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An efficient proline-based homogeneous organocatalyst with recyclability

Qiang Li, ^a Yuan Li, ^b Jingdong Wang, ^a Yingjie Lin, ^a Zhonglin Wei, ^a Haifeng Duan, ^a Qingbiao Yang,

many groups and has emerged as a class for broad employment, In this work, a homogeneous organocatalyst was developed for the which gained excellent isolated yield. In 2008, S. Luo et al. firstly asymmetric reduction of imines, which can be separated by constructed a magnetic nanoparticle (MNP)-supported chiral amine cyclodextrin-modified Fe3O4@SiO2 magnetic nanoparticles and catalyst. In recent years, increased attention has been paid on the then released back into a fresh reaction for more than seven times. development and application of supported catalysts in industries to Furthermore, a new catalytic mechanism is proposed and broaden the practical range of chiral organocatalysts.^{8, 9} Gradually, investigated through theoretical calculations.

^{*a} Fuguan Bai, ^{*b} and Yaoxian Li ^a

Asymmetric catalytic reduction of imines is one of the most important and efficient methods in the preparation of chiral amines in industrial and academic circles; chiral amines are a ubiquitous structure motif in enzymes, DNA and other natural products¹. Several synthetic methodologies have been developed for the synthesis of chiral amines². For instance, in 2004 Bruce H. Lipshutz et al. have reported an asymmetric reduction of imines using Cu-based catalysts with regard to both chemical yields and enantioselectivities.³ In 2013 Yuan gin Chang and co-workers reported a Fe-based catalyst material with high activity and is similar to a commercial Pt/C catalyst.⁴ Moreover, organocatalysts have been recently considered remarkable alternatives for asymmetric hydrogenation to gain chiral amines, considering their low toxicity, operational simplicity, and high efficiency.⁵ Among the reported strategies, L-proline and its derivatives have shown considerable catalytic efficiency in different organic transformations.⁶ Nowadays, widespread interest has been devoted on the development of new organocatalysts based on Lproline, especially its derivatives that can be utilized as chiral catalysts for reduction of imines to attain enantiomerically enriched amines with moderate optical yields.7

Organocatalysts have some superiority to metal catalysts, but many of them still suffered from some difficulties and disadvantages. For instance, the proline and its derivatives are difficult to be reused and recycled even though they are frequently consumed, thereby restricting these catalysts from practical applications. Therefore the immobilization of proline and its derivatives have been the focus of

supported¹² and cyclodextrin-supported¹³ catalytic methods. However, most immobilized catalysts are facing the same severe problem, that is, most of them will have a negative effect on the high activity of organocatalysts, leading to lower efficiency performance compared with their homogeneous counterparts. Most of them are jointed on bulk carriers and used as heterogeneous catalysts, which hamper the spatial configuration of catalysts. Thus, immobilized catalysts, such as MNP-supported catalyst, suffer from decreased activity and poor control in the process.14-16 In this work, we reported an efficient catalyst based on L-proline to promote the asymmetric reduction of imines, which can be recycled for seven times through self-assembly method¹⁷ based on host-guest molecular recognition¹⁸ using cyclodextrinmodified Fe₃O₄@SiO₂ magnetic nanoparticles (MNPs)¹⁹. The

cycle is shown in Figure. 1. Particularly, a different catalytic mechanism model is proposed. The trace of H₂O in the reaction system is critical as a bridge of hydrogen bond between the catalyst and substrate.²⁰ Furthermore, to investigate the mechanism, a theoretical calculation was conducted, which confirmed that H₂O can be beneficial in reducing the total energy of the catalytic system and can easily form π - π stacking.

other methods for the immobilization of organocatalysts have been attempted and achieved satisfactory results, such as dendrimer-

supported,¹⁰ metal nanoparticles-supported,¹¹ ionic liquid-

^{a.} College of Chemistry, Jilin University, E-mail: <u>vangqb@jlu.edu.cn;</u> Changchun 130021, P.R. China;

^{b.} Institute of Theoretical Chemistry, Laboratory of Theoretical and Computational Chemistry, Jilin University, Changchun 130023, P. R. China;

⁺ Footnotes relating to the title and/or authors should appear here.

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Figure.1. Recyclability of L-proline derivative.

FTIR was carried out to investigate the bonding information of the catalyst/Fe₃O₄@SiO₂- θ -CD MNPs. Figure. 2 shows the FTIR spectra of Fe₃O₄ (A), Fe₃O₄@SiO₂ (B), Fe₃O₄@SiO₂- θ -CD (C), and catalyst **a** /Fe₃O₄@SiO₂- θ -CD (D). The broad band centered at 467 cm⁻¹ and the band at 1091 cm⁻¹ were ascribed to the Fe–O and Si–O stretching vibrations. Therefore, SiO₂ was successfully deposited on the surface of the Fe₃O₄ MNPs. Bands at 2923 and 1654 cm⁻¹ were attributed to the alkane C–H stretching vibration and O–H bending vibration of cyclodextrin, which revealed the linkage of θ -CD and Fe₃O₄@SiO₂ MNPs. In addition, bands at 1400 and 1627 cm⁻¹ (C–C stretching of benzene skeleton) are found in Figure. 2 (D), which are exclusive and ascribed to the catalyst. Therefore, based on the data from FTIR, the resulting product of the catalyst/Fe₃O₄@SiO₂- θ -CD inclusion complex magnetic nanoparticles was doubtlessly prepared via host–guest self-assembly interactions



Figure. 2. The FTIR spectra of Fe_3O_4 (A), $SiO_2@Fe_3O_4$ (B), β -CD/SiO_2@Fe_3O_4 (C), and catalyst **a** MNPs (D).

Initially, solvents including polar and non-polar solvents were tested. Among the different solvents, which we have tried, CH_2CI_2 showed good results and has a short reaction time and high yield (89% ee). **Table 1** shows the time when the reaction was carried out at -30 °C within 48 h and when the reaction exhibited high yield **2a** with good enantioselectivity. When the amount of catalyst **a** decreased to 5 mol% (**Table 1**, entry 17), the yield and enantioselectivity decreased.

However, the reduction of **1a**, as catalyzed by catalyst by cataly



ee^c[%] Time[h] Entry solvent NRd 1 DMSO 96 rt ---2 1 DMF 48 0 55 3 Et₂O 48 0 36 0 4 CH₃OH 48 0 NRd ---3 5 THF 48 0 92 6 Toluene 48 0 72 0 7 Benzene 48 0 75 3 8 Ethyl acetate 48 0 64 5 9 CH₃CN 48 0 92 71 10 48 0 67 60 **CHCI**₃ CICH₂CH₂CI 48 42 11 0 95 12 CH₂Cl₂ 48 0 94 89 13 CH_2CI_2 48 -10 96 90 14 CH₂Cl₂ 72 -20 96 90 15 72 -30 92 CH₂Cl₂ 98 92 72 16 CH₂Cl₂ -40 87 17ª CH₂Cl₂ 72 -30 77 81 18^f CH₂Cl₂ 72 -30 94 0 19 CH_2CI_2 12 -30 81 85 20 90 CH₂Cl₂ 24 -30 89 92 21 98 CH₂Cl₂ 48 -30

^a The reactions were performed using 0.25mmol of imine and 0.75mmol of trichlorosilane with 0.025mmol of catalyst.

^b Isolated yields.

^c Determined by chiral HPLC.

^d No reaction

^e The reactions were performed using 0.25mmol of imine and 0.75mmol of trichlorosilane with 0.0125mmol of catalyst.

^F The reactions were performed using 0.25mmol of imine and 0.75mmol of trichlorosilane with 0.025mmol of catalyst **b**.

Variation of the ordinary imines **1a–r** was examined to obtain the substrate scope of the reaction and investigate the generality of catalyst **a** under the optimal reaction condition (**Table 1**). The results are summarized in **Table 2**. In the case of all amines, a dramatic difference in selectivity was observed, in that using electron-withdrawing groups obtained slightly low selectivity, which suggested that electronic interaction was supposed to be the key factor. Furthermore, imines with the same *p*-substituent group with either electron-withdrawing or electron-donating R₂ exhibited enantioselectivity that is marginally lower than that with R₁, which indicated that the difference of the *p*-substituent position may be crucial to the advantages of the steric configuration between the catalyst and the imines, such as **2e–2l**, exhibited enantioselectivity especially **2j**, which is higher than that in electron-withdrawing

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amines, like 2b-2d and 2m-2p, when the p-substituent groups are placed in R₁ or R₂. In the case of amines **2e–2h**, a significantly reduced yield and enantioselectivity were observed, which were fairly lower than those in 2i-2l, demonstrating that a steric repulsion occurred between the imines and catalyst. Thus, the *p*-substituents in R₂ are crucial in the steric properties, and the mechanism can account for the observed stereochemistry. The bulky adamantane group of the catalyst and the *p*-substituents of imines **b**-h stayed away from one another, given the steric repulsion, which was compared with the high level of enantioselectivity obtained from that with the psubstituents in R₁, such as imines i-I. Compared with 2e, another electron-rich group was placed in the phenyl moiety of R₁ for **2q**; then, the yield and enantioselectivity were increased as expected. However, further investigation with broad substrates to present more detailed comparison is required. When the methyl of imine was replaced with n-propyl as imine 1r, the yield and enantioselectivity of 2r were lower than that of 2a. We speculate that when the catalyst and HSiCl₃ get closer to the imines, the n-propyl moiety will afford more obstruction than methyl moiety due to the steric effect.

 Table 2. Reduction of imines 1a-r with trichlorosilane catalyzed by catalyst a



Entry	^a R1	R2	Х	product	Yield⁵ [%]	ee ^c [%]
1	C ₆ H₅	C ₆ H₅	CH₃	2a	96	92
2	C ₆ H₅	4-FC ₆ H₄	CH₃	2b	92	80
3	C ₆ H₅	4-BrC ₆ H₄	CH₃	2c	81	68
4	C ₆ H₅	4-IC ₆ H₄	CH₃	2d	70	73
5	C ₆ H ₅	4-CH ₃ OC ₆ H ₄	CH₃	2e	80	88
6	C ₆ H ₅	4-CH ₃ C ₆ H ₄	CH₃	2f	92	83
7	C ₆ H ₅	4-CH ₃ CH ₂ C ₆ H ₄	CH₃	2g	91	78
8	C ₆ H ₅	4-t-BuC ₆ H ₄	CH₃	2h	87	73
9	4-CH ₃ C ₆ H ₄	C ₆ H ₅	CH ₃	2i	96	87
10	4-CH ₃ CH ₂ C ₆ H ₄	C ₆ H ₅	CH ₃	2j	97	95
11	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	CH ₃	2k	92	90
12	4-t-BuC ₆ H ₄	C ₆ H ₅	CH ₂	21	91	93
13 14 15 16 17 18	4-FC ₆ H ₄ 4-BrC ₆ H ₄ 4-IC ₆ H ₄ 4-IC ₆ H ₄ 4-NO ₂ C ₆ H ₄ 4-CH ₃ OC ₆ H ₄ C ₆ H ₅	C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ C ₆ H ₅ 4-CH ₃ OC ₆ H ₄ C ₆ H ₅	CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ n-prop	2m 2n 2o 2p 2q 2yl 2r	88 91 90 56 95 70	85 88 87 51 93 64

^a The reactions were performed using 0.25mmol of imine and 0.75mmol of trichlorosilane with 0.025mmol of catalyst **a**. -30° C, 48h, CH₂Cl₂.

^b Isolated yields.

 $^{\rm c}\,$ Determined by chiral HPLC.

To provide an explanation on the mechanism of catalytic behavior, a new plausible transition state model was proposed on the basis of the available experimental data. Many researchers, such as Takuya Kanemitsu and Andrei V. Malkov, have independently shown the transition state for the reduction of imines with chiral organocatalysts.^{20, 21} A different transition state model was proposed for catalyst **a** in a similar method. The catalyst could coordinate with trichlorosilane and activate the reducing agent in a synergistic manner. The reaction was accelerated presumably through the coordination between the silicon atom and oxygen²² of the amide

group and a hydrogen bond between the imine nitrogen and anline hydrogen. In addition, the results presented in **Table C** (entry 1.8) showed that catalyst **b** can obtain high yield but without enantioselectivity. Arene–arene interactions between the catalyst and the substrates appear to be crucial in the formation of a steric transition state. However, as shown in **Table 2**, the catalyst obtained highly excellent yield and enantioselectivity when the *p*-substituent groups are placed in R₁ rather than in R₂. This finding revealed that the stability of steric configuration between catalyst and imines with bulky group on N-phenyl moiety of R₂ was disturbed by the adamantane moiety on catalyst **a**, as shown in Figure 3.

Furthermore, to investigate the effect of hydrogen bonding between catalyst and imines, anhydrous system was considered. Nevertheless, the reaction gave corresponding products that were rarely and toughly processed. However, when trace amounts of D_2O were added to the anhydrous solvent, the reaction returned to normal. Moreover, the increase of the product molecular mass was observed and measured by HRMS (Figure S5). Therefore, the hydrogen bonding was formed between O of water and H of catalyst. Then, the H of water and N of substrate moved to each other to form another hydrogen bond. This finding suggested that water plays an important role as a bridge in the hydrogen bonding formation. Therefore, these results are consistent with the proposed mechanism model. Consequently, the proposed interactions could result in the attack from the *Re* face of the imine **1a** to obtain the optically active amine (S)-**2**.

Re-face attact



Figure. 3. Proposed transition state of catalyst a

As shown in Figures S6, S7, and S8, blue fragments represent strong electrostatic interactions, such as hydrogen bond interaction, in the corresponding region. Red fragments imply intensive steric effects. Green region suggests low electron density, which corresponds to Van der Waals (VDW) interaction. In Figure S6, a blue portion near the H_2 - N_2 group and a blue-green one are shown near the H_1 -O part in the model A. Thus, strong hydrogen bonds were formed. In Figure S8, the colors are light blue and green blue near the H₂-N₂ group and the H_1 -O portion are presented separately in model C. Meanwhile, the corresponding scatter graph shows that the absolute values of the electrostatic interaction of model A, which range from -0.05 to -0.02, are higher than those of model C. The grass-green isosurface near H₁-N₂ in B exhibited the weakest hydrogen bond effect. Moreover, the green portion implies that VDW interaction exists between the phenyl of catalyst and N-phenyl of R₂ on imines in model A. However, the isosurface between the phenyl of catalyst and R₁ on imines shown as model C suggests little VDW interaction. Thus, model A is more stable than models B and C shown as Figure. S9.

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To classify the catalyst performance in a homogeneous catalysis/heterogeneous separation, the recyclability and optimal conditions of catalyst a should be examined. A series of eight consecutive runs were carried out, and the results are shown in Table s3. The magnetic cyclodextrin-modified Fe₃O₄@SiO₂ with large surface area²³ and outstanding stability²⁴ can be reused more than seven times. In addition, a little drop in activity was observed after five runs, which caused a slight decrease in yield and enantioselectivity (Table s3, entries 1-6). After each run, the recycled amount of catalyst a was detected by RP-HPLC (Figure S3). However, a 7.4 % loss was observed in each run, presumably including 2.7% loss in the process of extraction, 3% loss for the inclusion interaction of SiO₂ formed in the hydrolysis of HSiCl₃, and 1.7% loss in the process of self-assembly. With more than six runs, some catalysts were supplemented into the continual reaction, making the amount of catalyst approach an initial amount of 10 mol%, as shown in Figure 4. Moreover, significant increases in yield and enantioselectivity occurred, and the catalyst retrieved a high activity as that in the first run. Therefore, although a slight loss of catalyst occurred in the recyclable process, this self-assembly method can efficiently recycle almost all catalysts to support the high activity and catalyze the reaction for each run without any obvious loss of activity.



Figure. 4. Recyclability of catalyst **a** for the reduction of imine 1a. The reactions were performed using 0.25mmol of imine and 0.75mmol of trichlorosilane with 0.025mmol (10mol%, 10.9mg) of catalyst.

Conclusions

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We developed a homogeneous catalyst for the reduction of imines with recyclability. This method has several advantages, including homogeneous catalysis, heterogeneous efficient isolation of catalyst, and easy workup. The catalyst also has good activity performance (95% ee) and could be recycled up to eight runs with only a slight drop in activity. Once we supplemented some catalysts, the activity performed like a fresh catalyst. Moreover, a new mechanism model was proposed by investigating the n-n stacking for the catalyst and N-phenyl of imines and presenting water as a bridge, which was confirmed by theoretical calculations.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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A homogeneous organocatalyst for asymmetric reduction of imine can be reused for many cycles through self-assembly method using MNPs.

