 2007, **107**, 5656-5682.f) K. Maruoka, *Organic Process Research & Development*, 2008, **12**, 679-697.g) S.-s. Jew and H.-g. Park, *Chemical Communications*, 2009, 7090-7103.h) S. Shirakawa and K. Maruoka, *Angewandte Chemie International Edition*, 2013, **52**, 4312-4348.i) B. Xiang, K. M. Belyk, R. A. Reamer and N. Yasuda, *Angewandte Chemie International Edition*, 2014, **53**, 8375-8378.

19 As far as we known, there are few examples using C-2' modified cinchona-alkaloids as organocatalyst. For homogeneous catalysis,see :a) Y. Wu and L. Deng, *Journal of the American Chemical Society*, 2012, **134**, 14334-14337. b) J. Li, T. Du, G. Zhang and Y. Peng, *Chemical Communications*, 2013, **49**, 1330-1332. For phase-transfer catalysis. see: Ł. Woźniak, J. J. Murphy and P. Melchiorre, *Journal of the American Chemical Society*, 2015, **137**, 5678-5681.

20 C. Pan, X. Zeng, Y. Guan, X. Jiang, L. Li and H. Zhang, *Synlett*, 2011, **3**, 425-429.

21 T. C Bruice, J. B Noar, S. S Ball and U.V. Venkataram, U, *Journal of the American Chemical Society*, 1983, **105**, 2452-2463.

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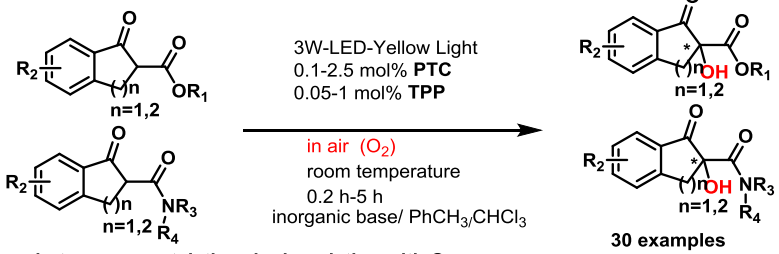

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- broad scope

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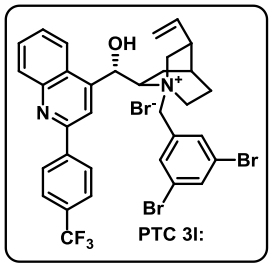
up to 99% yield
up to 90% ee



new series of C-2' phase transfer catalyst