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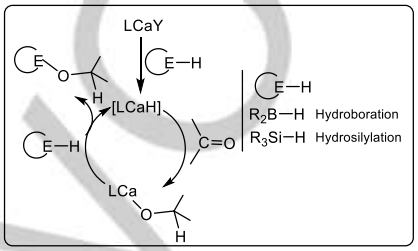
Beyond Hydrofunctionalization: A Well-Defined Calcium Compound Catalyzed Mild and Efficient Carbonyl Cyanosilylation

Sandeep Yadav,[a] Ruchi Dixit,[b] Kumar Vanka,[b] and Sakya S. Sen*[a]

Dedicated to Professor Dietmar Stalke on the occasion of his 60th birthday

Abstract: Organocalcium compounds have been reported as efficient catalysts for various transformations, for cases where one of the substrates contained a E–H (E=B, N, Si, P) bond. Here, we look at the possibility of employing an organocalcium compound for a transformation in which none of the precursors has a polar E–H bond. This study demonstrates the utilization of a well-defined amidinatocalcium iodide, [PhC(N*i*Pr)$_2$CaI] (**1**) for cyanosilylation of a variety of aldehydes and ketones with Me_3SiCN under ambient conditions without the need of any co-catalyst. The reaction mechanism involves a weak adduct formation between **1** and Me_3SiCN leading to the activation of the Si–C bond, which subsequently undergoes σ-bond metathesis with a C=O moiety. Such a mechanistic pathway is unprecedented in alkaline earth metal chemistry. Experimental and computational studies support the mechanism.

There is an increasing demand to explore efficient, sustainable catalysts based on earth-abundant elements that can rival precious metal catalysts in high-value transformations.[1-4] Among various earth-abundant elements, organocalcium compounds have recently garnered considerable interest due to their high terrestrial abundance, low-cost, non-toxicity regardless of concentration, and biocompatibility. A range of catalytic processes such as hydroamination, hydrophosphination, hydroboration, hydrosilylation, and the hydrogenation of C=C, C=O or C=N bonds involving hydrocarbon soluble calcium compounds has appeared in recent years through the studies from a number of research groups of whom Harder, Hill, Roesky, Westerhausen, Sarazin, and Ward are especially prominent.[5-20] A common feature of all aforementioned reactions is that one of the precursors contains an E–H bond that undergoes σ-bond metathesis with the organocalcium compound to generate the active catalyst. The latter undergoes an insertion reaction with the unsaturated C=X bond to generate a species that subsequently reacts with another molecule of E-H to form the product and regenerate the catalyst (Scheme 1). Therefore, the catalytic landscape of organocalcium compounds is primarily restricted to those processes where one of the substrates contains a polar E–H bond and is generally not known for those reactions where neither of the substrates possess an E–H bond.



Scheme 1. The tentative catalytic cycle for organocalcium catalyzed hydrofunctionalization of carbonyl compounds [Y=H, alkyl]. What happens if there is no E-H bond present in the substrates?

To expand the catalytic regime of hydrocarbon soluble well-defined calcium compounds, we have turned our attention towards the cyanosilylation of carbonyl compounds with Me_3SiCN,[21] where none of the substrates possessed an E–H bond. Unlike carbonyl hydroboration by heavier main group compounds, which is increasingly being reported in the literature,[22] the catalytic carbonyl cyanosilylation by compounds with heavier main group elements has seen only limited success with p-block elements from the groups of Roesky,[23-25] Nagendran,[26,27] and others.[28,29] Furthermore, cyanosilylation of carbonyl compounds has not been achieved thus far with any alkaline earth metal complex. Notable advances to this end have been made with lanthanide based polyoxometallates.[30] Our initial entrance into the calcium chemistry was through the preparation of soluble and easily accessible [PhC(N*i*Pr)$_2$CaI] (**1**).[31] After discovering that **1** efficiently catalyzes the hydroboration of aldehydes, ketones, and imines,[32] we sought to look into the viability of cyanosilylation of carbonyl compounds with the former to enhance the utility of **1** as a catalyst. Incentivized by the seminal works on electrostatic activation of multiple bonds by an early main group element by Clark and others,[33] we hypothesized that the electrostatic interaction between the Ca atom of **1** and Me_3SiCN will activate the Si-C bond to such a level that it would permit further nucleophilic attack from the carbonyl moiety. Here, we describe our initial efforts to define a catalytic, molecular cyanosilylation process based upon a calcium complex and provide a mechanistic appraisal based upon stoichiometric reactivity and DFT based calculations.

Calcium compound **1** was examined as a catalyst for cyanosilylation of a variety of aldehydes and ketones with Me_3SiCN, as illustrated in Scheme 2. A brief screening of solvents showed that that most of the organic solvents were suitable for the reaction. However, for aldehydes, toluene and for ketones, THF afforded the best results. Conversion of aldehydes was efficient at catalyst loadings of 2 mol % within 30 minutes

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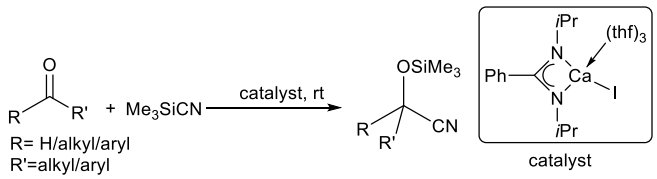
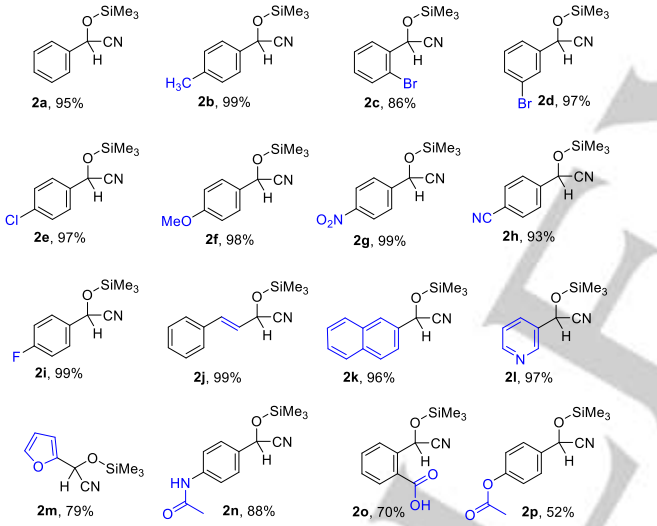
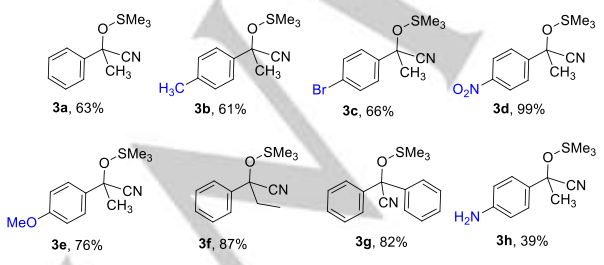
(entries **2a**-**2p**). As the experiments were monitored by ^{1}H NMR spectroscopy, most of the reactions were over before the reaction mixture could be analyzed. In fact, a visual evaluation of all such reactions qualitatively indicated that they were complete in less than 10 min. Electron donating as well as withdrawing groups were well tolerated. For the analogous reactions with substrates including naphthalene and heterocycles, the desired products were obtained in good yields (**2k**: 96%, **2l**: 97%, **2m**: 79%). Consistent with recent studies, 1,2-addition of Me_3SiCN to cinnamaldehyde was observed as a result of the highly electrophilic character of the carbonyl moiety (**2j**). Aldehydes were selectively and exclusively cyanosilylated in the presence of amide (**2n**), acid (**2o**) and ester (**2p**).

Scheme 2. The scope of cyanosilylation with aldehyde and ketone substrates.



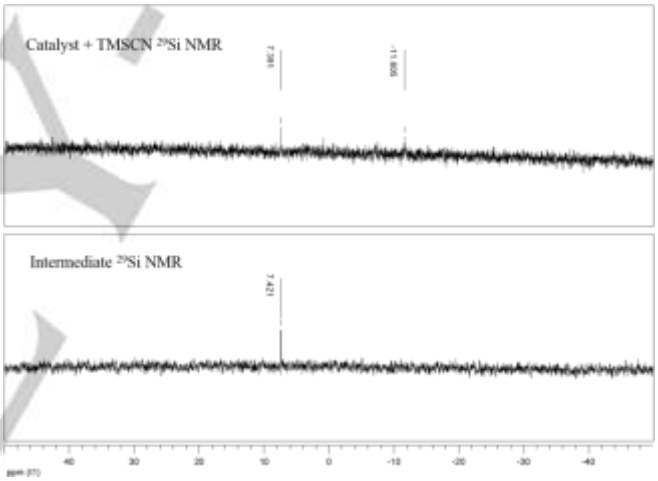


[a]Reaction conditions: 2 mol% catalyst, 30 min reaction at room temperature in toluene. Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethyl benzene as an internal standard.



[a]Reaction conditions: 3 mol% catalyst, 2 h reaction at room temperature in THF. Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethyl benzene as an internal standard.

Aromatic ketones were identified as equally suitable substrates for cyanosilylation, demonstrated by the conversion of acetophenone although marginally higher catalyst loadings (3 mol %) and extended reaction time (2 h) were necessary to achieve productive conversion. Even the sterically demanding benzophenone was converted to the corresponding cyanosilylated product (**3g**) under the same conditions in 82% yield, which had not been achieved with any other main group catalyst thus far. The cyanosilylation of a wide variety of aromatic ketones bearing various functional groups to the respective cyanohydrin trimethylsilyl ethers was successful under standard reaction conditions. The cyanosilylation of acetophenone derivatives with electron withdrawing substituents (**3c**, **3d**) took places smoothly. In contrast, acetophenone derivatives with electron donating substituents (**3b**, **3e**, **3h**) were not found to be very suitable for productive catalysis. Among the main group catalysts, the catalytic efficiency of **1** was found to be higher than our previously reported silane catalyst [PhC(N*t*Bu)$_2$Si(H)(Me)Cl] and comparable with other known aluminum catalysts reported by Zhi, Nagendran, Roesky and others.[23-27]



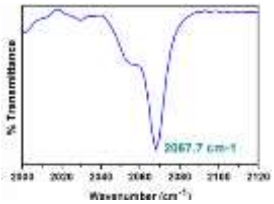


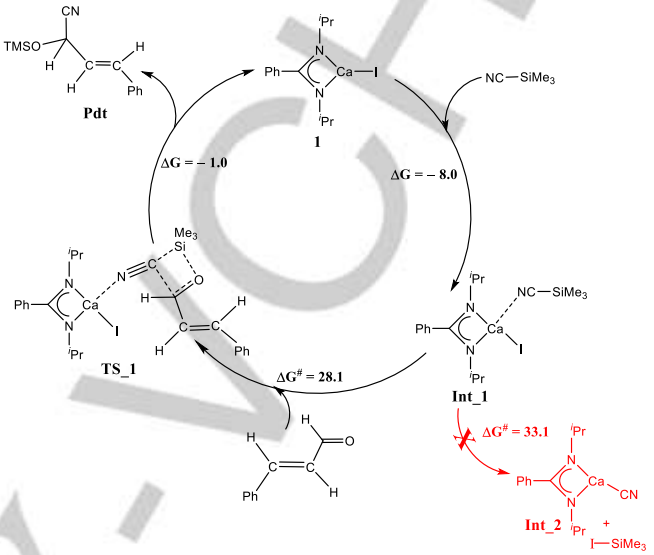
Figure 1. ^{29}Si NMR from the reaction the reaction mixture of **1** and Me_3SiCN (left). The above NMR was taken after 30 min, when both Me_3SiCN and **Int_2** were present; after 2 h all Me_3SiCN was consumed and only **Int_2** was left (below).The IR spectrum of the **Int_2** is on the right.

Efforts to gain some mechanistic insights were undertaken. Two possible pathways may be considered for the mechanism. By analogy to the mechanism proposed for organolanthanide catalyzed cyanosilylation of ketones,[34] the Ca-catalyst can undergo σ-bond metathesis with Me_3SiCN affording the "Ca-CN complex" (**Int_2**) that acts as the catalyst for the cycle. Alternatively, **1** can form an adduct with Me_3SiCN (**Int_1**) and activates the Si-C bond. As Me_3SiCN is more basic than THF, replacement of one of the THF molecules by Me_3SiCN is viable. The cycloaddition of the Si–C σ bond of the Me_3SiCN fragment to the O=C bond of the carbonyl moiety could result in the formation of cyanohydrin. In order to understand which mechanism is operational, a few stoichiometric reactions were

undertaken. The ^{1}H NMR spectrum of the 1:1 reaction of **1** and Me_3SiCN at ambient temperature shows the development of a new $SiMe_3$ peak at δ 0.06 ppm along with the free Me_3SiCN peak at δ 0.23 ppm. In the ^{29}Si NMR, a new peak developed at δ 7.39 ppm with the free Me_3SiCN peak at δ -11.6 ppm (Figure 1). No peak at δ 0.38 ppm in the ^{1}H NMR and δ 10.5 ppm in the ^{29}Si NMR negate the possibility of the metathesis reaction between **1** and Me_3SiCN and the formation of Me_3SiI during the reaction. Monitoring the NMR after 2 h showed the disappearance of the Me_3SiCN resonance and the presence of only one resonance at δ 7.39 ppm in the ^{29}Si NMR. New resonances appeared at the ^{13}C NMR spectrum at δ 1.59 and 127.43 ppm, which are different from those in Me_3SiCN (δ -1.95 and 127.62 ppm). The new resonances are indicative of the formation of a weakly bound adduct. The IR spectrum of the intermediate showed a CN stretching band at ν 2067.7 cm^{-1} (free Me_3SiCN at ν 2192 cm^{-1}). The decrease in stretching frequency indicates the decrease of triple bond character, which is anticipated due to electrostatic interaction between the C≡N bond and the calcium atom (Figure 1, right). Taken together, these data surmise that Me_3SiI was not formed during the catalytic cycle and suggests the possible formation of a weakly bound adduct, **Int_1**. The role of the calcium complex is to pre-orient the substrate as well as activate the C–Si bond in Me_3SiCN. By monitoring the reaction of **Int_1** with 1 equivalent of benzaldehyde by ^{1}H NMR, we observed the formation of the characteristic C-H resonance of the **Pdt** at δ 4.69 ppm

Full quantum chemical calculations have also been done using density functional theory (DFT) at the PBE/QZVP level of theory {for further details, please see the Supporting Information (SI) file}. Cinnamaldehyde was chosen as the substrate for the calculations because the obtained product yield was observed to be highest for this case (see Scheme 2, 2j). The mechanism obtained for this is shown in Scheme 3.

1 can react with trimethylsilyl cyanide (Me_3SiCN) to give **Int_1**, where the nitrogen of the cyanide group shows a weak interaction with the calcium of catalyst **1**.This intermediate complex, **Int_1**, is seen to being thermodynamically stable (ΔG = -8.0 kcal/mol), (see Scheme 1 below). Subsequent to this, there are two possible pathways that can be followed as the reaction proceeds. In the first possible pathway, **Int_1** can transform into **Int_2** (see FigureS1 in the SI file) *via* a four membered transitionstate,**TS_2**, with a free energy barrier **(**$\Delta G^{\#}$) of 33.1 kcal/mol and a reaction free energy (ΔG) of 2.5 kcal/mol. In the alternative pathway, nucleophilic attack by the carbonyl oxygen of the cinnamaldehyde can occur at the silicon centre of Me_3SiCN in **Int_1**. This will lead to the cyanide being transferred from the silicon centre to the electrophilic carbonyl carbon of the cinnamaldehyde, *via* a C-C bond formation reaction (see Scheme 1). This occurs through a four membered transition state (**TS_1**) and has a barrier of 28.1 kcal/mol. Therefore, a comparison of the two competing pathways shows that the second pathway is thermodynamically (by 3.5 kcal/mol) and kinetically (by 5.0 kcal/mol) more favourable than the first. Indeed, applying the Arrhenius equation to compare the rates, it is seen that the second pathway would be approximately 4000 times faster than first. Hence, it becomes clear that the reaction would proceed through the second pathway, where the transition state **TS_1** would lead to the formation of the product (**Pdt**) along with the regeneration of the catalyst **1**. The free energy profile with the intermediate and transition state structures are shown in Figure S1 in the SI file.



Scheme 3. The catalytic cycle and reaction mechanism for the cinnamaldehyde cyanosilylation reaction by catalyst **1**, calculated at the PBE/QZVP level of theory with DFT. ΔG and $\Delta G^{\#}$ represent the Gibbs free energy of reaction and the Gibbs free energy of activation respectively. All values are in kcal/mol.

In summary, organocalcium compounds are thus far known to catalyze hydroboration, hydroamination, hydrophosphination, and hydrosilylation of multiple bonds. We have introduced a well-defined organocalcium catalyst for cyanosilylation of carbonyl compounds, where none of the precursors contains a polar E-H bond. This is also the first report on an alkaline earth metal catalyzed cyaosilylation reaction. The catalyst is found to be very effective for the cyanosilyltion of a wide range of aldehydes and ketones under ambient conditions. As neither the precursor or nor the catalyst contains any E-H bond, the mechanism of the reaction is different from that proposed previously for organocalcium catalyzed reactions. Our combined experimental and computational studies (with DFT based calculations)lead us to conclude that the calcium complex forms a weak adduct with trimethylsilyl cyanide, leading to polarization of the Si-C bond and facilitates the carbonyl attack. The observation of cyanosilylation of carbonyl compounds with **1** will not only expand the catalytic regime of calcium complexes but reduce the gap between the chemistry of alkaline earth metals and transition metals/lanthanides in homogeneous catalysis.

Experimental Section

Experimental Details, details of DFT calculations, and representative NMR spectra are given in the supporting information.

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Keywords: Ca-catalysis • cyanosilylation • DFT• transition metal free catalysis • carbonyls

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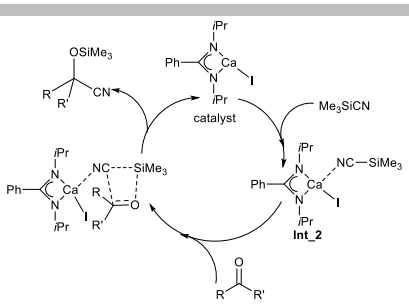
COMMUNICATION

Moving over from catalyzing only hydroelemenation reactions, this work describes the first use of a well-defined calcium compound for cyanosilylation of a range of aldehydes and ketones. Spectroscopic and DFT studies propose an unprecedented mechanism that involves a weak adduct formation between the catalyst and Me_3SiCN, followed by σ-bond metathesis with the C=O group.



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