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

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Summary

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 phosphine oxides, and phosphonates. The review covers the literature up to February 2008.

Keywords

hydrophosphinylation; hydrophosphonylation; phosphonates; phosphinates; phosphinylidene

1. Introduction

Phosphorus-carbon bond-forming reactions have been the object of intense interest in recent years.^[i] This review specifically covers reactions in which a phosphinylidene $[P(=O)H]$ functionality^[ii] 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.^[iii] 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, based on 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.

2. Addition of phosphinates (RO)P(O)H₂

Phosphinates are derivatives of hypophosphorous acid (H₃PO₂, HPA, phosphinic acid). They include salts of the parent acid, as well as its esters.^[iv] Hypophosphorous acid is an industrial commodity and is sold as aqueous solutions.^[v] It is prepared from elemental white phosphorus (P₄) 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 (P₄ + Cl₂ + 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.^[vi]

2.1. Alkenes

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

A few years ago, we reported novel conditions to effect the radical addition of hypophosphorous derivatives under neutral conditions and at room temperature, using a trialkylborane and air as the initiator.^[xiii] This reaction has a broad scope in terms of alkene and phosphinate reagent. Excellent selectivity for monoaddition is observed, even when an excess 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 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).^[xiv] Piettre similarly applied our reaction to the preparation of potentially biologically important α,α -difluoro-*H*-phosphinates (Scheme 6).^[xv]

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

We also discovered and developed the hydrophosphinylation of alkenes using palladium and nickel catalysts.^[xviii] 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 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.

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).^[xix] These studies lay the ground work for using 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 which 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.

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).^[xx] 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 part 5), or through the hydrolysis of P-Cl bonds, thus tremendously increasing cost and environmental impacts.

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.

The radical addition of hypophosphorous compounds has been examined with alkynes. Nifantev explored the reaction of HPA with alkynes (Equation 2).^[xxi] Using our R₃B/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, allowing easy purification.^[xxii] These compounds have great potential as bisphosphonate precursors, and other compounds such as 1,1-bisphosphinomethane derivatives.^[xxiii] 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*-phosphate esters with *E*-selectivity.^[16]

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(4)

3. R¹(RO)P(O)H *H*-phosphinates

3.1. Alkenes

The free-radical addition of *H*-phosphinates to alkenes is relatively well-known.^[xxv] 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) which are both general and atom-economical, and which take place under mild conditions. Although Aaron reported^[xxvi] 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 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 part 5) versus hypophosphites. It also explains why PhP(O)(OR)H are much more reactive since 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 of the bond dissociation energy. Early on, when we reported our Et₃B/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).^[xxvii]

In recent investigations, we have 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.^[xxviii] 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 traces of air (Scheme 14).^[xxix] Interestingly, the reaction proceeds with complete stereoselectivity as demonstrated by the addition of optically pure (*R*_{Pc})-PhP(O)(OMe)H to 1-octene. However, *experimental details and isolated yields are conspicuously lacking*. The reaction probably proceeds via a free radical mechanism.

3.2. Alkynes

The only literature examples of *H*-phosphinate P-H bond activation were reported by Tanaka^[xxx] and Han^[xxxi] (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 using copper (10 mol-%) as the catalyst, was reported by Fu (Equation 5).^[xxxiii] Again, a phenyl-*H*-phosphate ester was employed. A single example was provided.

(5)

4. Addition of secondary phosphine oxides R¹R²P(O)H

Mixed or symmetrical secondary phosphine oxides are important intermediates for the generation of bisphosphine oxides and alkenylphosphine oxides. These two classes of compounds have a wide spectrum of practical applications in biology, in ecology and in chemistry as extractants for the first one, as fire retardants and ligands for homogeneous catalyst for the second one. Diphenylphosphine oxide (Ph₂P(O)H) has been the most studied.

4.1. Alkenes

The addition of secondary phosphine 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 diphenylphosphine oxide to terminal alkenes in 1-octanol at high temperature (200 °C) in good yield.^[xxxiii] More recently, Han discovered and developed an efficient air-induced addition.^[29] This method has a larger scope (Equation 6) for secondary phosphine oxides and also alkenes (terminal or internal). A variety of functionalities are tolerated and yields are good to excellent (although only NMR 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.

(6)

4.2. Alkynes

The addition of secondary phosphine 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 alkenylphosphine oxides **1** (anti-Markovnikov addition) and **2** (Markovnikov addition) or 1,2-bis-phosphine oxides **3**.

(7)

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

In superbasic conditions (DMSO, KOH), reported by Indzhikyan,^[xxxv] diphenylphosphine oxide reacts with terminal alkynes to form exclusively bis-diphenylphosphine oxides compounds **3** in good yield (62–72 %). The authors suggested the electron-withdrawing effect of the diphenylphosphinoyl group favors further addition of a nucleophile, driving the reaction until the di-addition product. Recently, Bunlaksananusorn and Knochel reported one example of phosphine oxide, in their *t*BuOK-catalyzed addition of phosphines to alkenes.^[xxxvi] In the presence of *t*BuOK in DMSO, diphenylphosphine oxide reacted with a trisubstituted unsaturated pyridine to yield one diastereoisomer in 50 % (Equation 8).

(8)

More recently, the use of transition metals allowed the regio- and stereo-selective control in the addition of secondary phosphine oxides to alkynes. Tanaka and coworkers studied the addition of diphenylphosphine oxide to internal and terminal alkynes under Pd and Rh catalysis.^[xxxvii, xxxviii] They reported the regio- and stereoselective synthesis of *E*-alkenylphosphine oxides **1** in high yields using Pd(PPh₃)₄ and RhBr(PPh₃)₃ (Scheme 16). These conditions are mild and are compatible with different functionalities like halides, nitrile, protected amines, esters and unprotected alcohol. Addition to internal alkynes proceeds also in excellent yields but higher and longer heating is necessary.

In 2006, Love and coworkers published a study of rhodium pyrazolylborate complexes in addition of phosphine oxides to alkynes.^[xxxix] The authors showed these complexes catalyze the reaction but not as efficiently than ClRh(PPh₃)₄.

By adding a trace of phosphinic acid, dibutyl phosphate or phosphoric acid to the Pd-catalyzed reaction, Tanaka and coworkers changed the regioselectivity of the reaction (Scheme 17).^[xl] Markovnikov addition compounds **2** were mainly obtained. Terminal and internal alkynes react in these conditions, albeit the latter react more slowly. *cis*-[Me₂Pd(PPhMe₂)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)Ph₂ bond to form an alkenylpalladium species **5** which leads to the Markovnikov addition product by protonolysis with Ph₂P(O)H.

In 2007, Zhao and coworkers reported addition of secondary phosphine oxides to alkynes in the presence of a copper catalyst to form regio- and stereo-selectively *E*-alkenylphosphine oxides **1** (Scheme 18).^[xli] 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.

Interestingly, in all three above-mentioned metal-assisted reactions (Pd, Rh, Cu), 1-ethynylcyclohexene underwent selective addition of diphenylphosphine 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 diphenylphosphine oxide to alkynes.^[31] By slightly tuning the conditions (Ni catalyst, solvent), anti-Markovnikov or Markovnikov addition products are formed preferentially (Equation 9).

Lin and coworkers reported the synthesis of bisphosphine oxides **3** using Pd-catalysis.^[xlii] Treatment of terminal alkynes with 2.4 equivalents of diphenylphosphine oxide in the presence of 5 mol-% of Pd(PPh₃)₄ lead to bis-diphenylphosphine oxides in good yields.

Microwave-assisted addition was used in this area. Stockland and coworkers studied first Tanaka's and then Lin's reaction conditions under microwave irradiation, and also using supported catalysts.^[xliii] They reported microwave-assisted solventless reactions are faster (few minutes) and give good to high yields (60–90 %) using both homogeneous or solid-supported catalysts. Moreover, they studied the mechanism of the formation of the bis-diphenylphosphine oxides. 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)Ph₂ group as in the superbasic conditions. More recently, Stockland and coworkers applied microwave heating to the addition of secondary phosphine oxides to propargyl alcohols and ethynyl steroids, in the presence of rhodium as catalyst, in various solvents.^[xliv] 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*-Phosponates (RO)₂P(O)H

H-Phosponates 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.^[xlv] The authors reported the addition of different *H*-phosphonates (diethyl, dimethyl, dibutyl) to various terminal and internal alkenes, in the presence of 5 mol-% di-*tert*-butyl peroxide 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 with an excess of *H*-phosphonate to avoid polymerization. Some years later, Nifant'ev and coworkers reported an improvement of the radical reaction induced by decomposition of the benzoyl peroxide, by addition of catalytic amount of acetic or oxalic acid (Scheme 20).^[8a, xlvii] 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, this result has also been reported by Skortsov and coworkers^[xlviii] but in the case of internal double bonds, regioselectivity is poor. Nifant'ev and coworkers studied regio- and stereo-selectivity with different substituted pentenes and cyclohexenes.^[46] They concluded 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.

More recently, in 2004, a very nice and efficient radical hydrophosphonylation was reported by Ishii and coworkers using Mn(OAc)₂ under air (Scheme 21).^[xlviii] 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 lead to anti-Markovnikov compounds **6** in good yields (61–82 %). Internal alkenes have also been studied, cyclooctene, a symmetric alkene, forms one product in 78 % but in the case of *cis*-2-octene, the 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 with 72 % yield (Scheme 21).

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

(10)

Two groups, Russell^[1] and Knochel,^[36] reported the addition of *H*-phosphonates under basic conditions (*t*BuOK, DMSO) to styrene systems leading 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 to symmetrical cyclic internal alkenes (Scheme 22).^[li] 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(PPh₃)₄ (26 % yield, 10 mol-% catalyst) and RhCl(PPh₃)₃ (49 % yield) but Pt(CH₂=CH₂)(PPh₃)₂ was inactive. It is the air-sensitive *cis*-

$\text{PdMe}_2(\text{PPh}_2(\text{CH}_2)_4\text{PPh}_2)$ which 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 which 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 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.

In 2004, Skvortsov and coworkers published an exception to the non-reactivity of the other *H*-phosphonates.^[47] Diethyl *H*-phosphonate has been found to react with 2-allylmalonate in the presence of $\text{Pd}(\text{PPh}_3)_4$ to yield mainly the Markovnikov addition product. Recently, the authors reported additional studies on this reaction.^[lii]

In the specific case of vinylarenes, Beletskaya and coworkers discovered $[\text{CpPd}(\text{allyl})]/\text{CyPPh}_2$ (1:3 ratio, pre-incubated at 100 °C in dioxane during 40 min) led mainly to the Markovnikov addition product in excellent yields.^[liii] In the same publication, the authors reported the study of asymmetric addition using chiral mono- or bidentate ligands. Bidentate ligands as Josiphos ligands were identified as promising, and (*R,S*)-Binaphos with $\text{CpPd}(\text{allyl})$ afforded more than 90 % regioselectivity and enantioselectivities in the 50 % range (Equation 11).

(11)

In 2006, Xu and Han reported a palladium-catalyzed enantioselective addition to norbornenes using Josiphos ligands (Equation 12).^[liv] The authors modified the 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 then. Thus, the five-membered cyclic *H*-phosphonate **7** in the presence of $\text{Pd}(\text{OAc})_2/\text{Josiphos}$ ligand and Et_3N in a ratio 1/1.5/4 (5 mol-%) in dioxane heated at 100 °C during 81 h gave the best results in term of enantioselectivity and yield (Equation 12).

(12)

Following upon Tanaka's work, Pagenkopf and coworkers reported a rhodium-catalyzed addition of the *H*-phosphonate **7** to alkenes.^[lv] In the presence of a catalytic amount (5 mol-%) of $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$ (dppb), Wilkinson's catalyst ($(\text{PPh}_3)_3\text{RhCl}$, 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 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**).

The same regioselectivity (99 %) has been observed with various vinylarenes (two-fold excess), both electron-rich or electron-deficient, by Beletskaya and coworkers, using Wilkinson's catalyst (5 mol-%).^[53] Carpentier and coworkers also explored the transition metal-catalyzed hydrophosphonylation on an acyclic 1,6-diene system.^[lvi] As Tanaka had reported, they observed, using cyclic *H*-phosphonate **7**, the steric discrimination between unreactive internal double bonds and reactive terminal double bond. 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 phosphines (monodentate tricyclohexylphosphine, bidentate 1,6-bis(diphenylphosphino)hexane) or carbene ligands (IPr : 1,3-bis(2,6-diisopropylphenyl)-4,5-dimethylimidazol-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 allenenes.^[lvii] As with alkenes, addition to allenenes was only possible with the five-membered cyclic *H*-phosphonate **7**. $\text{PdMe}_2(\text{dppf})$ appeared to be the best catalyst. Under these conditions, *trans*-allyl phosphonates are obtained regio- and stereo-selectively in good to excellent yields (Scheme 24).

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

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

(13)

5.3. Alkynes

Radical additions have been reported but surprisingly only recently. First, Ishii and coworkers described one example of terminal alkyne in their addition catalyzed by Mn(II) under 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).^[lix] Moderate to good diastereoisomeric excesses were observed, depending on the alkyne substrate.

(15)

A much larger number of studies has 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 stereo-selectivity of the addition. Tanaka and coworkers reported the first example of such a reaction, using a palladium catalyst (Scheme 26).^[lx] Both Pd(0) and Pd(II) with less basic ligands (*cis*-PdMe₂(PPh₃)₂, Pd(CH₂=CH₂)(PPh₃)₂ and Pd(PPh₃)₄) gave the best results, but Pt(PEt₃)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, leading 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.

By changing from palladium to rhodium catalysts, Tanaka and coworkers inverted the regioselectivity of the addition (Scheme 26).^[lxi] Using the highly reactive five-membered cyclic *H*-phosphonate **7**, they obtained *E*-alkenylphosphonates in high yields with excellent regio- and stereo-selectivities. Wilkinson-type complexes RhX(PPh₃)₄ presented the highest catalytic activity. Under these conditions, internal alkenes are unreactive.

Genet, Beletskaya and coworkers reported an improvement of the Tanaka's reaction.^[lxii] Using commercially available Pd₂(dba)₃.CHCl₃ (1.5 mol-%) in the presence of triphenylphosphine (6–12 mol-%), the authors showed Markovnikov addition products are obtained in yields as good as with the air-sensitive Pd(PPh₃)₄ used by Tanaka.

In 2004, Han and coworkers published a nickel-catalyzed addition of dimethyl *H*-phosphonates to alkynes.^[31] Excellent regiocontrol has been 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.

Lin and coworkers reported the bis-addition of *H*-phosphonates to electron-deficient terminal alkynes to obtain bisphosphonates, in the presence of Pd(PPh₃)₄ (Scheme 28).^[lxiii] Only diethyl- and diisopropyl-*H*-phosphonates are able to undergo this bis-addition.

Finally, Han and coworkers just reported the double palladium-catalyzed dehydrogenative hydrophosphonylation of terminal alkynes with cyclic *H*-phosphonate **7**, leading to (*Z*)-bisphosphonyl-1-alkenes (Scheme 29).^[lxiv]

6. Conclusions & Outlook

While 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 authors' opinion, the modern research results and future directions may well lead to the challenging, or at least the re-thinking, of the current phosphorus trichloride-based economy. This is particularly true of hypophosphorous acid-based methodologies which bypass the need for PCl_3 entirely. On the other hand, hydrophosphonylation reactions, while becoming competitive with the classical Arbuzov phosphonate synthesis, still rely on PCl_3 -based dialkylphosphites 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 one hundred 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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Biographies

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 using hypophosphorous derivatives, and the medicinal chemistry of phosphorus-containing compounds.

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, in Dr. Jean-Luc Montchamp's 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.

References

- i. General reviews on P-C bond formation: Engel R, Cohen JJ. *Synthesis of Carbon-Phosphorus Bonds* (2nd ed.). 2003 Boca Raton CRC Press Wicht DK, Glueck DS, Togni A, Grützmacher H. Catalytic Heterofunctionalization. 2001; Weinheim Wiley-VCH Chapter 5 and references therein; Delacroix O, Gaumont A-C. *Curr. Org. Chem.* 2005; 9:1851–1882. Schwan AL. *Chem. Soc. Rev.* 2004; 33:218–224. [PubMed: 15103403] Tanaka M. *Top. Curr. Chem.* 2004; 232:25–54. Alonso F, Beletskaya IP, Yus M. *Chem. Rev.* 2004; 104:3079–3160. [PubMed: 15186189] Baillie C, Xiao J. *Curr. Org. Chem.* 2003; 7:477–514. Beletskaya IP, Kazankova MA. *Russ. J. Org. Chem.* 2002; 38:1391–1430.
- ii. Reviews on the phosphinylidene functionality: Nifant'ev EE. *Russ. Chem. Rev.* 1978; 47:835–858. Yudelevich VI, Sokolov LB, Ionin BI. *Russ. Chem. Rev.* 1980; 49:46–58. Stawinski J, Kraszewski A. *Acc. Chem. Res.* 2002; 35:952–960. [PubMed: 12437320]
- iii. For some relevant references on transition-metal catalyzed P-C bond formation via cross-coupling: Martorell G, Garcías X, Janura M, Saá JM. *J. Org. Chem.* 1998; 63:3463–3467. Hirao T, Masunaga T, Yamada N. *Bull. Chem. Soc. Jpn.* 1982; 55:909–913. Xu Y, Zhang J. *Synthesis.* 1984:778–780. Lei H, Stoakes MS, Schwabacher AW. *Synthesis.* 1992:1255–1260. Kazankova MA, Trostyanskaya IG, Lutsenko SV, Beletskaya IP. *Tetrahedron Lett.* 1999; 40:569–572. Al-Masum M, Kumuraswamy G, Livinghouse T. *J. Org. Chem.* 2000; 65:4776–4778. [PubMed: 10959896] Holt DA, Erb JM. *Tetrahedron Lett.* 1989; 30:5393–5396. Montchamp J-L, Dumond YR. *J. Am. Chem. Soc.* 2001; 123:510–511. Bravo-Altamirano K, Huang Z, Montchamp J-L. *Tetrahedron.* 2005; 61:6315–6329. Bravo-Altamirano K, Montchamp J-L. *Org. Lett.* 2006; 8:4169–4171. [PubMed: 16928101]
- iv. Bravo-Altamirano, K.; Montchamp, J-L., editors. *Encyclopedia of Reagents for Organic Synthesis (eROS)*. 2007. Phosphinic Acid, Alkyl Esters. (<http://www.mrw.interscience.wiley.com/eros/articles/rn00762/sect0-fs.html>)
- v. a) Fee, DC.; Gard, DR.; Yang, C-H. *Kirk-Othmer Encyclopedia of Chemical Technology*. 4th ed.. Vol. vol. 19. New York: Wiley; 1999. p. 19-73. b) *Kirk-Othmer Encyclopedia of Chemical Technology Home Page*. <http://www.mrw.interscience.wiley.com/kirk/>.
- vi. For examples of functional group interconversion related to H-phosphinic acids, see: Frank AW. *Chem. Rev.* 1961; 60:389–424. Sasse K. *Methoden der Organischen Chemie (Houben-Weyl)*. 1964 Stuttgart Thieme:294–337. band XII/1 Regitz M. *Methoden der Organischen Chemie (Houben-Weyl)*. 1982; vol. E2 Stuttgart Thieme Frank AW, Kosolapoff GM, Maier L. *Organic Phosphorus Compounds*. 1972; vol. 4 (chapter 10) New York Wiley Karanewsky DS, Badia MC. *Tetrahedron Lett.* 1986; 27:1751–1754. Frank AW. *J. Org. Chem.* 1961; 26:850–853. Soulier E, Clement J-C, Yaouanc J-J, des Abbayes H. *Tetrahedron Lett.* 1998; 39:4291–4294. Reviews: Montchamp J-L. *Specialty Chemicals Magazine*. 2006; 26:44. Montchamp J-L. *J. Organomet. Chem.* 2005; 690:2388–2406.
- vii. Williams RH, Hamilton LA. *J. Am. Chem. Soc.* 1955; 77:3411–3412.

- viii. Radical addition of hypophosphorous compounds: Nifant'ev EE, Magdeeva RK, Shchepet'eva NP. *J. Gen. Chem. USSR*. 1980; 50:1416–1423. Karanewsky DS, Badia MC, Cushman DW, DeForrest JM, Dejneka T, Loots MJ, Perri MG, Petrillo EW, Powell JR. *J. Med. Chem.* 1988; 31:204–212. [PubMed: 3336020]
- ix. Anderson NG, Coradetti ML, Cronin JA, Davies ML, Gardineer MB, Kotnis AS, Lust DA, Palaniswamy VA. *Org. Process Res. Dev.* 1997; 1:315–319.
- x. Aleksandrova IA, Ufimtseva LI. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1971; 6:1218–1219.
- xi. Dubert O, Gautier A, Condamine E, Piettre SR. *Org. Lett.* 2002; 4:359–362. [PubMed: 11820879]
- xii. For references on phosphorus-centered radicals, see: Leca D, Fensterbank L, Lacote E, Malacria M. *Chem. Soc. Rev.* 2005; 34:858–865. [PubMed: 16172675] Walling C, Pearson MS. *Top. Phosphorus Chem.* 1966; 3:1–56. Halmann H. *Top. Phosphorus Chem.* 1967; 4:49–84. Bentrude WG, Kochi JK. *Free Radicals*. 1973; vol. 2(chapter 22)New YorkWiley Bentrude WG, Hartley FR. *The Chemistry of Organophosphorus Compounds*. 1990; vol. 1(chapter 14)New YorkWiley For a discussion of the efficiency of radical reactions based on P-radicals, see: Jessop CM, Parsons AF, Routledge A, Irvine DJ. *Eur. J. Org. Chem.* 2006:1547–1554.
- xiii. Deprère S, Montchamp J-L. *J. Org. Chem.* 2001; 66:6745–6755. [PubMed: 11578230]
- xiv. Feng Y, Coward JK. *J. Med. Chem.* 2006; 49:770–788. [PubMed: 16420062]
- xv. Gautier A, Garipova G, Salcedo C, Balieu S, Piettre SR. *Angew. Chem. Int. Ed.* 2004; 43:5963–5967.
- xvi. Antczak MI, Montchamp J-L. *Synthesis*. 2006:3080–3084.
- xvii. Deprère S, Montchamp J-L. *J. Organomet. Chem.* 2002; 154:643–644.
- xviii. a) Deprère S, Montchamp J-L. *J. Am. Chem. Soc.* 2002; 124:9386–9387. [PubMed: 12167029] b) Deprère S, Montchamp J-L. *Org. Lett.* 2004; 6:3805–3808. [PubMed: 15469354] c) Bravo-Altamirano K, Abrunhosa-Thomas I, Montchamp J-L. *J. Org. Chem.* 2008; 73:2292–2301. [PubMed: 18275217] d) Ribière P, Bravo-Altamirano K, Antczak MI, Hawkins JD, Montchamp J-L. *J. Org. Chem.* 2005; 70:4064–4072. [PubMed: 15876098]
- xix. Bravo-Altamirano, K. Dissertation. Texas Christian University; 2007.
- xx. Bravo-Altamirano K, Montchamp J-L. *Tetrahedron Lett.* 2007; 48:5755–5759. [PubMed: 17940584]
- xxi. Nifant'ev EE, Solovetskaya LA, Maslennikova VI, Magdeeva RK, Sergeev NM. *J. Gen. Chem. USSR*. 1986; 56:680–688.
- xxii. Gouault-Bironneau S, Deprère S, Sutor A, Montchamp J-L. *Org. Lett.* 2005; 7:5909–5912. [PubMed: 16354097]
- xxiii. a) Unpublished results; b) Poster 447. Belabassi Y, Gouault-Bironneau S, Montchamp J-L. Practical synthesis of 1,1-bis-*H*-phosphinates by radical reaction of hypophosphorous acid with terminal alkynes. 232nd National Meeting of the ACS September 10–14, 2006San Francisco
- xxiv. Unpublished results.
- xxv. For the radical reactions of H-phosphinates: Piettre SR. *Tetrahedron Lett.* 1996; 37:2233–2236. Zeiss H-J. *Tetrahedron*. 1992; 38:8263–8270. Dingwall JG, Tuck B. *J. Chem. Soc. Perkin Trans. 1*. 1986:2081–2090. Pudovik AN, Konovalova IV, Guryleva AA. *J. Gen. Chem. USSR*. 1963; 33:2850–2853. Finke M, Kleiner H-J. *Liebigs Ann. Chem.* 1974:741–750.
- xxvi. Reiff LP, Aaron HS. *J. Am. Chem. Soc.* 1970; 92:5275–5276. The reaction proceeds stereoselectively at room temperature. There is no detailed experimental procedure.
- xxvii. Gautier A, Garipova G, Salcedo C, Balieu S, Piettre SR. *Angew. Chem. Int. Ed.* 2004; 43:5963–5967.
- xxviii. Ribière P, Montchamp J-L. unpublished results.
- xxix. Hirai T, Han L-B. *Org. Lett.* 2007; 9:53–55. [PubMed: 17192083]
- xxx. Han L-B, Zhao C-Q, Onozawa S-Y, Goto M, Tanaka M. *J. Am. Chem. Soc.* 2002; 124:3842–3843. [PubMed: 11942816]
- xxxi. Han LB, Zhang C, Yazawa H, Shimada S. *J. Am. Chem. Soc.* 2004; 126:5080–5081. [PubMed: 15099086]
- xxxii. Niu M, Fu H, Jiang Y, Zhao Y. *Chem. Commun.* 2007:272–274.
- xxxiii. Chauzov VA, Kostina LP. *J. Gen. Chem. USSR*. 1991; 61:1149.

- xxxiv. a) Solovetskaya LA, Sergeev NM, Magdeeva RK, Nifant'ev EE. *J. Gen. Chem. USSR*. 1985; 55:1072–1073. b) Nifant'ev EE, Solovetskaya LA, Magdeeva RK. *J. Gen. Chem. USSR*. 1985; 55:2010–2015.
- xxxv. Khachatryan RA, Grigoryan NY, Indzhikyan MG. *Russ. J. Gen. Chem.* 1994; 64:1143–1138.
- xxxvi. Bunlaksananusorn T, Knochel P. *Tetrahedron Lett.* 2002; 43:5817–5819.
- xxxvii. Han LB, Choi N, Tanaka M. *Organometallics*. 1996; 15:3259–3261.
- xxxviii. Han LB, Zhao CQ, Tanaka M. *J. Org. Chem.* 2001; 66:5929–5932. [PubMed: 11511276]
- xxxix. Van Rooy S, Cao C, Patrick BO, Lam A, Love JA. *Inorg. Chem.* 2006; 359:2918–2923.
- xl. Han LB, Hua R, Tanaka M. *Angew. Chem. Int. ed.* 1998; 37:94–96.
- xli. Niu M, Fu H, Jiang Y, Zhao Y. *Chem. Comm.* 2007:272–274. [PubMed: 17299636]
- xlii. Allen A Jr, Ma L, Lin W. *Tetrahedron Lett.* 2002; 43:3707–3710.
- xliii. Stone JJ, Stockland RA Jr, Reyes JM Jr, Kovach J, Goodman CC, Tilman ES. *J. Mol. Catal. A: Chem.* 2005; 226:11–21.
- xliv. Stockland RA Jr, Lipman AJ, Bawiec JA III, Morrison PE, Guzei IA, Findeis PM, Tamblin JF. *J. Organomet. Chem.* 2006; 691:4042–4053.
- xl. Stiles AR, Vaughan WE, Rust FF. *J. Am. Chem. Soc.* 1958; 80:714–716.
- xlvi. a) Nifant'ev EE, Magdeeva RK, Dolidze AV, Ingorokva KV, Samkharadze LO, Vasyanina LK, Bekker AR. *J. Gen. Chem. USSR*. 1991; 61:83–92. b) Nifant'ev EE, Magdeeva RK, Dolidze AV, Ingorokva KV, Vasyanina LK. *J. Gen. Chem. USSR*. 1993; 63:1201–1205.
- xlvi. Reznikov AN, Sokolova MV, Skvortsov NK. *Russ. J. Gen. Chem.* 2004; 74:1461–1462.
- xlvi. Tayama O, Nakano A, Iwahama T, Sakaguchi S, Ishii Y. *J. Org. Chem.* 2004; 69:5494–5496. [PubMed: 15287806]
- lxix. a) Jessop CM, Parsons AF, Routledge A, Irvine D. *Tetrahedron Lett.* 2003; 44:479–483. b) Jessop CM, Parsons AF, Routledge A, Irvine DJ. *Eur. J. Org. Chem.* 2006:1547–1554.
- l. Russell GA, Ngoviwatchai P. *J. Org. Chem.* 1989; 54:1836–1842.
- li. Han LB, Mirzaei F, Zhao CQ, Tanaka M. *J. Am. Chem. Soc.* 2000; 122:5407–5408.
- lii. Reznikov AN, Skortsov NK. *Russ. J. Gen. Chem.* 2007; 77:1170–1177.
- liii. Shulyupin MO, Franciò G, Beletskaya IP. *Adv. Synth. Catal.* 2005; 347:667–672.
- liv. Xu Q, Han LB. *Org. Lett.* 2006; 8:2099–2101. [PubMed: 16671791]
- lv. Reichwein JF, Patel MC, Pagenkopf BL. *Org. Lett.* 2001; 3:4303–4306. [PubMed: 11784203]
- lvi. Ajellal N, Thomas CM, Carpentier J-F. *Adv. Synth. Catal.* 2006; 348:1093–1100.
- lvii. Zhao CQ, Han LB, Tanaka M. *Organometallics*. 2000; 19:4196–4198.
- lviii. Mirzaei F, Han LB, Tanaka M. *Tetrahedron Lett.* 2001; 42:297–299.
- lix. Beaufils F, Dénès F, Renaud P. *Angew. Chem. Int. Ed.* 2005; 44:5273–5275.
- lx. Han LB, Tanaka M. *J. Am. Chem. Soc.* 1996; 118:1571–1572.
- lxi. Zhao CQ, Han LB, Goto M, Tanaka M. *Angew. Chem. Int. Ed.* 2001; 40:1929–1932.
- lxii. a) Goulioukina NS, Dolgina TM, Beletskaya IP, Henry J-C, Lavergne D, Ratovelomanana-Vidal V, Genet J-P. *Tetrahedron Asymmetry*. 2001; 12:319–327. b) Gulykina NS, Dolgina TM, Beletskaya IP. *Russ. J. Org. Chem.* 2003; 39:797–807.
- lxiii. Allen A Jr, Manke DR, Lin W. *Tetrahedron Lett.* 2000; 41:151–154.
- lxiv. Han L-B, Ono Y, Shimada S. *J. Am. Chem. Soc.* 2008; 130:2752–2753. [PubMed: 18257571]

$\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{H}$, hypophosphorous acid, HPA

$\text{R}^1 = \text{OR}$, $\text{R}^2 = \text{H}$, alkyl phosphinate ($\text{R} = \text{alkyl}$)

$\text{R}^1 = \text{OM}$, $\text{R}^2 = \text{H}$, hypophosphite ($\text{M} = \text{Na}$, NH_4 , PhNH_3 , etc.)

$\text{R}^1 = \text{OR}$, $\text{R}^2 = \text{alkyl or aryl}$, *H*-phosphinate ($\text{R} = \text{H}$, alkyl)

$\text{R}^1, \text{R}^2 = \text{alkyl or aryl}$, secondary phosphine oxide

$\text{R}^1, \text{R}^2 = \text{OR}$, *H*-phosphonate, dialkylphosphite ($\text{R} = \text{alkyl}$)

hydrophosphinylation

hydrophosphonylation

Scheme 1.

Hydrophosphinylation and hydrophosphonylation reactions.

Scheme 2.

Industrial preparation of phosphorus trichloride and hypophosphites.

Scheme 3.
Preparation of Monopril (Fosinopril)

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

Scheme 5.

Coward's radical hydrophosphinylation of vinylglycine.

TBPP (75 %)

TBPP or Et₃B/O₂ (85 %)

TBPP (83 %)

TBPP (80 %)

TBPP (78 %)

Et₃B/O₂ (63 %)

TBPP (76 %)

TBPP (70 %)

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

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

Scheme 8.

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

Substrate	Catalyst	Product	Isolated yield (%)
Hex	$\text{Pd}_2\text{dba}_3/\text{xantphos}$		100
$\text{Pd}_2\text{dba}_3/\text{xantphos}$		97
$\text{Pd}_2\text{dba}_3/\text{xantphos}$		95
$\text{Pr}-\text{C}\equiv\text{C}-\text{Pr}$	$\text{Pd}_2\text{dba}_3/\text{xantphos}$		91
NHCBz	$\text{Pd}_2\text{dba}_3/\text{xantphos}$		86

Scheme 9.

Environmentally-friendly synthesis of phosphonic acids.

Scheme 10.

Regiocontrolled hydrophosphinylation of terminal alkynes.

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

Scheme 12.

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

Scheme 13.

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

<i>H</i> -Phosphinate	R ³	NMR yield	Time/temp
	<i>n</i> -C ₈ H ₁₇	72 %	10 h/120 °C
	<i>n</i> -C ₂₀ H ₄₁	91 %	2 h/200 °C
	P(O)Ph ₂	97 %	12 h/120 °C
	<i>n</i> -C ₈ H ₁₇	77 %	10 h/120 °C

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

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

Scheme 16.
Palladium- and rhodium-catalyzed addition of $\text{Ph}_2\text{P}(\text{O})\text{H}$ to 1-octyne.

Scheme 17.
 Proposed mechanism in the Markovnikov hydrophosphinylation

R	Isolated yield	Reaction time
Ph	67 %	12 h
CH ₂ Ph	72 %	18 h

Scheme 18.

Copper-catalyzed hydrophosphinylation.

Solvent	Solvent-free	Water	THF	Ethyl lactate
Catalyst	(Ph ₃ P) ₃ RhCl	(Me ₂ PhP) ₃ RhMe ₃	(Ph ₃ P) ₃ RhCl	(Me ₂ PhP) ₃ RhMe ₃
Reaction time	60 min	10-15 min	10-15 min	20 min
Isolated yield	80 %	79 %	86 %	80 %

Scheme 19.
Microwave-assisted addition to ethynyl steroids.

Scheme 20.
Stiles and Nifant'ev radical additions.

Scheme 21.
Radical hydrophosphinylation of *H*-phosphonates with Mn(OAc)₂

Scheme 22.
Tanaka's Pd-catalyzed hydrophosphinylation.

R	Yield	Compound 8	Compound 9
H	85 %	0	1
TMS	99 %	1	0

Scheme 23.
Pagenkopf's regioselectivity studies.

Scheme 24.
Tanaka's allene hydrophosphonylation.

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

Scheme 26.
Alkyne hydrophosphonylation.

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

Ar :

90 %

89 %

87 %

87 %

72 %

Scheme 28.

1,2-Bisphosphonate synthesis via hydrophosphonylation.

R	CyCH ₂	<i>t</i> Bu	Me ₃ Si	Ph	Fc	(CH ₂) ₃ CN	(CH ₂) ₃ Cl
Isolated Yield %	53	58	62	71	56	75	71

Scheme 29.

Dehydrogenative Pd-catalyzed hydrophosphonylation of terminal alkynes.