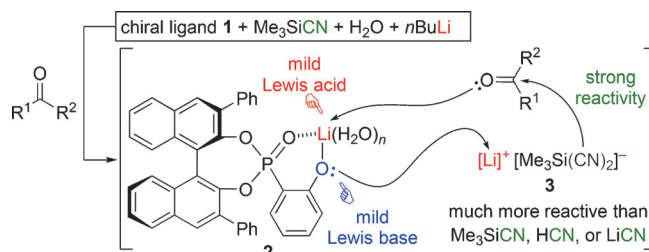# Enantioselective Cyanosilylation of Ketones with Lithium(I) Dicyanotrimethylsilicate(IV) Catalyzed by a Chiral Lithium(I) Phosphoryl Phenoxide

Manabu Hatano, Katsuya Yamakawa, Tomoaki Kawai, Takahiro Horibe, and Kazuaki Ishihara*

Abstract: A highly enantioselective cyanosilylation of ketones was developed by using a chiral lithium(I) phosphoryl phenoxide aqua complex as an acid/base cooperative catalyst. The pentacoordinate silicate generated in situ from Me_3SiCN/ LiCN acts as an extremely reactive cyano reagent. Described is a 30 gram scale reaction and the synthesis of the key precursor to (+)-13-hydroxyisocyclocelabenzine.

Optically active cyanohydrins are important compounds since they can readily provide α-hydroxy carboxylic acids, β-hydroxy amines, etc., which are used in many pharmaceuticals.[1] However, the catalytic enantioselective cyanosilylation of ketones is still challenging, since ketones are inherently much less reactive than aldehydes as a result of steric and electronic constraints.[2] Progress with such reactions using ketones are reported, however, there is room for improvement with regard to the substrate scope, reaction time (typically 24–48 h), and reaction scale.[3] To overcome the difficulties of the enantioselective cyanosilylation of unreactive simple ketones, we anticipated that the activation of the trimethylsilyl cyanide reagent by achiral additives could be effective. This strategy is highly promising as it may not depend on the use of strong, chiral Lewis acid catalysts to the activate substrates. In fact, even weak chiral Lewis acid catalysts might be appropriate. In this regard, we envisioned that the active lithium(I) dicyanotrimethylsilicate(IV)(**3**),[4] formed in situ, might be suitable for use with the chiral lithium(I) phosphoryl phenoxide aqua complex **2**, a newly designed and mild Lewis acid/Lewis base cooperative catalyst for the cyanosilylation of ketones (Scheme 1).[5–7] An advantage of this catalytic system is that we can simply use the chiral (*R*)-BINOL (1,1′-bi-2-naphthol)-derived ligand **1**, Me_3SiCN, water, and either *n*BuLi or LiOH as the same lithium(I) source to prepare both the active lithium(I) catalysts and lithium(I) silicates(IV) in situ.

We initially examined the reaction of acetophenone (**4a**) with **1** (10 mol%), *n*BuLi (10 mol%), Me_3SiCN (130 mol%),

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Scheme 1. Acid-base combined catalytic system with reactive lithium(I) dicyanotrimethylsilicate(IV) **3**.

and H_2O (0–130 mol%) in toluene at −78°C for 5 hours (Table 1, entries 1–6). The reaction was sluggish in the absence of water (entry 1). In contrast, the reactions were promoted in the presence of water, and the highest enantio-selectivity (92% *ee*) of **5a** was observed with the use of 60 mol% of H_2O (entry 4). The yield was improved with the use of 250 mol% of Me_3SiCN and 120 mol% of H_2O (entry 7). Finally, the use of 15 mol% of *n*BuLi provided **5a**

Table 1: Optimization of the reaction conditions.[a]

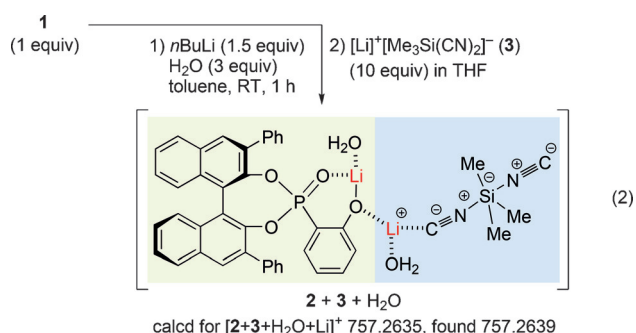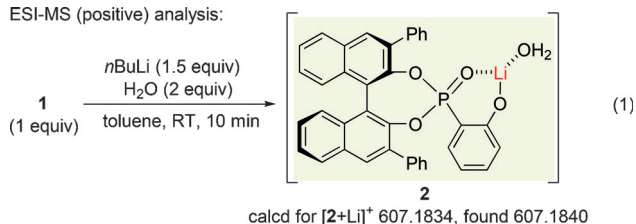| Entry	*n*BuLi (mol%)	Me_3SiCN (mol%)	H_2O (mol%)	Me_3SiOH (mol%)	$(Me_3Si)_2O$ (mol%)	Yield [%]	*ee* [%]
1	10	130	0	0	0	23	44
2	10	130	20	0	0	44	69
3	10	130	40	0	0	51	86
4	10	130	60	0	0	35	92
5	10	130	80	0	0	25	91
6	10	130	130	0	0	0	–
7	10	250	120	0	0	68	90
8	15	250	120	0	0	94	91
9	15[b]	250	120	0	0	98	90
10	15	250	120	50	0	90	91
11	15	250	120	0	50	91	89

[a] The reaction was carried out with **4a** (0.5 mmol), Me_3SiCN (130 or 250 mol%), **1** (10 mol%), *n*BuLi (10 or 15 mol%), and H_2O (0–130 mol%) in toluene at −78°C for 5 h. The cyanohydrin **6a** was not obtained in any of the cases. [b] LiOH was used in place of *n*BuLi.

in 94% yield with 91% *ee* (entry 8). LiOH reacted well in place of *n*BuLi (entry 9), although we have conventionally used *n*BuLi as a common catalytic lithium(I) source in cyanosilyations.[7] Water might be essential for the generation of active a monomeric species,[7,8] and we observed a signal, corresponding to **2,** as a major peak in ESI-MS analysis [Eq. (1); see the Supporting Information]. Most of the remaining water might be used to generate HCN (and Me₃SiOH) in situ as the reactions were run under the homogeneous reaction conditions. Notably, the active cyanide reagent in this reaction might not be HCN (entry 6), and the cyanohydrin **6a** was not obtained in any of the cases (entries 1–11). Moreover, Me₃SiOH and (Me₃Si)₂O, generated in situ, had almost no influence on the results (entries 10 and 11).


calcd for [**2**+Li]⁺ 607.1834, found 607.1840

calcd for [**2**+**3**+H₂O+Li]⁺ 757.2635, found 757.2639

For the mechanistic aspect, our catalytic system includes multiple cyano sources, such as Me₃SiCN, LiCN, HCN, and their relevant combinations [Eq. (3)]. In particular, based on the screening of the reaction conditions for **4a** in Table 1, a catalytic amount of LiCN, formed in situ, may play a key role (entry 8 versus entry 7).[9,10] To identify the active reagent in the system, we performed a ¹³C NMR analysis of a [D₈]THF solution containing a 1:1 molar ratio of Me₃SiCN ($\delta = -2.00$ ppm) and LiCN [Eq. (4); see the Supporting Information]. The pentacoordinate silicate [Li]⁺-[Me₃Si(CN)₂]⁻ (**3**)[4] was observed as the only peak at $\delta = 2.00$ ppm. Ionic LiCN is essential for generation of the silicate, since a 1:1 molar ratio of Me₃SiCN and HCN gave [H]⁺-[Me₃Si(CN)₂]⁻ (**3′**) in 8% conversion, even after 5 hours [Eq. (5); see the Supporting Information]. Based on these results, a catalytic amount (5 mol%) of **3**, formed in situ, might serve as the active reagent [Eq. (3)].[10,11] Overall, **2** [Eq. (1)] and **3** [Eq. (4)] could associate through a cooperative acid–base interaction. In support of this association, we observed the **2**+**3** complex in the ESI-MS analysis [Eq. (2), see the Supporting Information].

(reaction of **4a** for 5 h: 94%, 91% ee of **5a** [Table 1, entry 8])
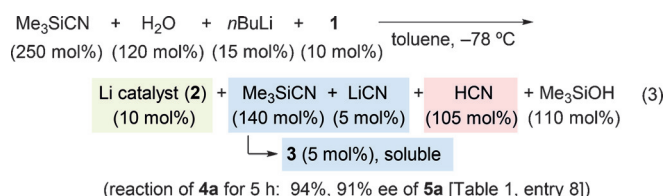
¹³C NMR analysis:
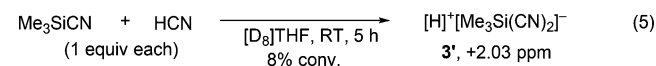
We show a possible catalytic cycle in Scheme 2. The transition state (TS) **7**[12] might involve the **2**+**3** complex, as shown in Equation (2), and **4**. After cyanation,[13] the product **5** is delivered via the lithium(I) cyanohydrin **8**. We could not detect **6** directly, even by in situ IR analysis (see the
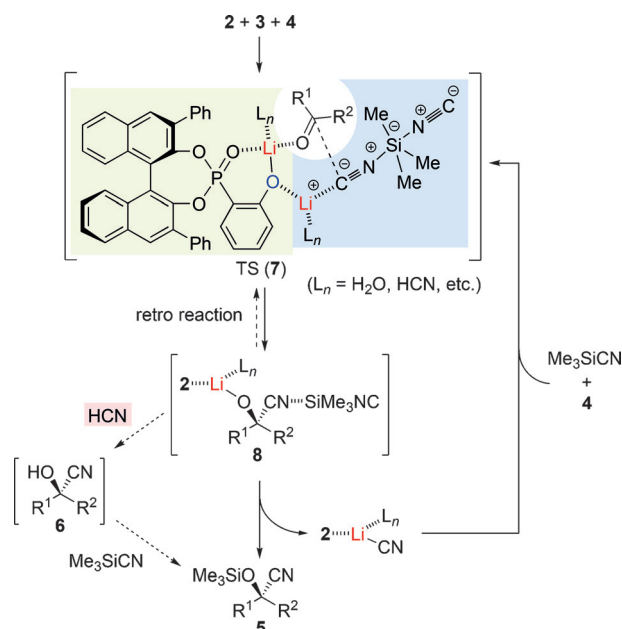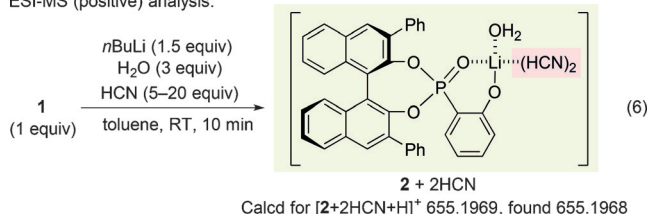

Scheme 2. Possible catalytic cycles.

Supporting Information), but we cannot completely rule out the transient generation of **6** by protonation[14,15] in an HCN buffer, and subsequent silylation[16] of **6**. Instead, it is likely that HCN is acting as a coordinating ligand(s) for the lithium(I) center of **2** and/or **3**, and the corresponding lithium(I)/L_n (L_n = H₂O and HCN) solvates might promote the release of **5** and the active species (e.g., L_n···**2**···LiCN) to regenerate **7**. In support of this assumption, we detected **2**·(HCN)₂ in the ESI-MS analysis when a large amount of HCN (10 ≈ 20 equiv)[17] was used in the presence of **2** [Eq. (6), see the Supporting Information]. Accordingly, in the presence of an excess amount of HCN (total of 205 mol% in situ), a large-scale reaction of **4a** was achieved (18.0 g, 150 mmol).

Additionally, by using only 5 mol% of the catalyst for a shorter reaction time (3 h), about 30 grams of **5a** were obtained with 90% *ee* after extraction, concentration, and filtration of the crude reaction mixture (no silica gel column chromatography) [Eq. (7)]. Moreover, **1** was easily recovered in 98% (>99% purity) after precipitation by washing with *n*-hexane and 1 M aqueous HCl.
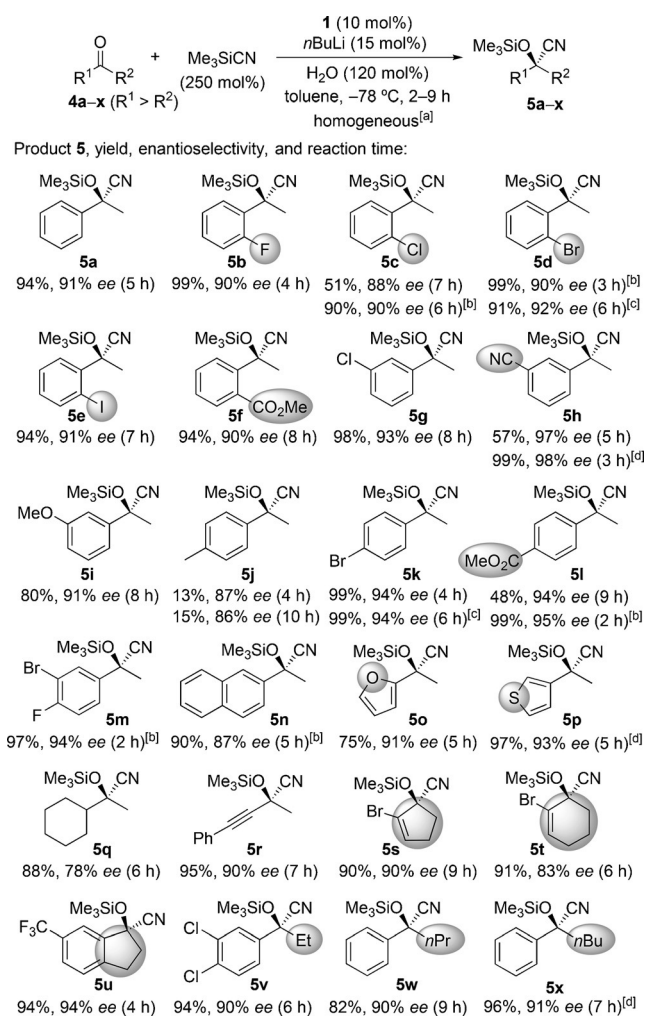
ESI-MS (positive) analysis:

$$\mathbf{1} \xrightarrow[\text{toluene, RT, 10 min}]{\substack{n\text{BuLi (1.5 equiv)} \\ \text{H}_2\text{O (3 equiv)} \\ \text{HCN (5–20 equiv)}}} \quad (6)$$

2 + 2HCN
Calcd for [**2**+2HCN+H]+ 655.1969, found 655.1968

30 gram scale synthesis:

$$\substack{\mathbf{4a} \quad + \quad \text{Me}_3\text{SiCN} \\ \text{150 mmol} \quad \text{(250 mol\%)} \\ \text{(18.0 g)}} \xrightarrow[\substack{\text{HCN (100 mol\%) in situ} \\ \text{H}_2\text{O (120 mol\%)} \\ \text{toluene, } -78\,°\text{C, 3 h}}]{\substack{\mathbf{1} \text{ (5 mol\%)} \\ n\text{BuLi (7.5 mol\%)}}} \substack{\mathbf{5a} \\ 90\% \\ (29.6\,\text{g}) \\ 90\%\ ee} \quad (7)$$

- reduced catalytic amount (5 mol%) in shorter time (3 h)
- without silica-gel column chromatography
- ligand **1** was recovered (98%)
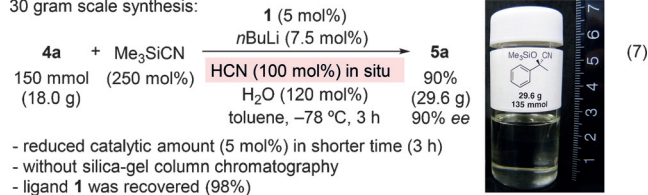
With the optimized reaction conditions in hand (Table 1, entry 8), we examined the scope with respect to the ketones **4** (Scheme 3). The *ortho*-, *meta*-, and *para*-substituted acetophenones were used successfully, and the corresponding products **5b–m** were obtained in high yields with high enantioselectivities (87–98% *ee*).[18] In particular, electron-withdrawing groups generally promoted the reaction, while an electron-donating group, such as a methyl group, decreased the reactivity, with recovery of the starting ketone **4j**.[19] Whereas sterically hindered *ortho*-substituted ketones are often problematic for use in conventional catalysis,[1–3] they were tolerated by our catalytic system (**5b–f**). Moreover, our catalyst was used for the unprecedented cyanosilylation of carbonyl- and cyano-substituted ketones (**5f**, **5h**, and **5l**), groups which may deactivate relatively strong Lewis acid catalysts.[1–3] The coordination of 2-furyl and 3-thienyl ketones, **4o** and **4p**, respectively, to the catalyst also proceeded smoothly. Cyclohexyl methyl ketone (**4q**), as a simple aliphatic ketone, showed moderate enantioselectivity (**5q**, 78% *ee*). In sharp contrast, acyclic and cyclic α,β-unsaturated aliphatic ketones (**4r–t**) delivered the corresponding products **5r–t** in high yields with good to high enantioselectivities (83–90% *ee*). Remarkably, our catalyst could be used for other nonmethyl ketones, such as 1-indanone, propiophenone, butyrophenone, and valerophenone derivatives, and the desired products **5u–x** were obtained with high enantioselectivities (90–94% *ee*). Overall, our catalytic system features a much shorter reaction time (2–9 h) than conventional systems.[1–3] It is noted again that cyanohydrins (**6**) were not obtained in any of the reactions.
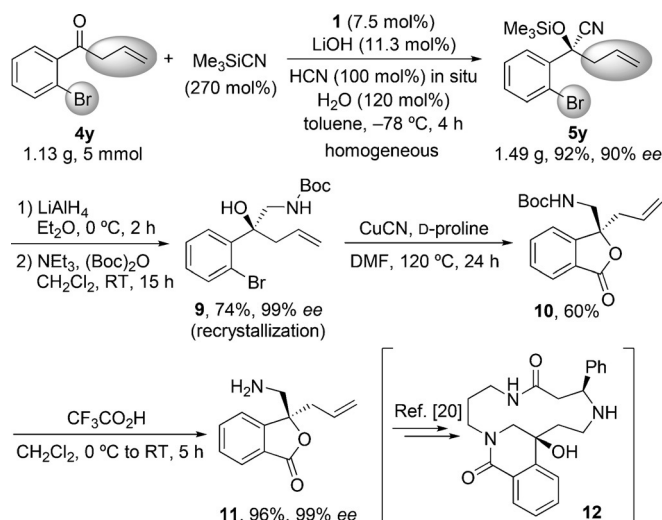
To demonstrate the synthetic utility of our catalytic system, we synthesized the key intermediate **11** which is used in the synthesis of (+)-13-hydroxyisocyclocelabenzine

$$\substack{\text{O} \\ \| \\ \text{R}^1 \overset{}{\frown} \text{R}^2 \\ \mathbf{4a–x}\ (\text{R}^1 > \text{R}^2)} + \substack{\text{Me}_3\text{SiCN} \\ \text{(250 mol\%)}} \xrightarrow[\substack{\text{H}_2\text{O (120 mol\%)} \\ \text{toluene, } -78\,°\text{C, 2–9 h} \\ \text{homogeneous}^{[a]}}]{\substack{\mathbf{1} \text{ (10 mol\%)} \\ n\text{BuLi (15 mol\%)}}} \substack{\text{Me}_3\text{SiO\ \ CN} \\ \text{R}^1 \overset{}{\frown} \text{R}^2 \\ \mathbf{5a–x}}$$

Product **5**, yield, enantioselectivity, and reaction time:

5a
94%, 91% *ee* (5 h)

5b (F)
99%, 90% *ee* (4 h)

5c (Cl)
51%, 88% *ee* (7 h)
90%, 90% *ee* (6 h)[b]

5d (Br)
99%, 90% *ee* (3 h)[b]
91%, 92% *ee* (6 h)[c]

5e (I)
94%, 91% *ee* (7 h)

5f (CO₂Me)
94%, 90% *ee* (8 h)

5g (Cl)
98%, 93% *ee* (8 h)

5h (NC)
57%, 97% *ee* (5 h)
99%, 98% *ee* (3 h)[d]

5i (MeO)
80%, 91% *ee* (8 h)

5j
13%, 87% *ee* (4 h)
15%, 86% *ee* (10 h)

5k (Br)
99%, 94% *ee* (4 h)
99%, 94% *ee* (6 h)[c]

5l (MeO₂C)
48%, 94% *ee* (9 h)
99%, 95% *ee* (2 h)[b]

5m (Br, F)
97%, 94% *ee* (2 h)[b]

5n
90%, 87% *ee* (5 h)[b]

5o (O)
75%, 91% *ee* (5 h)

5p (S)
97%, 93% *ee* (5 h)[d]

5q
88%, 78% *ee* (6 h)

5r (Ph)
95%, 90% *ee* (7 h)

5s (Br)
90%, 90% *ee* (9 h)

5t (Br)
91%, 83% *ee* (6 h)

5u (F₃C)
94%, 94% *ee* (4 h)

5v (Cl, Cl, Et)
94%, 90% *ee* (6 h)

5w (nPr)
82%, 90% *ee* (9 h)

5x (nBu)
96%, 91% *ee* (7 h)[d]

Scheme 3. Substrate scope in the catalytic enantioselective cyanosilylation of ketones **4**. [a] Unless otherwise noted, the reaction was carried out with **4** (0.5 mmol), Me₃SiCN (250 mol%), **1** (10 mol%), *n*BuLi (15 mol%), and H₂O (120 mol%) in toluene at −78°C. [b] 270 mol% of Me₃SiCN was used. [c] The reaction was carried out with **4** (1 mmol), Me₃SiCN (250 mol%), **1** (5 mol%), *n*BuLi (7.5 mol%), and H₂O (120 mol%) in toluene at −78°C for 6 h. [d] 300 mol% of Me₃SiCN was used.

(**12**),[20] a spermidine alkaloid with antibacterial and antitumor activities (Scheme 4). The bulky allyl 2-bromophenyl ketone (**4y**) was selected as the starting ketone. Fortunately, by using LiOH and **1** (7.5 mol%) in the enantioselective cyanosilylation of **4y** on a 1.13 gram scale, **5y** was obtained in 92% yield (1.49 g) with 90% *ee*. The compound **5y** was then transformed into **9** by reduction with LiAlH₄ and subsequent Boc protection (Boc = *tert*-butoxycarbonyl). A single recrystallization of **9** increased the enantiopurity to 99% without a serious loss of yield. Finally, the optically pure key intermediate **11** was obtained after a copper(I)-promoted lactonization to **10** and removal of the Boc group.

In summary, we have developed a highly enantioselective cyanosilylation of ketones with the use of a chiral lithium(I) phosphoryl phenoxide complex as an acid/base cooperative catalyst. An extremely reactive pentacoordinate silicate generated in situ from Me₃SiCN and LiCN acts as the key

Scheme 4. Synthesis of the key intermediate **11** which is used in the synthesis of (+)-13-hydroxyisocyclocelabenzine (**12**). DMF = N,N-dimethylformamide.

cyano reagent. In particular, our robust catalytic system was employed in a large-scale (30 gram) reaction. Also, a key intermediate in the synthesis of (+)-13-hydroxyisocyclocela-benzine was successfully synthesized in an optically pure form.

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[7] We previously developed a chiral lithium(I) binaphtholate aqua complex for aldehydes and a chiral lithium(I) phosphate for a very limited numbers of ketones. The reactions scarcely proceed with these catalysts (< 15% yield with < 10% *ee*) under the reaction conditions given in entry 8 of Table 1 (see the Supporting Information). Therefore, this catalytic system with the silicate **3** turned out to be different from our previous catalytic systems with Me₃SiCN. a) M. Hatano, T. Ikeno, T. Miyamoto, K. Ishihara, *J. Am. Chem. Soc.* **2005**, *127*, 10776; b) M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776.

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[10] We used a catalytic amount of isolated LiCN in a model reaction of **4a** with Me₃SiCN in toluene at −78°C (see the Supporting Information). As a result, a positive effect of LiCN on both yield and enantioselectivity was observed when compared to the control experiment in which LiCN was absent. However, isolated LiCN was not very soluble and caused, overall, lower efficiency under heterogeneous conditions, particularly in the yield, than soluble LiCN which was prepared in situ from Me₃SiCN, *n*BuLi, and H₂O under homogeneous conditions.

[11] Investigation of the reactions of aldehydes also supports that **3** might be more active than other reagents in situ. See the Supporting Information.

[12] Possible transition states, which might explain the absolute stereochemistry of **5**, are shown in the Supporting Information.

[13] The retro reaction of the tertiary cyanohydrin **8** to the TS **7** might be possible. Therefore, the reaction of **8** with a HCN buffer would also provide a slight bias on the equilibrium between **7** and **8**.

[14] On the basis of pK_a values in water (HCN: 9.1, Me$_3$SiOH: 12.7, H$_2$O: 15.8), HCN might act as a proton source. a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456; b) K. M. Delak, N. Sahai, *Chem. Mater.* **2005**, *17*, 3221.

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[16] In a control experiment, the isolated cyanohydrin **6a** was quickly trimethylsilylated within 1 minute under the standard reaction conditions. See the Supporting Information.

[17] A large amount of HCN (i.e., 105 mol %) under optimized conditions) is necessary to promote the reaction. A control experiment with 45 mol % of HCN showed significantly slow conversion (5 h, 41 % yield with 89 % *ee*). In contrast, another control experiment with 205 mol % of HCN showed fast conversion (2 h, 95 % yield with 91 % *ee*). See the Supporting Information.

[18] For some ketones, the use of either 270 or 300 mol % of Me$_3$SiCN gave better yields than the use of 250 mol % of Me$_3$SiCN.

[19] During the reaction, the inactive silylated ligand **13** was partially detected (see the Supporting Information), particularly when unreactive ketones such as **4j** were used. A routine workup/purification procedure always resulted in recovered **1** (90–95 %), and it could be reused after it was washed with 1M aqueous HCl.

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