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Phosphinate Chemistry in the 21st Century: A Viable Alternative to the Use of Phosphorus Trichloride in Organophosphorus Synthesis.

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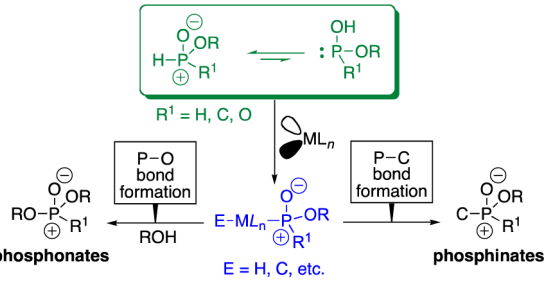
RECEIVED ON MARCH 11, 2013

CONSPECTUS

Organophosphorus compounds are important in everyday applications ranging from agriculture to medicine and are used in flame retardants and other materials. Although organophosphorus chemistry is known as a mature and specialized area, researchers would like to develop new methods for synthesizing organophosphorus compounds to improve the safety and sustainability of these chemical processes.



The vast majority of compounds that contain a phosphorus–carbon bond are manufactured using phosphorus trichloride (PCl_3) as an intermediate. However, these reactions require chlorine, and researchers would like to avoid the use of PCl_3 and develop safer chemistry that also decreases energy consumption and minimizes waste. Researchers have already proposed and discussed two primary strategies based on elemental phosphorus (P_4 or P_{red}) or on phosphine (PH_3) as alternatives to PCl_3. However, phosphinates, an important class of phosphorus compounds defined as any compound with a phosphorus atom attached to two oxygens, $R^1R^2P(O)(OR)$ (R^1/R^2 = hydrogen/carbon), offer another option.

This Account discusses the previously neglected potential of these phosphinates as replacements of PCl_3 for the preparation of organophosphorus compounds. Because of their strong reductive properties, industry currently uses the simplest members of this class of compounds, hypophosphites, for one major application: electroless plating. In comparison with other proposed PCl_3 surrogates, hypophosphorous derivatives can offer improved stability, lower toxicity, higher solubility, and increased atom economy. When their reducing power is harnessed to form phosphorus–carbon or phosphorus–oxygen bonds, these compounds are also rich and versatile precursors to organophosphorus compounds. This Account examines the use of transition metal-catalyzed reactions such as cross-coupling and hydrophosphinylation for phosphorus–carbon bond formation. Because the most important industrial organophosphorus compounds include compounds triply or quadruply bound to oxygen, I also discuss controlled transfer hydrogenation for phosphorus–oxygen bond formation. I hope that this Account will further promote research in this novel and exciting yet much underdeveloped area of phosphinate activation.

I. Introduction

Organophosphorus chemistry is one of the oldest subfields of organic chemistry with a rich tradition over its more than a century history (providing many named reactions, such as, Arbuzov, Michaelis–Becker, Perkow, Kabachnik–Fields, Wittig, and Wadsworth–Horner–Emmons). Not surprisingly, organophosphorus compounds play many key roles, from flame-retardants, metal extractants, and ancillary ligands for metals to agrochemicals such as pesticides to medicines. Furthermore they are key intermediates or components used in general organic synthesis.[1] Because of this, phosphorus chemistry is often considered to be a mature specialty field, perhaps not receiving much attention and recognition in the chemical community and *a fortiori* the public at large.

Phosphorus is an essential element in all fields of chemical science, including material science and inorganic chemistry. Even more importantly, phosphorus is a key building block in all known forms of life.[2] It is also a limiting nutrient in plant growth, explaining its huge economic and societal importance in the phosphate fertilizer industry. This is the main application of phosphorus, numbering in tens or

Published on the Web 08/02/2013 www.pubs.acs.org/accounts
10.1021/ar400071v

hundreds of millions of metric tons each year,[3] without which feeding the growing world population would simply be impossible. This is also true of various phosphorus-containing agrochemicals (such as the herbicides glyphosate and glufosinate, their associated genetically modified crops, the plant-growth regulator/ripening agent ethephon, etc.), which are less important in tonnage but are still essential to modern food production. The industrial synthesis of glyphosate is also a major consumer of phosphorus trichloride. Of course, many organic compounds (for example:, polyethylene) have a much larger share of industrial production than glyphosate and related organophosphorus compounds do; however, few have such an impact on the well-being of mankind.

In 1669, German alchemist Hennig Brandt first prepared elemental phosphorus (P_4) from the reduction of concentrated urine with sand and coal,[4] a chemical process eerily similar to today's industrial manufacture, except phosphate rock has fortunately replaced urine! Ironically, projected shortages of phosphate rock will necessitate a phosphorus recycling strategy likely to involve human and animal wastes either directly or through water treatment.[5] The problem of phosphorus availability is a looming crisis even more severe than dwindling supplies of fossil fuels, because there is simply no alternative for this irreplaceable element. It is vital not only for food production but also for any other commodities relying on agriculture, such as ethanol, biofuels, or any biorenewable chemical.[5]

Because of this, novel methods to better employ feedstocks for organophosphorus synthesis (let alone phosphate) are needed, and these need to address many issues such as increased safety, efficiency, and sustainability, less energy consumption, less waste product formation, etc. Current industrial processes rely on phosphorus trichloride (PCl_3), which is prepared by the reaction of elemental phosphorus with chlorine. Since the major industrial products do not contain reactive phosphorus−chlorine bonds, it is desirable to avoid the use of chlorine altogether. This Account examines the reactivity of phosphinates[6] as potential alternatives to PCl_3. In addition, it discusses catalytic reactions for the formation of phosphorus−carbon bonds. Compounds containing a P−C bond are an important subset of phosphorus-containing molecules.

The current industrial pathways for the synthesis of organophosphorus compounds are shown in Scheme 1.[3] Phosphate is reduced all the way down to P_4 and then oxidized to PCl_3, which serves as precursor to organophosphorus compounds such as phosphonates. The vast majority of organophosphorus compounds are made through PCl_3. A large portion of P_4 is also converted into inorganic compounds such as high purity phosphoric acid or sulfur-containing species (P_2S_5). Although P_4 is currently the main industrial intermediate, its poor solubility, high toxicity, and pyrophoricity make the so-called "P_4-activation" process (direct conversion of P_4 into P−C containing compounds) problematic.[7] Worse, once the phosphorus tetrahedron has reacted, the remaining P−P bonds have diminished reactivity, making it difficult to incorporate all four phosphorus atoms into a useful product. In fact, this is the reason PCl_3 remains the major practical intermediate since all phosphorus atoms are converted in the process. Some companies do employ phosphine (PH_3) on industrial scales to prepare various organophosphorus compounds, even though PH_3 is a highly toxic and pyrophoric gas.[8] Phosphine is also a byproduct in the preparation of phosphinates.

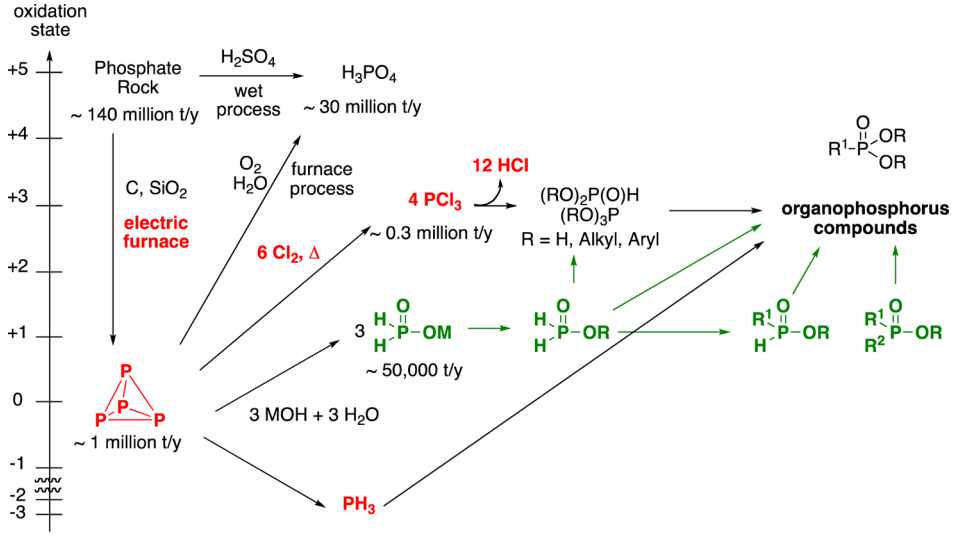
Phosphinates (hypophosphites, $H_2P(O)(OR)$) are made on an industrial scale (~50,000 t/y) through the alkaline hydrolysis of P_4.[3] Although the preparation of phosphinates is significant, it is currently reserved for a single major application called electroless plating (the Kanigen process). Despite much promise, phosphinates have not yet been employed in general industrial organophosphorus synthesis.[3] Because they have an established industrial production and are versatile intermediates with the fewest issues in terms of solubility, air-sensitivity, and toxicity, we are proposing that phosphinates are the *best already available* PCl_3 replacements.[9] As shown in Scheme 1, hypophosphites have an oxidation state (+1) exactly in the middle between PH_3 (−3) and H_3PO_4 (+5), making them ideal intermediates to access all other functionalities. For these reasons, we began developing the organic chemistry of phosphinates some 15 years ago.

This Account discusses some of the organic transformations of phosphinates, with the goal of illustrating the potential of phosphinate chemistry in the preparation of other phosphorus-containing compounds. Phosphorus chemistry is fundamental in sustaining humanity mostly through its agricultural importance. The world's population of seven billion would not be sustainable without the proper management of phosphorus.[5]

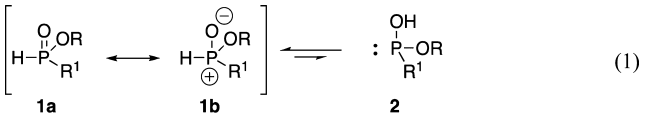
II. Phosphinate Chemistry

There are three kinds of phosphinates depending on the atoms (carbon, hydrogen, or both) attached to the P(O)(OR) moiety: phosphinates **1** (hypophosphorous acid derivatives,

SCHEME 1. Overview of Industrial Phosphorus Chemistry



hypophosphites, R^1 = H), *H*-phosphinates **1** (R^1 = C), and disubstituted phosphinates. When at least one hydrogen is attached, the phosphinylidene group, P(O)–H **1**, can tautomerize to the P–OH form, **2** (eq 1).[10]

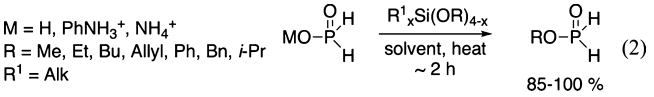


(1)

It should be noted here that although the conventional representation, P=O **1a**, is still ubiquitous, the phosphonium cation resonance form **1b** is a much better and more useful representation.[11]

Hypophosphites **1** (R^1 = H) are generally much more reactive than *H*-phosphinates (R^1 = Alk) because in eq 1, more donating R^1 groups make the tautomerization even less favorable. On the other hand, electron-withdrawing substituents help in stabilizing **2**. For most compounds, the equilibrium always lies heavily on the side of **1**, but small electronic differences affect this equilibrium significantly, and R^1 = aryl makes the availability of **2** more significant.

A. Preparation of Alkyl Phosphinates. Alkyl phosphinates (organic esters of H_3PO_2) can be prepared most easily through two esterification methods: alkoxysilane-mediated esterification (eq 2, Montchamp method) and Fischer-type Dean–Stark esterification with some alcohols (Nifantev method).[6d,12] Alkyl phosphinates are generally prepared and used in solution as decomposition (disproportionation) occurs upon attempted isolation. Whereas other methods are available, those have a more limited scope especially in terms of reaction scale and cost or solvent.[12] The two methods are also applicable to the esterification of *H*-phosphinic acids.



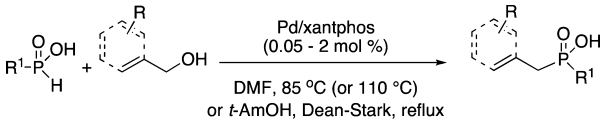
(2)

B. P–C Bond-Formation from Phosphinates. 1. Cross-Coupling. Schwabacher and Holt reported the palladium-catalyzed cross-coupling of hypophosphites early on.[13] In this process, the phosphorus species acts as the nucleophile as in many other cross-coupling processes. The scope was relatively narrow, and transfer hydrogenation was a significant competing pathway because of the strong reducing ability of hypophosphites.[14] Scheme 2 summarizes various mechanistic pathways for both hypophosphites and *H*-phosphinates (as well as any other species containing a P(O)–H moiety), except that significant differences exist: (1) transfer hydrogenation is more or less pronounced; (2) the tautomeric equilibrium (eq 1) is different and controls both the rate of nucleophilic attack (of M–X) and the rate of oxidative addition (into P–H).

We were able to develop very general conditions for the palladium-catalyzed cross-coupling of both hypophosphites[15] and *H*-phosphinates,[16] as summarized in Scheme 3. The reactions employ 2 mol % or less of palladium and simple ligands (PPh_3, dppp, dppf, or xantphos), with or without a solvent additive such as ethylene glycol (EG) or 1,2-dimethoxyethane (DME).

Cross-couplings with H_3PO_2 or *H*-phosphinic acids are also possible using allylic or benzylic alcohols directly (eq 3).[17] In these reactions, the leaving group necessary for oxidative addition is generated in situ via Fischer-like

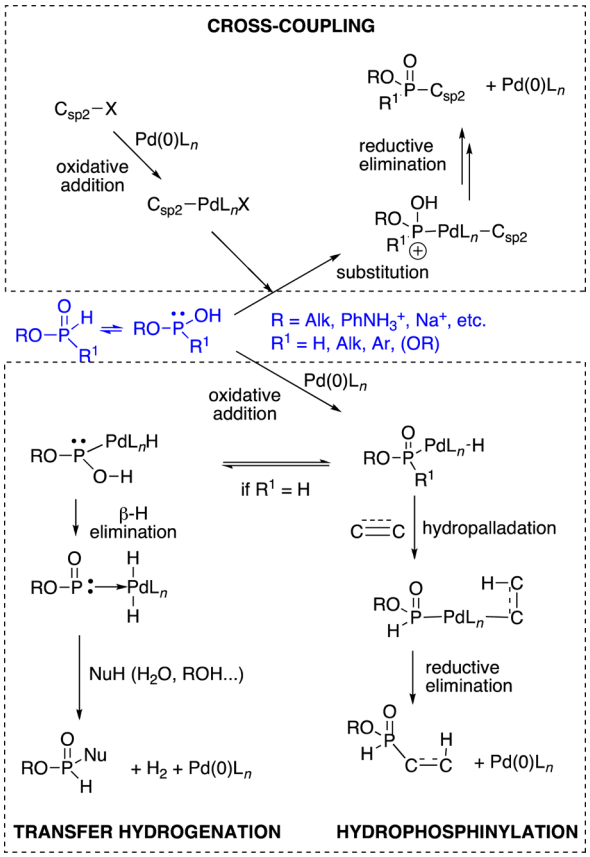
esterification. As expected, H_3PO_2 is more reactive and thus requires less forcing conditions (lower Pd loading, lower temperature, no need for water removal) than *H*-phosphinic acids, and allylation is easier than benzylation. Nonetheless, numerous phosphinic acids can be prepared in a single step and without protecting or activating groups.



(3)

R^1 = H: 34 examples, 32 - 98 % isolated yield
R^1 = C: 19 examples, 34 - 100 % isolated yield

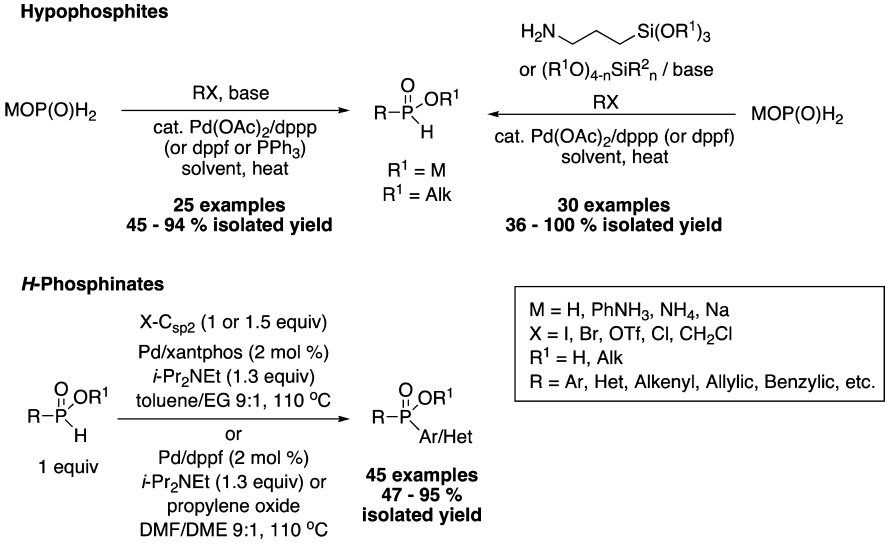
SCHEME 2. Mechanistic Pathways in Palladium-Catalyzed Reactions of Phosphinates



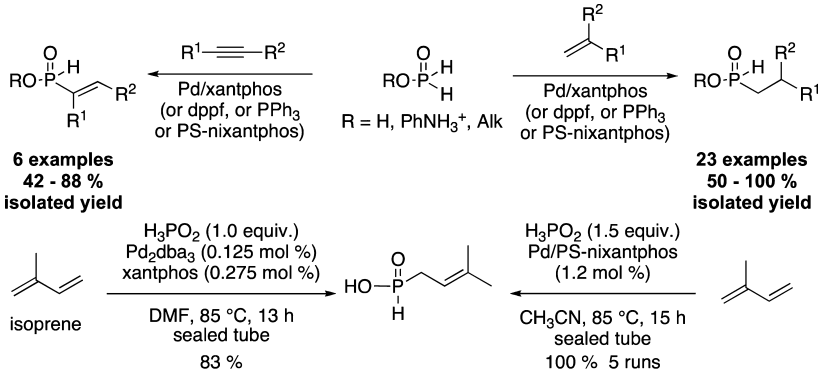
2. Addition Reactions (Hydrophosphinylation). The addition of phosphinates to unsaturated hydrocarbons is perhaps the most important and atom-efficient reaction for the preparation of organophosphorus intermediates. Cytec uses phosphine for this purpose, but phosphinates can be viable substitutes, completely avoiding the toxicity and air-sensitivity issues associated with PH_3.[9]

a. Transition Metal-Catalyzed Reactions. On the basis of the mechanism of cross-coupling and transfer hydrogenation (Scheme 2), we invented the metal-catalyzed hydrophosphinylation reaction.[18] Reasoning that a ligand (especially one slowing β-hydrogen elimination in the case of hypophosphites) should slow the formation of a metal hydride complexed to a phosphinidene oxide, we achieved the trapping of the intermediate metal hydride with alkenes or alkynes. The reaction has a broad scope (but fails with 1,2-disubstituted alkenes because the reverse β-hydrogen elimination is favored) and is successful even with commercial (50 wt %) aqueous H_3PO_2.[18] Although the turnovers can be high, we still developed a simple reusable catalyst based on polystyrene-supported nixantphos (PS-nixantphos).[18b] A summary of the reaction[18] and an example[19] are shown in Scheme 4.

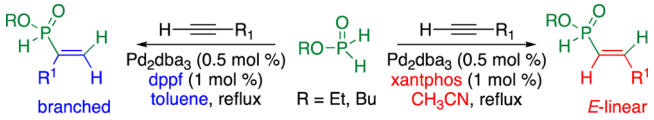
SCHEME 3. Palladium-Catalyzed Phosphinate Couplings



SCHEME 4. Hydrophosphinylation and Its Application to Isoprene



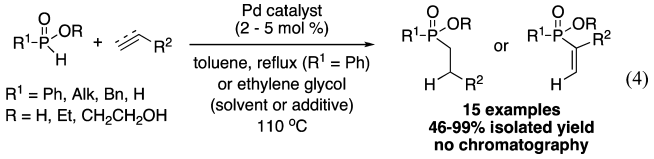
SCHEME 5. Regiocontrolled Hydrophosphinylation of Terminal Alkynes



11 examples, 66 - 100 % isolated yield

Regiocontrol can be also achieved in the hydrophosphinylation of terminal alkynes with alkyl phosphinates, based on ligand and solvent selection (Scheme 5).[18a] Selectivities vary depending on the alkyne employed and the conditions for phosphinate synthesis but are generally better than 5:1 and sometimes reach 98:2, with either the linear or the branched isomer dominating.

The Pd-catalyzed hydrophosphinylation of *H*-phosphinates is once again much more difficult than with hypophosphites (except in the phenyl-substituted case). However, we discovered that *H*-phosphinic acids undergo palladium-catalyzed addition to both alkenes and alkynes, using ethylene glycol as an additive (eq 4).[20]

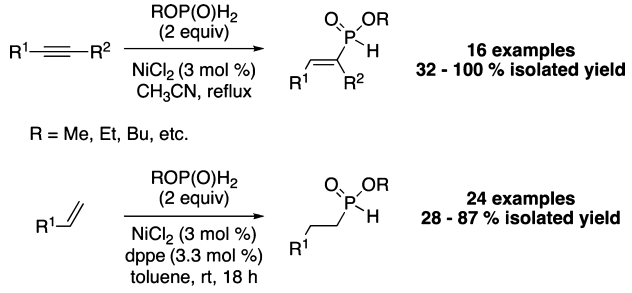


(4)

15 examples
46-99% isolated yield
no chromatography

Although palladium catalysis offers many opportunities in the synthesis of phosphinates and many reactions were accomplished using low catalyst loadings or with a reusable catalyst, we looked for a cheaper hydrophosphinylation catalyst, focusing on nickel. Catalysis with "cheap metals" is an intensely active field of research. However, one must bear in mind that it is not just the element that counts but the molar cost of the metal source itself and other factors like ligands, turnover numbers, etc. For example, anhydrous $NiCl_2$ is 2 orders of magnitude cheaper than $PdCl_2$, but

SCHEME 6. Nickel-Catalyzed Hydrophosphinylation



$Ni(cod)_2$ is as expensive as $PdCl_2$ and also requires rigorous inert atmosphere techniques.

In 2005, we reported a simple and inexpensive nickel-catalyzed hydrophosphinylation of alkynes using $NiCl_2$ (Scheme 6).[21] In this reaction, the alkyl hypophosphite serves three important roles: (1) it is the reagent added to the alkyne, but (2) it is also the reducing agent that converts Ni(II) into Ni(0) in situ, and (3) it is the P(III) tautomer ROP(OH)H serving as a loosely bound ligand to stabilize Ni(0) (if $NiCl_2 \cdot 6H_2O$ is employed, a fourth role is the drying of the catalyst).

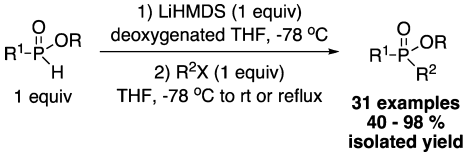
At that time, we knew that the reaction with alkenes was possible, but the results were unsatisfactory, especially when compared with the palladium method. We recently solved this problem by adding an external ligand (dppe was best, although other phosphines could be used) and conducting the reaction at room temperature.[22] The rationale for these conditions (external ligand and lower temperature) is that the addition to alkenes is slower than that to alkynes, so the active nickel catalyst's lifetime needs to be increased in order to achieve good conversions.

b. Free-Radical Reactions. Several free-radical reactions of hypophosphites have been described, and some are used industrially.[23] Our group has described the R_3B/air

system for the preparation of *H*-phosphinates[24] and 1,1-bis-*H*-phosphinates[25] and also the AIBN-initiated reaction of hypophosphite esters,[26] based on their slower thermal decomposition when prepared through the alkoxysilane method (eq 2).[12a] The reaction of *H*-phosphinates is also known[27] but is much more difficult and requires specialized initiators, except in some special cases like aryl-*H*-phosphinate esters (eq 1, R^1 = aryl), an exception we reported more than a decade ago.[24] Hypophosphites are also excellent, inexpensive, and nontoxic replacements for Bu_3SnH or $(Me_3Si)_3SiH$ in many radical reactions,[28] such as deoxygenation, dehalogenation, and even radical cyclizations, and they are the classic reagents in the reduction of diazonium salts.[29]

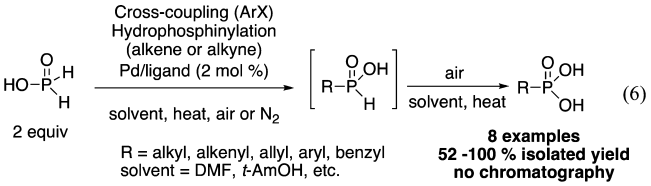
3. Alkylation. Phosphinates can be alkylated, in reactions analogous to the sila-Arbuzov[23] or Michaelis–Becker phosphonate syntheses. The reaction of hypophosphites through pyrophoric $(TMSO)_2PH$ can be used in some cases, although if the *H*-phosphinate is desired, it requires a large excess of reagent to prevent disubstitution, and phosphorus-rich polymers always form.[27,30] The lack of convenience and generality of this process was one of the origins of our research on phosphinate chemistry 15 years ago. Similarly, alkyl hypophosphites can be alkylated using strong bases (for example, *n*-BuLi at low temperature), but this reaction is also not always ideal and has limitations.[31] With reactive halides, alkylation with DBU (at or below room temperature) is much more convenient.[31a,32]

On the other hand, *H*-phosphinates can be alkylated more easily because decomposition is less problematic, and many conditions have been described in the literature. Our own contribution in this area is shown in eq 5.[33] As far as we know, it is still the only method that proceeds under equimolar conditions and works even with unreactive electrophiles (such as primary chloride and tosylate or secondary iodide). With unreactive electrophiles, moderate deoxygenation is necessary to avoid competing oxidation of the phosphonite anion $R^1P(OR)(OLi)$.



(5)

C. P–O Bond Formation from Phosphinates. Scheme 2 showed a reasonable mechanism for transfer hydrogenation,[14] which must be prevented (or slowed) when cross-coupling or hydrophosphinylation are desired. However, it is a useful reaction of itself, often employed to reduce various functionalities. In the research laboratory, formates are typically used because CO_2 is evolved, but industrially, hypophosphites are preferred because they are much cheaper and handling gas evolution is avoided. In these reactions, what happens to the reducing agent is often neglected, but as far as phosphinates are concerned, it occurred to us that there was an opportunity to develop some unique methodology for P–O bond formation (and ultimately other reactions depending on the nucleophile in Scheme 2). So far, we have reported two types of catalytic oxidative phosphorylation reactions: (1) the preparation of phosphonic acids (eq 6),[34] and (2) the preparation of *H*-phosphonate monoesters from H_3PO_2 (eq 7).[35] The former reaction exploits the various methodologies outlined earlier to prepare an *H*-phosphinate intermediate, which is then oxidized in situ by air. This allows the straightforward preparation of phosphonic acids in good yields, without the use of PCl_3 and protecting groups.



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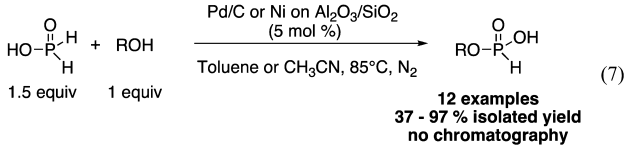
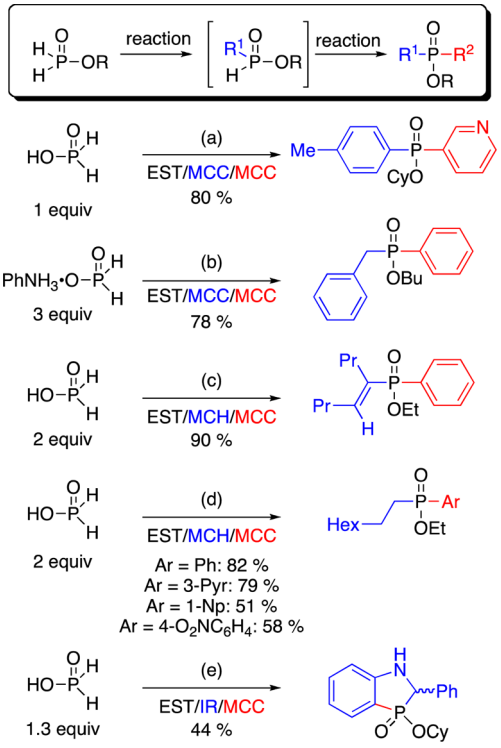


(7)

Although *H*-phosphonate monoesters do not contain P–C bonds and therefore are not organophosphorus compounds as we defined earlier, they are representative of the P(O)(OR) class. These compounds are key intermediates in the synthesis of a wide range of compounds, such as oligonucleotides, phospholipids, sugar phosphates, etc.; however, they have always been derived from PCl_3 previously.

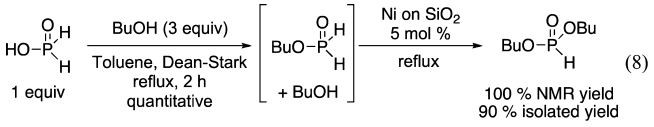
Finally, a critical bridge between our phosphinate-based chemistry and the established PCl_3 chemistry is the preparation of *H*-phosphonate diesters, $(RO)_2P(O)H$. This can be easily achieved as shown in eq 8.[36] As expected, ligandless conditions are ideal to favor transfer hydrogenation. Preliminary results also show that the catalytic oxidative phosphorylation of *H*-phosphinate esters with alcohols is a promising approach toward the preparation of *H*-phosphonate

SCHEME 7. Tandem Transformations[a]



[a]All yields are for isolated compounds. Abbreviations: EST, esterification (silicate or Dean–Stark); MCC, metal-catalyzed cross-coupling; MCH, metal-catalyzed hydrophosphinylation; IR, ionic reactions (alkylation, conjugate addition, etc.). Reagents and conditions: (a) (i) CyOH (2 equiv), toluene, reflux, Dean–Stark, 3 h; (ii) *p*-MeC_6H_4I (1 equiv), $Pd(OAc)_2$/dppf (2 mol %), *i*-Pr_2NEt (1.3 equiv), toluene/DME (9:1 v/v), 115 °C; (iii) 3-BrC_6H_4N (1 equiv), *i*-Pr_2NEt (1.3 equiv), 115 °C, 24 h, 80%; (b) (i) $(BuO)_4Si$ (3 equiv), CH_3CN, reflux, 2 h; (ii) $Pd(OAc)_2$/dppf (2 mol %), *i*-Pr_2NEt (1.3 equiv), $PhCH_2Cl$ (1 equiv), reflux, 16 h; (iii) PhBr (3 equiv), $Pd(OAc)_2$/xantphos (2 mol %), *i*-Pr_2NEt (3 equiv), toluene/EG (9:1 v/v), 115 °C, 24 h; (c) (i) 4-octyne (1 equiv), $(EtO)_3Si(CH_2)_3NH_2 \cdot TFA$ (2 equiv), $NiCl_2$ (3 mol %), CH_3CN, reflux, 2.5 h; (ii) PhI (1 equiv), $Pd(OAc)_2$/xantphos (2 mol %), *i*-Pr_2NEt (3 equiv), toluene/EG (9:1 v/v), 115 °C, 24 h; (d) (i) $Me_2Si(OEt)_2$ (2 equiv), toluene, reflux, 2 h; (ii) 1-octene (1 equiv), Pd/xantphos (2 mol %), toluene, reflux, 24 h; (iii) ArBr (2 equiv), *i*-Pr_2NEt (1.3 equiv), EG (10% v/v), 115 °C, 24 h; (e) (i) CyOH (2.0 equiv), toluene, reflux, Dean–Stark, 3 h; (ii) PhCHO (1 equiv), 2-iodoaniline (1 equiv), toluene, reflux, 24 h; (iii) $Pd(OAc)_2$/dppf (2 mol %), *i*-Pr_2NEt (1.3 equiv), DMF/DME (9:1 v/v), 115 °C, 24 h.

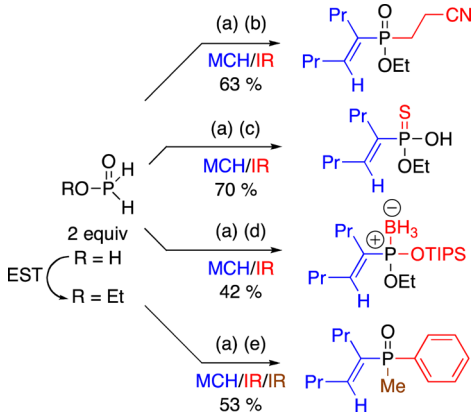
diesters. Research along these lines is currently being conducted in our laboratory.[36]



(8)

D. Tandem and Miscellaneous Reactions. 1. Tandem Reactions (Formation of Two or More Bonds to Phosphorus). Because many of the reactions described above are high yielding and clean, it is often possible to conduct tandem transformations without isolation of the intermediate *H*-phosphinate and at times without any solvent switch. Furthermore, because the *H*-phosphinate is always less

SCHEME 8. More Tandem Transformations[a]



[a]All yields are for isolated compounds. Reagents and conditions: for EST, $Me_2Si(OEt)_2$ (2 equiv), CH_3CN, reflux, 2 h; for MCH (nickel-catalyzed hydrophosphinylation), (a) 4-octyne (1 equiv), $NiCl_2$ (3 mol %), CH_3CN, reflux, 3 h; for IR (ionic reactions), (b) acrylonitrile (3 equiv), DBU (3 equiv), rt, 6 h; (c) S_8 (3 equiv), Et_3N (3 equiv), CH_3CN, rt, 12 h; (d) (i) TIPSCl (1.5 equiv), Et_3N (1.6 equiv), CH_3CN, 0 °C to rt, 14 h; (ii) $H_3B \cdot SMe_2$ (2 equiv), rt, 5 h; (e) (i) solvent removal; (ii) PhMgBr (3 equiv), THF, reflux, 3 h; (iii) CH_3I (3 equiv), THF, rt, 1 h.

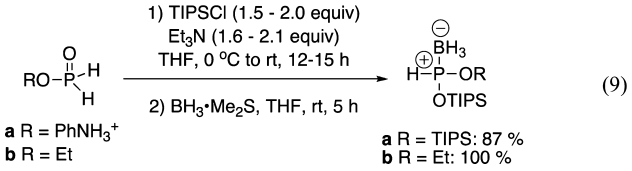
reactive than the hypophosphite, it is generally possible to prepare nonsymmetrical disubstituted phosphinates. Scheme 7 shows several combinations of reactions in tandem processes, with palladium-catalyzed cross-coupling as the last step.[16b,21] Keeping in mind that three new bonds are formed in these examples (one P–O through esterification and two P–C bonds; and actually a fourth C–N bond in the last example), the isolated yields are quite good (>80%/bond). Perhaps the most valuable processes involve doubly catalytic transformations, for which many possibilities exist (including some examples in eqs 3 and 4).

Of course, other tandem processes are possible. Equations 6 and 8 illustrated tandem P–C/P–O and P–O/P–O processes, respectively. Scheme 8 shows some examples of nickel-catalyzed hydrophosphinylation followed by other reactions.[21] The last example offers a one pot synthesis of a tertiary phosphine oxide via triple P–C bond formation.

2. Protected Hypophosphites. Although the direct use of hypophosphites is ideal, in some cases a protected version can be useful. As mentioned earlier, the direct base-mediated alkylation of hypophosphite esters is problematic; therefore the temporary masking of one of the P–H groups can solve this problem. A broadly useful class of such reagents was developed at Ciba-Geigy (ethyl 1,1-(diethoxyethyl)- and 1,1-(diethoxymethyl)-*H*-phosphinates, $RC(OEt)_2P(O)(OEt)H$, R = Me, H).[19] The reagents are prepared from the reaction of H_3PO_2 with orthoformate or orthoacetate and an acid catalyst. Cleavage of the acetal after functionalization unmasks the P(O)H moiety.

For example, Hall and co-workers have used these compounds for a variety of synthetic applications, which include an elegant preparation of nonsymmetrical secondary phosphine oxides avoiding PCl_3 completely.[37]

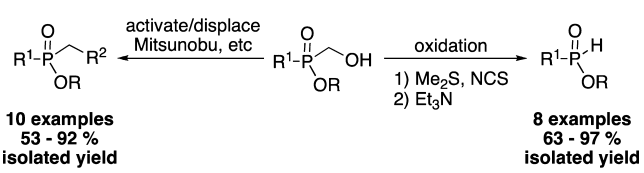
We have also been interested in the preparation of hypophosphite equivalents, as part of a program concerning the chemistry of phosphonite–borane complexes. We showed that $(EtO)_2P(BH_3)H$ can be synthesized easily, is stable to air and chromatographic purification, and undergoes useful reactions; however, its preparation requires both PCl_3 and $LiBH_4$.[38] Instead, a class of reagents derived from the H_3PO_2, P(III) tautomer can be prepared by silylation and borane complexation (eq 9).[38] The resulting reagents undergo base-promoted alkylation and radical hydrophosphinylation, and deprotection is accomplished using a range of conditions (HBF_4, tertiary amine, ROH reflux) in high yield.[38,39] Phosphonite–borane complexes are not only latent forms of *H*-phosphinates, they are also phosphonite precursors, and one example of decomplexation/Arbuzov reaction was demonstrated.[39d]



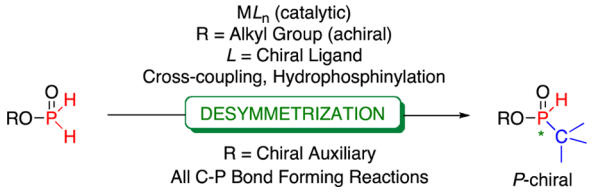
(9)

Another useful reagent is (hydroxymethyl)-*H*-phosphinic acid, easily prepared from H_3PO_2 and (para)formaldehyde. Our contribution in this area was published last year: not only can the hydroxymethyl moiety be elaborated into a range of functional groups while preserving the methylene carbon (as other researchers had partially established), but it can also be oxidatively cleaved to unmask the initial phosphinylidene moiety P(O)H.[40] We found that the Corey–Kim oxidation (R_2S/NCS then Et_3N) gives good yields for the deprotection of various (hydroxymethyl)phosphinyl compounds (Scheme 9).

SCHEME 9. Alkyl(hydroxymethyl)-*H*-phosphinate Esters as Versatile Building Blocks



3. Asymmetric Reactions. As Mislow demonstrated in the 1970s, *H*-phosphinate esters are configurationally stable under certain conditions.[41] These compounds remain configurationally stable over a useful range of conditions, as long as hydrolysis and oxidation are avoided. Therefore, a tantalizing prospect would be the asymmetric synthesis of *H*-phosphinates through the desymmetrization of hypophosphite esters, $ROP(O)H_2$. Since we have developed many new reactions, including transition metal-catalyzed processes, this was of obvious interest (eq 10).[42]



(10)

However, the vast majority of catalytic asymmetric reactions concern enantiofacial differentiation as opposed to the desymmetrization of tetrahedral structures (one notable exception is the enantioselective oxidation of sulfides into sulfoxides), and still relies on extensive (and also expensive/time-consuming) ligand-screening approaches. After we established a method for the determination of enantiomeric excess, we have looked at this problem and found that a ligand-based asymmetric desymmetrization process is beyond our capabilities.[42] Furthermore, limiting ourselves to metal-catalyzed reactions seemed futile. Instead, we quickly realized that auxiliary-based methods would be superior, not only because of the ease of screening but also because they should allow a much wider range of reactivity, not limited to metal catalysis. Recycling of the auxiliary should also be feasible. This work was published recently and concluded that 8-phenylmenthol was the best auxiliary with diastereomeric excesses around 70% (~5:1).[42]

But even chiral auxiliaries are generally used for enantiofacial discrimination. Current work in our laboratory is aimed at the design of a chiral auxiliary for tetrahedral compounds like hypophosphite esters. The preparation of *P*-chiral compounds is perhaps the "Holy Grail" of organophosphorus chemistry. Whereas many methods for the preparation of *P*-chiral compounds have been reported over the years, those are often experimentally complicated or expensive or limited in scope, as demonstrated by the paucity of commercially available *P*-chiral ligands.[43]

III. Conclusions and Outlook

This Account examined both the current usefulness of hypophosphites and *H*-phosphinates as PCl_3-replacements and also their further potential to revolutionize organophosphorus chemistry as a whole. Clearly, industrial processes will not be altered anytime soon based on the sheer amount

of industrial products that are being manufactured and the fact that retrofitting factories is a very expensive proposition. Nonetheless, hypophosphorous derivatives certainly constitute very promising alternatives to PCl_3, PH_3, and even elemental phosphorus. Our laboratory will continue to develop methodologies based on hypophosphites and *H*-phosphinates, as well as bridges (such as *H*-phosphonate synthesis) to bypass intermediates originating from PCl_3. A promising and general solution to the *P*-chiral problem, as well as alternatives to the preparation of P_4 are also currently being investigated.

In the final analysis, phosphorus chemistry remains one of the most critical fields for the advancement of mankind, no matter what the perception might be from experts and nonexperts alike. The phosphorus atom is key to sustaining the world population and life in general, perhaps only behind nitrogen and the Haber–Bosch process (which has been called "the most important process of the 20th century" and was credited for a population growth from 1.6 billion in 1900 to 6 billion in 2000). This is because phosphorus is not only needed in fertilizers but also affects agrochemicals needed in food production. In the end, concentrated sources of phosphate rock will disappear, perhaps in less than a century, so recycling and more sustainable strategies will have to be developed. Chlorine is produced from the electrolysis of sodium chloride (this process is also still responsible for significant mercury pollution because mercury cells are still in use in some parts of the world for chloralkali production) and is energy demanding. Perhaps even worse, both Cl_2 and PCl_3 are hazardous chemicals that have already resulted in major accidents. White phosphorus is toxic and pyrophoric, and in fact, it is not available through standard chemical suppliers and is typically converted on site into other compounds. Both chlorine and P_4 have been used in warfare with devastating effects. Red phosphorus, an amorphous form of elemental phosphorus, is much safer but therefore less reactive, requiring "superbasic" conditions to generate phosphide anions of limited synthetic value. Phosphine is a toxic gas and pyrophoric if not rigorously pure (traces of P_2H_4 cause combustion), used for its fumigant properties (for example, to kill rodents), and associated with the will-o'-the-wisp phenomenon. Therefore, environmentally benign phosphinates appear to be the ideal surrogates to PCl_3 and its derivatives, as well as superior to the other alternatives discussed above. Phosphinates not only have favorable safety, solubility, and stability properties and are manufactured on an industrial scale but also display excellent synthetic versatility and atom efficiency in the synthesis of organophosphorus compounds.

This material is based, in part, upon work supported by the National Science Foundation under Grant No. 0953368. The author acknowledges all co-workers, past and present, who contributed and are contributing to the development of phosphinate chemistry.

ABBREVIATIONS

DME, 1,2-dimethoxyethane; dppe, 1,2-bis(diphenylphosphino)-ethane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dppp, 1,3-bis(diphenylphosphino)propane; EG, ethylene glycol; PG, propylene glycol; PS-nixantphos, polystyrene-supported 4,6-bis(diphenylphosphino)phenoxazine; xantphos, 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene;

BIOGRAPHICAL INFORMATION

Prof. Jean-Luc Montchamp was born in Lyon, France, in 1967. He obtained his B.S. and M.S. degrees in chemistry in 1989 from the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL, now known as CPE). He obtained his Ph.D. from Purdue University in 1992, under the direction of Professor John W. Frost. After postdoctoral experiences at Michigan State University and the Scripps Research Institute, he returned to Purdue University for a postdoctoral stay with Professor Ei-ichi Negishi. He joined the faculty of Texas Christian University in 1998, where he is now full professor. He became a citizen of the United States in 2004. His research interests include the development of methodology for phosphorus–carbon and phosphorus–oxygen bond formation, especially using phosphinates, and the medicinal chemistry of phosphorus-containing analogs of natural products.

FOOTNOTES

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The authors declare no competing financial interest.

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