Potential chemical transformation of phosphonic acid derivatives and their applications in the synthesis of drugs

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Abstract

The chemical transformation of phosphonic acid is a well-considered mature area of research on account of the historical significant reactions such as Kabachnik–Fields, Mannich, Arbuzov, Michael–Becker, etc. Considerable advances have been made over last years especially in metal-catalyzed, free-radical processes and asymmetric synthesis using catalytic enantioselective. As a result, the aim of this synopsis is to make the reader familiar with advances in the approaches of phosphonic acids toward the synthesis of highly functionalized and valuable building blocks. Another purpose of this survey is to provide the current status of the applications of phosphonic acids in the synthesis of drugs.

1. Introduction

Among a wide range of interesting phosphorous compounds, the phosphonic acid family has attracted recognition as being one of the versatile synthons with useful medicinal and therapeutic properties [1–6]. Since its discovery by August Wilhelm Hofmann in 1855 [7], many studies and numerous users have blossomed contain such diverse applications as anti-depressant, anti-anticancer, anti-Alzheimer, antimicrobial, anti-parasitic, anti-hepatitis, antiproliferative, anti-inflammatory, etc [8–14]. This important class of compounds was also the used in agrochemicals [15] industrial applications [16], and ligands for transition metal complexes [17].

Bearing the significance and attractiveness of phosphonic acids chemistry in organic synthesis, exhaustive studies have been devoted to finding out convenient and efficient reactions [18–26]. During the past decades, several types of reactions leading to phosphonic acids have been reported, such as Kabachnik–Fields, Mannich, Arbuzov, Michael–Becker, etc. In this context, many chemical applications of this structural motif still remain unexplored, leaving a long way to be covered with special mention to asymmetric reactions [27–30]. This tutorial review has compiled recent and important contributions related to elegant and useful organic reactions of phosphonic acids. The results will be covered by the formation of phosphorous–carbon bonds, phosphorous–sulfur bonds, and phosphorous–nitrogen bonds. Moreover, we will present an overview of the development that has been made of the phosphonic drugs.

**Abbreviations and Acronyms:**

Ac, Acetyl; ACE, Angiotensin converting enzyme; AD, Alzheimer’s disease; AIBN, 2,2'-Azobisisobutyronitrile; Ala, Alanine; Alk, Alkyl; Aq, Aqueous; Ar, Aryl; BINOL, 1,1'-Bi-2,2'-naphthol; Bn, Benzyl; Boc, tert-Butyloxycarbonyl; BSA, N,O-bis(trimethylsilyl) acetamide; Bu/n-Bu, Normal (primary) butyl; Bz, Benzoyl; Cbz, Benzyloxy-carbonyl; cod, 1,5-Cyclooctadiene; C, Degrees celsius; c-Hex, Cyclohexane; DCC, Dicyclohexylcarbodiimide; DCM, Dichloromethane; d.r, Diastereomeric ratio; EC50, Half maximal inhibitory concentration; ee, Enantiomeric excess; eq, Equivalent weight; Et, ethyl; et al., and others; etc., and so forth; Fmoc, 9-fluorenylmethoxycarbonyl; GABA, γ-Aminobutyric acid; GERD, Gastroesophageal reflux disease; Gly, glycine; GSK, GlaxoSmithKline’s; h, hour(s); HCV, Hepatitis C virus; Hex/n-Hex, n-hexyl; HIV, Human Immunodeficiency Virus; HMDS, Hexamethyldisilazane; IBF, Isobutyl chloroformate; IC50, Half maximal inhibitory concentration; i-Pr, isopropyl; LDA, Lithium diisopropylamide; Leu, leucine; Me, methyl; Menth, menthol; Ms, methanesulfonyl (mesyl); MW, microwave; NMP, N-Methyl-2-pyrrolidone; NNRTIs, Non-Nucleoside reverse transcriptase inhibitors; NS3, Nonstructural protein 3; Pd(II), Triis(dibenzylidenacetone)dipalladium(0); Ph, Phenyl; Piv, Pivaloyl; Pr/n-Pr, Propyl; rt, room temperature; s-Bu, sec-buty1; t-Bu, tert-buty1; TFA, Trifluoroacetic acid; TFA, Trifluoroacetic acid; THF, Tetrahydrofuran; TMS, Trimethylsilyl; TEA, Triethylamine (Et3N); TEBAC, Triethylbenzyl ammonium chloride; TFA, Trifluoroacetic acid; TFA, Trifluoroacetic acid; TMS, Trimethylsilyl; p-Tol, para Tolyl; Ts, Tosyl; Val, Valine

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2. Reactions

2.1. Reactions involving the phosphorous–carbon bond formation

2.1.1. Silyl-Arbuzov reaction

Thottathil et al. reported an efficient method for the synthesis of phosphinic acids or esters from phosphonous acids or esters via silyl-Arbuzov reaction of 1 with bromoacetates in the presence of triethylamine (TEA) (Scheme 1) [31].

Hansen and Kehler disclosed an elegant route to the synthesis of sec-alkylmethylphosphinates from aldehydes or ketones and the easily obtainable ethyl methylphosphinate in the presence of HMDS (Scheme 2) [32].

2.1.2. Kabachnik–Fields reaction

The Kabachnik–Fields reaction is the three-component procedure using amines, oxo compounds, and hydrophosphoryl reagents afforded α-aminophosphine oxides [33–35]. However, the yields in this reaction
tend to be moderate, there are several advantages such as the cheapness and availability of starting materials and the broad scope of the reaction [33,34]. Indeed, many publications showed the use of special catalysts, such as a phthalocyanine–AlCl3 complex [36], metal triflates [37], Ln (OTf)3 [38,39], Ga2I6 [40], Bi(NO3)3 [41], SmI2 [42], InCl3 [43], and Mg(ClO4)2 [44,45], etc. in solvents, or without the use of any solvent [46–48].

Gruszecka et al. have demonstrated the synthesis of 4-amino-4-phosphinoylpentanoic acids 8 via the treatment of methyl 4-oxopentanoate 6 with phosphinic esters 7 in the presence of ammonia (Scheme 3) [49].

Microwave-assisted Kabachnik-Fields reaction of dibenzo[c,e][1,2]oxaphosphorine 11 as the P-reactant with paraformaldehyde 10 and secondary amines at 80°C in dry ethanol 9 for the corresponding aminomethyl-2-{2′-hydroxybiphenyl}phosphinic acids 12 (Scheme 4) [50].
Scheme 13.

\[
\text{Ar} \quad \text{N} \quad \text{=} \quad \text{N} \quad \text{Ar}
\]
\[(S)-35\]
\[
\text{H}_3\text{PO}_2, \text{THF}, 0^\circ\text{C}
\]
\[40\%\]
\[
\text{2:1}
\]
\[
(S, R)-36
\]
\[
(S, S)-37
\]
\[\text{Ar} = 2\text{-naphthyl}\]

Scheme 14.

\[
\text{RN} \quad \text{=} \quad \text{N} \quad \text{NR}
\]
\[38\text{a-d}\]
\[
\text{H}_3\text{PO}_2, \text{MeCN}, \Delta
\]
\[
39\text{a-d}
\]
\[39\text{a}; \text{R} = (S)-\text{CH(Me)Ph}, 97\%, 4:1:1 \text{ d.r.}\]
\[39\text{b}; \text{R} = (S)-\text{CH(CO}_2\text{Me})\text{Me}, 39\%, 2:1:1 \text{ d.r.}\]
\[39\text{c}; \text{R} = (S)-\text{CH(CO}_2\text{Et})\text{Bn}, 46\%, 2:1:1 \text{ d.r.}\]
\[39\text{d}; \text{R} = (S)-\text{CH(CO}_2\text{Me})-\text{t-Bu}, 47\%, 2:1:1 \text{ d.r.}\]

Scheme 15.

\[
\text{Ar} \quad \text{N} \quad \text{=} \quad \text{N} \quad \text{Me}
\]
\[40\text{a-c}\]
\[
\text{HP(OTMS)}_2, \text{CH}_2\text{Cl}_2, \text{rt}, 12 \text{ h}
\]
\[2\text{eOH}
\]
\[
(S, R)-41\text{a-c}
\]
\[41\text{a}; \text{Ar} = 2\text{-Py}, 19\%
\]
\[41\text{b}; \text{Ar} = 3\text{-Py}, 28\%
\]
\[41\text{c}; \text{Ar} = 4\text{-Py}, 8\%
\]

Scheme 16.

\[
\text{O} \quad \text{N} \quad \text{=} \quad \text{N} \quad \text{R}
\]
\[(S)-42\text{a-r}\]
\[
\text{Rb}_2\text{CO}_3, \text{CH}_2\text{Cl}_2, \text{rt}
\]
\[43\text{a, 44a}; \text{R} = \text{C}_6\text{H}_{5}, 46\%/50\%
\]
\[43\text{b, 44b}; \text{R} = 4\text{-MeC}_6\text{H}_{4}, 37\%/34\%
\]
\[43\text{c, 44c}; \text{R} = 2\text{-thienyl}, 45\%/47\%
\]
\[43\text{d, 44d}; \text{R} = 4\text{-MeC}_6\text{H}_{4}, 37\%/48\%
\]
\[43\text{e, 44e}; \text{R} = 4\text{-MeOC}_6\text{H}_{4}, 48\%/50\%
\]
\[43\text{f, 44f}; \text{R} = 4\text{-morpholinC}_6\text{H}_{4}, 29\%/36\%
\]
\[43\text{g, 44g}; \text{R} = 3,4\text{-}(\text{OCH}_2\text{O})\text{-C}_6\text{H}_{4}, 49\%/49\%
\]
\[43\text{h, 44h}; \text{R} = 2\text{-FC}_6\text{H}_{4}, 37\%/36\%
\]
\[43\text{i, 44i}; \text{R} = 4\text{-FC}_6\text{H}_{4}, 43\%/50\%
\]
\[43\text{j, 44j}; \text{R} = 4\text{-ClC}_6\text{H}_{4}, 46\%/48\%
\]
\[43k, 44k]; \text{R} = 4\text{-BrC}_6\text{H}_{4}, 41\%/35\%
\]
\[43l, 44l]; \text{R} = 2\text{-furyl}, 35\%/49\%
\]
\[43m, 44m]; \text{R} = 3\text{-pyridyl}, 50\%/35\%
\]
\[43n, 44n]; \text{R} = 2\text{-naphthyl}, 43\%/49\%
\]
\[43o, 44o]; \text{R} = 4\text{-biphenyl}, 49\%/49\%
\]
\[43p, 44p]; \text{R} = 4\text{-NCC}_6\text{H}_{4}, 41\%/48\%
\]
\[43q, 44q]; \text{R} = 4\text{-O}_2\text{NC}_6\text{H}_{4}, 32\%/38\%
\]
\[43r, 44r]; \text{R} = \text{n-Hex}, 45\%/30\%
2.1.3. Hydrophosphinylation of imines

Hydrophosphinylation of imines “Pudovki reaction” is one of the most common pathways to the synthesis of α-amino-H-phosphinates [51–53].

2.1.3.1. Using non-chiral phosphorus compounds and non-chiral imines. The reactions of various aldimines 14 with 13 afforded the corresponding amino phosphinic esters 15 without any stereoselectivity (Scheme 5) [54–57].

Cristau et al. reported the hydrophosphination of imines 17 with alkyl hypophosphites 16 led to the formation of aminoalkyl-hydroxymethylphosphinates 18 (Scheme 6) [58–60].

The reaction of H-phosphinates 19 to imines 20 in the presence of sodium ethoxide was also described for the formation of bisphosphinic ester 21 (Scheme 7) [61].
Cristau and coworkers have prepared α-aminophosphinate 24 by the treatment of H-phosphinates 22 to aromatic imines 23 (Scheme 8) [62].

Additionally, the reaction of phosphinate 25 with imine in the presence of BF3.Et2O, furnished aminophosphinates 27, including the core structure in the synthesis of phosphinopeptides toward Trypanosoma cruzi (Scheme 9) [63,64].

2.1.3.2. Using chiral phosphorus compounds and non-chiral imines. Diastereoselective synthesis of aminophosphinates 27 with a NCPCN pattern via the reaction of 2H-2-oxo-1,4,2-oxazaphosphinanes 26 as chiral reagents with aldimines in the presence of boron trifluoride (Scheme 10) [65].

Yokomatsu and co-workers reported the diastereoselective reaction of amino-H-phosphinates 30 to imine 31 catalyzed by Yb(OTf)3 as Lewis acids led to the formation of α,α′-diaminophosphinic ester 32 with de 94% (Scheme 11) [66,67].

2.1.3.3. Using chiral imine compounds and non-chiral phosphorus compounds. Lewkowski and co-workers have published the highly diastereoselective hydrophosphinylation of the chiral Schiff bases 33a–g with hypophosphorous acid in acetonitrile afforded the α-amino-H-phosphinic acids (R,S)-34a–g with high diastereoselectivities (Scheme 12) [68,69].

In a similar fashion, the treatment of hypophosphorous acid to the chiral aldimine 35 led to the formation of (S,R)-36 and (S,S)-37 in 2:1 diastereoisomeric ratio (Scheme 13) [70].

Lewkowski and co-workers have succeeded in the preparation of bis-phosphonous acids 39a–d by the treatment of H3PO2 with Schiff bases 38a–d in acetonitrile at reflux (Scheme 14) [71–73].

Diastereoselective hydrophosphinylation reaction of bis(tri-methylsilyl) phosphonate (BTSP) to chiral N-(diphenylmethyl) imines 40a–c in DCM followed by the treatment with MeOH gave 1-(diphenylmethylamino)-alkylphosphonous acids 41a–c (Scheme 15) [74,75].

Furthermore, Yuan and Zhang noted that the enantioselective reaction of ethyl diethoxymethylphosphinate to N-(tert-butanesulfinyl) ketimines (S)-42a–r in DCM using Rb2CO3 as a base gave the α-aminophosphinates (R,C,SS)-43a–r and (R,C,SS,SP)-44a–r as the major diastereoisomers (Scheme 16) [76].

The reaction of ethyl diethoxymethylphosphinate to (S)-sulfinamides 45a–g in the presence of Rh3CO3 furnished the phosphonates (R,SS)-46a–g in good yields (Scheme 17) [77].

Optically active α-aminophosphinates (R,C,SS)-48a–c can be prepared through the reaction of ethyl phenylphosphinates and enantiopure aldimines (S)-47a–c in toluene at 70°C (Scheme 18) [78,79].

Rossi et al. [80] reported that the reaction of the ethyl
Scheme 23.

\[
\begin{align*}
HHArF_4 &= HB(3.5-(CF_3)_2C_6H_3)4 \\
57 &\text{ HBArF}_4
\end{align*}
\]

58a; Ar = C_6H_5, R = Bn, 83%, 6:1 d.r., 94% ee.
58b; Ar = 4-FC_6H_4, R = Bn, 90%, 6:1 d.r., 90% ee.
58c; Ar = 4-ClC_6H_4, R = Bn, 90%, 4:1 d.r., 92% ee.
58d; Ar = 4-MeC_6H_4, R = Bn, 85%, 4:1 d.r., 90% ee.
58e; Ar = 2-naphthyl, R = Bn, 93%, 6:1 d.r., 91% ee.
58f; Ar = 2-furyl, R = Bn, 71%, 7:1 d.r., 94% ee.
58g; Ar = trans-C_6H_5CH=CH, R = Bn, 92%, 3:1 d.r., 90% ee.
58h; Ar = C_6H_5, R = 2-naphthyl-CH_2, 92%, 6.5:1 d.r., 94% ee.
58i; Ar = C_6H_5, R=4-FC_6H_5CH=CH_2, 92%, 16:1 d.r., 94% ee.
58j; Ar = C_6H_5, R = 4-MeC_6H_4CH=CH_2, 83%, 5:1 d.r., 86% ee.
58k; Ar = C_6H_5, R = trans-C_6H_5CH=CHCH_2, 82%, 7:1 d.r. 82% ee.

Scheme 24.

(R,S)-5a; R = C_6H_5, 35%, 100% d.e.
(R,S)-5b; R = 2-furyl, 100% d.e.
(R,S)-5c; R = c-C_8H_11, 32%, 100% d.e.
(R,S)-5g; R = ferrocenyl, 60% d.e.
(R,S)-5h; R = i-Pr, 49%, 100% d.e.
(R,S)-5i; R = i-Bu, 33%, 100% d.e.
(R,S)-5j; R = s-Bu, 36%, 100% d.e.
(R,S)-5k; R = pent-2-y1, 30%, 100% d.e.
(R,S)-5i; R = hept-3-yl, 35%, 100% d.e.
(R,S)-5m; R = C_8H_5CH_2, 20%, 100% d.e.
phenylphosphinate with the chiral imines 49a,b furnished the phosphinates 50a,b with good diastereoselectivities (Scheme 19).

Carbohydrate derivatives are used as efficient auxiliaries in various stereoselective chiral syntheses [81–83]. Chen and coworkers reported the stereoselective synthesis of phosphinates 52a–g via the reaction of ethylphenylphosphinate to aldimines 51a–g in the presence of SnCl4 as a catalyst in THF at room temperature (Scheme 20) [84].

The first asymmetric synthesis of α-aminophosphinic acids 60a–g in good diastereoisomeric ratios was carried out by Szabó et al. without using a catalyst via the treatment of the chiral imines 59a–g with ethyl phenylphosphinate (Scheme 21) [85].

2.1.3.4. Using chiral imine compounds and chiral phosphorus compounds. Zhao and coworkers [86] described the hydrophosphinylation of the Schiff base (R)-53 with the phenylphosphinate 54 at 80°C followed by crystallization afforded the optically pure phosphinate (R,S,R)-55 (Scheme 22).

2.1.3.5. Using chiral catalyst. A series of enantiomerically enriched α-amino phosphinate 58a–k were synthesized by the stereoselective reaction of the imines 56 with phosphinates in the presence of the guanidinium salt HBArF4 57 as a catalyst (Scheme 23) [87].
2.1.4. Phospha-Mannich reaction

Phospha-Mannich reaction of paraformaldehyde, 2-carboxyethylphosphonous acid, and formaldehyde or phosphorous acid afforded phosphinates that were used as labeling biomolecules in nuclear medicine (Scheme 24) [88].

The three-component reaction of (R)-α-methylbenzylamine, hypophosphorous acid, and aldehydes furnished the α-amino-H-phosphinic acids (R,S)-67a-m as single diastereoisomers (Scheme 25) [89].
Scheme 37.

\[
\begin{align*}
R^1 &= \text{H, i-Pr, i-Bu, sec-Bu, CH}_2\text{CH}_2\text{COOMe, CH}_2\text{OBz, Ph,} \\
R^1 &= \text{Me; R}^2 = \text{i-Pr} \\
R^1 &= \text{Ph; R}^2 = \text{Me} \\
R^1 &= \text{i-Bu; R}^2 = \text{H}
\end{align*}
\]

Scheme 38.

\[
\begin{align*}
\text{H}_2\text{N} &\text{POH} \quad \text{R} \\
\text{COOH} &\quad \text{COOH}
\end{align*}
\]

Scheme 39.

\[
\begin{align*}
\text{CbzHNAA} &\quad \text{NH}_2 \\
\text{CN} &\quad \text{100 °C, 1h} \\
\text{CbzHNAA} &\quad \text{NPOO} \quad \text{CO}_2\text{Et}
\end{align*}
\]

Scheme 40.

\[
\begin{align*}
\text{CbzHNAA} &\quad \text{NH}_2 \\
\text{CN} &\quad \text{100 °C, 1h} \\
\text{CbzHNAA} &\quad \text{NPOO} \quad \text{CO}_2\text{Et}
\end{align*}
\]
2.1.5. Hirao cross-coupling reactions: Montchamp has disclosed the synthesis of disubstituted aryl-alkenyl phosphate esters in Pd-catalyzed cross-coupling reactions of alkyl phosphinates with aryl and alkenyl bromides in the presence of Pd-catalysts (Scheme 26) [90].

Lu and co-workers demonstrated that a catalytic alkylation of phosphinates via palladium-catalyzed direct coupling of 2-vinyl/2-aryl-1,4,2-oxazaphosphinanes can be synthesized with aryl and alkenyl bromides in high diastereoselectivity mediated in the synthesis of phosphorus chirality (80–94%).

2.1.7. Amidoalkylation

2.1.7.1. None-stereoselective amidoalkylation. A facile and direct route for the preparation of N-protected α-aminoalkylphosphonic acids in moderate yields consists of the reaction of an aldehyde with benzaldehyde in the presence of triethylamine (Scheme 32) [104,105].

Pudovik and co-workers reported for the first time the reaction of H-phosphonates to aldehydes or ketones, i.e. heating under base-catalyzed conditions to give the methyl alkyl-(phenyl)-phosphonates [106]. Both Yamashita [107] and Hansen [32] used this approach to synthesize alkyl(2-aryl)phosphinates via the reaction of H-phosphonates to aldehydes or reactive ketones under amine-catalysis (Scheme 33).

Shibuya et al. [108] used Al-Li-BINOL complexes for the asymmetric synthesis of α,β-dihydroxyphosphinates and 2-alkoxy-2-aryl-1,4,2-oxazaphosphinyl phosphonates through palladocatalyzed arylation of phosphinates in the presence of palladium(II) acetate and trimethylamine afforded the corresponding phosphinates via α-hydroxyphosphinic acids (Scheme 31).

2.1.7.2. Stereoselective amidoalkylation. A three component condensation reaction of aldehydes, FmocNH2, and carbamoyl phosphonic acid in AcCl/AcOH to get pseudodipeptides that were directly suitable for solid-phase peptide synthesis (Scheme 37) [112].

Rozhko and Ragulin reported a mild procedure for the preparation of phosphonic acids through the amidoalkylation of phosphonous acids with benzaldehyde and acetamide in acetyl chloride at 0°C (Scheme 36) [110,111].

In similar fashion, Matzari and Yiotakis applied a three-component condensation reaction of aldehydes, FmocNH2, and carboxylic acids with benzaldehyde and acetamide in AcCl/AcOH to get pseudodipeptides that were directly suitable for solid-phase peptide synthesis (Scheme 37) [112].

Dmitriev and Ragulin described the reaction of bis-carbamates and phosphonic acids in a mixture of acetic anhydride and acetyl chloride or trifluoroacetic anhydride afforded α-aminoalkylphosphonic acids in high diastereoselectivity (80–94%).

2.1.8. Hydrophosphinylation of aldehydes

Several literature reports have noticed enantioselective synthesis of α-hydroxyphosphinic acids via hydrophosphinylation of aldehydes in the presence of base or by Lewis-acid [98–103]. Diastereoselective synthesis of α,β-dihydroxyphosphinates in high diastereoselectivity was attained by a chiral Allibis(binaoxphosphate) (ALB) or lithium phenoxide(PhOLi)-catalyzed hydrophosphinylation of aldehydes in the presence of triethylamine (Scheme 32) [104,105].

Pudovik and co-workers reported for the first time the reaction of H-phosphonates to aldehydes or ketones, i.e. heating under base-catalyzed conditions to give the methyl alkyl-(phenyl)-phosphonates [106]. Both Yamashita [107] and Hansen [32] used this approach to synthesize alkyl(2-aryl)phosphinates via the reaction of H-phosphonates to aldehydes or reactive ketones under amine-catalysis (Scheme 33).

Shibuya et al. [108] used Al-Li-BINOL complexes for the asymmetric synthesis of α,β-dihydroxyphosphinates and 2-alkoxy-2-aryl-1,4,2-oxazaphosphinyl phosphonates through palladocatalyzed arylation of phosphinates in the presence of palladium(II) acetate and trimethylamine afforded the corresponding phosphinates via α-hydroxyphosphinic acids. The reaction proceeded with highly retentive phosphorus chirality (80–94%).

2.1.7.2. Stereoselective amidoalkylation. A three component condensation reaction of N-Cbz-amino amides, aldehydes, and phosphines through alcoholysis gave the depsipeptides in the presence of base or by Lewis-acid [98–103]. Diastereoselective synthesis of α,β-dihydroxyphosphinates in high diastereoselectivity was attained by a chiral Allibis(binaoxphosphate) (ALB) or lithium phenoxide(PhOLi)-catalyzed hydrophosphinylation of aldehydes in the presence of triethylamine (Scheme 32) [104,105].
The alkyl trimethylsilyl phosphonate 119 has been used for P-Michael addition with acrylic acid 120 to give 121 after hydrolysis (Scheme 42) [123].

Enantioselective Michael addition of phosphinic acids 122 with acrylates 123 proceeded smoothly to afford phosphinyl dipeptidometics 124 in excellent yields (Scheme 43) [124].

An unprecedented coupling of a P–C and a C–C bond formation on a phosphinic dipptides 127 and 128 was reported by Yiotakis et al. [125] via Michael addition of α-N-benzyloxycarbonylaminoalkylphosphonous acid (R)-125 to acrylate 126 followed by a Claisen-type rearrangement (Scheme 44).

Michael addition of H-phosphinates 129 to 1,4-conjugated systems
involving silyl alkyl phosphonite intermediates afforded disubstituted phosphinic acid derivatives as a key step in the synthesis of inhibitors of various metalloproteases (Scheme 45) [126–128].

2.1.7.4. Diastereoselective Michael addition to olefins. Enantio- and diastereoselective Michael reaction of 1,4,2-oxazaphosphinanes to olefins furnished phosphinopeptides in very good to excellent yields (Scheme 46) [129].

Yamagishi et al. reported Michael addition of stereodefined phosphinates to t-butyl acrylate in the presence of magnesium alkoxide as a catalyst afforded a single isomer in excellent yield (Scheme 47) [130].

The diastereoselective synthesis of C-phosphinate (R,RP)-136 in 95% yield can be carried through Michael addition of phosphinate (R,RP)-135 to t-butyl acrylate in the presence of t-BuOMgBr (Scheme 48) [131,132].

2.1.8. Hydrophosphinylation reaction with alkenes

A stereospecific radical or base-catalyzed reaction of menthyl phenylphosphinate 137 to alkenes afforded optically pure alkyl-phenylphosphinates (Scheme 49) [133].

Hirai and Han noted the air-induced addition of reactive phosphinic acids 140 to alkenes for the selectively synthesis of the corresponding anti-Markovnikov adduct 141 requires a high temperature (Scheme 50) [134].

2.1.9. Hydrophosphinylation reaction with alkynes

There are many reports in the literature metal-catalyzed hydrophosphinylation of alkynes [135–138]. Tanaka developed a highly regioselective Pd-catalyzed stereospecific hydrophosphinylation of H-phosphinate 142 with alkynes 143 as the first straightforward synthesis of enantiomerically pure P-chiral alkenylphosphinates 144 and 145.
A similar procedure was reported by Han, where Ni-catalysis the addition of ethyl phenyl-H-phosphinate 146 to terminal alkynes 143 in a regioselective manner afforded 147 and 148 (Scheme 51) [136].

\[
\text{Han} \\
\text{EtO}_2\text{P} + \equiv \text{R} \xrightarrow{\text{Ni catalysts}} \text{O} \text{P} \equiv \text{R} \\
\text{R} = \text{Ph}, \text{n-C}_\text{6}\text{H}_{13}
\]

**Condition A:** 0.5 mol% Ni(PPh₃Me)$_4$, 1 M EtOH, rt, 5 h, 87-95% (ratio 12/13=5/95)

**Condition B:** 1 mol% Ni(cod)$_2$, 4 mol% PPhMe$_2$, 2 mol% PhP(O)OH, 1 M THF, rt, 2h, 89-93% (ratio 12/13=94/6)

\[
\text{Scheme } 51.
\]

**2.1.10. Reactions involving P-S bond formation**

**2.1.10.1. Direct thioesterification of phosphinic acids.** The MW-assisted direct thioesterification of phosphinic acids 151 using thiols 152 afforded thiophosphinates 153 in low yields of 36–40% (Scheme 53) [140].

\[
\text{Scheme } 53.
\]

**2.1.11. Reactions involving P-N bond formation**

**2.1.11.1. Direct amidation reaction of phosphinic acids.** Microwave-assisted the direct amidation of 1-hydroxy-3-phospholene 1-oxide 153 with amines 154 to give 1-alkylamino-3-phospholene oxides 155 in low yields (25–29%) (Scheme 54) [141].

\[
\text{Scheme } 54.
\]

**2.2. Reactions involving oxygen–carbon bond formation**

**2.2.1. Alkylating esterification of phosphinic acids**

**2.2.1.1. Using traditional methods.** It is known that direct esterification of alcohols is very difficult [142]. It is remarkable that the direct esterification of hypophosphorus acid 156 with alcohols 157 can be carried in the presence of different acidic catalysts in benzene or toluene afforded phosphinates 158 (Scheme 55) [143,144].

In similar fashion, phosphinates 161 can be synthesized via the transformation of acids 159 into their corresponding sodium or potassium salts 160 followed by the reaction with an alkyl halides (Scheme 56) [145–150].

In addition, the esterification of phosphinic acids 162 is achieved via the treatment with alcohols 163 in the presence of
dicyclohexylcarbodiimide (DCC) and \(N,N\)-dimethylaminopyridine (DMAP) in THF to furnish the corresponding phosphinates 164 (Scheme 57) [151–154].

The base-catalyzed esterification of chlorophospholene oxides 165 by alcohols 166 in the presence of \(\text{NEt}_3\) or \(\text{NaOMe}\) in different solvents afforded phosphinates 167 (Scheme 58) [155–157].

2.2.1.2. Using microwave (MW) technique. Quinn et al. have reported that microwave-assisted direct esterification of phenylphosphinic acids 168 with alcohols 169 at 160–180°C furnished phenyl-H-phosphinates 170 in high (73–90%) yields (Scheme 59) [158].

In a similar manner, the esterification of cyclic phosphinic acids 171 with alcohols 172 was also elaborated to furnish phosphinates 173.
Furthermore, it was found that this reaction will be more efficient and faster by using 1-n-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF₄] as a catalyst [161].

A solvent-free MW-assisted method was developed for the phase transfer that catalyzed the esterification of cyclic phosphinic acids 174 with alkyl halides in the presence of K₂CO₃ and afforded the corresponding phosphinates 175 in yields of 56–98% (Scheme 61) [162,163].

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Developer</th>
<th>Indication</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monopril</td>
<td>Bristol-Myers Squibb</td>
<td>Hypertension</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Lesogaberan</td>
<td>AstraZeneca</td>
<td>Gastroesophageal reflux</td>
<td>GABA₂ agonist</td>
</tr>
<tr>
<td>Fosdevirine</td>
<td>ViiV Healthcare</td>
<td>HIV disease</td>
<td>HIV-1 NNRTI</td>
</tr>
<tr>
<td>SGS-742</td>
<td>Novartis AG</td>
<td>Alzheimer’s disease</td>
<td>GABA₂ antagonist</td>
</tr>
<tr>
<td>GS-9256</td>
<td>Gilead Sciences</td>
<td>HCV disease</td>
<td>HCV NS3 protease inhibitor</td>
</tr>
</tbody>
</table>

(Scheme 60) [159,160].
3. Applications in drug synthesis

There are a number of phosphinic based drugs that are found currently in clinical trials (Table 1).

3.1. Fosinopril (Monopril): An ACE inhibitor prodrug

The synthetic approach towards Fosinopril is outlined in Scheme 62. A radical addition of hypophosphorous acid to 4-phenyl-1-butene produced the phosphinic acid. The Arbuzov reaction of with chloroacetic acid afforded the dialkyl phosphinic acid. Benzylation of led to , which was subsequently alkylated using racemic 1-chloro-2-methylpropyl propionate and then hydrogenolysis followed by resolution, provided enantioenriched , which was coupled with . Conversion of the acid to its sodium salt yielded Fosinopril sodium in 79% over the final two steps.

3.2. Lesogaberan: Drug for the treatment of gastroesophageal reflux

The stereoselective synthesis of Lesogaberan was accomplished through the reaction of alkyl iodide with bis(tri-methylsilyl) phosphonate followed by Boc deprotection of the amino-group using ion exchange chromatography afforded Lesogaberan (Scheme 63).

3.3. SGS742: Drug for the treatment of Alzheimer’s disease

In 1991, Baylis et al. [170] reported the synthesis of SGS-742 starting by Cbz-protection of 3-aminopropylphosphinic acid with CbzCl led to . Dialkyl phosphinic acid was obtained through the activation of by silylation with TMSCl followed by Arbuzov reaction with . Acidic hydrolysis of followed by treatment with propylene oxide afforded SGS-742 (Scheme 64).

3.4. Fosdevirine: Drug for the treatment of HIV

The enantioselective synthesis of Fosdevirine started with the preparation of dichlorophosphate derivative via the treatment of aryl halides or triflates with Mg or RLi and PCl₃. Derivatization of the with (+)- or (−)-menthyl chloroformate after crystallization from n-hexane. Subsequently, Pd₂(dba)₃ catalyzed P-allylation of with in the presence of triethylamine afforded . Optically active P-stereogenic transformed into withinversion of configuration using trimethyloxonium tetrafluoroborate (Meerwein salt) followed by acidic treatment. Finally, ammonolysis of afforded Fosdevirine (Scheme 65).
3.5. GS-9256: Drug for the treatment of HCV infection

The macrocyclic phosphinic acid GS-9256 was prepared through several steps (Scheme 66) [172]. The (1-amino-2-vinylcyclopropyl)-(2,6-difluoro-benzyl)-phosphinic acid ethyl ester 198 was coupled with the acid 199 in the presence of IBCF and NMM to give 200. Ring closing metathesis of phosphinate 200 in the presence of 1st generation Grubbs' catalyst afforded 201. Rh/Al₂O₃ catalysis was used for the hydrogenation of alkene 201, which led to the formation of 202. Substitution by 203 led to GS-9256 after ester removal.
4. Conclusions and future directions

The chemical transformation of phosphinic acid is a well-thought-out ripe area of research in the organic synthesis with an unprecedented, explosive growth over the last two decades. This account compliments the most relevant and potential strategies of using phosphinic acids toward the formation of $P-C$, $PO-C$, and $P-N$ bonds to be the appropriate route for the synthesis of the highly desired and functionalized phosphinic acid-based building blocks. Authors believe that the work in the future will direct towards the advances of asymmetric versions for the reactions outlined in this review to be more fully exploited once a frontier tool in the design and synthesis of new medicinal agents.

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