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Recent advances in phosphorus–carbon bond formation: synthesis of H-phosphinic acid derivatives from hypophosphorous compounds

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Abstract

This account summarizes the research conducted in our laboratory over the past five years. New methodologies were devised for the formation of P–C bonds with a focus on the reactions of hypophosphorous acid derivatives. Three types of reactions have been developed: palladium-catalyzed cross-coupling, room-temperature radical addition, and palladium-catalyzed addition. Our results are summarized in each of these areas and include some of our most recent data. (1) Our palladium-catalyzed cross-coupling has been extended to the direct coupling of alkyl phosphinates with a variety of aryl, heteroaryl, and even alkenyl electrophiles. (2) The addition of sodium hypophosphite under radical conditions is extended from alkenes to alkynes. (3) The catalytic addition of hypophosphorous compounds using palladium catalysts (hydrophosphinylation) is also discussed.

Keywords: Organophosphorus compounds; H-phosphinic acids; Organic synthesis; Hydrophosphinylation; Palladium cross-coupling

1. Introduction

Phosphorus–carbon bond formation remains an active and important research area, as new reactions are continuously being developed for the preparation of organophosphorus compounds such as phosphines, phosphonates, and phosphine oxides. Our laboratory has focused on H–phosphinic acid derivatives $R_1P(O)(OR)H$, a less developed class of compounds. H-phosphinates are potentially versatile intermediates (Scheme 1) for the synthesis of a variety of organophosphorus compounds, including phosphonates and phosphinates, as well as primary phosphines, secondary phosphine oxides, and dichlorophosphines, to name a few [1].

The most commonly employed methods to prepare H–phosphinates are summarized in Scheme 2. Each of these methods suffers from limitations in scope. The use of $(TMSO)_2PH$ is inconvenient and often requires a large excess of the reagent to avoid formation of symmetrically disubstituted phosphinates [2]. Decomposition and disproportionation also complicate handling and isolation. Only the most reactive alkyl halides produce a reasonable yield of product [2]. The radical reaction originally introduced by Nifant'ev et al. [3] and subsequently developed by Karanewsky et al. [4] suffers from the strongly acidic medium, thus limiting the substrates that can be employed. Hydrolysis or alcoholysis of dichlorophosphines is limited by the availability of the starting materials. The reaction of a Grignard reagent (and other organometallics) with $(RO)_2PCl$ [5,4] implies stability of the precursor toward Grignard formation. Gallagher devel-

Abbreviations: AHP, anilinium hypophosphite; Dba, dibenzylideneacetone; Dppf, 1,1′-bis(diphenylphosphino)ferrocene; Dppp, 1,3-bis(diphenylphosphino)propane; Nixantphos, 4,5-bis(diphenylphosphino)phenoxazine; Xantphos, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

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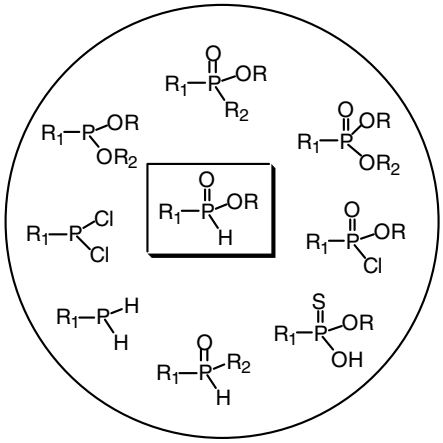


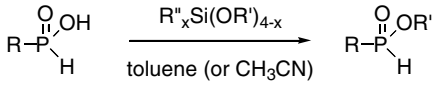
Scheme 1. Transformations of H-phosphinates.

oped the alkylation of *i*-PrOP(O)H_2, using sodium isopropoxide and an alkyl halide, but this reaction has rarely been used [6]. Finally, the Ciba–Geigy reagent [7] solves a number of these limitations, but relies on a protection–deprotection strategy, and the acidic cleavage of the acetal is not always compatible with functionalized compounds.

In connection with various projects requiring the synthesis of functionalized H-phosphinates, we became aware of the relative lack of convenient and general methods to access these intermediates. A program was thus initiated to develop novel methods for P–C bond formation based on hypophosphorous compounds ROP(O)H_2 as the starting materials. Progress toward this objective is outlined below.

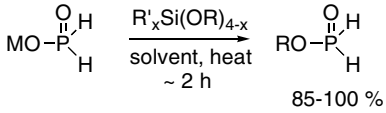
2. Results and discussion

2.1. Preparation of alkyl phosphinates ROP(O)H_2



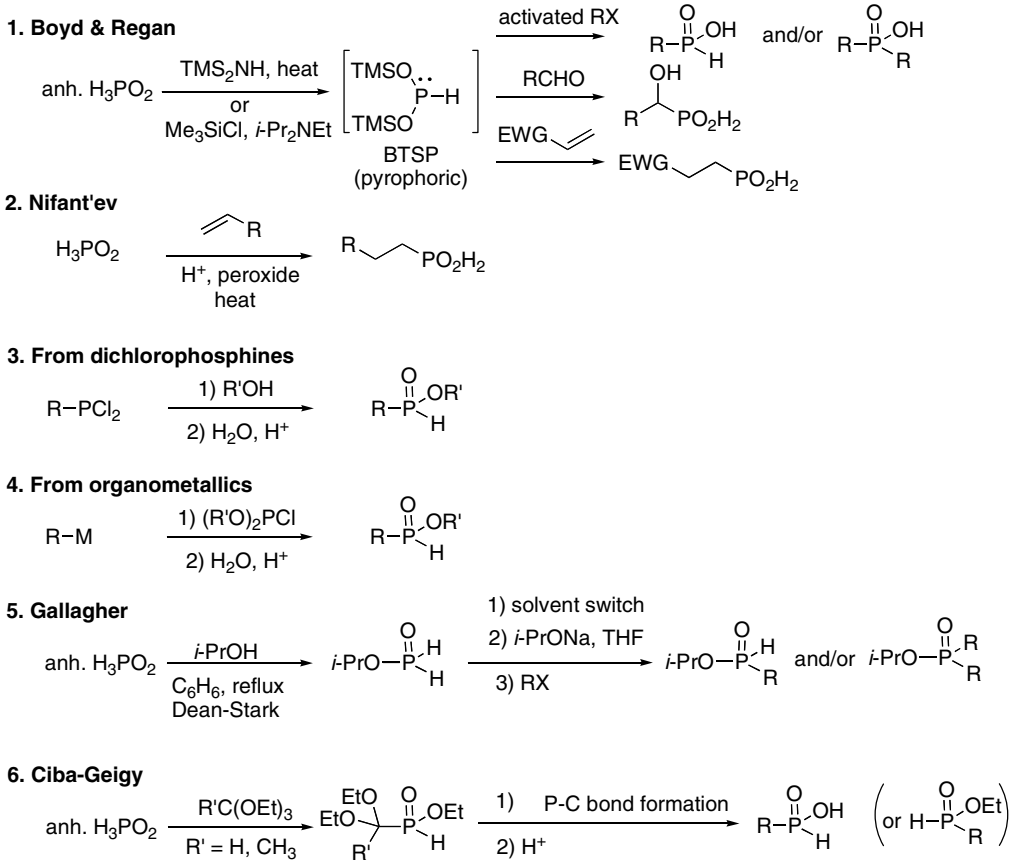
(1)

M = H, $PhNH_3$, NH_4
R = Me, Et, Bu, Allyl, Ph, Bn, *i*-Pr

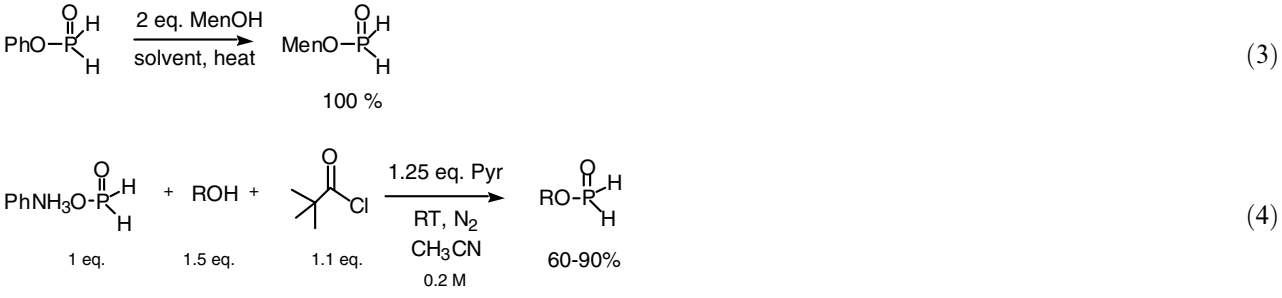


(2)

An important component of the methodologies we have developed, is the discovery of a novel preparation of alkyl phosphinates from hypophosphorous acid and its salts. Initially, we reported the selective esterification of H-phosphinic acids in the presence of dialkyl phosphinic acids using alkoxysilanes (Eq. (1)) [8]. This reaction is useful when a particular method gives a mixture of these two products which are otherwise difficult to separate, and it is also more convenient than most alternatives (CH_2N_2, or DCC/alcohol). We found that similar conditions can be applied to esterify hypophosphorous acid (and some salts) to provide alkyl phosphinates in high yield and in a variety of solvents (Eq. (2)) [9]. In addition, the alkyl phosphinates (which are used in situ) displayed unusual thermal stability, with only 10–20% decomposition at 85 °C for more than 20 h [9]. In fact, stock solutions of EtOP(O)H_2 in CH_3CN, THF, or toluene, were found to be stable at room temperature under nitrogen for over a month (less than 10% decomposition). Alkyl phosphinates for which the corresponding alkoxysilane is not commercially available can be prepared by transesterification of PhOP(O)H_2, or by a slightly modified Stawinski approach [10], using anilinium hypophosphite (AHP), PivCl, pyridine, and an alcohol (Eqs. (3) and (4), respectively). Finally, reaction of concentrated H_3PO_2 in CH_3CN with diphenyldiazomethane cleanly gives the corresponding benzhydryl phosphinate ($Ph_2CHOP(O)H_2$) [11]. The reaction of H_3PO_2 with diazoalkane was the first reported method to prepare alkyl phosphinates, but it is not commonly employed [12].

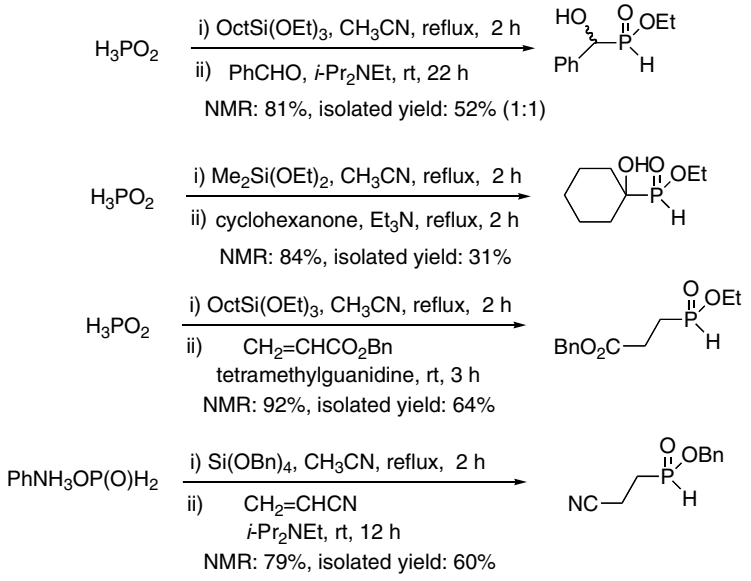


Scheme 2. Methods for the preparation of H-phosphinates.



2.2. Reactions of alkyl phosphinates with electrophiles

Alkyl phosphinates prepared by the alkoxysilane method react uneventfully with carbonyl compounds and Michael acceptors (Scheme 3) [9]. Gallagher has reported the only examples of alkylation with alkyl halides using *i*-PrOP(O)H_2/*i*-PrONa (Scheme 2, method 5) [6]. The lack of stability of the anions derived from alkyl phosphinates is well precedented [13], and the use of more hindered isopropyl phosphinate was considered essential to successful alkylation. We have found that alkyl phosphinates can be alkylated with BuLi at −78 °C, or with DBU at room temperature in acceptable yields (Scheme 4) [14]. While preliminary, these results show promise for the straightforward synthesis of a variety of H-phosphinate esters by alkylation. Nonetheless, significant improvements remain to be made, especially in the isolation procedure [15]. At this time, the DBU-promoted alkylation appears limited to the most reactive alkyl halides, but is very easy to conduct in practice.



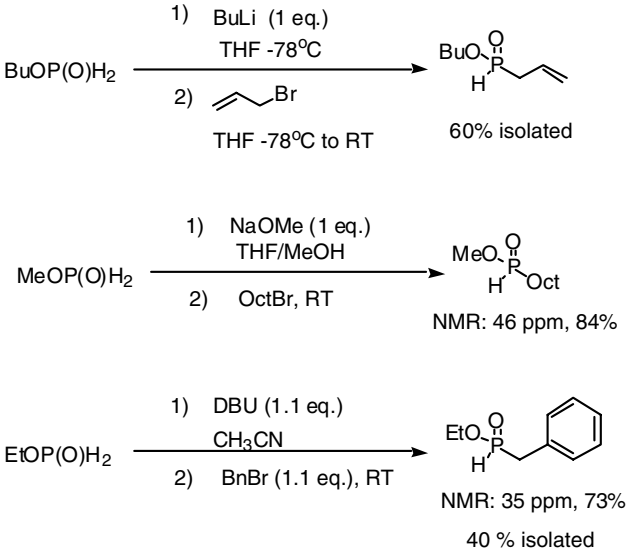
Scheme 3. Nucleophilic additions of alkyl phosphinates.

2.3. Palladium-catalyzed cross-coupling of anilinium hypophosphite (AHP) and alkyl phosphinates

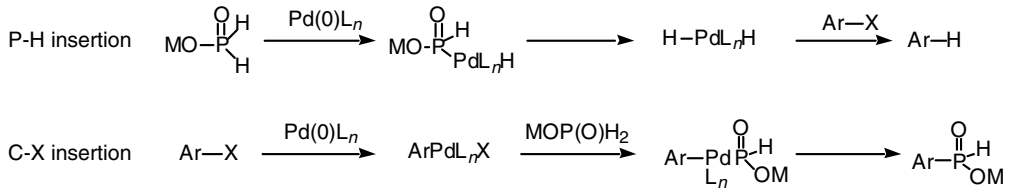
Schwabacher and co-workers [16] were first to report the palladium-catalyzed cross-coupling reaction of alkyl phosphinates with aryl iodides. Holt and Erb [17] reported one example of cross-coupling between triethylammonium hypophosphite and a steroid-derived dienyl triflate, but the generality of the reaction was not established. We, in turn, have investigated the palladium-catalyzed cross-coupling reactions of hypophosphorous compounds with a variety of electrophiles.

2.3.1. Cross-coupling reactions with AHP

Our initial contribution in this area dealt with the cross-coupling reactions of AHP [18], an easily prepared, relatively non-hygroscopic salt [19]. A major concern with the cross-coupling reactions of hypophosphorous compounds is the potential for competing transfer hydrogenation. Indeed, the preparatively useful transfer hydrogenation of alkenes, alkynes, aldehydes, ketones, and aryl halides is well precedented to take place with hypophosphorous acid or its sodium and amine salts, under the influence of virtually all transition-metals [20]. This reaction is believed to occur via insertion



Scheme 4. Alkylation of alkyl phosphinates.

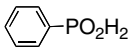
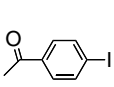
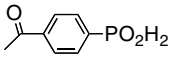
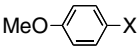
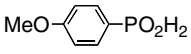
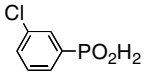
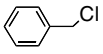
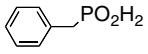
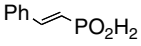
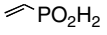
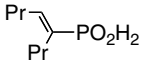
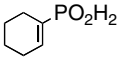


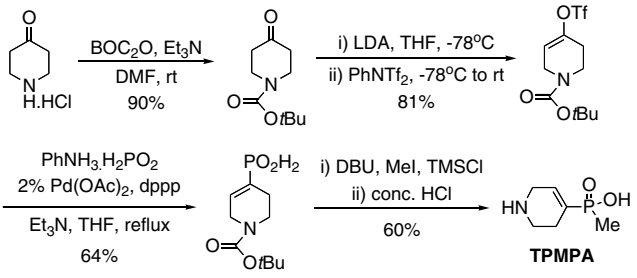
Scheme 5. Competing palladium insertion pathways.

of the metal into a P–H bond with subsequent formation of a metal hydride which is the catalytically active reducing agent. In order to achieve the desired P–C bond formation, the metal must instead insert into a C–X bond (Scheme 5). We expected that the ligands around the metal might control the relative rates of these two competing insertions.

As it turns out, even PPh_3 provides good control for cross-coupling over transfer hydrogenation with the more reactive aryl iodides, since palladium insertion into the C_{sp2}–I bond is facile [18]. However, the most general conditions employ dppp as the ligand [18]. With this ligand and $Pd(OAc)_2$, even substrates deactivated towards oxidative addition (for example bromoanisole) react in high yield. One example of a highly activated chloride was also reported [18]. However, we have not yet been able to employ unactivated aryl chlorides. With $Pd(OAc)_2$/dppp (2 mol% or less) as the catalyst, and Et_3N as the base, AHP successfully couples with aryl iodides, bromide, triflates,

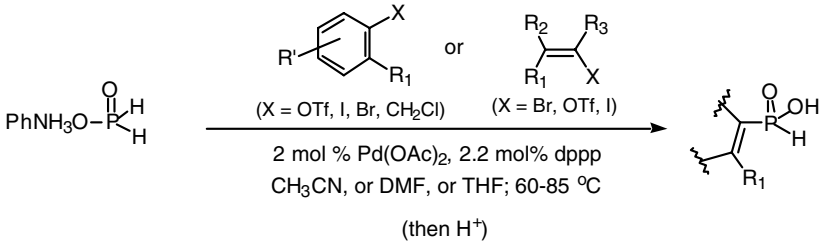
Table 1
Representative examples of the AHP coupling

Entry	Electrophile	H-phosphinate product	X	^{31}P NMR yield	Isolated yield
1			I Br OTf	97 81 81	87 – –
2			–	93	74
3			I Br	91 85	85 –
4			–	95	94
5			–	81	66
6			–	94	60
7			Br OTf	85 69	75 –
8			–	64	–
9			–	17	–
10			–	96	74



Scheme 6. AHP cross-coupling in the synthesis of TPMPA.

and with benzylic chlorides. Interestingly, the reaction still takes place to some extent without base, suggesting that the nucleophile is the P(III) form of the hypophosphorous compound. In addition, the reaction was quite tolerant to moisture and even to air, so that reagent grade solvents can be employed directly [18]. The reaction was then extended to include alkenyl electrophiles, particularly bromides and triflates [21]. Here also, dppp was found to be the ideal ligand, except with *Z*-substituted alkenyl halides for which dppf was superior. The palladium-catalyzed cross-coupling reaction of AHP with a variety of electrophiles (Eq. (5)) constitutes a useful P–C bond formation methodology and affords access to many H-phosphinates, which were previously difficult to obtain. Table 1 shows a few examples. This reaction was applied to the expeditious synthesis of the selective $GABA_C$ receptor antagonist (1,2,3,6-tetrahydropyridin-4-yl)-methyl phosphinic acid (TPMPA) (Scheme 6) [21]. The cross-coupling of AHP provides significant advantages over other approaches because the P–H bond of the intermediate H-phosphinate can be elaborated into a variety of compounds (Scheme 1).



(5)

2.3.2. Direct formation of H-phosphinate esters

More recently, we have focused on the Schwabacher-like cross-coupling of alkyl phosphinates. Schwabacher showed that aryl iodides can cross-couple successfully with $MeOP(O)H_2$ (prepared from $H_3PO_2/(MeO)_3CH$) but the scope was limited by transfer hydrogenation as well as the rapid thermal decomposition of methyl phosphinate [16a]. In subsequent work, the use of *t*-$BuOP(O)H_2$ was also demonstrated [16b]. Since our method to prepare alkyl phosphinates results in enhanced thermal stability, [9] the prospect of extending the Schwabacher cross-coupling seemed excellent. The combination of the AHP cross-coupling [18] with our selective esterification of H-phosphinic acids [8] would provide the same overall transformation. However, this two-step approach presents some problems: First, the manipulation is complicated by the fact that the intermediate phosphinate salts must be acidified prior to the esterification to obtain good yields of esters; and second, the esterification step often requires long reaction times (12–24 h). A single step process has obvious advantages, especially for substrates (such as nitrogen heterocycles) for which intermediate acidification is problematic, or for highly water-soluble H-phosphinic acids which cannot be extracted easily. The direct coupling of alkyl phosphinates provides H-phosphinate esters which can be purified by standard chromatographic techniques, and it minimizes manipulations and reaction time. We have found that alkyl phosphinates (prepared by the alkoxysilane method) couple successfully with aryl- and heteroaryl iodides, bromides, triflates, and benzylic chlorides (Eq. (6)) [22]. We have just extended the process to also include alkenyl halides [23]. Initially, DABCO was employed as the base, but generally Et_3N was found to give similar results. In some cases, the overall reaction may still proceed via the coupling of a salt followed by in situ esterification [22]. However, the HX which is produced during the coupling step must be essential to esterification, since the alkoxysilane esterification of pure H-phosphinate salts

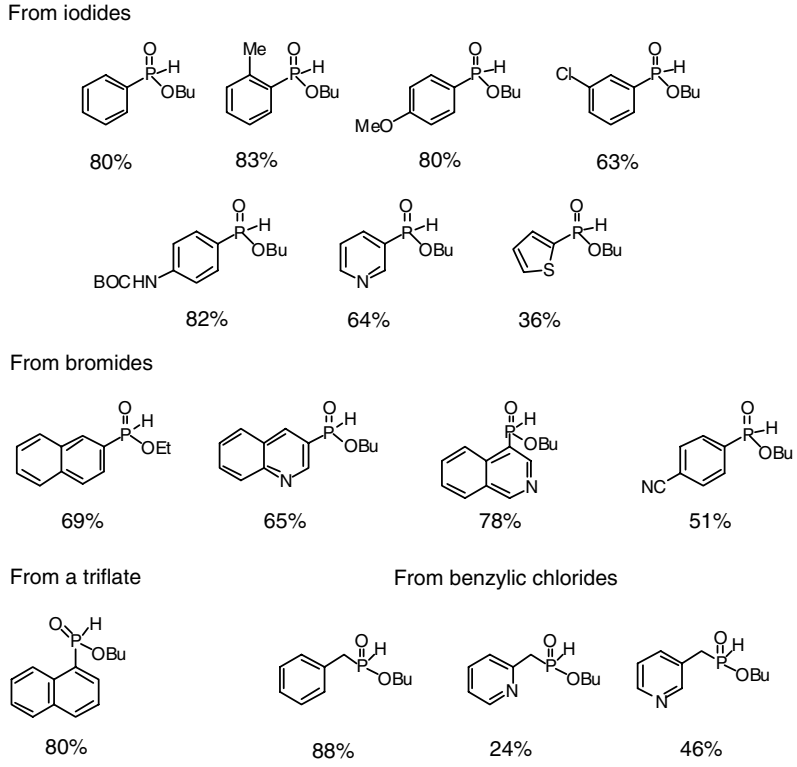
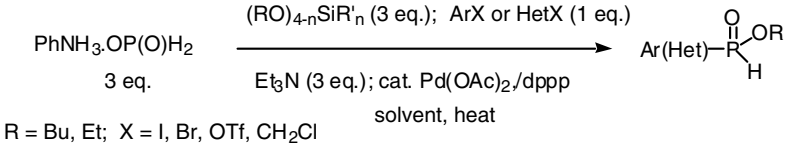


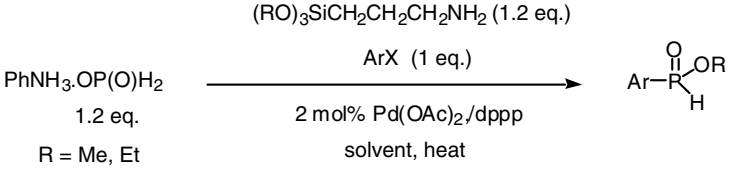
Chart 1. Synthesis of H-phosphinate esters via palladium-catalyzed cross-coupling.

is very inefficient [8]. At least in the case of aryl iodides, the cross-coupling appears to proceed in a single step (like in the identical Schwabacher reaction [16a]) since some reactions conducted in the absence of a base (and therefore without the possibility for the formation of a hypophosphite salt) occur in nearly quantitative yields. The mechanistic subtleties of the one-pot reaction are currently being examined [23].



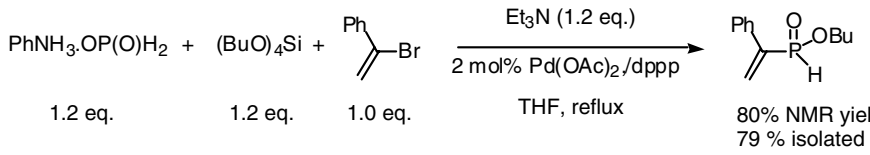
(6)

An interesting extension of the direct coupling was made with the use of aminosilicates (Eq. (7)) [22,23]. The commercially available 3-aminopropyltriethoxysilane serves three distinct purposes: it may act as the base for the palladium-catalyzed process (to shuttle from Pd(II) to Pd(0)), it provides the esterification reagent, and it simplifies the work-up since the silicate by-product can be removed by simple aqueous wash.



(7)

Some of the H-phosphinate esters synthesized are summarized in Chart 1 (all yields shown are isolated [15]). It should be noted that many of these compounds have never been prepared before. Thus the initial objective of expanding the scope of the Schwabacher coupling has now been accomplished, and a variety of H-aryl- and H-heteroarylphosphinates can be prepared conveniently in a single step. Finally, we have just extended this cross-coupling reaction to include alkenyl halides, and a full study is currently in progress [23]. A successful example is shown in Eq. (8).

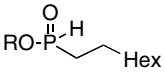
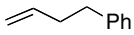
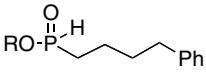
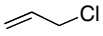
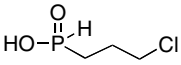
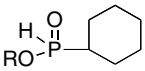
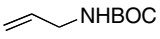
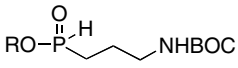
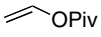
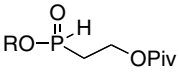
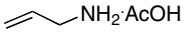
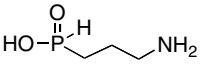
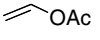
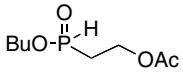
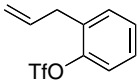
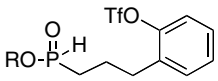


(8)

2.4. Radical reactions of hypophosphorous compounds

The addition of phosphorus-centered radicals to olefins has been known for several decades [24]. As early as 1955, Williams and Hamilton [25] investigated the use of aqueous H_3PO_2. Nifant'ev et al. [3] then significantly developed the reaction to the point where it has become a major preparative method for H-phosphinic acids. In fact, a slightly modified version of the Nifant'ev radical addition is used today in the manufacture of the heart drug Monopril [26]. In spite of the modern improvements in the reaction conditions [4] (AIBN initiator, refluxing EtOH), the medium is always strongly acidic and therefore not compatible with functionalized molecules.

Table 2
Scope of the radical hydrophosphinylation

Entry	Alkene	H-phosphinate product	R=	^{31}P NMR yield	Isolated yield
1			H	90	80[a]
			Me	–	96[b]
2			H	89	87[a]
			Me	85	55[d]
			Bu	76	65[c,e]
3			–	72	71[a]
4			H	96	86[a]
			Me	97	60[b]
			Bu	–	60[c]
5			H	100	51[a]
			Me	100	60[d]
6			H	77	49[a]
			Me	93	40[b]
7			–	100	42[a]
8			–	–	52[c]
9			H	82	80[a]
			Bu	62	59[c]

[a] Method A: (i) $NaH_2PO_2 \cdot H_2O$, alkene, Et_3B, air, MeOH, rt, 2 h and (ii) H^+.
[b] Method B: (i) conc. H_3PO_2, $(MeO)_3CH$, 1–2 h and (ii) dioxane, alkene, Et_3B, air, rt, 2 h.
[c] Method C: (i) aq. H_3PO_2, BuOH, cyclohexane, reflux, Dean–Stark trap, 4–6 h and (ii) alkene, Et_3B, air, rt, 2 h.
[d] Method D: (i) conc. H_3PO_2, $(MeO)_3SiCH_2CH_2CH_2NH_2$.TFA, CH_3CN, reflux, 2 h and (ii) alkene, Et_3B, air, rt, 2 h.
[e] Method E: (i) conc. H_3PO_2, $(BuO)_4Si$, cyclohexane or CH_3CN, reflux, 2 h and (ii) alkene, Et_3B, air, rt, 2 h.

To solve this significant limitation, we have developed a room-temperature radical hydrophosphinylation reaction, which proceeds under very mild conditions and has a broad scope [27]. Our process is based on the initiation of the radical reaction through trialkylboranes autooxidation. Alkyl radicals are then sufficiently reactive to form the desired hypophosphorous radical and to maintain a viable chain reaction at low temperature. In the classical thermal reaction, multiple additions of the initiator are always required.

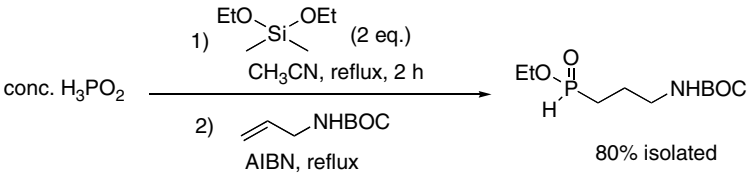
2.4.1. Alkenes

Using trialkylboranes (usually a commercial solution of Et_3B in hexane or THF) in an open reaction vessel successfully initiates the addition of hypophosphorous compounds to alkenes. Hypophosphorous acid, its salts (including AHP and NaH_2PO_2), and even alkyl phosphinates can be added to alkenes at room temperature [27]. With alkyl phosphinates, a substoichiometric amount of R_3B is sufficient to achieve good yields of addition, but the other starting materials are best used with 0.5–1.0 equivalent of R_3B. In our initial work [27], the alkyl phosphinates were prepared by the orthoformate method [28] (Fitch), or by the Dean–Stark method [29] (Nifant'ev), and thus were more sensitive to decomposition, or limited to a small set of solvents. Since then, we found our alkoxysilane method to be superior, both in terms of convenience and generality (alkyl group, reaction solvent) [9]. The radical-based hydrophosphinylation [27] has a very broad scope (Table 2) and is conveniently run at room temperature and in an open flask, thus making it an experimentally straightforward reaction which can be easily scaled-up. The reactions are usually complete in less than two hours. Nifant'ev and Koroteev [30] had studied the reaction of NaH_2PO_2 under neutral conditions, but this required multiple addition of a peroxide initiator in an autoclave, at high temperature.

For the first time, we have been able to prepare H-phosphinates in high yields from both acid- and base-sensitive alkenes (enol ethers, enol esters, and BOC-protected amines) [27]. Alkyl phosphinates are themselves sensitive to moisture and air, but the conditions we employ are sufficiently mild, and the reaction times sufficiently short, for decomposition to not be a major problem. Even alkyl chlorides, which would normally be reduced above ambient temperature, are well-tolerated, however, bromides are reduced under our conditions. A feature of the reaction is its very high selectivity for the formation of H-phosphinates: even when excess alkene is employed, the disubstituted phosphinates are minor products. This indicates the much higher reactivity toward radical formation of the phosphinylidene group (P(O)H) in hypophosphorous compounds over H-phosphinates. The only type of H-phosphinate ester which reacted in preparatively useful yield was PhP(O)(OR)H, but this has not been investigated thoroughly. The thermal radical reaction of H-phosphinate esters is also well known and has often been used to prepare disubstituted phosphinate esters.

A limitation of our radical hydrophosphinylation is the apparent electrophilicity of the P-centered radicals, so that polar electron-poor alkenes (such as Michael acceptors), and other substrates which give stabilized radicals (such as styrene) are mediocre substrates. In the case of allyltributyltin, we demonstrated a recycling stratagem which employed cyclohexyl bromide as a shuttle to improve chain propagation [27]. With Michael acceptors, the addition of $ROP(O)H_2$ can be conducted under basic conditions (Scheme 3), so the radical reaction is unnecessary.

With our new alkoxysilane methodology for the preparation of alkyl phosphinates, thermal decomposition is minimal even over an extended period of time [9]. Thus, more classical reaction conditions using AIBN could be contemplated. Although we have not yet conducted a full study of these conditions, the use of AIBN in refluxing CH_3CN gives satisfactory results, as shown in Eq. (9) [31].



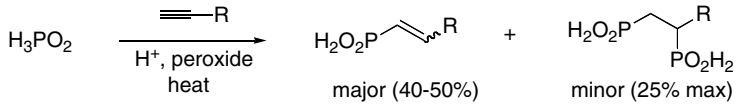
(9)

We have also studied the reactivity of 1,1-difluoroolefins to see if the corresponding α,α-difluorophosphinates could be prepared and serve as phosphate analogs. Unfortunately, although P–C bond-formation does occur, poor regiocontrol and variable amounts of reduction products were observed [32]. Improvements may still be possible, but it is unlikely this reaction may be developed into a generally applicable approach, unless regiocontrol can be improved. We have not yet tested all the possibilities with regards to the choice of hypophosphorous compound, or conditions (AIBN vs Et_3B). 1-Fluoroolefins have not been tried.

2.4.2. Alkynes

Once the radical hydrophosphinylation of alkenes developed, we turned our attention to alkynes. Nifant'ev, once again, had pioneered the hydrophosphinylation of alkynes using his conditions (Eq. (10)) [33]. Alkenyl-H-phosphinic

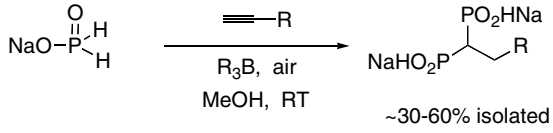
acids were always the major products (formed as a ~2:1 *trans*/*cis* mixture), and 1,2-bis-H-phosphinic acids were produced in variable but minor amounts.



(10)

Our palladium-catalyzed cross-coupling reaction [18,23] provides an alternative approach to alkenyl-H-phosphinates, especially because of its stereospecificity. It was hoped, however, that the radical reaction conducted at room temperature may lead to increased selectivity over the Nifant'ev approach. In addition, since we are able to use a broad range of hypophosphorous compounds as starting materials, we thought our radical reaction may lead to a useful P–C bond-forming reaction with alkynes. Our work in this area has not yet been published, except for some data contained in a patent application [34].

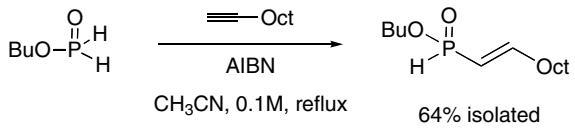
The most interesting starting material turned out to be NaH_2PO_2. Under conditions identical to those developed for alkenes ($NaH_2PO_2 \cdot H_2O$, MeOH, Et_3B, RT), the previously unknown 1,1-bis-H-phosphinates were produced from terminal alkynes (Eq. (11)) [34,35]. The formation of these compounds was completely unexpected, in light of the above-mentioned



(11)

literature precedent from Nifant'ev et al. [33]. Besides the fact that the reaction is trivial to run (as was the case with alkenes [27]), an added bonus is that disodium 1,1-bis-H-phosphinate salts spontaneously precipitate from the reaction mixture. This property seems to hold throughout the substrates we have investigated to date and provides a simple method to purify the products by filtration (and with a methanol wash if residual NaH_2PO_2 is present). The yields are generally moderate (30–60%), but this is compensated by the fact that reaction and purification are so straightforward. In addition, the yields can sometimes be improved by adjusting the number of equivalents of NaH_2PO_2, the concentration, and by using co-solvents to modulate solubility. Regardless of the terminal alkyne employed, the soluble portion of the reaction mixture generally contains only traces of other products deriving from P–C bond formation [35].

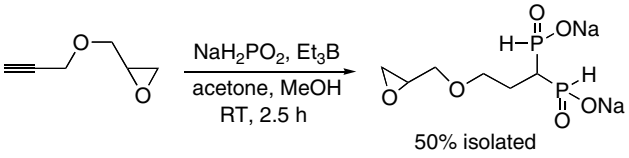
Interestingly, AHP leads mostly to the soluble 1,2-bis-H-phosphinates in good yields. The reason for the difference between AHP and NaH_2PO_2 is not completely clear at this time, but mechanistic issues are currently being investigated. Alkyl phosphinates react to give mixtures of *trans*/*cis* H-alkenylphosphinate stereoisomers with either the Et_3B or the thermal, AIBN-initiated protocol, and alkenyl-H-phosphinates can be obtained in reasonable yield (Eq. (12)) [31]. This may point to both steric and electronic factors influencing the course of the reaction, as bis-addition is not observed with the alkyl phosphinates.



(12)

Our radical hydrophosphinylation of alkynes gives potentially valuable products. The most important of these are undoubtedly the novel 1,1-bis-H-phosphinates, because those are precursors to the corresponding 1,1-bisphosphonates [36] via oxidation (H_2O_2, bleach). 1,1-Bisphosphonates are important medicinally, for example in the treatment of bone-related diseases [37]. Various molecules (drugs, proteins) have also been conjugated to 1,1-bisphosphonates for bone-targeting, but the syntheses of these conjugates typically require multistep sequences and protection–deprotection strategies [38]. Since the conditions for our radical hydrophosphinylation with NaH_2PO_2 are so mild, complex alkynes can be employed and conjugation can be conducted as the penultimate step (before oxidation) without resorting to phosphonate protecting groups. The oxidation of the H-phosphinate to the phosphonate is also very mild and should be compatible with many complex molecules. Alternatively, 1,1-bis-H-phosphinates with a reactive tether for subsequent conjugation can be synthesized. An example is shown in Eq. (13). Thus, the new reaction may constitute an original and expeditious approach toward biologically relevant bisphos-

phonates. Research along these lines is being actively pursued and includes plans to study the reaction in aqueous media. The 1,2-bis-H-phosphinates (obtained with AHP) may also be interesting, but as far as we know, these compounds have not been tested as pyrophosphate analogs.



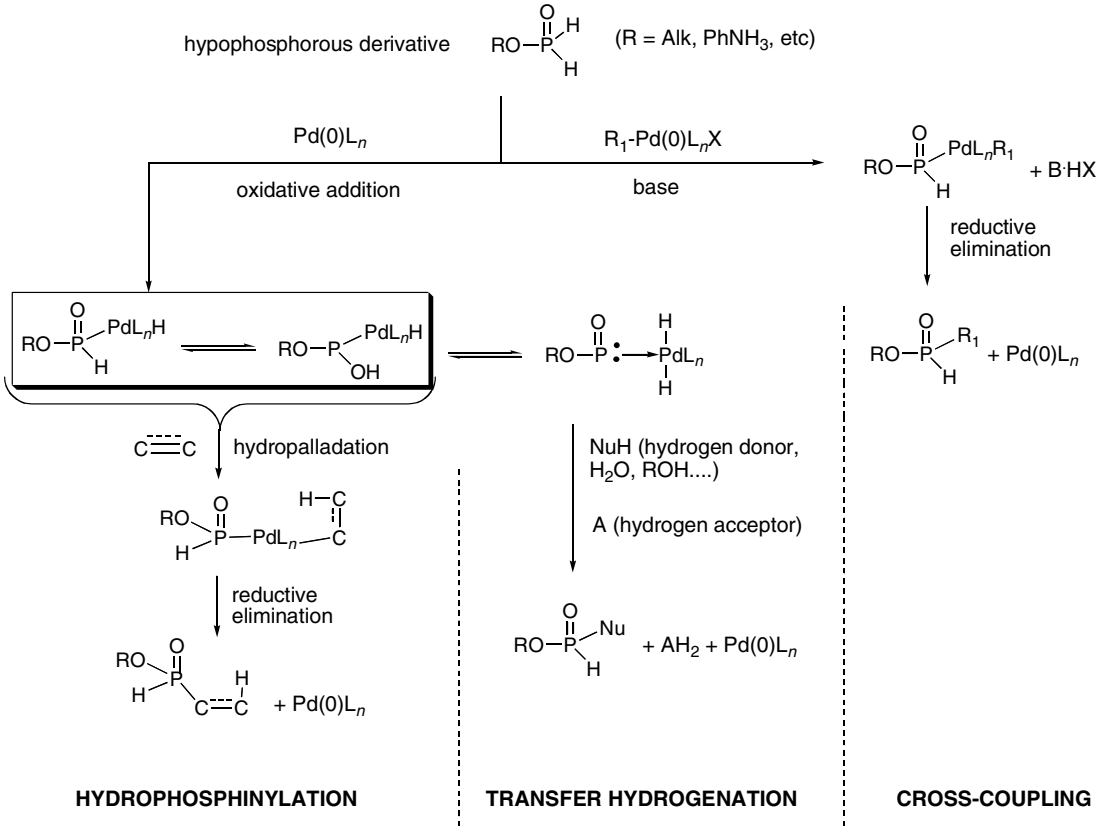
(13)

2.5. Palladium-catalyzed hydrophosphinylation

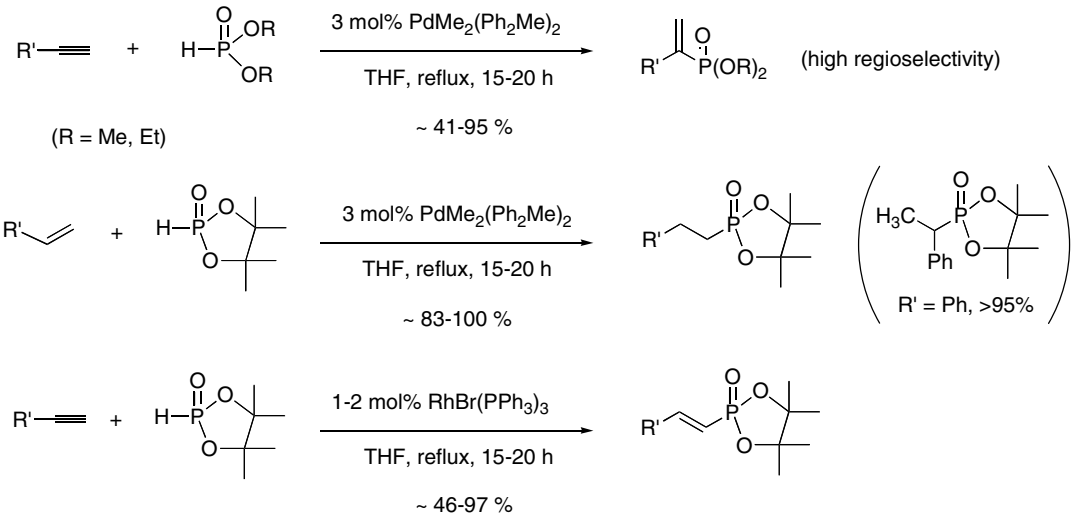
2.5.1. Homogeneous catalysis

During our work on the cross-coupling reactions of hypophosphorous compounds, [18,21] we realized that the competing transfer hydrogenation [20] pathway (Scheme 5) could provide unique synthetic opportunities for catalytic P–C bond formation, if the reactivity of the postulated phosphinyl palladium hydride intermediate (boxed structures in Scheme 7) could be harnessed before its decomposition to a palladium dihydride species. It was thought that the ligand could control the lifetime and reactivity of this species. This mechanism-based idea (Scheme 7), perhaps simplistic, turned out to be correct, at least in practice, and we were able to develop a unique catalytic P–C bond-forming reaction [39].

Prior to this, Tanaka had reported the catalytic hydrophosphonylation of alkenes and alkynes with H-phosphonates (Scheme 8), using palladium- and rhodium-based catalysts [40]. There are many theoretical and practical differences between Tanaka's hydrophosphonylation and our hydrophosphinylation, much like there are significant differences between the cross-coupling of H-phosphonates and the Schwabacher coupling of an alkyl phosphinate. An important theoretical distinction is the much higher reducing power of hypophosphorous compounds relative



Scheme 7. Mechanistic pathways in the Pd-catalyzed reactions of $ROP(O)H_2$.



Scheme 8. Tanaka hydrophosphonylation of alkenes and alkynes.

to H-phosphonates, while in practice H-phosphinate products are considerably more versatile intermediates than are phosphonates.

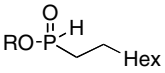
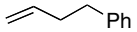
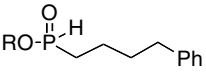
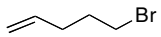
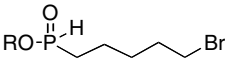
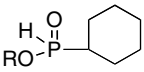
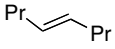
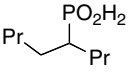
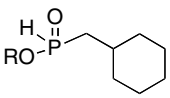
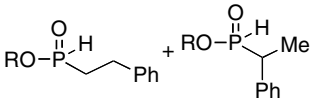
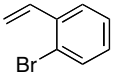
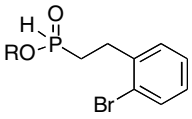
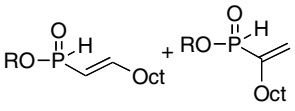
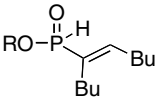
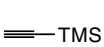
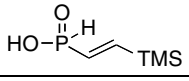
Tanaka established the insertion of palladium into the P–H bond of H-phosphonates, but this insertion was certainly not a surprise with H-phosphinates, considering the large body of literature on the transfer hydrogenation of H_3PO_2 and its derivatives, and our cross-coupling work. In addition, Tanaka's reaction uses relatively elaborate catalysts and with alkenes the hydrophosphonylation is limited to pinacol H-phosphonate. The latter is a significant limitation because the pinacol phosphonate esters require harsh conditions for cleavage [41]. Therefore the overall approach may not provide significant advantages over the classical Arbuzov or Michaelis–Becker phosphonate syntheses.

Our hydrophosphinylation reaction turns out to be very general and practical, and a variety of catalysts can be employed. While much of this work remains unpublished, we have already reported in a communication the successful reaction of H_3PO_2, AHP, and alkyl phosphinates with both alkenes and alkynes [39]. Some dienes and allenes also react [31]. Excellent selectivity for hydrophosphinylation is always observed, even though H-phosphonates [$(RO)_2P(O)H$] are present in the reaction mixture due to the catalyzed (and uncatalyzed) decomposition of the hypophosphorous starting materials. Even with alkynes, the Tanaka-like addition of these side-products [40a] is not observed. Several ligands were found to be capable of steering the reaction toward addition instead of transfer hydrogenation. N-Heterocyclic carbene (NHC) ligands can be employed [11] to give high yields of hydrophosphinylation (>80% yield), but some phosphine ligands remain superior (~100% yield). The two best ligands seem to be xantphos and dppf, but many other ligands which have been tested still deliver H-phosphinates in good yields when alkyl phosphinates are employed. For example, $Cl_2Pd(PPh_3)_2$/2 MeLi is quite successful, and we have since found that MeLi is often not necessary, and similarly high yields can be observed in its absence. Alkyl phosphinates are sufficiently strong reducing agents to generate the reactive Pd(0) catalyst from a variety of Pd(II) precatalysts (this was certainly established in the case of the base-free cross-coupling we mentioned earlier), and a variety of palladium sources can be employed ($PdCl_2$, $Pd(OAc)_2$, Pd_2dba_3, and Pd–C). Xantphos emerged as perhaps the most widely useful ligand to conduct the addition reaction with all the hypophosphorous compounds investigated. In fact, suppression of the transfer hydrogenation is so efficient that even aqueous H_3PO_2 can be employed. Very low catalyst loadings (as little as 0.02 mol% Pd) still provide good conversions [39].

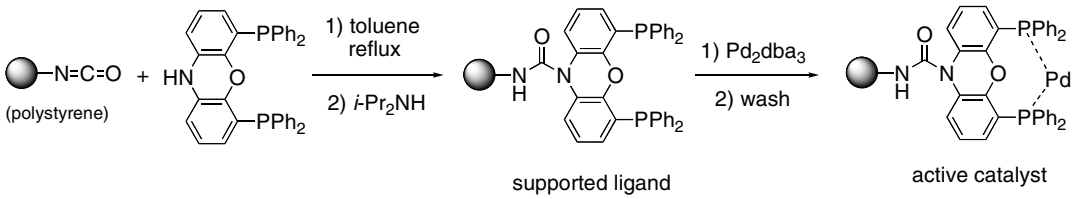
In many instances, the reaction can be conducted at room temperature.

Table 3 shows some examples of the Pd-catalyzed hydrophosphinylation. 1,2-Disubstituted alkenes are poor substrates, possibly because of the reversible dehydropalladation. In this case, radical hydrophosphinylation [27] is complementary in its scope and can be used instead. Functional groups are well-tolerated, and in the case of terminal alkynes, useful selectivity can be observed. This selectivity can be controlled depending on the catalyst employed: Pd/xantphos or Pd/dppf give the linear product (>3:1), whereas $Cl_2Pd(PPh_3)_2$/2MeLi gives the branched isomer (Eq. (14)).

Table 3
Palladium-catalyzed hydrophosphinylation[a]

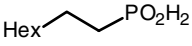
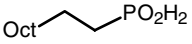
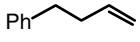
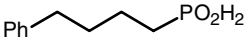
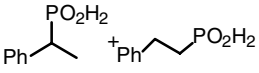
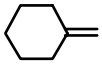
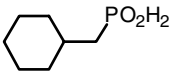
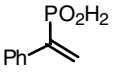
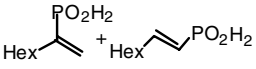
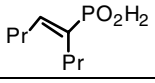
Entry	Alkene	H-phosphinate product	R=	^{31}P NMR yield	Isolated yield
1			H Bu	100 89	67[b] 76
2			H Et $PhNH_3$	100 100 100	92 84 –
3			H Et	100 100	83[b] 61
4			H Et	0 10	– –
5			–	45	–
6			H Bu	100 42	93 –
7			Bu	100	69 (4.4:1)
8			H Bu	100 81	81 –
9			Et Bu	75 78 (5:1)	70 (3.7:1) –
10			H Bu	100 35	88 –
11			–	64	57

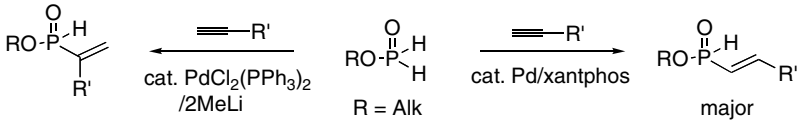
[a] All reactions were catalyzed by 0.025–0.5 mol% Pd_2dba_3, and 0.06–1.2 mol% xantphos in refluxing CH_3CN. Alkyl phosphinates $ROP(O)H_2$ (1.5 eq.) were prepared as shown in Eq. (2), using $(BuO)_4Si$ or $(EtO)_2SiMe_2$.
[b] Conducted at room temperature.



Scheme 9. Preparation of the polymer-supported catalyst.

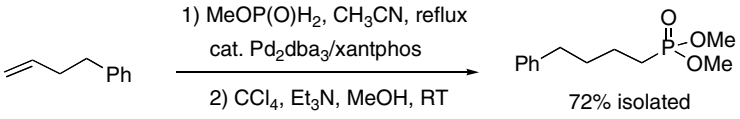
Table 4
Hydrophosphinylation with the heterogeneous catalyst

Entry	Substrate	Product	H_3PO_2	Conditions	Runs	Isolated yield%
1			50% aq	Reflux, N_2CH_3CN	3	70
2			50% aq	Reflux, N_2CH_3CN	4	50
3			50% aq	Reflux, N_2CH_3CN	3	96
4			50% aq	Reflux, N_2CH_3CN	5	90 (2:1)
5			conc.	Reflux, N_2CH_3CN	1	92
6			conc.	RT, N_2CH_3CN	1	42
7			conc.	Reflux, N_2CH_3CN	1	53 (2:1)
8			conc.	Reflux, N_2CH_3CN	1	46



(14)

The power of the Pd-catalyzed hydrophosphinylation lies in its broad scope as well as the synthetic flexibility provided by the H-phosphinate products (Scheme 1). For example, phosphonates can be obtained simply through known methods, as seen in Eq. (15). Tanaka's reaction would give the corresponding pinacol phosphonate which then requires manipulations for cleavage or transesterification [41]. Other more interesting tandem reactions for a second P–C bond formation in one pot are being studied.



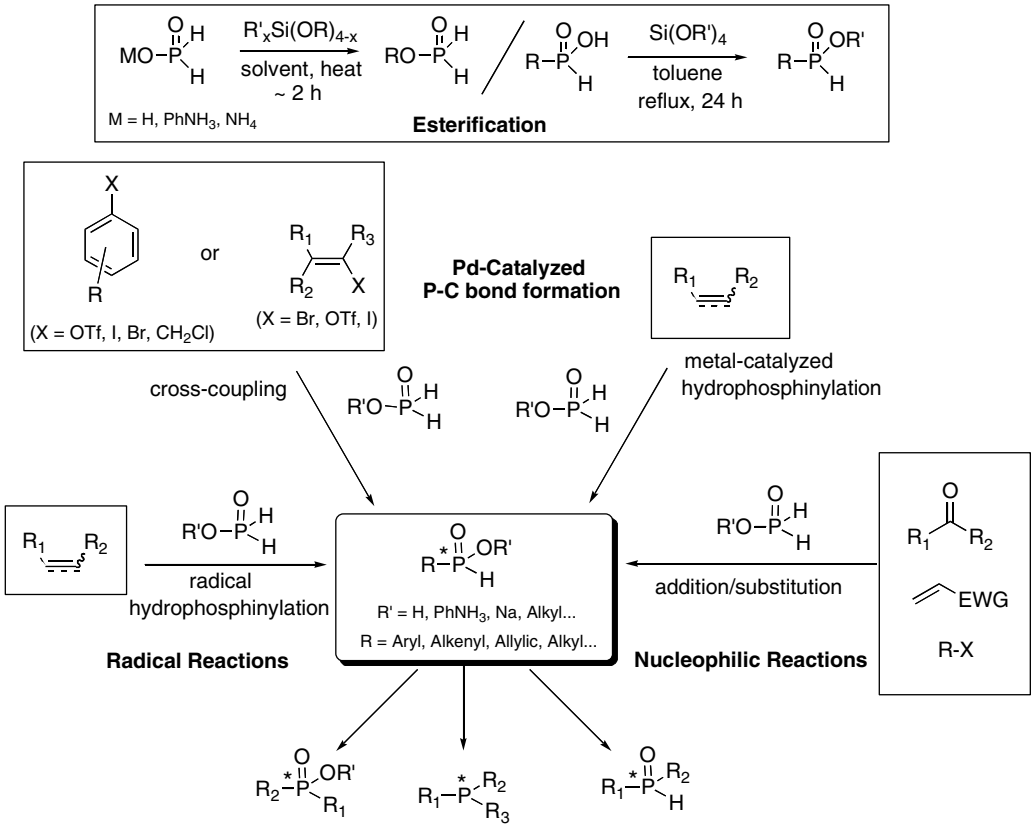
(15)

2.5.2. Heterogeneous catalysis

We have also developed a polymer-supported hydrophosphinylation catalyst [42]. Even if low catalyst loadings can be employed in the homogeneous version of the reaction (ca. 1 mol% Pd or less), palladium remains expensive and recycling is always desirable. The use of heterogeneous catalysts allows the recovery of the metal and simplifies purification. We already knew that palladium on carbon gives satisfactory result when xantphos is added [39]. However, even if xantphos is inexpensive and easy to prepare, a fully reusable catalyst would be ideal. We focused more particularly on the reaction of hypophosphorous acid, and we wanted an easily prepared and robust catalyst to maximize the possibility for application in other laboratories. We settled on a polystyrene framework to prepare a polymer-supported ligand in a single step from commercially available starting materials (Scheme 9) [43]. The active catalyst is obtained by treating the ligand with Pd_2dba_3 either in situ, or in a separate step. The resulting catalyst is air stable and does not require special handling precautions [42].

Hydrophosphinylation with hypophosphorous compounds takes place in good yield with the polymer-supported catalyst (Table 4). The scope is narrower than with the homogeneous system, particularly with alkynes. However, multiple runs can be conducted without addition of palladium. The polymer catalyst is also more air and water tolerant than its homogeneous counterpart, and provides an environmentally friendly synthesis of H-phosphinic acids from aqueous H_3PO_2. The ligand can even be employed with palladium on carbon to furnish a doubly heterogeneous reusable catalyst [42]. Since the reaction can be conducted under mild conditions (sometimes at room temperature) and in the presence of water and even air, and since the H-phosphinic acid products can be obtained in good purity via a simple extractive work-up, possible future applications include the preparation of radiolabeled organophosphorus compounds from T_3PO_2 or even H_3 [32]PO_2. We have shown that the polymeric catalyst can be employed to conduct deuteration of alkenes and alkynes (75–90% D-incorporation) [42].

The homogeneous and heterogeneous palladium-catalyzed hydrophosphinylation of unsaturated compounds provide a novel P–C bond forming reaction of broad applicability. The scope and mechanism of this reaction continue



Scheme 10. Methodological summary.

to be delineated and improvements remain to be made. In addition, the uses of chiral auxiliaries and chiral catalysts are also being investigated, particularly in the context of P-chiral compound synthesis [44]. Since chiral auxiliaries have generally been developed to induce diastereofacial differentiation, we are faced with the problem of finding an efficient auxiliary for a tetrahedral structure instead of a planar one. This will require designing an auxiliary for our specific purpose. Nonetheless, some encouraging results have been secured.

3. Conclusions and future directions

Several new methodologies for the preparation of H-phosphinic acids and esters have been and continue to be developed in our laboratory (Scheme 10). These reactions provide general methods for phosphorus–carbon bond formation which are valuable not only for the synthesis of H-phosphinates but also for a variety of other organophosphorus compounds which can be derived from them [1]. H-Phosphinates are ideal synthons in organophosphorus chemistry, but their use has been hampered by the paucity of synthetic methodology available. It is hoped that the synthetic potential of H-phosphinates will be more fully exploited once practical and general methods are available for their synthesis.

Practical and scalable reactions are the key to both academic and industrial applications. Our ultimate objective is to develop approaches for the preparation of virtually any H-phosphinate using chemistry which can be conducted in any laboratory with standard equipment and widely available, inexpensive, reagents and catalysts. In the past months, we have discovered a ligand-free $NiCl_2$-catalyzed hydrophosphinylation of alkynes with alkyl phosphinates [45,46]. This reaction bridges the gap which existed in the low-yielding Pd-catalyzed hydrophosphinylation of internal alkynes with alkyl phosphinates (see Table 3, entry 10). These results will be communicated in the near future [45]. We have also found that a number of our reactions can be conducted with microwave irradiation to furnish high yields of products in minutes.

Several reactions have been developed in our laboratory (Scheme 10) and the arsenal of phosphorus–carbon forming reactions continues to expand. Several methodological and synthetic opportunities are being created for new research. Perhaps the most intriguing and challenging one is in asymmetric synthesis. Because the configurational stability of P-chiral H-phosphinates has been previously established [47] future work will focus on the development of asymmetric versions for the reactions outlined in this account. The synthesis of P-chiral compounds remains a major frontier in organophosphorus chemistry, and while many obstacles remain, we are optimistic that, in time, they will be overcome.

Acknowledgments

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