Lewis Acid Catalysts

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Self-Assembled Nanocomposite Organic Polymers with Aluminum and Scandium as Heterogeneous Water-Compatible Lewis Acid Catalysts**

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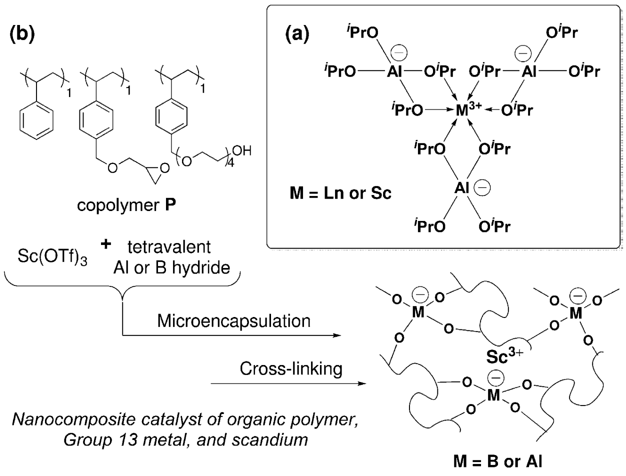
Abstract: *While water-compatible Lewis acids have great potential as accessible and environmentally benign catalysts for various organic transformations, efficient immobilization of such Lewis acids while keeping high activity and without leaching of metals even under aqueous conditions is a challenging task. Self-assembled nanocomposite catalysts of organic polymers, carbon black, aluminum reductants, and scandium salts as heterogeneous water-compatible Lewis acid catalysts are described. These catalysts could be successfully applied to various C−C bond-forming reactions without leaching of metals. Scanning transmission electron microscopy analyses revealed that the nanocomposite structure of Al and Sc was fabricated in these heterogeneous catalysts. It is noted that Al species, which are usually decomposed rapidly in the presence of water, are stabilized under aqueous conditions.*

Lewis acid catalysts are of great interest because they can realize various carbon–carbon (C−C) bond-forming reactions, which are essential for the production of fine chemicals, including pharmaceuticals.[1] While most metal Lewis acids easily decompose even in the presence of a small amount of water, some metal salts, such as lanthanide and scandium triflates ($Sc(OTf)_3$), were developed to be widely used as water-compatible Lewis acids.[1–3] These Lewis acids are useful not only for organic reactions in aqueous media but also for avoiding the use of dry organic solvents and strictly anhydrous conditions. On the other hand, heterogeneous catalysts are crucial for industrial use and environmentally benign organic synthesis, as well as high-throughput organic synthesis such as combinatorial chemistry and continuous flow synthesis.[4] Despite the great expansion of heterogeneous catalysis, the development of heterogeneous Lewis acid catalysts that can be used even in the presence of water with keeping high activity and without any leaching of metals is a challenging topic. Although several rational approaches have been attempted to realize these difficult tasks, successful examples are limited to composites of ionic liquids and solid supports,[5] metal organic frameworks as catalysts,[6] and mesoporous silica as a support.[5d,7]

We have been interested in the development of self-assembled nanocomposite catalysts of polymers, inorganic supports, and metal catalysts in accordance with our original immobilization methods: microencapsulation (MC) and polymer incarceration (PI).[8] Using these immobilization techniques, although we could immobilize water-compatible Lewis acids, we could not succeed in suppressing metal leaching in aqueous media.[9] Recently we developed Au-Pd-B bifunctional nanocomposite catalysts immobilized on polymer **P**-carbon black with a high specific surface area (namely polymer-incarcerated carbon black Au/Pd/B nanocomposites (PI/CB-Au/Pd/B)) for the integration of aerobic oxidation and Michael reactions.[10] Tetraalkoxy borate complexes derived from $NaBH_4$ and alcohol moieties in polymer side chains, which were originally introduced for cross-linking of polymer matrices to afford polymer-incarcerated catalysts after microencapsulation, were immobilized as an active catalyst for Michael reactions with metal nanoclusters.[11]

Inspired by this development and reports on complexes of lanthanide or scandium with tetraalkoxy aluminates (Scheme 1 a),[12] we designed self-assembled catalysts of group 13 metals, scandium salts, and polymer **P** as water-compatible heterogeneous Lewis acid catalysts (Scheme 1 b). Here we report the development of designed self-assembled catalysts and their application to various C−C bond-forming reactions in water or aqueous media, with complete suppression of metal leaching.



Scheme 1. a) Complexes of lanthanoids or scandium with a tetraalkoxy aluminate. b) Newly designed immobilized Sc catalyst prepared by self-assembly of polymer **P**, Group 13 metals, and scandium.

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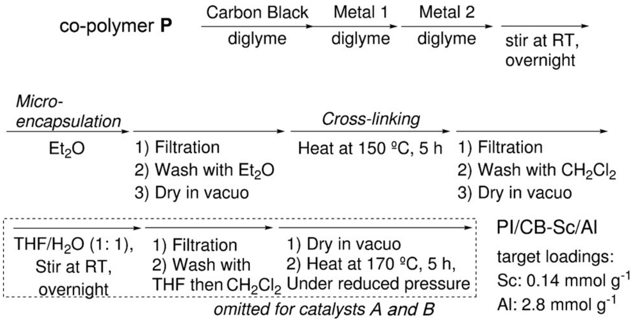
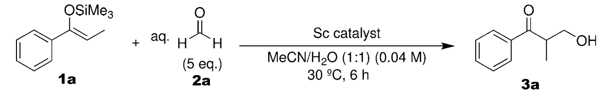
First, we prepared a composite catalyst derived from $Sc(OTf)_3$, $NaBH_4$, polymer **P** with cross-linking moieties, and carbon black with a high specific surface area following a method for PI/CB-metal nanocluster catalyst preparation. In this preparation, first polymer **P** was adsorbed on the surface of carbon black, and then metal catalysts were immobilized in the polymer matrix.[10] Both Sc and B were immobilized successfully to afford the desired catalyst, PI/CB-Sc/B **A**, and the metal loading was determined by inductive coupled plasma (ICP) analysis (Scheme 2, Table 1). The hydroxymethylation of silyl enol ether **1a** was conducted with an aqueous formaldehyde solution in MeCN as a solvent in the presence of PI/CB-Sc/B under ambient conditions. The desired product **3a** was obtained in moderate yield; however, a small amount of Sc and a significant amount of boron leaching were observed by ICP analysis, probably because of tetraalkoxyborate decomposition in the presence of water (Table 1, entry 1). We changed $NaBH_4$ to $Na[(CH_3OCH_2CH_2O)_2AlH_2]$ (Red-Al), and a nanocomposite catalyst, PI/CB-Sc/Al **B**, was prepared in the same manner. This catalyst could be collected by either filtration or centrifugation. Catalyst **B** gave a lower yield of the desired product in MeCN; however, no leaching of either Sc or Al was observed (entry 2). Encouraged by this result, we conducted hydroxymethylation with the addition of extra water because this reaction is known to be accelerated by water in the presence of water-compatible Lewis acids.[1b,2d,13] As we expected, a higher yield was observed (entry 3). Remarkably, absolutely no leaching of either metal was observed, while our previously developed PI-Sc catalysts without the introduction of an aluminum component led to significant scandium leaching for the same reaction even in the presence of a minimal amount of water.[9] The catalyst showed moderate to good activity in various co-solvent systems containing water without any leaching of metals, and the robustness of this catalyst against aqueous conditions was confirmed (see the Supporting Information). This is remarkable, because it is widely accepted that aluminum complexes easily decompose in the presence of water. The self-assembled nanocomposite structure of the Sc, Al, and polymer might be specially stabilized under thermodynamic conditions. A more Al-loaded catalyst with an aqueous washing step, PI/CB-Sc/Al **C**, gave a better result even with a shorter reaction time (6 h, entry 4). We also screened both aluminum and scandium sources. When $Sc(OTf)_3$ or $Sc(O\textit{i}Pr)_3$ and tetravalent aluminum hydrides were used, active catalysts could be prepared (entries 5, 7, and 8). On the other hand, catalysts derived from trivalent aluminum complexes (DIBAL, $AlCl_3$, $Al(O\textit{i}Pr)_3$) and $Sc(OTf)_3$ (**E**, **F**, **G**) showed very low activities (8-10% yield) with leaching of Al (0.4–5.9% leaching). We believe that the expected nanocomposite structure shown in Scheme 1b did not form in these cases. The choice of Sc salts was crucial for the catalytic activities, and catalyst **H** derived from $ScCl_3$ showed poor activity (entry 6).



Scheme 2. Preparation of polymer-incarcerated carbon black nanocomposite Sc-Al (PI/CB-Sc/Al) catalysts.

Table 1: Optimization of catalyst preparation.

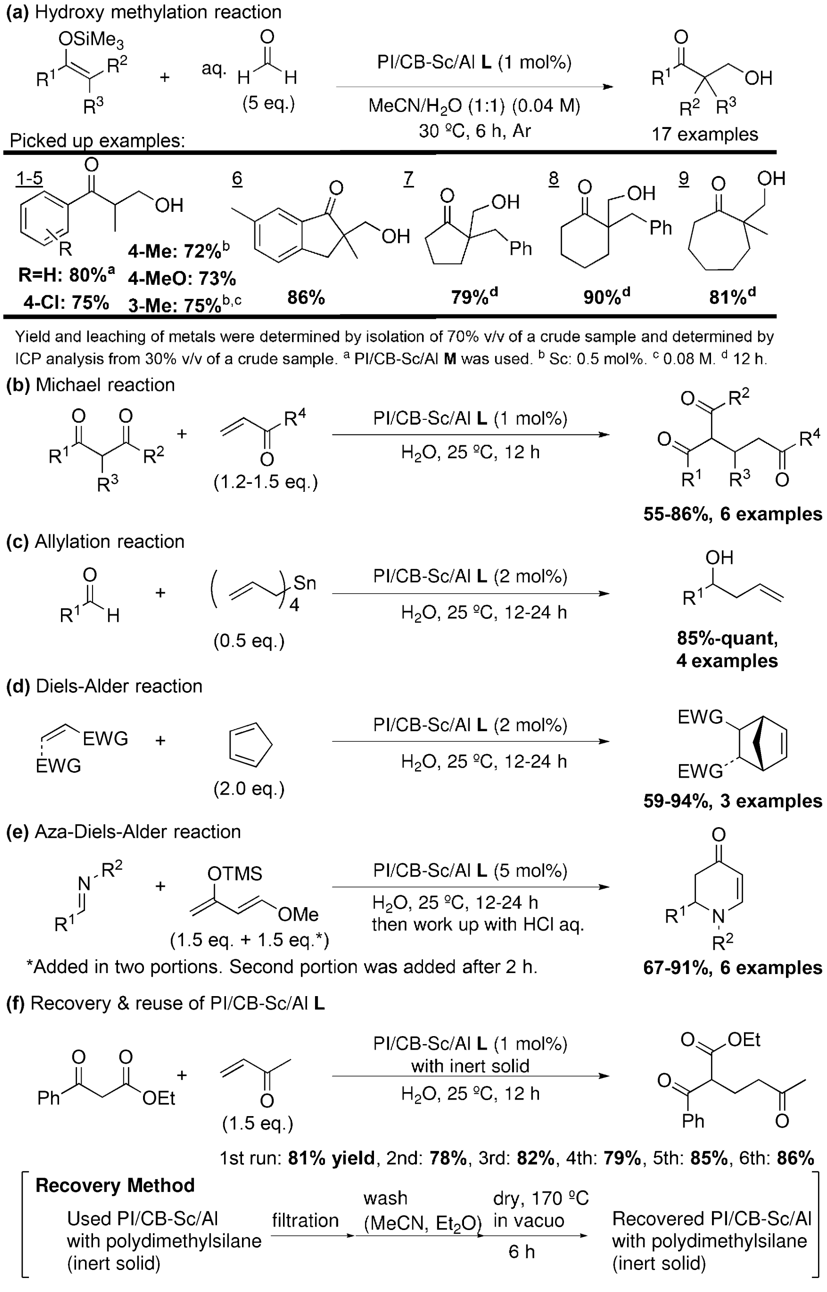


Entry	Cat.	Metal 1	Metal 2	Sc [mol%]	Yield [%][a]	Leaching [%][b] Sc	Al
1	**A**	$Sc(OTf)_3$	$NaBH_4$[c]	3	54[d]	0.14	15 (B)
2	**B**	$Sc(OTf)_3$	Red-Al[c]	3	21[d]	ND	ND
3	**B**	$Sc(OTf)_3$	Red-Al[c]	3	63[e]	ND	ND
4	**C**	$Sc(OTf)_3$	Red-Al	1	74	ND	ND
5	**D**	$Sc(OTf)_3$	$LiAlH_4$[f]	1	77	ND	ND
6	**H**	$ScCl_3{\cdot}6H_2O$	Red-Al	1	31	ND	ND
7	**I**	$Sc(O\textit{i}Pr)_3$	Red-Al	1	73	ND	ND
8	**J**	$Sc(O\textit{i}Pr)_3$	$LiAlH_4$[f]	1	63	ND	0.4
9	**K**	Red-Al	$Sc(OTf)_3$	1	78	ND	ND
10	**L**	$LiAlH_4$[f]	$Sc(OTf)_3$	1	77	ND	ND
11	**M**	$LiAlH_4$[f]	$Sc(O\textit{i}Pr)_3$	1	80 (75)[g]	ND	ND

[a] Corrected yield determined by isolation of 70% v/v of crude sample. [b] Corrected value determined by ICP analysis from 30% v/v of crude sample. ND = not detected (no peak of the metal was observed). [c] Target loading: 1.4 mmol g^{-1}. [d] In 0.4 M MeCN, for 17 h. [e] In 0.4 M, for 17 h. [f] $LiAlH_4$ was slowly added under Ar atmosphere during preparation. [g] Recovered catalyst was used.

Although the above-developed methods gave very active catalysts, a small amount of Al leaching and the formation of a concomitant over-reacted product through a second aldol reaction were sometimes observed, depending on the amounts of the catalysts. After extensive screening of the preparation methods, we found that the order of addition of Sc and Al sources was important to obtain good and stable results (entries 9–11). The catalysts **K**, **L**, and **M** prepared from $Sc(OTf)_3$/$Sc(O\textit{i}Pr)_3$ and Red-Al/$LiAlH_4$ were found to be highly active, and we adopted these catalysts for further investigations. We also confirmed that the reactions proceeded in heterogeneous phase by a filtration transfer test (see the Supporting Information), and a recovered catalyst can be used, keeping high activity (entry 11).[14]

The substrate scope of the hydroxy methylation reaction was surveyed (Scheme 3a). A commercially available formaldehyde aqueous solution could be used directly. Silyl enol ethers containing aromatic rings with both electron-withdrawing and electron-donating groups gave the desired hydroxy methylated compounds in good yields (entries 1–5). Silyl enol ethers derived from cyclic ketones were also applicable (entries 6–9). Substrates that gave a quaternary carbon center showed high yields regardless of their steric



Scheme 3. Scope of the reaction (details of substrate scope are shown in the Supporting Information).

hindrance. It is noted that we did not detect any leaching of Sc and Al in any substrate.

PI/CB-Sc/Al was also applicable to various C–C bond forming reactions in pure water without metal leaching. Michael reactions proceeded smoothly in pure water for both tertiary and quaternary carbon center formations under ambient conditions (Scheme 3b). PI/CB-Sc/Al was also effective for allylation of aldehydes using an allyltin reagent as nucleophile in pure water under ambient conditions (Scheme 3c). Both Diels–Alder and aza-Diels–Alder reactions also proceeded well in pure water at room temperature (Scheme 3d,e). In case of the aza-Diels–Alder reaction, reaction mechanism was confirmed as a stepwise process via a Mannich adduct followed by cyclization under acidic work-up. In all cases, various substrate combinations could be employed to afford the desired products in good to excellent yields. No additional surfactants were required for these reactions even in pure water, hence self-assembled nanocomposite of polymer-Sc-Al would provide highly effective amphiphilic reaction environments that can work in water. The heterogeneous catalyst could be recovered by simple procedures and reused to give the desired product in high yields for at least 6 runs (Scheme 3f; see the Supporting Information for more detail). We found that addition of inert solid facilitated recovery of the catalyst.

The structure of the PI/CB-Sc/Al **L** was analyzed by scanning transmission electron microscopy (STEM), energy-dispersive X-ray spectrometry (EDS), and scanning electron microscopy (SEM) (Figure 1). The STEM analysis (A-1) and SEM analysis (C-3) revealed that the polymer was highly dispersed over the spherical carbon black and formed a nanocomposite. Metal species are immobilized in the nanocomposite without the formation of clusters, but in a highly dispersed fashion. It is noted that Sc can be detected only in places where Al exists, judging from EDS mapping analyses (A-5 and A-6). EDS line analysis indicates the formation of a complex between Al and Sc because the amount of Sc is proportional to that of Al (A-2 and A-3). The catalyst used for 6 times recovery and reuse (Scheme 3 f) was also analyzed and similar morphology and elemental distributions were observed. In conjunction with the fact that PI/CB-Sc/Al **L** performed well for the various reactions in pure water and aqueous media without leaching of metals, and that trivalent Al species failed to form active catalysts or suppress metal leaching, these structural analyses strongly support the formation of complexes in which Sc and Al species are electrostatically coupled and immobilized together, such as the structure we proposed in Scheme 1.

According to SEM analyses, carbon black is 40–45 nm uniform sphere (Figure 1, C-1) and the diameter of particles slightly increases to 50–55 nm after formation of the nanocomposite with co-polymer **P** because co-polymer **P** adsorbs on the surface of carbon black. These nanocomposite particles agglomerate to form linked structure with void (C-2). Each nanocomposite unit slightly shrank (45–50 nm), keeping the linked structure after immobilization of Sc and Al followed by cross-linking (C-3).[15] The Brunauer–Emmett–Teller (BET) surface areas of catalysts **M** and **L** were calculated to be 84.3 $m^2 g^{-1}$ and 96.7 $m^2 g^{-1}$ respectively, and

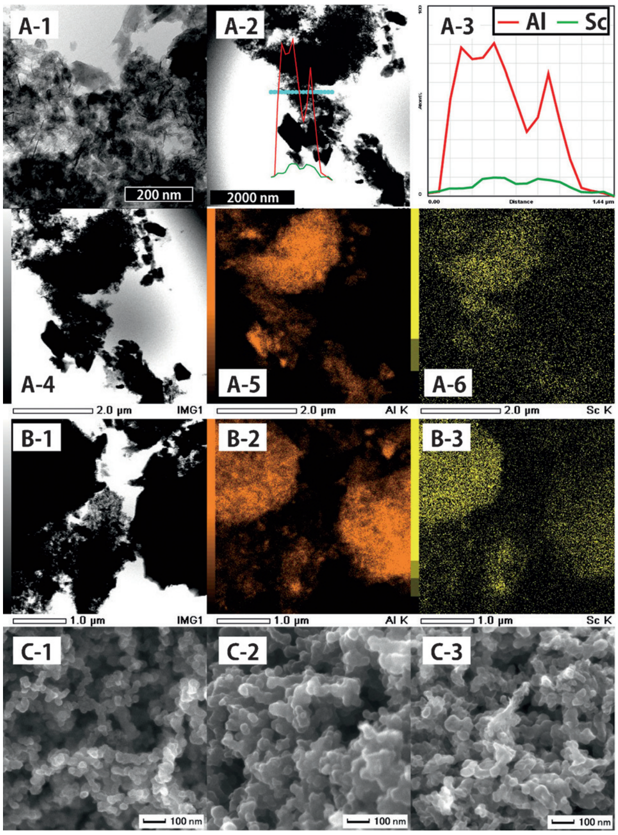


Figure 1. STEM images of PI/CB-Sc/Al **L** (A: before use; B: after use (see Scheme 3 f): A-1) STEM image, A-2,3) STEM-EDS line analysis, A-4,5,6) STEM-EDS mapping (BF image, Al mapping, Sc mapping); B-1,2,3) STEM-EDS mapping (BF image, Al mapping, Sc mapping). SEM images of C-1) carbon black, C-2) carbon black + polymer **P**, and C-3) PI/CB-Sc/Al **L**.

they are considered as non- or macroporous materials, based on the adsorption/desorption isotherm without hysteresis (see the Supporting Information). Mean pore diameters were also calculated as 10.8 nm and 8.6 nm for **M** and **L**, respectively. The "pore" corresponds to the void between the agglomerates of the nanocomposites, as seen in the SEM images. Judging from these structural analyses, both Sc and Al are immobilized within the polymer matrix dispersed over carbon black.[15] We believe that the reactions proceed inside of the polymer matrix that absorbs organic substrates and swells with them in water and aqueous media, resulting in high catalytic performance.

In conclusion, we have developed heterogeneous water-compatible Lewis acids that catalyzed various C–C bond-forming reactions in water or aqueous media under ambient conditions without any metal leaching: hydroxy methylation reactions using aqueous formaldehyde, Michael reactions, allylation of aldehydes, and Diels–Alder and aza-Diels–Alder reactions. The catalyst could be recovered and reused by simple operation, keeping activity. These heterogeneous catalysts were simply prepared by self-assembly of polymer, carbon black, Sc Lewis acids, and Al reductants in one pot, based on a modified procedure for MC and PI. Sc cations and tetravalent Al alkoxides are immobilized together with electrostatic attraction and retention of high catalytic activity, and the interaction might prevent leaching of either metal even under aqueous conditions. The choice of Sc and Al species is crucial for both catalytic activity and the prevention of metal leaching. It is noteworthy that Al species, which are usually decomposed rapidly in the presence of even a small amount of water, are stabilized under aqueous conditions. This unusual stability of the Al species against hydrolysis can be explained by multiple interactions of the hydroxy groups in the polymer and hydrophobic nature of the polymer support. Further application of these catalysts to other Lewis acid catalyzed reactions and an expansion of the strategy to immobilize other water-compatible Lewis acids are now ongoing.

Keywords: aluminum · C–C coupling · heterogeneous catalysis · Lewis acids · scandium

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[15] See the Supporting Information for a representation of PI/CB-Sc/Al.

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