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Catalytic cyanomethylation of carbonyl compounds and imines with highly basic phosphine

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Abstract

A highly basic phosphine, tris(2,4,6-trimethoxy phenyl)phosphine (TTMPP), catalyzes cyanomethylation using trimethylsilylacetonitrile ($TMSCH_2CN$) to give the corresponding products in good to high yields, with both carbonyl compounds and imines.

β-Hydroxy nitriles are useful intermediates in organic synthesis, for example, in the synthesis of γ-aminoalcohols and β-hydroxycarboxylic acids.[1] Thus, several methods have been developed for their synthesis. Generally, β-hydroxy nitriles are prepared by reacting alkaliacetonitriles with carbonyl compounds.[2] However, the resultant β-hydroxy nitriles are easily dehydrated to afford α,β-unsaturated nitriles, and the yield of product is sometimes unsatisfactory. Among several methods to overcome this problem,[3,4] cyanomethylation using trimethylsilylacetonitrile ($TMSCH_2CN$) is considered to be one of the most efficient methods because of their low basicity and high stability. On this basis, catalytic cyanomethylation procedures using TASF,[4c] CuF,[4d] and AcOLi[4e] have been developed to realize high yield and selectivity. However, the examples of the catalytic cyanomethylation are still scarce.

On the other hand, organocatalysis is currently being vigorously pursued because of its attractive features such as the metal-free conditions, experimental simplicity.[5] Tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) is known to be a highly basic phosphine owing to its multiple methoxy substitutions.[6] Many unique reactions have been reported using TTMPP as an organocatalyst.[7] We previously demonstrated that TTMPP catalyzes aldol, imine-aldol reactions via O–Si bond activation.[8] In this Letter, we report that TTMPP catalyzes the cyanomethylation of carbonyl compounds and imines by using $TMSCH_2CN$ via C–Si bond activation.

Initially, cyanomethylation of benzaldehyde with $TMSCH_2CN$ was examined in the presence of 10 mol % TTMPP in DMF at room temperature.[9] The desired product was obtained in 92% yield in 3 h (Table 1, entry 1). The product was obtained in moderate to low yield when other phosphines were used instead of TTMPP (Table 1, entries 1 vs 7–10). THF, DMPU, and toluene were also effective solvents in this TTMPP-catalyzed reaction. However, only trace amounts of product were obtained using CH_2Cl_2, MeOH, and acetonitrile.

In order to clarify the scope of this reaction, several aldehydes were examined in the presence of 10 mol % TTMPP (Table 2). Good results were obtained for both aromatics having an electron-donating or -withdrawing group and aliphatic aldehydes. Ketones also worked in the reaction, which proceeded smoothly with various ketones in the presence of 10 mol % TTMPP. 1,2-Adducts were obtained in good yields when α,β-unsaturated ketones were employed. Aliphatic ketones also worked well, although longer reaction times and 20 mol % TTMPP were required when compared to the reaction with aromatic ketones.

Imines were also examined in this TTMPP-catalyzed cyanomethylation.[10] The resultant β-amino nitriles are useful building blocks, as they are easily converted into either β-aminocarboxylic acid or 1,3-diamino compounds.[11] In

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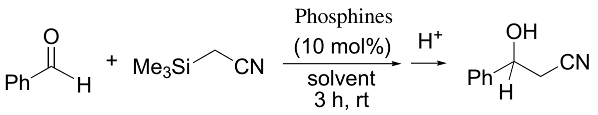
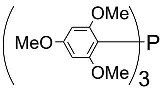
Table 1
Optimization of the reaction conditions



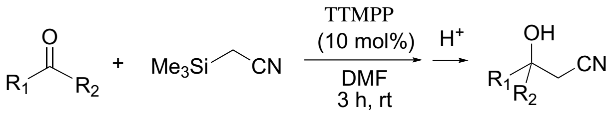
Entry	Phosphines	Solvent	Yield (%)
1	TTMPP	DMF	92
2[a]		DMF	46
3		THF	82
4		DMPU[b]	100
5		Toluene	93
6		CH_3CN	0
7		MeOH	0
8		CH_2Cl_2	0
9	TMPP[c]	DMF	62
10	Ph_3P	DMF	14
11	nBu$_3$P	DMF	0
12	tBu$_3$P	DMF	0

[a] 1 mol % of TTMPP was used.

[b] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

[c] Tris(4-methoxyphenyl)phosphine.

Table 2
TTMPP-catalyzed cyanomethylation of various aldehydes and ketones



Entry	R1	R_2	Yield[a] (%)
1	C_6H_5	H	92
2	$4\text{-}CH_3OC_6H_4$	H	95
3	$4\text{-}ClC_6H_4$	H	97
4	$4\text{-}CNC_6H_4$	H	80
5	1-Naphtyl	H	99
6	2-Naphtyl	H	80
7	(*E*)-PhCH=CH	H	98
8	$PhCH_2CH_2$	H	91
9	$n\text{-}C_8H_{17}$	H	85
10	Furyl	H	65
11	C_6H_5	CH_3	80
12[b]		CH_3	96
13	$4\text{-}CH_3OC_6H_4$	CH_3	69
14	$4\text{-}ClC_6H_4$	CH_3	73
15	$4\text{-}CF_3C_6H_4$	CH_3	81
16	$3\text{-}CH_3OC_6H_4$	CH_3	74
17	C_6H_5	C_2H_5	66
18	(*E*)-PhCH=CH	CH_3	80
19	(*E*)-PhCH=CH	C_6H_5	68
20[b]	C_5H_{11}	C_2H_5	65
21[b]	*cyclo*-C_6H_{10}		56

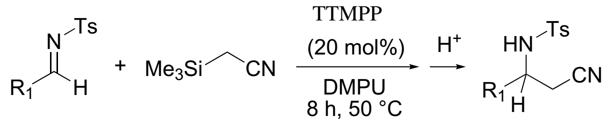
[a] Isolated yield.

[b] 20 mol % of TTMPP was used.

the present study, we screened solvents and aldimines and found that the corresponding β-amino nitrile was obtained in good yield using *N*-tosylaldimine in DMPU at 50 °C.[12] Other phosphines, such as triphenylphosphine and tributylphosphine did not catalyze this reaction. This fact clearly shows the superiority of TTMPP. Good to high yields of several β-amino nitriles were obtained under the same conditions (Table 3, entries 5–8). Unfortunately, we had no success with aliphatic aldimines under these conditions.

Although the mechanism of this reaction is not clear, a possible mechanism is illustrated in Scheme 1. First, TTMPP coordinates the silicon atom of the $TMSCH_2CN$ to form activated penta coordinated silicon species **1** (mainly in THF, toluene) or hexa coordinated silicon species **1′** (mainly in DMF, DMPU), and the C–Si bond is activated. Next, the nucleophilicity of the CH_2CN group is enhanced and it readily reacts with an electrophile to produce the alkoxide or amino ion **2** and silylphosphonium

Table 3
TTMPP-catalyzed cyanomethylation of various imines

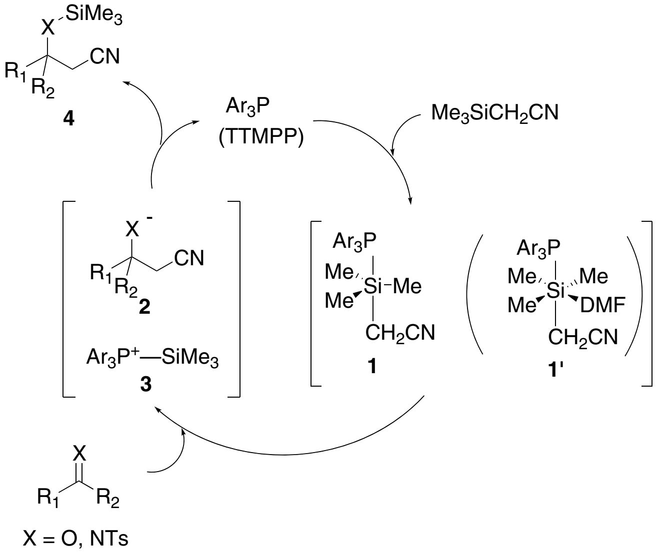


Entry	R_1	Yield (%)
1	C_6H_5	80
2[a]	C_6H_5	25
3[b]	C_6H_5	0
4[c]	C_6H_5	0
5	$4\text{-}CH_3OC_6H_4$	85
6	$4\text{-}ClC_6H_4$	75
7	$4\text{-}BrC_6H_4$	80
8	$4\text{-}NO_2C_6H_4$	75
9	Furyl	30

[a] TMPP was used instead of TTMPP.

[b] $P(^{t}Bu)_3$ was used instead of TTMPP.

[c] PPh_3 was uesd instead of TTMPP.



Scheme 1.

salt **3**. Finally, immediate silylation occurs to give the silylated adduct **4** with regeneration of TTMPP.

In summary, we demonstrated that TTMPP catalyzes cyanomethylation using $TMSCH_2CN$. TTMPP effectively activated the C–Si bond of $TMSCH_2CN$, and the reaction proceeded smoothly to afford the corresponding product. This reaction can be applied to not only carbonyl compounds but also imines. Further investigation along these lines, including stereoselective reactions, is currently underway.

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9. *Typical experimental procedure*: To a solution of TTMPP (26.6 mg, 0.05 mmol) in DMF (1 mL) was added benzaldehyde (53.1 mg, 0.5 mmol) and $TMSCH_2CN$ (105 mL, 0.75 mmol) at room temperature. After stirring for 3 h, the resultant mixture was quenched with 5% HCl–MeOH (2 mL). The mixture was extracted with EtOAc and organic layer was washed with brine and dried over anhydrous Na_2SO_4, and evaporated. The crude mixture was purified by preparative TLC to afford the desired product (67.8 mg, 92%) as colorless oil.
10. For cyanomethylation of imines, see: (a) Sun, P.; Zhang, Y. *Synth. Commun.* **1997**, *27*, 3175; (b) Kumagai, N.; Matsubara, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 12632; (c) Kawano, Y.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **2005**, 1134.
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12. *Typical experimental procedure for the reaction using imines as an electrophile*: To a solution of TTMPP (53.2 mg, 0.1 mmol) in DMPU (1 mL) was added *N*-tosylbenzaldimine (129.7 mg, 0.5 mmol) and $TMSCH_2CN$ (105 mL, 0.75 mmol) at room temperature. And the reaction mixture was warmed to 50 °C. After stirring for 8 h, the resultant mixture was quenched with water (2 mL). The mixture was extracted with EtOAc and organic layer was washed with brine and dried over anhydrous Na_2SO_4, and evaporated. The crude mixture was purified by preparative TLC to afford the desired product (120.0 mg, 80%) as white solid.