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REVIEW

The main directions of scientific activity of Academician V. P. Kukhar

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Abstract: This survey is dedicated to Academician Valery P. Kukhar on the occasion of his 80th birthday, to acknowledge his contribution to synthetic bioorganic chemistry.

Keywords: fluorinated amino acids; aminophosphonates; stereoselective synthesis; fluorine-containing synthons; phosphate mimetics.

Introduction

V. P. Kukhar (1942-2017) is a prominent Ukrainian scientist who made a significant contribution to the development of bioorganic chemistry in Ukraine. He graduated from Dnepropetrovsk Institute of Chemical Technology in 1963, and obtained his Cand. Chem. Sc. degree (1967) and Doctor Chem. Sc. degree (1974) from Institute of Organic Chemistry of the National Academy of Sciences of Ukraine (under the supervision of Academician Alexander Kirsanov). In 1987 he initiated the creation of the Institute of Bioorganic Chemistry of the National Academy of Sciences of Ukraine, and since that time he held the position of Director of the Institute and Head of the Department of Fine Organic Synthesis. During 50 years of research, the scientific achievements of Professor Kukhar are notable. They comprise more than 650 papers and 30 review articles published in world-recognized journals. He is also the author and editor of 6 books, including *Chemistry of Fluorine-Containing Amino Acids* (1994) and *Aminophosphonic and Amino-phosphinic Acids. Chemistry and Biological Activity* (2000). His activities also included numerous national and international collaborations, among others with research groups in Germany, France, Poland, Italy, Russia, and USA.

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Valery Kukhar scientific work has been honored both at home and abroad. He was a member of National Academy of Sciences of Ukraine and Head of State Fund for fundamental research of Ukraine. He was recipient of the GLOBAL-500 Prize (UNEP, 1993), San-Valentino Award (World Federation of Scientists, 1999), Ukrainian State Award in Science & Technology (1999), and the International Arbuzov Award for research in organophosphorus chemistry (2013). Valery Kukhar was a member of the OPCW Scientific Advisory Board and International Advisory Group for Chernobyl Shelter Fund, EBRD [1, 2].

The following gives a brief summary of selected examples of his research achievements made during his academic career at the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine.

1. Practical synthesis of fluorine-containing amino acids

The beginning of these studies can be traced back to the late 1980s when Valery Kukhar has initiated research program on the chemistry of fluorine-containing α- and β-amino acids and their mimetics of pharmaceutical and medicinal interest. The evolution of this research, starting from the synthesis of racemic amino acids and ending with stereochemically directed syntheses and preparation of fluorine-containing amino acids in enantiomerically pure state is well reflected in several books and reviews authored by Kukhar [3-14].

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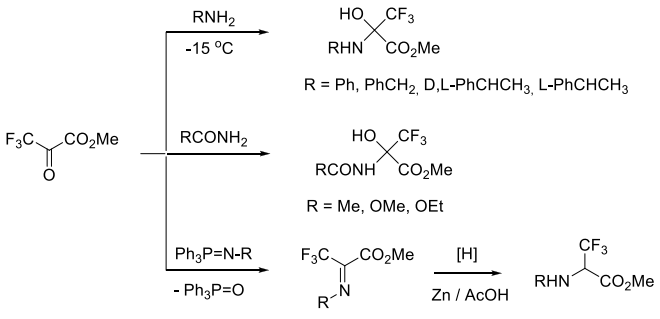
In the family of unnatural amino acids, fluorine-containing amino acids occupy a very special place due to unique properties of fluorine atom. It is well known that the substitution of hydrogen atoms with the fluorine leads to minimum possible steric changes in overall geometry and size of natural products. In sharp contrast, the presence of fluorine or fluorine-containing groups in organic molecules induces the opposite polarization (C-F vs. C-H) of the fluorinated moieties as well as overall electron distribution in molecules and strongly affects their reactivity and functional properties. On the biological level these changes can lead to significant alternation of the original biological activity or even to completely new mode "substrate-receptor" interactions. One of the most appreciated effects of selective fluorination of biological molecules is the rational control of stability of new pharmaceuticals against metabolic oxidative degradation. Another very important consequence of fluorination of natural molecules is that the presence of fluorine atoms and fluoroalkyl groups in an organic compound increase substantially their lipophilicity facilitating membrane permeability and hydrophobic binding. The fluorine substitution for hydrogen can also be efficiently used for quite unique tagging of the biologically active molecules, which is accurately readable by ^{19}F NMR, allows following, both in vitro and in vivo, their location, interactions and metabolic transformations. Due to the promising applications in the fields of bioorganic chemistry, it is not surprising that development of synthetic methods allowing reliable, convenient access to fluorinated amino acids and their derivatives, desirably in enantiomerically pure form to satisfy the need for systematic biological studies, became the subjects of intensive research activities.

In order to synthesize a family of *N*- and *C*-substituted trifluoroalanines, trifluoropyruvic acid was selected as convenient and readily available starting material. It was found that aniline, benzylamine, *D,L*- and *L*-(phenyl)-ethylamine reacted with carbonyl moiety of trifluoropyruvic acid at -15 °C to give stable *gem*-aminoalcohols. *N*-Substituted imines of trifluoropyruvic acid have been prepared via the Staudinger reaction of trifluoropyruvic with triphenylphosphazenes. Reduction of imines with Zn in AcOH results in *N*-substituted trifluoroalanines (Scheme 1) [15].

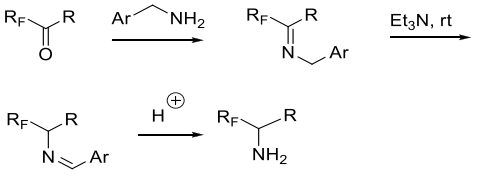


Scheme 1. Synthesis of *N*- and *C*-substituted trifluoroalanines.

Besides the amino acid synthesis, the trifluoropyruvic acid was found to be also attractive starting compound for preparation of *α*-trifluoromethyl-*α*-hydroxy acids. The latter still remain overlooked as potentially promising class of compounds for bioorganic and medicinal chemistry research. Kukhar and co-workers discovered that (*R,S*)-2-hydroxy-2-trifluoromethyl *trans*-octadec-4-enoic acid is a powerful activator of 5-lipoxygenase enzyme from potato tubers in enzymatic oxidation of linoleic acid. The activation seems to be results of both high lipophilicity of alkyl chain and increased by CF_3-group acidity of COOH function because its esterification resulted in a complete loss of the original activation activity and induced noticeable inhibitory activity of the same enzyme [16, 17].

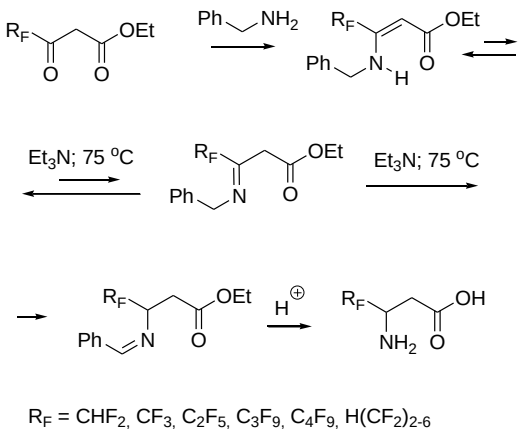
It has been established that the imines of methyl trifluoropyruvate are also very useful substrates for preparation of various trifluoromethyl substituted amino acids via *C*-alkylation or cycloaddition reactions. For instance, *N*-acylimines with highly electrophilic C=N bond R = CO_2Me, SO_2Ph) can be converted into 2-aryl- and 2-hetaryl-3,3,3-trifluoroalanines by action of activated aromatic and heterocyclic compounds [18].

In the late 1980s, Soloshonok and Kukhar found a new effective approach to fluoroalkyl amino acids, based on biomimetic base-catalyzed [1,3]-proton shift reaction. It was demonstrated that base-catalyzed isomerization of *α*-fluoro-*N*-(benzyl) imines, in particular substrates containing trifluoromethyl and poly(per)fluorinated groups, undergo the azomethine-azomethine isomerization under very mild conditions giving rise to the imine products which can be readily hydrolyzed under acidic conditions to afford the corresponding amino derivatives [19-21]. This finding made authors to conclude that they found a new synthetic procedure for reductive amination allowing in elegant biomimetic regime to dispense with the normally required hydrogenation step. Further research has demonstrated remarkable generality of this biomimetic approach for transamination of various fluorinated carbonyl compounds to amino derivatives [21]. In particular operationally convenient and practical methods are now available for biomimetic transamination of carbonyl compounds represented by alkyl and aryl aldehydes, alkyl/aryl ketones, and *α*-keto carboxylic acids (Scheme 2) [22-25].



Scheme 2. Approach to fluoroalkyl-amino acids based on base-catalyzed [1,3]-proton shift reaction.

A particular area of the biomimetic reaction is transamination of fluorinated *β*-keto esters to *β*-amino acids. It worth noting that the biomimetic transamination of non-fluorinated *β*-keto esters to *β*-amino acids is unknown and thermodynamically is not allowed as the corresponding 1,3-proton shift should result in the formation less C-H acid product. However, the fluoro-containing analogs prepared from keto esters and benzylamine underwent clean isomerization to Schiff bases upon heating at 75° C in the presence of triethylamine as a base-catalyst. The equilibrium between enamine and intermediate imine is virtually completely shifted towards the former, however the irreversible and relatively fast biomimetic 1,3-proton shift in imine leads to the formation of Schiff bases as the final reaction products. Acidic hydrolysis of imines easily gives rise to the target fluorinated *β*-amino acids in high overall yield. The reason for the dramatic difference in reactivity between the fluorinated and non-fluorinated *β*-keto acid esters is that the presence of fluorina ted group in imines renders the *α*-C-H proton substantially more acidic as compared with the acidity of the corresponding benzylic protons (Scheme 3) [26, 27].

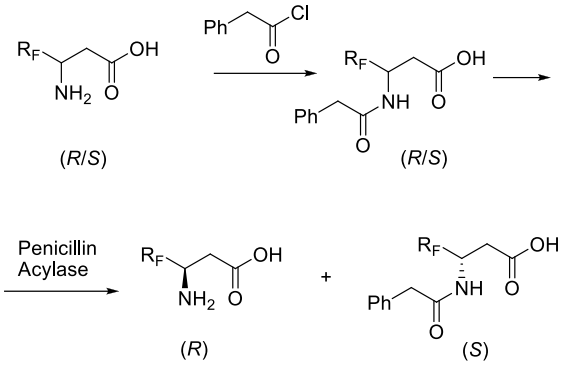


R_F = CHF_2, CF_3, C_2F_5, C_3F_9, C_4F_9, $H(CF_2)_{2\text{-}6}$

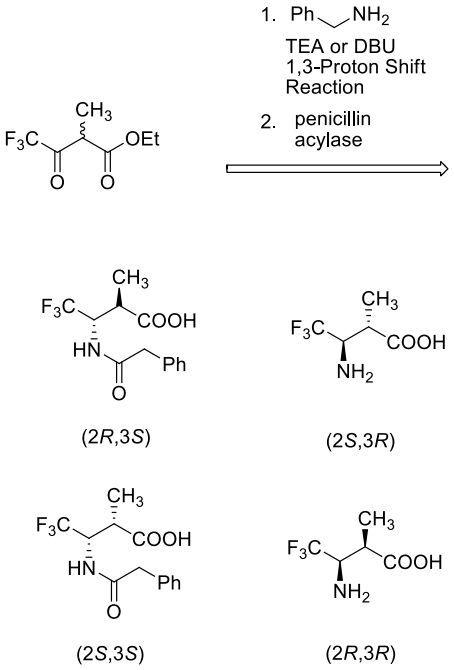
Scheme 3. Transamination of fluorinated *β*-keto esters to *β*-amino acids.

Racemic *β*-amino acids can be efficiently resolved to enantiomerically pure forms using biocatalytic methods [28, 29]. In particular, as shown in Scheme 4, amino acids were converted to the corresponding *N*-(phenyl)acetyl derivatives which were enantioselectively hydrolyzed in the presence of penicillin acylase to give (*R*)-configurated free amino acids and (*S*)-*N*-acyl derivatives which can be further hydrolyzed to free amino acids under routine acidic conditions. The stereoselectivity of the bio-catalytic step was exceptionally high allowing preparation of the target compounds with virtually complete (>48%) chemical yields and enantiomeric purity (>99% ee) [30, 31].

Interesting combination of the biomimetic transamination and penicillin acylase catalyzed resolution was used in the development of chemo-enzymatic protocol for preparation of enantiomerically pure fluorinated *β*-amino acids. Thus, starting from keto ester all four stereoisomers of *α*-alkyl-*β*-fluoroalkyl-*β*-amino acids were prepared in enantiomerically pure form and reasonable chemical yields (Scheme 5) [32]. Opportunity for catalytic enantiocontrolled synthesis of amino acids with application of monochiral base, as a catalyst for [1,3]-proton shift reaction was also demonstrated [33, 34].

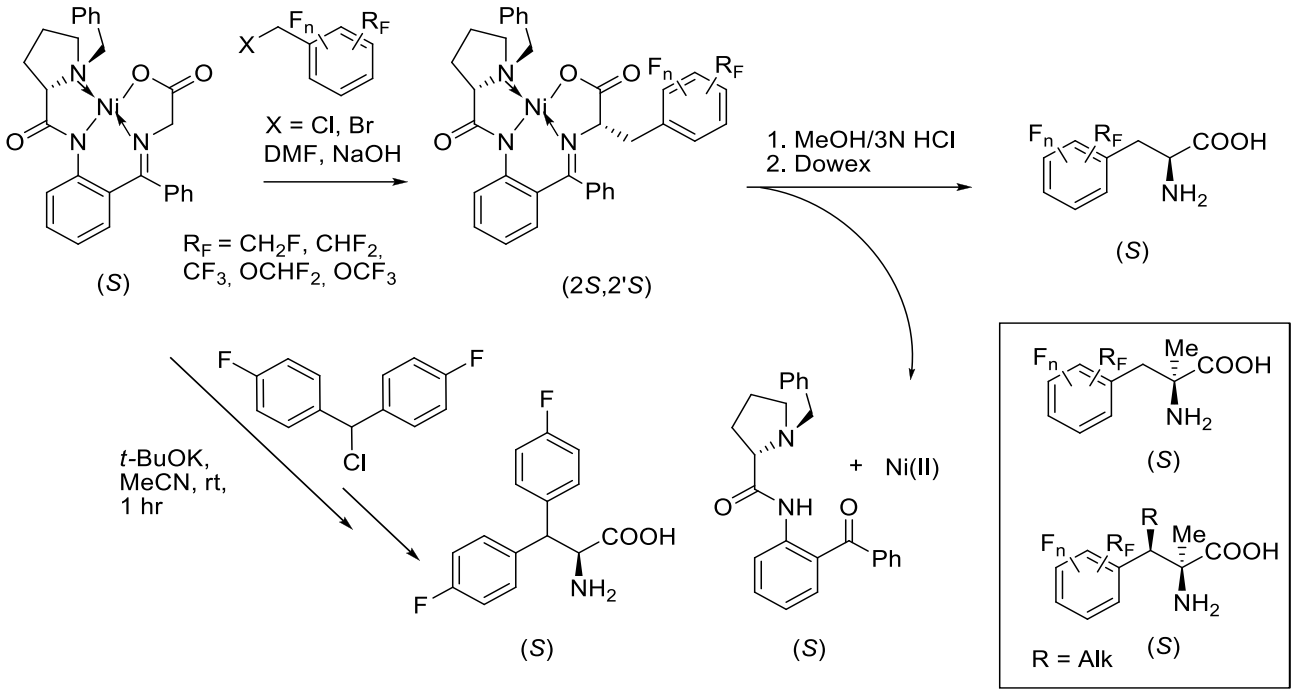


Scheme 4. Enantioselective hydrolysis of racemic amino acids.

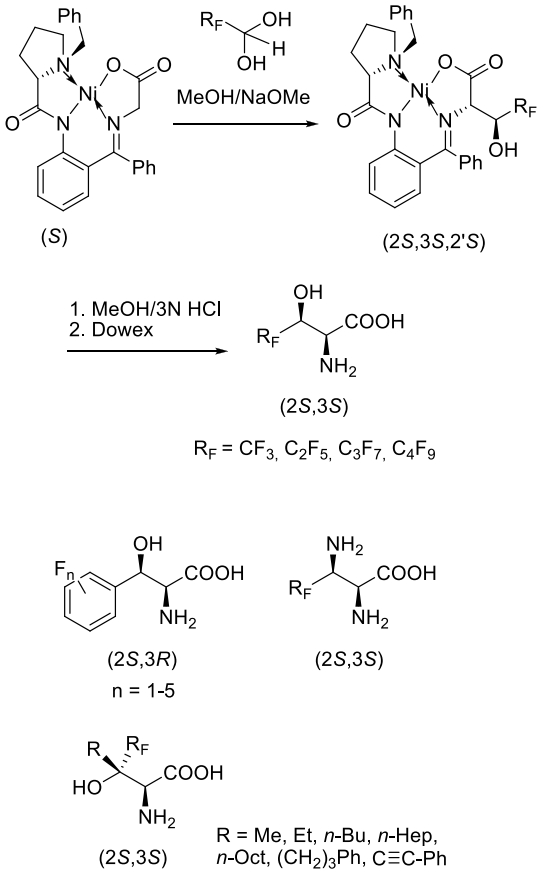


Scheme 5. Combination of the biomimetic transamination and penicillin acylaze catalyzed resolution.

One of the most interesting projects of Kukhar's laboratory is the asymmetric synthesis of fluorine-containing *α*-amino acids via homologation of the chiral Ni(II) Schiff's base complex of glycine with (*S*)-*o*-[*N*-(*N*´-benzylprolyl)amino]benzophenone [35, 36]. This area of research was initiated in collaboration with Prof. Belokon' and was developed by Dr. Soloshonok. At the beginning, authors studied the alkylation of Ni(II) complex with fluorinated benzyl halides. It was found that these reactions typically conducted in DMF solution and in the presence of NaOH, cleanly furnished the alkylation products in high diastereomeric purity and chemical yield. The (*S*) absolute configuration of the *N*-(benzyl) proline residue in the original complexes effectively induced the (*S*) stereo-chemistry of the newly formed stereogenic center of amino acids (Scheme 6).



Scheme 6. Asymmetric synthesis of fluorine-containing *α*-amino acids via homologation of the chiral Ni(II) Schiff's base complex of glycine with (*S*)-*o*-[*N*-(*N´*-benzylprolyl)amino]benzophenone.



Scheme 7. Stereoselective syntheses via chiral Ni(II) Schiff's base complex of glycine with (*S*)-*o*-[*N*-(*N´*-benzylprolyl)amino]benzophenone.

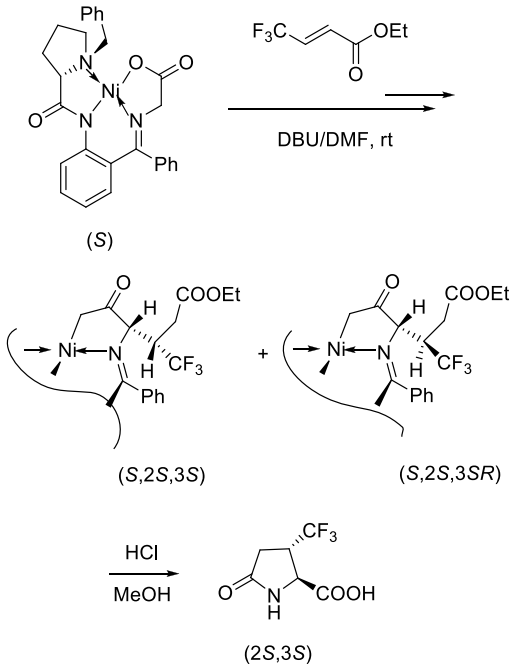
Another general approach for homologation of chiral nickel(II) complexes of Schiff's bases is aldol addition reactions allowing reliable synthetic access to the family of *α*-amino-*β*-hydroxy carboxylic acids. It was found that the perfluoroalkyl aldehydes, due to the high electrophilicity, can be easily used in the reactions with Schiff base as the corresponding hydrates, leading to the virtually irreversible formation of aldol addition products. The highest reaction rates were observed in methanol solutions in the presence of NaOMe [37]. The stereochemical outcome of these reactions was remarkably high favoring single (2*S*,3*S*,2´*S*) configured diastereomer out of four theoretically possible stereoisomeric products. Importantly, the trifluoromethyl, or more generally, perfluoroalkyl, group was shown to be the stereo-controlling substituent, mechanistically similar in the stereo-directing size to a *tert*-butyl. The target *α*-amino-*β*-hydroxy-*β*-perfluoroalkyl carboxylic acids (2*S*, 3*S*) were isolated from products in high chemical yield using the standard procedure (Scheme 7).

Using the same approach, a series of fluorinated derivatives of *β*-phenylserine (2*S*,3*R*), bearing from one to five fluorine atoms on the phenyl ring, were synthesized starting from the corresponding fluorinated benzaldehydes. The mode of the asymmetric induction in this case was the same and the different (2*S*,3*R*) absolute configuration is simply a consequence of the CIP priority rules [38].

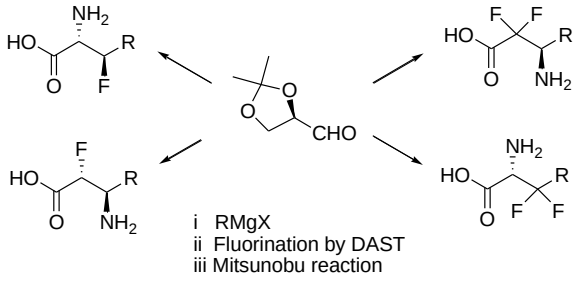
Application of imines derived from perfluoroalkyl aldehydes allowed to prepare quite a unique class of *α*,*β*-diamino-*β*-perfluoroalkyl carboxylic acids (2*S*,3*S*) [39]. Ni(II) complex of the Schiff base of glycine with (*S*)-o-[*N*-(*N*-benzylpropyl)amino]benzophenone readily reacts with ethyl 4,4,4-trifluorocrotonate in ethanol solution in the presence of DBU to afford a mixture of two diastereomers in ratio of

81:19, isolated with an excellent yield. The absolute configuration of the α-stereogenic center of the amino residues in complexes was assigned to be (*S*) by investigation of the chiroptical properties of the products (Scheme 8) [40].

Being interested in an efficient approach to biologically important compounds from easily accessible materials, Kukhar and co-workers turned attention to the application (*R*)-2,3-*O*-isopropylideneglyceraldehyde as a chiral synthon for the synthesis of optically pure mono- and difluorinated amino acids. Key steps of this methodology involve the Mitsunobu reaction for the introduction of amino function and incorporation of fluorine atom(s) by the fluorinating agent, morpholinotrifluorosulfurane (Scheme 9) [41].



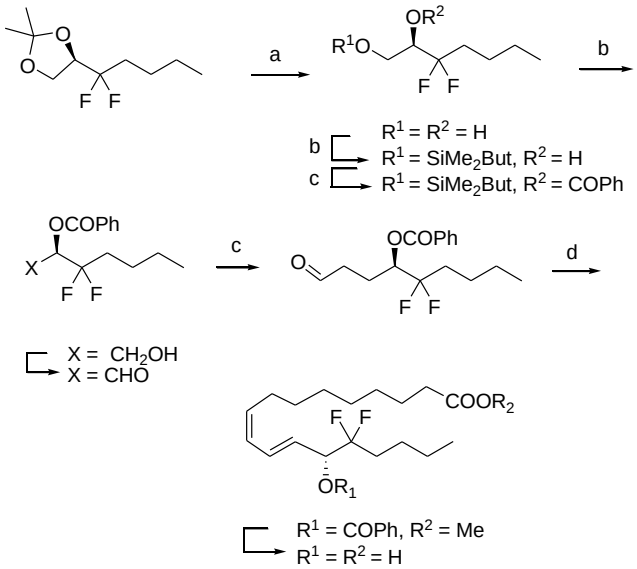
Scheme 8. Reaction of Ni(II) complex of the Schiff base of glycine with ethyl 4,4,4-trifluorocrotonate.



Scheme 9. (*R*)-2,3-*O*-isopropylideneglyceraldehyde as a chiral synthon.

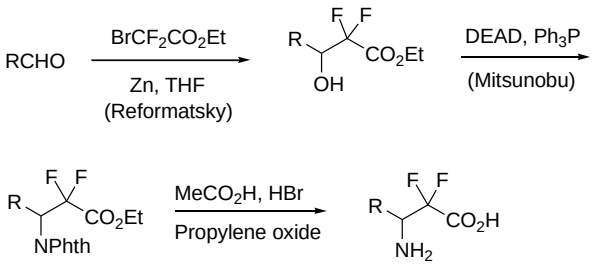
Another example including the efficient, stereoselective synthesis of (*R*)-14,14-difluorocoriolic acid starting from (*R*)-2,3-O-isopropylideneglyceraldehyde via the key intermediate (*R*)-3,3-difluoro-1,2-dihydroxyheptane has been reported by Kornilov and Sorochinsky (Scheme 10) [42]. The fluorinated analogue of coriolic acid was considered to be an attractive target for the synthesis, since coriolic acid possesses cation-specific ionophoric activity and plays a significant role in controlling thrombosis.

A three-stage synthesis of the fluorinated amino acids from aliphatic and aromatic aldehydes and ethyl bromodifluoroacetate has been carried out by Fokina and Kornilov using a combination of the Mitsunobu and Reformatsky procedures (Scheme 11) [43].



Reagents and conditions: a) 4N HCl-THF (1:4), 20 °C, 78%; b) *t*-BuMe$_2$SiCl, DMAP, CH_2Cl_2, 82%; c) PhCOCl, Py, CH_2Cl_2, 84%; d) dioxane-H_2O-HCl (10:2:5), 20 °C, 91%; e) $C_5H_5NH^+ClCrO_3^-$, 4A molecular sieves, 90%; f) Ph_3P=CHCHO, C_6H_6, reflux, 80%; g) Ph_3P=CH(CH$_2$)$_7$COOMe, 85%; h) LiOH, THF-H_2O (4:1), 20 °C, 45%

Scheme 10. Stereoselective synthesis of (*R*)-14,14-difluorocoriolic acid.

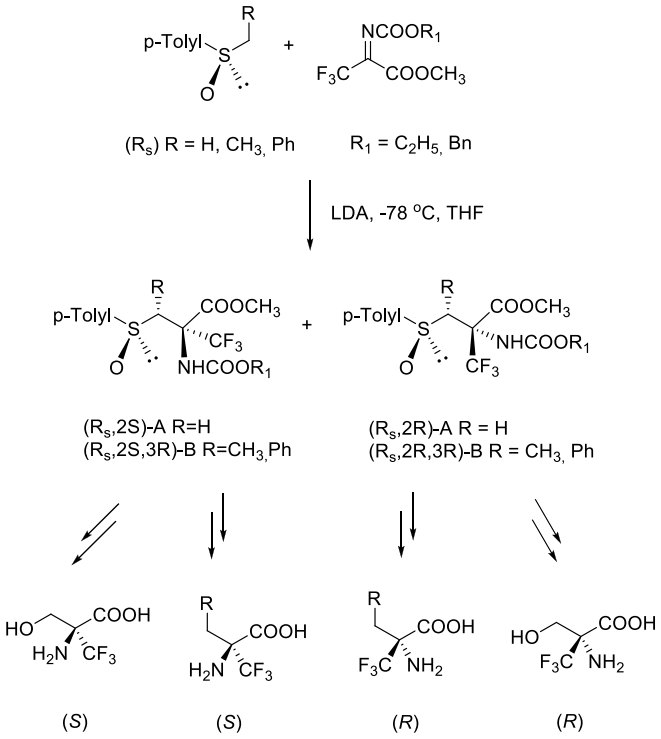


R = n-C_5H_{11}, n-C_4H_9, i-C_3H_7, 4-ClPh, 4-FPh

Scheme 11. Synthesis of fluorinated amino acids using a combination of the Mitsunobu and Reformatsky procedures.

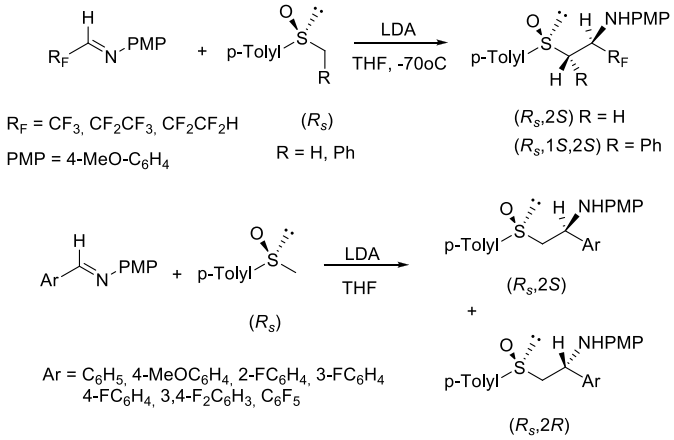
Sulfinyl group mediated asymmetric synthesis of fluorine-containing amines, amino alcohols and amino acids is another important area of scientific research of Kukhar and co-workers. The main advantages of the sulfinyl auxiliaries are: (a) existence of efficient methods for their preparation in enantiomerically pure form; (b) ease of chemical transformations into different functional groups or removal under mild conditions by reductive or eliminative methods; (c) high asymmetric induction exhibited in various reactions. In search for general diastereoselective approach to α-fluoroalkyl-α-amino acids, Kukhar's group in collaboration with Prof. Bravo (Italy) studied additions of α-lithiated alkyl *p*-tolyl sulfoxides to readily available *N*-acyl imines of trifluoropyruvate. They found that the reaction of *N*-acyl imines of methyl trifluoropyruvate with

the lithium anion of alkyl *p*-tolyl sulfoxides (R_s) in THF at -78º C regioselectively afforded the addition products at the imine carbon in good yields. Moderate diastereoselectivity and high enantioselectivity were observed in these addition reactions. Diastereomerically pure addition products were isolated by flash chromatography and/or fractional crystallization in moderate yields. Configuration assignments of the obtained *β*-amino sulfoxides were carried out by X-ray crystallography analysis as well as ^{1}H and ^{19}F NMR correlation. Pummerer rearrangement of both diastereomers **A** allowed extending this strategy to synthesis of *α*-trifluoromethylserines. Each of separated diastereomers **B** after well-optimized reduction, desulfurization and deprotection procedures provided a series of *α*-trifluoromethyl *α*-amino acids (Scheme 12) [44, 45].



Scheme 12. Sulfinyl group mediated asymmetric synthesis of fluorine-containing amino acids.

After achieving only moderate diastereoselectivity in the addition reactions to *N*-acyl imines, attention was turned to such electrophilic substrates as *N*-(*p*-methoxyphenyl)-aldimines bearing polyfluoroalkyl groups. The *N*-*p*-methoxyphenyl protective group was chosen because of its versatility. It can be readily cleaved to afford a free amine function, provides geometric homogenity of the imine functionality, and induces reasonably high electrophilicity of the C=N double bond allowing the imine nitrogen to form coordinated transition states. According to the ^{1}H, ^{13}C and ^{19}F NMR data the starting *N*-(*p*-methoxyphenyl)-aldimines, easily prepared by direct condensation between *p*-anisidine and perfluoroalkyl aldehydes in their commercially available hydrate or hemiacetal form, exist exclusively as (*E*)-geometric isomers that is critically important considering stereochemical outcome of the addition reactions [45, 46]. Condensation of the lithium anion of alkyl *p*-tolyl sulfoxides (R_s) with *N*-(*p*-methoxyphenyl) aldimines proceeded with high rate giving rise to addition products (R_s,2*S*) and (R_s,1*S*,2*S*) in excellent yields. The nature of the fluoroalkyl group in the starting imines had no particular influence on the stereochemical outcome of the addition reactions. Generally, high diastereoselectivity, more than 70% *de*, was achieved even for the case when two chiral centers were simultaneously created in the addition step. *α*-Fluoroalkyl-*β*-sulfinyl amines were found to be highly crystalline compounds thus allowing their purification to enantiomerically pure state by simple crystallization of crude reaction mixtures. The stereochemical outcome of these reactions were found to be quite different from that for *N*-(p-methoxyphenyl) aldimines derived from a series of aromatic aldehydes. It was demonstrated that stereochemistry of the irreversible additions between lithium derivatives of methyl *p*-tolyl sulfoxide (R_s) and aryl *N*-(*p*-methoxyphenyl) aldimines is function of reaction conditions and electronic properties of arylidene group of starting imines. High kinetically controlled (R_s,2*S*) diastereoselectivity of 84-90% *de* was achieved for the additions to imines bearing relatively electron rich *N*-arylidene group (Ar = C_6H_5, 4-$MeOC_6H_4$). Introduction of fluorine atoms on the benzylidene phenyl ring decreases the kinetically controlled (R_s,2*S*) diastereoselectivity and in the case of pentafluoro-benzylidene imine a mixture of corresponding diastereo-mers (R_s,2*S*) and (R_s,2*R*) was obtained in a ratio of 64:36 (Scheme 13). The stereochemical outcome can be explained by six-membered chair-like transition state where coordination of the metal to the sulfinyl oxygen and imine nitrogen could result in preferable attack of nucleophile to the *Re* face of the C=N bond in imine while the configuration of α-carbanion of benzyl *p*-tolyl sulfoxide is responsible for configuration of the new CSO stereogenic center [47].

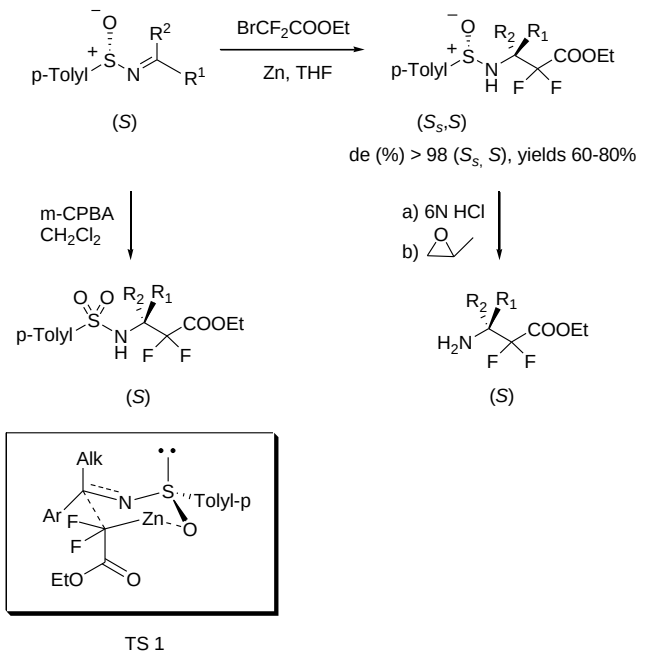


Scheme 13. Condensation of the lithium anion of alkyl *p*-tolyl sulfoxides (R_s) with *N*-(*p*-methoxyphenyl) aldimines.

The direct asymmetric synthesis of *α*,*α*-difluoro-*β*-amino acids has been realized by Sorochinsky et al. via Reformatsky reaction of ethyl bromodifluoroacetate with enantiomerically pure *N*-*p*-toluenesulfinyl imines. The enantiomerically pure *N*-*p*-toluenesulfinyl imines were treated with ethyl bromodifluoroacetate in the presence of activated Zn dust under high temperature to provide the desired *p*-toluenesulfinamides with the (S_s,3*S*)-absolute

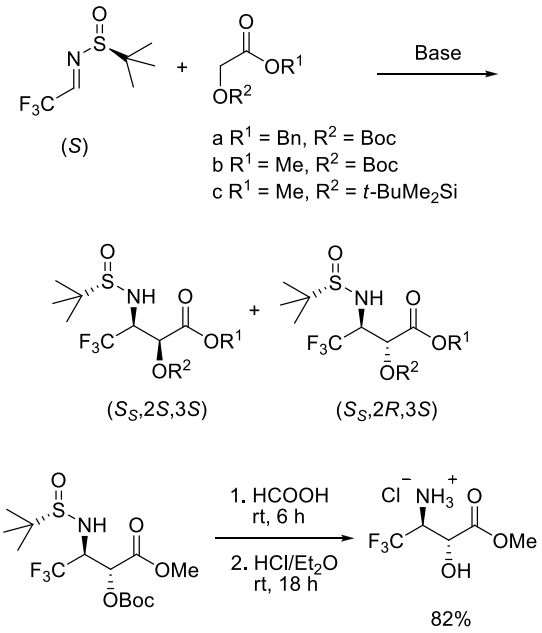
configuration of the major diastereomers and in highly diastereoselective manner. It was demonstrated that the diastereoselectivity of these addition reactions was noticeably influenced by the electron-donating or withdrawing character of the substituent on the aromatic ring, ranging from > 98 *de* for anisaldehyde-derived imine to 80-86% *de* for *p*-trifluoromethylphenyl- and 2-furyl-containing derivatives. At the same time the reactions of aliphatic imines proceeded with similar to the aromatic series rates but with lower diastereoselectivity (72-76% *de*) [48].

The Reformatsky reactions of acetophenone-derived *N*-sulfinyl ketimines giving the products possessing a quaternary stereogenic center were also studied. Thus, the acetophenone-derived ketimine afforded the expected addition product (S_s,*S*) in moderate yield, however, with excellent diastereoselectivity. The stereochemical outcome of the Reformatsky-type addition of ethyl bromo-difluoroacetate to sulfinketimines (*S*) has been explained by six-membered chair-like transition states TS 1 where the metal ion is chelated to the sulfinyl oxygen. Treatment of diastereomerically pure sulfinamides with 6*N* HCl and propylene oxide afforded the corresponding *α,α*-difluoro-*β*-amino acids in good isolated yields (Scheme 14).



Scheme 14. Synthesis of *α,α*-difluoro-β-amino acids via the Reformatsky reactions of acetophenone-derived *N*-sulfinyl ketimines.

Among the achievements of this period, it should be noted new asymmetric approach to *β*-trifluoro-methylisoserines (Scheme 15). The enantiopure (2*S*,3*S*)- and (2*R*,3*S*)-*β*-trifluoromethylisoserine derivatives have been prepared by Mannich-type addition of enolate derived from *O*-protected *α*-hydroxyacetates to (S_S)-*N*-*tert*-butanesulfinyl 3,3,3-trifluoroacetaldimine in good to excellent combined yield and good diastereoselectivity. Enantiopure *β*-trifluoromethylisoserines thus obtained are useful intermediates for synthesis of corresponding *N*,*O*-protected and partially deprotected aminoacids [49].



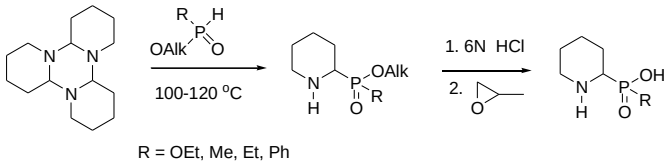
Scheme 15. Asymmetric approach to *β*-trifluoromethylisoserines.

2. Chemistry of aminophosphonic acids

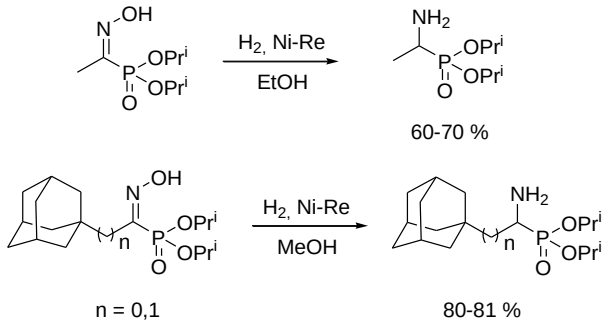
The Kukhar's saga on the study of mimetics of natural amino acids originates in the chemistry of aminophosphonic and aminophosphinic acids. These compounds occupy an important position in understanding of bioprocesses in living organisms and in a construction of new bioregulators – pharmaceuticals and agrochemicals. The tetrahedral configuration of pentavalent phosphorus atom mimics transition state in some enzyme-substrate interactions that can be used in the synthesis of new inhibitors and metal-complexing agents which have diagnostic and therapeutic applications. The importance of phosphonates has been revealed by discovery (Horiguchi and Kandatsu, 1959) of 2-aminoethanephosphonic acid ("*Ciliatine*") (AEP) in natural organisms. However, in those years, phosphonates remained poorly understood compounds and the development of convenient and effective procedures for their synthesis was an important task of preparative organophosphorus chemistry.

In 1987 Kukhar and Solodenko published the paper with the title "*Synthesis of (D,L)-2-phosphonopiperidines*". In this and subsequent articles they reported the synthesis of phosphorus analogues of 2-homoproline, a natural amino acid that plays an important role in the metabolism of lysine. 2,3,4,5-Tetrahydropyridine trimer and a number of *H*-phosphonates have been used in the Pudovik reaction which turned out to be more convenient than the use of imines of aldehydes. The simple heating of the reagents at 100-120 °C made it possible to obtain the desired compounds with yields of about 70% (Scheme 16) [50-53].

Some racemic α-aminophosphonates and their corresponding phosphonic acids were prepared via reduction of oximes of α-ketophosphonates by hydrogen over Raney nickel (Scheme 17) [54, 55].

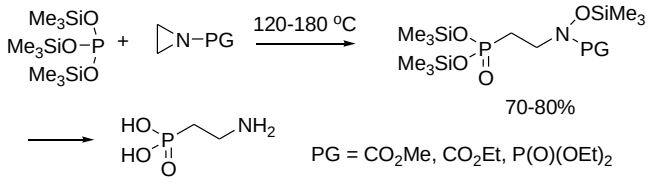


Scheme 16. Synthesis of (D,L)-2-phosphonopiperidines.



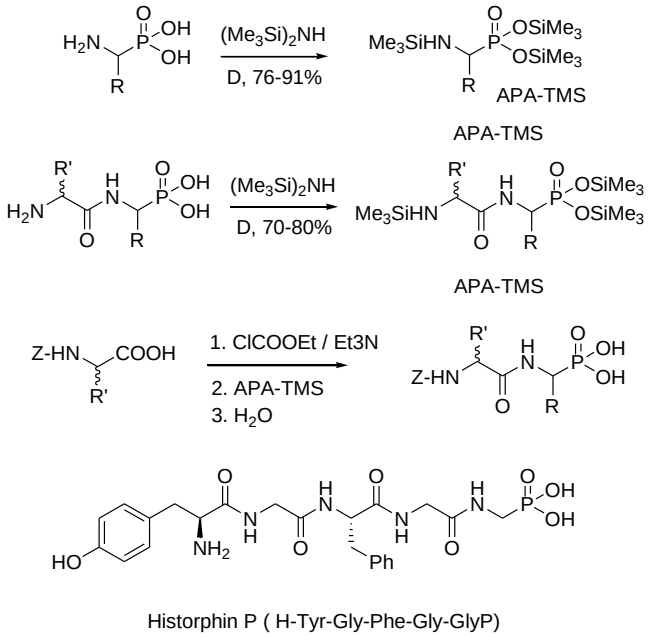
Scheme 17. Synthesis of racemic aminophosphonates *via* reduction of oximes of α-ketophosphonates by hydrogen over Raney nickel.

A particularly effective synthetic approach to functionalized phosphonates was the use of organosilicon methodologies that make it possible to obtain phosphonic acids under mild conditions and with high yield [56]. The advantage of "silyl" variants of aminophosphonate synthesis is that silyl substituents act as protecting groups, thus allowing the synthesis of phosphonates containing acid labile substituents. In addition, the conventional method for converting phosphonate esters into free phosphonic acids requires harsh reaction conditions which are usually not applicable to compounds with hydrolytically sensitive groups. In contrast to dialkyl esters, the trimethylsilyl esters of phosphonic acids can be hydrolyzed to corresponding phosphonic acids in neutral conditions at room temperature. From this point of view the trimethylsilyl esters of phosphonates present powerful platform to simplify route to desirable free phosphonic acids. In fact, the combination of phosphonate and trimethylsilyl group has given rise to new synthetic applications including the Arbuzov and Pudovik-Abramov reactions, Peterson condensation and fluoride-induced formation of α-phosphonylated carbanions. The effectiveness of the silicon methodology in amino-phosphonate chemistry is illustrated by the method developed by Lazukina and Kukhar to synthesize β-aminoethyl-phosphonic acid starting from tris(trimethyl-silyl)phosphite and functionalized aziridines (Scheme 18) [57].



Scheme 18. "Silyl" variant of aminophosphonate synthesis.

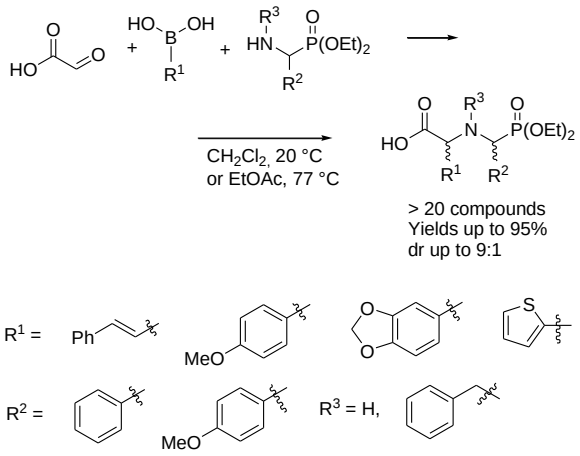
It is well known that the use of aminophosphonic acid esters for peptide synthesis is complicated by their instability, and the condensations with free amino-phosphonic acids often yield low yields. To overcome such difficulties, Kukhar and co-workers used trimethylsilyl derivatives in the synthesis of unprotected phospho-nopeptides with a *P*-terminal aminophosphonate residue. Heating of free aminophosphonic acids with an excess of hexamethyldisilazane gives TMS-protected aminophospho-nates with high yields while protecting the acid and amino functions. These compounds can in turn be involved in a standard procedure of peptide synthesis to give the desired phosphonopeptides. The effectiveness of the method was demonstrated by the synthesis of *P*-analogues tripeptides and pentapeptide of historphin P (H-Tyr-Gly-Phe-Gly-Gly^P) (Scheme 19) [58, 59].



Scheme 19. Synthesis of unprotected phosphinopeptides via "silyl" methodology.

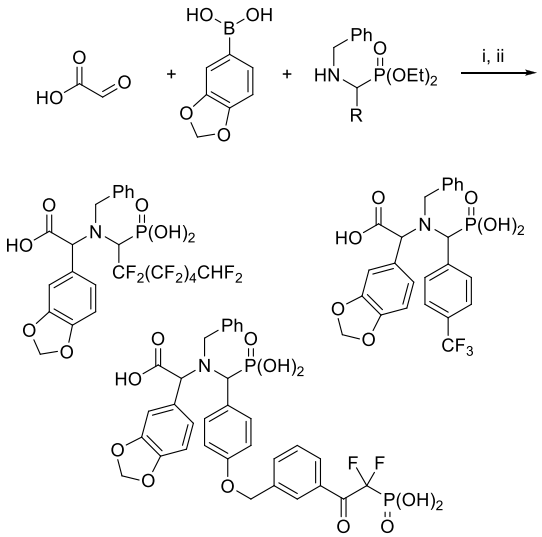
Kukhar and co-workers appear to be one of the pioneers in utilization of aminophosphonates as amine components in the Petasis boronic acid Mannich reaction (Scheme 20) [60-63]. Among multicomponent reactions, the Petasis three-component reaction has been focus of attention in the last decades due to a number of advantages. These are an availability of organoboron reagents in a large variety of structural configurations, compatibility with many functional groups allowing the facile synthesis of multifunctional molecules without the excessive use of protective groups, possibility of using water and alcohols as the reaction medium and low toxicity and environmental friendliness. With the use of α-aminophosphonates, several *N*-phosphonomethylglycine derivatives were prepared in good yield and high diastereoselectivity. On the whole, the regularities of the reaction are similar to those described earlier for the Petasis reaction involving organylamines: (a) for organylboronic acids, $RB(OH)_2$, the reactivity decreases in the following order of R^1: styryl > hetaryl > aryl; (b) diastereoselectivity of the reactions is higher in the

case of aminophosphonates with secondary amino group (*dr* > 9:1) as compared to phosphonates with primary amino group (*dr* > 7:3); (c) aprotic solvents of moderate polarity are the optimum reaction media. It should be noted that the conclusions on the stereochemistry of reaction products, made on the basis of theoretical calculations and X-ray diffraction studies, completely coincide [60].



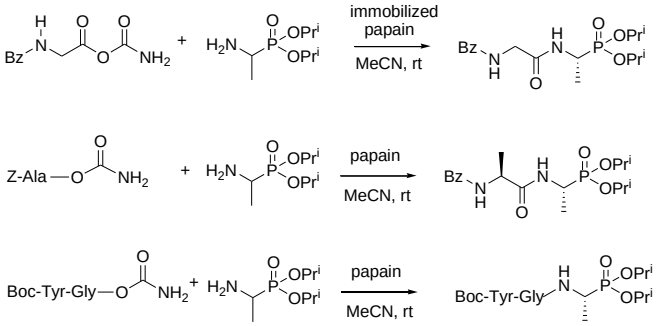
Scheme 20. Utilization of aminophosphonates as an amine component of Petasis reaction.

The Petasis reaction with aminophosphonates was applied to prepare a number of specially constructed compounds with additional functional groups in order to test of their biological activity as protein tyrosine phosphatase inhibitors and immunomodulatory agents (Scheme 21) [61-63].



Scheme 21. Application of the Petasis reaction for the synthesis of functionalized aminophosphonates.

In the biochemistry of aminophosphonic acids, stereochemical aspects play a very important role, since many *R*-amino acids (corresponding to the L-configuration of natural amino acids) change their activity when replaced with the *S*-configuration. Therefore, in order to study bioactivity, it is important to have both enantiomers of aminophosphonates. To solve this problem, Kukhar and co-workers used both traditional methods of asymmetric synthesis, based on the use of chiral induction groups, and specific enzymatic methods. The usefulness of enzymatic approaches to the synthesis of phosphonopeptides was first demonstrated by Solodenko and Kukhar on the example of synthesis of diisopropyl ester of 1-(*N*-benzyloxycarbonyl-glycilamino)ethylphosphonic acid (Scheme 22) [64]. Thus, racemic diisopropyl ester of 1-aminoethyl-phosphonic acid is converted to phosphonopeptides by treatment with *N*-benzyloxycarbonyl derivatives of amino acids in MeCN solution in the presence of a papain immobilized on polyamide carrier. Papain reveals high stereoselectivity in regard to racemic amino component: only L-amino-phosphonate is involved in the peptide bond formation. It allows the racemic aminophosphonates to be used for the synthesis of phosphonopeptides with moieties of optically active aminophosphonic acid at *P*-terminus. This approach was successfully used for the stereoselective papain-catalyzed synthesis of antimicrobial agent *Alafosfalin* [65, 66].

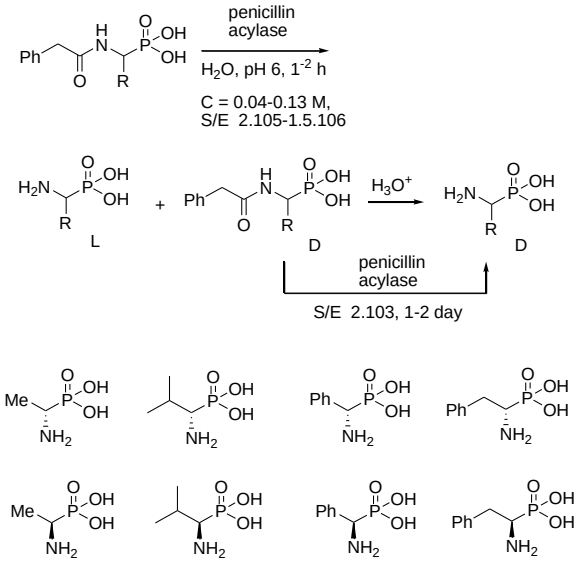


Scheme 22. Enzymatic approach to the synthesis of phosphonopeptides.

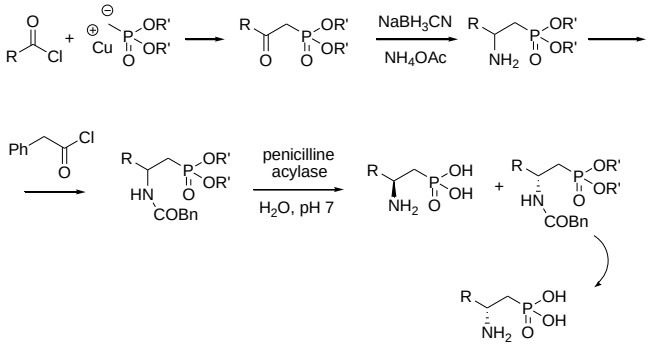
The broad substrate specificity of penicillin acylase makes it possible to use its catalytic properties for the separation of α- and β-aminophosphonates (Scheme 23 and 24). It turned out that in the case of *N*-phenylacetyl derivatives of β-aminophosphonates, the rate and enantioselectivity of hydrolysis depend on the nature of the substituents at the β-position of the carbon chain. If it is a phenyl radical, the hydrolysis proceeds like a series of α-aminophosphonate derivatives. If in the β-position there is a methyl group, then to achieve high stereoselectivity, monitoring of the process is necessary. Thus, both the α- and β-aminophosphonic acids can be separated into enantiomers by an enzymatic hydrolysis. The developed preparative procedures have some advantages in simplicity, number of steps, time consumption, as well as in the yields of the products. Moreover, it was shown that enantiomeric aminoalkylphosphonic acids can be easily incorporated into peptide chains. This finding is of great importance because the bioactivity of phosphonopeptides was shown to depend essentially on the stereochemistry of incorporated aminophosphonic acids which must correspond to L-configuration of natural amino acids [8].

Further studies performed in Kukhar's laboratory showed that organophosphorus compounds can act not only as substrates but also as inhibitors in relation to penicillin acylase. In particular, it has been found that aryl esters and

amides of benzylphosphonic acid are selective reversible competitive inhibitors of the enzyme from *E. coli* (EC 3.5.1.11). Inactivation of the enzyme is due to the phosphonylation of the hydroxy group of serine in its active site. The NMR spectrum of the "washed" inactivated complex with the enzyme shows a strong binding to the phosphonate. The new anionic inhibitors were the first representatives of this kind, other than the traditional neutral inhibitors of serine hydrolases [67, 68].



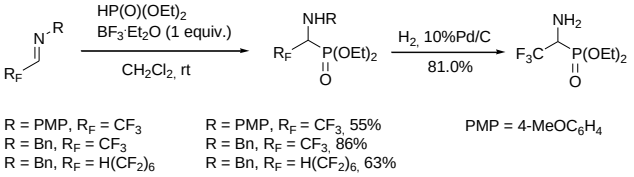
Scheme 23. Enzymatic approach to the synthesis α-amino-phosphonates.



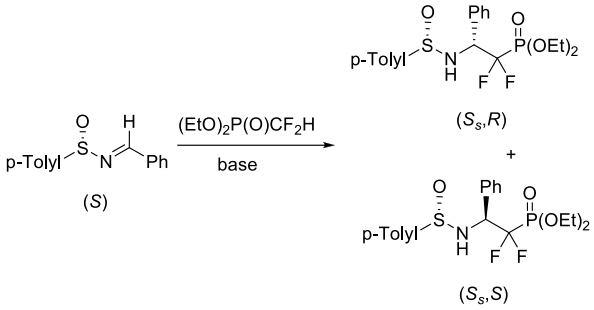
Scheme 24. Enzymatic approach to the synthesis β-amino-phosphonates.

Although diastereoselective nucleophilic addition of dialkyl phosphites to chiral aldimines is the most frequently employed strategy for the asymmetric synthesis of *α*-aminophosphonates, the synthetic potential of these reactions with fluorinated substrates remained largely unexplored. Kukhar and co-workers studied a behavior of fluorinated aldimines in the Pudovik reaction. Starting fluorinated aldimines have been obtained by condensation of hydrates or hemiacetals of the corresponding aldehydes with amines. It was found that the addition of diethyl phosphite to fluoroalkyl aldimines in CH_2Cl_2 proceeded smoothly in the presence of boron trifluoride etherate (1 equiv.) at room temperature to give the desired *α*-fluoroalkyl *α*-aminophosphonates. In particular, nucleophilic addition of diethyl phosphite in the presence of BF_3 was found to be a convenient method for the synthesis of racemic diethyl *α*-fluoroalkyl-*α*-aminophosphonates in good yield.

Addition of phosphonodifluoromethyl carbanion obtained by deprotonation of diethyl difluoromethyl-phosphonate with LDA in THF at -78 ºC to enantiomerically pure sulfinimine (*S*) proceeded smoothly to afford corresponding *N*-sulfinyl *α,α*-difluoro-*β*-amino phosphonate after mild acidic work up. In spite of relatively restricted nucleophilicity of phosphonodifluoromethyl carbanion, *N*-sulfinyl *α,α*-difluoro-*β*-aminophosphonate was obtained in good yield and diastereoselectivity. Due to its crystalline nature the major diastereomer could be readily obtained in optically pure form by single crystallization of the crude reaction mixture. The absolute stereochemistry of major diastereomer was determined to be (*S*s,*R*) by X-ray analysis (Scheme 26) [69, 70].

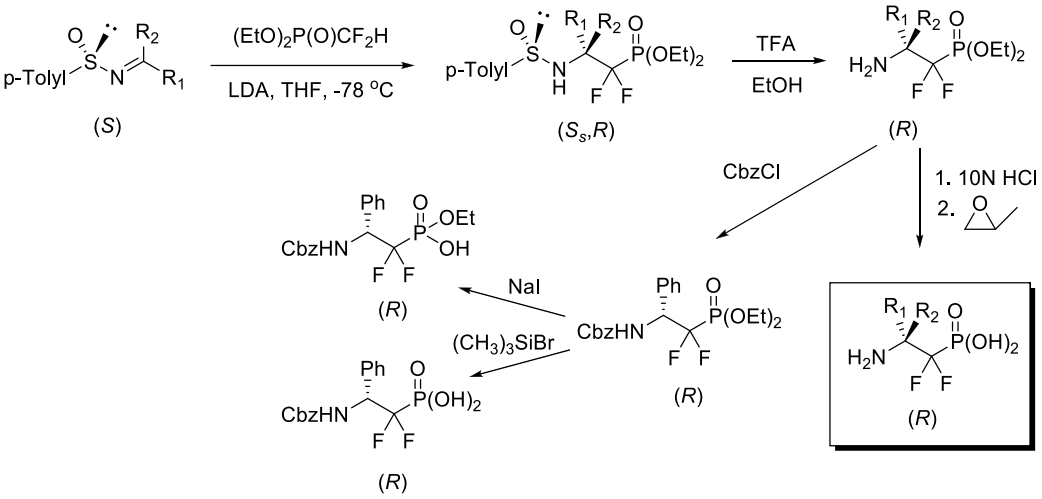


Scheme 25. Synthesis of *α*-fluoroalkyl *α*-aminophosphonates from fluorinated aldimines.



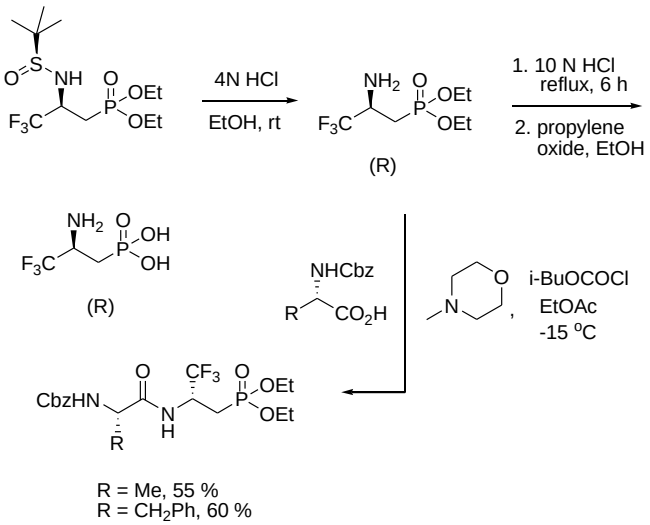
Scheme 26. Asymmetric synthesis of *N*-sulfinyl *α,α*-difluoro-*β*-aminophosphonate.

In accordance with previous experiments, addition of diethyl difluoromethylphosphonate to other *N*-sulfinyl-aldimines in THF using LDA as base proceeds in excellent diastereoselectivity (Scheme 27). The *N*-sulfinyl *α,α*-difluoro-*β*-aminophosphonate diastereomers were separated by chromatography or crystallization to give the major pure diastereomers (*S*s,*R*). Subsequent studies have demonstrated that *N-tert*-butanesulfinyl imine derived from fluoral is extremely useful building block for the asymmetric synthesis of fluorinated amines and related molecules due to excellent diastereoselectivity of nucleophilic addition reactions across C=N double bond and mild conditions for cleavage. Kukhar and co-workers applied this available chiral reagent as straightforward approach for the preparation of optical active phosphonotrifluoroalanine and its derivatives. In particular, it was established that the reaction of (*S*S)-*N-tert*-butanesulfinyl 3,3,3-trifluoro-acetaldiminewith dialkyl methylphosphonates emploing *n*-BuLi, LDA and LHMDS as deprotonating reagents provides the convenient stereoselective approach to *β*-tri-



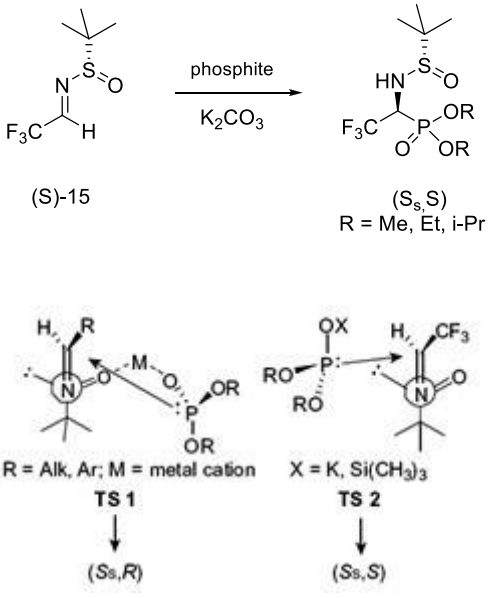
Scheme 27. Asymmetric synthesis of *α,α*-difluoro-*β*-aminophosphonic acids using sulfinimines.

fluoromethyl-*β*-aminophosphonic acids (Scheme 28). Various phosphonates participated successfully in the reaction to give the corresponding addition products in moderate to good yields and excellent diastereoselectivity (>90%). The stereochemistry of the major diastereomer was determined to be (*S*s,*R*) by X-ray analysis. Addition of *α*-phosphonate and α-phosphinate carbanions to *N*-sulfinyl-alkyl and aryl aldimines was proposed to proceed via open transition state model where *α*-phosphonate and *α*-phosphinate carbanions preferably added to the imine from the less hindered face to afford the major diastereomer adduct [71].



Scheme 28. Asymmetric synthesis of trifluoromethylated *β*-aminophosphonates and their incorporation into dipeptides.

Synthesis of fluorinated *α*-aminophosphonates required a direct reaction of (*S*s)-*N*-*tert*-butanesulfinyl 3,3,3-trifluoroacetaldimine with phosphites or dialkyl phosphites. However, treatment of *N*-*tert*-butanesulfinyl imine with dimethyl or diethyl phosphites in CH_2Cl_2 did not give any products at room temperature. On the other hand when combination of diethyl phosphite and potassium carbonate has been used the reaction with trifluoroacetaldimine proceeded at room temperature affording *N*-*tert*-butanesulfinyl *α*-aminophosphonate (*S*s,*S*) as major diastereoisomer in moderate chemical yield and diastereoselectivity. Diastereoselectivity could be raised to more satisfactory level by converting of diethyl phosphite *in situ* to its trimethylsilyloxy derivative. Indeed, the diethyl trimethylsilylphosphite reacts with trifluoroacetaldimine (*S*) in diastereoselective manner at 0 °C yielding *N*-*tert*-butanesulfinyl *α*-aminophosphonate (*S*s,*S*) in good yield and 84% *de*. Kukhar and co-workers also investigated the reaction of trifluoroacetaldimine with trimethylsilyl reagents derived from different dialkyl phosphites.

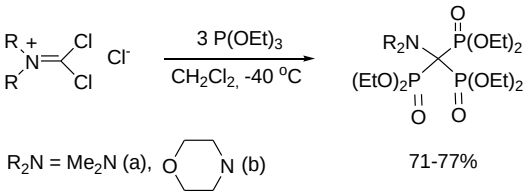


Scheme 29. Asymmetric synthesis of trifluoromethylated α-aminophosphonates.

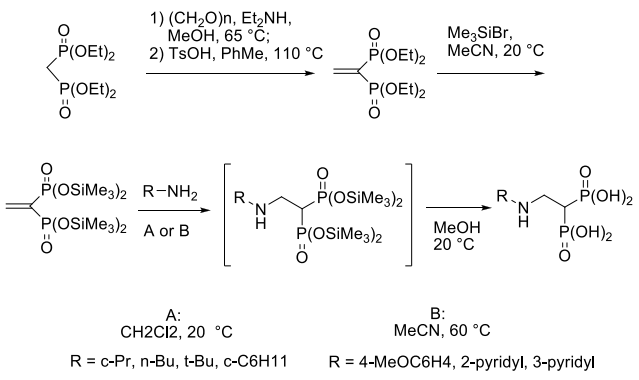
Using dipropyl trimethylsilyl phosphite brought about a slight increase in the yield of major diastereomer (S_S,S) while trimethylsilyl reagent derived from dimethyl phosphite led to lower overall yield and stereocontrol in favour of (S_S,S) isomer. The best result was achieved with diisopropyl trimethylsilyl phosphite furnishing stereoisomer (S_S,S) in high chemical yield and with good diastereoselectivity. The formation of the major diastereomers with the (*S*)-configuration of the chiral carbon atom in the addition of alkyl phosphites to weakly coordinate trifluoroacetaldimine may reasonably be explained by open transition state model where alkyl phosphites preferably added to imine from the less hindered face occupied by the lone pair of electrons on sulfur to afford the major diastereomer adduct (S_S,S). Such a transition-state model rationalizes the greater diastereoselectivity observed for the more sterically hindered diisopropyl trimethylsilyl phosphite relative to other dialkyl trimethylsilyl phosphites as well as diethyl phosphite (Scheme 29).

3. Synthesis of polyfunctional phosphate mimetics

There has been a considerable interest in the preparation and use of the geminal bis- and trisphosphonates, because of the widespread biomedical application of methylenebisphosphonates as mimetics of the endogenous metabolites, i.e., inorganic pyrophosphates (PP_i). A particularly interesting characteristic of trisphosphonates is the possibility of constructing systems based on Blackborn's conception of supercharged nucleotide analogues in which an additional negative charge is provided without elongation of the polyphosphate chain.



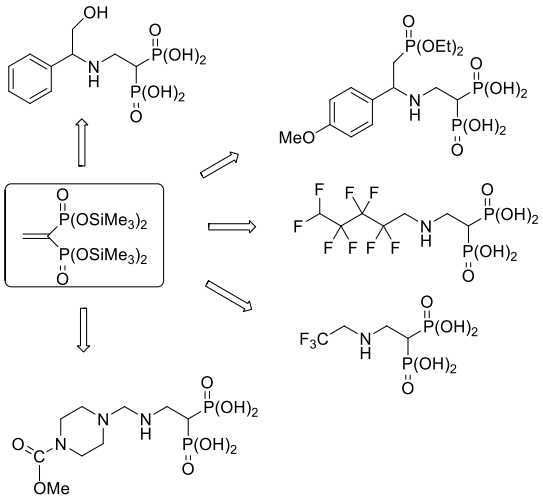
Scheme 30. Synthesis of methylidynetrisphosphonates.



Scheme 31. Synthesis of 2-aminoethylidene-1,1-bisphosphonates.

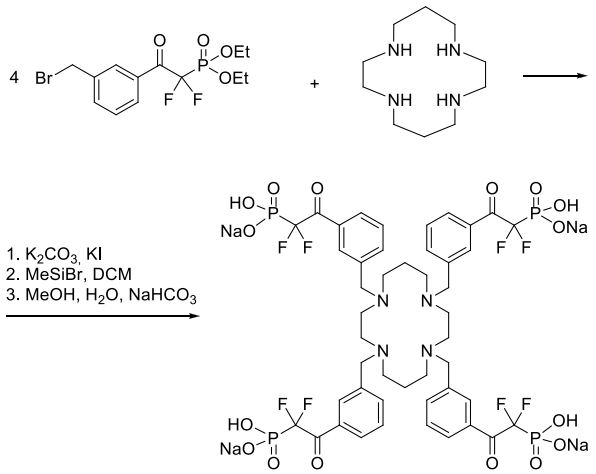
Study of the reaction of dichloromethaniminium chloride with triethyl phosphite, Kukhar, Pasternak and Kirsanov performed the first authentic synthesis of methylidynetrisphosphonates – representatives of geminal polyphosphonates bearing three phosphonate (PO_3H_2) groups at the bridged carbon atom (Scheme 30) [72]. In the scientific literature these compounds have been termed "Kukhar's phosphonates". Chemistry of methylidynetris-phosphonates has been reviewed by Kukhar and Romanenko [73].

The silicon methodology was successfully used in a straightforward synthesis of highly functionalized 2-amino-ethylidene-1,1-bisphosphonic acids via the Michael addition of amines to easily available tetrakis(trimethyl-silyl)ethenylidene-1,1-bisphosphonate (Scheme 31) [74, 75]. Treatment of the silyl esters with methanol at room temperature smoothly yielded the corresponding 2-aminoethylidene-1,1-bisphosphonic acids. The biological activity of functionalized 2-aminoethylidene-1,1-bis-phosphonic acids as immunomodulatory agents was a subject of special investigation (Scheme 32) [76].



Scheme 32. Examples of functionalized 2-aminoethylidene-1,1-bisphosphonates.

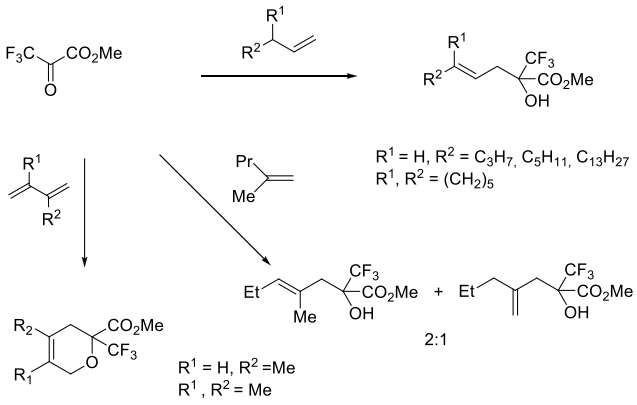
The Kukhar's research group in cooperation with Prof. I. Beletskaya and her co-workers also worked out the synthesis of phosphonates and bisphosphonates on the platform of tetraazamacrocycles (cyclames and cyclenes). Thus, studies of the biological activity of the cyclam bearing four benzyl-linked α,α-difluoro-β-ketophosphonate substituents, performed in the laboratory of Prof. A. Vovk, shoved that this compound can strongly inhibit activity of TC-PTP with IC_{50} value of 75 nM (Scheme 33). Comparison with the other tetraazamacrocyclic inhibitors indicated that this could be the consequence of the presence of both bioisosteric phosphonate moieties and the macrocyclic polyamine ring in the molecule. Kinetic and docking studies suggested that the macrocyclic inhibitor may bind to the active site of TC-PTP with open WPD-loop, preventing enzyme-substrate interaction. In addition, the obtained data demonstrated that cyclam- and cyclen-based inhibitors of TC-PTP with four α,α-difluoro-β-ketophosphonate fragments can display selectivity over PTP1B, CD45, SHP2, and PTPβ. This study paves the way for the synthesis and investigation of specific polyazamacrocycle-based PTP inhibitors that would enable the modulation of the signalling pathways in living cells [77, 78].



Scheme 33. Synthesis of tetraazamacrocycle-based inhibitor.

4. Fluorine-containing unsaturated synthons in practical synthesis of bioactive molecules

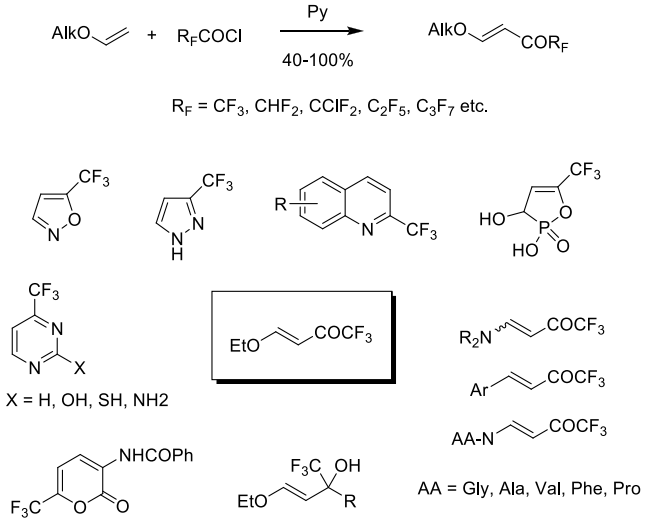
Different approaches have been applied to the synthesis of fluorinated unsaturated compounds. However, none of them seems to have general applicability, and difficulties were, generally, associated with selective introduction of fluorine in polyfunctional molecules. The application of the "synthon strategy" in such syntheses seemed therefore very expedient. In fact, during the entire scientific career of Kukhar, his favorite approach for the synthesis of fluorine-containing biologically active compounds was the application of fluorine-containing synthons in practical synthesis of bioactive molecules. This is particularly evident from the works performed by Valery Kukhar jointly with Dr. Igor Gerus, Dr. Alexander Sorochinsky and Dr. Vadim Soloshonok on the synthesis of amino acids sand unsaturated polyfunctional compounds with fluorine atom or fluorine containing groups.



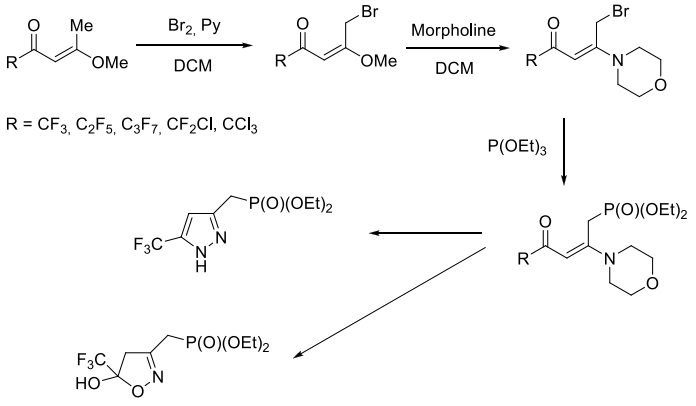
Scheme 34. Methyl trifluoropyruvate in "ene" reactions with 1-alkenes.

Thus, methyl trifluoropyruvate was found to be highly reactive in "ene" reactions with 1-alkenes (Scheme 34). Due to its exceptionally high electrophilicity these reactions can be conducted without any catalyst (usually Lewis acid is required) at ambient temperatures or moderate heating yielding α-allyl derivatives of trifluoromethyl lactic acid. The relative stereochemistry of the double bond in these compounds was shown by NMR spectra to be exclusively *trans*. 2-Methyl-1-pentene reacted exothermically with a keto ester to form a mixture of isomeric hydroxyl esters in a ratio of 2:1. In contrast, terminal diene did not react by "ene"-type mechanism, but via Diels-Alder reaction giving rise to (trifluoromethyl)pyrans [79].

Gerus and co-workers have developed chemistry of β-alkoxyvinyl polyfluoroalkyl ketones as basis for the construction of various trifluoromethyl containing heterocycles and aliphatic polyfunctional compounds (Scheme 35) [80-83]. Naturally, they used these synthons in the synthesis of polyfluoroalkyl containing amino acids – unknown analogues of γ-aminobutyric acid (GABA), Ornitine, Glutamic Acid, etc. The scheme below shows some transformations of β-alkoxyvinyl ketones into various organic compounds with trifluoromethyl group. β-Alkoxyvinyl ketones have been used in heterocyclic syntheses as well as a protective groups in peptide synthesis due to easy substitution of alkoxy group by amino function. In some cases, it was possible to realize a simple addition reaction on C=C bond without subsequent elimination, for example, to add alcohols and glycols. It is clear that these new products may be perspective synthons for the subsequent transformations of the acetal group [84-86].



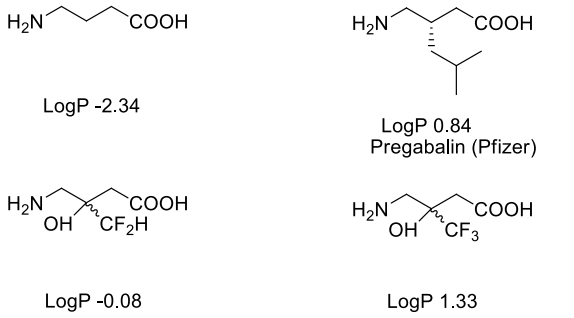
Scheme 35. β-Alkoxyvinyl polyfluoroalkyl ketones as synthons.



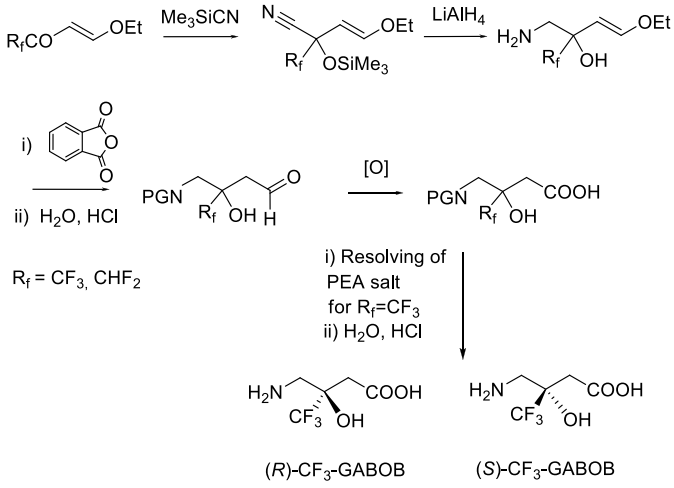
Scheme 36. Application of β-alkoxyvinyl polyfluoroalkyl ketones in heterocyclic synthesis.

A number of polyhalogenoalkyl-containing phosphonates with an enaminone core were synthesized from readily available *β*-alkoxyvinyl polyhalogenoalkyl ketones by successive bromination, amination, and Arbuzov reaction. The new phosphonates were used for the synthesis of five- and six-membered heterocycles bearing both trifluoromethyl and methylenephosphonate groups (Scheme 36) [87, 88].

It was known that GABA derivatives strongly affect the central nervous system. Kukhar and co-workers draw their attention on the fact that bioactive GABAs have at the *β*-position either a hydrophobic residue or hydroxy group. They found that *β*-polyfluoromethyl derivatives characterized much higher value of calculated LogP in comparison with parent GABA and have been very close to Pregabalin – Pfizer product. So, they synthesized a new type of GABA analogues which have both polyfluoroalkyl substituent and hydroxyl group at *β*-position (Scheme 37).



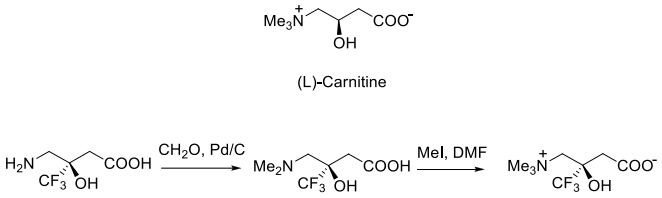
Scheme 37. Calculated *logP* of GABAs and their perfluoroalkyl analogues.



Scheme 38. Synthesis of optically active *β*-hydroxy-*β*-polyfluoromethyl GABAs.

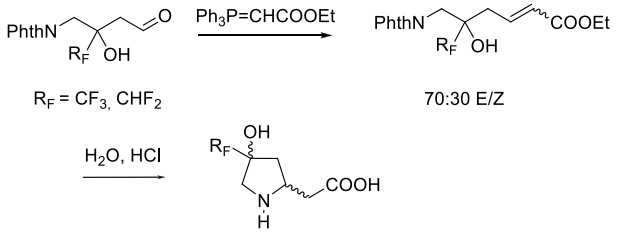
The addition of TMSCN to carbonyl group with following reduction of the cyanohydrines gives aminoalcohols in good yields. The salts of the aminoalcohols with L- or D-tartaric acid have been used for resolving of CF_3-containing intermediates [89-91]. Amino group in a racemic aminoalcohol has been protected with phthalic anhydride, and then alkoxyvinyl intermediate was hydrolyzed to aldehyde followed by oxidation to *β*-R_f-GABOBs (Scheme 38) [92].

Kukhar and co-worker also described the first synthesis of a fluorinated carnitine. L-Carnitine (3-hydroxy-4-trimethylammonium butyrate) is a small molecule to be found in almost all cells. The increase of the lipophilicity of carnitine molecule was achieved thanks to the introduction of the trifluoromethyl group. CF_3-containing GABOB was used as starting material for the synthesis of *β*-trifluoromethyl carnitine. Reductive methylation with following methylation of norcarnitine gave the desired CF_3-containing carnitine (Scheme 39) [93].

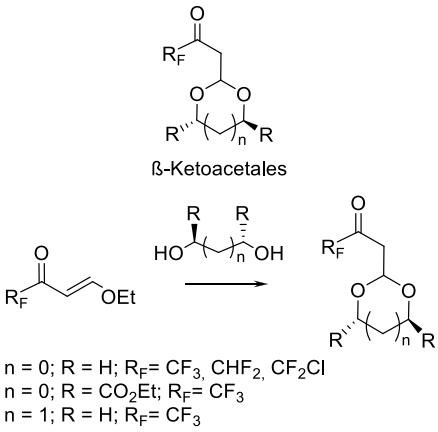


Scheme 39. Synthesis of a fluorinated carnitine.

Derivatives of 4-hydroxy-homoproline are potent GABA-uptake inhibitors. The polyfluoroalkyl substituted aldehydes were used as synthons for the synthesis of previous unknown homoprolines. Thus, the *β*-substituted acrylates were obtained by the Wittig reaction as a mixture of *cis*- and *trans*- isomers in essentially quantitative yield. Subsequent deprotection gives 4-hydroxy-4-polyfluoroalkyl homoproline as the result of intramolecular nucleophilic attack of the nitrogen atom on *β*-unsaturated carbon atom in high yields and good diastereoselectivity (Scheme 40) [94].



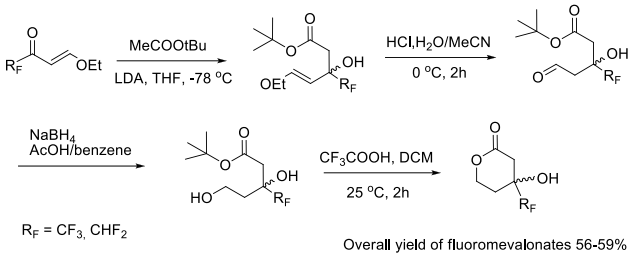
Scheme 40. Synthesis of 4-hydroxy-4-polyfluoroalkyl homoprolines.



Scheme 41. Fluorinated *β*-ketoacetales.

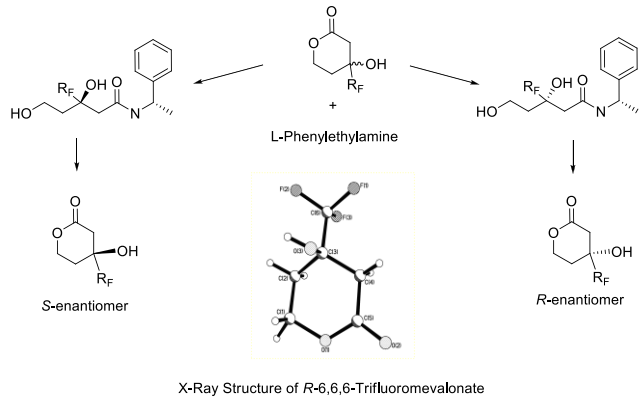
Another class of fluorinated acetyl acetaldehyde derivatives are fluorinated *β*-ketoacetales which can be easily prepared by the reaction of corresponding *β*-alkoxy enone with 1,2- or 1,3-diol (Scheme 41). The peculiarity of these derivatives is that they do not have reactive *β*-position for nucleophilic attack as in the case of *β*-alkoxy enones.

These compounds were used as the starting materials for the fluoromevalonate synthesis (Scheme 42) [95].

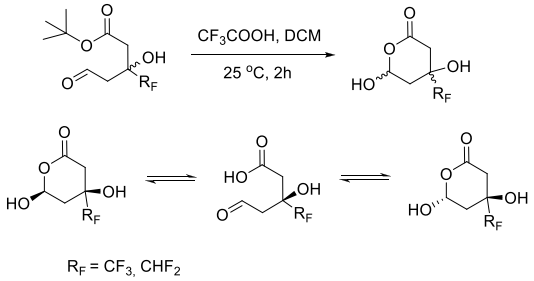


Scheme 42. Synthesis of 6,6,6-trifluoro- and 6,6-difluoro-mevalonates.

Separation of 6,6-difluoro- and 6,6,6-trifluoromevalonic acid enantiomers has also been performed. It was shown that reaction of trifluoromevalonolactone with L-phenyl-ethylamine gives diastereomeric amides, which can be separated by column chromatography. Hydrolysis of the amides leads to enantiomerically pure trifluoromevalonate. X-Ray analysis of (-)-6,6,6-trifluoromevalonate revealed *R*-configuration. Therefore (-)-trifluoromevalonate as well as natural (-)-mevalonate has *R*-configuration (Scheme 43) [85].



Scheme 43. Fluoromevalonate enantiomer resolution.



Scheme 44. Synthesis of racemic difluoromethyl- and trifluoromethyl analogues of mevaldinic acid.

The proposed scheme can also be used for synthesis of racemic difluoromethyl- and trifluoromethyl analogues of mevaldinic acid. On the basis of NMR-spectra it was shown that trifluoromevaldinic acid exists in solution as an equilibrium mixture of two diastereomeric lactoles and an acyclic form. Sodium salt of trifluoro and difluoromevaldinic acid obviously exists just in opened form (Scheme 44).

In conclusion, it should be noted that the studies described here are only a small part of the work that was carried out by the staff and students of Valery Kukhar. His never-ending enthusiasm for research in bioorganic chemistry has not only inspired all of his group members but has also unlighted researches working in the related areas such as ecology, resource conservation, replacement of chemical raw materials with renewable organic materials, and the safe use of chemicals [95]. Looking into the future, there are many prospects for finding useful applications of the chemistry developed by Kukhar and his co-workers, and there are plenty of opportunity for new discoveries, which we think will continue to offer scientific challenges.

Notes

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Основні напрями наукової діяльності академіка В. П. Кухаря

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Резюме: Ця стаття присвячена академіку Валерію Павловичу Кухарю з огляду на значний внесок його у розвиток синтетичної біоорганічної хімії та з нагоди його 80-річчя.

Ключові слова: фторовані амінокислоти; амінофосфонати; стереоселективний синтез; фторовмісні синтони; фосфатні міметики.