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Short communication

Highly efficient and recyclable chiral Pt nanoparticle catalyst for enantioselective hydrogenation of activated ketones

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ABSTRACT

Thermoregulated phase-separable chiral Pt nanoparticle catalyst exhibited excellent ee (> 99%) in the enantioselective hydrogenation of activated ketones for preparing chiral α-hydroxy acetals and chiral 1,2-diols. More importantly, the chiral catalyst could be easily separated by phase separation and directly reused in the next cycle without any loss in catalytic activity and enantioselectivity, even in the gram-scale reaction. The leaching of Pt was under the detection limit of the instrument.

1. Introduction

Chiral secondary alcohols are very important intermediates and auxiliaries in the asymmetric synthesis chemistry. For example, chiral α-hydroxy acetals not only can be converted to chiral 1,2-diols, chiral β-amino alcohols and chiral aldol derivatives [1–3], but also are necessary chiral building blocks for synthesis of lipoxine A [4], rhodinose [5], rocellaric acid [6], grayanotoxins [7] and amino sugars [8]. Meanwhile, chiral 1,2-diols are crucial components for synthesis of insect pheromones [9], δ-lactones [10], β-lactone esterase inhibitors [11], especially for anti-HIV pharmaceutical tenofovir [12] and many other biologically active substances [13]. Due to their great importance, much attention has been paid to exploring high-efficiency methods to obtain chiral α-hydroxy acetals [14–16] and chiral 1,2-diols [17–19]. Among them, the enantioselective hydrogenation of activated ketones is one of the most effective and atom economic methods for preparation of chiral α-hydroxy acetals and chiral 1,2-diols. In the past few decades, great progress with high enantioselectivity has been made in this reaction [20–26], however, studies about the recyclable chiral catalyst for enantioselective hydrogenation to obtain chiral α-hydroxy acetals and chiral 1,2-diols with excellent enantioselectivity has not been reported.

Based on our previous studies, the thermoregulated phase-separable chiral Pt nanoparticle catalyst was developed and successfully applied in asymmetric hydrogenation of a series of α-ketoesters with high catalytic activity, enantioselectivity, recyclability and general applicability [27]. The working principle can be simply described as follows: before reaction, the system consists of two phases, one is the upper organic phase and another is the chiral Pt nanoparticle catalyst phase. When the temperature rises above the critical solution temperature, the system turns into homogeneous phase in which the reaction runs efficiently. After reaction, with temperature decreasing the system becomes two-phase again. Therefore, the chiral Pt nanoparticle catalyst can be easily separated from products by simple phase separation and directly reused in the next cycle. Namely, the system is characterized by the homogeneous reaction coupled with biphase separation.

Encouraged by these results, we herein applied the thermoregulated phase-separable chiral Pt nanoparticle catalyst to enantioselective hydrogenation of various activated ketones for synthesizing chiral α-hydroxy acetals and chiral 1,2-diols with the aim to achieve excellent enantioselectivity and to realize the recyclability of the catalyst (Fig. 1).

2. Experimental

2.1. Materials and analyses

Unless otherwise noted, all chemicals were purchased from commercial sources without further purification. $PtCl_4$ (57.6% of Pt) was purchased from Japan. 1,1-Dimethoxyacetone **1a** (97%), cyclobutyl methyl ketone (97%) and 2-hexanone (98%) were from Alfa Aesar. 2,2-Diethoxyacetophenone 1h (96%) was purchased from Acros. Acetophenone (99%) was from Aladdin. 1-Hydroxybutan-2-one **1j** (98%), (1-hydroxycyclohexyl)(phenyl)methanone **1m** (98%) and 2-hydroxy-1-phenylethanone **1l** (97%) were from Ark. 3,3-Dimethoxybutan-2-one **1i** (97%), 3-hydroxy-2-butanone **1k** (97%) and 4-hydroxy-2-butanone (95%) were from Adamas. Pyruvic aldehyde (30 wt% in H_2O) was from Accela. 1,3-Propanediol (98%) and 4,4-dimethoxy-2-butanone (92%) were from Innochem. Ethyl alcohol, propanol, isopropanol, *n*-butanol, t-butyl alcohol, toluene, glacial acetic

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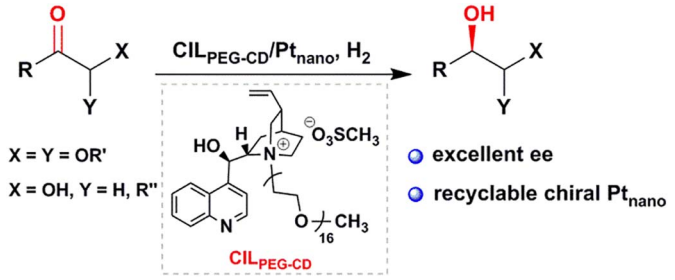


Fig. 1. Enantioselective hydrogenation of activated ketones catalyzed by the thermo-regulated phase-separable chiral Pt nanoparticles.

acid, *n*-heptane and cyclohexane were all analytical reagents and purchased from Kermel. 1-(1,3-Dioxan-2-yl)ethanone **1b**, 1,1-diethoxy-2-propanone **1c**, 1,1-dipropoxy-2-propanone **1d**, 1,1-dibutoxy-2-propanone **1e**, 1,1-diisopropoxy-2-propanone **1f** and 1,1-ditertbutoxy-2-propanone **1g** were synthesized as reported [28,29]. ^{1}H NMR was recorded on a Varian (400 MHz). Chemical shifts (δ) are denoted in ppm using residual solvent peaks as internal standard ($CDCl_3$, δ = 7.26 ppm). Chiral GC analyses were carried out on Fuli 9790 GC instrument equipped with an Agilent CP-Chirasil-Dex (25 m × 0.25 mm × 0.25 μm) and an FID detector (N_2 as a carrier gas). TEM (Transmission electron microscopic) images were carried out by using a Tecnai G^2 20 S-TWIN (200 kV) instrument. ICP-AES (Inductively coupled plasma atomic emission spectrometer) analyses were performed on Optima 2000 DV (detection limit is 10 ppm).

2.2. Preparation of the chiral Pt nanoparticle catalyst

As a typical example, a mixture of $PtCl_4$ (1.20 mg, 3.56×10^{-3} mmol) and CIL$_{PEG-CD}$ (32 mg, 2.85×10^{-2} mmol) was added to a 75 mL stainless-steel autoclave. The autoclave was flushed for three times with 2.0 MPa H_2 and then inflated to 4.0 MPa with H_2. After being stirred at 80 °C for 8 h, the reactor was cooled to room temperature and depressurized. The color of the mixture changed from claret to black, indicating the formation of the chiral Pt nanoparticle catalyst. The preparation of other chiral Pt nanoparticle catalysts with different ratios of CIL$_{PEG-CD}$ to Pt was carried out according to the same procedure.

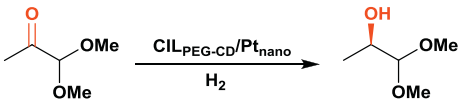
2.3. Enantioselective hydrogenation experiments

The enantioselective hydrogenation of 1,1-dimethoxyacetone 1a was used as a representative: The autoclave was charged with the above-prepared chiral Pt nanoparticle catalyst (32 mg, containing 3.56×10^{-3} mmol of Pt), CIL$_{PEG-CD}$ (12 mg), glacial acetic acid (1.6 g), toluene (1.0 g), *n*-heptane (0.3 g) and cyclohexane (50 mg, internal standard). The mixture was stirred for 30 min at 30 °C, and then 1,1-dimethoxyacetone **1a** (42 mg, **1a**/Pt = 100:1) was added. The reactor was flushed three times with 2.0 MPa H_2 and stirred under required hydrogen pressure at an appointed temperature for a designated time. After reaction, the autoclave was cooled in an ice-water bath and then depressurized. The lower chiral Pt nanoparticle catalyst phase was easily separated from the upper organic phase containing products by simple phase separation and directly reused in next catalytic cycle. The upper phase was directly analyzed by chiral GC and ^{1}H NMR.

2.4. Gram-scale reaction

The autoclave was charged with chiral Pt nanoparticle catalyst (0.80 g, containing 8.90×10^{-2} mmol of Pt), CIL$_{PEG-CD}$ (0.30 g), glacial acetic acid (40.0 g), toluene (25.0 g), *n*-heptane (7.50 g) and cyclohexane (1.25 g, internal standard). The mixture was stirred for 30 min at 30 °C, and then 1,1-dimethoxyacetone **1a** (1.05 g, 1a/Pt = 100:1) was added. The reactor was flushed three times with 2.0 MPa H_2 and stirred under 5.0 MPa H_2 at 30 °C for 3 h. After reaction, the autoclave was cooled in an ice-water bath and then depressurized. The lower chiral Pt nanoparticle catalyst phase was easily separated by simple phase separation and directly reused in next catalytic cycle. The upper phase was directly analyzed by chiral GC.

Table 1
Enantioselective hydrogenation of 1,1-dimethoxyacetone **1a** catalyzed by the thermo-regulated phase-separable chiral Pt nanoparticles.[a]



1a 2a

Entry	CIL$_{PEG-CD}$/Pt (mol/mol)	T (°C)	P_{H2} (MPa)	t (h)	Conv.[b] (%)	ee[b] (%)
1	4	30	5	3	49	89
2	5	30	5	3	80	> 99
3	7	30	5	3	92	> 99
4	8	30	5	3	> 99	> 99
5	8	25	5	3	37	> 99
6	8	35	5	3	86	> 99
7	8	40	5	3	60	95
8[c]	8	30	5	3	> 99	> 99
9	8	30	3	3	29	83
10	8	30	4	3	80	94
11	8	30	6	3	> 99	> 99
12	8	30	5	1	20	> 99
13	8	30	5	2	40	> 99
14	8	30	5	2.5	72	> 99

[a] Reaction conditions: 3.56×10^{-3} mmol of Pt, the corresponding amount of CIL$_{PEG-CD}$, toluene (1.0 g), *n*-heptane (0.3 g), glacial acetic acid (1.6 g), **1a**/Pt = 100 (mol/mol), cyclohexane (50 mg).
[b] Determined by chiral GC analysis.
[c] 2nd cycle of entry 7 at 30 °C.

3. Results and discussion

Our studies began by using 1,1-dimethoxyacetone **1a** as model substrate for enantioselective hydrogenation to screen the optimal reaction conditions. Firstly, a series of chiral Pt nanoparticle catalysts with different molar ratios of CIL$_{PEG-CD}$ to Pt were prepared and tested in the reaction (Table 1, entries 1–4). The results showed that the conversion greatly increased from 49% to > 99% with increasing the molar ratio from 4 to 8, while the > 99% ee was obtained and remained when the molar ratio was in the range of 5 to 8. Subsequently, the effect of reaction temperature was explored in the range of 25–40 °C. As shown in Table 1, when the temperature was increased from 25 to 30 °C, the conversion rapidly increased from 37% to > 99% (entry 5 *vs.* 4). This can be explained by the fact that the reaction system changes from two-phase to homogeneous phase at 30 °C. Meanwhile, the > 99% ee remained unchanged. However, once the temperature exceeded 30 °C, the decrease in the conversion or the ee was observed (entries 6–7 *vs.* 4). According to the reported literatures [20,30], it's most likely that the chiral modifier is either desorbed from the metal catalyst surface or hydrogenated at higher temperature. However, in our experiment no hydrogenation product of the chiral ionic liquid CIL$_{PEG-CD}$ was detected by ^{1}H NMR. To further illustrate this phenomenon, the catalyst of entry 7 was reused at 30 °C and the results indicated that the decrease was probably the result of desorption of CIL$_{PEG-CD}$ from Pt nanoparticle catalyst (entry 8 *vs.* 7). In addition, the dependence of the conversion and the ee on hydrogen pressure was investigated between 3 and 6 MPa (entries 4 and 9–11). The data showed that both the conversion and the ee increased with increasing hydrogen pressure until the > 99% conversion and ee were achieved at 5 MPa. With a further increase in the hydrogen pressure to 6 MPa, the conversion and the ee remained