Catal Lett (2010) 137:104–109
DOI 10.1007/s10562-010-0341-0

Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalyzed by SBA-15 Supported Ir(I) Complex Under Mild Conditions

**Yanbin Shen · Qiu Chen · Lan-Lan Lou · Kai Yu ·
Fei Ding · Shuangxi Liu**

Received: 19 January 2010 / Accepted: 3 April 2010 / Published online: 15 April 2010

Abstract A heterogeneous catalyst of Ir(I)-9-amino *epi*-cinchonine complex immobilized on the surface of mesoporous SBA-15 was firstly synthesized and used in the asymmetric transfer hydrogenation of aromatic ketones. Enhanced enantioselectivity compared with homogeneous catalyst was obtained at room temperature. Furthermore, the heterogeneous system with very low leaching of iridium can be easily regenerated.

Keywords 9-Amino *epi*-cinchonine · Immobilization · Asymmetric transfer hydrogenation

1 Introduction

Chiral secondary aromatic alcohols constitute one of the most important classes of building blocks in organic synthesis [1–7]. Asymmetric transfer hydrogenation of ketones is an attractive method to prepare chiral alcohols. Although a variety of homogeneous chiral Ir, Rh and Ru catalysts have been proved to be highly enantioselective in the asymmetric transfer hydrogenation of prochiral ketones [8–11], most of them have not been industrialized due to the high cost of noble metals and chiral ligands as well as the difficulties in removing trace amounts of toxic metals from organic products. To overcome these problems, homogeneous chiral catalysts can be immobilized on various supports such as organic polymers and inorganic supports. However, the heterogenized catalysts, in most cases, always suffer from lower catalytic activity and enantioselectivity compared to their homogeneous counterparts [12–14].

Cinchona alkaloids have a long and proud history in the field of asymmetric synthesis. Nowadays, cinchona alkaloids and their synthetic derivatives have been widely used in the asymmetric reaction. In particular, an osmium catalyst bearing cinchona alkaloid-type ligand has been well studied for asymmetric dihydroxylation of olefins [15–21]. In 2006, a catalyst with 9-amino cinchona alkaloids as ligand has been found to be effective in the asymmetric transfer hydrogenation of ketones, the catalyst could be recycled under homogeneous conditions, but it could not be recovered totally, and high iridium leaching was observed in the recycling process [22, 23].

Recently, the mesoporous materials as supports for chiral catalysts have drawn much more attention. The large surface area and ordered mesopore channels of mesoporous materials can help avoid the aggregation of catalytic active species and maintain excellent stereocontrol performance. The commercial availability of cinchona alkaloids and the virtues of mesoporous materials as supports encouraged us to investigate the heterogeneous catalysts' utility in asymmetric transfer hydrogenation. More importantly, they can be easily recycled via simple filtration.

In this paper, we report a highly ordered mesoporous SBA-15 anchored 9-amino *epi*-cinchonine-$[Ir(COD)Cl]_2$ complex for asymmetric transfer hydrogenation of aromatic ketones at room temperature. Enhancement of enantioselectivity was expected to be obtained from the heterogeneous catalyst due to the confinement effects of SBA-15 channel. The metal leaching during the reaction will be another concern. To the best of our knowledge, this is the first report on immobilization of 9-amino *epi*-cinchonine onto mesoporous materials.

Y. Shen · Q. Chen · L.-L. Lou · K. Yu · F. Ding · S. Liu (✉)
Institute of New Catalytic Materials Science, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China
e-mail: sxliu@nankai.edu.cn

2 Experimental

2.1 Preparation of 9-Amino *epi*-Cinchonine

9-Amino *epi*-cinchonine was synthesized following the method in literature [24]. 9-Amino *epi*-cinchonine **1** (slightly yellow oil, yield 65.2%). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85–0.99 (m, 1H), 1.08–1.15 (m, 1H), 1.48–1.60 (m, 3H), 2.05(s, 2H), 2.24–2.26 (m, 1H), 2.90–3.10 (m, 5H), 4.79 (d, J = 8.1 Hz, 1H), 5.01–5.04 (m, 2H), 5.87 (m, 1H), 7.54–8.36 (m, 5H), 8.91 (d, J = 4.5 Hz, 1H); IR (CH_2Cl_2) v 3392, 3308, 3056, 2952, 2868, 1663, 1637, 1590, 1569, 1506, 1459, 1260 cm^{-1}.

2.2 Preparation of Catalyst

The synthesis procedure towards the catalyst is shown in Scheme 1. The parent silica SBA-15 was prepared following the reported procedure [25]. The template was removed by calcination at 823 K in air for 6 h. Calcined SBA-15 (0.60 g) was treated with 0.90 mL of (3-mercaptopropyl)trimethoxysilane in refluxing anhydrous toluene for 24 h. The solid was washed with toluene followed by Soxhlet extraction with dichloromethane and dried under vacuum for 1 h, resulting in 1.73 mmol of S element per g of modified SBA-15 calculated from TG result. The sample is denoted as SH-SBA-15. Then 0.60 g of SH-SBA-15 was suspended in chloroform and refluxed with 0.22 g of 9-amino *epi*-cinchonine **1** and 0.06 g of AIBN as radical initiator for 24 h [26]. The sample was filtered followed by washing with chloroform, Soxhlet extraction and drying under vacuum for 1 h to yield **2** (1.74 wt% of N). The resulting catalyst was prepared in situ by mixing the solid **2** with $[Ir(COD)Cl]_2$ in *i*-propanol at room temperature for 4 h under N_2.

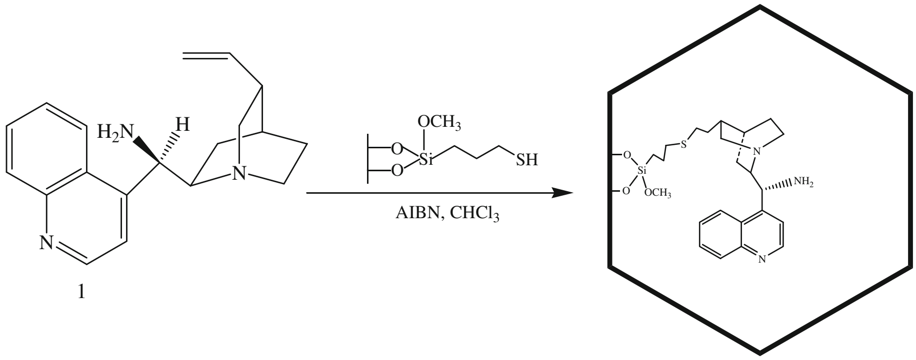
2.3 Characterization

Ir loading in the reaction solution was determined by inductively coupled plasma-atomic emission spectrometry (ICP-AES) on an ICP-9000 (N + M) spectrometer (TJA Co.). To accomplish this measurement, the solution was vapourized and then the sample was calcined. The remaining residue was dissolved in hydrogen fluoride and then dissolved by 5% hydrogen chloride. ^{1}H NMR spectra were recorded at 300 MHz using a Varian Mercury Vx-300 spectrometer. FT-IR spectra were recorded on a Bruker Vector 22 spectrometer using self-supporting wafers. Powder XRD patterns of the samples were obtained using a R/max-2500 diffractometer with Cu Kα source and a step size of 0.02°. Elemental analysis was conducted with a Perkin–Elmer 240C analyzer. N_2 adsorption–desorption analysis was carried out at 77 K on a Micromeritics TriStar 3000 apparatus. The analytical data were processed by the BET equation for surface areas and by the BJH model for pore size distributions. Enantiomeric excess (ee) values were determined by GC with β-DEX 325 chiral column, using a GC-7800 chromatograph equipped with a flame ionization detector.

2.4 Typical Procedure for the Asymmetric Transfer Hydrogenation

A general reaction run was as follows: $[Ir(COD)Cl]_2$ (8.4 mg) and the solid **2** (60.3 mg) were added to 5 mL of dry degassed *i*-propanol and stirred at room temperature for 4 h under N_2. Then KOH (2.8 mg) was added and the reaction mixture was stirred for another 10 min. The ketone was then added in portion (0.25 mmol) and the reaction was conducted at room temperature for two days. The reaction mixture was filtered and the reaction products were analyzed by GC. The homogeneous reaction was carried out with 9-amino *epi*-cinchonine (7.3 mg), $[Ir(COD)Cl]_2$ (8.4 mg), KOH (2.8 mg) and substrate (0.25 mmol) in 5 mL of *i*-propanol, at room temperature for 2 days.

After completion of the asymmetric transfer hydrogenation reaction, the heterogeneous catalyst was separated by filtration and then subjected to the next run with a new batch of KOH and the substrate, without the addition of any $[Ir(COD)Cl]_2$ or ligand.



Scheme 1 Depiction of the *epi*-cinchonine bound inside the hexagonal pores of SBA-15

3 Results and Discussion

3.1 Characterization of the Catalyst

SBA-15 possesses good thermal and hydrothermal stability, large surface area, well-ordered pore arrays and uniform pore size distribution. In this work, calcined SBA-15 is applied as the support for 9-amino *epi*-cinchonine **1**. The SH-SBA-15, sample **2** and catalyst of Ir(I)-9-amino *epi*-cinchonine complex were characterized by FT-IR spectroscopy, element analysis, N_2 adsorption-desorption experiments, powder XRD and ICP-AES. The FT-IR spectrum of SH-SBA-15 showed a vibration band at 2575 cm^{-1} assigned to SH group (Fig. 1a). The spectrum of **2** showed a absorption band at 1595 cm^{-1} assigned to the –C=N– stretchings of the quinoline ring, bands at 1511 and 1459 cm^{-1} which are presented in the spectrum of 9-amino *epi*-cinchonine can also be observed. These observations, together with the absence of the band attributed to SH group at 2575 cm^{-1}, demonstrated the successful immobilization of chiral 9-amino *epi*-cinchonine onto the SBA-15. The element analysis of **2** confirmed immobilization of 0.41 mmol/g of 9-amino *epi*-cinchonine **1**. The leaching of Ir from catalyst into the solution was determined by ICP, only $5.9 \times 10^{-2}\%$ Ir was detected in the liquid phase after the first run, which indicates that the Ir(I) complex is strongly bonded on the support.

The powder XRD pattern of **2** is showed in Fig. 2. Similar to calcined pure SBA-15, sample **2** showed one intense peak and two weak peaks indexable as (100), (110), and (200) reflections, respectively, suggesting that the hexagonal mesoporous structure (*p6mm*) could be well preserved. The decrease in the XRD peak intensity indicated that the modification and immobilization might disturb the ordered mesoporous structure to a certain degree. The N_2 adsorption–desorption isotherms and pore size distributions in Fig. 3 revealed that all of the SBA-15, SH-SBA-15 and **2** exhibited an isotherm typical of type IV with a steep increase in adsorption at $P/P_0 = 0.6$–0.8. A narrow and well-ordered mesopores can be observed in the pore size distribution. Some structural parameters are listed in Table 1. It's found

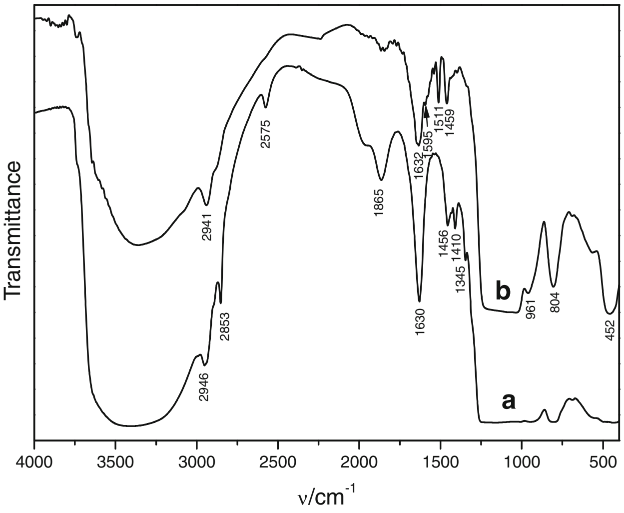


Fig. 1 FT-IR spectra of **a** SH-SBA-15 and **b** **2**

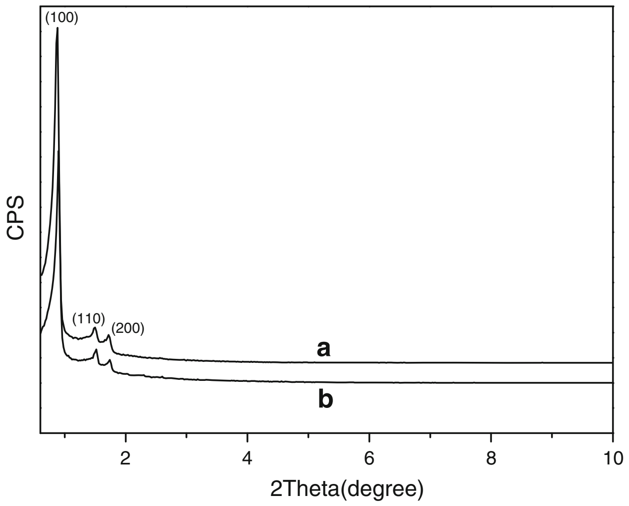


Fig. 2 Powder XRD patterns of **a** calcined SBA-15 and **b** **2**

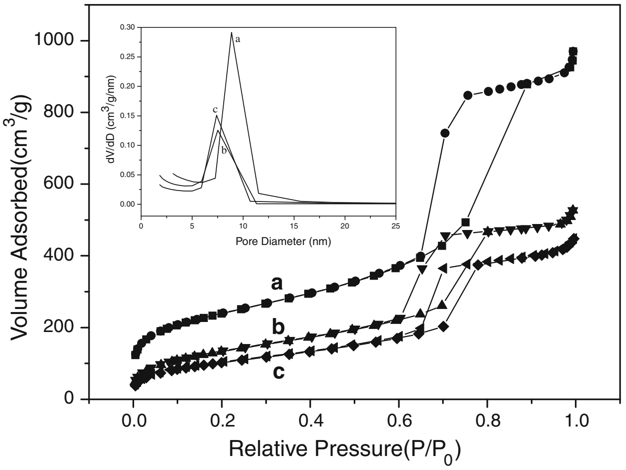


Fig. 3 N_2 adsorption-desorption isotherms and pore size distributions of **a** SBA-15, **b** SH-SBA-15 and **c** **2**

Table 1 Pore structural parameters of various materials

Sample	Mesopore volume (cm^3/g)	Surface area (m^2/g)	Pore diameter (nm)
Calcined SBA-15	1.37	859	8.8
SH-SBA-15	0.73	499	7.5
2	0.63	382	7.4
Fresh catalyst	0.34	227	5.0
Used catalyst[a]	0.27	193	4.4

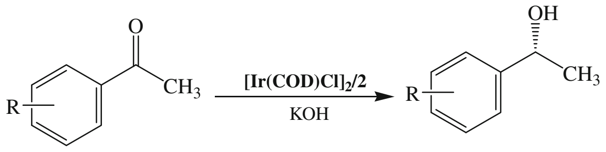
[a] The catalyst used for three runs

that incorporation of mercaptopropyl groups and ligands onto SBA-15 resulted in a gradual decrease in BET surface area, pore volume and pore size. This could be attributed to the coverage of pore surface of the calcined SBA-15 with mercaptopropyl groups and 9-amino *epi*-cinchonine, leading to an increase in the wall thickness.

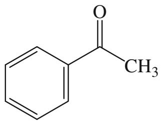
3.2 Catalytic Studies

The catalytic activity of catalyst was explored in the asymmetric transfer hydrogenation of aromatic ketones. *i*-Propanol serving as H-donor was applied in the Ir-catalyzed asymmetric reaction. The initial heterogeneous experiments were carried out using the acetophenone as a model substrate, as shown in Table 2, the asymmetric transfer hydrogenation reaction at room temperature provided (*S*)-1-phenylethanol in 94.0% conversion and 66.0% ee. This ee value is higher than the corresponding homogeneous catalyst (60.1%, entry 2 in Table 2). The increase in ee value may be mainly attributed to the confinement effects originating from the regular and adjustable pores of the support, which can give rise to significant effects on the microenvironment of the active sites [27–29]. On the basis of the excellent result, a series of aromatic ketones were examined as substrates in this work, in order to investigate the effects of the electronic property and position of substituent in the acetophenone. In general, substituted acetophenone was less effective than acetophenone under similar conditions. Electron donating substituent in the *ortho*-position, gave the product in higher ee value but with lower conversion compared with electron-withdrawing substituent (Table 2, entry 5 vs 3 and 7). Aromatic ketone incorporating chlorine group in the *ortho*-position afforded higher catalytic activity and enantioselectivity than that with the same group in the *para*-position (entry 7 vs 9). These results indicate that, unlike the reported results [30, 31], the catalytic activity and enantioselectivity of the reaction were affected by the electronic property and position of substituent. In view of the low catalytic activity of substituted acetophenones over heterogeneous catalyst,

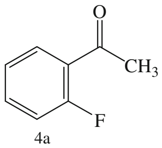
Table 2 Asymmetric transfer hydrogenation of aromatic ketones[a]



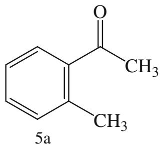
3a-7a 3b-7b



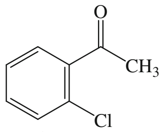
3a



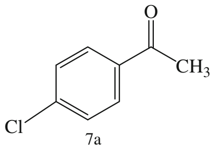
4a



5a



6a



7a

Entry	Substrate	Temp (K)	Conv. (%)[b]	ee (%)[c]
1	3a	298	94.0	66.0
2[d]	3a	298	97.6	60.1
3	4a	298	64.1	59.2
4[d]	4a	298	>99	54.5
5	5a	298	32.8	78.3
6[d]	5a	298	99.3	74.7
7	6a	298	80.0	64.6
8[d]	6a	298	98.3	63.9
9	7a	298	74.8	47.6
10[d]	7a	298	97.8	45.3
11	5a	313	53.5	69.8

[a] Reactions were performed in isopropanol for 2 days with ketone-Ir-ligand-KOH = 1:0.05:0.1:0.2

[b] Conversion % determined by GC with chiral column

[c] ee % determined by GC with BETA-DEX 325 chiral column. The absolute configuration was *S*

[d] Reaction performed using the homogeneous catalyst

Table 3 Recycle studies of the heterogeneous catalyst in the asymmetric transfer hydrogenation of acetophenone[a]

Entry	Conv. (%)	ee (%)	Leaching of Metal (%)
0	94.0	66.0	5.9×10^{-2}
1	97.8	67.0	1.4×10^{-2}
2	98.1	65.0	7.4×10^{-3}
3	53.3	58.4	6.3×10^{-3}
4[b]	95.7	64.6	–

[a] Reactions were performed in isopropanol at 298 K for 2 days

[b] The catalyst was washed thoroughly with isopropanol, acetone, ether and hexane

we just investigated the effects of temperature by using 2-methylacetophenone as a substrate. As the temperature was increased to 313 K, the catalytic activity increased from 32.8 to 53.5% for conversion (entries 5 and 11) but the enantioselectivity decreased slightly. It revealed that the enhancement of reaction temperature had a favourable effect on the catalytic activity. Next, the further investigation is necessary to give a detailed understanding of the factors that influenced the reaction.

Recovery and reusability of the catalytic system was evaluated by carrying out consecutive cycles for acetophenone. The catalyst was carefully separated from the reaction mixture by simple filtration and dried in a vacuum without any other treatment. It was found that the catalyst run 3 times still afforded almost the same conversion and ee value as the first run (Table 3, entries 0–2). But for the fourth run, both the ee value and conversion were observed to fall. To make clear what is responsible for the drop in the activity and enantioselectivity, the catalyst after three runs was characterized by TEM and N_2 adsorption-desorption experiments. The well-ordered array of channels can be clearly observed by TEM as shown in Fig. 4, indicating that the mesoporous structure of the catalyst retained good periodicity after three runs. The used catalyst was found to have a surface area of 193 m^2/g and a narrow distribution of pore size with a maximum at 4.4 nm as shown in Table 1, which is smaller than that of the fresh catalyst. Therefore, after the fourth run the catalyst was washed thoroughly with solvents. Excitingly, 95.7% conversion and 64.6% ee were observed in the fifth run, which is quite comparable to the conversion and ee of the first run. Thus the reason for the drop in activity and enatioselectivity is possibly that the catalytic active sites are covered by the adsorbed reactant, product, or impurities during the reaction. Iridium leaching from each recycle is also presented in Table 3, the amount of Ir leaching in the four runs was 5.9×10^{-2}%, 1.4×10^{-2}%, 7.4×10^{-3}% and 6.3×10^{-3}%, respectively. Total Ir leaching for four runs was less than 0.1%, which is lower than previous reports [23, 32, 33]. This noticeably low Iridium leaching might be resulted from the stable coordination of Ir-N complex, and also be owing to the formation of a strong bond between Ir(I) complexes and mesoporous SBA-15. Moreover, no further increase in the conversion occurred while fresh reactant was added to the filtrate after each reaction.

4 Conclusion

In summary, for the first time, 9-amino *epi*-cinchonine ligand was immobilized on mesoporous silica SBA-15 to produce an effective heterogeneous catalyst for the asymmetric transfer hydrogenation of aromatic ketones. This heterogeneous catalyst showed enhanced enantioselectivity compared to the corresponding homogeneous analogue. Moreover, total Ir leaching during four runs of the catalyst was less than 0.1%. The catalyst could be easily regenerated by solvent washing.

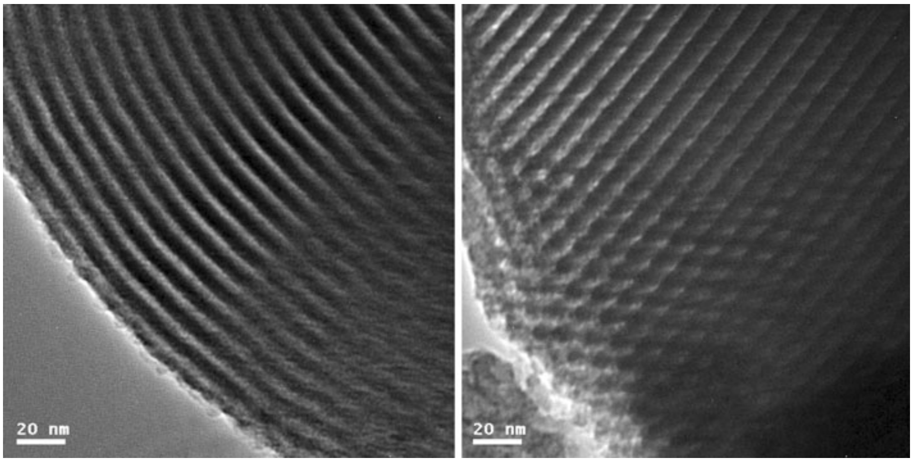


Fig. 4 TEM micrograph of the catalyst after three runs

Acknowledgements The authors are grateful to the National Natural Science Foundation of China (20773069) and the Research Fund for the Doctoral Program of Higher Education of China (200800551017) for financial support.

References

1. Ohkuma T, Doucet H, Pham T, Mikami K, Korenaga T, Terada M, Noyori R (1998) J Am Chem Soc 120:1086
2. Mikami K, Korenaga T, Yusa Y, Yamanaka M (2003) Adv Synth Catal 345:246
3. Sandoval CA, Ohkuma T, Muñiz K, Noyori R (2003) J Am Chem Soc 125:13490
4. Jing Q, Zhang X, Sun J, Ding K (2005) Adv Synth Catal 347:1193
5. Burk S, Franciò G, Leitner W (2005) Chem Commun 3460
6. Wu XF, Vinci D, Ikariyab T, Xiao JL (2005) Chem Commun 4447
7. Trindade AF, Gois PMP, Afonso CAM (2009) Chem Rev 109:418
8. Noyori R, Ohkuma T (2001) Angew Chem Int Ed 40:40
9. Gladiali S, Alberico E (2006) Chem Soc Rev 35:226
10. Wu XF, Li XH, Zanotti-Gerosa A, Pettman A, Liu JK, Mills AJ, Xiao JL (2008) Chem Eur J 14:2209
11. Aydemir M, Baysal A, Meric N, Gumgum B (2009) J Organomet Chem 694:2488
12. Bayston DJ, Travers CB, Polywka MEC (1998) Tetrahedron Asymmetr 9:2015
13. Sandee AJ, Petra DGI, Reek JNH, Kamer PCJ, van Leeuwen PWNM (2001) Chem Eur J 7:1202
14. Parambadath S, Singh AP (2009) Catal Today 141:161
15. Jacobsen EN, Markd I, Mungall WS, Schroder G, Sharpless KB (1988) J Am Chem Soc 110:1968
16. Kolb HC, VanNieuwenhze MS, Sharpless KB (1994) Chem Rev 94:2483
17. Lohray BB, Nandanan E, Bhushan V (1996) Tetrahedron Asymmetr 7:2805
18. Song CE, Yang JW, Ha H-J (1997) Tetrahedron Asymmetr 8:841
19. Lee HM, Kim S-W, Hyeon T, Kim BM (2001) Tetrahedron Asymmetr 12:1537
20. Motorina I, Crudden CM (2001) Org Lett 3:2325
21. Choudary BM, Chowdari NS, Jyothi K, Kantam ML (2002) Catal Lett 82:99
22. He W, Liu P, Zhang BL, Sun XL, Zhang SY (2006) Appl Organometal Chem 20:328
23. He W, Zhang BL, Jiang R, Liu P, Sun XL, Zhang SY (2006) Tetrahedron Lett 47:5367
24. Vakulya B, Varga S, Csámpai A, Soós T (2005) Org Lett 7:1967
25. Zhao DY, Feng JL, Huo Q, Melosh N, Fredrickson GH, Chmelka BF, Stucky GD (1998) Science 279:548
26. Yu P, He J, Guo CX (2008) Chem Commun 2355
27. Raynor SA, Thomas JM, Raja R, Johnson BFG, Bell RG, Mantle MD (2000) Chem Commun 1925
28. Basu S, Paul H, Gopinath CS, Bhaduri S, Lahiri GK (2005) J Catal 229:298
29. Li C, Zhang HD, Jiang DM, Yang QH (2007) Chem Commun 547
30. Liu GH, Yao M, Wang JY, Lu XQ, Liu MM, Zhang F, Li HX (2008) Adv Synth Catal 350:1464
31. Liu GH, Liu MM, Sun YQ, Wang JY, Sun CS, Li HX (2009) Tetrahedron Asymmetr 20:240
32. Maillard D, Pozzi G, Quici S, Sinou D (2002) Tetrahedron 58:3971
33. Yang CF, Jiang HY, Feng J, Fu HY, Li RX, Chen H, Li XJ (2009) J Mol Catal A 300:98