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Recent Developments in the Addition of Phosphinylidene-Containing Compounds to Unactivated Unsaturated Hydrocarbons: Phosphorus–Carbon Bond Formation by Hydrophosphinylation and Related Processes

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Keywords: Hydrophosphinylation / Phosphaalkenes / Phosphanes / Phosphorus / Phosphonates / Phosphinates

The reactions of phosphinylidene-containing compounds with *unactivated* unsaturated hydrocarbons are reviewed. The review is organized by phosphorus-containing functional group types. Free-radical and metal-catalyzed additions of $R^1R^2P(O)H$ to alkenes, alkynes, and related compounds deliver functionalized organophosphorus compounds $RP(O)R^1R^2$, including *H*-phosphinates, phosphinates, tertiary phosphane oxides, and phosphonates. The review covers the literature up to February 2008.

Outline

1. Introduction

Phosphorus–carbon bond-forming reactions have been the object of intense interest in recent years.[1] This review specifically covers reactions in which a phosphinylidene [P(=O)H] functionality[2] is added to an unactivated unsaturated hydrocarbon under various conditions, including transition-metal catalysis and free-radical processes. Additions to carbonyls, imines, and Michael acceptors and cross-coupling processes are not covered in this review.[3] Hydrophosphination[1c] (the addition of R^1R^2PH) and related reactions are also beyond the scope of the review.

The review is organized by phosphorus functionalities on the basis the degree of oxidation. Additions of a phosphorus atom bonded to one or two oxygen atoms are termed hydrophosphinylations, whereas hydrophosphonylation involves addition of a phosphorus atom bonded to three oxygen atoms (Scheme 1). The literature sometimes uses the term "hydrophosphorylation", but we feel this term is a misnomer for a P–C bond-forming reaction and is better adapted to the formation of P–O–C motifs. However, the relevant results have been included in this review.

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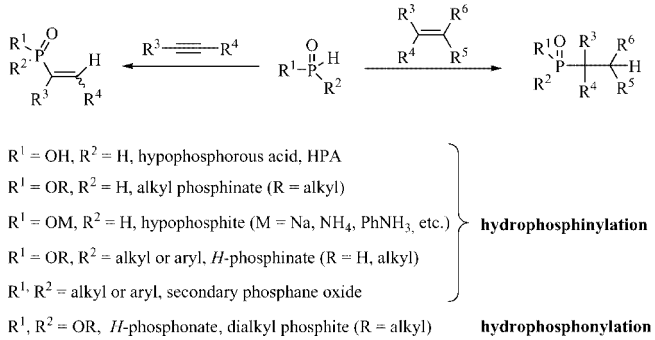
Laëtitia Coudray was born in 1978 in Blois, France. She received a Doctorate of Pharmacy in 2002 from the Université Paris XI, France. She conducted research at the Institut de Chimie des Substances Naturelles (ICSN), under the supervision of Dr. Joëlle Dubois, and she obtained a Ph.D. in Chemistry in 2005 from the Université Paris XI, France. She is currently pursuing post-doctoral research at Texas Christian University as a member of the Dr. Jean-Luc Montchamp team. Her research focuses on the development of new phosphorus–oxygen and phosphorus–carbon bond formations and the synthesis of small phosphorus-containing compounds with biological interests.

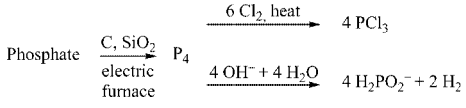
Jean-Luc Montchamp was born in Lyon, France. He completed his undergraduate studies at the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL), now known as CPE. He obtained his Ph.D. from Purdue University in 1992, under the direction of Professor John W. Frost. After some postdoctoral experiences at Michigan State University, and at the Scripps Research Institute, he returned to Purdue University for a postdoctoral stint with Professor Ei-ichi Negishi. He became Assistant Professor at Texas Christian University in 1998 and was promoted to Associate Professor in 2004. His research interests include the development of methodology for phosphorus–carbon bond formation, especially by using hypophosphorous derivatives, and the medicinal chemistry of phosphorus-containing compounds.



Scheme 1. Hydrophosphinylation and hydrophosphonylation reactions.

2. Addition of Phosphinates (RO)P(O)H_2

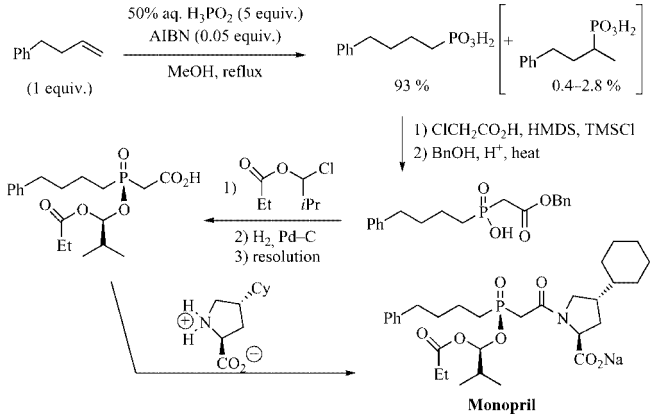
Phosphinates are derivatives of hypophosphorous acid (H_3PO_2, HPA, phosphinic acid). They include salts of the parent acid, as well as its esters.[4] Hypophosphorous acid is an industrial commodity and is sold as aqueous solutions.[5] It is prepared from elemental white phosphorus (P_4) through reaction with an inorganic base, followed by acidification (Scheme 2). HPA and its salts are therefore readily available, and their preparation is much more environmentally benign than that of phosphorus trichloride (P_4 + Cl_2 + heat), which is the precursor of many organophosphorus reagents currently used in P–C bond forming reactions, even if the chlorine atoms are typically not part of the final products (Scheme 2). Hypophosphorous derivatives are also more easily handled and less toxic than white phosphorus. With this in mind, methodologies based on HPA for the preparation of P–C bonds are nearly ideal and most atom economical. They also provide added flexibility in terms of the organophosphorus functionalities accessible from the same intermediate. In that sense, *H*-phosphinate derivatives are rather unique in that they possess an oxidation state in the middle of the range and can be derivatized into a plethora of other important functional groups.[6]



Scheme 2. Industrial preparation of phosphorus trichloride and hypophosphites.

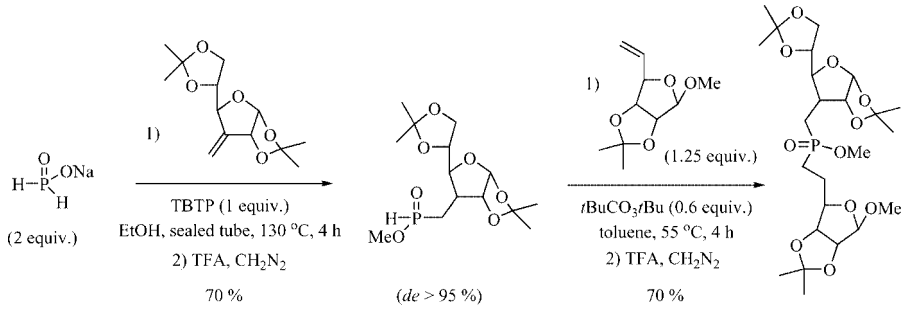
2.1. Alkenes

The addition of HPA to olefins under radical conditions was described in 1955 by Williams and Hamilton.[7] Some improvements and extension in scope were subsequently made, chiefly by Nifant'ev.[8] A modification of these conditions is currently used industrially for the side-chain preparation of the drug Monopril (Scheme 3).[9] Sodium hypophosphite has also been used directly in radical reactions, although its low solubility in organic solvents and the need for high initiation temperatures and large amounts of initiator make this reaction impractical. With alkyl hypophosphites, disubstitution is also often observed, as the harsh conditions are able to activate the intermediate *H*-phosphinate for further reaction (see Section 3).[10] In spite of this, Piettre reported an interesting study of this radical process for the synthesis of a DNA-dimer analog (Scheme 4).[11] The radical chain reactions of hypophosphorous compounds are generally inefficient.[12]

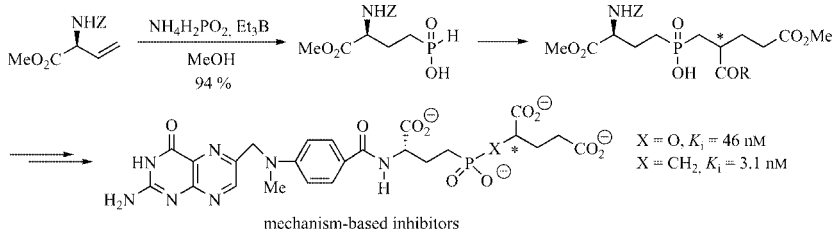


Scheme 3. Preparation of Monopril (Fosinopril).

A few years ago, we reported novel conditions to effect the radical addition of hypophosphorous derivatives under neutral conditions and at room temperature by using a trialkylborane and air as the initiator.[13] This reaction has a broad scope in terms of alkene and phosphinate reagent. Excellent selectivity for monoaddition is observed, even when an excess amount of the alkene is employed. The particularly mild conditions allow the presence of a variety of functional groups in the alkene substrate. Even alkyl phosphinates can be used as the phosphorus partners. In this



Scheme 4. Piettre's synthesis of a DNA dimer.



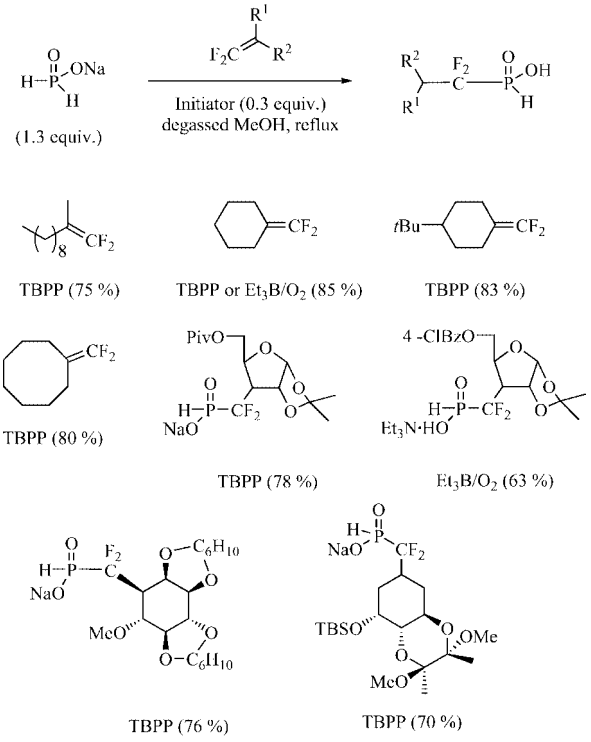
Scheme 5. Coward's radical hydrophosphinylation of vinylglycine.

particular case, a lower amount of initiator is satisfactory.[13] Sodium, anilinium, and ammonium hypophosphites are all useful reagents to hydrophosphinylate alkenes under radical conditions.

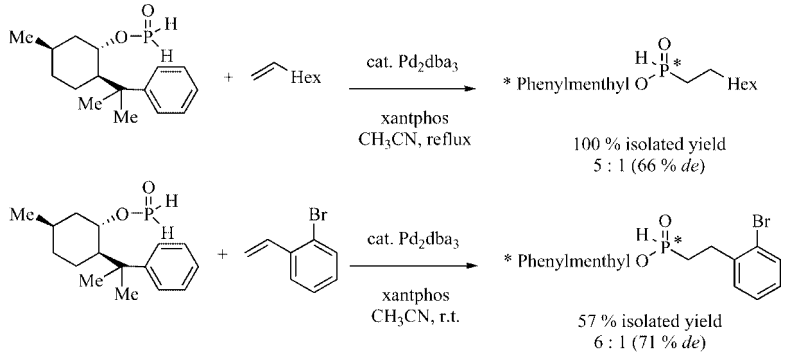
Coward and coworkers successfully applied our reaction to the hydrophosphinylation of vinylglycine. This intermediate was then elaborated into a potent inhibitor of folylpoly-γ-glutamate synthetase (Scheme 5).[14] Piettre similarly applied our reaction to the preparation of potentially biologically important α,α-difluoro-*H*-phosphinates (Scheme 6).[15]

More recently, the reaction of alkyl phosphinates was further developed by using AIBN as the initiator.[16] The reason for the success of these conditions lies in the exceptional thermal resistance of the alkyl phosphinates prepared by using our alkoxysilane esterification method.[17]

We also discovered and developed the hydrophosphinylation of alkenes by using palladium and nickel catalysts.[18] This reaction is akin to metal-catalyzed hydrosilylation. One special aspect of the reaction, which is most often not associated with other metal-catalyzed addition processes, is the competitive transfer hydrogenation (reduction) pathway that always competes with hydrophosphinylation (addition). Fortunately, hydrophosphinylation can be achieved efficiently by using appropriate ligands. Several ligands can be used with palladium, although xantphos is the most general in terms of scope, both from the standpoint of unsaturated hydrocarbon and the hypophosphorous reagent employed. In some cases, the reaction even proceeds at room temperature, and it is water tolerant. This novel P–C bond-forming reaction provides a major and novel entry into the preparation of *H*-phosphinic acid derivatives (including the Monopril side chain). Monosubstituted and *gem*-disubstituted alkenes are generally excellent substrates, but internal alkenes react poorly, except with HPA and anilinium hypophosphite. In the case of internal alkenes, our radical hydrophosphinylation is better suited, and the two types of hydrophosphinylations complement each other in terms of scope.



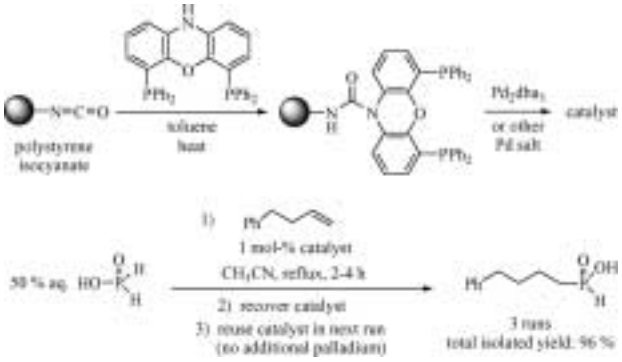
Scheme 6. Piettre's preparation of α,α-difluoro-*H*-phosphinates.



Scheme 7. P-chiral *H*-phosphinate synthesis from chiral phosphinates.

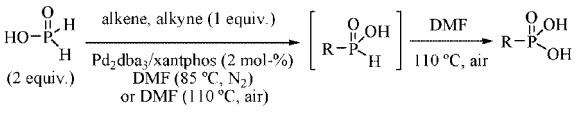
The reaction of chiral phosphinates was investigated as a way to prepare P-chiral *H*-phosphinate intermediates. A range of chiral auxiliaries has been tested and the best results thus far were obtained with 8-phenylmenthol (Scheme 7).[19] These studies lay the ground work for the use of a racemic auxiliary with a chiral catalyst to desymmetrize one of the two P–H bonds.

The palladium-catalyzed hydrophosphinylation proceeds with low catalyst loading (as little as 0.025 mol-% Pd).[18a] In spite of this, we developed a polystyrene-supported catalyst that can be prepared easily, in one step, from commercially available reagents.[18b] The supported catalyst was mainly applied to hydrophosphinylation with aqueous HPA, although alkyl phosphinates can be used as well (Scheme 8). This provides a green approach to *H*-phosphinic acid synthesis, because the catalyst can be recovered and reused in multiple runs, and it is water tolerant. Nickel-based catalysts were not competitive for alkene hydrophosphinylation as only about 70% conversions were obtained.[18d] As will be discussed later, the situation with internal alkyne is different.



Scheme 8. Polystyrene-supported hydrophosphinylation catalysts and application to the synthesis of the Monopril side chain.

Very recently, we developed a tandem hydrophosphinylation/air-oxidation process to prepare phosphonic acids directly from the corresponding alkene or other *H*-phosphinic acid precursors derived from our various methodologies (Scheme 9).[20] This appears to be an important milestone resulting in the first environmentally benign, direct synthesis of phosphonic acids. Because it proceeds mechanistically through initial formation of the *H*-phosphinic acid, this cannot be considered as the direct addition of phosphorous acid (in fact phosphorous acid does not add under our conditions); therefore, the reaction is discussed in this section. This catalytic hydrophosphinylation/oxidation reaction could become an important process to prepare phosphonic acids, as current methods always rely on protection/deprotection sequences (see hydrophosphonylation in Section 5) or the hydrolysis of P–Cl bonds, which thus tremendously increases the cost and environmental impact.

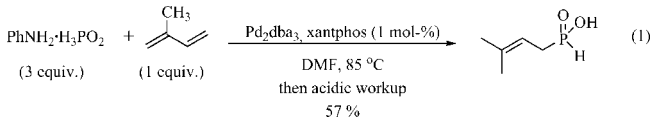


Substrate	Catalyst	Product	Isolated yield [%]
Hex	Pd_2dba_3/xantphos	Oct-P(O)(OH)H	100
	Pd_2dba_3/xantphos		97
Ph	Pd_2dba_3/xantphos	$Ph(CH_2)_4$-P(O)(OH)H	95
Pr—≡—Pr	Pd_2dba_3/xantphos		91
NHCbz	Pd_2dba_3/xantphos	$CbzHN(CH_2)_3$-P(O)(OH)H	86

Scheme 9. Environmentally friendly synthesis of phosphonic acids.

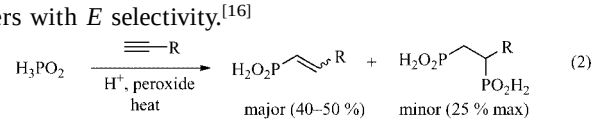
2.2. Allenes and Conjugated Dienes

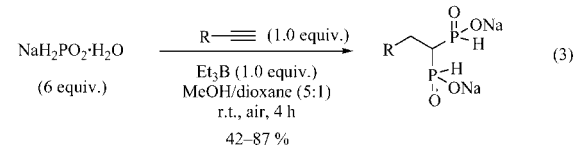
Hydrophosphinylation of 1,2- and 1,3-dienes was also investigated.[18c] With 1,3-dienes, the reaction is typically not very useful, as some mixtures of isomers are obtained and/or reduction takes place. Isoprene does give a good yield of methallyl-*H*-phosphinic acid [Equation (1)]. With 1,2-dienes (allenes),[18c] the reaction appears more general, although it largely depends on the substrate, and isomers are also usually formed.



2.3. Alkynes

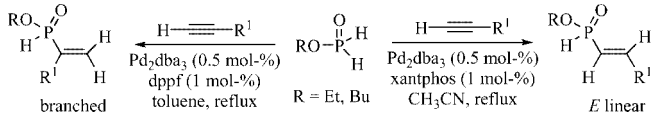
The radical addition of hypophosphorous compounds has been examined with alkynes. Nifant'ev explored the reaction of HPA with alkynes [Equation (2)].[21] By using our R_3B/air conditions, in general, only terminal alkynes react satisfactorily. Reaction with sodium hypophosphite gives the novel 1,1-bis-*H*-phosphinates in good yield [Equation (3)], and these products precipitate from the reaction mixture, which allows easy purification.[22] These compounds have great potential as bis(phosphonate) precursors, and other compounds such as 1,1-bis(phosphinomethane) derivatives.[23] Interestingly, anilinium hypophosphite tends to give 1,2-disubstitution instead. Alkyl phosphinates do not react under the trialkylborane conditions, but they react with AIBN as initiator to form alkenyl-*H*-phosphinate esters with *E* selectivity.[16]



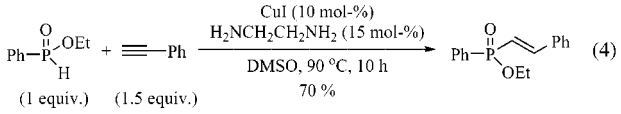


The palladium-catalyzed hydrophosphinylation of terminal alkynes can be employed to selectively form either

the linear (*E*)-1-alkenyl-*H*-phosphinates or branched 2-alkenyl-*H*-phosphinates, depending on ligand and solvent choice (Scheme 10).[24] Very good selectivities on the order of 10:1 can be achieved. Internal alkynes only react in good yield with HPA and anilinium hypophosphite, but not with alkyl phosphinates. Fortunately, a nickel-catalyzed reaction was developed to use alkyl phosphinates and internal alkynes [Equation (4)].[18d] Nickel chloride (0.5–4 mol-%) catalyzes the addition of alkylphosphinates in excellent yield, in the absence of added ligand. Regioselectivity is only good with sterically or electronically biased alkynes. With terminal alkynes, regiocontrol is poorer than in the alternative palladium-catalyzed reaction. Some tandem two- or three-step reaction sequences were demonstrated. Both palladium- and nickel-catalyzed hydrophosphinylations proceed under microwave heating to deliver a high yield of product in minutes.[18d,24]



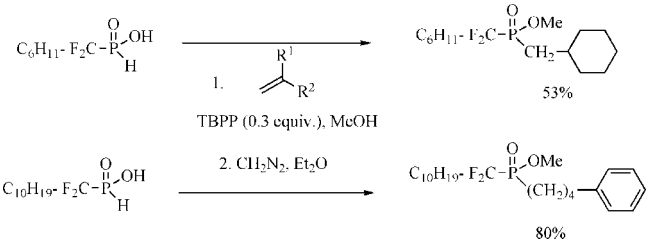
Scheme 10. Regiocontrolled hydrophosphinylation of terminal alkynes.



3. R¹(RO)P(O)H *H*-Phosphinates

3.1. Alkenes

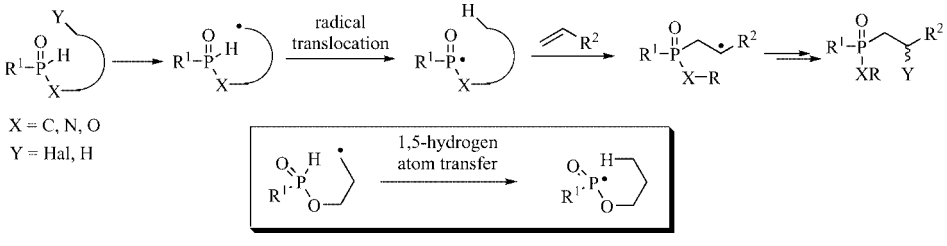
The free-radical addition of *H*-phosphinates to alkenes is relatively well known.[25] There are a few examples in the literature (see Scheme 4, for example), but careful analysis shows that these reactions are inefficient, often require specialized radical initiators or forcing conditions, and a wasteful stoichiometry (a large excess of one of the reactants is used, usually the alkene). There is a lack of methods (including radical additions) that are both general and atom economical and which take place under mild conditions. Although Aaron reported[26] the photoinitiated addition at low temperature (and incidentally with retention of stereochemistry at the P-chiral center), the reaction has apparently not been used preparatively. From our work on the free-radical reactions of hypophosphorous compounds, we noted that even in the presence of an excess amount of alkene, disubstitution does not take place to a significant extent.[13,16] This indicates the higher P–H bond dissociation energy in *H*-phosphinates and phosphites (a significant amount of free-radical work has been done recently with phosphites, see Section 5) versus hypophosphites. It also explains why PhP(O)(OR)H are much more reactive, as there might be a benzylic-like stabilization of the intermediate radical (computations show significant contribution of the aromatic ring to the SOMO) and the associated decrease in the bond-dissociation energy. Early on, when we reported our Et_3B/air protocol,[13] we showed that *H*-phosphinates do not undergo the reaction (similar results have generally been observed[8a]), with the notable exception of phenyl-*H*-phosphinate esters.[13] Thus, the development of general, practical, and mild conditions for the radical reactions of *H*-phosphinates remains a largely unresolved problem. Piettre reported the radical functionalization of α,α-difluoro-*H*-phosphinic acids (Scheme 11).[27]



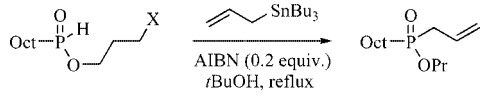
Scheme 11. Piettre's radical reactions of *H*-phosphinic acids.

In recent investigations, we probed the concept of radical translocation (Scheme 12) to improve the efficiency of these radical reactions through the use of 1,5-hydrogen transfer. As can be seen in Scheme 13, the idea seems to be quite successful, as the direct allylation of propyl octyl-*H*-phosphinate with allyl tributyltin under standard radical conditions does not proceed at all, whereas the 3-bromopropyl ester gives a very high yield of allylated product.[28] It appears that the concept can be applied to intermolecular reactions, although we have not yet fully investigated it.[28]

Most recently, Han reported the anti-Markovnikov addition of *H*-phosphinates to alkenes induced by trace amounts of air (Scheme 14).[29] Interestingly, the reaction proceeds with complete stereoselectivity, as demonstrated by the addition of optically pure (R_{Pc})-PhP(O)(OMen)H to 1-octene. However, *experimental details and isolated yields are conspicuously lacking*. The reaction probably proceeds by a free-radical mechanism.

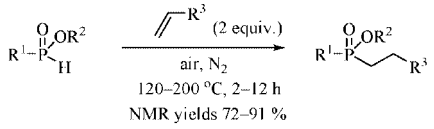


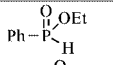
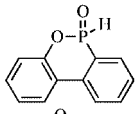
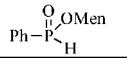
Scheme 12. The concept of radical translocation to improve the efficiency of chain reactions.



X = Br, 94 % isolated yield of product
X = H, 100 % unreacted starting material

Scheme 13. Radical translocation vs. standard conditions on the radical allylation of an *H*-phosphinate ester.



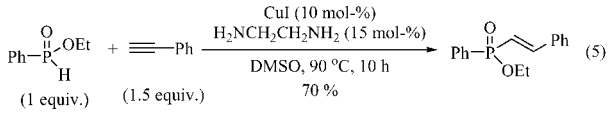
H-Phosphinate	R^3	NMR yield [%]	*t* [h] / *T* [°C]
	*n*-C_8H_{17}	72	10 / 120
	*n*-$C_{20}H_{41}$	91	2 / 200
	$P(O)Ph_2$	97	12 / 120
	*n*-C_8H_{17}	77	10 / 120

Scheme 14. Han's radical addition of *H*-phosphinates esters.

3.2. Alkynes

The only literature examples of *H*-phosphinate P–H bond activation were reported by Tanaka[30] and Han[31] (Scheme 15). In both cases, excellent regioselectivity was achieved. However, in both cases, only phenyl-*H*-phosphinate esters were employed, and as mentioned above these substrates are rather special. Although mechanistically different from the radical processes, the metal-catalyzed reactions of phenyl-*H*-phosphinates likely benefit from the benzylic-like position to facilitate P–H bond activation. Currently, there is still *no general catalytic addition of H-phosphinates* to unsaturated hydrocarbons.

A related reaction, but with the use of copper (10 mol-%) as the catalyst, was reported by Fu [Equation (5)].[32] Again, a phenyl-*H*-phosphinate ester was employed. A single example was provided.

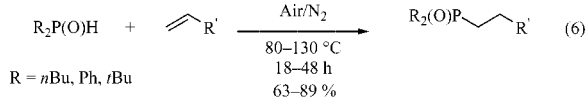


4. Addition of Secondary Phosphane Oxides $R^1R^2P(O)H$

Mixed or symmetrical secondary phosphane oxides are important intermediates for the generation of bis(phosphane oxide)s and alkenylphosphane oxides. These two classes of compounds have a wide spectrum of practical applications in biology, ecology, and chemistry as extractants for the former and as fire retardants and ligands for homogeneous catalyst for the latter. Diphenylphosphane oxide [$Ph_2P(O)H$] has been the most studied.

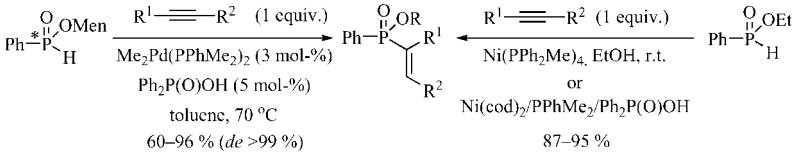
4.1. Alkenes

The addition of secondary phosphane oxides to unactivated olefins has been reported recently, and only under radical conditions in the absence of radical initiators [Equation (6)]. In all the examples, the anti-Markovnikov product is formed. Kostina described the addition of diphenylphosphane oxide to terminal alkenes in 1-octanol at high temperature (200 °C) in good yield.[33] More recently, Han discovered and developed an efficient air-induced addition.[29] This method has a larger scope [Equation (6)] for secondary phosphane oxides and also alkenes (terminal or internal). A variety of functionalities are tolerated and yields are good to excellent (although only NMR spectroscopic yields are reported and detailed conditions are absent). The study of the reaction mechanism showed it is consistent with a radical chain mechanism initiated by oxygen.

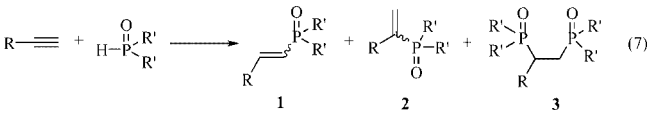


4.2. Alkynes

The addition of secondary phosphane oxides to alkynes has received more attention [Equation (7)]. It has been achieved in the presence of radical initiators, superbase, and transition metals to obtain alkenylphosphane oxides **1** (anti-Markovnikov addition) and **2** (Markovnikov addition) or 1,2-bis(phosphane oxide)s **3**.



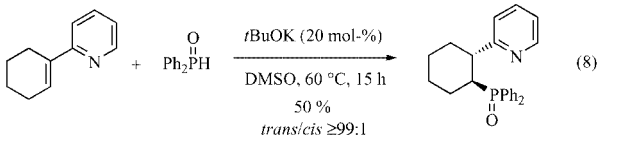
Scheme 15. Alkyne hydrophosphinylation with phenyl-*H*-phosphinate esters.



(7)

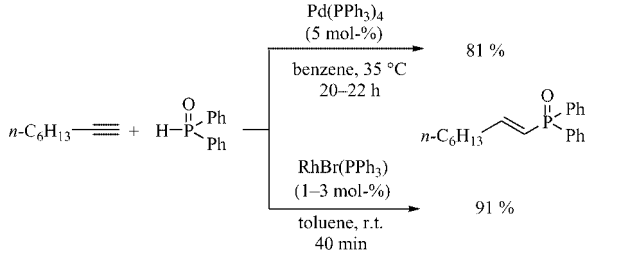
In 1985, Nifant'ev published the only studies concerning the radical approach.[34] He described addition of dibutylphosphane oxide and diarylphosphane oxides to terminal alkynes in the presence of a small amount of benzoyl peroxide at 90–95 °C in dioxane. Dibutylphosphane oxide leads to mixtures of (1-alkenyl)dibutylphosphane oxides **2** with a slight predominance of the *trans* isomer in yields of 45–70%. Diarylphosphane oxides tend to form bis(diphenylphosphane oxide)s **3** and quantitative reactions are observed when they are used in excess (3 equiv.).

In superbasic conditions (DMSO, KOH), reported by Indzhikyan,[35] diphenylphosphane oxide reacts with terminal alkynes to form exclusively bis(diphenylphosphane oxide)s **3** in good yield (62–72%). The authors suggested that the electron-withdrawing effect of the diphenylphosphinoyl group favors further addition of a nucleophile, which drives the reaction to the di-addition product. Recently, Bunlaksananusorn and Knochel reported one example of phosphane oxide in their *t*BuOK-catalyzed addition of phosphanes to alkenes.[36] In the presence of *t*BuOK in DMSO, the reaction of diphenylphosphane oxide with a trisubstituted unsaturated pyridine yields one diastereoisomer in 50% [Equation (8)].



(8)

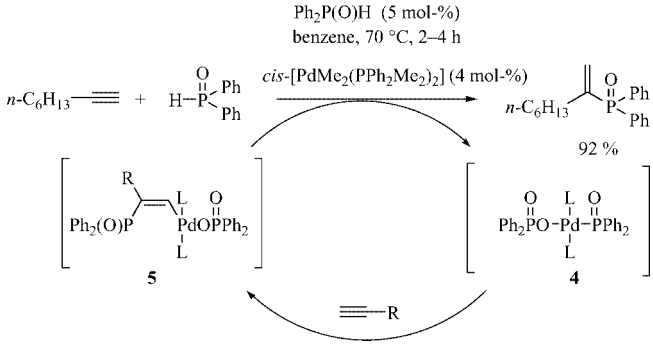
More recently, the use of transition metals allowed regio- and stereoselective control in the addition of secondary phosphane oxides to alkynes. Tanaka and coworkers studied the addition of diphenylphosphane oxide to internal and terminal alkynes under Pd and Rh catalysis.[37,38] They reported the regio- and stereoselective synthesis of (*E*)-alkenylphosphane oxides **1** in high yields by using $[Pd(PPh_3)_4]$ and $[RhBr(PPh_3)_3]$ (Scheme 16). These conditions are mild and compatible with different functionalities like halides, nitriles, protected amines, esters, and unprotected alcohols. Addition to internal alkynes proceeds also in excellent yields, but higher and longer heating is necessary.



Scheme 16. Palladium- and rhodium-catalyzed addition of $Ph_2P(O)H$ to 1-octyne.

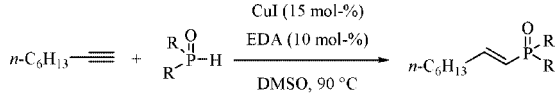
In 2006, Love and coworkers published a study of rhodium pyrazolylborate complexes in addition of phosphane oxides to alkynes.[39] The authors showed these complexes catalyze the reaction but not as efficiently than $[ClRh(PPh_3)_4]$.

By adding a trace amount of phosphinic acid, dibutyl phosphate, or phosphoric acid to the Pd-catalyzed reaction, Tanaka and coworkers changed the regioselectivity of the reaction (Scheme 17).[40] Markovnikov addition compounds **2** were mainly obtained. Terminal and internal alkynes react in these conditions, albeit the latter react more slowly. *cis*-$[Me_2Pd(PPhMe_2)_2]$ gave the best yields. To explain this new reactivity, the authors proposed a mechanism where a new palladium species **4** is involved (Scheme 17). Alkyne would insert into the Pd–$P(O)Ph_2$ bond to form alkenylpalladium species **5**, which leads to the Markovnikov addition product by protonolysis with $Ph_2P(O)H$.



Scheme 17. Proposed mechanism in the Markovnikov hydrophosphinylation.

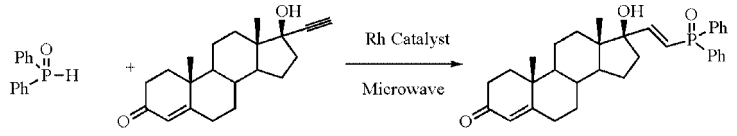
In 2007, Zhao and coworkers reported addition of secondary phosphane oxides to alkynes in the presence of a copper catalyst to form regio- and stereoselectively (*E*)-alkenylphosphane oxides **1** (Scheme 18).[41] After a screening of different amines and copper salts, the system CuI/ethylenediamine in a ratio 10 mol-%/15 mol-% in DMSO emerged as the optimum choice. Alkynes with unprotected alcohols undergo the reaction without leading to side products.



R	Isolated yield [%]	Reaction time [h]
Ph	67	12
CH_2Ph	72	18

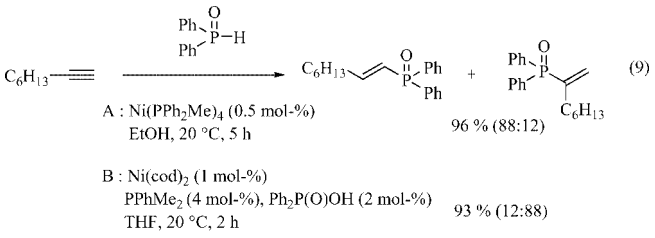
Scheme 18. Copper-catalyzed hydrophosphinylation.

Interestingly, in all three above-mentioned metal-assisted reactions (Pd, Rh, Cu), 1-ethynylcyclohexene underwent selective addition of diphenylphosphane oxide at the triple bond. Nickel catalysis has also been explored for alkyne hydrophosphinylation. In 2004, Han and coworkers reported the nickel-catalyzed addition of diphenylphosphane oxide to alkynes.[31] By slightly tuning the conditions (Ni catalyst, solvent), anti-Markovnikov or Markovnikov addition products are formed preferentially [Equation (9)].



	Solvent free	Water	THF	Ethyl lactate
Catalyst	$(Ph_3P)_3RhCl$	$(Me_2PhP)_3RhMe_3$	$(Ph_3P)_3RhCl$	$(Me_2PhP)_3RhMe_3$
Reaction time [min]	60	10–15	10–15	20
Isolated yield [%]	80	79	86	80

Scheme 19. Microwave-assisted addition to ethynyl steroids.



Lin and coworkers reported the synthesis of bis(phosphane oxide)s **3** by using Pd catalysis.[42] Treatment of terminal alkynes with diphenylphosphane oxide (2.4 equiv.) in the presence of $[Pd(PPh_3)_4]$ (5 mol-%) led to bis(diphenylphosphane oxide)s in good yields.

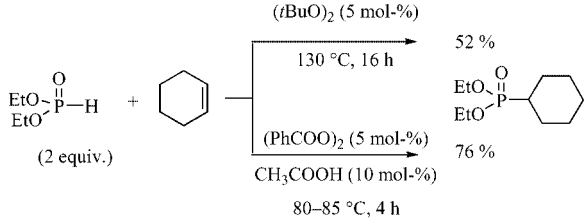
Microwave-assisted addition was used in this area. Stockland and coworkers studied first the reaction conditions of Tanaka and then those of Lin under microwave irradiation and also with the use of supported catalysts.[43] They reported that microwave-assisted solventless reactions are faster (few minutes) and give good-to-high yields (60–90%) with both homogeneous or solid-supported catalysts. Moreover, they studied the mechanism of the formation of the bis(diphenylphosphane oxide)s. They proved the first addition reaction is a metal catalysis, whereas the second addition is promoted by irradiation due to the presence of the activating $-P(O)Ph_2$ group, as in the superbasic conditions. More recently, Stockland and coworkers applied microwave heating to the addition of secondary phosphane oxides to propargyl alcohols and ethynyl steroids, in the presence of rhodium as catalyst, in various solvents.[44] Ethynyl steroids showed very good reactivity under these conditions to afford anti-Markovnikov addition products **2** in high yields (71–86% depending on the solvent, Scheme 19).

5. Addition of *H*-Phosphonates $(RO)_2P(O)H$

H-Phosphonates are important synthetic intermediates to obtain phosphonates as Wadsworth–Horner–Emmons reagents or numerous bioactive compounds. Their addition to alkenes, allenes, and alkynes has been, and continues to be, an area of intensive research, because it is the most atom-economical way to prepare organophosphonate diesters. As for the previous class of phosphorus compounds, radical addition, base-promoted, and transition-metal-catalysis reactions have been explored.

5.1. Alkenes

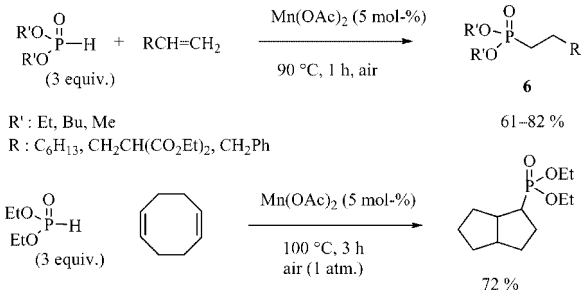
In 1958, Stiles and coworkers published the first study of radical addition of *H*-phosphonates to alkenes.[45] The authors reported the addition of different *H*-phosphonates (diethyl, dimethyl, dibutyl) to various terminal and internal alkenes in the presence of di-*tert*-butyl peroxide (5 mol-%) at 120–190 °C in moderate yields (25–77%). The proposed mechanism is addition of phosphite radical to the double bond then abstraction of the hydrogen atom from the *H*-phosphonate to complete the chain reaction. Therefore, the best yields are obtained when an excess amount of *H*-phosphonate is used to avoid polymerization. Some years later, Nifant'ev and coworkers reported an improvement in the radical reaction induced by decomposition of the benzoyl peroxide, by addition of a catalytic amount of acetic or oxalic acid (Scheme 20).[8a,46] Reactions of diethyl and diisopropyl *H*-phosphonate with terminal and internal unactivated double bonds are faster and proceed in good yields (75–90%). For terminal double bonds, only anti-Markovnikov products are obtained, and this result was also reported by Skortsov and coworkers[47] but in the case of internal double bonds, the regioselectivity is poor. Nifant'ev and coworkers studied regio- and stereoselectivity with different substituted pentenes and cyclohexenes.[46] They concluded that addition is influenced by the nature of the cycloalkene and the nature of the *H*-phosphonate, but *trans* addition is favored by increasing alkyl group size in the *H*-phosphonate.



Scheme 20. Stiles and Nifant'ev radical additions.

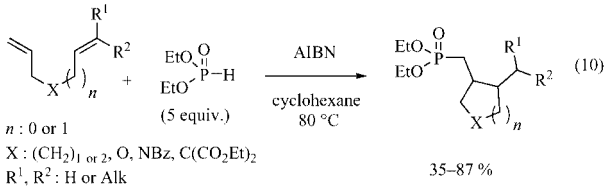
More recently, in 2004, a very nice and efficient radical hydrophosphonylation was reported by Ishii and coworkers with the use of $Mn(OAc)_2$ in air (Scheme 21).[48] The authors suggested Mn^{II} is oxidized by oxygen from air to Mn^{III}, which catalyzes the addition. Under these conditions, reactions of different *H*-phosphonates (diethyl, dimethyl, and dibutyl) to terminal alkenes led to anti-Mar-

kovnikov compounds **6** in good yields (61–82%). Internal alkenes were also studied: cyclooctene, a symmetric alkene, forms one product in 78%, but in the case of *cis*-2-octene, a mixture of two regioisomers is obtained. The authors also reported the cyclization of 1,5-cyclooctadiene under these conditions to give the *cis*-octahydropentalene product in 72% yield (Scheme 21).



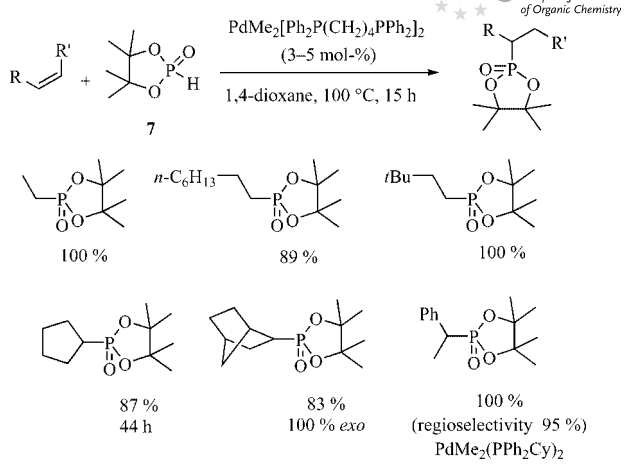
Scheme 21. Radical hydrophosphinylation of *H*-phosphonates with $Mn(OAc)_2$.

Parsons and coworkers reported also the cyclization of acyclic dienes by addition of *H*-phosphonates in the presence of AIBN.[49] Yields are moderate to excellent, depending upon the substitution of alkenes [Equation (10)].



Two groups, Russell[50] and Knochel,[36] reported the addition of *H*-phosphonates under basic conditions (*t*BuOK, DMSO) to styrene systems, which led to the anti-Markovnikov addition product in good yields.

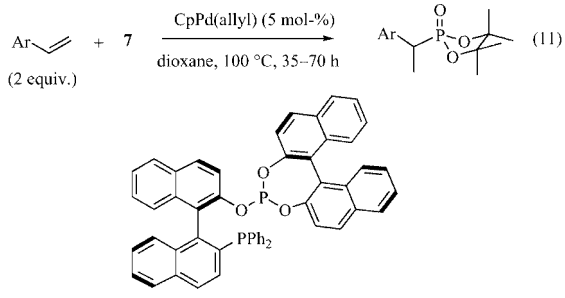
Transition metals, like palladium, nickel, rhodium, and platinum, have also been used to increase selectivity. It was not until 2000 that Tanaka and coworkers published the first palladium-catalyzed addition to terminal and symmetrical cyclic internal alkenes (Scheme 22).[51] Anti-Markovnikov addition products are mainly obtained in high yields except for styrene. Under similar conditions, acyclic internal alkenes appeared to be inert. Nickel and rhodium showed moderate activities: $Ni(PPh_3)_4$, 26% yield (10 mol-% catalyst); $[RhCl(PPh_3)_3]$, 49% yield, but $[Pt(CH_2{=}CH_2)(PPh_3)_2]$ was inactive. It is the air-sensitive *cis*-$[PdMe_2\{PPh_2(CH_2)_4PPh_2\}]$ that showed the best results. This work is the basis of all the studies in this area, because the authors reported the first and only *H*-phosphonate that proceeds in this reaction: the five-membered cyclic *H*-phosphonate **7** (4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, pinacol-*H*-phosphonate). The authors suggested that the high reactivity of this compound is associated with the reductive elimination step in the catalytic cycle, but to date, the exact reason remains unclear.



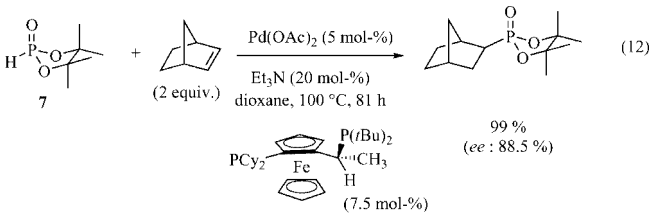
Scheme 22. Tanaka's Pd-catalyzed hydrophosphinylation.

In 2004, Skvortsov and coworkers published an exception to the nonreactivity of the other *H*-phosphonates.[47] Diethyl *H*-phosphonate was found to react with 2-allylmalonate in the presence of $[Pd(PPh_3)_4]$ to yield mainly the Markovnikov addition product. Recently, the authors reported additional studies on this reaction.[52]

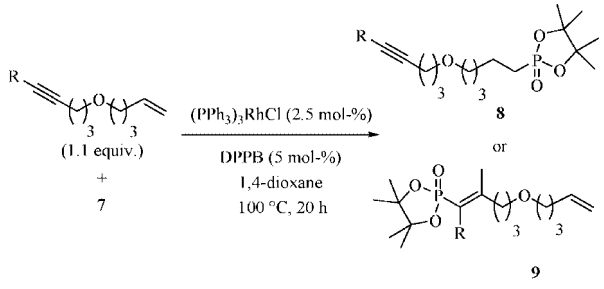
In the specific case of vinylarenes, Beletskaya and coworkers discovered $[CpPd(allyl)]/CyPPh_2$ (1:3 ratio, preincubated at 100 °C in dioxane over 40 min) led mainly to the Markovnikov addition product in excellent yields.[53] In the same publication, the authors reported the study of asymmetric addition by using chiral mono- or bidentate ligands. Bidentate ligands such as josiphos ligands were identified as promising, and (*R*,*S*)-binaphos with [CpPd(allyl)] afforded more than 90% regioselectivity and enantioselectivities in the 50% range [Equation (11)].



In 2006, Xu and Han reported a palladium-catalyzed enantioselective addition to norbornenes by using josiphos ligands [Equation (12)].[54] The authors modified five-membered cyclic *H*-phosphonate **7** by increasing the size of the substituents in order to enhance the enantioselectivity, but the reaction did not proceed. Thus, five-membered cyclic *H*-phosphonate **7** in the presence of $Pd(OAc)_2$/josiphos/Et_3N in a 1:1.5:4 (5 mol-%) ratio in dioxane heated at 100 °C for 81 h gave the best results in terms of enantioselectivity and yield [Equation (12)].



Following the work of Tanaka, Pagenkopf and coworkers reported a rhodium-catalyzed addition of *H*-phosphonate **7** to alkenes.[55] In the presence of a catalytic amount of $Ph_2P(CH_2)_4PPh_2$ (dppb) (5 mol-%), Wilkinson's catalyst {$[(PPh_3)_3RhCl]$, 2.5 mol-%} gave, with 1-octene, the anti-Markovnikov addition product in excellent yield (95%). Under these conditions, *trans* internal double bonds remain intact, and only terminal alkenes react. An interesting result was obtained by using enyne compounds (Scheme 23). Under these conditions, only addition to the triple bond was observed (compound **9**) but alkyne substitution with a TMS group prevents addition and only the double bond reacted (compound **8**).



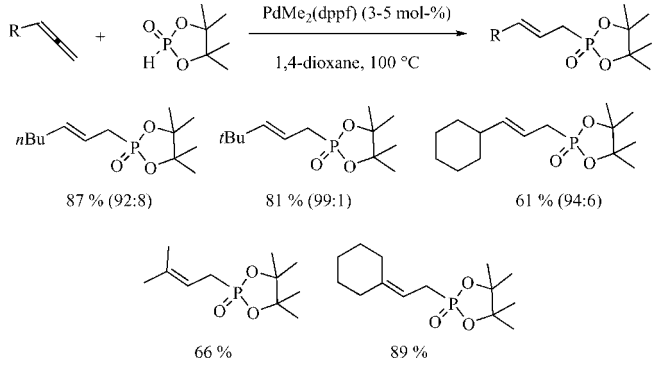
R	Yield of **8** [%]	Yield of **9** [%]
H	0	85
TMS	99	0

Scheme 23. Pagenkopf's regioselectivity studies.

The same regioselectivity (≥99%) was observed with various vinylarenes (twofold excess), both electron-rich or electron-deficient by Beletskaya and coworkers by using Wilkinson's catalyst (5 mol-%).[53] Carpentier and coworkers also explored the transition-metal-catalyzed hydrophosphonylation of an acyclic 1,6-diene system.[56] As Tanaka had reported, they observed by using cyclic *H*-phosphonate **7**, the steric discrimination between unreactive internal double bonds and reactive terminal double bonds. The latter reaction proceeds smoothly at 100 °C in dioxane, with palladium catalysts, and more rapidly with Wilkinson's catalyst, but cobalt or iridium catalysts were inactive. By adding phosphanes [monodentate tricyclohexylphosphane, bidentate 1,6-bis(diphenylphosphanyl)hexane] or carbene ligands [IPr: 1,3-bis(2,6-diisopropylphenyl)-4,5-dimethylimadozol-2-ylidene], they reported conversions above 90% with a rhodium catalyst loading as low as 0.04 mol-%.

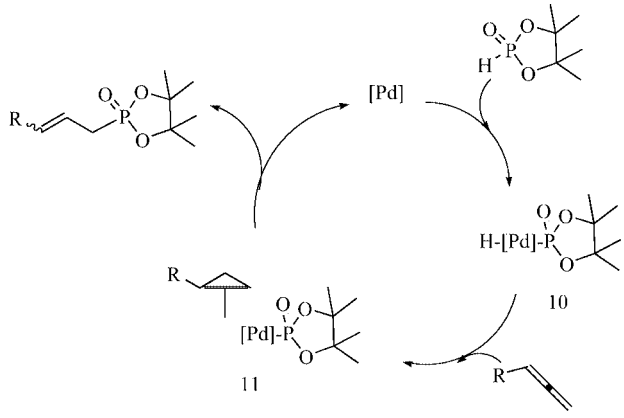
5.2. Allenes and Conjugated Dienes

Tanaka and coworkers also published the palladium-catalyzed addition of *H*-phosphonates to various allenes.[57] As with alkenes, addition to allenes was only possible with five-membered cyclic *H*-phosphonate **7**. $PdMe_2$(dppf) appeared to be the best catalyst. Under these conditions, *trans*-allyl phosphonates are obtained regio- and stereoselectively in good-to-excellent yields (Scheme 24).



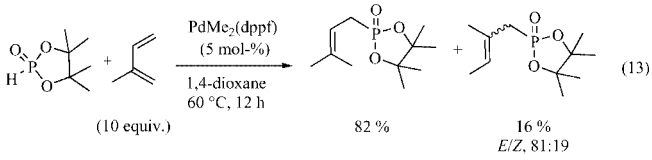
Scheme 24. Tanaka's allene hydrophosphonylation.

From NMR spectroscopic studies in deuterated solvents, the authors suggested the presence of π-allyl complex **11** formed between palladium–hydride **10** and the allenes (Scheme 25).



Scheme 25. Proposed catalytic cycle in the Pd-catalyzed allene hydrophosphonylation.

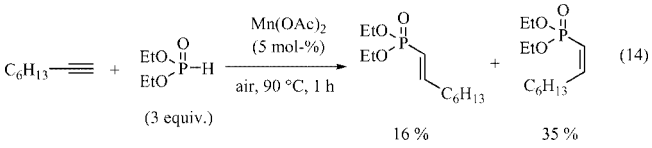
Tanaka further reported the transition-metal-catalyzed addition of pinacol-*H*-phosphonate **7** to 1,3-dienes.[58] Unfortunately, this reaction is neither stereoselective nor regioselective [Equation (13)]. The authors suggested a mechanism similar to the one shown in Scheme 25.



5.3. Alkynes

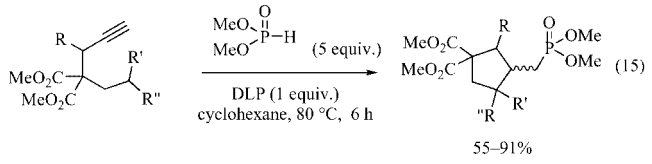
Radical additions have been reported but surprisingly only recently. First, Ishii and coworkers described one example of a terminal alkyne in their addition catalyzed by

Mn^{II} in air.[48] Only the anti-Markovnikov regioisomer is obtained, but the two stereoisomers are formed [Equation (14)].



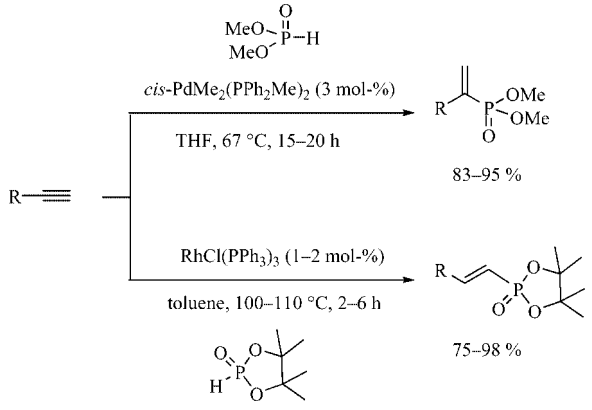
(14)

The second example was reported by Renaud and coworkers for the formation of cyclopentyl derivatives, which proceeds through radical translocation in the presence of dilauroyl peroxide (DLP) [Equation (15)].[59] Moderate-to-good diastereoisomeric excesses were observed, depending on the alkyne substrate.



(15)

A much larger number of studies have been published on the transition-metal-catalyzed addition of *H*-phosphonates to alkynes. These reactions are done in equimolar conditions, and depending on the metal employed, it gives the opportunity to change the regio- and stereoselectivity of the addition. Tanaka and coworkers reported the first example of such a reaction by using a palladium catalyst (Scheme 26).[60] Both Pd^0 and Pd^{II} with less basic ligands {*cis*-[$PdMe_2(PPh_3)_2$], [$Pd(CH_2{=}CH_2)(PPh_3)_2$], and [$Pd(PPh_3)_4$]} gave the best results, but [$Pt(PEt_3)_3$] also was successful. With aliphatic and aromatic terminal alkynes, *H*-phosphonates add regioselectively to the internal carbon of the triple bond, except in the presence of bulky groups such as a TMS, when only the terminal carbon is phosphonylated. Under these conditions, internal alkynes also react, albeit slowly, which leads to the *cis* isomer stereoselectively (in the case of 4-octyne). Alkenes appeared totally unreactive to the addition, consistent with the finding that only pinacol-*H*-phosphonate reacts with alkenes.

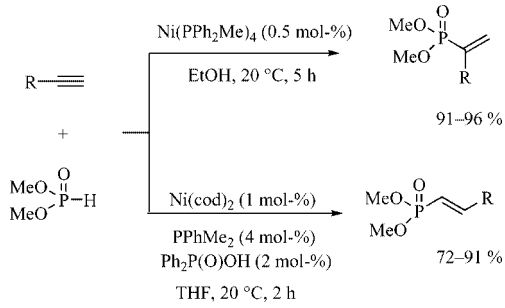


Scheme 26. Alkyne hydrophosphonylation.

By changing from palladium to rhodium catalysts, Tanaka and coworkers inverted the regioselectivity of the addition (Scheme 26).[61] By using the highly reactive five-membered cyclic *H*-phosphonate **7**, they obtained (*E*)-alkenylphosphonates in high yields with excellent regio- and stereoselectivities. Wilkinson-type complexes [$RhX(PPh_3)_4$] presented the highest catalytic activity. Under these conditions, internal alkenes are unreactive.

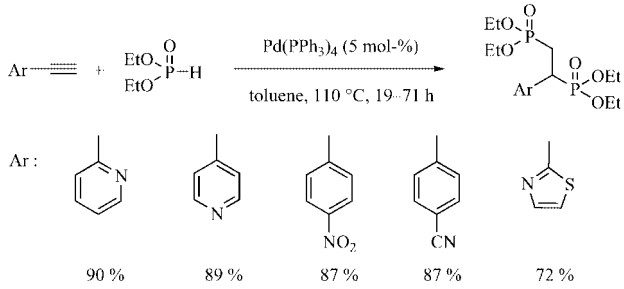
Genet, Beletskaya, and coworkers reported an improvement in Tanaka's reaction.[62] By using commercially available [$Pd_2(dba)_3$]·$CHCl_3$ (1.5 mol-%) in the presence of triphenylphosphane (6–12 mol-%), the authors showed Markovniknov addition products are obtained in yields as good as with the air-sensitive [$Pd(PPh_3)_4$] used by Tanaka.

In 2004, Han and coworkers published a nickel-catalyzed addition of dimethyl *H*-phosphonates to alkynes.[31] Excellent regiocontrol was obtained by slightly tuning the conditions (Scheme 27). Thus, anti-Markovnikov or Markovnikov addition products are formed by changing the Ni catalyst and the solvent.



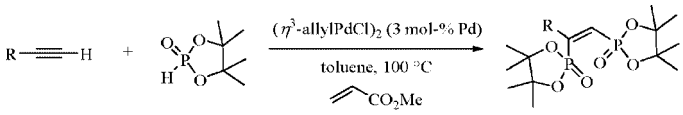
Scheme 27. Ni-catalyzed addition of *H*-phosphonates to alkynes.

Lin and coworkers reported the bis(addition) of *H*-phosphonates to electron-deficient terminal alkynes to obtain bis(phosphonate)s, in the presence of [$Pd(PPh_3)_4$] (Scheme 28).[63] Only diethyl- and diisopropyl-*H*-phosphonates are able to undergo this bis(addition).



Scheme 28. 1,2-Bis(phosphonate) synthesis by hydrophosphonylation.

Finally, Han and coworkers just reported the double palladium-catalyzed dehydrogenative hydrophosphonylation of terminal alkynes with cyclic *H*-phosphonate **7**, which leads to (*Z*)-bis(phosphonyl)-1-alkenes (Scheme 29).[64]



R	$CyCH_2$	*t*Bu	Me_3Si	Ph	Fe	$(CH_2)_3CN$	$(CH_2)_3Cl$
Isolated Yield [%]	53	58	62	71	56	75	71

Scheme 29. Dehydrogenative Pd-catalyzed hydrophosphonylation of terminal alkynes.

6. Conclusions & Outlook

Although P–C bond formation is often considered a mature area of research because of the historic reactions (Arbuzov, Michaelis–Becker, etc.), tremendous progress has been made over the last 15 years in metal-catalyzed and free-radical processes. As a result, a variety of organophosphorus compounds are becoming more and more available, and in ever more efficient and environmentally benign ways. Addition of phosphinylidene functionalities to unactivated unsaturated hydrocarbons is probably the most atom-economical process conceivable. In the opinion of the authors, the modern research results and future directions may well lead to the challenging of, or at least the rethinking of, the current phosphorus trichloride based economy. This is particularly true of hypophosphorous acid based methodologies, which bypass the need for PCl_3 entirely. In contrast, hydrophosphonylation reactions, while becoming competitive with the classical Arbuzov phosphonate synthesis, still rely on PCl_3-based dialkyl phosphites and protecting-group strategies.

As can be seen in this review, traditional organophosphorus chemistry based on partially oxidized precursors has found a renewed youth and relevance for the preparation of a wide variety of important compounds. There is little doubt that efforts will continue in order to deliver ever more efficient, high-yielding, and industrially relevant processes. After well over 100 years since the birth of organophosphorus chemistry, the 21st century should continue to see significant and steady improvements resulting from contributions in laboratories worldwide.

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