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Recent Advances in *H*-Phosphonate Chemistry. Part 2. Synthesis of C-Phosphonate Derivatives

Michal Sobkowski, Adam Kraszewski, and Jacek Stawinski

Abstract This chapter provides an overview of recent advances in the development of new methods and protocols for the formation of the P–C bond using *H*-phosphonate diesters as starting materials. Various chemical and stereochemical aspects of the transition metal-catalyzed cross-coupling and organocatalyst-promoted reactions which are relevant to the synthesis of structurally diverse C-phosphonate derivatives are surveyed.

Keywords Aminophosphonates · C-phosphonates · *H*-Phosphonates · Hydroxyphosphonates · Organic catalysis · Transition metal catalysis

Contents

M. Sobkowski (✉), A. Kraszewski (✉), and J. Stawinski (✉)
Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland
e-mail: msob@ibch.poznan.pl; Adam.Kraszewski@ibch.poznan.pl; jstaw@ibch.poznan.pl

Abbreviations

Al-salalen	1,2-Diaminocyclohexane-based Al-complexes
BHT	Butylated hydroxytoluene
BINOL-Al	Binaphthyl Al-complex; for the structure
BINOL-Ti	Binaphthyl Ti-complex
bipy	2,2′-Bipyridine
Cp_2ZrHCl	Bis(cyclopentadienyl)zirconium hydrogen chloride
Cpf	Cyclopalladated ferrocenylimines
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DIPEA	*N,N*-Diisopropylethylamine
DMA	*N,N*-Dimethylacetamide
dmphen	2,9-Dimethyl-1,10-phenanthroline
DPAP	2,2-Dimethoxy-2-phenylacetophenone
dpephos	Bis-[2-(diphenylphosphino)phenyl]ether
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	Dichloro[1,3-bis(diphenylphosphino)propane
KHMDS	Potassium bis(trimethylsilyl)amide
$Pd_2(dba)_3(CHCl_3)$	Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
PEG-600	Polyethylene glycol, MW 600 Da
Pht-M	Tetra-*tert*-butylphthalocyanine complexes
Pro	Proline
(*R*)-BINAP	(*R*)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Schiff-Al	Tridentate Schiff base Al(III) complexes
SDS	Sodium dodecylsulfate
(*S*)-TRIP	Binaphthyl-derived phosphoric acid
TAP	Tetraaminophosphonium salt
TBO-Al	Bis(8-quinolinato) dinaphthyl
TPP	Triphenylphosphine
TPPA	Phthalocyanine analogues
Tween-20	Polyoxyethylene sorbitan monolaurate
Xantphos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis-(diphenylphosphine)

1 Introduction

Four-coordinated phosphorus compounds containing P–C bonds (C-phosphonates and C-phosphinates) are stable, usually non-hydrolyzable by enzymes, and serve as isosteric analogues of phosphate esters [1–3]. Thus, they are ideal for use as target-specific modulators of a variety of biological processes, e.g., pesticides and therapeutics [4]. Compounds with single or multiple P–C bonds are also important synthetic intermediates [5] and find broad agricultural [6, 7] and industrial applications [8].

For the formation of the P–C(sp^3) bond, the most common approaches are still those involving the Michaelis–Arbuzov [9, 10] and the Michaelis–Becker reactions [11, 12], or the addition to a carbonyl group [13, 14]. However, in recent decades, the transition metal mediated P–C bond formation strategy has started to become widely used, especially in the synthesis of P–C(sp^2) derivatives [5, 15–18]. In the context of using *H*-phosphonate diesters as phosphorus partners for P–C bond formation, we discuss recent progress in the addition of these compounds to carbonyl derivatives (aldehydes, ketones, imines) and in the transition metal catalyzed cross-coupling reactions which afford products with P–C(sp), P–C(sp^2), and P–C(sp^3) bonds [17].

This review covers selected, important contributions to *H*-phosphonate chemistry in the last 5 years (2009–2013) towards C-phosphonate synthesis. Different aspects of *H*-phosphinate and *H*-phosphine oxide chemistry have recently been reviewed [17, 19–22].

2 Synthesis of α-Aminophosphonates and Related Compounds

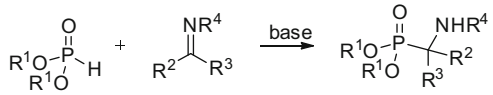
Addition of *H*-phosphonate diesters to a carbonyl group and its derivatives has been known for years as a convenient way to prepare α-functionalized C-phosphonates, especially α-aminophosphonates and α-hydroxyphosphonates [13, 14]. Because of a wide range of practical applications [5–8], recent research in this area has been focused on finding new catalysts and developing stereoselective approaches [23].

α-Aminophosphonates are typically formed in base catalyzed reactions of imines with *H*-phosphonate diesters (the Pudovik reaction [24]) or in a three-component one-pot reaction involving a carbonyl compound, an amine, and an *H*-phosphonate diester (the Kabachnik–Fields reaction [14, 25]). General forms for these reactions are shown in Scheme 1.

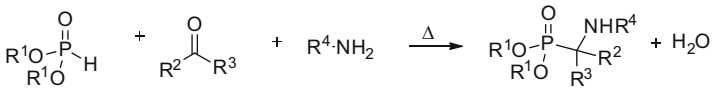
The Kabachnik–Fields reaction, because of its wide scope and experimental simplicity, has, in recent years, dominated the synthetic procedures for the preparation of aminophosphonates. This reaction is usually carried out with equimolar amounts of reactants with or without removal of water (e.g., molecular sieves, azeotropic distillation), and with or without a catalyst. The most significant modifications recently introduced consist of using microwave irradiation as an energy source [26, 27], ionic liquids as a reaction medium [13], and different types of catalysts [28]. Some mechanistic aspects of this reaction have also been investigated [14, 28].

A typical example is the preparation of α-aminophosphonates containing an adamantyl moiety (70–80% yield), using microwave heating in the presence of cadmium(II) iodide as a catalyst and molecular sieves (4 Å) as a dehydrating agent [27]. As substrates, various primary amines containing adamantyl fragments, 2-methylpropanal, and diethyl *H*-phosphonates were used. Since the reaction

The Pudovik reaction



The Kabatchnik-Fields reaction



R^1 = alkyl; R^2, R^3 = alkyl or aryl; R^4 = alkyl, aryl or H

Scheme 1 The Pudovik and the Kabachnik–Fields reactions

system in the Kabachnik–Fields reaction is rather complex, various bimolecular processes between the reactants may cause the formation of unexpected products, especially under microwave heating conditions [26].

The addition of phosphorus nucleophiles to imines (substrates in the Pudovik reaction and the putative intermediates in the Kabachnik–Fields reaction) is catalyzed by Lewis acids (e.g., $SnCl_2$, $SnCl_4$). However, because of the generation of water during the course of the Kabachnik–Fields reaction, these Lewis acids are often deactivated. To overcome this problem, micellar solutions of surfactants were used as catalysts. Sobhani and Vafaee [29] reported on the efficient formation of α-aminophosphonates (yields >90%) from aldehydes, amines, and diethyl *H*-phosphonate in the presence of sodium dodecylsulfate (SDS, Fig. 1) in aqueous solution. The nonionic surfactant Tween-20 (polyoxyethylene derivative of sorbitan monolaurate; Sorbitan-20; Fig. 1) was also used under environmentally friendly conditions for the one-pot, three-component synthesis of aminophosphonates [30]. The major advantages were claimed to be the wide scope of substrates, simple work-up, short reaction time (ca 30 min), and high yields.

Metallophthalocyanines, structurally related to metal porphyrins, are used as efficient catalysts in organic synthesis [31]. In 2003, Matveeva et al. [32] reported on the application of tetra-*tert*-butylphthalocyanine–metal complexes (Pht-M, Fig. 1) to the Kabachnik–Fields reaction. Various α-aminophosphonates derived from sterically hindered ketones were obtained in acceptable yields. These conditions were extended to reactions involving aminopyridines as amino components [33]. In toluene (110°C, 24–78 h), in the presence of molecular sieves (4 Å), 3-aminopyridine and diethyl *H*-phosphonate afforded the corresponding α-aminophosphonates, both with aldehydes and ketones, while 2- and 4-aminopyridines reacted only with aldehydes (yields ca. 70%). An eco-friendly version of this reaction was also developed using a water-soluble Cu(II) complex of a phthalocyanine analogue (TPPA, Fig. 1), in which the benzene rings were replaced by quaternary pyridine moieties [34]. Under aqueous conditions, in the

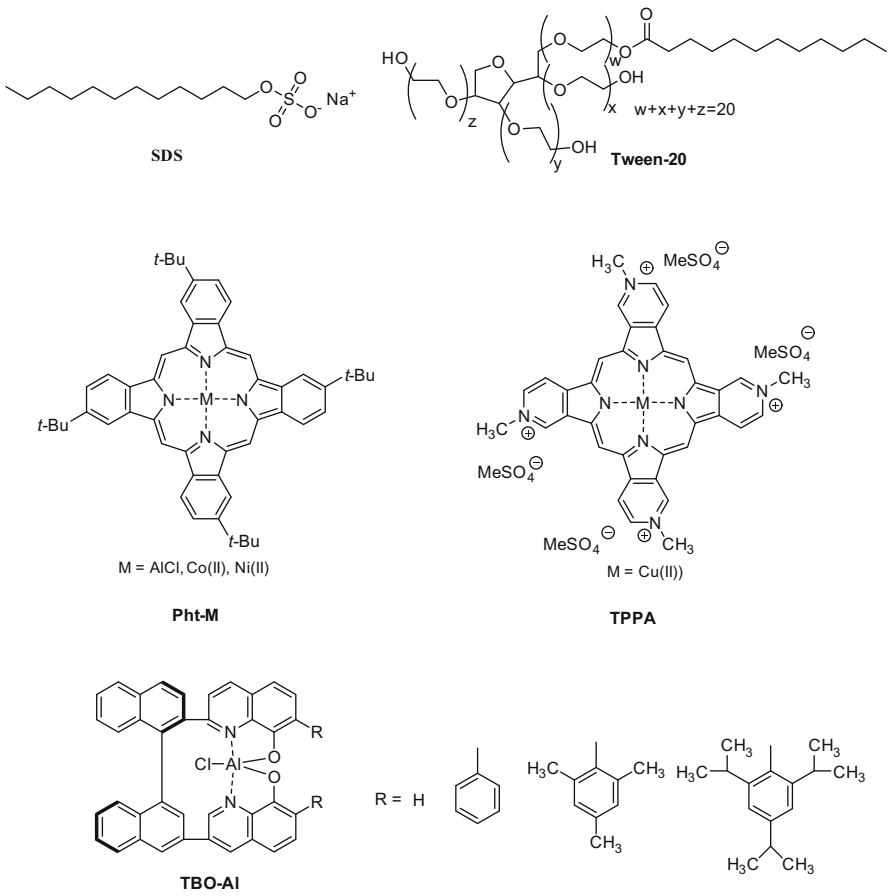
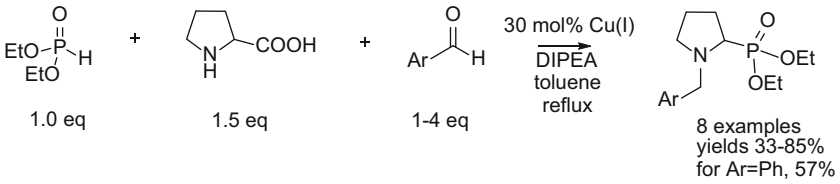


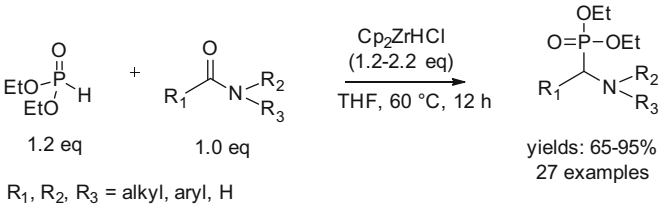
Fig. 1 Some surfactants and catalysts used in the synthesis of α-aminophosphonates

presence of a small amount of catalyst (0.16%), aminophosphonates derived from aromatic amines and diverse aldehydes (alkyl, aryl, allyl, heteroaryl) were formed in >90% yields in a short time (0.5–2 h).

A new, general protocol for the Kabachnik–Fields reaction, based on heterogeneous catalysis by H-beta zeolite, was developed by Choudhary et al. [35]; it was found to be applicable to aldehydes and ketones, as well as aliphatic and aromatic amines. Apart from high efficiency (yields ca. 90%), the major advantages of this method are operational simplicity, reusability of the catalyst, short reaction time, and tolerance to sensitive functional groups. Heterogeneous catalysts based on iron-doped single walled carbon nanotubes showed similar efficiency and usability [36]. Simple inorganic salts ($CaCl_2$ [37] and $KHSO_4$ [38]), phosphorofluoridic acid [39], and phenylboronic acid [40] have been advocated as superior, cheap catalysts for the Kabachnik–Fields reaction under solvent-free conditions. Tosyl



Scheme 2 Decarboxylative three-component coupling reaction for α-aminophosphonates



Scheme 3 Reductive phosphonylation of amides

chloride was also proposed as a catalyst for this reaction because of its ability to stabilize more nucleophilic, tervalent phosphite forms of *H*-phosphonates [41].

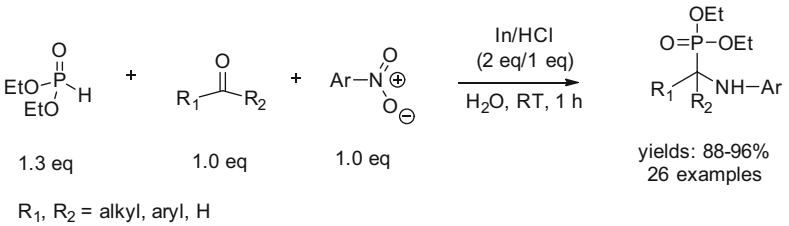
Despite the obvious advantages of using catalysts, for certain applications (e.g., synthesis of α-aminophosphonates containing rigid β-amino acids with the amino function at bridgehead positions) the uncatalyzed, thermal version of the Kabachnik–Fields reaction remains a viable option [42].

Apart from various modifications of the classical Kabachnik–Fields reaction, a handful of new methods for the preparation of α-aminophosphonates were recently developed. A copper/DIPEA-catalyzed reaction involving an aldehyde-induced decarboxylative coupling of proline with *H*-phosphonate diesters [43] is shown in Scheme 2. This reaction worked well with a variety of amino acids and turned out to be useful for the preparation of potential ligands for the organic synthesis of biologically important amino acid analogues. An uncatalyzed version of this reaction (absence of base and catalyst) was also developed [44].

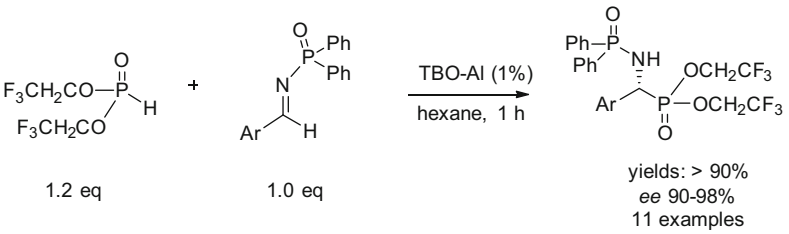
An interesting approach to α-aminophosphonate synthesis, based on in situ reduction of amides with bis(cyclopentadienyl)zirconium hydrogen chloride (Cp_2ZrHCl, the Schwartz's reagent) in the presence of dialkyl *H*-phosphonates, is presented in Scheme 3 [45]. The main advantages of this direct transformation of amides into aminophosphonates are a broad scope of substrates, mild reaction conditions, and good yields.

A distinct approach to α-aminophosphonates was developed using aromatic nitro compounds as the source of an amino component [46] (Scheme 4). This is a three-step, one-pot reaction which involves initial reduction of the nitro compound to an amine with In/HCl, followed by in situ reaction of the formed imine with *H*-phosphonate diester to afford the corresponding α-aminophosphonate derivative.

Since the synthesis of α-aminophosphonates produces a new chiral center on the α-carbon atom, these compounds are obtained in an enantioselective manner with



Scheme 4 Synthesis of aminophosphonates starting from nitro compounds



Scheme 5 Enantioselective synthesis of aminophosphonates using chiral catalyst

chiral auxiliaries. Because of the mechanistic complexity of the Kabachnik–Fields reaction, a Pudovik type of reaction with the preformed imine derivatives (see below) is normally used instead.

Scheme 5 depicts an enantioselective version of the Pudovik reaction using aldimines, an *H*-phosphonate diester, and a chiral catalyst TBO-Al (containing a chiral tethered bis(8-quinolinato) ligand) (Fig. 1) [47].

This catalytic system is very efficient both in yields of the formed α-aminophosphonates and degree of enantioselectivity ($ee > 90\%$) for various aromatic and heteroaromatic aldimines. With the growing interest in organocatalysis, new protocols were developed for enantioselective transformations of imines and related compounds into α-aminophosphonates. These transformations used quinine-squaramide [48] or chiral Brønsted acids [45] as catalysts [49, 50].

Regarding asymmetric synthesis employing the Kabachnik–Fields reaction, List et al. [51] described an impressive enantio- and diastereoselective protocol for the formation of β-branched α-aminophosphonates. The reactants consisted of racemic aldehydes, *p*-anisidine, and an *H*-phosphonate diester in the presence of chiral BINOL-derived phosphoric acid [(*S*)-TRIP, Fig. 2] (Scheme 6). This reaction was particularly challenging because it combined a dynamic kinetic resolution (at the level of imine formation) with the parallel creation of an additional stereogenic center on the α-carbon to the phosphorus center.

Another example of asymmetric synthesis of α-aminophosphonates is the addition of dialkyl *H*-phosphonates to *tert*-butylsulfinyl imines, where chirality is

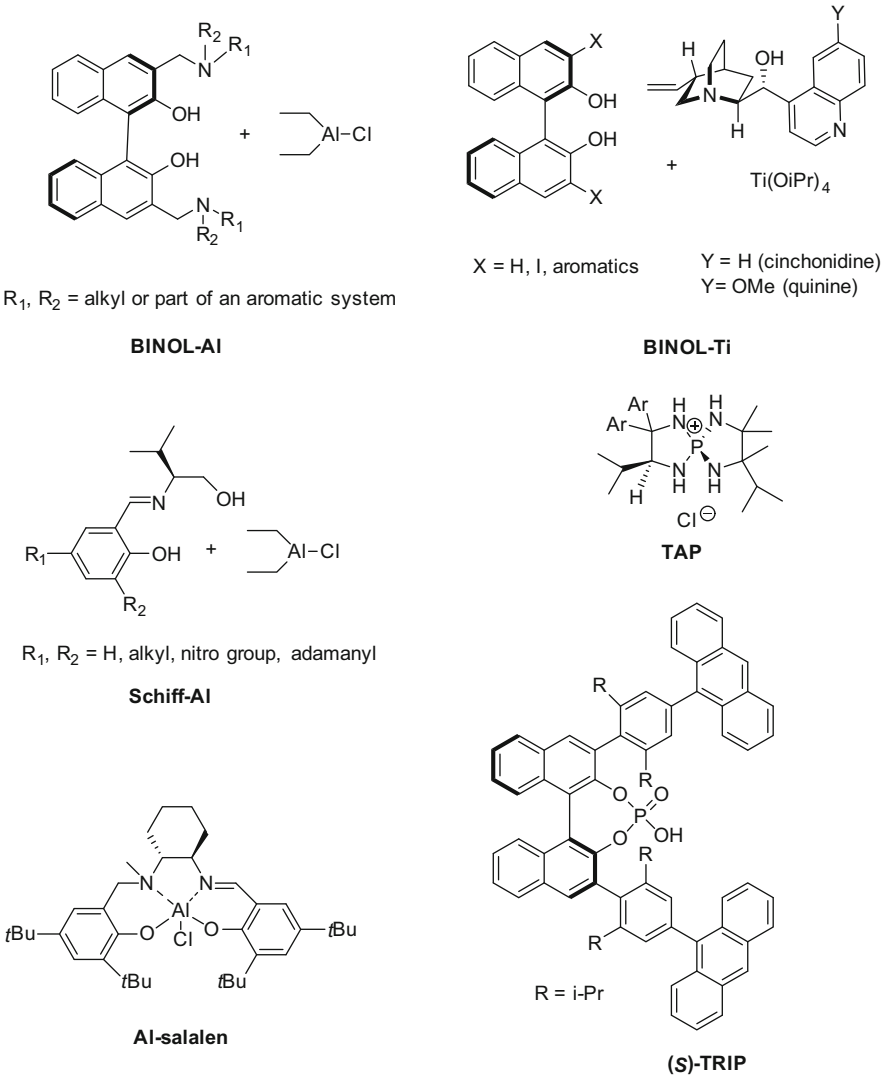
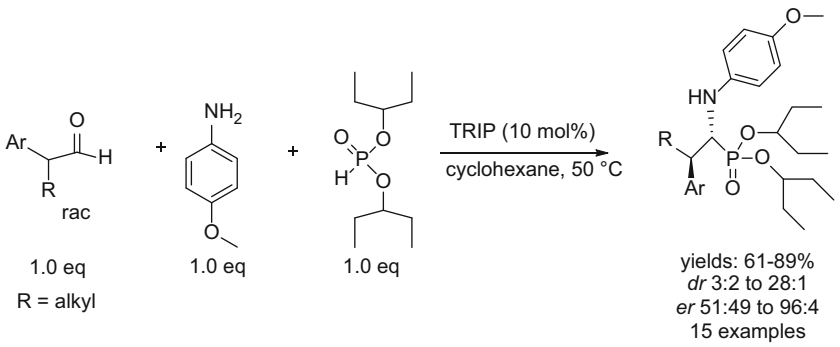
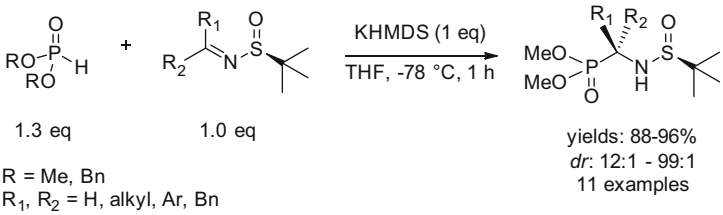


Fig. 2 Some catalysts used in the synthesis of α-amino- and α-hydroxyphosphonates

imparted by a chiral sulfinyl group [52] (Scheme 7). The reaction was carried out in the presence of potassium bis(trimethylsilyl)amide (KHMDS) as a base catalyst. The diastereoselectivity observed was usually high. Even a sterically hindered substrate (e.g., ketimine, derived from pinacolone) provided the α-aminophosphonates in high yield (94%) with a high diastereoselective selection (*dr* 99:1).



Scheme 6 Enantio- and diastereoselective Kabachnik–Field reaction



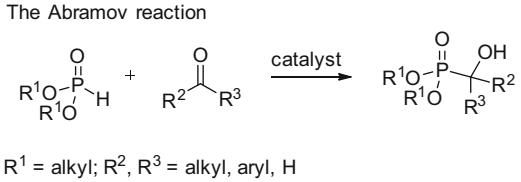
Scheme 7 Asymmetric synthesis of aminophosphonates

3 Synthesis of α-Hydroxyphosphonates and Related Compounds

α-Hydroxyphosphonates can be treated as analogs of natural phosphates and hydroxy carboxylic acids. As such, they attracted considerable interest as biologically active molecules, complexing agents, and important chemical intermediates [53, 54]. Preparative methods for α-hydroxyphosphonates are usually based on the addition of dialkyl *H*-phosphonates to aldehydes and ketones in an Abramov reaction [55] (Scheme 8). This experimentally simple reaction is further facilitated with catalyst addition [13, 53, 54].

Recently, basic alumina (chromatographic grade) was found to catalyze efficiently the addition of dimethyl *H*-phosphonates to a variety of carbonyl compounds (aldehydes and ketones) at room temperature under solvent-free conditions (reaction time ca. 72 h) [56]. To speed-up the reaction, microwave irradiation (in combination with a strong base, DBN) [57] and ultrasound excitation [58] (in the presence K_2HPO_4 as catalyst) were also used. In both cases, improved yields and shortened reaction times (5–45 min) were observed. To facilitate separation and recovery of the catalyst from the reaction mixtures, magnetic nanoparticles Fe_3O_4 with immobilized strong bases (guanidine) were proposed as novel, magnetic interphase nanocatalysts [59] (80°C, solvent-free conditions, aromatic and heteroaromatic aldehydes; yields 70–98%).

Scheme 8 Synthesis of α-hydroxyphosphonates using the Abramov reaction

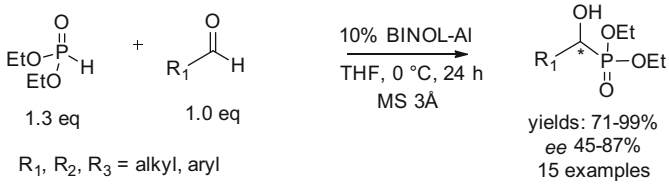


A highly efficient catalyst based on tetracoordinate lanthanide amides, $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$, was proposed by Xu and Shen [60]. A key factor affecting catalytic activity was the presence of LiCl. The reaction time was very short (5 min) and α-hydroxyphosphonates derived from aromatic aldehydes were obtained in high yields (>90%) using very little catalyst (0.1 mol%). This catalytic system was developed further by combining it with calix[4]pyrrole [61] to form dinuclear trivalent lanthanide amido complexes bearing tetra-anion calix[4]pyrrolyl ligands. Alternatively, the lanthanide catalyst could be combined with methylene-linked pyrrolyl-amino ligands [62] to form dinuclear lanthanide complexes. Both groups of catalysts turned out to be highly efficient for the hydrophosphonylation of aldehydes and inactivated ketones. Some mechanistic aspects of these lanthanide amide-catalyzed reactions have been investigated [60] as well. A high-valent oxo-molybdenum complex (MoO_2Cl_2) has also been suggested as a superior catalyst for the hydrophosphonylation of aldehydes [63]. Computational studies revealed that activation of the *H*-phosphonate diester started with coordination of the P=O group to molybdenum, followed by hydrogen transfer from the P–H bond to the Mo=O functionality [63].

In the last decade, the coordination chemistry of alkaline earth metals (Ca, Sr, Ba) became a major research area [64]. As a result, highly effective alkaline earth catalysts were developed for the sterically demanded hydrophosphonylation of aldehydes and inactivated ketones [65]. These heteroleptic complexes of type $[(Me_3Si)_2N]_2Ae(THF)_2$ (Ae=Ca, Sr, Ba), with or without multidentate ancillary ligands, exhibited exceptionally high reactivity in the Abramov reaction using as little catalyst as 0.02 mol% [65]. In most cases the reaction time under solvent-free conditions at room temperature was very short (1–10 min). Furthermore, for a given type of complex and for all carbonyl substrates investigated, the activity of the catalytic system always increased with the size of the metal atom (Ca < Sr < Ba) [53, 54].

For ketones known to be much less reactive than aldehydes in the Abramov reaction, the Lewis acid Ti(O*i*-Pr)$_4$ permitted efficient synthesis of quaternary α-hydroxyphosphonates [66]. Aromatic ketones, regardless of the electronic nature of an aryl moiety, showed high reactivity (yields >90%), while aliphatic ketones gave slightly lower yields (ca. 80%).

A new approach to α-hydroxyphosphonates was recently reported [67]. It makes use of alcohols or ethers as starting materials which are oxidized with $CuCl_2$/*tert*-butyl hydroperoxide to form in situ the corresponding carbonyl compounds. These are added to *H*-phosphonate diesters, affording α-hydroxyphosphonates in



Scheme 9 Enantioselective synthesis of α-hydroxyphosphonates using BINOL-Al catalyst

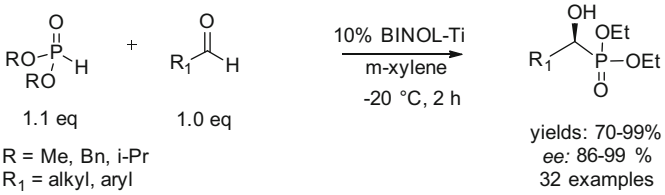
moderate to good yields [56]. This method can be convenient when the corresponding aldehyde is unavailable. The scope of this reaction remains to be established.

Since the biological activity of phosphonic acid derivatives is primarily determined by the absolute configuration of the α-carbon [68, 69], enantio/diastereoselective synthesis of α-hydroxyphosphonates has became a focus of synthetic endeavors in recent years [53, 54].

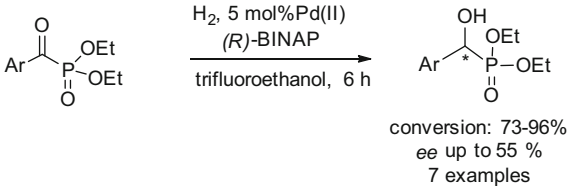
Feng et al. [70] developed a bifunctional chiral Al(III) complex of various BINOL derivatives (BINOL-Al, Fig. 2) for asymmetric hydrophosphonylation of aldehydes with *H*-phosphonate diesters (Scheme 9). This type of chiral catalyst binds both the electrophilic carbonyl substrate (via a metal center acting as a Lewis acid) and a nucleophilic phosphorus reagent (with the amine moiety acting as a Lewis base) in the transition state. This furnishes a strong stereoselection, affording α-hydroxyphosphonate derivatives with high enantioselectivity. The yields and the enantioselectivity may be improved by the presence of molecular sieves 3 Å [70]. A catalytic system as used for the enantioselective synthesis of α-aminophosphonates (TBO-Al) also worked well for the preparation of α-hydroxyphosphonates [47].

In addition, other Al(III) complexes containing chiral ligands were proposed for the enantioselective hydrophosphonylation of aldehydes. These are shown in Fig. 2 and include tridentate Schiff base Al(III) complexes (Schiff–Al) [71] and Al(III)-salalen complexes (Al–salalen) [72]. All these complexes were sterically and electronically adjusted to provide high enantioselective yields ($ee > 90\%$) in the addition process of *H*-phosphonate diesters to aldehydes (THF, −15°C, 24–60 h). A hydrogenated version of the chiral Schiff base in Fig. 2 was used for the enantioselective hydrophosphonylation of trifluoromethyl aromatic/heteroaromatic ketones (*ee* up to 90%) [73]. Computational studies on Schiff-Al [74] and Al-salalen [75] (Fig. 2) catalyzed hydrophosphonylation of benzaldehyde revealed some mechanistic aspects of these reactions. For the latter, calculations showed that the catalytic cycle involves formation of Al–phosphite (via P–H activation) as the catalytically active species, followed by coordination of benzaldehyde, nucleophilic addition, and deprotonation of *H*-phosphonate as the rate-determining step [66]. For the Schiff–Al-catalyzed reaction, the computations pointed to a dimer as a catalytically active species and to C–P bond formation as rate determining [65].

A self-assembled bifunctional catalyst based on BINOL derivatives and cinchona alkaloids (cinchonidine and quinine) coordinated by Ti(IV) cation was proposed by You et al. [76] (BINOL-Ti in Fig. 2 and Scheme 10). A modular



Scheme 10 Enantioselective synthesis of α-hydroxyphosphonates using BINOL-Ti catalyst



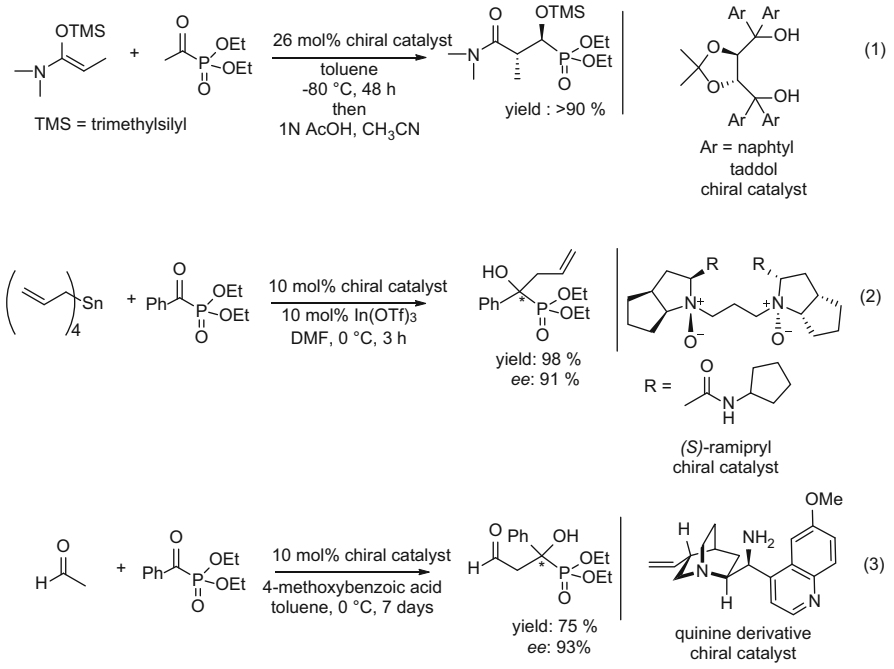
Scheme 11 Asymmetric hydrogenation of α-ketophosphonates

form of this catalyst is constructed from commercially available components which enable its steric and electronic properties to be tuned. This catalyst system seems to be more efficient in terms of yield and enantioselection compared to the one based on BINOL-Al.

The protocol developed by Ooi et al. [77] approaches the enantioselective synthesis of α-hydroxyphosphonate in a different way. This involves in situ formation of chiral dialkyl phosphite salt, a putative nucleophile in the Abramov reaction, from dialkyl *H*-phosphonate and a triaminoiminophosphorane [78], generated upon reaction of chiral tetraaminophosphonium salt TAP (Fig. 2) with KO*t*Bu. In THF, at −98°C, this chiral *P*-nucleophile adds to aromatic aldehydes in an enantioselective manner (*ee* 91–99%) to afford the corresponding α-hydroxyphosphonates in high yields (>90%) [77].

Apart from these protocols for P–C bond formation, enantioselective synthesis of α-hydroxyphosphonates can be realized via asymmetric hydrogenation or asymmetric addition to the carbonyl group of α-acylphosphonates. Although mechanistically different (formation of the P–C bond occurs via reaction of *H*-phosphonate diesters with acyl chlorides), we discuss these reactions here.

As shown in Scheme 11, asymmetric hydrogenation of α-ketophosphonates using chiral palladium catalysts [79] afforded various α-hydroxyphosphonates in excellent yields and with moderate enantioselectivity. Typical chiral ligands used for asymmetric hydrogenation [e.g., (*R*)-BINAP] can also be used for this purpose. Within the series of dialkyl benzoylphosphonates, the diisopropyl esters gave the highest *ee*. The reaction was strongly solvent-dependent and did not occur in nonfluorinated solvents (e.g., methanol, chloroform). In a ligand-free system (palladium on carbon), quantitative conversion into racemic hydroxyphosphonates occurred [79].



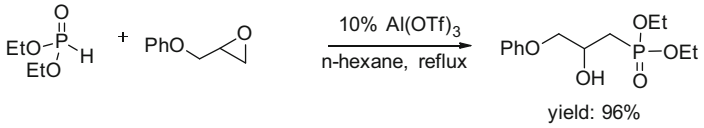
Scheme 12 Asymmetric addition to α-ketophosphonates to produce α-hydroxyphosphonates

Three additional examples of enantioselective synthesis of α-hydroxyphosphonates via addition to the carbonyl functionality of ketophosphonates are shown in Scheme 12. Reaction (1) represents the diastereoselective and enantioselective Mukaiyama aldol reaction catalyzed by various hydrogen-bond donors [80]. For the example shown, in the presence of a chiral taddol catalyst, the conversion was better than 90%, *dr* (anti/syn) 1:30, and *ee* 90%. This mild and general method provides access to α-hydroxyphosphonate derivatives with two chiral centers, using a commercially available chiral catalyst.

Reaction (2) shows a highly enantioselective allylation of aromatic α-ketophosphonates (conversion up to 98%, *ee* 91%) [81]. The bifunctional catalyst system, C_2-symmetric (*S*)-ramipryl and $In(OTf)_3$, provided Lewis base activation of tetraallyltin by the *N*-oxide functionalities, and indium(III) as Lewis acid, to activate aromatic α-ketophosphonate.

Reaction (3) is an example of a cross-aldol reaction between enolizable aldehyde (acetaldehyde) and an α-ketophosphonate. In the presence of an organocatalyst (9-amino-9-deoxy-*epi*-quinine), an enantioselective aldol coupling yielded β-formyl-α-hydroxyphosphonates (potential anticancer agents) [82] with high enantioselection (*ee* up to 93%).

In contrast to α-hydroxyphosphonates, the β-hydroxy derivatives received less attention as their preparations can be more complex [1]. However, a simple and



Scheme 13 Regioselective opening of epoxides by P-nucleophiles to produce β-hydroxyphosphonates

efficient synthesis of β-hydroxyphosphonate via opening of epoxides with phosphorus nucleophiles (phosphite triesters or *H*-phosphonate diesters) [83] was recently reported (Scheme 13). This reaction was recently extended to the synthesis of ribonucleoside 5′-β-hydroxyphosphonates by stereoselective opening of a chiral oxirane system in nucleoside derivatives with *H*-phosphonate diesters, in the presence of a silylating agent and BF_3 as a Lewis acid catalyst [84].

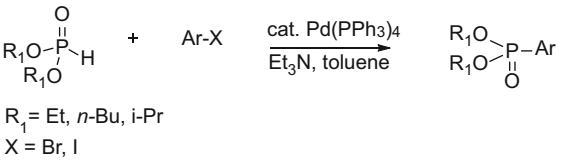
Other studies on biologically active hydroxyphosphonates involved determination of absolute configurations at the α-carbon of fosfazinomycins A and B from *Streptomyces lavendofoliae* containing an α-hydroxyphosphonate motif [85], delineation of decomposition pathways of aryl nucleoside α-hydroxyphosphonates [86] (potential anti-HIV agents), and development of an efficient method for the synthesis of nucleoside α-hydroxyphosphonate monoesters via iodine-promoted hydrolysis of the corresponding nucleoside aryl diesters [86].

4 Pd-Catalyzed Reactions

Transition metal-catalyzed formation of the P–C bond is an important method for preparing organophosphorus compounds [16, 19, 87], thus enabling the synthesis of C(sp^2)–P derivatives which are not accessible by the Michaelis–Arbuzov [9, 10] or Michaelis–Becker [11, 12] reactions. Cross couplings promoted by palladium are stereospecific and occur with retention of configuration at the stereogenic phosphorus center [88–90].

The first palladium(0)-catalyzed cross-coupling reaction between aryl and vinyl bromides and *H*-phosphonate diesters was reported by Hirao et al. [91, 92] (Scheme 14). This classic method has been significantly modified and improved in terms of type of catalyst, palladium source, and reaction conditions to meet the requirements of contemporary synthetic organic demands [16, 17].

By using $Pd(OAc)_2$ as a palladium source and dppf (see Fig. 3) as ligands, Montchamp et al. [93] expanded the scope of the Hirao reaction by including, among other things, activated aryl chlorides as substrates. Stockland et al. [94] developed a room temperature version of the Hirao reaction by using aryl iodides as substrates, $Pd(OAc)_2$ and dpephos (Fig. 3) as a catalytic system, and replacing *H*-phosphonate diesters with more powerful nucleophiles, i.e., their silver salts.



Scheme 14 The Hirao cross-coupling reaction of dialkyl *H*-phosphonates with C(sp^2)-X partners

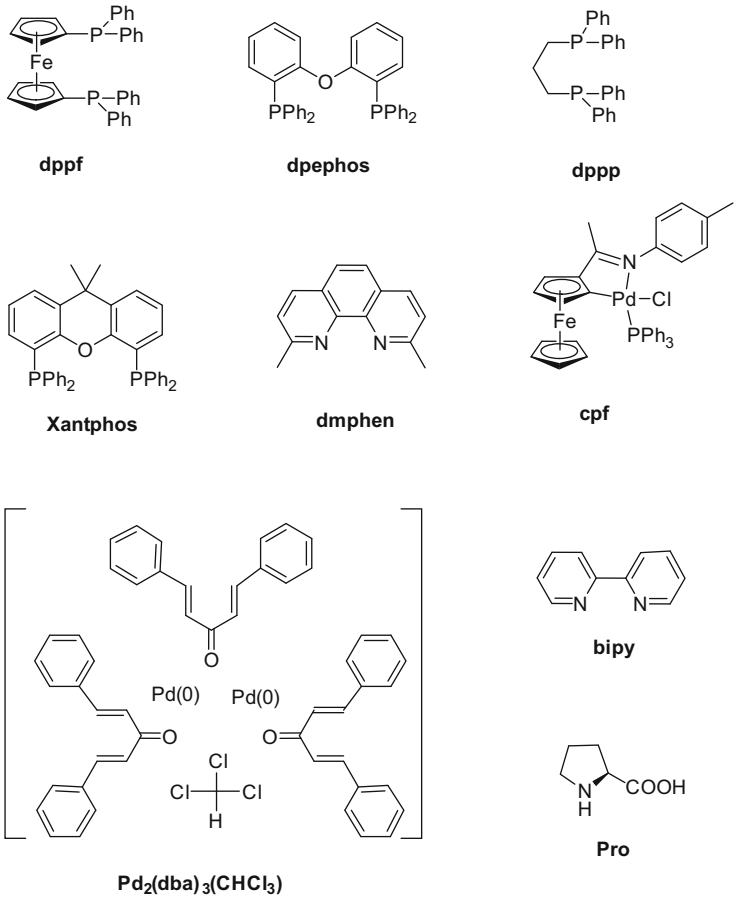


Fig. 3 Some ligands and catalysts/precatalysts used in a palladium-catalyzed cross-coupling reactions

Aminopyridines are poor substrates for the cross-coupling reactions because of the enhanced complexation of palladium. Thus, 2- and 4-aminopyridine derivatives (bromides) under original Hirao's conditions usually give low yields of the

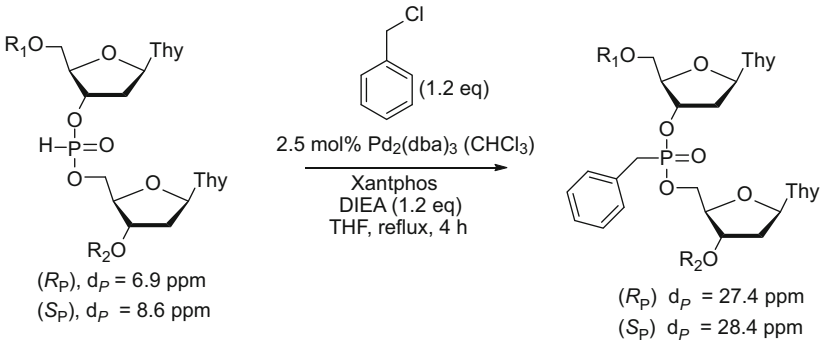
corresponding aminopyridylphosphonates. However, by using ethanol as the solvent and $Pd(OAc)_2$–triphenylphosphine (TPP) as the catalyst system, the yields can be significantly improved [95]. Efficient synthesis of arylphosphonates by the cross coupling of aryl imidazoylsulfonates with *H*-phosphonates, catalyzed by $Pd(OAc)_2$–dppp (Fig. 3) (iPr$_2$NEt as a base), was also reported [96]. The reaction showed good substrate generality and the best results (yields 85–97%) were obtained with dioxane as the solvent. Using $Pd(OAc)_2$ in combination with Xantphos (Fig. 3), an efficient cross coupling of 3-, 4-, and 5-halopyrazoles with *H*-phosphonate diesters, *H*-phosphinates, and secondary phosphine oxides was achieved (THF, 70°C, Et_3N) [97]. Finally, a general and environmentally friendly protocol was developed for the synthesis of arylphosphonates from the corresponding aryl halides (I, Br, Cl) and *H*-phosphonate diesters using standard Hirao catalyst, $Pd(PPh_3)_4$, in polyethylene glycol (PEG-600) (reaction times 15–25 h, yields 80–95%) [98].

Stereoselective synthesis of highly functionalized P-stereogenic nucleosides via a palladium-catalyzed P–C cross-coupling reaction was reported by Hayes et al. [99]. By using the $Pd(OAc)_2$–TPP catalyst system in THF with propylene oxide as a base, completely stereospecific coupling of nucleoside *H*-phosphonate diesters with nucleoside vinyl bromide was achieved. A general and efficient method for the microwave-assisted formation of the P–C bond was also developed. This method is applicable to complex, biologically relevant compounds such as cholesteryl and dinucleotide derivatives [100]. Using a prevalent palladium catalyst, $Pd(PPh_3)_4$, and Cs_2CO_3 as a base in THF, various aryl-, heteroaryl-, and vinylphosphonates were obtained in high yields (80–95%) within 10 min. Recently, a microwave-assisted synthesis of arylphosphonates from aryl bromides and dialkyl *H*-phosphonates, using $Pd(OAc)_2$ and NEt_3 in a Pd-ligand- and solvent-free system, was promoted as an environmentally benign variant of the Hirao reaction [101].

An interesting and rare side reaction was observed during the cross coupling of bromoanilines with diethyl *H*-phosphonate under Hirao's conditions [102]. Together with the expected products, diethyl aminoarylphosphonates, significant amounts (up to 30%) of diethyl phenylphosphonate were formed, which the authors ascribed to an aryl–aryl exchange process in the $Pd(PPh_3)_2ArX$ complexes.

In contrast to arylpalladium(II) complexes, activation and functionalization of benzylic derivatives by palladium is far less common [103]. This is particularly true for cross-coupling reactions with phosphorus nucleophiles, for which a new, efficient method for the synthesis of benzylphosphonate diesters was recently developed [104, 105]. This protocol makes use of $Pd(OAc)_2$ [104] or $Pd_2(dba)_3(CHCl_3)$ [105] as a palladium source and Xantphos (Fig. 3) as a supporting ligand. Various glyceryl, cholesteryl, and dinucleoside benzylphosphonates, with a diverse substitution pattern in the benzyl moiety, could be obtained. Some mechanistic aspects of this reaction were also investigated [105]. An example of the application of this method to the synthesis of dinucleoside benzylphosphonates is shown in Scheme 15.

The catalytic cycle of the Hirao reaction consists of the oxidative addition of a Pd(0)-complex to aryl (or vinyl, benzyl) halides to form arylpalladium(II) species, followed by ligand exchange with a phosphorus nucleophile (usually deprotonated



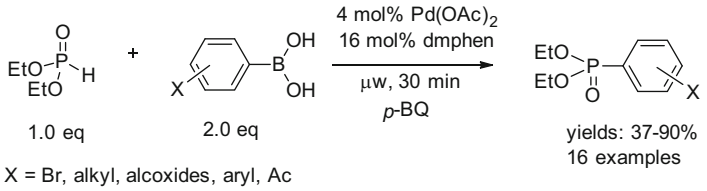
Thy = thymin-1-yl; R_1 = 4,4'-dimethoxytrityl; R_2 = *tert*-butyldimethylsilyl
DIEA = *N,N*-diisopropylethylamine

Scheme 15 Stereospecific synthesis of dinucleoside benzylphosphonates [104]

H-phosphonate), and reductive elimination which liberates the product (aryl-, vinyl-, or benzylphosphonate) and regenerates the Pd(0)-catalyst. Mechanistic aspects of this palladium-mediated cross coupling were investigated in depth in terms of palladium sources, supporting ligands, and the roles of various additives (halides, acetates) on the kinetics and efficiency of the catalytic cycle [106–109]. On this basis, a general, highly efficient protocol was developed for the synthesis of palladium-catalyzed arylphosphonates from *H*-phosphonate diesters and aryl electrophiles, in the presence of acetate ions [109]. The cross-coupling time (30 min vs 23 h, for phenyl triflate) was significantly shortened for bidentate and monodentate supporting ligands, as well as for different aryl electrophiles (iodo, bromo, and triflate derivatives) [100].

The stability, low toxicity, and easy availability of organobismuth compounds have made them attractive substrates in organic synthesis [110]. A novel and highly efficient cross coupling of triarylbismuths with a variety of H–P=O compounds was developed [111]. Since the C–Bi bond is week, it easily adds to Pd(0) species in the presence of 2,2′-bipyridine (bipy, Fig. 3). The catalytic cycle proceeds smoothly without the exclusion of moisture or air, and provides a convenient entry to various arylphosphonates. Some mechanistic aspects of this reaction were probed with DFT calculations [111].

Palladacycles are among the most efficient catalysts in the Heck-type reaction for C–C and C–X bond formation [112]. Wu, Yang, et al. [113] recently developed a new catalytic system based on cyclopalladated ferrocenylimines (cpf, Fig. 3) which efficiently performed synthesis of aryl- and benzylphosphonates. Also, inactive aryl chlorides with electron-donating substituents underwent cross coupling with diisopropyl *H*-phosphonates to afford the corresponding arylphosphonates in good to high yields (DMA, *t*BuOK, 130°C, 3 h). The same catalyst system (cyclopalladated ferrocenylimines, cpf), in combination with a weak, inorganic base (KF) was used for the cross coupling of aryl chlorides with



Scheme 16 Pd(II)-catalyzed arylphosphonate formation [115]

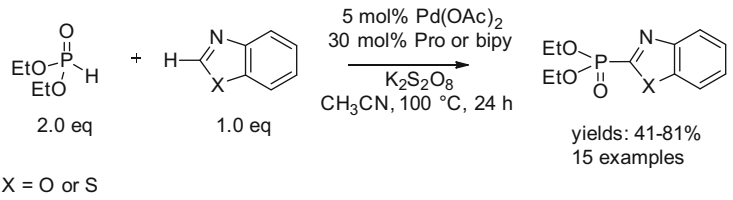
diisopropyl *H*-phosphonate in water [114]. In this case, however, addition of some isopropanol was necessary to suppress hydrolysis of the *H*-phosphonate diester. The method has wide substrate scope and conforms to the idea of green chemistry.

Larhead et al. [115] extended the Pd(II)-catalyzed oxidative Heck reaction [116] to P-arylation by cross coupling aryl boronic acids or aryl trifluoroborates with *H*-phosphonate diesters in the presence of $Pd(OAc)_2$ and rigid bidentate ligand dmphen (Fig. 3), under microwave irradiation (Scheme 16). The above coupling reactions were performed in DMF and occurred without the addition of acid or base. They were performed in the presence of *p*-benzoquinone (*p*-BQ), the most efficient reoxidant for the conversion of Pd(0) into the catalytically active Pd(II) species. Mechanistically, this reaction differs from Pd(0)-catalyzed arylations in the formation of aryl-palladium complexes via transmetallation instead of oxidative addition [104, 105].

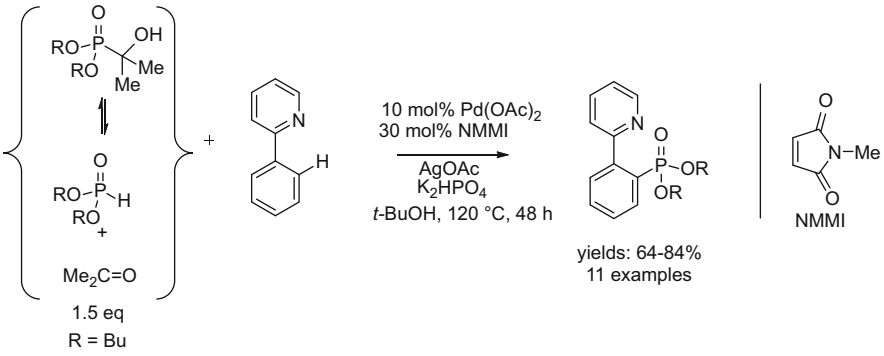
Recently, arylsulfinates have been proposed as new coupling partners in the Pd(II)-catalyzed formation of arylphosphonates [117]. In the presence of $PdCl_2/PPh_3$ as a catalyst system, tetrabutylammonium chloride as an additive, and Ag_2CO_3 as an oxidant, arylphosphonates with diverse substitution patterns could be obtained (yields 70–93%, 28 examples) [117].

In contrast to classical phosphonylation methods which require pre-functionalized Ar–H coupling partners (aryl halides, aryl boronic acid, etc.), a transition metal aromatic C–H activation recently emerged as a viable alternative for C–C and C–heteroatom bonds formation [118–121]. Scheme 17 depicts the first Pd-catalyzed direct phosphonylation of non-functionalized azoles with diethyl *H*-phosphonate (which occurs without the addition of acid or base) [122]. The method consists of an oxidative cleavage of the C–H and P–H bonds and proceeds probably via a Pd(II)/Pd(IV) catalytic cycle. An analogous catalyst system was used for direct phosphonylation (C–H activation) of coumarins with dialkyl *H*-phosphonates to produce the corresponding 3-phosphonylated coumarin derivatives in a highly regioselective manner, with moderate to good yields [123]. Although Pd(II)-catalyzed reactions typically proceed via a Pd(II)/Pd(0) catalytic cycle (Scheme 17), a Pd(IV) species [124] was postulated as an intermediate [122, 123].

A pyridine-directed, palladium-catalyzed phosphonylation of C(sp^2)–H bonds was reported by Murakami et al. [125] and Yu et al. [126]. A perennial problem in this type of reaction is a strong, competing coordination of phosphorus nucleophiles which may hamper the process of activation of less coordinative C–H bonds.



Scheme 17 Pd(II)-catalyzed direct phosphonylation of azoles with dialkyl *H*-phosphonates

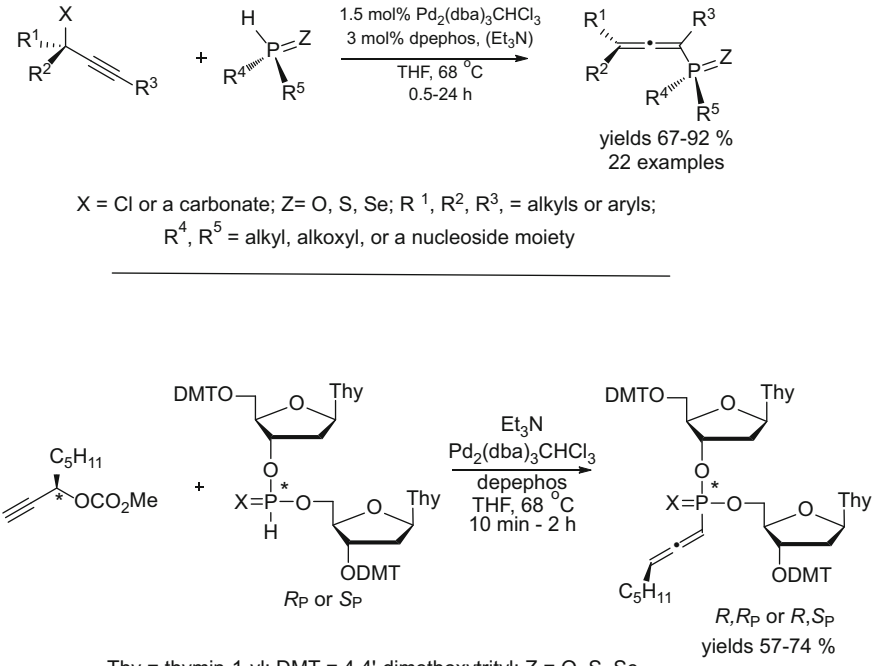


Scheme 18 Pyridine-directed palladium catalyzed phosphonylation of C(sp^2)-H bond

Scheme 18 presents the phosphonylation of 2-phenylpyridine via Pd(II)-catalyzed C–H bond activation [125]. To overcome the problem of catalyst deactivation caused by coordination by the *H*-phosphonate diesters, the corresponding α-hydroxyphosphonate was used as a substrate for a slow, in situ generation of the P-nucleophile.

Mechanistic studies revealed that the catalytic cycle for the reaction in Scheme 18 was of the Pd(II)/Pd(0) type, and silver acetate acted as an oxidant for regeneration of the Pd(II) catalyst. In addition, NMMI was found to be an indispensable reaction component which enabled reductive elimination of the products from the corresponding aryl(phosphonate)Pd(II) complexes. Also, Yu et al. [126] developed a catalytic system for C–H phosphonylation of 2-aminoaryl scaffolds, similar to the system shown in Scheme 18. In this instance, the Pd(II)-catalyst deactivation was attenuated by a slow addition of *H*-phosphonate diesters (ethyl, isopropyl), and *p*-benzoquinone was used to facilitate the reductive elimination step. The postulated Pd(II)/Pd(0) catalytic cycle was completed by oxidation of Pd (0)-species by silver acetate to afford arylphosphonate derivatives in up to 79% yields. This protocol did not work with dibenzyl and diphenyl *H*-phosphonates, but was compatible with various diarylphosphine oxides as coupling partners (yields of triarylphosphine oxides, 39–48%).

Although an allene moiety has been extensively used as a pharmacophore [127], allenylphosphonates have not been explored yet in this context [128]. However, a

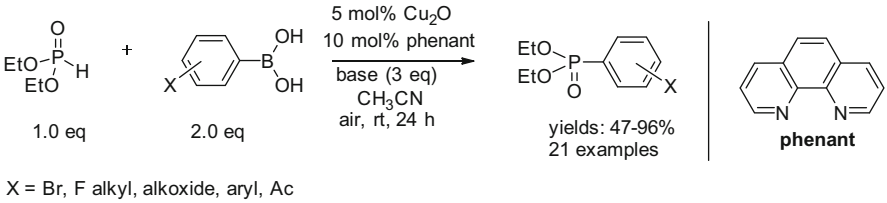


Scheme 19 Stereospecific synthesis of dinucleoside allenylphosphonates and their analogues [129, 130]

novel synthetic method was developed for the preparation of allenylphosphonates, applicable to biologically important natural product derivatives [129, 130]. The method shown in Scheme 19 is based on a palladium-catalyzed propargylic substitution with phosphorus nucleophiles, and represents a new means of formation of the P–C bond. With the proper choice of propargylic components and phosphorus nucleophiles (*H*-phosphonates and their analogues or *H*-phosphinate derivatives), complex organic structures can be generated. The reaction is stereospecific at the phosphorus center and occurs with complete center to axial chirality transfer in the propargylic partner moiety (Scheme 19). Some mechanistic aspects of this reaction were investigated through ab initio calculations [131].

5 Cu-, Ni-, and Other Metal-Catalyzed Reactions

Copper-catalyzed P–C bond formation has recently emerged as a cheaper and more convenient alternative to the Pd-catalyzed reactions. The first catalytic procedure for Cu(I)-mediated coupling of aryl halides with *H*-phosphonate diesters, based on the Ullmann-type of chemistry, was described in 2003 by Buchwald



Scheme 20 Copper-catalyzed cross coupling of arylboronic acids with *H*-phosphonate diesters

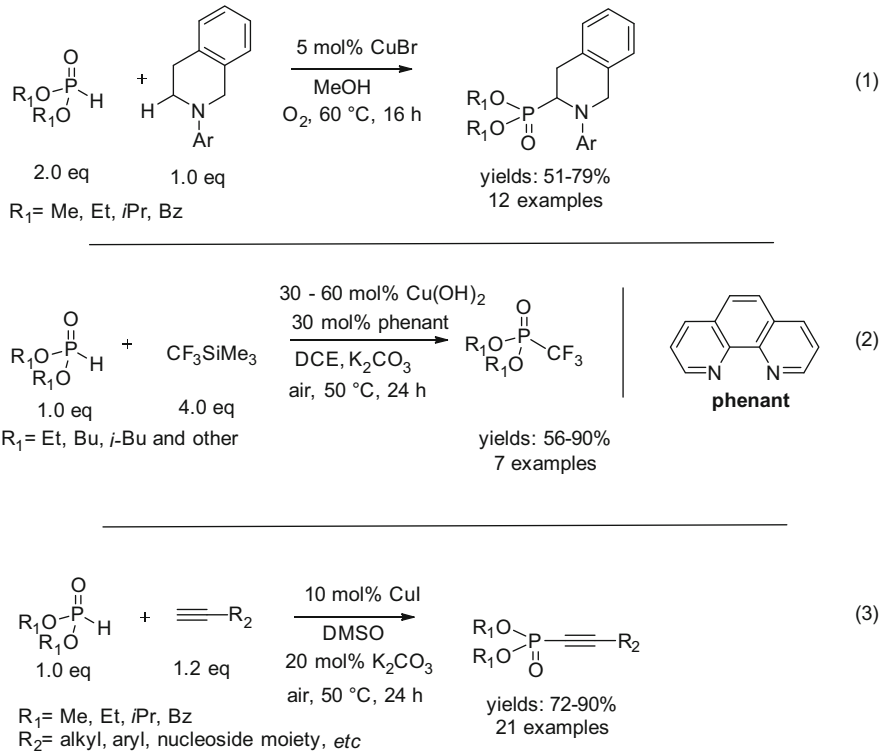
et al. [132]. Since then, the number of applications of copper as a catalyst has steadily increased [133–135].

Scheme 20 depicts a copper-catalyzed synthesis of arylphosphonates using arylboronic acid derivatives and diethyl *H*-phosphonate [136]. Among the bidentate-supporting ligands investigated, the best results were obtained with phenanthroline. The advantage of this method was that the cross coupling could be performed under milder conditions than those of the Hirao arylation protocol.

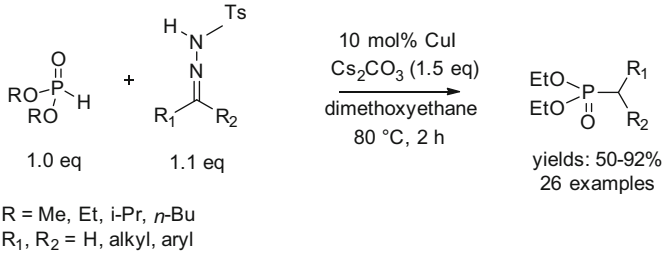
Some other examples for the catalytic construction of P–C linkages via an aerobic phosphonylation of sp^3 and *sp* C–H bonds are presented in Scheme 21. Reaction (1) depicts an efficient cross-dehydrogenative coupling of various dialkyl *H*-phosphonates via activation of an sp^3 C–H bond adjacent to the nitrogen atom in *N*-aryltetrahydroisoquinolines [137]. The reaction shows high regioselectivity and affords the corresponding α-aminophosphonates in high yields. Reaction (2) illustrates the first copper-catalyzed trifluoromethylation of *H*-phosphonate diesters in the presence of phenanthroline as a supporting ligand [138]. This method should allow for the introduction of the CF_3 group into biologically important compounds, thus modifying their electronic and hydrophobic properties. Finally, reaction (3) exemplifies an aerobic oxidative coupling of terminal alkynes with *H*-phosphonates, catalyzed by copper, to generate alkynylphosphonates in high yields under mild conditions [139]. This new method is highly general (examples include aromatic, aliphatic, and complex organic acetylenic compounds) and tolerates a variety of functional groups in the coupling partners (e.g., hydroxyl, alkoxyl, carboxyl, chloro, amino, etc.). In contrast to *H*-phosphonates and *H*-phosphinates, which reacted smoothly with terminal alkynes, no coupling products could be detected under the reaction conditions for secondary phosphine oxide $Ph_2P(O)H$. For this reaction, $CuSO_4$ [132] or recyclable silica-supported carbene-Cu(II) catalyst [140] was used.

Yang, Wu, et al. reported an alternative protocol for the synthesis of alkynylphosphonates via copper-mediated decarboxylative coupling in water, using 1,10-phenanthroline as a supporting ligand [141]. The reaction proceeded under mild conditions (60°C, 24 h) and afforded alkynylphosphonates in 51–88% yields. To suppress hydrolysis of *H*-phosphonate diesters, a few equivalents of isopropanol were used as an additive.

A copper-catalyzed reaction of *N*-tosylhydrazones with *H*-phosphonate diesters was recently investigated as a means for P–C(sp^3) bond formation

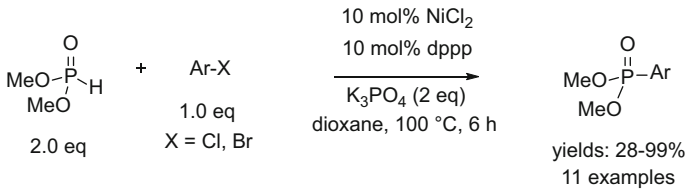


Scheme 21 Some copper-catalyzed aerobic oxidative coupling reactions



Scheme 22 Copper-catalyzed coupling of *H*-phosphonates with *N*-tosylhydrazones [142]

[142–144]. Scheme 22 shows a typical example of such a reaction which affords various alkyl- and benzylphosphonates [142]. This coupling reaction proceeds in good yields, does not require any ligand, and can be performed as a one-pot reaction from the corresponding carbonyl compounds, without isolation of tosylhydrazone intermediates. The above experimental conditions were extended to the cross coupling of *N*-tosylhydrazones with a secondary phosphine oxide $Ph_2P(O)H$ [143]. A modified version of this reaction was also developed, utilizing Cu(II)



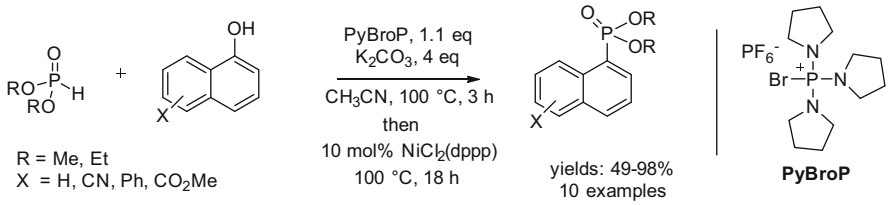
Scheme 23 Nickel-catalyzed coupling of *H*-phosphonates with aryl bromides [150]

precatalysts which undergo in situ reduction by tosylhydrazones to produce catalytically active Cu(I) species [144]. This protocol worked well with *H*-phosphonate diesters and $Ph_2P(O)H$, and with a variety of aliphatic and aromatic substrates bearing electron-rich as well as electron-deficient substituents. A Cu(I)-catalyzed direct oxyphosphonylation of alkenes with *H*-phosphonates in the presence of dioxygen to produce β-ketophosphonates [145], and a three-component, one-pot reaction of azides, alkynes, and *H*-phosphonates, to afford 1,2,3-triazolyl-5-phosphonates [146], were also recently reported.

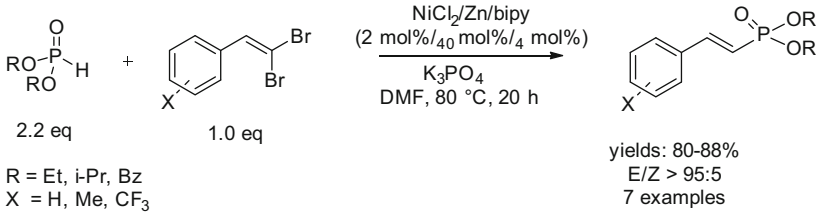
The reaction of trialkyl phosphites with aryl halides catalyzed by Ni(II)X_2 was developed in 1970 by Tavs [147], representing the first synthesis of a P–C bond catalyzed by transition metals; it is referred to as the Ni-catalyzed Arbuzov reaction or the Tavs reaction. It was postulated that the harsh conditions usually required for this reaction are necessary because of the high activation energy for the reduction of Ni(II) to Ni(0) and the oxidative addition step [148].

Tang et al. [149] recently developed milder reaction conditions for nickel-catalyzed cross coupling of aryl halides with $Ph_2P(O)H$, and these were modified by Han et al. [150] to become compatible with *H*-phosphonates as coupling partners (Scheme 23). Mechanistically, this reaction follows a pathway similar to the Hirao reaction pathway (see above), and the best results were obtained with 1,3-bis(diphenylphosphino)propane (dppp, Fig. 3) as a supporting ligand. Since aryl mesylates and tosylates are attractive substrates for cross-coupling reactions [151, 152], a method was developed for the nickel-catalyzed phosphonylation of this type of aromatic electrophiles with *H*-phosphonate diesters [153]. To facilitate cross coupling with these less reactive derivatives, zinc dust was used as a reducing agent for the in situ generation of an active Ni(0) catalyst. In addition, dppf (Fig. 3), a ligand with a bigger bite angle than dppp, was necessary. The reactions were carried out in DMF, in the presence of DIPEA as a base, and afforded the arylphosphonates in 55–90% yields [153]. The method is unsuitable for substrates with electron-donating groups or electron-withdrawing groups in the *para*-position of the aromatic ring. Recently, arylboronic acids were reported as new coupling partners with *H*-phosphonates, *H*-phosphinates, and *H*-phosphine oxides for nickel-catalyzed P–C bond formation [154].

For electron-deficient phenols which are usually difficult to phosphonylate, a new Ni-catalyzed cross-coupling protocol was developed (Scheme 24). The method involves activation of a phenol with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), followed by Ni-catalyzed coupling with *H*-phosphonate



Scheme 24 One-pot Ni(II)-catalyzed cross-coupling reaction mediated by PyBroP [155]



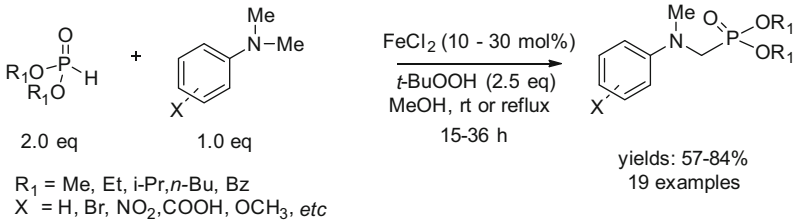
Scheme 25 Ni-catalyzed cross coupling of *gem*-dibromoalkenes with *H*-phosphonate diesters

diesters or diaryl phosphine oxides [155]. The reaction can be carried out as a one-pot procedure without the need for isolating the activated phenol intermediate.

Alkenyl–phosphorus compounds bearing a vinyl group attached to the phosphorus center are an important class of chemicals which are used extensively in pharmaceuticals and material sciences [156–158]. Scheme 25 depicts a new synthetic approach to vinylphosphonates, utilizing Ni(0)-catalysis [159]. The reaction consists of two steps: (1) the Hirao-type of reduction which generates a bromovinyl intermediate, followed by (2) Ni(0)-catalyzed cross coupling with *H*-phosphonate diesters. This is a highly stereospecific process which produces, in a one-pot procedure, the corresponding vinylphosphonate derivatives. Zinc dust acts as a reducing agent for converting Ni(II) into the catalytically active Ni(0) species which is stabilized by the supporting 2,2′-bipyridine (bipy, Fig. 3) ligand. A mechanism proposed for this reaction was substantiated by computational and ^{31}P NMR studies [159].

Although typical reactions for the synthesis of α-aminophosphonates are those of the Pudovik and the Kabachnik–Fields types (see Sect. 2, Scheme 1), these compounds are also accessible via transition metal-catalyzed cross couplings (e.g., see Scheme 21, Reaction 1). Scheme 26 shows an example of a selective C–H to C–P bond transformation with aryl tertiary amines which is catalyzed by $FeCl_2$ [160, 161].

Aniline derivatives bearing various alkyl groups, or having a nitrogen atom as part of their cyclic systems (e.g., pyrrolidine, piperidine), also smoothly underwent this oxidative α-phosphonylation. Mechanistic investigations showed that the reactions proceeded with intermediate *N*-aryl iminium ions (mediated by Fe/BuOOH), which were reactive enough to be intercepted by *P*-nucleophiles [160].



Scheme 26 Iron-catalyzed α-phosphonylation of the C(sp^3)-H bond in *N*,*N*-dimethylanilines [160]

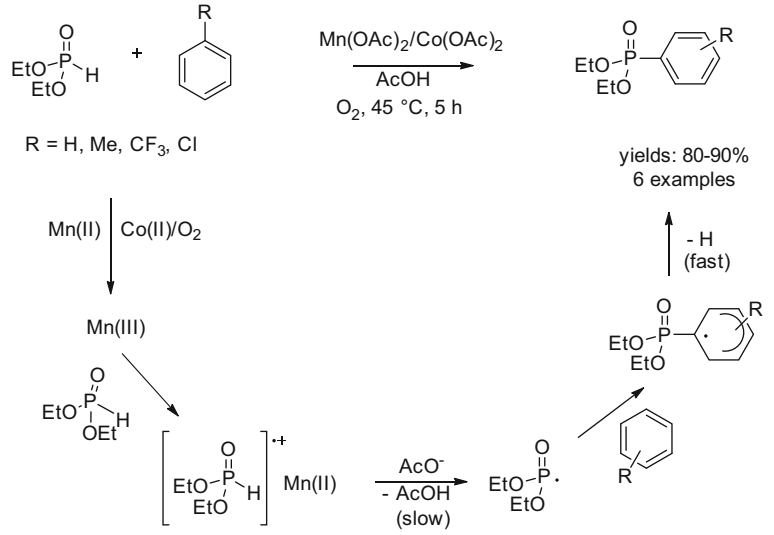
6 Free Radical Reactions

Because of the presence of a medium-strong P–H bond (ca 77 kcal/mol; actually weaker than the N–H or C–H bond), *H*-phosphonate diesters can relatively easily generate phosphorus-centered radicals which may undergo various transformations relevant to synthetic organic chemistry [162, 163]. In 1958, Stiles et al. [164] reported on the first radical addition of *H*-phosphonate diesters to various olefins using light or peroxides as initiators. However, it was not until recently that Ishii et al. [165] disclosed their results on manganese-mediated activation of *H*-phosphonate diesters, and that a free-radical phosphonylation, via C–H bond functionalization, became an important way to form the P–C bond [17].

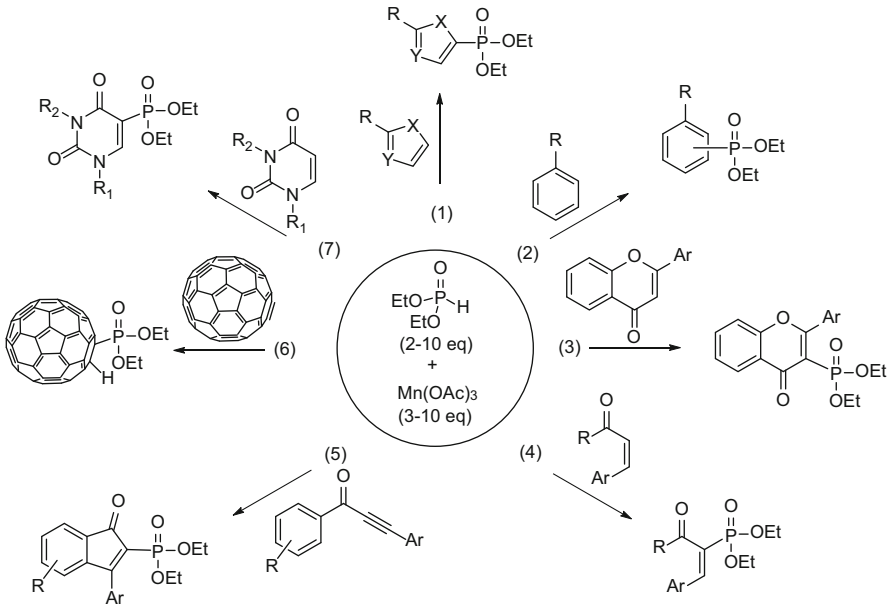
In 2006, Ishii et al. [153] developed the first catalytic phosphonylation of arenes using a $Mn(OAc)_2/Co(OAc)_2/O_2$ redox system [166] (Scheme 27).

The authors proposed that the reaction involved a phosphonyl radical intermediate, generated in situ by a one-electron oxidation of the *H*-phosphonate by Mn(III). This is followed by the addition of the radical to the aromatic system, and, ultimately, formation of arenephosphonates (see Scheme 27). Consistent with the proposed mechanism, the reaction was markedly accelerated by KOAc. In some instances, formation of bisphosphonylated products (up to 9%), was observed.

This method was further simplified by using Mn(III) as a stoichiometric oxidant. Some synthetic transformations based on this reaction are shown in Scheme 28. Zhang et al. [167] developed direct phosphonylation of heteroaromatic compounds, such as thiazoles, furans, and pyrroles (Reaction 1, Scheme 28). These transformations were carried out in acetic acid (3 h, 80°C), and afforded the phosphonylated products in high yields (84–95%) with complete regioselectivity. A free-radical mechanism, similar to the one shown in Scheme 27, was proposed. The same reaction conditions were recently applied to the phosphonylation of mono- and disubstituted arenes [168] (Reaction 2, Scheme 28). To secure high yields (80–90%), threefold molar excess of Mn(III) relative to the *H*-phosphonate component was required. The observed regioselectivity was rationalized on the basis of the assumed free radical mechanism [168]. The same authors observed that phosphonyl radicals generated from *H*-phosphonate diesters and Mn(III) added



Scheme 27 Free radical, manganese-catalyzed arene phosphonylation [166]



Scheme 28 Free radical, Mn(III)-catalyzed phosphonylation reactions

selectively to the three-position of flavones and coumarins (Reaction 3, Scheme 28), producing the corresponding phosphonates in moderate to good yields [168].

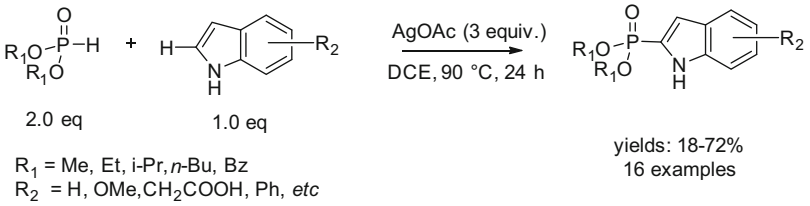
In contrast to aromatic/heteroaromatic phosphonylation, the synthesis of vinylphosphonates turned out to be more challenging. This was because of the competing polymerization of the alkenes used for the reaction, and problems with controlling regio- and stereo-(*E*/*Z*)-selectivity (Reaction 4, Scheme 28). To address these problems, Zhang et al. [169] developed reaction conditions for the regioselective phosphonylation of conjugated arylalkenes bearing a keto, nitro, or ester functionality in the α-position (Reaction 4, Scheme 28). Both the carbonyl and aryl groups in the substrates were necessary to control reactivity and regioselectivity of the phosphonylation process. Reaction 5 in Scheme 28 is similar to this wherein phosphonylated indenone derivatives are formed in 70–80% yield from the corresponding arylalkynes [169]. The reaction consists of the addition of a phosphonyl radical to the triple bond, followed by an intramolecular free radical cyclization.

Wang et al. [170] investigated phosphonylation of fullerene with *H*-phosphonate diesters or phosphine oxides mediated by Mn(III) (Reaction 6, Scheme 28). The phosphonylated fullerene shown in the scheme was formed in 62% yield; however, depending on the ratio of the reactants, other fullerene derivatives can be formed as major products (e.g., single bonded phosphonylated fullerene dimers or hydrophosphonylated fullerenes with the acetoxy group) [159].

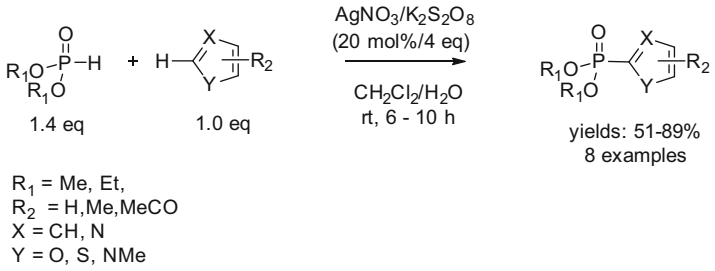
An efficient synthesis of 5-phosphonylated uracil derivatives (Reaction 7, Scheme 28) via an Mn(III)-mediated coupling of *H*-phosphonate diesters with various uracil precursors was also developed [171]. The starting materials for this reaction, besides simple alkyl derivatives, included ribo-, deoxy-, and dideoxyuridines; they afforded the phosphonylated products in 68–99% yields. As in the other protocols for this type of free radical reactions, acetic acid was used as a solvent. These reaction conditions were later extended to phosphonylation of pyridine-2-ones and pyrimidine-4-ones [172].

Apart from manganese, silver is another metal frequently used in free radical oxidation reactions [173]. Recently, Wan et al. [174] developed direct phosphonylation of indoles using Ag(I) as a stoichiometric oxidant (Scheme 29).

This method provides a convenient access to biologically important indolylphosphonates, albeit in moderate yields. A free radical mechanism for this reaction was proposed on the basis of influence of the substituents and sensitivity to radical inhibitors (butylated hydroxytoluene, BHT).



Scheme 29 Ag(I)-mediated oxidative coupling of indoles with *H*-phosphonate diesters



Scheme 30 Silver-catalyzed dehydrogenative phosphonylation of five-membered heteroarenes

A catalytic system for phosphonylation of various heteroaromatic compounds (Scheme 30) was developed [175] to reduce the amount of silver used.

It was hypothesized that Ag(II) was catalytically active in this reaction; it was formed from Ag(I) via oxidation with peroxydisulfate $K_2S_2O_8$ during the course of the reaction which converted the *H*-phosphonate diester into a cation radical. The mechanism is similar to the mechanism proposed by Effenberger et al. [173]. The best results were obtained in methylene chloride/water using 13 mol% of $AgNO_3$ and fourfold excess of the oxidant. These reaction conditions were extended to phosphonylation of pyridines and quinolines, but the yields were lower because of competing formation of the corresponding *N*-oxides [175]. To remedy this problem, an additional step was added to the synthetic protocol, namely the reduction of *N*-oxides with $Na_2S_2O_3$. This significantly increased the yields (53–81%) of pyridyl- and quinolylphosphonates.

A similar catalytic system was also successfully developed for dehydrogenative cross coupling of *H*-phosphonate diesters with arenes bearing strongly electron-withdrawing substituents (e.g., nitro, sulfonyl groups) [176]. This protocol for the C–H-functionalization (Ag_2SO_4, 10 mol%; $K_2S_2O_8$, 3 equiv.; CH_3CN/water, 1:1, v/v; 90°C; 1–12 h) has a broad substrate scope and is suitable for the preparation of *ortho*-phosphonylated aromatic compounds (yields 55–82%, 25 examples). This catalytic system also worked well in the phosphonylation of various pyrroles [177].

New types of electrophilic components, diaryliodonium salts [178], have recently been promoted as superior substrates for room temperature synthesis of arylphosphonates from *H*-phosphonate diesters. This reaction is catalyzed by CuCl (5 mol%), and affords the coupling products in high yields (75–95%) within 10 min. A free radical mechanism for this reaction was suggested.

Other free radical reactions, not involving metal catalysis, were also reported for C–P bond formation. These include photochemical activation of the P–H bond by eosin Y [179], 2,2-dimethoxy-2-phenylacetophenone (DPAP) [180], an Ru(II)- or Ir(III)-bipyridyl photocatalyst [181], a microwave-assisted reaction of dimethyl *H*-phosphonate with cyclohexane and alkene oxides [182], and radical telomerization of fluorinated alkenes with *H*-phosphonate diesters acting as telogens [183].

7 Other Types of Reactions

The addition of H–P=O compounds to unsaturated carbon frameworks (e.g., acetylenes, olefins, allenes, dienes, isocyanides) is another powerful strategy for preparing organophosphorus compounds. In these instances, Ni- and Pd-based catalysts are commonly used [184–187]. Chemical, stereochemical, and mechanistic aspects of these reactions, along with studies on the development of new catalysts, have been thoroughly covered in a recent review by Tanaka [188]; they are not the subject of this survey.

8 Final Remarks

Because of the chemical, biological, medicinal, and industrial importance of phosphorus compounds containing P–C bonds, synthetic methods for preparing C-phosphonates and related compounds are of great importance in contemporary bioorganic phosphorus chemistry. In this respect, *H*-phosphonate diesters, with their ability to act as nucleophiles, electrophiles, and P-centered free radicals, provide a plethora of mechanistic ways in which the phosphorus–carbon bond can be formed; they are unrivalled phosphorus substrates. Currently, both classical methods for P–C bond formation (the Michaelis–Arbuzov, the Michaelis–Becker, the Pudovik, the Abramov, and the Kabachnik–Fields reactions) and those based on organocatalysis or transition-metal catalyzed cross couplings are still viable synthetic options.

It seems that further progress in developing (1) enantioselective methods for the formation of C(sp^3)–P bonds using chiral auxiliaries, (2) broadening the scope of the reactions catalyzed by Fe, Cu, Ni, and various chiral organocatalysts, and (3) designing new methods for diverse, direct C–H bond functionalization under environmentally friendly conditions will all be of particular importance in the future.

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