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# Stereoselective Synthesis of $\alpha$ -Aminophosphonic Acids through Pudovik and Kabachnik-Fields Reaction

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Additional information is available at the end of the chapter

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## Abstract

Representative examples concerning the Pudovik and Kabachnik-Fields reactions as the main strategies for the stereoselective synthesis of  $\alpha$ -aminophosphonic acids are discussed, classifying these reactions according to the chiral auxiliary and chiral catalyst.

**Keywords:**  $\alpha$ -aminophosphonic acids,  $\alpha$ -aminophosphonates, stereoselective synthesis, Pudovik and Kabachnik-Fields

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## 1. Introduction

Optically active  $\alpha$ -aminophosphonic acids are the most important analogs of  $\alpha$ -amino acids, which are obtained by isosteric substitution of the planar and less bulky carboxylic acid ( $\text{CO}_2\text{H}$ ) by a sterically more demanding tetrahedral phosphonic acid functionality ( $\text{PO}_3\text{H}_2$ ). Several  $\alpha$ -aminophosphonic acids have been isolated from natural sources, either as free amino acids or as constituents of more complex molecules [1], such as the phosphonotriptide K-26 (**Figure 1**) [2].

The  $\alpha$ -aminophosphonic acids,  $\alpha$ -aminophosphonates, and phosphonopeptides are currently receiving significant attention in organic synthesis and medicinal chemistry as well as in agriculture, due to their biological and pharmacological properties. Additionally, the  $\alpha$ -aminophosphonic acids are used as key synthetic intermediates in the synthesis of phosphonic acids, phosphoramides, and phosphinates, which not only play an important role as protease inhibitors but also in the wide range of biochemical pathways (**Scheme 1**) [3].

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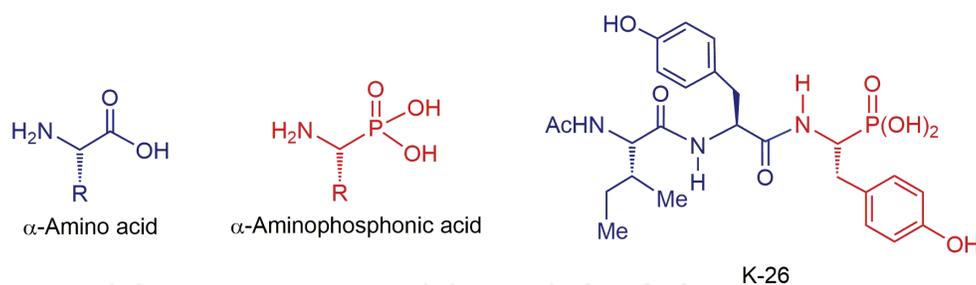
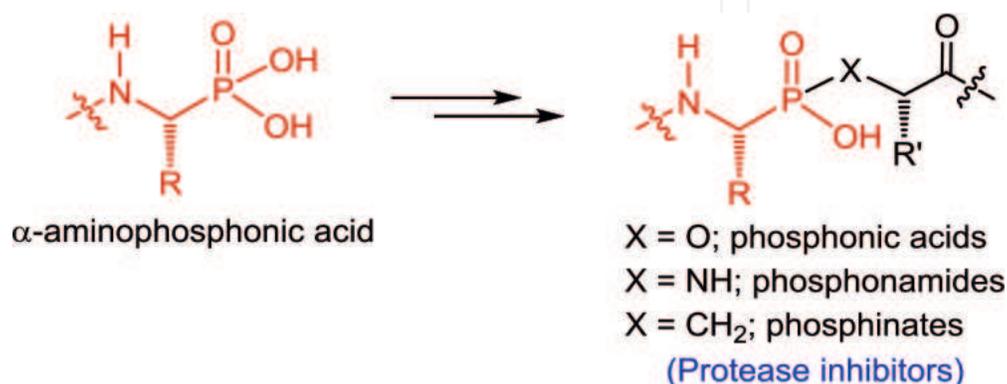


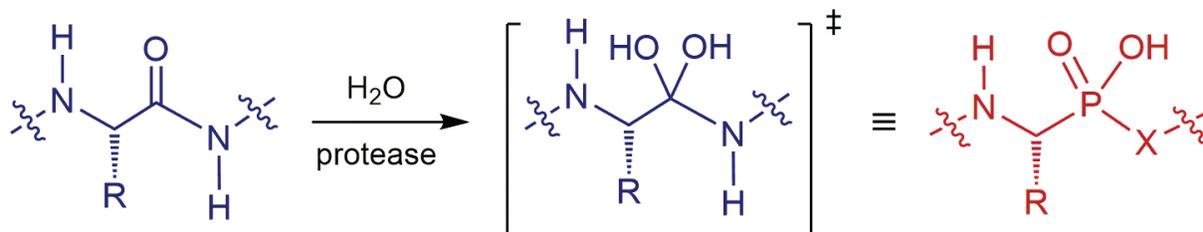
Figure 1.  $\alpha$ -Aminophosphonic acid analogs of  $\alpha$ -amino acids.



Scheme 1.

The inhibitory activity of the  $\alpha$ -aminophosphonic acids and their derivatives has been attributed to the tetrahedral geometry of the substituents around the phosphonic moiety mimicking the tetrahedral high-energy transition state of the peptide bond hydrolysis, favoring the inhibition of a broad spectrum of proteases and ligases (Scheme 2) [4].

Furthermore, it is well known that the biological activity of the  $\alpha$ -aminophosphonic acids and derivatives depends on the absolute configuration of the stereogenic  $\alpha$ -carbon to phosphorous [5]. For example, (*R*)-phospholeucine is a more potent inhibitor of leucine aminopeptidase than the (*S*)-phospholeucine [6], and (*S,R*)-alaphosphalin shows higher antibacterial activity against both Gram-positive and Gram-negative microorganisms than the other three diastereoisomers [7]. Additionally, the L-Pro-L-Leu-L-Trp<sup>P</sup> tripeptide acts as an MMP-8 enzyme inhibitor, wherein the peptide responsible for the biological activity is that in which the three amino acids have L configuration (Figure 2) [8].



Scheme 2.

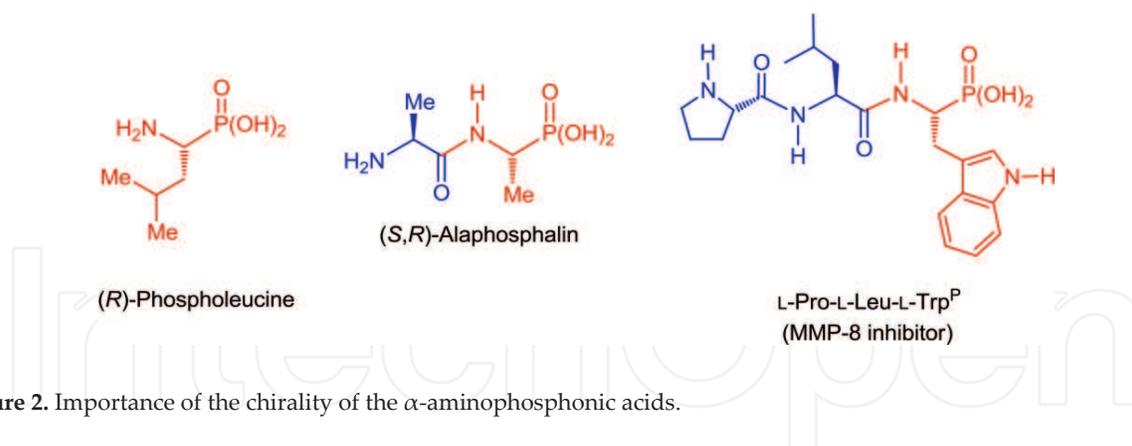
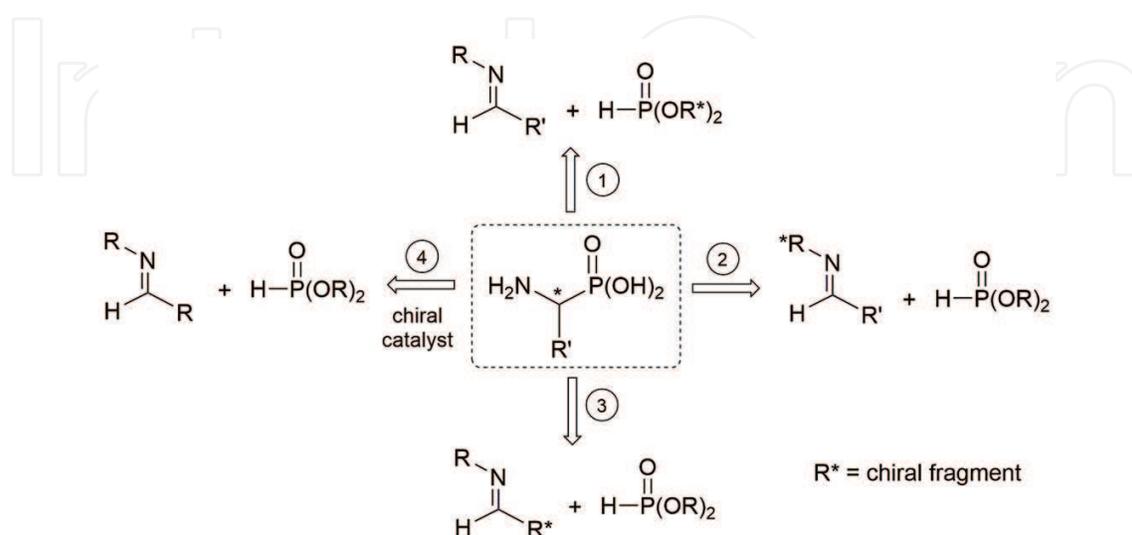


Figure 2. Importance of the chirality of the  $\alpha$ -aminophosphonic acids.

In view of the different biological and chemical applications of the  $\alpha$ -aminophosphonic acids, nowadays the development of suitable synthetic methodologies for their preparation in optically pure form is a topic of great interest and many reviews have been recently published concerning their stereoselective synthesis [9]. In this context, Pudovik and Kabachnik-Fields reactions the main synthetic strategies for the stereoselective synthesis of  $\alpha$ -aminophosphonic acids will be described in this chapter.

## 2. Stereoselective C-P bond formation (Pudovik methodology)

The diastereoselective and enantioselective hydrophosphonylation of aldimines and ketimines, called as the Pudovik reaction, involves the addition of a phosphorus nucleophile over the corresponding imine, in such a way that one or both of the reactants can incorporate a chiral auxiliary or nonchiral reagents may be reacted in the presence of a chiral catalyst (Scheme 3).



Scheme 3. Diastereo- and enantio-selective synthesis of  $\alpha$ -aminophosphonic acids by Pudovik methodology.

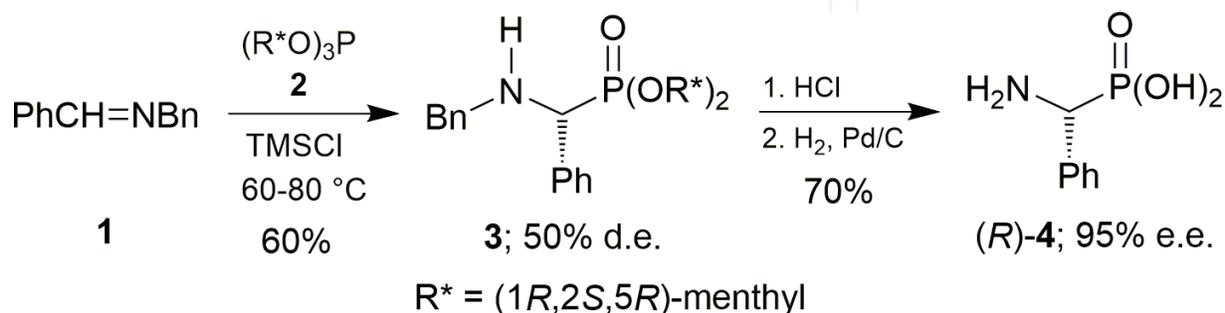
## 2.1. Chiral phosphorus compounds

One of the general methods for the synthesis of  $\alpha$ -aminophosphonic acids involves the diastereoselective hydrophosphonylation of achiral imines with chiral phosphites to introduce the phosphonate function, which by hydrolysis afforded the optically enriched  $\alpha$ -aminophosphonic acids. For example, the nucleophilic addition of chiral  $C_3$ -symmetric trialkyl phosphite **2**, obtained from the naturally occurring (1*R*,2*S*,5*R*)-(-)-menthol to the aldimine **1** in the presence of trimethylsilyl chloride (TMSCl) as an activator, provided the  $\alpha$ -aminophosphonate **3** in 60% yield and moderate induction at the  $\alpha$ -carbon atom (50% diastereoisomeric excess), which by hydrolysis with HCl in dioxane, followed by catalytic hydrogenolysis using Pd/C, produced the (*R*)-phosphophenyl glycine **4** in 70% yield and with 95% enantiomeric excess (**Scheme 4**) [10].

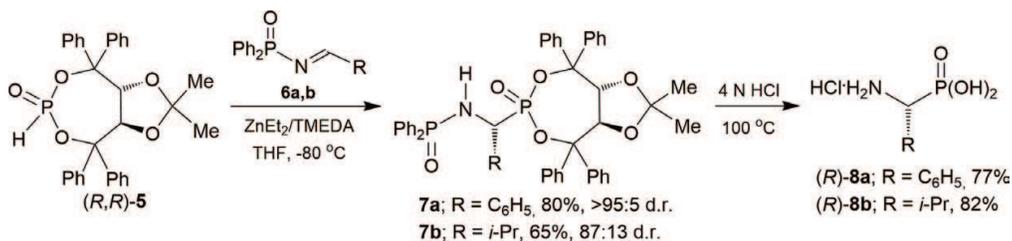
Palacios et al. [11] proposed also the chiral cyclic (*R,R*)- $\alpha,\alpha',\alpha',\alpha'$ -tetraphenyl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol (TADDOL) phosphite **5**, derived from natural tartaric acid, as a suitable phosphorus nucleophile in the stereoselective synthesis of  $\alpha$ -aminophosphonic acids. In this context, the diastereoselective hydrophosphonylation reaction of *N*-diphenylphosphinoyl aldimines **6a,b** with (*R,R*)-TADDOL-derived phosphite **5** in the presence of  $ZnEt_2$  and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at  $-80^\circ C$  afforded the  $\alpha$ -aminophosphonates **7a,b** in good yields and diastereoselectivities. Finally, the simultaneous hydrolysis of (*R,R*)-TADDOL phosphonate and diphenylphosphinoyl groups in the diastereoisomerically pure **7a,b** with 4 *N* HCl, led to the optically pure (*R*)- $\alpha$ -aminophosphonic acids hydrochlorides (*R*)-**8a,b** in 77 and 82% yield, respectively (**Scheme 5**).

Additionally, the (*R,R*)-TADDOL framework has also proved its usefulness as a chiral auxiliary in the diastereoselective addition of Grignard reagents to chiral  $\alpha$ -aminophosphonates. Thus, nucleophilic addition of chiral phosphite (*R,R*)-**5** to *N*-tosylbenzaldimine **9** in the presence of  $Et_3N$  in toluene, afforded the  $\alpha$ -aminophosphonate **10** in 93% and 77:23 diastereoisomeric ratio, which by oxidation and by treatment with trichloroisocyanuric acid (TCCA) and poly(4-vinylpyridine), gave the  $\alpha$ -ketiminophosphonate **11** in 82% yield. Addition of methylmagnesium bromide to **11**, furnished the quaternary  $\alpha$ -aminophosphonate **12** in good yield and 94:6 diastereoisomeric ratio, which by hydrolysis with 10 M HCl, produced the optically enriched (*S*)- $\alpha$ -aminophosphonic acid **13** in 80% yield (**Scheme 6**) [12].

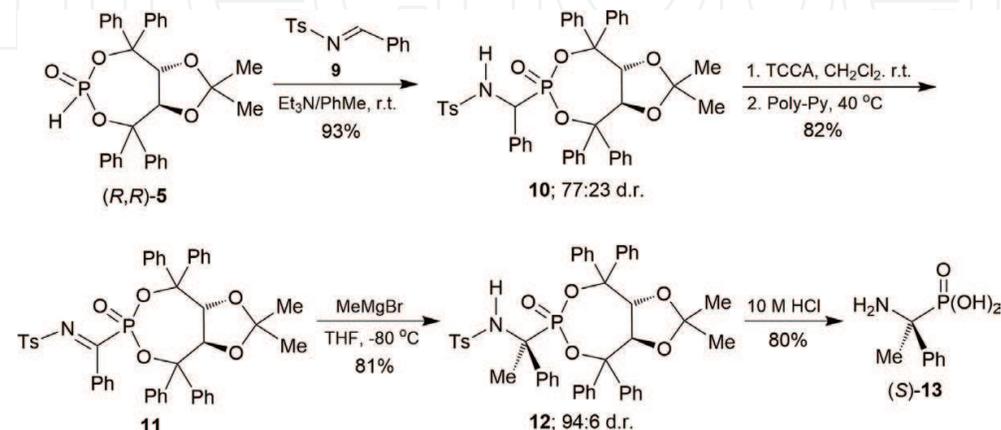
The Pudovik reaction has also been reported incorporating the chiral auxiliary attached not only to the phosphite residue, but also to the imine fragment. As a proof of concept, Olszewski and



Scheme 4.



Scheme 5.

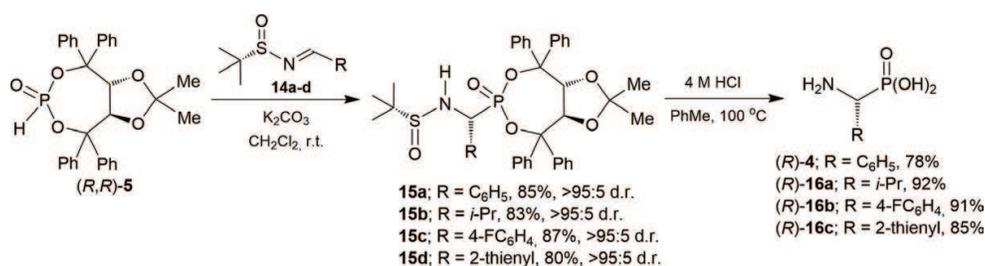


Scheme 6.

Majewski [13] reported the hydrophosphonylation reaction of (*S*)-*N*-*tert*-butylsulfinylaldimines **14a-d** with readily available chiral (*R,R*)-TADDOL phosphite **5** in the presence of potassium carbonate in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, obtaining the  $\alpha$ -aminophosphonates **15a-d** in 80–87% yield and diastereoisomeric ratio (>95:5 d.r.). Simultaneous removal of both chiral auxiliaries in **15a-d** by hydrolysis with 4 M HCl at 100°C, produced the (*R*)- $\alpha$ -aminophosphonic acids **4**, **16a-c** in 78–92% yield (Scheme 7).

## 2.2. Imines from chiral carbonyl compounds

The hydrophosphonylation of chiral Schiff bases is another general method for the synthesis of optically enriched  $\alpha$ -aminophosphonates, which can be performed by addition of alkyl phosphites to chiral imines readily obtained by condensation of chiral aldehydes with nonchiral



Scheme 7.

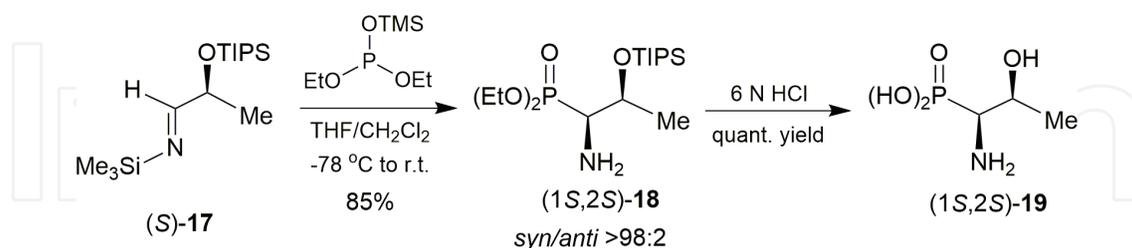
amines. In this context, Bongini et al. [14] carried out the synthesis of (*S,S*)-phosphothreonine **19** through nucleophilic addition of trimethylsilyl diethyl phosphite to the chiral imine (*S*)-**17**, obtained by condensation of (*S*)-2-triisopropylsilyloxy lactaldehyde and *N*-trimethylsilyl amine. The reaction proceeded in excellent way to give the  $\beta$ -silyloxy- $\alpha$ -aminophosphonate (*1S,2S*)-**18** in 85% yield and >98:2 *syn/anti* diastereoisomeric ratio. Cleavage of the *O*-SiMe<sub>3</sub> bond and hydrolysis of the diethyl phosphonate in (*S,S*)-**18** with 6 N HCl provided the (*1S,2S*)-phosphothreonine **19** in quantitative yield. Under identical conditions, the (*1R,2R*)-phosphothreonine **19** was obtained starting from the enantiopure aldimine (*R*)-**17** (Scheme 8).

### 2.3. Imines from chiral amino compounds

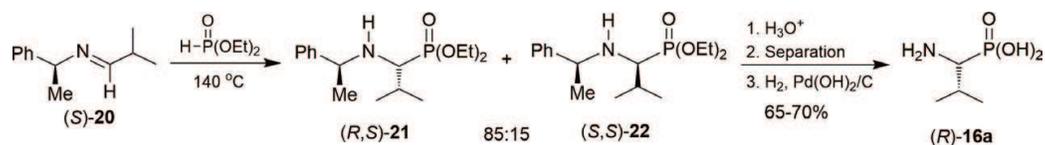
On the other hand, the stereoselective hydrophosphonylation of chiral Schiff bases can also be conducted by addition of alkyl phosphites to chiral imines readily obtained by condensation of nonchiral aldehydes with chiral amines. For example, the nucleophilic addition of dimethyl phosphite to the imine (*S*)-**20**, readily obtained from the condensation of isobutyraldehyde and (*S*)- $\alpha$ -methylbenzylamine at 140°C, under solvent-free conditions, afforded the  $\alpha$ -aminophosphonates (*R,S*)-**21** and (*S,S*)-**22** with a 85:15 diastereoisomeric ratio. Hydrolysis of the phosphonates in (*R,S*)-**21** and (*S,S*)-**22** followed by separation and hydrogenolysis using Pd(OH)<sub>2</sub>/C afforded the (*R*)-Val<sup>P</sup> **16a** in 65–70% yield. The (*S*)-Val<sup>P</sup> **16a** was obtained also from (*R*)- $\alpha$ -methylbenzylamine-derived imine (Scheme 9) [15].

On the other hand, Vovk et al. [16] carried out the addition of sodium diethyl phosphite to the imine (*S*)-**23**, obtaining the  $\alpha$ -aminophosphonate (*S,R*)-**24** in 98% yield and 95% diastereoisomeric excess. Hydrogenolysis of the chiral auxiliary in (*S,R*)-**24** and hydrolysis of the diethyl phosphonate with trimethylsilyl bromide (TMSBr) in chloroform followed by the treatment with methanol gave the enantiomerically pure (*R*)- $\alpha$ -aminophosphonic acid **25** (Scheme 10).

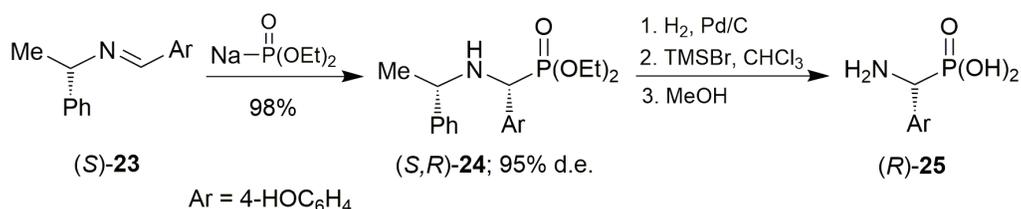
Nucleophilic addition of triethyl phosphite to the chiral base imines (*S*)-**26a-c** bearing (*S*)-1-( $\alpha$ -aminobenzyl)-2-naphthol, promoted by trifluoroacetic acid (TFA) in toluene at room



Scheme 8.



Scheme 9.

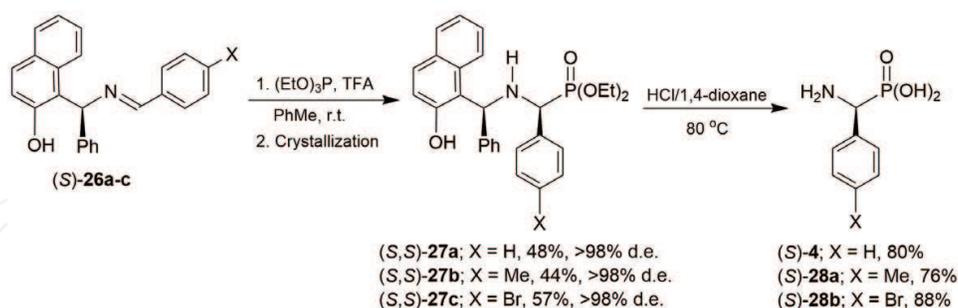


Scheme 10.

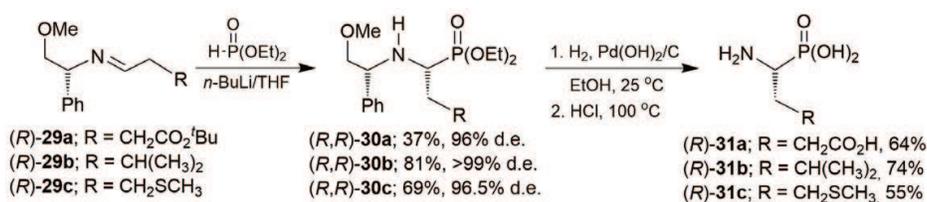
temperature and subsequent crystallization, provided the  $\alpha$ -aminophosphonates (*S,S*)-**27a-c** in 44–57% yield and with excellent diastereoisomeric excess (>98%), which by cleavage of the chiral auxiliary and hydrolysis of the diethyl phosphonate with HCl in 1,4-dioxane at 80°C, afforded the (*S*)- $\alpha$ -aminophosphonic acids **4**, **28a,b** in 76–88% yield (Scheme 11) [17]. Additionally, the (*R*)- $\alpha$ -aminophosphonic acid **4** was obtained also starting from the aldimine (*R*)-**26c**.

Smith et al. explored the generality of the diastereoselective addition of the lithium salt of diethyl phosphite to a variety of imines. Thus, addition of LiPO<sub>3</sub>Et<sub>2</sub> to aldimines (*R*)-**29a-c** bearing the methyl ether of (*R*)-phenylglycinol as chiral auxiliary, furnished the  $\alpha$ -aminophosphonates (*R,R*)-**30a-c** in 37–81% yield and 96 to >99% diastereoisomeric excess. Cleavage of the chiral fragment in (*R,R*)-**30a-c** by hydrogenolysis using Pd(OH)<sub>2</sub>/C followed by hydrolysis of the diethyl phosphonate with concentrated HCl at 100°C gave the enantiomerically pure (*R*)-Glu<sup>p</sup> **31a**, (*R*)-Leu<sup>p</sup> **31b**, and (*R*)-Met<sup>p</sup> **31c** in 55–74% yield (Scheme 12) [18].

The readily available chiral sulfinimides [19] containing an aryl- or *tert*-butylsulfinyl moiety represent valuable chiral auxiliaries in stereoselective synthesis [20]. In this regard [21], the nucleophilic addition of the lithium salt of the diethyl phosphite to the enantiopure imine



Scheme 11.



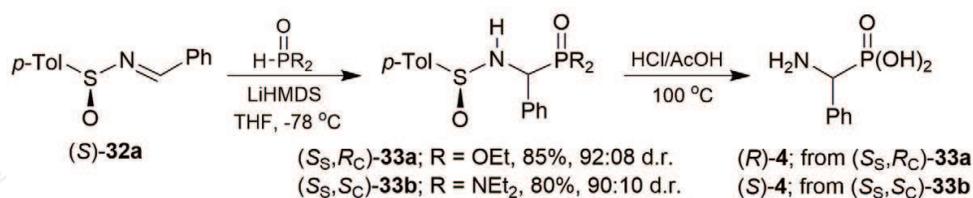
Scheme 12.

(*S*)-**32a** [22, 23], readily obtained by condensation of (*S*)-*p*-toluenesulfinamide with benzaldehyde gave the  $\alpha$ -aminophosphonate ( $S_S, R_C$ )-**33a** in 85% yield and 92:08 diastereoisomeric ratio. When the lithium salt of bis(diethylamido) phosphite was reacted with (*S*)-**32a**, the  $\alpha$ -aminophosphonate ( $S_S, S_C$ )-**33b** was obtained in good yield and diastereoselectivity [24]. Cleavage of the chiral auxiliary and hydrolysis of the diethyl phosphonate and diamidophosphite in ( $S_S, R_C$ )-**33a** and ( $S_S, S_C$ )-**33b** with hydrochloric acid in acetic acid at 100°C led to the enantiomerically pure (*R*)- and (*S*)-phosphophenyl glycine **4** (Scheme 13).

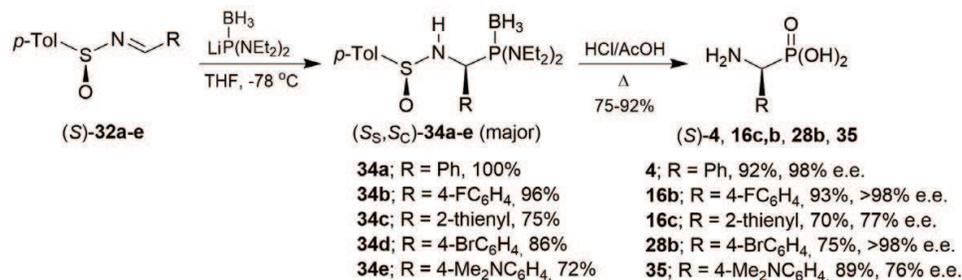
Mikolajczyk et al. [25] reported the addition of the lithium salt of the bis(diethylamido)phosphine borane complex to the *p*-toluenesulfinyl imines (*S*)-**32a-e** in THF at -78°C, obtaining mainly the ( $S_S, S_C$ )-**34a-e** diastereoisomers in 72–100% yield. Finally, cleavage of the *N*-sulfinyl auxiliary and hydrolysis of the bis(diethylamido)phosphine borane function with hydrochloric acid in acetic acid at reflux gave the (*S*)- $\alpha$ -aminophosphonic acids **4**, **16b,c**, **28b**, **35** in 75–93% yield and 76 to >98% enantiomeric excess. Under identical conditions, the (*R*)- $\alpha$ -aminophosphonic acids (*R*)-**4**, **16b,c**, **28b**, **35** were obtained from the imines (*R*)-**32a-e** (Scheme 14).

On the other hand, the addition of the lithium salt of diethyl phosphite to the enantiopure *p*-toluenesulfinyl imines (*S*)-**36a-c**, readily obtained by the  $\text{Ti}(\text{OEt})_4$  catalyzed condensation of (*S*)-*p*-toluenesulfinamide with the corresponding ketones [26], furnished the  $\alpha$ -aminophosphonates ( $S_S, R_C$ )-**37a-c** in 73–97% yield and excellent diastereoisomeric ratio (>99:1 d.r.). Cleavage of the chiral auxiliary and hydrolysis of the diethyl phosphonate in ( $S_S, R_C$ )-**37a-c** with 10 N HCl at reflux followed by the treatment with propylene oxide led to the (*R*)- $\alpha$ -aminophosphonic acids **38a-c** in 68–84% yield (Scheme 15) [23].

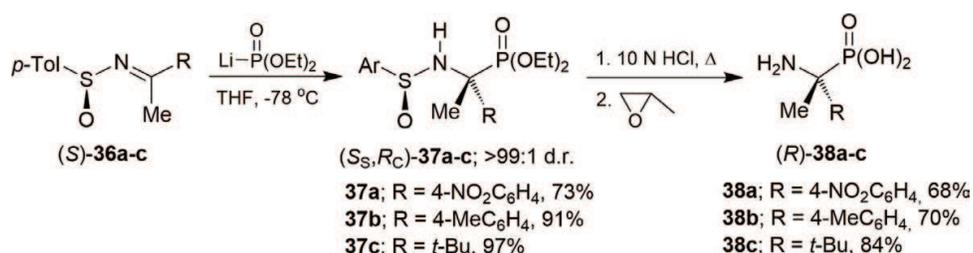
With the aim of obtaining the phosphonic analog of aspartic acid (*R*)-**42**, Mikołajczyk et al. [27] reported the nucleophilic addition of the lithium salt of diethyl phosphite to the enantiopure sulfinylaldimine (*S*)-**39** at -78°C in THF, obtaining the  $\alpha$ -aminophosphonate ( $R_C, S_S$ )-**40** in 62%



Scheme 13.



Scheme 14.

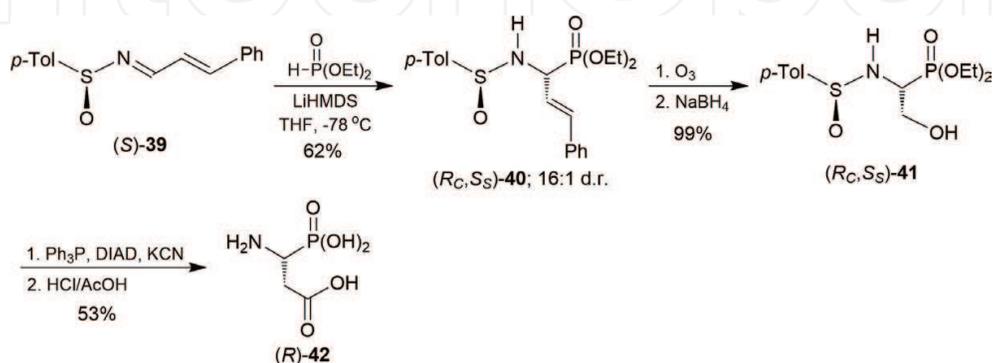


Scheme 15.

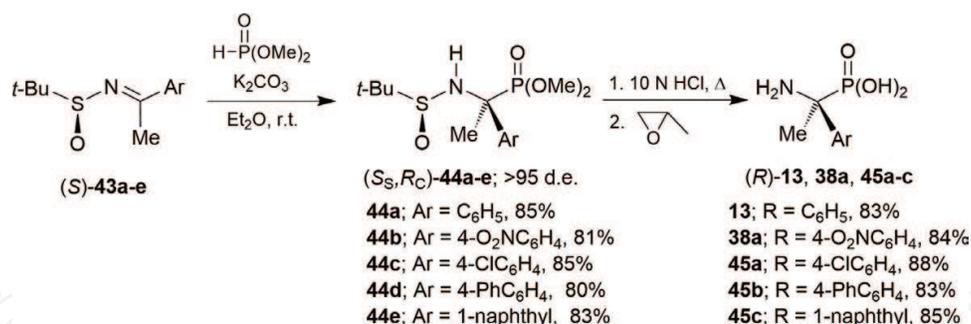
yield and 16:1 diastereoisomeric ratio. Ozonolysis of diastereoisomerically pure ( $R_C, S_S$ )-**40** followed by NaBH<sub>4</sub> reduction, provided the  $\alpha$ -aminophosphonate ( $R_C, S_S$ )-**41** in 99% yield, which under Mitsunobu reaction conditions led to the cyanide, that by hydrolysis with HCl in AcOH gave the phosphoaspartic acid ( $R$ )-**42** in 53% yield (Scheme 16).

The *N*-*tert*-butylsulfinyl group activates the imines for the nucleophilic addition, serves as a powerful chiral directing group and after the addition reaction is readily cleaved upon treatment of the product with acid. Competitive nucleophilic attack at the sulfur atom is minimized in the addition to *N*-*tert*-butylsulfinyl imines versus *N*-*p*-tolylsulfinyl imines, due to the greater steric hindrance and reduced electronegativity of the *tert*-butyl group relative to the *p*-tolyl moiety [28]. Under this context, reaction of the chiral *N*-*tert*-butylsulfinyl imines ( $S$ )-**43a-e** with dimethyl phosphite in the presence of K<sub>2</sub>CO<sub>3</sub> in Et<sub>2</sub>O at room temperature gave the  $\alpha$ -aminophosphonates ( $S_S, R_C$ )-**44a-e** in 80–85% yield and with >95% diastereoisomeric excess, which by simultaneous cleavage of the sulfinyl group and hydrolysis of the diethyl phosphonate with 10 N HCl at reflux, followed by treatment with propylene oxide, produced the ( $R$ )- $\alpha$ -aminophosphonic acids **13**, **38a**, **45a-c** in 83–88% yield (Scheme 17) [29].

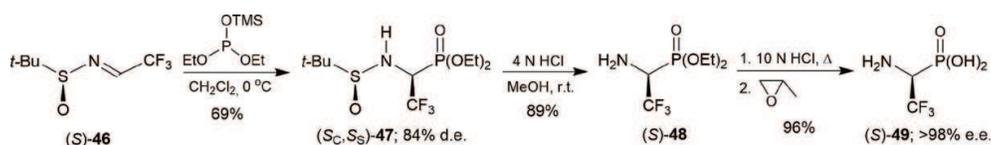
On the other hand, the addition of diethyl trimethylsilyl phosphite to chiral *N*-*tert*-butyl-sulfinyl-aldimine ( $S$ )-**46** afforded the  $\alpha$ -aminophosphonate ( $S_C, S_S$ )-**47** in 69% yield and 84% diastereoisomeric excess. Cleavage of the *N*-*tert*-butylsulfinyl group in ( $S_C, S_S$ )-**47** with 4 N HCl in methanol, produced the  $\alpha$ -aminophosphonate ( $S$ )-**48** in 89% yield. Finally, the hydrolysis of the diethyl phosphonate in ( $S$ )-**48** with 10N HCl at reflux followed by the treatment with propylene oxide gave the enantiomerically pure ( $S$ )-phosphonotrifluoroalanine **49** in 96% yield (Scheme 18) [30].



Scheme 16.



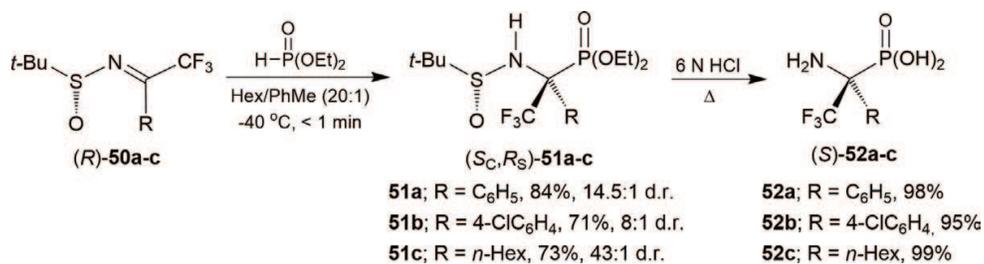
Scheme 17.



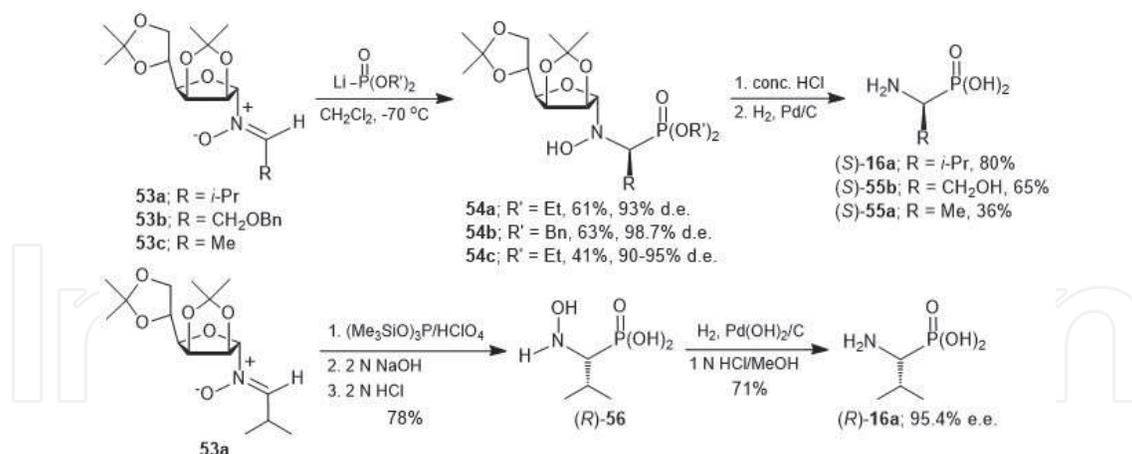
Scheme 18.

Lu et al. [31] reported the addition of diethyl phosphite to the enantiopure sulfanylketimines (*R*)-50a-c, to obtain the quaternary  $\alpha$ -aminophosphonates ( $S_C, R_S$ )-51a-c in 73–84% yield and 8:1–43:1 diastereoisomeric ratio. Cleavage of the *N*-*tert*-butylsulfanyl group and hydrolysis of the diethyl phosphonate in ( $S_C, R_S$ )-51a-c with 6 N HCl at reflux, led to the enantiomerically pure  $\alpha$ -aminophosphonic acids (*S*)-52a-c in excellent yield (Scheme 19).

On the other hand, the sugar-derived nitrones have also emerged as valuable synthetic intermediates in the stereoselective synthesis of  $\alpha$ -aminophosphonic acids. For example, the hydrophosphonylation reaction of the nitrones 53a-c with the lithium salt of diethyl or dibenzyl phosphite, provided the *N*-glycosyl- $\alpha$ -aminophosphonates 54a-c in 41–63% yield and 90–98.7% diastereoisomeric excess, which by hydrolysis of the sugar fragment and the phosphonate with concentrated HCl and subsequent cleavage of the N-OH bond by hydrogenation using Pd/C, afforded the optically enriched  $\alpha$ -aminophosphonic acids (*S*)-16a, 55a,b in 36–80% yield. Additionally, the nucleophilic addition of *tris*(trimethylsilyl) phosphite to the enantiomerically pure nitron 53c in the presence of HClO<sub>4</sub> followed by hydrolysis of the sugar fragment and the phosphonate, led to the *N*-hydroxyphosphovaline (*R*)-56 in 78%



Scheme 19.

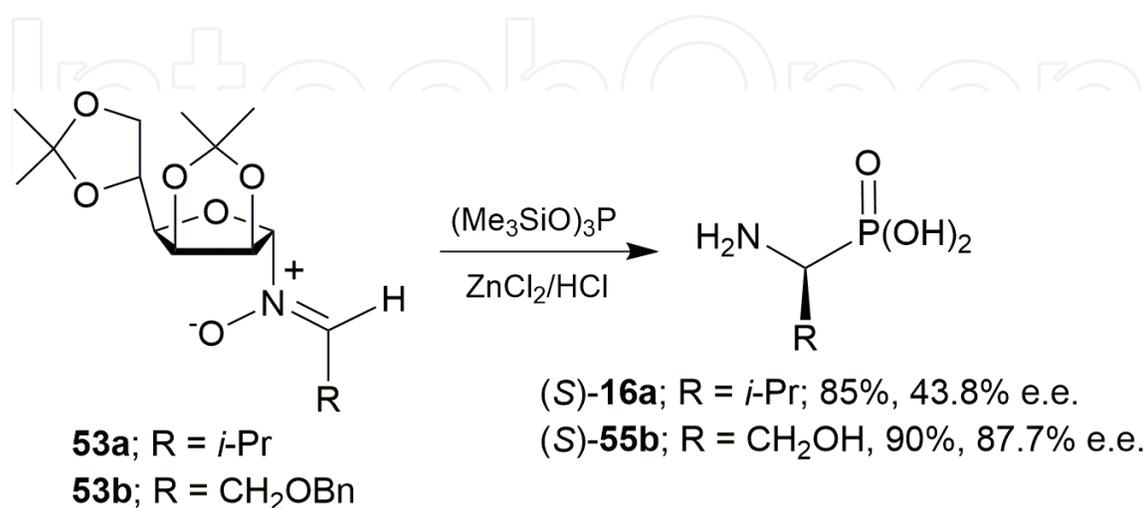


Scheme 20.

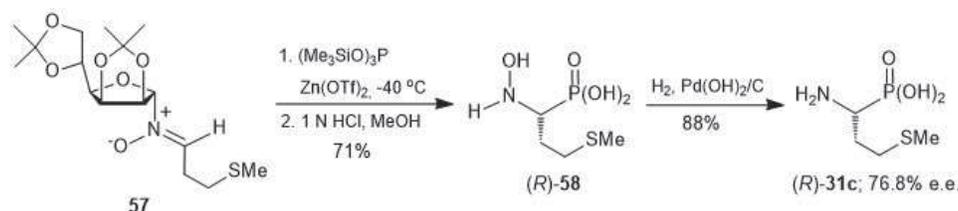
yield, which by hydrogenation of the N–OH bond and treatment with 1 N HCl, gave the (*R*)-Val<sup>P</sup> **16a** in 71% yield and 95.4% enantiomeric excess (Scheme 20) [32].

Huber and Vasella [33] reported the synthesis of optically enriched (*S*)-Val<sup>P</sup> **16a** and (*S*)-Ser<sup>P</sup> **55b** from the enantiopure nitrones **53a,b** with a slight modification of the reaction conditions. Thus, the nucleophilic addition of *tris*(trimethylsilyl) phosphite to the sugar-derived nitrones **53a,b** catalyzed by ZnCl<sub>2</sub>/HCl afforded directly the corresponding  $\alpha$ -aminophosphonic acids (*S*)-**16a**, **55b** in good yield and with 43.8 and 87.7% enantiomeric excess, respectively (Scheme 21).

Similarly, the addition of *tris*(trimethylsilyl) phosphite to the enantiopure nitrone **57** in the presence of Zn(OTf)<sub>2</sub> at –40°C and subsequent treatment with 1 N HCl in MeOH, led to the *N*-hydroxy- $\alpha$ -aminophosphonic acid (*R*)-**58** in 71% yield, which by cleavage of the N–OH bond by hydrogenation using Pd(OH)<sub>2</sub>/C, provided the (*R*)-Met<sup>P</sup> **31c** in 88% yield and 76.8% enantiomeric excess (Scheme 22) [33].



Scheme 21.



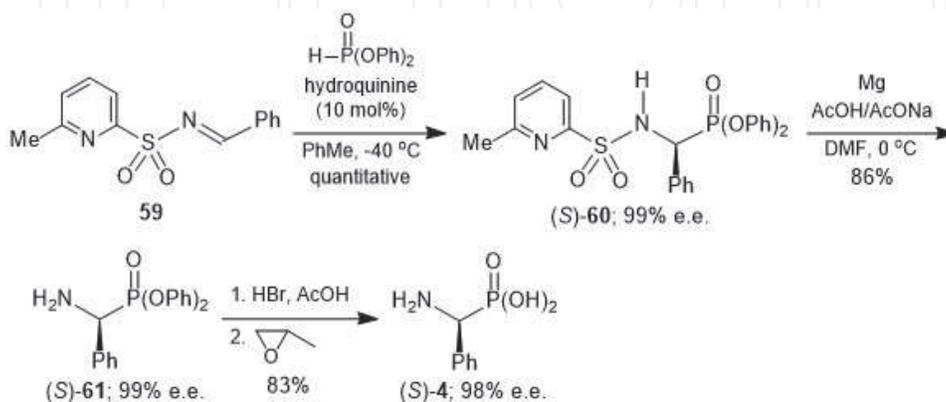
Scheme 22.

## 2.4. Chiral catalyst

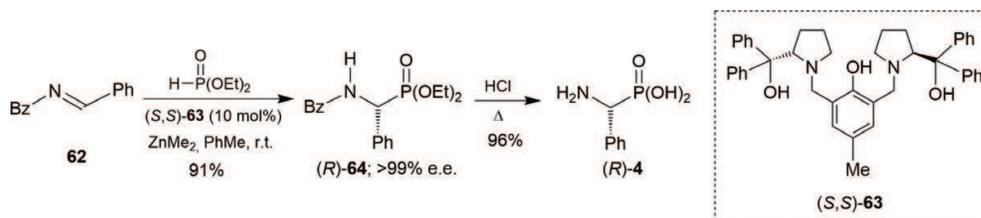
Catalytic asymmetric synthesis is one of the most important topics in modern synthetic chemistry and is considered the most efficient methodology to bring about the synthesis of enantiomerically pure compounds [34]. For example, the hydrophosphonylation reaction of *N*-sulfonylaldimine **59** with diphenyl phosphite in the presence of catalytic amounts of hydroquinine gave the (*S*)- $\alpha$ -aminophosphonate **60** in quantitative yield and excellent enantiomeric excess (>99%). Cleavage of the *N*-sulfonyl group in (*S*)-**60** by treatment with Mg in AcOH/AcONa and *N,N*-dimethylformamide (DMF) afforded the (*S*)- $\alpha$ -aminophosphonate **61** in 86% yield, which by hydrolysis of the diphenyl phosphonate with HBr in acetic acid followed by treatment with propylene oxide, produced the (*S*)-phosphophenyl glycine **4** in 83% yield and 98% enantiomeric excess (**Scheme 23**) [35].

In order to obtain the optically enriched (*R*)-phosphophenyl glycine **4**, Wang et al. [36] carried out the nucleophilic addition of diethyl phosphite to the *N*-benzoylimine **62** in the presence of catalytic amounts of (*S,S*)-**63** and ZnMe<sub>2</sub>, obtaining the (*R*)- $\alpha$ -aminophosphonate **64** in 91% yield and >99% enantiomeric excess. Simultaneous hydrolysis of the diethyl phosphonate and *N*-benzoyl group in (*R*)-**64** with concentrated HCl at reflux, produced the optically enriched (*R*)-phosphophenyl glycine **4** in 96% yield (**Scheme 24**).

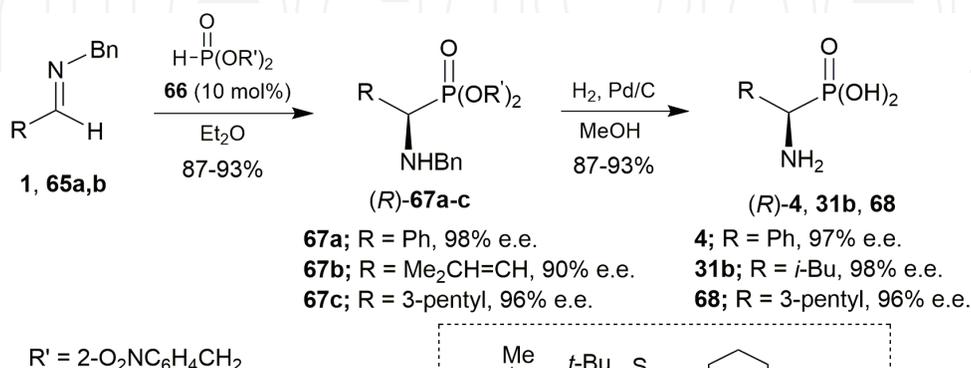
On the other hand, Joly and Jacobsen [37] reported that the addition of di(*o*-nitrobenzyl) phosphite to the achiral *N*-benzyl aldimines **1**, **65a,b** in the presence of catalytic amounts of the chiral urea **66**, produced the (*R*)- $\alpha$ -aminophosphonates **67a-c** in 87–93% yield and 90–98% enantiomeric excess. Finally, the simultaneous cleavage of the di(*o*-nitrobenzyl) phosphonate



Scheme 23.



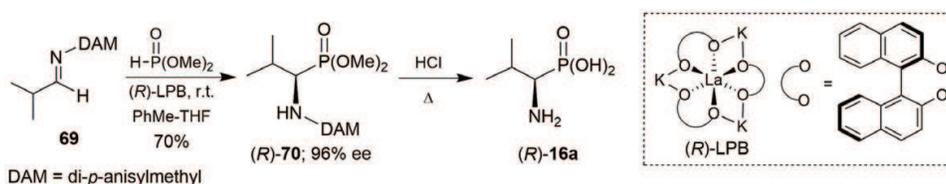
Scheme 24.



Scheme 25.

and *N*-Bn bond by hydrogenolysis in (*R*)-**67a-c** using Pd/C in MeOH afforded the enantiomerically enriched (*R*)- $\alpha$ -aminophosphonic acids **4**, **31b**, **68** in 87–96% yield and excellent enantioselectivity (**Scheme 25**).

Another exceptional example of the chiral catalyst approach is reported by Shibasaki et al. [38] who found that the catalytic hydrophosphonylation of the aldimine **69** in the presence of the lanthanoid-potassium-1,1'-bi-2-naphthol (BINOL) complex [(*R*)-LPB] afforded the (*R*)- $\alpha$ -aminophosphonate **70** in 70% yield and 96% enantiomeric excess. Cleavage of *p*-anisylmethyl fragment and simultaneous hydrolysis of the dimethyl phosphonate in (*R*)-**70** with concentrated HCl at reflux, produced the enantiomerically enriched (*R*)-Val<sup>P</sup> **16a** (**Scheme 26**).



Scheme 26.

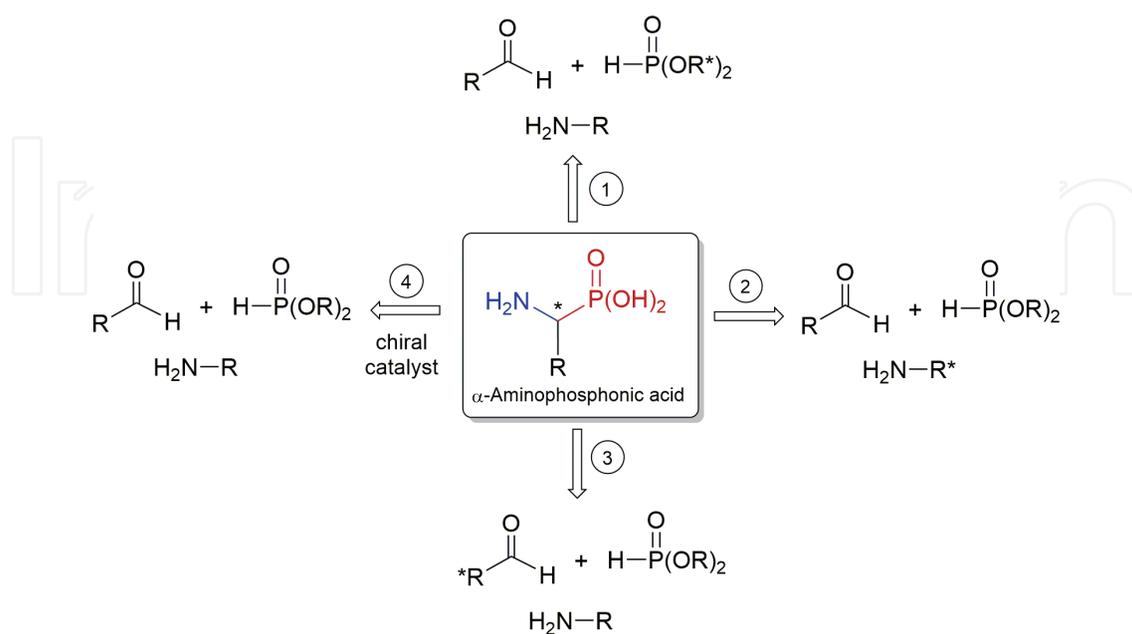
### 3. Stereoselective C-P bond formation (Kabachnik-Fields methodology)

Another important method for the stereoselective synthesis of  $\alpha$ -aminophosphonic acids is the “one-pot” three-component reaction, known as the Kabachnik-Fields reaction. In this process, the reactants (carbonyl compound, amine and the phosphorus nucleophile agent) are placed all together to give the diastereo or enantiomerically pure  $\alpha$ -aminophosphonates, which are easily transformed into the corresponding  $\alpha$ -aminophosphonic acids. To induce the stereochemistry in the  $\alpha$ -aminophosphonates, the chirality inducer may be at the source of phosphorus, in the amine, in the aldehyde or ketone, or in a chiral catalyst. Additionally, the reactions are carried out in solvent or under solvent free conditions (**Scheme 27**).

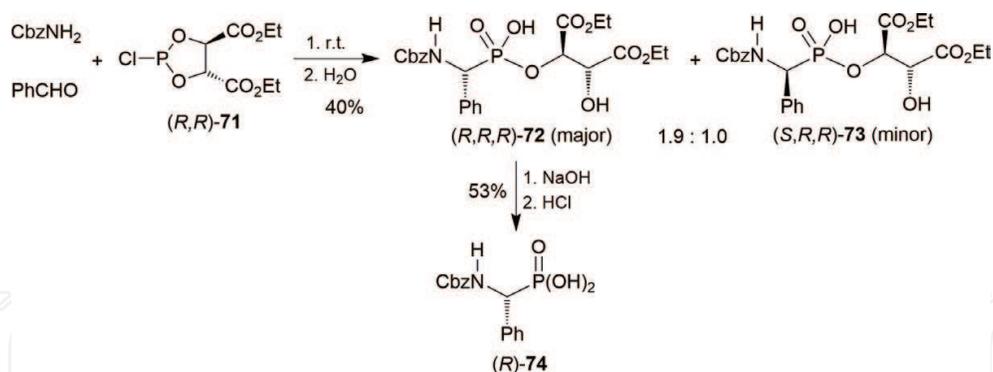
#### 3.1. Chiral phosphorus compounds

The “one-pot” three-component reaction of benzyl carbamate, benzaldehyde, and diethyl (*R,R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate **71**, readily obtained from the reaction of diethyl L-tartrate with phosphorous trichloride, followed by dioxaphospholane ring opening with H<sub>2</sub>O, led to the  $\alpha$ -aminophosphonates (*R,R,R*)-**72** and (*S,R,R*)-**73** in 40% yield and 1.9:1.0 diastereoisomeric ratio. Saponification of diastereoisomer (*R,R,R*)-**72** gave the (*R*)-*N*-Cbz-phosphophenyl glycine **74** in 53% yield (**Scheme 28**) [39].

On the other hand, Xu and Gao [40] carried out the stereoselective synthesis of the depsiphosphonopeptides **76** and **77**, as key intermediates in the synthesis of  $\alpha$ -aminophosphonic acids. Thus, the three-component reaction of (*R*)-1-carboethoxy phosphorodichloridite **75** with benzyl carbamate and benzaldehyde in benzene at room temperature and subsequent treatment with H<sub>2</sub>O, produced the depsiphosphonopeptides (*S,R*)-**76** and (*R,R*)-**77** in 86% yield and



**Scheme 27.** Diastereo and enantioselective synthesis of  $\alpha$ -aminophosphonic acids by Kabachnik-Fields methodology.



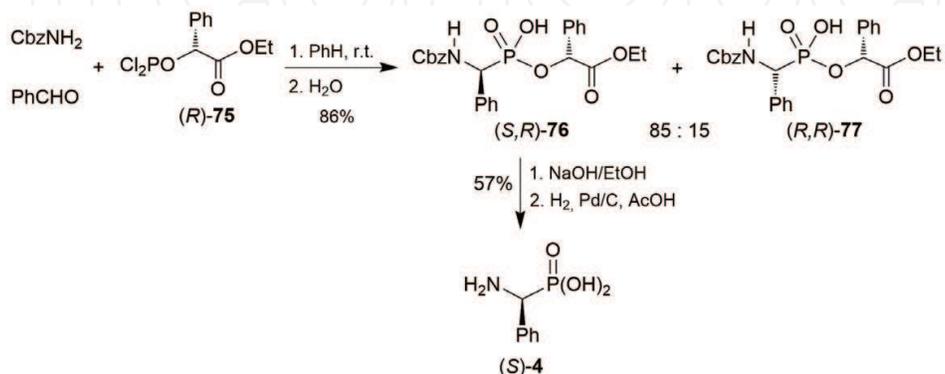
Scheme 28.

85:15 diastereoisomeric ratio. Saponification of the phosphonic ester in the diastereoisomerically pure  $(S,R)$ -76 followed by hydrogenolysis of  $N$ -Cbz bond using  $\text{Pd/C}$  in  $\text{AcOH}$  gave the enantiomerically pure  $(S)$ -phosphophenyl glycine **4** in 57% yield (Scheme 29).

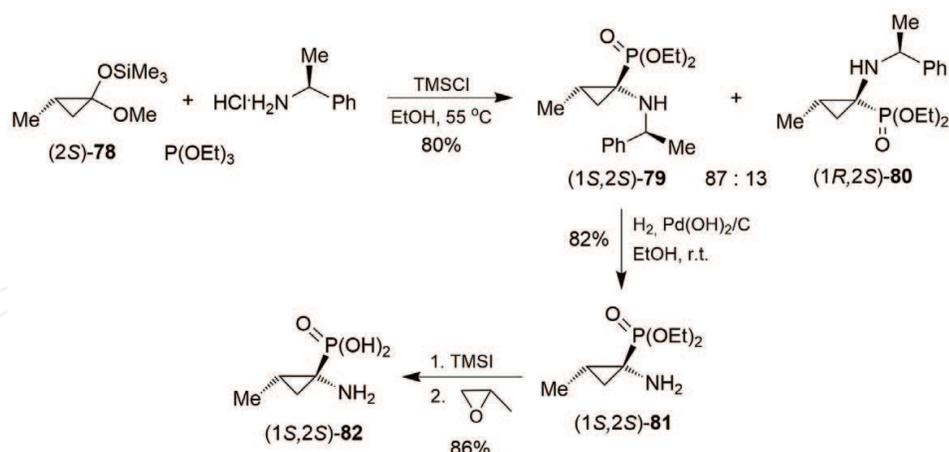
### 3.2. Chiral carbonyl compounds

In order to prepare conformationally restricted  $\alpha$ -aminophosphonic acids, Fadel et al. [41] carried out the  $\text{TMSCl}$  promoted three-component reaction of the chiral ketal  $(2S)$ -78 with  $(S)$ - $\alpha$ -methylbenzylamine hydrochloride and triethyl phosphite in  $\text{EtOH}$  at  $55^\circ\text{C}$ , obtaining the  $\alpha$ -aminophosphonates  $(1S,2S)$ -79 and  $(1R,2S)$ -80 in 80% yield and 87:13 diastereoisomeric ratio. Cleavage of the methylbenzyl fragment by hydrogenolysis in the major diastereoisomer  $(1S,2S)$ -79 using  $\text{Pd}(\text{OH})_2/\text{C}$  in  $\text{EtOH}$  at room temperature, provided the  $\alpha$ -aminophosphonate  $(1S,2S)$ -81 in 82% yield, which by hydrolysis of the diethyl phosphonate with trimethylsilyl iodide ( $\text{TMSI}$ ) followed by treatment with propylene oxide, produced the enantiomerically pure  $(1S,2S)$ -1-amino-2-methylcyclopropane phosphonic acid **82** in 86% yield (Scheme 30).

Similarly, the one-pot reaction of chiral ketal  $(2S)$ -78,  $(R)$ -phenylglycinol and triethyl phosphite catalyzed by  $\text{TMSCl}$  in ethanol at  $55^\circ\text{C}$ , led to the  $\alpha$ -aminophosphonates  $(1S,2S)$ -83 and  $(1R,2S)$ -84 in 71% yield and 89:11 diastereoisomeric ratio. Hydrogenolysis of diastereoisomerically pure  $(1S,2S)$ -83 over Pearlman's catalyst in  $\text{EtOH}$ , provided the  $\alpha$ -aminophosphonate



Scheme 29.

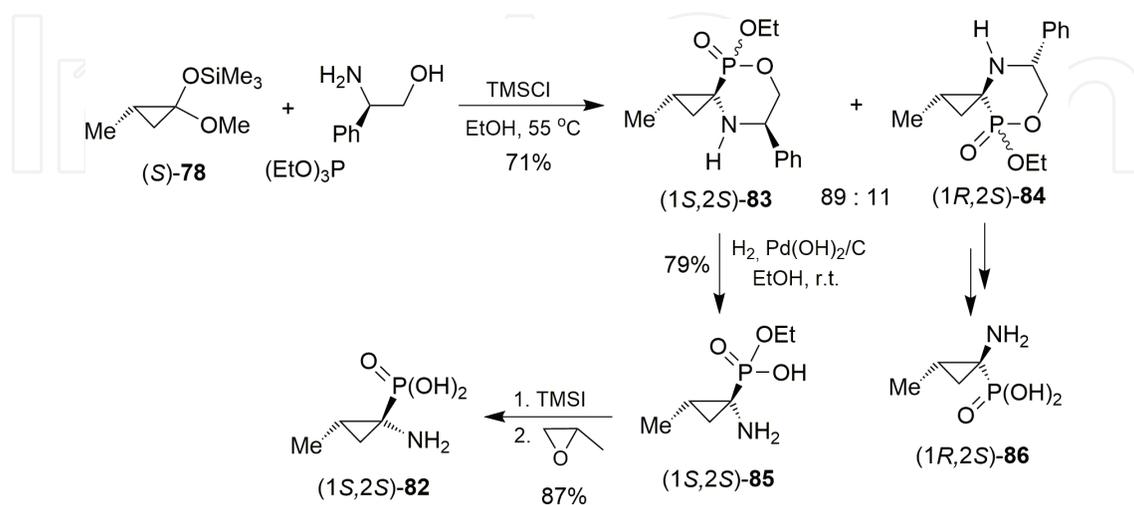


Scheme 30.

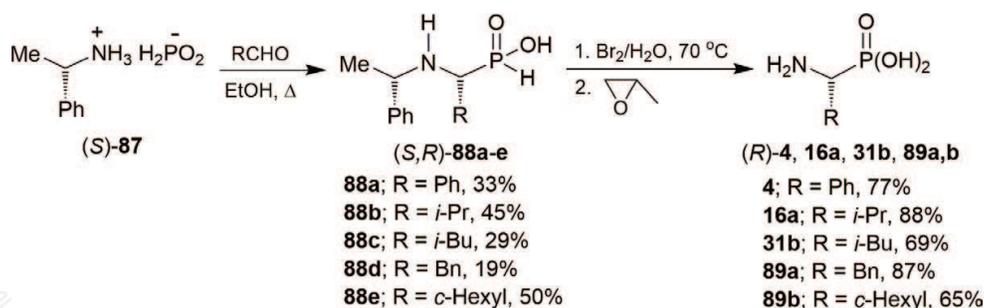
monoester (1*S*,2*S*)-85 in 79% yield. Finally, hydrolysis of (1*S*,2*S*)-85 with TMSI followed by treatment with propylene oxide afforded the enantiomerically pure  $\alpha$ -aminophosphonic acid (1*S*,2*S*)-82 in 87% yield. In a similar way, the  $\alpha$ -aminophosphonate (1*R*,2*S*)-84 was transformed into  $\alpha$ -aminophosphonic acid (1*R*,2*S*)-86 (Scheme 31) [42].

### 3.3. Chiral amino compounds

The “one-pot” three-component reaction of (*S*)- $\alpha$ -methylbenzylamine, anhydrous hypophosphorous acid and different aldehydes in EtOH at reflux, furnished the corresponding  $\alpha$ -aminophosphonous acids (*S*,*R*)-88a-e as a single diastereoisomers in 19–50% yield, which by treatment with bromine water solution at 70°C and subsequent treatment with propylene oxide, gave the enantiomerically pure (*R*)- $\alpha$ -aminophosphonic acids 4, 16a, 31b, 89a,b in 65–88% yield (Scheme 32). Using (*R*)- $\alpha$ -methylbenzylamine as starting material, the (*S*)- $\alpha$ -aminophosphonic acids 4, 16a, 31b, 89a,b were obtained in good yields [43].



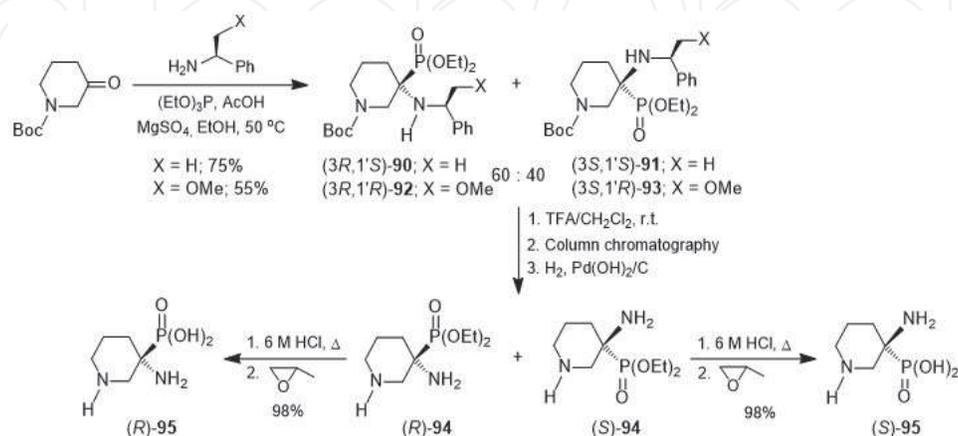
Scheme 31.



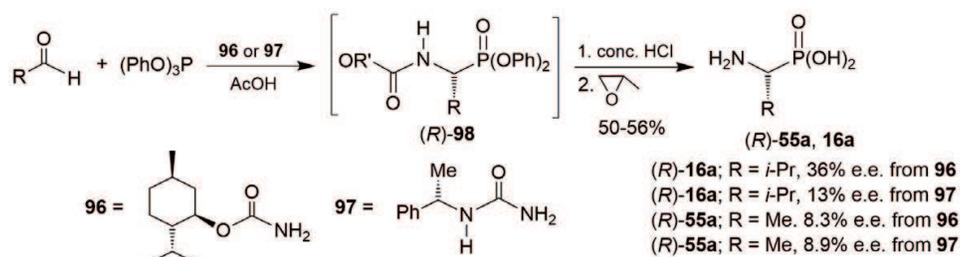
Scheme 32.

On the other hand, Fadel et al. [44] carried out the “one-pot” reaction of *N*-Boc-piperidin-3-one, (*S*)- $\alpha$ -methylbenzylamine ( $X = H$ ), triethyl phosphite and AcOH as catalyst in ethanol at 50°C, to obtain the quaternary  $\alpha$ -aminophosphonates (3*R*,1'*S*)-90 and (3*S*,1'*S*)-91 in 75% yield and 60:40 diastereoisomeric ratio. The use of (*S*)- $\alpha$ -methoxymethylbenzylamine ( $X = OMe$ ) as chiral amine in this three-component reaction afforded the  $\alpha$ -aminophosphonates (3*R*,1'*R*)-92 and (3*S*,1'*R*)-93 in 55% yield and with the same diastereoisomeric ratio (60:40). Cleavage of *N*-Boc bond with TFA at room temperature, chromatographic separation, and removal of the chiral fragment by hydrogenolysis using Pd(OH)<sub>2</sub>/C in each pure diastereoisomer, furnished the quaternary (*R*)- and (*S*)- $\alpha$ -aminophosphonates 94 in good yield. Finally, the hydrolysis of diethyl phosphonate in (*R*)- and (*S*)-94 with 6 M HCl at reflux followed by treatment with propylene oxide gave the enantiomerically pure  $\alpha$ -aminophosphonic acids (*R*)- and (*S*)-95 in 98% yield (Scheme 33).

Enantiomerically pure carbamates and urea have also shown a potential as chiral auxiliaries in the stereoselective synthesis of  $\alpha$ -aminophosphonic acids. For example, the “one-pot” reaction of carbamate 96, readily obtained from naturally occurring (–)-menthol or the urea 97 derived from (*S*)- $\alpha$ -methylbenzylamine, with acetaldehyde or propionaldehyde and triphenyl phosphite in the presence of acetic acid as catalyst, provided the  $\alpha$ -aminophosphonates (*R*)-98, which by hydrolysis with concentrated HCl followed by treatment with propylene oxide, afforded the (*R*)-Ala<sup>P</sup> 55a and (*R*)-Val<sup>P</sup> 16a in moderate yield but low enantiomeric excess (Scheme 34) [45].



Scheme 33.

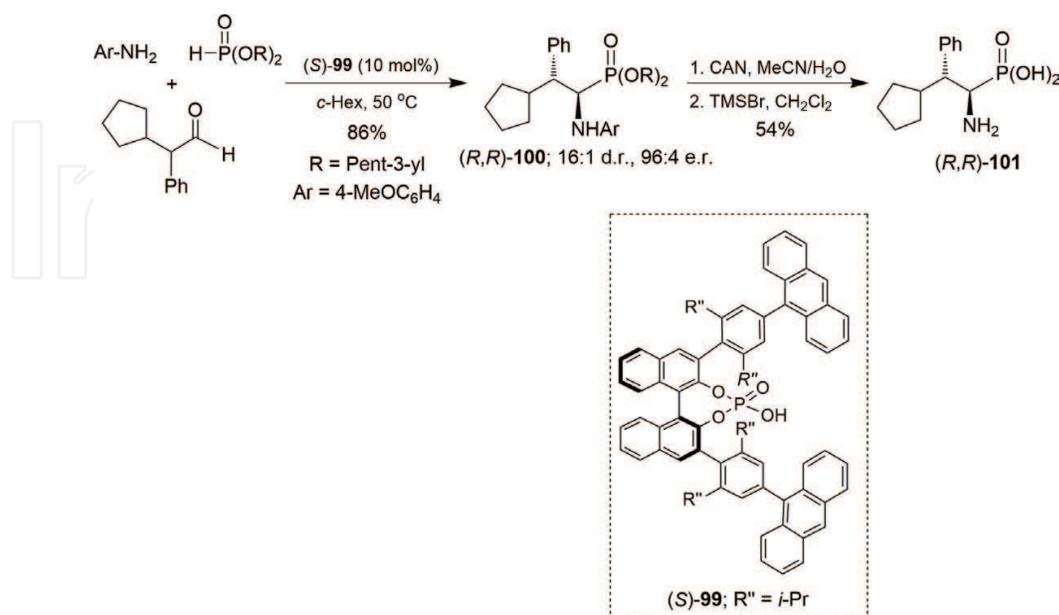


Scheme 34.

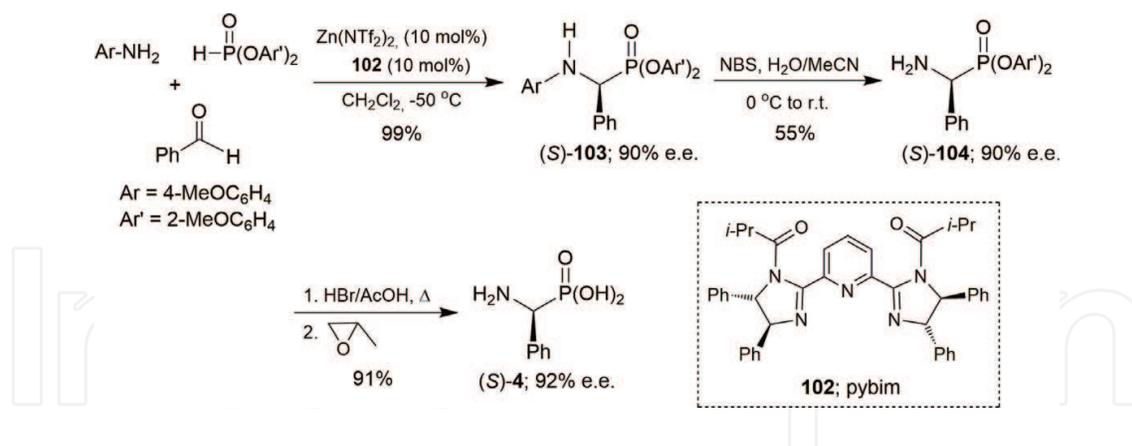
### 3.4. Chiral catalyst

The development of methodologies under chiral catalysis protocols has become one of the most relevant issues in the field of modern synthetic chemistry [46]. In this respect, List et al. [47] described the Kabachnik-Fields reaction of 2-cyclopentyl-2-phenylacetaldehyde, *p*-anisidine and di-(pent-3-yl) phosphite in the presence of catalytic amounts of the chiral phosphoric acid (*S*)-**99** in cyclohexane at 50°C, obtaining the (*R,R*)- $\alpha$ -aminophosphonate **100** in 86% yield with both high diastereoisomeric and enantiomeric ratio. Removal of *p*-methoxyphenyl fragment with cerium ammonium nitrate (CAN) followed by the hydrolysis of the diethyl phosphonate in (*R,R*)-**100** with TMSBr, produced the optically enriched (*R,R*)- $\alpha$ -aminophosphonic acid **101** in 54% yield (**Scheme 35**).

In another example, Shibata et al. [48] reported that the reaction of benzaldehyde, *p*-anisidine, and di-(*o*-methoxyphenyl) phosphite in the presence of catalytic amounts of Zn(NTf<sub>2</sub>)<sub>2</sub> and **102** as chiral ligand in CH<sub>2</sub>Cl<sub>2</sub> at -50°C gave the (*S*)- $\alpha$ -aminophosphonate **103** in 99% yield and 90% enantiomeric excess. Removal of *p*-methoxyphenyl group in (*S*)-**103** was accomplished



Scheme 35.



Scheme 36.

by treatment with *N*-bromosuccinimide (NBS), obtaining the (*S*)- $\alpha$ -aminophosphonate **104** in 55% yield without racemization, which by hydrolysis of the phosphonate with HBr/AcOH followed by treatment with propylene oxide, led to the optically enriched (*S*)-phosphophenyl glycine **4** in 91% yield and 92% enantiomeric excess (**Scheme 36**).

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