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Synthesis of new proazaphosphatranes and their application in organic synthesis

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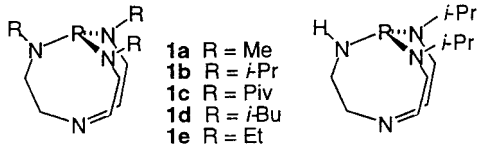
Abstract—We report herein the synthesis of the new proazaphosphatrane strong bases $P(RNCH_2CH_2)_3N$ (R=Me_3CCH_2, Me_2CHCH_2) and $P(HNCH_2CH_2)_2NCH_2CH_2N$-*i*-Pr (**1g**). The new azaphosphatranes $[HP(RNCH_2CH_2)_3N]Cl$ (R=Me_3CCH_2, Me_2CHCH_2) have P–N_{ax} distances of 2.047 and 1.958 Å, respectively. We also report the synthesis of the tetramine precursor proazaphosphatrane **1g** [namely, $(H_2NCH_2CH_2)_2NCH_2CH_2NH$-*i*-Pr] in 41% yield and the use of a complexation–extraction technique to separate it from a mixture containing the di- and tri-isopropyl substituted analogs. Using a ^{31}P NMR technique, we report the pK_a value for $\mathbf{1gH}^+$ (34.49). The catalytic properties of three bases $P(RNCH_2CH_2)_3N$ (R=*i*-Pr, Piv, *i*-Bu) are compared in the synthesis of several β-hydroxy nitriles, β-nitroalkanols, α,β-unsaturated esters and for the Michael addition of allyl alcohol to α,β-unsaturated ketones. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The proazaphosphatrane nonionic bases **1a**,[1] **1b**,[2]and **1f**,[3a] first synthesized in our laboratories, have been found to be efficient catalysts and promoters for many reactions. Thus, proazaphosphatranes catalyze the trimerization of isocyanates,[4] the dehydrohalogenation of alkyl halides,[5] the synthesis of α,β-unsaturated nitriles,[6] β-hydroxy nitriles,[7] and homoallylic alcohols,[8] the transesterification of esters,[9] the deprotection of acylated alcohols[9] and silylated alcohols,[10] the synthesis of β-nitroalkanols,[11] the synthesis of α,α-dicyano-α,β-olefins,[12] Michael addition reactions,[13] the silylation of hindered alcohols,[14] the conjugation of methylene-interrupted double bonds,[15] the synthesis of glutaronitriles,[16] the synthesis of benzofurans,[17] and the synthesis of oxazolines.[18]



1f

1g **1h**

We have also been able to utilize these bases stoichiometrically in other syntheses, such as Wittig products,[19] α,β-unsaturated esters[20] and oxazoles.[21] Compound **1a** (available from Strem Chemicals) has been extensively studied and found to be superior in the aforementioned reactions to other nonionic bases, such as DBU and proton sponge.[22] Recent studies with **1a**, **1b**, and **1f** suggest that these bases have slightly different basicities.[2,3,6] Furthermore, we have found that **1b** is superior to **1a** in a number of reactions as a result of its higher basicity and better stability with respect to oligomerization.[7,8,20] It is thus imperative that new homologous proazaphosphatranes be synthesized in order to facilitate studies aimed at understanding the effect of the PN_3 nitrogen substituents on the basicity and catalytic properties of this class of compounds. More economical and convenient syntheses of such trisubstituted proazaphosphatranes are also important to investigate, because in our experience, proazaphosphatrane bases bearing an *R* group at each PN_3 nitrogen are more stable to oligomerization than the less substituted analogs.

Previously we attempted to use acetaldehyde for the synthesis of $N(CH_2CH_2NHEt)_3$ (the precursor to **1e**) via the reduction of the intermediate *tris*-aldimine formed from $N(CH_2CH_2NH_2)_3$ (**2**).[2] However, oligomerization of the intermediate aldimine was faster than its reduction and consequently, the tetramine $N(CH_2CH_2NHEt)_3$ had to be prepared by a less convenient procedure.[23] This was achieved by reacting $N(CH_2CH_2NH_2)_3$ (**2**) with acetic anhydride followed by reducing the resulting *tris*-amide with LAH. Although the *tris*-aldimine derived from acetaldehyde in this case proved to be unsuitable, we believed that higher aldehydes might lead to *tris*-aldimines that are less prone to oligomerization because of steric hindrance. We therefore

Keywords: proazaphaphosphatrane; nonionic base; pK_a; catalysis; phosphazane base.

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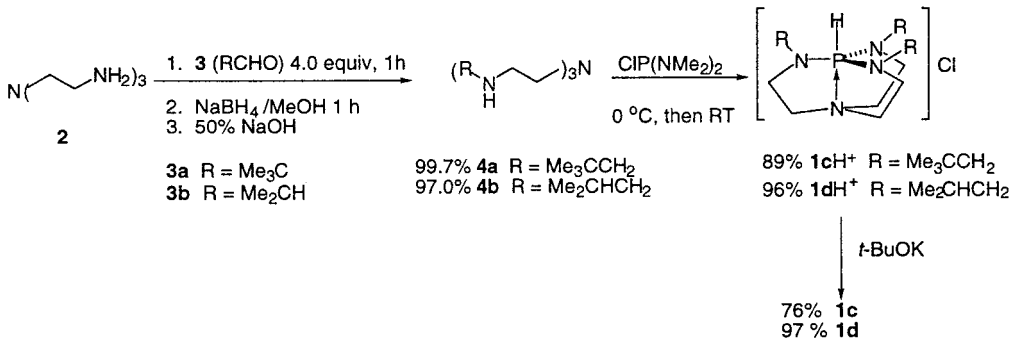


Scheme 1.

decided to investigate the reaction of pivalaldehyde (**3a**) and isobutyraldehyde (**3b**) with **2**, and we report herein the synthesis of proazaphosphatranes **1c** and **1d**, respectively, derived from these aldehydes.

We have previously reported the synthesis of proazaphosphatrane **1b**[2] and its less substituted analog **1f**.[3] Preliminary results have indicated that **1h** may be more basic than **1a**, although the pure base could not be isolated.[24] We thus tentatively concluded that if we could prepare proazaphosphatrane **1g**, it might exceed **1a**, **1b** and **1f** in basicity. Using a ^{31}P NMR technique we report the pK_a value for **1g**H$^+$ in MeCN and compare it to the pK_a values we measured recently[25] for **1c**H$^+$ and **1d**H$^+$ in the same solvent. We also compare the catalytic properties of **1b**, **c** and **d** in the synthesis of several β-hydroxy nitriles, β-nitroalkanols, α,β-unsaturated esters and for the Michael addition of allyl alcohol to α,β-unsaturated ketones.

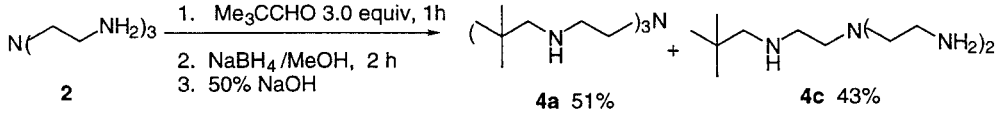
2. Results and discussion

2.1. Synthesis of N(CH$_2$CH$_2$NHCH$_2$CMe$_3$)$_3$ (4a), [HP(Me$_3$CCH$_2$NCH$_2$CH$_2$)$_3$N]Cl, [1cH]Cl and P(Me$_3$CCH$_2$NCH$_2$CH$_2$)$_3$N (1c)

The preparation of **4a** was achieved by stirring a 1:4 mixture of **2** and pivalaldehyde for 1 h and then reducing the intermediate aldimine with sodium borohydride in methanol. The excess borohydride was quenched with 50% aqueous sodium hydroxide to afford **4a** in 99.7% yield (Scheme 1). This synthesis of **4a** is more convenient than that recently reported by Scheer et al. (who provided no physical data for the pure tetramine).[26] The Scheer synthesis was carried out by reacting the tetramine **2** with pivaloyl anhydride followed by the reduction of the triamide thus produced with lithium aluminum anhydride. When the amount of pivalaldehyde in Scheme 1 was reduced to 3.0 equiv., conversion to **4a** decreased to 51% owing to the formation of the less substituted derivative **4c** (43%, Scheme 2). The tetramine **4a** is not appreciably soluble in acetonitrile and consequently, it was necessary to prepare [**1c**H]Cl in a solvent system composed of methylene chloride and ethyl ether. The [**1c**H]Cl thus successfully prepared in 89% yield (Scheme 1) was then deprotonated in THF to afford **1c** in 76% yield with an overall yield of 67%. The use of methylene chloride alone led to inconsistent results, while ether failed to induce a clean reaction. Although the reaction was successful in THF, the product could not be purified. The weak acid [**1c**H]Cl displayed a ^{31}P signal at 2.29 ppm, which is significantly downfield (by ~12 ppm) compared with that of the analogous cations **1a**H$^+$ and **1b**H$^+$.[2] However, X-ray crystallography (Fig. 1) showed that the P–N$_{ax}$ distance (2.047 Å) in cation **1c**H$^+$ was within experimental error (i.e. within 3×esds) of those found in the analogous cations [**1a**H$^+$ (1.967 Å), **1b**H$^+$ (1.946 Å) and **1f**H$^+$ (2.078 Å) reported earlier from our laboratories.[2] The N$_{eq}$PN$_{eq}$ angles of 118–119° are also comparable to those in the aforementioned analogs reported previously.[2] The proazaphosphatrane base **1c** displayed a ^{31}P NMR signal at 144.3 ppm in C_6D_6, which upon the addition of two drops of nitromethane, rapidly disappeared to be replaced by a single ^{31}P signal at 2.29 ppm. This experiment strongly indicates that the conjugate acid of the new proazaphosphatrane **1c** has a pK_a value of at least 28 in acetonitrile, since the pK_a of nitromethane in CH_3CN is 28.[27a] The strong basicity of this proazaphosphatrane was recently confirmed by measuring the pK_a (32.84) of its conjugate acid **1c**H$^+$ in equilibrium with EtN=P(NMe$_2$)$_2$N=P(NMe$_2$)$_3$ in acetonitrile by a ^{31}P NMR method.[25]

2.2. Synthesis of N(CH$_2$CH$_2$NHCH$_2$CHMe$_2$)$_3$ (4b), [HP(Me$_2$CHCH$_2$NCH$_2$CH$_2$)$_3$N]Cl {[1dH]Cl} and P(Me$_2$CHCH$_2$NCH$_2$CH$_2$)$_3$N (1d)

The synthesis of **4b** was achieved analogously to that of **4a** as discussed above. Thus **2** was reacted with isobutyraldehyde in a small amount of *t*-butyl alcohol or methanol, followed by reduction with sodium borohydride in methanol to afford a 97% yield of **4b** after distillation (Scheme 1). When isobutyraldehyde was not first dissolved in an



Scheme 2.

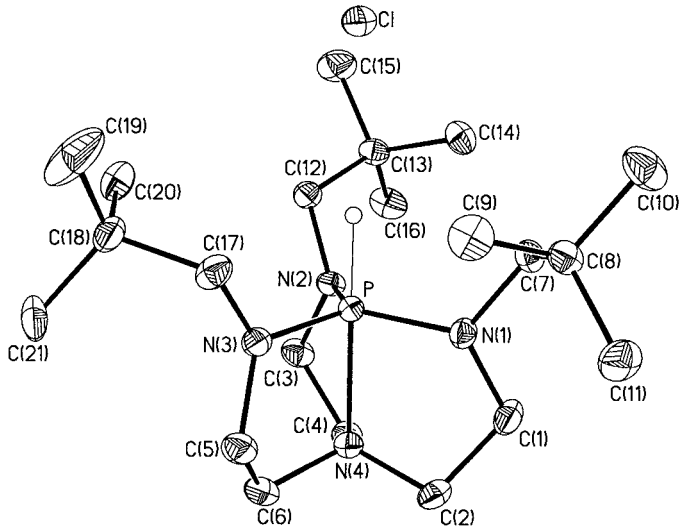


Figure 1. Computer drawing of the molecular structure of **1c**H$^+$. Ellipsoids are at the 30% probability level.

alcohol, the isolated yield of **4b** decreased to 89%. Ring closure to [**1d**H]Cl was achieved in acetonitrile in 96% yield in a manner analogous to that described above for [**1c**H]Cl. However, scale-up of the reaction led to lower yields as a result of the limited solubility of **4b** in this solvent. This problem was circumvented upon altering the solvent system to methylene chloride or THF. This afforded 87–95% yields of [**1d**H]Cl depending on the scale of the reaction. Compound [**1d**H]Cl was deprotonated in THF using potassium *t*-butoxide, followed by extraction with pentane to afford **1d** in 97% yield. Compound **1d** was thus obtained in three steps in 82–89% overall yield. The lower limit occurred in large scale syntheses (0.5 mol) in which stirring difficulties were encountered. Nevertheless, **1d** is the least expensive proazaphosphatrane we have prepared so far. It is worth mentioning that the ring closure reaction was unsuccessful in ether.

The P–N_{ax} distance in cation **1d**H$^+$ (Fig. 2) is 1.958 Å, which is within experimental error (i.e. within 3×esds) of those reported for **1a**H$^+$ and **1b**H$^+$.[2] The $N_{eq}PN_{eq}$ angle of 119–120° is also close to those reported for the same analogs.[2] However, the ^{31}P NMR chemical shift (−7.1 ppm) of **1d**H$^+$ is shifted downfield by over 2 ppm compared to that of the analogs **1a**H$^+$ and **1b**H$^+$.[2] The molecular structure obtained for **1d**H$^+$ reveals that two molecules crystallize with four solvent ($CHCl_3$) molecules in the monoclinic unit.

Compound **1d** was obtained as a colorless oil that solidifies to form a white solid upon storage at −4°C for 24 h. When formation of solid **1d** did not occur, the colorless liquid was frozen in a dry ice-acetone bath, which was then allowed to warm to −4°C in the freezer to form a white solid that was kept at or below −4°C. However, **1d** can be used in the liquid form. Thus far, we have observed no change in either the physical data (^{31}P NMR and ^{1}H NMR spectra) or the chemical properties of **1d** upon storing the compound in either the liquid or solid state for up to 30 days. A liquid sample of **1d** stored at room temperature over the same time period, also showed no change in either the ^{1}H NMR or ^{31}P NMR spectrum. For reasons that are not yet clear, a sample of isolated **1d** left in an open tube for 24 h showed no formation of the oxide in contrast with **1a**, **1b**, and **1f**. The

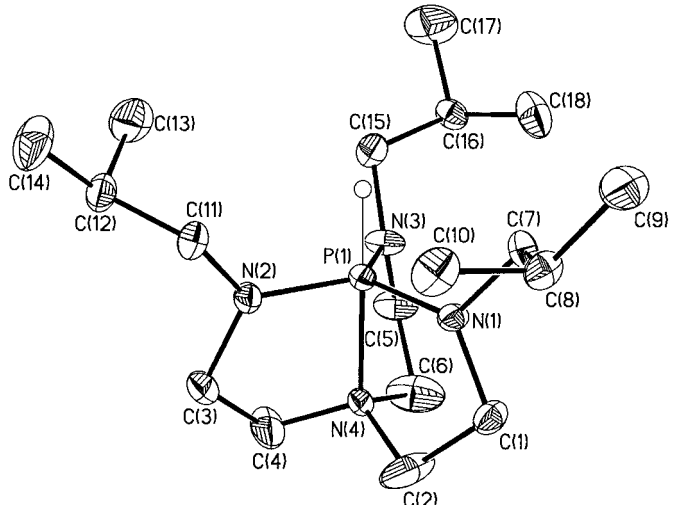
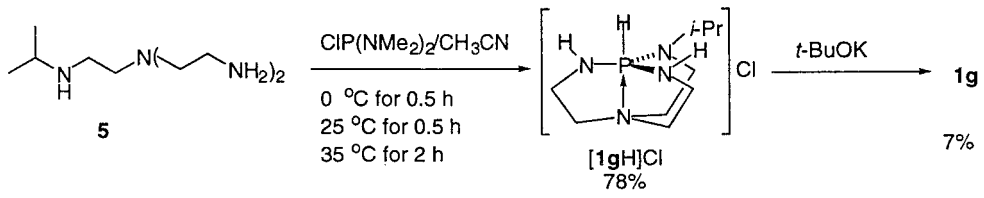


Figure 2. Computer drawing of the molecular structure of **1d**H$^+$. Ellipsoids are at the 30% probability level.



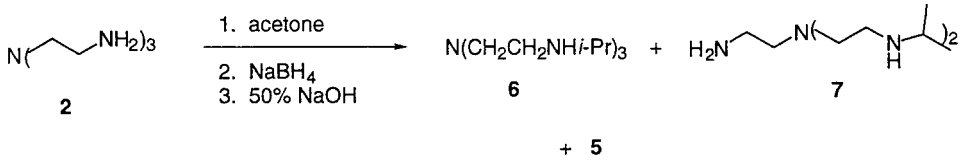
Scheme 3.

base **1d** showed a single ^{31}P NMR signal at 130.9 ppm. Upon addition of nitromethane to the solution of this compound in C_6D_6, this peak instantaneously disappeared and was replaced by a single peak at −8.2 ppm (**1d**H^+) which is characteristic of pentacoordinate phosphorus. The downfield δ ^{31}P value compared with that in $CDCl_3$ (−7.1 ppm) reflects a solvent effect. We recently reported a pK_a value of 33.53 for **1d**H^+ in MeCN.[25]

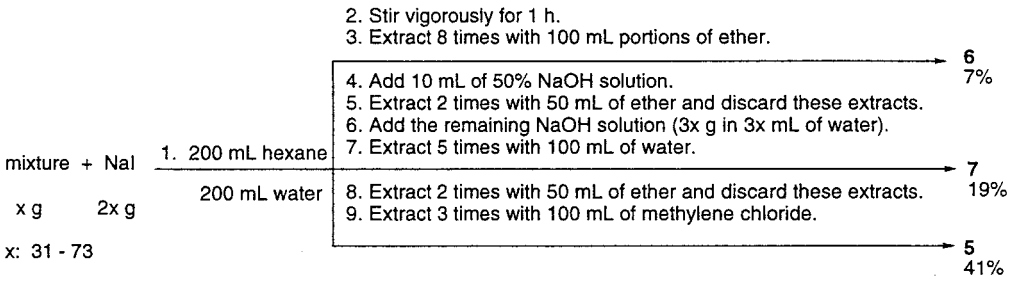
2.3. Synthesis of $(H_2NCH_2CH_2)_2NCH_2CH_2NHCHMe_2$ (5), $HP(HNCH_2CH_2)_2NCH_2CH_2NCHMe_2]Cl$ {[**1g**H]Cl} and $P(HNCH_2CH_2)_2NCH_2CH_2NCHMe_2$ (**1g**)

The synthesis of **1g** in Scheme 3 (to be discussed shortly) required a viable route to tetramine **5**. Although syntheses of the more highly substituted analogs **6**[2] and **7**[3] in Scheme 4 were reported previously from our laboratories, neither report mentioned the monosubstituted analog **5** because we did not observe its presence in the product mixture. Subsequently, we have noticed that **5** forms in varying amounts during preparations of both **6** and **7**. Therefore, a study aimed at optimizing the formation of **5** was initiated. Compound **5** was obtained as the major product (Scheme 4) by reducing the amount of acetone used in the reaction to 3.2 equiv. and also by reducing the time of addition of sodium borohydride to 3 h. However, none of the three products could be isolated from the mixture of products by distillation because they consistently distilled together. Purification based on the difference in the solubility of their sodium iodide complexes was achieved according to Scheme 5. A mixture of **5**, **6** and **7** was stirred in a 1:1 mixture of hexane and water for 1 h in the presence of sodium iodide. Separation of the organic layer, followed by extraction of the aqueous layer with ether afforded **6**, which does not form a complex with sodium iodide that is water-insoluble. The aqueous layer was then treated with 50% aqueous sodium hydroxide to pH 11 in order to free **7**. This basic aqueous solution was extracted with ether and dried over anhydrous potassium carbonate. The sodium iodide-**5** complex remained as an insoluble viscous oil above the aqueous layer which was extracted with methylene chloride to afford an oily material that was distilled to afford pure **5**.

The conversion of **5** to the hydrochloride [**1g**H]Cl was effected as shown in Scheme 3. In this process, **5** was added to $ClP(NMe_2)_2$ in acetonitrile at 0°C. The reaction mixture was stirred for 0.5 h at this temperature, followed by stirring at room temperature for an additional 0.5 h. The reaction mixture was placed in a warm water bath (35°C) and stirred for 2 h. The material that precipitated was filtered under vacuum and washed with cold acetonitrile to afford the pure salt [**1g**H]Cl. Alternatively, the reaction mixture was stirred at room temperature overnight to afford the hydrochloride salt [**1g**H]Cl in comparable yields to that described above. Attempted deprotonation of [**1g**H]Cl with potassium *tert*-butoxide in THF, followed by extraction with pentane, afforded a liquid material with ^{31}P NMR spectral peaks at 124 and 134 ppm. The two peaks were found to persist when $MeNO_2$ was added to a solution of the product in C_6D_6, and therefore we concluded that this material could not be **1g**. The second step in Scheme 3 was then repeated in



Scheme 4.



Scheme 5.

Table 1. Comparison of the efficiency of **1b** as a catalyst or promoter versus **1c** and **1d**

Reaction	Mol% of **1**/°C/h	Yield with **1d** (%)	Yield with **1c** (%)	Yield with **1b** (%)[a]
2-methylcyclohexanone+MeCN	10/25/6[b]	93	–[c]	84[7]
2-butanone+MeCN	10/25/6[6]	96	–[c]	88[7]
p-anisaldehyde+MeCN	30/-5/6[b]	91	trace	60[7]
p-chlorobenzaldehyde+MeCN	30/0/6[b]	89	trace	71[7]
3-pentanone+$MeNO_2$	10/25/3[b]	76	78	60[11]
benzaldehyde+*n*-$PrNO_2$	20/25/2[b]	96	95	97[11]
p-anisaldehyde+CH_3CO_2Et	30/0/6	91(96)	trace	60[21]
p-chlorobenzaldehyde+$EtCO_2Me$	30/50/6	95	trace	9521
4-hexen-3-one+CH_2:$CHCH_2OH$	20/70/3	96	96	71[13]
mesityl oxide+CH_2:$CHCH_2OH$	20/70/3	88	81	40[13]

[a] Obtained from referenced reports from our laboratories.
[b] In the presence of 2.2 equiv. of $MgSO_4$.
[c] No detectable amount of product was formed.

benzene. The product isolated exhibited a ^{31}P NMR chemical shift at 100.9 ppm in C_6D_6. This peak rapidly disappeared on addition of $MeNO_2$ to a C_6D_6 solution of the product with the subsequent appearance of a peak at −32.6 ppm, which is characteristic of **1g**H^+. This slight variation in the chemical shift of **1g**H^+ is assumed to originate from a solvent effect which we have noted for several azaphosphatranes. The peak at 100.9 ppm for the mono-isopropyl-substituted **1g** (although slightly shifted in the presence of MeCN to 101.4 ppm) also agrees favorably with the trend observed for disubstituted **1f** and trisubstituted **1b**, whose ^{31}P NMR chemical shifts are 110.5[3] and 117[2] ppm, respectively. It should be mentioned that the use of a slight excess of potassium *tert*-butoxide in benzene in the second step afforded an oily material that exhibited seven ^{31}P signals with none corresponding to the desired product. This is probably due to the deprotonation of an N–H proton followed by oligomerization of the bicyclic product.

Compound **1g** was very unstable to oligomerization even at −4°C where it did so in 24 h, although crude **1g** dissolved in benzene and kept in the freezer for up to seven days did not oligomerize substantially. We previously observed that **1f** oligomerized when kept at room temperature for a week, but was stable for longer periods of time when kept below −4°C.[3] Attempts at preparing the unsubstituted proazaphosphatrane **1h** have remained unsuccessful so far because of oligomerization side reactions, although it could be observed in solution and stable derivatives have been isolated.[1,28] The ^1H and ^{13}C NMR spectra of **1g** were not sufficiently clean to allow elemental analysis and/or HRMS. An attempt at redistillation was unsuccessful because of the small amount of material in hand. However, the observed purity (93% by ^{31}P NMR analysis) was sufficient for NMR characterization. The rest of the material, as determined by ^{31}P NMR analysis, was the corresponding oxide whose presence is attributed to adventitious oxygen that readily reacted with **1g**.

The pK_a value of 34.49 measured herein for **1g**H^+ (34.49) in MeCN was obtained by equilibrating a 1:1 mixture of EtN=P(NMe_2)N=P(NMe_2)$_3$ and pure [**1g**H]Cl. The measurement made in this way is therefore unaffected by purification difficulties encountered with **1g**. However, it was necessary to record the ^{31}P NMR spectrum in 10–30 min to avoid oligomerization of **1g** in the reaction mixture.

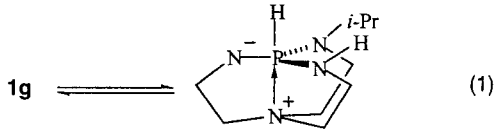
2.4. Comparison of the catalytic properties of 1b, 1c and 1d

Because the preparation of **1d** is less expensive than any of the other proazaphosphatrane bases we have prepared so far, we selected it for the comparison of its efficiency as a catalyst for several reactions for which **1b** has already proven to be a superior base. We also compared these key reactions using **1c**. We thus utilized both **1c** and **1d** for the catalytic synthesis of several β-hydroxy nitriles, β-nitroalkanols and α,β-unsaturated esters, and for the oxa-Michael addition of allyl alcohol to α,β-unsaturated ketones. Pertinent data for these reactions collected in Table 1 reveal that **1d** is generally at least as efficient as **1b**, and in some cases more efficient. The most noteworthy of these reactions is the preparation of a β-hydroxy nitrile from *p*-anisaldehyde and acetonitrile in the presence of 2.2 equiv. of magnesium sulfate. Previously we found that this reaction proceeds in relatively modest yield (78%) in the presence of **1b** as the catalyst. In the presence of **1d**, the conversion of *p*-anisaldehyde is 96% at 0°C but with relatively enhanced formation of the α,β-unsaturated nitrile (14% compared to 4% using **1b**). However, by reducing the reaction temperature to −5°C, a similar conversion is obtained, but with only 3% formation of the α,β-unsaturated nitrile (as observed by ^1H NMR spectroscopic integration) with a corresponding 91% isolated yield of the β-hydroxy nitrile. Similarly, the β-hydroxy nitrile obtained from the reaction of *p*-chlorobenzaldehyde and acetonitrile proceeded in superior yield with **1d** as did the preparation of β-hydroxy nitriles from 2-methylcyclohexanone and 2-butanone. The reaction of mesityl oxide and 4-hexen-3-one with allyl alcohol provided two additional examples in which **1d** is superior to **1b**. We previously reported[11] a relatively low yield of nitroaldol product in the reaction of 3-pentanone with nitromethane (see also Table 1). We find here that **1d** affords a much better yield (Table 1). Table 1 also shows that **1c** is not a useful catalyst for the synthesis of β-hydroxy nitriles or for the synthesis of α,β-unsaturated esters. The poor reactivity of **1c** in MeCN is probably associated with the lower basicity of this catalyst and its lower solubility in this solvent. However, **1c** is highly effective for the addition of allyl alcohol to enones[13] and for the promotion of the

Henry (nitroaldol) reaction in the presence of magnesium sulfate.[11]

3. Conclusion

Despite their sterically hindered nature, **1c** and **1d** are strong nonionic bases (pK_a in MeCN: 32.84 and 33.53 respectively[25]) with normal $P–N_{ax}$ bond distances (2.047 and 1.958 Å) for their protonated forms **1c**H^+ and **1d**H^+, respectively. The somewhat larger pK_a of base **1g** in this solvent (34.49) suggests that if this measurement can be trusted for this unstable material, the possibility of equilibrium (1) arises in which the anionic amide site of the zwitterion contributes to the basicity. Here it may be mentioned that the ^{31}P NMR evidence for such an equilibrium was put forth for **1f**.[3a] The more sterically hindered base **1d** is at least as efficient and sometimes more efficient than **1b** in the syntheses shown in Table 1.



(1)

4. Experimental

All ring closure and deprotonation reactions were carried out under nitrogen. *Tris*(2-aminoethyl)amine (**2**) was distilled before use. The aldehydes (Aldrich) were used as received. The solvents THF, pentane, benzene, methylene chloride and acetonitrile were dried according to standard procedures.[29] ^1H and ^{13}C NMR spectra were recorded on a Bruker VXR300 or Bruker DRX400 instrument and calibrated using TMS as an internal standard. ^{31}P NMR spectra were recorded on a Bruker DRX 400 instrument. The bases **1a**,[1] **1b**,[2] and **1f**[3] were prepared according to previously reported methods, although **1a** is commercially available (Strem).

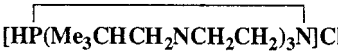
4.1. Preparation of $N(CH_2CH_2NHCH_2CMe_3)_3$, 4a

To 14.6 g (0.100 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask placed in an ice bath was added over 20 min 49 mL of a commercially available solution of 89% pivalaldehyde in *tert*-butyl alcohol. The mixture was allowed to stir at room temperature for 1 h after which 100 mL of methanol was added. The resulting solution was allowed to cool to 5°C, and then 11.1 g of powdered sodium borohydride was added portion-wise over 1 h, at the end of which time unreacted sodium borohydride could be seen as a white solid. The reaction mixture was quenched by the addition of 60 mL of a 50% aqueous sodium hydroxide solution. At this point, a solid precipitated which was dissolved by the addition of 100 mL of water. The reaction mixture was extracted with hexane (4×100 mL) and the hexane extracts were combined and treated with 50 mL of 1.0 M aqueous sodium iodide. The hexane layer was separated and the aqueous layer was extracted with 3×50 mL of hexane. The hexane extracts were combined and then dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure, followed by distillation under vacuum, afforded 34.9 g (99.7%) of the pale product **4a** (bp 160°C/2 Torr) that was ^1H NMR pure. ^1H NMR ($CDCl_3$): δ 2.64 (t, J=5.6 Hz 6H), 2.48 (t, J=6 Hz, 6H), 2.34 (s, 6H), 0.99 (s, 27H). ^{13}C NMR ($CDCl_3$): δ 63.2, 55.7, 49.9, 32.3, 28.5. HRMS Calcd for $C_{21}H_{49}N_4$ 357.3957. Found m/e ($M+H^+$) 357.3956.

4.2. Preparation of $N(CH_2CH_2NHCH_2CMe_3)_3$, 4a and $(H_2NCH_2CH_2)_2NCH_2CH_2NHCH_2CMe_3$, 4c

To 14.6 g (0.100 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask placed in an ice bath, was added over 20 min 36.0 mL of a commercially available solution of 80% pivalaldehyde in *tert*-butyl alcohol. The mixture was allowed to stir for 1 h after which 100 mL of methanol was added. The resulting solution was allowed to cool to 5°C and then 9.50 g of powdered sodium borohydride was added portion-wise over 1 h, at the end of which time unreacted sodium borohydride was present as a white solid. The reaction mixture was quenched by the addition of 60 mL of 50% aqueous sodium hydroxide. At this point, a solid precipitated, which was dissolved by the addition of 100 mL of water, and then the reaction mixture was extracted with ether (4×100 mL). The ether extracts were combined and dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure afforded a mixture of the title products. The separation of these products was accomplished as follows. The product mixture was dissolved in 50 mL of hexane in a 500 mL round-bottomed flask followed by the addition of 50 mL of a 1.00 M aqueous solution of NaI. The mixture was stirred for 0.5 h, the organic layer was separated and the aqueous layer was extracted with 4×100 mL of hexane to afford a solution of $N(CH_2CH_2NHCH_2CMe_3)_3$ (**4a**) that was purified as detailed in the previous paragraph to afford a 51% yield (14.6 g) of the tetramine **4a**. The aqueous layer was placed in a water bath and 50 mL of 50% aqueous sodium hydroxide was added slowly (to avoid a strong exotherm) and then the mixture was extracted with 4×60 mL of ether. The ether extracts were combined and dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure followed by distillation at 140°C/500 milliTorr afforded 9.31 g (43%) of **4c**. ^1H NMR (C_6D_6): δ 2.52–2.61 (overlapping region, 6H), 2.40 (t, J=5.5 Hz, 2H), 2.30 (s, 2H), 2.25 (t, J=6 Hz, 4H), 0.96 (s, 9H). ^{13}C NMR (C_6D_6): δ 63.3, 58.5, 55.3, 49.7, 41.0, 32.2, 28.4.

4.3. Preparation of



[HP(Me$_3$CHCH$_2$NCH$_2$CH$_2$)$_3$N]Cl, [1cH]Cl

To 50 mmol of $ClP(NMe_2)_2$, prepared in situ in 125 mL of methylene chloride by the slow addition of 1.5 mL (17 mmol) of PCl_3 to 6.1 mL (33 mmol) of $P(NMe_2)_3$ at 0°C in an ice bath, was added under nitrogen 17.8 g (50.0 mmol) of $N(CH_2CH_2NHCH_2CMe_3)_3$ (**4a**) dissolved in 50 mL of methylene chloride. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. After the addition of **4a**, 100 mL of dry ether was added, and the reaction mixture was stirred for 48 h at room temperature after which the volatiles were removed under

reduced pressure. The residue was partitioned between 10 mL of water and 50 mL portions of methylene chloride until the methylene chloride extracts afforded no residue. The organic extracts were combined and dried over anhydrous magnesium sulfate, and then the volatiles were removed under reduced pressure to afford an oily material that was dissolved in 30 mL of methylene chloride. Ether was added until a slight turbidity was seen. The flask was then placed in the freezer for at least 2 h. After decantation of the supernatant, the white material that precipitated was washed with 2×15 mL of ice-cold ether to afford 18.3 g (89%) of [**1c**H]Cl. ^{1}H NMR ($CDCl_3$): δ 5.43 (d, J= 4.98 Hz, 1 Hz) 3.63 (s, 6H), 3.26 (t, J=5 Hz, 6H), 2.68 (td, J=1.2 Hz, 20 Hz, 6H), 0.89 (s, 27H). ^{13}C NMR ($CDCl_3$): δ 61.1 (d, J=11 Hz), 48.0 (d, J=7.4 Hz), 42.2 (d, J=6.0 Hz), 33.5 (d, J=3.8 Hz). ^{31}P NMR ($CDCl_3$): δ 2.29.

4.4. Preparation of $P(Me_3CCH_2NCH_2CH_2)_3N$, 1c

To a mixture of 6.77 g (16.1 mmol) of ([**1c**H]Cl) and 3.60 g (32.2 mmol) of *t*-BuOK in a Schlenk flask was added 100 mL of dry THF under nitrogen. The reaction mixture was stirred for 2 h at room temperature after which THF was distilled off under vacuum. Then 150 mL of pentane was added to the reaction mixture under nitrogen and stirring was continued for one more hour. The reaction mixture was allowed to settle and the clear upper layer was vacuum transferred by means of a canula into a 500 mL Schlenk flask through a fritted glass. Another portion of pentane (100 mL) was added under nitrogen and the mixture was stirred for 0.5 h after which the entire mixture was transferred by canula onto the fritted glass under nitrogen. The mixture was allowed to filter slowly under vacuum. After filtration was complete, the solvent was removed under vacuum to afford 4.71 g (76% yield) of the base **1c** as a white solid that was found to be 98% pure by ^{1}H NMR spectroscopy and essentially pure by ^{31}P NMR spectroscopic analysis. ^{1}H NMR (C_6D_6): δ 2.86–2.95 (overlapping region, 18H), 1.01 (d, J=10 Hz, 27H). ^{13}C NMR (C_6D_6): δ 66.6 (d, J=43.8 Hz), 51.8 (d, J=1 Hz), 51.2 (d, J=6.8 Hz), 34.4 (d, J=2.8 Hz), 28.3 (d, J=2.5 Hz). ^{31}P NMR (C_6D_6): δ 144.3. HRMS (EI) Calcd for $C_{21}H_{45}N_4P$: 384.3332. Found m/e $(M)^+$: 384.3394.

4.5. Preparation of $N(CH_2CH_2NHCH_2CHMe_2)_3$, 4b

To 14.6 g (0.100 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask was added dropwise over 20 min, 36 mL (28.8 g, 0.400 mol) of isobutyraldehyde dissolved in 10 mL of *tert*-butyl alcohol. The mixture was allowed to stir at room temperature for 1 h after which 100 mL of methanol was added. The resulting colorless solution was allowed to cool to 5°C in an ice bath and then 11.1 g of powdered sodium borohydride was added portion-wise over 1 h, at the end of which time unreacted sodium borohydride was present as a white solid. The reaction mixture was quenched by the addition of 60 mL of aqueous 50% sodium hydroxide followed by the addition of 100 mL of water to dissolve the precipitated inorganic material. The reaction mixture was extracted with 4×100 mL of hexane. The hexane extracts were combined and then treated with 50 mL of 1.0 M sodium iodide. The hexane layer was separated and then the aqueous layer was washed with 3×50 mL of hexane. The hexane extracts were combined and dried over anhydrous potassium carbonate followed by removal of the volatiles under reduced pressure. The crude product was distilled under vacuum to afford 30.5 g (97%) of **4b** as a pale liquid (bp 160°C/2 Torr). ^{1}H NMR ($CDCl_3$): δ 2.60 (t, J=5.8 Hz, 6H), 2.46 (t, 5.6 Hz, 6H), 2.40 (d, J=6.4 Hz, 6H), 1.72 (m, 3H), 1.25 (s, 3H), 0.95 (d, J=6.4 Hz, 18H). ^{13}C NMR ($CDCl_3$): δ 59.1, 55.2, 48.9, 29.5, 21.4. HRMS Calcd for $C_{18}H_{45}N_4$: 315.3479. Found m/e $(M+H^+)$: 315.3486.

4.6. Preparation of [HP(Me2CHCH2NCH2CH2)3N]Cl, [1dH]Cl

To 50.0 mmol of $ClP(NMe_2)_2$, prepared in situ in 125 mL of acetonitrile by the slow addition of 1.5 mL (16.7 mmol) of PCl_3 to 6.1 mL (33.3 mmol) of $P(NMe_2)_3$ at 0°C in an ice bath, was slowly added under nitrogen 15.7 g (50 mmol) of tetramine **4b** dissolved in 50.0 mL of acetonitrile. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. A white precipitate was observed to form gradually. After completion of the addition, the reaction mixture was stirred for 2 h at room temperature after which 100 mL of ether was added. Stirring was continued for two additional hours after which the volatiles were removed under reduced pressure. The residue was then partitioned between 100 mL of acetonitrile and 100 mL of hexane. The hexane fraction, upon removal of the volatiles under vacuum afforded 0.3 g of unreacted $N(CH_2CH_2NHCH_2CHMe_2)_3$ (**4b**). The acetonitrile fraction afforded a residue, which was dissolved in a minimum amount of THF and then ether was added until no more precipitation was observed with further addition of ether (total ~150 mL). The flask was then placed in the freezer for at least 2 h after which the clear layer was decanted from the residue. The residue was washed with 20 mL of cold THF and then dried under vacuum to afford 18.1 g (96% yield) of white solid [**1d**H]Cl. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J=6.4 Hz, 18H), 1.83 (septet, J=6.8 Hz,, 3H), 2.61 (m, 6H), 3.10 (m, 6H), 3.56 (d, J=6.8 Hz, 6H), 5.14 (d, J=4.99 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 55.7 (d, J=12.7 Hz), 47.0 (d, J=7.8 Hz), 39.6 (d, J=5.9 Hz), 26.8 (d, J=4.7 Hz), 20.0 (s). ^{31}P NMR ($CDCl_3$): δ −7.1 (s).

4.7. Preparation of $P(Me_2CHCH_2NCH_2CH_2)_3N$, 1d

To a mixture of 13.7 g (36.0 mmol) of [**1d**H]Cl and 8.09 g (72.2 mmol) of *t*-BuOK in a 500 mL Schlenk flask was added under nitrogen 100 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature after which THF was distilled off under vacuum. Pentane (150 mL) was then added to the reaction mixture under nitrogen and stirring was continued for an additional hour. The reaction mixture was then allowed to settle and the clear upper layer was vacuum transferred by means of a canula into a 500 mL Schlenk flask through a glass frit. Another portion of pentane (100 mL) was added under nitrogen to the residue in the reaction flask and then the mixture was stirred for 0.5 h after which it was transferred by canula into a fritted glass tube under nitrogen. After the mixture was allowed to filter slowly under vacuum, the solvent was

removed from the filtrate under vacuum and the crude base was then transferred under nitrogen by means of a syringe into a 50 mL round-bottomed flask. Distillation at 132°C/210 milliTorr afforded 12.0 g (97% yield) of the product **1d**. ^{1}H NMR (C_6D_6): δ 0.93 (d, J=6.8 Hz, 18H), 1.82 (septet, J=6.4 Hz, 3H), 2.75 (overlapping region, 12H). ^{13}C NMR (C_6D_6): δ 59.1 (d, J=37 Hz), 55.3 (s), 52.1 (d, J=2.85 Hz), 47.2 (d, J=7.1 Hz), 29.2 (d, J= 27.3 Hz), 21.2 (d, J=14.4 Hz). ^{31}P NMR (C_6D_6): δ 130.9. HR MS (EI) Calcd for $C_{18}H_{39}N_4P$: 342.2912. Found *m/e* $(M)^+$ 342.2913. Anal. Calcd for $C_{18}H_{39}N_4P$: C, 63.12; H, 11.48, N, 16.36; P, 9.04. Found: C, 62.95; H, 11.41; N, 16.31, P, 9.02.

4.8. Preparation of 5, 6, and 7

To a solution of 76 g (0.52 mol) of *tris*(2-aminoethyl)amine (**2**) and 81.0 g of anhydrous sodium acetate in 500 mL of water was added 225 mL of glacial acetic acid in a 3.0 L three-necked flask. The mixture was stirred by means of a mechanical stirrer at 500 rpm while it cooled to room temperature. The mixture was then placed in an ice/salt bath and cooled to 5°C after which 110 mL (1.67 mol) of acetone was added over 15 min. The solution was allowed to stir for 5 min and then 55 g (1.50 mol) of powdered sodium borohydride was added portion-wise over 3 h while the temperature was kept to 5–10°C. After completion of the addition, the reaction mixture was allowed to stir in the ice bath for 30 additional minutes after which it was quenched with 200 g of sodium hydroxide dissolved in 300 mL of water. Extraction of the mixture with 4×100 mL of methylene chloride, followed by drying of the combined extracts over anhydrous potassium carbonate and removal of the extract solvent under reduced pressure afforded 73.1 g of the product mixture. The separation of this mixture was effected as follows. To the above 73.1 g of mixture dissolved in 200 mL of hexane was added 142 g of sodium iodide followed by 200 mL of water. The mixture was stirred vigorously for 1 h and then it was extracted with 6×100 mL of ether. After the addition of 10 mL of 50% aqueous sodium hydroxide, two more extracts obtained with 2×50 mL of ether were collected and dried over anhydrous potassium carbonate. The volatiles from these two last extracts were then removed under reduced pressure to afford 329 mg of a material that was discarded. When these last extracts contained substantial amounts of **6**, as determined by ^{1}H NMR spectroscopy of the residue, extraction was continued until the extracts produced no more residue upon removal of the volatile components. All the organic layers were then combined, dried over anhydrous potassium carbonate, and the volatiles subsequently removed under reduced pressure to afford crude **6** that was distilled at 85–90°C/200 milliTorr to afford 9.91 g (7% yield) of **6**.[2] To the aqueous layer was then carefully added by slow addition to avoid an exothermic reaction, 210 g of sodium hydroxide dissolved in 220 mL of water. The reaction mixture was allowed to cool to room temperature, and then it was extracted with 6×100 mL of ether while ensuring that no oily droplets were collected with the organic fraction. The ether extracts were combined and dried over anhydrous potassium carbonate. The volatiles were removed under reduced pressure and the crude product was distilled at 110–120°C/250 milliTorr affording 22.7 g (19% yield) of **7**.[3] The aqueous layer remaining at this point displayed the presence of a viscous oily layer that was extracted with 3×100 mL of methylene chloride. The extracts were dried over anhydrous potassium carbonate followed by removal of the solvent under reduced pressure to afford crude **5** that was distilled to afford 40.1 g (41% yield) of **5** as a yellowish liquid (bp 137°C/200 milliTorr) that was 98% pure by ^{1}H NMR spectroscopy. ^{1}H NMR (C_6D_6): δ 2.89 (septet, J=6.4 Hz, 1H), 2.54 (t, J=6 Hz, 6H), 2.39 (s, 2H), 2.24 (t, J=6 Hz, 4H), 0.98–1.05 (overlapping region, 11H). ^{13}C NMR (C_6D_6): δ 58.4, 55.4, 49.5, 46.2, 40.9, 23.8.

4.9. Preparation of [HP(NHCH$_2$CH$_2$)$_2$NCH$_2$CH$_2$NCHMe$_2$]Cl, [1gH]Cl

To 50.0 mmol of $ClP(NMe_2)_2$, prepared in situ in 100 mL of dry acetonitrile by the slow addition of 1.5 mL (16.7 mmol) of PCl_3 to 6.1 mL (33.3 mmol) of $P(NMe_2)_3$ at 0°C in an ice bath, was added under nitrogen 9.40 g (50.0 mmol) of **5** dissolved in 50 mL of acetonitrile. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. The reaction mixture was stirred for 0.5 h at 0°C and then for 0.5 h at room temperature. The reaction flask was then placed in a water bath warmed to 35°C, and stirring was continued for two additional hours during which time a white precipitate formed. The precipitate was filtered by means of a medium glass frit, washed with 2×20 mL portions of ice-cold dry acetonitrile and then dried under vacuum to afford 9.96 g (78%) of [**1g**H]Cl. ^{1}H NMR (D_2O): δ 5.61 (d, 1H J=320 Hz), 3.46 (septet, J=4.8 Hz, 1H), 2.96 (overlapping region, 12H), 1.00 (d, 6H). ^{13}C NMR (D_2O): δ 49.0 (d, J=11.3 Hz), 47.7 (d, J=8.3 Hz), 47.4 (d, J=15.1 Hz), 32.9 (d, J=5.3 Hz), 32.5 (d, J=2.3 Hz), 20.3 (d, J=5.3 Hz). ^{31}P NMR (D_2O): δ 32.7. MS (ESI) Calcd for $C_9H_{22}N_4P$: 217.2, Found *m/e* $(M-HCl)^+$: 217.3.

4.10. Preparation of P(HNCH$_2$CH$_2$)$_2$NCH$_2$CH$_2$NCHMe$_2$, 1g

To a mixture of 6.31 g (25.0 mmol) of [**1g**H]Cl and 2.80 g (25.0 mmol) of *t*-BuOK in a 500 mL Schlenk flask, was added under nitrogen 100 mL of dry benzene. The reaction mixture was stirred for 2 h at room temperature and then it was allowed to stand until it separated into two layers. The clear upper layer was transferred under vacuum by means of a canula into a 500 mL Schlenk flask through a glass frit. Another portion of benzene (100 mL) was added to the residue of the reaction mixture and then the mixture was stirred for 0.5 h after which the mixture was transferred under nitrogen by canula into the glass frit and filtered slowly under vacuum. After filtration was complete, the solvent was distilled under vacuum and the crude base was transferred under nitrogen by means of a syringe into a 50 mL round-bottomed flask. Distillation at 143°C/200 milliTorr afforded 378 mg (7% yield) of **1g**. ^{1}H NMR (C_6D_6): δ 2.67 (septet, J=4 Hz, 1H), 2.55 (t, J=8 Hz, 6H), 2.39 (t, J=8 Hz, 2H), 2.24 (t, J=6 Hz, 4H), 1.23 (d, J=16 Hz, 6H), 0.92 (bs, 2H). ^{13}C NMR (C_6D_6): δ 58.4 (d, J=11.3 Hz), 55.3 (d, J=12.1 Hz), 49.5 (d, J=2.3 Hz), 46.2 (s), 40.9 (s), 23.9 (d, J=0.8 Hz). ^{31}P NMR (C_6D_6): δ 101.4.

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