Synthesis and applications of new polymer bound catalysts

by

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CHAPTER 1. INTRODUCTION

Catalysis plays an important role in our world. From drug synthesis to polymer production, the use of catalysts allows society to improve the quality of life. Two important classes of catalysts are based on anions, and phosphoramides.

Anion catalysis

Anionic catalysts play a large role in organic chemistry. The tungstate anion, for example, is an extremely effective catalyst for the epoxidation of electron-deficient olefins, such as allyl alcohol, and α,ß-unsaturated acids.[1] A tungsten-containing anionic cluster has also been found to be a useful reusable heterogenous catalyst for the Michael addition of thiols to α,ß-unsaturated ketones.[2]

Nonmetallic anions can also function as effective catalysts. Michael adducts of α,ß-unsaturated ketones and amines or thiols are afforded through the use of sodium dodecyl sulfate.[3] The fluoride ion, both homogenously[4] and supported on alumina,[5] is a versatile catalyst for Michael additions. The selective silylation of ribonucleosides has been found to be catalyzed by the perchlorate ion[6] and this ion also catalyzed the methanolysis of methyl perchlorate in benzene.[7] The authors suggested that perchlorate deprotonates methanol in the catalytic process. Phosphate ion has been found to catalyze hydrogen peroxide decomposition.[8] Here, phosphate serves to deprotonate hydrogen peroxide, and the deprotonated compound is decomposed by chromate. The hydrolysis of 1,3-diphenyl-2-imidazolinium chloride is also catalyzed by phosphate.[9] In this reaction, phosphate acts as a base in the breakdown of a water-complexed substrate to produce N-(2-anilinoethyl)formanilide as the product. The oxidation of thioethers to sulfoxides by iodine has been found to be catalyzed by the arsenate ion.[10] Selenite ion catalyzes the reduction of

cytochrome c by glutathion.[11] A selenopersulfide is proposed to be the reactive intermediate. Selenite also catalyzes the absorption of carbon dioxide by water.[12] This reaction is also effectively catalyzed by arsenite or sulfite. Two possible mechanisms are proposed, the first of which involves nucleophilic attack of aqueous carbon dioxide by the catalyst. In the second mechanism, the catalyst deprotonates a water molecule adjacent to the carbon dioxide. The hydroxide ion produced then nucleophilicly attacks the carbon dioxide to produce carbonic acid.

The nitrate ion has also shown interesting catalytic activity. When used with a bismuth counterion, it is not only an effective Michael addition catalyst,[13] but it is also useful in the deprotection of oximes,[14] electrophilic substitution of indoles,[15] Paal-Knorr synthesis of pyrroles,[16] and glycosylation of alcohols.[17] Bismuth is not the only counterion that can be employed. Imino Diels-Alder reactions are catalyzed by urea nitrate[18] and tetrabutylammonium nitrate has been found to be an efficient catalyst for the selective silylation of ribonucleosides.[6] The authors found evidence that a nitrate coordinated silicon is the active species in this reaction.

Catalysis by phosphoramides and proazaphosphatranes and their derivatives

Phosphoramides are a class of widely soluble Lewis basic catalysts that show a wide variety of catalytic activity. Hexamethylphosphoramide (HMPT) is the most widely used of this group. It has proven useful in the synthesis of chalcogen complexes of aluminum.[18] HMPT has also proven useful in the ortho arylation of phenols.[20] In this reaction, a phosphite is made with the phenol which undergoes ortho metalation by rhodium. The cleavage of disilanes with various nucleophiles is facilitated with catalytic amounts of HMPT.[21] A method of catalyzing the Michael reaction utilizing HMPT has been found.[22]

HMPT is useful for the addition of trialkylaluminum compounds to epoxides wherein the phosphorus coordinates to the aluminum.[23] The dimerization of alkanes is carried out utilizing catalytic amounts of HMPT.[24]

Derivatives of HMPT are also useful in organic synthesis. HMPT sulfide is used as a catalyst for Pauson-Khand reactions wherein only one atmosphere of carbon monoxide is needed.[25] Syntheses of nylons are catalyzed by an iminophosphorane made from HMPT.[26]

Proazaphosphatranes are strong, non-ionic bases that exhibit a broad range of catalytic activity. This phenomenon has been well documented in two recent reviews.[27] The tethering of proazaphosphatranes to solid-supports has met with rather limited success, however. A protonated azaphosphatrane salt supported on a Merrifield resin was used as a procatalyst with NaH to deprotonate the salt and thus perform proazaphosphatrane-catalyzed dehydrohalogenations,[28] but attempts to isolate the supported free base met with failure.

Derivatives of proazaphosphatranes have also been shown to be useful in catalysis. Iminophosphoranes have been used in the acetylation of alcohols with vinyl acetate.[29] This catalyst was also immobilized on a solid support, and showed impressive catalytic activity in the same reaction.[29] Proazaphosphatrane sulfide was found to be useful catalytically in titanium tetrachloride-assisted Baylis-Hillman reactions.[30]

Chapter contents

Nitric acid has been shown to be a weak acid in acetonitrile.[31] It is conceivable that a nitrate salt of a weakly Lewis acidic cation could furnish a "naked" nitrate anion as a basic catalyst in a variety of reactions in non-aqueous solvents. Such a nitrate salt could also be bound to a polymeric support via the cation, thereby allowing for reclamation and recycling of the nitrate ion. This subject is dealt with in Chapter 2, wherein my contributions consisted

of performing all the reactions with the polymer supported catalyst and carrying out the experiments necessary to shed light on the reaction mechanisms. Chapter 3 contains a description of the structure and catalytic properties of an azidoproazaphosphatrane. This compound is an air-stable versatile catalyst that has proven useful not only homogenously, but also when bound to a solid support. The synthesis of a polymer bound proazaphosphatrane containing a trivalent phosphorus is presented in Chapter 4. Such a compound has been sought after by our group for a number of years. Not only does the synthesis I have accomplished for it allow for easier separation of proazaphosphatrane catalysts from reaction mixtures, but recycling of the base is made much simpler. Proazaphosphatranes are useful homogeneous catalysts that activate atoms in other reagents, thus enhancing their reactivity. The next chapters deal with two such reactions with aldehydes and ketones, namely silylcyanations with trialkylsilylcyanides (Chapters 5 and 6) and reductions with poly(methylhydrosiloxane), in Chapter 7. In Chapter 5, Zhigang Wang performed the initial optimization and scoping of the reaction, while repetitions of the scoping experiments for reproducibility, determination of diastereomeric ratios, and experiments aimed at elucidating aspects of the mechanism were performed by me. The proazaphosphatrane coordinates to the silicon atom in both cases, thereby allowing the aforementioned reactions to proceed under much milder conditions. Proazaphosphatranes are also effective Brønsted-Lowry bases. This is illustrated in Chapter 8 wherein a wide variety of conjugate addition reactions are catalyzed by proazaphosphatranes. In that chapter, repeitions of the nitroalkane addition reactions for reproducibility, improved spectral data for the products and comparisons of literature yields of all reactions were performed by me.

Finally, Chapter 9 contains a conclusion of the work presented, and my suggestions for future projects.

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CHAPTER 2. $[HP(HNCH_2CH_2)_3N]NO_3$: AN EFFICIENT HOMOGENOUS AND SOLID-SUPPORTED PROMOTER FOR AZA AND THIA-MICHAEL REACTIONS AND FOR STRECKER REACTIONS

An invited paper submitted for a Symosium in Print on Organocatalysis to Tetrahedron

Brandon M. Fetterly, Nirmal K. Jana, and John G. Verkade

Abstract: In the presence of a catalytic amount of the title azaphosphatrane nitrate salt, amines and thiols react readily with Michael acceptors. The title salt is also an efficient promoter for the one pot synthesis of α-amino and α-amidonitriles. By anchoring the title salt to Merrifield Resin, a reusable heterogenous catalyst is obtained for these reactions. Evidence is presented for catalysis attributable solely to the NO_3^- ion.

1. Introduction

The Michael reaction has been a useful tool for the organic, medicinal and biochemist for several decades.[1] This transformation is an efficient and commonly used route to the formation of C-C,[2] C-O,[3] C-N,[4] and C-S[5] bonds and it facilitates, for example, the synthesis of important amino alcohols and versatile intermediates for a large number of natural products,[6] heterocycles,[7] peptides[8] and chiral auxiliaries.[9] Protected *beta*-amino carbonyl compounds and *beta*-thiocarbonyl compounds can also be prepared *via* aza-Michael and thia-Michael reactions, respectively.[10]

Michael reactions are facilitated homogenously by protic acid catalysts,[11] base catalysts,[2a,c,3] or Lewis acid catalysts.[4,5] Recently, bismuth nitrate[4b] and also palladium tetrafluoroborate and chloride complexes[4f] have been reported to catalyze the production of

beta-amino and *beta*-thio carbonyl compounds in the presence of *alpha,beta*-unsaturated ketones.

α-Aminonitriles, often synthesized by a Strecker reaction,[12] are highly useful synthons for the preparation of α-amino acids[13] and nitrogen and sulfur-containing heterocycles[14] such as imidazoles and thiadiazoles. Acyclic α-amidonitriles,[15] are versatile synthons for the synthesis of diverse heterocyclic compounds,[16] and they are normally prepared by acylation of an α-aminonitrile.[15b,c,16,17a-e,18,19] Strecker reactions are generally carried out in aqueous solution with a variety of cyanide ion sources, including trimethylsilyl cyanide (TMSCN)[17] which appears to be most useful and also relatively safe.

A variety of homogenous catalysts containing Lewis acidic metal ions have been reported for the Strecker reaction.[15b,c,16b,17e,18a,c,e] The Strecker reaction is also known to proceed via the nucleophilic addition of cyanide to an imine in the absence of a catalyst, albeit with long reaction times (2-3 days).[19] Many of the reported methodologies for this reaction involve the use of relatively expensive reagents, extended reaction times and/or tedious work-up procedures leading to the generation of considerable amounts of waste, which in a substantial number of instances is toxic.

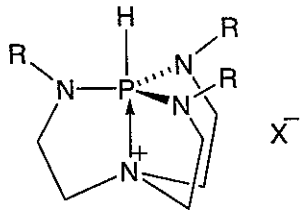
By contrast with α-aminonitriles, few reports were found describing the preparation of α-amidonitriles.[15] These two-step methods require relatively long reaction times and relatively tedious work-up procedures that generate comparatively large quantities of toxic waste.[15]

Catalysts bound to cross-linked polystyrene solid supports are well known and have been utilized for a myriad of organic transformations.[20] Azaphosphatrane **1a** supported on crosslinked polystyrene has been shown to be an effective procatalyst in

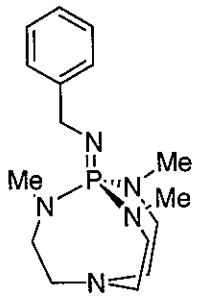
dehydrohalogenations and debrominations with NaH.[21] Acylation of alcohols has been achieved using polymer-supported iminoproazaphosphatrane **2**.[22]

Polymer-supported catalysts are also known for the Michael reaction, such as acids,[23] cinchona alkaloids,[24] catalytic lithium and aluminum ions complexed by a ligand linked to the polymer,[2b] or fluoride ion.[25] Unfortunately, these catalysts have only been tested on a small number of amines. Moreover, repeated recycling of these polymers was either not discussed or the polymer mounted catalysts required periodic reactivation.

Although resin bound catalysts for the Strecker reaction are known, such catalysts either involve the use of toxic metals[26] or of multistep syntheses.[27]



	R	X
1a	H	Cl^-
1b	H	NO_3
1c	H	CF_3CO_2
1d	H	CF_3SO_3
1e	Me	NO_3
1f	Me_2CHCH_2	Cl
1g	Me_2CHCH_2	NO_3



2

Our interest in thia- and aza-Michael reactions was piqued by the efficacy of bismuth nitrate as a catalyst and particularly by the apparent co-catalytic role of the nitrate ion.[4b] To insure that the nitrate ion in our experiments would be essentially free of Lewis acid-Lewis base interactions with its counter cation, in contrast to the likelihood of such interactions between the bismuth(III) cation and nitrate ion, we chose to investigate the nitrate salts of three azaphosphatranes, namely, **1b**, **e** and **g** because of the opportunity for positive charge delocalization in the azaphosphatrane cations. Here we report the synthesis of these salts and compare their efficiencies as catalysts with previously synthesized **1c, d,** and **f**[28] for the aza and thia-Michael reactions of amines and thiols at room temperature with *alpha,beta*-unsaturated ketones, *alpha,beta*-unsaturated esters and *alpha,beta*-unsaturated nitriles. We also report here a simple one-pot, three-component protocol for the preparation of a variety of α-aminonitriles using **1b**[28] as a promoter in reactions wherein nitrate ion is demonstrated to be the catalytically active species. A one-pot, four-component coupling method for the synthesis of α-amidonitriles using **1b** is also described.

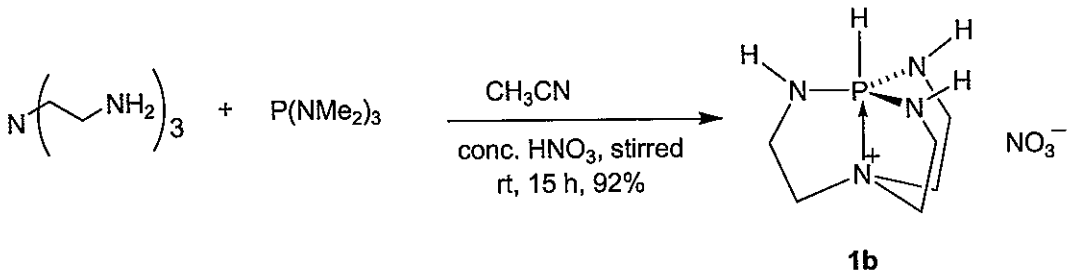
2. Results and Discussion

2.1 Homogenously catalyzed Michael reactions

Initially, we attempted to use the deprotonated form of **1e** [i.e., $P(MeNCH_2CH_2)_3N$] as a base catalyst for the aza-Michael reaction of aniline with methyl vinyl ketone, but to no

avail. We found, however, that although 10 mole % of the chloride salt **1f** gave no detectable yield of product in this reaction, 10 mole % of the nitrate salts **1e** and **1g** afforded a 78 and a 72% product yield after 30 h at room temperature, respectively. Because **1b** is considerably easier and cheaper to synthesize than **1e** or **1g**, we continued our investigations with **1b,** which was prepared from commercially available starting materials in a single step as shown in Scheme 1.

Scheme 1. Synthesis of **1b**

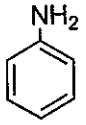
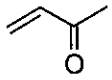
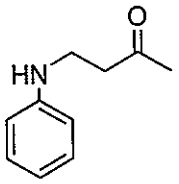
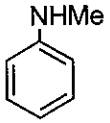
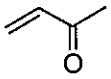
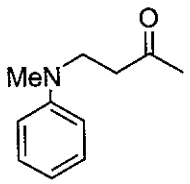
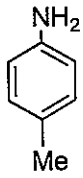
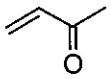
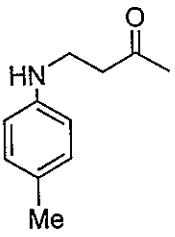
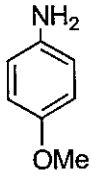
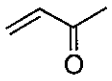
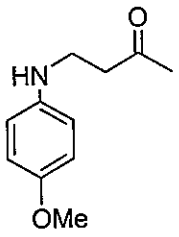
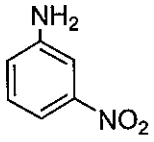
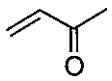
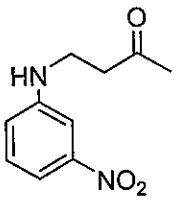
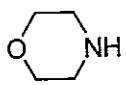
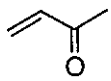
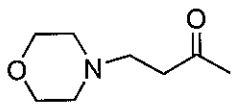
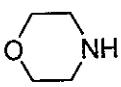
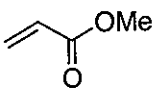
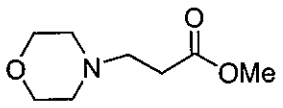


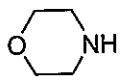
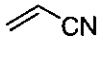
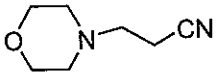
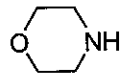
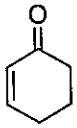
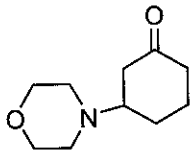
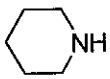
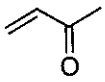
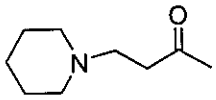
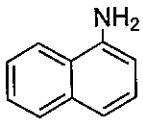
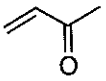
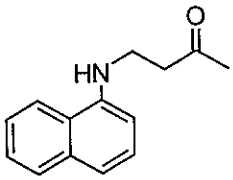
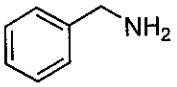
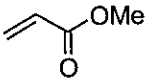
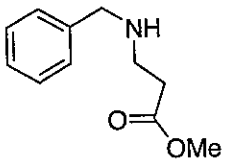
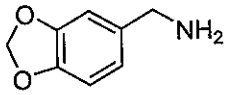
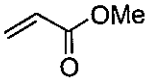
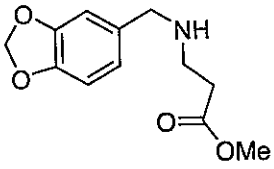
1b

When we screened the trifluoroacetate and triflate salts of **1b** (**1c** and **1d**, respectively) in the reaction of aniline with methyl vinyl ketone under the aforementioned conditions, the reactions were quite slow, furnishing product yields of 70% and 72% after 40 h using **1c** and after 48 h using **1d**, respectively. We also tested 10 mol % solution concentrations of HNO_3, $NaNO_3$, $NaNO_3$ in the presence of 15-crown-5, CAN, $Bu_4N(NO_3)$, 1-butyl-3-methylimidazolium chloride and 1-ethyl-3-methylimidazolium nitrate in this reaction, all of which provided unimpressive yields of 40, 32, 20, 0, 30, 45 and 50%, respectively, after 40 h. We attribute these poor results to anion-cation interactions that significantly exceed those experienced with the cation in **1b** wherein the positive charge is very well delocalized among the phosphorus and the four nitrogens as can be represented by the five resonance structures that can be drawn.

In the presence of 10 mol % of **1b**, reactions of methyl vinyl ketone with the anilines in Table 1 (entries 1-5) gave reasonable to good yields, except for relatively poorly nucleophilic 3-nitroaniline which contains the strongly electron withdrawing nitro group. With morpholine and the acceptors shown in entries 6-10 in Table 1, the corresponding aza-Michael products were realized in good to excellent yields. Piperidine and 1-aminonaphthalene when reacted with methyl vinyl ketone, gave good yields of the expected aza-Michael reaction product (Table 1, entries 10-11) although the reaction involving 1-aminonaphthalene required warming to 50 ^{0}C to accelerate the reaction. Benzylamine and piperonylamine also participated well in the aza-Michael reaction, giving the anticipated products in excellent yields (entries 12-13 in Table 1).

TABLE 1. Room temperature aza-Michael reactions in the presence of **1b** as a promoter..

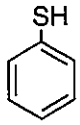
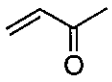
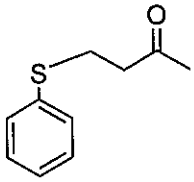
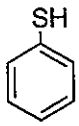
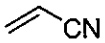
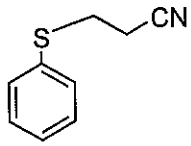
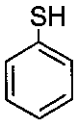
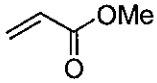
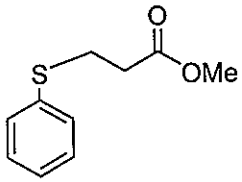
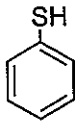
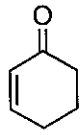
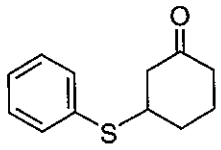
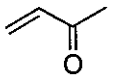
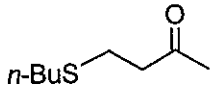
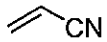
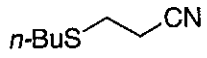
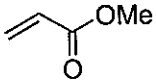
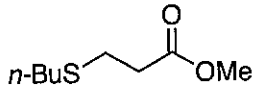
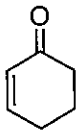
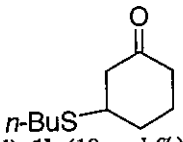
Entry	Donor	Acceptor	Time (h)	Product	Yield w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. Yield (%)[c]
1			30		NR	78	80-90[4f]
2			40			68	___[d]
3			40			83	73[10g]
4			40			84	76[10g]
5			50		NR	27	___[e]
6			20		40	90	87-88[4g,k]
7			20		50	86	91[4g]

Entry	Donor	Acceptor	Time (h)	Product	Yield w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. Yield (%)[c]
8			20		45	98	82[4g]
9			20			85	60[4j]
10			20		40	88	87-90[4e,l]
11			20			85[f]	___[e]
12			48		70	98	60-70[4g,h,l]
13			48		60	96	___[g]

[a]Conditions: amine (2.0 mmol), acceptor (2.5 mmol), **1b** (10 mol %) and CH_3CN (3 mL). [b]Isolated yields. [c]Literature yields. [d]This compound was reported earlier in ref. 7b, but no yield was given. [e]New compound. [f]Heated at 50 °C. [g]Although this compound has been reported and characterized,[4m] its yield and nmr spectral data were not given.

Thiophenol when allowed to react with a variety of acceptors in the presence of 10 mol % of **1b**, afforded the corresponding thia-Michael reaction products in excellent yields after 40 h at room temperature (Table 2, entries 1-4). Butanethiol also provided thia-Michael products in excellent yields after 48 h (Table 2, entries 5-8).

TABLE 2. Room temperature thia-Michael reactions promoted by **1b**.

Entry	Donor	Acceptor	Time (h)	Product	w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. Yield (%)[c]
1			40			95	66-72[5a,c]
2			40		30	98	92[5a]
3			40		20	98	92[5a]
4			40			94	65-92[4b,5a]
5	*n*-BuSH		48			90	70[5a]
6	*n*-BuSH		48			98	88[5a]
7	*n*-BuSH		48		NR	99	90[5a]
8	*n*-BuSH		48			93	73[4b]

[a]Conditions: thiol (2.0 mmol), acceptor (2.5 mmol), **1b** (10 mol %) and CH_3CN (3 mL). [b]Isolated yields. [c]Literature yields.

Our protocol is simple and of good scope, giving product yields that are better in 12 of the 17 reactions for which literature yields could be found (as seen in Tables 1 and 2). In 3 additional instances among those 17 cases, the yields realized with **1b** were about the same as

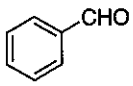
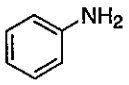
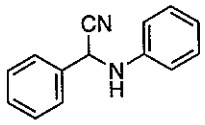
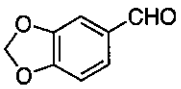
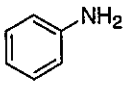
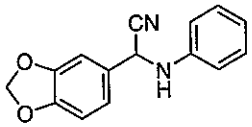
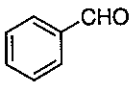
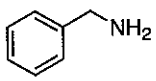
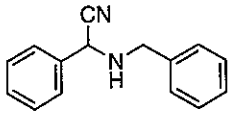
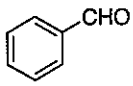
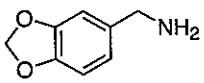
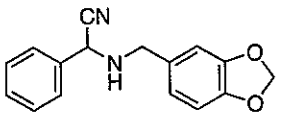
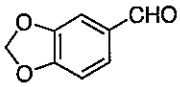
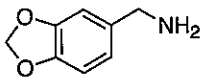
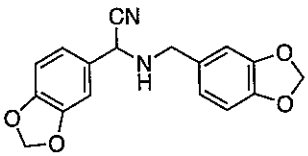
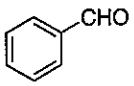
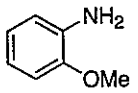
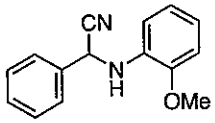
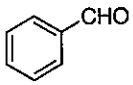
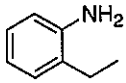
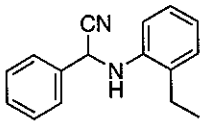
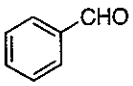
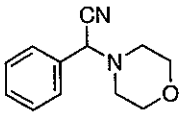
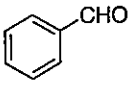
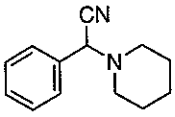
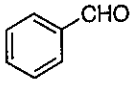
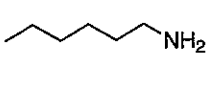
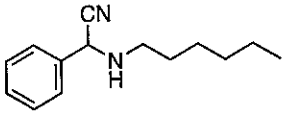
the maximum yield found in the literature, and in only one case was the yield roughly the same as the minimum literature yield.

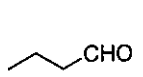
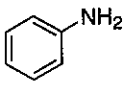
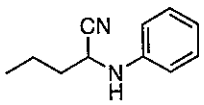
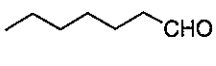
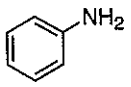
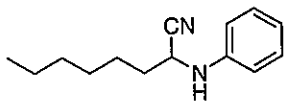
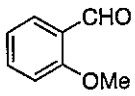
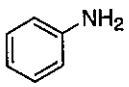
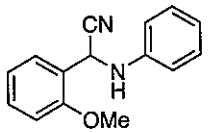
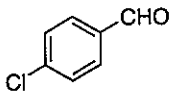
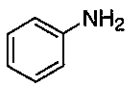
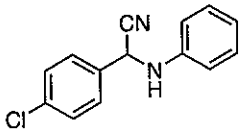
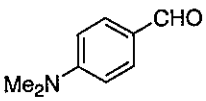
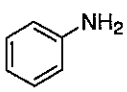
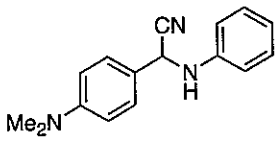
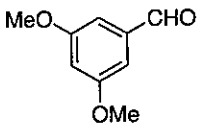
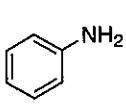
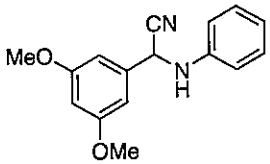
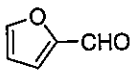
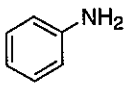
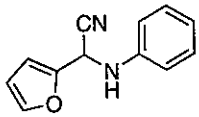
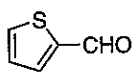
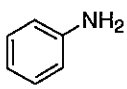
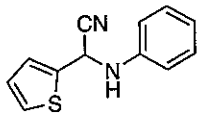
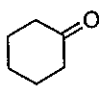
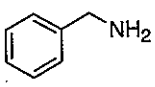
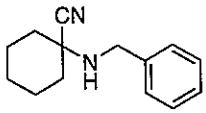
2.2 Homogenously catalyzed Strecker reactions

For the Strecker reaction, we initially examined **1c** and **1d** as promoters (20 mol%) for the three-component model reaction employing benzaldehyde, aniline and TMSCN in acetonitrile at room temperature for 12 h. Although the yields were disappointing (75% and 60%, respectively) the same reaction with 20 mol % of **1b** provided a 94% yield of the desired product. The use of dichloromethane as a solvent in this reaction gave a poor yield (40%) in a very slow (12 h) reaction probably owing to incomplete solution of **1b**.

Benzaldehyde (1.0 mmol) reacted with a variety of amines (1.0 mmol) in the presence of 20 mol % of **1b** and TMSCN (1.2 mmol) in CH_3CN to give excellent product yields (Table 3, entries 1, 3-4, 6-10). Secondary amines (Table 3, entries 8 and 9) reacted relatively quickly to give 98% product yields and *n*-hexylamine (entry 10) also gave a high yield of product of 83%. Piperonal reacted with amines, giving the corresponding α-aminonitrile in excellent yield (entries 2 and 5). Aliphatic aldehydes also reacted well with aniline, affording good product yields (entries 11 and 12). Aniline reacted with substituted aromatic aldehydes, affording 85-90% product yields (entries 13-16) and the heterocycles in entries 17 and 18 gave a 93 and 95% yield of desired product, respectively. Reactions of the type reported here are very sluggish without promoter **1b**, as was shown for the reaction in entry 1, in which case, 3 days were necessary to achieve a 90% product yield.

TABLE 3. Room temperature preparation of α-aminonitriles using **1b** as a promoter[a]

Entry	Aldehyde	Amine	Product	Time (h)	% Yield w/ **1b**[b]	Lit. Yield (%)[c]
1				12	94	d, 75-92[15b,16a,d]
2				15	91	97[15b]
3				12	90	d, 73-96[15a,b]
4				8	93	e
5				12	90	e
6				15	92	f[15a,c]
7				15	90	e
8				8	98	d, 82[15b]
9				15	98	d, 78[16c]
10				15	92	d, 83[17f]

Entry	Aldehyde	Amine	Product	Time (h)	% Yield w/ **1b**[b]	Lit. Yield (%)[c]
11				25	82	75[15a]
12				25	80	e
13				12	88	74[15a]
14				15	90	d, 75-91[15a,16a]
15				15	88	97[15b]
16				25	85	e
17				15	93	94[15c]
18				20	95	97[15c]
19				15	82	d, 66[15b]

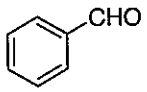
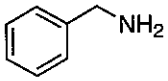
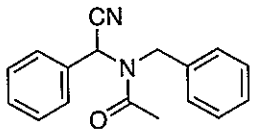
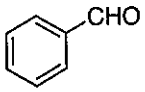
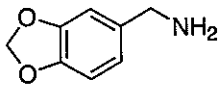
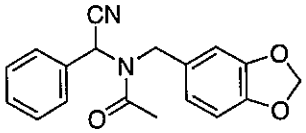
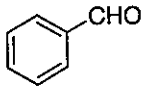
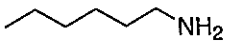
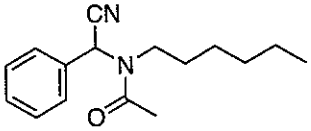
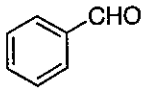
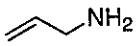
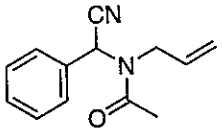
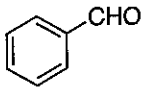
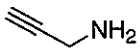
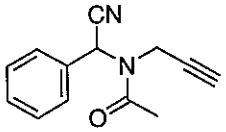
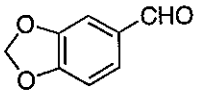
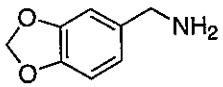
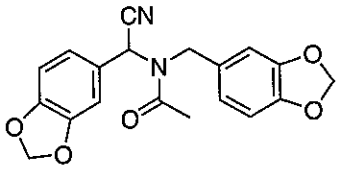
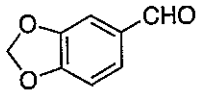
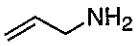
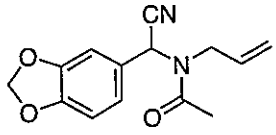
[a]Conditions: aldehyde or ketone (1.0 mmol), amine (1.0 mmol), TMSCN (1.2 mmol), **1b** (20 mol %) and CH_3CN (3 mL). [b]Isolated yields. [c]Literature yields. [d]Three-component coupling reaction. [e]New compound. [f]The yield was reported as quantitative.

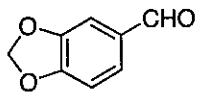
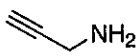
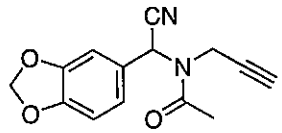
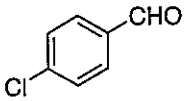
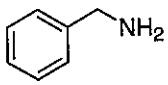
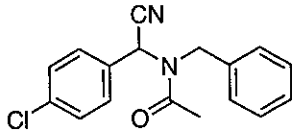
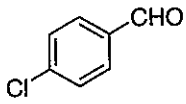
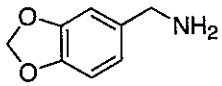
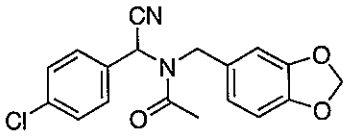
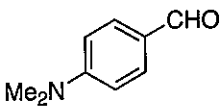
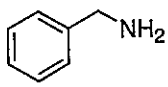
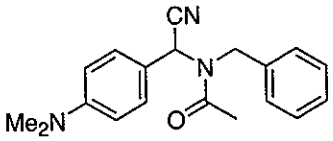
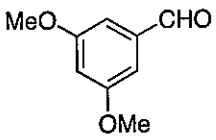
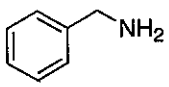
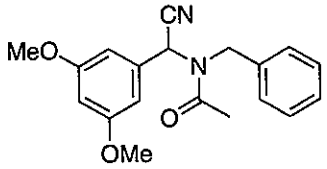
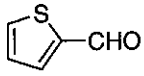
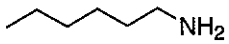
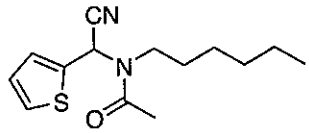
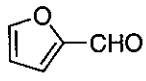
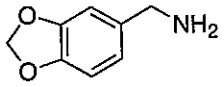
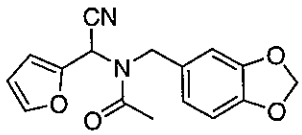
To our knowledge, only two reports of Strecker-type reactions with ketones appear in the literature.[17b,29] In one case $InCl_3$ was the catalyst for cyclohexanones[17b] and in the second, elevated pressure in the absence of a catalyst was employed for aliphatic and aromatic ketones.[29] Although the reaction of acetophenone with aniline and TMSCN in the presence of

20 mol% of **1b** at room temperature gave no detectable product after 25 hours, the reaction of cyclohexanone with benzylamine and TMSCN under the same conditions gave an 82% product yield after 15 hours (entry 19).

From Table 3 it is seen that, of the literature yields reported for three-component reactions (entries 1, 3, 8-10, 14 and 19), our protocol delivers a substantially higher yield in four of the seven cases, and yields that are near or at the upper end of the literature range in the other three cases. In the remaining entries in which literature yields were reported for perhaps less risky two-step syntheses (entries 2, 6, 8, 11, 13 and 15-18) our one-pot methodology produced higher yields in three of the nine cases, very comparable yields in two cases and lower yields in four instances.

TABLE 4. Room temperature preparation of α-amidonitriles using **1b** as a promoter and acetic anhydride as the acetylating reagent.[a]

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)[b]
1				25	82
2				25	84
3				25	85
4				30	86
5				35	60
6				25	70
7				35	73

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)[b]
8				35	50
9				25	74
10				25	76
11				30	65
12				25	80
13				25	75
14				30	72

[a]Conditions: aldehyde (1.0 mmol), amine (1.0 mmol), TMSCN (1.2 mmol), $(CH_3CO)_2O$ (2.0 mmol), **1b** (30 mol %) and CH_3CN (3 mL). [b]Isolated yields. None of the products in Table 2 have been described in the literature.

For the four-component one-pot synthesis of α-amidonitriles, we employed 20 mol% of **1b**, benzaldehyde (1.0 mmol), benzylamine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol) and acetic anhydride (1.0 mmol). After 20 h at room temperature, a 40% yield (based on benzaldehyde) of the coupling product was realized. Increasing the quantity of acetic anhydride to 1.5 mmol improved the product yield to only 60%. After further attempts to increase the yield by changing relative concentrations of the reactants, we found that a

mixture of 30 mol% of **1b**, benzaldehyde (1.0 mmol), benzylamine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol) and acetic anhydride (2.0 mmol) stirred at room temperature for 25 hours gave a good yield (82%) of product (entry 1 in Table 4). We also observed that after addition of the TMSCN, it was advantageous to quickly add the acetic anhydride in order to avoid decreased yields. Substituting acetyl chloride for acetic anhydride gave no detectable amount of product. Using 30 mol % of the commercially available catalysts $InCl_3$ or $Bi(NO_3)_3$ gave only acylated amine.

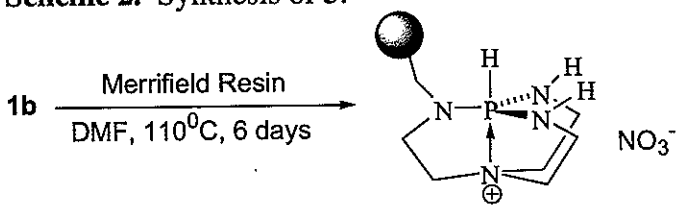
Stirring a mixture of benzaldehyde, **1b**, an amine, TMSCN and acetic anhydride as specified in Table 4, gave product yields ranging from 60-86% yields as shown in entries 1-5 of this table. Extending this chemistry to reactions of a variety of aryl aldehydes with different amines, 50-80% yields of the corresponding coupling products were realized (Table 4, entries 6-12). The relatively low yields obtained in the case of propargylamine may be due to side reactions associated with its reactivity with the aldehyde and/or with acetic anhydride. The heterocycles in entries 13 and 14 gave in each case reasonable product yields. Although none of the products in Table 4 were found in the literature, the yields for the fourteen products listed in this table are good (80-86%) in five instances, moderate (60-75%) in eight cases and modest in only one (50%).

A drawback of our four-component methodology is that no coupling product stemming from aniline as a reagent was detected. This result may be attributed to steric hindrance provided by the phenyl group. Thus our protocol is effective, however, with benzyl amine (entries 1, 9, 11 and 12 in Table 4).

2.3 Heterogeneously catalyzed Michael reactions

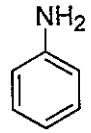
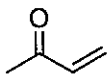
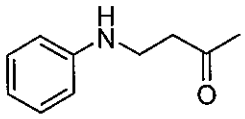
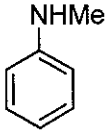
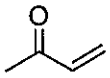
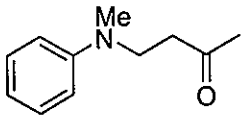
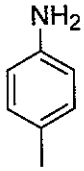
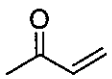
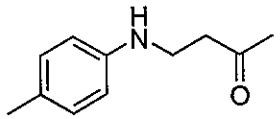
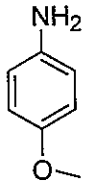
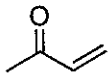
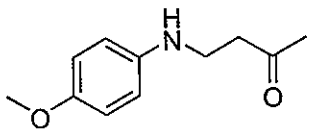
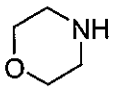
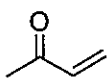
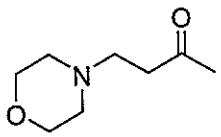
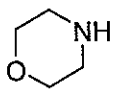
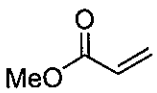
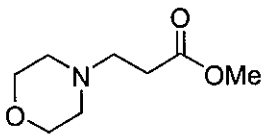
We reported the synthesis of the triflate salt of a polymer-bound azaphosphatrane several years ago[21] and we synthesized **3** by an analogous route (Scheme 2). Our conditions for the nitrate-catalyzed Michael additions are mild (Tables 5 and 6). It is seen in Table 5 that electron neutral (entries 1 and 2) and electron rich anilines (entries 3 and 4) react readily with methyl vinyl ketone, but higher temperatures are sometimes needed for sterically hindered or electron rich anilines(Table 5, entries 2-4). Aliphatic amines also react with various Michael acceptors (Table 5, entries 5-9) providing the desired products in very good to excellent yields. 1-Aminonaphthalene, on the other hand, required a reaction temperature of 60°C to afford a product yield (Table 5, entry 10) comparable to other products in this table. The same reaction at room temperature produced only a 30% yield. Benzylic amines (Table 5 entries 11 and 12) also react cleanly to give the desired products in excellent yields.

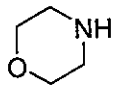
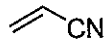
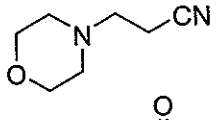
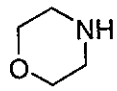
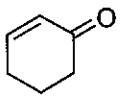
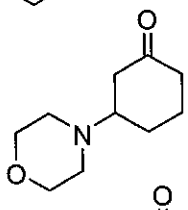
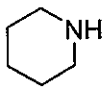
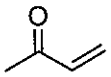
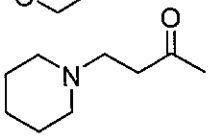
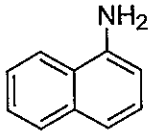
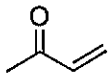
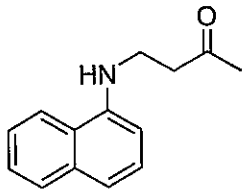
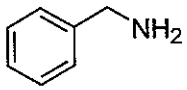
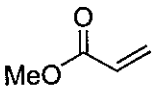
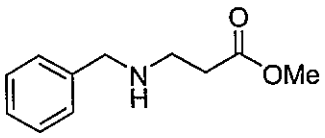
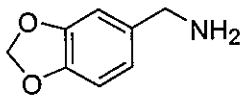
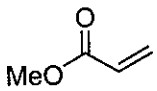
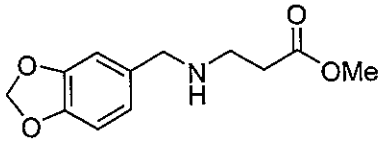
Scheme 2. Synthesis of **3**.



3

Table 5. Room temperature aza-Michael reaction in the presence of **3** as a promoter.

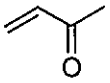
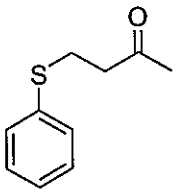
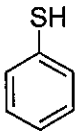
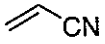
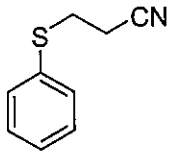
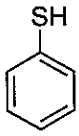
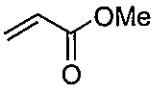
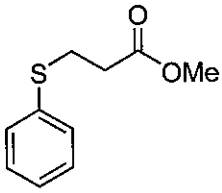
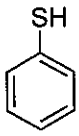
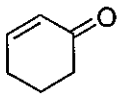
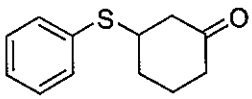
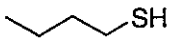
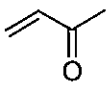
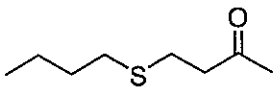
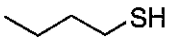
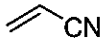
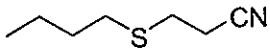
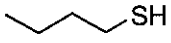
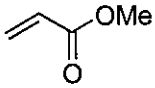
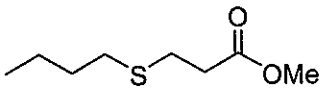
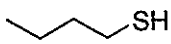
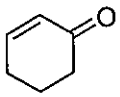
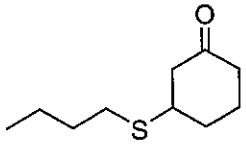
Entry[a]	Donor	Acceptor	Product	Yield (%)
1				80
2[b]				70
3[b]				92
4[b]				92
5				99
6				99

Entry[a]	Donor	Acceptor	Product	Yield (%)
7				82
8				89
9				99
10[b]				84
11				95
12				99

[a]Conditions: amine (1.5 mmol), acceptor (1.9 mmol), **3** (10 mol %) and CH_3CN (2 mL). Reactions were run for 24 h at room temperature. [b]Reaction temperature was 60°C.

Upon extending our protocol to thiols, excellent yields of products were found in all cases (Table 6). It should also be noted that no electrophilic substitution was observed when an aromatic thiol was employed as the Michael donor (Table 6, entries 1-4).

Table 6. Room temperature thia-Michael reactions promoted by **3**.

Entry[a]	Donor	Acceptor	Product	Yield (%)
1				99
2				99
3				99
4				99
5				99
6				99
7				99
8				99

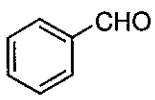
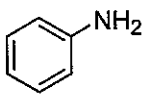
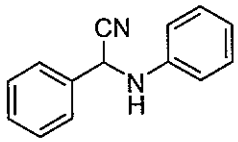
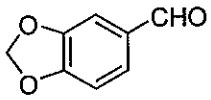
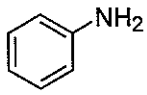
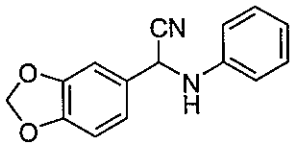
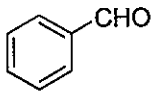
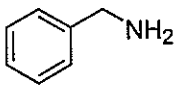
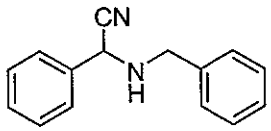
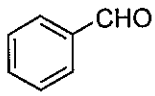
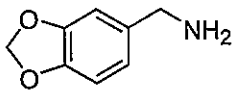
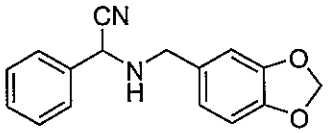
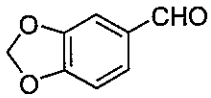
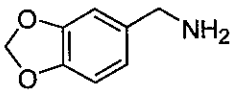
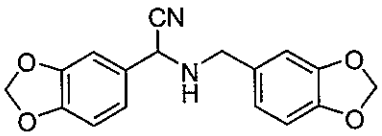
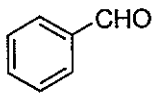
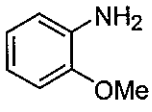
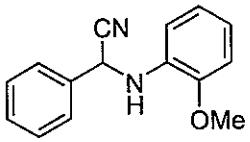
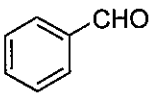
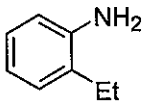
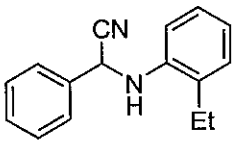
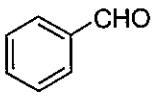
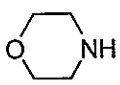
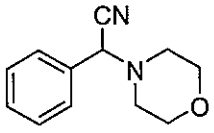
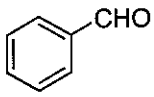
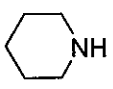
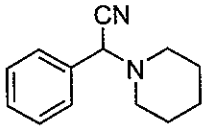
[a]Conditions: thiol (1.5 mmol), acceptor (1.9 mmol), **3** (10 mol %) and CH_3CN (2 mL). Reactions were run for 48 h at room temperature.

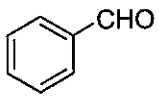
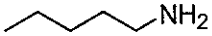
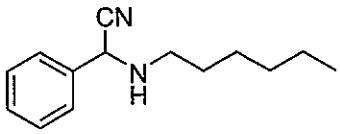
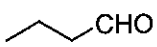
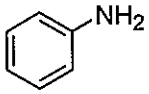
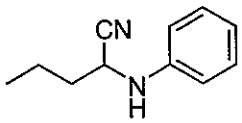
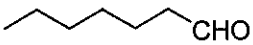
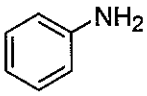
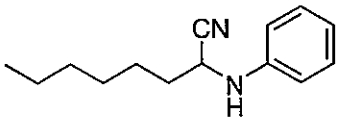
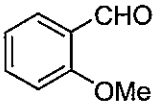
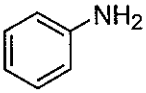
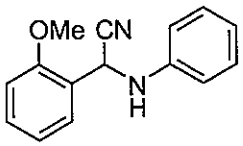
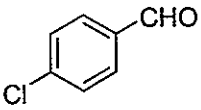
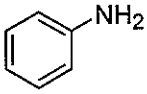
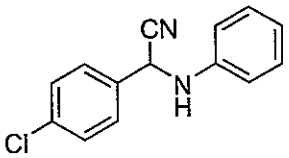
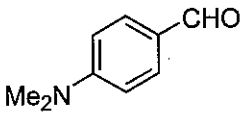
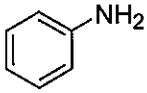
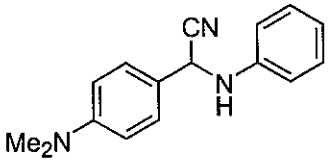
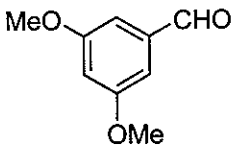
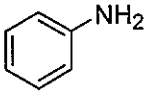
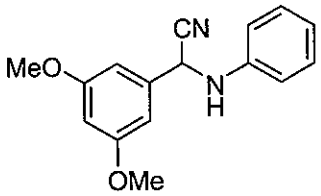
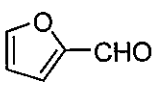
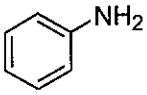
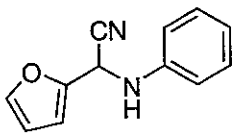
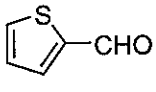
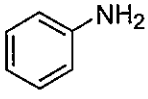
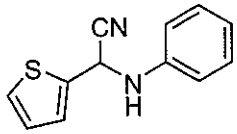
Workup is simplified in many cases because column chromatography can be avoided. In cases where there are no aromatic groups on the amine, the polymeric catalyst is filtered from the reaction mixture, and washed well to remove any remaining traces of products and starting materials. After removal of the volatile compounds and solvent on a vacuum line, the desired products are NMR pure.

2.4 Heterogeneously catalyzed Strecker reactions

Results of the Strecker-type reactions promoted by **3** are summarized in Table 7. The isolated yields are seen to be excellent in all cases, and both aromatic and aliphatic amines react well. The same cannot be said for aromatic and aliphatic aldehydes. While aromatic aldehydes were willing participants in the reaction, the reactions with aliphatic aldehydes proved sluggish (Table 7 entries 11 and 12). Moreover, the yields in these reactions, while impressive, are slightly lower than those achieved with the various benzaldehydes tested.

Table 7 Room temperature preparation of α-aminonitriles using **3** as a promoter.

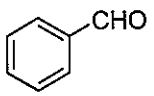
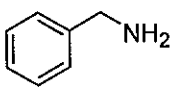
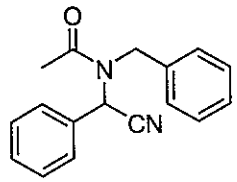
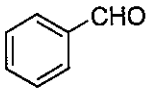
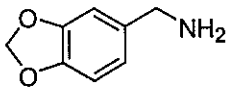
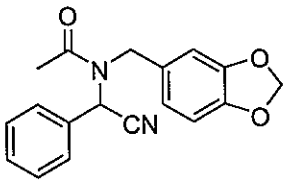
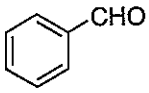
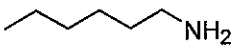
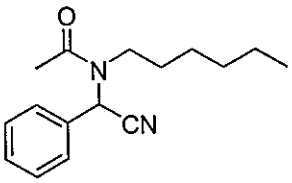
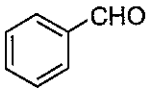
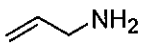
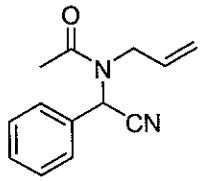
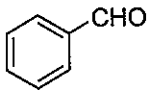
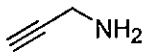
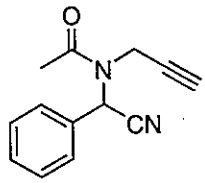
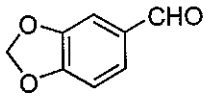
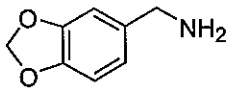
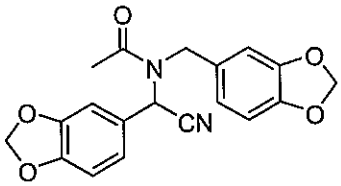
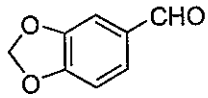
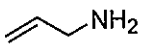
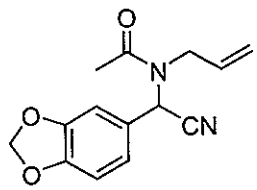
Entry	Aldehyde	Amine	Product	Time	Yield (%)
1				12	99
2				15	99
3				12	99
4				8	99
5				12	99
6				15	99
7				15	99
8				8	99
9				15	99

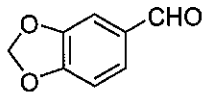
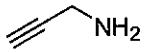
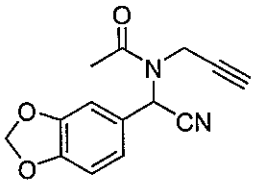
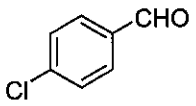
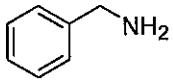
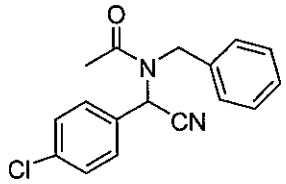
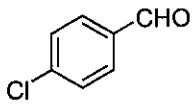
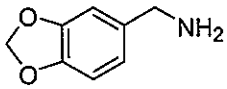
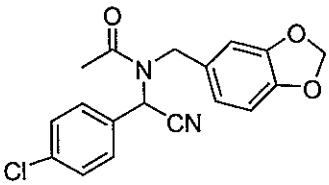
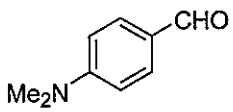
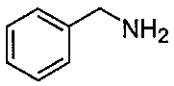
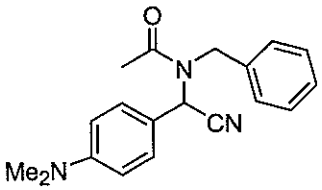
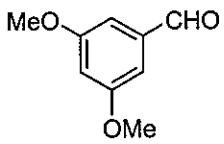
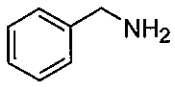
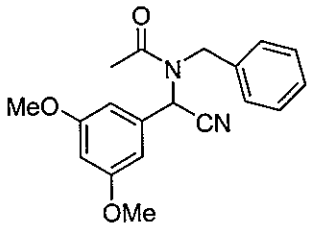
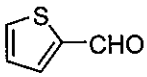
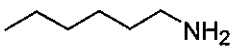
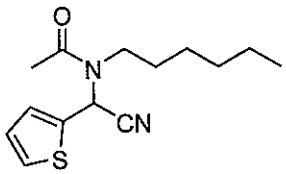
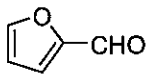
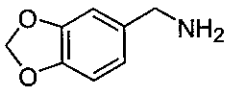
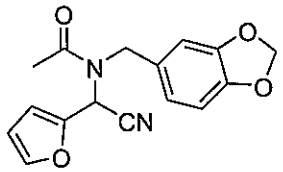
Entry	Aldehyde	Amine	Product	Time	Yield (%)
10				15	99
11				25	90
12				25	90
13				12	99
14				15	99
15				15	97
16				25	89
17				15	95
18				20	99

[a]Conditions: aldehyde or ketone (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), **3** (20 mol %) and CH_3CN (2 mL).

Because we observed excellent results for the synthesis of Reissert compounds homogenously promoted by **1b** (Table 4) we decided to extend that work with the utilization of the heterogeneous catalyst **3**, the results of which are contained in Table 8. Benzaldehyde participated well in this reaction, giving products with various amines in 80-90% yield (Table 8, entries 1-5). Other functionalized benzaldehdyes gave products in varying yields (Table 8, entries 6-12). It is not clear why low product yields were obtained in a few cases (Table 8, entries 8 and 12). Heterocycles gave the desired coupling products in modest to good yield (Table 8, entries 13-14).

Table 8 Room temperature preparation of α-amidonitriles using **3** as a promoter and acetic anhydride as the acetylating reagent.

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)
1				25	90
2				25	90
3				25	89
4				30	80
5				35	80
6				25	60
7				35	71

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)
8				35	29
9				25	90
10				25	90
11				30	80
12				25	29
13				25	47
14				30	80

[a]Conditions: aldehyde (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), $(CH_3CO)_2O$ (3.0 mmol), **3** (30 mol %) and CH_3CN (2 mL).

2.5 Catalyst reusability

The re-usability of polymer-bound nitrate salt **3** was evaluated in the Michael addition of aniline to methyl vinyl ketone as a model system. We found that when precautions were taken to avoid moisture, polymer **3** can be recycled up to twenty times without loss of activity. However, when water (1 equiv. based on the amine) was added, the amount of desired product isolated decreased sharply after four cycles. It is likely that hydroxide ion formed in the reaction of the amine with the water allows nitrate ion to be exchanged from the cationic polymer resin into the reaction solution. The catalytic activity of **3** is easily recovered, however, by washing the nitrate-depleted resin with aqueous sodium nitrate.

Furthermore, we found that resin bound azaphosphatrane nitrate catalyst **3** can be recycled twenty times with no loss of catalytic activity in the three component coupling of purified benzaldehyde, aniline, and trimethylsilylcyanide. However, when the benzaldehyde and aniline were taken from previously opened bottles exposed to air, the resin recycled only eleven times. The twelfth reaction required twice as much time to achieve a similar yield as the previous eleven uses of the catalyst. The thirteenth cycle failed to give any product after 24 hours. The catalyst can be reactivated, however, upon treatment with 3M aqueous sodium nitrate. The reactivated catalyst behaved identically to a freshly prepared sample.

When we tested the reusability of polymer-bound promoter **3** a second time in the four-component coupling reaction of benzaldehyde, benzylamine, TMSCN, and acetic anhydride the isolated product yield dropped from 90% to 73%. We conjectured that the water and acetate ion side products in the reaction displaced nitrate ion from **3**, thereby decreasing its effectiveness in the reaction. These problems were easily overcome by a simple washing of the polymer with aqueous sodium nitrate. The regenerated polymer then behaved identically to a fresh sample in the reaction.

2.6 Mechanistic considerations

Representative reactions chosen from Tables 1 and 2, when carried out under the same conditions in the absence of catalyst **1b**, either produced no detectable amount of product or gave substantially lower product yields. To compare the efficacy of **1b** with $Bi(NO_3)_3$, we also carried out the reaction in entry 1 of Table 1 with the latter salt, albeit with only 3.3 mol % in order to maintain 10 mol % of nitrate ion concentration in the reaction mixture. The product yield in that reaction (80%) was close to the 78% yield realized with **1b**. This result suggests (a) that the bismuth ion is not active as a catalyst whereas nitrate is, (b) that the bismuth ion is as active as naked nitrate (and that the nitrate is completely inactivated owing to anion-cation interactions), or (c) that the situation is somewhere between these two extremes (a more likely scenario in our view).

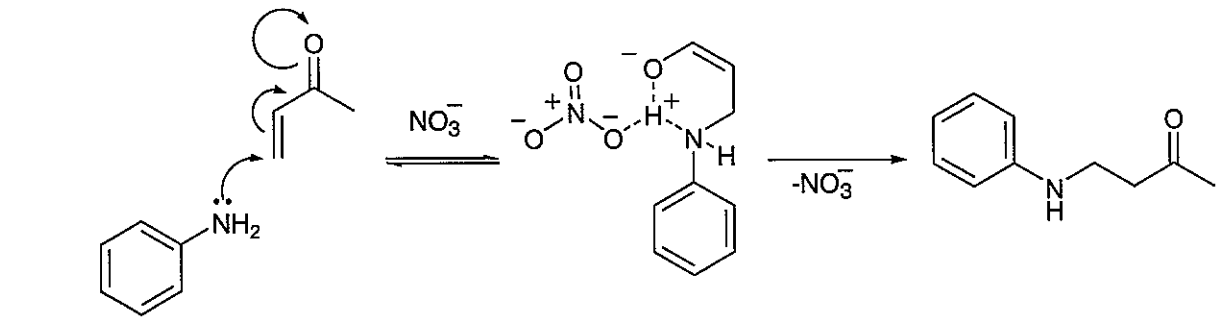
We have also performed a competition experiment between aniline and benzylamine which showed that the nucleophilicity of the amine plays an important role in this reaction. Here we observed that methyl acrylate reacted selectively with benzylamine to give the desired product in nearly quantitative yield while aniline was recovered unreacted.

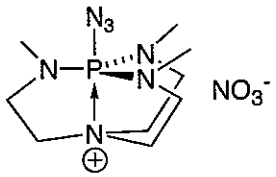
To investigate whether or not the P-H and N-H bonds in **1b** play a role in the reaction, we utilized nitrate salt **4**.[30] This salt behaved identically when used in place of **1b** in the Michael addition of aniline to methyl vinyl ketone. Since **4** contains no groups that might be deprotonated to produce nitric acid *in situ*, we can rule out dissociation of **1b** in solution to produce an active catalytic species.

The results taken *in toto* prompt us to propose the mechanism in Scheme 3. Initially, the amine adds to the electron deficient carbon atom of the Michael acceptor and nitrate ion

in this case acts as a "proton shuttle", utilizing hydrogen bonding to facilitate transfer of the proton from nitrogen to oxygen.

Scheme 3. Proposed mechanism of nitrate catalyzed aza- and thia-Michael reactions.





4

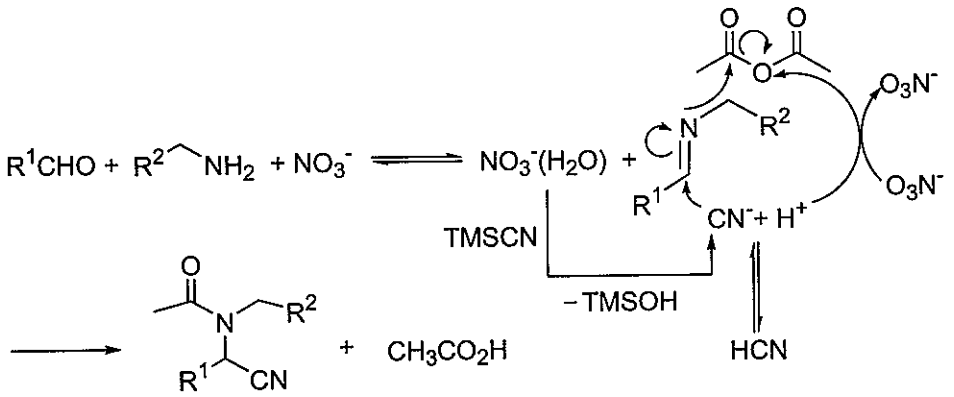
In order to gain some insight into the origin of the acceleration of the three-component reactions described here are accelerated by **1b**, a mixture of benzaldehyde (0.1 mmol) and aniline (0.1 mmol) in CD_3CN (0.7 mL) was monitored by ^1H NMR spectroscopy for a period of 12 hours at room temperature with and without 20 mol % of **1b** present. It was found that imine formation is fourteen times faster in the presence of **1b** than in its absence. The same monitoring experiment was carried out for the reaction of TMSCN (0.100 mmol, 13.3 microliters) with H_2O (0.100 mmol, 1.80 microliters) in CD_3CN (0.7 mL) in the absence and presence of **1b** (20 mol%). Here we observed that the peak position of TMSCN disappeared too quickly compared with product resonances, thus precluding a conclusion. However, when a solution of N-benzylidene aniline (1 mmol), TMSCN (1.2 mmol) and 20 mol % of **1b** in 3 mL of acetonitrile was stirred at room temperature for 12 h, a 94% yield of the expected product was obtained. When the same reaction was carried out in the absence

of a promoter, a 50% yield of the product was obtained. From these experiments it is clear that **1b** promoted both imine formation and cyanide addition.

Other nitrate ion sources (20 mol %) were also tested in a model reaction of benzaldehyde, aniline and TMSCN. Both sodium nitrate and 1,1,3,3-tetramethylguanidinium nitrate were ineffective, a result that can be attributed to the observed incomplete solution of these salts. When 15-crown-5 was added to the sodium nitrate, an 89% yield of the desired product was isolated, which supports the notion that effective inhibition of anion-cation interactions is important. The somewhat higher yield (94% in entry 1 of Table 3) indicates that this inhibition is somewhat stronger for **1b**. CAN proved to be completely ineffective, leading to a large number of spots on TLC. Tetrabutylammonium nitrate was only mildly efficacious, permitting isolation of a 49% yield of product.

On the basis of the foregoing observations, we suggest that the nitrate ion acts as a proton shuttle in these transformations (Scheme 4) and that the nitrate ion is rendered quite "naked" by delocalization of the positive charge among the four nitrogens and the phosphorus atom in the cation of **1b**. It may be noted that this cation is relatively modest in size compared with a $[Na(15\text{-crown-}5)]^+$ or a $[NBu_4]^+$ species, for example.

Scheme 4. Proposed mechanism of four-component coupling reactions catalyzed by **1b.**



3. Conclusion

We have developed a novel and efficient azaphosphatrane nitrate catalyst that operates at room temperature in nearly all cases, not only for aza- and thia-Michael reactions, but also for Strecker and the four-component coupling reactions involving Strecker transformations. When bound to a solid support, this catalyst shows excellent catalytic activity at room temperature in the aforementioned reactions, and it is also recyclable . Investigations are currently underway of the catalytic activity of other anions that behave as strong bases in non-aqueous solvents[31] and which are also rendered "naked" by cations of the phosphatrane type.

4. Experimental Section

4.1. General Considerations: All reactions were conducted under argon. All solvents were collected from a Grubbs-type two column solvent purification system and kept under 4 Å molecular sieves. NMR spectrometers employed were a Varian VXR-300 for ^{1}H and ^{13}C spectra and a Varian VXR-400 for ^{31}P spectra. Standards for the NMR spectra were TMS (^{1}H, internal), 85% H_3PO_4 (^{31}P, external). High resolution mass spectra were recorded on a KRATOS MS-50 spectrometer. Silica gel (J. T. Baker, 40-140 mesh) was used for column chromatography. All chemicals were purchased from Aldrich or Fisher.

4.2 Preparation of 1b: HMPT (10 mmol) was added to an ice-cold acetonitrile (25 mL) solution of *tris*(2-aminoethyl)amine (10 mmol) under argon and the mixture was stirred at room temperature for 30 min. A solution of HNO_3 [conc. HNO_3 (69%) 12 mmol] in acetonitrile (5 mL) was slowly added to the reaction mixture and the byproduct Me_2NH was allowed to escape while stirring at room temperature for 15 h. The solvent was distilled under

vacuum, and the residue was washed with ether and dried under vacuum to afford the solid product.

4.3. Preparation of 1e and 1g: To a stirred solution of $P(MeNCH_2CH_2)_3N$ or $P(i\text{-}BuNCH_2CH_2)_3N$ (1 mmol) in acetonitrile (5 mL) was added HNO_3 [conc. HNO_3 (69%) 1.5 mmol, 0.1 mL] drop wise very slowly. After stirring the solution at room temperature for 6 h, the solvent was removed under vacuum and the residue was washed with hexane and then ether. The residue was dried under vacuum to afford the solid product in 95% (**1e**) and 94% (**1g**) yields, respectively.

4.4. General procedure for aza and thia-Michael reactions promoted by 1b: To a stirred acetonitrile (3 mL) solution of **1b** (10 mol %) was added an amine or thiol (2 mmol) followed by stirring at room temperature under argon. An acceptor (2.5 mmol) was added to the reaction mixture followed by stirring at room temperature for 20-50 h (see Tables 1 and 2). The solvent was evaporated to dryness and the product was purified by chromatography over silica gel using 5% ether-in-hexane for Table 2, entries 1 and 3; 10% ether-in-hexane for Table 2, entries 2 and 4-8; 20% ether-in-hexane for Table 1, entries 1, 2, and 5 and; 50% ether-in-hexane for Table 1, entries 3 and 4; and ether for Table 1, entries 6-10, 12, and 13 as eluent. ^1H and/or ^{13}C NMR data are reported for known compounds in the literature references and our corresponding data compared well.

4.5. General procedure for the synthesis of α-aminonitriles promoted by 1b: A mixture of **1a** (20 mol %), aldehyde (1.0 mmol), amine (1.0 mmol) and trimethylsilyl cyanide (1.2 mmol) was stirred in acetonitrile (3 mL) under argon at room temperature for 8-25 h. The solvent was evaporated to dryness and the product was purified by silica gel column chromatography using 5% ether-in-hexane for Table 3 entries 1, 2, 6, 7, 9-12, 14, and 19;

10% ether-in-hexane for Table 2, entries 3, 4, 13, and 15-18; 20% ether-in-hexane for Table 2, entry 5; and 25% ether-in-hexane for Table 2, entry 8 as eluents. ^{1}H and/or ^{13}C NMR data are reported for known compounds in the literature references and our corresponding data compared well.

4.6. General procedure for the synthesis of α-amidonitriles promoted by 1b: A mixture of **1a** (30 mol %), aldehyde (1.0 mmol), amine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol) and acetic anhydride (2.0 mmol) in acetonitrile (3 mL) was stirred under argon at room temperature for 25-35 h. The reaction mixture was evaporated to dryness and the product was purified by column chromatography over silica gel using 50% ether-in-hexane for Table 2 entries 1-5, and 7-14 and ether for Table 3, entry 6 as eluent.

4.7. General procedure for Michael addition promoted by 3: The Michael donor (1.5 mmol) the acceptor (2.25 mmol) and acetonitrile (2 mL) were combined and then the mixture was added to **3** whose catalyst capacity was calculated from the phosphorus elemental analysis (1.98 mmol/g). The weight of **3** used was 106 mg (10 mol % based on the Michael donor). The reaction mixture was stirred and after the conditions in the Tables 5 and 6 had been met, the polymer was filtered off and washed with ~10 mL of acetonitrile. The solvent and volatiles were then removed from the acetonitrile solution under reduced pressure (~40 microns Hg). Products were then subjected to column chromatography on silica gel where necessary to give the pure compound.

For the reuse of **3**, the procedure in the previous paragraph was followed for an aniline/MVK/**3** mixture which was stirred for 24 hours at room temperature. Stirring was then stopped, the solution was allowed to settle and then the supernatant was decanted by

cannula and the polymer was washed with ~10 mL of acetonitrile. Another aniline/MVK mixture was then cannulated into the polymer catalyst and the procedure was repeated.

4.8. General procedure for the Strecker-type reaction promoted by 3: The catalyst (20 mol % based on the aldehyde and amine) was weighed into a 10 mL round bottomed flask. The aldehyde (1.5 mmol), amine (1.5 mmol), and TMSCN (1.8 mmol) were premixed in acetonitrile (2 mL) and cannulated into the flask containing the catalyst. The reaction was then stirred magnetically at room temperature until the conditions in Table 7 had been met. The catalyst was then filtered off and washed with ~10 mL of acetonitrile. The product was purified by a short path silica gel column using mixtures of 5-25% ether in hexane as the eluent. Exact solvent mixtures are given in Section 4.5.

For the reuse of **3**, the procedure for the experiment in the previous paragraph was followed. After the reaction time indicated in Table 7 for a benzaldehyde/aniline/TMSCN reaction mixture, stirring was stopped and the polymer was allowed to settle. The supernatant was then carefully cannulated off, and a new mixture of starting materials was cannulated in. The experiment was then repeated. The product was purified as described in the preceding paragraph.

4.9. General procedure for the four component coupling promoted by 3: The catalyst (30 mol % based on the aldehyde and amine) was weighed into a 10 mL round bottomed flask. The aldehyde (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), and acetic anhydride (3.0 mmol) were premixed in acetonitrile (2 mL) and cannulated into the flask with the catalyst. The reaction was then stirred magnetically at room temperature until the conditions in Table 8 had been met. The catalyst was then filtered off and washed with ~10 mL of acetonitrile.

The product was then purified by a short path silica gel column using solvent mixtures given in Section 4.6.

For the reuse of **3**, the procedure in the previous paragraph was followed. After the reaction time indicated in Table 7 for a benzaldehyde/aniline/TMSCN/acetic anhydride reaction mixture, stirring was stopped and the polymer was allowed to settle. The supernatant was then carefully cannulated off, and a new mixture of starting materials was cannulated in. The experiment was then repeated. The product was purified as described in the previous paragraph.

4.10. Reactivation of 3: Samples of used **3** from previous experiments (approximately 500 mg) were combined into a 100 mL flask followed by the addition of 30 mL of a 3M aqueous sodium nitrate solution. The suspension was stirred for 2 h at room temperature and filtered. The polymer was washed with water, 3M sodium nitrate, water, methanol, THF, and ether (~20 mL each). The polymer was then dried under reduced pressure at room temperature for 24 hours.

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SUPPLEMENTARY MATERIALS

1b: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.47-4.90 (d, J = 469.8 Hz, 1H), 3.75 (brs, 1H), 3.66 (brs, 1H), 3.04-3.01 (m, 12H), 2.66 (brs, 1H). ^{13}C NMR (CD_3CN, 75.5 MHz): δ 50.6, 38.5, 34.3. ^{31}P NMR (CD_3CN, 400 MHz): δ -45.1. HRMS (M^+): calcd. for $C_6H_{16}N_5O_3P$ 237.09908; found, 237.09970. The NMR spectra were very comparable to those reported earlier for the corresponding chloride salt.[11]

1d: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.11-4.46 (d, J = 494.6 Hz, 1H), 3.10-2.94 (m, 12H), 2.75-2.55 (m, 9H). ^{13}C NMR (CD_3CN, 75.5 MHz): δ 48.4, 48.3, 42.3, 42.2, 35.2, 34.9. ^{31}P NMR (CD_3CN, 400 MHz): δ -9.47.

1f: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.07-4.38 (d, J = 505.0 Hz, 1H), 3.13-3.00 (m, 12H), 2.73-2.65 (m, 6H), 1.85-1.76 (m, 3H), 0.82-0.85 (d, J = 6.7 Hz, 18H). ^{13}C NMR (CD_3CN, 75.5 MHz): δ 56.8, 56.6, 48.4, 48.3, 40.4, 40.3, 28.1, 28.1, 20.6. ^{31}P NMR (CD_3CN, 400 MHz): δ -5.89. The NMR spectra were very comparable to those reported earlier for the corresponding chloride salt.[11]

4-Phenylaminobutan-2-one (Table 1, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14-7.20 (m, 2H), 6.59-6.74 (m, 3H), 3.97 (brs, 1H), 3.41 (t, J = 6.1 Hz, 2H), 2.74 (t, J = 6.1 Hz, 2H), 2.1 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.1, 147.8, 129.4, 117.8, 113.2, 42.8, 38.5, 30.5.

4-Methyl-4-phenylaminobutan-2-one (Table 1, entry 2): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23-7.28 (m, 2H), 6.71-6.76 (m, 3H), 3.65 (t, J = 7.0 Hz, 2H), 2.94 (s, 3H), 2.71 (t, J = 7.0 Hz, 2H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.1, 148.8, 129.4, 116.8, 112.6, 47.4, 40.4, 38.6, 30.7.

4-(4′-Methylphenylamino)butan-2-one (Table 1, entry 3): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04-7.01 (d, J = 8.0 Hz, 2H), 6.58-6.55 (d, J = 8.0 Hz, 2H) , 3.82 (brs, 1H), 3.41 (t, J = 6.1 Hz, 2H), 2.74 (t, J = 6.1 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.2, 145.5, 129.9, 126.9, 113.3, 42.7, 38.8, 30.3, 20.5.

4-(4′-Methoxyphenylamino)butan-2-one (Table 1, entry 4): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.79-6.76 (d, J = 8.9 Hz, 2H), 6.59-6.56 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H), 3.69 (brs, 1H), 3.34 (t, J = 6.1 Hz, 2H), 2.70 (t, J = 6.1 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.3, 152.4, 142.0, 114.9, 114.6, 55.8, 42.7, 39.6, 30.3.

4-(3′-Nitrophenylamino)butan-2-one (Table 1, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23-7.52 (m, 3H), 6.83-6.87 (m, 1H), 4.44 (s, 1H), 3.45 (t, J = 6.1 Hz, 2H), 2.78 (t, J = 6.1 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.3, 149.2, 130.4, 119.7, 112.7, 106.7, 42.7, 38.7, 30.9. HRMS (M^+): calcd. for $C_{10}H_{12}N_2O_3$ 208.08479; found, 208.08510.

4-Morpholinobutan-2-one (Table 1, entry 6): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (t, J = 4.6 Hz, 4H), 2.58 (t, J = 4.6 Hz, 4H), 2.38 (t, J = 4.6 Hz, 4H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.2, 67.4, 54.1, 53.7, 41.6, 30.7.

Methyl-3-morpholinopropionate (Table 1, entry 7): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.65-3.68 (d, J = 6.5 Hz, 7H), 2.65 (t, J = 7.0 Hz, 2H), 2.41-2.50 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.4, 67.5, 54.6, 54.0, 52.3, 32.5.

3-Morpholinopropionitrile (Table 1, entry 8): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.71 (t, J = 4.6 Hz, 4H), 2.68 (t, J = 7.0 Hz, 2H), 2.48-2.53 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 118.2, 66.1, 53.0, 52.5, 15.1.

3-Morpholinocyclohexanone (Table 1, entry 9): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (t, J = 4.6 Hz, 4H), 1.92-2.64 (m, 11H), 1.49-1.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 210.5, 67.3, 63.5, 49.6, 44.4, 41.3, 27.9, 22.3.

4-Piperidinobutan-2-one (Table 1, entry 10): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54-2.55 (d, J = 2.5 Hz, 4H), 2.30 (s, 4H), 2.10 (s, 3H), 1.33-1.53 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.2, 54.6, 53.5, 41.6, 30.3, 26.1, 24.4.

4-Naphthylaminobutan-2-one (Table 1, entry 11): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78-7.81 (m, 2H), 7.25-7.47 (m, 4H), 6.61-6.64 (m, 1H), 3.78 (brs, 1H), 3.58 (t, J = 6.1 Hz, 2H), 2.85 (t, J = 6.1 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.5, 143.2, 134.5, 128.7, 126.6, 125.9, 124.9, 123.9, 120.2, 117.8, 104.5, 42.5, 38.7, 30.5. HRMS (M^+): calcd. for $C_{14}H_{15}NO$ 213.11536; found, 213.11570.

Methyl-3-benzylaminopropionate (Table 1, entry 12): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17-7.27 (m, 5H), 3.74 (s, 2H), 3.62 (s, 3H), 2.84 (t, J = 6.5 Hz, 2H), 2.48 (t, J = 6.5 Hz, 2H), 1.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.4, 140.3, 128.5, 128.2, 127.1, 53.9, 51.7, 44.6, 34.7.

Methyl-3-piperonylaminopropionate (Table 1, entry 13): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.72-6.80 (m, 3H), 5.90 (s, 2H), 3.67 (s, 2H), 3.65 (s, 3H), 2.84 (t, J = 6.5 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 1.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.4, 147.8, 146.6, 134.2, 121.3, 108.7, 108.2, 100.9, 53.6, 51.8, 44.4, 34.7.

4-Thiophenylbutan-2-one (Table 2, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12-7.28 (m, 5H), 3.06 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 206.7, 135.8, 129.6, 129.1, 126.4, 43.2, 30.2, 27.6.

3-Thiophenylpropionitrile (Table 2, entry 2): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.41 (m, 5H), 3.08 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 133.2, 131.2, 129.3, 127.6, 118.0, 30.1, 18.2.

Methyl-3-thiophenylpropinate (Table 2, entry 3): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17-7.34 (m, 5H), 3.63 (s, 3H), 3.13 (t, J = 7.2 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.1, 135.2, 130.0, 129.0, 126.6, 51.8, 34.2, 29.0.

3-Thiophenylcyclohexanone (Table 2, entry 4): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23-7.40 (m, 5H), 3.34-3.42 (m, 1H), 2.62-2.68 (m, 1H), 2.07-2.38 (m, 5H), 1.63-1.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.4, 132.9, 132.8, 128.8, 127.5, 45.6, 45.5, 40.6, 30.9, 23.8.

4-Thiobutylbutan-2-one (Table 2, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.66 (s, 4H), 2.45 (t, J = 7.4 Hz, 2H), 2.11 (s, 3H), 1.30-1.53 (m, 4H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 207.0, 43.8, 32.1, 31.7, 30.1, 25.8, 22.0, 13.7.

3-Thiobutylpropionitrile (Table 2, entry 6): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54-2.78 (m, 6H), 1.34-1.57 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 118.5, 32.0, 31.6, 27.7, 21.9, 19.0, 13.7.

Methyl-3-thiobutylpropionate (Table 2, entry 7): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.63 (s, 3H), 2.71 (t, J = 7.4 Hz, 2H), 2.54 (t, J = 7.4 Hz, 2H), 2.46 (t, J = 7.4 Hz, 2H), 1.30-1.52 (m, 4H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 51.8, 34.8, 31.8, 31.6, 26.9, 22.0, 13.7.

3-Thiobutylcyclohexanone (Table 2, entry 8): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.97-3.03 (m, 1H), 2.63-2.68 (m, 1H), 2.50 (t, J = 7.4 Hz, 2H), 2.06-2.36 (m, 5H), 1.31-1.72 (m, 6H),

0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.1, 48.4, 42.9, 41.1, 31.9, 31.8, 30.3, 24.4, 22.2, 13.8.

Anilinophenylacetonitrile (Table 3, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63-7.26 (m, 7H), 6.94-6.78 (m, 3H), 5.45-5.42 (d, J = 7.8Hz, 1H), 4.08-4.05 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.9, 134.1, 129.8, 129.7, 129.5, 127.4, 120.4, 118.7, 114.3, 50.4.

α-(Phenylamino)-1,3-benzodioxole-5-acetonitrile (Table 3, entry 2): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.24 (m, 2H), 7.09-6.74 (m, 6H), 6.00 (s, 1H), 5.32-5.29 (d, J = 7.8 Hz, 1H), 4.07-4.04 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 148.3, 148.2, 144.3, 129.3, 127.4, 120.7, 199.9, 188.0, 113.9, 108.4, 107.4, 101.4, 49.6.

N-Benzyl-2-phenylglycinonitrile (Table 3, entry 3): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59-7.31 (m, 10H), 4.77 (s, 1H), 4.11-3.95 (dd, J = 32.4, 13.1 Hz, 2H), 1.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 138.2, 134.9, 129.1, 129.0, 128.7, 128.5, 127.7, 127.4, 118.9, 53.5, 51.3.

2-Phenyl-2-(N-piperonylamino)acetonitrile (Table 3, entry 4): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.40 (m, 5H), 6.92-6.77 (m, 3H), 5.94 (s, 2H), 4.74 (s, 1H), 3.99-3.84 (dd, J = 33.4, 12.9 Hz, 2H), 1.88 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 147.6, 146.7, 134.4, 131.6, 128.7, 128.6, 126.9, 121.4, 118.4, 108.4, 107.9, 100.7, 52.9, 50.7. HRMS (M^+): calcd. for $C_{16}H_{14}N_2O_2$ 266.10553; found, 266.10600.

α-[(1,3-Benzodioxol-5-ylmethyl)amino]-1,3-Benzodioxole-5-acetonitrile (Table 3, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01-6.75 (m, 6H), 5.97 (s, 2H), 5.94 (s, 2H), 4.63 (s, 1H), 3.95-3.80 (dd, J = 33.4, 12.9 Hz, 2H), 1.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ

148.3, 148.2, 148.0, 147.2, 132.0, 128.7, 121.8, 120.9, 118.9, 108.7, 108.5, 108.3, 107.9, 101.6, 100.2, 52.9, 51.0. HRMS (M^+): calcd. for $C_{17}H_{14}N_2O_4$ 310.09536; found, 310.09610.

α-[(2-Methoxyphenyl)amino]-benzeneacetonitrile (Table 3, entry 6): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.66-7.47 (m, 5H), 6.98-6.84 (m, 4H), 5.49-5.46 (d, J = 7.8 Hz, 1H), 4.73-4.71 (d, J = 7.8 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 147.6, 134.7, 134.3, 129.6, 129.4, 127.4, 121.4, 119.7, 118.4, 111.8, 110.2, 55.6, 50.0.

2-[N-(2-Ethylanilino)]-2-phenylacetonitrile (Table 3, entry 7): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68-7.50 (m, 5H), 7.28-7.20 (m, 2H), 6.97-6.90 (m, 2H), 5.52-5.50 (d, J = 6.1 Hz, 1H), 4.04-4.02 (d, J = 6.1 Hz, 1H), 2.56-2.50 (q, J = 5.6 Hz, 2H), 1.28 (t, J = 5.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 142.3, 134.3, 129.7, 129.5, 128.6, 127.4, 127.3, 120.3, 118.5, 112.0, 50.3, 23.9, 13.2. HRMS (M^+): calcd. for $C_{16}H_{16}N_2$ 236.13135; found, 236.13180.

α-Phenyl-4-morpholineacetonitrile (Table 3, entry 8): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55-7.35 (m, 5H), 4.82 (s, 1H), 3.76-3.65 (m, 4H), 2.59-2.56 (t, J = 4.5 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.6, 129.1, 128.9, 128.1, 115.3, 66.7, 62.5, 50.0.

Phenylpiperidinoacetonitrile (Table 3, entry 9): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.33 (m 5H), 4.83 (s, 1H), 2.52 (m, 4H), 1.66-1.47 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 133.7, 128.8, 128.7, 127.9, 115.7, 63.1, 51.0, 25.9, 24.1.

α-(Hexylamino)-benzeneacetonitrile (Table 3, entry 10): ^1H NMR ($CDCl_3$, 300MHz): δ 7.55-7.37 (m, 5H), 4.79 (s, 1H), 2.87-2.69 (m, 3H), 1.56-1.30 (m, 9H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 135.2, 128.9, 128.8, 127.4, 119.1, 54.7, 47.5, 31.7, 29.7, 26.9, 22.7, 14.1.

2-Anilinovaleronitrile (Table 3, entry 11): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.24 (m, 2H), 6.90-6.71 (m, 3H), 4.26-4.18 (m, 1H), 3.76-3.73 (d, J = Hz, 1H), 1.98-1.90 (m, 2H), 1.69-1.44 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.1, 129.7, 120.2, 119.8, 114.2, 45.8, 35.7, 19.2, 13.6.

2-(N-Anilino)-2-octanitrile (Tabe 3, entry 12): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.24 (m, 2H), 6.90-6.71 (m, 3H), 4.25-4.17 (dd, J = 15.8, 7.2 Hz, 1H), 3.76-3.73 (d, J = 8.9 Hz, 1H), 1.99-1.91 (m, 2H), 1.63-1.58 (m, 2H), 1.42-1.30 (m, 6H), 0.91 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.1, 129.7, 120.2, 119.8. 114.2, 46.1, 33.7, 31.7, 28.8, 25.8, 22.7, 14.2. HRMS (M^+): calcd. for $C_{14}H_{20}N_2$ 216.16265; found, 216.16310.

2-Methoxy-α-(phenylamino)-benzeneacetonitrile (Table 3, entry 13): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50-7.24 (m, 4H), 7.04-6.78 (m, 5H), 5.58 (s, 1H), 4.32 (s, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 156.9, 145.2, 131.1, 129.6, 128.9, 122.5, 121.3, 120.1, 118.8, 114.4, 111.5, 55.9, 45.9.

Anilino(4-chlorophenyl)acetontrile (Table 3, entry 14): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55-7.41 (m, 4H), 7.29-7.24 (m, 2H), 6.93-6.88 (m, 1H), 6.77-6.74 (m, 2H), 5.41 (s, 1H), 4.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.6, 135.8, 132.6, 129.8, 129.7, 128.8, 120.8, 118.0, 114.5, 49.9.

4-(Dimethylamino)-α-(phenylamino)-benzeneacetonitrile (Table 3, entry 15): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.24 (m, 4H), 6.90-6.72 (m, 5H), 5.29-5.26 (d, J = 7.8 Hz, 1H), 3.97-3.95 (d, J = 7.8 Hz, 1H), 2.95 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.2, 145.1, 129.6, 128.4, 121.1, 119.9, 118.9, 114.1, 112.6, 49.8, 40.5.

2-(N-Anilino)-2-(3,5-dimethoxyphenyl)acetonitrile (Tabe 3, entry 16): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.24 (m, 2H), 6.92-6.69 (m, 5H), 6.49-6.48 (m, 1H), 5.35-5.32 (d, J = 8.0 Hz, 1H), 4.13-4.10 (d, J = 8.0 Hz, 1H), 3.79 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.6, 144.8, 136.2, 129.7, 120.4, 118.3, 114.3, 105.4, 101.4, 55.7, 50.4. HRMS (M^+): calcd. for $C_{16}H_{16}N_2O_2$ 269.12900; found, 269.12960.

α-Anilino-2-furanacetonitrile (Table 3, entry 17): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (s, 1H), 7.46-7.24 (m, 2H), 6.93-6.76 (m, 3H), 6.58-6.57 (d, J = 3.3 Hz, 1H), 6.42-6.41 (q, J = 1.8 Hz, 1H), 5.47 (s, 1H), 4.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 146.2, 144.2, 144.1, 129.8, 120.9, 116.7, 114.7, 111.1, 109.8, 44.5.

α-(Phenylamino)-2-thiopheneacetonitrile (Table 3, entry 18): ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.39-7.27 (m, 4H), 7.06-6.92 (m, 2H), 6.81-6.78 (m, 2H), 5.63 (s, 1H), 4.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 144.2, 136.9, 129.7, 127.4, 127.3, 127.2, 120.8, 117.7, 114.7, 46.2.

2-(*N*-Acyl, *N*-benzylamino)-2-phenylacetonitrile (Table 4, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41-7.29 (m, 8H), 7.09-7.04 (m, 3H), 4.59-4.42 (m, 2H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$,

75.5 MHz): δ 171.7, 135.7, 132.3, 129.5, 129.2, 128.8, 127.8, 126.3, 116.5, 49.7, 48.7, 22.1. HRMS (M^+): calcd. for $C_{17}H_{16}N_2O$ 264.12626; found, 264.12660.

2-(*N*-Acyl, *N*-piperonylamino)-2-phenylacetonitrile (Table 4, entry 2): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.34 (m, 5H), 7.04 (s, 1H), 6.68-6.46 (m, 3H), 5.87 (s, 2H), 4.48-4.30 (m, 2H), 2.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.5, 148.1, 147.2, 132.3, 129.4, 129.2,

127.7, 119.8, 116.5, 108.4, 106.9, 101.2, 49.4, 48.4, 22.0. HRMS (M^+): calcd. for $C_{18}H_{16}N_2O_3$ 308.11609; found, 308.11660.

2-(*N*-Acyl, *N*-hexylamino)-2-phenylacetonitrile (Table 4, entry 3): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43-7.37 (m, 5H), 7.00 (s, 1H), 3.28-3.07 (m, 2H), 2.19 (s, 3H), 1.66-1.56 (m, 1H), 1.56-1.15 (m, 7H), 0.83-0.79 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.8, 132.7, 129.4, 129.2, 127.5, 117.1, 47.8, 46.5, 31.1, 29.2, 26.6, 22.5, 21.3, 13.9. HRMS (M^+): calcd. for $C_{16}H_{22}N_2O$ 258.17321; found, 258.17350.

2-(*N*-Acyl, *N*-allylamino)-2-phenylacetonitrile (Table 4, entry 4): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44-7.37 (m, 5H), 7.03 (s, 1H), 5.64-5.51 (m, 1H), 5.14-5.06 (m, 2H), 3.94-3.77 (m, 2H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.3, 132.4, 129.5, 129.3, 127.6, 118.2, 116.7, 48.5, 48.0, 21.6. HRMS (M^+): calcd. for $C_{13}H_{14}N_2O$ 214.11061; found, 214.11110.

2-(*N*-Acyl, *N*-propargylamino)-2-phenylacetonitrile (Table 4, entry 5): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.40 (m, 5H), 6.97 (s, 1H), 4.03-3.85 (m, 2H), 2.31 (s, 3H), 2.23 (t, J = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.94, 131.5, 129.7, 129.3, 127.8, 116.1, 76.8, 73.8, 48.0, 35.2, 21.8. HRMS (M^+): calcd. for $C_{13}H_{12}N_2O$ 212.09496; found, 212.09530.

2-(*N*-Acyl, *N*-piperonylamino)-2-piperonylacetonitrile (Table 4, entry 6): ^1H NMR ($CDCl_3$, 300 MHz): δ 6.97-6.69 (m, 5H), 6.55-6.50 (m, 2H), 5.97 (s, 2H), 5.92 (s, 2H), 4.48-4.34 (m, 2H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.6, 148.7, 148.6, 148.3, 147.3, 129.6, 126.1, 121.8, 119.9, 116.6, 113.9, 108.6, 108.5, 108.2, 106.9, 101.8, 101.4, 49.4, 48.2, 22.2. HRMS (M^+): calcd. for $C_{19}H_{16}N_2O_5$ 352.10592; found, 352.10660.

2-(*N*-Acyl, *N*-allylamino)-2-piperonylacetonitrile (Table 4, entry 7): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.00-6.80 (m, 4H), 6.00 (s, 2H), 5.57-5.56 (m, 1H), 5.19-5.09 (m, 2H), 3.95-

3.80 (m, 2H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.3, 148.8, 148.7, 132.5, 126.2, 121.7, 118.3, 116.9, 108.7, 108.1, 101.9, 48.4, 47.8, 21.8. HRMS (M^+): calcd. for $C_{14}H_{14}N_2O_3$ 258.10044; found, 258.10110.

2-(*N*-Acyl, *N*-propargylamino)-2-piperonylacetonitrile (Table 4, entry 8): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04-6.82 (m, 4H), 6.01 (s, 2H), 4.03-3.88 (m, 2H), 2.31 (s, 3H), 2.26 (t, J = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.9, 148.9, 148.7, 125.2, 121.9, 116.2, 108.7, 108.2, 101.9, 76.8, 73.8, 47.8, 35.0, 21.9. HRMS (M^+): calcd. for $C_{14}H_{12}N_2O_3$ 256.08479; found, 256.08510.

2-(*N*-Acyl, *N*-benzylamino)-2-(4-chlorophenyl)acetonitrile (Table 4, entry 9): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.29 (m, 7H), 7.06-7.04 (m, 3H), 4.60-4.46 (m, 2H), 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.7, 135.7, 135.4, 131.1, 129.5, 129.3, 129.1, 128.1, 126.5, 49.9, 48.3, 22.1. HRMS (M^+): calcd. for $C_{17}H_{15}ClN_2O$ 298.08729; found, 298.08780.

2-(*N*-Acyl, *N*-piperonylamino)-2-(4-chlorophenyl)acetonitrile (Table 4, entry 10): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.27 (m, 4H), 7.00 (s, 1H), 6.70-6.67 (m, 1H), 6.54-6.46 (m, 2H), 5.92 (s, 2H), 4.49-4.35 (m, 2H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.5, 148.3, 147.4, 135.5, 131.1, 129.3, 129.1, 120.1, 116.1, 108.5, 107.1, 101.4, 49.8, 47.9, 22.1. HRMS (M^+): calcd. for $C_{18}H_{15}ClN_2O_3$ 342.07712; found, 342.07800.

2-(*N*-Acyl, *N*-benzylamino)-2-(4-*N*,*N*-dimethylaminophenyl)acetonitrile (Table 4, entry 11): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.01 (m, 8H), 6.68-6.65 (d, J = 8.7 Hz, 2H), 4.55-4.40 (m, 2H), 2.97 (s, 6H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.7, 151.1, 136.3, 129.1, 128.9, 127.7, 126.4, 119.1, 117.3, 112.4, 49.2, 48.3, 40.5, 22.3. HRMS (M^+): calcd. for $C_{19}H_{21}N_3O$ 307.16846; found, 307.16920.

2-(*N*-Acyl, *N*-benzylamino)-2-(3,5-dimethoxyphenyl)acetonitrile (Table 4, entry 12): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.01 (m, 6H), 6.54-6.41 (m, 3H), 4.95-4.41 (m, 2H), 3.74 (s, 6H), 2.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.8, 161.4, 135.8, 134.4, 128.9, 127.9, 126.4, 116.5, 105.9, 101.3, 55.6, 49.8, 48.8, 22.1. HRMS (M^+): calcd. for $C_{19}H_{20}N_2O_3$ 324.14739; found, 324.14820.

2-(*N*-Acyl, *N*-hexylamino)-2-thiophenoacetonitrile (Table 4, entry 13): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.02 (m, 2H), 6.99-6.96 (m, 2H), 3.34-3.17 (m, 2H), 2.16 (s, 3H), 1.71-1.61 (m, 1H), 1.33-1.19 (m, 7H), 0.85-0.80 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.6, 135.6, 128.4, 127.9, 127.0, 116.7, 46.6, 43.9, 31.3, 29.4, 26.7, 22.6, 21.4, 14.1. HRMS (M^+): calcd. for $C_{14}H_{20}N_2OS$ 264.12964; found, 264.13010.

2-(*N*-Acyl, *N*-piperonylamino)-2-furfurylacetonitrile (Table 4, entry 14): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (m, 1H), 6.98 (s, 1H), 6.70-6.47 (m, 4H), 6.33-6.31 (m, 1H), 5.91 (s, 2H), 4.59-4.44 (m, 2H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.4, 148.3, 147.2, 145.0, 144.2, 129.6, 119.5, 115.2, 111.7, 111.1, 108.5, 106.6, 101.3, 49.6, 42.8, 21.9. HRMS (M^+): calcd. for $C_{16}H_{14}N_2O_4$ 298.09536; found, 298.09610.

CHAPTER 3. POLYMER-SUPPORTED CATALYST FOR OXA-MICHAEL REACTIONS

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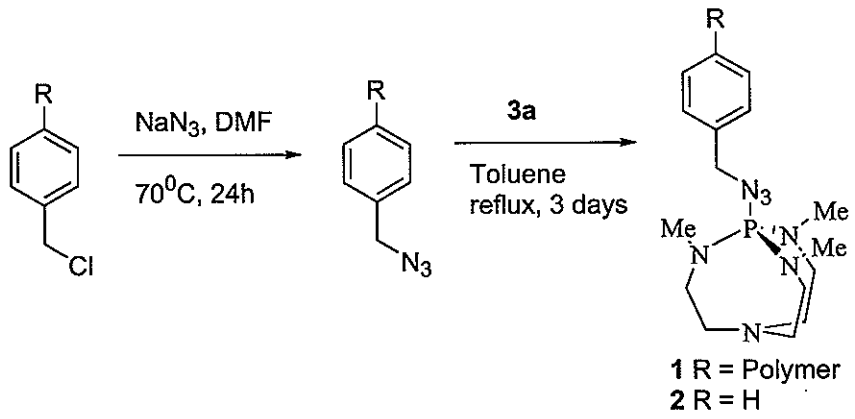
Abstract: Oxa-Michael additions to various acceptors were efficiently catalyzed at room temperature by a re-usable and easily regenerated polymer-supported catalyst bearing the $C_6H_5CH_2N_3P(MeNCH_2CH_2)_3N$ moiety. Even traditionally sensitive functionalities, such as esters and acid chlorides, were easily tolerated.

The Michael reaction is a highly utilized tool in organic chemistry, and also in medicinal and biochemistry.[1] A wide variety of donor reagents have been used for this reaction, including those containing sulfur,[2] nitrogen,[2a,3] oxygen,[4] and carbon.[5] Oxa-Michael addition is useful to the synthetic chemist in peptide synthesis,[4f] heterocycle formation[4e,k,l] and in the synthesis of β-alkoxy carbonyl compounds.[4i] Strong bases such as *t*-BuOK,[4e,k,l] NaOH,[4g] and NaH[4h,j,m,p] are commonly employed in this transformation. The addition of alcohols to epoxides,[6] α, β-unsaturated ketones[6e] and α, β-unsaturated nitriles[4b] has been realized with palladium, ruthenium, and vanadium catalysts. A novel bifunctional (Ni^{+2}/Cs^{+1}) catalyst affords enantioselective Michael addition products of carbon nucleophiles in respectable yields and good selectivity.[7] Proazaphosphatrane catalysts for oxa-Michael reactions are also known,[8] but transesterification competes when α, β-unsaturated esters are employed.[9] Three examples of polymer-supported catalysts are also known for the oxa-Michael reaction, that employ either Nafion, or a polyoxime complex of cobalt or copper in the Michael addition of methanol to acrolein.[10]

In an earlier publication from our laboratories, polymer supported azidoproazaphosphatrane **1** shown in Scheme 1 was reported to catalyze the acylation of alcohols with vinyl acetate in good yield.[11] However, the structure of the catalyst was incorrectly reported to be the corresponding iminophosphorane arising from dinitrogen loss from **1**. Herein we provide conclusive evidence for the correct structure of catalyst **1** and its use as an effective catalyst in the oxa-Michael reaction.

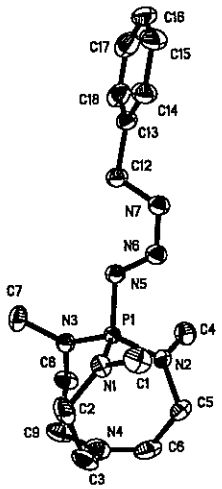
Scheme 1. Synthesis of **1** and **2**



In our initial description of the synthesis of polymer-supported catalyst **1**, our group reported that the structure of the phosphorus cage moiety was that of an imino- rather than an azidophosphorane. However, the ^{31}P NMR chemical shift of the polymer-bound compound did not match well with another example of a proazaphosphatrane imine found in the literature (11.8 ppm).[12] This prompted us to synthesize **2**,[11] as a small-molecule model compound of the polymer-supported analogue. A crystal and molecular structure of **2** clearly shows the presence of the azido group (Fig. 1). Because the ^{31}P NMR chemical shift of **2** (δ 37.9[11]) and the polymer-bound analogous structure (δ 36.35) are nearly identical, we conclude that the structure of **1** also contains the azido group. It should also be noted that the P:N ratio from elemental analysis is 1:7.02, further supporting the presence of the

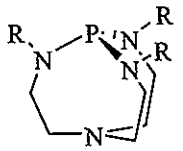
azidophosphine moiety. The P-N_3 bond distance of 1.6199(12) Å in **2** is similar to that in other azidophosphines reported.[13] The N-N-N bond angle of 116.65(12)°, on the other hand differed significantly from the angle we reported earlier for the structure of 1,3,5-cis-$[N(CH_2CH_2NMe)_3PN_3]_3C_6H_9$ [112.58(12)°].[13]

Figure 2. Crystal and molecular structure of **2**



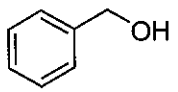
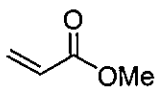
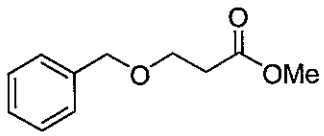
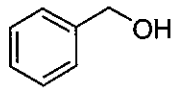
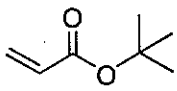
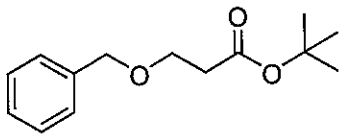
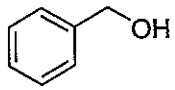
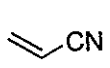
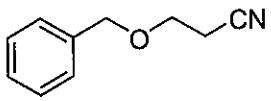
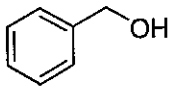
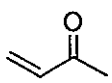
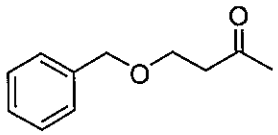
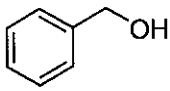
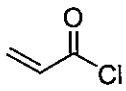
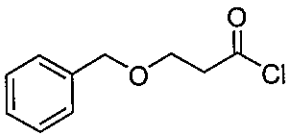
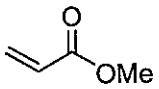
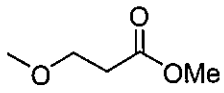
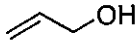
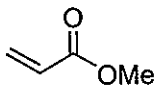
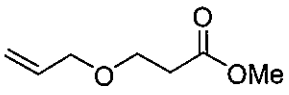
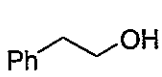
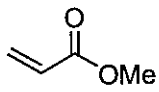
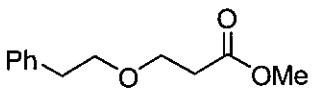
Although our group reported the use of the free proazaphosphatrane base **3b** as a catalyst in oxa-Michael reactions,[8] comparatively harsh conditions were required, and the protocol was restricted to primary alcohols which afforded product yields of 40-96%. Thus, we began the present study by screening benzyl alcohol as the Michael donor, the use of which has also been demonstrated in an oxa-Michael step in a recent synthesis of Bleomycin A_2.[4d] When benzyl alcohol, methyl acrylate and catalyst **1** were stirred in acetonitrile at room temperature for 14 hours, the desired conjugate addition product was obtained in 95% isolated yield (Table 1, entry 1) along with a 5% yield (as measured by GC-MS) of the transesterification reaction product. When the acceptor was changed to *t*-butyl acrylate, we

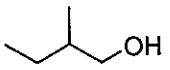
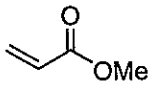
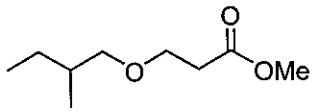
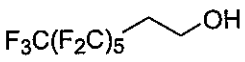
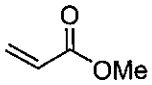
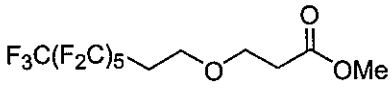
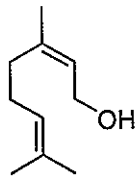
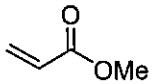
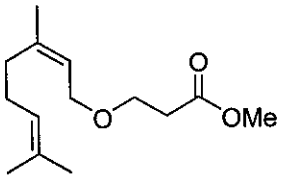
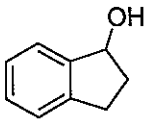
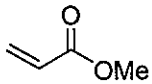
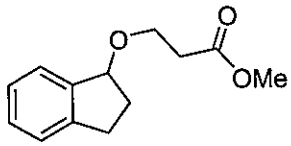
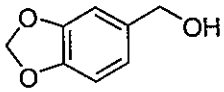
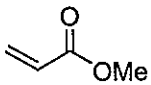
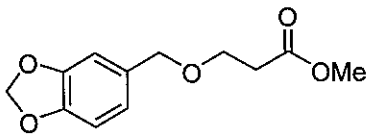
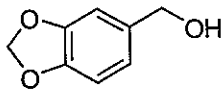
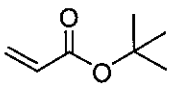
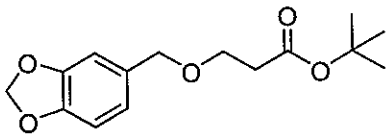
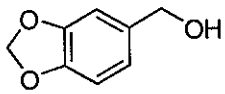
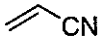
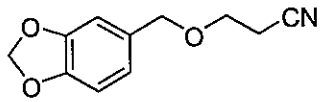
found no evidence for transesterification, but the yield of the desired product decreased to 75% (Table 1, entry 2). Remarkably, an acid chloride in the presence of benzyl alcohol provides the desired Michael addition product in nearly quantitative yield (Table 1, entry 5). To our knowledge, this is the first report of such a transformation rather than the expected reaction of an acid chloride with an alcohol. We speculate that the kinetics of the Michael addition are faster than those of the transesterification. Methyl acrylate functions quite efficiently in these reactions without competitive transesterification (Table 1, entries 6-11) and importantly, products from competitive transesterification were not observed in any of these cases. In contrast to the failure of secondary alcohols to function as Michael donors in our earlier methodology,[8] 1-indanol participates well under our conditions to give the 1,4 addition product exclusively in 90% yield (Table 1, entry 12). In the presence of *iso*-propanol, methyl acrylate or acrylonitrile were completely unreactive under our conditions. This may be associated with the benzylic nature of 1-indanol. The Michael addition of three tertiary alcohols, namely, linalool, *t*-butanol, and 2-phenyl-2-butanol also failed with methyl acrylate and acrylonitrile even when the reactions were carried out for up to 30 h at room temperature or at 60°C. Piperonyl alcohol is also a willing participant in this reaction, adding to methyl acrylate to give the desired product in 97% yield (Table 1, entry 13) although 3% of the transesterified product is also observed (GC-MS). With *t*-butyl acrylate, no transesterification was observed (TLC, GC-MS) and the desired product was isolated in nearly quantitative yield (Table 1, entry 14).



3a R = Me
3b R = *i*-Pr

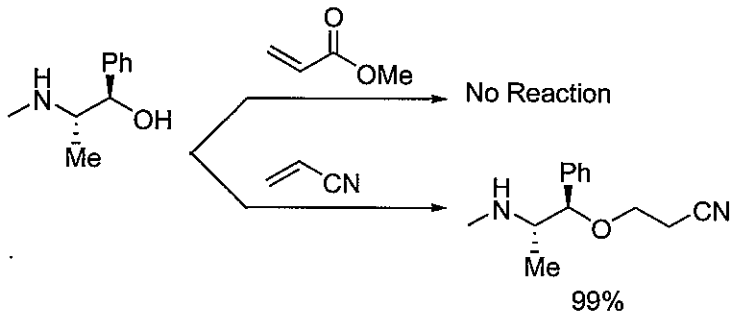
Table 1. Room Temperature Michael Reactions of Alcohols

Entry	Donor	Acceptor	Product	Time (h)	Yield (%)
1				14	95
2				16	75
3				14	99
4				30	66
5				14	99
6	CH_3OH			15	99
7				20	99
8				20	99

Entry	Donor	Acceptor	Product	Time (h)	Yield (%)
9				15	99
10				15	99
11				24	99
12				72	90
13				30	97
14				30	99
15				30	99

The Michael addition of ephedrine was also attempted with two substrates (Scheme 2). With methyl acrylate as the acceptor, none of the desired product was found to form after 30 h, and only a small amount of what appeared (by GC-MS) to be transesterified product was observed. With acrylonitrile as the acceptor, however, a nearly quantitative yield of product was achieved after 30 h. This amino nitrile is a potentially useful precursor to the corresponding amino acid via facile hydrolysis.

Scheme 2. Oxa-Michael Reaction with Ephedrine as the Donor

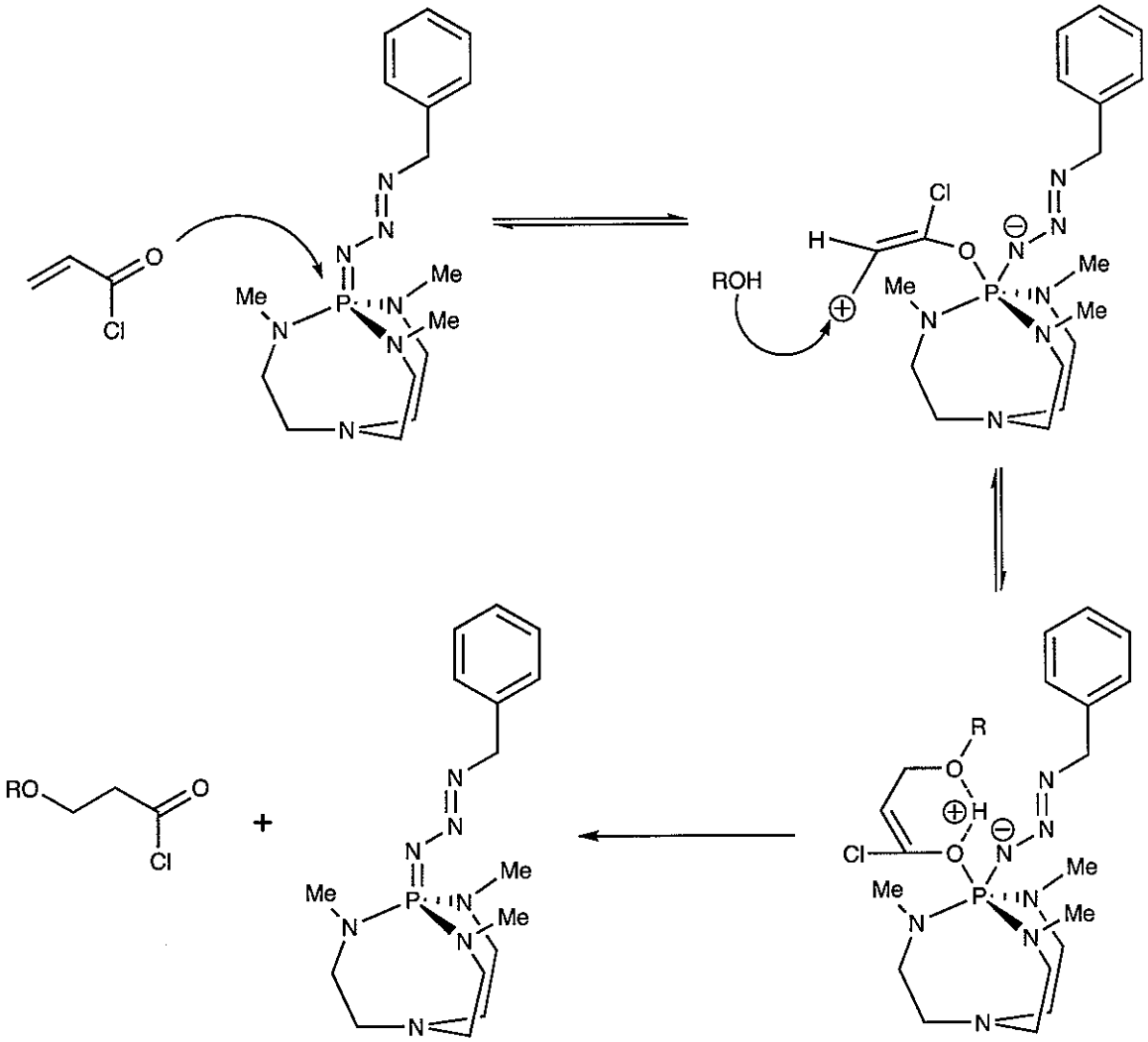


The re-usability of our polymer-bound catalyst was investigated in the reaction of benzyl alcohol with methyl acrylate. This test reaction also allowed us to determine whether re-use might lead to increased transesterification. Polymer-supported catalyst **1** could be effectively re-used three times with product yields ranging from 91-95%. Upon the fourth re-use, the yield of the reaction was only 50% with the balance being transesterification product. However, treatment with *t*-BuOK regenerated polymer catalyst **1**, which then behaved identically to a fresh sample on re-use.

In order to gain insight regarding the manner in which the azidophosphine moiety might catalyze the oxa-Michael reaction involving acryloyl chloride, a 1:1 mixture of this compound and the small-molecule analog catalyst **2** in CD_3CN was monitored by ^{31}P NMR

spectroscopy. The chemical shift of **2** by itself (37.9 ppm) moved to -1.23 ppm. We believe this remarkably strong (ca 39 ppm) upfield shift may be associated with coordination of the carbonyl oxygen with the Lewis acidic phosphorus of **2** as illustrated in Scheme 3, thus expanding the coordination number of phosphorus. This coordination then polarizes the C-C double bond of the Michael acceptor, making it more susceptible to nucleophilic attack by an alcohol than the carbonyl carbon. After proton transfer, the enol irreversibly tautomerizes to give the product. Efforts to isolate this adduct have thus far failed.

Scheme 3. Proposed Mechanism of Michael Addition Catalyzed by **1**



In summary, polymer-supported catalyst **1** efficiently facilitates the oxa-Michael addition of primary and some secondary alcohols at room temperature. Although the re-usability of **1** is modest, it is easily regenerated to full strength. Catalyst **1** also tolerates well the presence of sensitive functionalities, such as esters and acid chlorides, affording the desired coupling products in excellent isolated yields in the vast majority of cases.

Experimental

Acetonitrile and THF were purified over a Grubbs-type two-column system[14] and stored over 4 Å molecular sieves. Benzyl alcohol and methyl acrylate used for polymer catalyst re-use experiments were purified according to known procedures.[15] All other solvents and reagents were used as received, and standard Schlenk techniques were employed.[16] Compounds **1** and **2** were synthesized by previously reported methods.[11]

General Procedure for Michael Reaction of Alcohols: A mixture of Michael donor (1.5 mmol) and acceptor (2.25 mmol) in acetonitrile (2 mL) was added to polymer catalyst **1** (9 mol % of the azidophosphine moiety based on the donor). The reaction mixture was stirred according to the conditions stated in Table 1 and in Scheme 2, and the polymer was filtered off and washed with ~10 mL of acetonitrile. Volatiles were then removed under reduced pressure (~40 microns Hg) from the solution. Impure residues were then subjected to column chromatography on silica gel to give the pure product. Chromatographic solvents used are included in the Supporting Information.

Polymer Re-use Experiment. Benzyl alcohol (1.5 mmol) methyl acrylate (2.25 mmol) and acetonitrile (2 mL) were combined and added to the polymer catalyst (9 mol % of the azidophosphine moiety based on benzyl alcohol) and stirred for 14 hours at room temperature. Stirring was then stopped and the solution was allowed to settle. The

supernatant was decanted via cannula, followed by washing the polymer with ~10 mL of acetonitrile. This procedure was repeated by cannulation of another solution of aniline and methyl vinyl ketone in acetonitrile onto the polymer catalyst.

Reactivation of 1. Substantially deactivated polymer from a series of five re-use experiments was added to a suspension of KO-*t*-Bu (6.75 mmol) in THF (15 mL). The suspension was stirred for 3 days at room temperature and then filtered. The polymer was washed sequentially with ~15 mL portions of THF, DMF, THF, DMF and THF. The fully reactivated polymer was then dried under reduced pressure for 24 hours.

References:

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SUPPLEMENTARY MATERIALS

All numbered references refer to those in the manuscript.

Methyl 3-benzyloxypropionate (Table 1, entry 1)[4r]: 5% Ether-hexane was used as the chromatography eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.55 (t, J = 6.4 Hz, 2H), 3.62 (s, 3H), 3.68 (t, J = 6.4 Hz, 2H), 4.46 (s, 2H), 7.18-7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.0, 51.8, 65.7, 73.2, 127.7, 128.3, 128.5, 138.2, 172.1.

***t*-Butyl 3-benzyloxypropionate (Table 1, entry 2)[4m]:** 5% Ether-hexane was used as the chromatography eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 9H), 2.46 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 4.46 (s, 2H), 7.18-.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.2, 36.5, 66.1, 73.2, 80.6, 127.7, 127.8, 128.5, 138.4, 171.0.

3-Benzyloxypropionitrile (Table 1, entry 3)[4b]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.48 (t, J = 6.4 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 4.46 (s, 2H), 7.21-7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.5, 64.2, 72.8, 117.6, 127.3, 127.6, 128.1, 136.9.

4-Benzyloxy-2-butanone (Table 1, entry 4)[4l]: 10% Ether-hexane was used as the chromatography eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H), 2.64 (t, J = 6.4 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 4.44 (s, 2H), 7.23-7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 30.2, 43.5, 64.9, 72.9, 76.4, 126.0, 126.7, 127.4, 137.8, 206.9.

3-Benzyloxypropionyl chloride (Table 1, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.74 (t, J = 6.5 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 5.06 (s, 2H), 7.24-7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 37.8, 39.1, 66.9, 128.5, 128.6, 128.8, 135.7, 170.3. This compound was reported in *J. Med. Chem.* **1999**, *42*, 706.

Methyl 3-methoxypropionate (Table 1, entry 6)[8]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (T, J = 6.4 Hz, 2H), 3.34 (s, 3H), 3.63 (s, 3H), 3.68 (t, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.0, 51.9, 59.0, 68.2, 181.0.

Methyl 3-allyloxypropionate (Table 1, entry 7)[8]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.59 (t, J = 6.4 Hz, 2H), 3.72 (m, 5H), 5.15-5.29 (m, 2H), 5.82-5.93 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.1, 51.9, 65.7, 72.2, 117.4, 134.7, 172.3.

Methyl 3-phenethyloxypropionate (Table 1, entry 8): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.61 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 3.64-3.78 (m, 7H), 7.23-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 35.1, 36.3, 51.8, 66.3, 72.1, 126.3, 128.4, 129.0, 138.9, 172.2. HRMS (M^+): calcd. For $C_{12}H_{16}O_3$ 208.10994; found, 208.11020.

Methyl 3-butyloxy(2'-methyl)propionate (Table 1 entry 9): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84-1.11 (m, 9H), 1.13-1.64 (m, 3H), 2.56 (t, J = 6.5 Hz, 2H), 3.17-3.33 (m, 2H), 3.67-4.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.5, 16.7, 26.4, 34.9, 35.2, 51.8, 66.4, 76.6, 172.4. HRMS (M^+): calcd. For $C_9H_{18}O_3$ 174.12559; found, 174.12580.

Methyl 3,3,4,4,5,5,6,6,7,7,8,8-tridecafluorooctyloxypropionate (Table 1, entry 10): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28-2.45 (m, 2H), 2.55 (t, J = 6.5 Hz, 2H), 3.66 (s, 3H), 3.71 (t, J = 6.5 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 31.2, 34.5, 51.4, 62.6, 66.3, 108.0-120.0 (m, CF_2 & CF_3), 171.6. HRMS (M^+): calcd. For $C_{12}H_{11}O_3F_{13}$ 450.05006; found, 450.05095.

Methyl 3-geranyloxypropionate (Table 1, entry 11)[4q]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56 (d, 3H), 1.63 (s, 6H), 2.00-2.07 (m, 4H), 2.53-2.58 (m, 2H), 3.65 (m, 5H), 3.95-3.98 (d, J = 6.8 Hz, 2H), 5.02-5.07 (m, 1H), 5.27-5.32 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.9, 18.2, 26.2, 26.9, 35.5, 40.1, 52.1, 65.8, 67.9, 121.2, 124.5, 132.1, 140.9, 172.6.

Methyl 3-indanyloxypropionate (Table 1, entry 12): 10% Ether-hexane was used as the chromatography eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.04-2.15 (m, 1H), 2.31-2.42 (m, 1H), 2.63 (t, J = 6.4 Hz, 2H), 2.77-2.87 (m, 1H), 3.03-3.13 (m, 1H), 3.70 (s, 3H), 3.83 (t, J = 6.4 Hz, 2H), 4.95-4.99 (m, 1H), 7.21-7.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 30.7, 32.7, 35.7, 52.2, 64.4, 84.0, 125.4, 125.6, 126.9, 128.9, 143.1, 144.4, 172.7. HRMS (M^+): calcd. for $C_{13}H_{15}O_3$ 220.10994; found, 220.11030.

Methyl 3-piperonyloxypropionate (Table 1, entry 13): 10% Ether-hexane was used as the chromatography eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (t, J = 6.4 Hz, 2H), 3.65 (s, 3H), 3.67 (t, J = 6.4 Hz, 2H), 4.38 (s, 2H), 5.89 (s, 2H), 6.72-6.79 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 34.9, 51.7, 65.3, 72.9, 100.9, 121.3, 131.9, 147.2, 147.8, 171.9. HRMS (M^+): calcd. for $C_{12}H_{14}O_5$ 238.08412; found, 238.08460.

***t*-Butyl 3-piperonyloxypropionate (Table 1, entry 14):** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43 (s, 9H), 2.49 (t, J = 6.4 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 4.40 (s, 2H), 5.91 (s, 2H), 6.74-6.81 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.2, 36.5, 65.8, 73.0, 80.7, 101.1, 108.1, 108.5, 121.3, 132.2, 147.2, 147.9, 171.0. HRMS (M^+): calcd. for $C_{15}H_{20}O_5$ 280.13107; found, 280.13150.

3-Piperonyloxypropionitrile (Table 1, entry 15): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (t, J = 6.4 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 4.44 (s, 2H), 5.92 (s, 2H), 6.76-6.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.9, 64.3, 73.1, 101.1, 108.1, 108.4, 117.9, 121.4, 131.1, 147.4, 147.9. HRMS (M^+): calcd. for $C_{11}H_{11}NO_3$ 205.07389; found, 205.07420.

3-Ephedrinyloxypropionitrile (Scheme 2): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04-1.06 (d, J = 6.8 Hz, 3H), 2.23-2.53 (m, 4H), 2.57 (t, J = 6.4 Hz, 2H), 2.66-2.91 (m, 1H), 3.48-3.53 (m, 2H), 4.39-4.41 (d, J = 4.7 Hz, 1H), 7.23-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ

17.9, 19.3, 38.7, 49.8, 63.6, 64.5, 85.3, 118.3, 126.9, 127.9, 128.6, 140.3. HRMS (M^+): calcd. for $C_{13}H_{18}N_2O$ 218.14191; found, 218.14220.

CHAPTER 4. A POLYMER SUPPORTED PROAZAPHOSPHATRANE: SYNTHESIS AND CATALYTIC PROPERTIES

Brandon M. Fetterly and John G. Verkade

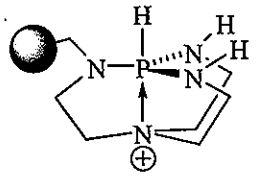
Submitted as a Disclosure to ISURF.

Abstract: A polymer-supported proazaphosphatrane is described. This resin-bound compound is an effective catalyst for the trimerization of isocyanates to isocyanurates, and for the synthesis of diaryl ethers. The polymer catalyst was recycled 20 times in the latter reaction without observable loss of activity.

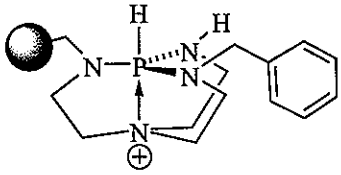
Polymer supported reagents and catalysts have garnered much attention in recent years.[1] The ease of product separation afforded by the use of these reagents has greatly simplified the work of the laboratory chemist. Proazaphosphatranes are a class of non-ionic strongly basic compounds whose utility in solution in a wide variety of catalytic and stoichiometric reactions has been well documented.[2] The ability to recycle such compounds by immobilizing them on a polymer support has been a target of our group for some time. Herein we report the synthesis of a polymer bound proazaphosphatrane and demonstrate its catalytic activity in the trimerization of isocyanates to isocyanurates and in the synthesis of diaryl ethers via electrophilic aromatic substitution.

Initially, compound **1** was synthesized and shown to be an effective precursor to the formation of the corresponding proazaphosphatrane in situ during reactions aimed at dehydrohalogenation, but attempts to isolate the free polymer bound compound met with

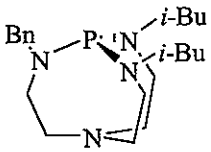
failure.[3] At that point, it was thought that increased steric bulk was needed to protect the proazaphosphatrane from oligomerization, a reaction that is known to occur in the polymer unbound analog $P(HNCH_2CH_2)_3N$.[4] Therefore, **2** was synthesized,[5] but unfortunately attempts to obtain the corresponding polymer mounted proazaphosphatrane were also unsuccessful.



1



2



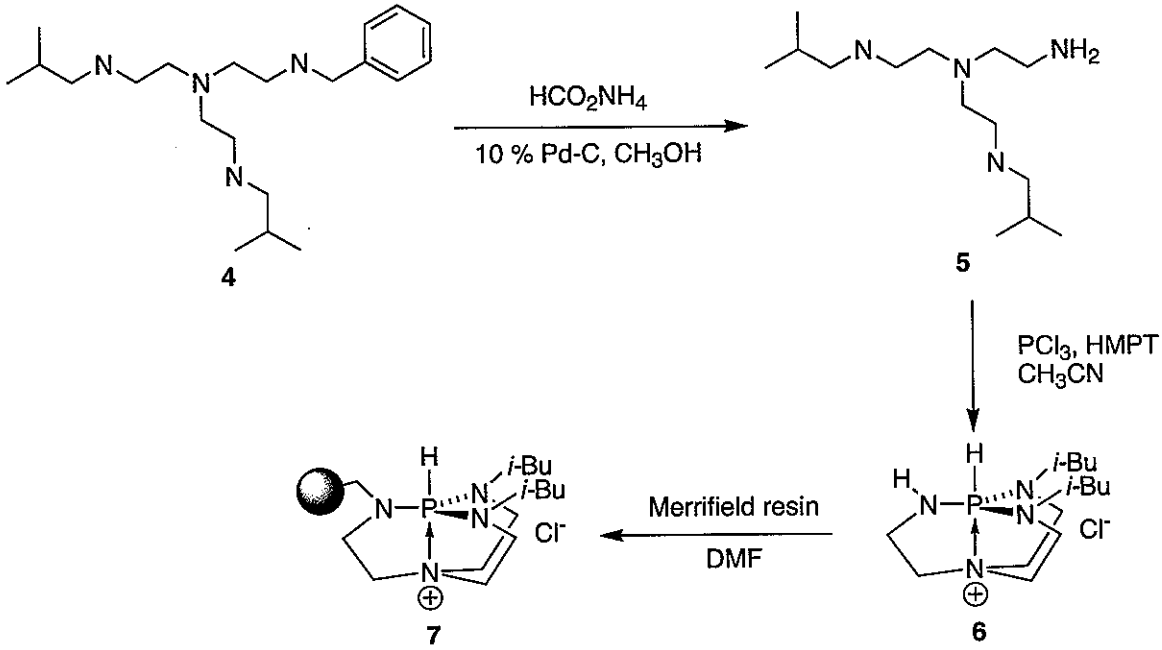
3

It was then decided that it would be desirable to substitute the remaining N-H bond in **2** in the next attempt to synthesize a polymer bound proazaphosphatrane. Toward that end, the synthesis of di-isopropyl tren [$(i\text{-}PrNCH_2CH_2)NCH_2CH_2NH_2$] was investigated for use as the azaphosphatrane precursor, but the yield (7%) was low.[6] A recent synthetic achievement by our goup,[7] namely, compound **3** which was synthesized for a different purpose, provided an alternative more efficient route to an analogous polymer-mounted azaphosphatrane. We recognized, however, that **3**, which we had synthesized in 58% yield, was a promising precursor to the synthesis of a polymer mounted proazaphosphatrane.

We began our synthesis of such the polymer mounted proazaphosphatrane **7** in Scheme 1 with compound **4**[7] which was debenzylated using a known procedure[8] to give **5**, as shown in this scheme. Compound **4** was then cyclized to produce azaphosphatrane salt **6** which we then attached to Merrifield resin via a method developed previously for the amination of such a resin,[3] to give compound **7**. It was then necessary to determine optimum conditions for the deprotonation of **7** to give the polymer bound proazaphosphatrane base.

When KO*t*-Bu was used, the polymer became dark brown after only a few minutes. No deprotonation was observed by solid state ^{31}P NMR spectroscopy of the product after workup. Although NaH did not lead to any darkening of the polymer in the reaction

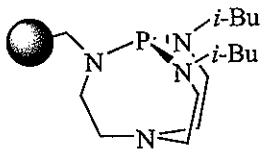
Scheme 1. Synthesis of Polymer Bound Azaphosphatrane **7**



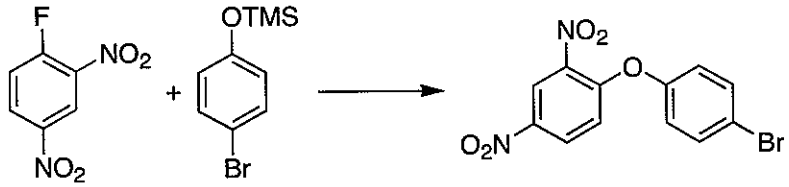
mixture, it proved to be impossible to remove from the polymer after the reaction because of its limited solubility in toluene, DMF, and ether. This prompted us to use commercially available sodium hexamethyldisilazide (NaHMDS) as a base, because of its solubility in toluene. The NaCl side product is soluble in the DMF wash. After stirring a toluene solution of **7** and NaHMDS for two days at room temperature, no discoloration of the polymer was observed.

To demonstrate that we had indeed made polymer bound azaphosphatrane **8**, we tested its catalytic properties in two reactions. First, we investigated the trimerization of isocyanates to isocyanurates, a reaction that is known to proceed cleanly via

proazaphosphatrane catalysis with $P(MeNCH_2CH_2)_3N$[9] and $P(i\text{-}PrNCH_2CH_2)_3N$.[10] We found that the polymer bound catalyst **8** gave trimerized product cleanly at room temperature. With the homogenous catalyst $P(MeNCH_2CH_2)_3N$, the reaction was complete within a few minutes. The polymer bound catalyst required a reaction time of 10 hours to give completely solidified product. Unfortunately, we found that recycling of the catalyst was not feasible to evaluate in this reaction because the only solvents that would dissolve the reaction mixture were halogenated solvents. These solvents have been shown to react with $P(MeNCH_2CH_2)_3N$,[11] and we saw noticeable darkening of the polymer bead during product dissolution in chloroform, dichloromethane, and 1,2-dibromoethane. Examination of **8** as a catalyst in the synthesis of a diaryl ether[12] (reaction 1) revealed production of the product in nearly quantitative yield. Although both the homogenous and the heterogeneous catalyst gave products in room temperature reactions, the heterogeneous catalyst **8** required about twice as much time to show reaction completion by TLC. Catalyst **8** was easily recycled 20 times with no observable loss in reaction yield and with no necessity to lengthen the reaction time.



8



(1)

In conclusion, we have developed a polymer-bound proazaphosphatrane (**8**) that shows excellent catalytic activity. This polymer also shows promising recycling capability.

Experimental

Preparation of 5: Under argon atmosphere, **4** (3.0 mmol, 1.05 g) and an equal mass of 10 % Pd-C catalyst were taken into dry methanol (20 mL). Anhydrous ammonium formate (15.0 mmol, 0.95 g) was added. The mixture was then refluxed with stirring for 6 hours. The catalyst was removed by filtration through a Celite pad, which was then washed with 20 mL of chloroform. The combined organics were then subjected to solvent removal on a rotovapor apparatus to give the desired product in nearly quantitative yield.**6**

Preparation of 6: Under argon atmosphere, a solution containing of PCl_3 (8.9 mmol, 0.78 mL) in 5 mL of acetonitrile was added all at once to a solution of HMPT (17.7 mmol, 3.22 mL) in 25 mL of acetonitrile. This solution was then cooled with an ice bath and then **5** (26.6 mmol, 6.87 g) in 25 mL of acetonitrile was added over a period of 15 minutes. Ether was then added until the solution became turbid. The mixture was then cooled to 0 °C to crystallize the product from the ether-acetonitrile solution. Filtration of the product and washing with 25 mL of ether gave **6** in nearly quantitative yield.

Preparation of 7: Under argon atmosphere, **6** (12.8 mmol), Merrifield peptide resin (2.88 mmol Cl^-/g, 4.34 g) and 60 mL of DMF was vigorously stirred at 110 °C for 6 days. Then the reaction mixture was cooled to room temperature and 40 mL of methanol was added. After the mixture was stirred for 5 minutes, it was filtered to give a solid, which was successively washed with THF, triethylamine, methanol, THF, ether, THF, and ether (10 mL each). The solid product was dried under reduced pressure.

Deprotonation of 7: Under argon atmosphere, **7** (1.00 g) was charged to a round bottom flask. NaHMDS in toluene (20 mL of a 0.6 M solution) was cannulated into the flask and the suspension was stirred for 3 days. The solid remaining after filtration of the reaction mixture

was successively washed with ether, DMF, and ether (20 mL each). The solid product was dried under reduced pressure.

Catalyzed trimerization of phenylisocyanate: Polymer mounted catalyst **8** (5.00 μmol based on an elemental analysis of **7**, 3.0 mg) was weighed under argon atmosphere. Phenylisocyanate (2.0 mL) was then added and the suspension was stirred at room temperature until it solidified (10 h). Chloroform (ca 5 mL) was added to dissolve the solid product. The polymer was then filtered off and the chloroform was removed on a rotovapor apparatus to give phenylisocynurate in nearly quantitative yield.

Catalyzed synthesis of a diaryl ether: Polymer-supported proazaphosphatrane **8** (0.15 mmol, 90 mg) was weighed under argon atmosphere. A solution of Sanger's reagent (1.5 mmol, (0.19 mL) and (*p*-bromophenoxy)trimethylsilane (1.65 mmol, 0.32 mL) in toluene (2 mL) was cannulated into the flask. The suspension was stirred for 2 hours, after which the starting material was consumed as shown by TLC using hexane as an eluent. Compound **8** was then filtered off and the toluene was removed under reduced pressure to give the product in reaction 1 in nearly quantitative yield.

Polymer recycling experiment: A reaction mixture for the synthesis of the diaryl ether in reaction 1 was prepared as described in the previous paragraph. After 2 hours, stirring was stopped and the suspension was allowed to settle. The supernatant was carefully cannulated off, and a new solution of the reaction mixture in toluene was cannulated into the reaction vessel.

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CHAPTER 5. $P(MeNMCH_2CH_2)_3N$: AN EFFECTIVE PROMOTER FOR TRIMETHYLSILYLCYANATION OF ALDEHYDES AND KETONES

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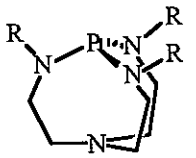
The addition of cyanotrialkylsilanes to carbonyl compounds, and especially the development of catalysts for this transformation, has attracted considerable attention owing to the utility of cyanohydrin trialkysilylethers as well as cyanohydrins as versatile intermediates in organic synthesis.[1] A variety of catalysts have been developed[2] for such reactions including Lewis acids,[3] Ti(IV) Schiff base complexes[4] $Cu(OTf)_2$[5], KCN/18-crown-6[6], tetracyanoethylene,[7] solid acidic montmorillonite, and solid bases such as CaO and MgO.[8] Several optically active catalysts for asymmetric cyanohydrin formation are also effective.[9] Although uncatalyzed cyanosilylations have been reported,[10] reactions of ketones with TMSCN under such conditions are extremely sluggish. Kobayashi was the first to report the trimethylsilycyanation of aldehydes catalyzed by Lewis bases such as amines, tributylphosphine, triphenylantimony and triphenylarisine.[11] The reactions were carried out under mild conditions to afford cyanohydrin silylethers in high yield. However, no mention was made of ketones as substrates for this reaction. In our continuing efforts to expand the synthetic applications of strong nonionic bases of type **1**,[12] first synthesized in our laboratories,[13] we found earlier that **1b** promotes the allylation of aromatic aldehydes with allyltrimethylsilane,[14] and that **1a** efficiently promotes the reduction of aldehydes and ketones with PMHS.[15]



1a, R = Me
1b, R = *i*-Pr
1c, R = (S)-PhCHMe

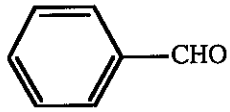
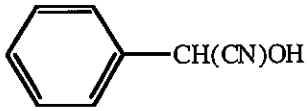
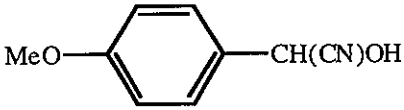
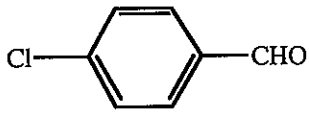
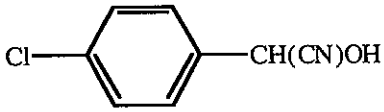
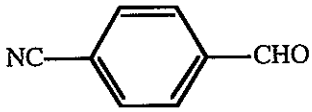
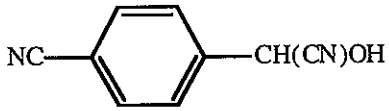
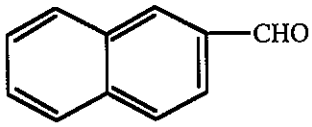
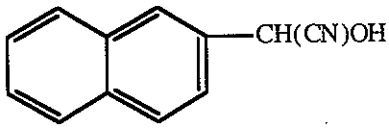
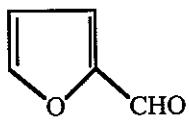
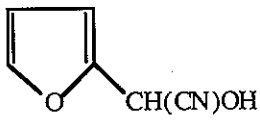
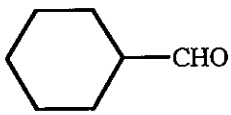
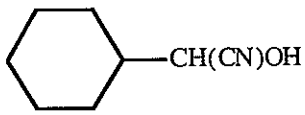
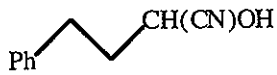
Herein we report that **1a** is an effective promoter for the addition of trimethylsilyl cyanide to aldehydes and ketones under mild conditions, giving rise to cyanohydrins and cyanohydrin silyethers, respectively, in high yields (reactions 1 and 2). When the reaction of benzaldehyde or heptaldehyde

$$\text{RCHO} + \text{TMSCN} \xrightarrow[\text{THF}]{\text{1. 1a, 10 mol\%, THF}\ \text{2. aq HCl/ether}} \text{RCH(OH)CN} \quad (1)$$

$$\text{R'COR"} + \text{TMSCN} \longrightarrow \text{R'C(OTMS)CNR"} \quad (2)$$

was carried out with TMSCN in the presence of (10 mol%) **1a,** the transformations were found to be complete in 30 minutes at room temperature as monitored by TLC. However, the corresponding cyanohydrins were observed together with the cyanohydrin silylethers. Desilylation persisted even when the reaction temperature was decreased to 0°C. The cyanohydrins were exclusively obtained in high yields by treating the reaction mixture with aqueous HCl. The results of these experiments are shown in Table 1. This table shows that *para*-methoxybenzaldehyde also reacts with TMSCN to give the corresponding substituted cyanohydrin in 94% yield. However, aromatic aldehydes bearing electron withdrawing Cl or CN substituents gave the corresponding cyanohydrins in low yields. Other aldehydes such as naphthaldehyde, furaldehyde and cyclohexanecarboxaldehyde gave the corresponding cyanohydrins in good to high yields (83 – 92%). When the optically active strong base **1c**[13c] was employed to promote the cyanohydration of benzaldehyde with TMSCN, the cyanohydrin was isolated in high yields (95%) but no enantioselectivity was observed.

Table 1. The reduction of aldehydes with TMSCN using **1a** as a promoter[a]

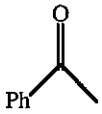
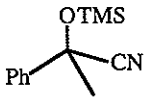
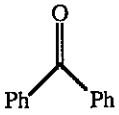
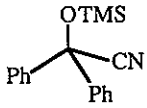
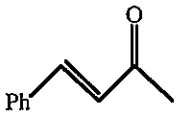
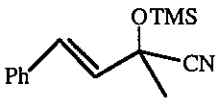
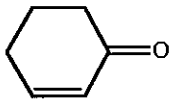
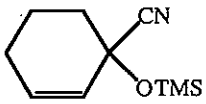
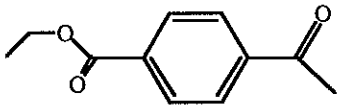
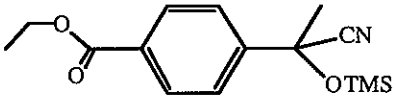
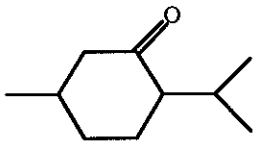
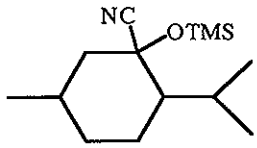
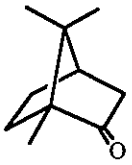
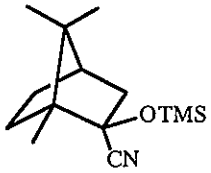
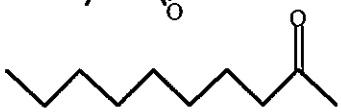
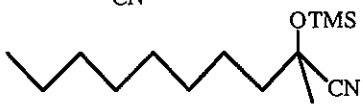
entry	aldehyde	reaction condition T (°C)/t (h)	product	yield (%)[b,c]
1		0/1		92 (92)
2		0/1		94
3		rt/0.5		68 (23)
4		rt/0.5		59
5		rt/0.5		83
6		0/1		84
7		0/2		90
8		0/1		92
9	$CH_3(CH_2)_5CHO$	rt/0.5	$CH_3(CH_2)_5CH(CN)OH$	95 (95)

[a]All reaction were conducted under argon. THF was freshly distilled over Na and stored over 4 Å molecular sieves. [b]Isolated yields are based on the aldehyde. [c]Yields in parentheses are with HMPT.

As shown in Table 2, the reaction of both aromatic and aliphatic ketones (entries 1, 2

and 9) with TMSCN proceeded smoothly at room temperature to give the corresponding cyanohydrin silylethers in high yields. α,β-Unsaturated ketones (entries 3 and 4) react with TMSCN to give 1,2-addition products regioselectively; no 1,4-adducts were observed. The reaction of 4-*t*-butylcyclohexanone with TMSCN in the presence of **1a** affords a mixture of axial and equatorial cyanide in a ratio of 84:16. Also worth mentioning are the reactions of the two chiral ketones, namely (-)-methone and (1R)-(+)-camphor with TMSCN (entries 7 and 8 respectively). (-)-Menthone reacted with TMSCN to give the cyanohydrin silylether in 94% yield, although diastereoselectivity was poor and the product was isolated as a mixture of diastereomers (66:34). For the reaction of (1R)-(+)-camphor, the yield was only 33%, but diastereoselectivity was excellent since only one diastereomer was observed.

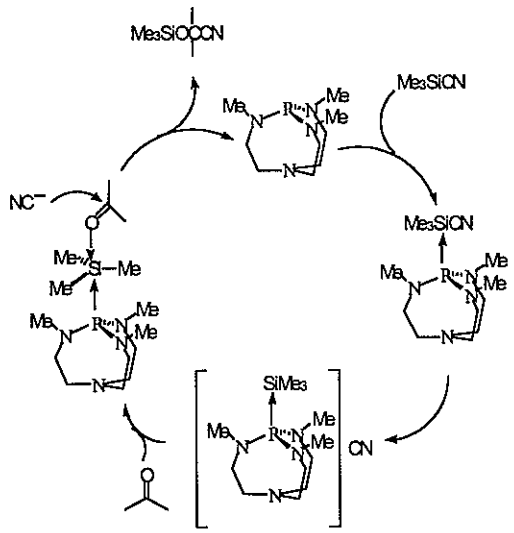
Table 2. The reduction of ketones with TMSCN using **1a** as a promoter[a]

entry	ketones	product	yield (%) [b]
1			94 (24)[f]
2			91
3			86
4[c]			54
5			88
6[d]			89 (84:16) [e]
7			94 (66:34) [e]
8[c]			33[c](NR)[f]
9[d]			90

[a] All reactions were conducted at room temperature for 1 h under argon unless stated otherwise. THF was freshly distilled from Na and stored over 4Å molecular sieves. [b]Isolated yields are based on the ketone. [c] Reaction time was 5 h. [d]Reaction time was 0.5 h. [e]The diastereomeric ratio was determined by ^{13}C NMR spectroscopic integration. [f]Results are with HMPT as the promoter.

The cyanation intermediate in our reactions is assumed to involve a pentacoordinate silicon formed from **1** and TMSCN as shown in Scheme 1, analogous to that suggested by Kobayashi with an amine, a phosphine, a stibine, or an arsine.[11] Neither Kobayashi nor we have any evidence for such an intermediate in the reaction of aldehydes and ketones with TMSCN. However, we have adduced evidence that bases of type **1** coordinate to four-coordinate silicon in trimethylsilyl allyations of aromatic aldehydes[14] and in reductions of aldehydes and ketones with PMHS.[15] It is likely that the pathway for the trimethylsilylcyantion of aldehydes and ketones (Scheme 1) involves

Scheme 1.



ion formation since we have found evidence for such a mechanism in the case of the trimethylsilyl allylation of aromatic aldehydes.[14] The step at which ionization occurs in Scheme 1 is open to question.

Experimental

Typical procedure for reaction of aldehydes with TMSCN. To a solution of **1a** (0.15 mmol) in THF (2.0 mL) was added TMSCN (1.8 mmol) at 0°C, followed by addition of the

aldehyde (1.5 mmol). After the reaction conditions stated in Table 1 had been met, an aqueous solution of HCl (1M, 5 mL) and ether (20 mL) was added and the mixture was then stirred at room temperature for another 1 h. The phases were separated and the water layer was washed with ether (3 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL) and then dried over $MgSO_4$. The solvent was removed with a rotary evaporator and then under reduced pressure on a vacuum line to give the crude product which was purified by flash chromatography (hexane : ethyl acetate = 10 : 1) to give the cyanohydrin.

Typical procedure for the reaction of ketones with TMSCN. To a solution of **1a** (0.15 mmol) in THF (2.0 mL) was added TMSCN (1.8 mmol) at room temperature, followed by addition of the ketone (1.5 mmol). After the reaction conditions stated in Table 2 had been met, the solvent was removed under reduced pressure on a vacuum line to give the crude product which was purified by flash chromatography (hexane : ethyl acetate = 100 : 1) to give the cyanohydrin silylether.

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SUPPLEMENTARY MATERIALS

Mandelonitrile: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1999**, 1(2), 1483B.

***p*-Methoxymandelonitrile**: The ^{1}H NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173.

***p*-Chloromandelonitrile**: The ^{1}H NMR spectra compared favorably with that reported in *Synthesis*, **1990**, 575.

***p*-Cyanomandelonitrile**: The ^{1}H NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173.

2-Naphthaleneglycolonitrile: The NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1992**, *65*, 111.

2-Furanglycolonitrile: The NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1992**, *65*, 111. .

Cyclohexaneglycolonitrile: The ^{1}H NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379. .

2-Hydroxy-4-phenylbutyronitrile: The ^{1}H NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379.

2-Hydroxyoctanenitrile: The ^{1}H NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173.

α–(Trimethylsiloxy)-hydratroponitrile: These NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016.

α-Phenyl-α-(trimethylsilyloxy)-benzeneacetonitrile: These NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016.

2-Methyl-4-phenyl-2-(trimethylsilyloxy)-(*E*)-3-butenenitrile: These NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016.

1-(Trimethylsilyloxy)-2-cyclohexene-1-carbonitrile: These NMR spectra compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016.

2-(Trimethylsiloxy)-2-(*p*-carboethoxyphenyl)propionitrile: ^{1}H NMR ($CDCl_3$): δ 0.18 (s, 9H), 1.39 (t, 3H), 1.84 (s, 3H), 4.38 (q, 2H), 7.59-7.63 (m, 2H), 8.04-8.09 (m, 2H). ^{13}C NMR ($CDCl_3$): 1.1 (($\underline{C}H_3$)Si), 14.4, 33.6, 61.2, 71.4($\underline{C}$-CN), 121.2, 124.7, 130.1, 131.0, 146.8, 166.0; HRMS (EI) Calcd for CHONSi: 291.12907, Found: 291.12956 m/e(M^+)

4-(1,1-Dimethylethyl)-1-(trimethylsilyloxy)-cyclohexanecarbonitrile: The ^{13}C NMR spectrum compared favorably with that reported in *Tetrahedron* **1983**, *39*, 777.

1-Cyano-1-(trimethylsiloxy)-2-*iso*-propyl-5-methyl-cyclohexane: Isolated as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$): 0.21, 0.22 (s, 9H), 0.83-1.01 (m, 10H), 1.21-1.46 (m, 3H), 1.67-1.75 (m, 5H), 2.01-2.25 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 1.2 (($\underline{C}H_3$)$_3$Si), 1.6 (($\underline{C}H_3$)$_3$Si), 17.2, 18.3, 20.2, 21.6, 23.1, 23.5, 23.6, 25.8, 26.7, 29.6, 30.4, 34.1, 34.3, 47.9, 49.8, 50.6, 53.3, 73.6 ($\underline{C}$-CN), 73.9 ($\underline{C}$-CN), 121.6 (C≡N), 122.8 (C≡N); Anal. Calcd. For CHONSi: 253.18619. Found: 253.18653.

1,7,7-Trimethyl-2-(trimethylsilyloxy])-bicyclo[2.2.1]heptane-2-carbonitrile: *Tetrahedron asymmetry* **1994**, *5*, 1599. ^{1}H NMR ($CDCl_3$): δ 0.22 (s, 9H), 0.87 (s, 3H), 0.94 (s, 3H), 0.98 (s, 3H), 1.10-1.20 (m, 1H), 1.54-1.82 (m, 4H), 2.04 (d, 1H), 2.15-2.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 1.1 (($\underline{C}H_3$)$_3$Si), 10.6, 20.5, 21.2, 26.6, 31.8, 45.2, 48.0, 48.8, 54.2, 78.7 ($\underline{C}$-CN), 122.2 (C≡N).

2-Methyl-2-(trimethylsilyloxy)-decanenitrile: ^{1}H NMR ($CDCl_3$): δ 0.23 (s, 9H), 0.88 (t, 3H), 1.27-1.34 (m, 12H), 1.55 (s, 3H), 1.69 (dd, 2H). ^{13}C NMR ($CDCl_3$): δ 1.4 (($\underline{C}H_3)_3Si$), 14.2, 22.7, 24.3, 29.0, 29.3, 29.5, 31.9, 69.8 ($\underline{C}$-CN), 122.3 (C≡N); Anal. Calcd. For CHONSi:255.20184. Found: 255.20227.

CHAPTER 6. $P(RNCH_2CH_2)_3N$: EFFICIENT CATALYSTS FOR THE CYANOSILYLATION OF ALDEHYDES AND KETONES

Brandon M. Fetterly and John G. Verkade

A paper presented at the 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002, Organic Abstracts paper 344.

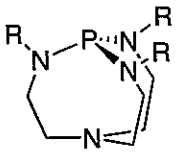
Abstract: The 1,2-addition of trialkylsilylcyanides to aldehydes and ketones produces the corresponding protected cyanohydrins in good to excellent yields when carried out at 0 °C to room temperature in the presence of catalytic amounts of the nonionic strong base $P(RNCH_2CH_2)N$ (R = Me, *i*-Pr) in THF. These catalysts are easily removed from the product by hydrolysis or column filtration through silica gel.

Introduction

Cyanohydrins and cyanohydrin trialkylsilylethers are versatile intermediates in organic synthesis.[1] It is therefore no surprise that many catalysts have been developed for the reaction of trimethylsilylcyanide (TMSCN) with aldehydes and ketones.[2] However, trimethylsilyl groups are easily removed under a variety of reaction conditions.[3] This problem can be solved by using bulkier trialkylsilylcyanides such as *tert*-butyldimethylsilyl cyanide (TBSCN) or *tert*-butyldiphenylsilyl cyanide (TBDPSCN). These compounds produce TBS or TBDPS-protected alcohols, respectively, which contain two of the most popular silyl protecting groups used, being approximately 10^4 times more resistant to hydrolysis than the corresponding TMS protected alcohol. Such protected alcohols are stable to a variety of organic transformations carried out on other functional groups in the molecule, and the silyl groups are easily removed by a variety of methods.[3] Despite the usefulness of

TBS and TBDPS-protected cyanohydrins, a one step conversion to this functionality from aldehydes and ketones is still rare.[4]

We have previously reported the exceedingly strong nonionic bases **1a** and **1b**.[5] Bases of this type have been shown to catalyze a variety of organic reactions, including but not limited to efficient preparations of nitroalcohols,[6] α,β-unsaturated nitriles,[7] β-hydroxy nitriles,[8] glutaronitriles,[9] alkenes,[10] and α,β-unsaturated esters.[11]



1a R = Me
1b R = *i*-Pr

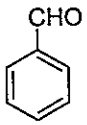
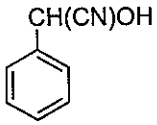
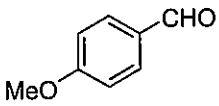
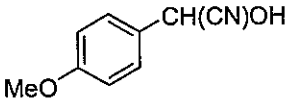
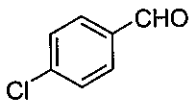
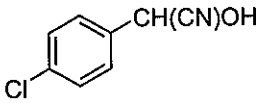
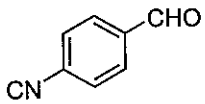
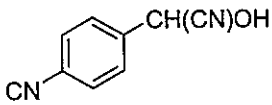
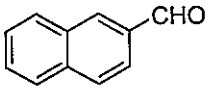
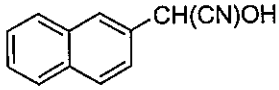
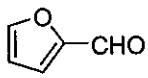
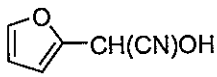
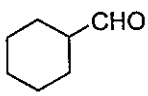
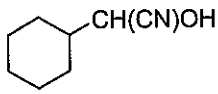
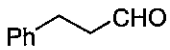
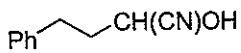
Here we report improvements to a procedure previously published by our group. The previous procedure involves the use of 10 mol % **1a** to afford products in moderate to excellent yields at room temperature. We now show that the use of **1b** gives yields that are not only better in most cases to those previously published, but also affords these yields in the presence of a lower catalyst loading.

Results and Discussion

Trimethylsilylcyanation of aldehdyes and ketones. After testing a series of phosphorus containing compounds, we concluded that base **1b** is the optimal catalyst for reactions of this type. Unfortunately, we still observed desilylation when the reactions were performed with aldehydes, the results of which are summarized in Table 1. This table shows that the low yields previously associated with using aromatic aldehydes bearing electron withdrawing groups has been solved simply by changing the catalyst from **1a** to **1b**. It is not presently clear why this is the case. Other aldehydes, such as furfural,

hydrocinnamaldehyde, and heptaldehyde give the corresponding cyanohydrins in very good to excellent yields (89-99%).

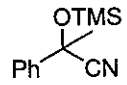
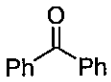
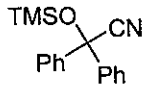
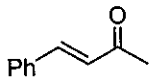
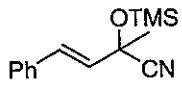
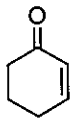
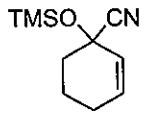
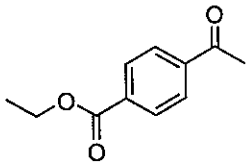
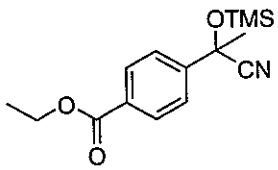
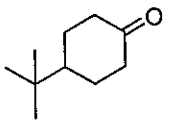
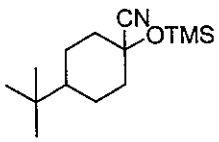
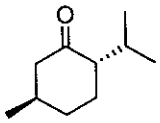
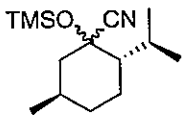
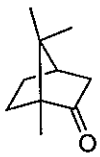
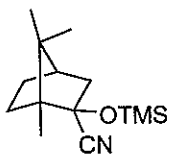
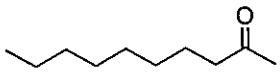
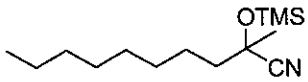
Table 1. The reaction of aldehydes with TMSCN using **1b** as a catalyst.

Entry	Aldehyde	Reaction Condition T (°C)/t (h)/catalyst (%)	Product	Yield (%)
1		0/1/1		97[b]
2		0/1/3		98
3		rt/0.5/5		99[c]
4		rt/0.5/3		97
5		rt/0.5/3		99
6		0/1/3		89
7		0/2/3		99
8		0/1/3		98
9	$CH_3(CH_2)_5CHO$	rt/0.5/3	$CH_3(CH_2)_5CH(CN)OH$	95

[a]All reactions were conducted under argon. THF was freshly distilled over Na and stored over 4 Å molecular sieves. 3 mol % catalyst was used unless stated otherwise. [b]1 mol % catalyst was used. [c]5 mol % catalyst was used.

The results of the trimethylsilylcyanation of ketones are shown in Table 2. Ketones of various types react smoothly with TMSCN for afford the corresponding products in good to excellent yields. α,β-Unsaturated ketones (entries 3 and 4) react solely in 1,2 style, and no Michael addition products are detected. Also of note, is the reaction of TMSCN with chiral ketones (entries 7 and 8). (-)-Menthone affords and excellent yield of product, but diastereoselectivity is nonexistent. (1R)-(+)-Camphor, on the other hand, was found to give only one diastereomeric product, but the overall yield for this reaction is only 26%, and 10 mol % catalyst is required to afford it.

Table 2. The reaction of ketones with TMSCN using **1b** as a catalyst.

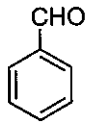
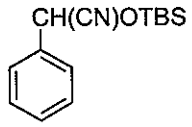
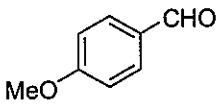
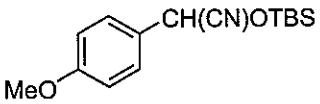
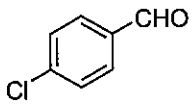
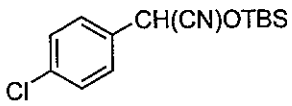
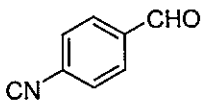
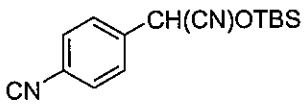
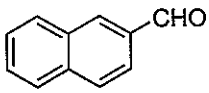
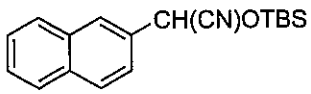
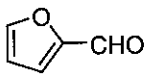
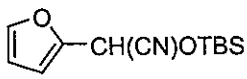
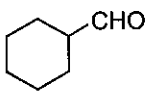
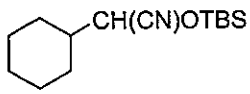
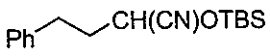
Entry	Ketone	Product	Yield (%)
1			90
2			87[e]
3			99
4[b]			99
5			99
6[c]			85 (79:21)[d]
7			99 (53:47)[d]
8[b]			26[f]
9[c]			99

[a]All reactions were conducted at room temperature for 1 h under argon with 3 mol % catalyst unless stated otherwise. THF was freshly distilled from Na and stored over 4 Å molecular sieves. [b]Reaction times was 5 h. [c]Reaction time was 0.5 h. [d]The diastereomeric ratio was determined by ^{13}C NMR spectroscopic integration. [e]5 mol % catalyst was used. [f]10 mol % catalyst was used.

***t*-Butyldimethylsilylcyanation of aldehydes and ketones.** The products obtained from the reaction of aldehydes and ketones with TMSCN are partially hydrolyzed by

adventitious water in the reaction mixture. Therefore, we decided to use a trialkylsilylcyanide that affords a product that is more difficult to hydrolyze.[3] To achieve this, we chose TBSCN. Although we found that the title catalysts hydrolyze TBS ethers, the reaction requires longer times and higher temperatures than those used herein.[12] Under our reaction conditions, no desilylation products are found in reactions with aldehydes. Furthermore, the reactions proceeded much more cleanly than those in which TMSCN was used, as shown in Table 3.

Table 3. The reaction of aldehdyes with TBSCN using **1b** as a catalyst.

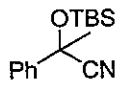
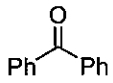
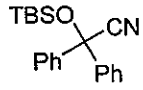
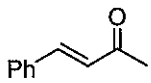
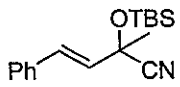
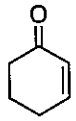
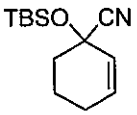
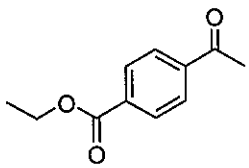
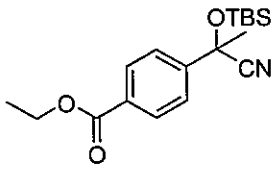
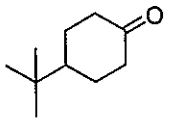
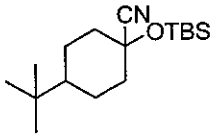
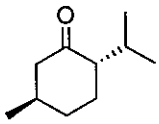
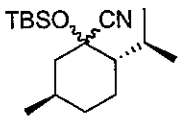
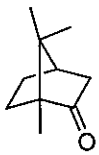
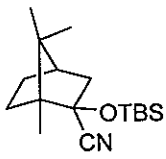
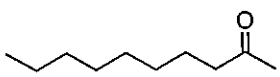
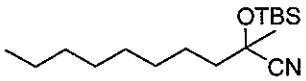
Entry	Aldehyde	Reaction Condition T (°C)/t (h)	Product	Yield (%)
1		0/1		99
2		0/1		99
3		rt/0.5		99
4		rt/0.5		99
5		rt/0.5		99
6		0/1		99
7		0/2		99
8		0/1		99
9	$CH_3(CH_2)_5CHO$	rt/0.5	$CH_3(CH_2)_5CH(CN)OTBS$	99

[a]All reactions were conducted under argon. THF was freshly distilled over Na and stored over 4 Å molecular sieves. 3 mol % catalyst was used.

The results of the reactions with ketones are shown in Table 4. Acetophenone (entry 1) requires 7 mol % catalyst to see the same product yield that was realized with 3 mol %

catalyst for other ketones. Also of note is the nearly two-fold increase in yield in the reaction of (1R)-(+)-camphor with TBSCN, again with no loss of diastereoselectivity. Using TBSCN instead of TMSCN in the reaction of (-)-methone, on the other hand, does not give any significant diastereoselectivity increase.

Table 4. The reaction of ketones with TBSCN using **1b** as a catalyst.

Entry	Ketone	Product	Yield (%)
1			99[e]
2			99
3			98
4[b]			99
5			99
6[c]			99 (63:37)[d]
7			99 (61:39)[d]
8[b]			42[f]
9[c]			99

[a]All reactions were conducted at room temperature for 1 h under argon with 3 mol % catalyst unless stated otherwise. THF was freshly distilled from Na and stored over 4 Å molecular sieves. [b]Reaction time was 5 h. [c]Reaction time was 0.5 h. [d]The diastereomeric ratio ws determined by ^{13}C NMR spectroscopic integration. [e]7 mol % catalyst was used. [f]10 mol % catalyst was used.

Although other methods are known to give these products, they either involve much longer reaction times, or the use of Lewis acid or crown ether catalysts.[4]

Proazaphosphatranes of type **1** used here serve as superior catalysts for *t*-butyldimethylsilylcyanation of aldehydes and ketones.

Conclusions

A wide range of aldehydes and ketones undergo trialkylsilylcyanation in generally excellent yield, with the use of non-ionic proazaphosphatrane bases. Alkyl and aryl aldehydes and ketones react cleanly under mild conditions, tolerating many different types of functional groups. The catalyst is easily removed, affording NMR pure products in many cases.

Experimental

Typical procedure for reaction of aldehydes with TMSCN. To a solution of TMSCN (1.8 mmol) and the aldehyde (1.5 mmol) in THF (2.0 mL) was added **1b** (1 to 5 mol% of aldehyde, as specified in Table 1) at 0 °C. After the reaction conditions stated in Table 1 had been met, an aqueous solution of HCl (1M, 5 mL) and ether (20 mL) was added and the mixture was then stirred at room temperature for another hour. The phases were separated and the water layer was washed with brine (2 x 20 mL) and dried over $MgSO_4$. The solvent was removed with a rotary evaporator to give the crude product which was purified by flash chromatography (hexane:ethyl acetate = 10:1) to give the cyanohydrin.

Typical procedure for the reaction of ketones with TMSCN. To a solution of TMSCN (1.8 mmol) and the ketone (1.5 mmol) in THF (2.0 mL) was added **1b** (3 to 10 mol% of ketone, as specified in Table 2) at room temperature. After the reation conditions stated in Table 2 had been met, the reaction mixture was loaded onto a small silica gel column for elution (ether:methanol = 20:1). Removal of the solvent from the eluate under

reduced pressure afforded the crude product which was purified by flash chromatography (hexane:ethyl acetate = 100:1) to give the cyanohydrin silyl ether.

Typical procedure for the reaction of aldehydes and ketones with TBSCN. To a solution of TBSCN (1.8 mmol) and the aldehyde or ketone (1.5 mmol) in THF (2.0 mL) was added **1b** (3 to 10 mol% of aldehyde or ketone, as specified in Tables 3 and 4) at 0 °C. After the reaction conditions in Tables 3 and 4 had been met, the reaction mixture was loaded onto a small silica gel column (ether:methanol = 20:1). Removal of the solvent from the eluate under reduced pressure afforded the crude product which was purified where necessary by flash chromatography (hexane:ethyl acetate = 100:1) to give the cyanohydrin silyl ether.

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CHAPTER 7. P(*i*-BuNCH$_2$CH$_2$)$_3$N: AN EFFICIENT CATALYST FOR THE REDUCTION OF ALDEHYDES AND KETONES

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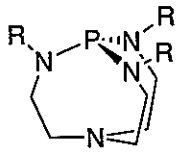
A paper to be submitted to the Journal of Organic Chemistry

Abstract: The reduction of aldehydes and ketones using polymethylhydrosiloxane (PMHS) produces the corresponding alcohols in excellent yields when carried out at 0°C in the presence of catalytic amounts of the commercially available nonionic strong base P(i-BuNCH$_2$CH$_2$)$_3$N in THF. The products are easily removed from the reaction mixture via hydrolysis and chromatography.

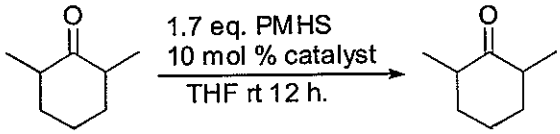
Hydrosilylation is one of the premier methods for the synthesis of alcohols from carbonyl compounds.[1] The hydrosilylation agent of choice in recent years has been polymethylhydrosiloxane (PMHS) and its use has been well documented.[2]

The versatility of nonionic bases of type **1** in stochometric and catalytic organic reactions are well known.[3] Because, these compounds can show marked differences in catalytic activity, we decided to investigate other bases of this type along with related phosphines in a reaction known to proceed with **1a** (Table 1).[4] As seen in this table, a variety of phosphorus compounds were tested as catalysts in a model reaction, and only bases of type **1** were found to give substantial amounts of products. This could be attributed to the partial tansannulation that has been suggested on the basis of NMR evidence in complexes of **1** with PMHS.[4] It was decided that **1c** was the optimal catalyst for this reaction, and it was used for the rest of the work.



1a R = Me
1b R = *i*-Pr
1c R = *i*-Bu

Table 1.



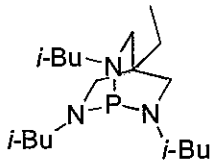
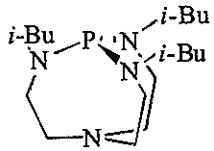
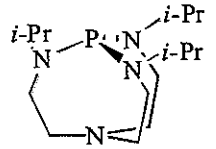
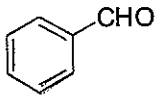
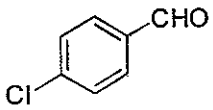
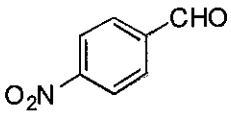
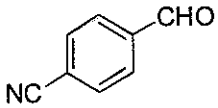
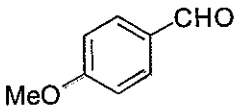
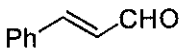
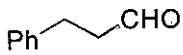
Entry	Catalyst	Yield (%)
1	HMPT	0
2	$(i\text{-}Bu_2N)_3P$	trace
3		trace
4		90
5		79

Table 2 shows that aldehydes are easily reduced with excellent tolerance to a variety of functional groups. Furthermore, no aldol condensation products that are known to occur with bases of this type were found in the reaction mixture when aliphatic aldehydes are used.[5] Unfortunately, when the reduction of hydrocinnamaldehyde was quenched with aqueous sodium hydroxide, no desired product was observed. Instead, the two products obtained were the dehydration product, allylbenzene, and its isomer 1-phenyl-1-propene. It

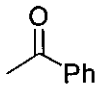
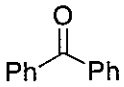
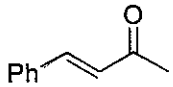
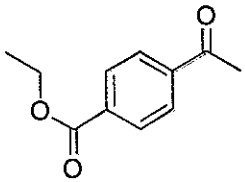
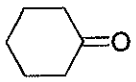
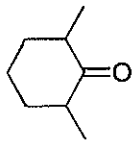
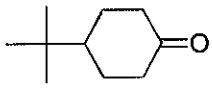
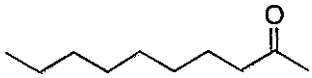
is known that fluoride ion is an effective agent for the cleavage of Si-O bonds.[6] When fluoride ion was used in the quench, the desired product was isolated in excellent yield.

Table 2

aldehyde	mol % catalyst	yield %
	3	99
	1	99
	1	99
	1	99
	1	99
	10	99
$H_2C{=}CH(CH_2)_8CHO$	3	98
	5	99

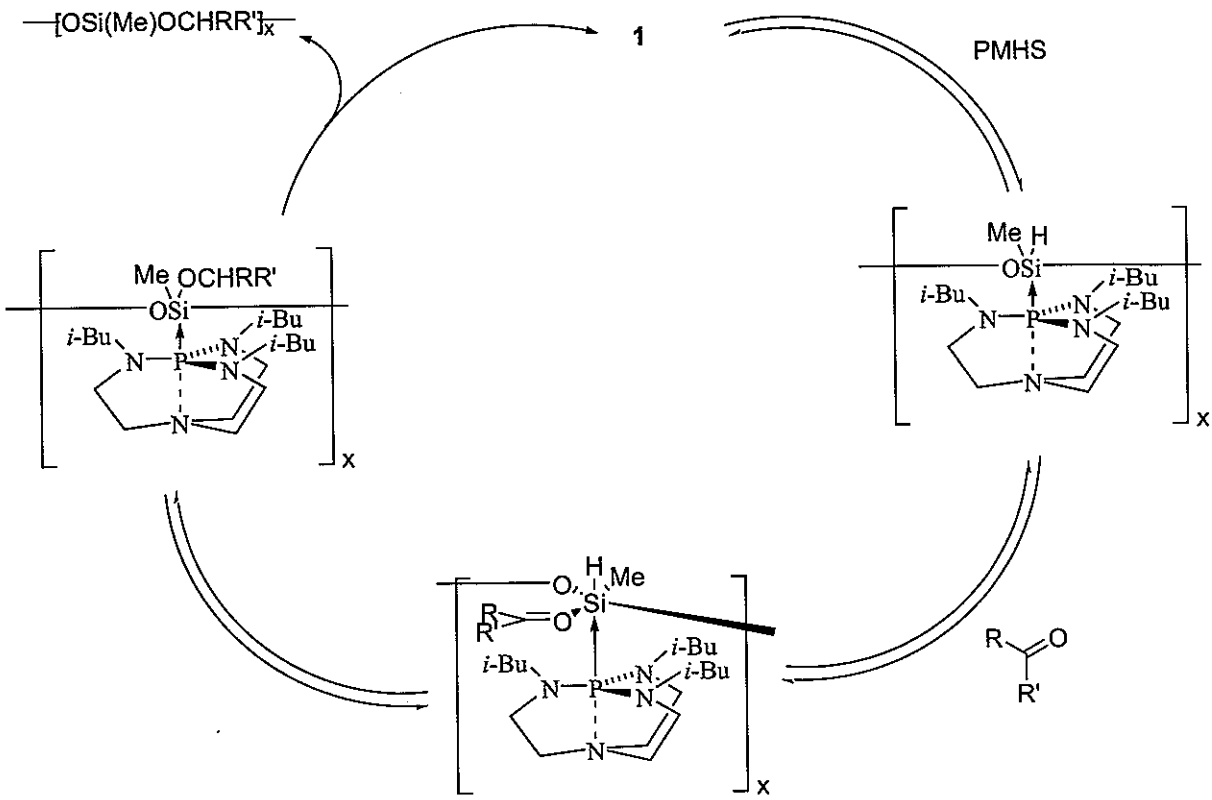
In Table 3, the results of ketone reductions with PMHS are shown. Products are obtained in excellent yield in all cases although two substrates did not survive the hydroxide quenching step intact. Thus *trans*-4-phenyl-3-butene-2-one gave the dehydrated product and the ester functionality of ethyl 4-acetylbenzoate was partially hydrolyzed. Both of these problems were solved, however, when fluoride was used in the quench, and the desired products were obtained in both cases.

Table 3

ketone	mol % catalyst	yield %
	3	98
	10	99
	3	98
	5	99
	1	99
	10	90
	3	99
	5	98

This reaction is assumed to proceed by the mechanism described earlier for reductions with other hypervalent hydrosilicates.[7] As shown in Scheme 1, the phosphorus atom first coordinates to the silicon, and then the silicon atom becomes coordinated by a carbonyl group thus forming a hexacoordinate silicon complex. Hydrogen transfer then leads to formation of the silyl ether which hydrolyzes in the aqueous workup to give the free alcohol.

Scheme 1.



Experimental

A typical reaction procedure follows. PMHS (0.1 mL, 1.70 mmol) and the aldehyde or ketone (1.0 mmol) were dissolved in dry THF (2.0 mL) under argon at 0 °C. Proazaphosphatrane **1c** (10 mol % based on the carbonyl) was then added with magnetic stirring. The reaction was allowed to stir for the specified amount of time (1 h for aldehydes and 12 h for ketones) while warming to room temperature. In the case of sodium hydroxide quenching, 5 mL of a 10% NaOH solution and ether (10 mL) was added, and the mixture was stirred for another hour. When this quench procedure proved troublesome, 0.5 mL of 48% aqueous HF and 5 mL of acetonitrile was added to the reaction mixture at 0 °C. This mixture was stirred for one hour and then, 25 mL of a 1M $NaHCO_3$ solution was added followed by stirring for another hour. Finally, 30 mL of ether was added. The phases were

separated and the organic layer was washed with brine (3 × 10 mL) and dried over $MgSO_4$. Solvent was removed on a rotovapor apparatus to give the crude product which was purified by flash chromatography (10% ethyl acetate in hexane). The ^{1}H and ^{13}C NMR for all compounds are reported in the literature and our data compared well.

Acknowledgement The authors thank the Donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research through a grant.

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SUPPLEMENTARY MATERIALS

Benzyl alcohol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 326B.

4-Chlorobenzyl alcohol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 351C.

4-Nitrobenzyl alcohol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 697C.

4-Cyanobenzyl alcohol: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1973**, *38*, 2786.

4-Methoxybenzyl alcohol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 352B.

***trans*-3-Phenyl-prop-2-en-1-ol:** These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 392C.

Undec-10-en-1-ol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(1)*, 218A.

3-Phenyl-1-propanol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 387C.

1-Phenylethanol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 327A.

Diphenylmethanol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(2)*, 336A.

***trans*-4-Phenylbut-3-en-2-ol:** These NMR spectra compared favorably with that reported in *Tetrahedron* **1998**, *54*, 5129.

Ethyl 4-(1-hydroxy)ethylbenzoate: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1993**, *58*, 2880.

***trans*-4-*t*-Butylcyclohexanol:** These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1994**, *59*, 6378.

2-Decanol: These NMR spectra compared favorably with that reported in *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* **1993**, *1(1)*, 182B.

CHAPTER 8. $P(RNCH_2CH_2)_3N$: EFFICIENT 1,4-ADDITION CATALYSTS

Philip B. Kisanga, Palanichamy Ilankumaran, Brandon M. Fetterly and John G. Verkade

A paper published in the *Journal of Organic Chemistry* **2002**, *67*, 3555.

Abstract The 1,4-addition of primary alcohols, higher nitroalkanes and a Schiff's base of an α-amino ester to α,β-unsaturated substrates produces the corresponding products in moderate to excellent yields when carried out at –63 to 70 °C in the presence of catalytic amounts of the nonionic strong bases $P(RNCH_2CH_2)_3N$ (R = Me, *i*-Pr, *i*-Bu) in isobutyronitrile. Diastereoselectivity for the *anti* form of the product is high in the case of the Schiff's base in the absence of lithium ion. These catalysts are easily removed from the product by either column filtration through silica gel or *via* aqueous work-up.

Introduction

Michael addition is one of the most efficient and effective routes to the formation of C-C bonds.[1] This reaction is widely applied in organic synthesis[2] and several new versions of the reaction have recently been introduced.[3] Michael addition reactions of electron deficient alkenes have been used to produce difunctionalized synthons that have been used extensively in organic synthesis.[2] 1,5-Diketones (prepared by Michael addition of α-nitroketones to α,β-unsaturated ketones)[4] have been used to prepare 2-cyclohexenones,[5] and β-nitroketones can be reduced to β-aminoketones.[1,6] Alternatively, the nitro group can be removed[7] leaving behind a β-alkyl substituent on the carbonyl product.

The commonly employed anionic alkyl synthons for Michael addition are those derived from nitroalkanes,[8] ethyl cyanocarboxylates,[9] and malonates.[10] Such Michael donors have been extensively studied, and their limitations (such as double additions,[11] requirement

for a large excess of the nitroalkane,[12] restrictions in the types of Michael acceptors[13] tolerated, and the low to moderate product yields encountered[10b]) have been largely overcome by newer methodologies.

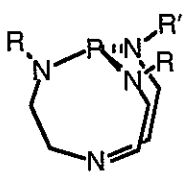
The newer approaches are by no means devoid of drawbacks, however. Among recent developments are the use of Amberlyst A-27,[14] and sodium hydroxide solution in the presence of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant.[15] However, the Amberlyst A-27[14] process requires reaction times ranging from four hours (for MVK) to 25 hours for the reactions of higher nitroalkanes with β-substituted methyl vinyl ketones. The sodium hydroxide method[15] affords only modest product yields in the reaction of secondary nitroalkanes, even with MVK.[15] The yields in both processes range from moderate to high for most substrates. Michael addition reactions of higher nitroalkanes to α,β-unsaturated carbonyl compounds generally require lengthy reaction times and yields are only moderate. Although reactions employing alumina are rapid, four equivalents of the rather expensive higher nitroalkanes are required.[7b]

Oxa-Michael addition reactions have been reported and the protected β-hydroxy carbonyl compounds so produced are of significant importance in organic synthesis.[16] Reports describing such reactions include descriptions of UV irradiation of cycloalkenones in methanol to produce the β-methoxy cyclic ketones;[16] reactions promoted by NaOMe,[17a] KH,[17b] and potassium *t*-butoxide;[17c] and the cyanoethylation of alcohols by a Mg-Al hydrotalcite prepared in a process requiring 450 °C for up to 12 hours.[18a] Several other catalysts have also been used for the cyanoethylation of alcohols but their utility has not been extended to other α,β-unsaturated compounds.[18b,c] Recently, vanadium complexes have been reported to induce hydroalkoxylation of α,β-unsaturated ketones and epoxides.[19] However,

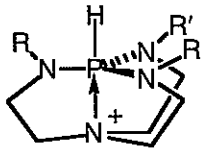
the use of transition metals introduces environmental concerns. To our knowledge, no general reaction has been reported in which β-alkoxy ketones can be prepared via Michael addition. Thus there still exists a need for new methodologies for the preparation of β-alkoxy ketones.

Michael addition reactions of Schiff's bases of α-amino esters have long been known to constitute a convenient method for functionalizing α-amino esters at the *alpha* position.[20] However, this transformation has a propensity to undergo a competing cycloaddition.[20b] The ratio of Michael addition to cycloaddition product has been found to depend upon the metal ion employed to chelate the enolate produced upon deprotonation. Although the use of DBU in this reaction has been observed to give an *alpha*-functionalized α-amino ester as the exclusive product,[21] a stoichiometric amount of LiBr is required to provide sufficient cation concentration for chelation. It is worth noting that a weaker base such as triethylamine produces only the cycloadduct even in the presence of LiBr.[22]

We have previously reported that the proazaphosphatranes **1a**,[23a] **1b**,[23b] and **1c**[23c] are exceedingly strong nonionic bases[23d] for the catalytic deprotonation of activated methyl and



	R	R′	
1a	Me	Me	**2a**
1b	*i*-Pr	*i*-Pr	**2b**
1c	*i*-Pr	H	**2c**
1d	*i*-Bu	*i*-Bu	**2d**



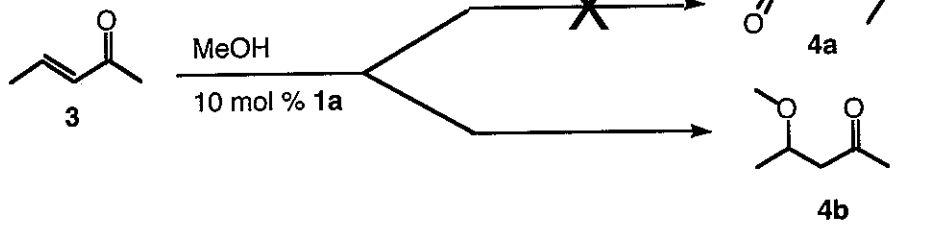
methylene groups. Thus, they deprotonate nitroalkanes, acetonitrile, alkyl halides and carboxylic acid esters leading to efficient preparations of nitroalcohols,[24] α,β-unsaturated nitriles,[25] β-hydroxy nitriles,[26] glutaronitriles,[27] alkenes[28] and α,β-unsaturated esters,[29] for example. In such reactions, bases of type **1** are protonated to form the corresponding cations **2a-d**.

We report herein the use of **1a**-**1c**[23] and the most recently synthesized member of this family **1d**[30] as catalysts for the 1,4-addition of alcohols, nitroalkanes and a Schiff's bases of an α-amino ester to α,β-unsaturated carbonyl compounds. We also show that these catalysts effect the hydroalkoxylation of α,β-unsaturated ketones in a most efficient manner and that they are very efficient catalysts in the absence of any metal ion for the Michael addition of the Schiff's bases of the α-amino ester.

Results and Discussion

Hydroalkoxylation of α,β-unsaturated carbonyl compounds. We first observed a Michael addition reaction promoted by bases of type **1** when we attempted to dimerize (*E*)-3-penten-2-one (**3**) in the presence of 10 mol % of **1a** in methanol (Scheme 1) in analogy to the dimerization of α,β-unsaturated nitriles previously reported from our laboratories by us under similar conditions.[27] Although none of the

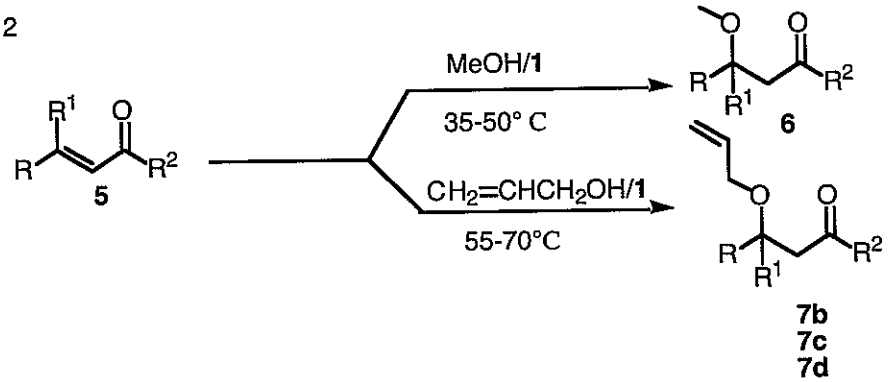
Scheme 1



expected dimer (**4a**) was observed, we were able to isolate 20-30% of the corresponding β-methoxy ketone **4b**. When the reaction was repeated with MVK (**5a**) and with 2-cyclohexen-1-one (**5b**), we isolated the respective β-methoxy compounds in 33% (**6a**) and 24% (**6b**) yield (Scheme 2). Catalysts **1a** and **1b** each afforded similar yields within experimental error. We determined earlier that the protonation of proazaphosphatranes of type **1** to form

cation **2** is slow and incomplete in alcohols at room temperature[23a,29] In the present work, hydroalkoxylation reactions utilizing 10 mol % of **1a** or **1b** at this temperature led to substantial substrate oligomerization with only 20-30% of hydroalkoxylation product that was observed to flow through the chromatography column. At 50 ^{0}C all of **1a** and **1b** is rapidly protonated, substantial hydromethoxylation of MVK and of 2-cyclohexenone occurred in 10-15 minutes, and additional hydromethoxylation occurred over an additional 15 minutes at room temperature to afford the corresponding

Scheme 2



a: R = R^1 = H, R^2 = Me

b: R = H, R^1, R^2 = $(CH_2)_3$

c: R = R^1 = R^2 = Me

d: R = H, R^1 = Me, R^2 = Et

e: R = R^1 = H, R^2 = OMe

f: R = Me, R^1 = H, R^2 = OEt

g: R = H, R^1 = Ph, R^2 = Me

h: R = H, R^1 = CO_2Me, R^2 = OMe

i: R = H, R^1 = Me, R^2 = OMe

β-methoxy ketones in 65% and 76% yield, respectively. Base **1c** afforded a lower yield (52-61%) probably owing to its relative instability to oligomerization.[23c] Because of its low boiling point (38 °C) MVK was added to the warm mixture of MeOH and catalyst in a septum-sealed tube whose contents were stirred at 50 °C for 10 min, followed by stirring at room temperature for an additional 20 min. When 15 mol % of **1d** was used as the catalyst at

35 °C, an excellent yield of the desired product **6a** was obtained from MVK (**5a**) in 24 h (Table 1). Repetition of this reaction with **1a** and with **1b** at the same temperature resulted in the isolation of only trace amounts of the product **6a** after column chromatography. Subtle differences in reactions catalyzed by proazaphosphatranes have recently been observed by us[29,30a] and a rationale for these differences will be reported in due course. Higher alcohols such as *t*-butyl alcohol and 2-propanol resisted addition to (*E*)-3-penten-2-one (**3**), 2-cyclohexen-1-one (**5b**) or 4-hexen-3-one (**5d**) when reacted at 50–70 °C in the presence of up to 30 mol % of the proazaphosphtranes **1a**, **1b** or **1d**.

Table 1. The reaction of α,β–unsaturated carbonyl compounds with alcohols in the presence of **1**.

Michael Acceptor	Michael Donor	base/ mol%	reaction conditions	pro-duct	% yield	lit. yield[a]
3-penten-2-one (**3**)	MeOH	**1a**/10	50 °C; 1 h	**4b**	78	N.A.
MVK (**5a**)	MeOH	**1a**/10	50 °C; 0.5 h	**6a**	65	96[b]
2-cyclohexenone (**5b**)	MeOH	**1b**/20	50 °C; 0.5 h	**6b**	76	71[c]
(*E*)-PhCHCHCOMe (**5g**)	MeOH	**1b**/10	50 °C; 2 h	—	—	—
4-hexen-3-one (**5d**)	MeOH	**1b**/10	50 °C; 0.5 h	**6d**	96	93[d]
4-hexen-3-one (**5d**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7d**	71	N.A.
4-hexen-3-one (**5d**)	Me_3COH	**1b**/20	70 °C; 3 h	—	—	—
2-cyclohexenone (**5b**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7b**	58	N.A.
mesityl oxide (**5c**)	MeOH	**1b**/10	50 °C; 0.5 h	**6c**	79	70[e]
mesityl oxide (**5c**)	Me_2CHOH	**1b**/20	70 °C; 3 h	—	—	—
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7c**	40	N.A.
MVK (**5a**)	MeOH	**1c**/20	50 °C; 0.5 h	**6a**	61	96[b]
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1d**/20	55 °C; 7 h	**7c**	89	N.A.
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	**7c**	88	N.A.
4-hexen-3-one (**5d**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	**7d**	94	N.A.
mesityl oxide (**5c**)	Me_2CHOH	**1d**/20	70 °C; 3 h	—	—	—
MVK (**5a**)	MeOH	**1d**/10	35 °C; 24 h	**6a**	62	96[b]
MVK (**5a**)	MeOH	**1d**/15	35 °C; 24 h	**6a**	93	96[b]

Table 1 Continued. The reaction of α,β–unsaturated carbonyl compounds with alcohols in the presence of **1**.

Michael Acceptor	Michael Donor	base/ mol%	reaction conditions	pro- duct	% yield	lit. yield[a]
2-cyclohexenone (**5b**)	MeOH	**1d**/10	50 °C; 3 h	**6b**	89	71[c]

[a]Based on reactions mediated by base. [b]Kabashima, H.; Katou, T.; Hattori, H. *A ppl. Catal. A.* **2001**, *214*, 121. [c]Ref. 16b [d]Horiuchi, C. A.; Ochiai, K.; Fukunishi, H. Chem. *Lett.* **1994**, *2*, 185. [e]Lechevallier, A.; Huet, F.; Conia, J. M. *Tetrahedron* **1983**, *39*, 3317.

Allyl alcohol on the other hand reacted at 70 °C over 3 h to afford high yields of β-allyloxy carbonyl products using **1b** or **1d** (Table 1). Hence, mesityl oxide (**5c**) reacted with allyl alcohol in the presence of 20 mol % of **1b** or **1d** at 70 °C to afford **7c** in 40 or 88% yield, respectively, in 3 h. On the other hand, 4-hexen-3-one (**5d**) reacted more efficiently under similar conditions to afford the corresponding β-allyloxy ketone **7d** (Scheme 2) in 71% and 94% yield in the presence of **1b** and **1d**, respectively (Table 1). At the lower temperature of 55 °C, however, allyl alcohol also reacted very efficiently with mesityl oxide (**5c**) in the presence of **1d** to give the corresponding β-allyloxy ketone **7c** in 89% yield. This is probably due to the higher solubility of anticipated for **1d** which allows the occurrence of an efficient reaction at this relatively low temperature. Both **1a** and **1b** failed to produce any appreciable amount of the desired product under these mild reaction conditions.

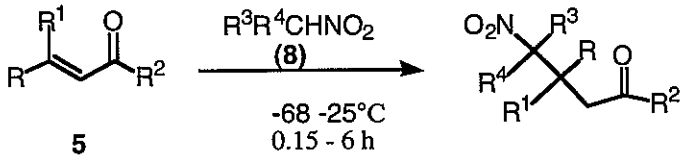
To the best of our knowledge, there is only a single report for the preparation of 4-allyloxy-4-methylpentan-2-one (**7c** in Scheme 2) and its analogues (which are valuable intermediates in ketyl-olefin radical cyclization reactions).[31] This was achieved by treating the corresponding alcohols with $CaSO_4$, allyl bromide and silver oxide for 10 h to afford the desired β-alkoxy ketone in 44% yield. Although the inability of 4-phenyl-2-but-3-enone (**5g**) to react with methanol or allyl alcohol in the presence of **1b** or **1d** under our conditions is disappointing, this result can be rationalized in terms of the resonance stability of this substrate which would be interrupted by hydroalkoxylation.

α,β-Unsaturated esters [represented by methyl acrylate (**5e**) and (*E*)-ethyl crotonate (**5f**)] reacted with methanol in the presence of 10 mol % of **1d** in 2 h to afford the β-methoxylation products, and in the latter case also the transesterified product. When reacted with 3.0 equiv of methanol in a solvent such as THF or Me_2CHCN, **5f** gave a 14:15 mixture of $MeCH(OMe)CH_2CO_2Et$ (**7f**) and $MeCH(OMe)CH_2CO_2Me$, respectively, in 83% total yield, which were inseparable upon attempted column chromatography. Reducing the amount of methanol below 3.0 equiv afforded total yields that were less than 50%. Hence, hydroxymethoxylation of α,β-unsaturated esters under our conditions is of limited practical utility because of transesterification. Mild conditions for the transesterification of esters in the presence of catalysts of type **1** have been reported previously from our laboratories.[32]

Michael addition of nitroalkanes. The Michael addition of the lower nitroalkanes nitromethne or nitropropane to MVK and 2-cyclohexeneonone **5b** catalyzed by **1a – 1d** afforded only modest product yields (Table 2). These reactions required a lower temperature (-63 °C) in order to suppress the competing facile nitroaldol reaction which becomes particularly efficient when the nitroalkane is used as the solvent.[24] By employing the Michael addition of nitromethane to mesityl oxide as a model reaction, we discovered a strong dependency of this transformation on the solvent. Because an increase in the ratio of nitromethane or its use as a solvent led to the formation of nitroaldols from the Michael adduct, we investigated several solvents for the reaction. From the first four entries in Table 2, it is seen that isobutyronitrile is the best solvent for the Michael addition of nitromethane to mesityl oxide. The same reaction of MVK with nitromethane, however, produced several products including nitroaldols and double Michael addition products as indicated by ^{1}H NMR spectroscopy. This problem was overcome by carrying out the reaction at –63 °C for 10-15

min affording a 78% yield (Table 2). Recently, the same reaction was reported to proceed in 98% yield at a higher temperature (0 °C) in the presence of the less basic charge-neutral catalyst TBD.[33] Using the reaction of nitromethane (**8a**) with mesityl oxide (**5c**) as a model, 0.1 equiv of each of the bases **1a-1d** (data for reactions employing **1a**, **1c** and **1d** not shown in Table 2) were found to promote a quantitative reaction of (*E*)-ethyl crotonate (**5f**) with $MeNO_2$ (99% isolated yield of **9j**) in *i*-PrCN. Thus this reaction is influenced more by the solvent than by the proazaphosphatrane base used. Neither **5g** nor **5h** afforded any Michael adduct upon reaction with $MeNO_2$ for up to 24 h with up to 20 mol % of **1b** in *i*-PrCN.

Scheme 3



8a: $MeNO_2$
8b: *n*-$PrNO_2$
8c: *i*-$PrNO_2$
8d: nitrocyclohexane

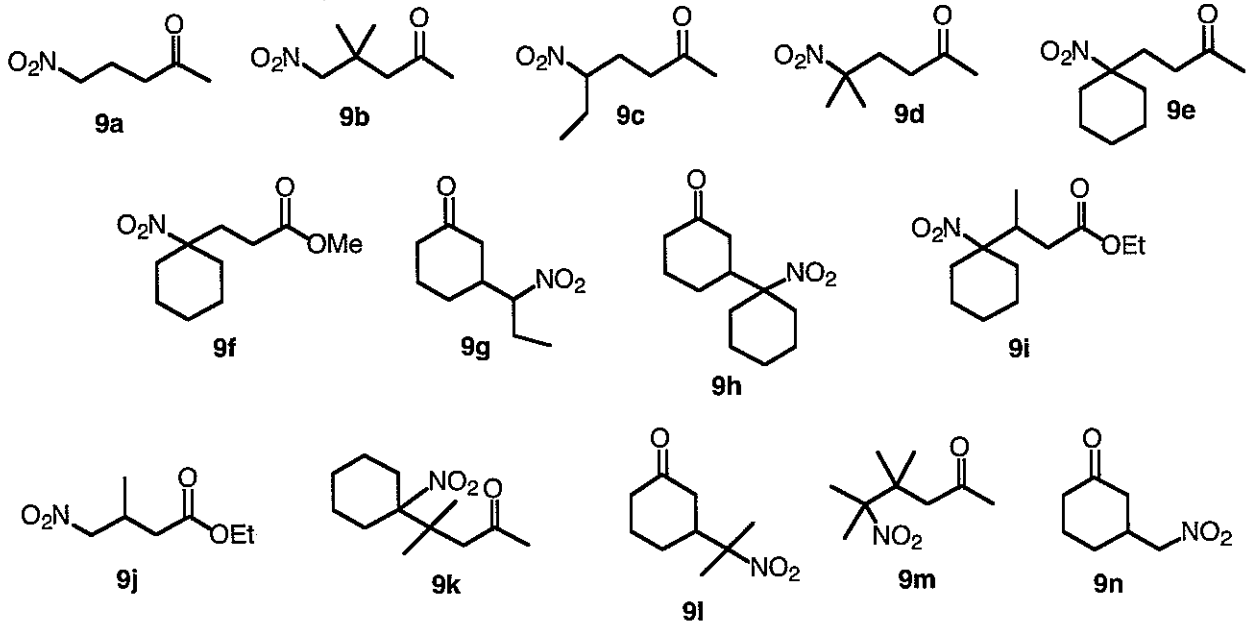


Table 2. The Michael addition of nitroalkanes to α,β-unsaturated carbonyl compounds in the presence of **1**.

Michael acceptor	Michael donor	conditions base[b]/ °C / h.	product	% yield of **9**	lit.[b] yield
mesityl oxide (**5c**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5	**9b**	99	93[c]
mesityl oxide (**5c**)	$MeNO_2$[d] (**8a**)	**1b**/RT/0.5	**9b**	95	93[c]
mesityl oxide(**5c**)	$MeNO_2$[e] (**8a**)	**1b**/RT/0.5	**9b**	91	93[c]
mesityl oxide (**5c**)	$MeNO_2$[f] (**8a**)	**1b**/RT/0.5	**9b**	92	93[c]
2-cyclohexenone (**5b**)	$MeNO_2$[d] (**8a**)	**1b**/RT/0.5	**9n**	89	99.8[g8]
MVK (**5a**)	$MeNO_2$ (**8a**)	**1b**/-63/0.15	**9a**	78	98[h]
MVK (**5a**)	*n*-$PrNO_2$ (**8b**)	**1b**/-63/0.15	**9c**	81	95[i]

Table 2 Continued. The Michael addition of nitroalkanes to α,β-unsaturated carbonyl compounds in the presence of **1**.

Michael acceptor	Michael donor	conditions base[b]/ °C / h.	product	% yield of **9**	lit.[b] yield
MVK (**5a**)	*i*-$PrNO_2$ (**8c**)	**1b**/RT/0.25	**9d**	99	95[j]
MVK (**5a**)	nitrocyclohexane (**8d**)	**1b**/RT/0.25	**9e**	93	80[k]
2-cyclohexenone (**5b**)	Me_2CHNO_2 (**8c**)	**1b**/RT/0.5	**9l**	99	100[l]
CH_2:$CHCO_2Me$ (**5e**)	nitrocyclohexane (**8d**)	**1b**/RT/4	**9f**	100	85[m]
(*E*)-ethyl crotonate (**5f**)	nitrocyclohexane (**8d**)	**1b**/RT/4	**9i**	100	NA
2-cyclohexenone (**5b**)	*n*-$PrNO_2$ (**8b**)	**1b**/-63/0.25	**9g**	71	93[i]
(*E*)-ethyl crotonate (**5f**)	$MeNO_2$ (**8a**)	**1b**/-63/0.25	**9j**	99	96[n]
2-cyclohexenone (**5b**)	nitrocyclohexane (**8d**)	**1b**/RT/1	**9h**	99	77[l]
mesityl oxide (**5c**)	nitrocyclohexane (**8d**)	**1d**/RT/1	**9k**	95°	NA
MVK (**5a**)	nitrocyclohexane (**8d**)	**1d**/RT/0.25	**9e**	99	80[n]
CH_2:$CHCO_2Me$ (**5e**)	nitrocyclohexane (**8d**)	**1d**/RT/1	**9f**	99	85[m]
(E)-ethyl crotonate (**5f**)	nitrocyclohexane (**8d**)	**1d**/RT/1	**9i**	99	NA
mesityl oxide (**5c**)	*i*-$PrNO_2$ (**8c**)	**1d**/RT/0.33	**9m**	99	14[p]

[a] Based on reactions mediated by bases. [b] The amount of base used was 10 mol % in isobutyronitrile unless stated otherwise. [c] Perrin, C.L.; Thoburn, J. D.; Elsheimer, S. *J. Org. Chem.* **1991**, *56*, 7034. [d] The solvent was THF. [e] The solvent was benzene. [f] The solvent was ether. [g] Kabashima, H.; Tsuji, H.; Shibuya, T.; Hattori, H. *J. Mol. Catal. A: Chem.* **2000**, *155*, 23. [h] Ref. 33. [i] Mdoe, J. E. G.; Clark, J. H.; Macquarrie, D. J. *Synlett.* **1998**, *6*, 625. [j] Clark, J. H.; Miller, J. M.; So, K. *J. Chem. Soc., Perkin Trans. 1.* **1978**, *9*, 941. [k] Ref. 34b. [l] Ref. 11b. [m] *J. Chem. Res. Miniprint* **1989**, *1*, 116. [n] Floch, L.; Kubán, J.; Gogová, A.; Zálupsky, P.; Jakubík, T.; Prónayová, N. *Molecules* **1996**. *1*, 175. [o] The amount of **1d** used was 20 mol %. [p] Papat, J. B.; Black, D. S. C. *Aust. J. Chem.* **1968**, *21*, 2483.

Michael additions with higher nitroalkanes, such as 2-nitropropane (**8c**) and nitrocyclohexane (**8d**), proceeded smoothly in 0.15-6 h. Our methodology constitutes a distinct improvement for Michael addition of nitrocyclohexane (**8d**) to 2-cyclohexenone (**5b**), mesityl oxide (**5c**) or (*E*)-ethyl crotonate (**5f**) which occurs quantitatively under mild conditions in 4-6 h (Table 2). Likewise, the Michael addition of 2-nitropropane (**8c**) to **5a**, **5b**, and **5c** occurred quantitatively in 0.5-3 h. Although both DBU and TMG have been reported as catalysts for these transformations,[33] reaction times of up to 48 hours are required

for either catalyst to afford the Michael adducts in only poor to modest yields.[33] Thus, proazaphosphatranes of type **1** used here serve as superior catalysts for Michael addition of nitroalkanes and especially of higher nitroalkanes.

Michael additions of nitrocycloalkanes to α,β-unsaturated esters afford intermediates that are useful in the synthesis of spirolactams.[7c] Triton B has been used for the Michael additions of nitrocyclohexane to α,β-unsaturated esters to give the corresponding Michael adducts in 64% yield.[7c] Lower yields (70%) and longer reaction times (up to 10 h) were also the case in reactions employing Amberlyst A21.[14] Our methodology gives **9e** in 99% yield in one hour at room temperature in the presence of **1d**. Our approach also improves on a reported process in which 1-nitrocyclohexene was reacted with α,β-unsaturated esters in methanol in the presence of $NaBH_4$ to afford Michael addition products (e.g. **9f**) in 62-95% yield over 24 h.[34] It is worth mentioning that the procedure and the work-up in that reported procedure[34] is cumbersome compared with ours.

Michael addition of $Me_3CCH{:}NCH_2CO_2Me$. The reaction of the title Schiff's base was found to proceed smoothly in the presence of 0.1 equiv of **1b** (Scheme 4 and Table 3). When 10 mol % of **1d** was employed, the conversion obtained for the reaction of methyl acrylate (**5e**) with $Me_3CCH{:}NCH_2CO_2Me$ was found to be equal to that employing **1b** within experimental error. Although base-catalyzed reactions of this type have been reported previously using Et_3N and DBU, the formation of the Michael adduct rather than cycloaddition product depended on the presence of Li^+.[21,22] The efficiency of bases of type **1** in this reaction is demonstrated by their ability to induce a clean Michael addition of the imine with various α,β-unsaturated compounds in the absence of Li^+. Hence, methyl crotonate (**5i**), methyl acrylate (**5e**), mesityl oxide (**5c**), 2-cyclohexenone (**5b**), (*E*)-3-

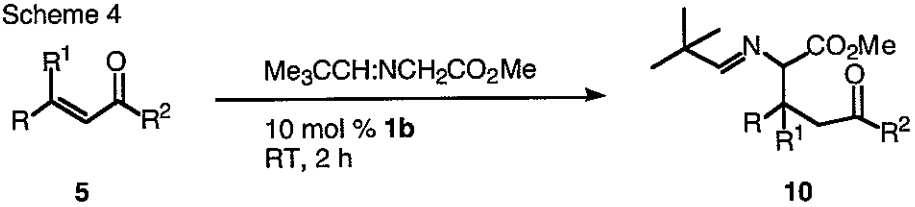
pentenone (**3**), dimethyl maleate (**5h**), and (*E*)-4-phenyl butenone (**5g**) afforded the corresponding products in 72-97% yield (Table 3).

Table 3. Michael addition of $Me_3CCH{:}NCH_2CO_2Me$ in the presence of **1b**.

Michael acceptor	yield (*anti:syn*)[a] of **10x**[b]	lit. yield[c]
methyl acrylate (**5e**)	72	N.A.[d,e]
methyl crotonate (**5i**)	76 (9:1)	77 (single, anti)[e]
mesityl oxide (**5c**)	86	N.A.
2-cyclohexenone (**5b**)	97 (single)	N.A.
(*E*)-3-penten-2-one (**3**)	85 (7:1)	80 (single, anti)[e]
dimethyl maleate (**5h**)	94 (single)	99 (single, anti)[e]
(*E*)-4-phenyl-3-buten-2-one (**5g**)	91 (single)	97 (single, anti)[e]

[a]Determined by ^{1}H NMR integration based on a comparison with literature spectra.[22] [b]Where **x** is the letter index of the corresponding Michael acceptor **5** except in the case of the fifth entry where the product is **10j**. [c] Based on reactions mediated by bases. [d]Isolated as a mixture of products. [e]Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.

Scheme 4



5 **10**

b: R = H, R^1, R^2 = $(CH_2)_3$
c: R = R^1 = R^2 = Me
e: R = R^1 = H, R^2 = OMe
g: R = H, R^1 = Ph, R^2 = Me
h: R = H, R^1 = CO_2Me, R^2 = OMe
i: R = H, R^1 = Me, R^2 = OMe
j: R = H, R^1 = R^2 = Me

Chelation has consistently been cited as a possible reason for the higher diastereoselectivities observed in the Michael addition reaction of the *N*-lithiated azomethine ylides (or lithium enolates) produced upon deprotonation of the imines.[21] For reasons that are not presently clear, we observe high diastereoselectivity and high yields (Table 3) with (*E*)-3-

penten-2-one (**2**), methyl crotonate (**5i**), dimethyl maleate (**5h**) and (*E*)-4-phenyl-3-buten-2-one (**5g**) despite the absence of a metal ion. It is interesting that the reaction of methyl acrylate with $Me_3CCH{:}NCH_2CO_2Me$ in the presence of DBU and LiBr reported by other investigators[21] gives only the double Michael adduct in 71% yield whereas our method affords the desired mono adduct in 72% yield.

Conclusions

We have shown that proazaphosphatranes are efficient catalysts for the Michael addition of primary alcohols, higher nitroalkanes and Schiff's bases to α,β-unsaturated carbonyl compounds. However, Michael addition of alcohols to unsaturated esters is hindered by competing transesterification. The Michael addition of nitroalkanes was found to have limited success with nitromethane owing to its nitroaldol reaction with the products formed from MVK and cyclohexenone. Michael addition of the Schiff's base $Me_3CCH{:}NCH_2CO_2Me$ proceeds smoothly with high diastereoselectivity in the absence of a chelating metal ion. As can be seen from Tables 1 – 3, to the best of our knowledge our product yields exceed those in the literature by at least 4% in eleven cases, are reasonable to excellent in fourteen cases not reported in the literature, are within ± 3% in nine cases and are worse by 4% or more in eight cases.

Experimental Section

All reactions were conducted under nitrogen. Isobutyronitrile (Aldrich) was dried over 4 Å molecular sieves and stored under nitrogen. The unsaturated compounds (Aldrich) were used as received. The melting points of the products are uncorrected. The bases **1a**,[23a] **1b**[23b] and **1c**[23c] were prepared according to our previously reported methods. $Me_3CCH{:}NCH_2CO_2Me$ was prepared according to a published procedure.[22]

General procedure for the Oxa-Michael addition of alcohols to α,β-unsaturated substrates. The required weight of the proazaphosphatrane **1** was weighed in a small test tube under nitrogen. To this was added 3.0 mL of the alcohol and then the colorless solution was heated in an oil bath that had been preheated to the required temperature (Table 1) under stirring for 2-3 minutes. The Michael acceptor (2.00 mmol) was then added in one portion and stirring was continued for the time periods specified in Table 1. At the end of the reaction time, the reaction mixture was added to 20 mL of brine and then extracted with 3 x 30 mL of ether. The extract was dried over anhydrous sodium sulfate and the volatiles were removed in *vacuo* to afford the crude alkoxy ketones that were purified (when necessary) as detailed below. Alternatively, the reaction mixture was allowed to cool to room temperature, loaded onto a small silica gel column and eluted with 70 mL of 5% methanol in ether. Removal of the volatiles under reduced pressure afforded the crude alkoxy ketones that (when necessary) were also purified. Products requiring purification were purified by elution on a silica gel column using ether in hexane. The ratio of ether was increased in 5% increments and the products eluted at 40% ether in hexane.

General procedure for the Michael addition of nitroalkanes to α,β-unsatuarated substrates. The base (0.2 mmol) was weighed into a small test tube under nitrogen and a small stirring bar was added. To this was added 2.0 mL of the appropriate solvent (Table 2) followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 min at the temperature given in Table 2 after which 2.0 mmol of the Michael acceptor was added in one portion. After stirring had been continued for the required time, the reaction mixture was loaded onto a small silica gel column and eluted with 5% MeOH in ether. Removal of the solvent under reduced pressure afforded the crude product that was then fractionated on a

silica gel column using an eluent system made up of hexane and EtOAc, wherein the EtOAc was increased in concentration by 5% increments. The products eluted with 20% EtOAc in hexane.

General Procedure for the Michael addition of $Me_3CCH{:}NCH_2CO_2Me$ to α,β-unsatuarated substrates. The base (0.2 mmol) was weighed in a small test tube under nitrogen and a small stirring bar was added. To this was added 2.0 mL of isobutyronitrile followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 minutes at room temperature after which 2.0 mmol of the Michael acceptor was added in one portion and stirring was continued for 2 h. The reaction mixture was added to 20 mL of ethyl acetate and then the mixture was washed with 10 mL of water and 10 mL of brine. The organic layer was dried over anhydrous sodium sulfate and the volatiles were removed under reduced pressure to afford the Michael adduct. However, these compounds were too labile to be purified by column chromatography. This result is in accord with previous reports by Yamamoto *et al.*[21a] and Kanemasa and co-workers.[21b] The Michael adducts were essentially NMR-pure and only the ^1H NMR and ^{13}C NMR spectra were recorded.

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SUPPLEMENTARY MATERIALS

^{1}H and ^{13}C NMR Data

4b: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1988**, *53*, 2199.

6a: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1988**, *53*, 2199.

6b: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1985**, *50*, 4173.

6c: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron* **1984**, *40*, 315.

6d: The ^{1}H NMR spectrum compared favorably with that reported in *J. Organomet. Chem.* **1975**, *93*, 33.

7c: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1995**, *60*, 872.

7d: ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3 H J = 7.4 Hz), 1.18 (d, 3 H J = 6.3 Hz), 22.38-2.48 (overlapping region, 3 H), 2.73 (dd, 1 H), 3.92-4.02 (overlapping region, 3 H), 5.16 (dd, 2H), 5.90 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 210.0, 135.1, 116.6, 71.5, 69.7, 49.6, 37.2, 19.9, 7.6.

9a: The ^{1}H NMR spectrum compared favorably with that reported in *J. Chem. Soc. Perkin Trans. 1*, **1992**, *5*, 601.

9b: The ^{1}H NMR spectrum compared favorably with that reported in *J. Chem. Soc., Perkin Trans. 1* **1990**, 457.

9c: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1996**, *61*, 3209.

9d: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1996**, *61*, 3209.

9e: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron Letters* **1996**, *37*, 8027.

9f: The ^{1}H NMR spectrum compared favorably with that reported in *J. Chem Res. MiniPrint* **1989**, *1*, 116.

9h: Reported in *J. Org. Chem.* **1987**, *52*, 1601 but no NMR data were given. The ^{1}H NMR ($CDCl_3$): δ 1.54-1.21 (overlapping region, 4 H), 1.81-1.56 (overlapping region, 6 H), 1.958 (d, 1 H), 2.137 (m, 4 H), 2.5 (m, 4 H). ^{13}C NMR ($CDCl_3$: δ 209.6, 94.0, 47.0, 42.5, 41.0, 32.0, 31.5, 31.0, 25.7, 24.7, 24.6, 24.1, 22.3, 22.3. HRMS Calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1365.

9i: ^{1}H NMR ($CDCl_3$): δ 0.95 (d, 3H), 1.32 – 1.47 (overlapping region, 6H), 1.68 – 1.72 (overlapping region, 5H), 2.05 (m, 1H), 2.44 (m, 4H), 4.13 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 172.3, 94.2, 60.7, 38.9, 36.5, 31.9, 31.4, 22.3, 14.7, 14.2. HRMS Calcd. for $C_{12}H_{22}NO_4$ 244.1549, found $MH^+/2$ 244.1545.

9j: The ^{1}H NMR spectrum compared favorably with that reported in *Synthesis* **1989**, 953.

9k: ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 6H), 1.15-1.28 (overlapping region, 3H), 1.43-1.82 (overlapping region, 5H), 2.15 (s, 3H), 2.47(s, 2H), 2.53 (broad d, 2H). ^{13}C NMR ($CDCl_3$): δ 22.38, 22.83, 24.69, 29.31, 33.14, 40.23, 48.37, 99.09, 207.76.

9l: Reported in *J. Org. Chem.* **1987**, *52*, 1601 but no NMR data were given. ^{1}H NMR ($CDCl_3$): δ 1.20-1.39 (overlapping region, 2H), 1.44 (s, 3H), 1.47 (s, 3H), 1.50-1.71 (overlapping region, 2H), 1.98-2.39 (overlapping region, 5 H). ^{13}C NMR ($CDCl_3$): δ 19.79,

22.66, 23.08, 24.35, 25.88, 40.68, 42.55, 46.52, 90.70, 208.90. HRMS: Calcd for $C_9H_{15}NO_3$: 185.10519, found: 185.10557.

9m: The ^{1}H NMR spectrum compared favorably with that reported in *J. Aust. Chem.* **1968**, 2483.

9n: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron* **1996**, *52*, 8209.

9o: The ^{1}H NMR spectrum compared favorably with that reported in *J. Chem. Res. Miniprint* **1989**, *1*, 116.

CHAPTER 9. CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

In this research, we have shown the utility of the azaphosphatrane cation as a weakly interacting counterion with nitrate. This has been demonstrated with the use of an azaphosphatrane nitrate as a catalyst/promoter, both homogenously and heterogeneously. The specific role of nitrate ion as a promoter has been illustrated in both aza and thia-Michael reactions and in Strecker-type three component one-pot couplings. The Strecker reaction was further extended through the use of acetic anhydride as an amine protecting agent, thereby providing a four component one-pot coupling reaction.

The utility of azaphosphatrane cations as weakly coordinating counterions for nitrate demonstrated in this report, may be extendable to other anions. With the exception of perchloric acid, other strong acids behave as weak acids in acetonitrile.[1] Thus the corresponding anions of these acids are much more basic in acetonitrile than in water. In addition to nitrate, anions such as sulfate, phosphate, carbonate, and fluoride could prove to be useful catalysts in the presumable absence of significant cation-anion interactions. Transformations in which such anions may be catalytically useful are Michael reactions of amines and thiols with various acceptors,[2] the oxidation of thioethers,[3] and as polarization agents in Diels-Alder reactions.[4]

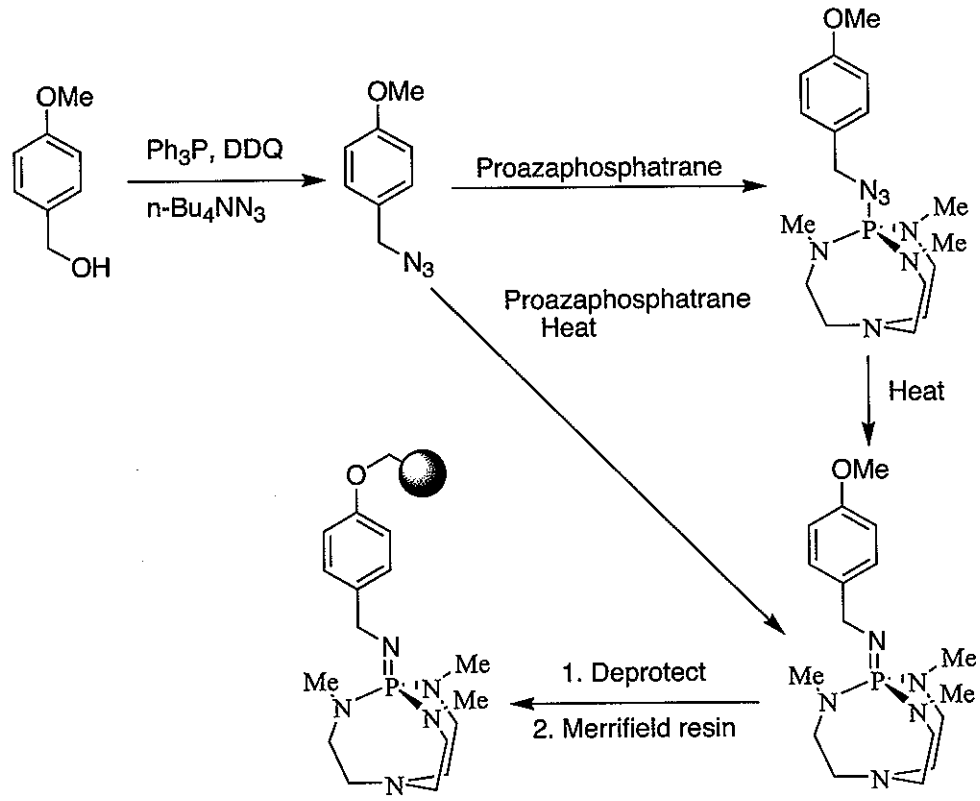
In this thesis a polymer-supported proazaphosphatrane earlier postulated to be an iminoproazaphosphatrane was shown to be an azidoproazaphosphatrane. The polymer-supported azidoproazaphosphatrane showed extraordinary selectivity as a catalyst for the oxa-Michael reaction in the presence of usually sensitive functionalities. The catalyst recycles well and is also easily regenerated.

Polymer-bound azidoproazaphosphatranes have been shown earlier by our group to be useful air-stable catalysts in the acetylation of alcohols with vinyl acetate,[5] and in oxa-Michael addition, as described in this thesis. These catalysts could prove useful in other reactions where traditional strong bases are used either catalytically or stochiometrically. The air-stable nature of azidoproazaphosphatranes could greatly simplify organic methodologies, while its polymer-supported form would make product isolation easier and less time consuming. Reactions wherein carbonyl substrate activation occurs are obvious candidate reactions, such as the nitroaldol (Henry) reaction,[6] the Michael addition of malonates and malonate derivatives or of nitroalkanes,[6c] and the synthesis of β-hydroxy nitriles via the coupling of aldehydes with acetonitrile.[6a,7] It may even be possible to dehydrate these compounds *in situ* to produce α,β-unsaturated nitriles directly in a one-pot cascade transformation.[8]

It would also be interesting to investigate the factors and conditions governing the evolution of nitrogen from azidoproazaphosphatranes in their conversion to iminoproazaphosphatranes. The azidoproazaphosphatranes encountered in this work were surprisingly stable.

The basicity of iminoproazaphosphatranes has been investigated previously, leading to an estimated pK_a of about 22.[9] A relatively simple synthesis of iminoproazaphosphatranes, as illustrated in Scheme 1 may open the door to a new non-nucleophilic base that is useful both stochiometrically and catalytically. If useful, this new iminoproazaphosphatrane should be attached to a polymer support through deprotection of the phenol and attachment to Merrifield resin.

Scheme 1 Synthesis of imimoprozaphosphatrane



After earlier considerable efforts by others in the group, a proazaphosphatrane has successfully been chemically immobilized on a polymer support herein. This new heterogeneous catalyst bearing a trivalent phosphorus has been applied successfully to the trimerization of isocyanates to isocyanurates and to the synthesis of diaryl ethers.

In the present research, proazaphosphatranes have proven to be useful catalysts in reactions of aldehydes and ketones with silicon reagents in the use of trimethylsilylcyanide for efficiently producing cyanohydrins and protected cyanohydrins. These catalysts also allow commercially available poly(methylhydrosiloxane) to be utilized in the reduction of aldehydes and ketones. In these reactions, the proazaphosphatrane is suggested to expand the coordination sphere of silicon, thereby producing reactive intermediates that operate under mild conditions.

The synthesis of a polymer-bound proazaphosphatrane described herein also opens up many possibilities for future work. The diverse chemistry of homogenously catalytic polymer-unbound proazaphosphatranes previously described[10] should be explored with the polymer-bound proazaphosphatrane, as well as the reactions described in the previous paragraph. Important examples of catalytic reactions homogeneously catalyzed by proazaphosphatranes as described by others include the dehydration of aldoximes to nitriles,[11] and the silylation[12] and desilylation[13] of alcohols. The use of the polymer-bound proazaphosphatrane as a solid-supported ligand in palladium-catalyzed coupling reactions, such as the Suzuki[14] and Stille[15] couplings, are also worthy of investigation. The potential for recovery of the expensive palladium from spent solid catalyst would greatly increase the economic feasibility of widespread use and possible commercial application of these generally useful transformations.

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