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Direct Synthesis of α,*β*-Unsaturated Nitriles Catalyzed by Nonionic Superbases

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We report herein the use of 3−30 mol % of a new class of tricyclic strong nonionic Lewis bases $P(MeNCH_2CH_2)_3N$ and $P(HNCH_2CH_2)(i\text{-}PrNCH_2CH_2)_2N$ for the direct catalytic synthesis of a variety of functionalized α,*β*-unsaturated nitriles in high yields from aldehydes and acetonitrile or benzyl cyanide at 40−50 °C. Evidence for a novel mechanistic pathway proposed for this reaction in a polar protic solvent such as methanol, and a nonpolar aprotic solvent such as benzene is also presented. Under these conditions, primary and secondary aliphatic aldehydes do not condense satisfactorily with acetonitrile to give the α,*β*-unsaturated nitrile, and ketones do not condense with either benzyl cyanide or acetonitrile.

Introduction

The direct conversion of carbonyl compounds to α,*β*-unsaturated nitriles in the presence of nitriles (i.e., without isolating and dehydrating the intermediate *β*-hydroxynitrile) is of considerable economic interest since such nitriles serve as versatile intermediates in the synthesis of a variety of products such as perfumes,[1] sex pheromones,[2] vitamin A,[3] and pigments.[4] Classical methods leading directly to α,*β*-unsaturated nitriles generally employ sodium hydroxide,[5] potassium hydroxide[6] or potassium carbonate[7] as a base and sodium ethoxide[8] or sodium methoxide[9] as a catalyst. The base-promoted condensations are carried out in heterogeneous media, whereas the base-catalyzed condensations are carried out in homogeneous media. However, side reactions occur under these conditions, such as self-condensation of the nitrile, aldol condensation of the carbonyl (in the case of an enolizable aldehyde or ketone), the Cannizzaro reaction (for aromatic aldehydes and aliphatic aldehydes with no α-hydrogen), and retroreaction of the *β*-hydroxynitrile intermediate.[7,10] Hence, α,*β*-unsaturated nitriles are generally obtained from aliphatic aldehydes by the Wittig−Horner reaction.[11] Moreover, the compatibility of the classical routes with base-sensitive functional groups is poor.[6]

An indirect approach for the preparation of α,*β*-unsaturated nitriles involves the condensation of a carbonyl compound with acetonitrile using strong ionic bases such as *n*-butyllithium in organic solvents giving the *β*-hydroxy nitrile, which is then isolated and thermally dehydrated in the presence of a strong acid such as phosphoric acid.[12] However, acetonitrile undergoes numerous base-catalyzed side reactions, and the bases required to deprotonate acetonitrile often nucleophilically attack this reagent.[6]

Metals have also been employed to assist in the formation of α,*β*-unsaturated nitriles. Thus, although aldehydes in the presence of Cl(TMS)CHCN and Zn give rise to α,*β*-unsaturated nitriles in refluxing THF, the nitrile must be provided in the derivatized form shown.[13] Similarly, $RCH_2CHCNCO_2CH_2CH{=}CH_2$ (preformed from $NCCH_2CO_2H$ in a two-step reaction) decomposes thermally to $RCH{=}CHCN$, CO_2, and C_3H_6 in the presence of Pd and PPh_3.[14] At 60 °C, $PhCH_2CN$ has been found to condense with PhCHO in the presence of $RuH_2(PPh_3)_4$ and additives such as 1,2-bis(diphenylphosphino)ethane to give $PhCH{=}CPh(CN)$ ($E/Z = 1/6$) in 87% yield.[15] A more recent synthesis of α,*β*-unsaturated nitriles utilizes cationic surfactants such as cetyltrimethylammonium chloride in the presence of sodium hydroxide as the catalyst in an aqueous medium. The drawbacks here are the same as those encountered in the classical methods.[4]

The above approaches are less convenient and less versatile than the one we report herein. They also provide only low to moderate yields of product, and routes employing metallic species pose environmental problems.

Recently, we discovered an efficient method for the synthesis of esters using **1** (first reported from our laboratories) as a promoter.[16] A chiral fluorescent auxiliary,[17] alkenes (via dehydrohalogenation),[18] pyrroles,[19] oxazoles,[19] porphyrins,[19] *C*-acyl-α-amino acid esters,[19] and

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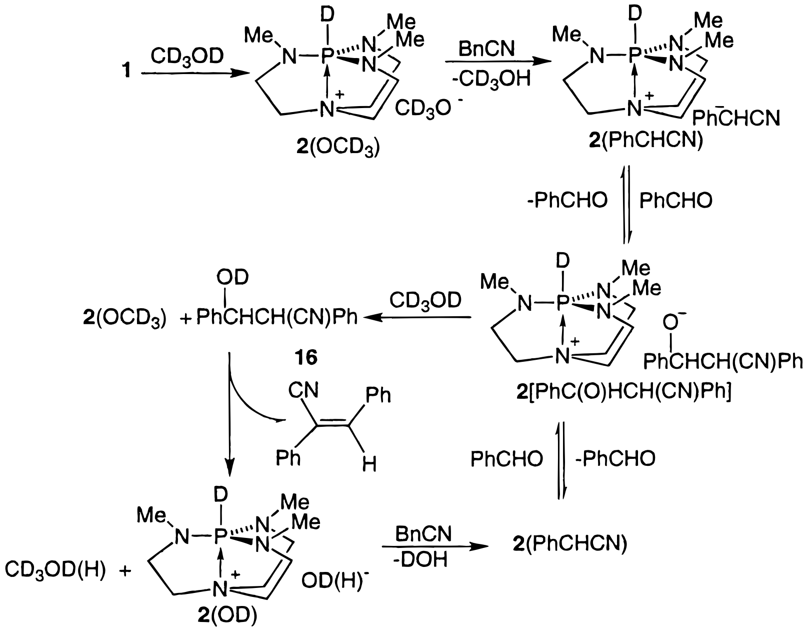
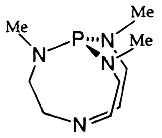
Scheme 1



benzyl ethers[20] are all made in high yields using **1** as a stoichiometric base. An indication of the strength of this base is the pK_a of its conjugate acid, which is 41.2 in acetonitrile.[21] Silyl ethers[22,23] and isocyanurates[24] are made by superior routes using **1** as a catalyst. The growing versatility of **1** as a catalyst and strong nonionic base in synthetic organic chemistry has led to its commercial availability.[25]



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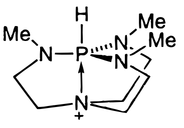

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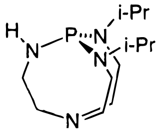

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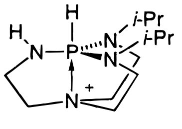

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Strong nonionic bases are widely used in synthetic organic transformations because of the generally milder conditions they permit[26] and the enhanced reactivity of the weakly bound ion pairs they provide by deprotonation of a substrate (in contrast to the strongly bound ion pairs formed by ionic bases).[27] The unusually strong basicities of **1** and of **3** (whose synthesis we recently described[28]) arise in large measure from the formation of three five-membered rings in their corresponding conjugate acids **2** and **4**, respectively, after proton abstraction from a substrate.[21]

Herein, we report the application of **1** and the first member of a new class of strong nonionic Lewis bases, **3**, to the direct synthesis of a variety of functionalized α,β-unsaturated nitriles from aldehydes using acetonitrile and benzyl cyanide. The effect of solvent on the synthesis of 2,3-diphenylpropenenitrile from benzaldehyde and benzyl cyanide is also discussed. Evidence for the novel mechanistic pathway of this reaction in a polar protic solvent such as methanol and in a nonpolar aprotic solvent such as benzene is also presented.

Results and Discussion

Benzyl Cyanide Condensations with Aldehydes. The deprotonation of benzyl cyanide with ionic bases followed by condensation with a variety of aldehydes is well documented.[10] However, the use of nonionic bases in this reaction for the direct synthesis of α,β-unsaturated nitriles has to our knowledge not been reported. We therefore decided to explore this possibility in the belief that **1** as a strong nonionic and weakly nucleophilic base would eliminate or at least reduce the side reactions observed with classical methods and in the hope that it could be used as a catalyst despite the possibility that the water eliminated during the reaction could conceivably deactivate the catalytic activity of **1** by protonation to form **2**(OH).

It has been reported that, by using the indicated bases, 2,3-diphenylpropenenitrile could be synthesized in the following (sometimes variable) yields: 40% aqueous NaOH, 80−95%;[10] 10 mol % NaOEt, 83−91%;[8] 0.03 equiv of $RhH_2(PPh_3)_4$ and dppe in THF, at 60 °C, 87%;[15] 12 mol % NaOH/0.1 equiv of cetyltrimethylammonium chloride, 86%;[4] 1 equiv of K_2CO_3, 95%;[7] 1 equiv of NaOH/0.05 equiv of poly(ethylene glycol), 71%.[5] The variable yields in the presence of ionic bases may be associated with the higher dielectric constant they confer on the medium, which polarizes the aldehyde C=O, thus rendering this functionality more susceptible to Cannizzaro side reactions. By employing **1** as a catalyst, 2,3-diphenylpropenenitrile

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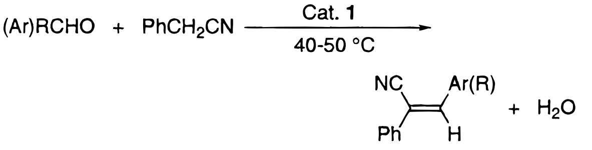
Table 1. Conditions for the Synthesis of α,β-Unsaturated Nitriles from Benzyl Cyanide Using 1 in Catalytic Amounts

aldehyde	equiv of **1**	*T* (°C)/ time (h)	solvent	eluent ratio[a]	% yield
benzaldehyde	0.03	50/6	neat	80:20	98
			THF		98
			C_6H_6		98
5	0.1	40/3	MeOH	80:20	99
6	0.1	40/3	MeOH		*b*
7	0.1	50/6	MeOH	50:50	99
	0.1	50/6	THF	50:50	50
8	0.1	40/3	MeOH	50:50	*c*
			THF	50:50	*d*
9	0.1	50/6	MeOH	80:20	99
10	0.1	40/3	MeOH	80:20	98
11	0.1	45/6	MeOH	95:5	98
12	0.1	50/24	THF	80:20	95
13	0.1	45/6	MeOH	95:5	88
14	0.1	50/6	MeOH	80:20	99
MeCHO	0.1	45/3	MeOH	90:10	98[e]

[a] Hexanes/ethyl acetate. [b] The OH group in **6** is deprotonated (Lensink, C.; Xi, S. K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478). [c] 100% BnCN, 85% vanillin acetate and 8% vanillin (*Aldrich Library of ^{13}C and ^1H FT-NMR Spectra*, 1st ed.; Aldrich, Milwaukee, Vol. 2, No. 959A) were recovered using gradient elution techniques starting from 50 mL of 10% ethyl acetate and increasing the polarity of the eluent in steps of 10% up to the eluent ratio indicated in this table. [d] Starting materials were recovered. [e] Because of the volatility of MeCHO (bp 21 °C), 2 equiv was used. Product yield is based on benzyl cyanide.

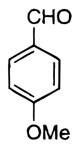
was obtained in 98% yield in a variety of solvents such as THF, C_6H_6, and MeOH and also in the absence of solvent under identical conditions (Table 1). The superiority of **1** over other typically employed nonionic bases was also demonstrated. Thus, reaction of 2.0 mmol of benzyl cyanide in THF at 50 °C for 6 h with 2.0 mmol of benzaldehyde in the presence of 0.2 mmol of the indicated catalyst revealed the chromatographically obtained yields (cf. details in Table 1) of 2,3-diphenylpropenenitrile: 1,1,3,3-tetramethyl guanidine, 20%; 1,8-diazabicyclo-[5.4.0]undec-7-ene, 20%; **1**, 98%. When CH_3CN was used as the solvent, only a 90% yield of 2,3-diphenylpropenenitrile was obtained using **1** as a catalyst. Although the lower yield in this case might be attributed to a decrease in catalyst **1** concentration caused by its partial conversion to **2**(CH_2CN) via deprotonation of CH_3CN,[21] we find that the ^{31}P resonance for the deuterated form of cation **2** in solutions of **1** in rigorously dried CD_3CN is barely detectable. Moreover, no cinnamonitrile arising from the reaction of acetonitrile anion and benzaldehyde was detected.

Table 1 indicates the efficiency and the scope of our method for the condensation/dehydration of benzyl cyanide with a variety of functionalized aldehydes as summarized in reaction 1. It has been reported that the synthesis of 1-methyl-2-phenylpropenenitrile using condensing agents such as alcoholic ammonia, piperidine, and acetic acid−acetic anhydride were unsuccessful, with excessively alkaline solutions leading to the formation of large amounts of resinous tarry material.[29] Thus, 1-methyl-2-phenylpropenenitrile was prepared in only 36% yield in ethanol at −5 °C using 20 mol % of sodium ethoxide as a catalyst,[29] whereas our method gave a 98% yield of product using 0.1 equiv of **1**. Even sterically hindered trimethyl acetaldehyde gave a 95% yield of the corresponding α,β-unsaturated nitrile under our conditions. In Table 1, it is seen that aliphatic aldehydes bearing α−protons were converted to the corresponding α,β-unsaturated nitriles in 88−98% yields; yields that are significantly higher than those reported in the literature (70−80%[7]). In our reaction involving **13**, the byproduct was shown to be the aldol product.



(1)

The best method in the literature for the preparation of α,β-unsaturated nitriles from aromatic aldehydes and benzyl cyanide gave variable yields (90−95%) depending on the structure of the aromatic aldehyde.[7] Except for **6** and **8** (see later), however, our approach consistently gave near-quantitative yields of α,β-unsaturated nitriles from aromatic aldehydes (Table 1) even in the case of the sterically hindered aromatic aldehyde **9**. Because the use of undistilled benzyl cyanide produces products that can be more deeply colored than those obtained with distilled benzyl nitrile,[8] this reactant was distilled before use.



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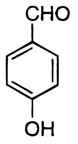

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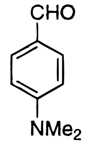

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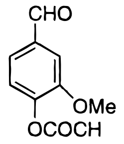

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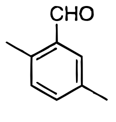

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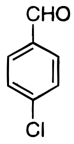

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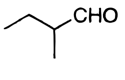

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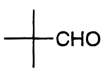

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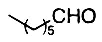

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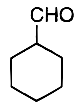

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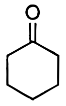

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On the basis of the chemical shift of the aromatic protons in the ^1H NMR spectra, it can be concluded that the aromatic rings are coplanar with the double bond framework of the α,β-unsaturated nitriles obtained from benzylnitrile and **5**−**7**, **9**−**14**, acetaldehyde, and benzaldehyde. The configuration of these products is exclusively *E* (see later).[4,5,30]

The proposed pathways associated with reaction 1 in polar protic solvents and in nonpolar aprotic solvents are depicted in Schemes1 and 2, respectively. The ^{31}P NMR of **1** in CD_3OD showed only a 1:1:1 triplet at −10 ppm, which we assigned to cation **2** (in deuterated form) on the basis of nearly the same ^{31}P NMR chemical shift (1:1 doublet) observed for protio-**2** in the proton-coupled spectrum.[21] Upon addition, benzyl cyanide is deprotonated by deuteriomethoxide anion, and the resulting

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(29) Knowles, E. C.; Cloke, J. B. *J. Am. Chem. Soc.* **1932**, *54*, 2036.

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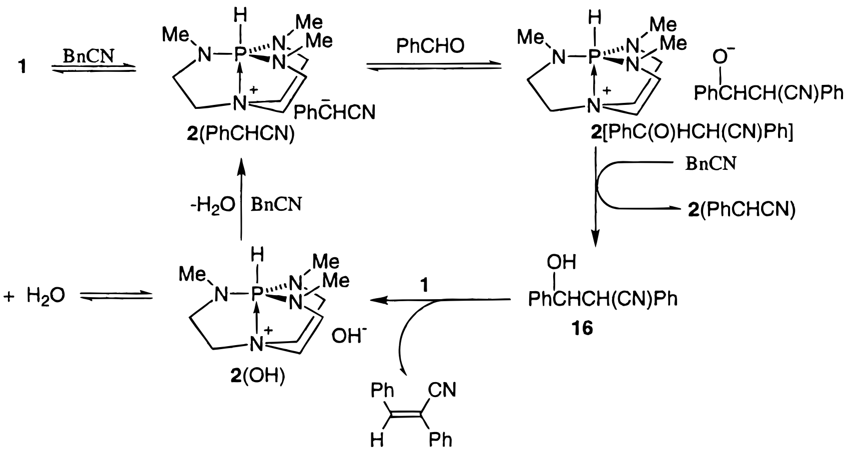
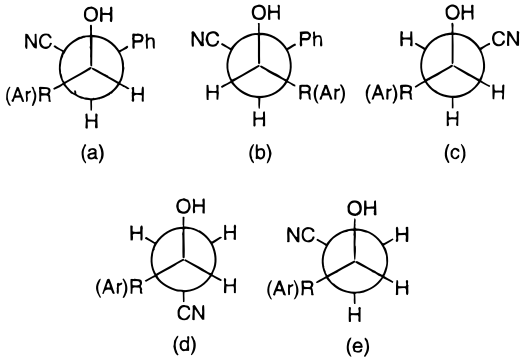
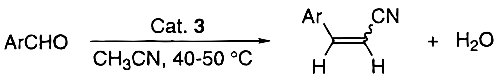
Scheme 2





PhCHCN$^-$ carbanion can react with benzaldehyde to give **2**[PhC(O)HCH(CN)Ph], the anion of which provides β-deuteriooxynitrile **16** in the presence of CD_3OD. The dehydration of β-deuteriooxynitrile **16** is facilitated by **2**(OCD_3), giving **2**(OD) and α,β-unsaturated nitrile. The **2**(OCD_3) then deprotonates benzyl cyanide, thus regenerating **2**(PhCHCN) for re-entry into the catalytic cycle. This pathway is supported by the fact that the dehydration of **16** was incomplete in MeOH at 50 °C in 6 h, whereas under the same conditions in the presence of 10 mol % of **1** it is complete in 6 h. Thus, in a polar protic solvent such as methanol, **1** initiates the reaction via deprotonation of methanol. In a nonpolar aprotic solvent such as benzene, however, **1** initiates the reaction via deprotonation of benzyl cyanide with subsequent dehydration of the intermediate β-hydroxy nitrile **16** (Scheme 2). This pathway is supported by the observation that **16** did not dehydrate in a relatively nonpolar solvent such as THF at 50 °C in 6 h. On the other hand, dehydration of **16** was complete in 6 h under the same conditions in the presence of 10 mol % of **1**. Further support for the pathway in Scheme 2 comes from the ^{1}H NMR spectrum of an equimolar mixture of **1** and benzyl cyanide in C_6D_6, which indicated 43% deprotonation of the benzyl cyanide. This partial deprotonation of $PhCH_2CN$ is not suprising since the **2**(PhCHCN) ion pair may be relatively unstable with respect to **1** and $PhCH_2CN$ in a nonpolar solvent such as C_6D_6. It is noted here that compound **16** can be synthesized in quantitative yield by a modification of our method that will be reported in due course.[31]

The exclusive formation of the **E** configuration of the α,β-unsaturated nitriles derived from $PhCH_2CN$ and aldehydes **5**−**7** and **9**−**14** can be rationalized on the basis of a dominant steric effect expressed by the (Ar)R and the phenyl groups in the β-hydroxy nitrile intermediates (schematically shown in Newman projections a and b) prior to deprotonation of the posterior carbon.



(2)

Acetonitrile Condensations with Aldehydes. The novel nonionic base **3**, which we synthesized recently, deprotonates acetonitrile to a larger extent than **1**.[28] In view of the fact that an attempted preparation of cinnamonitrile using 20 mol % of **1** at 50 °C in acetonitrile in 6 h failed, we reacted benzaldehyde with acetonitrile in the presence of 10 mol % of **3** at 50 °C, giving a 5.5:1 mixture of (*E*)- and (*Z*)-cinnamonitrile in 98% yield (Table 2). This contrasts the reported synthesis of (*E*)- and (*Z*)-cinnamonitrile (3:1) in 82% yield using 1 equiv of KOH at 82 °C.[6] Acetonitrile condenses with 4-methoxybenzaldehyde (**5**) in the presence of 1 equiv of KOH to give 81% of the α,β-unsaturated nitrile in an *E*/*Z* ratio of 2, whereas our methodology increases the yield to 99% and the *E*/*Z* ratio to 9 (Table 2).[6] To the best of our knowledge, aldehydes **7** and **9** have not been reported as a substrate for this reaction. Interestingly, 4-chlorobenzaldehyde (**10**) gave a 96% yield of the corresponding α,β-unsaturated nitrile, which is superior to the 57% yield reported in the literature.[6] Even the sterically hindered aldehyde **9** gave a 89% yield of the corresponding α,β-unsaturated nitrile. The aliphatic aldehyde **13** in the presence of MeCN gave only the aldol product in 99% yield for reasons that are not yet clear. Secondary aliphatic aldehydes **11** and **14** apparently produced the intermediate α,β-unsaturated nitrile, which subsequently underwent Michael addition to give novel compounds that will be reported later. Interestingly, the tertiary aliphatic aldehyde **12** gave exclusively the *Z* isomer of the corresponding α,β-unsaturated nitrile in 92% yield. These results contrast a literature report that aliphatic aldehydes (unspecified) do not condense satisfactorily with acetonitrile in the presence of potassium hydroxide.[6] Furthermore, **12** was reported to resist reaction with cyanoacetic acid to give the corresponding α,β-unsatur-

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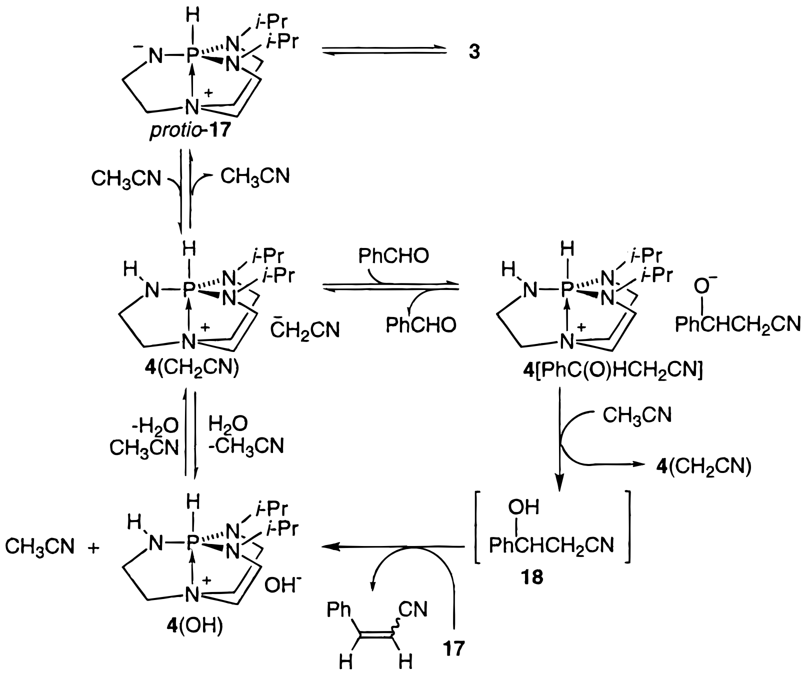
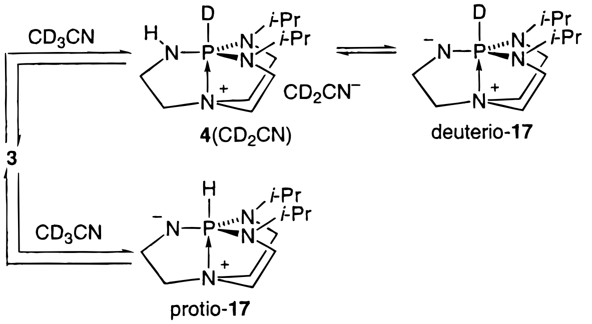
(31) D'Sa, B. A.; Verkade, J. G. Manuscript in preparation.

Scheme 3



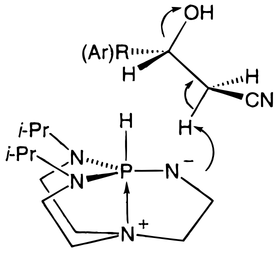
Scheme 4



ated nitrile in the presence of pyridine as a catalyst at 190 °C under 1000 psi.[32]

The proposed pathway for the formation of α,β-unsaturated nitrile using a catalytic amount of **3** is shown in Scheme 3. We have shown by ^{31}P NMR spectroscopy that, in CH_3CN, **3** exists in equilibrium with ca. 15% of its tautomer protio-**17** shown in Scheme 3.[28] When **3** is dissolved in CD_3CN, the tautomer is almost exclusively in the deuterated form with only a barely detectable peak assignable to the isotopomer of this tautomer achieved by direct rearrangement (Scheme 4). Regardless of the pathway to **17** in Scheme 3, the amide ion of this zwitterionic tautomer is expected to function as an ionic base, deprotonating CH_3CN much more rapidly than the neutral phosphorus in its parent **3**. It should be noted that no ^{31}P NMR peak for the deuterated form of cation **4** can be observed for CD_3CN solutions of **3** even after several days. These observations do not preclude the formation of **4**(CH_2CN) or **4**(CD_2CN) in rapid equilibria in Schemes 3 and 4, respectively, since their concentrations may be undetectably small. Thus, the **4**(CH_2CN) so formed in Scheme 3 can then condense with benzaldehyde to give the β-hydroxy nitrile **18**, which subsequently dehydrates to the α,β-unsaturated nitrile product. The tautomer of **3** (i.e., **17**) appears to be required for the dehydration of **18** since both **3** and **1** are almost equally strong bases,[28] and **1** does not catalyze this reaction.

Because the use of **3** in the reactions of CH_3CN with aldehydes gives rise to significantly higher *E*/*Z* ratios for the products than those achieved through the use of OH^- ion reported in the literature,[6] we conclude that tautomer **17** of **3** prefers to deprotonate the rotameric form of intermediate **16** shown as Newman projection c in preference to d or e. That the order for the populations of rotamers c–e is c > d > e is expected on steric grounds. A possible reason the order of deprotonation preference by **3** follows this decreasing steric order more strongly with **3** than with OH^- can be visualized in the approach of rotamer c to the zwitterionic form **17** of base **3** as shown in f below. When van der Waals radii of the atoms are taken into account, rotamer c can be visualized to approach **17** more comfortably than d. Although the steric interactions involved with e and **17** are similar to those with c and **17**, the relative population of e is small.



(f)

Vanillin Acetate (8), Cyclohexanone (15), and *p*-Hydroxybenzaldehyde (6) as Substrates. It is not suprising that vanillin acetate (**8**) gave only starting materials in the presence of benzyl cyanide and **1** in THF or benzene, since the intermediate β-hydroxy nitriles formed in such equilibria do not spontaneously dehydrate in a nonpolar aprotic solvent, an observation that has ample precedent in the literature.[12] Attempts to carry out this reaction in MeOH in the presence of a catalytic

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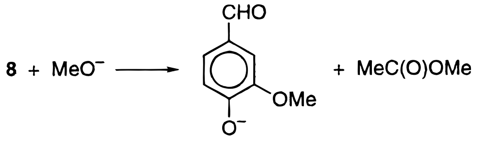
[32] Lee, C. K.; Shin, J. Y. *OPPI Briefs* **1990**, *22*, 94.

Table 2. Conditions for the Synthesis of α,β-Unsaturated Nitriles from Acetonitrile Using 3 in Catalytic Amounts

aldehyde	equiv of **3**	T (°C)/ time (h)	eluent ratio	E/Z[a] ratio	% yield
benzaldehyde	0.1	50/6	75:25[b]	5.5:1	98
5	0.3	40/3	80:20[b]	9:1	99
6	0.3	40/3			*c*
7	0.3	40/3	80:20[b]	9:1	99
8	0.3	40/3			*d*
9	0.3	40/3	80:20[e]	7.7:1	89
10	0.3	40/3	80:20[b]	9:1	96
12	0.3	45/3	90:10[e]	∞	92
13	0.3	40/3	80:20[b]		*f*

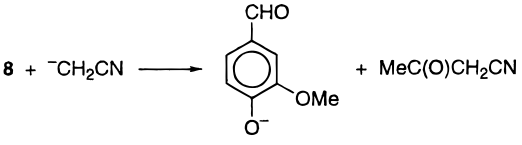
[a] Determined by ^{1}H NMR spectroscopy. [b] Hexanes/ethyl acetate. [c] The OH group in **6** is deprotonated. [d] 70% vanillin acetate and 27% vanillin (*Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*, 1st ed.; Aldrich: Milwaukee, Vol. 2, No. 959A) was isolated by chromatography (see Discussion). [e] Pentane/ethyl ether. [f] A quantitative yield of aldol product was obtained.

amount of **1** (Table 1) or with MeCN (which served additionally as the solvent) using **3** as a catalyst (Table 2) were also not successful. From the reaction in MeOH, BnCN was recovered quantitatively along with 85% of the vanillin acetate and 8% vanillin. This can be understood from the pathway proposed in Scheme 1 wherein the MeO$^-$, which is formed by deprotonation of MeOH with **1**, attacks the vanillin acetate (**8**) as shown in reaction 3. The vanillin anion so produced subsequently became protonated by the chromatographic eluent (50:50 hexanes/ethyl acetate), which was not dried prior to use. The 8% vanillin recovered in the chromatography is reasonably close to the 10% expected on the basis of the ~0.1 mol % of **1** initially present. Reactions carried out in benzene or THF or with no solvent led only to the recovery of starting materials.



(3)

The reaction of vanillin acetate with MeCN, wherein ~30 mol % of **3** was present gave rise to 27% vanillin and 70% vanillin acetate after chromatography. Here, it seems likely that the pathways in Schemes 3 and 4 operate, wherein deprotonation of MeCN by **3** leads to reaction 4. Again, chromatography with undried eluent would lead to reprotonation of this anion. The acetoacetonitrile produced in this reaction could not be isolated by chromatography. This may be due to its polymerization[33] and possibly its reaction with the unrecovered vanillin and/or vanillin acetate. (Acetoacetonitrile is known to react with aldehydes.[34]) Further evidence for conversion of the acetoacetonitrile to an unidentified product after its formation in reaction 4 is the observation that the analogue 4,4-dimethyl-3-oxopentanenitrile after deprotonation with 3 equiv of **3** (as observed by ^{31}P NMR spectroscopy) was recovered in reprotonated form upon chromatography of the mixture. A repetition of this experiment with acetoacetonitrile failed. The presence of $MeC(O)CH_2CN$ in reaction 4 was confirmed, however, by reacting 1 equiv of **3** with 1 equiv of vanillin acetate in CD_3CN followed by quenching the reaction with 2 drops of D_2O, drying the mixture over anhydrous Na_2SO_4, and distilling of the mixture at 60 °C/500 mTorr. The ^{1}H NMR spectrum of the distillate (a solution of acetoacetonitrile in CD_3CN) compared favorably with that reported earlier for this β-ketonitrile.[34]



(4)

Cyclohexanone (**15**) fails to react with BnCN in the presence of **1** in MeOH at 40 °C or with CH_3CN in the presence of a catalytic amount **3** at 40 °C. This may be associated with the relatively low dielectric environment in our reactions, compared with those incorporating ionic bases. Thus, the ketonic carbonyl is not polarized to as large a degree, thus rendering the carbonyl carbon less susceptible to nucleophilic attack. By polarizing the carbonyl group of a variety of ketones (including cyclohexanone) with Mg^{2+}, however, CH_3CN in the presence of **3** effects high conversions to the corresponding β-hydroxy nitrile from 25 to 40 °C.[31] The presence of Mg^{2+} in a mixture of cyclohexanone, BnCN, and **1** in MeOH failed to cause any observable reaction at 40 °C. The latter observation can be attributed to one or a combination of the following: solvation of Mg^{2+} by MeOH, the larger steric encumbrance encountered by $PhCHCN^-$ compared with CH_2CN^-, and the poorer nucleophilicity of $PhCHCN^-$ compared with CH_2CN^-.

p-Hydroxybenzaldehyde (**6**) failed to condense with BnCN or CH_3CN. Because phenols are easily deprotonated by strong nonionic bases such as **1** and **3**,[21] this observation is easily understood.

Conclusions

The novel routes described herein are convenient for synthesizing α,β-unsaturated nitriles by the condensation/dehydration of benzyl cyanide with a variety of functionalized aromatic and aliphatic aldehydes in the presence of the catalytic nonionic base **1** and by the condensation/dehydration of acetonitrile with aromatic aldehydes and tertiary aliphatic aldehydes using catalytic amounts of the novel base **3**. The proton α to the nitrile group in **18** is less acidic compared with that of **16**, and hence, the stronger zwitterionic base **17** is required for dehydration of **18**. Evidence for different mechanistic pathways for the reaction involving benzyl cyanide and **1** in a polar protic solvent such as methanol and a nonpolar aprotic solvent such as benzene has been adduced. With either **1** or **3**, primary and secondary aliphatic aldehydes do not give the corresponding α,β-unsaturated nitriles with acetonitrile. Ketones do not condense with either benzyl cyanide or acetonitrile under our conditions, perhaps owing to an insufficiently high dielectric environment.

Experimental Section

THF, toluene, and benzene were distilled from Na–benzophenone under nitrogen. Acetonitrile and methanol were distilled from calcium hydride. Benzyl cyanide, *p*-hydroxy-

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(33) Vinick, F. J.; Pan, Y.; Gschwend, H. W. *Tetrahedron Lett.* **1978**, 4221.

(34) Perez, J. D.; Yranzo, G. I.; Wunderlin, D. A. *J. Org. Chem.* **1982**, *47*, 982.

(35) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *75*, 578.

benzaldehyde, *p*-chlorobenzaldehyde, 2-methylbutyraldehyde, trimethylacetaldehyde, heptaldehyde, cyclohexanecarboxaldehyde, 2,5-dimethylbenzaldehyde, acetaldehyde, and vanillin acetate were purchased from Aldrich Chemical Co. and were used as received except for benzyl cyanide, which was distilled before use. *p*-Methoxybenzaldehyde was purchased from Acros Chemical Co. and was used without further purification. *p*-(Dimethylamino)benzaldehyde and benzaldehyde were purchased from Fisher Scientific and were used as received. All reactions were carried out under N_2. Although the nonionic base **1** is commercially available,[25] we prepared it according to our previously published method[34] and stored it under N_2. The nonionic base **3** was synthesized according to our method[28] and stored under N_2 at −4 °C. The products were characterized by MS and ^{13}C NMR spectroscopy and were found to be >98% pure by ^1H NMR analysis.

Condensation Conditions for Aldehydes 4−14 and 12 with Benzyl Cyanide Using a Catalytic Amount of 1. In a 20 mL test tube was dissolved a catalytic amount of **1** (Table 1) in 3.0 mL of methanol, THF, or C_6H_6. To this was added 0.23 mL (2.0 mmol) of benzyl cyanide. After the mixture was stirred for 0.5 min, 2.0 mmol of the aldehyde was added with continued stirring at the temperature stated in Table 1. After the reaction time given in Table 1, the α,*β*-unsaturated nitriles obtained in >98% yield were purified by flash column chromatography using the eluent stated in Table 1. The α,*β*-unsaturated nitriles obtained in <98% yield were purified by silica gel column chromatography using the gradient elution technique. Thus, after the column was loaded with the crude α,*β*-unsaturated nitrile, the polarity of the solvent was increased in steps of 5% using 50 mL of eluent in each step, starting from 50 mL of 100% hexanes and ending with the ratio indicated in Table 1.

Preparation of 1-Methyl-2-phenylpropenenitrile. In a 20 mL test tube was dissolved 0.04 g (0.20 mmol) of **1** (Table 1) in 3.0 mL of methanol. To this was added 0.23 mL (2.0 mmol) of benzyl cyanide. After the mixture was stirred for 0.5 min, 0.44 mL (4.0 mmol) of acetaldehyde was added with continued stirring at 45 °C. After 3 h, the crude 1-methyl-2-phenylpropenenitrile was purified by column chromatography using the gradient elution technique. Thus, after the column was loaded with the crude product, the polarity of the solvent was increased in steps of 2% using 50 mL of eluent in each step, starting from 50 mL of 100% hexanes and ending with the ratio indicated in Table 1.

Condensation Conditions for Aldehydes 4−10 and 12 with Acetonitrile Using a Catalytic Amount of 3. In a 20 mL test tube was dissolved a catalytic amount of **3** (Table 2) in 1.0 mL of acetonitrile. After the mixture was stirred for 0.5 min, 0.4 mmol of the aldehyde dissolved in 1 mL of acetonitrile was added with continued stirring at the temperature stated in Table 2. After the reaction time given in Table 2, the crude α,*β*-unsaturated nitriles were purified by column chromatography using the eluent given in Table 2.

Supporting Information Available: ^1H and ^{13}C NMR and mass spectral data (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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