The application of a novel pro-azaphosphatrane in catalytic cycles and as a novel ligand

Patrick Alan McLaughlin

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The application of a novel pro-azaphosphatrane in catalytic cycles and as a novel ligand

by

Patrick Alan McLaughlin

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
1998
This is to certify that the Doctoral dissertation of
Patrick Alan McLaughlin
has met the requirements of Iowa State University

Signature was redacted for privacy.

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For the Major Program
Signature was redacted for privacy.

For the Graduate College
Dedication

I dedicate this work in its entirety to my loving parents, Thomas V. and Linda M. McLaughlin. Mom and Dad, you are truly my heroes and I love you very much. Thank you for my life and everything else that you have cooperated with God in giving me.
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ABSTRACT

The exceptionally strong non-ionic base P(NMeCH₂CH₃)₃N is herein applied as a reagent and a catalyst in a variety of interesting organic and inorganic syntheses. First, we noted the substantially enhanced reaction of an organic halide/pseudohalide with organostannanes in the presence of Pd(0) (in the form of Pd₂dba, dba = (PhCH=CH₂CO) and strong non-ionic bases is due to reaction of the base with dba. This novel base effect apparently stems from the inability of the reacted dba to coordinate to Pd(0), thus allowing Pd(0) to act in a ligandless capacity in Stille cross-coupling reactions. The formation of styrene in THF and in MeCN at two different temperatures was evaluated by HPLC with a series of strong nonionic bases and Group 15 weak ligands. Based on these data, DBU and P(MeNCH₂CH₂)₃N were used in scaled-up syntheses of p-methylacetophenone and p-vinylacetophenone, giving yields that were comparable or superior to those obtained with phosphine or arsine ligands used traditionally.

In addition, we demonstrate that in the presence of water and excess PPh₃, fluoride ion catalyzes the reduction of (Ph₃P)₂PdCl₂ under mild conditions to Pd(PPh₃)₄ in good yields while Ph₃P is oxidized to Ph₃P=O. The inactivation of catalytic F⁻ by formation of highly stable HF₂⁻ and other polyhydrogen fluorides that can form in the reaction is prevented by adding a strong non-ionic base such as P(MeNCH₂CH₂)₃N.
Pd(ddpb)₂ and Pd₂(dpmm)₃ are synthesized in high yields by incorporating this strong non-ionic base into the catalyzed synthesis.

Also, the exceptionally strong base P(NMeCH₂CH₃)₃N is herein applied as an excellent catalyst in the Knoevenagel condensation. Aromatic aldehydes are converted to the corresponding tri-substituted alkenes in excellent yields (>98%). In addition, ketones and aliphatic aldehydes are converted to their condensates in high yield.

Finally, P(NMeCH₂CH₃)₃N is capable of forming adducts with various Lewis acids, resulting in a P-Nₓ bonding distance ranging from the van der Waal's radii of 3.34 Å
to 1.976 Å as in the molecule H-P(NMeCH₂CH₂)₃N. We report herein the formation of 
{[(PNMeCH₂CH₂)₃N]₂AuCl} adduct, with a corresponding transannular bond of 3.171 Å. 
Although X-Ray analysis of [(F-P(NMeCH₂CH₂)₃N)F] has not been completed, NMR 
spectroscopic evidence suggests a high degree of transannulation in this compound.
GENERAL INTRODUCTION

Dissertation Organization

This dissertation contains five papers in the format required for journal publication, describing the research I performed at Iowa State University. Preceding these papers is a literature review of the synthesis, characterization, and applications of the pro-azaphosphatrane P(NMeCH₂CH₂)₃N. In the literature review and the papers, the literature citations, schemes, figures, and tables pertain only to the chapters in which they appear. A general summary succeeds the final paper.

A general review of pro-azaphosphatrane 1

Nearly a decade ago, we reported the unusually robust P-H bond in the conjugate acid of compound 1, namely 2.¹ The exceedingly weak acidity of 2 was demonstrated by its resistance to deprotonation by DBU in DMSO, n-BuLi in THF, CaH₂ in CH₂Cl₂, and KOH in refluxing toluene.¹ Later we showed that 2 (pKₐ = 41 in MeCN) is a much weaker acid than [H-DBU]+ (pKₐ = 24 in MeCN). Thus 1 is a very strong non-ionic base, with a growing number of applications in organic synthesis.

Strong non-ionic bases (such as 1, Proton Sponge, DBU, or P₄-t-Bu) have a variety of attractive features that make them convenient for use in organic synthesis, including the milder reaction conditions they permit,³ the enhanced reactivity of the more naked anions in the poorly associated ion pairs formed upon deprotonation of the substrate by such bases (in contrast to ionic bases),⁴ and the better solubility of non-ionic bases in organic solvents at room temperature and below required for some reactions.⁵ In addition, salts of 2 are easily separated from reaction mixtures,⁶ thus allowing conversion to 1 according to literature methods.⁷ ⁸ Because 1 is an exceptionally strong non-ionic base, it may allow pathways not available to weaker non-ionic bases, thus providing opportunity for expansion of its chemistry.
The basicity of 1 can be attributed to a great extent to the ability of the phosphorus to receive electron density from the axial nitrogen atom. Thus, whereas 1 is tricovalent, 2 is pentacovalent, featuring an axial four-electron-three-centered bond.

When undergoing transannulation from 1 to 2, the geometry of 1 as a whole changes drastically in several ways. The transannulation observed in the protonation of 1 to form 2 has been suggested as a model for the $S_{N2}$ formation of a five coordinate intermediate, with the unusual feature that the nucleophilic atom is forced to invert by virtue of its bridgehead position in 1. Although one might expect the presence of only two possibilities when 1 is attached to various Lewis acids, namely transannulated and nontransannulated, Laramay, Tang, and Verkade have shown that there is a progression of intermediate P-N distances and N-P-N angles (determined by X-ray means) for a series of derivatives of 1 (Figure 1). As is indicated in this figure, the P-N bond angle ranges from 3.33 Å (3.34 Å being the sum of van der Waal's radii) in the case of trans-Cl$_2$Pt(1)$_2$ to 1.967 Å in the case of 2, while the N-P-N angles increasing from 104.5° to 119.6°. Thus, a stepwise establishment of the P-N bond is demonstrated, suggesting interesting potential applications in the fields of organic and inorganic synthesis where flexibility in the basicity of phosphorus may be advantageous.

In the exploration of the chemical consequences of partial transannulation in the aforementioned systems, the synthesis of a series of quasi-azaphosphatrane cations was undertaken. In this work, 3 was reacted with a variety of alkyl halides. It is interesting to note that 3 is stabilized by transannulation, whereas the corresponding adduct between P(NR$_2$)$_3$ and CS$_2$ rearranges rapidly. When 3 was reacted with MeI, 4 was produced, accompanied by the shortening of the transannular distance from 3.008 Å in 3 to 2.771 Å in 4 (with corresponding changes in the N-P-N bond angles of 110.3° to 113.4°, respectively). Thus, a more complete picture of the influence of small substrate effects,
Figure 1. A plot of $P-N_{eq}$ distances against $N_{eq}-P-N_{eq}$ angles when 1 is attached to various Lewis acids.
on partial transannulation was achieved through these

Because 1 proved to be an exceptionally strong base, work was undertaken by our
group to examine the strength of the corresponding imidophosphine 5 and 6, and to
compare the basicities of these compounds with 1, PhN=P(NMe₂)₃, MeN=P(NMe₂)₃ and
P₄-t-Bu (via the pKᵢ values of their conjugate acids). Equilibrium studies revealed that the
ordering of the basicities of these species in CD₃CN was:

P₄-t-Bu > 1 > 6 > MeN=P(NMe₂)₃ > DBU > 3 > PhN=P(NMe₂)₃

These studies established that 1 is 17 orders of magnitude more basic than the traditionally
used nonionic base DBU.

The previous two studies led to the application of 1 to the catalytic trimerization
of isocyanates. It was observed that most catalysts for the trimerization of isocyanates
were Lewis bases, and that the efficiency of the catalyst was dependent on the structural

stability of a zwitterionic intermediate such as 7. Having investigated the stability of
products such as 3 and the superior basicity of 1, the accidental discovery of the catalytic
formation of triaryl isocyanurates (Scheme 1) could be rationalized. Compound 5 also
demonstrated the ability to trimerize isocyanate albeit less efficiently. Our group was also
able to demonstrate the greater efficiency of 1 in the high-yield synthesis α-C-acyl amino
acid esters from oxazoles, and porphyrins from pyrroles or dipyrrromethanes compared
with other strong non-ionic bases, such as DBU or Proton Sponge.
Our group has successfully employed 1 as a nucleophilic promoter in the acylation of alcohols\textsuperscript{15} and as a catalyst in the silylation of hindered alcohols\textsuperscript{16} (Schemes 2 and 3, respectively).

Our group was also able to show the superiority of 1 over DBU in the dehydrohalogenation of primary and secondary alkyl halides to alkenes,\textsuperscript{17} and to demonstrate the use of 1 in selective mono-alkylation of active-methylene compounds.\textsuperscript{18}

Pro-azaphosphatrane 1 holds much promise for subsequent studies. Herein, it has been applied as an efficacious component of the catalyst system in the Stille cross-coupling reaction, as a reagent in the fluoride catalyzed formation of Pd(0) phosphine formation of Pd(0) phosphine complexes, in the formation of substituted alkenes by the Knoevenagel condensation, and as an interesting ligand when attached to Au(I) and F\textsuperscript{−}. 
Scheme 2

\[
\text{[2] O}_2\text{CPh} + \text{RO}_{2}\text{CPI}
\]
Scheme 3

TBDMSCI

ROH + Et₃N

ROTBDMS + Et₃NHCl

1
References


(3) Schwesinger, R. Chimia 1985, 39, 269.


A NOVEL BASE ENHANCEMENT FOR THE STILLE CROSS-COUPLING REACTION

A paper submitted to the Journal of the American Chemical Society
Patrick A. McLaughlin and John G. Verkade*

Abstract

The substantially enhanced reaction of an organic halide/pseudohalide with organostannanes in the presence of Pd(0) (in the form of Pd$_2$dba$_3$, dba = (PhCH=CH)$_2$CO) and strong non-ionic bases is due to reaction of the base with dba. This novel base effect apparently stems from the inability of the reacted dba to coordinate to Pd(0), thus allowing Pd(0) to act in a ligandless capacity in Stille cross-coupling reactions. The formation of styrene was evaluated by HPLC in THF and in MeCN at two different temperatures with a series of strong nonionic bases and Group 15 weak ligands. Based on these data, DBU and P(MeNCH$_2$CH$_2$)$_3$N were used in scaled-up syntheses of $p$-methylacetophenone and $p$-vinylacetophenone, giving yields that were comparable or superior to those obtained with phosphine or arsine ligands used traditionally.

Introduction

The use of transition-metal catalysts in cross-coupling reactions is an extremely powerful tool in organic synthesis. The Stille reaction, an exceptionally versatile transformation of this kind, involves the coupling of an unsaturated organic halide or triflate with an organostannane. This cross-coupling route has been applied to key steps in the synthesis of natural products, carbon-nitrogen bond formation in aryl amines, stereospecific cross-coupling reactions of unsymmetrical dienes, and the synthesis of functional polymers, among numerous other applications in organic synthesis. The Stille reaction is attractive because it is compatible with most functional groups. Moreover, organostannane reagents (which are generally stable to air and moisture) are becoming increasingly available.
The Stille reaction is especially useful in carbon-carbon bond formation with substrates not very susceptible to the $S_{n2}$ pathway, as illustrated in reaction 1:

$$R^1X + R^2SnBu_3 \xrightarrow{\text{catalyst}} R^1R^2 + XSnBu_3$$

(1)

$R^1 = \text{aryl, vinyl, allyl, acyl}$; $R^2 = \text{aryl, vinyl, allyl}$; $X = \text{Br, I, OTf}$

The generally accepted mechanism for the Stille reaction (Scheme 1) consists of the oxidative addition of the organic halide/pseudohalide to the palladium complex, followed by transmetalation of an organic group on the organostannane by the palladium complex. The transmetalation is driven by the formation of the very strong tin halide/pseudohalide.
bond, and is followed by the reductive elimination of the coupled organic product. In this mechanism, the nature of the “PdL_n” moiety plays a key role. A good σ-donor ligand augments the ability of the palladium to oxidatively add the organic halide/pseudohalide. However, dissociation of the ligand is required for both oxidative addition and reductive elimination, and good σ-donors tend to dissociate less readily than poor σ-donors. Furthermore, good σ-donors have been shown to decrease the rate of transmetalation, which is the rate-determining step in most cross-coupling reactions. Thus, a compromise must be reached in the choice of a suitable ligand.

In solutions of Pd(PPh₃)₄, equilibria exist among the tetracoordinated, tri-, and dicoordinated species (equations 2 and 3). Currently, the dicoordinated palladium center is believed to be the active catalyst in Stille cross-couplings.

\[
Pd(PPh₃)₄ \rightleftharpoons Pd (PPh₃)₂ + PPh₃ \quad (2)
\]

\[
Pd(PPh₃)₃ \rightleftharpoons Pd (PPh₃)₂ + PPh₃ \quad (3)
\]

Several studies suggested that PPh₃ was the best candidate ligand in the Stille reaction because of its intermediate strength as a σ-donor. However, “weak ligands”, such as Ph₃As and tris(2-furyl)phosphine (TFP) were demonstrated by Farina to be more efficacious in Stille cross-coupling reactions because of their improved lability during oxidative addition, reductive elimination, and transmetalation. Reactions employing these weak ligands resulted in better turnover rates and higher product yields under milder reaction conditions than analogous reactions with traditional phosphine ligands, such as PPh₃.

Although a wide choice of PdL₄ complexes can be used in Stille cross-coupling, a mixture of Pd₂dba₃ [dba = (PhC=CH)₂C=O] and an appropriate amount of ligand necessary to generate the catalyst in situ is also commonly employed. Thus Pd₂dba₃ is
relatively stable and this method avoids the necessity to synthesize and purify the PdL₄ pro-catalyst.

Recently we have been exploring the applications of pro-azaphosphatrane 1, first reported from our laboratories,¹⁰,¹¹,¹²,¹³ as a superior non-ionic base in the synthesis of acylated alcohols,¹⁴ porphyrins,¹⁵ α-C-acylamino acids,¹⁶ trans-olefins,¹⁶,¹⁷ a chiral auxiliary-bearing isocyanide,¹⁸ and mono-alkylated β-dicarbonyls;¹⁹ and as an efficient catalyst for the trimerization of isocyanates²⁰ and the protective silylation of alcohols.²¹ Compound 1, when acting as a phosphorus Lewis base, is able to retain its bicyclic transannulated structure with a variety of Lewis acids. With other Lewis acids it becomes partially transannulated, and in the presence of very strong Lewis acids such as the proton, it achieves full transannulation (2).²²,²³ From the unusually strong basicity observed for 1 (pKₐ of 2 = 41 in MeCN¹³) it is reasonable to suppose that donation of the axial nitrogen lone pair to the phosphorus strengthens the sigma donor properties of the phosphorus. Our hope was that the flexibility of the transannular interaction in 1 could be advantageous in Stille cross-coupling reactions, wherein 1 could conceivably act as a good σ-donor during the oxidative addition of the organic halide or triflate, but could then also act as a poor σ-donor during transmetalation. Although a striking enhancement of Stille cross-coupling was observed with 1, we report here evidence that this result is attributable to a heretofore unreported destruction of the ligand in the Pd₂dba₂ pro-catalyst in these reactions by strong nonionic bases of which 1 is an example.
Results and Discussion

A. Reactions at 60 °C in THF

\[
\text{Ph}_3I + \text{Bu}_3\text{Sn} \xrightarrow{\text{Pd}_2\text{dba}_3, \text{base or ligand}} \text{Ph} - \text{Bu}_3\text{Sn} \quad (4)
\]

Farina studied the rate of Stille cross-coupling reactions with various ligands in THF at 60 °C, the best of which were Ph$_3$As and TFP. In order to compare the efficiency of pro-azaphosphatrane 1 with such ligands and the strong nonionic bases Proton Sponge, DBU, P$_4$f-Bu, and P$_4$Et, experiments were run under identical conditions using the model reaction 4. Average conversions to styrene for this reaction are collected in Table 1.

The use of the weak ligands Ph$_3$As and TFP gave rise to a great improvement in product conversion compared with that obtained with the more traditional Ph$_3$P ligand or with no ligand present. Our hope that pro-azaphosphatrane 1 would compete favorably with these ligands was not realized, and in fact its acyclic analogue P(NMe$_2$)$_3$ was somewhat more effective than 1. When P$_4$f Bu, P$_4$Et, and DBU were used as bases in reaction 4, however, significant increases in conversions over those obtained with pro-azaphosphatrane 1 were observed, suggesting the possibility of a base effect. On the other hand, when proton sponge was used, a much smaller conversion was observed than with 1.

The longer reaction time of 20 hours was also investigated for selected ligands and bases in reaction 4 (Table 2) in order to determine whether or not these reactions had run
their course in 6 hours. While insignificant to modest increases in conversions were seen with the weak ligands Ph$_3$As and TFP, modest to significant conversion increases were seen in reactions involving the bases DBU and P$_4$-t-Bu, again indicating the presence of a base effect.

**B. Reactions at 60 °C in MeCN**

\[
\text{Pd}_{2}\text{dba}_3 \xrightleftharpoons{\text{base or ligand}} \text{MeCN, 60 °C} \xrightarrow{\text{base or ligand}} \text{MeCN, 60 °C} + \text{Bu}_3\text{SnI} \quad (5)
\]

Based on our observation that conversions to styrene in THF increased in the presence of a strong base compared with those in the absence of ligand or base, we hypothesized that the base effect involves a reaction of the base with the dba, either by forming a monomeric or oligomeric zwitterionic salt, or by inducing anionic living polymerization. Since a more polar environment would be expected to facilitate both possible pathways, acetonitrile (reaction 5) was investigated as a solvent (Table 3) at the temperature employed in THF (reaction 4).

The "weak ligands" each gave comparable conversions to styrene in reaction 5 and they outperformed the strong bases. The strong bases, however, did show remarkable increases in styrene conversions in acetonitrile over those observed in THF under identical reaction conditions. This result supported our hypothesis that the base effect involves a reaction of the base with dba. The strong bases, with the exception of P$_2$-Et, also showed remarkably similar styrene conversions in reaction 5.

Because augmented conversions to styrene were observed upon increasing the reaction time in THF to 20 hours, selected ligands and bases were chosen for 20-hour reactions in acetonitrile (Table 4). While no significant increase in the conversion to styrene was observed for the weak ligand TFP, a modest increase in the conversion was
observed for Ph₃As. Increased conversions of about the same magnitude were observed for pro-azaphosphatrane 1, Proton Sponge, and P₄-t-Bu. DBU, however, outperformed TFP and matched the conversion (within experimental error) to styrene obtained with Ph₃As.

C. Reactions at 80 °C in MeCN

Because the base effect for the reaction of interest here is more pronounced in acetonitrile than in THF, the effect of increased reaction temperature was examined for a series of six-hour reactions with selected ligands and bases (reaction 6, Table 5). Not unexpectedly, all of the reactions gave higher conversions to styrene. However, now the strong bases 1 and DBU compared very favorably with the weak ligands Ph₃As and TFP in conversions to styrene. Moreover, these conversions are very close to those achieved in acetonitrile at 60 °C over twenty hours, indicating that a modest increase in temperature results in competitive conversions in a considerably shorter reaction time.

Conversions to styrene using selected ligands and bases in reaction 6 were also obtained after twenty hours at 80 °C (Table 6). Here, DBU and TFP led to modest increases in conversions, while 1 and Ph₃As gave rise to small decreases in conversions for reasons that are not obvious to us.

D. Preparative scale reactions

Several attempts were made to acquire isolated yields of styrene in scaled-up versions of these reactions, but all failed because of problems in the isolation of styrene from the reaction mixture. These failures were due to problems in separation of the styrene from other organic materials using column chromatography, and/or to polymerization of the
styrene in the presence of Pd(0) complexes and/or Pd metal that appeared to form during attempted distillation. Therefore, we examined reactions 7 and 8 in which the products were easily isolated and purified. In reaction 7, the presence of DBU resulted in a 94% yield and the use of 1 gave a 92% yield, compared with a 95% yield using the weak ligand TFP. In this reaction, LiCl has proven to be useful in inducing

\[
\text{LiCl} + \text{Pd}_{2}\text{dba}_3, \text{DBU or 1} \rightarrow \text{NMP, 2h, RT} \rightarrow \begin{array}{c}
\text{94%, 92%}
\end{array}
\]

Our efforts to find a synthesis wherein the base effect showed an improvement in yield over that achieved with a weak ligand was realized in the transfer of a methyl group from tetramethyltin (reaction 8). Despite the mediocre product yields in this reaction

\[
\text{LiCl} + \text{Pd}_{2}\text{dba}_3, \text{DBU or 1} \rightarrow \text{NMP, 48h, 60 °C} \rightarrow \begin{array}{c}
\text{82%, 80%}
\end{array}
\]

the presence of Ph\textsubscript{3}As (69%) and TFP (52%), this methodology is considered of substantial utility because alkyl groups are much more reluctant to cross-couple than π-bonded moieties.\textsuperscript{25} The isolated yield of the cross-coupled product in the presence of DBU was a gratifying 82% and it was 80% when 1 was used.

**E. Reactions of 1 and DBU with Pd\textsubscript{2}dba\textsubscript{3} and dba**

The results presented in the preceding sections is consistent with the idea that reaction of the base with dba prevents coordination of dba to the palladium and that the reaction product(s) is even less effective as a palladium ligand, thus allowing this metal to
function more effectively in an extremely "ligandless" environment. That dba is not innocent in Stille cross-coupling was demonstrated in experiments showing that dba competes quite effectively with phosphines for coordination to Pd(0) in Pd(dba)$_2$.

Thus an investigation of the reactions of two representative bases (I and DBU) with Pd$_2$dba$_3$ and dba were carried out. These reaction mixtures were analyzed by NMR (¹H, ¹³C, ³¹P) and by mass spectroscopies (Tables 7-10).

When a deuterio-acetonitrile solution of Pd$_2$dba$_3$ was treated with eight equivalents of I at 60 °C for 6 hours, the vinyl/phenyl resonances of dba that were resolved in the absence of I appeared as one broad resonance (7.1 to 7.7 ppm). A broad peak assigned to the vinyl/phenyl region with a range of several ppm (centered at 129 ppm) was also observed in the ¹³C NMR spectrum. The methyl/methylene region of I, though well resolved in the ¹H NMR spectrum, was very complex, indicating the formation of several products. In addition, a doublet at 5.28 ppm indicative of the phosphorus proton in 2 (presumably formed by the abstraction of a proton from dba) was also observed. The ³¹P NMR spectrum, obtained from an anaerobically sealed NMR tube reaction, revealed the presence of the oxide 3 (23 ppm) of I, suggesting that I abstracts an oxygen from the carbonyl carbon in dba during the course of the reaction, forming the robust phosphoryl bond. In addition, several resonances between 3 and 10 ppm in the ³¹P NMR were observed, suggesting that I bonds to dba, forming a zwitterion which can subsequently oligomerize (Scheme 2). Furthermore, 2 (-10 ppm) was observed in the ³¹P NMR spectrum, in addition to deuterio-2 (presumably formed by the deprotonation of deuterio-
acetonitrile). The latter species has been observed previously in CD₃CN solutions of 1.¹⁷,²⁸ The presence of 2 suggests the formation of dba anions (4), which can oligomerize according to Scheme 2. A similar broadening of the phenyl/vinyl region was observed in both the ¹H and ¹³C NMR spectra when an identical reaction using d₆-THF as the solvent was run. Here, the presence of compound 2 was verified in the ¹H NMR spectrum and the ³¹P NMR spectrum clearly revealed resonances for compounds 2 and 3, and the peaks associated with the supposed oligomers formed from 1 and dba.

Mass spectral analysis of these reaction mixtures also supported the hypothesis that dba is attacked by 1. Pd₂dba₃ was treated with eight equivalents of 1 at 60 °C for 6 hours in both THF and MeCN. The solvent from each reaction mixture was then removed under vacuum and the residue was submitted for mass spectral analysis, employing both EI and CI techniques.

Scheme 2

![Scheme 2 diagram](image)

(Table 8). The MeCN solution showed ions of mass 232(EI) corresponding to 3 or dba minus dihydrogen, 234(EI) corresponding to dba, 451(CI) indicative of an adduct of 1 and one dba, and 465(CI) indicative of a dimer of dba minus two dihydrogen molecules. The
THF solution showed identical ion masses when the same techniques were employed, with the addition of ions of mass 233(CI) and 235(CI) indicative of the aforementioned moieties for 232(EI) and 234(EI), and an ion of mass 685(CI) indicative of 1(dba)₂.

The possibility of a reaction of dba with 1 in the absence of Pd(0) was also investigated. A solution containing three equivalents of dba was treated with eight equivalents of 1 at 60 °C for 6 hours in both d₃-MeCN and d₅-THF. Both the ¹H and ¹³C NMR spectra (for both solvents) showed the characteristic broadening of the protons in the vinyl/phenyl regions of the respective spectra (Table 7), indicative of a reaction between the base and dba in the absence of Pd(0). In addition, the ¹H NMR spectrum suggested the presence of cation 2 in both the d₃-MeCN and the d₅-THF reactions. The ³¹P NMR spectrum, in addition to confirming the formation of 2, indicated the presence of oligomers and 3 for both solvent systems. For mass spectral analysis (EI and CI), a pair of reactions identical to the preceding ones were carried out in MeCN and THF. The solvent in each of these reactions was then removed under vacuum and the residues were analyzed mass spectroscopically (Table 8). The MeCN solution showed ions of mass 232(EI) corresponding to 3 or dba minus dihydrogen, 234(EI) corresponding to dba, and 467(CI) indicative of a dimer of dba minus dihydrogen. The THF solution showed identical ion masses when the same techniques were employed, in addition to masses at 233(CI) and 235(CI), corresponding to the aforementioned moieties listed for 232(EI) and 234(EI).

Presumably, these products were formed during the course of the reaction (rather than in the mass spectrometer) based on the observation of the broadening of the vinyl/phenyl region in the ¹H and ¹³C NMR spectra, and the additional peaks observed in the ³¹P NMR spectra.

When deuterio-acetonitrile and deuterio-THF solutions of Pd₂dba₂ were treated with eight equivalents of DBU under conditions identical to those described above for reactions involving 1, the same broadening of the phenyl/vinyl region of dba was observed in the ¹H
and $^{13}$C spectra (Table 9) as was observed when 1 was used as the base in both solvents. Whereas 1 appears to have three modes of reaction with dba (deoxygenation, deprotonation, and induction of living oligomerization), thereby creating more naked palladium(0), DBU appears to have only one reaction mode according to NMR spectroscopy, namely, deprotonation of the dba followed by its oligomerization, with subsequent deprotonation of [DBU-H]$^+$ by the dba anionic oligomer. To support this idea, DBU was reacted with a range of equivalents of triflic acid ranging from 0.00 to 1.00 in deuterio-acetonitrile, while one of the $^1$H NMR resonances was monitored. When 0.14 equivalents of strong acid had been added to the solution of DBU, a resonance corresponding to unprotonated DBU (2.26 ppm) disappeared and a new resonance appeared at 2.32 ppm. The latter resonance shifted downfield to 2.48 ppm when a total of 0.54 equivalents of acid had been added, and stopped moving at 2.59 ppm when 1.00 equivalents of the acid had been added. This supported the idea that the protonated and deprotonated forms of DBU are in equilibrium on the NMR time scale. When reactions in $d_2$-MeCN and $d_6$-THF between Pd$_2$dbaj and eight equivalents of DBU were allowed to react according to the above-mentioned conditions, the 2.26 ppm peak was observed in the $^1$H NMR spectra of both solutions, indicating that DBU is largely in the unprotonated form after these reactions. This result in conjunction with the broadening in the vinyl/phenyl proton and carbon region in the respective NMR spectra suggests that DBU induces oligomerization of the dba in Pd$_2$dbaj. This was further confirmed by mass spectral analysis of the residues of reactions of Pd$_2$dbaj with DBU at 60 °C for 6 hours in THF and in MeCN (Table 10). The MeCN solution residue showed no ion at mass 232(EI), suggesting that 3 is responsible for this mass ion when Pd$_2$dbaj is treated with 1 (see above). In addition, ions of mass 234(EI) corresponding to dba, 389(CI) corresponding to a 1:1 DBU(dbaj) zwitterion, and at 469(CI) indicative of a dimer of dba were observed. The THF solution showed identical ion masses when the same techniques were employed,
with the exceptions of ions of mass 232(EI), indicating the presence of dba minus one
dihydrogen, and the absence of the DBU(dba) zwitterion at 389, suggesting that this
species is not formed when the less polar solvent THF is employed.

The reaction of DBU with dba in the absence of Pd(0) was also investigated. Three
equivalents of dba were treated with eight equivalents of DBU at 60 °C in MeCN and in
THF for six hours (Table 9). Even after 20 hours, no broadening of the vinyl/phenyl
resonances was observed in either the \(^1\)H or \(^{13}\)C NMR spectra for these reactions (Table 9).
Interestingly, DBU does not appear to induce detectable oligomerization of dba in the
absence of Pd(0), in contrast to our observation with 1 (see above). As expected, the \(^1\)H
NMR spectra of these reaction mixtures revealed that DBU was unprotonated at the end of
each of these reactions. The products of these 60 °C six-hour reactions in the absence of
Pd(0) were also analyzed mass spectroscopically (Table 10). Here ions of mass 233(CI)
indicative of dba minus one dihydrogen; 234(EI) and 235(CI) indicative of dba; and
469(CI) indicative of a dimer of dba were detected in the MeCN solution residue. Ions of
mass 232(EI) indicative of dba minus one dihydrogen; 234(EI) indicative of dba; and
469(CI) indicative of a dimer of dba were detected in the solution residue of THF.
However, these ion masses exhibited smaller intensities by a factor of approximately two
compared with those detected when the reaction was run in the presence of Pd(0). Because
no broadening was observed in the vinyl/phenyl region of the \(^1\)H and \(^{13}\)C NMR spectra of
either of these reactions, DBU apparently does not react to an NMR-detectable extent with
dba in the absence of Pd(0). The appearance of ion masses indicative of dba dimer, despite
this observation, suggests that this species can be formed in the mass spectrometer.

Conclusion

In the selection of catalyst systems available for use in Stille cross-coupling
reactions, the use of a strong non-ionic base has been shown to be an excellent potential
alternative to the use of traditional phosphine ligands such as PPh\(_3\), or weak ligands such
as TFP and Ph$_3$As. Thus the use of a base to create a "ligandless" environment via
destruction of the dba ligand provides conversions/yields that are as good, and in some
cases better, than the use of Group 15 ligands. A strong base is particularly effective for
the transfer of a methyl group from tetramethyltin, which heretofore has been problematic.
Moreover, the use of DBU would be less expensive (DBU, $39.50; Ph$_3$As, $351; 1, $900;
and TFP, $6965 per mole). The use of nonionic strong bases in other difficult Stille
cross-couplings promises to be an interesting area for future work.

**Experimental Section**

Reactions were carried out under an inert atmosphere using Schlenk techniques.
NMR spectra were obtained on a Varian VXR-300 instrument. HPLC analyses were
performed on a Hewlett-Packard Series 1050 instrument equipped with a UV detector set at
274.4 nm. A Bondclone 10 C-18 (300 x 3.9 mm, 10 micron) column was used for the
HPLC analyses. A 30% acetonitrile/70% water eluent was employed. Mass spectrometry
experiments were performed using a Finnigan TSQ 700 instrument. The system was
configured in the electron impact ionization (EI) mode and in the chemical ionization (CI)
mode. The first quadrupole was used as a mass analyzer with a scan from m/z 35 to m/z
700 with a rate of 1.2 seconds per scan. The second and third quadrupoles were kept in
the RF-only mode. Unit mass resolution was achieved using FC43 as a calibration and
tuning reference gas. The electron energy was 70 eV in all EI experiments. Ammonia was
used in all the CI experiments. Small amounts of sample (less than 1 µG) were placed in a
glass vial and introduced using a solid probe device. The probe temperature was elevated
as appropriate up to 500 °C.

**Chemicals.** Dry acetonitrile was obtained by distillation from CaH$_2$, dry THF
was obtained by distillation from Na/benzophenone, and dry NMP was obtained from
Aldrich in Sure-seal containers. P$_4$-r-Bu as a 1.0 M solution in hexanes and neat P$_2$-Et
were purchased from Fluka. Pro-azaphosphatrane 1, 4-(triflyloxy)acetophenone, and
vinyltributyl tin$^{29}$ were prepared and purified according to literature methods. P(NMe$_2$)$_3$ was distilled at reduced pressure (48-50 °C, 12 mm Hg) prior to use. All other reagents were obtained from Aldrich or Acros and were used without further purification.

**Coupling of iodobenzene and vinyltributyltin with Pd$_2$dba$_3$.** Pd$_2$dba$_3$ (10.0 mg, 0.0218 mmol Pd) was placed in a Schlenk tube which was then purged with argon. THF (4.53 mL) was added to dissolve the catalyst, followed by the addition of iodobenzene (0.120 mL, 1.07 mmol). After a period of 10 minutes, the tube was placed in an oil bath at 60 °C and vinyltributyltin was added (0.351 mL, 1.20 mmol). The reaction was stirred for six hours, after which time an aliquot was withdrawn for HPLC analysis via syringe. Heating was continued for an additional fourteen hours, after which a second aliquot was withdrawn for HPLC analysis.

**Coupling of iodobenzene and vinyltributyltin using a ligand/base with Pd$_2$dba$_3$ in THF.** These reactions were run according to the previous procedure except that a solid ligand/base Ph$_3$P, Ph$_3$As, TFP, 1, or Proton Sponge (0.0877 mmol) was placed in the Schlenk tube prior to the addition of solvent. A liquid ligand/base P(NMe$_2$)$_3$, DBU, P$_2$-Et, or P$_4$-r-Bu (0.0877 mmol was placed in the Schlenk tube immediately after the addition of solvent. See Table 1 for HPLC analyses. Heating was continued for another fourteen hours in the case of Ph$_3$P, Ph$_3$As, TFP, DBU and P$_4$-r-Bu, after which a second aliquot was withdrawn for HPLC analysis (Table 2).

**Coupling of iodobenzene and vinyltributyltin with ligands and bases in MeCN.** A series of 60 °C reactions was run in the same manner as the six-hour reactions in THF described above except that acetonitrile was used as the solvent for the six-hour reaction time (Table 3). In the case of no ligand and the ligands/bases Ph$_3$P, Ph$_3$As, TFP, 1, DBU and P$_4$-r-Bu, the reaction time was also extended to 20 hours (Table 4). Two series of 80 °C reactions were run in the same manner as the preceding two series (Tables 5 and 6).
**General Method for HPLC analysis.** In order to compensate for matrix effects on the UV absorption detector and for drift in the UV lamp over time, the method of standard additions was employed in the analysis of the styrene produced. A 0.100 mL aliquot of the reaction mixture was placed in each of four 5-mL volumetric flasks. A standard solution of styrene was prepared in the appropriate solvent (THF or acetonitrile) and increasing volumes of this standard solution (0.100 mL, 0.200 mL, and 0.300 mL) were added to the second, third, and fourth volumetric flask, respectively. All the volumetric flasks were diluted to volume with the same solvent in which the reaction was run, and then the solutions were analyzed by HPLC. A graph of peak height versus concentration was prepared using Microsoft Excel, and the concentration of the original aliquot was extrapolated from this graph. The coefficients of correlation obtained for these graphed data were very good (0.999 or better) in most cases. Because all reaction mixtures were of constant volume, calculation of the total amount of styrene present was easily done, and a conversion to product was calculated. Even when the coefficient of correlation was poorer than 0.999, reproducibility of the conversions was very good. In all cases, at least three experimental conversions were used to calculate the average conversion reported (Tables 1-6). Taking into account the methods of introduction of the sample, conversions reported are precise to within 2%.

**Preparative scale coupling of 4-(triflyloxy)acetophenone and vinyltributyltin using DBU.** The title triflate (1.00 g, 3.73 mmol) was dissolved in NMP (10 mL) and anhydrous LiCl (0.484 g, 11.4 mmol), Pd$_2$dba$_3$ (69 mg, 0.15 mmol Pd), and DBU (0.045 mL, 0.30 mmol) were added. After 10 minutes at room temperature, vinyltributyltin (1.31 mL, 4.48 mmol) was added and the reaction was stirred at room temperature for 2 h. The reaction mixture was then diluted with a saturated solution of KF (30 mL), extracted with hexanes (50 mL) and then the two phases were separated. The organic layer was dried and evaporated under vacuum. A portion (1.72 g
of 4.82 g) of the crude product remaining was further purified via silica gel flash chromatography (5% ethyl acetate in hexanes) followed by Kugelrohr distillation (50 °C at 60 mtorr) giving p-vinylacetophenone (184 mg, 94%) whose ¹H NMR spectrum obtained agreed well with that reported in the literature.⁹

**Preparative scale coupling of 4-(triflyloxy)acetophenone and vinyltributyltin using 1.** This reaction was carried out and the product was purified in a manner identical to that in the preceding method, except that 1 (65 mg, 0.30 mmol) was employed instead of DBU as the base, giving p-vinylacetophenone (176 mg, 92%). The ¹H NMR spectrum of the product agreed well with that reported in the literature.⁹

**Preparative scale coupling of 4-(triflyloxy)acetophenone and tetramethyltin using DBU.** This reaction was carried out and the product was purified in a manner identical to that given above, except that tetramethyltin (0.620 mL, 4.98 mmol) was used instead of vinyltributyltin, giving p-methylacetophenone (152 mg, 82%). The ¹H NMR spectrum of the product obtained agreed well with that reported in the literature.⁹

**Preparative scale coupling of 4-(triflyloxy)acetophenone and tetramethyltin using Ph₃As.** This reaction was carried out and the product was purified in a manner identical to that given above, except that Ph₃As (91 mg, 0.30 mmol) was used as the base and tetramethyltin (0.620 mL, 4.98 mmol) was used instead of vinyltributyltin, giving p-methylacetophenone (97 mg, 69%). The ¹H NMR spectrum of the product obtained agreed well with that reported in the literature.⁹
Preparative scale coupling of 4-(triflyloxy)acetophenone and tetramethyltin using TFP. This reaction was carried out and the product was purified in a manner identical to that given above, except that TFP (69 mg, 0.30 mmol) was used as the base and tetramethyltin (0.620 mL, 4.98 mmol) was used instead of vinyltributyltin, giving p-methylacetophenone (110 mg, 52%). The \(^1\)H NMR spectrum of the product obtained agreed well with that reported in the literature.\(^9\)

Acknowledgments

We thank the National Science Foundation and the ISU Institute for Physical Research and Technology for grant support of this research.

References


Table 1. Average yields for reaction 4 carried out for 6 hours.\textsuperscript{a}

<table>
<thead>
<tr>
<th>ligand/base</th>
<th>conversion to styrene (%)\textsuperscript{b}</th>
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<tbody>
<tr>
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<td>7</td>
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<tr>
<td>Ph\textsubscript{3}P</td>
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</tr>
<tr>
<td>Ph\textsubscript{2}As</td>
<td>90</td>
</tr>
<tr>
<td>TFP</td>
<td>96</td>
</tr>
<tr>
<td>P(NMe\textsubscript{2})\textsubscript{3}</td>
<td>47</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>DBU</td>
<td>62</td>
</tr>
<tr>
<td>P\textsubscript{2}-Et</td>
<td>61</td>
</tr>
<tr>
<td>P\textsubscript{4}-t-Bu</td>
<td>49</td>
</tr>
<tr>
<td>Proton Sponge</td>
<td>18</td>
</tr>
</tbody>
</table>

\textsuperscript{a} A 1:4 Pd:ligand/base ratio was employed with \textbf{Pd\textsubscript{2}dba\textsubscript{3}} as the Pd source.

\textsuperscript{b} Reaction conversions were determined using HPLC analysis.
Table 2. Average yields for reaction 4 carried out for 20 hours.\textsuperscript{a}

<table>
<thead>
<tr>
<th>ligand/base</th>
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<tbody>
<tr>
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<tr>
<td>Ph\textsubscript{3}P</td>
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<tr>
<td>Ph\textsubscript{3}As</td>
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<td>TFP</td>
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<td>DBU</td>
<td>69</td>
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<tr>
<td>P\textsubscript{4}-t-Bu</td>
<td>61</td>
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</tbody>
</table>

\textsuperscript{a} A 1:4 Pd:ligand/base ratio was employed with Pd\textsubscript{2}dba\textsubscript{3} as the Pd source.

\textsuperscript{b} Reaction conversions were determined using HPLC analysis.
Table 3. Average yields for reaction 5 carried out for 6 hours.\(^a\)

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<td>$\text{Ph}_3\text{As}$</td>
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<tr>
<td>TFP</td>
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<tr>
<td>$\text{P(NMe}_2\text{)}_3$</td>
<td>64</td>
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<tr>
<td>1</td>
<td>73</td>
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<tr>
<td>DBU</td>
<td>68</td>
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<td>$\text{P}_2\text{Et}$</td>
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<td>$\text{P}_4\text{-r-Bu}$</td>
<td>67</td>
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<tr>
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<td>69</td>
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</table>

\(^a\) A 1:4 Pd:ligand/base ratio was employed with $\text{Pd}_2\text{dba}_3$ as the Pd source.

\(^b\) Reaction conversions were determined using HPLC analysis.
Table 4. Average yields for reaction 5 carried out for 20 hours.\textsuperscript{a}

<table>
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<td>TFP</td>
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<td>1</td>
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<td>DBU</td>
<td>93</td>
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<tr>
<td>P\textsubscript{4}-t-Bu</td>
<td>70</td>
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<tr>
<td>Proton Sponge</td>
<td>76</td>
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</tbody>
</table>

\textsuperscript{a} A 1:4 Pd:ligand/base ratio was employed with Pd\textsubscript{2}dba\textsubscript{2} as the Pd source.

\textsuperscript{b} Reaction conversions were determined using HPLC analysis.
Table 5. Average yields for reaction 6 carried out for 6 hours.a

<table>
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<tr>
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<td>TFP</td>
<td>87</td>
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<td>1</td>
<td>85</td>
</tr>
<tr>
<td>DBU</td>
<td>90</td>
</tr>
</tbody>
</table>

a A 1:4 Pd:ligand/base ratio was employed Pd₂dba₃ as the Pd source.

b Reaction conversions were determined using HPLC analysis.
Table 6. Average yields for reaction 6 carried out for 20 hours.\textsuperscript{a}

<table>
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<th>ligand/base</th>
<th>conversion to styrene (%)\textsuperscript{b}</th>
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<tbody>
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<tr>
<td>Ph\textsubscript{3}P</td>
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<td>Ph\textsubscript{3}As</td>
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<td>96</td>
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<td>1</td>
<td>83</td>
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<tr>
<td>DBU</td>
<td>92</td>
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</table>

\textsuperscript{a} A 1:4 Pd:ligand/base ratio was employed with Pd\textsubscript{2}dba\textsubscript{3} as the Pd source.

\textsuperscript{b} Reaction conversions were determined using HPLC analysis.
Table 7. NMR study of the reaction of 1 with dba in the presence and absence of palladium(0) in THF and in MeCN at 60 °C for six hours.

<table>
<thead>
<tr>
<th>system</th>
<th>solvent</th>
<th>(^1)H observations</th>
<th>(^13)C observations</th>
<th>(^{31})P observations</th>
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<tr>
<td>1 + Pd(_2)dba(_3)</td>
<td>MeCN</td>
<td>vinyl/phenyl</td>
<td>vinyl/phenyl</td>
<td>2 and 3 observed, oligomers</td>
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<td>broadening, 2 present</td>
<td>broadening</td>
<td>suggested</td>
</tr>
<tr>
<td>1 + dba(^b)</td>
<td>MeCN</td>
<td>vinyl/phenyl</td>
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<td>broadening, 2 present</td>
<td>broadening</td>
<td>suggested</td>
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</tbody>
</table>

\(^a\) The molar ratio of 1 to Pd\(_2\)dba\(_3\) was 8:1.

\(^b\) The molar ratio of 1 to dba was 8:3.
Table 8. Mass spectral study of the reaction of 1 with dba in the presence and absence of palladium(0) in THF and in MeCN at 60 °C for six hours.$^a$

<table>
<thead>
<tr>
<th>reactants (solvent)</th>
<th>technique employed to observe ions of mass</th>
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<tr>
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<tr>
<td>$1 + \text{Pd}_2\text{dba}_3$ (MeCN)</td>
<td>EI</td>
</tr>
<tr>
<td>$1 + \text{dba}$ (MeCN)</td>
<td>EI</td>
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<tr>
<td>$1 + \text{Pd}_2\text{dba}_3$ (THF)</td>
<td>EI, CI$^b$</td>
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<tr>
<td>$1 + \text{dba}$ (THF)</td>
<td>EI, CI$^b$</td>
</tr>
</tbody>
</table>

$^a$ The molar ratio of base to dba was 8:1.

$^b$ The ion mass detected was one mass unit higher than listed because of CI technique.

$^c$ The ion mass detected was 465.

$^d$ The ion mass detected was 467.
Table 9. NMR study of the reaction of DBU with dba in the presence and absence of palladium(0) in THF and in MeCN at 60 °C for six hours.

<table>
<thead>
<tr>
<th>system</th>
<th>solvent</th>
<th>$^1$H observations</th>
<th>$^{13}$C observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBU + Pd$_2$dba$_3$</td>
<td>MeCN</td>
<td>vinyl/phenyl broadening, no</td>
<td>vinyl/phenyl broadening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[DBU-H]$^+$</td>
<td></td>
</tr>
<tr>
<td>DBU + dba$^{bc}$</td>
<td>MeCN</td>
<td>no vinyl/phenyl broadening, no</td>
<td>no vinyl/phenyl broadening, no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[DBU-H]$^+$</td>
<td>[DBU-H]$^+$</td>
</tr>
<tr>
<td>DBU + Pd$_2$dba$_3$</td>
<td>THF</td>
<td>vinyl/phenyl broadening, no</td>
<td>vinyl/phenyl broadening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[DBU-H]$^+$</td>
<td></td>
</tr>
<tr>
<td>DBU + dba$^{bc}$</td>
<td>THF</td>
<td>no vinyl/phenyl broadening, no</td>
<td>no vinyl/phenyl broadening, no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[DBU-H]$^+$</td>
<td>[DBU-H]$^+$</td>
</tr>
</tbody>
</table>

$^a$ The molar ratio of DBU to Pd$_2$dba$_3$ was 8:1.

$^b$ The molar ratio of DBU to dba was 8:3.

$^c$ The longer reaction time of 20 hours was employed since no reaction was observed at six hours.
Table 10. Mass spectral study of the reaction of DBU with dba in the presence and absence of palladium(0) in THF and in MeCN at 60 °C for six hours.\textsuperscript{a}

<table>
<thead>
<tr>
<th>reactants (solvent)</th>
<th>technique employed to observe ions of mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>232</td>
</tr>
<tr>
<td>DBU + Pd\textsubscript{2}dba\textsubscript{3} (MeCN)</td>
<td>not observed</td>
</tr>
<tr>
<td>DBU + dba (MeCN)</td>
<td>Cl\textsuperscript{b}</td>
</tr>
<tr>
<td>DBU + Pd\textsubscript{2}dba\textsubscript{3} (THF)</td>
<td>EI</td>
</tr>
<tr>
<td>DBU + dba (THF)</td>
<td>EI</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The molar ratio of base to dba was 8:1.

\textsuperscript{b} The ion mass detected was one mass unit higher than listed because of CI technique.
FLUORIDE-CATALYZED REDUCTION OF PALLADIUM(II) TO PALLADIUM(0) PHOSPHINE COMPLEXES

A paper submitted to Organometallics
Patrick A. McLaughlin and John G. Verkade*

Abstract

Here we demonstrate that in the presence of water and excess PPh₂, fluoride ion catalyzes the reduction of (Ph₂P)₂PdCl₂ under mild conditions to Pd(PPh₃)₄ in good yields while Ph₃P is oxidized to Ph₃P=O. The inactivation of catalytic F⁻ by formation of highly stable HF₂⁻ and other polyhydrogen fluorides that can form in the reaction is prevented by adding a strong non-ionic base such as P(MeNCH₂CH₂)₃N. Pd(ddpb)₂ and Pd₂(dppm)₃ are synthesized in high yields by incorporating this strong non-ionic base into the catalyzed synthesis.

Introduction

Tetracoordinate Pd(0) phosphine complexes are widely used as catalysts in organic synthesis. Interesting among the several routes to these compounds is the formation of a Pd(0) complex in quantitative conversion via a redox transmetalation involving Pd(II) and Pt(0).¹ In more traditional preparations Pd(II) halide complexes are reduced to the corresponding bis-(diphosphine)Pd(0) or tetrakis-(phosphine)Pd(0) analogues with NaBH₄ (11% to 68% yields)² in the presence of the phosphine or diphosphine, or to tetrakis-(phosphine)Pd(0) complexes with hydrazine in the presence of phosphines (90-95% isolated yields).³⁴ (PPh₃)₂PdCl₂ complexes can also be reduced efficiently to (PPh₃)₄Pd by employing NaOH in the presence of a phase-transfer catalyst (84% yield),⁵ with alkaline alkoxides (90% yield),⁶ or with acetate ion in the presence of excess phosphate (quantitative conversion).⁷ Displacement reactions of dba (dba = dibenzylideneacetone) and PPh₃ from Pd(db)₂ and Pd(PPh₃)₂, respectively, by P(CH₂OH)₃ have been employed to synthesize the water-soluble complex Pd[P(CH₂OH)₃]₄ in good yields (89% and 77%
yields, respectively). The dicoordinate Pd(0) complex Pd(PPh₃)₂ is made by reduction of Cl₂Pd(PPh₃)₂ with RLi (quantitative conversion). The Pd(PPh₃)₂ can be further treated with PPh₃ to form Pd(PPh₃)₄. In addition, the dimer (Ph₃P)₂Pd₂ has been synthesized by the treatment of [Ph₃P-Pd(OAc)₂]₂ with H₂ or Na/Hg (95% yields). Finally, PdCl₂ has been reduced to (PET₃)₄Pd by potassium metal in the presence of excess PET₃ (91% yield).

In 1992 the novel redox reaction 1 was reported from our laboratories. Here Pd(II) bis-phosphine complexes are reduced to tetrakis-phosphine Pd(0) complexes while part of the excess phosphine is oxidized to R₃P=O. The formation of an R₃PF₂ phosphorane intermediate in the reduction and its subsequent reaction with water present in the reaction mixture to give R₃P=O (Scheme 1) was demonstrated by NMR spectroscopy.

\[
(R_3P)_2PdCl_2 + 2F^- + H_2O + 3PR_3 \rightarrow (R_3P)_4Pd + 2Cl^- + 2HF + R_3P=O \quad (1)
\]

Although reaction 1 could be taken to imply that fluoride is acting as a catalyst, HF readily forms very robust HF₂⁻ as well as other stable polyhydrogen fluorides. Evidence for the robustness of these anionic species was the failure to produce any significant product in reaction 1 when an attempt was made to generate fluoride from KHF₂ in the presence of the very strong non-ionic base 2-(dimethylamino)pyridine (DMAP, pKₐ = 13 in acetonitrile). It was of interest, therefore to seek a non-ionic base that could deprotonate the hydrogen fluoride species in reaction 1, thereby liberating fluoride ion and demonstrating its catalytic role.

Recently we have been exploring the application of pro-azaphosphatrane 1, first reported from our laboratories, as a superior non-ionic base in the synthesis of acylated alcohols, porphyrins, α-C-acylamino acids, trans olefins, chiral auxiliary-bearing isocyanides, and mono-alkylated β-dicarbonyls, and as an efficient catalyst for the trimerization of isocyanates and the protective silylation of alcohols. The very stable conjugate acid 2 of commercially available 1 has a pKₐ (41 in MeCN) which is about 17 units larger than the conjugate acid of DBU, a strong non-nucleophilic base widely used...
in synthetic applications. We show here that reaction 1 is catalytic in fluoride in the presence of the very strong non-ionic bases 1, DBU, and P₄-t-Bu; the latter possessing a base strength very comparable to that of 1. We also report that the tetracoordinated palladium(0) product of reaction 1 is contaminated with ca. 6% of an uncharacterized impurity that can be removed by column chromatography.

![Chemical structures](image)

**Experimental Section**

Reagent grade PdCl₂ (Aldrich), PPh₃ (Aldrich), the phosphazene base P₄-t-Bu (Fluka), and n-Bu₄NF•3H₂O (Aldrich) were used as received. DBU (Aldrich) was distilled under reduced pressure (0.07 torr, 48 °C) prior to use. Pro-azaphosphatrane 1 was synthesized and purified according to literature methods.³¹P NMR spectra were acquired on a Bruker AC 200Mz instrument. All organic solvents were distilled under nitrogen. In addition, chloroform was degassed using the freeze-pump-thaw method. All experiments were carried out under an inert atmosphere.

**Synthesis of Pd(PPh₃)_4 using catalytic fluoride and 1.** Method A: PdCl₂ (0.100 g, 0.563 mmol) and PPh₃ (0.817 g, 3.11 mmol) were dissolved in 15 mL of DMSO, and the reaction mixture was heated in an oil bath at 140 °C. Heating was discontinued after 15 minutes (the time required to dissolve all reactants) and a solution of n-Bu₄NF•3 H₂O
(0.029 g, 0.11 mmol) in 5 mL of DMSO was added via syringe. The remaining water (3.5 μL, 0.19 mmol) was added via a microliter syringe, followed by the addition of 1 (0.25 g, 1.2 mmol) in 5 mL of DMSO. The yellow solution was allowed to cool to room temperature during which time a yellow solid precipitated. Ethanol (30 mL) was added to the vessel and the reaction mixture was stirred overnight to effect complete precipitation. The product was isolated by filtration, rinsed with two 10-mL portions of cold ethanol (5 °C) and 10 mL of diethyl ether. The product was dried in vacuo (395 mg, 94% crude). This crude mixture was purified using a silica gel column employing degassed chloroform as the eluent (81% yield). $^3$P NMR (CDCl$_3$) δ 19 (lit. 19), mp: 190-194 °C (lit. 19). \[\text{Method B:} \text{PdCl}_2 (0.050 g, 0.28 \text{mmol}) \text{and PPh}_3 (0.370 g, 1.43 \text{mmol}) \text{were dissolved in 15 mL of DMSO. The reaction mixture was heated in an oil bath at 80 °C for 15 minutes (the time required to dissolve all reactants) and then a solution of n-Bu$_4$NF·3 H$_2$O (0.014 g, 0.054 mmol) in 5 mL of DMSO was added via syringe. The remaining water (2.0 μL, 0.11 mmol) was added via syringe, and this was followed by the addition of 1 (0.12 g, 0.56 mmol) in 5 mL of DMSO. The yellow solution was allowed to cool to room temperature during which time a yellow solid precipitated. Ethanol (30 mL) was added to the vessel and the reaction mixture was stirred overnight to complete precipitation. The product was isolated by filtration, rinsed with two 10-mL portions of cold ethanol (5 °C) and 10 mL of diethyl ether. The product was dried in vacuo (314 mg, 96% crude and purified as in Method A above (82% yield).} \]

$^3$P NMR (CDCl$_3$) δ 19 (lit. 19), mp: 190-194 °C (lit. 19). \[\text{Synthesis of Pd(PPh}_3)_4 \text{using catalytic fluoride and P}_4\text{-t-Bu.} \text{ This reaction was identical to that in Method B, except that P}_4\text{-t-Bu (0.564 mL of a 1.0 M solution in hexane, 0.56 mmol) was used as a base instead of 1. The product was isolated as described above,}\]
dried in vacuo (294 mg, 90% crude) and purified as in Method A above (77% yield). \(^{31}P\) NMR (CDCl\(_3\)) \(\delta 19\) (lit.\(^{12}\) 19).

**Synthesis of Pd(PPh\(_3\))\(_4\) using catalytic fluoride and DBU.** This reaction was identical to that in Method B, except that DBU (0.085 mL, 0.56 mmol) was used as a base instead of 1. The product was isolated as described above, dried in vacuo (237 mg, 73% crude) and purified as in Method A above (62% yield). \(^{31}P\) NMR (CDCl\(_3\)) \(\delta 19\) (lit.\(^{12}\) 19).

**Synthesis of Pd(dppb)\(_2\) using catalytic fluoride and 1. Method A:** This reaction was identical to that which gave Pd(PPh\(_3\))\(_4\) in Method A above, except that the phosphine used was dppb (0.364 g, 0.854 mmol) and no chromatography was required to give \(^{31}P\) NMR-spectroscopically pure Pd(dppb)\(_2\) (187 mg, 69%). \(^{31}P\) NMR (CD\(_2\)D\(_2\)): \(\delta 12\) (br) (lit.\(^{12}\) 12).

**Method B:** This reaction was identical to that which gave Pd(PPh\(_3\))\(_4\) in Method B above, except that the phosphine used was dppb (0.364 g, 0.854 mmol) and no chromatography was required to give \(^{31}P\) NMR-spectroscopically pure Pd(dppb)\(_2\) (211 mg, 78%). \(^{31}P\) NMR (CD\(_2\)D\(_2\)): \(\delta 12\) (br) (lit.\(^{12}\) 12).

**Synthesis of Pd\(_2\)(dppm)\(_3\) using catalytic fluoride and 1.** This reaction was identical to that which gave Pd(PPh\(_3\))\(_4\) in Method B above, except that the phosphine used was dppm (0.328 g, 0.854 mmol) and no chromatography was required to give \(^{31}P\) NMR-spectroscopically pure Pd\(_2\)(dppm)\(_3\) (164 mg, 85%). \(^{31}P\) NMR (CD\(_2\)D\(_2\)): \(\delta 14\) (br) (lit.\(^{12}\) 14).

**Results and Discussion**

Previously, it was demonstrated that stoichiometric F– in reaction 1 afforded an 80% yield of crude Pd(PPh\(_3\))\(_4\) in DMSO as the solvent.\(^{12}\) In the presence of the strong non-ionic bases 1, P\(_4\)-t-Bu, and DBU, F– is observed in the present work to behave catalytically, effecting the transformation of PdCl\(_2\) to Pd(PPh\(_3\))\(_4\) in DMSO in improved yields of crude product (96%, 90%, and 73%, respectively). The observation of comparable yields of product using 1 (pK\(_a\) = 41 in acetonitrile\(^{16}\)) and P\(_4\)-t-Bu (pK\(_a\) = 42 in
acetonitrile\textsuperscript{18}) is in accord with the similar strengths of these bases,\textsuperscript{17} while the lower yield observed with DBU (pK\textsubscript{a} = 24 in acetonitrile\textsuperscript{18}) can be attributed to its considerable weaker basicity.\textsuperscript{18} It may be noted here that unlike P\textsubscript{4}-r-Bu, in which protonation occurs on the imino nitrogen, 1 is protonated on the phosphorus giving 2 (which was observed in the $^{31}$P NMR spectrum of the filtrate). A preparation of Pd(PPh\textsubscript{3})\textsubscript{4} in the presence of 1 was

\[
1 + \text{H}_2\text{O} \rightleftharpoons 2 + \text{OH}^- \quad (2)
\]

attempted in the absence of fluoride anion leaving all other conditions identical. As was mentioned above, it has been reported previously that hydroxide anion is capable of reducing Pd(II) in the presence of phosphines to give Pd(PR\textsubscript{3})\textsubscript{4}.\textsuperscript{5} Thus, we tested the possibility that hydroxide in equilibrium 2 is formed in sufficiently high concentration to effect the reduction of Pd(II). However, the $^{31}$P NMR spectrum of a solution of the precipitate showed no resonance indicative of the formation of Pd(PPh\textsubscript{3})\textsubscript{4}. These results are consistent with the postulate we put forth earlier\textsuperscript{12} that the catalytic fluoride ion concentration was reduced to ineffectively low values by HF\textsubscript{2} and polyhydrogen fluorides in our original synthesis. Whereas Pd(dbbp)\textsubscript{2} had previously been isolated in 65\% yield using stoichiometric fluoride at 140 °C,\textsuperscript{12} it was isolated here in 69\% yield using 1 and catalytic fluoride at the same temperature. The yield was further increased to 78\% by performing the reaction at lower temperature (80 °C) in the presence of 1 and catalytic fluoride. Pd\textsubscript{2}(dppm)\textsubscript{3}, which had previously been isolated in 86\% yield using stoichiometric fluoride at 140 °C,\textsuperscript{12} was herein isolated in 85\% yield at 80 °C (although a longer reaction time was necessary) using 1 as the base.

An impurity in the Pd(PPh\textsubscript{3})\textsubscript{4} amounting to approximately 6\% of the mixture was discovered by $^{31}$P NMR spectroscopy (δ 33) in carrying out reaction 1 as originally described by us\textsuperscript{12} as well as in all of our preparations described here. Column chromatography with degassed chloroform as the eluent permitted removal of this impurity.
Thus the best yield of pure Pd(PPh₃)₄ obtained in the present work was 82%. Pyridine, acetonitrile, and NMP were investigated as alternative solvents to DMSO for reaction 1 wherein R₃P is Ph₃P, but product yields with both stoichiometric and catalytic fluoride were at most half of what was achieved in DMSO. No impurities were detected in the chelating phosphine products.

While the best yield of pure Pd(PPh₃)₄ in the present work is less than that obtained with some of the previously reported methods, our present results support our hypothesis that fluoride ion is a catalyst in reaction 1, and that this reaction offers an alternative route to Pd(0) phosphine complexes, at least for chelating phosphine ligands. A unique feature of reaction 1 is that the source of electrons in the oxidation product Ph₃P=O is fluoride ion whereas the oxygen source is the weak base H₂O. This contrasts similar reactions reported earlier with the more basic anions hydroxide⁵, alkoxide⁶ and acetate⁷ wherein the oxygen in these species serve both purposes. Thus the function of the H₂O in reaction 1 is solely to hydrolyze the Ph₃PF₃ formed by the catalytic redox action of the fluoride anion (Scheme 1). The nucleophilic anions in these redox reactions involving fluoride, hydroxide⁵, alkoxide⁶ and acetate⁷ must attack phosphorus at some point. Whether they do so by migrating to the phosphorus subsequent to metal coordination or directly (see paths a and b in Scheme 1 for the present case of the fluoride ion) is not yet clear.

Pro-azaphosphatrane 1 appears to be of potentially wide use as a non-nucleophilic base in organometallic and transition metal chemistry owing to its solubility in a wide variety of polar and nonpolar solvents, the ease with which its protonation can be monitored by ³¹P NMR spectroscopy, its facile recovery from product salts of 2 (which are generally insoluble in nonpolar solvents), and its rather poor metal ligating properties, especially when there is an opportunity for a deprotonation reaction to occur, and its commercial availability (Strem). Efforts to expand the utility of 1 and several of its even more basic analogues as deprotonating agents are underway.
Acknowledgments

We thank the National Science Foundation for financial support of this research in the form of a grant.

References


P(NMeCH₂CH₂)₃N: A GENERALLY SUPERIOR PROMOTER OF THE KNOEVENAGEL CONDENSATION

A paper to be submitted to *Journal of Organic Chemistry*

Patrick A. McLaughlin and John G. Verkade*

Abstract

The exceptionally strong base P(NMeCH₂CH₂)₃N (1) is herein applied as a generally superior promoter in the Knoevenagel condensation of carbonyls with malonitrile. Aromatic aldehydes, ketones, and secondary aldehydes are converted to their corresponding alkenes in 98-99%, in 84-93%, and in 98% yields, respectively. Reactions are carried out with 5 mol% of the promoter at room temperature in two hours.

Introduction

The Knoevenagel condensation, generalized in reaction 1, is of great synthetic utility in the manufacture of a wide variety of compounds, including the preparation of chromophores,¹ the synthesis of non-linear optical materials,² ³ narrow bandgap polymers,⁴ steroid derivatives,⁵ and substituted benzenes and pyridines in one-pot syntheses.⁶ This reaction has been studied with a wide variety of catalysts.⁷ Catalysts and reaction conditions employed to condense malonitrile and aromatic aldehydes, for example, include alkali and alkaline earth carbonates (10-47 mol%, dioxane, 90 °C for 10 - 120 min, 5-90%),⁸ piperidine (2-3 mol%, alcohol, 25 °C for 5 min, 38-96% yield),⁹ a,b piperidine (2 mol%, neat, microwave irradiation for 2-5 min, 90-97% yield),¹⁰ silica gel (500 mg per 4.6 mmol of aldehyde, methylene chloride, 25 °C for 70 h, 95% yield),¹¹ silica supported amines (10-12 g per 10 mmol of aldehyde, neat or in toluene followed by passage through
column to catalyze reaction, 25 °C, 83-91% yield),

zinc chloride (10 mol%, neat, 100 °C for 10 min, 91-97% yield),
bismuth chloride (10 mol%, neat, 80 °C for 15 min, 71-75% yield),
modified weakly acidic ion-exchange resin (20 mg per 2 mmol of aldehyde, benzene, 25 °C for 5 hours, 90-92% yield),
phosphate ore or sodium phosphate (5-8 g per 6 mmol of benzaldehyde, methanol, 20 °C for 5-7 min, 90% yield),
magnesium oxide (600 mol%, neat, 25 °C for 5-10 min, 91-94% yield),
aluminum oxide (300 mol%, neat, 25 °C for 3 min, 96% yield),
AIPO4-Al2O3 (185 mol% AIPO4:74 mol% Al2O3, neat, 25 °C for 15 min, 77-81% yield),
kobalt fluoride (25 mol% for all reactions, benzene, 25 °C for 1 hour, 84% yield; ethanol, 25 °C for 1 hour, 93% yield; DMF, 25 °C for 1 hour, 99% yield),
cadmium iodide (10 mol%, benzene, 75 °C for 5 min, 92-95% yield).
Aliphatic aldehydes have also been catalytically condensed with malonitrile using piperidine (5 mol%, neat, RT for 5 min, 98% yield),
bismuth chloride (10 mol%, neat, 80 °C for 15 min, 71% yield),
magnesium oxide (600 mol%, neat, 25 °C for 10 min, 93% yield),
aluminum oxide (300 mol%, neat, 25 °C for 3 min, 88% yield),
AIPO4-Al2O3 (185 mol% AIPO4:74 mol% Al2O3, neat, 25 °C for 30 min, 75% yield),
cadmium iodide (10 mol%, benzene, 75 °C for 5 min, 80% yield).
Finally, ketones have been catalytically condensed with malonitrile using piperidine (2-3 mol%, alcohol, 25 °C for 5 min, 30% yield),
modified weakly acidic ion-exchange resin (20 mg per 2 mmol of ketone, benzene, 25 °C for 5 min - 3 h, 47-86% yield),
magnesium oxide (600 mol%, neat, 25 °C for 5 min, 40% yield),
aluminum oxide (200-300 mol%, neat, 50-100 °C for 3-30 min, 81-98% yield),
AIPO4-Al2O3 (185 mol% AIPO4:74 mol% Al2O3, neat, 25 °C for 30 min, 31-52% yield),
and potassium fluoride (25 mol%, benzene, 60 °C for 6 h, 75% yield).

Our group has recently been investigating the applications of pro-azaphosphatrane 1, first reported from our laboratories, as a superior non-ionic base used as a promoter in the synthesis of acylated alcohols, as a reagent in the preparation of porphyrins,
acylamino acids, trans oleins, chiral auxiliary-bearing isocyanides, and mono-
alkylated \( \beta \)-dicarbonyls; and as an efficient catalyst for the trimerization of isocyanates and the protective silylation of alcohols. The very stable conjugate acid 2 of commercially available 1 has a \( pK_a \) approximately 17 units larger than the conjugate acid of DBU, a strong non-nucleophilic base widely used in synthetic applications. As reported herein, commercially available pro-azaphosphatrane 1 is also an efficient promoter for the conversion of a variety of aldehydes and ketones to the corresponding Knoevenagel condensates at room temperature.

**Results and Discussion**

\[ \text{\textit{CD}_3\text{CN}} \rightleftharpoons \text{\textit{CD}_2\text{CN}^-} \] (2)

It has been observed that pro-azaphosphatrane 1 reacts with deuterio-acetonitrile (\( pK_a \) of acetonitrile = 25) to form a small amount of the corresponding deuterated salt of 1, namely, \( 2'(\text{CD}_2\text{CN}) \) in an equilibrium (reaction 2). All attempts to isolate this salt failed, because removal of the solvent causes the equilibrium to shift too rapidly to the right. However, the malonitrilate (\( pK_a = 11 \)) of 2 was easily made in quantitative yield from the reaction of 1 with malonitrile in toluene (reaction 3). That this equilibrium lies far...
to the right was demonstrated by a $^{31}$P NMR spectrum of an equimolar mixture of 1 and CH$_2$(CN)$_2$ in CD$_3$CN in which no unreacted 1 was detected. Salt 3 when reacted with benzaldehyde under mild conditions, resulted in the quantitative formation of 4 (reaction 4). On the basis of this result, we hypothesized that 1 could be used as an efficient promoter in the Knoevenagel condensation.

The large quantities of catalysts often required to induce condensations (especially in the case of the heterogenous catalysts) and/or the heating employed in some of the aforementioned reactions are potentially avoided through the use of a strong non-ionic base, such as 1. Such bases permit milder reaction conditions because in contrast to ionic bases they feature enhanced reactivity owing to the more naked anions in the poorly associated ion pairs they form upon deprotonation of the substrate and because they possess better solubility in organic solvents at room temperature and below as is required for some reactions. Thus only 5 mol% of 1 was needed to induce virtually complete condensation of the aldehydes and ketones in Table 1 (with the exception of p-hydroxybenzaldehyde for which 10 mol% was required). In Scheme 1, 1 probably reacts with malonitrile to form 2[CH(CN)$_2$], the malonitrilate anion of which subsequently attacks a carbonyl group forming an alkoxide intermediate which can then deprotonate another malonitrile molecule, generating the corresponding alcohol and another malonitrilate ion that continues the reaction. The alcohol eliminates water, the driving force for this reaction being the formation of the conjugated alkene. The yields of the condensates of aromatic aldehydes (Table 1) exceeded those every other catalyst found in the literature. These high yields are achieved despite steric effects or electron-withdrawing/donating substituents on the aromatic aldehyde (factors which greatly reduced yields provided by some of the
Promoter 1 also achieved ketone condensation better than all previous reported catalysts, with the exception of aluminum oxide (which employed 200-300 mol% of catalyst). For the condensation of secondary aldehydes, promoter 1 is superior to MgO, Al₂O₃, and AlPO₄-Al₂O₃, and is competitive with piperidine for the condensation of secondary aldehydes. Attempts to convert primary aldehydes into the corresponding alkenes were met with very low conversions.

Though here used in relatively small amounts, promoter 1 could, in principle, be recovered after isolation of the product by chromatography or extractive work-ups (see Experimental Section). Thus the silica gel column could be extracted with an acidified (e.g., HCl) polar solvent (e.g., MeCN), and the aqueous extract could similarly acidified. The extracts could be reduced in volume and evaporated, respectively. The residueu in the latter case would then be dissolved in MeCN and the MeCN solutions would be treated with KO-ι-Bu to recover 1 by sublimation.\textsuperscript{33,34}

Scheme 1

\[ \text{CH}_2(\text{CN})_2 + \text{H}_2\text{O} \rightarrow \text{CH(CN)}_2^- \]

\[ \text{NC-CN} \quad \text{R} \quad \text{R'} \quad + \text{H}_2\text{O} \]

\[ \text{CH}_2(\text{CN})_2 \]

\[ \text{O} \quad \text{R} \quad \text{R'} \]

\[ \text{NC-CN} \quad \text{R} \quad \text{R'} \quad \text{W} \quad \text{O}^- \]

\[ \text{CH}_2(\text{CN})_2 \]
Experimental Section

Materials. Pro-azaphosphatrane 1 (commercially available from Strem) was synthesized and purified according to literature methods. Acetonitrile was distilled from CaH$_2$ under a nitrogen atmosphere. Malonitrile was distilled at reduced pressure (50 °C, 600 mtorr) prior to use. All other reagents were purchased from Aldrich and were used without subsequent purification. Product purity was confirmed by $^1$H and $^{13}$C NMR spectroscopies using CDCl$_3$ as the solvent.

Preparation of 2[CH(CN)$_2$]. Malonitrile (91 mg, 1.4 mmol) was placed in a flask and dissolved in toluene (15 mL). Pro-azaphosphatrane 1 (299 mg, 1.38 mmol) was added to the flask as a solution in toluene (3 mL). Within a few minutes, 2[CH(CN)$_2$] was formed as a precipitate. The precipitate was filtered, washed with diethyl ether, and dried in vacuo to remove residual solvent, yielding the salt (388 mg, 99%).

General Procedure for the Reaction of Malonitrile with Carbonyl Compounds in the presence of 1. Malonitrile (4.70 mmol) was placed in a flask and dissolved in acetonitrile (10 mL). Pro-azaphosphatrane 1 (5 mol%) was added to the flask as a solution in acetonitrile (1 mL), causing the solution to become brown. The carbonyl compound was added to the reaction mixture, which was then allowed to stir for two hours at room temperature. The solvent was removed by rotary evaporation under reduced pressure. One of two methods of purification was employed, depending on the nature of the product. In the first method, the crude product was purified by silica gel chromatography (30:70 ethyl acetate/hexanes eluent). The eluent was then removed via rotary evaporation under reduced pressure, giving the pure compound. In cases where chromatography proved ineffective, the crude product was dissolved in toluene (120 mL) and any excess malonitrile and/or salt 2 was extracted with water (4 x 20 mL). The organic layer was separated, dried with MgSO$_4$, filtered, and evaporated via rotary evaporation, giving NMR-pure product.
Preparation of benzylidenemalonitrile (4). Benzaldehyde (0.462 mL, 4.54 mmol) was added to a solution of malonitrile (0.300 g, 4.54 mmol) and 1 (0.048 mg, 0.22 mmol) according to the general procedure. Chromatography gave the straw colored product 4 (686 mg, 98% yield).

Preparation of p-chlorobenzylidenemalonitrile (5). p-Chlorobenzaldehyde (0.636 g, 4.52 mmol) was added to a solution of malonitrile (0.310 g, 4.70 mmol) and 1 (0.049 g, 0.23 mmol) according to the general procedure. After extraction of the toluene solution with water according to the method described in that procedure, product 5 was obtained (686 mg, 99% yield).

Preparation of p-hydroxybenzylidenemalonitrile (6). p-Hydroxybenzaldehyde (0.509 g, 4.50 mmol) was added to a solution of malonitrile (0.312 g, 4.73 mmol) and 1 (116 mg, 0.536 mmol) according to the general procedure. After extraction of the toluene solution with water according to the method described in that procedure, product 6 was obtained (686 mg, 99% yield). The use of 5 mol% of 1 resulted in a poorer conversion ('H NMR spectroscopy, 70%).

Preparation of 2,5-(dimethyl)benzylidenemalonitrile (7). 2,5-(Dimethyl)benzaldehyde (0.695 g, 5.18 mmol) was added to a solution of malonitrile (0.342 g, 5.18 mmol) and 1 (56 mg, 0.26 mmol) according to the general procedure. After extraction of the toluene solution with water according to the method described in the general procedure, product 7 was obtained (944 mg, 99% yield).

Preparation of 2,5-(dimethoxy)benzylidenemalonitrile (8). 2,5-(Dimethoxy)benzaldehyde (0.768 g, 4.62 mmol) was added to a solution of malonitrile (0.308 g, 4.67 mmol) and 1 (0.049 g, 0.23 mmol) according to the general procedure. After extraction of the toluene solution with water according to that procedure, product 8 was obtained (986 mg, 99% yield).
Preparation of 1,1-dicyano-2-cyclohexylethene (9).
Cyclohexanecarboxyaldehyde (0.662 mL, 5.46 mmol) was added to a solution of malonitrile (0.361 g, 5.46 mmol) and 1 (0.059 g, 0.27 mmol) according to the general procedure. Chromatography gave product 9 (686 mg, 98% yield).

Preparation of cyclohexylidenemalonitrile (10). Cyclohexanone (0.455 mL, 4.39 mmol) was added to a solution of malonitrile (0.290 g, 4.39 mmol) and 1 (0.049 g, 0.23 mmol) according to the general procedure. After extraction of the toluene solution with water according to that procedure, product 10 was obtained (598 mg, 93% yield).

Preparation of 1,1-dicyano-2-propylpent-1-ene (11). 4-Heptanone (0.626 mL, 4.47 mmol) was added to a solution of malonitrile (0.307 g, 4.65 mmol) and 1 (0.049 g, 0.23 mmol) according to the general procedure. After extraction of the toluene solution with water according to the method described in that procedure, a portion of the organic product (546 mg of crude product) was further purified by Kugelrohr distillation (40 °C, 60 mtorr) yielding product 11 (480 mg, 88% yield).

Acknowledgment
We thank the Donors of the Petroleum Research Fund administered by the American Chemical Society for support of this work in the form of a grant.

Supporting Materials.
'H and 13C NMR spectral data. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masterhead page for ordering information and Internet access instructions.

References


(36) Schwesinger, R. Chimia 1985, 39, 269.


**Table 1.** Reaction of aldehydes and ketones with malonitrile in acetonitrile for 2 hours at RT in the presence of 5 mol% 1.\(^a\)

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<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
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<td>93%</td>
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<tr>
<td><img src="image15" alt="Image" /></td>
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<td>84%</td>
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</table>

\(^a\) 5 mol% of 1 was used in all cases except for the reaction giving 6, in which case 10 mol% was present.
Supporting Information

P(NMeCH₂CH₂)₃N: A Generally Superior Promoter of the Knoevenagel Condensation

Patrick A. McLaughlin and John G. Verkade*

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111

¹H and ¹³C NMR Data

1. 2[CH(CN)₂]: ¹H NMR δ 2.69 (d, 9 H, J = 18 Hz), 3.13 (m, 6 H), 3.34 (m, 6 H), 5.30 (d, 1 H, J = 223 Hz); ¹³C δ -1.57, 34.53 (d), 41.28 (d), 47.33 (d), 132.09.

2. 4: ¹H NMR δ 7.18 (m, 1H), 7.55 (m, 2H), 7.77 (s, 1 H), 7.90 (d, 2H, J = 12 Hz) compares favorably with that shown in Aldrich FT-NMR 1(2), 1509C.

²C NMR δ 82.35, 112.39, 113.53, 129.34, 130.48, 130.69, 134.42, 159.87.

3. 5: ¹H NMR δ 7.46 (d, 2H, J = 9 Hz), 7.67 (s, 1 H), 7.79 (d, 2H, J = 9 Hz) and ¹³C NMR δ 83.15, 112.53, 113.34, 129.14, 130.15, 131.98, 141.09, 158.31 compare favorably with those shown in J. Chem. Soc., Perkin Trans. 2, 1976, 6, 729.

4. 6: ¹H NMR δ 7.11 (d, 2H, J = 9 Hz), 8.00 (d, 2H, J = 9 Hz), 8.26 (s, 1 H) and ¹³C NMR δ 77.99, 114.76, 115.79, 117.40, 124.54, 134.59, 160.84, 163.76 compare favorably with those shown in J. Chem. Soc., Perkin Trans. 2, 1976, 6, 729.

5. 7: ¹H NMR δ 2.38 (s, 3 H), 2.40 (s, 3 H), 7.25 (m, 2 H), 7.89 (s, 1 H), 8.07 (s, 1 H); ¹³C NMR δ 19.00, 20.63, 83.02, 112.44, 113.79, 128.26, 129.62, 131.13, 134.95, 136.58, 136.67, 158.17.

6. 8: ¹H NMR δ 3.80 (s, 3 H), 3.87 (s, 3 H), 6.92 (d, 1 H, 9 Hz) 7.17 (dd, 1 H, J = 9 Hz, 3 Hz), 7.74 (d, 1 H, J = 3 Hz), 8.29 (s, 1 H) compares favorably with that shown in Can. J. Chem. 1965, 43, 2585. ¹³C NMR δ 55.77, 56.23, 80.78, 111.05, 112.71, 113.13, 114.31, 120.06, 124.17, 153.36, 153.70, 154.04.

7. 9: ¹H NMR δ 1.48 (m, 10 H), 2.66 (m, 1 H), 7.12 (d, 1H, 10 Hz) compares favorably with that shown in Rec. J. R. Neth. Chem. Soc. 1980, 99, 6. ¹³C NMR δ 24.41, 24.88, 30.55, 42.01, 87.56, 110.56, 111.93, 173.81.
8. 10: $^1$H NMR 1.69 (m, 6 H), 2.59 (m, 4 H) compares favorably with that shown in J. Am. Chem. Soc. 1995, 117, 12436. $^{13}$C NMR 24.8, 27.8, 34.56, 82.0, 111.5, 185.

9. 11: $^1$H NMR 0.94 (t, 6 H, 7.5 Hz), 1.55 (m, 4 H), and 2.48 (t, 4 H, 7.5 Hz); $^{13}$C NMR 8 13.23, 20.87, 36.92, 84.98, 109.52, 11.67, 186.54. Bull. Soc. Chim. Fr. 1975, 1670.
PREPARATION OF \{\text{Au}[\text{P(NMeCH}_2\text{CH}_2)_3\text{N}]_2\}\text{Cl}

A note submitted to *Inorganic Chemistry*

Patrick A. McLaughlin and John G. Verkade*

Abstract

P(\text{NMeCH}_2\text{CH}_2)_3\text{N} (1) is capable of forming adducts with various Lewis acids, resulting in a P-N* bond distance ranging from the sum of the van der Waal's radii (3.34 Å) to a fully transannulated P-N* bond (1.976 Å) as in the molecule H-P(\text{NMeCH}_2\text{CH}_2)_3\text{N} (2). We report herein the formation of a bis-(1)gold(I) adduct, with a corresponding transannular bond of 3.171 Å.

Introduction

We have previously reported the extraordinary Lewis basicity of proazaphosphatranne 1, first reported from our laboratories \(^1\) as a superior non-ionic base used as a reagent in the synthesis of acylated alcohols, \(^5\) porphyrins, \(^6\) \(\alpha\)-C-acylamino acids, \(^6\) trans olefins, \(^7,8\) chiral auxiliary-bearing isocyanides, \(^9\) and mono-alkylated \(\beta\)-dicarbonyls; \(^10\) and as an efficient catalyst for the trimerization of isocyanates \(^11\) and the protective silylation of alcohols. \(^12\) We have also studied its coordination to a variety of Lewis acids. \(^13,14\) In those studies we compared the varying degrees of transannulation exhibited in structures of the products (determined by X-ray means) with the sum of the van der Waals radii (3.34 Å) of the bridgehead atoms. Full transannulation occurs in cation 2 (1.976 Å). We report title the title compound and its structure determined by X-ray crystallography.
Figure 1. Perspective view and atom-labeling scheme for the cation of 3, namely
\[
\{[(P(NMeCH_2CH_2)_2N]Au}\]^+,
\]
with atoms represented by their 30\% probability ellipsoids. Hydrogens have been eliminated for clarity.
Results and Discussion

Synthesis and Characterization. The title compound 3(Cl) was synthesized as a tan powder in quantitative yield according to reaction 1. A computer drawing of the

\[ [(\text{Me}_2\text{S})\text{AuCl}] + 2 \text{I} \rightarrow 3(\text{Cl}) + \text{Me}_2\text{S} \quad (1) \]

of the complex is shown in Figure 1. Selected bond distances and bond angles are listed in Tables 1 and 2, respectively, and atomic coordinates are given in Table 3. The P-Au-P angle is almost perfectly linear, at 179.11°. The average P-N distance is 3.171 Å. This compound is more transannulated than any previously synthesized transition metal complex of 1.

Experimental Section

Reagent grade (Me2S)AuCl (Aldrich) was used as received. Pro-azaphosphatrane 1 was synthesized and purified according to literature methods.\(^{1,2}\) \(^{13}\)C and \(^{31}\)P NMR spectra were acquired on a Bruker AC 200Mz instrument. \(^1\)H NMR spectra were acquired on a Variac VX-R-300 instrument. Acetonitrile was dried with CaH\(_2\) under nitrogen and ether was dried with Na/benzophenone under nitrogen. Experiments were carried out under argon.

Synthesis of 3. To (Me2S)AuCl (0.100 g, 0.340 mmol) dissolved in 2 mL of acetonitrile was added a solution of 1 (0.147 g, 0.680 mmol) dissolved in 1 mL of acetonitrile. The reaction was allowed to proceed for 2 hours at room temperature, followed by removal of the solvent and Me2S by evaporation. The product was placed in a warm water bath (35 °C) under vacuum (50 mtorr) in order to ensure complete removal of these species. Compound 3 was isolated (0.225, 99.6%) as a tan colored powder. NMR

\(^1\)H 1.93 (m), 2.77 (m), 2.87 (m). \(^{13}\)C 34.75 (m), 50.36 (\(J_{C-P} = 32\) Hz), \(^{31}\)P 132.29.

Anal. Calcd for 3 (C\(_{12}\)H\(_{42}\)N\(_8\)P\(_2\)AuCl): C, 32.51; H 6.37; Cl 5.33. Found: C, 31.37; H, 6.43; Cl, 5.07.
X-Ray structure determination of 3(Cl). A crystal of compound 3(Cl) was attached to a glass fiber and mounted on the Siemens SMART system for a data collection at 173(2) K. An initial set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames are oriented such that orthogonal wedges of reciprocal space were surveyed. This produces orientation matrices determined from 89 reflections. Final cell constants are calculated from a set of 5001 strong reflections from the actual data collection. Please refer to Table 4 for additional crystal and refinement information.

The data collection technique used for this specimen is generally known as a hemisphere collection. Here a randomly oriented region of reciprocal space is surveyed to the extent of 1.3 hemispheres to a resolution of 0.84 Å. Three major swaths of frames are collected with 0.30° steps in α. In the event the lattice is triclinic some additional sets of frames are collected to better model the absorption correction.

The space group P2₁/n was determined based on systematic absences and intensity statistics. A successful direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Several full-matrix least squares/difference Fourier cycles were performed which located the remainder of the non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters.

The complex was found as expected. The position of the Au atom gives the data the appearance of being C-centered; all otherwise primitive reflections are systematically weakened. This appearance led to initial incorrect choice of lattice and space group that provided a bizarre solution. The present solution is most certainly correct. During the final stages of refinement it was noticed that many reflections with l = 10, in particular F_o^2 >> F_c^2. A small rotational twin was verified with the following twin law: [1.0 0.0 0.70, 0.0]
The twin law implies that all reflections with \( l = 0, 3, 7, 10, 13, \) and \( 17 \) have exact overlaps with those from the twin component. The reflection data were corrected for this with UNTWIN by creating a SHELXTL HKLF reflection file. The minor twin component was determined to be about 5% of the mass of the main crystal. This improved the residuals from 0.048 to 0.041.

**Conclusions**

We have been able to prepare an interesting gold(I) compound of 1, which shows partial transannulation to a greater degree than what has previously been seen with transition metals. Investigation into how the transannular distance changes when gold(I) is oxidized to gold(III) in this system are underway.

**Acknowledgment**

The authors thank the National Science Foundation for support of this research in the form of a grant. In addition, we thank Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory, who provided the crystallographic report.

**References**


(15) Young, V. “Crystal Structure Report C_{18}H_{42}AuClN_8P_2”.

(16) SHELXTL-Plus V5.0, Siemens Industrial Automation, Inc., Madison, WI.

(17) UNTWIN, V. G. Young, Jr., University of Minnesota, 1997.
Table 1: All Bond Distances (Å) and Their Estimated Standard Deviations for the cation of 3.

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Table 2: All Angles (deg) and Their Estimated Standard Deviations for the cation of 3.

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<td>C(1)-N(1)-P(1)</td>
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<td>122.4(5)</td>
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<td>N(1)-C(2)-C(3)</td>
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<td>C(4)-N(2)-P(1)</td>
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<tr>
<td>N(4)-C(6)-C(5)</td>
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<td>C(8)-N(3)-C(7)</td>
<td>116.4(6)</td>
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<td>C(8)-N(3)-P(1)</td>
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Table 3: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (× 10^3) for 3. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Table 4 (continued)

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$^a$ U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.
Table 4: Crystal structure and refinement data for 3.

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PREPARATION OF [F-P(NMeCH₂CH₂)₃N][F]

A note submitted to Inorganic Chemistry

Patrick A. McLaughlin and John G. Verkade*

Abstract

P(NMeCH₂CH₂)₃N (1), in addition to being an exceptionally strong non-ionic base, can act as a nucleophile. Herein, 1 reacts with carbonyl difluoride to form [FP(NMeCH₂CH₂)₃N][F] (3a) in high yield (86%). The synthesis and characterization of 3a are discussed herein.

Introduction

We have previously reported the extraordinary Lewis basicity of pro-azaphosphatrane 1, first reported from our laboratories¹-³ as a superior non-ionic base used as a reagent in the synthesis of acylated alcohols,⁵ porphyrins,⁶ α-C-acylamino acids,⁶ trans olefins,⁷,⁸ chiral auxiliary-bearing isocyanides,⁹ and mono-alkylated β-dicarboxyls;¹⁰ and as an efficient catalyst for the trimerization of isocyanates¹¹ and the protective silylation of alcohols.¹² Furthermore, we have studied its coordination to a variety of Lewis acids.¹³,¹⁴ In these studies, the varying degrees of transannulation of the P-Nax bond for derivatives of 1 were examined, with these bond distances ranging from the sum of the van der Waals radii (3.34 Å) to the fully transannulated bond as observed in compound 2 (1.97 Å), and the Neq-P-Neq bond angles ranging from 104.5° to 119.6°, respectively. Halogens were investigated for their Lewis acidity, and synthesis of compounds 3b-3d were accomplished, although the synthesis of 3a proved elusive.
Herein, the synthesis, characterization, and potential applications for 3a are discussed.

\[
\begin{align*}
\text{Me}^+ - & \text{F}^- \\
\text{Me}^- & 1) \text{toluene, } 30 \text{ min, } -77 \, ^\circ\text{C} \\
& 2) \text{warm to RT, } 30 \text{ min} \\
\end{align*}
\]

1) toluene, 30 min, -77 °C
2) warm to RT, 30 min

\[
\begin{align*}
\text{F}^+ + \text{CO} \quad (1)
\end{align*}
\]

Results and Discussion.

Synthesis and Characterization. The new compound was synthesized in quantitative yield according to reaction 1. Selected characterization data of compound 3a are given in the experimental section. It was noted in previous studies\textsuperscript{15} that two indications of a fully transannulated compound are the upfield resonance in the \( ^{31}\text{P} \) NMR (the resonance is at -41 for 3a, compared to the resonance at 120 for 1), and the coupling between the phosphorus and the carbons attached to the axial nitrogen, which is present in this molecule. Attempts to recrystallize 3a have been successful in a variety of solvents (MeOH, THF, MeCN), but X-Ray analysis has been problematic due to a solvent dependency observed in the crystals. Further attempts are underway.

Experimental Section

Pro-azaphosphatrane 1 was synthesized and purified according to literature methods.\textsuperscript{23} \( ^{13}\text{C} \) and \( ^{31}\text{P} \) NMR spectra were acquired on a Bruker AC 200Mz Instrument. \( ^1\text{H} \) and \( ^{19}\text{F} \) NMR spectra were acquired on a Varian VXR 300 instrument. Toluene was dried with Na/benzophenone. Experiments were carried out under an inert atmosphere.

Synthesis of 3a. 1 (1.01 g, 4.67 mmol) was placed in a Schlenk flask and purged with argon, followed by subsequent evacuation of the gas by vacuum pump. Toluene (30 mL) was added to completely dissolve 1. The flask was placed in a dry ice/acetone bath (-77 °C) and allowed to cool for 15 minutes, after which carbonyl
difluoride (229 mL, 8.97 mmol) was added to the reaction vessel. The reaction was allowed to stir at -77 °C for thirty minutes, followed by warming to room temperature for thirty minutes. The salt was filtered, washed with ether, and dried in vacuo, yielding 3a (1.02, 86%). \( ^1\text{H NMR} \ 2.72 \,(\text{dd}, 9\text{H}, \ ^3\text{J}_{\text{pp}} = 10 \text{ Hz}, \ ^4\text{J}_{\text{pp}} = 3 \text{ Hz}), 3.19 \,(\text{m}, 12 \text{ H}).\]

\( ^{13}\text{C NMR} \ 36.4 \,(\text{d}, \ J = 14.6 \text{ Hz}), 44.7 \,(\text{d}, 14.0 \text{ Hz}), 47.6 \,(\text{d}, 10.5 \text{ Hz}).\]

\( ^{19}\text{F NMR} \ 2.08 \,(\text{fluoride anion}), 92.9 \,(\text{d}, \ J_{\text{pp}} = 723 \text{ Hz}).\]

\( ^{31}\text{P NMR} \ -41 \,(\text{d}, \ J_{\text{pp}} = 729 \text{ Hz}).\]

**Conclusions**

We have been able to prepare a formerly unattainable derivative of 1, namely 3a. This compound has been shown to have a slightly larger transannular bond than that of 3b, consistent with theoretical calculations.

**Acknowledgment**

The authors thank the National Science Foundation for support of this research in the form of a grant.

**References**


GENERAL SUMMARY

P(NMeCH₂CH₂)₃N (1) is a fascinating molecule with a wide range of applications in organic and inorganic synthesis. Our investigations of its chemistry has revealed its utility as a viable co-catalyst in Stille-cross coupling reactions (in addition to the utility of other strong non-ionic bases in this reaction). This base effect, previously unreported to our knowledge, promises utility in dealing with problematic syntheses where traditional ligands have failed. In addition, we have seen how 1 is utilized in the formation of Pd(0) complexes, allowing fluoride to act catalytically. The superior basicity of 1 has demonstrated great utility in the formation of tri-substituted alkenes through the Knoevenagel condensation, competitive or superior to other catalysts used in the past. Finally, structural studies, both based on NMR and X-Ray crystallography, have revealed interesting features with gold(I) and F(I) derivatives of 1.

The vast possibilities and enormous potential the rich chemistry of 1 allows in the fields of organic and inorganic syntheses promises to be an interesting avenue to further investigations.
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There are so many who have supported me throughout my graduate school career and my life that I hardly know where to begin.

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