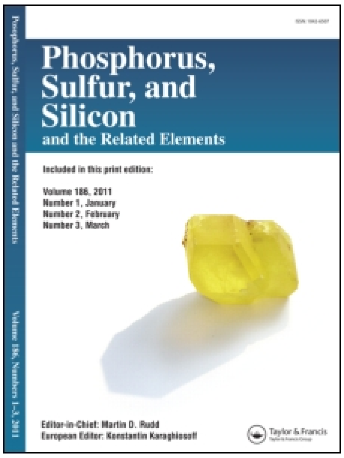

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$P(RNCH_2CH_2)_3N$: Superbasic and Catalytic Cages

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$P(RNCH_2CH_2)_3N$: SUPERBASIC AND CATALYTIC CAGES

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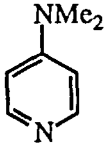
In contrast to acyclic $P(NR_2)_3$, the title pro-azaphosphatrane cages (first reported from our laboratories) are exceedingly strong nonionic bases that protonate to give the extraordinarily weak acids $HP(RNCH_2CH_2)_3N^+$ (pK_a in MeCN, ~41). Thus we have found that commercially available $P(MeNCH_2CH_2)_3N$ is a superior nonionic base for the synthesis of porphyrins, alkenes, C-monoalkylation of esters and β-hydroxy nitriles. We have also discovered that $P(RNCH_2CH_2)_3N$ cages function as superior catalysts for the synthesis of β-hydroxy nitriles, α,β-unsaturated nitriles and silyl-protected alcohols. Protective acylations of alcohols are very efficiently promoted by $P(MeNCH_2CH_2)_3N$.

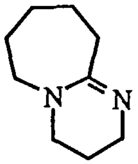
Keywords: pro-azaphosphatranes; nonionic base; catalysis; silylation; acylation

INTRODUCTION

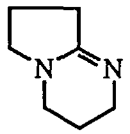
Strong nonionic non-nucleophile bases such as DMAP, DBU, DBN, Proton Sponge® and TMG have long been utilized in organic synthesis. During the last few years we have synthesized a series of new bases of the nonionic type such as **1a**-**7a** which are proving to be superior bases and catalysts in a variety of useful synthetic applications.[1-17]



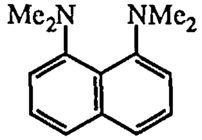
DMAP



DBU



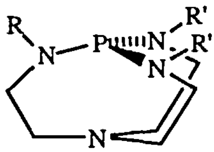
DBN



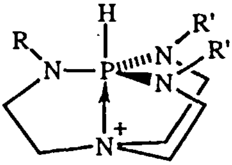
Proton Sponge®

HN=C$(NMe_2)_2$

TMG

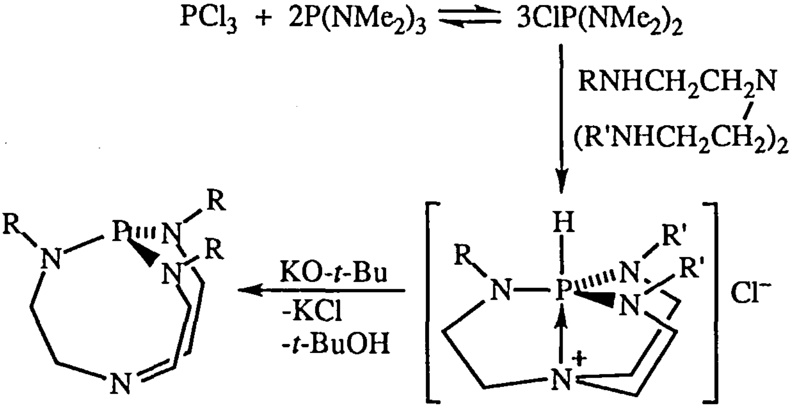


	R	R'	
1a	H	H	**1b**
2a	Me	Me	**2b**
3a	Et	Et	**3b**
4a	*i*-Pr	*i*-Pr	**4b**
5a	$PhCH_2$	$PhCH_2$	**5b**
6a	H	*i*-Pr	**6b**
7a	Me_3Si	Me_3Si	**7b**



These bases are synthesized in 70-80% yields via Scheme I wherein intermediates **1b**-**7b** (which are rather unexpectedly protonated on the phosphorus rather than on a nitrogen) are subsequently deprotonated with the strong ionic base KO-*t*-Bu. The X-ray structures of several of the intermediates (**1b**, **2b** and **4b**) confirm the five-coordinate tbp phosphorus coordination geometry shown, and the $P-N_{ax}$ distance is close to 2.0 Å. By contrast, this distance in **4a** and **7a** (*ca.*

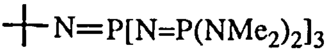
SCHEME I



1a-7a **1b-7b**

3.3 Å) is close to the van der Waals sum and N_{ax} has a nearly trigonal planar coordination geometry.

The superior basicity of a cage such as **1a** stems from the stability of the three five-membered ring systems present in its conjugate acid **1b** in which the transannular $N_{ax} \rightarrow P$ bond enriches the electron density of phosphorus, thereby favoring a strong P-H bond. Thus the pK_a of **2b**, for example, is 41 in MeCN which contrasts that of H^+DBU (24) in the same solvent. Although the pK_a of the conjugate acid of **8** (42 in



$t\text{-}Bu\text{-}N{=}P[N{=}P(NMe_2)_2]_3$

8

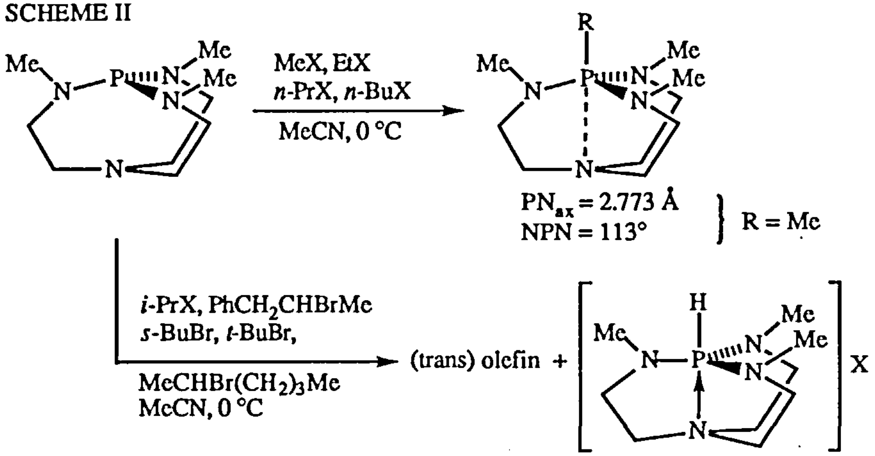
MeCN) is close to that of **2b**, it should be noted that base **8** becomes protonated on the P=N-*t*-Bu nitrogen rather than on phosphorus.[18] Within our series of bases the basicity order is **3a** > **4a** > **2a** for reasons that are not clear.

The reactions discussed below for some of our bases fall into two categories: stoichiometric consumption of base and catalysis by the base.

STOICHIOMETRIC DEHYDROHALOGENATION

Summarized in Scheme II are reactions observed with alkyl halides and **2a**. Unless a conjugated product can be obtained, primary RX give rise to phosphonium salts which are apparently only partially transannulated. Secondary and tertiary RX readily provide *trans* olefin in 85-98% yield by a pathway that involves prior deprotonation of the solvent MeCN for less reactive substrates RX and direct deprotonation of reactive substrates.

SCHEME II



STOICHIOMETRIC PORPHYRIN SYNTHESIS

A convenient "one-pot" synthesis we developed for octaethyl porphyrin using **2a** is depicted in Scheme III. The major improvement in overall yield of product (62%) by our approach over that reported in the literature using other bases (22-45%) is due mainly to the formation in step 3 of pyrrole carboxylates in quantitative yield. Furthermore the precipitated salts containing **2b** can easily be isolated and the base **2a** recovered for recycling.

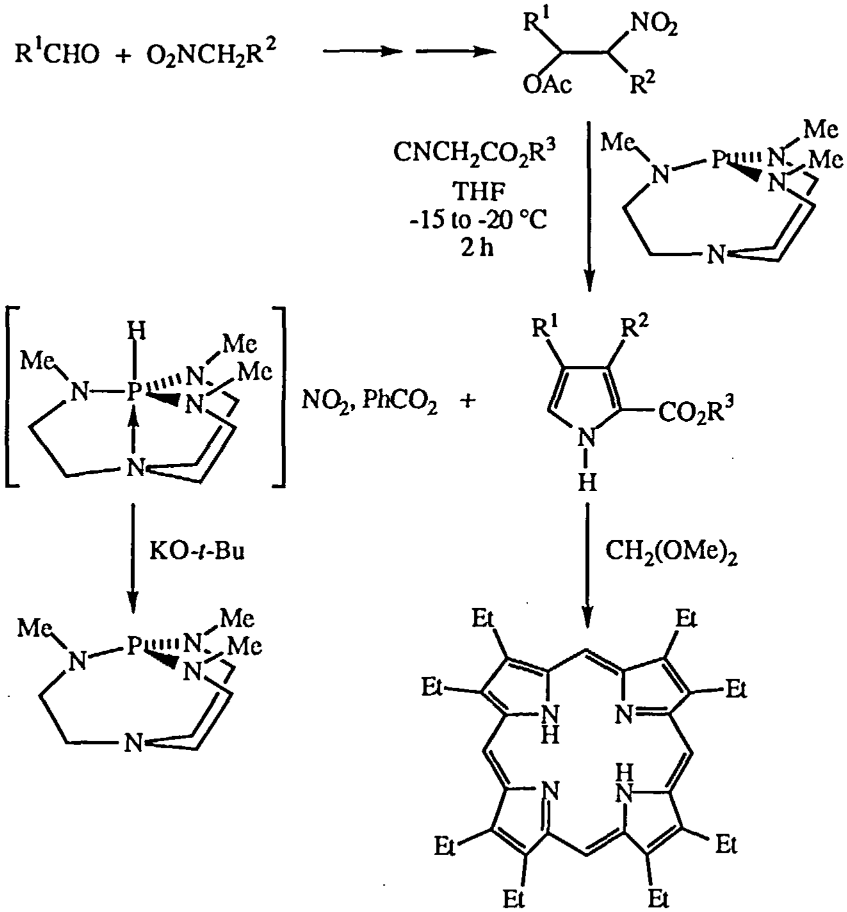
STOICHIOMETRIC C-MONOALKYLATION OF ESTERS

Selective C-monoalkylation of esters such as those shown in Scheme IV is generally difficult owing to side reactions including C-dialkylation and also O-alkylation. We have shown that selective C-monoalkylation can be achieved in generally excellent yield using **2a**.

STOICHIOMETRIC β-HYDROXYNITRILE SYNTHESIS

As shown in Scheme V for one of the systems we have investigated, the yield is very high. Here the alkoxy intermediate is trapped as a silyl

SCHEME III

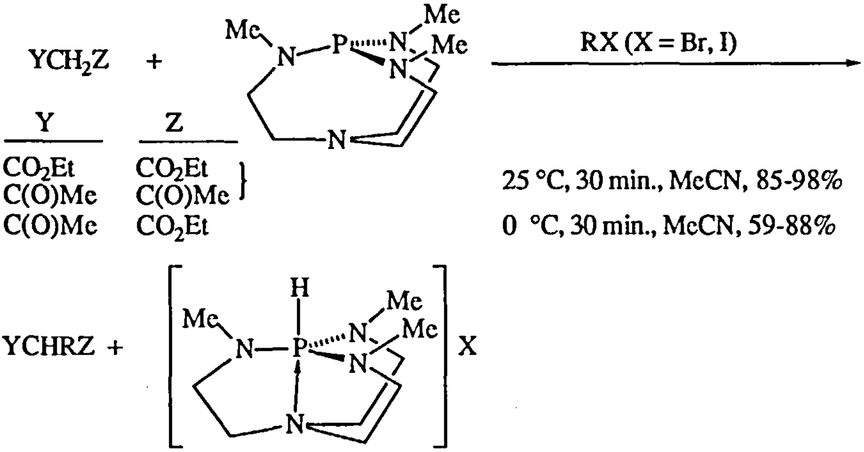


ether by Me_3SiCl which is subsequently converted to the β-hydroxy nitrile by cleavage with MeOH.

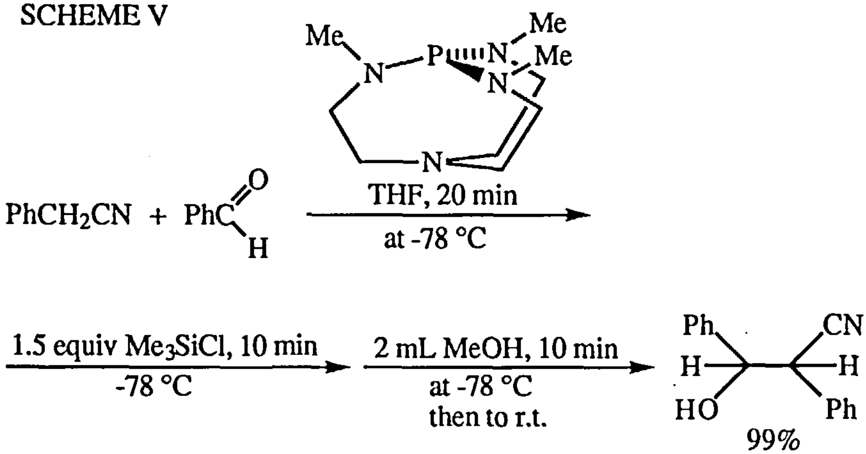
CATALYTIC SYNTHESIS OF β-HYDROXY NITRILES

By employing **4a**, or the latest novel member of this family of bases **6a**, in place of **2a**, the reaction of ketones with MeCN can be made catalytic (Scheme VI). Here it is believed that the alkoxy intermediate deprotonates intermediate **4b** or **6a**, respectively, thus regenerating the

SCHEME IV



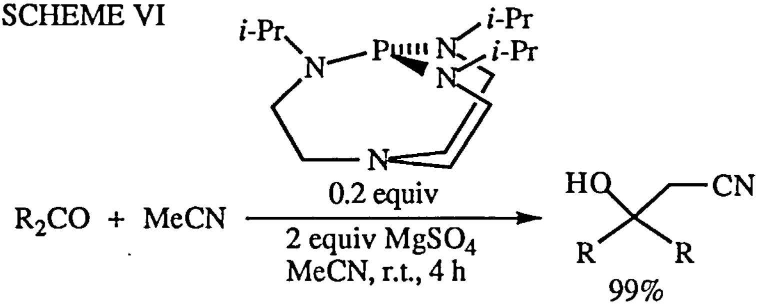
SCHEME V



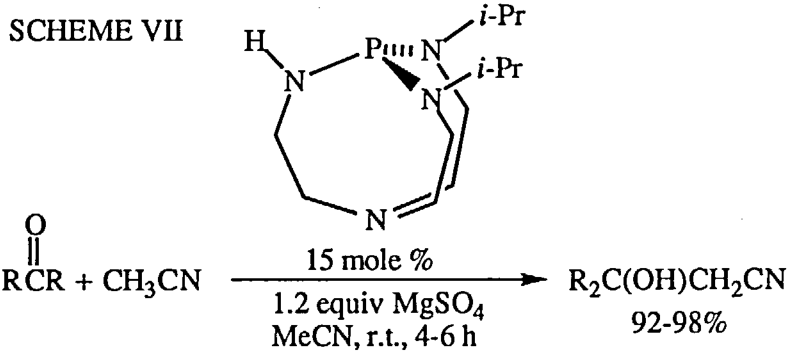
base in the catalytic cycle. The probable role of Mg^{2+} in this scheme is to activate the carbonyl carbon of the ketone by complexing its oxygen.

Even with 6a as a catalyst, however, ketones do not react with acetonitrile unless magnesium ion is present to activate the carbonyl carbon (Scheme VII).

SCHEME VI



SCHEME VII

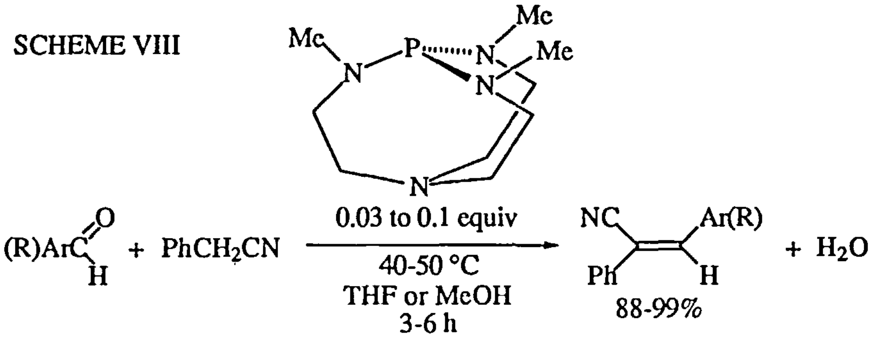


CATALYTIC SYNTHESIS OF α,β-UNSATURATED NITRILES

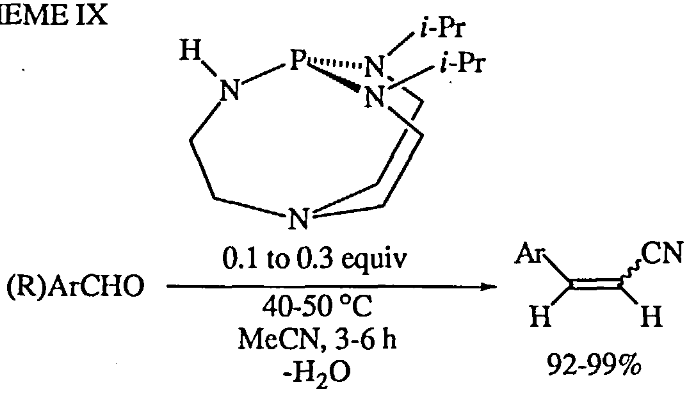
Benzyl cyanide reacts readily with most aryl and alkyl aldehydes in the presence of **4a** to give excellent yields of the *E* isomeric product as shown in Scheme VIII. Primary aldehydes are to be avoided, however, owing to aldol condensation. With the more powerful base **6a**, acetonitrile is caused to react with aryl aldehydes and tertiary alkyl aldehydes to give excellent yields of products as shown in Scheme IX. Because **6a** is very probably in tautomeric equilibrium with zwitterionic **6c**, which features an anionic amide site, alkyl aldehydes possessing a hydrogen on the alpha carbon undergo side reactions of the aldol or Michael addition types. By increasing the acidity of the cyano reagent to

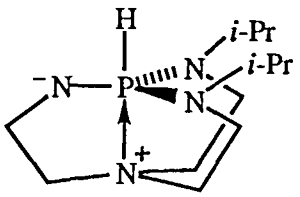
$CH_2(CN)_2$, **2a** readily functions as a catalyst for its condensation to a variety of aryl ketones (Scheme X).

SCHEME VIII

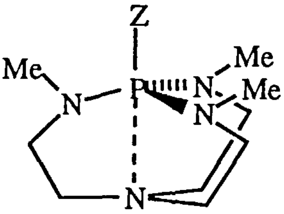


SCHEME IX





6c

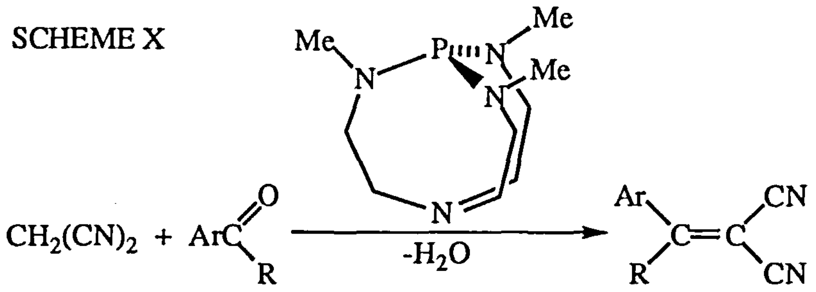


	Z
9	$SiR_2(t\text{-}Bu)$
10	C(O)R

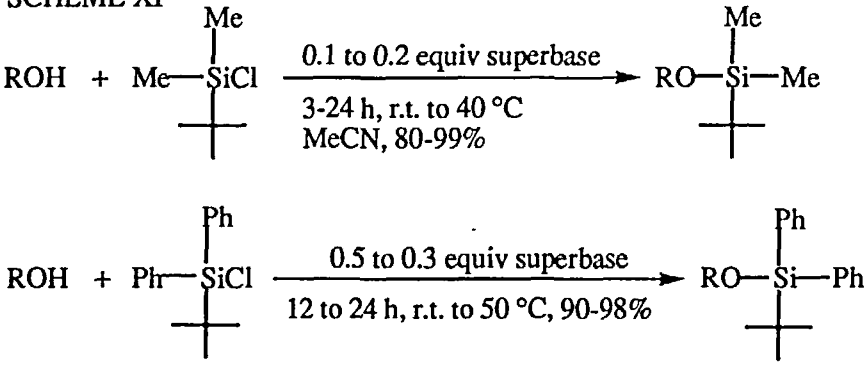
CATALYZED SILYLATION OF ALCOHOLS

The protection of alcohols by silyl ether formation is an important transformation in organic chemistry for which catalyst **2a** is superior to DMAP, DBU or TMG (Scheme XI). In this reaction, evidence has

SCHEME X



SCHEME XI



been adduced for **9** as the silylation intermediate.

PROTECTIVE ACYLATION OF ALCOHOLS

These reactions (Scheme XII) are promoted rather than catalyzed by **2a**. Product yields are superior to those achieved with promoters **8**, DBU, PBu$_3$ or DMAP and acid-sensitive alcohols are also easily acylated. The acylation intermediate in our reactions was shown to be **10**.

SCHEME XII

$$ROH + Ac_2O \xrightarrow[\text{MeCN, 68-96\%}]{\text{0.16-1.0 h, r.t.}} ROAc + HOAc$$

$$ROH + (PhCO)_2O \xrightarrow[C_6H_6\text{, 90-99\%}]{\text{0.16-1.5 h, r.t.}} RO_2CPh + HO_2CPh$$

Acknowledgments

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