A novel thermoregulated phase-transfer catalysis system for chiral nano-Pt-catalyzed asymmetric hydrogenation

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Abstract
The chiral ionic liquid CILTPT-MS \([\text{CH}_3(\text{OCH}_2\text{CH}_2)_{16}\text{CD}]^+ [\text{CH}_3\text{SO}_3]^-\) (CD = cinchonidine) is found to exhibit cloud point character. Due to this cloud point character, a CILTPT-MS-stabilized chiral nano-Pt catalyst is prepared and utilized to realize transfer in a H\(_2\)O–1-pentanol biphasic system by simply changing the temperature. Therefore, a fluorine-free, thermoregulated phase-transfer catalysis system is developed and applied to the asymmetric hydrogenation of \(\alpha\)-ketoesters with enantiomeric excess of \(>99\%\) and excellent conversion. In addition, the chiral nano-Pt catalyst can be easily separated and reused efficiently.

Keywords
\(\alpha\)-ketoesters, asymmetric hydrogenation, chiral nano-Pt catalyst, fluorine-free, thermoregulated phase-transfer catalysis system

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Introduction
The technology behind obtaining optically pure chiral molecules plays an increasingly important role in pharmaceutical research.\(^1\)–\(^3\) Although many highly efficient homogeneous chiral catalysts have been reported to synthesize chiral molecules,\(^4\)–\(^6\) the simple separation and recycling of chiral catalysts remains a big problem.\(^7\)–\(^8\) Fortunately, heterogeneous chiral catalysis can overcome the abovementioned problems, but for many heterogeneous chiral catalysts, the enantioselectivity problem limits their practical applications.\(^9\) Therefore, it is worthwhile to develop new catalytic systems that not only achieve the separation and recycling of chiral catalysts, but can also lead to high enantioselectivities.

In the past decade, the phase transfer of a catalyst in an aqueous–organic biphasic system has been extensively studied as a way to realize the separation and recycling of catalysts.\(^10\)–\(^13\) Among these studies, ionic liquids (ILs), as effective phase-transfer vehicles, have received significant attention.\(^11\)–\(^14\) In our previous study, a thermoregulated phase-transfer catalysis system was developed based on the cloud point (Cp) of the chiral ionic liquid CIL\(_{\text{TPPT}}\) \([\text{CH}_3(\text{OCH}_2\text{CH}_2)_{16}\text{CD}]^+ [\text{PF}_6]^-\) (CD = cinchonidine).\(^15\) The CIL\(_{\text{TPPT}}\)-stabilized chiral Pt nanocatalyst could realize transfer in a H\(_2\)O–1-pentanol biphasic system. Hence, the chiral Pt nanocatalyst can be easily separated and recycled. However, up to now, almost all the ILs involved in phase transfer of a catalyst are limited to using fluorine-containing anions,\(^10\)–\(^13\) which are expensive and environmentally unfriendly. This of course pertains to our previously reported thermoregulated phase-transfer catalysis system.\(^15\) Therefore, developing new thermoregulated phase-transfer catalysis systems without fluorine-containing anions is important.

In this paper, CIL\(_{\text{TPPT-MS}}\) \([\text{CH}_3(\text{OCH}_2\text{CH}_2)_{16}\text{CD}]^+ [\text{CH}_3\text{SO}_3]^-\) (CD = cinchonidine) was investigated and found to exhibit Cp character. As a result of the Cp character, a chiral nano-Pt catalyst stabilized by CIL\(_{\text{TPPT-MS}}\) was prepared, which can easily transfer between the H\(_2\)O–alcohol biphasic system by changing temperature. The first fluorine-free, thermoregulated phase-transfer catalysis system containing a CIL\(_{\text{TPPT-MS}}\)-stabilized chiral nano-Pt catalyst has been developed and applied to the asymmetric hydrogenation of \(\alpha\)-ketoesters.

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Our investigations started with the Cp detection of CIL TPT-MS. The experimental results indicated that the Cp was higher than 100 °C. Taking into consideration the literature reports that inorganic salts have obvious effects on decreasing the Cp, the effects of different inorganic salts on the Cp were investigated. As shown in Figure S1 (see the Online Supporting Information), a decrease in Cp was observed on increasing the inorganic salt concentration. This may be due to the decreasing number of hydrogen bonds between water and the polyether chains in CIL TPT-MS when inorganic salts are present. Among these inorganic salts, K3PO4·3H2O has the most dramatic effect on decreasing the Cp. The corresponding Cp was 51 °C when the K3PO4·3H2O concentration was 4.8 wt%. Besides, the influence of the CIL TPT-MS concentration on Cp was also detected (Figure 1). The corresponding Cp was 74 °C when the CIL TPT-MS concentration was 0.5 wt%. The results in Figure 1 indicate that the Cp evidently decreased on increasing the CIL TPT-MS concentration. Furthermore, the Cp decreased to 61 °C when the CIL TPT-MS concentration was increased to 3.0 wt%.

The thermoregulated phase-transfer of a chiral nano-Pt catalyst

Based on the Cp of CIL TPT-MS, the thermoregulated phase-transfer of CIL TPT-MS in a H2O–organic biphasic system was attempted in the presence of K3PO4·3H2O. The results clearly showed that the CIL TPT-MS possessed thermoregulated phase-transfer properties in a H2O–alcohol (such as 1-butanol, 1-pentanol, 1-hexanol, and cyclohexanol) biphasic system. Furthermore, the UV-Vis spectra also proved the phase-transfer phenomenon of the CIL TPT-MS in the H2O–1-pentanol biphasic system (Figure 2). However, the phase transfer did not occur when the organic phase was toluene or n-heptane.

After investigating the phase-transfer properties, the CIL TPT-MS was used as a stabilizer of a nano-Pt catalyst. The results indicated that the chiral nano-Pt catalyst stabilized by CIL TPT-MS dispersed very well and exhibited a mean diameter of 1.9 ± 0.4 nm (see Figure S2, A1-2 in the Online Supporting Information). Moreover, the catalytically active precursor for synthesizing optically active α-hydroxy esters.

The asymmetric hydrogenation of α-ketoesters catalyzed by the chiral nano-Pt catalyst

After the construction of this novel thermoregulated phase-transfer catalysis system, its catalytic efficiency was evaluated in the asymmetric hydrogenation of α-ketoesters. Such compounds have been studied extensively, serving as effective precursors for synthesizing optically active α-hydroxy esters.

In addition, with the purpose to test the stability of the chiral nano-Pt catalyst, continuous phase-transfer experiments in the H2O–1-pentanol biphasic system were attempted through heating and cooling. No sign of aggregation was visually noticed after five transfer cycles. Moreover, the transmission electron microscope (TEM) images of the freshly prepared chiral nano-Pt catalyst and that after five cycles showed that the particle size had only slightly increased from 1.9 to 2.2 nm (see Figure S2, B1-2 in the Online Supporting Information). These results confirmed that the CIL TPT-MS-stabilized chiral nano-Pt catalyst displayed good stability.

Figure 1. Effects of the CIL TPT-MS concentration on Cp (2.5 wt% K3PO4·3H2O).

Cp: cloud point.
On further increasing the temperature to 50 °C, the conversion of MBF remained unchanged; however, the ee began to decrease (Table 2, entries 2, 6, and 7). In addition, the H₂ pressure has a significant effect on the ee. The results indicated that when the H₂ pressure was higher than 2 MPa, the ee decreased significantly (Table 2, entries 2, 8, and 9). Therefore, the optimized reaction conditions for the asymmetric hydrogenation of MBF were established with >99% conversion and >99% ee (see Table 2, entry 2).

With optimized conditions in hand, the recyclability of the chiral nano-Pt catalyst was evaluated. After the reaction, the upper alcohol phase containing the products can be simply separated and the lower catalyst-containing aqueous phase was reused in the next cycle. As shown in Table 3, the chiral nano-Pt catalyst showed good recyclability without loss of ee after the catalyst had been used 3 times. Although the conversion decreased to 86% in the fourth cycle, prolonging the reaction time from 20 min to 30 min also achieve a conversion of >99% (Table 3, entry 4).

In the recycling experiments, the factors that may lead to a decrease in the conversion were further investigated. First, the size of the chiral nano-Pt catalyst was determined by TEM (Figure 4), and the results indicated that the diameter of the chiral nano-Pt catalyst had slightly increased from 2.6 ± 0.4 nm (freshly prepared) to 3.0 ± 0.4 nm after three cycles. In addition, the Pt leaching into the 1-pentanol phase was detected by inductively coupled plasma atomic emission spectroscopy (ICP-AES) at the end of the reaction. These results are presented in Table S2 (see the Online Supporting Information) and indicate that the Pt leaching gradually decreased in each cycle experiment. The average Pt leaching was 1.2 wt%. Therefore, we speculate that the increasing Pt nanoparticle size and the Pt leaching maybe the reasons for the decreased catalytic performance during the recycling experiments.

Moreover, with the purpose of obtaining further information on the nature of the chiral nano-Pt catalyst, mercury poisoning experiments were conducted, which are widely used to determine whether the catalyst was heterogeneous.
Asymmetric hydrogenation of MBF catalyzed by the CIL$_{TPT-MS}$-stabilized chiral nano-Pt catalyst.

| Entry | CIL$_{TPT-MS}$/Pt (mol/mol) | $P_{H_2}$ (MPa) | Temperature ($^\circ$C) | Conversion $^a$ (%) | ee$^a$ (%) |
|-------|----------------------------|----------------|------------------------|---------------------|-----------|
| 1     | 10                         | 2              | 40                     | >99                 | 80        |
| 2     | 12.5                       | 2              | 40                     | >99                 | >99       |
| 3     | 15                         | 2              | 40                     | >99                 | 82        |
| 4     | 20                         | 2              | 40                     | >99                 | 64        |
| 5     | 12.5                       | 2              | 30                     | >99                 | 78        |
| 6     | 12.5                       | 2              | 45                     | >99                 | 86        |
| 7     | 12.5                       | 2              | 50                     | >99                 | 72        |
| 8     | 12.5                       | 3              | 40                     | >99                 | 84        |
| 9     | 12.5                       | 5              | 40                     | >99                 | 76        |

MBF: methyl benzoylformate; ee: enantiomeric excess; GC: gas chromatography.

Reaction conditions: the as-prepared chiral nano-Pt catalyst (1.78 × 10$^{-3}$ mmol) and a certain amount of CIL$_{TPT-MS}$ were stirred in a mixture of H$_2$O (1.000 g), acetic acid (0.500 g), K$_3$PO$_4$·3H$_2$O (50.0 mg), and 1-pentanol (2.000 g) for 30 min at 40 °C, and then MBF (MBF/Pt = 150, molar ratio) was added. Time = 20 min.

$^a$Determined by chiral GC.

Conclusion

The CIL$_{TPT-MS}$ was found to exhibit Cp character. On the basis of the Cp, the first fluorne-free, thermoregulated phase-transfer catalysis system has been developed and explored for the asymmetric hydrogenation of $\alpha$-ketoesters. High ee values and conversions were obtained for the asymmetric hydrogenation of $\alpha$-ketoesters, and the chiral nano-Pt catalyst showed good recyclability. More importantly, it is expected that this fluorne-free, thermoregulated phase-transfer catalysis system will provide an approach for designing more environmentally friendly phase-transfer catalytic systems.

Experimental

Chemicals

The CIL$_{TPT-MS}$ was prepared as reported. MBF (99%), isoamyl pyruvate (97%), and ethyl 3-chlorobenzoyleformate (96%) were obtained from J&K Chemical (Shanghai, China). PtCl$_2$ (99.9%) was obtained from Alfa Aesar (Ward Hill, MA, USA). Ethyl 4-methyl-2-oxopentanoate was purchased from Ark Pharm (Chicago, USA). Pyruvic acid (Z)-3-hexenyl ester (95%) was purchased from TCI (Tokyo, Japan). Chemicals such as 1-pentanol, 1-hexanol, cyclohexane, cyclohexanol, 1-butanol, and acetic acid were purchased from Kermel (Tianjin, China). NaCl, KCl, Na$_2$SO$_4$, KBr, NaNO$_3$, and K$_2$PO$_4$·3H$_2$O were supplied from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). All these chemicals were analytical grade and were used without further purification.
In a typical experiment, PtCl₄ (0.60 mg, 1.78 × 10⁻³ mmol), the chiral ionic liquid CILTPT-MS (20.00 mg, 1.78 × 10⁻³ mmol), and H₂O (0.400 g) were added to a Teflon-lined standard stainless-steel autoclave (75 mL). The mixture was stirred at 70 °C for 7 h under hydrogen (4 MPa). The autoclave was allowed to cool and depressurized. The change of the color of the solution to black indicated the formation of the chiral nano-Pt catalyst.

**Catalytic applications**

The hydrogenation of MBF served as a standard model reaction. The reaction was performed in a Teflon-lined standard stainless-steel autoclave (75 mL). The chiral nano-Pt catalyst, CILTPT-MS, H₂O, K₃PO₄·3H₂O, 1-pentanol, cyclohexane (internal standard), and acetic acid were injected into the autoclave and the mixture stirred for 30 min. Next, MBF was added and the autoclave was flushed with H₂ three times and pressurized with H₂ up to the desired pressure. The reactor was held at the given temperature for the appropriate amount of time. After completion of the reaction, the reactor was depressurized and allowed to cool. The 1-pentanol phase was separated and

Table 4. Mercury poisoning experiments on the asymmetric hydrogenation of MBF catalyzed by the chiral nano-Pt catalyst.

| Entry | Hg/Pt (molar ratio) | Time of addition of Hg (min) | Time (min) | Conversion (%)a |
|-------|---------------------|-----------------------------|------------|----------------|
| 1     | –                   | –                           | 20         | >99            |
| 2     | 1000                | 0                           | 20         | 4              |
| 3     | –                   | –                           | 10         | 46             |
| 4     | 1000                | 10                          | 20         | 46             |

MBF: methyl benzoylformate; GC: gas chromatography.

**Preparation of the chiral nano-Pt catalyst stabilized by CILTPT-MS**

In a typical experiment, PtCl₄ (0.60 mg, 1.78 × 10⁻³ mmol), the chiral ionic liquid CILTPT-MS (20.00 mg, 1.78 × 10⁻³ mmol), and H₂O (0.400 g) were added to a Teflon-lined standard stainless-steel autoclave (75 mL). The mixture was stirred at 70 °C for 7 h under hydrogen (4 MPa). The autoclave was allowed to cool and depressurized. The change of the color of the solution to black indicated the formation of the chiral nano-Pt catalyst.

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| 3     | –                   | –                           | 10         | 46             |
| 4     | 1000                | 10                          | 20         | 46             |

MBF: methyl benzoylformate; GC: gas chromatography.

**Reaction conditions:** 1.78 × 10⁻³ mmol of Pt, CILTPT-MS/Pt = 12.5 (molar ratio), H₂O (1.000 g), K₃PO₄·3H₂O (50.0 mg), 1-pentanol (2.000 g), and acetic acid (0.500 g), Temp = 40 °C, P_H₂ = 2 MPa, MBF (MBF/Pt = 150:1, mol/mol).

aDetermined by chiral GC using cyclohexane as an internal standard.
analyzed by chiral gas chromatography (GC). The enantio-
meric excess is expressed as $ee\% = 100 \times \frac{|R - S|}{(R + S)}$.

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Table 5. Asymmetric hydrogenation of different $\alpha$-ketoesters.

| Entry | Substrate | Conversion (%)a | ee (%)a |
|-------|-----------|----------------|---------|
| 1b    |           | >99            | >99     |
| 2c    |           | >99            | >99     |
| 3d    |           | >99            | >99     |
| 4e    |           | >99            | >99     |

ee: enantiomeric excess; GC: gas chromatography.

Reaction conditions: $H_2$O (1.000 g), 1-pentanol (2.000 g), K$_3$PO$_4$·3H$_2$O (50.0 mg), and acetic acid (0.500 g), Temp = 40 °C, $P_{H_2}$ = 2 MPa.

The conversion and ee values were determined by chiral GC.

Chiral nano-Pt catalyst (1.78 $\times$ 10$^{-3}$ mmol), substrate/CILTPT -MS/Pt = 100:10:1, molar ratio, time = 30 min.

Chiral nano-Pt catalyst (1.78 $\times$ 10$^{-3}$ mmol), substrate/CILTPT -MS/Pt = 100:12:1, molar ratio, time = 40 min.

Chiral nano-Pt catalyst (3.56 $\times$ 10$^{-3}$ mmol), substrate/CILTPT -MS/Pt = 100:8:1, molar ratio, time = 120 min.

Chiral nano-Pt catalyst (1.78 $\times$ 10$^{-3}$ mmol), substrate/CILTPT -MS/Pt = 100:12:1, molar ratio, time = 60 min.