

Neutral π -Nucleophile-Catalyzed Cyanation of Aldehydes and Ketones

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Received 8 February 2007

Abstract: 1-Methoxy-2-methyl-1-(trimethylsiloxy)propene, a neutral π -nucleophile, was found to be able to efficiently catalyze the cyanation (cyanosilylation and cyanocarbonation) of various aldehydes and ketones, and this study provided the first illustration of using a neutral π -nucleophile for the development of synthetically useful organocatalysis.

Key words: π -nucleophile, cyanosilylation, cyanocarbonation, aldehydes, ketones

It is well established that some nucleophilic organic compounds such as tertiary amines,¹ phosphines² and sulfides³ can efficiently catalyze a wide variety of chemical transformations by activating or generating nucleophiles with their nucleophilic nitrogen, phosphorous and sulfur, respectively (Figure 1). Neutral (non-anionic) π -nucleophiles exhibit nucleophilicity toward many electrophiles in various carbon–carbon bond-forming reactions⁴ and in molecular interactions.⁵ However, to our knowledge, the possibility of using neutral π -nucleophiles as organocatalysts⁶ to promote chemical reactions has not yet been explored. Based on their nucleophilicity, we envisaged that neutral π -nucleophiles could activate some nucleophiles in a way, to some extent, similar to the activation by nucleophilic heteroatoms. Since neutral π -nucleophiles are reactive species toward some electrophiles, the reaction to test this hypothesis should be carefully selected to avoid consuming them. With these considerations, we initiated the investigation on the potential of neutral π -nucleophiles to act as organocatalysts for nucleophile–electrophile reactions.

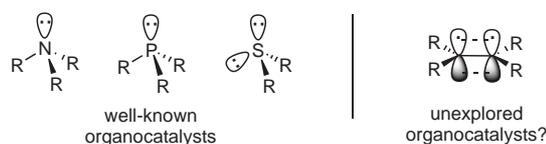


Figure 1 Some nucleophilic organic compounds: tertiary amines, phosphines, sulfides and neutral π -nucleophiles

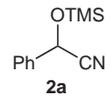
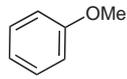
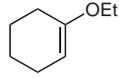
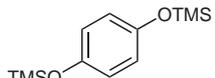
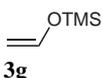
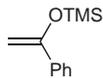
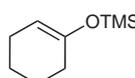
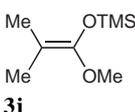
The cyanation of aldehydes and ketones^{7–10} was selected as a model reaction for our investigation since this reaction is synthetically important for the carbon–carbon bond

formation and is also known to be readily catalyzed by nucleophilic catalysts bearing heteroatoms such as nitrogen and phosphorus.^{8a–i} Thus, to a mixture of benzaldehyde (**1a**) and trimethylsilyl cyanide (TMSCN) at 25 °C was added 10 mol% of a readily available neutral π -nucleophile catalyst,¹¹ and in two hours each of the reaction mixtures was analyzed by gas chromatographic analysis. Although most of the neutral π -nucleophiles examined in Table 1 showed sluggish catalytic activities, commercially available 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (**3j**) was identified as a highly effective catalyst, with which the reaction proceeded in 99.7% conversion (entry 11, Table 1). Further optimization of the reaction conditions led to a clean cyanosilylation of benzaldehyde (**1a**) with only 1 mol% of catalyst **3j** (vide infra).

As shown in Table 2, the substrate scope for the neutral π -nucleophile-catalyzed cyanosilylation of aldehydes and ketones is very general.¹² A variety of conjugated and unconjugated aldehydes **1a–j** were completely transformed to their corresponding cyanohydrin silyl ethers **2a–j** in the presence of only 1 mol% of catalyst **3j** at ambient temperature (entries 1–10, Table 2). The cyanosilylation of cyclic ketones **1k–l** (entries 11 and 12, Table 2) and functionalized ketones **1n,o** and **1r,s** (entries 14, 15, 18, 19, Table 2), proceeded in quantitative yields with 2–5 mol% of catalyst **3j**. Higher catalyst loading up to 15 mol% and elevated temperature (50 °C) were needed for conjugated ketones **1p,q** (entries 16 and 17, Table 2) to proceed in 100% conversion. This reaction tolerated acid-sensitive functionality such as the acetal group (in **1n** and **1s**) well, and readily enolizable ketone **1o** could also provide quantitative yield. Given the clean, solvent-free reaction, and the volatile properties of both catalyst **3j** and TMSCN,¹³ simple evaporation of the reaction mixture (after the complete consumption of aldehyde or ketone) under reduced pressure could afford the desired product in quantitative yield. Therefore, this catalytic approach to synthesize cyanohydrin silyl ethers is not only conceptually new, but also superior to the previously reported Lewis acid or Lewis base mediated approaches in terms of yield, functional group tolerance, and experimental simplicity.¹⁴

Good to excellent selectivity was observed in the cross-over cyanosilylation of aldehydes and ketones catalyzed by neutral π -nucleophile **3j** (Table 3). Aliphatic aldehyde **1j** was found to be much more reactive than both conjugated aldehydes (entries 1 and 2, Table 3) and ketones (entries 3–5, Table 3). Similarly, an aliphatic ketone exhibited higher reactivity than a conjugated one (entry 6,

Table 1 Neutral π -Nucleophile-Catalyzed Cyanosilylation of Benzaldehyde (**1a**)^a

PhCHO + TMSCN 1a (1.1 equiv)		catalyst (10 mol%) neat, 25 °C, 2 h	 2a
Entry	Cat.		Conv. ^a (%)
1	–		<1.0
2	 3a		3.9
3	 3b		1.8
4	 3c		<1.0
5	 3d		2.1
6	 3e		3.6
7	 3f		<1.0
8	 3g		1.5
9	 3h		10.4
10	 3i		7.8
11	 3j		99.7

^a Determined by GC analysis.

Table 3). Notably, an α -acetal group can greatly activate a ketone toward this cyanosilylation (entries 7 and 8, Table 3).

Under all the above cyanosilylation conditions, no product resulting from the reaction between aldehyde (or ketone) and catalyst **3j** was detected by both ¹H NMR and GC analysis. The fact that no structural change for catalyst **3j** was observed by the ¹H NMR analysis of the reaction mixture during and after the cyanosilylation of benzaldehyde (**1a**, entry 11, Table 1) excludes the possibility for catalyst **3j** to decompose to other silicon species as the origin of the observed catalysis.

In order to gain more insights into the activation mechanism by catalyst **3j** and extend this catalysis to other cyanating agents without silyl groups, further investigation was carried out with ethyl cyanofornate that can be activated by nucleophilic tertiary amines.^{9a-d} As shown in Table 4, catalyst **3j** could also efficiently catalyze the cyanocarbonation of various aldehydes to afford the desired cyanohydrin carbonates in excellent to quantitative yields, though a higher catalyst loading (5–25 mol%) was required than that for the corresponding cyanosilylation. Furthermore, the lack of cyanohydrin silyl ether in each of the above cyanocarbonations disfavored the proposal for catalyst **3j** to act as a silicon Lewis acid in that the trialkylsilyl group of catalyst should be transferred to the product in a typical silicon Lewis acid catalyzed carbon–carbon bond-forming reaction of carbonyl compounds.¹⁵

Alternative activation mechanism by catalyst **3j** in the cyanation of aldehydes and ketones can be originated from its π -nucleophilicity. The activation of TMSCN by catalyst **3j** was observed in the IR spectra, which showed that the isocyanide stretching band at 2088 cm⁻¹, as compared to the cyanide stretching band at 2190 cm⁻¹, increased significantly with the addition of catalyst **3j**.^{16,17} However, at present the mechanistic detail for the activation of cyanating agent by catalyst **3j** remains unclear.¹⁸

In summary, 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**3j**), a commercially available neutral π -nucleophile, was found to be able to efficiently catalyze the cyanation (cyanosilylation and cyanocarbonation) of aldehydes and ketones. The mild reaction conditions, excellent functional-group tolerance, excellent to quantitative yield, and the simple protocol for product purification illustrate the practically attractive features of this catalysis. By providing the first illustration of using neutral π -nucleophile as organocatalyst for a nucleophile–electrophile reaction, the current study demonstrates a new concept for the development of synthetically useful organocatalysis. Investigations are underway to extend this concept to develop a broad range of synthetically important reactions.

Acknowledgment

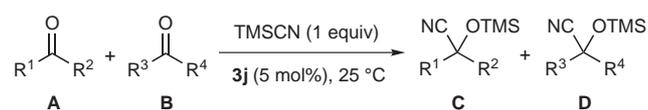
We are grateful for the financial support from the National Natural Science Foundation of China (No. 20672105) and the University of Science and Technology of China.

Table 2 Neutral π -Nucleophile-Catalyzed Cyanosilylation of Aldehydes and Ketones^a

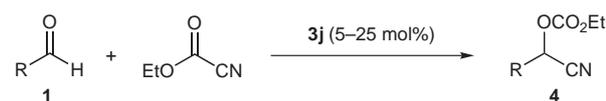
Entry	Substrate	Cat. (mol%)	Temp (°C)	Time (h)	Yield ^b (%)
1		1	19	30	>99
2	1b : X = OMe, Y = Z = H	1	19	36	>99
3	1c : X = Cl, Y = Z = H	1	19	25	>99
4	1d : X = Z = H, Y = Cl	1	19	11	>99
5	1e : X = Y = Cl, Z = H	1	19	11	>99
6	1f : X = Y = H, Z = NO ₂	1	19	25	>99
7		1	19	10	>99
8	1g 	1	19	36	>99
9	1h 	1	21	10	>99
10	1j : n = 2	1	24	18	>99
11		5	16	84	>99
12	1l : n = 2	2	19	36	>99
13		5	25	50	>99
14	1m 	5	22	18	>99
15	1n 	5	50	50	>99
16	1o 	15	50	80	>99
17	1p 	15	50	80	>99
18	1r : X = CO ₂ Et	5	22	18	>99
19	1s : X = CH(OEt) ₂	5	23	18	>99

^a The reaction was performed by the treatment of aldehyde or ketone (0.50 mmol) with TMSCN [0.60 mmol (0.75 mmol for entries 15–17)] and catalyst **3j** (1–15 mol%).

^b Isolated yields.

Table 3 Neutral π -Nucleophile-Catalyzed Crossover Cyanosilylation of Aldehydes and Ketones^a

Entry	R ¹	R ²	R ³	R ⁴	Time (h)	Product		Selectivity ^b C:D
						C	D	
1	BnCH ₂	H	Ph	H	5	2j	2a	86:14
2	BnCH ₂	H	PhCH=CH	H	5	2j	2h	91:9
3	BnCH ₂	H	<i>n</i> -Pent	Me	5	2j	2m	>99:1
4	BnCH ₂	H	(MeO) ₂ CH	Me	5	2j	2n	84:16
5	BnCH ₂	H	Ph	Me	5	2j	2q	>99:1
6	<i>n</i> -Pent	Me	Ph	Me	62	2m	2q	73:27
7	<i>n</i> -Pent	Me	(MeO) ₂ CH	Me	20	2m	2n	9:91
8	(EtO) ₂ CH	Ph	Ph	Me	20	2s	2q	86:14

^a A:B:TMSCN = 1:1:1.^b Determined by ¹H NMR analysis after no more transformation was detected by GC analysis.**Table 4** Neutral π -Nucleophile-Catalyzed Cyanocarbonation of Aldehydes^a

Entry	Aldehyde	Product	Cat. (mol%)	Temp (°C)	Time (h)	Yield ^b (%)
1	1a	4a	5	25	11	>99
2	1b	4b	5	25	15	>99
3	1c	4c	10	24	12	>99
4	1e	4e	5	22	58	>99
5	1f	4f	5	25	11	>99
6	1g	4g	5	25	9	>99
7	1h	4h	25	31	8	>99
8	2-MeOC ₆ H ₄ CHO (1s)	4s	5	28	20	>99
9	Me ₂ CHCHO (1t)	4t	25	30	72	90

^a The reaction was performed by the treatment of aldehyde (0.50 mmol) with NCCO₂Et [0.55 mmol (0.60 mmol for entries 7 and 9)] and catalyst **3j** (5–25 mol%).^b Isolated yields.

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- (11) Most of the neutral π -nucleophiles listed in Table 1 are electron-rich substituted enol ethers. However, electron-rich enamines and the silyl enol derivatives of amides are excluded from the survey since they react readily with aldehydes at r.t. For the silyl enol derivatives of amides, see: Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *113*, 9672.
- (12) **General Procedure**
A mixture of aldehyde or ketone **1a–s** (0.50 mmol), TMSCN (0.60–0.75 mmol) and catalyst **3j** (1–15 mol%) was allowed to stand in a vial at 16–50 °C (indicated in Table 2). The reaction was monitored by GC or TLC. After the aldehyde or ketone was completely consumed, the reaction mixture was subject to a reduced pressure of 5–10 mmHg at 25–50 °C to remove catalyst **3j** and the remaining TMSCN, and the desired product **2a–s** was obtained in quantitative yield. Cyanohydrin silyl ethers **2a–s** are known compounds, see ref. 8–10.
- (13) The boiling point of catalyst **3j** is 57 °C/15 mmHg, and that of TMSCN is 118 °C.
- (14) For previously reported methods, the extractive procedures and/or column chromatography are needed to purify the products. See references 7–10, and references cited therein.
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- (17) No significant IR change was observed for benzaldehyde (or ethyl cyanofornate) with the addition of catalyst **3j**.
- (18) Based on its π -nucleophilicity, we speculate that catalyst **3j** may activate the cyanating agent with its π -system through association. However, to our knowledge, this type of π -based catalysis has not been reported previously.