Tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP): Efficient Catalysts for the Cyanosilylation and Cyanocarbonation of Aldehydes and Ketones

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Abstract: A variety of aldehydes and ketones were transformed to their corresponding cyanohydrin silyl ethers in good to excellent yields in the presence of 1-5 mol% of tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP). Cyanohydrin carbonates were also readily prepared using 5-10 mol% of TTMPP as an organocatalyst.

Keywords: organocatalysis; cyanosilylation; cyanohydrin carbonate; phosphines; cyanation

Introduction

The addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds is one of the most popular strategies to afford cyanohydrins, which can be conveniently converted into various important polyfunctionalized building blocks for the synthesis of many natural products and bioactive molecules, including α-hydroxyl carbonyl compounds and β-amino alcohols [1-7]. Consequently, many catalytic systems, such as metal salts, organocatalysts, inorganic solid acids and bases, have been developed to enhance the efficiency of this transformation. Organophosphorous compounds have also been employed. Mukaiyama reported that Bu$_3$P and Ph$_3$P act as catalysts for the cyanosilylation with aldehydes [8]. Plumet [9,10] and Tian [11] independently reported that phosphonium salts-catalyzed cyanosilylation with aldehydes and ketones. Verkade’s base (cycloazaphosphine) also acts as a good catalyst in this reaction [12]. In search of other useful organophosphorous catalysts, we have now...
examined the use of a highly basic phosphine, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), as a catalyst.

TTMPP is known to be a highly basic phosphine owing to its extensive methoxy-substitution [13]. Based on this property, some unique catalytic reactions have been reported [14-19]. We have also reported that TTMPP acts as a good Lewis base catalyst in the reaction with silylated nucleophiles via O-Si and C-Si bond activation [20-25]. Herein we wish to report an efficient catalytic cyanosilylation of various aldehydes and ketones using TTMPP as a catalyst.

Results and Discussion

Initially, the reactions of different aldehydes with trimethylsilyl cyanide in the presence of 1 mol% of TTMPP in DMF at room temperature were examined. For both aromatics having an electron-donating or -withdrawing group and aliphatic aldehydes, the reaction proceeded quite smoothly and the desired products were obtained at high yield within 30 min (Table 1). The product was obtained in lower yield when other phosphines, such as Bu₃P, Ph₃P and TMPP were used instead of TTMPP (Table 1, entries 1 vs. 10-12). The reaction also smoothly proceeded in THF. However, the reactions performed in MeCN and toluene were inferior when compared to those in DMF and THF.

**Table 1. Cyanosilylation of various aldehydes.** [a]

| Entry | Phosphines     | Aldehyde     | solvent | Yield (%) |
|-------|----------------|--------------|---------|-----------|
| 1     | TTMPP          | C₆H₅CHO      | DMF     | 98        |
| 2     |                 | 4-CH₃OC₆H₄CHO |         | 99        |
| 3     |                 | 4-ClC₆H₄CHO  |         | 95        |
| 4     |                 | 4-NO₂C₆H₄CHO |         | 98        |
| 5     |                 | α-Naphthaldehyde |      | 92        |
| 6     |                 | β-Naphthaldehyde |    | 90        |
| 7     |                 | C₆H₅HCHO     |         | 95        |
| 8     |                 | C₆H₅CH₂CH₂CHO |         | 92        |
| 9     |                 | cyclo-C₆H₁₁CHO |        | 93        |
| 10    | TMPP[b]        | C₆H₅CHO      |         | 45        |
| 11    | Ph₃P           |              |         | 30        |
| 12    | sBu₃P          |              |         | 68        |
| 13    | TTMPP          |              |         | 95        |
| 14    |                 | CH₃CN        |         | 55        |
| 15    |                 | toluene      |         | 30        |

[a] Reactions were carried out on a 0.5 mmol scale with 1.2 equiv of TMSCN.
[b] Tris(4-methoxyphenyl)phosphine.
Table 2. TTMPP-Catalyzed cyanosilylation of various ketones.\textsuperscript{[a]}

| Entry | Ketones (3) | Temp (°C) | Yield (%) |
|-------|-------------|------------|-----------|
| 1     |             | r.t.       | 97        |
| 2\textsuperscript{[b],[c]} |             |            | 99        |
| 3     |             |            | 95        |
| 4     |             |            | 93        |
| 5     |             |            | 98        |
| 6     |             |            | 90        |
| 7     |             |            | 93        |
| 8     |             |            | 94        |
| 9     |             |            | 76        |
| 10\textsuperscript{[d]} |             | r.t.       | trace     |
| 11    |             | 50 °C      | 97        |
| 12    |             |            | 96        |
| 13    |             |            | 95        |
| 14    |             |            | 95        |

\textsuperscript{[a]} Reactions were carried out on a 0.5 mmol scale with 1.2 equiv of TMSCN.  
\textsuperscript{[b]} 1 mol% of TTMPP was used.  
\textsuperscript{[c]} Reaction time: 5 h.  
\textsuperscript{[d]} Reaction time: 24 h.

Next, we investigated the scope of this TTMPP-catalyzed reaction of ketones (Table 2). In the case of aliphatic ketones, the reaction proceeded smoothly in the presence of 5 mol% of TTMPP in DMF at room temperature. Good results were obtained for both acyclic and cyclic ketones. This reaction also proceeded smoothly when 1 mol% of TTMPP was used. Only 1,2-addition products were observed for unsaturated ketones. On the other hand, for the typical aromatic ketone acetophenone, only a trace amount of the product was obtained at room temperature even after 24 h. Then, the reaction was carried out at the elevated temperature. The desired product was obtained in 95% yield at 50 °C in
DMF within 1 h. Under the same conditions, a variety of aromatic ketones were transformed to their corresponding cyanohydrin silyl ethers in high yield.

Cyanocarbonation [26-33] of aldehydes and ketones with cyanoformate was also examined (Table 3). Cyanohydrin carbonates are configurationally stable and significantly less prone to hydrolysis than cyanohydrin trimethylsilyl ethers. We examined the scope of this TTMPP-catalyzed reaction of aldehydes and ketones using methyl cyanoformate. Good results were obtained for both aromatics having an electron-donating or -withdrawing group and aliphatic aldehydes in the presence of 5 mol% of TTMPP in THF at room temperature. The reaction also proceeded smoothly with various aliphatic ketones in the presence of 10 mol% TTMPP, but was unsuccessful with aromatic ketones under these conditions.

**Table 3. TTMPP-Catalyzed cyanocarbonation of aldehydes and ketones.**[^a]  

| Entry | Carbonyl Compound (3) | Time (h) | Yield (%) |
|-------|-----------------------|----------|-----------|
| 1     | C₆H₅CHO               | 1 h      | 98        |
| 2     | 4-CH₃OC₆H₄CHO         | 4 h      | 85        |
| 3     | 4-ClC₆H₄CHO           |          | 95        |
| 4     | 4-BrC₆H₄CHO           |          | 98        |
| 5     | 4-NO₂C₆H₄CHO          |          | 88        |
| 6     | α-Naphthaldehyde      | 1 h      | 98        |
| 7     | β-Naphthaldehyde      |          | 85        |
| 8     | C₆H₅CHO               | 4 h      | 87        |
| 9     | C₆H₅CH₂CH₂CHO         |          | 92        |
| 10    | *cyclo*-C₆H₁₀CHO      |          | 88        |
| 11[^b] | C₆H₁₃COCH₃            | 20 h     | 75        |
| 12[^b] | C₆H₅CH₂CH₂COCH₃       |          | 85        |
| 13[^b] | C₆H₅COCH₃             | 24 h     | 5         |
| 14[^b],[^c] | C₆H₅COCH₃ | 48 h     | 10        |

[^a]: Reactions were carried out on a 0.5 mmol scale with 1.5 equiv of methyl cyanoformate;[^b] 10 mol% of TTMPP was used;[^c] At 50 °C.

**Experimental**

**General**

All reactions were performed under an argon atmosphere using oven-dried glassware. Flash column chromatography was performed using silica gel Wakogel C-200. Preparative thin-layer chromatography was carried out on silica gel Wakogel B-5F. Dehydrate DMF, THF, toluene and
CH₃CN were purchased from Wako Chemical. Other commercially available reagents were used as received without further purification. ¹H NMR and ¹³C NMR spectra were recorded on a JEOL JMN-GS400 spectrometer (399.65 MHz for ¹H and 100.40 MHz for ¹³C).

General Procedure for the TTMPP-Catalyzed Cyanosilylation of Aldehydes and Ketones

To a solution of TTMPP (0.05 mmol) in DMF (1 mL) was added aldehyde or ketone (0.5 mmol) and trimethylsilyl cyanide (0.60 mmol) at room temperature. After stirring for 30 min, the resultant mixture was quenched with water. The mixture was extracted with EtOAc and organic layer was washed with brine and dried over anhydrous Na₂SO₄, and evaporated. The crude mixture was purified by column chromatography on silica gel (EtOAc-hexane = 1:10) to give the corresponding product. The products are all known compounds identified by their spectroscopic data and comparison with literature values [8-12,34]. The purity of the product was confirmed by ¹H NMR analysis.

General Procedure for the TTMPP-Catalyzed Cyanocarbonation of Aldehydes

To a solution of TTMPP (0.05 mmol) in THF (1 mL) was added aldehyde (0.5 mmol) and methyl cyanoformate (0.75 mmol) at room temperature. After stirring for 30 min, the resultant mixture was quenched with water. The mixture was extracted with Et₂O and organic layer was washed with brine and dried over anhydrous Na₂SO₄, and evaporated. The crude mixture was purified by column chromatography on silica gel (EtOAc-hexane = 1:3) to give the corresponding product. The products are all known compounds identified by their spectroscopic data and comparison with literature values [27-33]. The purity of the product was confirmed by ¹H NMR analysis.

α-(Trimethylsilyloxy)phenylacetonitrile: ¹H-NMR (400 MHz, CDCl₃) δ 0.21 (s, 9H), 5.45 (s, 1H), 7.35 – 7.50 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ −0.3, 63.4, 119.1, 126.0, 128.4, 129.0, 136.0.

2-Trimethylsilyloxy-2-phenylpropanenitrile: ¹H-NMR (400 MHz, CDCl₃) δ 0.17 (s, 9H), 1.85 (s, 3H), 7.35 – 7.56 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 1.0, 33.5, 71.5, 121.3, 124.8, 128.4, 141.9.

α-(Methoxycarboxy)phenylacetonitrile: ¹H-NMR (400 MHz, CDCl₃) δ 3.87 (s, 3H), 6.28 (s, 1H), 7.39 – 7.55 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 55.9, 66.6, 115.6, 127.8, 129.1, 130.6, 131.1, 153.9.

Conclusions

In conclusion, we demonstrated that TTMPP catalyzes cyanosilylation reactions using TMSCN. TTMPP effectively activated the C-Si bond of TMSCN, and the reaction proceeded smoothly to afford the corresponding products. This reaction can be applied to wide variety of aldehydes and ketones. Cyanohydrin carbonates could also be readily prepared with methyl cyanoformate using 5-10 mol% of TTMPP as catalyst.
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**Sample Availability:** Samples of the compounds of interest are available from the authors.