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To be cited as: *ChemCatChem* 10.1002/cctc.202000309

Link to VoR: http://dx.doi.org/10.1002/cctc.202000309

A Journal of ChemPubSoc Europe

WILEY-VCH www.chemcatchem.org

ChemCatChem 10.1002/cctc.202000309

Three Coordinated Organoaluminum Cation for Rapid and Selective Cyanosilylation of Carbonyls under Solvent-Free Conditions

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Abstract: The well-defined three coordinated electronically unsaturated cationic organoaluminum complex $[(\{(2,6\text{-}i\mathrm{Pr}_2\mathrm{C}_6\mathrm{H}_3\mathrm{N})\mathrm{P}(\mathrm{Ph}_2)\}_2\mathrm{N})\mathrm{AlMe}]^+[\mathrm{MeB}(\mathrm{C}_6\mathrm{F}_5)_3]^-$ (**1**), has been utilized to catalyze the cyanosilylation of aldehydes and ketones under mild and solvent-free conditions. Moreover, catalyst **1** showed high chemoselective cyanosilylation of aldehydes over ketones, nitriles and olefins. The multinuclear NMR investigations revealed that cyanosilylation proceeds via Lewis adduct formation between **1** and TMSCN thereby activating TMSCN (Si-CN bond) followed by nucleophilic attack of the carbonyl oxygen at the Si center of the activated silane and formation of the product.

The cyanosilylation of carbonyl functional group is one of the most fundamental carbon–carbon bond forming reactions.[1] The resultant cyanohydrins are important intermediates that can be easily converted into numerous organic and biological compounds like α-hydroxy acids, 1,2-diols, α-amino alcohols, β-amino alcohols, etc.[2] The cyanosilylation of carbonyl compounds with trimethylsilylcyanide (TMSCN) is the most commonly used method. As a rare example, cyanosilylation of aldehydes was demonstrated without the use of any catalyst where solvent (DMF) acts as nucleophilic activator.[3a] In a recent report, this reaction was achieved even in the absence of solvent but with higher temperature and reaction time[3b] whereas under similar conditions ketones showed poor reactivity. Thus, for the cyanosilylation of ketones the use of catalyst is necessary. Activation of TMSCN and transfer of the cyano group to a carbonyl compound can be initiated by metal salts, organocatalyst, Lewis acid, Lewis bases, and heterogeneous catalyst.[4]

Very recently, due to remarkable reactivity the main group catalysts have attracted much attention for cyanosilylation of aldehyde and ketones in comparison to transition metal catalysts.[5] A few main-group catalysts based on Li,[6] Mg,[7] Ca,[8] B,[9] Al,[10] Si,[11] Ge,[12] Sn,[12] and Bi[13] have been utilized to access the cyanosilylation of carbonyl group. The combination of chiral Lewis acidic oxazaborolidinium ion and Ph_3PO catalytic system has also been reported for asymmetric cyanosilylation.[14a] In this context, cyanosilylation of carbonyls catalyzed by main group catalysts can be considered still at its infancy and far from matching the extensive research already accomplished with expensive transition metal catalysts.

In terms of catalysis, the Lewis acidic complexes of group 13 have proved to be potentially useful. In 2009, Kadam and Kim first reported the application of commercially available strong Lewis acid $B(C_6F_5)_3$ for cyanosilylation of aldehydes and ketones under solvent free conditions.[9] Roesky et al. demonstrated the catalytic efficiency of neutral aluminum complexes towards cyanosilylation of carbonyl compounds.[10a,b] In 2016, Zhou and co-workers used a three-component system of salen-aluminum complex, phosphoranes and Ph_3PO for enantioselective cyanosilylation of ketones and enanones.[14b] In 2017, Nagendran et al. synthesized a coordinatively saturated aluminum cation stabilized with non-bulky aminotroponate ligand with triflate counterion and utilized it to promote the cyanosilylation of carbonyl compounds under mild conditions[10c] (Figure 1). Notably, among the reported examples the cationic nature of coordinatively saturated pentacoordinated aluminum complex enhance the catalytic activity in comparison to the neutral tetracoordinated Al complexes.[10c] Inspiring from these pioneering results and further to improve the catalytic efficiency, we set out to employ unsaturated cationic aluminum complex for

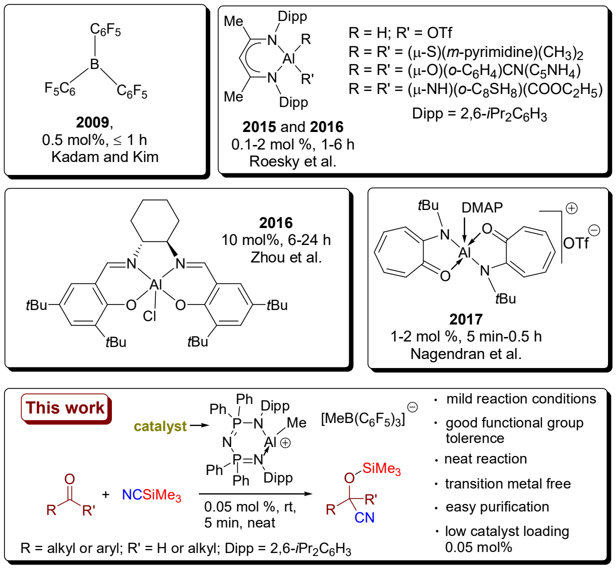

Figure 1. Well defined group 13 catalysts used for cyanosilylation of carbonyls and the aluminum cation used as a catalyst in this work.

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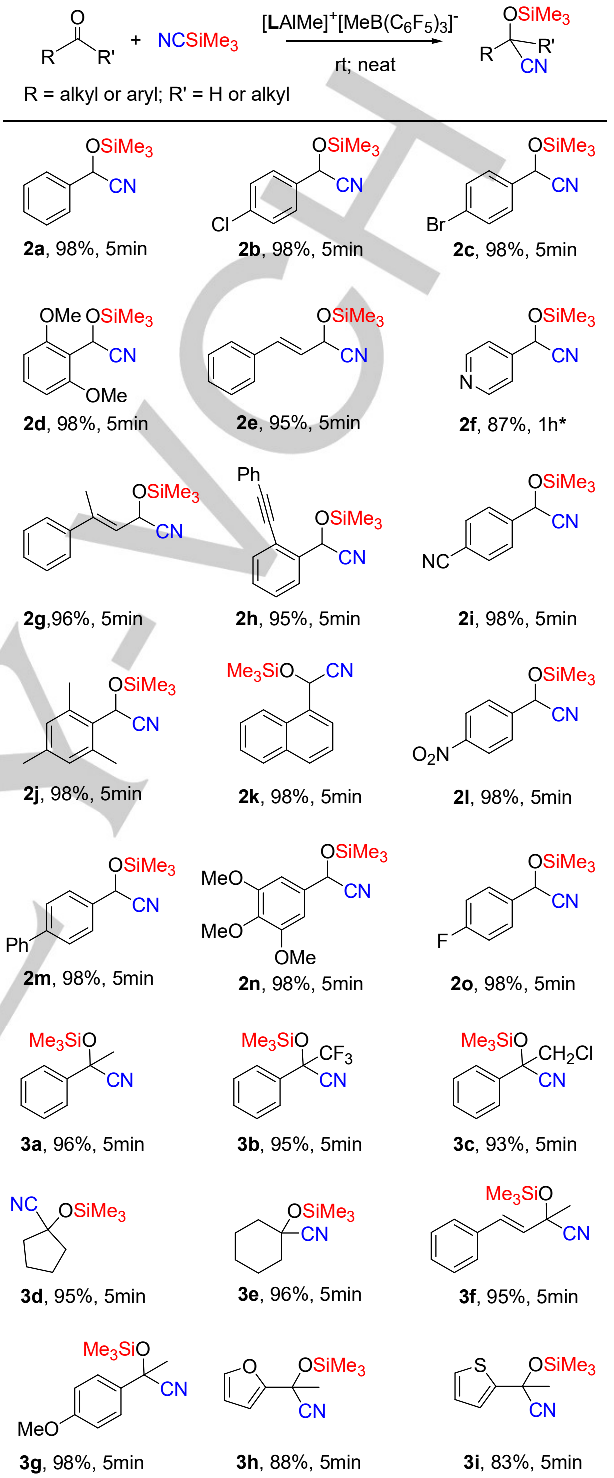
caynosilylation reaction. To the best of our knowledge, there is no example of an isolable, structurally characterized, low coordinated electronically unsaturated organoaluminum cation that has been used in cyanosilylation reaction. The main advantage of a cationic (electronically unsaturated) and coordinatively unsaturated (two or three coordinated) Al center is to ensure strong Lewis acid character and therefore its high reactivity.[15,16]

Previously, we reported on electronically unsaturated three coordinated Al cations, ($[\mathbf{L}AlMe]^{+}[MeB(C_6F_5)_3]^{-}$ (**1**) and $[\mathbf{L}AlH]^{+}[HB(C_6F_5)_3]^{-}$)[17] (**1'**) (**L** = $[\{(2,6\text{-}i\text{Pr}_2C_6H_3N)P(Ph_2)\}_2N]$) and demonstrated that their Gutmann Lewis acidity[18] is comparable to the popular Lewis acid $B(C_6F_5)_3$. The DFT calculations revealed the NBO charge of +2.01 on Al centre in **1** and support its high Lewis acidic nature. Further application of this cation was demonstrated by performing hydrofunctionalization of the carbonyls through hydroboration process.[17]

The present work extends the utility of Lewis acid character of the Al cation to catalyze reactions beyond hydrofunctionalization. The catalytic activity of **1** was evaluated for cyanosilylation of aldehydes and ketones. Compound **1** showed excellent activity with a very low catalyst loading (0.05 mol%) under neat conditions and the reaction completed within 5 min. The present catalyst is also important due to its ability to work without solvent as recently solvent-free methods have started to attracted prominence due to the environmental concerns.[19] Moreover, catalyst **1** displayed chemo-/regio-selective cyanosilylation of aldehydes over functional groups like olefins, alkynes, and nitriles and chemoselective cyanosilylation of aldehydes over ketones.

In the initial attempts, the reaction of benzaldehyde and TMSCN was performed both in toluene and under neat conditions with 5 mol % of catalyst **1** at room temperature which afforded the quantitative conversion of benzaldehyde to the corresponding cyanohydrin trimethylsilylether, ($PhCH(CN)OSiMe_3$) **2a**. Further, different reaction temperature and catalyst loadings were applied to optimize the reaction conditions. After optimizing an efficient catalytic protocol, the use of very low catalyst (0.05 mol%) has allowed the formation of desired product **2a** with excellent yield (98%) at room temperature (28 ℃) within 5 min (Table S1). Interestingly, when the model reaction was performed in the absence of catalyst **1** the trace amount of product formation was observed after 24 h which suggested that use of catalyst **1** promotes the cayanosilayation of the carbonyl group. The cyanosilylation of other substrates such as 4-bromobenzaldehyde and 1-(furan-2-yl)ethanone was also performed in the absence of catalyst **1** and no conversion was observed after 5min. However, the addition of catalyst **1** to the same sample resulted in the formation of desired product with 99% conversion within 5 min which authenticate the vital role of catalyst **1** to accelerate the catalytic reaction. Subsequently, under optimized reaction conditions, diverse range of aldehydes and ketones were smoothly converted to their corresponding cyanohydrin trimethylsilylethers in very good yields and results are summarized in Table 1 (**2b-2o** and **3a-3i**). Both electron donating and withdrawing substituted aldehyde and ketones gave excellent yields of their respective cyanohydrin products. Halogenated benzaldehydes could be easily converted to their respective cyanohydrin trimethylsilylethers (**2b** and **2c**) and no σ-bond metathesis between halogen moiety and the Me_3SiCN was observed. The cyanosilylation of aliphatic and heterocyclic substrates were also investigated and their corresponding products were obtained with high yields. In our attempts to further explore the substrate scope we have also been able to demonstrate the good chemo-

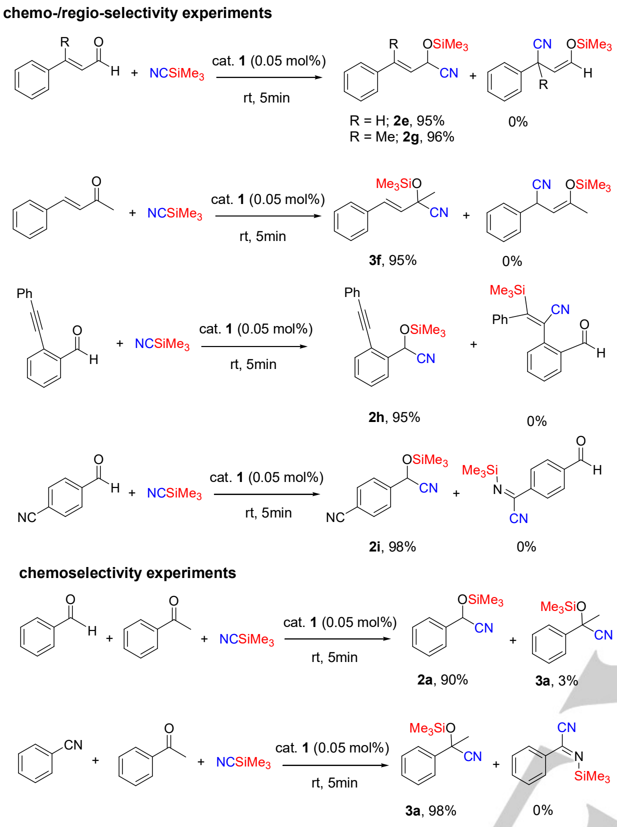
Table 1. Substrate scope for cyanosilylation of carbonyls[a],[b]



2a, 98%, 5min
2b, 98%, 5min
2c, 98%, 5min
2d, 98%, 5min
2e, 95%, 5min
2f, 87%, 1h*
2g,96%, 5min
2h, 95%, 5min
2i, 98%, 5min
2j, 98%, 5min
2k, 98%, 5min
2l, 98%, 5min
2m, 98%, 5min
2n, 98%, 5min
2o, 98%, 5min
3a, 96%, 5min
3b, 95%, 5min
3c, 93%, 5min
3d, 95%, 5min
3e, 96%, 5min
3f, 95%, 5min
3g, 98%, 5min
3h, 88%, 5min
3i, 83%, 5min

[a] Reaction conditions: aldehyde or ketone (1.0 mmol), Me_3SiCN (1.0 mmol), and catalyst **1** (0.05 mol%), rt as 25-28 ℃. [b] Yields have been calculated based on the products isolated by extraction in pentane. *1.5 mol% catalyst was used for **2f**.

and regio-selectivity of our catalyst towards carbonyl in the presence of different functional groups like olefins, alkyne and nitrile.

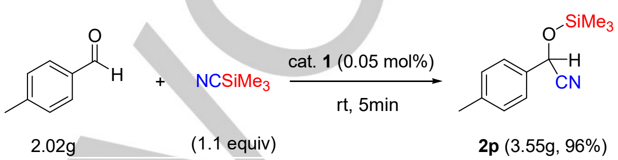


Scheme 1. Chemo-/regio-selective cyanosilylation of aldehydes and ketones catalyzed by **1**. Yields of the isolated products after extraction in pentane.

The *α,β*-unsaturated carbonyls such as cinnamaldehyde, 3-phenylbut-2-enal, 4-phenylbut-3-en-2-one, and 2-(phenylethynyl)benzaldehyde bearing both olefin (alkene, alkyne) and carbonyl functionality were examined. These reactions showed the reduction of only carbonyl functionality in a regioselective manner to their 1,2-adducts giving high yield of the products **2e**, **2g**, **3f**, and **2h** respectively and the C-C unsaturated systems remained intact (Scheme 1). Also, in case of 4-cyanobenzaldehyde the selective cyanosilylation of aldehyde functionality over the nitrile group was observed with high yield of the product **2i** (98%) with the reaction time of 5min (Table 1). These results clearly showed that olefins, alkyne and nitrile are well tolerated under mild reaction conditions without forming any other reduced products.

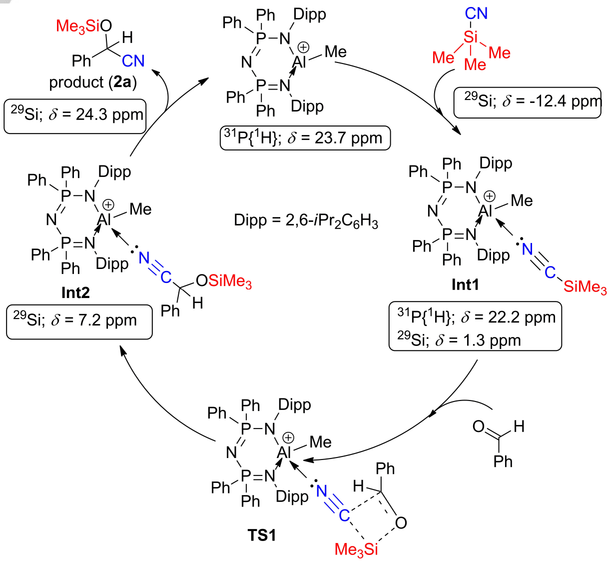
The cyanosilylation reaction of 4-pyridinecarboxaldehyde with 0.05 mol% catalyst loading afforded the desired product with a low conversion (8%). Increasing the catalyst loading to 1.5 mol% results in the formation of the corresponding product **2f** with 87% yield after 1 hour (Table 1). Higher catalyst loading and reaction time in this case can probably be accounted for the Lewis adduct formation between pyridine nitrogen and the Lewis acidic cationic Al center of the catalyst. However, in the case of 1-(furan-2-yl)ethanone and 1-(thiophen-2-yl)ethanone good conversions were observed (88 and 83% for **3h** and **3i**, respectively) with 0.05 mol% catalyst within the reaction time of 5min.

The excellent performance of the catalyst, in terms of short reaction time, very low catalyst loading, solvent free reactions and high chemoselectivity, in contrast to many important previous reports,[10] prompted us to test the applicability of the catalyst for scaled-up reactions. To check this aspect of the catalyst, a reaction between *p*-tolualdehyde (16.6 mmol) and Me_3SiCN was performed successfully by using 0.0008 mmol (0.05 mol%, 11 mg) of **1** that gave product, 2-(*p*-tolyl)-2-((trimethylsilyl)oxy)acetonitrile (**2p**) in quantitative (96%) isolated yield (3.55 g, TOF 384/min) at 28 °C under solvent-free conditions (Scheme 2).



Scheme 2. Cyanosilylation of *p*-tolualdehyde by **1** in a scaled-up reaction.

To gain insights on mechanistic investigations, we further performed various in-situ NMR experiments. Based on the observations from these NMR experiments and the previous reports,[10] a catalytic scheme has been proposed for the cyanosilylation of carbonyls using the methyl aluminum cation **1** (Scheme 3). Ideally, the methyl aluminum cation can form Lewis adducts with either carbonyl oxygen or Me_3SiCN however, the adduct formation with the latter would be a preferred [20] pathway leading to the formation of **Int1**. The **Int1** was clearly observed when an stoichiometric reaction of **1** and Me_3SiCN was performed in C_6D_6, an apparent downfield chemical shift of the ^{29}Si NMR signal from -12.4 ppm (for Me_3SiCN in C_6D_6) to 1.3 ppm (for the Lewis adduct of **Int1**) was supportive of this.[17] Further, an upfield shift in the $^{31}P\{^1H\}$ NMR signal from 23.7 ppm



Scheme 3. Proposed mechanism for the cyanosilylation of PhCHO with Me_3SiCN using $[LAlMe]^+[MeB(C_6F_5)_3]^-$ (**1**) as the catalyst. The weekly coordinating counter anion $[MeB(C_6F_5)_3]^-$ of the catalyst is not participating in the reaction and therefore has not been shown in the scheme.

(for **1**) to 22.2 ppm also corroborates with the proposed adduct **Int1**. In the ^{1}H NMR spectrum of the **Int1**, two septets (3.04 and 3.73 ppm) and four doublets (1.18, 0.87, 0.66 and 0.46 ppm) for the 2,6-iPr$_2$C$_6$H$_3$ moieties of the ligand were observed that are similar to our previous observations for an unsymmetrical tetra coordinated cationic Al center[17] whereas, the planar arrangement around Al center of cation **1** gave one septet and two doublets.[17] We believe that this adduct formation leads to the activation of Si-CN bond of Me$_3$SiCN. At this stage, after the addition of benzaldehyde, nucleophilic attack of the carbonyl oxygen at the Si center of the activated Me$_3$SiCN occurred leading to the transfer of cyanide moiety from Si center to the electrophilic carbonyl carbon involving sigma bond metathesis possibly via a cyclic four membered transition state **TS1**. Simultaneous regeneration of the catalyst **1** was evident by reappearance of the signal at 23.7 ppm in the ^{31}P{^{1}H} NMR spectrum of the reaction mixture. Further, in ^{29}Si NMR spectrum of reaction mixture the appearance of signal at 24.3 ppm indicates elimination of product **2a** from **Int2**. Probably due to the steric reasons it forms a very labile adduct with the cationic Al center and thus enabling the catalyst to be available for the next reaction cycle.

In summary, we have developed a new efficient and sustainable catalyst for the chemoselective cyanosilylation of aldehydes and ketones. The current procedure employed a methyl aluminum cation [**L**AlMe]$^+$[MeAl(C$_6$F$_5$)$_3$]$^-$ as the catalyst and Me$_3$SiCN as a cyanide precursor to prepare cyanohydrin trimethylsilylethers in a homogeneous process. Solvent-free, room temperature conditions, very low catalyst loadings, atom-economical process, and short reaction duration are attractive features of this catalyst. The pronounced Lewis acidity of the cationic aluminum center facilitates this reaction and opens up new avenues in the area of main group catalysis compared to expensive heavier transition elements. The reaction conditions optimized here can also be extended for scaled up synthesis making the whole process adoptable.

Acknowledgements

We acknowledge IISER Mohali for NMR central facility and for all other infrastructural support. The authors thank Dr. S. Venkataramani and Dr. S. A. Babu for useful discussions. S. R. and M. B. acknowledge IISER Mohali for PhD fellowships.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: cyanosilylation • organoaluminum catalyst • carbonyl • chemoselecetivity • cationic aluminum complex

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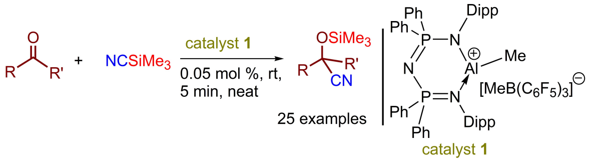

Cationic organoaluminum complex with Al center in three coordinated geometry as well as in electronically unsaturated state is an example of highly Lewis acidic main group compound. The coordination of TMSCN to the cationic Al center activates the Si-CN bond in the former to catalyze cyanosilylation of carbonyls under RT and solvent free conditions.