

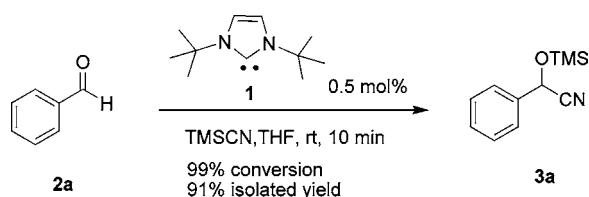
## Activation of TMSCN by N-Heterocyclic Carbenes for Facile Cyanosilylation of Carbonyl Compounds

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N-Heterocyclic carbenes were found to be highly effective organocatalysts in activating TMSCN for facile cyanosilylation of carbonyl compounds. Cyano transfer from TMSCN to aldehydes and ketones proceeds at room temperature in the presence of only 0.01–0.5 mol % of N-heterocyclic carbene (**1**), leading to a range of trimethylsilylated cyanohydrins in very good to excellent yields. These conditions are extremely mild and simple and tolerate various functional groups.

N-Heterocyclic carbenes (NHCs) have attracted considerable attention in recent years. They have been extensively studied and employed as ligands in a variety of transition-metal-catalyzed processes.<sup>1</sup> Owing to their strong  $\sigma$ -donating properties, N-heterocyclic carbenes can also act as organocatalysts.<sup>2</sup> N-Heterocyclic carbenes have been used to catalyze organic transformations such as nucleophilic substitutions,<sup>3</sup> benzoin- and Stetter-type reactions,<sup>4</sup> homoenolate formations,<sup>5</sup> transesterification reactions,<sup>6</sup> and trimerization of isocyanates.<sup>7</sup> It was believed that the key step in the NHC-catalyzed nucleophilic substitutions or benzoin- or Stetter-type reactions involves the attack of the carbene at the carbonyl group of the aldehydes to form the “Breslow intermediate” which functions like an acyl anion equivalent (Umpolung). For transesterification reactions,

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an NHC–acyl intermediate was suggested by Waymouth and Hedrick.<sup>6e</sup> In a recently reported NHC-catalyzed amide bond formation<sup>8</sup> reaction, it was proposed that NHC functions as a carbon-centered Brønsted base.

Recently, we have reported our discovery of an efficient NHC-catalyzed trifluoromethyl transfer reaction from TMSCF<sub>3</sub> to carbonyl compounds.<sup>9</sup> To our best knowledge, this reaction serves as the first example to show that a silicon-based reagent such as TMSCF<sub>3</sub> can be activated by N-heterocyclic carbenes for nucleophilic addition reactions. As part of our continued efforts to gain more insight into this unprecedented mode of reactivity for NHCs, we now wish to disclose a facile NHC-catalyzed cyanation reaction between TMSCN and carbonyl compounds using as little as 0.01–0.5 mol % catalyst loadings.

Cyanohydrins represent one of the most valuable synthons that can be elaborated into a variety of useful synthetic building blocks, such as  $\alpha$ -hydroxy acids,  $\alpha$ -hydroxy aldehydes, 1,2-diols, and  $\alpha$ -amino alcohols.<sup>10</sup> Because of their importance in organic synthesis and life science research, a large body of work has been devoted to the development of cyanohydrin synthesis. The most commonly used method to prepare cyanohydrins involves the cyanosilylation of carbonyl compounds using TMSCN. Transfer of a cyano group from TMSCN to carbonyl compounds can be catalyzed by a plethora of reagents<sup>11–13</sup> including Lewis acids, Lewis bases, metal alkoxides, bifunctional catalysts, iodine, and inorganic salts. Among these methods, the *metal-free, organic-molecule-catalyzed processes* are particularly attractive because of the mildness of the reaction conditions and the potential for the development of an asymmetric version of this transformation. However, there are only a limited number of such examples existing in the literature.<sup>12,13</sup> For example, it has been reported that Lewis bases such as triethylamine, tributylphosphine, triphenylarsine, trisaminophosphines, and triphenylantimony catalyze cyanosilylation of car-

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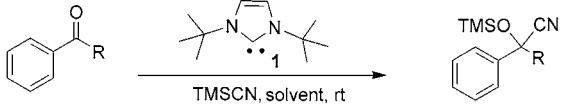
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bonyl compounds with TMSCN.<sup>12d,f,i,j</sup> Guanidine was also successfully employed as a catalyst for this reaction.<sup>12h,k</sup> More recently, certain amine *N*-oxides have been shown to be effective catalysts for the cyanide addition to both aldehydes and ketones using TMSCN as the cyanide source.<sup>12a–c,e,g</sup> In these reactions, nucleophilic activation of TMSCN by amine *N*-oxides was proposed as a key step in the catalytic cycle.<sup>12c</sup> During our search for a new type of organocatalyst for this transformation, we decided to investigate the possibility of using nucleophilic *N*-heterocyclic carbenes to catalyze cyanosilylation of carbonyl compounds with TMSCN.

On the basis of our experience with NHC-catalyzed trifluoromethyl addition reactions with TMSCF<sub>3</sub>,<sup>9</sup> we postulated that the carbon–silicon bond in TMSCN could be activated by NHCs for cyano transfer in an analogous fashion. Indeed, when a THF solution of benzaldehyde and TMSCN was treated with 0.5 mol % of 1,3-di-*tert*-butylimidazol-2-ylidene (**1**, *t*Bu, Table 1) at room temperature, the cyanide addition occurred almost instantaneously to give trimethylsilylated cyanohydrin **3a** with 99% conversion in 10 min (entry 1). 1,3-Di-(1-adamantyl)imidazol-2-ylidene (IAd) was found to exhibit similar catalytic activity. Both *t*Bu and IAd carbenes have good thermal stability<sup>14</sup> and can be easily handled in the laboratories. NHC-catalyzed cyanide addition to benzaldehyde also proceeded

TABLE 1. Cyanosilylation of Benzaldehyde and Acetophenone



entry	R	solvent	catalyst loading	time	% conversion (% isolated yield)
1	H	THF	0.5 mol %	10 min	99 (91)
2	H	THF	0.01 mol %	4 h	97 (83)
3	Me	DMF	0.5 mol %	1 h	95 (80)
4	Me	DMF	0.1 mol %	16 h	95 (74)

smoothly in a number of other solvents such as methylene chloride, MTBE, and acetonitrile. The catalyst loading was studied on a ~100 mmol scale, and we were delighted to find that only a minute amount of NHC **1** (0.01 mol %) was required to catalyze the cyanation of benzaldehyde at room temperature in THF (97% conversion within 4 h, entry 2).

An NHC-catalyzed reaction between acetophenone and TMSCN is very sluggish in THF. Switching the reaction solvent to DMF greatly accelerated the rate of the reaction, giving 95% conversion within 1 h at room temperature in the presence of 0.5 mol % of the catalyst **1** (entry 3). When 0.1 mol % of NHC **1** was used in the cyanation of acetophenone in DMF, the same conversion (95%) was achieved after 16 h at room temperature (entry 4). It should be noted that in the absence of NHC (**1**) no reaction occurs between benzaldehyde and TMSCN in THF or between acetophenone and TMSCN in DMF after 17 h at room temperature. The low catalyst loading that is needed for this reaction underscores the extraordinary catalytic activity of NHCs in activating silicon-based reagents such as TMSCN. In contrast, for the previously reported organocatalysts, 5 mol % of phenolic amine *N*-oxide (6 h at room temperature)<sup>12a</sup> or 30 mol % NMO (8 h at room temperature)<sup>12b</sup> was employed to promote complete conversion of acetophenone to the corresponding trimethylsilylated cyanohydrin **3b**.

The scope of this method was examined by using a number of representative carbonyl compounds (Table 2). For these preparative experiments, 0.5 mol % catalyst loading was used. Benzaldehyde as well as enolizable aliphatic aldehydes (entries 1–3) underwent NHC-catalyzed cyanosilylation in excellent yields. Cyanide addition to the sterically hindered pivalaldehyde occurred rapidly at room temperature (entry 4).

Cyanosilylation reactions of ketones were carried out at room temperature by using DMF as the solvent.  $\alpha$ -Keto ester **2f** was subjected to the NHC-catalyzed cyanation reaction to afford product **3f** in 79% yield (entry 5). Acetophenone and *p*-nitroacetophenone (entries 6–7) were smoothly converted into the corresponding tertiary trimethylsilylated cyanohydrins under NHC catalysis. Cyanation of cyclic and acyclic aliphatic ketones (entries 8–9) was found to proceed efficiently. It is of particular

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TABLE 2. NHC-Catalyzed Cyanosilylation of Carbonyl Compounds

entry	substrate	solvent (time)	product	isolated yield
1		THF (10 min) <sup>a</sup>		91%
2		THF (10 min) <sup>a</sup>		95%
3		THF (10 min) <sup>a</sup>		93%
4		THF (10 min) <sup>a</sup>		87%
5		DMF (0.5 h) <sup>b</sup>		79%
6		DMF (1 h) <sup>b</sup>		80%
7		DMF (2 h) <sup>b</sup>		81%
8		DMF (2 h) <sup>b</sup>		84%
9		DMF (2.5 h) <sup>b</sup>		79%
10		DMF (0.5 h) <sup>b</sup>		81%
11		DMF (2 h) <sup>b</sup>		83%
12		DMF (2 h) <sup>b</sup>		83%
13		DMF (2.5 h) <sup>b</sup>		86%

<sup>a</sup> Method A: To a THF solution of aldehyde and TMSCN (1.0 equiv) at room temperature was added carbene (**1**, 0.5%), and the reaction was stirred at room temperature for the time indicated above. <sup>b</sup> Method B: To a DMF solution of ketone and TMSCN (1.1 equiv) at room temperature was added carbene (**1**, 0.5 mol %), and the reaction was stirred at room temperature for the time indicated above.

interest to note that cyanosilylation of sterically hindered ketone **2j** (entry 10) and relatively unreactive ketones **2k** and **2l** (entries 11–12) was readily achieved under our standard reaction

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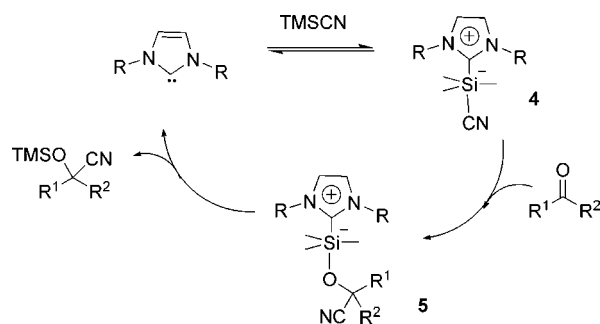


FIGURE 1. Proposed reaction pathway.

conditions (0.5 mol % NHC **1**, room temperature, 2 h). As a comparison, amine *N*-oxide-catalyzed cyanosilylation of  $\alpha$ -tertralone (**2k**) required a long reaction time (~15 h at room temperature) as well as significantly higher catalyst loading.<sup>12a,b</sup> Finally, we have shown that cyanide addition to 2-bromoacetophenone was also successful (entry 13).

We propose that the NHC-catalyzed cyanosilylation reaction follows a nucleophilic catalysis pathway, as illustrated in Figure 1.<sup>12c,19</sup> NHC interacts with TMSCN to form a reactive pentavalent silicon complex **4** which transfers a cyano group to the carbonyl compound. Subsequently, the intermediate **5** fragments to furnish the desired product while regenerating the carbene catalyst.

In conclusion, we have described a highly efficient cyanosilylation reaction of carbonyl compounds by using *N*-heterocyclic carbene **1** as an organocatalyst. Ketones and aldehydes undergo facile cyanosilylation at room temperature in the presence of only 0.01–0.5 mol % of NHC **1**, leading to a range of trimethylsilylated cyanohydrins in very good to excellent yields. Compared to the previously reported organocatalysts for cyanosilylation reactions with TMSCN,<sup>12</sup> *N*-heterocyclic carbene has exhibited higher catalytic activity as evidenced by the shorter reaction time and much lower catalyst loading. These conditions are metal-free, extremely mild, and simple and tolerate various functional groups. Importantly this methodology further exemplifies the remarkable ability of NHCs to activate silicon-based reagents such as TMSCN and TMSCF<sub>3</sub>. Efforts to further extend NHC catalysis to other fundamental organic transformations are ongoing.

## Experimental Section

**General Procedures.** All reactions were performed in oven-dried glassware under nitrogen with magnetic stirring. All commercial reagents were used as received. Flash chromatography was performed using 230–400 mesh silica gel.

**Cyanosilylation of Benzaldehyde.** A dry flask with a stir bar was purged with N<sub>2</sub> and charged with anhydrous THF (6 mL), benzaldehyde (1.0 mL, 10.0 mmol, 1.0 equiv), and finally TMSCN (1.3 mL, 10.0 mmol, 1.0 equiv). 1,3-Di-*tert*-butylimidazol-2-ylidene (9 mg, 0.05 mmol, 0.005 equiv) was added at room temperature. After 10 min, HPLC analysis shows the complete consumption of benzaldehyde. The reaction mixture was concentrated and loaded directly onto a silica gel column (eluting with 90:10 hexanes/MTBE) to give **3a** (1.87 g, 91%) as a colorless oil.

**Cyanosilylation of Acetophenone.** A dry flask with a stir bar was purged with N<sub>2</sub> and charged with anhydrous DMF (5 mL), acetophenone (0.59 mL, 5.0 mmol, 1.0 equiv), and finally TMSCN (0.73 mL, 5.5 mmol, 1.1 equiv). 1,3-Di-*tert*-butylimidazol-2-ylidene (4.5 mg, 0.025 mmol, 0.005 equiv) was added at room temperature.

After 1 h, HPLC analysis shows the complete consumption of acetophenone. The reaction mixture was diluted with MTBE (40 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, concentrated, and loaded onto a silica gel column (eluting with 90:10 hexanes/EtOAc) to give **3b** (0.88 g, 80%) as a colorless oil.

**Supporting Information Available:** <sup>1</sup>H NMR and <sup>13</sup>C NMR data as well as copies of <sup>1</sup>H NMR spectra for isolated products **3a–m**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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