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P(*i*-PrNCH$_2$CH$_2$)$_3$N as a Lewis Base Catalyst for the Synthesis of *β*-Hydroxynitriles Using TMSAN

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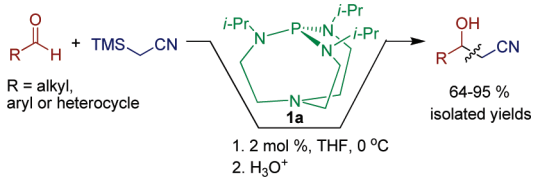

Proazaphosphatrane **1a** was found to be an efficient catalyst for synthesis of *β*-hydroxynitriles via the reaction of trimethylsilylacetonitrile (TMSAN) with aldehydes under mild reaction conditions and typically low catalyst loading (ca. 2 mol %). A variety of functional groups were tolerated, and good to excellent product yields were obtained.

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Carbon−carbon bond-forming reactions are extensively utilized in modern organic synthesis,[1] and one of the most common approaches to this process is via nucleophilic addition to carbonyl compounds.[1] *β*-Hydroxynitriles are important building blocks in many natural product syntheses[2] owing to the stability of nitriles to handling[3] and the versatility of the nitrile group to conversion to a variety of other functionalities such as amines,[4a] amides,[4b] aldehydes,[4c] esters,[4d] alcohols,[4e] or carboxylic acids.[5]

Generally, *β*-hydroxynitriles have been synthesized with the aid of an equivalent amount of strong alkali metal base (for example, $(CH_3)_2CHMgBr$, BuLi, or alkali amides) to deprotonate the α proton of acetonitrile or benzyl nitrile to generate a nucleophile that attacks the carbonyl group.[6] Low yields commonly encountered with these methods[6] have been attributed[7] to reversibility of the reaction or facile product dehydration to give α,*β*-unsaturated nitriles.

More recently, several other methods aimed at improving the yields of *β*-hydroxynitrile syntheses have appeared in the literature.[8] Using an equivalent amount of *n*-BuLi, additional TMSCl was added to trap the alkoxide, resulting in a favorable shift of the equilibrium.[8a] Other reported methods include the use of toxic metal catalysts such as Mn/$PbCl_2$/TMSCl,[8d] $Hg(ONC)_2$,[3] and $PbCl_2$/Ga.[8k] A two-step synthesis of *β*-hydroxynitriles has been reported involving the prior generation of an aryl anion using aryl halide in an electrochemical cell,[8e] which then deprotonates acetonitrile for subsequent addition of the resulting anion to ketones, aldehydes, alkyl halides, and esters. However, this method is cumbersome, providing only poor to moderate product yields (52−74%). Another commonly utilized approach is the use of 1,2-epoxides in the presence of a nitrile or $LiClO_4$/KCN to promote nucleophilic ring-opening of the epoxide. However, this method generally favors the use of aliphatic epoxides, and yields vary from 35 to 98%.[8f−8j] Additional reported methods for the synthesis of *β*-hydroxynitriles involve multistep approaches.[8l,8m]

TMSAN has been utilized for prior formation of the *O*-silyl ether in several attempts to overcome the reaction reversibility problem. In one such reaction, *β*-hydroxynitriles were produced in 70−73% yield via acid hydrolysis of the *O*-silyl adduct formed via the use of toxic potassium cyanide as the catalyst.[9a] The use of KF as a catalyst resulted in quantitative conversion of the *O*-silyl ether to product, but 25 mol % of KF was required, and only benzaldehyde was explored as a substrate.[9b] KF (50 mol %) loaded on alumina

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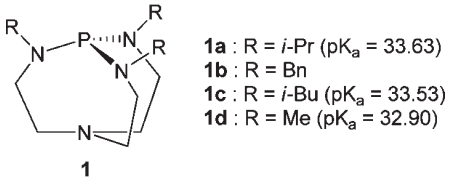


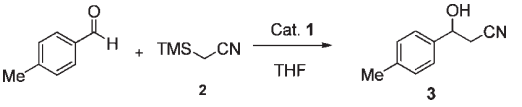
FIGURE 1. Proazaphosphatranes.

with prior catalyst activation at 673 K using benzaldehyde as the sole substrate gave a low yield of product plus 15% of α,β-unsaturated nitrile.[9d] Utilizing 10 mol % of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) at −15 °C resulted in product yields of 20−93% for a variety of aldehydes and ketones.[9c] Using 2.5 mol % of $[Cu(PPh_3)_3]$-$[(EtO)_3SiF_2]$ as a catalyst in the presence of 1.2 equiv of $(EtO)_3SiF$ as an additive for the cyanomethylation of aldehydes using TMSAN[5] gave good product yields (75−100%), but no scope of functional groups was reported. The use of LiOAc and CsOAc as Lewis base catalysts has been described,[7] and although the yields are good, a high catalyst loading (10 mol %) as well as a relatively inconvenient solvent (DMF) is required. Piperidine (24 mol %) functioned as a catalyst under microwave conditions in the absence of solvent, but product yields were low to moderate (ca. 38−73%), and reactions were typically conducted at elevated temperature (85 °C).[9e] Recently, Kitazaki et al. reported the use of tris(2,4,6-trimethoxyphenyl)phosphine (10 mol %) for TMSAN addition to aldehydes and ketones with product yields of 56−99% and to imines with 0−85% product yields in DMF and DMPU.[9f]

We previously found[10] that proazaphosphatranes (**1**) bearing various organic groups on the PN_3 nitrogens (Figure 1) are strongly basic with pK_a values of the their P-protonated N_{basal}→P transannulated conjugate acids in the range 32−34 in MeCN.[11] To the extent that N_{basal}→P transannulation may be occurring during reactions catalyzed by **1**, the nucleophilicity of the phosphorus may be enhanced.[10b] We previously reported reactions in which proazaphosphatranes can activate silicon functionalities as, for example, in the silylation of alcohols using silyl chloride,[12a,12b] synthesis of cyanohydrins from the addition of trimethylsilyl nitrile to carbonyl compounds,[12c,12d] desilylation of TBDMS ethers,[12e] nucleophilic aromatic substitution of aryl fluorides with aryl silyl ethers,[12f,12g] allylation of aromatic aldehydes,[12h] and reduction of aldehydes and ketones using poly(methylhydrosiloxane).[12i]

In the present work, we report the use of proazaphosphatrane **1a** as an efficient catalyst for the synthesis of β-hydroxynitriles from aldehydes with TMSAN as shown in the Abstract graphic.

TABLE 1. Survey of Proazaphosphatranes as Catalysts for the Synthesis of β-Hydroxynitriles[a]



entry	catalyst	mol %	yield of **3**[b] (%)
1[c]	**1a**	10	30
2	**1a**	10	46
3[d]	**1a**	10	45
4	**1a**	5	56
5	**1a**	4	74
6	**1a**	2	91[e]
7	**1a**	1	86
8	**1b**	2	87[e]
9	**1c**	2	90[e]
10	**1d**	2	90[e]

[a]Reaction conditions: (a) aldehyde (2 mmol), TMSAN (2.4 mmol), THF (2 mL), 0 °C, 24 h, 1 N HCl (3 mL). [b]Isolated yield after silica gel column chromatography. [c]Reaction was carried out at rt. [d]Reaction was carried out at −15 °C. [e]Average of three runs.

To optimize the reaction conditions, we chose the reaction of *p*-tolualdehyde with TMSAN (Table 1) as a model. We selected proazaphosphatrane **1a** as the screening catalyst owing to its efficiency in this reaction and its commercial availability.[13] Using 10 mol % of **1a** at room temperature, dehydration to the corresponding α,β-unsaturated nitrile dominated β-hydroxynitrile formation (Table 1, entry 1). Lowering the temperature to 0 °C under the same conditions increased the yield of the desired product to 46% (entry 2), but lowering the temperature to −15 °C revealed essentially no change in product yield (entry 3).

Since higher loading of a basic catalyst can lead to undesired formation of α,β-unsaturated nitrile via a Peterson olefination pathway,[14] we reduced the catalyst loading to 5 mol % and found that the yield of β-hydroxynitrile was substantially enhanced (Table 1, entry 4). Further lowering of the catalyst loading increased the yield of β-hydroxynitrile to 74 and 91% (entries 5 and 6, respectively). However, lowering the catalyst loading below 2% inhibited completion of the reaction, resulting in only a good product yield (86%, entry 7). Thus, we decided to proceed with 2 mol % catalyst at 0 °C to screen proazaphosphatranes **1b**−**d**, and those results are also summarized in Table 1 (entries 8−10). We found that changing the R group on the PN_3 nitrogens gave comparable yields of the desired product, although **1a** was slightly better than the others. We do not have a reasonable explanation for this observation.

Given the higher activity of **1a** as a catalyst and its commercial availability, we proceeded with **1a** under the conditions optimized in Table 1, entry 6, to extend the scope of our protocol for the synthesis of β-hydroxynitriles. Thus, a variety of aromatic and aliphatic aldehydes were employed under the optimized conditions in Table 1, entry 6. The product yields shown in Table 2 are comparable in most

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TABLE 2. Scope of the Reaction of Aldehydes with TMSAN Catalyzed by 1a[a]

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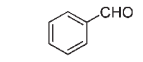
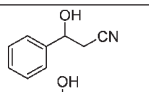
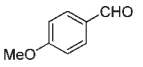
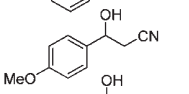
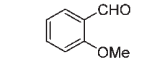
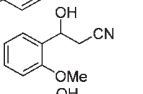
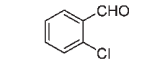
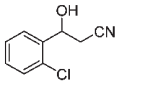
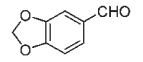
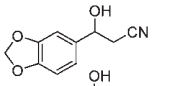
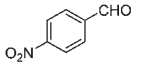
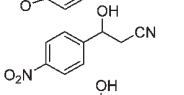
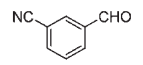
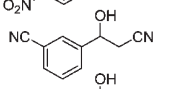
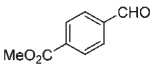
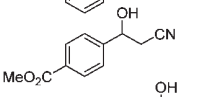
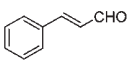
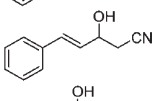
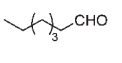
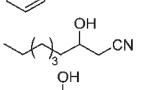
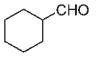
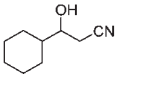
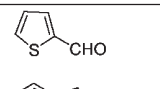
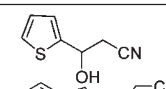
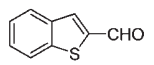
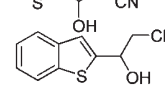
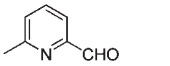
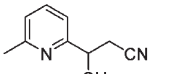
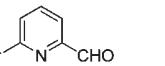
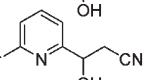
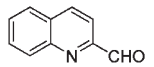
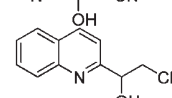
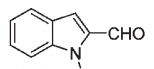
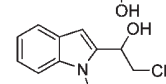
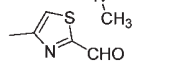
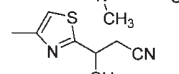
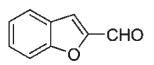
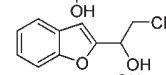
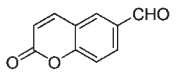
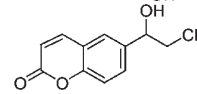
1			89	62-100[c-h]
2			83	80-96[e,f,g,i]
3			77	-
4			94	-
5			82	-
6			94	94[g]
7			89	-
8			93	73[e]
9			94	45-99[c,e,f,i]
10			85	80[f]
11			86	80-86[f,g]

[a]Reaction conditions: (a) aldehyde (2 mmol), TMSAN (2.4 mmol), **1a** (2 mol %), THF (2 mL), 0 °C, 24 h, 1 N HCl (3 mL). [b]Isolated yield after column chromatography. [c]See ref 9a. [d]See ref 9b. [e]See ref 9c. [f]See ref 5. [g]See ref 7. [h]See ref 9e. [i]See ref 9f.

cases to those reported in the literature. Both electron-donating and -withdrawing groups afforded excellent isolated yields, with only a trace of or no dehydrated product detectable by ^{1}H NMR spectroscopy. Electron-donating groups such as methyl (Table 1, entry 6), methoxy at both para and ortho positions (Table 2, entries 2 and 3), and halogen (Table 2, entry 4) were tolerated under our conditions, giving excellent isolated product yields. Electron-withdrawing groups such as *p*-nitro (entry 6), *m*-cyano (entry 7), and *p*-ester (entry 8) were also well tolerated, affording the desired respective products in excellent isolated yields. *trans*-Cinnamaldehyde gave the desired product in good isolated yield (entry 9) with no observable evidence from NMR spectroscopy of the corresponding Michael addition product. Aliphatic enolizable aldehydes also gave good isolated product yields (Table 2, entries 10 and 11). Unfortunately, our methodology was ineffective for the ketones tested (acetophenone, 4-chloroacetophenone, and benzophenone).

With a range of 5- and 6-membered ring heterocycle-bearing aldehydes possessing representation of O-, N- and S-heterocycle types, good to excellent yields of the desired product were obtained (Table 3). Thus, the thiophenic aldehydes in entries 1 and 2 gave very good and excellent product yields, respectively; the pyridinyl aldehydes in entries 3 and 4 and quinolyl aldehyde in entry 5 afforded the corresponding products in

TABLE 3. Scope of the Reaction of Heterocyclic Aldehydes with TMSAN Catalyzed by 1a[a]

entry	aldehyde	product	yield (%)[b]
1			88
2			93
3			92
4			87
5			93 (97)[c]
6			81
7			95
8			64
9			70
10			81 (99,[c] 65[d])

[a]Reaction conditions: (a) aldehyde (2 mmol), TMSAN (2.4 mmol), **1a** (2 mol %), THF (2 mL), 0 °C, 24 h, 1 N HCl (3 mL). [b]Isolated yield after column chromatography. [c]See ref 7. [d]See ref 9f.

SCHEME 1. Proposed Mechanism of TMSAN Addition to Aldehydes

excellent to good yields, respectively; N-containing 2-formyl-1-methylindole gave an excellent isolated product yield (entry 6); the S,N-heterocycle in entry 7 facilitated an excellent yield of product; and the benzofuran, coumarin, and furan carboxaldehydes in entries 8, 9, and 10 permitted a modest, moderate, and good yield of products, respectively. The moderate product yield in entry 9 was pleasantly surprising in view of the sensitivity of lactones to acid and base.

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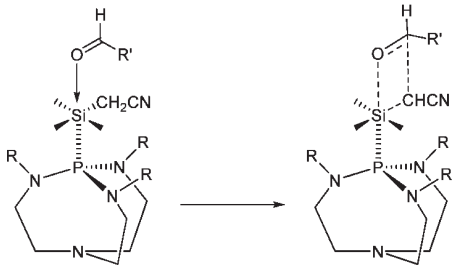
SCHEME 2. Alternative Proposed Mechanism of TMSAN Addition to Aldehydes



A proposed mechanistic pathway for the addition of TMSAN to aldehydes is shown in Scheme 1. To obtain some insight into this pathway, we carried out ^{29}Si NMR experiments at −40 °C in which a THF solution of TMSAN (δ^{29}Si 5.02 ppm in THF) was treated with an equimolar amount of **1a**. A new peak, which then appeared at δ^{29}Si 9.16, was attributed to the tetracoordinate silicon species **B** in which the anionic CH_2CN^- has been displaced. This chemical shift is in the same region as a peak we reported previously for a 1:1 mixture of TMSCN and **1d** in C_6D_6 (δ^{29}Si 7.5) in which CN^- had been displaced. If the anion had not been displaced in both cases, an upfield rather than a downfield shift from the parent TMSX molecule would have been observed since the silicon would have become 5-coordinate.[12c] We used similar reasoning to account for the formation of both α- and γ-addition products in the reaction of crotyltrimethylsilane with aldehydes in the presence of **1a**.[12h] After transient **A** forms **B** in Scheme 1, an aldehyde molecule reacts with CH_2CN^- to form the alkoxide shown, which after trimethylsilylation is acid-hydrolyzed to give the corresponding β-hydroxynitrile as the final product, plus the regenerated catalyst **1a**. Although we have ^{29}Si NMR evidence consistent with the formation of **B**, we have no convincing ^{31}P NMR evidence for this species. ^{31}P chemical shifts for PR_4^+ cations are generally in the range of 90−140 ppm.[15] The chemical shift for **B** is 119 ppm at −40 °C in THF, which is virtually unchanged from the value of **1a** under the same conditions. This result perhaps suggests a minimal perturbation of the phosphorus shielding environment as a result of a weak Si−P interaction.

Since six-coordinate silicon species are also well-known, **A** in Scheme 1 may undergo nucleophilic attack by the carbonyl oxygen of the aldehyde to give rise to the six-coordinate intermediate **C** shown in Scheme 2. This intermediate may then decompose to product and regenerated catalyst **1a** via the 4-center intermediate depicted in **D**. The unreactivity of ketones in our protocol can be rationalized on the basis of their increased steric hindrance in the formation of intermediates **C** and **D**.

In summary, commercially available **1a** is an excellent catalyst for the synthesis of β-hydroxynitriles via the reaction of TMSAN with aldehydes. Our reaction conditions are mild, and our catalyst loadings are the lowest we were able to find in the literature for this transformation. In the case of aryl aldehydes, both electron-withdrawing and -donating groups are well tolerated, both heterocyclic and aliphatic aldehydes function well, and both acid- and base-sensitive functionalities favor the reaction. Comparing our yields to the maximum yields for seven different methods in the literature using seven different catalyst systems, our yields were lower in two cases, comparable (±5%) in four cases, and higher in one case. For the two literature yields that were larger than ours, one literature preparation involved the use of LiOAc in DMF and in the other 2.5 mol % of $[Cu(PPh_3)_3][(EtO)_3SiF_2]$ and 120 mol % of $(EtO)_3SiF$ as an additive were present. In Table 3 our yields for two substrates when compared to the maximum yields in the literature were comparable in one case (±5%) and lower in the other; the literature method for these two cases involved the use of 10 mol % of LiOAc in DMF. From an environmental standpoint, it is worth noting that our catalyst is metal-free.

Experimental Section

General Reaction Procedure. A round-bottom flask was charged with the required amount of proazaphosphatrane (**1**) (2 mol %) in a nitrogen-filled glovebox. Anhydrous THF (2.0 mL) was added to the flask via syringe, followed by addition of TMSAN (2.40 mmol) at 0 °C via syringe under an argon atmosphere. The reaction mixture was stirred at 0 °C for 15 min, and then aldehyde (2.0 mmol) was added over a period of 5−10 min. The reaction mixture was stirred for 24 h at 0 °C, and then it was quenched with 3 mL of aqueous HCl (1 N). The reaction mixture was stirred at 0 °C for 1 h, and then it was neutralized with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The crude product was purified by column chromatography on silica gel using 10% EtOAc/hexanes, except for heterocyclic substrates, in which case 20−25% EtOAc/hexanes was used as the eluent.

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Supporting Information Available: Complete experimental details, references to the known compounds, copies of ^{1}H and ^{13}C NMR spectra for all products, and HRMS spectral reports for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) *Handbook of Phosphorus Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press Inc.: Boca Raton, 1991.

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