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Reactivity of Primary Phosphines and Primary Phosphine Sulfides towards Imines

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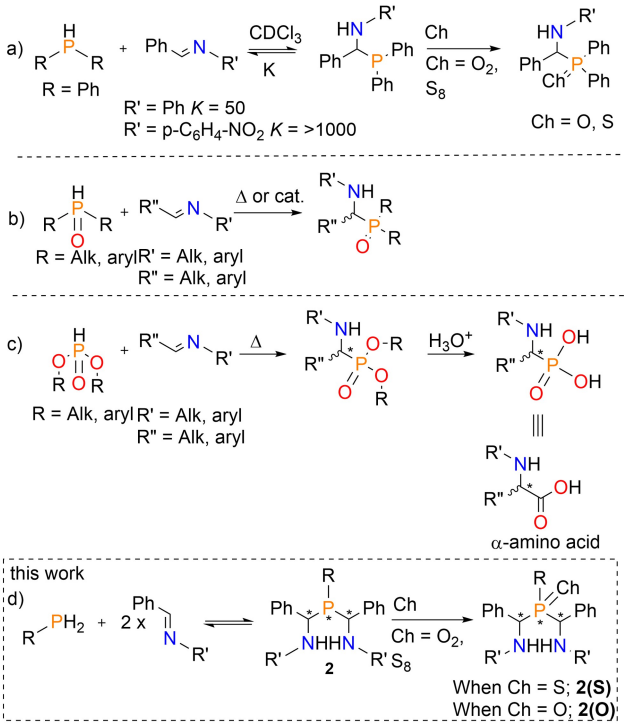
Abstract: Reactivity of primary phosphines with two stoichiometric equivalents of imine results in the formation of bis-α-aminophosphines (**2a–e**), which can be subsequently oxidized in the presence of S_8 or H_2O_2 to generate air stable bis-α-aminophosphine sulfides (**2b–m(S/O)**). To elucidate the mechanism of this three-component reaction, Hammett analysis, kinetic isotope effect (KIE), and trapping experiments were performed. Ultimately a P(V)–P(III) tautomerization is invoked, followed by nucleophilic attack by the P(III) species to generate the desired products.

Introduction

Hydrophosphination is the addition of a P–H bond to an unsaturated unit, most commonly C=C and C≡C bonds, and is the most atom economical method for preparing organophosphines.[1] There are a number of key reports on the hydrophosphination reaction of both alkenes and alkynes via a variety of methods, most notably using transition metal catalysts, or through radical initiated chemistry.[2] The hydrophosphination of unsaturated units such as imines (R–C=N–R'), has been the subject of far fewer reports.[3–7] It is noteworthy that the hydrophosphination of imines does not require additives or catalysts in order to proceed, and most likely progresses because of the intrinsic nucleophilic/electrophilic reactivity of the reaction partners. The resulting product of the hydrophosphination of an imine is an α-aminophosphine, which is typically unstable to isolation. This difficulty arises from an equilibrium between the parent phosphine/imine and the α-aminophosphine (Scheme 1a) that is regulated by the electronics of the corresponding imine.[3] The hydrophosphination product can be favoured with imines bearing strong electron withdrawing groups in the *para*-position of the *N*-aryl substituent (Scheme 1a). Irreversible P(III)→P(V) oxidation of the α-aminophosphine with chalcogens (O_2, S_8) allows for the isolation of the α-aminophosphine chalcogenides[5] (Scheme 1a). The same P(V) products can instead be accessed by imine hydrophosphorylation using a P(V) precursor (Scheme 1b). Given the prochiral carbon centre in the imine, stereoselective catalysts have been developed to facilitate this reaction selectively (Scheme 1b).[7,8,9–11] The most common hydrophosphorylation reactions are the Pudovik or the Kabachnik-Fields (KF) reactions that employ secondary phosphonate reagents and yield α-aminophosphonate products (Scheme 1c).[12–14] Such products are widely used in biochemical



Scheme 1. Reactivity of P(III) and P(V) species towards imines. a) equilibrium between 2° P(III) and substituted imines. b) Addition of 2° phosphine oxide P(V) and imine. c) Pudovik reaction between dialkylphosphite and imine. Reactions using in situ generated imine are classified as Kabachnik-Fields reaction. Subsequent acid hydrolysis generates unnatural α-amino acids. d) Scope of this report.

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research as unnatural analogues of α-amino acids (Scheme 1c).[15–18]

To the best of our knowledge, there has been only one reported example of the addition of primary phosphines (R–PH_2) to imines to form the *bis*-α-aminophosphine motif.[19] Diastereoselective formation of oxygen-sensitive P(III) products was achieved with a samarium ene-diamido catalyst, though there is no mention of a dynamic equilibrium. The apparent dearth in the literature of hydrophosphination with primary phosphines is likely driven by a combination of unpleasant odour, pyrophoricity, and instability towards oxygen of the phosphorus precursors. Previous work has focused on addition of 1° phosphines (R–PH_2) and 1° phosphine oxides/sulfides (R–P(O/S)H_2) to carbonyl groups and the subsequent formation of bis-α-hydroxyphosphine chalcogenide products.[20–23] However, expansion to other unsaturated units remains mostly unexplored. There have been no mechanistic studies regarding the addition of a primary phosphine chalcogenide to an electrophile. The use of 1° phosphines and 1° phosphine sulfides and their corresponding reactivity towards imines as well as the determination of the underlying mechanism are the topic of this study (Scheme 1d).

Results and Discussion

The reaction involving 1° phosphines and imines was performed using a 1:2 stoichiometric ratio of phosphine to imine at 25 °C in acetonitrile and monitored by $^{31}P\{^1H\}$ and ^{31}P NMR spectroscopy over an 18-hour period (Figure 1c). Using N-benzylidene isopropylimine (Ph–C=N–*i*-Pr) as a model substrate, and *i*-$BuPH_2$ as a model phosphine, after 18 h 70% of the primary phosphine was consumed, and 5 new signals appeared in the $^{31}P\{^1H\}$ NMR spectrum (Figure 1a, 1c). Two signals correspond to 2° phosphines **1a** ($\delta_P = -47.0$ and -49.5; $^1J_{P-H} =$ 201 Hz) and three signals to 3° phosphines **2a** ($\delta_P = 6.4$, -2.1 and -6.4). The number of products is a consequence of the formation of diastereomers after P–H bond addition. Phosphine inversion barriers are determined to be between 132 and 203 kJ/mol,[24,25] typically not amenable to inversion at room temperature.[26] Therefore, two chiral centres are formed in 2° products **1** and three in 3° products **2** (Figure 1b). The two 2° phosphine signals correspond to the enantiomer pairs (S_c, S_p)/(R_C, R_P) and (S_c, R_P)/(R_C, S_P) in an approximate 1:1 ratio. The three 3° phosphine resonances correspond to the enantiomer pairs (R_C, S_p, S_C)/(S_C, S_P, R_c) and (S_C, R_p, R_C)/(R_C, R_P, S_C), and the (R_C, R_C)/(S_C, S_C) meso-compounds which have a pseudo-chiral centre on phosphorus (Figure 1b).[20] Statistically a 1:1:2 mixture of the three diastereomers (R_C, S_p, S_C)/(S_C, S_P, R_c):(S_C, R_p, R_C)/(R_C, R_P, S_C):(R_C, R_C)/(S_C, S_C) was anticipated, however, the distribution is approximately 10:30:60. As the first addition proceeds by generating an approximate 1:1 mixture of diastereomers of the secondary phosphine, it is our hypothesis that the second addition proceeds with some stereoselectivity due to steric interactions, thus resulting in the nonstatistical distribution. This trend in diastereomer distribution is observed with all other phosphine/imine combinations, although with slight deviations

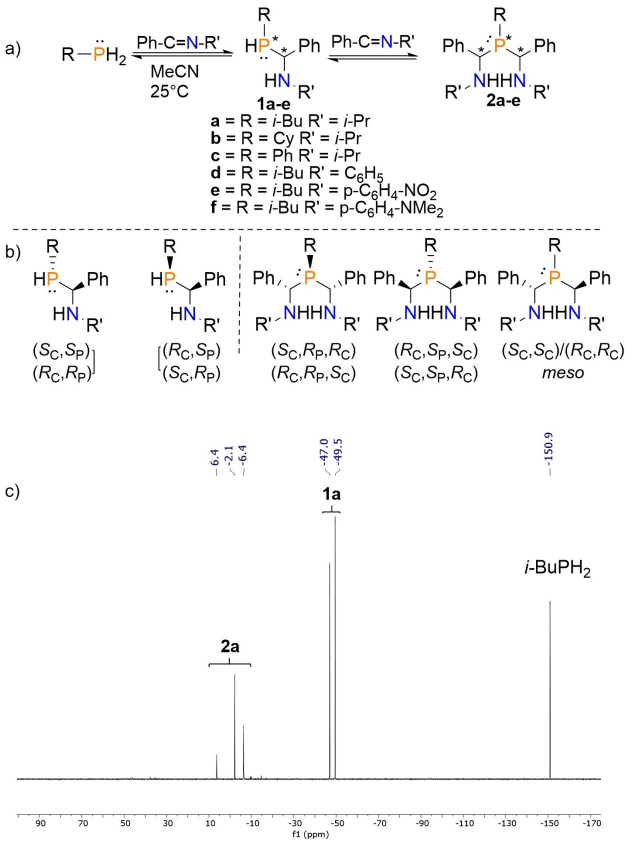
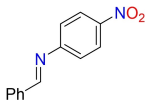
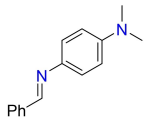


Figure 1. a) Reaction of phosphine and two equivalents of Ph–C=N-R'. b) Diastereomers generated from the reaction. Chiral centres denoted by *. c) Representative $^{31}P\{^1H\}$ NMR spectrum of crude reaction mixture containing *i*-$BuPH_2$, **1a**, and **2a**.

between substrates. To confirm the presence of an equilibrium process, the reaction mixture of the model reagents was subjected to gentle heating at 70 °C for three hours. It was noted that the starting 1° phosphine began to reform, from 29% to 55% relative integration. The quantities of the 2° and 3° phosphines began to decrease, from 42% and 29% to 23% and 20%, respectively.

The scope of the hydrophosphination reaction was evaluated under optimized reaction conditions (Table 1). The reactivity of the reagents *i*-$BuPH_2$ and Ph–C=N–*i*-Pr (Entry a) was first compared to other 1° phosphines ($CyPH_2$, $PhPH_2$; Entries b-c). While the two alkyl phosphines (R = *i*-Bu and Cy) were consumed in similar quantities (73% and 65%, respectively), the product distribution varied substantially. With lower steric bulk, *i*-$BuPH_2$ gave 2° and 3° phosphine products in a ca. 4:3 ratio, whereas the more encumbered cyclohexyl derivative exclusively produced the 2° products **1b**. A lower conversion efficiency was achieved with $PhPH_2$ (≈40%), which is consistent with its sluggish addition to C=C bonds and underscores that more electron rich phosphines drive the equilibrium toward hydrophosphination products.[27] The ratio of **1c**:**2c** is 3:1, and this reflects the intermediate steric profile of Ph as compared to *i*-Bu and Cy.

Table 1. Phosphine addition to Ph–C=N-R′ substituted imines.

Entry	R–PH_2	Imine[a]	Conv [%][b]		**1** [%]	**2** [%]	K_{obs}[c]
a	*i*-$BuPH_2$		37	71	42	29	6.1
b	$CyPH_2$		30	65	65	0	3[d]
c	$PhPH_2$		13	40	30	10	2.1
d	*i*-$BuPH_2$		8	23	13	10	1.0
e	*i*-$BuPH_2$		90	90	22	68	17
f	*i*-$BuPH_2$		0	16	13	3	0.5

[a] Reactions performed in MeCN at 25 °C and monitored by $^{31}P\{^1H\}$ spectroscopy after 18 h of reaction time. [b] Conversion given after 2 h (left column) and 18 h of reaction time (right column). Conv = ((**1** + **2**)/(**1** + **2** + *i*-$BuPH_2$))*100. [c] K_{obs} = [**2**]/([R–PH_2]*[imine]^2). [d] K_{obs} = [**1**]/([R–PH_2]*-[imine]), where concentrations were determined by relative integrations by $^{31}P\{^1H\}$ spectroscopy with a delay time of 5 sec.

The reaction was next assessed for the addition of *i*-$BuPH_2$ to imines bearing different aryl groups in the R′ position (Entries d–f). Compared to the *i*-Pr *N*-substituted imine, the unsubstituted Ph derivative gave substantially lower conversion of 23% (Entry d). Whereas the strong electron withdrawing nitro- group *para*- to the imine nitrogen showed dramatically higher conversion of 90% (Entry e) and a ratio **1e** to **2e** of 1:3.1, the strongly electron donating NMe_2 in the same position (Entry f) inhibited the reactivity, giving only 16% conversion and 3% formation of **2f**. The distribution of products provides insight into the equilibrium constants (Table 1). The relative equilibrium constants show trends similar to those observed by Andrieu, in which electron withdrawing imines were shown to have much larger equilibrium constants than do unsubstituted imines.[3]

During the formation of **1a–f** and **2a–f**, reactions with the aliphatic phosphines showed qualitatively faster rates than those with the aromatic phosphine (Table 1). These relative rates mimic those observed in the hydrophosphination of olefins.[27] A corresponding electronic trend for the imine was observed for Entries d-f. The NO_2-substituted imine resulted in 89% conversion in only 15 minutes, as well as forming 68% of the double addition product **2e**, while the NMe_2 substituted imine resulted in 16% conversion after 18 h, with only 3% of the double addition product **2f** observed. Interestingly, whilst comparing Entries a and d, it was noted that the more electron-withdrawing phenyl imine had slower reactivity than the aliphatic imine, which was not anticipated. However, the slow reaction with the *N*–Ph imine is hypothesized to occur due to increased steric bulk of the aryl group.

In all cases, isolation of the α-aminophosphine products **1a–f** and **2a–f** was precluded by the aforementioned equilibrium. Oxidation of α-aminophosphine compounds to the corresponding phosphine oxides or sulfides has proven effective to isolate products with a similar bonding motif (see Scheme 1a).[5] We reasoned that addition of S_8 to reaction mixtures would readily afford the bis-α-aminophosphine sulfide products, even from reactions with unfavourable K_{eq} for the hydrophosphination step. To test this strategy, S_8 was added to a reaction mixture of *N*-benzyildene aniline (Ph–C=N–Ph), with *i*-$BuPH_2$, **1d** and **2d** present in a 76:13:10 ratio (Figure 2). Within 10 min, samples of the reaction mixture assessed using $^{31}P\{^1H\}$ NMR spectroscopy revealed that the P(III) compounds were completely consumed, and new signals emerged that were shifted substantively downfield, consistent with oxidation of P(III) to P(V) (Figure 2b). The corresponding ^{31}P NMR spectra showed the two signals at $\delta_P \approx 35$, split into doublets with $^1J_{P-H} = 451$ Hz, and confirmed their assignment as the 2° phosphine sulfide diastereomers **1d(S)**. The multiplicity of the signals at δ_P ~65 did not change, and therefore these correspond to the 3° phosphine sulfide diastereomers **2d(S)**. The number of observed diastereomers is the same after oxidation, since the chirality is retained with a sulfur atom on phosphorus in lieu of the lone pair. Over one hour, **1d(S)** reacts with Ph–C=N–Ph in solution to form the tertiary **2d(S)** products (Figure 2b). This indicates that the 2° P(V) compounds **1d(S)** undergo P–H bond addition to the imine faster than the P(III) precursor *i*-$BuPH_2$ (see below). Therefore, a general one-pot reaction of primary phosphine, S_8 and imine should readily afford the air-stable bis-α-aminophosphine sulfide products.

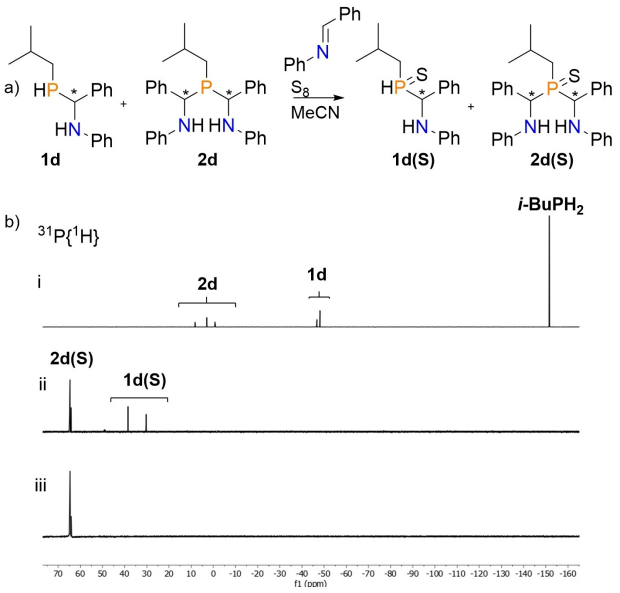


Figure 2. a) Reaction of α-aminophosphines **1d** and **2d** in the presence of S_8 and imine to generate bis-α-aminophosphine sulfide **2d(S)**; b) $^{31}P\{^1H\}$ NMR spectra of (**i**) **1d** and **2d** (**ii**) **1d(S)** and **2d(S)** generated 10 minutes after addition of S_8(**iii**) **2d(S)** generated 1 h after the addition of S_8.

Upon complete conversion to **2 d(S)**, the diastereomeric mixture can be separated via column chromatography, and diastereomers were individually characterized by multinuclear NMR spectroscopy, mass spectrometry, and IR spectroscopy. In the ^{1}H NMR spectrum of the major diastereomer of **2 d(S)**, there were two signals corresponding to the α-hydrogens. These signals were observed as a doublet of doublets, as a function of both coupling to the P atom as well as to the hydrogen bound to the adjacent secondary amine ($^{2}J_{P-H}$ = 11.6; $^{3}J_{H-H}$ = 9.3 Hz). The 2° amine hydrogens were observed as slightly broadened signals at δ_H = 5.03 and 5.33, which did not exhibit a correlation to a carbon upon collection of a ^{1}H–^{13}C HSQC spectrum. The two minor diastereomers each have only one signal for an α-hydrogen in the ^{1}H NMR spectrum. This shows the C_2 symmetry of the minor diastereomers, which can be assigned as the (R_C, S_P, S_C)/(S_C, S_P, R_C)and (S_C, R_P, R_C)/(R_C, R_P, S_C)enantiomer pairs. The major product can thus be assigned to the (R_C, R_C)/(S_C, S_C)) *meso* compounds.

A one-pot protocol using 1° phosphine, S_8 and imine was next employed to synthesize a range of isolable bis-α-aminophosphine sulfides (Figure 3). With the phenyl-substituted imine, a range of alkyl and aryl primary phosphines was successfully utilized to afford **2 b(S)**, **2 c(S)**, **2 d(S)** and **2 e(S)**. It is worth noting, that under these oxidizing conditions $CyPH_2$ gives 75% yield of the *bis*-addition product **2 b(S)**. This contrast with the analogous P(III) reactivity without S_8, which leads to only the mono addition product **1 b**. The primary phosphine

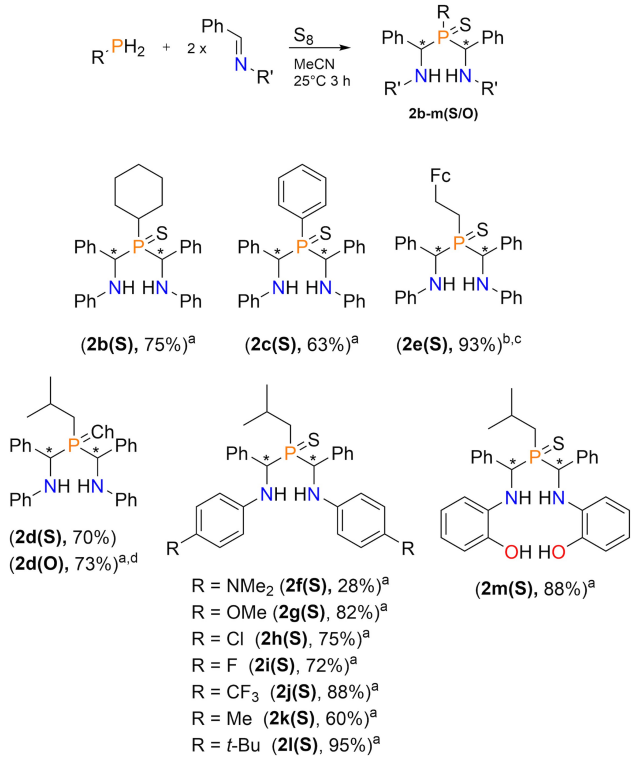


Figure 3. General reaction between 1° phosphine, imine, and chalcogen. Footnotes : [a] Isolated products as mixtures of diastereomers. [b] Fc=Bis(η^5-cyclopentadienyl)iron), [c] Reaction performed under air. [d] Added excess $H_2O_{2(aq)}$ to mixture of 1 equiv. phosphine and 2 equiv. imine.

$FcCH_2CH_2PH_2$ (Fc=Bis(η^5-cyclopentadienyl)iron), is air stable,[28] which allowed the reaction to be carried out under air to give **2 e(S)** in excellent 93% yield without oxide formation. The most readily available phosphine, *i*-$BuPH_2$ was used to examine functional group compatibility with various imines having substituted aryl groups. The reaction was compatible with aryl amines, ether, aryl halides, alkyl donors, and phenols (i.e. products: **2 f(S)**–**2 m(S)**). However, the *p*-NMe_2-substituted product **2 f(S)** was only isolated in 28% yield. This is due to a combination of poor solubility that hinders chromatographic purification and competing acid/base chemistry (see below). The *o*-OH substituted product was isolated in 88% yield (**2 m(S)**), which showed the reaction is compatible with acidic phenol functionalities. The protocol is amenable to the installation of other chalcogens. The bis-α-aminophosphine oxide **2 d(O)** was prepared in 73% yield on the treatment of a mixture of *i*-$BuPH_2$ and Ph–C=N–Ph with excess of $H_2O_{2(aq)}$.

Crystals of **2 c(S)** and **2 d(O)** suitable for X-ray diffraction were obtained from a sample of one of the minor isomers, which was isolated from the diastereomeric mixture by column chromatography, and the structures confirmed the expected atom connectivity (Figure 4). The C_α-N bond lengths are in the expected range (ca. 1.45 Å) for a C–N single bond.[29] The P(1)-S(1) and P(1)-O(1) bonds are 1.9595(4) and 1.492(2) Å, respectively, and are similar to previously reported P–Ch bond lengths.[20,23,30–32] The isomers of **2 c(S)** and **2 d(O)** crystallized in the $P2_{1/m}$ and P-1 space groups, respectively, which precludes assignment of absolute stereochemistry. However, in both structures the two α-carbons have opposite signs, which is consistent with the ^{1}H NMR data that support C_2 symmetry for the minor diastereomers. Attempts to grow crystals of the major diastereomers or of the other bis-α-aminophosphine sulfide derivatives remain unsuccessful.

Qualitatively, the relative rate of formation of the *bis*-α-aminophosphine sulfide products **2(S)** is much faster than that for the corresponding phosphine products **2**. In situ analysis of the reaction of *i*-$BuPH_2$, S_8 and PhHC=NPh revealed the mono-addition phosphine sulfide **1 d(S)** as a major intermediate. These two observations indicate that phosphine oxidation likely occurs prior to P–H bond addition to the imine. Thus, for the mechanistic analysis we considered the reactivity of primary

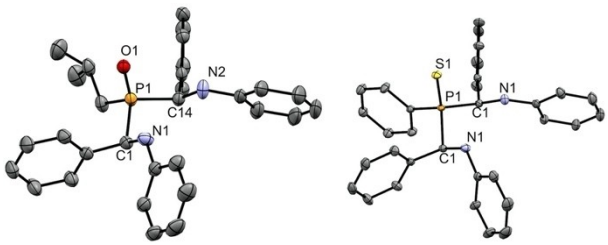
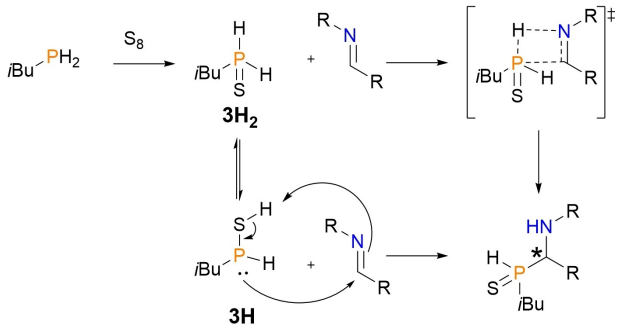


Figure 4. Thermal displacement plots of a minor diastereomer of **2 d(O)** (left) at 30% probability and of **2 c(S)** (right) at 50% probability. Hydrogen atoms and a residual DCM solvent molecule in **2 d(O)** (left) omitted for clarity. Select bond lengths (Å) and bond angles (deg). **2 d(O)**: P(1)–O(1) = 1.492(2), C(1)–N(1) = 1.433(4), C(14)–(N2) = 1.437(4) P(1)–C(1)–N(1) = 108.50(19). P(1)–C(14)–N(2) = 108.67(19). **2 c(S)**: P(1)–S(1) = 1.9595(4), (C1)–(N1) = 1.4500(7), P(1)–C(1)–N(1) = 107.79(3).

phosphine sulfide **3H$_2$**. The accepted mechanistic routes for the addition of related H-phosphonates ((RO)$_2$P(O)H) to imines involve reactivity via P(V) or the P(III) tautomer ((RO)$_2$P(OH)).[33–35] The corresponding routes for a primary phosphine sulfide are presented in Scheme 2. The first route would involve concerted addition of the P–H bond of the P(V) intermediate **3H$_2$** to the C=N double bond (Scheme 2: top). The second possibility would require tautomerization of **3H$_2$** to the P(III) species **3H** that could undergo nucleophilic attack and proton transfer steps in a stepwise or concerted fashion (Scheme 2: bottom). The P(V) – P(III) tautomerization is well established,[33,36–39] which supports the viability of both **3H$_2$** and **3H** as intermediates.

To investigate the plausible pathways, the independent synthesis of **3H$_2$** was carried out using *i*-BuPH$_2$ and S$_8$ in MeCN (Figure 5a). Analysis of the reaction mixture by ^{31}P{^{1}H} NMR spectroscopy reveals a singlet for the starting P(III) compound ($\delta_P = -150.1$) and a new singlet at $\delta_P = -18.0$ (Figure 5b). The dramatic downfield shift of the latter is diagnostic of P(III) to P(V) oxidation. In the ^{31}P NMR spectrum the product signal is a pseudo triplet of quartets, rather than an expected triplet of



Scheme 2. Pathways for the formation of α-aminophosphine sulfides, via a 4-membered transition state (top), or a nucleophilic attack and proton transfer of **3H** to the imine (bottom).

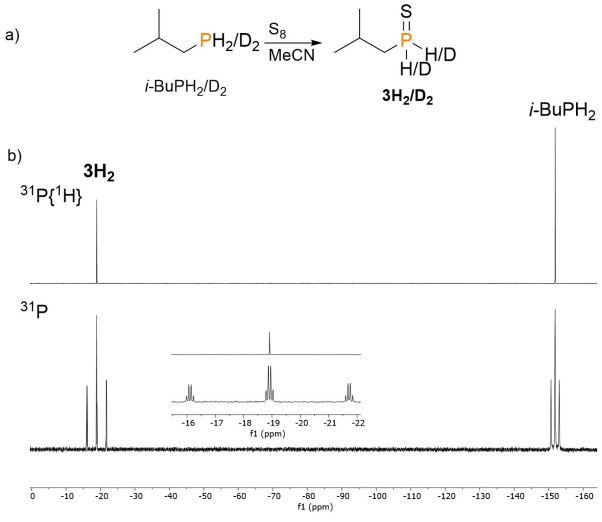


Figure 5. a) Synthesis of **3H$_2$** and **3D$_2$**. b) ^{31}P{^{1}H} and ^{31}P NMR spectra of an incomplete reaction mixture containing *i*-BuPH$_2$, S$_8$, and **3H$_2$** (inset) **3H$_2$** resonance depicting a pseudo triplet of quartets.

triplet of doublets. (Figure S10) The observed multiplicity is a consequence of coincidentally similar values for $^2J_{P-H}$ and $^3J_{P-H}$ for coupling to the CH$_2$ and CH protons, respectively. The large $^1J_{P-H}$ coupling of 455 Hz is consistent with values of other 1° phosphine sulfides.[20,23] Isolation of **3H$_2$** proved impractical since decomposition occurred upon removal of the volatiles. Compound **3H$_2$** was prepared via oxidation of the primary phosphine with excess S$_8$ over 16 h at 25 °C, and filtered solutions were used directly for mechanistic studies. Over extended periods of time (ca. 24 h) samples of **3H$_2$** would gradually decompose, likely through a myriad of known disproportionation mechanisms.[21] Samples could be preserved for extended periods by freezing in liquid nitrogen.

Treatment of **3H$_2$** with two stoichiometric equivalents of *N*-benzylidene-aniline (PhHC=NPh) gave complete conversion to bis-α-aminophosphine sulfide **2d(S)** within 5 min at 25 °C, as judged by ^{31}P{^{1}H} NMR spectroscopy. This is in stark contrast to the reaction of the corresponding P(III) reagent with the same imine, which took >2 h, and only reached a maximum 23% conversion (Table 1, Entry d). The rates of **3H$_2$** addition to C=N groups were determined at −20 °C by monitoring the consumption of the phosphine sulfide by ^{31}P{^{1}H} NMR spectroscopy. The reactions were conducted under pseudo first order conditions with various imines bearing aryl groups featuring electron-donating and -withdrawing groups *para* to nitrogen (Figure 6a). A plot of the relative rate constants (log(k_R/k_H)) vs. the Hammett *para*-substituent constants (σ) gives two lines of different slope for derivatives with electron-donating vs. -withdrawing substituents. The overall concave-up fit is indicative of a change in mechanism or transition state from electron-rich to -poor imines.

The substituted imine with an *N,N'*-dimethyl amine donor group was an outlier in the Hammett analysis, giving an unexpectedly low rate for P–H bond addition (Figure 6b). To

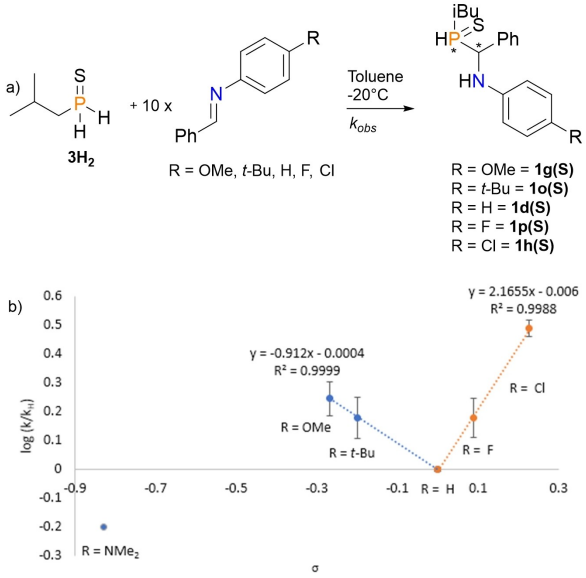
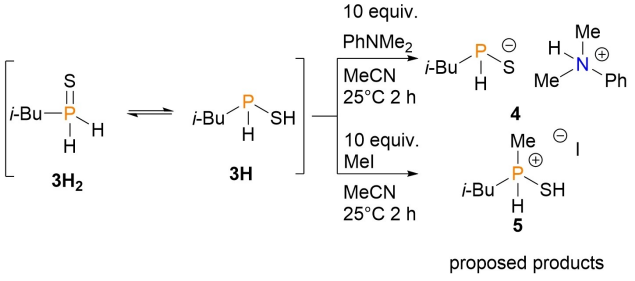


Figure 6. a) Reaction conditions for rate analysis. b) Hammett analysis displaying concave-up fit.

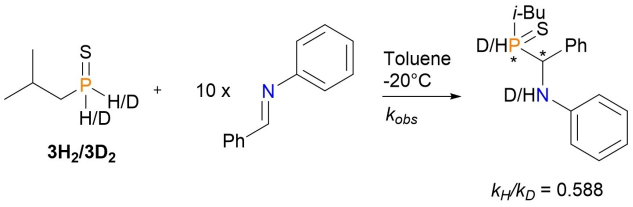
elucidate the reason for the low rate, a reaction between $\mathbf{3H_2}$ and *N,N′*-dimethylaniline was performed (Scheme 3). Several new products were observed in both the $^{31}P\{^1H\}$ and ^1H NMR spectra. Notably, a broad peak emerged at $\delta_H = 11.3$ that corresponds to protonation of the dimethyl amino group. In the $^{31}P\{^1H\}$ spectra, the major product is observed at $\delta_P = 31.0$, which splits into a pseudo doublet of quartets when subjected to the ^1H coupled experiment. The larger coupling constant is in the range expected for a P–H moiety ($^1J_{P-H} = 442$ Hz). The smaller coupling interactions are consistent with those previously observed with $\mathbf{3H_2}$ to the methylene and methine protons of the *i*-Bu group. Thus, the product is assigned as the ammonium sulfide salt **4**. The operational acid could be either P(V) species $\mathbf{3H_2}$ or the P(III) tautomer **3H**. While pK_a values for 1° phosphine chalcogenides are not known, the 2° phosphine sulfide $Me_2P(S)H$ is ca. 9 orders of magnitude more acidic than the corresponding oxide (p$K_{a(DMSO)}$: $Me_2P(S)H = 17.6$,; $Me_2P(O)H = 27.1$,).[40] Successful protonation of *N,N′*-dimethylaniline indicates $\mathbf{3H_2}$/**3H** is more acidic than the ammonium (p$K_{a(MeCN)} = 11.43$, $[PhN(H)Me_2]^+$).[41] The acidity of $\mathbf{3H_2}$/**3H** indicates that a proton transfer step is viable and possibly mechanistically relevant for P–H bond addition to an imine.

To investigate the nucleophilicity of the invoked P(III) species **3H**, a trapping experiment was performed by treating $\mathbf{3H_2}$ with an excess of iodomethane (Scheme 3). Reaction monitoring by $^{31}P\{^1H\}$ and ^{31}P NMR spectroscopy revealed complete consumption of $\mathbf{3H_2}$ after two hours. Several new signals in similar intensity appeared in the range 30–40 ppm. While this is not a clean reaction, one of the product signals ($\delta_P = 38.9$) is a doublet of septets, which is consistent with coupling for a P–H moiety ($^1J_{P-H} \approx 480$ Hz) and between phosphorus and hydrogens of *i*-Bu and the installed Me group ($^2J_{PH(methyl)} \approx {}^2J_{PH(methylene)} \approx {}^3J_{PH(methine)}$). The large $^1J_{P-H}$ is in agreement with previously reported phosphonium compounds bearing a P–H bond,[42] therefore we assign the observed signal to phosphonium **5**. Formation of **5** indirectly supports an equilibrium between the P(V) compound $\mathbf{3H_2}$ and the nucleophilic P(III) compound **3H**.

To gain more insight into the mechanism of P–H addition to imines, the deuterated phosphine sulfide compound *i*-$BuP(S)D_2$ $\mathbf{3D_2}$ was synthesized analogously to $\mathbf{3H_2}$. The isotopologues have similar chemical shifts in the $^{31}P\{^1H\}$ NMR spectrum, however, the doubly deuterated species at $\delta_P = -19.2$ is a 1:2:3:2:1 pentet from coupling to the two I = 1 deuterium



Scheme 3. Trapping of **3H** in situ via addition of iodomethane or dimethylaniline to produce proposed products **4** and **5**.



Scheme 4. Parallel KIE experiment using $\mathbf{3H_2}$ and $\mathbf{3D_2}$.

nuclei. A stoichiometric mixture of $\mathbf{3H_2}$ and $\mathbf{3D_2}$ underwent an H/D exchange, and formation of the mixed species *i*-BuP(S)HD was observed by $^{31}P\{^1H\}$ NMR spectroscopy as a 1:1:1 triplet at $\delta_{P=} -18.7$. To avoid H/D exchange, the KIE experiments were conducted in parallel as opposed to a one-pot competition for the addition to *N*-benzylidene-aniline (Scheme 4). A KIE of 0.588 was observed, indicating an *inverse* kinetic isotope effect. With the established P(V)–P(III) tautomerization phenomenon, the proposal of an inverse equilibrium isotope effect (IEIE) arising from the pre-equilibrium between **3H** and $\mathbf{3H_2}$ species is reasonable. The incorporation of deuterium perturbs the equilibrium constant to favour **3D**. In the presence of a greater concentration of reactive **3D**, the rate of addition to imine would subsequently be increased, thus giving a net inverse kinetic isotope effect. Unfortunately, due to the influence of the IEIE on the overall KIE, we were unable to identify an isotope effect for the subsequent step of the mechanism.

The inverse equilibrium isotope effect indicates that P–H bond addition to PhHC=NPh proceeds via the P(III) tautomer **3H**. Subsequently, proton transfer and nucleophilic attack occur to give the observed α-aminophosphine sulfide products. Separate reactions of the tautomeric mixture of $\mathbf{3H_2}$ and **3H** with a Brønsted base or an electrophile show that both proton transfer and nucleophilic attack are each viable steps. A Hammett analysis revealed that the mechanism differs for imines with either electron-donating or -withdrawing *N*-substituents. We propose that for electron-rich imines, proton transfer occurs first followed by nucleophilic attack. The order would be reversed for electron poor imines, which would be less basic but more electrophilic. While this hypothesis is consistent with our data, we cannot conclusively exclude the possibility of a different mechanism for imines other than PhHC=N-Ph, such as a concerted/P(V)pathway.

Conclusion

We have generated *bis*-α-aminophosphine and *bis*-α-aminophosphine chalcogenides from primary phosphines, imines, and S_8 or H_2O_2. The underlying mechanism for the addition of a primary phosphine sulfide to an imine was explored. The data is consistent with reactivity via the P(III) tautomer involving stepwise proton transfer and nucleophilic attack. A change in mechanism was identified, depending on the electronics of the imine and likely reflected the relative order of proton transfer and P–C bond formation. The generated products are readily

tuneable motifs and could find potential applications as mixed hard/soft multidentate ligands or as non-selective metal sequestration agents once installed on a suitable support. Utilization of primary phosphines in this transformation allows for a potential wide array of *bis*-substituted phosphine chalcogenides.

Experimental Section

2 d(S): Under an atmosphere of N_2, to a solution of imine (0.199 mmol, 2.05 equiv) in dried MeCN (10 ml) was added S_8 (0.05 mmol, 1/2 equiv) and 1° phosphine (0.097 mmol, 1 equiv). The solution was stirred at room temperature (21 °C) for 1–3 h. Reaction completion was monitored by analysis of reaction aliquots via $^{31}P\{^1H\}$ NMR spectroscopy until no starting phosphine remained. The solvent was removed under vacuum to afford a pale-yellow residue. This residue was then subjected to flash column chromatography (3:7 DCM:Hexanes) on silica gel to remove excess starting materials. The diastereomeric mixture was then subjected to gradient flash column chromatography (2:8→4:6 DCM:Hexanes) on silica gel to separate diastereomers. Major diastereomer denoted by ▲, and minor diastereomer with the higher frequency ^{31}P NMR chemical shift is denoted by ●, and minor diastereomer with the lower frequency ^{31}P NMR chemical shift is denoted by ■. Isolated a white powder as a mixture of diastereomers prior to separation (33 mg, 70%).

2 d(S)●: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.28 (m, Ar, 10H), 7.10 (t, ^3J = 7.7 Hz, Ar, 4H,), 6.72 (t, ^3J = 7.3 Hz, Ar, 2H), 6.60 (d, ^3J = 8.0 Hz, Ar, 4H), 5.34 (br s, N*H*, 2H), 4.90 (d, $^2J_{P-H}$ = 12.4 Hz, NC*H*P, 2H), 1.56 (n, ^3J = 6.7 Hz, $CH_2CH(CH_3)_2$, 1H). 1.24 (dd, ^2J = 10.4 Hz, ^3J = 6.5 Hz, $CH_2CH(CH_3)_2$, 2H), 0.72 (d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$, 6H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 146.6, 146.4, 135.63, 135.61, 129.2, 128.9, 128.8, 128.63, 128.60, 128.31, 128.27, 118.9, 114.7, 56.8, 56.3, 32.4, 31.9, 24.5, 24.4, 23.6, 23.6. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 65.3. FTIR (ATR, cm^{-1}): 3325 (w, ν(N–H)), 2959 (w), 1601 (s), 1502 (s), 1453 (m), 1431 (m), 1311 (m), 1274 (m), 1066 (w), 746 (s), 689 (s), HRMS: calcd. for $[C_{30}H_{33}N_2PSH]^+$ *m/z* = 507.1994, obs *m/z* 507.2000 [−1.1 ppm].

2 d(S)▲: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.4 (m, Ar, 2H), 7.3–7.23 (m, Ar, 4H), 7.22–7.14 (m, Ar, 3H), 7.12–7.04 (m, Ar, 2H), 7.02–6.92 (m, Ar, 2H), 6.73–6.65 (m, Ar, 1H), 6.64–6.55 (m, Ar, 3H), 6.34–6.24 (m, Ar, 2H), 5.46 (br s, N*H*, 1H), 5.10 (br t, ^3J = 8.5 Hz, N-*H*, 1H), 4.72 (d, $^2J_{P-H}$ = 10.5 Hz, NC*H*P, 1H), 4.29 (dd, $^2J_{P-H}$ = 10.5 Hz, ^3J = 10.1 Hz, NC*H*P, 1H). 1.86–1.62 (m, $CH_2CH((CH_3)_2)$, 2H) and $CHHCH(CH_3)_2$), 1.48–1.36 (m, $CHHCH(CH_3)_2$), 1H) 0.97 (d, ^3J = 6.5 Hz, $CH(CH_3)(CH_3)$, 3H), 0.69 (d, ^3J = 6.5 Hz, $CH(CH_3)(CH_3)$, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 146.9, 146.7, 145.0, 144.8, 136.0, 135.9, 129.2, 128.9, 128.7, 128.6, 128.5, 128.5, 128.4, 127.4, 118.6, 118.0, 59.6, 59.1, 53.7, 53.2, 35.3, 34.8, 24.9, 24.8, 24.3, 24.3, 24.1, 24.1, $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 64.1, FTIR (ATR, cm^{-1}): 3352 (w, ν(N–H)), 2957 (w), 1599 (s), 1499 (s), 1453 (m), 1431 (m), 1311 (m), 1262 (m), 1077 (w), 1027 (w) 747 (s), 690 (s), HRMS: calcd. for $[C_{30}H_{33}N_2PSNa]^+$ m/z = 507.1994, obs m/z 507.1996 [-0.3 ppm].

2 d(S)■: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, Ar, 4H), 7.25–7.16 (m, Ar, 6H), 7.12–7.06 (m, Ar, 4H), 6.74–6.68 (m, Ar, 2H), 6.55–6.50 (m, Ar, 2H), 4.84 (br, N-*H*, 2H), 4.67 (d, $^2J_{P-H}$ = 15.8 Hz, NC*H*P, 2H). 2.07 (n, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$, 1H,). 1.24 (dd, ^2J = 9.1 Hz, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$, 2H), 0.91 (d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$, 6H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 145.6, 145.5, 134.3, 129.2, 128.5, 128.5, 128.3, 128.3, 128.2, 128.2, 119.1, 114.5, 57.1, 56.5, 33.7, 33.3, 24.8, 24.7, 24.3, 24.3, $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 63.7, FTIR (ATR, cm^{-1}): 3341 (w, ν(N–H)), 2958 (w), 1600 (s), 1505 (s), 1455 (m), 1428 (m), 1309 (m), 1262 (m), 1063 (w), 749 (s), 690 (s), HRMS: calcd. for $[C_{30}H_{33}N_2PSNa]^+$ m/z = 507.1994, obs m/z 507.1970 [+4.7 ppm].

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: imine · main group · mechanism · nucleophilicity · primary phosphine

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