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Catalytic cyanosilylation of ketones with simple phosphonium salt

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Abstract—In the presence of 1–5 mol % of benzyltriphenylphosphonium chloride, a wide variety of unconjugated and conjugated, acyclic and cyclic ketones were transformed to their corresponding cyanohydrin silyl ethers in excellent yields.
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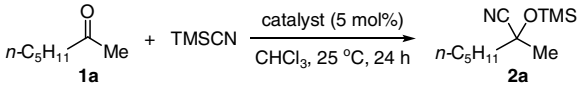
Organocatalysis is currently being vigorously pursued because of its attractive features such as the metal-free conditions, experimental simplicity and the ease to recover the organocatalysts.[1] A number of the applications of organocatalysts in the cyanation reaction of carbonyl compounds,[2,3] which is an important carbon–carbon bond forming reaction to produce versatile cyanohydrins that can be elaborated into a variety of synthetically useful building blocks such as α-hydroxy acids, α-hydroxy aldehydes (or ketones) and β-amino alcohols,[4] have been developed despite the fact that a plethora of other types of reagents are able to catalyze this reaction.[5] Besides organic amines, N-oxides, phosphines, carbenes and ammonium salts, the catalytic potential of phosphonium salts in the cyanosilylation of carbonyl compounds has also been investigated. In 2003, Plumet and co-worker reported that methyltriphenylphosphonium iodide could efficiently catalyze the cyanosilylation of aldehydes,[2u] but this phosphonium salt failed to do so with ketones: There is only one example reported with highly reactive cyclobutanone; the reaction took 72 h.[2v] Herein we wish to report an efficient catalytic cyanosilylation of various ketones with readily available benzyltriphenylphosphonium chloride.

Phosphonium salts were successfully employed to catalyze several other types of organic reactions,[6] and their catalytic activities could be greatly influenced by the nature of the four groups attached to the atom of phosphine and the corresponding counterion. With this consideration, we envisaged that the modification of phosphonium salts could lead to an efficient cyanosilylation of ketones. Furthermore, the ease to synthesize phosphonium salts can greatly facilitate the improvement of their catalytic activities. The search for an effective phosphonium salts to catalyze the cyanosilylation of ketones was launched with the evaluation of the readily available analogues of methyltriphenylphosphonium iodide. Thus, to a solution of 2-heptanone (**1a**) in chloroform at room temperature was added trimethylsilyl cyanide (TMSCN) and 5 mol % of phosphonium salt, and the yield was determined by GC analysis. As indicated by the data summarized in Table 1, the catalytic ability of a phosphonium salt is tightly associated with the nature of both phosphonium cation and counterion.

Table 1. Survey of readily available phosphonium salts[a]



Entry	Catalyst	Yield[b] (%)
1	None	<1.0
2	$Ph_3P^+MeI^-$	5.0
3	$Ph_3P^+CH_2CO_2EtBr^-$	<1.0
4	$Ph_3P^+CH_2CO_2MeCl^-$	13
5	$Ph_3P^+CH_2CH{=}CH_2Br^-$	6.5
6	$Ph_3P^+CH_2CH{=}CH_2Cl^-$	89
7	$Ph_3P^+BnBr^-$	2.6
8	$Ph_3P^+BnCl^-$	**92**

[a] The reaction was performed by the treatment of **1a** (0.25 mmol) in chloroform (50 μL) at room temperature with TMSCN (0.30 mmol) and phosphonium salt (5 mol %).
[b] Determined by GC analysis.

Keywords: Organocatalysis; Phosphonium salts; Cyanation; Cyanosilylation; Ketones.
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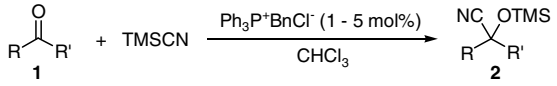
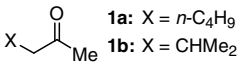
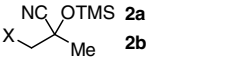
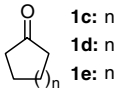
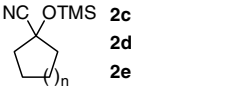
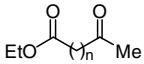
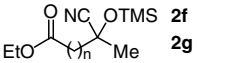
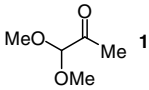
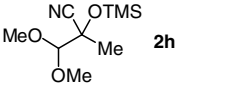
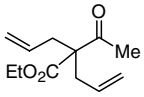
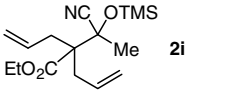
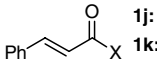
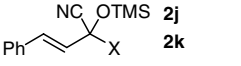
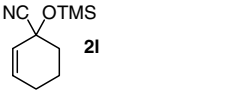
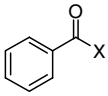
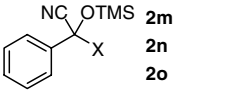
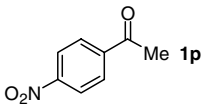
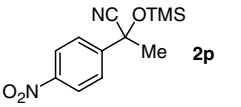
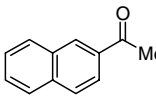
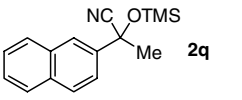
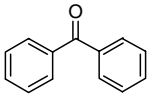
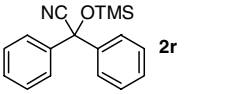
Although most of the phosphonium salts shown in Table 1 led to sluggish reactions, benzyltriphenylphosphonium chloride, prepared from inexpensive triphenylphosphine and benzyl chloride, was identified as an effective catalyst, with which the reaction proceeded in 92% yield (Table 1, entry 8).

Next, we investigated the substrate scope for this phosphonium salt-catalyzed cyanosilylation of ketones. As summarized in Table 2, in the presence of 1–5 mol % of benzyltriphenylphosphonium chloride a wide variety of unconjugated and conjugated, acyclic and cyclic ketones were transformed to their corresponding cyanohydrin silyl ethers in excellent yields.[7] Remarkably, only 1,2-addition products were observed for unsaturated ketones such as **1j–l** (Table 2, entries 10–12). In addition, this reaction well tolerated acid-labile functionality such as the acetal group in **1h** and **1o** (Table 2, entries 8 and 15), and readily enolizable ketone (**1g**) could also provide the corresponding product in excellent yield (Table 2, entry 7).

As illustrated in Table 1, the proper choice of phosphonium cation and counterion is the key for the successful

Table 2. Phosphonium salt-catalyzed cyanosilylation of ketones[a]



Entry	Ketone	TMSCN (equiv)	Catalyst (mol %)	Temperature (°C)	Time (h)	Product	Yield[b] (%)
1	 **1a:** X = *n*-C_4H_9 **1b:** X = $CHMe_2$	1.2	5	25	24	 **2a** **2b**	86
2		1.5	5	50	24		92
3	 **1c:** n = 1 **1d:** n = 2 **1e:** n = 3	1.2	5	25	24	 **2c** **2d** **2e**	90
4		1.2	1	25	4		98
5		1.5	5	50	24		98
6	 **1f:** n = 0 **1g:** n = 1	1.2	1	25	4	 **2f** **2g**	93
7		1.2	1	25	4		96
8	 **1h**	1.2	1	25	4	 **2h**	98
9	 **1i**	1.5	5	50	48	 **2i**	90
10	 **1j:** X = Me **1k:** X = Ph	1.5	5	50	24	 **2j** **2k**	99
11		1.5	5	50	24		98
12	 **1l**	1.5	5	50	24	 **2l**	94
13	 **1m:** X = Me **1n:** X = CO_2Et **1o:** X = $CH(OEt)_2$	1.5	5	50	48	 **2m** **2n** **2o**	95
14		1.2	1	25	4		99
15		1.2	1	25	5		98
16	 **1p**	1.5	5	50	7	 **2p**	98
17	 **1q**	1.5	5	50	24	 **2q**	99
18	 **1r**	1.5	5	50	48	 **2r**	94

[a] The reaction was performed by the treatment of ketone (0.50 mmol) in chloroform (0.10 mL) at 25 or 50 °C with TMSCN (0.60 or 0.75 mmol) and catalyst (1–5 mol %).

[b] Isolated yield.

cyanosilylation of ketones, and presumably a double-activation mechanism is responsible for this catalysis. On the one hand, the phosphonium cation may activate ketone due to its Lewis acidity resulting from the presence of 3d orbitals.[6a] On the other hand, the counterion, Cl^-, has been demonstrated by Ohkuma and co-workers to be able to activate nucleophile TMSCN.[8] The activation of TMSCN by benzyltriphenylphosphonium chloride was evidenced by the appearance of a new cyanide stretching band at 2254 cm^{-1}, different from that for TMSCN (2190 cm^{-1}) and TMSN = C (2088 cm^{-1}), in the IR spectrum of the 1:1 mixture.[9] Since it is necessary for both phosphonium cation and Cl^- to be dissociated from each other before the effective activation of ketone and TMSCN, respectively, the decent Lewis acidity of phosphonium cation seems to be essential for the phosphonium salt to efficiently practice double activation.

In summary, benzyltriphenylphosphonium chloride was identified as a highly effective organocatalyst to promote the cyanosilylation of a wide variety of unconjugated and conjugated, acyclic and cyclic ketones. This protocol not only presents a new organocatalytic synthesis of cyanohydrin silyl ethers, but also adds a synthetically useful entry into the catalysis with phosphonium salts. Further development of its asymmetric variant is ongoing.

Acknowledgments

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7. *General procedure*: To a solution of ketone (0.50 mmol) in dry chloroform (0.10 mL) were added TMSCN (0.60 or 0.75 mmol) and benzyltriphenylphosphonium chloride (1–5 mol %), and the mixture was allowed to stand at 25 or 50 °C (indicated in Table 2). The reaction was monitored with GC and/or TLC, and directly purified by silica gel column chromatography to give the desired product in excellent yield. For new compound **2i**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.24$ (s, 9H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.70 (s, 3H), 2.44–2.56 (m, 2H), 2.61–2.70 (m, 2H), 4.12–4.24 (m, 2H), 5.03–5.16 (m, 4H), 5.73–5.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 1.4$, 14.2, 25.8, 37.0, 37.2, 57.0, 61.3, 74.5, 118.0, 118.6, 121.1, 133.9, 134.4, 171.8; IR (neat) $\nu = 3079$, 1735, 1639, 1444 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{27}NO_3Si$ (M^+), 309.1760; found, 309.1761.
8. The chloride anion of LiCl was proposed to activate TMSCN to form a pentavalent silicon compound Li[$(CH_3)_3SiCl(NC)$] in the cyanosilylation of carbonyl compounds, see Ref. 5o.
9. For the IR study on the activation of TMSCN with Ph_3PO, see Ref. 5v. For IR spectral data on TMSCN and TMSNC, see: Seckar, J. A.; Thayer, J. S. *Inorg. Chem.* **1976**, *15*, 501.