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# New methods for high-throughput synthesis*

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*Abstract*: New methodologies for library synthesis have been developed. They are based on new carbon–carbon bond-formation reactions in the solid-phase and organic synthesis using polymer-supported catalysts. We have immobilized alkyl glyoxylate equivalents onto resins and prepared novel polymer-supported imines. We have also developed unprecedented polymer-supported catalysts such as microencapsulated scandium trifluoromethanesulfonate [MC $Sc(OTf)_3$], osmium tetroxide (MC $OsO_4$), and palladium triphenylphosphine [MC $Pd(PPh_3)$] for high-throughput synthesis.

## INTRODUCTION

Combinatorial chemistry is now of great interest not only in the field of drug discovery [1] but also in many other fields such as material sciences and asymmetric catalysis. Since high-throughput screening technology has been rapidly developed, the key to successful implementation for combinatorial chemistry is shifting to library synthesis. Organic chemists play a key role in synthesis, and their goal is to prepare large numbers of structurally distinct molecules efficiently. It is, of course, possible to prepare large numbers of compounds by traditional organic synthesis, but often using much manpower and time. It is indeed questionable whether these syntheses are truly efficient. The authors think that new methodologies are needed to prepare large numbers of molecules (compound libraries), just as new methodologies for natural product synthesis were required 40 years ago (Fig. 1). Our goal is to develop new methods for library synthesis. "High-throughput synthesis" provides powerful tools to reach this goal. In this article, new methods for high-throughput synthesis are described. They are based on new carbon–carbon bond-formation reactions in the solid-phase and organic synthesis using polymer-supported catalysts.

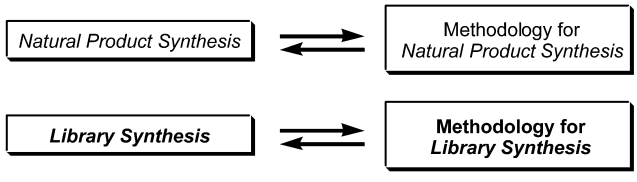


**Fig. 1** Methodology for library synthesis.

## ORGANIC SYNTHESIS ON SOLID SUPPORTS

The solid-phase synthesis has some advantages compared with the solution-phase synthesis. For example, procedures in the solid-phase synthesis are very simple because unreacted reagents and excess compounds can be removed by simple filtration. Thus, automation is easily lead in the solid-phase synthe-

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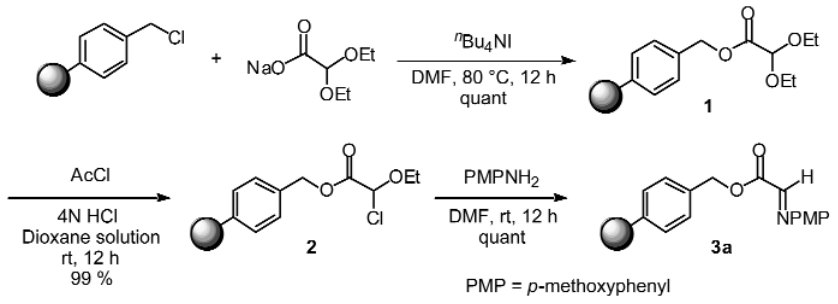
sis. Furthermore, it is expected that unstable compounds are stabilized when immobilized on polymer supports, and indeed, in our previous work, we immobilized commonly unstable silyl enol ethers on resins and successfully used them in several carbon–carbon bond-forming reactions.

α-Imino acetates are useful building blocks for the synthesis of nitrogen-containing biologically important compounds such as α-amino acids, β-amino alcohols, etc. However, they are often unstable at room temperature due to rapid decomposition and polymerization, and have to be prepared just before use. Thus, we decided to immobilize alkyl glyoxylate equivalents onto resins and prepared novel polymer-supported imines.

Polymer-supported α-imino acetates were prepared according to Scheme 1 [2]. Sodium diethoxyacetate, which was readily prepared from commercially available ethyl diethoxyacetate by hydrolysis, was treated with chloromethylated resin at 80 °C for 12 h in DMF to form diethoxyacetate resin (**1**). Subsequent chlorination was performed using acetyl chloride in a hydrogen chloride dioxane solution at room temperature for 12 h to give 2-chloro-2-ethoxyacetate resin (**2**). The loadings of **1** and **2** were determined by chlorine titration (Volhard's method). The reaction of **2** with *p*-anisidine was found to proceed smoothly at room temperature in DMF to give 2-(4'-methoxyphenyl)iminoacetate resin (**3a**) quantitatively. In these transformations in the solid-phase, $^{13}C$ swollen-resin magic-angle spinning NMR (SR-MAS NMR) analysis [3] provided a powerful tool to optimize the reaction conditions of each step and to determine the structures of these resins (**1**, **2**, and **3a**) (Fig. 2).




**Scheme 1** Synthesis of polymer-supported α-imino acetate.

Polymer-supported α-imino acetate (**3a**) thus prepared was used in Mannich-type reactions with silyl nucleophiles (Scheme 2). In the presence of 20 mol % scandium trifluoromethanesulfonate [scandium triflate; $Sc(OTf)_3$], **3a** was treated with the silyl enolate derived from methyl isobutyrate at room temperature for 20 h in $CH_2Cl_2$–$CH_3CN$ (1:1). The resulting resin was treated with NaOMe at room temperature for 1 h in THF to afford the desired α-amino acid derivative (**4**) in 76% yield. When ytterbium trifluoromethanesulfonate [ytterbium triflate; $Yb(OTf)_3$] was used as a catalyst, the yield was slightly reduced. Various types of silyl enolates derived from esters as well as thioesters and ketones reacted smoothly to afford the corresponding α-amino acid derivatives, which are an interesting class of biologically important compounds. When Danishefsky's diene was used as a nucleophile, 2-methoxycarbonyl-1-(4'-methoxyphenyl)-1,2,3,4-tetrahydropyridin-2-one (**5**) was obtained in 69% yield.

We further studied aza Diels–Alder reactions of **3** for the preparation of tetrahydroquinoline derivatives. In the presence of 20 mol % $Sc(OTf)_3$, **3a** reacted with dihydrofuran at room temperature for 20 h in $CH_2Cl_2$–$CH_3CN$ (1:1) to give 2-methoxycarbonyltetrahydroquinoline derivative in 72% yield after cleavage from the polymer support. Other examples are examined, and in all cases the desired reactions proceeded smoothly in the solid-phase to afford the corresponding tetrahydroquinoline derivatives in good to excellent yields. Since aza Diels–Alder adducts formed in the solid-phase were unstable under cleavage conditions, we protected imino-nitrogens as their Boc groups before cleavage. The Boc groups were deprotected simultaneously when the adducts were cleaved from the polymer support.

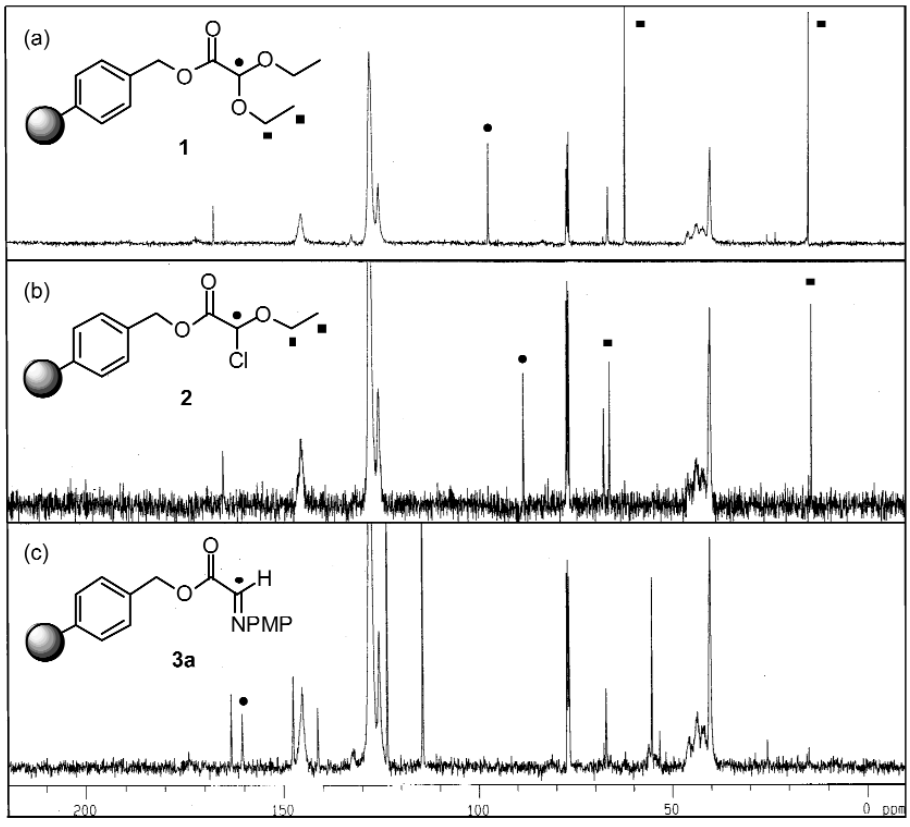
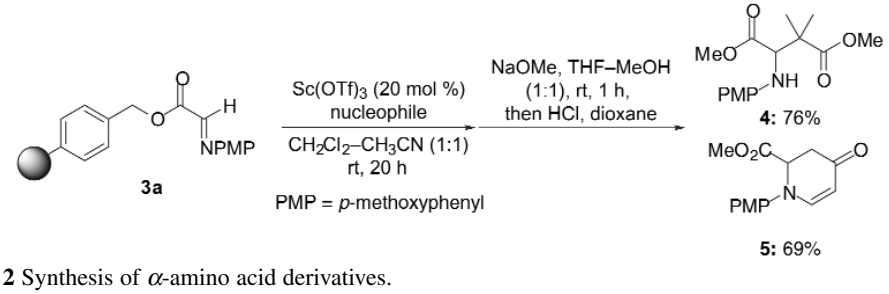



**Fig. 2** $^{13}C$ Swollen-resin magic-angle spinning (SR-MAS) NMR spectra of (a) diethoxyacetate resin (**1**); (b) α-chloro-α-ethoxyacetate resin (**2**); (c) α-iminoacetate resin (**3a**) ($CDCl_3$).




**Scheme 2** Synthesis of α-amino acid derivatives.

## LIBRARY SYNTHESIS USING IMMOBILIZED CATALYSTS

Although polymer-supported substrates (reagents) have often been used for library synthesis, there are some disadvantages in this method. Firstly, the reactions of polymer-supported reagents are sometimes slow, and differences in reactivity between the substrates can lead to lack of diversity of the library. Secondly, the loading level of polymer-supported substrates is generally low (<0.8 mmol/g in most cases), and large-scale preparation is difficult. To overcome these problems, a new methodology for library synthesis has been developed. *The new method does not use polymer-supported reagents, but uses polymer-supported (immobilized) catalysts in multicomponent reactions (MCRs).*

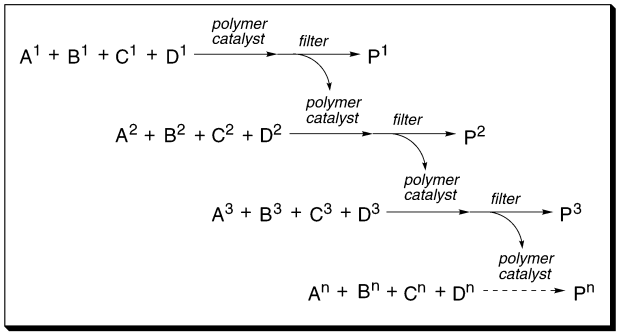
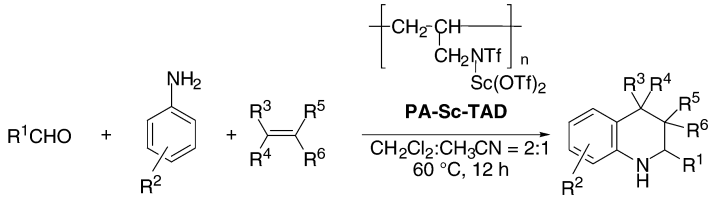



**Fig. 3** Multicomponent reactions using polymer-supported catalysts.

Immobilized catalysts in organic synthesis offer several advantages, such as simplification of product work-up, separation, isolation, and reuse of the catalyst [4]. A general scheme for library synthesis using an immobilized catalyst in MCRs is shown in Fig. 3. In the presence of an immobilized catalyst, equimolar amounts of multicomponents (A–D in Fig. 3) are combined. If the reaction proceeds smoothly, the catalyst is separated by simple filtration, and the product is obtained by concentrating the filtrate. The recovered catalyst can be reused in the following reactions. The procedures are very simple, and the application to multiple parallel synthesis using an automation system is a possibility.

## QUINOLINE LIBRARY

An example of library synthesis using an immobilized catalyst in MCRs has been shown in the synthesis of a large number of quinoline derivatives. Three-component coupling reactions using lanthanide triflate as the catalyst had been previously developed. Many combinations of aldehydes, amines, and alkenes were used in this reaction, and a large quinoline library could be prepared. A novel immobilized scandium catalyst, polyallylscandium trifylamide ditriflate (PA-Sc-TAD), has been developed and successfully used for the synthesis of a quinoline library (Scheme 3) [5]. A characteristic feature of this method, when compared with conventional combinatorial synthetic technology using polymer-supported reagents, is that syntheses on more than the 100 mg scale with a large array of diverse molecular entries have been achieved with high purities (high yields and high selectivities). There are over 200 commercially available aromatic aldehydes, aliphatic aldehydes, heterocyclic aldehydes, and glyoxals and glyoxylates, more than 200 aromatic amines, and 50 alkenes (and alkynes) that would be applicable to this reaction. Therefore, a quinoline library of more than a million compounds with high quantity and quality could be prepared by using an automated system based on this method. Moreover, the tetrahydroquinoline derivatives thus obtained were easily oxidized to dihydroquinoline or quinoline derivatives, which could double or triple the size of the library.




**Scheme 3** Synthesis of quinoline library.

## NOVEL IMMOBILIZED CATALYSTS

A key step for library synthesis using immobilized catalysts would be to develop truly efficient polymer-supported catalysts. Microcapsules have been used for coating and isolating substances until their activity is needed. Their application to medicine and pharmacy has been extensively studied [6]. The idea is to apply this microencapsulation technique to the immobilization of catalysts onto polymers (Fig. 4). That is, catalysts would be physically enveloped by thin films of polymer, and at the same time immobilized by interaction between π electrons of the benzene rings of the polystyrene, which is used as a polymer backbone, and vacant orbitals of the catalysts (metal compounds).

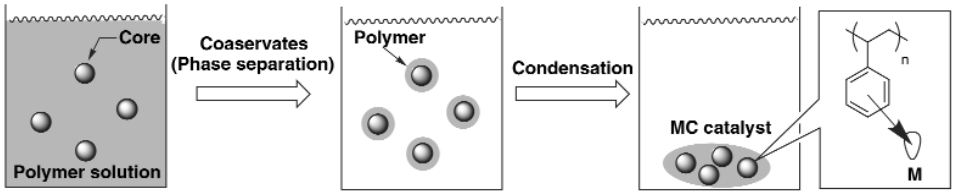
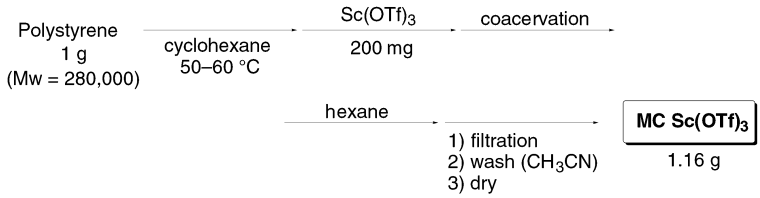



**Fig. 4** Microencapsulation technique for the immobilization of catalysts onto polymers.

## MICROENCAPSULATED SCANDIUM TRIFLATE [MC $Sc(OTf)_3$]

Scandium triflate was chosen as the first Lewis acid catalyst to be immobilized [7]. $Sc(OTf)_3$ is a new type of water-stable Lewis acid, and many useful synthetic reactions using $Sc(OTf)_3$ have been developed. Microencapsulated $Sc(OTf)_3$ [MC $Sc(OTf)_3$] was prepared according to a standard procedure using polystyrene (Scheme 4). 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 because of 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. These results demonstrate that the interaction between $Sc(OTf)_3$ and the benzene rings of polystyrene is a key to immobilizing $Sc(OTf)_3$.




**Scheme 4** Preparation of microencapsulated $Sc(OTf)_3$ catalyst.

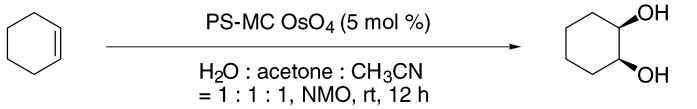
MC $Sc(OTf)_3$ was successfully used in several fundamental and important Lewis acid-catalyzed carbon–carbon bond-forming reactions. The reactions could be carried out in both batch (using normal vessels) and flow systems (using circulating columns). It was found that MC $Sc(OTf)_3$ can activate carbonyl compounds such as aldehyde and α,β-unsaturated ketone. Several reactions proceeded smoothly using MC $Sc(OTf)_3$ to give the corresponding products in high yields. It was also found that MC $Sc(OTf)_3$ effectively activated aldimines, and that typical synthetic reactions using aldimines proceed-

ed smoothly. 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 $Sc(OTf)_3$, as shown by preliminary kinetic studies. The polymer catalyst was recovered quantitatively by simple filtration and could be reused. The activity of the recovered catalyst did not decrease, even after several uses. MC $Sc(OTf)_3$ has also been successfully used in three-component reactions such as Mannich-type, Strecker, and quinoline-forming reactions for the synthesis of biologically interesting compound libraries.

## MICROENCAPUSULATED OSMIUM TETROXIDE (MC $OsO_4$)

$OsO_4$ was successfully immobilized onto a polymer using the microencapsulation technique [8]. Styrene-based, microencapsulated osmium tetroxide (PS-MC $OsO_4$) was easily recovered quantitatively by simple filtration and could be reused several times without loss of activity (Table 1). No contamination of $OsO_4$ in the products occurred under the conditions used. Moreover, PS-MC $OsO_4$ was found to be effective in dihydroxylation of various olefins (Fig. 5).

**Table 1** 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 |

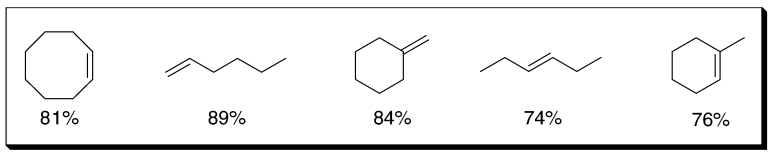
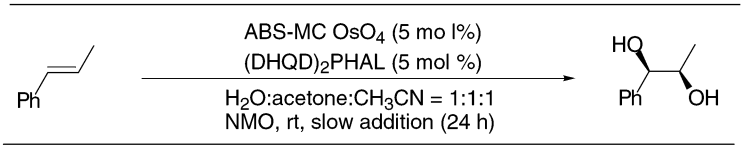



**Fig. 5** Dihydroxylation of olefins using PS-MC $OsO_4$.

In addition, the microencapsulated osmium catalyst was applied to asymmetric dihydroxylation of olefins [9]. The osmium catalyst for the asymmetric dihydroxylation of olefins was prepared using an acrylonitrile-butadiene-polystyrene (ABS). ABS-based $OsO_4$ (ABS-MC $OsO_4$) thus prepared was first tested in achiral dihydroxylation of olefins. In the presence of ABS-MC $OsO_4$ (5 mol %), various olefins were treated with *N*-methylmorpholine *N*-oxide (NMO) in $H_2O$–acetone–$CH_3CN$ (1:1:1) to give the corresponding diols in high yield. Styrene was not a good substrate in the dihydroxylation using PS-MC $OsO_4$ because styrene dissolved PS-MC $OsO_4$.

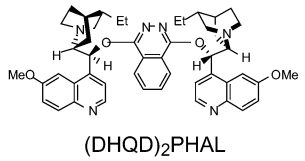
This catalyst was successfully used in asymmetric dihydroxylation of olefins, according to the Sharpless procedure. β-Methylstyrene was oxidized in the presence of catalytic amounts of ABS-MC $OsO_4$ and 1,4-bis-(9-*O*-dihydroquinidinyl)phthalazine [$(DHQD)_2PHAL$; a chiral source], and a stoichiometric amount of NMO (a cooxidant) to give the corresponding diols in high yields with high enantiomeric excesses (ees) (Table 2). The osmium catalyst and the chiral source were recovered quantitatively and were reused without loss of activity. A 100-mmol-scale asymmetric synthesis was successfully demonstrated. Several examples of ABS-MC $OsO_4$-catalyzed asymmetric dihydroxylation of olefins are summarized in Fig. 6.

**Table 2** Asymmetric dihydroxylation of olefin using ABS-MC $OsO_4$.




| Run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Yield (%) | 84 | 84 | 84 | 85 | 82 |
| ee (%) | 84 | 95 | 94 | 96 | 95 |
| Recovery[a,b] | quant | quant | quant | quant | quant |

[a]Recovery of ABS-MC $OsO_4$. [b]Recovery of $(DHQD)_2PHAL$ = >95%.




$(DHQD)_2PHAL$

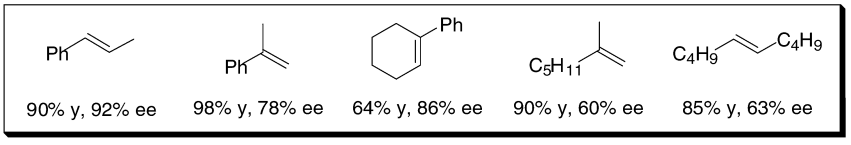



**Fig. 6** Asymmetric dihydroxylation of various olefins.

## PEM-BASED NOVEL MICROENCAPUSULATED OSMIUM TETROXIDE (PEM–MC $OsO_4$)

The reaction procedure based on ABS-MC $OsO_4$ requires a slow addition of olefins, and hence incurs some problems such as a tedious procedure and the difficulty of using insoluble substances. Thus, we developed recoverable and reusable osmium-catalyzed asymmetric dihydroxylation of olefins without the slow addition of olefins using microencapsulated osmium tetroxide derived from a novel polymer support.

On the basis of several experiments and consideration, we designed phenoxyethoxymethyl-polystyrene (PEM-polystyrene) shown in Fig. 7 [10]. Preparation of a new type of microencapsulated osmium tetroxide (PEM-MC $OsO_4$) was performed according to a standard method.

PEM-MC $OsO_4$ thus prepared was first tested in asymmetric oxidation of styrene using $(DHQD)_2PHAL$ in several solvents. In $H_2O$-acetone, moderate chemical yields, good enantiomeric excesses, and high recovery of the catalyst were obtained. It is noted that the PEM-MC $OsO_4$ was recovered quantitatively by simple filtration, and that no leaching of the osmium from PEM-MC $OsO_4$ occurred. In order to increase the chemical yields, we examined separate addition of the cooxidant and

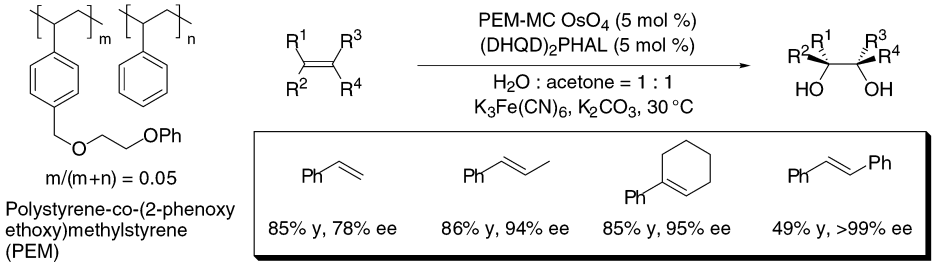



**Fig. 7** Asymmetric dihydroxylation of olefins using PEM-MC $OsO_4$.

the base, because it was observed that the desired reaction stopped halfway. When $K_3Fe(CN)_6$ (2.0 equiv.) and potassium carbonate (2.0 equiv.) were added at first, and they were added again after 3 h, the best result was obtained.

This system was applied to other olefins, and the results are shown in Fig. 7. In most cases, the desired diols were obtained in good yields with high enantiomeric excesses. It is noteworthy that a wide variety of olefins are applicable in this system.

## MICROENCAPSULATED TRIPHENYLPHOSPHINE PALLADIUM [MC Pd($PPh_3$)]

Palladium catalyst was successfully immobilized onto a polymer using the microencapsulation technique. Preparation of a new type of microencapsulated palladium catalyst [MC Pd($PPh_3$)] was performed according to a standard method [11]. MC Pd($PPh_3$) thus prepared was first used in the allylation reaction. When allyl methyl carbonate was combined with dimethyl phenylmalonate in the presence of 20 mol % MC Pd($PPh_3$) and 20 mol % of $PPh_3$, the reaction proceeded smoothly. 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 Fig. 8. Malonates and $\beta$-ketoesters smoothly reacted under these conditions to afford the corresponding allylation adducts in high yields.

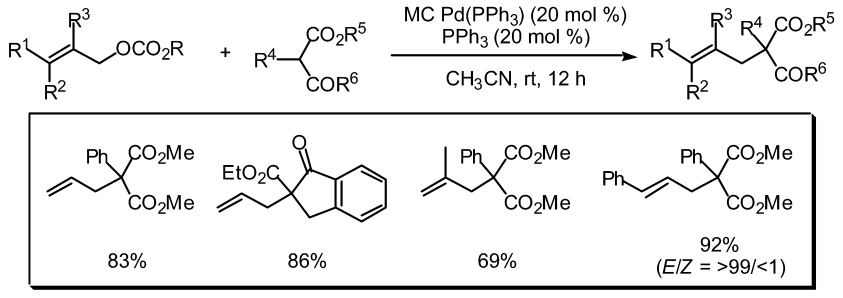



**Fig. 8** Allylic substitution using MC Pd($PPh_3$).

In addition, Suzuki coupling reactions 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. In these reactions, the best results were obtained by using tri-*o*-tolylphosphine [P(*o*-Tol)$_3$] as an external ligand.

## CONCLUSIONS

Several new methods for high-throughput synthesis have been discussed. It was demonstrated that development of carbon–carbon bond-forming reactions in the solid-phase is crucial. We have developed new polymer-supported reagents such as polymer-supported α-imino acetates, which were successfully used in several carbon–carbon bond-forming reactions, leading to large numbers of biologically important compounds. We have also developed unprecedented polymer-supported catalysts, microencapsulated catalysts, which show high activities and can be recovered quantitatively and reused by a simple procedure. These methods provide versatile tools for library synthesis.

## ACKNOWLEDGMENTS

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## REFERENCES

1. (a) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop. *J. Med. Chem.* **37**, 1233 (1994); (b) M. A. Gallop, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop. *J. Med. Chem.* **37**, 1385 (1994); (c) G. Lowe. *Chem. Soc. Rev.* **37**, 309 (1995); (d) N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Seele. *Tetrahedron* **51**, 8135 (1995); (e) J. S. Früchtel, G. Jung. *Angew. Chem., Int. Ed. Engl.* **35**, 17 (1996); (f) L. Al. Thompson and J. A. Ellman. *Chem. Rev.* **96**, 555 (1996); (g) N. K. Terrett. *Combinatorial Chemistry*, Oxford University Press, Oxford (1998).
2. (a) S. Kobayashi, R. Akiyama, H. Kitagawa. *J. Comb. Chem.* **2**, 438 (2000); (b) S. Kobayashi, R. Akiyama, H. Kitagawa. *J. Comb. Chem.* **3**, 196 (2001).
3. S. Kobayashi, R. Akiyama, T. Furuta, M. Moriwaki. *Mol. Online* **2**, 35 (1998).
4. S. Kobayashi and S. Nagayama. *J. Org. Chem.* **61**, 2256 (1996).
5. (a) S. Kobayashi, S. Nagayama, T. Busujima. *Tetrahedron Lett.* **51**, 9221 (1996); (b) S. Kobayashi and S. Nagayama. *J. Am. Chem. Soc.* **118**, 8977 (1996).
6. M. Donbrow. *Microcapsules and Nanocapsules in Medicine and Pharmacy*, CRC Press, Boca Raton (1992).
7. S. Kobayashi and S. Nagayama. *J. Am. Chem. Soc.* **120**, 2985 (1998).
8. S. Nagayama, M. Endo, S. Kobayashi. *J. Org. Chem.* **63**, 6094 (1998).
9. S. Kobayashi, M. Endo, S. Nagayama. *J. Am. Chem. Soc.* **121**, 11229 (1999).
10. S. Kobayashi, T. Ishida, R. Akiyama. *Org. Lett.* **3**, 2649 (2001).
11. R. Akiyama and S. Kobayashi. *Angew. Chem., Int. Ed.* **40**, 3469 (2001).