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Microreactors

Safe Use of a Toxic Compound: Heterogeneous OsO_4 Catalysis in a Nanobrush Polymer Microreactor**

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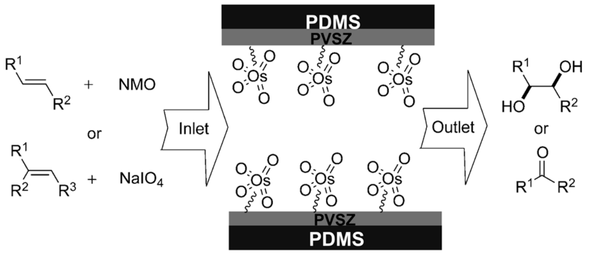
Some catalysts are toxic and volatile, this volatility allows permeation of the toxin throughout its environment, and yet these catalysts are, in many cases, essential for organic synthesis. Therefore, in recent years, much attention has been given to immobilization and reuse of these catalysts, mostly on solid supports in bulk reaction systems.

Osmium tetroxide (OsO_4) is such a catalyst. It is an excellent catalyst for dihydroxylation and oxidative cleavage of olefins, but it is highly toxic, hazardous, expensive, and volatile in nature. To overcome these issues, many researchers have developed different strategies for its immobilization or encapsulation on polymers and inorganic substrates.[1] However, all of these supported catalyst systems need a high loading of osmium to achieve good conversions in reasonable reaction times compared to homogeneous reactions. Despite various attempts to recycle the catalyst, the recovery and reuse of osmium is still a very difficult task, as leaching of osmium is inevitable in a bulk reaction system under mechanical agitation for good mixing.[1l,n]

These difficulties suggest the use of microfluidic systems, which have already been shown to offer various advantages over traditional large-scale batch chemistry.[2] In particular, the microreactor is a suitable system for the synthesis and use of potentially hazardous compounds, as only very small amounts of compounds/reagents are handled. Therefore, the robust immobilization of toxic catalysts on microreactor channel is a promising strategy to increase safety and reaction efficiency, while reducing environmental impact.[3]

Herein, we present the concept behind and the fabrication of a microreactor that allows the safe use of OsO_4 without leaching or spill problems of this toxic catalyst, and yet permits its use at the molecular level in a durable and reusable manner. The microreactor is a poly(dimethysiloxane) (PDMS) microchannel reactor, the modified wall surface of which is covered with a nanobrush polymer coating that is in turn used to immobilize the costly and highly toxic OsO_4 catalyst for complete utilization. Immobilization of OsO_4 onto nanobrush-like poly(4-vinylpyridine) (P4VP) on the inner wall of the microreactor is more convenient and efficient than a packed-bed microreactor, because there are few problems with blocking/clogging or pressure drop in a continuous flow system.[4] The silicone rubber PDMS has been the most widely used for manufacturing microfluidic devices, owing to its simplicity, low cost, and easy fabrication (only requiring a photomask and photoresist) versus other complicated techniques. However, plain PDMS is not suitable for organic reactions, as it swells in organic solvents.[5] Therefore, the surface of the PDMS channel was modified using a photo/thermal-curable preceramic polyvinylsilazane (PVSZ) polymer to form a protective coating layer, as reported from our own work.[6] The PVSZ-coated PDMS is not only resistant to organic solvents, but also allows attachment of a nanobrush-like P4VP polymer layer to the PVSZ wall by a "grafting-to" approach.

For the attachment, a method was developed to covalently bond the P4VP nanobrush layer to the inner wall of the PVSZ-modified PDMS microchannel. The P4VP polymer chains contain tertiary nitrogen atoms in the *para* position of a repeating pyridine unit that can be used for the immobilization of OsO_4.[1k] Scheme 1 shows dihydroxylation and oxidative cleavage reactions (See the Supporting Information for details) that take place inside the microchannel, the surface of which is covered with OsO_4 immobilized on P4VP nanobrushes, which is attached to the microchannel wall. In this approach, the mono-hydroxyl-terminated P4VP polymer with a molecular weight around 52 kDa (M_n) and a narrow polydispersity was initially synthesized by a radical polymerization technique mediated by hydroxytetramethylpiperidine (HO-TEMPO; Figures S2 and S3). The monohydroxy-terminated P4VP was then converted into NCO-terminated P4VP by treatment with excess hexamethylene diisocyanate at



Scheme 1. Continuous flow dihydroxylation and oxidative cleavage of olefins in the PVSZ/PDMS-based microreactor with immobilized OsO_4 catalyst on P4VP polymer nanobrushes.

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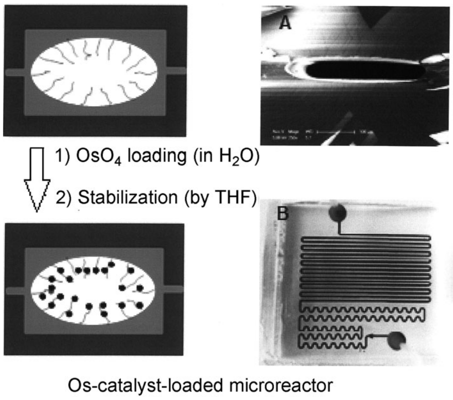


Figure 1. OsO_4 immobilization on P4VP nanobrush anchored microreactor; A) Cross-sectional SEM images of P4VP–NCO coated microchannel, B) Optical image of the fabricated microreactor with immobilized OsO_4. Microchannel dimension: 90 cm long, 500 μm wide, ca. 85 μm high.

elevated temperature. The free NCO stretching peak at 2260 cm^{-1} and N–H stretching peak from the urethane group at 3420 cm^{-1} were confirmed by FTIR analysis (Figure S3B).

Figure 1 illustrates the immobilization of OsO_4 and stabilization in a microreactor (Figure S1). Two identical PDMS channels were fabricated that are 500 μm wide and 40–45 μm high. The concave surface was treated with plasma and then spin-coated with PVSZ. The two PVSZ-coated channels were carefully aligned, and consolidated by UV irradiation for 30 min followed by thermal curing at 150 °C in open atmosphere for 2 h with a controlled heating and cooling rate. Open exposure to a humid atmosphere during the curing step caused partial hydrolysis of the Si–H and Si–NH–Si bonds of the PVSZ polymer into silanol (Si–OH) groups.

Further modification of the microchannel surface was conducted through the grafting-to approach, which takes advantage of the dual functionalities on the channel wall and the linear P4VP polymer nanobrushes. The single-end-functionalized P4VP-NCO polymer (0.5 wt. %) was dissolved in anhydrous chloroform and continuously passed through the channel for 1 h at a rate of 100 μL min^{-1} using a syringe pump at 60 °C. The NCO group of the polymer was very reactive towards the silanol group of the PVSZ surface and formed urethane bridges to covalently bond the P4VP chain to the chemically stable microreactor channel wall.

P4VP-NCO can also react with the remaining –NH– functional groups of partially hydrolyzed PVSZ, which provides an alternative reaction route.[7] FTIR analysis confirmed that the NCO stretching peak at 2260 cm^{-1} disappeared and the N–H stretching peak from the urethane group at 3420 cm^{-1} remained, which is an indication of a bridge between the P4VP polymer and the PVSZ surface (Figure S4C). The channel was further washed with chloroform to remove any unreacted P4VP and then the nanobrush-decorated microreactor was dried under vacuum. It is believed that the nanobrushes were covalently bound by coupling between –NCO at the chain end of the linear brush P4VP polymers and the –OH/–NH– functionalized PVSZ layer on the substrate. The protective PVSZ layer on the PDMS channel was very stable, with no degradation during modification in organic solvent at elevated temperature (Figure S5). To estimate the thickness of the nanostructure on the channel wall, a PVSZ-coated layer on a silicon wafer was grafted by keeping the wafer in P4VP-NCO polymer solution for 1 h at 60 °C; AFM analysis then confirmed that the thickness is around 85 nm (Figure S6). It is significant that the thickness of the nanobrush layer is close to the theoretical value calculated based on the degree of polymerization. (L = ca. $N^{2/3}$, where L and N are the thickness and the degree of polymerization of the polymer chains, respectively).[8] The surface morphology was also investigated by AFM at different scales (Figure S7), and it is clear that the P4VP layer fully covered the PVSZ coated surface with a dense globular structure, with a size distribution that is ca. 30–50 nm wide and ca. 2–10 nm high. The observed morphology resembles the characteristic nature of polymer brushes obtained through the grafting-to approach.[9]

To immobilize OsO_4 catalyst on the nanobrush P4VP polymer, the microreactor was connected to a syringe pump through PTFE tubing with airtight joints to prevent leakage or exposure to the toxic OsO_4 catalyst. An OsO_4 solution (0.1 wt. %) in water was infused continuously through the channel at 100 μL min^{-1} at room temperature for 40 min. The amount of immobilized OsO_4 inside the microreactor could be quantified by an in-house method using ICP-MS instruments (Table S1). Figure 2 shows that about 50 μg of OsO_4 in total was immobilized inside the microreactor channel (90 cm long, 500 μm wide, ca. 85 μm high), which had been coated with a P4VP nanobrush layer with a molecular weight of 52 kDa g mol^{-1}, in 40 min of flow time.

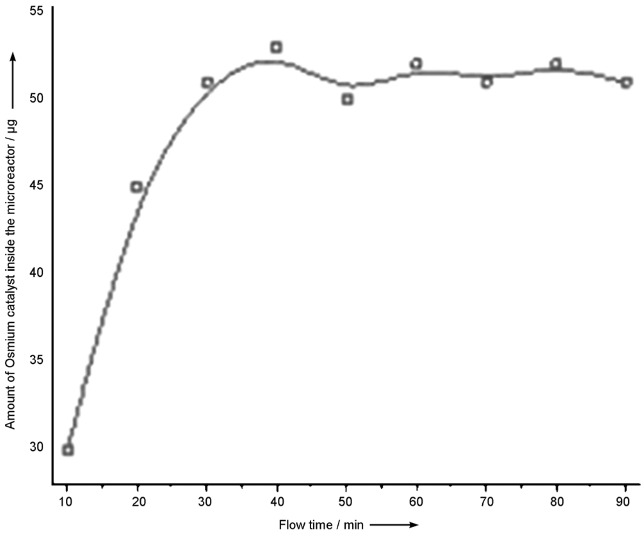


Figure 2. Amount of immobilized OsO_4 as a function of flow time in different microreactors with identical channel dimensions (90 cm long, 500 μm wide, ca. 85 μm high) when OsO_4 (0.1 wt. %) solution was infused with a flow rate of 100 μL min^{-1}.

The microchannel loaded with OsO_4–P4VP showed a yellowish tint and the catalytic activity almost vanished after 1 day, even in a closed environment. This is presumably due to the instability of OsO_4. Therefore, further treatment was conducted to enhance the stability of the immobilized catalyst by continuously feeding THF as a reducing agent through the channel after loading the OsO_4, and the yellow color turned to dark blue, indicating the formation of an oxo-osmium(VI) pyridine complex. Hermann and co-workers reported that THF as a reducing agent lowered the oxidation state of osmium to the osmium(VI) oxide complex. They found that the structure was more stable in open atmosphere than OsO_4 and that identical catalytic activity to OsO_4 was maintained in the presence of oxidizing agents.[10]

Furthermore, the distribution of osmium metal inside the channel was determined by observing the horizontally cut OsO_4-P4VP nanobrush microchannel using a high resolution SEM. Both EDX (energy dispersive X-ray spectroscopy) Os mapping and EDX spectra confirmed the uniform distribution of osmium throughout the channel surface (Figure 3; see also Figure S8).

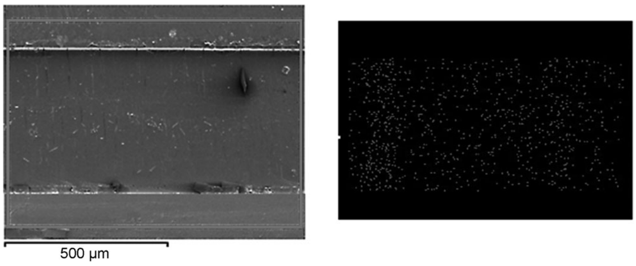
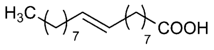
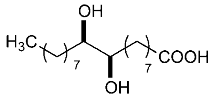
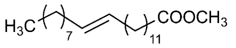
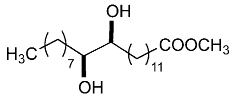
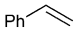
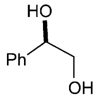
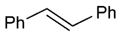
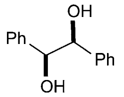
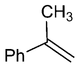
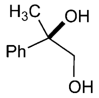


Figure 3. Horizontal cross-sectional SEM image of the OsO_4–P4VP nanobrush microchannel and the corresponding EDX mapping of Os metal (see also Figure S4 for EDX spectra).

With the osmium oxide bonded nanobrush microreactor prepared, the catalytic performance and the efficiency of the microreactor were investigated in two reactions: dihydroxylation and oxidative cleavage of olefins. Both of these reactions are quite important in both academia and industry for the production of active intermediates that are required for the syntheses of natural products, pharmaceuticals, and fine chemicals.

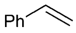
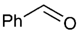
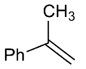
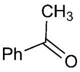
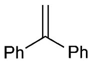
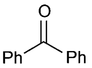
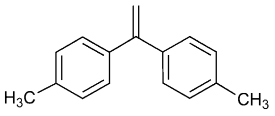
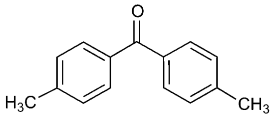
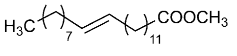
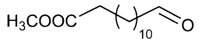
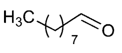
For dihydroxylation reactions, *N*-methylmorpholine *N*-oxide (NMO) was used as a co-oxidant in an acetone/water mixture (10:1).[1m] A 72 cm long microchannel was fabricated for this study, including an 18 cm long serpentine mixing zone. For the dihydroxylation, biomass-based aliphatic and aromatic olefins were selected. As shown in Table 1, the reactions reached 99 % conversion in 10 min. Only 0.002 mol % of OsO_4 was needed in the microfluidic reactor to catalyze the reaction of 10 mmol of olefins with excellent conversion (based on 50 µg of OsO_4), this is 50 times more efficient than bulk reaction systems.[1m,n] Furthermore, the productivity of around 1.0 $mmol\,h^{-1}$ remained the same, even when the microreactor was continuously used for 10 h under identical conditions, thus indicating good durability. Reusability of the reactor and the catalyst was also confirmed by running the same experiment and observing no significant change in the results after the reactor had been stored for three months after fabrication. Oxidative cleavage reactions were performed in a THF/water mixture in the presence of $NaIO_4$ as an oxidant. As shown in Table 2, these reactions, with an average productivity of around

Table 1: Dihydroxylation of olefins in the OsO_4–P4VP nanobrush microreactor[a]

Entry	Substrate	Product	Conversion[b] (Yield)[c] [%]
1			99 (92)
2			98 (93)
3			98 (94)
4			99 (95)
5			99 (94)

[a] All reactions were performed at room temperature for 10 min using one microreactor for each product with identical reactor dimensions (l = 90 cm, w = 500 µm, h = ca. 85 µm, volume = ca. 40 µL), acetone/water (10:1) as solvent, olefin (10 mmol), and NMO (1 equiv). [b] Conversions were determined by GCMS using anisole as an internal standard. The average of three independent runs in the same microreactor is given in the table. [c] Yield of isolated product.

Table 2: Oxidative cleavage of olefins in the OsO_4–P4VP nanobrush microreactor.[a]

Entry	Substrate	Product	Conversion[b] (Yield)[c] [%]
1			99 (91)
2			99 (92)
3			98 (94)
4			99 (93)
5		A  B 	99 (A: 75) (B: 67)

[a] All reactions were performed at room temperature for 7 min using one microreactor for each product with identical reactor dimensions (l = 90 cm, w = 500 µm, h = ca. 85 µm, volume = ca. 40 µL), THF/water (2:1) as solvent, olefin (10 mmol), and $NaIO_4$ (2 equiv). [b] Conversions were determined by GCMS using anisole as an internal standard. The average of three independent runs in the same microreactor is given in the table. [c] Yield of isolated product.

1.3 mmol h^{-1}, were faster than the dihydroxylation reactions, reaching more than 98 % conversion within 7 min of reaction time. The reaction times were optimized for both dihydroxylation and oxidative cleavage by periodically checking the conversions at different residence times. The height of the microchannel for this P4VP nanobrush system was varied with the width fixed at 500 μm. It was found that a height of less than 100 μm is desirable for better performance, this is presumably due to better access of the reactants to the catalyst under flow conditions. The osmium content in the reaction mixtures was analyzed by ICP-MS to check for leaching during these reactions, and was found to be in the range of 30–50 PPB level in both reactions.

The superiority of the present microfluidic polymeric nanobrush strategy over other supported systems can be explained by the excellent solubility and wettability of the nanobrushes in the reaction medium. Thus, the reagents readily diffuse and reach all of the catalytic units on the nanobrush, which is not so readily accomplished in an insoluble-solid-supported catalytic system. The dihydroxylation and oxidative cleavage results clearly demonstrate that a tiny amount of OsO_4 anchored to the P4VP nanobrush layer is sufficient for excellent reaction efficiency, presumably owing to a uniform distribution of catalyst at the molecular level without aggregation and to complete utilization of loaded catalyst dispersed on the nanobrush. The results also revealed the durability and reusability of the microreactor without spillage of hazardous catalyst, which has not yet been demonstrated with any solid-supported bulk-reaction systems.

In conclusion, we have devised a nanobrush microreactor for use in heterogeneous catalytic processes, in particular ones involving toxic, volatile, or expensive catalysts, using a simple microfluidic platform in the PVSZ-PDMS microreactor. The method of immobilization of hazardous OsO_4 on the nanobrush P4VP layer was shown to be a safe, efficient, and green process, with little environmental impact, and allowed reactions to be conducted in a time- and chemical-saving manner, as compared to spill-over bulk processes. The concept and method can be easily extended to other hazardous-metal-catalyst systems in glass- or metal- based microreactors after appropriate surface modifications for high throughput screening and upscale production.

Experimental Section

Monohydroxyl-terminated P4VP was synthesized by standard Schlenk techniques, and further functionalized with NCO groups. The same NCO-P4VP nanobrush polymer was used for all microreactor fabrication. To perform the dihydroxylation and oxidative cleavage reactions, the OsO_4–P4VP nanobrush microreactor was connected to a programmable syringe pump through PTFE tubing with an internal diameter of 500 μm. All of the reactions were carried out at room temperature.

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