

# Renaissance of immobilized catalysts. New types of polymer-supported catalysts, 'microencapsulated catalysts', which enable environmentally benign and powerful high-throughput organic synthesis

Shū Kobayashi\* and Ryo Akiyama

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: skobayas@mol.f.u-tokyo.ac.jp

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Immobilized catalysts have been reinvestigated from two aspects; as keys to environmentally benign chemical processes and high-throughput organic synthesis for combinatorial chemistry. While most known polymer-supported catalysts are less active than the corresponding original catalysts, new types of polymer-supported catalysts, microencapsulated catalysts, have been developed. The catalysts were immobilized on to polymers using physical envelopment by polymer backbones and interaction between  $\pi$  electrons of benzene rings of the polystyrenes used as polymer backbones and vacant orbitals of the catalysts. Microencapsulated Sc, Os, Pd and Ru catalysts have been successfully prepared and high activities have been attained. In all cases, no leaching of the catalysts occurred, and the immobilized catalysts were recovered quantitatively by simple filtration and reused without loss of activity. It is noted that this method enables direct immobilization of metals onto polymers, and that normally unstable species such as Pd(0)(PPh<sub>3</sub>) can be kept stable by this immobilization technique. It is expected that other metal catalysts can be immobilized using this microencapsulation technique.

## Introduction

Immobilized catalysts have been of great interest due to several advantages, such as simplification of product work-up, separation, isolation, and reuse of the catalysts.<sup>1</sup> However, their use in organic synthesis has been rather limited because immobilized catalysts are less active than the corresponding original catalysts in many cases. On the other hand, we have recently been

reinvestigating immobilized catalysts mainly from two aspects. First, chemical processes with little waste are expected using immobilized catalysts, because they can be recovered and reused. This leads to more environmentally benign chemical processes. Second, use of immobilized catalysts is expected to be a key to high-throughput organic synthesis. Recent advances in combinatorial chemistry have required synthesis of large numbers of structurally distinct compounds efficiently. For this purpose, even modern organic synthesis with efficient reactions which attain high yields and high selectivities does not work well. We think new methodologies for the preparation of large numbers of compounds (compound library) are needed.<sup>2</sup> While solid-phase syntheses provide one of the efficient methods, we have recently proposed a new method for the synthesis of compound libraries using immobilized catalysts.<sup>3</sup>

Through these research works, we have recognized the importance of developing truly efficient polymer-supported catalysts, and reached an idea of microencapsulated catalysts. Microcapsules have been used for coating and isolating substances until such time as their activity is needed, and their application to medicine and pharmacy has been extensively studied.<sup>4</sup> Recently, much progress has been made in this field; for example, the size of microcapsules achievable has been reduced from a few  $\mu\text{m}$  to nanometers. Our idea is to apply this microencapsulation technique to the immobilization of catalysts onto polymers. That is, catalysts would be physically enveloped by polymer thin films, and at the same time, immobilized by the interaction between  $\pi$  electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbitals of the catalysts (metal compounds) (Fig. 1).

In this article, use of new types of polymer-supported catalysts, microencapsulated catalysts, is summarized.

## Microencapsulated scandium trifluoromethanesulfonate [MC Sc(OTf)<sub>3</sub>]

First, scandium triflate was chosen as a Lewis acid to be immobilized.<sup>5</sup> Sc(OTf)<sub>3</sub> is a new type of water-compatible Lewis acid,<sup>6</sup> and many useful synthetic reactions using Sc(OTf)<sub>3</sub> have been developed.<sup>7</sup> Microencapsulated Sc(OTf)<sub>3</sub> (MC Sc(OTf)<sub>3</sub>) was prepared as follows: Polystyrene (1.000 g) was dissolved in cyclohexane (20 mL) at 50–60 °C, and to this solution was added powdered Sc(OTf)<sub>3</sub> (0.200 g) as a core. The mixture was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coaservates were found to envelop the solid core dispersed in the medium. Microcapsules formed at this stage were physically soft, and hexane (30 mL) was added to harden the capsule walls. The mixture was stirred at room temperature for 1 h, and the capsules were washed with acetonitrile several times and dried at 50 °C. Judging from the recovered Sc(OTf)<sub>3</sub> (0.080 g), 0.120 g of Sc(OTf)<sub>3</sub> was microencapsulated according to this procedure. The weight of the capsules was 1.167 g which contain acetonitrile. MC Sc(OTf)<sub>3</sub> thus prepared can be stored at room temperature for more than several months.

A scanning electron microscopy (SEM) micrograph and scandium energy dispersive X-ray (EDX) map of MC Sc(OTf)<sub>3</sub> revealed that small capsules of MC Sc(OTf)<sub>3</sub> adhered to each

*Shū Kobayashi studied chemistry at the University of Tokyo and received his Ph.D. in 1988 (Professor Teruaki Mukaiyama). After spending 11 years at the Science University of Tokyo (SUT), he moved to the Graduate School of Pharmaceutical Sciences, the University of Tokyo, in 1998. His research interests include development of new synthetic methods, development of novel catalysts (especially chiral catalysts), organic synthesis in water, solid-phase organic synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He received the first Springer Award in Organometallic Chemistry in 1997, IBM Award in 2001 and Nagoya Silver Medal in 2002.*

*Ryo Akiyama was born in 1974 in Niigata. He studied chemistry at the Science University of Tokyo (SUT), and took his Master degree at SUT in 1999 and Ph.D. degree at the University of Tokyo in 2002 under the supervision of Professor Shū Kobayashi. He is now a postdoctoral fellow in Cambridge, UK (Professor Steven V. Ley). His research interest includes development of new synthetic methods and polymer-supported catalysts.*

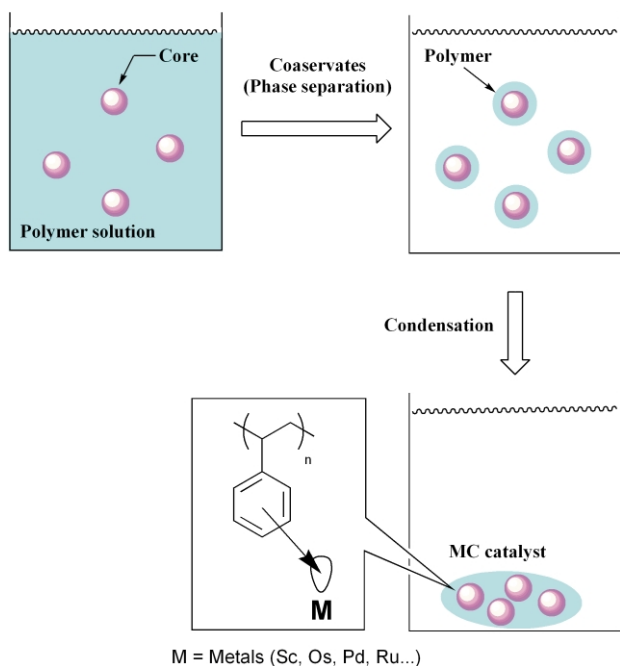
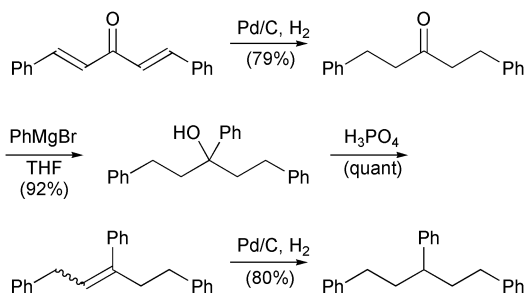


Fig. 1 Microencapsulation technique.

other, probably due to the small size of the core, and that  $\text{Sc}(\text{OTf})_3$  was located all over the polymer surface. The importance of the benzene rings of the polystyrene in immobilizing  $\text{Sc}(\text{OTf})_3$  was demonstrated by control experiments using polybutadiene or polyethylene instead of polystyrene. Whereas 43% of  $\text{Sc}(\text{OTf})_3$  (where 100% is the amount of  $\text{Sc}(\text{OTf})_3$  immobilized by polystyrene) was bound using polybutadiene, no  $\text{Sc}(\text{OTf})_3$  was observed in the microcapsules prepared using polyethylene.<sup>8</sup>

In addition, we measured the  $^{45}\text{Sc}$  NMR spectra of the monomeric  $\text{Sc}(\text{OTf})_3$ , a mixture of  $\text{Sc}(\text{OTf})_3$  and 1,3,5-triphenylpentane and MC  $\text{Sc}(\text{OTf})_3$ . 1,3,5-Triphenylpentane was used as a polystyrene analogue, which was synthesized from *trans,trans*-dibenzylideneacetone according to Scheme 1. In the presence of benzene rings,  $^{45}\text{Sc}$  NMR signals were shifted downfield compared to monomeric  $\text{Sc}(\text{OTf})_3$  (Table 1). These results demonstrate that the interaction between  $\text{Sc}(\text{OTf})_3$  and the benzene rings of polystyrene is a key to immobilizing  $\text{Sc}(\text{OTf})_3$ .



Scheme 1 Synthesis of 1,3,5-triphenylpentane.

MC  $\text{Sc}(\text{OTf})_3$  was successfully used in several fundamental and important Lewis acid-catalyzed carbon–carbon bond-forming reactions. All reactions were carried out in a 0.5 mmol scale in acetonitrile or nitromethane using MC  $\text{Sc}(\text{OTf})_3$  containing *ca.* 0.120 g of  $\text{Sc}(\text{OTf})_3$ . The reactions could be carried out in both batch (using normal vessels) and flow systems (using circulating columns). It was found that MC  $\text{Sc}(\text{OTf})_3$  effectively activated aldimines. Imino aldol (Scheme 2),<sup>7d</sup> aza Diels–Alder (Scheme 3),<sup>7d,e</sup> cyanation (Scheme 4),<sup>7f</sup> and alkylation (Scheme 5)<sup>7g</sup> reactions of aldimines proceeded smoothly using MC  $\text{Sc}(\text{OTf})_3$  to afford synthetically useful  $\beta$ -

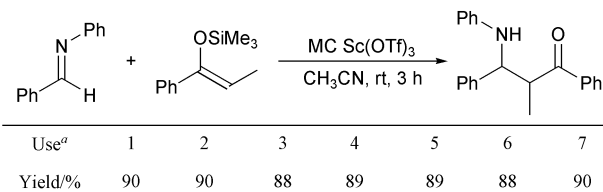
amino ester, tetrahydroquinoline,  $\alpha$ -aminonitrile and homoallylic amine derivatives, respectively, in high yields. Although it is well known that most Lewis acids are trapped and sometimes decomposed by basic aldimines and/or products, MC  $\text{Sc}(\text{OTf})_3$  effectively catalyzed the reactions in all cases. One of the most remarkable and exciting points is that the ability of MC  $\text{Sc}(\text{OTf})_3$  to activate aldimines was superior to that of monomeric  $\text{Sc}(\text{OTf})_3$ , which was shown by kinetic studies. The polymer catalyst was recovered quantitatively by simple filtration and could be reused. The activity of the recovered catalyst did not decrease even after several uses.

MC  $\text{Sc}(\text{OTf})_3$  has also been successfully used in three-component reactions such as Mannich-type (Scheme 6),<sup>7h</sup> Strecker (Scheme 7),<sup>7f</sup> and quinoline-forming (Scheme 8) reactions,<sup>7i</sup> which provide efficient methods for the preparation of biologically interesting compound libraries.<sup>9</sup>

Table 1 NMR experiments<sup>a</sup>

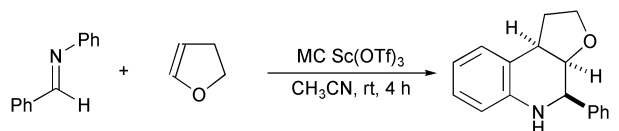
Sample	$^{45}\text{Sc}$ NMR peak shift data/ $\delta$
$\text{Sc}(\text{OTf})_3$	–182.2
$\text{Sc}(\text{OTf})_3$ + 1,3,5-triphenylpentane	–168.4
MC $\text{Sc}(\text{OTf})_3$	–163.9

<sup>a</sup>  $\text{ScCl}_3$  was used as an external standard ( $\delta = 0$ ) in  $\text{CD}_3\text{CN}$ .



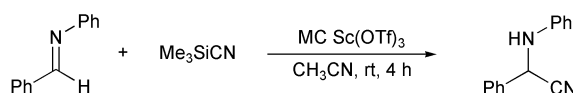
<sup>a</sup> Recovered catalyst was used successively (Use 2,3,4,...)

Scheme 2 Imino aldol reaction (flow system).



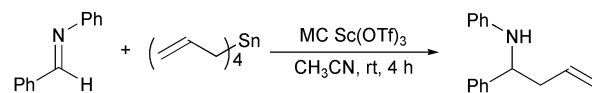
1st use, 80% yield; 2nd use, 78% yield; 3rd use, 78% yield

Scheme 3 Aza Diels–Alder reaction (flow system).



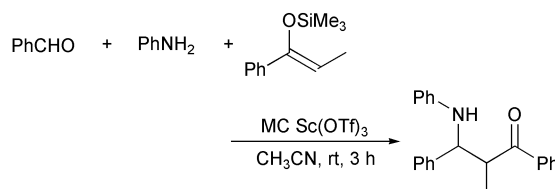
1st use, 77% yield; 2nd use, 77% yield; 3rd use, 76% yield

Scheme 4 Cyanation reaction (flow system).



1st use, 85% yield; 2nd use, 87% yield; 3rd use, 83% yield

Scheme 5 Allylation reaction (flow system).

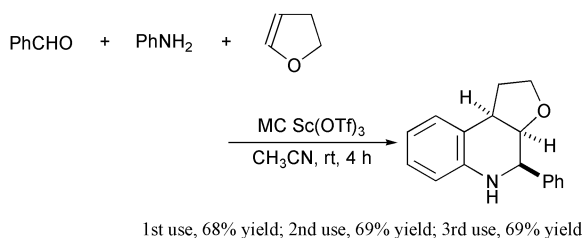


1st use, 90% yield; 2nd use, 96% yield; 3rd use, 93% yield

Scheme 6 Mannich-type reaction (flow system).

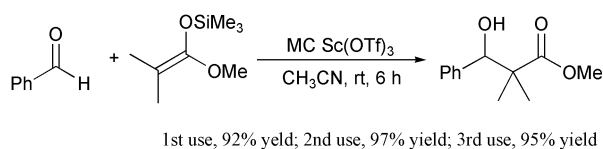


**Scheme 7** Strecker reaction (flow system).

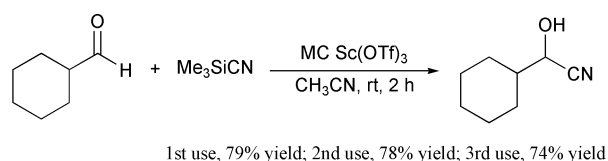


**Scheme 8** Qinaldin synthesis (flow system).

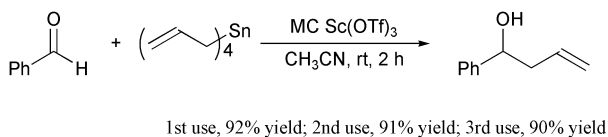
It was also found that MC Sc(OTf)<sub>3</sub> can activate carbonyl compounds such as aldehydes and  $\alpha,\beta$ -unsaturated ketones. Aldol reaction (Scheme 9),<sup>7i</sup> cyanation (Scheme 10), and allylation (Scheme 11)<sup>7k</sup> of aldehydes proceeded smoothly using MC Sc(OTf)<sub>3</sub> to give the corresponding aldol, cyanohydride, and homoallylic alcohol derivatives in high yields. Michael reaction of an  $\alpha,\beta$ -unsaturated ketone with a silyl enol ether (Scheme 12)<sup>7j</sup> and a Diels–Alder reaction of an oxazolindione derivatives with cyclopentadiene (Scheme 13)<sup>6</sup> also proceeded smoothly using MC Sc(OTf)<sub>3</sub>. Moreover, a Friedel–Crafts acylation was performed to produce an aromatic ketone in a good yield (Scheme 14).<sup>7l</sup> Friedel–Crafts alkylation and acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry.<sup>10</sup> While the alkylation reaction proceeds in the presence of a catalytic amount of a Lewis acid, the acylation reaction generally



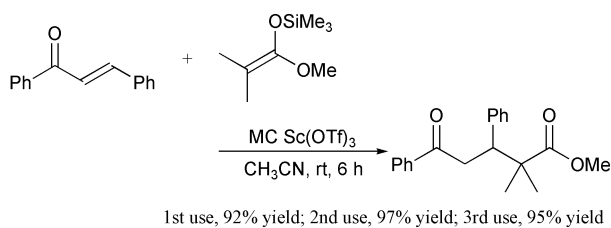
**Scheme 9** Aldol reaction (batch system).



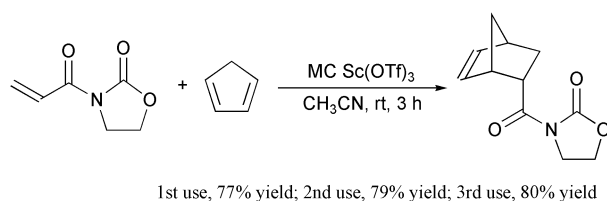
**Scheme 10** Cyanation reaction of aldehyde (batch system).



**Scheme 11** Allylation reaction of aldehyde (Batch system).

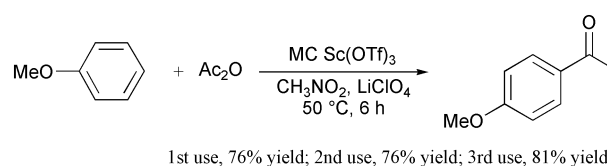


**Scheme 12** Michael reaction (batch system).



**Scheme 13** Diels–Alder reaction (batch system).

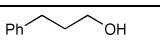
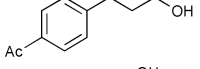
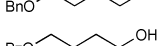
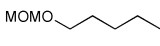
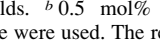
requires more than a stoichiometric amount of a Lewis acid such as aluminium chloride (AlCl<sub>3</sub>), due to consumption of the Lewis acid by coordination to the products, aromatic ketones. It should be noted that a catalytic amount of MC Sc(OTf)<sub>3</sub> has high activity in the Friedel–Crafts acylation and that MC Sc(OTf)<sub>3</sub> can be recovered easily by simple filtration and reused without loss of activity.



**Scheme 14** Friedel–Crafts acylation (batch system).

MC Sc(OTf)<sub>3</sub> was successfully used in other transformations. Oriyama and coworkers reported that reactions of alcohols with methallylsilanes proceeded smoothly in the presence of a catalytic amount of MC Sc(OTf)<sub>3</sub> to afford the corresponding alkyl silyl ethers in high yields.<sup>11</sup> It should be noted that MC Sc(OTf)<sub>3</sub> was more effective than monomeric Sc(OTf)<sub>3</sub> (Table 2). In the cases of alcohols containing other functional groups such as ketones, ethers, esters and acetals, the reactions worked well using MC Sc(OTf)<sub>3</sub>, and the yields of the corresponding TBS ethers were higher than those in the case of using monomeric Sc(OTf)<sub>3</sub>.

**Table 2** Synthesis of TBS ethers using MC Sc(OTf)<sub>3</sub>

ROH	Yield (%) <sup>a</sup>
	98 <sup>b</sup>
	93 (59) <sup>c</sup>
	92 (61)
	95 (74)
	85 (32)

<sup>a</sup> Isolated yields. <sup>b</sup> 0.5 mol% of MC Sc(OTf)<sub>3</sub> and 1.2 equiv. of methallylsilane were used. The reaction was performed for 1 h. <sup>c</sup> Values in parentheses are yields in the case of using monomeric Sc(OTf)<sub>3</sub>.

## Microencapsulated osmium tetroxide [MC OsO<sub>4</sub>]

### Polystyrene-based MC OsO<sub>4</sub> [PS-MC OsO<sub>4</sub>]

Osmium tetroxide (OsO<sub>4</sub>) is the most reliable reagent for the dihydroxylation of olefins to give the corresponding vicinal diols.<sup>12</sup> The reaction proceeds in the presence of a catalytic amount of OsO<sub>4</sub> using a cooxidant such as metal chlorates, hydrogen peroxide, *tert*-butyl hydroperoxide, potassium ferricyanide, or most commonly, *N*-methylmorpholine *N*-oxide (NMO). Although a number of substrates have been successfully applied to this dihydroxylation, few fruitful industrial

applications have been accomplished, probably because OsO<sub>4</sub> is highly toxic, expensive, volatile, and cannot be recovered.

Immobilized osmium catalysts are expected to solve these problems, and indeed such efforts have been made; however, recovery and reuse of polymer catalysts has not been satisfactory in almost all cases.<sup>13</sup> We intended to apply the microencapsulation technique for immobilizing osmium tetroxide.<sup>14</sup> Styrene-based, microencapsulated osmium tetroxide (PS-MC OsO<sub>4</sub>) was easily prepared by the same procedure as that of the preparation of MC Sc(OTf)<sub>3</sub>. One gram of polystyrene and 200 mg of OsO<sub>4</sub> were used, and *ca.* 180 mg of OsO<sub>4</sub> were immobilized. Unencapsulated OsO<sub>4</sub> was recovered from the washings.

PS-MC OsO<sub>4</sub> was first used in dihydroxylation of cyclohexene, and several solvents and cooxidants were examined (Table 3). All the reactions were carried out on a 10 mmol scale using PS-MC OsO<sub>4</sub> containing *ca.* 0.12 g of OsO<sub>4</sub> (5 mol%) in a batch system. When a solvent such as H<sub>2</sub>O–acetone or H<sub>2</sub>O–<sup>t</sup>BuOH (which is used in typical OsO<sub>4</sub>-catalyzed dihydroxylation) was used, lower yields were obtained. However, the yield was dramatically improved when acetonitrile was added to the H<sub>2</sub>O–acetone solution. We also examined several cooxidants. While the reaction was successfully carried out using NMO, only a moderate yield was obtained using trimethylamine *N*-oxide, and much lower yield was observed using hydrogen peroxide or potassium ferricyanide.

**Table 3** Effect of solvents and cooxidants

Solvent	Cooxidant	Yield (%)
H <sub>2</sub> O–acetone (2:1)	NMO	15
H <sub>2</sub> O– <sup>t</sup> BuOH (2:1)	NMO	20
H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1:1:1)	NMO	84
H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1:1:1)	Me <sub>3</sub> NO	57
H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1:1:1)	H <sub>2</sub> O <sub>2</sub>	30
H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1:1:1)	<sup>t</sup> BuOOH	18
H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1:1:1)	K <sub>3</sub> Fe(CN) <sub>6</sub>	0

Several examples of PS-MC OsO<sub>4</sub>-catalyzed dihydroxylation of olefins in the presence of NMO in H<sub>2</sub>O–acetone–acetonitrile are summarized in Table 4. Cyclic and acyclic exo as well as internal olefins worked well under these conditions. Moreover, bulky olefins such as 1-methylcyclohexene and 2-methyl-2-butene also reacted smoothly in the presence of PS-MC OsO<sub>4</sub> to afford the corresponding diols in high yields. The polymer catalyst was recovered quantitatively by simple filtration and could be reused several times without loss of activity (Table 5), indicating that no OsO<sub>4</sub> was released from the polymer catalyst during or after the reaction. This was first confirmed by the qualitative analysis of OsO<sub>4</sub> using iodometry as follows: PS-MC OsO<sub>4</sub> (1.12 g) was stirred in H<sub>2</sub>O–acetone–CH<sub>3</sub>CN (1:1:1, 9 mL) at room temperature for 24 h. After filtration, the resulting filtrate was treated with potassium iodide and HCl. The solution was titrated with sodium thiosulfate in the presence of starch, and no formation of iodine was observed. Since the titration is very sensitive, these results indicate that no contamination OsO<sub>4</sub> in the products occurred. No leaching of OsO<sub>4</sub> was also confirmed later by MIP-MS analysis. Finally, a kinetic study on the conversion of the starting olefin was performed by using OsO<sub>4</sub> and PS-MC OsO<sub>4</sub> in a model dihydroxylation of cyclohexene using NMO as a cooxidant (Table 6). It was found that the reaction proceeded slightly faster using OsO<sub>4</sub> than using PS-MC OsO<sub>4</sub> (Fig. 2). While an 81% yield of the diol was obtained using OsO<sub>4</sub> for 3 h, a 75% yield was obtained using PS-MC OsO<sub>4</sub> under the same reaction conditions.

PS-MC OsO<sub>4</sub> was successfully applied to several total syntheses.<sup>15</sup> For example, in analogue-syntheses and assess-

**Table 4** Dihydroxylation of olefins using PS-MS OsO<sub>4</sub><sup>a</sup>

Olefin	Product	Yield (%)
		<i>n</i> = 1; 84 <i>n</i> = 2; 81 R = (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ; 89 R = (CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> ; 68
		83
		84
		78
		74
		76
		R = CH <sub>3</sub> ; 63 R = (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ; 83 <sup>b</sup>

<sup>a</sup> All reactions were carried out using PS-MC OsO<sub>4</sub> (5 mol%) and NMO in H<sub>2</sub>O–acetone–CH<sub>3</sub>CN (1:1:1) at room temperature for 6–48 h. <sup>b</sup> Carried out at 60 °C.

**Table 5** Recovery and reuse of PS-MC OsO<sub>4</sub>

Run	1	2	3	4	5
Yield of product (%)	84	84	83	84	83
Recovery of catalyst (%)	quant.	quant.	quant.	quant.	quant.

**Table 6** Kinetic study on the conversion of the starting olefin

Time/min	1	10	30	60	180
Yield (OsO <sub>4</sub> ) (%)	11	79	78	78	81
Yield (PS-MC OsO <sub>4</sub> ) (%)	—	7	37	55	75

ment of biological potency of Callistatin A, oxidative cleavage of the olefin (**1**) using PS-MC OsO<sub>4</sub> followed by NaIO<sub>4</sub> treatment afforded hydroxyaldehyde **2** in 95% yield (Scheme 15).<sup>15a</sup>

In the synthesis of 2-acetoxypiperidines, the ene-carbamate (**3**) was oxidized to give *N*-benzyloxycarbonyl-2,3-dihydroxypiperidine (**4**) using OsO<sub>4</sub>.<sup>15b</sup> In this dihydroxylation procedure, PS-MC OsO<sub>4</sub> was observed to lead to the *cis*-diol without epimerization at the 2-position, whereas epimerization occurred when K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O was used (Table 7).

In addition, Oshima and coworkers used PS-MC OsO<sub>4</sub> in deprotection of an allyl ether (Scheme 16).<sup>15c</sup> Deallylation of glycoside (**5**) using PdCl<sub>2</sub> did not give Furanodictine A but oxazoline as a major product. On the other hand, treatment of **5** with Wilkinson's catalyst in 10% aqueous ethanol followed by oxidative cleavage of 1-propenyl glycoside with PS-MC OsO<sub>4</sub> allowed to complete the synthesis of Furanodictine A.

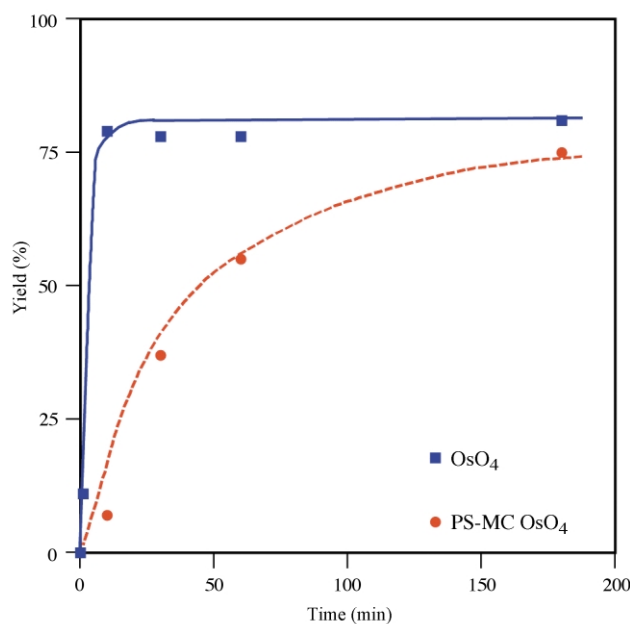
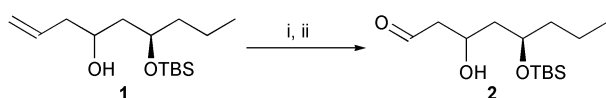


Fig. 2 Kinetic study on dihydroxylation of cyclohexene.



Scheme 15 Oxidative cleavage of olefin (**1**). Reagents and conditions: (i) PS-MC OsO<sub>4</sub> (5 mol%), NMO (5.0 equiv.), H<sub>2</sub>O–acetone–CH<sub>3</sub>CN (1 : 1 : 1), rt, 7 d. (ii) NaIO<sub>4</sub> (5.0 equiv.), Et<sub>2</sub>O–H<sub>2</sub>O (1 : 1), rt, 1.5 h (2 steps 95%).

Table 7 Dihydroxylation of ene-carbamate (**3**)



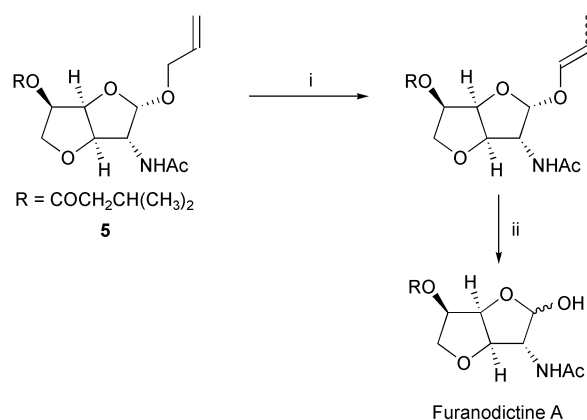
Entry	Conditions	Yield (%)	<i>cis</i> : <i>trans</i> <sup>a</sup>
1	PS-MC OsO <sub>4</sub> (5 mol%), NMO H <sub>2</sub> O–acetone–CH <sub>3</sub> CN (1 : 1 : 1)	79	100:0
2	K <sub>2</sub> OsO <sub>4</sub> ·2H <sub>2</sub> O (1.7 mol%) K <sub>3</sub> Fe(CN) <sub>6</sub> , K <sub>2</sub> CO <sub>3</sub> , <sup>t</sup> BuOH–H <sub>2</sub> O (1 : 1)	73	80:20

<sup>a</sup> Determined by <sup>1</sup>H NMR.

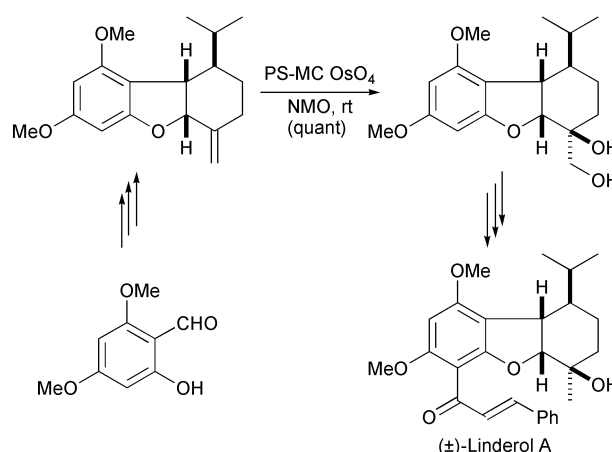
Furthermore, PS-MC OsO<sub>4</sub> was used in the first total synthesis of (±)-Linderol A by Ohta and coworkers (Scheme 17).<sup>15d</sup> After Wittig olefination of the ketone with methylenetriphenylphosphine, dihydroxylation using a catalytic amount of PS-MC OsO<sub>4</sub> in the presence of NMO afforded the corresponding diol as a single isomer in quantitative yield.

### Poly(acrylonitril-*co*-butadiene-*co*-styrene)-based MC OsO<sub>4</sub> [ABS-MC OsO<sub>4</sub>]

Osmium-catalyzed asymmetric dihydroxylation of olefins provides one of the most efficient methods for the preparation of chiral diols.<sup>16</sup> Although high yields and stereoselectivities have been attained in many substrates, high cost of osmium and ligands as well as high toxicity of osmium catalysts, which may contaminate products, have obstructed the use in industry. Soluble and insoluble polymer-supported ligands have been developed by several groups,<sup>17,18</sup> but complete recovery and reuse of the osmium have not yet been accomplished.<sup>19</sup> Microencapsulated osmium tetroxide, which has first achieved complete recovery and reuse of the osmium component in achiral oxidations, was then intended to apply to asymmetric catalysis.



Scheme 16 Deprotection of allyl ether. Reagents and conditions: (i) RhCl(PPh<sub>3</sub>)<sub>3</sub> (20 mol%), DABCO (20 mol%), EtOH–H<sub>2</sub>O (9 : 1), reflux, 2 h. (ii) PS-MC OsO<sub>4</sub> (5 mol%), NMO (1.3 equiv.), H<sub>2</sub>O–acetone–CH<sub>3</sub>CN (1 : 1 : 1), rt, 9 h (2 steps 56%).




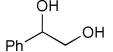
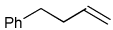
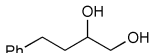

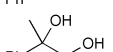

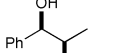

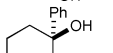

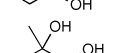

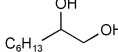

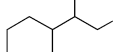

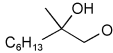
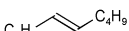
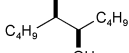
Scheme 17 The first total synthesis of (±)-Linderol A.

In the initial studies, PS-MC OsO<sub>4</sub> was applied to asymmetric oxidation. After many trials, however, the yields and selectivities as well as recovery of the catalyst were not satisfactory, so then the polymer support was changed. Several polymer supports and preparative conditions were examined, and finally the desired osmium catalyst for the catalytic asymmetric dihydroxylation of olefins was prepared using an acrylonitrile–butadiene–styrene (ABS) copolymer and tetrahydrofuran according to the general procedure.<sup>20</sup>

ABS-based OsO<sub>4</sub> (ABS-MC OsO<sub>4</sub>) thus prepared was first tested in achiral dihydroxylation of olefins. In the presence of ABS-MC OsO<sub>4</sub> (5 mol%), styrene was treated with *N*-methylmorpholine *N*-oxide (NMO) in H<sub>2</sub>O–acetone–acetonitrile (1 : 1 : 1). Although styrene was not a good substrate in the dihydroxylation using PS-MC OsO<sub>4</sub> because styrene dissolved PS-MC OsO<sub>4</sub>, the desired product, 1-phenyl-1,2-ethanediol, was obtained in 93% yield using ABS-MC OsO<sub>4</sub>. The catalyst was recovered quantitatively, and the recovered catalyst was used in the second, third and fourth runs, and no loss of activity was observed (93, 90, 87 and 89% yields, respectively, and ABS-MC OsO<sub>4</sub> was recovered quantitatively in all cases). Several other olefins were then examined, and the results are summarized in Table 8. Various olefins including cyclic and acyclic, terminal, mono-, di-, tri- and tetra-substituted olefins worked well to give the corresponding diols in high yields.

Encouraged by these promising results, asymmetric dihydroxylation of olefins was then performed according to the Sharpless procedure.<sup>21</sup> *trans*-Methylstyrene was chosen as a model, and several reaction conditions were examined. When 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ((DHQD)<sub>2</sub>PHAL, Fig. 3) was used as a chiral source and *trans*-methylstyrene was

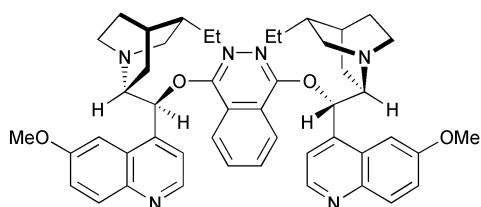
**Table 8** Achiral dihydroxylation of olefins using ABS-MC OsO<sub>4</sub><sup>a</sup>

Olefin	Product	Yield (%)
		94
		82
		quant.
		95
		87
		83 <sup>b</sup>
		73
		74
		82
		77

<sup>a</sup> All reactions were carried out using ABS-MC OsO<sub>4</sub> (5 mol%) and NMO in H<sub>2</sub>O–acetone–CH<sub>3</sub>CN (1:1:1) at room temperature for 12 h. <sup>b</sup> Carried out at 60 °C.

slowly added over 24 h to the mixture of ABS-MC OsO<sub>4</sub>, (DHQD)<sub>2</sub>PHAL (5 mol% each) and NMO, the desired diol was obtained in 88% yield with 84% ee. The osmium catalyst was recovered quantitatively by simple filtration and the chiral ligand was also recovered by simple acid/base extraction (>95% recovery). The recovered catalyst and the chiral source were reused several times and no loss of activity was observed even after the fifth use (Table 9). Higher enantioselectivities were obtained in the second, third, fourth and fifth runs compared to the 1st run. A clear explanation for these results has not been made, but the following control experiment and the standard Sharpless conditions that require an excess of a chiral ligand to osmium may suggest a solution. The control experiment performed was oxidation of *trans*-methylstyrene. *trans*-Methylstyrene was slowly added over 24 h to a mixture of fresh ABS-MC OsO<sub>4</sub> (5 mol%), (DHQD)<sub>2</sub>PHAL (10 mol%) and NMO, and the desired diol was obtained in 91% ee.





This system was applied to other olefins and the results are summarized in Table 10. In most cases, the desired diols were obtained in high yields with high enantiomeric excesses. The yield and selectivities obtained are comparable to those obtained using OsO<sub>4</sub>. For example, 73% yield and 95% ee were obtained in the oxidation of *trans*-methylstyrene using 5 mol% of unencapsulated OsO<sub>4</sub>, 10 mol% of (DHQD)<sub>2</sub>PHAL and NMO (slow addition, 24 h).

**Fig. 3** (DHQD)<sub>2</sub>PHAL.**Table 9** Reuse of ABS-MC OsO<sub>4</sub>

Run	Yield (%)	Ee (%)	Recovery <sup>a,b</sup>
1	88	84	quant.
2	75	95	quant.
3	97	94	quant.
4	81	96	quant.
5	88	95	quant.

<sup>a</sup> Recovery of ABS-MC OsO<sub>4</sub>. <sup>b</sup> Recovery of (DHQD)<sub>2</sub>PHAL ≥95%.

**Table 10** Asymmetric dihydroxylation using ABS-MC OsO<sub>4</sub>

Olefin	ABS-MC OsO <sub>4</sub> (mol%)	Chiral ligand (mol%)	Yield (%)	Ee (%)
	5	10	75	91
	2.5	5	90	92
	1	2	97	86 <sup>a</sup>
	1	2	91	89 <sup>b</sup>
	5	5	98	78
	5	5	64	86
	5	5	90	60
	2.5	5	85	63
	5	5	36	85

<sup>a</sup> 20 mmol-scale experiment was performed. <sup>b</sup> 100 mmol-scale experiment was performed.

The asymmetric reaction was conducted in a 100 mmol-scale experiment. To a mixture of ABS-MC OsO<sub>4</sub> (1.0 mmol, 1.0 mol%), (DHQD)<sub>2</sub>PHAL (2.0 mmol, 2.0 mol%) and NMO (130 mmol) was slowly added *trans*-methylstyrene (100 mmol) over 24 h. The desired diol was obtained in 91% yield with 89% ee, and >95% of ABS-MC OsO<sub>4</sub> and the chiral ligand was recovered.

### Poly(4-phenoxyethoxymethylstyrene-*co*-styrene)-based MC OsO<sub>4</sub> [PEM-MC OsO<sub>4</sub>]

ABS-MC OsO<sub>4</sub> has achieved catalytic asymmetric dihydroxylation with complete recovery and reuse of the catalyst without loss of activity. However, this reaction required a slow addition of olefins, and hence incurred some problems such as a tedious procedure and difficulty of using insoluble substances. Thus, it was next planned to develop recoverable and reusable osmium-catalyzed asymmetric dihydroxylation of olefins without slow addition of olefins.<sup>22,23</sup>

In the initial studies, it was intended to apply ABS-MC OsO<sub>4</sub> to the asymmetric dihydroxylation under Sharpless conditions: *i.e.* two-phase conditions with potassium hexacyanoferrate (K<sub>3</sub>Fe(CN)<sub>6</sub>) as a cooxidant (Table 11). In the presence of ABS-MC OsO<sub>4</sub> and (DHQD)<sub>2</sub>PHAL (5 mol% each), styrene was treated with K<sub>3</sub>Fe(CN)<sub>6</sub> (2.0 equiv.) and potassium carbonate (2.0 equiv.) in H<sub>2</sub>O–<sup>t</sup>BuOH (1:1) for 5 h, and the desired diol was obtained in 81% yield with 94% ee. The recovered catalyst was reused three times, and no loss of activity was observed (entry 1). However, it was revealed that a small amount of OsO<sub>4</sub> was leached from the support.

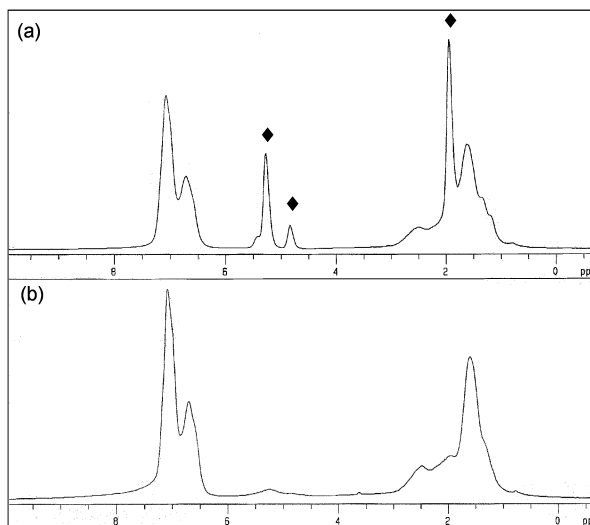
<sup>1</sup>H NMR spectra of ABS-MC OsO<sub>4</sub> was taken using a swollen-resin magic angle spinning (SR-MAS) NMR technique.<sup>24</sup> It was revealed that the olefin moiety of the ABS polymer derived from the butadiene monomer was oxidized by

**Table 11** Study of several polymers

Entry	MC OsO <sub>4</sub>	Yield (%) (ee (%), recovery (%))		
		1st	2nd	3rd
1	ABS <sup>a</sup>	81 (94, 88)	83 (94, 74)	84 (94, 74)
2	PS <sup>b</sup>	4 (—, 97)	—	—
3	AS <sup>c</sup>	5 (—, 99)	—	—

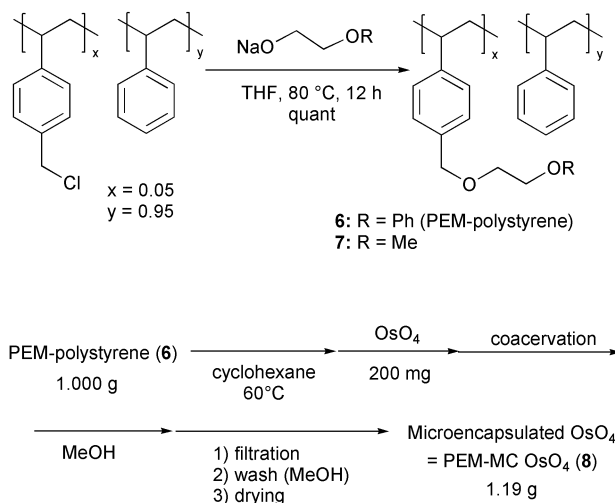
<sup>a</sup> ABS = poly(acrylonitrile-*co*-butadiene-*co*-styrene). <sup>b</sup> PS = polystyrene.  
<sup>c</sup> AS = poly(acrylonitrile-*co*-styrene).

osmium tetroxide, presumably during the microcapsule formation (Fig. 4). Other polymer supports such as polystyrene (PS) and poly(acrylonitrile-*co*-styrene) (AS) were then examined. However, these polymers were not effective under the reaction conditions. It was assumed that the diol moiety of the polymer support was very effective in two-phase dihydroxylation, probably due to the hydrophilic property of the cooxidant. However, leaching of OsO<sub>4</sub> occurred in ABS-MC OsO<sub>4</sub>, because this polymer was too hydrophilic and a part of the polymer was dissolved in the H<sub>2</sub>O-*t*-BuOH solution. On the other hand, PS and AS are lipophilic and were difficult to react with the cooxidant.

**Fig. 4** <sup>1</sup>H Swollen-Resin Magic Angle Spinning (SR-MAS) NMR spectra of (a) ABS polymer and (b) ABS-MC OsO<sub>4</sub> (CDCl<sub>3</sub>). ◆: Butadiene moiety.

Based on these experiments and consideration, a new polymer, phenoxyethoxymethyl-polystyrene (PEM-polystyrene, **6**), shown in Scheme 18 was designed. This polymer was readily synthesized from chloromethyl-polystyrene by etherification. PEM-based microencapsulated OsO<sub>4</sub> was prepared according to the standard procedure.

PEM-MC OsO<sub>4</sub> (**8**) thus prepared was first tested in asymmetric oxidation of styrene using (DHQD)<sub>2</sub>PHAL in H<sub>2</sub>O-alcohol solutions (Table 12, entries 1–3). Although the desired products were obtained in good yields in the first run, the activity of the catalyst decreased significantly in the second and third runs. In H<sub>2</sub>O-THF, the results were similar to those in H<sub>2</sub>O-alcohols (entry 4). On the other hand, in H<sub>2</sub>O-acetone, moderate chemical yields, good enantiomeric excesses, and high recovery of the catalyst were obtained (entry 5). Use of polymer **7** instead of **6** was not effective. It seemed that the phenylether moiety of **6** was required for good recovery. It is noted that the osmium catalyst **8** was recovered quantitatively by simple filtration, and that no leaching of the osmium from **8**

**Scheme 18** Synthesis of PEM-MC OsO<sub>4</sub> (**8**).**Table 12** Effect of linkers and solvents

Entry	Solvent <sup>a</sup>	Yield (%) (ee (%), recovery (%))		
		1st	2nd	3rd
1	A	77 (94, 94)	37 (80, 86)	NR <sup>d</sup> (—, 84)
2 <sup>b</sup>	A	93 (93, 93)	34 (90, 90)	3 (—, 83)
3	B	65 (92, 86)	4 (—, 82)	—
4	C	80 (80, 74)	Trace (—, 61)	—
5	D	35 (77, quant.)	56 (79, quant.)	53 (79, quant.)
6 <sup>b</sup>	D	44 (76, quant.)	49 (78, 94)	60 (78, 90)
7 <sup>c</sup>	D	85 (78, quant.)	66 (78, quant.)	84 (78, quant.)

<sup>a</sup> A, H<sub>2</sub>O-*t*-BuOH (1:1); B, H<sub>2</sub>O-*i*-PrOH (1:1); C, H<sub>2</sub>O-THF (1:1); D, H<sub>2</sub>O-acetone (1:1). <sup>b</sup> Polymer **7** was used instead of **6** (see Scheme 18). <sup>c</sup> Cooxidant (2.0 equiv.) and base (2.0 equiv.) were added at first, and then added again after 3 h. <sup>d</sup> NR = No reaction.

occurred, which were carefully confirmed by fluorescence X-ray analysis.

In order to increase the chemical yields, separate addition of the cooxidant and the base was examined, because it was observed that the desired reaction stopped halfway (Table 12). When K<sub>3</sub>Fe(CN)<sub>6</sub> (2.0 equiv.) and potassium carbonate (2.0 equiv.) were added at first, and they were added again after 3 h, the best result was obtained (entry 7).

This system was applied to other olefins, and the results are summarized in Table 13. In most cases, the desired diols were obtained in good yields with high enantiomeric excesses. It is noteworthy that a wide variety of olefins were applicable in this system and that the catalyst was recovered quantitatively by simple filtration without loss of activity and that no leaching of the osmium occurred.

### Microencapsulated palladium catalysts [MC Pd(PPh<sub>3</sub>)<sub>3</sub>]

While palladium catalysts find widespread utility in a variety of transformations in organic synthesis,<sup>25</sup> these are expensive, air-sensitive, and cannot be recovered in many cases. Immobilized palladium catalysts have been expected to solve these problems, and several polymer-supported palladium catalysts have been developed for allylic substitution,<sup>26,27a-c,f</sup> oligomerization,<sup>26c,28,29</sup> decarboxylation,<sup>26d</sup> hydrogenation,<sup>27h,29</sup> isomerization,<sup>30</sup> telomerization,<sup>31</sup> Suzuki coupling<sup>27c,d,i,32</sup> and the

**Table 13** Asymmetric dihydroxylation of olefins using PEM-MC OsO<sub>4</sub> (**8**)

Entry	Olefin	Time/h	Yield (%)	Ee (%)
1		3 + 2	85 (80) <sup>a</sup>	78 (–82) <sup>a</sup>
2		3 + 2	86	94
3		3 + 2	85	76
4		5 + 4	85	95
5		3 + 2	41	91
6 <sup>b</sup>		3 + 2 + 2 + 2 <sup>c</sup>	66	>99
7 <sup>b</sup>		3 + 2	51	>99

<sup>a</sup> (DHQD)<sub>2</sub>PHAL (5 mol%) was used instead of (DHQD)<sub>2</sub>PHAL. <sup>b</sup> Methanesulfonamide (1.0 equiv.) was added. <sup>c</sup> One equivalent each of K<sub>3</sub>Fe(CN)<sub>6</sub> and K<sub>2</sub>CO<sub>3</sub> was added four times.

Mizoroki–Heck reaction,<sup>27g,i,29c,33</sup> etc. In these cases, however, recovery and reuse of the polymer catalysts have not been satisfactory.<sup>27</sup> We have found that palladium catalyst was successfully immobilized onto a polymer using the microencapsulation technique.<sup>34</sup>

Preparation of the microencapsulated palladium catalyst was performed according to the standard procedure. First, polystyrene (1.000 g) was dissolved in cyclohexane (20 mL) at 40 °C, and to this solution was added tetrakis(triphenylphosphine)palladium(0) (Pd(PPh<sub>3</sub>)<sub>4</sub>, 0.200 g) as a core. Pd(PPh<sub>3</sub>)<sub>4</sub> was dissolved completely. The mixture was stirred for 1 h at this temperature. The color of the mixture changed from brown to black at this stage. The mixture was slowly cooled to 0 °C, and coarservates (phase separation) were found to envelop the core dispersed in the medium, and hexane (30 mL) was added to harden the capsule walls. The mixture was left to stand at room temperature for 12 h, and the catalyst capsules were then washed with acetonitrile several times and dried at room temperature for 24 h. From the washings, it was found that three equivalents of triphenylphosphine (PPh<sub>3</sub>) were recovered and one equivalent of PPh<sub>3</sub> remained in the catalyst capsules. <sup>31</sup>P SR-MAS NMR spectra of the catalyst capsules were measured, and only one peak of PPh<sub>3</sub> coordinating to the palladium was observed. From these results, it was assumed that the catalyst was encapsulated as Pd(PPh<sub>3</sub>) (microencapsulated Pd(PPh<sub>3</sub>)).

Microencapsulated Pd(PPh<sub>3</sub>) (MC Pd(PPh<sub>3</sub>)) thus prepared was first used in the allylation reaction of allyl methyl carbonate (**9**) with dimethyl phenylmalonate (**10**). When **9** was combined with **10** in the presence of 20 mol% MC Pd(PPh<sub>3</sub>), the reaction did not proceed at all. However, it was found that the reaction proceeded smoothly after adding PPh<sub>3</sub> (external ligand). The effect of the amounts of PPh<sub>3</sub> was examined, and the results are shown in Table 14. The best results were obtained when 20 mol% of PPh<sub>3</sub> was used. It should be noted that the palladium catalyst was recovered quantitatively and reused, and that the high activity of the catalyst was maintained even after the fifth use.

Several examples of the MC Pd(PPh<sub>3</sub>)-catalyzed allylation reactions of *C*-nucleophiles with allylic carbonates are summarized in Table 15. Malonates and β-ketoesters smoothly reacted under these conditions to afford the corresponding allylation adducts in high yields. While the reaction of ethyl acetoacetate with (*E*)-cinnamyl methyl carbonate (**12**) gave a mixture of *E*:*Z*

**Table 14** Effect of the amounts of triphenylphosphine

MC Pd(PPh <sub>3</sub> ) (mol%)	PPh <sub>3</sub> (mol%)	Yield (%) (recovery (%))		
		1st	2nd	3rd
5	0	0	—	—
5	5	97 (quant.)	75 (quant.)	57 (quant.)
20	0	0	—	—
20	10	94 (quant.)	61 (99)	30 (99)
20	20	83 (quant.)	90 (quant.)	84 (quant.) <sup>a</sup>
20	40	92 (quant.)	81 (99)	77 (quant.)
20	60	69 (95)	58 (98)	65 (99)

<sup>a</sup> 4th, 94 (quant.); 5th, 83 (quant.).

stereoisomers (*E*:*Z* = 64:36), only *E* isomers were obtained in the reactions of **10** with **12** and (*Z*)-carbonate **13**. The recovery was quantitative in all cases and the recovered catalyst could be reused.

MC Pd(PPh<sub>3</sub>) was successfully used in other reactions. Allyl acetate reacted with dimethyl phenylmalonate in the presence of MC Pd(PPh<sub>3</sub>), PPh<sub>3</sub>, *N,O*-bis(trimethylsilyl)acetamide (BSA), and a catalytic amount of potassium acetate, to afford the corresponding adduct in 90% yield (Scheme 19). In addition, Suzuki coupling reactions<sup>35</sup> of boronic acids with aryl bromides were found to proceed smoothly in the presence of MC Pd(PPh<sub>3</sub>) to afford the corresponding adducts in high yields (Scheme 20). 2-Bromothiophene also worked well. In these reactions, the best results were obtained by using tri-*o*-tolylphosphine (P(*o*-Tol)<sub>3</sub>) as an external ligand. A catalytic asymmetric allylation reaction was also successfully carried out using MC Pd(PPh<sub>3</sub>) and a chiral ligand (Scheme 21). The

**Table 15** Allylic substitution using MC Pd(PPh<sub>3</sub>)<sup>a</sup>

Entry	Allylic carbonate	Nucleophile	Product	Yield (%)
1	<b>9</b>	<b>10</b>		83
2	<b>9</b>			86
3	<b>9</b>			60
4	<b>11</b>	<b>10</b>		69
5	<b>12</b>	<b>10</b>		92 <sup>b</sup>
6	<b>12</b>			79 <sup>c</sup>
7	<b>13</b>	<b>10</b>		64 <sup>b</sup>

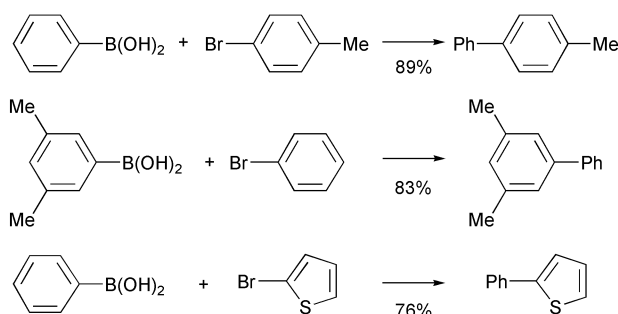
<sup>a</sup> All reactions were carried out using MC Pd(PPh<sub>3</sub>) (20 mol%) and PPh<sub>3</sub> (20 mol%) in CH<sub>3</sub>CN at room temperature for 12 h. <sup>b</sup> *E*:*Z* = >99: <1. <sup>c</sup> *E*:*Z* = 64:36.



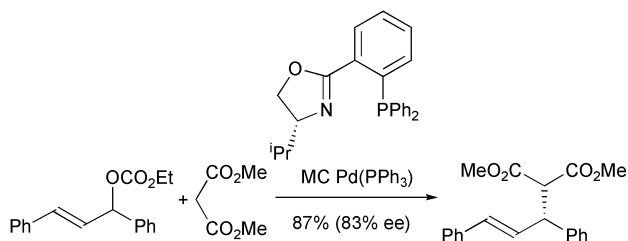
reaction of 1,3-diphenyl-2-propen-1-yl ethyl carbonate (1.0 equiv.) with dimethyl malonate (3.0 equiv.) was performed in the presence of MC Pd(PPh<sub>3</sub>) (20 mol%), 2-(*o*-diphenylphosphinophenyl)-(4*R*)-isopropylloxazoline (20 mol%),<sup>36</sup> BSA (3.0 equiv.) and potassium acetate (0.10 equiv.) under reflux conditions in acetonitrile. The allylation adduct was obtained in 87% yield with 83% ee.



**Scheme 19** Allylic substitution of allyl acetate with **10**. Reagents and conditions: MC Pd(PPh<sub>3</sub>) (20 mol%), PPh<sub>3</sub> (20 mol%) BSA (3.0 equiv.), KOAc (0.10 equiv.), CH<sub>3</sub>CN, reflux, 12 h.



**Scheme 20** Suzuki coupling. Reagents and conditions: MC Pd(PPh<sub>3</sub>) (20 mol%), P(*o*-Tol)<sub>3</sub> (20 mol%), K<sub>3</sub>PO<sub>4</sub> (2.0 equiv.), CH<sub>3</sub>CN, reflux, 6 h.



**Scheme 21** Asymmetric allylic substitution. Reagents and conditions: MC Pd(PPh<sub>3</sub>) (20 mol%), chiral ligand (20 mol%), BSA (3.0 equiv.), KOAc (0.10 equiv.), CH<sub>3</sub>CN, reflux, 12 h.

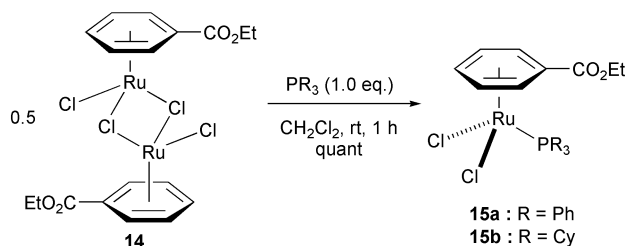
For the structure of MC Pd(PPh<sub>3</sub>), we assume 18-electron Pd(0) that is coordinated by PPh<sub>3</sub> and the benzene ring(s) of polystyrene. After adding an external ligand, 14- or 16-electron Pd(0) would be formed and the catalytic reaction proceeds. The coordination of the external ligand to Pd(0) was confirmed by <sup>31</sup>P SR-MAS NMR analysis, which revealed that the recovered catalyst in Suzuki coupling reactions contained P(*o*-Tol)<sub>3</sub>.

## Polymer-supported arene-ruthenium complexes [PS-RuCl<sub>2</sub>(PR<sub>3</sub>)]

Arene-ruthenium complexes are very useful precatalysts for several organic reactions such as transfer hydrogenation,<sup>37</sup> Diels–Alder reaction,<sup>38</sup> olefin cyclopropanation,<sup>39</sup> enol formate formation,<sup>40</sup> cyclization of dienyalkyne,<sup>41</sup> and olefin metathesis,<sup>42</sup> etc. While the catalysts prepared from the arene-ruthenium complexes are air- and moisture-sensitive, expensive, and cannot be recovered in many cases, immobilized catalysts are expected to solve these problems. Although several polymer-supported ruthenium complexes have been reported,<sup>43</sup> these involve problems such as tedious procedures for the preparation of the complexes, low activity compared with the original catalysts, and difficulty of applying the catalysts to other reactions. Therefore, development of more versatile polymer-supported ruthenium complexes is strongly demanded. Since microencapsulation techniques have been successfully

applied to Sc, Os and Pd, it was decided to develop a new type polymer-supported ruthenium catalyst based on the technique.

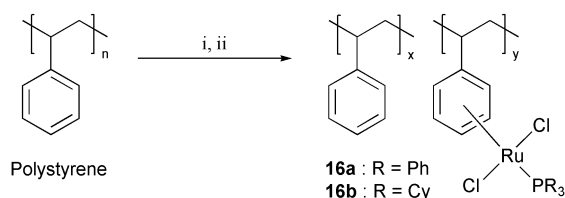
The idea is to utilize the benzene rings of polystyrene as ligands to immobilize arene–metal complexes. However, it has been known that arene-displacement reactions at Ru(II) are often sluggish.<sup>44</sup> Thus, [Ru(η<sup>6</sup>-C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>Et)Cl<sub>2</sub>]<sub>2</sub> (**14**) was carefully chosen as the starting material, because it was reported that an intramolecular arene exchange proceeded in good yield using **14** instead of [Ru(η<sup>6</sup>-*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>.<sup>45</sup> Dimer **14** was easily prepared according to the literature procedure,<sup>44,45</sup> and treatment of **14** with triphenylphosphine or tricyclohexylphosphine gave [Ru(η<sup>6</sup>-C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>Et)Cl<sub>2</sub>]<sub>2</sub> (**15a**: R = Ph, **15b**: R = Cy) quantitatively (Scheme 22).



**Scheme 22** Preparation of monomeric catalysts **15**.

Preparation of the polymer-supported arene ruthenium complexes using **15** was successfully performed based on a procedure, which is similar in part to that of formation of microcapsules (Scheme 23).<sup>46</sup> Polystyrene (5.00 g) was dissolved in cyclohexane (100 mL) at 65 °C, and to this solution was added **15a** (0.20 g). Complex **15a** was not dissolved and a suspension solution was obtained. The mixture was stirred at 120 °C for 24 h, and then at 65 °C for 1 h. The reaction was monitored by TLC. Complex **15a** disappeared and ethyl benzoate appeared. The mixture was slowly cooled to 0 °C. Coarsening (phase separation) occurred to envelop the core dispersed in the medium to form catalyst capsules, and hexane (100 mL) was added to harden the capsule walls. The mixture was left to stand at room temperature for 12 h, and the catalysts were then washed with acetonitrile several times and dried at room temperature for 24 h to give polymer-supported ruthenium complex **16a**. The procedure for **16b** is similar to the preparation of **16a**. The structure of **16** was confirmed by NMR analysis. The <sup>31</sup>P SR-MAS NMR spectra of the catalysts were measured, and only one peak of PR<sub>3</sub> (**16a**: R = Ph: δ 25.7, **16b**: R = Cy: δ 28.5) coordinating to the ruthenium was observed. [Ru(η<sup>6</sup>-*p*-cymene)(PPh<sub>3</sub>)Cl<sub>2</sub>] was prepared and <sup>31</sup>P NMR of this complex was measured (δ 23.1). [Ru(η<sup>6</sup>-*p*-cymene)(P-Cy<sub>3</sub>)Cl<sub>2</sub>] was reported in literature (δ 26.0).<sup>42c</sup> From these results, it was concluded that the catalyst was supported as arene–RuCl<sub>2</sub>(PR<sub>3</sub>) (polymer-supported arene–RuCl<sub>2</sub>(PR<sub>3</sub>) (**16**, PS-RuCl<sub>2</sub>(PR<sub>3</sub>))). To the best of our knowledge, this is the first example of a polymer-supported ruthenium catalyst, in which the benzene rings of the polymer coordinated to the ruthenium to immobilize the catalyst onto the polymer.

PS-RuCl<sub>2</sub>(PR<sub>3</sub>) (**16**) was first used in ring-closing olefin metathesis (RCM). We prepared a polymer-supported cationic ruthenium allenylidene complex according to the Dixneuf and Fürstner method.<sup>42b,c</sup> Thus, PS-RuCl<sub>2</sub>(PPh<sub>3</sub>) (**16a**), tricyclohexylphosphine (PCy<sub>3</sub>), 1,1-diphenyl-2-propynol (**17**) and sodium



**Scheme 23** Synthesis of polymer-supported arene–RuCl<sub>2</sub>(PR<sub>3</sub>) (**16**). Reagents and conditions: (i) cyclohexane, 65 °C, 1 h. (ii) **15a** or **15b**, 120 °C, 24 h then 65 °C, 1 h then 0 °C.

hexafluorophosphate (NaPF<sub>6</sub>) were mixed in several solvents, and the mixture was stirred for 1 h under reflux conditions. Signals of the <sup>31</sup>P SR-MAS NMR spectra of the activated ruthenium catalyst (**18a**, Fig. 5) thus prepared were observed at

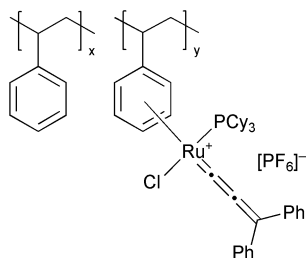


Fig. 5 Activated ruthenium catalyst **18a**.

$\delta$  50.8 and  $-144.0$ . The <sup>31</sup>P NMR spectrum of the monomeric ruthenium complex has already been measured [<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta$  58.8 (PCy<sub>3</sub>),  $-140.8$  (PF<sub>6</sub><sup>-</sup>)].<sup>40c,47</sup> Catalyst **18a** was then tested in RCM of *N,N*-diallyl-*p*-toluenesulfonamide (**19**) in hexane (Table 16). It was found that the choice of solvents was crucial. While the desired product was obtained in good yield in the first run in <sup>i</sup>PrOH–hexane (1 : 1), the activity of the catalyst decreased significantly in the second and third runs (entry 2). On the other hand, the yield of the desired product was very low in <sup>i</sup>PrOH (entry 1). In <sup>i</sup>PrOH–hexane (1 : 10), moderate chemical yields were obtained. The activity of the catalyst was maintained even after the third use (entries 3 and 4). In all reactions, no leaching of ruthenium metal were confirmed by fluorescence X-ray analysis.

Table 16 Effect of solvents in the preparation of the active catalyst

Entry	Solvent	Yield (%) (recovery (%))		
		1st	2nd	3rd
1	<sup>i</sup> PrOH	8 (quant.)	9 (quant.)	—
2	<sup>i</sup> PrOH–hexane (1 : 1)	78 (quant.)	48 (quant.)	16 (quant.)
3	<sup>i</sup> PrOH–hexane (1 : 10)	42 (quant.)	69 (quant.)	71 (quant.)
4	<sup>i</sup> PrOH–hexane (1 : 10) <sup>a</sup>	49 (98)	72 (quant.)	77 (quant.)

<sup>a</sup> **16b** was used instead of **16a**.

In order to increase the chemical yields, reactivation conditions of the recovered catalysts in RCM were next examined (Table 17). After careful investigations, the best results were obtained when a mixture of the recovered catalyst, PCy<sub>3</sub>, and **17** was stirred for 1 h under reflux conditions and, after addition of NaPF<sub>6</sub>, further stirred for 12 h at room temperature (method C). Several other examples of the PS Ru-catalyzed ring-closing metathesis of olefins were then tested, and the results are summarized in Table 18. Six- as well as five-membered rings were smoothly formed under these conditions, while sterically hindered diethyl diallylmalonate was less reactive (entry 4). It should be noted that recovery of the catalyst was quantitative in all cases, and that the recovered catalyst could be reused without loss of activity. In addition, the structure of the recovered catalyst was confirmed by <sup>31</sup>P SR-MAS NMR analysis. Signals were observed at  $\delta$  50.8 and  $-144.0$ , which were completely consistent with those of the original catalyst **18a**.

Table 17 Reactivation conditions of the catalyst

Entry	Method	Conditions	Yield (%)		
			1st	2nd	3rd
1	A	PCy <sub>3</sub> , <b>17</b> , reflux, 1 h	40	72	77
2	B	PCy <sub>3</sub> , NaPF <sub>6</sub> , <b>17</b> , rt, 12 h	63	56	49
3	C	PCy <sub>3</sub> , <b>17</b> , reflux, 1 h then NaPF <sub>6</sub> , rt, 12 h	69	73	85
4 <sup>c</sup>	C	As above	75	81	98 <sup>f</sup>
5 <sup>c,d</sup>	C	As above	71	85	88
6 <sup>c,e</sup>	C	As above	97	18	12
7 <sup>c,g</sup>			80	—	—

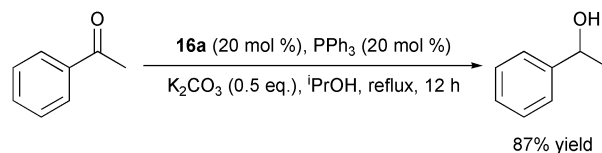
<sup>a</sup> Catalyst **18a** was reactivated under method A–C in <sup>i</sup>PrOH–hexane (1 : 10). <sup>b</sup> Recovery of the catalysts was quantitative. <sup>c</sup> Hexane–toluene (10 : 1) was used as a solvent in RCM. <sup>d</sup> 10 mol% of **18a** was used. <sup>e</sup> 5 mol% of **18a** was used. <sup>f</sup> 4th, 83% (recovery: quant.); 5th, 82% (recovery: quant.); 6th, 89% (recovery: quant.); 7th, 92% (recovery: quant.). <sup>g</sup> [(*p*-cymene)RuCl(PCy<sub>3</sub>)(=C=C=CPh<sub>2</sub>)]<sup>+</sup>[PF<sub>6</sub>]<sup>-</sup> was used instead of **18a**.

Table 18 Ring-closing olefin metathesis using **18a**<sup>a</sup>

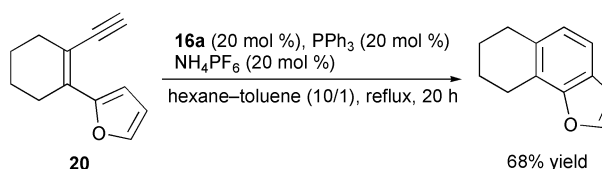
Entry	Substrate	Product	Yield (%)
1			98
2			92
3			57 <sup>b</sup>
4			72
5			66
6			82

<sup>a</sup> All reactions were carried out using **18a** (20 mol%) in hexane–toluene (10 : 1) under reflux conditions for 12 h. <sup>b</sup> Reaction was carried out for 24 h.

PS-RuCl<sub>2</sub>(PPh<sub>3</sub>) (**16a**) was successfully used in other reactions. Acetophenone was reduced smoothly in the presence of **16a** to afford the corresponding alcohol in high yield (Scheme 24). In addition, **16a** catalyzed cyclization of dienyllalkyne (**20**) in good yield (Scheme 25).



Scheme 24 Hydrogenation of acetophenone using **16a**.



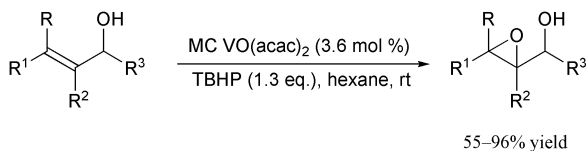
Scheme 25 Cyclization of dienyllalkyne using **16a**.

## Conclusion

New types of polymer-supported catalysts, microencapsulated catalysts, have been discussed. The catalysts were developed based on a microencapsulation technique for binding catalysts to polymers utilizing physical envelopment by polymer backbones and interaction between  $\pi$  electrons of benzene rings of the polystyrenes used as polymer backbones and vacant orbitals of the catalysts. They are indeed unprecedented polymer-supported catalysts, and immobilization of Sc, Os, Pd and Ru catalysts has been demonstrated, and high activities have been attained. In all cases, no leaching of the catalysts occurred, and the immobilized catalysts were recovered quantitatively by simple filtration and reused without loss of activity. It is noted that this method enables direct immobilization of metals onto polymers, and that normally unstable species such as Pd(0)(PPh<sub>3</sub>) can be kept stable by this immobilization technique. It is expected that other metal catalysts can be immobilized using this microencapsulation technique, and that these catalysts contribute to environmentally benign and powerful high-throughput organic synthesis.

## Notes in proof

After completing this article, Gibson and Swamy reported a microencapsulated metathesis catalyst.<sup>48</sup> Ley and coworkers also published elegant examples of polyurea-encapsulated palladium catalysts.<sup>49</sup> Furthermore, Lattanzi and Leadbeater prepared microencapsulated VO(acac)<sub>2</sub> (MC VO(acac)<sub>2</sub>), which was used in epoxidation of allylic alcohols using *tert*-butyl hydroperoxide as an oxidant (Scheme 26).<sup>50</sup> The reactions proceeded smoothly in hexane at room temperature. The MC VO(acac)<sub>2</sub> was reusable without significant loss of activity.



Scheme 26 Allylic alcohol epoxidation using MC VO(acac)<sub>2</sub>.

## Acknowledgements

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