

Polymer–Micelle Incarcerated Scandium as a Polymer-Supported Catalyst for High-Throughput Organic Synthesis

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High-throughput organic synthesis (HTOS) is a powerful tool for lead discovery and lead optimization in modern medicinal chemistry. Recently, many methodologies for HTOS, such as solid-phase syntheses and solution-phase syntheses, using polymer-bound reagents or scavengers have been reported.^{1,2} As one of the most efficient methodologies for HTOS, the use of immobilized catalysts has also attracted much attention.³ On the other hand, Lewis acid catalysts are now of great interest because of their utility for activation of various carbon–carbon bond-forming reactions and others, and they provide among the most important methods in organic syntheses.⁴ In this context, much effort has been devoted to the development of solid-supported Lewis acid catalysts for HTOS, and some immobilizing methods using organic polymers or inorganic materials as solid supports have been reported.⁵ However, activities of such supported Lewis acids are lower in many cases compared with those of the original Lewis acids, presumably because rather strong interactions between the Lewis acid metals and their supports, which work as Lewis bases, result in decreasing Lewis acidities. Therefore, development of truly efficient and general methods for immobilization of Lewis acids, which can be applied to many reactions, is desired. We now report here novel polymer-supported scandium triflate ($\text{Sc}(\text{OTf})_3$) utilizing polymer micelles, which has high activity in several synthetically useful carbon–carbon bond-forming reactions.

Since $\text{Sc}(\text{OTf})_3$ is a water-compatible Lewis acid and is now one of the standard Lewis acids often used in organic synthesis,⁶ we decided to immobilize this Lewis acid onto polymers. Although we and other groups have already synthesized some examples of polymer-supported $\text{Sc}(\text{OTf})_3$ and derivatives,⁷ catalytic activity, scope of reaction, and/or catalyst loadings are still unsatisfactory in most cases. Recently, we developed a new immobilizing technique for metal catalysts, a polymer incarcerated (PI) method.⁸ This method is based on microencapsulation and cross-linking, and phosphine-free polymer incarcerated $\text{Pd}(0)$ (PI Pd) was prepared from $\text{Pd}(\text{PPh}_3)_4$. Since ligand exchanges were used for the preparation of PI Pd , it was not clear whether Lewis acids, such as $\text{Sc}(\text{OTf})_3$, could be immobilized utilizing this method.

We first examined several reaction conditions for the preparation of polymer-supported $\text{Sc}(\text{OTf})_3$ based on the PI method. It was found that choice of solvents at the stage of microencapsulation was key to the preparation (Table 1). While toluene–hexane and THF–cyclohexane–hexane were efficient for immobilizing $\text{Sc}(\text{OTf})_3$ (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).⁹ These results suggest that $\text{Sc}(\text{OTf})_3$ may locate in hydrophilic parts of random copolymer **1**.^{8d,10} It is noted that the PI method can also be successfully used for the preparation of immobilized $\text{Sc}(\text{OTf})_3$. Moreover, interesting information was obtained by transmission electron microscopic (TEM) analysis of the polymer solutions (Figure 1). Although random aggregation of copolymer **1**– $\text{Sc}(\text{OTf})_3$

Table 1. Solvent Effects in Microencapsulation of $\text{Sc}(\text{OTf})_3$

microencapsulation			
1	$\text{Sc}(\text{OTf})_3$ solvent rt 1) washed (toluene, CH_2Cl_2) 2) dried	coacervation poor solvent 1) filtered 2) washed (hexane) 3) dried	cross-linking no solvent 120 °C, 2 h
→ PI or PMI $\text{Sc}(\text{OTf})_3$			
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

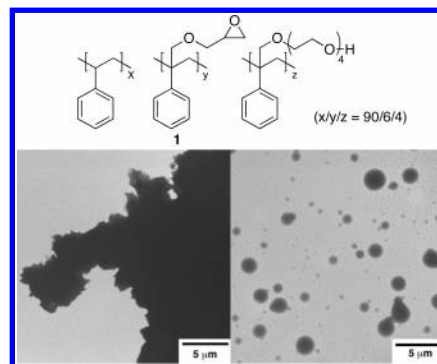


Figure 1. TEM images of **1**– $\text{Sc}(\text{OTf})_3$ solutions in toluene (left) and THF–cyclohexane.

Table 2. Comparison of Catalytic Activity of PI $\text{Sc}(\text{OTf})_3$ and PMI $\text{Sc}(\text{OTf})_3$ in Mukaiyama Aldol Reaction

		$\text{PhCHO} + \text{CH}_3\text{C}(\text{OMe})=\text{CHOSiMe}_3$ (1.3 equiv)		$\xrightarrow[\text{solvent, rt, 3 h}]{\text{Sc catalyst (5 mol\%)}}$ $\xrightarrow{\text{H}^+}$			
				yield (%)			Sc leaching (%)
entry	solvent	Sc catalyst	1st	2nd	3rd		
1	CH_3CN	PI $\text{Sc}(\text{OTf})_3$	85	87	85		ND ^b
2	toluene	PI $\text{Sc}(\text{OTf})_3$	70	64	71		ND ^b
3	CH_2Cl_2	PI $\text{Sc}(\text{OTf})_3$	83	83	83		ND ^b
4	CH_2Cl_2	PI $\text{Sc}(\text{OTf})_3$	84 ^a				ND ^c
5	CH_2Cl_2	PMI $\text{Sc}(\text{OTf})_3$	92 ^a	96	94		ND ^c

^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%).

was observed in toluene, spherical micelles were formed in THF–cyclohexane, and $\text{Sc}(\text{OTf})_3$ 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 as polymer incarcerated $\text{Sc}(\text{OTf})_3$ (PI $\text{Sc}(\text{OTf})_3$) and the latter as polymer–micelle incarcerated $\text{Sc}(\text{OTf})_3$ (PMI $\text{Sc}(\text{OTf})_3$).

PI $\text{Sc}(\text{OTf})_3$ and PMI $\text{Sc}(\text{OTf})_3$ were first used in the Mukaiyama aldol reaction¹¹ to compare their catalytic activity (Table 2). PI $\text{Sc}(\text{OTf})_3$ worked well in several solvents, and the desired product was obtained in good yields (entries 1–3). Moreover, it was

Table 3. Mannich-type Reaction Using PMI Sc(OTf)₃

entry	R ¹	X	R ²	R ³	Y	time (h)	yield (%)
1	Ph	Ph	Me	Me	OMe	3	96 ^{b,c}
2 ^a	2-thienyl	Ph	Me	Me	SEt	4	97
3 ^a	PhCH ₂ CH ₂	NHBz	Me	Me	OMe	24	80
4 ^a	EtO ₂ C	NHBz	Me	Me	OMe	24	73
5 ^a	Ph	Ph	H	H	Ph	3	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%). ^c Second use, 99%; third use, 97%.

Table 4. 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 CH₃CN 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%.

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). We tested other substrates, and in all cases, PMI Sc(OTf)₃ had higher catalytic activity than PI Sc(OTf)₃.¹² The higher activity of PMI Sc(OTf)₃ compared with that of PI Sc(OTf)₃ may be ascribed to construct the larger catalytic surface area in PMI Sc(OTf)₃ by formation of spherical micelles shown in Figure 1. Moreover, PMI Sc(OTf)₃ showed higher activity than MC Sc(OTf)₃, previously developed by our group.^{7c,12} It is noted that these catalysts were recovered quantitatively by simple filtration and that the same levels of yields were obtained even after the third use.

PMI Sc(OTf)₃ was successfully used as a catalyst in other reactions, such as Mannich-type¹³ and Michael¹⁴ reactions (Tables 3 and 4). 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 3). PMI Sc(OTf)₃ was also available for the reaction of less reactive acylhydrazones (entries 3 and 4).^{12,15} Moreover, it was confirmed that PMI Sc(OTf)₃ was an effective catalyst for Michael reactions (Table 4), one of the powerful methods for the synthesis of 1,5-dioxo units.¹⁴ In the presence of 5 mol % of PMI Sc(OTf)₃, the desired Michael reactions proceeded smoothly,^{12,16} and again, no Sc leaching was observed. It is noted that, to our knowledge, the highest catalytic activity in terms of TON (>7500) has been attained in the Michael reaction.

In summary, we have developed a novel immobilization technique for Sc(OTf)₃, a polymer–micelle incarcerated (PMI) method. To the best of our knowledge, this is the first example of immobilization of Lewis acids utilizing polymer micelles. PMI Sc(OTf)₃ is highly active in several fundamental carbon–carbon bond-forming reactions. The catalyst is recovered quantitatively by simple filtration and reused several times without loss of catalytic activity, and no Sc leaching was observed in all reactions (<0.1 ppm).¹⁷ In addition, several solvents are available, and these aspects are suitable for HTOS. The PMI method is operationally simple and might be applied to a wide range of Lewis acid catalysts. Further study into the immobilization of other Lewis acid catalysts is now in progress.

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Supporting Information Available: Tables of details in Mukaiyama aldol, Mannich-type, and Michael reactions, and experimental details (PDF). This material is available free of charge via Internet at <http://pubs.acs.org>.

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- (16) PMI Sc(OTf)₃ is also available and reusable in CH₂Cl₂ or toluene.
- (17) Metal leaching is a serious issue especially in pharmaceutical industry. However, most literature of immobilized Lewis acids ignores this important aspect. As far as we know, this is the lowest leaching level so far reported.

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