New developments in azaphosphatrane systems ZP(RNCH2CH2)3N

Xiaodong Liu
Iowa State University

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New developments in azaphosphatrane systems ZP(RNCH₂CH₂)₃N

by

Xiaodong Liu

A dissertation submitted to the graduate faculty in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Inorganic Chemistry

Major Professor: John G. Verkade

Iowa State University

Ames, Iowa

2000

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Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

Xiaodong Liu

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

Signature was redacted for privacy.

For the Graduate College
DEDICATION

To my wife, parents and sister for their love and encouragement
and

my dream to be a chemist
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ABSTRACT

Compounds of the type ZP(RNCH₂CH₂)₂N where Z = a lone pair are proving to be versatile reagents and catalysts for an ever increasing number of organic transformations. These properties stem from the extraordinary basicity and low nucleophilicity of the phosphorus atom when certain Z substituents induce the bridgehead nitrogen to transannulate (even partially) to the phosphorus.

In this work, several novel azaphosphatranes have been successfully synthesized and characterized, where R = a bulky group (R₃Si) (1f-i, 1f and 2g in chapter 3), or a chiral group (5-7 in chapter 5). A stable polymer-based azaphosphatrane (4 in chapter 4) was also synthesized from a commercially available Merrifield resin. In addition, the synthesis of commercially available P(MeNCH₂CH₂)₂N (1 in chapter 1) was remarkably improved in terms of chemical cost, labor cost, yield, safety and preparation time.

It has been found that the cations HP(CH₃NCH₂CH₂)₂N⁺, HP(HNCH₂CH₂)₂N⁺ and HP[N(polymer)CH₂CH₂]N(CH₂CH₂NH)₂⁺ (2, 3 and 4 in chapter 4) serve as efficient procatalysts for dehydrohalogenation of organic bromides using NaH as an inexpensive stoichiometric hydride source in CH₃CN at room temperature; that compound 6 in chapter 5 is an efficient derivatizing agent for the direct determination of enantiomeric ratios of chiral azides by means of ³¹P and ¹H NMR spectroscopy; that N(CH₂CH₂NMe)₂P=O (3 in chapter 7) is an efficient catalyst in a mild procedure for the silylation of primary alcohols, secondary alcohols, hindered secondary alcohols and of hindered phenols, in the presence of t-butyldimethyldisilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCI); and that P(MeNCH₂CH₂)₂N (2a in chapter 8) functions as a highly selective reagent for providing epoxides with trans/cis ratios as high as 99/1.

Cation [O=P(i-PrNCH₂CH₂)₂CH₃]⁺ (3 in chapter 6) features the longest distance between the bridgehead atoms (3.56 Å) so far recorded for phosphatranes despite a non-tetrahedral CN_bridgehead_C angle (~114°). The 70.8° N_bridgehead_CCN torsion angles in the bridging
moieties of 3 produce a substantial twist along the $C_3$ axis of the structure that does not easily allow racemization of the cage.

Benzene is formed at room temperature under acidic conditions from the novel trisubstituted cyclohexane derivative 1 (in chapter 9). The dominant reaction in the decomposition of the isolable thermally stable Staudinger intermediate in the presence of HA is the formation of benzene, nitrogen and $[H_2N=PR_3]A$. 
CHAPTER 1. GENERAL INTRODUCTION

Dissertation Organization

This dissertation consists of ten chapters. The first chapter is a general introduction containing a general review and a statement of the research project. The subsequent eight chapters represent research results that have been published or submitted for journal publication, except for Chapter 2 which discloses an invention submitted to Iowa State University Research Foundation (ISURF) as a Record of Invention. The numbering of compounds, figures, schemes, tables, and references are independent in each chapter. The last chapter is a summary of the results achieved and a prospective outlook for the proazaphosphatrane chemistry. All contributors to the work presented herein are acknowledged in each chapter and a general acknowledgment is given in the end of this dissertation.

General Review and the Project Statement

Phosphorus is very important to our world since it can be made into many useful products which are play critical role in our everyday life. For example, phosphorus is the key element in agriculture chemicals (such as insecticides and herbicides), medicinal compounds (such as anticancer, antiviral, and antibacterial agents), catalyst systems based on metal-coordinated tertiary phosphines (for Oxo hydroformylation, olefin hydrogenation, and Reppe olefin polymerization), flame retardants (for fabrics and plastics), additives in the petroleum products, and etc.¹

Phosphorus chemistry started from the nineteenth century and has drawn increasing attention over time, especially from the beginning of twentieth century, accelerated by the pioneering work in the laboratory of Karl Arnold August Michaelis and in the school of Aleksandr Erminingel’dovich Arbusov. In the last few decades, this field has become an
international arena. Since the late 1970s, the chemistry of atranes of groups 13 to 15 has been extensively studied by the Verkade group and others because of their intrinsic interest and the potential use as precursors for metal and nonmetal nitrides for a variety of electronic applications and as hard-surface coatings for protection against corrosion and wear. In 1989, the first proazaphosphatrane P(MeNCH$_2$CH$_2$)$_3$N (1a) was synthesized by the Verkade group. Following its synthesis, its analogues 1b–d have been synthesized and fully characterized by this group. The unusual phosphorus basicity of proazaphosphatranes is reflected in the protonation of proazaphosphatranes A to their conjugated acid form B. The driving force for this process is the formation of three stable five-member rings from two strained eight-member rings, which is accompanied by transannular interaction from the bridgehead N to the bridgehead P.

In recent years we have been exploring the chemistry of proazaphosphatranes such as 1a–f, some of which are proving to be exceedingly potent catalysts, promoters and strong nonionic bases that facilitate a variety of useful organic transformations. For example, 1a is an efficient catalyst for the trimerization of aryl and alkyl isocyanates that function as additives in the manufacture of nylon-6, for the protective silylation of a wide variety of sterically hindered and deactivated alcohols, and for the acylation of such substrates.
Proazaphosphatrane 1a is much stronger as a base than DBU,\(^\text{10}\) a commonly used nonionic base in organic synthesis. Thus it is a superior base for the synthesis of porphyrins,\(^\text{11}\) for the dehydrohalogenation of secondary and tertiary halides,\(^\text{12}\) and for the synthesis of a chiral fluorescence agent.\(^\text{13}\) As a result of such applications, 1a has become commercially available.\(^\text{14}\) Recently, we have discovered that 1a and 1b are also efficient nonionic base catalysts for transesterification,\(^\text{15}\) \(\beta\)-nitroalkanol synthesis,\(^\text{16}\) Michael additions,\(^\text{17}\) \(\beta\)-hydroxy nitrile synthesis,\(^\text{18}\) and \(\alpha,\beta\)-unsaturated nitrile synthesis.\(^\text{19}\)

Encouraged by the promising results of the proazaphosphatrane chemistry, the goal of the present research is to develop new proazaphosphatrane systems. Thus, we were interested in (1) developing a more economical method for the synthesis of commercially available base 1a (presently $238/g), (2) synthesizing new proazaphosphatranes bearing bulky substituents or chiral groups, and also polymer-supported systems, (3) studying the properties and structural features of new systems, and (4) extending the application of proazaphosphatranes in organic synthesis.

References


CHAPTER 2. AN IMPROVED SYNTHESIS OF OUR PATENTED AND
COMMERCIALY AVAILABLE SUPERBASE/CATALYST P(MeNCH₂CH₂)₃N

An invention disclosure submitted to ISURF for Patent Application
Xiaodong Liu and John G. Verkade

Abstract

A new, easier and more economical method has been developed for the synthesis
P(MeNCH₂CH₂)₃N in three steps and in 68% overall yield. This compound is proving to be a
versatile reagent and catalyst for an ever increasing number of organic transformations
requiring extraordinary basicity and low nucleophilicity.

Introduction

Compounds of the type P(RNCH₂CH₂)₃N where R = Me,¹ PhCH₂,² Et,³ i-Pr,³
CH₂CHMe₂,⁴ CH₂CMe₃,⁴ are proving to be versatile reagents and catalyst for a variety of
organic transformations. Compound 1 (Scheme 1) first synthesized in our laboratories.¹

Scheme 1

a. ClCO₂Et, C₆H₆/H₂O, 5°C/2 h, RT/8 h, 85%.  b. LiAlH₄, THF, reflux, 12 h, 88%.

c. P(NMe₂)₃, PCl₃, CH₃CN, RT, 6 h, 90%.  d. KO-t-Bu, CH₃CN, RT, 1 h, 82%.
possesses unusually high basicity and readily protonates to give cation 2 whose \( pK_a \) in CH\(_3\)CN is 32.9.\(^6\) Thus for example, 1 acts as a strong nonionic base in stoichiometric reactions, such as synthesis of a fluorescence agent,\(^7\) porphyrins,\(^8\) olefins\(^9\) and monoalkylated active methylene systems.\(^10\) Compound 1 is also an efficient catalyst in alcohol acylation with anhydrides,\(^11\) protective alcohol silylation,\(^12\) isocyanate trimerization\(^13\) and in \( \alpha,\beta \)-unsaturated nitrile synthesis.\(^14\) It is noteworthy that 1 has been patented by the DuPont Company\(^15\) and by the US Department of the Navy\(^16\) for the catalytic synthesis of Nylons and for propellant stabilization, respectively. Compound 1 is commercially available from Strem Chemical Co.\(^17\)

The present method for making 1 shown in Scheme 1 has disadvantages including long reaction time, labor intensiveness, and safety concerns resulting from the use of excess LiAlH\(_4\) in the reduction step. The overall yield in this four-step synthesis 55%. Thus, a more facile and economical method is desired. Here we report that 1 can be synthesized in 68% overall yield from (H\(_2\)NCH\(_2\)CH\(_2\)N in a newly developed three-step procedure.

**Results and Discussion**

The sequence of reactions starting with commercially available starting materials is shown in Scheme 2. The first step gives 3(CF\(_3\)CO\(_2\)) in quantitative yield using our earlier method.\(^2\) The second step is the reaction of 3(CF\(_3\)CO\(_2\)) with 3.1 equiv. of Me\(_2\)SO\(_4\) in the

### Scheme 2

\[
\text{N(CH}_2\text{CH}_2\text{NH}_2\text{)} \xrightarrow{a} \text{N}(\text{CH}_2\text{CH}_2\text{NH}_2\text{)}_\text{H} \xrightarrow{b} \text{Me}_\text{N}(\text{CF}_3\text{CO}_2\text{)} \xrightarrow{c} \text{Me}_\text{N}(\text{CF}_3\text{CO}_2\text{)} \]

a. CF\(_3\)CO\(_2\)H, P(NEt\(_2\))\(_3\), CH\(_3\)CN, RT, 10 h, 99%.

b. 4.0 equiv NaH, 3.1 equiv Me\(_2\)SO\(_4\), CH\(_3\)CN, 20°C, 10 h, 78%.

c. 1.5 KO-t-Bu, THF, RT, 2 h, 88%.
presence of 4.0 equiv. of NaH in CH$_3$CN at room temperature. After purification, the salt 2 with a mixture of counter ions CF$_3$CO$_2^-$ and MeSO$_4^-$ is obtained as a white crystalline solid in good yield (78%). Step 3 is carried out by our previous literature procedure.$^{18}$

The key step in Scheme 2 is the direct methylation of 3 to 2. In the present work, NaH deprotonates the N$_{Me}^+$H groups stepwise upon which S$_N^2$ attack of the anionic nitrogen on the methylation reagent gives the methylated cage compound 2, as shown in Scheme 3. This reaction pathway was confirmed by monitoring reactions with $^{31}$P NMR spectroscopy, in which the mono (2a) and di (2b) methylated intermediates were observed before 2 was formed as the final product.

Scheme 3

![Scheme 3 diagram](image)

When KO-t-Bu was used as the base in step 2, methylation was not clean. Thus 2, 2a, 2b and the phosphonium cation 4 formed as final products when 2 was reacted with 3.1 equiv. of Me$_2$SO$_4$ in the presence of 4.0 equiv. of KO-t-Bu in CH$_3$CN at room temperature.

Excess NaH was used in our experiments to insure complete alkylation. However, it was found that NaH also deprotonates 2 to give 1, although much more slowly than the reaction involving KO-t-Bu, in which further reaction of 1 with Me$_2$SO$_4$ to form 4 is observed. Thus, the amount of Me$_2$SO$_4$ must be carefully controlled: too much results in the
formation of undesired 4 and too little leads to incomplete methylation. Mel was initially used as the methylation agent but because of its low boiling point (42.5 °C), it was difficult to control the quantity of Mel added to the reaction mixture. The lower cost and higher boiling point (188 °C) of Me₂SO₄ led to its use in place of Mel.

To reduce the cost of the chemicals, several cheaper acids, such as CH₃CO₂H, HCl, CH₃SO₃H and CF₃CO₂H, were used in place of expensive CF₃SO₂H. It was found that CH₃CO₂H and CH₃SO₃H gave impure product in low yields and HCl gave 3 as an insoluble product in CH₃CN even though the yield was quantitative. With CF₃CO₂H, pure 3 was obtained as the CF₃CO₂⁻ salt in quantitative yield and this salt had better solubility in CH₃CN. With the use of this salt in step 2, the methylated product 2 was formed with a mixture of CF₃CO₂⁻ and MeSO₄⁻ anions in an approximately 1 : 2 ratio based on MS(ESI) and ¹H NMR results. It is noted that when 3(OTf) was used for the methylation step, only OTf⁻ was found in the methylated product. Concern that MeSO₄⁻ would methylate 1 to 4 subsequent to the deprotonation step proved to be unfounded since no formation of 4 and 100% conversion of 1 occurred.

Step 1 and Step 2 of our procedure were carried out in CH₃CN because of its excellent solvent properties for 2(CF₃CO₂⁻, MeSO₄⁻) and its ready removal under vacuum after the reaction. DMF was found to be a better solvent for the reaction involving NaH because of a faster reaction rate, but its high boiling point (153 °C) prevented easy removal. As stated in the Experimental Section, 3(CF₃CO₂⁻) reacts with 3.1 equiv. of Me₂SO₄ in the presence of 4.0 equiv. of NaH using CH₃CN as the solvent. After 10 hours at room temperature, a 100% conversion was obtained, 95% of which was desired product 2, with 2b and 4 being minor byproducts (<5%). After work-up and purification, 2(CF₃CO₂⁻, MeSO₄⁻) was obtained as a white crystalline solid in 78% isolated yield. After deprotonation with KO-t-Bu, 1 was obtained as a white solid in 88% isolated yield (99% conversion).
Experimental Section

All solvents were used as purchased unless stated otherwise and all reactions were carried out under argon. All other chemicals were purchased from Aldrich Chemical Company and were used without further purification. $^1$H and $^{13}$C NMR spectra were recorded on a Varian VXR-300 NMR spectrometer. $^{31}$P NMR spectra were recorded on a Bruker WM-200 NMR spectrometer using 85% $H_3PO_4$ as the external standard. ESI mass spectra were measured using a Finnigan TSQ700 spectrometer.

Synthesis of \([\text{HP(HNCH}_2\text{CH}_2\text{N)}\text{CF}_3\text{CO}_2], 3\text{CF}_3\text{CO}_2\) To a 500 mL RB flask was added (H$_2$NCH$_2$CH$_2$)$_3$N (14.6 g, 100 mmol) followed by the addition of CH$_3$CN (250 mL). After flushing with Ar for about 10 min, the flask was placed in an ice water bath and the reaction mixture was magnetically stirred. After 5 min, P(NMe$_2$)$_3$ (16.3 g, 100 mmol) was syringed into the above solution. After stirring at room temperature for 15 min, a solution of CF$_3$CO$_2$H (11.4 g, 100 mmol) in CH$_3$CN (50 mL) was added to the solution. After further stirring at room temperature for 10 hrs, all volatiles were removed under reduced pressure, and hexanes (300 mL) were added. The product 3(CF$_3$CO$_2$) was obtained as a white solid in quantitative yield upon filtration and drying in vacuum for 2 hrs. The $^{31}$P, $^1$H and $^{13}$C NMR data of the product were consistent with those in literature.

Synthesis of \([\text{HP(MeNCH}_2\text{CH}_2\text{N)}\text{CF}_3\text{CO}_2], \text{MeSO}_4, 2\text{CF}_3\text{CO}_2, \text{MeSO}_4\) In a glove-box, NaH (5.00 g, 200 mmol) was placed in a 1 L RB flask followed by the addition of CH$_3$CN (400 mL). After flushing with Ar for about 10 min, 3(CF$_3$CO$_2$) (14.5 g, 50.0 mmol) was added, the flask was then placed in an ice water bath and the reaction mixture was magnetically stirred. After 5 min, Me$_2$SO$_4$ (19.5 g, 155 mmol) in CH$_3$CN (200 mL) was introduced to the above suspension over about 20 min. The suspension was continuously stirred and kept in the ice water bath until the ice melted and the water had warmed to room temperature. After 10 hrs of stirring at room temperature, 1.0 mL of H$_2$O was added. After stirring at room temperature for 10 more min, all volatiles were removed by rotary
evaporation at below 50 °C, giving a brown to yellow solid which was then dissolved in 100 mL of distilled water. To this aqueous solution was added 2.0 g of KOH, and then it was extracted with Et₂O (3 x 200 mL) to extract organic impurities. NaCl was added to the resulting aqueous solution until some solid NaCl remained. Methylene chloride (5 x 200 mL) was used to extract product from the aqueous phase, and the organic extracts were collected and dried over MgSO₄ (20 g). After filtration, the volatiles were removed by rotary evaporation, giving a yellowish solid which was dissolved in THF (40 mL) followed by precipitation with hexanes (300 mL). The final product was obtained as a white solid (13.0 g, 78%) after recrystallization from THF (30 mL) and hexanes (30 mL) at -20 °C for 24 hrs and drying under vacuum at RT for 24 hrs. ³¹P, ¹H NMR and MS(ESI) spectra confirmed the identity and purity (98%) of the products.¹

**Synthesis of P(MeNCH₂CH₂)₃N, 1** To a 500 mL RB flask was added KO-t-Bu (6.55 g, 58.5 mmol) followed by the addition of dry THF (150 mL, distilled from Na). After flushing with Ar for about 10 min, a solution of 2(CF₃CO₂, MeSO₄) (13.0 g, 39.0 mmol) in dry THF (100 mL) was syringed into the above solution. After stirring at room temperature for 3 hrs, all volatiles were removed under reduced pressure followed by extraction with pentane (2 x 300 mL). Then all volatiles in the extracts were removed under reduced pressure, giving the product 1 as a white solid (7.41 g, 88%) upon sublimation (60 °C / 0.2 Torr). The ³¹P, ¹H and ¹³C NMR spectroscopic data were consistent with those in literature.¹

**Acknowledgment** The authors are grateful to the National Science Foundation for a grant in support of this research.

**References**

17. Strem Chemical Inc., Newburyport, MA.
CHAPTER 3. SYNTHESIS AND STRUCTURAL FEATURES OF NEW STERICALLY HINDERED AZAPHOSPHATRANE SYSTEMS:

\[ \text{ZP(RNCH}_2\text{CH}_2\text{)}_2\text{N} \]


Xiaodong Liu, Yuniu Bai and John G. Verkade

ABSTRACT

The synthesis of \([\text{ZP(RNCH}_2\text{CH}_2\text{)}_3\text{N}]\text{CF}_3\text{SO}_3\) wherein \(Z = \text{H}^+\) and \(R = \text{SiMe}_3\) (1f), \(\text{SiEt}_3\) (1g), \(\text{SiPh}_3\) (1h), \(\text{SiPh}_2\text{Me}\) (1i) and \(\text{Li}\) (1j) are reported along with that of 2f wherein \(Z = \text{Ip}\) and \(R = \text{SiMe}_3\). Also described are the transformations of 1j to 1f-i, 2f to \(\text{OP(Me}_3\text{SiNCH}_2\text{CH}_2\text{)}_3\text{N}\) (3b), 5 to 3b, and 2f to \(\text{SP(Me}_3\text{SiNCH}_2\text{CH}_2\text{)}_3\text{N}\) (3a). The structures of 2f and 3a determined by X-ray means are also presented. Compound 2f displays a bridgehead-bridgehead distance of 3.360(7) Å while that in 3a is 3.152(7) Å. The smaller distance in the latter by ca. 0.1 Å is attributed to the wider NPN bond angle by ca. 5° in 3a. VT \(^{31}\text{P}\) NMR studies revealed no evidence for transannulation or tautomerism in 3b.

**Keywords:** azaphosphatrace, steric hindrance

1. Introduction

In recent years we have been exploring the chemistry of azaphosphatranes such as 1a-e; particularly as it is related to the deprotonated parents of these cations, namely, their corresponding proazaphosphatranes 2a-e.[1-14] Some of these proazaphosphatranes are proving to be exceedingly potent catalysts, promoters and strong nonionic bases that facilitate a variety of useful organic transformations. For example, 2b is a superior catalyst for the trimerization of aryl and alkyl isocyanates to isocyanurates (equation 1) that are useful as
additives in the manufacture of Nylon-6.[1] Compound 2b is a superior catalyst for the

\[
\begin{array}{c|c}
\text{R} & \\
\hline
\text{la} & \text{H} \\
\text{lb} & \text{Me} \\
\text{lc} & \text{Et} \\
\text{ld} & \text{i-Pr} \\
\text{le} & \text{Bn} \\
\text{lf} & \text{SiMe}_3 \\
\text{lg} & \text{SiEt}_3 \\
\text{lh} & \text{SiPh}_3 \\
\text{li} & \text{SiPh}_2\text{Me} \\
\text{lj} & \text{Li} \\
\end{array}
\]

protective silylation of a wide variety of sterically hindered and deactivated alcohols,[12] and it is also an excellent promoter for the acylation of such substrates.[10] Proazaphosphatrane 2b is 17 pK units stronger as a base than DBU[2], a commonly used nonionic base in organic synthesis. Thus 2b has facilitated a substantial improvement in the synthesis of porphyrins,[5] for the dehydrohalogenation of secondary and tertiary halides[14] and in the synthesis of a chiral fluorescence agent.[15] As a result of these as well as currently emerging applications, 2b has become commercially available.[16]

\[
\begin{array}{c}
3\text{ArNCO} \xrightarrow{2b} \\
\end{array}
\]

All of these transformations are crucially dependent upon the ability of the bridgehead nitrogen in 2b to form a partial or full coordinate bond to the phosphorus.[17] In support of this hypothesis we observed, for example, that the acyclic analogue P(NMe\_2)\_3 is ineffective in all of the aforementioned reactions.

The first proazaphosphatrane for which we were able to obtain crystals suitable for an X-ray structural study was 2d. A curious feature we observed in this structure is the virtually planar geometry around the bridgehead nitrogen (angle sum = 358.7°).[8] This geometry was attributed to van der Waals repulsions among the methylene protons adjacent to the bridgehead nitrogen, which tended to draw the nitrogen from a downwardly directed pyramidal
sp³ geometry into a nearly planar sp³ hybridized geometry. The planarity of the bridgehead nitrogen is mainly responsible for the transannular N-P distance of 3.29 Å in 2d which is only about 2% shorter than the van der Waals sum of 3.35 Å.[8]

With the above considerations in mind, we sought to synthesize and structurally characterize a proazaphosphatrane that engenders even greater steric encumbrance around the phosphorus than 2d, in order to determine if the bridgehead-bridgehead distance would be elongated, and if so, whether the bridgehead nitrogen would be more pyramidal, or the NPN bond angles [angle sum = 309.7(7)° in 2d] would be sterically compressed.

Here we report the synthesis of 1f-j and of 2f, and the conclusion from the X-ray structure of 2f that although its transannular distance is slightly [0.06(1) Å] longer than that in 2d, both bridgehead bond angle sums are unchanged from those in 2d. Also described are the conversions of 1j to 1f-i, 2f to 3b, 5 to 3b and 2f to 3a. Evidence is also presented for the formation of 6(CF₃SO₃) in the synthesis of 1f. The molecular structural parameters for 3a determined herein by X-ray means are compared with those determined earlier for 4.[18]
2. Results and Discussion

2.1 Syntheses

Although the trilithio azaphosphatrane $1j(CF_3SO_3)$ could be isolated in 90% yield via step one in Scheme 1, compounds $1f-i$ derived from $1j(CF_3SO_3)$ by silylation in step two of this scheme were obtained in better yields and with greater convenience by generating $lj$ in situ followed by trisilylation. In view of the relative ease with which trisilylation of $lj(CF_3SO_3)$ occurred to give the corresponding salts $lg-i$ (51-63% yield) it was surprising to observe that $lj$ upon reaction with $Me^iCl$ (the least sterically hindered silylating agent employed) gave rise to a 3:1 mixture of the desired product $lf$ and what is probably $6(CF_3SO_3)$ the disilylated product. Evidence for the latter compound is its $^{31}P$ chemical shift (-34.3 ppm) which is upfield as is the case for cation $7$ (-23.2 ppm[8]). The reason(s) for the incomplete silylation here are not obvious. Attempts to deprotonate $1f-i$ with KO-$r$-Bu, the base of choice for these strong nonionic bases, succeeded only in the case of $lf(CF_3SO_3)$. For reasons that are not clear severe decomposition occurred when $lg-i$ were treated with KO-$r$-Bu.

Proazaphosphatrane $2f$, obtained in 58% overall yield from $1a(CF_3SO_3)$, was oxidized to $3b$ with $(Me_3SiO)_2$ (Scheme 1) in 94% yield. The oxide $3b$ was also derived from $5$ in 51% overall yield according to Scheme 2, presumably via intermediate $8$ which was not isolated. Proazaphosphatrane $2f$ reacts with sulfur as shown in Scheme 1 to give crystalline $3a$ in 76% yield.
We had previously synthesized 5 from 1a by allowing the latter to react with molecular oxygen.\cite{18} The yield of 5 was improved here (71\%) over that reported earlier (48\%\cite{18}) by reacting 1a with (Me$_3$SiO)$_2$.

2.2 NMR studies. A plot of the $^{31}$P chemical shifts of protonated pro-azaphosphatranes (summarized in Table 1) against the degree of R substitution for hydrogen shown in Figure 1 reveals some interesting trends. Trisubstituted alkyl and benzyl species display a comparatively narrow (~4 ppm) $\delta^{31}$P range (which is downfield) relative to their silyl counterparts (~14 ppm). These relationships, though largely preserved, become less pronounced as the number of non-hydrogen R groups decreases. Interestingly, the $\delta^{31}$P values progress upfield with decreasing R substitution until the value of -45.2 ppm is reached when all the R groups are replaced by hydrogens (1a). The trisubstituted lithium compound 1j displays a $\delta^{31}$P value (-17.7 ppm) that lies between the ranges for its trialkyl and trisilyl analogues. The orders in the $\delta^{31}$P values at each level of R substitution do not follow an obvious trend.
In efforts to determine if the Me$_3$Si groups on 3b are sufficiently electronegative (via N$\rightarrow$Si pi-bonding effects) to induce sufficient transannulartion (i.e., 3'b) to affect the $^{31}$P NMR chemical shift, and also to see whether evidence for tautomer 3''b could be found (owing to the superior strength of the Si-O bond and perhaps steric congestion among the equatorial Me$_3$Si groups) VT $^{31}$P and $^1$H NMR studies were carried out. It was observed that the position of the $^{31}$P peak is independent of temperature, although the $^1$H NMR spectrum of compound 3b is temperature dependent. At 298K, the resonance of the methylene protons showed two sets of multiplets (2.00-2.30 and 2.40-2.80 ppm). With increasing temperature, the peaks in the 2.00-2.30 ppm range began to combine with some of the peaks in 2.40-2.80 ppm range to form a broad peak at approximately 2.42 ppm, while the remaining peaks in 2.40-2.80 ppm range became sharper. At 343 K, the resonance of the methylene protons showed one broad peak at 2.42 ppm and one appearing to be a doublet of triplets at 2.79 ppm. It is suggested that at lower temperatures, compound 3b is rigid due to slow conformational inversion of the rings. Thus the protons of the methylene groups are not equivalent, displaying separated multiplet character in the $^1$H NMR spectrum. At higher temperatures, the structure becomes more flexible, rendering the protons of the methylene groups equivalent on the NMR time scale, thus accounting for the appearance of one doublet of triplets.

$$\text{lg(CF}_3\text{SO}_3) + 2b \rightleftharpoons 2g + 1b$$

$$\text{lh(CF}_3\text{SO}_3) + 2b \rightleftharpoons 2h + 1b$$

Efforts to compare the basicities of lg(CF$_3$SO$_3$) and lh(CF$_3$SO$_3$) with 2b were partially successful. $^{31}$P NMR monitoring of reactions 2 and 3 in CD$_3$CN showed that for reaction 2 in CD$_3$CN, 1b (along with its P-D analogue) and 2g (101 ppm) were formed, as well as 9 (97.0 ppm) owing to hydrolysis by adventitious water. In an analogous reaction of 1b and 2b, 1b (along with its P-D analogue) and 2h ($\delta^{31}$P = 105 ppm) were formed, as well as some partially hydrolyzed product 10 ($\delta^{31}$P = 99.1 ppm). Both experiments suggest, however, that 2b is more basic than lg or lh. Although these equilibria lie far to the right,
the extreme sensitivity of 2g and 2h to moisture made calculation of an equilibrium constant unwarranted.

This moisture sensitivity was also shown for 2f by monitoring its $^{31}$P NMR spectrum upon treatment with 3 equiv of H$_2$O in CD$_3$CN (see Experimental Section). The results are summarized in Scheme 3. Some support for the lack of formation of 1f(OH) in the first step of this scheme is the absence of a $^{31}$P NMR peak at $-24.5$ ppm and the persistence of cation 12 for up to one week. The reduced hydrolytic sensitivity of cations such as 1f, 12 and 13 may be attributed to the presence of N$_x$→P transannulation that reduces the electrophilicity of the silicon substituents. By contrast, untransannulated 3b hydrolyzes completely to 5 in 2 hours at room temperature as shown by comparison of its $^{31}$P, $^1$H and mass spectra which compared favorably to data we published earlier.[19]

**Scheme 3**

2.3 Structural considerations. Compound 2f (Fig. 2) is only the second pro-azaphosphatrane that has thus far provided crystals suitable for X-ray analysis, the first being 1d.[8] The bridgehead-bridgehead distances in these two compounds [2f, avg 3.360(7) Å; 2d, 3.293(2) Å], average NPN angles [2f, 103.3(2)°; 2d, 103.24(7)°] and average CNC angles [2f, 119.3(5)°; 2d, 119.6(2)°] are quite comparable. Thus any changes in stereoelectronic effects have a minimal effect on the overall geometry of the cage core.

Compound 3a (Fig. 3) is only the second pro-azaphosphatrane sulfide in addition to 14 to have been structured by X-ray means. The bridgehead-bridgehead distances [3a,
3.152(7); 14, 3.177(4) Å, average NPN angles (3a, 107.9(2)°; 14, 106.7(1)°) and average CNC angles (3a, 119.8(5)°; 14, 119.4(3)°) are again very comparable, as are the P-S distances (3b, 1.952(2) Å; 14, 1.957(1) Å). The smaller bridgehead-bridgehead distance by ca. 0.27 Å in 2f compared with 3a appears to be associated with the wider NPN angle in the latter compound (by ca. 5°) which tends to lift the nearly planar bridgehead nitrogen somewhat more strongly toward the phosphorus.

![Chemical Structures]

2.4 Catalytic properties of 2f

Like 2b[1] and 2d[8], 2f is a potent catalyst for reaction 1 in which Ar = Ph. Thus at room temperature, PhNCO is exothermically trimerized to the corresponding phenyl isocyanurate at room temperature in 97% yield. This result demonstrates that the zwitterionic intermediate 15, like its analogue of 2b[1] and of 2d[8], can form despite the formidable steric bulk provided by the SiMe$_3$ groups.

3. Experimental Section

3.1. General Procedures

Acetonitrile was dried with CaH$_2$. THF, toluene, benzene, and pentane were dried with sodium. All solvents were freshly distilled from their respective drying agents and all reactions were carried out under argon. $^1$H and $^{13}$C NMR spectra were recorded on a Varian VXR-300 NMR spectrometer or a Bruker WM-200 NMR spectrometer. $^{31}$P NMR spectra were recorded on a Bruker WM-200 NMR spectrometer using 85% H$_3$PO$_4$ as the external standard. High resolution mass spectra were recorded on a KRATOS MS-50 spectrometer and ESI mass spectra were performed using FINNIGAN TSQ700 spectrometer. Elemental
analyses were performed in the Instrument Services Laboratory of the Chemistry Department at Iowa State University. Compounds 1a(CF$_3$SO$_3$)[19] and 2b[20] were synthesized according to our previously published methods.

3.2. [HP(LiNCH$_2$CH$_2$)$_3$N](CF$_3$SO$_3$), 1j(CF$_3$SO$_3$)

A suspension of 1a(CF$_3$SO$_3$) (0.324 g, 1.00 mmol) in THF (50 mL) was cooled to -78 °C under argon. N-butyllithium (1.28 mL, 3.20 mmol) as a 2.5 M solution in hexane was added and the reaction mixture was stirred while it warmed slowly to room temperature. Stirring was continued for 4 h at room temperature. The volatiles were then removed in vacuo and the residue was washed with cold (0 °C) pentane (20 mL). After drying the residue in vacuo, 1j(CF$_3$SO$_3$) was obtained as a white powder (3.10 g, 90%) and was used in the following reaction without further purification. Attempts to purify this compound consistently resulted in less pure material. $^{31}$P (CD$_3$CN): δ -17.67 (bds). $^1$H (CD$_3$CN): δ 2.59-2.80 (bdm, 12H, N$_{eq}$CH$_2$ and N$_{ax}$CH$_2$ resonance overlapped), 6.27 (d, 1H, PH, $^1$J$_{PH} = 460$ Hz). $^{13}$C (CD$_3$CN): δ 37.62 (bds, N$_{ax}$CH$_2$), 50.63 (bds, N$_{eq}$CH$_2$).

3.3. [HP(Me$_3$SiNCH$_2$CH$_2$)$_3$N](CF$_3$SO$_3$), 1f(CF$_3$SO$_3$)

Both isolated 1j(CF$_3$SO$_3$) and 1j(CF$_3$SO$_3$) generated in situ used in this reaction gave similar results. Here the procedure for the preparation of 1f(CF$_3$SO$_3$) using 1j(CF$_3$SO$_3$) synthesized in situ as a starting material is described and the in situ method is also employed in subsequent preparations. A suspension of 1j(CF$_3$SO$_3$) generated in situ from 1a(CF$_3$SO$_3$) (3.24 g, 10.0 mmol) in THF (300 mL) was cooled to -78 °C under argon. Trimethylsilyl chloride (4.37 g, 40.0 mmol) was slowly added with a syringe. The mixture (in a flask closed by a septum) was allowed to warm slowly to room temperature and was stirred at that temperature for an additional 10 h. The volatiles were removed in vacuo and the residue was extracted with acetonitrile (3 x 25 mL). The extract was filtered and the solvent was removed in vacuo to give a powder which was washed with pentane (1 x 50 mL). The $^{31}$P and $^1$H NMR spectra of this white powder in CD$_3$CN indicated that a mixture of 1f(CF$_3$SO$_3$) and 5(CF$_3$SO$_3$)
was formed in approximately a 3:1 ratio (see Discussion). The ratio of trimethylsilyl chloride was increased to six equivalents and the reaction time was extended from 10 h to 48 h in an attempt to synthesize pure 1f(CF₃SO₃). However, the product mixture ratio remained unchanged. Although attempts to isolate pure 1f(CF₃SO₃) from this mixture were not successful, the mixture was used in the following reaction to prepare 2f.

3.4. \(P(Me, SiNCH₂CH₂)₃N, 2f\)

A suspension of 1.05 g of the above-described mixture of 1f(CF₃SO₃) and 5(CF₃SO₃) in THF (80 mL) was added to a suspension of KO-t-Bu (0.336 g, 3.00 mmol) in THF (20 mL) at room temperature. After the reaction mixture was stirred for 2 h at room temperature, the volatiles were removed in vacuo and the residue was extracted with toluene (1 x 50 mL). The extract was filtered and the solvent was removed in vacuo. Colorless crystalline 2f was obtained upon sublimation at 80 °C/0.5 Torr (0.451 g, 58% overall yield based on 1a).

3.5. \([HP(Et₃SiNCH₂CH₂)₃N](CF₃SO₃), 1g(CF₃SO₃)\)

The synthesis of 1g(CF₃SO₃) was analogous to that of 1f(CF₃SO₃) except that triethylsilyl chloride (4.55 g, 40.0 mmol) was used instead of trimethylsilyl chloride. The product 1g(CF₃SO₃) was obtained as a white powder (4.02 g, 60%). ³¹P (CD₃CN): δ -25.99. ¹H (CD₃CN): δ 0.80 (q, 18H, Nₚₜ(CH₂CH₃)₃), ²JHH = 8.0 Hz). ³JHH = 0.98 (t, 27H, Nₚₜ(CH₂CH₃)₃), ³JHH = 8.0 Hz), 2.85 (bdm, 6H, Nₚₜ(CH₂CH₃)₃), 3.03 (dt, 6H, Nₚₜ(CH₂CH₃)₃), ³JHH = 16.0 Hz, ³JHH = 6.0 Hz), 6.28 (d, 1H, PH, ¹JPH = 504 Hz). ¹³C (CD₃CN): δ 5.14 (d, CH₂CH₃, ³JPC = 2.5 Hz), 7.65 (s, CH₂CH₃), 38.52 (s, Nₚₜ(CH₂CH₃)₃), 52.84 (d, Nₚₜ(CH₂CH₃)₃). MS (ESI) m/z: 517.2 (cation 1g).
3.6. [HP(Ph₂SiNCH₂CH₂)₃N]([CF₃SO₃])₂, 1h(CF₃SO₃)

The synthesis of 1h(CF₃SO₃) was analogous to that of 1f(CF₃SO₃) except that triphenylsilyl chloride (11.8 g, 40.0 mmol) was used instead of trimethylsilyl chloride. The product 1h(CF₃SO₃) was obtained as a white powder (5.61 g, 51%). ³¹P (CD₃CN): δ -19.64. ¹H (CD₃CN): δ 2.88 (bddd, 6H, NαCH₂), 3.58 (dt, 6H, NeqCH₂, ¹JPH = 16.0 Hz, ¹JHH = 6.0 Hz), 6.92 (d, 1H, PH, ¹JPH = 532 Hz), 7.07-7.49 (m, 45H, C₆H₅). ¹³C (CD₃CN): δ 42.57 (s, NαCH₂), 52.07 (d, N, qCH₂, ³JPC = 10.0 Hz), 129.35 (s, C₆H₅), 131.64 (s, C₆H₅), 132.43 (d, C₆H₅, ³JPC = 1.5 Hz), 137.29 (s, C₆H₅). MS (ESI) m/z: 949.1 (cation 1h).

Elemental analysis calculated for C₆₁H₅₈N₄Si₃O₃PSF₃: C, 66.64; H, 5.32; N, 5.10. Found: C, 66.87; H, 5.68; N, 4.87.

3.7. [HP(Ph₂MeSiNCH₂CH₂)₃N]([CF₃SO₃])₂, 1i(CF₃SO₃)

The synthesis of 1i(CF₃SO₃) was analogous to that of 1f(CF₃SO₃) except that diphenylmethylsilyl chloride (9.72 g, 40.0 mmol) was used instead of trimethylsilyl chloride. The product 1i(CF₃SO₃) was obtained as a white powder (5.45 g, 63%). ³¹P (CD₃CN): δ -34.25. ¹H (CD₃CN): δ 0.42 (d, 9H, CH₃), 4.15-4.31 (m, 12H, NeqCH₂ and NαCH₂ overlapped), 6.65 (d, 1H, PH, ¹JPH = 494 Hz), 7.35-7.52 (m, 30H, C₆H₅). ¹³C (CD₃CN): δ - 0.98 (d, CH₃, ³JPC = 3.1 Hz), 40.25 (s, NαCH₂), 50.62 (d, NeqCH₂, ³JPC = 11.6 Hz), 129.50 (s, C₆H₅), 131.62 (s, C₆H₅), 135.10 (s, C₆H₅), 135.64 (s, C₆H₅). MS (ESI) m/z: 762.9 (cation 1i).

3.8. S=P(Me₃SiNCH₂CH₂)₃N, 3a

Elemental sulfur (0.039 g, 1.20 mmol) was added to a solution of 2f (0.390 g, 1.00 mmol) in benzene (20 mL) at 0 °C. After stirring the reaction mixture for 12 h at room temperature, it was filtered and the solvent in the filtrate was slowly evaporated to give product 3b as a colorless crystalline solid (0.332 g, 76%). ³¹P (C₆D₆): δ 65.30. ¹H (C₆D₆): δ 0.44 (s, 27H, CH₃), 2.11-2.26 and 2.53-2.82 (bddd, 12H, NeqCH₂ and NαCH₂ overlapped). ¹³C (C₆D₆): δ 2.55 (s, CH₃), 47.34 (d, NeqCH₂, ³JPC = 3.0 Hz), 55.00 (s, NαCH₂). HRMS m/z...
calculated for $\text{C}_{15}\text{H}_{39}\text{N}_4\text{SPSi}_3$: 422.19410. Found: 422.19367 (37.8, M*). Elemental analysis calculated for $\text{C}_{15}\text{H}_{39}\text{N}_4\text{SPSi}_3$: C, 42.61; H, 9.30; N, 13.25. Found: C, 42.89; H, 9.43; N, 13.15.

3.9. $O=\text{P(Me}_3\text{SiCH}_2\text{CH}_2)\text{N}$, 3b

Method A. Bistrimethylsilyl peroxide (0.214 g, 1.20 mmol) was added to a solution of 2f (0.390 g, 1.00 mmol) in pentane (20 mL) at 0 °C. After 10 h at room temperature, the reaction mixture was filtered and the solvent was evaporated in vacuo to give 3b as a white solid (0.340 g, 84%) which was further purified by sublimation at 80 °C/0.5 Torr (0.321 g, 94 %). $^3\text{P} (\text{C}_6\text{D}_6)$: δ 24.11. $^1\text{H} (\text{C}_6\text{D}_6)$: δ 0.34 (d, 27H, CH$_3$, $^4J_{\text{PH}} = 3.0$ Hz), 2.14-2.71 (bdm, 12H, $N_{\text{eq}}\text{CH}_2$ and $N_{\text{ax}}\text{CH}_2$). $^{13}\text{C} (\text{C}_6\text{D}_6)$: δ 1.58 (d, CH$_3$, $^3J_{\text{PC}} = 1.5$ Hz), 47.16 (d, $N_{\text{eq}}\text{CH}_2$, $^2J_{\text{PC}} = 2.3$ Hz), 54.96 (s, $N_{\text{ax}}\text{CH}_2$). HRMS m/z calculated for $\text{C}_{15}\text{H}_{39}\text{N}_4\text{PSi}_3\text{O}$: 406.21694. Found: 406.21209.

Method B. A suspension of 5 (0.190 g, 1.00 mmol) in THF (50 mL) was cooled to -78 °C under argon. N-butyllithium (1.28 mL, 3.20 mmol) as a 2.5 M solution in hexane was then added with a syringe and after 30 min the reaction mixture was allowed to warm slowly to room temperature where it was stirred for an additional 3 h. The reaction mixture was then cooled to -78 °C and trimethylsilyl chloride (0.443 g, 4.00 mmol) was slowly added. The reaction mixture was again allowed to warm slowly to room temperature where it was stirred for an additional 12 h. All the volatiles were then removed in vacuo and the residue was extracted with toluene (1 × 50 mL). The extract was filtered through Celite and the toluene in the filtrate was removed in vacuo. The residue was sublimed at 80 °C/0.5 Torr to give product 3b as a white solid (0.212 g, 51%).

3.10. $O=\text{P(HNCH}_2\text{CH}_2)\text{N}$, 5

Although we reported this compound previously [19], we found that the action of bistrimethylsilyl peroxide instead of molecular oxygen on 1a gave a higher yield of 5 in less time. To a suspension of 1a($\text{CF}_3\text{SO}_3$) (3.24 g, 10.0 mmol) in THF (150 mL) at room
temperature was added a solution of KO-t-Bu (1.35 g, 12.0 mmol) in acetonitrile (20 mL) followed by the addition of bistrimethylsilyl peroxide (2.02 g, 12.0 mmol) over a period of 10 min. The reaction mixture was stirred at room temperature for 12 h and then filtered. The crude product was obtained as a yellowish solid from the filtrate by evaporation in vacuo. Compound 5 (1.35 g, 71%, lit. 48%) was recrystallized from methanol as colorless crystals. The $^{31}$P, $^1$H, $^{13}$C NMR and mass spectral data were consistent with those in the literature.[19]

3.11. Hydrolysis of 2f

Water (6 μL, 0.3 mmol) was added at room temperature via syringe to a solution of 2f (40 mg, 0.10 mmol) in CD$_3$CN (0.6 mL) in a NMR tube. After shaking the NMR tube for 1 min, the reaction mixture was allowed to stand at room temperature. A $^{31}$P NMR spectrum of the reaction mixture was taken 30 min, 90 min and 480 min after the reagents had been mixed. After 30 min, the $^{31}$P NMR spectra showed, that in addition to decreased signal intensity for the starting material 2f, there appeared a new signal at 92.0 ppm and a triplet at −33.0 ppm whose members were of equal intensity. After 90 min, the signal for the starting material vanished completely, the signal at 92.0 ppm decreased and the triplet, now at −35.0 ppm, greatly increased. After 480 min, the signals at 92.0 and −35.0 ppm disappeared while a new signal at −42.0 ppm was observed that persisted for a week (see Results and Discussion).

3.12. Catalytic Trimerization of PhNCO by 2f

To a solution of 2f (0.41 g, 1.0 mmol) in dry benzene (20 mL) under argon was added (by syringe) phenyl isocyanate (6.00 g, 99% pure, 50.0 mmol, Aldrich). After the mixture was stirred at room temperature for 2 min, a white precipitate rapidly formed, transforming the reaction mixture into a solid mass. The solid was allowed to cool to room temperature and 30 mL of dry benzene was added. After stirring at room temperature for 1 h, the resulting suspension was filtered in vacuo, further washed with 15 mL of dry benzene, and finally dried in vacuo to give phenyl isocyanurate as a white solid (5.82 g, 97%). The $^1$H and $^{13}$C NMR and mass spectroscopic data matched those in the literature.[6]
3.13. $^1$H VTNMR of $O=P(Me_3SiNCH_2CH_2)_2N$, 3b

Solutions of 3b (41 mg, 0.10 mmol) in CD$_3$CN (0.6 mL) and C$_6$D$_6$ (0.6 mL) were prepared. $^{31}$P NMR spectra of 3a in CD$_3$CN were taken at 251 K, 261K, 293 K, 323 K and 341 K. $^1$H NMR spectra of 3a in C$_6$D$_6$ were also taken at 298 K, 323 K, and 343 K.

3.14. X-ray Structural Determinations of 2f and 3a

A crystal of 2f was mounted on a glass fiber on the Siemens P4 for a data collection at 213(2) ± 1K. The cell constants for the data collection were determined from reflections found from a 360° rotation photograph. Twenty five reflections in the range of 18-31° θ were used to determine precise cell constants. Pertinent data collection and reduction information are given in Table 2. Lorentz and polarization corrections and a nonlinear correction based on the decay in the standard reflections were applied to the data. A series of azimuthal reflections was collected and a semi-empirical absorption correction was applied to the data. The space group $P\bar{1}$ was chosen based on systematic absences and intensity statistics. This assumption proved to be correct as determined by a successful direct-methods solution [21] and subsequent refinement. All non-hydrogen atoms were placed directly from the E-map. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogens were treated as riding-atoms with individual isotropic displacement parameters. Final refinements were carried out.[21-23] Selected bond angles and distances are collected in Table 3.

A crystal of 3a was mounted on a glass fiber on the Enraf-Nonius CAD4 for data collection at 293(2) ± 1K. The cell constants for the data collection were determined from reflections found from a 360° rotation photograph. Twenty five reflections in the range of 4.27-15.77° θ were used to determine precise cell constants. Pertinent data collection and reduction information is given in Table 2. Lorentz and polarization corrections and a nonlinear correction based on the decay in the standard reflections were applied to the data. A series of azimuthal reflections was collected for this specimen and a semi-empirical absorption correction was applied to the data. The space group $P2_1/c$ was chosen based on systematic absences and...
intensity statistics. This assumption proved to be correct as determined by a successful direct-methods solution[21] and subsequent refinement. All non-hydrogen atoms were placed directly from the E-map and they were refined with anisotropic displacement parameters. The hydrogen atoms were treated as riding-atoms with individual isotropic displacement parameters. The hydrogen atoms on the main body of the molecule were placed from successive difference fourier maps and refined isotropically. Final refinements were then carried out.[21-23] Selected bond angles and distances are collected in Table 4.

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References


[16] Strem Chemical Inc., Newburyport, MA.


[21] SHELXTL-PLUS, Siemens Analytical Xray, Inc., Madison, WI.


TABLE 1. $^{31}$P NMR Chemical shifts for protonated proazaphosphatranes
HP(RNCH$_2$CH$_2$)$_3$N$^*$.  

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<td>Ph$_3$Si</td>
<td>2</td>
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<tr>
<td>Ph$_3$Si</td>
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<tr>
<td>MePh$_2$Si</td>
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</tr>
<tr>
<td>MePh$_3$Si</td>
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<td>-43.1</td>
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</tbody>
</table>

$^a$R is defined here as a substituent other than hydrogen. Thus 1a possesses a hydrogen on each equatorial nitrogen. $^b$Chemical shifts were measured in CD$_3$CN unless stated otherwise. $^c$DMSO. $^d$CDCl$_3$. $^e$M. A. H. Laramay, J. G. Verkade, J. Am. Chem. Soc. 112 (1990) 9421. $^f$P. B. Kisanga, J. G. Verkade, to be published.
TABLE 2. Crystallographic Data for 2f and 3a.

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<tr>
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<th>C₁₅H₃₉N₄PSi₃</th>
<th>C₁₅H₃₀N₄PSSi₃</th>
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<tr>
<td>Empirical formula</td>
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<td>C₁₅H₃₀N₄PSSi₃</td>
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<tr>
<td>Formula weight</td>
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<td>413.73</td>
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<td>Crystal color, habit</td>
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<td>(c, \text{ Å}^3)</td>
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<td>Max, min difference peak ((e^\text{2}\text{Å}^3))</td>
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<td>0.430</td>
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</table>

^a\(R = \Sigma||F_o||-|F_c||/\Sigma|F_c||; R_w = [\Sigma|w(F_o^2-|F_c|^2)/\Sigma|w|F_c|^2]|^{1/2}. ^b\)Goodness of fit = \([w(F_o^2-|F_c|^2)/(n_{\text{obs}}-n_{\text{par}})]^{1/2}. \)
TABLE 3. Selected Bond Angles and Bond Distances in 2f.

<table>
<thead>
<tr>
<th>Bond Angles (deg)</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>N(3A)-P(1A)-N(2A)</td>
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<td>N(1B)-P(1B)-N(2B)</td>
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<tr>
<td>N(3A)-P(1A)-N(1A)</td>
<td>102.6(2)</td>
<td>N(1B)-P(1B)-N(3B)</td>
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<tr>
<td>N(2A)-P(1A)-N(1A)</td>
<td>104.2(2)</td>
<td>N(2B)-P(1B)-N(3B)</td>
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<td>C(4A)-N(4A)-C(6A)</td>
<td>120.6(5)</td>
<td>C(4B)-N(4B)-C(6B)</td>
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<tr>
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<td>119.9(5)</td>
<td>C(4B)-N(4B)-C(2B)</td>
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<tr>
<td>C(6A)-N(4A)-C(2A)</td>
<td>117.8(5)</td>
<td>C(6B)-N(4B)-C(2B)</td>
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</table>

<table>
<thead>
<tr>
<th>Bond Distances (Å)</th>
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<tr>
<td>P(1A)-N(3A) 1.705(5)</td>
<td>Si(1A)-N(1A) 1.735(5)</td>
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<td>P(1A)-N(2A) 1.715(5)</td>
<td>Si(2A)-N(2A) 1.737(5)</td>
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</tr>
<tr>
<td>P(1A)-N(1A) 1.711(5)</td>
<td>Si(3A)-N(3A) 1.732(5)</td>
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<tr>
<td>P(1B)-N(1B) 1.711(4)</td>
<td>Si(1B)-N(1B) 1.745(5)</td>
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<td>Si(2B)-N(2B) 1.747(4)</td>
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<td>P(1B)-N(3B) 1.720(4)</td>
<td>Si(3B)-N(3B) 1.730(4)</td>
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TABLE 4. Selected Bond Angles and Distances in 3a.

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<tr>
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<td>N(2)-P-N(3) 107.9(2)</td>
<td>N(1)-P-S 110.7(2)</td>
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<tr>
<td>N(2)-P-N(1) 107.9(2)</td>
<td>C(4)-N(4)-C(6) 120.1(6)</td>
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<tr>
<td>N(3)-P-N(1) 107.9(2)</td>
<td>C(4)-N(4)-C(2) 119.4(5)</td>
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<tr>
<td>N(2)-P-S 111.6(2)</td>
<td>C(6)-N(4)-C(2) 119.8(5)</td>
<td></td>
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<tr>
<td>N(3)-P-S 110.8(2)</td>
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<table>
<thead>
<tr>
<th>Bond Distances (Å)</th>
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<tr>
<td>P-N(2) 1.653(5)</td>
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<td>P-N(3) 1.661(5)</td>
<td>P-S 1.952(2)</td>
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Figure 1. Plot of $^{31}$P NMR chemical shifts of protonated pro-azaphosphatranes against the number of non-hydrogen R groups.
Figure 2. Computer drawing of 2f with thermal ellipsoids at the 50% probability level.
Figure 3. Computer drawing of 3b with thermal ellipsoids at the 50% probability level.
CHAPTER 4. FREE AND POLYMER-BOUND TRICYCLIC AZAPHOSPHATRANE HP(RNCH₂CH₂)₃N⁺: PROCATALYSTS IN DEHYDROHALOGENATIONS AND DEBROMINATIONS WITH NaH


Xiaodong Liu, Zhengkun Yu and John G. Verkade

Abstract

The commercially available nonionic base P(CH₃NCH₂CH₂)₃N (1a) was shown earlier to be superior to DBU as a stoichiometric reagent for the conversion of primary and secondary alkyl halides to alkenes (Arumugam, S.; Verkade, J. G. J. Org. Chem. 1997, 62, 4827). The precursor cation HP(CH₃NCH₂CH₂)₃N⁺ (2) to 1a, which is more stable and less expensive, is reported herein to be an efficient procatalyst for these reactions and also for the debromination of vicinal dibromides using NaH as a relatively inexpensive stoichiometric hydride source in CH₃CN at room temperature. In dehydrohalogenations requiring more than ca. 10 h, the CH₂CN ion also acts as a base. By itself, NaH does not function well or at all under the same conditions. A catalytic cycle is proposed in which hydride deprotonates cation 2 liberating catalytic 1a. The cations HP(HNCH₂CH₂)₃N⁺ (3) and HP[N(polymer)CH₂CH₂N(CH₂CH₂NH)₂⁺ (4) are also shown to function as procatalysts for the efficient dehydrohalogenation of RX and for the debromination of vicinal dibromides. The preparation of the heterogeneous procatalyst 4 (OTf) is also described.

Introduction

The introduction of double bonds into organic systems via the elimination of hydrogen halides is a widely applicable transformation. Although typical organic bases, such as Et₃N, N,N-dimethylaniline, pyridine, and quinoline have been employed as dehydrohalogenation reagents, they often result in unsatisfactory yields. Over the past 30 years, DBU and DBN
have become popular dehydrohalogenation reagents owing to their non-nucleophilic nature and greater basicity.\textsuperscript{2,3} However, these reagents frequently require heating and must be used in stoichiometric excess. Moreover, yields are often only moderate. Dehalogenations have been used as a means for the purification of olefins,\textsuperscript{4} for the temporary protection of double bonds,\textsuperscript{5} and for generating a new double bond as part of a synthetic sequence.\textsuperscript{6} Dehalogenations from vicinal dihalides are promoted by a variety of nucleophiles, including halide and hydride ions, as well as neutral sulfur, phosphorus, nitrogen and oxygen compounds.\textsuperscript{7} Recently\textsuperscript{8,9} we found that the commercially available proazaphosphatrane 1a, reported for the first time by our group,\textsuperscript{10} is superior to DBU as a dehydrohalogenation reagent for primary and secondary alkyl halides. Solid 2(X), which is produced in these reactions (X = Cl, Br, OTf) can be converted back to 1a by treatment with KO-r-Bu.\textsuperscript{11}

Here we report that NaH deprotonates 2(Cl), 3(OTf) and 4(OTf), thus allowing for the possibility that neutral 1a-c can act as a catalyst in dehydrohalogenations. By itself NaH is not an efficient dehydrohalogenation reagent, but it is considerably less expensive than other bases, such as DBN, DBU or KO-r-Bu. Because 2(Cl) is stable to air for months without degradation, it seemed to us that it, as well as 3(OTf) and 4(OTf) could function as
procatalysts for dehydrohalogenations of alkyl halides in the presence of NaH. Here we report that 0.1 equiv of any of these procatalysts in the presence of excess NaH (2.5 equiv) in CH$_3$CN are not only efficient dehydrohalogenation media at room temperature, but that these mixtures also debrominate vicinal dibromides effectively.

**Results and Discussion**

That NaH can deprotonate cation 2 in CH$_3$CN to give 1a is shown by a $^{31}$P NMR spectrum of a CH$_3$CN solution of a 3.0/1.0 equiv ratio of NaH to 2(Cl). Thus only one resonance at 119 ppm corresponding to 1a was observed after 20 min at room temperature. The combination of a catalytic amount of procatalyst 2(G), 3(OTf) or 4(OTf) (0.1 equiv) and excess NaH (2.5 equiv) was therefore employed as a dehydrohalogenation and debromination medium for the compounds in Table 1. In the dehydrohalogenation of 7 with the above combination in CD$_3$CN using 2(Cl) at room temperature, 83% and 99% conversions were obtained after 1 h and 2 h, respectively, without detectable side reactions according to $^1$H NMR and GC-mass spectroscopic analysis. By comparison, 2.5 equiv of NaH only used without 2(Cl) in the same reaction gave rise to considerably slower reactions (i.e., 11% and 72% conversions after 1 h and 2 h, respectively). This observation prompted us to test our three procatalyst systems on the additional substrates 5-14 in Table 1 in the presence of NaH both with and without procatalysts.

It was found that except for 14, which afforded no detectable product in any case, the conversions (95-99%) of the products formed from substrates 5-12 (33-94% conversions for 13) treated with 0.1 equiv of each procatalyst and 2.5 equiv of NaH exceeded those obtained with 2.5 equiv of NaH by itself (<1-82%) by remarkable margins. It is noted that an electron-withdrawing group $\beta$ to the halogen (5-8) leads to high conversions with procatalyst/NaH in only 2 h, owing to rapid E2 elimination caused by activation of the hydrogen on the $\beta$ carbon. Evidence for abstraction of such a hydrogen by 1a was presented earlier.$^9$ Substrates 9 and
13 required more time to give high conversions of corresponding alkenes. Interestingly, 13 gave two isomers (1-heptene and trans-2-heptene in 87 and 94% total conversions using 2(Cl) and 3(OTf), respectively) while only one isomer (trans-2-heptene) was observed using 1.1 equiv of 1a. It is of interest that the dibromides 10 and 11 each gave the corresponding debrominated product with all three procatalysts. This contrasts the result for these substrates described in our earlier publication in which only monobromoalkene was reported to form in the presence of a stoichiometric quantity of 1a. Repetition of these experiments with 10 and 11 in the presence of a stoichiometric amount of 1a now reveals that their corresponding debrominated products (see Experimental Section) were undoubtedly also formed in our earlier experiments.

We believe the pathway shown in Scheme 1 for 2(Cl) reasonably accounts for the formation of these debrominated products. Thus step 1 occurs in the stoichiometric experiment and this is followed by step 2 under catalytic conditions. As with the use of PPh₃ in such reactions, initial nucleophilic attack of the phosphorus of 1a on a bromine is followed by the formation of cation 15 with elimination of the second bromine from the substrate as Br⁻. When 2(Cl)/NaH is used, 15(Br) can be further reduced and deprotonated by NaH to regenerate 1a. In separate ¹H NMR experiments, 10 mol% of 2(Cl)/2.5 equiv of NaH and 2.0 equiv of PPh₃ were used to debrominate 10 in CD₃CN at 35 °C. It was found that debromination by 2(Cl)/NaH is much more efficient than by PPh₃: 99% conversion vs <30% conversion in 2 h. The literature describes the use of PPh₃ for debromination promoted under
considerably harsher conditions (xylene/150-160 °C/250 min), and the yield is only moderate (76%).

A possible dehydrohalogenation pathway for substrates requiring extended reaction times (beyond ca. 10 h) in the presence of 1 in CH₂CN was proposed earlier, in which evidence was put forth that the -CH₂CN abstracts a proton from the substrates.⁹ Thus the main phosphorus-containing compound observed in the dehydrohalogenation of 13 in D₃CCN is the deuterio analogue of 2, which displayed a triplet signal at -10.0 ppm in ³¹P NMR spectrum.⁹

**Scheme 2**

\[
\begin{align*}
&\text{NaX} + H_2 \\
&\text{NaH} \\
&\text{1a} \\
&\text{RX} \\
&\text{olefin}
\end{align*}
\]

**Scheme 3**

\[
\begin{align*}
&\text{NaX} + H_2 \\
&\text{NaH} \\
&\text{1a} \\
&\text{RX} \\
&\text{CH₃CN} + X^- \\
&\text{olefin}
\end{align*}
\]

Catalytic cycles that account for the aforementioned direct and indirect dehydrohalogenations are shown in Schemes 2 and 3, respectively, for cation 2. The first step in Scheme 2 involves NaH deprotonation of cation 2 to give 1a, the effective dehydrohalogenation agent for substrates with activating groups. The signal at 119 ppm in the ³¹P NMR spectrum observed at the end of these reactions is characteristic of 1a. In the second step, 1a reacts with activated alkyl halides to give corresponding olefin products. That the first step in Scheme 2 is the rate-determining is supported by the detection of only a single ³¹P NMR signal at -10.0 ppm before completion of the reaction. This peak corresponds to cation 2 as noted above. The peak at 119 ppm corresponding to 1a was not observed until the reaction was complete, which is in accord with the supposition that the concentration of 1a during the reaction is low and that the reaction
rate of alkyl halides with 1a is fast compared with the regeneration of 1a from 2 by NaH. A similar conclusion can be drawn from the cycles in Scheme 3 in which the process on the left is again the slow step. In this scheme, however, deprotonation of CH₃CN by 1a is faster than deprotonation of RX by 1a. All of the reactions were accompanied by the formation of H₂ gas bubbles. It should be mentioned that procatalyst 2(Cl) can be rather simply recovered chromatographically (see Experimental Section).

In our earlier work,¹⁴ attempts to isolate the neutral form 1b from 3(OTf) resulted in oligomeric product, suggesting that intermolecular oligomerization occurs subsequent to the deprotonation step. However, as shown in Table 1, 3(OTf) is as effective as 2(Cl) for both dehydrohalogenation and debromination, which suggests the formation of 1b as an intermediate that reacts more quickly with the substrate than it does intermolecularly to form oligomer. Additional evidence supporting the formation of 1b stems from an NMR experiment in which a ³¹P NMR signal was observed at 91 ppm upon adding 2.0 equiv of KO-t-Bu to 3(OTf) in THF at room temperature. The catalytic reaction pathways for 3(OTf) are analogous to those shown in Schemes 2 and 3. Although this procatalyst cannot be recovered after use in such reactions owing to oligomerization of 1b, 3(OTf) is much less expensive to synthesize than 2(Cl) and is very comparable in efficiency.

Whereas the synthesis of 2(Cl)¹⁰ and 3(OTf)¹⁴ have been reported, that of 4(OTf) (Scheme 4) has not. Although the protonated form 4(OTf) was successfully synthesized, attempts to isolate its neutral form 1c by deprotonation with KO-t-Bu or NaH, at room temperature or 60 °C, for 1 to 6 days have thus far failed for reasons that are not clear. Survival of cation 4 is signalled by its CPMAS ³¹P NMR chemical shift at −15.9 ppm (see Experimental Section). However, the results in Table 1 show that 0.1 equiv of 4(OTf) in the presence of excess NaH (2.5 equiv) in CH₃CN effectively allowed both dehydrohalogenation and debromination, although more slowly than 2(Cl) and 3(OTf) (Table 1). Thus we believe that in the presence of NaH, 1c is generated in situ and that it functions as the catalyst. The
advantage of this approach in which both the NaH and the procatalyst and catalyst are insoluble is easy isolation of spectroscopically pure products (ca. 95%) by filtration of the reaction mixture followed by evaporation. Moreover, the procatalyst is easily recovered by washing and drying the filter cake.

**Scheme 4**

\[
\begin{align*}
\text{N} & \rightarrow \text{H} \quad \text{H} \\
3(\text{OTf}) \quad \text{b} & \quad \text{polymer} \\
-67.0 \text{ ppm} & \\
\end{align*}
\]

\[
\begin{align*}
\text{a. P(NMe}_2\text{)}_3 & , \text{HOTf, CH}_2\text{Cl}_2, \text{RT, Ar, 30 min, 99%}. \\
\text{b. Merrifield's peptide resin, DMF, 110°C, 6 days.} \\
\text{c. KO-\text{-}t-\text{-}Bu or NaH, THF, RT or 60°C, 1 - 6 days.}
\end{align*}
\]

**Experimental Section**

CH\text{\textsubscript{3}}CN and CD\text{\textsubscript{3}}CN were distilled from CaH\text{\textsubscript{2}}. All other solvents were used as purchased. All chemicals were obtained from Aldrich Chemicals and were used without purification unless otherwise noted. All reactions were carried out at room temperature under Ar. Both 2(Cl)\textsuperscript{10} and 3(OTf)\textsuperscript{14} were prepared according to our previously published methods.

**Preparation of Polymer-Based Azaphosphatrane 4(OTf).** Under Ar, a mixture of 3(OTf) (4.15 g, 12.8 mmol), Merrifield's peptide resin (5.00 g, 1% cross-linked 200-400 mesh, ca. 2.5 mmol Cl/g) and 60 mL of DMF was vigorously stirred at 110 °C for 6 days. Then the reaction mixture was cooled to room temperature and 40 mL of MeOH was added. After the mixture was shaken for 5 min, it was filtered to give a solid which was
successively washed with THF, Et$_2$N, MeOH, THF, Et$_2$O, THF and Et$_2$O (10 mL each).

After drying in vacuo, 4.56 g of a pale yellow-brown solid 4(OTf) was obtained. Solid state $^{31}$P NMR (MAS): $\delta$ -15.6 ppm. Elemental analysis: P 3.27%; N 5.15%. P : N ratio: Calcd., 1.8; found, 1.6. Loading: 1.0 mmol of 3(OTf)/g of 4(OTf).

**Attempted Deprotonation of 4(OTf).** Under Ar, 4(OTf) (1.0 g, ~1.0 mmol) was added to a suspension of KO-t-Bu (1.12 g, 10 mmol) or 95% pure NaH (0.24 g, 10 mmol) in THF or DMF (20 mL). Then the reaction mixture was vigorously stirred at room temperature or 60 °C for 1 to 6 days. The solid remaining after filtration of the reaction mixture was successively washed with THF, DMF and THF (20 mL each). After drying in vacuo, 2.0 to 2.5 g of a pale brown solid was recovered. Solid state $^{31}$P NMR (MAS): $\delta$ -15.9 ppm.

**General Procedure for Dehydrohalogenation or Debromination.** The combination of 2(Cl), 3(OTf) (0.10 mmol) or 4(OTf) (0.10 g, ~0.10 mmol) and NaH (0.1 g, 2.5 mmol, 60% in mineral oil) or NaH (0.10 g, 2.5 mmol, 60% in mineral oil) by itself was added to 3 mL of CD$_3$CN at room temperature under Ar. After stirring for 10 min, the alkyl halide (1.0 mmol) was added to above suspension, and the resulting mixture was stirred at room temperature. The reaction was monitored by $^1$H NMR spectroscopy. After the reaction time stated in Table 1, an $^1$H NMR spectrum was recorded from which conversions were obtained by integration of peak areas. GC-mass spectra were recorded for some substrates to confirm the identity of the products. The reaction was then quenched by 0.1 mL of MeOH, and the resulting mixture was filtered and washed with CH$_3$CN (2 x 10 mL). The cake was saved for the recovery of catalyst when 4(OTf) was employed as the procatalyst. The filtrate was dried over MgSO$_4$, followed by evaporating about 95% of the solvent under vacuum. The resulting crude product was purified by chromatography on a silica gel column using the eluents stated in Table 1. The product was obtained upon evaporation of the solvent, and was identified by $^1$H and $^{13}$C NMR spectroscopies.
NMR Reaction of 10 with PPh₃. In a 5 mm NMR tube was placed 10 (17 mg, 0.05 mmol) followed by a mixture of PPh₃ (27 mg, 0.10 mmol) in CD₃CN (0.75 mL). The NMR tube was placed in an ultrasonic bath for 2 h and then the ¹H NMR spectrum was recorded. The reaction mixture was 35 °C. See Results and Discussion.

NMR Reaction of 10 with 2(Cl)/NaH. In a 5 mm NMR tube was placed 10 (17 mg, 0.05 mmol) and NaH (5.00 mg, 1.25 mmol, 60% in mineral oil) followed by a solution of 2(Cl) (3 mg, 0.01 mmol) in CD₃CN (0.75 mL). The NMR tube was placed in an ultrasonic bath for 2 h and then the ¹H NMR spectrum was recorded. The reaction temperature was 35 °C. See Results and Discussion.

NMR Reactions of 10 and 11 with 1a. In a 5 mm NMR tube was placed 10 or 11 (0.05 mmol) followed by a solution of 1a (17 mg, 0.75 mmol) in CD₃CN (0.75 mL). Then this NMR tube was placed in an ultrasonic bath for 2 h and then the ¹H NMR spectrum was recorded. The reaction temperature was 35 °C. ¹H NMR spectra of the reaction mixture showed that the reaction was complete in 1 h and that the products were the corresponding debrominated alkenes. This result was confirmed by GC-mass spectroscopy.

Recovery of 2(Cl). After chromatographic separation of the olefin products, the silica gel columns were washed with 100 mL of a solution of CH₂Cl₂ (95%) and CH₃OH (5%) followed by washing with 100 mL of CH₃OH. After collecting the pure CH₃OH fraction and evaporation of the solvent under vacuum, 2(Cl) was recovered as a white solid in 60-80% yield. The ³¹P, ¹H and ¹³C NMR spectra are consistent with those of a standard sample of 2(Cl).

Recovery of 4(OTf). The filter cake from five experiments (0.50 g of 4(OTf)) was placed in a 100 mL round-bottomed flask followed by addition of 30 mL of distilled H₂O. The resulting suspension was stirred at room temperature for 2 h followed by filtration. The cake was washed with H₂O, MeOH, THF and Et₂O (20 mL each) and then it was dried in vacuo for
24 h to give 4(OTf) as a pale yellow-brown solid (0.45 g, 90% mass recovery). Solid state $^{31}$P NMR (MAS): $\delta$ -15.7 ppm.

Acknowledgment  The authors are grateful to the ISU Center for Advanced Technology Development for grant support of this research.

References

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Identification was made by comparing $^1$H and $^{13}$C NMR spectral data with those in the references indicated. Conversions were determined by $^1$H NMR integration of signals for olefin products to corresponding alkyl halides. GC-mass spectral analysis was used to confirm the olefin products and to check for detectable side products. Isolated yields were obtained by chromatography and purity was determined by $^1$H NMR spectroscopy. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(1), 1358B. Butcher, M.; Mathews, R. J.; Middleton, S. Aust. J. Chem. 1973, 26, 2067. The reaction solution turned blue within 1 min which suggested the possibility of a side reaction between NaH and the NO$_2$ group in substrate. However, the GC-mass spectrum showed the olefin product listed as the only detectable product and thus the formation of side products was assumed to be negligible. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(2), 23A. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(2), 24A. See reference 5.


From direct filtration of the reaction mixture followed by drying under vacuum. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(1), 18B.

Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(1), 25B. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(1), 73C.
CHAPTER 5. \( P[(S,S,S)-\text{PhHMeCNCH}_2\text{CH}_2]_3\text{N} \): A NEW CHIRAL \( ^{31}\text{P} \) AND \( ^1\text{H} \) NMR SPECTROSCOPIC REAGENT FOR THE DIRECT DETERMINATION OF ee VALUES OF CHIRAL AZIDES


Xiaodong Liu, Palanichamy Ilankumaran, Ilia A. Guzei and John G. Verkade

**Abstract**

A facile and economical procedure for the synthesis of the \( C_3 \) chiral \( \alpha \)-phenylethylamino trisaminoamine \( [(S,S,S)-\text{PhHMeCNHCH}_2\text{CH}_2]_3\text{N} \) in good yield is reported. The corresponding bicyclic proazaphosphatranne \( P[(S,S,S)-\text{PhHMeCNHCH}_2\text{CH}_2]_3\text{N} \), its bicyclic phosphoryl derivative and its tricyclic \( P \)-protonated azaphosphatranne were also synthesized and characterized. It is found that the proazaphosphatranne is an efficient derivatizing agent for the direct determination of enantiomeric ratios of chiral azides by means of \( ^{31}\text{P} \) and \( ^1\text{H} \) NMR spectroscopy.

**Introduction**

In recent years we have been exploring the chemistry of proazaphosphatranes such as \( 1a-f \), some of which are proving to be exceedingly potent catalysts, promoters and strong nonionic bases that facilitate a variety of useful organic transformations. For example, \( 1b \) is an 

![Diagram](attachment:image.png)
efficient catalyst for the trimerization of aryl and alkyl isocyanates that function as additives in
the manufacture of nylon-6,7 for the protective silylation of a wide variety of sterically hindered
and deactivated alcohols,8 and for the acylation of such substrates.9 Proazaphosphatrane 1b is
much stronger as a base than DBU,10 a commonly used nonionic base in organic synthesis.
Thus it is a superior base for the synthesis of porphyrins,11 for the dehydrohalogenation of
secondary and tertiary halides,12 and for the synthesis of a chiral fluorescence agent.13 As a
result of such applications, 1b has become commercially available.14 Recently, we have
discovered that 1b and 1c are also efficient nonionic base catalysts for transesterification.15 β-
nitroalkanol synthesis,16 Michael additions,17 β-hydroxy nitrile synthesis,18 and α,β-
unsaturated nitrile synthesis.19

Chiral azides are important starting materials for the synthesis of amines that are used as
ligands, chiral auxiliaries, pharmaceutical intermediates and building blocks for the asymmetric
synthesis of natural products.20 Although amines can be made in several ways, the azide
reduction method is often employed because it is facile and well documented in the literature.
Hence numerous methods have been developed to synthesize azides in enantiomeric forms.21
While a variety of approaches can be taken to establish the enantiomeric purity of chiral
compounds,31P NMR spectroscopic analysis is very popular because of the attractive features
of this nucleus.22 Several derivatizing agents have been developed for such analyses of chiral
alcohols, amines and thiols.21 However, no derivatizing agent has been reported for the direct
determination of ee values of chiral azides by means of 31P or 1H NMR spectroscopy.
We report herein a simple and efficient procedure for the synthesis of the C₃ chiral tripodal trisaminoamine 3 from commercially available inexpensive (S)-α-phenylethylamine 4, and the conversion of 3 to the corresponding tricyclic azaphosphatrane 5Cl which can be deprotonated to the bicyclic proazaphosphatrane 6. The new chiral nonionic base 6 is found to be an excellent tagging agent for the direct determination of enantiomeric excesses of chiral azides using ³¹P and ¹H NMR spectroscopy. Upon oxidation, proazaphosphatrane 6 yields the new C₃-chiral phosphine oxide 7.

Scheme 1

Results and Discussion

Synthesis of 3. The synthetic route to the chiral trisaminoamine 3 is shown in Scheme 1. In the first step, nitrilotriacetic acid 8 is condensed with 3.0 equiv of 4 in the presence of P(OPh)₃ using pyridine as the solvent at 100 °C to give (S,S,S)-amidoamine 9. The synthesis of 9 reported earlier required tedious column chromatography for purification and the yield was only moderate (65%). In the present work, spectroscopically pure 9 was obtained in a good yield (85%) upon recrystallization from THF/hexanes at -20 °C. To ensure complete reduction of all three amido groups of 9 to give optically pure 3, it was necessary to carry out the second step in the presence of excess LiAlH₄ in refluxing THF for five days. The yield of 3 (82%) is surprisingly good.
The only two tripodal chiral trisaminoamines that have been reported possess chiral centers at the beta carbon of the tertiary nitrogen\textsuperscript{24,25} as shown in Schemes 2 and 3. The synthesis of 11 involves nucleophilic ring opening of the aziridine derived from 10.\textsuperscript{24} The drawbacks of this synthesis are that the enantiopure amino alcohol used as the starting material is expensive, and five steps are required to obtain the desired product. Although (S)-proline 12, the starting material for 13, is readily available and inexpensive, seven synthetic steps are required to obtain the final product, including two condensations, three LiAlH$_4$ reductions, a protection and a deprotection.\textsuperscript{25} By contrast, our route to 3 utilizes inexpensive nitrilotriacetic acid 8 and (S)-(−)-α-phenylethylamine 4, only two steps are required to obtain the final product and the work-up is quite simple involving only extraction and recrystallization. Moreover, the chiral substituents can be readily replaced with other chiral amines in order to tune the steric and electronic properties of the proazaphosphatrane derivatives. Chiral 3 represents the first example of a tripodal trisaminoamine in which the chiral centers are not on the CH$_2$CH$_2$ moiety.

**Synthesis of 5(Cl), 6 and 7.** The protonated azaphosphatrane 5(Cl) shown in Scheme 4 was synthesized according to our established procedure for analogs of this cation.\textsuperscript{3}
Scheme 4

However, formation of the tricyclic phosphatrane cage was not complete even after one week of reaction. Thus only 75% conversion and a 62% isolated yield were realized, which is considerably lower than the 95% conversion and 90% isolated yield for the analogous synthesis of 2b. Raising the temperature to 60 °C gave no improvement in either yield or purity of the product. The main impurity is 3•3HCl (see Experimental Section). The formation of 3•3HCl may be due to steric hindrance of the α-phenylethyl groups which could lower the rate of cage formation relative to protonation of 3. In the presence of KO-t-Bu, using THF as the solvent, 5(Cl) was easily converted into proazaphosphatrane 6 in 82% yield within 2 h. Oxidation of 6 with (Me₃SiO)₂ in benzene gave 7 in 90% yield.

Structural considerations. The computer drawing of 5(Cl) in Figure 1 features a P-Nₓ distance of 1.967(10) Å (which is 40% shorter than the sum of the P and N van der Waals radii[26]), a nearly tetrahedral bridgehead nitrogen [avg ∠CNₓC = 112.54(7)°] and a nearly ideal trigonal bipyramidal phosphorus with N_eq-P-N_eq angles averaging 119.4(10)°. All these metrics are consistent with a fully transannulated structure. The P-Nₓ distance of cation 5 is within experimental error of those of the less sterically hindered analogs 2b[26] and 2c[5] (as judged by the 3 x esd criterion). The remaining bond distances and angles (Table 2) are unremarkable and the crystallographic data are collected in Table 3.

Compound 6 is the first example of a chiral proazaphosphatrane characterized by X-ray crystallography (Figure 2). Its geometry around P is pyramidal [avg. ∠N_eqPN_eq = 104.16(14)°], but the bridgehead axial nitrogen (angle sum = 357.3°) possess an essentially planar configuration. This planarity is attributed to van der Waals repulsions among the methylene protons adjacent to the bridgehead nitrogen, which tend to draw the nitrogen from a
downward directed pyramidal $sp^3$ geometry into a hybridized nearly planar $sp^2$ geometry. The transannular N-P distance of 3.274 Å in 6 is only about 2% shorter than the van der Waals sum of 3.35 Å and is very close to that of 1e (3.293 Å). The remaining bond distances and angles are unremarkable (Table 4) and the crystallographic data are collected in Table 3.

Like its nonchiral analogue 14, compound 7 (Figure 3) displays a nearly tetrahedral geometry around bridgehead P [avg $\angle N_{eq}PN_{eq} = 107.81(13)^\circ$] and a nearly planar trigonal geometry around the bridgehead nitrogen [avg $\angle CN_{ax}C = 119.999(6)^\circ$], compared with $107.6(1)^\circ$ and $118.9(2)^\circ$, respectively, in 14. The P-N$_{ax}$ distance in 7 [3.081(5) Å] is about 8% shorter than the sum of the P and N van der Waals radii but it is still very close to the P-N$_{ax}$ distance in 14 [3.152(3) Å]. The remaining bond distances and angles (Table 5) are unremarkable and crystallographic data are summarized in Table 3.

**Pro-azaphosphatrane 6 as a chiral derivatizing agent for chiral azides.**

In previous work we showed that proazaphosphatrane 1b reacts with organic azides to give iminophosphines quantitatively. In the present work, diastereomeric iminophosphine derivatives were quantitatively prepared by heating the chiral proazaphosphatrane 6 with enantiomeric mixtures of azides in $C_6D_6$ at 50 °C in an NMR tube for 2 h, as represented in
reaction 1. The $^1$H and proton-decoupled $^{31}$P NMR spectra of these derivatives were obtained directly without further purification. To evaluate the derivatizing ability of 6, (±)-neomenthyl azide was reacted with 6 in C$_6$D$_6$ at 50 °C for 2 h. Two $^{31}$P NMR singlets (32.55 and 31.41 ppm) in a very nearly 1:1 ratio (Table 1), indicated the expected presence of a racemic mixture. $^1$H NMR spectra also showed good diastereomeric peak separations for the benzylic proton H$_a$ in the proazaphosphatracene moiety and H$_b$ attached to the α-carbon in the azide moiety (5.65, 5.79 ppm and 4.18, 4.32 ppm, respectively) thus facilitating verification of ee values obtained by $^{31}$P NMR spectroscopy.

When (-)-neomenthyl azide was reacted under the same conditions, only one singlet was observed at 31.44 ppm in the $^{31}$P NMR spectrum and two multiplets in the $^1$H NMR spectrum (5.65 and 4.32 ppm), corresponding to H$_a$ and H$_b$ respectively, in 15 thus relating the NMR data to a specific enantiomer. A 1:1 mixture of (±) and (-)-neomenthyl azide employed to test the reliability of this method gave a ratio of (-) to (+) enantiomers from both the $^{31}$P and $^1$H NMR spectra of very nearly 3:1 as expected. When commercially available chiral phosphorus triamide 16 was used in a parallel reaction for comparison, no diastereomeric differentiation was observed. After reacting 16 with (±)-neomenthyl azide in C$_6$D$_6$ at 50 °C for 2 h, only one singlet (30.3 ppm) was observed in the $^{31}$P NMR spectrum. Although the corresponding $^1$H NMR spectrum indicated some chemical shift separation of the N-methyl group protons in moiety 16 of the corresponding diastereomers, the multiplet character of the peaks gave rise to excessive overlap, thus preventing adequate integration. These observations may be attributable to the presence of only two chiral centers in 16 which apparently do not generate a sufficiently chiral environment around phosphorus in 16 to allow
differentiation of the diastereomeric products spectroscopically. In chiral proazaphosphatrane 6 and hence in the iminophosphine product 15, the three chiral substituents held rigidly by the cage structure probably afford an enhanced chiral phosphorus environment. The azide substrates 17–22 used in this work and the results of the NMR measurements on the diastereomeric derivatives are given in Table 1.

In general, the phosphorus imine derivatives examined by decoupled $^{31}$P NMR spectroscopy displayed excellent diastereomeric peak separation, allowing accurate integration and quantitative determination of the diastereomeric ratios. $^1$H NMR analysis also gave good diastereomeric peak separation, although the spectra were more complex due to P-H and H-H coupling, as well as overlap with closely neighboring signals. The advantage of decoupled $^{31}$P NMR spectroscopic analysis is that no signals other than the two singlets associated with the diastereomeric derivatives are observed in the spectra. For substrate 22, however, no evidence for the expected diastereomeric derivatives appeared in the $^{31}$P NMR spectrum, and only a peak for cation 5 (-10 ppm) which is characteristic of the protonated form of 6 was observed. This result is attributed to facile deprotonation of the azido carbon, which was confirmed by the disappearance of the NMR spectroscopic resonance of this hydrogen. Both the $^1$H an $^{13}$C NMR were quite complicated, however, suggesting that side reactions of the anion ensued.

**Experimental Section**

CH$_3$CN was dried with CaH$_2$. THF and Et$_2$O were dried with sodium, and other solvents were dried with molecular sieves. All solvents were freshly distilled before use and all reactions were carried out under an Ar atmosphere. The racemic azides used in this work were synthesized by heating NaN$_3$ with the corresponding bromides in DMF at 60 °C for 24 h. Chemicals employed were purchased from Aldrich Chemical Company and were used without further purification. Elemental analyses were performed in the Instrument Services Laboratory of the Chemistry Department at Iowa State University.
Synthesis of (S,S,S)-Tris(2-(α)-methylbenzylcarbamoylmethyl)amine 9. Although the synthesis of 9 has been reported, an easier procedure is described here. Nitrilotriacetic acid 8 (19.1 g, 100 mmol) was added to 250 mL of pyridine. The slurry was stirred vigorously while (S)-(-)-(α)-methylbenzylamine 4 (37.0 g, 305 mmol) was introduced. The solution was warmed to 50 °C and P(OPh)$_3$ (99.2 g, 320 mmol) was added. The reaction mixture was kept at 100 - 105 °C for 10 h followed by removing pyridine via vacuum distillation. The resulting yellow oil was dissolved in 600 mL of CHC$_3$ and then sequentially, distilled H$_2$O (3 x 600 mL), 10% aqueous NaHCO$_3$ (10 x 600 mL), distilled H$_2$O (3 x 600 mL) and brine (2 x 600 mL) were used to wash the organic phase. The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure, giving the crude product as a pale yellow solid. Recrystallization of the crude product from THF (200 mL) and hexanes (50 mL) at -20 °C for 24 h gave pure 9 as a white solid (42.5 g, 85%). $^1$H and $^{13}$C NMR data were consistent with those in literature.

Synthesis of (S,S,S)-Tris(2-(α)-methylbenzylamino-ethyl)amine 3. A solution of 9 (10.0 g, 20.0 mmol) in THF (150 mL) was added dropwise at room temperature to a suspension of LiAlH$_4$ (20.0 g, 520 mmol) in THF (300 mL). This mixture was vigorously stirred and heated under reflux for 5 days after which it was cooled to room temperature. Then 50 mL of 10% aqueous KOH was slowly added and the resulting mixture was heated under reflux until the salts turned white. After cooling the reaction mixture to room temperature, the salts were removed by filtration. The salts were again heated under reflux for 1 h in a mixture of THF (400 mL) and H$_2$O (10 mL). After removal of the salts by filtration, the THF layers were combined and concentrated under reduced pressure. The resulting yellow oil was placed in a 20% aqueous KOH (50 mL) solution and extracted with CH$_2$Cl$_2$ (2 x 70 mL). After drying the extract over MgSO$_4$ and concentrating it under reduced pressure, 3 was obtained as a pale yellow oil (7.51 g, 82%) which was used in the following reaction without
further purification. The sample for characterization was purified by silica gel column chromatography using a mixture of CH₂Cl₂ and MeOH (10:1) as the eluent.

**Synthesis of (S,S,S)-Tris(2-(α)-methylbenzylamino-ethyl)amine hydrochloride 3·3HCl.** Crude 3 (4.60 g, 10.0 mmol) was placed in a 10% aqueous HCl (50 mL) solution. After stirring at room temperature for 2 hrs, CH₂Cl₂ (4 x 50 mL) was used to extract the product. After drying over MgSO₄, complete evaporation under reduced pressure, and purification of the residue by silica gel column chromatography using a mixture of CH₂Cl₂ and MeOH (10:1) as the eluent, 3·3HCl was obtained as a white solid (2.20 g, 48%).

**Synthesis of (S,S,S)-Azaphosphatrane 5(Cl).** To a solution of PCl₃ (47.0 mg, 0.33 mmol) in CH₃CN (10 mL) was added P(NMe₂)₃ (110 mg, 0.67 mmol) at 0 °C with a syringe. The resulting solution was stirred at 0 °C for 1 hr and then a solution of 3 (458 mg, 1.00 mmol) in CH₃CN (2 mL) was added. After stirring at room temperature for 12 h, the volatiles were removed under vacuum. The residue was then purified by silica gel column chromatography using a mixture of CH₂Cl₂ and MeOH (15:1) as the eluent, giving 5(Cl) (330 mg, 62%) as a white solid upon drying over MgSO₄ and evaporation under vacuum. A crystal for X-ray analysis was obtained by diffusing Et₂O into a solution of 5(Cl) in CH₃CN at room temperature for 3 days.

**Synthesis of Chiral-Proazaphosphatrane 6.** A solution of 5(Cl) (330 mg, 0.63 mmol) in THF (10 mL) was added at room temperature to a suspension of KO-t-Bu (125 mg, 1.10 mmol) in THF (20 mL). After the reaction mixture was stirred for 2 h at room temperature, the volatiles were removed in vacuo and the residue was extracted with benzene (2 x 50 mL). The extract was filtered and the solvent was removed under vacuum giving 6 as a white solid (250 mg, 82%). A crystal for X-ray analysis was obtained by slow evaporation of a solution of 6 in THF at room temperature.
Synthesis of Chiral-Proazaphosphatrane oxide 7. Bistrimethylsilyl peroxide (180 mg, 1.00 mmol) was added to a solution of 6 (250 mg, 0.51 mmol) in benzene (10 mL) at 0 °C. After standing for 5 h at room temperature, the reaction mixture was filtered and the solvent was evaporated in vacuum to give 7 as a white solid (230 mg, 90%). The crystal for X-ray analysis was obtained by dissolving 7 in hot THF followed by cooling at -20 °C for 24 h.

Crystallographic structural determinations of 5(Cl), 6, 7. The systematic absences in the diffraction data were consistent with space groups \( R3 \) and \( \overline{R3} \) for 5(Cl) and 7, and for space groups \( P2_1 \) and \( P2_1/m \) for 6. In all cases the \( E \)-statistics strongly suggested the non-centrosymmetric space groups. The chosen chiral space groups \( R3 \) for 5(Cl) and 7, and \( P2_1 \) for 6 yielded chemically reasonable and computationally stable refinement results. The structures were solved using direct methods that provided locations for most non-hydrogen atoms from the \( E \)-map.\(^{27}\) The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. In the case of 5(Cl) the empirical absorption corrections were based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.\(^{28}\) In the case of 7 the semi-empirical absorption correction data were collected by the \( \psi \)-scan technique. Absorption corrections were not required for 6 because the variations in the integrated \( \psi \)-scan intensities were less than 10%. In the structure of 5(Cl), the cation and anion reside on a threefold crystallographic axis that passes through atoms P, N(2), H(0A) and Cl. This structure was refined with a fixed phosphorous-hydrogen distance of 1.400(1) Å. Structures 6 and 7 were refined with soft restraints on thermal displacement parameters to conserve data. Molecule 7 occupies a crystallographic threefold axis that passes through atoms P, O, and N(2).
General procedure for $^1$H and $^{31}$P NMR spectral determination of $ee$ values of chiral azides with 6. To an azide (0.05 mmol) in an NMR tube sealed with a rubber septum was added a solution of 6 (29 mg, 0.06 mmol) in C$_6$D$_6$ (0.6 mL) at room temperature under an Ar atmosphere. The NMR tube was then heated at 50°C for 2 h. After cooling the NMR tube to room temperature, the $^{31}$P and $^1$H NMR spectra were recorded and the $ee$ value of the racemic azide was determined from both NMR peak integrations (Table I).

Acknowledgment The authors are grateful to the Donors of the Petroleum Research Fund administered by the American Chemical Society for a grant in support of this research.

Supporting Information Available: Analytical and spectral data (NMR and mass) for 3, 3-HCl, 5(Cl), 6, 7 and 18. Complete X-ray data for 5(Cl), 6 and 7. This material is free of charge via the Internet at http://pubs.acs.org.

References


27. All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrich, Bruker Analytical X-ray Systems, Madison, WI).

Table 1. $^{31}$P and $^1$H NMR data for azides derivatized by 6.

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<td>racemic</td>
<td>32.26 (0.82)</td>
<td>5.19 (0.07)</td>
<td>50.2:49.8 (50.5:49.5)</td>
</tr>
<tr>
<td>Me</td>
<td>racemic</td>
<td>31.72 (0.30)</td>
<td>4.78 (0.09)</td>
<td>50.2:49.8 (51.0:49.0)</td>
</tr>
<tr>
<td>21$^i$</td>
<td>racemic</td>
<td>31.97 (0.56)</td>
<td>5.72 (0.15)$^k$</td>
<td>51.0:49.0 (50.5:49.5)</td>
</tr>
<tr>
<td>22$^l$</td>
<td>racemic</td>
<td>na$^m$</td>
<td>na$^m$</td>
<td>na$^m$</td>
</tr>
</tbody>
</table>

$^a$ Average of both signals and (separation between both signals). $^b$ Average of both signals and (separation between both signals) of the proton on the alpha-carbon of the azide moiety unless otherwise stated. $^c$ The ratio of the two diastereomers determined by $^{31}$P and ($^1$H) NMR integrations. $^d$ Synthesized according to the procedure described in Synthesis, 1990, 130. $^e$ Authentic sample synthesized from (-)-menthol via a Mitsanobu transformation. $^f$A mixture composed of racemic and pure (-)-isomer in a 1:1 ratio. $^g$ Synthesized from the reaction of the corresponding iodide with sodium azide in refluxing acetone. $^h$ Synthesized according to the procedure described in Synthesis, 1990, 130. $^i$ Synthesized according to the procedure described in Synthesis, 1990, 130. $^j$ Synthesized according to the procedure described in Synthesis, 1990, 130. $^k$ Synthesized according to the procedure described in J. Am. Chem. Soc. 1954, 1231. $^l$ The average of both signals and (the difference between both signals) of the three benzylic protons in the azaphosphatrane moiety. $^m$ Synthesized by the PCC oxidation of 21. The $^1$H NMR spectrum compared favorably with that reported in J. Org. Chem. 1994, 59, 2902. $^n$ Elimination of HN$_3$ gave cation 5.
Table 2. Crystallographic Data for 5(C1), 6 and 7.

<table>
<thead>
<tr>
<th></th>
<th>5(C1)</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>formula</strong></td>
<td>C$<em>{30}$H$</em>{40}$ClN$_4$P</td>
<td>C$<em>{30}$H$</em>{39}$N$_4$P</td>
<td>C$<em>{30}$H$</em>{39}$N$_4$P</td>
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<td><strong>formular weight</strong></td>
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<td>502.62</td>
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<td>rhombohedral</td>
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<td><strong>space group</strong></td>
<td>R3</td>
<td>P2$_1$</td>
<td>R3</td>
</tr>
<tr>
<td><strong>crystal color, habit</strong></td>
<td>colorless rod</td>
<td>colorless block</td>
<td>colorless block</td>
</tr>
<tr>
<td><strong>a, Å</strong></td>
<td>15.7922(10)</td>
<td>9.245(3)</td>
<td>14.5268(10)</td>
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<tr>
<td><strong>b, Å</strong></td>
<td>15.7922(10)</td>
<td>14.7103(8)</td>
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<tr>
<td><strong>c, Å</strong></td>
<td>9.8706(6)</td>
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<td>11.3942(18)</td>
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<td><strong>V, Å$^3$</strong></td>
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<td>1379.3(7)</td>
<td>2082.4(4)</td>
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<td><strong>Z</strong></td>
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<td>2</td>
<td>3</td>
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<tr>
<td><strong>D(calc), g cm$^{-3}$</strong></td>
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<td>1.172</td>
<td>1.202</td>
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<td><strong>temperature, K</strong></td>
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<td>296(2)</td>
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<td>semi-empirical</td>
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<tr>
<td><strong>radiation</strong></td>
<td>MoK$\alpha$ ($\lambda = 0.71073$ Å)</td>
<td>CuK$\alpha$ ($\lambda = 1.54178$ Å)</td>
<td>CuK$\alpha$</td>
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<td><strong>$\mu$, mm$^{-1}$</strong></td>
<td>0.216</td>
<td>1.058</td>
<td>1.095</td>
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<tr>
<td><strong>$\theta$ range,$^\circ$</strong></td>
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<td>2.06-56.54</td>
<td>2.62-56.35</td>
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<tr>
<td><strong>no. of measd reflect.</strong></td>
<td>19563</td>
<td>2475</td>
<td>844</td>
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<tr>
<td><strong>no. of obsd reflect.</strong></td>
<td>1963</td>
<td>2034</td>
<td>691</td>
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<td><strong>R,</strong> $^a$%</td>
<td>2.26</td>
<td>3.62</td>
<td>3.83</td>
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<tr>
<td><strong>R,$^a$,$^b$%</strong></td>
<td>6.16</td>
<td>9.54</td>
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<td><strong>GOF</strong></td>
<td>1.054</td>
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$^a$Quantity minimized = $R(wF^2) = \Sigma[w(F_o^2-F_c^2)^2]/\Sigma[(wF_o^2)^2]^{1/2}$; $R = \Sigma\Delta(F_o)/\Sigma(F_o)$. $\Delta = |F_o-F_c|$. 

Table 3. Selected Bond Lengths (Å) and Angles (deg) for 5(Cl).a

<table>
<thead>
<tr>
<th>Bond Distances</th>
<th>Bond Angles</th>
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<tr>
<td>P-N(1) 1.6752(10)</td>
<td>N(1)-C(3) 1.4818(15)</td>
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<tr>
<td>N(1)-C(1) 1.4577(15)</td>
<td>N(2)-C(2) 1.4888(13)</td>
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<td>N(1)-P-N(1)#2 119.404(10)</td>
<td>C(3)-N(1)-P 121.88(8)</td>
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<tr>
<td>C(1)-N(1)-C(3) 117.04(10)</td>
<td>C(2)#2-N(2)-C(2) 112.54(7)</td>
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<td>C(1)-N(1)-P 121.06(8)</td>
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</tbody>
</table>

*aSymmetry transformations used to generated equivalent atoms: #1 -y,x-y,z; #2 -x+y,-x,z
Table 4. Selected Bond Lengths (Å) and Angles (°) for 6.

<table>
<thead>
<tr>
<th>Bond Lengths</th>
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<th>Bond Angles</th>
<th></th>
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</thead>
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<tr>
<td>P-N(1)</td>
<td>1.694(3)</td>
<td>N(1)-P-N(2)</td>
<td>103.91(14)</td>
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<tr>
<td>P-N(3)</td>
<td>1.703(3)</td>
<td>N(1)-P-N(3)</td>
<td>104.15(15)</td>
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<tr>
<td>N(1)-C(7)</td>
<td>1.470(5)</td>
<td>C(1)-N(1)-C(7)</td>
<td>117.0(3)</td>
</tr>
<tr>
<td>N(2)-C(15)</td>
<td>1.476(4)</td>
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<td>115.5(2)</td>
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<td>N(3)-C(23)</td>
<td>1.474(4)</td>
<td>C(3)-N(2)-C(15)</td>
<td>116.9(3)</td>
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<td>N(4)-C(2)</td>
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<td>N(3)-C(5)</td>
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<td>N(4)-C(4)</td>
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Table 5. Selected Bond lengths (Å) and angles (°) for 7.

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<td>O-P-N(1)</td>
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<td>C(1)-N(1)-P</td>
<td>124.4(3)</td>
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<td>N(1)-C(3)-C(5)</td>
<td>109.0(3)</td>
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*Symmetry transformations used to generate equivalent atoms: #1 -y,x-7,z.*
Figure 1. The molecular structure of cation 5 of 5(Cl) drawn with thermal ellipsoids at the 30% probability level. All hydrogen atoms except the H atom on the phosphorus were omitted for clarity.
Figure 2. The molecular structure of 6 drawn with the thermal ellipsoids are shown at the 30% probability level. The hydrogen atoms have been omitted for clarity.
Figure 3. The molecular structure of 7 drawn with the thermal ellipsoids are shown at the 30% probability level. The hydrogen atoms have been omitted for clarity.
Supporting Information

$^{31}$P, $^1$H, $^{13}$C NMR and MS Spectral Data and Analyses

$(S,S,S)$-Tris(2-(α)-methylbenzylamino-ethyl)amine 3:  $^1$H NMR (CDCl$_3$): $\delta$ 1.33 (d, 9H, $J = 6.4$ Hz), 2.12 (br, 3H), 2.45-2.55 (m, 12H), 3.71 (q, 3H, $J = 6.4$ Hz), 7.21-7.33 (m, 15H, Ph).  $^{13}$C NMR (CDCl$_3$): $\delta$ 24.4, 45.4, 54.0, 58.5, 126.7, 126.9, 128.5, 145.8.  HRMS (EI) calcd for C$_{30}$H$_{44}$N$_4$: 458.3410, found 458.3410 [M-CH$_2$N(H)C(H)MePh].  Anal. calcd for C$_{30}$H$_{44}$N$_4$: C, 78.56; H, 9.23; N, 12.21.  Found: C, 78.95; H, 9.27; N, 12.05.

$(S,S,S)$-Tris(2-(α)-methylbenzylamino-ethyl)amine hydrogen-chloride 3•HCl:  $^1$H NMR (CDCl$_3$): $\delta$ 1.94 (d, 9H, $J = 6.4$ Hz), 1.99 (m, 3H), 2.55 (m, 3H), 3.45 (m, 3H), 4.36 (s, 3H), 7.33 (m, 9H, Ph), 7.66 (m, 6H, Ph), 9.43 (br, 3H), 10.38 (br, 3H).  $^{13}$C NMR (CDCl$_3$): $\delta$ 20.8, 42.0, 51.2, 60.2, 128.5, 129.4, 129.5, 136.0.  Anal. calcd for C$_{30}$H$_{45}$N$_4$Cl$_3$: C, 63.44; H, 7.93; N, 10.36.  Found: C, 63.75; H, 8.02; N, 9.73.

$(S,S,S)$-Azaphosphatrane 5(Cl):  $^{31}$P NMR (CDCl$_3$): $\delta$ -10.5;  $^1$H NMR (CDCl$_3$): $\delta$ 1.40 (d, 9H, $J = 6.8$ Hz), 2.95 (br, 3H), 3.21 (br, 3H), 3.42 (br, 3H), 3.80 (br, 3H), 4.47 (dq, 3H, $J = 18.4$ Hz, $J = 6.4$ Hz), 5.93 (d, 1H, $J = 500$ Hz), 7.23-7.40 (m, 15H, Ph);  $^{13}$C NMR (CDCl$_3$): $\delta$ 18.7 (d, $J = 5.2$ Hz), 34.2 (d, $J = 7.1$ Hz), 46.5 (d, $J = 8.2$ Hz), 53.7 (d, $J = 17.0$ Hz), 126.2, 127.8, 129.0, 141.8 (d, $J = 4.4$ Hz).  MS (ESI): m/z 487.3 (cation).  Anal. calcd for C$_{30}$H$_{42}$N$_4$OPCl: C, 66.60; H, 7.77; N, 10.36.  Found: C, 66.75; H, 7.88; N, 10.35.

$(S,S,S)$-Proazaphosphatrane 6:  $^{31}$P NMR (C$_6$D$_6$): $\delta$ 126.5;  $^1$H NMR (C$_6$D$_6$): $\delta$ 1.40 (d, 9H, $J = 6.8$ Hz), 2.95 (br, 3H), 3.21 (br, 3H), 3.42 (br, 3H), 3.80 (br, 3H), 4.47 (dq, 3H, $J$
= 18.4 Hz, $J = 6.4$ Hz), 5.93 (d, 1H, $J = 500$ Hz), 7.23-7.40 (m, 15H, Ph); $^{13}$C NMR ($C_6D_6$): $\delta$ 18.7 (d, $J = 5.2$ Hz), 34.2 (d, $J = 7.1$ Hz), 46.5 (d, $J = 8.2$ Hz), 53.7 (d, $J = 17.0$ Hz), 126.2, 127.8, 129.0, 141.8 (d, $J = 4.4$ Hz). HRMS (EI) calcd for $C_{30}H_{39}N_4P$ 486.2912, found 486.2816.

(S,S,S)-Proazaphosphatrane oxide 7: $^{31}$P NMR (CDCl$_3$): $\delta$ 22.0; $^1$H NMR (CDCl$_3$): $\delta$ 1.54 (d, 9H, $J = 7.2$ Hz), 2.30-2.50 (m, 6H), 2.60-2.90 (m, 6H), 5.22 (dq, 3H, $J = 9.2$ Hz, $J = 6.8$ Hz), 7.19-7.58 (m, 15H); $^{13}$C NMR (CDCl$_3$): $\delta$ 19.1 (d, $J = 1.9$ Hz), 43.9 (d, $J = 3.3$ Hz), 52.4, 55.1 (d, $J = 5.9$ Hz), 126.8, 127.6, 128.1, 144.4 (d, $J = 2.9$ Hz). HRMS (EI) calcd for $C_{30}H_{39}N_4OP$ 502.2862, found 502.2860. Anal. calcd for $C_{30}H_{39}N_4OP$: C, 71.71; H, 7.77; N, 11.16. Found: C, 71.23; H, 7.92; N, 10.98.

(S,S,S)-Tris(2)-(α)-methylbenzylcarbamoylmethyl)amine 9: $^1$H and $^{13}$C NMR data compared favorably with that reported in reference 23 (Inorg. Chem. 1997, 36, 3210).

Azide 18: $^1$H NMR (CDCl$_3$): $\delta$ 3.20 (dd, 1H), 3.31 (s, 3), 3.49 (dd, 1H), 4.36 (dd, 1H), 7.30-7.41 (m, 5H, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 5.65, 56.96, 83.29, 126.79, 128.53, 128.82, MS (Cl): 195 (M+NH$_4^+$), 138.73, 121.
CHAPTER 6. \([\text{O} = \text{P}(\text{i-PrNCH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NCH} \cdot \text{CH}_3)]^+\): NOVEL EFFECT OF QUATERNIZATION ON THE STRUCTURAL METRICS OF THE BICYCLIC CAGE

A paper published in the Heteroatom Chemistry, 1999, 10, 255.

Xiaodong Liu, Brad Logsdon, Robert A. Jacobson and John G. Verkade*

Abstract

The title cation features the longest distance between the bridgehead atoms (3.56 Å) so far recorded for phosphatrane cages despite a non-tetrahedral CN\text{bridgehead}C angle (~114°). The 70.8° N\text{bridgehead}CCN torsion angles in the bridging moieties produces a substantial twist along the C\text{3} axis of the structure that does not easily allow racemization of the cage. The resulting rigidity of the twisted cage gives rise to AB patterns for the methylene protons of this cation and its analogues.

Introduction

Cage structures of type A (pro-azaphosphatranes) have been the subject of intense study in our laboratories in recent years because of their unusual phosphorus basicity, their remarkable catalytic activity in a variety of synthetically useful reactions, and the architectural diversity they display in the presence of electron pair acceptors. Compounds of type A possess P-N\text{ax} distances (3.29 Å, R = i-Pr\text{1}; 3.36 Å, R = SiMe\text{3}) that are 2% to
approximately 0% shorter than the sum of the P-N$_{ax}$ van der Waals radii (3.35 Å) and axial nitrogens with virtually trigonal planar geometries attributable to steric rather than electronic reasons (see later). Pro-azaphosphatranes of type A fully transannulate to structures of type B (azaphosphatranes) with P-N$_{ax}$ bond lengths that are 40 ± 2% shorter than the sum of the P-N van der Waals radii when Z = H$^+$ [2.0778(4) Å, R = H; 1.967(8) Å, R = Me$^-$; 1.964(2) Å, R = i-Pr$^-$] or Cl$^+$ [1.937(8)Å, R = Me$^-$]. Increasingly longer P-N$_{ax}$ distances are observed in B (R = Me) in the order Z = H$^+$ < MeSC(NPh)$^+$ < HPhN$^+$ < MeS(S)C$^+$ < Me$^+$ < S$_2$C < 1/2Cl$_2$Hg < O < S < cis-Br(OC)$_2$Re until at Z = 1/2trans-Cl$_2$Pt a maximum of 3.33 Å is reached, which substantially matches the van der Waals radii sum.

The exceedingly strong Lewis basicity of non-ionic bases of type A ($pK_a$ of B (R = Me) = 32.9 in CH$_3$CN) has been utilized by our group to improve substantially the synthesis of pyrrois,$^9$ oxazoles,$^9$ porphyrins,$^9$ α-C-acylaminoacids$^8$ a chiral fluorescing agent,$^{10}$ alkenes via dehydrohalogenation reactions$^{11}$ and alkylated products of active methylene substrates.$^{12}$ It has been used by others for the improved synthesis of isoindoles from nitroaromatics$^{13}$ and as a thermal stabilizer for dinitramide salts used as propellent oxidizers.$^{14}$ The flexibility of the transannular distance in A has been shown by us to play a crucial role in its ability when R = Me to act as a superior catalyst for the protective silylation of alcohols,$^{15}$ the synthesis of isocyanurates from isocyanates,$^{15}$ the synthesis of α,β-unsaturated nitriles$^{17}$ and also as a very efficient promoter of alcohol acylation by anhydrides.$^{18}$ Others have discovered that A is a useful catalyst for anionic ring-opening polymerization of lactams to nylons.$^{19}$ The question of when bond formation occurs as the transannulation distance decreases has also been addressed.$^{20}$

Only where Z = O or S have species of type C been found, though none have been subjected to structural analysis by X-ray means until now. Compounds 1a and 2a were reported earlier by us to form as a mixture with their regioisomers 1b and 2b, respectively, when the corresponding alkyl iodide was added to the parent proazaphosphatrane wherein Z
= S. The upfield $^{31}\text{P}$ chemical shifts of 1b and 2b suggested that transannulation is present in these compounds. When analogous reactions were carried out for the corresponding unquaternized parents (R = Me or i-Pr) wherein Z = O, only one regioisomer was obtained in each case, namely, 3-6 according to NMR spectroscopic analysis. Here we report on the structural metrics for 3 which we were able to obtain recently by means of an X-ray diffraction study.

**Results and Discussion**

Although quaternization of N$_{ax}$ in forming 3 was expected to produce an elongation of the cage, it was not clear at the outset whether a bridgehead nitrogen in a bicyclic molecule of this type could assume at least a nearly tetrahedral geometry. Thus the virtually planar geometry of N$_{ax}$ in A is attributable to van der Waals repulsions among the hydrogens on the methylene groups adjacent to the N$_{ax}$ and such repulsions would presumably be intensified by downward pyramidalization of N$_{ax}$ upon attack of an electrophile. Indeed, the CN$^\text{C}$ angle of 3 [avg 113.9(10)$^\circ$], whose structure is shown in Figure 1, is substantially greater than the tetrahedral angle. Although this result is consistent with augmentation of the aforementioned van der Waals repulsions, other more subtle strain-inducing geometry changes may also be occurring.

It is interesting to observe that the P-N$_{ax}$ distance in 3 (3.56 Å) is 6% longer than the van der Waals sum, and that this P-N$_{ax}$ distance constitutes a record axial elongation for phosphatrane cages. This elongation over the P, N van der Waals radii contrasts the 2.7%
shortening of this distance $[3.564(7) \, \text{Å}]$ over the Si,N van der Waals sum in the recently reported structure of $\{\text{trans-}(\text{PPh}_3)_2\text{Os(O)Cl}[\text{Si(OCH}_2\text{CH}_2)_3\text{NMe}])\text{CF}_3\text{SO}_3\}$. However, the CN$_{\alpha}$C angle in this complex [avg. 113.9°$^{23}$] is essentially the same as in 3 and this is probably so for the same reason(s) as it is in the [HC(CH$_2$CH$_2$)$_3$NH]$^+$ cation wherein this angle has an average of 115.5° and the CC$_{\text{bridgehead}}$C angle averages 113.9°$^{25}$.

![Diagram](https://via.placeholder.com/150)

Comparison of the structure determined for a parent analogue of 3, namely, 7, reveals that the NPN angle of 3 [avg. 106.2(5)°] is within experimental error of that of 7 [avg. 107.6(1)°$^{24}$] whereas the CN$_{\alpha}$C angle decreases by ca 6° upon quaternization of N$_{\alpha}$. The CN$_{\alpha}$C angle decrease from 7 to 3 causes a concomitant enlargement of the N$_{eq}$CC angle by ca 3° while the CCN$_{\alpha}$ angle remains constant within experimental error [i.e., 3σ(esd)]. The decrease of ca. 3° seen in the internal PN$_{eq}$C angle from 7 to 3 may be associated with the presence of the more bulky i-Pr group on N$_{eq}$ in the latter. A major consequence of the CN$_{\alpha}$C angle decrease in 3 is the induction of a twist of the cage (avg. N$_{\alpha}$CCN$_{eq}$ torsion angle = 70.8°) that is larger than that in 7 (avg. 58.2°). The inflexibility, with respect to a racemizing twisting motion along the C$_2$ axis, that results from these torsional angles of the bridges of 3-6 gives rise to the appearance of AB patterns for the bridging-methylene protons in the $^1$H NMR spectra of these compounds.$^6$ These rigid structures are quite robust and in the case of 3, the AB pattern persists up to 80 °C. Moreover, in the $^1$H NMR spectrum of 3, two sets of CH(CH$_3$)$_2$ protons are also observed. We also observed that O=P(i-PrNCH$_2$CH$_2$)$_3$N, the unquaternized parent of 3 is a good catalyst for the protective silylation of alcohols.$^{26}$ By contrast, its quaternized analogue 3 displays no detectable catalytic
properties in such reactions. Because the positive charge in 3 is localized at the opposite end of the cage from the active silylation site, which is the phosphoryl oxygen, we tentatively conclude that the catalytic activity of the unquaternized parent is at least in part associated with a flexibility of the cage that permits some degree of transannulation in the silylated intermediate 8.

**Experimental Section**

Compound 3, prepared according to our preparation reported earlier, was recrystallized from a CH$_3$CN solution at room temperature by allowing ether vapor to diffuse into it. After 48 hours, crystals suitable for X-ray diffraction were obtained.

A crystal of approximate dimensions 0.2 mm x 0.2 mm x 0.2 mm was arbitrarily oriented on a glass fiber. Data were collected on a Siemens P4 computer-controlled diffractometer with MoKα radiation (0.71073 Å). Cell constants and an orientation matrix for data collection were obtained from a least squares refinement using 38 setting angles. The data were collected at room temperature using a variable omega scan. Three representative reflections were measured for every one hundred reflections collected to check the stability of the crystal. No significant decay was observed. Due to the rapid loss of intensities as 2θ was increased, reflections were collected only to 2θ = 45°. Lorentz polarization corrections were applied to the data but no absorption correction was applied because of the small value of μ. The structure was solved by a combination of heavy atom methods and direct methods and was refined using SHELXL-93. All non-hydrogen atoms were refined anisotropically.

Scattering factors were taken from Cromer and Waber. All calculations were performed on a PC with a Pentium processor. Details of the data collection and refinement of this structure are reported in Table 1. Atomic coordinates, displacement parameters, bond
lengths, and angles for the structure have been deposited at the Cambridge Crystallographic Data Center.

Acknowledgments We thank the Donors of the Petroleum Research Fund administered by the American Chemical Society for a grant supporting this work. We also are grateful to the Ames Laboratory of the DOE for financial support.

References


### Table 1. Crystallographic Data for 3.

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$^aR = [\Sigma(F_o - k|F_i|)/\Sigma F_o]$, $R_w = [\Sigma w(F_o - k|F_i|)^2/\Sigma w F_o^2]^{1/2}$. $^b$GOF = $[\Sigma w(F_o - k|F_i|)^2/(N_{\text{observations}} - N_{\text{variables}})]^{1/2}$. 
Figure 1. ORTEP view of 3 (Ellipsoids are drawn at the 50% probability level).
CHAPTER 7. ELECTRON RICH O=PR₃ COMPOUNDS: CATALYSTS FOR ALCOHOL Silylation

A paper submitted to the Heteroatom Chemistry

Xiaodong Liu and John G. Verkade

Abstract

The catalytic effect of a group of R₃P=O compounds was studied in a mild procedure for the silylation of primary alcohols, secondary alcohols, hindered secondary alcohols and of hindered phenols, in the presence of t-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCl). It was found that R₃P=O is an efficient catalyst in such reaction when R is a good electron donating group, such as Me₂N or n-Bu and as NMe(CH₂) in N(CH₂CH₂NMe)₃P=O (3). However, R₃P=O is a weak or ineffective catalyst when R is a poor electron donating group, such as Ph or O-n-Bu or as CH₂N-o-CH₂C₅H₄N in N(CH₂CH₂N-o-CH₂C₅H₄N)₃P=O. Compound 3, synthesized by oxidation of commercially available N(CH₂CH₂NMe)₃P, displayed the best catalytic properties for alcohol silylation in terms of efficiency, stability and safety.

Introduction

Protection of the organic hydroxyl group is necessary for avoiding undesired reactions with oxidizing agents and electrophiles during the course of multi-step syntheses. Among the many trialkylsilyl reagents used to protect this functionality, t-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCl) are two of the most popular. A variety of methods has been reported for the derivatization of alcohols with the TBDMS and TBDPS moieties. These reactions have been most satisfactorily achieved by reacting the alcohol with a molar excess of imidazole using dimethyl formamide (DMF) as a solvent, or with catalysts such as DMAP, 1,1,3,3-tetramethylguanidine and ethyldiisopropylamine.
More recently, the silylation of primary and secondary alcohols in 69-99% yields using TBDPCl in DMF with catalysts, such as AgNO₃, NH₄NO₃, or NH₄ClO₄ has been described.³⁴

Proazaphosphatranes of type 1⁶ have been shown to be very strong nonionic bases that function as superior deprotonating agents,⁷ as a superior catalysts⁸ and as efficient promoters⁹ in a variety of synthetically useful organic transformations. For the very effective and mild silyl protection of a wide variety of OH-containing organic substrates catalyzed by 1⁸b a mechanism involving intermediates 2a and 2b detected with 1 was postulated on the basis of NMR evidence. In an earlier study of the chemistry of 3, we discovered that the phosphoryl group of this compound is capable of catalyzing the conversion of isocyanates to isocyanurates¹⁰ and that it is also a good donor to Lewis bases including silanes, forming cationic adducts such as 4a-4f.¹¹ This prompted us to evaluate the catalytic activity of 3 in alcohol silylation reactions.

Herein we report on the silyl protection of a wide variety of alcohols, including primary alcohols, secondary alcohols, hindered secondary alcohols and of hindered phenols using 3, O=P(NMe₂)₃ and O=P(n-Bu)₃ as the catalysts (equation 1) under mild conditions. Among these catalysts, 3 displays the best overall catalytic properties in terms of efficiency, stability and safety. A comparison of the efficiency of these catalysts with the commonly used catalyst
ROH (1°, 2° and phenols) – catalysis or other O=PR₃ catalysts

MeCN, Et₃N, rt - 35°C

$t$-BuMe₂SiCl or $t$-BuPh₂SiCl

$t$-BuMe₂SiOR → $t$-BuMe₂SiOR + Et₃NHCl

DMAP₁² is also presented. The phosphine oxides O=PPh₃ and O=P(O-n-Bu) and 5₁² were found to be poor to nonfunctioning catalysts for alcohol silylation.

Results and Discussion

In preliminary NMR monitoring reactions (see Experimental Section), we found that TBDMS silylation of benzyl alcohol (6) is accelerated in the presence of 3. Thus in CD₃CN, 2.1 h was required to effect 99% silylation of 6 (according to ¹H NMR integration) in the presence of 0.5 equiv of 3, while 10.5 h was required to obtain the same conversion in the absence of a catalyst. When O=P(NMe₂)₃, an acyclic analogue of 3, was used as the catalyst in CD₃CN in the same reaction, only 1.3 h was required for 99% conversion. In the nonpolar solvent C₆D₆, 11 h is required for 99% silylation of 6 using 0.5 equiv of 3 as a catalyst while no reaction was observed during 12 h in the absence of a catalyst. When the coordinating solvent DMF was used in the presence of 0.5 equiv of 3, silylation of 6 was complete in 1.9 h. Although DMF seemed to be a somewhat better solvent than CH₃CN in terms of reaction rate, CH₃CN was the solvent of choice because of its lower boiling point and its ability to give yields comparable with those obtained in DMF. For a more complete comparison, reactions were carried out on a preparative scale for three different hydroxyl compounds including
primary alcohol 6, secondary alcohol 10 and hindered phenol 14 (Table 1) in the presence of one of the six phosphoryl compounds 3 shown in this table. In addition, DMAP, a commonly used silylation catalyst \(^2\) was also compared. The results are listed in Table 1.

Table 1 shows that O=PR\(_3\) wherein R is a good electron donating group, such as n-Bu, NMe\(_2\) or NMe(CH\(_2\))\(_2\) (in 3), considerably accelerates silylation for all three substrate alcohols whereas the lack of a good electron donating group leads to a poor catalyst (O=PPh\(_3\) and 5) or an ineffective one O=P(O-n-Bu)\(_3\)). In general, the catalytic efficiency for alcohol silylation of these phosphoryl compounds follows the increasing electron donor ability of the phosphoryl oxygen in the order O=P(O-n-Bu)\(_3\) < O=PPh\(_3\) < 5 < O=P(n-Bu)\(_3\), O=P(NMe\(_2\))\(_3\), 3. Of all the phosphoryl compounds tested, 3 seems most effective, although the advantage is admittedly somewhat marginal compared with O=P(n-Bu)\(_3\) or O=P(NMe\(_2\))\(_3\). We believe that the slight superiority of 3 in this respect may be associated with the stronger donor character of the oxygen in this compound than that in its acyclic analogue O=P(NMe\(_2\))\(_3\) owing to an N\(_{ax}\)→P transannular interaction that can occur in an intermediate or transition state.\(^1\) However, the P=O group is more sterically hindered in the rigid cage structure of 3 by the upwardly directed Me groups each of which resides on a planar nitrogen. Such a bulk effect may compromise the higher character of 3 to some extent. Thus 3 does not show a remarkable advantage over its acyclic analogues O=P(n-Bu)\(_3\) and O=P(NMe\(_2\))\(_3\). The poorer performance of compound 5 is attributed to the withdrawing nature of the pyridyl groups in the CH\(_2\)NCH\(_2\)-o-C\(_6\)H\(_4\)N moieties and the large cone angle swept out by the CH\(_2\)-o -C\(_6\)H\(_4\)N segment of the CH\(_2\)-o -C\(_6\)H\(_4\)N groups.

Compared with 3, the catalytic activity of DMAP in the silylation of alcohols is about the same for the primary alcohol 6 and the hindered phenol 14, but less efficient for the hindered secondary alcohol 10 (see later for additional discussion). At room temperature, silylations of 6, 10, and 14 using 2 equiv of imidazole were faster than the combination of 10 mol\% 3 and 1.1 equiv of Et\(_3\)N (98% conversion vs 90% for 6 in 0.4 h, 97% vs 88% for 10 in
4 h, and 67% vs 50% for 14 in 8 h, respectively). However, when 10 mol% of imidazole and 1.1 equiv of Et₃N was used, much slower conversions at room temperature were observed than with 10 mol% of 3 and 1.1 equiv of Et₃N (67% vs 90% for 6 in 0.4 h, 53% vs 88% for 10 in 4 h, and 25% vs 50% for 14 in 8 h, respectively). Thus, on a mole-for-mole basis, 3 is more efficient than imidazole. That a base such as Et₃N as well as a catalyst is necessary for efficient silylations was shown by the lack of detectable silylation of 6 by TBDMSCl in the presence of 10 mol% of 3 or O=P(NMe₂)₃ when Et₃N was absent.

In Table 2, it is shown that of 3 catalyzes the TBDMS silylation of primary alcohols 6-8 and phenols 12 and 13 within 0.5 h at room temperature in excellent isolated yields (>91%) while the secondary alcohols 9-11 require a longer reaction time (6 h) to give excellent product yields (>91%) of silylated products. The hindered phenol 14 gave only a moderate yield of silyl ether (55%) in 12 h. The tertiary alcohol 15 is resistant to silylation with TBDMSCl, giving no detectable yield after 48 h. For each substrate, silylations catalyzed by DMAP and in the absence of catalyst were also conducted for comparison. It should be noted that for the primary alcohol 6, the less hindered secondary alcohol 11, and phenols (12-14), 3 shows about the same efficiency as DMAP. However, for the primary alcohols 7 and 8, and the hindered secondary alcohols 9 and 10, 3 is somewhat marginally more efficient than DMAP. Except for the TBDMS silylation of phenols 12 and 13, silylations in the absence of catalysts proceed in considerably lower conversions (20-70%).

Table 3 shows that with 0.10 equiv of 3 as a catalyst at 35°C, the primary alcohols (6 and 7) and phenol (12 and 13) are silylated with TBDPSCI within 6 h and 4 h, respectively, in high conversions (95-99%), while the secondary alcohol 9 is more difficult to silylate, giving 74% conversion over 24 h. It is noted that 11 and the acid-sensitive alcohol 8 require longer reaction times but give good conversions (94% and 97%, respectively) to silylated products. The hindered secondary alcohol 10 is reluctant to silylate with TBDPSCI, giving only a 30% conversion of product in 24 h.
Although several mechanistic pathways can be considered that rationalize the ability of electron rich O=PR₃ compounds to catalyze hydroxyl silylation, we believe the one shown in Scheme 1 is the most plausible on the basis of present evidence. This pathway could be facilitated in the case of the somewhat superior catalyst 3, by transannulation of the bridgehead nitrogen to the phosphorus to form intermediates B and/or C wherein phosphorus is five-coordinate. An analogous pathway has been suggested as a working hypothesis in the ring opening of epoxides with SiCl₄ promoted by O=P(NMe₂)₃. Further support for the pathway in Scheme 1 comes from our previously reported isolation and characterization of 4e and 4f.¹¹ ¹H and ³¹P NMR spectroscopic data suggest the presence of transannulation in these compounds as well as in 4e and 4d.¹¹ Further supporting the cycle in Scheme 1 in which ion formation is involved, is the fact that the catalyzed silylations occur in the polar solvent CH₃CN. By contrast, silylation is much slower in benzene (see above). There is considerable evidence in the
literature indicating that pentacoordinate silicon compounds tend to be more reactive to nucleophilic substitution than four-coordinate silicon species.\textsuperscript{14} This evidence also supports the cycle in Scheme 1.

**Conclusion**

Compounds of the type $O=PR_3$, in which $R$ is a good electron donating group are excellent catalysts for alcohol and phenol protective silylations under mild conditions using TBDMSCl and TBDPSCI. The advantages of these catalysts are (1) The yields or conversions of the silylated alcohols and phenols are generally superior, (2) Acetonitrile can be used instead of the often used but comparatively nonvolatile DMF, (3) The $O=PR_3$ catalysts are highly stable under the reaction conditions employed, (4) These catalysts are soluble in both polar and nonpolar solvents, and (5) 3, though more expensive than $O=P(NMe_2)_3$, can be recovered in good yield and is less volatile than $O=P(NMe_2)_3$, which is a well-known nasal carcinogen and should be avoided if a substitute is available.

**Experimental Section**

CH$_3$CN and CD$_3$CN were distilled from CaH$_2$, and Et$_2$O and benzene were dried with sodium. All solvents were freshly distilled before use and all reactions were carried out under Ar. Catalysts 3\textsuperscript{6} and 5\textsuperscript{12} were prepared according to methods developed in our laboratories. Silica gel sheets were purchased from J. T. Baker. All other chemicals were purchased from Aldrich Chemical Co. and were used as received.

**NMR monitoring experiments for the catalytic silylation of 6.** In a 5 mm NMR tube was dissolved 0.05 mmol of catalyst (when catalysts were used) in 0.75 mL of solvent (CD$_3$CN, C$_6$D$_6$ or DMF). To this solution was added 0.11 mmol of $t$-BuMe$_2$SiCl followed by the addition of NEt$_3$ (15 $\mu$L, 0.11 mmol). After shaking the tube for 2 min, 6 (10 $\mu$L, 0.10 mmol) was added followed by recording $^1$H NMR spectra at various time intervals.
The reaction temperature was 20 °C. The time interval between each spectrum was 1 min for spectra 1-20, 10 minutes for spectra 21-30, 30 minutes for spectra 31-40, 1 hour for spectra 41-45, and 4 hours for each spectrum thereafter. One minute was required to complete each spectrum.

**General procedure for silylations with t-BuMe₂SiCl TBDMSCl or t-BuPh₂SiCl TBDPSCI.** In a 10 mL test tube capped with a rubber septum was dissolved 0.1 equiv of a catalyst in 2 mL of CD₃CN. To this was added 1.0 mmol of the alcohol followed by the addition of NEt₃ (0.15 mL, 1.1 mmol). After stirring the mixture for 5 min, 1.1 mmol of the silylating agent was added with continued stirring at room temperature (25°C) for t-BuMe₂SiCl and at 35 °C for t-BuPh₂SiCl. 'H NMR spectra were taken to obtain the conversion based on 'H NMR integration of characteristic resonances, and the product identity was confirmed by GC-mass spectroscopy. After the reaction time stated in the tables, 0.02 mL of H₂O was added with stirring. The mixture was filtered, and the residue was washed with Et₂O (2 x 5 mL) followed by evaporating ca 95% of the solvent under vacuum. The resulting crude silyl ether was purified chromatographically on a silica gel column using a mixture of 95% hexane and 5% ethyl acetate as the eluent. The product was obtained upon drying over anhydrous MgSO₄ and evaporation of the eluent. The identifying 'H and ¹³C NMR spectra compared favorably with those in the literature given Supporting Information Available.

**General procedure for the recovery of 3.** After chromatographic separation of the silyl ether product, the silica gel column was washed with an additional 100 mL of a solution of 90% hexanes and 10% ethyl acetate followed by washing with 100 mL of CH₃OH. After collecting the pure CH₃OH fraction and evaporating the solvent under vacuum, 3 was recovered as a white solid in 60-75% yields. The ³¹P, ¹H and ¹³C NMR spectra were identical to those of an authentic sample of 3.
Acknowledgment  The authors are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the ISU Center for Advanced Technology Development for grant support of this research.

Supporting Information Available: $^1$H and $^{13}$C NMR spectra data and mass spectral molecular weights (7 pages).

References


12. Liu, X.; Verkade, J. G. to be published.

Table 1. Comparison of seven catalysts for alcohols with TBDMSCl.\textsuperscript{a}

<table>
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<tr>
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<th>O=PPPh\textsubscript{3}</th>
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<th>O=P(n-Bu)\textsubscript{3}</th>
<th>O=P(NMe\textsubscript{2})\textsubscript{3}</th>
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<th>DMAP</th>
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<td>63</td>
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\textsuperscript{a}See Experimental Section for conditions. \textsuperscript{b}Based on \textsuperscript{1}H integrations in which the error limit is about 1% absolute. Conversions are reproducible within this error limit for at least two separate runs on each substrate.
Table 2. Comparison of 3 and DMAP in alcohol silylation with TBDMSCl.\(^a\)

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<th>DMAP(^d)</th>
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\(^a\)See Experimental Section for conditions. \(^b\)Based on \(^1\)H integrations of characteristic resonances. The conversions are reproducible for at least two separate runs on each substrate. The error limit is about 1% absolute. \(^c\)After column chromatography, the purity was >95% by \(^1\)H NMR spectroscopy. The yields are the highest values observed in each case. \(^d\)10 mol% catalyst. \(^e\)No detectable reaction.
Table 3. TBDPSCI Alcohol silylations catalyzed by 3.\textsuperscript{a}

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<td>4</td>
<td>98</td>
</tr>
<tr>
<td>(\text{C}(\text{O})\text{H}_2\text{OH} )</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}See Experimental Section for conditions. \textsuperscript{b}Based on \(^1\text{H}\) integrations in which the error limit is about 1% absolute. Conversions are reproducible within this error limit for at least two separate runs on each substrate. New compounds were characterized by \(^1\text{H}, ^{13}\text{C}\) NMR, and HRMS(EI) spectroscopies. \textsuperscript{c}10 mol\% catalyst. \textsuperscript{d}No detectable reaction.
CHAPTER 8. P(MeNCH₂CH₂)₃N: A HIGHLY SELECTIVE REAGENT FOR SYNTHESIZING TRANS EPOXIDE FROM ARYL ALDEHYDES

A paper to be published in the *Journal of Organic Chemistry*

Xiaodong Liu and John G. Verkade

Abstract

In contrast to its acyclic analogue P(NMe₂)₃ (1), which in benzene at room temperature reacts with two aryl aldehyde molecules bearing electron withdrawing groups to give the corresponding diaryl epoxide as an isomeric mixture (trans/cis ratios: 72/28 - 51/49), P(MeNCH₂CH₂)₃N (2a) under the same reaction conditions is found to be a highly selective reagent that provides epoxides with trans/cis ratios as high as 99/1. These reactions are faster with 2a, because its phosphorus atom is apparently more nucleophilic than that in 1. Thus it is found that 2a more easily forms 1:1 and 1:2 adducts with one or two molecules of aldehyde, respectively. These adducts apparently are intermediates in the formation of the product epoxide and the corresponding phosphine oxides of 1 and 2a.

Introduction

Epoxides are important starting materials in organic synthesis. The most frequently used method to generate them is to oxidize olefins with peroxides. However, for the preparation of epoxides with sensitive structural features, this method is not always applicable. For converting aryl aldehydes possessing electron withdrawing groups to the corresponding epoxides, Mark *et al.* found that P(NMe₂)₃ (1) is a reagent that provides a
simple and mild approach often leading to high yields of product. Moreover, this transformation tolerates sensitive functional groups (such as pyridyl) that oxidative methods do not. The use of 1 has therefore constituted a practical synthetic approach. Although trans epoxides are always major products with reagent 1, stereoselectivity is usually poor since trans/cis ratios between 2.6/1 and 1.1/1 are generally realized, depending on the substrate. Thus, finding a stereoselective synthesis of epoxides from aryl aldehydes has remained challenging.

\[
\begin{array}{c}
\text{label} \\
\text{a} \\
\text{b} \\
\text{c} \\
\text{d} \\
\text{e}
\end{array}
\]

In recent years we have been exploring the chemistry of proazaphosphatrane 2a-e, some of which are proving to be exceedingly potent catalysts, promoters and strong nonionic bases that facilitate a variety of useful organic transformations. For example, 2a is an efficient catalyst for the trimerization of aryl and alkyl isocyanates that function as additives in the manufacture of Nylon-6, for the protective silylation of a wide variety of sterically hindered and deactivated alcohols, and for the acylation of alcohols. Proazaphosphatrane 2a is a much stronger base than DBU, a commonly used nonionic base in organic synthesis. Thus 2a is a superior base for the synthesis of porphyrins, the dehydrohalogenation of secondary and tertiary halides, and for the synthesis of a chiral fluorescence agent. As a result of these and other emerging applications, 2a has become commercially available.

\[
\begin{align*}
2 \text{ Ar-CHO} + \\
\text{2a} \\
\text{RT/C}_6\text{H}_6 \\
\rightarrow \\
\text{O} \\
\text{Me} \\
\text{Ar} \\
\text{Ar} \\
\text{3}
\end{align*}
\] (1)
We report herein a facile, efficient, and highly selective procedure for the synthesis of trans epoxides from aryl aldehydes bearing electron-withdrawing groups. For comparison of conversions and stereoselectivity, both 1 and 2a were used in parallel reactions. We also find that the more bulky proazaphosphatrane 2b does not lead to epoxides, although color changes do occur.

**Results and Discussion**

That 2a becomes oxidized to 3 in the reaction of two aryl aldehyde molecules in benzene to give the corresponding epoxide was shown by $^{31}$P and $^1$H NMR spectroscopic analysis of a C$_6$D$_6$ solution of a 2.0/1.0 equiv ratio of 9a to 2a (Table 1). Only one $^{31}$P resonance at 20.2 ppm corresponding to oxide 3$^{10}$ was observed after 12 h at room temperature. In the $^1$H NMR spectrum, the CHO proton resonance also disappeared after 12 h and a singlet at 3.95 ppm corresponding to the oxirane proton was observed (99% conversion). By comparison of $^1$H and $^{13}$C NMR spectroscopic data in the literature, the epoxide 9b present in the reaction mixture was found to be almost pure trans (trans/cis ratio = 98/2). Simply filtering the reaction mixture and washing the filtered solid with cool benzene afforded $^1$H-NMR spectroscopically pure trans-9b in 75% yield. For comparison, the use of 1 under the same conditions led to a considerably slower reaction and lower stereoselectivity (85% conversion with a trans/cis ratio of 69/31). The isolated yield of epoxide in both bases, however, was virtually the same (74% with 1 and 75% with 2a) because a substantial amount of starting material is converted to intermediate adducts with 2a while no such adducts survive in the reaction with 1 (see later). The improved stereoselectivity realized with 2a prompted us to evaluate this reagent with the substrates in Table 1. Compound 1 was used in parallel reactions to obtain conversions, yields and trans/cis ratios for comparison with the data realized with 2a, and these data are also included in this table.
Table 1 reveals that substrates 12a, 13a and 14a afforded no detectable or very slow reaction rates, respectively, with 0.5 equiv of 1, although a 28% conversion to product was realized with 0.5 equiv of 2a (trans/cis ratio = 92/8) in the case of substrate 12a. Faster reactions were observed for substrates 4a-11a with 0.5 equiv of 2a (95-100% conversions) than those carried out with 0.5 equiv of 1 (5-95% conversions). However, the faster conversions with 2a did not necessarily lead to higher product yields, owing to formation of comparatively robust 1:2 adducts of 2a and the aldehyde substrate (see later), which gave rise to higher conversions of starting materials but to lower isolated yields of epoxide. Thus for substrates 4a, 6a, and 7a, compound 1 gave higher isolated yields than with 2a although the conversions were lower.

For all the substrates tested except 13a and 14a (which did not react), compound 2a gave excellent stereoselectivity (trans/cis ratios: 92/8 - 99/1) based on 1H NMR integration of the reaction mixtures, while 1 gave isomeric mixtures (trans/cis ratios from 51/49 to 72/28) under the same conditions. The reactions were also substrate dependent: for the aryl aldehydes with electron-withdrawing groups (i.e., 4a-7a), nearly quantitative conversions (>99%) were achieved within 1 h using 2a. For the delocalized polyaromatic aldehydes (i.e., 8a-11a), high conversions (95-99%) were realized within 12-14 h with 2a. Epoxide formation was more sluggish for substrate 12a and 60 h were necessary to obtain a 28% conversion with 2a while less than 2% conversion was observed with 1. However, 2a did provide good stereoselectivity (trans/cis ratio = 92/8) despite the low conversion. In the case of ketone 13a and 14a, no detectable formation of corresponding epoxide 13b and 14b was observed even after 120 h and 24 h respectively, probably because of steric hindrance present in the substrate. Moreover, aryl aldehydes bearing electron-donating groups such as 2,5-dimethyl-benzaldehyde and 2-methoxybenzaldehyde yielded no detectable epoxide formation over two days under the same reaction conditions. These results are consistent with earlier work wherein it was shown that relatively electrophilic aldehydes promote epoxide formation. It should be noted that
although the trans/cis ratios of chromatographically purified epoxides 4b-8b were the same as those displayed by the corresponding reaction mixtures, we observed that when filtration was used to purify the product, higher trans/cis ratios were achieved for the isolated epoxides (9b-11b) than those observed for the corresponding reaction mixtures. Here, the trans-epoxides were less soluble than their cis isomers in benzene.

Scheme 1

Two reaction pathways have been considered for 1.\(^4\)\(^6\) The one put forth by Mark et al. in Scheme 1\(^4\) involves phosphorus nucleophilically attacking an aldehyde carbonyl carbon to form the 1:1 adduct 15 wherein the oxygen attacks a second molecule of the aldehyde to form the 1:2 adduct 16 (for which three resonance forms are shown). Epoxide formation would occur by carbanion attack in 16c directly on the opposite benzyl carbon to give trans epoxide, or by carbanion attack on the benzylic carbon in an S\(_{\text{N}}\)2 manner after rotation of the O-CHAr bond to give the cis epoxides. However, this mechanism was questioned by Ramirez\(^6\) who proposed an alternative pathway (Scheme 2) wherein the phosphorus in 1 first electrophilically attacks the carbonyl oxygen of the aryl aldehyde to form a 1:1 adduct (17) on the grounds that the phosphorus of 1 should exhibit an even greater tendency to electrophilically attack the
carbonyl oxygen than the phosphorus of trialkyl phosphites that were reported to give isolable adducts of type 18b in Scheme 2. Thus after 17 is formed, a second molecule of the aldehyde attacks 17 to give a mixture of erythro (18a) and threo (18b) 1:2 adducts. If the erythro form is predominant, as might be expected for steric reasons, the trans-epoxide formed by loss of the oxide of 1 should predominate over the cis product. However, 1 gave rise to poor stereoselectivity, with trans/cis ratios generally ranging from 1.1 to 2.6, probably owing to similar steric hindrance in the erythro and threo forms of the adduct formed from a variety of substituted aryl aldehydes. It was also reported that when cyclic 19 was employed instead of 1 in the reaction with 4-nitrobenzaldehyde, the corresponding 1:2 adducts containing pentavalent phosphorus (21a and 21b in Scheme 3) were isolated as a mixture in 60% yield in a 1:1 ratio.

In the present work, when 0.5 equiv 2a was allowed to react with 4a in C_6D_6 at room temperature, the ^{31}P NMR spectrum of the reaction mixture exhibited three resonances (20.6,
22.7, and 22.8 ppm) in a 20:4:1 ratio. The signal at 20.6 ppm is characteristic of the oxide and the other two are believed to be associated with the 1:1 and 1:2 adducts formed as intermediates. Mass spectroscopy (ESI) of the same reaction mixture revealed a large peak at 468 daltons corresponding to the 1:2 adduct, and a considerably smaller signal at 337 daltons attributable to the 1:1 adduct. Thus, it is reasonable to assign the large $^{31}$P NMR peak at 22.7 ppm to the 1:2 adduct and the smaller one at 22.8 ppm to the 1:1 adduct. The $^1$H NMR spectrum of the reaction mixture failed to give unambiguous evidence for the ratio of these two adducts owing to peak overlaps. These observations are consistent with the reported result from the reaction of cyclic 19 in Scheme 3 with 4-nitrobenzaldehyde to give the 1:2 adduct. However, no evidence for the formation of the 1:1 adduct was reported. Based on the $^{31}$P
NMR chemical shifts of the 1:1 and 1:2 adducts observed in our work (which are much closer to those of a P-O bonded adduct\textsuperscript{24} than to that of a carbon bonded\textsuperscript{30} adduct of 2a) the reaction pathway proposed by Ramirez\textsuperscript{6} (Scheme 2) seems to be supported by our results. Since 2a like 19 is a cyclic aminophosphine, the reaction pathway in Scheme 4 is analogous to that of 19 in Scheme 3. We also note that when more bulky substrates such as 9a were allowed to react with 0.5 equiv of 2a, similar evidence of the presence of a mono and diadduct was obtained from \textsuperscript{31}P NMR and mass (ESI) spectroscopies. However, the ratio of 3 to 1:2 adduct to 1:1 adduct was 30 : 5 : 1, implying a higher production of 9b from 9a compared with the production of 4b from 4a (Table 1). Efforts to isolate a pure adduct of 4a with 2a or of 9a with 2a in a 1:1 or 2:1 ratio at \(-78\) °C (in toluene) or room temperature always resulted in a mixture of 3, the 1:2 adduct, and the 1:1 adduct. Attempts to purify the 1:1 or 1:2 adduct by recrystallization also failed.
As mentioned earlier, when the cyclic aminophosphine 19 was allowed to react with an aryl aldehyde bearing an electron-withdrawing group, a 1:2 adduct (trans:cis ratio 1:1) was isolated. The cis-isomer isolated from this mixture refluxing in ethanol gave the trans epoxide. However, the isomeric mixture of the 1:2 adducts of 2a observed in the present work gave no evidence of decomposition in this manner under the same conditions. During silica gel column chromatographic purification, however, these adducts did dissociate to give the starting aldehyde. Attempts to improve product yields by prolonging the reaction time, changing the reaction temperature or using different solvents such as THF, toluene or CH$_2$Cl$_2$ failed. By contrast, the reaction of 1 with these aldehydes provided no detectable quantities of the corresponding 1:1 or 1:2 adducts.

Although 1 reacts with one equiv of benzaldehyde to produce a 1:1 adduct,4 aryl aldehydes bearing electron-withdrawing groups give epoxides as the dominant products and whose stereochemistry is only somewhat preferentially trans. On the other hand, when 19 was employed, an isomeric mixture of trans and cis (1:1) 1:2 intermediate adducts was obtained from which the pure cis 1:2 adduct intermediate could be isolated. The cis 1:2 adduct gave pure trans-epoxide in 86% yield but in <20% overall yield from the aldehyde. It was found in the present work that 1 reacts much more slowly with aryl aldehydes bearing electron withdrawing groups than 2a (see Table 1). Owing to the possibility of transannular interaction from the axial nitrogen to the bridgehead phosphorus in 2a, this base is stronger and perhaps more nucleophilic. Thus 2a was expected to be more reactive with an aldehyde carbonyl group than 1, and this is reflected in Table 1. It is conceivable the use of acyclic 1 or cyclic 19 for epoxide formation from aldehydes, steric differences between cis and trans 1:2 adduct intermediates are relatively small, owing to P-N bond rotation of at least one phosphorus substituent, resulting in poor stereoselectivity. On the other hand, the structure of 2a is rigid and the 1:2 adduct intermediate must adopt a less steric hindered conformation (Scheme 4). Somewhat surprisingly, the present work showed that the cis 1:2 adduct (23b) is apparently
the more stable isomer. It is speculated that the steric hindrance between the aromatic rings in 23a and the methyl groups in 2a is higher than that in 23b owing to a folding of the five-membered ring in 23b away from the methyl group on the mirror plane to an “envelope” conformation with phosphorus in the “flap” position. The greater bulk and rigidity of the intermediate 1:2 adduct of 2a than the analogue with 1 is thus perhaps responsible for the greater stereoselectivity of base 2a as shown in Table 1. However, the cause for the survival of the 1:2 isomeric intermediate adduct of 2a in refluxing ethanol remains unclear.

Interestingly, the isolated cis 1:2 adduct 21b in Scheme 3 and the almost exclusively formed analogue 23b in Scheme 4 give rise to trans epoxide. This is best understood in terms of heterolytic cleavage of a P-O bond to form a zwitterion followed by rotation about the ArC-CAr bond and subsequent nucleophilic attack of the alkoxide oxygen on the adjacent aryl carbon in an $S_N^2$ fashion to give the trans product. By inference the 1:2 adducts 21a and 23a lead to cis epoxides. This conclusion coupled with the stereoselectivity for trans epoxide in our reaction supports our assignment of the cis configuration to greatly predominant 1:2 adduct isomer 23b. Compound 2b, a more sterically hindered analogue of 2a, was also allowed to react with substrates 4a-9a under the same conditions as with 2a. Surprisingly, no epoxide products were generated according to $^1$H and $^{31}$P NMR spectroscopy. Instead, a remarkable color change from colorless to dark red was observed, which may be associated with a charge-transfer complex between the aminophosphine phosphorus as the donor and the aryl aldehyde bearing an electron-withdrawing group as the acceptor as was postulated to form as an intermediate in the reaction of 1 with aryl aldehydes. The failure of 2b to facilitate epoxide formation may well be due to the steric hindrance around the phosphorus that prevents it from nucleophilically attacking the carbonyl group of a substrate, thus restricting the interaction to charge-transfer.
Experimental Section

Benzene (C₆H₆ and C₆D₆), toluene, and THF were dried with sodium. CH₂Cl₂ was dried with CaH₂. All reactions were carried out under an Ar atmosphere. Chemicals employed were purchased from Aldrich Chemicals and were used without purification unless otherwise noted. Compounds 2a¹² and 2b¹³ were prepared according to our previously published methods. NMR, MS (ESI) and HRMS (EI) spectroscopic measurements were performed in the Instrument Services Laboratory of the Chemistry Department at Iowa State University.

General procedure for converting aryl aldehydes to epoxides with 1 or 2a. To a solution of an aryl aldehyde (2.00 mmol) in C₆D₆ (3.0 mL) at room temperature under an Ar atmosphere was slowly added a solution of 1 or 2a (1.05 mmol) in C₆D₆ (1.5 mL). The reaction was monitored by ¹H and ³¹P NMR spectroscopies. After the reaction time stated in Table 1, a ¹H NMR spectrum was recorded from which the conversion and the trans/cis ratio of the product were obtained by integration. For known compounds, these spectra were also compared with those recorded in the literature. The product epoxide was then isolated and purified by silica gel column chromatography, or filtration followed by washing (see Table 1). The identities of the purified product were confirmed by ¹H and ¹³C NMR spectroscopies. In the case of new compounds, HRMS (EI) data are also given (see Supporting Information).

Acknowledgment The authors are grateful to the Donors of the Petroleum Research Fund administered by the American Chemical Society for a grant in support of this research. The authors thank Dr. Palanichamy Ilankumaran for valuable discussions.

Supporting Information ¹H, ¹³C NMR and HRMS (EI) spectroscopic data (6 pages).
References


22. Strem Chemical Company.


Table 1. Epoxidation of Aryl-aldehydes with 1 and 2a.a

<table>
<thead>
<tr>
<th>Arylaldehyde</th>
<th>Productb</th>
<th>Reaction time (h)</th>
<th>Work-up method</th>
<th>% conversions with 2a</th>
<th>Yield with 2a (trans:cis)%</th>
<th>Yield with 1 (trans:cis)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N&lt;sub&gt;C&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>4a</td>
<td>0.5</td>
<td>col. chrom.</td>
<td>100 (98:2)</td>
<td>95 (51:49)</td>
<td>81 (51:49)</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>5a</td>
<td>0.5</td>
<td>col. chrom.</td>
<td>100 (94:6)</td>
<td>85 (56:44)</td>
<td>50 (57:43)</td>
</tr>
<tr>
<td>Br&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>6a</td>
<td>1.0</td>
<td>col. chrom.</td>
<td>99 (95:5)</td>
<td>94 (70:30)</td>
<td>69 (70:30)</td>
</tr>
<tr>
<td>N&lt;sub&gt;N&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>7a</td>
<td>0.5</td>
<td>col. chrom.</td>
<td>100 (92:8)</td>
<td>65 (63:37)</td>
<td>52 (63:35)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>8a</td>
<td>14</td>
<td>col. chrom.</td>
<td>95 (95:5)</td>
<td>&lt; 5 (53:47)</td>
<td>na (na)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>9a</td>
<td>12</td>
<td>filtration</td>
<td>99 (98:2)</td>
<td>85 (61:39)</td>
<td>74 (69:31)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>10a</td>
<td>14</td>
<td>filtration</td>
<td>98 (99:1)</td>
<td>48 (63:37)</td>
<td>37 (72:28)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>11a</td>
<td>14</td>
<td>filtration</td>
<td>96 (99:1)</td>
<td>73 (52:48)</td>
<td>64 (52:48)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>12a</td>
<td>60</td>
<td>na</td>
<td>28 (92:8)</td>
<td>&lt; 2 (na)</td>
<td>na (na)</td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>13a</td>
<td>120</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
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<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;CHO</td>
<td>14a</td>
<td>24</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

Reactions were carried out in C<sub>6</sub>D<sub>6</sub> or C<sub>6</sub>H<sub>6</sub> at room temperature under Ar. Identification was made by comparing 1H and 13C NMR spectroscopic data with those in the references indicated. New compounds were
Table 1. (continued)

fully characterized by $^1$H, $^{13}$C NMR and HRMS (EI) spectroscopies. *Conversions were determined by $^1$H NMR integration of signals of the methine proton in the epoxide product to the aldehyde proton in corresponding reactant. *The trans:cis ratios were obtained by integrating the relevant $^1$H NMR signals in the reaction mixture, or of the isolated epoxide isomer mixture (see Results and Discussion). *Isolated yields were obtained by the indicated methods and purity was determined by $^1$H NMR spectroscopy. *See reference 4. *Silica gel column chromatography using a mixture of hexanes (95%) and ethyl acetate (5%) as the eluent. *Minami, T.; Matsuzaki, N.; Ohshiro, Y.; Agawa, T. J. Chem. Soc. Perkin Trans. 1, 1980, 1731. *Clark, K. B.; Bhattacharyya, K.; Das, P. K.; Scaiano, J. C.; Schaap, A. P. J. Org. Chem. 1992, 57, 3706. *See reference 23. *Since the product is insoluble in benzene, filtration followed by washing with benzene and drying in vacuo was employed to give $^1$H NMR pure product. *See Supporting Information. *Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(2), 222A. Aldrich Library of $^{13}$C and $^1$H FT NMR spectra, 1993, 1(2), 221C. *D'Auria, M.; Mauriello, G. Photochem. Photobiol., 1994, 606, 542. °No observable reaction. °No epoxide formation was observed.
Supporting Information

$^1$H, $^{13}$C NMR and HRMS Spectroscopic Data

**Compound trans-10b:** $^1$H NMR (CDCl$_3$): $\delta$ 4.58 (s, 2H), 7.54-8.82 (m, 18H). $^{13}$C NMR (CDCl$_3$): $\delta$ 61.02, 122.69, 123.09, 123.47, 123.73, 126.90, 127.02, 127.05, 127.10, 129.08, 130.28, 130.33, 130.49, 131.57, 131.67. HRMS (EI) calcd for C$_{30}$H$_{20}$O 396.151415, found 396.151402.

**Compound trans-11b:** $^1$H NMR (CDCl$_3$): $\delta$ 4.91 (s, 2H), 8.00-8.30 (m, 18H). $^{13}$C NMR (CDCl$_3$): $\delta$ 61.78, 122.26, 122.40, 124.80, 124.93, 125.39, 125.54, 125.70, 126.34, 127.72, 127.78, 128.42, 129.14, 130.79, 130.99, 131.36, 131.60. HRMS (EI) calcd for C$_{34}$H$_{20}$O 444.151415, found 444.152167.
CHAPTER 9. FACILE FORMATION OF BENZENE FROM A NOVEL CYCLOHEXANE DERIVATIVE

A paper submitted to the *Organic Letter*
Xiaodong Liu, Guangtao Zhang and John G. Verkade

The observation of benzene formation from cyclohexane derivatives is rare. In one of the two reports we were able to find for such a transformation, cyclohexanedione dioximes were treated with polyphosphoric acid,[1a] while the second report described the oxidative aromatization of substituted cyclohexanes with Pd(OAc)$_2$ and Na$_2$Cr$_2$O$_7$ in CF$_3$CO$_2$H.[1b] Both reactions require elevated temperatures (95-105 °C[1a] and 90 °C[1b]) and provide low yields of corresponding aromatic product (14-35%[1a] and trace to 29%[1b]) for aliphatic substituted cyclohexanes. Here we report that the reaction of 1 with PhCO$_2$H at room temperature to give benzene in 56% yield within 1 h is the first example of the aromatization of a cyclohexane derivative under very mild conditions.

In view of the apparent considerable basicity of compounds of type 3,[2] we had originally decided to investigate the possibility that the cyclohexane ring of 4 might be
forced to invert conformationally in the presence of a proton so that the proton would be a bridgehead atom that could interact simultaneously with a lone pair on each of the three imino nitrogens via covalent and hydrogen bonding to form a stable cationic adamantane-like structure. It eventually became clear, however, that the reaction of 2 with cis-1,3,5-triazido cyclohexane gave the triazido derivative 1 as an isolable thermally stable Staudinger intermediate, rather than the expected iminophosphine 4. During the short time we had erroneously believed (on the basis of preliminary evidence) that the latter compound had been formed, we reacted this substance with acids and discovered serendipitously and quite surprisingly that benzene was a major product. Compound 1 is very stable to thermolytic decomposition to the corresponding tris-iminophosphine derivative 4 even at 100°C/0.5 Torr for 10 h or in refluxing toluene for 24 h. Recrystallization of 1 from hot CH₃CN yielded colorless crystals suitable for X-ray crystallographic analysis. All three azido substituents are equatorial as expected, and the azido fragments have the usual E-configuration. All three cage moieties lie on the same side of cyclohexane ring, giving the structure a bowl-like appearance. The cage moieties possess pyramidal geometry around phosphorus [avg. \( \angle N_{eq}PN_{eq} = 108.77(7)^\circ \)], but a planar conformation at the bridgehead nitrogen [avg. \( \angle CN_{eq}C = 119.90(14)^\circ \)] for reasons we have discussed previously for analogous systems. The bridgehead-bridgehead distance of 3.1053(15) Å indicates the absence of transannular N→P interaction.

\[
\begin{align*}
R_3P + N_3R' & \rightarrow R_3PN_3R' \quad \text{[A]} \\
\begin{array}{c}
\text{[R}_3P \overset{N}{\text{N}}R']^+ \\
\end{array} & \rightarrow R_3P=NR' + N_2 \quad \text{[B]}
\end{align*}
\]

The Staudinger reaction is a two-step process involving the initial electrophilic addition of an alkyl or aryl azide to a P'' center followed by N₂ elimination from the intermediate phosphazide A to give the iminophosphine B in reaction 1. Steric hindrance at the P''' center does not hinder the electrophilic addition step, but it does suppress decomposition, since steric requirements in the four-membered ring transition state are much
more rigorous than those in the addition transition state.\textsuperscript{[31]} Donor character on the part of the P\textsuperscript{III} substituents stabilizes phosphazides,\textsuperscript{[31]} and this factor apparently also operates in 1 to give it thermal stability. The unusual resistance of 1 to thermolysis may be enhanced by the rigidity of the cage structure which by virtue of the planar geometry around MeN nitrogens, maintaining a methyl group in close proximity to the phosphorus-azido linkage.

Surprisingly, when 1 was treated with acids such as PhCO\textsubscript{2}H, CH\textsubscript{3}CO\textsubscript{2}H, or CF\textsubscript{3}CO\textsubscript{2}H in CH\textsubscript{3}CN at room temperature, an exothermic reaction accompanied by the rapid formation of N\textsubscript{2} (confirmed by GC-MS) and benzene (confirmed by \textsuperscript{1}H NMR and GC mass spectrosocopies) occurred. In the case of PhCO\textsubscript{2}H, benzene was provided in 56\% yield (using toluene as a reference in the GC-MS experiment) within 1 h. Upon evaporation of the reaction mixture to dryness, crude [5H]+PhCO\textsubscript{2} was isolated. Upon deprotonation of this salt with KO'Bu in THF, the iminophosphine 5 was obtained in 40\% yield after sublimation.

Upon treatment of 5 with PhCH\textsubscript{2}CH\textsubscript{2}Br in benzene and recrystallization of the product, crystals of [5H]+Br\textsuperscript{–} were isolated. The molecular structure of this salt determined by X-ray means reveals a transannular distance of 2.859(2) \textAA{} which is suggestive of some transannular interaction. This tentative conclusion is mildly corroborated by the rather wide N\textsubscript{eq}PN\textsubscript{eq} angle [112.03(9)°] although the angles around the bridgehead [119.59(18)°] confer an essentially planar conformation around this atom. The somewhat reduced transannulated distance may also be associated with steric factors that are currently obscure.

In contrast to our observation with 1, weak acids have been reported to combine with phosphazides to give stable 1:1 adducts in solution,\textsuperscript{[5a]} while strong acids cleave phosphazides to the corresponding amine and phosphine oxide.\textsuperscript{[5b]} There is, however, a report describing the reaction of triphenylmethyl azido triphenylphosphine with acetic acid that gives N\textsubscript{2}, Ph\textsubscript{3}CO\textsubscript{2}CCH\textsubscript{3} and Ph\textsubscript{3}P=NH.\textsuperscript{[5c]} In this reaction Ph\textsubscript{3}C\textsuperscript{–} was postulated to be an intermediate, as we believe is similarly the case in our reaction (D in Scheme 1). However, in this scheme the carbocation facilitates proton abstraction by the product base 5 to form a C=C bond.
NMR studies showed that 1 does not undergo decomposition in the presence of acid at -30°C at an observable rate, although it does protonate. Thus addition of PhCO₂H to a solution of 1 in CD₃CN led to an initial dramatic upfield shift of the ³¹P NMR resonance of the reaction mixture from 37.2 ppm to an asymptotically reached value of -11.0 ppm after 22.4 equiv PhCO₂H had been added. This result strongly suggests that protonation in a rapidly established equilibrium is accompanied by the formation of species containing five-coordinated phosphorus arising from transannulation in the cage moieties. At high acid concentration, all three cage moieties are apparently transannulated. That transannulation plays a role in the excellent leaving group properties exhibited by the cage moieties in 1 is strongly suggested by preliminary results in our laboratories on its acyclic *tris*-hexamethyl phosphoramidate analogue, which reacts about ten times slower with acid and is also significantly more susceptible to side reactions.
To better understand the mechanism of benzene formation in our reaction, we followed it over time by ESI-mass spectroscopy. During the reaction of 1 with PhCO₂H, two intermediates [6H]⁺ (m/z = 597) and [7H]⁺ (m/z = 338) were detected which disappeared upon reaction completion, while the product [5H]⁺ (m/z = 232) increased over time. Two additional species [8H]⁺ (m/z = 541) and [9H]⁺ (m/z = 310) were observed as minor products (see below). These observations give the reaction pathway in Scheme 1 further credence. The reaction begins with protonation of the exocyclic axial N atom, which activates N₂ elimination to give 5 and a carbocation. Then 5 serves as a base that quickly extracts a proton from the β carbon in the cyclohexane moiety to generate a new C=C bond. To gain further support for this mechanism, the proposed intermediate 6 was synthesized. When it was treated with PhCO₂H, the same products were observed as with 1.

**Scheme 2**

\[
C \quad \xrightarrow{\text{[6H]⁺ (m/z = 597), [7H]⁺ (m/z = 338)}} \quad \text{[5H]⁺ (m/z = 232)} \quad \xrightarrow{\text{[8H]⁺ (m/z = 541), [9H]⁺ (m/z = 310)}} \quad \text{[5H]⁺ (m/z = 232)} + N_2
\]

The formation of impurities [8H]⁺ and [9H]⁺ in the reaction of 1 with PhCO₂H may result from the competitive side reaction shown in Scheme 2. After protonation, a four-membered ring transition state E could form by rearrangement followed by evolution of N₂ to give the protonated iminophosphine F.

Further investigations aimed at broadening the scope of these reactions and at applying them in organic synthesis are underway.

**Experimental Section**

Compounds 1⁴ and 1,3,5-cis-triazidocyclohexane⁶ were synthesized according to the literature procedures. Compounds whose syntheses are described below were
characterized by $^1$H, $^{13}$C, $^{31}$P (where applicable) and mass (including high resolution and electrospray) spectroscopies, and elemental analyses.

The synthesis of 1 was achieved by allowing 1,3,5-cis-triazidocyclohexane to react with 3 equiv of 2 in MeCN at 0°C. After stirring for 3 h and solvent evaporation, 1 was obtained in 92% yield after washing with ether and drying.

The isolation and characterization of 5 was achieved by combining 1 with PhCO$_2$H in a 1:4 molar ratio at 0°C. After stirring at ambient temperature for 4 h followed by solvent evaporation, the residue was dissolved in THF and treated with 6 equiv of KO'Bu. After stirring the reaction mixture at ambient temperature for 2 h, followed by solvent evaporation, extraction of the residue with pentane and solvent evaporation, 5 was obtained in 40% yield upon vacuum sublimation of the residue. Compound 5 was converted to the conjugate acid [5H]Br by combining equimolar amounts of 5 and PhCH$_2$CH$_2$Br in C$_6$D$_6$ at room temperature. After 3 h, a 99% conversion of PhCH$_2$CH$_2$Br to PhCH=CH$_2$ had occurred was determined by $^1$H NMR integration. The precipitate that had formed was filtered and washed with Et$_2$O to give pure [5H]Br (90%) upon drying.

The formation of 3,5-cis-diazidohexa-1-ene was observed in the present work as a minor product by $^1$H NMR spectroscopy, during the synthesis of 1,3,5-cis-triazidocyclohexane. This mixture, when subjected to silica gel column chromatography, gave 3,5-cis-diazidohexa-1-ene in 10% yield.

The previous product was combined with 2 in a 1:2 molar ratio in MeCN at 0°C and the reaction mixture was allowed to stir at ambient temperature for 3 h. After evaporating the solvent and washing the residue with ether, 6 was obtained in 85% yield.

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Reference


Supporting Information

NMR, Mass Spectroscopic, Elemental analyses, and X-ray analysis Data

1: $^{31}$P (CD$_3$CN): $\delta$ 37.11. $^1$H (CD$_3$CN): $\delta$ 1.56-1.60 (m, 6H, CH$_2$), 2.65 (d, 27H, N$_{ax}$CH$_3$, $J_{PH}$ = 7.6 Hz), 2.77 (t, 18H, N$_{ax}$CH$_2$, $J_{HH}$ = 4.8 Hz), 2.88 (dt, 18H, N$_{eq}$CH$_2$, $J_{PH}$ = 12.8 Hz, $J_{HH}$ = 4.8 Hz), 3.38 (m, 3H, CH). $^{13}$C (CD$_3$CN): $\delta$ 35.67 (d, N$_{cq}$CH$_3$, $J_{PC}$ = 3.5 Hz), 39.42 (s, CH$_2$), 50.32 (s, N$_{eq}$CH$_3$), 52.27 (s, N$_{eq}$CH$_3$), 66.34 (s, CH). ESI-MS m/z: 856 (M$^+$). HRMS m/z calculated for C$_{33}$H$_{72}$N$_{16}$P$_3$: 856.54894. Found: 771.53235 (M-3N$_2$)$^+$. Elemental analysis calculated for C$_{33}$H$_{72}$N$_{16}$P$_3$: C, 46.30; H, 8.48; N, 34.36. Found: C, 46.29; H, 8.57; N, 34.07.

5: $^{31}$P (C$_6$D$_6$): $\delta$ 36.93. $^1$H (C$_6$D$_6$): $\delta$ 2.43 (t, 6H, N$_{ax}$CH$_2$, $J_{HH}$ = 4.8 Hz), 2.58 (dt, 6H, N$_{eq}$CH$_2$, $J_{PH}$ = 12.0 Hz, $J_{HH}$ = 4.8 Hz), 2.71 (d, 9H, N$_{ax}$CH$_3$, $J_{PH}$ = 7.6 Hz). $^{13}$C (C$_6$D$_6$): $\delta$ 35.58 (d, N$_{cq}$CH$_3$, $J_{RC}$ = 6.3 Hz), 49.71 (s, N$_{eq}$CH$_3$), 51.57 (d, N$_{eq}$CH$_3$, $J_{PC}$ = 2.3 Hz). HRMS m/z calculated for C$_6$H$_{22}$N$_2$P: 231.16231. Found: 231.16257 (M$^+$).

[5H]$^1$Br: $^{31}$P (CDCl$_3$): $\delta$ 34.38. $^1$H (CDCl$_3$): $\delta$ 2.69 (t, 6H, N$_{ax}$CH$_2$, $J_{HH}$ = 4.8 Hz), 2.82 (m, 6H, N$_{eq}$CH$_2$), 2.86 (d, 9H, N$_{ax}$CH$_3$, $J_{PH}$ = 7.5 Hz). $^{13}$C (CDCl$_3$): $\delta$ 36.29 (d, N$_{eq}$CH$_3$, $J_{PC}$ = 4.8 Hz), 49.72 (s, N$_{ax}$CH$_2$), 50.34 (d, N$_{eq}$CH$_2$, $J_{PC}$ = 3.7 Hz). ESI-MS m/z: 232 (for cation). Elemental analysis calculated for C$_6$H$_{22}$N$_2$PBr: C, 34.63; H, 7.43; N, 22.43. Found: C, 34.66; H, 7.41; N, 22.11.

3,5-cis-diazidohexa-1-ene: $^1$H (CDCl$_3$): $\delta$ 1.65 (m, 1H), 2.05-2.21 (m, 1H), 2.25-2.50 (m, 2H), 3.60-3.70 (m, 1H), 4.01-4.10 (m, 1H), 5.67-5.73 (m, 1H), 5.85-5.95 (m, 1H). $^{13}$C (CDCl$_3$): $\delta$ 30.69 (s), 33.95 (s), 55.11 (s), 56.61 (s), 126.16 (s), 128.31 (s). ESI-MS m/z: 164 (M$^+$).
6: $^{31}$P (CD$_3$CN): δ 37.02, 37.23. $^1$H (CD$_3$CN): δ 1.60-1.77 (m, 2H), 2.00-2.10 (m, 1H), 2.11-2.22 (m, 1H), 2.65 (d, 18H, N$_{eq}$CH$_3$, J$_{PH}$ = 7.6 Hz), 2.77 (t, 12H, N$_{ax}$CH$_2$, J$_{HH}$ = 4.8 Hz), 2.90 (dt, 12H, N$_{eq}$CH$_3$, J$_{PH}$ = 7.6 Hz, $^3$J$_{HH}$ = 4.8 Hz), 3.52-3.59 (m, 1H), 4.00-4.03 (m, 1H), 5.52-5.54 (m, 1H), 5.71-5.77 (m, 1H). $^{13}$C (CD$_3$CN): δ 31.41 (s), 34.64 (s), 35.79 (s), 49.29 (s), 51.25 (s), 63.51 (s), 65.75 (s), 126.12 (s), 130.95 (s). ESI-MS m/z: 597 (MH$^+$). HRMS m/z calculated for C$_{24}$H$_{50}$N$_{14}$P$_2$: 596.381816. Found: 540.37012 (M-2N$_2$)$^\cdot$. 


Figure 1. ORTEP view of 1 (30% probability thermal ellipsoids): hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: P(1)-N(3) 1.6134(13), P(1)-N(4) 1.6370(13), P(1)-N(6) 1.6438(12), P(1)-N(5) 1.6491(13), P(1)-N(7) 3.1549(14), N(1)-N(2) 1.2556(17), N(1)-C(1) 1.4721(18), N(2)-N(3) 1.3720(17); N(3)-P(1)-N(4) 116.14(7), N(3)-P(1)-N(6) 103.05(6), N(4)-P(1)-N(6) 107.65(7), N(3)-P(1)-N(5) 112.20(7), N(4)-P(1)-N(5) 107.33(7), N(6)-P(1)-N(5) 110.30(6), N(2)-N(1)-C(1) 110.94(12), N(1)-N(2)-N(3) 112.58(12), N(2)-N(3)-P(1) 113.78(10), C(15)-N(7)-C(12) 120.31(13), C(15)-N(7)-C(9) 120.04(13), C(12)-N(7)-C(9) 118.94(13), N(1)-C(1)-C(6) 109.90(12), N(1)-C(1)-C(2) 108.85(11).
Figure 2. ORTEP view of [5H]*Br (50% probability thermal ellipsoids). Selected bond lengths [Å] and angles [°]: P-N(1) 1.6257(17), P-N(2) 1.6338(18), P-N(3) 1.6326(17), P-N(4) 1.6277(16), P-N(5) 2.852(2); N(1)-P-N(4) 104.15(8), N(1)-P-N(3) 105.98(10), N(4)-P-N(3) 115.05(9), N(1)-P-N(2) 110.28(10), N(4)-P-N(2) 110.92(9), N(3)-P-N(2) 110.13(9), C(6)-N(5)-C(3) 119.80(17), C(6)-N(5)-C(9) 119.88(18), C(3)-N(5)-C(9) 119.10(17).
CHAPTER 10. GENERAL CONCLUSION

Concluding Remarks

In this work, the following results have been achieved:

(1) A new, easier and more economical method has been developed for the synthesis of our patented superbase \( \text{P(MeNCH}_2\text{CH}_2\text{N} \) \( 1a \) in three steps and in 68% overall yield.\(^1\) This commercial reagent \( 1a \) is proving to be a versatile reagent and catalyst for an ever increasing number of organic transformations requiring extraordinary basicity and low nucleophilicity.

(2) A series of novel highly sterically hindered azaphosphatranes \( \{\text{ZP(RNCH}_2\text{CH}_2\text{)}}_3\text{N} \) \( \text{CF}_3\text{SO}_3 \) wherein \( Z = H^+ \) and \( R = \text{SiMe}_3, \text{SiEt}_3, \text{SiPh}_3, \text{SiPh}_2\text{Me} \) have been synthesized along with proazaphosphatranne \( 1c \) wherein \( Z = \text{Ip} \) and \( R = \text{SiMe}_3 \). Also described are the transformations of \( 1c \) to \( \text{O=P(Me}_3\text{SiNCH}_2\text{CH}_2\text{)})_3\text{N} \) (2a) and to \( \text{S=P(Me}_3\text{SiNCH}_2\text{CH}_2\text{)})_3\text{N} \) (2b). The structures of \( 1c \) and \( 2b \) determined by X-ray means are also presented.\(^2\) Compound \( 1c \) displays a bridgehead-bridgehead distance of 3.360(7) Å while that in \( 2b \) is 3.152(7) Å. The smaller distance in the latter by ca. 0.1 Å is attributed to the wider NPN bond angle by ca. 5° in \( 1c \). VT \( ^{31}\text{P} \) NMR studies revealed no evidence for transannulation or tautomerism in \( 2a \).

(3) The precursor cation \( \text{HP(CH}_3\text{NCH}_2\text{CH}_2\text{))}_3\text{N}^+ \) to \( 1a \), which is more stable and less expensive, is reported herein to be an efficient procatalyst for dehydrohalogenation and also for the debromination of vicinal dibromides using NaH as a relatively inexpensive
stoichiometric hydride source in CH$_3$CN at room temperature. In dehydrohalogenations requiring more than ca. 10 h, the $\text{CH}_2\text{CN}$ ion also acts as a base. By itself, NaH does not function well or at all under the same conditions. A catalytic cycle is also proposed. The cations HP(HNCH$_2$CH$_2$)$_2$N$^+$ and HP[N(polymer)CH$_2$CH$_2$]N(CH$_2$CH$_2$NH)$_2$$^+$ (3) are also shown to function as procatalysts for the efficient dehydrohalogenation of RX and for the debromination of vicinal dibromides. The preparation of the heterogeneous procatalyst 3 (OTf) is also described.

(4) A facile and economical procedure for the synthesis of the C$_3$ chiral-phenylethylamino trisaminoamine [(S,S,S)-PhHMeCNHCH$_2$CH$_2$]$_3$N in good yield is reported. The corresponding bicyclic proazaphosphatrane P[(S,S,S)-PhHMeCNCH$_2$CH$_2$]$_3$N 1d, its bicyclic phosphoryl derivative and its tricyclic P-protonated azaphosphatrane were also synthesized and characterized. It is found that the proazaphosphatrane is an efficient derivatizing agent for the direct determination of enantiomeric ratios of chiral azides by means of $^{31}$P and $^1$H NMR spectroscopy.

(5) The compounds 4a – 4d were synthesized, among which the cation [O=P(i-PrNCH$_2$CH$_3$)$_2$CH$_3]$ 4c features the longest distance between the bridgehead atoms (3.56 Å) so far recorded for phosphatrane cages, despite a non-tetrahedral CN$_{bridgehead}$C angle (114°). The 70.8° N$_{bridgehead}$CCN torsion angles in the bridging moieties produces a substantial twist along the C$_3$ axis of the structure that does not easily allow racemization of the cage. The resulting rigidity of the twisted cage gives rise to AB patterns for the methylene protons of this cation and its analogues.
(6) The catalytic effect of a group of R₃P=O compounds has been studied in a mild procedure for the silylation of primary alcohols, secondary alcohols, hindered secondary alcohols and of hindered phenols, in the presence of t-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCI). It is found that R₃P=O is an efficient catalyst in such reactions when R is a good electron donating group, such as Me₂N or n-Bu and as NMe(CH₂) in N(CH₂CH₂NMe)₃P=O. However, R₃P=O is a weak or ineffective catalyst when R is a poor electron donating group, such as Ph or O-ₙ-Bu or as CH₂N-o-CH₂C₅H₄N in N(CH₂CH₂N-o-CH₂C₅H₄N)₃P=O. Compound 2c, synthesized by oxidation of commercially available N(CH₂CH₂NMe)₃P la, displays the best catalytic properties for alcohol silylation in terms of efficiency, stability and safety.

(7) In contrast to its acyclic analogue P(NMe₂)₃, which in benzene at room temperature reacts with two aryl aldehyde molecules bearing electron withdrawing groups to give the corresponding diaryl epoxide as an isomeric mixture (trans/cis ratios: 72/28 - 51/49), P(MeNCH₂CH₂)₃N (la) under the same reaction conditions is found to be a highly selective reagent that provides epoxides with trans/cis ratios as high as 99/1. These reactions are faster with la, because its phosphorus atom is apparently more nucleophilic than that in P(NMe₂)₃. Thus it is found that la more easily forms 1:1 and 1:2 adducts with one or two molecules of aldehyde, respectively. These adducts apparently are intermediates in the formation of the product epoxide and the corresponding phosphine oxides of P(NMe₂)₃ and la.

(8) The dominant reaction in the decomposition of the starting material 5, an unusually thermally stable Staudinger intermediate, in the presence of HA is the formation of benzene, nitrogen and [H₂N=PR₃]⁺A⁻ (6H⁺A⁻). Evidence for a transannulated cage intermediate is presented. A competing reaction produces the corresponding cyclohexenyl and the 1,3-cyclohexadienyl derivatives (7 and 8), along with nitrogen. The tris-iminophosphine cyclohexane derivative of the starting material expected as a thermal
decomposition product was not observed to form in refluxing toluene or at 100 °C in vacuum.

**Current Progress and Suggestion for Future Work**

During the past decade, there has been a steady flow of publications on phosphatrane chemistry from our group and there is no sign of abatement. The results presented herein are a small part of the total of contribution made by past and present coworkers to this academically and industrially exceedingly interesting and significant field.

Currently, this author is working on the synthesis of new proazaphosphatranes with different R group on the N_eq in the cage moiety, aiming at structural and electronic modification of the basicity and ligand properties. Thus the new proazaphosphatranes 1e^9 and 1f^10 have been successfully synthesized and structurally characterized. Preliminary results showed that both are weaker bases than 1a, although they have similar catalytic activities.

P(NMe₂)₃ is a well-known ligand in coordination chemistry that has provided hundreds of complexes for structural and reactivity studies. Since P(MeNCH₂CH₃)₃N 1a is the bicyclic analogue of P(NMe₂)₃, its metal complexes could also be interesting. A few metal complexes (9 – 11) involving 1a have been synthesized in this group,^11 and their structural features have been elucidated. Recently, Au(I) complexes 12^12 and 13^13 have also been obtained by reacting Me₅SAu(I)Cl with one and two equivalents of 1a, respectively.
The donor properties of 1a towards Au(I) were studied by testing its ability to remain coordinated in the presence of other phosphines such as P(NMe₂)₃ and PPh₃. It was found that 1a is a better donor ligand than P(NMe₂)₃, which is better than PPh₃ when coordinated to Au(I).

Another new finding is that for the first time 1a and 1b have been found to cleave the C-F bonds in CF₃I to give exclusively 14a and 14b, respectively, in which the transannular bridgehead-bridgehead bond is among the shortest found thus far. However, P(NMe₂)₃, the acyclic analogue of 1a in the presence of CF₃I gives little or no analogous C-F cleavage products, 15 being formed instead under the same conditions (see Scheme 2).

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**Scheme 1**

Cl—Au—SMe₂ À Cl—Au—SMe₂

CH₃CN/RT/30 min

Me₂N⁺P(NMe₂)₃⁺Cl⁻

**Scheme 2**

R

14a Me + :CF₂

14b i-Pr

15
Since our proazaphosphatranes have been proving to be efficient bases/catalysts in a variety of useful organic transformations, immobilizing them on a polymer will be of great interest because of the following advantages. Polymeric reagents are easily separated which saves time, uses less solvent, and is therefore more environmentally benign.

Scheme 3

In our previous work, polymer-supported azaphosphatrane 3 was synthesized from Merrifield resin and used as a catalyst in dehydrohalogenation of organic halides with NaH.\textsuperscript{4} However, it is found that deprotonation of 3 to its pure free base form is difficult, perhaps due to inefficient mass transport of the deprotonation base in the reaction resulting from steric bulk of polymer back-bone. Therefore, it is conceivable that an appropriate linker is required between the polymer back-bone and the reactive site (i.e., the phosphorus cage moiety). Scheme 3 shows one possible route to achieve this goal. It is noted that linkers with different lengths should be evaluated to obtain the optimum result. In this way, the
A deprotonation reagent can easily access the phosphorus to liberate the free phosphorus base and the phosphorus will be more accessible to the reactants.

Very recently, a novel ylide-like base 21 and its polymer-supported analogue 22 were synthesized and used in some N and C alkylation reactions. However, the synthesis and reactivity of the polymer-supported base were not described in detail, which results in the speculation that some problems may exist, such as less reactivity and/or difficulty in the isolation of pure polymeric base 22. Using the same approach given in Scheme 3, various linkers can be used to install the reactive site well away from the steric hindrance of the polymer back-bone (see Scheme 4).
If our superbases, such as 1a, are converted into the ylide-like polymer-supported bases, high basicity is expected. It is believed that the nonnucleophilic nature of 22 is due to the steric bulk of the polymer back-bone.\(^{15}\) However, if a polymeric ylide-like base 25 in the Scheme 4 is more accessible, then its nucleophilicity could be enhanced to facilitate Wittig reactions in the presence of aldehydes or ketones.

Although phosphatrane chemistry continues to be thoroughly and systematically studied for its synthetic, mechanistic, and application implications, there remain many fundamental questions to be answered, important properties to be studied, and new applications to be explored.

References

1. Liu, X.; Verkade, J. G. (submitted to ISURF for patent application)

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