

# A dream combination for catalysis: highly reactive and recyclable scandium(III) triflate-catalyzed cyanosilylations of carbonyl compounds in an ionic liquid†

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The catalytic activity of lanthanide triflates, particularly scandium triflate, increased dramatically in [bmim][SbF<sub>6</sub>], allowing the cyanosilylation of a variety of aldehydes and ketones with a turnover frequency up to 48 000 mol h<sup>-1</sup> and a total turnover number of 100 000.

The development of a recyclable catalytic system with high reactivity that enables economical and environmental sustainability is one of the most exciting challenges in chemistry. Emerging ionic liquids (ILs) have attracted increasing attention as novel vehicles for catalyst immobilization. Different types of metallic catalysts can be immobilized in ILs, allowing the recovery and reuse of both the catalyst and IL.<sup>1</sup> In addition to these advantages, unique reactivity and selectivity that cannot be achieved in conventional organic solvents are also observed in ILs.<sup>2</sup> As part of our continuing studies on catalysis in ionic liquids,<sup>3</sup> Song and ourselves collaboratively reported that metal triflate-catalyzed reactions, such as three-component reactions,<sup>3a</sup> Diels–Alder reactions,<sup>3b</sup> and Friedel–Crafts alkylation,<sup>3b</sup> were much faster in ionic liquids than in conventional organic solvents. In particular, hydrophobic ionic liquids with a non-coordinating anion, such as PF<sub>6</sub><sup>-</sup> and SbF<sub>6</sub><sup>-</sup>, exhibited positive ionic liquid effects that were attributed to *in situ* anion exchange between the catalyst and ionic liquid causing them to become a more electrophilic Lewis acid.<sup>3i</sup> With the aim of exploiting the synergic effects of lanthanide triflates in ionic liquids,<sup>4</sup> this study developed highly effective and environmentally benign catalytic cyanosilylation reactions of aldehydes and ketones in an ionic liquid with a turnover frequency (TOF) up to 48 000 mol h<sup>-1</sup> and a total turnover number (TON) of 100 000.

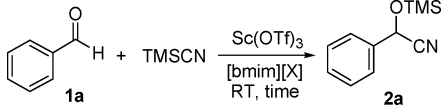
Cyanohydrins have demonstrated considerable synthetic potential as useful building blocks in organic synthesis. Hence, many catalytic methods, including asymmetric reactions, have been explored.<sup>5</sup> Among the various catalysts examined, Lewis acid-catalyzed cyanosilylations with trimethylsilylcyanide (TMSCN) have been investigated most extensively.<sup>6</sup> Therefore, it is not surprising to expect that the Lewis acidic rare-earth triflates may be effective catalysts for cyanosilylation reactions. Lanthanide triflates, particularly scandium(III) triflate, are

ubiquitous in many Lewis acid-catalyzed reactions, mainly due to the pioneering work by Kobayashi.<sup>7</sup> However, only a few lanthanide triflates, such as Yb(OTf)<sub>3</sub><sup>8</sup> and Sc(OTf)<sub>3</sub>,<sup>9</sup> have been investigated for the cyanosilylation of carbonyl compounds, and their catalytic activities are lower or merely comparable to those of other active catalysts, such as Cu(OTf)<sub>2</sub>,<sup>10a</sup> ZnI<sub>2</sub>,<sup>10b</sup> LiClO<sub>4</sub>,<sup>10c</sup> and LiCl.<sup>10d</sup> Moreover, there are no reports on lanthanide triflate-catalyzed cyanosilylation of carbonyls in ionic liquids. Although, Loh *et al.* indicated that ionic liquids have their own catalytic activity for the cyanosilylation of aldehydes, their efficiencies were quite low.<sup>11</sup> Based on these observations, we hypothesized that a combination of lanthanide triflates with an ionic liquid would accelerate the cyanosilylation reaction with high recyclability.

The initial experiments on the reaction of benzaldehyde (**1a**) and TMSCN were carried out without a catalyst in 1-butyl-3-methylimidazolium (bmim)-based ionic liquids with different anions, such as BF<sub>4</sub><sup>-</sup>, SbF<sub>6</sub><sup>-</sup>, and PF<sub>6</sub><sup>-</sup>.<sup>‡</sup> Although the efficiency was relatively lower than that reported by Loh *et al.*,<sup>11</sup> only the ionic liquid with the SbF<sub>6</sub><sup>-</sup> anion, [bmim][SbF<sub>6</sub>], showed appreciable catalytic activity with 34% conversion (entry 1, Table 1). Accordingly, the cyanosilylation was carried out first with 0.5 mol% of Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>]. All the benzaldehyde was converted to the corresponding cyanosilyl ether **2a** within 5 min (entry 2, Table 1), even in the presence of 0.1 mol% catalyst (entry 3, Table 1). 40% conversion was achieved in 5 min when the Sc(OTf)<sub>3</sub> loading was decreased further to 0.01 mol%, indicating a TOF (defined as moles of product per mole of catalyst per hour) of 48 000 mol h<sup>-1</sup> (entry 4, Table 1). More than 99% conversion was achieved when the reaction time was extended to 30 min, thus indicating that the Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>] is one of the most reactive catalysts reported (entry 5, Table 1). In contrast, significantly decreased conversions were observed in other ionic liquids, [bmim][BF<sub>4</sub>] (entry 6, Table 1) and [bmim][PF<sub>6</sub>] (entry 7, Table 1) and in CH<sub>2</sub>Cl<sub>2</sub> (entry 8, Table 1). The catalytic activities of various lanthanide triflates and In(OTf)<sub>3</sub> were also investigated using a loading of 0.1 mol% in [bmim][SbF<sub>6</sub>]. As shown in Fig. 1, Gd(OTf)<sub>3</sub> (97%), Ho(OTf)<sub>3</sub> (97%), Er(OTf)<sub>3</sub> (97%), Tm(OTf)<sub>3</sub> (99%), Y(OTf)<sub>3</sub> (96%), and In(OTf)<sub>3</sub> (96%) also exhibited excellent activity. Other lanthanide triflates, such as Ce(OTf)<sub>3</sub> (87%), Sm(OTf)<sub>3</sub> (91%), Eu(OTf)<sub>3</sub> (86%), Tb(OTf)<sub>3</sub> (93%), Lu(OTf)<sub>3</sub> (94%), and La(OTf)<sub>3</sub> (93%), showed comparable activity with conversions ranging from 86 to 94%. On the other hand, Pr(OTf)<sub>3</sub> (<5%), Nd(OTf)<sub>3</sub> (<5%), and Dy(OTf)<sub>3</sub> (28%) showed extremely low catalytic activity. These results suggested that an appropriate choice of metal triflate and

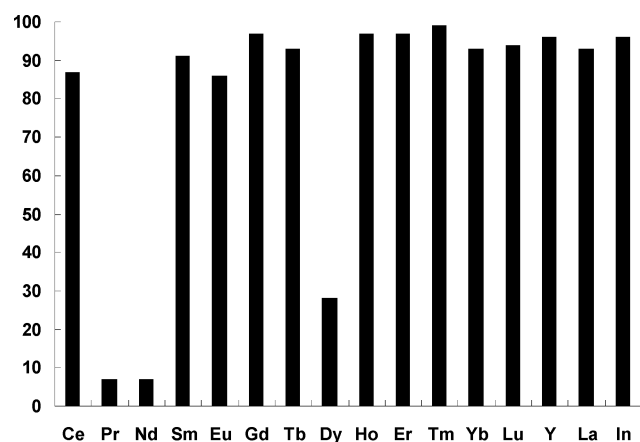
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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra for **2a–2t**, and **3a**, **3d**, **3i**, **3k**, **3m**. See DOI: 10.1039/b900254e

**Table 1** Sc(OTf)<sub>3</sub>-catalyzed cyanosilylation of benzaldehyde with TMSCN in an ionic liquid<sup>a</sup>


Entry	Sc(OTf) <sub>3</sub> (mol%)	Solvent	Time	Conv. (%) <sup>b</sup>
1	—	[bmim][SbF <sub>6</sub> ]	24 h	34
2	0.5	[bmim][SbF <sub>6</sub> ]	5 min	>99
3	0.1	[bmim][SbF <sub>6</sub> ]	5 min	>99 (98) <sup>c</sup>
4	0.01	[bmim][SbF <sub>6</sub> ]	5 min	40
5	0.01	[bmim][SbF <sub>6</sub> ]	30 min	>99
6	0.1	[bmim][BF <sub>4</sub> ]	5 min	11
7	0.1	[bmim][PF <sub>6</sub> ]	5 min	<5
8	0.1	CH <sub>2</sub> Cl <sub>2</sub>	5 min	7

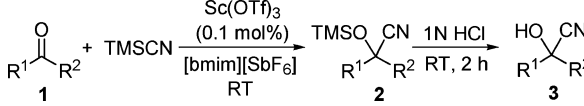
<sup>a</sup> Reaction conditions: benzaldehyde (1.0 mmol), TMSCN (1.2 mmol) in [bmim][X] (1.0 mL) at room temperature. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis with the average of three reactions. <sup>c</sup> Parentheses denote the isolated yield as cyanohydrine after acidic hydrolysis of the cyanosilyl ether with 1 N aqueous HCl solution for 2 h at room temperature.



**Fig. 1** Yields obtained with different lanthanide triflates. *Reaction conditions:* benzaldehyde (1.0 mmol), TMSCN (1.2 mmol), and Ln(OTf)<sub>3</sub> (0.1 mol%) in [bmim][SbF<sub>6</sub>] (1.0 mL) at room temperature for 5 min. The conversion was determined by <sup>1</sup>H NMR from the average three times reactions.

ionic liquid could generate a highly effective catalytic system for cyanosilylation of carbonyl compounds. The high catalytic activity of metal triflates in [bmim][SbF<sub>6</sub>] is ascribed to the anion exchange between Sc(OTf)<sub>3</sub> and [bmim][SbF<sub>6</sub>] resulted in a more Lewis acidic catalyst.<sup>31</sup>

The present catalytic system worked with a broad range of substrates. Various aldehydes were investigated in the presence of 0.1 mol% of Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>] for 5 min. As shown in Table 2 (entries 1–13, Table 2), all aromatic (**1b–1h**) and heteroaromatic aldehydes (**1i** and **1j**),  $\alpha,\beta$ -unsaturated (**1k**) and aliphatic aldehydes (**1l–1n**) were uniformly transformed into the corresponding cyanohydrine trimethylsilyl ethers (**2b–2n**) in quantitative yields. Some of the selected cyanosilyl ethers (**2a**, **2d**, **2i**, **2k**, and **2m**) were hydrolyzed to the corresponding cyanohydrine with excellent yields (entry 3, Table 1 and entries 3, 8, 10, 12, Table 2). The reaction can also be extended to a variety of ketones. It has been reported that, compared to aldehydes, the lanthanide triflates are known to be less reactive

**Table 2** Sc(OTf)<sub>3</sub>-catalyzed cyanosilylation of various aldehydes and ketones in [bmim][SbF<sub>6</sub>]<sup>a</sup>


Entry	1	Product	Yield (%) <sup>b</sup>
1	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO ( <b>1b</b> )	<b>2b</b>	>99
2	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO ( <b>1c</b> )	<b>2c</b>	>99
3	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO ( <b>1d</b> )	<b>2d (3d)</b>	>99 (94)
4	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO ( <b>1e</b> )	<b>2e</b>	>99
5	4-ClC <sub>6</sub> H <sub>4</sub> CHO ( <b>1f</b> )	<b>2f</b>	>99
6	4-PhOC <sub>6</sub> H <sub>4</sub> CHO ( <b>1g</b> )	<b>2g</b>	96
7	2-Naphthaldehyde ( <b>1h</b> )	<b>2h</b>	100
8	2-Furaldehyde ( <b>1i</b> )	<b>2i (3i)</b>	>99 (98)
9	2-Thiophenecarboxaldehyde ( <b>1j</b> )	<b>2j</b>	>99
10	<i>Trans</i> -C <sub>6</sub> H <sub>4</sub> CH=CHCHO ( <b>1k</b> )	<b>2k (3k)</b>	>99 (95)
11	PhCH <sub>2</sub> CH <sub>2</sub> CHO ( <b>1l</b> )	<b>2l</b>	>99
12	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CHO ( <b>1m</b> )	<b>2m (3m)</b>	>99 (95)
13	(CH <sub>3</sub> ) <sub>2</sub> CHCHO ( <b>1n</b> )	<b>2n</b>	>99
14	PhCOCH <sub>3</sub> ( <b>1o</b> )	<b>2o</b>	>99
15	PhCOCH <sub>2</sub> CH <sub>3</sub> ( <b>1p</b> )	<b>2p</b>	>99
16	PhCOPh ( <b>1q</b> )	<b>2q</b>	>99
17	1-Indanone ( <b>1r</b> )	<b>2r</b>	>99
18	$\alpha$ -Tetralone ( <b>1s</b> )	<b>2s</b>	>99
19	Cyclohexanone ( <b>1t</b> )	<b>2t</b>	>99

<sup>a</sup> Reaction conditions: carbonyl **1** (1.0 mmol), TMSCN (1.2 mmol), and Sc(OTf)<sub>3</sub> (0.1 mol%) in [bmim][SbF<sub>6</sub>] (1.0 mL) at room temperature for 5 min for aldehydes and 2 h for ketones. <sup>b</sup> Parentheses denote the isolated yield as cyanohydrine after acidic hydrolysis of the cyanosilyl ether with 1 N aqueous HCl solution for 2 h at room temperature.

toward cyanosilylation of ketones. For example, cyanosilylation of acetophenone with TMSCN using 5 mol% of Yb(OTf)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> provided the corresponding cyanosilyl ether in 41% after 21 h reaction.<sup>10c</sup> To our delight, all aromatic and aliphatic ketones (**1o–1t**) reacted with TMSCN in the presence of 0.1 mol% of Sc(OTf)<sub>3</sub> for 2 h to yield the corresponding cyanohydrine silyl ethers (**2o–2t**) quantitatively (entries 14–19, Table 2).

The excellent recyclability of this catalytic system was examined with the reaction between benzaldehyde and TMSCN in the presence of 0.01 mol% of Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>] at room temperature for 30 min. After extracting the reaction mixture with *n*-hexane, the ionic liquid containing Sc(OTf)<sub>3</sub> was reused for the next run. No leaching of Sc into organic layer was observed. As shown in Table 3, the recovered Sc(OTf)<sub>3</sub> immobilized in [bmim][SbF<sub>6</sub>] could be reused 10 times without any loss of catalytic activity achieving a total turnover number of almost 100 000. These results clearly show that a combination of Sc(OTf)<sub>3</sub> with the ionic liquid increases both its catalytic activity and stability.

In summary, this study examined the catalytic activity of lanthanide triflates in the cyanosilylation of benzaldehyde with TMSCN in an ionic liquid. A highly reactive, recyclable and environmentally benign catalytic system consisting of Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>] was developed. With this catalytic system, various cyanohydrine silyl ethers were obtained from a wide range of aldehydes and ketones in quantitative yield. Anion exchange between Sc(OTf)<sub>3</sub> and [bmim][SbF<sub>6</sub>], which makes the catalyst more Lewis acidic, might be responsible for the excellent catalytic activity of Sc(OTf)<sub>3</sub> in [bmim][SbF<sub>6</sub>]. The ionic

**Table 3** Recycling of Sc(OTf)<sub>3</sub> and [bmim][SbF<sub>6</sub>] in the cyanosilylation of benzaldehyde with TMSCN<sup>a</sup>

$$\text{Ph-CHO} + \text{TMSCN} \xrightarrow[\text{[bmim][SbF}_6\text{], RT, 30 min}]{\text{Sc(OTf)}_3 \text{ (0.01 mol\%)}} \text{Ph-CH(OTMS)-CN}$$

Run <sup>b</sup>	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Conv.(%)	>99	>99	98	96	>99	>99	97	97	>99	>99

<sup>a</sup> Reaction conditions: benzaldehyde (5.0 mmol), TMSCN (6.0 mmol) and Sc(OTf)<sub>3</sub> (0.01 mol%) in [bmim][SbF<sub>6</sub>] (5.0 mL) at room temperature for 30 min. <sup>b</sup> The product was extracted with *n*-hexane (50 mL × 3) and the ionic liquid containing Sc(OTf)<sub>3</sub> was reused for the next run.

liquid containing Sc(OTf)<sub>3</sub> could also be recovered and reused for several reaction cycles without any loss of catalytic activity. Studies aimed at applying this combination of lanthanide triflate with an ionic liquid to asymmetric cyanosilylations and to other catalytic reactions are currently under way.

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### Notes and references

‡ General procedure for the cyanosilylation of carbonyl compounds: a solution of Sc(OTf)<sub>3</sub> (0.1 mol%) in [bmim][SbF<sub>6</sub>] (1.0y) was stirred for 10 min at room temperature. A carbonyl compound (1.0 mmol) and TMSCN (1.2 mmol) were added successively, and the reaction mixture was stirred for 5 min for aldehydes (2 h for ketones) at room temperature under a nitrogen atmosphere. The reaction mixture was extracted with *n*-hexane (10 mL × 3), and the combined *n*-hexane layer was concentrated to give the corresponding cyanosilylated **2**. The results are shown in Tables 1 and 2. For catalyst recycling, the reaction was carried out in the presence of 0.01 mol% of Sc(OTf)<sub>3</sub>, and the recovered ionic liquid layer containing Sc(OTf)<sub>3</sub> was dried under a vacuum pump, and reused for the catalyst recycling test (Table 3). The hydrolysis of cyanohydrine trimethylsilyl ethers was carried out. The crude cyanosilyl ether obtained from the above reaction was treated with 1 N HCl (3.0 mL), and stirred for 2 h at room temperature. The reaction mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5), and the combined organic layer was washed with a saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated to give the cyanohydrine.

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