Tetrahedron 65 (2009) 17–49

Contents lists available at ScienceDirect

Tetrahedron

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

Tetrahedron report number 856

An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives

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ARTICLE INFO

Article history:
Received 18 September 2008
Available online 8 October 2008

Keywords:
α-Aminophosphonic acids
α-Aminophosphonates
Stereoselective Synthesis
Resolution
Chiral pool

Contents

Abbreviations: ABSA, 4-acetamidobenzenesulfonyl azide; Ac, acetyl; acac, acetylacetone; BINAP, 2,20-bis(diphenylphosphanyl)-1,10-binaphthyl; BINOL, 1,10-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BtH, benzotriazole; BuLi, butyl lithium; CALB, *Candida antarctica* lipase B; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; DAM, di-*p*-anisylmethyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DMTP, dimethyl thiophosphite; dr, diastereoisomeric ratio; ee, enantiomeric excess; HFIP, hexafluoroisopropyl alcohol; HIV, human immunodeficiency virus; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; LPDE, lithium perchlorate diethyl eter; KHMDS, potasium bis(trimethylsilyl)amide; MBA, methylbenzylamine; MMPs, matrix metalloproteinases; MS, molecular sieves; Ms, methanesulfonyl (mesyl); NaHMDS, sodium bis(trimethylsilyl)amide; PEAphos, phosphineaminophosphine; PKAP, porcine kidney alkaline phosphatase; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PTPases, protein tyrosine phosphatases; QN, quinidine; rt, room temperature; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDMSOTf, *tert*-butyldimethylsilyl triflate; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMSBr, trimethylsilyl; Tol, tolyl; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, *p*-toluenesulfonyl (tosyl).

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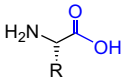
0040-4020/$ – see front matter
doi:10.1016/j.tet.2008.09.083

1. Introduction

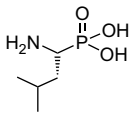
α-Aminoalkylphosphonic acids **1** are structurally analogous to α-amino acids **2**, obtained by isosteric substitution of the planar and less bulky carboxylic acid (CO_2H) by a tetrahedral phosphonic acid functionality (PO_3H_2). Several aminophosphonic, aminophosphinic, and aminophosphonous acids have been isolated from various natural sources, either as free amino acids or as constituents of more complex molecules.[1] Many natural and synthetic aminophosphonic acids, their phosphonate esters and short peptides incorporating this unit exhibit a variety of biological properties.[2] Their diverse applications include enzyme inhibitors[3] such as synthase,[4] HIV protease,[5] renin,[6] phosphatase activity,[7] PTPases,[8] and potent antibiotics,[9] as antibacterial agents,[10] antiviral,[11] antifungal,[12] herbicides,[13] and antitumor agents.[14] Their role for antibody generation is also well documented.[15] In addition, the incorporation of cyclic amino acids of medium ring size into key positions in peptide chains plays an important synthetic role, and constitutes the most prominent pathway to conformationally constrained peptidomimetics, a tool in modern drug discovery.[16]

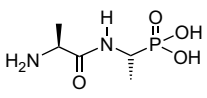

α-aminophosphonic acid, **1**


α-amino acid, **2**

In addition, α-aminophosphonic acids and their monoalkyl esters are also of interest in hydrometallurgy in order to extract metals[17] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides.[18,19]

It is well known that the biological activity of α-aminophosphonic acids and derivatives depends on the absolute configuration of the stereogenic α-carbon to phosphorous.[20] For example, (*R*)-phospholeucine **3** is a more potent inhibitor of leucine aminopeptidase than the *S* enantiomer,[21] and (*S*,*R*)-alafosfalin **4** shows higher antibacterial activity against both Gram-positive and Gram-negative microorganisms than the other three diastereoisomers.[22]


(*R*)-phospholeucine, **3**

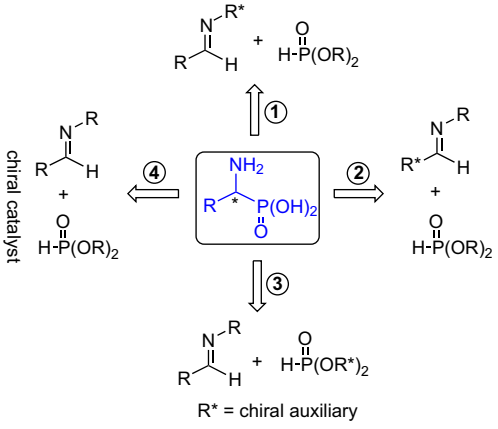

(*S*,*R*)-alafosfalin, **4**

In view of the different biological and chemical applications of the α-aminophosphonic acids and derivatives, in the last 35 years the development of suitable synthetic methodologies for their preparation in optically pure form has been a topic of great interest in several research groups. In this context, several protocols for efficient asymmetric synthesis of α-aminophosphonic acids and derivatives have emerged in recent years and several reviews have been published.[23] Now we would like to report herein an update of the stereoselective synthesis of α-aminophosphonic acids and their derivatives from 1998 to 2007. The principal synthetic strategies for α-aminophosphonic acids and their derivatives in an optically pure form can be classified into C–P bond formation using the Strecker-type process, C–C bond formation derived from diastereoselective alkylation of phosphonoglycine equivalents, C–N bond formation derived from diastereoselective electrophilic amination, catalytic hydrogenation of dehydroaminophosphonates, resolution, and chiral pool processes.

2. Stereoselective synthesis of α-aminophosphonic acids and derivatives

2.1. Stereoselective C–P bond formation

The nucleophilic addition of a dialkyl or diaryl phosphite to imines or oxoiminium derivatives, the Pudovik reaction,[24] is one of the most convenient methods for the preparation of α-aminophosphonates, key intermediates in the synthesis of α-aminophosphonic acids. In this context, the stereoselective synthesis of α-aminophosphonates can be carried out by four routes: (1) addition of alkyl phosphites to chiral imines readily obtained by condensation of aldehydes with chiral amines, (2) addition of alkyl phosphites to chiral imines readily obtained by condensation of chiral aldehydes with non-chiral amines, (3) addition of chiral alkyl phosphites to non-chiral imines, and (4) addition of non-chiral alkyl phosphites to non-chiral imines in the presence of a chiral catalyst (Scheme 1).

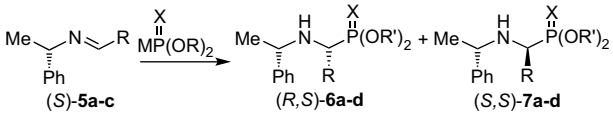


Scheme 1.

2.1.1. Addition of alkyl phosphites to imines derived from chiral amines

The first synthesis of enantiomerically pure α-aminophosphonic acids was described by Gilmore and McBride in 1972.[25] They reported that the addition of diethyl phosphite to the imine (*S*)-**5a**, readily obtained by condensation of benzaldehyde and (*S*)-α-methylbenzylamine [(*S*)-α-MBA], afforded the α-aminophosphonates (*R*,*S*)-**6a** and (*S*,*S*)-**7a** (X=O) with a 66:34

diastereoisomeric ratio.[26] A better diastereoselectivity was obtained when the addition of diethyl phosphite to the imine (*S*)-**5c** derived from cyclohexanecarboxaldehyde (R=cyclohexyl) was carried out, affording the α-aminophosphonates (*R*,*S*)-**6c** and (*S*,*S*)-**7c** (X=O) with a 83:17 diastereoisomeric ratio.[27] Recently, Vovk et al.[28] found that the reaction of the imine (*S*)-**5b** (R=4-HOC_6H_4) with an excess of sodium diethyl phosphite solution gave the α-aminophosphonates (*R*,*S*)-**6b** and (*S*,*S*)-**7b** (X=O) in 98% yield and 95% diastereoisomeric excess. On the other hand, Thompson et al.[29] reported that the addition of dimethyl thiophosphite (DMTP) to the imine (*R*)-**5a** (R=Ph) led to the α-aminophosphonothionates (*R*,*S*)-**6d** and (*S*,*S*)-**7d** (X=S) in 64% yield and 76:24 diastereoisomeric ratio (Scheme 2).



Product	R	R'	X	M	yield (%)	(*R*,*S*) : (*S*,*S*)
a	Ph	Et	O	H	[a]	66 : 34
b	4-HOC_6H_4	Et	O	Na	98	97.5 : 2.5
c	*c*-Hexyl	Et	O	H	70	83 : 17
d	Ph	Me	S	H	64	76 : 26

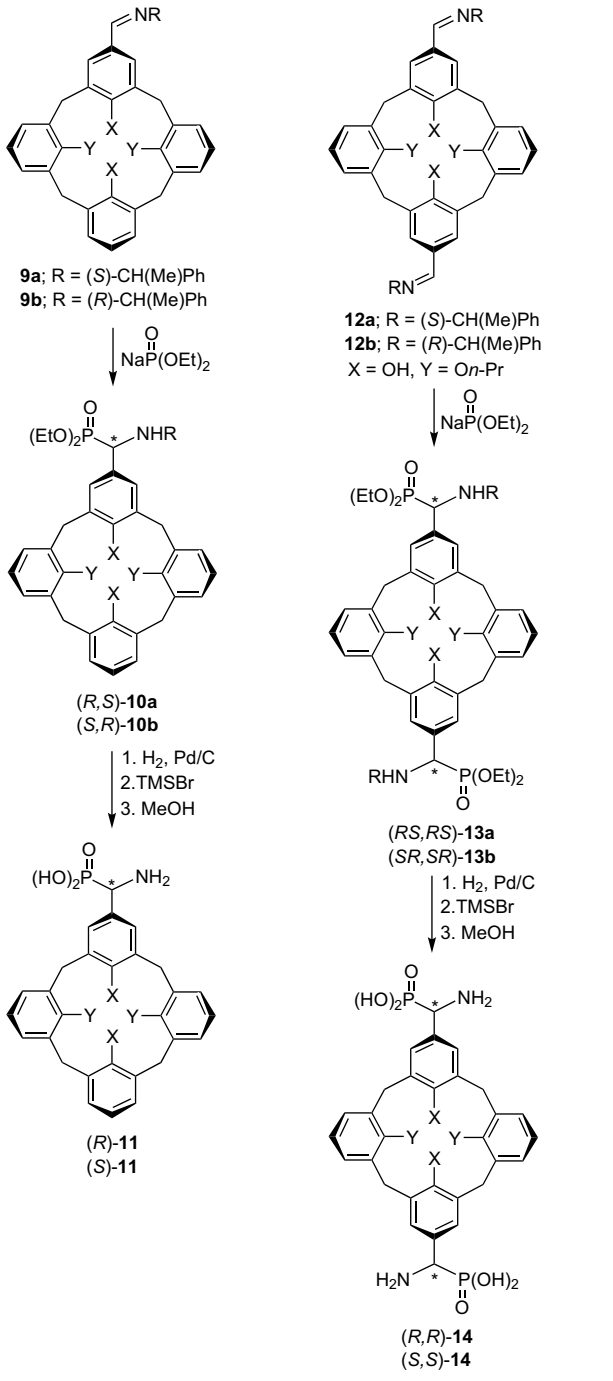
[a]Yield not reported

Scheme 2.

Hydrogenolysis of (*R*,*S*)-**6a** (R=Ph, X=O) and (*R*,*S*)-**6b** (R=4-HOC_6H_4, X=O) followed by hydrolysis with trimethylsilyl bromide (TMSBr) gave the enantiomerically pure (*R*)-α-aminophosphonic acids **8a**,**b** (Scheme 3).

Scheme 3.

This methodology has been used in the preparation of calix[4]arene α-aminophosphonic acids, which show inhibitory activity toward porcine kidney alkaline phosphatase.[28] In this context, addition of the sodium salt of diethyl phosphite to iminocalix[4]arenes **9a**,**b** and **12a**,**b**, easily obtained through the condensation of mono- or 1,3-diformylcalix[4]arenes with (*S*)- or (*R*)-α-MBA, afforded the corresponding α-aminophosphonates **10a**,**b** and **13a**,**b** in 60–80% yield and 75–85% diastereoisomeric excess. Hydrogenolysis of the chiral auxiliary in **10a**,**b** and **13a**,**b**, followed by hydrolysis of the phosphonic esters with TMSBr and methanol, gave the mono- and di-α-aminophosphonic acids **11** and **14** in quantitative yield (Scheme 4).



Scheme 4.

The inhibitory activity of α-aminophosphonic acids (*R*)-**8b** (R=4-HOC_6H_4), **11**, and **14** toward porcine kidney alkaline phosphatase (PKAP) depends considerably on the absolute configuration at the α-carbon atoms. For example, the K_i value for (*S*)-**11** is about two times smaller than that of the enantiomer (*R*)-**11**, and (*R*,*R*)-**14** binds to PKAP about 50 times stronger than the (*S*,*S*)-**14** enantiomer.

A molecular mechanics study on this type of reaction has revealed that the diastereoisomeric excess values and the induced direction are controlled by the conformation of the imine substrate.[30] In imines such as (*S*)-**5**, conformations **A** and **C** are destabilized because of allylic 1,3-strain (Fig. 1).[31] Thus, addition of alkyl phosphites to the more stable imine **B** bearing (*S*)-α-MBA takes place by the *re*-face, generating the (*R*,*S*)-**6** diastereoisomer as the major product. As a consequence, the imines bearing (*S*)-α-MBA give rise to (*R*)-α-aminophosphonic acids, whereas using (*R*)-α-MBA affords the (*S*)-α-aminophosphonic acids.

Petneházy et al.[32] found that the addition of ethyl phenylphosphinate **15** to the imines (*S*)-**5a** and (*S*)-**5d**–**f** at 70 °C in toluene afforded the α-aminophosphinates **16a** and **16d**–**f** with a predominance of two of the four diastereoisomers. Hydrolysis of **16a** and **16d**–**f** with HCl or HBr solution in glacial acetic acid gave the corresponding derivatives **17a** and **17d**–**f** which by hydrogenolysis led to the α-aminophosphinic acids **18a** and **18d**–**f** with good to excellent diastereoisomeric ratio (80:20 to 100:0) (Scheme 5).[33]

On the other hand, addition of diethyl phosphite to the imines (*R*)-**19a**, obtained in excellent yield by condensation of (*R*)-phenylglycine *tert*-butyl ester with cyclohexanecarboxaldehyde, in

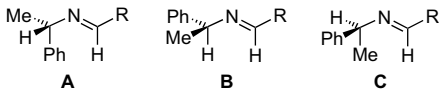
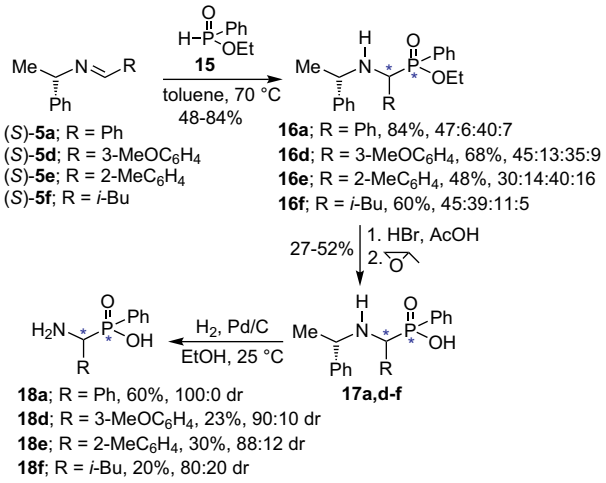


Figure 1. Conformers for the imine (*S*)-**5**.



Scheme 5.

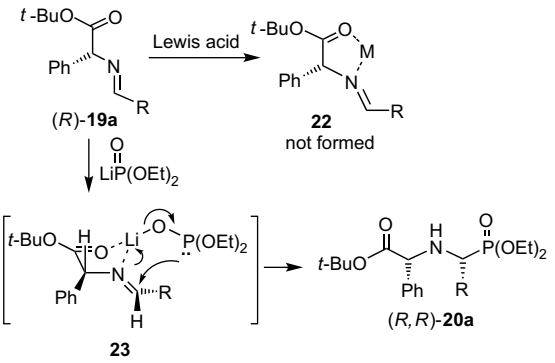


Figure 2. Transition-state for the addition of $LiP(O)(OEt)_2$ to (*R*)-**19a**.

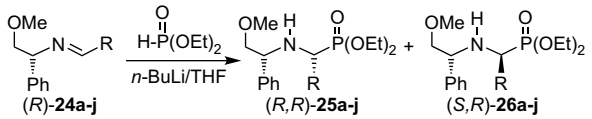
the presence of Lewis acids such as $ZnCl_2$, $MgBr_2$, and trifluoroacetic acid (TFA), afforded the corresponding α-aminophosphonates (*R*,*R*)-**20a** and (*R*,*S*)-**21a** (Table 1, entries 1–4).[34] All three catalysts led to increased rates of addition, indicative of the desired imine activation, but none afforded an increase of the diastereoselectivity. The poor diastereoselectivity obtained indicated that the chelate **22** was not formed. A lower diastereoselectivity was obtained in the addition of diethyl or dimethyl phosphite to the imines **19b**,**c** derived from (*R*)-leucine benzyl ester (Table 1, entries 5–7).[35] Similar results were obtained in the reaction of the imines (*R*)-**19e**–**h** with diethyl thiophosphite (Table 1, entries 8–11). However, the addition of the lithium salt of diethyl phosphite, prepared by treatment of diethyl phosphite with *n*-BuLi in THF at −78→25 °C, to the imine **19a** gave the α-aminophosphonates (*R*,*R*)-**20a** and (*R*,*S*)-**21a** in 80% yield and high diastereoselectivity (Table 1, entry 12).

The high diastereoselectivity has been explained as result of the coordination of the nucleophile with the corresponding imine (*R*)-**19**, generating the chelate **23**, with a trans relationship between the nucleophile and the stereodirecting phenyl group, and the addition of dialkyl phosphite on the *re*-face of the imine double bond (Fig. 2).

A most effective diastereoselectivity in favor of diastereoisomer (*R*,*R*)-**25** was obtained in the addition of lithium diethyl phosphite to the imines **24a**–**j** bearing methoxymethyl ether derived from (*R*)-phenylglycinol (Table 2, entries 1–10).[36]

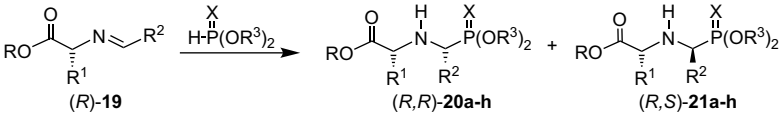
In order to explain the results obtained in Table 2, the authors suggest a chelated intermediate **27** analogous to the structure **23**

Table 2
Addition of diethyl phosphite to the imines (*R*)-**24a**–**j**



Entry	Product	R	Yield (%)	**25**/**26**
1	**a**	Ph	90	7.3:1
2	**b**	*c*-Hexyl	68	49:1
3	**c**	*c*-HexylCH$_2$	70	114:1
4	**d**	*i*-Pr	82	55:1
5	**e**	*i*-Bu	81	114:1
6	**f**	Me	77	41:1
7	**g**	*n*-Hexyl	78	49:1
8	**h**	BnOCH$_2$	36	49:1
9	**i**	MeSCH$_2$CH$_2$	69	55:1
10	**j**	*t*-BuO$_2$CCH$_2$CH$_2$	37	49:1

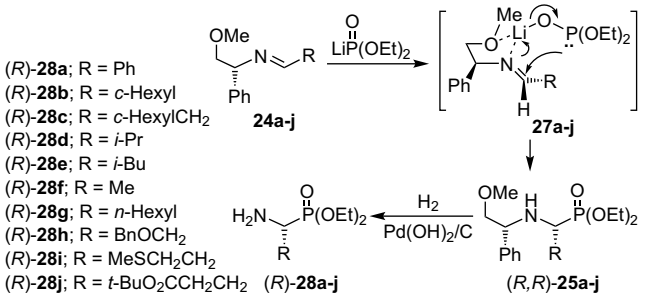
Table 1
Addition of alkyl phosphites to the imines (*R*)-**19**



Entry	Product	R	R^1	R^2	R^3	X	Conditions	Yield (%)	**20**/**21**	Ref.
1	**a**	*t*-Bu	Ph	*c*-Hexyl	Et	O	Toluene/rt	87	69:31	34
2	**a**	*t*-Bu	Ph	*c*-Hexyl	Et	O	Toluene, $ZnCl_2$/rt	84	74:26	34
3	**a**	*t*-Bu	Ph	*c*-Hexyl	Et	O	Toluene, $MgBr_2$/rt	40	69:31	34
4	**a**	*t*-Bu	Ph	*c*-Hexyl	Et	O	Toluene, TFA/rt	46	57:43	34
5	**b**	Bn	*i*-Bu	Ph	Et	O	Neat/100 °C	78	50:50	35
6	**c**	Bn	*i*-Bu	Ph	Me	O	Neat/100 °C	73	50:50	35
7	**d**	Bn	*i*-Bu	2-Furyl	Me	O	Neat/100 °C	74	50:50	35
8	**e**	Me	Me	Ph	Me	S	Toluene/rt	17[a]	47:53	29
9	**f**	Me	CH_2OH	Me	Me	S	Toluene/rt	33[a]	45:55	29
10	**g**	Me	CH_2OH	*i*-Pr	Me	S	Toluene/rt	15[a]	70:30	29
11	**h**	Me	CH_2OH	Ph	Me	S	Toluene/rt	62[a]	27:73	29
12	**a**	*t*-Bu	Ph	*c*-Hexyl	Et	O	*n*-BuLi/THF	80	98:02	34

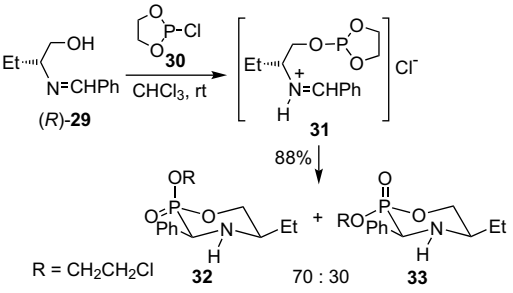
[a] The configuration of chiral auxiliary was (*S*) and the products were (*S*,*S*)-**20** and (*S*,*R*)-**21**.

(Fig. 2). Thus, the enantiofacial preference for attack on the aldimine carbon by the phosphorous atom is due to the formation of a highly organized cyclic transition-state **27** by chelation with the lithium cation, and the *anti* disposition of the phenyl and phosphite groups presumably directs the addition to the *re*-face of the imine, affording the α-aminophosphonates (*R*,*R*)-**25a–j** as the principal products,[37] which by hydrogenolysis over $Pd(OH)_2$ afforded the enantiomerically pure (*R*)-α-aminophosphonates **28a–j** (Scheme 6).



Scheme 6.

The intramolecular version of nucleophilic addition of phosphites to imines was reported by Dimukhametov et al.[38] In this context, the reaction of the chlorophosphite **30** with (*R*)-*N*-(benzylidene)-2-aminobutan-1-ol **29** gave the phosphite **31**, which, after intramolecular cyclization followed by a Michaelis–Arbuzov reaction,[39] afforded the 1,4,2-oxazaphosphinanes **32** and **33** in 88% yield and 70:30 diastereoisomeric ratio, which are precursors of chiral α-aminophosphonic acids (Scheme 7).



Scheme 7.

To explain the stereochemistry of this reaction, the authors suggest that the nucleophilic attack by the phosphite group on the electrophilic C=N group proceeds stereospecifically by the *re*-face, generating the *R* configuration at the α-C atom to phosphorous as the principal product. The attack on the *si*-face is hindered and, in this case, the ethyl group would have to adopt an unfavorable axial position in the transition-state (Fig. 3).

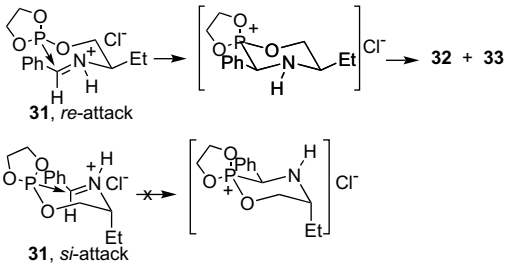
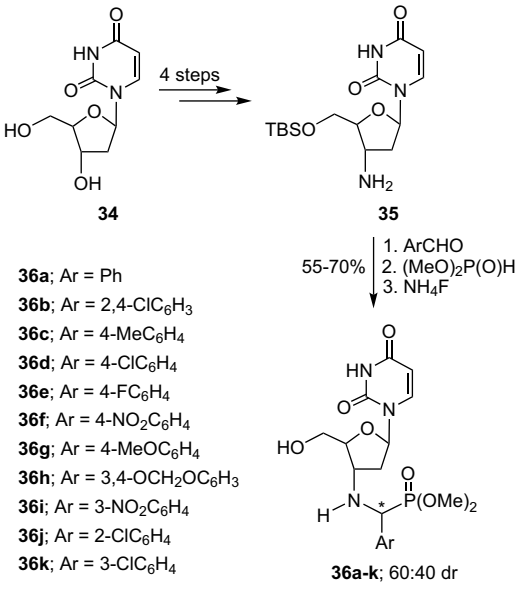


Figure 3. Intramolecular cyclization of **31**.

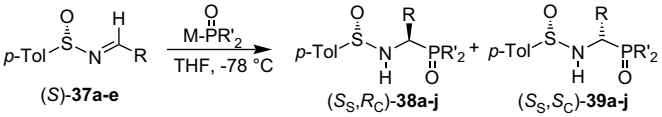
Recently, Chen et al.[40] reported the synthesis of the α-aminophosphonate derivatives **36a–k** from 2′-deoxyuridine **34**. In this context, nucleophilic addition of dimethyl phosphite to the corresponding imines obtained from condensation of the arylaldehydes with the amine **35** obtained in four steps from **34**, followed by treatment with ammonium fluoride, provided the α-aminophosphonates **36a–k** in 55–70% yield and 60:40 diastereoisomeric ratio (Scheme 8). The configurations of the three chiral carbon atoms of **35** are known, but the newly formed chiral carbon atom resulting from the addition reaction was not established.



Scheme 8.

The chiral sulfinimides readily available[41] containing an arylsufinyl moiety constitute valuable target molecules in asymmetric synthesis.[42] For example,[43] the addition of the lithium or sodium salts of alkyl phosphites to the *p*-toluenesulfinyl imines (*S*)-**37a–e**[44,45] gave the *N*-sulfinyl-α-aminophosphonates **38a–i** and **39a–i** in moderate yield and excellent diastereoselectivity, with preference of (S_S,R_C)-**38a–i** (Table 3, entries 1–12). On the other hand, the reaction of the lithium salt of bis(diethylamido) phosphite with (*S*)-**37a** afforded the α-aminophosphonates (S_S,R_C)-**38j** and (S_S,S_C)-**39j**

Table 3
Addition of the salts of alkyl phosphites to the imines (*S*)-**37a–e**



Entry	Product	R	R′	M	Yield (%)	**38**/**39**	Ref.
1	**a**	Ph	OEt	Li	85	92:08	43a
2	**a**	Ph	OEt	Na	80	96:04	43a
3	**b**	4-$MeOC_6H_4$	OEt	Li	50	92:08	43a
4	**b**	4-$MeOC_6H_4$	OEt	Na	50	95:05	43a
5	**c**	*n*-Pr	OEt	Li	78	92:08	43b
6	**d**	2-Furyl	OMe	Li	[a]	94:06	46b
7	**e**	2-Thienyl	OMe	Li	[a]	95:05	46b
8	**f**	Ph	OMe	Na	[a]	88:12	46a
9	**f**	Ph	OMe	Li	[a]	94:06	46a
10	**g**	Ph	O*i*-Pr	Li	82	74:26	46b
11	**h**	4-$MeOC_6H_4$	O*i*-Pr	Li	55	93:07	46b
12	**i**	*n*-Pr	O*i*-Pr	Na	86	99:01	43b
13	**j**	Ph	NEt_2	Li	[a]	10:90	46a

[a] Yield 75–80%.

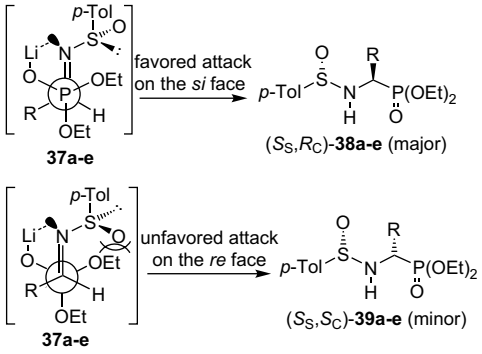
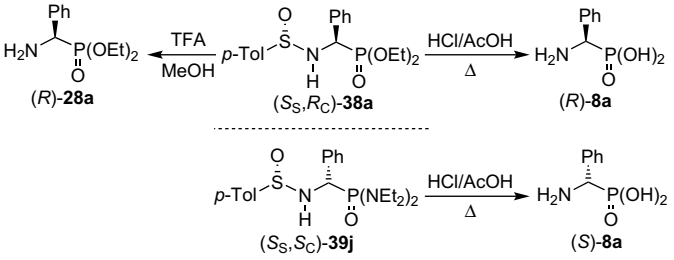


Figure 4. Addition of $LiP(O)(OEt)_2$ to the imine (*S*)-**37a**.

in good diastereoselectivity and with a preference of diastereoisomer (S_S,S_C)-**39j** (Table 3, entry 13).[46]

The high diasteroselectivity obtained in the addition of the lithium salts of alkyl phosphites to the *p*-toluenesulfinyl imines (*S*)-**37a–i** may be rationalized by assuming a coordination of lithium to the nitrogen lone pair, facilitating the delivery of the phosphorus atom to the prochiral trigonal carbon center from the face opposite to the sulfinyl oxygen atom (Fig. 4).[43] However, a model to explain the opposite configuration observed in the addition of bis(diethylamido) phosphite to the *p*-toluenesulfinyl imine (*S*)-**37a** has not yet been elucidated.[46]

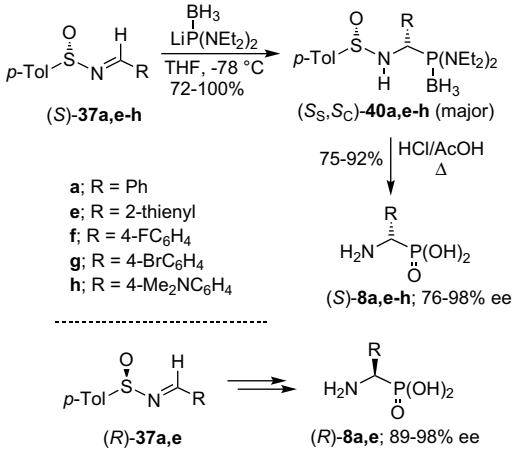
Removal of the *N*-sulfinyl auxiliary in the diastereoisomer (S_S,R_C)-**38a** (R=Ph) by acidic hydrolysis with TFA in methanol gave the enantiomerically pure α-aminophosphonic diethyl ester (*R*)-**28a** (R=Ph), whereas the hydrolysis with hydrochloric acid in acetic acid at reflux produced the enantiomerically pure (*R*)-phosphophenylglycine **8a** (R=Ph). In a similar way, hydrolysis of (S_S,S_C)-**39j** afforded the (*S*)-phosphophenylglycine **8a** (Scheme 9).



Scheme 9.

On the other hand, addition of the lithium salt of the bis(diethylamido)phosphine borane complex to the enantiopure *p*-toluenesulfinyl imines (*S*)-**37a** and (*S*)-**37e–h** in THF at −78 °C, afforded the corresponding derivatives (S_S,S_C)-**40a** and (S_S,S_C)-**40e–h** as principal diastereoisomers in high yield, which by treatment with hydrochloric acid in AcOH at reflux led to the enantiomerically pure (*S*)-α-aminophosphonic acids **8a** and **8e–h** in good yield. In a similar way, the imines (*R*)-**37a**,**e** were transformed into the (*R*)-α-aminophosphonic acids **8a**,**e** (Scheme 10).[47]

The diastereoselectivity obtained in the addition of the lithium salt of bis(diethylamido)phosphine to the *p*-toluenesulfinyl imines (*S*)-**37a** and (*S*)-**37e–h** is opposite to that observed with lithium dialkyl phosphites. These results have been explained in terms of the transition-state model **D**, in which the lithium cation is coordinated to the nitrogen lone pair, facilitating the delivery of the phosphorous atom to the prochiral trigonal carbon center from the less-hindered face occupied by the lone pair of electrons at sulfur (Fig. 5).



Scheme 10.

Recently, Gallina et al.[48] have described the preparation of *N*-arylsulfonylaminophosphonic acids (*R*)-**44a–i** using the addition of lithium dialkyl phosphites to enantiopure sulfinimines **41** as the key step. In this context, the addition of lithium dialkyl phosphites to the imine (*S*)-**41**, obtained by condensation of *iso*-butyraldehyde with (*S*)-*p*-bromobenzenesulfinamide,[49] afforded mixtures of (S_S,R_C)-**42a–c** and (S_S,S_C)-**43a–c** in good yield and diastereoselectivity (Scheme 11). Diastereoisomerically pure (S_S,R_C)-**42a–c** were transformed into (*R*)-α-aminophosphonic acids **44a–i**, which showed a selective inhibition of matrix metalloproteinases (MMPs).

Recently, Chen and Yuan[50] reported the nucleophilic addition of dialkyl phosphites to the *N-tert*-butylsulfinyl imines in order to obtain enantiomerically pure α-aminophosphonic acids. The *N-tert*-butylsulfinyl group activates the imines for the nucleophilic addition and 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.[51] Thus, the nucleophilic addition of lithium dimethyl phosphite to *N-tert*-butylsulfinyl imines (*S*)-**45a–p** in the presence of K_2CO_3 in dichloromethane or ethyl ether[52] at rt provided the phosphonates (S_S,R_C)-**46a–p** in good yield and with moderate to excellent diastereoselectivity (Table 4).

Acidic hydrolysis of diastereoisomerically pure (S_S,R_C)-**46a**, **46h**, and **46j–n** with 10 N HCl under reflux followed by treatment with propylene oxide led to the enantiomerically pure α-aminophosphonic acids (*R*)-**8a** and quaternary (*R*)-**47a–f**, analogues of α-methyl α-amino acids, which are of considerable interest because their incorporation into peptides results in an improvement in their rigidity,[53] resistance to protease enzymes, and often an enhancement of the bioactivity[54] (Scheme 12).

Davis et al.[45] reported that the addition of lithium diethyl phosphite to the enantiopure imines (*S*)-**48a–g**, readily obtained by condensation of (*S*)-*p*-toluenesulfinamide with the appropriate

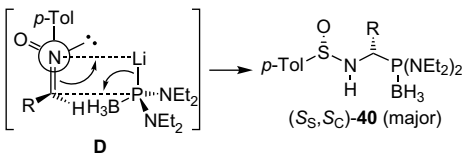
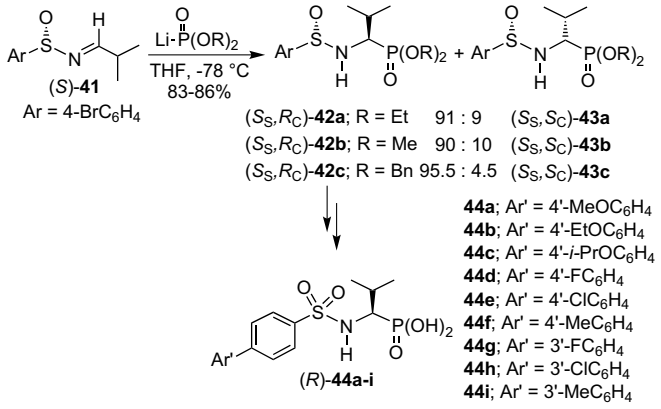
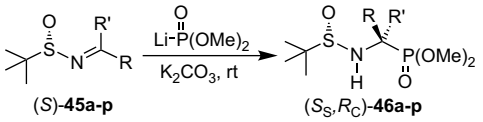


Figure 5. Transition-state for the formation of (S_S,S_C)-**40**.

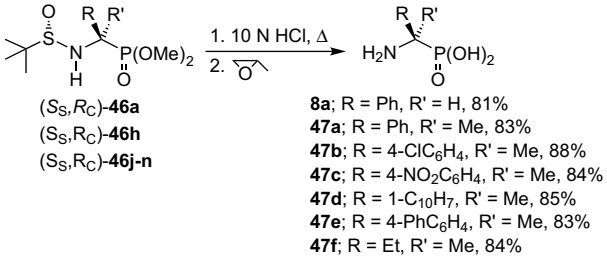


Scheme 11.

Table 4
Addition of lithium dimethyl phosphite to (*S*)-**45a–p**



Product	R	R′	Solvent	Yield (%)	de (%)
46a	Ph	H	CH_2Cl_2	81	81.8
46b	4-$MeOC_6H_4$	H	CH_2Cl_2	78	85.2
46c	4-MeC_6H_4	H	CH_2Cl_2	81	80.2
46d	4-ClC_6H_4	H	CH_2Cl_2	82	72.4
46e	Et	H	CH_2Cl_2	80	77.0
46f	*i*-Pr	H	CH_2Cl_2	79	85.1
46g	*t*-Bu	H	CH_2Cl_2	77	86.9
46h	Ph	Me	Et_2O	85	>95
46i	4-MeC_6H_4	Me	Et_2O	82	>95
46j	4-ClC_6H_4	Me	Et_2O	85	>95
46k	4-$NO_2C_6H_4$	Me	Et_2O	81	>95
46l	1-Naphthyl	Me	Et_2O	83	>95
46m	4-PhC_6H_4	Me	Et_2O	80	>95
46n	Et	Me	CH_2Cl_2	73	72.4
46o	*n*-Bu	Me	CH_2Cl_2	75	>95
46p	*t*-Bu	Me	CH_2Cl_2	73	>95

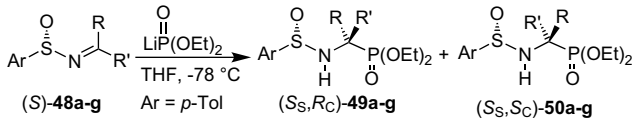


Scheme 12.

ketone in the presence of $Ti(OEt)_4$,[55] gave the α-aminophosphonates (*S*S,*R*C)-**49a–g** in good yield and excellent diastereoselectivity, except for the imine (*S*)-**48g** derived from 2-hexanone, where the α-aminophosphonates (*S*S,*R*C)-**49g** and (*S*S,*S*C)-**50g** were obtained with 82:18 dr (Table 5).[56]

The high diastereoselectivity obtained in the addition of lithium diethyl phosphite to the enantiopure *p*-toluenesulfinyl imines (*S*)-**48a–g** has been explained in terms of the transition-state model **E**, in which the lithium cation is coordinated to both sulfinyl and phosphonate oxygens in a seven-membered twisted-chair-like transition-state and assuming that the sulfinyl imine has the

Table 5
Addition of lithium diethyl phosphite to (*S*)-**48a–g**



Sulfinimine	R	R′	Yield (%)	**49**/**50**
48a	Me	4-$MeOC_6H_4$	73	>99:1
48b	Me	4-MeC_6H_4	91	>99:1
48c	Me	Ph	92	>99:1
48d	Et	Ph	93	>99:1
48e	Me	4-$NO_2C_6H_4$	93	>99:1
48f	Me	*t*-Bu	97	>99:1
48g	Me	*n*-Bu	71	82:18

favored geometry, this is a plausible rationalization for the preferential formation of (*S*S,*R*C)-**49a–g**. By contrast, the twisted-chair transition-state **F** leading to the minor products (*S*S,*S*C)-**50a–g** has the bulky aryl and *p*-tolyl groups in the energetically unfavorable axial positions (Fig. 6).

Removal of the *N*-sulfinyl auxiliary in the diastereoisomerically pure (*S*S,*R*C)-**49b**,**e**,**f** with TFA in methanol produced the enantiomerically pure α-aminophosphonates (*R*)-**51a–c**, whereas the acidic hydrolysis of (*S*S,*R*C)-**49b**,**e**,**f** with 10 N HCl at reflux followed by treatment with propylene oxide gave the enantiomerically pure (*R*)-α-aminophosphonic acids **47c**,**g**,**h** (Scheme 13).

An aza-Darzens reaction of (*S*)-**37** with the lithium anion of diethyl chloromethylphosphonate **52** in THF at −78 °C afforded the α-chloro-β-amino derivatives (*S*S,1*S*,2*R*)-**53** and (*S*S,1*R*,2*R*)-**54** in good yield (72–98%) and with a moderate to excellent diastereoisomeric ratio (54:46 to 92:8).[57] Identical results were obtained using diethyl bromomethyl-, iodomethyl- or tosylmethylphosphonate. Reaction of diastereoisomerically pure (*S*S,1*S*,2*R*)-**53** with sodium hydride gave the aziridines (*S*S,2*S*,3*R*)-**55** in 64–85% yield via S_N2 inversion α to phosphorus, which by treatment with TFA provided (2*S*,3*R*)-**56** in 70–82% yield. Catalytic hydrogenation under Pd/C, HCO_2NH_4 conditions produced the (*S*)-α-aminophosphonates **28k–p** in 67–98% yield (Scheme 14).[58,59]

On the other hand, an aza-Darzens reaction of the imine (*S*)-**37a** with the lithium anion of diethyl 1-chloroethylphosphonate **57** in THF at −78 °C afforded the α-chloro-β-amino derivative (*S*S,2*R*,3*R*)-**58** in 56% yield, and an unseparable mixture of (*S*S,2*S*,3*R*)-**59** and (*S*S,2*S*,3*S*)-**59** in 23% yield. Reaction of diastereoisomerically pure (*S*S,2*R*,3*R*)-**58** with NaH gave the aziridine (*S*S,2*R*,3*R*)-**60** in 69% yield, which by treatment with TFA led to (2*R*,3*R*)-**61** in 76% yield. Finally, catalytic hydrogenation under Pd/C, HCO_2NH_4 conditions gave the diethyl (*R*)-α-methylphosphophenylalanine diethyl ester **51d** in 92% yield. In a similar way, the mixture of **59** was converted into (*S*)-**51d** in 43% overall yield, after three steps (Scheme 15).[60]

The formation of (*S*S,2*R*,3*R*)-**58** was explained through a transition-state model **G**, in which the lithium anion derived from **57** attacks the sulfiminine (*S*)-**37a** on the *si*-face, whereas the *re*-face is sterically shielded by the sulfinyl oxygen in the six-membered transition-state (Fig. 7).

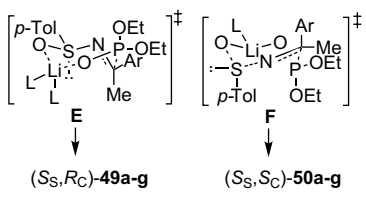
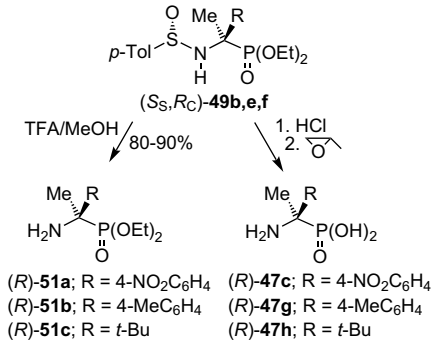
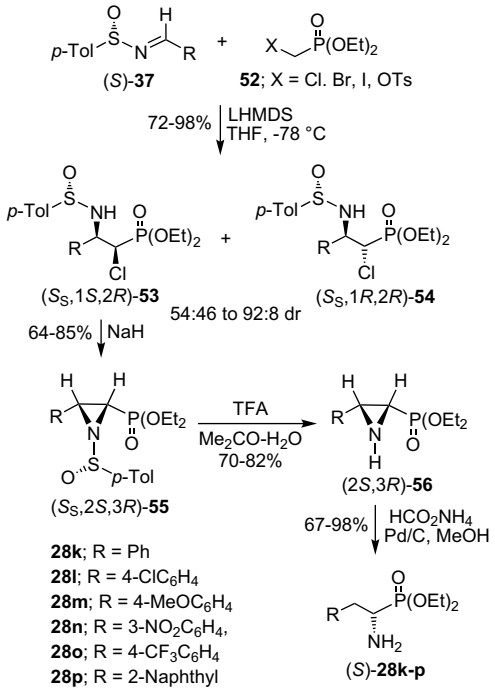


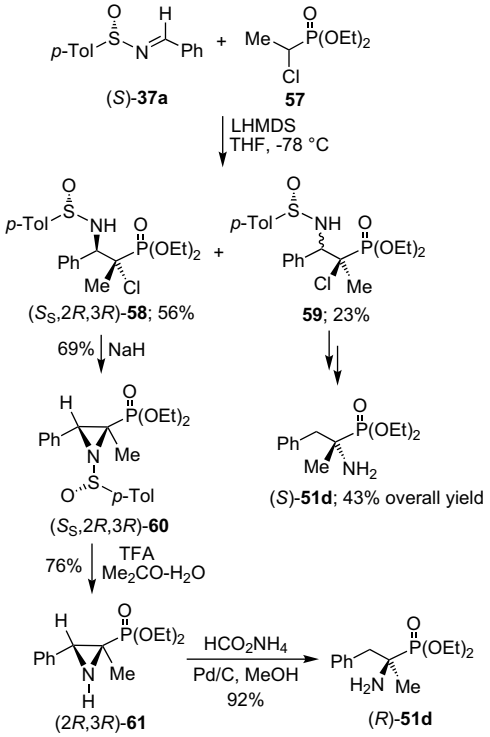
Figure 6. Rationalization for the formation of (*S*S,*R*C)-**49a–g**.



Scheme 13.



Scheme 14.



Scheme 15.

Another important methodology used in the synthesis of α-aminophosphonates is the Kabachnik–Fields reaction,[61] which is an efficient three-component reaction of aldehydes or ketones, amines, and phosphites under solvent-free conditions.[62] The first asymmetric synthesis of α-aminophosphonates via a one-pot, three-component reaction was reported by Heydari et al.[63] They carried out the reaction of dimethyl phosphite with imines derived from (*S*)-α-MBA, prepared in situ, in the presence of lithium perchlorate diethyl ether (LPDE), obtaining the α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in good yield and moderate diastereoselectivity (Table 6, entries 1–4). In a similar way, a one-pot, three-component reaction of diethyl phosphite, with arylaldehydes and (*S*)-α-MBA, in the presence of LPDE and trimethylsilyl chloride (TMSCl), gave the phosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in good yield and moderate diastereoselectivity (Table 6, entries 5–8).[64]

Nucleophilic addition of phosphites to imines catalyzed by base or acids under three-component conditions is the most convenient methodology for the synthesis of α-aminophosphonates. Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, and $MgBr_2$ have been used.[65] However, these reactions cannot be carried out in a one-pot reaction with carbonyl compounds, amine, and dialkyl phosphite, because the imines and water that exist during the imine formation can decompose or deactivate the Lewis acids.[66] This disadvantage has been overcome by a recent procedure described by Qian and Huang,[67] by using a combination of a lanthanide triflate as catalyst in the presence of 4 Å molecular sieves or magnesium sulfate in dichloromethane as the best solvent. However, although this procedure affords excellent yields for aromatic aldehydes, only low to moderate yields were obtained for aliphatic aldehydes, which is attributed to the aromatic aldehydes having a higher reactivity than aliphatic aldehydes. For example, a three-component reaction of benzaldehyde, (*S*)-α-MBA and diethyl phosphite, in the presence of a catalytic amount of ytterbium triflate (10 mol %) and anhydrous $MgSO_4$ at rt, gave the α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in excellent yield and 57:43 diastereoisomeric ratio. Similar results were obtained when *p*-methoxybenzaldehyde was used (Table 6, entries 9 and 10). The α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** were obtained with a better diastereoisomeric ratio (83:17) when the three-component reaction of benzaldehyde, (*S*)-α-MBA, and diethyl phosphite was carried out in the presence of a catalytic amount of indium(III) chloride (10 mol %) in dry THF at reflux or under sonication (Table 6, entry 11).[68] The reaction of 2-formylpyridine under identical conditions led to the α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in 90% yield and 78:22 diastereoisomeric ratio (Table 6, entry 12). This methodology afforded excellent yields for aliphatic and aromatic aldehydes, as well as open-chain, cyclic, and aromatic ketones.

A one-pot reaction of methylcyclopropanone acetal (2*S*)-**62**, obtained in two steps from commercially available methyl (*S*)-3-

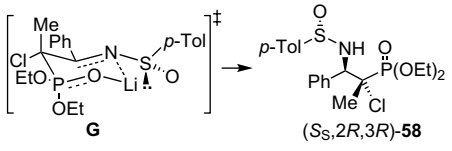
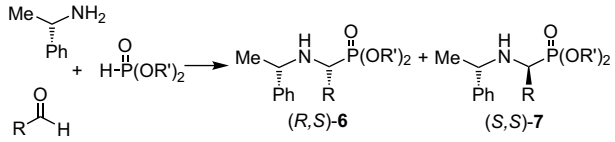


Figure 7. Proposed predominant transition-state for phosphonate addition to the sulfinimine **37a**.

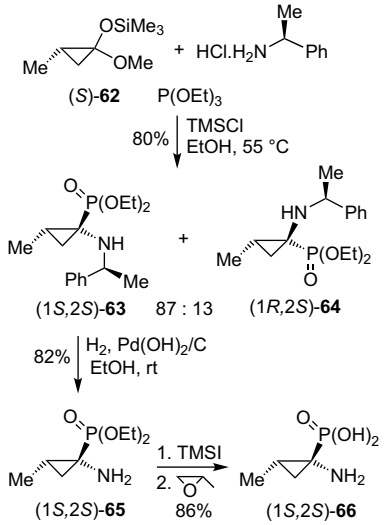
Table 6
One-pot, three-component synthesis of (*R*,*S*)-**6** and (*S*,*S*)-**7**



Entry	R	R′	Conditions	Yield (%)	**6**/**7**	Ref.
1	*i*-Pr	Me	A	95	79:21	63
2	*t*-Bu	Me	A	96	82:18	63
3	*c*-Hexyl	Me	A	92	80:20	63
4	Bn	Me	A	90	83:17	63
5	Ph	Et	B	95	75:25	64
6	4-ClC_6H_4	Et	B	97	78:22	64
7	4-$NO_2C_6H_4$	Et	B	96	80:20	64
8	PhCH=CH_2	Et	B	93	70:30	64
9	Ph	Et	C	92	57:43	67
10	4-$MeOC_6H_4$	Et	C	88	57:43	67
11	Ph	Et	D	90	83:17	68
12	2-Py	Et	D	90	78:22	68

Conditions: A. LPDE, B. LPDE/TMSCl, C. $Yb(OTf)_3/MgSO_4$, D. $InCl_3$.

hydroxy-2-methylpropionate,[69] with (*S*)-α-MBA hydrochloride and triethyl phosphite, in the presence of a catalytic amount of TMSCl in ethanol at 55 °C, afforded the α-aminophosphonates (1*S*,2*S*)-**63** and (1*R*,2*S*)-**64** in 80% yield and 87:13 diastereoisomeric ratio. The selectivity was not altered when (*R*)-α-MBA or (*S*)-1-(1-naphthyl) ethylamine was used as the chiral auxiliary. Hydrogenolysis of diastereoisomerically pure (1*S*,2*S*)-**63**, in the presence of Pearlman's catalyst, afforded the α-aminophosphonate (1*S*,2*S*)-**65** in 82% yield, which, by hydrolysis with trimethylsilyl iodide (TMSI) followed by treatment with propylene oxide, gave (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **66** in 86% yield (Scheme 16).[70]



Scheme 16.

The diastereoselectivity obtained in the nucleophilic addition of triethyl phosphite to the iminium intermediate **67** takes place from the less-hindered face (*si*-face) opposite to the methyl group on the cyclopropane with a relative *like* approach, affording (1*S*,2*S*)-**63** as the principal product (Fig. 8).

In a similar way, a one-pot reaction of methylcyclopropanone acetal (2*S*)-**62** with (*R*)-phenylglycinol and triethyl phosphite in the presence of a catalytic amount of TMSCl in ethanol at 55 °C afforded the spirophosphonates **68** and **69** in good yield, and with the trans

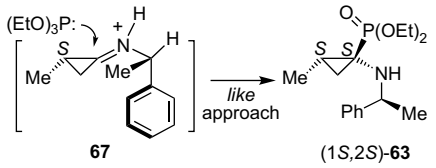
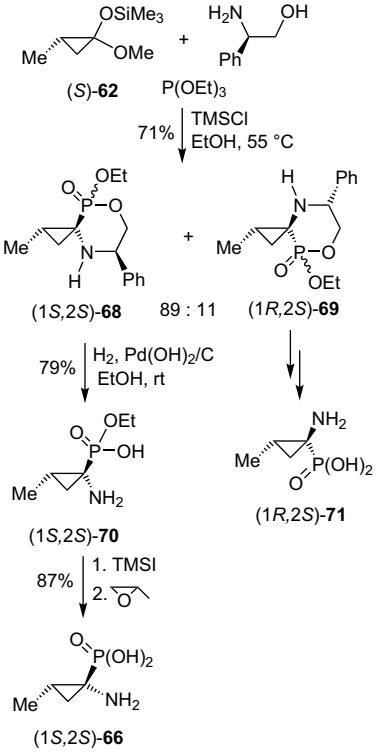


Figure 8. Transition-state proposed for addition of $(EtO)_3P$ to **67**.

isomer as the major product (ratio 89:11). Reaction of (2*S*)-**62** with (−)-norephedrine and triethyl phosphite under the same conditions gave the spirophosphonates in low yield and diastereoisomeric ratio. Hydrogenolysis of diastereoisomerically pure **68**, in the presence of a catalytic amount of Pearlman's catalyst, afforded the cyclic α-aminophosphonate **70** in 79% yield, which, by hydrolysis with TMSI followed by treatment with propylene oxide, gave the cyclic α-aminophosphonic acid (1*S*,2*S*)-**66** in 87% yield. Under identical conditions, **69** was transformed into (1*R*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **71** (Scheme 17).[71]

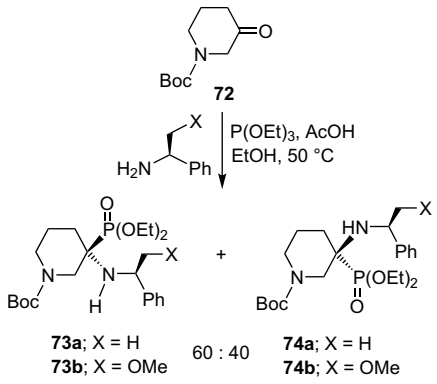


Scheme 17.

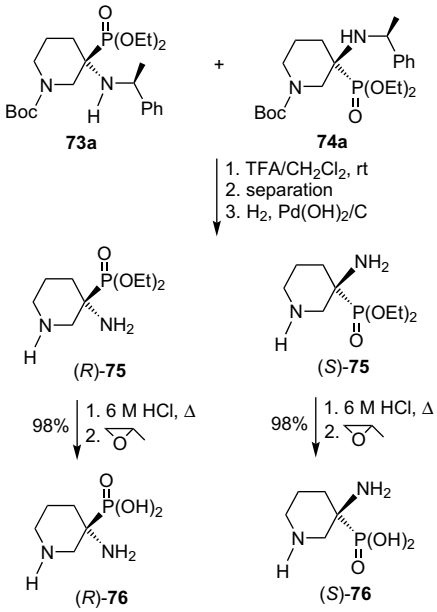
Recently, Fadel et al.[72] described that the three-component reaction of *N*-Boc-3-piperidinone **72**, (*S*)-α-MBA (X=H), and triethyl phosphite, in the presence of AcOH and anhydrous $MgSO_4$ at 50 °C, gave the α-aminophosphonates (*R*,*S*)-**73a** and (*S*,*S*)-**74a** in 75% yield and 60:40 dr. Similar results were obtained when (*S*)-α-methoxymethylbenzylamine (X=OMe) was used, providing the α-aminophosphonates (*R*,*S*)-**73b** and (*S*,*S*)-**74b** (Scheme 18).

Cleavage of the *N*-Boc protecting group in **73a**/**74a** with TFA at rt, followed by chromatographic separation and hydrogenolysis over $Pd(OH)_2$ of each diastereoisomer, gave the phosphonates (*R*)-**75** and (*S*)-**75** in good yield, which, by hydrolysis with aqueous HCl solution followed by treatment with propylene oxide, provided the enantiomerically pure α,β-diaminophosphonic acids (*R*)-**76** and (*S*)-**76** in quantitative yield (Scheme 19).[73]

On the other hand, a three-component reaction of several aliphatic aldehydes with (*R*)-phenylglycinol and dimethyl



Scheme 18.



Scheme 19.

phosphite, in the presence of 5 M LPDE, afforded the α-aminophosphonates (*R*,*R*)-**25** and (*S*,*R*)-**26** in excellent yield and good diastereoselectivity, the diastereoisomer (*R*,*R*)-**25** predominating (Table 7, entries 1–3).[63] In a similar way, reaction of aromatic aldehydes, the methoxymethyl ether of (*S*)-phenylglycinol or (*S*)-1-methoxy-3-methyl-2-butylamine and diethyl phosphite, in the presence of a catalytic amount of ytterbium triflate (10 mol %) and

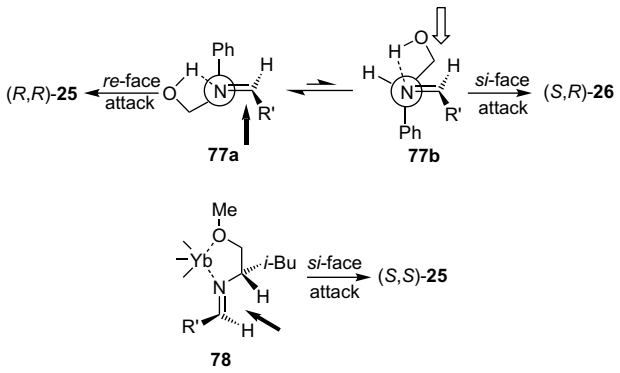
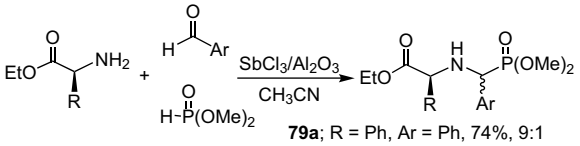


Figure 9. Transition-state in the formation of **25** and **26**.

anhydrous $MgSO_4$ at rt, gave the α-aminophosphonates (*S*,*S*)-**25** and (*R*,*S*)-**26** in good yield and moderate diastereoselectivity in favor of diastereoisomer (*S*,*S*)-**25** (Table 7, entries 4–7).[67]

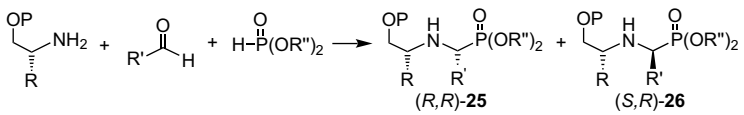
The high diasteroselectivity obtained using (*R*)-phenylglycinol has been explained on the basis of the aza analogue of the Anh–Eisenstein hypothesis,[74] where the nucleophilic attack on the imine **77** should take place antiperiplanar to the phenyl group to give the diastereoisomer (*R*,*R*)-**25** as the principal product.[63] For the addition of diethyl phosphite to the imines derived from the methoxymethyl ether of (*S*)-phenylglycinol or (*S*)-1-methoxy-3-methyl-2-butylamine in the presence of a catalytic amount of ytterbium triflate, the authors suggest the model **78** transition-state in which the $Yb(OTf)_3$ is chelated by the nitrogen and the methoxy group, and the nucleophilic attack on the imine should take place antiperiplanar to the α-*i*-Bu group (Fig. 9).[67]

Very recently, Kapoor et al.[75] have reported the synthesis of α-aminophosphonates **79a**–**e** from (*S*)-phenylglycine and (*S*)-phenylalanine. In this context, the reaction of arylaldehydes with amino acid esters and dimethyl phosphite, in the presence of antimony trichloride adsorbed on alumina as an efficient and recyclable catalyst, gave the mixtures of α-aminophosphonates **79a**–**e** in moderate yield and diastereoisomeric ratio (Scheme 20).



Scheme 20.

Table 7
One-pot, three-component synthesis of α-aminophosphonates (*R*,*S*)-**25** and (*S*,*S*)-**26**

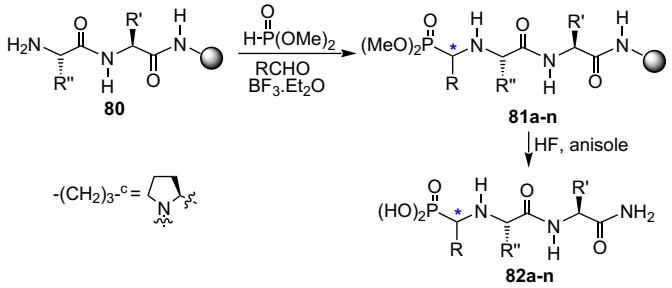


Entry	P	R	R′	R″	Conditions	Yield (%)	**25**/**26**	Ref.
1	H	Ph	*i*-Pr	Me	2.0 M, LPDE, −15 °C	90	88:12	63
2	H	Ph	*t*-Bu	Me	2.0 M, LPDE, −15 °C	95	91:09	63
3	H	Ph	*c*-Hexyl	Me	2.0 M, LPDE, −15 °C	94	90:10	63
4	Me	Ph	Ph	Et	$Yb(OTf)_3/MgSO_4$	95	78:22	67[a]
5	Me	Ph	4-$MeOC_6H_4$	Et	$Yb(OTf)_3/MgSO_4$	91	78:22	67[a]
6	Me	*i*-Bu	Ph	Et	$Yb(OTf)_3/MgSO_4$	82	74:26	67[a]
7	Me	*i*-Bu	4-$MeOC_6H_4$	Et	$Yb(OTf)_3/MgSO_4$	81	74:26	67[a]

[a] The configuration of chiral auxiliary was (*S*) and the principal product was the diastereoisomer (*S*,*S*)-**25**.

Houghten et al.[76] have reported the preparation of α-aminophosphonates bearing peptides under a three-component reaction. Thus, the reaction of aldehyde, resin-bound peptides **80**, and dimethyl phosphite, in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ (10 mol %), gave the α-aminophosphonates **81a–n**, which, by hydrolysis with HF and anisole, gave the α-aminoalkyl phosphonopeptides **82a–n**. The results are shown in Table 8.

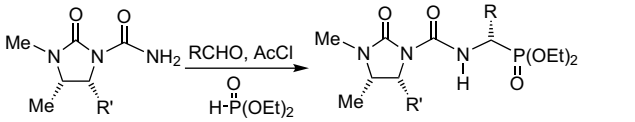
Table 8
One-pot preparation of **82a–n**



Product	R	R′	R″	Yield (%)	Ratio
82a	Ph	Bn	Bn	85	80:20
82b	Ph	Bn	HO_2CCH_2	79	40:60
82c	Ph	Bn	$-(CH_2)_3-$	82	90:10
82d	Ph	Bn	Me	83	34:66
82e	Pr	Bn	Me	88	20:80
82f	Pr	Bn	HO_2CCH_2	86	nd[a]
82g	Pr	Bn	Bn	92	nd[a]
82h	Bu	Bn	*i*-Pr	80	40:60
82i	Bu	Me	Bn	71	nd[a]
82j	Ph	Me	Bn	53	nd[a]
82k	Pr	Me	Bn	65	nd[a]
82l	Bu	H	Bn	88	63:37
82m	*i*-PrC_6H_4	Bn	$-(CH_2)_3-$	75	20:80
82n	*i*-PrC_6H_4	Bn	Me	70	44:56

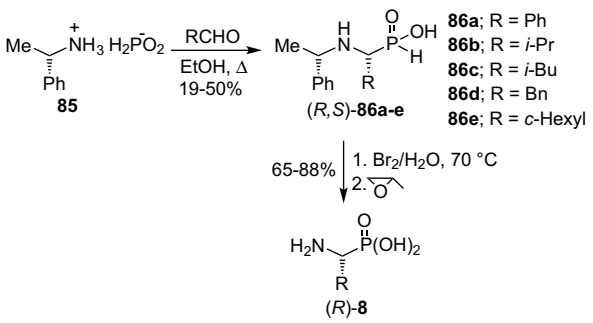
[a] Stereochemistry not determined (nd).

A three-component reaction of chiral amides **83a**,**b** with aldehydes and diethyl phosphite, in the presence of acetyl chloride at 0 °C, afforded the α-aminophosphonates **84a–d** in moderate yield and excellent diastereoselectivity,[77] which is consistent with a front-side attack of the phosphorous nucleophile on the *s-cis*/*E* conformation of the *N*-acylimine intermediate (Scheme 21). Hydrolysis of **84a** gave the (*S*)-phosphophenylglycine **8**.[78]



Scheme 21.

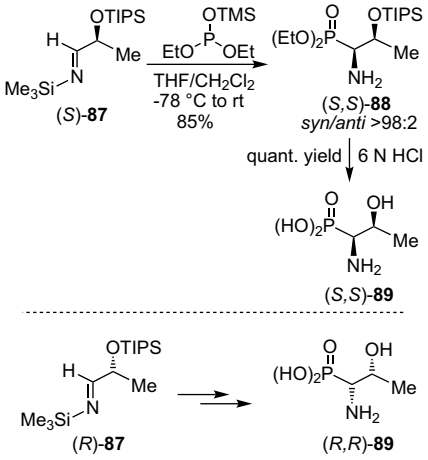
On the other hand, the reaction of a chiral hypophosphorous acid salt **85**, obtained by addition of (*S*)-α-MBA to anhydrous hypophosphorous acid, with aldehydes at reflux in ethanol gave the corresponding *N*-protected α-aminophosphonous acids **86a–e** as a single diastereoisomer, which, by treatment with bromine–water solution at 70 °C followed by the addition of propylene oxide, afforded the (*R*)-α-aminophosphonic acids **8** (Scheme 22). (*S*)-α-Aminophosphonic acids **8** were obtained using (*R*)-α-MBA.[79]



Scheme 22.

2.1.2. Addition of alkyl phosphites to imines derived from chiral aldehydes and ketones

In order to obtain diasteroisomerically pure phosphothreonine **89**, Bongini et al.[80] reported that the nucleophilic addition of trimethylsilyl diethyl phosphite to the imine (*S*)-**87**, readily obtained by condensation of (*S*)-2-triisopropylsilyloxy lactaldehyde with *N*-trimethylsilylamine, provided the β-silyloxy-α-aminophosphonate (*S*,*S*)-**88** in 85% yield and >98:2 *syn*/*anti* diastereoisomeric ratio. Acidic hydrolysis of (*S*,*S*)-**88** with 6 N HCl at reflux gave the phosphothreonine (*S*,*S*)-**89**. In a similar way, addition of trimethylsilyl diethyl phosphite to the imine (*R*)-**87**, followed by acidic hydrolysis, afforded the (*R*,*R*)-phosphothreonine **89** (Scheme 23).



Scheme 23.

The high diasteroselectivity in the addition of trimethylsilyl diethyl phosphite to the imine (*S*)-**87** is characterized by two important features: (1) the α-silyloxy group induces a high degree of *syn* diastereoselectivity, without a chelating Lewis acid; and (2) with increasing bulkiness of the silicon protecting group, an enhancement of the *syn* diastereoselectivity was observed. Computational studies showed that a pentacoordinate silicon group may be involved in the determination of the diastereoselectivity of the reaction. It should be noted that the reaction proceeds at −78 °C and, at this temperature, the $(EtO)_2P–OSiMe_3$ tautomeric structure is stabilized and strongly promotes the nucleophilic reactivity via a concerted [2+3] cycloaddition reaction (Fig. 10).

Recently, Davis and Prasad reported[81] that the addition of the potassium salt of diethyl or dimethyl phosphite to the enantiopure *O*-protected α-hydroxy sulfinimine (S_S,2*S*)-**90**, readily obtained by condensation of (*S*)-*p*-toluenesulfinamide with the appropriate *O*-protected α-hydroxy aldehyde in the presence of $Ti(OEt)_4$, afforded the α-aminophosphonates (S_S,1*R*,2*S*)-**91a–d** in good yield and 94% de.[82] Low diastereoselectivity was obtained when the

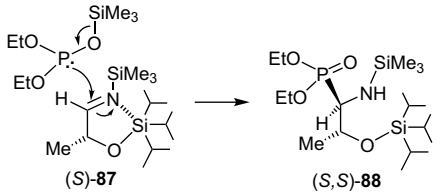
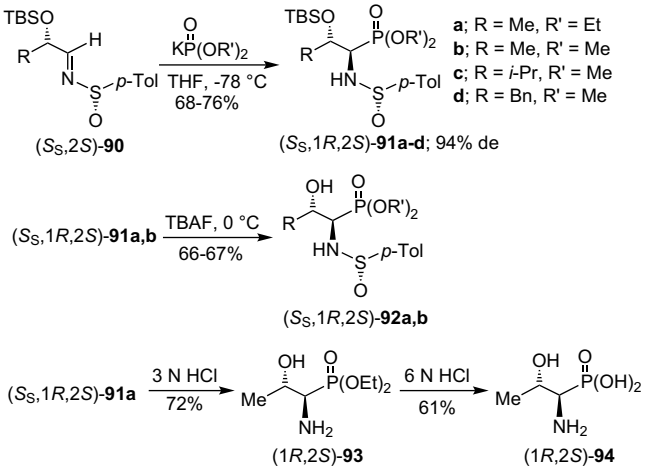


Figure 10. Transition-state proposed for addition of $(EtO)_2POSiMe_3$ to (*S*)-**87**.

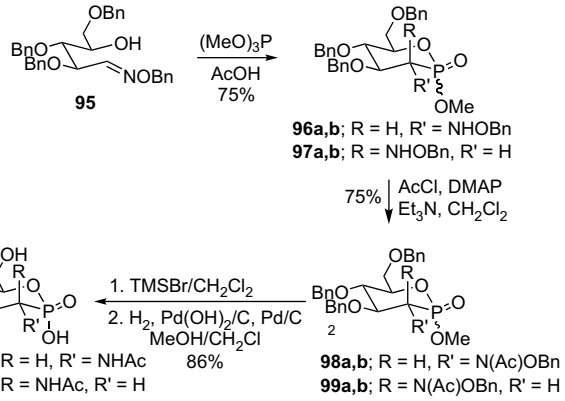
lithium or sodium salts of the alkyl phosphites were used. Treatment of (*S*S,1*R*,2*S*)-**91a**,**b** with tetra-*n*-butylammonium fluoride (TBAF) at 0 °C gave the β-hydroxy derivatives **92a**,**b** in 66–67% yield, whereas hydrolysis of (*S*S,1*R*,2*S*)-**91a** with 3 N HCl at reflux led to the α-amino-β-hydroxyphosphonate (1*R*,2*S*)-**93** in 72% yield, which, by hydrolysis with 6 N HCl at reflux, produced the α-amino-β-hydroxyphosphonic acid (1*R*,2*S*)-**94** in 61% yield (Scheme 24).



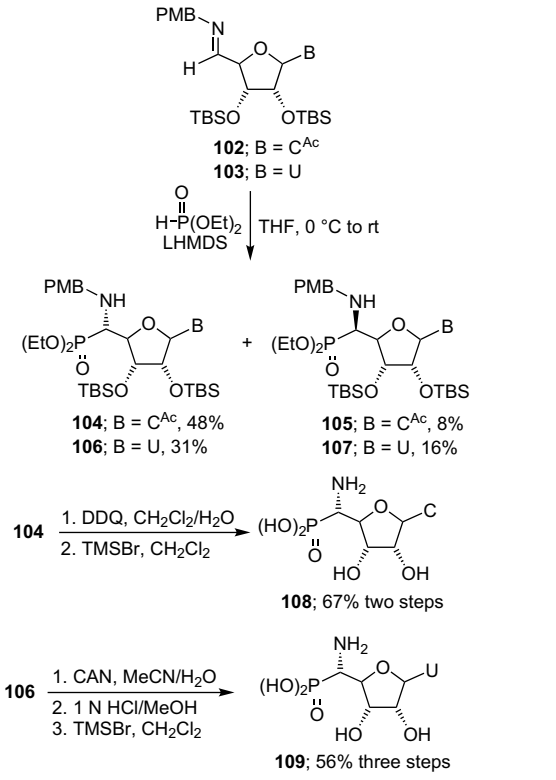
Scheme 24.

Addition of trimethyl phosphite to the oxime **95**, readily obtained by condensation of *O*-benzyl hydroxylamine and 2,3,5-tri-*O*-benzyl D-arabinose,[83] afforded a mixture of the D-*gluco* and D-*manno* isomers **96** and **97**, each consisting of a pair of two isomeric phosphonates (**a** and **b**). The cyclization into the phosphonates was spontaneous under these reaction conditions. Acetylation of **96a** gave the corresponding *N*-acetyl D-*gluco* derivative **98a**, whereas acetylation of the remaining mixture of isomers led to the other D-glucophosphonate **98b** and D-mannose analogues **99a**,**b**. Hydrolysis of the methyl esters **98a**,**b** and **99a**,**b** and chromatographic separation, followed by hydrogenolysis of each isomer, gave the *N*-acetyl-D-glucosamine phosphonate **100** and *N*-acetyl-D-mannosamine phosphonate **101** as the free acids (Scheme 25).[84]

Nucleophilic addition of lithium diethyl phosphite to the nucleosyl imines **102** and **103**, prepared by condensation of protected cytidine[85] and uridine,[86] respectively, with *p*-methoxybenzylamine, for the cytidine series gave the α-aminophosphonates **104** and **105** in a 6:1 ratio, and, for the uridine series, afforded **106** and **107** in a 2:1 ratio. Oxidation of the *p*-methoxybenzyl (PMB) protective group in the α-aminophosphonate **104** with DDQ, followed by hydrolysis of the phosphono esters with TMSBr, provided the α-aminophosphonic acid **108** directly in good yield. Presumably, the HBr generated in situ from an excess of TMSBr was sufficient to remove the TBS group. On the other hand, treatment of **106** under oxidative conditions with ceric ammonium nitrate (CAN) to remove the PMB protective group, followed by hydrolysis of the phosphono ester with TMSBr, afforded the α-aminophosphonic acid **109** in good yield (Scheme 26).[87]



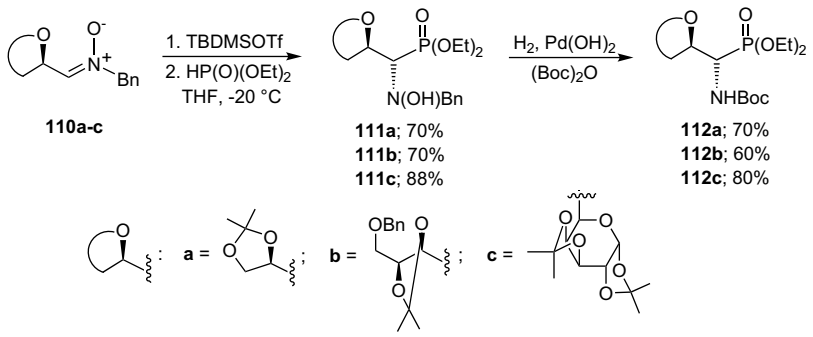
Scheme 25.



Scheme 26.

Addition of diethyl phosphite to *N*-benzyl nitrones derived from chiral α-alkoxy aldehydes has been a methodology used for the synthesis of polyhydroxylated α-aminophosphonates. For example, Pollini et al.[88] reported that the nucleophilic addition of diethyl phosphite to *N*-benzyl nitrones **110a**–**c**, readily obtained from D-glyceraldehyde, L-threose, and D-galactose, in the presence of *tert*-butyldimethylsilyl triflate (TBDMSOTf) afforded exclusively the *syn*-adducts **111a**–**c** in good yield, which, by catalytic hydrogenation over $Pd(OH)_2/C$ in the presence of di(*tert*-butyl)dicarbonate $(Boc)_2O$ gave the α-*N*-Boc-aminophosphonates **112a**–**c** in moderate yields (Scheme 27).

The high diastereoselectivity obtained in the addition of diethyl phosphite to **110a** has been explained in terms of the two transition-state structures **113** and **114**, in which the silicon atom of the trialkylsilyl group coordinates to both the nitrone oxygen atom and one of the oxygen atoms of the dioxolane ring, α-chelation or β-chelation, respectively (Fig. 11). The formation of the *anti*



Scheme 27.

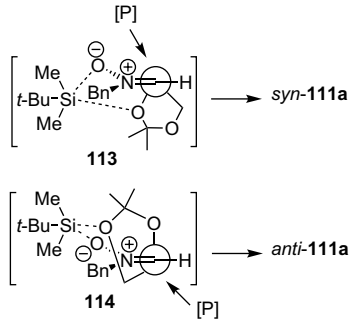


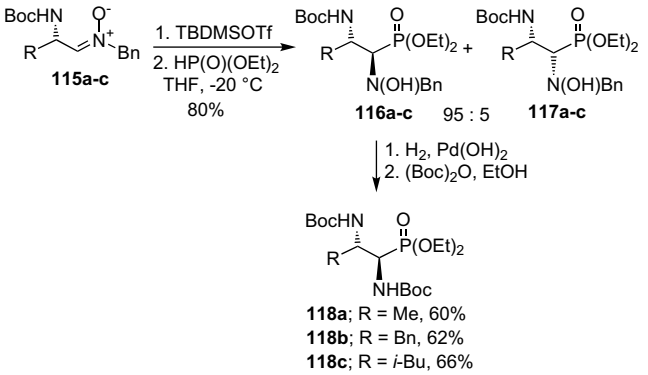
Figure 11. Models for addition of $HP(O)(OEt)_2$ to **110a**.

diastereoisomer suggests that the addition of diethyl phosphite occurs preferentially at the *si*-face of the nitrone in the β-chelate model **114**.

On the other hand, treatment of TBDMSOTf-precomplexed nitrones **115a–c** with diethyl phosphite in THF at −20 °C afforded the α,β-diaminophosphonates **116a–c** and **117a–c** in good yield and 95:5 dr. Catalytic hydrogenation of **116a–c** over $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ gave the *N*,*N*-diprotected α,β-diaminophosphonates **118a–c** in moderate yields (Scheme 28).[88]

In a similar way, treatment of *N*,*N*-diprotected α-amino nitrones **119a–d** with TBDMSOTf, followed by nucleophilic addition of diethyl phosphite, afforded exclusively the *syn*-adducts **120a–d** in good yield. Catalytic hydrogenation of **120a–d** over $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ provided the *N*,*N*-diprotected α,β-diaminophosphonates **121a–d** in moderate yield (Scheme 29).[88]

In order to explain the observed *syn*/*anti* stereoselectivity in the nucleophilic addition reaction of diethyl phosphite to the nitrones **115a–c** and **119a–d**, the authors have postulated two transition-state structures **122** and **123** (Fig. 12), in which the silicon atom of the trialkylsilyl group coordinates to both the nitrone oxygen atom and the carbamate group. The difference between these conformations exists on the outside and inside positions of the medium-sized substituent. The addition of diethyl phosphite to the *N*-monosubstituted derivatives **115a–c** should occur from the less-hindered side of the cyclic chelate **122**, leading the *anti* products **116a–c**, whereas the addition to the *N*,*N*-disubstituted α-nitrones **119a–d** should take place from the less-hindered side of the cyclic chelate **123** (*re*-attack), to give exclusively the *syn*-adducts **120a–d**.



Scheme 28.

2.1.3. Addition of chiral alkyl phosphites to non-chiral and chiral imines

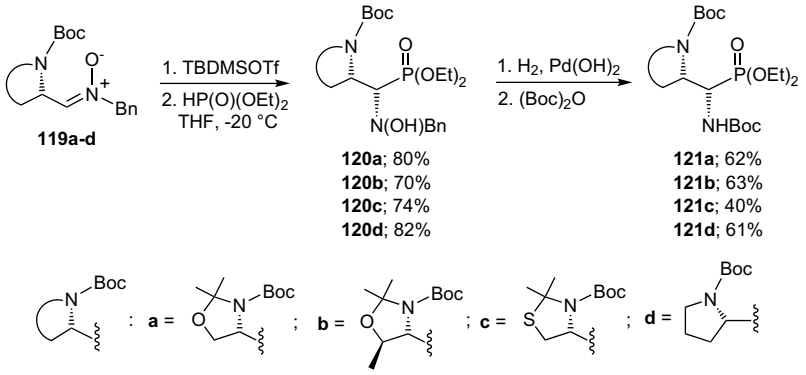
The chiral auxiliary can be attached not only to the imine fragment, but also to the phosphite residue. In this context, chiral C_3-symmetric trialkyl phosphites have been studied as starting reagents for the preparation of chiral organophosphorous compounds. For example, nucleophilic addition of tris[(1*R*,2*S*,5*R*)-menthyl] phosphite **125**, readily obtained from the reaction of (1*R*,2*S*,5*R*)-menthol with phosphorous trichloride, to the imine **124** in the presence of TMSCl afforded the α-aminophosphonates **126** in good yield and moderate diastereoselectivity (de=50%). Hydrolysis of the diastereoisomerically pure **126** with HCl in dioxane, followed by catalytic hydrogenolysis over Pd/C, gave the (*R*)-phosphophenylglycine **8a** with ca. 95% ee (Scheme 30).[89]

Recently, Kolodiazhnyi et al.[90] reported that the addition of chiral dialkyl phosphites **127a**,**b** [R*=(1*R*,2*S*,5*R*)-menthyl and (1*S*)-*endo*-bornyl] to the chiral imines derived from (*S*)- and (*R*)-α-MBA is accompanied by a double asymmetric induction at the α-carbon atom. Thus, addition of **127a** to the imine (*S*)-**5** at 80 °C gave the α-aminophosphonate (*R*,*S*)-**128** in 60% yield and 92% de, whereas addition of **127a** to the imine (*R*)-**5** led to α-aminophosphonate (*S*,*R*)-**128** in 50% yield and 50% de.[91] In a similar way, nucleophilic addition of chiral di-[(1*S*)-*endo*-bornyl] phosphite **127b** to (*S*)-**5** provided the α-aminophosphonate (*R*,*S*)-**129** in 60% yield and 86% de, whereas addition of **127b** to (*R*)-**5** afforded the α-aminophosphonate (*S*,*R*)-**129** in 70% yield and 60% de (Scheme 31). Hydrolysis of diastereoisomerically pure (*R*,*S*)-**128** and (*S*,*R*)-**128** with HCl in dioxane, followed by catalytic hydrogenolysis over Pd/C, gave the (*S*)- and (*R*)-phosphophenylglycine **8a**, respectively.

On the other hand, addition of tris[(1*R*,2*S*,5*R*)-menth-2-yl] phosphite **125** to the imine **124** in the presence of $BF_3 \cdot OEt_2$ afforded the α-aminophosphonate **126** with 30% de. In a similar way, addition of **125** to the imine (*S*)-**5** in the presence of $BF_3 \cdot OEt_2$ gave the α-aminophosphonate (*S*,*S*)-**130** with 70% de (Scheme 32).

It is noteworthy that the reactions of tri[(1*R*,2*S*,5*R*)-menthyl] phosphite **125** and di[(1*R*,2*S*,5*R*)-menthyl] phosphite **127a** with Schiff bases differ in their steric results and led to the diastereoisomers with opposite absolute configuration at the α-carbon atom.

The reaction of chiral P–H spirophosphoranes **131** with long-chain aldimines **132** is a methodology used for the synthesis of α-aminophosphonic acid amphiphiles **135** in both enantiopure



Scheme 29.

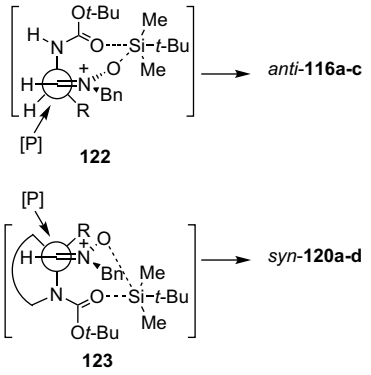
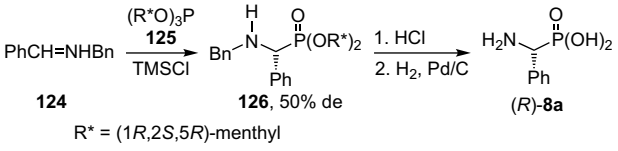
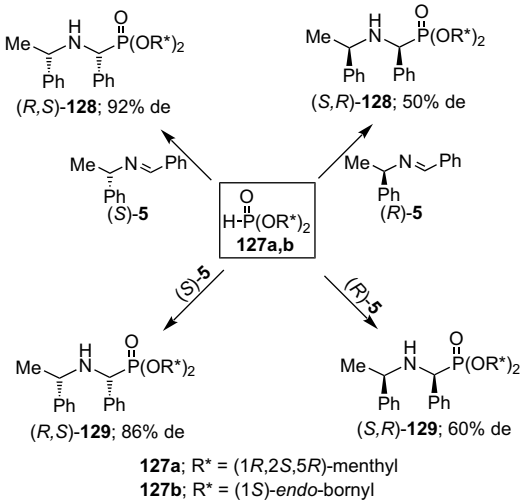


Figure 12. Models for addition of $HP(O)(OEt)_2$ to nitrones **115** and **119**.

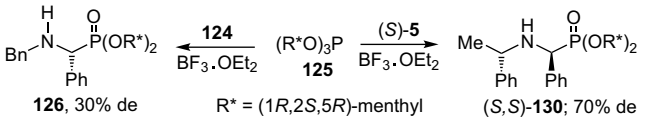


Scheme 30.

forms.[92] In this context, reaction of the aldimine **132** ($R'=C_{18}H_{37}$) with the spirophosphorane **131a**, readily obtained from (*S*)-α-hydroxyisovaleric acid,[93] followed by selective hydrolysis of **133**, afforded the derivative **134a** with 15:85 dr. In a similar way,

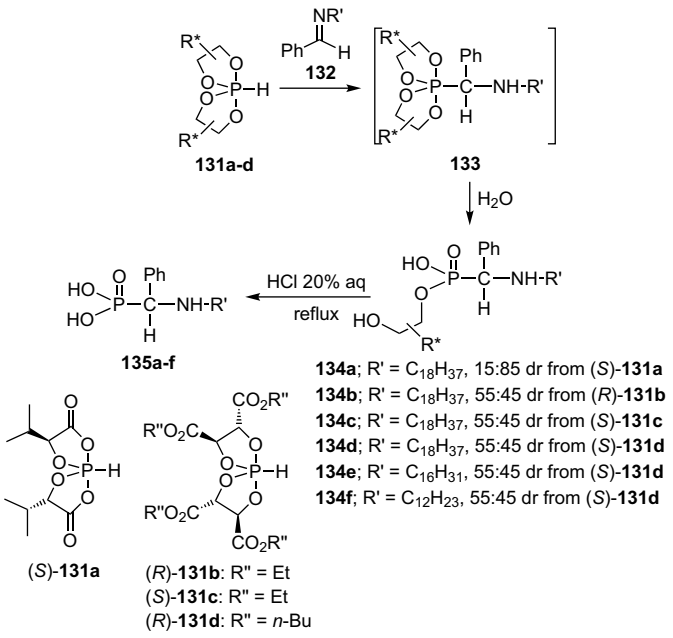


Scheme 31.



Scheme 32.

nucleophilic addition of spirophosphoranes **131b–d**, obtained from tartaric acid esters, to the aldimines **132** ($R'=C_{18}H_{37}$, $R'=C_{16}H_{31}$, $R'=C_{12}H_{23}$), followed by the selective hydrolysis of **133**, gave the derivatives **134b–f** with 55:45 dr in all cases. The lack of diastereoselectivity obtained for **134b–f**, compared with **134a**, might be due to the structural lability of the spirophosphoranes **131b–f**. The absence of the carbonyl intracyclic group may also reduce the acidity and the reactivity of the P–H bond. Finally, acidic hydrolysis of diastereosiomerically pure **134a–f** afforded the α-amino-phosphonic acid amphiphiles **135a–f** in both enantiopure forms (Scheme 33).

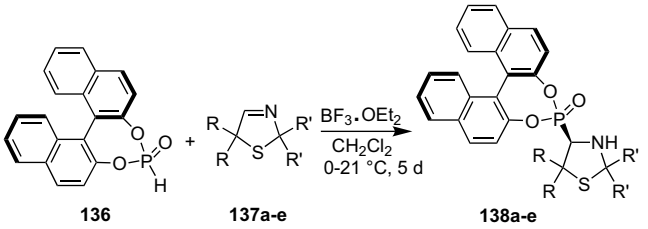


Scheme 33.

Since the chiral auxiliary might be easily removed by hydrolysis of the phosphonic ester, Martens et al.[94] carried out the addition of chiral BINOL-phosphite **136** to achiral 3-thiazolines **137a–e** in the presence of $BF_3\cdot OEt_2$, obtaining the corresponding thiazolidinyl phosphonates **138a–e** in moderate yield and excellent

diastereoselectivity. It is noteworthy that the stereoselectivity of the BINOL-phosphite **136** seems to be independent of the steric demands of the nearby substituents R. In contrast, the nature of the more distant substituent R′ of the *N*,*S*-acetalic carbon atom influences the diastereoselectivity to a larger extent (Table 9).[95]

Table 9
Addition of chiral BINOL-phosphite **136** to achiral 3-thiazolines **137a–e**

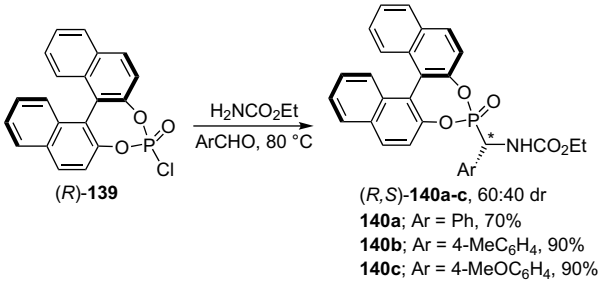


136 **137a-e** **138a-e**

Product	R/R	R′/R′	Yield (%)	dr
138a	Me/Me	Me/Me	47	83:17
138b	Me/Me	$-(CH_2)_5-$	47	>95:5
138c	$-(CH_2)_5-$	Me/Me	37	80:20
138d	$-(CH_2)_5-$	$(CH_2)_5-$	68	>95:5
138e	H/H	$-(CH_2)_5-$	30	>95:5

Removal of the chiral auxiliary and cleavage of the *N*,*S*-acetal[94] might be performed by acidic hydrolysis, as has been described in the literature, thus maintaining the chiral information of the released α-aminophosphonic acid.

Swamy et al.[96] reported the utility of chiral cyclic chlorophosphites derived from BINOL as scaffolds for the one-pot synthesis of α-aminophosphonates under solvent-free conditions. In this context, treatment of the chlorophosphite (*R*)-**139** with urethane and arylaldehydes at 80 °C yielded the α-aminophosphonates **140a–c** in good yield and 60:40 dr, with the (*R*,*S*) diastereoisomers as the principal products (Scheme 34).



(*R*)-**139**

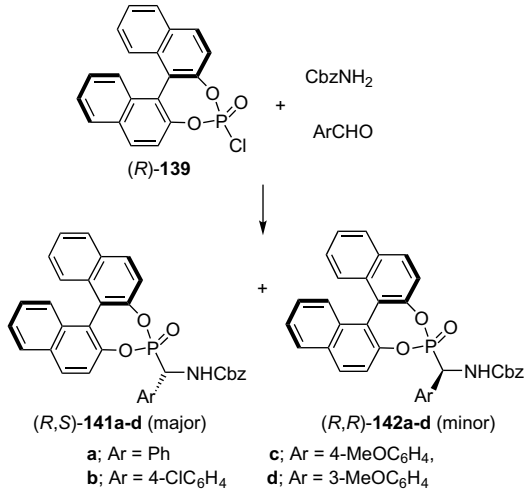
(*R*,*S*)-**140a-c**, 60:40 dr
140a; Ar = Ph, 70%
140b; Ar = 4-MeC_6H_4, 90%
140c; Ar = 4-$MeOC_6H_4$, 90%

Scheme 34.

In a similar way, the reaction of (*R*)-**139** with benzyl carbamate and arylaldehydes afforded the α-aminophosphonates **141a–d** and **142a–d** in good yield, and diastereoisomeric ratios from 1.1:1 to 1.8:1, with the (*R*,*S*)-**141a–d** diastereoisomers as the principal products (Scheme 35).[97]

On the other hand, treatment of diethyl (*R*,*R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate **143**, readily prepared from diethyl L-tartrate and phosphorus trichloride, with benzyl carbamate and arylaldehydes, followed by the addition of H_2O, led to the α-aminophosphonates **144a–f** and **145a–f** in good yield, and diastereoisomeric ratios from 1.7:1 to 2.5:1, with (*R*,*R*,*R*)-**144a–d** diastereoisomers as the principal products. Saponification of diastereoisomerically pure **144a** and **145a** afforded the (*R*)- and (*S*)-*N*-Cbz-phosphophenylglycine **146a**, respectively (Scheme 36).[97]

Using this Mannich-type multicomponent reaction, Xu and Gao[98] prepared the depsiphosphonopeptides **148** and **149**, which are analogues of naturally occurring peptides. Thus, reaction of

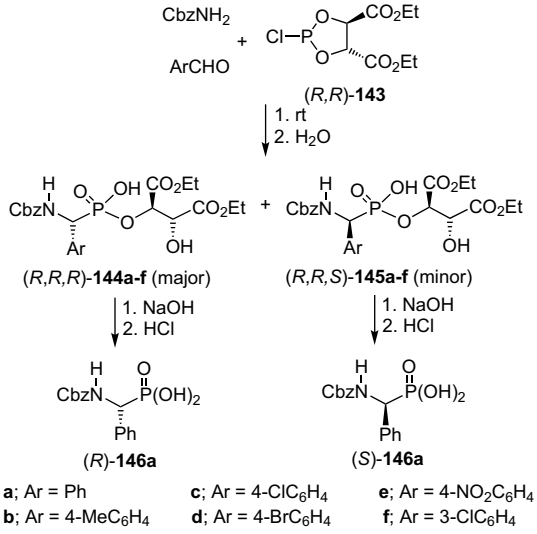


(*R*)-**139**

(*R*,*S*)-**141a-d** (major) (*R*,*R*)-**142a-d** (minor)

a; Ar = Ph **c**; Ar = 4-$MeOC_6H_4$,
b; Ar = 4-ClC_6H_4 **d**; Ar = 3-$MeOC_6H_4$

Scheme 35.



(*R*,*R*)-**143**

(*R*,*R*,*R*)-**144a-f** (major) (*R*,*R*,*S*)-**145a-f** (minor)

(*R*)-**146a** (*S*)-**146a**

a; Ar = Ph **c**; Ar = 4-ClC_6H_4 **e**; Ar = 4-$NO_2C_6H_4$
b; Ar = 4-MeC_6H_4 **d**; Ar = 4-BrC_6H_4 **f**; Ar = 3-ClC_6H_4

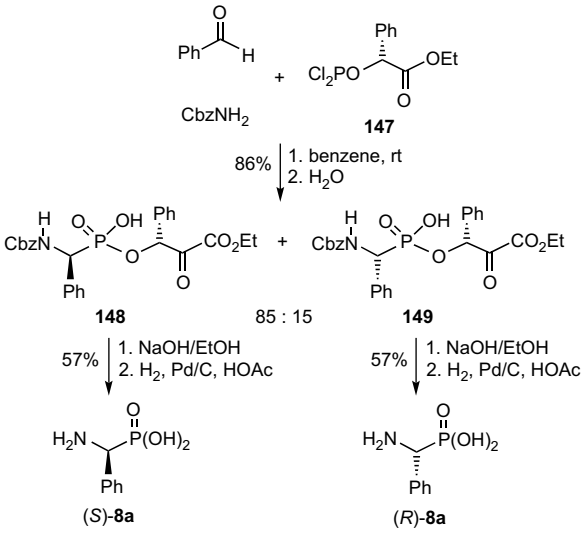
Scheme 36.

1-carboethoxy phosphorodichloridite **147** with benzyl carbamate and benzaldehyde in anhydrous benzene, followed by hydrolysis, afforded the depsiphosphonopeptides **148** and **149** in 86% yield and 85:15 dr. Saponification of diastereoisomerically pure **148** and **149**, followed by cleavage of the Cbz protective group provided the enantiomerically pure (*S*)- and (*R*)-phosphophenylglycine **8a**, respectively (Scheme 37).

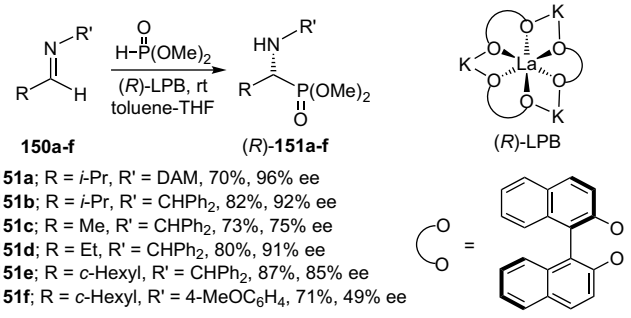
2.1.4. Catalytic asymmetric addition of alkyl phosphites to non-chiral imines

Catalytic enantioselective synthesis is one of the most important topics in modern synthetic chemistry, because it provides the most efficient methodology to approach in the preparation of enantiomerically pure compounds.[99] In this context, Shibasaki et al.[100] reported the first catalytic hydrophosphonylation of imines. Thus, addition of dimethyl phosphite to the imines **150a–f** in the presence of a lanthanoid/potassium/BINOL complex [(*R*)-LPB] gave the (*R*)-α-aminophosphonates **151a–f** in moderate to high enantiomeric excess (Scheme 38).

Another approach for the synthesis of chiral α-aminophosphonates is the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of non-chiral imines. For example, Akiyama et al.[101] reported that hydrophosphonylation of the imines **152a–k** catalyzed by the cyclic phosphoric acid **153**, derived from



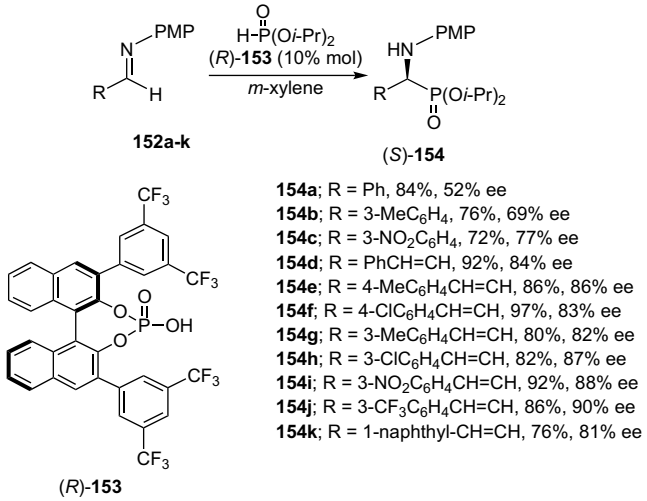
Scheme 37.



Scheme 38.

(*R*)-BINOL, afforded the (*S*)-α-aminophosphonates **154a**–**k** in good yield and enantioselectivity (Scheme 39).

In order to explain the high chiral induction, the authors proposed a nine-membered transition-state (Fig. 13), wherein the phosphonic acid (*R*)-**153** plays two roles: (1) the phosphonic acid hydrogen activates the imine as a Brønsted acid; and (2) the phosphoryl oxygen activates the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base, thereby



Scheme 39.

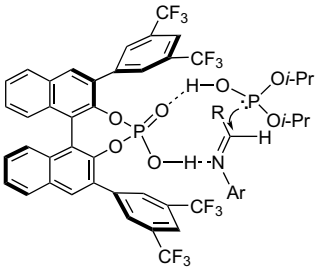
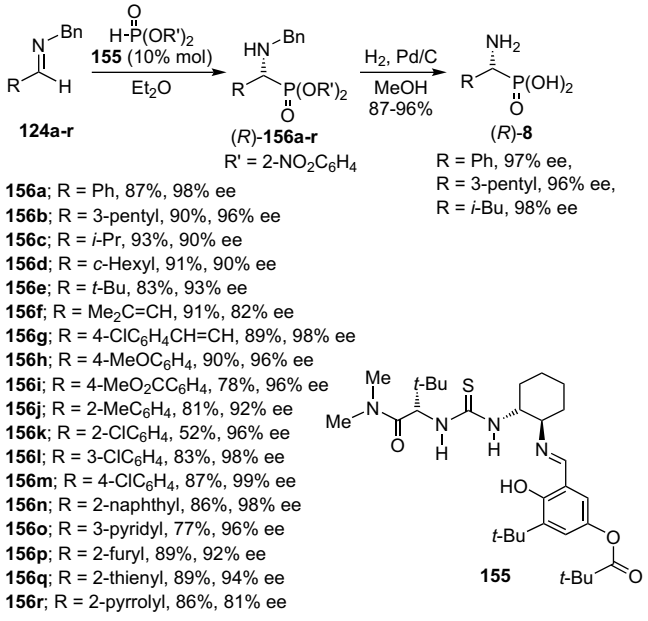


Figure 13. Plausible reaction mechanism of **152a**–**k**.

promoting *re*-facial attack on the imine and increasing the enantioselectivity by a proximity effect.

On the other hand, Joly and Jacobsen[102] found that the nucleophilic addition of di(*o*-nitrophenyl) phosphite to the *N*-benzyl imines **124a**–**r**, in the presence of a chiral urea **155** as catalyst, gave the (*R*)-α-aminophosphonates **156a**–**r** in excellent yield and enantioselectivity. Hydrogenolysis of **156a**, **156b**, and **156f** afforded the enantiomerically enriched (*R*)-α-aminophosphonic acids **8** (Scheme 40).

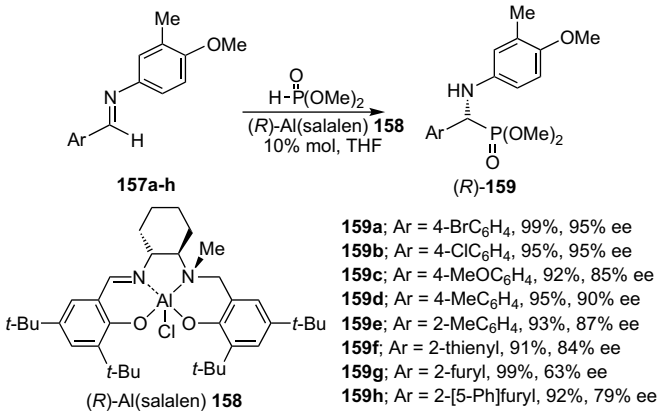


Scheme 40.

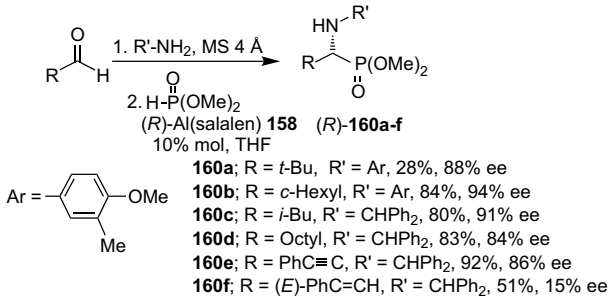
Recently, Katsuki et al.[103] reported that the asymmetric hydrophosphonylation of aromatic aldimines **157a**–**h** bearing a 4-methoxy-3-methylphenyl group as the *N*-protecting group, in the presence of the complex (*R*)-Al(salalen) **158** as catalyst, gave the (*R*)-α-aminophosphonates **159a**–**h** in excellent yield and good enantioselectivity. When the imine carried an electron-withdrawing *p*-substituent, the enantioselectivity was improved up to 95% ee; however, the presence of an electron-donating *p*-substituent decreased the enantioselectivity to 85% ee (Scheme 41).[104]

One-pot hydrophosphonylation of aldehydes, 4-methoxy-3-methylaniline or diphenylmethylamine, and dimethyl phosphite, in the presence of the complex (*R*)-Al(salalen) **158** as catalyst, afforded the (*R*)-α-aminophosphonates **160a**–**f** in good enantioselectivity (Scheme 42).[103,105]

On the other hand, addition of diethyl phosphite to *N*-Boc-protected imines **161a**–**i** at 20 °C, in the presence of quinine (QN) **162** as chiral catalyst, provided the (*R*)-α-aminophosphonates **163a**–**i** in moderate yield and enantioselectivity. An enhanced



Scheme 41.

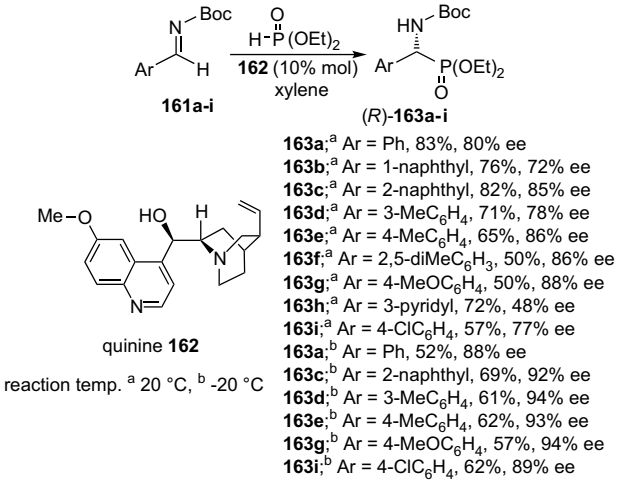


Scheme 42.

enantioselectivity was observed when the reaction was carried out at −20 °C (Scheme 43).[106]

In order to explain the high chiral induction, the authors proposed that the imine is activated by hydrogen bonding with the acidic hydroxyl group in the quinine, and that the phosphite–phosphonate equilibrium toward the phosphite form could give rise to attack at the electrophilic azomethine carbon (Fig. 14).[106]

In 1998, Shibasaki et al.[107] described for the first time the catalytic and enantioselective hydrophosphonylation of cyclic imines. In this context, nucleophilic addition of dimethyl phosphite to thiazolines **137**, catalyzed by (*R*)-YbPB **164**, afforded the corresponding 4-thiazolidinyl phosphonates (*S*)-**165a**–**e** in good yield and enantiomeric excess (Scheme 44).



Scheme 43.

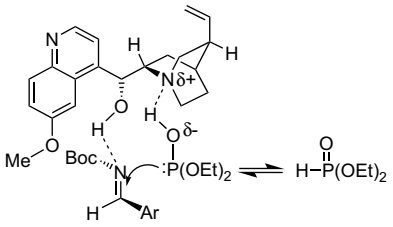
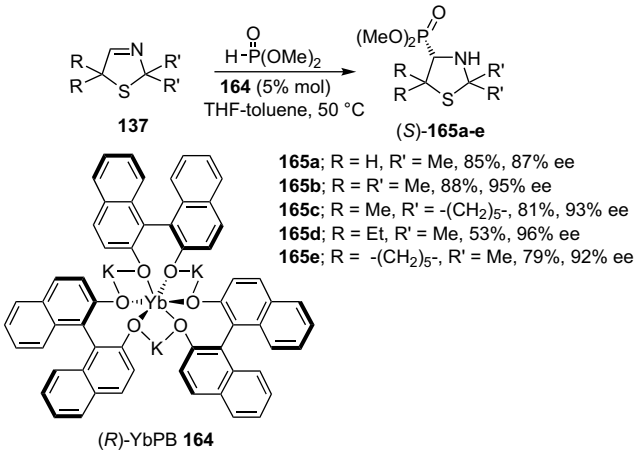


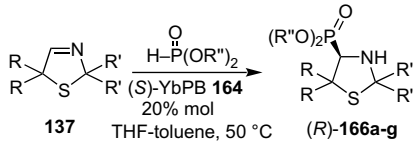
Figure 14. Proposed mechanism for addition of $(EtO)_2P(O)H$ to **161** catalyzed by QN.



Scheme 44.

In a similar way, enantioselective hydrophosphonylation of cyclic imines **137** using cyclic phosphites, catalyzed by (*S*)-YbPB **164**, provided the 4-thiazolidinyl phosphonates (*R*)-**166a**–**g** in excellent enantiomeric excess and high chemical yields (Table 10).[108]

Table 10
Catalytic and enantioselective hydrophosphonylation of **137**



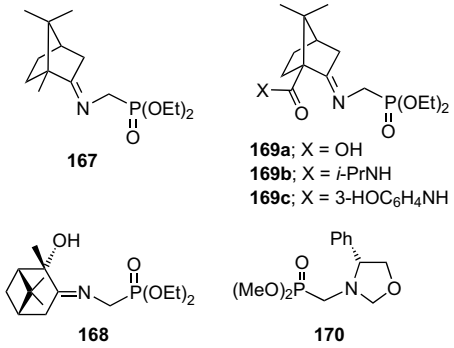
Product	R/R	R′/R′	R″/R″	Yield (%)	ee (%)
166a	Me/Me	Me/Me	$-(CH_2)_3-$	99	97
166b	Me/Me	Me/Me	$-CH_2C(Me)_2CH_2-$	90	92
166c	Me/Me	Me/Me	$-CH_2CH{=}CHCH_2-$	87	93
166d	Me/Me	$-(CH_2)_5-$	$-(CH_2)_3-$	61	97
166e	Me/Me	$-(CH_2)_5-$	$-CH_2C(Me)_2CH_2-$	82	98
166f	$-(CH_2)_5-$	Me/Me	$-(CH_2)_3-$	85	97
166g	$-(CH_2)_5-$	Me/Me	$-CH_2C(Me)_2CH_2-$	69	96

2.2. Stereoselective C–C bond formation

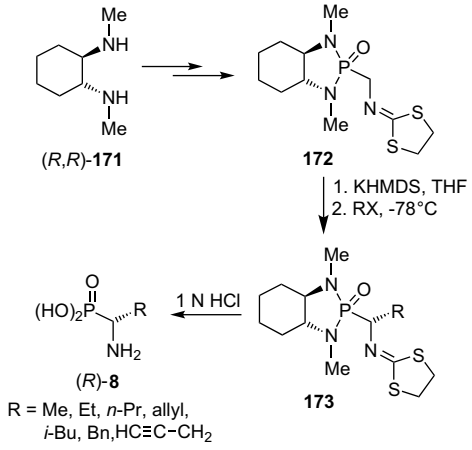
2.2.1. Alkylation of phosphoglycine derivatives

The chiral Schiff bases formed from esters of glycine and chiral carbonyl compounds are one of the most popular approaches for the asymmetric synthesis of α-amino acids.[109] In a similar way, the chiral Schiff bases prepared from phosphoglycine have also been used in the asymmetric synthesis of α-aminophosphonic acids. For example, the Schiff base **167** derived from (*R*)-camphor and phosphoglycine diethyl ester was used by Schöllkopf[110] for the asymmetric synthesis of α-aminophosphonic acids. On the other hand, the Schiff base **168** derived from (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one and phosphoglycine diethyl ester has been used by Roumestant

et al.[111] for the stereoselective synthesis of α-aminophosphonic acids. Jommi et al.[112] reported that the chiral Schiff bases **169a–c** obtained by condensation of (+)-ketopinic acid with phosphoglycine diethyl ester are important compounds for the asymmetric synthesis of α-aminophosphonic acids. Alkylation of the oxazolidine **170** derived from (*R*)-phenylglycinol has also been used in the enantioselective synthesis of α-aminoalkylphosphonic acids.[113]



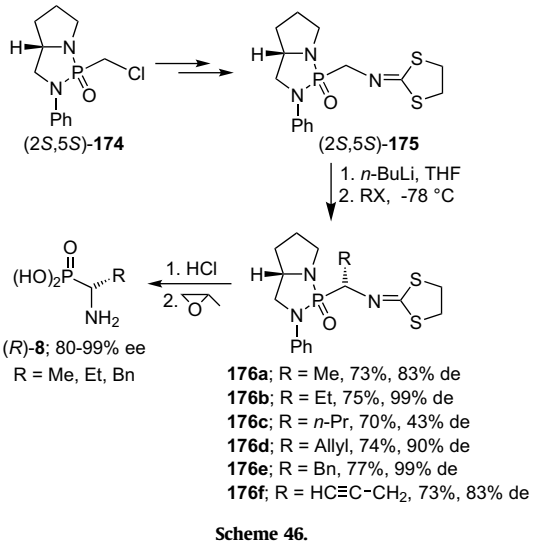
In 1990, Hanessian and Bennani[114] reported the enantioselective synthesis of α-aminoalkylphosphonic acids (*R*)-**8** via the diastereoselective alkylation of bicyclic phosphonoamide **172**, which was easily prepared from the (*R*,*R*)-diamine **171**. Acidic hydrolysis of **173** gave the α-aminoalkylphosphonic acids (*R*)-**8** (Scheme 45).



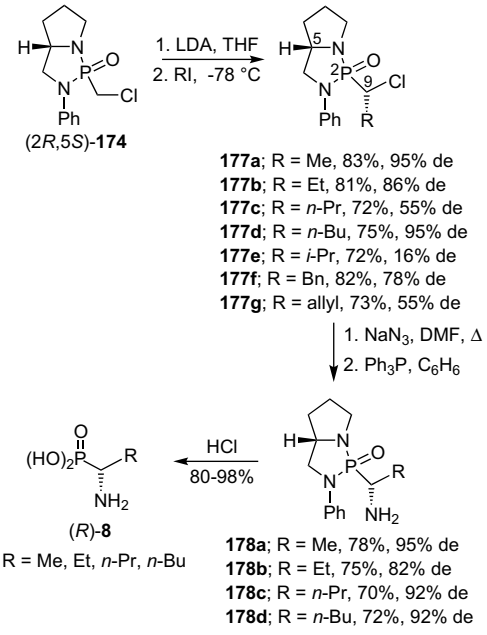
Scheme 45.

Recently, Cheng-Ye and Qian-Yi[115] reported a facile and efficient asymmetric synthesis of α-aminophosphonic acids (*R*)-**8** via the diastereoselective alkylation of the bicyclic phosphonoamide **175**. Thus, treatment of (2*S*,5*S*)-**175**, readily obtained from (2*S*,5*S*)-**174** derived from (*S*)-2-anilinomethylpyrrolidine, with *n*-BuLi in THF at −78 °C followed by addition of an alkyl halide, afforded the alkylated products **176a–f** in moderate yield and with moderate to excellent diastereoselectivity (43–99%). Acidic hydrolysis of **176a**,**b** and **176e** gave the (*R*)-α-aminoalkylphosphonic acids **8** with excellent enantiomeric excess (Scheme 46).[116]

On the other hand, treatment of the bicyclic chloromethylphosphonoamide (2*R*,5*S*)-**174** with lithium diisopropylamide (LDA) in THF at −78 °C, followed by addition of alkyl iodide, afforded the alkylated products (2*R*,5*S*,9*S*)-**177a–g** in good yield (72–83%) and with low to good levels of diastereoselectivity (16–95% de). Nucleophilic displacement on chloro derivatives **177a–d** by azide ion and subsequent treatment under Staudinger reaction[117] conditions gave the α-aminophosphonoamides **178a–d** in good yield and diastereoselectivity (82–95% de). Acidic hydrolysis of **178a–d** led to the (*R*)-α-aminophosphonic acids **8** (Scheme 47).[118,119]



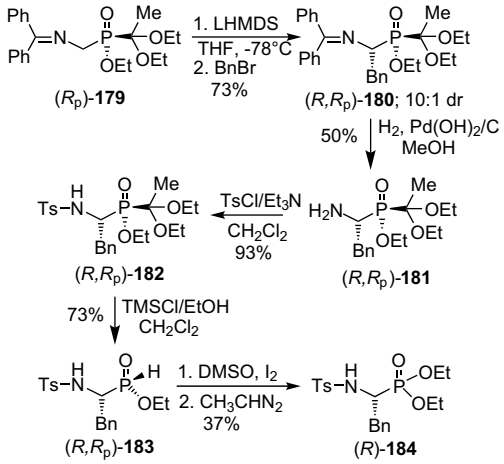
Scheme 46.



Scheme 47.

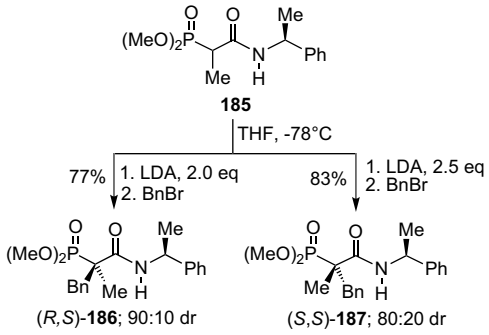
Recently, Yokomatsu et al.[120] reported the diastereoselective synthesis of α-aminophosphonate **184** by a highly diastereoselective alkylation of phosphoglycine derivative (R_P)-**179**. In this context, treatment of (R_P)-**179** with LHMDS in THF at −78 °C followed by addition of benzyl bromide afforded the benzylated product (*R*,R_P)-**180** in 73% yield and 10:1 diastereoisomeric ratio,[121] which, by hydrogenolysis over $Pd(OH)_2$/C and subsequent tosylation of free amine (*R*,R_P)-**181**, gave the *N*-tosyl derivative (*R*,R_P)-**182** in 93% yield. Deprotection of the ketal moiety in (*R*,R_P)-**182** with TMSCl and EtOH provided the compound (*R*,R_P)-**183** in 73% yield.[122] Finally, oxidation of (*R*,R_P)-**183** with DMSO and I_2 followed by esterification with diazoethane led to the enantiomerically pure (*R*)-α-aminophosphonate **184** in 37% yield (Scheme 48).

Recently, we have reported the first stereochemical reversal in the benzylation reaction of the phosphonoamide **185**[123] by changing the LDA equivalents. In this context, the enolization of **185** with freshly prepared LDA (2.0 equiv) in THF at −78 °C, followed by the addition of benzyl bromide, afforded the quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** in 77% yield and 90:10



Scheme 48.

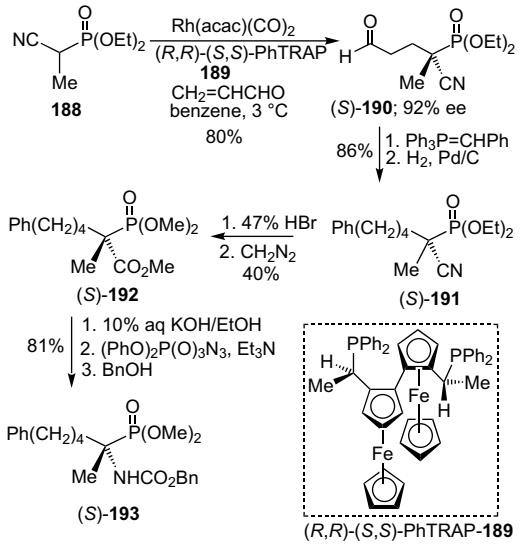
diastereoisomeric ratio, with a predominance of (*R*,*S*)-**186**. However, when the enolate of **185** was generated with LDA (2.5 equiv) at −78 °C, followed by the addition of benzyl bromide, the quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** were formed in 83% yield and 20:80 dr, but now with a predominance of (*S*,*S*)-**187** (Scheme 49).[124] The quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** could be transformed into the quaternary α-aminophosphonic acids after several reactions including a Curtius rearrangement.[125]



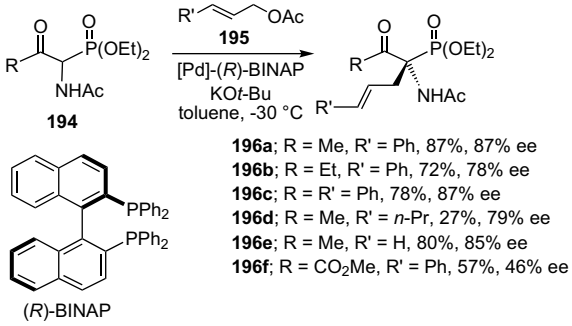
Scheme 49.

Asymmetric Michael addition of diethyl (1-cyanoethyl)-phosphonate **188** to acrylaldehyde, in the presence of Rh(acac)$(CO)_2$ and (*R*,*R*)-(*S*,*S*)-PhTRAP **189** in dry benzene, afforded the quaternary optically active (4-oxoalkyl)phosphonate **190** in 80% yield and 92% ee, which, by treatment with benzyltriphenylphosphonium ylide and subsequent hydrogenation of the newly formed carbon–carbon double bond, led to the cyano derivative **191** in 86% yield. Complete hydrolysis of **191** using 47% HBr followed by esterification with diazomethane led to the dimethyl ester **192** in 40% yield. Selective hydrolysis of the carbomethoxy group in **192** and subsequent Curtius rearrangement[125] followed by treatment with benzyl alcohol gave the quaternary α-aminophosphonate **193** in 81% yield (Scheme 50).[126]

On the other hand, asymmetric allylation of α-acetamido β-ketophosphonate **194** at −30 °C with allyl acetates **195** using potassium *tert*-butoxide as base, in the presence of 1 mol% of a chiral catalyst prepared in situ from (*R*)-BINAP and [Pd(π-allyl)(cod)]BF_4, afforded the α-allyl α-aminophosphonates **196a**–**e** in 78–87% ee. However, the allylation reaction of α-acetamido β-carbomethoxyphosphonate gave **196f** with only low enantioselectivity (Scheme 51).[127]

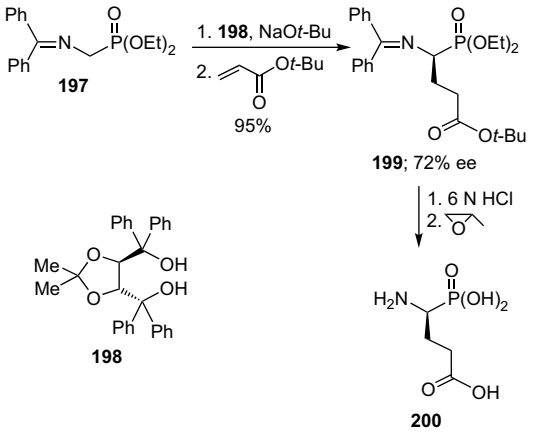


Scheme 50.



Scheme 51.

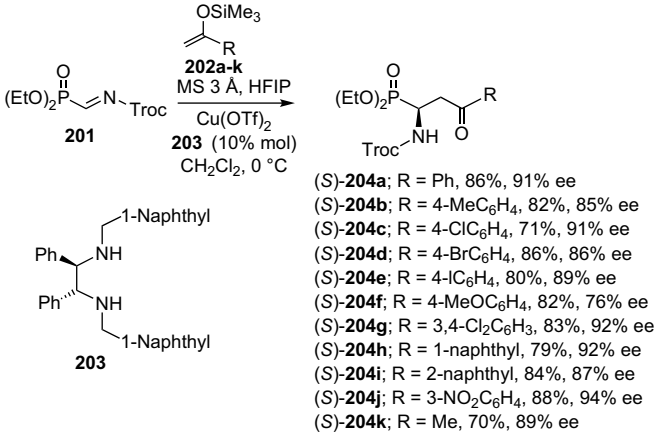
Recently, Jászay et al.[128] have reported the synthesis of (*S*)-phosphoglutamic acid **200** via a catalytic enantioselective Michael addition. In this context, treatment of the achiral Schiff base **197**, derived from phosphoglycine, with sodium *tert*-butoxide, followed by the addition of *tert*-butyl acrylate in the presence of TADDOL **198**, produced the α-aminophosphonate **199** in 95% yield and 72% ee.[129] Acidic hydrolysis of **199** using 6 N HCl gave the (*S*)-phosphoglutamic acid[130] **200** (Scheme 52).



Scheme 52.

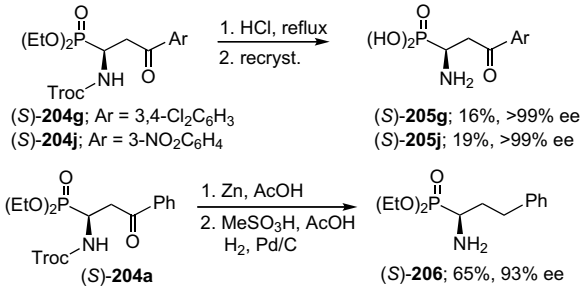
2.2.2. Nucleophilic addition to iminophosphonates

Catalytic enantioselective carbon–carbon bond-forming reactions have been used for the asymmetric synthesis of α-aminophosphonates. For example, the addition of silicon enolates **202a–k**, derived from aromatic and aliphatic ketones, to *N*-acyl-α-iminophosphonate **201**, catalyzed by the chiral copper(II) complex derived from $Cu(OTf)_2$ and diamine **203**, in the presence of hexafluoroisopropyl alcohol (HFIP) at 0 °C, gave the γ-keto-α-aminophosphonates **204a–k** in good yield (70–88%) and enantioselectivity (76–94% ee) (Scheme 53).[131]



Scheme 53.

Treatment of **204g** and **204j** with concentrated HCl at reflux followed by recrystallization afforded the γ-keto-α-aminophosphonic acids **205g** and **205j**, respectively, with excellent enantioselectivity. The reaction of **204a** with zinc powder in acetic acid, followed by hydrogenolysis over Pd/C in acetic acid and methanesulfonic acid, provided the α-aminophosphonate **206** with good enantioselectivity (Scheme 54).

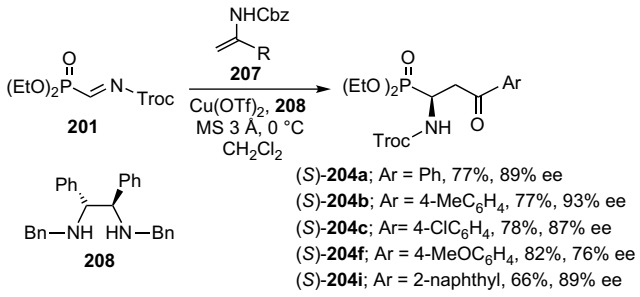


Scheme 54.

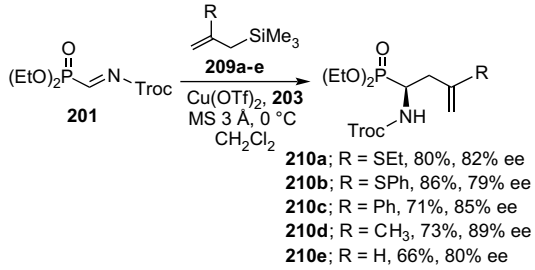
In a similar way, the reaction of α-iminophosphonate **201** with the enamines **207** in the presence of $Cu(OTf)_2$ and chiral diamine **208** in dichloromethane at 0 °C, followed by hydrolysis, provided the corresponding γ-keto-α-aminophosphonates **204** in good yield (66–82%) and enantioselectivity (76–93% ee) (Scheme 55).[132,133]

Kobayashi et al.[134] reported the first example of catalytic enantioselective allylations of α-iminophosphonates for the synthesis of α-allyl α-aminophosphonates **210**. In this context, the allylation reaction of *N*-acyl-α-iminophosphonate **201** with the allylsilanes **209a–e**, in the presence of $Cu(OTf)_2$ and the chiral diamine **203** in dichloromethane at 0 °C, led to the α-aminophosphonates **210** in good yield (66–86%) and enantioselectivity (79–89% ee) (Scheme 56).

Recently, Dodda and Zhao[135] reported the first enantioselective synthesis of α-aminopropargylphosphonates **214a–m** through the

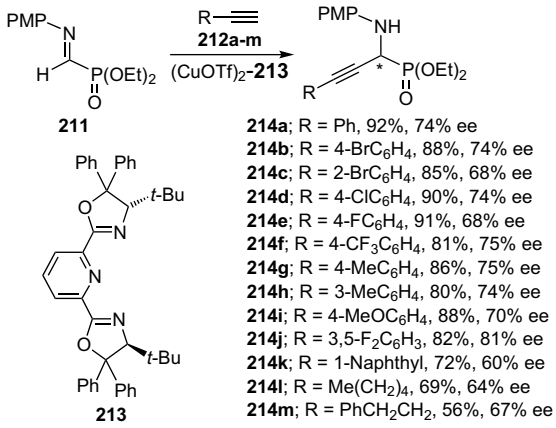


Scheme 55.



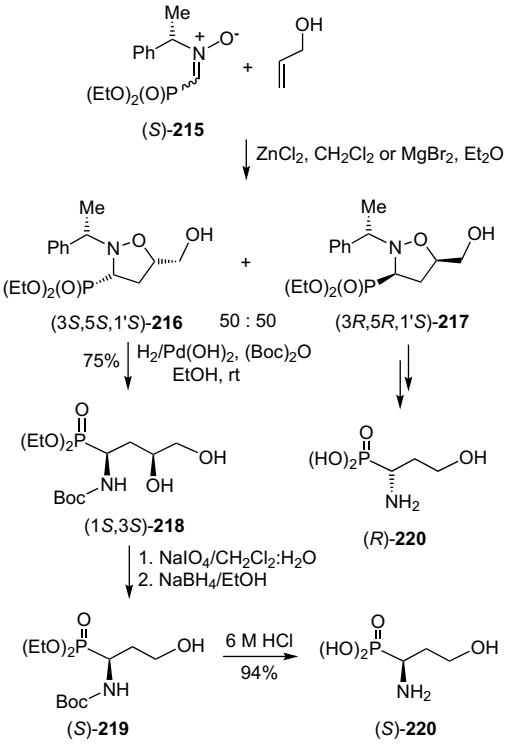
Scheme 56.

direct addition of terminal alkynes **212** to α-iminophosphonate **211** in the presence of a $(CuOTf)_2$/bisoxazoline **213** complex as chiral catalyst. In general, high yields (56–92%) and good levels of asymmetric induction (60–81% ee) were obtained (Scheme 57).



Scheme 57.

Carbon–carbon bond formation via a 1,3-dipolar cycloaddition reaction has been used for the synthesis of (*R*)- and (*S*)-phosphohomoserine **220**.[136] In this context, 1,3-dipolar cycloaddition of the nitrone (*S*)-**215** with allyl alcohol in the presence of $ZnCl_2$ or $MgBr_2$ gave an unseparable mixture of cis-isomers, (3*S*,5*S*,1′*S*)-**216** and (3*R*,5*R*,1′*S*)-**217**, in a 50:50 ratio.[137,138] Hydrogenation of diastereoisomerically pure (3*S*,5*S*,1′*S*)-**216** in the presence of $(Boc)_2O$ led to the *N*-Boc-aminodiol (1*S*,3*S*)-**218** in 75% yield, which, by treatment with sodium metaperiodate, followed by reduction of the aldehyde generated with $NaBH_4$, provided the corresponding alcohol (*S*)-**219**. Finally, acidic hydrolysis of (*S*)-**219** with 6 M HCl and subsequent treatment with propylene oxide afforded the enantiomerically pure (*S*)-phosphohomoserine **220** in 94% yield. In a similar fashion, the diastereoisomerically pure (3*R*,5*R*,1′*S*)-**217** was transformed into (*R*)-phosphohomoserine **220** (Scheme 58).

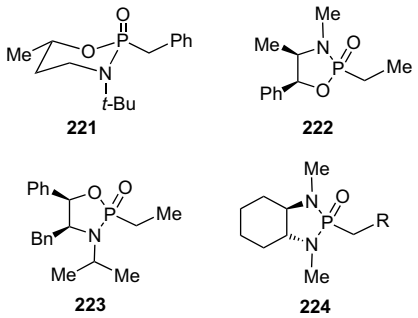


Scheme 58.

2.3. Stereoselective C–N bond formation

2.3.1. Stereoselective electrophilic amination

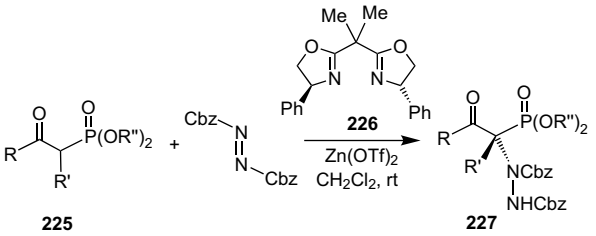
Another approach for the asymmetric synthesis of α-aminophosphonic acids is the stereoselective electrophilic amination of chiral α-phosphonate carbanions. In this context, several chiral oxazaphosphorinanes and oxazaphospholanes and diazophospholanes, derived from alkylphosphonic dichlorides and the appropriate chiral amino alcohols or diamines, have been used as key substrates in the electrophilic amination. For example, Denmark et al.[139] reported the asymmetric synthesis of α-aminophosphonic acids from **221** via stereoselective electrophilic amination. On the other hand, the chiral oxazaphospholanes **222**[140] and **223**[141] have also been used in the synthesis of α-aminophosphonic acids. Similar results have been obtained using the diazaphospholane **224**.[142]



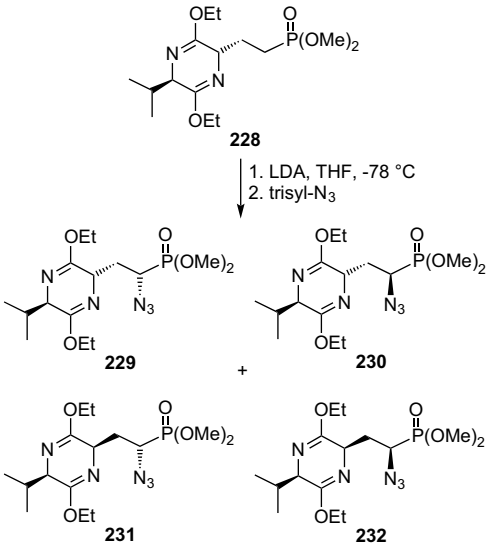
Recently, Jørgensen et al.[143] reported that the enantioselective α-amination of β-ketophosphonates **225** with dibenzyl azodicarboxylate, in the presence of a catalyst formed by combination of the chiral bisoxazoline **226** and $Zn(OTf)_2$, afforded the corresponding aminated products **227** in good yield (75–98%) and excellent enantioselectivity (85–95% ee) (Table 11).

Recently, Ruiz et al.[144] reported that the treatment of the bis-lactim ether **228** with LDA in THF at −78 °C, followed by the addition of trisyl-N_3, gave the phosphonates **229** and **230** derived from azidation by a complete retention of the 2,5-trans configuration of the bis-lactim ether, and the phosphonates **231** and **232**, products of the racemization of the bis-lactim **229** at position 2. The mixture of the phosphonates **229**, **230**, **231**, and **232** was obtained in 80% yield and a 7:7:1:1 ratio (Scheme 59).[145]

Table 11
Catalytic enantioselective α-amination of **225**



Entry	R	R′	R″	Yield (%)	ee (%)
1	Ph	Me	Et	85	92
2	2-Naphthyl	Me	Et	93	92
3	Bn	Me	Et	60	95
4	Me	Me	Et	75	85
5	Ph	Allyl	Et	85	98
6	Ph	Me	Me	97	94
7	$-(CH_2)_3-$		Et	98	95
8	$-(CH_2)_4-$		Et	98	94

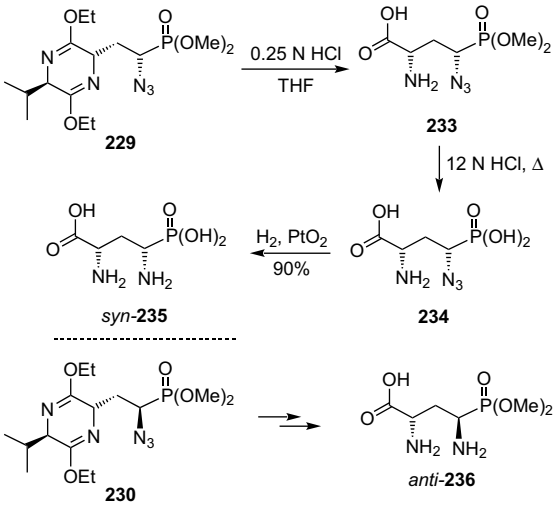


Scheme 59.

Mild acid hydrolysis of diastereoisomerically pure **229** with 0.25 N HCl provided the compound **233**, which, by acid hydrolysis with 12 N HCl at reflux, led to the α-azidophosphonic acid **234**. Finally, catalytic hydrogenation of **234** over PtO_2 gave the α-aminophosphonic acid *syn*-**235** in 90% yield, an AP_4 derivative.[146] In a similar way, **230** was transformed into *anti*-**236** (Scheme 60).

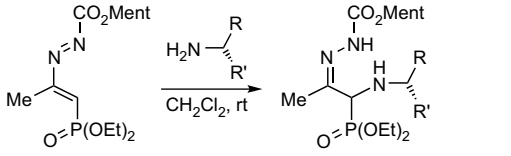
2.3.2. Addition of amines to enaminophosphonates

Palacios et al.[147] reported that the addition of (*R*)-α-MBA (R=Me, R′=Ph) and ethyl (*S*)-valinate (R=CO_2Et, R′=*i*-Pr) to 1,2-diaza-1,3-butadiene **237** afforded the α-aminophosphonates **238** and **239**, respectively, in good yield, but with very low diastereoselectivity (<10% ds) (Scheme 61). Similar results were obtained in the addition of non-chiral amines to **237**.



229 **233** **234** *syn*-**235** **230** *anti*-**236**

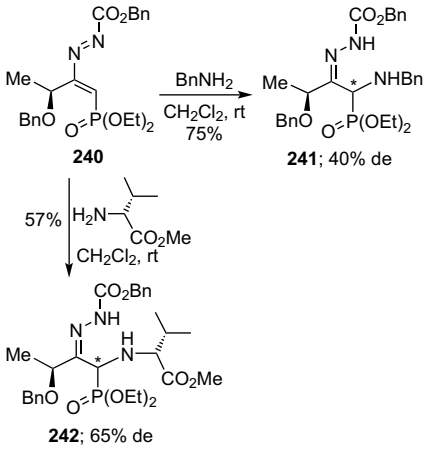
Scheme 60.



237 **238**; R = Me, R' = Ph, 83% **239**; R = CO_2Et, R' = *i*-Pr, 79%

Scheme 61.

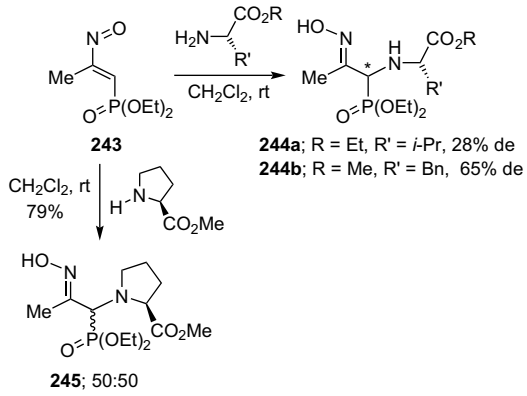
The same authors reported that the Michael addition of benzylamine to 1,2-diaza-1,3-butadiene **240**, derived from L-lactic acid, gave the corresponding α-aminophosphonate **241** in 75% yield and 40% de. In a similar way, addition of (*S*)-valine methyl ester to **240** afforded an unseparable diastereoisomeric mixture **242** in 57% yield and moderate diastereoselectivity (Scheme 62).



240 **241**; 40% de **242**; 65% de

Scheme 62.

Phosphonyl nitrosoalkenes are reactive intermediates as Michael acceptors toward nucleophilic reagents such as ammonia, amines, and enantiomerically pure α-amino esters. For example, addition of L-valine ethyl ester hydrochloride to nitrosoalkene **243** afforded the α-aminophosphonate **244a** as a non-separable diastereoisomeric mixture in 82% yield and 28% de. In a similar way, Michael addition of L-phenylalanine methyl ester hydrochloride to **243** gave the α-aminophosphonate **244b** in 80% yield and 65% de. However, no diastereoselection was observed when L-proline methyl ester hydrochloride was added to **243**, and both diastereoisomers of **245** were obtained as an equimolecular mixture (Scheme 63).[148]



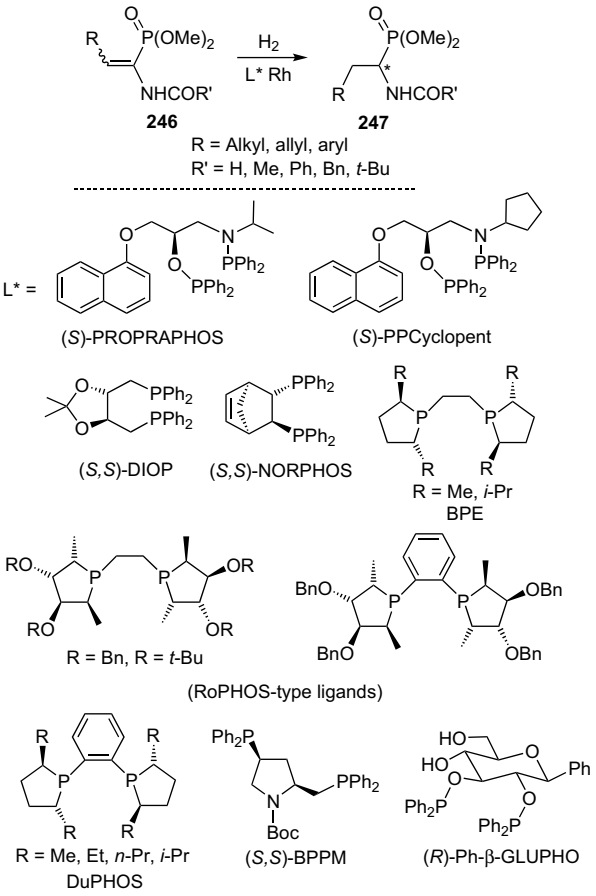
243 **244a**; R = Et, R' = *i*-Pr, 28% de **244b**; R = Me, R' = Bn, 65% de **245**; 50:50

Scheme 63.

2.4. Stereoselective C–H bond formation

2.4.1. Catalytic hydrogenation of dehydroaminophosphonates

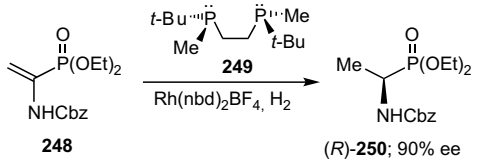
Catalytic asymmetric hydrogenation of dehydroaminophosphonates[149] of the type **246** is another methodology available for the synthesis of optically pure α-aminophosphonic acids and their derivatives. In this context, from 1985 to 1999 several catalysts have been used in the hydrogenation of **246**, obtaining the α-aminophosphonates **247** in good yields and with excellent levels of enantioselectivity (Scheme 64).[150]



246 **247**

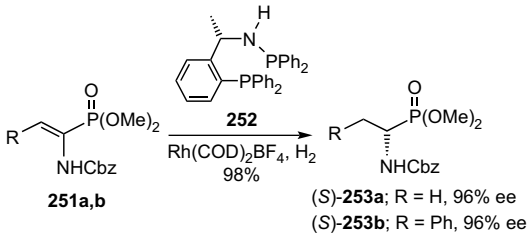
Scheme 64.

In 2004, Imamoto et al.[151] reported that the catalytic hydrogenation of dehydroaminophosphonate **248** in the presence of a rhodium complex and (*R*,*R*)-*t*-BuBisP* **249** gave the (*R*)-α-aminophosphonate **250** in 90% ee (Scheme 65).



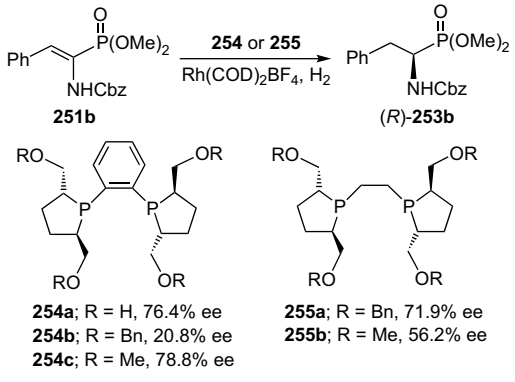
Scheme 65.

Recently, Hu et al.[152] reported that the chiral phosphineaminophosphine (PEAphos) **252** readily obtained from (*S*)-MBA promoted excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dehydroaminophosphonates **251a**,**b**, and the corresponding (*S*)-α-aminophosphonates **253a**,**b** were obtained in excellent yield and enantioselectivity (96% ee) (Scheme 66).



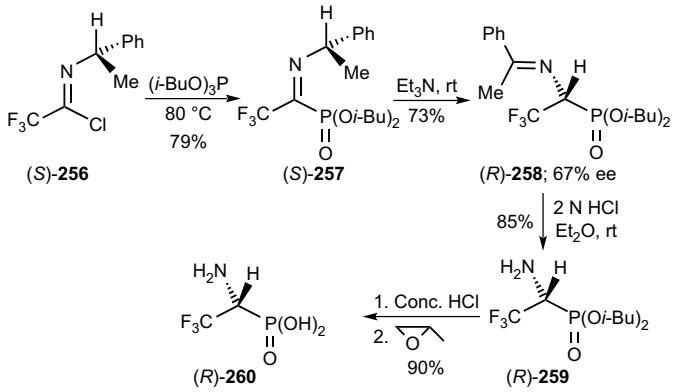
Scheme 66.

On the other hand, asymmetric hydrogenation of dehydroaminophosphonate **251b**, in the presence of a rhodium complex and bis(phospholanes) **254** or BASPHOS **255**, gave the (*R*)-α-aminophosphonate **253b** in moderate enantioselectivity (20.8–78.8% ee) (Scheme 67).[153]



Scheme 67.

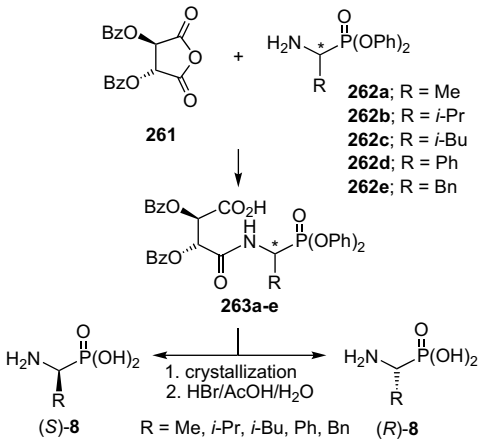
1-Amino-2,2,2-trifluoroethanephosphonic acid (*R*)-**260** has been obtained by a base-catalyzed [1,3]-proton shift reaction of diisobutyl 1-*N*-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **257**.[154] In this context, the reaction of chloroimine (*S*)-**256** with triisobutyl phosphite at 80 °C, gave the (*S*)-α-iminophosphonate **257** in 79% yield, which, by a [1,3]-proton shift induced by triethylamine, afforded the α-aminophosphonate (*R*)-**258** in 73% yield and 67% ee. Acidic hydrolysis of the imine group in (*R*)-**258** with 2 N HCl produced the α-aminophosphonate (*R*)-**259** in 85% yield. Finally, treatment of (*R*)-**259** with concentrated hydrochloric acid, followed by the addition of propylene oxide, afforded the (*R*)-α-aminophosphonic acid **260** in 90% yield (Scheme 68).[155]



Scheme 68.

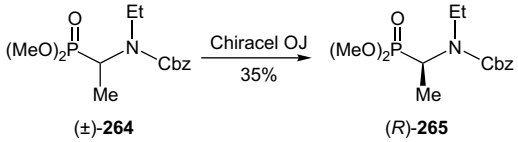
2.5. Resolutions

Optically active α-aminophosphonic acids can also be obtained by resolution. For example, the reaction of dibenzoyl L-tartaric anhydride **261** with diphenyl α-aminophosphonates (±)-**262a**–**e** provided the amides **263a**–**e**. Hydrolysis of diastereoisomerically pure **263a**–**e** obtained by crystallization gave both enantiomers of (*S*)- and (*R*)-α-aminophosphonic acids **8** in high yields (Scheme 69).[156]



Scheme 69.

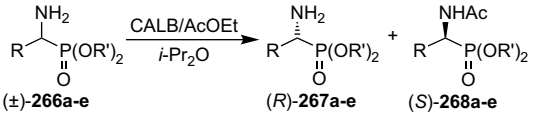
On the other hand, resolution of (±)-**264** on a 500-g scale, using simulated moving-bed chromatography on Chiracel OJ, gave the (*R*)-α-aminophosphonate **265** in 35% yield and 99% ee (Scheme 70).[157]



Scheme 70.

The biocatalytic resolution of racemic molecules has attracted the interest of synthetic chemists for several decades.[158] In this context, Yuan et al.[159] reported that the CALB-catalyzed acylation of (±)-**266a**–**e**, using ethyl acetate as the acetylating reagent, produced the optically enriched (*R*)-**267a**–**e** and (*S*)-**268a**–**e** in good yield and enantioselectivity (Table 12).

Table 12
CALB-catalyzed enantioselective acetylation of (±)-**266a–e**

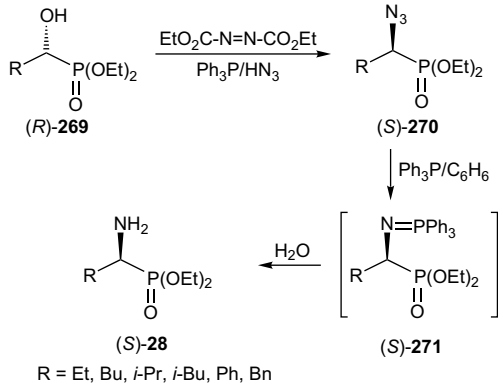


Substrate	R	R′	267		268	
			Yield (%)	ee (%)	Yield (%)	ee (%)
266a	Me	Et	41	99.7	48	90
266b	Me	*n*-Pr	42	90	42	98
266c	Me	*i*-Pr	44	96	43	98
266d	Et	Et	73	18	10	100
266e	CF_3	Et	[a]	—	—	—

[a] No reaction.

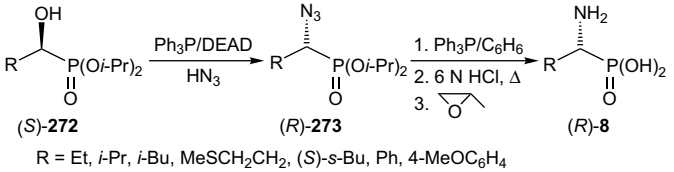
2.6. Chiral pool

The hydroxy group in enantiomerically pure α-hydroxyalkylphosphonates can be replaced by an amino function using the Mitsunobu reaction.[160] For example, treatment of (*R*)-α-hydroxyphosphonates **269** under Mitsunobu conditions, using triphenylphosphine (Ph_3P), diethyl azodicarboxylate (DEAD), and hydrazoic acid, afforded the (*S*)-α-azidophosphonates **270** with complete inversion of configuration.[161] Reduction of the azido group in **270** under Staudinger reaction conditions,[117] with Ph_3P followed by hydrolysis of the iminophosphoranes **271**, gave the (*S*)-α-aminophosphonates **28** in good yield (50–88%) and enantioselectivity (40–82% ee) (Scheme 71).[162]



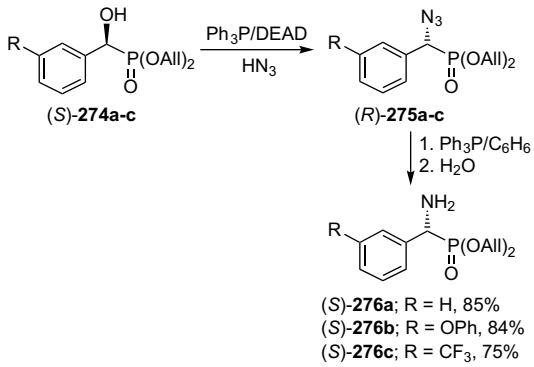
Scheme 71.

In a similar way, treatment of (*S*)-α-hydroxyphosphonates **272** (92–99% ee) with Ph_3P/DEAD/HN_3 gave the (*R*)-α-azidophosphonates **273** with good yield and 68–90% ee, which, by reduction of the azido group with Ph_3P, followed by acidic hydrolysis, led to the (*R*)-α-aminophosphonic acids **8** in 59–85% yield (Scheme 72).[163]



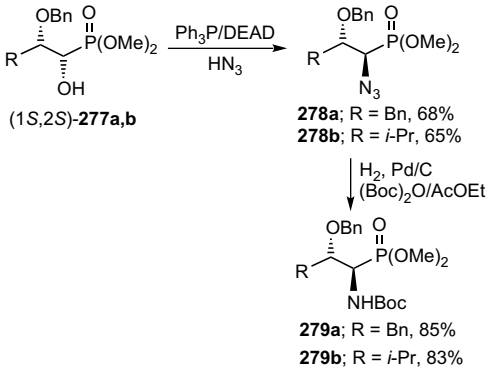
Scheme 72.

On the other hand, treatment of (*S*)-α-hydroxyphosphonates **274a–c** with Ph_3P/DEAD/HN_3 gave the (*R*)-α-azidophosphonates **275a–c** in 88–98% yield, which, by reduction of the azido group with PPh_3, led to the (*R*)-α-aminophosphonates **276a–c** in 75–85% yield (Scheme 73).[164]



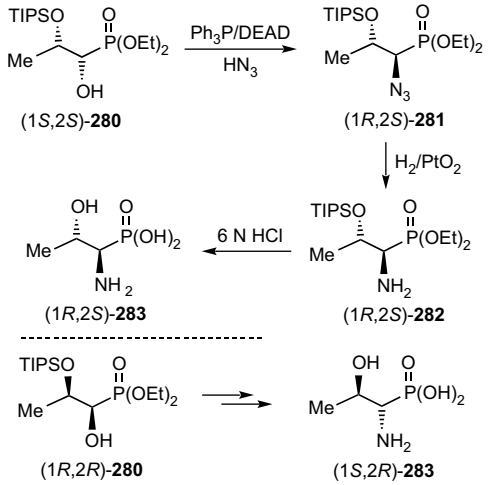
Scheme 73.

α-Amino-β-hydroxyphosphonic acids can be obtained from α,β-dihydroxyphosphonates via Mitsunobu azidation. For example, reaction of **277a,b** with Ph_3P/DEAD/HN_3 afforded the α-azidophosphonates **278a,b** in moderate yield, which, by catalytic hydrogenation over Pd/C, in the presence of $(Boc)_2O$, provided the *N*-Boc-α-aminophosphonates **279a** and **279b** in 85% and 83% yield, respectively (Scheme 74).[165]



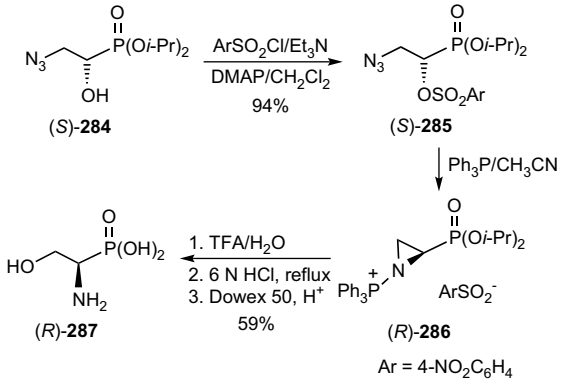
Scheme 74.

In a similar way, treatment of (1*S*,2*S*)-**280** with Ph_3P/DEAD and HN_3 led to α-azidophosphonate **281**, which, by catalytic hydrogenation over PtO_2, followed by acidic hydrolysis of **282**, gave the (1*R*,2*S*)-phosphothreonine **283**. Under identical conditions, (1*R*,2*R*)-**280** was transformed into (1*S*,2*R*)-**283** (Scheme 75).[166]



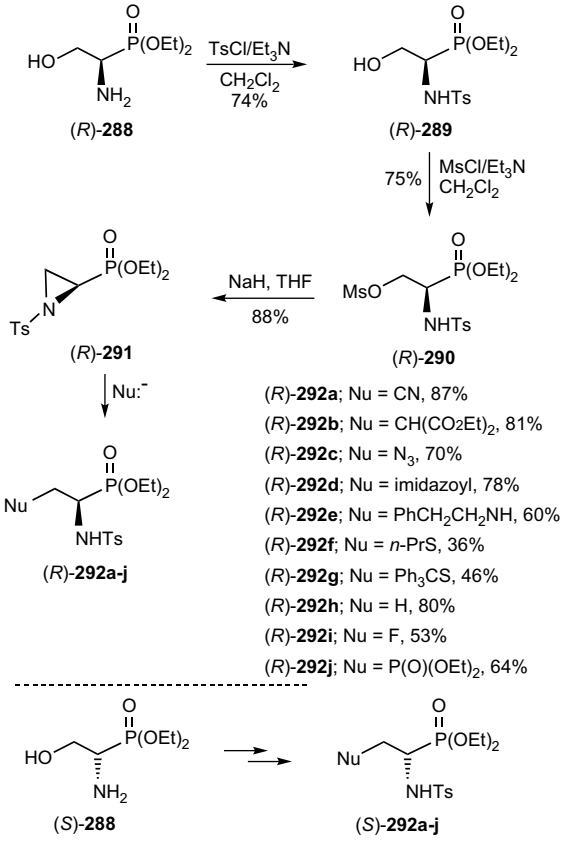
Scheme 75.

On the other hand, reaction of (*S*)-**284** with *p*-nitrobenzenesulfonyl chloride furnished the corresponding nosylate (*S*)-**285** in 94% yield, which, under Staudinger reaction conditions gave the corresponding aziridine (*R*)-**286**. Regioselective opening of the aziridine (*R*)-**286** with TFA, followed by acidic hydrolysis with hydrochloric acid and subsequent ion exchange, afforded the (*R*)-phosphoserine **287** in 59% yield (Scheme 76).[167]



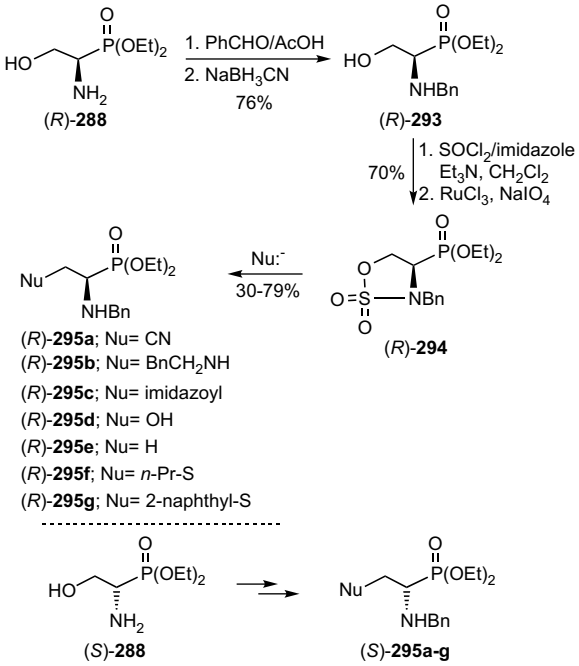
Scheme 76.

Treatment of phosphoserine diethyl ester (*R*)-**288** with tosyl chloride afforded the corresponding *N*-tosylate (*R*)-**289** in 74% yield, which, by reaction with mesyl chloride, afforded the *O*-mesylate derivative (*R*)-**290** in 75% yield. Reaction of (*R*)-**290** with NaH in THF gave the aziridine-2-phosphonate (*R*)-**291** in 88% yield, which, by reaction with several nucleophiles, gave the α-aminophosphonates (*R*)-**292a–j** in 36–87% yield. In a similar way, the α-aminophosphonates (*S*)-**292a–j** were obtained from (*S*)-**288** (Scheme 77).[168]



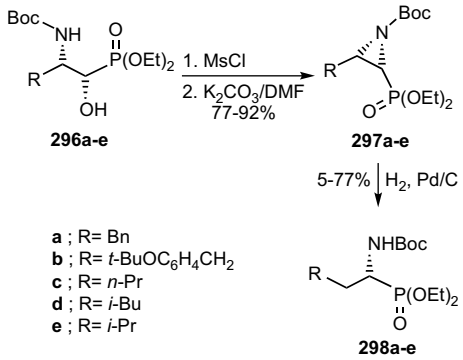
Scheme 77.

On the other hand, reaction of phosphoserinate (*R*)-**288** with benzaldehyde, followed by reduction with sodium cyanoborohydride in acetic acid, afforded the *N*-benzyl aminophosphonate (*R*)-**293** in 76% yield. Treatment of (*R*)-**293** with thionyl chloride and subsequent oxidation with sodium periodate in the presence of ruthenium chloride gave the sulfonamide (*R*)-**294** in 70% yield, which, by reaction with several nucleophiles, provided the α-aminophosphonates (*R*)-**295a–g**. In a similar way, (*S*)-**295a–g** were obtained from (*S*)-**288** (Scheme 78).[169]



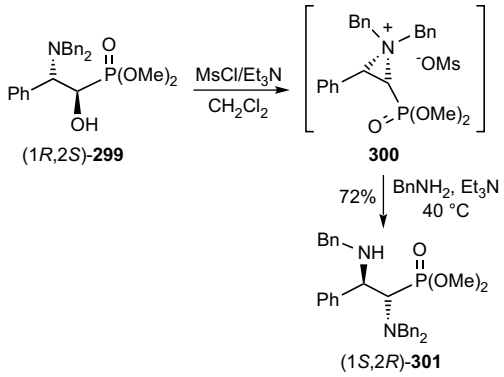
Scheme 78.

Pousset and Larchevêque[170] reported that the catalytic hydrogenation of *N*-Boc-aziridine-2-phosphonates **297a–e**, readily obtained from 3-amino-2-hydoxyphosphonates **296a–e** in 77–92% yield, furnished the *N*-Boc-α-aminophosphonates **298a–e** in moderate yield (5–77%) and high enantioselectivity (Scheme 79).



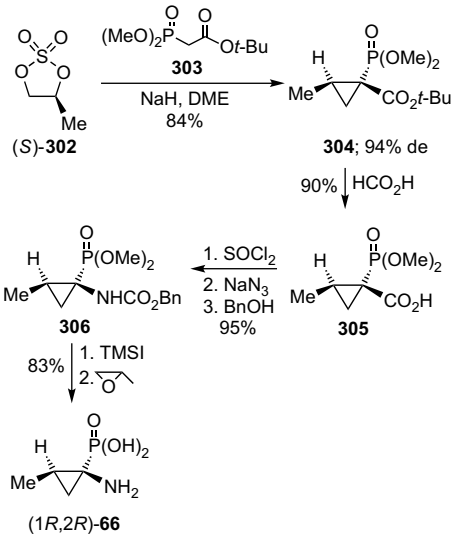
Scheme 79.

On the other hand, treatment of α-hydroxyphosphonate (1*R*,2*S*)-**299** with mesyl chloride in the presence of triethylamine followed by the addition of benzylamine gave the α,β-diaminophosphonate (1*S*,2*R*)-**301** in 72% yield. Transformation of (1*R*,2*S*)-**299** into (1*S*,2*R*)-**301** with inversion of configuration takes place through the participation of the aziridium ion **300** (Scheme 80).[171]



Scheme 80.

Treatment of sulfate (*S*)-**302**, readily obtained from (*S*)-1,2-propanediol, with dimethyl *tert*-butoxycarbonylmethylphosphonate **303** and NaH gave the cyclopropane derivative **304** in 84% yield and 94% de. Acidic hydrolysis of **304** with formic acid afforded the carboxylic acid derivative **305** in 90% yield, which, by treatment with thionyl chloride, followed by Curtius rearrangement using sodium azide and subsequent addition of benzyl alcohol, furnished the *N*-protected aminophosphonate **306** in 95% yield. Finally, hydrolysis of **306** with TMSI followed by treatment with propylene oxide led to the enantiomerically pure (1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid **66** in 83% yield (Scheme 81).[172] The aminophosphonic acid **66** is an analogue of (1*S*,2*R*)-allo-norcoronamic acid.[173]



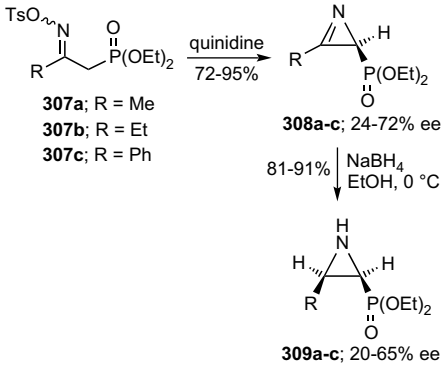
Scheme 81.

2.7. Stereoselective synthesis of azaheterocyclic phosphonic acids and derivatives

Azaheterocyclic phosphonates are considered to be one of the most biologically important classes of heterocyclic compounds. In this context, in 2004, Stevens et al.[174] published a review on the synthetic methods for azaheterocyclic phosphonates and their biological activity and, recently, De Kimpe et al.[175] published another review on the synthesis and reactivity of *C*-heteroatom-substituted aziridines, including *C*-phosphorus-substituted aziridines. We will now describe here only some examples and an update of the stereoselective synthesis of azaheterocyclic phosphonic acids and their derivatives.

2.7.1. Aziridin-2-ylphosphonic acids and derivatives

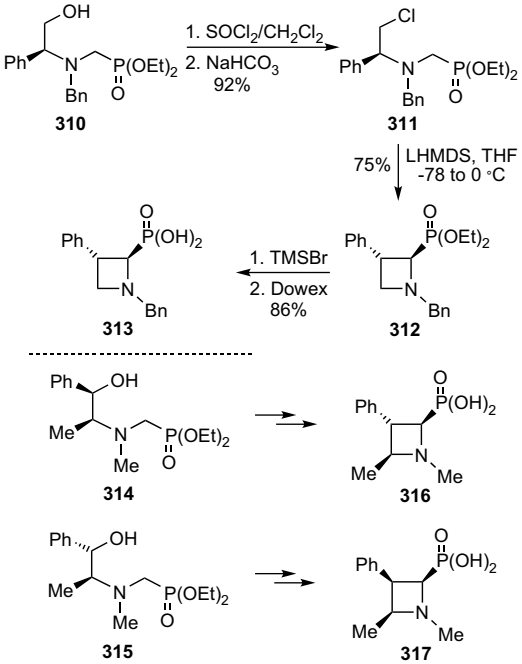
Palacios et al.[176,177] reported that the treatment of *O*-tosyl oximes **307a–c** with quinidine afforded the 2*H*-azirine-2-phosphonates **308a–c** in good yield (72–95%) and moderate enantioselectivity (24–72% ee). When (−)-sparteine, hydroquinidine, or quinine was used as a base, **308a–c** were obtained with low enantioselectivity. Reduction of **308a–c** with $NaBH_4$ in ethanol gave the 2-phosphorylated *cis*-aziridines **309a–c** in 81–91% yield and with 20–65% ee (Scheme 82).



Scheme 82.

2.7.2. Azetidin-2-ylphosphonic acids and derivatives

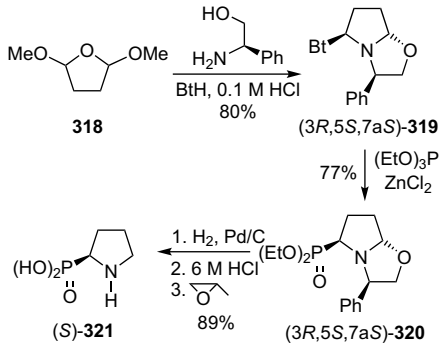
The stereoselective synthesis of azetidin-2-ylphosphonates has been scarcely explored. The first asymmetric synthesis of azetidine-2-phosphonates of the type **313**, **316**, and **317** was reported by Couty et al.[178] In this context, treatment of the aminophosphonate **310** derived from (*S*)-*N*-benzyl phenylglycinol,[179] with thionyl chloride in dichloromethane, followed by the addition of $NaHCO_3$ gave the chloro derivative **311** in 92% yield. Reaction of **311** with LHMDS in THF afforded only the 1,3-*trans* azetidine **312** in 75% yield, which, by hydrolysis of the phosphonate moiety with TMSBr, followed by purification by ion-exchange chromatography, led to azetidin-2-ylphosphonic acid **313** in 86% yield. In a similar way, aminophosphonates **314** and **315** derived from (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-pseudo-ephedrine, respectively, afforded the aminophosphonic acids **316** and **317** in good yield (Scheme 83).



Scheme 83.

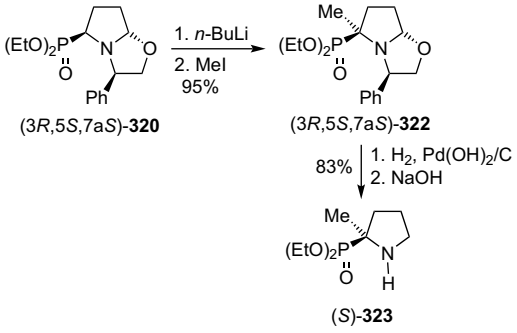
2.7.3. Pyrrolidin-2-ylphosphonic acids and derivatives

Reaction of 2,5-dimethoxytetrahydrofuran **318** with (*R*)-phenylglycinol and benzotriazole (BtH), via a double Robinson–Schopf condensation,[180] afforded the bicyclic derivative (3*R*,5*S*,7a*S*)-**319** in 80% yield, which, by an Michaelis–Arbuzov reaction with triethyl phosphite in the presence of $ZnCl_2$, gave the corresponding phosphonate (3*R*,5*S*,7a*S*)-**320** as a single diastereoisomer in 77% yield. Hydrogenolysis of **320**, followed by acidic hydrolysis of the phosphonate moiety with 6 M HCl and subsequent treatment with propylene oxide led to (*S*)-phosphoproline **321** in 89% yield (Scheme 84).[181]



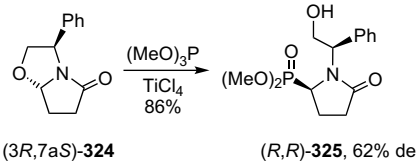
Scheme 84.

On the other hand, treatment of (3*R*,5*S*,7a*S*)-**320** with *n*-BuLi, followed by the addition of MeI, afforded the methylated product (3*R*,5*S*,7a*S*)-**322** in 95% yield, high diastereoselectivity, and with retention of configuration. Hydrogenolysis of **322** over Pd/H_2 gave the quaternary phosphoproline diethyl ester (*S*)-**323** in 83% yield (Scheme 85).[182]



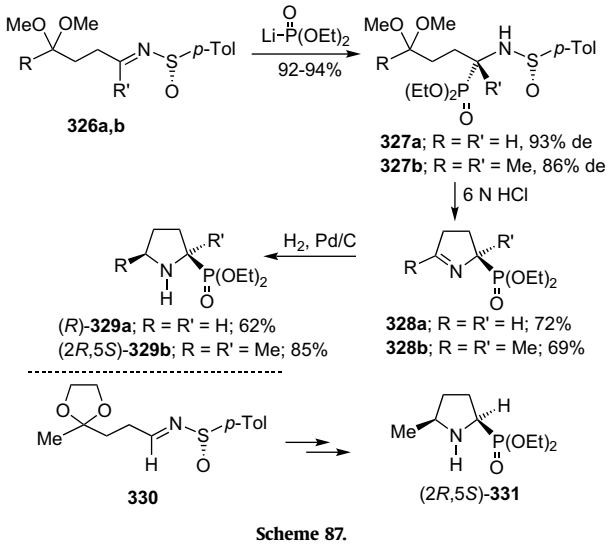
Scheme 85.

Addition of trimethyl phosphite to the bicyclic lactam **324**, readily obtained from (*R*)-phenylglycinol, in the presence of $TiCl_4$ gave the phosphonylated pyrrolidinone **325** in 86% yield and 62% de (Scheme 86).[183]



Scheme 86.

Treatment of the chiral sulfinyl imines **326a**,**b** with lithium diethyl phosphite gave the α-aminophosphonates **327a**,**b** in good yield and moderate diastereoselectivity. Cleavage of the sulfinyl group and hydrolysis of the acetal gave the aminocarbonyl derivative, which cyclized to afford the iminophosphonates **328a**,**b**. Finally, catalytic hydrogenation of **328a**,**b** led to the cyclic α-aminophosphonates **329a**,**b**. In a similar way, the chiral sulfinyl mine **330** furnished the α-aminophosphonate (2*R*,5*S*)-**331** (Scheme 87).[184]



Scheme 87.

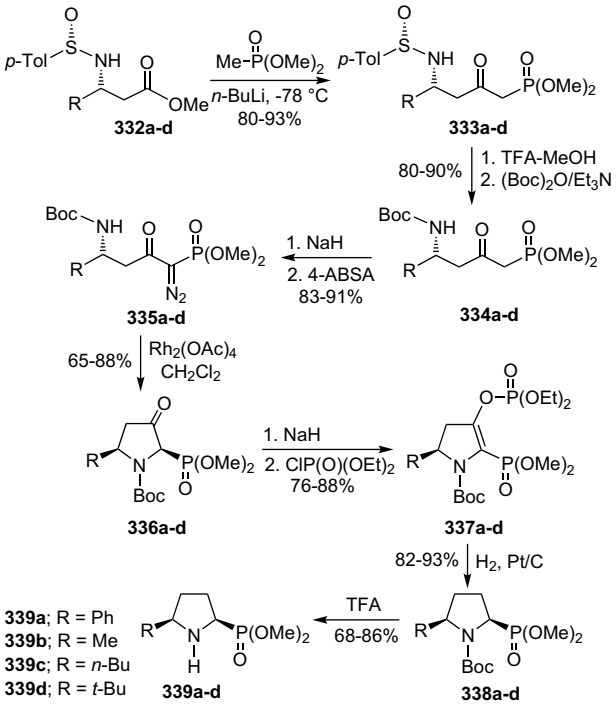
Davies et al.[185] reported the synthesis of *cis*-5-substituted pyrrolidine-2-phosphonates **339a**–**d** using metal/carbenoid NH insertion. In this context, reaction of β-amino esters **332a**–**d** with lithium dimethyl methylphosphonate gave the corresponding δ-amino-β-ketophosphonates **333a**–**d**, which, by treatment with TFA, followed by reaction with $(Boc)_2O$, afforded the derivatives **334a**–**d** in 80–90% yield. Reaction of **334a**–**d** with NaH and 4-acetamidobenzenesulfonyl azide (4-ABSA) furnished the diazo derivatives **335a**–**d** in excellent yield (83–91%), which, by treatment with $Rh_2(OAc)_4$, led to the 3-oxo-pyrrolidine phosphonates **336a**–**d**. Removal of the 3-oxo group in **336a**–**d** by treatment with NaH, followed by the addition of diethyl chlorophosphonate, and subsequent hydrogenation of **337a**–**d** provided the cyclic phosphonates **338a**–**d** in good yield. Finally, cleavage of the Boc protective group in **338a**–**d** with TFA afforded the *cis*-5-substituted pyrrolidine-2-phosphonates **339a**–**d** in 68–86% yield (Scheme 88).[186]

Reaction of (2*R*,5*R*)-**336a** with NaH, followed by the addition of allyl bromide[187] in the presence of 18-crown-6, gave the quaternary phosphonate (2*R*,5*R*)-**340** in 35% yield, which, by treatment with TFA, afforded the pyrrolidine phosphonate (2*R*,5*R*)-**341** in 76% yield as a single diastereoisomer, the product derived from retention of configuration. Catalytic hydrogenation of **341** gave the acyclic α-amino-β-ketophosphonate (*R*)-**342** in 95% yield (Scheme 89).[188]

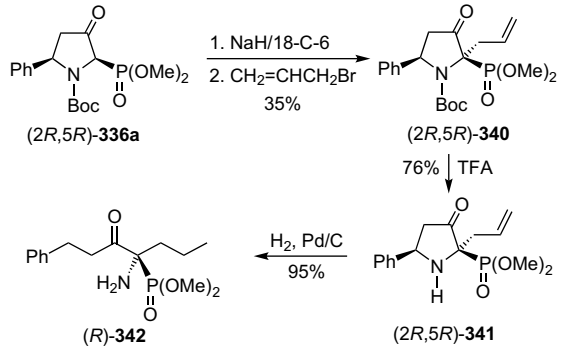
Reduction of L-pyroglutamic acid derivative **343** with super hydride in THF at −78 °C, followed by acetylation and subsequent treatment with trimethyl phosphite, in the presence of $BF_3 \cdot OEt_2$, gave the cyclic phosphonates **344** and **345** in moderate to good yield (45–80%) and with diastereoselectivities from 1:1.5 to 1:1.9 (Scheme 90).[189]

Decarboxylation–phosphorylation reactions of α-amino acids afford the α-aminophosphonates in good yield.[190] For example, treatment of the (4*R*)-acetoxyproline derivative **346** with $PhI(OAc)_2/I_2$ under sunlight, followed by reaction with $(MeO)_3P$ in the presence of $BF_3 \cdot OEt_2$, afforded the α-aminophosphonate **347** and its epimer **348** in 64% and 15% yield, respectively (Scheme 91).[191]

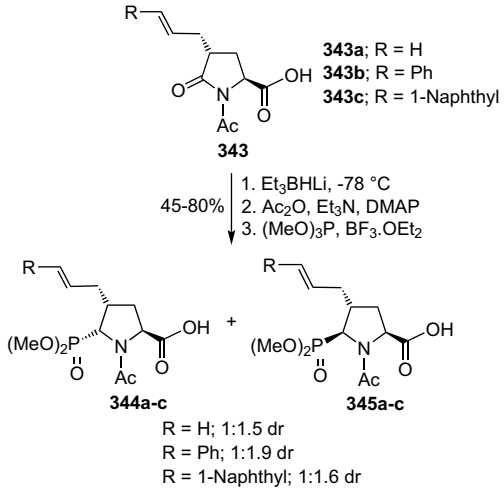
A better result was obtained in the oxidative decarboxylation of **349**. In this context, anodic oxidation of **349** afforded a 1:1 mixture



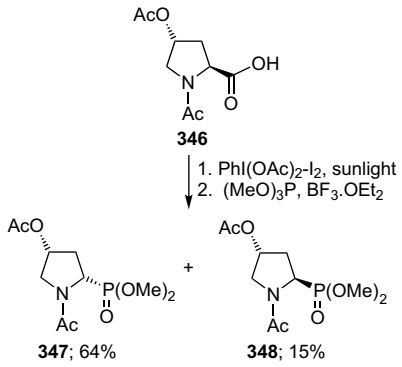
Scheme 88.



Scheme 89.

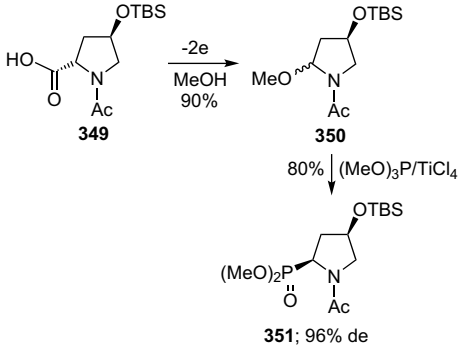


Scheme 90.



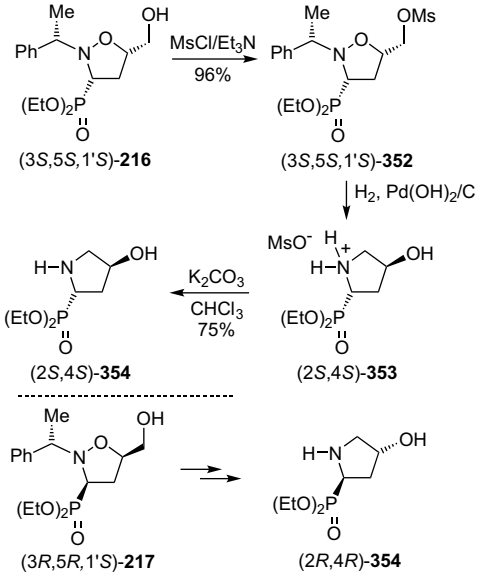
Scheme 91.

of **350** in 90% yield, which, by treatment with trimethyl phosphite in the presence of $TiCl_4$, gave the cyclic phosphonate **351** in 80% yield and 96% de (Scheme 92).[192]



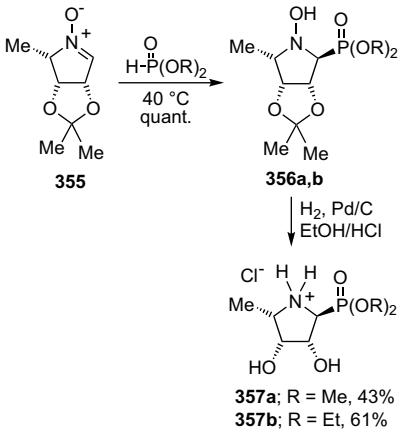
Scheme 92.

On the other hand, reaction of (3*S*,5*S*,1′*S*)-**216** with mesyl chloride in the presence of triethylamine gave the mesylated derivative (3*S*,5*S*,1′*S*)-**352** in 96% yield, which, by hydrogenolysis, followed by treatment of the product obtained (**353**) with K_2CO_3, furnished (2*S*,4*S*)-**354** in 75% yield. In a similar way, reaction of (3*R*,5*R*,1′*S*)-**217** gave (2*R*,4*R*)-**354** (Scheme 93).[137a]



Scheme 93.

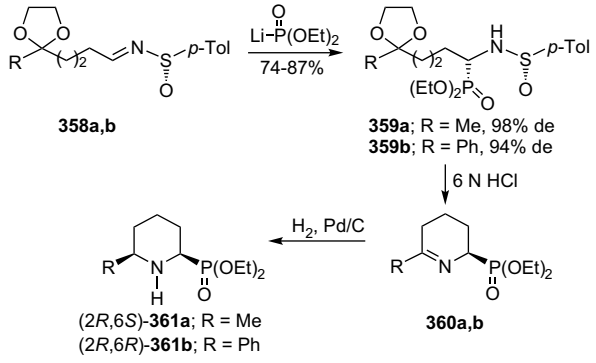
Addition of dimethyl or diethyl phosphite to the nitrone **355** at 40 °C gave the corresponding *N*-hydroxy phosphonates **356a**,**b** in quantitative yield. *O*,*N*-Bis-deprotection in **356a**,**b** by hydrogenolysis over Pd/C in EtOH and aqueous 1 N HCl afforded the pyrrolidine phosphonates **357a**,**b** as the hydrochlorides in 43% and 61% yield, respectively (Scheme 94).[193]



Scheme 94.

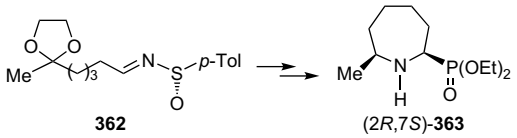
2.7.4. Piperidin-2-ylphosphonic acids and derivatives

Davis et al.[184] described the stereoselective synthesis of piperidin-2-yl-phosphonates **361a**,**b** from the chiral sulfinyl imines **358a**,**b**. In this context, reaction of the imines **358a**,**b** with lithium diethyl phosphite afforded the α-aminophosphonates **359a**,**b** in good yield and excellent diastereoselectivity. Cleavage of the sulfinyl group and acidic hydrolysis of the ketal in **359a**,**b** gave the aminocarbonyl derivative, which, by cyclization, afforded the iminophosphonates **360a**,**b**. Finally, catalytic hydrogenation of **360a**,**b** led to the cyclic α-aminophosphonates (2*R*,6*S*)-**361a** and (2*R*,6*R*)-**361b** (Scheme 95).[194]



Scheme 95.

In a similar way, the cyclic α-aminophosphonate (2*R*,7*S*)-**363** was obtained in moderate yield and diastereoselectivity from the chiral sulfinyl imine **362** (Scheme 96).[194]



Scheme 96.

3. Concluding remarks

In spite of the recognized relevance of the α-aminophosphonic acids, it is obvious that there is a very important gap between the possibilities that these compounds offer in relation to their corresponding counterparts, the α-amino acids. Nevertheless, during the last few years, these α-aminophosphonic acids have attracted considerable attention and, in this way, numerous papers have been published on their stereoselective synthesis. The authors of this report have covered all advances related to the synthesis of these important compounds and, although there is a long way to go, many of these procedures are already competitive and can be applied to the synthesis of these compounds in an enantiomerically pure form and on a multigram scale. The authors are convinced that all of these efforts will contribute to future advances in the understanding of these important compounds.

Acknowledgements

This work was carried out with the financial support of CONACYT-MEXICO (Project 62271) and financial support from the Ministerio de Educación y Ciencia–FEDER (project CTQ2007-62245) and Gobierno de Aragón (group E40 and project MI041/2007) is gratefully acknowledged. This project has been funded as whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under contract number N01-CO-12400. The content of this publication does not necessarily reflect the view or the policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. We thank Dr. Ana Isabel Jiménez and Dr. Victoria Labastida for their valuable help.

References and notes

1. (a) Horiguchi, M.; Kandatsu, M. *Nature* **1959**, *184*, 901–902; (b) Bayer, E.; Gugel, K. H.; Hägele, K.; Hagenmaier, H.; Jessipow, S.; Konig, W. A.; Zähner, H. *Helv. Chim. Acta* **1972**, *55*, 224–239; (c) Kamiya, T.; Hemmi, K.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1980**, *21*, 95–98.
2. (a) Vassiliou, S.; Xeilari, M.; Yiotakis, A.; Germbecka, J.; Pawełczak, M.; Kafarski, P.; Mucha, A. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 3187–3200; (b) El Kaïm, L.; Grimaud, L.; Hadrot, S. *Tetrahedron Lett.* **2006**, *47*, 3945–3947; (c) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *Tetrahedron Lett.* **2001**, *42*, 4491–4494; (d) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, UK, 2000; (e) De Lombaert, S.; Blanchard, L.; Stamfort, L. B.; Tan, J.; Wallace, E. M.; Satoh, Y.; Fitt, J.; Hoyer, D.; Simonsbergen, D.; Moliterni, J.; Marcopoulos, N.; Savage, P.; Chou, M.; Trapani, A. J.; Jeng, A. Y. *J. Med. Chem.* **2000**, *43*, 488–504; (f) De Lombaert, S.; Stamfort, L. B.; Blanchard, L.; Tan, J.; Hoyer, D.; Diefenbacher, C. G.; Wei, D.; Wallace, E. M.; Moskal, M. A.; Savage, P.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1059–1064; (g) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little, D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323–1326; (h) For comprehensive review, see: Kafarsky, P.; Lejczak, B. *Phosphorous, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215; (i) McLeod, D. A.; Brinkworth, R. I.; Ashley, J. A.; Janda, K. D.; Wirsching, P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 653–658.
3. (a) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237; (b) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652–1661; (c) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Leo, G. C.; Franz, J. E. *J. Org. Chem.* **1988**, *53*, 4069–4074; (d) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603–1609.
4. (a) Emgenbroich, M.; Wulff, G. *Chem.—Eur. J.* **2003**, *9*, 4106–4117; (b) Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han, C. Y.; Lin, K.-C.; Pajengraa, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphorous, Sulfur Silicon Relat. Elem.* **1993**, *76*, 375–378.
5. (a) Senten, K.; Daniëls, L.; Var der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Comb. Chem.* **2003**, *5*, 336–344; (b) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625–6628.
6. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587–5590.
7. Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996**, *4*, 1693–1701.

8. (a) Burke, T. R., Jr.; Barchi, J. J., Jr.; George, C.; Wolf, G.; Shoelson, S. E.; Yan, X. *J. Med. Chem.* **1995**, *38*, 1386–1396; (b) Bruke, T. R., Jr.; Kole, H. K.; Roller, P. P. *Biochem. Biophys. Res. Commun.* **1994**, *204*, 129–134; (c) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29–40.
9. (a) See Ref. 8c; (b) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Haga, S.; Sugi, H.; Tanigawa, K.; Suzuki, Y.; Fukawa, K.; Irino, O.; Saita, O.; Yamabe, S. *Heterocycles* **1981**, *16*, 1205–1242; (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845–2853; (d) Lejczak, B.; Kafarski, P.; Sztajer, H.; Mastalerz, P. *J. Med. Chem.* **1986**, *29*, 2212–2217; (e) Okada, Y.; Iguchi, S.; Mimura, M.; Yagyu, M. *Chem. Pharm. Bull.* **1980**, *28*, 1320–1323.
10. (a) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641–2655; (b) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123–8129; (c) Liu, W.; Rogers, C. J.; Fisher, A. J.; Toney, M. D. *Biochemistry* **2002**, *41*, 12320–12328; (d) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031–1033; (e) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141–1143; (f) Kim, K. S.; Hurh, E. Y.; Youn, J. N.; Park, J. I. *J. Org. Chem.* **1999**, *64*, 9272–9274; (g) Bird, J.; De Melo, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158–169; (h) Pratt, R. F. *Science* **1989**, *246*, 917–919; (i) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 677–683; (j) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 684–695; (k) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 696–705; (l) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56–58.
11. Huang, J.; Chen, R. *Heteroat. Chem.* **2000**, *11*, 480–492.
12. (a) Maier, L.; Diel, P. J. *Phosphorous, Sulfur Silicon Relat. Elem.* **1994**, *90*, 259–279; (b) Maier, L.; Diel, P. J. *Phosphorous, Sulfur Silicon Relat. Elem.* **1991**, *57*, 57–64.
13. (a) Yager, K. M.; Taylor, C. M.; Smith, A. B., III. *J. Am. Chem. Soc.* **1994**, *116*, 9377–9378; (b) Natchev, I. A. *Liebigs Ann. Chem.* **1988**, 861–867.
14. Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierré, A. *J. Med. Chem.* **1991**, *34*, 1998–2003.
15. Smith, A. B., III; Taylor, C. M.; Bencovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 6853–6856.
16. (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785–2798; (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers (Pept. Sci.)* **2001**, *60*, 396–419; (c) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers (Pept. Sci.)* **1997**, *43*, 219–266; (d) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; (e) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267.
17. Jagodic, V.; Herak, M. J. *J. Inorg. Nucl. Chem.* **1970**, *32*, 1323–1332.
18. Bligh, S. W. A.; Choi, N.; Green, D. St. C.; Hudson, H. R.; McGrath, C. M.; McPartlin, M.; Pianka, M. *Polyhedron* **1993**, *12*, 2887–2890 and references therein.
19. (a) Bulman, R. A. In *Trace Metals and Fluoride in Bones and Teeth*; Priest, N. O., van de Vyver, F. L., Eds.; CRC: Boca Raton, FL, 1990; p 271; (b) Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
20. (a) Drag, M.; Pawelczak, M.; Kafarski, P. *Chirality* **2003**, *15*, S104–S107; (b) See Ref. 9c; (c) See Ref. 10k.
21. (a) Stamper, C.; Bennett, B.; Edwards, T.; Holz, R. C.; Ringe, D.; Petsko, G. *Biochemistry* **2001**, *40*, 7035–7046; (b) Kafarzki, P.; Lejczak, B.; Szewczyk, J. *Can. J. Chem.* **1983**, *61*, 2425–2430.
22. (a) Solodenko, V. A.; Kukhar, V. P. *Tetrahedron Lett.* **1989**, *32*, 66–75; (b) Polyak, M. S. *Antibiot. Med. Biotekhnol.* **1987**, *32*, 66–75.
23. (a) Uziel, J.; Genêt, J. P. *Russ. J. Org. Chem.* **1997**, *33*, 1521–1542; (b) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorous, Sulfur Silicon Relat. Elem.* **1994**, *92*, 239–264; (c) See Ref. 2a.
24. (a) Pudovik, A. N. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865–869; (b) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868–3935.
25. (a) Gilmore, W. F.; McBride, H. A. *J. Am. Chem. Soc.* **1972**, *94* 4361–4361; (b) For the addition of the sodium salt of diethyl phosphite to imines, see: Failla, S.; Finocchiaro, P.; Hägele, G.; Kalchenko, V. I. *Phosphorous, Sulfur Silicon Relat. Elem.* **1997**, *128*, 63–77.
26. The diastereosiomeric ratio of this reaction was determined by Glowiak, T.; Sawka-Dobrowolska, W.; Kowalik, J.; Mastalerz, P.; Soroka, M.; Zon, J. *Tetrahedron Lett.* **1977**, *18*, 3965–3968.
27. See Ref. 15.
28. Cherenok, S.; Vovk, A.; Muravyova, I.; Shivanyuk, A.; Kukhar, V.; Lipkowski, J.; Kalchenko, V. *Org. Lett.* **2006**, *8*, 549–552.
29. Tongcharoensirikul, P.; Suarez, A. I.; Voelker, T.; Thompson, C. M. *J. Org. Chem.* **2004**, *69*, 2322–2326.
30. Li, S.; Wang, G.; Li, Y.; Yuan, C. Y. *Acta Chim. Sinica* **1993**, *51*, 1195–1202.
31. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860; (b) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017; (c) Kraus, G. A.; Jeon, I. *Org. Lett.* **2006**, *8*, 5315–5316.
32. Szabó, A.; Jászay, Z. M.; Hegedűs, L.; Tőke, L.; Petneházy, I. *Tetrahedron Lett.* **2003**, *44*, 4603–4606.
33. For the application of phosphinic acids in biochemistry, biology, and medicine, see: Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629–647.
34. (a) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888; (b) See Ref. 12a.
35. Alonso, E.; Alonso, E.; Solís, A.; Del Pozo, C. *Synlett* **2000**, 698–700.
36. Smith, A. B., III; Yager, K. M.; Phillips, B. W.; Taylor, C. M. *Org. Synth.* **1998**, *75*, 19–29.
37. Neither sodium nor potassium salt of diethyl phosphite prepared by treatment of diethyl phosphite with NaHMDS or KHMDS in THF gave any detectable α-aminophosphonates (*R*,*R*)-**25** and (*S*,*R*)-**26** even after several days at rt.
38. Dimukhametov, M. N.; Bajandina, E. V.; Davydova, E. Y.; Litvinov, I. A.; Gubaidullin, A. T.; Dobrynin, A. B.; Zyablikova, T. A.; Alfonsov, V. A. *Heteroat. Chem.* **2003**, *14*, 56–61.
39. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.
40. Shang, Z.-Q.; Chen, R.-Y.; Huang, Y. *Heteroat. Chem.* **2007**, *18*, 230–235.
41. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229–6232.
42. (a) Ordoñez, M.; Guerrero-de la Rosa, V.; Labastida, V.; Llera, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2675–2686; (b) Han, Z.; Krishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Sennayake, C. H. *Org. Lett.* **2002**, *4*, 4025–4028; (c) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705; (d) *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoseletive Synthesis*; Mikolajczyk, M., Drabowicz, J., Kielbasinski, P., Eds.; CRC: New York, NY, 1997; (e) *Organosulfur Chemistry: Synthetic and Stereochemical Aspects*; Page, P., Ed.; Academic: London, 1998; Vol. 2; (f) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899–1930.
43. (a) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532–7533; (b) Lefebvre, I. M.; Evans, S. A., Jr. *Phosphorous, Sulfur Silicon Relat. Elem.* **1999**, *144–146*, 397–400.
44. For the synthesis of chiral sulfinimines, see: Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555–2563 and references therein.
45. Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757–1760.
46. (a) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991–3994; (b) Mikolajczyk, M. *J. Organomet. Chem.* **2005**, *690*, 2488–2496.
47. Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2571–2576; (c) For diastereoselective addition of phosphite anions to enantipure 2-aziridine-sulfinimines, see: Li, B. F.; Zhang, M.-J.; Hou, Z.-X.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 2902–2906.
48. (a) Biasone, A.; Tortorella, P.; Campestre, C.; Agamennone, M.; Preziuso, S.; Chiappini, M.; Nuti, E.; Carelli, P.; Rossello, A.; Mazza, F.; Gallina, C. *Bioorg. Med. Chem.* **2007**, *15*, 791–799; (b) Pochetti, G.; Gavuzzo, E.; Campestre, C.; Agamennone, M.; Tortorella, P.; Consalvi, V.; Gallina, C.; Hiller, O.; Tschesche, H.; Mazza, F. *J. Med. Chem.* **2006**, *49*, 923–931.
49. Capozzi, M. A.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933–5936.
50. Chen, Q.; Yuan, C. *Synthesis* **2007**, 3779–3786.
51. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.
52. Addition of dimethyl phosphite to the *N*-*tert*-butylsulfinyl aldimines (*S*)-**45a–g** in the presence the other bases as LHMDS, CaH_2, Et_3N, KF, CsF, Li_2CO_3, and Na_2CO_3 gave the phosphonates (S_S,R_C)-**46a–g** with low diastereoselectivity.
53. For the synthesis of α,α-disubstituted amino acids, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; (d) Alias, M.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapena, Y. *Tetrahedron* **1998**, *54*, 14963–14974; (e) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220–8225.
54. See, for example: (a) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918–5924; (b) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790–791; (c) Roos, E. L.; López, M. C.; Brook, M. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1993**, *58*, 3259–3268; (d) Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704–717; (e) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245–7248; (f) Nájera, C.; Abellán, T.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, *15*, 2809–2820; (g) Belokon, Y. N.; Fuentes, J.; North, M.; Steed, J. W. *Tetrahedron* **2004**, *60*, 3191–3204.
55. (a) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704–8708; (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403–1406; (c) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50–56.
56. Addition of bis(*N*,*N*-diethylamino)phosphite to **48b** afforded the α-aminophosphonate with opposite configuration; however, this compound was unstable under hydrolysis conditions, and decomposition occurred.
57. Reaction of (*S*)-*N*-*tert*-butylsulfinyl or (*S*)-2,4,6-trimethyl-phenylsulfinyl imines with the anion of **52** gave directly the corresponding aziridines in excellent diastereoselectivity.
58. (a) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249–252; (b) Kim, D. Y.; Suh, K. H.; Choi, S.; Mang, J. Y.; Chang, S. K. *Synth. Commun.* **2000**, *30*, 87–95; (c) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345–6352; (d) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410–2419; (e) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894–6898.
59. For the synthesis of enantiomerically pure α-aminophosphonates from aziridines, see: Hanessian, S.; Bennani, Y. L.; Herve, Y. *Synlett* **1993**, 35–36.
60. Davies, F. A.; McCoull, W.; Titus, D. D. *Org. Lett.* **1999**, *1*, 1053–1055.
61. Kabachnik, M. I.; Medved, T. Y. *Dokl. Akad. Nauk SSSR* **1952**, 689–691.
62. For the recent synthesis of non-chiral α-aminophosphonates via one-pot three-component reaction, see: (a) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263–1270; (b) Kaboudin, B.; Jafari, E. *Synthesis* **2007**, 1823–1826; (c) Bhattacharya, A. K.; Kaur, T. *Synthesis* **2007**, 745–748; (d) Prasad, G. S.; Krishna, J. R.; Manjunath, M.; Reddy, O. V. S.; Krishnaiah, M.; Reddy, C. S.; Puranik, V. G. *Arkivoc* **2007**, *xiii*, 133–141; (e) Kaboudin, B.; Moradi, K.; Sardarian, A. R. *Arkivoc* **2007**, *xiii*, 210–217; (f) Kasthuraiah, M.; Kumar, K. A.; Reddy, C. S.; Reddy,

C. D. *Heteroat. Chem.* **2007**, *18*, 2–8; (g) Hua, F.; Meijuan, F.; Xiaoxia, L.; Guo, T.; Yufen, Z. *Heteroat. Chem.* **2007**, *18*, 9–15; (h) Wu, J.; Sun, W.; Xia, H.-G.; Sun, X. *Org. Biomol. Chem.* **2006**, *4*, 1663–1666; (i) Mu, X. J.; Lei, M.-Y.; Zou, J.-P.; Zhang, W. *Tetrahedron Lett.* **2006**, *47*, 1125–1127; (j) Kudrimoti, S.; Bommena, V. R. *Tetrahedron Lett.* **2005**, *46*, 1209–1210; (k) Zahouily, M.; Elmakssoudi, A.; Mezdar, A.; Rayadh, A.; Sebti, S. *J. Chem. Res.* **2005**, 324–327; (l) Reddy, K. R.; Reddy, K. S.; Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Reddy, V. V. N. *Chem. Lett.* **2005**, *34*, 444–445; (m) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synthesis* **2005**, 2606–2608; (n) Kabachnik, M. M.; Zobnina, E. V.; Beletskaya, I. P. *Synlett* **2005**, 1393–1396; (o) Van der Veken, P.; El Sayed, I.; Joossens, J.; Stevens, C. V.; Augustyns, K.; Haemers, A. *Synthesis* **2005**, 634–638; (p) Zhan, Z.-P.; Yang, R.-F.; Li, J.-P. *Chem. Lett.* **2005**, *34*, 1042–1043; (q) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989–2991.
63. Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 6729–6732.
64. Saidi, M. R.; Azizi, N. *Synlett* **2002**, 1347–1349.
65. Laschat, S.; Kunz, H. *Synthesis* **1992**, 90–95.
66. Zon, J. *Pol. J. Chem.* **1981**, *55*, 643–646.
67. Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125–4128.
68. See Ref. 10e.
69. (a) Fadel, A.; Canet, J.-L.; Salaün, J. *Synlett* **1990**, 89–91; (b) Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305–320.
70. (a) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153–2159; (b) For the reaction of (±)-**62**, see: Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267–2276.
71. Fadel, A.; Tesson, N. *Tetrahedron: Asymmetry* **2000**, *11*, 2023–2031.
72. Louaisil, N.; Rabasso, N.; Fadel, A. *Synthesis* **2007**, 289–293.
73. For the synthesis of quaternary acyclic α,β-diaminophosphonic acids, see: Studer, A.; Seebach, D. *Heterocycles* **1995**, *40*, 357–378.
74. (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70; (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908–910; (c) See Ref. 31b; (d) Chakraborty, T. K.; Azhar, H. K.; Venkat, R. G. *Tetrahedron* **1995**, *51*, 9179–9190.
75. Satish-Kumar, A.; Taneja, S. C.; Hundal, M. S.; Kapoor, K. K. *Tetrahedron Lett.* **2008**, *49*, 2208–2212.
76. Rinnová, M.; Nefzi, A.; Houghten, R. A. *Tetrahedron Lett.* **2002**, *43*, 4103–4106.
77. For the synthesis of α-aminophosphonates using chiral amides, see: (a) Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1996**, *7*, 21–24; (b) Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3177–3181; (c) Huber, J. W., III; Gilmore, W. F. *Tetrahedron Lett.* **1979**, *33*, 3049–3052.
78. Ross, G. H. P.; Balasubramaniam, S. *Synth. Commun.* **1998**, *28*, 3877–3884.
79. (a) Hamilton, R.; Walker, B.; Walker, B. J. *Tetrahedron Lett.* **1995**, *36*, 4451–4454; Also, see: (b) Drag, M.; Grembecka, J.; Pawelczak, M.; Kafarski, P. *Eur. J. Med. Chem.* **2005**, *40*, 764–771; (c) See Ref. 20a; (d) Drag, M.; Grembecka, J.; Kafarski, P. *Phosphorous, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1591–1595.
80. (a) Bongini, A.; Camerini, R.; Panunzio, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1467–1476; (b) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045–8048.
81. Davis, F. A.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 7249–7253.
82. For the synthesis of α-amino-β-hydroxyphosphonates, see: (a) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247–2250; (b) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769–5772; (c) See Ref. 80a; (d) See Ref. 60; (e) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843–844; (f) De Risi, C.; Perrone, D.; Dondoni, A.; Pollini, G. P.; Bertolasi, V. *Eur. J. Org. Chem.* **2003**, 1904–1914.
83. Finch, P.; Iskander, G. M.; Siriwardena, A. H. *Carbohydr. Res.* **1991**, *210*, 319–325.
84. Hanessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667–2674.
85. Chen, X.; Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 9331–9339.
86. Zhu, X. F.; Williams, H. J.; Scott, A. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2305–2306.
87. Chen, X.; Wiemer, D. F. *J. Org. Chem.* **2003**, *68*, 6108–6114.
88. (a) See Ref. 82f; (b) De Risi, C.; Dondoni, A.; Perrone, D.; Pollini, G. P. *Tetrahedron Lett.* **2001**, *42*, 3033–3036.
89. Kolodiazhnyi, O. I.; Sheiko, S.; Grishkun, E. V. *Heteroat. Chem.* **2000**, *11*, 138–143.
90. (a) Kachkovskii, G. A.; Andrushko, N. V.; Sheiko, S. Y.; Kolodiazhnyi, O. I. *Russ. J. Gen. Chem.* **2005**, *75*, 1735–1743; (b) Kolodiazhnyi, O. I. *Phosphorous, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2111–2114; (c) Sergei, S.; Irina, G.; Eugeni, G.; Kolodiazhnyi, O. I. *Phosphorous, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2269–2270; (d) Kolodiazhnyi, O. I.; Sheiko, S. Y. *Russ. J. Gen. Chem.* **2001**, *71*, 1155–1156; (e) Kolodiazhnyi, O. I.; Sheiko, S. Y. *Russ. J. Gen. Chem.* **2001**, *71*, 977–978.
91. Similar results were obtained in the addition of **127a** to the chiral imines obtained by condensation from (*S*)- and (*R*)-α-MBA with *p*-$Me_2NC_6H_4CHO$, *p*-$NO_2C_6H_4CHO$, *p*-FC_6H_4CHO, and *p*-BrC_6H_4CHO. Electron-acceptor substituents in aromatic ring reduced the stereoselectivity, whereas electron donors increases it.
92. (a) Déjugnat, C.; Etemad-Moghadam, G.; Rico-Lattes, I. *Chem. Commun* **2003**, 1858–1859; (b) Vercruysse, K.; Déjugnat, C.; Munoz, A.; Etemad-Moghadam, G. *Eur. J. Org. Chem.* **2000**, 281–289.
93. (a) Munoz, A.; Garriges, B.; Koenig, M. *Tetrahedron* **1980**, *36*, 2467–2482; (b) Koenig, M.; Munoz, A.; Garriges, B.; Wolf, R. *Phosphorous, Sulfur Silicon Relat. Elem.* **1979**, *6*, 435–451.
94. Schlemminger, I.; Willecke, A.; Maison, W.; Koch, R.; Lützen, A.; Martens, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2804–2816.
95. For the preliminary asymmetric addition of chiral cyclic phosphites to achiral 3-thiazolines, see: Hoppe, I.; Schöllkopf, U.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1067–1068.
96. Swamy, K. C. K.; Kumaraswamy, S.; Kumar, K. S.; Muthiah, C. *Tetrahedron Lett.* **2005**, *46*, 3347–3351.
97. Liu, H.; Cai, S.; Xu, J. *J. Pept. Sci.* **2006**, *12*, 337–340.
98. Xu, J.; Gao, Y. *Synthesis* **2006**, 783–788.
99. (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022; (b) Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8938–8940 and references therein; (c) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; John Wiley & Sons: New York, NY, 2000.
100. Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656–6657.
101. Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583–2585.
102. Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.
103. Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986.
104. The addition of diethyl phosphite to imines catalyzed by bis-*gluco*-18-crown-6 or monoaza-15-crown-5 gave the α-aminophosphonates with only low enantioselectivity, see: Jaszay, Z. M.; Nagy, E.; Bako, P.; Petnehazy, I.; Töke, L. Supplement to Chimica Oggi *Chem. Today* **2006**, *24*, 24–26.
105. For the one-pot synthesis of α-aminophosphonates using β-cyclodextrin (β-CD) in water at reflux, see: Kaboudin, B.; Sorbiun, M. *Tetrahedron Lett.* **2007**, *48*, 9015–9017.
106. Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269–6272.
107. Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089–3103.
108. (a) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818–4825; (b) Yamakoshi, K.; Harwood, S. J.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 2565–2568.
109. (a) Chen, F.-Y.; Uang, B.-J. *J. Org. Chem.* **2001**, *66*, 3650–3652; (b) Laue, K. W.; Muck-Lichtenfeld, C.; Haufe, G. *Tetrahedron* **1999**, *55*, 10413–10424; (c) Meyer, L.; Poirier, J.-M.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094–8095; (d) Yeh, T.-L.; Liao, C.-C.; Uang, B.-J. *Tetrahedron* **1997**, *53*, 11141–11152; (e) Tabcheh, M.; El Achqar, A.; Pappalardo, A.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4611–4618; (f) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009–6010; (g) McIntosh, J. M.; Cassidy, K. C. *Can. J. Chem.* **1988**, *66*, 3116–3119.
110. (a) Shöllkopf, U.; Schütze, R. *Liebigs Ann. Chem.* **1987**, 45–49; (b) Groth, U.; Richter, L.; Shöllkopf, U. *Liebigs Ann. Chem.* **1992**, 903–909; (c) Groth, U.; Richter, L.; Shöllkopf, U. *Tetrahedron* **1992**, *48*, 117–122; (d) For the synthesis of phosphonic analogue of diaminopimelic acid (P-DAP) using **167**, see: Song, Y.; Niederer, D.; Lane-Bell, P. M.; Lam, L. K. P.; Crawley, S.; Palcic, M. M.; Pickard, M. A.; Pruess, D. L.; Vederas, J. C. *J. Org. Chem.* **1994**, *59*, 5784–5793.
111. (a) Ouazzani, F.; Roumestant, M.-L.; Viallefont, P.; El Hallaoui, A. *Tetrahedron: Asymmetry* **1991**, *2*, 913–917; (b) Hannour, S.; Roumestant, M.-L.; Viallefont, P.; Riche, C.; Martinez, J.; El Hallaoui, A.; Ouazzani, F. *Tetrahedron: Asymmetry* **1998**, *9*, 2329–2332.
112. (a) Jommi, G.; Miglierini, G.; Pagliarin, R.; Sello, G.; Sisti, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1131–1134; (b) Ferrari, M.; Jommi, G.; Miglierini, G.; Pagliarin, R.; Sisti, M. *Synth. Commun.* **1992**, *22*, 107–123; (c) Cabella, G.; Jommi, G.; Pagliarin, R.; Sello, G.; Sisti, M. *Tetrahedron* **1995**, *51*, 1817–1826.
113. (a) Maury, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1992**, *33*, 6127–6130; (b) Also, see: Maury, C.; Gharbaoui, T.; Royer, J.; Husson, H. P. *J. Org. Chem.* **1996**, *61*, 3687–3693.
114. Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465–6468.
115. Cheng-Ye, Y.; Qian-Yi, C. *Chin. J. Chem.* **2005**, *23*, 1671–1676.
116. Diastereoselective alkylation of (2*R*,5*S*)-**175** followed by the acidic hydrolysis led to the (*S*)-α-aminophosphonic acids **8**.
117. (a) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406; (b) Tian, W. Q.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299–4308 and references therein.
118. (a) Yuan, C.; Li, S.; Wang, G. *Heteroat. Chem.* **2000**, *11*, 528–535; (b) Yuan, C.; Li, S.; Cui, S.; Wang, G. *Phosphorous, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1731–1734.
119. Diastereoselective alkylation of (2*R*,5*R*)-**174** and subsequent reactions gave the (*S*)-α-aminophosphonic acids **8**.
120. (a) Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2886–2893; (b) Yamagishi, T.; Haruki, T.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 9210–9217.
121. Alkylation of (S_P)-**179** afforded (*S*,S_P)-**180** in 74% yield and with 10:1 diastereoisomeric ratio.
122. For the synthesis of α-amino-α′-hydroxyphosphinates from reaction of (*R*,R_P)-**183** with several alkyl and aryl aldehydes, see: Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Synthesis* **2007**, 3226–3232.
123. For the practical and efficient synthesis of (*E*)-α,β-unsaturated amides bearing (*S*)-α-MBA from phosphonoamides of the type **185** via Horner–Wadsworth–Emmons reaction, see: (a) Ordóñez, M.; Hernández-Fernández, E.; Montiel-Pérez, M.; Rojas-Cabrera, H.; Fernández-Zertuche, M.; García-Barradas, O. *Tetrahedron: Asymmetry* **2007**, *18*, 2427–2436; (b) Hernández-Fernández, E.; Fernández-Zertuche, M.; García-Barradas, O.; Muñoz-Muñiz, O.; Ordóñez, M. *Synlett* **2006**, 440–444.
124. Ordóñez, M.; Hernández-Fernández, E.; Xahuentitla, J.; Cativiela, C. *Chem. Commun.* **2005**, 1336–1338.
125. (a) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717–5720; (b) Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107–4110; (c) Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, *68*, 9453–9455; (d) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368; (e) Smith, P. A. S. *Org. React.* **1946**, *3*, 337–449.
126. (a) Sawamura, M.; Hamashima, H.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2559–2562; (b) Also, see Ref. 82a.
127. Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837–839.
128. Jászay, Z. M.; Németh, G.; Pham, T. S.; Petneházy, I.; Grün, A.; Tőke, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3837–3840.

129. For the catalytic enantioselective synthesis of α-aminophosphonates from **197**, see: Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 679–682.
130. (a) Ma, D.; Ma, Z.; Jian, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889–893; (b) Lejczak, B.; Kafarski, P.; Mastalerz, P. *J. Chromatogr.* **1985**, *324*, 455–461; (c) Antczak, K.; Szewczyk, J. *Phosphorous, Sulfur Silicon Relat. Elem.* **1985**, *22*, 247–251.
131. Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558–6559.
132. Kiyohara, H.; Matsubara, R.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 5333–5335.
133. For the synthesis of non-chiral α-aminophosphonates via addition of enamines to α-iminophosphonates, see: Risch, N.; Piper, S.; Winter, A.; Lefarth-Risse, A. *Eur. J. Org. Chem.* **2005**, 387–394.
134. Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615–1617.
135. (a) Dodda, R.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 4339–4342; (b) For the synthesis of non-chiral α-imino-propargylphosphonates, see: Dodda, R.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 165–167.
136. Piotrowska, D. G.; Głowacka, I. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2787–2790.
137. (a) Piotrowska, D. G.; Głowacka, I. E. *Tetrahedron: Asymmetry* **2007**, *18*, 1351–1363; (b) For the preparation of isoxazolidines from *N*-glycosyl-*C*-dialkoxyphosphorylated nitrones, see: Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1953–1964.
138. For the cycloaddition reactions of nonchiral phosphonitrones, see: (a) Piotrowska, D. G. *Tetrahedron Lett.* **2006**, *47*, 5363–5366; (b) Piotrowska, D. G. *Tetrahedron* **2006**, *62*, 12306–12317.
139. Denmark, S. E.; Chatani, N.; Pansare, S. V. *Tetrahedron* **1992**, *48*, 2191–2208.
140. Jommi, G.; Miglierini, G.; Pagliarin, R.; Sello, G.; Sisti, M. *Tetrahedron* **1992**, *48*, 7275–7288.
141. Pagliarin, R.; Papeo, G.; Sello, G.; Sisti, M. *Tetrahedron* **1996**, *52*, 13783–13794.
142. (a) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272–1274; (b) Maffre, D.; Dumy, P.; Vidal, J.-P.; Escale, R.; Girard, J.-P. *J. Chem. Res., Synop.* **1994**, 30–31.
143. Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772–5773.
144. Fernández, M. C.; Díaz, A.; Guillín, J. J.; Blanco, O.; Ruiz, M.; Ojea, V. *J. Org. Chem.* **2006**, *71*, 6958–6974.
145. For the stereoselective azidation of chiral α-alkyl phosphonoamides, see Ref. 142a.
146. (a) Jiao, X.; Chen, W.; Hu, B. *Synth. Commun.* **1992**, *22*, 1179–1186; (b) Fernández, M. C.; Quintela, J. M.; Ruiz, M.; Ojea, V. *Tetrahedron: Asymmetry* **2002**, *13*, 233–237; (c) Reyes-Rangel, G.; Marañon, V.; Avila-Ortiz, C. G.; Anaya de Parrodi, C.; Quintero, L.; Juaristi, E. *Tetrahedron* **2006**, *62*, 8404–8409; (d) See Ref. 144 and references therein; (e) Sibille, P.; López, S.; Brabet, I.; Valenti, O.; Oueslati, N.; Gaven, F.; Goudet, C.; Bertrand, H.-O.; Neyton, J.; Marino, M. J.; Amalric, M.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2007**, *50*, 3585–3595.
147. (a) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M. *Tetrahedron* **2005**, *61*, 2815–2830; (b) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M. *Tetrahedron Lett.* **2004**, *45*, 4345–4348.
148. de los Santos, J. M.; Ignacio, R.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2007**, *72*, 5202–5206.
149. For the preparation of dehydroaminophosphonates of the type **246**, see: (a) Quiclet-Sire, B.; Zard, S. Z.; Zhang, H. *J. Organomet. Chem.* **2002**, *643–644*, 404–408; (b) Błażewska, K.; Gajda, T. *Tetrahedron* **2004**, *60*, 11701–11707.
150. For catalytic asymmetric synthesis of α- and β-aminophosphonic acid derivatives, see: (a) Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630–636; For related references, see: (b) Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555–559; (c) Schmidt, U.; Oehme, G.; Krause, H. *Synth. Commun.* **1996**, *26*, 777–781; (d) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031–8034; (e) Schmidt, U.; Krause, H. W.; Oehme, G.; Michalik, M.; Fischer, C. *Chirality* **1998**, *10*, 564–572; (f) Grassert, I.; Schmidt, U.; Ziegler, S.; Fischer, C.; Oehme, G. *Tetrahedron: Asymmetry* **1998**, *9*, 4193–4202; (g) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387–390.
151. Gridnev, I. D.; Yasutake, M.; Imamoto, T.; Beletskaya, I. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5385–5390.
152. Wang, D.-Y.; Huang, J.-D.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2011–2014.
153. Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2001**, 4615–4624.
154. For the synthesis of non-chiral 1-amino-2,2,2-trifluoroethanephosphonates, see: (a) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, 3891–3897; (b) Rassukana, Y. V.; Kolotylo, M. V.; Sinitsa, O. A.; Pirozhenko, V. V.; Onys'ko, P. P. *Synthesis* **2007**, 2627–2630.
155. Xiao, J.; Zhang, X.; Yuan, C. *Heteroat. Chem.* **2000**, *11*, 536–540.
156. (a) See, Ref. 21b; (b) Wagner, J.; Lerner, R. A.; Barbas, C. F., III. *Bioorg. Med. Chem.* **1996**, *4*, 901–916; (c) Also, see: Kowalik, J.; Sawka-Dobrowolska, W.; Głowiak, T. *J. Chem. Soc., Chem. Commun.* **1984**, 446–447.
157. (a) Auberson, Y. P.; Acklin, P.; Bischoff, S.; Moretti, R.; Ofner, S.; Schmutz, M.; Veenstra, S. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 249–254; (b) See also: Lämmerhofer, M.; Hebenstreit, D.; Gavioli, E.; Lindner, W.; Mucha, A.; Kafarski, P.; Wieczorek, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2557–2565; (c) Caccamese, S.; Failla, S.; Finocchiaro, P.; Hägele, G.; Principato, G. *J. Chem. Res., Synop.* **1992**, 242–243.
158. (a) Ou, L.; Xu, Y.; Ludwig, D.; Pan, J.; Xu, J. H. *Org. Process Res. Dev.* **2008**, *12*, 192–195; (b) Snyder, P. W.; Johannes, M. S.; Vogen, B. N.; Clark, R. L.; Toone, E. J. *J. Org. Chem.* **2007**, *72*, 7459–7461; (c) Adam, W.; Lukacs, Z.; Saha-Moller, C. R.; Schreier, P. *J. Am. Chem. Soc.* **2000**, *122*, 4887–4892; (d) Burgess, K.; Jennings, L. D. *J. Org. Chem.* **1990**, *55*, 1138–1139.
159. Yuan, C.; Xu, C.; Zhang, Y. *Tetrahedron* **2003**, *59*, 6095–6102.
160. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Castro, B. R. *Org. React.* **1983**, *29*, 1–162; (c) Hughess, D. L. *Org. React.* **1992**, *42*, 335–356; (d) Hughess, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; (e) Dodge, J. A.; Jones, S. A. *Rec. Res. Devel. Org. Chem.* **1997**, *1*, 273–283; (f) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772; (g) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855–3864; (h) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069–5072.
161. For the synthesis of non-chiral α-aminophosphonates from α-hydroxyphosphonates under solvent-free conditions using microwave irradiation, see: Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051–1053.
162. (a) Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *3*, 377–378; (b) Gajda, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965–1972; (c) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121–6131.
163. (a) Hammerschmidt, F.; Wuggenig, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1709–1721; (b) Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933–4946.
164. Skropeta, D.; Schwörer, R.; Schmidt, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3351–3354.
165. (a) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930–7933; (b) Yokomatsu, T.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Synlett* **1995**, 847–849.
166. (a) See Ref. 80a; (b) Simov, B. P.; Wuggenig, F.; Lämmerhofer, M.; Lindner, W.; Zarbl, E.; Hammerschmidt, F. *Eur. J. Org. Chem.* **2002**, 1139–1142.
167. Hammerschmidt, F.; Lindner, W.; Wuggenig, F.; Zarbl, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2955–2964.
168. Dolence, E. K.; Roylance, J. B. *Tetrahedron: Asymmetry* **2004**, *15*, 3307–3322.
169. Dolence, E. K.; Mayer, G.; Kelly, B. D. *Tetrahedron: Asymmetry* **2005**, *16*, 1583–1594.
170. Pousset, C.; Larchevêque, M. *Tetrahedron Lett.* **2002**, *43*, 5257–5260.
171. Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2003**, *59*, 8405–8410.
172. Hercouet, A.; Le Corre, M.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197–199.
173. (a) Gaucher, A.; Olliver, J.; Marguerite, J.; Paugam, R.; Salaün, J. *Can. J. Chem.* **1994**, *72*, 1312–1327; (b) Cativiela, C.; Díaz-de-Villegas, M. D.; Jiménez, A. I. *Tetrahedron: Asymmetry* **1995**, *6*, 177–182; (c) Hercouet, A.; Bessieres, B.; Le Corre, M. *Tetrahedron: Asymmetry* **1996**, *7*, 283–284.
174. Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.
175. Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135.
176. (a) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363–5366; (b) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; López de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689–700.
177. For the synthesis and application of racemic 2-phosphorylated aziridines, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2005**, *70*, 8895–8901; (b) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148.
178. Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2002**, *43*, 4633–4636.
179. For the preparation of diethyl phosphonate **310**, see Ref. 110c.
180. (a) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762–768; (b) Schopf, C. *Angew. Chem.* **1937**, *50*, 779–787; (c) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035; (d) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth. Coll. Vol.* **1998**, *9*, 176–180.
181. (a) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979–1985; (b) Dinér, P.; Amedjkouh, M. *Org. Biomol. Chem.* **2006**, *4*, 2091–2096.
182. Amedjkouh, M.; Westerlund, K. *Tetrahedron Lett.* **2004**, *45*, 5175–5177.
183. Baussanne, I.; Chiaroni, A.; Royer, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1219–1224.
184. Davis, F. A.; Lee, S. H.; Xu, H. *J. Org. Chem.* **2004**, *69*, 3774–3781.
185. Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett.* **2004**, *6*, 4523–4525.
186. For the synthesis of substituted pyrrolidine phosphonates, see: Dondas, H. A.; Durust, Y.; Grigg, R.; Slater, M. J.; Sarker, M. A. B. *Tetrahedron* **2005**, *61*, 10667–10682.
187. The alkylation reaction of **336a** with iodomethane and benzyl bromide gave complex mixtures.
188. Davis, F. A.; Xu, H.; Wu, Y.; Zhang, J. *Org. Lett.* **2006**, *8*, 2273–2276.
189. Hanessian, S.; Gauchet, C.; Charron, G.; Marin, J.; Nakache, P. *J. Org. Chem.* **2006**, *71*, 2760–2778.
190. For the conversion of racemic cyclic α-amino acids into cyclic α-aminophosphonic acids, see: Kaname, M.; Mashige, H.; Yoshifuji, S. *Chem. Pharm. Bull.* **2001**, *49*, 531–536.
191. Boto, A.; Gallardo, J. A.; Hernández, R.; Saavedra, C. J. *Tetrahedron Lett.* **2005**, *46*, 7807–7811.
192. Zhao, Y.; Cao, S.; Li, Y.; Ma. Y. Faming Zhuanli Shenqing Gongkai Shoumingshu, CN 10797226, 1993; *Chem. Abstr.* **1995**, *122*, 183469.
193. Chevrier, C.; Le Nouën, D.; Defoin, A.; Tarnus, C. *Eur. J. Org. Chem.* **2006**, 2384–2392.
194. For the stereoselective synthesis of piperidin-2-yl-phosphonic acids and derivatives, see: (a) Maury, C.; Wang, Q.; Gharbaoui, T.; Chiadmi, M.; Tomas, A.; Royer, J.; Husson, H. P. *Tetrahedron* **1997**, *53*, 3627–3636; (b) Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655–658; (c) Kaname, M.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron Lett.* **2001**, *42*, 2713–2716; (d) Kaname, M.; Yoshinaga, K.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron Lett.* **1999**, *40*, 7993–7994; (e) Kaname, M.; Yoshinaga, K.; Arakawa, Y.; Yoshifuji, S. *Chem. Pharm. Bull.* **2004**, *52*, 160–162.

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