Pergamon

SCIENCE DIRECT®

TETRAHEDRON

Tetrahedron 59 (2003) 7819–7858

Tetrahedron report number 652

Proazaphosphatranes: a synthesis methodology trip from their discovery to vitamin A

John G. Verkade[a,*] and Philip B. Kisanga[b]

[a]*Department of Chemistry, 1605 Gilman Hall, Iowa State University, Ames, IA 50011-3111, USA*
[b]*Syracuse Research Center, Albany Molecular Research Inc., 7001 Performance Drive, North Syracuse, NY 13212, USA*

Received 24 June 2003

Contents

Keywords: proazaphosphatranes; azaphosphatranes; nonionic bases; catalysis.

* Corresponding author. Tel.: +1-515-294-5023; fax: +1-515-294-0105; e-mail: jverkade@iastate.edu

doi:10.1016/S0040-4020(03)01204-3

1. Introduction

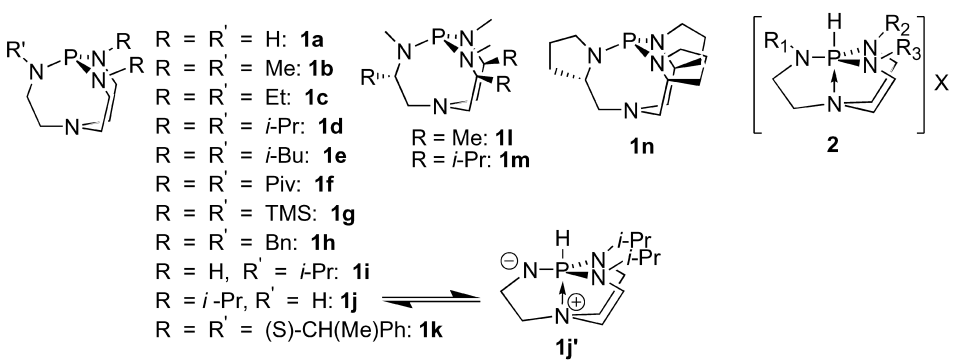
Several reviews have appeared in recent years on the synthesis and chemistry of proazaphosphatranes.[1] In this report we emphasize aspects of this chemistry that will hopefully pique the interest of organic chemists, particularly those in the community who are attracted to synthesis methodology.

Proazaphosphatranes, such as those of type **1**, have an aesthetically pleasing prolate cage framework in which one end of the 'football' is flattened owing to van der Waals interactions among the methylene protons adjacent to the axial nitrogen.[1] The first proazaphosphatrane, **1a**, was synthesized in our laboratories a little more than a decade ago.[2] In contrast to proazaphosphatranes, azaphosphatranes have oblate frameworks that feature a transannular N→P bond in the 3.3.3.0 tricyclic cage as in the case of cations of type **2** in which the PN_3 end of the proazaphosphatrane football is flattened and its bottom is puckered upward. Induction of transannulation is not restricted to a proton because fluoronium and chloronium cations, for example, are also capable of stabilizing this configuration.[1] The transition from a proazaphosphatrane to an azaphosphatrane configuration can be effected very gradually through a series of neutral stable 'quasiazaphosphatranes' that have been structured by X-ray analysis (Scheme 1).

The ca. 3 Å bridgehead–bridgehead distance in a proazaphosphatrane thus shortens gradually over a series of 'quasiazaphosphatranes' to about 2 Å in azaphosphatranes. Proazaphosphatranes were accidentally discovered to be exceedingly strong nonionic Bronsted and Lewis bases. The original motivation for synthesizing them was to use them as 'double-ended' ligands for connecting metal species via the bridgehead atoms into organometallic polymers. This goal was never realized, however, owing to the poor ligation properties of the bridgehead nitrogen that is constrained to adopt a trigonal geometry in **1**. We were fascinated to discover, however, that the strongest site of Bronsted basicity in proazaphosphatranes is the phosphorus atom and not one of the nitrogens. Moreover, the P–H moiety in **2** required *t*-BuO^- for efficient deprotonation!

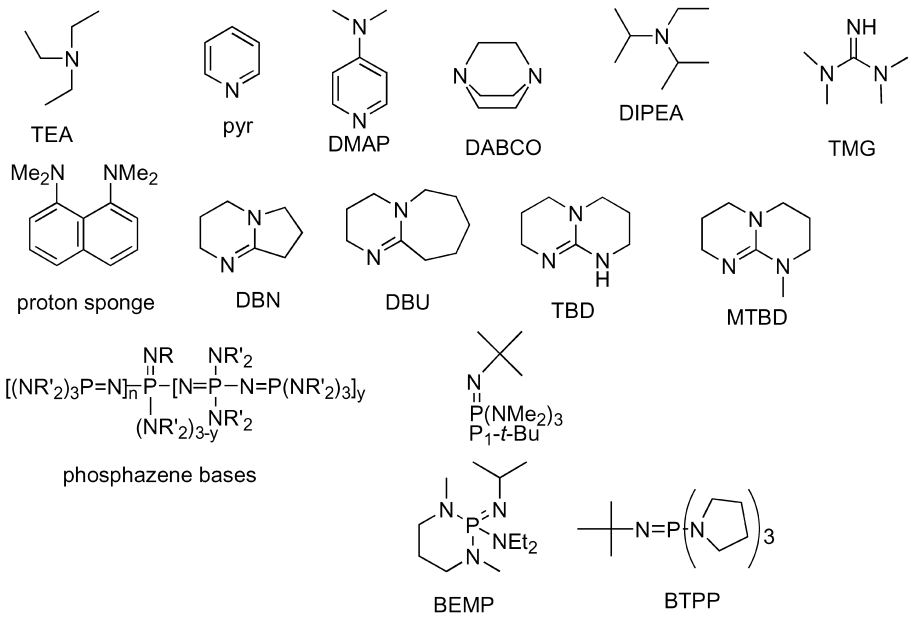
Nonionic bases have been used by organic chemists for generations. Among the more or less routinely used members of this class of bases are those shown below. Proazaphosphatranes are unique in that, unlike all of the commonly utilized nonionic bases (including the phosphazene series), proazaphosphatranes become protonated on their phosphorus atom rather than on one of their nitrogen atoms.

Nonionic nitrogen bases have been found to be extremely useful in transformations such as dehydrohalogenations,[3] the Henry reaction,[4] silylations[5] and alcohol acylations,[6] to name but a few. In the last decade, proazaphosphatranes have become valuable in an ever-growing list of transformations. Noteworthy is our observation that this class of bases, together with the phosphazene bases, are closing the gap between ionic and nonionic bases in applications to stoichiometric and catalytic reactions because of the extraordinary basicity[7] and relatively weak nucleophilicity



Scheme 1.

of non-ionic bases. With pK_a values spanning a large range (17–42) proazaphosphatranes and phosphazenes facilitate reactions previously restricted to ionic bases such as NaH, potassium *t*-butoxide, LDA and NaHMDS. During most reactions involving proazaphosphatranes (both stoichiometric and catalytic) the putative protonated bulky cation **2** is formed and consequently anions thus produced are essentially naked and more reactive. Organic transformations facilitated by proazaphosphatranes also tend to be more selective, which aids product purification. These transformations are also generally quite devoid of side reactions (which often accompany reactions of ionic bases) and so it is not uncommon for crude products to exceed 95% purity.



A considerable number of proazaphosphatranes of type **1** have been synthesized to date[1a] and the usefulness of **1b**,[1] **1d**[8] and **1e**[9] in particular have resulted in their commercial availability from Aldrich Chemical Co. Although these compounds are rather closely analogous in structure, they can differ considerably in their efficacy as catalysts and as stoichiometric bases. It should be stated at this point, however, that in many cases, further exploration is required to identify the best proazaphosphatrane to employ. In addition to proazaphosphatranes **1a**–**1j**, the chiral proazaphosphatranes **1k**–**1n** have also been reported although they do not as yet appear to possess significant ability to act as catalysts for asymmetric induction.[1a]

2. Synthesis of proazaphosphatranes

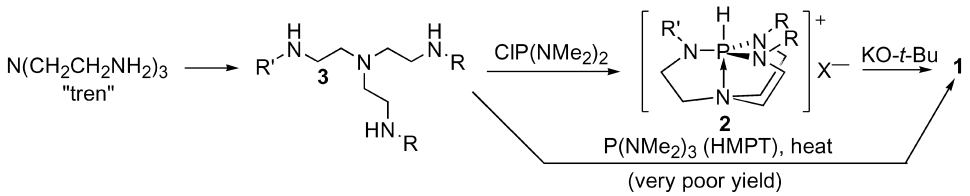
The synthesis of proazaphosphatranes is accomplished via a generally short sequence of reactions that starts with tris(2-ethylamino)amine ('tren') which is converted into the corresponding mono-, di- or trialkylated tetramine[1,2,8,9] which is then converted to an azaphosphatrane of type **2**. Product **2** is then deprotonated to a proazaphosphatrane by a strong ionic base, typically potassium *t*-butoxide (Scheme 2). Early attempts at converting the alkylated tetramine directly into the corresponding proazaphosphatrane met with limited success[2a] and these efforts were reviewed earlier.[1b]

2.1. Synthesis of monosubstituted proazaphosphatranes

Monoalkylated proazaphosphatranes are characterized by higher reactivities and basicities perhaps due to their ability to exist in a tautomeric amide form. As a result of this highly active amide nitrogen, monosubstituted proazaphosphatranes are quite unstable to ring opening oligomerization. This reaction has been discussed for the disubstituted analogue[10] which is relatively stable (see Section 2.2). So far, only one member of the title group has succumbed to synthetic efforts, namely, **1i**.[9] The synthesis of this compound was achieved by reacting tris(2-aminoethyl) amine (tren) with acetone in the presence of a sodium acetate/acetic acid buffer. By carefully controlling the reaction temperature, addition time and the ratio of acetone to tris(2-ethylamine), conversion to the mono-imine was maximized whereupon it was reduced with sodium borohydride giving a mixture of the mono-, di- and trisubstituted tren derivatives which were separated via a sodium iodide complexation technique.[9,10] The pure monosubstituted tren thus obtained was cyclized with bis(dimethylamino)chlorophosphine to afford the corresponding azaphosphatrane salt **2**, which was deprotonated with potassium *t*-butoxide to afford **1i** in the unimpressive overall yield of 2%. Efforts are underway to create more stable analogues of **1i** with more sterically bulky tren derivatives.

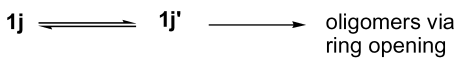
2.2. Synthesis of disubstituted proazaphosphatranes

Only one member of this class of proazaphosphatanes has been successfully prepared to date, namely, **1j**.[10] This was achieved by preparing *N*,*N*′-diisopropyl tren in a process



Scheme 2.

analogous to that described above for mono-isopropyl tren.[9] This intermediate was reacted with hexamethylphosphoramide in the presence of triflic acid to afford the corresponding azaphosphatrane triflate which was then deprotonated with potassium *t*-butoxide to afford the free base **1j**. This base is unstable to the atmosphere owing to oxidation and also apparently to a transaminative ring opening oligomerization, perhaps initiated by the nucleophilic amide in tautomer **1f′** in Scheme 3. However, the base is stable for months when stored at 4°C under an inert atmosphere.



Scheme 3.

2.3. Synthesis of trisubstituted proazaphosphatranes

This class of proazaphosphatranes has been by far the most studied because of their stability. The most often used method for their preparation[1,8] (depicted in Scheme 2) is the pathway involving the stable intermediate salt **2**X (X= anion). Proazaphosphatrane **1g** (R=TMS) was prepared via the route shown in Scheme 4.[11]

2.4. Synthesis of chiral proazaphosphatranes

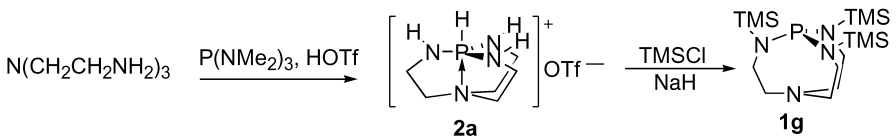
Three nonracemic proazaphosphatranes have been reported to date. Proazaphosphatranes **1l** and **1m** were prepared by similar routes in which the chiral tetramines were obtained from amino alcohols[12] as shown in Scheme 5. However, the deprotonation of the azaphosphatranes using a number of bases such as NaH and NaHDMS proved difficult. An estimated 70% conversion was realized using potassium *t*-butoxide in acetonitrile.[13]

For the preparation of chiral **1k**,[14] nitrilotriacetic acid was condensed with 3 equiv. of (*S*)-methylbenzylamine to afford the corresponding triamide which was reduced with LAH to give the expected tetramine. Proazaphosphatrane **1k** was made from the tetramine via the additional two steps shown in Scheme 2 for analogous proazaphosphatranes.

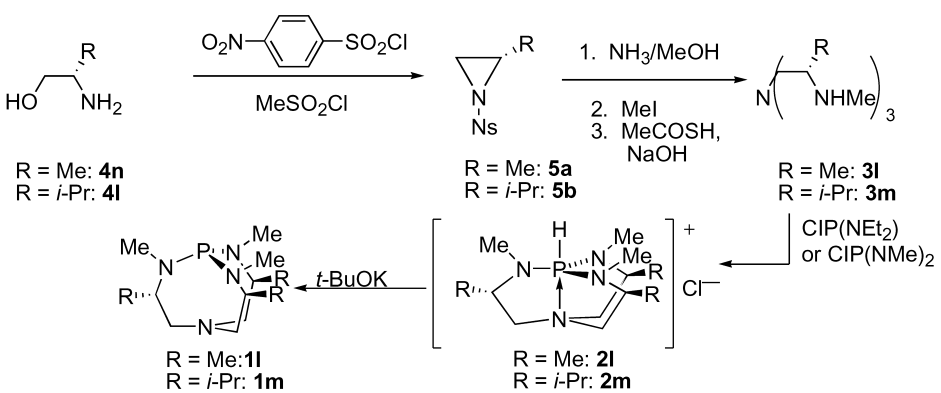
The synthesis of the chiral proazaphosphatrane **1n**[15] was achieved in seven steps starting from proline as shown in Scheme 6. Conversion of **3n** to **1n** followed that in Scheme 2.

3. Reactivity of proazaphosphatranes

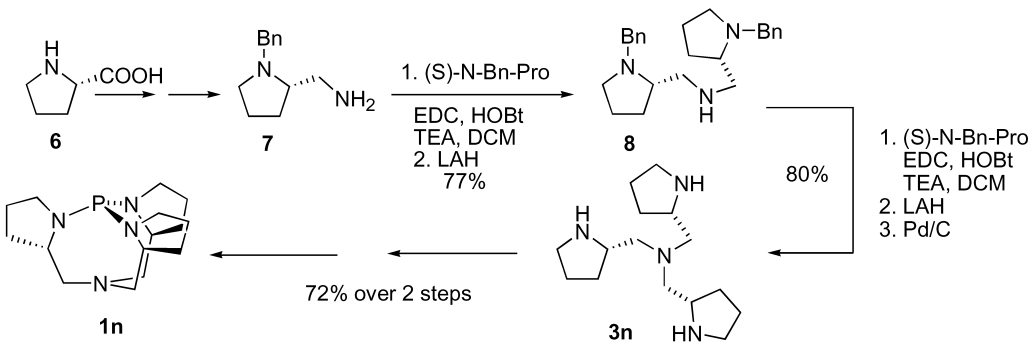
Proazaphosphatranes **1** are highly basic compounds with pK_a values for their protonated forms **2** of about 32–34 units.[7a] The strong basicity of these compounds has been attributed to their ability to undergo facile transannulation,[1,2] as has been verified by X-ray crystallographic experiments.[1] Computer modeling studies[16] demonstrate that the P–N_{ax} distance in **2** (ca. 2.0 Å) is considerably shorter than the sum of the van der Waals radii of these atoms (ca. 3.4 Å) but somewhat longer than a P–N covalent bond distance (ca. 1.85 Å). Unlike phosphazene bases, which protonate on a P=NR nitrogen and delocalize the positive charge to other



Scheme 4.



Scheme 5.



Scheme 6.

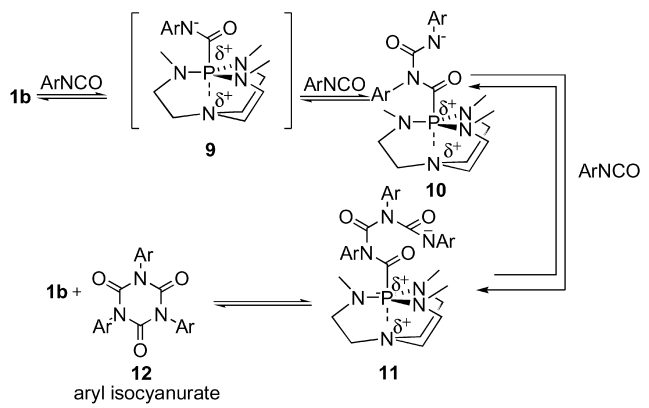
P–NR_2 nitrogens in the molecule,[7a,17] proazaphosphatranes protonate on phosphorus (**2**) which also allows positive charge delocalization to the nitrogens.[1,2]

Proazaphosphatranes combine with oxygen to form the corresponding oxides[11,18] and with water to afford the corresponding hydroxide, albeit[8,19] in rather slow reactions. Proazaphosphatranes also react with sulfur and organic azides to give the corresponding sulfides[2d,11] and iminophosphoranes,[20] respectively. The latter compounds, though somewhat less basic than the parent proazaphosphatranes, also behave as strong nonionic bases and so their reactions will be included in this report.

4. Application of proazaphosphatranes in nucleophilic reactions

4.1. Trimerization of isocyanates

This catalytic reaction (shown in Scheme 7) which occurs rapidly and exothermically at room temperature, was among the first discovered for proazaphosphatranes.[21] The isocyanurate products are highly useful activators in the industrial polymerization of ε-caprolactam to nylon-6 with low unreacted monomer content and highly stable melt viscosity. The speed of the trimerization decreases with the catalyst order **1d**>**1b**>**1c**, and under the same conditions the acylic analogue $P(NMe_2)_3$ produces only low yields of the dimer, an undesirable impurity in the product isocyanurate, which is not detected when proazaphosphatranes are used.[21]



Scheme 7.

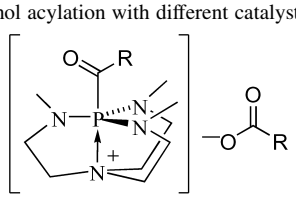
For Lewis bases known to catalyze this reaction, it has been proposed that their activity depends on their basicity and/or the stability of zwitterionic intermediates.[21] In the case of **1b**, both ^{31}P NMR and mass spectrometric evidence for the first intermediate in Scheme 7 allowed us to formulate with some confidence the pathway shown in this scheme.

4.2. Acylation of alcohols

Although the acylation of alcohols has been extensively studied and there are numerous commercially available catalysts for this transformation, reactions that proceed with high yields for highly-hindered alcohols continue to be of considerable interest. Traditional methods for this reaction include those using acetic anhydride or acetyl chloride.[22] Newer reactions have appeared, including those utilizing tributylphosphine, 4-pyrrolidinopyridine (PPY) and DMAP, the last apparently being the most popular base. The toxicity of DMAP and the low flash-point of tributylphosphine are disadvantages of these reagents.

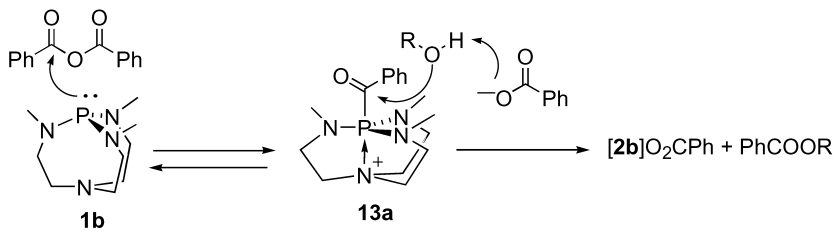
Proazaphosphatrane **1b** efficiently catalyzes the acylation of hindered alcohols affording the desired products in excellent yields with only a 10% molar excess of the acylating agent. Under similar conditions, both DMAP and tributylphosphine require a 50% molar excess of the acylating reagent.[23] For example, **1b** gave 99% conversions to acylated and benzoylated (±)-menthol in NMR experiments, whereas under similar reaction conditions, DMAP, DBU, tributyl-phosphine and the phosphazene base P_4-*t*-Bu {*t*-BuN=P[N=P(NMe_2)$_3$]$_3$} gave the inferior results shown in Table 1. Although P_4-*t*-Bu is much more basic

Table 1. (±)-Menthol acylation with different catalysts



13a: R = Ph
13b: R = Me

Entry	Catalyst	Conversion (%)
1	DMAP	76
2	Bu_3P	74
3	P_4-*t*-Bu	49
4	DBU	<1



Scheme 8.

than **1b**, it has a lower reactivity, which is probably associated with this catalyst's reactive site (i.e., the *t*-BuN═P nitrogen) which is quite different from the phosphorus in proazaphosphatranes. We suppose that the P→C═O moiety in the intermediate acylium adducts **13a** and **13b** is more reactive than the corresponding N→C═O moiety involving the *t*-BuN═P nitrogen in P_4-*t*-Bu.

Since acetic anhydride and pyridine are known to form a small but detectable amount of *N*-acylated intermediate in an equilibrium reaction,[23] acylation was attempted in pentane using $P(NMe_2)_3$ or NEt_3 as promoters. However, <1% of the acylation product was realized,[23] making it unlikely that **1b** is *N*-acylated in our acylations. Evidence for P-acylation of **1b** to give intermediate **13a** was supported by ^1H, ^{13}C and ^{31}P NMR spectroscopy, and VT NMR experiments on these nuclei showed that **13a** is favored at low temperatures.[23] The relatively high percentage of **13a** in equilibrium with **1b** in Scheme 8 at room temperature may be due to the stabilizing effect of at least partial transannular bond formation.

We believe that the extensive delocalization of positive charge among the nitrogens in cations **13a** and **13b** (as in cation **2**) permits substantial nakedness of the ion pair, thereby making its anion more available for the deprotonation step in (Scheme 8) and the acyl group more vulnerable to nucleophilic attack by RO^- in the general base catalysis portion of this scheme.[23] This mechanism is analogous to that proposed for acylations involving DMAP.[24] Remarkable is the observation that the extraordinary basicity of **1b** in this apparently kinetically controlled reaction does not result in its premature protonation and death as a catalyst.

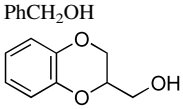
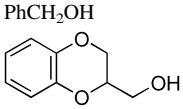
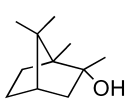
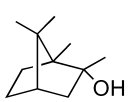
Examples of acylation reactions mediated by proazaphosphatranes are shown in Table 2.

Iminophosphoranes such as **16a** and **16b** (reactions (1) and (2)) are also highly effective homogeneous catalysts for selectively acylating primary alcohols in the presence of secondary alcohols when reacted with enol esters (namely, (P)**16a**; reaction (3)).[25] [This process is also promoted by polymer supported **16a** and its corresponding acyclic analogue (P)**16b** (reaction (4)) derived from HMPT (hexamethylphosphoramide)].

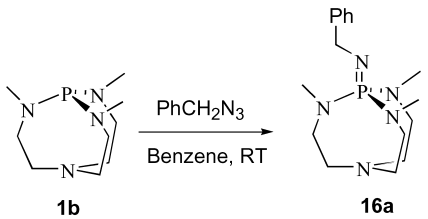
Alcohols are typically completely acylated in 8–17 h except for geraniol (**17a**; reaction (5)) which required 38 h to afford **17b** (94% isolated yield). These iminophosphoranes were found to be compatible with acid-labile functionalities as in ketal **14a** in Table 2 which was acylated (99%) in 15 min and epoxy alcohol **18a** (reaction (6)) which was acylated (99%) by vinyl acetate in the presence of **16a**. Furthermore, the chiral oxazoline **19a**, a disulfide and a TBDMS-protected alcohol survived well.[25] As with phosphazene bases such as P_4-*t*-Bu, the acylium adduct intermediate in these reactions with our iminophosphoranes probably contains a P═NR→C═O moiety. It is worth mentioning that a process using $Sc(OTf)_3/Ac_2O$ was reported to afford multiple products with **17a** and related substrates.[26]

Polymer-supported iminophosphoranes (P)**16a** and (P)**16b** are also effective for acylating alcohols using vinyl acetate, although reactions employing (P)**16b** were found to be more sluggish.[25] Thus, for example, **16a** catalyzed the acylation of benzyl alcohol (99%) in 8 h (whereas (P)**16b** gave a similar yield in 21 h). Catalyst (P)**16a** also facilitated acylation of the

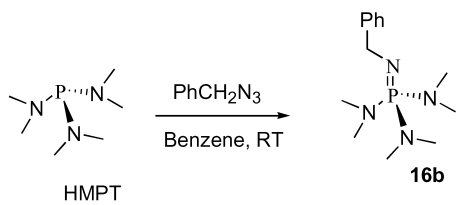
Table 2. Acylation of alcohols with **1b** in different solvents

Alcohol	Reagent	Reaction time (h)	Yield (%)	Alcohol	Reagent	Reaction time (h)	Yield (%)
$PhCH_2OH$	Ac_2O in MeCN	0.16	79	$PhCH_2OH$	Bz_2O in PhH	0.16	99
	Ac_2O in MeCN	0.25	89		Bz_2O in PhH	0.25	94
							
14				**14**			
	Ac_2O in MeCN	1.0	68		Bz_2O in PhH	1.0	90
15				**15**			
Menthol	Ac_2O in MeCN	1.0	93	Menthol	Bz_2O in PhH	1.5	90

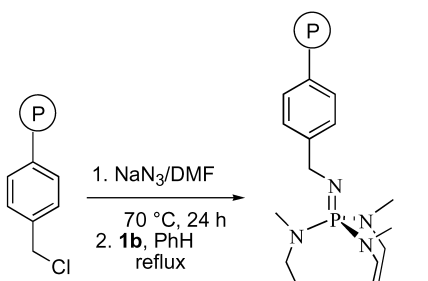
chiral oxazoline **19a** (87%) in 14 h



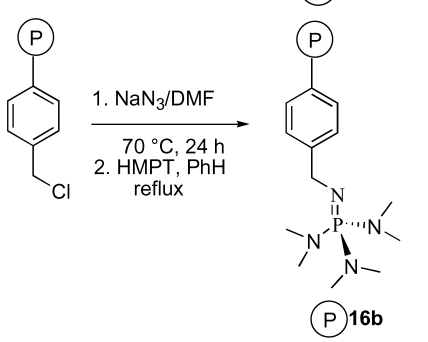
(1)



(2)

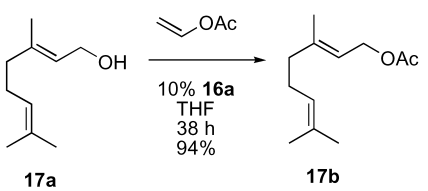


(3)

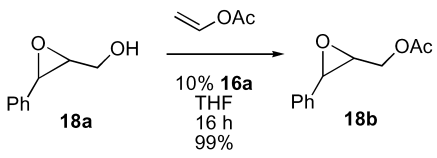


(4)

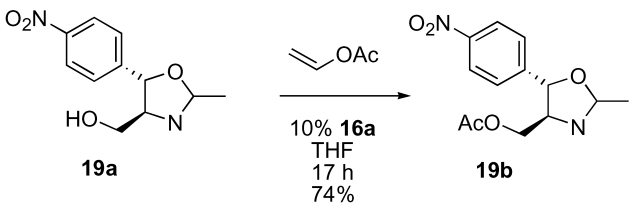
Alcohol acylations with vinyl acetates are more facile with **1b** and **1d**[27] than with their less basic iminophosphoranes derivatives. (As examples, see reactions (6)–(9)). Excellent yields are observed with primary and secondary alcohols with reaction times ranging from 2 to 41 h for the reaction of more sterically hindered alcohols with 2-propenyl acetate, for example, in the presence of **1b** and **1d**. On the other hand, benzyl alcohol is acylated (99%) by **1b** in the presence of vinyl acetate in 2 h. However, no reaction was observed for 1-methyl-1-cyclohexanol with 2-propenyl acetate even after 24 h. A chiral oxazoline was also esterified without observable racemization.[27] Like the reactions catalyzed by iminophosphoranes,[25] proazaphosphatranes tolerate acid and base-sensitive functionalities, and thus providing a substantial advantage over Cp*Sm·thf and [$ClBu_2SnOSnBu_2Cl$] as catalysts.[27]



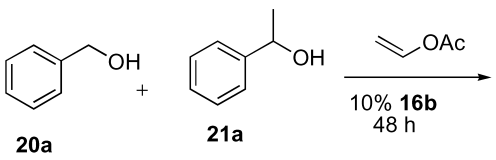
(5)



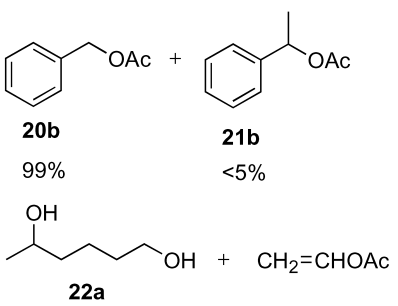
(6)

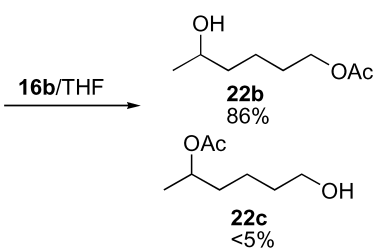


(7)



(8)





(9)

4.3. Silylation of alcohols

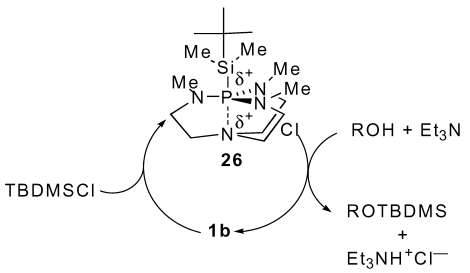
This reaction is by far the most often employed for protecting alcoholic OH groups in organic synthesis.[28] *t*-Butyldimethylsilyl chloride (TBDMSCl) and *t*-butyldiphenylsilyl chloride (TBDPSCl) are the most popular silylation agents because of their stability to weakly acidic and basic conditions as a result of steric protection of the silicon to nucleophilic attack. The protection of sterically hindered alcohols and phenols with TBDMSCl has been difficult to accomplish under traditional conditions such as TBDMSCl/imidazole, Et_3N/TMG, Et_3N/DBU, 18-crown-6, DBU/potassium carbonate, *i*-Pr_2NEt, Et_3N/DMAP, and lithium sulfide in solvents such as DMF acetonitrile and methylene chloride.[28] This problem became quite apparent in a total synthesis of maytansine[29] and of 1,4-bis(*tert*-butyldimethylsiloxy)-2,5-di-*tert*-butylbenzene for electrochemical studies.[30] To overcome this problem the more reactive silylating agents TBDMS perchlorate and TBDMS triflate

Table 3. Silylation of benzyl alcohol using **1b** in different solvents

Solvent	Yield (%)	Solvent	Yield (%)
Pentane	43	THF	92
Ether	46	MeCN	100
Benzene	78	DMF	100

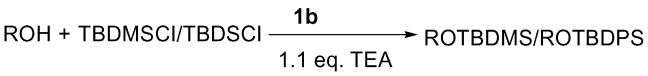
were prepared. Although these reagents are effective for silylating tertiary and hindered alcohols in high yield, TBDMS perchlorate is not commercially available and its explosive nature requires extreme care in its handling.

A very efficient and mild procedure for the silylation of a wide variety of alcohols (including primary, secondary, allylic, propargylic, benzylic, hindered secondary, tertiary, acid-sensitive and base-sensitive alcohols, and also hindered phenols) using TBDMSCl involves the use of **1b** as the catalyst (reaction (10)).[28] The reactions are carried out in acetonitrile as a solvent at temperatures ranging from 24 to 40°C. Under rare conditions, DMF may be used as a solvent at temperatures ranging from 24 to 80°C (Table 3). This table also shows that the yields of the silylated alcohols depend on the polar solvents to afford the highest yields. This dependence is rationalized in terms of a mechanism in which an ionic species is formed as an active intermediate, although such an intermediate (as depicted in Scheme 9) was not detected in variable temperature NMR experiments using equimolar amounts of **1b** and TBDMSCl, TBDMS triflate, TBDPSCl, or triphenylsilyl chloride (TIPSCl) in CD_3CN or C_6D_6 from −10°C to +40°C. However, such an intermediate was supported by the aforementioned spectroscopic experiments involving less hindered **1a**.[23,25] It may be mentioned here that although silylation intermediates analogous to those suggested in Scheme 9 derived from DMAP, DBU and TMG have been postulated, none has been observed directly.[28b] In Scheme 9 the ion pair intermediate (especially in polar solvents) facilitates nucleophilic attack at silicon. This mechanism is analogous to that proposed for silylations involving DBU. It is interesting that the equimolar amount of NEt_3 used in the



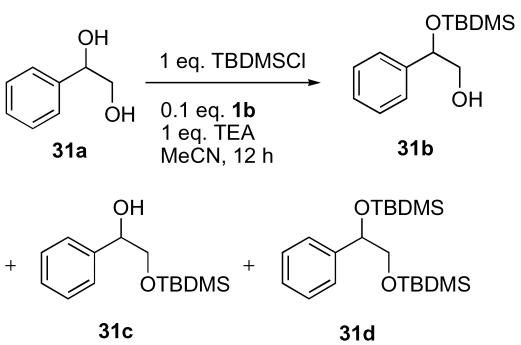
Scheme 9.

reaction does not effectively catalyze our reactions, nor does its hydrochloride (which forms during the reaction) protonate catalyst **1b** before silylation is complete. This observation indicates that silylation is kinetically favored over alcohol deprotonation. The examples shown in Table 4 for alcohol silylation demonstrate that yields are typically greater than 80%



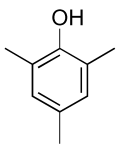
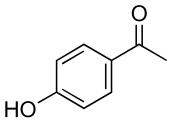
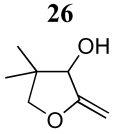
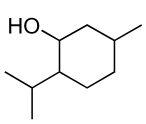
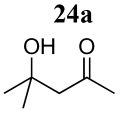
(10)

Of particular note is the selectivity of this methodology in protecting secondary alcohols in the presence of primary alcohols. This selectivity was demonstrated by the protection of alcohol **31a** in which the ratio of isolated products from a reaction of a 1:1 mixture of reactants was 97:0:3 (**31b**:**31c**:**31d**)[28b]



(11)

Table 4. Silylation of alcohols using 20 mol% of **1b**

Alcohol	Reagent	Reaction time (h)	Yield (%)	Alcohol	Reagent	Reaction time (h)	Yield (%)
PhCH(OH)Me **21**	TBDMSCl in MeCN	3	99	$Me(CH_2)_6C H_2OH$ **28**	TBDMSCl in MeCN	0.2	99
	TBDMSCl in MeCN **1b**	12	85		TBDMSCl in MeCN 10% **1b**	2	99
 **26**				 **29**			
 **27**	TBDMSCl in DMF	12	86	 **24a**	TBDMSCl in MeCN	3	99
$PhCCCH_2OH$ **28**	TBDMSCl in MeCN	24	96	 **30**	TBDMSCl in DMF	24	80

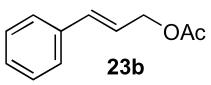
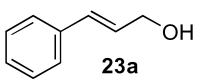
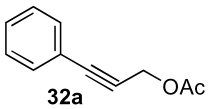
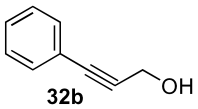
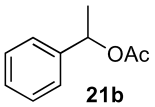
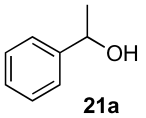
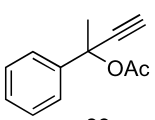
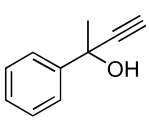
The chiral proazaphosphophatrane **1m**, although an efficient silylation catalyst, was found by others to be incapable of effectively inducing asymmetric silylation.[15] This is perhaps due to the long distance of the silicon atom from the chiral center in the intermediate.

The oxidized form of **1b**,[11,18] namely, **1b**=O is also an effective catalyst for the silylation of a variety of alcohols,[19] including primary, secondary and tertiary as well as representative sterically hindered phenols. Interestingly, the yields in these reactions parallel those obtained with **1b**. Perhaps the reduced basicity of the P=O oxygen is compensated by the high degree of oxophilicity of the silicon in the P=O→Si moiety of the proposed intermediate.

4.4. Deprotection of alcohols

4.4.1. Deacylation of protected alcohols. Although a wide range of reagents have been used for the deacylation of alcohols, the use of a base in alcohol, such as potassium carbonate in methanol, is common.[27] Recently, DIBAL-H has been shown to effect clean deacylation for pivaloate esters. However, this reagent is pyrophoric and must be handled carefully. Proazaphosphatrane **1b** has recently been found to catalyze the clean deacylation of acetates in 20 min in methanol.[27] As shown in Table 5, the reaction tolerates allylic as well as propargylic alcohols that are reduced by DIBAL-H. Thus, for example, **33a** is deprotected to the corresponding alcohol (96%) with no observed side products.[27]

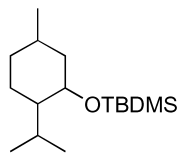
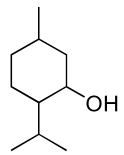
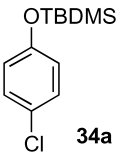
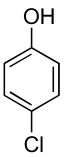
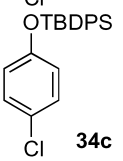
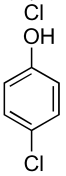
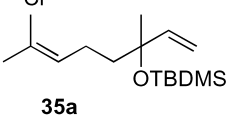
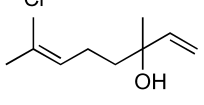
Table 5. Deprotection of acetates catalyzed by **1b** in methanol

Alcohol	Product	Reaction time (min)	Yield (%)
 **23b**	 **23a**	20	100
 **32a**	 **32b**	20	100
 **21b**	 **21a**	220	99
 **33a**	 **33b**	2460	96

4.4.2. Desilylation of silyl ethers. Protic acids, Lewis acids, transition metal compounds and Lewis bases have been used to deprotect silyl ethers to regenerate their parent alcohols.[31] TBDMS ethers of primary, secondary and tertiary alcohols and also phenolic TBDMS ethers are desilylated to their corresponding alcohols and phenols, respectively, in DMSO at 80°C (68–94%) in the presence of 0.2–0.4 equiv. of **1b**.[31] In the presence of a catalytic amount of **1d**, 85–97% yields of alcohols were obtained from the corresponding TBDMS ethers. Under the same reaction conditions, both catalysts afford lower alcohol yields (22–45% yield) in the deprotection of TBDPS ethers.

Faster reaction rates were observed in acetonitrile compared with DMSO. Since both solvents were found to be deprotonated by **1b** and **1d**, possible reaction pathways were proposed involving nucleophilic attack of the anion of the solvent molecule [$^{-}CH_2CN$ or $^{-}CH_2S(O)CH_3$] at the Si–O bond of a silyl ether. Another possible scenario involves prior activation of the silyl ether by the catalyst via P→Si interaction (in an intermediate analogous to that shown in Scheme 9) followed by nucleophilic attack of the solvent anion on silicon. Both ^{1}H and ^{31}P NMR data were consistent with either of these mechanisms. Further support for a reaction pathway of the aforementioned type, rather than the usual base-promoted silyl cleavage, was provided by the failure of TBDMS ethers to desilylate in the presence of 40 mol% **1b** in C_6D_6 even at 50°C over 62 h. Selected examples of silyl ether deprotections catalyzed by **1b** are shown in Table 6.[31]

Table 6. Deprotection of silyl ethers using **1b** at 80°C in DMSO

Alcohol	Product	Reaction time (h)	Yield (%)
 **(D,L)-24c**	 **(D,L)-24a**	36	85
 **34a**	 **34b**	24	94
 **34c**	 **34b**	36	45
 **35a**	 **35b**	36	81

4.5. Desulfurization of organosulfur compounds

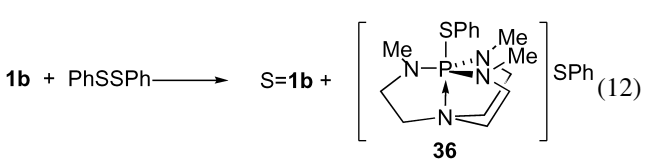
Desulfurization of organosulfur compounds has been studied for more than four decades. A variety of trivalent phosphorus reagents have been used to convert disulfides to mono sulfides, trisulfides to disulfides or monosulfides, β-keto sulfides to ketones and sulfenimides to amines.[32] These reagents have also been employed to remove sulfur from thioethers, thiols and organometallic dithiocarboxylates, and oxygen from sulfones.

Table 7. Desulfurization of organosulfur compounds using **1b**

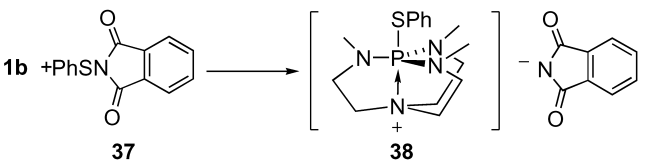
Sulfide	Solvent	**1b** (equiv.)	Temperature/time (°C/h)	Products (yield, %)
PrS_3Pr	THF	1.0	rt/4	PrS_2Pr (95.0), PrSPr (2.2)
BnS_3Bn	THF	2.2	rt/1.5	BnS_2Bn (94.0), BnSBn (2.8)
BnS_3Bn	THF	2.2	rt/3	BnSBn (>99)
PrS_2Pr	C_6H_6	1.1	40/26	PrSPr (100)
i-PrS_2*i*-Pr	PhMe	1.1	110/17	*i*-PrS*i*-Pr (30)
i-PrS_2*i*-Pr	PhMe	1.1	110/64	*i*-PrS*i*-Pr (100)
PhS_2Ph	THF	1.0	rt/48	PhSPh (<5)
t-BuS_2*t*-Bu	PhMe	1.1	110/65	*t*-BuS*t*-Bu (45.0)

Proazaphosphatrane **1b** has been found to stoichiometrically convert trisulfides chiefly to disulfides along with monosulfides as minor products at room temperature.[32] When the concentration of **1b** was increased, further desulfurization of trisulfides could be effected to give monosulfides, which in principle could be desulfurized further to afford the corresponding alkenes.[32] The products were often recovered in good to high yields at room temperature or up to 110°C over periods ranging from 3 to 65 h. As an example, propylene sulfide in the presence of **1b** was found to give exclusively propylene at room temperature, and somewhat unexpectedly, S=PPh_3 was desulfurized in moderate yield, although S=$P(NMe_2)_3$ and S=$P(-n\text{-}Bu)_3$ were resistant to this process. In comparison reactions the acyclic analogues $P(NMe_2)_3$ and $P(NEt_2)_3$ were considerably less effective desulfurization reagents and this may be attributable to the possibility for transannulation in **1b** during the transformation.[32] Further examples of sulfides which were desulfurized are shown in Table 7.

Some insight into the probable pathway of these reactions is afforded by a consideration of the nature of intermediates observed in some of these reactions. Although **1b** did not efficiently desulfurize phenyl disulfide, raising the temperature from 80 to 160°C led to the formation of the thiophosphine S=**1b** as a minor product and [PhS**1b**]SPh (**36** in reaction (12)) as the major component in reaction (12), analogues of which have been observed with $P(NR_2)_3$ in similar reactions.[32] In the reaction of **1b** with organic thiocyanates, virtually complete conversion to the corresponding cyanide was observed in 10–14 h between 35 and 40°C. However, when the reaction with EtSCN was carried out at room temperature, NMR evidence was adduced for [EtS**1b**]CN, which decomposed on warming to give EtCN presumably by nucleophilic attack of $^-$CN on the carbon of the Et–S bond in [EtS**1b**]CN.[32] The reaction of **1b** with *N*-(phenylthio)phthalimide (**37** in reaction (13)) at room temperature cleanly led to quantitative formation of [PhS**1b**]phthalimide (**38**) which was isolated and characterized.[32] Although no definitive evidence could be obtained for the presence or absence of transannulation in the aforementioned salts of RS**1b**$^+$ cations, it is likely from the previous discussion associated with reaction (13) that these cations are probably partially transannulated.



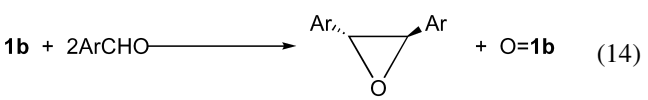
(12)



(13)

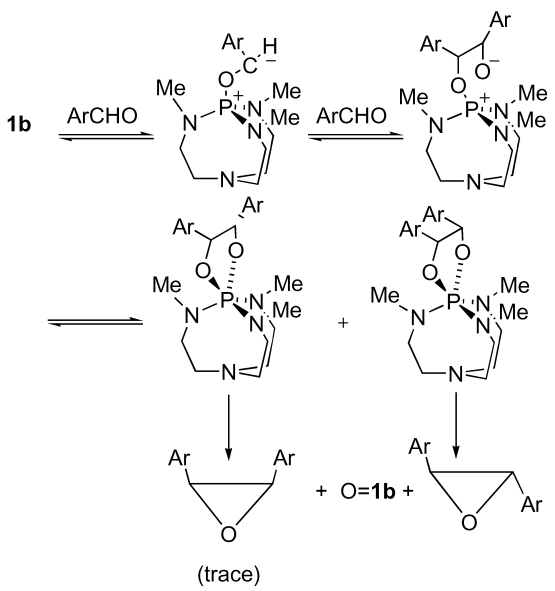
4.6. Removal of an oxygen atom from aldehydes to form epoxides

The preparation of epoxides is an important transformation in organic synthesis and it is generally accomplished by the oxidation of the corresponding olefin with peroxides.[33] However, the preparation of peroxides bearing sensitive functional groups is not usually successful under such conditions. The trisaminophosphine HMPT has been used to convert aryl aldehydes bearing electron withdrawing groups to the corresponding epoxides,[34] but this method suffers from low selectivity since a mixture of the *trans* and *cis* products is usually obtained with selectivity ranging from 1.1:1 to 2.6:1 for the *trans* product. Approaches leading to symmetric epoxides have been plagued by a number of draw-backs, such as formation of side products, low yields, and the use of toxic reagents.[35] Bases of type **1** are highly selective reagents for the synthesis of symmetric *trans* epoxides with selectivities ranging from 94:6 to absolute.[33] In this reaction, the base is converted into its oxide as shown in Eq. (14). Because the reactions are carried out in benzene, O=**1b** is easily separated from the reaction mixture by filtration



(14)

These reactions are faster with **1b** than with $P(NMe_2)_3$ because the phosphorus atom of **1b** is apparently more nucleophilic (perhaps via transannulation at some point in the reaction path) and/or because of stereoelectronic factors associated with constraint of the bicyclic structure. An enhanced basicity accompanying this greater nucleophilicity could account for the substantial amount of intermediate 1:1 and 2:1 adducts of aldehydes formed from **1b**, while no such adducts survive in the same reactions with $P(NMe_2)_3$.[33] Both ^{31}P NMR and mass spectral evidence for adducts with a 1:1 and a 2:1 ratio of aldehyde to **1b** was obtained for the case of *para*-cyanobenzaldehyde. We attributed the high stereoselectivity of **1b** to induce formation of *trans* epoxides to the rigidity of the structure of **1b** which allows the 2:1 adduct intermediate to adopt a less sterically hindered



Scheme 10.

conformation as shown in Scheme 10. Somewhat surprisingly, the spirocyclic *cis* diadduct shown in this scheme is less sterically hindered than its *trans* counterpart (also shown).[33] It was speculated that steric hindrance between the aromatic rings in the *trans* diadduct and the methyl groups in **1b** is higher than that in the *cis* isomer, owing to a folding of the five-membered ring in the *cis* isomer away from the methyl group on the mirror plane to an 'envelope' conformation with phosphorus in the 'flap' position. Although it is not clear, the *cis*-adduct may epimerize via the zwitterionic intermediate shown, thus permitting formation of the *trans* adduct which subsequently decomposes to *trans* epoxide. The greater bulk and rigidity of the 2:1 adduct of **1b** than that in the analogous $P(NMe_2)_3$ species is thus perhaps responsible for the greater stereoselectivity of **1b**. It is interesting that proazaphophatrane **1d** did not facilitate this reaction, probably owing to its greater steric bulk.[33]

A few examples of some of the epoxides prepared by this protocol are shown in Table 8.

Two ketones tested in this reaction (namely, acetophenone and 4-cyanoacetophenone) did not form detectable amounts of epoxide with either **1b** or HMPT.

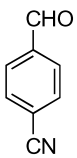
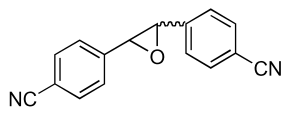
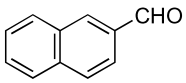
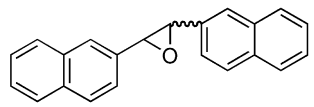
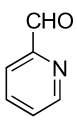
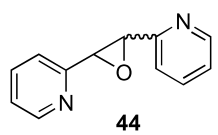
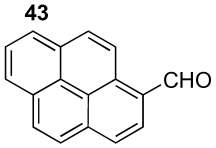
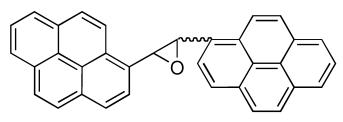
4.7. Removal of nitrogen from azides

Azides react with proazaphosphatranes to produce the corresponding iminophosphoranes or azidophosphoranes which are also useful in organic synthesis. Thus, proazaphosphatrane **1b** reacts with benzyl azide to produce $BnN{=}P(NMeCH_2CH_2)_3N$, a useful catalyst for alcohol acylation and for transesterification. An analogous approach was used to prepare a polymer-supported iminophosphorane for such reactions.[25]

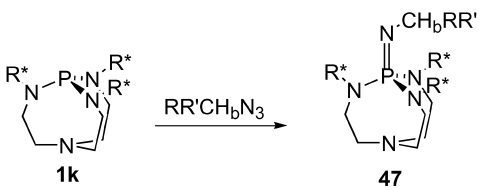
Because chiral azides are starting materials for the synthesis of chiral amine ligands, chiral auxiliaries, pharmaceutical intermediates, and building blocks for the asymmetric synthesis of natural products, an efficacious method of determining their chiral purity is highly desirable.[14] Phosphorus-containing tagging agents have been very attractive for the analyses of chiral alcohols, amines and thiols owing to the attractive features of this nucleus in ^{31}P NMR spectroscopic analysis.

Interestingly, no derivatizing agent had been reported for

Table 8. Preparation of epoxides in the presence of **1b** or HMPT

Aldehyde	Product	Reaction time (h)	Yield (%) with **1b** (*trans*/*cis*)	Yield (%) with HMPT (*trans*/*cis*)
 **39**	 **40**	0.5	64 (98:2)	81 (51:49)
 **41**	 **42**	14	75 (100:0)	74 (69:31)
 **43**	 **44**	0.5	42 (92:8)	52 (65:35)
 **45**	 **46**	14	69 (100:0)	64 (52:48)

the direct determination of ee values of chiral azides by ^{31}P or ^{1}H NMR spectroscopy until we synthesized pseudo-C_3 **1k**.[14] When a chiral azide is reacted with **1k** in an NMR tube at 50°C for 2 h (reaction (15)) substantial separations of the ^{31}P NMR chemical shifts for the diastereomeric product (ca. 1 ppm) allowed the ratios of the iminophosphorane diastereomers to be measured accurately.[14] These ratios were very close to those expected for commercially purchased racemic and chirally pure organic azides as well as for various mixtures of two such enantiomeric substrates. These ratios were also in good agreement with those measured by ^{1}H NMR spectroscopic integration of the H_b proton shifts in the tagged product (see reaction (15))



(15)

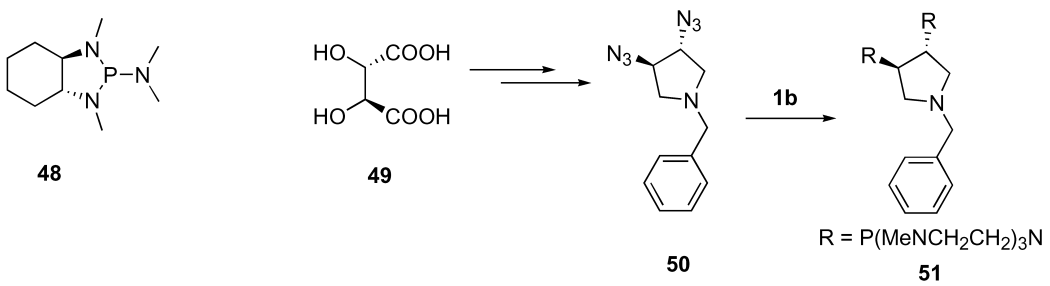
The commercially available chiral phosphoramide **48** when employed in comparison studies afforded no observable diastereomeric differentiation either by ^{31}P or by ^{1}H NMR analysis. This result may be rationalized on the fact that the three chiral centers in **1k** are held rigidly in place, thus perhaps providing a more enhanced chiral phosphorus environment.[14]

The reaction of proazaphosphatranes with organic azides has recently been carried out in our laboratories for the preparation of several more exotic imidophosphorane bases from chiral sources such as tartaric acid (Scheme 11), glucose acetate (Scheme 12) and an alkaloid moiety (Scheme 13).[20]

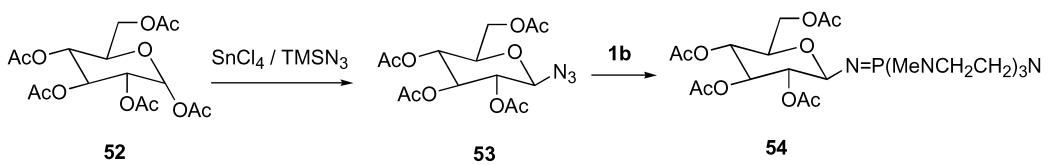
4.8. Transesterification of esters

Ester transesterification is an important transformation in which an ester is transformed into a more useful one. In addition to the use of strong acids and ionic bases as catalysts for this purpose, catalytic amounts of Ti(O-*i*-Pr)$_4$, DBU/LiBr or certain organometallic compounds in the presence of an alcohol are also utilized.[27]

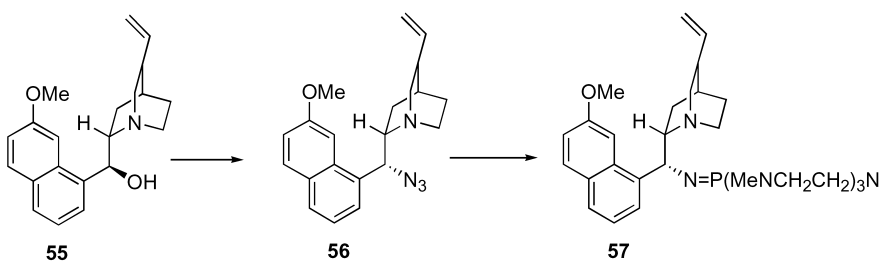
Proazaphosphatrane **1b** catalyzes the transesterification of esters with high selectivity and in excellent yields at room temperature (Table 9).[27] This approach is also effective for amino acid esters which are very useful protecting groups in peptide synthesis. Hence, Boc-Val-Phe-OMe (**60a** in Table 9) underwent smooth transesterification in allyl alcohol in the presence of **1d**, affording **60c** (96%) with a diastereomeric ratio of 98:2. The less hindered base **1b**, however, gave a 55:45 mixture of epimers (**60b**) at the phenylalanine residue.[27] Acetonide **61a** was completely epimerized in the presence of **1b** or **1d**. The use of catalytic amounts of these proazaphosphatranes for transesterifications is more efficient than the DBU/LiBr process in which 50% loading is required or the DBU approach which employs 500 mol% loading.[36]



Scheme 11.

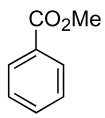
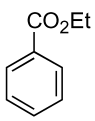
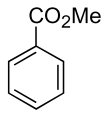
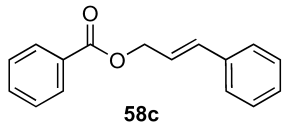
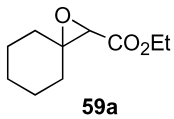
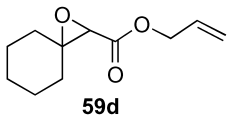
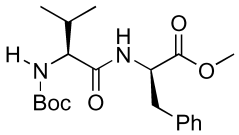
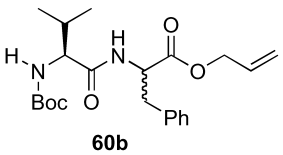
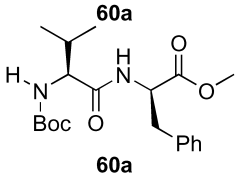
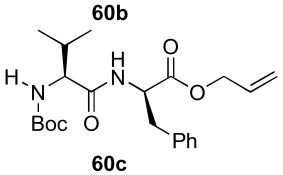
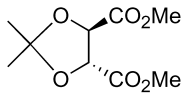
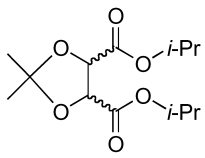
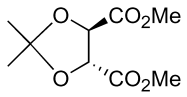
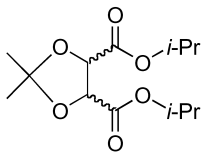


Scheme 12.



Scheme 13.

Table 9. Transesterification of esters using **1b** as a catalyst (10–15 mol%)

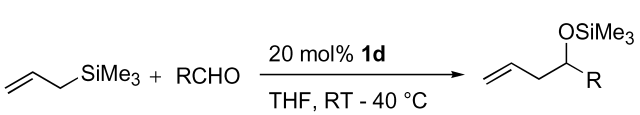
Ester	Alcohol	Product	Reaction time (h)	Yield (%)
 **58a**	EtOH	 **58b**	4	89
 **58a**	$PhCH{=}CHCH_2OH$	 **58c**	24	91
 **59a**	$CH_2{=}CHCH_2OH$	 **59d**	5	91
 **60a**	$CH_2{=}CHCH_2OH$	 **60b**	17	96
 **60a**	$CH_2{=}CHCH_2OH$	 **60c**	4	96a
 **61a**	*i*-PrOH	 **61b**	18	95
 **61a**	*i*-PrOH	 **61c**	21	81[a]

[a] The base used was **1d**.

4.9. Allylation of aromatic aldehydes

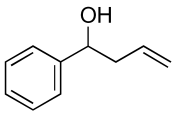
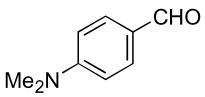
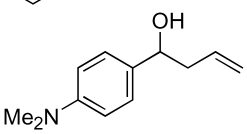
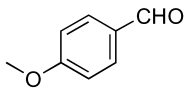
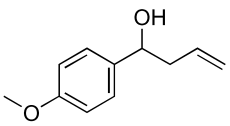
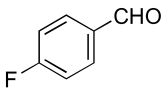
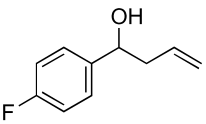
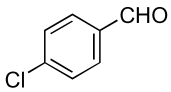
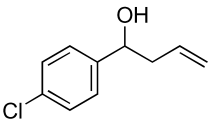
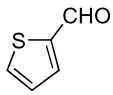
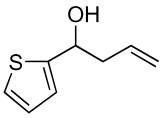
The formation of homoallylic alcohols by the addition of allyl silanes to aldehydes under Lewis acid conditions has been extensively studied owing to facile formation of functionalized C–C bonds under such conditions.[37] Recent interest in Lewis-base mediated allylation of aldehydes has been sparked by the mild conditions under which this transformation can occur. Although several reagents have been reported for the Lewis acid mediated reaction, apparently the only Lewis base to our knowledge reported in the literature for this reaction is the fluoride ion for which refluxing THF is required to be effective.[38]

It was gratifying to discover in our laboratories that sub-stoichiometric amounts of **1d** provides a mild entry into the allylation of a variety of aldehydes (reaction (16)).[38] Both HMPT and **1b** were inefficient in this reaction. As shown in Table 10, aromatic aldehydes bearing an electron donating group (e.g. **64a** and **65a**) possess lower reactivity under our conditions and gave poor yields. Reactions with *para*-cyanobenzaldehyde (**39**) and *para*-nitrobenzaldehyde (**67**) gave deep red solutions which are attributed to the formation of a complex with **1d** of presently unknown constitution.[38] Both of these reaction mixtures were EPR silent suggesting that ionic complexes were perhaps formed. This assumption was substantiated by ^{31}P NMR studies in THF in which only a ^{31}P signal at -10.7 ppm associated with cation $\mathbf{1dH^+}$ is observed. However, the source of the proton in $\mathbf{1dH^+}$ is presently not known. In the reaction of *para*-cyanobenzaldehyde (**39**), an 81% yield of an epoxide was generated

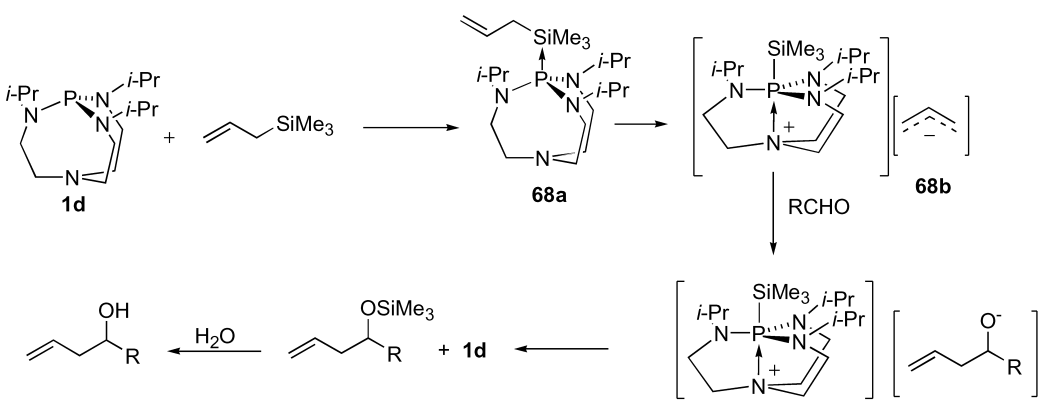


(16)

Table 10. Allylation of aldehydes in the presence of 20 mol% of **1d**

Aldehyde	Product	Reaction time (h)/temperature (°C)	Yield (%)
PhCHO		72/rt	74
 **62a**	 **62b**	84/40	57
 **63a**	 **63b**	84/40	52
 **64a**	 **64b**	72/rt	77
 **65a**	 **65b**	84/rt	59
 **66a**	 **66b**	72/rt	80

The reaction of allyltrimethylsilane with aldehydes in the presence of **1d** is assumed to proceed in a manner similar to that of other allylation reactions promoted by Lewis bases. Thus **1d** can be expected to coordinate with allyltrimethylsilane to form a pentacoordinate silicon species that may also feature a pentacoordinate phosphorus (Scheme 14). One option for this intermediate is to coordinate further with an aldehyde oxygen to form a hexacoordinate silicon species, thus allowing completion of the reaction ring transition state.[38] Another possibility is that the C–Si bond of the pentacoordinate silicon intermediate cleaves to form an allylic anion, which then adds to the aldehyde to give α,γ-addition products. To determine which pathway is followed, crotyltrimethylsilane (*E*/*Z*=88:12) was reacted with benzaldehyde under the same conditions.[38] Although the reaction was very sluggish, both α and γ-addition products formed in roughly equal ratio were isolated as a mixture. This strongly suggests that an allylic anion is generated during the reaction (as illustrated in Scheme 14), and that at least partial transannulation of the phosphorus cage occurs while the silyl ether is finally hydrolyzed in work-up to give the homoallylic alcohol.[38] Due to the



Scheme 14.

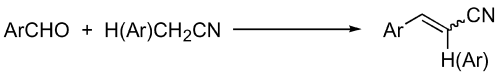
electron withdrawing nature of the *para*-chlorobenzaldehyde, electrophilic attack of the silyl group on the silyl ether is probably the slow step in the reaction, thus perhaps accounting for a lower yield of product.

5. Reactions in which a CH deprotonation occurs

5.1. Reactions of nitriles

Nitriles bearing acidic α-hydrogen atoms can be deprotonated by proazaphosphatranes to produce an equilibrium mixture that contains both the corresponding protonated base (**2**) and the free base **1**. However, benzyl cyanide, because of its low pK_a value, is essentially completely deprotonated by proazaphosphatranes, and the product carbanion can undergo a variety of reactions depending on conditions such as temperature, solvent and other species available in the reaction mixture. The following sections detail a number of useful proazaphosphatrane-mediated transformations involving nitriles.

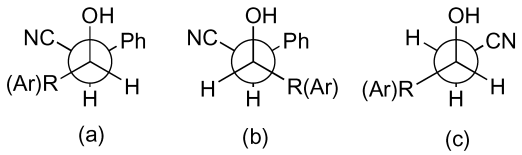
5.1.1. Direct synthesis of α,β-unsaturated nitriles. Direct production of α,β-unsaturated nitriles by the reaction of carbonyl compounds with nitriles (reaction (17)), without the necessity of isolating and dehydrating the intermediate β-hydroxy nitrile, is of considerable economic interest because α,β-unsaturated nitriles are versatile intermediates in the production of perfumes,[39] sex pheromones,[40] vitamin A[41] and pigments,[42] for example. However, traditional direct approaches to α,β-unsaturated nitriles (**69** in reaction (17)) usually utilize an alkali metal alkoxide or some other ionic base as a catalyst which lead to undesired side reactions such as self-condensation of the nitrile, aldol condensation of the carbonyl compound, Cannizzaro reactions and/or retro-reaction of the β-hydroxy nitrile intermediate.[43] As a result, α,β-unsaturated nitriles have generally been prepared from aliphatic aldehydes via a Wittig–Horner reaction. An example of an indirect route to α,β-unsaturated nitriles involves the reaction of a carbonyl compound with $LiCH_2CN$ obtained by deprotonating acetonitrile with strong ionic bases such as *n*-BuLi. This produces the intermediate β-hydroxy nitrile which is isolated and thermally dehydrated in the presence of a strong acid. Both traditional direct methods as well as indirect routes to α,β-unsaturated nitriles are therefore inefficient[39]

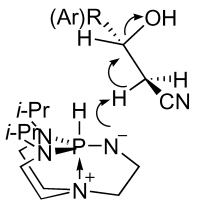


(17)

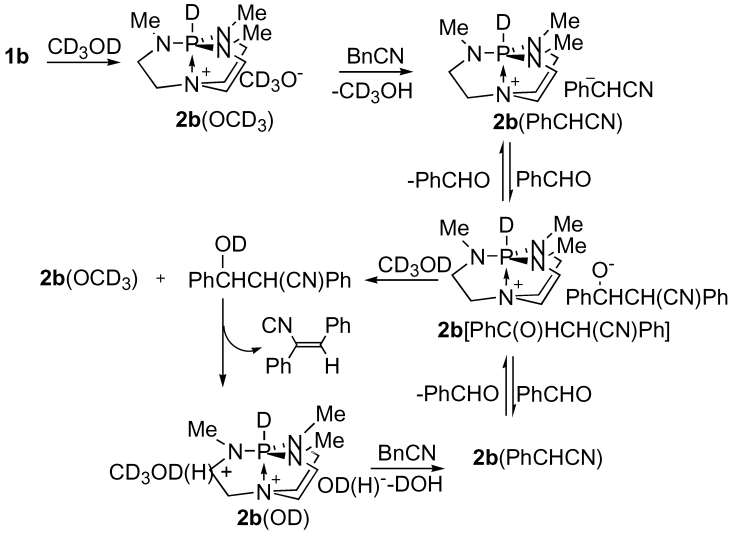
69

Proazaphosphatranes **1b**, **1j** or **1e** facilitate a direct catalytic synthesis of α,β-unsaturated nitriles in high yields, typically 89–99%, by reacting aldehydes with acetonitrile or benzyl cyanide at 40–50°C.[39] These reactions take place in both polar protic and nonpolar aprotic solvents, and the corresponding pathways proposed (for which ^{31}P NMR evidence for the deuterio-cations was adduced) are given in Schemes 15 and 16 for **1b**. While the yield is high for most of the substrates investigated (Table 11), 4-hydroxybenzaldehyde (**72**) resisted conversion due to deprotonation of the phenolic OH.[39] The reaction of vanillin acetate also did not afford the desired product because of a deacylation[27] reaction of this substrate leading to vanillin. The requirement for a higher loading of **1j** observed in this study is probably due to its tendency to competitively oligomerize.[39] With benzyl cyanide, exclusively *E* product configurations are observed. This is reasoned on the basis of a dominant steric effect expressed by the (Ar)R and the phenyl groups in the β-hydroxy nitrile intermediates (schematically shown in Newman projections (a) and (b) below) prior to deprotonation of the posterior carbon.[39]



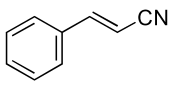
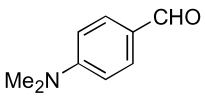
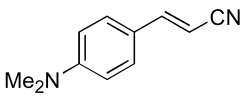
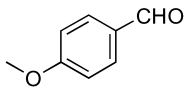
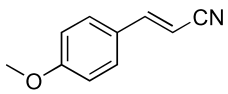
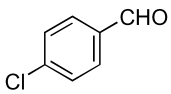
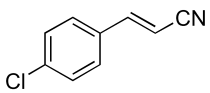
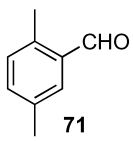
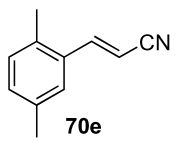
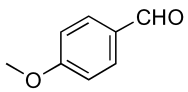
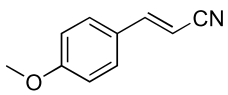
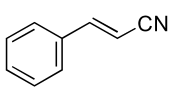
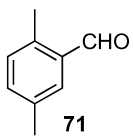
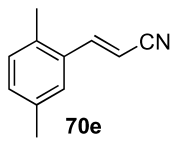
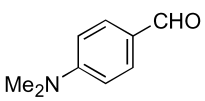
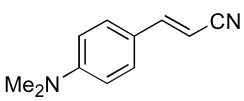
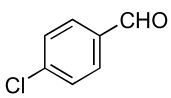
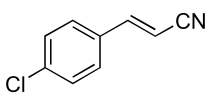


73



Scheme 15.

Table 11. Direct synthesis of α,β-unsaturated nitriles

Aldehyde	Product	Reaction time (h)/temperature (°C)/base (mol equiv.)/solvent	Yield (%)
PhCHO	 **70a**	60/50/**1b**(0.3)/THF, neat or PhH	98
 **62a**	 **70b**	6/50/**1b**/(0.1)/MeOH	99
 **63a**	 **70c**	3/40/**1b**(0.1)/MeOH	99
 **65a**	 **70d**	3/40/**1b**(0.1)/MeOH	98
 **71**	 **70e**	6/50/**1b**(0.1)/MeOH	99
 **63a**	 **70c**	3/40/**1j**(0.3)/MeOH	99
PhCHO	 **70a**	6/50/**1j**(0.1)/MeOH	98
 **71**	 **70e**	3/40/**1j**(0.3)/MeOH	89
 **62a**	 **70b**	3/40/**1j**(0.3)/MeOH	99
 **65a**	 **70d**	3/40/**1j**(0.3)/MeOH	96

Proazaphosphatrane **1j**, which is more basic than **1b**, efficiently catalyzed the condensation/dehydration of aromatic aldehydes and tertiary aliphatic aldehydes.[39] The use of **1j** in these reactions gives rise to products with unusually high *E*/*Z* ratios which are rationalized on the basis of preferential deprotonation of the rotameric form shown above as Newman projection (c), which in turn depends primarily on a sterically better interaction of the base with rotamer c as shown in **73**. With either **1b** or **1j**, aliphatic aldehydes give aldol products, and secondary aldehydes lead to novel Michael addition products which are described in Section 5.1.2. Ketones do not condense with either benzyl cyanide or acetonitrile under our conditions.[39]

5.1.2. α,β-Dimerization of α,β-unsaturated nitriles. The preparation of olefin dimers is of interest because these compounds are useful for making copolymers. A variety of reactions are known for the conversion of α,β-unsaturated

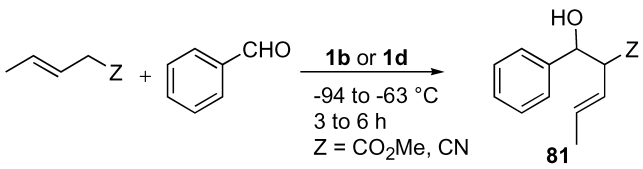
nitriles to glutaronitriles. However, these reactions proceed with low yields and are of limited scope.[44]

In the presence of **1b** or **1j**, acetonitrile reacts with secondary aldehydes to produce α,β-dimers of the corresponding α,β-unsaturated nitriles (Scheme 17) via a proposed pathway in which an α,β-unsaturated nitrile is deprotonated by the base to a canonical anion with the negative charge concentrated on the α-carbon. This stabilized anion undergoes a facile Michael addition to an already formed α,β-unsaturated nitrile to form the observed dimers after a 1,3-proton shift. We observed no detectable β,β-dimer product and only the α-carbon of the delocalized anion adds in a Michael fashion to a second molecule of the unsaturated nitrile. Secondary aldehydes are assumed to form the corresponding α,β-unsaturated nitriles which are subsequently deprotonated by the nonionic base to form an allylic anion that can then undergo Michael addition to a second molecule of the α,β-unsaturated nitrile. This concept has since been explored further and has led to a 1,2-addition reaction of allylic anions discussed in Section 5.1.3.

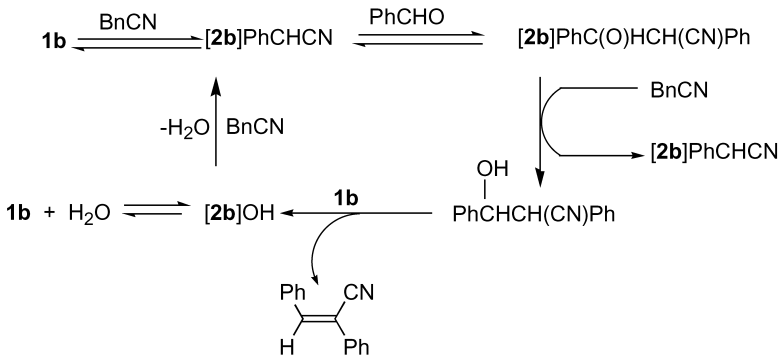
Selected examples of dimerizations of unsaturated nitriles are given in Table 12 which demonstrate that these reactions are highly efficient. The reaction of 1-(cyclohexenyl) acetonitrile forms a 90% yield of isolated product in addition to a 10% yield of the isolated rearranged cyclohexylidine–acetonitrile.

5.1.3. 1,2-Addition reactions of activated allylic synthons. Stabilized allylic anions have been employed in organic synthesis for the construction of C–C bonds; a process that has been found to give rise to both α and γ-alkylation, since the resonance forms of this ion place negative charges on both the α and γ-carbon atoms.[45]

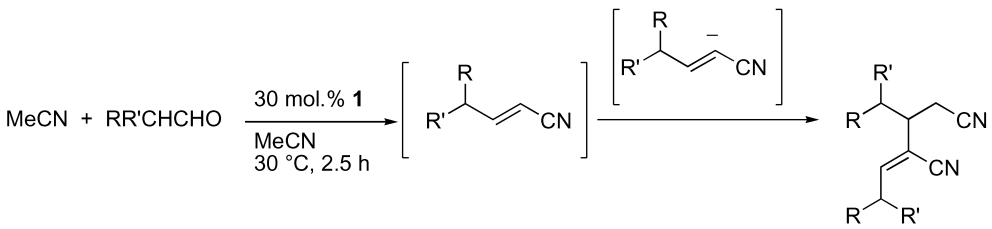
Proazaphosphatranes bases **1b** and **1d** (20–40 mol%) were found to catalyze the reaction of activated allylic compounds with aromatic aldehydes (as in reactions (18)–(20)) to produce either a β,γ-unsaturated product (**81**) or a Baylis–Hillman product (**83**), depending on the starting allylic compound.[46] These addition products are useful intermediates for the synthesis of substituted tetrahydrofurans via base-promoted electrophilic cyclizations. The formation of products in Scheme 18 as a 1:1 mixture of diastereomers is assumed to originate from polarization of the double bond by the methyl group; a process that places a partial negative charge adjacent to an anionic carbon, thus favoring a 1,3-proton shift and the subsequent deprotonation reaction shown in Scheme 18



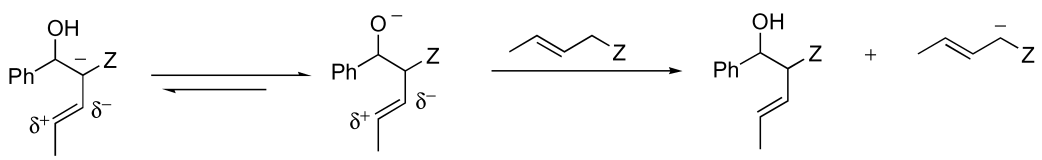
(18)



Scheme 16.

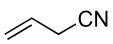
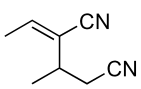
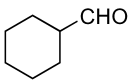
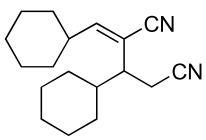
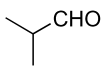
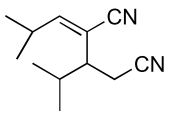
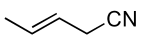
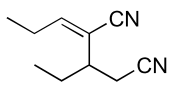
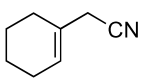
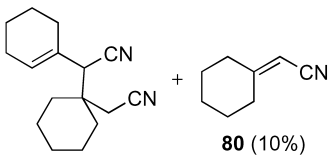


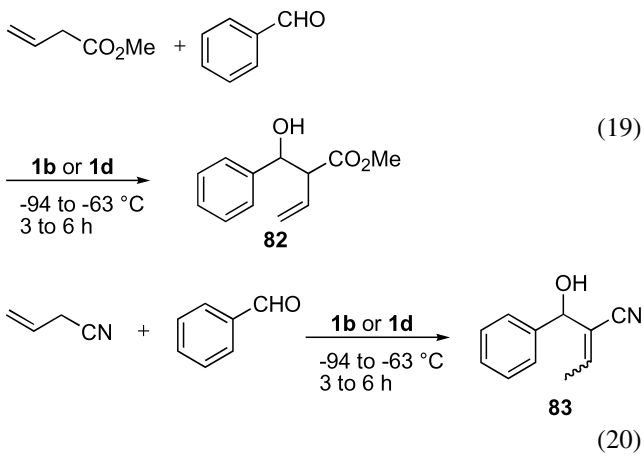
Scheme 17.



Scheme 18.

Table 12. Dimerization of unsaturated nitriles

Substrate	Product	Reaction time (h)/temperature (°C)/base (mol equiv.)/solvent	Yield (%)
	 **74**	1/30/**1b** or **1j** (0.1)/PhH	94
 **75a**	 **75b**	2.5/30/**1b** or **1d**/(0.3)/MeCN	98
 **76a**	 **76b**	2.5/30/**1b** or **1d**/(0.3)/MeCN	81
 **77a**	 **77b**	2.5/40/**1b** or **1d**/(0.3)PhH	98
 **78**	 **80** (10%) **79**	2.5/40/**1d**/(0.3)/PhH	90



(19)

(20)

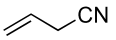
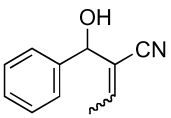
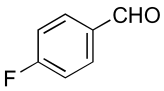
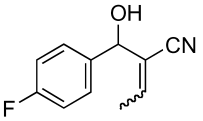
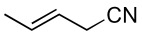
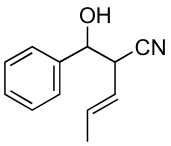
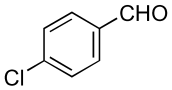
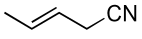
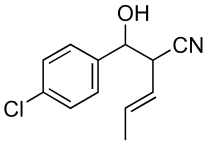
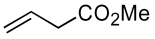
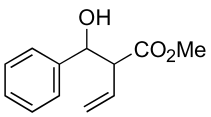
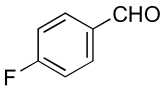
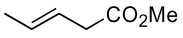
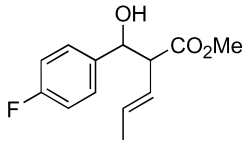
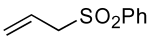
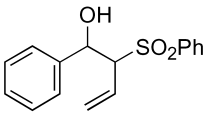
The reaction of allyl cyanide on the other hand results in an allylic transposition to produce a Baylis–Hillman product exclusively.[46] Although the Baylis–Hillman reaction has been studied for decades,[47] high pressure and lengthy reaction times are normally required and generally employ a bulky base such as DABCO. With proazaphosphatranes, the product we observed in reaction (20) forms under very mild conditions and in a very short time compared with both older as well as more recent literature approaches. One significant feature of our reaction is its facile nature with aromatic aldehydes (Table 13) which have traditionally been problematic under typical Baylis–Hillman conditions.

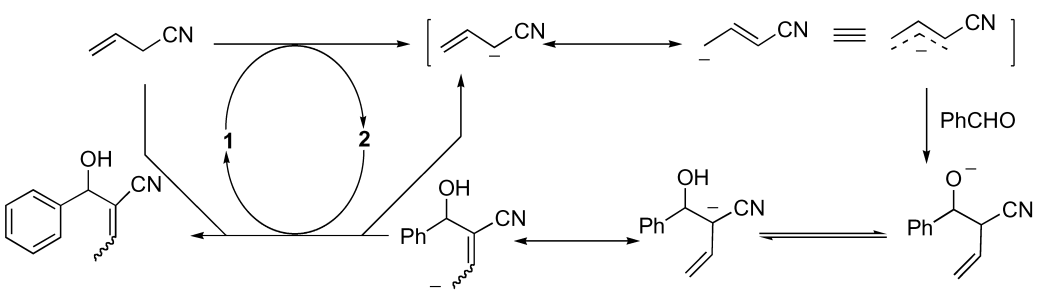
Unlike the nucleophilic pathway proposed for traditional Baylis–Hillman reactions, the transformation shown in reaction (20) is proposed to proceed through an allylic anion produced by deprotonation of allyl cyanide by the proazaphosphatrane. The allylic anion thus produced could add to the aldehyde to afford an intermediate alkoxide anion which is sufficiently basic to deprotonate allyl cyanide, thus possibly facilitating a catalytic reaction. However, it seems more likely that the alkoxide undergoes a facile 1,3-proton shift, giving a terminal carbanion that deprotonates either allyl cyanide or the protonated base **2**, with resultant regeneration of the proazaphosphatrane that then re-enters the catalytic cycle in Scheme 19. This mechanism received some support from NMR evidence.[46]

Benzaldehyde and 4-chloro and 4-fluorobenzaldehyde in Table 13 afforded the Baylis–Hillman products when reacted with allyl cyanide and gave the β,γ-unsaturated products when reacted with 3-pentenenitrile or methyl 3-pentenoate. Not surprisingly, *p*-nitrobenzaldehyde resisted addition under our conditions.[46]

5.1.4. Synthesis of β-hydroxy nitriles. The title nitriles are versatile intermediates in organic synthesis for making 1,3-amino alcohols. Such intermediates can be prepared by a variety of methods which are scarcely devoid of drawbacks, however. Among these are poor to moderate yields, toxicity of a catalyst or solvent, fire or explosion hazard, lengthy reactions times, multistep syntheses, and the requirement of cryogenic temperatures.[48] We found that proazaphosphatranes **1b**, **1d** and **1j** efficiently catalyze the

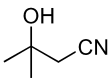
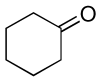
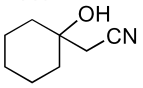
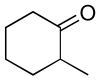
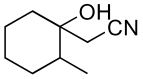
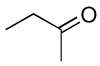
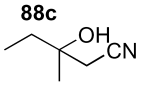
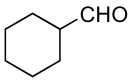
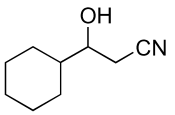
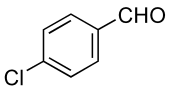
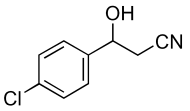
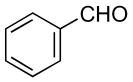
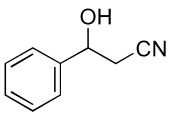
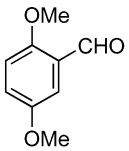
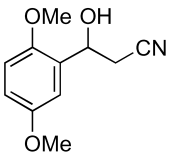
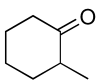
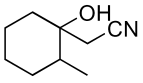
Table 13. 1,2-Addition of allylic synthons

Aldehyde	Allylic substrate	Product	Reaction conditions	Yield (%)
PhCHO		 **83**	−63°C, 3 h, 40 mol% **1d**	88
 **64a**		 **84**	−63°C, 3 h, 40 mol% **1d**	88
PhCHO		 **81**	−94°C, 3 h, 40 mol% **1d**	94
 **65a**		 **85**	−78°C, 3 h, 40 mol% **1d**	87
PhCHO		 **82**	−63°C, 3 h, 20 mol% **1d**	88
 **64a**		 **86**	−84°C, 3 h, 40 mol% **1d**	95
PhCHO		 **87**	−78°C, 3 h, 25 mol% **1d**	63



Scheme 19.

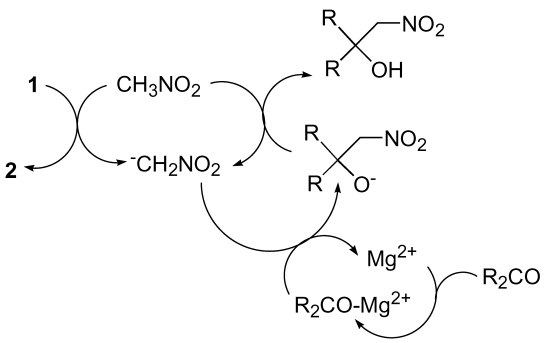
Table 14. Preparation of β-hydroxy nitriles in the presence of 0.2 equiv. of **1d** and 2.2 equiv. of $MgSO_4$

Substrate	Product	Isolated yield (%)	α,β-Unsaturated product observed[a] (%)	Residual substrate observed[a] (%)
Acetone	 **88a**	99	0	0
 **89b**	 **88b**	99	0	0
 **89c**	 **88c**	54	22	20
 **89d**	 **88d**	97	0	0
 **75a**	 **88e**	95	0	<1
	 **88f**	88[a]	4	0
	 **88g**	96[a]	2	0
 **65a**	 **88h**	84[a]	0	15
 **89c**	 **88c**	95[b]	0	0

Compound **1b** was used in this reaction.
[a] Reaction was carried at 0°C and quenched with MeOH at this temperature before work-up.
[b] 10 mol% **1e** for 6 h at room temperature.

reaction of aldehydes with acetonitrile to give β-hydroxynitriles in very good to excellent yields. In several such reactions, **1e** was found to be much more reactive than **1f**. Our reaction is quite parallel to our synthesis of α,β-unsaturated nitriles except that it works well only when 2.2 equiv. of magnesium sulfate (or magnesium bromide) as a Lewis acid are present in the reaction mixture in order to stop the reaction at the β-hydroxy nitrile stage. No other Lewis acid among those tried ($AlCl_3$, BF_3, $BF_3{\cdot}OEt_2$ and HgI_2) was found to be suitable. Ketones participating in this reaction afford β-hydroxy nitriles as the only products, perhaps because of the sterically hindered nature of the tertiary alcohols produced which prevents further deprotonation by the bulky **2**/$^{-}CH_2CN$ ion pair. Aldehydes on the other hand form secondary alcohols which are less sterically hindered and can be easily deprotonated leading to the formation of detectable amounts of α,β-unsaturated nitriles. Primary aldehydes, however, undergo aldol condensations.[48] Table 14 illustrates the application of this methodology with representative carbonyl compounds.

Erosion in selectivity for the desired product with aromatic aldehydes was controlled by carrying out the reaction at 0°C and then quenching the reaction mixture at this temperature with methanol prior to warming to room temperature.[48] Contrary to our observation with **1j**, **1b** does not produce substantial quantities of the corresponding undesired α,β-unsaturated nitrile, and **1b** gives higher yields of the desired β-hydroxy nitrile. This is rationalized by the relatively stronger basicity of **1j** (resulting from its ability



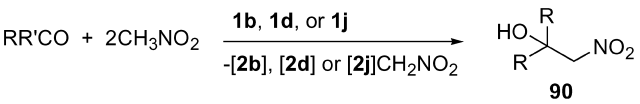
Scheme 20.

to exist in a transannulated zwitterionic amide form shown in the Introduction) which is less sterically hindered. Base **1j** is therefore better capable of effecting dehydration of the desired product. When **1b** was used as the catalyst for the reaction of benzaldehyde with benzyl cyanide instead of acetonitrile, the corresponding undesired α,β-unsaturated nitrile was formed quantitatively. However, the desired product was realized (99%) when the reaction was carried at −78°C in THF.[48]

5.2. Promotion of the nitroaldol (Henry) reaction

The Henry reaction is the most convenient for the preparation of β-nitroalkanols which are important and versatile intermediates in organic synthesis.[49] These compounds are easily transformed into nitroalkenes, 2-amino alcohols, and α-nitro ketones. 2-Aminoalcohols have been extensively used in the synthesis of biologically active compounds such as epinephrine and anthracycline antibiotics. α-Nitroketones have also been used as valuable intermediates in the synthesis of several natural products. In addition to being used as synthetic intermediates, β-nitroalkanols are important compounds because of their fungicidal properties. Classical methods for the Henry reaction include condensation of carbonyl compounds with a nitroalkane in the presence of an ionic base. Although this approach is quite simple and inexpensive, it is limited by its susceptibility to base-catalyzed elimination of water. Another limitation of the classical Henry reaction is the necessity for removal of the base before work-up because acidification may lead to the Nef reaction[50] (a degradation of the nitro compound to a carbonyl derivative) if extreme care is not exercised. The use of primary amines and Et_3N as condensing agents has led to the formation of 1,3-dinitro compounds and water elimination has also been observed in such preparations. More recent developments include the use of TMG, for example, but high product yields are not observed with ketones even when such reactions are observed.[4]

Proazaphosphatrane **1b**, **1d** and **1j** catalyze the nitroaldol reaction at room temperature in the presence of $MgSO_4$ in generally excellent yields.[49] Aldehydes react quantitatively in 5–60 min whereas ketones require up to 3 h with nitromethane and up to 7 h with higher nitroalkanes. In a comparison of the effectiveness of **1f** with **1e** and **1d** in these reactions, **1e** and **1d** were more efficacious. The simplicity of reaction (21) stems from the fact that the catalytic amount of base present is protonated during the transformation to form the **2b**, **2d** or **1j** salts cited. The proposed pathway of the reaction involving aldehydes using proazaphosphatranes of type **1** as the catalyst is shown in Scheme 20. Among the magnesium salts we tried, it is interesting that $MgSO_4$ was the only one that was effective as an activator of the carbonyl group. Moreover, ketone self-condensation was not problematic under our conditions. This observation may be associated with the weaker basicity of the nitronate ion compared with the alkoxide in Scheme 20. Thus the nitronate anion is unable to deprotonate the starting ketone; a process that would lead to self-condensation. Once the nitronate adds to the ketone, the alkoxide produced deprotonates preferentially the more acidic nitroalkane which is present in excess. Selected examples from a variety of the reactions we reported[49] are shown in Table 15 which shows that all the substrates afford high yields of the desired β-nitroalkanols. However, this methodology was ineffective for sterically hindered ketones such as 2,6-dimethylcyclohexanone and 2,4-dimethylpentanone, perhaps because of the bulky nature of the azaphosphatrane counter ion[49]



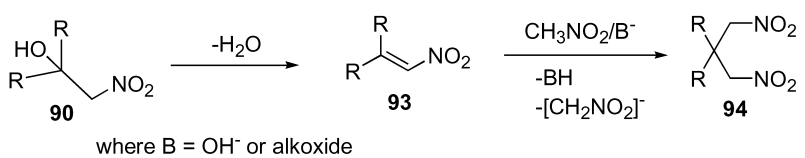
(21)

A side reaction observed in these transformations is the formation of a dinitro compound **94** arising from dehydration of the nitroaldol product followed by a Michael addition of nitronate to the unsaturated intermediate **93** as shown in Scheme 21. This side product was observed when the reaction was allowed to proceed for longer reaction times (typically 18 h) in the absence of a Lewis acid. However, the side reaction was easily controlled by the use of magnesium sulfate and reducing the reaction time to 1–6 h.

5.3. Synthesis of oxazoles and α-*C*-acyl amino acid esters

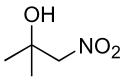
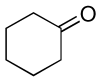
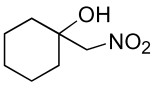
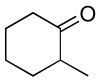
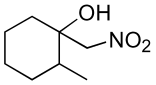
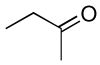
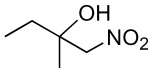
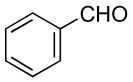
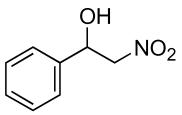
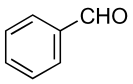
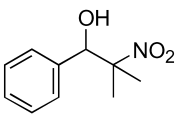
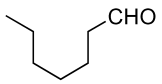
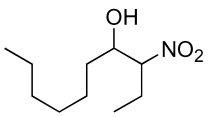
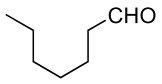
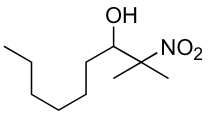
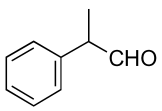
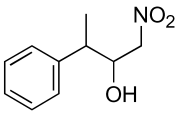
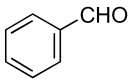
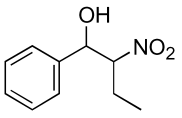
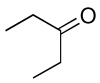
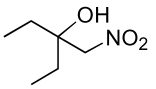
Oxazoles are widely reported in the literature as synthetic intermediates in the preparation of a number of pharmaceutically useful α-*C*-acyl amino acids used in the preparation of β-hydroxy amino acids, especially β-aryl serine and amino alcohols including sympathomimetic agents such as ephedrine and epinephrine.[51] Syntheses of oxazoles typically require the presence of a large excess of TEA or DBU over lengthy reaction times.

Proazaphosphatrane **1b** is a highly efficient base for preparing oxazoles in nearly quantitative yields in 1.5 h



Scheme 21.

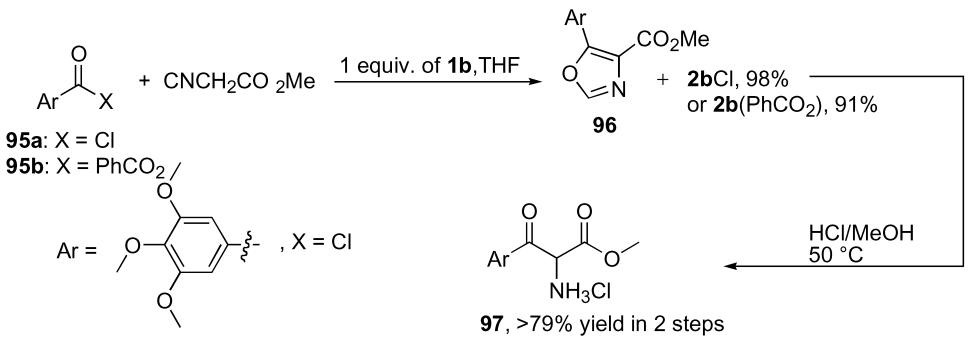
Table 15. The Henry reaction promoted by 10 wt% **1** in the presence of 2.2 equiv. $MgSO_4$

Substrate	Nitroalkane	Product	Catalyst (time)	Isolated yield (%)
Acetone	$MeNO_2$	 **90a**	**1d** (3 h)	91
 **89b**	$MeNO_2$	 **90b**	**1d** (3 h)	96
 **89c**	$MeNO_2$	 **90c**	**1d** (3 h)	40
 **89d**	$MeNO_2$	 **90d**	**1d** (3 h)	67
	$MeNO_2$	 **90e**	**1d** (40 min)	96
		 **91a**	**1d** (4 h)	95
 **92a**	$CH_3CH_2CH_2NO_2$	 **91b**	**1d** (1.25 h)	99
 **92a**		 **91c**	**1d** (4 h)	99
 **92c**	$MeNO_2$	 **90f**	**1d** (40 min)	88
	$CH_3CH_2CH_2NO_2$	 **91d**	**1e**[a] (2 h)	96
 **92d**	$MeNO_2$	 **90g**	**1f** (3 h)	78

[a] 20 mol%.

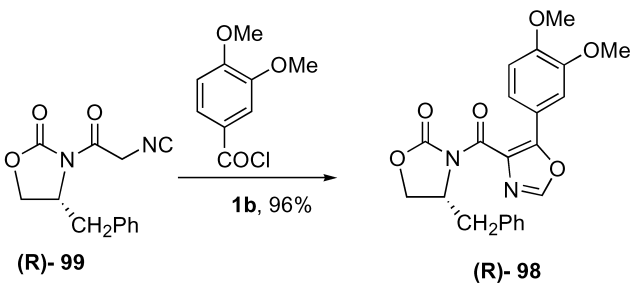
from acid chlorides or anhydrides in the presence of isocyanates (Scheme 22).[52] Acid hydrolysis of these products affords α-*C*-acyl amino acids in high yields. This process is advantageous over those employing DBU or TEA because the **2b** salts formed are easily separated from the product in high yield by filtration for subsequent recovery of the free base.

Proazaphosphatrane **1b** was also employed to construct oxazole rings in the synthesis of strongly fluorescent (*R*)-**98** and (*S*)-**98** prepared from the chiral auxiliary-bearing isocyanides (*R*)-**99** and (*S*)-**99**, respectively, which we also synthesized for the first time.[53] Optically active fluorescent materials with high quantum yields and/or strong circular



Scheme 22.

dichroism signals are rare, but they are important standards in fluorescence-detected circular dichroism for on-column capillary electrophoresis (FDCD-CE).[53] The new oxazoles (*R*)-**98** and (*S*)-**98** were found to have high fluorescence quantum yields of 0.99 in EtOH.

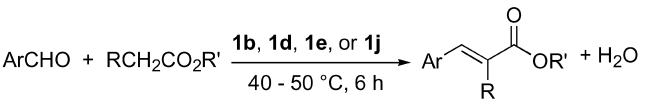


(22)

5.4. Direct synthesis of *E*-α,β-unsaturated esters

The most commonly used methods for the preparation of *E*-α,β-unsaturated esters are the Wittig and the Wittig–Horner–Wadsworth, Peterson and Julia-Lithgoe olefinations, and the Perkin reaction (which gives low to modest yields of α?β-unsaturated acids even at elevated temperatures) in addition to a number of reactions involving a variety of organometallic compounds.[54] Most of these reactions have limitations which include low selectivity for the *E* isomers, requirements for high temperatures and/or toxic reagents, low yields and added cost as a result of the need to prepare required intermediates.

In the presence of proazaphosphatranes as stoichiometric reagents, α,β-unsaturated esters **101** and **102** are formed as the sole products with excellent *E* stereoselectivity upon reacting ethyl acetate (**100a**) or methyl propionate (**100b**) in isobutyronitrile with a variety of aromatic aldehydes at 40–50°C for 2–6 h.[54] Among the proazaphosphatranes evaluated in this reaction were **1b**, **1d**, **1j** and **1e**. Some comparative studies showed that **1d** is as effective as **1e** for this reaction[9] as shown in Table 16. Reaction (23) is convenient because cheaper esters (e.g. ethyl acetate or methyl propionate) can be used as solvents, leading to an improved *E* selectivity, especially in the case of the preparation of trisubstituted alkenes[54]



(23)

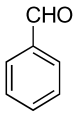
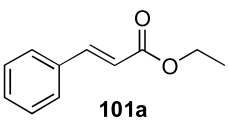
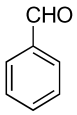
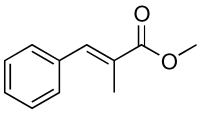
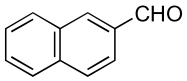
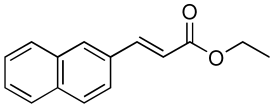
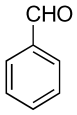
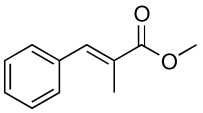
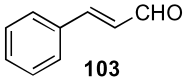
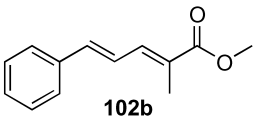
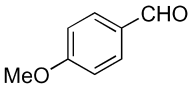
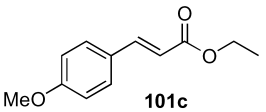
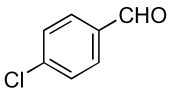
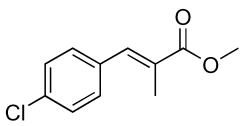
The necessity for using isobutyronitrile as the solvent in reaction (27) instead of acetonitrile stemmed from the ease with which the latter solvent was deprotonated by **1d** followed by reaction with aldehydes to form β-hydroxynitriles[48] and α,β-unsaturated nitriles.[39,44] Experimental evidence was presented that was consistent with a greater deprotonating ability (basicity) of **1d** in the solvent acetonitrile, and/or prior deprotonation of acetonitrile by **1d** with subsequent deprotonation of the ester or ketone by the $^{-}CH_2CN$ ion produced.[54] In addition, evidence was given for either a stronger basicity of **1d** in ethyl acetate/isobutyronitrile mixtures or that a proton transfer equilibrium is reached more rapidly via the $^{-}CH_2CN$ or the $^{-}C(Me_2)CN$ ion.[54] The reaction described here is less successful for the preparation of α,β-unsaturated ketones. The proposed pathway for the stoichiometric reaction shown in Scheme 23 is initiated by a pre-equilibrium that apparently lies far to the left.

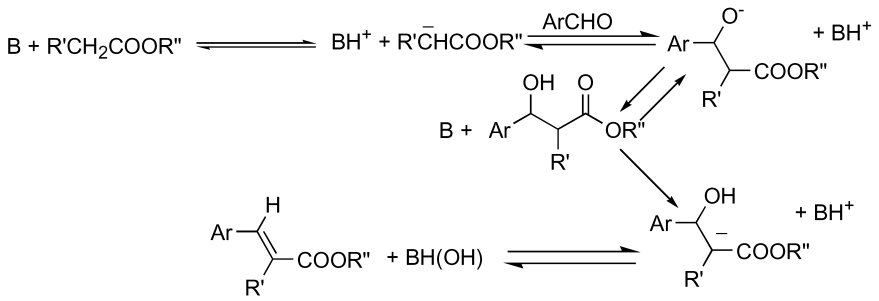
5.5. Synthesis of 3-substituted coumarins

Despite the wide spread application of coumarins in organic synthesis, newer routes to this class of compounds continue to attract attention.[55] Among recent approaches to these compounds is the use of flash vacuum pyrolysis in an attempt to circumvent the problem of variable yields and tedious work-ups encountered in Wittig olefination–cyclizations.[56] A rhodium-catalyzed process was recently introduced, but this approach produced a mixture of coumarins and benzofurans.[56]

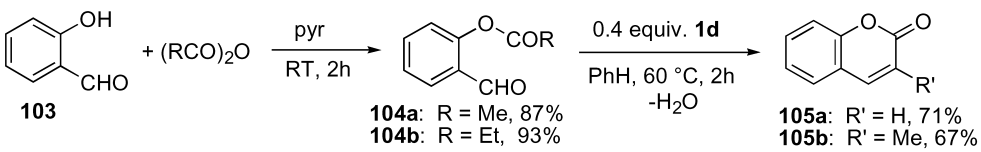
Proazaphosphatrane **1d** was found to promote the cyclization of the intermediate aldehydes **104** in benzene (Scheme 24) in a process that can be envisaged as an intramolecular version of our preparation of α,β-unsaturated esters.[54] Yields observed in this scheme are modest but because of the moderate temperatures used, our approach represents a reasonable alternative to other literature processes such as pyrolysis and Witting-olefination cyclizations.

Table 16. Direct preparation of α?β-unsaturated esters in the presence of 1.06 equiv. of **1**

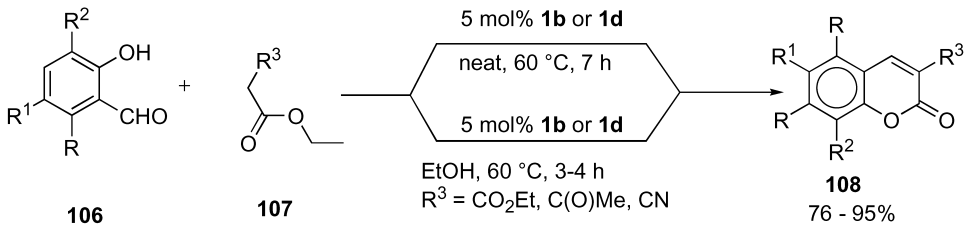
Substrate	Product	Base/temperature/reaction time (h)/solvent	Yield (%) (*E*/*Z*)
	 **101a**	**1d**/40/2/Me_2CHCN	96 (100:0)
	 **102a**	**1d**/40/2/Me_2CHCN	91 (10:1)
 **41**	 **101b**	**1d**/50/6/EtOAc	96 (100:0)
	 **102a**	**1d**/50/6/$EtCO_2Me$	93 (100:0)
 **103**	 **102b**	**1d**/50/6/$EtCO_2Me$	64 (100:trace)
 **63a**	 **101c**	**1e**/50/6/EtOAc	91(100:0)
 **65a**	 **102c**	**1e**/50/6/$EtCO_2Me$	95(100:0)



Scheme 23.



Scheme 24.



Scheme 25.

The Knoevenagel condensation has often been used to prepare 3-substituted coumarins. Highly efficient reactions have recently been reported involving the condensation of salicylaldehydes with malonates in which yields of 92–94% were realized.[56] However, the temperatures employed are somewhat elevated (100–120°C). Reactions using ethyl cyanoacetate in benzene or isobutyronitrile were not as successful with **1d** because up to 1.5 equiv. of the base and 1.2 equiv. of ethyl cyanoacetate were required to achieve a high yield (94%) of the desired coumarin. However, by carrying out the reaction neat or in ethyl alcohol, 76–95% yields were observed in the presence of only 5% **1d** or **1b** at 60°C for 3–4 h (Scheme 25).[56] While the observed yields (80–95%) in our protocol are not superior to those reported in the literature, the mild reaction conditions and the shorter reaction times render it an attractive practical alternate route to coumarins.

5.6. Synthesis of substituted benzofuran-2-ethyl carboxylates

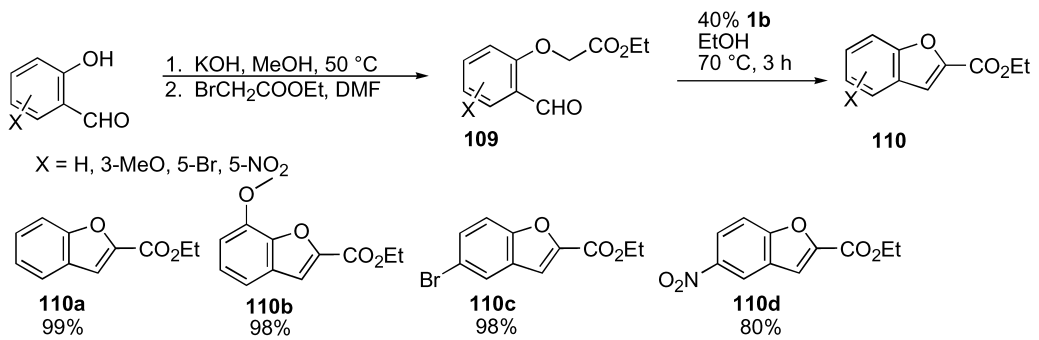
Benzofurans constitute a class of compounds that are popular for forming the core structure of fluorogenic reagents, CNS depressants, bacteriostatic agents, inflammation inhibitors, angiotensin II type I receptor antagonists, antitumor antibiotics and analgesic agents.[57] The commonly encountered problem with literature processes is low yields (44% in the case of DBU[57]) and the fact that indirect synthetic routes have to be taken.

Using **1b** as a catalyst in refluxing ethanol, an efficient direct synthesis to a variety of functionalized ethyl 2-benzofuran carboxylates in very high yields (80–99%) was achieved. The required aldehydes for this reaction were prepared from commercially available 2-hydroxyaldehydes (80–95%) using a modified literature procedure.[57] Proazaphosphatrane **1b** induced an intramolecular aldol cyclization of the intermediate aldehydes to afford the title compounds after thermal dehydration.[57] Several other bases studied gave inferior yields. Thus when X=H, observed yields were **1b**, 98%; DBU, 60%; DMAP, 0%; DABCO, 0%; sodium ethoxide, 0%; diisopropylethylamine, 0%. High yields utilizing **1b** were also observed for products **110a-d** shown in Scheme 26. The phosphazene base P_4-*t*-Bu has recently been found by us to promote the related formation of benzofurans for which **1b** was found to be ineffective.[58]

5.7. Michael addition of nitroalkanes and Schiff bases of α-amino esters

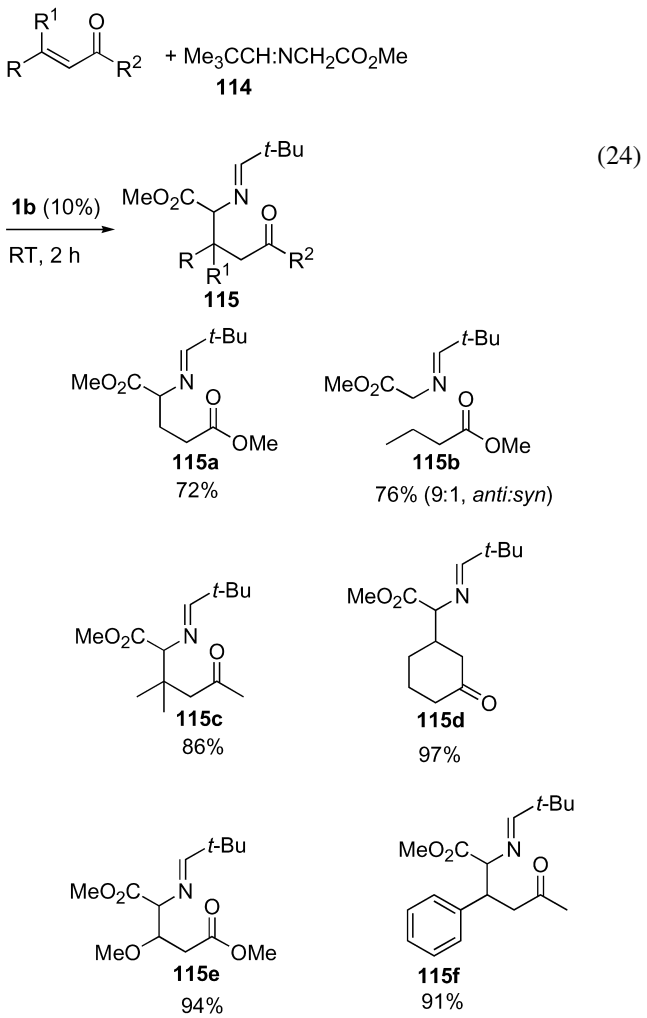
Michael addition is perhaps one of the most efficient reactions for the construction of C–C bonds as is manifested by the substantial attention it continues to receive in the literature and the newer versions that continue to be introduced.[59] Traditionally, this reaction has been achieved by adding anions generated from nitroalkanes, ethylcyanocarboxylates and malonates to Michael acceptors such as α,β-unsaturated carbonyl compounds. Historic limitations have largely been overcome by newer methodologies.[60] However, these more recent approaches are still more problematic because of long reaction times, modest product yields in many cases and the requirement for excess nitroalkane. Michael adducts prepared from Schiff bases have traditionally been used to prepare α-amino esters functionalized at the α-position although this reaction has been reported to undergo a competing cycloaddition process, depending on the presence of added metal ions.[61]

Higher nitroalkanes [such as 2-nitropropane (**112d**) in Table 17] and nitrocyclohexane (**112b**), and Schiff bases of α-amino esters (**114** in reaction (28)) undergo a facile Michael addition to α,β-unsaturated substrates to produce the corresponding products (**115**) in moderate to excellent yields when carried out at −63°C to room temperature in the presence of catalytic amounts of **1b**, **1d** or **1e** in isobutyronitrile.[9,60] Noteworthy is the observation that these catalysts do not require a metal ion (such as Li^+) to facilitate Michael adduct synthesis as has been observed for



Scheme 26.

reactions in which DBU or Et_3N is utilized.[61]



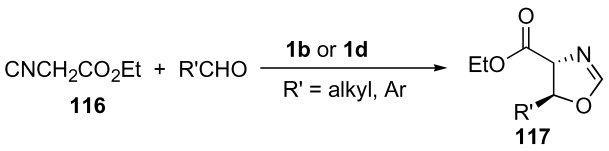
(24)

high yields (up to 94%) were obtained in Michael additions of nitromethane using the less basic catalyst TBD at 0°C.[62] With proazaphosphatrane **1d**, a high yield (78%) was observed upon reacting nitromethane with cyclohexenone at −63°C.[60]

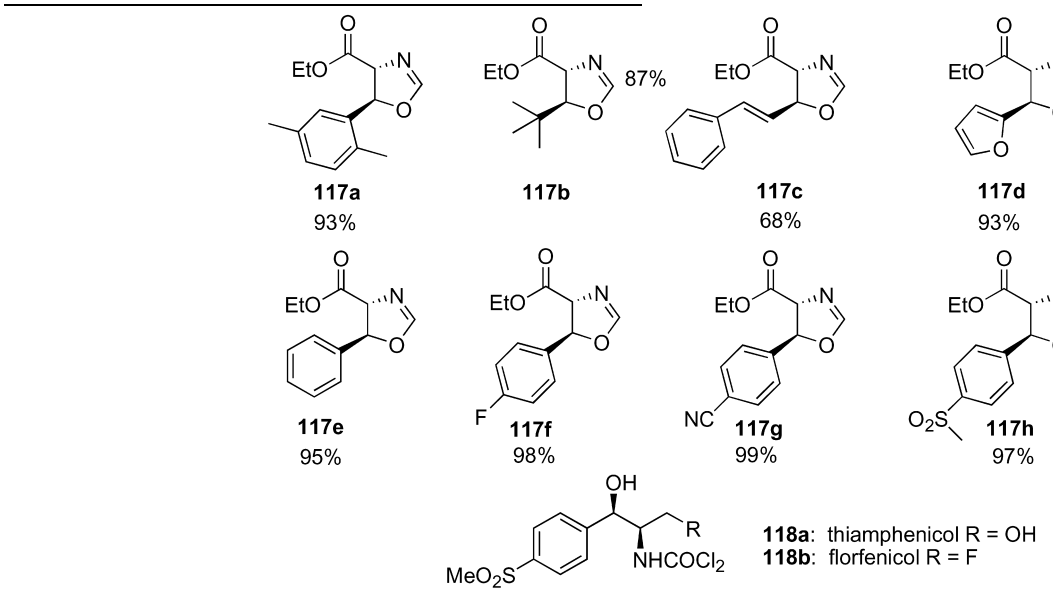
5.8. Diastereoselective synthesis of oxazolines

Oxazolines are versatile intermediates in the synthesis of β-substituted serines[63] which are widely used in the synthesis of various antibiotics such as hypeptin[64] and leucinostatin.[65] Although ethyl isocyanoacetate is ideal for the synthesis of oxazolines, via deprotonation using mild bases and subsequent addition to aldehydes, this reaction has been plagued by its lack of diastereoselectivity.[66]

Proazaphosphatranes **1b** and **1d** serve as efficient catalyst systems for the synthesis of oxazoline alkyl carboxylates in isobutyronitrile in good to excellent yields with diastereoselectivities in excess of 95:5 (reaction (25)).[66] The oxazoline carboxylate derived from *p*-methylsulfonylbenzaldehyde (**117h**, which was synthesized in 97% yield) is of particular interest because an analogous oxazoline was previously used as an intermediate in the synthesis of the broad spectrum antibiotics thiamphenicol (**118a**) and florfenicol (**118b**).[67] Aliphatic aldehydes bearing α-protons gave complex mixtures consisting of the desired compounds, Knoevenagel products and other species that were not identified.[66]



(25)

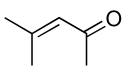
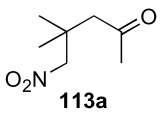
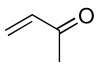
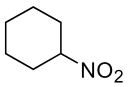
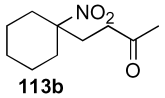
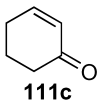
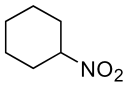
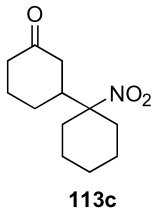
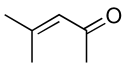
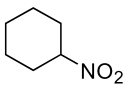
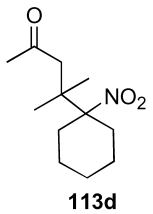
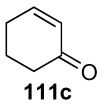
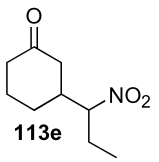
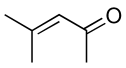
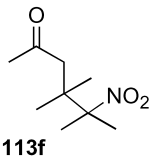


Lower nitroalkanes such as nitromethane (**112a**) afford paltry yields under our conditions owing to nitroaldol reaction with the products formed from methyl vinyl ketone and cyclohexenone, for example.[60] However, this methodology complements a recently reported process wherein

6. Deprotonation of proton-bearing heteroatoms

Several reactions have been observed resulting from the deprotonation of a hydrogen bonded to nitrogen or oxygen. Although there is no report for the deprotonation of the

Table 17. Michael addition of nitroalkanes in the presence of catalytic amounts of **1** in isobutyronitrile

Substrate	Nitroalkane	Product	Base/temperature (°C)/time (h)	Yield (%)
 **111a**	$MeNO_2$ **112a**	 **113a**	**1d**/rt/0.5	99
 **111b**	 **112b**	 **113b**	**1e**/rt/0.25	93
 **111c**	 **112b**	 **113c**	**1d**/rt/1	99
 **111a**	 **112b**	 **113d**	**1e**/rt/1	95
 **111c**	*n*-$PrNO_2$	 **113e**	**1d**/−63°C/0.25	71
 **111a**	*i*-$PrNO_2$ **112d**	 **113f**	**1d**/rt/0.33	99

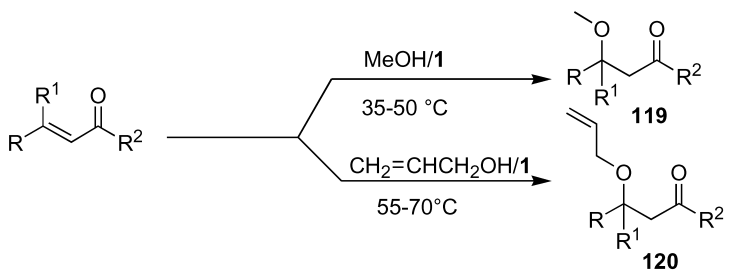
amine N–H proton using proazaphosphatranes, the corresponding amide N–H is readily deprotonated by these bases.

6.1. Oxa-Michael addition of alcohols

The preparation of β-alkoxyketones is an important process because the protected β-hydroxy carbonyl compounds so produced are of significance in organic synthesis. Literature reports for this transformation are limited.[9,60] We serendipitously discovered the proazaphosphatrane-catalyzed 1,4-addition of alcohols when we attempted dimerization of pent-3-en-2-one in methanol.[9,60]

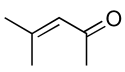
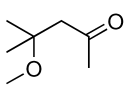
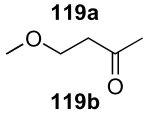
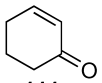
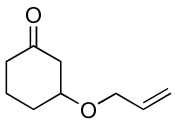
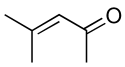
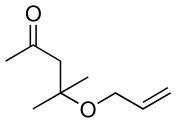
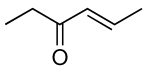
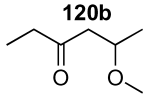
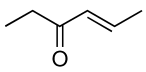
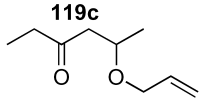
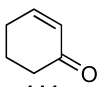
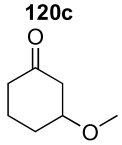
In reactions mediated by catalytic amounts of proazaphosphatranes, good to excellent yields of hydroalkoxylated products were obtained under the conditions indicated in Scheme 27 using **1b**, **1d** or **1e**.[9,60] When compared under similar conditions, **1f** and **1e** were more efficient for the addition of allyl alcohol than **1d**. Higher alcohols, such as *t*-butyl alcohol and 2-propanol, did not add to α,β-unsaturated ketones under these conditions (Table 18). Although this reaction is not completely general, it is appears to be more general than other literature procedures.

Because the addition of methanol to ethyl crotonate (as an



Scheme 27.

Table 18. Oxa-Michael addition reactions mediated by pro-azaphosphatranes

Substrate	Alcohol	Product	Base/Temperature (°C)/Time (h)	Yield (%)
 **111a**	MeOH	 **119a**	**1d**/50/0.5	79
 **111b**	MeOH	 **119b**	**1d**/50/0.5	65
 **111c**	CH_2=$CHCH_2OH$	 **120a**	**1d**/70/3	58
 **111a**	CH_2=$CHCH_2OH$	 **120b**	**1e**/70/3	88
 **111d**	MeOH	 **119c**	**1e**/50/0.5	96
 **111d**	CH_2=$CHCH_2OH$	 **120c**	**1e** or **1f**/70/3	96
 **111c**	MeOH	 **119d**	**1e**/70/3	89

attempted example of hydroxy-methylation of esters) led to transesterification,[27] hydroxymethylation of α,β-unsaturated esters in the presence of proazaphosphatranes presently appears to be of limited practical utility.

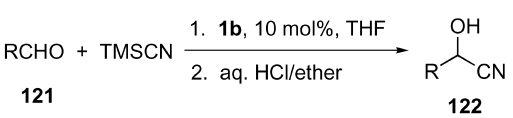
6.2. Polymerization of lactams

The reaction of lactams with **1b** as a catalyst at elevated temperatures gives high molecular weight polyamides.[68] For example, heating ε-caprolactam at 203°C in the presence of catalytic amounts of **1b** gave a polymer with a stable melt viscosity. This reaction mimics that observed with anionic catalysts with the advantage that trace amounts of moisture can be tolerated. At 270°C, other lactams also gave high molecular weight polymers such as nylon 6, 7, and 66 using either **1b** or one of several phosphazene bases.

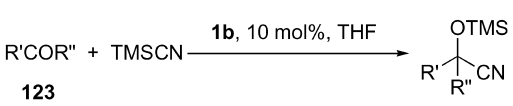
7. Other additions to aldehydes and ketones

7.1. Reaction of aldehydes and ketones with trimethylsilyl cyanide

Cyanohydrin trialkysilylethers and cyanohydrins continue to play a significant role in organic synthesis. As a result, considerable attention has been given to these compounds and a variety of catalysts have been developed for the title reaction including Lewis acids, transition metal complexes, 18-crown-6 complexes of alkali metals, tetracyanoethylene, Lewis bases and alkaline earth bases.[69] In a rare example of a Lewis base-mediated trimethylsilylcyanation of carbonyl compounds, **1b** was found to be an effective catalyst for the addition of trimethylsilyl cyanide to aldehydes and ketones under mild conditions, giving cyanohydrins and cyanohydrin silyethers, respectively, in moderate to high yields (reactions (26) and (27))[70]



121 **122** (26)



123 **124** (27)

Under the mild conditions employed, aldehydes formed a mixture of the corresponding cyanohydrins and cyanohydrin silylethers.[70] Desilylation was observed even when the reaction temperature was carried out at 0°C. As a result, the crude product was treated with aq. HCl to afford the cyanohydrins as the only products in high yields. Aromatic aldehydes bearing electron withdrawing

Cl or CN substituents gave low yields of the product cyanohydrins. Optically active **1k** also produced cyanohydrins (95%) with benzaldehyde but no enantioselectivity was observed.[70]

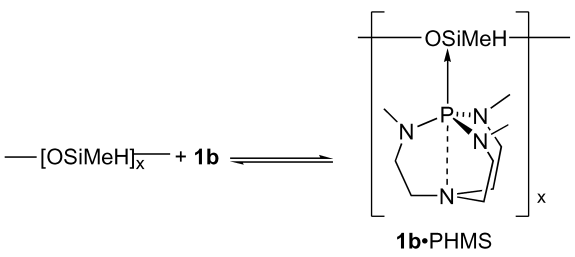
Both aromatic and aliphatic ketones smoothly produced cyanohydrin silylethers at room temperature in moderate to high yields in the presence of **1b** (reaction (31)). With α,β-unsaturated ketones, 1,2-addition products were regioselectively produced. 4-*t*-Butylcyclohexanone and (−)-menthone generated the desired cyanohydrin silylethers in high yields with poor diastereoselectivity, while (1*R*)-(+)-camphor gave a low product yield but diastereoselectivity was excellent.[70]

The trimethylsilylcyanation intermediate in our reactions appears (on the basis of ^{31}P and ^{1}H NMR evidence) to involve a pentacoordinate silicon formed from **1b** and TMSCN as shown in Scheme 28. Such an intermediate is analogous to that suggested in the literature for an amine, a phosphine, a stibine, or an arsine ligand.[70] The lack of enantioselectivity induced in the trimethylcyanation of prochiral benzaldehyde by the use of **1k** could well be associated with the considerable distance between the chiral region and the aldehyde functionality as is depicted in Scheme 28 for **1b**.[70]

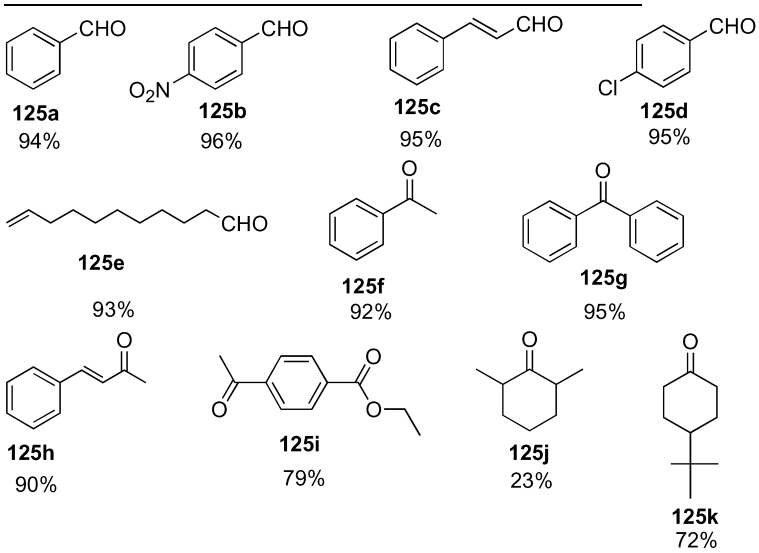
7.2. Reduction of aldehydes and ketones with poly(methylhydrosiloxane)

Hydrosilylation of carbonyl compounds is one of the most effective methods for the synthesis of alcohols. Asymmetric versions of these reactions have also been introduced in which chiral diols or chiral aminoalcohols are used as complexing ligands with organosilicon reagents.[71] The recent introduction of the use of polymethylhydrosiloxane (PMHS) has been quite popular for the reduction of imines,[71d] azides[71e] and esters[71f] in the presence of a catalyst. Although aldehydes and ketones can be reduced by PMHS in the presence of fluoride, bis(dibutylacetoxy)tin or $ZnCl_2$, the yields are modest and/or harsh reaction conditions must be employed.[72]

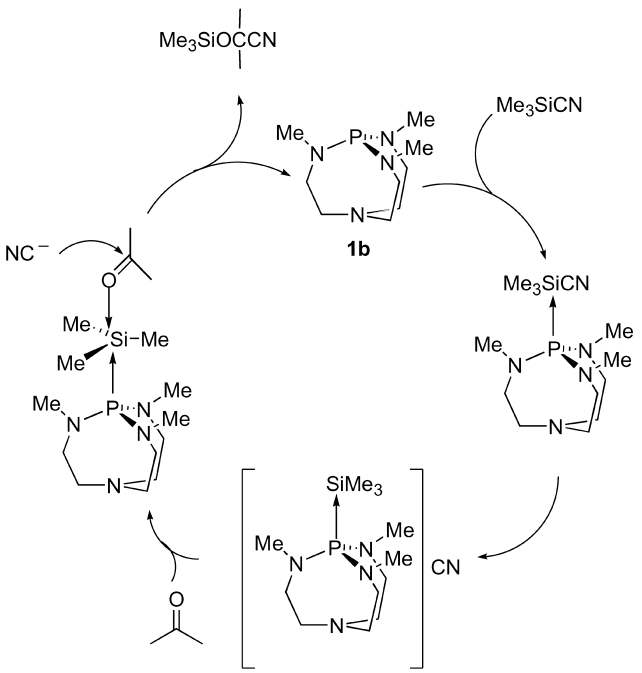
In the presence of **1b** as a catalyst, a variety of aromatic and aliphatic aldehydes and aliphatic ketones were efficiently reduced to the corresponding alcohols in high yields.[72] This reaction was found to be compatible with various functionalities such as aromatic chloro, nitro, cyano, and methoxy groups in addition to isolated as well as conjugated double bonds. Although aliphatic aldehydes undergo aldol condensation in the presence of proazaphosphatranes,[48] they were efficiently reduced to the corresponding alcohols (92–96%) in 1 h.[72] We assume that under our reaction conditions an equilibrium is rapidly established between **1b**, PMHS, and the P→Si coordinated adduct which lies sufficiently far toward the adduct (reaction (28)) that aldol condensation via initial deprotonation of the aldehyde by **1b** is effectively suppressed. The analogous reduction of sterically hindered aromatic and aliphatic ketones occurred in yields of 79–95 and 64–74%, respectively, in 12 h.[72] It was also shown that aldehydes are reduced much more rapidly than ketones, thus allowing for a chemoselective reduction of an aldehyde in the presence of ketones. The carbonyl compounds below were reduced in the yields shown, wherein the adverse role of steric hindrance in the postulated intermediate **1b**·PHMS is evident in sterically hindered **125j**, for example.



(28)



A mechanistic rationale proposed for this reaction parallels that put forth earlier in the literature for the reduction of carbonyl compounds with hypervalent hydrosilicates.[72] The pentacoordinate silicate coordinates a carbonyl group with concomitant formation of a hexacoordinate hydrosilicate followed by H transfer to the carbonyl carbon to form the silylether linkage. The alcohol is formed during workup in aqueous NaOH or in HF/CH_3CN. When $P(NMe_2)_3$ (in which transannulation is not possible) was employed under the conditions used, no detectable reduction product was



Scheme 28.

observed. The ^{29}Si NMR spectral evidence was also presented which supports the presence of five-coordinate silicon intermediacy.[72]

8. Elimination of HX

8.1. Ylide generation for Wittig and related reactions

A variety of bases have been reported in the literature for generating ylides for the Wittig (Scheme 29) and Wittig-Horner (reaction (29)) products, and **1b** is also an efficient base for preparing alkenes via these reactions.[73] Thus, **1b** deprotonates $[RCH_2PPh_3]X$ and $RCH_2P(O)(OEt)_2$ to their corresponding ylides and anions, respectively, under mild conditions. As indicated in Scheme 29, aldehydes such as benzaldehyde give the corresponding olefins (70–92%) with *E*/*Z* selectivities comparable to those reported with classical bases

$$\underset{\textbf{126b}}{RCH_2P(O)(OEt)_2} \xrightarrow{\textbf{1b},\ (Ar)R'CHO} \underset{\textbf{128b}}{(Ar)R'CH{=}CHR} \qquad (29)$$

The reaction of proazaphosphatrane **1b** with various alkyl halides has also been used to generate the ylides **1b**=CHR (**127b**) after dehydrohalogenation with strong bases such as sodium bis(trimethylsilyl)amide (NaHMDS).[74] These semi-stabilized ylides react with aldehydes to form exclusively *E*-olefins.

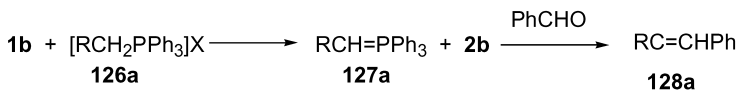
8.2. Preparation of sulfur ylides

Sulfur ylides have traditionally been prepared via the reaction of sulfonium salts with ionic bases such as alkali metal alkoxides, amides and hydrides. Less stable ylides are usually prepared by the deprotonation of the sulfonium salt with a strong base such as LDA or *n*-BuLi.[75] Such ylides are nucleophilic alkylidene transfer reagents in reactions with electron-deficient functional groups as in epoxide formation from carbonyl compounds. Ylides can also undergo conjugate addition with structurally appropriate Michael acceptors resulting in cyclopropanation.[75]

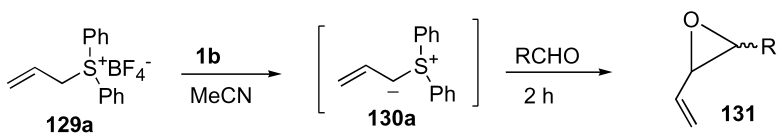
Proazaphosphatrane **1b** was found to deprotonate sulfonium salts to produce both somewhat stable and nonstable ylides in acetonitrile.[76] These ylides readily react with aromatic aldehydes (Schemes 30 and 31) to give oxiranes, generally in (70–96%) without evidence of sigmatropic rearrangement as is sometimes seen with the use of *n*-BuLi. It should be noted that the product of Scheme 29 corrects the structure erroneously shown earlier[76] as an allyl oxirane. Although THF or ether can be used as solvents for this reaction, they tend to give lower yields (Table 19).

8.3. Selective monoalkylation of diactivated methylene compounds

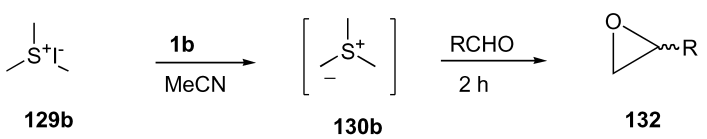
Alkylations and acylations of active methylene compounds such as malonic esters, β-diketones, and β-keto esters are



Scheme 29.

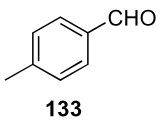
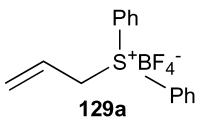
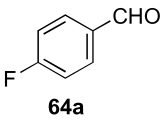
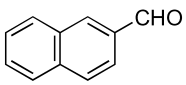
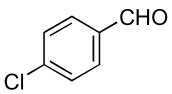
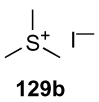
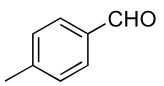
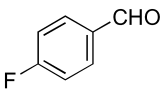


Scheme 30.



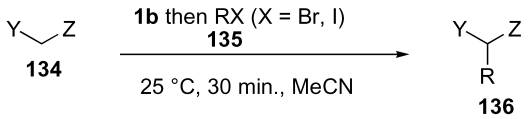
Scheme 31.

Table 19. Preparation of oxiranes using **1b**

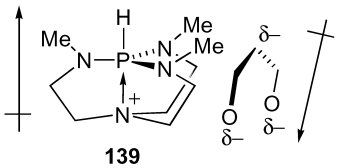
Substrate	Sulfonium	Yield of oxirane (%)	*trans*/*cis*
 **133**	 **129a**	90	82:18
 **64a**		92	71:29
 **41**		88	68:32
 **65a**	 **129b**	83	
 **133**		79	
 **64a**		75	

important reactions in organic synthesis because the monosubstituted product can be converted into useful compounds such as ketenes or esters.[77] Such products can also be converted into α,β-unsaturated esters and ketones. However, attempts to monosubstitute diactivated methylene compounds generally lead to concurrent disubstitution, condensation reactions and significant *O*-alkylation if the equilibrium concentration of the enol tautomer is relatively high as with β-keto esters and β-diketones.[77] The use of a nonionic base such as DBU does not seem to overcome all of these problems and in addition only moderate yields are realized despite relatively long reaction times.[78]

Base **1b** mediates selective monoalkylation of symmetrical diactivated methylene compounds under mild conditions, and the yields are generally high to excellent (85–98%, reaction (30) and Table 20).[78] Quantitative conversions are typically observed with no detectable amounts of a dialkylated product. With unsymmetrical diactivated methylene compounds, residual starting material was observed at the end of the reaction time, in addition to some dialkylated produc. However, reasonable yields of the desired monoalkylated products were also obtained (59–88%).[78] We speculate that the observed preferential *C* to *O*-alkylation is attributable to steric protection and charge neutralization of the negatively charged enolate oxygens by the large diffusely charged cation of the ion pair **139**.[78]



(30)



139

8.4. Dehydrohalogenation of alkyl halides

Dehydrohalogenation is of great utility in organic synthesis because of the ease with which this reaction introduces unsaturation into organic molecules. This is demonstrated by its wide spread application in the synthesis of a variety of biologically active compounds including prostaglandins, Vitamin A and polyenes.[79,80] Because organic bases such as Et_3N, DMAP, pyridine and quinoline usually lead to unsatisfactory yields for such reactions, more basic and nonnucleophilic bases such as DBN and DBU have been employed. However, these reagents are usually required in large excess with heating to afford product but yields are usually not high.[79,80]

Proazaphosphatrane **1b** was found to promote the dehydrohalogenation of a number of halides. In cases where

Table 20. Monoalkylation of deactivated methylene compounds using **1b**

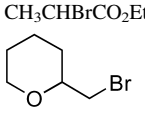
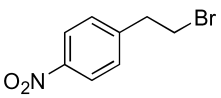
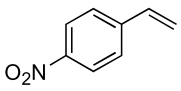
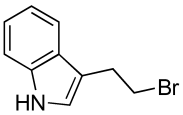
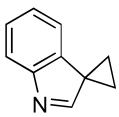
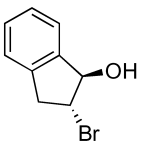
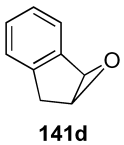
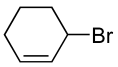
RX **135**	Yield (%) of $CHR(CO_2Et)_2$ **136**	Yield (%) of $CHR(COMe)_2$ **137**	Yield (%) of $MeCOCHRCO_2Et$ **138**
MeI (**135a**)	98	96	71
EtI (**135b**)	92	85	78
i-PrI (**135c**)	98	86	70
$CH_2{=}CH{-}CH_2Br$ (**135d**)	94	94	80
$PhCHBrCH_3$ (**135e**)	92	98	87
$CH_3CHBrCO_2Et$ (**135f**)	93	95	88
 **135g**	88	86	59

Table 21. Elimination of HX from alkyl halides using **1b**

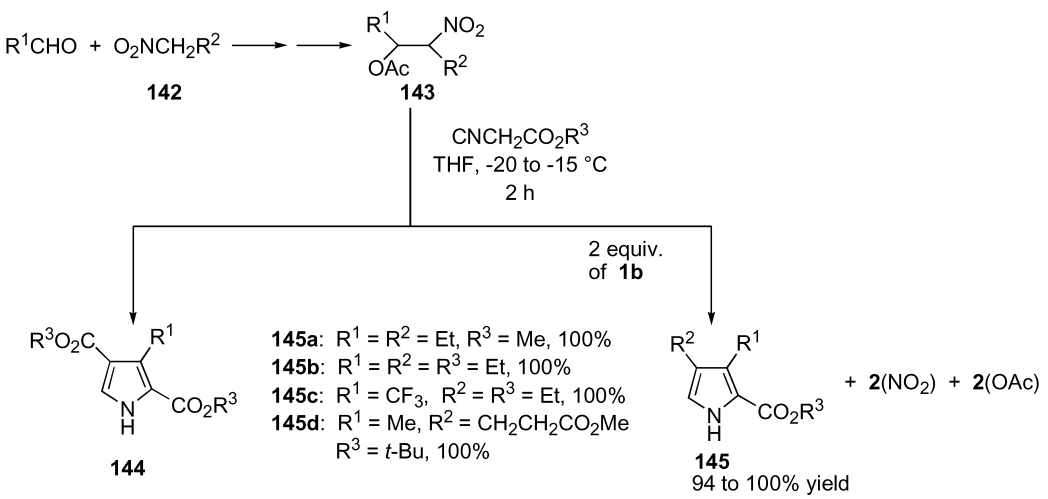
Substrate	Product	Time (h)	Yield (%) with **1**	Conversion with DBU (%)
 **140a**	 **141a**	1/12	98	87
$BrCH_2CH_2COCl$ **140b**	$CH_2{=}CHCOCl$ **141b**	1/12	90	18
 **140c**	 **141c**	1/12	98	87
 **140d**	 **141d**	1/12	92	85
 **140e**	 **141e**	24	85	50

epoxide or lactone formation was possible, these reactions occurred in preference to alkene formation (Table 21).[80a] It is interesting that rates of elimination employing **1b** are enhanced in acetonitrile. NMR studies carried out in CD_3CN showed that **1b** dedeuterates the solvent, giving deutereo-**2b**, and the $^{-}CD_2CN$ anion that promotes the reaction. Because the *t*-Bu^+ ion is more stable than the *i*-Pr^+ ion under the S_N1 conditions favored in a polar solvent such as acetonitrile, our observation of a faster reaction of *t*-BuBr with **1b** than of *i*-PrBr by a factor of about 3 is therefore rationalized. This observation is also consistent with the strong E2 component expected in these dehydrohalogenations.[80a]

8.5. Synthesis of pyrroles

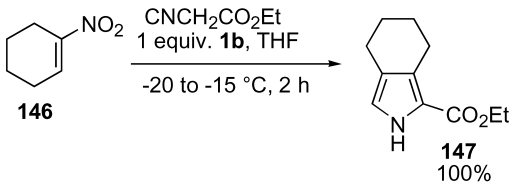
Substituted pyrroles are important intermediates in the synthesis of bioactive porphyrins, bile pigments, drugs and agrochemicals. As an example, octaethylporphyrin (OEP) is widely used for biological modeling studies because of its high symmetry, relatively good solubility, and stability.[52]

Using **1b**, an efficient 'one pot' process was developed for the synthesis of α-(alkoxycarbonyl) pyrroles and also for a more efficient synthesis of OEP in (62%) which is significantly higher than yields previously reported by other methods (22–45%).[52] Thus, **1b** leads to quantitative yields of α-(alkoxycarbonyl) pyrroles under exceedingly mild conditions. Unlike the salts of DBU or guanidine, the salts of **2b** shown in Scheme 32 are insoluble in THF and are readily separated for recovery of **1b**. We believe that the strong basicity of **1b** facilitates rapid and complete elimination of HOAc



Scheme 32.

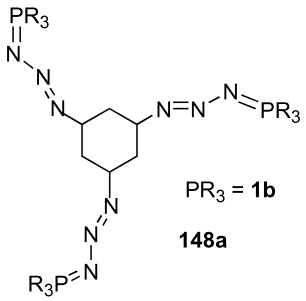
in the first step and the rapid conversion of the isocyano acetate to the enolate followed by a Michael addition of the enolate to the alpha-nitro olefin, even at low temperature (Scheme 32). The enolate may well be more nucleophilic compared with similar anions obtained by deprotonation of isocyanoacetate with ionic bases or with nonionic bases such as DBU or guanidine, owing to effective charge delocalization in cation **2b** as was discussed earlier. The pathway in Scheme 33 is supported by reaction (31) in which 1-nitrocyclohex-1-ene (**146**) reacts with isocyanoacetate in the presence of **1b** to afford the expected 2-pyrrole ethylcarboxylate **147**



146 **147** 100% (31)

8.6. Accidental synthesis of benzene

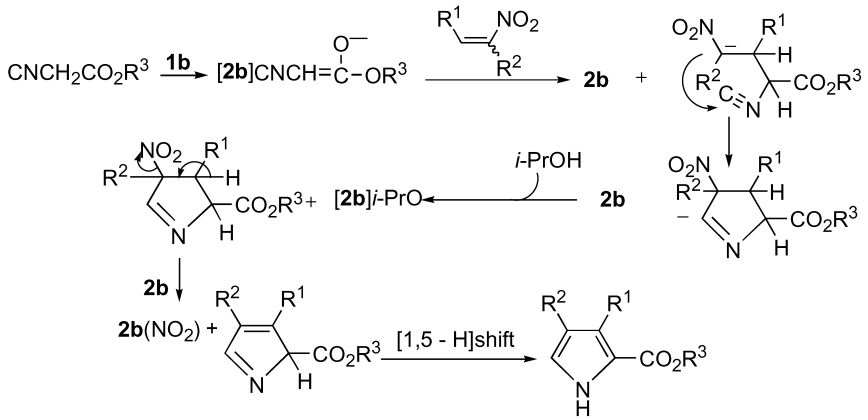
The preparation of benzene via aromatization of cyclohexane derivatives at elevated temperatures (90°C and above) is well known. However, this process has apparently not been reported to occur at room temperature. While the synthesis of benzene to be described using the precursor **148a** shown above is quite impractical, it readily takes place at room temperature and proceeds by a novel pathway that also produces interesting side products.[81]



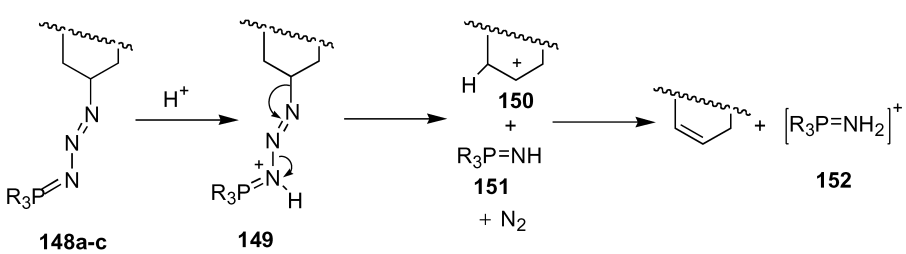
148a

Compound **148a** is remarkably thermally stable to loss of dinitrogen to give the corresponding trisimidophosphorane even at 100°C under vacuum for 10 h. This stability was attributed to the well known contribution of steric hindrance and phosphine basicity to the stability of such Staudinger intermediates.[81]

In the presence of weak acids, such as benzoic acid, however, **148a** rapidly and exothermically decomposes with the evolution of nitrogen gas to afford a 56% yield of benzene via the proposed pathway shown in Scheme 34. Here, removal of the proton from the carbocation **150** is facilitated by the quite basic imidophosphorane **151**, whose protonated product **152** was demonstrated to be partially transannulated.[81] The role of transannulation in Scheme 33 was very strongly suggested by the immediate and dramatic upfield ^{31}P NMR shift to −11 ppm in the starting material **148a** observed at low temperature when acid was added. That transannulation plays a key role in causing the three N_3PR_3 groups on the starting compound to function as

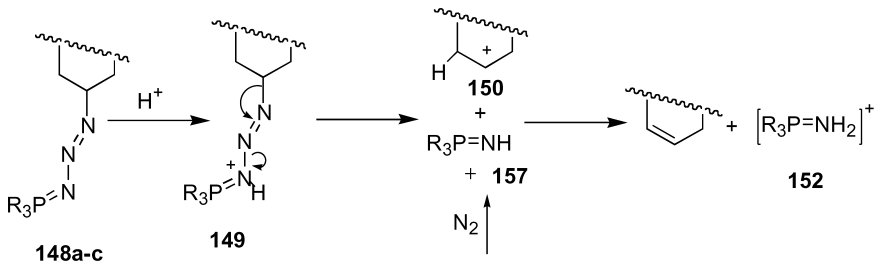


Scheme 33.



148a-c **149**

Scheme 34.



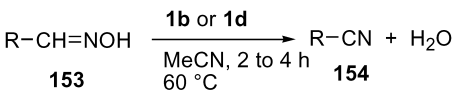
Scheme 35.

excellent leaving groups is supported by the observation that when $PR_3{=}P(NMe_2)_3$ was employed, the acid-induced decomposition to form benzene was about 10 times slower. The low yield of benzene observed in our reaction stems from the observation of the intermediates **148d** and **148e** by mass spectroscopy. Thus, for example, after one N_3PR_3 group departs, one of the two azidophosphorane substituents remaining on the ring (**148b**) finds itself in a sterically less encumbered environment and therefore thermally decomposes before protonation occurs to form **148d**. Similarly, **148e** could form from **148c** (Scheme 35).

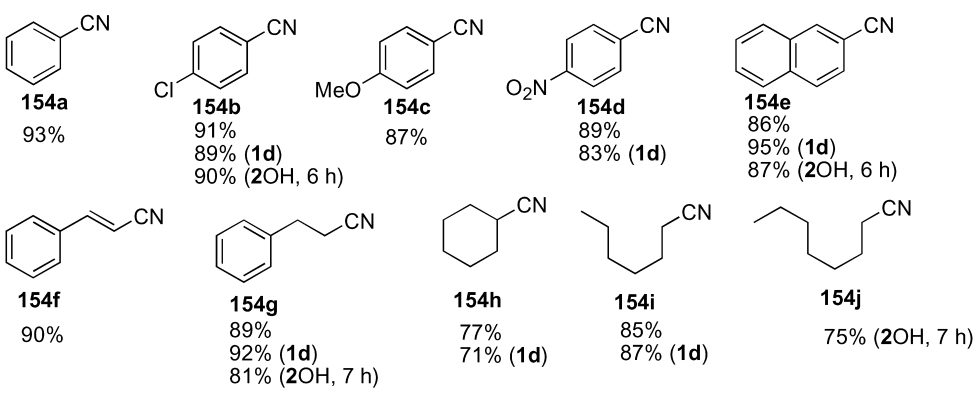
8.7. Dehydration of aldoximes to form nitriles

A broad variety of reagents have been reported for the dehydration of aldoximes to nitriles.[82] However, most of these reactions have a number of disadvantages. For example, dehydration with solid reagents such as montmorillonite KSF, zeolites, and envirocat EPZG require high reaction temperatures or lengthy reaction times. Triethylamine/sulfur dioxide and sulfuryl chloride promote a fast and mild preparation of nitriles from aldoximes, but these reagents have to be prepared at cryogenic temperatures.[83]

Proazaphosphatranes **1b** and **1d** have been found to dehydrate aldoximes in good yield in a mild reaction that works well for both aliphatic and aromatic aldoximes (reaction (32)).[83] With aliphatic aldoximes, this reaction is complete in 2 h at room temperature, while the reaction with aromatic aldoximes is achieved in 3–4 h at 60°C in the presence of 0.4 equiv. of **1b** or 0.3 equiv. of the stronger base **1d**.[83]



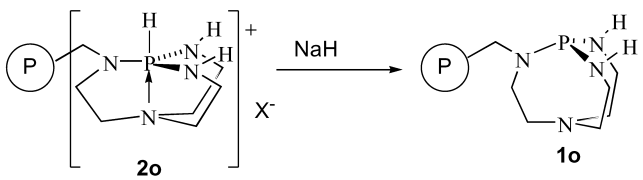
(32)



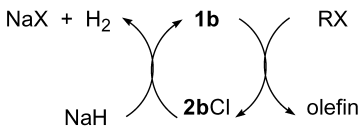
The novel hydroxide **2**[OH] is formed in this reaction. Thus to shed some light on the mechanism of this transformation, and to establish that the reaction is not catalyzed by the **2**[OH] formed in the process, [**2b**]OH[8] was used in this reaction in place of **1b**. Although [**2b**]OH also catalyzed the conversion of aldoximes into nitriles, longer reaction times (6–7 h) were required. This suggests that **1b** and **1d** are more catalytically active than [**2b**]OH and [**2d**]OH, respectively, in deprotonating aldoximes; a process that is expected to predominant in the early stages of the reaction.

8.8. Dehydrohalogenation using in situ-generated proazaphosphatranes

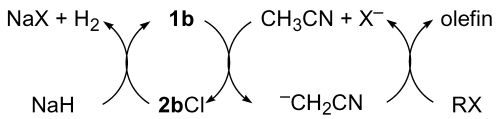
By analogy with the use of **1b** discussed in Section 8.4 for the dehydrohalogenation of organic halides,[80] we investigated the use of solid **2b**(X) for this reaction, since the byproduct in that process (X=Cl, Br, OTf) can be converted back to **1b** by treatment with strong ionic bases.[2,8,9] This suggested that an in situ production of neutral **1a**, **1b** or the polymer-bound analogue of **1a** (namely, **1o** in reaction (33)) could then function as a dehydrohalogenation catalyst. This approach was supported by the observation that NaH by itself did not efficiently dehydrohalogenate halides.[84] Indeed, 0.1 equiv. of any of these procatalysts efficiently dehydrohalogenated halides in the presence of excess sodium hydride in CH_3CN at room temperature. Upon completion of the reaction, filtration afforded the desired products in over 95% purity from the filtrate



(33)



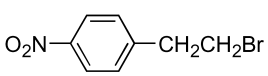
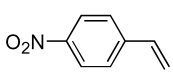
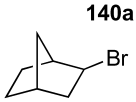
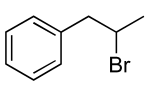
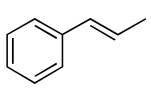
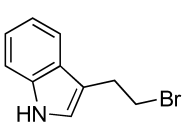
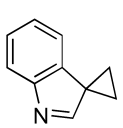
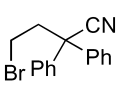
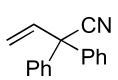
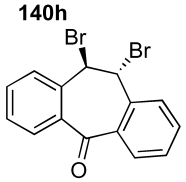
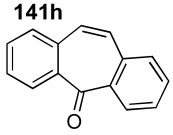
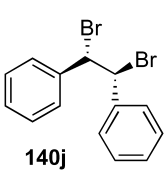
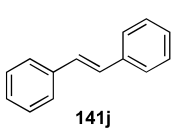
Scheme 36.

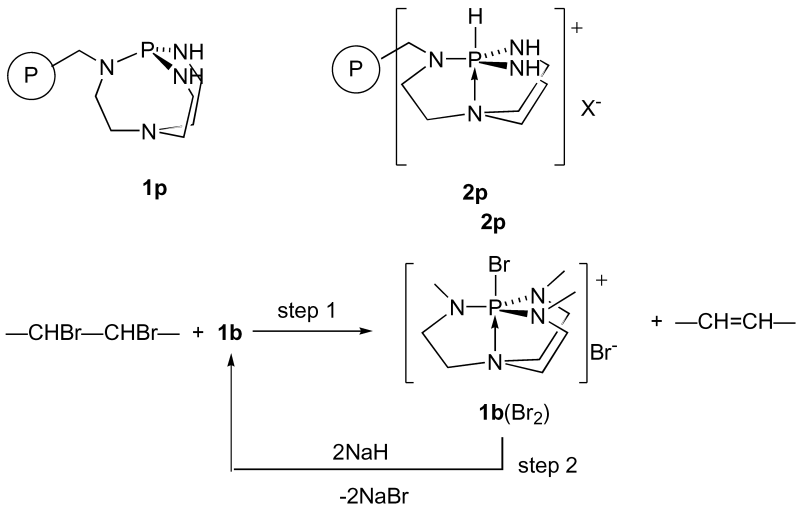


Scheme 37.

The pathway shown in Schemes 36 and 37 for **2b**(Cl) reasonably accounts for the formation of the alkene products in the absence and presence of acetonitrile as a solvent, respectively. Since reactions of organic halides with activating groups can be carried out in a nonprotic solvent, direct deprotonation of the substrate by a proazaphosphatrane such as **1b** must occur (Scheme 36). An indirect dehydrohalogenation pathway apparently occurs with **1b** in CH_3CN (Scheme 37), since in D_3CCN, the main phosphorus-containing compound observed in the ^{31}P NMR spectrum was the deuterio analogue of **2b**.[84] The first step in Scheme 36 involves NaH deprotonation of cation **2** to give **1**, the effective dehydrohalogenation agent for substrates with activating groups. In the second step, **1** reacts to give corresponding olefin products.[84] It was shown by ^{31}P NMR spectroscopy that the peak corresponding to **1a**, for example, was not observed until the reaction was complete, which accords with the supposition that the concentration of **1a** during the reaction is low and that the reaction rate of alkyl halides with **1a** is fast compared with the regeneration of **1a** from its corresponding cation **2** by NaH. A similar conclusion can be drawn from the cycles in Scheme 37 in which the process on the left is the slow step as in Scheme 36. In Scheme 37, however, deprotonation of CH_3CN by **1a** is faster than deprotonation of RX.[84]

Table 22. The use of in situ-generated proazaphosphatranes in dehydrohalogenation

Substrate	Product	Reaction time (h)	Conversion (yield) in %			
			2a(OTf)/NaH	**2b**(Cl)/NaH	**2p**(OTf)/NaH	NaH
 **140a**	 **141a**	1	99(94)	99	95(92)	43
 **140f**	 **141f**	100	0	0	0	0
 **140g**	 **141g**	2	99	98(91)	95(90)	25
 **140c**	 **141c**	1	99	99(85)	99(90)	25
 **140h**	 **141h**	6	78	99(95)	97(92)	19
 **140i**	 **141i**	2	99	99(92)	97(90)	25
 **140j**	 **141j**	2	98	99(94)	98(92)	39



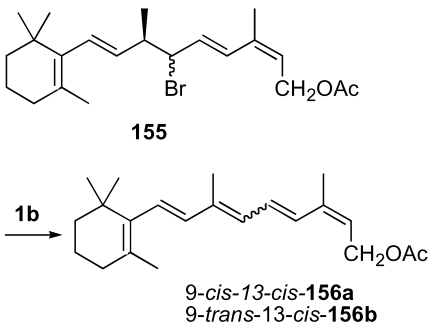
Scheme 38.

The debromination (rather than dehydrohalogenation) of **140i** and **140j** in Table 22 could occur via Scheme 38 in which step 1 is stoichiometric and step 2 takes place under catalytic conditions. Initial nucleophilic attack of the phosphorus of **1a** on a bromine is followed by the formation of the bromophosphonium cation with elimination of the second bromine from the substrate as Br^-.[84] When **2b**(Cl)/NaH is used, the bromophosphonium cation can be reduced and deprotonated by NaH to regenerate **1b**. In separate ^1H NMR experiments, 10 mol% of **2b**(Cl)/2.5 equiv. of NaH and with 2.0 equiv. of PPh_3 were used to debrominate **140j** in CD_3CN at 35°C. It was found that debromination with **2b**(Cl)/NaH was much more efficient than with PPh_3/NaH which is generally used under considerably harsher conditions (e.g. xylene/150–160°C/250 min) to afford only moderate product yields.[84]

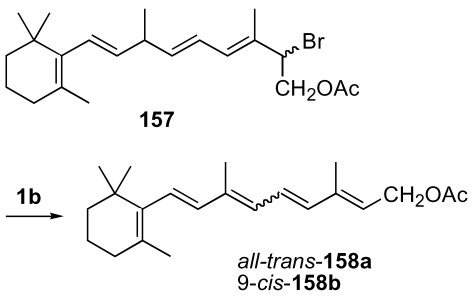
It may be noted that attempts to isolate **1a** from salts of **2** have previously resulted in oligomeric products. However, as shown from the examples in Table 22, **2a**(OTf) is as effective as **2b**(Cl) for both dehydrohalogenation and debromination, which suggests the formation of **1a** as an intermediate that reacts more quickly with substrates than it does intermolecularly to form oligomers.

8.9. Dehydrohalogenation in the preparation of vitamin A

Proazaphosphatrane **1b** has recently been reported to promote an efficient dehydrohalogenation reaction in the synthesis of all-*trans* vitamin A, the synthesis of which has been studied extensively.[85] Using compound **1b**, it was possible to carry out the conversions shown in reactions (34) and (35) in which the requirement of an all-*trans* system of double bonds has been introduced.[85] Although the reaction using **1b** was less efficient in refluxing benzene than that using DBU or DBN, switching the solvent system to acetonitrile afforded a clean reaction. Studies employing CD_3CN demonstrated that the basic anion CD_2CN^- produced upon deprotonation of CD_3CN was responsible for catalyzing the reaction. The use of **1b** to dehydrobrominate vitamin A derivative **157** to give **158** in reaction (35) was recently described in a patent[86]



(34)



(35)

9. Conclusions

Proazaphosphatranes are becoming broadly useful in organic synthesis methodology as stoichiometric bases and as catalysts, with new applications continuing to be discovered. In their catalytic applications, proazaphosphatranes do not always behave equally well, thus providing opportunities for further fine tuning of their activities by changing substitution patterns, especially on the nitrogens adjacent to phosphorus. Under current development are recyclable polymer and mesoporous silica-bound proazaphosphatranes, as well as chiral versions that may yet prove fruitful in asymmetric synthesis.

Acknowledgements

It is truly an honor to express my deep gratitude to the enthusiastic and creative graduate students, postdoctorals and visiting faculty whom I am proud to have as co-authors of publications listed in the references. The results described herein could not have been obtained without the generous financial support of the National Science Foundation, the Donors of the Petroleum Research Fund administered by the American Chemical Society, the United States Department of Agriculture and the United Soybean Board.

References

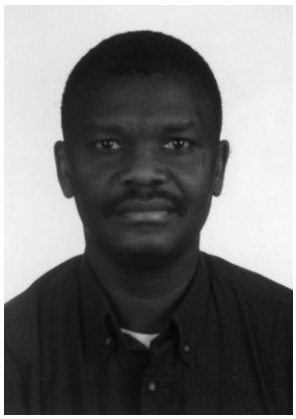
1. (a) Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1–44, and references therein. (b) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233–295. (c) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483–489.
2. (a) Lensink, C.; Xi, S.-K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478–3479. (b) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421–9422. (c) Tang, J.-S.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903–2904. (d) Tang, J.-S.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 1660–1664.
3. Baciocchi, E. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; pp 1173–1227, Part 2.
4. Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.
5. Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228–7230, and references therein.
6. Nahmani, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733–3735, and references therein.
7. (a) Kisanga, P. B.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431–5432. (b) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satich, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, *7*, 1055–1081.
8. Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69–79.
9. Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467–475.
10. D'Sa, B. A.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1997**, *123*, 301–312.
11. Liu, X.; Bai, Y.; Verkade, J. G. *J. Organomet. Chem.* **1999**, *582*, 16–24.
12. Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2655–2662.
13. Lake, F.; Hagberg, L.; Svensson, M.; Moberg, C. *Collect. Czech. Chem. Commun.* **2000**, *65*, 570–576.
14. Liu, X.; Ilankumaran, P.; Guzei, I. A.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 701–706.
15. Ishihara, K.; Karumi, Y.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 5692–5695.
16. Windus, T. L.; Schmidt, M. W.; Gordon, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 11449–11455.
17. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.
18. Liu, X.-D.; Verkade, J. G. *Inorg. Chem.* **1998**, *37*, 5189–5197.
19. Liu, X.; Verkade, J. G. *Heteroat. Chem.* **2001**, *12*, 21–26.
20. Ilankumaran, P.; Zhang, G.; Verkade, J. G. *Heteroat. Chem.* **2000**, *11*, 251–253.
21. Tang, J.-S.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896–898, and references therein.
22. Baker, R. H.; Bordwell, F. G. *Organic Synthesis*; *Collect. Vol. 3*, Wiley: New York, 1995; p 141.
23. D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963–2966, and references therein.
24. Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
25. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 9063–9066, and references therein.
26. (a) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420–2421. (b) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422–2423.
27. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086–3089.
28. (a) D'Sa, B. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 12832–12833, and references therein. (b) D'Sa, B. A.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 5057–5061, and references therein.
29. Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613–6615.
30. Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999–5004.
31. Yu, Z.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 2065–2068, and references therein.
32. Yu, Z.; Verkade, J. G. *Heteroat. Chem.* **1999**, *7*, 544–547.
33. Liu, X.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 4560–4564, and references therein.
34. Agarwal, S. C.; Van Duuren, B. L. *J. Org. Chem.* **1975**, *40*, 2307–2310.
35. (a) Minami, T.; Matsuzaki, N.; Ohshiro, Y.; Agawa, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1731–1738. (b) Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35–38. (c) Zhong, Q.; Shao, J.; Liu, C.; Lu, R. *Synth. Commun.* **1991**, *21*, 869–876. (d) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Lee, H. Y.; Reid, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 5973–5974.
36. Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.
37. For reviews see: (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
38. Wang, Z.; Kisanga, K.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 6459–6461, and references therein.
39. D'Sa,; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961–3967, and references therein.
40. Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Shichid, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195–7201.
41. Mori, K. *Synthetic Chemistry of Insect Pheromones and Juvenile Hormones*; *Recent Developments in the Chemistry of Natural Carbon Compounds*; Akademia Kiado: Budapest, 1979; Vol. 9. p 11.
42. Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F. *Tetrahedron* **1994**, *50*, 11499–11508.
43. (a) Ladhar, F.; Gharbi, E. *Synth. Commun.* **1991**, *21*, 413. (b) Arseniyadis, S.; Skyler, K.; Watt, D. S. *Org. React.* **1984**, *31*, 1–364.
44. Kisanga, P.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1998**, *63*, 10057–10059, and references therein.

45. Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665–722.
46. Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426–430, and references therein.
47. For some recent examples see: (a) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem.* **2002**, *67*, 7135–7137. (b) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609–611. (c) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219–223. (d) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405.
48. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090–3094, and references therein.
49. Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298–4303, and references therein.
50. For recent literature on the Nef reaction see: (a) Hwu, J. R.; Gilbert, B. A. *J. Am. Chem Soc.* **1991**, *113*, 5917–5918. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233–5235. (c) Gil, M. V.; Roman, E.; Serrano, J. A. *Tetrahedron Lett.* **2000**, *41*, 10201–10205. (d) Shahi, S. P.; Vankar, Y. D. *Synth. Commun.* **1999**, *29*, 4321–4325.
51. (a) Warmus, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 271. (b) Roush, W. R.; Murphy, M. *J. Org. Chem.* **1992**, *57*, 6622–6629. (c) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merrit, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403–4405.
52. Tang, J.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793–7802.
53. Tang, J. S.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 8750–8754.
54. Kisanga, P.; D'Sa, B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 8047–8052, and references therein.
55. For recent literature see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305–6306. (b) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643–3646. (c) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1033–1035.
56. Kisanga, P.; Fei, X.; Verkade, J. *Synth. Commun.* **2002**, *32*, 1135–1144, and references therein.
57. D'Sa, B.; Kisanga, P.; Verkade, J. G. *Synlett* **2001**, *5*, 670–672, and references therein.
58. Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. *Org. Lett.* **2000**, *2*, 2409–2410.
59. For some recent examples see: (a) Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Lett.* **2001**, *3*, 3753–3755. (b) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339–1350. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688–6696. (d) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713–719.
60. Kisanga, P. B.; Ilankumaran, P.; Fetterly, B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555–3560, and references therein.
61. (a) Bey, P.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 3249–3253. (b) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411–4417.
62. Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. *Tetrahedron Lett.* **2000**, *41*, 1607–1610.
63. (a) Hining, H.; Seufer-Waserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841. (b) Gaparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367. (c) Togni, A.; Pastor, S. D.; Ribs, G. *J. Organomet. Chem.* **1990**, *381*, C21.
64. Shoji, J.; Hinoo, H.; Hattori, T.; Hirooka, K.; Kimura, Y.; Yoshida, T. *J. Antibiot.* **1989**, *42*, 1460–1464.
65. Hukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *J. Antibiot.* **1983**, *36*, 1613–1630.
66. Kisanga, P.; Ilanakumaran, P.; Verkade, J. G. *Tetrahedron Lett.* **2001**, *42*, 6263–6266, and references therein.
67. (a) Wu, G.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. *J. Org. Chem.* **1997**, *62*, 2996–2998. (b) Kaptein, B.; van Dooren, T. J. G. M.; Boesten, W. H. J.; Sonke, T.; Duchateau, A. L. L.; Broxterman, Q. B.; Kamphuis, J. *Org. Process Res. Dev.* **1998**, *2*, 10–17. (c) Nagata, T.; Oka, H. *J. Agric. Food Chem.* **1996**, *44*, 1280–1284.
68. Memeger W., Jr.; Campbell, G. C.; Davidson, F. *Macromolecules* **1996**, *29*, 6475–6480.
69. (a) Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702–2704. (b) Brunel, J.-M.; Legrand, O.; Buono, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1979–1984. (c) Gama, A.; Flores-López, L. Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Walsh, P. J. *Tetrahedron: Asymmetry* **2002**, *13*, 149–154.
70. Wang, Z.; Fetterly, B.; Verkade, J. G. *J. Organomet. Chem.* **2002**, *646*, 161–166.
71. For recent examples see: (a) Mimoun, H. *J. Org. Chem.* **1999**, *64*, 2582–2589. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779–2788. (c) Terstiege, I.; Maleczka R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342–343. (d) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713–715. (e) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2796–2797. (f) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474.
72. Wang, Z.; Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 8021–8023, and references therein.
73. Wang, Z.; Verkade, J. G. *Heteroat. Chem.* **1998**, *9*, 687–689, and references therein.
74. Wang, Z.; Zhang, G.; Guzei, I.; Verkade, J. G. *J. Org. Chem.* **2001**, *66*, 3521–3524.
75. For recent examples see: (a) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407–2409. (b) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620–5623. (c) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756. (d) Zhang, X.; Qu, Z.; Ma, Z.; Shi, W.; Jin, X.; Wang, J. *J. Org. Chem.* **2002**, *67*, 5621–5625.
76. Fei, X.-S.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 538–540, and references therein.
77. For recent examples see: (a) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235–5237. (b) Pine, S. H.; Shen, G.; Bautista, J.; Sutton, C.; Yamada, W.; Apodaca, L. *J. Org. Chem.* **1990**, *55*, 2234–2237.
78. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3677–3679, and references therein.
79. For recent examples see: (a) Jha, S. C.; Joshi, N. N. *J. Org. Chem.* **2002**, *67*, 3897–3899. (b) Amadji, M.; Vadecard, J.; Cahard, D.; Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *J. Org. Chem.* **1998**, *63*, 5541–5546.
80. (a) Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827–4828. (b) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. *Heteroat. Chem.* **1996**, *7*, 455–460, and references therein.
81. Liu, X.; Zhang, G.; Verkade, J. G. *Tetrahedron* **2001**, *42*, 4449–4451, and references therein.

82. Hart-Davis, J.; Battioni, P.; Boucher, J.-L.; Mansuy, D. *J. Am. Chem. Soc.* **1998**, *120*, 12524–12530.
83. Fei, X.-S.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 541–543, and references therein.
84. Liu, X.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4840–4843, and references therein.
85. Wróblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 420–425, and references therein.
86. Seko, S.; Konya, N.; Takahashi, T. Eur. Pat. Appl. 1092108, 2001; *Chem. Abstr*. **2001**, *134*, 295968.

Biographical sketch

John Verkade was born in Chicago to Dutch immigrant parents. He earned his BS degree in chemistry at the University of Illinois Urbana campus in 1956 and his MA degree in chemistry at Harvard University in 1958. Upon graduation he returned to the University of Illinois where he obtained his PhD degree in 1960 in inorganic chemistry with a sole minor in organic chemistry under the guidance of the late Professor Stan Piper. He then joined the Chemistry Department at Iowa State University where he is now Professor of Chemistry and University Professor. His current research emphases include the improvement of organic transformation methodologies through the synthesis of new 'green' homogeneous and heterogeneous organononmetallic and organometallic catalyst systems, and the conversion of biomass and biomass components to value-added nonfood products.



Philip Kisanga was born in Yambio in South Sudan. He received his BS (Honors) in Chemistry from the University of Cairo followed by the MA in Organic Chemistry from the University of Northern Iowa (Cedar Falls) under the tutelage of Professor Kirk P. Manfredi. After leaving UNI, he pursued graduate studies with Professor John G. Verkade at Iowa State University researching the synthesis of proazaphosphatranes and their applications in organic synthesis. After graduating in 1999, he joined Professor Ross A. Widenhoefer's group at Duke University for postdoctoral training. In 2000, he accepted a Research Scientist position with Aldrich Chemical Company. He joined Albany Molecular Research (Syracuse Research Center) in 2001 where he is Senior Research Scientist I in the Chemical Development group.