# Asymmetric transfer hydrogenation over Ru–TsDPEN catalysts supported on siliceous mesocellular foam†

**Xiaohua Huang[a] and Jackie Y. Ying*[ab]**

*Received (in Cambridge, UK) 26th October 2006, Accepted 8th January 2007*
*First published as an Advance Article on the web 8th February 2007*
**DOI: 10.1039/b615564b**

**A siliceous mesocellular foam-immobilized Ru–TsDPEN complex exhibited excellent catalytic reactivity, enantioselectivity and reusability in the asymmetric transfer hydrogenation of an imine and ketones.**

Since Noyori *et al.*'s first report of the ruthenium–(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine [(*S*,*S*)-TsDPEN] complex as a highly effective and enantioselective catalyst in the asymmetric transfer hydrogenation of carbonyl and imino groups,[1] this catalyst has been widely explored for various reaction profiles of substrates and experimental conditions.[2] For practical and environmentally friendly application in industrial processes, this catalyst has been immobilized onto insoluble supports by several groups.[3] A heterogenized catalyst allows for ease of separation from the products by filtration and centrifugation, and enables expensive complexes to be readily recovered for reuse.

Compared to polymeric matrices that are often used for anchoring organometallic complexes, silica supports have the advantage of high mechanical strength, chemical robustness, and thermal stability.[4] Silica could also be tailored with different pore structure and particle morphology. In particular, mesoporous silica has emerged as a new class of nanostructured material, with successful applications in catalysis, membrane separation, electronics and optics, *etc*.[5] Siliceous mesocellular foam (MCF) has a unique 3-dimensional pore structure, whose cell-like pores (20–50 nm) are connected by windows of a smaller opening (9–26 nm).[6,7] The ultralarge and uniform pore size of MCF would facilitate the mass transport of substrates,[8,9] and allow bulky catalytic complexes to be immobilized within the pores without steric effects. Herein, MCF and silica gel (which is commonly used for column chromatography) were employed as insoluble support materials for a chiral organoruthenium complex, and the activities of the resulting heterogenized catalysts were evaluated for asymmetric transfer hydrogenation.[10]

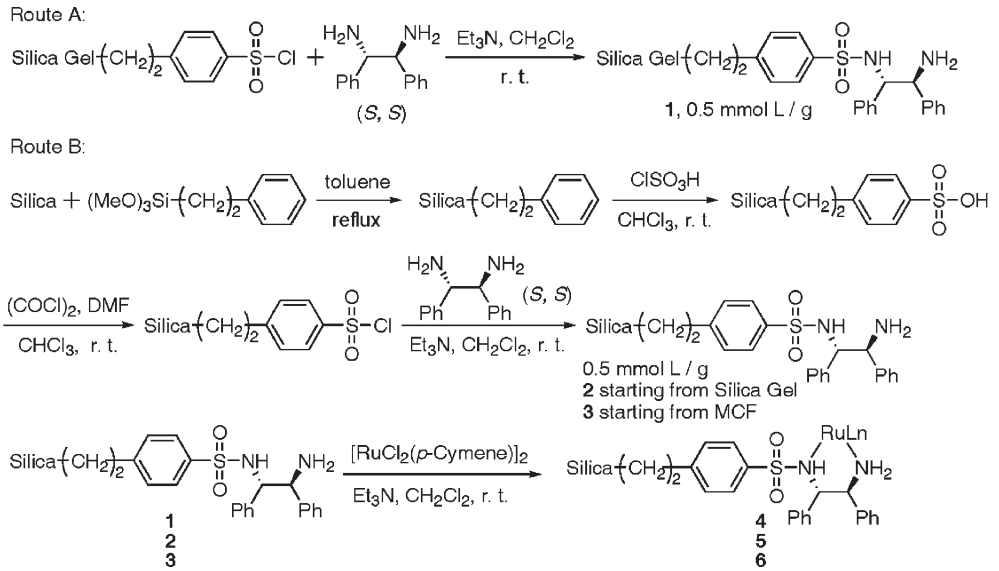
The chiral ligand, (*S*,*S*)-TsDPEN, was covalently grafted onto the silica supports through their surface silanol groups (Scheme 1). In route A, the commercially available 4-ethyl benzenesulfonyl chloride-functionalized silica gel (from Sigma-Aldrich) was stirred with (1*S*,2*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-DPEN] in dichloromethane using triethylamine as the base. The immobilized ligand obtained was designated as **1**. In route B, unfunctionalized silica gel was stirred with phenethyltrimethoxysilane in refluxing toluene for 24 h, followed by sulfonation using chlorosulfonic acid in chloroform to yield the immobilized 4-ethyl benzenesulfonic acid on silica gel.[11] Reacting this sulfonic acid with oxalyl chloride assisted by *N*,*N*-dimethylformamide (DMF) in dichloromethane produced the immobilized 4-ethyl benzenesulfonyl chloride on silica gel. Subsequent mixing of this material with [(*S*,*S*)-DPEN] in dichloromethane using triethylamine as the base provided the desired (*S*,*S*)-TsDPEN covalently grafted on silica gel, designated as **2**. Ligand **3** was also prepared by route B, except that MCF was employed as the support instead of silica gel. MCF was prepared with a surface area of 567 $m^2\ g^{-1}$, a pore size of 26 nm, a window size of 15 nm and a total pore volume of 1.9 $cm^3\ g^{-1}$, according to the published procedure.[7] The ligand immobilized on silica was characterized using several spectroscopic methods (see ESI†). In particular, Raman spectroscopy was employed to confirm the structure of the desired product. The ligand-immobilized MCF, **3**, was also characterized by nitrogen adsorption analysis. Compared to the MCF support, it possessed a lower surface area of 313 $m^2\ g^{-1}$, a smaller pore volume of 1.1 $cm^3\ g^{-1}$, and a smaller pore size (15 nm) and window size (10 nm). The significant reductions in pore volume, pore size and surface area of MCF after ligand immobilization could be attributed to the fixation of the ligands within the pore structure, instead of on the external surface of MCF. The chiral Ru–TsDPEN complex was generated *in situ* by mixing the immobilized ligand (**1**, **2** or **3**) with di-$\mu$-chlorobis[(*p*-cymene)chlororuthenium(II)] in a mixture of dichloromethane and triethylamine at room temperature for 1 h (see Scheme 1). The immobilized ruthenium complex on silica was designated as **4**, **5** or **6**, respectively.

1-Substituted 1,2,3,4-tetrahydroisoquinoline alkaloids, specifically salsolidine, have been of great interest to synthetic chemists because of their important physiological activities, especially that related to the pathogenesis of Parkinson's disease.[12] Thus, we have selected the preparation of salsolidine, starting from the imine and using transfer hydrogenation, as the model reaction to compare the catalytic reactivity and enantioselectivity of the immobilized Ru complexes (Table 1).

Catalyst **4**, which could be readily prepared from commercially available reagents, catalyzed the transfer hydrogenation using a formic acid–triethylamine complex (5 : 2) as the hydride source in excellent product yield (94%) and moderate enantioselectivity (78% ee) (Table 1). After the 12-h run, the catalyst was separated from the product and excess reagent by washing with $CH_2Cl_2$ and

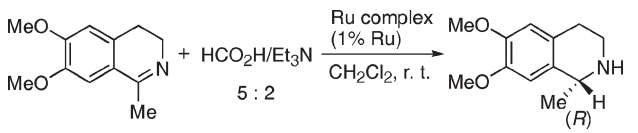
[a]*Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA*
[b]*Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669, Singapore. E-mail: jyying@ibn.a-star.edu.sg; Fax: (+65) 6478-9020*

† Electronic supplementary information (ESI) available: General experimental procedures, catalyst preparation, general procedure for transfer hydrogenation, characterization of products, physical mixture of Ru–TsDPEN and MCF, and catalyst performance optimization. See DOI: 10.1039/b615564b




**Scheme 1** Ligand and Ru complex preparation. Ligand loading is calculated from nitrogen analysis.

**Table 1** Enantioselective synthesis of salsolidine using catalysts **4**, **5** and **6**




| Entry | Ru Complex | Yield (%)[a] | ee (%)[b] | Successive runs |
|---|---|---|---|---|
| 1 | **4** | 94–95 | 78–81 | Two |
| 2 | **5** | 95–97 | 86–87 | Three |
| 3 | **6** | 95–100 | 90–91 | Six |

[a] Yields were based on GC analysis and isolated material. Configuration was determined from the sign of rotation of the product. [b] Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H).

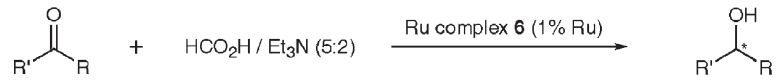
centrifugation. It was subjected to the second run by adding another batch of imine in $CH_2Cl_2$ and formic acid–triethylamine complex. Full conversion of imine, and 95% product yield with 81% ee were obtained in the second run. However, starting from the third run, a decrease in catalytic activity was observed, which led to the incomplete consumption of imine. Catalyst **5** provided a higher ee of 86%, but its reusability was limited to three consecutive runs. For catalysts **4** and **5**, the yields would decrease to 80% in the third and fourth runs, respectively, while the ee's remained the same (see Table S1 in ESI†).

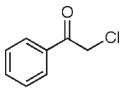
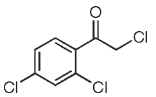
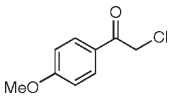
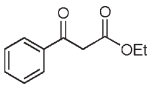
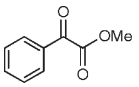
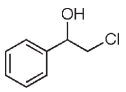
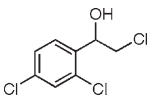
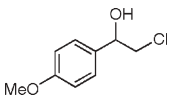
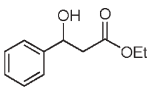
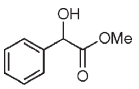
In contrast, catalyst **6** achieved salsolidine with an ee of 91%, with full conversion of the reactant and excellent product yield (100%). Its enantioselectivity was comparable to that obtained by the homogeneous Ru–TsDPEN catalyst,[13] but its reactivity was lower. The reduced activity of catalyst **6** might be attributed to the immobilization of another side-product on MCF, which could act as an inhibitory ligand to Ru.[14] Nevertheless, catalyst **6** successfully preserved its catalytic activity and excellent enantioselectivity after six consecutive runs.[15] In an attempt to further improve the reactivity and enantioselectivity of the catalyst, the reaction was run using the formic acid–triethylamine complex in other ratios (2 : 1 and 1 : 1) and other solvents (*e.g.* acetonitrile, DMF, ethyl acetate and tetrahydrofuran (THF)). The reaction was also run neat. These alternative conditions did not improve the catalytic performance, and, in some cases, inferior results were obtained. It has been reported that the capping of residual silanol groups on the silica gel surface could provide heterogenized catalysts with improved performance.[9,16] Thus, we tried to control the surface chemistry of our silica support by capping the silanol groups with hexamethyldisilazane (HMDS) or 1-(trimethylsilyl)imidazole. However, a significant loss of reactivity was observed in this case, probably due to the nonselective capping of amino groups in the ligand as well. To examine the metal retention in catalyst **6** after reaction, ruthenium content was analyzed for the solid catalyst after six consecutive runs and for the organic solution from each run after catalyst removal by centrifuge. 2–5 ppm of Ru were found to have leached into the organic solution from each run, which amounted to a total loss of ~11% of the loaded Ru after six runs. Elemental analysis of **6** after six runs showed 17% loss in Ru and 7% loss in ligand.

Encouraged by the performance and stability of catalyst **6**, this immobilized catalyst was further examined in the asymmetric transfer hydrogenation of ketones in 12-h runs (Table 2). 2-Chloroacetophenone was converted to chiral 2-chlorophenethanol by catalyst **6** with a yield of 94–100% and an ee of 97–98%. The ready conversion of 2-chlorophenethanol to styrene oxide, with retention of enantiopurity at the chiral benzylic carbon, in combination with the heterogeneous hydrogenation presents another practical method to prepare this important class of chiral building block.[17] A β-ketoester could also be readily converted to a β-hydroxyester in excellent yield (90–95%) and ee (96–97%) when isopropanol was used as the solvent at 45 °C. While only 71–73% ee could be achieved for the reaction with an α-ketoester as the substrate, this modest enantioselectivity was still noteworthy compared to the 59% ee obtained with the homogeneous Ru–TsDPEN catalyst.[18] In all the reactions presented in Table 2, catalyst **6** was used successfully over six runs with negligible changes in activities and enantioselectivities.

**Table 2** Asymmetric transfer hydrogenation of ketones using catalyst **6**




| | | | | | |
|---|---|---|---|---|---|
| Ketone |  |  |  |  |  |
| Product (*R*) |  |  |  |  |  |
| Solvent/temperature | $CH_2Cl_2$/rt | $CH_2Cl_2$/rt | $CH_2Cl_2$/rt | *i*PrOH/45 °C | *i*PrOH/rt |
| Yield (%)[a] | 94–100 | 97–99 | 88–94 | 90–95 | 95–98 |
| ee (%)[b] | 97–98 | 90–92 | 97 | 96–97 | 71–73 |

[a] Yields were based on GC analysis and isolated material. Configuration was determined from the sign of rotation of the product. [b] Enantiomeric excess was determined by HPLC analysis.

In summary, TsDPEN has been successfully anchored onto silica supports. Siliceous MCF was shown to be a superior support to conventional silica gel. The Ru complex immobilized on MCF demonstrated excellent reactivity, enantioselectivity and reusability in the asymmetric transfer hydrogenation of an imine and ketones.

This work was sponsored by the Singapore-MIT Alliance. The authors thank Timothy McClure (MIT Center for Materials Science and Engineering) for his assistance in Raman spectroscopy. This work made use of the National Science Foundation MRSEC Shared Experimental Facilities (DMR-02-13282) and Laser Facilities (CHE-01-11370) at MIT.

## Notes and references

1 S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 285.
2 R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; M. J. Palmer and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045.
3 C. Saluzzo and M. Lemaire, *Adv. Synth. Catal.*, 2002, **344**, 915 and references therein; X. Li, X. Wu, W. Chen, F. E. Hancock, F. King and J. Xiao, *Org. Lett.*, 2004, **6**, 3321; X. Li, W. Chen, W. Hems, F. King and J. Xiao, *Tetrahedron Lett.*, 2004, **45**, 951; Y.-C. Chen, T.-F. Wu, J.-G. Deng, H. Liu, Y.-Z. Jiang, M. C. K. Choi and A. S. C. Chan, *Chem. Commun.*, 2001, 1488.
4 E. F. Vansant, P. Van Der Voort and K. C. Vrancken, in *Studies in Surface Science and Catalysis*, ed. B. Delmon and J. T. Yates, Elsevier, Amsterdam, 1995, vol. 93; M. H. Valkenberg and W. F. Hölderich, *Catal. Rev. Sci. Eng.*, 2002, **44**, 321; C. E. Song and S.-g. Lee, *Chem. Rev.*, 2002, **102**, 3495.
5 A. Stein, B. J. Melde and R. C. Schroden, *Adv. Mater.*, 2000, **12**, 1403; J. Y. Ying, C. P. Mehnert and M. S. Wong, *Angew. Chem., Int. Ed.*, 1999, **38**, 56; J. Y. Ying, C. P. Mehnert, J. S. Lettow and D. Huang, *US Pat.*, 6 544 923, 2003; J. Y. Ying, *Chem. Eng. Sci.*, 2006, **61**, 1540.
6 D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka and G. D. Stucky, *Science*, 1998, **279**, 548; P. Schmidt-Winkel, W. W. Lukens, Jr., P. Yang, D. I. Margolese, J. S. Lettow, J. Y. Ying and G. D. Stucky, *Chem. Mater.*, 2000, **12**, 686; J. S. Lettow, Y. J. Han, P. Schmidt-Winkel, P. Yang, D. Zhao, G. D. Stucky and J. Y. Ying, *Langmuir*, 2000, **16**, 8291; J. S. Lettow, T. M. Lancaster, C. J. Glinka and J. Y. Ying, *Langmuir*, 2005, **21**, 5738.
7 P. Schmidt-Winkel, W. W. Lukens, Jr., D. Zhao, P. Yang, B. F. Chmelka and G. D. Stucky, *J. Am. Chem. Soc.*, 1999, **121**, 254.
8 Y.-J. Han, J. T. Watson, G. D. Stucky and A. Butler, *J. Mol. Catal. B: Enzym.*, 2002, **17**, 1; J. K. Park, S.-W. Kim, T. Hyeon and B. M. Kim, *Tetrahedron: Asymmetry*, 2001, **12**, 2931; Y. Han, S. S. Lee and J. Y. Ying, *Chem. Mater.*, 2006, **18**, 643.
9 T. M. Lancaster, S. S. Lee and J. Y. Ying, *Chem. Commun.*, 2005, 3577; S. S. Lee, S. Hadinoto and J. Y. Ying, *Adv. Synth. Catal.*, 2006, **348**, 1248; S. S. Lee and J. Y. Ying, *J. Mol. Catal. A: Chem.*, 2006, **256**, 219.
10 P. N. Liu, P. M. Gu, F. Wang and Y. Q. Tu, *Org. Lett.*, 2004, **6**, 169; P.-N. Liu, P.-M. Gu, J.-G. Deng, Y.-Q. Tu and Y.-P. Ma, *Eur. J. Org. Chem.*, 2005, 3221; P. N. Liu, J. G. Deng, Y. Q. Tu and S. H. Wang, *Chem. Commun.*, 2004, 2070. Mesoporous MCM-41 and SBA-15 were reported to be worse supports for the Ru–TsDPEN catalyst than silica gel in the asymmetric transfer hydrogenation.
11 R. D. Badley and W. T. Ford, *J. Org. Chem.*, 1989, **54**, 5437.
12 T. S. Kaufman, *Tetrahedron: Asymmetry*, 2004, **15**, 1203.
13 N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916; G. D. Williams, R. A. Pike, C. E. Wade and M. Wills, *Org. Lett.*, 2003, **5**, 4227.
14 The N/S molar ratio for *N*-sulfonylated-1,2-diamine should be 2, but the elemental analysis of ligand **3** showed a N/S molar ratio of 1.8 (see ESI†). The slight reduction in the N/S molar ratio could be due to the formation of small amounts of the *N*,*N*′-disulfonylated-1,2-diamine compound (which has a N/S molar ratio of 1) on MCF. Although an excess of 1,2-diphenylethylenediamine was used to react with 4-ethyl benzenesulfonyl chloride immobilized on MCF to suppress the formation of *N*,*N*′-disulfonylated-1,2-diamine, the latter was still found in small quantities on the high surface area MCF support. Consequently, catalyst **6** likely involved Ru supported by a mixture of *N*-sulfonylated-1,2-diphenylethylenediamine and *N*,*N*′-disulfonylated-1,2-diphenylethylenediamine ligands, giving a similar enantioselectivity but lower reactivity compared to the homogeneous Ru–TsDPEN catalyst.
15 A minimum of three batches of each catalyst (**4**, **5** and **6**) were prepared, and consistent reactivities were observed for each catalyst.
16 D. Rechavi and M. Lemaire, *Org. Lett.*, 2001, **3**, 2493; S. J. Bae, S.-W. Kim, T. Hyeon and B. M. Kim, *Chem. Commun.*, 2000, 31.
17 T. Hamada, T. Torii, K. Izawa, R. Noyori and T. Ikariya, *Org. Lett.*, 2002, **4**, 4373.
18 D. Sterk, M. S. Stephan and B. Mohar, *Tetrahedron Lett.*, 2004, **45**, 535.