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**A Heterogeneous Silica-Supported Scandium/
Ionic Liquid Catalyst System for Organic
Reactions in Water****

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Yuichiro Mori, and Shū Kobayashi**

Organic reactions in water are of current interest in organic synthesis.^[1] In addition to environmental and economical advantages, unique reactivity and selectivity that are not achieved in organic solvents are often observed in water, and several interesting and useful reactions have been exploited with water as the solvent. Lewis acids are frequently used to accelerate organic transformations,^[2] but the moisture sensitivity of the majority of Lewis acids render them unsuitable for use in aqueous solvent systems. To address this stability issue, water-compatible Lewis acids have been developed,^[3] and several Lewis acid catalyzed reactions, including asymmetric reactions, have been studied in aqueous media.^[4] However, many of these reactions proceed sluggishly in pure water, presumably because most organic materials are not soluble in the medium. We solved this problem by generating hydrophobic reaction environments in water by

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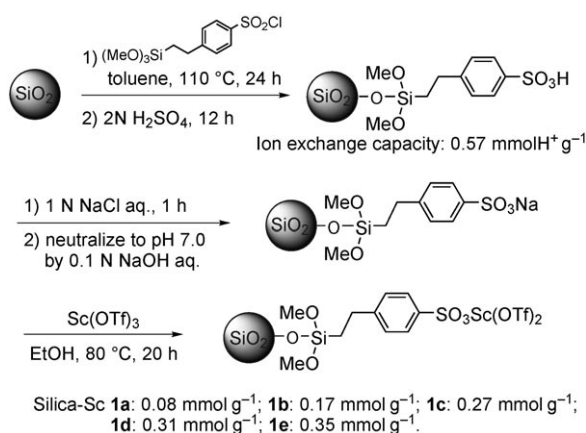
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Supporting information (experimental details and spectral data of products) for this article is available on the WWW under <http://www.angewandte.org> or from the author.

utilizing Lewis acid–surfactant combined catalysts (LASCs)^[5] or styrene-based hydrophobic polymer-supported catalysts.^[6] In these cases, however, substrate scope, catalysts loadings, and recovery and reuse of catalysts are not yet satisfactory. In the course of our investigations into the development of more efficient catalysts in water, we reasoned that hydrophobic ionic liquids (ILs) might interact with silica-supported metal catalysts to create hydrophobic reaction environments in water.^[7] Herein we describe a silica gel supported scandium system with an ionic liquid, a novel heterogeneous catalyst that works very efficiently in several carbon–carbon bond-forming reactions in water.^[8] An asymmetric version of this system involving a chiral scandium catalyst is also reported.

The silica gel supported scandium catalysts were prepared according to a modified literature method (Scheme 1, Figure 1 a).^[9] The scandium catalysts thus prepared were added to a solution of ionic liquid in ethyl acetate, and the solvent



Scheme 1. Preparation of silica gel supported Sc.

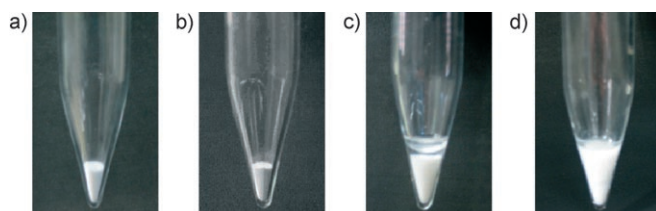


Figure 1. View of catalyst and reaction systems. a) Silica-Sc; b) silica-Sc-IL; c) silica-Sc-IL, water, and substrates before mixing; d) mixture from (c) during the reaction (after mixing).

was removed under reduced pressure to afford powdery and free-flowing solid silica-Sc-IL (Figure 1 b). Interestingly, silica-Sc and silica-Sc-IL could not be differentiated by sight. When substrates and water were added to silica-Sc-IL, the phases did not mix (Figure 1 c), but formed a colloidal suspension upon stirring (Figure 1 d).

Silica-Sc-IL (**1**) was first tested in Mukaiyama aldol reactions. Several reaction conditions were examined in the model reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methyl-1-propene (**2a**) (Table 1). To our great delight, the reaction took place smoothly in water, and the best yields were obtained with 0.27 mmol g^{−1} loading of

Table 1: Mukaiyama reaction conditions with silica-Sc-IL.

$\text{PhCHO} + \text{2a} \xrightarrow[\text{solvent, 15 °C, 24 h}]{\text{silica-Sc-IL IL (30 wt\%)}} \text{Ph-C(Ph)(OH)-C(=O)SEt}$					
Entry	Catalyst	Sc [mol %]	Solvent	IL ^[e]	Yield [%]
1	1a	1.6	H ₂ O	[DBIm]SbF ₆	50
2	1b	3.4	H ₂ O	[DBIm]SbF ₆	81
3	1c	5.4	H ₂ O	[DBIm]SbF ₆	97
4	1d	6.2	H ₂ O	[DBIm]SbF ₆	73
5 ^[a]	–	0	H ₂ O	[DBIm]SbF ₆	0
6	1c	5.4	hexane	[DBIm]SbF ₆	26
7	1c	5.4	Et ₂ O	[DBIm]SbF ₆	22
8 ^[b]	1c	5.4	–	[DBIm]SbF ₆	25
9 ^[c]	1c	5.4	H ₂ O	–	31
10	1c	5.4	H ₂ O	[DBIm]NTf ₂	64
11	1c	5.4	H ₂ O	[DBIm]PF ₆	76
12	1c	5.4	H ₂ O	[BMIm]SbF ₆	54
13 ^[d]	1c	5.4	H ₂ O	[DBIm]SbF ₆	69

[a] Without catalyst; [b] without solvent; [c] without IL; [d] 15 wt % of IL was used; [e] [DBIm] = 1-butyl-3-decylimidazolium; [BMIm] = 1-butyl-3-methylimidazolium.

scandium (**1c**; Table 1, entry 3). The reaction proceeded sluggishly in hexane, ether, and also under solvent-free conditions (Table 1, entries 6–8). These results clearly show that the reaction progressed much faster in water than in organic solvents or in the absence of solvent, and that the use of water as a solvent is essential for the silica-Sc-IL-catalyzed aldol reaction. Although the reaction also proceeded sluggishly without ionic liquid (Table 1, entry 9), moderate to good yields were obtained by using other ionic liquids (Table 1, entries 10–12). When half the amount of ionic liquid was used, the reaction was accelerated relative to the background level; however, the reaction was not complete within 24 h (Table 1, entry 13). These experiments clearly showed that silica-Sc-IL and ionic liquid formed a hydrophobic reaction environment in water. It should be noted that water-labile reagents such as **2a** can be used effectively in water under the conditions, and that, to the best of our knowledge, this is the first demonstration of the combination of silica gel supported metal catalysts with ionic liquids to create an efficient hydrophobic environment for organic reactions in water.^[10]

A range of other substrates were surveyed for Mukaiyama aldol reactions with silica-Sc-IL **1c** (Table 2). In all cases, aldehydes reacted smoothly with silicon enolates in water to afford the desired aldol adducts in high yields. The scandium catalyst was reused at least three times with only a slight decrease in yields (Table 2, entry 1). In a typical experimental procedure,^[11] hexane was added to extract the product after the reaction was completed. We carefully checked both the water and organic phases for evidence of metal leaching. Inductively coupled plasma (ICP) analysis revealed that 0.1 % of the Sc (relative to the total Sc content) had leached into the water phase, whereas no leaching into the organic phase was detected.

We then tested Michael reactions of indole derivatives with enones (Table 3). The reactions also proceeded smoothly in water to afford the desired Michael adducts in high yields. Turnover numbers as high as 4560 were obtained (Table 3,

Table 2: Mukaiyama aldol reactions in water.

$\text{R}^1\text{CHO} + \text{R}^2\text{C}(\text{OSiMe}_3)=\text{R}^3\text{R}^4 \xrightarrow[\text{H}_2\text{O}, 15^\circ\text{C}, 24\text{ h}]{\text{silica-Sc-IL } \mathbf{1c} (5.4\text{ mol}\%), [\text{DBIm}]\text{SbF}_6 (30\text{ wt}\%, 12\text{ mol}\%)}$ $\text{R}^1\text{CH}(\text{OH})\text{C}(\text{R}^2)(\text{R}^3)\text{R}^4$			
2b: $\text{R}^2 = \text{CH}_3$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{Ph}$ 2c: $\text{R}^2 = \text{H}$, $\text{R}^3, \text{R}^4 = -(\text{CH}_2)_3-$			
Entry	R ¹	Enolate	Yield [%]
1	Ph	2a	97 (95 ^[a] , 90 ^[b])
2	4-MeOC ₆ H ₄	2a	81
3	4-ClC ₆ H ₄	2a	90
4	(E)-PhCH=CH ₂	2a	87
5	PhCH ₂ CH ₂	2a	64
6 ^[c]	Ph	2b	71 ^[d]
7	Ph	2c	84 ^[e]

[a] Reused in the second run; [b] reused in the third run; [c] 50 wt % of IL and 2a (0.75 mmol) were used at 20°C; [d] *syn/anti* = 49:51; [e] *syn/anti* = 60:40.

Table 3: Silica-Sc-IL-catalyzed Michael reactions of indoles.^[a]

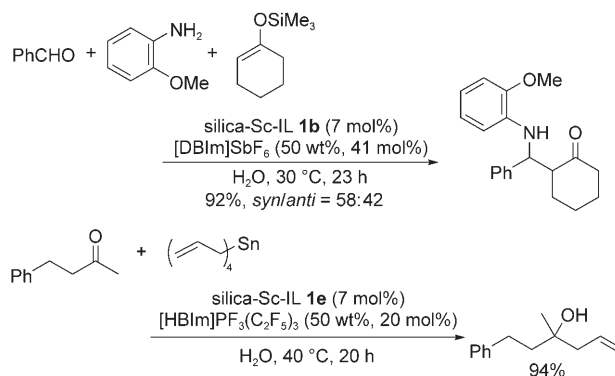
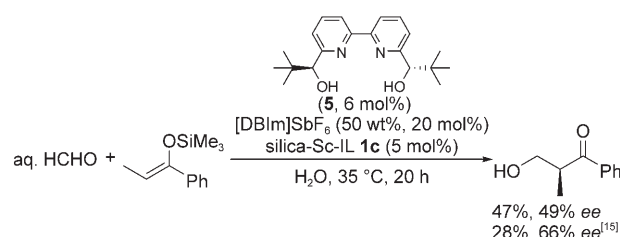
$\text{Indole } \mathbf{3} + \text{Enone } \mathbf{4} \xrightarrow[\text{H}_2\text{O}, 30^\circ\text{C}]{\text{silica-Sc-IL } \mathbf{1}, [\text{DBIm}]\text{SbF}_6}$					
Entry	Sc [mol %]	3 ^[b]	4 ^[c]	t [h]	Yield [%]
1	1a (1.6)	3a	4a	4	96
2	1f ^[d] (0.02)	3a	4a	12	93
3	1a (1.6)	3b	4a	4	92
4	1a (1.6)	3c	4a	4	88
5	1a (1.6)	3d	4a	4	87
6	1a (1.6)	3e	4a	4	74
7	1a (1.6)	3a	4b	4	89
8	1a (1.6)	3a	4c	4	88
9	1e (7.0)	3a	4d	20	70

[a] 50 wt %, 20 mol %; [b] 3a: indole; 3b: 5-bromoindole; 3c: 5-methoxyindole; 3d: 1-methylindole; 3e: 2-methylindole; [c] 4a: methyl vinyl ketone; 4b: ethyl vinyl ketone; 4c: phenyl propenyl ketone; 4d: cyclopenten-2-one; [d] 1f: silica-Sc(OSO₂C₈F₁₇)₂ (0.001 mmol g⁻¹).

entry 2). Other substrates were treated under standard conditions, and in all cases the desired Michael adducts were obtained in high yields.

We further investigated the applicability of the catalyst system to other reactions in water. We selected a three-component Mannich reaction of aldehydes, amines, and silicon enolates, and an allylation reaction of a ketone with tetraallyl tin (Scheme 2).^[12] In all cases, the reactions proceeded smoothly in water to afford the desired products in high yields. It is noted that silica-Sc-IL can be widely used as a Lewis acid catalyst in several important carbon–carbon bond-forming reactions in water.

Finally, a catalytic asymmetric version of this system was tested with silica-Sc-IL and a chiral ligand (Scheme 3). In the presence of silica-Sc-IL and chiral bipyridine **5**,^[13] the silicon enolate derived from propiophenone was treated with an aqueous solution of formaldehyde in water.^[14] Remarkably, the reaction proceeded at 35°C to afford the desired hydroxymethylated ketone in 47% yield and 49% ee.^[15] Although the yield and the enantioselectivity were moderate,


Scheme 2. Mannich (top) and allylation (bottom) reactions.

Scheme 3. Catalytic asymmetric hydroxymethylation.

this is the first example of an enantioselective reaction with a supported chiral scandium catalyst in water. Investigations aimed at improving the yield and enantiomeric excess of the reaction are now in progress.

In summary, we developed a novel heterogeneous scandium catalyst system, which works well in several carbon–carbon bond-forming reactions in water and has been applied to a catalytic asymmetric reaction. It has been shown for the first time that the combination of silica gel supported metal catalysts with an ionic liquid creates a hydrophobic reaction environment in water. This concept may be applicable to other catalysts based, for example, on metal complexes, and investigations along this line are underway.

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Keywords: heterogeneous catalysis · hydrophobic effect · ionic liquids · Lewis acids · scandium

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