Asymmetric bifunctional primary aminocatalysis on magnetic nanoparticles†

Sanzhong Luo,*[a] Xiaoxi Zheng[a] and Jin-Pei Cheng*[ab]

Received (in Cambridge, UK) 28th July 2008, Accepted 8th September 2008
First published as an Advance Article on the web 6th October 2008
DOI: 10.1039/b812958d

MNP-supported chiral primary amine catalysts were developed and evaluated as asymmetric bifunctional enamine catalysts in direct aldol reaction, showing essentially unchanged activity and stereoselectivity after 11 recycles.

As structural and functional mimics of type I aldolases, simple chiral primary amine catalysts have been shown to be versatile enamine catalysts that attain new level of catalysis beyond the reach of classical secondary amine catalysts.[1] However, large catalyst loadings were normally employed in order to overcome the intrinsic lower turnover of primary aminocatalysis in many of these cases. Heterogenization of primary amine catalysts would be an effective way to improve their catalytic efficiency *via* catalyst recovery and reuse.[2] In this regard, heterogeneous bifunctional primary amine catalysis has recently been achieved using mesoporous silica as support.[3] Unfortunately, those mesoporous primary amine catalysts are still of low activity and only achiral catalysis has been attempted. To the best of our knowledge, asymmetric heterogeneous primary aminocatalysis has not been reported so far. As a continuation of our efforts toward developing efficient primary aminocatalysis,[4] we present herein the first example of magnetic nanoparticle (MNP) supported chiral primary amine catalysts.

Magnetic nanoparticles (MNPs) have recently appeared as a new type of catalyst support because of their easy preparation and functionalization, large surface area ratio, facile separation *via* magnetic force as well as low toxicity and price.[5] These fascinating features have made MNPs a promising alternative to porous/mesoporous catalyst supports. Accordingly, MNPs have been successfully utilized to immobilize enzymes[5c] and chiral transition metal catalysts.[6] However, MNP-supported asymmetric organocatalysts have not been attempted so far, though a few examples of achiral organocatalysts have recently been reported.[7] In this context, we explored the use of MNP for immobilizing chiral primary amine catalysts, selecting chiral primary–tertiary diamine type catalysts developed in our group (Fig. 1).[4] Besides serving as enamine catalysts

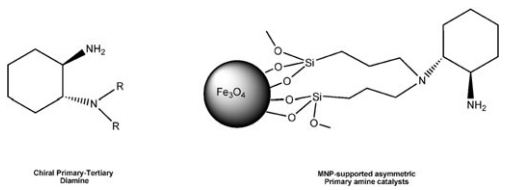
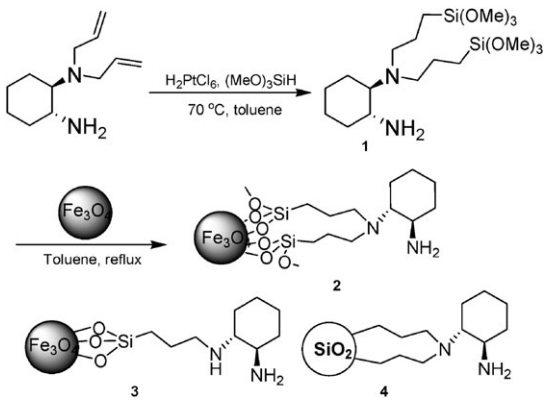


Fig. 1

themselves, the cyclohexanediamines are also preferred skeletons for bifunctional thiourea catalysts and chiral ligands in transitional metal catalysts,[8] and so the successful immobilization of this series of catalysts may therefore open the door to a range of asymmetric recoverable catalysts.

The MNP-supported chiral primary amine **2** was prepared following the procedure shown in Scheme 1. We chose magnetite nanoparticles as the support as these nanoparticles were easily prepared *via* co-precipitation.[9] The magnetite nanoparticles were first protected with a layer of silica to prevent aggregation. The obtained SiO_2–MNP was treated with trimethoxysilane **1** in refluxing toluene to afford the MNP-supported catalyst **2** with 0.39 mmol g^{-1} loading of chiral amine. Trimethoxysilane **1** was prepared *via* Pt-catalyzed hydrosilylation of the allylated precursors in toluene. After complete conversion of the starting material as judged by ^1H NMR (>90% purity), the filtered toluene solution of **1** was directly used for subsequent immobilization without further purification.[10]

TEM image confirmed the nanometre dimensions (spherical particles, 8–10 nm) of the catalyst as well as the existence of silica coating (1–2 nm coating, Fig. 2, a). Magnetization curves



Scheme 1 Preparation of MNP-supported chiral primary amine catalysts.

[a] *Beijing National Laboratory for Molecular Sciences (BNLMS), Centre for Chemical Biology, Institute of Chemistry, Chinese Academy of Science, Beijing, 100190, China. E-mail: luosz@iccas.ac.cn; Fax: +86-10-62554449; Tel: +86-1062554446*
[b] *Department of Chemistry and State-key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, China; E-mail: chengjp@mail.most.gov.cn*

† Electronic supplementary information (ESI) available: Experimental details and characterization of catalysts. See DOI: 10.1039/b812958d

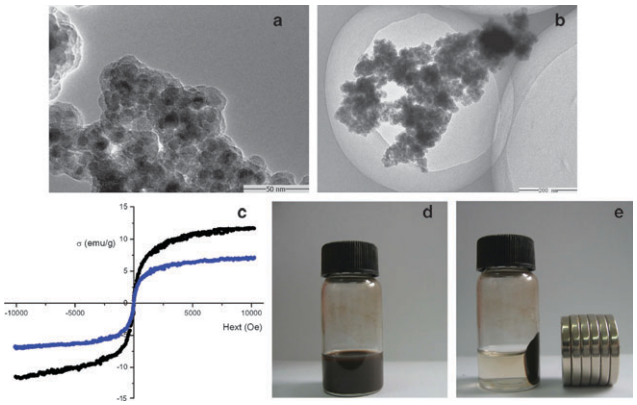


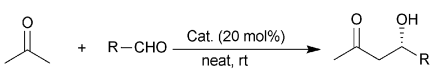
Fig. 2 TEM images of freshly prepared catalyst **2** (a) and catalyst **2** after 11 cycles of reuse (b); (c) magnetization curves of silica-coated MNP (black line) and catalyst **2** (blue line); (d) catalyst **2** dispersion in methanol; (e) catalyst separation with a small magnet.

measured under room temperature showed that the MNP-supported catalyst **2** is superparamagnetic (Fig. 2, c). The MNP catalysts are well dispersed in a range of solvents such as water, alcohols, THF and CH_2Cl_2 and easily separated by a small magnet placed nearby (Fig. 2, d and e). The zeta-potentials of MNPs before and after functionalization were determined to be −40.6 mV and +49.0 mV, respectively, indicating good stability of the MNP-supported catalysts in aqueous conditions (Fig. S5 in ESI†).

For comparison, MNP-supported primary–secondary diamine **3**[11] and silica supported chiral primary amine **4** (commercial amorphous silica for column chromatography, 200–300 mesh) was prepared with a loading of 1.42 mmol g^{-1} and 0.47 mmol g^{-1}, respectively.

The MNP-supported catalyst **2** was next evaluated in the typical enamine-based direct aldol reaction of acetone. As shown in Table 1, an acidic additive was found to be essential for the catalysis of **2** and the reaction barely occurred in the absence of acidic additive (Table 1, entries 1 *vs.* 2). This behavior closely resembles its non-supported counterpart.[4a] In consistence with the non-supported catalysis, stronger Brønsted acids such as TfOH gave slightly better enantio-

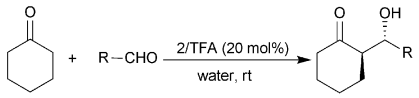
Table 1 Asymmetric direct aldol reaction of acetone catalyzed MNP supported catalyst



Entry	Cat.	R	Additive	Time/h	Yield (%)[a]	Ee (%)[b]
1	**2**	4-NO_2Ph	None	48	Trace	—
2	**2**	4-NO_2Ph	TFA	48	86	66
3	**2**	4-NO_2Ph	TfOH	48	84	73
4	**3**	4-NO_2Ph	TFA	24	25	48
5	**4**	4-NO_2Ph	TfOH	48	30	80
6	**2**	2-NO_2Ph	TfOH	32	92	69
7[c]	**2**	2-NO_2Ph	[c]	32	90	69
8	**2**	3-NO_2Ph	TfOH	48	91	66
9	**2**	4-CF_3Ph	TfOH	96	87	67
10	**2**	1-Naphth	TfOH	96	91	67

[a] Isolated yields. [b] Ee value of *anti* isomer, determined by chiral HPLC. [c] The 9th reuse of the catalyst **2** employed in entry 6 reaction, no extra TfOH was added for reuse.

Table 2 Asymmetric direct aldol reaction of cyclohexanone[a]



Entry	R	Time/h	*anti* : *syn*[b]	Yield (%)[c]	Ee (%)[d]
1	4-NO_2Ph	24	11 : 1	98	98
2[e]	4-NO_2Ph	24	11 : 1	94	94
3[f]	4-NO_2Ph	24	9 : 1	96	95
4[g]	4-NO_2Ph	24	3 : 1	53	84
5	3-NO_2Ph	28	10 : 1	89	92
6[e]	3-NO_2Ph	28	10 : 1	89	92
7	2-NO_2Ph	28	8 : 1	92	87
8[e]	2-NO_2Ph	28	10 : 1	89	85
9	4-CF_3Ph	48	6 : 1	81	88
10[e]	4-CF_3Ph	48	6 : 1	78	88
11	4-ClPh	96	6 : 1	76	92
12	1-Naphth	48	2 : 1	60	91

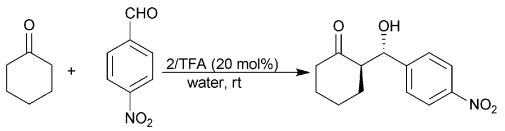
[a] 0.25 mmol reaction in 0.1 mL water. [b] Determined by ^{1}H NMR. [c] Isolated yields. [d] Ee value of *anti* isomer, determined by chiral HPLC. [e] In 0.5 mL of water. [f] Reaction under neat conditions. [g] Catalyst **4** was used.

selectivity (Table 1, entry 3 *vs.* 2). Though the selectivity was inferior to that obtained in homogeneous catalysis, the current results clearly indicated that asymmetric primary amino-catalysis could be successfully transferred to the surface of magnetic nanoparticles. In addition, the relative lower catalytic efficiency in the catalysis of MNP supported primary–secondary diamine catalyst **3** (Table 1, entry 4) or silica-supported catalyst **4** (Table 1, entry 5 and Table 2, entry 4) also highlighted the advantages of the primary–tertiary diamine skeleton along with its nano-sized support.

The application of catalyst **2** was then examined and some of the results are summarized in Tables 1 and 2. Both the direct aldol reactions of acetone and cyclohexanone worked very well in the presence of **2**, affording the desired aldol products with high yields and high stereoselectivities (Table 1, entries 6–10 and Table 2). Notably, the reactions of cyclohexanone proceeded smoothly under "on-water" conditions,[12] showing slightly improved diastereoselectivity over the reactions under neat conditions. In these cases, the use of the weakly acidic additive TFA was sufficient for effective catalysis and large amounts of water were tolerated in the reaction to give results equally as good as that in a small amount of water (Table 2, entries 2, 5, 7 and 9). The supported catalysis of **1** was generally limited to aromatic aldehydes; the reactions with aliphatic aldehydes gave poor yields.

The magnetically driven separation and recycling of MNP-supported catalyst **2** were quite easy and simple. After the reaction, ethyl acetate was added to dilute the reaction mixture and the organic layer was simply decanted, assisted by the use of a magnet, to afford the desired products. The MNP catalyst is quickly concentrated to the side wall of the reaction vial once a magnet is placed nearby (Fig. 2, c). The separated catalyst was directly used for the next run without any pretreatment. No extra acid, *e.g.* TFA and TfOH, was needed in the recycling experiments, suggesting the initially formed diamine–Brønsted acid bifunctional moiety was maintained in the extensive recycling and reuse. Thus, the catalyst could be

Table 3 Recycle and reuse of catalyst **2**[a]



Cycle	Time/h	*anti* : *syn*[b]	Yield (%)[c]	Ee (%)[d]
1	24	11 : 1	98	98
2	24	11 : 1	97	95
3	24	11 : 1	98	94
4	24	12 : 1	98	97
5	24	11 : 1	98	95
6	24	13 : 1	97	96
7	24	12 : 1	96	96
8	24	9 : 1	95	93
9	24	3 : 1	95	86
10	24	3 : 1	92	87
11	24	4 : 1	90	89

[a] 0.25 mmol reaction in 0.1 mL water. [b] Determined by ^{1}H NMR. [c] Isolated yields. [d] Ee value of *anti* isomer, determined by chiral HPLC.

reused nine times with essentially no loss of activity and enantioselectivity in the reaction of acetone (Table 1, entry 7, for details see Table S3 in ESI†). The recyclability and reusability were also examined in the reaction of cyclohexanone, showing unchanged activity in up to eleven cycles with slightly reduced stereoselectivity in the last three cycles (Table 3). TEM images showed that after eleven reuses catalyst **2** still maintained nanospheric dimensions as well as the silica coating but with slight aggregation (Fig. 2, b). These results prove the robustness of the MNP-supported primary amine catalysts.

In conclusion, we have developed the first example of MNP-supported chiral primary amine catalysts. The MNP-supported catalyst **2** demonstrated high activity and stereoselectivity in the enamine-based direct aldol reactions. The reactions occurred smoothly under "on-water" conditions and the catalysts could be easily recycled *via* magnetic force and reused for up to 11 times with essentially no lose of activity and stereoselectivity. Further development of MNP-supported catalysts using the diaminocyclohexane skeleton is currently under way in our laboratory.

This work was supported by the Natural Science Foundation of China (NSFC 20421202 20632060 and 20702052), the Ministry of Science and Technology (MoST) and the Institute of Chemistry, Chinese Academy of Sciences (ICCAS).

Notes and references

1 For recent examples, see: (*a*) S. G. Davies, R. L. Sheppard, A. D. Smith and J. E. Thomson, *Chem. Commun*., 2005, 3802–3804; (*b*) Z. Jiang, Z. Liang, X. Wu and Y. Lu, *Chem. Commun*., 2006, 2801–2803; (*c*) S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc*., 2007, **129**, 288–289; (*d*) H. Huang and E. N. Jacobsen, *J. Am. Chem. Soc*., 2006, **128**, 7170–7171; (*e*) M. P. Lalonde, Y. G. Chen and E. N. Jacobsen, *Angew. Chem., Int. Ed*., 2006, **45**, 6366–6370; (*f*) S. B. Tsogoeva and S. Wei, *Chem. Commun*., 2006, 1451–1453; (*g*) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes and Y. Xu, *Chem.–Eur. J*., 2006, **12**, 5383–5397; (*h*) A. Córdova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist and W.-W. Liao, *Chem. Commun*., 2005, 3586; (*i*) W. Zou, I. Ibrahem, P. Dziedzic, H. Sundén and A. Córdova, *Chem. Commun*., 2005, 4946; (*j*) I. Ibrahem, W. Zou, M. Engqvist, Y. Xu and A. Córdova, *Chem.–Eur. J*., 2005, **11**, 7024; (*k*) Y. Xu, W. Zou, H. Sundén, I. Ibrahem and A. Córdova, *Adv. Synth. Catal*., 2006, **348**, 418; (*l*) Y. Xu and A. Córdova, *Chem. Commun*., 2006, 460; (*m*) Y. Liu, H. Cui, Y. Zhang, K. Jiang, W. Du, Z. He and Y. Chen, *Org. Lett*., 2007, **9**, 3671–3674; (*n*) L. Cheng, X. Han, H. Huang, M. Wong and Y. Lu, *Chem. Commun*., 2007, 4143–4145; (*o*) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F. Tanaka and C. F. Barbas, III, *Angew. Chem., Int. Ed*., 2007, **46**, 5572–5575; (*p*) N. Utsumi, M. Imai, F. Tanaka, S. S. V. Ramasastry and C. F. Barbas, III, *Org. Lett*., 2007, **9**, 3445–3448; (*q*) X. Wu, Z. Jiang, H.-M. Shen and Y. Lu, *Adv. Synth. Catal*., 2007, **349**, 812–816; (*r*) X.-Y. Xu, Y.-Z. Wang and L.-Z. Gong, *Org. Lett*., 2007, **9**, 4247–4249.

2 For heterogenization of organocatalysts, see: (*a*) M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev*., 2003, **103**, 3401–3429; (*b*) M. Benaglia, *New J. Chem*., 2006, **30**, 1525–1533; (*c*) F. Cozzi, *Adv. Synth. Catal*., 2006, **348**, 1367–1390; For selected reviews of organocatalysis, see: (*d*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed*., 2004, **43**, 5138; (*e*) A. Berkessel and H. Groger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; (*f*) J. Seayad and B. List, *Org. Biomol. Chem*., 2005, **3**, 719–724.

3 For examples, see: (*a*) R. K. Zeidan, S. J. Hwang and M. E. Davis, *Angew. Chem., Int. Ed*., 2006, **45**, 6332–6335; (*b*) R. K. Zeidan and M. E. Davis, *J. Catal*., 2007, **247**, 379–382; (*c*) S. Huh, H.-T. Chen, J. W. Wiench, M. Pruski and V. S.-Y. Lin, *Angew. Chem., Int. Ed*., 2005, **44**, 1826–1830.

4 (*a*) S. Z. Luo, H. Xu, J. Y. Li, L. Zhang and J.-P. Cheng, *J. Am. Chem. Soc*., 2007, **129**, 3074–3075; (*b*) S. Z. Luo, H. Xu, L. Zhang, J. Y. Li and J.-P. Cheng, *Org. Lett*., 2008, **10**, 653–656; (*c*) S. Z. Luo, J. Y. Li, L. Zhang, H. Xu and J.-P. Cheng, *Chem.–Eur. J*., 2008, **14**, 1273–1281; (*d*) S. Z. Luo, H. Xu, L. J. Chen and J.-P. Cheng, *Org. Lett*., 2008, **10**, 1775.

5 For examples, see: (*a*) T.-J. Yoon, W. Lee, Y.-S. Oh and J.-K. Lee, *New J. Chem*., 2003, **27**, 227; (*b*) A.-H. Lu, W. Schmidt, N. Matoussevitch, H. Bönnemann, B. Spliethoff, B. Tesche, E. Bill, W. Kiefer and F. Schüth, *Angew. Chem., Int. Ed*., 2004, **43**, 4303; (*c*) H. M. R. Gardimalla, D. Mandal, P. D. Stevens, M. Yen and Y. Gao, *Chem. Commun*., 2005, 4432; (*d*) P. D. Stevens, J. Fan, H. M. R. Gardimalla, M. Yen and Y. Gao, *Org. Lett*., 2005, **7**, 2085; (*e*) Y. Zheng, P. D. Stevens and Y. Gao, *J. Org. Chem*., 2006, **71**, 537; (*f*) D. Lee, J. Lee, H. Lee, S. Jin, T. Hyeon and B. M. Kim, *Adv. Synth. Catal*., 2006, **348**, 41; (*g*) R. Abu-Reziq, H. Alper, D. Wang and M. L. Post, *J. Am. Chem. Soc*., 2006, **128**, 5279; (*h*) N. T. S. Phan, C. S. Gill, J. V. Nguyen, Z. J. Zhang and C. W. Jones, *Angew. Chem., Int. Ed*., 2006, **45**, 2209–2212; (*i*) N. T. S. Phan and C. W. Jones, *J. Mol. Catal. A: Chem*., 2006, **253**, 123–131.

6 A. Hu, G. T. Yee and W. Lin, *J. Am. Chem. Soc*., 2005, **127**, 12486.

7 (*a*) M. Kawamura and K. Sato, *Chem. Commun*., 2006, 4718; (*b*) C. Ó. Dálaigh, S. A. Corr, Y. Gun'ko and S. J. Connon, *Angew. Chem., Int. Ed*., 2007, **46**, 4329; (*c*) M. Kawamura and K. Sato, *Chem. Commun*., 2007, 3404; (*d*) S. Z. Luo, X. X. Zheng, H. Xu, X. L. Mi, L. Zhang and J.-P. Cheng, *Adv. Synth. Catal*., 2007, **349**, 2431.

8 For a review, see: A. G. Doyle and E. N. Jacobsen, *Chem. Rev*., 2007, **107**, 5713.

9 T.-J. Yoon, J. S. Kim, B. G. Kim, K. N. Yu, M.-H. Cho and J.-K. Lee, *Angew. Chem., Int. Ed*., 2005, **44**, 1068–1071.

10 Compound **1** was easily polymerized when concentrated, the toluene solution of **1** was therefore used directly without purification. Consistent purity (>90%) was maintained in different batches as proved by NMR.

11 Catalyst **3** was prepared without the silica coating.

12 For an example of on-water reaction, see: S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed*., 2005, **44**, 3275–3279; For a review on asymmetric heterogeneous aqueous catalysis, see: Y. Uozumi, *Pure Appl. Chem*., 2007, **79**, 1481.