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Asymmetric synthesis of fluorine- and phosphorus-containing analogues of aminoacids

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Abstract. The available literature data on the methods for the asymmetric synthesis of fluorine- and phosphorus-containing aminoacids are surveyed. The chemical and enzymic methods of the asymmetric synthesis of the above compounds are considered. The bibliography includes 139 references.

I. Introduction

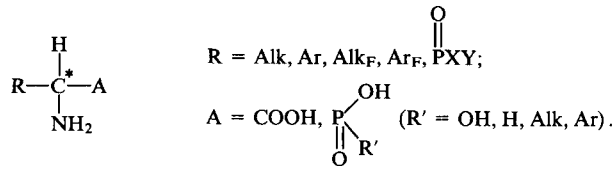
The synthesis of organoelement analogues of natural products and in the first place of element-containing aminoacids is one of the most vigorously developing fields in modern organic chemistry.[1] There exist natural element-containing aminoacids; bromine-,[2] chlorine-,[3] fluorine-,[4] and phosphorus-containing aminoacids[5, 6] have been isolated from various sources. The unique biological activity of natural element-containing aminoacids has served as a powerful stimulus which initiated vigorous research in this field.

Numerous element-containing aminoacids have been synthesised hitherto, among which special emphasis must be laid on fluorine- and phosphorus-containing aminoacids. The majority of these aminoacids are metabolites of the 'normal' aminoacids. They exhibit the properties of highly selective (as regards the specificity of their activity) inhibitors of enzyme reactions and they possess high carcinostatic, bactericidal, cytotoxic, and other forms of biological activity. Thus more than 20 studies devoted to various aspects of the synthesis and biological activity of fluorine-,[7–24] phosphorus-,[25–35] boron-,[36] and selenium-containing aminoacids[37] have now been published.

Analysis of the literature data shows that the most urgent problem in the chemistry of organoelement aminoacids is that of the development of methods of synthesis of these compounds in an enantiomerically pure form, which is dictated by modern requirements in biology and medicine. Unfortunately, in most cases racemic synthesis is considered in the reviews quoted above and the main aspects of the asymmetric synthesis of element-containing aminoacids (the nature of the enantioselectivity, the optical purity, and the absolute configuration) are hardly discussed.

The present review deals with the methods of asymmetric synthesis of fluorine- and phosphorus-containing aminoacids published up to the middle of 1992 inclusive. We were guided by the fundamental classical definition of asymmetric synthesis, given in the monograph of Morrison and Mosher,[38] as a process in which a prochiral molecule or its fragment is converted into a chiral molecule with unequal amounts of the stereoisomeric products. The process takes place under the influence of chiral reagents, part of the initial molecule, or the catalyst. The methods of synthesis of enantiomerically pure or optically active organoelement aminoacids (C – F, C – P) involving the direct introduction of the element into complete aminoacid enantiomers or involving enzymic or chemical separation of racemic compounds will therefore not be considered in the present review.

The entire data are described in five main sections depending on the type of bond formed at the chiral centre of the α-aminoacid, while syntheses using enzymes have been collected in a separate section.



II. Enantioselective formation of the C – C bond

The asymmetric synthesis of element-containing aminoacids is most widely represented by examples of the enantioselective formation of the C – C bond on alkylation of chiral Schiff bases. These can be readily obtained from the esters of the simplest aminoacids and chiral carbonyl compounds, which can be regenerated and used in new syntheses. The formation of Schiff bases increases the CH acidity of the aminoacid fragment and permits the generation of a carbanion under the influence of bases of different strengths and its subsequent reactions with various electrophiles.[39]

Camphor and its derivatives are frequently used as the chiral carbonyl compound in the above synthesis, which is due to their ready availability in both enantiomerically pure forms.

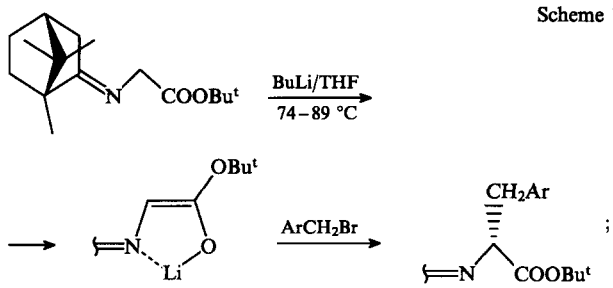
V P Kukhar', N Yu Svistunova, V A Solodenko, V A Soloshonok Institute of Bioorganic Chemistry and Petrochemistry, Academy of Sciences of the Ukraine, Murmanskaya ul. 1, 252660 Kiev-94, Fax (7-044) 543 5152

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In most cases the chiral Schiff base is deprotonated with butyllithium or lithium diisopropylamide and the carbanion formed is made to react with alkyl halides, carbonyl compounds, or Michael acceptors.

Thus the (*R*)-enantiomers of *p*-fluoro- and *p*-trifluoromethylphenylalanines have been synthesised[40] by alkylating the Schiff base formed from the *tert*-butyl ester of glycine and (*R*)-camphor with the corresponding benzyl bromides (Scheme 1).

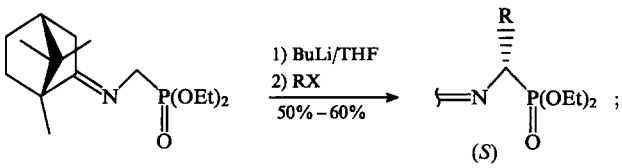
Scheme 1



Ar = 4-FC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$.

The attack by the lithium derivative comes predominantly from the *re*-side [the side opposite to the C(8) atom of camphor], affording products with a diastereo-isomeric excess (d.e.) > 98% (F) and 79% (CF_3), which is controlled kinetically. It is of interest to note that high values of d.e. are observed in this synthesis only when benzyl and allyl halides are used as alkylating agents (in the case of EtBr, d.e. = 33%). This has been attributed[40] to the additional $\pi-\pi$ interaction in the transition state between the π-system of benzyl or allyl halides, which has a positive character after the partial dissociation of the C–Br bond, and the π-system of the enolate. This hypothesis has been confirmed by the dependence of the d.e. on the nature of the substituent in the benzene ring and benzyl bromide. A series of (*S*)-α-aminoalkylphosphonic acids have been synthesised by a similar procedure using the Schiff base obtained from (*R*)-camphor and diethyl aminomethylphosphonate (the phosphonoglycine synthon),[41] the maximum enantioselectivity of the alkylation being achieved, as in the study of McIntosh et al.,[40] in the case of allyl and benzyl halides (Scheme 2).

Scheme 2



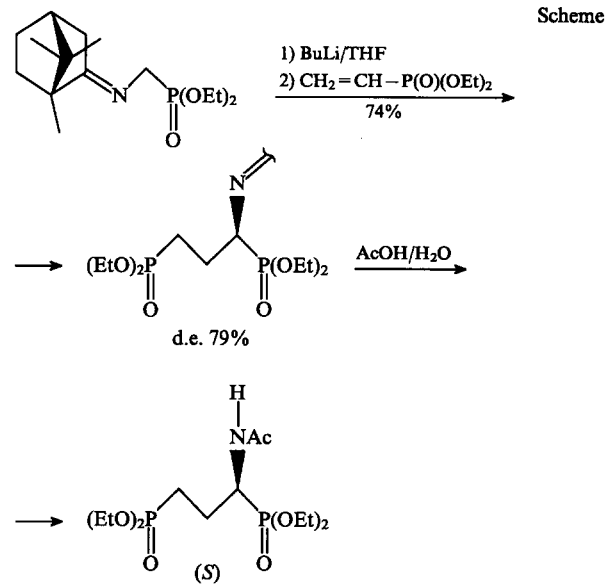
R	$CH_2CH=CH_2$	$PhCH_2$	$CH_2-C\equiv CH$
d.e. (%)	>95	>95	71

R	Me	Et	Pr	$MeOCH_2$
d.e. (%)	11	69	77	56

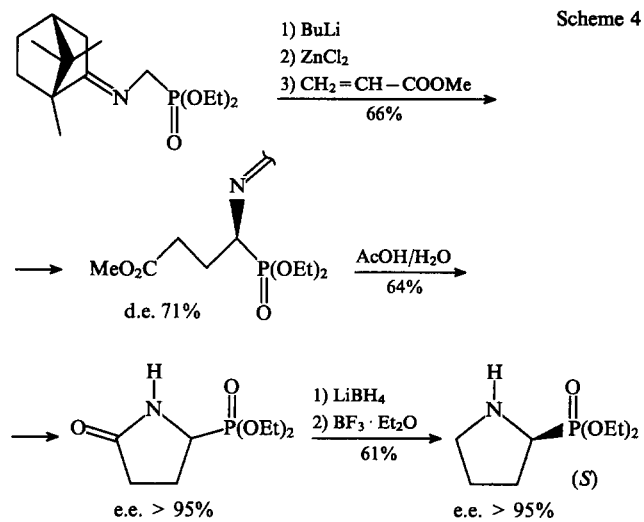
The possibilities of the phosphonoglycine synthon may be expanded by using it for the Michael addition to activated carbon–carbon double bonds.[42]

The kinetically controlled addition of vinylphosphonate or methyl acrylate to the lithium derivative of the Schiff base takes place with high values of the d.e., affording esters of the phosphono-analogues† of (*S*)-Glu$^{\alpha,\omega\text{-P}}$ and (*S*)-Glu$^{\alpha\text{-P}}$. The ester of (*S*)-phosphonoproline was obtained from the latter in two stages (Scheme 3 and 4).

Scheme 3



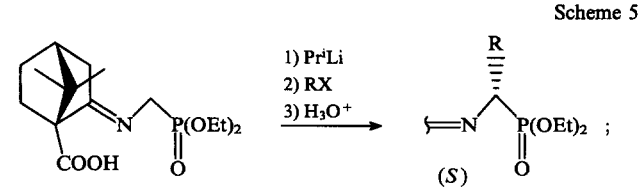
Scheme 4



e.e. = enantiomeric excess.

The use of (*R*)-ketopinoic acid (a camphor derivative), instead of camphor itself, for the synthesis of the chiral phosphonoglycine synthon hardly affects the enantioselectivity of the alkylation and leads to the (*S*)-phosphonic acid with high values of d.e. only in the case of the allyl and benzyl derivatives (Scheme 5).[43]

Scheme 5

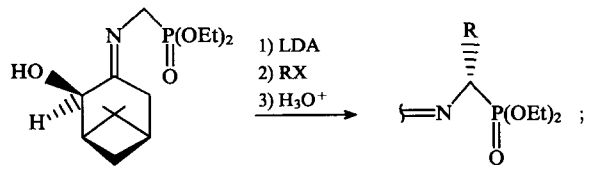


R	Me	Et	CH_2Ph	$CH_2CH=CH_2$
Yield (%)	67	68	93	65
d.e. (%)	15.1	62	79	92

† Three-letter designations of aminoacids with the superscript 'P' are used to designate the phosphorus analogues of natural aminoacids. In the case of the phosphorus analogues of aspartic and glutamic acids, the additional superscripts α, β, and γ, indicating the position of the phosphorus-containing group, are introduced.

The phosphonoglycine synthon, obtained from (1*R*, 2*R*, 5*R*)- or (1*S*, 2*S*, 5*S*)-2-hydroxypinan-3-one, gives a more stable stereochemical result which depends little on the nature of the alkylating agent (Scheme 6).[41, 44–46]

Scheme 6



(1*R*, 2*R*, 5*R*) (1*S*, 2*S*, 5*S*) (*R*) (*S*)

R	Me	Et	$PhCH_2$	$CH_2=CHCH_2$
Yield (%)	90	85	71	70
d.e. (%)	74–85	95	83	74

R	$CH_2-C\equiv CH$	$(CH_2)_5I$	$(CH_2)_2OTHP$
Yield (%)	85	72	85
d.e. (%)	83	69	~100

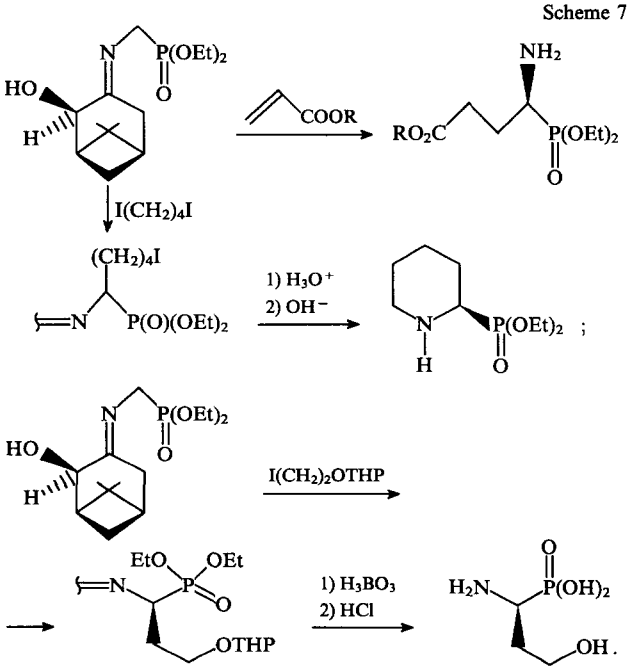
LDA = *N*-lithium diisopropylamide, OTHP = *O*-tetrahydropyranyl.

In this case, phosphonic aminoacids can be obtained with a high optical purity even when their alkyl groups are small.

The nature of the asymmetric induction in the alkylation of the Schiff base obtained from phosphonoglycine and hydroxypinanone has not been discussed,[44, 45] but one can postulate the important role of the hydroxy-group in the α-position relative to the C=N bond in the coordination of the metal during the reaction. Thus the replacement of LDA by *tert*-BuOK in this synthesis leads to the alkylation of the hydroxyl (MeI) and a decrease in the diastereoselectivity of the alkylation of the Schiff base from 85% to 45% (R = Me).

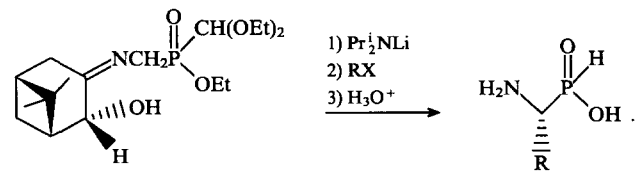
The use of α,ω-dihaloalkanes makes it possible to obtain cyclic phosphonic aminoacids (proline homologues), which is illustrated in relation to the synthesis of (*S*)- or (*R*)-homoproline, while the Michael addition of methyl acrylate affords the α-phosphonic analogue of glutamic acid with 87% enantiomeric purity, from which the esters of (*S*)- and (*R*)-Pro^{P} were obtained in several stages (Scheme 7).[44]

Scheme 7



The only example of the asymmetric synthesis of α-aminoalkylphosphonous acids also involves the stereoselective alkylation of a chiral Schiff base obtained from (1*R*, 2*R*, 5*R*)-2-hydroxy-3-pinanone and ethyl aminomethyl(diethoxymethyl)-phosphinic acid with benzyl bromide (d.e. > 99%) and methyl iodide (d.e. 56%).[47] After the hydrolysis of the alkylation products under mild conditions, optically active phosphonous analogues of phenylalanine (*R*)-Phe^{P-H} (d.e. > 99%) and alanine (*R*)-Ala^{P-H} (d.e. 46%) were isolated (Scheme 8).

Scheme 8



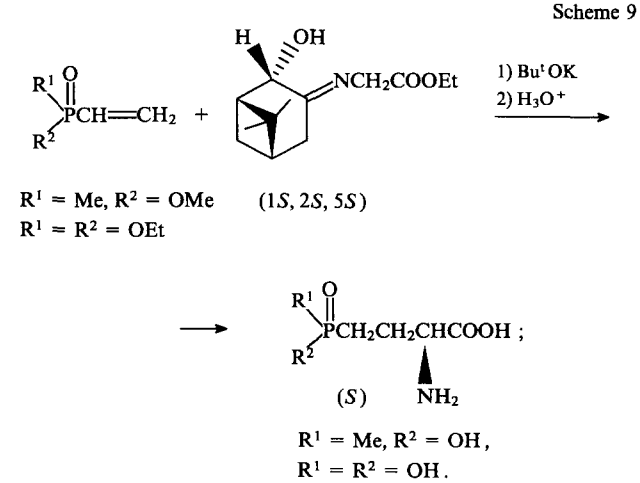
(1*R*, 2*R*, 5*R*) (*R*)

The use of the Schiff base derived from (1*S*, 2*S*, 5*S*)-2-hydroxy-3-pinanone leads to the formation of another enantiomer of the phosphonous analogue of phenylalanine–(*S*)-Phe^{P-H} (e.e. > 99%).

The authors note the dependence of the stereoselectvity of the alkylation of the Schiff base on the nature of its acid function: the diastereoselectivity of the benzylation ($PhCH_2Br$) increases appreciably in the sequence COOEt < $P(O)(OEt)_2$ < P(O)·$\cdot(OEt)CH(OEt)_2$ and amounts to 75%, 83%, and 99% respectively.

The addition of chiral Schiff bases derived from hydroxypinanones to vinylphosphonates and vinylphosphinates has been used for the asymmetric synthesis of α-amino-γ-phosphonobutyric acid [(*S*)-(+)-Glu$^{\gamma\text{-P}}$] and (*S*)-(+)-phosphinotricin [(*S*)-(+)-Glu$^{\gamma\text{-P-Me}}$] as well as their (*R*)-(−)-enantiomers (Scheme 9).[48]

Scheme 9



R^1 = Me, R^2 = OMe (1*S*, 2*S*, 5*S*)
$R^1 = R^2$ = OEt

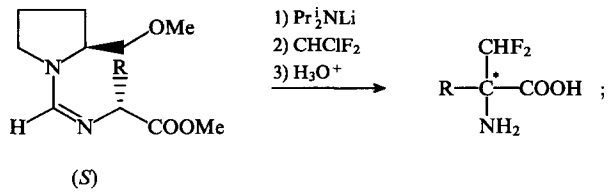
R^1 = Me, R^2 = OH,
$R^1 = R^2$ = OH.

The stereoselectivity of the process is appreciably higher in addition to vinylphosphinate (d.e. 73% and 79%) than in addition to vinylphosphonate (45% and 50%) and decrease by 25% – 30% in the presence of additives which effectively solvate the cation (hexamethylphosphoramide, crown-ether). On this basis, the authors conclude that the coordination of the electron pairs of the nitrogen atom and of the oxygen atom of the phosphoryl group to the metal ion (K^+) exerts a decisive influence on the stereoselectivity of the addition reaction.

The use of chiral inducing reagents of another type — proline derivatives — in the asymmetric synthesis of element-containing aminoacids has been demonstrated in relation to the synthesis of α-difluoromethylalanine and α-difluoromethylphenylalanine by alkylating with chlorodifluoromethane the lithio-derivative of

the Schiff base obtained from (*S*)-1-dimethoxymethyl-2-methoxymethylpyrrolidine and the esters of the corresponding aminoacids (Scheme 10).[49]

Scheme 10



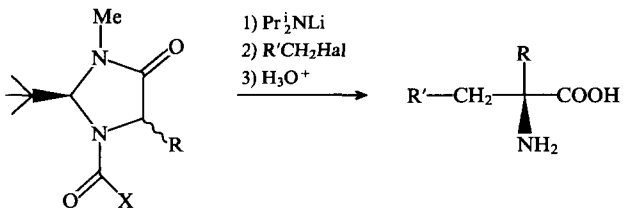
(*S*)

R = Me, CH_2Ph.

The enantioselectivity of the reaction and the absolute configuration of the aminoacids formed are not discussed in the above communication.[49] However, the [1,5]-asymmetric induction occurring in this instance is as a rule weak.[50]

The alkylation of rigid cyclic synthons usually takes place with a higher diastereoselectivity than in the case of linear systems. The advantages of using cyclic synthons have been demonstrated particularly convincingly in the studies by Seebach et al.,[51] Schöllkopf,[51] and Belokon' et al.[53] Thus the lithio-derivative obtained from (*S*)-1-*tert*-butoxycarbonyl-2-(*tert*-butyl)-3-methyl-4-imidazolidinone (R = H) is alkylated diastereospecifically with *p*-fluoro- or pentafluoro-benzyl bromides, affording, after the hydrolysis of the alkylation products, (*S*)-*p*-fluoro- and (*S*)-pentafluoro-phenylalanines with an optical purity >98% (Scheme 11).[54, 55]

Scheme 11



R = H, Me; R′ = 4-FC_6H_4, C_6F_5, 2-FC_6H_4, 3-FC_6H_4; X = CH_2Ph, $OCMe_3$.

The alkylation of the alanine synthon (R = Me) with fluorobenzyl halides led to the formation of the isomeric (*S*)-α-methyl derivatives of *o*-, *m*-, and *p*-fluorophenylalanines with an equally high optical purity.[56]

The lithio-derivative of imidazolidinone (R = H) as well as another chiral glycine synthon used by Seebach, namely benzyl-(*R*)-2-(*tert*-butyl)-5-oxo-3-oxalidine carboxylate, have been used in the synthesis of (2*S*, 3*S*)-trifluorothreonine‡ and (2*S*, 3*R*)-*p*-trifluoromethyl- and (2*S*, 3*R*)-*o*-fluorophenylserines (Scheme 12).[57, 58]

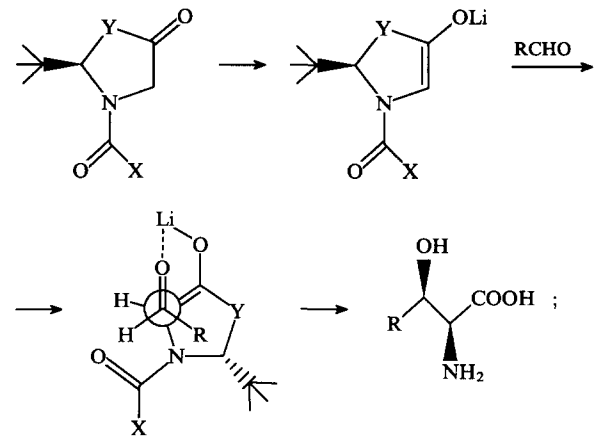
The high stereoselectivity of the reaction can be explained by the preference for one of the possible transition states in which minimum steric interactions and maximum overlap of the donor and acceptor π-systems of the reacting molecules are insured.

The alkylation of the lithio-derivative of the chiral bislactim ether with ω-phosphonoalkyl bromides (Schöllkopf's method) takes place with a high stereoselectivity, which has been used for the asymmetric synthesis of optically active carboxylic α-amino-ω-phosphono-acids and their esters (Scheme 13).[59]

The phosphorus-containing bislactim ether formed in the first stage can be realkylated, which ultimately leads to α-substituted γ-phosphonic analogues of (*S*)-glutamic acid.

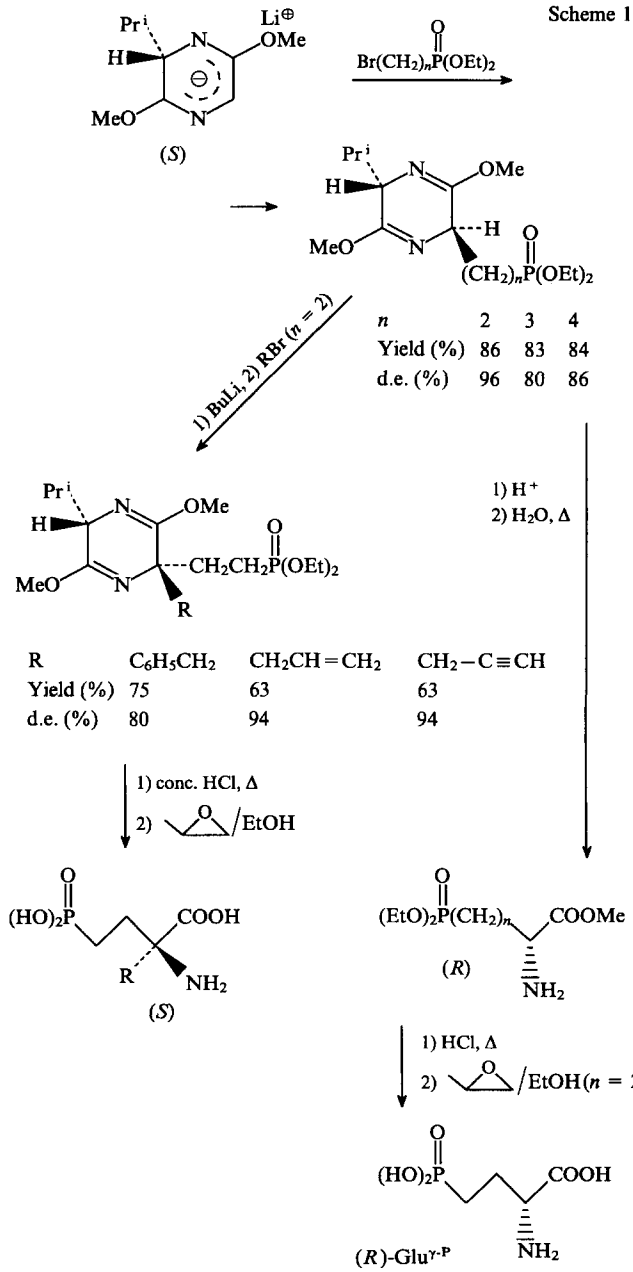
‡ Seebach et al.[58] erroneously attributed the (2*S*, 3*R*)-configuration to the aminoacid obtained.

Scheme 12



R = CF_3, 4-$CF_3C_6H_4$, 4-FC_6H_4; X = Ph, $PhCH_2O$; Y = O, NMe.

Scheme 13

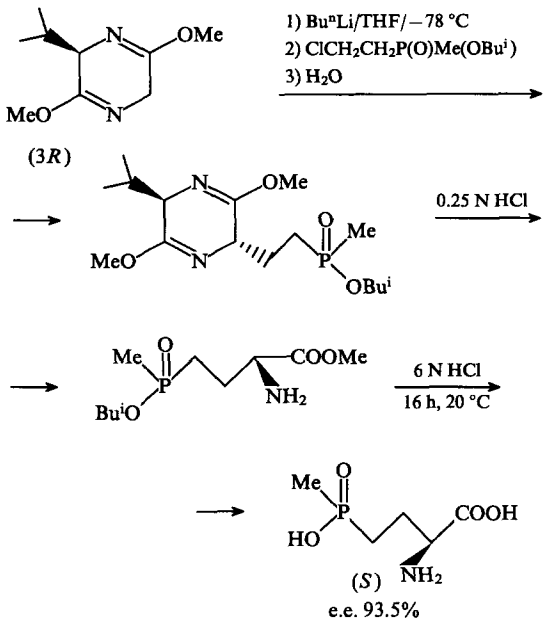


n	2	3	4
Yield (%)	86	83	84
d.e. (%)	96	80	86

R	$C_6H_5CH_2$	$CH_2CH=CH_2$	$CH_2-C\equiv CH$
Yield (%)	75	63	63
d.e. (%)	80	94	94

Both enantiomers of phosphinotricin were obtained by Schöllkopf's method involving the alkylation of the lithio-derivative of the bislactim ether containing a valine residue as the stereodifferentiating group (Scheme 14).

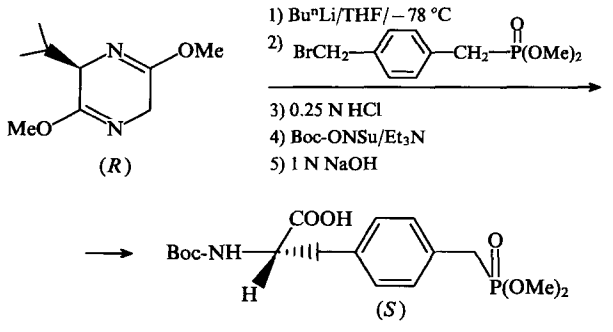
Scheme 14



As in all the syntheses by Schöllkopf's method, in this case the chiral anion is alkylated with a high degree of stereoselectivity (93.5%), affording phosphorus-containing (*S*)- or (*R*)-amino-acids when the (*R*)- or (*S*)-bislactim ethers are used respectively.[60]

The same method has been employed to synthesise an analogue of phosphonotyrosine—*p*-phosphonomethyl-(*S*)-phenyl-alanine, which was subsequently incorporated in the peptide chain of angiotensin in the search for biologically active peptides (Scheme 15).

Scheme 15

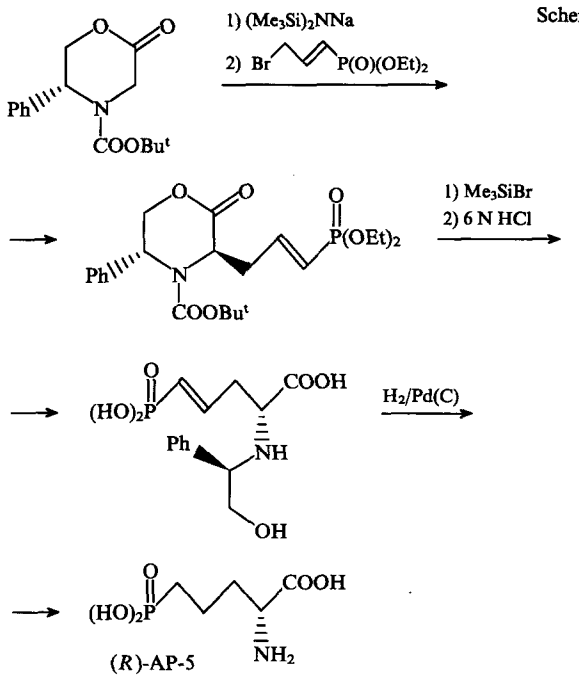


In order to estimate the optical purity of the product, the P- and N- substituted aminoacid was condensed with the methyl ester of (*S*)-leucine and the content of the diastereoisomeric dipeptides obtained was determined by high performance liquid chromatography (HPLC): the ratio of the (*S*,*S*)- and (*R*,*S*)-dipeptides was 95.3 : 4.7.[61]

Alkylation of the chiral oxazinone, obtained from D-phenyl-glycinol, has been used in the first enantioselective synthesis of (*R*)-(−)-2-amino-5-phosphonopentanoic acid (AP-5).[62] This compound is a selective antagonist of *N*-methyl-D-aspartate and is widely used in biochemical research.[63] The glycine synthon employed requires an active alkylating agent. In this instance, 3-phosphonoallyl bromide was used for this purpose (Scheme 16).

After the removal of the protecting groups and the hydrogenation of the carbon–carbon double bond, the target phosphorus-containing aminoacid was obtained in a high yield, its optical purity being estimated as 'high' from high performance liquid chromatographic data and the analysis of the NMR data for the diastereoisomeric precursors.

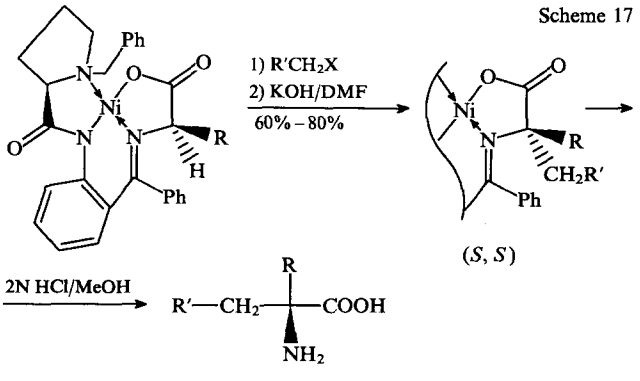
Scheme 16



In Belokon's chiral glycine synthon, the carboxy-group of the Gly (or Ala) fragment is not esterified and is not bound in a ring by a covalent bond, as in the previous methods. Nevertheless, the nickel(II) complexes of the glycine Schiff base are rigid cyclic systems in which [1,7]-asymmetric induction occurs as a result of the distortion of the chelate rings, which leads, when (*S*)-proline is used, to the shielding of the *re*-side of the methylene group of glycine by the benzene ring of the *o*-aminobenzophenone fragment. In order to generate the corresponding carbanion in these complexes, it is sufficient to use ordinary KOH in a dry organic solvent (DMF, MeCN), or NEt$_3$, or diazabicyclooctane in methanol or CHCl$_3$.

Alkylation with the appropriate fluorine-substituted benzyl chlorides or bromides of the nickel(II) complex of the Schiff base obtained from glycine and (*S*)-2-[*N*-(benzylprolyl)amino]-benzophenone afforded a series of (*S*)-phenylalanines containing from one to five fluorine atoms (as well as other halogens—Cl and Br) in the benzene ring as well as the trifluoromethyl group in the *para*- or *meta*-position.[64, 65] The attempts to obtain by this method (*S*)-*o*-trifluoromethylphenylalanine were unsuccessful, apparently owing to the steric effect of the trifluoromethyl group. The use of the nickel(II) complex of the Schiff base derived from alanine makes it possible to obtain fluorine-substituted α-methylphenylalanine derivatives (Scheme 17).

Scheme 17

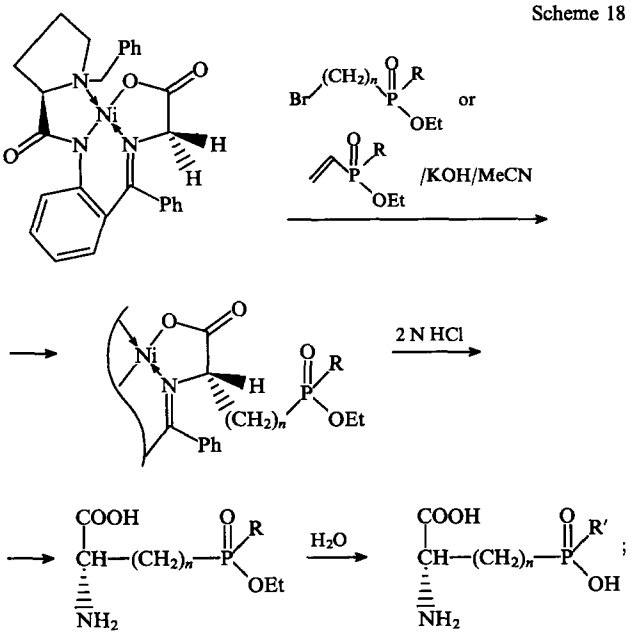


R = H, Me; R' = 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-Cl,6-FC$_6$H$_3$, 4-CF$_3$C$_6$H$_4$, 2-F,6-BrC$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$; X = Br, Cl.

The high chemical (50% – 80%) and optical (~90% d.e.) yields in the stage involving the alkylation of the nickel complexes render this method preparative.

The (*S*)-enantiomers of ω-phosphonic and ω-phosphinic analogues of carboxylic α-aminoacids have been obtained by alkylating the nickel complex of glycine with the corresponding phosphonoalkyl bromides or, in a synthesis of homoglutamic acid and phosphinotricin, with vinyl phosphonate and vinyl phosphinate (Scheme 18).[66, 67]

Scheme 18



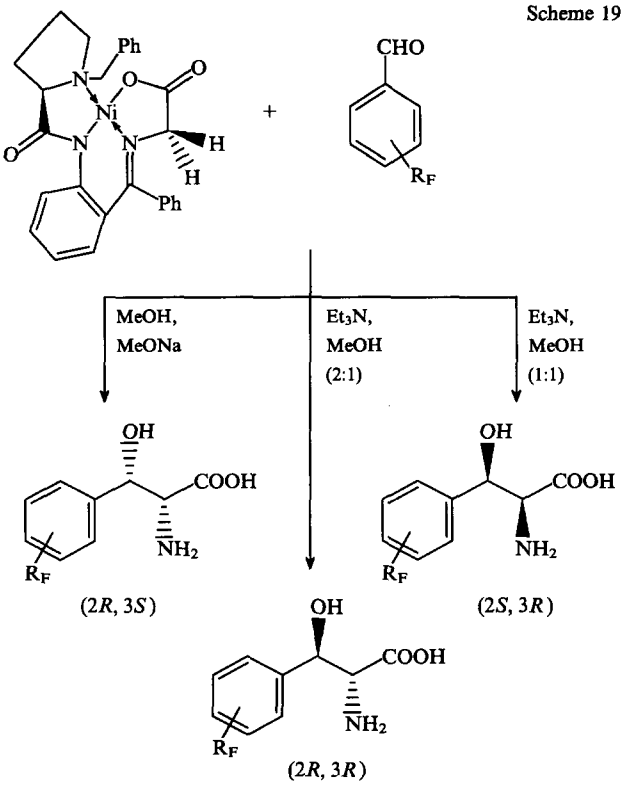
n = 2, 3; R = Me, OEt; R′ = Me, OH.

The enantioselectivity of the alkylation of the nickel complex with the diesters of ω-haloalkylphosphonic acids is >90%, while the kinetically controlled Michael addition takes place with only 60% diastereoselectivity. However, thermodynamic control (in the presence of MeONa) leads[67] to a 95 : 5 ratio of the diastereoisomeric complexes.

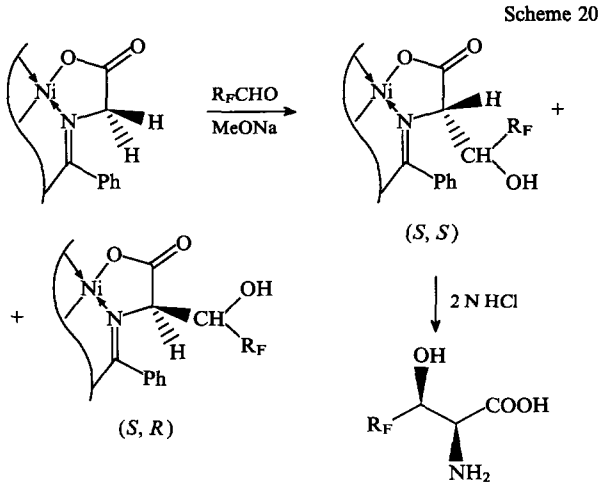
From the standpoint of the stereochemical result (diastereoselectivity of the alkylation), the method considered has no advantage over the Seebach or Schöllkopf methods in the synthesis of α-aminoacids, while its application to the synthesis of α-amino-β-hydroxyacid produces a unique result associated with the fact that at high pH the ionised β-hydroxy-group of the aminoacid fragment can substitute the carboxy-group at the nickel atom in the coordination plane, which results in the inversion of the absolute configuration at the α-carbon.[68] Thus, depending on the conditions in the condensation of the nickel(II) complexes of the Schiff bases obtained from glycine and fluorobenzaldehydes, the corresponding β-(fluorophenyl)serines with the absolute (2*R*, 3*S*)-, (2*R*, 3*R*)-, and (2*S*, 3*R*)-configurations respectively of the chiral atoms were obtained in an optically pure form (Scheme 19).[69–71]

An interesting example of the critical influence of the fluorine-containing substituent on the stereochemical outcome of the reaction has been demonstrated in the condensation of a chiral glycine complex with aliphatic perfluorinated aldehydes.[71] The interaction of fluoral or its hydrate (hemiacetal) with the glycine complex in methanol under the influence of MeONa leads to the formation of (2*R*, 3*S*)-4,4,4-trifluorothreonine, whereas acetaldehyde afford (2*R*, 3*S*)-threonine under analogous conditions (Scheme 20).[68]

Scheme 19



Scheme 20

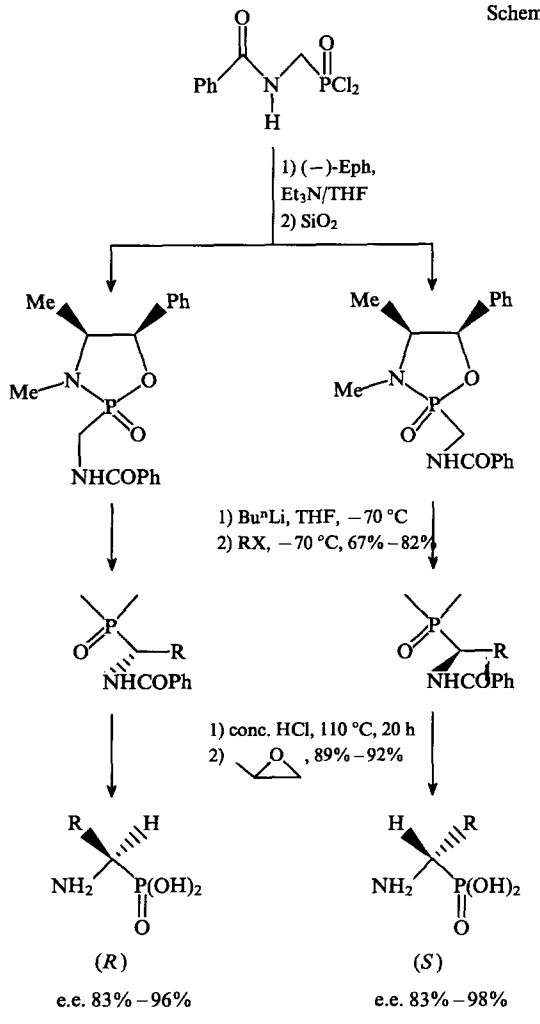


The same method has been used to synthesise (2*R*, 3*S*)- and (2*S*, 3*R*)-ω-phosphonic analogues of glutamic and homoglutamic acids with a β-hydroxy-group.[72, 73] The phosphonate group in the ω-position in the corresponding aldehyde does not exert in this instance any influence on the stereochemistry of the reaction.

In the examples examined above, the chiral auxiliary reagent is bound to the amino-group of the glycine or phosphonoglycine synthon. In an alternative approach, the chiral auxiliary reagent is bound to the acid functional group of the aminoacid. In the case of carboxylic α-aminoacids, it led to disappointingly low optical yields[50] but in the synthesis of phosphonic α-aminoacids it afforded a remarkable result. This was based on the possibility of obtaining cyclic esters, amides, or amidoesters in which the stereodifferentiating fragment is bound directly to the phosphorous atom ('chiral phosphorus').

Thus epimeric (with respect to the phosphorus atom) 2-benzamidomethyl-3,4-dimethyl-2-oxo-5-phenyl-2λ^5-1,3,2-oxazaphospholidines have been obtained from the dichloride of *N*-benzamidomethylphosphonic acid and (−)-ephedrine (Eph). After resolution on SiO_2, they were used[74] in the synthesis of the (*R*)- and (*S*)-enantiomers of Ala^P, Phe^P, and 1-aminobut-3-enylphosphonic acid (Scheme 21).

Scheme 21



RX = MeI, $PhCH_2Br$, $CH_2=CHCH_2I$.

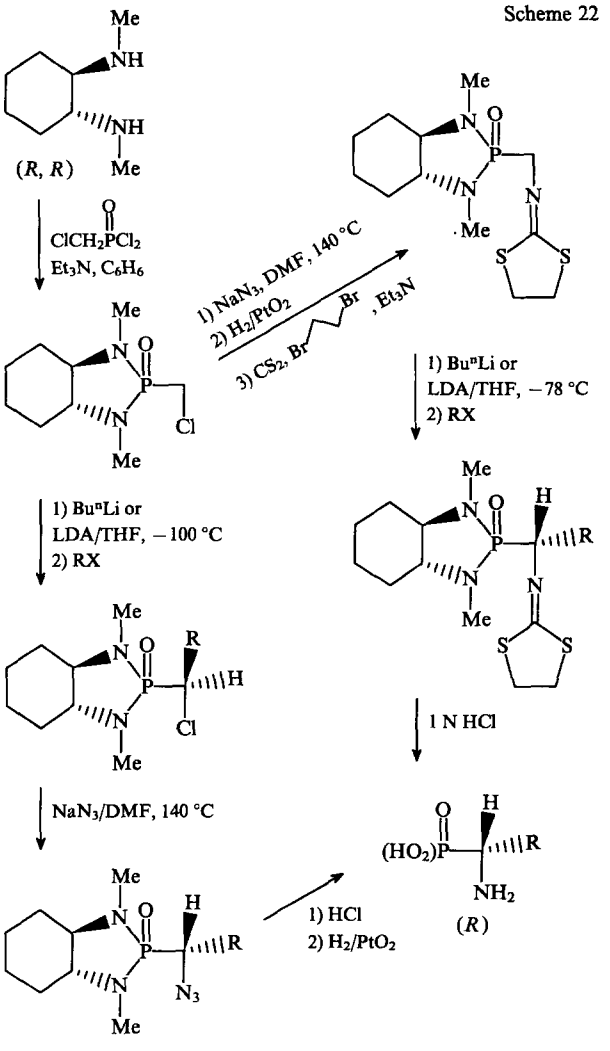
The diastereoselectivity of the alkylation reaction depends on the bulk of the substituent in the alkylating agent and is in the range form 58%−73% (MeI) to 84%−92% ($PhCH_2Br$). The chemical yield of the alkylation product is 67%−82%.

It is of interest to note that the diastereoselectivity of the alkylation of oxazaphospholidines diastereoisomeric with respect to the phosphorus atom is not the same. Thus in the case of the diastereoisomer with the (S^P)-configuration, this parameter is appreciably higher (up to 15%).

A method has been described in which a ligand with C_2 symmetry, namely (1*S*, 2*S*)- or (1*R*, 2*R*)-1,2-bis(methylamino)-cyclohexane, was used as the chiral inducing fragment bound to the phosphorus atom.[75, 76] The chiral methyliminodithiolan obtained from it can be alkylated with a high degree of diastereoselectivity (up to 98% d.e.), affording, after the removal of the protecting groups, phosphonic α-aminoacids in a satisfactory chemical yield and with a satisfactory chemical purity (Scheme 22).[75]

Another version of the method involves the alkylation of the chiral chloromethylphosphonate with subsequent replacement of chlorine by the amino-group and leads to optically active phosphonic α-aminoacids with the same stereoconfiguration,

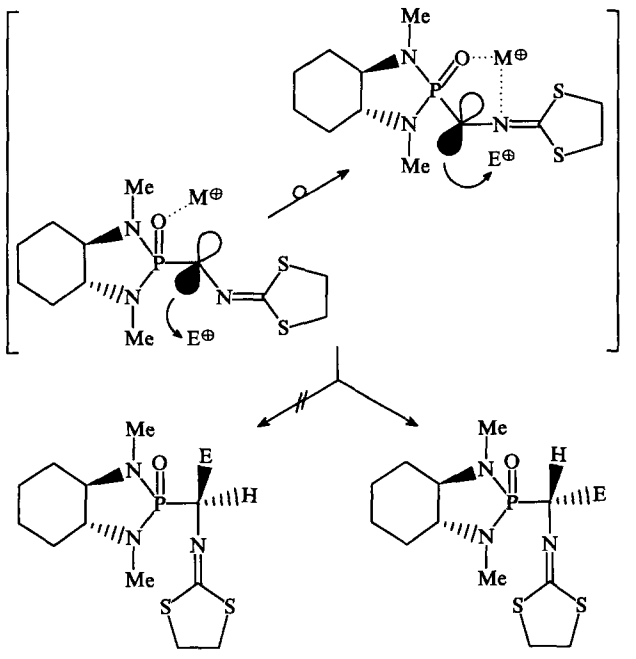
Scheme 22



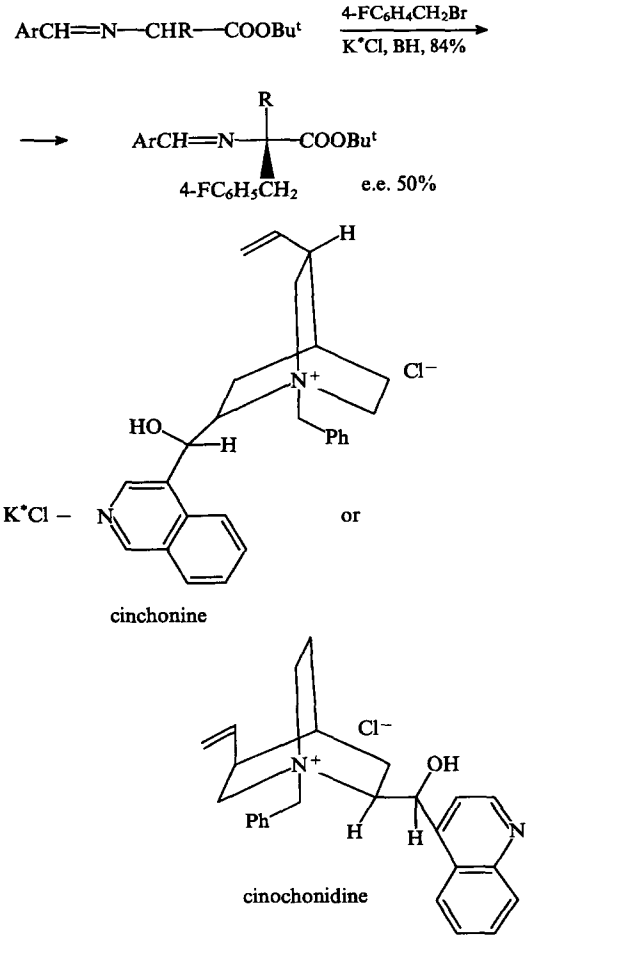
despite the fact that the sequence of reactions employed involves the replacement of chlorine by the azido-group as a result of a reaction of the S_N2 type with inversion of the configuration at the C_α- atom. This is associated with the fact that in the given instance, while a high degree of stereoselectivity in the alkylation reaction is retained, the absolute configuration of the alkylation product is different from that in the alkylation of the corresponding methyliminodithiolan. The authors assume[75] that in the case of the methyliminodithiolan the metallation of the latter is followed initially by the formation of a chelate with participation of the nitrogen atom in the iminothiolan fragment, leading to the complete inversion of the configuration of the carbanion, and then by alkylation predominantly the 'opposite side' of the anion (Scheme 23).

There is no doubt that the most effective method of using optically pure compounds in asymmetric synthesis involves their application as catalysts. Major advances in asymmetric catalysis have been achieved in the hydrogenation of unsaturated bonds, while instances of the enantioselective formation of a C−C bond in the presence of a chiral catalyst are still fairly rare.[50] Two widely known methods for the catalytic asymmetric synthesis of α-aminoacids, developed by O'Donnell and Hayashi, have been used successfully for the preparation of element-containing aminoacids. Thus alkylation with alkyl halides of the Schiff bases of the *tert*-butyl esters of glycine or alanine under phase transfer conditions in the presence of quaternary salts of cinchonine or cinochonidine makes it possible to obtain the corresponding α-aminoacids, including *p*-fluorophenylalanine, with a moderate enantiomeric excess (Scheme 24).[77, 78]

Scheme 23



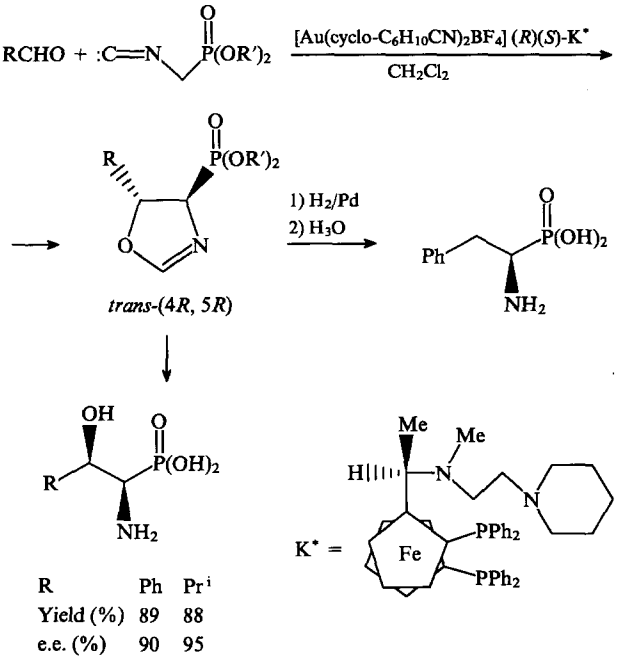
Scheme 24



The use of the quaternary cinchonine salt as the catalyst yields an excess of the (*R*)-aminoacid, while 'pseudoenantiomeric catalysis' by the cinochonidine salt leads to the formation of (*S*)-4-fluorophenylalanine.

Optically pure α-phosphonic analogues of phenylalanine and β-alkyl(aryl)serines can be obtained by the asymmetric aldol reaction [condensation ?] between isocyanomethylphosphonates and various aldehydes in the presence of catalytic amounts of chiral ferrocenylphosphine complexes of gold(I) (Scheme 25).[79–81]

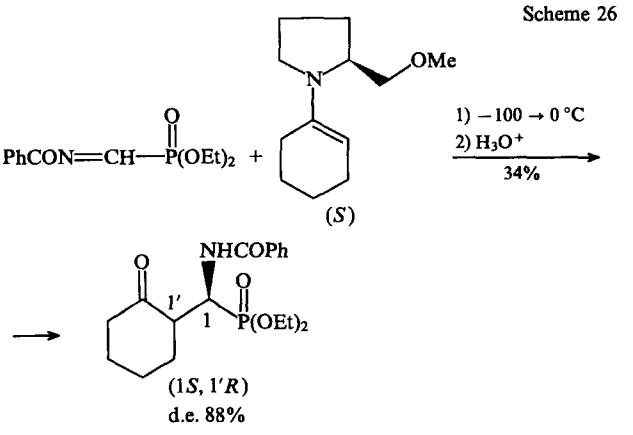
Scheme 25



The highest enantioselectivities of the reaction (94%) were obtained when diphenyl isocyanomethylphosphonate was used. It is noteworthy that only one hundredth of a mole of the catalyst is sufficient for effective asymmetric catalysis in this reaction.

The only example of the asymmetric synthesis of phosphonic aminoacids (with formation of a C–C bond) using the substituent group itself as the chiral auxiliary group is the nucleophilic addition of a chiral enamine to an acyliminoalkylphosphonate,[82] which affords the target aminoacid with a 88% diastereoisomeric excess (Scheme 26).

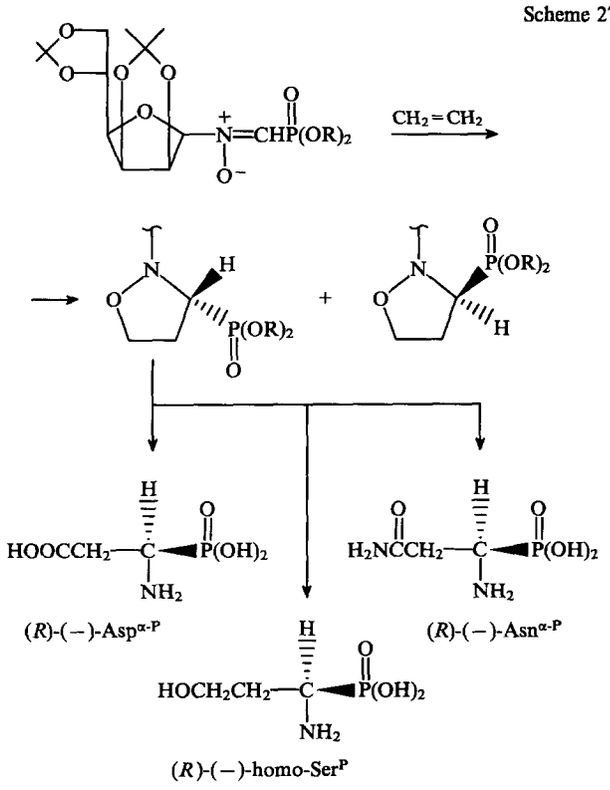
Scheme 26



N-Glycosyl-*C*-dialkoxyphosphonylnitrones based on α-D-mannofuranose combine with ethylene, forming diastereoselective cyclic adducts (yield 80%–85%) in proportions of 3 : 1, diastereoisomers with the configuration of the aminoalkylphosphonate fragment corresponding to that of natural L-aminoacids being formed preferentially. After the chromatographic separation, the dominant diastereoisomers were converted in high yields[83] into (*R*)-(–)-phosphonic analogues of homoserine, aspartic acid, and asparagine (Scheme 27).

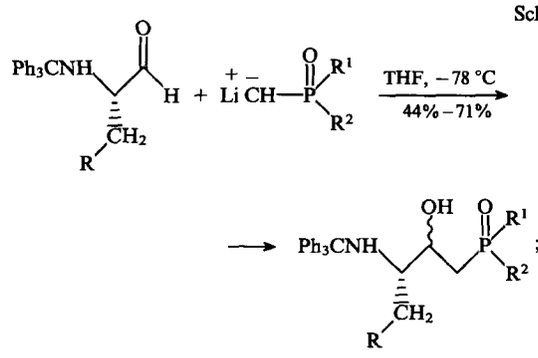
Phosphonic acid analogues of statine—an unusual natural carboxylic γ-amino-β-hydroxy-acid with two chiral centres [4-(*S*)-amino-3-(*S*)-hydroxy-6-methylheptanoic acid], forming part of the natural peptide pepstatin,[84] have been synthesised by

Scheme 27



adding a stabilised anion, generated from the dialkyl ester of methylphosphonic acid by treatment with butyllithium or sodium bis(trimethylsilyl)amide, to enantiomeric α-(*N*-trimethylamino)-aldehydes obtained from the corresponding *L*-aminoacids.[85] It was found that the diastereoselectivity of the addition depends only slightly on the nature of this group in the initial amino-aldehyde and on the ester groups in the phosphonate anion: the ratio of the (2*R*, 3*S*)- and (2*S*, 3*S*)-diastereoisomers formed varies within narrow limits—from 2.3 : 1 to 3.0 : 1 (Scheme 28).

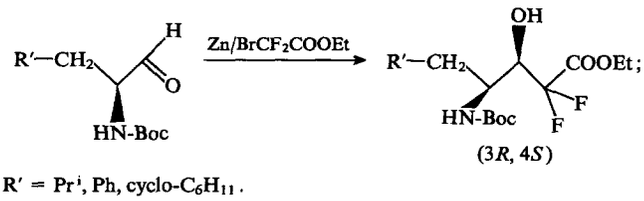
Scheme 28



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

The possibility of introducing the esters of bromodifluoroacetic acid into the Reformatskii reaction[86] has been used in the asymmetric synthesis of 2,2-difluoro-substituted analogues of statine (Scheme 29).

Scheme 29



R' = Pr^i, Ph, cyclo-C_6H_{11}.

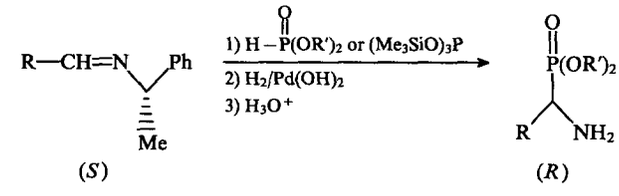
Two methods have been proposed for the condensation of *N-tert*-butoxycarbonyl-(*S*)-leucinal with bromodifluoroacetic ester in the presence of activated zinc.[87–91] Refluxing of the reagents in tetrahydrofuran (THF) affords a mixture of the (3*R*, 4*S*)- and (3*S*, 4*R*)-diastereoisomers in proportions of ~9 : 1, which is associated with the partial racemisation of the initial (*S*)-leucinal on heating. Milder condensation conditions at low temperatures under the influence of ultrasound lead to a 7 : 3 mixture of the (3*R*, 4*S*)- and (3*S*, 4*R*)-diastereoisomers. Almost the same stereochemical result was obtained on using the (*S*)-enantiomers of α-aminoaldehydes containing the phenyl or cyclohexyl group instead of the isopropyl group.

III. Enantioselective formation of the C–P bond

The nucleophilic addition of hydrophosphoryl compounds with a carbon–nitrogen double bond has been used extremely widely for the asymmetric synthesis of phosphonic α-aminoacids. This approach was used for the first time more than twenty years ago, and, although the optical yield of the aminoacids in these syntheses is as a rule not very high, the method still continues to attract the attention of investigators in view of its simplicity and accessibility.

In the first syntheses of this type,[92–95] the Schiff bases derived from α-phenylethylamine enantiomers were used as the chiral inducing agent. The addition of acid phosphites to the corresponding aldimines under the conditions of acid catalysis (organic and inorganic acids, Lewis acids) takes place with a fairly high diastereoselectivity only in the case of bulky substituents in the aldehyde fragment in the initial aldimine (R = Ph, Pr^i; up to 80% d.e.) and decreases on passing to small aliphatic substituents (R = Me, Et) (Scheme 30). The attempts to increase the stereoselectivity of the addition by increasing the bulk of the substituent in the second reactant (the phosphite), by employing tris-(trimethylsilyl) phosphate, did not produce the desired result.[95]

Scheme 30



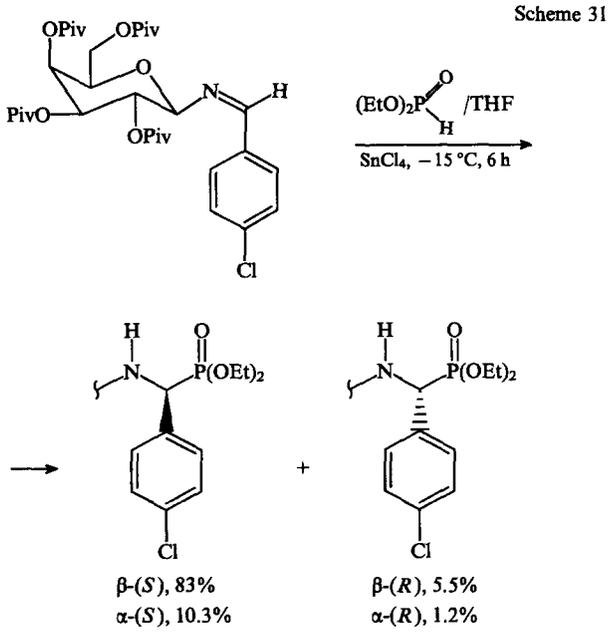
R = Me, Et, Pr^i, Ph.

A satisfactory result, within the framework of this method, has been obtained using Schiff bases obtained from aldehydes and pivaloylated glycosylamines (Scheme 31).

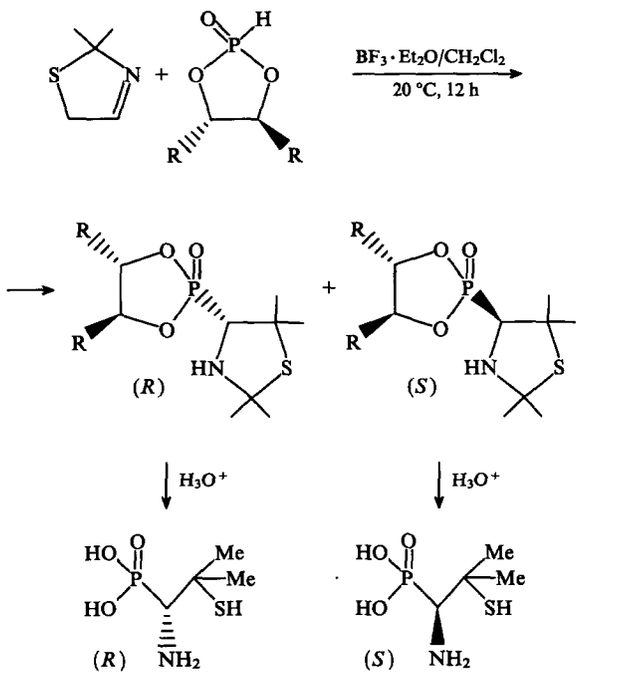
The nucleophilic addition of the acid phosphite in the reaction catalysed by $SnCl_4$ proceeds with high chemical and optical yields, affording as the main product (*S*)-amino-substituted phosphonates when β-D-galactosylimine (shown in Scheme 31) is used and (*R*)-amino-substituted phosphonates when α-D-arabino-pyranosylimine is used.[96] The resolution of the optical isomers is complicated in this case by the α,β-anomerisation of the products, but it can be achieved effectively by a combination of crystallisation and chromatographic methods.

In the syntheses of this type, the chiral inducing group can also be located at the phosphorus atom (nucleophilic diastereoselective addition of the chiral phosphite to the achiral azomethine), which has been demonstrated in relation to the synthesis of the enantiomers of the phosphonic analogue of penicillamine,[97] where the diastereoisomers are formed in the first stage in the proportions (*R*) : (*S*) = 2 : 1 (Scheme 32).

Scheme 31



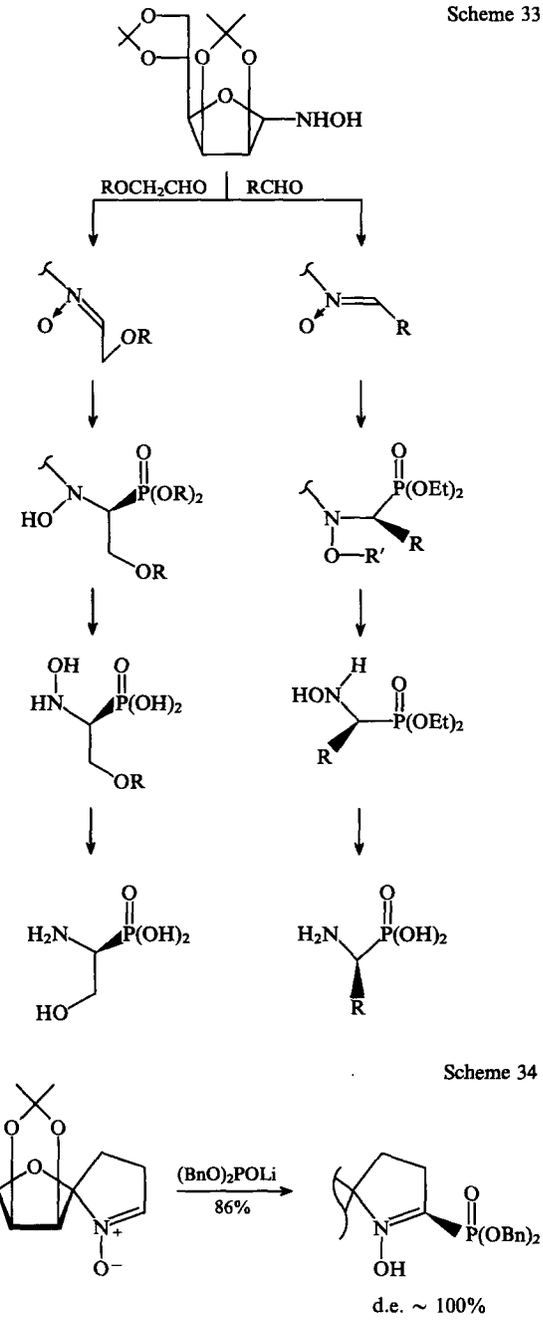
Scheme 32



Hydrophosphoryl compounds can be added to, apart from Schiff bases, a series of other compounds with a C=N bond, which has been used for the asymmetric synthesis of α-amino-substituted phosphonic acids. Considerable advances have been achieved by Vasella and coworkers,[98-100] who investigated the reactions involving the addition of phosphites to *N*-α-D-mannofuranosylnitrones (Scheme 33).

This method[98] makes it possible to obtain aminoacids with small alkyl substituents (Ala^P, Val^P) in high optical yields, although the chemical yield does not exceed 50%. The diastereoselectivity of the addition of lithium dialkyl phosphites to *N*-glycosyl-*C*-alkylnitrones is 78%–93%, decreasing appreciably when potassium dialkyl phosphites are used.[98] We may note that 100% diastereoselectivity is observed in addition of lithium dibenzyl phosphite to *N*-glycosylspironitrone (Scheme 34).[100]

Scheme 33



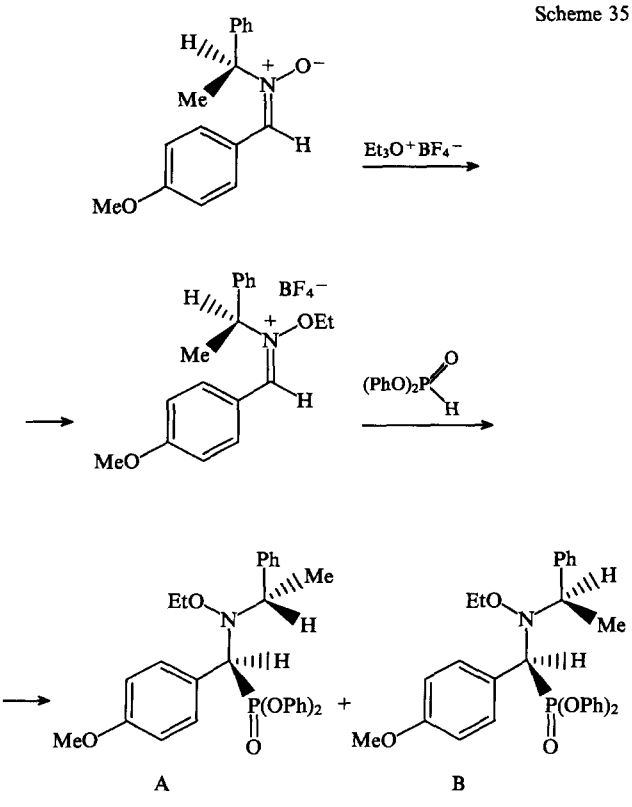
Scheme 34

The synthetic possibilities of the method are not limited to the synthesis of α-aminoalkylphosphonic acids. One of the advantages of the method is the possibility of isolating optically active *N*-hydroxy-α-aminoalkylphosphonic acids which cannot be obtained by other methods. In addition, the use of the corresponding aldehydes with protected functional groups makes it possible to obtain β-hydroxy-α-aminoalkylphosphonic acids (Ser^P) and γ-alkylthio-α-aminoalkylphosphonic acids (Met^P).[99]

It has been found that *N*-glycosyl-*C*-arylnitrones do not interact with the anions of dialkyl phosphites but do readily combine with tris(trimethylsilyl)phosphite in the presence of Lewis acids ($ZnCl_2$, $HClO_4$) with a diastereoselectivity of 79%–93%, which has been used to obtain optically active phosphonic analogues of phenylglycine.[99] The interesting inversion of the absolute configuration of the α-aminoalkylphosphonate on changing the relative amount of the catalyst present ($ZnCl_2$) is noteworthy. This made it possible to obtain both enantiomers of the phosphonic analogue of phenylglycine using the same reagents.

After *O*-ethylation, the nitrone with the chiral α-phenylethyl substituent at the nitrogen atom gives rise to an oxoiminium salt,[101] which combines diastereoselectively with diphenyl phosphite to form two diastereoisomers in proportions of 3 : 2. The absolute configurations of the diastereoisomers, which can be resolved by chromatography on an alumina column, were determined, but the authors suggest that the diastereoisomer A should be formed preferentially as a result of the attack on the C = N bond from the *si*-side (Scheme 35).

Scheme 35



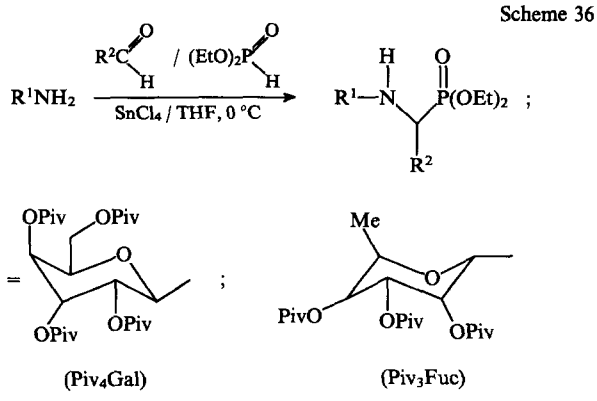
The *N*-acyliminoester obtained from (−)-ω-camphanic acid combines with dialkyl phosphites to form diastereoisomeric adducts from which optically active phosphonic analogues of phenylalanine [(+)- and (−)-Phe^P] were obtained[102] by the reductive elimination of the alkylthio-group and subsequent hydrolysis.

Other methods for the formation of the carbon–phosphorus bond, widely used in the synthesis of racemic α-aminoalkylphosphonic acids,[31] are represented by only isolated examples in the asymmetric synthesis of aminoalkylphosphonates. Thus β-D-galactosylamine and β-L-fucopyranosylamine have been used as the amino components in the Kabachnik – Fields reaction. Asymmetric induction, leading preferentially to (*S*)- and (*R*)-α-aminoalkylphosphonates respectively (from 42 to 96% d.e.), was then observed.[96] The level of this induction was virtually the same as in the addition of acid phosphites to the Schiff bases derived from the corresponding glycosylamines (Scheme 36).

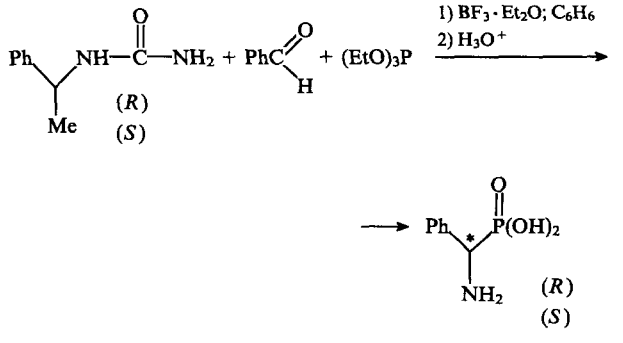
The intereaction of neutral phosphites with aldehydes and ureas or carbamates (a non-classical version of the Arbuzov reaction) has also been used for the asymmetric synthesis of a series of α-aminoalkylphosphonic acids. *N*-Monosubstituted ureas, obtained from (*R*)- and (*S*)-α-phenylethylamine,[103] or carbamates based on (−)-menthol or 1,7,7-trimethylspiro{bicyclo-[2.2.1]heptane-3,2′-indan}-2-ol, obtained from (*R*)-(+)-camphor, were introduced into the reaction (Scheme 37).[104]

The optical purity of the aminoalkylphosphonic acids obtained by this method — the phosphonic analogues of alanine, valine, and phenylglycine, as well as 1-amino-propylphosphonic acid — is low (e.e. = 8.3% – 42.2%), but one should note the inversion of the stereochemical outcome of this reaction relative to the reaction,

Scheme 36



Scheme 37



examined above, involving the addition reaction of acid phosphites with the C = N double bond. Thus, when the urea based on (*R*)-α-phenylethylamine is used, (*R*)-aminoalkylphosphonic acids are formed preferentially, while the addition of acid phosphites to aldimines based on (*S*)-α-phenylethylamine leads to (*S*)-aminoalkylphosphonates.[92, 103]

In the presence of titanium tetrachloride, triethyl phosphite effects the stereoselective opening of the homochiral acetals based on (+)-(2*S*, 4*S*)-pentanediol. The principal diastereoisomers, which are readily separated by column chromatography, were converted by the Swern oxidation into α-hydroxyalkylphosphonates with the (*R*)-configuration (e.e. > 95%), which were converted in their turn into α-azidoalkylphosphonates via reactions which occur with inversion of the configuration of the chiral centre (the Mitsunoba reaction or the reaction of sodium azide with the corresponding methanesulphonate) (Scheme 38).[105]

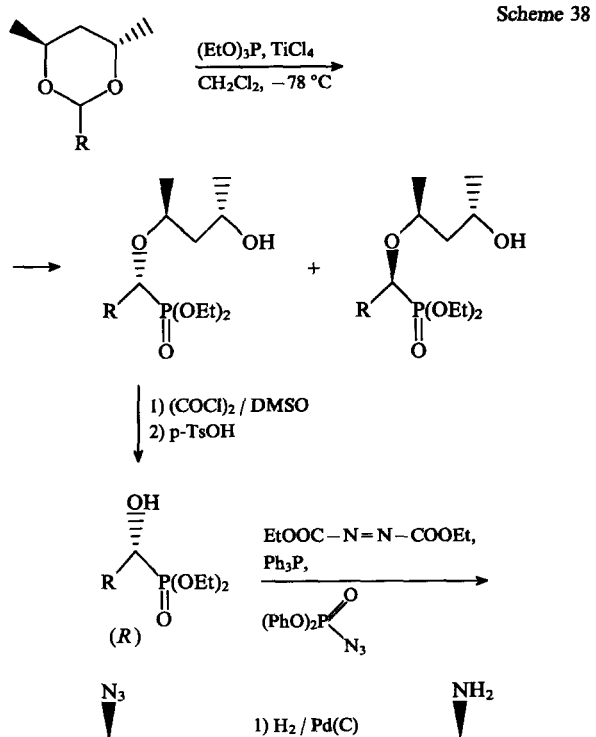
The catalytic hydrogenation of the azides leads to α-aminoalkylphosphonates, the hydrolysis of which afforded (*S*)-α-aminoalkylphosphonic acids (Val^P and Leu^P).

The base-catalysed diastereoselective addition of dimethyl phosphite to the chiral aldehyde obtained from L-phenylalanine leads to the formation of diastereoisomeric β-amino-α-hydroxyalkylphosphonates. Depending on the solvent and base used, the ratio of the *anti*- and *syn*-isomers varies from 1.2 : 1 (DBU/DMF) to 12 : 1 (KF/DMF) (Scheme 39).[106] The *anti*-diastereoisomer was used to synthesise an effective renin inhibitor.

IV. Enantioselective formation of the C–H bond

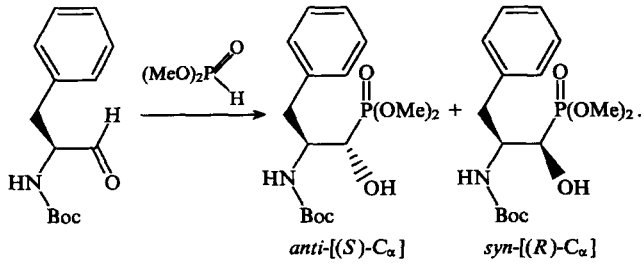
The reduction of the prochiral derivatives of α,β-dehydroaminoacids to the corresponding optically active aminoacids is one of the most vigorously developing fields of asymmetric synthesis. The rigidity of the intermediate complexes between the α,β-dehydroaminoacids and the catalyst is an important factor influencing the enantioselectivity of the reduction. It has been suggested that this factor is the cause of the lower optical yields in the reduction of (*E*)-dehydroaminoacids compared with the (*Z*)-isomers.[107]

Scheme 38



R	Pr^i	Bu^i	$PhCH_2$
d.e. (%)	86	88	82

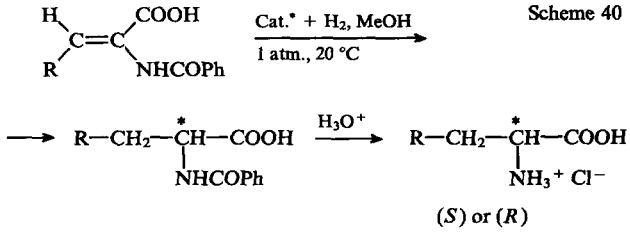
Scheme 39



The wide scale employment of rhodium catalysts is restricted by the necessity to select both the catalyst and the reaction conditions for each new substrate.[50]

In a recently published study,[108] a whole series of rhodium catalysts for the reduction of the corresponding (*Z*)-α-*N*-benzamido-β-(fluorophenyl)acrylic acids or their esters were investigated in order to achieve the asymmetric synthesis of fluorine-substituted phenylalanines. The best result (e.e. ≃ 90%) was obtained using rhodium complexes with PROPRAPHOS and *O*, *N*-bis(diphenylphosphino)-2-*exo*-hydroxy-3-*endo*-methylaminonorbornene as the chiral ligand (Scheme 40).

Scheme 40



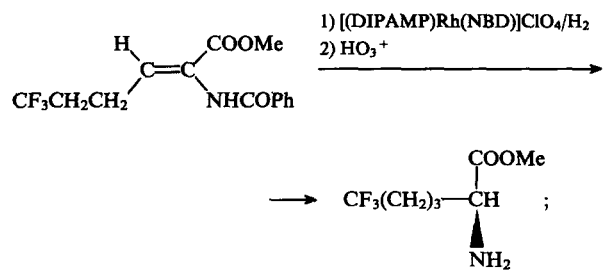
(*S*) or (*R*)

R = 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, C_6F_5.

It is noteworthy that in the reduction of (*Z*)-α-*N*-benzamido-β-pentafluorophenylacrylic acid a higher optical yield is observed than in the reduction of the monofluoro-substituted analogue under identical conditions.

Methyl (*Z*)-α-*N*-benzamido-β-3,3,3-trifluoropropylacrylate was reduced to the methyl ester of (*S*)-*N*-benzoyl-6,6,6-trifluoronorleucine in the presence of the rhodium complex of (1*R*, 2*R*)-1,2-ethanediylbis[(*o*-anisylphenyl)phosphine] (DIPAMP) with the same optical yield (e.e. = 90%) (Scheme 41).[109, 110]

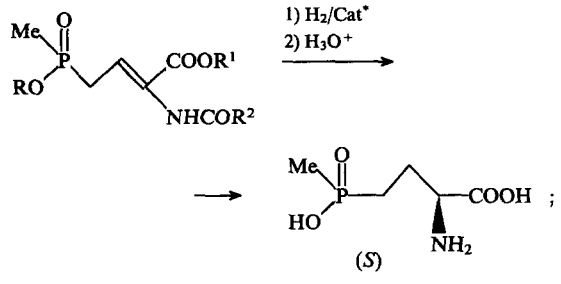
Scheme 41



NBD = *norbornadiene*

The asymmetric synthesis of phosphorus-containing amino-acids using rhodium catalysts was demonstrated in relation to the synthesis of (*S*)-phosphinotricin (Scheme 42).[111]

Scheme 42



Cat* = (*R*, *R*)-NORPHOS, (*S*, *S*)-CHIRAPHOS

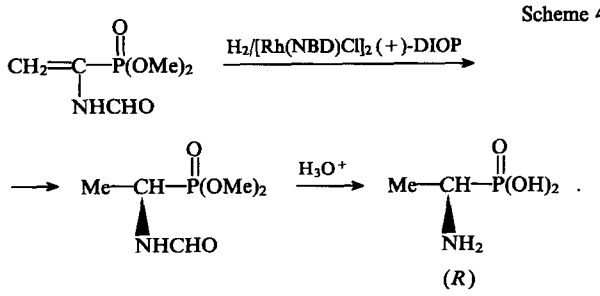
The best optical yield in the reduction stage was obtained using the rhodium complex of (*S*, *S*)-CHIRAPHOS (e.e. 91%).

In the cases examined above, the presence of fluorine or phosphorus atoms in the substituent in the γ-position in the corresponding acrylic acid does not apparently exert a significant influence on the catalytic process. The study of the possibility of using rhodium catalysts in the synthesis of α-aminoalkylphosphonic acids in which the phosphono-group adjoins the C=C double bond and can participate in the formation of the transition complex with the rhodium catalysts has therefore aroused much interest.

Schöllkopf et al.[112] showed that α-(*N*-formamido)vinylphosphonate, obtained by the Horner–Wittig reaction from *N*-formamidomethylenediphosphonate and paraformaldehyde, can be reduced in the presence of the rhodium complex of (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane [(+)-DIOP], which results in the formation of (*R*)-(−)-α-(*N*-formamido)ethylphosphonate with an enantiomeric excess of 76% (Scheme 43).

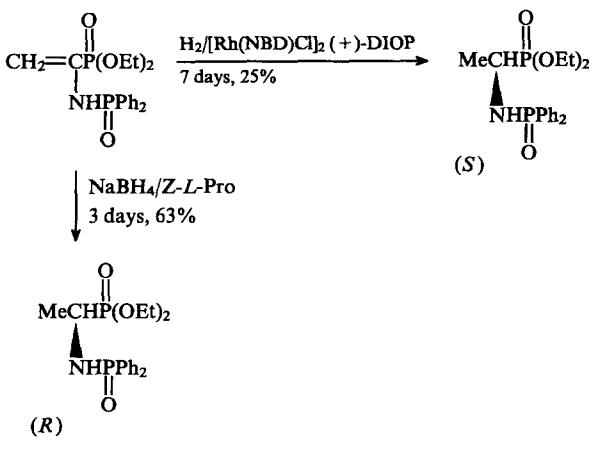
The attempts to use (+)-DIPAMP or (+)-NORPHOS instead of (+)-DIOP as the chiral ligands were unsuccessful—hydrogenation did not take place at the normal pressure. The asymmetric hydrogenation process in the presence of rhodium catalysts depends not only on the chiral ligand employed but also on the structure of the substrate. Thus the reduction of α-(*N*-diphenylphosphinylamino)vinylphosphonate in the presence of the chiral rhodium catalyst based on (+)-DIOP takes place extremely slowly and with a low asymmetric induction [e.e. ~ 3%;

Scheme 43



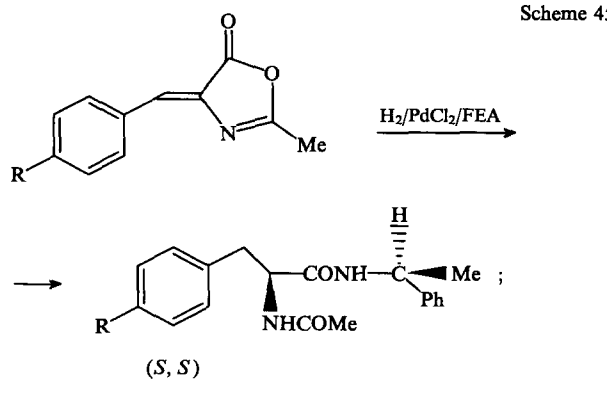
(*S*)-aminoalkylphosphonate predominates]. It is of interest that the reduction of this substrate with sodium tetrahydroborate in the presence of *N*-benzyloxycarbonyl-*L*-proline results in the preferential formation[113] of the (*R*)-aminoalkylphosphonate (e.e. 12%) (Scheme 44).

Scheme 44



The hydrogenation of azlactones in the presence of $PdCl_2$ and added (*S*)-α-phenylethylamine (PEA) (up to 55% d.e.) has been used to synthesise fluoro-derivatives of (*S*)-phenylalanine (Scheme 45).[114, 115]

Scheme 45

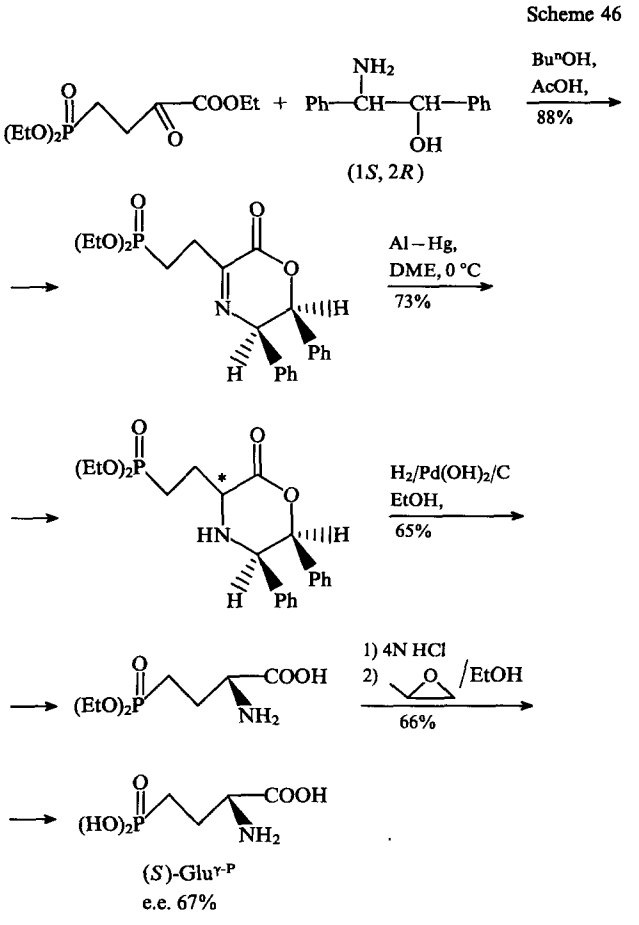


R = F, $OCHF_2$.

The dihydrooxazinone obtained from the ester of a γ-phosphono-α-ketoacid and the optically active (+)-*erythro*-2-hydroxy-1,2-diphenylethylamine, acted upon by aluminium amalgam, undergoes stereoselective reduction with formation of the corresponding tetrahydrooxazinone, which is subsequently converted by a standard procedure into the γ-phosphonic analogue of (*S*)-glutamic acid (e.e. 67%) (Scheme 46).[116]

The hydrogenation of the C=N double bond takes place more effectively in the presence of catalysts such as Raney nickel and platinum or palladium on carbon but under these conditions there is also simultaneous decomposition of the oxazinone ring,

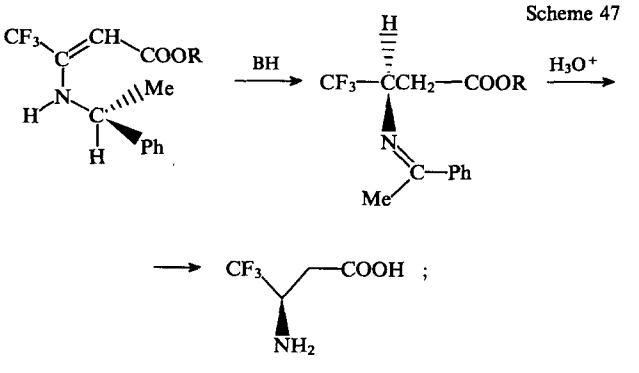
Scheme 46



playing the role of the stereodifferentiating fragment, which results in the formation of the racemic product.

The asymmetric version of the general method of synthesis of α-difluoromethylamines and -aminoacids via the irreversible isomerisation of α-trifluoromethyl-*N*-benzylimines[117] has been proposed for the enantioselective synthesis of (*S*)- and (*R*)-β-trifluoromethyl-β-alanine (Scheme 47).

Scheme 47



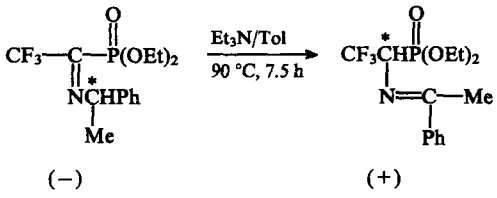
R = Me, Et.

The isomerisation in the above process, the [1,3]-proton shift, takes place on heating in the presence of bases (DBU, DBO) with a moderate enantioselectivity (up to 75% e.e.), which is determined by the preferential proton transfer from the *re*- or *si*-sides of the intermediate [1,3]-azaallyl anion. The catalytic version of this isomerisation [chiral enamine, chiral base (cinchonidine)] has also been examined but the asymmetric outcome of the reaction did not exceed 10% e.e.

N-(α-phenylethyl)trifluoroacetimidoylphosphonate, obtained from (−)-α-phenylethylamine, also undergoes a [1,3]-H shift on heating in the presence of triethylamine, which proceeds with a

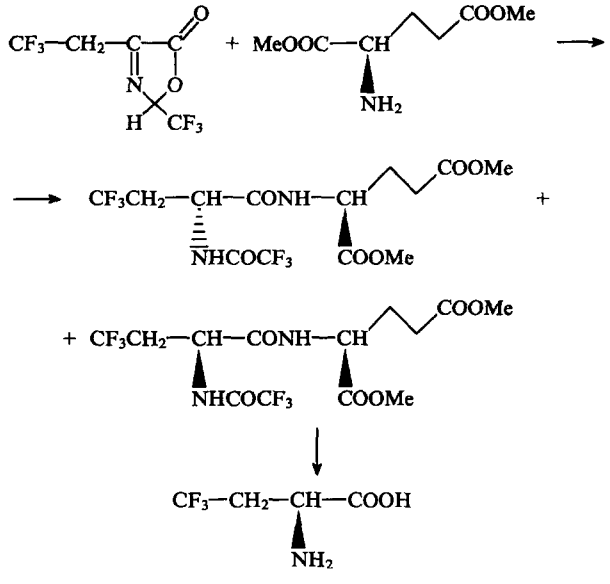
low asymmetric induction (e.e. 22%) and results in the formation of an optically active phosphonic analogue of trifluoroalanine (Scheme 48).[119]

Scheme 48



An asymmetric process has been proposed for the synthesis of the *L*-enantiomer of 4,4,4-trifluoro-2-aminobutyric acid. It consists of the stereoselective opening of the ring in 4-(2,2,2-trifluoroethyl)-2-trifluoromethyl-Δ^3-5-oxazolinone by the dimethyl ester of *L*-glutamic acid, which affords a mixture of diastereoisomeric dipeptides in the proportions (*L*, *L*) : (*D*, *L*) = 83 : 17. Optically pure *L*-4,4,4-trifluoro2-aminobutyric acid has also been obtained after repeated crystallisation of a diastereoisomeric mixture with subsequent elimination of the *L*-glutamic acid residue (Scheme 49).[120]

Scheme 49



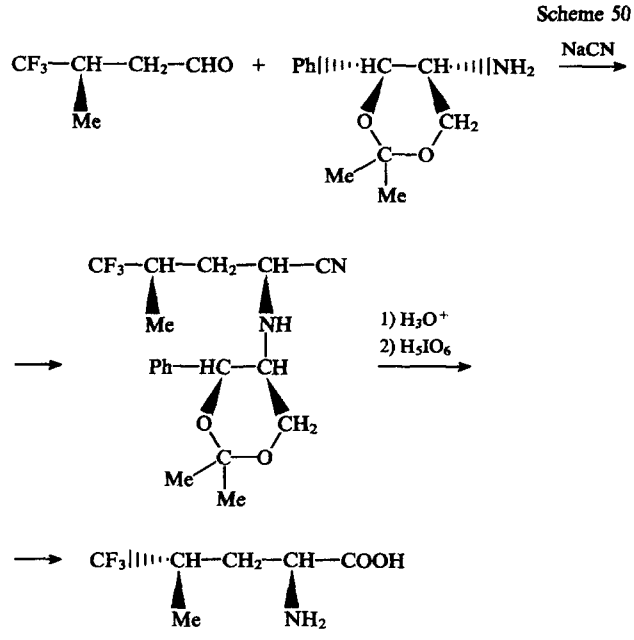
V. Enantioselective formation of the C–N bond

The asymmetric synthesis of (2*S*, 4*R*)-5,5,5-trifluoroleucine from the optically pure (3*R*)-3-trifluoromethylbutanal and (4*S*, 5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane was carried out by the strecker reaction.[121] The reaction takes place with a moderate diastereoselectivity (d.e. 60%), affording the target aminoacid with the α-(*S*)-configuration of the chiral carbon atom (Scheme 50).

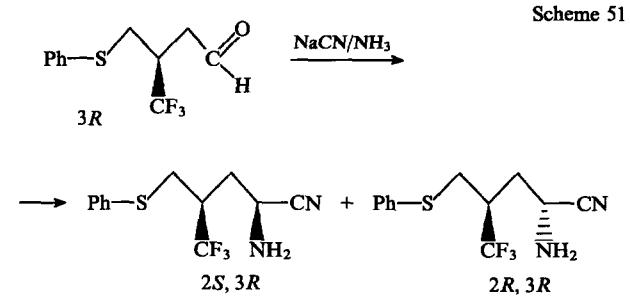
The asymmetric induction is apparently determined in this instance by the stereochemical structure of the substituent at the nitrogen atom, while the chiral centre in the aldehyde fragment has virtually no stereodifferentiating effect. Thus the Strecker synthesis using the 4-phenylthio-derivative of (3*R*)-3-trifluoromethylbutanal affords a mixture of the corresponding diastereoisomeric aminonitriles in proportions of ~1 : 1, from which the optically pure (2*R*, 3*R*)- and (2*R*, 3*S*)-5,5,5-trifluoroleucines were obtained after resolution, the hydrolysis of the nitrile group, and desulphurisation (Scheme 51).[122]

The use of ω-formylalkylphosphonates and (*S*)-α-phenylethylamine in the Strecker synthesis makes it possible to achieve the asymmetric synthesis of the (*S*)-enantiomers of the ω-phosphonic

Scheme 50

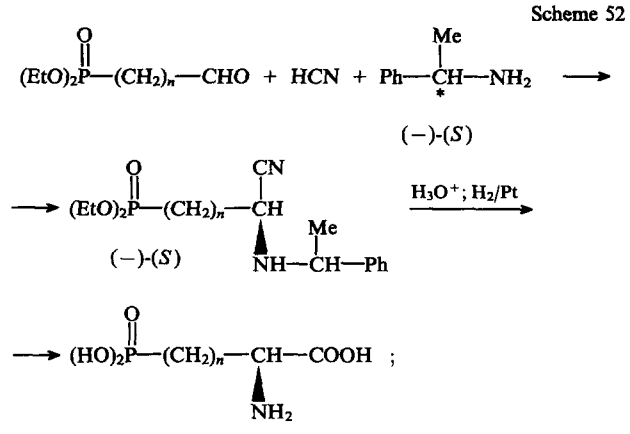


Scheme 51



analogues of aspartic and glutamic acid with e.e. up to 50% (Scheme 52).[123]

Scheme 52

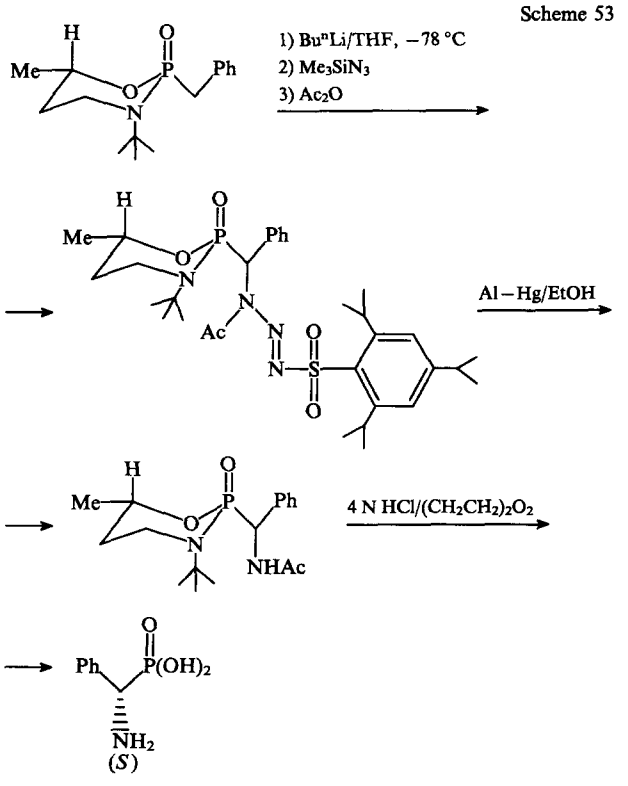


n = 1, 2.

The asymmetric electrophilic amination of stabilised phosphorus-containing carbanions, developed recently by Denmark, is a promising aspect of the asymmetric synthesis of α-aminoalkylphosphonic acids. The electrophilic amination of a series of chiral oxazaphosphorinanes and oxaphospholidines, obtained from the dichlorides of alkylphosphonic acids and the corresponding chiral 1,3- or 1,2-aminoalcohols has been investigated.[124] Trimethylsilyl azide was used as the aminating agent. It was established that the stereochemical outcome of the reaction depends on the structure of the stereodifferentiating aminoalcohol fragment, the nature of the *P*-alkyl substituent,

and the choice of the amination method and it has been shown that under optimum conditions it is possible to achieve an extremely high level of asymmetric induction. This was demonstrated in relation to the synthesis of the (*S*)-enantiomer of the phosphonic analogue of phenylglycine with an optical purity of 92% in accordance with Scheme 53.

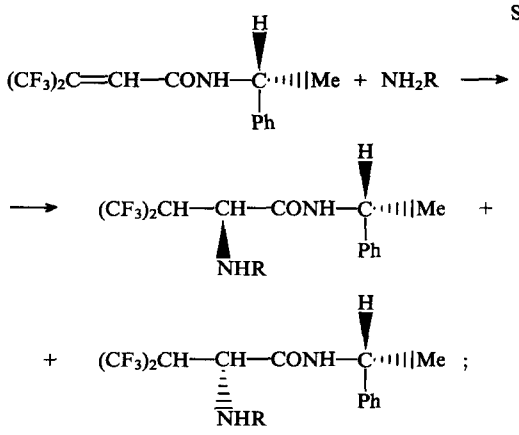
Scheme 53



When the *P*-benzyl substituent in the oxazaphoshorinane was replaced by the ethyl substituent or the 2-phenylethyl group, an appreciable decrease in the stereoselectivity of the amination was observed.

A simpler but much less effective method of asymmetric amination has been investigated by Solodin and coworkers[125, 126] in order to synthesise optically active hexafluorovaline (Scheme 54).

Scheme 54

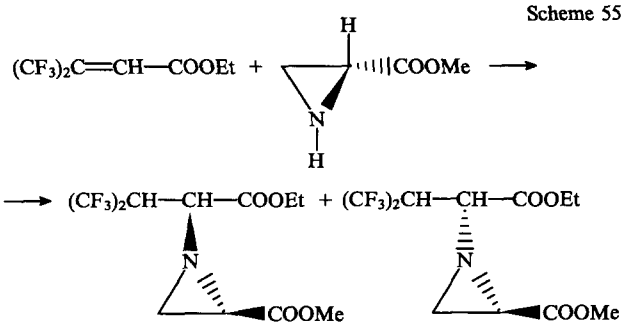


R = H, CH_2Ph.

It has been stated[125] that the addition of ammonia or benzylamine to the chiral *N*-phenylethylamide of 3,3-bis-(trifluoromethyl)acrylic acid leads to the formation of the corresponding hexafluorovaline derivatives with 20% – 41% d.e. However, neither the nature of the asymmetric induction nor the fact that the diastereoisomer is formed in excess were discussed.

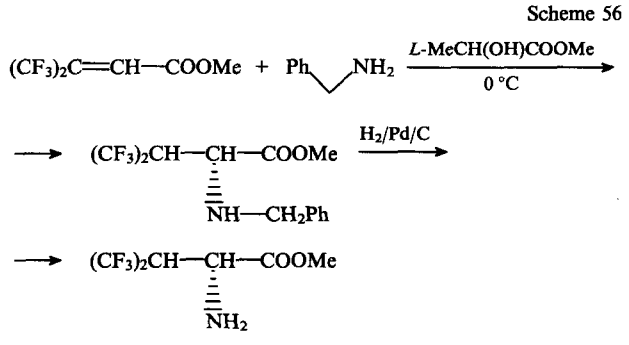
The asymmetric synthesis of hexafluorovaline derivatives can be achieved also by the addition of the chiral esters of (*S*)- or (*R*)-aziridine-2-carboxylic acids to ethyl 3,3-bis(trifluoromethyl)-acrylate. The stereochemical aspects of the addition were not discussed (Scheme 55).[126]

Scheme 55



The addition of benzylamine to methyl 3,3-bis(trifluoro-methyl)acrylate in a chiral medium (solution in *L*-methyl lactate) made it possible to obtain the methyl ester of (*R*)-hexafluoro-valine with a low optical purity (9.2%) (Scheme 56).[125]

Scheme 56



VI. Asymmetric synthesis with the use of enzymes

One of the promising methods of the industrial production of the *L*-enantiomers of proteinogenic aminoacids is their enzymic synthesis.[127] The enantiomeric purity of the aminoacids obtained approaches 100%. Salt suspensions in the culture liquid, disrupted cells, or the purified enzymes in a free state can be used as the source of enzymes effecting the asymmetric synthesis. The economy and simplicity of the method ensure a lower, compared with the chemical asymmetric synthesis, cost of the aminoacids obtained. This field is developing particularly vigorously at the present time in Japan.

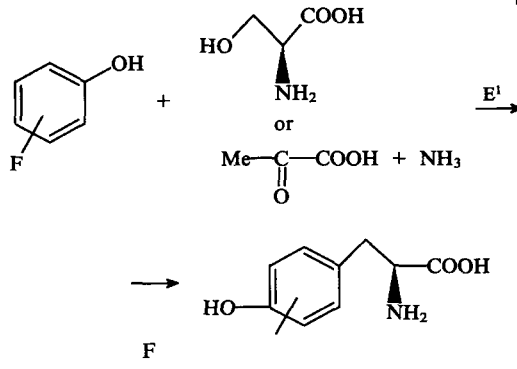
The possibility of obtaining element-containing aminoacids by enzymic synthesis arises from the fact that the majority of the enzymes used in this method have a fairly broad substrate specificity.

Thus β-tyrosinase (E^1), used successfully for the synthesis of various halogen-containing (Cl, Br) tyrosine analogues, was also employed to obtain (*S*)-2-fluoro- and (*S*)-3-fluoro-tyrosines in 75 and 50% yields respectively (Scheme 57).[128–133]

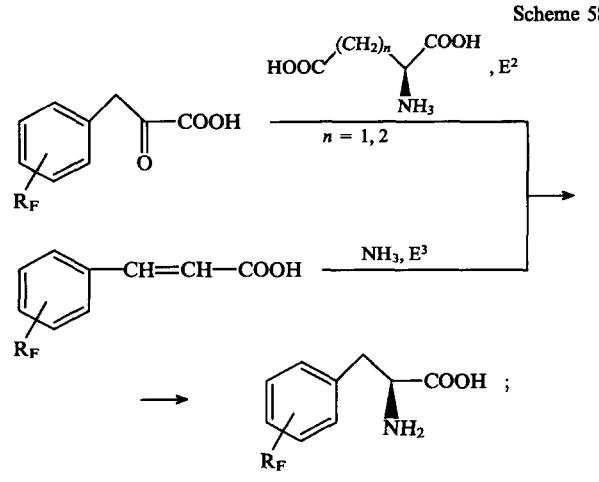
Fluorophenols and (*S*)-serine or a mixture of pyruvic acid and ammonia are used as starting compounds in the synthesis.

β-Phenylpyruvic acid with fluorine atoms or the trifluoro-methyl group in the benzene ring can be converted into the corresponding fluorine-substituted (*S*)-phenylalanines with a chemical yield up to 90% using the transaminase (E^2) from *Alcaligenes falcalis* and aspartic or glutamic acid as the donor of the amino-group (Scheme 58).[14, 132, 134]

Scheme 57



Scheme 58



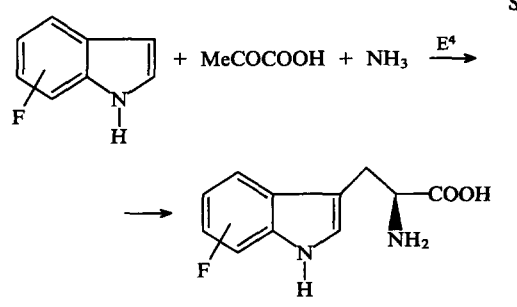
R_F = F, F_5, CF_3.

The rate of the enzymic transamination of phenylpyruvic acid depends on the nature of the substituents in the benzene ring and decreases appreciably on passing from the monofluoro- to the pentafluoro-, and trifluoro-methyl derivatives.

Phenylalanine ammonium lyase (E^3), can also be used for the synthesis of fluorophenylalanines, but this enzyme is more substrate-specific than the transaminase and cannot be employed for the synthesis of trifluoromethylphenylalanines.[14]

All the isomeric (*S*)-4-, (*S*)-5-, (*S*)-6-, and (*S*)-7-fluoroindoles as well as the (*S*)-5,7-di- and (*S*)-trifluoroindoles can also be obtained with an optical yield up to 90% from the corresponding fluoroindoles, pyruvic acid, and ammonia in the presence of tryptophanase (E^4) (Scheme 59).[14, 135]

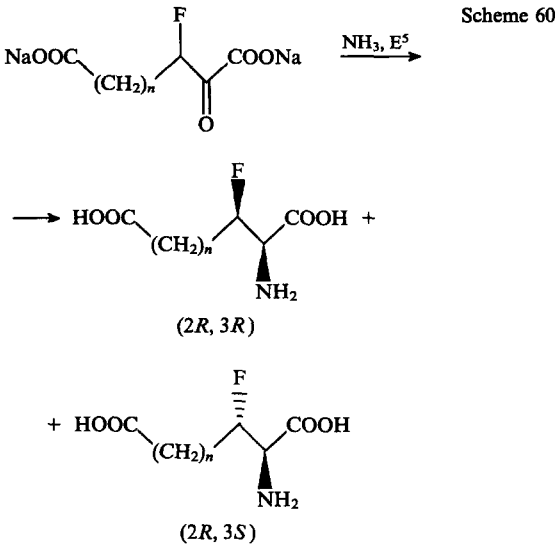
Scheme 59



The methods examined have also been used to synthesise ^{13}N- and ^{11}C-labelled aromatic fluoro-derivatives of amino-acids.[133, 135]

Optically pure (2*R*, 3*R*)- and (2*R*, 3*S*)-3-fluoroglutamic acids have been synthesised effectively from (*R*, *S*)-3-fluoro-2-oxo-glutaric acid under the influence of glutamate dehydrogenase (E^5) (Scheme 60).[136, 137]

Scheme 60



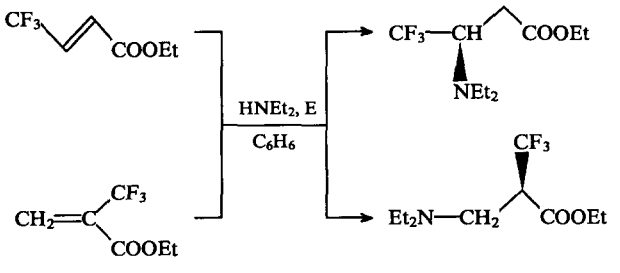
n = 0, 1.

The (2*R*, 3*R*)- and (2*R*, 3*S*)-diastereoisomers are formed in almost identical chemical and stereochemical yields (e.e. 97 and 98% respectively), which indicates the absence of any kind of stereodifferentiating effect on the fluorine atom in the initial racemate of 3-fluoro-2-oxoglutaric acid.

The racemate of 3-fluoro-2-oxosuccinic acid was converted by similar procedure in the presence of aspartate dehydrogenase into a mixture of the diastereoisomeric (2*R*, 3*R*)- and (2*R*, 3*S*)-3-fluoroaspartic acids, isolated in an optically pure form by ion exchange chromatography.[138]

Yet another example of the use of enzymes in the asymmetric synthesis of fluorine-containing aminoacids is the Michael addition of diethylamine in benzene to esters of trifluoromethylacrylic acids catalysed by lipases, amidases, or esterases.[139] The enantiomeric purity of the (−)-β-diethylamino-derivatives of aminoacids obtained in the reaction catalysed by the lipase MY from *Candida cylindracea* approaches 40%, but the absolute configuration of the aminoacid was not discussed (Scheme 61).[13]

Scheme 61



	Yield (%)	e.e. (%)
Lipase MY	47	37
α-Chymotrypsin	36	19
Esterase (from pig liver)	41	8

* *
*

As can be seen from the foregoing, the asymmetric synthesis of element-containing analogues of carboxylic aminoacids has passed through the foundation stage and is now in the dynamic development stage. Both traditional methods of synthesis of aminoacids (for example the alkylation of glycine synthons or the hydrogenation of α,β-dehydroaminoacids) as well as specific approaches associated with the characteristic features of the

chemistry of the corresponding elements are used for the asymmetric synthesis of element-containing aminoacid analogues. The latter appraoches are particularly valid in relation to phosphonic analogues of aminoacids, for the synthesis of which special methods of the chemistry of organophosphorus compounds have been used — the addition of hydrophosphoryl compounds to azomethines and aldehydes and the Arbuzov and Kabachnik–Fields reactions. The development of the methods of asymmetric synthesis has led to the availability of a wide range of optically active fluorine- and phosphorus-containing aminoacid analogues. On the other hand, by no means all the problems associated with the synthesis of specific enantiomerically pure element-containing aminoacid analogues with a high optical purity have found optimum solutions within the framework of the existing methods, which means that further development of the methods of asymmetric synthesis is required.

It may be expected that further research in the field of the asymmetric synthesis of element-containing aminoacid analogues will be directed primarily to the search for new highly effective chiral reagents and to the development of catalytic methods for the asymmetric synthesis of the of these compounds. There is no doubt that the use of enzymes also constitutes a promising approach to the synthesis of enantiomerically pure element-containing aminoacid analogues.

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