ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c7cc00892a

Received 3rd February 2017,
Accepted 23rd February 2017

DOI: 10.1039/c7cc00892a

rsc.li/chemcomm

A thermoregulated phase-separable chiral Pt nanocatalyst for recyclable asymmetric hydrogenation of α-ketoesters†

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The design and preparation of a chiral Pt nanocatalyst system possessing thermoregulated phase-separation property and its application in recyclable asymmetric hydrogenation of α-ketoesters are presented.

In transition-metal-catalyzed reactions, a daunting challenge is the recovery of metal catalysts and ligands.[1] Conventional strategies have mainly relied on the heterogenization of homogeneous catalyst systems by means of immobilization of the ligands and/or metal catalysts on solid supports such as polymer resins[2] and inorganic materials.[3] Alternatively, ionic-liquids have also been intensively investigated.[4] Although these efforts have greatly advanced the technologies of transition-metal-catalyzed reactions, the majority were concentrated on non-asymmetric reactions. In contrast, the studies on asymmetric transformations are much less developed due to the considerably increased difficulties in achieving high yield and enantioinduction simultaneously. While a few chiral heterogeneous catalyst systems that adsorb the metal catalysts and chiral modifiers on a solid matrix such as SiO_2,[5] Al_2O_3,[6] carbon nanotubes,[7] or mesoporous materials[8] have been reported, the recyclability of those catalyst systems remains to be improved due to metal leaching. In addition, as an inherent disadvantage, heterogeneous catalysts usually exhibit a lower catalytic efficiency than the homogeneous ones.[9]

Therefore, the development of a conceptually new chiral catalyst system that displays good integrative performances including high activity, excellent enantioinduction, broad generality, and easy recoverability and reusability, remains a clear requirement in transition-metal-catalyzed asymmetric reactions. Hinted by our previous discovery that a PEG-based ionic liquid (PEG = polyethylene glycol) exhibits electrosteric stabilization properties (*i.e.*, the steric and electrostatic stabilization arising from PEG chain and ammonium salt moiety, respectively) for transition metal nanoparticles and a distinctive critical solution temperature (CST),[10] we designed a novel chiral nanoparticle catalyst using a PEG-based chiral ionic liquid (CIL) as a stabilizer and chiral modifier, coined here as a thermoregulated phase-separable chiral catalyst (TPSCC). The working diagram of TPSCC is depicted in Fig. 1. At a temperature lower than the CST, the CIL phase containing chiral nanoparticle catalyst is immiscible with the upper phase organic solution containing reaction substrates (left vessel). However, when the temperature is elevated to a value higher than the CST, the biphasic system becomes miscible which virtually allows the reaction to proceed homogeneously (middle vessel). After the completion of the reaction, the homogeneous system separates into two phases again by the temperature falling to a value lower than CST (right vessel). Thus, the upper phase containing chiral products and the lower phase containing the chiral ionic liquid and nanoparticle catalyst can be easily separated *via* phase separation. Apparently, such a catalytic system takes advantage of both heterogeneous and homogeneous systems, and thereby, would be indisputably appealing in the area of catalytic reactions. The successful demonstration of such a new asymmetric catalyst system will be presented herein.

The PEG-based $CIL_{PEG\text{-}CD}$ was prepared *via* a two-step procedure from $CH_3(OCH_2CH_2)_{16}OH$ (PEG-750) and cinchonidine (CD) according to the reported literature[11] (Fig. 2, see the ESI† for detailed reaction procedure). After a brief examination of several less polar organic solvents, we found that the $CIL_{PEG\text{-}CD}$ exhibited

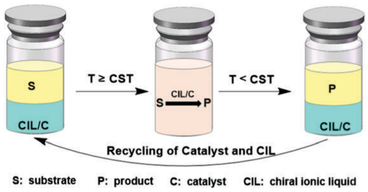

Fig. 1 Schematic illustration of the thermoregulated phase-separable catalyst system.

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† Electronic supplementary information (ESI) available: Experimental procedures, GC charts, and copies of NMR spectra. See DOI: 10.1039/c7cc00892a

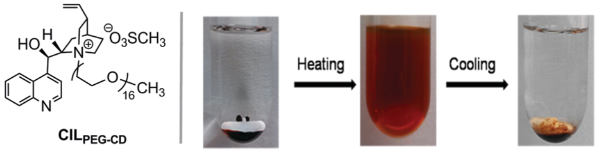


Fig. 2 Structure of a PEG-based chiral ionic liquid (CIL_{PEG-CD}) and its thermoregulated phase-separation property.

perfect thermoregulated phase-separable ability in a mixture of *n*-heptane and toluene. Namely, CIL_{PEG-CD} was immiscible with the *n*-heptane and toluene mixture at room temperature (Fig. 2, left tube). However, when heated to a temperature higher than CST, the biphasic system could be merged into a uniform and stable single phase (middle tube), which upon cooling down, re-separated into a biphasic system with the upper organic phase almost colorless as seen by the naked eye (right tube). More interestingly, we observed that the value of CST can be flexibly tuned within a broad range from *ca.* room temperature to >160 °C by changing the ratio of *n*-heptane to toluene (Table 1, entries 1–5). In stark contrast, only a negligible change of CST was observed when the ratio of *n*-heptane to toluene remained unchanged but just the total amounts of solvent were varied (entries 6–11). This property would be an important advantage of CIL_{PED-CD} when alteration of a reaction type or scale is under consideration.

Having unambiguously demonstrated the thermoregulated phase-separable property of CIL_{PEG-CD}, we then shifted our attention to its application as a stabilizer and chiral modifier of transition metals in catalytic asymmetric reactions. Accordingly, the CIL_{PEG-CD} stabilized Pt nanoparticles were easily prepared through the reduction of $PtCl_4$ with H_2 (see the ESI† for details). For comparison, catalysts stabilized by CD·HCl and PEG-750 were also prepared respectively in the same manner. As clearly shown in Fig. 3, the catalyst prepared from CIL_{PEG-CD} dispersed very well (Fig. 3a). In contrast, severe aggregation was observed for catalysts prepared from CD·HCl and PEG-750 (Fig. 3b and c). In good agreement with these observations, the TEM analysis revealed that the catalyst stabilized by CIL_{PEG-CD} formed equigranular nanoparticles within a size range of 3.1 ± 0.3 nm (Fig. 5a, *vide infra*). Since prior literature has suggested that either ammonium salts[12] or PEG[13] could serve independently as a stabilizer to stabilize the metal nanoparticles by electrostatic stabilization and steric stabilization, respectively, here, the formation of well dispersed Pt nanoparticles from CIL_{PEG-CD} may be attributed to a precise combination of both stabilizing functions. Thus, the use of CIL_{PEG-CD} not only endows the nanoparticle catalyst with the thermoregulated phase-separable property, but also stabilizes the nanoparticles through electrosteric stabilization effects.

Table 1 Critical solution temperature (CST) of the CIL_{PED-CD} in *n*-heptane and toluene mixtures[a]

Entry	*n*-Heptane (g)	Toluene (g)	Ratio	CST (°C)
1	1.50	1.50	1 : 1	>160
2	1.00	2.00	1 : 2	135
3	0.75	2.25	1 : 3	80
4	0.60	2.40	1 : 4	56
5	0.50	2.50	1 : 5	28
6	0.50	1.50	1 : 3	80
7	1.00	3.00	1 : 3	80
8	1.50	4.50	1 : 3	80
9	2.00	6.00	1 : 3	80
10	2.50	7.50	1 : 3	80
11	4.00	12.00	1 : 3	80

[a] General method for measuring CST: to a thick-walled tube was added CIL_{PEG-CD} (0.3 g), *n*-heptane, and toluene. The tube was then sealed and the mixture was heated slowly under stirring until a homogeneous and transparent solution was formed. After standing for 2 h, the homogeneous solution was cooled down slowly, and the point at which the CIL_{PEG-CD} precipitated out was defined as the CST.

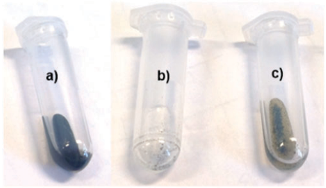
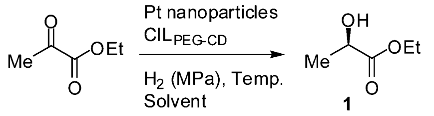


Fig. 3 Photograph of Pt nanoparticles stabilized by different stabilizers: (a) electrosteric stabilization by CIL_{PEG-CD}; (b) electrostatic stabilization by CD·HCl salt; and (c) steric stabilization by PEG-750.

Next, we investigated the asymmetric catalytic efficiency of the CIL_{PEG-CD} stabilized Pt nanoparticle catalyst. To this end, the asymmetric hydrogenation of α-ketoesters was examined with the aim of developing a highly efficient method for enantioselective synthesis of chiral α-hydroxy esters. α-Hydroxy esters are important building blocks or starting materials in organic synthesis.[14] Although asymmetric reaction methods for accessing such compounds have been extensively reported,[15] there remain considerable challenges stemming from one or more of the concerns such as low conversion efficiency, unsatisfactory enantioinduction, and poor reusability of catalysts and/or chiral modifiers.

Initial optimization of the reaction conditions was carried out using ethyl pyruvate as the model substrate (Table 2). The reaction was less effective at 20 °C (entry 1). Delightedly, complete conversion and >99% ee were obtained when the reaction temperature was elevated to 30 °C (entry 2). The absolute configuration of the product was assigned to be R as compared with an authentic sample.[16] A further increase of the temperature by 35 °C to 40 °C resulted in an apparently reduced enantioinduction although complete conversion was observed (entries 3 and 4). These results indicate that the enantioselectivity of this transformation was thermally sensitive. In addition, the reaction efficiency was also apparently affected by the pressure of H_2 (entries 2 *vs.* 5 and 6) and the ratio of CIL_{PEG-CD} to Pt nanocatalyst (entries 2 *vs.* 7–9). 5.0 MPa of H_2 and 15 : 1 of CIL_{PEG-CD} to Pt nanocatalyst were optimal as shown by the comparison of the conversion rate, TOF, and ee%. Here, we should mention that prior to the addition of the α-ketoester substrate, premixing of Pt nanoparticles and CIL_{PEG-CD} in a toluene, *n*-heptane, and glacial acetic acid mixture was necessary because diminished enantioselectivity was observed when ethyl pyruvate was added simultaneously with other substances (entries 2 *vs.* 10). Thus, through an extensive screening of various parameters, we could establish the optimized conditions as listed in entry 2. Under these conditions, the enantioselective hydrogenation proceeded efficiently in a quantitative yield and >99% ee. Finally, to further verify the crucial role of CIL_{PEG-CD}

Table 2 Optimization of conditions using $\mathrm{CIL_{PEG\text{-}CD}}$ stabilized Pt nanoparticles as the catalyst[a]



Entry	T (°C)	P_{H_2} (MPa)	CIL/Pt (mol/mol)	Conv.[b] (%)	TOF (h^{-1})	ee[c] (%)
1	20	5	15 : 1	48	480	82
2	30	5	15 : 1	>99	990	>99
3	35	5	15 : 1	>99	990	91
4	40	5	15 : 1	>99	990	83
5	30	3	15 : 1	90	900	82
6	30	4	15 : 1	98	980	88
7	30	5	5 : 1	>99	990	73
8	30	5	10 : 1	>99	990	85
9	30	5	20 : 1	>99	990	80
10[d]	30	5	15 : 1	>99	990	85

[a] Reaction conditions: 0.60 mg (1.78×10^{-3} mmol) of Pt nanoparticles and a certain amount of $\mathrm{CIL_{PEG\text{-}CD}}$ (added according to the ratio to Pt nanoparticles shown in the table) were stirred in a mixture of toluene (1.0 g), *n*-heptane (0.3 g), and glacial acetic acid (1.3 g) for 30 min at rt, then ethyl pyruvate (52 mg, substrate/Pt = 250 : 1, mol/mol) was added. The reaction mixture was stirred at a designated temperature for 15 min. [b] Determined by GC with cyclohexane as the internal standard. [c] Determined by chiral GC analysis. [d] All the substances were added simultaneously.

as a powerful stabilizer for stabilizing the Pt nanocatalyst, we compared the hydrogenation reaction with the other conditions identical to the standard ones but by just replacing the $\mathrm{CIL_{PEG\text{-}CD}}$ stabilized Pt nanocatalyst with a Pt catalyst stabilized by CD·HCl and PEG-750, respectively. However, the reaction proved to be futile with the substrate remaining intact.

Thus, with the optimized conditions in hand, we evaluated the recyclability of the Pt nanocatalyst and $\mathrm{CIL_{PEG\text{-}CD}}$ system by implementing the following operations: after the completion of the reaction, the autoclave was depressurized to atmospheric pressure and cooled in an ice-water bath; then, the lower phase containing the $\mathrm{CIL_{PEG\text{-}CD}}$ and $\mathrm{CIL_{PEG\text{-}CD}}$ stabilized Pt nanoparticles were separated by phase separation and reused directly in the next catalytic cycle. The results showed that the nanoparticle catalyst system displayed very good recyclability. Namely, complete conversion as well as excellent enantioselectivity of >99% ee was definitely maintained after eight reaction cycles (Fig. 4). In addition, TEM analysis revealed that the morphology and size of Pt nanoparticles remained almost unchanged after eight catalytic cycles (Fig. 5a *vs.* b). Moreover, a detection of Pt leaching in the upper organic phase by ICP-AES indicated that the contents of Pt were under the minimum detectable boundary of the instrument. These results firmly confirmed that the $\mathrm{CIL_{PEG\text{-}CD}}$ stabilized Pt nanocatalyst possesses an excellent integrative performance as judged from the recyclability, stability, catalytic activity, and enantioselectivity.

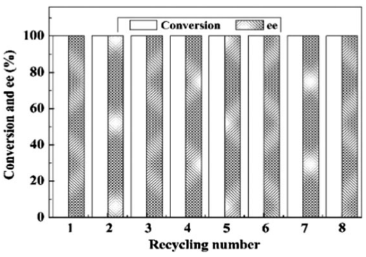


Fig. 4 Recyclability of $\mathrm{CIL_{PEG\text{-}CD}}$ stabilized Pt nanoparticles.

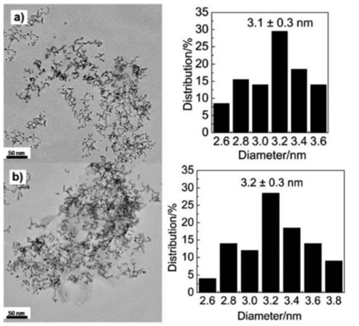


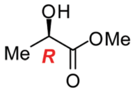
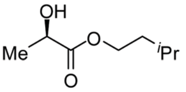
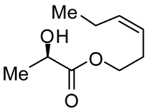
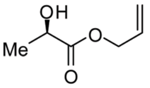
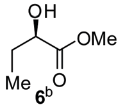
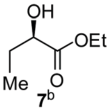
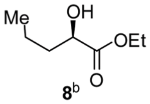
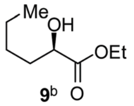
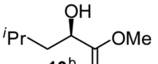
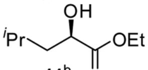
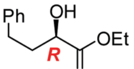
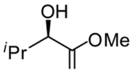
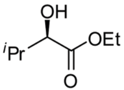
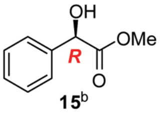
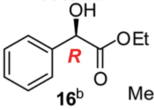
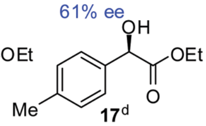
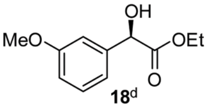
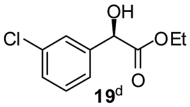
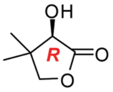
Fig. 5 TEM images and particle size histograms of newly prepared Pt nanoparticles (a) and after eight catalytic cycles (b) (200 particles, respectively).

Finally, to show the general applicability of the method, we examined the catalytic efficiency by varying the structural nature of substrates (Table 3). The results showed that the catalyst system is compatible with a variety of substrates including both aliphatic and aromatic α-ketoesters. Complete conversion and >99% ee were observed for most of the substrates. The purity of each product was identical with the corresponding conversion rate since no other by-products were formed as clearly seen from GC analysis (ESI†). Notably, for substrates decorated either by inner or terminal olefinic functionality, the hydrogenation proceeded chemoselectively at the site of carbonyl group with the olefinic groups remaining intact (**4** and **5**). This would be interesting since the highly chemoselective hydrogenation of carbonyl and olefin remains a considerably challenging issue.[17] The absolute configuration of **1**, **2**, **12**, **15**, **16**, and **20** was assigned as R by a comparison with authentic samples,[18] and that of other products was assigned by analogy. It should be mentioned that among 20 examples being examined, five substrates afforded moderate to moderately high enantioselectivity (**8**, **13**, **14**, **17**, and **20**). The reasons are not clear at this stage because of the complexity of the reaction system. This issue deserves a detailed clarification in our future studies.

In summary, we have successfully designed and developed a thermoregulated phase-separable chiral Pt nanocatalyst for highly efficient enantioselective hydrogenation of α-ketoesters. Excellent yields and enantioselectivities were obtained for an array of substrates. Moreover, the catalyst system displayed good recyclability without compromising the catalytic efficiency after eight cycles. The new method represents the first example that has realized the recyclability of a metal catalyst and chiral modifier by adopting a thermoregulated phase-separation strategy, which combines the advantages of both heterogeneous and homogeneous catalyst systems. Most significantly, the results presented herein would have a more profound implication beyond this work toward the *de novo* design of conceptually and methodologically new asymmetric catalyst systems. The development of new chiral catalyst system and further extension of our current method will be the focus of our future work.

This research was supported by the National Natural Science Foundation of China (21373039, 21173031).

Table 3 Asymmetric hydrogenation of various α-ketoesters catalyzed by CIL_{PEG-CD} stabilized Pt nanoparticles[a]

 **2** *t* = 10 min > 99% conv TOF = 1485 > 99% ee	 **3** *t* = 2 h > 99% conv TOF = 124 > 99% ee	 **4** *t* = 1 h > 99% conv TOF = 248 > 99% ee	 **5** *t* = 1 h > 99% conv TOF = 248 > 99% ee
 **6**^{b} *t* = 10 min > 99% conv TOF = 594 > 99% ee	 **7**^{b} *t* = 15 min > 99% conv TOF = 396 > 99% ee	 **8**^{b} *t* = 10 min 94% conv TOF= 564 77% ee	 **9**^{b} *t* = 3 h > 99% conv TOF = 33 80% ee
 **10**^{b} *t* = 20 min > 99% conv TOF = 297 > 99% ee	 **11**^{b} *t* = 20 min > 99% conv TOF = 297 > 99% ee	 **12**^{c} *t* = 15 min > 99% conv TOF = 792 > 99% ee	 **13**^{b} *t* = 30 min > 99% conv TOF = 198 61% ee
 **14**^{b} *t* = 1 h > 99% conv TOF = 99 60% ee	 **15**^{b} *t* = 30 min > 99% conv TOF = 198 > 99% ee	 **16**^{b} *t* = 1 h > 99% conv TOF = 99 > 99% ee	 **17**^{d} *t* = 3 h 93% conv TOF = 16 76% ee
 **18**^{d} *t* = 3 h 82% conv TOF = 14 85% ee	 **19**^{d} *t* = 3 h > 99% conv TOF = 17 > 99% ee	 **20**^{e} *t* = 5 min > 99% conv TOF = 11880 47% ee	

[a] Unless otherwise noted, the reactions were performed under the optimized conditions; the conversion rate was determined by GC with cyclohexane as the internal standard; the unit of TOF is defined as per hour; the ee% were determined by chiral GC; all reactions were repeated three times. [b] 1.20 mg (3.56×10^{-3} mmol) of Pt nanoparticles, substrate/CIL_{PEG-CD}/Pt = 100 : 7.5 : 1, toluene (1.0 g), *n*-heptane (0.3 g), and glacial acetic acid (1.6 g). [c] 0.60 mg (1.78×10^{-3} mmol) of Pt nanoparticles, substrate/CIL_{PEG-CD}/Pt = 200 : 15 : 1, toluene (1.0 g), *n*-heptane (0.3 g), and glacial acetic acid (1.6 g). [d] 1.20 mg (3.56×10^{-3} mmol) of Pt nanoparticles, substrate/CIL_{PEG-CD}/Pt = 50 : 7.5 : 1, toluene (1.0 g), *n*-heptane (0.3 g), and glacial acetic acid (1.6 g). [e] 0.6 mg (1.78×10^{-3} mmol) of Pt nanoparticles, substrate/CIL_{PEG-CD}/Pt = 1000 : 15 : 1, toluene (1.0 g), *n*-heptane (0.3 g), and glacial acetic acid (1.3 g).

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