



## A tricyclic aluminum alkoxide catalyst for aldehyde trimethylsilylcyanation

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### ABSTRACT

Trimethylsilylcyanation of aldehydes is efficiently accomplished with a low concentration of catalyst **1** under mild conditions in acetonitrile. This protocol tolerates a variety of electron-rich, neutral, and deficient aryl, heterocyclic, and alkyl aldehydes. At the end of the reaction, catalyst **1** precipitates from solution, allowing it to be recycled three times.

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Cyanohydrins and cyanohydrin trialkylsilylethers are intermediates in the synthesis of natural products such as L-Biotin<sup>1</sup> and 20S-Amoptothecin.<sup>2</sup> Because of the utility of such intermediates, extensive investigations aimed at the development of improved Lewis acid and Lewis base catalysts for the reaction of trimethylsilylcyanide with aldehydes and ketones have been reported. Lewis acid catalysts include a titanium isopropoxide Schiff base complex,<sup>3</sup> titanium complexes,<sup>4</sup> aluminum complexes,<sup>5</sup> aluminum compounds bearing chiral ligands,<sup>6</sup> complexes of lanthanide(III),<sup>7</sup> samarium(III) chloride,<sup>8</sup> scandium(III) triflate,<sup>9</sup> indium(III) bromide,<sup>10</sup> and potassium-exchanged zirconium hydrogen phosphate.<sup>11</sup> Useful Lewis base catalysts include proazaphosphatranes,<sup>12</sup> cesium fluoride,<sup>13</sup> N-heterocyclic carbenes,<sup>14</sup> and trialkylamines.<sup>15</sup> The aforementioned monofunctional catalysts generally lead to high product yields from both aldehydes and ketones. In addition, chiral Lewis acid–Lewis base bifunctional catalysts have been reported that give rise to chirally induced reactions of trimethylsilylcyanide with aldehydes and ketones, providing products in moderate to excellent enantiomeric excesses.<sup>16</sup> Typically such bifunctional chiral catalysts contain a Lewis basic phosphine, phosphine oxide, or a sulfur group; and a Lewis acidic aluminum, titanium, or zirconium functionality. Zerovalent metals such as palladium and platinum have also been shown to promote the trimethylsilylcyanation of aldehydes and ketones.<sup>17</sup>

Lewis acid trimethylsilylcyanation catalysts are frequently aluminum species owing to the relatively low cost and toxicity of this metal. A drawback, however, is the frequent requirement of high mole percentages and even molar excesses of such catalysts.<sup>5,6</sup>

In 2006 we reported the synthesis of a novel tricyclic aluminum alkoxide (alumatrane dimer **1** in Fig. 1) and demonstrated its ability to form monomeric alumatranes in the presence of an oxygen or nitrogen donor.<sup>18</sup> In that paper it was also shown that alumatrane **1** in the presence of benzaldehyde and trimethylsilylcyanide in toluene at room temperature formed the corresponding cyanohydrin trialkylsilylether in quantitative yield.<sup>18</sup> Recently we described the first example of a trivalent alumatrane (**2** in Fig. 1) wherein the aluminum center possesses an empty (axial) coordination site.<sup>19</sup>

Herein we report the utility of alumatrane dimer **1** as a Lewis acid low concentration trimethylsilylcyanation catalyst for aryl, alkyl, and heteroaryl aldehydes. Initially, we determined the minimum concentration of **1** required for completion of such a reaction under mild conditions. Because of the unstable nature of the cyanohydrins, all products were isolated as their trimethylsilyl ethers.

As shown in Table 1, entries 1 and 2, only 72% and 49% yields, respectively, of the desired products were achieved in toluene in the presence of 5 and 2.5 mol % of dimer **1**. For this type of reaction, a polar solvent is generally needed to obtain high yields with low

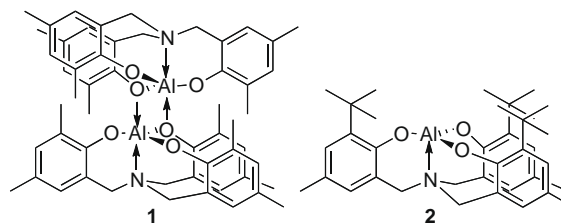
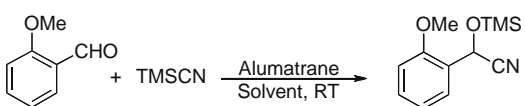


Figure 1. Alumatranes.

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**Table 1**  
Optimization study



Entry	Alumatrane <sup>a</sup> (mol %)	Solvent	Yield <sup>b,c</sup> (%)
1	5	Toluene	72
2	2.5	Toluene	49
3	5	CH <sub>3</sub> CN	98
4	2.5	CH <sub>3</sub> CN	96
5	0.5	CH <sub>3</sub> CN	94
6	0.5	CH <sub>3</sub> CN	67 <sup>d</sup>
7	None	CH <sub>3</sub> CN	24

<sup>a</sup> Alumatrane **1** was present in all cases except where noted otherwise.

<sup>b</sup> Reaction conditions: 2 mmol *o*-anisaldehyde, 3.5 mmol TMSCN, 5 mL solvent, 12 h, rt.

<sup>c</sup> Average of two runs.

<sup>d</sup> Alumatrane **2** was used at 70 °C.

mole percentages of catalyst.<sup>3–6,16</sup> The reaction shown in Table 1 failed in THF, however. As we have previously shown, dimer **1** is symmetrically cleaved in THF to form the corresponding monomeric alumatrane–THF adduct in high yield.<sup>18</sup>

Compound **1** is quite insoluble in acetonitrile. We have observed that adduct formation of **1** is characterized by splitting of the dimer and increased solubility of the adduct in organic solvents as in the case of the benzaldehyde adduct in acetonitrile and toluene, and of the THF adduct in pentane.<sup>18</sup> A <sup>13</sup>C NMR spectrum of the supernatant liquid above a suspension of **1** in acetonitrile that had been stirred for two days at room temperature revealed no new nitrile carbon peak as would be expected for the acetonitrile adduct, assuming acetonitrile exchange was slow on the NMR time scale. The reaction between *o*-anisaldehyde and trimethylsilyl cyanide in the presence of 5 mol % of dimer **1** in acetonitrile gave a nearly quantitative yield of the desired product (Table 1, entry 3) and when 2.5 mol % of alumatrane dimer **1** was employed, the yield decreased only slightly to 96% (Table 1, entry 4). Even at 0.5 mol % catalyst loading, the product yield was very high (Table 1, entry 5). The highest reported yield of this trimethylsilylcyanohydrin is 99% which was achieved in the presence of 2.8 mol % of a silica-supported imadazolium hydroxide in methylene chloride in 30 minutes.<sup>20</sup> Interestingly, despite the monomeric nature of **2** (which unlike **1** does not require dissociation to act as a catalyst) 1 mol % of **2** provided only a 67% yield of the product in the reaction shown in Table 1 (entry 6) at 70 °C. This unimpressive behavior can be attributed to steric hindrance provided by the three *t*-Bu groups in **2**. In contrast to alumatrane **1**, **2** is soluble in a wide range of solvents including toluene, acetonitrile, and tetrahydrofuran. It may be noted that the reaction of *o*-anisaldehyde with trimethylsilyl cyanide does proceed in acetonitrile in the absence of catalyst, but the product yield is only 24%. For the remainder of this report, 0.5 mol % of dimer **1** was used unless noted otherwise.

The wide variety of aryl aldehydes amenable to our protocol (Table 2) demonstrates the excellent substrate functional group tolerance of dimer **1**. The coupling of the electron-donating *m*- and *p*-anisaldehyde with trimethylsilyl cyanide proceeded smoothly to achieve 98% and 94% isolated yields of the desired products, respectively (Table 2, entries 1 and 2). Electron-deficient aldehydes are also effective in our protocol. Thus, 4-nitrobenzaldehyde in the presence of trimethylsilyl cyanide gave the corresponding cyanohydrin trimethylsilyl ether in 94% yield (Table 2, entry 3). Furthermore, 3- and 4-cyanobenzaldehyde gave 89% and 93% yields of the corresponding desired products (Table 2, entries 4 and 5, respectively). In a previous literature report, the reaction of 4-cyanobenzaldehyde with trimethylsilyl cyanide gave a product yield of only 72% using 0.5 mol % of an ammonium salt of DBU in

methylene chloride in which the DBU moiety acts as a base catalyst.<sup>21</sup> In the presence of methyl 4-formylbenzoate, trimethylsilyl cyanide gave a 92% yield of the desired product (Table 2, entry 6). This result is consistent with the notion that dimer **1** prefers to form a carbonyl adduct with the aldehyde oxygen rather than with the ester oxygen. In the presence of methyl benzoate, no adduct formation with dimer **1** was detected by NMR spectroscopy (see Supplementary data).

A variety of electron-neutral aryl aldehydes also worked well in our methodology. Thus, 2-naphthaldehyde reacted with trimethylsilyl cyanide to produce 91% of the desired product (Table 2, entry 7). *p*-Tolualdehyde and benzaldehyde led to 85% and 92% yields, respectively, of their corresponding cyanohydrin trimethylsilyl ethers (Table 2, entries 10 and 11, respectively). Sterically hindered electron-neutral aryl aldehydes, such as 1-naphthaldehyde and *o*-tolualdehyde, reacted smoothly to give 81% and 89% of their respective desired products (Table 2, entries 8 and 9, respectively).

With 4-chlorobenzaldehyde, a poor product yield of 45% was obtained when 0.5 mol % of dimeric **1** was employed in the presence of trimethylsilyl cyanide. However, the use of 1.25 mol % of **1** afforded an 82% yield of the desired product (Table 2, entry 12). Similarly, 1.25 mol % of dimer **1** led to improved yields in the reactions of piperonal and  $\alpha,\alpha,\alpha$ -trifluorotolualdehyde with trimethylsilyl cyanide (Table 2, entries 13 and 14, respectively).

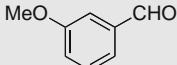
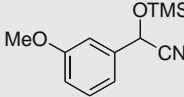
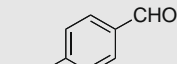
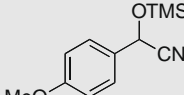
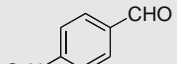
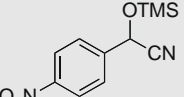
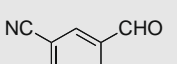
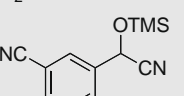
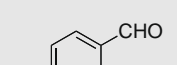
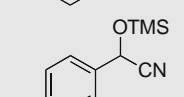
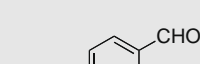
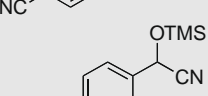
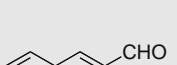
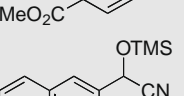
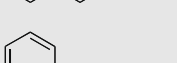
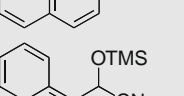
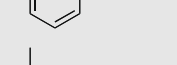
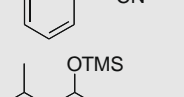
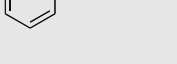
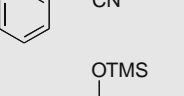
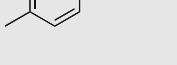
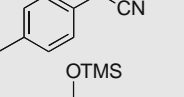
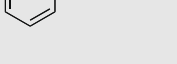
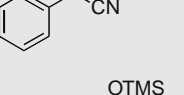
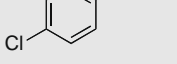
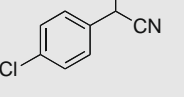
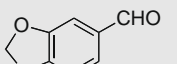
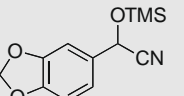
We also screened a variety of heterocyclic and alkyl aldehydes using catalyst **1** as shown in Table 3. Somewhat surprisingly, these reactions also proceeded well employing only 0.5 mol % of dimer **1**. Thus 2-pyridine-carboxaldehyde and 3-pyridine-carboxaldehyde afforded 91% and 86% yields of the desired products (Table 3, entries 1 and 2, respectively). The reaction between 6-methyl-2-pyridine-carboxaldehyde and trimethylsilyl cyanide afforded the new product shown in Table 3, entry 3 in 94% isolated yield. 2-Thiophene- and 3-thiophenecarboxaldehyde also functioned well in our protocol, giving 90% and 77% yields of the corresponding products (Table 3, entries 4 and 5, respectively). It might have been expected that a thiophene–aluminum adduct would form, as was produced with tetrahydrofuran and **1**.<sup>18</sup> Using catalyst **1** in the reaction of 4-methyl-2-thiazolecarboxaldehyde with trimethylsilyl cyanide, a new product was synthesized in 91% yield (Table 3, entry 6).

Alkyl aldehydes also provided corresponding cyanohydrin trimethylsilyl ethers in our procedure. When *trans*-cinnamaldehyde was used in the reaction, 80% of the desired product was obtained (Table 3, entry 7). Straight-chain alkyl aldehydes are also amenable to our approach, providing 85% and 81% of the desired products (Table 3, entries 8 and 9, respectively).

During our trimethylsilylcyanation reactions, a white precipitate consisting of the acetonitrile-insoluble dimer **1** was observed upon reaction completion. Pleasingly, the precipitated material in the reaction shown in Table 4 was successfully recycled three times, although the yield decreased significantly in the fourth cycle. The decrease in catalytic activity is attributable to the presence of adventitious moisture, mechanical loss of some of the 8.8 mg of **1** used, or the slight solubility of **1** in pentane and acetonitrile; or some combination of these factors.

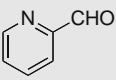
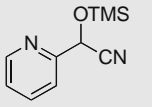
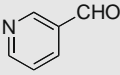
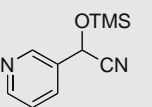
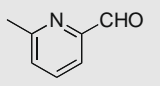
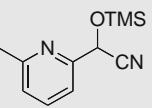
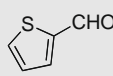
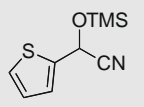
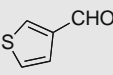
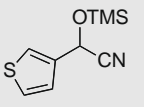
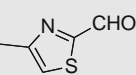
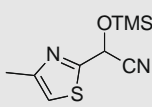
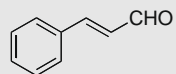
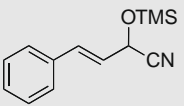
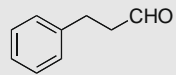
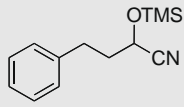
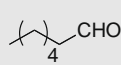
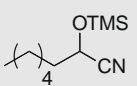
Since all the products shown in Tables 2 and 3 possess a chiral carbon center, the issue of synthesizing a chiral alumatrane arises. Of the Lewis acid catalyst systems for carbonyl trimethylsilylcyanation published in the literature, those based on titanium complexes of chiral Schiff bases appear to be widely used<sup>3,4</sup> and since the first publication on such a catalyst by Oguni,<sup>3c</sup> more efficient chiral Schiff bases have been developed for this purpose.<sup>3a,b,d</sup> Literature reports of aluminum Lewis acid catalysts for carbonyl trimethylsilylcyanation<sup>4,5,16</sup> have also appeared. Thus Pu et al. developed a catalyst system in which 10 mol % of Me<sub>2</sub>AlCl and 20 mol % of a chiral BINOL ligand in the presence of 40 mol % HMPA successfully converted aryl aldehydes to cyanohydrin

**Table 2**  
Trimethylsilylcyanation of aryl aldehydes

Entry	Aldehyde	Product	Yield <sup>a,b,c</sup> (%)
1			98 (Lit: 78–100)
2			94 (Lit: 33–100)
3			94 (Lit: 22–100)
4			89
5			93 (Lit: 70–72)
6			92 (Lit: 90)
7			91 (Lit: 78–100)
8			81 (Lit: 76–98)
9			89 (Lit: 80–100)
10			85 (Lit: 62–100)
11			92 (Lit: 16–100)
12			45 82 <sup>d</sup> (Lit: 63–100)
13			30 83 <sup>d</sup> (Lit: 55–99)
14			52 96 <sup>d</sup> (Lit: 95–100)

<sup>a</sup> Reaction conditions: 2 mmol aldehyde, 3.5 mmol TMSCN, 5 mL CH<sub>3</sub>CN, rt. 0.5 mol% **1** was used in all cases except where noted otherwise.<sup>b</sup> Average of two runs.<sup>c</sup> Most of the yields reported in the literature references pertain to products whose ee values ranged from 50% to 99%.<sup>d</sup> 1.25 mol% **1** was used.

**Table 3**  
Trimethylsilylcyanation of hetero and alkyl aldehydes

Entry	Aldehyde	Product	Yield <sup>a,b,c</sup> (%)
1			91 (Lit: 88–92)
2			86 (Lit: 90–99)
3			94
4			90 (Lit: 90–99)
5			77 (Lit: 82)
6			91
7			80 (Lit: 81–100)
8			85 (Lit: 81–100)
9			81 (Lit: 89–99)

<sup>a</sup> Reaction conditions: 2 mmol aldehyde, 3.5 mmol TMSCN, 5 mL CH<sub>3</sub>CN, rt.

<sup>b</sup> Average of two runs.

<sup>c</sup> Most of the yields reported in the literature references pertain to products whose ee values ranged from 50% to 99%.

trimethylsilyl ethers in moderate to high yields with enantioselectivities >90%.<sup>5</sup> Hoveda and co-workers reported asymmetric trimethylsilylcyanation of ketones using 1 mol % Al(O<sup>i</sup>Pr)<sub>3</sub> in the presence of 1 mol % of a peptide as an external ligand to obtain moderate to high yields of products with >80% enantioselectivities.<sup>6a</sup> An advantage of a chiral alumatrane (on which work is underway in our laboratories) is that no external ligand or base is required for catalyst function.

**Table 4**  
Recyclability of alumatrane dimer 1

Entry	Cycle	Time (h)	Yield <sup>a,b</sup> (%)
1	1	2	94
2	2	3	93
3	3	7	90
4	4	10	85

<sup>a</sup> Reaction conditions: 2 mmol *o*-anisaldehyde, 3.5 mmol TMSCN, 5 mL CH<sub>3</sub>CN, rt.

<sup>b</sup> Average of two runs.

In summary, we have demonstrated the usefulness of low concentrations of alumatrane dimer **1** for the room-temperature trimethylsilylcyanation of aldehydes. Our protocol tolerates a variety of electron-rich, neutral, and deficient aryl aldehydes; heterocyclic aldehydes; and alkyl aldehydes. Relative to the highest product yields recorded in the literature (see [Supplementary data](#)) two compounds were achieved in higher yield. Lower yields than the highest previously reported were obtained for nineteen compounds and of those, six were at or within 5%, four compounds were within 10%, four compounds were at or within 15%, and five compounds were within 20% of the highest yield reported. Three products are new. As demonstrated in entries 12–14 in [Table 2](#), product yields achieved by our methodology that poorly compete with maximum literature yields can be significantly enhanced with higher (but still catalytic) concentrations of **1**. We have also shown that the alumatrane can be recovered for recycling. Our alumatranes are the first aluminum catalysts for trimethylsilylcyanation that require no added ligand or base. Ketones did not trimethylsilylate under our conditions. Further explorations of the synthetic usefulness of alumatranes, including chiral ones, are in progress.

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### Supplementary data

Complete experimental procedures and characterizational data for all known and unknown compounds are provided. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.06.138](https://doi.org/10.1016/j.tetlet.2009.06.138).

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