De novo synthetic design for air-stable *bis* primary phosphines: Synthetic, catalytic and biomedical motifs

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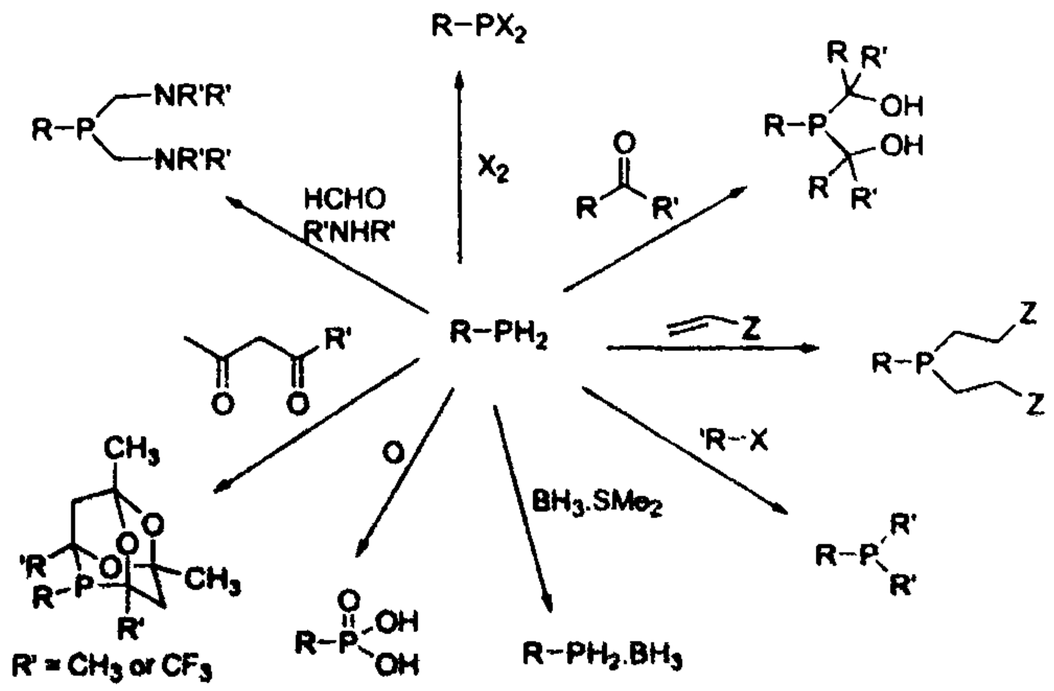
The syntheses of a series of 'hitherto unknown' air-stable functionalized bisprimary phosphines are described. Elegant syntheses of bisprimary phosphines with P_2N_2 (20) and P_2S_2 (24) frameworks were achieved by using 3-aminopropyl phosphine 3 and 3-bromopropyl phosphine 23 as building blocks. The highlights of these synthetic approaches involve the user-friendly synthons 3-aminopropyl phosphine 3 and 3-bromoproyl phosphine 23 and also the chemoselectivity in the aminolysis of acid ester 19 with 3-aminopropylphosphine 3. Ultimately, the first ever crystal structure of amido functionalized bisprimary phosphine is also reported. The successful conjugation of P_2N_2COOH 20 and P_2S_2COOH 24 to the peptides without oxidizing $-PH_2$ groups further demonstrated the stability and usefulness of compounds 20 and 24 in potential catalytic and biomedical applications.

PRIMARY and secondary phosphines (RPH_2 and R_2PH) constitute an important class of organophosphorus compounds[1–3]. Their facile participation in a number of chemical reactions that include, nucleophilic addition reactions with unsaturated species, substitution reactions with acid halides, reactions with alkali metals and a host of reactions at the P^{III} center (Scheme 1) have resulted in the development of a large number of new chemical products of commercial significance[1–8]. Primary phosphines, in particular, have proven to be versatile starting materials for the development of hydroxyalkyl phosphines ($R_x(CH_2OH)_yP$) via formylation of P–H bonds with aldehydes (Scheme 1)[9,10]. The ease of transformation of P–H bonds into P–C bonds is, undoubtedly, a synthetic novelty and the hydroxymethylated-phosphorus compounds have provided a diverse range of chemical, catalytic, biological and biomedical applications[11–18]. In particular, hydroxyalkyl phosphines have attained prominence for use as biocides[11], flame retardants[12,13], and environment protection agents[14]. Hydroxymethyl phosphines and their corresponding phosphonium salts have also found applications as ligands towards transition metals for the development of water-soluble catalysts for use under aqueous organic biphasic media[15,16].

Primary phosphine ligands are unique in that P^{III} centers are functionalized with the lightest element in the periodic table and therefore, possess higher vapour pressures. This feature has provided recent impetus in the application of primary phosphines as ligands in the development of new materials for use in chemical vapour deposition[17]. Most recently, functionalized hydroxymethyl phosphines have shown efficacy as complexing agents in the development of *in vivo* stable radiometal complexes for use in nuclear medicine[18].

Despite the rich chemistry, of general interest to organic, inorganic and biochemists, research on the development of precursor primary phosphine synthons has been mostly limited to simple alkyl or aryl substituted primary and secondary phosphines (e.g. RPH_2; R=CH_3, C_6H_5). A serious impediment to using primary and secondary phosphines, as general-purpose reagents to unravel



Scheme 1.

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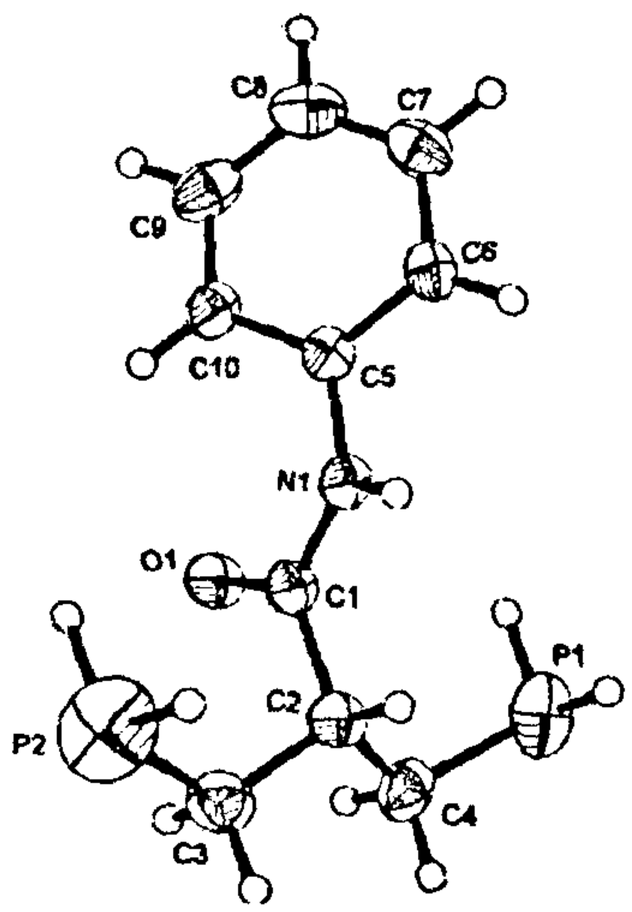
new chemistry, is associated with their unpleasant pyrophoric nature and extreme hydrolytic, thermal and oxidative instabilities. While examples of air and thermally stable mononuclear primary phosphines are rare, directed synthetic strategies to produce new generations of amine, amide or carboxylate functionalized primary phosphines may pave further progress in their fundamental and applied chemistry. In particular, design and development of *bis* primary phosphines (e.g. H_2PRPH_2) with 'user friendly' properties (e.g. good oxidative stability, low volatility) would be an important determinant towards the development of new chemistry and also for exploring further technological advances. As part of our ongoing research on the fundamental main group and organic chemistry of functionalized phosphorus compounds[19] we report, herein, *de novo* synthetic design for the development amide, carboxylate and thioether functionalized primary bisphosphines (Figure 1) featuring unprecedented oxidative and thermal stability characteristics. This research account summarizes latest results on (i) The utility of 3-aminopropyl primary phosphine **3** ($NH_2(CH_2)_3PH_2$) in the design and development of air stable amide and carboxylate functionalized *bis* primary phosphines via novel 'no-solvent' mediated *bis* aminolysis pathway (Scheme 2); (ii) unprecedented chemoselectivity in the reaction of 3-aminopropyl primary phosphine **3** with an ester in the presence of free acid (Scheme 2 and 5); (iii) the first example of a structurally characterized amide functionalized *bis* primary phosphine **13**; (iv) utility of bromopropyl phosphine as building block in the synthesis of carboxylate functionalized dithia *bis* primary phosphine; and (v) utility of carboxylate functionalized P_2N_2 and P_2S_2 primary bisphosphine frameworks in peptide conjugate chemistry.



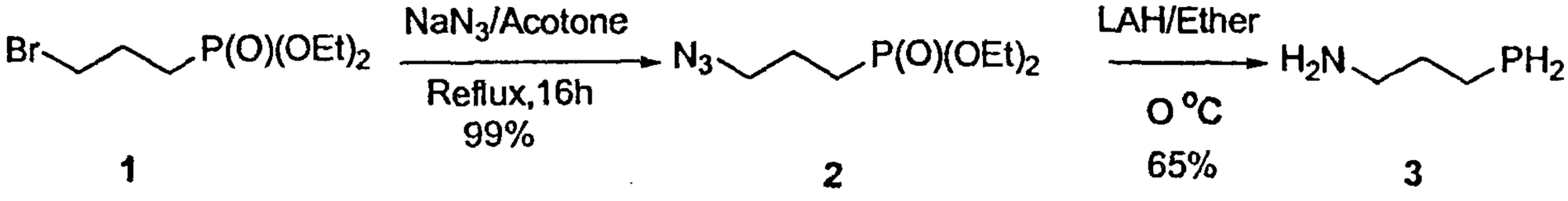
igure 1. Crystal structure of the amide functionalized bisprimary hosphines **6**.

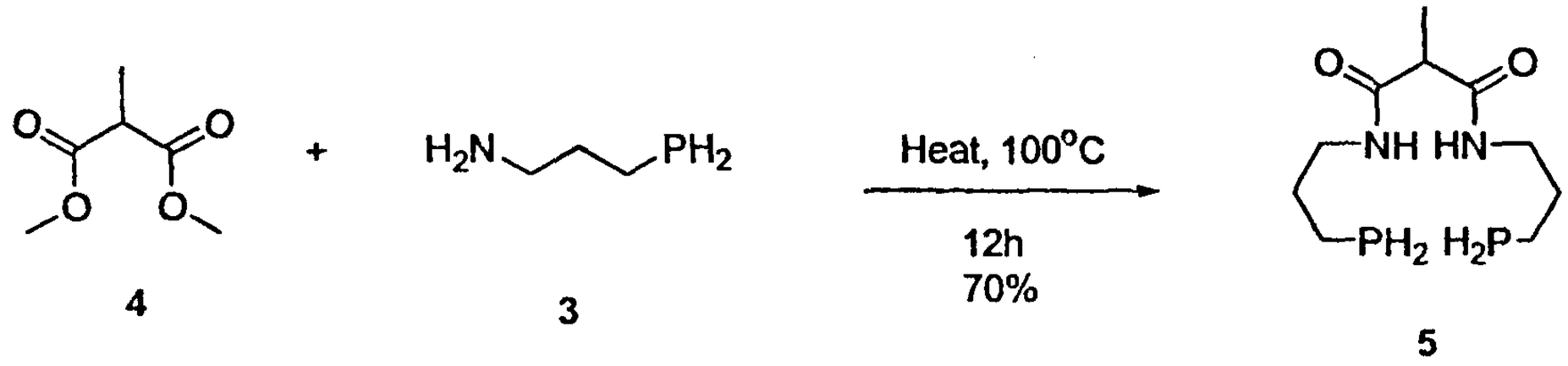
The reactions of primary phosphines, reported to date, mostly comprised of the utility of dangerously unstable and difficult to access phosphine gas (PH_3) and also alkali metal phosphides (e.g. MPH_2, M=Li or Na)[1–3]. The utility of 3-aminopropyl phosphine, $H_2N(CH_2)_3PH_2$ **3**, and bromopropyl phosphine $Br(CH_2)_3PH_2$ **14** as building blocks for the development of new and novel bisprimary phosphines (**5**, **10**, **20**, **24** and **29**), as described in the preceding sections, is unique because they are nonpyrophoric, thermally and oxidatively stable and are readily accessible in large quantites via non-phosphine gas synthons. The amide, carboxylate and thioether functionalized primary phosphines **5**, **6**, **10**, **14**, **15**, **20** and **24** reported, herein (Schemes 2–5 and 7) represent rare examples of air stable *bis* primaryphosphines with potential applications in catalysis and biomedicine (as discussed in the preceding sections).

Synthetic design for amide functionalized bisprimary phosphines

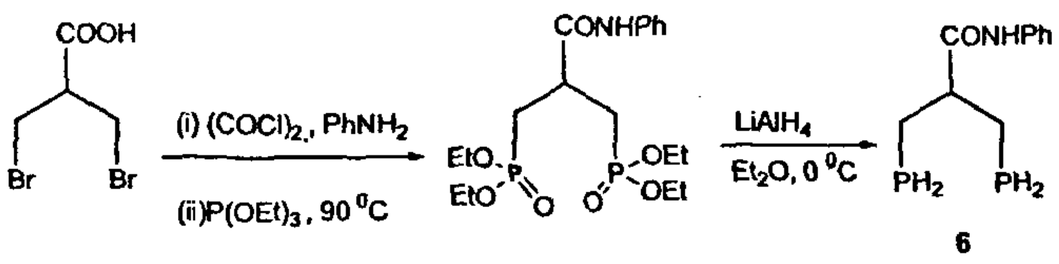
The synthon, 3-aminopropyl phosphine **3**, was synthesized via Arbuzov reaction of 1,3-dibromopropane with triethyl phosphite followed by conversion of the (3-bromopropyl)-phosphonic acid diethyl ester **1** to the corresponding azide **2** (Scheme 2). Further, (3-azidopropyl)-phosphonic acid diethyl ester **2** upon reduction with LAH gave 3-amino propyl phosphine **3** in 65% yield. 3-Aminopropylphoshine **3** is non-pyrophoric and is moderately stable in air. It can be stored for extended periods in nitrogen atmosphere as a neat colourless liquid. In the past, this compound was accessible via dangerous and often impractical routes that involved the use of PH_3 gas[20]. In sharp contrast, the reaction outlined in Scheme 2 to produce 3-aminopropyl phosphine **3** is simple, straightforward and consequently large quantities of this compound are readily accessible[21].

The demonstration that 3-aminopropyl phosphine **3** can be used as a building block to design functionalized phosphine **5** is depicted in Scheme 2. The reaction of aminopropyl phosphine **3** with 2-methyl malonic acid dimethyl ester **4** occurred at 100°C in the absence of solvent media to produce the new diamidodiphosphino, 2-methyl-*N*,*N*′-*bis*-(3-phosphanyl-propyl)-malonamide **5** (N_2P_2) in 70% yields. The amido functionalized primary phosphine **5** is an air stable crystalline solid and represents a rare example of an air stable primary *bis* phosphine[9,19]. The molecular constitution of **5** was confirmed by ^1H, ^{13}C and ^{31}P NMR spectroscopy and high-resolution mass spectrometry. Additional example of an air stable amide functionalized *bis* primary phosphine **6** is depicted in Scheme 3. The *bis* primary phosphine **6** produced single crystals upon slow evaporation of its solution in ethyl acetate and hexane (1:1).





Scheme 2.



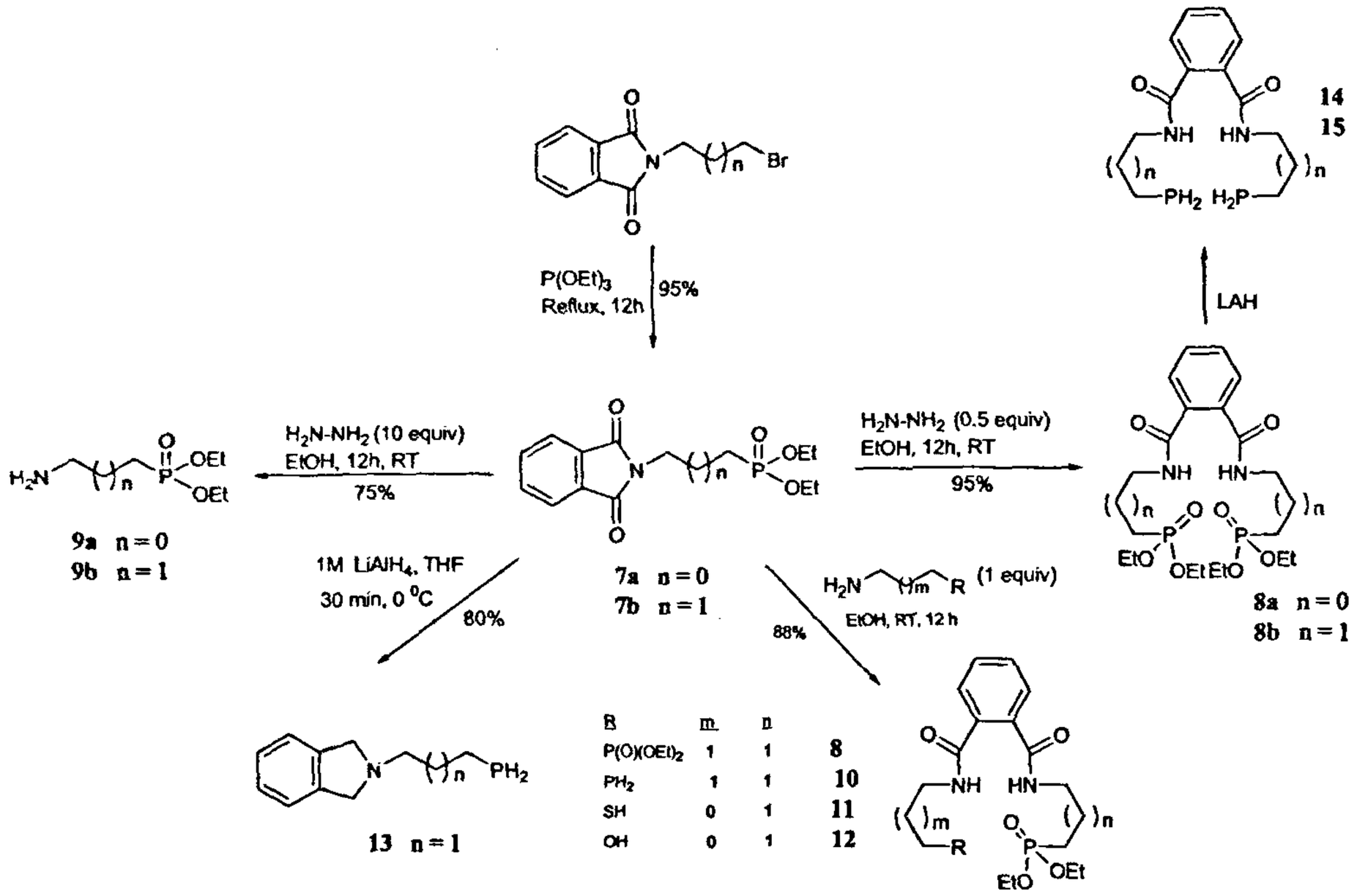
Scheme 3.

The molecular structure of **6**, shown in Figure 1, represents the first ever-reported crystal structure of a bis-primary phosphine compound[22].

Facile ring opening reactions of phthalimides as a new strategy for amide functionalized phosphonates, primary phosphines and novel water-soluble bisphosphines

Commercially available *N*-(bromoalkyl) phthalimides were converted to phthalimides **7** in near-quantitative yields utilizing the well known Michaelis–Arbuzov reaction by refluxing with 5-fold excess of triethyl phosphite for 12 h (Scheme 4)[23]. Treatment of **7** with 10-fold excess of hydrazine resulted in diethyl-aminoalkyl phosphonates **9** exclusively, via well known Gabriel synthetic pathway[24], in 75% yields (Scheme 4). Whereas, the treatment of phthalimides **7** with 0.5 equivalent of hydrazine in ethanol at room temperature for 12 h produced ring-opened bisphosphonates **8**, in near quantitative yields. The products **8** were formed as a result of ring opening of phthalimide by *in situ* generated nucleophiles **9**. When phthalimide **7** was treated with 0.5 equivalent of hydrazine, only 50% of **7** reacted to produce **9** and in turn, **9** further reacted with the remaining 50% of **7** to produce the novel ring-opened products **8**. The stoichiometric reaction of compounds **7** with **9** under similar experimental conditions produced bisphosphonates **8b** in near quantitative yields. Similar nucleophilic ring-opening reaction of *N*-methylphthalimide with ethylenediamine, to produce an adduct containing two units of *N*-methylphthalimide and one unit of ethylenediamine (*N,N'*-(*N,N'*-dimethyl)-diphthalamidoethane), was reported by Wolfe co-workers[25]. However, to date, there is no literature precedence of similar reactions for the synthesis of phosphorus containing ligands.

The generality of nucleophile assisted ring-opening reaction of phthalimide **7b** was tested by subjecting it to interact with 2-aminoethanol and 2-aminoethanethiol (Scheme 4). These reactions produced the corresponding phosphonates **11** and **12** in near-quantitative yields. The scope of this nucleophile-assisted ring opening was further tested by interacting 3-aminopropyl phosphine with **7b**. This reaction produced the first example of phosphine containing phosphonate **10** in 88% yield. The proton coupled phosphorus NMR of **10** clearly shows the presence of a P^{III} center (–135.1 ppm, J_{P-H} = 196 Hz) and P^{V} center (+ 34.3 ppm) within the same molecule. Compound **10** exemplifies the importance of 's' character of phosphorus center on the magnitude of phosphorus–carbon coupling constant across one bond. For example, the primary phosphine is expected to exhibit lower s character as compared to the phosphonate P^{V} in **10**. Therefore, in the ^{13}C NMR spectrum of compound **10**, P–C coupling was not observed for α–C to PH_2. However, α–C to $P(O)(OEt)_2$ showed a P–C coupling of 140.6 Hz. Compound **10** is unique in that it provides an example of an organophosphorus compound wherein P^{III} hydride and P^{V} phosphonate functionalities co-exist within the same molecule. Compounds that contain disparate three and five oxidation state phosphorus centers are

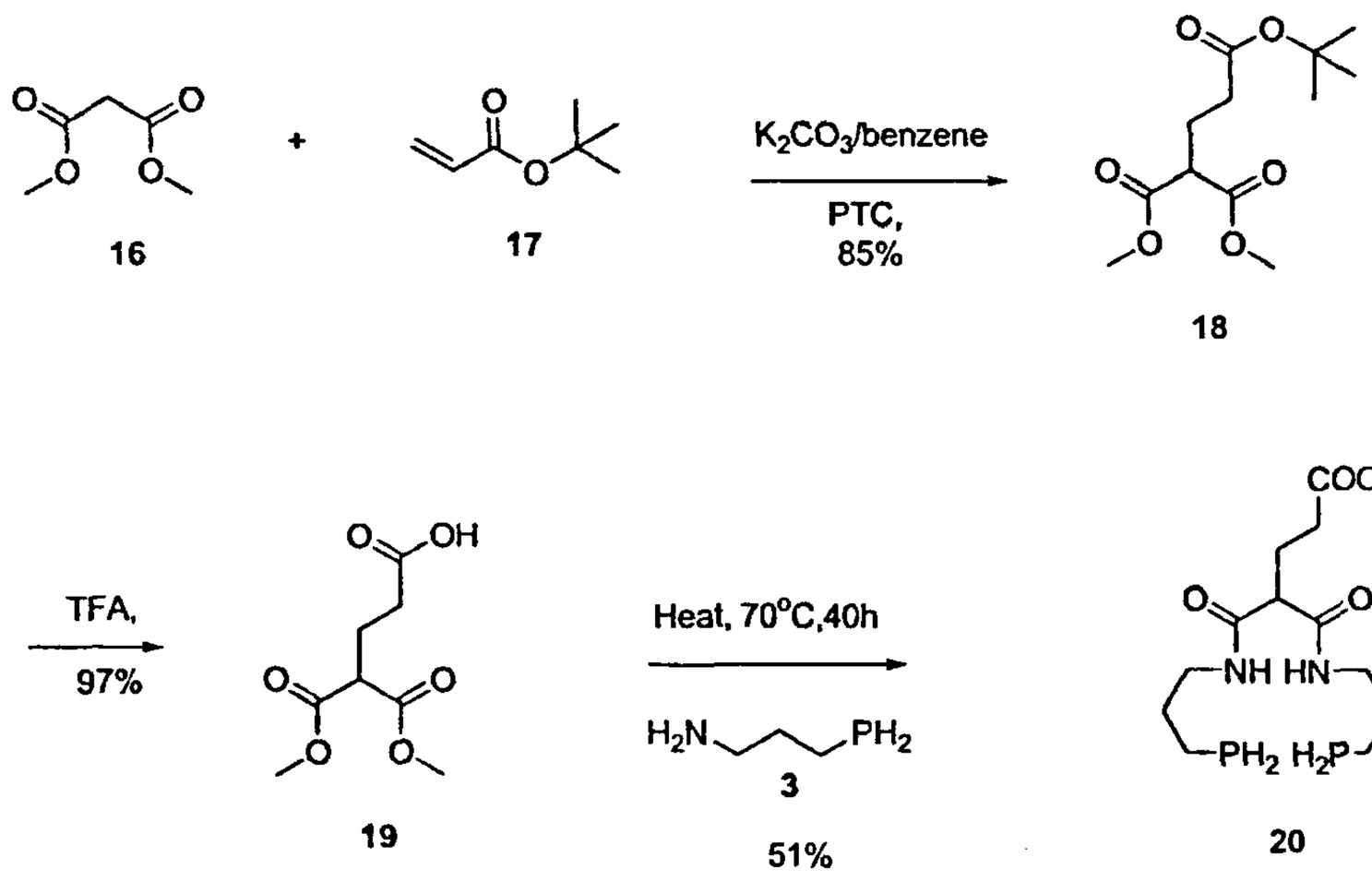


Scheme 4.

difficult to synthesize using traditional synthetic methods. In this context, the ease with which **10** is produced, via the reaction summarized in Scheme 4, provides a novel pathway for the development of hetero oxidation state organophosphorus compounds. All new compounds were characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and mass spectrometric methods.

It is interesting to note that reduction of bisphosphonates **8** with $LiAlH_4$ in dry THF at 0°C was selective in terms of reducing only phosphonates, although amide groups are susceptible for reduction under these conditions. The novel bisphosphines **14** and **15** were obtained in 80% yield, as air-stable, pale yellow solids. The formation of bisphosphines **14** and **15** was confirmed by ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopic and high-resolution mass spectrometric methods. The characteristic triplet splitting of the peak at –146.7 ppm (with $J_{P-H} = 195.6$ Hz) in the proton coupled ^{31}P NMR spectrum of **14** indicates the presence of two protons attached to the phosphorus center. It is interesting to note that ^{31}P NMR parameters of **14** are comparable with that of a simple primary phosphine compound $H_2P–CH_2–CO–NH–Ph$ (– 144.5 ppm, $J_{P-H} = 198$ Hz) reported by Issleib and co-workers[26]. It is also important to recognize that the amide function in **14** is four bonds away from PH_2 whereas it is disposed across two bonds in $H_2P–CH_2–CO–NH–Ph$. The presence of $–PH_2$ groups in **14** and **15** was further confirmed by the observation of characteristic band at 2282 cm^{-1} attributed to P–H stretch in the IR spectra. The peak at 169.1 ppm in ^{13}C NMR spectrum of **14** (and a band at 1632 cm^{-1} in IR spectrum) clearly indicated the presence of amide C=O group. The ^{13}C NMR resonance due to α–C (to PH_2) in **14** was observed at 14.6 ppm ($J_{P-C} = 10.5$ Hz) and is comparable with the reported spectral data by Issleib and co-workers for a series of *N*-substituted 2-aminoethylphosphines[27]. It may be noted that in the propyl analogue, **15**, P–C coupling was not observed for α–C to PH_2. Compounds **14** and **15** represent rare examples of alkyl primary phosphines with unusual stability towards air-oxidation. Recently Goodwin *et al.* and Brynda *et al.* have also reported high oxidative stability to primary phosphines functionalized with bulky substituents[28–30].

The reduction reaction of compound **7b** with $LiAlH_4$ under similar experimental conditions produced the primary phosphine **13**, in which both imide and phosphonate groups were reduced (Scheme 4). The primary phosphine **13** is an air-stable white crystalline solid, which was purified on a silica gel column. The triplet splitting in proton-coupled ^{31}P NMR spectrum (134.8 ppm, $J_{P-H} = 192.4$ Hz) of **13** was found to be in accordance with that of 3-(*N,N'*-dimethylamino)-propylphosphine (–138.9 ppm, $J_{P-H} = 193.7$ Hz) reported by Braver *et al.*[31]. The reduction of the imide groups in **7** to produce **13** is, presumably, due to the general tendency of imides to be more susceptible for reduction than amides.



Scheme 5.

The results outlined in Scheme 4 demonstrate synthetic utility of the nucleophile-mediated ring-opening of phthalimides **7**. The methodology described, herein, can be used in the design and development of hitherto unknown amide functionalized novel phosphonates and phosphines.

Synthesis of amide, thioether and carboxylate functionalized bisprimary phosphine framework

Combination of carboxylate and PH_2 groups within the same molecule, as in the compound: 4,4-*bis*-(3-phosphanyl-propylcarbamoyl)-butyric acid **20** (N_2P_2COOH, Scheme 5), will present unique prospects for attachment of phosphines to chemical and biochemical vectors via the traditional –COOH activation protocols. Subsequent transformation of $-PH_2$ bonds in to phosphorous-carbon linkages, via reactions shown Scheme 1 will generate versatile range of P^{III} compounds with finely-tuned substituents on phosphorus centers. But, the co-existence of –COOH and $-PH_2$ functionalities within the same molecule would be difficult. This is because the reaction conditions that are used to reduce a $-P(O)(OEt)_2$ group to a $-PH_2$ group can also result in the reduction of –COOH groups. Therefore, preformed primary phosphines, that contain reactive functionalities on their backbone (e.g. **3** and **23**), can be used as building blocks to produce such compounds containing reduction-sensitive groups (e.g. COOH). The synthetic utility of 3-aminopropyl phosphine **3** for the development of a novel –COOH functionalized bisamidobisprimary phosphine, 4,4-*bis*-(3-phosphanyl-propylcarbamoyl)-butyric acid **20** is depicted in Scheme 5. The reactions involved Michael addition of *t*-butyl acrylate **16** to malonic acid dimethyl ester **17** to produce the intermediate adduct, 2-methoxycarbonyl-pentanedioc acid 5-*tert*-butyl ester 1-methyl ester **18**, which upon treatment with trifluroacetic acid (TFA) produced the corresponding diester acid, 2-methoxycarbonyl-pentanedioc acid 1-methyl ester **19**, in near-quantitative yield. It is remarkable to note that the reaction of $NH_2(CH_2)_3(PH_2)$ **3** with the diester acid **19** is highly selective because the –COOH group remained unattacked whereas the reaction occurred smoothly and selectively at the –COOMe groups to produce the novel carboxylate functionalized diamide bisprimary phosphine, 4,4-*bis*-(3-phosphanyl-propylcarbamoyl)butyric acid **20** in 51% yield[21]. The proton-coupled phosphorus NMR spectrum confirmed the presence of $-PH_2$ units in **20** (Figure 2).

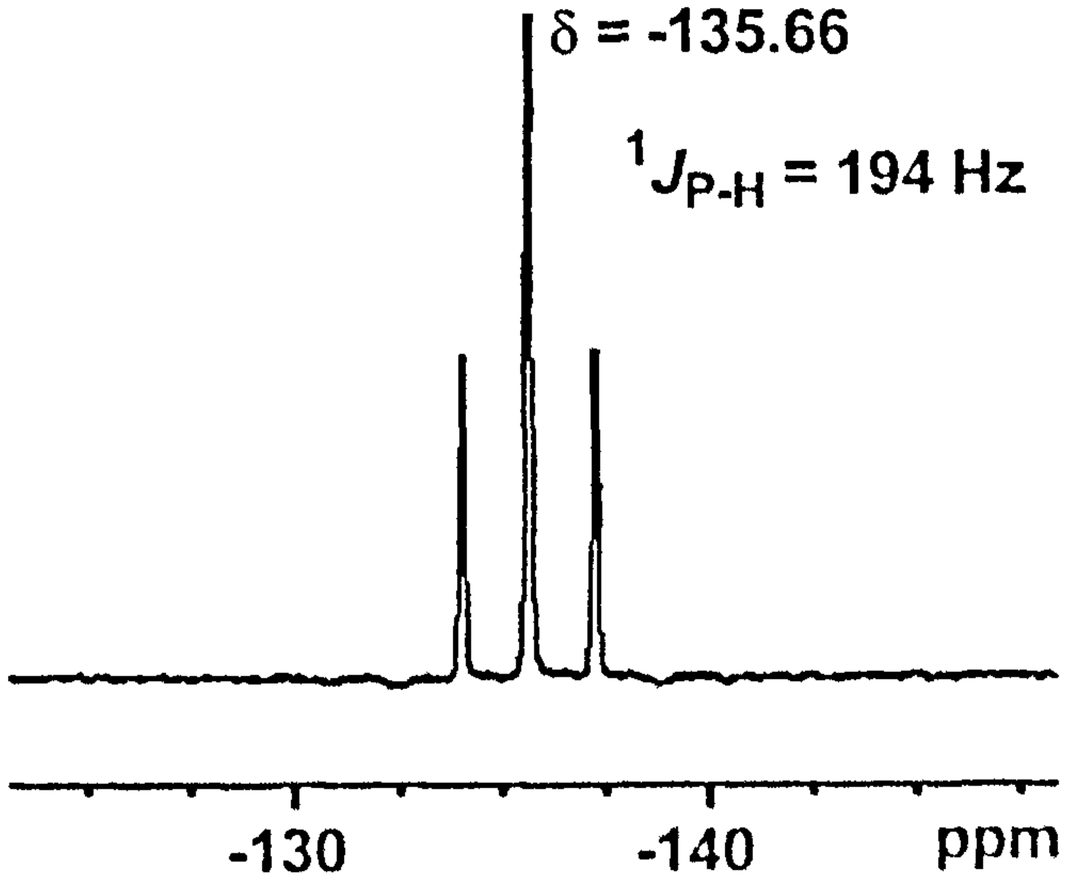
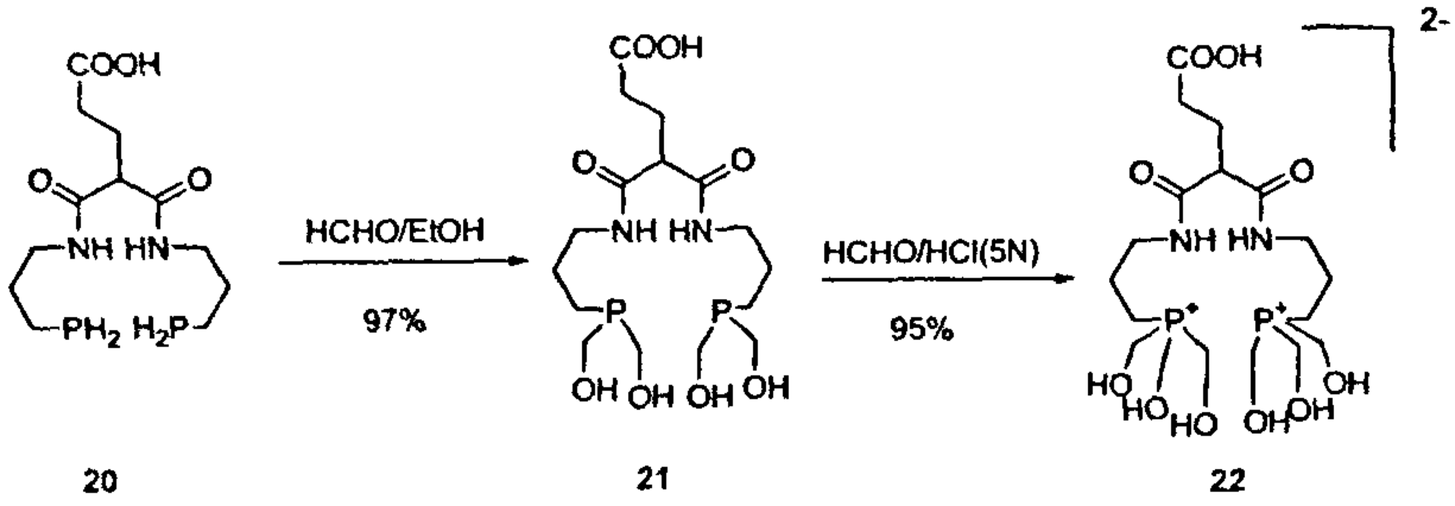
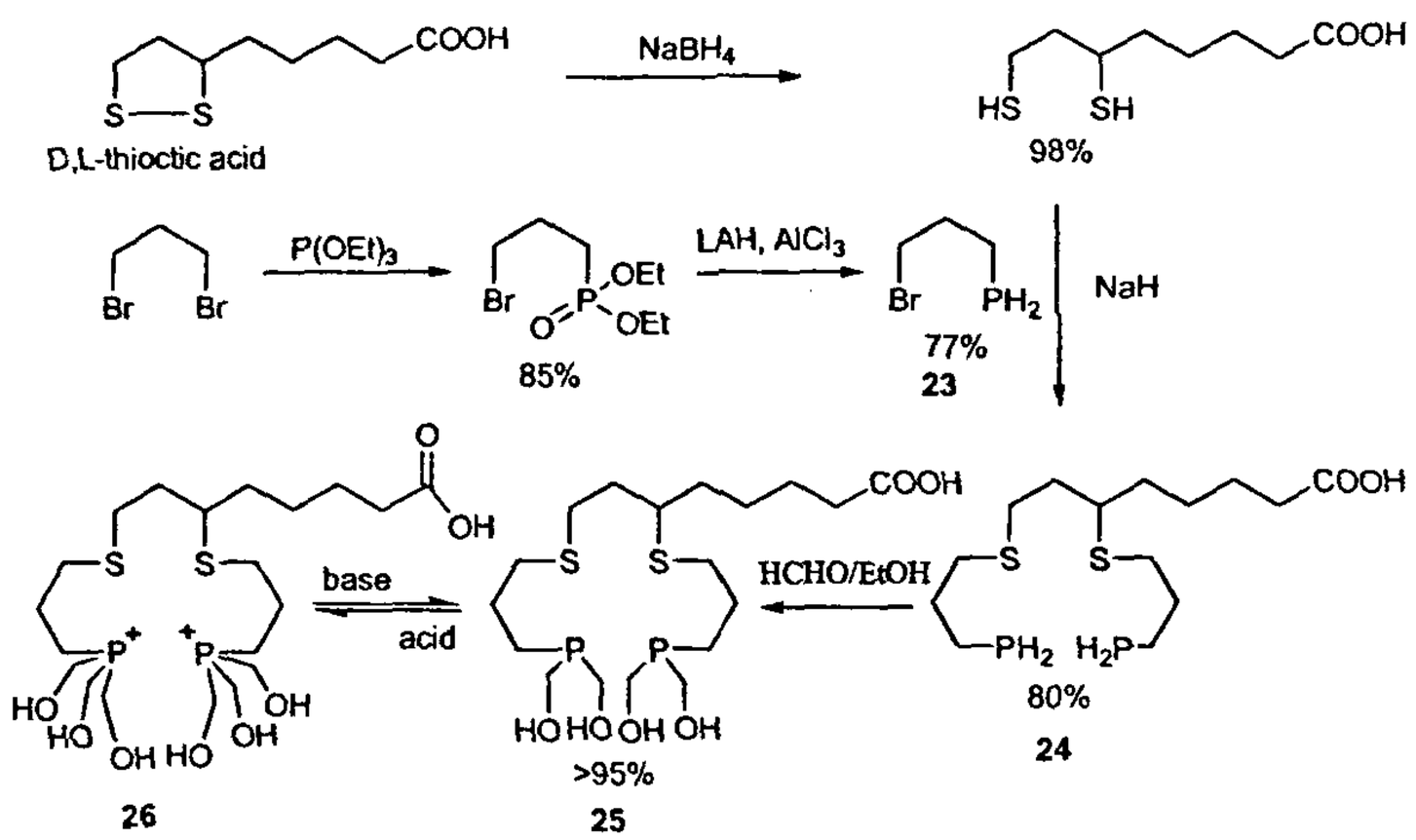


Figure 2. Proton-coupled ^{31}P NMR spectrum of **20**.



20 21 22

Scheme 6.



26 25

Scheme 7.

The new bisprimary phosphine **20** was characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and high-resolution mass spectrometry. It is important to recognize that the aminolysis of **4** and **19** with 3-aminipropylphosphine **3**, when carried out in the presence of solvents (benzene or toluene), resulted in complex side reactions and products **5** and **20** were formed as only minor byproducts.

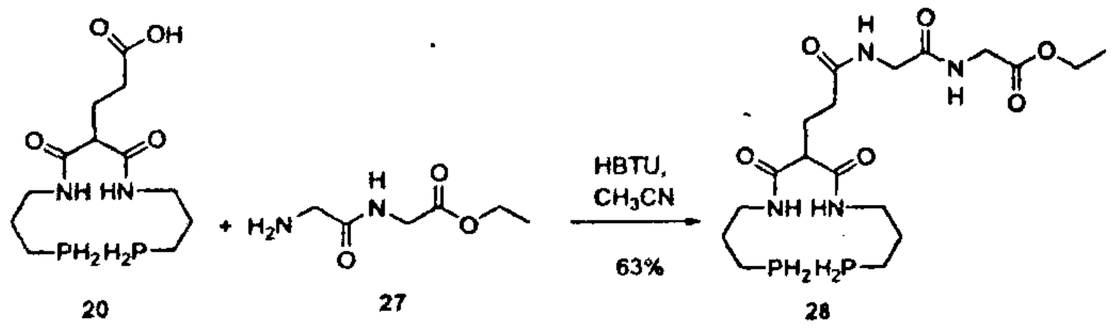
Formylation of P–H bonds in **20**, using formaldehyde in ethanol, produced hydroxymethyl functionalized bisphosphine, 4,4-*bis*[3-hydroxymethyl-phosphanyl)-propyl carbamoyl]butyric acid **21**, in near-quantitative yields. Compound **21** was oxidatively stable in aqueous media for extended periods of time. Further, hydroxymethyl functionalized bisphosphine **21** was converted to the corresponding phosphonium salt **22** for characterization purposes (Scheme 6).

Another approach to the synthesis of carboxylate functionalized primary phosphine ligand framework is shown in Scheme 7. It involves the use of bromopropyl phosphine **23** as a key synthon which was recently obtained in our laboratory by the reduction of diethyl-3-bromopropylphosphoante with dichloroaluminium hydride[19]. Reaction of **23** with dianion of 6,8-dithiooctanoic acid produced the COOH-functionalized P_2S_2-primary phosphine framework **24**. The proton-coupled ^{31}P NMR of **24** showed two merged triplets ($^{1}J_{P-H}$ = 193.2 Hz) and confirmed the presence of two different phosphanyl groups. The thermally stable P^{III} hydride **24** was then formylated with 37% formaldehyde in ethanol to produce the corresponding water-soluble phosphane framework **25** in near-quantitative yields (Scheme 7). Compounds **23–26** were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and HR-FAB mass spectrometry[19].

Implications of carboxylate functionalized bisprimary phosphines N_2P_2COOH 20 and P_2S_2COOH 24

The carboxylate-containing ligating frameworks of the type N_2P_2–COOH **20** and P_2 S_2–COOH **24** present opportunities for use in a number of different chemical, catalytic and biomedical motifs[22]. The carboxylate

groups in **20** and **24** are used to incorporate peptides or proteins on the ligating bisphosphine framework. The secondary and tertiary structure of peptides to which they are attached may subsequently help in controlling the reactivity of phosphine-coordinated transition metals. Specifically, the chirality and related important stereospecific characteristics associated with biomolecules (e.g. peptides or proteins) may be transferred to the transition metals if peptides are immobilized with chelating units that are capable of coordinating with transition metals[32]. This approach of conjugating catalytically active transition metals to chiral biomolecules provides a straightforward route to harvest chiral compounds with potential applications in enantioselective catalysis. The incorporation of phosphines onto peptides (and proteins) will also help to engineer metal binding sites that may eventually provide conformational integrity, biospecificity, and enhanced enzymatic activities[32,33]. In addition, bioconjugation of cytotoxic transition metals to receptor avid peptides may eventually provide effective vehicles for delivering cytotoxic moieties to specific tumours through receptor-mediated agonist or antagonist interaction[34]. In this context, peptides (or receptor-binding biomolecules) containing phosphine substituents are important in the design and development of tumour-specific radiopharmaceuticals[35,36]. Despite significant catalytic and biomedical applications offered by such peptides (and proteins), synthetic strategies for producing bioconjugates are still in their infancy. To demonstrate the feasibility of linking –COOH groups of P_2N_2–COOH **20** and P_2S_2–COOH **24** with peptides (and proteins), a synthetic protocol for linking compound **20** with a dipeptide, gly gly ethyl ester hydrochloride **27**, has been developed as outlined in Scheme 8. This method involved activation

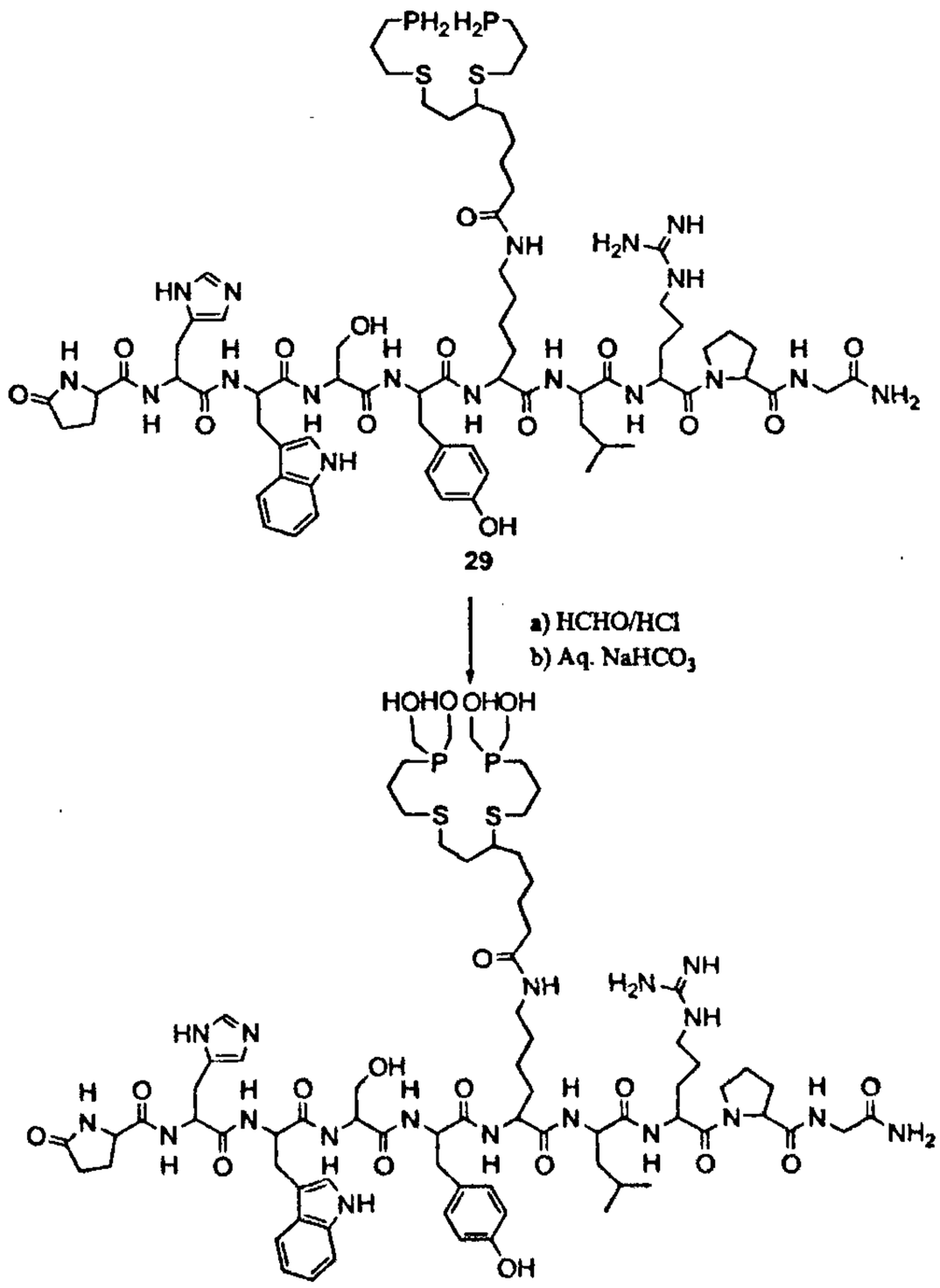


20 + 27 → 28

Scheme 8.

of the carboxylate of P_2N_2–COOH **20** using HBTU followed by interaction with the $-NH_2$ group of Gly–Gly peptide **27**. The resulting P_2N_2 Gly–Gly peptide conjugate, {2-[4,4-*bis*-(3-phosphanyl-propylcarbamoyl)-butyryalamino]-acetylamino}-acetic acid ethyl ester **28**, was produced in 63% yields.

To demonstrate the feasibility of linking P_2S_2–COOH compound **24** to biomolecules, a P_2S_2 –D-Lys conjugate of a leutinizing hormone releasing hormone peptide, the D-Lys^6-LHRH conjugate **29**, was synthesized by automated solid-phase peptide synthesis (SPPS; Scheme 9). This method involved repeated use of a variety of chemicals in high concentrations (including trifluoroacetic acid (TFA)) for cleavage of peptide bound resin. Peptide **29** was purified by HPLC and analysed by ^{31}P NMR spectroscopy and mass spectrometry. These data demonstrated that the peptide conjugate **29** was formed in high yields with no modification of PH_2 groups. These results also confirm that the PH_2 groups of **20** and **24** are resistant to oxidation and are unreactive towards other functional groups in the peptides and the reagents used in SPPS. The synthesis of biomolecules which contain $-PH_2$ groups allows their conversion to hydrophilic alkyl phosphanes. Thus formaldehyde reacted rapidly with the PH_2 groups of **29** to produce the peptide–functionalized phosphane **30** (Scheme 9) now



Scheme 9.

containing additional P–C bonds. Either PH_2 groups or their derivatized analogues PR_2 may be used as a part of the chelator framework of biomolecules to form well-defined metalated conjugates by complexation with transition metals.

Conclusions

The chemistry described, herein, demonstrates for the first time that primary phosphines containing amide, thioether and carboxylate groups possess high oxidative and thermal stabilities. Furthermore, the –COOH groups of primary phosphines **20** and **24** provide an elegant strategy for their incorporation on peptide backbones. Metalated analogues of the peptide **28–30** and related biomolecules may open up new avenues in the design of chiral transition metal compounds for catalytic applications. Moreover, the metallation of functionalized peptides with cytotoxic metals (e.g. Pt^{II}), will also enable the design and development of site-specific drugs for delivery of cytotoxic agents to specific cancerous sites through receptor-mediated agonist-antagonist interactions. Therefore, the new synthetic design for functionalized air-stable bisprimary phosphines and their bioconjugate chemistry reported, herein, has implications in both catalysis and biomedicine fields.

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