Bioorganic Chemistry 90 (2019) 103039

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

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

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ARTICLE INFO

*Keywords:*
Kabachnik–Fields reaction
Hydrophosphinylation
Phospha-Mannich Reaction
Hirao cross-coupling reactions
Amidoalkylation
Michael addition
Synthesis of drugs

ABSTRACT

The chemical transformation of phosphinic acid is a well-considered mature area of research on account of the historical significant reactions such as Kabachnik–Fields, Mannich, Arbuzov, Michaelis–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 phosphinic acids toward the synthesis of highly functionalized and valuable buildings blocks. Another purpose of this survey is to provide the current status of the applications of phosphinic acids in the synthesis of drugs.

## 1. Introduction

Among a wide range of interesting phosphorous compounds, the phosphinic acid family has attracted recognition as being one of the versatile synthons with useful medicinal and therapeutic properties [1–6]. Since its discovery by of August Wilhelm Hofmann in 1855 [7], many studies and numerous users have blossomed contain such diverse applications as anti-depressant, anti-anticancer, anti-Alzheimer, anti-microbial, anti-parasitic, anti-hepatitis, antiproliferative, anti-influenza, anti-HIV, anti-malarial agents, *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 phosphinic 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 phosphinic acids have been reported, such as Kabachnik–Fields, Mannich, Arbuzov, Michaelis–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 phosphinic 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 phosphinic 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*-Butoxycarbonyl; 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, *N,N'*-dicyclohexylcarbodiimide; DCM, Dichloromethane; de, Diastereomeric excess; DIPEA, (*N,N*-Diisopropylethylamine); DMAP, 4-(Dimethylamino)pyridine; d.r, Diastereomeric ratio; $EC_{50}$, Half maximal effective 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; IBCF, Isobutyl chloroformate; $IC_{50}$, Half maximal inhibitory concentration; *i*-Pr, isopropyl; LDA, Lithium diisopropylamide; Leu, leucine; Me, methyl; Menth, menthyl; Ms, methanesulfonyl (mesyl); MW, microwave; NMP, *N*-Methyl-2-pyrrolidone; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NS3, Nonstructural protein 3; $Pd_2(dba)_3$, Tris(dibenzylideneacetone)dipalladium(0); Ph, Phenyl; Piv, Pivaloyl; Pr/*n*-Pr, Propyl; rt, room temperature; s-Bu, *sec*-butyl; *t*-Bu, *tert*-butyl; *TEA*, Triethylamine ($Et_3N$); TEBAC, Triethylbenzyl ammonium chloride; TFA, Trifluoroacetic acid; THF, Tetrahydrofuran; TMS, Trimethylsilyl; *p*-Tol, para Tolyl; Tr/Trt, Triphenylmethyl/Trityl; Ts, Tosyl; Val, Valine

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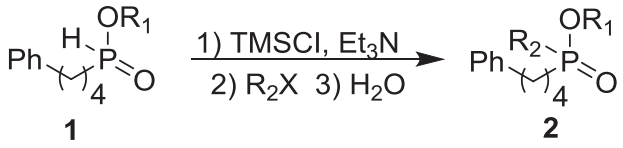
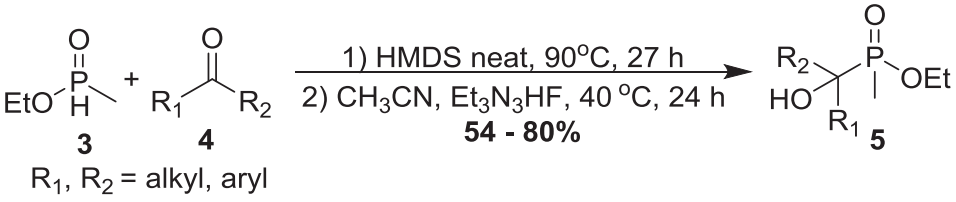
https://doi.org/10.1016/j.bioorg.2019.103039
Received 28 December 2018; Received in revised form 28 May 2019; Accepted 3 June 2019
Available online 10 June 2019




**1** **2**

**2a:** $R_1$ = Et; $R_2X$ = $BrCH_2CO_2Et$; 99%
**2b:** $R_1$ = H; $R_2X$ = $BrCH_2CO_2Et$; 99%
**2c:** $R_1$ = H; $R_2X$ = $BrCH_2CO_2Bz$; 71%
**2d:** $R_1$ = $C(CH_3)_3$; $R_2X$ = $BrCH_2CO_2Bz$; 88%
**2e:** $R_1$ = Et; $R_2X$ = $BrCH_2CH_2CO_2Et$; 96%
**2f:** $R_1$ = Et; $R_2X$ = $CH_3CH(Br)CO_2Et$; 74%
**2g:** $R_1$ = Et; $R_2X$ = $BrCH_2CO_2H$; 97%
**2h:** $R_1$ = H; $R_2X$ = $BrCH_2CO_2H$; 28%
**2i:** $R_1$ = Et; $R_2X$ = $Ph(CH_2)_4I$; 91%
**2j:** $R_1$ = H; $R_2X$ = $Ph(CH_2)_4I$; 48%

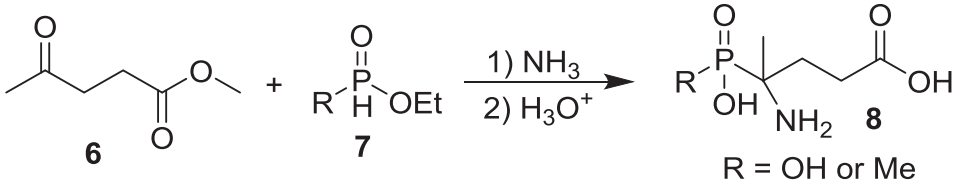
**Scheme 1.**




**3** **4** **5**

$R_1$, $R_2$ = alkyl, aryl

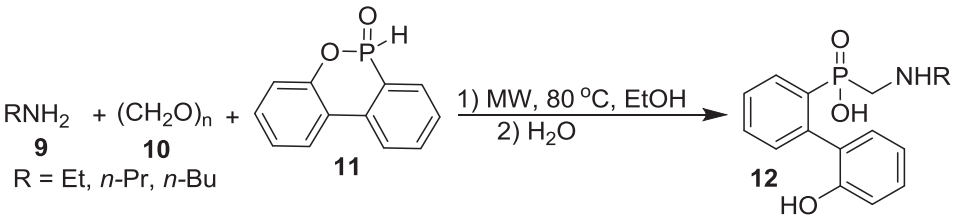
**Scheme 2.**




**6** **7** **8**

R = OH or Me

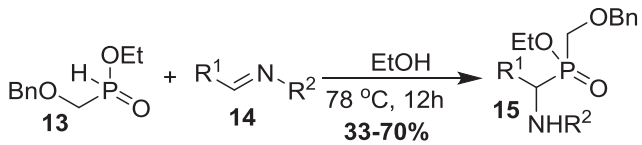
**Scheme 3.**




**9** **10** **11** **12**

R = Et, *n*-Pr, *n*-Bu

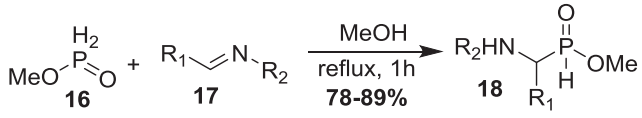
**Scheme 4.**




**13** **14** **15**

$R^1$ = Ph, $CH_2CHMe_2$, *c*-Hex
$R^2$ = Bn, $CHPh_2$

**Scheme 5.**




**16** **17** **18**

$R_1$ = Ph, H, Me
$R_2$ = Me, *n*-Bu, *n*-Pent, Bn

**Scheme 6.**

## 2. Reactions

### 2.1. Reactions involving the phosphorous–carbon bond formation

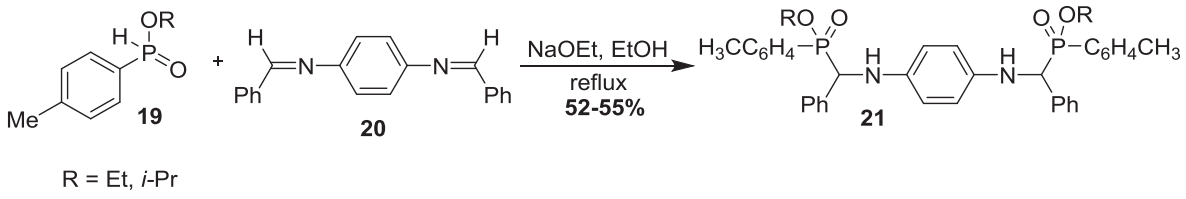
#### 2.1.1. Silyl-Arbuzov reaction

Thottathil et al. reported an efficient method for the synthesis of phosphinic acids or esters **2** from phosphonous acids or esters **1** *via* silyl-Arbuzov reaction of **1** with bromoacetates in the presence of trimethylsilyl chloride (TMS-Cl) and triethylamine (TEA) (Scheme 1) [31].

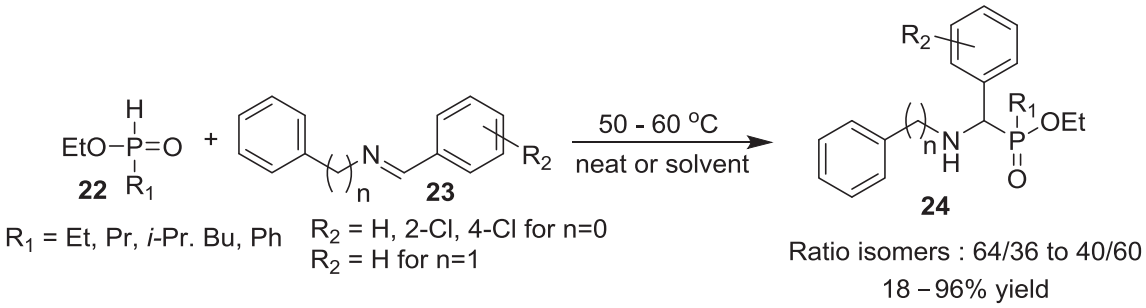
Hansen and Kehler disclosed an elegant route to the synthesis of sec-alkylmethylphosphinates **5** from aldehydes or ketones **4** and the easily obtainable ethyl methylphosphinate **3** in the presence of HMDS (Scheme 2) [32].

#### 2.1.2. Kabachnik–Fields reaction

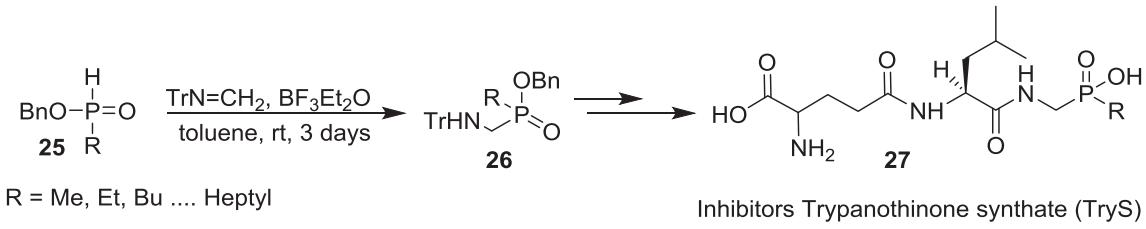
The Kabachnik–Fields reaction is the three-component procedure using amines, oxo compounds, and hydrophosphoryl reagents afforded α-aminophosphine oxides [33–35]. However, the yields in this reaction




**Scheme 7.**

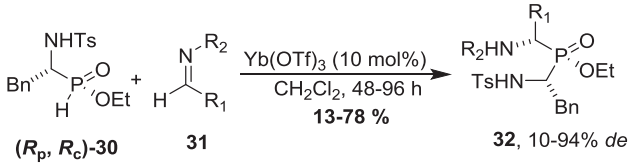



**Scheme 8.**



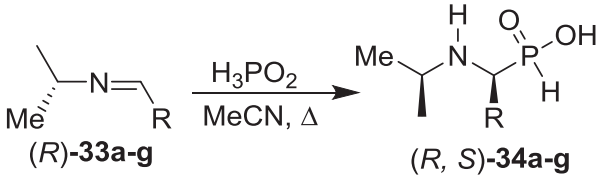

**Scheme 9.**


**Scheme 10.**




**$R_1$** = -$C_6H_5$, -$(CH_3)_3C$, -$(CH_3)_2CH$, -2-Furyl, 1-Naphthyl, 2-Naphthyl
**$R_2$** = -$C_6H_5$, -$C_6H_5CH_2$

**Scheme 11.**



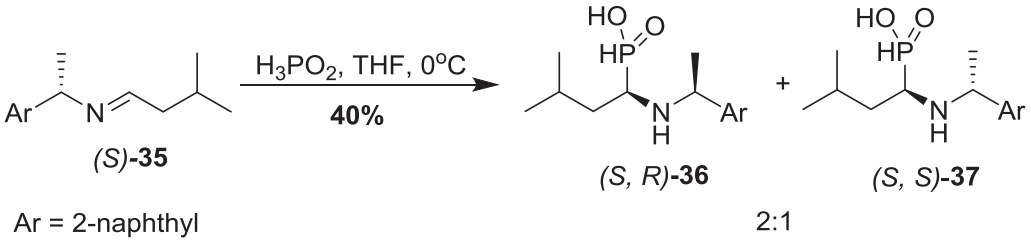

(*R, S*)-**34a;** R = $C_6H_5$, 44%, 100% d.e.
(*R, S*)-**34b;** R = 2-furyl, 39%, 100 % d.e.
(*R, S*)-**34c;** R = *c*-$C_6H_{11}$, 39%, 100% d.e.
(*R, S*)-**34d;** R = 4-$O_2NC_6H_4$, 65%, 100% d.e.
(*R, S*)-**34e;** R = 2-$MeOC_6H_4$, 54%, 100% d.e.
(*R, S*)-**34f;** R = $C_6H_5CH$=CH, 49%, 100% d.e.
(R, S)-**34g;** R = Ferrocenyl, 65%, 50% d.e.

**Scheme 12.**

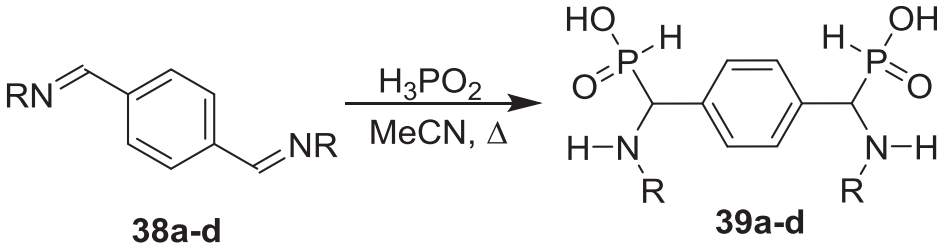
tend to be moderate, there are several advantages such as the cheapness and availability of starting materials and the broad scope of the reaction [33,34]. Indeed, many publications showed the use of special catalysts, such as a phthalocyanine–$AlCl_3$ complex [36], metal triflates [37], Ln $(OTf)_3$ [38,39], $Ga_2I_6$ [40], $Bi(NO_3)_3$ [41], $SmI_2$ [42], $InCl_3$ [43], and $Mg(ClO_4)_2$ [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].

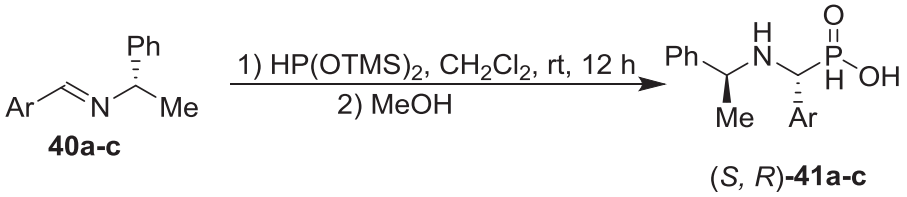



**Scheme 13.**



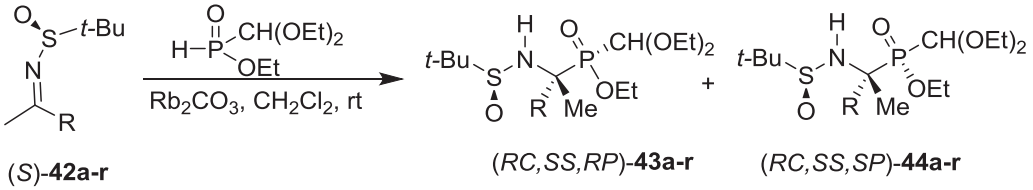

**39a;** R = *(S)*-CH(Me)Ph, 97%, 4:1:1 d.r.
**39b;** R = *(S)*-CH($CO_2$Me)Me, 39%, 2:1:1 d.r.
**39c;** R = *(S)*-CH($CO_2$Et)Bn, 46%, 2:1:1 d.r.
**39d;** R = *(S)*-CH($CO_2$Me)-*i*-Bu, 47%, 2:1:1 d.r.

**Scheme 14.**



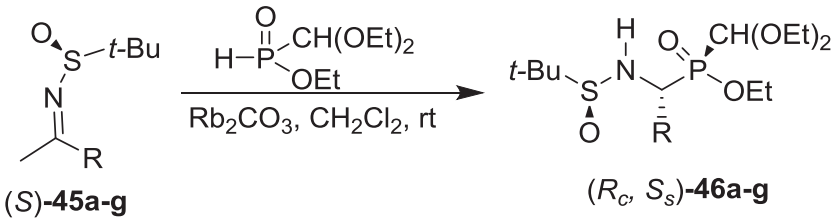

(*S, R*)-**41a;** Ar = 2-Py, 19%
(*S, R*)-**41b;** Ar = 3-Py, 28%
(*S, R*)-**41c;** Ar = 4-Py, 8%

**Scheme 15.**



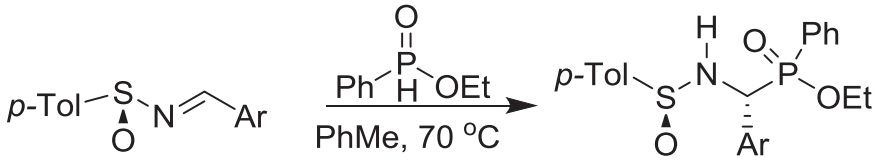

**43a, 44a;** R = $C_6H_5$, 46%/50%
**43b, 44b;** R = 4-Me$C_6H_4$, 37%/34%
**43c, 44c;** R = 2-thienyl, 45%/47%
**43d, 44d;** R = 4-Me$C_6H_4$, 37%/48%
**43e, 44e;** R = 4-MeO$C_6H_4$, 48%/50%
**43f, 44f;** R = 4-morpholin$C_6H_4$, 29%/36%
**43g, 44g;** R = 3,4-($OCH_2O$)-$C_6H_4$, 49%/49%
**43h, 44h;** R = 2-F$C_6H_4$, 37%/36%
**43i, 44i;** R = 4-F$C_6H_4$, 43%/50%
**43j, 44j;** R= 4-Cl$C_6H_4$, 46%/48%
**43k, 44k;** R = 4-Br$C_6H_4$, 41%/35%
**43l, 44l;** R = 2-furyl, 35%/49%
**43m, 44m;** R = 3-pyridyl, 50%/35%
**43n,44n;** R = 2-naphthyl, 43%/49%
**43o, 44o;** R = 4-biphenyl, 49%/49%
**43p, 44p;** R = 4-N$CC_6H_4$, 41%/48%
**43q, 44q;** R = 4-$O_2NC_6H_4$, 32%/38%
**43r, 44r;** R = *n*-Hex, 45%/30%

**Scheme 16.**



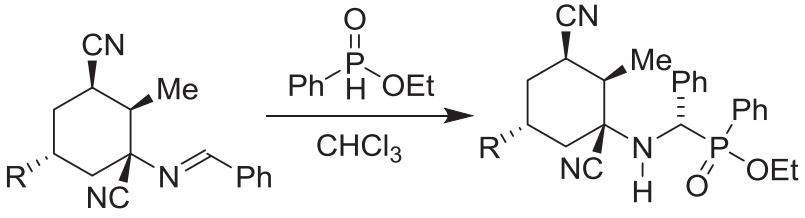

**20a;** R = PhthN$(CH_2)_3$, 92%
**20b;** R = $BnSCH_2$, 91%
**20c;** R = $EtOCO(CH_2)_2$, 87%
**20d;** R = $BnOCH_2$, 50%
**20e;** R = (*R*)-MeCH(OBn), 92%
**20f;** R = 3'-indolyl-$CH_2$, 96%
**20g;** R = *i*-Pr, 70%

**Scheme 17.**




**48a;** Ar = 2-$ClC_6H_4$, 22%
**48b;** Ar = 3-$MeOC_6H_4$, 35%
**48c;** Ar = $C_6H_5$, 19%

**Scheme 18.**




**9a;** R = $HO(CH_3)_2C$-, 96%, 8:46:3:43
**9b;** R = $CH_2$=C(Me)-, 80%, 7:51:5:37

**Scheme 19.**

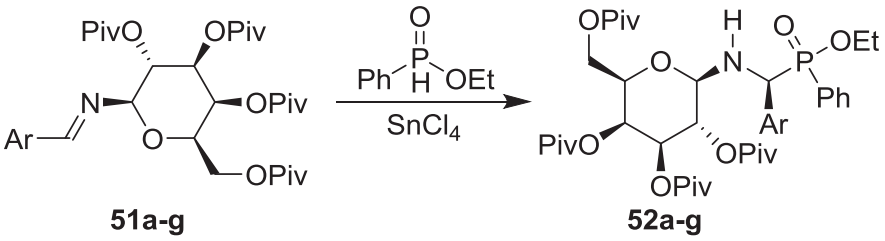
*2.1.3. Hydrophosphinylation of imines*

Hydrophosphinylation of imines "Pudovki reaction" is one of the most common pathways to the synthesis of *α*-amino-*H*-phosphinates hydrophosphinylation of aldimines and ketimines with hydrogenphosphinate ester [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].

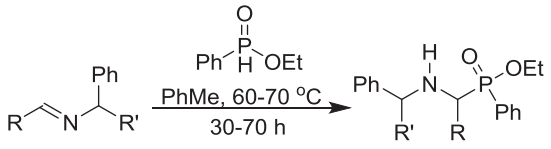
The reaction of *H*-phosphinates **19** to imines **20** in the presence of sodium ethoxide was also described for the formation of bisphosphinic ester **21** (Scheme 7) [61].




51a-g 52a-g

**52a;** Ar = 4-$BrC_6H_4$, 86%, > 82% d.r.
**52b;** Ar = 4-$FC_6H_4$, 92%, > 76% d.r.
**52c;** Ar = 4-$ClC_6H_4$, 84%, > 86%, d.r.
**52d;** Ar = 4-$O_2NC_6H_4$, 79%, > 88% d.r.
**52e;** Ar = 4-$MeOC_6H_4$, 82%, > 74% d.r.
**52f;** Ar = 4-$MeC_6H_4$, 95%, > 81% d.r.
**52g;** Ar = $C_6H_5$, 91%, > 73% d.r.

**Scheme 20.**




59a-g 60a-g

**60a;** R = 3-$MeOC_6H_4$, R' = Me, 68% , 45 : 13 : 35 : 9 d.r.
**60b;** R = 2-$MeC_6H_4$, R' = Me, 48%, 30 : 14 : 40 : 16 d.r.
**60c;** R = *i*-Bu, R' = Me, 60%, 45 : 39 : 11 : 5 d.r.
**60d;** R = 3-$MeOC_6H_4$, R' = $CH_2OMe$, 62%, 30 : 33 : 19 : 18 d.r.
**60e;** R = 2-$MeC_6H_4$, R' = $CH_2OMe$, 40% , 42 : 4 : 41 : 14 d.r.
**60f;** R = *i*-Bu, R' = $CH_2OMe$, 60%, 42 : 10 : 35 : 13 d.r.
**60g;** R = Ph, R' = Me, 84% , 47 : 6 : 40 : 7 d.r.

**Scheme 21.**

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 $BF_3.Et_2O$, 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 aminoalkyl-P-substituted phosphorus heterocycles **29** with a NCPCN pattern *via* the reaction 2*H*-2-oxo-1,4,2-oxazaphosphinanes **28** 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 the (*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 $H_3PO_2$ with Schiff bases **38a–d** in acetonitrile at reflux (Scheme 14) [71–73].

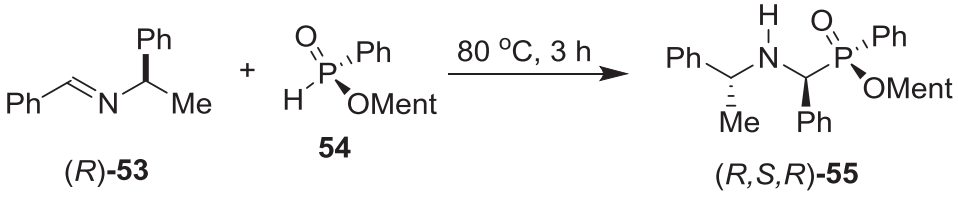
Diastereoselective hydrophosphinylation reaction of bis(trimethylsilyl) phosphonate (BTSP) to chiral N-(diphenylmethyl) imines **40a–c** in DCM followed by the treatment with MeOH gave 1-(diphenylmethylamino)-alkylphosphonous acids **41a–c** (Scheme 15) [74,75].

Furthermore, Yuan and Zhang noted that the enantioselective reaction of ethyl diethoxymethylphosphinate to *N*-(*tert*-butanesulfinyl) ketimines (*S*)-**42a–r** in DCM using $Rb_2CO_3$ as a base gave the *α*-aminophosphinates (*RC,SS,RP*)-**43a–r** and (*RC,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 $Rb_2CO_3$ furnished the phosphinates (*RC, SS*)-**46a–g** in good yields (Scheme 17) [77].

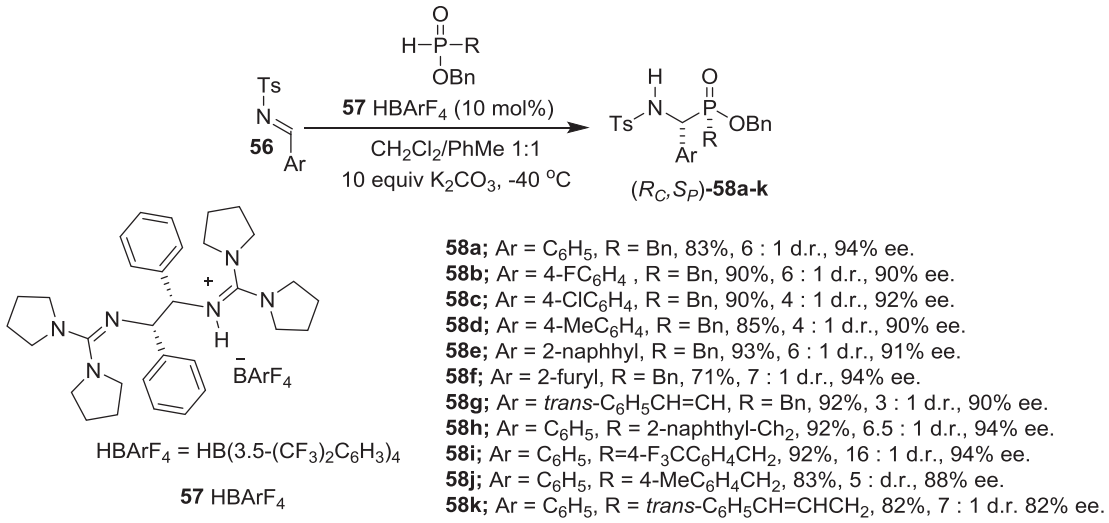
Optically active *α*-aminophosphinates (*RC,SS*)-**48a–c** can be prepared through the reaction of ethyl phenylphosphinate and enantiopure aldimines (*S*)-**47a–c** in toluene at 70 °C (Scheme 18) [78,79].

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



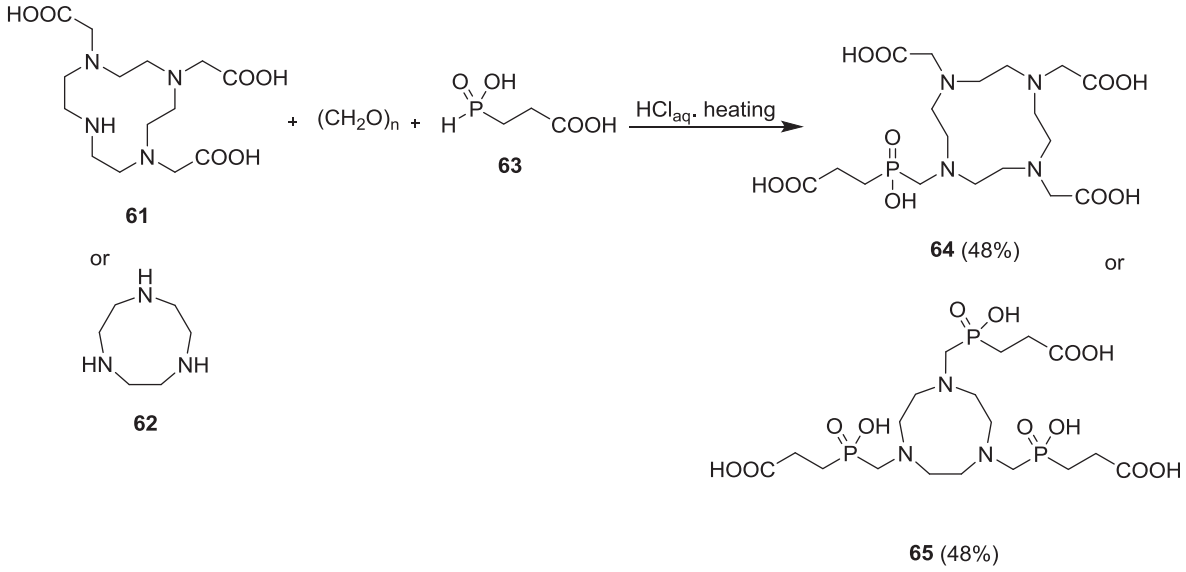

(*R*)-**53** **54** (*R,S,R*)-**55**

**Scheme 22.**

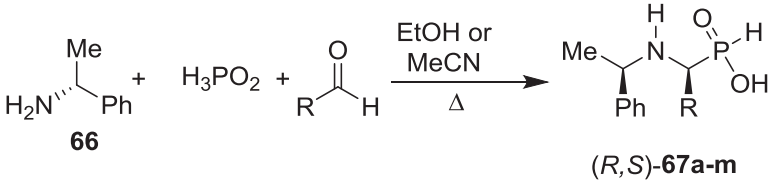



**58a;** Ar = $C_6H_5$, R = Bn, 83%, 6 : 1 d.r., 94% ee.
**58b;** Ar = 4-$FC_6H_4$ , R = Bn, 90%, 6 : 1 d.r., 90% ee.
**58c;** Ar = 4-$ClC_6H_4$, R = Bn, 90%, 4 : 1 d.r., 92% ee.
**58d;** Ar = 4-$MeC_6H_4$, R = Bn, 85%, 4 : 1 d.r., 90% ee.
**58e;** Ar = 2-naphhyl, R = Bn, 93%, 6 : 1 d.r., 91% ee.
**58f;** 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-$F_3CC_6H_4CH_2$, 92%, 16 : 1 d.r., 94% ee.
**58j;** Ar = $C_6H_5$, R = 4-$MeC_6H_4CH_2$, 83%, 5 : d.r., 88% ee.
**58k;** Ar = $C_6H_5$, R = *trans*-$C_6H_5CH$=$CHCH_2$, 82%, 7 : 1 d.r. 82% ee.

**Scheme 23.**

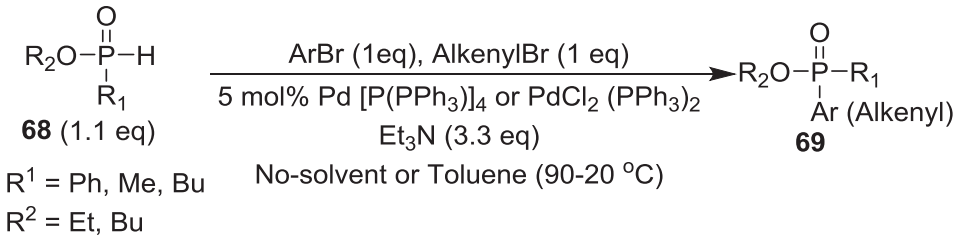



**Scheme 24.**

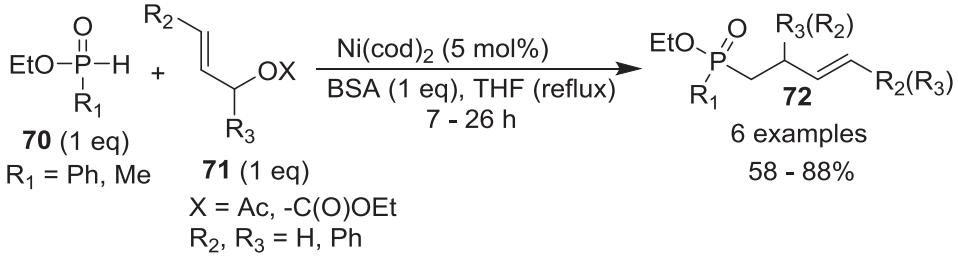



(*R,S*)-**5a;** R = $C_6H_5$, 35%, 100% d.e.
(*R,S*)-**5b;** R = 2-furyl, 100% d.e.
(*R,S*)-**5c;** R = *c*-$C_6H_{11}$, 32%, 100% d.e.
(*R,S*)-**5g;** R = ferrocenyl, 60% d.e.
(*R,S*)-**5h;** R = *i*-Pr, 49%, 100% d.e.
(*R,S*)-**5i;** R = *i*-Bu, 33%, 100% d.e.
(*R,S*)-**5j;** R = *s*-Bu, 36%, 100% d.e.
(*R,S*)-**5k;** R = pent-2-yl, 30%, 100% d.e.
(*R,S*)-**5l;** R = hept-3-yl, 35%, 100% d.e.
(*R,S*)-**5m;** R = $C_6H_5CH_2$, 20%, 100% d.e.

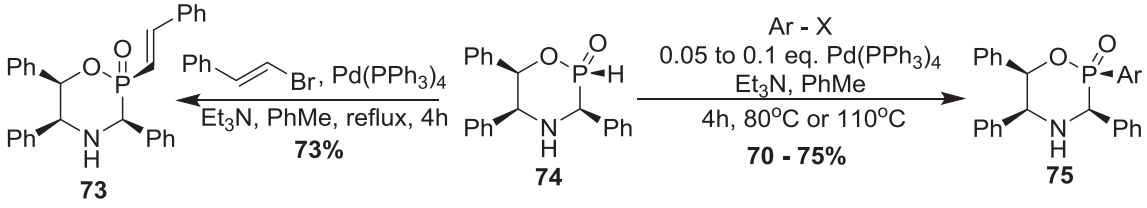
**Scheme 25.**



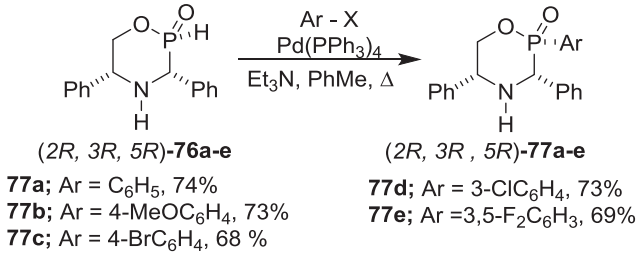

**Scheme 26.**



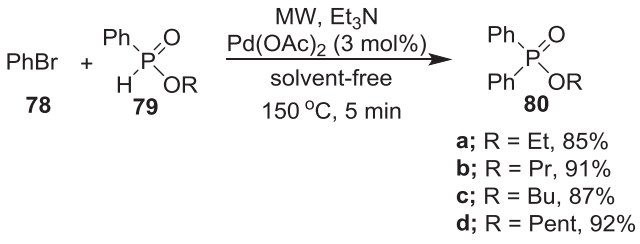

**Scheme 27.**




**Scheme 28.**




**Scheme 29.**




**Scheme 30.**

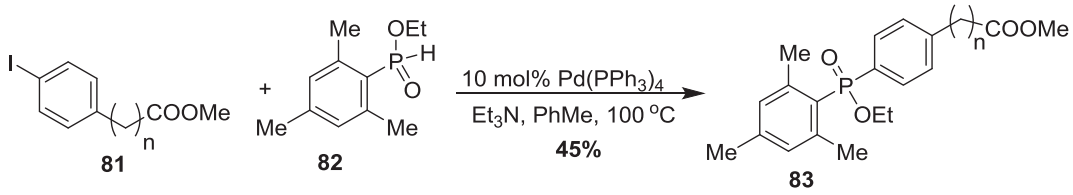
phenylphosphinate with the chiral imines **49a,b** furnished the phosphinates **50a,b** with good diastereoselectivities (Scheme 19).

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 ethyl phenylphosphinate to aldimines **51a–g** in the presence of $SnCl_4$ as a catalyst in THF at room temperature (Scheme 20) [84].

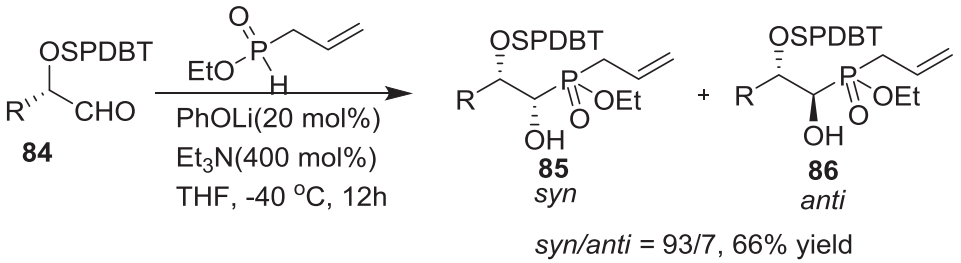
The first asymmetric synthesis of *α*-aminophosphinic acids **60a–g** in good diastereoisomeric ratio was carried by Szabó et al. without using a catalyst *via* the treatment of chiral imines **59a–g** with ethyl phenylphosphinate (Scheme21) [85].

*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).

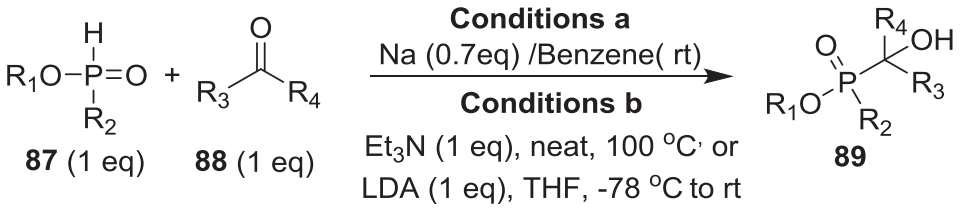
*2.1.3.5. Using chiral catalyst*. A series of enantiomerically enriched α-amino phosphinate **58a–k** were synthesized by the stereoselective reaction of the imines **56** with phosphinates in the presence of the guanidinium salt $HBArF_4$ **57** as a catalyst (Scheme 23) [87].



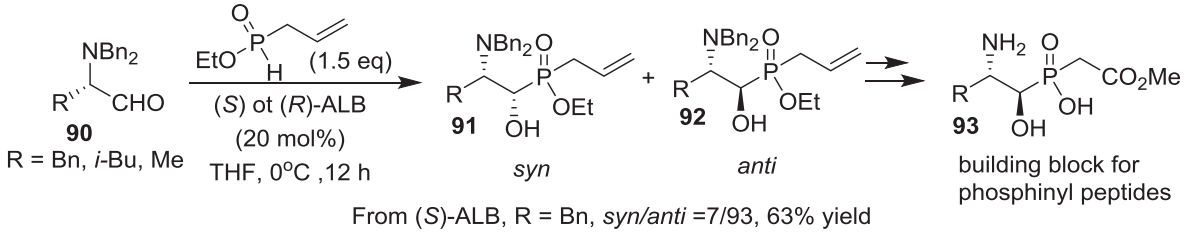

**Scheme 31.**



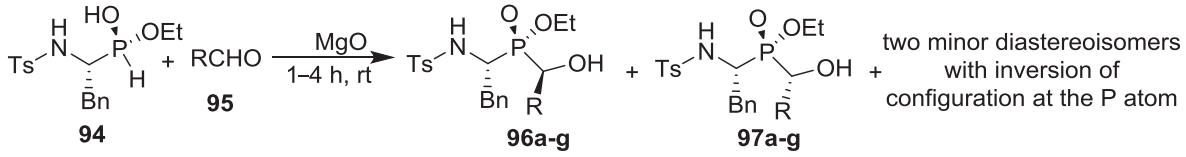

**Scheme 32.**




**Scheme 33.**

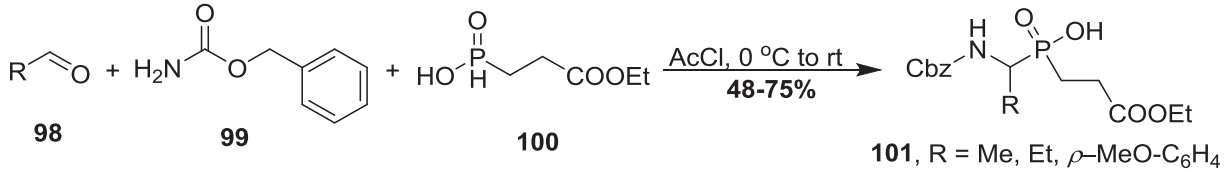



**Scheme 34.**




**96a, 97a**: R = Ph, 81%
**96b, 97b**: R = 1-naphthyl, 79%,
**96c, 97c**: R = 2-naphthyl, 51%
**96d, 97d**: R = 2-furyl, 65%
**96e, 97e**: R = CH=CHPh, 60%
**96f, 97f**: R = $(CH_2)_4Me$, 14%
**96g, 97g**: R = 4-$O_2NC_6H_4$, 46%

**Scheme 35.**

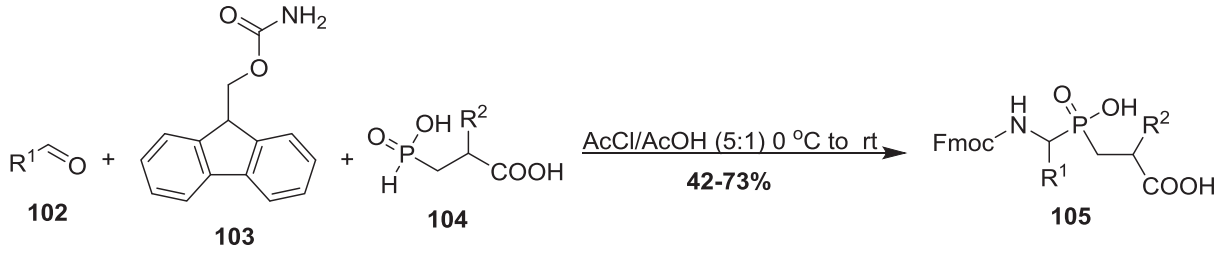


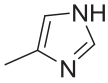

**Scheme 36.**

*2.1.4. Phospha-Mannich reaction*

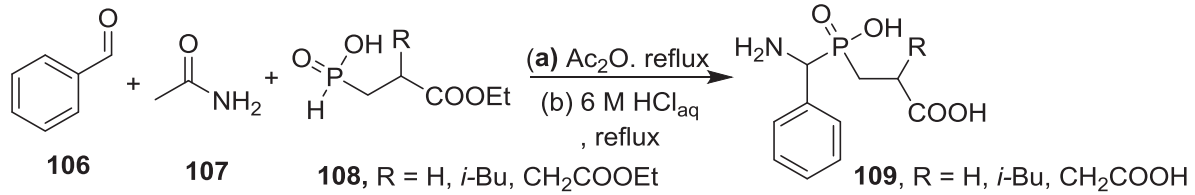
Phospha-Mannich reaction of paraformaldehyde, 2-carboxyethylphosphonous acid **63** and **61** or **62** afforded phosphinates (**64** and **65**) that used as labeling biomolecules in nuclear medicine (Scheme 24) [88].

The three-component reaction of (*R*)-α-methylbenzylamine **66**, hypophosphorous acid and aldehydes furnished the α-amino-*H*-phosphinic acids (*R*,*S*)-**67a-m** as single diastereoisomers (Scheme 25) [89].

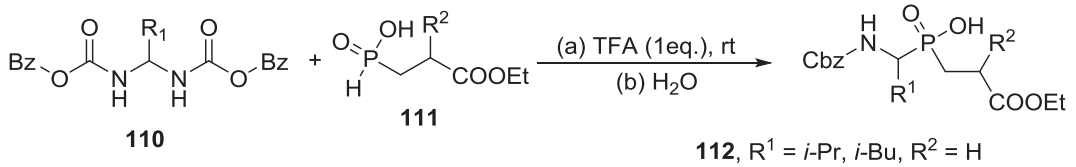



$R^1$ = H, *i*-Pr, *i*-Bu, *sec*-Bu, $CH_2CH_2COOMe$, $CH_2OBz$, Ph,  ; $R^2$ = Bz
$R^1$ = Me; $R^2$ = *i*-Bu
$R^1$ = Ph; $R^2$ = Me
$R^1$ = *i*-Bu; $R^2$ = H

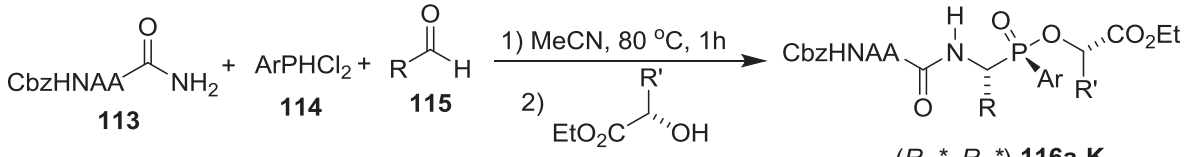
**Scheme 37.**




**Scheme 38.**

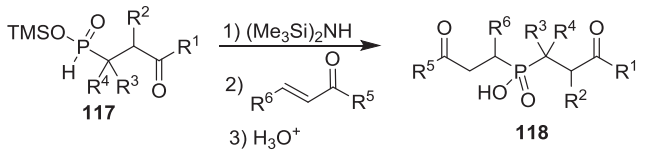



**Scheme 39.**




**116a;** AA = Gly, R = $C_6H_5$, Ar = $C_6H_5$, R' = H, 64%, 60 : 40 d.r.
**116b;** AA = Gly, R = $C_6H_5$, Ar = 4-Me$C_6H_4$, R' = H, 60%, 69: 31 d.r.
**116c;** AA = Gly, R = $C_6H_5$, Ar = 4-Cl$C_6H_4$, R'=H, 65%, 66 : 34 d.r.
**116d;** AA = Gly, R = 4-Me$C_6H_4$.Ar = $C_6H_5$, R' = H, 66%, 66 : 34 d.r.
**116e;** AA = Gly, R = 4-Cl$C_6H_6$, Ar = $C_6H_5$, R'=H, 61%, 62 : 38 d.r.
**116f;** AA = Gly, R = *i*-Pr, Ar = $C_6H_5$, R' = H, 59%, 69. 31 d.r.
**116g;** AA = Gly, R = 4-Me$C_6H_4$, Ar = $C_6H_5$, R' = (*S*)-Me, 62%, 50 : 26 : 12 : 12 d.r.
**116h;** AA = Gly, R = 4-Me$C_6H_4$, Ar = $C_6H_5$, R' = (*S*)-$C_6H_5$, 66% N.D.
**116i;** AA= -Ala, R = $C_6H_5$, Ar = $C_6H_5$, R' = H, 60%, 76 : 24 d.r.
**116j;** AA = (*S*)-Val, R = 4-Me$C_6H_4$, Ar = $C_6H_5$, R' = H, 50%, N.D.
**116k;** AA = Gly-Gly, R = 4-Me$C_6H_4$, Ar = $C_6H_5$, R'=H, 56%, 77: 23 d.r.

**Scheme 40.**




$R^1$ = Me, $R^2$ = H, $R^3$ = H, $R^4$ = H : 74%
$R^1$ = Et, $R^2$ = H, $R^3$ = H, $R^4$ = H : 89%
$R^1$ = *n*-Pr, $R^2$ = H, $R^3$ = H. $R^4$ = H : 87%
$R^1$ = Et, $R^2$ = H, $R^3$ = Me, $R^4$ = H : 80%
$R^1$ = Me, $R^2$ = H, $R^3$ = *n*-Bu, $R^4$ = H: 77%
$R^1$ = Me, $R^2$ = H, $R^3$ = Me, $R^4$ = Me : 80%
$R^1$ , $R^4$ = -$(CH_2)_2$-, $R^2$ = H, $R^3$ = H : 91%
$R^1$ , $R^4$ = -$(CH_2)_3$-, $R^2$ = H, $R^3$ = H : 87%
$R^1$ = Me, $R^2$, $R^3$ = -$(CH_2)_2$-, $R^4$ = H : 79%
$R^1$ = *n*-Pr, $R^2$ = H, $R^3$ = H, $R^4$ = H, $R^5$ = nPr, $R^6$ = H : 87%
$R^1$ = *n*-Pr , $R^2$ = H, $R^3$ = H, $R^4$ = H, $R^5$ = Et, $R^6$ = Me : 83%
$R^1$ = Et, $R^2$ = H, $R^3$ = H, $R^4$ = H, $R^5$ = OEt, $R^6$ = H : 79%
$R^1$ = OMe, $R^2$ = Me, $R^3$ = H, $R^4$ = H, $R^5$ = OEt, $R^6$ = H : 77%

**Scheme 41.**

*2.1.5. Hirao cross-coupling reactions:*

Montchamp has disclosed the synthesis of disubstituted aryl-alkenyl phosphinate esters **69** through Pd-catalyzed cross-coupling reactions of alkyl phosphinates **68** with aryl and alkenyl bromides in the presence of Pd-catalysts (Scheme 26) [90].

Lu and co-workers demonstrated that a catalytic allylation of phosphinates **70** *via* cross coupling with allylic acetates or carbonates **71** using BSA/Ni$(cod)_2$ as catalyst gave phosphinates **71** (Scheme 27) [91].

Pirat et al. noted that 2-vinyl/2-aryl-1,4,2-oxazaphosphinanes **73**/**75** can be synthesized *via* palladium-catalyzed direct coupling of 2-vinyl/2-aryl-halides with oxazaphosphinane **74** (Scheme 28) [92].

Pirat et al. [93] reported that the asymmetric synthesis of oxazaphosphinanes (*2R,3R,5R*)-**77a-e** as single diastereoisomers took place through pallado-catalyzed arylation of (*2R,3R,5R*)-**76** with aryl halides and $Et_3N$ in PhMe at reflux (Scheme 29) [94].

Under microwave conditions, Hirao reaction of aryl bromides **78** and alkyl phenyl-H-phosphinates **79** in the presence of palladium(II) acetate and trimethylamine afforded the corresponding phosphinates **80** (Scheme 30) [95,96].

Schuman et al. [97] noted that palladium-catalyzed coupling of iodo compound **81** with phosphinate **82** take place in the presence of quatrotriphenylphosphine as an efficient procedure for preparing 4-(4-carboxybutyl)-phenyl(2,4,6-trimethylphenyl)phosphinic ester **83** (Scheme 31).

*2.1.6. 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 *syn-α,β*-dihydroxyphosphinates **85,86** in high diastereoselectivity was attained by a chiral AlLibis(binaphtoxide) (ALB) or lithium phenoxide(PhOLi)-catalyzed hydrophosphinylation of aldehydes **84** 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)-phosphinates [106]. Both Yamashita [107] and Hansen [32] used this approach to synthesize alkyl(*sec*-alkyl)phosphinates **89** *via* the reaction of *H*-phosphonates **87** to aldehydes or reactive ketones **88** under amine-catalysis (Scheme 33).

Shibuya et al. [108] used Al-Li-BINOL complexes for the asymmetric synthesis of *α,α*-dihydroxyphosphinates **91** and **92** by the reaction of methyl phosphinate with aldehydes **90**. This methodology was applied in the preparation of *β*-amino-*α*-hydroxyphosphinates **93** as intermediates in the synthesis of phosphinyl peptides (Scheme 34) [98].

Diastereoselective hydrophosphinylation of phosphinate **94** with aldehydes **95** in the presence of magnesium oxide without solvent afforded novel α-amino-α'-hydroxyphosphinates **96a–g** and **97a–g** in ratio ~ 1:1 in all cases (Scheme 35) [109]. The reaction proceeded with highly retentive 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*-aminoalkylphosphinic acids **101** in moderate yields consists of the reaction of an aldehyde **98**, carbamate **99**, and a *β*-alkoxycarboxylphosphonous acid **100** in acetyl chloride at 0 °C (Scheme 36) [110,111].

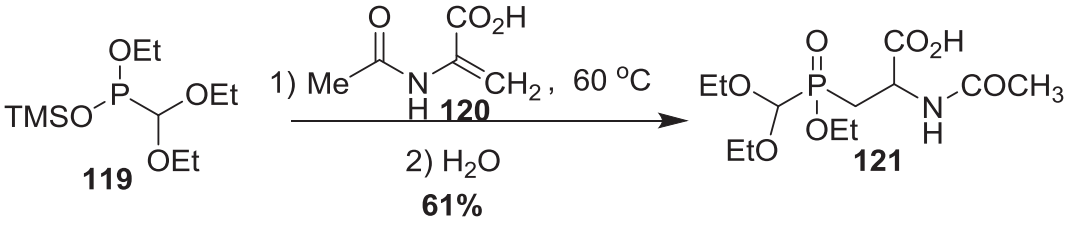
In similar fashion, Matziari and Yiotakis applied a three-component condensation reaction of aldehydes **102**, $FmocNH_2$ **103**, and carboxylic phosphonous acid **104** ($R_2$ = H, Me, *i*-Bu, Bzl) in AcCl/AcOH to get pseudodipeptides **105** that were directly suitable for solid-phase peptide synthesis (Scheme 37) [112].

Rozhko and Ragulin reported a mild procedure for the preparation of phosphinic acids **109** through the amidoalkylation of phosphonous acids **108** with benzaldehyde **106** and acetamide **107** in acetic anhydride followed by acid hydrolysis (Scheme 38) [113].

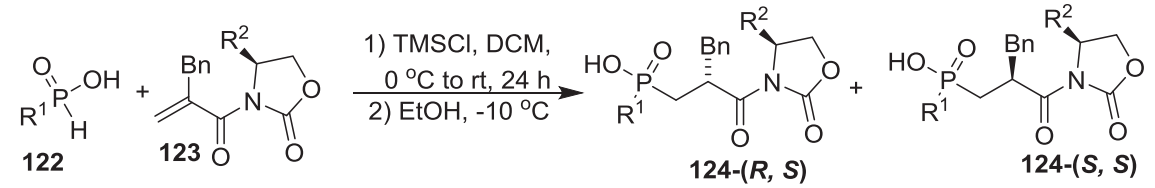
Dmitriev and Ragulin described the reaction of biscarbamates **110** and phosphonous acids **111** in a mixture of acetic anhydride and acetyl chloride or trifluoroacetic anhydride afforded *α*-aminoalkylphosphinic acids **112** (Scheme 39) [114–116].

*2.1.7.2. Stereoselective amidoalkylation.* A three component condensation reaction of *N*-Cbz-amino amides **103**, aldehydes **115**, and phosphines **114** followed by alcoholysis gave the depsipeptides **116a–k** (Scheme 40) [117].

*2.1.7.3. Michael addition to olefins.* The construction of phosphinic acids **118** *via* a P-Michael addition using the silylation of 117 with HMDS followed by 1,4-addition to olefins (Scheme 41) [118,119]. Moreover, the same reaction take place smoothly in solid-phase organic chemistry [120–122].



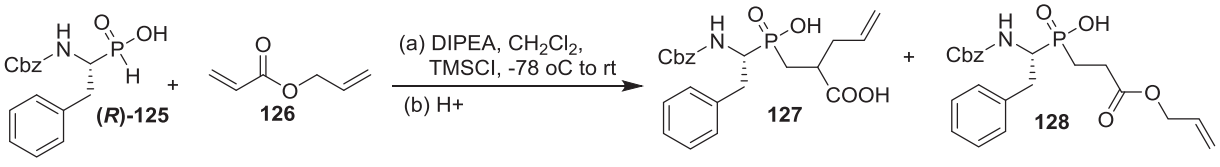

**Scheme 42.**




$R^1$ = BnCH(NHAc), naphthyl, $Ph(CH_2)_2$
$R^2$= Bn, $Ph_2CH$

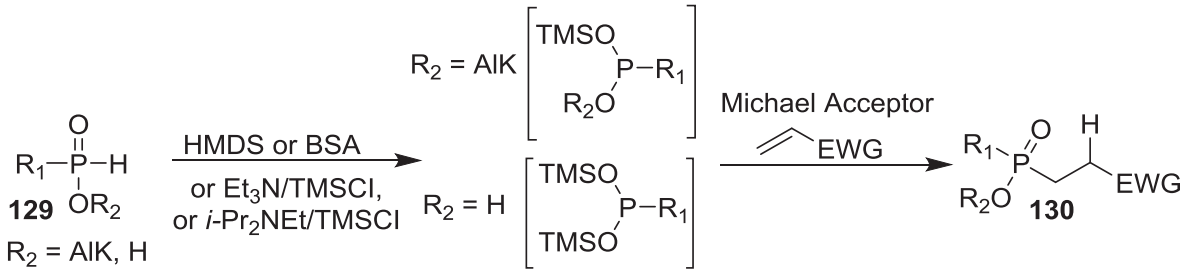
**a;** $R^1$ = BnCH(NHAc), $R^2$= Bn, 94%, *(R, S)/(S, S)*: 3/1
**b;** $R^1$ =BnCH(NHAc), $Ph_2CH$, 90%, *(R, S)/(S, S)*: 86/1
**c;** $R^1$ = naphthyl, $R^2$= Bn, 78%, *(R, S)/(S, S)*: 5/1
**d;** $R^1$ = naphthyl, $Ph_2CH$, 73%, *(R, S)/(S, S)*: 55/1
**e:** $R^1$ = $Ph(CH_2)_2$, $R^2$= Bn, 91%, *(R, S)/(S, S)*: 12/1
**f:** $R^1$ = $Ph(CH_2)_2$, $Ph_2CH$, 90%, *(R, S)/(S, S)*: 54/1

**Scheme 43.**

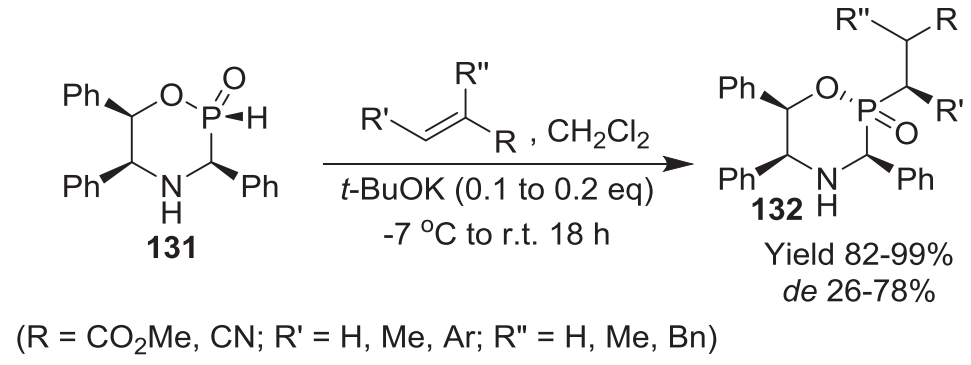



**Product ratio: 55:45**

**Scheme 44.**




**Scheme 45.**




(R = $CO_2Me$, CN; R' = H, Me, Ar; R" = H, Me, Bn)

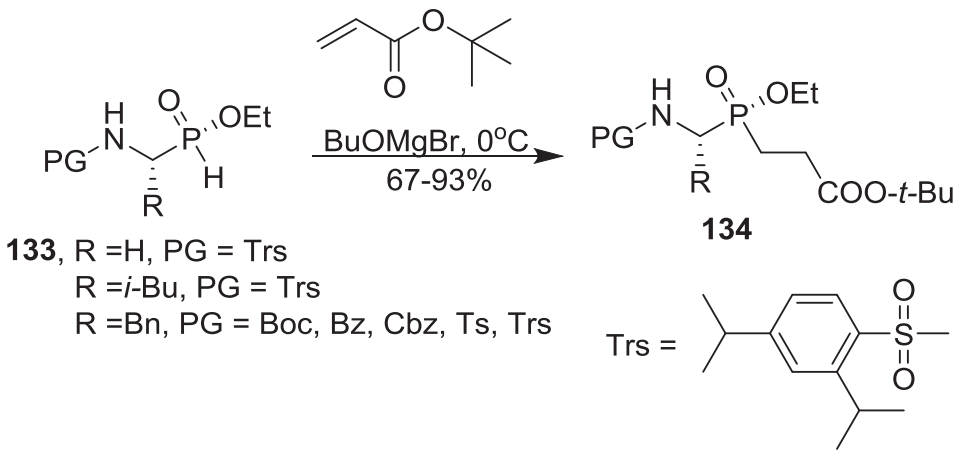
**Scheme 46.**

The alkyl trimethylsilyl phosphonate **119** has been used for *P*-Michael addition with acrylic acid **120** to give **121** after hydrolysis (Scheme 42) [123].

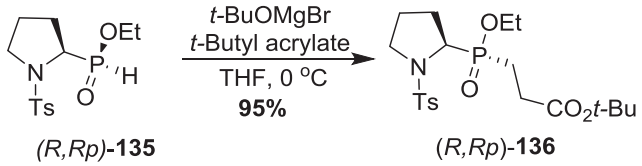
Enantioselective Michael addition of phosphinic acids **122** with acrylates **123** proceeded smoothly to afford phosphinyl dipeptidomimetics **124** in excellent yields (Scheme 43) [124].

An unprecedented coupling of a P—C and a C—C bond formation on a phosphinic dipeptides **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).

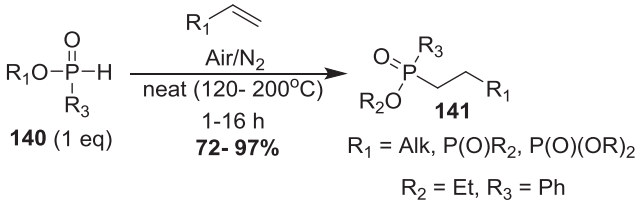
Michael addition of *H*-phosphinates **129** to 1,4-conjugated systems




**Scheme 47.**




**Scheme 48.**




**Scheme 50.**

involving silyl alkyl phosphonite intermediates afforded disubstituted phosphinic acid derivatives **130** 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 **131** to olefins furnished phosphinopeptides **132** in very good to excellent yields (Scheme 46) [129].

Yamagishi et al. reported Michael addition of stereodefined phosphinates **133** to *t*-butyl acrylate in the presence of magnesium alkoxide as a catalyst afforded a single isomer **134** in excellent yield (Scheme 47) [130].

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

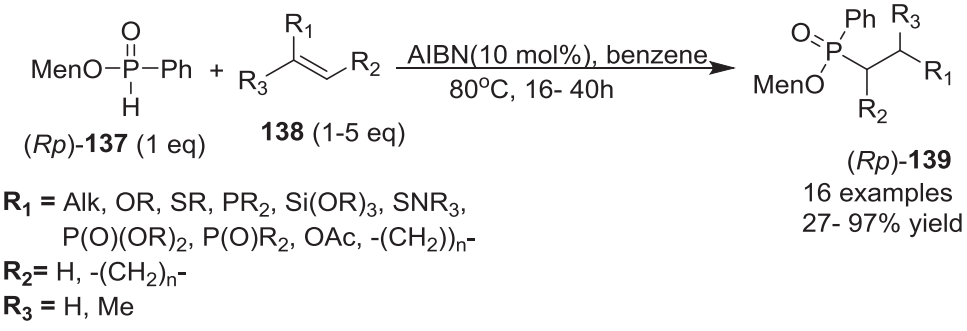
*2.1.8. Hydrophosphinylation reaction with alkenes*

A stereospecific radical or base-catalyzed the reaction of menthyl phenylphosphinate **137** to alkenes **138** afforded optically pure alkylphenylphosphinates **139** (Scheme 49) [133].

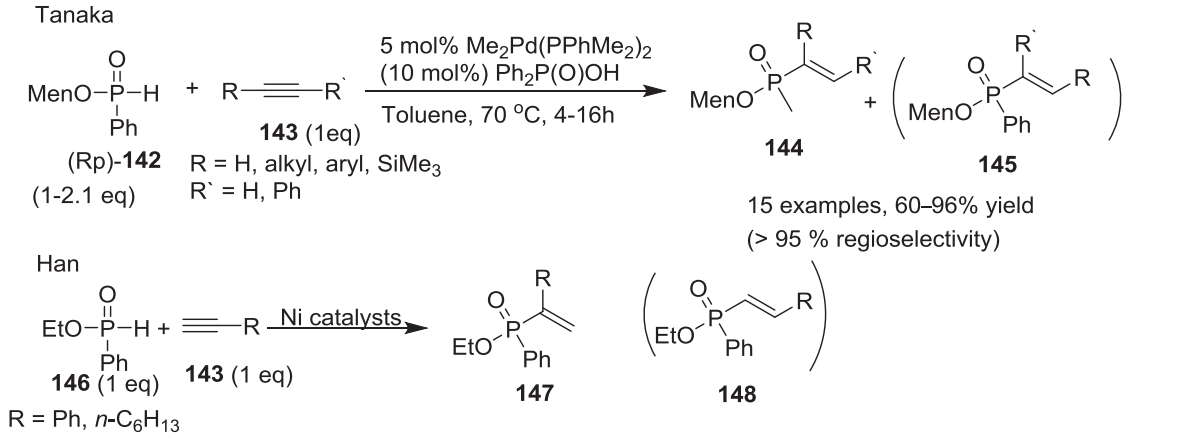
Hirai and Han noted the air-induced addition of reactive phosphinic acids **140** to alkenes for the selectively synthesis of the corresponding anti-Markovnikov adduct **141** requires a high temperature (Scheme 50) [134].

*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**

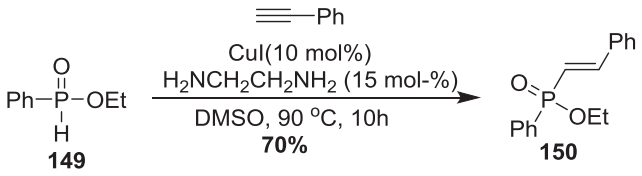



**Scheme 49.**

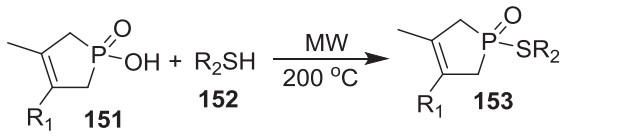



**Condition A**: 0.5 mol% $Ni(PPh_2Me)_4$, 1 M EtOH,rt, 5 h, 87-95% (ratio 12/13=5/95)
**Condition B**: 1 mol% $Ni(cod)_2$, 4 mol% $PPhMe_2$, 2 mol% PhP(O)OH, 1 M THF, rt, 2h, 89-93%(ratio12/13=94/6)

**Scheme 51.**

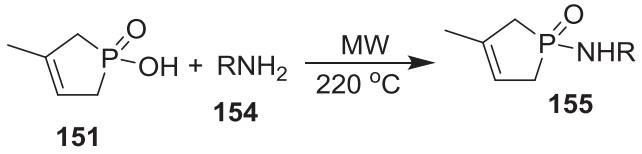



**Scheme 52.**



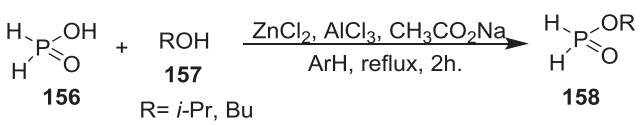

**a;** $R_1$ =H, $R_2$ = $C_4H_9$, 38%
**b;** $R_1$ = H , $R_2$ = $C_5H_{11}$, 40%
**c;** $R_1$ = $CH_3$, $R_2$ = $C_5H_{11}$, 36%

**Scheme 53.**



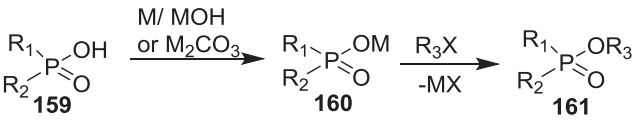

**a;** R =$(CH_2)_5CH$, 26%
**b;** R = $CH_3(CH_2)_5$ ,25%
**c;** R = $C_4H_9$, 29%

**Scheme 54.**




**Scheme 55.**

(Scheme 51) [136]. 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) [137,138].




$R_1$, $R_2$ = alkyl, aryl
M =Na, K
$R_3$ = alkyl, aminoalkyl

**Scheme 56.**

Fu et al. reported the copper-catalyzed addition of phenyl-*H*-phosphinate ester **149** to ethynylbenzene forming **150** under copper catalyst system CuI/ethylenediamine (Scheme 52) [139].

*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].

*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].

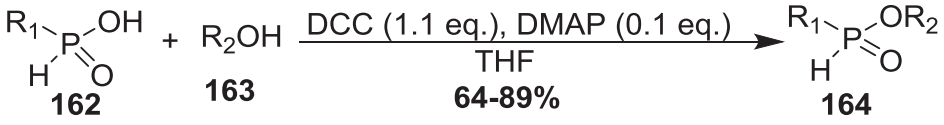
*2.2. Reactions involving oxygen–carbon bond formation*

*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].

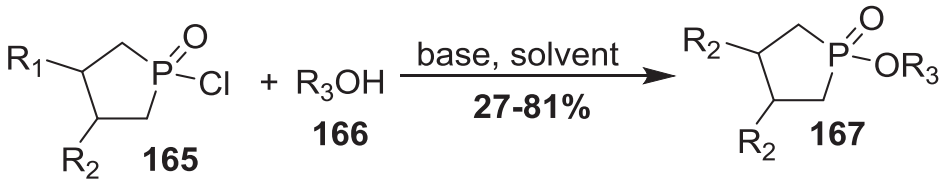
In similar fashion, phosphinates **161** can be synthesized *via* the transformation of acids **159** into their corresponding sodium or potassium salts **160** followed by the reaction with an alkyl halides (Scheme 56) [145–150].

In addition, the esterification of phosphinic acids **162** is achieved *via* the treatment with alcohols **163** in the presence of



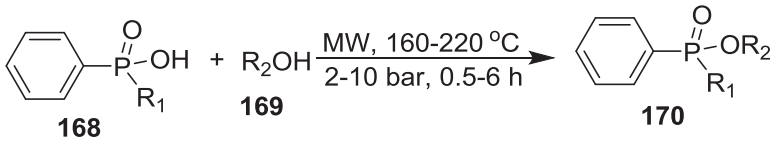

Scheme 57.

$R_1$ = aryl, alkyl
$R_2OH$ = EtOH, *i*-PrOH, BuOH, *t*-BuOH, etc.



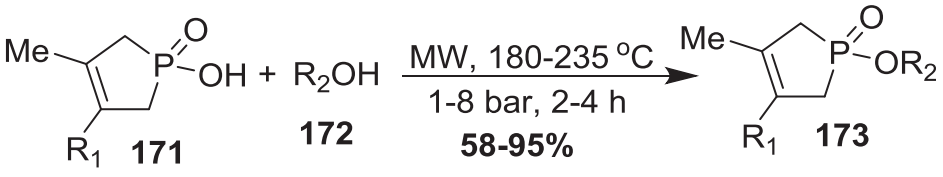

$R_1$, $R_2$ : H, Me
$R_3$: Me, Et, Pent, $C_1$-$C_{12}$ alkyl
Solvent: $Et_2O$, PhH, $CH_2Cl_2$, PhMe
Base: $NEt_3$, NaOMe

Scheme 58.




**a;** $R_1$ =H, $R_2$ = $C_2H_5$, 80%
**b;** $R_1$ = H , $R_2$ = $C_4H_9$, 90%
**c;** $R_1$ = H, $R_2$ = $CH_3(CH_2)_7$, 84%
**d;** $R_1$ = Ph, $R_2$ = $CH_3(CH_2)_7$, 42%

Scheme 59.




$R_1$: H, Me
$R_2$: Bu, *i*-Oct

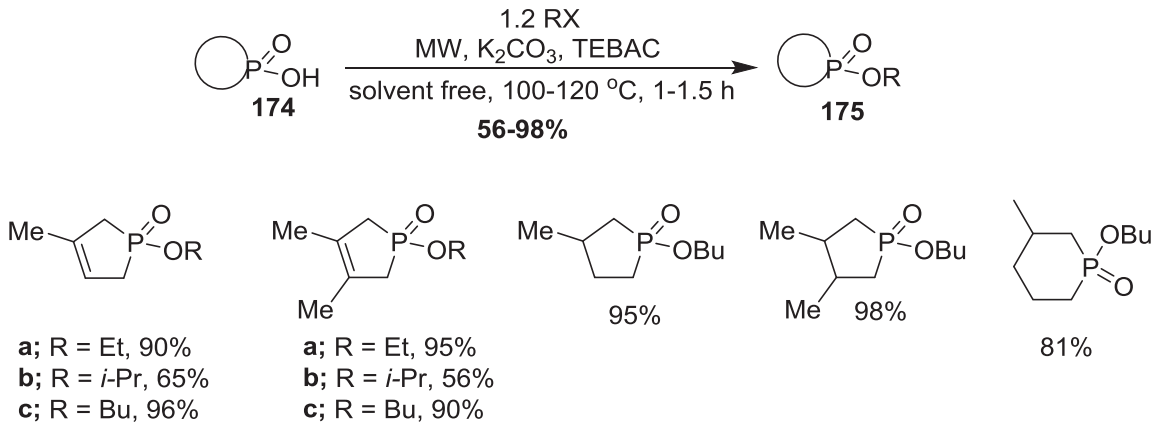
Scheme 60.

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 $NEt_3$ or NaOMe in different solvents afforded phosphinates **167** (Scheme 58) [155–157].

*2.2.1.2. Using microwave (MW) technique.* Quin 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].

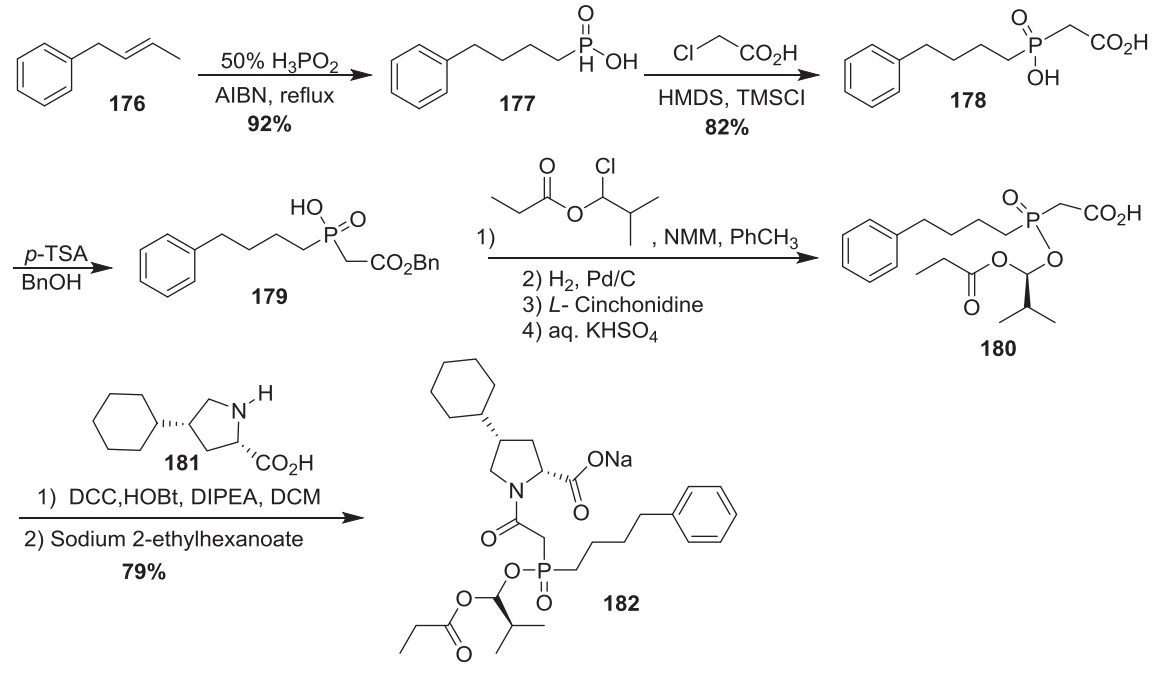
In a similar manner, the esterification of cyclic phosphinic acids **171** with alcohols **172** was also elaborated to furnish phosphinates **173**




**Scheme 61.**

**Table 1**
List of phosphinic acid drugs in clinical development.

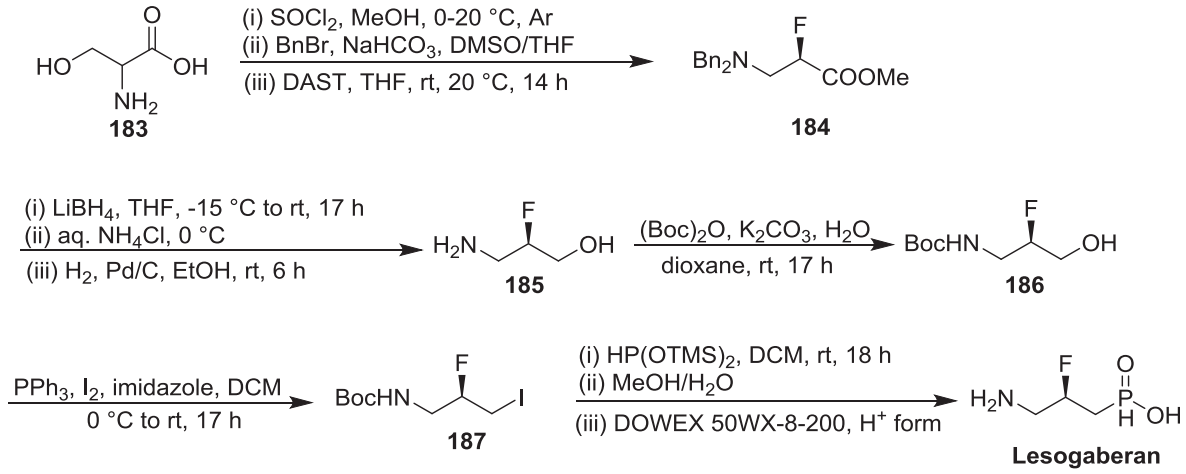
| Drug | Developer | Indication | Mechanism of action |
|---|---|---|---|
| Monopril | Bristol-Myers Squibb | Hypertension | ACE inhibitor |
| Lesogaberan | AstraZeneca | Gastroesophageal reflux | $GABA_B$ agonist |
| Fosdevirine | ViiV Healthcare | HIV disease | HIV-1 NNRTI |
| SGS-742 | Novartis AG | Alzheimer's disease | $GABA_B$ antagonist |
| GS-9256 | Gilead Sciences | HCV disease | HCV NS3 protease inhibitor |



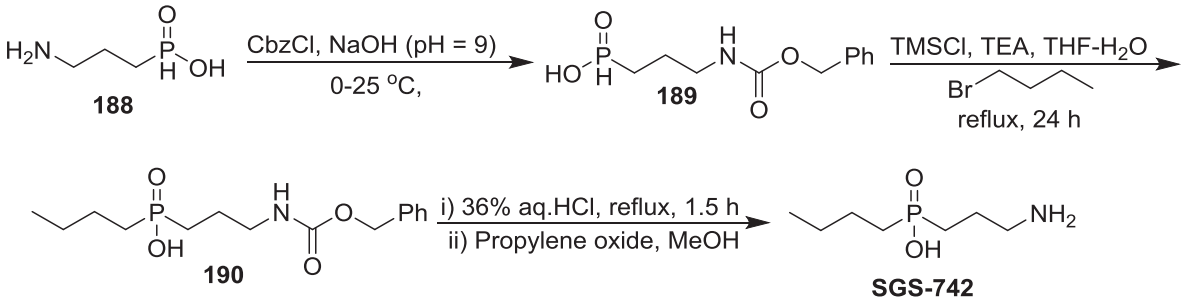

**Scheme 62.**

(Scheme 60) [159,160]. Furthermore, it was found that this reaction will be more efficient and faster by using 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [bmim][$BF_4$] as a cataylst [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 $K_2CO_3$ and afforded the corresponding phosphinates **175** in yields of 56–98% (Scheme 61) [162,163].




**Scheme 63.**




**Scheme 64.**

## 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 **182** is outlined in Scheme 62. A radical addition of hypophosphorous acid to 4-phenyl-1-butene **176** produced the phosphinic acid **177** [164]. The Arbuzov reaction of **177** with chloroacetic acid afforded the dialkyl phosphinic acid **178** [165]. Benzylation of **178** led to **179**, which was subsequently alkylated using racemic 1-chloro-2-methylpropyl propionate and then hydrogenolysis followed by resolution, provided enantioenriched **180**, which was coupled with **181**. Conversion of the acid to its sodium salt yielded Fosinopril sodium **182** in 79% over the final two steps [166].

### 3.2. Lesogaberan: Drug for the treatment of gastroesophageal reflux

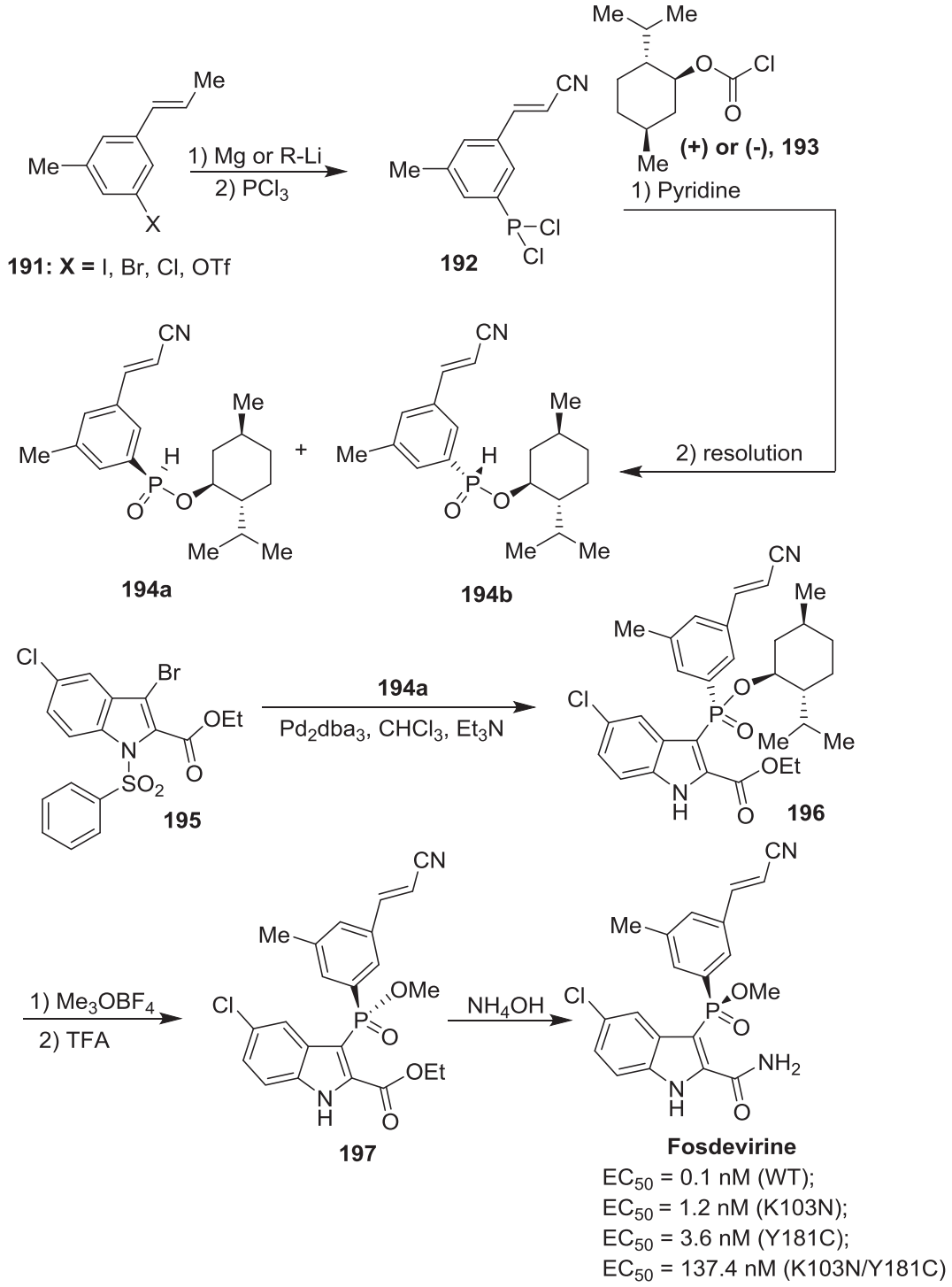
The stereoselective synthesis of Lesogaberan was accomplished through several steps beginning from the conversion of DL-serine **183** to the $\alpha$-fluoro-$\beta$-amino ester **184** [167]. After reduction of the ester group of **184** by $LiBH_4$, the Bn-protecting group was removed by hydrogenation conditions using Pd/C (10%) to give **185**. Then, upon treatment of **185** with $(Boc)_2O$ the carbamate **186** was formed. The treatment of alcohol **186** with $PPh_3$ and iodine afforded the corresponding iodo compound **187**. Subsequent conversion to the phosphinic acid was accomplished through the reaction of alkyl iodide **187** with bis(trimethylsilyl) phosphonate followed by Boc deprotection of the amino-group using ion exchange chromatography afforded Lesogaberan (Scheme 63) [168,169].

### 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 **188** with CbzCl led to **189**. Dialkyl phosphinic acid **190** was obtained through the activation of **189** by silylation with TMSCl followed by Arbuzov reaction with *n*-BuBr. Acidic hydrolysis of **190** with 36% HCl followed by treatment with propylene oxide afforded **SGS-742** (Scheme 64).

### 3.4. Fosdevirine: Drug for the treatment of HIV

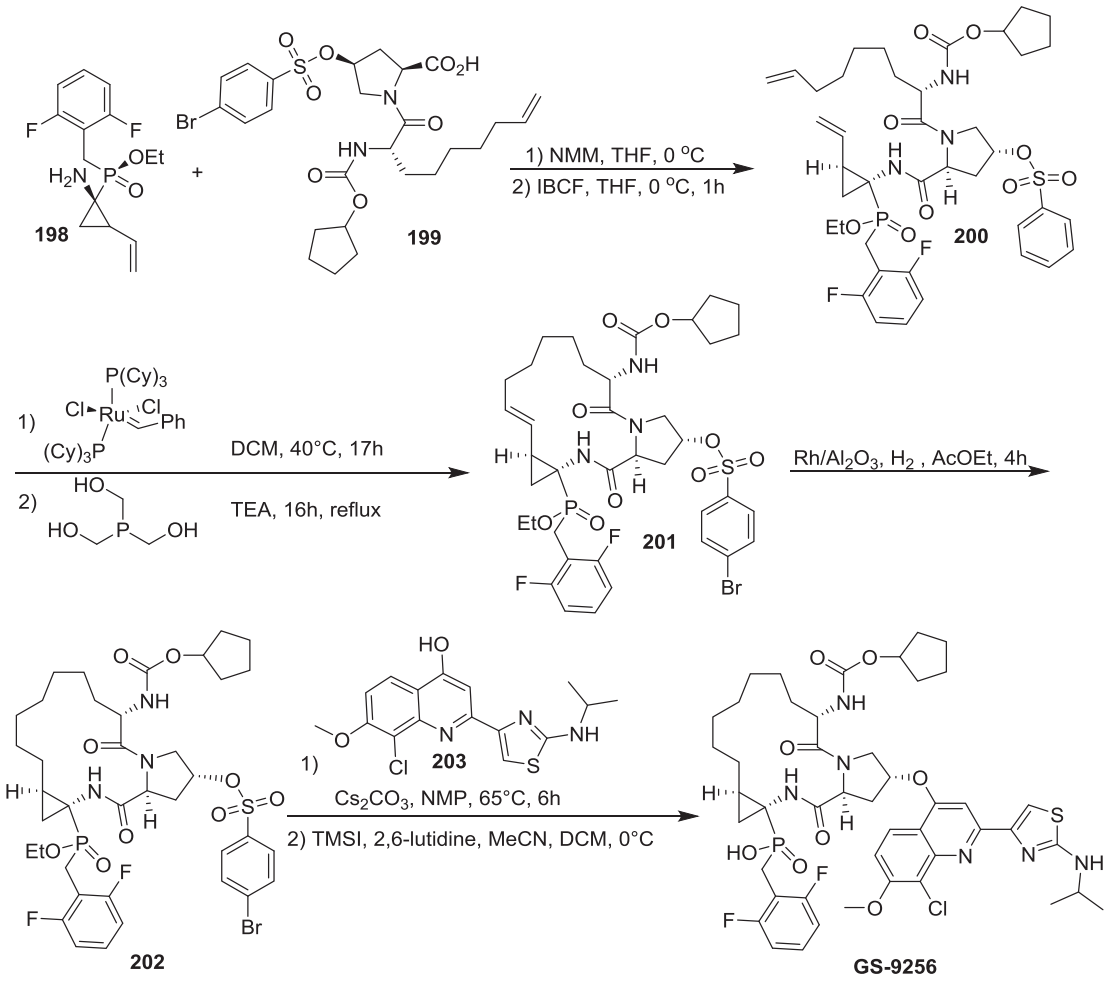
The enantioselective synthesis of Fosdevirine started with the preparation of dichlorophosphite derivative **192** *via* the treatment of aryl halides or triflates **191** with Mg or RLi and $PCl_3$. Derivatization of the **192** with (+)- or (−)-menthyl chloroformate **193** in the presence of pyridine produced two diastereoisomers, **194a** and **194b** after crystallization from *n*-hexane. Subsequently, $Pd_2(dba)_3$ catalyzed P-allylation of **194a** with **195** in the presence of triethylamine afforded **196**. Optically active P-stereogenic **196** transformed into **197** with inversion of configuration using trimethyloxonium tetrafluoroborate (Meerwein salt) followed by acidic treatment. Finally, ammonolysis of **197** afforded Fosdevirine (Scheme 65) [171].




**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**. $Rh/Al_2O_3$ 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.




**Scheme 66.**

## 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 compliment covers the most relevant and potential strategies of using phosphinic acids toward the formation of P—C bonds, PO—C bonds, and P—N bonds to be the appropriate route for the synthesis of the highly desired and functionalized phosphinic acid-based buildings 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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