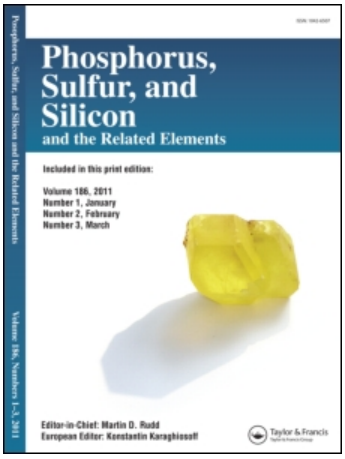

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Asymmetric Synthesis of Phosphorus Analogs of Amino Acids

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Review

ASYMMETRIC SYNTHESIS OF PHOSPHORUS ANALOGS OF AMINO ACIDS

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Data available in literature on asymmetric synthesis of phosphorus analogs of amino acids are summarized. The methods described are arranged according to the type of bond formation during a chiral center creation. The asymmetric synthesis was shown to be in dynamic development and can be considered as a valuable approach for production of optically active phosphorus analogs of amino acids.

Key words: Phosphorus analogs of amino acids, asymmetric synthesis, stereoselectivity, optically active compounds.

I. INTRODUCTION

An idea of the synthesis of amino acid phosphorus analogs belongs to the nature: several aminophosphonic, aminophosphinic and aminophosphonous acids (APA) have been isolated from various natural sources either as free amino acids or as constituents of more complex compounds (peptides).[1–3] Many natural and synthetic APA have been shown to possess promising biological activities.[4,5] Due to their structural analogy to natural amino acids, APA can act as false substrates in the course of amino acid metabolism and exhibit the properties of antibiotics, enzyme inhibitors, and other forms of biological activity. For example, the phosphonic analog of glycine is a growth regulator in plants,[6] the phosphonic analog of phenylalanine is a specific competitive inhibitor of phenylalanyl-t-RNA-synthetase,[7] and the phosphonodipeptide alafosfalin is a potent antimicrobial agent.[8]

The importance of stereochemistry in chiral compounds for their biological activity is definitely displayed in the APA series. For example, the (S)-enantiomer of 2-amino-4-phosphonobutanoic acid is 20–40 times more active than the (R)-enantiomer in suppression of glutamate-mediated neurotransmission,[9] and the activity of 2-amino-5-phosphonopentanoic acid as the N-methyl-D-aspartate antagonist has been attributed mainly to its (R)-enantiomer.[10] Similarly, the herbicidal activity of (S)-phosphinothricin is twice as high as that of the racemic compounds.[11]

In view of these findings, the development of methods for preparation APA in optically pure form and especially asymmetric syntheses APA are important and are currently attracting considerable attention.

Several reviews have been published in recent years on the preparation of particular classes of APA, their reactivity and application,[12–14] including optically

active 1-aminoalkylphosphonic acids.[15] However, attention to the stereodifferential approaches to the preparation of optically active APA has been lacking, and this is the subject of the present review. It is devoted to the asymmetric syntheses of APA where a prochiral group is transformed into a chiral one in an enantioselective (or enantiospecific) manner to produce enantiomerically enriched (or enantiomerically pure) products.

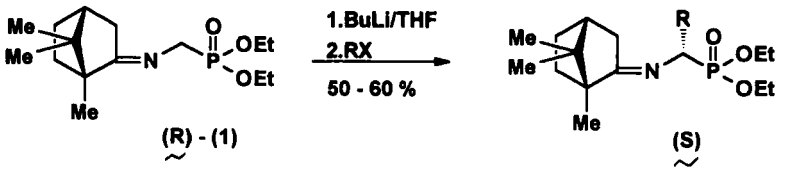
The review consists of 4 parts according to the type of the bond formed (C—C, C—P, C—H, or C—N) resulting in the creation of the chiral center. Special attention is paid to more recent results.

II. ENANTIOSELECTIVE C—C BOND FORMING REACTIONS

The most general approach for asymmetric synthesis of APA includes the alkylation reaction of chiral Schiff bases, formed from esters of aminomethylphosphonic acid (phosphonic analog of glycine, Gly^{P},†) and appropriate carbonyl compounds which can be regenerated without losing optical purity and reused in further syntheses. The formation of Schiff bases facilitates the proton abstraction from the methylene group and consequently promotes further reaction of the generated carbanion with electrophilic reagents.

The most commonly used carbonyl compounds in these syntheses are camphor and its derivatives which are readily available in two enantiomerically pure forms.

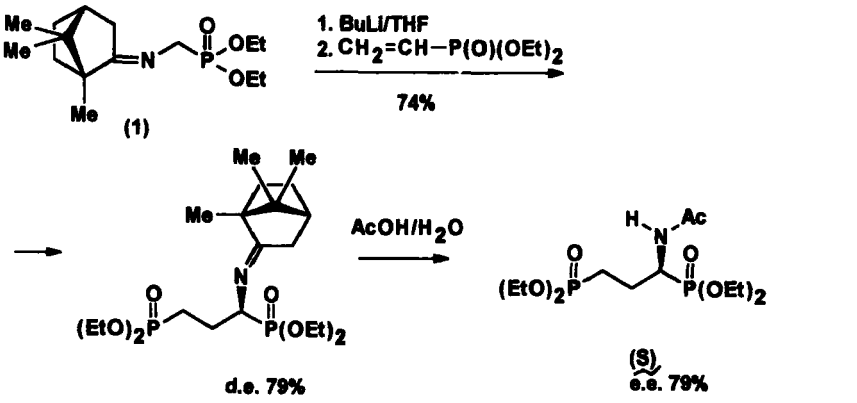
Thus, the lithium derivative of Schiff base (**1**) prepared from (**R**)-camphor and diethyl aminomethylphosphonate reacts with various alkyl, allyl or benzyl halides to yield the corresponding (**S**)-α-aminophosphonic acids with 11% to 95% diastereomeric excess (d.e.). The best diastereoselectivity was achieved when benzyl or allyl halides were used for alkylation of Schiff base (**1**).[16]

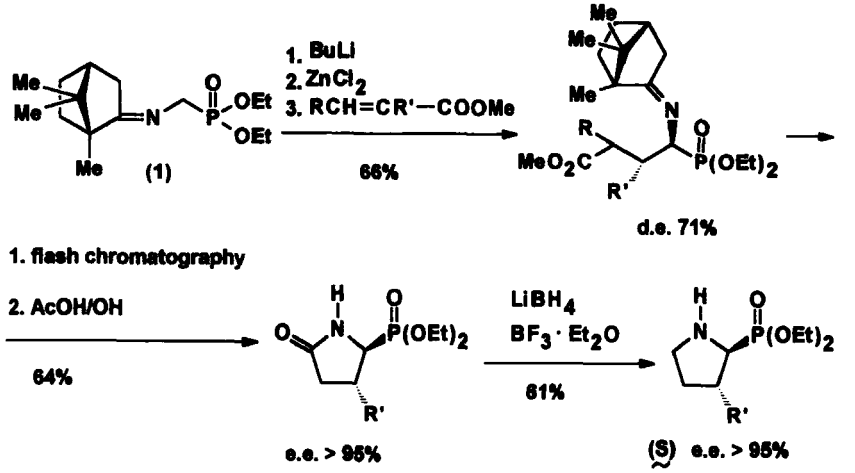


R=	$CH_2CH{=}CH_2$;	$PhCH_2$;	$CH_2{-}C{\equiv}CH$;	Me ;	Et ;	Pr ;	CH_3OCH_2
d.e.:	>95%	>95%	71%	11%	69%	77%	56%

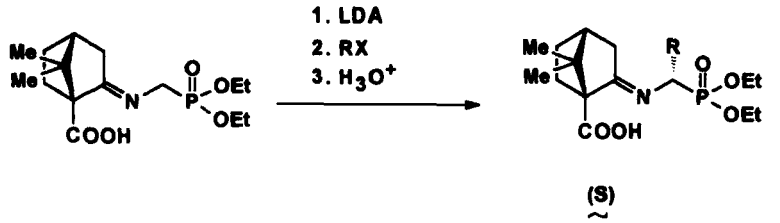
Kinetically controlled Michael addition of chiral phosphonoglycine Schiff base (**1**) to diethyl vinylphosphonate or methyl acrylate proceeds with high diastereoselectivity to give the esters of α, γ-di- and α-monophosphonic analogs of (**R**)-glutamic acid [(**S**)-$Glu^{\alpha,\gamma\text{-}P}$ and (**S**)-$Glu^{\alpha\text{-}P}$]. The later was transformed into (**S**)-pyrrolidine-2-phosphonic acid diethyl ester.[17,18]

†Phosphorus analogs of natural amino acids are designated the generally accepted three-letter symbols for amino acids with the superscript indexes "P" for aminophosphonic, "P-H" for aminophosphonous, and "P-R" for aminophosphinic acids; in addition, superscript indexes "α," "β," "γ" and "ω" indicate the position of phosphorus acid moiety for analogs of dicarboxylic amino acids.

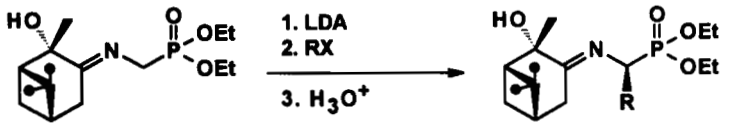




Substitution of (**R**)-(+)-ketopinic acid for camphor in its Schiff base with diethyl aminomethylphosphonate gave nearly the same results in view of diastereoselectivity and chemical yields: diethyl (**S**)-α-aminoalkylphosphonates were obtained with high enantiomeric excess (e.e.) only when benzyl or allyl halides were used on an alkylation step.[19]



R =	Me;	Et;	CH_2Ph;	$CH_2CH{=}CH_2$
d.e.	15.1%	62%	79%	92%
yield	67%	68%	93%	65%

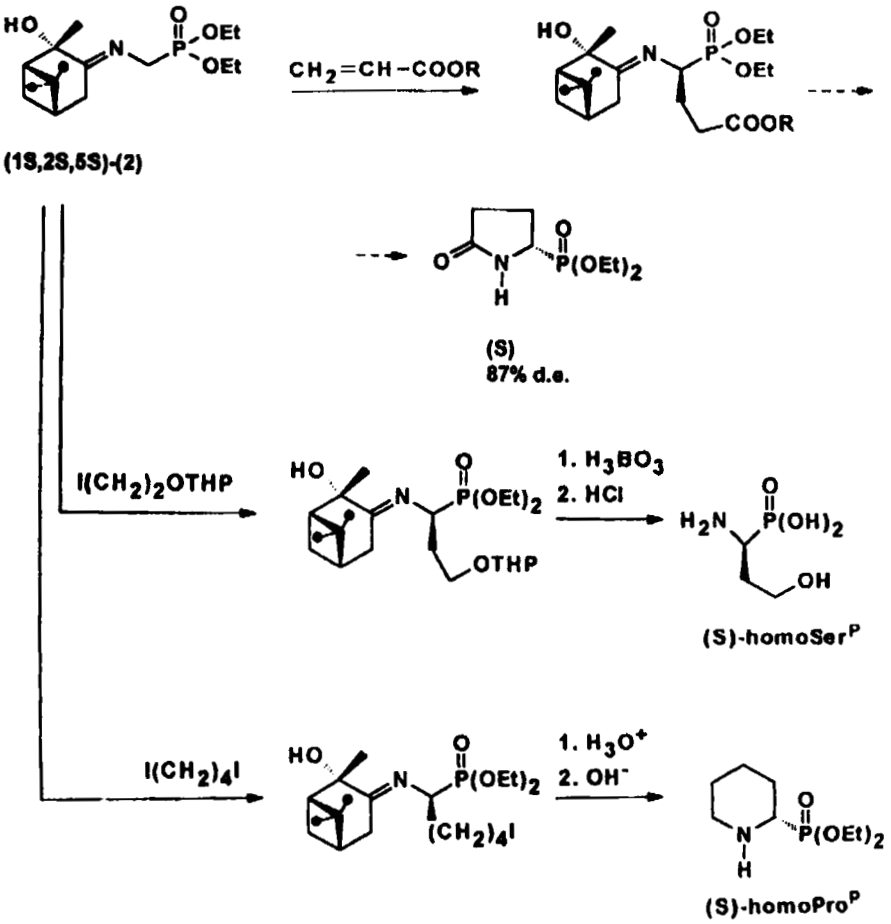


(1S,2S,5S)-(2) (S)

R=	Me;	Et;	$PhCH_2$;	$CH_2=CHCH_2$;	$CH_2-C\equiv CH$;	$I(CH_2)_5I$;	$I(CH_2)_2OTHP$
yield	90%	85%	71%	70%	85%	72%	85%
d.e.	85%	95%	33%	74%	83%	69%	~100%

In contrast to the two cases mentioned above, an application of enantiomerically pure 2-hydroxypinan-3-one as chiral auxiliary allows to obtain α-aminophosphonic acids in high e.e. even with small alkyl groups.[16,20–22]

Thus, the lithium derivative of Schiff base (2) formed from (1**R**, 2**R**, 5**R**)-(+)-2-hydroxypinan-3-one and diethyl aminomethylphosphonate was alkylated with various alkyl halides to give (**R**)-α-aminophosphonic acid derivatives in 70–90%



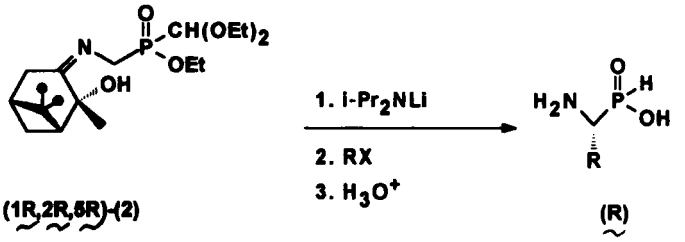
chemical yield and 69–100% d.e. (benzyl bromide, unexpectedly, only gave 33% d.e.). The application of Schiff base (**2**) derived from (1S, 2S, 5S)-(−)-2-hydroxypinan-3-one gave the corresponding (S)-α-aminophosphonic acids.[20]

The nature of diastereoselectivity in these syntheses has not been discussed but one can assume an important role of the hydroxyl group at α-position to the C=N double bond in coordination of a metal cation during the alkylation step. For example, substitution of the t-BuOK for LDA results in alkylation of the hydroxyl group and reduction of diastereoselectivity from 85% to 42% (for R = Me).[20]

The phosphonic analogs of homoserine and homoproline were also synthesized through the alkylation of Schiff base (**2**) derived from diethyl aminomethylphosphonate and enantiomers of 2-hydroxypinan-3-one. For this aim the tetrahydropyranyl ether of 2-iodoethanol (for homoSer^P)[22] or α,ω-diiodobutane (followed by cyclisation to homoPro^P) were employed.[20]

The Michael addition of Schiff base (**2**) to alkyl acrylate was performed in good yield and diastereoselectivity (d.e. 87%). Hydrolysis of the Schiff base afforded the optically active pyroglutamic acid analog.[20]

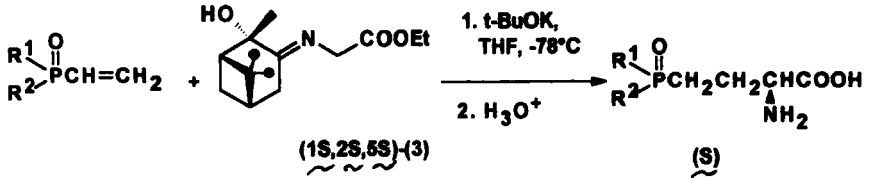
The only example of asymmetric synthesis of α-aminoalkylphosphonous acids also involves the stereoselective alkylation of the corresponding Schiff base (**2**) with 2-hydroxypinan-3-one as a chiral auxiliary. In this case C—C bond formation proceeds with high diastereoselectivity for benzyl bromide (>99% d.e.) and with moderate one for methyl iodide (56% d.e.).[23] The (1S, 2S, 5S)-2-hydroxypinan-3-one as a chiral auxiliary gave (S)-α-aminoalkylphosphonous acids, and application of (1R, 2R, 5R)-2-hydroxypinan-3-one afforded (R)-α-aminoalkylphosphonous acids.



(1R,2R,5R)-(2) (R)

It should be noted that the diastereoselectivity of benzylation of Schiff base (**2**) depends upon the nature of its acidic function and increases in the following order: COOEt (75% d.e.), $P(O)(OEt)_2$, (83% d.e.), $P(O)(OEt)CH(OEt)_2$ (99% d.e.).[23]

Asymmetric synthesis of (+)-phosphinothricin, (+)-2-amino-4-phosphonobutanoic acid, and their enantiomers has been achieved by the Michael addition of the chiral Schiff base (**3**) to corresponding vinyl phosphorus compounds.[24]



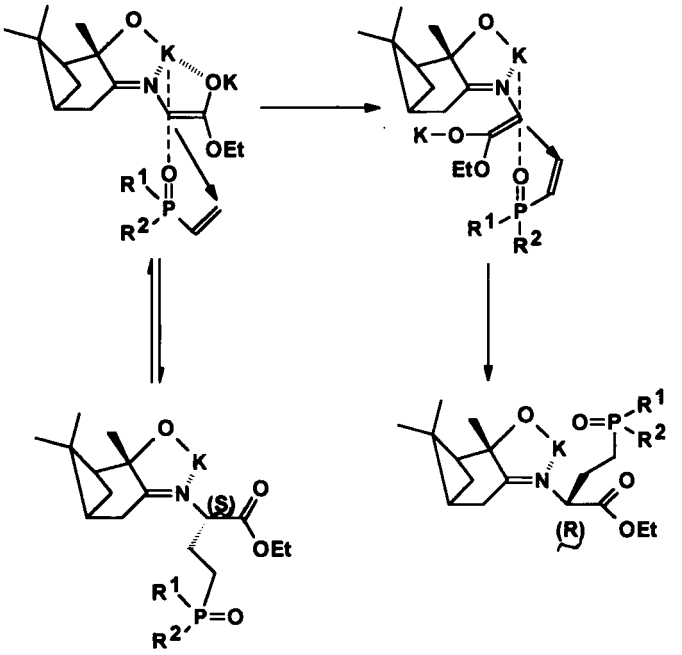
(1S,2S,5S)-(3) (S)

R^1=Me, R^2=MeO
R^1= R^2=EtO

R^1=Me, R^2=OH
R^1= R^2=OH

In order to explain the high chiral induction observed (up to 79% d.e.) for the addition to vinyl phosphorus compounds it was assumed that the coordination of the lone electron pairs on the nitrogen atom of Schiff base and the oxygen atom of phosphoryl group to the potassium cation plays a central role in this highly stereoselective addition.[24]

More detailed studies revealed the strong influence of the temperature on the stereochemical result of this process. Thus, at 0°C the Michael addition of the Schiff base derived from (1S, 2S, 5S)-2-hydroxypinan-3-one to the corresponding vinyl phosphorus compounds led to (R)-Glu$^{\gamma\text{-P-Me}}$ (e.e. 69%) and (R)-Glu$^{\gamma\text{-P}}$ (e.e. 68%) rather than to their (S)-enantiomers which were formed at −78°C. The authors assumed that addition of a dianion always takes place from the face opposite to the β-methyl group in the pinanone, but at elevated temperature the potassium enolate adopts the cisoid conformation thus leading to the inversion of stereochemical result of the process.[25]

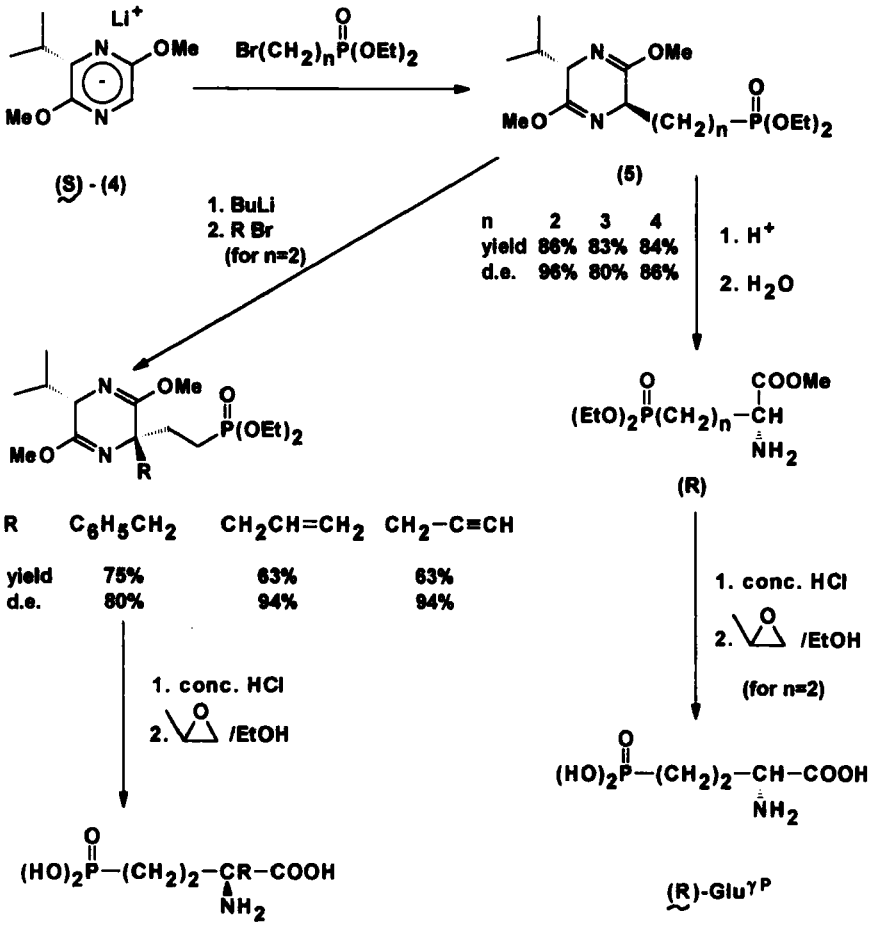


Well known methods for the asymmetric synthesis of α-amino carboxylic acids developed by U. Schöllkopf and Yu. Belokon' were successfully applied for preparation of enantiomerically pure ω-phosphono-α-amino alkylcarboxylic acids.

Thus, alkylation of the lithium derivative of bis-lactim ether (4) by ω-phosphonoalkyl halides proceeds with excellent diastereoselectivity to yield the corresponding ω-phosphonic analogs of glutamic and homoglutamic acid.[26,27]

The bis-lactim ether (5) with exocyclic 2-ethyl phosphonate residue formed on a first stage also can be alkylated to give α-substituted γ-phosphonic analogs of (S)-glutamic acid.

Both R- and S-enantiomers of phosphinothricin are prepared in high chemical yield with 93.5% e.e. by the same procedure starting from bis-lactim ether (4) and 2-chloroethyl methyl phosphinate.[27]

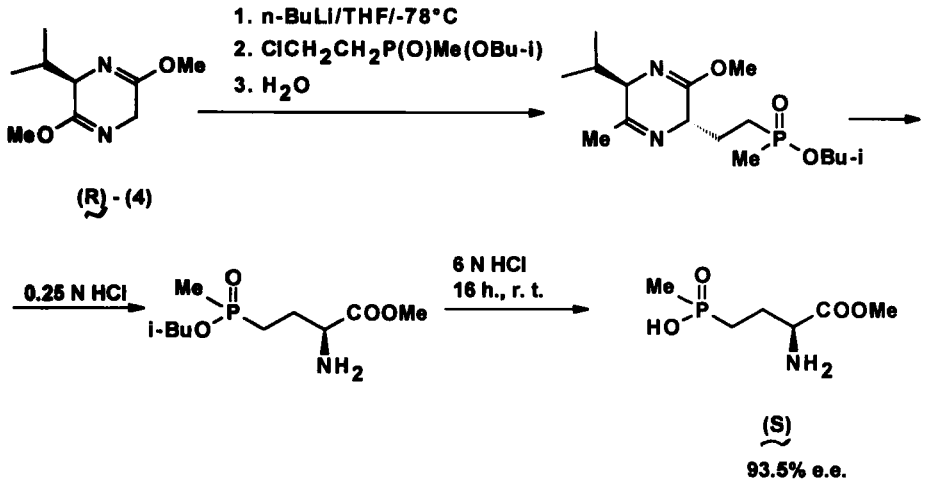


The unusual amino acid *p*-phosphonomethyl-(S)-phenylalanine was prepared *via* alkylation of bis-lactim ether (**4**) with *p*-dimethylphosphonomethyl benzyl bromide in optical purity more than 90% e.e.[28]

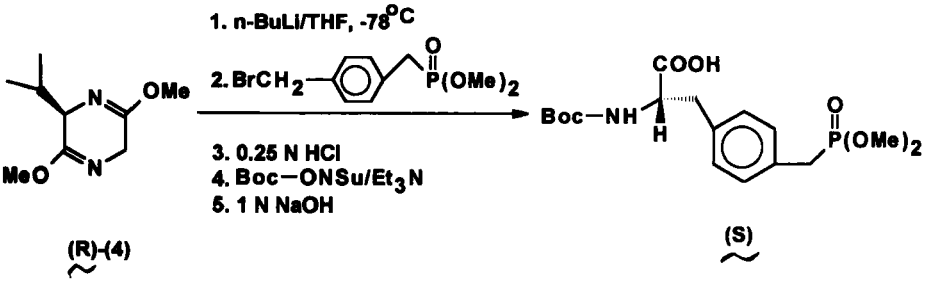
A highly selective and experimentally simple procedure for the efficient asymmetric synthesis of enantiopure (S)-phosphinothricin and α-amino-ω-phosphono carboxylic acids by the alkylation of glycine in its chiral Schiff's base Ni(II)-complex with a chiral auxiliary namely (S)-o-[(N-benzylprolyl)-amino]benzophenone was recently described by authors of this review.[29,30] Alkylation of complex (**6**) with appropriate alkyl halides was conducted at room temperature using powdered KOH as a base. The mixture of alkylated diastereoisomers [d.e. 90% of (S,S)-isomer] was separated on silica gel to give diastereoisomerically pure products.

The mild conditions of decomposition of the diastereoisomerically pure Ni(II)-complexes allowed to isolate novel amino acids with free carboxy groups and esterified phosphonic and phosphinic groups.

The relatively high CH-acidity of the glycine fragment in the complex (**6**) allowed to conduct its Michael addition to corresponding vinylphosphonates or vinylphosphinates under a variety of conditions by using various inorganic and organic bases.

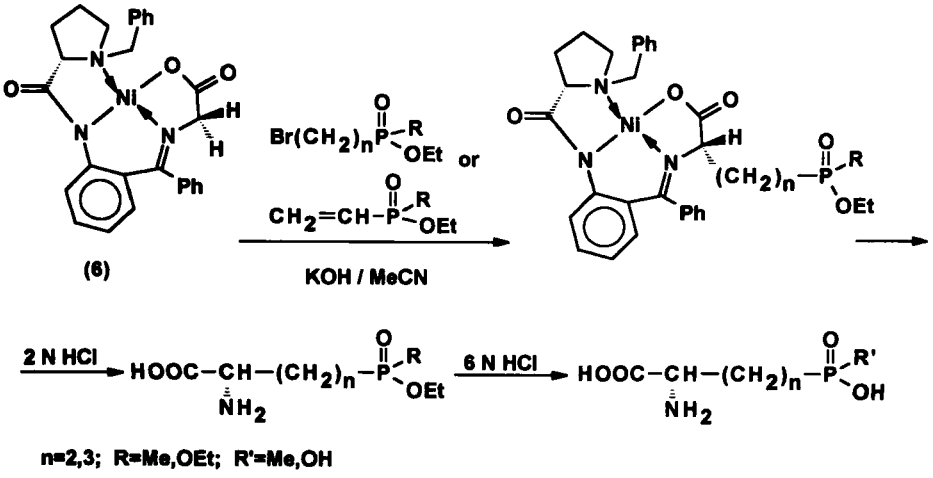


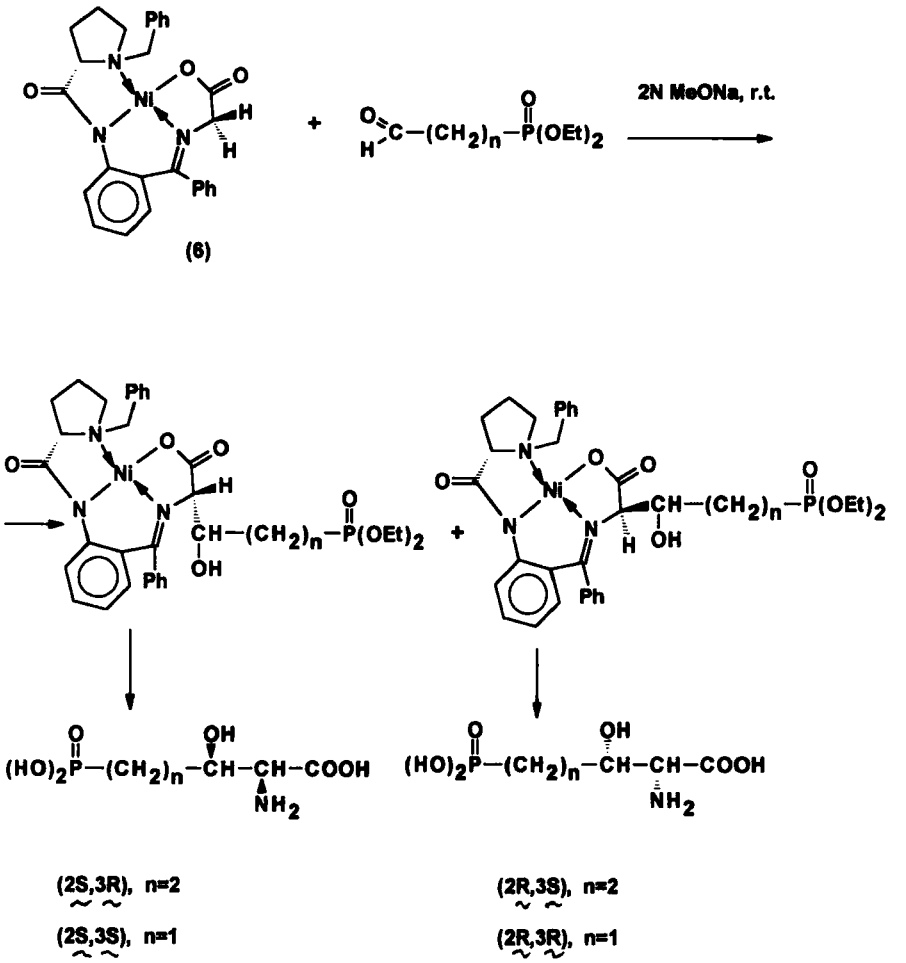
However, the diastereoselectivity of the addition was lower in comparison with the alkylation reaction. The optical yield of (S)-phosphinothricin and (S)-2-amino-4-phosphonobutanoic acid prepared by this method may be increased from 30% to



90% after epimerization of the diastereomeric complexes in the presence of sodium methoxide prior to decomposition.[29,30]

A similar procedure was employed for the preparation of α-amino-β-hydroxy alkylphosphonic acids *via* condensation of complex (**6**) with an appropriate alde-

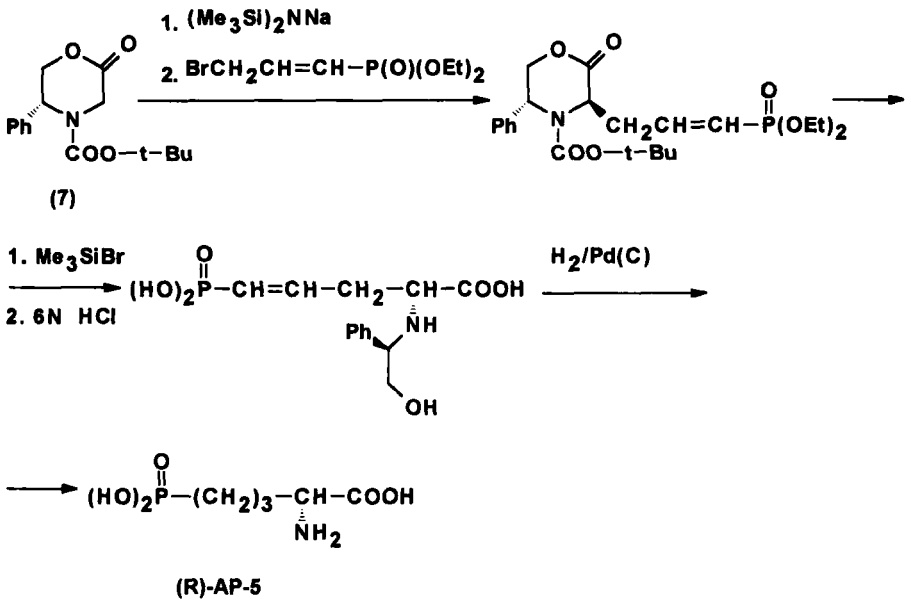




hyde containing a dialkyl phosphonate group in ω-position.[31,32] The reactions were carried out in 2N MeONa at 25°C to give the mixture (3:1) of the corresponding complexes of (**R**)-*threo*- and (**S**)-*threo*-α-amino-β-hydroxy-ω-phosphonocarboxylic acids. Diastereoisomerically and enantiomerically pure (2**R**, 3**R**)- and (2**S**, 3**S**)-2-amino-3-hydroxy-4-phosphonobutanoic acids as well as (2**R**, 3**S**)- and (2**S**, 3**R**)-2-amino-3-hydroxy-5-phosphonopentanoic acids were obtained after chromatographic purification on silica gel and decomposition of the corresponding complexes by the action of 0.2 N HCl.

The first asymmetric synthesis of (**R**)-(−)-2-amino-5-phosphonopentanoic acid (AP-5) was achieved by alkylation of the chiral oxazinone (**7**) prepared from D-phenylglycinol.[33] This amino acid is a selective NMDA antagonist and has found wide application in biochemical investigations.[34]

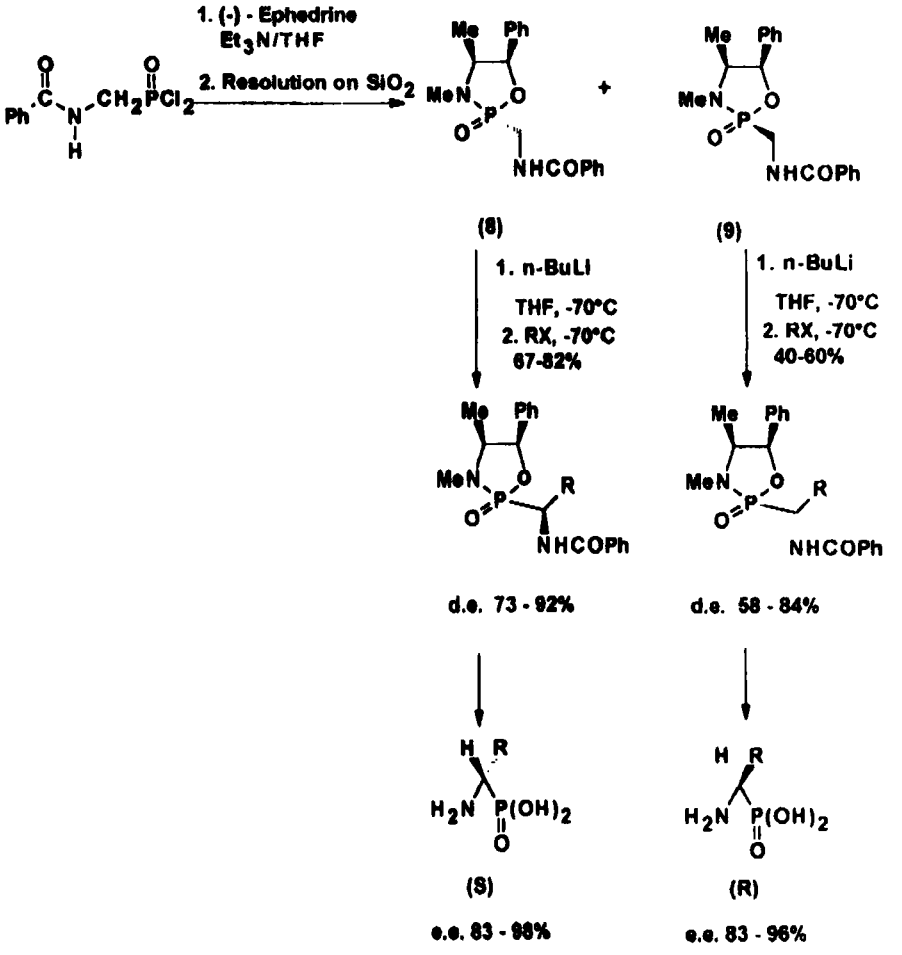
It should be noted that attempts to alkylate the chiral oxazinone (**7**) directly with diethyl 3-bromopropylphosphonate failed. The more active reagent 3-(diethylphosphono)allyl bromide gave a successful result. Further reduction of the C=C double bond can be conducted in one stage together with removal of the chiral auxiliary by palladium-catalyzed hydrogenolysis.



In the above described syntheses, chiral auxiliary groups have been connected with the amino group of glycine (or its phosphorus analogs) derivatives. The alternative approach with the chiral auxiliary group bonded to the phosphonic residue gave excellent results in asymmetric syntheses of α-aminophosphonic acids. This feature of tetracoordinated phosphorus allows to use chiral cyclic esters, amides or amido esters in which the phosphorus atom as a part of the chiral auxiliary can play a decisive role in stereoselectivity of C—C bond formation.

Two chiral 1,3,2-dioxaphosphorinanes formed from aminomethylphosphonate derivatives and *d,l*-2,4-pentandiol or 2-methyl-2,4-pentandiol were alkylated with moderate stereoselectivity (d.e. <50%) but gave asymmetric induction of the opposite sense. These results may be explained by differences in the dominating conformations of the dioxaphosphorinanes used.[35]

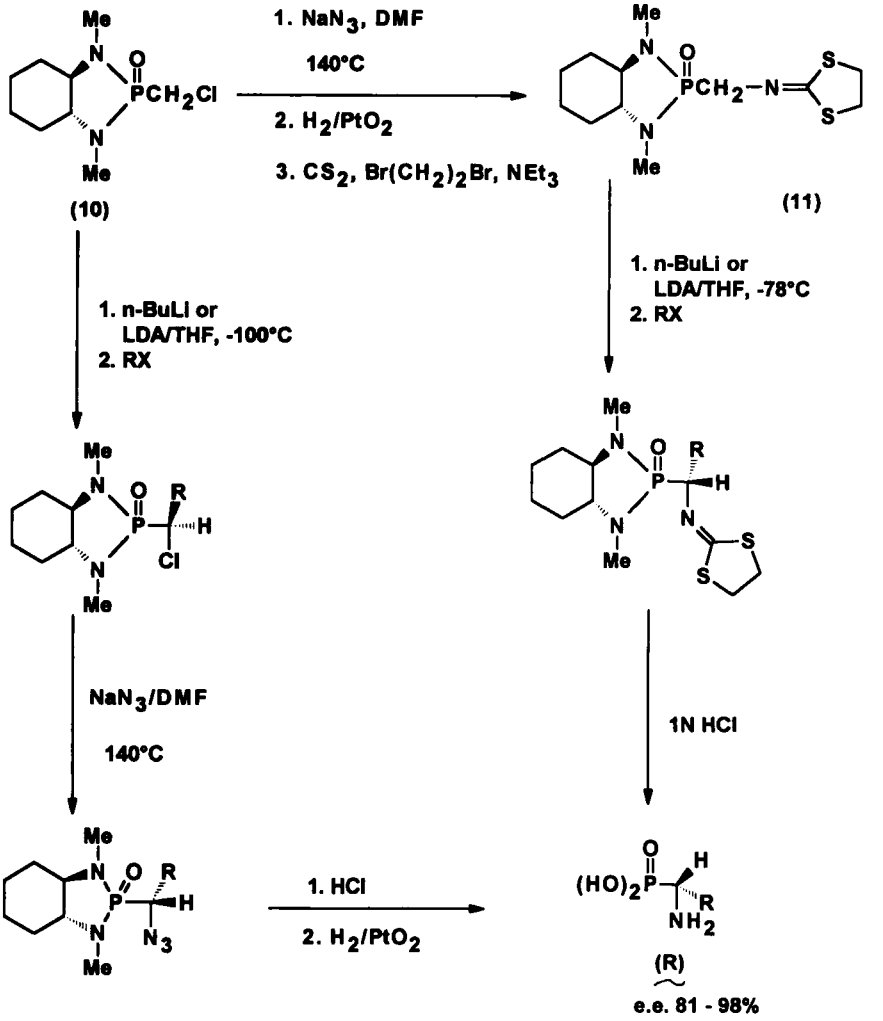
In comparison with dioxaphosphorinanes, the oxazaphospholidine and diazaphospholidine chiral auxiliaries seem to be more efficient as stereodifferential groups in similar asymmetric alkylations. Thus, the reaction of (N-benzoyl)aminomethyl phosphonic dichloride with ephedrine leads to an epimeric mixture of corresponding oxazaphospholidines (**8**) and (**9**) which can be easily resolved by column chromatography on silica gel. The diastereoselectivity of alkylating optically pure oxazaphospholidines was shown to be dependent on the nature (bulkiness) of the alkyl halide and the configuration of the phosphorus atom in starting diastereomer. Thus, the lower stereoselectivity was observed (NMR ^{31}P determination) for preparation of alanine^P (MeI, 58–73% d.e.) and a higher one for phenylalanine^P synthesis ($PhCH_2Br$, 84–92% d.e.). However, the resulting **R**- and **S**-Ala^P were isolated in higher optical purity (e.e. 96% and 98%, respectively) in comparison with **R**- and **S**-Phe^P (e.e. 83% each). The stereoselectivity of alkylating oxazaphospholidine (**8**) was 10–15% higher than alkylating its analog (**9**) under the same reaction conditions.[36]



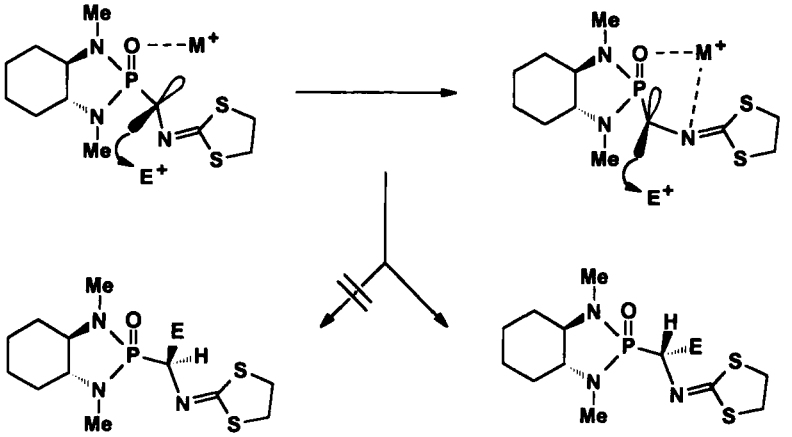
This is a rare example of preparing both **R**- and **S**-aminophosphonic acids using the same chiral auxiliary.

The C_2-symmetrical template (**11**) derived from (1**S**, 2**S**)- or (1**R**, 2**R**)-1,2-bis-(N-methylamino)cyclohexane and chloromethylphosphonic dichloride was alkylated with high diastereoselectivity to give after splitting off the protective groups the corresponding α-aminophosphonic acids in good overall yields and optical purity.[37,38]

An alternative approach is the direct alkylation of chloro derivative (**10**) followed by substitution of the chlorine atom with an amino group. This procedure gave optically active α-aminophosphonic acids with the same absolute configuration of their chiral center despite this route involving an additional S_N2-type reaction. The explanation is the alteration of electrophilic attack (with the same high level of diastereoselectivity) owing to preceded conformational rearrangement of the carbanion generated from iminomethyldithiolane (**11**).[38]



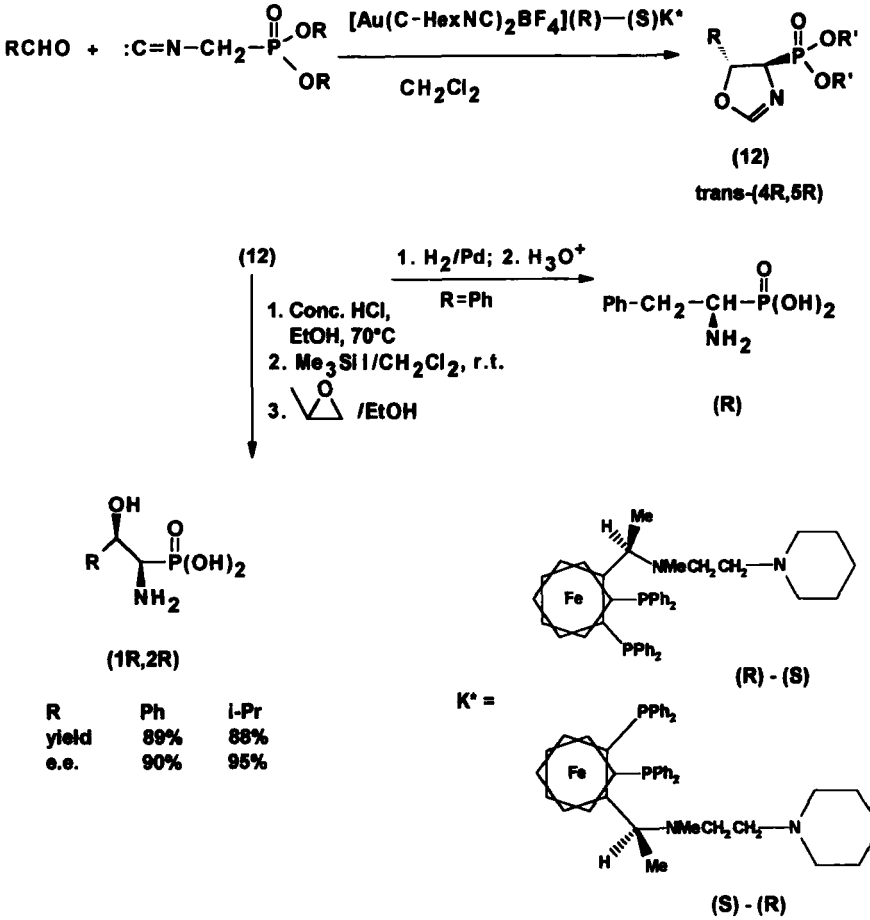
Undoubtedly, the most efficient way of application of enantiomerically pure compounds in asymmetric syntheses is their usage as catalysts. The notable results

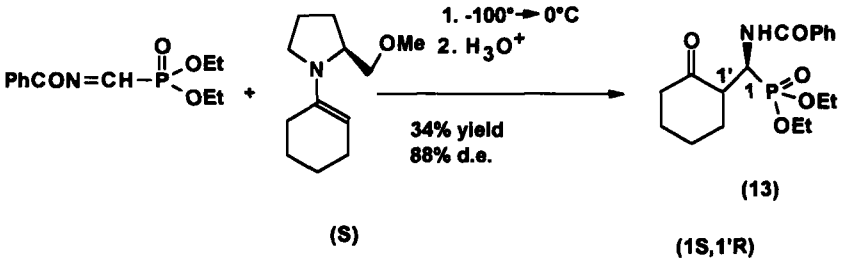


were achieved in the field of enantioselective catalytic hydrogenation of C=C double bonds while the examples of catalytic asymmetric C—C bond forming reaction are rare.

An efficient asymmetric synthesis of phosphonic analogs of phenylalanine and β-alkyl(aryl)serines through gold(I)-catalyzed asymmetric aldol reaction of (isocyanomethyl)phosphonates with aldehydes was proposed by T. Hayashi.[39,40]

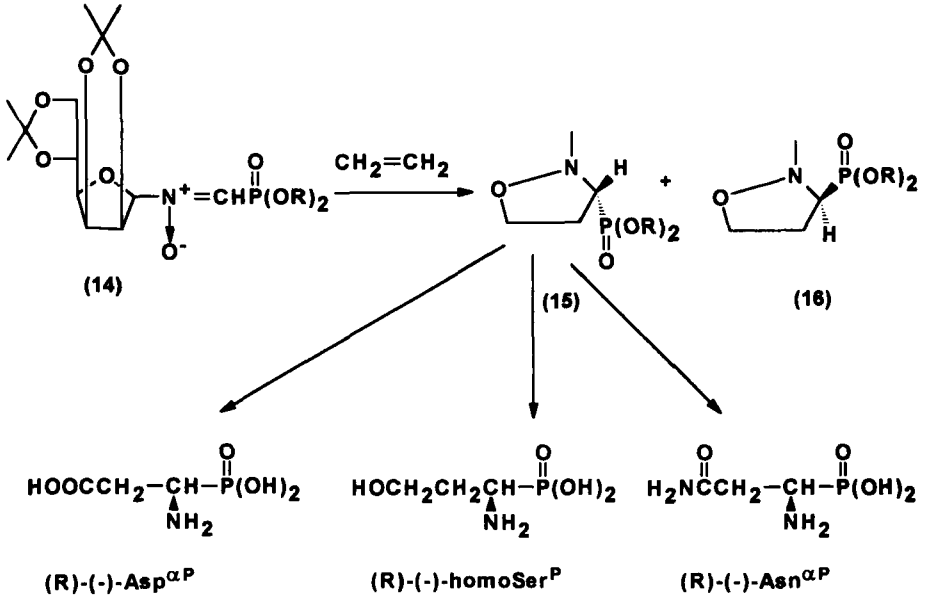
Thus, diethyl (isocyanomethyl)phosphonate was subjected to aldol reaction with aldehydes in the presence of 1 mol% of the gold(I) catalyst bearing a chiral ferrocenylphosphine ligand (**R**)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(**S**)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine [(**R**)-(**S**)-(K*)]. The aldol reaction of diethyl (isocyanomethyl)phosphonate proceeded smoothly at 40–60°C to give a high yield of 5-alkyl(aryl)-2-oxazoline-4-phosphonates (**12**) with excellent enantioselectivity (88–96%) and diastereoselectivity (>98% trans). Palladium-catalyzed hydrogenolysis of oxazoline (**12**) (R = Ph) followed by acidic hydrolysis of the resulting formamide gave (**R**)-(1-amino-2-phenylethyl)phosphonic acid, the phosphonic acid analog of phenylalanine. Treatment of oxazoline (**12**) with conc. HCl formed the corresponding amino ester hydrochloride which was converted by the reaction with iodotrimethylsilane to (1**R**, 2**R**)-(1-amino-2-hydroxy-2-phenylethyl)phosphonic acid.



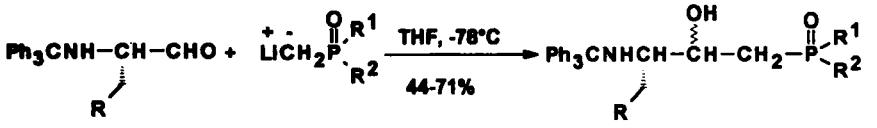


The only example of an asymmetric synthesis of aminophosphonic acids by C—C bond forming reactions in which the alkylating reagent serves as a chiral auxiliary is the nucleophilic addition of a chiral enamine to acylimino phosphonate.[41] The desired product (**13**) was isolated with 88% d.e.

N-Glycosyl-C-dialkoxyphosphonoylnitrones (**14**) were found to react with ethylene to give a mixture of diastereomeric cyclic products (**15**) and (**16**) in ratio 3:1, respectively (chemical yields 80–85%). After resolution on silica gel optically pure (**15**) and (**16**) were elaborated into the free α-phosphonic analogs of aspartic acid, asparagine, and homoserine.[42] The modest diastereoselectivity of the cycloaddition of ethylene to nitrone (**14**) may be rationalized by an (E)/(Z)-equilibration of the nitrone occurring easily under conditions of thermal reaction.



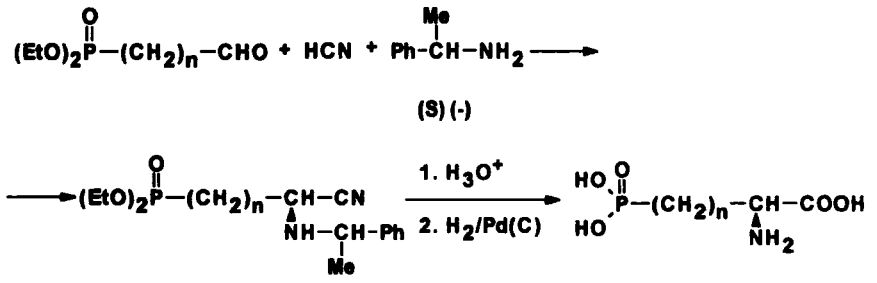
Phosphonic analogs of unusual the amino acid statine [4-(S)-amino-3-(S)-hydroxy-6-methylheptanoic acid] which forms part of the natural pentapeptide pepstatin[43] were prepared *via* addition of lithium derivative of dialkyl methyl phosphonate to enantiopure N-protected aldehydes (**17**) formed from corresponding (L)-amino acids.[44] It was shown that the diastereoselectivity of the addition reaction was nearly uncontrolled neither by the nature of alkyl residue in the starting aldehydes (**17**) nor by the nature of dialkylphosphonic group. The ratio of (2**R**, 3**S**)- and (2**S**, 3**S**)-diastereoisomers formed was changed in narrow limits from 2.3:1 to 3.0:1.[44]



(17)

R=i-Pr, cyclo-C_6H_{11}, Ph; R^1=R^2=MeO, BuO; R^1R^2=$O(CH_2)_3O$

The asymmetric synthesis of ω-phosphonic analogs of (S)-aspartic and (S)-glutamic acids has been carried out by the Strecker reaction from optically pure (S)-α-phenylethylamine and ω-(diethylphosphono)-ethanal or -propanal, respectively. The asymmetric induction achieved in these syntheses was not high (50% d.e.).[45]

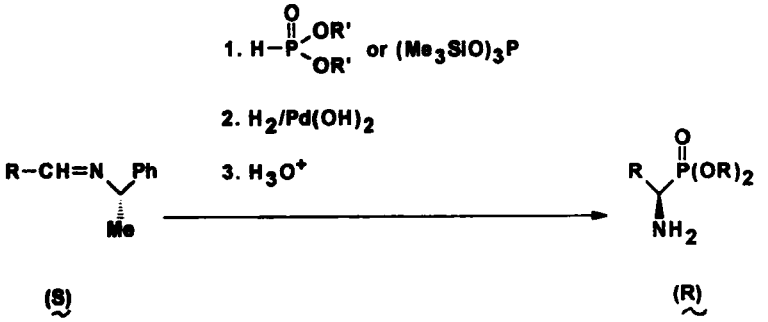


n= 1, 2

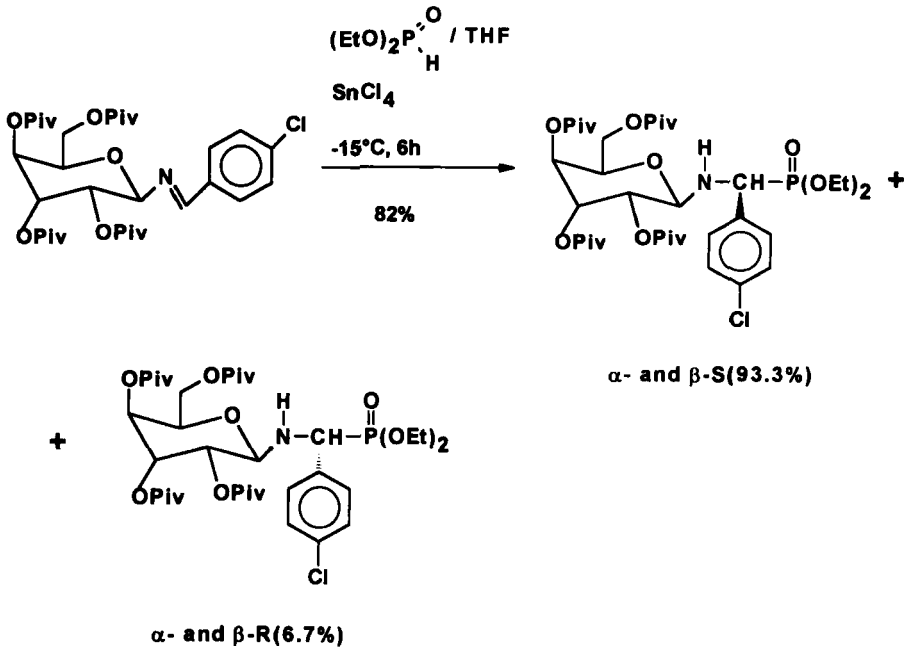
III. ENANTIOSELECTIVE C—P BOND FORMING REACTIONS

The nucleophilic addition of dialkyl(aryl) hydrogen phosphite to the C=N double bond proved to be a very useful approach for asymmetric synthesis of α-aminophosphonic acids. For the first time this methodology was described more than 20 years ago and despite of the rather low diastereoselectivity of addition step the method is still attractive owing to its simplicity and availability of reagents.

In the first syntheses of this type the Schiff bases derived from an appropriate aldehyde and enantiopure α-phenylethylamine—as chiral auxiliary—were examined.[46–48]

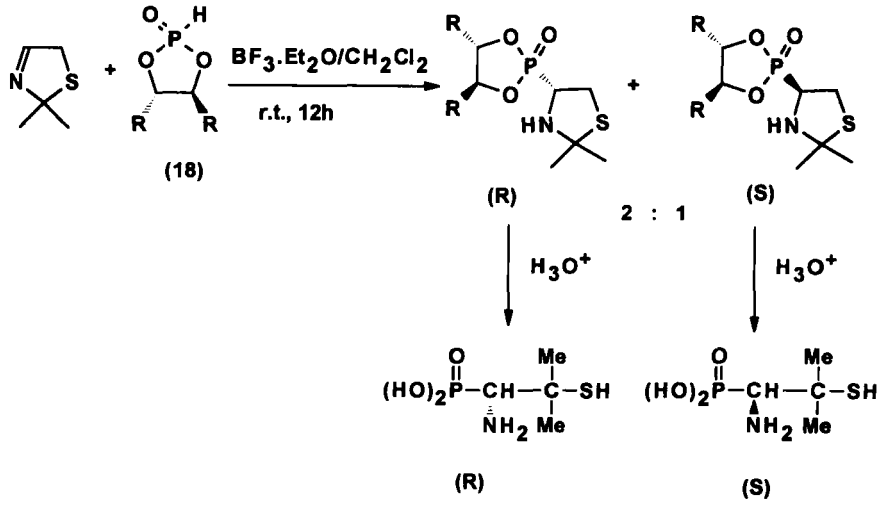


R=Me, Et, i-Pr, Ph



The acid-catalyzed (organic, inorganic, and Lewis acids) addition of dialkyl phosphites to aldimines proceeds with high diastereoselectivity only in the cases of bulky radicals in the aldehyde residue of starting aldimine (R=Ph, i—Pr; up to 80% d.e.) and strongly decreases when small aliphatic groups (R=Me, Et) are present.[47] The attempts to improve the diastereoselectivity of the addition reaction by increasing the bulkiness of the second component of the reaction—phosphite—using it as trimethylsilyl ester, unfortunately, failed.[48]

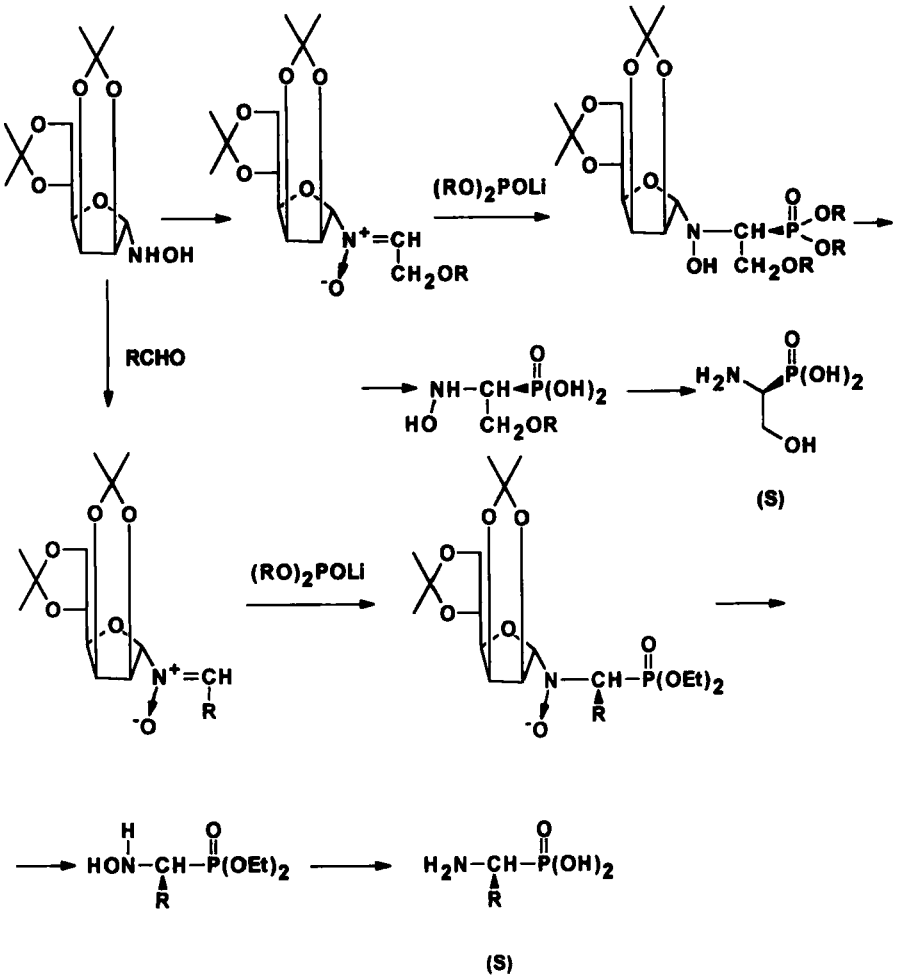
Pretty good results were achieved *via* Lewis acid catalyzed addition of diethyl phosphite to O-pivaloylated N-benzylidene-β-D-galactosylamine or N-benzylidene-α-D-arabinopyranosylamine.[49]

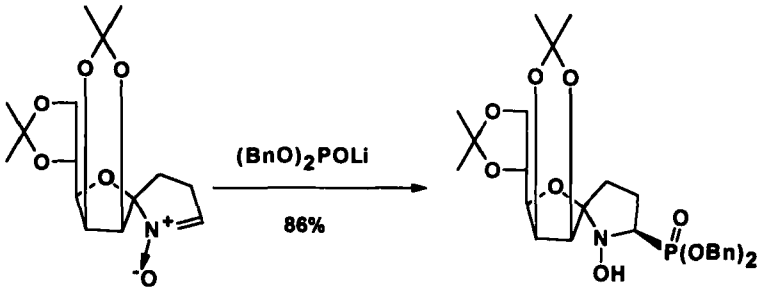


The $SnCl_4$-catalyzed nucleophilic addition of dialkyl phosphites proceeds with high chemical and optical yields to give (S)-α-aminophosphonic acid derivatives from β-D-galactosylamine (see the equation above) and (R)-α-aminophosphonic acid derivatives from α-D-arabinopyranosylamine as the chiral auxiliaries.[49] The resolution of optical isomers formed in this reaction is hindered with the α,β-anomerisation of products, however, in many cases, recrystallization or flash chromatography allow the enrichment of the major diastereomer.

In the asymmetric syntheses of APA by C—P bond forming reactions the chiral auxiliary can be attached not only to the amine fragment but also to the dialkyl phosphite residue. Thus, diastereoselective addition of chiral phosphite (**18**) to azomethine was realized in the synthesis of both enantiomers of phosphonic analog of penicillamine.[50] The diastereoisomeric products were formed in the ratio 2:1.

A considerable contribution to the asymmetric synthesis of α-aminophosphonic acids *via* stereoselective C—P bond forming reactions was made by A. Vasella *et al.* who had studied the nucleophilic addition reactions of dialkyl phosphites to N-glycosylnitrones.[51–53]



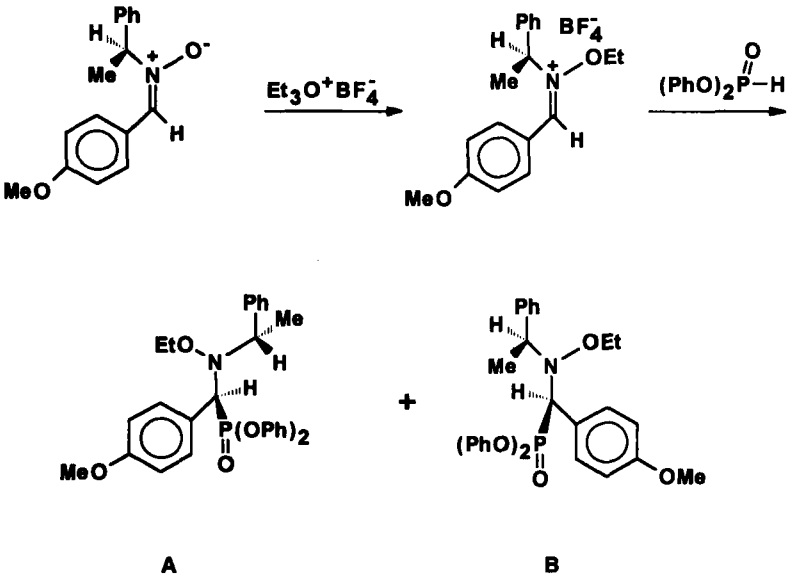


d.e. ~100%

The method allows to obtain α-aminophosphonic acids with small alkyl groups (Ala^P, Val^P) in high optical yields, although a chemical yields in these syntheses are not better than 50%. The diastereoselectivity of adding lithium dialkyl phosphites to the N-glycosyl-C-alkylnitrones is 91–93%. The addition of potassium dialkyl phosphites shows a much lower diastereoselectivity.[51] Notable is the 100% diastereoselectivity in the nucleophilic addition of lithium dibenzyl phosphite to the N-glycosyl spironitrone.[52]

Synthetic potentialities of this methodology are not limited to preparation of α-aminoalkylphosphonic acids. One of the advantages of the method is the possibility of isolating optically active N-hydroxy-α-aminophosphonic acids which are not easily accessible by other approaches. The application of the appropriate aldehydes with protected functional groups allows to produce β-hydroxy-α-aminophosphonic acids (Ser^P) and γ-alkylthio-α-aminophosphonic acids (Met^P).[53]

N-glycosyl-C-arylnitrones are inert to action of dialkyl phosphite anions but can be easily involved into addition reactions with tris(trimethylsilyl)phosphite under catalysis by Lewis acids.[53] Thus, the reaction between tris(trimethylsilyl)phosphite and N-glycosyl-C-arylnitrones gave the corresponding optically active N-hydroxy-



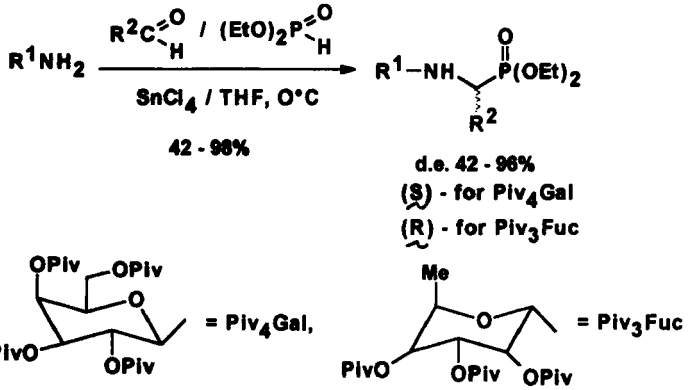
A B

α-aminophosphonic acids, and hence the free phosphonic analogs of phenylglycine in yields up to 92% and with an enantiomeric excess up to 97%. The absolute configuration of the resulting phosphonates depends on the nature and—in one case ($ZnCl_2$)—on the quantity of the catalyst. Thus, catalysis with trace quantities of $ZnCl_2$, gave (−)-(**S**)-α-aminophosphonic acids while an equimolar amount of $ZnCl_2$ yielded (+)-(**R**)-enantiomers.

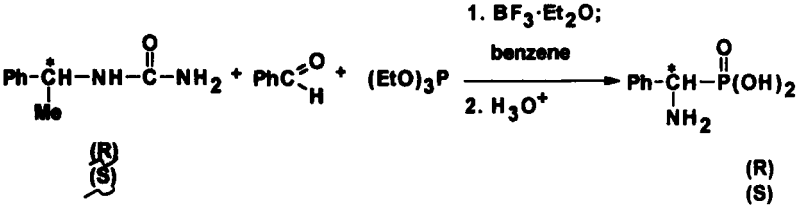
The nitrone bearing chiral α-phenylethyl fragment was converted to its oxoiminium salt with following addition of diphenyl phosphite to give two diastereoisomers in ratio 3:2. The effective resolution of diastereomers was achieved by means of column chromatography on alumina. The absolute configuration of optically pure diastereomers was not established although the authors assumed that the dominant isomer (A) resulted from the *si*-face attack of the C=N double bond.[54]

The N-acylimino derivative of (−)-ω-camphanic acid in reaction with dialkyl phosphites gives diastereoisomeric products which after separation were hydrolyzed to optically active enantiomers of Phe^P.[55]

Other methods of organophosphorus chemistry for C—P bond formation in asymmetric syntheses of aminophosphonic acids are rarely applied. Thus, β-D-galactosylamine and β-L-fucopyranosylamine were involved in a Kabachnik-Fields reaction to give the corresponding (**S**)- and (**R**)-α-aminophosphonate, respectively, in e.e. from 42% to 96% which corresponds to the values obtained in the addition reactions of dialkyl phosphites to Schiff bases formed from the same glycosylamines.[49]

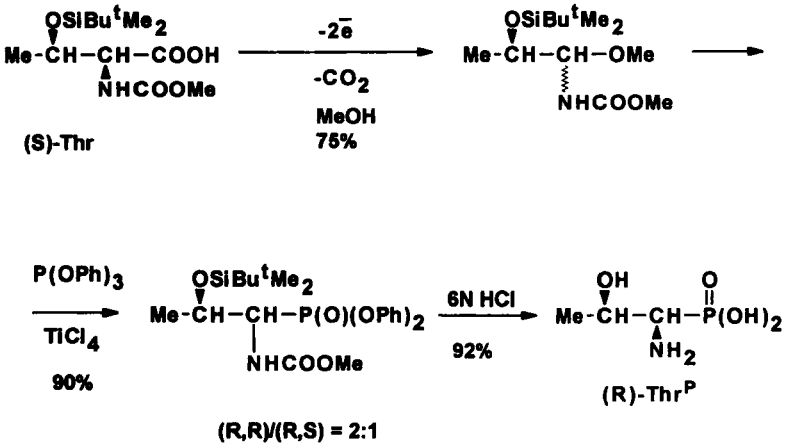


The asymmetric version of Arbusov reaction (or its modifications) was one of the first approaches used to obtain optically active α-aminophosphonic acids. In these syntheses chiral N-monosubstituted ureas [formed from (**S**)- or (**R**)-α-phenylethylamine][56] or chiral carbamates {formed from (−)-menthol or 1,7,7-trimethylspiro[bicyclo-[2,2,1]-hepten-3,2-indane]-2-ol [(**R**)-(+)-camphor derivative]}[57] were used.

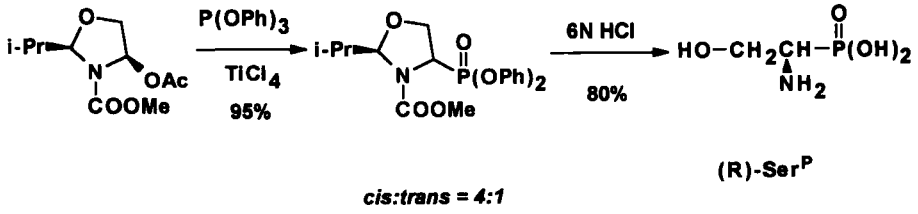


The optical purity of aminophosphonic acids obtained by this procedure is low (e.e. from 8.3 to 42.2%). A remarkable feature of this reaction is the inversion of the absolute configuration in comparison with the addition described above of dialkyl phosphites to the C=N double bond. Thus, when optically active ureas derived from (**R**)-α-phenylethylamine are employed, the reaction with aldehydes affords the corresponding (**R**)-aminophosphonic acids as the main products.[56] Contrary, the addition of dialkyl phosphites to aldimines derived from (**R**)-α-phenylethylamine gave aminophosphonic acids with (**S**) configuration of chiral carbon atom.[46,56]

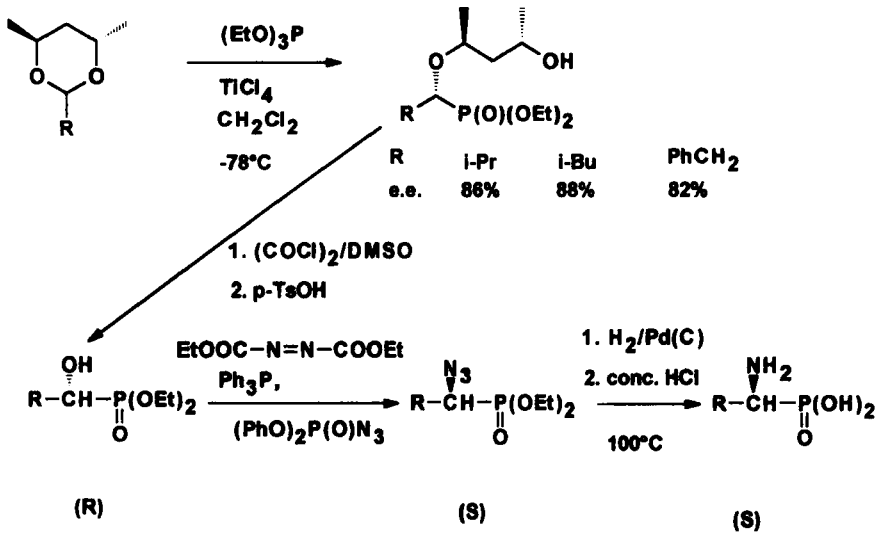
$TiCl_4$-Catalyzed reactions of phosphites with N,O-acetals obtained by oxidative electrolytic decarboxylation of N-acylated amino acids and peptides in protic media result in low to moderate diastereoselectivity. Pure diastereoisomers obtained after crystallyzation were transformed into the optically active phosphonic analogs of threonine.[58]



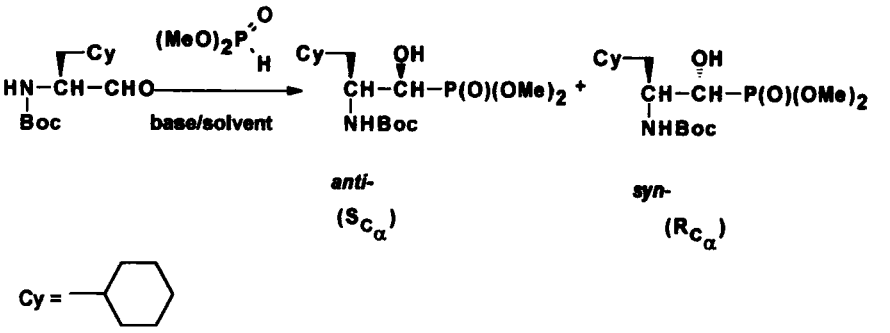
Starting with the cyclic N,O-acetal prepared from L-serine methyl ester and isobutyraldehyde, the phosphonic analog of L-serine was obtained in a similar manner.[58]



Recently, triethyl phosphite was found to open stereoselectively enantiopure acetals derived from (+)-(2S, 4S)-pentanediol. Major diastereoisomers, readily separated by column chromatography on silica gel, were converted by Swern oxidation into the corresponding α-hydroxyphosphonates. Further transformation of the alcohols to the corresponding azides in a S_N2 process was readily achieved by the Mitsunobu reaction. Catalytic hydrogenation of the azides with 10% Pd/C in ethanol under atmospheric pressure afforded corresponding amino esters which were hydrolyzed to free aminophosphonic acids (Val^P and Leu^P).[59]



Stereoselective base-catalyzed addition of dimethyl phosphite to a chiral aldehyde (formed from L-phenylalanine) gave the mixture of diastereomeric β-amino-α-hydroxy phosphonates. In dependence on solvent and base employed the ratio of *syn*- and *anti*-isomers changed from 1.2:1.0 (DBU/DMF) to 12:1 (KF/DMF).[60]

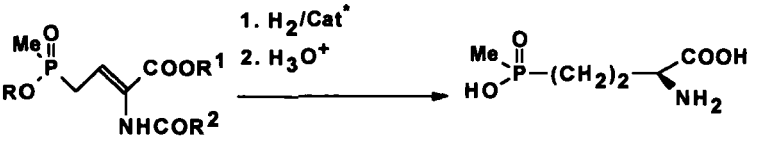


IV. ENANTIOSELECTIVE C—H BOND FORMING REACTIONS

While the asymmetric hydrogenation of α-acylamido acrylic acid derivatives, which leads to the formation of corresponding optically active α-amino carboxylic acids, has been extensively investigated, only a few reports have appeared on the synthesis of their phosphorus analogs.

Thus, asymmetric synthesis of both enantiomers of phosphinothricin was achieved *via* asymmetric hydrogenation of α-acylamido acrylate in the presence of rhodium (I) complexes derived *in situ* from the chiral bis(phosphines) (S,S)-DIOP, (R)-PROPHOS, (R,R)-NORPHOS, and (S,S)-CHIRAPHOS and equimolar amounts of chloronorbornadien-rhodium dimer.[61]

The enantioselectivity of the reaction was found to depend essentially on the solvent polarity and the concentration of the substrate. The highest enrichment of (S)-phosphinothricin was achieved with the (R,R)-NORPHOS catalyst system (e.e.

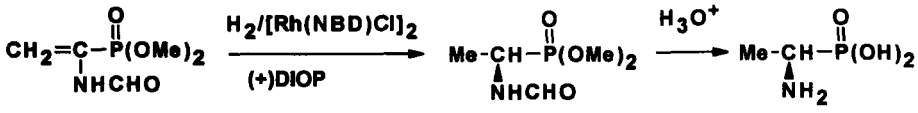


(S)

Cat* = (S,S)-DIOP; (R)-PROPHOS; (R,R)-NORPHOS;

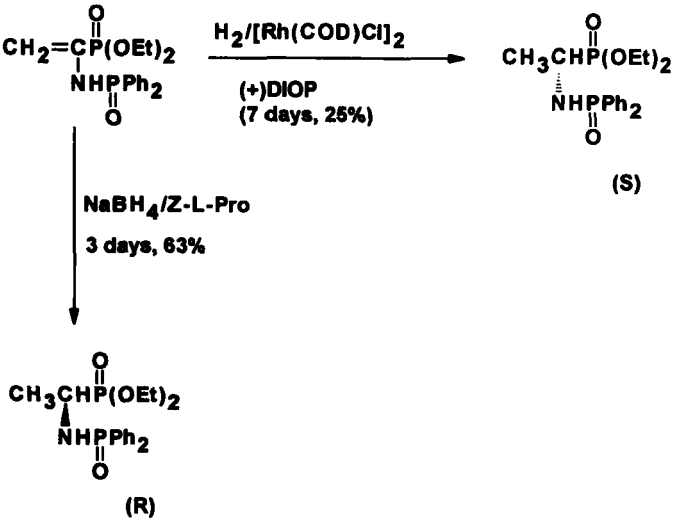
90.8%), while the (S,S)-CHIRAPHOS-derived catalyst afforded the (**R**)-enantiomer with e.e. of 91%.

In the case mentioned above the methyl phosphinate moiety is separated from the double C=C bond by a methylene group and seems to have no substantial influence on the catalytic process. An interesting example of asymmetric hydrogenation of N-[1-(dimethoxyphosphoryl)-1-alkenyl formamides was described by U. Schöllkopf.[62] In this case the dialkyl phosphonic moiety attached immediately to the C=C double bond can be expected to influence on the intermediate complex formation with the catalyst. Indeed, it was shown that hydrogenation of the (N-formyl)dehydroaminophosphonic acid ester (**19**) using a rhodium catalyst in the presence of (+)-DIOP as a chiral ligand takes place much more sluggishly in comparison with hydrogenation of α,β-dehydro amino carboxylic acid esters.[62]



(19) (R)-Ala^P

U. Schöllkopf supposed that this is due to the bulkiness of the dimethoxyphosphoryl group (the diethoxyphosphoryl derivative was practically inert towards hydrogenation). The initially formed N-formyl aminophosphonate was hydrolyzed to



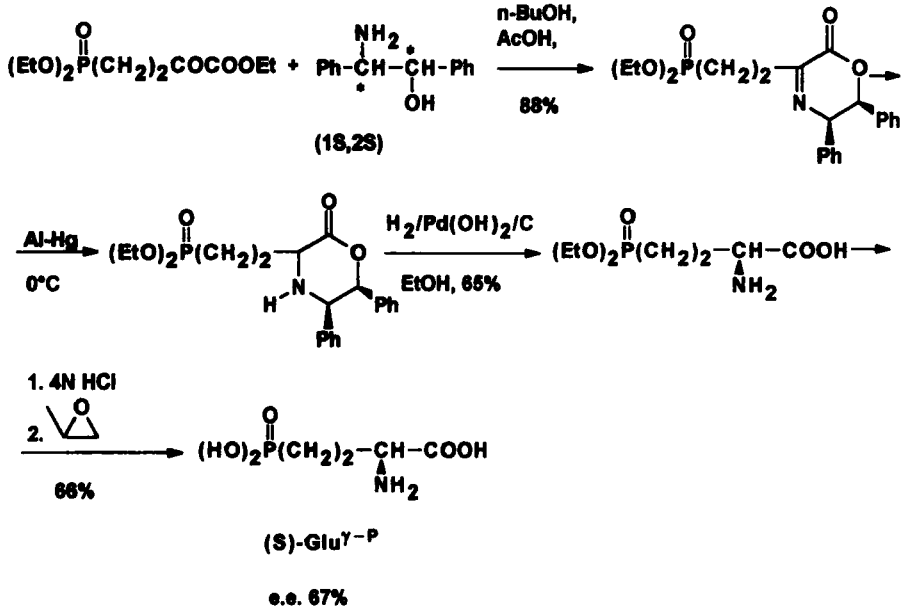
give the phosphonic analog of alanine with e.e. 76%; by a single crystallization from water/methanol the optical purity of (R)-Ala^P was increased to 93%.

Attempts to use catalysts with (+)-DIPAMP and (+)-NORPHOS ligands under the normal hydrogen pressure were unsuccessful.

It is known that optical yields in the rhodium catalyzed hydrogenation of dehydroamino acid derivatives depend not only on the chiral ligand employed but also on the structure of the substrate. Thus, substitution of diethyl 1-diphenylphosphinoamino-1-methylidenemethanephosphonate for N-[1-(dimethoxyphosphoryl)ethyl]formamide in the hydrogenation reaction in the presence of Rh-(+)-DIOP catalyst results in nearly complete loss of enantioselectivity (3% e.e. of (S)-enantiomer).[63]

It is interesting to note that the reduction of this substrate with $NaBH_4$ in the presence of N-benzyloxycarbonyl-L-proline gave preferably (12% e.e.) (R)-enantiomer of alanine^P derivative.[63]

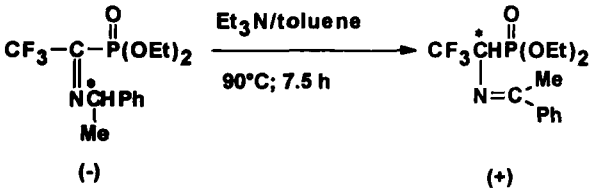
Enantioselective C—H bond formation with a reduction of a C=N double bond was described recently for asymmetric synthesis of (S)-(+)-2-amino-4-phosphonobutanoic acid.[64] The procedure includes cyclic condensation of ethyl-4-diethoxyphosphonyl-2-oxo-butanoate with (L)-*erythro*-(+)-1,2-diphenyl-2-hydroxyethylamine, followed by the aluminium amalgam catalyzed reduction and hydrolysis of the intermediates to free aminophosphonic acid isolated in 67% e.e.



Raney nickel, platinum, or palladium on charcoal were found to be much more effective catalysts than aluminium amalgam but the reduction of the C=N double bond in the presence of these catalysts always suffered from the simultaneous destruction of the oxazine ring which plays a key role in the chiral induction, and so, the racemic product was isolated.

Another example of an enantioselective C—H bond forming reaction in the asymmetric synthesis of α-aminophosphonic acids is a base-catalyzed 1,3-proton

shift in Schiff base derived from diethyl 2,2,2-trifluoro-1-oxoethylphosphonate and (−)-α-phenylethylamine as a chiral auxiliary group.[65]

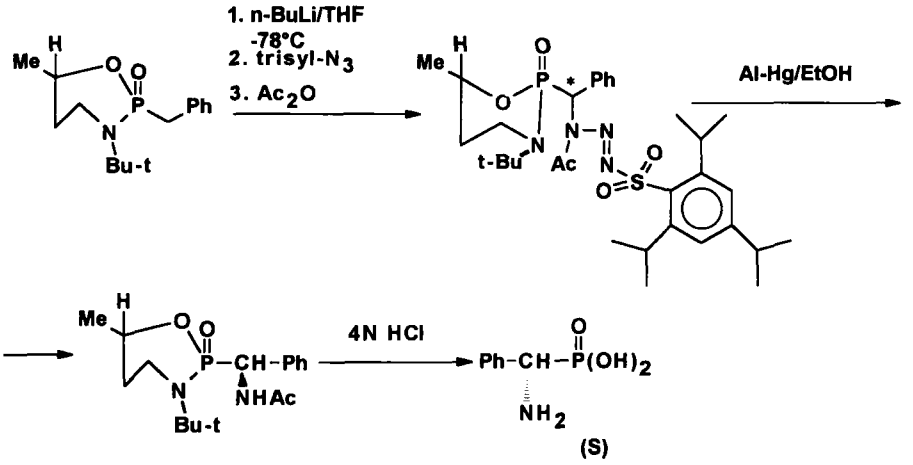


The mechanism of this transformation seems to be similar to the generally accepted one for an isomerisation of α-keto carboxylic acid derivatives.[66] But, in contrast to α-keto carboxylic acids transamination reactions, in this case enantioselectivity of proton transfer is low (22% e.e.). Apparently due to the high acidity of the C_α-H fragment, racemisation can take place. The absolute configuration of the phosphonic analog of trifluoroalanine obtained has not been established.[65]

V. ENANTIOSELECTIVE C—N BOND FORMING REACTIONS

One of the most promising approaches to the asymmetric synthesis of α-aminophosphonic acids is a stereoselective electrophilic amination of chiral phosphorus-stabilized anions which have been developing by S. E. Denmark *et al.*[67] Thus, several chiral oxazaphosphorinanes and oxazaphospholidines derived from alkylphosphonic dichloride and appropriate optically pure amino alcohols were examined as substrates for the amination process. The asymmetric induction was shown to be dependent upon the chiral auxiliary, the nature of the P-alkyl substituent and the amination procedure. Trisyl azide (2,4,6-triisopropylphenylsulfonyl azide) was found to be the most efficient reagent for the amination process. The best optical yield (92% e.e.) was achieved in the synthesis of phosphonic analog of phenylglycine.

Substitution of ethyl or 2-phenylethyl groups for a P-benzyl group resulted in substantial decrease of stereoselectivity of the amination.[67]



VI. CONCLUSIONS

Recently the asymmetric synthesis of phosphorus analogs of amino acids which started in the early 1970s is attracting the growing interest of investigators. Both traditional methods of amino acid synthesis (for example, the alkylation of the glycine synthon enolates or the hydrogenation of N-acyldehydro-α-amino acids) and specific approaches of organophosphorus chemistry (for example, Arbusov and Kabachnik-Fields reactions or addition of dialkyl phosphites to azomethines and aldehydes) find application for asymmetric syntheses of APA. The specific properties of phosphorus open some new possibilities even for the traditional approaches. Thus, in glycine^{P} synthon alkylations the tetracoordinated phosphorus atom can be involved itself in stereodifferential group formation.

A large number of optically active APA are available by the developed methodology of asymmetric synthesis. However, in some cases chiral APA are obtained in low or moderate optical yields thus prompting the search for more efficient methods. Apparently, the further development of APA asymmetric syntheses will be directed towards search and usage of new efficient chiral auxiliaries and a frequent application of catalytic variants in asymmetric syntheses. In view of the microbial production of some phosphorus analogs of amino acids,[2,68] the possibility of the enzyme usage to create the chiral centers in APA must also be taken into consideration.

The asymmetric synthesis of APA is in a stage of dynamic development and can be considered as a valuable approach for obtaining optically active phosphorus analogs of amino acids.

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