# “Microencapsulated” and Related Catalysts for Organic Chemistry and Organic Synthesis

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## Contents

## 1. Introduction

“Green Chemistry”[1] is spreading all over the world. Green Chemistry (environment-friendly chemistry) is chemical technology for eradication of environmental pollution by changing from conventional processes to environmentally friendly processes, which do not produce or use environmental pollutants or dangerous substances, and also by replacing conventional chemical products with environmentally friendly or harmless ones. Furthermore, it is thought that Green Chemistry is a paradigm shift of chemistry or a basic technology for chemistry for the 21st century. For continuous development of human beings, realization of symbiosis in chemistry and the environment is the most important subject in this century.

In promotion of Green Chemistry, synthetic organic chemistry has played an important role, and it has changed many synthetic processes to environmentally friendly ones. The requirements for environmentally friendly processes are (1) reduction of waste, (2) use of materials with low toxicity toward the human body and environment with no production of harmful materials, (3) reduction of assistant materials such as solvents and separating agents, (4) use of starting materials that can be renewable, (5) minimum energy consumption, (6) development of catalytic reactions rather than stoichiometric reactions, etc.

In synthetic organic chemistry, one of the most direct ways to satisfy these requirements is use of truly efficient catalytic reactions. In stoichiometric reactions, large amounts of activating agents are needed to drive desired reactions, and moreover, after reactions are complete, a large amount of waste forms along with the desired products. In catalytic reactions, on the other hand, one catalyst molecule can react with infinite starting materials in principle, and waste can be reduced. Furthermore, since catalytic reactions reduce activation energy, reactions can proceed at lower temperatures in a short time, and thus, catalytic reactions can contribute significantly to energy conservation.

While relatively simple organic compounds can be activating agents for catalytic reactions, most catalysts are bulk of metal, metal oxide,[2a] and organometallic complexes,[3] which are combined with inorganic and organic ligands. Many highly active and selective metal catalysts have been developed. In addition, solid catalysts, in which metal clusters are immobilized onto carbon, alumina, inorganic materials, etc., have been widely used especially in industrial productions. It can be said that these solid catalysts are suitable for Green Chemistry in terms of effective use for limited natural resources, because these catalysts can be separated from a reaction mixture by simple filtration and can be recycled.

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Ryo Akiyama was born in 1974 in Niigata. He studied chemistry at 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. After his postdoctoral work in Cambridge, U.K. (Professor Steven V. Ley), he joined Professor Kobayashi’s group as a postdoctoral fellow of SORST and a group leader of ERATO, Japan Science and Technology Corporation (JST). His research interest includes development of new synthetic methods and polymer-supported catalysts.

Shū Kobayashi was born in 1959 in Tokyo, Japan. He studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences, University of Tokyo, as full professor. In April 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, Faculty of Science, the University of Tokyo. Professor Kobayashi is also director of the ERATO project of the Japan Science Agency (JST). He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), and Philipps-University of Marburg (1997). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Ciba-Geigy Research Foundation Award (1994), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Organic Reactions Lecturer (2002), Nagoya Silver Medal (2002), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), Howard Memorial Lecturer (2006), C.S. Hamilton Award (2007), and Merck-Cambridge Lecturer (2007).

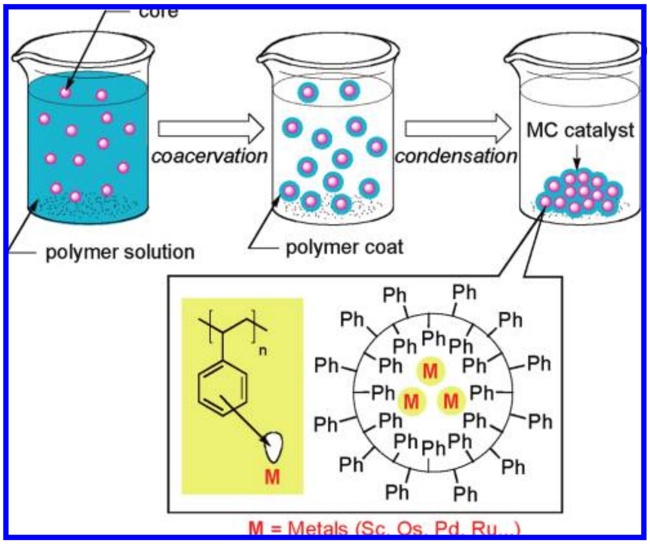


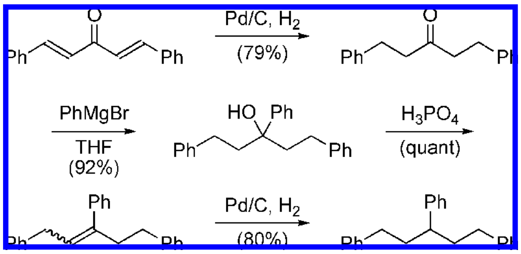
**Figure 1.** Microencapsulation technique.

However, a drawback is that reactivity of immobilized metal catalysts is often lower than that of the corresponding original catalysts. Moreover, in many cases, recovered catalysts have lower reactivity than that of fresh catalysts, and in such cases labor and energy consumption are needed for recycling catalysts.

To address these issues, several groups have investigated highly active immobilized metal catalysts,[2b,c] which can be recovered and reused without leaching of metals. In addition to the above-mentioned materials, such as carbon and alumina, synthetic polymers, silica, zeolite, clays, etc. have been investigated as supports. In most cases, however, tedious procedures are needed for preparation of complexes, and low activity is observed compared with that of the original catalysts. When the catalyst activity is evaluated, turnover number (TON) and turnover frequency (TOF) of the catalyst are often used as an index that shows how many molecules of a starting material can be converted to a desired product by one catalyst in total or per unit time. That is, the catalyst that has higher TON and TOF is more efficient and even more desirable from a viewpoint of Green Chemistry.

As a new method for immobilizing metal catalysts onto polymers, the microencapsulation method was first introduced in 1998.[4] Before that, microcapsules had been used for coating and isolating substances until their activity is needed. Their application to medicine and pharmacy was extensively studied.[5] The idea of the new method is to apply the microencapsulation technique for immobilization of catalysts onto polymers (Figure 1). That is, catalysts would be physically enveloped by thin films of polymers (polystyrene derivatives in many cases) and at the same time immobilized by interaction between $\pi$ electrons of the benzene rings of the polystyrenes, which are used as a polymer backbone, and vacant orbitals of the catalysts (metal compounds). The catalysts were new types of heterogeneous catalysts and were named as “microencapsulated (MC) catalysts”. Microcapsules in these catalysts are backbones of immobilized catalysts such as cross-linked polymers and inorganic materials such as silica gel and alumina, and thus are completely different from conventional microcapsules that are used for protection. After that, polymer incarcerated (PI) catalysts, which are more robust against many solvents, were developed based on the MC technique. In this review, we describe such unprecedented polymer-supported catalysts as MC catalysts and PI catalysts, which can create recoverable, reusable, and highly active heterogeneous metal catalysts for several organic reactions. While MC and PI catalysts are heterogeneous catalysts, they are very different

**Scheme 1. Synthesis of 1,3,5-Triphenylpentane**



from conventional heterogeneous catalysts in many aspects. Therefore, we describe more details of these catalysts in this review, which may be a little bit different from other review articles. On the other hand, we will not discuss other immobilized catalysts in this review, which are treated in detail in other contributions to this issue.

## 2. Polystyrene-Based Catalysts

### 2.1. Microencapsulated Scandium Trifluoromethanesulfonate [MC Sc(OTf)$_3$]

Sc(OTf)$_3$ is a new type of water-compatible Lewis acid,[6] and many useful synthetic reactions using Sc(OTf)$_3$ have been developed.[7] Microencapsulated Sc(OTf)$_3$ [MC Sc(OTf)$_3$] was prepared as follows:[4] Polystyrene (1.000 g) was dissolved in cyclohexane (20 mL) at 50−60 °C, and powdered Sc(OTf)$_3$ (0.200 g) was added to this solution as a core. The mixture was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coacervates were found to envelop the solid core dispersed in the medium, 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)$_3$ (0.080 g), 0.120 g of Sc(OTf)$_3$ was microencapsulated according to this procedure. The weight of the capsules, which contain acetonitrile, was 1.167 g. MC Sc(OTf)$_3$ 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)$_3$ revealed that small capsules of MC Sc(OTf)$_3$ adhered to each other, probably due to the small size of the core, and that Sc(OTf)$_3$ was located all over the polymer surface. The importance of the benzene rings of the polystyrene in immobilizing Sc(OTf)$_3$ was demonstrated by control experiments using polybutadiene or polyethylene instead of polystyrene. Whereas 43% of Sc(OTf)$_3$ (where 100% is the amount of Sc(OTf)$_3$ immobilized by polystyrene) was bound using polybutadiene, no Sc(OTf)$_3$ was observed in the microcapsules prepared using polyethylene.[8]

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

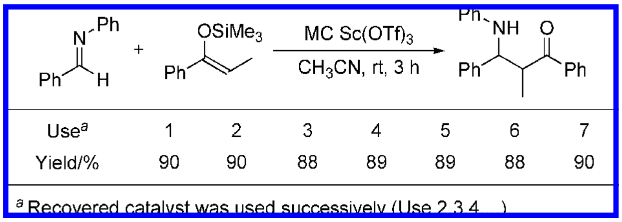
Recently, experimental and theoretical studies of $^{45}$Sc NMR interactions in solids were reported.[9] Several scandium salts such as Sc(acac)$_3$, Sc(TMHD)$_3$ Sc(NO$_2$)$_3$•5H$_2$O, Sc(OAc)$_3$, ScCl$_3$•6H$_2$O, ScCl$_3$•THF, and ScCp$_3$ were examined. In this study, solid-state $^{45}$Sc, $^{13}$C, and $^{19}$F NMR experiments are also applied to characterize the structures of microcrystalline Lewis acid catalyst Sc(OTf)$_3$ (for which the crystal structure is unknown) and noncrystalline and polystyrene microencapsulated Sc(OTf)$_3$.

**Table 1. NMR Experiments[a]**

| sample | $^{45}$Sc NMR peak shift data (ppm) |
|---|---|
| Sc(OTf)$_3$ | −182.2 |
| Sc(OTf)$_3$ + 1,3,5-triphenylpentane | −168.4 |
| MC Sc(OTf)$_3$ | −163.9 |

[a] ScCl$_3$ was used as an external standard ($\delta = 0$) in CD$_3$CN.

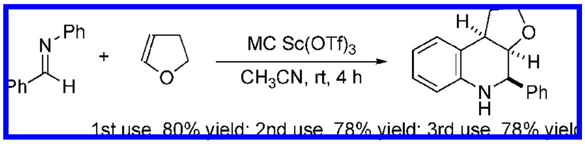
**Scheme 2. Imino Aldol Reaction (Flow System)**



| Use[a] | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Yield/% | 90 | 90 | 88 | 89 | 89 | 88 | 90 |

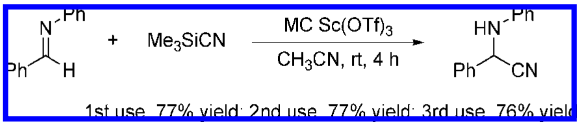
[a] Recovered catalyst was used successively (Use 2,3,4, ...)

**Scheme 3. Aza-Diels−Alder Reaction (Flow System)**



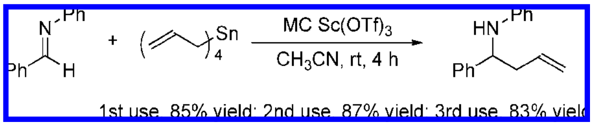
1st use, 80% yield; 2nd use, 78% yield; 3rd use, 78% yiel

**Scheme 4. Cyanation Reaction (Flow System)**



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

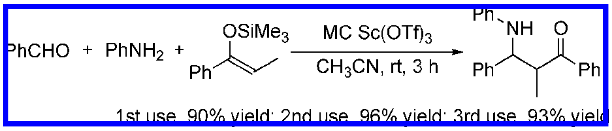
**Scheme 5. Allylation Reaction (Flow System)**



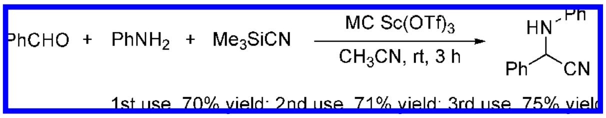
1st use, 85% yield; 2nd use, 87% yield; 3rd use, 83% yiel

MC Sc(OTf)$_3$ was successfully used in several fundamental and important Lewis acid-catalyzed carbon−carbon bond-forming reactions. All reactions were carried out on a 0.5 mmol scale in acetonitrile or nitromethane using MC Sc(OTf)$_3$ containing ca. 0.120 g of Sc(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 Sc(OTf)$_3$ effectively activated aldimines. Imino aldol (Scheme 2),[7d] aza-Diels−Alder (Scheme 3),[7d,e] cyanation (Scheme 4),[7f] and alkylation (Scheme 5)[7g] reactions of aldimines proceeded smoothly using MC Sc(OTf)$_3$ to afford synthetically useful $\beta$-amino ester, tetrahydroquinoline, α-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 or products, MC Sc(OTf)$_3$ effectively catalyzed the reactions in all cases. One of the most remarkable and exciting points is that the ability of MC Sc(OTf)$_3$ to activate aldimines was superior to that of monomeric Sc(OTf)$_3$, which was shown by kinetic studies. The polymer catalyst was recovered quantitatively by simple filtration and could be

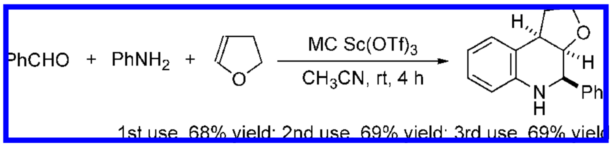
**Scheme 6. Mannich-type Reaction (Flow System)**



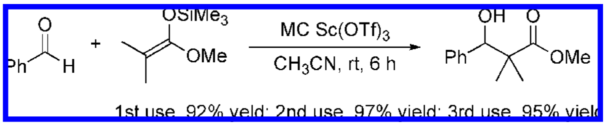
**Scheme 7. Strecker Reaction (Flow System)**



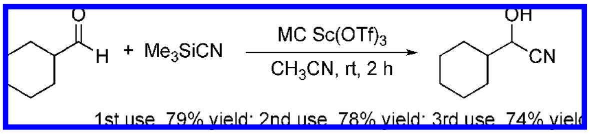
**Scheme 8. Qinoline Synthesis (Flow System)**



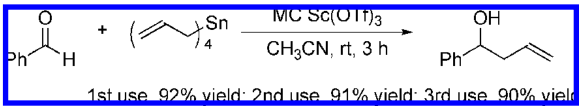
**Scheme 9. Aldol Reaction (Batch System)**



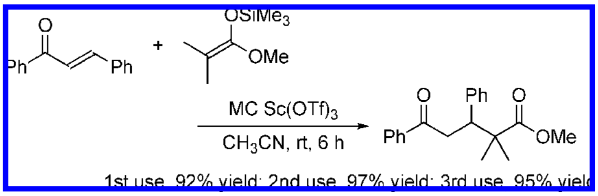
**Scheme 10. Cyanation Reaction of Aldehyde (Batch System)**



**Scheme 11. Allylation Reaction of Aldehyde (Batch System)**



**Scheme 12. Michael Reaction (Batch System)**

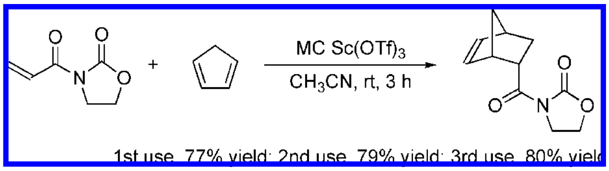


reused. The activity of the recovered catalyst did not decrease even after several uses.

MC Sc(OTf)$_3$ has also been successfully used in three-component reactions such as Mannich-type (Scheme 6),[7h] Strecker (Scheme 7),[7f] and quinoline-forming (Scheme 8)[7i] reactions, which provide efficient methods for the preparation of biologically interesting compound libraries.[10]

It was also found that MC Sc(OTf)$_3$ could activate carbonyl compounds such as aldehydes and $\alpha,\beta$-unsaturated ketones. Aldol (Scheme 9),[7i] cyanation (Scheme 10), and allylation (Scheme 11)[7k] of aldehydes proceeded smoothly using MC Sc(OTf)$_3$ 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)[7j] and a Diels−Alder reaction of an oxazolidinone derivative with cyclopentadiene (Scheme 13)[6] also proceeded smoothly using MC Sc(OTf)$_3$. Moreover, a Friedel−Crafts acylation was performed to produce an aromatic ketone in a good yield (Scheme 14).[7l] Friedel−Crafts alkylation and acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry.[11] While the alkylation reaction proceeds in the presence of a catalytic amount of Lewis acid, the acylation reaction generally requires more than a stoichiometric amount of Lewis acid such as aluminum chloride ($AlCl_3$), 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)$_3$ has high activity in the Friedel−Crafts acylation and that MC Sc(OTf)$_3$ can be recovered easily by simple filtration and reused without significant loss of activity.

**Scheme 13. Diels−Alder Reaction (Batch System)**



**Scheme 14. Friedel−Crafts Acylation (Batch System)**

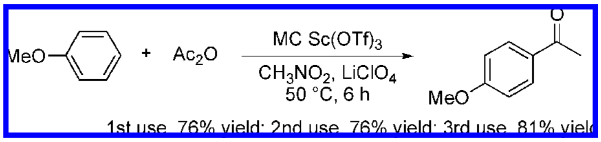
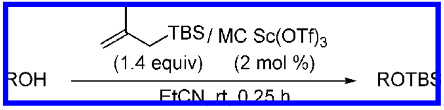
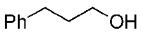
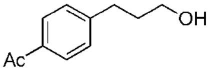
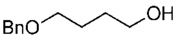
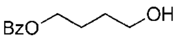
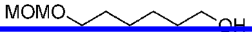


**Table 2. Synthesis of TBS Ethers Using MC Sc(OTf)$_3$**



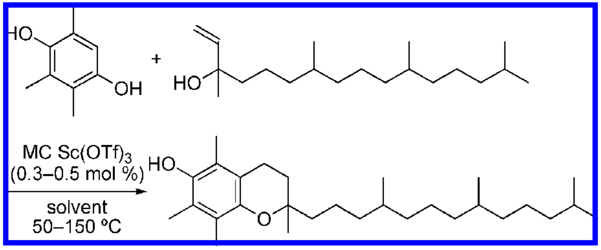
| ROH | Yield (%)[a] |
|---|---|
|  | 98[b] |
|  | 93 (59)[c] |
|  | 92 (61) |
|  | 95 (74) |
|  | 85 (32) |

[a] Isolated yields. [b] MC Sc(OTf)$_3$ (0.5 mol %) and 1.2 equiv of methallylsilane were used. The reaction was performed for 1 h. [c] Numbers in parentheses are yields using monomeric Sc(OTf)$_3$.

MC Sc(OTf)$_3$ was successfully used in other transformations. The reactions of alcohols with methallylsilanes proceeded smoothly in the presence of a catalytic amount of MC Sc(OTf)$_3$ to afford the corresponding alkyl silyl ethers in high yields.[12] Interestingly again, MC Sc(OTf)$_3$ was more effective than monomeric Sc(OTf)$_3$ (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)$_3$, and the yields of the corresponding *tert*-butyldimethylsilyl (TBS) ethers were higher than those in the case of using monomeric Sc(OTf)$_3$.

The synthesis of D,L-$\alpha$-tocophenol using MC Sc(OTf)$_3$ was reported (Table 3).[13] The acid-catalyzed $\alpha$-tocophenol synthesis consists of Friedel−Crafts reaction followed by a cyclization reaction. It is known that alcohols and preferably tertiary allylic alcohols like isophytol are easily dehydrated

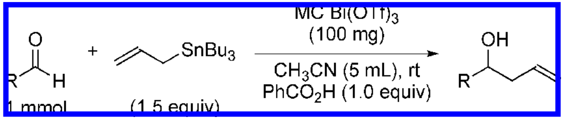
**Table 3. Synthesis of D,L-α-Tocophenol Using MC Sc(OTf)$_3$**

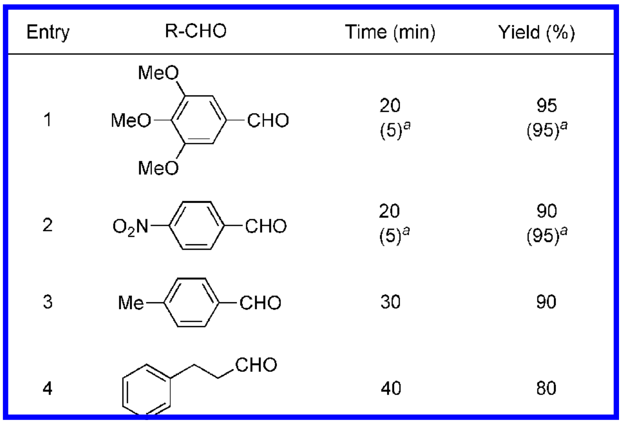


| solvent | yield (%)[a] |
|---|---|
| toluene | 52.3 |
| toluene[b] | 5.6 |
| nitromethane | 26.2 |
| acetonitrile | 1.4 |
| propylene carbonate[c] | 86.8 |
| propylene carbonate[c,d] | 68.4 |

[a] Yield is based on isophytol, determined by GC analysis of the crude product. [b] 50 °C. [c] Two-phase system with heptane (1/1). [d] 60 °C.

**Table 4. MC Bi(OTf)$_3$-Catalyzed Allylation of Aldehydes**

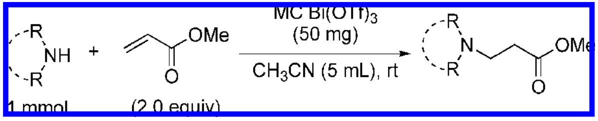


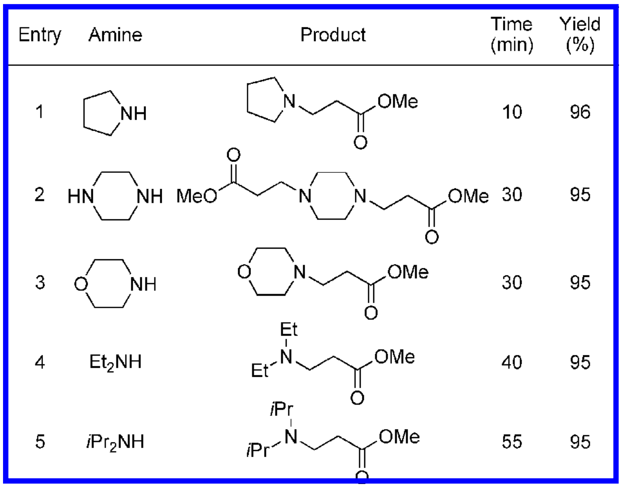


| Entry | R-CHO | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | MeO, MeO, MeO, CHO | 20<br>(5)[a] | 95<br>(95)[a] |
| 2 | O$_2$N, CHO | 20<br>(5)[a] | 90<br>(95)[a] |
| 3 | Me, CHO | 30 | 90 |
| 4 | CHO | 40 | 80 |

[a] With Bi(OTf)$_3$.

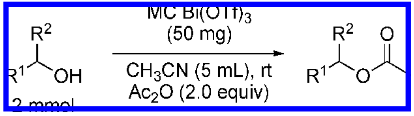
**Table 5. MC Bi(OTf)$_3$-Catalyzed Michael-type Addition of Aliphatic Amines**

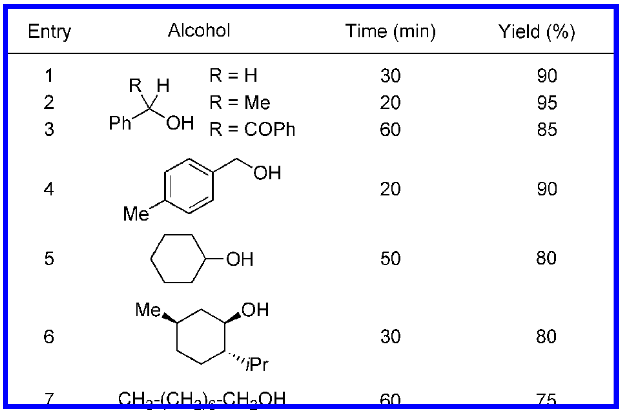




| Entry | Amine | Product | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | NH | N, OMe, O | 10 | 96 |
| 2 | HN, NH | MeO, O, N, N, OMe, O | 30 | 95 |
| 3 | O, NH | O, N, OMe, O | 30 | 95 |
| 4 | Et$_2$NH | Et, Et, N, OMe, O | 40 | 95 |
| 5 | *i*Pr$_2$NH | *i*Pr, *i*Pr, N, OMe, O | 55 | 95 |

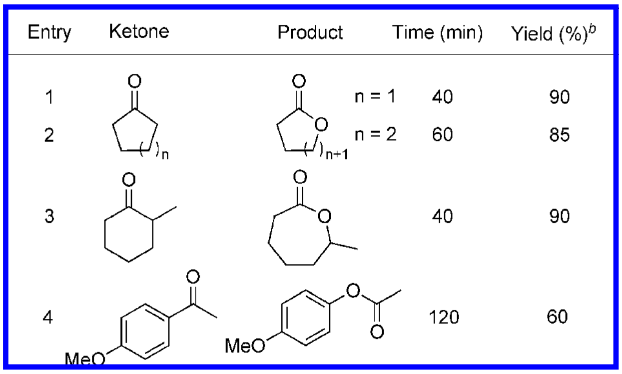
**Table 6. MC Bi(OTf)$_3$-Catalyzed Acetylation of Alcohols**





| Entry | Alcohol | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | R H, Ph OH; R = H | 30 | 90 |
| 2 | R = Me | 20 | 95 |
| 3 | R = COPh | 60 | 85 |
| 4 | Me, OH | 20 | 90 |
| 5 | OH | 50 | 80 |
| 6 | Me, OH, *i*Pr | 30 | 80 |
| 7 | CH$_3$-(CH$_2$)$_6$-CH$_2$OH | 60 | 75 |

**Table 7. MC Bi(OTf)$_3$-Catalyzed Baeyer−Villiger Oxidation[a]**



| Entry | Ketone | Product | Time (min) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | O, ( )$_n$ | O, O, ( )$_{n+1}$; n = 1 | 40 | 90 |
| 2 | | n = 2 | 60 | 85 |
| 3 | O | O, O | 40 | 90 |
| 4 | MeO, O | MeO, O, O | 120 | 60 |

[a] Reaction conditions: ketone (1 mmol), *m*-CPBA (2 mmol), MC Bi(OTf)$_3$ (100 mg), CH$_3$CN (5 mL). [b] Isolated yield.

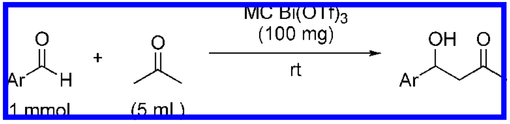
in the presence of acid.[14] The advantages of this procedure were high yield and selectivity, no waste, and mild reaction conditions. While the best results were obtained in a polar solvent such as propylene carbonate, the MC catalyst could not be recovered. In polar solvents at a range of 50−100 °C, leaching of the metal was observed and catalytic activity decreased even after one experiment.

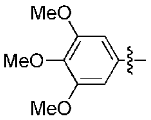
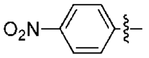
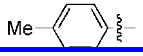
## 2.2. Microencapsulated Bismuth Trifluoromethanesulfonate [MC Bi(OTf)$_3$]

Microencapsulated bismuth trifluoromethanesulfonate [MC Bi(OTf)$_3$] was prepared by using a standard microencapsulation procedure.[15] MC Bi(OTf)$_3$ was used in allylation of aldehydes (Table 4), Michael-type addition of aliphatic amines to methyl acrylate (Table 5), acylation of alcohols (Table 6), Baeyer−Villiger oxidation (Table 7), and aldol reaction (Table 8).[15a]

In allylation reactions, as shown in Table 4, benzoic acid acted as a rate-accelerating agent, and in the absence benzoic acid, the activity of the Lewis acid was immediately restored.[16] MC Bi(OTf)$_3$ showed higher activity than MC Sc(OTf)$_3$ here and similar activity to homogeneous Bi(OTf)$_3$.[17]

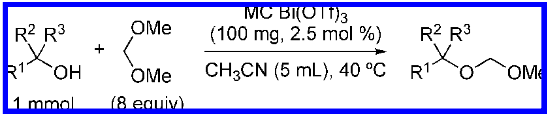
**Table 8. MC $Bi(OTf)_3$-Catalyzed Aldol Reaction**

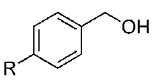
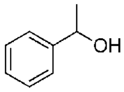
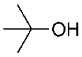
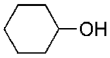
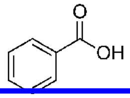


| Entry | Aldehyde (Ar) | Time (min) | Yield (%)[a] |
|---|---|---|---|
| 1 |  | 40 | 90 |
| 2 |  | 30 | 90 |
| 3 |  | 50 | 85 |

[a] Isolated yield.

**Table 9. MC $Bi(OTf)_3$-Catalyzed Methoxymethylation of Alcohols and a Carboxylic Acid**



| Entry | Substrate | | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  | R = H | 2.5 | 85 (83, 81, 80, 80)[b] |
| 2 | | R = Me | 4 | 75 |
| 3 |  | | 3 | 88 |
| 4 |  | | 8 | 46 |
| 5 |  | | 7.5 | 60 |
| 6 |  | | 2 | 80 |

[a] Isolated yield. [b] Yields of first, second, third, and fourth cycles.

On the other hand, primary and secondary alcohols underwent selective acetylation with heterogeneous MC $Bi(OTf)_3$ in the presence of aromatic alcohols. This selectivity was not observed in the case using homogeneous $Bi(OTf)_3$.

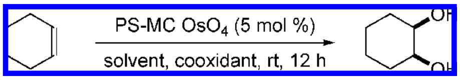
MC $Bi(OTf)_3$ also catalyzes methoxylmethylation reactions of alcohols and a carboxylic acid with dimethoxymethane in acetonitrile under reflux conditions (Table 9).[15b] The encapsulated catalyst exhibits a truly heterogeneous nature throughout the reactions.

## 2.3. Microencapsulated Osumium Tetroxide [MC $OsO_4$]

### 2.3.1. Polystyrene-Based MC $OsO_4$ [PS-MC $OsO_4$]

Osmium tetroxide ($OsO_4$) is the most reliable reagent for dihydroxylation of olefins to give the corresponding vicinal diols.[18] The reaction proceeds in the presence of a catalytic amount of $OsO_4$ 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 $OsO_4$ is highly toxic, expensive, and volatile and cannot be recovered.

**Table 10. Effect of Solvents and Cooxidants**



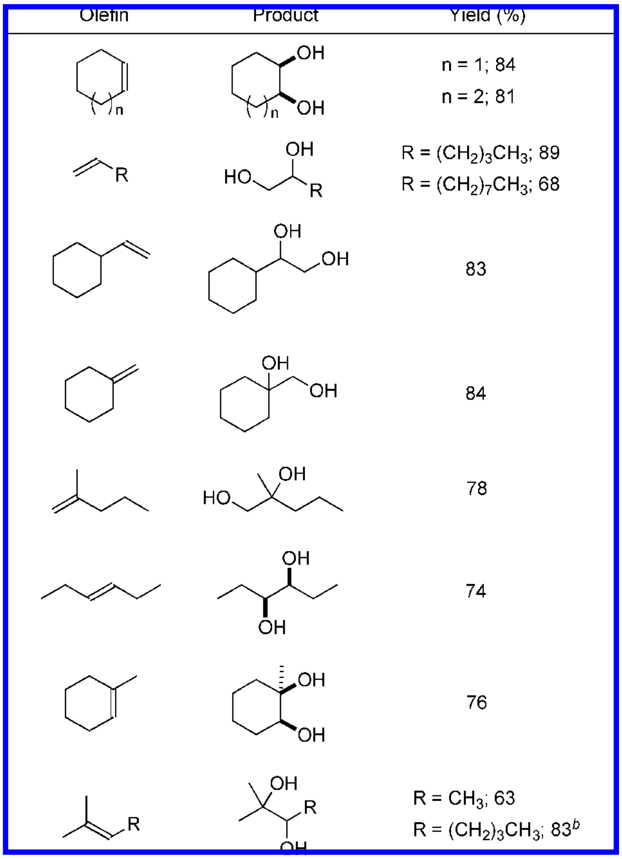
| solvent | cooxidant | yield (%) |
|---|---|---|
| $H_2O$−acetone (2/1) | NMO | 15 |
| $H_2O$−*t*BuOH (1/1) | NMO | 20 |
| $H_2O$−acetone−$CH_3CN$ (1/1/1) | NMO | 84 |
| $H_2O$−acetone−$CH_3CN$ (1/1/1) | $Me_3NO$ | 57 |
| $H_2O$−acetone−$CH_3CN$ (1/1/1) | $H_2O_2$ | 30 |
| $H_2O$−acetone−$CH_3CN$ (1/1/1) | *t*BuOOH | 18 |
| $H_2O$−acetone−$CH_3CN$ (1/1/1) | $K_3Fe(CN)_6$ | 0 |

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.[19] The microencapsulation technique was used for immobilizing $OsO_4$.[20] Styrene-based, microencapsulated osmium tetraoxide (PS-MC $OsO_4$) was easily prepared by the same procedure as that for the preparation of MC $Sc(OTf)_3$. For example, 1 g of polystyrene and 200 mg of $OsO_4$ were used, ca. 180 mg of $OsO_4$ was immobilized, and unencapsulated $OsO_4$ was recovered from the washings.

PS-MC $OsO_4$ was first used in dihydroxylation of cyclohexene, and several solvents and cooxidants were examined (Table 10). All the reactions were carried out on a 10 mmol scale using PS-MC $OsO_4$ containing ca. 0.12 g of $OsO_4$ (5 mol %) in a batch system. When a solvent such as $H_2O$−acetone or $H_2O$−*t*BuOH (which is used in typical $OsO_4$-catalyzed dihydroxylation) was used, lower yields were obtained. The yield was, however, dramatically improved when acetonitrile was added to the $H_2O$−acetone solution. Several cooxidants were examined, and while the reaction was successfully carried out using NMO, moderate yield was obtained using trimethylamine *N*-oxide, and much lower yield was observed using hydrogen peroxide or potassium ferricyanide.

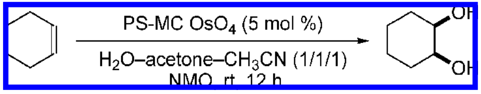
Several examples of PS-MC $OsO_4$-catalyzed dihydroxylations of olefins in the presence of NMO in $H_2O$−acetone−acetonitrile are summarized in Table 11. Cyclic and acyclic exo as well as internal olefins worked well under these conditions. Moreover, bulky olefins such as 1-methylcyclohexene and 2-methyl-2-butene also reacted smoothly in the presence of PS-MC $OsO_4$ 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 12), indicating that no $OsO_4$ was released from the polymer catalyst during or after the reaction. This was first confirmed by the qualitative analysis of $OsO_4$ using the iodometry. Since the titration is very sensitive, the result indicated that no contamination $OsO_4$ in the products occurred. A preliminary kinetic study on the conversion of the starting olefin was performed by using $OsO_4$ and PS-MC $OsO_4$ in a model dihydroxylation of cyclohexene using NMO as a cooxidant (Table 13). It was found that the reaction proceeded slightly faster using $OsO_4$ than using PS-MC $OsO_4$ (Figure 2). While an 81% yield of the diol was obtained using $OsO_4$ for 3 h, a 75% yield was obtained using PS-MC $OsO_4$ under the same reaction conditions.

**Table 11. Dihydroxylation of Olefins Using PS-MC $OsO_4$[a]**



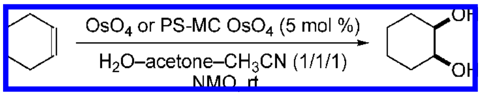
[a] All reactions were carried out using PS-MC $OsO_4$ (5 mol %) and NMO in $H_2O$−acetone−$CH_3CN$ (1/1/1) at room temperature for 6−48 h. [b] 60 °C.

**Table 12. Recovery and Reuse of PS-MC $OsO_4$**



| | run | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| yield of product (%) | 84 | 84 | 83 | 84 | 83 |
| recovery of catalyst (%) | quant | quant | quant | quant | quant |

**Table 13. Kinetic Study on the Conversion of the Starting Olefin**



| | time (min) | | | | |
|---|---|---|---|---|---|
| | 1 | 10 | 30 | 60 | 180 |
| yield ($OsO_4$) | 11 | 79 | 78 | 78 | 81 |
| yield (PS-MC $OsO_4$) | | 7 | 37 | 55 | 75 |

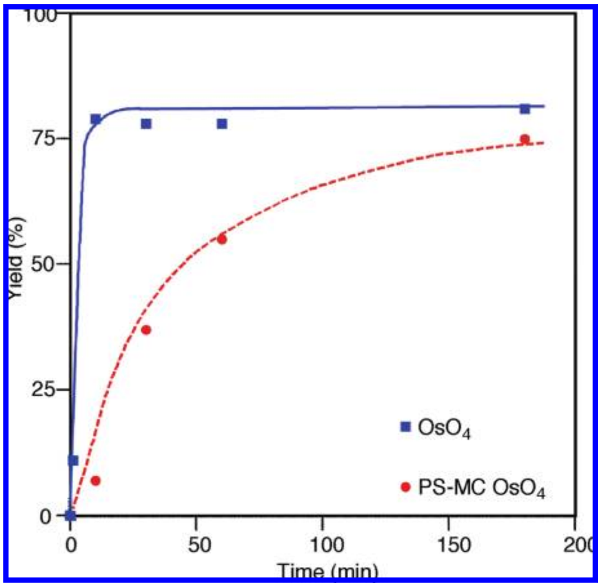
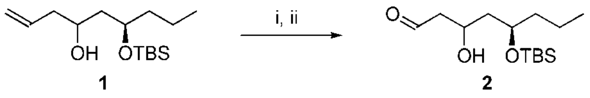


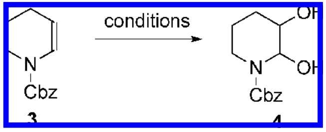
**Figure 2.** Kinetic study on dihydroxylation of cyclohexene.

**Scheme 15. Oxidative Cleavage of Olefin (1)[a]**



[a] Reagents and conditions: (i) PS-MC $OsO_4$ (5 mol %), NMO (5.0 equiv), $H_2O$−acetone−$CH_3CN$ (1/1/1), rt, 7 d; (ii) $NaIO_4$ (5.0 equiv), $Et_2O$−$H_2O$ (1/1), rt, 1.5 h (2 steps 95%).

**Table 14. Dihydroxylation of Ene-carbamate (3)**



| conditions | yield (%) | *cis*/*trans*[a] |
|---|---|---|
| PS-MC $OsO_4$ (5 mol %), NMO, $H_2O$−acetone−$CH_3CN$ (1/1/1) | 79 | 100/0 |
| $K_2OsO_4\cdot 2H_2O$ (1.7 mol %), $K_3Fe(CN)_6$, $K_2CO_3$, *t*BuOH−$H_2O$ (1/1) | 73 | 80/20 |

[a] Determined by $^1$H NMR.

PS-MC $OsO_4$ was successfully applied to several total syntheses.[21] For example, in analogue syntheses and assessment of biological potency of callystatin A, oxidative cleavage of the olefin (**1**) using PS-MC $OsO_4$ followed by $NaIO_4$ treatment afforded hydroxyaldehyde **2** in 95% yield (Scheme 15).[21a]

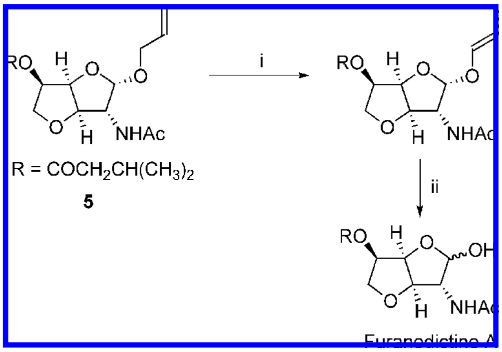
In the synthesis of 2-acetoxypiperidines, the ene-carbamate (**3**) was oxidized to give *N*-benzyloxycarbonyl-2,3-dihydroxypiperidine (**4**) using $OsO_4$.[21b] In this dihydroxylation procedure, PS-MC $OsO_4$ led to *cis*-diol without epimerization at the 2-position, whereas epimerization occurred when $K_2OsO_4\cdot 2H_2O$ was used (Table 14).

In addition, PS-MC $OsO_4$ was used for deprotection of an allyl ether (Scheme 16).[21c] Deallylation of glycoside (**5**) using $PdCl_2$ 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 $OsO_4$ allowed completion of the synthesis of furanodictine A.

Furthermore, PS-MC $OsO_4$ was used in the first total synthesis of (±)-linderol A (Scheme 17).[21d] After Wittig olefination of the ketone with methylenetriphenylphosphine, dihydroxylation using a catalytic amount of PS-MC $OsO_4$ in the presence of NMO afforded the corresponding diol as a single isomer in quantitative yield.

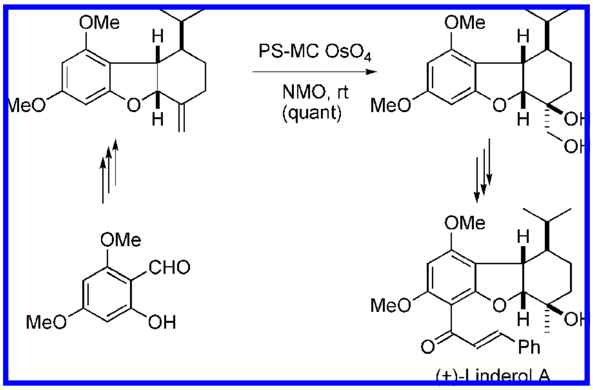
New ceramide trafficking inhibitors, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12) and a series of its analogues, were synthesized in diastereomerically and enantiomerically pure forms, and the

**Scheme 16. Deprotection of Allyl Ether**[a]

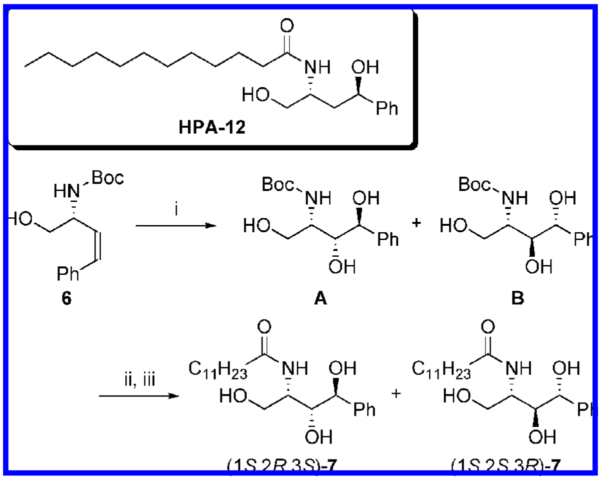


[a] Reagents and conditions: (i) $RhCl(PPh_3)_3$ (20 mol %), DABCO (20 mol %), $EtOH-H_2O$ (9/1), reflux, 2 h; (ii) PS-MC $OsO_4$ (5 mol %), NMO (1.3 equiv), $H_2O$−acetone−$CH_3CN$ (1/1/1), rt, 9 h (2 steps 56%).

**Scheme 17. The First Total Synthesis of (±)-Linderol A**



**Scheme 18. Synthesis of 2-Hydroxy Analogues of HPA-12**[a]



[a] Reagents and conditions: (i) PS-MC $OsO_4$ (5 mol %), NMO (1.4 equiv), $H_2O$−acetone−$CH_3CN$ (1/1/1), rt, 36 h (92%, **A**/**B** = 68/32); (ii) HCl, MeOH, reflux; (iii) $C_{11}H_{23}CO_2C_6H_4$(*p*-$NO_2$), $Et_3N$, rt (2 steps 74% from **A**, 70% from **B**).

structure−activity relationship was investigated.[21e] In this work, dihydroxylation of olefin **6** was carried out using PS-MC $OsO_4$ to give triols, **A** and **B**, in good yields. These diastereomers were separated by chromatography on silica gel, and then they were converted to the desired (1*S*,2*R*,3*S*)- and (1*S*,2*S*,3*R*)-**7** in the same manner (Scheme 18).

Moreover, PS-MC $OsO_4$ was used in the structure determination of a novel long chain polyacetylene, lembehyne A (Figure 3), which was isolated from an Indonesian marine sponge of *Haliclona* sp.[22]

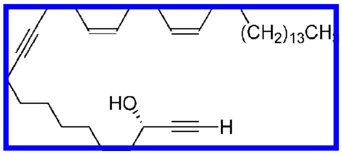


**Figure 3.** Structure of lembehyne A.

### 2.3.2. Poly(acrylonitrile-co-butadiene-co-styrene)-Based MC $OsO_4$ [ABS-MC $OsO_4$]

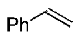
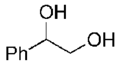
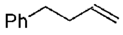
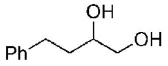
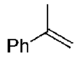
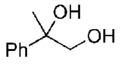
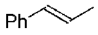
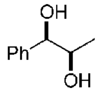
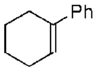
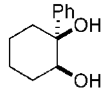
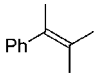
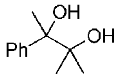
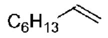
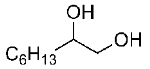
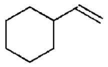
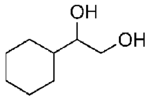
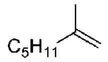
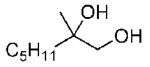
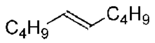
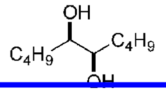
Osmium-catalyzed asymmetric dihydroxylation of olefins provides one of the most efficient methods for the preparation of chiral diols. Although high yields and stereoselectivities have been attained in many substrates, the high cost of osmium and ligands, as well as the high toxicity of osmium catalysts, which may contaminate products, have obstructed its use in industry. Soluble and insoluble polymer-supported ligands have been developed by several groups,[23,24] but complete recovery and reuse of the osmium have not yet been accomplished.[25] Microencapsulated osmium tetroxide, which first achieved complete recovery and reuse of the osmium component in achiral oxidations, was then applied to asymmetric catalysis after many trials; however, the yields and selectivities as well as recovery of the catalyst were not satisfactory.

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 a general procedure.[26]

ABS-based microencapsulated $OsO_4$ (ABS-MC $OsO_4$) was first tested in achiral dihydroxylation of olefins. In the presence of ABS-MC $OsO_4$ (5 mol %), styrene was treated with *N*-methylmorpholine *N*-oxide (NMO) in $H_2O$−acetone−acetonitrile (1/1/1). Although styrene was not a good substrate in the dihydroxylation using PS-MC $OsO_4$ because styrene dissolved PS-MC $OsO_4$, the desired product, 1-phenyl-1,2-ethanediol, was obtained in 93% yield using ABS-MC $OsO_4$. The catalyst was recovered quantitatively, and the recovered catalyst was used in the second, third, and fourth runs, and no significant loss of activity was observed (93%, 90%, 87%, and 89% yields, respectively, and ABS-MC $OsO_4$ was recovered quantitatively in all cases). Several other olefins were then examined, and the results are summarized in Table 15. Various olefins including cyclic and acyclic, terminal, and 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.[27] *trans*-Methylstyrene was chosen as a model, and several reaction conditions were examined. When 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine [$(DHQD)_2PHAL$, Figure 4] was used as a chiral source and *trans*-methylstyrene was slowly added over 24 h to the mixture of ABS-MC $OsO_4$, $(DHQD)_2PHAL$ (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 significant loss activity was observed even after the fifth use (Table 16). Higher enantioselectivities were obtained in the second, third, fourth, and fifth runs compared with the first run. A clear explanation for these results was not made, but

**Table 15. Achiral Dihydroxylation of Olefins Using ABS-MC $OsO_4$[a]**

| Olefin | Product | Yield (%) |
|---|---|---|
|  |  | 94 |
|  |  | 82 |
|  |  | quant |
|  |  | 95 |
|  |  | 87 |
|  |  | 83[b] |
|  |  | 73 |
|  |  | 74 |
|  |  | 82 |
|  |  | 77 |

[a] All reactions were carried out using ABS-MC $OsO_4$ (5 mol %) and NMO in $H_2O$−acetone−$CH_3CN$ (1/1/1) at room temperature for 12 h. [b] Carried out at 60 °C.

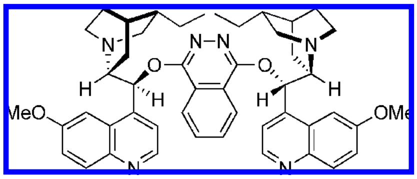
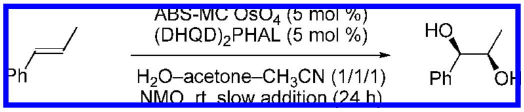


**Figure 4.** $(DHQD)_2PHAL$.

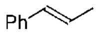
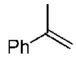
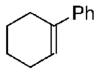
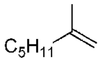
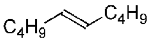
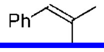
**Table 16. Reuse of ABS-MC $OsO_4$**



| run | yield (%) | ee (%) | recovery[a] |
|---|---|---|---|
| 1 | 88 | 84 | quant |
| 2 | 75 | 95 | quant |
| 3 | 97 | 94 | quant |
| 4 | 81 | 96 | quant |
| 5 | 88 | 95 | quant |

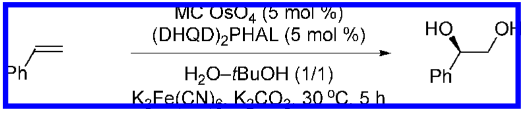
[a] Recovery of ABS-MC $OsO_4$; recovery of $(DHQD)_2PHAL$ was >95%.

**Table 17. Asymmetric Dihydroxylation Using ABS-MC $OsO_4$**

| Olefin | ABS-MC $OsO_4$ /mol % | Chiral Ligand /mol % | Yield /% | ee /% |
|---|---|---|---|---|
|  | 5<br>2.5<br>1 | 10<br>5<br>2 | 75<br>90<br>97 | 91<br>92<br>86[a] |
|  | 5 | 5 | 98 | 78 |
|  | 5 | 5 | 64 | 86 |
|  | 5 | 5 | 90 | 60 |
|  | 2.5 | 5 | 85 | 63 |
|  | 5 | 5 | 36 | 85 |

[a] A 20 mmol scale experiment was performed.

**Table 18. Study of Several Polymers**



| entry | MC $OsO_4$ | yield (%) [ee (%), recovery (%)] first | second | third |
|---|---|---|---|---|
| 1 | ABS[a] | 81 [94, 88] | 83 [94, 74] | 84 [93, 74] |
| 2 | PS[b] | 4 [−, 97] | | |
| 3 | AS[c] | 5 [−, 99] | | |

[a] ABS = poly(acrylonitrile-*co*-butadinene-*co*-styrene). [b] PS = polystyrene. [c] AS = poly(acrylonitrile-*co*-styrene).

the following control experiment and the standard Sharpless conditions, which require an excess of a chiral ligand to osmium, may suggest a solution. The control experiment was oxidation of *trans*-methylstyrene, *trans*-methylstyrene was slowly added over 24 h to a mixture of fresh ABS-MC $OsO_4$ (5 mol %), $(DHQD_2)PHAL$ (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 17. 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 $OsO_4$.

The asymmetric reaction was conducted in a 100 mmol scale experiment. To a mixture of ABS-MC $OsO_4$ (1.0 mmol, 1.0 mol %), $(DHQD)_2PHAL$ (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 $OsO_4$ and the chiral ligand was recovered.

### *2.3.3. Poly(4-phenoxyethoxymethylstyrene-co-styrene)-Based MC $OsO_4$ [PEM-MC $OsO_4$]*

ABS-MC $OsO_4$ 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 incured some problems such as a relatively tedious procedure and difficulty using insoluble substances. ABS-MC $OsO_4$ was applied to the asymmetric dihydroxylation under Sharpless conditions: that is, two-phase conditions with potassium hexacyanoferrate [$K_3Fe(CN)_6$] as a cooxidant (Table 18). In the presence of ABS-MC $OsO_4$ and $(DHQD)_2PHAL$ (5 mol % each), styrene was treated with $K_3Fe(CN)_6$ (2.0 equiv) and potassium

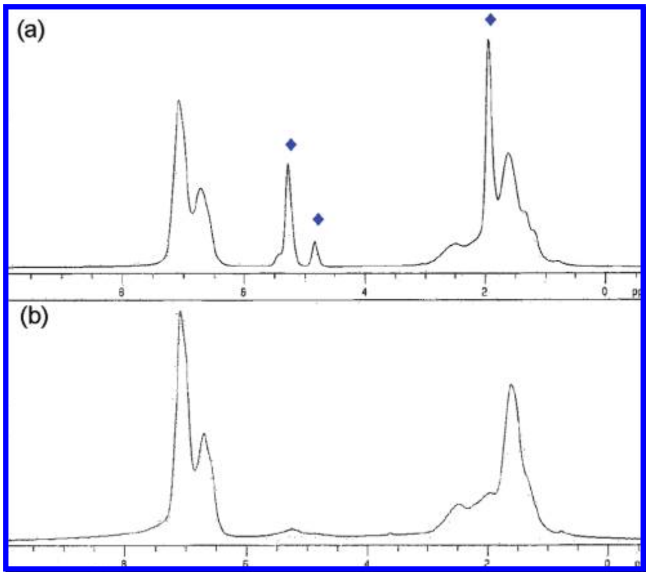
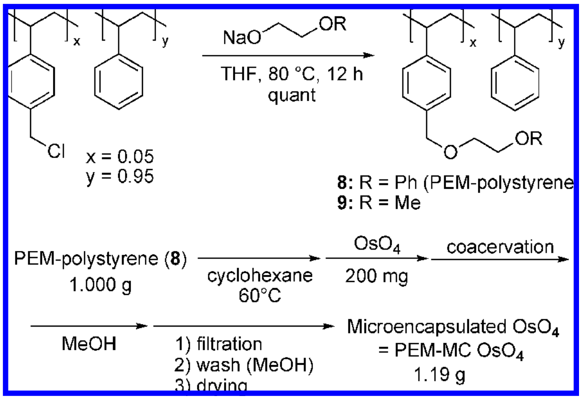


**Figure 5.** $^1H$ swollen-resin magic angle spinning (SR-MAS) NMR spectra of (a) ABS polymer and (b) ABS-MC $OsO_4$ ($CDCl_3$). Blue ◆ indicates the butadiene moiety.

**Scheme 19. Synthesis of PEM-MC $OsO_4$**

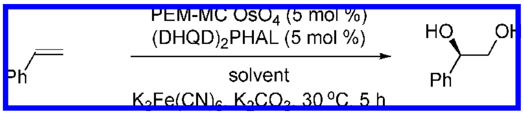


carbonate (2.0 equiv) in $H_2O-tBuOH$ (1/1) for 5 h, and the desired diol was obtained in 84% yield with 84% ee. The recovered catalyst was reused three times, and no loss of activity was observed (entry 1). However, it was revealed that a small amount of $OsO_4$ was leached from the support.

$^1H$ NMR spectra of ABS-MC $OsO_4$ using a swollen-resin magic angle spinning (SR-MAS) NMR technique[28] revealed that the olefin moiety of the ABS polymer derived from the butadiene monomer was oxidized by osmium tetroxide, presumably during the microcapsule formation (Figure 5). Other polymer supports such as polystyrene (PS) and poly(acrylonitrile-*co*-styrene) (AS) were examined; however, these polymers were not effective under the reaction conditions. The diol moiety of the polymer support was assumed to be very effective in two-phase dihydroxylation, probably due to the hydrophilic property of the cooxidant. However, leaching of $OsO_4$ occurred in ABS-MC $OsO_4$, because this polymer was too hydrophilic and a part of the polymer was dissolved in the $H_2O-tBuOH$ solution. On the other hand, PS and AS are lipophilic and were difficult to react with the cooxidant.

Based on these experiments and considerations, a new polymer, phenoxyethoxymethyl-polystyrene (PEM-polystyrene, **8**), was designed as shown in Scheme 19.[29,30] This polymer was readily synthesized from chloromethyl-polystyrene by etherification, and PEM-based microencapsulated $OsO_4$ was prepared according to a standard procedure.

**Table 19. Effect of Linkers and Solvents**



| entry | solvent[a] | yield (%) (ee (%), recovery (%)) first | second | third |
|---|---|---|---|---|
| 1 | A | 77 (94, 94) | 37 (80, 86) | NR (−, 84) |
| 2[b] | 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[b] | D | 44 (76, quant) | 49 (78, 94) | 60 (78, 90) |
| 7[c] | D | 85 (78, quant) | 66 (78, quant) | 84 (78, quant) |

[a] Solvent A, $H_2O-tBuOH$ (1/1); solvent B, $H_2O-iPrOH$ (1/1); solvent C, $H_2O-THF$ (1/1); solvent D, $H_2O$−acetone (1/1). [b] Polymer **9** was used instead of **8** (see Scheme 19). [c] Cooxidant (2.0 equiv) and base (2.0 equiv) were added at first, and then added again after 3 h.

PEM-MC $OsO_4$ thus prepared was first tested in asymmetric oxidation of styrene using $(DHQD)_2PHAL$ in $H_2O$−alcohol solutions (Table 19, entries 1−3). Although the desired products were obtained in good yields in the first run, activity of the catalyst decreased significantly in the second and third runs. In $H_2O-THF$, the results were similar to those in $H_2O$−alcohol (entry 4). On the other hand, in $H_2O$−acetone, moderate chemical yields, good enantiomeric excesses, and high recovery of the catalyst were obtained (entry 5). Use of polymer **9** instead of **8** was not effective. It seemed that the phenylether moiety of **8** was required for good recovery. It is noted that the osmium catalyst was recovered quantitatively by simple filtration and that no leaching of the osmium from polymer support occurred.

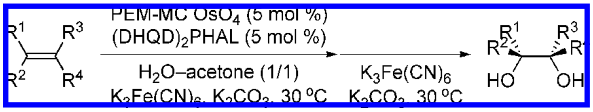
In order to increase the chemical yields, separate addition of the cooxidant and the base was tried, because it was observed that the desired reaction stopped halfway (Table 12). When $K_3Fe(CN)_6$ (2.0 equiv) and potassium carbonate (2.0 equiv) were added at first, and they were added again after three hours, the best result was obtained (entry 7).

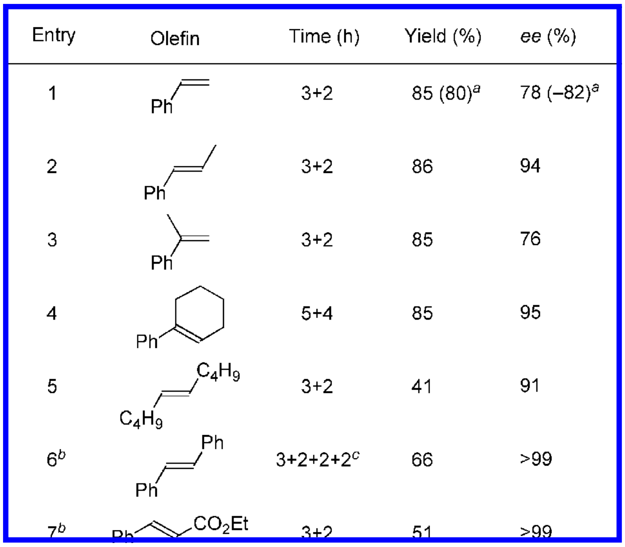
This system was applied to other olefins, and the results are summarized in Table 20. In most cases, the desired diols were obtained in good yields with high enantiomeric excesses. A wide variety of olefins were applicable in this system, catalyst was recovered quantitatively by simple filtration without significant loss of activity, and no leaching of the osmium occurred.

Organic reactions in water without the use of any harmful organic solvents are now of great interest in organic synthesis, because water is a safe, economical, and environmentally benign solvent.[31] Recently, several surfactant-type Lewis or Brønsted acids were developed and used as catalysts for carbon−carbon bond-forming reactions (the Mukaiyama aldol reaction,[32] the Mannich-type reaction,[33] etc.[34]) in water. In these reactions, hydrophobic emulsion particles or droplets, which are essential for efficient catalysis, are formed in the presence of small amounts of catalysts and hydrophobic substrates.

In the PEM-MC $OsO_4$-catalyzed reactions, it was assumed that the reaction proceeded on the surface area of PEM-MC $OsO_4$ and that the hydrophilic part of the PEM polymer acted as a surfactant. It would be possible to conduct the reactions in water without using any organic cosolvents.[35] Dihydroxylations of styrene were carried out in water using PEM-MC

**Table 20. Asymmetric Dihydroxylation of Olefins Using PEM-MC $OsO_4$**

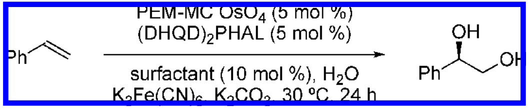




| Entry | Olefin | Time (h) | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 1 | Ph | 3+2 | 85 (80)[a] | 78 (−82)[a] |
| 2 | Ph | 3+2 | 86 | 94 |
| 3 | Ph | 3+2 | 85 | 76 |
| 4 | Ph | 5+4 | 85 | 95 |
| 5 | $C_4H_9$<br>$C_4H_9$ | 3+2 | 41 | 91 |
| 6[b] | Ph<br>Ph | 3+2+2+2[c] | 66 | >99 |
| 7[b] | Ph, $CO_2Et$ | 3+2 | 51 | >99 |

[a] $(DHQ)_2PHAL$ (5 mol %) was used instead of $(DHQD)_2PHAL$. [b] Methanesulfonamide (1.0 equiv) was added. [c] One equivalent each of $K_3Fe(CN)_6$ and $K_2CO_3$ was added four times.

**Table 21. Effect of Several Types of Surfactants**



| entry | surfactant | yield (%) | ee (%) | leaching (%)[g] |
|---|---|---|---|---|
| 1 | **10** | 82 | 68 | 26.4 |
| 2 | Span 20 | 77 | 54 | 8.0 |
| 3 | Tween 20 | quant | 77 | 3.5 |
| 4 | Triton WR-1339[a] | 91 | 76 | 2.7 |
| 5 | Triton CF-10[a] | 84 | 76 | 7.4 |
| 6 | Triton X-100 | 84 | 75 | 5.3 |
| 7 | Triton X-405 | 68 | 75 | 1.6 |
| 8[b] | Triton X-405 | 80, 86[e], 83[f] | 74, 73[e], 73[f] | 1.8, 1.6[e], 1.5[f] |
| 9[b],[c] | Triton X-405 | 86, 82[e], 83[f] | 74, 76[e], 75[f] | nd[g], nd[e], nd[f] |
| 10[b],[c] | Triton X-405[d] | 76, 74[e], 76[f] | 74, 74[e], 70[f] | nd, nd[e], nd[f] |

[a] Surfactant (2 mg/mL) was used. [b] The ligand was directry added. [c] The reaction mixture was neutralized by aqueoous $H_2SO_4$ (2 N) to quench the reaction. [d] Triton X-405 (3 mol %) was used. [e] Second run. [f] Third run. [g] nd = not detected.

$OsO_4$ (5 mol %), 4-methylmorpholine (NMM, 5 mol %) or $(DHQD)_2PHAL$ (5 mol %), $K_3Fe(CN)_6$, and $K_2CO_3$ (3.0 equiv). In the NMM case, when the reaction time was 6 h, the corresponding diol was obtained in low yield (45%), which could be improved by prolonging the reaction time from 6 to 24 h (65%). On the other hand, when $(DHQD)_2PHAL$ was used as a ligand, lower enantiomeric excess was observed even when the osmium−ligand complex was preprepared.

To improve the chemical yields and enantiomeric excesses further, several kinds of additives were tested. As a result, when a zwitterionic-type surfactant was added, the chemical yield and enantioselectivity were improved dramatically (Table 21, entry 1; see Figure 6 for structures of surfactants). However, significant leaching of the osmium component was observed by fluorescent X-ray analysis, presumably because the ammonium part of the surfactant strongly coordinated to the osmium. Based on this consideration, nonionic surfactants were examined. It was found that surfactants containing poly(ethylene glycol) parts were more effective and that Triton X-405 suppressed the leaching of the osmium component effectively (entry 7). At this stage, it was also observed that prepreparation of the osmium−ligand complex was not required to improve the chemical yield and enantiomeric excess. The ligand was then directly added to the reaction mixture. The desired product was obtained in better yield, and no deactivation of the catalyst was observed even after the third use (entry 8). To suppress Os leaching completely, the reaction mixture was neutralized with aqueous $H_2SO_4$ to convert the osmium species from osmate(VIII) to osmium(VIII) entirely. As a result, no osmium leaching occurred, and high yields and enantioselectivity were retained during the reuse of the catalyst (entry 9). It was also found that the reaction proceeded smoothly even using only 3 mol % Triton X-405 (entry 10).

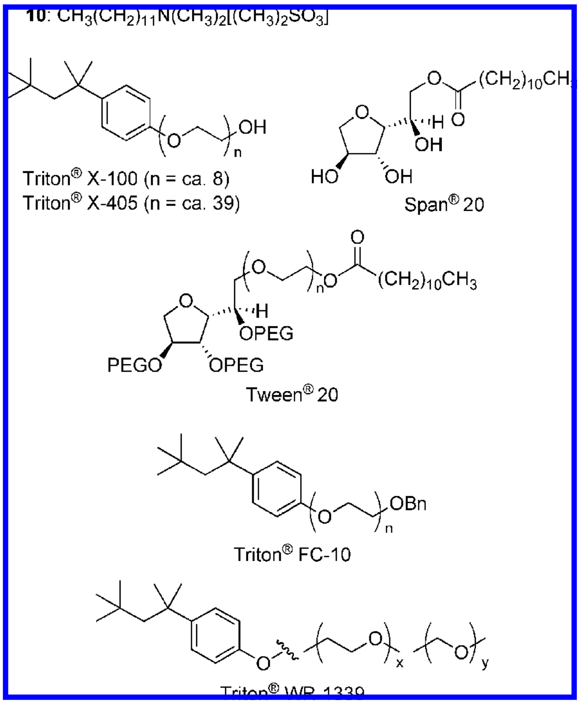


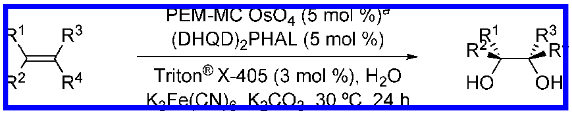
**Figure 6.** Structures of surfactants.

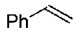
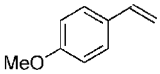
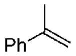
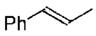
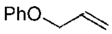
This system was applied to other olefins, and the results are summarized in Table 22. In most cases, the desired products were obtained in good yields using water as the sole solvent. It should be noted that the reaction system did not require the addition of excess amounts of the cooxidant and the base separately and that the catalyst was separated from the reaction mixture easily by simple filtration without leaching of the osmium component.

### *2.3.4. Cross-Linked Polystyrene-Based Osmium Catalyst [PSresin-MC Os]*

A novel microencapsulated osmium catalyst using cross-linked polystyrene was developed.[36] The concept of this method may go beyond that of microencapsulation, because polymers are usually dissolved in appropriate solvents according to a standard microencapsulation technique (Scheme 20). The catalyst was successfully used in asymmetric dihydroxylation in water (Scheme 21) and was recovered quantitatively by simple filtration and reused several times

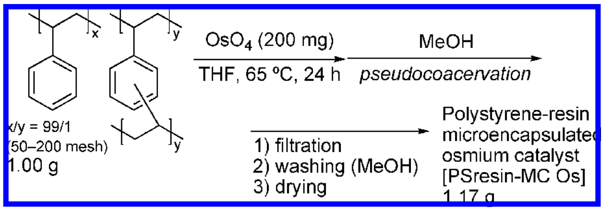
**Table 22. Asymmetric Dihydroxylation of Olefins Using Water As a Solvent**



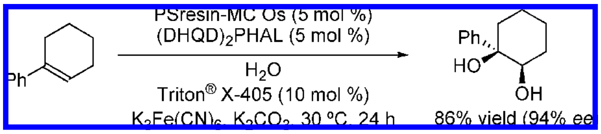
| Entry | Olefin | Yield (%) | *ee* (%)[b] |
|---|---|---|---|
| 1 |  | 76 | 74 |
| 2 |  | 68 | 89 |
| 3[c] |  | 85 | 80 |
| 4 |  | 76 | 92 |
| 5 |  | 79 | 55 |
| 6 |  | 76 | 66[d] |

[a] Leaching of the osmium component was not observed in each reaction. [b] Enantiomeric excesses were determined by chiral HPLC analysis. [c] Triton X-405 (5 mol %) was used. [d] The ee value obtained from $^1H$ NMR analysis of the di-MTPA ester of the corresponding 1,2-diol.

**Scheme 20. Preparation of the Polystyrene-Resin Microencapsulated Osmium Catalyst**



**Scheme 21. Asymmetric Dihydroxylation of Olefin Using PSresin-MC Os**



without loss of activity. The shape of the catalyst was maintained even after several uses. Moreover, no leaching of the Os component was detected.

### 2.3.5. *Polysulfone-Based Microencapsulated Osumium Tetroxide [Polysulfone-MC $OsO_4$]*

Another recoverable and reusable microencapsulated osmium tetroxide catalyst derived from polysulfone was reported (Figure 7).[37]

This catalyst could be used in asymmetric dihydroxylation of olefins without the need of slow addition of the olefin in high yields with excellent enantio- and diastereoselectivities (Table 23). After completion of the reaction, the catalyst could be recovered by simple filtration.

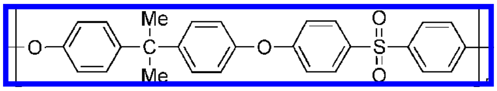
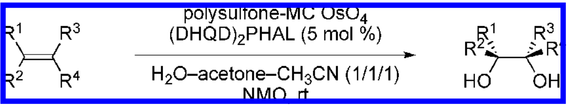
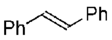
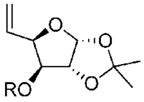
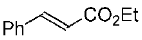
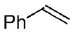
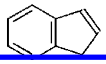


**Figure 7.** Polysulfone.

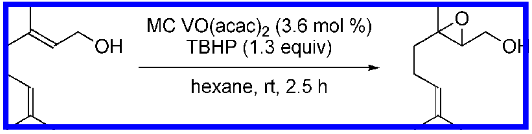
**Table 23. Asymmetric Dihydroxylation of Olefins Using Polysulfone-MC $OsO_4$**



| Olefin | | Time (min) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|
|  | | 30 | 94 | 96 |
|  | (R = Bn) | 25 | 92 | 99 |
| | (R = Bz) | 25 | 90 | 99 |
|  | | 25 | 86 | 92 |
|  | | 25 | 89 | 90 |
|  | | 30 | 92 | 89 |

[a] Isolated yield after column chromatography. [b] Enantiomeric excesses were determined by chiral HPLC analysis.

**Table 24. Reuse of MC $VO(acac)_2$ in the Epoxidation of Geraniol and Determination of Metal Leaching**



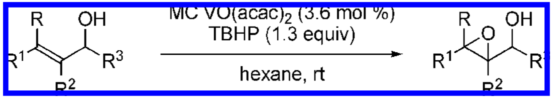
| run | yield of epoxide (%) | metal leaching |
|---|---|---|
| 1 | 93 | 0.097% |
| 2 | 84 | 550 ppm |
| 3 | 83 | 275 ppm |
| 4 | 81 | 118 ppm |
| 5[a] | 5 | |

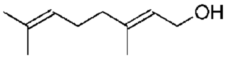
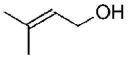
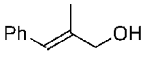
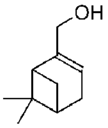
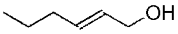
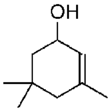
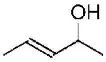
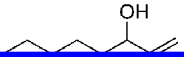
[a] Using 0.1 mol % of $VO(acac)_2$ in the place of MC $VO(acac)_2$

## 2.4. Microencapsulated $VO(acac)_2$ [MC $VO(acac)_2$]

Microencapsulated $VO(acac)_2$ [MC $VO(acac)_2$] was prepared using a standard protocol.[38] The MC $VO(acac)_2$ can be stored in air at room temperature for several months without loss of activity. To test the MC $VO(acac)_2$ as a catalyst for epoxidation reactions, the *tert*-butyl hydroperoxide (TBHP) mediated epoxidation of geraniol was investigated (Table 24). It was found that acetonitrile, toluene, and diethyl ether led to low yields of the product and pronounced metal leaching. However, somewhat surprisingly, at room temperature a 93% yield of the product was obtained in hexane. The aliphatic hydrocarbons are not effective as solvents for oxidation reactions catalyzed by the original $VO(acac)_2$. Furthermore, it is noteworthy that these results are obtained at room temperature, while elevated temperature is often used in the case of epoxidation using $VO(acac)_2$ or other supported oxyvanadium complexes in other solvents such as benzene. Therefore, the activity of $VO(acac)_2$ is totally changed by encapsulation. Being able to perform the reaction in hexane has significant advantages over the use of benzene or chlorocarbons in terms of ease of use, environmental impact, and toxicity. The MC $VO(acac)_2$ was reusable without significant loss of activity after the fourth use. The leaching of the metal in each run was determined by ICP analysis and found to decrease from 0.097% in the

**Table 25. MC $VO(acac)_2$/TBHP Epoxidation of Allylic Alcohols**



| Allylic Alcohol | Time (h) | Yield of Epoxide (%) | dr[a] |
|---|---|---|---|
|  | 2.5 | 93 | |
|  | 2 | 90 | |
|  | 8 | 87 | |
|  | 1.5 | 96 | |
|  | 5 | 84 | |
|  | 5 | 55 | |
|  | 13 | 81 | >98/<2[b] |
|  | 14 | 57 | 60/40[c] |
|  | 22 | 70 | 72/25[c] |

[a] Determined by $^1H$ NMR. [b] The *cis/trans* ratio. [c] The *erythro/threo* ratio.

first run down to 118 ppm in the fourth run. To evaluate the contribution derived from small quantities of $VO(acac)_2$ released during the reactions, the epoxidation of geraniol was conducted under the same reaction conditions using 0.1 mol % of $VO(acac)_2$ in place of MC $VO(acac)_2$. After the same reaction time, the epoxide was formed in only 5% yield. This proves that the high catalytic activity came from MC $VO(acac)_2$.

This system was applied to other olefins, and the results are summarized in Table 25. The reactivity was dependent on the nucleophilic character of the double bonds and steric factors.

## 2.5. Microencapsulated Methylrhenium Trioxide [MC MTO]

Novel heterogeneous methylrhenium trioxide (MTO) was prepared using poly(4-vinylpyridine) (PVP), poly(4-vinylpyridine-*N*-oxide) (PVPN), and polystyrene (PS) as polymeric supports.[39] These catalysts can be used for epoxidation of olefins using $H_2O_2$ as an oxygen atom donor (Scheme 22).[39a,d] Furthermore, the catalyst activity was maintained for at least five recycling experiments.

These catalysts were applied to the selective oxidation of phenol and anisole derivatives to quinines.[39b,c] In this oxidation, PVP/MTO and PVPN/MTO catalysts were stable enough to perform at least five recycling experiments with similar conversions and selectivities (Table 26).

**Scheme 22. Microencapsurated MTO Catalyzed Epoxidation of Olefins**

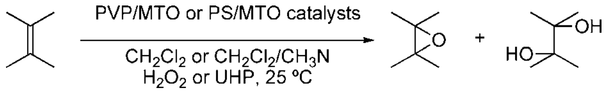
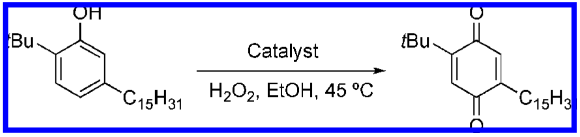


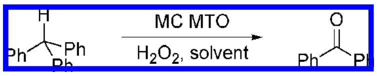
**Table 26. Stability of Poly(4-vinylpyridine)/MTO Catalyst[a]**



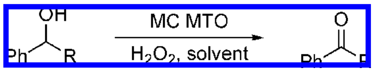
| | conversion (%)[b] | | | | |
|---|---|---|---|---|---|
| catalyst | run 1 | run 2 | run 3 | run 4 | run 5 |
| PVP-25%/MTO | 75 (98) | 76 (93) | 71 (97) | 75 (96) | 76 (97) |
| PVPN-2%/MTO | 62 (96) | 65 (91) | 63 (93) | 60 (98) | 61 (96) |

[a] Unless otherwise specified, all the reactions were performed in ethanol (5 mL) at 45 °C with $H_2O_2$ (35% aqueous solution) using a catalyst loading factor of 1.0. [b] Values of the benzoquinone yields are given in parentheses and are normalized to 100% of conversion.

**Scheme 23. Oxidation of Triphenylmethane**

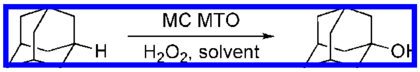


**Scheme 24. Oxidation of Secondary Alcohols[a]**



[a] R = Ph or Me.

**Scheme 25. Oxidation of Adamantane**



Microencapsulated MTO was also shown to act as an efficient and selective catalyst for oxy-functionalization of C−H bonds in representative hydrocarbon derivatives (leading to the corresponding alcohols or ketones) using $H_2O_2$ as an oxidant (Schemes 23−25).[39e]

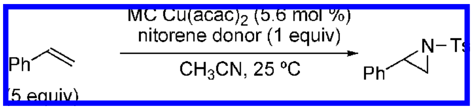
## 2.6. Microencapsulated $Cu(acac)_2$ [MC $Cu(acac)_2$]

MC $Cu(acac)_2$ was successfully prepared from $Cu(acac)_2$ and polystyrene and used in the aziridination of olefins.[40a] Aziridination of styrene was conducted using different nitrene donors such as chloramines-T, bromamine-T and PhI═NTs, and the leaching of the metal in these nitrene donors was determined by atomic absorption spectrometry (Table 27). The results confirmed that PhI═NTs was the best nitrene donor for MC $Cu(acac)_2$.

A variety of alkenes were examined for this MC $Cu(acac)_2$-catalyzed aziridination using PhN═NTs. As shown in Table 28, the desired aziridines were obtained in good yields using both aromatic and aliphatic olefins.

In order to confirm that this process was truly heterogeneous, the catalyst was removed after the reaction by filtration, fresh aliquots of reactants were added to the filtrate, and no product formation was observed. Furthermore, the recovered catalyst could be reused for several cycles with consistent activity (Table 29).

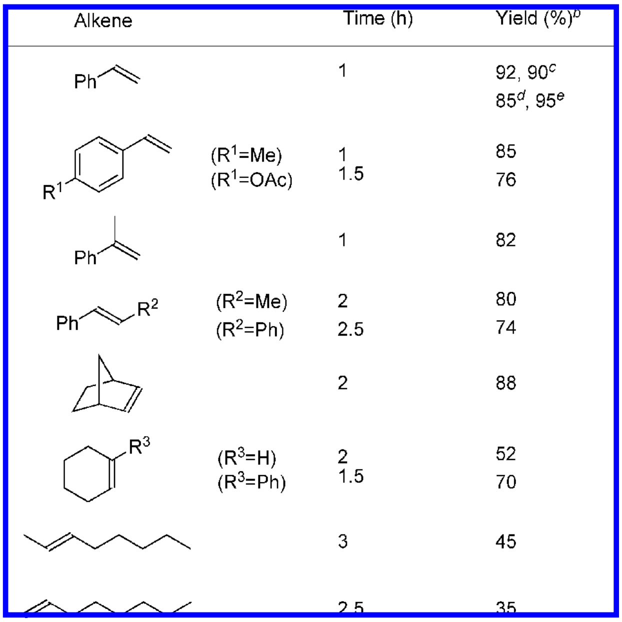
**Table 27. Aziridination of Styrene Using Various Nitrene Donors**



| nitrene donor | time (h) | yield (%)[a] | Cu leaching (wt %) |
|---|---|---|---|
| PhI═NTs | 1 | 92 | 0.025 |
| chloramine-T | 6 | 36 | 16.56 |
| bromamine-T | 6 | 45 | 10.28 |

[a] Isolated yield.

**Table 28. MC Cu(acac)$_2$-Catalyzed Aziridination of Alkenes[a]**



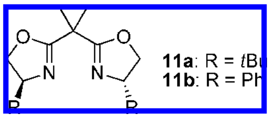
| Alkene | | Time (h) | Yield (%)[b] |
|---|---|---|---|
| Ph | | 1 | 92, 90[c]<br>85[d], 95[e] |
| R$^1$ | (R$^1$=Me)<br>(R$^1$=OAc) | 1<br>1.5 | 85<br>76 |
| Ph | | 1 | 82 |
| Ph, R$^2$ | (R$^2$=Me)<br>(R$^2$=Ph) | 2<br>2.5 | 80<br>74 |
| | | 2 | 88 |
| R$^3$ | (R$^3$=H)<br>(R$^3$=Ph) | 2<br>1.5 | 52<br>70 |
| | | 3 | 45 |
| | | 2.5 | 35 |

[a] Unless otherwise specified, reaction conditions were $CH_3CN$, 25 °C, alkene/PhI═NTs = 5:1. [b] Isolated yield of aziridine based on PhI═NTs. [c] With used catalyst. [d] Styrene/PhI═NTs = 1:1 molar ratio. [e] With 10 mol % of Cu(acac)$_2$.

These catalysts were also applied to sulfimidation of sulfides using PhI═NTs as a nitrene donor (Table 30).[40b]

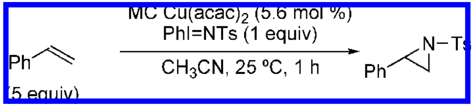
While complete conversion was observed in the reaction using the recovered catalyst, there was absolutely no conversion in the reaction using the filtrate. After the reaction, the filtrate was analyzed for leaching of copper metal using atomic absorption spectrometer. The result indicated leaching of 0.49% of Cu in MC Cu(acac)$_2$ during the reaction. Furthermore, the recovered catalyst was reused several times with consistent activity.

Asymmetric sulfimidation using 4,4′-disubstituted bis(oxazolines) **11a** and **11b** as chiral ligands was also examined (Table 31).



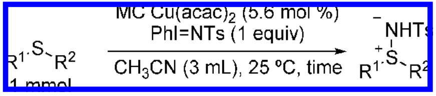
**11a**: R = *t*B
**11b**: R = Ph

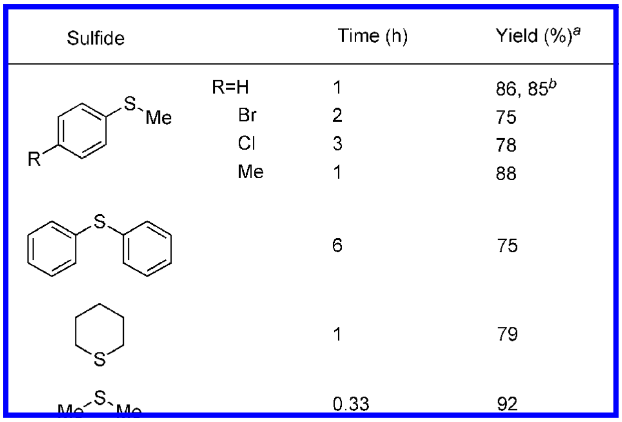
**Table 29. Recovery and Reuse of MC Cu(acac)$_2$**



| cycle no. | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| isolated yield (%) | 92 | 92 | 92 | 90 | 90 |

**Table 30. MC Cu(acac)$_2$-Catalyzed Sulfimidation of Sulfides**

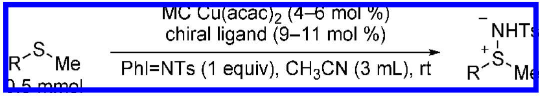


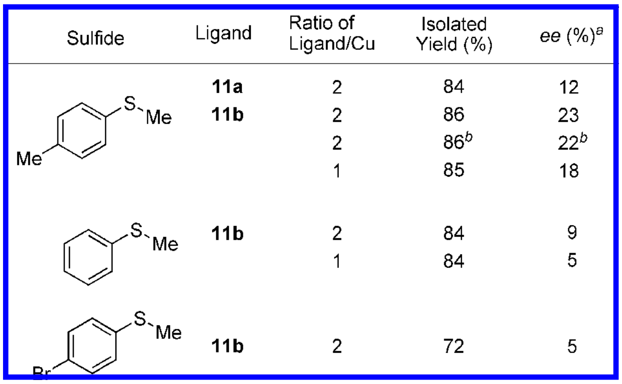


| Sulfide | | Time (h) | Yield (%)[a] |
|---|---|---|---|
| R | R=H<br>Br<br>Cl<br>Me | 1<br>2<br>3<br>1 | 86, 85[b]<br>75<br>78<br>88 |
| | | 6 | 75 |
| | | 1 | 79 |
| Me S Me | | 0.33 | 92 |

[a] Isolated yield of aziridine based on PhI═NTs. [b] With used catalyst.

**Table 31. Asymmetic Sulfimidation of Sulfides Using MC Cu(acac)$_2$**





| Sulfide | Ligand | Ratio of Ligand/Cu | Isolated Yield (%) | *ee* (%)[a] |
|---|---|---|---|---|
| Me | **11a** | 2 | 84 | 12 |
| | **11b** | 2 | 86 | 23 |
| | | 2 | 86[b] | 22[b] |
| | | 1 | 85 | 18 |
| | **11b** | 2 | 84 | 9 |
| | | 1 | 84 | 5 |
| Br | **11b** | 2 | 72 | 5 |

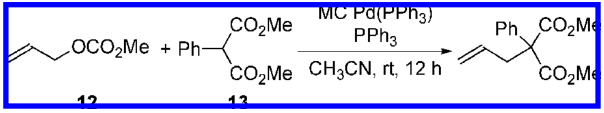
[a] Values were determined by chiral HPLC analysis. [b] With a reused catalyst.

## 2.7. Microencapsulated Palladium [MC Pd]

While palladium catalysts find widespread utility in a variety of transformations in organic synthesis,[41] these are expensive and 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,[42,43a−c,f] oligomerization,[42c,44,45] decarboxylation,[42d] hydrogenation,[43h,45] isomerization,[46] telomerization,[47] Suzuki coupling,[43c,d,i] the Mizoroki−Heck reaction,[43g,i,45c,49] etc. In these cases, however, recovery and reuse of the polymer catalysts have not necessarily been satisfactory. Palladium catalyst was successfully immobilized onto a polymer using the microencapsulation technique.[50]

Preparation of the microencapsulated palladium (MC Pd) was performed according to a standard procedure. First, polystyrene (1.000 g) was dissolved in cyclohexane (20 mL)

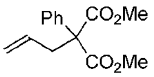
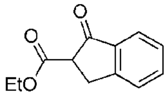
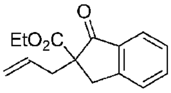
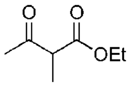
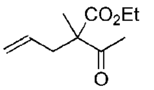
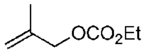
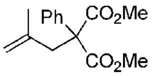
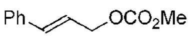
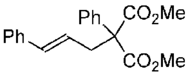
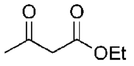
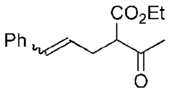
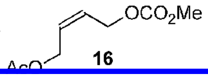
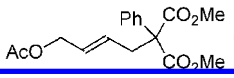
**Table 32. Effect of the Amounts of Triphenylphosphine**



| MC Pd(PPh$_3$) (mol %) | PPh$_3$ (mol %) | yield (%) (recovery (%)) | | |
|---|---|---|---|---|
| | | first | second | third |
| 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)[a] |
| 20 | 40 | 92 (quant) | 81 (99) | 77 (quant) |
| 20 | 60 | 69 (95) | 58 (98) | 65 (99) |

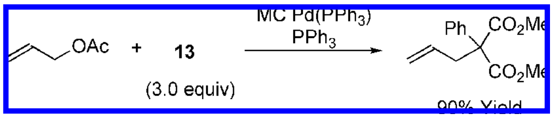
[a] Fourth, 94 (quant); fifth, 83 (quant).

**Table 33. Allylic Substitution Using MC Pd(PPh$_3$)[a]**

| Entry | Allylic carbonate | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **12** | **13** |  | 83 |
| 2 | **12** |  |  | 86 |
| 3 | **12** |  |  | 60 |
| 4 |  **11** | **13** |  | 69 |
| 5 |  **15** | **13** |  | 92[b] |
| 6 | **15** |  |  | 79[c] |
| 7 |  **16** | **13** |  | 64[b] |

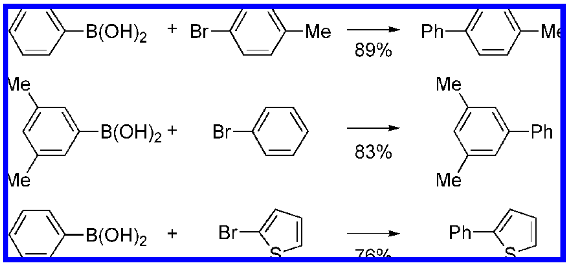
[a] All reactions were carried out using MC Pd(PPh$_3$) (20 mol %) and PPh$_3$ (20 mol %) in CH$_3$CN at room temperature for 12 h. [b] $E/Z$ = >99/<1. [c] $E/Z$ = 64/36.

**Scheme 26. Allylic Substitution of Allyl Acetate with 13[a]**



[a] Reagents and conditions: MC Pd(PPh$_3$) (20 mol %), PPh$_3$ (20 mol %), BSA (3.0 equiv), KOAc (0.10 equiv), CH$_3$CN, reflux, 12 h.

**Scheme 27. Suzuki Coupling[a]**



[a] Reagents and conditions: MC Pd(PPh$_3$) (20 mol %), P($o$-Tol)$_3$ (20 mol %), K$_3$PO$_4$ (2.0 equiv), CH$_3$CN, reflux, 6 h.

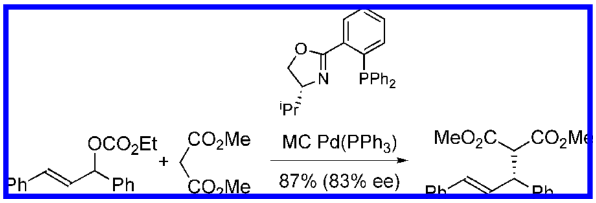
at 40 °C, and tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$, 0.200 g] was added to this solution as a core. Pd(PPh$_3$)$_4$ was dissolved completely. The mixture was stirred for 1 h at this temperature. The color of the mixture changed from brown to black at this stage. The mixture was slowly cooled to 0 °C, and coacervates (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 3 equiv of triphenylphosphine (PPh$_3$) was recovered and 1 equiv of PPh$_3$ remained in the catalyst capsules. $^{31}$P SR-MAS NMR spectra of the catalyst capsules showed only one peak of PPh$_3$ coordinating to the palladium. From these results, it was assumed that the catalyst was encapsulated as Pd(PPh$_3$) [microencapsulated Pd(PPh$_3$)].

Microencapsulated Pd(PPh$_3$) [MC Pd(PPh$_3$)] thus prepared was first used in the allylation reaction of allyl methyl carbonate (**12**) with dimethyl phenylmalonate (**13**). When **12** was combined with **13** in the presence of 20 mol % MC Pd(PPh$_3$), the reaction did not proceed at all. However, it was found that the reaction proceeded smoothly after adding PPh$_3$ (external ligand). The effect of the amounts of PPh$_3$ was examined, and the results are shown in Table 32. The best results were obtained when 20 mol % of PPh$_3$ 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$_3$)-catalyzed allylation reactions of C-nucleophiles with allylic carbonates are summarized in Table 33. Malonates and $\beta$-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 (**15**) gave a mixture of $E/Z$ stereoisomers ($E/Z$ = 64/36), only $E$ isomers were obtained in the reactions of **13** with **15** and ($Z$)-carbonate **16**. The recovery was quantitative in all cases, and the recovered catalyst could be reused.

MC Pd(PPh$_3$) was successfully used in other reactions. Allyl acetate reacted with dimethyl phenylmalonate in the presence of MC Pd(PPh$_3$), PPh$_3$, $N$,$O$-bis(trimethylsilyl)acetamide (BSA), and a catalytic amount of potassium acetate to afford the corresponding adduct in 90% yield (Scheme 26). In addition, Suzuki coupling reactions[51] of boronic acids with aryl bromides were found to proceed smoothly in the presence of MC Pd(PPh$_3$) to afford the corresponding adducts in high yields (Scheme 27). 2-Bromothiophene also worked well. In these reactions, the best results were obtained by using tri-$o$-tolylphosphine [P($o$-Tol)$_3$] as an external ligand. A catalytic asymmetric allylation reaction was also successfully carried out using MC Pd(PPh$_3$) and a chiral ligand (Scheme 28). The 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$_3$) (20 mol %), 2-($o$-diphenylphosphinophenyl)-(4$R$)-isopropyloxazoline (20 mol %),[52] BSA (3.0 equiv), and potassium acetate

**Scheme 28. Asymmetric Allylic Substitution**[a]



[a] Reagents and conditions: MC Pd($PPh_3$) (20 mol %), chiral ligand (20 mol %), BSA (3.0 equiv), KOAc (0.10 equiv), $CH_3CN$, reflux, 12 h.

**Scheme 29. Synthesis of NCPS-$PPh_3$/Pd**

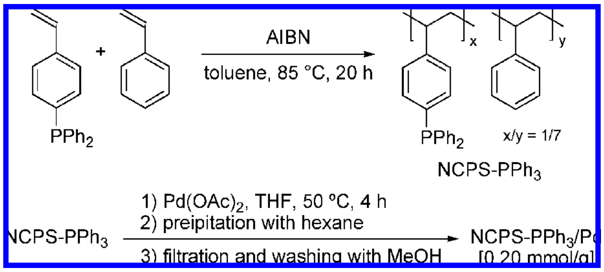
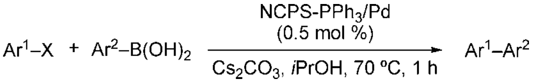


**Table 34. Synthesis of Biaryl Compounds**



| entry | $Ar^1$−X | $Ar^2$ | isolated yield (%) |
|---|---|---|---|
| 1 | Ph−I | Ph− | 90 |
| 2 | Ph−I | 4-MeO−$C_6H_4$− | 98 |
| 3 | Ph−I | 3,4-$(MeO)_2$−$C_6H_3$− | 86 |
| 4 | Ph−I | 2-Me−$C_6H_4$− | 83 |
| 5 | Ph−I | 2,6-$Me_2$−$C_6H_3$− | 12 |
| 6 | 4-MeO−$C_6H_4$−I | Ph− | 88 |
| 7 | 4-MeO−$C_6H_4$−I | 4-MeO−$C_6H_4$− | 97 |
| 8 | 4-MeO−$C_6H_4$−I | 2-Me−$C_6H_4$− | 85 |
| 9 | 4-MeO−$C_6H_4$−Br | Ph− | 74 |
| 10 | 4-MeOC−$C_6H_4$−I | Ph− | 83 |
| 11 | 4-MeOC−$C_6H_4$−I | 4-MeO−$C_6H_4$− | 73 |
| 12 | 4-MeOC−$C_6H_4$−I | 2-Me−$C_6H_4$− | 87 |
| 13 | 4-MeOC−$C_6H_4$−Br | Ph− | 85 |
| 14 | 4-MeOC−$C_6H_4$−Br | 4-MeO−$C_6H_4$− | 97 |
| 15 | 3-$NO_2$−$C_6H_4$−I | Ph− | 78 |
| 16 | 3-$NO_2$−$C_6H_4$−I | 4-MeO−$C_6H_4$− | 78 |
| 17 | 3-$NO_2$−$C_6H_4$−I | 2-Me−$C_6H_4$− | 80 |
| 18 | Ph−I | Ph− | 89[a] |

[a] Reaction was performed in refluxing $H_2O$ overnight with 0.005 mol % catalyst.

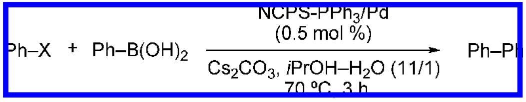
(0.10 equiv) under reflux conditions in acetonitrile. The allylation adduct was obtained in 87% yield with 83% ee.

For the structure of MC Pd($PPh_3$), 18-electron Pd(0) that is coordinated by $PPh_3$ and the benzene ring(s) of polystyrene was assumed. After addition of an external ligand, 14- or 16-electron Pd(0) would be formed and the catalytic reaction would proceed. The coordination of the external ligand to Pd(0) was confirmed by $^{31}P$ SR-MAS NMR analysis, which revealed that the recovered catalyst in Suzuki coupling reactions contained P(*o*-Tol)$_3$.

Non-cross-linked polystyrene supported triphenylphosphine (NCPS-$PPh_3$) microencapsulated palladium was developed (Scheme 29) and used as a heterogeneous catalyst in Suzuki−Miyaura coupling reactions without external addition of phosphine ligand (Table 34).[53]

Generally, approximately 95−97% of the catalyst could be recovered for reuse at the end of each reaction, presumably due to the small reaction scale. In a large scale experiment, the catalyst could be recovered and reused with only minimal palladium leaching (Table 35).

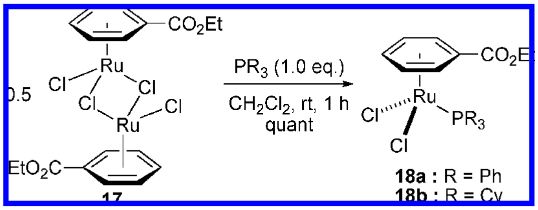
**Table 35. Synthesis of Biaryl Compounds**



| cycle | isolated yield (%) | Pd leaching (%)[a] |
|---|---|---|
| no substrate | | 0.0186 |
| 1 | 91 | 0.2137 |
| 2 | 83 | 0.1097 |
| 3 | 79 | 0.0644 |
| 4 | 73 | 0.0055 |
| 5 | 66 | 0.1375 |

[a] Amount of initial palladium found in the reaction mixture, as determined by ICP-MS analysis.

**Scheme 30. Preparation of Monomeric Catalysts 18**



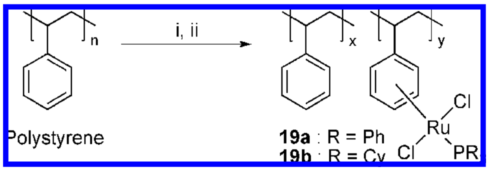
## 2.8. Microencapsulated Methathesis Catalyst

Arene−ruthenium complexes are very useful precatalysts for several organic reactions such as transfer hydrogenation,[54] Diels−Alder reaction,[55] olefin cyclopropanation,[56] enol formate formation,[57] cyclization of dienylalkyne,[58] olefin metathesis,[59] etc. While the catalysts prepared from the arene−ruthenium complexes are air- and moisture-sensitive and 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,[60] these involve problems such as tedious procedures for the preparation of the complexes, low activity compared with the original catalysts, and difficulty applying the catalysts to other reactions. Therefore, development of more versatile polymer-supported ruthenium complexes is strongly demanded.

A new type of polymer-supported ruthenium catalyst was developed based on the microencapsulated technique. However, the preparation method is a little different from that of other MC catalysts. The idea is to utilize the benzene rings of polystyrene as ligands to immobilize arene−metal complexes. It has been known that arene-displacement reactions at Ru(II) are often sluggish.[61] Thus, $[Ru(\eta^6\text{-}C_6H_5CO_2Et)Cl_2]_2$ (**17**) was carefully chosen as the starting material, because it was reported that an intramolecular arene exchange proceeded in good yield using **17** instead of $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$.[62] Dimer **17** was easily prepared according to the literature procedure,[61,62] and treatment of **17** with triphenylphosphine or tricyclohexylphosphine gave $[Ru(\eta^6\text{-}C_6H_5CO_2Et)Cl_2]_2$ (**18a**, R = Ph; **18b**, R = Cy) quantitatively (Scheme 30).

Preparation of the polymer-supported arene−ruthenium complexes using **18** was successfully performed based on a procedure that was similar in part to that of preparation of microcapsules (Scheme 31).[63] Polystyrene (5.00 g) was dissolved in cyclohexane (100 mL) at 65 °C, and **18a** (0.20 g) was added to this solution. Complex **18a** was not

**Scheme 31. Synthesis of Polymer-Supported Arene−RuCl$_2$(PR$_3$) (19)**[a]



[a] Reagents and conditions: (i) cyclohexane, 65 °C, 1 h; (ii) **18a** or **18b**, 120 °C, 24 h, then 65 °C, 1 h, then 0 °C.

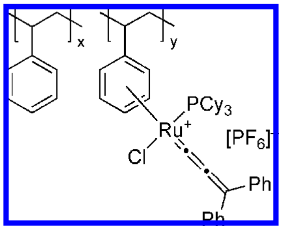
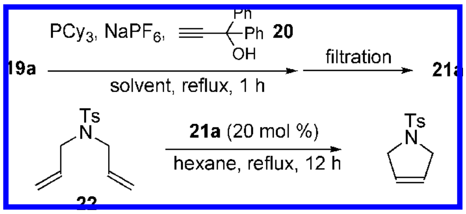


**Figure 8.** Activated ruthenium catalyst **21a**.

dissolved, and a suspension 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 **18a** disappeared, and ethyl benzoate appeared. The mixture was slowly cooled to 0 °C. Coacervation (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 **19a**. The procedure for the preparation of **19b** is similar to that of **19a**. The structure of **19** was confirmed by NMR analysis. The $^{31}$P SR-MAS NMR spectra of the catalysts were measured, and only one peak of PR$_3$ (**19a**, R = Ph, $\delta = 25.7$; **19b**, R = Cy, $\delta = 28.5$) coordinating to the ruthenium was observed. [Ru($\eta^6$-*p*-cymene)(PPh$_3$)Cl$_2$] was prepared, and $^{31}$P NMR of this complex was measured ($\delta = 23.1$). [Ru($\eta^6$-*p*-cymene)(PCy$_3$)Cl$_2$] was reported in literature ($\delta = 26.0$).[59c] From these results, it was concluded that the catalyst was supported as arene−RuCl$_2$(PR$_3$) (polymer-supported arene−RuCl$_2$(PR$_3$) [**19**, PS-RuCl$_2$(PR$_3$)]). 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$_2$(PR$_3$) (**19**) was first used in the ring-closing olefin metathesis (RCM). A polymer-supported cationic ruthenium allenylidene complex according to the Dixneuf and Fürstner method was prepared.[59b,c] Thus, PS-RuCl$_2$(PPh$_3$) (**19a**), tricyclohexylphosphine (PCy$_3$), 1,1-diphenyl-2-propynol (**20**), and sodium hexafluorophosphate (NaPF$_6$) were mixed in several solvents, and the mixture was stirred for 1 h under reflux conditions. Signals of the $^{31}$P SR-MAS NMR spectra of the activated ruthenium catalyst (**21a**, Figure 8) thus prepared were observed at 50.8 and −144.0 ppm. $^{31}$P NMR of monomeric ruthenium complex was already measured [$^{31}$P NMR (CDCl$_3$): 58.8 (PCy$_3$), −140.8 (PF$_6^-$)].[59c,64] Catalyst **21a** was then tested in RCM of *N*,*N*-diallyl-*p*-toluenesulfonamide (**22**) in hexane (Table 36). It was found that the choice of solvents was crucial. While the desired product was obtained in good yield in the first run in *i*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 *i*PrOH (entry 1). In *i*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.

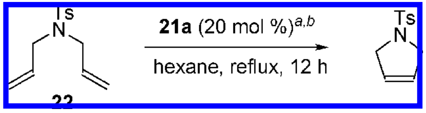
**Table 36. Effect of Solvents in the Preparation of the Active Catalyst**



| entry | solvent | yield (%) (recovery (%)) first | second | third |
|---|---|---|---|---|
| 1 | *i*PrOH | 8 (quant) | 9 (quant) | |
| 2 | *i*PrOH-hexane (1/1) | 78 (quant) | 48 (quant) | 16 (quant) |
| 3 | *i*PrOH-hexane (1/10) | 42 (quant) | 69 (quant) | 71 (quant) |
| 4 | *i*PrOH-hexane (1/10)[a] | 49 (98) | 72 (quant) | 77 (quant) |

[a] Compound **19b** was used instead of **19a**.

**Table 37. Reactivation Conditions of the Catalyst**



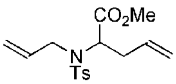
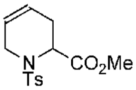
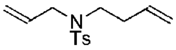
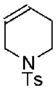
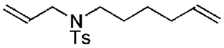
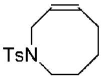
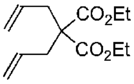
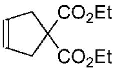
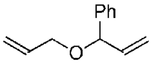
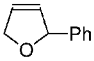
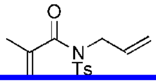
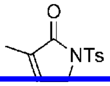
| entry | method | conditions | yield (%) first | second | third |
|---|---|---|---|---|---|
| 1 | A | PCy$_3$, 20, reflux, 1 h | 40 | 72 | 77 |
| 2 | B | PCy$_3$, NaPF$_6$, 20, rt, 12 h | 63 | 56 | 49 |
| 3 | C | PCy$_3$, 20, reflux, 1 h then NaPF$_6$, rt, 12 h | 69 | 73 | 85 |
| 4[c] | C | 75 | 81 | 98[f] | 88 |
| 5[c,d] | C | 71 | 85 | 88 | 88 |
| 6[c,e] | C | 97 | 18 | 12 | 88 |
| 7[c,g] | | | 80 | | |

[a] Catalyst **21a** was reactivated under methods A−C in *i*PrOH−hexane (1/10). [b] Recovery of the catalysts was quantitative. [c] Hexane−toluene (10/1) was used as a solvent in RCM. [d] 10 mol % of **21a** was used. [e] 5 mol % of **21a** was used. [f] Fourth, 83% (recovery quant); fifth, 82% (recovery quant); sixth, 89% (recovery quant); seventh, 92% (recovery quant). [g] [(*p*-Cymene)RuCl(PCy$_3$)(=C=C=CPh$_2$)]$^+$[PF$_6$]$^-$ was used instead of **21a**.

In order to increase the chemical yields, reactivation conditions of the recovered catalysts in RCM were next examined (Table 37). After careful investigation, the best results were obtained when a mixture of the recovered catalyst, PCy$_3$, and **20** was stirred for 1 h under reflux conditions and, after addition of NaPF$_6$, further stirred for 12 h at rt (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 38. Six-membered rings 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 $^{31}$P SR-MAS NMR analysis. Signals were observed at 50.8 and −144.0 ppm, which were completely consist with those of the original catalyst **18a**.

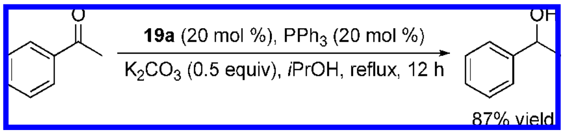
PS-RuCl$_2$(PPh$_3$) (**19a**) was successfully used in other reactions. Acetophenone was reduced smoothly in the

**Table 38. Ring-Closing Olefin Metathesis Using 21a**[a]

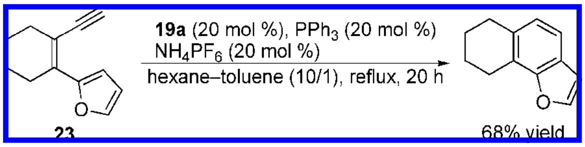
| Enrty | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 98 |
| 2 |  |  | 92 |
| 3 |  |  | $57^b$ |
| 4 |  |  | 72 |
| 5 |  |  | 66 |
| 6 |  |  | 82 |

[a] All reactions were carried out using **21a** (20 mol %) in hexane−toluene (10/1) under reflux conditions for 12 h. [b] Reaction was carried out for 24 h.

**Scheme 32. Hydrogenation of Acetophenone Using 19a**



**Scheme 33. Cyclization of Dienylalkyne Using 19a**



presence of **19a** to afford the corresponding alcohol in high yield (Scheme 32). In addition, **19a** catalyzed cyclization of dienylalkyne (**23**) in good yield (Scheme 33).

A saturated *N*-heterocyclic carbene metathesis catalyst, **24**, was also immobilized using the microencapsulation technique (Figure 9).[65] The resulting material was tested in the ring-closing metathesis using a standard substrate, *N*,*N*-diallyltosylamide. After some experiments, $H_2O$−MeOH (4/1) was shown to be the best solvent. The microencapsulated catalyst could be recycled and retained significant activity over fourth cycles (Scheme 34). However, in the first run, 540 ppm ruthenium was detected in the metathesis product as a result of leaching from the polymer.

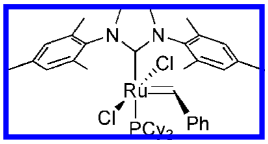
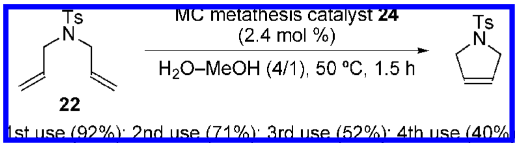


**Figure 9.** *N*-Heterocyclic carbene catalyst **24**.

**Scheme 34. Ring-Closing Metathesis Using MC Metathesis Catalyst 24**



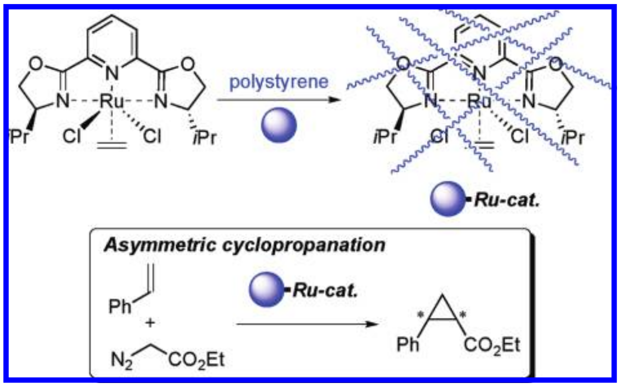


**Figure 10.** Microencapsulation of pybox−Ru chiral catalyst.

Microencapsulated chiral pybox−Ru catalysts were also reported (Figure 10).[66] In the cyclopropanation reaction, these catalysts allow 60−68% yields with enantioselectivities in the range 75−85% ee. The catalyst is soluble in a reaction solvent and is re-encapsulated at the end of the reaction.

## 3. Polymer Incarcerated Catalysts

### 3.1. Polymer Incarcerated Palladium [PI Pd]

A microencapsulation technique for binding catalysts to polymers has been reviewed. Utilizing this technique, unprecedented polymer-supported catalysts, microencapsulated Lewis acids, oxidants, and transition metal complexes have been prepared. The catalysts thus prepared have been demonstrated to be effective in many useful organic reactions. In all cases, the catalysts were recovered quantitatively by simple filtration and reused without significant loss of activity. This new technique will be applicable to the preparation of many other polymer-supported catalysts and reagents. On the other hand, some problems exist in these catalysts. In the microencapsulation method, it is necessary to dissolve the polymer support in an organic solvent. Therefore, it was found that the resulting microencapsulated catalysts were dissolved or swelled in some cases, and leaching of metals from supports occurred.

To address these issues, a new method for immobilizing metal catalysts onto polymers, “the polymer incarcerated (PI) method”, was developed.[67] This term was inspired by the elegant work of Cram[68] on carcerands, hemicarcerands, and their complexes (Figure 11).

In the PI method, a catalyst is first microencapsulated. Namely, a polymer is dissolved in an appropriate solvent, and a catalyst is added to this polymer. After cooling, microcapsules formed are washed and dried to afford a microencapsulated catalyst. It has already been shown that the catalyst locates not only inside the capsules but also on the surface or close to the surface of the capsules. The microcapsules formed are then cross-linked to afford the desired catalyst.

First, palladium was chosen as a transition metal to be immobilized. Based on this idea, epoxide-containing copolymers (**25a**−**c**), which were prepared by radical polymerization of styrene, 4-vinylbenzyl glycidyl ether, and methacrylic acid or alcohol (**26** or **27**) were prepared (Figure 12). Copolymer (**25a**−**c**) was dissolved in THF at room temperature, and $Pd(PPh_3)_4$ was added to this solution as a core. After hexane was added, coacervates were found to

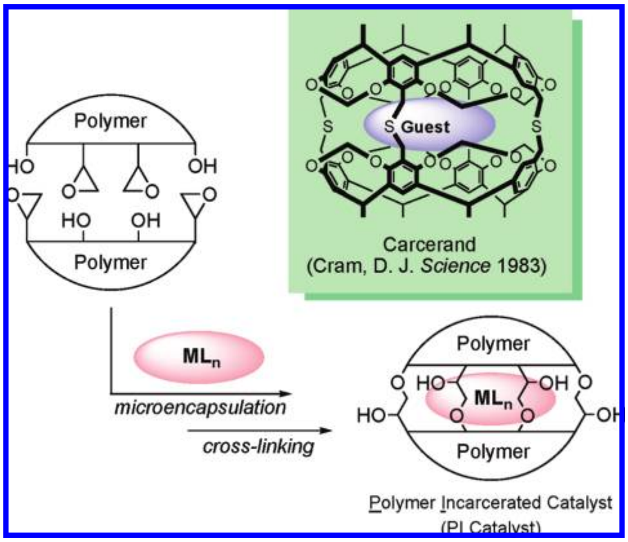


**Figure 11.** Polymer incarcerated catalysts.

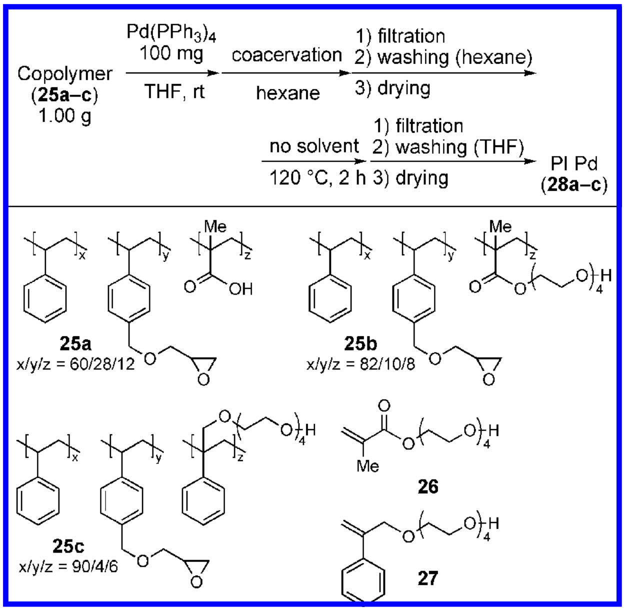
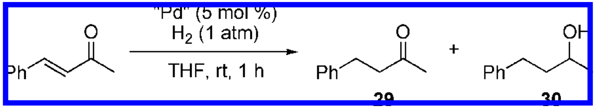


**Figure 12.** Preparation of polymer incarcerated (PI) Pd (**28a**−**c**) from copolymers **25a**−**c**.

**Table 39. Hydrogenation of Benzalacetone Using PI Pd**[a]



| "Pd" | yield (%)[c] first | second | third | fourth | fifth |
|---|---|---|---|---|---|
| PI Pd **28a**[b] | 81 | | | | |
| PI Pd **28b**[b] | 93 | 80 | 88 | 82 | 87 |
| PI Pd **28c**[b] | 85 | 80 | 87 | 91 | 90 |
| 5% Pd/C | 91 | | | | |
| $Pd(PPh_3)_4$ | 0 | | | | |

[a] Unless otherwise noted, the hydrogenation of olefin (0.5 mmol) was carried out in the presence of PI Pd (5 mol %) in THF (5 mL) and an atmosphere of hydrogen (1 atm) for 1 h. Catalysts **28b** and **28c** were recovered and reused after simple filtration and drying. [b] No peaks of palladium metal were observed in XRF analysis. [c] **29**/**30** = 95/5.

envelop the core dispersed in the medium. The mixture was left to stand at room temperature to form microcapsules containing Pd. After filtration, washing, and drying, the catalyst capsules were then stirred at 120 °C for 2 h to afford polymer incarcerated palladium (PI Pd). During this preparation, 4 equiv of $PPh_3$ was recovered from the washings, and no $PPh_3$ was observed in PI Pd measured by $^{31}P$ SR-MAS NMR and X-ray photoelectron spectroscocy (XPS) analyses. From these results, it was assumed that phosphine-free Pd(0) was formed by using the PI method. It should be noted that normally unstable ligand-free Pd(0) was readily prepared and could be stored at room temperature in air.

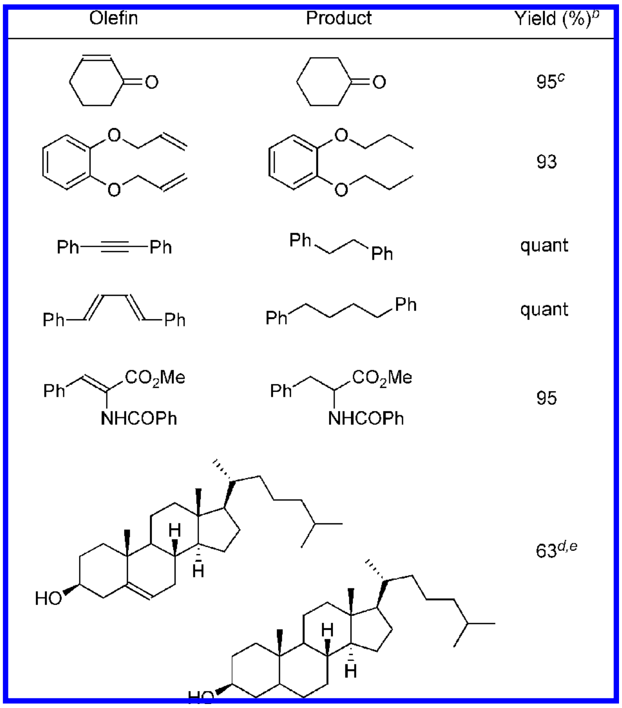
PI Pd (**28a**−**c**) thus prepared were first used in hydrogenation. While several homogeneous catalysts have been used in reduction reactions, heterogeneous catalysts have often been employed in many synthetic stages in laboratories as well as industry.[69] Although Pd/C is one of the most popular heterogeneous catalysts, leaching of Pd and ignition are known to be serious problems especially when reduction is performed in large-scale experiments. PI Pd was tested in hydrogenation of benzalacetone, and the results are shown in Table 39. Among the PI Pd ctatlysts tested, **28c** gave the best results (entries 1−3).[70] The reduction was completed within 1 h in THF under ordinary pressure, and it should be noted that the catalyst was recovered quantitatively by simple filtration and that the same yields were obtained even after the fifth use. Moreover, it was confirmed by fluorescence X-ray analysis that no leaching of Pd from the catalyst occurred. The activity of PI Pd was comparable to that of 5% Pd/C (entry 4), but no ignition occurred using PI Pd. It is also noteworthy that PI Pd was much more active than the original catalyst, $Pd(PPh_3)_4$. The reaction did not proceed at all using $Pd(PPh_3)_4$ under the same reaction conditions (entry 5). Furthermore, it was revealed that the reduction also proceeded smoothly using <0.1 mol % of PI Pd.

Reduction of other substrates using PI Pd **28c** was surveyed, and in all cases, the reactions proceeded smoothly to afford the desired products in high yields (Table 40).

PI Pd catalysts **28a**−**c** were then applied to allylic substitution reactions, a representative carbon−carbon bond-forming reaction.[71] The reaction of allyl methyl carbonate (**12**) with dimethyl phenylmalonate (**13**) was chosen as a model, and several reaction conditions were examined (Table 41). It was found that the allylation reaction proceeded in the presence of PI Pd (5 mol %) and $PPh_3$ (5 mol %) in THF under reflux conditions. While **28a** gave lower yields, the activity of **28b** and **28c** was high, and the desired allylation adducts were obtained in excellent yields. The catalysts were recovered by simple filtration and reused several times. In the case of **28b**, however, leaching of palladium from **28b** occurred in the fourth and the fifth use. On the other hand, no leaching of palladium was observed in the reactions using **28c** even after the fifth use, and the reactions proceeded smoothly to afford the desired adducts in high yields in all cases.

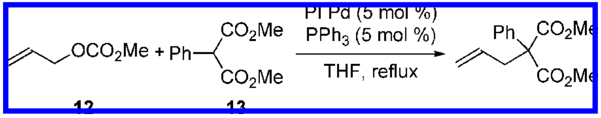
Several examples of allylic substitution reactions using the PI Pd **28c** are summarized in Table 42. Malonates and $\beta$-ketoesters smoothly reacted under these conditions to afford the corresponding allylation products in high yields. Moreover, PI Pd **28c** was successfully applied to carbon−oxygen bond-forming reactions. Namely, phenol or naphthol derivatives smoothly reacted with **12** to afford the corresponding allyl phenyl or allyl naphthyl ethers in high yields. It should be noted that 4-nitrophenol also worked well to produce allyl 4-nitrophenyl ether quantitatively. It was already reported that the reactivity of phenol or naphthol derivatives having electron-withdrawing groups such as a nitro group decreased significantly even using very reactive homogeneous pal-

**Table 40. Hydrogenation of Other Examples Using PI Pd 28c**[a]



[a] Unless otherwise noted, the hydrogenation of olefin (0.5 mmol) was carried out in the presence of PI Pd **28c** (5 mol %) in THF (5 mL) and an atmosphere of hydrogen (1 atm) for 1 h. [b] Isolated yield. [c] Determined by gas chromatography. [d] Reaction was carried out in dichloromethane (5 mL) for 24 h. [e] Determined by $^1H$ NMR.

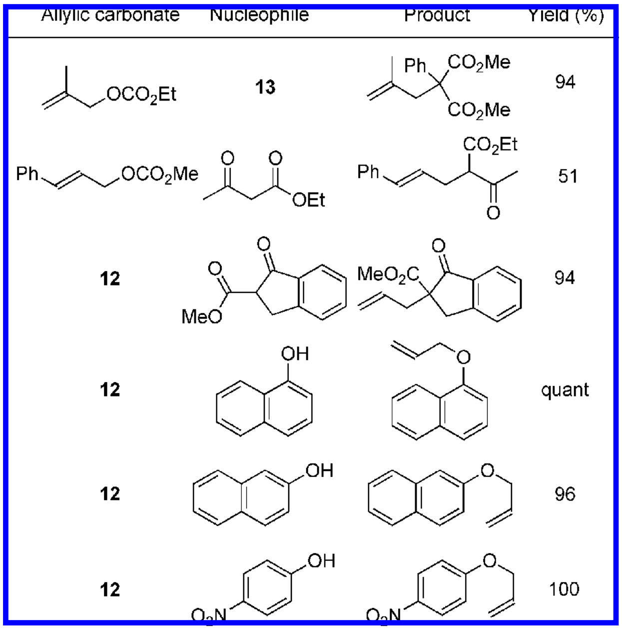
**Table 41. Allylation Reaction of Allyl Methyl Carbonate (12) with Dimethyl Phenylmalonate (13)**



| PI Pd | time (h) | yield (%) first | second | third | fourth | fifth |
|---|---|---|---|---|---|---|
| **28a** | 12 | 54 | 82 | 97[a] | | |
| **28b** | 12 | quant | 85 | 90 | 95[a] | 82[a] |
| **28b** | 2 | 96 | 97 | 100 | | |
| **28c** | 12 | 95 | 100 | 94 | 94 | 71 |
| **28c** | 2 | 88 | 94 | 98 | 87 | 98 |

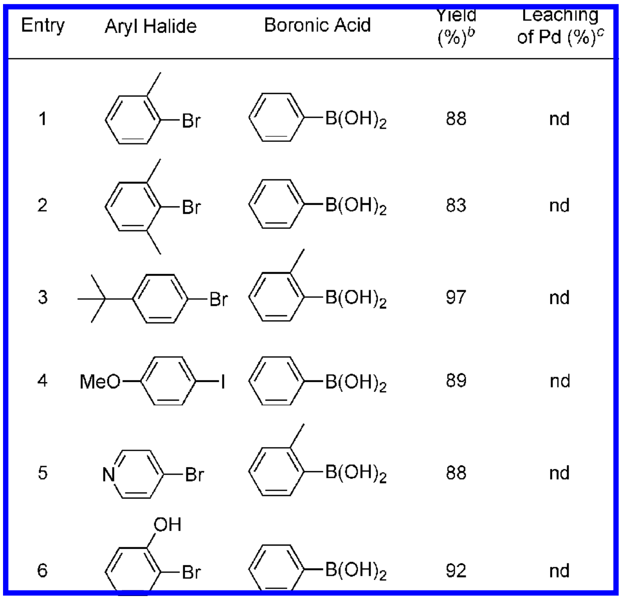
[a] A small amount of leaching of Pd was observed.

**Table 42. Allylation Reaction Using PI Pd 28c**[a]



[a] All reactions were carried out using PI Pd **28c** (5 mol %) and $PPh_3$ (5 mol %) in tetrahydrofulran under reflux for 2 h.

**Table 43. PI Pd-Catalyzed Suzuki–Miyaura Coupling of Various Substrates**[a]



[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 2.0 equiv of $K_3PO_4$, 5 mol % of PI Pd **28c** (0.15 mmol/g), 5 mol % of P(*o*-MeOPh)$_3$, toluene–$H_2O$ (4/1), reflux, 2 h. [b] Isolated yield. [c] Measured by XRF analysis. nd = not detected (<0.94%).

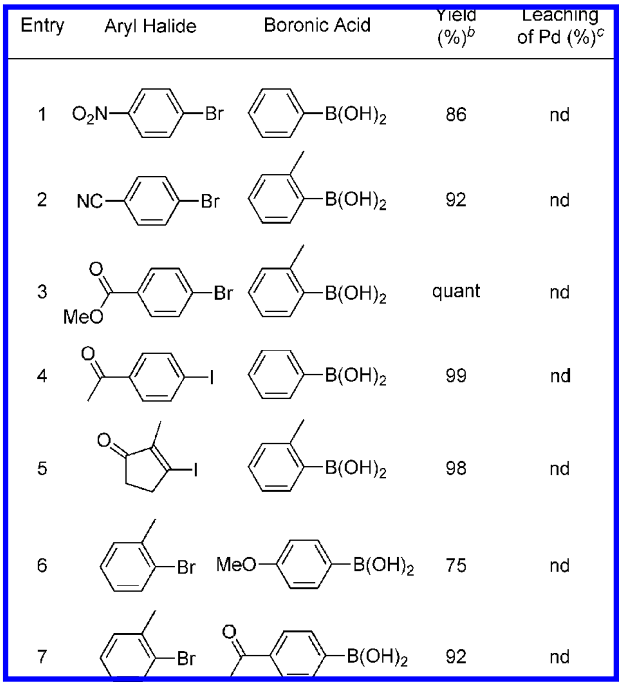
ladium systems. In this reaction, it was exciting to demonstrate that PI Pd **28c** was more reactive than the homogeneous Pd catalysts.

Moreover, PI Pd is also a highly efficient reusable catalyst for Suzuki–Miyaura coupling.[72] Various coupling reactions proceeded smoothly by using PI Pd **28c** (Tables 43 and 44). PI Pd was recovered by simple filtration and reused several times without loss of activity, and no leaching of the palladium was detected under optimized conditions. It is noted that the activity of PI Pd is even higher than that of homogeneous palladium catalysts. A characteristic feature of PI Pd as an immobilized catalyst is that the activity of the catalyst is remarkably improved by changing the external phosphine ligands.

The minimum amount of the catalyst that could be used to mediate several coupling reactions was evaluated (Table 45). Reactions that use very small amounts of the catalyst also afforded the desired coupling products with high turnover numbers (TONs). The maximum TON reached 53 600 (entry 5).

PI Pd was applied to the preparation of acridone derivatives.[73] Acridone analogues are promising antiviral agents[74] as well as fluorescent labels[75] in biodiagnostics. In the field of antitumor binding agents, acridones are important precursors for the creation of acridine derivatives with potential anticancer activity.[76] Acridones are usually prepared by Ullmann condensation of anilines with 2-bromobenzoic acids to give *N*-phenyl anthranilic acids, which undergo ring closure with sulfuric acid.[77] However, this method requires

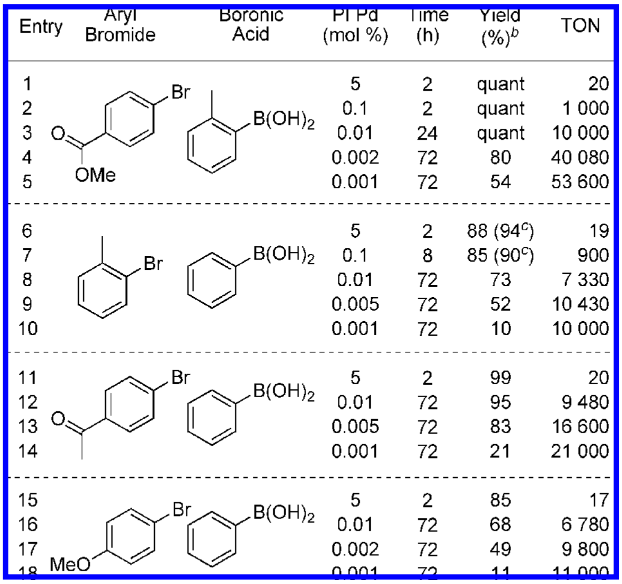
**Table 44. PI Pd-Catalyzed Suzuki−Miyaura Coupling of Various Substrates**[a]



| Entry | Aryl Halide | Boronic Acid | Yield (%)[b] | Leaching of Pd (%)[c] |
|---|---|---|---|---|
| 1 | $O_2N$ Br | $B(OH)_2$ | 86 | nd |
| 2 | NC Br | $B(OH)_2$ | 92 | nd |
| 3 | O MeO Br | $B(OH)_2$ | quant | nd |
| 4 | O I | $B(OH)_2$ | 99 | nd |
| 5 | O I | $B(OH)_2$ | 98 | nd |
| 6 | Br | MeO $B(OH)_2$ | 75 | nd |
| 7 | Br | O $B(OH)_2$ | 92 | nd |

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 2.0 equiv of $K_3PO_4$, 5 mol % of PI Pd **28c** (0.15 mmol/g), 5 mol % of P(*o*-MeOPh)$_3$, toluene-$H_2O$ (4/1), reflux, 2 h. [b] Isolated yield. [c] Measured by XRF analysis. nd = not detected (<0.94%).

**Table 45. The Minimum Amount of the Catalyst**[a]



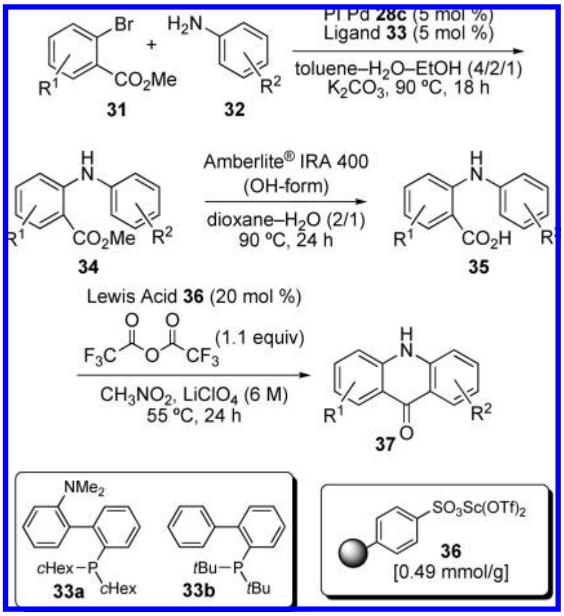
| Entry | Aryl Bromide | Boronic Acid | PI Pd (mol %) | Time (h) | Yield (%)[b] | TON |
|---|---|---|---|---|---|---|
| 1 | Br O OMe | $B(OH)_2$ | 5 | 2 | quant | 20 |
| 2 | | | 0.1 | 2 | quant | 1 000 |
| 3 | | | 0.01 | 24 | quant | 10 000 |
| 4 | | | 0.002 | 72 | 80 | 40 080 |
| 5 | | | 0.001 | 72 | 54 | 53 600 |
| 6 | Br | $B(OH)_2$ | 5 | 2 | 88 (94[c]) | 19 |
| 7 | | | 0.1 | 8 | 85 (90[c]) | 900 |
| 8 | | | 0.01 | 72 | 73 | 7 330 |
| 9 | | | 0.005 | 72 | 52 | 10 430 |
| 10 | | | 0.001 | 72 | 10 | 10 000 |
| 11 | Br O | $B(OH)_2$ | 5 | 2 | 99 | 20 |
| 12 | | | 0.01 | 72 | 95 | 9 480 |
| 13 | | | 0.005 | 72 | 83 | 16 600 |
| 14 | | | 0.001 | 72 | 21 | 21 000 |
| 15 | Br MeO | $B(OH)_2$ | 5 | 2 | 85 | 17 |
| 16 | | | 0.01 | 72 | 68 | 6 780 |
| 17 | | | 0.002 | 72 | 49 | 9 800 |
| 18 | | | 0.001 | 72 | 11 | 11 000 |

[a] Reaction conditions: 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 2.0 equiv of $K_3PO_4$, 5 mol % of PI Pd **28c** (0.15 mmol/g), 5 mol % of P(*o*-MeOPh)$_3$, toluene−$H_2O$ (4/1), reflux, 2 h. [b] Isolated yield. [c] GC yield.

harsh conditions and suffers from tedious workup and purification.

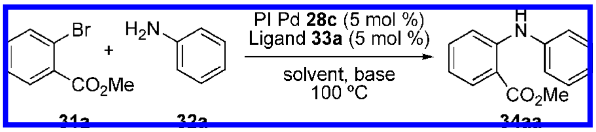
Synthetic scheme of acridone derivatives **37** using polymer-supported catalysts is shown in Scheme 35. The initial step involves the formation of *N*-phenyl anthranilic acid ester **34** according to the Pd-catalyzed amination.[78,79]

**Scheme 35. Procedure for the Synthesis of Acridone Derivatives**



First, the effect of solvents and bases was examined in the model reaction of methyl 2-bromobenzate (**31a**) with aniline (**32a**) in the presence of PI Pd **28c** and ligand **33a**[79] (Table 46). It was found that serious palladium leaching occurred when toluene was used as a solvent (entry 1); however, the addition of water and ethanol remarkably suppressed the leaching of palladium and showed higher catalytic activity (entries 2−5). Furthermore, the use of $K_2CO_3$ rather than $K_3PO_4$ as a base was more effective to suppress the leaching (entry 5).

**Table 46. Effect of Reaction Conditions in PI Pd-Catalyzed Amination**



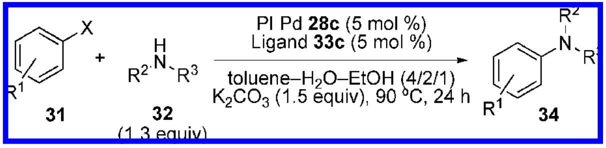
| entry | solvent | base | time (h) | yield %)[a] | leaching of Pd (%)[b] |
|---|---|---|---|---|---|
| 1 | toluene | $K_3PO_4$ | 18 | 46 | 76 |
| 2 | toluene−$H_2O$ (4/1) | $K_3PO_4$ | 18 | 78 | 7 |
| 3 | toluene−$H_2O$ (4/1) | $K_2CO_3$ | 12 | 34 | nd |
| 4 | toluene−$H_2O$−EtOH (4/2/1) | $K_3PO_4$ | 12 | 78 | 2 |
| 5 | toluene−$H_2O$−EtOH (4/2/1) | $K_2CO_3$ | 24 | 79 | nd |

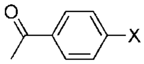
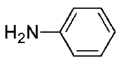
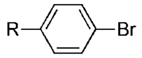
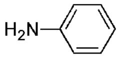
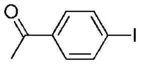
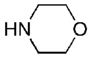
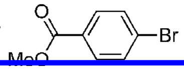
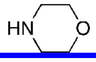
[a] Isolated yield. [b] Determined by XRF analysis; nd = not detected.

To confirm the catalytic activity of PI Pd **28c** in the amination of aryl halides, substrate generality of aryl halides and amines was briefly surveyed (Table 47). Both aryl iodides and aryl bromides gave the desired products in good yields without leaching of palladium (entries 1−5). Furthermore, aryl chloride also gave the aminated product in moderate yield without leaching of palladium (entry 3). In the case of secondary amines such as morpholine, however, aminated products were obtained in lower yields, and leaching of Pd was observed under the same reaction conditions (entries 6 and 7).

Palladium-catalyzed hydrogenation is frequently used not only in laboratories but also in industry. While immobilized palladium catalysts, such as Pd/C and Pd/$Al_2O_3$, have been often employed, leaching of the palladium from the supports, moderate yields of recovery, contamination of the palladium

**Table 47. PI Pd-Catalyzed Amination**



| Entry | Aryl Halide | Amine | | Yield (%)[a] | Leaching of Pd (%)[b,c] |
|---|---|---|---|---|---|
| 1 |  |  | X = Br | 68 | nd |
| 2 | | | X = I | 93 | nd |
| 3 | | | X = Cl | 64 | nd |
| 4 |  |  | R = CN | 80 | nd |
| 5 | | | R = $CO_2Me$ | 88 | nd |
| 6 |  |  | | 43 | 21 |
| 7 |  |  | | 24 | 11 |

[a] Isolated yield. [b] Determined by XRF analysis. [c] nd = not detected.

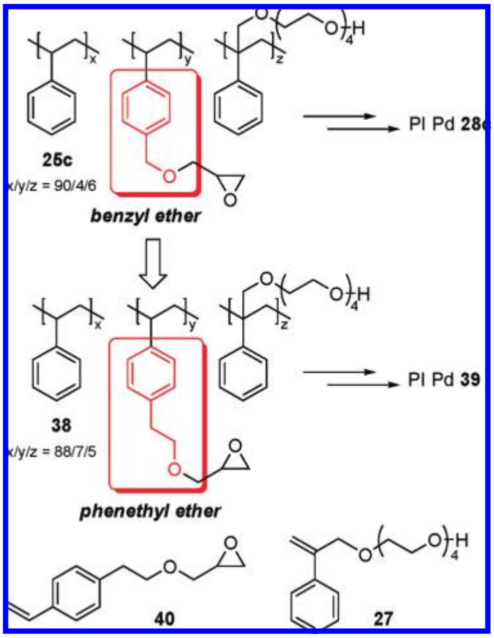


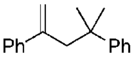
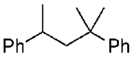
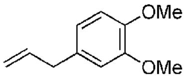
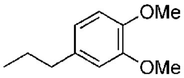
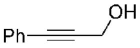
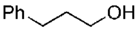
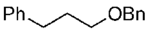
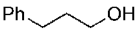
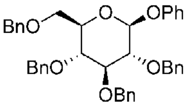
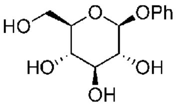
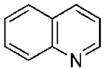
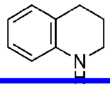
**Figure 13.** Preparation of more resistant PI Pd **39**.

to products, and poisoning by sulfur are sometimes serious problems, especially in the manufacture of pharmaceuticals.

It was revealed that PI Pd **28c** derived from polymer **25c** consisting of phosphine-free palladium(0) effectively catalyzed hydrogenation of olefins in THF under atmospheric pressure. Moreover, the catalyst was recovered completely by simple filtration and could be reused several times without loss of activity. On the other hand, it was assumed that the benzyl ether moieties of PI Pd **28c** would be cleaved in the hydrogenation under harsh conditions such as high hydrogen pressure and high temperature.

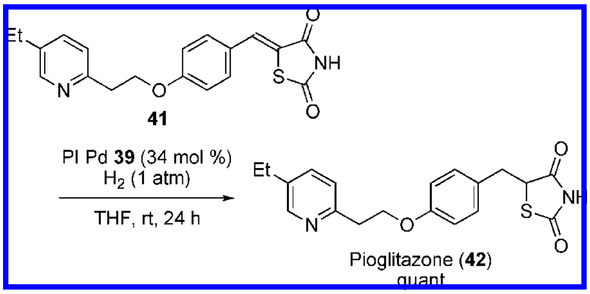
A new copolymer **38** for more resistant PI Pd **39**, which has no benzylic ether moiety, was designed.[80] Copolymer **38** was synthesized by radical copolymerization of styrene, epoxide monomer **40**, and tetra(ethylene glycol) monomer **27** (Figure 13). PI Pd **39** was prepared from $Pd(PPh_3)_4$ and polymer **38** according to the method for the preparation of **28c**.

**Table 48. Hydrogenation of Several Substrates Using PI Pd 39**[a]

| Substrate | Time (h) | Product | Yield (%) |
|---|---|---|---|
|  | 1 |  | quant |
|  | 1 |  | quant |
|  | 1 |  | 93 |
| PhOBn | 18 | PhOH | 89[b] |
|  | 5 |  | 98 |
|  | 72 |  | 87 |
| $PhNO_2$ | 18 | $PhNH_2$ | 93[b] |
|  | 24 |  | quant |

[a] All reactions were carried out using 5 mol % PI Pd **39** in THF under atmospheric hydrogen pressures at room temperature. The leaching of the palladium to the reaction mixture was measured by XRF analysis. No peaks of palladium were detected in any entry. [b] Determined by GC analysis.

**Scheme 36. Hydrogenation for Antidiabetic Agent Using PI Pd 39**

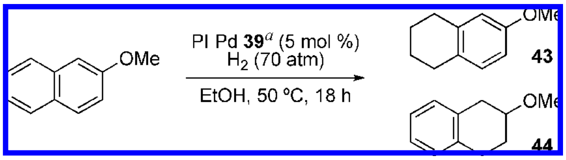


Several substrates were hydrogenated using PI Pd **39**, and the results are summarized in Table 48. In addition to normal C−C double and triple bonds, benzyl ethers, nitrobenzene, and quinoline were easily hydrogenated under atmospheric pressure at room temperature.

PI Pd **39** was also applied to the reduction of less reactive substrate **41**, which is an intermediate for the synthesis of an antidiabetic agent, pioglitazone (**42**). This agent is expected to effectively ameliorate the abnormal glucose and lipid metabolism associated with non-insulin-dependent diabetes mellitus or obesity.[81] It is known that the yields of the hydrogenation of **41** using conventional catalysts are not satisfactory, probably because this substrate has catalytic-poison nitrogen and sulfur moieties in the molecule. The hydrogenation of **41** using PI Pd **39** under atmospheric pressure proceeded smoothly to afford **42** quantitatively (Scheme 36). No contamination of the palladium was detected by X-ray fluorescence (XRF) analysis, and PI Pd **39** could be recovered and reused.

On the other hand, 2-methoxynaphthalene was hydrogenated under 70 atm of hydrogen pressure at 50 °C (Table 49). PI Pd **39** was successfully recovered and reused even

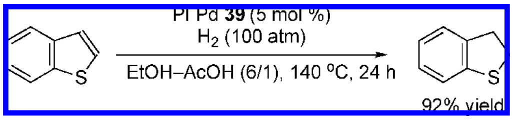
**Table 49. Reuse of PI Pd 39 under Harsh Conditions**



| entry | yield (%)[b] | ratio of **43**/**44**[c] | recovery of **39** (%) |
|---|---|---|---|
| 1 | 100 | 73/27 | quant |
| 2 | 100 | 74/26 | quant |
| 3 | 100 | 74/26 | quant |
| 4 | 99 | 74/26 | quant |
| 5 | 100 | 74/26 | quant |

[a] All reactions were carried out using 5 mol % PI Pd **39** in THF under atmospheric $H_2$ pressure at rt. The leaching of the palladium to the reaction mixture was measured by XRF analysis. No peaks of palladium were detected in any entry. [b] Isolated yield. [c] Determined by GC analysis.

**Scheme 37. Hydrogenation of Benzothiophene Using PI Pd 39**



under high hydrogen pressure at elevated temperature without loss of activity, and leaching of the palladium was not detected by XRF analysis in all runs.

Furthermore, a remarkable result was obtained in the hydrogenation of benzothiophene. In the petrochemical industry, the hydrotreatment of petroleum feedstocks is conducted in refineries, and sulfur compounds are converted to hydrocarbons and $H_2S$ via a hydrodesulfurization (HDS) process. Among the sulfur compounds, thiophenes are quite abundant and benzothiophene is among the most difficult to degrade.[83] The HDS process is typically performed at high hydrogen pressures (>200 atm) and temperatures (300−450 °C) in the presence of sulfided metal-based catalysts such as nickel- and cobalt-promoted $MoS_2$ and $WS_2$ supported on alumina, and benzothiophene is hydrogenated to dihydrobenzothiophene during the HDS process.[84] It is noted that the hydrogenation of benzothiophene using PI Pd **39** under milder conditions compared with HDS conditions proceeded in excellent yield without leaching of the palladium (Scheme 37).[85] The excellent activity of PI Pd **39** is possibly due to the highly dispersed palladium in the polymer, and the surrounding benzene rings of the polymer may protect the palladium from poisoning by sulfur.

PI Pd-catalyzed Suzuki−Miyaura couplings proceed in high yields in the presence of an externally added phosphine ligand such as tris(*o*-methoxyphenyl)phosphine without leaching of palladium.[72] In this case, however, the phosphine ligand is lost during filtration of the catalyst, and addition of the phosphine ligand is necessary in every recycling use. New PI Pd catalysts using polymer supports that contain the diphenylphosphino group instead of adding external phosphine ligands were investigated (Scheme 38) and were applied to Suzuki−Miyaura couplings (Table 50).[86]

In the reactions using both electron-rich and electron-deficient aryl halides, the corresponding biaryl coupling products were obtained in high yields without any leaching of the palladium. Furthermore, PI Pd was recovered by simple filtration and could be reused several times (Table 51). Even after the fifth use, the same yields were obtained. It was confirmed by XRF analysis that no leaching of Pd from the catalysts occurred in all cases.

**Scheme 38. Praparation of Phosphinated PI Pd 46**

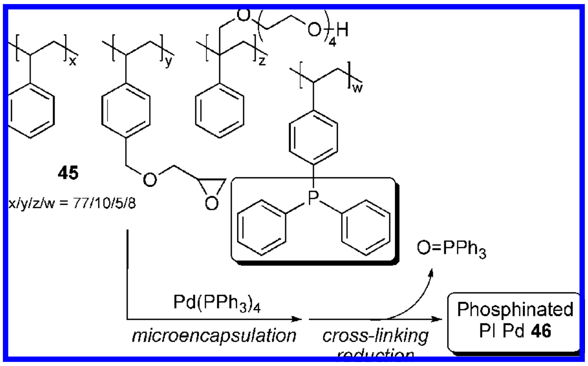
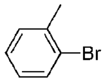
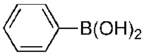
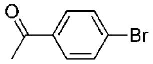
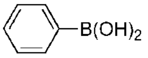
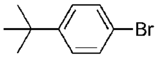
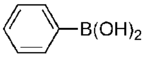
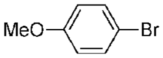
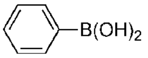
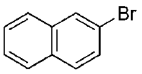
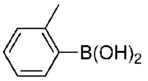
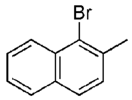
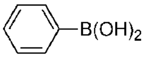
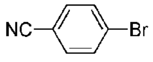
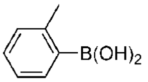
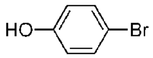
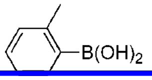
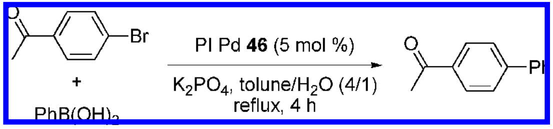


**Table 50. Phosphinated PI Pd-Catalyzed Suzuki−Miyaura Coupling of Various Substrates without External Phosphine Ligand[a]**

| Entry | Aryl Halide | Boronic Acid | Yield (%)[b] | Leaching of Pd (%)[c] |
|---|---|---|---|---|
| 1 |  |  | 96 | nd |
| 2 |  |  | quant | nd |
| 3 |  |  | quant | nd |
| 4 |  |  | 84 | nd |
| 5 |  |  | 94 | nd |
| 6 |  |  | 85 | nd |
| 7 |  |  | 85 | nd |
| 8 |  |  | 92 | nd |

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 1.5 equiv of $K_3PO_4$, 3 mol % PI Pd **46** (0.36 mmol/g, P/Pd = 2.1), toluene/$H_2O$ (4/1), reflux, 4 h. [b] Isolated yield. [c] Determined by XRF analysis; nd = not detected (<0.94%).

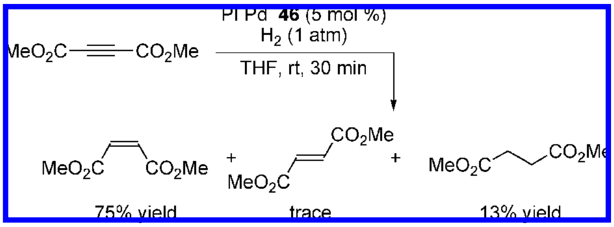
**Table 51. Recovery and Reuse of Phosphinated PI Pd 46**



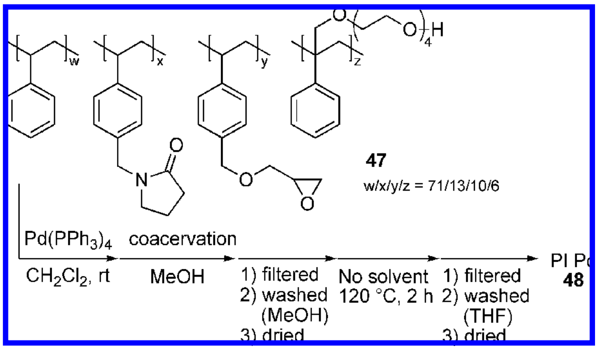
| run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| yield of product[a] (%) | quant | quant | 98 | 99 | quant |
| leaching of Pd[b] (%) | nd | nd | nd | nd | nd |

[a] Isolated yield. [b] Determined by XRF analysis; nd = not detected (<0.94%).

**Scheme 39. Phosphinated PI Pd-Catalyzed Semi-hydrogenation**



**Scheme 40. Preparation of PI Pd 48 from Copolymer 47**



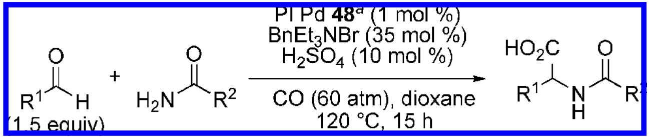
The possibility that the phosphines in the polymer support might act as a poisoning agent of the metal, realizing both chemoselective hydrogenation and suppression of metal leaching, was also considered. Thus, we investigated the chemoselective semihydrogenation of alkynes using phosphinated PI Pd catalysts prepared from polymer supports possessing diphenylphosphino groups as potential poisoning agents of palladium was investigated.[87]

After several examinations, it was found that phosphinated PI Pd **46** served as an effective catalyst for the selective semihydrogenation of alkynes without the addition of poisoning agents and without strict control of $H_2$ consumption (Scheme 39).

Amidocarbonylation has a great potential for the synthesis of *N*-acylamino acids due to a wide substrate scope and from an atom economical point of view. *N*-Acyl-α-amino acids are formed in one step from the reaction of an aldehyde, an amide, and carbon monoxide in the presence of a transition metal.[88] Cobalt catalysts were first discovered in early 1970s,[89] while Pd catalysts were recently disclosed.[90] Catalytic activities of rhodium, iridium, and ruthenium complexes in this amidocarbonylation were also reported.[91] Moreover, the first example of platinum-catalyzed amidocarbonylation has been reported.[92] Among these transition metals, the most active metal so far is Pd, and TON reaches 60 000 in certain cases, although Pd catalysts are expensive and air-sensitive and cannot be recovered in many cases. To solve these problems, several polymer-supported Pd catalysts have been developed; however, recovery and reuse of polymer catalysts has not been satisfactory.

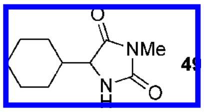
After several investigations, the PI Pd **48** derived from polymer **47** was found to be the best (Scheme 40).[93] Several examples of PI Pd-catalyzed amidocarbonylation using PI Pd **48** (1 mol %), $BnEt_3NBr$ (35 mol %), and $H_2SO_4$ (10 mol %) are summarized in Table 52. In most cases, the desired *N*-acyl-α-amino acids were obtained in moderate to high yields. It is noted that aromatic aldehydes, as well as several types of aliphatic aldehydes, could be applicable to this reaction, though reaction conditions were not optimized yet.

**Table 52. PI Pd-Catalyzed Amidocarbonylation**



| entry | $R^1$ | $R^2$ | yield (%)[b] |
|---|---|---|---|
| 1 | *c*-Hex | Me | quant (96)[c,d] |
| 2 | *c*-Hex | $(CH_2)_4Me$ | 75[c] |
| 3 | *c*-Hex | Ph | 20[c] |
| 4 | *c*-Hex | NHMe | 20[c,e] |
| 5 | $PhCH_2CH_2$ | Me | 49[c,f] |
| 6 | *i*-Pr | Me | 67 |
| 7 | *t*-Bu | Me | 55 |
| 8 | Ph | Me | 78 |
| 9 | *p*-$CF_3C_6H_4$ | Me | 46[g] |
| 10 | *p*-$MeOC_6H_4$ | Me | 38 |
| 11 | *a*-Naph | Me | 58[g] |
| 12 | *b*-Naph | Me | 44[h] |

[a] Unless otherwise noted, the loading level of the palladium was 1.04 mmol/g. [b] Isolated yields. [c] Yield was determined by HPLC analysis. [d] The loading level of the palladium was 0.820 mmol/g. [e] The product was identified as **49**.



49

[f] The reaction mixture was stirred at rt for 6 h before introducing CO. [g] The loading level of the palladium was 0.629 mmol/g. [h] The reaction was performed for 24 h.

## 3.2. Polymer-Micelle Incarcerated (PMI) Palladium

Colloidal metal particles and metal clusters have attracted much interest because of their unique properties and potential applicability to microelectronics,[94] chemical sensing,[95] data storage,[96] catalysts,[97] etc. While smaller nanosized structure is desired in these fields, formation of nanoclusters necessarily requires stabilization to prevent aggregation, which would eradicate most of their desirable advantages compared with bulk materials of identical composition. Recently, a number of stabilizing methods have been developed for controlled formation of Pd nanoclusters.[98] A standard strategy involves the use of weakly coordinated metals such as $Pd(OAc)_2$ and $PdCl_2$, which are complexes of a soft acid and a hard base as starting materials. More stable complexes with softer bases of stabilizing agents (e.g., surfactants, functionalized polymers, dendrimers, or micelles of block copolymers) are then used to load the metals. Finally, the desired metal colloids are prepared by subsequent chemical reactions, typically reduction.[99] The Pd nanoclusters thus prepared range in diameter from 1 to 40 or 50 nm. Among several preparation methods, the use of micelles of amphiphilic polymers to stabilize Pd clusters seems promising. The formation of nanometer-sized Pd colloids in an amphiphilic block copolymer, polystyrene-*b*-poly(4-vinylpyridine), was reported.[100] $Pd(OAc)_2$ was used as a precursor, which was first coordinated by a nitrogen atom of the polymer employed and then reduced to form the desired colloidal Pd. Several reducing agents were examined, which revealed that the size and the catalytic activity of the Pd colloids were influenced by the choice of reducing agents.[100] It is also known that the stability of the polymer micelles and micellization behavior are influenced by several other factors, including concentration, temperature, and chemical structure of the polymer, and that various morphologies, such as spherical, rods, vesicles, and lamellae micelles, can be formed.[101]

While the PI Pd **28c** showed high catalytic activity in hydrogenation,[67] allylation,[67] and Suzuki−Miyaura coupling reactions,[72] the structure of the Pd clusters was not well regulated. An idea was that, if stable polymer micelles could be formed, smaller-sized, well-organized Pd(0) clusters could be generated.

Although copolymer **25c** has an amphiphilic nature, it is hard to form clear micelles because hydrophilic epoxy branches are attached to the hydrophobic benzene rings. Therefore, a new copolymer **50**,[102] which was expected to form clearer and more stable micelles by phase separation between the benzene rings and the epoxy or tetra(ethylene glycol) (TEG) moieties across the polymer backbone, was designed. Copolymer **50** was also expected to be able to adopt several micelle morphologies upon cross-linking between the epoxy and the alcohol moieties of the polymer side chains.

Copolymer **50** (500 mg) thus prepared and $Pd(PPh_3)_4$ (500 mg, 0.43 mmol) were then dissolved in dichloromethane (DCM, 10 mL), and *tert*-amyl alcohol (*t*AmOH) (50 mL) was slowly added to this solution. After being stirred for 8 h at room temperature, the mixture was observed by transmission electron microscopic (TEM) analysis. Very clear spherical micelles were formed, and the diameters of the micelles were 200−500 nm. On the other hand, micelles prepared from copolymer **25c** and $Pd(PPh_3)_4$ using the identical procedure are not spherical. The different behavior of these polymers is thought to be due to the structural differences along the polymer backbone as mentioned previously.

Since the TEM image of **51b** prepared in the MeOH/DCM solvent system did not reveal a recognizable Pd cluster (presumably too small, TEM detection limit 1 nm), the structure was examined by X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS). The XANES spectrum of **51b** shows a similar feature to that of metallic Pd, which is characterized by two prominent peaks. This shows that **51b** has similar coordination symmetry to the Pd metal of face-centered cubic (fcc) structure. The spectrum of **51b** is clearly different from that of PdO. Note that the characteristic feature of the fcc metal in the spectrum of **51b** seems a little weak, suggesting that the Pd metal species in the catalyst would have a Pd metal fcc structure of very short-range order, suggesting that very small Pd metal particles were formed in the polymer support.

To clarify the local structure around the Pd atoms of **51b**, nonlinear curve-fitting analyses of the Fourier-filtered EXAFS of the first and the second shells, corresponding to Pd−C (or Pd−O) and Pd−Pd shells, were conducted by a least-squares method.

As a result, we revealed the formation of stable, subnanometer Pd clusters contained within micelles produced from random copolymers using a novel method (Figure 14). To the best of our knowledge, the Pd clusters formed in this work are the smallest reported to date (average cluster diameter ≈ 0.7 nm).

It was found that the networked Pd micelles **51b** catalyzed the hydrogenation of quinoline to afford 1,2,3,4-tetrahydroquinoline quantitatively under hydrogen at atmospheric pressure and room temperature (Scheme 41). According to the kinetic profile of the reduction, it is noted that no induction period was observed. These results and the previous XAFS data would suggest the presence of Pd(0) in **51b**.

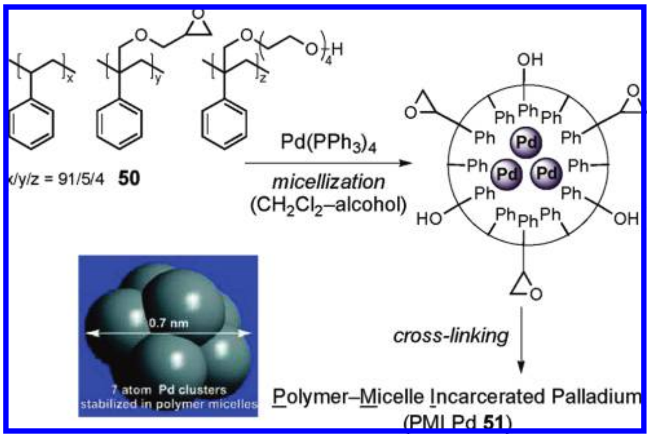


**Figure 14.** Polymer-micelle incarcerated palladium.

**Scheme 41. Hydrogenation of Quinoline**

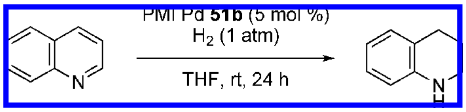
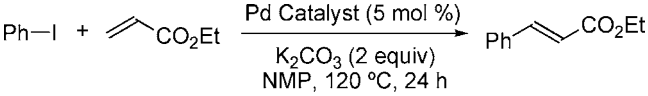


**Table 53. Heck Reaction Using Pd-Containing Micelles−the Effect of Polymer and Solvent System**



| Pd catalyst[a] | solvent system[b] | yield of cinnamate (%)[c] | Pd leaching (ppm)[d] |
|---|---|---|---|
| **28c** | hexane/THF | 87 | 78.7 |
| **28c′** | MeOH/DCM | 80 | 71.8 |
| **51a** | hexane/THF | 88 | 92.0 |
| **51b** | MeOH/DCM | 93 | nd |

[a] The loading of Pd was determind by XRF analysis after decomposition. **28c** = 0.81 mmol/g; **28c′** = 0.67 mmol/g; **51a** = 0.65 mmol/g; **51b** = 0.62 mmol/g. [b] Solvents for micellization. The ratio of poor solvent to good solvent was 3 to 1. In all cases, micelles have networked structure, and diameter of micelles was 20−50 nm. Both results were determined by TEM observation. [c] Isolated yield. [d] The concentration of leached Pd was measured by XRF analysis; nd = not detected (<5 ppm).

Catalytic activities of the Pd micelles were examined in the Heck reaction of iodobenzene with ethyl acrylate;[103] the results are summarized in Table 53. When PI Pd (from copolymer **25c**) prepared in either solvent system (hexane/THF (**28c**) or MeOH/DCM (**28c′**)) was used, the same level of leaching of the Pd to the reaction mixture was observed. In both **28c** and **28c′**, Pd coordinated with the benzene rings of the polymers was thought to exist both inside and outside of the structure. On the other hand, while the networked Pd-polymer micelles **51b** did not show any leaching at all, the micelles **51a** showed significant leaching of Pd. These results indicate that Pd was located in the hydrophobic part of the micelles (inside for **51b** and outside for **51a**).

On the other hand, the micelles containing Pd could be fixed on several supports such as a glass surface, a hydroxylated resin **52**, or an aminated resin **53** (Figure 15), which would be also used as catalysts. To a solution of the Pd-polymer micelles in the *t*AmOH/DCM system, a glass, hydroxylated resin **52**, or aminated resin **53** was added, and the mixtures were allowed to stand overnight to allow

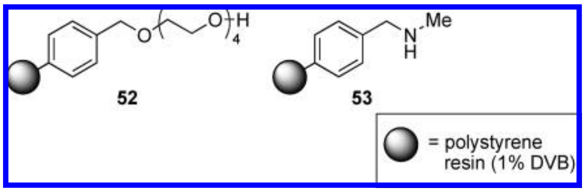
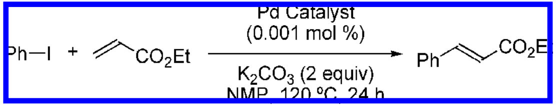


**Figure 15.** Hydroxylated resin **52** and aminated resin **53**.

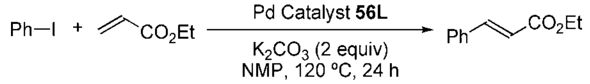
**Table 54. Heck Reaction Using Various Pd-Containing Micelles**



| Pd catalyst[a] | solvent system[b] | observed structure[c] | diameter of micelles[c] (nm) | yield (%)[d] | TON[e] |
|---|---|---|---|---|---|
| **28c** | A | networked | 20−50 | 52 | 52 300 |
| **51b** | B | networked | 20−50 | 83 | 82 500 |
| **57**[f] | C | sphere | 200−500 | 81 | 81 400 |
| **58**[g] | C | broken[h] | | 19 | 19 400 |
| **55** | C | sphere | 200−500 | 78 | 78 200 |
| **56** | C | sphere, rod[i] | 100−500 | 65 | 64 500 |
| 5% Pd/C | | | | 31 | 30 800 |

[a] The loading of Pd was determind by XRF analysis after decomposition. **28c** = 0.81 mmol/g; **51b** = 0.62 mmol/g; **57** = 0.81 mmol/g; **58** = 1.73 mmol/g; **55** = 0.009 mmol/g; **56** = 0.037 mmol/g. [b] Solvents for micellization. The ratio of solvents was 3 to 1 for hexane/THF (A) and MeOH/DCM (B) and 5 to 1 for *t*AmOH/DCM (C). [c] Determined by TEM observation. [d] Isolated yield. [e] TON denotes turnover number. [f] Sealed tube was used for cross-linking. [g] MW irradiation was used for cross-linking. [h] The micelles were disrupted, and 1−5 nm sized Pd clusters were observed. [i] Cross-linked sphere or rod micelles were observed.

**Table 55. Minimized Catalyst and Reuse**



| Pd catalyst **56L** (mol %)[a] | yield of cinnamate (%)[b] | TON[c] |
|---|---|---|
| 0.001 | 93 | 93 400 |
| 0.001[d] | 90 | 90 000 |
| 0.0003 | 85 | 284 660 |

[a] Catalyst **56L** was prepared by the same procedure for **56** except for the amount of resin **52** (5-fold increase). The loading of palladium in **56L** was determined by XRF analysis after decomposition: 0.8 μmol/g. [b] Isolated yield. [c] TON denotes turnover number. [d] Recovered catalyst from entry 1 was used.

precipitation of the micelles onto the supports. The supports with the micelles were washed with MeOH and then dried and heated at 120 °C for 2 h. After being washed with THF, spherical micelles were observed on the glass (**54**) and the hydroxylated resin (**55**). It was assumed that the immobilization of the micelles onto the supports by binding the epoxides to silanols on the glass or the alcohols on the resin and cross-linking of the polymer side chains occurred by heating at 120 °C at the same time. In the case of the aminated resin, the micelle morphology partially changed to a rodlike structure (**56**). Since the epoxides of polymer **50** would react with the amine moieties on the resin before cross-linking of the polymer side chains, the morphology might be partially changed. Subsequent heating at 120 °C led to the morphologies of the micelles being fixed by the cross-linking of the polymer side chains. Conversely, the aggregates of the micelles of polymer **50** without Pd on a glass did not form micelles, but rather a membrane was observed. This result also suggests that the micelles were stabilized by interaction between Pd and the polymer.

Catalytic activities of the various micelles were compared in the Heck reaction (Table 54). While PI Pd **28c** and the disrupted micelles **58** obtained by MW irradiation gave lower yields, all of the other cross-linked Pd micelles exhibited considerably high catalytic activities; the catalytic turnover numbers (TONs) were greater than 60 000. 5% Pd/C gave lower yield and TON. It is noteworthy that despite the considerable difference in the shapes of the various micelles, the catalytic activities were almost the same. This indicates that the surface area of the catalyst construct hardly affects the catalytic activity. Remarkably high catalytic activity was observed using low loading of micelle catalyst **58L**, which was prepared according to the same procedure as that for **58** except for the amount of the resin (a 5-fold increase of resin **54** was used as a support) and the TON was over 280 000 (Table 55). Moreover, catalyst **58L** could be reused without significant loss of activity at 0.001 mol %.

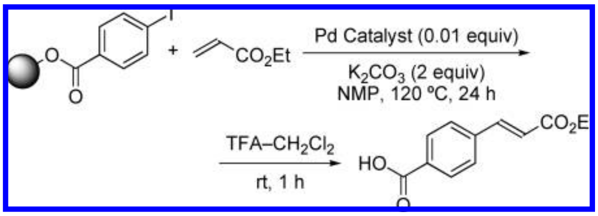
Although leaching of Pd to the reaction mixture was not detected by fluorescence X-ray (XRF) analysis in this system, the detection limit (5 ppm) was not sufficient to deny the possibility that a very small amount of leached Pd catalyzed the reaction. The catalytic activity of the filtrate was then carefully checked. After the coupling reaction of iodobenzene (50 mmol) with ethyl acrylate (75 mmol) in the presence of 0.01 mol % **51b** and potassium carbonate (100 mmol) in *N*-methyl-2-pyrrolidinone (NMP, 50 mL), the catalyst was removed by simple filtration. To the filtrate were added iodobenzene (50 mmol), ethyl acrylate (75 mmol), and potassium carbonate (100 mmol) again, and the mixture was further stirred for 24 h at 120 °C. No additional formation of the Heck product was observed, thus indicating that no Pd leaching occurred. A kinetic study and a hot leaching test were also conducted. The kinetic profile shows a short induction period, and it is noted that a similar kinetic profile was observed in the Heck reaction using Pd(OAc)$_2$. The reaction did not proceed at all after hot filtration (hot leaching test)[105] of the catalyst. These results suggest that an active Pd species for the Heck reaction may be produced in the initial stages of the reaction and that the active species may exist not in a solution but inside the support.

Further evidence that no Pd leaching occurred was garnered from experiments based on the “three-phase tests”[106] consisting of anchoring one of the substrates onto a solid support in addition to using the solid catalyst. If an active species is really heterogeneous, transformation should be hardly observed for the anchored substrate. Wang resin-bound aryl iodide was prepared and was then employed in Heck reactions with ethyl acrylate in the presence of **51b**, 5% Pd/C, or Pd(PPh$_3$)$_4$ (Table 56). While Pd(PPh$_3$)$_4$ gave the Heck adduct in 48% yield after cleavage from the support, the adducts were obtained in only 2% and 10% yields using **51b** and Pd/C, respectively. Although a very small amount of Pd might exist in the solution when **51b** was used in this “three-phase test” (which promoted the Heck reaction to afford the adduct in 2% yield), the result of the hot leaching test mentioned above indicates that no active species exists in the solution. These results suggest that most of the active Pd species was held inside the micelles and that catalytic turnover predominantly took place there too.

## 3.3. Polymer Incarcerated Ruthenium Catalyst

The polymer incarcerated method was applied to ruthenium catalysts; dichlorotris(triphenylphosphine)ruthenium

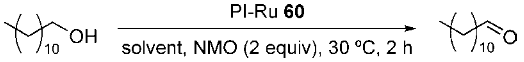
**Table 56. Three-Phase Test**



| entry | Pd catalyst | yield of cinnamate (%)[b] |
|---|---|---|
| 1 | **51b**[a] | 2 |
| 2 | 5% Pd/C | 10 |
| 3 | $Pd(PPh_3)_4$ | 48 |

[a] The loading of palladium was 0.62 mmol/g. [b] Determined by $^1H$ NMR analysis.

**Table 57. Effect of Solvents and Additives**



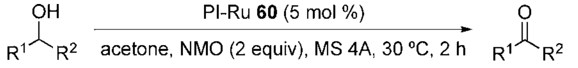
| entry | PI Ru (mol %) | solvent | yield[a] (%) [leaching[b] (%)] | | |
|---|---|---|---|---|---|
| | | | first | second | third |
| 1 | 15 | toluene | 33 [nd] | 28 [nd] | 19 [nd] |
| 2 | 15 | THF | 31 [nd] | 27 [2.4] | 31 [nd] |
| 3 | 15 | DMF | 57 [6.8] | 50 [nd] | 48 [nd] |
| 4 | 15 | $CH_3CN$ | 41 [nd] | 48 [nd] | 42 [nd] |
| 5 | 15 | $CH_2Cl_2$ | 48 [nd] | 45 [nd] | 56 [nd] |
| 6 | 15 | acetone | 61 [nd] | 70 [nd] | 73 [nd] |
| 7 | 5 | acetone | 64 [nd] | 72 [nd] | 65 [nd] |
| 8[c] | 5 | acetone | quant [nd] | 96 [nd] | 92 [nd] |

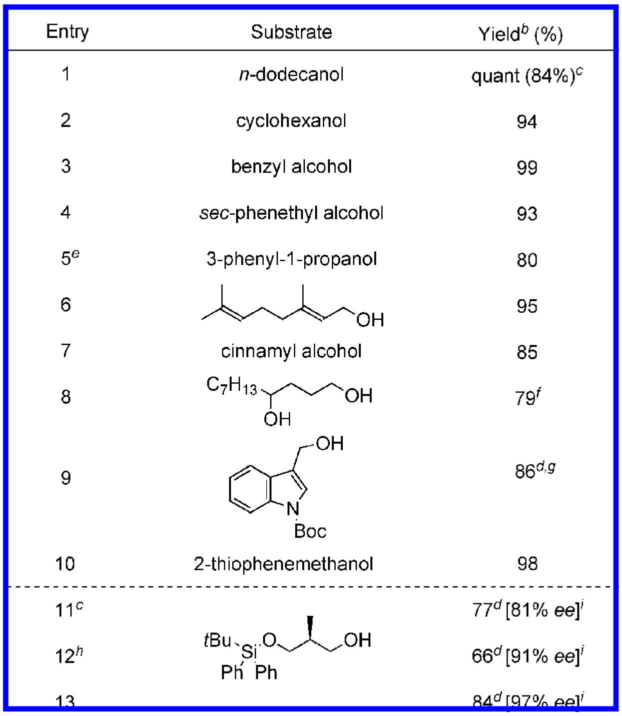
[a] Yields were determined by GC analysis. [b] Leachings were measured by XRF analysis; nd = not detected. [c] MS 4 Å (500 mg/mmol) was used.

$[RuCl_2(PPh_3)_3]$ was chosen as a starting catalyst[107] because it was thought that the three $PPh_3$ groups of $RuCl_2(PPh_3)_3$ would be eliminated during immobilization to create a more Lewis acidic, less hindered active catalyst. Epoxide-containing copolymer **25c** was dissolved in THF at room temperature, and $RuCl_2(PPh_3)_3$ was added to this solution. Hexane was then added to form microcapsules, which were filtered, washed, and dried. The microcapsules were next heated at 120 °C for 3.5 h to afford polymer incarcerated Ru (PI Ru **59**).[108] PI Ru **59** was preliminarily oxidized using 5 equiv of *N*-methylmorpholine-*N*-oxide (NMO) in acetone−2-propanol (1/9) at room temperature for 12 h before being subjected to oxidation reactions.

PI Ru **60** thus prepared was initially examined in the oxidation of dodecanol using NMO as a co-oxidant in a batch system (Table 57). Several solvents were tested, and it was found that the oxidation proceeded smoothly in acetone to afford dodecanal in good yield using 15 mol % of PI Ru at 30 °C for 2 h (entry 6). The catalyst was recovered quantitatively by simple filtration and reused three times without loss of activity. In addition, no leaching of Ru was detected by fluorescence X-ray (XRF) analysis. When the catalyst loading was reduced to 5 mol %, similar results were obtained. Finally, the yield was dramatically improved by adding molecular sieves (MS) 4 Å (entry 8). Molecular sieves would remove water that is generated during the oxidation and would prevent deactivation of the catalyst as well as further oxidation of the aldehyde to the corresponding carboxylic acid.

**Table 58. PI Ru-Catalyzed Oxidation of Various Substrates**[a]





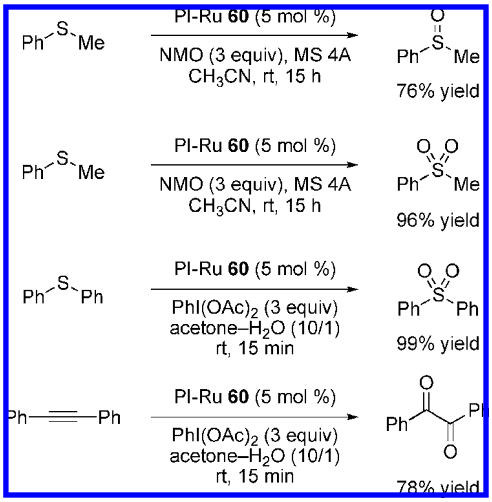
| Entry | Substrate | Yield[b] (%) |
|---|---|---|
| 1 | *n*-dodecanol | quant (84%)[c] |
| 2 | cyclohexanol | 94 |
| 3 | benzyl alcohol | 99 |
| 4 | *sec*-phenethyl alcohol | 93 |
| 5[e] | 3-phenyl-1-propanol | 80 |
| 6 | OH | 95 |
| 7 | cinnamyl alcohol | 85 |
| 8 | $C_7H_{13}$ OH OH | 79[f] |
| 9 | OH N Boc | 86[d,g] |
| 10 | 2-thiophenemethanol | 98 |
| 11[c] | *t*Bu Si O OH Ph Ph | 77[d] [81% *ee*][i] |
| 12[h] | | 66[d] [91% *ee*][i] |
| 13 | | 84[d] [97% *ee*][i] |

[a] MS 4 Å (500 mg/mmol) was used. The leaching of Ru to the reaction mixture was measured by XRF and ICP analyses. No peaks for Ru were detected in any entry (<0.5 ppm). [b] Yields were determined by GC analysis. [c] $RuCl_2(PPh_3)_3$ (5 mol %) was used instead of PI Ru. [d] Isolated yield. [e] The reaction was performed for 0.5 h. [f] The product is shown in parentheses. [g] An 86% yield using PI Ru (1 mol %) for 4 h; an 89% yield using PI Ru (0.5 mol %) for 15 h. [h] TPAP (5 mol %) in acetonitrile was used instead of PI Ru. [i] Enantiomeric excess of the product was determined by chiral HPLC analysis.

Under the optimized conditions, several alcohols were oxidized, and the results are summarized in Table 58. Primary and secondary, aliphatic and aromatic, and even allylic alcohols were oxidized smoothly in the presence of PI Ru **60** to afford the corresponding carbonyl compounds in high yields (entries 1−7). It should be noted that the yields were better than those using the parent metal source, $RuCl_2(PPh_3)_3$. Heterocyclic alcohols also worked well (entries 9 and 10), and a 1,4-dihydroxy compound gave the corresponding lactone directly (entry 8). For optically active aldehydes having a stereogenic center at the 2-position, it is well-known that partial racemization occurs during oxidation and that a racemic aldehyde is formed in many cases. Indeed, when optically pure alcohol (>99% ee) was oxidized using $RuCl_2(PPh_3)_3$, the corresponding aldehyde was obtained in 77% yield with 81% ee (entry 11). While a somewhat better result was obtained using tetra-*n*-propylammonium perruthenate (TPAP)[109] (66% yield, 91% ee, entry 12), PI Ru **60** was excellent so that the desired aldehyde was obtained in 84% yield with almost no racemization (97% ee, entry 13). We assume that the polymer serves to reduce the basicity of the reaction mixture to prevent the partial racemization of the aldehyde.

For the use of PI Ru in other oxidation reactions, the oxidation of sulfides and an acetylene derivative was briefly examined (Scheme 42). In the presence of PI Ru **60** (5 mol %) and MS 4 Å, thioanisole was treated with NMO in acetonitrile at room temperature for 15 h to afford methyl phenyl sulfoxide in 76% yield. On the other hand, methyl phenyl sulfone was obtained in high yield using (diacetoxyiodo)benzene $[PhI(OAc)_2]$ as a co-oxidant. Thus, thioanisole

**Scheme 42. PI Ru Catalyzed Oxidation of Other Substrates**



was treated with $PhI(OAc)_2$ in the presence of PI Ru **60** (5 mol %) in acetone−water (10/1) at room temperature for 15 min to afford methyl phenyl sulfone in 96% yield. Diphenyl sulfide gave diphenyl sulfone in 99% yield under the same reaction conditions. The system was also used for the oxidation of diphenylacetylene, and benzyl was obtained in good yield under mild reaction conditions. It is noted that, in all cases, the Ru catalyst was recovered by simple filtration and reused without loss of activity. Moreover, no leaching of Ru was observed in all cases.

PI Ru was then applied to a flow system. Flow systems are now very important not only in industry but also in high-throughput organic synthesis related to combinatorial library generation.[110] Whereas many immobilized catalysts have been developed, those that can be applied to flow systems are limited. Our flow system was set up as shown in Figure 16. PI Ru **60** and $MgSO_4$ were placed into a column, and an acetone solution of an alcohol and NMO was passed through the column. Under the conditions shown in the scheme, the substrate mixture came in contact with the catalyst in the column for approximately 20 min. After passing through the column, the alcohol was converted to the aldehyde almost quantitatively (Table 59). It is noted that high conversions and yields were maintained even after 8 h of continuous flow and that no leaching of Ru was observed. Applications to large-scale synthesis as well as combinatorial chemistry using this flow system are underway.

The structure of PI Ru was investigated. In the initial plan, the three $PPh_3$ groups of $RuCl_2(PPh_3)_3$ would be eliminated during immobilization to create a more active catalyst. For the activity of the newly created immobilized catalyst (PI Ru **60**), higher activity of PI Ru **60** compared with that of $RuCl_2(PPh_3)_3$ was demonstrated in several cases. Elemental analyses of PI Ru **60** support our working hypothesis. The Ru catalyst was analyzed just after microencapsulation (before cross-linking), PI Ru before activation (PI Ru **59**), and PI Ru after activation (PI Ru **60**). In all cases, the same levels of Ru loadings were observed, and 2 equiv of chlorine to Ru was detected. More importantly, almost all of the $PPh_3$ was removed during the preparation of PI Ru **60**. Analyses by EXAFS also support this structure.

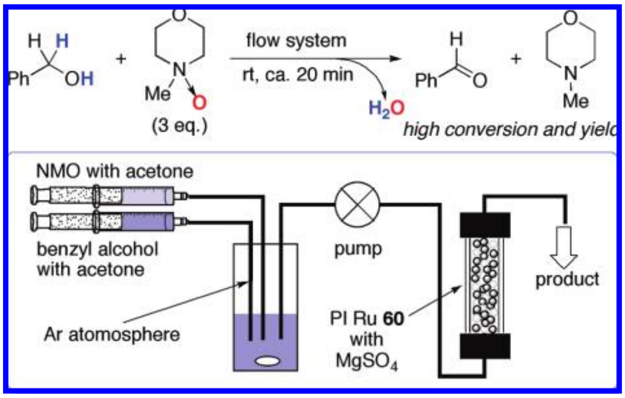


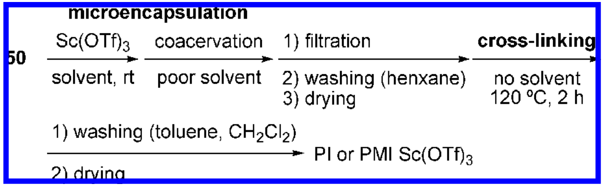
**Figure 16.** PI Ru catalyzed oxidation using flow system.

**Table 59. Results of PI Ru Catalyzed Oxidation Using a Flow System**[a]

| time (h) | conversion (%)[b] | yield (%)[b] |
|---|---|---|
| 0−1.05 | >99 | 94 |
| 1.05−2.10 | >99 | 92 |
| 2.10−3.15 | >99 | 87 |
| 3.15−4.20 | >99 | >99 |
| 4.20−5.25 | 99 | 95 |
| 5.25−6.30 | 98 | 88 |
| 6.30−7.35 | 96 | 89 |
| 7.35−8.40 | 94 | 92 |

[a] Benzyl alcohol (1.99 mg/mL) and 6.94 mg/mL NMO acetone solution were passed through a column containing 40.3 mg of PI Ru (loading level is 0.312 mmol/g) with $MgSO_4$. Flow rate was 0.08 mL/min. [b] Conversion and yield was calculated based on the total starting material as an average of 1.05 h.

**Table 60. Solvent Effects in Microencapsulation of $Sc(OTf)_3$**



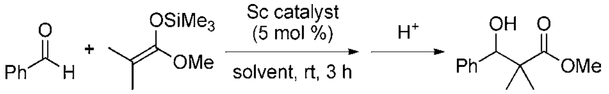
| entry | solvent | poor solvent | Sc loading (mmol/g) |
|---|---|---|---|
| 1 | toluene | hexane | 0.191 |
| 2 | THF−*c*Hex (1/3) | hexane | 0.185 |
| 3 | $CH_2Cl_2$ | MeOH | not loaded |

## 3.4. Polymer-Micelle Incarcerated Scandium Trifluoromethanesulfonate [PMI $Sc(OTf)_3$] and Ruthenium Catalyst [PMI Ru]

In microencapsulated $Sc(OTf)_3$ [MC $Sc(OTf)_3$] (section 2.1), catalytic activity, scope of reaction, solvent, and catalyst loadings are still unsatisfactory. The polymer incarcerated method to immobilization of $Sc(OTf)_3$ was investigated.

Several reaction conditions for the preparation of polymer-supported $Sc(OTf)_3$ based on the PI method were investigated.[111] It was found that choice of solvents at the stage of microencapsulation was key to the preparation (Table 60). While toluene−hexane and THF−cyclohexane−hexane were efficient for immobilizing $Sc(OTf)_3$ (entries 1 and 2), the catalyst was not loaded at all in microencapsulation before cross-linking using $CH_2Cl_2$−MeOH, which was efficient for immobilization of Pd (entry 3).[112] These results suggest that $Sc(OTf)_3$ may locate in hydrophilic parts of random copolymer **50**.[102,113] It is noted that the PI method can also be successfully used for the preparation of immobilized $Sc(OTf)_3$. Moreover, interesting information was obtained by transmission electron microscopic (TEM) analysis of the polymer solutions. Although random aggregation of copolymer **50**−$Sc(OTf)_3$ was observed in toluene, spherical micelles

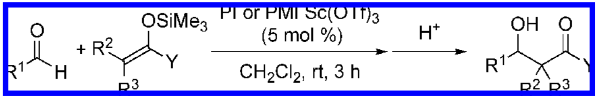
**Table 61. Comparison of Catalytic Activity of PI Sc(OTf)$_3$ and PMI Sc(OTf)$_3$ in Mukaiyama Aldol Reaction**



| entry | solvent | Sc catalyst | yield (%) | | | Sc leaching[b] (%) |
|---|---|---|---|---|---|---|
| | | | first | second | third | |
| 1 | $CH_3CN$ | PI Sc(OTf)$_3$ | 85 | 87 | 85 | nd |
| 2 | toluene | PI Sc(OTf)$_3$ | 70 | 64 | 71 | nd |
| 3 | $CH_2Cl_2$ | PI Sc(OTf)$_3$ | 83 | 83 | 83 | nd |
| 4 | $CH_2Cl_2$ | PI Sc(OTf)$_3$ | 94[a] | | | nd |
| 5 | $CH_2Cl_2$ | PMI Sc(OTf)$_3$ | 92[a] | 96 | 94 | nd |

[a] Corrected yield. Half of the crude compound was used for ICP analysis. [b] Determined by XRF analysis [nd = not detected in all runs (<2.2%)]. [c] Determined by ICP analysis after the first use (ND < 0.05%).

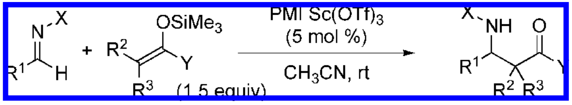
**Table 62. Substrate Scope for Mukaiyama Aldol Reaction**



| entry | catalyst | R$^1$ | R$^2$ | R$^3$ | Y | yield (%) |
|---|---|---|---|---|---|---|
| 1 | PI | 4-Me-Ph | Me | Me | OMe | 90 |
| 2 | PI | 2-Me-Ph | Me | Me | OMe | 93 |
| 3 | PI | 4-Cl-Ph | Me | Me | OMe | 93 |
| 4 | PI | $PhCH_2CH_2$ | Me | Me | OMe | 70 |
| 5 | PI | 2-furyl | Me | Me | OMe | 75 |
| 6 | PMI | 2-furyl | Me | Me | OMe | 85 |
| 7 | PI | 2-thienyl | Me | Me | OMe | 93 |
| 8 | PI | Ph | H | Me | SEt | 80[b] |
| 9 | PI | Ph | H | H | SEt | 83 |
| 10 | PI | Ph | Me | H | Ph | 70[c] |
| 11 | PMI | Ph | Me | H | Ph | 78[d] |
| 12 | Sc(OTf)$_3$ | Ph | Me | H | Ph | 50[e] |
| 13[a] | PMI | Ph | Me | H | Ph | 74[f] |
| 14[a] | MC Sc(OTf)$_3$ | Ph | Me | H | Ph | 57[g] |

[a] Reaction conditions: catalyst (5 mol %) in $CH_3CN$ at rt for 3 h. [b] Ratio *syn*/*anti* = 35/65. [c] Ratio *syn*/*anti* = 58/42. [d] Ratio *syn*/*anti* = 60/40. [e] Ratio *syn*/*anti* = 56/44. [f] Ratio *syn*/*anti* = 50/50. [g] Ratio *syn*/*anti* = 47/53.

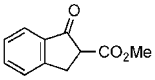
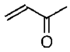
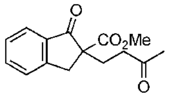
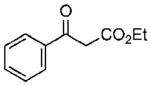
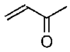
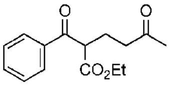
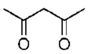
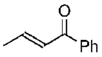
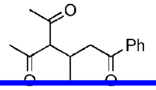
**Table 63. Mannich-type Reaction Using PMI Sc(OTf)$_3$**



| entry | R$^1$ | X | R$^2$ | R$^3$ | Y | yield (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | Ph | Me | Me | OMe | 96[b] |
| 2 | 2-thienyl | Ph | Me | Me | SEt | 97 |
| 3 | $PhCH_2CH_2$ | NHBz | Me | Me | OMe | 80 |
| 4 | $EtO_2C$ | NHBz | Me | Me | OMe | 73 |
| 5 | Ph | Ph | H | H | Ph | 80 |

[a] With 5 mol % of PMI Sc(OTf)$_3$. [b] Corrected yield. Half of the crude compound was used for ICP analysis. No Sc leaching was observed (ND < 0.05%); second use, 99%; third use, 97%.

**Table 64. Michael Reaction Using PMI Sc(OTf)$_3$**

| Entry | Donor | Acceptor | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  |  | 4 | 92[b,c] |
| 2 |  |  |  | 9 | 92 |
| 3 |  |  |  | 6 | 81 |

[a] Reaction conditions: PMI Sc(OTf)$_3$ (5 mol %), acceptor (2.0 equiv) in $CH_3CN$ at room temperature. [b] Corrected yield. Half of the crude compound was used for ICP analysis. No Sc leaching was observed (ND < 0.05%). [c] Second use, 94%; third use, 92%.

were formed in THF–cyclohexane, and Sc(OTf)$_3$ seemed to be encapsulated into these spherical micelles. These different shapes are ascribed to the polarity of the solvents. To distinguish these catalysts, the former was named polymer incarcerated Sc(OTf)$_3$ [PI Sc(OTf)$_3$] and the latter polymer-micelle incarcerated Sc(OTf)$_3$ [PMI Sc(OTf)$_3$].

PI Sc(OTf)$_3$ and PMI Sc(OTf)$_3$ were first used in the Mukaiyama aldol reaction[7i,114] to compare their catalytic activity (Table 61). PI Sc(OTf)$_3$ worked well in several solvents, and the desired product was obtained in good yields (entries 1–3). Moreover, it was confirmed by XRF and ICP analyses that no leaching of Sc occurred. On the other hand, PMI Sc(OTf)$_3$ was found to be more effective (entry 5).

Other substrates were tested, and in all cases, PMI Sc(OTf)$_3$ had higher catalytic activity than PI Sc(OTf)$_3$ (Table 62). The higher activity of PMI Sc(OTf)$_3$ compared with that of PI Sc(OTf)$_3$ may be ascribed to the larger catalytic surface area in PMI Sc(OTf)$_3$ by formation of spherical micelles. Moreover, PMI Sc(OTf)$_3$ showed higher activity than MC Sc(OTf)$_3$. It is noted that these catalysts were recovered quantitatively by simple filtration and that the same yields were obtained even after the third use.

PMI Sc(OTf)$_3$ was successfully used as a catalyst in other reactions, such as Mannich-type[7d] and Michael reactions[115] (Tables 63 and 64). Although it is well-known that most Lewis acids are trapped and sometimes decomposed by basic compounds, PMI Sc(OTf)$_3$ was effective for the activation of imines to form amines, and no Sc leaching was observed (Table 63). PMI Sc(OTf)$_3$ was also available for the reaction of less reactive acylhydrazones[116] (entries 3 and 4). Moreover, it was confirmed that PMI Sc(OTf)$_3$ was an effective catalyst for Michael reactions (Table 64), one of the powerful methods for the synthesis of 1,5-dioxo units. In the presence of 5 mol % PMI Sc(OTf)$_3$, the desired Michael reactions proceeded smoothly,[117] and again, no Sc leaching was observed. It is noted that the highest catalytic activity in terms of TON (>7500) has been attained in the Michael reaction.

The polymer-micelle incarcerated (PMI) method was applied to immobilized ruthenium catalyst for the oxidation of alcohols and sulfides (Figure 17).[118] In this study, it was found that choice of micelle-forming conditions and polymer structures played a key role in obtaining higher catalytic activities.

P$_1$MI Ru and P$_2$MI Ru were first used in the oxidation of a sulfide to compare their catalytic activities. When PI Ru, P$_1$MI Ru, and P$_2$MI Ru were used as the catalysts, reactions proceeded smoothly in an acetone–water cosolvent system in the presence of 2.2 equiv of iodobenzene diacetate [PhI(OAc)$_2$] to afford the desired sulfone in high yields.

In the presence of 0.5 mol % of each catalyst, the reaction was complete within 220 min in the case of PI Ru and 70 and 120 min in the cases P$_1$MI Ru and P$_2$MI Ru, respectively. All the catalysts could be recovered and reused several times by simple filtration and washing (Table 65). It is noted that no leaching of ruthenium was observed by fluorescence X-ray (XRF) analysis. In the cases of PI Ru and P$_2$MI Ru, longer

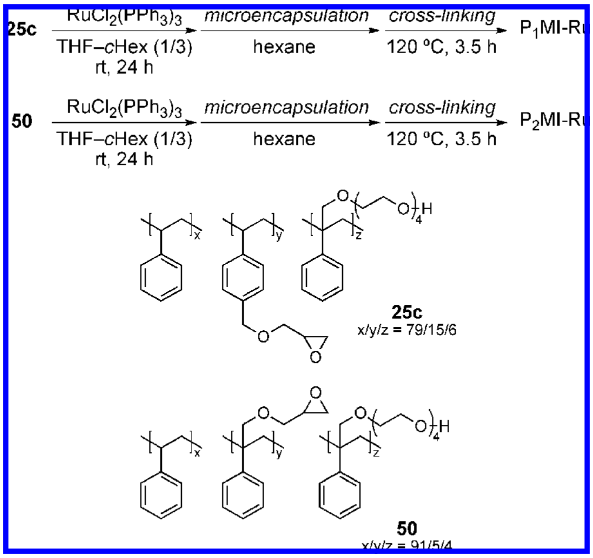
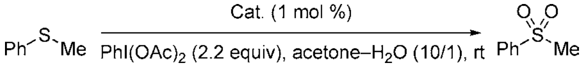


**Figure 17.** Preparation of polymer-micelle incarcerated (PMI) Ru from copolymers **25c** and **50**.

**Table 65. Oxidation of a Sulfide Using PI Ru and PMI Ru**



| entry | catalyst | yield[a] (%) [time (h)][b] | | | |
|---|---|---|---|---|---|
| | | first | second | third | fourth |
| 1 | PI Ru | quant [2.0] | 98 [2.5] | 80 [2.5] | 94 [2.5] |
| 2 | $P_1$MI Ru | quant [0.5] | 87 [0.5] | 97 [0.5] | 99 [0.5] |
| 3 | $P_2$MI Ru | 96 [0.5] | 96 [1.0] | 89 [1.1] | quant [1.3] |

[a] Isolated yield. No peaks of ruthenium were observed by XRF analysis (<1.1%). [b] Time until sulfoxide was completely consumed (confirmed by TLC).

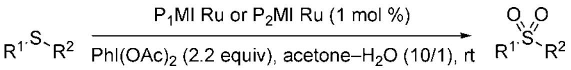
reaction times were needed for reactions to get to completion in the second use, while in the case of $P_1$MI Ru, the reactivity was completely maintained for at least four uses. The higher activity of $P_1$MI Ru and $P_2$MI Ru compared with the PI Ru could be ascribed to the formation of stable micelle morphologies with a large surface area. Although $P_2$MI Ru has a larger surface area than $P_1$MI Ru, $P_1$MI Ru has a higher catalytic activity in the oxidation of sulfides. This could be explained by the quantity of hydrophilic parts in the polymers (21% hydrophilic parts in **25c** vs 9% in **50**). As described above, ruthenium is mainly located in the hydrophilic parts of the polymer, which are at the outer layer of micelles when a THF(−cyclohexane)/hexane microencapsulation system is employed. In the slower second step, oxidation of a sulfoxide to a sulfone, the hydrophilic sulfoxide and $PhI(OAc)_2$ might be located at a hydrophilic catalytic site. On the other hand, the generated sulfone and iodobenzene, which are relatively hydrophobic, might be easily eliminated from the catalytic site to the outer layer. Therefore, in $P_1$MI Ru derived from **25c** containing more hydrophilic parts, there are more ruthenium metal species located in the hydrophilic parts than in $P_2$MI Ru, and the catalytic turn-over frequency is also higher.

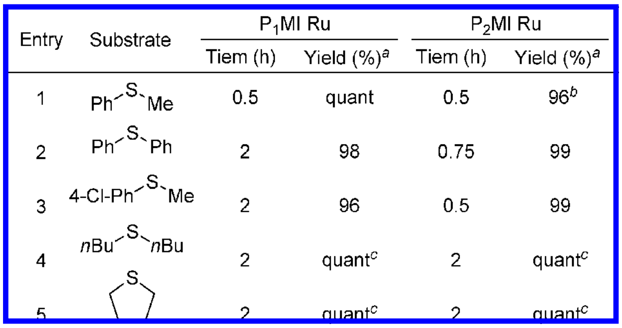
Under these conditions, aromatic (even with electron-withdrawing groups), aliphatic, and cyclic sulfides were smoothly oxidized in the presence of either $P_1$MI Ru or $P_2$MI Ru to afford the desired products in high yields (Table 66).

$P_1$MI Ru and $P_2$MI Ru were used in the oxidation of alcohols in the presence of 2 equiv of *N*-methylmorpholine-*N*-oxide (NMO). PI Ru, $P_1$MI Ru, and $P_2$MI Ru were preliminarily treated with 20 equiv of NMO in an acetone−isopropyl alcohol (*i*PrOH) (1/9) solvent at room temperature for 12 h before application to the oxidation reactions. Both PI Ru and $P_2$MI Ru did not work well in the oxidation of benzyl alcohol without MS 4 Å (Table 67, entries 1, 2). When 0.5 g/mmol of MS 4 Å were added to the reaction mixture, $P_2$MI Ru worked well to afford benzaldehyde in high yield (entry 5). In the cases of PI Ru and $P_1$MI Ru, the desired product was obtained in moderate yields (entries 3, 4). $P_2$MI Ru could be reused several times after recovery by simple filtration and washing, although after second use 7.5 h was needed to complete the reaction. Lower catalyst loading of $P_2$MI Ru also produced the product in high yield, albeit with prolonged reaction time (entry 7). That $P_2$MI Ru was the best catalyst for oxidation of alcohols was thought to be due to the greater surface area as well as hydrophilicity of the polymers that determined the reactivities in the case of oxidation of sulfides.

Under these conditions, the substrate scope was surveyed using $P_1$MI Ru and $P_2$MI Ru (Table 68). In most cases, high to excellent yields were obtained in the oxidation of both primary and secondary alcohols. Moreover, no ruthenium leaching was observed in all cases.

**Table 66. Oxidation of Sulfides**

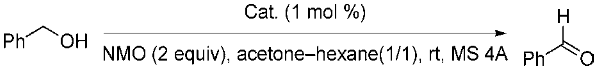




| Entry | Substrate | $P_1$MI Ru | | $P_2$MI Ru | |
|---|---|---|---|---|---|
| | | Tiem (h) | Yield (%)[a] | Tiem (h) | Yield (%)[a] |
| 1 | Ph-S-Me | 0.5 | quant | 0.5 | 96[b] |
| 2 | Ph-S-Ph | 2 | 98 | 0.75 | 99 |
| 3 | 4-Cl-Ph-S-Me | 2 | 96 | 0.5 | 99 |
| 4 | *n*Bu-S-*n*Bu | 2 | quant[c] | 2 | quant[c] |
| 5 | S | 2 | quant[c] | 2 | quant[c] |

[a] Isolated yield. No peaks of ruthenium were observed by XRF analysis (<1.1%). [b] Quantitative yield, using 0.1 mol % of $P_2$MI Ru for 11 h. [c] Determined by GC.

**Table 67. Oxidation of an Alcohol Using PI Ru and PMI Ru**



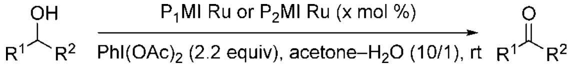
| entry | catalyst (mol %) | MS 4 Å (0.5 g/mmol) | time (h) | yield (%)[a] |
|---|---|---|---|---|
| 1 | PI Ru (1) | − | 2.5 | 47 |
| 2 | $P_2$MI Ru (1) | − | 2.5 | 51 |
| 3 | PI Ru (1) | + | 2.5 | 59 |
| 4 | $P_1$MI Ru (1) | + | 2.5 | 75 |
| 5 | $P_2$MI Ru (1) | + | 2.5 | 93 |
| 6 | $P_2$MI Ru (2) | + | 2.5 | 93[b] |
| 7 | $P_2$MI Ru (0.3) | + | 24 | 91 |

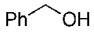
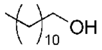
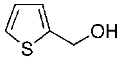
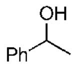
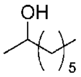
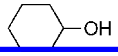
[a] Determined by GC. No peaks of ruthenium were observed by XRF analysis. [b] Second, 85% for 7.5 h; third, 85% for 7.5 h.

## 3.5. Polymer Incarcerated Palladium Derived from Palladium(II)

Tetrakistriphenylphosphine palladium(0) [$Pd(PPh_3)_4$] was successfully immobilized by the polymer incarcerated method to form phosphine-free polymer-incarcerated Pd(0) (PI Pd). Although it was thought that a ligand exchange from phosphine to copolymers would be the key to successful

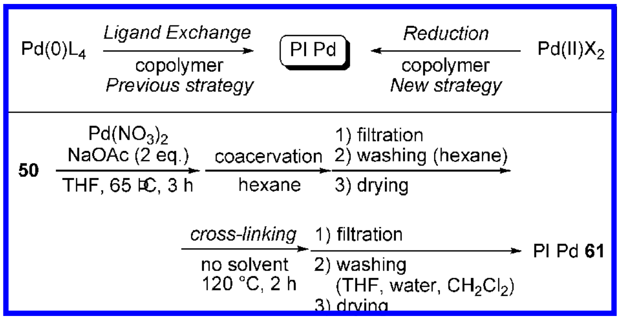
**Table 68. Oxidation of Alchols**



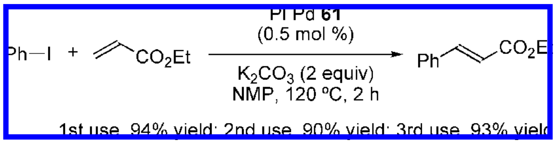
| Entry | Substrate | $P_1$MI Ru | | $P_2$MI Ru | |
|---|---|---|---|---|---|
| | | Tiem (h) | Yield (%)[a] | Tiem (h) | Yield (%)[a] |
| 1 |  | 2.5 | 75 | 2.5 | 93 |
| 2 |  | 12 | 66 | 2.5 | 67 |
| 3 |  | 2.5 (12) | 74 (83) | 2.5 | 81 |
| 4 |  | 12 | 73 | 12 | 82 |
| 5 |  | 12 | 50 | 12 (12[b]) | 45 (83[b]) |
| 6 |  | 12 | 65 | 12 (12[b]) | 60 (85[b]) |

[a] Determined by GC. No peaks of ruthenium were observed by XRF analysis. [b] Catalyst at 2 mol % was used.

**Scheme 43. Two Strategies for the Polymer Incarcerated Method**



**Scheme 44. Heck Reaction Using PI Pd 61**



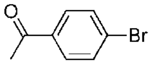
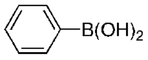
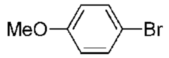
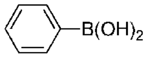
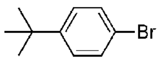
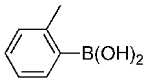
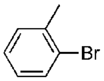
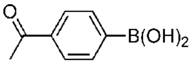
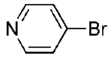
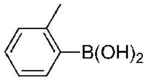
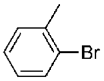
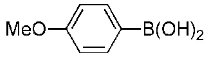
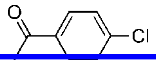
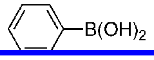
immobilization (Scheme 43), four triphenylphosphine moieties were lost during the preparation. It was expected that PI Pd could be alternatively prepared from inexpensive Pd(II) salts under suitable reduction conditions (Scheme 43, new strategy).[119] After several investigations, a new practical immobilization method of Pd was achieved.

PI Pd thus prepared showed high catalytic activity in the Mizoroki−Heck reaction (Scheme 44) and the Suzuki−Miyaura coupling with a range of substrates including an aryl chloride (Table 69). In all cases, the Pd catalyst was recovered quantitatively without leaching and reused several times without significant loss of activity.

## 3.6. Polymer Incarcerated Platinum [PI Pt]

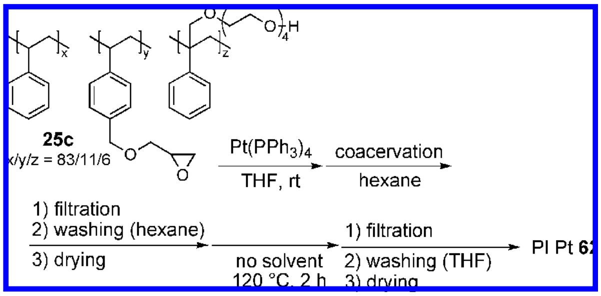
Hydrosilylation of alkenes and alkynes not only is an important industrial process but also provides very useful synthetic tools in laboratories.[120] While metal catalysts based on Rh and Mn are known in this process,[121,122] Pt complexes are the catalyst of choice since Speier's pioneering discovery.[123] Indeed, Pt catalysts work well with alkyl and alkoxysilanes as well as chlorosilanes without deactivation. On the other hand, immobilization of Pt catalysts on either inorganic or organic supports has been investigated.[124−126]

**Table 69. PI Pd 61-Catalyzed Suzuki−Miyaura Coupling of Various Substrates[a]**

| Entry | Aryl Halide | Boronic Acid | Yield (%)[b] | Leaching of Pd (%)[c] |
|---|---|---|---|---|
| 1 |  |  | quant | nd |
| 2 |  |  | 96 | nd |
| 3 |  |  | quant | nd |
| 4 |  |  | 97 | nd |
| 5[d] |  |  | quant | nd |
| 6 |  |  | 92 | nd |
| 7[e] |  |  | 92 | nd |

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 1.0 equiv of $K_3PO_4$, 5 mol % of PI Pd **61** (0.44 mmol/g), 5 mol % of P(*o*-MeOPh)$_3$, toluene−$H_2O$ (4/1), reflux, 2 h. [b] Isolated yield. [c] Measured by XRF analysis; nd = not detected (<0.94%). [d] $K_3PO_4$ (2.0 equiv) was used. [e] 2-(Dicyclohexylphosphino)biphenyl was used as a ligand. Reaction time was 6 h.

**Scheme 45. Preparation of PI Pt from Pt(PPh$_3$)$_4$**



Whereas some active heterogeneous Pt catalysts have been developed, their activity and selectivity are often decreased with repeated use, presumably because most Pt catalysts currently used are sensitive to air oxidation. To address this issue, Pt catalysts have been immobilized on polymer-supported phosphines, amines, etc.; however, applicability of these catalysts is limited due to the presence of ligands.[124,126]

The immobilization of a platinum catalyst was investigated by using the polymer incarcerated (PI) method.[127] PI Pt was prepared from copolymer **25c** and Pt(PPh$_3$)$_4$ (Scheme 45). A solution of **25c** and Pt(PPh$_3$)$_4$ in THF was coacervated by addition of hexane (microencapsulation). The resulting precipitate was washed, dried, and heated (cross-linked) to give PI Pt **62**.

It was revealed by elemental analysis that the P atom remained in PI Pt (P/Pt = 0.88), while it was reported that PI Pd prepared from **25c** and Pd(PPh$_3$)$_4$ contained no

**Scheme 46. PI Pt-Catalyzed Hydrosilylation of 4-Phenyl-1-butene**

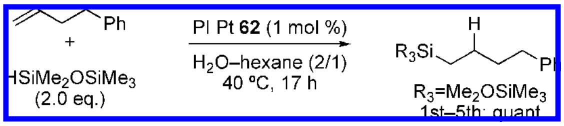
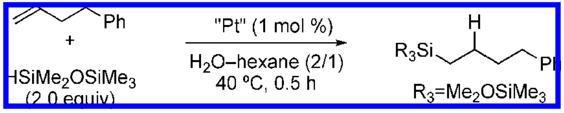


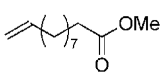
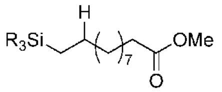
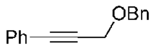
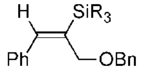
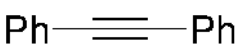
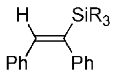
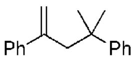
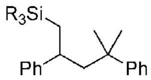
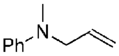
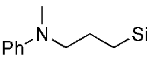
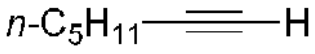
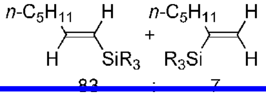
**Table 70. Comparison of Catalytic Activity**



| entry | "Pt" | additive (1 mol %) | yield (%)[a] [leaching (%)[b]] |
|---|---|---|---|
| 1 | PI Pt **62** | | 99 [nd] |
| 2 | Pt/C | | 99 |
| 3 | $Pt(PPh_3)_4$ | | 7 |
| 4 | $PtO_2$ | | 87 |
| 5 | PI Pt **62** | $PPh_3$ | 0 |
| 6 | PI Pt **62** | $Ph_3P{=}O$ | quant |

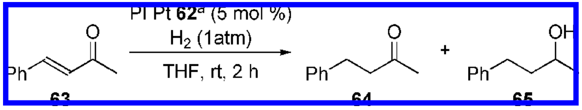
[a] Determined by $^1H$ NMR analysis using durene as an internal standard. [b] Measured by XRF analysis; nd = not detected (<2.6%).

**Table 71. PI Pt 62-Catalyzed Hydrosilylation of Various Substrates**[a]

| Entry | Substrate | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  | 3 |  | 90 |
| 2 |  | 17 |  | quant |
| 3[c] |  | 1 |  | quant |
| 4 |  | 17 |  | 81 |
| 5 |  | 17 |  | 83[d] |
| 6[c] |  | 16 |  | 82 |

[a] All reactions were carried out with pentamethyldisiloxane (2 equiv) using 1 mol % of **62** (the loading level of platinum = 0.768 mmol/g) in hexane–$H_2O$ (2/1) under Ar at 40 °C. The leaching of platinum was measured by XRF and ICP analyses. No peaks of the platinum were detected in any entry. [b] Determined by $^1H$ NMR analysis using durene as an internal standard. [c] Triethoxysilane (2 equiv) was used. [d] Isolated yield.

**Table 72. PI Pt-Catalyzed Hydrogenation of Benzalacetone**



| run | yield (%)[b] | ratio of **64**/**65** |
|---|---|---|
| 1 | quant | 95/5 |
| 2 | quant | 95/5 |
| 3 | quant | 94/6 |
| 4 | quant | 94/6 |
| 5 | quant | 94/6 |

[a] All reactions were carried out using 5 mol% of **62** (the loading level of platinum = 0.768 mmol/g) in THF under atmospheric $H_2$ pressure at rt. The leaching of platinum was measured by XRF and ICP analysis. No peaks of platinum were detected in any entry. [b] Determined by $^1H$ NMR analysis using durene as an internal standard.

phosphine. Although it was difficult to remove the P component from PI Pt **62** completely, this PI Pt was applied to hydrosilylation.[128] Initially, hydrosilylation of 4-phenyl-1-butene with pentamethyldisiloxane in several solvents was tested using PI Pt **62**. It was found that leaching of Pt was observed when THF or $H_2O$ was used as the sole solvent, while hexane suppressed the leaching to afford hydrosilylated product in high yield. However, reactivity was decreased significantly in the second run. On the other hand, the reaction in hexane–$H_2O$ (1/2) proceeded quantitatively without leaching of Pt, and the catalyst was recovered by simple filtration quantitatively and could be reused five times without loss of activity (Scheme 46).

The catalytic activity of PI Pt **62** was compared with that of common heterogeneous or homogeneous catalysts. The effect of additives on reactivity was also investigated (Table 70). The reaction was found to proceed using PI Pt even within 30 min (entry 1). Pt/C, which was known to be an effective catalyst for hydrosilylation of alkyne, showed almost the same activity, whereas the reaction did not proceed well when $Pt(PPh_3)_4$[129] was used as a catalyst (entries 2 and 3). In addition, $PtO_2$, which was recently found to be an effective catalyst for hydrosilylation,[130] gave an inferior result under the conditions (entry 4). While addition of $PPh_3$ to PI Pt completely suppressed the reaction, triphenylphosphine oxide ($Ph_3P{=}O$) did not affect the reactivity (entries 5 and 6). These results also support that the P atom in PI Pt **62** remains as $Ph_3P{=}O$.

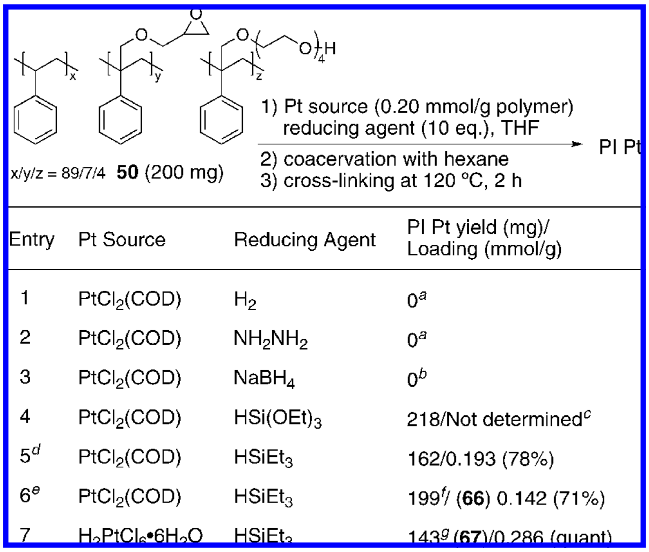
The substrate scope of PI Pt **62** catalyzed hydrosilylation is shown in Table 71. The reactions proceeded smoothly to afford the desired products in good to high yields in all cases.

PI Pt **62** also can be used in hydrogenation of olefin. Hydrogenation of benzalacetone (**65**) was conducted smoothly to afford reduced products **64** and **65** in high yield, and recovery and reuse of the catalyst were attained without loss of activity even after the fifth use (Table 72). No leaching of Pt was detected by XRF analysis in all runs.

PI Pt catalysts were conveniently prepared from $PtCl_2(COD)$ or $H_2PtCl_9 \cdot 6H_2O$ and styrene copolymers via reduction of the Pt sources, coacervation, and cross-linking.[131]

The preparation of PI Pt was first examined using $PtCl_2(COD)$ and copolymer **50** according to PI method by using THF and hexane as solvents (Table 73). As reducing agents, hydrogen and hydrazine afforded no immobilized platinum clusters, because the reduction of $PtCl_2(COD)$ was too fast and platinum metal precipitated immediately (entries 1 and 2). In the case of sodium borohydride, no cross-linking proceeded after the coacervation with hexane (entry 3). As a reducing agent, silanes were tried next and triethylsilane gave a satisfactory result to afford the desired PI Pt (entry 5). In this catalyst, the cluster size of Pt was less than 1 nm by transmission electron microscopy (TEM) analysis. However, this procedure was not reproducible presumably due to poor solubility of $PtCl_2(COD)$ in THF. In fact, when the solvent was changed to dichloromethane, which dissolved $PtCl_2(COD)$ well, PI Pt **66** was obtained reproducibly (entry 6). The Pt loading value of this PI Pt determined by fluorescence X-ray analysis (XRF) was 0.142 mmol/g. Hydrogen hexachloroplatinate hexahydrate ($H_2PtCl_6 \cdot 6H_2O$) was also found to be a good platinum source of the PI Pt **67**

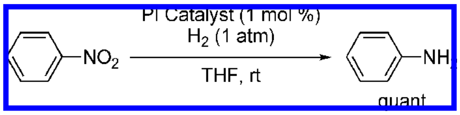
**Table 73. Preparation of PI Pt from Pt Salts and Copolymer 50**



| Entry | Pt Source | Reducing Agent | PI Pt yield (mg)/ Loading (mmol/g) |
|---|---|---|---|
| 1 | $PtCl_2(COD)$ | $H_2$ | 0[a] |
| 2 | $PtCl_2(COD)$ | $NH_2NH_2$ | 0[a] |
| 3 | $PtCl_2(COD)$ | $NaBH_4$ | 0[b] |
| 4 | $PtCl_2(COD)$ | $HSi(OEt)_3$ | 218/Not determined[c] |
| 5[d] | $PtCl_2(COD)$ | $HSiEt_3$ | 162/0.193 (78%) |
| 6[e] | $PtCl_2(COD)$ | $HSiEt_3$ | 199[f]/ (**66**) 0.142 (71%) |
| 7 | $H_2PtCl_6{\bullet}6H_2O$ | $HSiEt_3$ | 143[g] (**67**)/0.286 (quant) |

[a] Pt metal precipitated. [b] No cross-linking proceeded. [c] Huge clusters were obtained. [d] Not reproducible. [e] Dichloromethane and methanol were used as solvents. [f] Clusters of less than 1 nm size were observed by TEM analysis. [g] Clusters of 2−3 nm size were observed.

**Table 74. Hydrogenation of Nitrobenzene Catalyzed by PI Catalysts**



| entry | Pt source | time (h) | leaching (%)[a] |
|---|---|---|---|
| 1 | PI Pt **66** from $PtCl_2(COD)$ | 1 | *b* |
| 2 | PI Pt **62** from $Pt(PPh_3)_4$ | 6 | 19 |
| 3 | PI Pd **28c** | 3 | *b* |

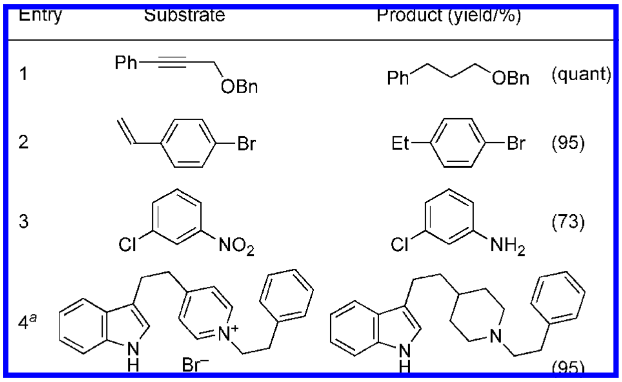
[a] Measured by XRF analysis. [b] Not detected (<2%).

(entry 7). PI Pt **67** with a higher loading level (0.286 mmol/g) was prepared from $H_2PtCl_6{\cdot}6H_2O$ and triethylsilane by a similar procedure. In this case, THF and hexane were used as solvents and the cluster size of this PI Pt observed by TEM was 2−3 nm.

The reactivity of the PI Pt catalysts prepared was tested by hydrogenation of nitrobenzene in THF under atmospheric pressure of hydrogen (Table 74). As expected, with 1 mol % of the PI Pt catalyst prepared from $PtCl_2(COD)$, the reaction completed within 1 h to give aniline quantitatively, and no leaching of Pt from the catalyst was observed by XRF analysis. By contrast, 6 h was required to finish the same hydrogenation with the PI Pt prepared from $Pt(PPh_3)_4$ and 19% leaching of the platinum was observed. For comparison, PI Pd was also applied to this reaction. Reactivity of the PI Pd was moderate to complete the hydrogenation in 3 h. It should be noted that the PI Pt from $PtCl_2(COD)$ gave higher activity than the PI Pt prepared from $Pt(PPh_3)_4$. In addition, the PI Pt from $PtCl_2(COD)$ could be reused at least 5 times repeatedly for the reaction without loss of activity and no Pt leaching was observed in each run. It should be also mentioned that the cluster size of the PI Pt did not change after five runs.

Next the PI Pt catalyst was applied to the hydrogenation of various alkenes and alkynes and selective reduction with PI Pt catalyst was also tried by using multifunctionalized substrates (Table 75).

**Table 75. Selective Hydrogenation Catalyzed by PI Pt[b]**



| Entry | Substrate | Product (yield/%) |
|---|---|---|
| 1 | | (quant) |
| 2 | | (95) |
| 3 | | (73) |
| 4[a] | | (95) |

[a] The reaction was conducted in methanol−THF (1/1) under 5 atm pressure of hydrogen with 5 mol % PI Pt **67**. No leaching of Pt was observed by ICP analysis (<0.06%). [b] In all entries, reaction time was 1 h. In all entries except entry 4, the reactions were performed in THF at room temperature under atmospheric pressure of hydrogen with 1 mol % of PI Pt **66**. No leaching of Pt was observed by XRF analysis (<2%).

## 3.7. Polymer Incarcerated Catalysts for Oxidation Using Molecular Oxygen

The selective oxidation of alcohols is one of the most important transformations in organic synthesis.[132] While several metal-based oxidizing reagents have been developed, these reagents usually require stoichiometric amounts of metal oxidants, and thus a large amount of waste is formed. In this respect, the oxidation of alcohols using molecular oxygen catalyzed by reusable heterogeneous catalysts is ideal from an environmental and atom-economical point of view.[133] Although the hydroxyapatite (HAP)-bound RuHAP[134] and PdHAP,[135] as well as $Ru/Al_2O_3$,[136] $Au/CeO_2$,[137] and Au−Pd/$TiO_2$,[138] are excellent catalysts for the aerobic oxidation of alcohols, they work only at high temperatures or under solvent-free conditions in most cases. Oxidation reactions at room temperature in appropriate solvents are necessary for alcohols such as those with high melting points or low stability at high temperatures, but examples of these room-temperature reactions are very limited.[139] Moreover, satisfactory results were obtained in only limited cases when catalysts were reused.[139a] Therefore, the development of reusable catalysts for the liquid-phase aerobic oxidation of alcohols under mild conditions, especially at room temperature, is an attractive and challenging subject in both organic synthesis and green chemistry.

Stability of gold nanoclusters was studied, and polymer **68**, which contained alcohol and epoxide moieties in higher molar ratio, was selected. The polymer-incarcerated gold nanocluster catalysts (PI Au) were first prepared as shown in Scheme 47.[140] The solution of ($AuClPPh_3$) in a small amount of THF was slowly added to a mixture of polymer **68** and $NaBH_4$ in THF at room temperature. The color of the solution immediately turned wine red. Hexane was then added to form microcapsules, which were filtered, washed, and dried under vacuum. The microcapsules were next heated at 150 °C for 5 h to cross-link the side chains and then washed with THF and water to afford PI Au (**69**) as a deep-purple solid. Small gold nanoclusters (around 1 nm) were observed by TEM analysis, and elemental analysis showed no contamination from phosphorus.

PI Au nanoclusters **69a** thus prepared were used for the aerobic oxidation of (±)-1-phenylethanol. The reaction

**Scheme 47. Preparation of PI Au**

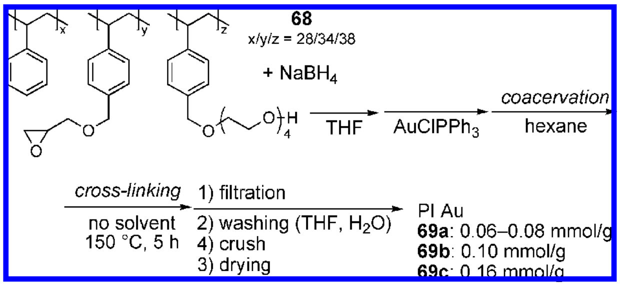
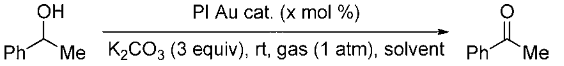


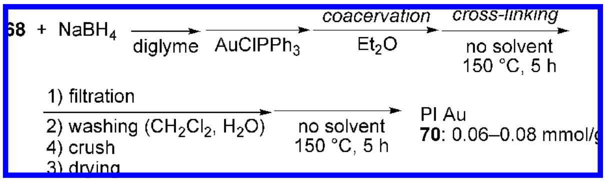
**Table 76. Oxidation of (±)-1-Phenylethanol Using the PI Au Nanoclusters**[a]



| entry | PI Au | $x$ | solvent | time (h) | gas | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **69a** | 3 | $CH_2Cl_2/H_2O$ (1/1) | 24 | $O_2$ | >99 |
| 2 | **69a** | 3 | toluene/$H_2O$ (1/1) | 24 | $O_2$ | 98 |
| 3 | **69a** | 3 | BTF/$H_2O$ (1/1) | 24 | $O_2$ | 99 |
| 4 | **69b** | 3 | BTF/$H_2O$ (1/1) | 24 | $O_2$ | 72 |
| 5 | **69c** | 3 | BTF/$H_2O$ (1/1) | 24 | $O_2$ | 85 |
| 6 | **69a** | 1 | BTF/$H_2O$ (1/1) | 3 | $O_2$ | 74 |
| 7 | **70** | 1 | BTF/$H_2O$ (1/1) | 3 | $O_2$ | 96 |
| 8 | **70** | 1 | BTF/$H_2O$ (1/1) | 3 | $O_2$ | 18[c] |
| 9 | **70** | 1 | BTF/$H_2O$ (1/1) | 5 | $O_2$ | >99 |
| 10 | **70** | 1 | BTF/$H_2O$ (1/1) | 5 | air | 88 |

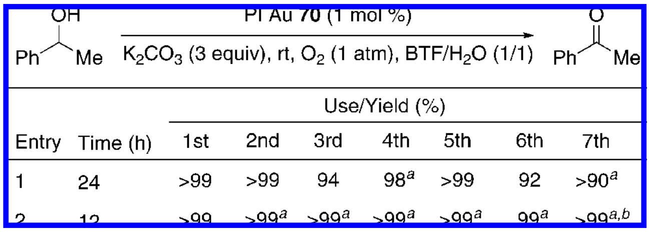
[a] Reaction conditions: substrate (0.5 mmol), solvent (6 mL), rt, 1 atm; BTF = benzotrifluoride. [b] Determined by GC analysis. [c] Base-free conditions.

**Scheme 48. Preparation of PI Au 70**



proceeded in a dichloromethane/water solvent mixture at room temperature and under oxygen at atmospheric conditions in the presence of **71a** (3 mol %) and potassium carbonate to afford acetophenone quantitatively (Table 76, entry 1). The reaction also proceeded smoothly in toluene/water and benzotrifluoride/water solvent mixtures (entries 2 and 3). It is notable that in all cases no metal leaching was detected by inductively coupled plasma (ICP) analysis (<0.04%). Examination of the relationship between the reactivities and the loadings of the gold catalysts revealed that use of a lower loading gave higher activity, which could be rationalized by the fact that a lower catalyst loading contained smaller clusters (compare entries 3−5). Furthermore, it was found that a slight modification of the preparation method of the PI Au nanoclusters (Scheme 48) greatly increased their catalytic activity (entries 6 and 7). It was proven that the reaction was promoted by a base and that the reaction did not proceed at all in the absence of water or base (entry 8). The nanoclusters **70** thus prepared were highly active, and the oxidation reaction reached completion when a catalyst loading of only 1 mol % was used (entry 9). The nanoclusters **70** showed high reactivity even when the reaction was carried out in air rather than under oxygen (entry 10).

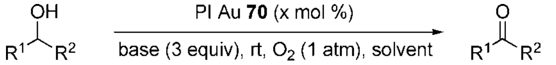
**Table 77. Recovery and Reuse of PI Au 70**

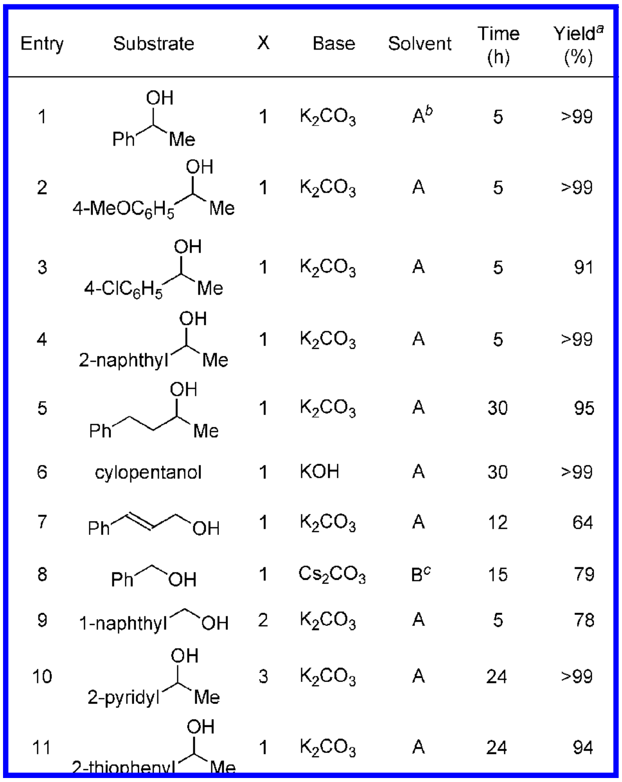


| Entry | Time (h) | Use/Yield (%) 1st | 2nd | 3rd | 4th | 5th | 6th | 7th |
|---|---|---|---|---|---|---|---|---|
| 1 | 24 | >99 | >99 | 94 | 98[a] | >99 | 92 | >90[a] |
| 2 | 12 | >99 | >99[a] | >99[a] | >99[a] | >99[a] | 99[a] | >99[a,b] |

[a] The recovered catalyst was heated at 150 °C for 5 h without solvent in air before use. [b] Eighth, >99%; ninth, 99%, tenth, >99%.

**Table 78. Oxidation of Various Alcohols Catalyzed by PI Au 70**





| Entry | Substrate | X | Base | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | OH<br>Ph Me | 1 | $K_2CO_3$ | A[b] | 5 | >99 |
| 2 | OH<br>4-MeOC$_6$H$_5$ Me | 1 | $K_2CO_3$ | A | 5 | >99 |
| 3 | OH<br>4-ClC$_6$H$_5$ Me | 1 | $K_2CO_3$ | A | 5 | 91 |
| 4 | OH<br>2-naphthyl Me | 1 | $K_2CO_3$ | A | 5 | >99 |
| 5 | OH<br>Ph Me | 1 | $K_2CO_3$ | A | 30 | 95 |
| 6 | cylopentanol | 1 | KOH | A | 30 | >99 |
| 7 | Ph OH | 1 | $K_2CO_3$ | A | 12 | 64 |
| 8 | Ph OH | 1 | $Cs_2CO_3$ | B[c] | 15 | 79 |
| 9 | 1-naphthyl OH | 2 | $K_2CO_3$ | A | 5 | 78 |
| 10 | OH<br>2-pyridyl Me | 3 | $K_2CO_3$ | A | 24 | >99 |
| 11 | OH<br>2-thiophenyl Me | 1 | $K_2CO_3$ | A | 24 | 94 |

[a] Determined by GC analysis. [b] Solvent A, BTF/$H_2O$ (1/1); solvent B, diglyme.

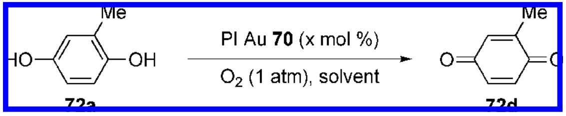
The catalyst was recovered by simple filtration and reused without significant loss of activity (Table 77). The recovered catalyst could be heated at 150 °C for 5 h to facilitate its reuse.

Several alcohols were then oxidized in an oxygen or air atmosphere in the presence of 1−3 mol % of **70**, and results were summarized in Table 78. The PI Au catalyst **70** could also be used for the aerobic oxidation of alcohols under solvent- and base-free conditions.

Next, PI Au **70** was also used in aerobic oxidation of hydroquinones to quinones.[141] PI Au was used in the aerobic oxidation of methylhydroquinone (**72a**) to toluquinone (**72d**) under atmospheric oxygen (Table 79).

Several hydroquinone derivatives and catechols were oxidized by PI Au under atmospheric oxygen or air (Tables 80 and 81). Hydroquinone (**71a**) was oxidized smoothly to give 1,4-quinone in good yield even in the presence of 0.5 mol % of the catalyst or under atmospheric air (entries 1

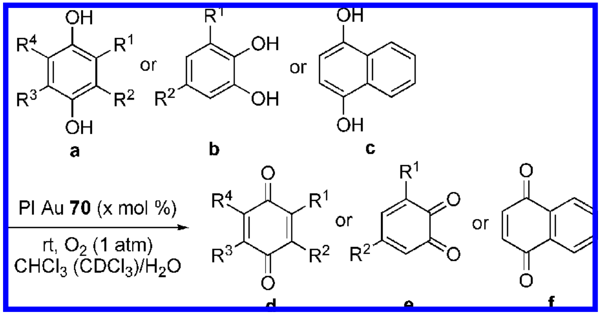
**Table 79. Aerobic Oxidation of Methylhydroquinone (72a) to Toluquinone (72d) in the presence of PI Au 70 (1 mol %) under $O_2$**

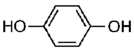
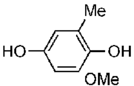
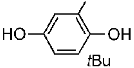
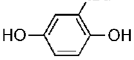
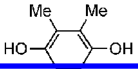


| entry | solvent (mL/mmol substrate) | *T* (°C) | *t* (h) | conversion (%) | selectivity (%)$^{a,b}$ | yield (%)$^{a}$ |
|---|---|---|---|---|---|---|
| 1 | BTF (4.0) | rt | 12 | 12 | 25 | 3 |
| 2 | BTF (4.0)/$H_2O$ (4.0) | rt | 12 | 73 | 51 | 37 |
| 3 | toluene (4.0)/$H_2O$ (4.0) | rt | 12 | 82 | 29 | 24 |
| 4 | $CH_2Cl_2$ (4.0)/$H_2O$ (4.0) | rt | 12 | 85 | 24 | 20 |
| 5 | $CH_2Cl_2$ (7.6)/$H_2O$ (0.4) | rt | 5.5 | 98 | 96 | 94 |
| 6 | $CH_2Cl_2$ (7.6)/$H_2O$ (0.4) | rt | 5.5 | >99 | 93 | 93 |
| 7 | $CH_2Cl_2$ (22.8)/$H_2O$ (1.2) | rt | 1 | >99 | >99 | >99 |
| 8 | $CH_2Cl_2$ (22.8)/$H_2O$ (1.2) | rt | 1 | >99 | >99 | >99 |
| 9 | $CH_2Cl_2$ (4.0)/$H_2O$ (4.0) | 0 | 6 | 88 | 67 | 57 |
| 10 | $CH_2Cl_2$ (7.6)/$H_2O$ (0.4) | 0 | 6 | 91 | 91 | 83 |
| 11 | $CH_2Cl_2$ (8.0) | 0 | 6 | 13 | >99 | 13 |
| 12 | $CHCl_3$ (7.6)/$H_2O$ (0.4) | rt | 1 | 98 | >99 | 98 |

[a] Determined by GC analysis. [b] Selectivity = yield of **72d**/conversion. [c] Atmospheric air was used instead of $O_2$. [d] No leaching of Au to the reaction mixture was observed by ICP analysis.

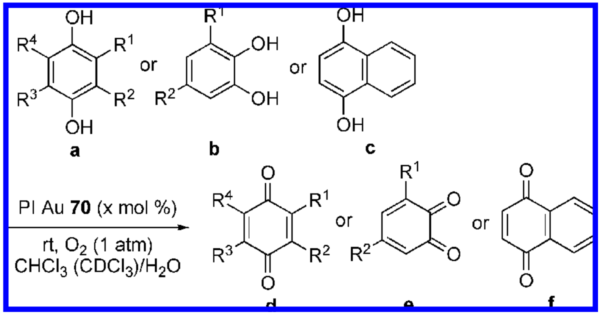
**Table 80. PI Au-Catalyzed Oxidation of Hydroquinones and Catechols (1)**

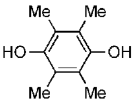
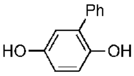
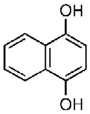
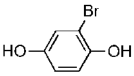
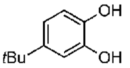
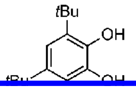


| Entry | Substrate /Product | Substrate | $CH(D)Cl_3/H_2O$ (mL/mmol substratr) | *X* | *t* (h) | Yield (%)$^{a}$ |
|---|---|---|---|---|---|---|
| 1 | **71a/71d** |  | 47.6/0.4 | 0.5 | 1 | 86$^{b}$ |
| 2 | | | 47.6/0.4 | 1 | 2 | 84$^{b,c}$ |
| 3 | **72a/72d** |  | 20.0/1.0 | 0.25 | 3 | >99$^{b}$ |
| 4 | **73a/73d** |  | 22.4/1.6 | 1 | 1 | >99$^{b}$ |
| 5 | **74a/74d** |  | 22.4/1.6 | 0.5 | 2.5 | 98$^{a}$ |
| 6 | **75a/75d** |  | 22.4/1.6 | 0.5 | 1 | 92$^{a}$ |

[a] Isolated yield. [b] Yield was determined by GC analysis. [c] Atmospheric air was used instead of $O_2$.

**Table 81. PI Au-Catalyzed Oxidation of Hydroquinones and Catechols (2)**



| Entry | Substrate /Product | Substrate | $CH(D)Cl_3/H_2O$ (mL/mmol substratr) | *X* | *t* (h) | Yield (%)$^{a}$ |
|---|---|---|---|---|---|---|
| 7 | **76a/76d** |  | 22.4/1.6 | 0.5 | 1 | 93$^{a}$ |
| 8 | **77a/77d** |  | 22.4/1.6 | 0.5 | 6.5 | 98$^{a}$ |
| 9 | **78c/78f** |  | 22.4/1.6 | 0.5 | 3 | 97$^{a}$ |
| 10 | **79a/79d** |  | 47.2/0.4<br>$NaHCO_3$ (1 equiv) | 1 | 3 | 55$^{b}$ |
| 11 | **80b/80e** |  | 23.2/1.6<br>$K_2CO_3$ (0.1 equiv) | 1 | 23 | 76$^{d}$ |
| 12 | **81b/81e** |  | 22.4/1.6<br>$K_2CO_3$ (0.1 equiv) | 1 | 28 | 96$^{a}$ |

[a] Isolated yield. [b] Yield was determined by GC analysis. [d] Yield was determined by $^{1}H$ NMR spectroscopy using an internal standard. $CDCl_3$ was used as a solvent.

and 2). Hydroquinones with alkyl substituents **72**−**76a** were also oxidized to afford the corresponding quinone derivatives in excellent yields (entries 3−7). Phenylhydroquinone (**77a**) and naphthoquinone (**78c**) were also converted to the oxidized products under the same conditions (entries 8 and 9). While oxidation of electron-poor bromohydroquinone (**79a**) was slow, the reaction was accelerated by addition of a base, affording bromoquinone in moderate yield (entry 10). Oxidation of catechols **80b** and **81b** was also accelerated by a base, providing the corresponding *o*-quinones in high yields (entries 11 and 12). It should be noted that in most cases analytically pure products were obtained in excellent yields by simple phase separation without further purification.

Although the extensive mechanistic study has not yet been conducted, a possible mechanism of aerobic oxidation of hydroquinones catalyzed by PI Au is shown in Figure 18.

More recently, a novel polystyrene−silica gel-supported gold(III) catalyst (MC Au(III) on $SiO_2$) has been devel-

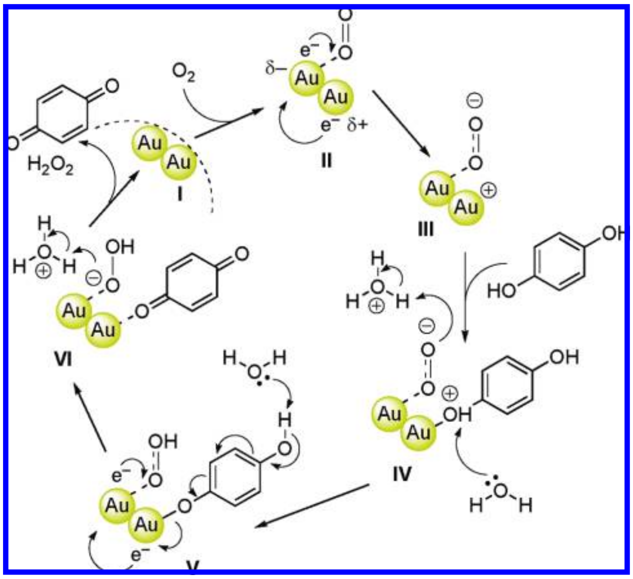


**Figure 18.** Assumed mechanism.

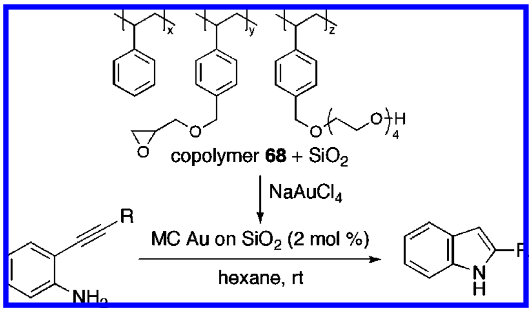


**Figure 19.** Novel gold(III) polymer-supported catalyst for indole library synthesis.

**Scheme 49. Preparation of PI Metal Catalysts**

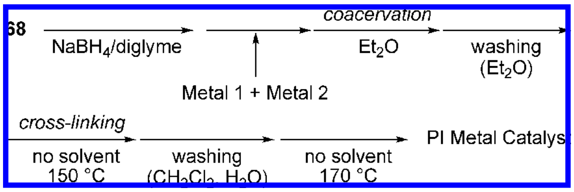
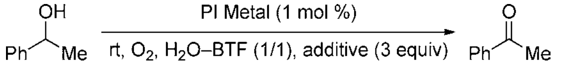


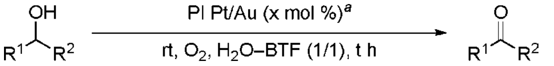
**Table 82. Activity of PI Metal Catalysts**



| entry | metal 1 | metal 2 | ratio | additive | yield (%) 12 h | yield (%) 3 h |
|---|---|---|---|---|---|---|
| 1 | $AuClPPh_3$[a] | $Pd(OAc)_2$ | 1/1 | | >99 | 72 |
| 2 | $AuClPPh_3$[a] | $Na_2PtCl_6$ | 1/1 | | >99 | 95 |
| 3 | $AuClPPh_3$[a] | $Ni(OAc)_2$ | 1/1 | | 72[b] | |
| 4 | $AuClPPh_3$[a] | $NiCl_2(PPh_3)_2$ | 1/1 | | 72[b] | |
| 5 | $AuClPPh_3$[a] | $Ni(PPh_3)_4$ | 1/1 | | 57[b] | |
| 6 | $AuClPPh_3$[a] | AgOCOPh | 1/1 | | 0[b] | |
| 7 | $AuClPPh_3$[a] | $HIr(PPh_3)_3$ | 1/1 | | 51[b] | |
| 8 | $AuClPPh_3$[a] | None | | $K_2CO_3$ | >99 | 95 |
| 9 | $AuClPPh_3$[a] | None | | | 49 | 18 |
| 10 | $Pd(OAc)_2$ | None | | $K_2CO_3$ | 0 | |
| 11 | $Pd(OAc)_2$ | None | | | 0 | |
| 12 | $Pd(OAc)_2$ | None | | $K_2CO_3$ | 11 | |
| 13 | $Na_2PtCl_6$ | None | | | 5 | 1 |
| 14 | $AuClPPh_3$[a] | $Na_2PtCl_6$ | 4/1 | | | 74 |
| 15 | $AuClPPh_3$[a] | $Na_2PtCl_6$ | 2/1 | | | 82 |
| 16 | $AuClPPh_3$[a] | $Na_2PtCl_6$ | 1/2 | | | 88 |

[a] Catalyst loading based on Au. [b] Reaction time was 24 h.

**Table 83. Substrate Scope of PI Pt/Au Catalyzed Aerobic Oxidation of Alcohols**



| entry | product | *x* | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | acetophenone | 1 | 5 | >99 |
| 2 | benzaldehyde | 1 | 5 | 93 |
| 3 | *p*-tolualdehyde | 1 | 5 | 88 |
| 4 | *o*-tolualdehyde | 1 | 5 | 84 |
| 5 | *p*-anisaldehyde | 1 | 5 | 90 |
| 6 | *p*-chlorobenzaldehyde | 2 | 5 | 86 |
| 7 | 2-acetonaphthaldehyde | 1 | 18 | >99 |
| 8 | 1-naphthaldehyde | 1 | 18 | 93 |
| 9 | cinnamaldehyde | 1 | 36 | 94 |
| 10 | 4-phenyl-2-butanone | 3 | 72 | >99 |
| 11 | 2-butanone | 1 | 8 | 67 |
| 12 | cyclopentanone | 2 | 115 | 90 |
| 13 | 2-acetylthiophene | 2 | 96 | 94 |
| 14 | 2-acetylpyridine | 1.5 | 48 | 80 |

[a] Catalyst loading based on Au. Ratio of Pt to Au is 1:1. [b] Determined by GC analysis.

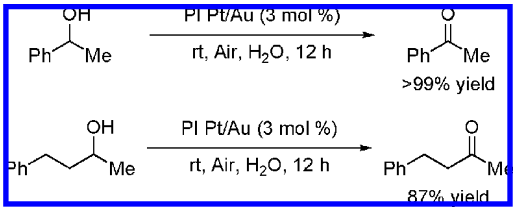
oped and successfully applied to indole library synthesis (Figure 19).[142] Initially, polymer-incarcerated (PI) Au(III) was prepare from copolymer **68** and sodium tetrachloroaurate(III) via coacervation in THF−hexane and cross-linking by heating according to the standard method. Unexpectedly, this potential catalyst had no activity toward the reaction for the conversion of alkynyl aniline to the indole. Several investigations revealed that MC Au(III) on $SiO_2$ afforded the best result in terms of the yield, gold leaching, and reusability.

While PI Au **70** has high activity for oxidation at room temperature, a drawback is that basic conditions are needed. Under basic conditions, the selective oxidation of primary alcohols to aldehydes is difficult. In light of recent reports where several groups have demonstrated that doping a secondary metal component into metal catalysts is advantageous for the activity and selectivity of various reactions, combinations of gold and second metals were investigated (Scheme 49).[133,143−145]

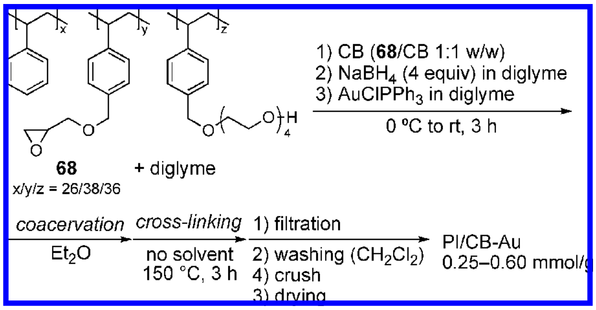
The PI bimetallic clusters were then tested for catalytic activity in the aerobic oxidation of alcohols.[146] When palladium and platinum were used as dopants, the desired ketone was obtained quantitatively (Table 82, entries 1 and 2). It is noted that the oxidation proceeded smoothly at room temperature in the absence of base. Nickel and iridium were also promising dopants, while the catalyst prepared with silver showed no activity (entries 3−7). Remarkably, the catalysts prepared from pure gold metal required addition of a base for high productivity (entries 8 and 9), while the catalysts prepared from either Pd or Pt metal showed little or no activity regardless of the presence of the base (entries 10−13). The ratio of gold to platinum was varied (entries 14−16), which revealed that a 1:1 mixture provided the most active catalyst.

With the optimized conditions in hand, several alcohols were then oxidized under atmospheric oxygen in the presence of 1−3 mol % of the PI Pt/Au catalyst. Aromatic secondary alcohols were oxidized smoothly to afford the corresponding ketones quantitatively (Table 83, entries 1 and 7). Although aliphatic ketones had relatively low reactivity, the desired ketones were also obtained in high yields by prolonging the reaction time (entries 10−12). It has been well documented

**Scheme 50. Aerobic Oxidation of Alcohols in Water Open to Air at Room Temperature**



**Scheme 51. Preparation of PI CB−Au**



that the oxidation of primary alcohols to carboxylic acids readily occurs under traditional methodologies. However, aromatic and allylic primary alcohols, which had both electron-donating and electron-withdrawing groups, were oxidized smoothly under the same conditions as those of secondary alcohols to afford the corresponding aldehydes in excellent yields without formation of carboxylic acids (entries 2−6, 8 and 9). Alcohols including heteroatoms such as sulfur and nitrogen, which are known to strongly coordinate to gold nanoparticles, could also be oxidized smoothly to give the desired ketones in high yields (entries 13 and 14).

Furthermore, it was found that the aerobic oxidations also proceeded smoothly in water without organic solvents under air (Scheme 50). Notably, this is the first example of aerobic oxidation of alcohols at room temperature under base-free conditions in water using heterogeneous catalysts.

The recovery and reuse of the developed PI Pt/Au catalyst was examined. It was found that the activity of the catalyst was maintained by treatment of the recovered catalyst with hydrogen under heating conditions. It should be noted that this recovery method enabled us to reuse the catalyst at least six times without loss of activity.

Novel polymer-incarcerated, carbon-stabilized gold nanoclusters were also developed for the aerobic oxidation of alcohols (Scheme 51).[147] The inclusion of carbon black (CB) in the composition of the catalyst, together with an amphiphilic copolymer, enhances the stability of gold nanoclusters probably via synergistic $\pi-\pi$ interactions among the three components, which enables an increase of the metal loading amount up to 0.60 mmol/g. Secondary alcohols could be oxidized smoothly to afford analytically pure products in excellent yields after simple phase separation without further purification. The catalyst could be recovered and reused several times without significant loss of activity or metal leaching in the reaction medium.

While various alkyl-substituted hydroquinones were smoothly oxidized, reactions with EWG-substituted hydroquinones in the presence of PI Au **70** either did not proceed or proceeded slowly with the aid of an added base. After further investigations, polymer-incarcerated platinum nanoclusters (PI Pt **82**) prepared following the same procedure for PI Au **70** were developed (Scheme 52).[148] In this catalytic system, a wide range of hydroquinone and catechol derivatives, including tetrachlorohydroquinone, are smoothly oxidized under ambient conditions with low catalyst loading (Table 84).

**Scheme 52. Preparation of PI Pt 82**

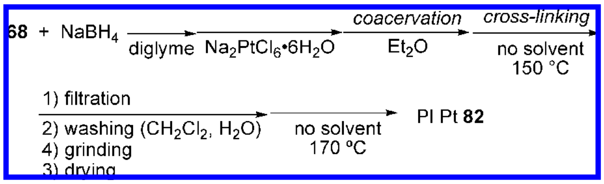
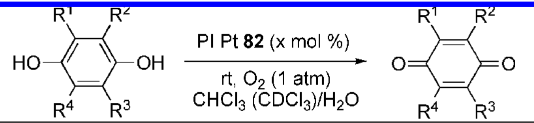
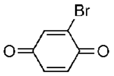
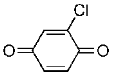
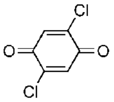
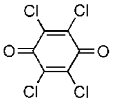
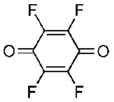
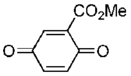
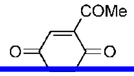


**Table 84. PI Pt-Catalyzed Aerobic Oxidation of Hydroquinones**

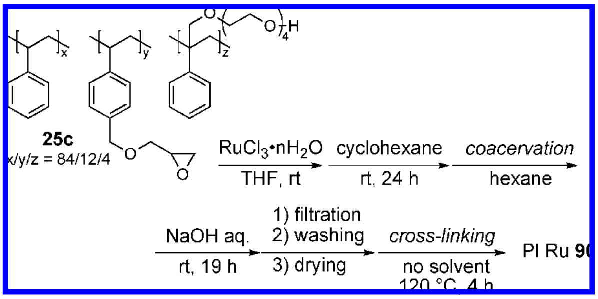


| Entry | Substrate /Product | Product | Amount of PI Pt (mol %) | t (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **83a/83b** |  | 1 | 0.5 | 80[a] |
| 2 | **84a/84b** |  | 0.5 | 7 | 93[a] |
| 3 | **85a/85b** |  | 1 | 3 | 99[a] |
| 4 | **86a/86b** |  | 1 | 3 | 99[a] |
| 5 | | | 0.5 | 3 | 90[b] |
| 6 | **87a/87b** |  | 1 | 3 | 65[a] |
| 7 | **88a/88b** |  | 2 | 3 | 92[c] |
| 8 | **89a/89b** |  | 2 | 6 | 88[b] |

[a] Yield determined by GC (internal standard, anisole), standard curve method. [b] Yield of isolated product. [c] Yield was determined by $^1$H NMR analysis (internal standard, acetophenone).

A polymer-incarcerated ruthenium (PI Ru **90**) catalyst for the oxidation of alcohols with molecular oxygen has been developed. The catalyst was prepared from a polystyrene-based copolymer with ruthenium chloride hydrate as the metal source (Scheme 53).[149a] The choice of ruthenium species was important to obtain high catalytic activity as well as for the suppression of leaching of ruthenium. In the presence of 5 mol % PI Ru **90** and 15 mol % 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO), alcohols were oxidized using molecular oxygen at atmospheric pressure to afford the corresponding aldehydes or ketones in good to excellent yields (Table 85). The catalyst could be recovered and reused at least ten times without loss of activity (Table 86). Furthermore, a novel organic-inorganic hybrid ruthenium (HB Ru) catalyst for the oxidation of alcohols with molecular oxygen has been developed.[149b] In the presence of HB Ru corresponding to 5 mol % loading of ruthenium, the alcohols were oxidized with molecular oxygen or air at atmospheric pressure without any

**Scheme 53. Preparation of PI Ru 90 from $RuCl_3 \cdot nH_2O$**



additives to afford the corresponding aldehydes or ketones in good to excellent yields.

## 3.8. Application of the Polymer Incarcerated Method to a Microreactor

Multiphase catalytic reactions have played important roles not only in the research laboratory but also in the chemical and pharmaceutical industries.[150] They are classified according to the phases involved, such as gas−liquid, gas−liquid−liquid, or gas−liquid−solid reactions. Although numerous multiphase catalytic reactions are known and many are used in industry, these reactions are still difficult to conduct when compared with homogeneous reactions because the efficiency of interaction and mass transfer between different phases is extremely low, and thus in most cases the reaction rates are slow. In general, to accelerate multiphase catalytic reactions, some treatment producing high interfacial area between the two or three reacting phases, for example, vigorous stirring or additional equipment, is needed, and the development of more effective, simple devices that can produce such a high interfacial area between different phases is a much sought-after goal.

To achieve truly efficient multiphase catalytic reactions, a new device, which has a very small channel (nano- to micrometer in width and depth and centimeter to meter in length) in a glass plate, was developed.[151] A similar device, the so-called "microchannel reactor", is used mainly in the field of analytical chemistry.[152] The device has a very large specific interfacial area per unit volume. In concrete figures, this area rises to 10 000−50 000 $m^2/m^3$, as opposed to only 100 $m^2/m^3$ for the case of conventional reactors used in chemical processes.[153] A solid catalyst was immobilized on the wall of the microchannel, and then liquid and gas materials were flowed into the channel. Provided that the flow is well controlled, it should be possible to pass the gas through the center of the channel, and the liquid along the inner surface of the channel at a particular gas pressure (Figure 20).[154] In this system, truly efficient gas−liquid−solid reactions might occur, because effective interaction of the three phases is expected due to the extremely large interfacial areas and the short path required for molecular diffusion in the very narrow channel space.

To put the above idea into practice, hydrogenation catalyzed by palladium as a model gas−liquid−solid reaction was demonstrated.[155]

An active Pd catalyst was immobilized on the wall of the glass channel. Although there have been several reports concerning immobilization of metals on a glass wall,[156] lowered reactivity and leaching of the metals during reactions are sometimes serious problems. To address the issue, a microchannel reactor having a channel 200 $\mu$m in width, 100 $\mu$m in depth, and 45 cm in length was selected. First, amine groups were introduced onto the surface of the glass channel to form **92** (Figure 21). Microencapsulated palladium (**91**), prepared from $Pd(PPh_3)_4$ and copolymer **50** in dichloromethane−*t*-amyl alcohol, was used as the Pd source. A colloidal solution of the MC Pd **91** was passed through the microchannel to form **93**, which was heated at 150 °C for 5 h. During the heating, cross-linking of the polymer occurred, and the desired Pd-immobilized microchannel was successfully prepared.

Hydrogenation was conducted, and the reactions proceeded smoothly to afford the desired products quantitatively within 2 min for a variety of substrates (Table 87). The system could also be applied to deprotection reactions.

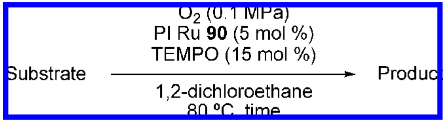
Supercritical carbon dioxide ($scCO_2$) was used in hydrogenation reactions in microchannel reactors to increase productivity of the reaction in each channel.[157] $scCO_2$ has attracted much interest as an ideal solvent because of its abundance, low cost, and nontoxicity. While $scCO_2$ has a liquid-like aspect, allowing dissolution of many organic compounds, it has also a gas-like aspect, retaining very high miscibility with other gases including hydrogen. Therefore, $scCO_2$ provides a quite effective environment for heterogeneous reactions using gas materials, and a variety of examples of hydrogenation reactions in $scCO_2$ have been reported.

The overall system for hydrogenation reactions using $scCO_2$ is shown in Figure 22. A cell that was durable under high pressure and into which substrates were injected was connected with a 200 mL autoclave, used to make $scCO_2$ containing dissolved hydrogen. The pressure inside the channel was controlled by a back-pressure regulator, which was positioned at the end of the microchannel reactor. A typical experimental method for conducting the reaction was as follows: first, the substrate was supplied into the cell, which was kept at 50 °C. Hydrogen and $CO_2$ were entered successively into the autoclave kept at 50 °C, where $scCO_2$ containing dissolved hydrogen was prepared. Finally, this fluid was transferred via the cell into the channel, kept at ca. 60 °C, where the dissolved substrate was converted to the desired product. During the reaction, $CO_2$ was supplied continuously at a constant flow rate, and the product was collected at the exit of the back-pressure regulator.

Under the conditions, a variety of substrates were converted to the desired products in nearly quantitative yields (Table 88). Surprisingly, the reaction time (mean residence time of the substrate inside the channel) was estimated to be *less than 1 s* in each case, and a quite efficient hydrogenation system has been achieved.

A practical and highly productive system for hydrogenation reactions utilizing capillary column reactors was also developed. The system occupies less space than ordinary batch systems, is low cost and easy to handle, and shows feasibility toward large-scale chemical synthesis (Figure 23).[158] Palladium-containing micelles were immobilized onto the inner surface of the capillaries. Nine palladium-immobilized capillaries were assembled and connected to a T-shaped connector, and hydrogen and a substrate solution were fed to capillaries via the connector. Hydrogenation of 1-phenyl-1-cyclohexene proceeded smoothly to give phenylcyclohexane in quantitative yield (Scheme 54). The capillaries themselves occupy only ca. 0.4 mL and a high space−time yield has been achieved (124.3 mg/17 min/0.4

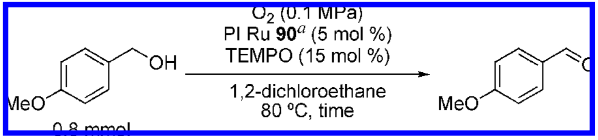
**Table 85. Oxidation of Various Alcohols Catalyzed by PI Ru 90**[a]



| entry | substrate | time (h) | conversion (%)[b] | yield (%)[b] | leaching (%)[c] |
|---|---|---|---|---|---|
| 1 | benzyl alcohol | 2.5 | >99 | 96 | <0.018 |
| 2[d] | benzyl alcohol | 2.5 | 57 | 49 | 1.19 |
| 3 | 4-methoxybenzyl alcohol | 3 | >99 | 96 [95][e] | <0.017 |
| 4 | 4-methylbenzyl alcohol | 3 | >99 | 99 | <0.017 |
| 5 | 2-methylbenzyl alcohol | 3 | >99 | 97 | 0.048 |
| 6 | 4-chlorobenzyl alcohol | 5 | >99 | 97 | 0.68 |
|  |  | (7) | (>99) | (94) | (<0.027) |
| 7 | cinnamyl alcohol | 5 | >99 | 94 | 0.72 |
|  |  | (6) | (>99) | (91) | (0.20) |
| 8 | 1-naphthalenemethanol | 8 | >99 | 96 | 0.22 |
|  |  | (7) | (>99) | (98) | (<0.046) |
| 9 | furfuryl alcohol | 11 | >99 | 91 | 0.22 |
|  |  | 21 | >99 | 90 | <0.046 |
| 10 | 2-thiophenemethanol | 5 | >99 | 94 | <0.017 |
| 11[f] | 1-decanol | (6) | (92) | (70) | (0.44) |
| 12[g] | (±)-1-phenethanol | (21) | (>99) | (92) | (0.16) |
| 13[f,g] | 2-adamantanol | (28) | (>99) | (93) | (0.10) |

[a] Unless otherwise stated, the reactions were carried out under atmospheric pressure of $O_2$ in 0.2 mmol of alcohol. The values shown in parentheses were based on the reactions in the presence of 100 mol % of $K_2CO_3$. [b] Determined by GC analysis. [c] Determined by ICP analysis. [d] PI Ru **59** was used instead of PI Ru **90**. [e] Isolated yield is shown in square brackets. The reaction was carried out on a 1.0 mmol scale of the alcohol for 4 h. [f] Ten mole percent PI Ru **90** and 30 mol % TEMPO were used. [g] In chlorobenzene at 100 °C.

**Table 86. Recovery and Reuse of PI Ru Catalyst**



| run | time (h) | conversion (%)[b] | yield (%)[b] | leaching (%)[c] |
|---|---|---|---|---|
| first | 4 | >99 | 98 | 0.40 |
| second | 6.5 | >99 | 98 | 0.33 |
| third | 10 | >99 | 97 | 0.47 |
| fourth | 10 | >99 | 97 | 0.068 |
| fifth | 10 | >99 | 97 | 0.049 |
| sixth | 10 | >99 | 97 | <0.031 |
| seventh | 10 | >99 | 98 | <0.034 |
| eighth | 24 | >99 | 97 | 0.066 |
| ninth | 16 | >99 | 97 | 0.038 |
| tenth | 12 | >99 | 97 | <0.036 |

[a] Loading 0.376 mmol/g. [b] Determined by GC analysis. [c] Determined by ICP analysis.

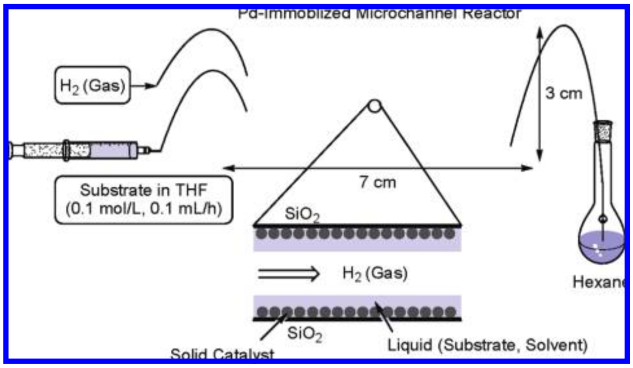


**Figure 20.** Experimental hydrogenation system using a microreactor.

mL). In addition, leaching of palladium was not detected by ICP analysis after reactions.

## 4. Polyurea-Encapsulated Catalyst (EnCat)

### 4.1. Polyurea-Encapsulated Palladium [Pd EnCat]

Another microencapsulation technology has been developed that allows effective recovery and reuse of transition metal catalysts.

Microcapsules can be prepared by an *in situ* interfacial polymerization approach,[159] which involves dispersing an organic phase containing polyfunctional monomers or oligomers (along with the material to be encapsulated) into an aqueous phase containing a mixture of emulsifiers and protective colloid stabilizers. This resulting oil-in-water emulsion undergoes *in situ* interfacial polymerization with the monomers/oligomers reacting spontaneously at the phase interface to form microcapsule walls. The permeability and size of these microcapsules and the coordinating properties of the polymer matrix may be tuned by varying the nature of monomers/oligomers, other reagents, and conditions used in the encapsulation procedure. Efficient entrapment of transition-metal based catalysts requires the design of systems possessing ligating functionality in order to retain the metal species. These systems should be physically robust and chemically inert to reaction conditions while also being cost-effective. Polyurea microcapsules[160] were found to be suitable by virtue of their chemical structure—a backbone of urea functionality—that could ligate and thus retain catalytically active metal species.

The scope and utility of $Pd(OAc)_2$ encapsulated in polyurea was investigated in a range of synthetically significant applications. Using a laboratory overhead stirrer fitted with a 50 mm rotary blade, a solution containing polymethylene polyphenylene diisocyanate (SUPRASEC 5025, average functionality of 2.7) and $Pd(OAc)_2$ in dichloroethane was dispersed at 800 rpm for 1 min into an aqueous solution of sodium lignosulfonate (Reax 100M), poly(vinyl alcohol) (Goshenol GL03) and the polyoxypropylene polyoxyethylene ether of butyl alcohol (TergitolXD). This resulted in an oil-in-water microemulsion with particle size range of 20−250

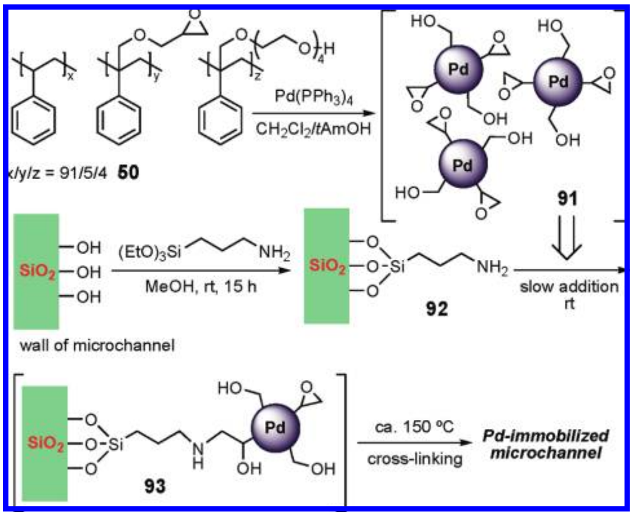
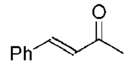
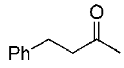
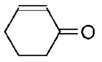
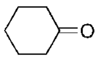
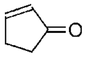
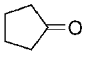
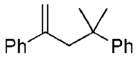
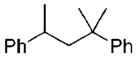
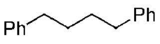
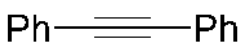
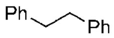
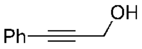
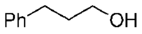
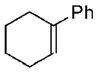
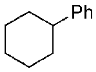
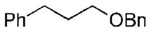
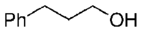
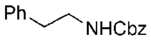
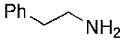
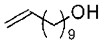
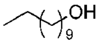
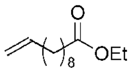
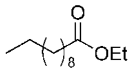
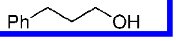
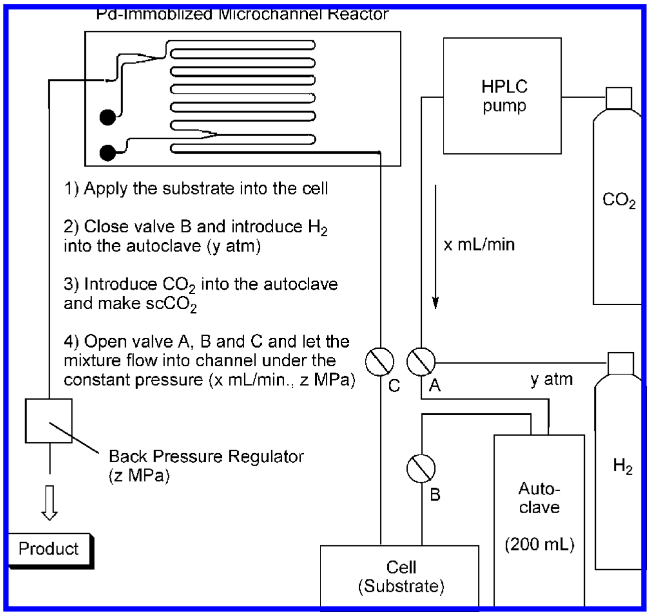


**Figure 21.** Immobilization of the Pd catalyst on the microchannel.

**Table 87. Hydrogenation Using the Pd-Immobilized Microchannel**[a]

| Entry | Substrate | Product |
|---|---|---|
| 1[b] |  |  |
| 2 |  |  |
| 3 |  |  |
| 4 |  |  |
| 5 |  |  |
| 6[c] |  |  |
| 7 |  |  |
| 8 |  |  |
| 9[d] |  |  |
| 10[d] |  |  |
| 11[e] |  |  |
| 12[e] |  |  |
| 13[f] |  |  |

[a] Unless otherwise noted, the reaction conditions were 1 mL/min $H_2$ in THF at room temperature for 2 min, and yields were quantitative (side products are noted) as determined by $^1H$ NMR. [b] Three percent 4-phenyl-2-butanol was obtained. [c] Isolated yield was 97%. [d] Ethanol was used as a solvent. Flow rate of the substrate was 0.05 mL/hr. The reaction was conducted at ca. 50 °C. Actual residence time was <1 min. [e] The reaction was conducted at ca. 50 °C. [f] Conditions were $H_2$ (2 mL/min) and 1,2-dichloroethane at ca. 50 °C.



1) Apply the substrate into the cell

2) Close valve B and introduce $H_2$ into the autoclave (y atm)

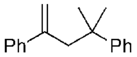
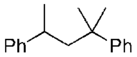
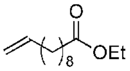
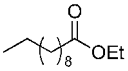
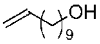
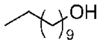
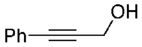
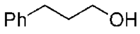
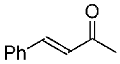
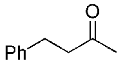
3) Introduce $CO_2$ into the autoclave and make $scCO_2$

4) Open valve A, B and C and let the mixture flow into channel under the constant pressure (x mL/min., z MPa)

**Figure 22.** System for hydrogenation reactions.

**Table 88. Hydrogenation Using the Pd-Immobilized Microchannel**[a]

$$\text{Substrate (0.20 mmol)} \xrightarrow[\substack{scCO_2\ (z = 9\ \text{MPa}),\ \text{liq. } CO_2 : y = 1.0\ \text{mL/min} \\ \text{ca. 50 °C (channel : ca. 60 °C), 2 h}}]{\substack{\text{Pd-immobilized microchannel reactor} \\ H_2\ (x = 9\ \text{atm})}} \text{Produc}$$

| Entry | Substrate | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  |  | 94 |
| 2 |  |  | 96 |
| 3 |  |  | quant |
| 4 |  |  | 91 |
| 5 |  |  | 92[b] |
| 6 |  |  | 91 |

[a] Isolated yield. [b] NMR yield.

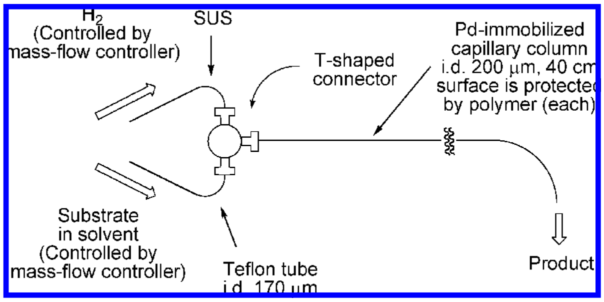
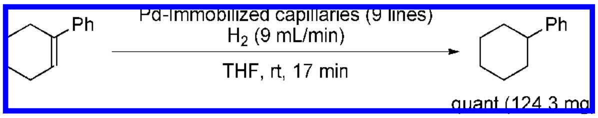


**Figure 23.** The system for the hydrogenation reaction using one Pd-immobilized capillary.

μm, which was gently shaken for 16 h. The wall-forming reaction (Scheme 55) is initiated when some of the peripheral isocyanate groups are hydrolyzed at the oil−water interface to form amines, which in turn react with other unhydrolyzed isocyanates to form a urea-linked polymeric coating resulting in insoluble and permeable polyurea microcapsules with a particle size ranging between 20−250 μm (average size 150

**Scheme 54. Hydrogenation Reaction Using Assembled Pd-Immobilized Capillaries**



**Scheme 55. Schematic Representation of the Polyurea Wall-Forming Reaction Occurring at the Oil−Water Interface**

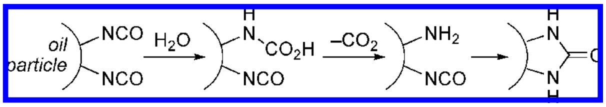
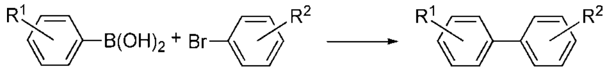


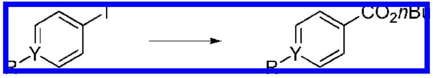
**Table 89. Cross-Coupling Reactions Using Pd EnCat**



| entry | $R^1$ | $R^2$ | yield (%)[b] |
|---|---|---|---|
| 1 | *p*-OMe | *p*-OMe | 87 |
| 2 | *p*-OMe | *p*-F | 89 |
| 3 | *p*-OMe | *p*-$NO_2$ | 91 |
| 4 | *o*-OMe | *o*-OMe | 71 |
| 5 | *p*-Ac | *p*-OMe | 84 |
| 6 | *p*-Ac | *p*-F | 90 |
| 7 | *p*-Ac | *p*-$NO_2$ | 97 |
| 8 | H | *p*-OMe | 94 |
| 9 | H | *p*-F | 93 |
| 10 | H | *p*-$NO_2$ | 97 |

[a] Pd EnCat (5 mol %), toluene−$H_2O$−EtOH (4/2/1), $K_2CO_3$, 80 °C, 6−12 h. [b] Based on isolated yield.

**Table 90. Carbonylation Reactions Using Pd EnCat**



| entry | transformation[a] | yield (%) |
|---|---|---|
| 1 | R = Me, Y = C | 89 |
| 2 | R = OMe, Y = C | 99 |
| 3 | R = COMe, Y = C | 95 |
| 4 | no R, Y = N | 93 |

[a] Pd EnCat (3 mol %), CO, *n*BuOH, $Et_3N$, 90 °C.

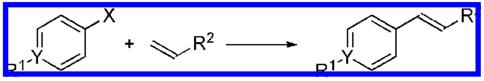
*μ*m). The microcapsules were filtered and washed several times with deionized water and a range of organic solvents and dried. According to X-ray fluorescence (XRF) and inductively coupled plasma (ICP) analysis, the average palladium content in these polyurea microcapsules (Pd EnCat) was found to be 0.4 mmol/g.

These microcapsules were tested for catalytic activity in Suzuki-type reactions involving the cross-coupling of aryl boronic acids with aryl bromides (Table 89).[161] The microcapsules were recovered by a simple filtration and reused four times without significant loss in activity, and subsequent ICP analysis of the crude product (obtained by filtration, concentration, and drying) detected palladium levels (w/w) at 13 ppm corresponding to 0.2% leaching of the original Pd content of the capsules.

Pd EnCat could also be applied to other reactions such as carbonylation reactions (Table 90), Heck reactions (Table 91) and Stille couplings (Table 92).[162]

In carbonylation, ICP analysis of the crude reaction mixture of entry 1 in Table 90 (after filtration and drying) indicated 79 ppm Pd (wt/wt), corresponding to 1% leaching of the original Pd content of the capsules.

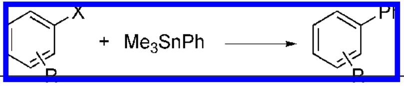
**Table 91. Heck Reactions Using Pd EnCat**



| entry | method | transformation[a] | | | | yield (%) |
|---|---|---|---|---|---|---|
| | | $R^1$ | X | Y | $R^2$ | |
| 1 | i | $NO_2$ | Br | C | $CO_2nBu$ | 91 |
| 2 | i | $NO_2$ | Br | C | Ph | 93 |
| 3 | i | | I | N | $CO_2nBu$ | 98 |
| 4 | i | OMe | Br | C | $CO_2nBu$ | 25 |
| 5 | ii | H | Br | C | $CO_2nBu$ | 99 |
| 6 | ii | OMe | Br | C | $CO_2nBu$ | 99 |
| 7 | ii | F | Br | C | $CO_2nBu$ | 75 |
| 8 | ii | $NO_2$ | Br | C | $CO_2nBu$ | 95 |
| 9 | ii | $NO_2$ | Cl | C | $CO_2nBu$ | 58 |

[a] Reagents and conditions: method i, Pd EnCat (2.5 mol %), IPA, $nBu_4NOAc$, 90 °C; method ii, $scCO_2$, Pd EnCat (0.4 mol %), $nBu_4NOAc$, 100 °C.

**Table 92. Stille Reactions Using Pd EnCat**



| entry | method | transformation[a] | | yield (%) |
|---|---|---|---|---|
| | | X | R | |
| 1 | i | Br | *p*-$NO_2$ | 99 |
| 2 | i | Br | *p*-OMe | 88 |
| 3 | i | Br | *p*-F | 82 |
| 4 | i | Br | *o*-OMe | 74 |
| 5 | ii | Br | H | 50 |
| 6 | ii | Br | *p*-OMe | 45 |
| 7 | ii | Br | *p*-$NO_2$ | >34 |
| 8 | ii | Cl | *p*-$NO_2$ | 50 |

[a] Reagents and conditions: method i, Pd EnCat (2.5 mol %), IPA−toluene (1/1), $nBu_4NOAc$, 90 °C; method ii, $scCO_2$, Pd EnCat (0.4 mol %), 100 °C.

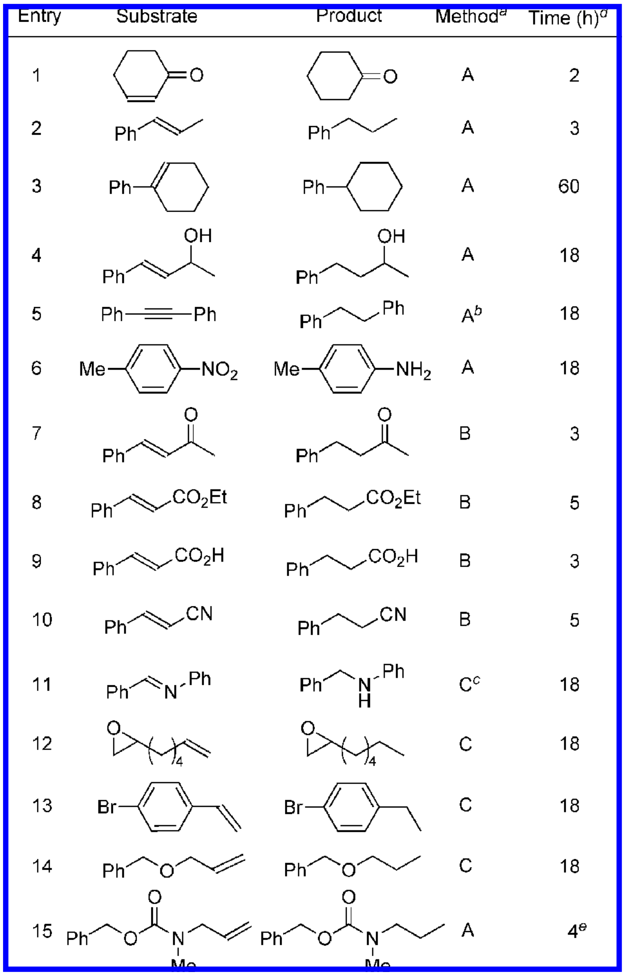
Treatment of 1-bromo-4-nitrobenzene with *n*-butyl acrylate in isopropyl alcohol in the presence of Pd EnCat (2.5 mol %) and $nBu_4NOAc$ afforded the requisite unsaturated ester in 91% yield (Table 91, entry 1). A range of substrates was treated under the same conditions to yield the products in good yields (entries 2−4). However, the reaction with 4-bromoanisole was less successful, yielding only 25% of the desired product. Under these conditions, the crude reaction mixture contained 60 ppm Pd, a loss of 2.8% of the original Pd content of the capsules.

Heck reactions were carried out in $scCO_2$ (entries 5−9). Under these conditions, yields were generally higher than those in IPA despite a lower catalyst loading.

The utility of Pd EnCat in $scCO_2$ is further demonstrated by similar Stille reactions (Table 92, entries 5−8). In these cases, however, yields are generally lower than those observed in conventional solvents.

Polyurea microcapsules containing palladium acetate (Pd EnCat) were also applied to hydrogenation reactions.[163] Pd EnCat was prereduced under $H_2$ (50 bar) for two days, and hydrogenations were then carried out with this reduced catalyst. The reactions were performed on a 1 mmol scale (with respect to substrate) using 5 mol % of prereduced Pd EnCat under an atmosphere of $H_2$ maintained by an inflated balloon or under higher pressure using an autoclave. The studies carried out revealed that these Pd microcapsules are effective in the hydrogenations of alkenes, alkynes, and imine and nitro functionalities (Table 93).

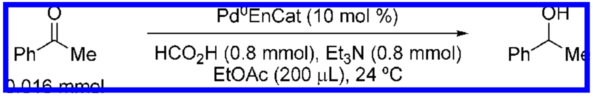
**Table 93. Hydrogenations using Pd EnCat**



| Entry | Substrate | Product | Method[a] | Time (h)[a] |
|---|---|---|---|---|
| 1 | | | A | 2 |
| 2 | | | A | 3 |
| 3 | | | A | 60 |
| 4 | | | A | 18 |
| 5 | | | A[b] | 18 |
| 6 | | | A | 18 |
| 7 | | | B | 3 |
| 8 | | | B | 5 |
| 9 | | | B | 3 |
| 10 | | | B | 5 |
| 11 | | | C[c] | 18 |
| 12 | | | C | 18 |
| 13 | | | C | 18 |
| 14 | | | C | 18 |
| 15 | | | A | 4[e] |

[a] Conditions: method A, Pd EnCat (5 mol %), EtOH, rt, $H_2$ (balloon); method B, Pd EnCat (5 mol %), EtOH−MeCN (1/1), 60 °C, $H_2$ (balloon); method C, Pd EnCat (5 mol %), EtOH, rt, $H_2$ (50 bar). [b] EtOH−-MeCN (1/1) was used as solvent. [c] MeCN was used as solvent. [d] Complete conversion to products was observed by GC or LCMS. [e] 93% Yield plus 7% cleavage prouct.

**Table 94. Recycling Experiment**



| run | first | second | third | fourth | fifth |
|---|---|---|---|---|---|
| yield (%) | 99 | 98 | 98 | 97 | 96 |
| time (h) | 21 | 22 | 24 | 26 | 28 |

Transfer hydrogenation was also carried out by using formic acid and triethylamine.[164] After several investigations, it was found that better performance in terms of reactivity and stability of the polyurea-encapsulated Pd(0) ($Pd^0$ EnCat) prepared from Pd EnCat was achieved by using HCOOH and $Et_3N$ in the molar ratio of 1:1 (instead of 5:2 used conventionally for other catalysts). The stability of the catalyst was further improved by adding ethyl acetate.

The efficiency and stability of the newly established catalytic system was examined in detail with acetophenone as a substrate. Reduction proceeds to completion giving excellent isolated yields through five successive recycle runs (Table 94). Interestingly, no traces of methylene compounds from further hydrogenolysis or products from the over-reduction of the aromatic ring were detected by either NMR or GC. A clear advantage of this catalyst over Pd/C was also noticed when propiophenone was reduced using 10% Pd/C under otherwise identical conditions (Scheme 56).

**Scheme 56. Transfer Hydrogenation of Propiophenone**

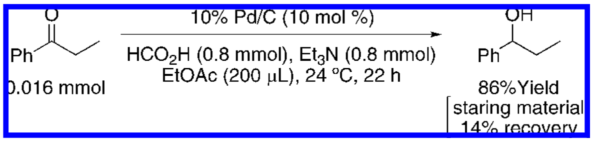
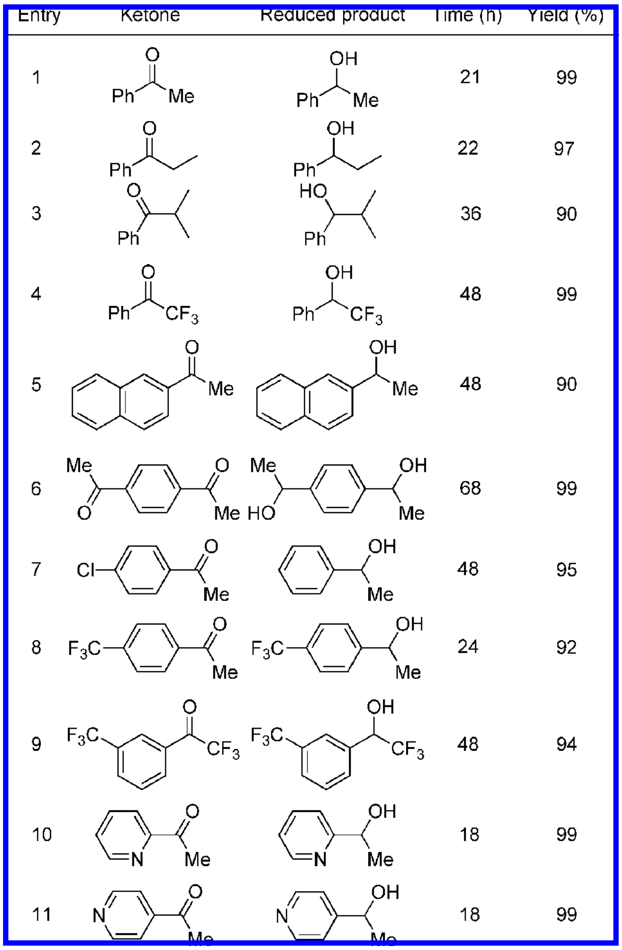


**Table 95. Reduction of Aromatic Ketones Using $Pd^0$ EnCat/$HCO_2H/Et_3N$[a]**



| Entry | Ketone | Reduced product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | | | 21 | 99 |
| 2 | | | 22 | 97 |
| 3 | | | 36 | 90 |
| 4 | | | 48 | 99 |
| 5 | | | 48 | 90 |
| 6 | | | 68 | 99 |
| 7 | | | 48 | 95 |
| 8 | | | 24 | 92 |
| 9 | | | 48 | 94 |
| 10 | | | 18 | 99 |
| 11 | | | 18 | 99 |

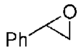
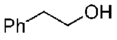
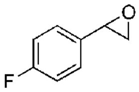
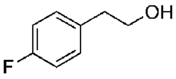
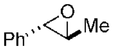
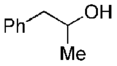
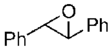
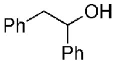
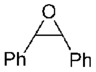
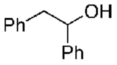
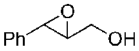
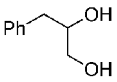
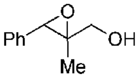
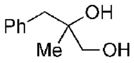
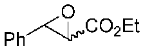
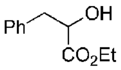
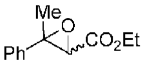
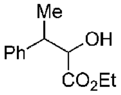
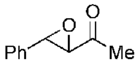
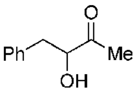
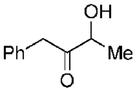
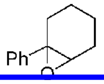
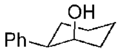
[a] Reagents and conditions: $Pd^0$ EnCat (10 mol %), EtOAc (200 μL), $HCO_2H$ (0.8 mmol), $Et_3N$ (0.8 mmol), ketone (0.016 mmol), 24 °C. Catalyst was reused for 5 times.

The newly prepared catalyst ($Pd^0$ EnCat) is clearly more reactive than Pd/C with higher conversion within the same reaction time (Table 95).

A variety of benzylic epoxides were subjected to the same hydrogenolysis conditions, and good yields of the homobenzylic alcohol were consistently obtained (Table 96).[165]

The regioselective reduction of terminal epoxides is a particularly attractive synthetic route to substituted alcohols due to the recent advances in the area of catalytic epoxidation of terminal olefins. To further expand the scope of this catalytic system, epoxyalkane substrates were investigated. The hydrogenolysis of 3-phenylepoxypropane was very slow under transfer hydrogenation conditions. However, a very encouraging result was obtained by using the same catalyst (preformed by the reduction with $HCO_2H$) under conven-

**Table 96. Pd$^0$ EnCat-Catalyzed Hydrogenolysis of Benzylic Epoxides**[a]

| Entry | Substrate | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 4 | 84 |
| 2 |  |  | 24 | 82 |
| 3 |  |  | 3 | 90 |
| 4 |  |  | 5 | 99 |
| 5 |  |  | 5 | 93 |
| 6 |  |  | 5 | 95 |
| 7 |  |  | 3 | 93 |
| 8 |  |  | 13 | 92 |
| 9 |  |  | 24 | 94 |
| 10 |  |  6<br>:<br> 1 | 6 | 87 |
| 11 |  |  | 7 | 84 |

[a] Reagents and conditions: Pd$^0$ EnCat (5 mol %), $HCO_2H$ (4 equiv), $Et_3N$ (4 equiv), EtOAc, 23 °C.

**Scheme 57. Hydrogenolysis of 3-Phenylepoxypropane**

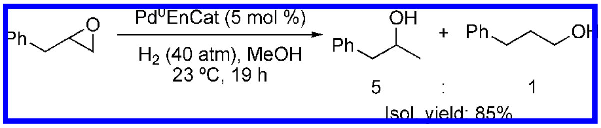
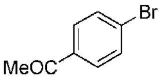
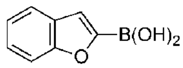
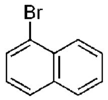
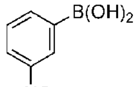
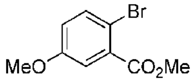
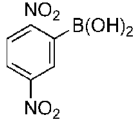
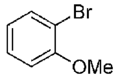
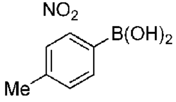
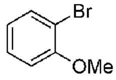
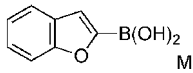
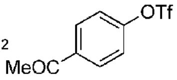
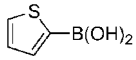
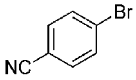
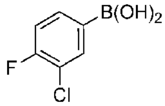
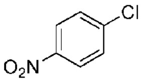
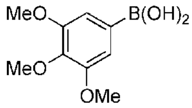
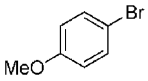
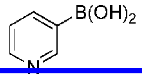
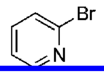
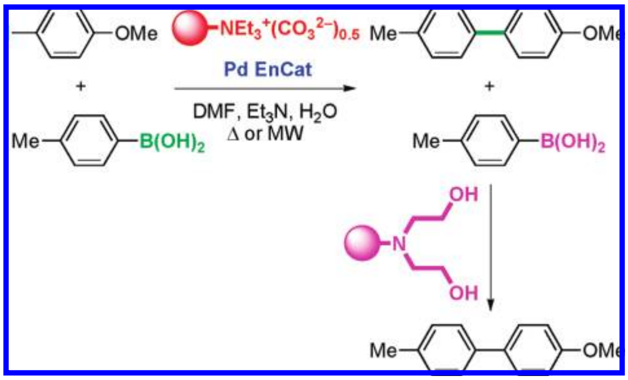


**Table 97. Sequential Processing of Multiple Substrates in Flow**[a]

| Entry | Boronic acid | Halide | Yield (%)[b] [Purity (%)[c]] | |
|---|---|---|---|---|
| | | | Bach[d] | Flow[e] |
| 1 | $PhB(OH)_2$ |  | 88 [>98] | 90 [>98] |
| 2 |  |  | 84 [82] | 87 [>98] |
| 3 |  |  | 94 [64] | 94 [>98] |
| 4 |  |  | 94 [54] | 92 [92] |
| 5 |  |  | 70 [40] | 88 [94] |
| 6 |  |  | 100 [30] | 97 [91] |
| 7 |  |  | 72 [26] | 76 [>98] |
| 8 |  |  | 82 [23] | 89 [>98] |
| 9 |  |  | 92 [16] | 94 [91] |
| 10 |  |  | 81 [<10] | 95 [82] |

[a] Reagents and conditions: halide (1 equiv), boronic acid (1 equiv), $Bu_4NOAc$ (2 equiv) in EtOH, Pd EnCat, EtOH, microwave irradiation. [b] Isolated yield. [c] Purity measured by LC-MS and $^1H$ NMR spectroscopy. [d] 120 °C, 10 min. [e] Flow rate 0.1 mL/min, 50 W with external cooling.

**Scheme 58. Polymer-Assisted Solution-Phase (PASP) Approach**

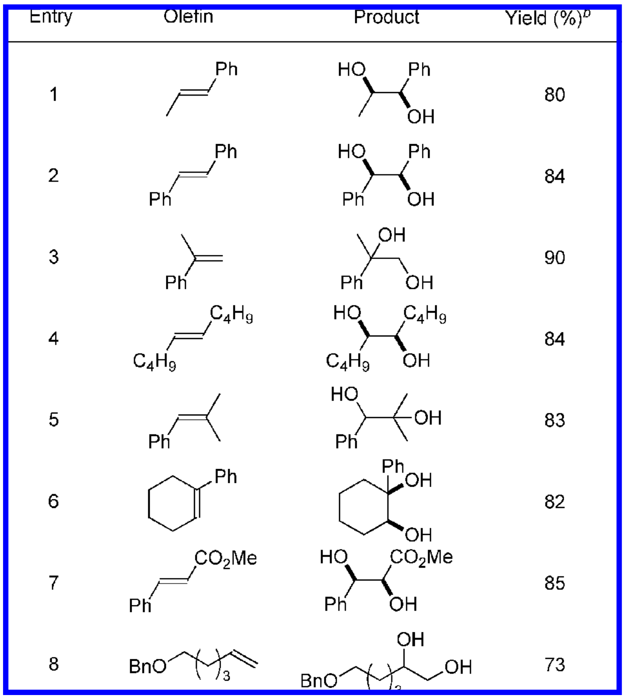


tional hydrogenation conditions (Pd$^0$ EnCat/$H_2$/methanol), suggesting that the application of this catalytic system may be extended to a wider range of epoxides (Scheme 57).

The catalyst was further applied to microwave-assisted Suzuki coupling reactions.[166] The catalyst system is highly efficient when used in conjunction with microwave heating, showing enhanced reactivity and a prolonged lifetime. A small library of biaryl compounds has been generated in a relatively short period of time by this approach. Furthermore, the yields and product purities were dramatically improved when simultaneous cooling was employed as microwave energy was supplied to the reaction system (Table 97).

Finally, a practical protocol for performing Suzuki coupling reactions was developed. A combination of polymer-supported reagents afforded biaryls in excellent yields and purities without the need for purification, either by aqueous workup or by column chromatography (Scheme 58). More recently, the PdA1qEn hybrid catalyst was developed, in which palladium nanoparticles were stabilized and encapsulated in combination of polyurea and an ionic liquid (Aliquat 336). This novel composite material is used as a recyclable and robust catalyst in hydrogenation reaction.[167]

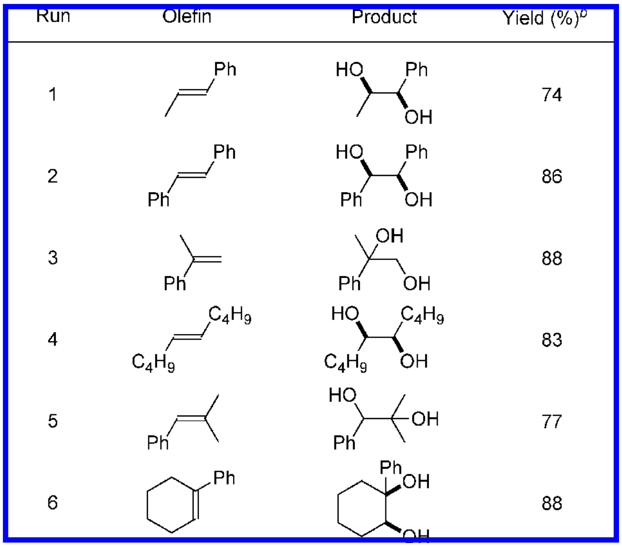
**Table 98. Dihydroxylations of Olefins Using Os EnCat**[a]



| Entry | Olefin | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | | | 80 |
| 2 | | | 84 |
| 3 | | | 90 |
| 4 | | | 84 |
| 5 | | | 83 |
| 6 | | | 82 |
| 7 | | | 85 |
| 8 | | | 73 |

[a] Reagents and conditions: Os EnCat (5 mol %), NMO, acetone$-$H$_2$O (10/1), rt, 12$-$24 h. [b] Based on isolated yields.

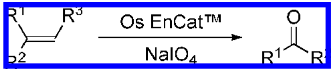
**Table 99. Recycling Experment with Os EnCat**[a]



| Run | Olefin | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | | | 74 |
| 2 | | | 86 |
| 3 | | | 88 |
| 4 | | | 83 |
| 5 | | | 77 |
| 6 | | | 88 |

[a] Reagents and conditions: Os EnCat (5 mol %), NMO, acetone$-$H$_2$O (10/1), rt, 12$-$24 h. [b] Based on isolated yields.

**Table 100. Oxidative Cleavage of Olefins Using Os EnCat**[a]



| entry | $R^1$ | $R^2$ | $R^3$ | yield (%) |
|---|---|---|---|---|
| 1 | $n$-$C_6H_{13}$ | H | H | 66[b] (100)[c] |
| 2 | Ph | H | H | 92[b] |
| 3 | Ph | H | Me | 79 |
| 4 | H | Ph | Ph | 99 |
| 5 | Ph | H | Ph | 98[b] |
| 6 | Ph | H | $CO_2Me$ | 95[b] |
| 7 | $n$-$C_6H_{13}$ | H | $n$-$C_6H_{13}$ | 55[b] (100)[c] |
| 8 | Ph | Ph | H | 99[b] |

[a] Reagents and conditions: Os EnCat (2 mol %), NaIO$_4$ (3 equiv), THF$-$H$_2$O (2/1), rt, 1$-$8 h. [b] Isolated and identified as the phenyl hydrazone. [c] GC yield. [d] Isolated yield of the alcohol formed upon treatment of crude product with PhMgBr.

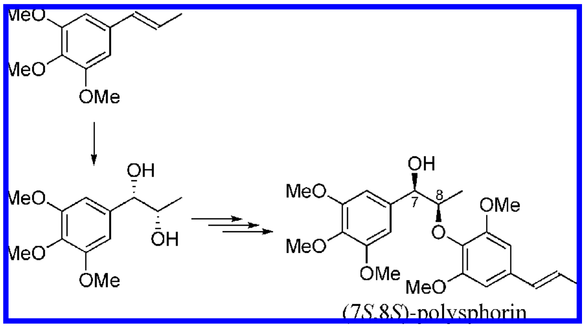


**Figure 24.** Synthesis of the antimalarial natural product polysphorin.

## 4.2. Polyurea-Encapsulated Osmium Tetroxide [Os EnCat]

Immobilization of osmium tetroxide was also investigated in a polyurea matrix using an *in situ* interfacial polymerization approach.[168] These microcapsules (Os EnCat) have been effectively used in the dihydroxylation of olefins (Table 98).

The microcapsules were recovered by simple filtration and reused five times, showing no significant loss of activity. (Table 99).

Osmium tetroxide is used as a catalyst for the generation of carbonyl compounds from olefins by oxidative cleavage of the formed glycols using sodium periodate (NaIO$_4$). This has also been carried out using Os EnCat. Treatment of a range of olefins with Os EnCat (2 mol %) and NaIO$_4$ (3 equiv) in THF$-$H$_2$O (2/1) gave the required carbonyl compounds in good yields (Table 100). Os EnCat was easily recovered by simple filtration and reused several times.

Asymmetric dihydroxylation using Os EnCat was investigated for development of a general asymmetric route to both enantiomers of polysphorin (Figure 24).[169]

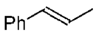
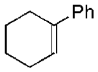
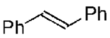
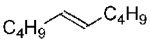
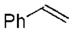
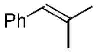
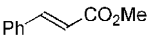
Optimization studies using Os EnCat with *trans*-$\beta$-methylstyrene showed that the best yield and ee were obtained using 5 mol % of the catalyst in THF$-$water. Eight substrates were screened successfully under the optimized conditions (Table 101).

Experiments were also conducted with *trans*-$\beta$-methylstyrene to test catalyst recycling, and the reactions proceeded in near quantitative yields with no drop of ee’s over the first three runs. However, in the fourth cycle, the yield dropped dramatically to 19%, indicating that the recycling of the Os EnCat was not consistently reproducible for the asymmetric application. Similar observations were encountered while conducting experiments using (DHQD)$_2$PHAL and NMO in acetone$-$water (10/1) solvent system.

## 5. Conclusion and Perspective

New types of polymer-supported catalysts, microencapsulated and related catalysts, have been discussed.[170] The catalysts were developed based on the 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

**Table 101. Asymmetric Dihydroxylations Using Os EnCat**[a]

| Olefin | Yield (%, isolated) | *ee* (%)[b] |
|---|---|---|
|  | 97–99 | 94 |
|  | 91 | 97 |
|  | 88 | >99 |
|  | 97 | 90 |
|  | 96 | 82 |
|  | 89 | 87 |
|  | 94 | >99 |
|  | 83 | 51 |

[a] Reagents and conditions: Os EnCat (5 mol %), $(DHQD)_2PHAL$ (5 mol %), $MeSO_2NH_2$ (1 equiv), $K_3Fe(CN)_6$ (3 equiv), $K_2CO_3$ (3 equiv), THF−$H_2O$ (1/1), rt, 24−48 h. [b] Determined by $^1H$ NMR analysis of the bis-Mosher ester.

polymer backbones and vacant orbitals. The catalysts thus prepared are effective in many useful organic reactions. In most cases, the catalysts are recovered quantitatively by simple filtration and reused without loss of activity. The catalysts have comparable activities to homogeneous catalysts in many cases, and sometimes even higher activities.

While many catalysts have been immobilized by using these new techniques, mechanistic aspects, including immobilization and catalytic activity, have not been clarified yet. On the other hand, applications of these catalysts to flow systems are promising, and some industrial trials have already started. It is expected that many other catalysts can be immobilized using these techniques and that these catalysts can contribute to environmentally benign and powerful high-throughput organic synthesis.

## 6. Note Added after Print Publication

During the publication of this manuscript, the Publisher inadvertently published Figure 16 as both Figure 16 and Figure 19. The electronic version of this paper has been updated to reflect the correct figures.

## 7. References

(1) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (b) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
(2) (a) *Handbook of Heterogeneous Catalysis*; Ertl, G., Knötzinger, H., Weitkamp, J., Eds.; Verlag Chemie: Weinheim, Germany, 1997; Vol. 5. (b) Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557. (c) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.
(3) (a) Parshall, G. W.; Ittle, S. D. *Homogeneous Catalysis*; Wiley: New York, 1992. (b) *Applied Homogeneous Catalysis by Organometallic Complexes*; Cornils, B., Herrmann, W. A., Eds.; Verlag Chemie: Weinheim, Germany, 1996.
(4) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985.
(5) Donbrow, M. *Microcapsules and Nanoparticles in Medicine and Pharmacy*; CRC Press: Boca Raton, FL, 1992.
(6) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.
(7) (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (c) Kobayashi, S *Synlett* **1994**, 689. For selected examples, see: (d) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (e) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195. (f) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115. (g) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049. (h) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773. (i) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423. (j) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472. (k) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958. (l) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.
(8) Steric factors (physical envelopment) would also contribute the remarkable immobilizing ability of polystyrene compared with poor immobilization of polybutadiene and polyethylene.
(9) Rossini, A. J.; Schurko, R. W. *J. Am. Chem. Soc.* **2006**, *128*, 10391.
(10) (a) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
(11) For leading references on Friedel−Crafts acylation, see: (a) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 733. (c) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, p 293. (d) Kobayashi, S.; Komoto, I.; Matsuo, J.-i. *Adv. Synth. Catal.* **2001**, *343*, 71.
(12) Suzuki, T.; Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2000**, *41*, 8903.
(13) Schager, F.; Bonrath, W. *Appl. Catal. A: Gen.* **2002**, *202*, 117.
(14) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 902.
(15) (a) Choudary, B. M.; Sridhar, Ch.; Sateesh, M.; Sreedhar, B. *J. Mol. Catal. A: Chem.* **2004**, *212*, 237. (b) Sreedhar, B.; Swapna, V.; Sridhar, Ch. *Catal. Commun.* **2005**, *6*, 293.
(16) Asponall, H. C.; Greeves, N.; Mclver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283.
(17) Choudary, B. M.; Chidara, S.; Raja Sekhar, C. H. V. *Synlett* **2002**, 1694.
(18) (a) Schötertder, M. *Chem. Rev.* **1980**, *80*, 187. (b) Singh, H. S. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., Ed. Plenum: New York. 1986, Chapter12. (c) Haines, A. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 10, p 437.
(19) (a) Cainelli, G.; Contento, M.; Manescalahi, F.; Plessi, L. *Synthesis* **1989**, 45. (b) Herrmann, W. A.; Kratzer, R. M.; Blumel, J.; Friedrich, H. B.; Fischer, R. W.; Apperley, D. C.; Mink, J.; Berkesi, O. *J. Mol. Catal. A: Chem.* **1997**, *120*, 197.
(20) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.
(21) (a) Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (c) Kikuchi, H.; Saito, Y.; Komiya, J.; Takaya, Y.; Honma, S.; Nakahata, N.; Ito, A.; Oshima, Y. *J. Org. Chem.* **2001**, *66*, 6982. (d) Yamashita, M.; Ohta, N.; Kawasaki, I.; Ohta, S. *Org. Lett.* **2001**, *3*, 1359. (e) Nakamura, Y.; Matsubara, R.; Kitagawa, H.; Kobayashi, S.; Kumagai, K.; Yasuda, S.; Hanada, K. *J. Med. Chem.* **2003**, *46*, 3688.
(22) Aoki, S.; Matsui, K.; Tanaka, K.; Satari, R.; Kobayashi, M. *Tetrahedron* **2000**, *56*, 9945.
(23) For reviews, see: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, *21*, 1. (c) Salvsdori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181.
(24) (a) Lee, H. M.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1537. (b) Motorina, I.; Crudden, C. M. *Org. Lett.* **2001**, *3*, 2325. (c) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kumar, N. S.; Kantam, M. L. *Chem. Commun.* **2002**, 586.
(25) Since amine ligands coordinate to osmium under equilibrium conditions, recovery of the osmium using polymer-supported ligands is generally difficult.
(26) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229.
(27) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
(28) The usefulness of the SR-MAS NMR technique for structure determination of resins directly without cleavage from polymer supports has been demonstrated through the development of several useful reactions using the cross-linked polystyrene-based resins in the solid-phase in our laboratories: (a) Kobayashi, S.; Akiyama, R.; Furuta, T.; Moriwaki, M. *Mol. Online* **1998**, *2*, 35. (b) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345. (c) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211. (d) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341. (e) Aoki, Y.; Kobayashi, S. *J. Comb. Chem.* **1999**,

*1*, 371. (f) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143. (g) Kobayashi, S.; Akiyama, R.; Kitagawa, H. *J. Comb. Chem.* **2000**, *2*, 438. (h) Kobayashi, S.; Akiyama, R.; Kitagawa, H. *J. Comb. Chem.* **2001**, *3*, 196.

(29) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649.

(30) Recently, osmium tetroxide was immobilized onto a silica-anchored tetrasubstituted olefin or by an ion-exchange technique: (a) Sevrens, A.; De Vos, D. E.; Fiermans, L.; Verpoort, F.; Grobet, P. J.; Jacobs, P. A *Angew. Chem., Int. Ed.* **2001**, *40*, 586. (b) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 5341.

(31) (a) *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueoous Media*; John Wiley & Sons: New York, 1997.

(32) (a) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H *Tetrahedron Lett.* **1997**, *38*, 4559. (b) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389. (c) Manabe, K.; Kobayashi, S. *Synlett* **1999**, 547. (d) Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3773. (e) Kobayashi, S.; Mori, Y.; Nagayama, S.; Manabe, K. *Green Chem.* **1999**, 175. (f) Manabe, K.; Mori, Y.; Nagayama, S.; Odashima, K.; Kobayashi, S. *Inorg. Chim. Acta* **1999**, *298*, 158. (g) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **1999**, *55*, 11203. (h) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *112*, 7202. (i) Mori, Y.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2815. (j) Kokubo, M.; Ogawa, C.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6909.

(33) (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545. (b) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (c) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (d) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.

(34) (a) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19. (c) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669. (d) Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107. (e) Kobayashi, S.; Lam, W.-L.; Manabe, K. *Tetrahedron Lett.* **2000**, *41*, 6115. (f) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174. (g) Kobayashi, S.; Kakumto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* **2001**, *41*, 247. (h) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593. (i) Ogawa, C.; Azoulay, S.; Kobayashi, S. *Heterocycles* **2005**, *66*, 201. (j) Boudou, M.; Ogawa, C.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 2585. (k) Aoyama, S.; Kobayashi, S. *Chem. Lett.* **2006**, *35*, 238. (l) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311. (m) Nagano, T.; Kobayashi, S. *Chem. Lett.* **2008**, 1042.

(35) Ishida, T.; Akiyama, R.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 576.

(36) Ishida, T.; Akiyama, R.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1189.

(37) Reddy, S. M.; Srinivasulu, M.; Reddy, Y. V.; Narasimhulu, M.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 5285.

(38) Lattanzi, A.; Leadbeater, N. E. *Org. Lett.* **2002**, *4*, 1519.

(39) (a) Saladino, R.; Neri, V.; Pellicia, A. R.; Caminiti, R.; Saduo, C. *J. Org. Chem.* **2002**, *67*, 1323. (b) Saladino, R.; Neri, V.; Mincione, E.; Filippone, P. *Tetrahedron* **2002**, *58*, 8493. (c) Saladino, R.; Mincione, E.; Attanasi, O. A.; Filippone, P. *Pure Appl. Chem.* **2003**, *75*, 265. (d) Saladino, R.; Andreoni, A.; Neri, V.; Crestini, C. *Tetrahedron* **2005**, *61*, 1069. (e) Bianchini, G.; Crucinanelli, M.; Crestini, C.; Saladino, R. *Top. Catal.* **2006**, *40*, 221.

(40) (a) Kantam, M. L.; Kavita, B.; Neeraja, V.; Haritha, Y.; Chaudhuri, M. K.; Dehury, S. K. *Tetrahedron Lett.* **2003**, *44*, 9029. (b) Kantam, M. L.; Kavita, B.; Neeraja, V.; Haritha, Y.; Chaudhuri, M. K.; Dehury, S. K. *Adv. Synth. Catal.* **2005**, *347*, 641.

(41) Reviews:(a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Tuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons: Chichester, U.K., 1995. (c) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (e) Poli, G.; Giambastiant, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (f) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley and Sons: New York, 2002. (g) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.

(42) (a) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (b) Bergbreiter, D. E.; Chen, B.; Lynch, T. J. *J. Org. Chem.* **1983**, *48*, 4179. (c) Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1989**, *54*, 2726. (d) Bergbreiter, D. E.; Chen, B.; Weatherford, D. A. *J. Mol. Catal.* **1992**, *74*, 409. (e) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112. (f) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940.

(43) Recently, some excellent polymer-supported palladium catalysts for allylic substitution have been reported: (a) Uozumi, Y.; Danjo, H.; Hayashi, T *Tetrahedron Lett.* **1997**, *38*, 3557. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303. (c) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y *Tetrahedron* **1999**, *55*, 14341. Also for Suzuki coupling: (d) Jang, S.-B. *Tetrahedron Lett.* **1997**, *38*, 1793. (e) Fenger, I.; Drian, C. L *Tetrahedron Lett.* **1998**, *39*, 4287. For using biphasic systems: (f) Bergbreiter, D. E.; Liu, Y. S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 4250. (g) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y. S. *J. Am. Chem. Soc.* **1999**, *121*, 9531. (h) Chechik, V.; Crooks, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1243. (i) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M *J. Am. Chem. Soc.* **2000**, *122*, 9058.

(44) (a) Pittman, C. U.; Wuu, S. K.; Jacobson, S. E. *J. Catal.* **1976**, *44*, 87. (b) Pittman, C. U., Jr.; Ng, Q. *J. Organomet. Chem.* **1978**, *153*, 85.

(45) (a) Bruner, H.; Bailar, J. C *Inorg. Chem.* **1973**, *12*, 1465. (b) Terasawa, M.; Kaneda, K.; Imanaka, T.; Teranishi, S. *J. Catal.* **1978**, *51*, 406. (c) Kaneda, K.; Terasawa, M.; Imanaka, T.; Teranishi, S. *Fundam. Res. Homogeneous Catal.* **1973**, *3*, 671. (d) Baralt, E.; Holy, N. *J. Org. Chem.* **1984**, *49*, 2626. (e) Bar-Sela, G.; Warshawsky, A. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 1303. (f) Mani, R.; Mahadevan, V.; Srinvasan, M. *React. Polym.* **1991**, *14*, 263. (g) Zhang, Y.; Liao, S.; Xu, Y. *Tetrahedron Lett.* **1994**, *35*, 4599. (h) Selvaraj, P. C.; Mahadevan, V.; Srinvasan, M. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 105. (i) Card, R. J.; Liesner, C. E.; Neckers, D. C. *J. Org. Chem.* **1979**, *44*, 1095.

(46) (a) Card, R. J.; Neckers, D. C. *J. Org. Chem.* **1978**, *43*, 2958. (b) King, R. B.; Hanse, R. M. *J. Org. Chem.* **1979**, *44*, 1092.

(47) Kaneda, K.; Kurosaki, H.; Terasawa, M.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1981**, *46*, 2356.

(48) Uozumi, Y.; Danjo, H.; Hayashi, T *J. Org. Chem.* **1999**, *64*, 3384.

(49) (a) Terasawa, M.; Kaneda, K.; Imanaka, T.; Teranishi, S. *J. Organomet. Chem.* **1978**, *162*, 403. (b) Andersson, C.-M.; Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3891. (c) Zhang, Z. Y.; Hu, H. W.; Kao, T. Y. *React. Polym., Ion Exch. Solvents* **1988**, *9*, 249. (d) Zhang, Z. Y.; Pan, Y.; Hu, H. W.; Kao, T. Y. *Synth. Commun.* **1990**, *20*, 3563. (e) Jang, S.-B. *Tetrahedron Lett.* **1997**, *3*, 4421.

(50) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3469.

(51) For reviews, see: (a) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 91. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 49. (f) *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Miley: West Sussex, UK, 2002. (g) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (h) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (i) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1995. (j) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(52) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coate, S. W. *Tetrahedron Lett.* **1993**, *34*, 3149.

(53) He, H. S.; Yan, J. J.; Shen, R.; Zhuo, S.; Toy, P. H. *Synlett* **2006**, 563.

(54) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Jiang, Y.; Jiang, Q.; Zhang, X. J. *J. Am. Chem. Soc.* **1998**, *120*, 3817.

(55) (a) Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. A. *Chem. Commun.* **1997**, 1352. (b) Carmona, D.; Cativiela, C.; Elipe, S.; Lahoz, F. J.; Lamata, M. P.; Víu, M. P. L.-R.; Oro, L. A.; Vega, C.; Viguri, F. *Chem. Commun.* **1997**, 2352.

(56) (a) Simal, F.; Demonceau, A.; Noels, A. F *Tetrahedron Lett.* **1998**, *39*, 3493. (b) Simal, F.; Dominique, J.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett.* **1999**, *40*, 1653.

(57) Neveaux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.

(58) Craig, A. M.; Malinda, E. P. *J. Am. Chem. Soc.* **1996**, *118*, 11319.

(59) For ring-closing olefin metathesis, see: (a) Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758. (b) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315. (c) Fürstner, A.; Liebl, M.; Lehmann, C. W.; Picquet, M.; Kunz, R.; Bruneau, C.; Touchard, D.; Dixneuf, P. H. *Chem.—Eur. J.* **2000**, *6*, 1847. For ring-opening metathesis polymerization, see: (d) Hafner, A.; Mühlebach, A.; van der Schaaf, P. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2121. (e) Demonceau, A.; Stumpf, A. W.; Saive, E.; Noels, A. F. *Macromolecules* **1997**, *30*, 3127.

(60) For ring-closing olefin metathesis, see: (a) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657. (b) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896. (c) Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898. (d) Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.;

Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4251. For asymmetric hydrogenation, see: (e) Fan, Q. H.; Ren, C. Y.; Yeung, C. H.; Hu, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **1999**, *121*, 7407. (f) Ohkuma, T.; Takeno, H.; Noyori, R. *Adv. Synth. Catal.* **2001**, *343*, 369. (g) Fan, Q. H.; Deng, G. J.; Lin, C. C.; Chan, A. S. C *Tetrahedron: Asymmetry* **2001**, *12*, 1241. For other reactions, see: (h) Leadbeater, N. E.; Scott, K. A.; Scott, L. J. *J. Org. Chem.* **2000**, *65*, 3231. (i) Leadbeater, N. E. *J. Org. Chem.* **2001**, *66*, 2168.

(61) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

(62) Therrien, B.; Ward, T. R.; Pilkington, M.; Hoffmann, C.; Gilardoni, F.; Weber, J. *Organometallics* **1998**, *17*, 330.

(63) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2002**, *42*, 2602.

(64) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.—Eur. J.* **2001**, *7*, 4811.

(65) Gibson, S. E.; Swamy, V. M. *Adv. Synth. Catal.* **2002**, *344*, 619.

(66) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A. *Tetrahedron* **2005**, *61*, 12107.

(67) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412.

(68) (a) Cram, D. J. *Nature* **1992**, *356*, 29. (b) Cram, D. J. *Science* **1983**, *219*, 1177. We are grateful to Professor Craig A. Merlic (UCLA) for his suggestion of this term. .

(69) (a) Trimm, D. L. *Design of Industrial Catalysts*; Elsevier: Amsterdam, 1980. (b) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985. (c) Satterfield, C. N. *Heterogeneous Catalysis in Industrial Practice*, 2nd ed.; McGraw-Hill: New York, 1991.

(70) Hydrogenation did not proceed at all using a polystyrene-based microencapsulated palladium catalyst.[50]

(71) (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (c) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

(72) Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* **2004**, *6*, 1987.

(73) Nishio, R.; Wessely, S.; Sugiura, M.; Kobayashi, S. *J. Comb. Chem.* **2006**, *8*, 459.

(74) (a) Fujiwara, M.; Okamoto, M.; Okamoto, M.; Watanabe, M.; Machida, H.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. *Antiviral Res.* **1999**, *43*, 189. (b) Akanitapichat, P.; Bastow, K. F. *Antiviral Res.* **2002**, *53*, 113.

(75) (a) Faller, T.; Hutton, K.; Okafo, G.; Gribble, A.; Camilleri, P.; Games, D. E. *Chem. Commun.* **1997**, 1529. (b) Bahr, N.; Tierney, E.; Reymond, J.-L. *Tetrahedron Lett.* **1997**, *38*, 1489.

(76) (a) Tabarrini, O.; Cecchetti, V.; Fravolini, A.; Nocentini, G.; Barzi, A.; Sabatini, S.; Miao, H.; Sissi, C. *J. Med. Chem.* **1999**, *42*, 2136. (b) Dzierzbicka, K.; Kolodziejczyk, A. M.; Wysocka-Skrzela, B.; Mysliwski, A.; Sosnowska, D. *J. Med. Chem.* **2001**, *44*, 3606. (c) Antonini, I. *Curr. Med. Chem.* **2002**, *9*, 1701. (d) Dzierbicka, K.; Kolodziejczyk, A. M. *J. Med. Chem.* **2003**, *46*, 183.

(77) Albert, A. *The Acridines*, 2nd ed.; Edward Arnold Publishing Ltd.: London, 1966.

(78) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (c) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

(79) (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (e) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820. (f) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.

(80) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871.

(81) (a) Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H. *Arzneim.-Forsch.* **1990**, *40*, 37. (b) Sugiyama, Y.; Taketomi, S.; Shimura, Y.; Sohda, T.; Meguro, K.; Fujita, T. *Arzneimforsch./Drug Res.* **1990**, *40*, 253. (c) Sugiyama, Y.; Shimura, Y.; Ikeda, H. *Arzneimforsch./Drug Res.* **1990**, *40*, 436.

(82) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Shoda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.

(83) Active homogeneous ruthenium catalysts for HDS have been reported. (a) Borowski, F. A.; Sabo-Etienne, S.; Donnadieu, B.; Chaudret, B *Organometallics* **2003**, *22*, 4803. (b) Bianchini, C.; Meli, A.; Moneti, S.; Oberhauser, W.; Vizza, F.; Herrera, V.; Fuentes, A.; Sanchez-Delgado, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 7071. (c) Rojas, I.; L.; Linares, F.; Valencia, N.; Bianchini, C *J. Mol. Catal.* **1999**, *144*, 1.

(84) (a) Topsøe, H.; Clause, B. S.; Massoth, F. E. *Hydrotreating Catalysis*; Springer-Verlag: Berlin, 1996. (b) Scherzer, J.; Gruia, A. J. *Hydrocracking Science and Technology*; Marcel Dekker: New York, 1996. (c) Gates, B. C. *Catalytic Chemistry*; John Wiley: New York, 1992; Chapter 5, p 390. (d) Whitehurst, D. D.; Isoda, T.; Mochida, I. *Adv. Catal.* **1998**, *42*, 345. (e) van den Berg, J. P.; Lucien, J. P.; Germaine, G.; Thielemans, G. L. B. *Fuel Process. Technol.* **1993**, *35*, 119. (f) Prins, R.; de Beer, V. H. J.; Somorjai, G. A. *Catal. Rev.-Sci. Eng.* **1989**, *31*, 1.

(85) It was confirmed that catalytic activity of **39** was higher than that of Pd/C: 5% Pd/C gave the reduced product in 14% yield; 54% yield was obtained using PI Pd **39** under the same conditions (10 atm, 140 °C for 24 h in THF).

(86) Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4831.

(87) Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 992.

(88) Review: Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010.

(89) Wakamatsu, H.; Uda, J.; Yamakami, N. *J. Chem. Soc., Chem. Commun.* **1971**, 1540.

(90) Beller, M.; Eckert, M.; Vollmüller, F.; Bogdanovic, S.; Geissler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1494.

(91) Drauz, K.; Burkhardt, O.; Beller, M.; Eckert, M. German Patent DE 100 12 251 A1, 1999.

(92) Sagae, T.; Sugiura, M.; Hagio, H.; Kobayashi, S. *Chem. Lett.* **2003**, *32*, 160.

(93) Akiyama, R.; Sagae, T.; Sugiura, M.; Kobayashi, S. *J. Organomet. Chem.* **2004**, *689*, 3806.

(94) (a) Schmid, G. *Chem. Rev.* **1992**, *92*, 1709. (b) *Nanoparticles and Nanostructured Films*; Fendler, J. H., Ed.; Wiley-VCH: Weinheim, Germany, 1998. (c) Shipway, A. N.; Katz, E.; Willner, I. *Chem. Phys. Chem.* **2000**, *1*, 18. (d) Andres, R. P.; Bielefeld, J. D.; Henderson, J. I.; Janes, D. B.; Kolagunata, V. R.; Kubiak, C. P.; Mahoney, W. J.; Osifchin, R. G. *Science* **1996**, *273*, 1690.

(95) Emory, S. R.; Haskins, W. E.; Nie, S. *J. Am. Chem. Soc.* **1998**, *120*, 8009.

(96) Sun, T.; Seff, K. *Chem. Rev.* **1994**, *94*, 857.

(97) (a) *Cluster and Colloids*; Schmid, G., Ed.; Wiley-VCH: Weinheim, Germany, 1994. (b) Lewis, L. N. *Chem. Rev.* **1993**, *93*, 2693.

(98) Beck, A.; Horváth, A.; Sárkány, A.; Guczi, L. , In *Nanotechnology in Catalysis*; Zhou, B., Hermans, S., Somorjai, G. A., Eds. Kluwer Academic: New York. 2004; Vol. 1, Chapter 5.

(99) (a) Förster, S.; Antonietti, M. *Adv. Mater.* **1998**, *10*, 195. (b) Lu, P.; Teranishi, T.; Asakura, K.; Miyake, M.; Toshima, N. *J. Phys. Chem. B* **1999**, *103*, 9673. (c) Dutta, A. K.; Ho, T.; Zhang, L.; Stroeve, P. *Chem. Mater.* **2000**, *12*, 1042. (d) Ding, J. H.; Gin, D. L. *Chem. Mater.* **2000**, *12*, 22. (e) Rheingans, O.; Hugenberg, N.; Harris, J. R.; Fischer, K.; Maskos, M. *Macromolecules* **2000**, *33*, 4780. (f) Corbierre, M. K.; Cameron, N. S.; Sutton, M.; Mochrie, S. G. J.; Lurio, L. B.; Rühm, A.; Lennox, R. B. *J. Am. Chem. Soc.* **2001**, *123*, 10411. (g) Pavel, F. M.; Mackay, R. A. *Langmuir* **2000**, *16*, 8568. (h) Sohn, B. H.; Seo, B. H. *Chem. Mater.* **2001**, *13*, 1752. (i) Hatano, T.; Takeuchi, M.; Ikeda, A.; Shinkai, S. *Org. Lett.* **2003**, *5*, 1395.

(100) Klingelhöfer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Förster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116.

(101) (a) Zhang, L.; Eisenberg, A. *Science* **1995**, *268*, 1728. (b) Henselwood, F.; Liu, G. *Macromolecules* **1997**, *30*, 488. (c) Harada, A.; Kataoka, K. *Science* **1999**, *283*, 65. (d) Jenekhe, S. A.; Chen, X. L. *Science* **1999**, *283*, 372. (e) Won, Y. Y.; Davis, H. T.; Bates, F. S. *Science* **1999**, *283*, 960. (f) Discher, B. M.; Won, Y. Y.; Ege, D. S.; Lee, J. C.-M.; Bates, F. S.; Discher, D. E.; Hammer, D. A. *Science* **1999**, *284*, 1143. (g) Svensson, M.; Alexandridis, P.; Linse, P. *Macromolecules* **1999**, *32*, 637.

(102) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 2125.

(103) Reviews: (a) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4. (d) De Meijere, A.; Braese, S. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, U.K., 1999. (e) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(104) TOF = 11 800. TON and TOF in other immobilized Pd including nanoparticles: (a) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2004**, *60*, 4097 (TON = 1 150 000, TOF = 12 000; iodobenzene and methyl acrylate). (b) Mandal, S.; Roy, D.; Chaudhari, R. V.; Sastry, M *Chem. Mater.* **2004**, *16*, 3714 (TOF = 4256; iodobenzene and styrene). (c) Hagiwara, H.; Sugawara, Y.; Isobe, K.; Hoshi, T.; Suzuki, T *Org. Lett.* **2004**, *6*, 2325 (TON = 68 400, TOF = 8000; iodobenzene and cyclohexyl acrylate). (d) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K *J. Am. Chem. Soc.* **2002**, *124*, 11572 (TON = 49 000; 4′-iodoacetophenone and butyl acrylate). (e) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem.—Eur. J.* **2002**, *8*, 622 (TON =

18 000, TOF = 9000; bromobenzene and styrene). (f) Rahim, E. H.; Kamounah, F. S.; Frederiksen, J.; Christensen, J. B *Nano Lett.* **2001**, *1*, 499 (TON = 36 800, TOF = 3066; 1-bromo-2-iodo-benzene and acrylic acid). (g) Le Bars, J.; Specht, U.; Bradley, J. S.; Blackmond, D. G *Langmuir* **1999**, *15*, 7621 (TON = 100 000, TOF = 80 000; 4-bromo-benzaldehyde and butyl acrylate). (h) Klingelhöfer, S.; Heitz, W.; Greiner, A.; Oestreich, S.; Förster, S.; Antonietti, M. *J. Am. Chem. Soc.* **1997**, *119*, 10116 (TON = 56 600; 4′-bromoacetophenone and styrene).

(105) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B *J. Org. Chem.* **2003**, *68*, 1177.

(106) (a) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112. (b) Rebek, J.; Broun, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454. (c) Collman, J. P.; Kosydar, K. M.; Bressan, M.; Lamanna, W.; Garrett, T. *J. Am. Chem. Soc.* **1984**, *106*, 2569. (d) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (e) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317. (f) Baleizão, C.; Corma, A.; Garcia, H.; Leyva, A. *J. Org. Chem.* **2004**, *69*, 439. (g) Yu, K.; Sommer, W.; Weck, M.; Jones, C. W. *J. Catal.* **2004**, *226*, 101. (h) See also ref 105.

(107) (a) Sharpless, K. B.; Akashi, K.; Oshima, K *Tetrahedron Lett.* **1976**, *17*, 2503. See also: (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.

(108) Kobayashi, S.; Miyamura, H.; Akiyama, R.; Tasuku, I. *J. Am. Chem. Soc.* **2005**, *127*, 9251.

(109) Review: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(110) Reviews: (a) Jas, G.; Kirschning, A. *Chem.—Eur. J.* **2003**, *9*, 5708. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650. See also: (c) Kirschning, A.; Altwicker, C.; Dräger, G.; Kunz, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 3995. (d) Solodenko, W.; Wen, H.; Leue, S.; Stuhlmann, F.; Sourkouni-Argirusi, G.; Jas, G.; Schönfeld, H.; Kunz, I. U.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3601.

(111) Takeuchi, M.; Akiyama, R.; Kobayash, S. *J. Am. Chem. Soc.* **2005**, *127*, 13096.

(112) The loading level of the polymer-supported $Sc(OTf)_3$ was determined by XRF analysis.

(113) Control experiments strongly suggested that the tetra(ethylene glycol) moieties in copolymer **50** played an important role in the immobilization of Sc(OTf).

(114) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

(115) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4.

(116) (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054. (c) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143.

(117) PMI $Sc(OTf)_3$ is also available and reusable in $CH_2Cl_2$ or toluene.

(118) Miyamura, H.; Akiyama, R.; Ishida, T.; Matsubara, R.; Takeuchi, M.; Kobayashi, S. *Tetrahedron* **2005**, *61*, 12177.

(119) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375.

(120) (a) *Comprehensive Handbook on Hydrosilylation*; Marciniec, B., Ed.; Pergamon Press: Oxford, England, 1992. and references therein. (b) Ojima, I. *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; p 1479. (c) Harrod, J. F.; Chark, A. J. In *Organic Synthesis via Metal Carbonyls*; Wender, I., Pino, P., Eds.; Wiley: New York, 1977, p 673.

(121) (a) Michalska, Z. M.; Strzelec, K.; Sobczak, J. W. *J. Mol. Catal. A: Chem.* **2000**, *156*, 91. (b) Michalska, Z. M.; Ostaszewski, B.; Strzelec, K. *J. Organomet. Chem.* **1995**, *496*, 19.

(122) Hilal, H. S.; Suleiman, M. A.; Jondi, W. M.; Khalaf, S.; Masoud, M. M. *J. Mol. Catal. A: Chem.* **1999**, *144*, 47.

(123) Speier, J. L.; Webster, J. A.; Barrnes, G. H. *J. Am. Chem. Soc.* **1957**, *79*, 974.

(124) For reviews, see: (a) Hartley, F. R. *Supported Metal Complexes: A New Generation of Catalysts*; D. Reidel Publishing Co.: Dordrecht, The Netherlands, 1985; Chapter 7, p 204. (b) *Comprehensive Handbook on Hydrosilylation*; Marciniec, B., Guilinski, J., Kornetka, Z. W., Marciniec, B., Eds.; Pergamon Press: Oxford, U.K., 1992; Chapter 2, p 84.

(125) Miao, Q. J.; Fang, Z.-P.; Cai, G. P. *Catal. Commun.* **2003**, *4*, 637.

(126) Recently, an effective polystyrene and polymethacrylate resin-supported Pt catalyst has been reported. See: (a) Drake, R.; Sherrington, D. C.; Thomson, S. J. *React. Funct. Polym.* **2004**, *60*, 65. (b) Drake, R.; Dunn, R.; Sherrington, D. C.; Thomson, S. J. *J. Mol. Catal. A: Chem.* **2001**, *177*, 49. (c) Drake, R.; Dunn, R.; Sherrington, D. C.; Thomson, S. *J. Chem. Commun.* **2000**, 1931. Immobilization of platinum catalysts using pyridine, phosphine, and nitrile ligand are reported; see: (d) Michalska, Z. M.; Strzelec, K.; Sobezak, J. W. *J. Mol. Catal. A: Chem.* **2000**, *156*, 91. (e) Kan, C.; Yuan, Q.; Luo, X.; Kong, X. *Polym. Adv. Technol.* **1995**, *7*, 76. (f) Michalska, Z. M.; Ostaszewski, B.; Zientarska, J. *React. Polym.* **1991−1992**, *16*, 213.

(127) Hagio, H.; Sugiura, M.; Kobayashi, S. *Synlett* **2005**, 813.

(128) TEM analysis of PI Pt **62** disclosed that Pt dispersed on the polymer uniformly, and no formation of large clusters was observed. Hydrosilylation using Pt colloids as catalysts have been reported. See: (a) Stein, J.; Lewis, L. N.; Gao, Y.; Scott, R. A *J. Am. Chem. Soc.* **1999**, *121*, 3693. (b) Boardman, L. D. *Organometallics* **1992**, *11*, 4194. (c) Lewis, L. N.; Lewis, N.; Uriarte, R. J. In *Homogeneous Transition Metal Catalyzed Reactions*; Moser, W. R.; Slocum, D. W., Eds.; Advances in Chemistry Series 230; American Chemical Society: Washington, DC, 1992; p 541. (d) Lewis, L. N.; Uriarte, R. J.; Lewis, N. *J. Mol. Catal.* **1991**, *66*, 105. (e) Lewis, L. N.; Uriarte, R. J. *Organometallics* **1990**, *9*, 621. (f) Lewis, L. N. *J. Am. Chem. Soc.* **1990**, *112*, 5998. (g) Lewis, L. N.; Lewis, N. *J. Am. Chem. Soc.* **1986**, *108*, 7228.

(129) Fink, W. *Helv. Chim. Acta* **1971**, *54*, 1304.

(130) Sabouraut, N.; Mignani, G.; Wagner, A.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 2117.

(131) Miyazaki, Y.; Hagio, H.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 2529.

(132) (a) Hill, C. L. *Advances in Oxygenated Processes*; JAI Press: London, 1988; Vol. 1. (b) Hundlucky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.

(133) For a review, see: Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037.

(134) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2000**, *122*, 7144.

(135) (a) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572. (b) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 10657.

(136) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538.

(137) Abad, A.; Concepcîn, C.; Corma, A.; García, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4066.

(138) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362.

(139) (a) Ji, H.-B.; Ebitani, K.; Mizugaki, T.; Kaneda, K. *Catal. Commun.* **2002**, *3*, 511. (b) Martín, S.; Suárez, D. F. *Tetrahedron Lett.* **2002**, *43*, 4475. (c) Colemane, K. S.; Coppe, M.; Thomas, C.; Osborn, J. A. *Tetrahedron Lett.* **1999**, *40*, 3723. (d) Muldoon, J.; Brown, S. N. *Org. Lett.* **2002**, *4*, 1043. (e) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Peduli, G. F. *Chem. Commun.* **2002**, 688. (f) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, 109.

(140) Miyamura, H.; Matsubara, R.; Miyazaki, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4151.

(141) Miyamura, H.; Shiramizu, M.; Matsubara, R.; Kobayashi, S. *Chem. Lett.* **2008**, *37*, 360.

(142) Miyazaki, Y.; Kobayashi, S. *J. Comb. Chem.* **2008**, *10*, 355.

(143) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362.

(144) Kristian, N.; Yan, Y.; Wang, X. *Chem. Commun.* **2008**, 353.

(145) (a) Chen, M.; Kumar, D.; Yi, C.-W.; Goodman, D. A. *Science* **2005**, *310*, 291. (b) Ahang, J.; Sasaki, K.; Sutter, E.; Adzic, R. R. *Science* **2007**, *315*, 220. (c) Venezia, A. M.; Parola, V. L.; Nicoli, V.; Deganello, G. J. *J. Catal.* **2002**, *212*, 56. (d) Scott, R. W.; J.; Wilson, O. M.; Oh, S.-K.; Kenik, E. A.; Crooks, R. M *J. Am. Chem. Soc.* **2004**, *126*, 15583. (e) Dimitratos, N.; Villa, A.; Wang, D.; Porta, F.; Su, D.; Prati, L. *J. Catal.* **2006**, *244*, 113. (f) Edwards, J. K.; Solsona, B. E.; Landon, P.; Carley, A. F.; Herzing, A.; Kiely, C. J.; Hutchings, G. J. *J. Catal.* **2005**, *236*, 69. (g) Scott, R. W.; J.; Sivadinarayana, C.; Wilson, O. M.; Yan, Z.; Goodman, D. W.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 1380. (h) Zhou, S.; Mcllwrath, K.; Jackson, G.; Eichhorn, B *J. Am. Chem. Soc.* **2006**, *128*, 1780. (i) The reactivity of Au is also changed by various impurities. See: Iizuka, Y.; Kawamoto, A.; Akita, K.; Date, M.; Tsubota, S.; Okumura, M.; Haruta, M. *Catal. Lett.* **2004**, *97*, 203. (j) Wang, D.; Villa, A.; Porta, F.; Su, D.; Prati, L. *Chem. Commun.* **2006**, 1956.

(146) Miyamura, H.; Matsubara, R.; Kobayashi, S. *Chem. Commun.* **2008**, 2031.

(147) Lucchesi, C.; Inasaki, T.; Miyamura, H.; Matsubara, R.; Kobayashi, S. *Adv. Synth. Catal.* **2008**, *350*, 1996.

(148) Miyamura, H.; Shiramizu, M.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8093.

(149) (a) Matsumoto, T.; Ueno, M.; Kobayashi, J.; Miyamura, H.; Mori, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2007**, *349*, 531. (b) Matsumoto, T.; Ueno, M.; Wang, N.; Kobayashi, S. *Chem. Asian J.* **2008**, *3*, 239.

(150) Mills, P. L.; Chaudhari, R. V. *Catal. Today* **1997**, *37*, 367.

(151) (a) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*,

4735. (b) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406. (c) Bellefon, C.; Tanchoux, N.; Caravieilhes, S.; Grenouillet, P.; Hellel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442. (d) Hisamoto, H.; Saito, T.; Tokeshi, M.; Hibara, A.; Kitamori, T. *Chem. Commun.* **2001**, 2662. (e) Yoshida, J-i.; Suga, S. *Chem.—Eur. J.* **2002**, *8*, 2650. (f) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (g) Tokeshi, M.; Minagawa, T.; Uchiyama, K.; Hibara, A.; Sato, K.; Hisamoto, H.; Kitamori, T. *Anal. Chem.* **2002**, *74*, 1565. (h) Hisamoto, H.; Shimizu, Y.; Uchiyama, K.; Tokeshi, M.; Kikutani, Y.; Hibara, A.; Kitamori, T. *Anal. Chem.* **2003**, *75*, 350. (i) Ueno, M.; Hisamoto, H.; Kitamori, T.; Kobayashi, S. *Chem. Commun.* **2003**, 936.

(152) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors*; Wiley-VCH, Weinheim, Germany, 2000.

(153) *Microreactor, Epoch-making Technology for Synthesis*; Yoshida, J-i., Ed.; CMC: Japan, 2000.

(154) (a) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883. (b) Serizawa, A.; Feng, Z.; Kawara, Z. *Exp. Therm. Fluid. Sci.* **2002**, *26*, 703.

(155) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, U.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305.

(156) (a) Greenway, G. M.; Haswell, S. J.; Morgan, D. O.; Skelton, V.; Styring, P. *Sens. Actuators B* **2000**, *63*, 153. (b) Ouyang, X.; Besser, R. S. *Catal. Today* **2003**, *84*, 33.

(157) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Commun.* **2005**, 2567.

(158) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1889.

(159) Mars G. J.; Scher, H. B. In *Controlled Delivery of Crop Protecting Agents*; Wilkens, R. M., Ed.; Taylor and Francis: London, 1990; p 65.

(160) Scher, H. B. U.S. Patent 4,285,720, 1980.

(161) Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmeida, N. *Chem. Commun.* **2002**, 1132.

(162) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A, J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134.

(163) (a) Bremeyer, B.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. *Synlett* **2002**, 1843. (b) Ley, S. V.; Steawrt-Liddon, A. J. P.; Pears, D.; Pemi, R. H.; Treacher, K. *Beilstein J. Org. Chem.* **2006**, *2*, 15.

(164) Yu, J.-Q.; Wu, H.-C.; Ramarao, C.; Spencer, J. B.; Ley, S. V. *Chem. Commun.* **2003**, 678.

(165) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. *Org. Lett.* **2003**, *5*, 4665.

(166) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem.—Eur. J.* **2006**, *12*, 4407.

(167) Toubiana, J.; Chidambaram, M.; Santo, A.; Sasson, Y. *Adv. Synth. Catal.* **2008**, *350*, 1230.

(168) Ley, S. V.; Ramarao, C.; Lee, A.-L.; Østergaard, N.; Smith, S. C.; Shirley, I. M. *Org. Lett.* **2003**, *5*, 185.

(169) Lee, A.-L.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3957.

(170) Very recently, polysilane-supported Pd and Pt catalysts have been prepared by using microencapsulation techique for the first time, and used successfully in several organic reaction. See: (a) Oyamada, H.; Akiyama, R.; Hagio, H.; Naito, T.; Kobayashi, S. *Chem. Commun.* **2006**, 4297. (b) Oyamada, H.; Naito, T.; Miyamoto, S.; Akiyama, R.; Hagio, H.; Kobayashi, S. *Org. Biomol. Chem.* **2008**, *6*, 61.

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