

# Design and Development of Functionalized Water-Soluble Phosphines: Catalytic and Biomedical Implications

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Water is an environmentally (and biologically) benign solvent, and therefore, development of chemistry in aqueous media has long been a desirable goal for chemists. In particular, chemistry of water-soluble transition metal compounds has gained considerable prominence in recent years because of their usefulness in biphasic (aqueous–organic) catalysis<sup>1</sup> and biomedicine.<sup>2</sup> High solubility of transition metal compounds in water becomes a primary requirement in the design and development of catalysts for use under biphasic media because

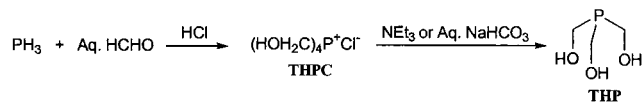
Kattesh V. Katti was born in Dharwad, India, in 1956. He received B.Sc. and M.Sc. degrees, in 1977 and 1979, from Karnataka and Mysore Universities, India, respectively. He carried out graduate studies, in cyclophosphazene chemistry, under the direction of Professor S. S. Krishnamurthy at the Indian Institute of Science, Bangalore, India, and received his Ph.D. degree in 1984. In 1985, he was awarded the Alexander von Humboldt fellowship to work in Professor H. W. Roesky's research group at the University of Gottingen, Germany, and in 1987, he worked in Professor R. G. Cavell's research group as a Research Associate at the University of Alberta, Edmonton, Canada. Since 1990, he has been a faculty member at the University of Missouri—Columbia and is currently Associate Professor of Radiology with a joint appointment at the Research Reactor as Senior Research Scientist. His research interests include main group and transition metal chemistry with a focus on the design and synthesis of chemical and biological conjugates for use in nuclear medicine, biomaterials, and catalysis.

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Scheme 1



of the need for efficient separation and recovery of expensive transition metal catalysts (in aqueous media) from organic products. Additionally, the ability of specific transition metals to exert therapeutic (and diagnostic) influence on certain diseases has provided increased impetus in the development of new water-soluble and in vivo-stable transition metal compounds.<sup>2,3</sup> Of the various ligands available to stabilize specific oxidation states of transition metals and to produce aqueous soluble coordination compounds, functionalized phosphines are the most attractive class of ligands because of their versatile coordination chemistry. While aqueous soluble di- or trisulfonated arylphosphines, such as P(*m*-C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na)<sub>3</sub>, have largely been employed in the development of highly active water-soluble transition metal catalysts,<sup>1</sup> hydrophilic alkylphosphines are being highly sought after in order to gain specific structure–activity advantages in both catalytic and biomedical applications. In this context, the formylation of PH<sub>3</sub>, first reported by Hoffman et al., to produce tetrakis(hydroxymethyl)phosphonium chloride (THPC) has provided one of the earliest examples for the synthesis of hydrophilic alkylphosphines (Scheme 1).<sup>4</sup> Water-soluble tris(hydroxymethyl)phosphine (THP) was produced upon reaction of THPC with a suitable base (e.g., triethylamine or sodium bicarbonate buffer) (Scheme 1).<sup>5</sup> The transition metal chemistry of THP and other functionalized phosphines, over the years, has enabled the development of a wide spectrum of water-soluble transition metal/organometallic compounds for potential use in biphasic catalysis<sup>5,6</sup> and biomedicine.<sup>7,8</sup>

The ease of transformation of P–H bonds into P–C bonds (as outlined in Scheme 1) is, undoubtedly, a synthetic novelty and the (hydroxymethyl)phosphorus compounds have provided a diverse range of chemical, catalytic, biological, environmental, and biomedical applications.<sup>5–10</sup> Despite the potential academic interest and scope for further technological advances, formylation reactions of functionalized phosphorus hydrides and, especially, of multinuclear phosphorus hydrides (i.e., bis-, tris-, or tetraphosphines) have, surprisingly, remained largely unexplored.

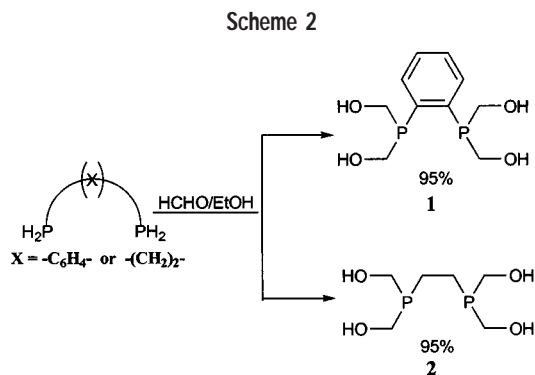
It must be recognized that PH<sub>3</sub>, in its pure form, is an extremely hazardous chemical compound. It ignites in air at about 150 °C and decomposes to produce phosphoric acid.<sup>11</sup> In its impure form, PH<sub>3</sub> gas is spontaneously inflammable at room temperature and this insta-

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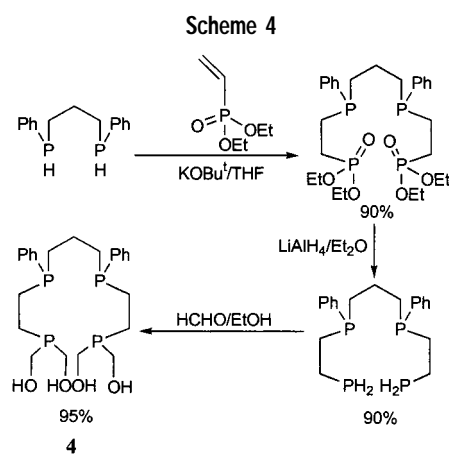
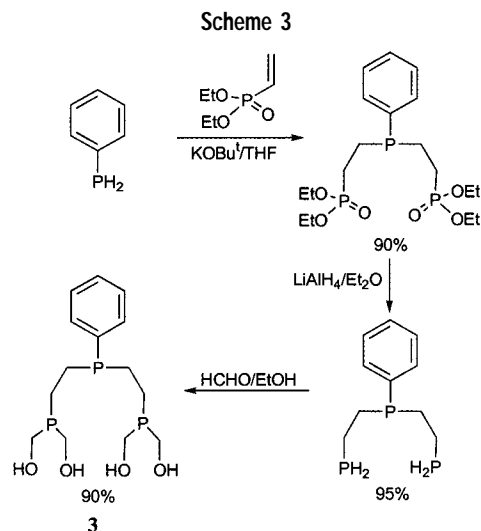


bility has been attributed to traces of diphosphine,  $P_2H_4$ , and also  $P_4$ .<sup>11</sup> These unfavorable properties of  $PH_3$  and related phosphorus(III) hydrides have, presumably, impeded their widespread use as precursors in the development of new water-soluble phosphines via formylation reactions. Therefore, the development of new and functionalized phosphorus(III) hydrides, which are safe to handle, would be an important determinant for future advances in their formylation reactions. We have a long-standing interest in the design and development of functionalized phosphines for catalytic and biomedical applications.<sup>12,13</sup> We discuss, herein, promising and versatile strategies for producing stable and well-defined multifunctional and multinuclear phosphorus(III) hydrides followed by their utility as synthons for the development of a new generation of water-soluble phosphines via formylation reactions of P–H bonds.

The purpose of this Account is, therefore, to review recent advances in phosphorus chemistry research at the University of Missouri–Columbia. This Account begins with discussions of results of the generation of new phosphorus(III) hydrides of simple di- and triphosphines followed by descriptions of the incorporation of thioether, amino, and carboxylate subunits to produce highly functionalized phosphines. We then demonstrate how these multifunctional phosphorus hydrides can be formylated, even in partially aqueous media, to produce structurally diverse water-soluble (hydroxymethyl)phosphines. Finally, solution properties and reactions of (hydroxymethyl)phosphines with transition metals are discussed with particular relevance to the potential utility of water-soluble transition metal complexes in biphasic catalysis and biomedicine.

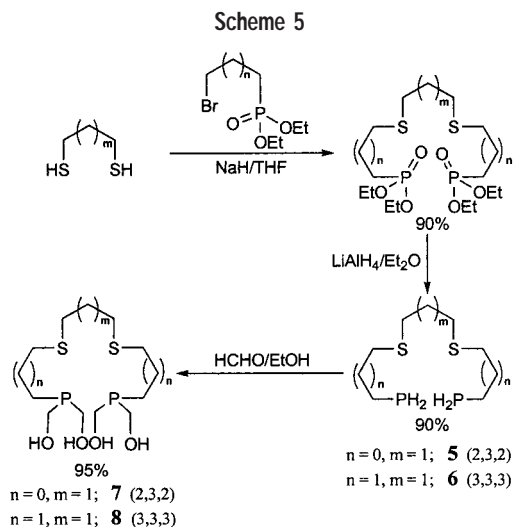
## Synthesis and Formylation of Multinuclear Phosphines

Our entry into the area of formylation reactions of multinuclear phosphorus(III) hydrides began with the successful synthesis of 1,2-bis(bis(hydroxymethyl)phosphino)benzene, **1**, or -ethane, **2**, via formylation of the respective 1,2-bis(phosphino)benzene or -ethane analogues (Scheme 2).<sup>14,15</sup> Early reports on the formylation of 1,2-bis(phosphino)ethane and related analogues used harsh reaction conditions that involved employing high temperatures ( $>80\text{ }^\circ\text{C}$ ) and longer durations under sealed



setups.<sup>16</sup> It is important to recognize that phosphorus(III) hydrides are toxic and pyrophoric. Therefore, we wished to see if formylation reactions of phosphorus(III) hydrides can be carried out using mild conditions (unsealed apparatus and at lower temperatures). Such “user-friendly” reaction conditions would provide safety from explosion hazards and, more importantly, enhance the applicability of formylation reactions to, hitherto unexplored, multinuclear phosphorus(III) hydride compounds. In fact, our laboratory, for the first time, demonstrated that formylation reaction of 1,2-bis(phosphino)benzene or -ethane (Scheme 2) can be carried out (using 37% formaldehyde) in ethanol in unsealed glass wares, at  $25\text{ }^\circ\text{C}$  or lower, to produce the corresponding hydroxymethylated 1,2-bis(bis(hydroxymethyl)phosphino)benzene, **1**, or -ethane, **2**, respectively, in excellent yields.<sup>14,15</sup>

We quickly tested the efficacy of this new formylating strategy on the tri- and tetranuclear phosphorus(III) hydrides developed recently in our laboratory (Schemes 3 and 4).<sup>17,18</sup> The formylation of these multinuclear  $P^{III}$  hydrides occurred readily in diethyl ether, even at  $0\text{ }^\circ\text{C}$ , to produce a new and interesting class of water-soluble triphosphine, **3**, and tetraphosphine, **4**, functionalized with hydroxymethyl units on the  $P^{III}$  centers.

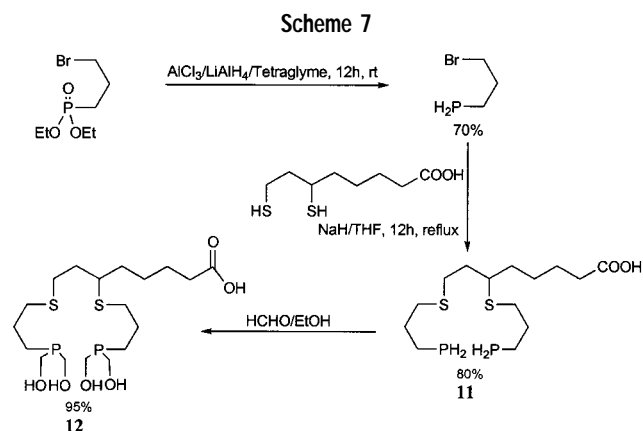
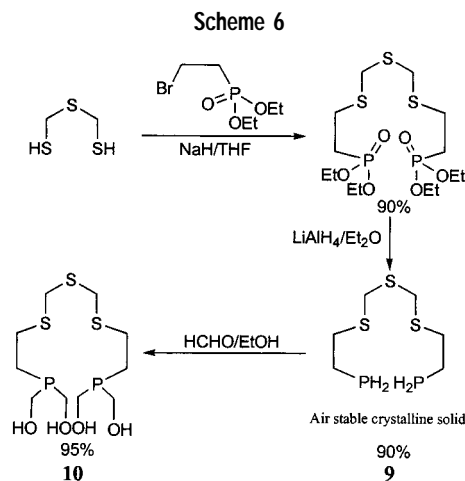


## Formylation of Functionalized Phosphorus(III) Hydrides

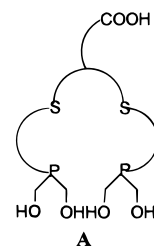
The hazardous nature of  $\text{PH}_3$  and the relative difficulties in the synthesis and handling of  $\text{H}_2\text{P}(\text{X})\text{PH}_2$  ( $\text{X} = \text{C}_6\text{H}_4$  or  $(\text{CH}_2)_2$ ) may appear as serious impediments for the development of new phosphorus(III) hydrides. However, as we have designed new chemical backbones with appended  $-\text{PH}_2$  units, we have experienced some surprises. For example, the thioether-functionalized bis-(phosphines) ( $\text{P}_2\text{S}_2$ ), **5** and **6** (Scheme 5), obtained via a two step synthetic pathway, are stable at room temperature as neat liquids, and their solutions in common organic solvents can be stored for extended periods of time.<sup>19,20</sup> As outlined in Scheme 5, the thioether-functionalized phosphorus(III) hydrides, of varying alkyl chain lengths (e.g., 2–3–2 or 3–3–3) that connect thioether units to the  $\text{PH}_2$  center, can be synthesized with the choice of appropriate dithiols (e.g.,  $\text{HS}-(\text{CH}_2)_n-\text{SH}$ ;  $n = 3, 4$ ) and (bromoalkyl)phosphonate precursors (e.g.,  $\text{Br}-(\text{CH}_2)_n-\text{P}(\text{O})(\text{OEt})_2$ ;  $n = 2$  or  $3$ ).<sup>19,20</sup> Formylation of  $\text{P}_2\text{S}_2$  phosphorus hydrides **5** and **6** occurred via reaction with aqueous formaldehyde in ethanol to produce the first examples of thioether-functionalized (hydroxymethyl)-phosphines **7** and **8** in good yields (Scheme 5).<sup>19,20</sup>

Another example of a thioether-functionalized phosphorus(III) hydride came with the synthesis of  $\text{P}_2\text{S}_3$  framework, **9**, as shown in Scheme 6. This new phosphine is a white, thermally stable, crystalline solid and can be stored for extended periods ( $>2$  years) in unsealed glass vials. In fact, exposure of this phosphorus(III) hydride to atmospheric moisture/oxygen did not result in any decomposition. To the best of our knowledge, this is the first phosphorus(III) hydride with unusual thermal- and oxidative-stability features.

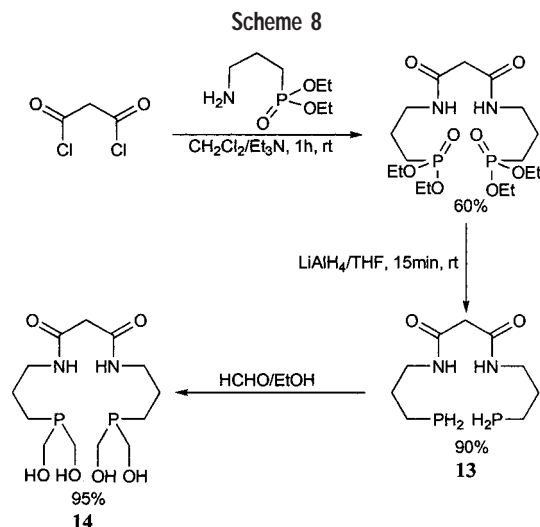
The reaction sequences described in Schemes 5 and 6 involve a reduction step to reduce phosphonate compounds to their corresponding phosphorus(III) hydrides using lithium aluminum hydride ( $\text{LiAlH}_4$ ). If the (bromoalkyl)phosphonate or the dithiol derivatives are bonded to other organic functionalities, such as carboxylic acids or halides, the  $\text{LiAlH}_4$  reduction pathway, in addition to



reducing the  $-\text{P}(\text{O})(\text{OEt})_2$  functionalities to  $\text{PH}_2$ , would also reduce the organic functional groups. Therefore, new strategies must be developed in order to produce highly functionalized phosphorus(III) hydrides and phosphines. The  $-\text{COOH}$  functionalized  $\text{P}_2\text{S}_2$  framework (**A**), for ex-



ample, will have applications in biomedicine and catalysis. The  $-\text{COOH}$  group can be conjugated to specific biomolecular vectors (e.g., proteins or peptides), and such bioconjugates can be used to produce water-soluble transition metal or radiometal complexes (vide infra). Our approach to the  $\text{P}_2\text{S}_2-\text{COOH}$  (**A**) ligand framework involved using (bromopropyl)phosphine ( $\text{Br}(\text{CH}_2)_3\text{PH}_2$ ), as a key synthon. This synthon was recently developed in our laboratory via reduction of the corresponding phosphonate using dichloroaluminum hydride ( $\text{AlHCl}_2$ , commonly referred to as dichloroalane) as an active reductant (Scheme 7). It must be realized that the generation of dichloroalane is difficult as it involves a highly exothermic reaction of  $\text{AlCl}_3$  with  $\text{LiAlH}_4$ . Dichloroalane is a reductant



of choice here because it selectively reduces phosphonates and does not reduce alkyl bromides whereas traditional reducing agents are nonselective.<sup>21</sup> The (bromoalkyl)-phosphine, upon reaction with dihydrolipoic acid, produced the corresponding  $-\text{COOH}$ -functionalized  $\text{P}_2\text{S}_2$  framework, **11**, as outlined in Scheme 7. It is important to recognize that (bromopropyl)phosphine can be used as a versatile synthon to produce compounds in which chemical functionalities that are susceptible to reduction (e.g.,  $-\text{COOH}$  or amides) and highly reduced chemical frameworks (e.g.,  $-\text{PH}_2$ ) coexist (e.g.,  $(\text{PH}_2)_2\text{S}_2-\text{COOH}$ , **11**) as in Scheme 7. The thermally stable  $\text{P}^{\text{III}}$  hydrides, **9** and **11**, were formylated, using 37% formaldehyde, in ethanol to produce the corresponding water-soluble phosphine compounds **10** and **12**, respectively, in  $>90\%$  yields.

Our synthesis of amide-functionalized phosphorus(III) hydride  $(\text{PH}_2)_2\text{N}_2$ , **13**, and its subsequent formylation to produce hydroxymethylated bisphosphine **14** is illustrated in Scheme 8. Although amide functionalities are prone to reduction with  $\text{LiAlH}_4$ , the short duration of reaction, necessary for reduction of phosphonate to  $-\text{PH}_2$ , generally, did not affect the amide bonds (Scheme 8). Amides are considered to be versatile ligands because of their ability to undergo deprotonation reactions upon interaction with transition metals. In this context, the combination of phosphine and amide ligating units in one ligand, provided by **14**, presents attractive features for use in the development of novel water-soluble transition metal compounds.

## Solution Behavior and Oxidative Stability

Most of the (hydroxymethyl)phosphines (HMP), as described in Schemes 2–8, are soluble in water because of the presence of hydrophilic  $-\text{CH}_2\text{OH}$  substituents. These compounds also exhibit high oxidative stability in aqueous media. The aqueous solutions of the HMP compounds **1–3**, **7**, **8**, **10**, **12**, and **14** exhibit a natural pH of 4–5. However, upon addition of hydrochloric acid, they are transformed into phosphonium salts. These phosphonium salts upon titration with bases, such as triethylamine or sodium bicarbonate buffer solution, revert back to the

free HMP compounds. The large difference in the chemical shifts of phosphonium salts and the free phosphines allow such acid–base equilibria to be followed by  $^{31}\text{P}$  NMR spectroscopy. Traditionally, trivalent phosphorus compounds can be transformed into their phosphonium chlorides. However, many of them exhibit marked oxidative instability in basic media. In this context, the well-defined acid–base equilibria and the oxidative stability in the pH range 2–8.5 demonstrated for HMP compounds is remarkable. The pronounced influence of  $-\text{CH}_2\text{OH}$  groups in providing high oxidative inertness to HMP compounds is a significant factor in further applications of such ligands, under aqueous media, in biphasic catalysis and biomedicine.

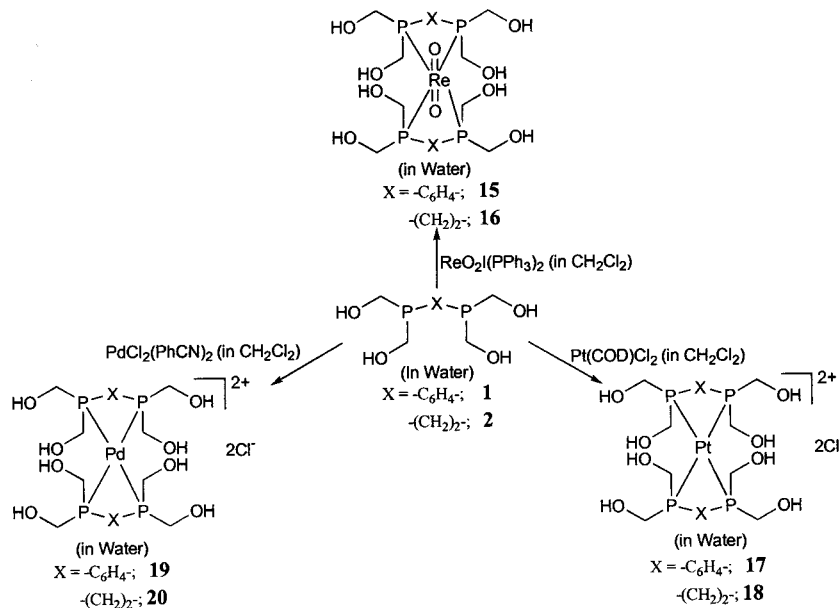
## Coordination Chemistry

The (hydroxymethyl)phosphines are excellent chelating agents for use in the coordination chemistry of early and late transition metals. Their aqueous solubility, in particular, allows reactions in “aqueous–organic” biphasic media. For example, the bisphosphines **1** and **2**, dissolved in water, react with  $\text{Pt}^{\text{II}}$ ,  $\text{Pd}^{\text{II}}$ , and  $\text{Re}^{\text{V}}$  precursors, dissolved in  $\text{CH}_2\text{Cl}_2$ , under biphasic conditions to produce the corresponding water-soluble metal chelates **15–20** in near quantitative yields as outlined in Scheme 9.<sup>14,15,22,23</sup> These reactions are “strictly” biphasic because upon vortexing of solutions of ligands (in aqueous media) and metal precursors (dissolved in organic solvents), more than 95% of the resulting complexes are selectively partitioned into the aqueous phase. These complexes, **15–20**, can be isolated from the reaction mixture as analytically pure compounds upon simple separation from the organic phase.

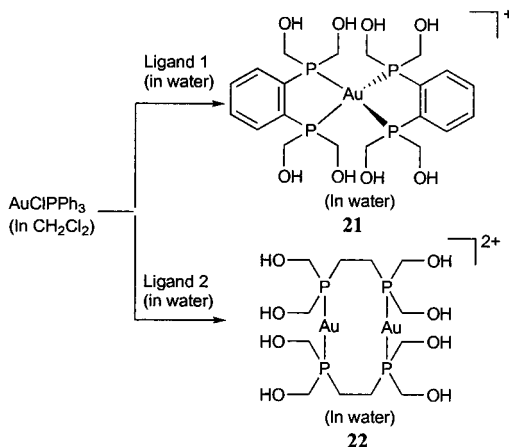
Scheme 10 summarizes results obtained from the reactions of **1** and **2** with a gold(I) precursor and exemplify the rich coordination chemistry of these ligands. The compounds **21** and **22** represent rare examples of water-soluble and kinetically inert gold complexes in tetrahedral and linear geometries, respectively.<sup>24,25</sup>

While the reactions summarized in Schemes 9 and 10 provide examples of transition metal complexes that possess a ratio of 1:2 between the metal center and the coordinated ligand, for specific biomedical (vide infra) and also for some catalytic applications, it is important to have a ratio of 1:1 between a transition metal and ligand. In this context, the tripodal phosphine (described in Scheme 3) and the thioether- or amide-functionalized bisphosphines (outlined in Schemes 5–8) provide ample opportunities for tuning the geometries and coordination numbers of transition metal centers. For example, the tridentate phosphine **3**, upon reaction with  $\text{Pd}^{\text{II}}$ ,  $\text{Pt}^{\text{II}}$ , and  $\text{Rh}^{\text{I}}$  precursors, produced the corresponding tripodally coordinated water-soluble novel transition metal compounds as outlined in Scheme 11.<sup>17,18</sup> Phosphorus NMR spectroscopy was used as a diagnostic tool to confirm tripodal coordination in **23–25** (Scheme 11).<sup>17,18</sup> The  $^{195}\text{Pt}$  NMR spectrum of **24** clearly established the tripodal linkage of the metal center with the two disparate  $\text{P}^{\text{III}}$

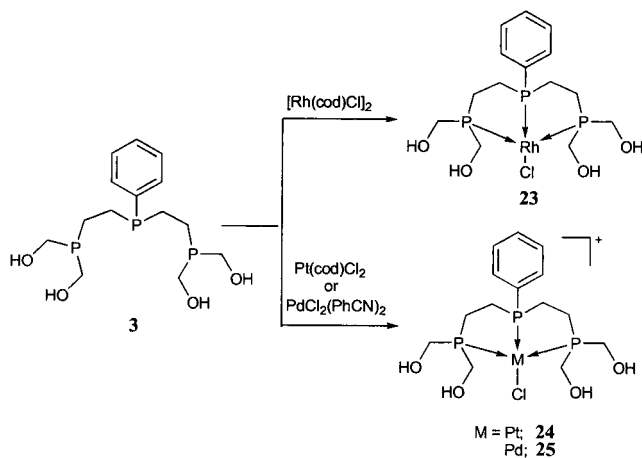
Scheme 9



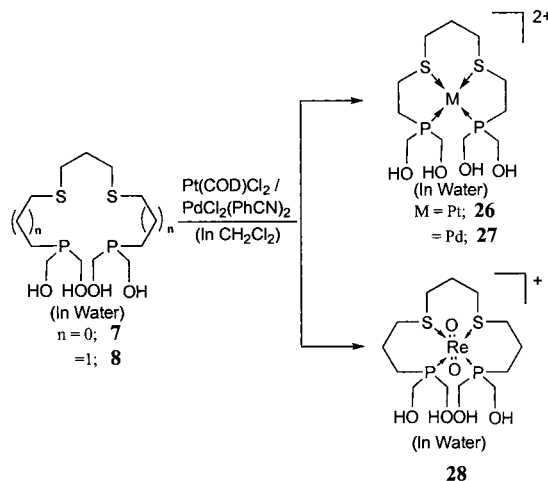
Scheme 10



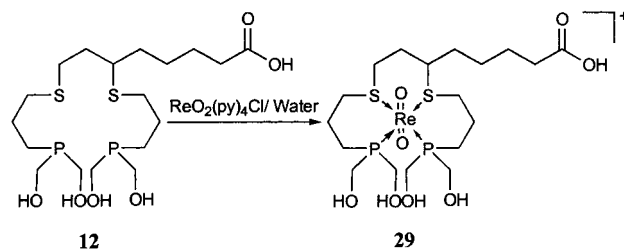
Scheme 11



Scheme 12



Scheme 13



centers.<sup>18</sup> The coordination chemistry of the water-soluble HMP ligands, as outlined in Scheme 12, justifies the importance of heteroatomic thioether electron donors in achieving 1:1 metal-to-ligand ratios for  $Pd^{II}$ ,  $Pt^{II}$ , and  $Re^V$  (compounds **26–28**).<sup>19,20</sup> In sharp contrast, the

simple (hydroxymethyl)bisphosphines **1** and **2** produced transition metal complexes with similar metals in 1:2 metal-to-ligand stoichiometry.<sup>14,15</sup>

The reaction of  $P_2S_2-COOH$ , **12**, with  $ReO_2(py)_4Cl$  ( $py = pyridine$ ) to produce a water-soluble and kinetically inert  $Re^V$  complex **29** is of particular significance because of its potential applications in nuclear medicine (Scheme 13).<sup>26</sup> This reaction presents prospects of using radio-metals of diagnostic (e.g.,  $^{99m}Tc$ ,  $\gamma$  emitter) and therapeutic (e.g.,  $^{186/188}Re$ ,  $\beta$  emitter) importance to produce

**Table 1. X-ray Crystallographic Data of Transition Metal Complexes Derived from (Hydroxymethyl)phosphines**

coordination compounds of (hydroxymethyl)phosphines	P–M distances (Å)	geometry around metal center	ref
[ReO <sub>2</sub> {(HOH <sub>2</sub> C) <sub>2</sub> PC <sub>6</sub> H <sub>4</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl, <b>15</b>	2.461(1); 2.456(1)	octahedral	22
[ReO <sub>2</sub> {(HOH <sub>2</sub> C) <sub>2</sub> PCH <sub>2</sub> CH <sub>2</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl, <b>16</b>	2.480(2); 2.472(2)	octahedral	22
[Pt{(HOH <sub>2</sub> C) <sub>2</sub> PCH <sub>2</sub> CH <sub>2</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl <sub>2</sub> , <b>18</b>	2.304(1); 2.315(1)	square planar	14
[Pd{(HOH <sub>2</sub> C) <sub>2</sub> PC <sub>6</sub> H <sub>4</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl <sub>2</sub> , <b>19</b>	2.312(1); 2.322(1)	square planar	15
[Au{(HOH <sub>2</sub> C) <sub>2</sub> PC <sub>6</sub> H <sub>4</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl, <b>21</b>	2.354(2); 2.378(2); 2.368(11); 2.368(11)	distorted tetrahedral	25
[Au <sub>2</sub> {(HOH <sub>2</sub> C) <sub>2</sub> PCH <sub>2</sub> CH <sub>2</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl <sub>2</sub> , <b>22</b>	2.304(4); 2.316(3); 2.307(3); 2.305(4)	linear	25
[Pd{(HOH <sub>2</sub> C) <sub>2</sub> P(CH <sub>2</sub> ) <sub>2</sub> S(CH <sub>2</sub> ) <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl <sub>2</sub> , <b>27</b>	2.266(7); 2.285(7)	square planar	19
[ReO <sub>2</sub> {(HOH <sub>2</sub> C) <sub>2</sub> P(CH <sub>2</sub> ) <sub>2</sub> S(CH <sub>2</sub> ) <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub> P(CH <sub>2</sub> OH) <sub>2</sub> } <sub>2</sub> ]Cl <b>28</b>	2.425(10); 2.418(10)	octahedral	20

radiolabeled bifunctional chelates. The carboxylate group of **12** (or its radiolabeled analogues) can be activated using standard procedures to produce bioconjugates upon reactions with –NH<sub>2</sub> groups of biomolecules (peptides and proteins).<sup>27</sup> Design and synthesis of bifunctional chelating agents, such as compound **12**, have gained considerable interest in recent years because of their utility in the development of radiolabeled biomolecules for use in tumor-specific diagnosis or therapy of cancer.<sup>28</sup>

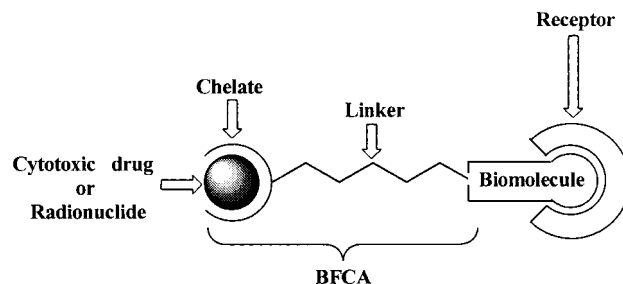
## Structures and Kinetic Inertness

Detailed characterization of all the new water-soluble HMP phosphines and, in some instances, their phosphorus(III) hydrido precursors have been carried out using multinuclear NMR spectroscopy and various other analytical techniques. Also, the X-ray crystallographic investigation of representative examples of metal complexes have, indirectly, confirmed the molecular constitution of the parent water-soluble phosphine ligands.<sup>14,15,19,20,22,25</sup> The salient features of X-ray crystallographic parameters of specific metal complexes are summarized in Table 1.

A common feature underlying all the (hydroxymethyl)-phosphine–metal complexes, described in Schemes 9–13, is that they are soluble in aqueous media. The ones that possess a greater number of –CH<sub>2</sub>OH groups per metal center show a tendency for increased water solubility. All the metal complexes are stable in water (at pH 5–7) for extended periods of time (several months). In fact, the Pd<sup>II</sup>, Pt<sup>II</sup>, and Re<sup>V</sup> complexes (**15**–**20**) are resistant to decomposition even upon subjecting them to boiling temperatures in water. The high kinetic inertness in aqueous media may be attributed to efficient shielding of the metal centers by anion-repelling –CH<sub>2</sub>OH groups. The hydroxy or chloride (OH<sup>–</sup> or Cl<sup>–</sup>) anions are, presumably, kept from attacking the metal centers because of the electronic repulsive force exerted by the plethora of –CH<sub>2</sub>OH groups that surround the metal center. The strong hydration between –CH<sub>2</sub>OH and water molecules may also create an effective shield to reduce or eliminate nucleophile-mediated dechelation of the metal centers. Clearly, more detailed studies must be carried out in order to explain the observed kinetic inertness in protic media.

## Relevance to Biomedicine

An aspect of paramount importance in drug delivery is to achieve high specificity at diseased (or tumor-bearing) sites in the body. Site-specific delivery not only is expected to increase drug efficiency but also minimizes



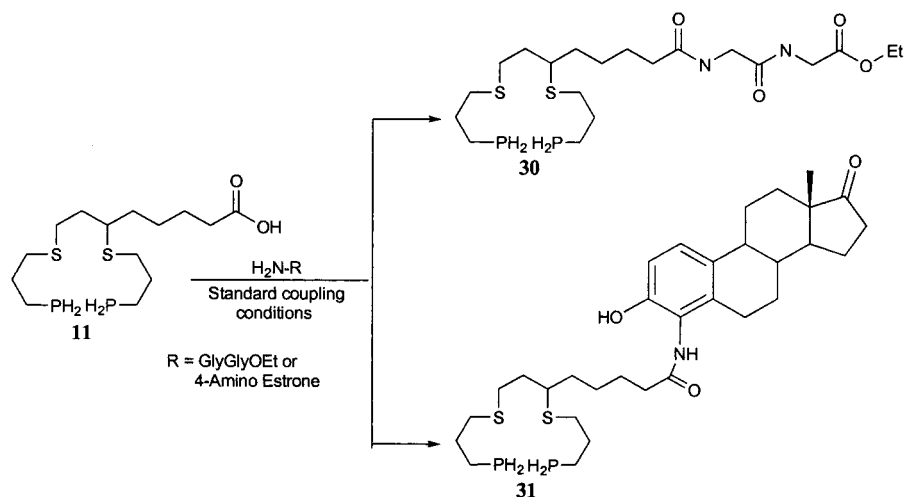
**FIGURE 1.** Bifunctional chelating agent (BFCA) linking a radionuclide (or cytotoxic drug) to a specific biomolecule for site specificity.

toxic side effects that are caused by nontarget uptake of drugs. Strategies for targeting of specific drugs, including metal-based pharmaceuticals or radiopharmaceuticals (e.g., cisplatin or radiolabeled diagnostic or therapeutic agents), are being developed by conjugating drug molecules to target-specific biomolecular vectors (e.g., peptides or proteins).<sup>28,29</sup> The strong affinity of certain peptides (or proteins) for receptors expressed by specific cancers (or other diseases) makes such targeting strategies attractive.<sup>28,29</sup> An approach, as outlined in Figure 1, utilizes bifunctional chemical frameworks whereby drug moieties (i.e., traditional pharmaceuticals or radiopharmaceuticals) are brought into conjugation with target-directing vehicles (i.e., biomolecules). To target specific metal-containing drugs or radiometal-containing pharmaceuticals (e.g., technetium-99m imaging agents), it is important, first, to design ligands that will stabilize metal or radiometal complexes under in vivo conditions. In this context, our recent studies have demonstrated that HMP ligands produce well-defined complexes with <sup>99m</sup>Tc (and other radiometals) and that these radiolabeled compounds have excellent stability under in vivo conditions.<sup>27,30–32</sup> Additionally, the bifunctional chelating agent P<sub>2</sub>S<sub>2</sub>–COOH, **11**, can be conjugated to specific biomolecules to produce peptide, **30**, or steroid, **31**, conjugates, respectively (Scheme 14).<sup>33</sup> These new bioconjugates will provide realistic prospects as synthons for the development of site-specific pharmaceuticals.

## Models for Biphasic Catalysis

The chemistry of water-soluble transition metal complexes has attracted considerable attention in recent years because of their potential usefulness in biphasic catalysis. The rhodium complex of the water-soluble trisulfonated triphenylphosphine (TPPTS), currently being used on an industrial scale, for the formylation of propylene into *n*-butanal, is a premier example of a performance-effective

Scheme 14



biphasic catalyst.<sup>34</sup> In biphasic catalysis, the reactants and the products stay in the organic phase while the catalyst remains in the aqueous phase. The preferential solubility of HMP complexes **15–28** in aqueous media and their selective partition from the organic into aqueous media present prospects for their utility in biphasic catalysis. The chemical modification of the traditional sulfonated arylphosphines is difficult, making it impractical to tune the lipophilicities of these ligands. Systematic variations in the lipophilicities of ligands and their metal complexes are important in the development of “counterphase transfer catalysts” wherein a catalyst from the aqueous phase will interact with the lipophilic substrate molecules from the organic phase.<sup>35</sup> As the number of carbon centers in the chemical frameworks of the water-soluble phosphines (**1–4**, **7**, **8**, **10**, **14**) increases (Schemes 1–8), the lipophilic property of the individual ligands also increases accordingly. Therefore, our new approach to ligand design affords phosphines of appropriate aqueous solubility and lipophilicity for use in the development of counterphase transition metal catalysts.

## Concluding Remarks and Outlook

In sharp contrast to the experimental difficulties of handling  $\text{PH}_3$ , the high thermal stability, oxidative inertness, and nonvolatile characteristics of functionalized phosphorus hydrides (as demonstrated in this Account) should lead to an increase in the utility of such and related phosphorus(III) hydrides in future chemical research. Our research has also demonstrated that phosphorus(III) hydrides can be incorporated into a spectrum of chemical frameworks and their formylation reactions occur under mild conditions to produce a structurally diverse range of functionalized water-soluble phosphines. Sulfonated arylphosphines have become ubiquitous for use in the development of water-soluble catalytically active transition metal/organometallic compounds. However, the water-soluble chelating and multifunctional (hydroxymethyl)-phosphines, as described in this Account, offer complementary and new dimensions to the design and development

of well-defined aqueous-soluble transition metal compounds with potential applications in catalysis and biomedicine.

It must be recognized that the formaldehyde-mediated formylation reactions, described in Schemes 2–8, represent just a “tip of the ice berg” because such reactions when carried out using a large number of readily available aliphatic and aromatic aldehydes will result in a multitude of new phosphines. Formylations of specific phosphines using a select choice of functionalized aldehydes are currently underway in our laboratory.

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