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The Synthesis of Heteroleptic Phosphines

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Heteroleptic phosphines (R_2PR^1) are a class of essential ligands for inorganic and organometallic chemistry. However, the syntheses of these phosphines are often fraught with laborious synthetic hurdles. Consequently, a renewed interest in innovative synthetic methods to access heteroleptic phosphines is emerging. This Perspective presents an overview of modern synthetic approaches to heteroleptic phosphines as well as a discussion of the strengths and limitations of these synthetic methods. A major emphasis is placed on simple and direct routes to phosphines and significant synthetic innovations for P-C bond-forming reactions.

Introduction

The challenging nature of phosphine chemistry has thwarted the development of new phosphine ligands. In consequence, phosphine syntheses remain virtually unchanged after nearly a century of research.[1–3] It is astounding how little progress has been made in the development of new phosphine syntheses when contrasted with the importance of phosphines in modern inorganic chemistry. This situation is changing, however, because a revival of research in organophosphine synthesis has recently begun, bringing with it the promise of new inorganic complexes, catalysts,[4] materials,[5] medicinal compounds,[6] and organic reagents.[7–9]

Since their discovery in 1847[10,11] and their development throughout the first half of the 20th century, phosphines have established themselves as an essential class of ligands for organometallic and inorganic chemistry. Twentieth century inorganic chemists identified phosphines as superb ligands for transition metals and exploited them to great effect. Phosphine-metal complexes have been the fulcrum for an astounding number of influential processes and studies that have shaped chemistry and the world today.[12,13]

Early phosphine syntheses were hindered by the exceptional air-sensitivity of alkyl phosphines and a general lack of air-free techniques. By the mid-20th century, a rigorous set of air-free protocols was standard in inorganic laboratories and the synthesis of phosphines developed into standardized procedures.[13] Aryl phosphines, usually triphenyl phosphine (PPh_3), became commonplace as ligands owing to their air-stability and ease of synthesis.

Phosphine chemistry entered a golden age during the 1960's through 1980's when classics were established in the field. Exemplary phosphines that emerged out of this era include 1,2-bis(diphenylphosphino)ethane (dppe)[14], 1,1'-bis(diphenylphosphino)ferrocene (dppf)[15], and 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP)[16] (Figure 1a). Of late, the application of phosphines has seen a resurgence with modern "designer" phosphines[‡] that display complex or chiral architecture such as 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos),[17] (*S*)-1-[(R_P)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine (Josi-Phos),[18] and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos)[19] (Figure 1b).

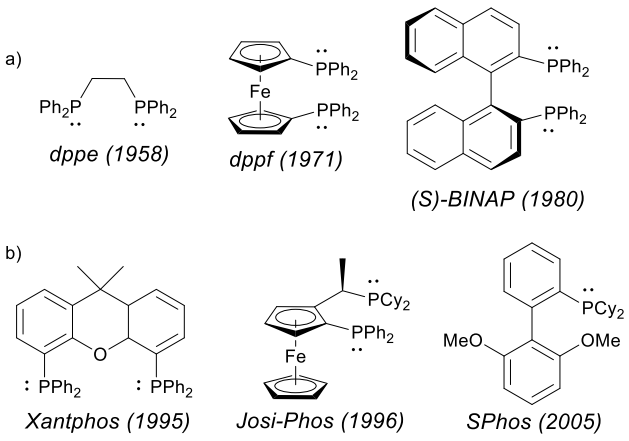

Figure 1. Examples of (a) classic heteroleptic phosphines and (b) designer heteroleptic phosphines.

The power of designer phosphines is nicely illustrated by Pd-catalyzed cross-coupling reactions in which designer phosphines are often required to form active catalytic Pd(0) complexes.[20] The identity of the phosphine ligand can change what products are formed in a reaction by changing the catalytic cycle. For example, PCy_3 forms $(L)_2Pd(0)$ complexes and stabilizes Pd(0/II) oxidation states, while P^tBu_3 forms lower coordination number catalytic complexes $(LPd(I)X)_2$ and LPd(0) and stabilizes Pd(0/I) oxidation states. The different coordination modes and oxidation states for these complexes change the cross-coupling chemoselectivity.[21] Proutiere *et al.* showed that the hybrid heteroleptic phosphine $P(^tBu)_2(^iPr)$

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forms $(LPd(I)X)_2$, LPd(0), and $L_2Pd(0)$ complexes, which allows modulation of chemoselectivity based on how many equivalents of ligand are used.[22,23] The ability to design a phosphine for directed influence at a metal center in a tailored fashion is a key advent in inorganic and organometallic chemistry. Developing new syntheses of phosphines drives these fields toward new frontiers.

This Perspective will discuss synthetic strategies to make heteroleptic phosphines. Both modern and classic strategies to make heteroleptic phosphines will be assessed with a focus on modern synthetic approaches. This Perspective should serve as a primer for organophosphorus chemistry and its application to phosphine syntheses.

Nomenclature

When discussing organophosphorus chemistry, a nomenclature is necessary to facilitate organophosphorus's many common forms. Although the nomenclature is somewhat cumbersome, it is an essential part of discussing the chemistry and is reviewed in Figure 2.

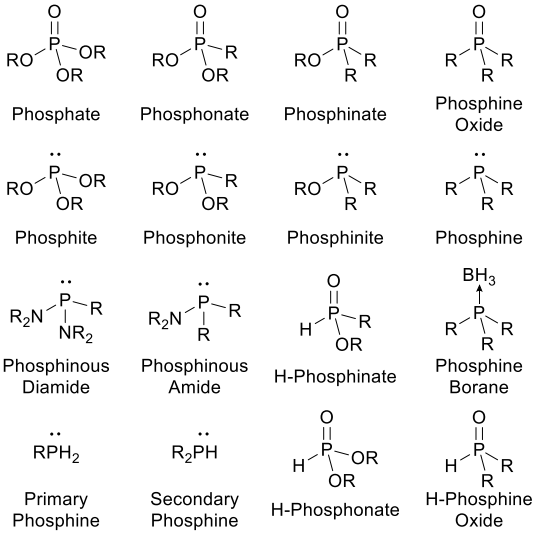


Figure 2. Nomenclature for common organophosphorus species relevant to the synthesis of heteroleptic phosphines.

Types of Phosphines

For this Perspective, it is helpful to divide phosphines into three categories: 1) homoleptic phosphines, 2) heteroleptic phosphines, and 3) asymmetric (or P-chiral) phosphines (Figure 3). Homoleptic phosphines have three identical organic substituents on phosphorus, such as PPh_3. Heteroleptic phosphines are defined as having the general structure R_2PR^1, where R and R^1 are distinct. Asymmetric phosphines have three distinct groups connected to phosphorus which, due to the large inversion barrier of a phosphine lone pair,[24] make these phosphines chiral.

Despite the severely limited architectures available with homoleptic phosphines, they are good "general-use" ligands. P-

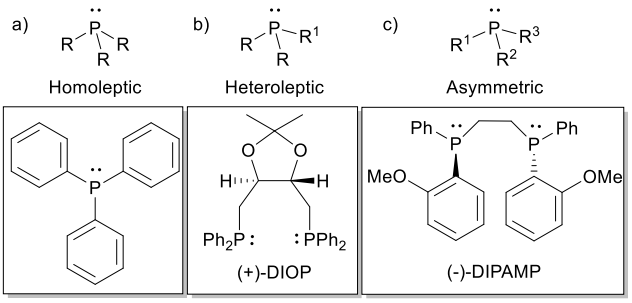


Figure 3. Definition of the three general types of phosphines: a) homoleptic, b) heteroleptic, and c) asymmetric. Examples are shown in the boxes below.

chiral phosphines are useful in asymmetric syntheses, although they are incredibly laborious to synthesize and thus generally impractical. (However, an excellent body of research has been done and is continuing on this subject.[25-27]) In contrast to homoleptic and asymmetric phosphines, heteroleptic phosphines are both synthetically accessible and tailorable. Furthermore, heteroleptic phosphines make excellent polydentate phosphines and can also be chiral (*e.g.*, (+)-DIOP, Figure 2). In comparison to P-chiral phosphines, it is often easier to synthetically install controlled chirality in one of the R groups of a heteroleptic phosphine. Chiral heteroleptic phosphine syntheses can therefore take advantage of well-established main-group chemistry to achieve ligand chirality while avoiding the laborious drawbacks of a P-chiral phosphine synthesis. Overall, heteroleptic phosphines represent a ligand class that is exceptional in versatility and practicality for both synthesis and performance.[1]

General Considerations in Phosphine Synthesis

Phosphines have their drawbacks. Compared to most ligands, phosphines are: readily oxidized (O_2-instability), difficult to handle (they are profoundly malodorous and pyrophoric), and typically extremely difficult to purify (due to instability on silica, non-crystallinity, and very high boiling points). These qualities are more pronounced with alkyl phosphines than with aryl phosphines, which has made the synthesis and study of aryl phosphines more attractive, even though alkyl phosphines often have more favourable properties.

The convoluted nature of phosphorus syntheses arises from several factors including stable oxidation states of III and V, multiple coordination modes (up to 6 coordinate), pseudo-rotations, radical chemistry, and lower redox potentials (*e.g.*, both dehydrocoupling and oxidation are much easier for P species than N analogues).[28,29] These factors make organophosphorus chemistry considerably more sensitive to reaction conditions than typical first-row main-group chemistry. Syntheses can also be complicated by the Lewis basicity of phosphines. The basicity of phosphines can be tailored by changing the electronics of the substituents at phosphorus. More electron-withdrawing groups at phosphorus or π-conjugated groups increase the π-accepting ability of the phosphine, and thus decrease the σ-donating (*i.e.*, basicity)

ability of the phosphorus lone pair.[30-33] Alkyl phosphines are much better σ-donors and much weaker π-acceptors than aryl phosphines. Protonated tertiary phosphines typically have pK_a's from ~2 to 8,[34] making them moderately basic to acidic – something to keep in mind if using an acidic workup.

Heteroleptic Phosphine Synthesis

The synthesis of heteroleptic phosphines can be broken down into two general routes: those involving P(III), or trivalent phosphorus, and those involving P(V), or oxidized tetravalent phosphorus. Because P(III) species are typically air-sensitive and P(V) species are not, these two general synthetic approaches are very different. Each category is further divided into electrophilic chemistry, nucleophilic chemistry, radical chemistry, and metal-mediated chemistry. Herein, the general strategies will be discussed in the context of their strengths and limitations based on our laboratory's experience and the recent scientific literature.

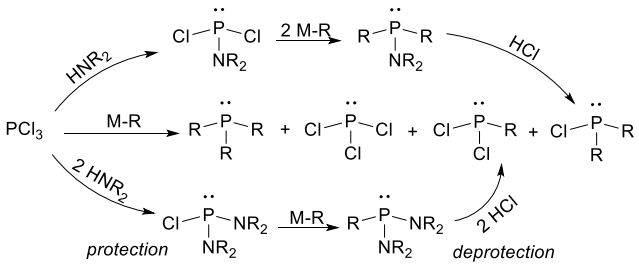
Phosphorus (III) Syntheses

P(III) molecules are readily oxidized by molecular oxygen and most species must be handled rigorously air-free. Trivalent phosphorus species are slow to oxidize in O_2 if they are sufficiently kinetically or thermodynamically stabilized. For example, Barder *et al.* showed that sterically shielding the lone pair of phosphines kinetically slows oxidation considerably.[35] With respect to thermodynamics, oxidation of P(III) can be controlled by the lone-pair's ability to participate in O_2 chemistry. When electronegative or electron-withdrawing groups are bonded to the P(III), the basicity of the phosphine is decreased and oxidation is prevented (*e.g.*, PCl_3 and PPh_3 are O_2-stable, whereas $PhPCl_2$ and PEt_3 are not). Syntheses starting from P(III) precursors typically require air-free techniques from start to finish – increasing the time and labor required. However, the advantage of a P(III) synthesis is that a reduction step from P(V) to P(III) is not necessary.

Phosphorus(III) Electrophiles

Electrophilic P(III) species are typically derived from P-Cl molecules. Trichlorophosphine (PCl_3) is a readily available starting material and relatively O_2-stable, and for these reasons it serves as a convenient starting point for most phosphine syntheses. For a heteroleptic phosphine synthesis, however, PCl_3 has significant synthetic drawbacks. Directly generating the heteroleptic $RPCl_2$ or R_2PCl species from PCl_3 is not trivial because controlling the number of nucleophiles that will add to PCl_3 is very difficult. This lack of selectivity is likely caused by the extreme electrophilicity of P-Cl species. Even carefully selected reaction conditions still yield the desired product in a mixture. In and of itself, this would not normally be problematic except for the difficulty in isolating the product out of the mixture. To avoid this lack of selectivity, a typical work-around is to "protect" electrophilic sites with amide fragments (Scheme 1).[36] This approach is higher yielding but has the drawbacks of requiring several extra synthetic steps (protection/deprotection) while maintaining O_2 and H_2O free conditions for the phosphinous amide or phosphinous diamide intermediate. In addition, the purification can still be challenging.§

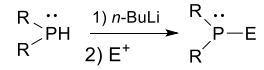
Purifications of P-Cl compounds are difficult for several reasons: 1) incompatibility with silica, 2) $RPCl_2$ and R_2PCl species are considerably more O_2 sensitive than PCl_3, and 3) incompatibility with H_2O. These compounds must therefore undergo air-free distillation for purification, typically requiring large-scale reactions (>10 grams).



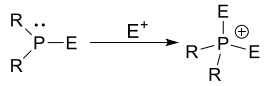
Scheme 1. Generation of heteroleptic phosphine precursors from PCl_3 using amine protecting groups to achieve selective stoichiometry. M-R = organometallic nucleophile.

Nucleophiles from Trivalent Phosphorus

Using nucleophiles generated from trivalent phosphorus species is another strategy for P-C bond formation. Secondary and primary phosphines are easily deprotonated by organometallic reagents (pK_a typically ~25-35)[37] to produce phosphide species (Equation 1). Phosphides are transient and quite nucleophilic, making this strategy good for reluctant electrophiles. Careful stoichiometry must be observed with electrophiles using this synthetic approach or over-alkylation may occur at the phosphine lone-pair, producing the persistent and stable phosphonium species (Equation 2).

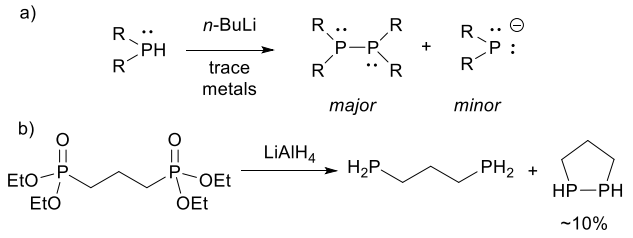


(1)



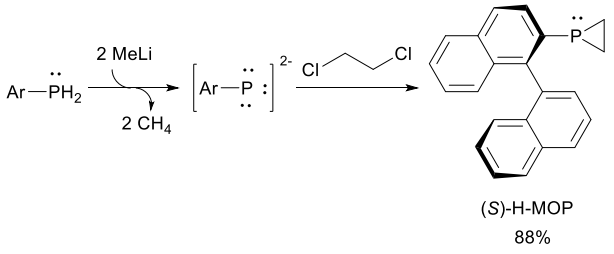
(2)

A side reaction that often occurs instead of phosphide anion generation is dehydrocoupling of primary or secondary phosphines (Scheme 2a). Under reducing conditions and in the presence of trace metals or Lewis acids, reduction of the phosphorus to a P-P bond can occur in competition with deprotonation. This is common when deprotonating either primary or secondary alkyl phosphines. Dehydrocoupling of phosphines is also common when reducing an alkyl phosphorus species (*i.e.*, an alkyl phosphonate or phosphinate) to a primary or secondary phosphine (Scheme 2b). The P-P species thus generated is often difficult to remove from reaction mixtures and contributes to side reactions. Dehydrocoupling can be promoted with transition metal catalysts[38] as well as strong Lewis acids.[39]



Scheme 2. Common conditions for unintended dehydrocoupling during a) generation of a phosphide intermediate and b) reduction of phosphonates.

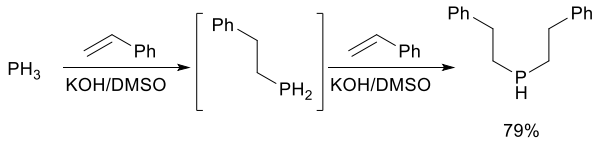
Dehydrocoupling is rarely a problem with aryl phosphines or sterically hindered phosphines. For example, Ficks *et al.* showed the binapthyl phosphine (*S*)-H-MOP can be synthesized using a primary phosphine precursor that is notably O_2-stable (Scheme 3).[40] The large biaryl group allows the phosphorus di-anion to be generated as an intermediate. Though they are somewhat rare, there are several known O_2-stable primary phosphines.[41] Tertiary phosphines made from these O_2-stable primary phosphines are also typically oxygen resistant. Bulky aryl phosphines are good candidates for phosphide generation because the anions are typically more persistent and do not undergo side reactions as readily as alkyl phosphines.



Scheme 3. Generation of a phosphide dianion as an intermediate in the synthesis of a heteroleptic phosphine.

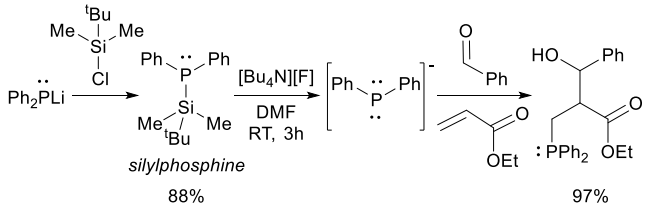
Phosphine gas (PH_3), typically used to make homoleptic phosphines, can also be used to generate heteroleptic phosphines. Note that PH_3 gas is extremely dangerous due to its acute toxicity (>1 ppm) and highly pyrophoric nature.[42] Nonetheless, PH_3 can be generated on-site using red phosphorus and $NaOH/H_2O$. When PH_3 is bubbled through strongly basic media (KOH in dimethylsulfoxide), the phosphide (PH_2^-) species is generated and can be used to add across aryl or heteroaryl conjugated unsaturated hydrocarbons.[43] The pK_a values of PH_3 and RPH_2 are low enough that these species are deprotonated under the reaction conditions, Scheme 4. (Note: the pK_a of R_2PH is too high, making the secondary phosphine the product of the reaction in these cases.) The advantage of this approach is the selectivity of P-C bond formation at the terminal carbon (due to resonance stabilization of the carbanion at the benzyl position) and strict double addition to form a secondary phosphine selectively and in good yields.

A modern approach to generating the phosphide anion is fluoride-induced desilylation. Starting with a silylphosphine, the phosphide can be generated by the introduction of a fluoride anion. This approach has been exploited to great effect by the



Scheme 4. An example of how the generation of a phosphide from PH3 will selectively make secondary phosphines.

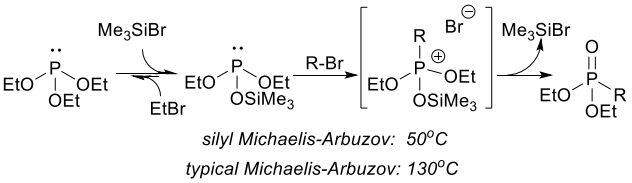
Hayashi group (Scheme 5).[44] The silylphosphine can be generated from either an electrophilic (*e.g.*, P-Cl) or a nucleophilic (*e.g.*, phosphide anion) phosphorus source and a silicon precursor. The resulting silylphosphine is more easily handled, purified, and stored than P-H or P-Cl precursors. The gentle *in situ* formation of a phosphide anion provides better kinetic control over the reactivity, excellent selectivity, and yields. Using fluoride to generate the phosphide is gentle enough to carry out in the presence of electrophiles, unlike organometallic generation of phosphides where electrophiles must be introduced in a second step. The *in situ* procedure allows for cascade or multi-step reactions to take place in one-pot, generating selective and complex architectures from simple precursors.[44]



Scheme 5. Fluoride-induced desilylation of a silylphosphine to generate a phosphide, which undergoes a two-step reaction to generate a complex heteroleptic phosphine in a one-pot reaction.

Phosphorus(III) Nucleophiles

Perhaps the most well-known strategy to synthetically incorporate phosphorus into a molecule is the Michaelis-Arbuzov reaction, which converts an alkyl phosphite and alkyl halide to a phosphonate. This reaction takes advantage of a phosphite's ability to act as a modest nucleophile for P-C functionalization. The Michaelis-Arbuzov reaction has been thoroughly studied and is discussed in-depth elsewhere.[45] In practice, Michaelis-Arbuzov reactions require high temperatures (~130°C) and generally harsh conditions. A valuable modification to the Michaelis-Arbuzov is to first silylate the phosphite (using catalytic (5%) trimethylsilylhalide), which lowers the activation barrier for reactivity considerably (Scheme 6).[46] This modification also helps mitigate side reactions of

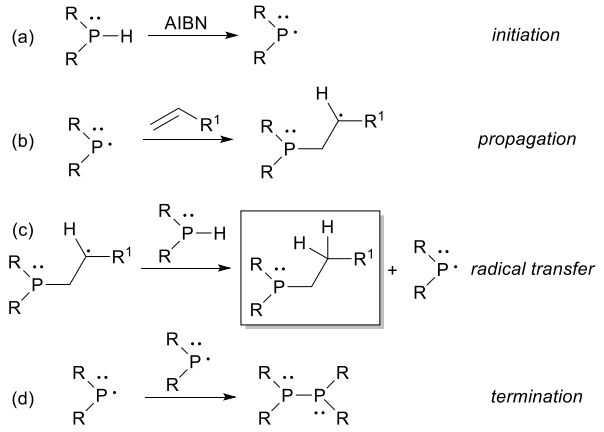


Scheme 6. Silyl-modified Michaelis-Arbuzov reaction of $P(OEt)_3$ with an alkyl bromide.

phosphite with the alkyl halide (*e.g.*, EtBr in Scheme 6) generated during the reaction. The alkyl halide generated in the reaction must still be systematically removed (typically using a Dean-Stark apparatus), which is easier at lower temperatures where the side reaction is slower.

Radicals from Trivalent Phosphorus

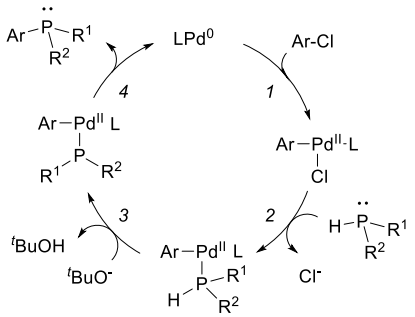
P-H bonds can be readily homolyzed using standard non-peroxide radical initiators such as azobisisobutyronitrile (AIBN), Scheme 7a.[47] The phosphine radical is exceptionally stable for a radical species and undergoes well-behaved radical chemistry. Access to this radical chemistry makes hydrophosphination across unsaturated hydrocarbons a very reliable reaction (Scheme 7). Often times, discrete species with few side reactions can be isolated from a radical reaction with primary or secondary phosphines with alkenes. Regioselectivity for this radical reaction is anti-Markovnikov. A low effective concentration of radicals helps mitigate unfavorable termination steps (Scheme 7d). Electron-rich alkenes tend to react under milder conditions than electron-poor alkenes. For heteroleptic phosphine syntheses, this strategy requires either a primary or a secondary phosphine as a precursor and produces ethylene-linked functionalization at the phosphorus (PCH_2CH_2R).



Scheme 7. Radical chain mediated hydrophosphination of a P-H bond across an alkene. Desired product is boxed for clarity.

Cross-Coupling Trivalent Phosphorus

For aryl P-C functionalization, palladium-mediated cross-coupling is an emerging field. Akin to Buchwald-Hartwig cross-coupling, trivalent phosphorus cross-coupling allows secondary phosphines to be coupled to aryl halides. In a seminal study, Surry *et al.* were able to cross-couple a myriad of secondary phosphines (both alkyl and aryl) with aryl chlorides using the commercially available bidentate phosphine, 1,1'-bis-(diisopropylphosphino)ferrocene (DiPPF), for the palladium catalyst (Scheme 8). Bidentate phosphines are typically required for palladium mediated H-phosphine oxide[48] and H-phosphonate[49] cross-couplings.¶ This reaction is particularly useful because aryl chlorides are both cheaper and more amenable to late-stage functionalization than aryl bromides.



Scheme 8. An example of Buchwald-Hartwig-type Pd-catalyzed cross-coupling of an aryl chloride with a secondary phosphine. Catalytic steps are: 1) oxidative addition, 2) ligand exchange, 3) deprotonation, and 4) reductive elimination. L = DiPPF (a bidentate phosphine).

The only limitation to this study is that the secondary phosphines were all *sec*-alkyl or aryl derivatives.

Phosphorus (V) Syntheses

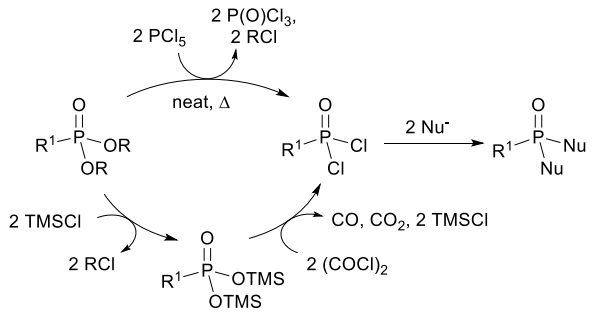
In the preparation of heteroleptic phosphines, it is often synthetically advantageous to start with an oxidized form of phosphorus. Phosphorus(V) species are typically tetravalent with a formal double bond at phosphorus; examples include phosphates, phosphonates, phosphinates, etc. (Figure 1). Phosphorus(V) starting materials can also be highly cost-effective because they are typically much cheaper and more varied than P(III) precursors. Phosphorus(V) synthetic chemistry is currently undergoing a modernization with a renewed interest in developing milder conditions and broader substrates for synthesis.[50]

Starting a synthesis with P(V) species is attractive for several reasons: 1) O_2 stability, 2) H_2O stability, and 3) silica stability. Benchtop chemistry can be used in these syntheses. This approach typically culminates in a tertiary phosphine oxide that is reduced to the desired phosphine, generating the air-sensitive product at the end of the synthesis. In its own right, P(V) reduction to P(III) is a growing field. However, there are currently many ways to reduce phosphine oxides to phosphines using a wide range of reagents and conditions.[51–53] Thus, reduction is typically not a difficult step in phosphine synthesis as long as it is substrate-compatible. For brevity, the P(V) compounds discussed here will focus on oxo-P(V) derivatives, that is, $R_3P(O)$ species. The analogous phosphorus sulfide ($R_3P=S$) and phosphorus imine ($R_3P=NR$) derivatives have also been studied; however, they are less synthetically relevant.

Phosphorus(V) Electrophiles

As a starting material, trichlorophosphine oxide ($P(O)Cl_3$) offers few advantages over PCl_3 so $P(O)Cl_3$ is typically not used. On the other hand, phosphonic dichlorides ($RP(O)Cl_2$) and phosphinic chlorides ($R_2P(O)Cl$) can be used as P(V) electrophiles. These species are not generated directly from $P(O)Cl_3$, rather from the chlorination of phosphonates ($RP(O)(OR)_2$) or phosphinates ($R_2P(O)(OR)$). Most synthetic methods do not isolate these

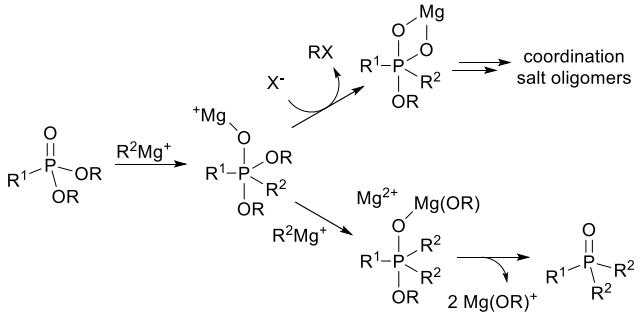
chlorinated species, rather they are reacted after *in situ* generation. Generally, phosphorus pentachloride (PCl_5) or trimethylsilylchloride (TMSCl) followed by oxalyl chloride ($(COCl)_2$) is used for chlorination (Scheme 9).‖ These chlorination conditions are strongly acidic, which are not amenable to many functional groups. Chlorination can be problematic in its own right because of the undesirable and highly reactive by-products generated and harsh conditions required. The lack of isolation or purification of the chlorinated intermediate as standard procedure shows the difficulty in handling these compounds. Yields vary wildly, though our experience has been that very low yields (<20%) should be expected for this two-step conversion to heteroleptic phosphine oxides.



Scheme 9. Indirect conversion of a phosphonate to a phosphine oxide going through a phosphonic dichloride intermediate.

For decades, the question of why phosphonates cannot undergo direct nucleophilic attack (akin to an ester) had gone unanswered. Attempts at direct conversion of phosphonates to phosphine oxides using organometallic reagents were unsuccessful. Grignard reagents offered the best results: low yields (~20%) of phosphine oxide with complete consumption of starting material.[54,55]

A recent development in our laboratory showed that direct and high-yielding P-C functionalization at phosphonates was possible without decomposition or the need for multistep chlorination.[56] In a typical reaction of a Grignard reagent with phosphonate, a pentavalent phosphorus intermediate quickly reacts with free halide in solution to form coordination salt oligomers (Scheme 10, top route). This reaction is mechanistically similar to the Michaelis-Arbuzov reaction and accounts for the complete consumption of phosphonate starting material and low yields of phosphine oxide. By



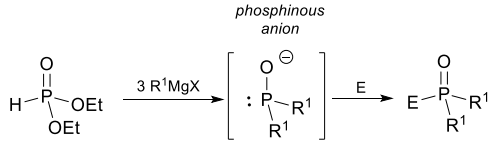
Scheme 10. Direct conversion of a phosphonate to a phosphine oxide showing the proposed intermediates to (top) coordination salt oligomers in the presence of halides and (bottom) a phosphine oxide in the absence of halides.

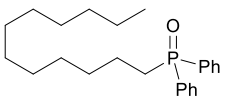
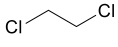
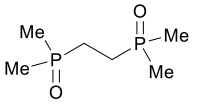
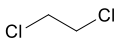
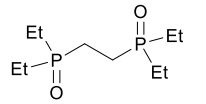
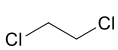
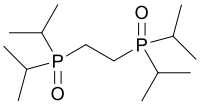
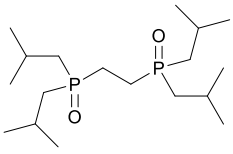
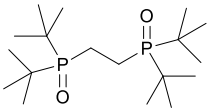
removing the free halide from solution using a sodium salt (sodium trifluoromethanesulfonate), oligomer formation was eliminated and yields improved dramatically (Scheme 10, bottom route). This direct conversion of a phosphonate to a phosphine oxide is considerably simpler, higher yielding, and has a large substrate scope compared to the traditional two-step chlorination route (Scheme 9).

Tetravalent Phosphorus Electrophiles

In a related reaction, H-phosphonates can be used as a convenient starting material to make H-phosphine oxides and tertiary phosphine oxides using Grignard reagents (Table 1). Several well-established protocols can be used to directly convert H-phosphonates to heteroleptic phosphine oxides. It is notable that unlike phosphonates, H-phosphonates do not undergo side reactions with halogens in solution (similar to Scheme 10 top route). Rather, the first equivalent of Grignard reagent acts to deprotonate the H-phosphonate, generating the

Table 1. H-Phosphonate reaction with Grignard reagents to form either H-phosphine oxides or heteroleptic phosphine oxides. [a]From reference 57, [b]From: L. R. Doyle, A. Heath, C. H. Low and A. E. Ashley, *Adv. Synth. Catal.*, 2014, **356**, 603-608.



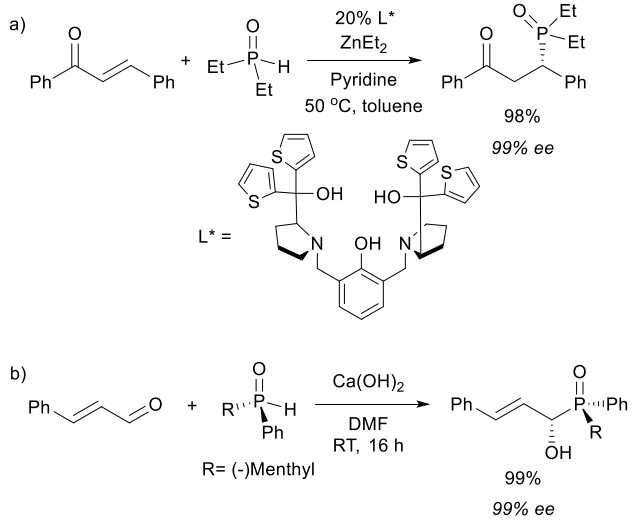
R^1	E	Product	Isolated Yield
Me	H^+		63[a]
Et	H^+		52[a]
Ph	$C_{12}H_{25}Br$		88[a]
Me			84[b]
Et			78[b]
^{i}Pr			76[b]
^{i}Bu			92[b]
^{t}Bu			85[b]

anion, which quickly and exothermically reacts with two additional Grignard reagents to form the deprotonated phosphinous anion (Table 1). The phosphorus anion reacts with soft electrophiles at the phosphorus to generate a tertiary phosphine oxide.[57] The synthesis of a wide range of phosphine oxides can be made this way from simple starting materials. Oxophilic electrophiles such as TMSCl can be used to generate the phosphinite by reacting at the oxygen instead of the phosphorus.

Nucleophiles from Tetravalent Phosphorus

Generating a phosphide-type anion from an oxidized phosphorus species is almost exclusively done by deprotonating an H-phosphorus precursor. This methodology works well, although the persistence of the phosphorus anion generated *in situ* varies depending on the identity of the H-phosphorus precursor, solvent, and cation. In general, cryogenic conditions and organometallic bases produce good yields of products, though this must be experimentally determined for reliable yields. This strategy can also be applied to secondary phosphine-boranes.[58]

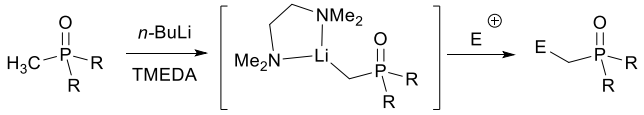
H-phosphonates (pK_a ~9-23) are more acidic than H-phosphinates (pK_a ~20-23), which in turn are more acidic than H-phosphine oxides (pK_a ~21-27).[37] As one would expect, electron withdrawing groups and aromatic moieties at phosphorus lower the pK_a, whereas alkyl and electron donating groups raise the pK_a. If the proton is acidic enough, sometimes KOH/DMSO or $Ca(OH)_2$/DMF mixtures are basic enough to generate the phosphorus anion. As first noted by Hays, unless an oxophilic electrophile (*e.g.*, silyl chloride) is used, the phosphorus is the predominant nucleophile, not the oxygen.[57] The P-C bond formation can selectively undergo Michael-type addition to ketone conjugated alkenes (Scheme 11a)[59,60] or direct carbonyl addition (Scheme 11b),[61] depending on the catalyst or the phosphorus cation. This simple strategy can be used to great effect, especially for chiral syntheses.



Scheme 11. H-Phosphine oxides as nucleophiles for alkene conjugated carbonyls showing a) zinc-mediated Michael addition to the alkene and b) calcium-mediated direct carbonyl addition.

Nucleophiles from α-Methyl Carbanion

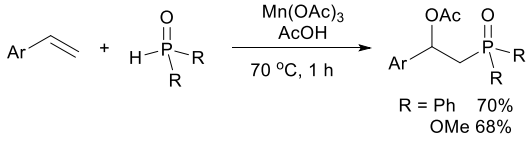
α-Methyl phosphine oxides can be deprotonated using organolithiates in conjunction with *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) to generate an α-carbanion. This carbanion can be reacted with an electrophile, creating a C-C bond β to the phosphorus (Scheme 12). This is especially advantageous when R = CH_3. From trimethyl phosphine oxide, alkyl dimethyl phosphine oxides can be directly generated. Though this approach is equally valid with alkyl phosphines,[62] the hydrogens at the α-carbon become considerably more acidic (and carbanion better behaved) when using the phosphine oxide, phosphine borane, or phosphine sulfide (R_3P=S).[63] This approach is not valid for phosphonates or phosphinates because of the electrophilic nature of the P-OR bond which reacts quickly with alkyl lithiates.



Scheme 12. Phosphine oxide α-methyl carbanion generation for C-C bond formation β to the phosphorus.

Radical from Tetravalent Phosphorus

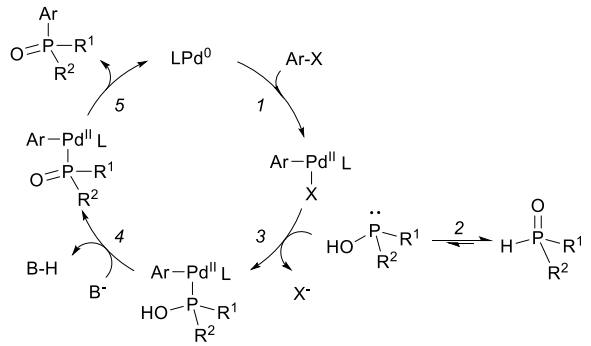
H-Phosphonates, H-phosphinates, and H-phosphine oxides undergo radical chemistry in a nearly identical fashion to secondary and primary phosphines. A major step forward in this field was the discovery of metal-mediated radical acetoxyphosphorylation. The simultaneous installation of two functional groups across unsaturated alkenes produces more complex architectures in one step compared to standard hydrophosphination. In a preliminary finding by Zhou *et al.*, both H-phosphine oxides and H-phosphonates can be added regioselectively with an acetoxy group across conjugated alkenes (Scheme 13).[64]



Scheme 13. Mn(III)-mediated radical acetoxyphosphorylation of alkenes with both H-phosphine oxides and H-phosphonates.

Cross-Coupling Tetravalent Phosphorus

One of the quickly growing subfields in organophosphorus chemistry is the development of H-phosphonate,[48–49,65–69] H-phosphinate,[70,71] and H-phosphine oxide cross-coupling reactions[72–74] to form P-C bonds (Scheme 14). There has been serious interest in these transformations during the last decade and these reactions are now standard practice in organophosphorus synthesis. Cross-couplings to form P-C bonds are more sensitive to conditions than "typical" C-C bond-forming reactions, with phosphine oxides often being more finicky than phosphonates. Typically, several literature



Scheme14. An example of Pd-catalyzed cross-coupling of an aryl halide with a secondary P(V) species. Catalytic steps are: 1) oxidative addition, 2) P(V)-P(III) tautomerization, 3) ligand exchange, 4) deprotonation, and 5) reductive elimination. L is typically a bidentate phosphine ligand.

preparations must be screened before a cross-coupling reaction has been optimized for any specific substrate. Both palladium[75] and nickel[76] cross-coupling protocols for H-phosphonates, H-phosphinates, and H-phosphine oxides are reasonably robust across a variety of substrates. In spite of these advances, cross-coupling of P-H species is still in need of standard protocols that are universally reliable and mechanistically well understood.

Looking Forward

Although the modern organophosphorus chemist has more synthetic tools than ever before, the ability to make P-C bonds as easily as first-row main-group bonds to carbon is still a distant dream. The differences in first- and second-row main-group chemistry provide a high degree of variance in reactivity and sensitivity to subtle changes in conditions. The exploitation of these differences is the fuel that drives phosphine chemistry toward new and seminal discoveries.

One such area of research uses borane as a protecting group for phosphines.[49] This approach is an excellent way to take advantage of air- and silica-stability of phosphine-boranes. Also, phosphine boranes are easily deprotected to yield phosphines. (Heating with amines will typically free the phosphine.) Considering the diversity of chemistry discussed in this Perspective, it is readily apparent that borane-protected phosphorus syntheses have been minimally exploited.[77,78] Typically, borane is used as a late-stage protecting group; however, it could be used throughout the synthesis. The ability of phosphine-borane derivatives of phosphinites and phosphonites to undergo nucleophilic attack or be deprotonated to a phosphide is not well established. Cross-coupling of phosphine-boranes is also an underdeveloped field that shows much promise for the future of organophosphine synthesis.

The ability to gently and selectively reduce P(V) species to P(III) is an ongoing challenge for chemists. In a recent example of research in this area, the Gilheany group showed the ability to reduce P=O bonds while retaining the weaker (more easily reduced) P-N bonds of aminophosphine oxides.[79] Selective reduction of P(V) was thought impossible based on the large discrepancy in bond strengths and reduction potentials of P=O and P-N bonds. The ability to selectively reduce P=O bonds will grant access to more diverse functionality at P(V) precursors and will open up new routes to heteroleptic phosphines. As such, the development of selective reduction for P(V) species will continue to be a key area of modern phosphine chemistry.

Conclusions

The last decade has seen a renewed interest in organophosphorus chemistry. New chemistries for reliable P(III) and P(V) syntheses of heteroleptic phosphines have emerged. Many chemists, however, still rely on traditional P-Cl derived synthetic routes and aryl phosphines for research. The new synthetic methods grant access to ligands like alkyl phosphines that currently represent an underutilized class of heteroleptic phosphines due to the considerable synthetic hurdles associated with their synthesis. As new syntheses of heteroleptic phosphines come online, inorganic and organometallic chemistry will surely flourish. The new organophosphorus synthetic methods will also have a serious impact on other fields including medicinal chemistry, biochemistry, materials science, solid state chemistry, and catalysis. From a global perspective, the new syntheses will serve to expand our understanding of the idiosyncratic nature of second-row main-group chemistry.

Acknowledgements

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Notes and References

‡ Designer ligands have structures that are strictly tailored for a specific chemical purpose. Typically, these ligands represent synthetically fine-tuned structures because they evolved from previously studied structures.

§ Preliminary work with 2,2'-biphenol as a bidentate P-Cl protecting group has also shown promise, where the P-O bond is sensitive to organolithiates, but not organomagnesium reagents.[80]

¶ The Tavs Reaction is another trivalent phosphorus cross-coupling reaction. It serves as an alternative to H-phosphonate cross-coupling and uses alkyl phospites with aryl halides to form aryl phosphonates.[81]

‖ Thionyl chloride also works well as a chlorinating agent for phosphonates to phosphinic dichlorides.

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