ChemComm
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Aqueous enantioselective hydrogenation of methyl 2-acetamidoacrylate with Rh–MeDuPHOS occluded in PDMS

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Received (in Cambridge, UK) 10th October 2001, Accepted 21st November 2001
First published as an Advance Article on the web 7th February 2002

A new chiral heterogeneous catalytic system obtained by occlusion of the Rh–MeDuPHOS complex in a polydimethylsiloxane film was tested in the asymmetric hydrogenation of methyl 2-acetamidoacrylate in aqueous medium.

Over the past 30 years,[1] economic incentives[2] and scientific challenges have led to significant progress in the R&D of enantioselective homogeneous and heterogeneous catalysts for the production of pure enantiomers from prochiral substrates. Transition metal complexes with biphosphine ligands, such as BINAP [2,2-bis(diphenylphosphino)-1,1′-binaphthyl][3–5] and DuPHOS [1,2-bis(phospholano)benzene],[6–8] have proved to be excellent homogeneous catalysts in various asymmetric hydrogenation reactions. Attempts have been made to heterogenize these complexes so as to combine advantages of heterogeneous catalysts (high stability, facile catalyst recycling, and the possibility for continuous operation) with the inherent advantages of homogeneous catalysis (high activity and enantioselectivity).

Different approaches to the heterogenization of chiral metal complexes have recently been reviewed.[9,10] These include immobilization of chiral transition metal complexes *via* covalent bonding to organic[11] and inorganic[12] supports or *via* ionic interactions.[13] Potential alternatives to these methods are entrapment of metal complexes in silica matrices by sol–gel methods[14] or occlusion of the complexes in polydimethylsiloxane (PDMS) films.[15,16] A disadvantage of the methods described above for heterogenization of the catalysts is that recyling is impeded by leaching of the metal complex and/or loss of activity and enantioselectivity.[9,10]

Most organic chemical reactions take place in organic solvents, but the advantages of being able to use water as the solvent are self-evident: water is cheap, environmentally benign and non-hazardous. To the best of our knowledge, this paper reports the first successful asymmetric hydrogenation in an aqueous medium by means of the Rh–MeDuPHOS complex (Fig. 1) occluded in a PDMS matrix. The entrapped catalyst is well dispersed in the polymer matrix, and the strongly hydrophobic polymer selectively sorbs the organic substrate from the reaction mixture to facilitate the reaction.

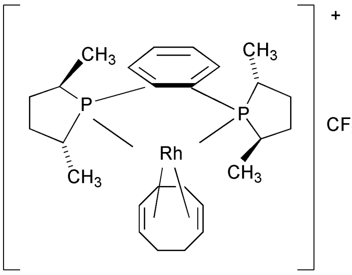


Fig. 1 Rh–MeDuPHOS complex.

DOI: 10.1039/b109234k

The chiral complex was heterogenized by occlusion in a PDMS film as previously reported.[15,16] Before curing, a weighed amount of silica (Hi-sil 233, Cabot, predried at 120 °C) was stirred into a mixture of PDMS and cross-linker in dichloromethane, followed by the addition of Pt catalyst (for cross-linking). Approximately 10 μmol of Rh–MeDuPHOS in a small volume of dichloromethane (~2 mL) was added dropwise to the PDMS solution. After 20 to 30 min, the homogeneous solution obtained was poured into a Petri dish to allow slow evaporation of the solvent and subsequent curing. Curing time of 5–6 h resulted in a ~1000 μm thick membrane. Leaching of the complex and solvent sorption were evaluated by immersing 2 g of the catalyst-entrapped PDMS film in 20 mL of various solvents. The extent of leaching of the metal complex from the polymer matrix was measured by analyzing the liquid phase on a PQ3/VG ICP-MS system with an accuracy of ~1 ppt. The sorption of the solvents was determined by weighing the film pieces before and after immersion in the solvent.

The asymmetric hydrogenation of methyl 2-acetamidoacrylate, a precursor of an alanine derivative, was selected as a test reaction (Scheme 1). A 25 mL reactor with a magnetic stirrer was used for both the homogeneous and the heterogeneous reactions. In heterogeneously catalyzed reactions, the film was added as pieces to the reaction medium under nitrogen atmosphere. Samples were withdrawn periodically to determine the reaction rate, and the enantiomeric excess as a function of time. The samples were analyzed by a Hewlet Packard GC on a chiral 7503 WCOT fused silica column (CP-Chiracil-Dex CB). Reuse of the catalyst was tested by replacing the liquid phase reaction and washing the PDMS film with the reaction solvent before addition of new substrate.

Selection of the solvent is a key element in the development of the heterogeneous catalytic system. In our previous study,[16] we focused on the preparation of the optimal polymer film with respect to catalytic activity. In this work, we dealt with the problem of catalyst leaching by choosing the type of solvent for the reaction so as to minimize leaching while preserving the activity and enantioselectivity of the catalyst. However, addi-

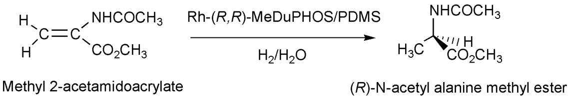
Table 1 Leaching of Rh–MeDuPHOS from PDMS films with 20 wt% silica and sorption of solvents in the polymer film (Conditions: 10 μmol of Rh–MeDuPHOS, 20 mL solvent, 25 °C, 24 h)

Solvent	Solubility of complex in solvent	Sorption of the solvent in PDMS (g/g)	% Leaching
Methanol	High	0.049	31
Dichloromethane	High	1.152	52
Xylene	Low	1.177	2.9
Heptane	Low	1.456	0.7
Water	Low	0.065	0.9
Xylene + methanol (10:1, v/v)	—	0.954	65
Water + methanol (10:1, v/v)	—	0.063	1

Table 2 Enantioselective hydrogenation of methyl 2-acetamidoacrylate with Rh–MeDuPHOS complex occluded in a PDMS film (Reaction conditions: 25 °C, 2 bars, 0.1 g methyl 2-acetamidoacrylate, 10 μmol catalyst, 15 mL solvent)

Catalyst	Solvent	Sorption of the solvent in PDMS (g/g)	TOF (h^{-1})[a]	Ee (%)
Homogeneous RhMeDuPhos	Methanol	—	320	99.1
Homogeneous RhMeDuPhos	Methanol/water[b]	—	210	99.0
RhMeDuPhos/PDMS (10 wt% Si)	Water	0.035	9.9	93.1
RhMeDuPhos/PDMS (15 wt% Si)	Water	0.037	10.6	92.8
RhMeDuPhos/PDMS (20 wt% Si)	Water	0.049	12.6	96.9
RhMeDuPhos/PDMS (20 wt% Si) (Reuse)[c]	Water	0.049	12.6	91.1
Pt catalyst/PDMS (10 wt% Si)[d]	Water	0.035	100	0

[a] After 3 h. [b] 9 mL methanol and 9 mL water. [c] Reuse of the catalysts from previous entry. [d] 0.4 μmol extra platinum crosslinking catalyst instead of Rh–MeDuPhOS.



Scheme 1 Asymmetric hydrogenation of methyl 2-acetamidoacrylate catalyzed by Rh–MeDuPHOS complex in PDMS.

tional considerations were taken into account, since in some cases the solvent acts as a temporary ligand in the catalytic cycle.[3] We found that leaching occurred with all the solvents that dissolved the catalyst, even when the degree of sorption of the solvent by the polymer film was very low (*e.g.* methanol), as shown in Table 1. Poor solvents for the complex like water, heptane or xylene yielded negligible leaching. However, when methanol was added to xylene, leaching was very high, probably due to the good solubility of the complex in methanol and high degree of swelling of the PDMS film in xylene. The results of sequential replacement of methanol or water every 24 h (typical reaction time) are shown in Fig. 2. The potential advantage of water as solvent in this reaction is evident.

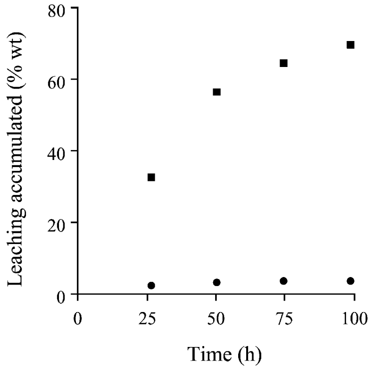


Fig. 2 Cumulative leaching of the complex in (■) methanol and (●) water. (10 μmol of Rh–MeDuPHOS occluded in 1 g of PDMS films with 20 wt.% silica.)

A series of catalytic experiments were thus carried out in an aqueous medium (Table 2). A blank reaction was carried out with pure catalyst in water. No reaction took place. Although addition of water to methanol in a homogeneous reaction (entry 2) decreased the reaction rate, the enantioselectivity of the reaction was not affected. The data shown in Table 2 indicate that reactions carried out in aqueous systems with the PDMS occluded RhMeDuPhos catalysts yielded excellent results in terms of enantioselectivity of the catalyst. A comparison cannot be made with the analogous homogeneous system, since the complex does not dissolve in water. However, the activity and, to a lesser extent, the enantioselectivity are lower for the heterogeneous system. A possible reason for the small decrease in the enantiomeric excess is the symmetric reduction of methyl 2-acetamidoacrylate by the platinum catalyst used to catalyze the crosslinking reaction of the PDMS film. Evidence for this was provided by an experiment in which the Rh–MeDuPHos was replaced with additional Pt catalyst, leading to a complete loss of enantioselectivity in the film. The low activity of the PDMS occluded catalysts is probably a result of mass-transfer limitations in the 1 mm thick film.

The catalytic activity could be increased by increasing the content of silica in the film. The presence of silica probably attracted water, leading to a higher amount of substrate into the film. Increasing the silica content up to 20 wt% substantially increased the water sorption. With a content of silica above 20 wt%, a brittle film was obtained. A slight decrease in enantioselectivity was observed in the reuse of the heterogeneous catalyst, but without loss of activity. Dissolved oxygen may be the reason for the reduction in enantiometric excess between runs. The possibility of a homogeneous-catalyzed reaction due to the low leaching in water was excluded since by adding fresh substrate to a filtrate from a reaction at low conversion no asymmetric hydrogenation of the enamide was detected.

In conclusion, the ability to heterogenize a transition metal complex by occlusion in a polymer film, with a non-dissolving solvent as the reaction medium, is reported for the first time and is demonstrated for the water/Rh–MeDuPHOS/PDMS system. Due to the insolubility of the transition metal complex in water, the reported catalytic system is truly recyclable and thus represents an excellent example of 'green' chemistry.

Notes and references

1 R. A. Sheldon, *Chirotechnology*, Marcel Dekker Inc., New York, 1993.
2 S. C. Stinson, *Chem. Eng. News*, 2000, **23**, 55.
3 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley, New York, 1994.
4 K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa and H. Takaya, *J. Org. Chem.*, 1994, **59**, 3064.
5 S. Akutagawa, 'Asymmetric Synthesis by Metal BINAP Catalysts', *Appl. Catal.*, 1995, **128**, 171.
6 M. J. Burk, *ChemTracts-Org. Chem.*, 1998, **11**, 787.
7 M. J. Burk, *J. Am. Chem. Soc.*, 1991, **113**, 8518.
8 M. J. Burk, *J. Am. Chem. Soc.*, 1995, **117**, 4423.
9 K. Fodor, S. G. A. Kolmschot and R. A. Sheldon, *Enantiomer*, 1999, **4**, 497.
10 P. A. Jacobs, I. F. J. Vankelecom and D. De Vos, *Chiral Catalyst Immobilisation and Recycling*, Wiley-VCH, Weinheim, Germany, 2000.
11 D. J. Bayston, J. L. Fraser, M. R. Ashton, A. D. Baxter, M. E. C. Polywka and E. Moses, *J. Org. Chem.*, 1998, **63**, 3137.
12 B. F. G. Johnson, S. A. Raynor, D. S. Shephard, T. Machmeyer, J. M. Sanker, S. G. Bromley, R. Oldroyd, L. Gladden and M. D. Mantle, *Chem. Commun.*, 1999, 1167.
13 D. Tas, D. Jeanmart, R. F. Parton and P. Jacobs, *Stud. Surf. Sci. Catal.*, 1997, **108**, 493.
14 F. Gelman, D. Avnir, H. Schumann and J. Blum., *J. Mol. Catal.*, 1999, **146**, 123.
15 I. F. J. Vankelecom and P. A. Jacobs, *Catal. Today*, 1999, **1**, 1905.
16 I. Vankelecom, A. Wolfson, S. Geresh, M. Landau, M. Gottlieb and M. Herskowitz, *Chem. Commun.*, 1999, 2407.