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Asymmetric α-hydroxylation of β-dicarbonyl compounds by C-2′ modified cinchonine-derived phase-transfer catalysts in batch and flow microreactors

Xiao-Fei Tang[a,b], Jing-Nan Zhao[a], Yu-Feng Wu[a], Ze-Hao Zheng[a], Cun-Fei Ma[a], Zong-Yi Yu[a], Lei Yun[a], Guang-Zhi Liu[a], and Qing-Wei Meng[a]

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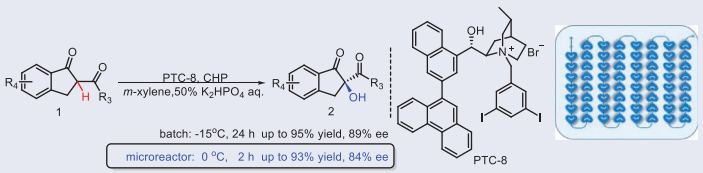
ABSTRACT

The asymmetric α-hydroxylation of β-dicarbonyl compounds was catalyzed by C-2′-modified cinchonine-derived phase-transfer catalysts. Excellent yields (up to 95%) and good enantioselectivities (up to 89% ee) were obtained. The reaction was carried out in a flow microreactor and similar results were obtained (up to 93% yield, 84% ee), the residence time was shortened from 24 h in batch to 2 h.

GRAPHICAL ABSTRACT



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KEYWORDS
Asymmetric; microreactor; oxidation

Introduction

In recent decades, microreactors have been widely applied in the synthesis of fine chemicals and pharmaceuticals.[1] Microreactors are considered to have advantages in improving safety, heat/mass transfer efficiency, and automation.[2] However, the reported reactions using microreactors are still mainly used for the synthesis of achiral compounds.[3,4] There are only a few examples of microreactors being used to achieve a homogeneous asymmetric reaction in only one fluid phase,[5,6] such as the Aldol reaction and Michael addition reaction.[7,8] Because of its mass transferability, microreactors have already been applied to the gas–liquid and liquid–liquid catalytic reactions.[9,10] Until 2004, de Bellefon's group reported the heterogeneous gas–liquid asymmetric hydrogenation catalyzed by the chiral rhodium-based catalysts in the microreactors.[11] Then, Newton and Ley reported the asymmetric hydrogenation catalyzed by the chiral iridium- and rhodium-based catalysts in a tube-in-tube gas–liquid flow reactor.[12]

α-Hydroxy-β-dicarbonyl compounds are important structural cores in various natural products and pharmaceuticals.[13] In particular, they have been used as the key

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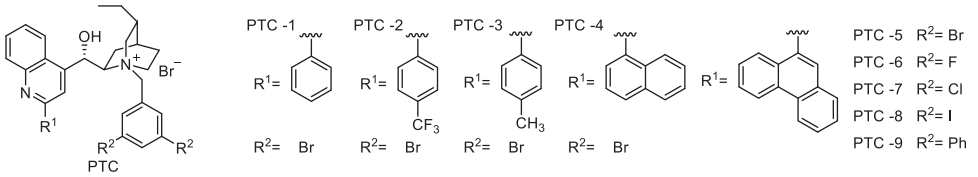


Scheme 1. The PTCs used for α-hydroxylation.

intermediate in the synthesis of the insecticide, indoxacarb. Although we have reported asymmetric photooxygenation of β-dicarbonyl compounds in the flow photomicroreactors,[14] the photomicroreacotors are very expensive. Therefore, we hope to use peroxide as an oxidant to achieve this asymmetric oxidation reaction in the flow microreactors.

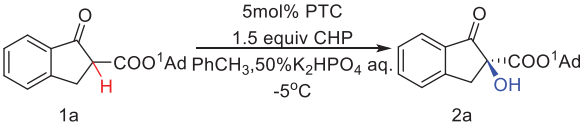
According to Deng's method,[15] we synthesized a series of C-2′-modified cinchonine-derived PTCs by the Suzuki–Miyaura coupling reaction. Furthermore, we hope to use these PTCs to achieve asymmetric α-hydroxylation of β-dicarbonyl compounds in a microreactor. This not only expands the application of C-2′-modified cinchonine-derived PTCs, but also realizes heterogeneous liquid-liquid asymmetric oxidation by flow microreactors.

Results and discussion

According to the previous work,[15,16] we synthesized a series of C-2′-modified cinchonine-derived PTCs as shown in Scheme 1, and the catalysts and reaction conditions were the screened further. Firstly, the reaction was carried out with C-2′-substituted phenyl catalyst **PTC-1**, product **2a** obtained in 93% yield and 81% ee (Table 1, entry 1). The electron-withdrawing substituted catalyst **PTC-2** gave the product **2a** with similar yield and enantioselectivity (Table 1, entry 2). However, with the electron-donating substituted catalyst **PTC-3**, **2a** was obtained in 84% yield with 73% ee (Table 1, entry 3). The 1-naphthalenyl-substituted catalyst **PTC-4** and 9-phenanthrenyl-substituted catalyst **PTC-5** afforded **2a** with good yields and enantioselectivities (89–95% yield, 79–82% ee, Table 1, entries 4-5). Catalyst **PTC-5** achieved a better enantioselectivity than the others. Then, a benzyl substituent PTCs were examined. It was found that 3,5-iodo groups in the benzylic position **PTC-8** resulted in a higher enantioselectivity than 3,5-fluoro, 3,5-chloro, 3,5-bromo and 3,5-phenyl groups (95% yield and 85% ee, Table 1, entries 5–9). The reaction conditions were investigated. The reaction performed in *m*-xylene provided the product **2a** in 96% yield with 86% ee (Table 1, entry 10). Performing the reaction at **–15**°C could improve the enantioselectivity (95% yield and 88% ee, Table 1, entry 11). Finally, the enantioselectivity could be further improved by decreasing the substrate concentration (Table 1, entry 12).

Having established the optimal reaction conditions, the scope of substrates were examined (Table 2). The nonsubstituted indanone 1-adamantyl ester **1a** was obtained with best result (95% yield, 89% ee, Table 2, **2a**). Substitutes of 1-indanone-derived 1-adamantly β-keto esters were investigated initially. The aromatic rings of indanone were substituted by electron-withdrawing groups (–F, –Cl, –Br), the desired products **2b-2d** were obtained in excellent yields (86–94%) and good enantioselectivities (83–85% ee). The electron-donating (–CH_3, –OCH_3) substrates provided the corresponding

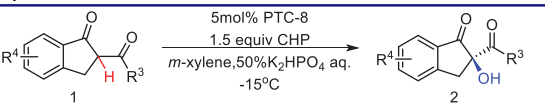
Table 1. Screening of PTCs of α-hydroxylation of β-keto ester 1a.[a]

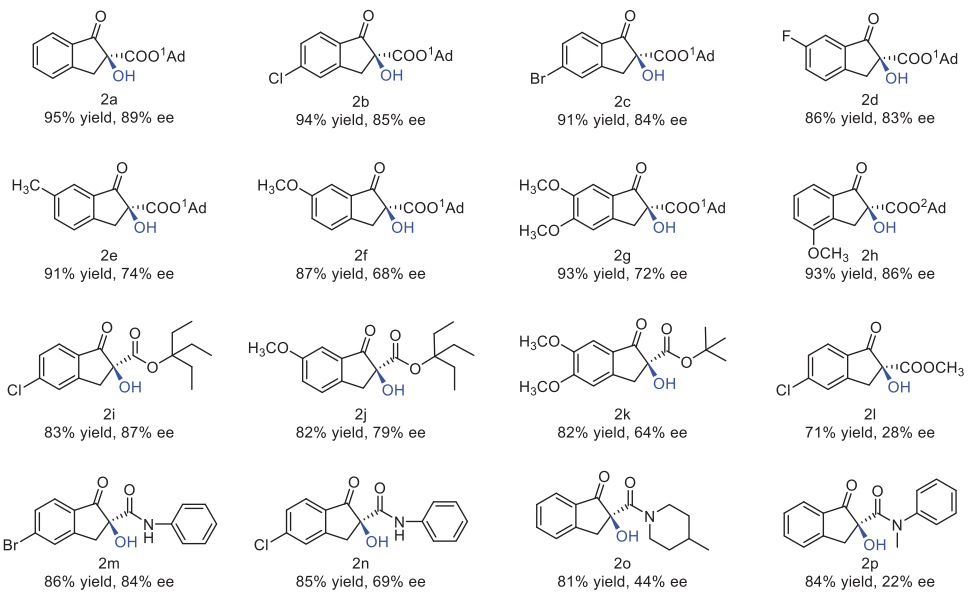


Entry	Cat.	Solvent	T/°C	Yield/%[b]	ee/%[c]
1	PTC-1	Toluene	–5	93	81
2	PTC-2	Toluene	–5	93	80
3	PTC-3	Toluene	–5	84	73
4	PTC-4	Toluene	–5	89	79
5	PTC-5	Toluene	–5	95	82
6	PTC-6	Toluene	–5	86	69
7	PTC-7	Toluene	–5	93	75
8	PTC-8	Toluene	–5	95	85
9	PTC-9	Toluene	–5	90	82
10	PTC-8	*m*-Xylene	–5	96	86
11	PTC-8	*m*-Xylene	–15	95	88
12[d]	PTC-8	*m*-Xylene	–15	95	89

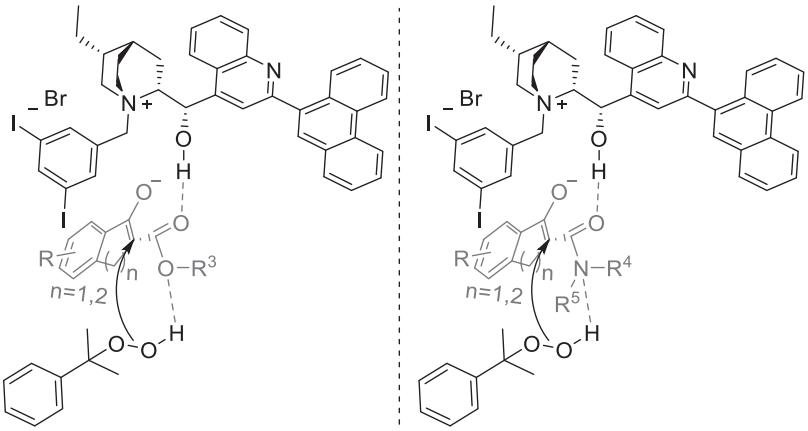
[a]Unless otherwise specified, the reaction was performed with β-keto ester 1a (31.0 mg, 0.1 mmol), 1.5 equiv. cumene hydroperoxide (CHP), 5 mol% catalyst, 4 mL $PhCH_3$, 2 mL 50% K_2HPO_4 at –5 °C.
[b]Isolated yields.
[c]Determined by HPLC analysis (Chiralcel AD-H) with hexane/2-propanol (80:20) as the eluent.
[d]8 mL *m*-xylene.

Table 2. Substrate scope[a].





[a]General Conditions: substrate 1 (0.1 mmol), 1.5 equiv CHP and 5 mol% PTC-8 in 8 mL *m*-xylene, and 2 mL 50% K_2HPO_4 at –15 °C for 24 h. All yields were isolated yields, and enantiomeric excess was determined by chiral HPLC.



Scheme 2. Plausible transition state.

products **2e–2g** in 87–93% yields with 68–74% ee. Next, the ester group on 1-indanone derivatives was investigated. The 2-adamantyl ester product **2h** was produced in excellent yield and good enantioselectivity (93% yield, 86% ee). The product **2i** was obtained in satisfactory yield and enantioselectivity (83% yield, 87% ee). The substrates **1j–1k** with electron-donating groups in 5- and 6-substituted of indanone gave the corresponding products **2j–2k** with good yields and moderate enantioselectivities (82% yield, 64–79% ee). The methyl ester product **2l** was obtained in 71% yield with 28% ee probably because of the steric hindrance. Finally, the scope of the β-keto amides was examined. The 5-position of indanone substituted by bromo and chloro groups could be successfully transformed into the desired products **2m** and **2n** with good yields (85–86%) and enantioselectivities (69–84% ee). Meanwhile, the product **2o** was obtained in 81% yield with 44% ee. Substrate **1p** with methyl and phenyl in the N-position transformed into the corresponding product **2p** in 84% yield and only 22% ee. The enantioselectivity of β-keto amide was decreased with the increased amount of substituents. Therefore, a plausible transition state was proposed in Scheme 2. The substrate formed an enolate anion under basic conditions. Then, three different types of interactions could exist: (1) an ion-pair interaction between the anion of the substrate and the cation of the PTC; (2) hydrogen bonding between the carbonyl group of the substrate and the C-9 hydroxy group of the PTCs; (3) hydrogen bonding between the H (–OOH) of CHP and the O (ester group) or N (amide group) of the substrate. With the increase of the substituents of β-keto amide, the hydrogen bond stability between the CHP and substrates decreases, which leads to the enantioselectivity of the products decreasing.

Next, we attempted to transfer this reaction in flow micoreactors as shown in Figure 1 (Corning Advanced Flow Reactor). Due to the limitations of the microreactor material (glass reactor), reaction conditions were not exactly the same as in batch. The organic phase was prepared by dissolving substrates **1a** (0.1 mmol), **PTC-8** (5 mol%) and CHP (1.5 equiv) in *m*-xylene (8 mL). The aqueous phase was a K_2HPO_4 solution (10% K_2HPO_4). The organic phase and aqueous phase were introduced through pump 1 and pump 2 at a flow rate of 1.5 mL/min. The product **2a** was obtained in 93% yield with 78% ee at 0 °C (Table 3, entry 1). At the same time, the residence time was drastically shortened from 24 h in the batch to 2 h in the flow microreactors. Using toluene as

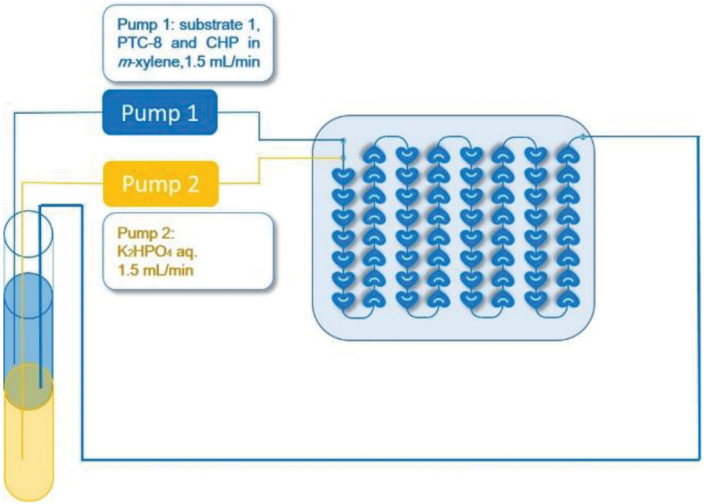
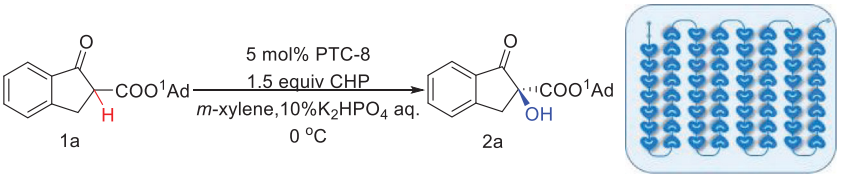


Figure 1. Schematic representation of microreactor for asymmetric oxidation of β-dicarbonyl compounds.

Table 3. Optimization of the reaction conditions for α-hydroxylation of β-keto ester **1a** in the flow microreactors.[a]

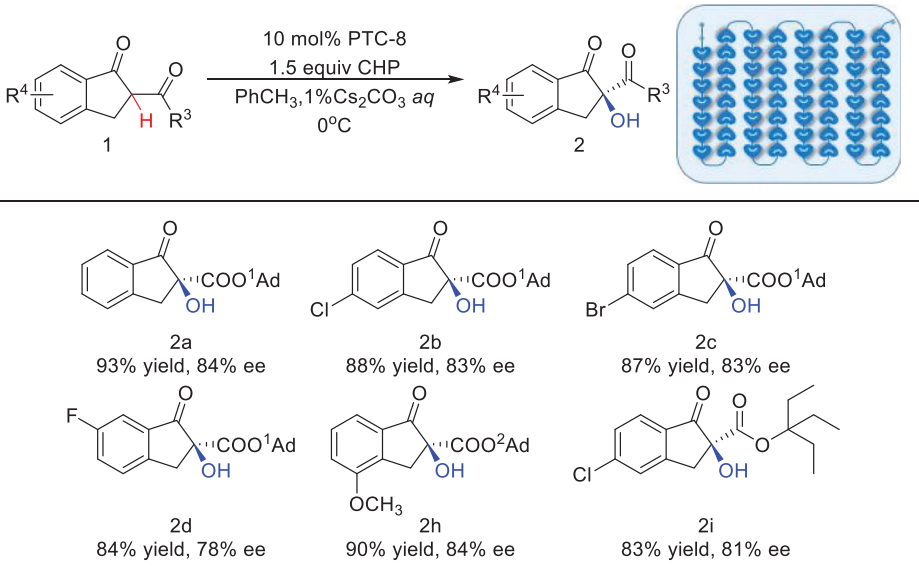


Entry	Base	Solvent	T/°C	Yield/%[b]	ee/%[c]
1	10% K_2HPO_4	*m*-Xylene	0	92	78
2	10% K_2HPO_4	Toluene	0	93	80
3	1% K_2HPO_4	Toluene	0	87	80
4	1% Cs_2CO_3	Toluene	0	91	82
5	1% Cs_2CO_3	Toluene	10	93	81
6	1% Cs_2CO_3	Toluene	20	94	81
7[d]	1% Cs_2CO_3	Toluene	0	93	84
8[e]	3.3% Cs_2CO_3	Toluene	0	95	83
9[e,f]	3.3% Cs_2CO_3	Toluene	0	24	83

[a]pump 1: substrate 1a (0.1 mmol), 5 mol% PTC-8 and 1.5 equiv CHP in 8 mL *m*-xylene, 1.5 mL/min; pump 2: 10% K_2HPO_4 aq.1.5 mL/min.
[b]Isolated yields.
[c]Determined by HPLC analysis (Chiralcel AD-H) with hexane/2-propanol (80:20) as the eluent.
[d]10 mol% PTC-8.
[e]β-Keto ester 1a (31.0 mg, 0.1 mmol), 10 mol% PTC-8 and 1.5 equiv. CHP in 4 mL $PhCH_3$, 2 equiv. Cs_2CO_3 in 2 mL H_2O ($\approx$3.3% Cs_2CO_3) at 0 °C in batch.
[f]Reaction time 2 h.

solvent in microreactors, the enantioselectivity was increased to 80% ee (Table 3, entry 2). Then, the basic solution, reaction temperature and catalyst loading were screened (Table 3, entries 3–7). The product **2a** was obtained from higher enantioselectivity with 1% Cs_2CO_3 aqueous solution (Table 3, entries 3–4). By performing the reaction at 10 or 20 °C, the stereoselectivity was decreases slightly (Table 3, entries 5–6). By increasing

Table 4. Substrate scope in the flow microreactors.[a]



[a]pump1: substrate 1 (0.1 mmol), 10 mol% PTC-8 and 1.5 equiv CHP in 8 mL $PhCH_3$, 1.5 mL/min; pump2: 1% Cs_2CO_3 aq. 1.5 mL/min. All yields were isolated yields, and enantiomeric excess was determined by chiral HPLC.

the **PTC-8** loading to 10 mol%, product **2a** was obtained in 93% yield with 84% ee (Table 3, entry 7). Comparing entry 7 and entry 8 in Table 3, the product **2a** was obtained with 93% yield and 84% ee in the microreactors, and 95% yield and 83% ee in batch. From here, the enantioselectivity was increased and the reaction time was shorted from 24 h to 2 h in the microreactors. When the reaction time was 2 h, the product **2a** was obtained in only 24% yield and 83% ee in batch (Table 3, entry 9). Hence, the optimum conditions for the asymmetric oxidation of β-dicarbonyl compounds were identified as follows: 0.1 mmol substrate 2, 10 mol% **PTC-8** and 1.5 equiv CHP in 8 mL toluene, and 1% Cs_2CO_3 aqueous solution at 0 °C, and the flow rates of organic phase and aqueous phase were 1.5 mL/min. After that, the substrate scope was investigated (Table 4). For substrates **1b–1d**, **1h** and **1i** were transformed into the corresponding products (**2b–2d**, **2h** and **2i**) in excellent yields (83–93%) and good enantioselectivities (78–84% ee). Meanwhile, the reaction residence time was greatly shortened from 24 h in batch to 2 h in the flow microreactor.

Conclusion

The asymmetric oxidation of β-dicarbonyl compounds catalyzed by the C-2′-modified cinchonine-derived PTCs and the corresponding products were obtained in excellent yields and enantioselectivities. At the same time, the flow microreactors had been used to achieve a heterogeneous liquid–liquid asymmetric oxidation reaction. Good yields and enantioselectivities were obtained and the residence time could be greatly shortened

by flow microreactors. We will further expand the application of C-2′-cinchonine-derived PTCs and flow microreactors to other asymmetric reactions.

Experimental part

Analytical TLC was visualized with UV light at 254 nm. Thin-layer chromatography was carried out on TLC aluminum sheets with silica gel $60F_{254}$. Purification of reaction products was carried out with chromatography on silica gel 60 (200–300 mesh). Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at 20 °C (10 cm cell, c given in g/100 mL). ^{1}H NMR (400 MHz MHz) spectra was obtained at 25 °C; ^{13}C NMR (101 MHz) were recorded on a VARIAN INOVA-400M and AVANCE II 400 spectrometer at 25 °C. Chemical shifts are reported as δ (ppm) values relative to TMS as internal standard and coupling constants (J) in Hz. High-resolution mass spectrometry data were obtained with UPLC/Q-Tof Mass Spectrometer and were determined by electrospray ionization (ESI). The enantiomeric excess (ee) 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 with an injection volume of 20 μL at a flow rate of 1 mL/min.

General procedure for the asymmetric α-hydroxylation of β-dicarbonyl compounds

Substrate 1 (0.1 mmol), PTC-8 (5 mol %), CHP (1.5 equiv) and 50% K_2HPO_4 aq. (2 mL) were added to a test tube equipped with a stirring bar and dissolved in *m*-xylene (8 mL) at −15 °C. After completion of the reaction (confirmed by TLC), the mixture was diluted with EtOAc (50 mL), washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, 5/1) to afford the product **2a–2p**. The ee of the product was determined by chiral HPLC.

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