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A Microencapsulated Lewis Acid. A New Type of Polymer-Supported Lewis Acid Catalyst of Wide Utility in Organic Synthesis

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The utility of polymer catalysts is now well-recognized because of their ease of workup and of separation of products and catalysts, from the economical point of view, and in application to industrial processes, etc.[1,2] In general, catalysts are immobilized on polymers via coordinate or covalent bonds. While the stability of polymer catalysts having coordinate bonds is often low, preparation of polymer catalysts having covalent bonds can be troublesome and their activities are generally lower than those of the monomer catalysts.[2] On the other hand, Lewis acid-catalyzed reactions are of great current interest because of the unique reactivities and selectivities that can be achieved as well as for the mild conditions used.[3] Although many of them have been applied in industry,[3] there are few examples of polymer-supported Lewis acids.[4] Recently, we have developed polymer-supported scandium Lewis acids based on Nafion[5] and a polyacryronitrile derivative;[6] however, their reactivity was lower than for the monomeric Lewis acids. We now report here an unprecedented polymer-supported Lewis acid, *a microencapsulated Lewis acid*, which is readily prepared, has higher activity than the monomeric Lewis acid, is recoverable and reusable, and can be applied to many synthetic reactions.

Microcapsules have been used for coating and isolating substances until such time as their activity is needed, and their application to medicine and pharmacy has been extensively studied.[7] Recently, much progress has been made in this field; for example, the size of microcapsule achievable has been reduced from a few micrometers to nanometers.[7,8] Our idea is to apply this microencapsulation technique to the immobilization of Lewis acid catalysts onto polymers. That is, Lewis acids would be physically enveloped by polymer thin films and perhaps stabilized by the interaction between π electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbitals of the Lewis acids.[9] Scandium trifluoromethanesulfonate (scandium triflate, Sc(OTf)$_3$)[10] was chosen as the Lewis acid to be immobilized. Sc(OTf)$_3$ is a new type of water-stable Lewis acid we have discovered,[11] and many useful synthetic reactions using Sc(OTf)$_3$ have been developed.[12] Preparation of the microencapsulated Sc(OTf)$_3$ (MC Sc(OTf)$_3$) was performed as follows: Polystyrene (1.000 g) was dissolved in cyclohexane (20 mL) at 40 °C, and to this solution was added powdered Sc(OTf)$_3$ (0.200 g) as a solid 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.[13,14]

A scanning electron microscopy (SEM) micrograph and scandium energy-dispersive X-ray (EDX) map of MC Sc(OTf)$_3$ prepared are shown in Figure 1. It was found that small capsules of MC Sc(OTf)$_3$ adhered to each other, probably due to the small size of the core. Judging from the scandium mapping, Sc(OTf)$_3$ was located all over the polymer surface. A possible role for the benzene rings of the polystyrene in immobilizing Sc(OTf)$_3$ was suggested by control experiments using polybutadiene or polyethylene instead of polystyrene. While 43% of Sc(OTf)$_3$ (100% = 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 may indicate that there is an interaction between Sc(OTf)$_3$ and the benzene rings of polystyrene.[15]

We then used MC Sc(OTf)$_3$ 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[16,17] using MC Sc(OTf)$_3$ containing ca. 0.120 g of Sc(OTf)$_3$. The reactions were 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 1),[12b] aza Diels−Alder,[12b,c,17] cyanation,[12d,17] and allylation[12e,17] reactions of aldimines proceeded smoothly using MC Sc(OTf)$_3$ to afford respectively the synthetically useful β-amino ester, tetrahydroquinoline, α-aminonitrile, and homoallylic amine derivatives in high yields. Although it is well-known that most Lewis acids are trapped and sometimes decomposed by basic aldimines, MC Sc(OTf)$_3$ worked well in all cases. One

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[13] 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 was 1.167 g which contained acetonitrile. MC Sc(OTf)$_3$ thus prepared can be stored at room temperature for more than a few months.

[14] IR (KBr): 3062, 3030 (νCH), 1946, 1873, 1805 (δCH), 1601, 1493 (benzene rings), 1255 (ν_{as}SO$_2$), 1029 (ν_sSO$_2$), 756 (νC−S), 696 (νS−O) cm^{-1}. Cf., Sc(OTf)$_3$: 1259 (ν_{as}SO$_2$), 1032 (ν_sSO$_2$), 769 (νC−S), 647 (νS−O) cm^{-1}. Polystylene: 3062, 3026 (νCH), 1944, 1873, 1803 (δCH), 1600, 1491 (benzene rings) cm^{-1}.

[15] Steric factors (physical envelopment) would also contribute the remarkable immobilizing ability of polystyrene compared to poor immobilization of polybutadiene and polyethylene.

[16] Nitromethane was used in Friedel−Crafts acylation (Scheme 5).

[17] Details are shown in the Supporting Information.

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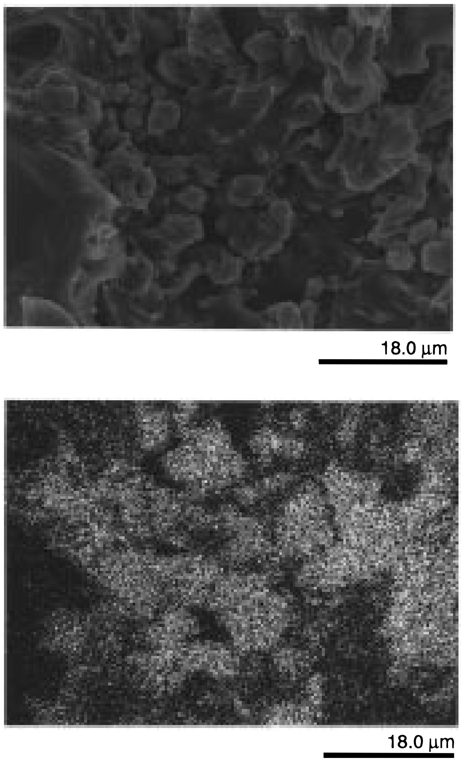
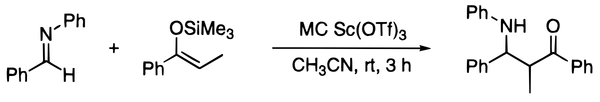


Figure 1. Scanning electron microscopy (SEM) micrograph (top) and scandium energy dispersive X-ray (EDX) map (bottom) of MC Sc(OTf)$_3$.

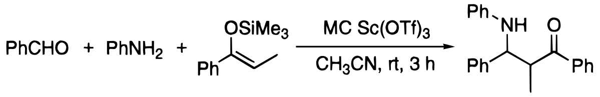
Scheme 1. Imino Aldol Reaction (Flow System)



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

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

Scheme 2. Mannich-Type Reaction (Flow System)



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

of the most remarkable and exciting points is that the activating ability of MC Sc(OTf)$_3$ for aldimines was revealed to be superior to that of monomeric Sc(OTf)$_3$ by preliminary kinetic studies.[17,18] The polymer catalyst was recovered quantitatively by simple filtration and could be reused. The activity of the recovered catalyst did not decrease even after seven uses (Scheme 1). MC Sc(OTf)$_3$ could also be successfully used in three-component reactions such as Mannich-type (Scheme 2),[12f] Strecker,[12d,17] and quinoline-forming reactions.[12g,17] These reactions are known to be useful for the synthesis of biologically interesting compound libraries.[19]

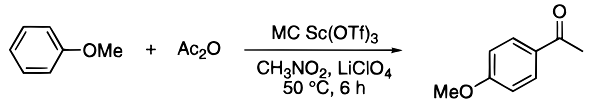
Scheme 3. Aldol Reaction (Batch System)

1st use, 92% yield; 2nd use, 97% yield; 3rd use, 95% yield

Scheme 4. Michael Reaction (Batch System)

1st use, 92% yield; 2nd use, 97% yield; 3rd use, 95% yield

Scheme 5. Friedel-Crafts Acylation (Batch System)



1st use, 76% yield; 2nd use, 76% yield; 3rd use, 81% yield

It was also found that MC Sc(OTf)$_3$ was effective for the activation of carbonyl compounds. The polymer scandium catalysts such as Nafion−Sc,[5] polyallylscandium trifylamide ditriflate (PA-Sc-TAD)[6] we have previously prepared were found to have only a low ability to activate aldehydes. On the other hand, MC Sc(OTf)$_3$ efficiently activated aldehydes, and aldol (Scheme 3),[12h] cyanation, and allylation[12i,17] reactions of aldehydes proceeded smoothly to give the corresponding aldol, cyanohydrin, and homoallylic alcohol derivatives in high yields. Michael reaction of an α,β-unsaturated ketone with a silyl enol ether (Scheme 4)[12h] and a Diels−Alder reaction of an oxazolidinone derivative with cyclopentadiene[11,17] also worked well using MC Sc(OTf)$_3$. Moreover, a Friedel−Crafts acylation proceeded smoothly to produce an aromatic ketone in a good yield (Scheme 5).[12j] Friedel−Crafts alkylation and acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry.[20] While the alkylation reaction proceeds in the presence of a catalytic amount of a Lewis acid, the acylation reaction generally requires more than a stoichiometric amount of a Lewis acid, usually aluminum chloride (AlCl$_3$), due to consumption of the Lewis acid by coordination to the aromatic ketone products. It should be noted that MC Sc(OTf)$_3$ has high activity in the Friedel−Crafts acylation and can be recovered easily by simple filtration and reused without loss of activity.

In conclusion, we have developed a microencapsulation technique for binding catalysts to polymers. Utilizing this technique, an unprecedented polymer-supported, microencapsulated Lewis acid has been prepared. The catalyst thus prepared has been demonstrated to be effective in many useful carbon−carbon bond-forming reactions. In all cases, the catalyst was recovered quantitatively by simple filtration and reused without loss of the activity. This new technique for binding monomeric compounds to polymers will be applicable to the preparation of many other polymer-supported catalysts and reagents.

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Supporting Information Available: Experimental details and reaction yields (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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