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Cat-in-a-Cup: Facile Separation of Large Homogeneous Catalysts**

*Anil V. Gaikwad, Vittorio Boffa, Johan E. ten Elshof, and Gadi Rothenberg**

We present herein a simple and practical concept and device for homogeneous catalyst separation. The device is a two-layered ceramic membrane cylinder that allows the diffusion of reactant and product molecules in and out, but keeps the catalyst trapped inside. The concept is demonstrated for the enantioselective transfer hydrogenation of acetophenone to (*S*)-phenylethyl alcohol with large molecular catalysts anchored on Fréchet-type dendrimers. The robustness, low cost, and high precision of the ceramic membranes make them ideal for such practical applications.

Catalyst separation and recycling is the bane of homogeneous catalysis, both for lab-scale experiments and large industrial processes.[1] Various ingenious solutions are available: selective product crystallization, catalyst precipitation and filtration, flash distillation of the product, or extraction of the catalyst using, for example, supercritical solvents[2] (one can also tether the homogeneous complex onto a solid support, for example, polymers,[3–5] zeolites,[6,7] or silica,[8] but then it is no longer homogeneous catalysis). One relatively new concept combines nanoporous membranes and high-molecular-weight transition-metal complexes.[9] Such membranes can effectively filter species a few nanometers in diameter (nanofiltration) to tens and hundreds of nanometers (ultrafiltration).[10] These diameters match those of dendrimers and macromolecules, respectively. Current applications include hydrovinylation,[11] allylic amination,[12] and Kharasch addition.[13]

Unfortunately, many of these solutions require dedicated membrane reactor technology, which is often incompatible with conventional laboratory equipment. Moreover, organic polymer membranes are prone to swelling and leaching. To solve this problem, we turned to ceramic membranes.[14–17] As we recently showed, these can be designed and tailored to nanometric dimensions.[16,17] Herein, we present a novel and simple tool for separating homogeneous catalysts using a multilayered porous membrane cylinder (Figure 1). We demonstrate the utility of this "cat-in-a-cup" concept in the ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone.

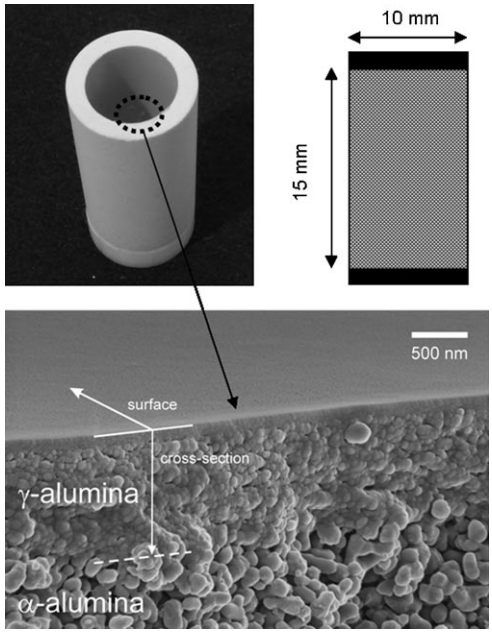

Figure 1. Top: Photo and schematic of the multilayered porous catalyst separation cup; pore diameter 4 nm, molecular weight cutoff 1000 Da. Bottom: HRSEM image of a cross section of the membrane cup showing the α-alumina and γ-alumina layers.

Our porous membrane cups are basically cylinders made of a thin nanoporous γ-alumina layer coated onto a macroporous α-alumina membrane (Figure 1).[18,19] They are closed with teflon caps on both sides. The cups are 15 mm tall and have an inner diameter of 7 mm. The molecular-weight cutoff of the γ-alumina layer is 1000 Da. Although this is higher than most homogeneous complexes, it is well within the size range of dendrimers and oligomers.

There are different approaches for making high-molecular-weight homogeneous catalysts, for example, the covalent binding of ligands to soluble oligomers or polymers demonstrated by Plenio and co-workers.[5,20] Herein, we chose to attach a "dendrimer anchor" to the homogeneous complex.[21–24] This creates a dendritic catalyst with a controllable structure that can be separated by nanofiltration.[25] We synthesized a third-generation Fréchet-type dendrimer scaffold (MW 1240 Da),[24] attaching to it a Ru^{II} complex with (*S*,*S*)-*N*-arenesulfonyl-1,2-diphenylethylenediamine ligands (TsDPEN). This complex, developed by Noyori and Ikar-

[*] A. V. Gaikwad, Prof. Dr. G. Rothenberg
Van't Hoff Institute for Molecular Sciences
University of Amsterdam
Nieuwe Achtergracht 166, 1018 WV Amsterdam (The Netherlands)
Fax: (+31) 20-525-5604
E-mail: g.rothenberg@uva.nl
Homepage: http://www.science.uva.nl/~gadi/
V. Boffa, Dr. Ir. J. E. ten Elshof
MESA+ Institute for Nanotechnology, University of Twente
PO Box 217, 7500 AE Enschede (The Netherlands)

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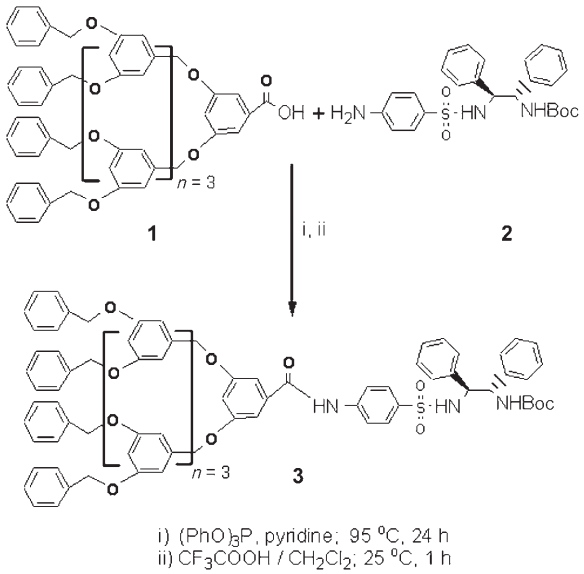
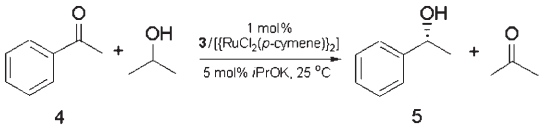
iya,[26] is known as a good asymmetric transfer hydrogenation catalyst. Moreover, Chen et al. showed that attaching this complex to a dendrimer did not diminish its catalytic activity.[27–29] The core functionalized dendritic ligand was prepared by condensing the chiral (*S,S*)-DPEN **2** with third-generation polyether dendrons **1**, followed by removal of the Boc group (Scheme 1; Boc = *tert*-butyloxycarbonyl). The dendritic ruthenium complex was prepared by mixing the dendrimer ligand with $[\{RuCl_2(cymene)\}_2]$ at 25 °C in THF (see the Supporting Information for full experimental details).



Scheme 1. Ts-DPEN ligand formation with third-generation dendrimer.

We then tested the catalyst in the asymmetric transfer hydrogenation of acetophenone (**4**) with *i*PrOH in the presence of *i*PrOK as base [Eq. (1)]. The reaction reached



(1)

65 % conversion after 48 h and had high selectivity for (*S*)-1-phenylethanol (**5**; 95 % *ee*). No reverse reaction was observed. Subsequently, we tested the same catalyst using our cat-in-a-cup system under otherwise identical reaction conditions. We used a 25 mL glass reactor, constructed in-house, in which the alumina cylinder rests on a stainless steel stand above a magnetic stirrer (Figure 2). The membrane "cup" was first placed under vacuum to remove oxygen from the pores. Then, it was immersed in *i*PrOH for 2 h,[30] after which the Ru^{II} complex (0.6 mL, 0.03 mM) was injected into the cup under N_2. The cup was then sealed with a teflon cap, and placed in the reactor together with *i*PrOH (20 mL). The reagents and base were added, and the mixture was stirred at 25 °C. Samples were taken every 2 h and analyzed by GC. After 24 h, the membrane cup was removed and kept in

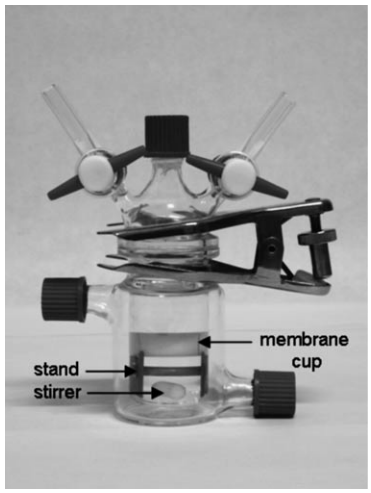


Figure 2. The reactor used for the "cat-in-a-cup" experiments.

*i*PrOH under N_2 for 24 h. During this period, we continued sampling the reaction mixture. The cup was then replaced in the reactor and the reaction was continued for another 24 h. Figure 3 shows the results. The clear stepwise behavior of the

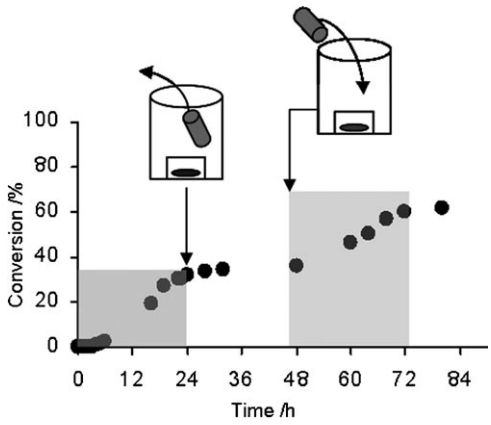


Figure 3. Stepped reaction profile for acetophenone conversion, showing the removal and replacement of the membrane cup at 24 h intervals. Reaction conditions: acetophenone (0.23 mL, 2 mmol), pentadecane (internal standard, 1 mmol), and *i*PrOK (0.1 mL, 10 mmol) stirred under N_2 in *i*PrOH (20 mL) at 25 °C under nitrogen.

reaction profile supports our hypothesis that the catalyst indeed stays inside the membrane cup. Inductively coupled plasma mass spectrometry (ICP-MS) analysis showed that less than 0.3 % of the Ru leached into solution. The slight increase observed in the second 12-hour period is well within the experimental measurement error limits.

A series of control experiments were run to examine the background reaction effects (Figure 4). No conversion was observed in the absence of catalyst or when only the dendritic ligand was present. Reactions in the presence of the ruthenium precursor salt, the Ru complex, and the Ru–dendrimer complex all gave similar conversions, but only the latter two showed enantioselectivity (93–95 % *ee* in both cases). These reactions were also repeated without the

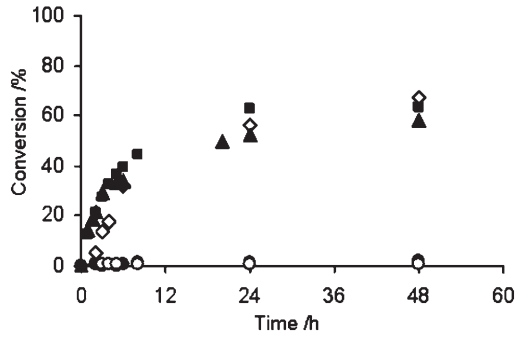


Figure 4. Reaction profiles of the control experiments: ○: reaction without catalyst; ●: dendritic ligand only; ◇: ruthenium salt precursor only; ■: with catalyst but without dendritic ligand; ▲: with catalyst and dendritic ligand. Reaction conditions are as in Figure 3.

membrane cup, by placing the various catalysts in standard Schlenk reactors. The results were identical, affirming that the lack of enantioselectivity in the last three cases is not due to diffusion processes through the membrane. A separate series of extraction experiments followed by ICP-MS analysis showed that the membrane cup retained greater than 99.7% of the Ru metal after stirring for 3 days in *i*PrOH. Preliminary studies show that the ceramic membrane is highly stable between pH 3 and pH 7, and that no membrane fouling was observed.

Indeed, catalyst recovery is only part of the problem in homogeneous systems. Recovery per se is often possible if you allow catalyst destruction. Conversely, recovery and recycling is more challenging. Our concept has the potential to allow the latter, as shown by the recycling experiments in Figure 5. In these experiments, the same catalyst "cup" was used in two different runs and gave practically identical conversions, selectivities, and reaction rates. These results also show that the Ru catalyst retained in the membrane remains in the form of the dendrimer-supported complex. Note that the experimental system was cleaned carefully between the two runs to preclude the possibility of residual activity due to catalyst contamination.

In summary, we have shown that multilayered ceramic membranes can be combined with large molecular ligands to give a simple and effective separation tool for homogeneous catalysis research. We hope that this cat-in-a-cup approach will be adopted and applied by the general catalysis community.

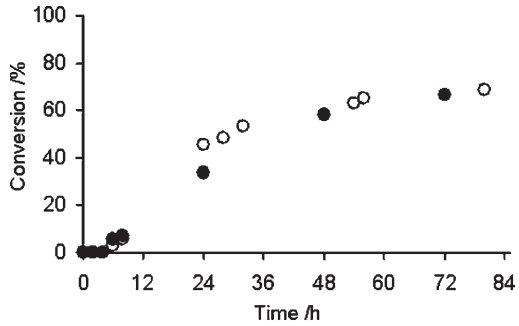


Figure 5. Time-resolved reaction profiles for two consecutive experiments using the same catalyst "cup" (● and ○ symbols denote the first and second run, respectively) Reactions conditions for both runs are as in Figure 3.

Experimental Section

A detailed description of the material and instrumentation, preparation of membrane cup, and its SEM analysis is given in the Supporting Information. General procedure for preparing the dendritic Ru^{II} catalyst: All reactions were carried out in standard Schlenk vessels under nitrogen. Third generation dendrimer **1** was prepared as described by Fréchet.[24] Ligands **2** and **3** were prepared by using the method of Chen et al.[27] Then, $[\{RuCl_2(cymene)\}_2]$ (6.5 mg, 0.01 mmol), dendritic ligand **3** (1.1 equiv of Ru), and NEt_3 (6.5 μL, 0.04 mmol) were stirred in THF at room temperature for 2 h. All the intermediate dendrimers and ligands were analyzed by ^1H NMR and ^{13}C NMR spectroscopy.

Procedure for asymmetric transfer hydrogenation of acetophenone in the membrane reactor: The membrane pellet was kept under vacuum overnight to remove the air from the pores and thus prevent any interference of oxygen. Then it was immersed in the distilled and dried *i*PrOH under nitrogen for 2 h. The catalyst solution in 0.6 mL THF was injected into the cup under nitrogen, and the cup was sealed with a teflon cap. The cup was placed on the stand in the membrane reactor. *i*PrOH (20 mL) was injected in the reactor and then acetophenone **4** (0.23 mL, 2 mmol), pentadecane (internal standard, 1 mmol), and *i*PrOK (0.1 mL, 10 mmol) were added, and the samples were analyzed by GC.

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[1] G. Rothenberg, *Catalysis: Concepts and green applications*, Wiley-VCH, Weinheim, **2008**.
[2] P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, *99*, 475.
[3] S. Bastin, R. J. Eaves, C. W. Edwards, O. Ichihara, M. Whittaker, M. Wills, *J. Org. Chem.* **2004**, *69*, 5405.
[4] S. Itsuno, M. Takahashi, Y. Arakawa, N. Haraguchi, *Pure. Appl. Chem.* **2007**, *79*, 1471.
[5] A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685.
[6] H. Siklova, E. Leitmannova, P. Kacer, L. Cerveny, *React. Kinet. Catal. Lett.* **2007**, *92*, 129.
[7] M. L. Kantam, B. P. C. Rao, B. M. Choudary, B. Sreedhar, *Adv. Synth. Catal.* **2006**, *348*, 1970.
[8] P. N. Liu, P. M. Gu, F. Wang, Y. Q. Tu, *Org. Lett.* **2004**, *6*, 169.
[9] C. Mueller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.* **2005**, 4011.
[10] I. F. J. Vankelecom, *Chem. Rev.* **2002**, *102*, 3779.
[11] E. B. Eggeling, N. J. Hovestad, J. T. B. H. Jastrzebski, D. Vogt, G. van Koten, *J. Org. Chem.* **2000**, *65*, 8857.
[12] D. de Groot, B. F. M. de Waal, J. N. H. Reek, A. P. H. J. Schenning, P. C. J. Kamer, E. W. Meijer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2001**, *123*, 8453.
[13] A. W. Kleij, R. A. Gossage, R. J. M. Klein Gebbink, N. Brinkmann, E. J. Reijerse, U. Kragl, M. Lutz, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **2000**, *122*, 12112.
[14] A. Julbe, D. Farrusseng, C. Guizard, *J. Membr. Sci.* **2001**, *181*, 3.
[15] S. R. Chowdhury, P. T. Witte, D. H. A. Blank, P. L. Alsters, J. E. ten Elshof, *Chem. Eur. J.* **2006**, *12*, 3061.
[16] M. B. Thathagar, J. E. ten Elshof, G. Rothenberg, *Angew. Chem.* **2006**, *118*, 2952; *Angew. Chem. Int. Ed.* **2006**, *45*, 2886.

[17] A. V. Gaikwad, A. Holuigue, M. B. Thathagar, J. E. ten Elshof, G. Rothenberg, *Chem. Eur. J.* **2007**, *13*, 6908.
[18] For a detailed overview of this type of synthesis, see: N. Benes, A. Nijmeijer, H. Verweij in *Recent Advances in Gas Separation by Microporous Ceramic Membranes* (Ed.: N. K. Kanellopoulos), Elsevier, Amsterdam, **2000**, pp. 335–372.
[19] T. Van Gestel, C. Vandecasteele, A. Buekenhoudt, C. Dotremont, J. Luyten, B. Van der Bruggen, G. Maes, *J. Membr. Sci.* **2003**, *214*, 21.
[20] M. an der Heiden, H. Plenio, *Chem. Eur. J.* **2004**, *10*, 1789.
[21] H. P. Dijkstra, N. Ronde, G. P. M. van Klink, D. Vogt, G. van Koten, *Adv. Synth. Catal.* **2003**, *345*, 364.
[22] H. P. Dijkstra, C. A. Kruithof, N. Ronde, R. van de Coevering, D. J. Ramon, D. Vogt, G. P. M. van Klink, G. van Koten, *J. Org. Chem.* **2003**, *68*, 675.
[23] For recent reviews on dendritic catalysts, see: a) G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem.* **2001**, *113*, 1878; *Angew. Chem. Int. Ed.* **2001**, *40*, 1828; b) D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991; c) R. M. Crooks, M. Zhao, L. Sun, V. Chechik, L. K. Yueng, *Acc. Chem. Res.* **2001**, *34*, 181; d) L. J. Twyman, A. S. H. King, I. K. Martin, *Chem. Soc. Rev.* **2002**, *31*, 69; e) R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717; f) Q.-H. Fan, Y. M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385.
[24] C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638.
[25] H. P. Dijkstra, G. P. M. Van Klink, G. Van Koten, *Acc. Chem. Res.* **2002**, *35*, 798.
[26] a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521; b) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562; c) K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285.
[27] Y. C. Chen, T. F. Wu, J. G. Deng, H. Liu, Y. Z. Jiang, M. C. K. Choib, A. S. C. Chan, *Chem. Commun.* **2001**, 1488.
[28] Y. C. Chen, T. F. Wu, J. G. Deng, H. Liu, X. Cui, J. Zhu, Y. Z. Jiang, M. C. K. Choi, A. S. C. Chan, *J. Org. Chem.* **2002**, *67*, 5301.
[29] Y. C. Chen, T. F. Wu, L. Jiang, J. G. Deng, H. Liu, J. Zhu, Y. Z. Jiang, *J. Org. Chem.* **2005**, *70*, 1006.
[30] S. R. Chowdhury, D. H. A. Blank, J. E. ten Elshof, *J. Phys. Chem. B* **2005**, *109*, 22414.

