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New developments in azaphosphatrane systems ZP(RNCH2CH2)3N

Xiaodong Liu
Iowa State University

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New developments in azaphosphatrane systems ZP(RNCH$_2$CH$_2$)$_3$N

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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For the Major Program

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For the Graduate College

DEDICATION

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

and

my dream to be a chemist

TABLE OF CONTENTS

ABSTRACT

Compounds of the type $ZP(RNCH_2CH_2)_3N$ 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 (R_3Si) (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 $P(MeNCH_2CH_2)_3N$ (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 $HP(CH_3NCH_2CH_2)_3N^+$, $HP(HNCH_2CH_2)_3N^+$ and $HP[N(polymer)CH_2CH_2]N(CH_2CH_2NH)_2^+$ (2, 3 and 4 in chapter 4) serve as efficient procatalysts for dehydrohalogenation of organic bromides using NaH as a inexpensive stoichiometric hydride source in CH_3CN 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 ^{31}P and ^1H NMR spectroscopy; that $N(CH_2CH_2NMe)_3P=O$ (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-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCl); and that $P(MeNCH_2CH_2)_3N$ (2a in chapter 8) functions as a highly selective reagent for providing epoxides with trans/cis ratios as high as 99/1.

Cation $[O=P(i-PrNCH_2CH_2)_3CH_3]^+$ (3 in chapter 6) 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 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.[2] In

1989, the first proazaphosphatrane $P(MeNCH_2CH_2)_3N$ (1a) was synthesized by the Verkade

group.[3] Following its synthesis, its analogues 1b – d have been synthesized and fully

characterized by this group.[4,5] The unusual phosphorus basicity of proazaphosphoatranes 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.

	R
1a	Me
1b	i-Pr
1c	Et
1d	CH_2Ph
1e	CH_2CHMe_2
1f	CH_2CMe_3

A   B
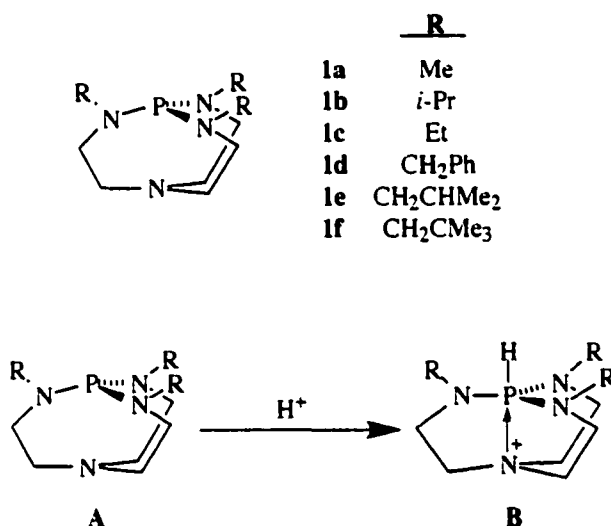
In recent years we have been exploring the chemistry of proazaphosphatranes such as

1a - f,[2-6] 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,[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 **1a** 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, **1a** has become commercially

available.[14] Recently, we have discovered that **1a** and **1b** are also efficient nonionic base

catalysts for transesterification,[15] β-nitroalkanol synthesis,[16] Michael addtions,[17] β-hydroxy

nitrile synthesis,[18] and α,β-unsaturated nitrile synthesis.[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.

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CHAPTER 2. AN IMPROVED SYNTHESIS OF OUR PATENTED AND COMMERCIALLY AVAILABLE SUPERBASE/CATALYST P(MeNCH$_2$CH$_2$)$_3$N

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(MeNCH$_2$CH$_2$)$_3$N 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(RNCH$_2$CH$_2$)$_3$N where R = Me,[1] PhCH$_2$,[2] Et,[3] i-Pr,[3] CH$_2$CHMe$_2$,[4,5] CH$_2$CMe$_3$,[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
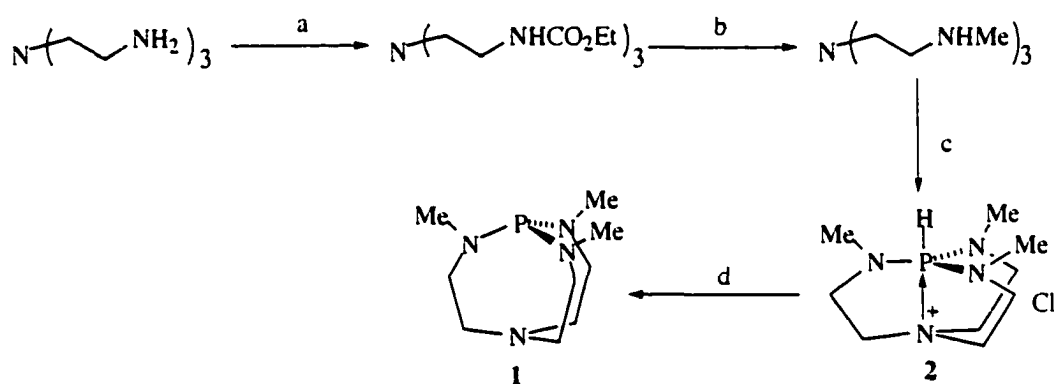
a. ClCO$_2$Et, C$_6$H$_6$/H$_2$O, 5°C/2 h, RT/8 h, 85%.   b. LiAlH$_4$, THF, reflux, 12 h, 88%.

c. P(NMe$_2$)$_3$, PCl$_3$, CH$_3$CN, RT, 6 h, 90%.   d. KO-t-Bu, CH$_3$CN, RT, 1 h, 82%.

possesses unusually high basicity and readily protonates to give cation **2** whose pK_a in

CH_3CN 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 mono-

alkylated 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

α,β-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 $(H_2NCH_2CH_2)_3N$ 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 $3(CF_3CO_2)$ in quantitative yield using our earlier

method.[2] The second step is the reaction of $3(CF_3CO_2)$ with 3.1 equiv. of Me_2SO_4 in the

Scheme 2

$N(CH_2CH_2NH_2)_3 \xrightarrow{a}$ **3** $\xrightarrow{b}$ **2** $\xrightarrow{c}$ **1**
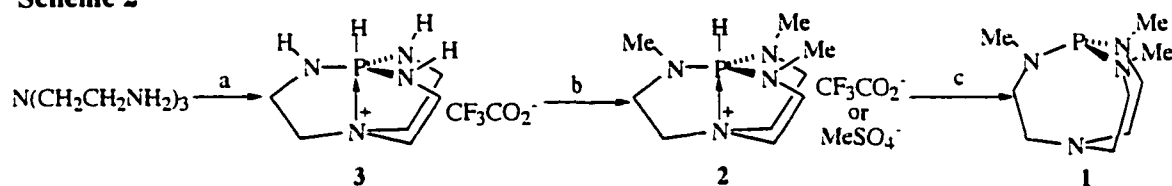
a. CF_3CO_2H, $P(NMe_2)_3$, CH_3CN, RT, 10 h, 99%.

b. 4.0 equiv NaH, 3.1 equiv Me_2SO_4, CH_3CN, 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_3CN at room temperature. After purification, the salt **2** with a mixture of counter ions $CF_3CO_2^-$ 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_{eq}-H groups stepwise upon which S_N2 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
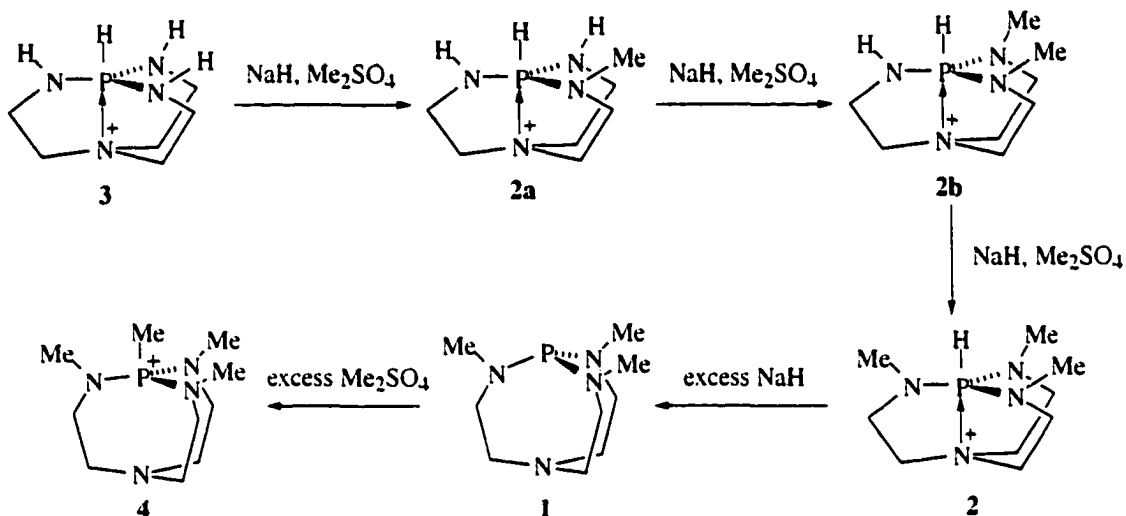
When KO-*t*-Bu was used as the base in step 2, methylation was not clean. Thus **2**, **2a**, **2b** and the phosphonium cation **4** formed as final products when **2** was reacted with 3.1 equiv. of Me_2SO_4 in the presence of 4.0 equiv. of KO-*t*-Bu in CH_3CN at room temperature.

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_2SO_4 to form **4** is observed. Thus, the amount of Me_2SO_4 must be carefully controlled: too much results in the

formation of undesired 4 and too little leads to incomplete methylation. MeI 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 MeI added to the reaction mixture. The lower cost and higher boiling point (188 °C) of Me_2SO_4 led to its use in place of MeI.

To reduce the cost of the chemicals, several cheaper acids, such as CH_3CO_2H, HCl, CH_3SO_3H and CF_3CO_2H, were used in place of expensive CF_3SO_3H. It was found that CH_3CO_2H and CH_3SO_3H gave impure product in low yields and HCl gave 3 as an insoluble product in CH_3CN even though the yield was quantitative. With CF_3CO_2H, pure 3 was obtained as the $CF_3CO_2^-$ salt in quantitative yield and this salt had better solubility in CH_3CN. With the use of this salt in step 2, the methylated product 2 was formed with a mixture of $CF_3CO_2^-$ and $MeSO_4^-$ 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 $MeSO_4^-$ 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 CH_3CN because of its excellent solvent properties for $2(CF_3CO_2^-, MeSO_4^-)$ 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, $3(CF_3CO_2)$ reacts with 3.1 equiv. of Me_2SO_4 in the presence of 4.0 equiv. of NaH using CH_3CN 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, $2(CF_3CO_2^-, MeSO_4^-)$ 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 [HP(HNCH$_2$CH$_2$)$_3$N][CF$_3$CO$_2$], 3(CF$_3$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.[2]

Synthesis of [HP(MeNCH$_2$CH$_2$)$_3$N][CF$_3$CO$_2^-$, MeSO$_4^-$], 2(CF$_3$CO$_2^-$, 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 Et_2O (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 $MgSO_4$ (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. ^{31}P, ^{1}H NMR and MS(ESI) spectra confirmed the identity and purity (98%) of the products.[1]

Synthesis of P(MeNCH$_2$CH$_2$)$_3$N, 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 $2(CF_3CO_2^-, MeSO_4^-)$ (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 ^{31}P, ^{1}H and ^{13}C NMR spectroscopic data were consistent with those in literature.[1]

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CHAPTER 3. SYNTHESIS AND STRUCTURAL FEATURES OF NEW STERICALLY HINDERED AZAPHOSPHATRANE SYSTEMS: ZP(RNCH₂CH₂)₃N

Xiaodong Liu, Yuniu Bai and John G. Verkade
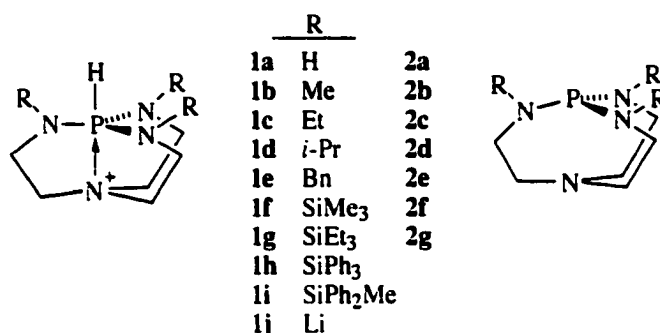
ABSTRACT

The synthesis of [ZP(RNCH$_2$CH$_2$)$_3$N]CF$_3$SO$_3$ wherein Z = H$^+$ and R = SiMe$_3$ (**1f**), SiEt$_3$ (**1g**), SiPh$_3$ (**1h**), SiPh$_2$Me (**1i**) and Li(**1j**) are reported along with that of **2f** wherein Z = lp and R = SiMe$_3$. Also described are the transformations of **1j** to **1f-i**, **2f** to OP(Me$_3$SiNCH$_2$CH$_2$)$_3$N (**3b**), **5** to **3b**, and **2f** to SP(Me$_3$SiNCH$_2$CH$_2$)$_3$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}P NMR studies revealed no evidence for transannulation or tautomerism in **3b**.

*Keywords:* azaphosphatrane, 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

	R	
1a	H	**2a**
1b	Me	**2b**
1c	Et	**2c**
1d	*i*-Pr	**2d**
1e	Bn	**2e**
1f	SiMe₃	**2f**
1g	SiEt₃	**2g**
1h	SiPh₃	
1i	SiPh₂Me	
1j	Li	

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]

$$3\text{ArNCO} \xrightarrow{\text{2b}} \qquad (1)$$
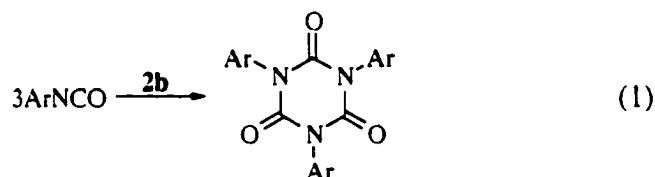
All of these transformations are crucially dependent upon the ability of the bridgehead

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

sp^3 geometry into a nearly planar sp^2 hybridized geometry. The planarity of the bridgehead nitrogen is mainly responsible for the transannular N-P distance of 3.29Å in **2d** which is only about 2% shorter than the van der Waals sum of 3.35Å.[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**(CF_3SO_3) 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]
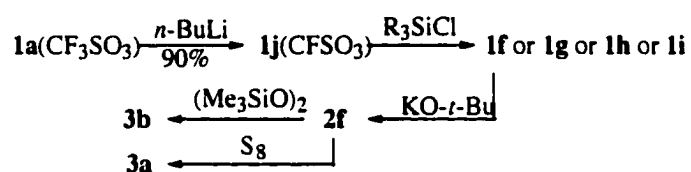

3a: Z = S
3b: Z = O

4

5

6
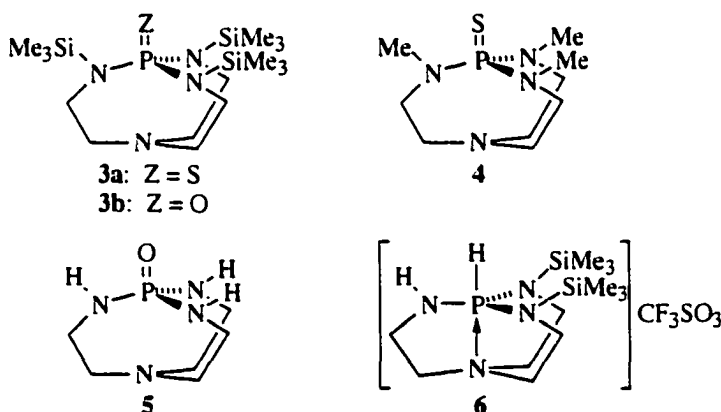
2. Results and Discussion

2.1 Syntheses

Although the trilithio azaphosphatrane **1j**(CF$_3$SO$_3$) could be isolated in 90% yield via

step one in Scheme 1, compounds **1f-i** derived from **1j**(CF$_3$SO$_3$) by silylation in step two of

this scheme were obtained in better yields and with greater convenience by generating **1j** in situ

followed by trisilylation. In view of the relative ease with which trisilylation of **1j**(CF$_3$SO$_3$)

Scheme 1

$$\textbf{1a}(CF_3SO_3) \xrightarrow[90\%]{n\text{-BuLi}} \textbf{1j}(CFSO_3) \xrightarrow{R_3SiCl} \textbf{1f} \text{ or } \textbf{1g} \text{ or } \textbf{1h} \text{ or } \textbf{1i}$$

$$\textbf{3b} \xleftarrow{(Me_3SiO)_2} \textbf{2f} \xleftarrow{KO\text{-}t\text{-}Bu}$$
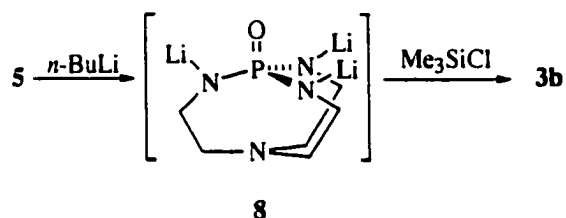
$$\textbf{3a} \xleftarrow{S_8}$$

occurred to give the corresponding salts **1g-i** (51-63% yield) it was surprising to observe that

1j upon reaction with Me$_3$SiCl (the least sterically hindered silylating agent employed) gave

rise to a 3:1 mixture of the desired product **1f** and what is probably **6**(CF$_3$SO$_3$) 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

7
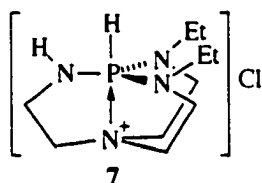
here are not obvious. Attempts to deprotonate **1f-i** with KO-t-Bu, the base of choice for these

strong nonionic bases, succeeded only in the case of **1f**(CF$_3$SO$_3$). For reasons that are not

clear severe decomposition occurred when **1g-i** were treated with KO-t-Bu.

Proazaphosphatrane **2f**, obtained in 58% overall yield from **1a**(CF$_3$SO$_3$), was oxidized

to **3b** with (Me$_3$SiO)$_2$ (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.

Scheme 2

$$5 \xrightarrow{n\text{-BuLi}} \left[\begin{array}{c} \text{Li} \\ \text{N} - \overset{\overset{\displaystyle O}{\|}}{P} \cdots \text{N} \overset{\text{Li}}{\underset{\text{Li}}{\diagdown}} \\ \text{N} \end{array} \right] \xrightarrow{\text{Me}_3\text{SiCl}} \quad 3b$$

8

We had previously synthesized **5** from **1a** by allowing the latter to react with molecular oxygen.[18] The yield of **5** was improved here (71%) over that reported earlier (48%[18]) by reacting **1a** with $(\text{Me}_3\text{SiO})_2$.

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) δ^{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 δ^{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 δ^{31}P value (-17.7 ppm) that lies between the ranges for its trialkyl and trisilyl analogues. The orders in the δ^{31}P values at each level of R substitution do not follow an obvious trend.

3'b

3"b
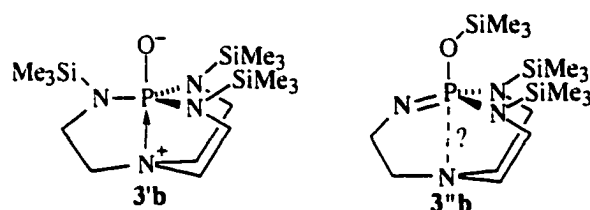
In efforts to determine if the Me_3Si groups on **3b** are sufficiently electronegative (via

$N{\rightarrow}Si$ 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_3Si groups) VT ^{31}P and ^1H NMR studies were carried out. It was observed that

the position of the ^{31}P peak is independent of temperature, although the ^1H 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 ^1H 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.

$$1g(CF_3SO_3) + 2b \rightleftharpoons 2g + 1b \qquad (2)$$
$$1h(CF_3SO_3) + 2b \rightleftharpoons 2h + 1b \qquad (3)$$
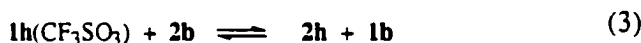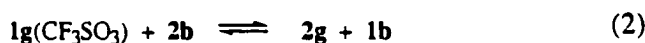
Efforts to compare the basicities of $1g(CF_3SO_3)$ and $1h(CF_3SO_3)$ with **2b** were

partially successful. ^{31}P NMR monitoring of reactions 2 and 3 in CD_3CN showed that for

reaction 2 in CD_3CN, **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 **1g** or **1h**. Although these equilibria lie far to the right,

	R
9	SiEt₃
10	SiPh₃
11	SiMe₃
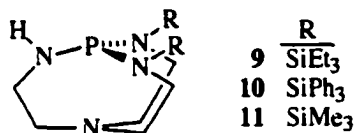
the extreme sensitivity of **2g** and **2h** to moisture made calculation of an equilibrium constant unwarranted.

This moisture sensitivity was also shown for **2f** by monitoring its ^{31}P NMR spectrum upon treatment with 3 equiv of H_2O in CD_3CN (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 $N_{ax} \rightarrow P$ 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
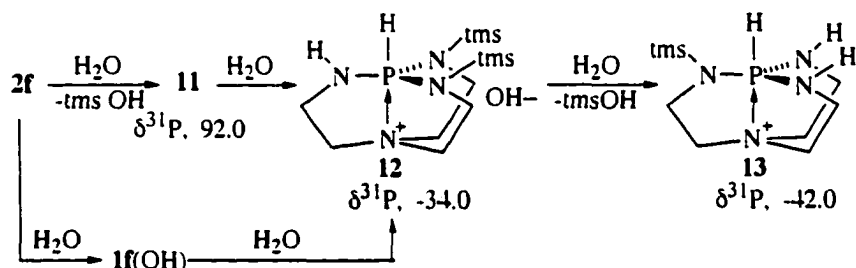
2.3 Structural considerations. Compound **2f** (Fig. 2) is only the second pro-azaphosphatrane that has thus far provided crystals suitable for X-ray analysis, the first being **1d**.[8] The bridgehead-bridgehead distances in these two compounds [**2f**, avg 3.360(7) Å; **2d**, 3.293(2) Å], average NPN 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.

14   **15**
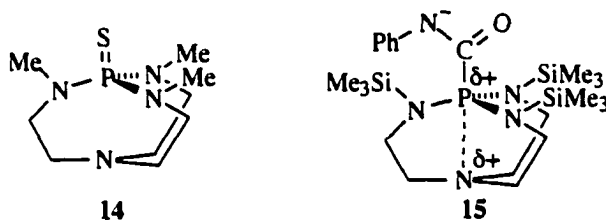
2.4 Catalytic properties of 2f

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. ^1H 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_3PO_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 $1a(CF_3SO_3)$[19] and $2b$[20] were synthesized according to our previously published methods.

3.2. $[HP(LiNCH_2CH_2)_3N](CF_3SO_3)$, $1j(CF_3SO_3)$

A suspension of $1a(CF_3SO_3)$ (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, $1j(CF_3SO_3)$ 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_3CN): δ -17.67 (bds). ^1H (CD_3CN): δ 2.59-2.80 (bdm, 12H, $N_{eq}CH_2$ and $N_{ax}CH_2$ resonance overlapped), 6.27 (d, 1H, PH, $^1J_{PH}$ = 460 Hz). ^{13}C (CD_3CN): δ 37.62 (bds, $N_{ax}CH_2$), 50.63 (bds, $N_{eq}CH_2$).

3.3. $[HP(Me_3SiNCH_2CH_2)_3N](CF_3SO_3)$, $1f(CF_3SO_3)$

Both isolated $1j(CF_3SO_3)$ and $1j(CF_3SO_3)$ generated in situ used in this reaction gave similar results. Here the procedure for the preparation of $1f(CF_3SO_3)$ using $1j(CF_3SO_3)$ synthesized in situ as a starting material is described and the in situ method is also employed in subsequent preparations. A suspension of $1j(CF_3SO_3)$ generated in situ from $1a(CF_3SO_3)$ (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 ^1H NMR spectra of this white powder in CD_3CN indicated that a mixture of $1f(CF_3SO_3)$ and $5(CF_3SO_3)$

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(CF_3SO_3). However, the product mixture ratio remained

unchanged. Although attempts to isolate pure 1f(CF_3SO_3) from this mixture were not

successful, the mixture was used in the following reaction to prepare 2f.

3.4. P(Me₃SiNCH₂CH₂)₃N, 2f

A suspension of 1.05 g of the above-described mixture of 1f(CF_3SO_3) and 5(CF_3SO_3)

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). ^{31}P

(C_6D_6): δ 99.67. ^{1}H (C_6D_6): δ 0.24 (d, 27H, CH_3, $^4J_{PH}$ = 3.0 Hz), 2.68 (bdm, 12H, $N_{eq}CH_2$

and $N_{ax}CH_2$ overlapped). ^{13}C (C_6D_6): δ 1.18 (d, CH_3, $^3J_{PC}$ = 9.0 Hz), 40.95 (d, $N_{eq}CH_2$, $^2J_{PC}$

= 4.5 Hz), 54.93 (d, $N_{ax}CH_2$, $^3J_{PC}$ = 3.0 Hz). HRMS m/z calculated for $C_{15}N_{39}N_4Si_3P$:

390.22202. Found: 390.22155 (27.1, M$^+$). Elemental analysis calculated for $C_{15}H_{39}N_4Si_3P$:

C, 46.11; H, 10.06; N, 14.34. Found: C, 45.40; H, 10.21; N, 14.44.

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

The synthesis of 1g(CF_3SO_3) was analogous to that of 1f(CF_3SO_3) except that

triethylsilyl chloride (4.55 g, 40.0 mmol) was used instead of trimethylsilyl chloride. The

product 1g(CF_3SO_3) was obtained as a white powder (4.02 g, 60%). ^{31}P (CD_3CN): δ -25.99.

^{1}H (CD_3CN): δ 0.80 (q, 18H, $N_{eq}Si(CH_2CH_3)_3$, $^3J_{HH}$ = 8.0 Hz), 0.98 (t, 27H,

$N_{eq}Si(CH_2CH_3)_3$, $^3J_{HH}$ = 8.0 Hz), 2.85 (bdm, 6H, $N_{ax}CH_2$), 3.03 (dt, 6H, $N_{eq}CH_2$, $^3J_{PH}$ =

16.0 Hz, $^3J_{HH}$ = 6.0 Hz), 6.28 (d, 1H, PH, $^1J_{PH}$ = 504 Hz). ^{13}C (CD_3CN): δ 5.14 (d,

CH_2CH_3, $^3J_{PC}$ = 2.5 Hz), 7.65 (s, CH_2CH_3), 38.52 (s, $N_{ax}CH_2$), 52.84 (d, $N_{eq}CH_2$, $^2J_{PC}$ =

11.1 Hz). MS (ESI) m/z: 517.2 (cation 1g).

3.6. [HP(Ph₃SiNCH₂CH₂)₃N](CF₃SO₃), 1h(CF₃SO₃)

3.6. [HP(Ph₃SiNCH₂CH₂)₃N](CF₃SO₃), 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%). ^{31}P (CD₃CN): δ -19.64.

^{1}H (CD₃CN): δ 2.88 (bdm, 6H, N$_{ax}$CH₂), 3.58 (dt, 6H, N$_{eq}$CH₂, $^3J_{PH}$ = 16.0 Hz, $^3J_{HH}$ = 6.0

Hz), 6.92 (d, 1H, PH, $^1J_{PH}$ = 532 Hz), 7.07-7.49 (m, 45H, C₆H₅). ^{13}C (CD₃CN): δ 42.57 (s,

N$_{ax}$CH₂), 52.07 (d, N$_{eq}$CH₂, $^2J_{PC}$ = 10.0 Hz), 129.35 (s, C₆H₅), 131.64 (s, C₆H₅), 132.43 (d,

C₆H₅, $^3J_{PC}$ = 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), 1i(CF₃SO₃)

3.7. [HP(Ph₂MeSiNCH₂CH₂)₃N](CF₃SO₃), 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%). ^{31}P (CD₃CN): δ -

34.25. ^{1}H (CD₃CN): δ 0.42 (d, 9H, CH₃, $^4J_{PH}$ = 1.8 Hz), 2.97-3.21 (m, 12H, N$_{eq}$CH₂ and

N$_{ax}$CH₂ overlapped), 6.65 (d, 1H, PH, $^1J_{PH}$ = 494 Hz), 7.35-7.52 (m, 30H, C₆H₅). ^{13}C

(CD₃CN): δ - 0.98 (d, CH₃, $^3J_{PC}$ = 3.1 Hz), 40.25 (s, N$_{ax}$CH₂), 50.62 (d, N$_{eq}$CH₂, $^3J_{PC}$ = 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

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%). ^{31}P (C₆D₆): δ 65.30. ^{1}H (C₆D₆): δ 0.44 (s,

27H, CH₃), 2.11-2.26 and 2.53-2.82 (bdm, 12H, N$_{eq}$CH₂ and N$_{ax}$CH₂ overlapped). ^{13}C

(C₆D₆): δ 2.55 (s, CH₃), 47.34 (d, N$_{eq}$CH₂, $^2J_{PC}$ = 3.0 Hz), 55.00 (s, N$_{ax}$CH₂). HRMS m/z

calculated for $C_{15}H_{39}N_4SPSi_3$: 422.19410. Found: 422.19367 (37.8, M^+). Elemental

analysis calculated for $C_{15}H_{39}N_4SPSi_3$: C, 42.61; H, 9.30; N, 13.25. Found: C, 42.89; H,

9.43; N, 13.15.

3.9. $O=P(Me_3SiNCH_2CH_2)_3N$, 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

%). ^{31}P (C_6D_6): δ 24.11. ^1H (C_6D_6): δ 0.34 (d, 27H, CH_3, $^4J_{PH}$ = 3.0 Hz), 2.14-2.71 (bdm,

12H, $N_{eq}CH_2$ and $N_{ax}CH_2$). ^{13}C (C_6D_6): δ 1.58 (d, CH_3, $^3J_{PC}$ = 1.5 Hz), 47.16 (d, $N_{eq}CH_2$,

$^2J_{PC}$ = 2.3 Hz), 54.96 (s, $N_{ax}CH_2$). HRMS m/z calculated for $C_{15}H_{39}N_4Si_3PO$: 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 x 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. $O=P(HNCH_2CH_2)_3N$, 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**(CF_3SO_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. ^1H VTNMR of $O=P(Me_3SiNCH_2CH_2)_3N$, 3b

Solutions of **3b** (41 mg, 0.10 mmol) in CD_3CN (0.6 mL) and C_6D_6 (0.6 mL) were

prepared. ^{31}P NMR spectra of **3a** in CD_3CN were taken at 251 K, 261K, 293 K, 323 K and

341 K. ^1H NMR spectra of **3a** in C_6D_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

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

R^a	number of R groups $\neq$ H	δ^{31}P (ppm)	reference
(1a)	0	-45.2	_^{e}
Me (1b)	3	-10.0^c	18
Me	2	-21.4^c	18
Me	1	-35.5^c	18
Et (1c)	3	-13.5^d	8
Et	2	-23.2^d	8
Et	1	-33.6^d	8
i-Pr (1d)	3	-11.8^d	8
i-Pr	2	-21.7^d	8
i-Pr	1	-32.3^d	_^{f}
PhCH$_2$ (1e)	3	-11.0^d	_^{e}
Me$_3$Si (1f)	3	-24.5	this work
Me$_3$Si	2	-34.3	this work
Me$_3$Si	1	-42.0	this work
Et$_3$Si (1g)	3	-25.9	this work
Et$_3$Si	2	-38.8	this work
Et$_3$Si	1	-43.0	this work
Ph$_3$Si (1h)	3	-19.6	this work
Ph$_3$Si	2	-36.0	this work
Ph$_3$Si	1	-42.4	this work
MePh$_2$Si (1i)	3	-34.3	this work
MePh$_2$Si	2	-39.3	this work
MePh$_2$Si	1	-43.1	this work

^{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**.

Empirical formula	$C_{15}H_{39}N_4PSi_3$	$C_{15}H_{30}N_4PSSi_3$
Formula weight	390.74	413.73
Crystal color, habit	clear, rectangular	colorless plate
Crystal dimensions (mm)	0.4 x 0.2 x 0.2	0.4 x 0.3 x 0.08
Crystal system	triclinic	monoclinic
2θ	25 (18-31°)	25 (4.27-15.77°)
Lattice parameters		
a, Å	10.304(5)	17.841(4)
b, Å	14.963(7)	9.532(2)
c, Å^3	16.753(8)	15.611(3)
α,°	78.51(4)	111.38(3)
β, °	86.66(4)	2397.2(20)
γ, °	71.28(3)	
Space group	P$\bar{1}$	P2$_1$/n
Z	4	4
d_{calcd} g/cm^3	1.083	1.112
$\mu_{(CuK\alpha)}$mm^{-1}	2.479	0.347
Diffractometer	Siemens P4	Enraf-Nonius CAD4
Radiation, graphite monochromated	CuK$_\alpha$ (λ = 1.54178Å)	MoK$_\alpha$ (0.71073Å)
Temperature	213(2)	293(2)
Scan type	2θ:θ	ω-2θ
$2\theta_{max}$	108.74	54.94
No. of reflections measured	5884	5664
Corrections	Lorentz-polarization absorption (trans. factors 0.708-0.814)	Lorentz-polarization absorption (trans. factors 0.758-0.626)
No. observations [I ≥ 2σ(I)]	4208	2230
No. variables	415	217
Residuals: R; R$_w^a$	0.0699, 0.1830	0.0777, 0.1573
Goodness-of-fit indicator^b	1.113	1.191
Max, min difference peak (e$^-$/Å^3)	0.690	0.430

^{a}R = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$; R$_w$ = $[\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|]^{1/2}$. ^{b}Goodness of fit = $[w(|F_o|-|F_c|)^2/(n_{obs}-n_{par})]^{1/2}$.

TABLE 3. Selected Bond Angles and Bond Distances in 2f.

Bond Angles (deg)			
N(3A)-P(1A)-N(2A)	103.1(2)	N(1B)-P(1B)-N(2B)	103.8(2)
N(3A)-P(1A)-N(1A)	102.6(2)	N(1B)-P(1B)-N(3B)	103.4(2)
N(2A)-P(1A)-N(1A)	104.2(2)	N(2B)-P(1B)-N(3B)	102.7(2)
C(4A)-N(4A)-C(6A)	120.6(5)	C(4B)-N(4B)-C(6B)	119.8(5)
C(4A)-N(4A)-C(2A)	119.9(5)	C(4B)-N(4B)-C(2B)	118.7(5)
C(6A)-N(4A)-C(2A)	117.8(5)	C(6B)-N(4B)-C(2B)	119.1(5)
Bond Distances (Å)			
P(1A)-N(3A)	1.705(5)	Si(1A)-N(1A)	1.735(5)
P(1A)-N(2A)	1.715(5)	Si(2A)-N(2A)	1.737(5)
P(1A)-N(1A)	1.711(5)	Si(3A)-N(3A)	1.732(5)
P(1B)-N(1B)	1.711(4)	Si(1B)-N(1B)	1.745(5)
P(1B)-N(2B)	1.715(4)	Si(2B)-N(2B)	1.747(4)
P(1B)-N(3B)	1.720(4)	Si(3B)-N(3B)	1.730(4)

TABLE 4. Selected Bond Angles and Distances in 3a.

Bond Angles (°)			
N(2)-P-N(3)	107.9(2)	N(1)-P-S	110.7(2)
N(2)-P-N(1)	107.9(2)	C(4)-N(4)-C(6)	120.1(6)
N(3)-P-N(1)	107.9(2)	C(4)-N(4)-C(2)	119.4(5)
N(2)-P-S	111.6(2)	C(6)-N(4)-C(2)	119.8(5)
N(3)-P-S	110.8(2)		
Bond Distances (Å)			
P-N(2)	1.653(5)	P-N(1)	1.675(4)
P-N(3)	1.661(5)	P-S	1.952(2)

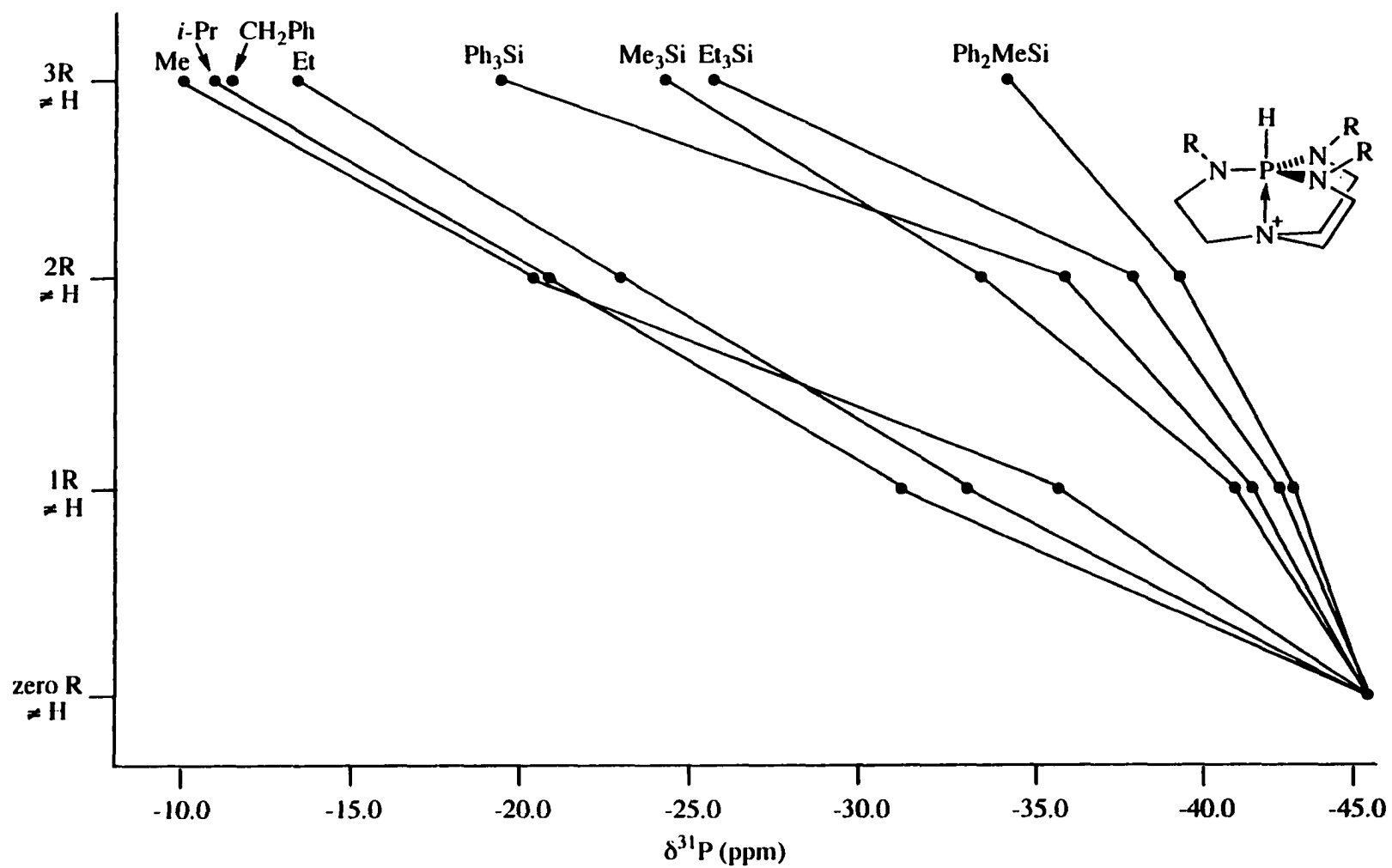Figure 1. Plot of ^{31}P NMR chemical shifts of protonated pro-azaphosphatranes against the number of non-hydrogen R groups.
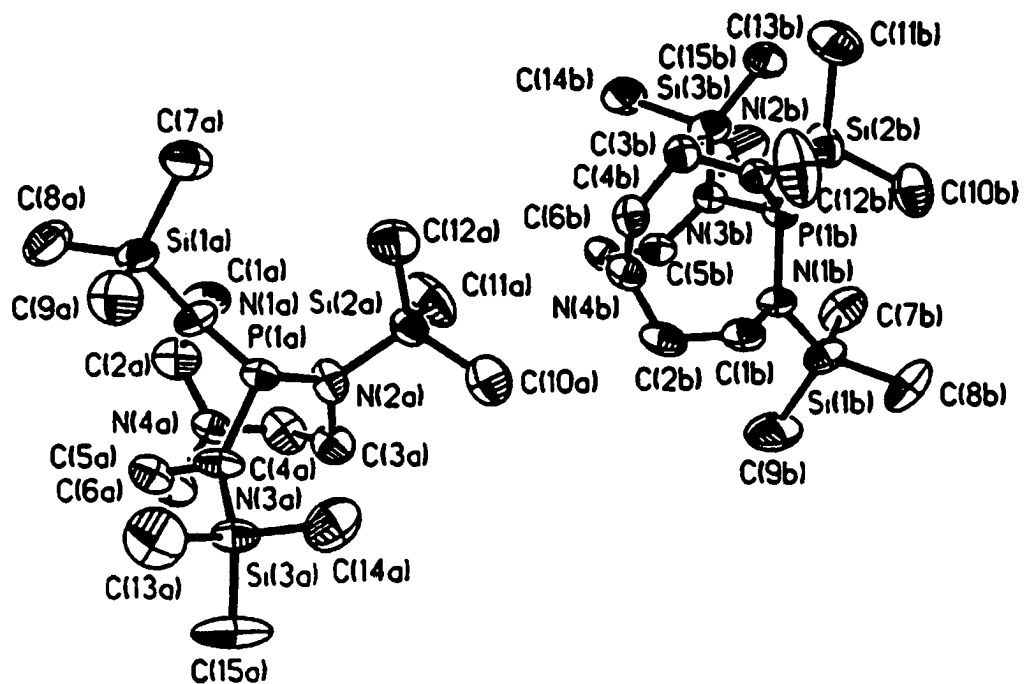
31

Figure 2. Computer drawing of **2f** with thermal ellipsoids at the 50% probability level.
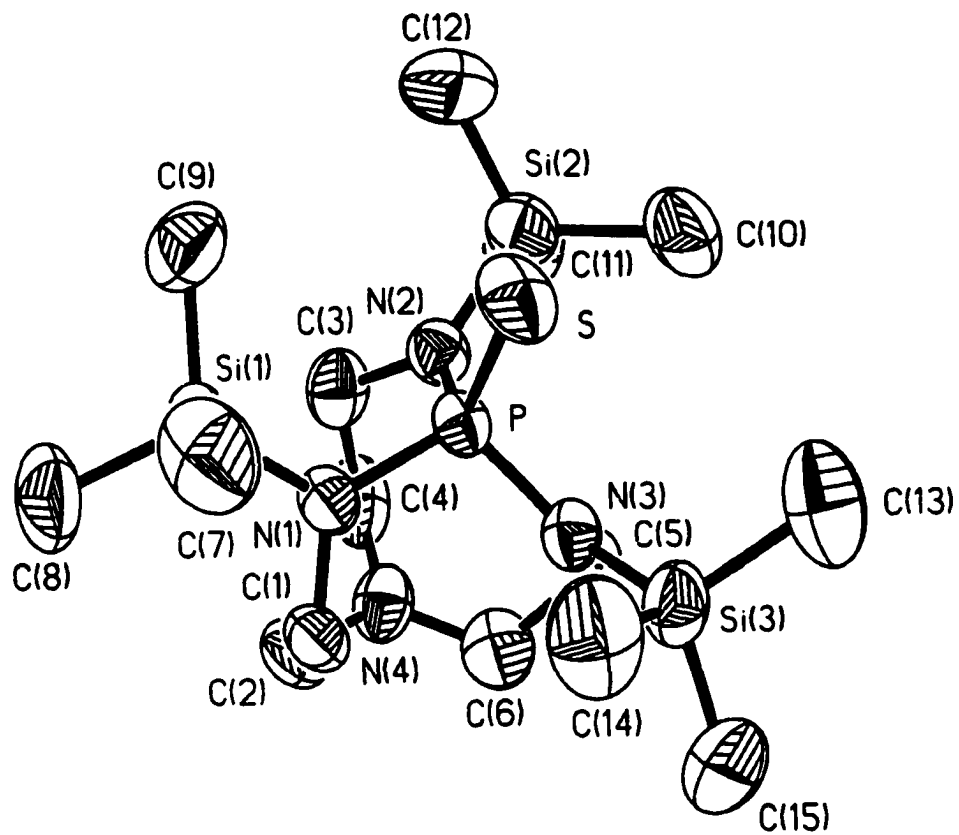
Figure 3. Computer drawing of **3b** with thermal ellipsoids at the 50% probability level.

CHAPTER 4. FREE AND POLYMER-BOUND TRICYCLIC AZAPHOSPHATRANE HP(RNCH₂CH₂)₃N⁺: PROCATALYSTS IN DEHYDROHALOGENATIONS AND DEBROMINATIONS WITH NaH

A paper published in the *Journal of Organic Chemistry*, **1999**, *64*, 4840

Xiaodong Liu, Zhengkun Yu and John G. Verkade

Abstract

The commercially available nonionic base $P(CH_3NCH_2CH_2)_3N$ (**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 $HP(CH_3NCH_2CH_2)_3N^+$ (**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 CH_3CN at room temperature. In dehydrohalogenations requiring more than *ca.* 10 h, the $^-CH_2CN$ 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 $HP(HNCH_2CH_2)_3N^+$ (**3**) and $HP[N(polymer)CH_2CH_2]N(CH_2CH_2NH)_2^+$ (**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.[1] Although typical organic bases, such as Et_3N, 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.[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,[4] for the temporary protection of double bonds,[5]

and for generating a new double bond as part of a synthetic sequence.[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.[7] Recently[8,9] we

found that the commercially available proazaphosphatrane 1a, reported for the first time by our

group,[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-t-Bu.[11]

	R	R'
1a	Me	Me
1b	H	H
1c	polymer	H

2(X)
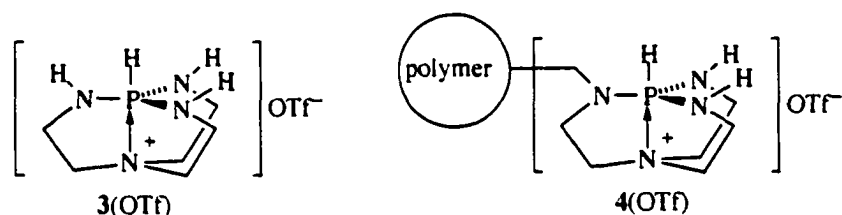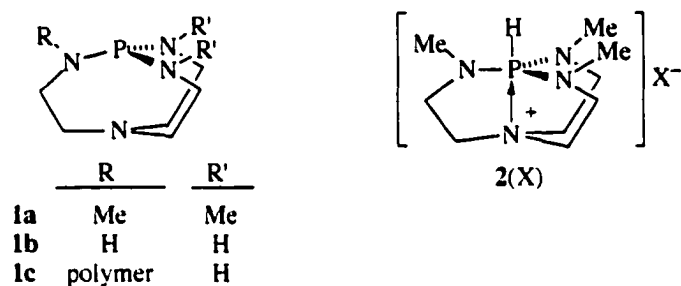
3(OTf)

4(OTf)

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-t-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_3CN 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_3CN to give 1a is shown by a ^{31}P NMR

spectrum of a CH_3CN 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(Cl), 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_3CN 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 β 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 β 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.[9] 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.[9] 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.[9]

Scheme 1
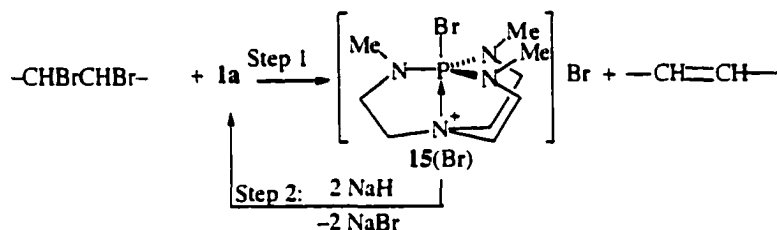
We believe the pathway shown in Scheme 1 for 2(Cl) reasonably accounts for the formation of these debrominated products. Thus step 1 occurs in the stoichiometric experiment and this is followed by step 2 under catalytic conditions. As with the use of PPh_3 in such reactions,[12] initial nucleophilic attack of the phosphorus of 1a on a bromine is followed by the formation of cation 15[13] 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 ^{1}H NMR experiments, 10 mol% of 2(Cl)/2.5 equiv of NaH and 2.0 equiv of PPh_3 were used to debrominate 10 in CD_3CN at 35 °C. It was found that debromination by 2(Cl)/NaH is much more efficient than by PPh_3: 99% conversion vs <30% conversion in 2 h. The literature describes the use of PPh_3 for debromination promoted under
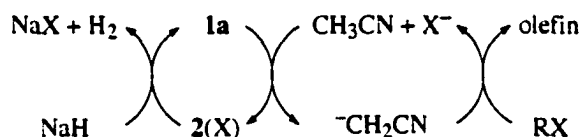
considerably harsher conditions (xylene/150-160 °C/250 min), and the yield is only moderate (76%).[12]

A possible dehydrohalogenation pathway for substrates requiring extended reaction times (beyond *ca.* 10 h) in the presence of **1** in CH_3CN was proposed earlier, in which evidence was put forth that the ⁻CH_2CN abstracts a proton from the substrates.[9] Thus the main phosphorus-containing compound observed in the dehydrohalogenation of **13** in D_3CCN is the deuterio analogue of **2**, which displayed a triplet signal at -10.0 ppm in ³¹P NMR spectrum.[9]

Scheme 2

$$NaX + H_2 \quad \diagdown \diagup \quad \textbf{1a} \quad \diagdown \diagup \quad RX$$
$$NaH \quad \diagup \diagdown \quad \textbf{2(X)} \quad \diagup \diagdown \quad olefin$$

Scheme 3

$$NaX + H_2 \quad \diagdown \diagup \quad \textbf{1a} \quad \diagdown \diagup \quad CH_3CN + X^- \quad \diagdown \diagup \quad olefin$$
$$NaH \quad \diagup \diagdown \quad \textbf{2(X)} \quad \diagup \diagdown \quad {}^-CH_2CN \quad \diagup \diagdown \quad RX$$
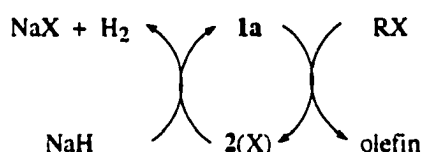
Catalytic cycles that account for the aforementioned direct and indirect dehydrohalogenations are shown in Schemes 2 and 3, respectively, for cation **2**. The first step in Scheme 2 involves NaH deprotonation of cation **2** to give **1a**, the effective dehydrohalogenation agent for substrates with 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
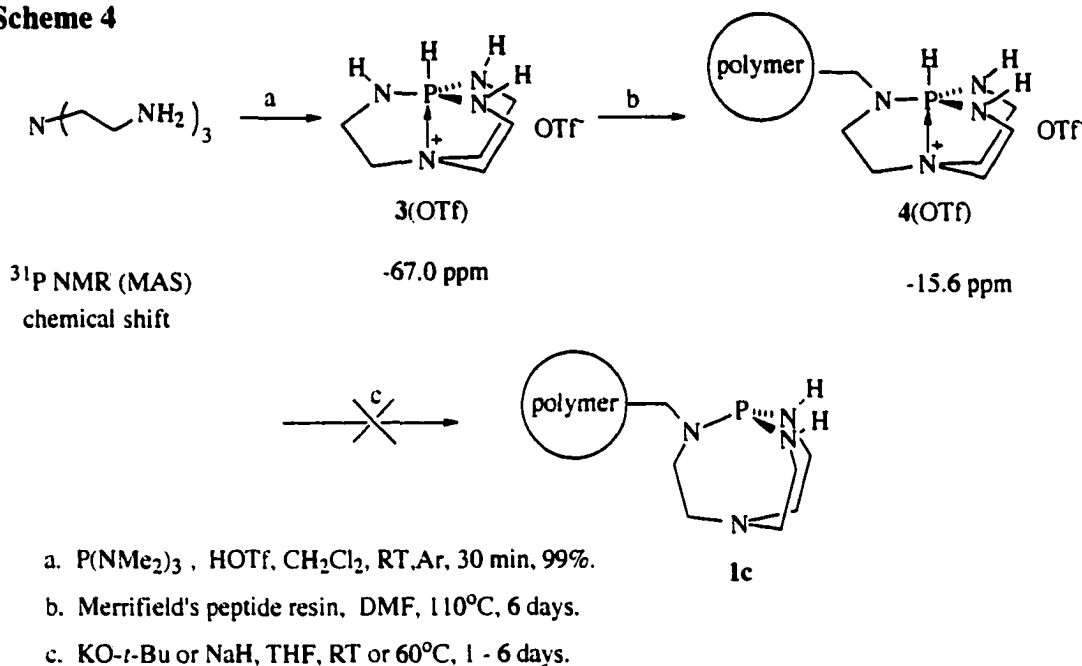
rate of alkyl halides with **1a** is fast compared with the regeneration of **1a** from **2** by NaH. A similar conclusion can be drawn from the cycles in Scheme 3 in which the process on the left is again the slow step. In this scheme, however, deprotonation of CH_3CN by **1a** is faster than deprotonation of RX by **1a**. All of the reactions were accompanied by the formation of H_2 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 subequent 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 ^{31}P 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 ^{31}P 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 CH_3CN 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

3(OTf)   4(OTf)

^{31}P NMR (MAS)   -67.0 ppm   -15.6 ppm
chemical shift

1c

a. P(NMe₂)₃, HOTf, CH₂Cl₂, RT,Ar, 30 min, 99%.
b. Merrifield's peptide resin, DMF, 110°C, 6 days.
c. KO-*t*-Bu or NaH, THF, RT or 60°C, 1 - 6 days.

Experimental Section

CH$_3$CN and CD$_3$CN were distilled from CaH$_2$. 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)[10] and 3(OTf)[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, Et₃N, MeOH, THF, Et₂O, THF and Et₂O (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): δ -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): δ -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 CD₃CN 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 CH₃CN (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 MgSO₄, 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
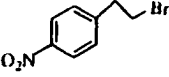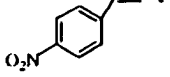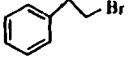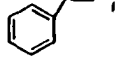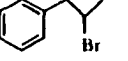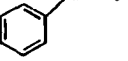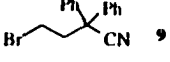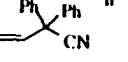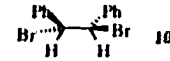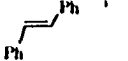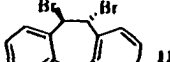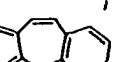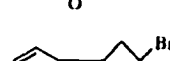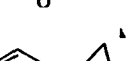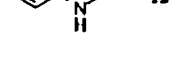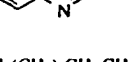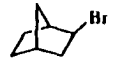
24 h to give 4(OTf) as a pale yellow-brown solid (0.45 g, 90% mass recovery). Solid state
^{31}P NMR (MAS): δ -15.7 ppm.

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Table 1. Dehydrobromination and debromination of alkyl halides with 2(Cl)/NaH, 3(OTf)/NaH, 4(OTf)/NaH and NaH alone.

substrate	product[a]	reaction time (h)	eluent	% conversion[b] (yield[c])			
				2(Cl)/NaH	3(OTf)/NaH	4(OTf)/NaH	NaH only
Br~CN **5**	=CN [d]	0.6	na	99	99	99	82
O₂N–C₆H₄–CH₂CH₂Br **6**	O₂N–C₆H₄–CH=CH₂ [e]	1	hexanes	99	99 (94)	95 (92)	43
C₆H₅–CH₂CH₂Br **7**	C₆H₅–CH=CH₂ [f]	2	hexanes	99 (92)	99	97 (91)	72
C₆H₅–CH₂CH(Br)CH₃ **8**	C₆H₅–CH=CHCH₃ [g]	2	hexanes	98 (91)	99	95 (90)	25
Ph Ph CN Br **9**	Ph Ph CN [h]	2		60	59	37	3
		6	CH₂Cl₂	99 (95)	78	97 (92)	19
Br Ph Ph Br **10**	Ph Ph [i]	2	CH₂Cl₂	99 (94)	98	98 (92)	39
Br Br (dibenzosuberone) **11**	(dibenzosuberone) [j]	2	CH₂Cl₂	99 (92)	99	97 (90)	25
indole–CH₂CH₂Br **12**	indole spiro [k]	1	.	99 (85[m])	99	99 (90[n])	81
CH₃(CH₂)₄CH(Br)CH₃ **13**	CH₃(CH₂)₄CH=CH₂[o] trans-CH₃(CH₂)₃CH=CHCH₃[p]	36	na	22 65	24 70	8 25	<1
norbornyl–Br **14**	norbornene [q]	100	na	0	0	0	0

44

Table I. (continued)

[a]Identification was made by comparing ^1H and ^{13}C NMR spectral data with those in the references indicated. [b]Conversions were determined by ^1H 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. [c]Isolated yields were obtained by chromatography and purity was determined by ^1H NMR spectroscopy. [d]Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(1), 1358B. [e]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. [f]Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(2), 23A. [g]Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(2), 24A. [h]See reference 5. [i](a)Kropp, P. J.; Crawford, S. D. J. Org. Chem. 1994, 59, 3102. (b) Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(2), 36A. [j](a) Rupard, J. H.; Paulis, T. D.; Janowsky, A.; Smith, H. E. J. Med. Chem. 1989, 32, 2261. (b) Jones, A. J.; Gardner, P. D.; Grant, D. M.; Litchman, W. M.; Boekelheide, V. J. Am. Chem. Soc. 1970, 92, 2395. [k]Johansen, J. E.; Christie, D.; Rapoport, H. J. Org. Chem. 1981, 56, 4914. The reaction was carried out in dry THF intead of CH_3CN. [l]The product decomposed during attempted chromatographic separation. [m]From bulb-to-bulb distillation at 120 °C/0.1 torr. [n]From direct filtration of the reaction mixture followed by drying under vacuum. [o]Aldrich Library of ^{13}C and ^1H Ft NMR spectra, 1993, 1(1), 18B. [p]Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(1), 25B. [q]Aldrich Library of ^{13}C and ^1H FT NMR spectra, 1993, 1(1), 73C.

CHAPTER 5. P[(S,S,S)-PhHMeCNCH₂CH₂]₃N: A NEW CHIRAL ³¹P AND ¹H NMR SPECTROSCOPIC REAGENT FOR THE DIRECT DETERMINATION OF ee VALUES OF CHIRAL AZIDES
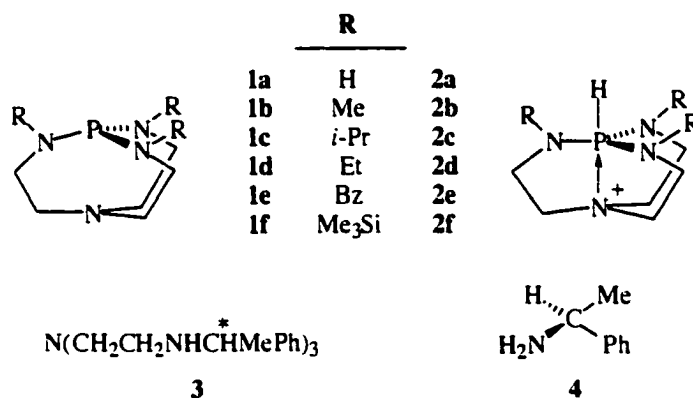
Xiaodong Liu, Palanichamy Ilankumaran, Ilia A. Guzei and John G. Verkade

Abstract

A facile and economical procedure for the synthesis of the C_3 chiral α-phenylethylamino trisaminoamine [(S,S,S)-PhHMeCNHCH₂CH₂]₃N in good yield is reported. The corresponding bicyclic proazaphosphatrane P[(S,S,S)-PhHMeCNCH₂CH₂]₃N, 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 ³¹P and ¹H NMR spectroscopy.

Introduction

In recent years we have been exploring the chemistry of proazaphosphatranes such as **1a-f**,[1-6] 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


	R	
1a	H	**2a**
1b	Me	**2b**
1c	*i*-Pr	**2c**
1d	Et	**2d**
1e	Bz	**2e**
1f	Me₃Si	**2f**

N(CH₂CH₂NHCHMePh)₃

3

H⸳⸳C⸳Me / H₂N⸳C⸳Ph

4

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 addtions,[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, ^{31}P 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.[21e] However, no derivatizing agent has been reported for the direct determination of *ee* values of chiral azides by means of ^{31}P or ^{1}H NMR spectroscopy.

5Cl   6   7
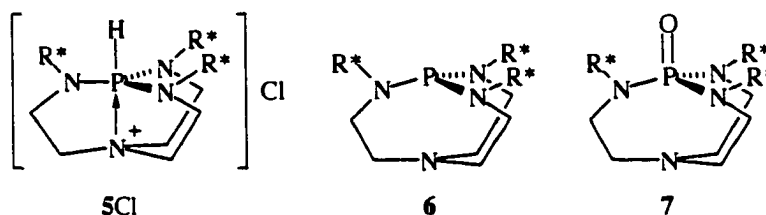
We report herein a simple and efficient procedure for the synthesis of the C_3 chiral

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 ^{31}P and ^{1}H NMR spectroscopy. Upon oxidation, proazaphosphatrane **6** yields the

new C_3-chiral phosphine oxide **7**.

Scheme 1
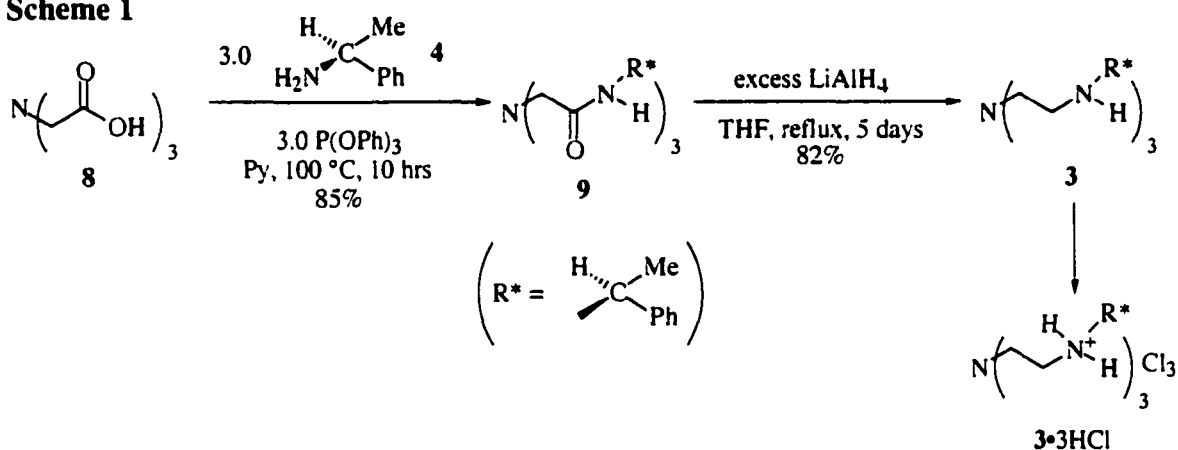
Results and Discussion

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[23] 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 LiAlH$_4$ in refluxing THF for five days. The

yield of **3** (82%) is surprisingly good.

**Scheme 2**

10 → (5 steps) → 11
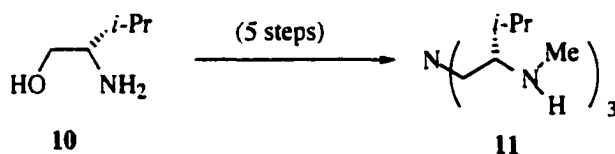
Scheme 3

12 → (7 steps) → 13
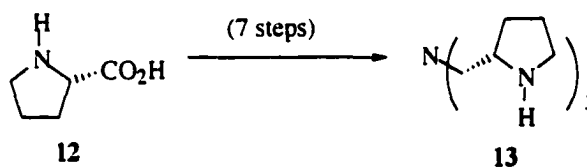
The only two tripodal chiral trisaminoamines that have been reported possess chiral centers at the beta carbon of the tertiary nitrogen[24,25] as shown in Schemes 2 and 3. The synthesis of **11** involves nucleophilic ring opening of the aziridine derived from **10**.[24] The drawbacks of this synthesis 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.[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.[3]

Scheme 4
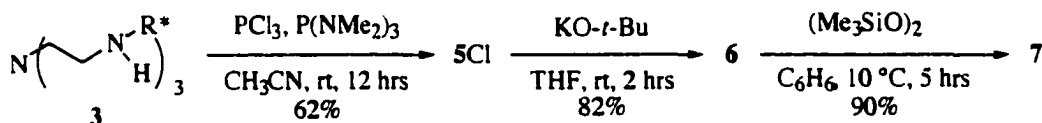
However, formation of the tricyclic phosphatrane cage was not complete even after one week of reaction. Thus only 75% conversion and a 62% isolated yield were realized, which is considerably lower than the 95% conversion and 90% isolated yield for the analogous synthesis of **2b**. Raising the temperature 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 $(Me_3SiO)_2$ in benzene gave **7** in 90% yield.

Structural considerations. The computer drawing of **5**(Cl) in Figure 1 features a $P-N_{ax}$ 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 $\angle CN_{ax}C = 112.54(7)°$] 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 $P-N_{ax}$ 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. $\angle N_{eq}PN_{eq} =$ 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.[5] 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 **1c**[5] (3.293 Å). The remaining bond distances and

angles are unremarkable (Table 4) and the crystallographic data are collected in Table 3.


14
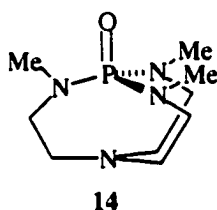
Like its nonchiral analogue **14**,[7] compound **7** (Figure 3) displays a nearly tetrahedral

geometry around bridgehead P [avg$\angle N_{eq}PN_{eq}$ = 107.81(13)°] and a nearly planar trigonal

geometry around the bridgehead nitrogen [avg $\angle CN_{ax}C$ = 119.999(6)°], compared with

107.6(1)° and 118.9(2)°, respectively, in **14**.[7] 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].[7] 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[10] 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

(1)
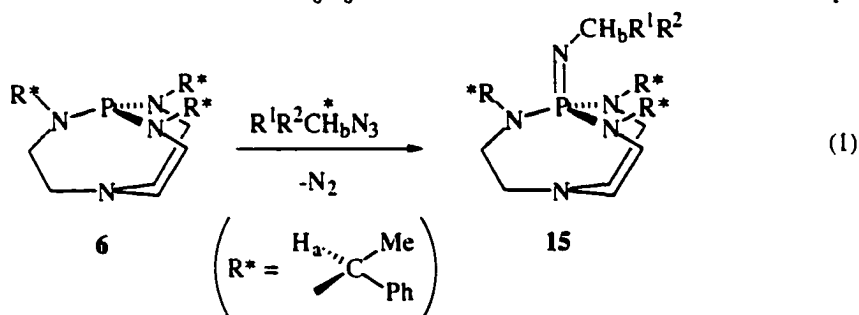
reaction 1. The ^{1}H and proton-decoupled ^{31}P NMR spectra of these derivatives were obtained

directly without further purification. To evaluate the derivatizing ability of **6**, (±)-neomenthyl

azide was reacted with **6** in C_6D_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 proazaphosphatrane 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.

16
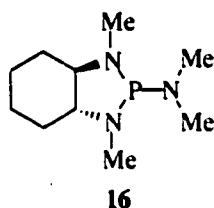
When (-)-neomenthyl azide was reacted under the same conditions, only one singlet

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_6D_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 deprontonaton of the azido carbon, which was confirmed by the disappearance of the NMR spectroscopic resonance of this hydogen. Both the ^{1}H an ^{13}C NMR were quite complicated, however, suggesting that side reactions of the anion ensued.

Experimental Section

CH_3CN was dried with CaH_2. THF and Et_2O 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,[23] 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 $CHCl_3$ and then sequentially,

distilled H_2O (3 x 600 mL), 10% aqueous $NaHCO_3$ (10 x 600 mL), distilled H_2O (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%). ¹H and ¹³C NMR data were

consistent with those in literature.[23]

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_2O (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_2Cl_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 CH_2Cl_2 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, CH_2Cl_2 (4 x 50 mL) was used to extract the product. After drying over $MgSO_4$, complete evaporation under reduced pressure, and purification of the residue by silica gel column chromatography using a mixture of CH_2Cl_2 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 PCl_3 (47.0 mg, 0.33 mmol) in CH_3CN (10 mL) was added $P(NMe_2)_3$ (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 CH_3CN (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 CH_2Cl_2 and MeOH (15:1) as the eluent, giving **5(Cl)** (330 mg, 62%) as a white solid upon drying over $MgSO_4$ and evaporation under vacuum. A crystal for X-ray analysis was obtained by diffusing Et_2O into a solution of **5(Cl)** in CH_3CN 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 $R\bar{3}$ 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 ψ-scan technique. Absorption corrections were not
required for **6** because the variations in the integrated ψ-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_6D_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 1).

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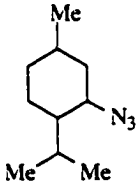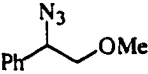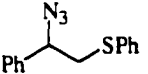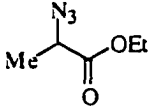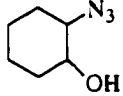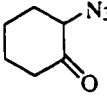
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27. All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrich, Bruker Analytical X-ray Systems, Madison, WI).

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

substrate	actual ratio	$\delta\,^{31}P\,(\Delta\,\delta)$ (ppm)[a]	$\delta^1H\,(\Delta\,\delta)$ (ppm)[b]	measured ratio[c]
17[d] (Me-substituted cyclohexyl azide, menthyl)	racemic	31.98 (1.14)	4.21 (0.14)	49.0:51.0 (49.1:50.9)
	(-)isomer[e]	32.66	4.18	100 : 0
	75:25[f]	31.98 (1.14)	4.21 (0.14)	75.2:24.8 (74.9:25.1)
18[g] (Ph-CH(N$_3$)-CH$_2$-OMe)	racemic	32.06 (0.63)	4.42 (0.22)	50.8:49.2 (50.2:49.8)
19[h] (Ph-CH(N$_3$)-CH$_2$-SPh)	racemic	32.26 (0.82)	5.19 (0.07)	50.2:49.8 (50.5:49.5)
20[i] (Me-CH(N$_3$)-C(O)-OEt)	racemic	31.72 (0.30)	4.78 (0.09)	50.2:49.8 (51.0:49.0)
21[j] (2-azidocyclohexanol)	racemic	31.97 (0.56)	5.72(0.15)[k]	51.0:49.0 (50.5:49.5)
22[l] (2-azidocyclohexanone)	racemic	na[m]	na[m]	na[m]

[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]H NMR compared favorably with that reported in *J. Chem. Soc. Perkin Trans. 1*, **1974**, 2287. [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(Cl), 6 and 7.[a]

	5(Cl)	6	7
formula	$C_{30}H_{40}ClN_4P$	$C_{30}H_{39}N_4P$	$C_{30}H_{39}N_4P$
formular weight	523.08	486.62	502.62
crystal system	rhombohedral	monoclinic	rhombohedral
space group	R3	$P2_1$	R3
crystal color, habit	colorless rod	colorless block	colorless block
a, Å	15.7922(10)	9.245(3)	14.5268(10)
b, Å	15.7922(10)	14.7103(8)	14.5268(10)
c, Å	9.8706(6)	10.918(4)	11.3942(18)
V, Å^3	2131.9(2)	1379.3(7)	2082.4(4)
Z	3	2	3
D(calc), g cm^{-3}	1.222	1.172	1.202
temperature, K	173(2)	293(2)	296(2)
diffractometer	Bruker CCD-1000	Siemens P4RA	Siemens P4RA
absorption correction	Empirical (SADABS)	none	semi-empirical
radiation	MoKα (λ = 0.71073 Å)	CuKα (λ = 1.54178 Å)	CuKα
μ, mm^{-1}	0.216	1.058	1.095
θ range, °	2.54-26.50	2.06-56.54	2.62-56.35
no. of measd reflect.	19563	2475	844
no. of obsd reflect.	1963	2034	691
R, %[a]	2.26	3.62	3.83
R$_w$, %[a]	6.16	9.54	10.05
GOF	1.054	1.058	1.030

[a]Quantity minimized = $R(wF^2) = \Sigma[w(F_o^2-F_c^2)]/\Sigma[(wF_o^2)^2]^{1/2}$; $R = \Sigma\Delta/\Sigma(F_o)$, $\Delta = |(F_o-F_c)|$.

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

Bond Distances

P-N(1)	1.6752(10)	N(1)-C(3)	1.4818(15)
N(1)-C(1)	1.4577(15)	N(2)-C(2)	1.4888(13)

Bond Angles

N(1)-P-N(1)#2	119.404(10)	C(3)-N(1)-P	121.88(8)
C(1)-N(1)-C(3)	117.04(10)	C(2)#2-N(2)-C(2)	112.54(7)
C(1)-N(1)-P	121.06(8)		

[a]Symmetry 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.

Bond Lengths			
P-N(1)	1.694(3)	P-N(2)	1.689(3)
P-N(3)	1.703(3)	N(1)-C(1)	1.455(5)
N(1)-C(7)	1.470(5)	N(2)-C(3)	1.468(4)
N(2)-C(15)	1.476(4)	N(3)-C(5)	1.461(4)
N(3)-C(23)	1.474(4)	N(4)-C(4)	1.437(5)
N(4)-C(2)	1.439(5)	N(4)-C(6)	1.440(5)
Bond Angles			
N(1)-P-N(2)	103.91(14)	N(1)-P-N(3)	104.15(15)
N(2)-P-N(3)	104.42(14)	C(1)-N(1)-C(7)	117.0(3)
C(1)-P-N(3)	125.5(3)	C(7)-N(1)-P	115.5(2)
C(3)-N(2)-C(15)	116.9(3)	C(3)-N(2)-P	125.6(2)
C(15)-N(2)-P	115.9(2)	C(5)-N(3)-C(23)	116.2(3)
C(5)-N(3)-P	124.9(2)	C(23)-N(3)-P	115.5(2)
C(4)-N(4)-C(2)	120.2(4)	C(4)-N(4)-C(6)	119.2(4)
C(2)-N(4)-C(6)	119.8(3)		

Table 5. Selected Bond lengths (Å) and angles (°) for 7.[a]

Bond Lengths

P-O	1.482(5)	N(1)-C(3)	1.499(5)
P-N(1)	1.654(3)	N(2)-C(2)	1.435(4)
N(1)-C(1)	1.449(5)		

Bond Angles

N(1)#1-P-N(1)	107.81(12)	N(1)-C(3)-C(4)	112.4(4)
C(1)-N(1)-C(3)	116.0(3)	O-P-N(1)	111.09(12)
C(3)-N(1)-P	119.4(3)	C(1)-N(1)-P	124.4(3)
C(2)-N(2)-C(2)#1	120.0(3)	N(2)-C(2)-C(1)	112.0(4)
N(1)-C(1)-C(2)	114.0(3)	N(1)-C(3)-C(5)	109.0(3)

[a]Symmetry transformations used to generate equivalent atoms: #1 -y,x-7,z.
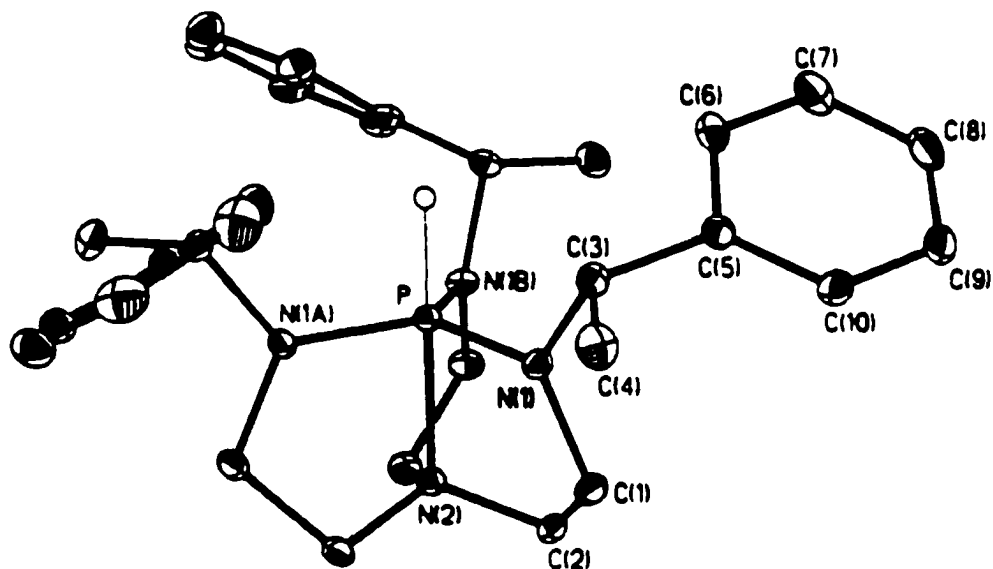
Figure 1. The molecular structure of cation 5 of 5(Cl) drawn with thermal ellipsoids at the 30% probability level. All hydrogen atoms except the H atom on the phosphorus were omitted for clarity
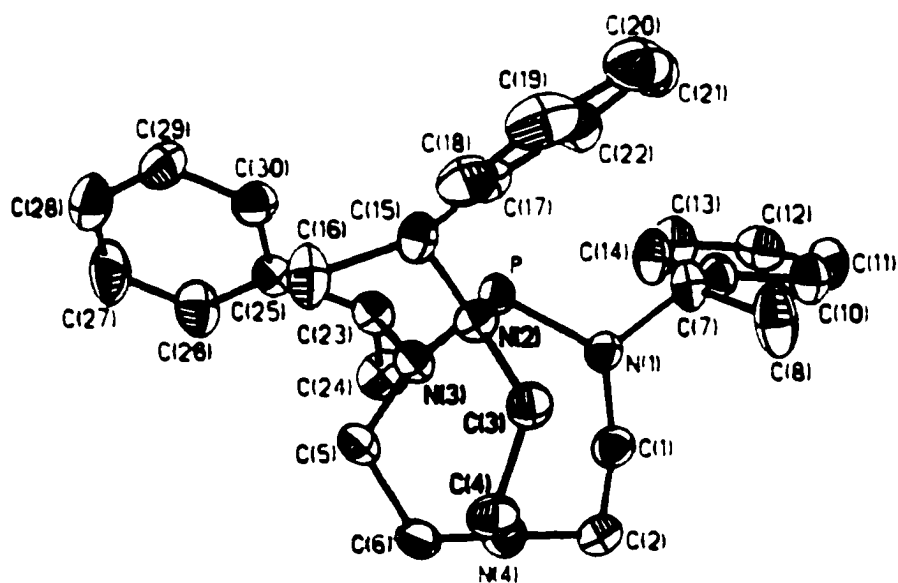
Figure 2. The molecular structure of 6 drawn with the thermal ellipsoids are shown at the 30% probability level. The hydrogen atoms have been omitted for clarity.
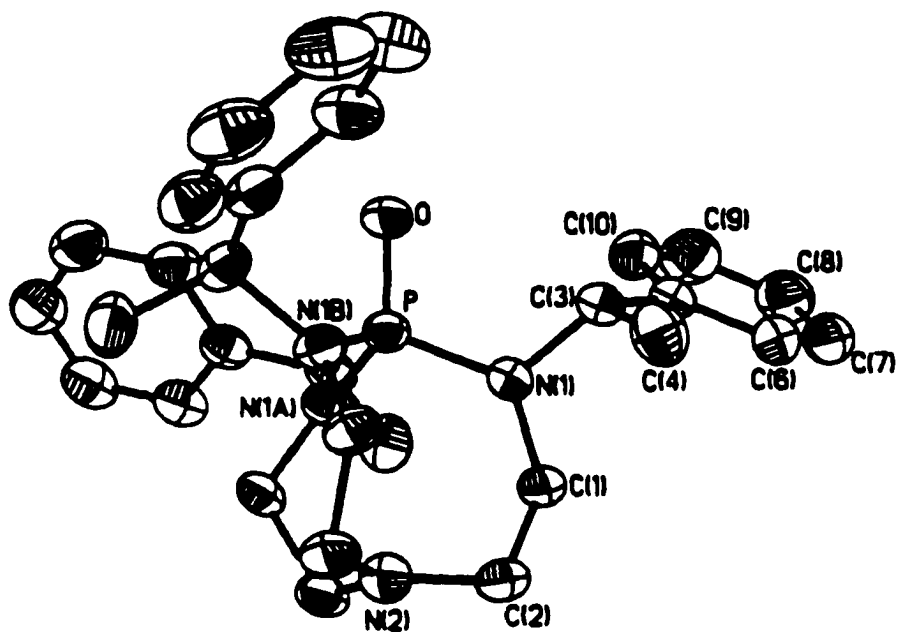
Figure 3. The molecular structure of 7 drawn with the thermal ellipsoids are shown at the 30% probability level. The hydrogen atoms have been omitted for clarity.

Supporting Information

³¹P, ¹H, ¹³C NMR and MS Spectral Data and Analyses

(*S*,*S*,*S*)-Tris(2-(α)-methylbenzylamino-ethyl)amine 3: ¹H NMR (CDCl₃): δ 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). ¹³C NMR (CDCl₃): δ 24.4, 45.4, 54.0, 58.5, 126.7, 126.9, 128.5, 145.8.

HRMS (EI) calcd for C₃₀H₄₂N₄ 458.3410, found 324.2840 [M-CH₂N(H)C(H)MePh]⁺. Anal.

calcd for C₃₀H₄₂N₄: 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:

¹H NMR (CDCl₃): δ 1.94 (d, 9H, *J* = 6.4 Hz), 1.99 (m, 3H), 2.55 (m, 3H), 3.26 (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). ¹³C NMR (CDCl₃): δ 20.8, 42.0, 51.2, 60.2, 128.5, 129.4, 129.5, 136.0. Anal. calcd

for C₃₀H₄₅N₄Cl₃: C, 63.44; H, 7.93; N, 9.87. Found: C, 63.75; H, 8.02; N, 9.73.

(*S*,*S*,*S*)-Azaphosphatrane 5(Cl): ³¹P NMR (CDCl₃): δ -10.5; ¹H NMR (CDCl₃): δ

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); ¹³C

NMR (CDCl₃): δ 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 C₃₀H₄₂N₄OPCl: C, 66.60; H, 7.77; N, 10.36. Found: C, 66.75; H, 7.88; N,

10.35.

(*S*,*S*,*S*)-Proazaphosphatrane 6: ³¹P NMR (C₆D₆): δ 126.5; ¹H NMR (C₆D₆): δ 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): δ 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$_3$): δ 22.0; ^{1}H NMR (CDCl$_3$):

δ 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$_3$): δ 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$_3$): δ 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$_3$): δ 5.65, 56.96, 83.29, 126.79, 128.53, 128.82,

MS (CI): 195 (M+NH$_4$$^+$), 138.73, 121.

CHAPTER 6. [O=P(*i*-PrNCH₂CH₂)₃NCH₃]⁺: NOVEL EFFECT OF QUATERNIZATION ON THE STRUCTURAL METRICS OF THE BICYCLIC CAGE
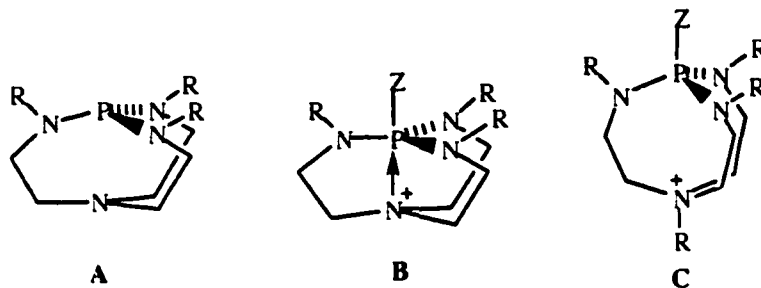
Xiaodong Liu, Brad Logsdon, Robert A. Jacobson and John G. Verkade*

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 $CN_{bridgehead}C$ 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.

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_{ax} distances (3.29 Å, R = *i*-Pr¹; 3.36 Å, R = SiMe₃²) that are 2% to

A   B   C

approximately 0% shorter than the sum of the P-N_{ax} van der Waals radii (3.35 $\AA^3$) 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) $\AA$, R = H^4; 1.967(8) $\AA$, R = Me^5; 1.964(2) $\AA$,

R = i-Pr^1] or Cl^+ [1.937(8)$\AA$, R = Me^6]. 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_2C < 1/2Cl_2Hg

≈ O < S < cis-Br(OC)$_4$Re until at Z = 1/2$trans$-Cl_2Pt a maximum of 3.33 $\AA$ is reached[7], 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 $CH_3CN)^8$ has been utilized by our group to improve substantially the synthesis

of pyrrols,[9] oxazoles,[9] porphyrins,[9] α-C-acylaminoacids[9] 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 promotor 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
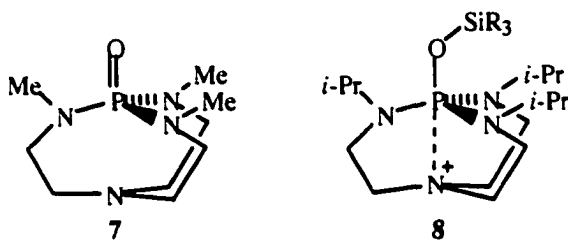
	Z	R	R'	
1a	S	Me	Me	1b
2a	S	Me	Et	2b
3	O	i-Pr	Me	
4	O	i-Pr	Et	
5	O	Me	Me	
6	O	Me	Et	

= S.[21] The upfield ^{31}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.[6] 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}[1,22] and such repulsions would presumably be intensified by downward pyramidalization of N_{ax} upon attack of an electrophile. Indeed, the $CN_{ax}C$ angle of **3** [avg 113.9(10)°], 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) Å] over the Si,N van der Waals sum in the recently

reported structure of {*trans*-(PPh₃)₂Os(O)Cl[Si(OCH₂CH₂)₃NMe]}CF₃SO₃.[23] However, the

$CN_{ax}C$ angle in this complex [avg. 113.90[23]] is essentially the same as in **3** and this is

probably so for the same reason(s) as it is in the [HC(CH₂CH₂)₃NH]⁺ cation wherein this

angle has an average of 115.5° and the $CC_{bridgehead}C$ angle averages 113.9°.[25]

7　　　　**8**

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 $CN_{ax}C$ angle decreases by *ca* 6° upon quaternization of N_{ax}. The

$CN_{ax}C$ angle decrease from **7** to **3** causes a concomitant enlargement of the $N_{eq}CC$ angle by

ca 3° while the CCN_{ax} angle remains constant within experimental error [i.e., 3x(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

$CN_{ax}C$ angle decrease in **3** is the induction of a twist of the cage (avg. $N_{ax}CCN_{eq}$ 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_3 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 ¹H 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 ¹H NMR spectrum of **3**,

two sets of CH(C*H₃*)₂ protons are also observed. We also observed that O=P(*i*-

PrNCH₂CH₂)₃N, 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,[5] was recrystallized from a CH_3CN 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 $MoK\alpha$ 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 hundered 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 $2\theta = 45°$. 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.[27] 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.

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Table 1. Crystallographic Data for **3**.

Formula	$C_{16}H_{38}IN_4O_2P$
F.W.	476.37
Crystal System	monoclinic
Space Group	$P2_1/n$
a (Å)	9.243(4)
b (Å)	15.230(4)
c (a)	16.332(8)
β (°)	93.93(4)
Z	4
F(000)	984
D_{calcd} (g/cm^{-3})	1.380
μ(MoKα) (cm^{-1})	14.81
Scan Mode	ω
θ-range (°)	3-22.5
Octants of reciprocal space explored	+h, +/- k, +/- l
Measured reflections	4838
Unique refl. with I>3σ(I)	941
Final R and R_w indices[a]	0.387, 0.1589
No. of variables	217
GOF[b]	0.840

[a] $R = [\Sigma(F_o - k|F_c|)/\Sigma F_o]$. $R_w = [\Sigma w(F_o - k|F_c|)^2/\Sigma w F_o^2]^{1/2}$. [b] $GOF = [\Sigma w(F_o - k|F_c|)^2/(N_{observations} - N_{variables})]^{1/2}$.

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 $R_3P=O$ 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 $R_3P=O$ is an efficient catalyst in such reaction when R is a good electron donating group, such as Me_2N or n-Bu and as $NMe(CH_2)$ in $N(CH_2CH_2NMe)_3P=O$ (3). However, $R_3P=O$ is a weak or ineffective catalyst when R is a poor electron donating group, such as Ph or O-n-Bu or as CH_2N-o-$CH_2C_5H_4N$ in $N(CH_2CH_2N$-o-$CH_2C_5H_4N)_3P=O$. Compound 3, synthesized by oxidation of commercially available $N(CH_2CH_2NMe)_3P$, 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.[1] Among the many trialkylsilyl reagents used to protect this functionality, t-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDMSCl) are two of the most popular.[2] A variety of methods has been reported for the derivatization of alcohols with the TBDMS and TBDPS moieties.[3] These reactions have been most satisfactorily achieved by reacting the alcohol with a molar excess of imidazole using dimethyl formamide (DMF) as a solvent,[4,5] or with catalysts such as DMAP,[2f] 1,1,3,3-tetramethylguanidine[2a] and ethyldiisopropylamine.[2e]

More recently, the silylation of primary and secondary alcohols in 69-99% yields using

TBDPCl in DMF with catalysts, such as $AgNO_3$, NH_4NO_3, or NH_4ClO_4 has been described.[3d]

Proazaphosphatranes of type 1[6] have been shown to be very strong nonionic bases that

function as superior deprotonating agents,[7] as a superior catalysts[8] and as efficient promoters[9]

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 1[8b] 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

isocyanurates[10] 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.

4a R = R' = Me, R" = t-Bu
4b R = R' = Ph, R" = t-Bu
4c R = R' = R" = Me
4d R = R' = R" = Ph
4e R = R' = Cl, R" = Me
4f R = R' = R" = Cl

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,

$O=P(NMe_2)_3$ and $O=P(n\text{-}Bu)_3$ 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

$$\text{O=P(catalyst)} \quad \text{or other O=PR}_3 \text{ catalysts}$$

ROH
(1°, 2° and phenols)

MeCN, Et₃N, rt - 35°C
t-BuMe₂SiCl or t-BuPh₂SiCl

$$\left.\begin{array}{l} t\text{-BuMe}_2\text{SiOR} \\ t\text{-BuPh}_2\text{SiOR} \end{array}\right\} + \text{Et}_3\text{NHCl} \qquad (1)$$
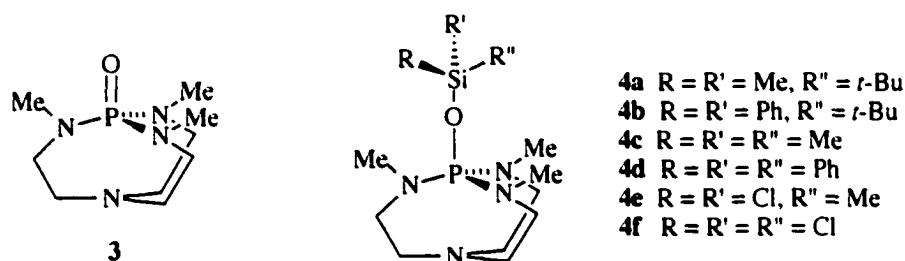
Py-o-H₂C ... O=P ... o-CH₂Py / o-CH₂Py

5
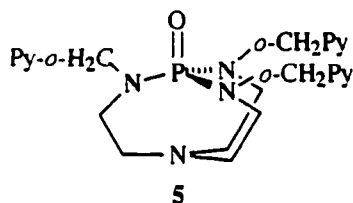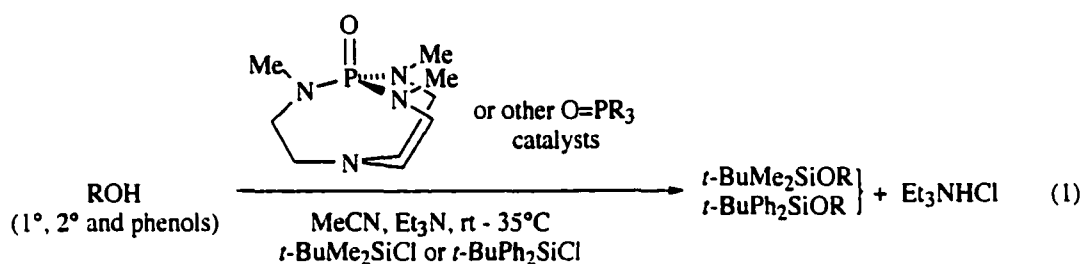
DMAP^{2f} is also presented. The phosphine oxides O=PPh₃ and O=P(O-n-Bu) and **5**[12] were found to be poor to nonfunctioning catalysts for alcohol silylation.

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$_2$) (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.[11] 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$_5$H$_4$N moieties and the large cone angle swept out by the CH$_2$-o -C$_5$H$_4$N segment of the CH$_2$-o -C$_5$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 Et_3N was used, much slower conversions at room temperature were observed than with 10 mol% of **3** and 1.1 equiv of Et_3N (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 Et_3N 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 $O=P(NMe_2)_3$ when Et_3N 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 TBDPSCl 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 TBDPSCl, giving only a 30% conversion of product in 24 h.

Scheme 1
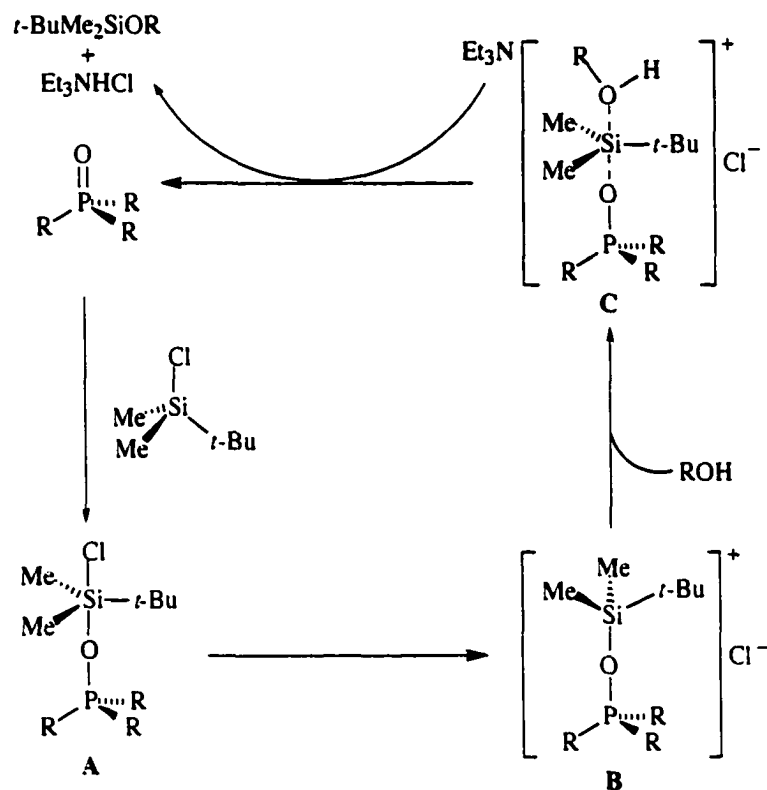
Although several mechanistic pathways can be considered that rationalize the ability of electron rich $O=PR_3$ compounds to catalyze hydroxyl silylation, we believe the one shown in Scheme 1 is the most plausible on the basis of present evidence. This pathway could be facilitated in the case of the somewhat 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 $SiCl_4$ promoted by $O=P(NMe_2)_3$.[13] Further support for the pathway in Scheme 1 comes from our previously reported isolation and characterization of **4e** and **4f**.[11] ^{1}H and ^{31}P NMR spectroscopic data suggest the presence of transannulation in these compounds as well as in **4c** 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 CH_3CN. 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.[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 TBDPSCl. 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[6] and 5[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 μL, 0.11 mmol). After shaking the tube for 2 min, 6 (10 μL, 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 TBDPSCl. In a 10 mL test tube capped with a rubber septum was dissolved 0.1 equiv of a catalyst in 2 mL of CD_3CN. To this was added 1.0 mmol of the alcohol followed by the addition of NEt_3 (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. ^1H NMR spectra were taken to obtain the conversion based on ^1H 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 H_2O was added with stirring. The mixture was filtered, and the residue was washed with Et_2O (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 $MgSO_4$ and evaporation of the eluent. The identifying ^1H and ^{13}C 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 CH_3OH. After collecting the pure CH_3OH fraction and evaporating the solvent under vacuum, 3 was recovered as a white solid in 60-75% yields. The ^{31}P, ^1H and ^{13}C NMR spectra were identical to those of an authentic sample of 3.
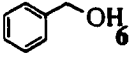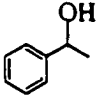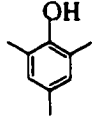
Supporting Information Available: ^{1}H and ^{13}C NMR spectra data and mass spectral molecular weights (7 pages).

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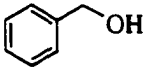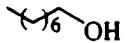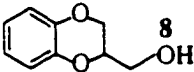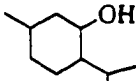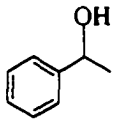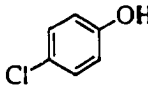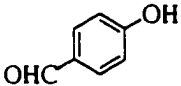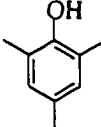
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Table 1. Comparison of seven catalysts for alcohols with TBDMSCl.[a]

substrates	reaction time (h)	% conversions[b]							
		no cat.	O=P(O-n-Bu)$_3$	O=PPh$_3$	5	O=P(n-Bu)$_3$	O=P(NMe$_2$)$_3$	3	DMAP
6	0.5	70	72	80	91	98	97	98	95
10	6	41	29	60	71	94	93	99	85
14	12	20	22	26	33	58	53	63	65
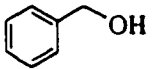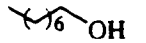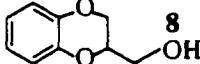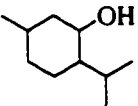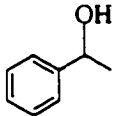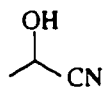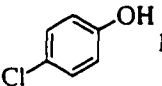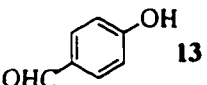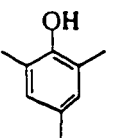
[a]See Experimental Section for conditions. [b]Based on ^{1}H integrations in which the error limit is about 1% absolute. Conversions are reproducible within this error limit for at least two separate runs on each substrate.

Table 2. Comparison of 3 and DMAP in alcohol silylation with TBDMSCl.[a]

substrate	reaction time (h)	conversions[b] (yields[c]) (%)		
		3[d]	DMAP[d]	no cat.
(benzyl alcohol) **6**	0.5	98 (91)	95	70
7	0.5	98 (92)	88	45
8	2	97 (91)	90	44
9	6	97 (93)	60	31
10	6	99 (91)	85	41
11	6	99 (94)	99	65
12	0.2	99 (95)	99	91
13	0.2	99 (94)	99	90
14	12	63 (55)	65	20
t-BuOH **15**	48	—[e]	—[e]	—[e]

[a]See Experimental Section for conditions. [b]Based on ¹H 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 ¹H NMR spectroscopy. The yields are the highest values observed in each case. [d]10 mol% catalyst. [e]No detectable reaction.

Table 3. TBDPSCl Alcohol silylations catalyzed by 3.[a]

substrates		reaction time (h)	conversions[b] (%)	
			3[c]	no cat.
	6	6	95	47
	7	6	99	50
	8	24	97	39
	9	24	74	25
	10	24	30	9
	11	24	94	59
	12	4	97	78
	13	4	98	85
	14	50	-[d]	-[d]

[a]See Experimental Section for conditions. [b]Based on ^{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. New compounds were characterized by ^{1}H, ^{13}C NMR, and HRMS(EI) spectroscopies. [c]10 mol% catalyst. [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 $P(NMe_2)_3$ (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), $P(MeNCH_2CH_2)_3N$ (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.[1-3] 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.[4] For converting aryl aldehydes possessing electron withdrawing groups to the corresponding epoxides, Mark *et al.* found that $P(NMe_2)_3$ (1) is a reagent that provides a

1
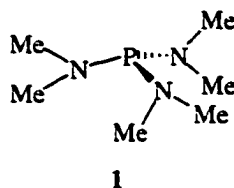
simple and mild approach often leading to high yields of product.[4] Moreover, this

transformation tolerates sensitive functional groups (such as pyridyl) that oxidative methods do

not. The use of 1 has therefore constituted a practical synthetic approach.[5-8] 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,[4] depending on the substrate.

Thus, finding a stereoselective synthesis of epoxides from aryl aldehydes has remained

challenging.

R	label
Me	a
i-Pr	b
Et	c
Bz	d
Me₃Si	e
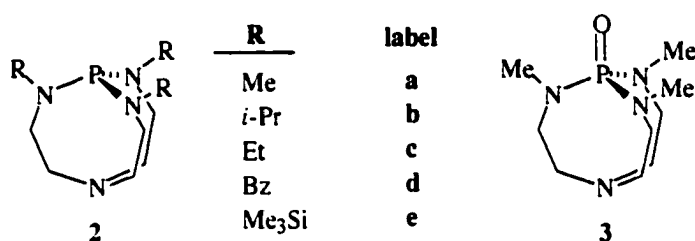
In recent years we have been exploring the chemistry of proazaphosphatranes such as

2a-e[9-14] 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,[15] for the protective silylation of a wide variety of sterically

hindered and deactivated alcohols,[16] and for the acylation of alcohols.[17] Proazaphosphatrane 2a

is a much stronger base than DBU,[18] a commonly used nonionic base in organic synthesis.

Thus 2a is a superior base for the synthesis of porphyrins,[19] for the dehydrohalogenation of

secondary and tertiary halides,[20] and for the synthesis of a chiral fluorescence agent.[21] As a

result of these and other emerging applications, 2a has become commercially available.[22]

2 Ar-CHO + —RT/C₆H₆→ + (1)
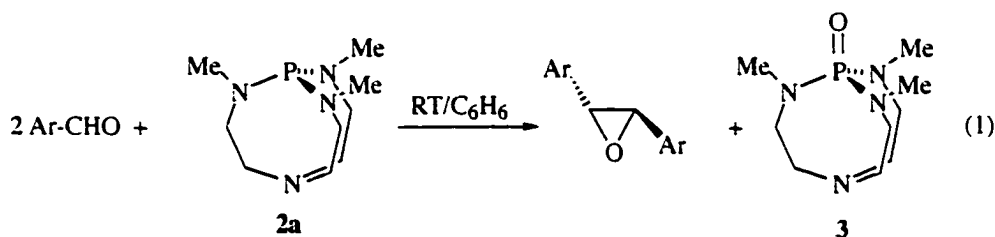
We report herein a facile, efficient, and highly selective procedure for the synthesis of *trans* epoxides from aryl aldehydes bearing electron-withdrawing groups. For comparison of conversions and stereoselectivity, both 1 and 2a were used in parallel reactions. We also find that the more bulky proazaphosphatrane 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_6D_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,[23] the epoxide 9b present in the reaction mixture was found to be almost pure *trans* (*trans/cis* ratio = 98/2). Simply filtrering the reaction mixture and washing the filtered solid with cool benezene 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 ^{1}H 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[4] 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
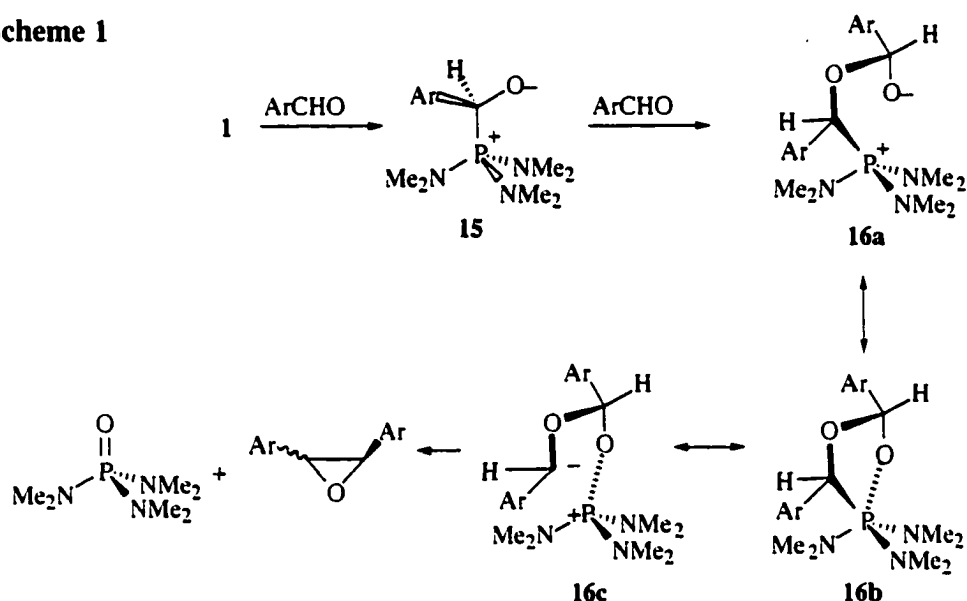
Two reaction pathways have been considered for **1**.[4,6] The one put forth by Mark *et al.* in Scheme 1[4] involves phosphorus nucleophilically attacking an aldehyde carbonyl carbon to form the 1:1 adduct **15** wherein the oxygen attacks a second molecule of the aldehyde to form the 1:2 adduct **16** (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_N2 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

Scheme 2

17

18a   +   18b
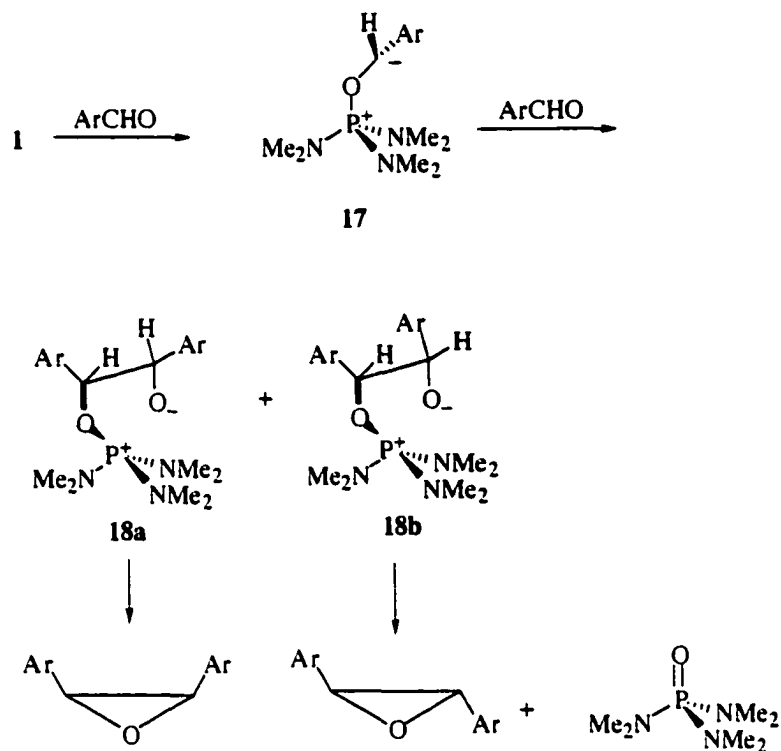
carbonyl oxygen than the phosphorus of trialkyl phosphites that were reported to give isolable

adducts of type **18b** in Scheme 2.[6] 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,[4] probably owing

to similar steric hindrance in the *erythro* and *threo* forms of the adduct formed from a variety of

substituted aryl aldehydes.[4,6] It was also reported[6] 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

3,[10] 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

Scheme 3

19   20

21a   21b
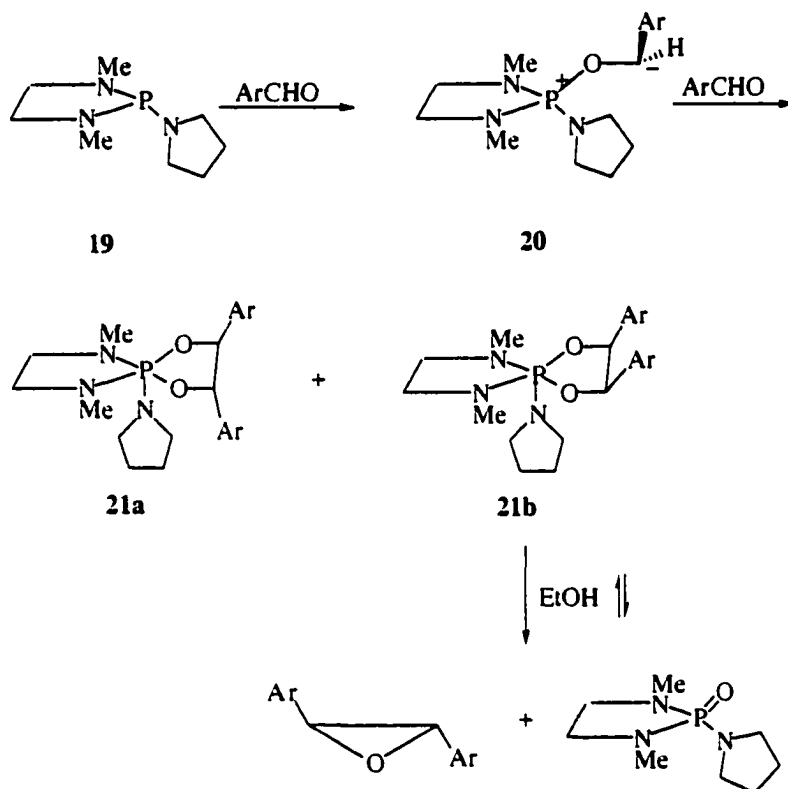
spectrum of the reaction mixture failed to give unambiguous evidence for the ratio of these two

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.[6] Based on the [31]P

Scheme 4
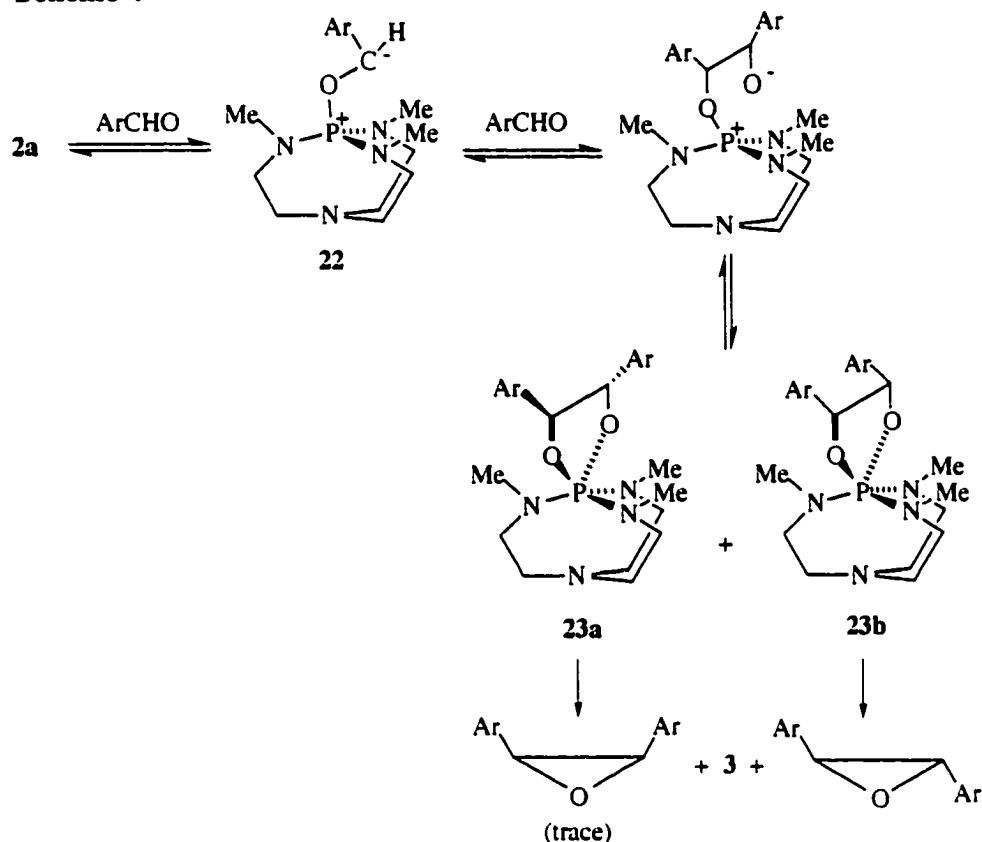
NMR chemical shifts of the 1:1 and 1:2 adducts observed in our work (which are much closer

to those of a P-O bonded adduct[24] than to that of a carbon bonded[20] adduct of **2a**) the reaction

pathway proposed by Ramirez[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 ^{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.[6] 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_2Cl_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.[6] The cis 1:2 adduct gave pure trans-epoxide in 86% yield but in <20% overall yield from the aldehyde.[6] 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_N2 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 ^1H 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.[6] 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 (C_6H_6 and C_6D_6), toluene, and THF were dried with sodium. CH_2Cl_2 was dried with CaH_2. 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 2a[12] and 2b[13] 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 C_6D_6 (3.0 mL) at room temperature under an Ar atmosphere was slowly added a solution of 1 or 2a (1.05 mmol) in C_6D_6 (1.5 mL). The reaction was monitored by ^1H and ^{31}P 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 ^{13}C NMR spectroscopies. In the case of new compounds, HRMS (EI) data are also given (see Supporting Information).

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

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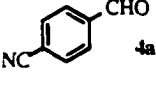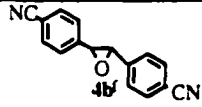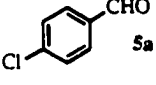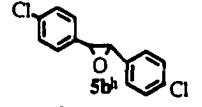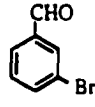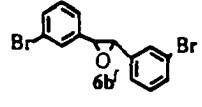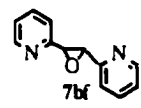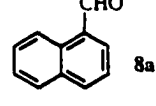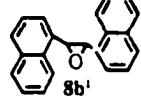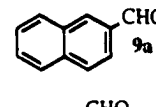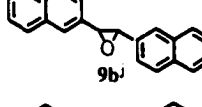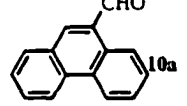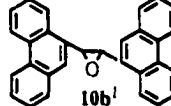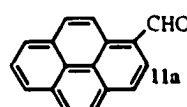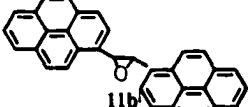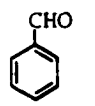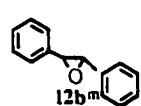
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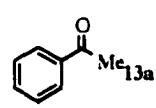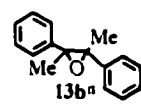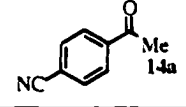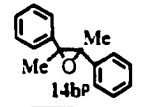2. Simandi, L. I. *"Catalytic Activation of Dioxygen by Metal Complexes"*, Kluwer Academic Publishers: Dordrecht, 1992, p 109.

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

arylaldehyde	product[b]	reaction time (h)	work-up method	%conversions[c](*trans:cis*)[d] yields[e](*trans:cis*)[d]	
				with 2a	with 1
4a	4b[f]	0.5	col.[g] chrom.	100(98:2) 64(98:2)	95(51:49) 81(51:49)
5a	5b[h]	0.5	col.[g] chrom.	100(94:6) 55(95:5)	85(56:44 50(57:43)
6a	6b[f]	1.0	col.[g] chrom.	99(95:5) 51(96:4)	94(70:30) 69(70:30)
7a	7b[f]	0.5	col.[g] chrom.	100(92:8) 42(92:8)	65(63:37) 52(65:35)
8a	8b[i]	14	col.[g] chrom.	95(95:5) 72(99:1)	< 5(53:47) na(na)
9a	9b[j]	12	filtra-tion[k]	99(98:2) 75(100:0)	85(61:39 74(69:31)
10a	10b[i]	14	filtra-tion[k]	98(99:1) 70(100:0)	48(63:37) 37(72:28)
11a	11b[i]	14	filtra-tion[k]	96(99:1) 69(100:0)	73(52:48) 64(52:48)
12a	12b[m]	60	na	28(92:8) na (na)	< 2 (na) na (na)
13a	13b[n]	120	na	na[o]	na[o]
14a	14b[p]	24	na	na[p]	na[p]

[a]Reactions were carried out in C_6D_6 or C_6H_6 at room temperature under Ar. [b]Identification was made by comparing ^{1}H and ^{13}C 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. [c]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. [d]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). [e]Isolated yields were obtained by the indicated methods and purity was determined by ^{1}H NMR spectroscopy. [f]See reference 4. [g]Silica gel column chromatography using a mixture of hexanes (95%) and ethyl acetate (5%) as the eluent. [h]Minami, T.; Matsuzaki, N.; Ohshiro, Y.; Agawa, T. *J. Chem. Soc. Perkin Trans. 1*, **1980**, 1731. [i]Clark, K. B.; Bhattacharyya, K.; Das, P. K.; Scaiano, J. C.; Schaap, A. P. *J. Org. Chem.* **1992**, *57*, 3706. [j]See reference 23. [k]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. [l]See Supporting Information. [m]*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. [n]D'Auria, M.; Mauriello, G. *Photochem. Photobiol.*, **1994**, *606*, 542. [o]No observable reaction. [p]No epoxide formation was observed.

Supporting Information

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

Compound *trans*-10b: ^{1}H NMR (CDCl$_3$): δ 4.58 (s, 2H), 7.54-8.82 (m, 18H). ^{13}C NMR (CDCl$_3$): δ 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$_3$): δ 4.91 (s, 2H), 8.00-8.30 (m, 18H). ^{13}C NMR (CDCl$_3$): δ 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

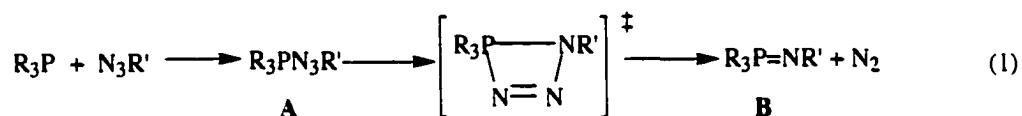A paper submitted to the *Organic Letter*

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 $Na_2Cr_2O_7$ in CF_3CO_2H.[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 $PhCO_2H$ 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
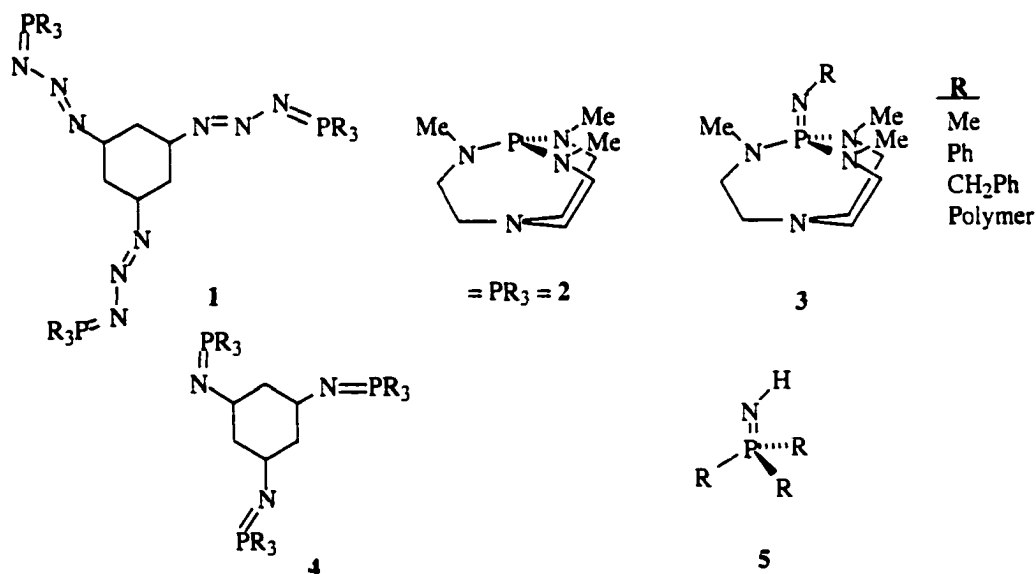
forced to invert conformationally in the presence of a proton so that the proton would be a bridgehead atom that could interact simultaneously with a lone pair on each of the three imino nitrogens via covalent and hydrogen bonding to form a stable cationic adamantane-like structure. It eventually became 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 CH_3CN 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.[3b] 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. $\angle N_{eq}PN_{eq} = 108.77(7)°$], but a planar conformation at the bridgehead nitrogen [avg. $\angle CN_{ax}C = 119.90(14)°$] for reasons we have discussed previously for analogous systems.[4] The bridgehead-bridgehead distance of 3.1053(15) Å indicates the absence of transannular N→P interaction.[4]

$$R_3P + N_3R' \longrightarrow R_3PN_3R' \longrightarrow \left[\begin{array}{c} R_3P\text{---}NR' \\ \diagdown \diagup \\ N= N \end{array} \right]^{\ddagger} \longrightarrow R_3P{=}NR' + N_2 \qquad (1)$$
$$A \phantom{\longrightarrow R_3PN_3R' \longrightarrow \left[\begin{array}{c} R_3P\text{---}NR' \\ \diagdown \diagup \\ N= N \end{array} \right]^{\ddagger} \longrightarrow } B$$

The Staudinger reaction is a two-step process involving the initial electrophilic addition of an alkyl or aryl azide to a P^{III} center followed by N_2 elimination from the intermediate phosphazide A to give the iminophosphine B in reaction 1.[3] Steric hindrance at the P^{III} 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.[3] Donor character on the part of the

P[III] substituents stabilizes phosphazides,[3] 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 $PhCO_2H$, CH_3CO_2H, or CF_3CO_2H

in CH_3CN at room temperature, an exothermic reaction accompanied by the rapid formation

of N_2 (confirmed by GC-MS) and benzene (confirmed by ^1H NMR and GC mass

spectroscopies) occurred. In the case of $PhCO_2H$, 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 $[5H]^+PhCO_2^-$ was isolated. Upon deprotonation of this salt

with KO^{t}Bu in THF, the iminophosphine 5 was obtained in 40% yield after sublimation.

Upon treatment of 5 with $PhCH_2CH_2Br$ in benzene and recrystallization of the

product, crystals of $[5H]^+Br^-$ were isolated. The molecular structure of this salt determined

by X-ray means reveals a transannular distance of 2.859(2) Å which is suggestive of some

transannular interaction. This tentative conclusion is mildly corroborated by the rather wide

$N_{eq}PN_{eq}$ 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,[5a] while strong acids cleave phosphazides

to the corresponding amine and phosphine oxide.[5b] There is, however, a report describing

the reaction of triphenylmethyl azido triphenylphosphine with acetic acid that gives N_2,

$Ph_3CO_2CCH_3$ and $Ph_3P=NH$.[5c] In this reaction Ph_3C^+ 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.

Scheme 1
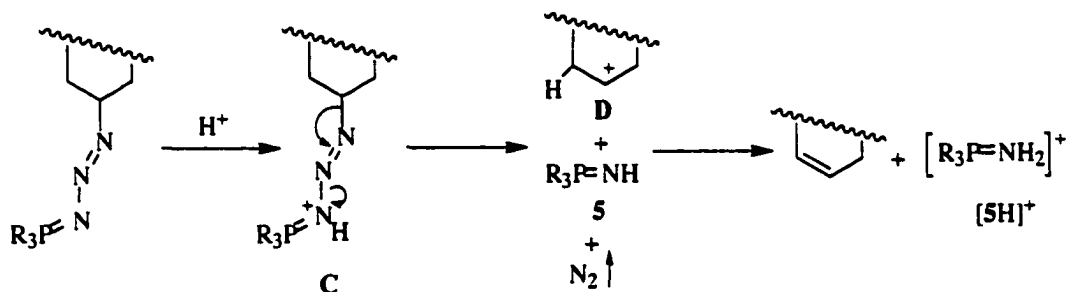
NMR studies showed that 1 does not undergo decomposition in the presence of acid

at –30°C at an observable rate, although it does protonate. Thus addition of $PhCO_2H$

to a solution of 1 in CD_3CN led to an initial dramatic upfield shift of the ^{31}P NMR resonance

of the reaction mixture from 37.2 ppm to an asymptotically reached value of –11.0 ppm after

22.4 equiv $PhCO_2H$ 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

phosphoramide analogue, which reacts about ten times slower with acid and is also

significantly more susceptible to side reactions.
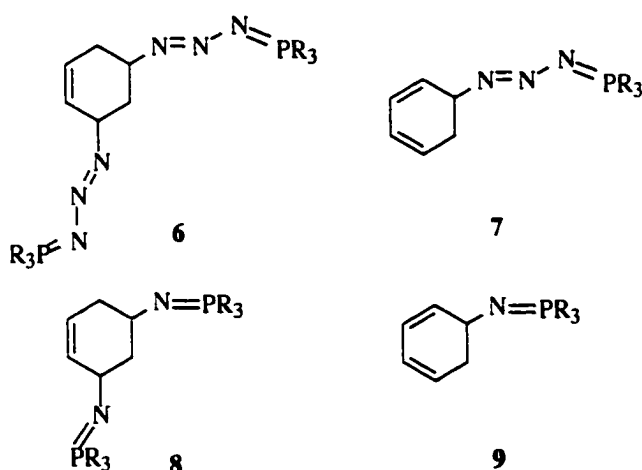
To better understand the mechanism of benzene formation in our reaction, we followed it over time by ESI-mass spectroscopy. During the reaction of 1 with $PhCO_2H$, two intermediates [6H]$^+$ (m/z = 597) and [7H]$^+$ (m/z = 338) were detected which disappeared upon reaction completion, while the product [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 N_2 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 $PhCO_2H$, the same products were observed as with 1.

Scheme 2
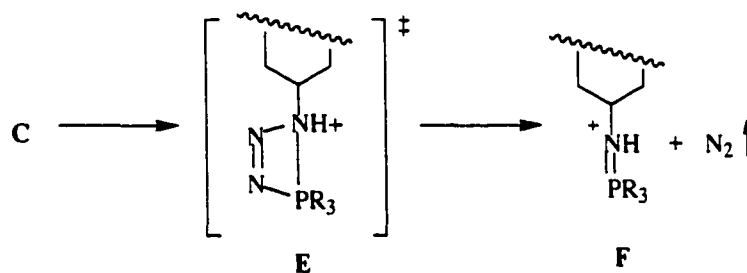
The formation of impurities [8H]$^+$ and [9H]$^+$ in the reaction of 1 with $PhCO_2H$ may result from the competitive side reaction shown in Scheme 2. After protonation, a four-membered ring transition state E could form by rearrangement followed by evolution of N_2 to give the protonated iminophosphine F.

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

Experimental Section

Compounds 1[4d] and 1,3,5-cis—triazidocyclohexane[6] 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^{t}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.

Drs. Ilya Guzei, Kamel Harrata and Natesan Thirupathi for providing X-ray data, mass spectroscopic data and experimental assistance, respectively.

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Supporting Information

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

1: ^{31}P (CD$_3$CN): δ 37.11. ^{1}H (CD$_3$CN): δ 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, ^{3}J$_{HH}$ = 4.8 Hz), 3.38 (m, 3H, CH). ^{13}C (CD$_3$CN): δ 35.67 (d, N$_{eq}$CH$_3$, J$_{PC}$ = 3.5 Hz), 39.42 (s, CH$_2$), 50.32 (s, N$_{ax}$CH$_2$), 52.27 (s, N$_{eq}$CH$_2$), 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$_{21}$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$_6$): δ 36.93. ^{1}H (C$_6$D$_6$): δ 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, ^{3}J$_{HH}$ = 4.8 Hz), 2.71 (d, 9H, N$_{ax}$CH$_3$, J$_{PH}$ = 7.6 Hz). ^{13}C (C$_6$D$_6$): δ 35.58 (d, N$_{eq}$CH$_3$, J$_{PC}$ = 6.3 Hz), 49.71 (s, N$_{ax}$CH$_2$), 51.57 (d, N$_{eq}$CH$_2$, J$_{PC}$ = 2.3 Hz). HRMS m/z calculated for C$_9$H$_{22}$N$_5$P: 231.16231. Found: 231.16257 (M$^+$).

[5H]$^+$Br$^-$: ^{31}P (CDCl$_3$): δ 34.38. ^{1}H (CDCl$_3$): δ 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$_3$): δ 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$_9$H$_{23}$N$_5$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$_3$): δ 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$_3$): δ 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$_2$, 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$_2$)$^+$.
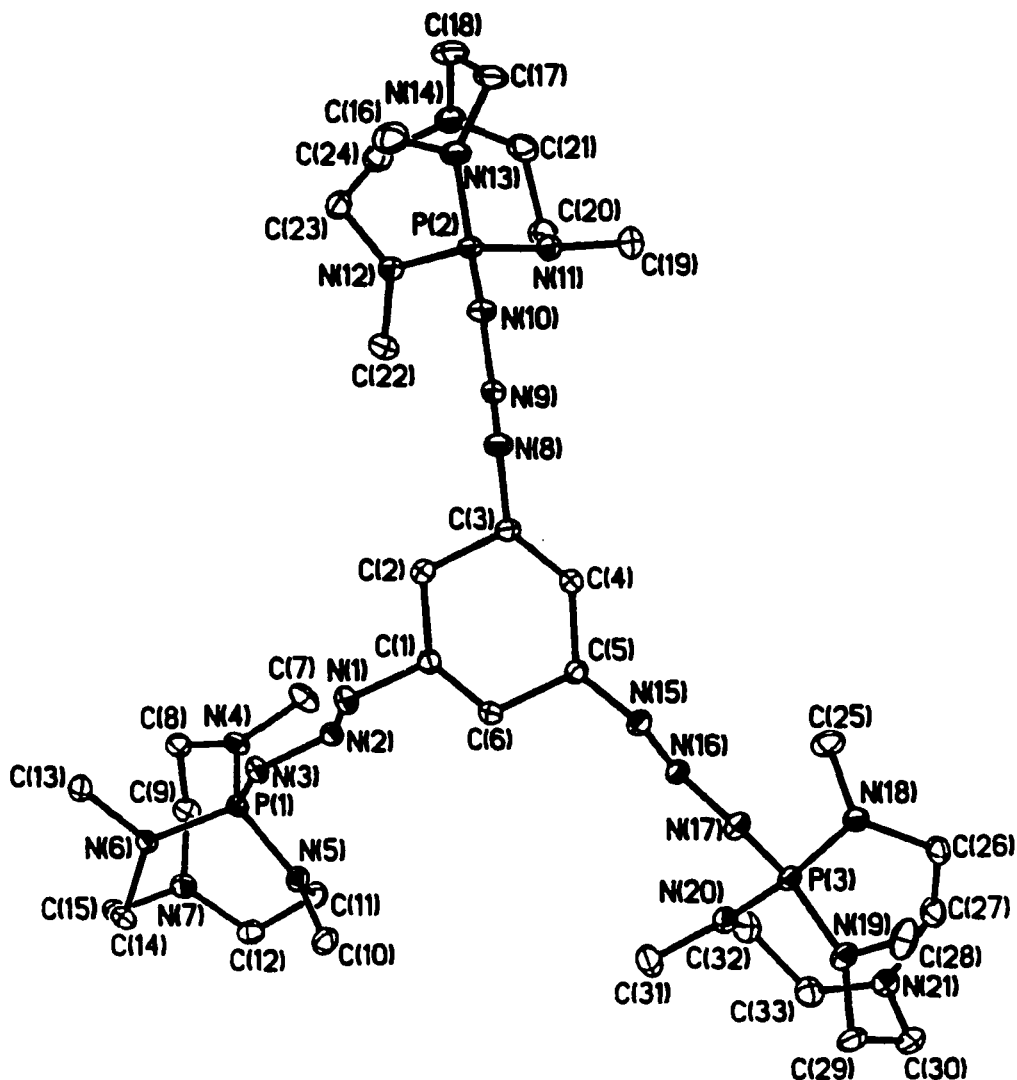
Figure 1. ORTEP view of **1** (30% probability thermal ellipsoids): hydrogen atoms and
solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: P(1)-
N(3) 1.6134(13), P(1)-N(4) 1.6370(13), P(1)-N(6) 1.6438(12), P(1)-N(5) 1.6491(13), P(1)-
N(7) 3.1549(14), N(1)-N(2) 1.2556(17), 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)-
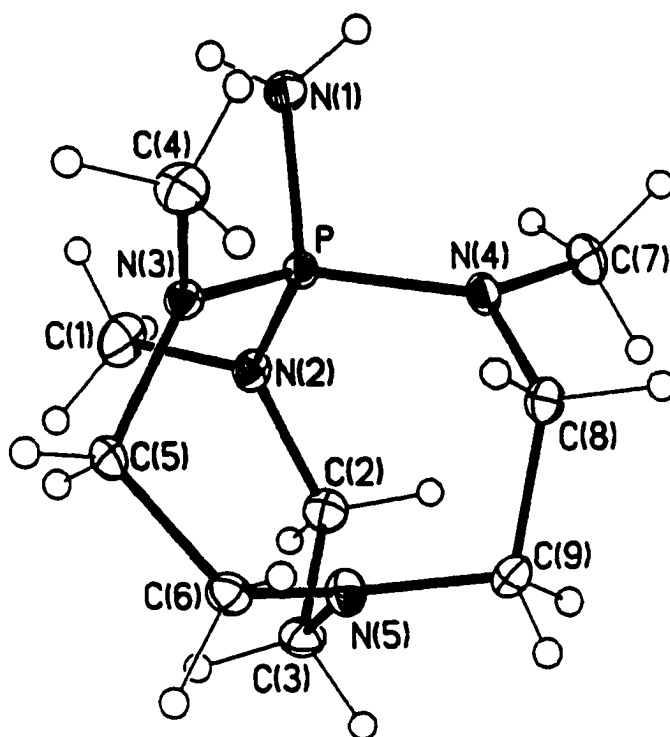C(1)-C(2) 108.85(11).

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).
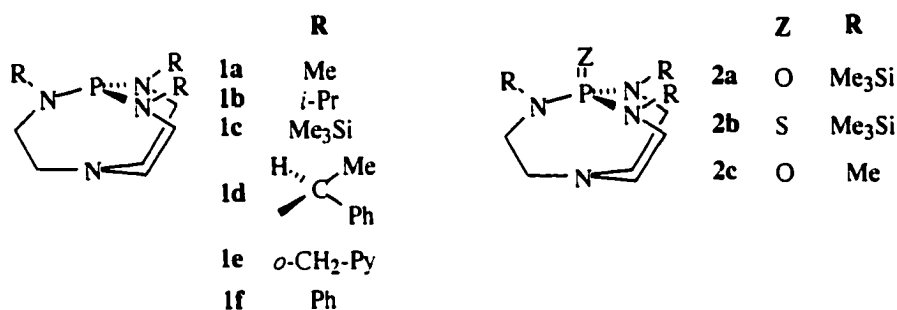
CHAPTER 10. GENERAL CONCLUSION

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 $P(MeNCH_2CH_2)_3N$ **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.

	R			**Z**	**R**
1a	Me		**2a**	O	Me$_3$Si
1b	*i*-Pr		**2b**	S	Me$_3$Si
1c	Me$_3$Si		**2c**	O	Me
1d	$\overset{H}{\underset{}{}}C\overset{Me}{\underset{Ph}{}}$				
1e	*o*-CH$_2$-Py				
1f	Ph				

(2) A series of novel highly sterically hindered azaphosphatranes $[ZP(RNCH_2CH_2)_3N]CF_3SO_3$ wherein $Z = H^+$ and $R = SiMe_3$, $SiEt_3$, $SiPh_3$, $SiPh_2Me$ have been synthesized along with proazaphosphatrane **1c** wherein $Z = lp$ and $R = SiMe_3$. Also described are the transformations of **1c** to $O=P(Me_3SiNCH_2CH_2)_3N$ (**2a**) and to $S=P(Me_3SiNCH_2CH_2)_3N$ (**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}P NMR studies revealed no evidence for transannulation or tautomerism in **2a**.

(3) The precursor cation $HP(CH_3NCH_2CH_2)_3N^+$ 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_3CN at room temperature.[3] In dehydrohalogenations requiring more than *ca.* 10 h, the $^-CH_2CN$ 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 $HP(HNCH_2CH_2)_3N^+$ and $HP[N(polymer)CH_2CH_2]N(CH_2CH_2NH)_2^+$ (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.

|	R	R'
4a	Me	Me
4b	Me	Et
4c	*i*-Pr	Me
4d	*i*-Pr	Et
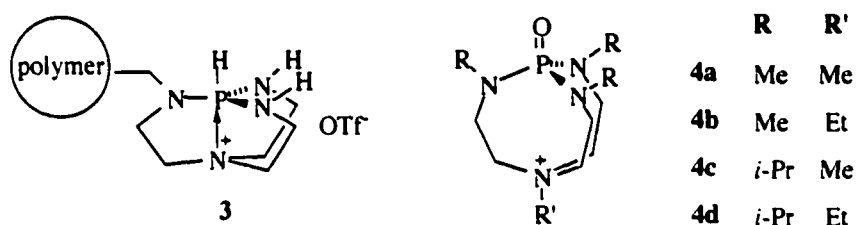
(4) A facile and economical procedure for the synthesis of the C_3 chiral-phenylethylamino trisaminoamine [(S,S,S)-PhHMeCNHCH$_2$CH$_2$]$_3$N in good yield is reported. The corresponding bicyclic proazaphosphatrane P[(S,S,S)-PhHMeCNCH$_2$CH$_2$]$_3$N 1d, its bicyclic phosphoryl derivative and its tricyclic P-protonated azaphosphatrane were also synthesized and characterized.[4] 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$_2$)$_3$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.[5]

(6) The catalytic effect of a group of $R_3P=O$ 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 (TBDPSCl).[6] It is found that $R_3P=O$ is an efficient catalyst in such reactions when R is a good electron donating group, such as Me_2N or n-Bu and as $NMe(CH_2)$ in $N(CH_2CH_2NMe)_3P=O$. However, $R_3P=O$ is a weak or ineffective catalyst when R is a poor electron donating group, such as Ph or O-n-Bu or as CH_2N-o-$CH_2C_5H_4N$ in $N(CH_2CH_2N$-o-$CH_2C_5H_4N)_3P=O$. Compound 2c, synthesized by oxidation of commercially available $N(CH_2CH_2NMe)_3P$ 1a, displays the best catalytic properties for alcohol silylation in terms of efficiency, stability and safety.

(7) In contrast to its acyclic analogue $P(NMe_2)_3$, 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), $P(MeNCH_2CH_2)_3N$ (1a) 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.[7] These reactions are faster with 1a, because its phosphorus atom is apparently more nucleophilic than that in $P(NMe_2)_3$. Thus it is found that 1a 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 $P(NMe_2)_3$ and 1a.

(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 $[H_2N=PR_3]^+A^-$ (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 matereial expected as a thermal
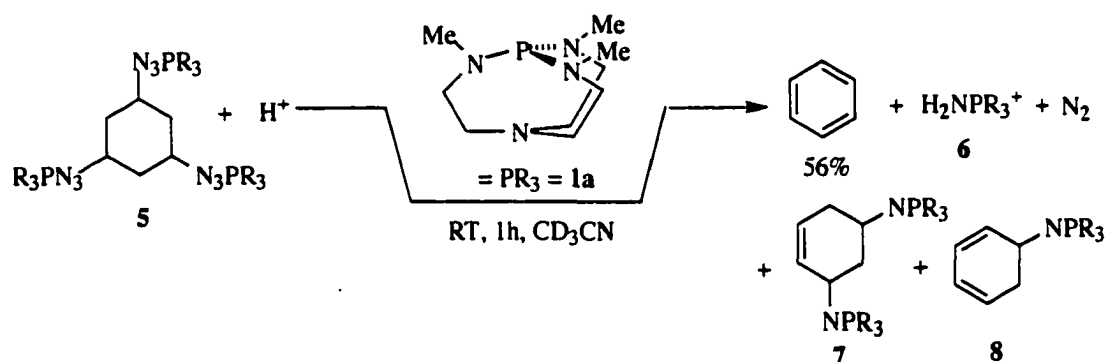
decomposition product was not observed to form in refluxing toluene or at 100 °C in vacuum.[8]

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.

$P(NMe_2)_3$ is a well-known ligand in coordination chemistry that has provided hundreds of complexes for structural and reactivity studies. Since $P(MeNCH_2CH_2)_3N$ 1a is the bicyclic analogue of $P(NMe_2)_3$, 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 $Me_2SAu(I)Cl$ with one and two equivalents of 1a, respectively
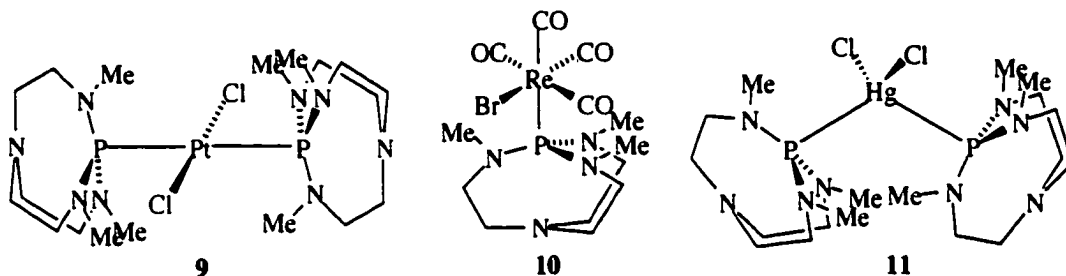
(Scheme 1). The donor properties of **1a** towards Au(I) were studied by testing its ability to remain coordinated in the presence of other phosphines such as $P(NMe_2)_3$ and PPh_3. It was found that **1a** is a better donor ligand than $P(NMe_2)_3$ which is better than PPh_3 when coordinated to Au(I).

Scheme 1
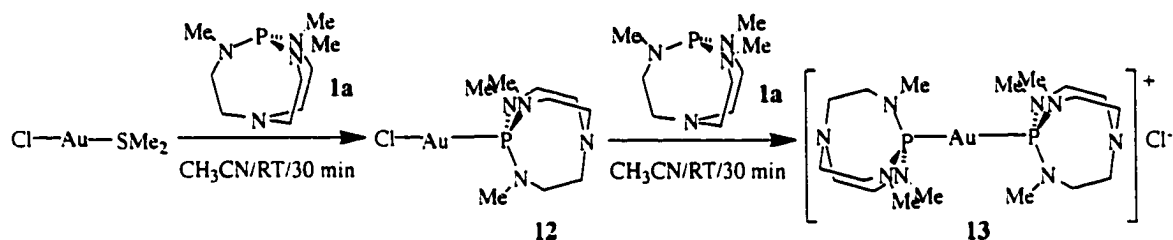

Another new finding is that for the first time **1a** and **1b** have been found to cleave the C-F bonds in CF_3I to give exclusively **14a** and **14b**, respectively, in which the transannular bridgehead-bridgehead bond is among the shortest found thus far. However, $P(NMe_2)_3$, the acyclic analogue of **1a** in the presence of CF_3I gives little or no analogous C-F cleavage products, **15** being formed instead under the same conditions (see Scheme 2).[14]

Scheme 2
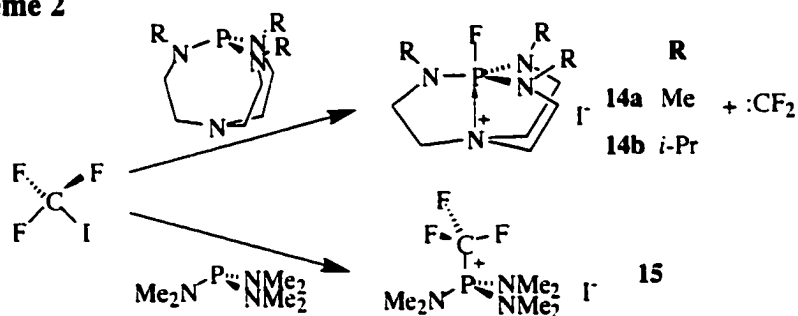
Since our proazaphosphatranes have been proving to be efficient bases/catalysts in a variety of useful organic transformations, immobilizing them on a polymer will be of great interest because of the following advantages. Polymeric reagents are easily separated which saves time, uses less solvent, and is therefore more environmentally benign.

Scheme 3
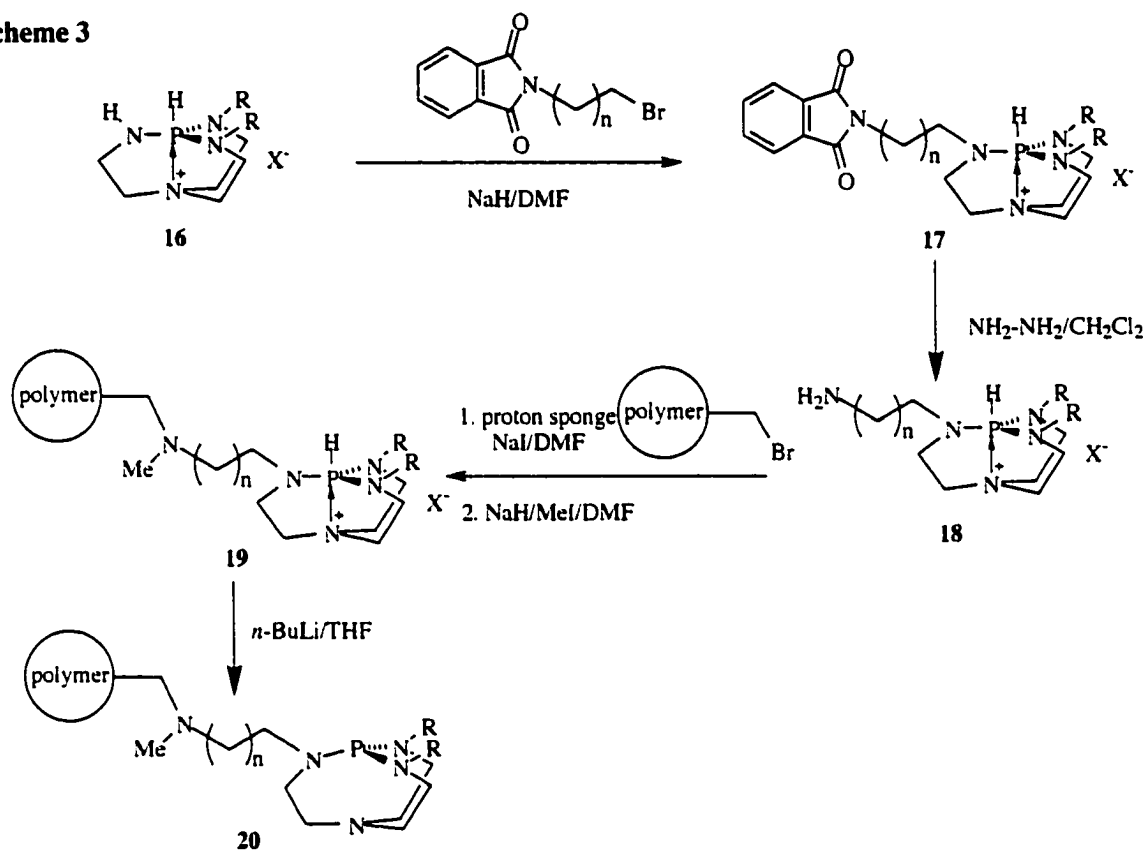
In our previous work, polymer-supported azaphosphatrane 3 was synthesized from Merrifield resin and used as a catalyst in dehydrohalogenation of organic halides with NaH.[4] However, it is found that deprotonation of 3 to its pure free base form is difficult, perhaps due to inefficient mass transport 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

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.[15] However, the synthesis and

21

22
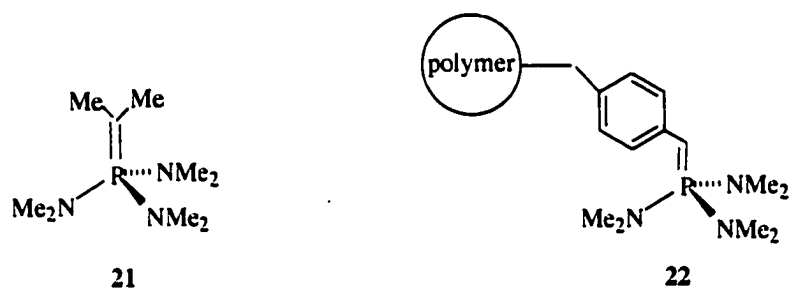
reactivity of the polymer-supported base were not described in detail, which results in the speculation that some problems may exist, such as less reactivity and/or difficulty in the isolation of pure polymeric base **22**. Using the same approach given in Scheme 3, various linkers can be used to install the reactive site well away from the steric hindrance of the polymer back-bone (see Scheme 4).

Scheme 4
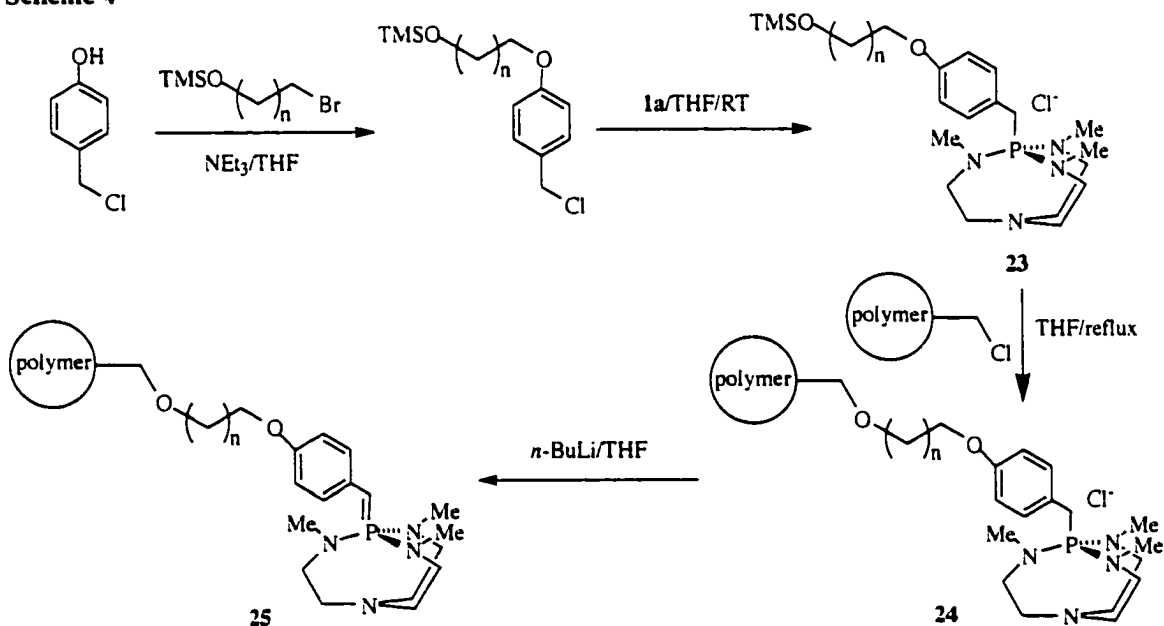
If our superbases, such as **1a**, are converted into the ylide-like polymer-supported bases, high basicity is expected. It is believed that the nonnucleophilic nature of **22** is due to the steric bulk of the polymer back-bone.[15] However, if a polymeric ylide-like base **25** in the Scheme 4 is more 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.

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ACKNOWLEDGMENTS

I would like to thank Professor John G. Verkade, my research adviser, for his kind support, valuable guidance, unceasing encouragement and for providing a freely and stimulating scientific environment during my graduate study.

I would also like to thank the other members in my Program of Study Committee Professor Robert J. Angelici, Professor Gordon J. Miller, Professor Robert S. Houk and Professor Steve W. Martin, for their effort in reading and improving this dissertation.

I would like to thank the following persons who helped me in different ways:

The past and present members of the Verkade group for the valuable help.

Drs. Zhiwen Wan, Ruili Huang, Chen Wang, Xuemei Wang, Hanrong Gao, Chaozhong Li, Weidong Wang, Hui Su, Fusheng Wei, Ms. Xiaoxia Li, and Mr. Jinyuan Chen for the wonderful friendship and help.

Dr. Dave Scott and Dr. Shu Xu for the assistance in NMR spectroscopy,

Dr. Kamel Harrata and Mr. Charles Baker for mass spectroscopic data,

Dr. Ilia A. Guzei and Dr. Leonard Thomas for the crystallographic results, and

My special thanks go to my wife, baby-girl, parents and sister for the love and support.

My appreciation also goes to the NSF, the Petroleum Research Foundation and the ISU Center for Advanced Technology Development for grant support of this research.