Valery P. Kukhar (1942-2017)

Scientific contribution

It is tragic for family, friends and colleagues that Valery P. Kukhar passed away on Mars 28, 2017, at the age of 75. Until the last days of his life he retained a deep interest in scientific research in the field of bioorganic, heteroatom and organoelement chemistry and did not stop actively participating in the work of the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of the Ukraine created by him, in 1989. The breadth of his scientific interests, deep scientific intuition and charismatic communication style will long be remembered. Prof. Kukhar published about 700 research papers and about 35 scientific reviews. He was also the co-author or editor of the well-known books "*Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*" (Wiley & Sons, 2000), "*Fluorine-containing Amino Acids: Synthesis and Properties*" (Wiley & Sons, 1995), "*Amino Acids, Peptides and Proteins in Organic Chemistry*" (Wiley-VCH, 2009), "*Химия биорегуляторных процессов*" (Наукова Думка, 1992).[1-4] His last scientific report was made at the XXIV Ukrainian Conference on Organic Chemistry in the beautiful city of Poltava, Ukraine, on September 19, 2016, and was entitled "*Carbon-hydrogen bond activation. New tools for organic synthesis*". For many years he was one of the world's leaders in the field of aminophosphonate chemistry and was awarded the prestigious International Arbuzov's Prize for a set of scientific results in the development of phosphorus chemistry in 2013.[5]

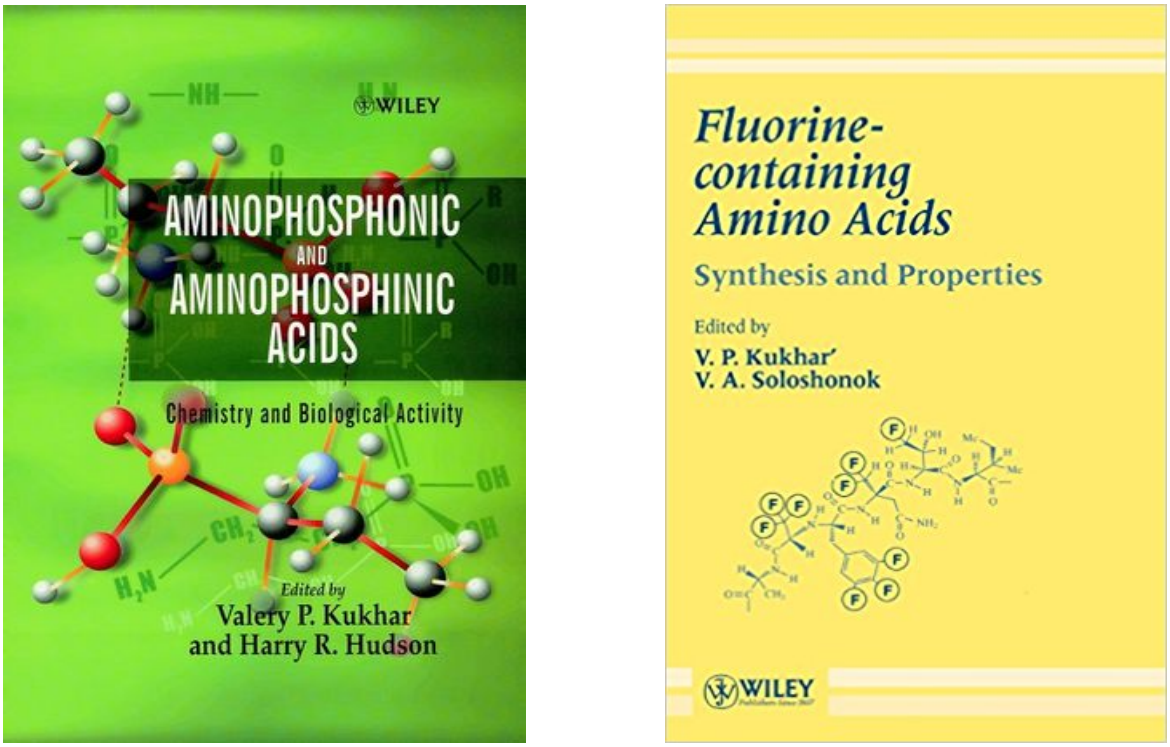


Figure 1. Books published under the editorship of Valery P. Kukhar

Valery Kukhar began his career as a research worker in organic chemistry by joining the group of Dr. Elena Abrazhanova at Dnepropetrovsk Chemical Engineering Institute while being a second-years student. Dr. E.A. Abrazhanova has been at that time the dean of the Faculty of Organic Chemistry. She was a post-graduate student of Professor Alexander Kirsanov (1898-1994), who in 1949-1951 headed the Department of Organic Chemistry at the Dnepropetrovsk Metallurgical Institute. Dr. E. Abrazhanova had been engaged in the study of phosphazo compounds, a classic subject of investigation of his scientific teacher. It was not surprising that she drew Valery Kukhar into synthetic organoelement chemistry and introduced him to her scientific direction. Kukhar's first experimental results concerning arenesulfamides were published in the *Журнал Общей Химии* (Journal of General Chemistry),[6] which at that time was the leading Soviet chemical journal. There is no doubt that the young chemist was extremely fortunate to be involved in the scientific atmosphere of a modern chemistry, which was provided by highly educated and highly intelligent university's teachers. Valery Kukhar had graduated from the Dnepropetrovsk Chemical Engineering Institute in 1963. He had plans to become a process engineer, but his time with Dr. Elena Abrazhanova was to change that forever, much to the benefit of the field of organoelement chemistry research. Nevertheless, Kukhar retained close contact and collaboration with the engineer community throughout his carrier. In 1963, having a diploma of Chemical Engineering Institute, Valery Kukhar moved to Kiev and became a post-graduate student of Alexander Kirsanov, an outstanding chemist and a remarkable man, who was a Director of the Institute of Organic Chemistry of Academy of Science of the Ukraine and head of the Department of Organophosphorus Compounds. Alexander Vasil'evich Kirsanov was one of the students of Academician A.E. Chichibabin (1871-1945), who in turn was a pupil of Academician V.V. Markovnikov (1838-1904), who had passed the school of A.M. Butlerov (1821-1886), a student of Justus von Liebig (1803-1873) himself. For all these majestic figures of organic chemistry there were inherent depth of thinking and a vivid flight of ideas. Here are some memories left by Kukhar about his teacher:

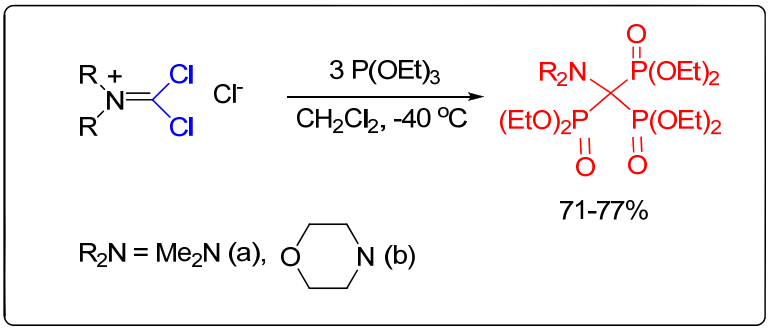
"The most striking feature of the character of Alexander Vasil'evicha was an unceasing attraction to a new, yet unknown. He loved "chemical secrets" and their "investigation", was generous to new brilliant ideas and valued such traits from employees. For him, the main thing was not the "scientific pursuit" of a scientist, but his desire for creative interesting work and the ability to translate interesting ideas... He advised us not to follow others but to go our own way. Since then, these words have been, and still are, my motto." [7]

Valery Kukhar was working hard on his thesis for the degree of PhD in chemistry (Candidate of Chemical Sciences), which he successfully defended on March 11, 1967. The topic of his thesis was "*Phosphorylation of dicarboxylic acid nitriles*".[8] After defending the thesis, Kukhar continues to work at the Institute of Organic Chemistry as a junior, then senior research fellow. It was a stormy and happy period of his life. At this time he married Natalia Mirian (also a professional chemist and scientist), from whom he lived his whole life and raised a son (Alexey) and daughter (Natalia). His major chemistry topics in this period of his scientific career were halogenated polycyanohydrocarbons, α-haloalkylamines and their phosphorylated derivatives. The theme of Kukhar's thesis for degree of Doctor of Chemical Sciences (1974) was "*N-Chloroalkylamines and their derivatives*".[9] Scientific opponents on

his doctoral defense were prominent Soviet scientists Academician I. Knunyants, Professor A. Yasnikov and Professor A. Dombrovsky. In his thesis Kukhar sums up his years of theoretical and experimental studies of trichloroalkylamines and phosphorylated derivatives of α-chloroalkylamines – trichlorophosphazo-α,α-dichloroalkanes. Academician Knunyants called this cycle of works elegant («изящным», *рус*.).[10]

Figure 2. Alexander V. Kirsanov and Valery P. Kukhar (about 1975)

Among the many interesting and important reactions found by Kuhar is to single out one that has gained wide popularity. Studying the reaction of dichloromethaniminium chloride with triethyl phosphite, Kukhar, Pasternak and Kirsanov performed the first authentic synthesis of methylidyntrisphosphonates – representatives of geminal polyphosphonates bearing three phosphonate (PO_3H_2) groups at the bridged carbon atom.[11] In the scientific literature these compounds have been termed "Kukhar's phosphonates".[12]



There has been a considerable interest in the preparation and use of the geminal trisphosphonates, $XC(PO_3R_2)_3$, 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.[13]

Figure 3. Photo of Kukhar's scientific group in the early 1970's. Back row (left to right): Valery Kukhar, Marina Furmanova, Viktor Matsnev, Elene Pashinik, Alexander Boyko. Front row (left to right): Valentina Pasternak, Ludmila Vasilenko and Tamara Kasheva

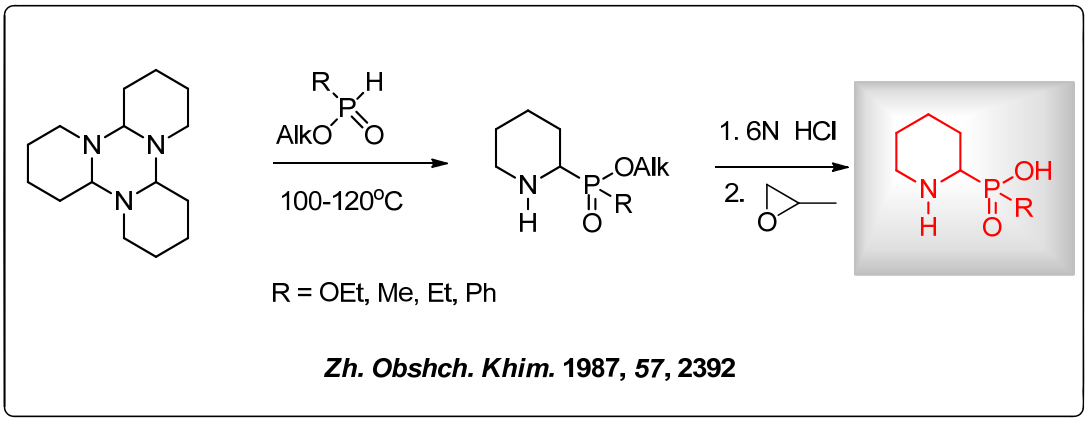
In the early 1980s, at the suggestion of the President of Academy of Sciences of the Ukrainian SSR Boris E. Paton, Valery Kuhar established the Institute of Bioorganic Chemistry and Petrochemistry whose task was the development of scientific research on the border of organic chemistry, biology and medicine**.** Since that time, organoelement mimetics of natural amino acids is "a sharpening stone" in the activity of the Laboratory of Fine Organic Synthesis headed by Prof. Kukhar.

Figure 4. Group photo taken in 1978 shows Valery Kukhar (centre facing) and his co-workers. Back Row (left to right): A. Pavlenko, A. Sorochynsky, O. Kolodiazhnyi, L. Salogub, A. Aleksandrov, L. Kovalevskaya, A. Boyko, E. Ruchko, V. Vishnevskaya, S. Vdovenko, A. Kisilenko, V. Gamaleya, V. Matsnev, S. Moshchitskyi. Front Row (left to rigth): M. Furmanova, L. Lazukina, V. Kukhar, T. Kasheva and E. Pashinnik

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

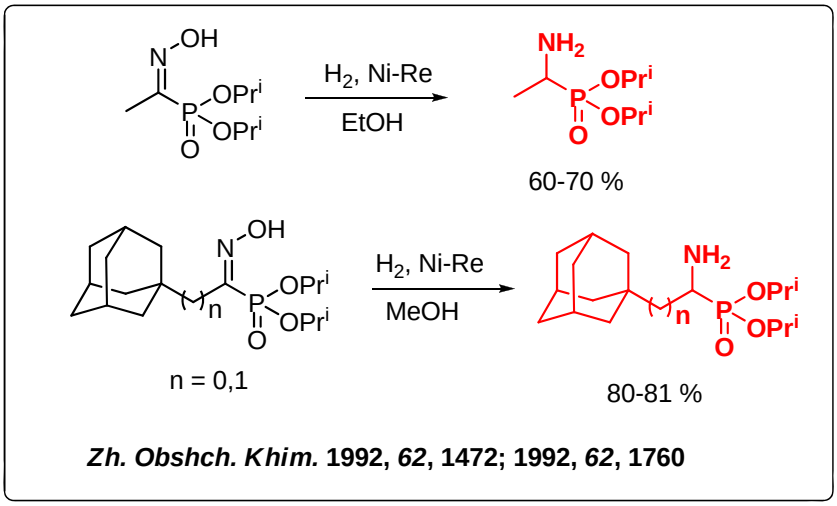
that can be used in the synthesis of new inhibitors and metal-complexing agents which have diagnostic and therapeutic applications. The importance of phosphonates has been revealed by discovery (Horiguchi and Kandatsu, 1959) of 2-aminoethanephosphonic acid ("*Ciliatine*") (AEP) in natural organisms. 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 Valery Kukhar and Vladimir 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%.[14-17]



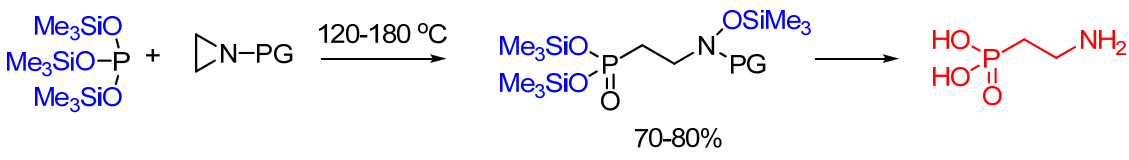
***Zh. Obshch. Khim.* 1987, *57*, 2392**

Some racemic α-aminophosphonates and their corresponding phosphonic acids were prepared via reduction of oximes of α-ketophosphonates by hydrogen over Raney nickel.[18,19]



***Zh. Obshch. Khim.* 1992, *62*, 1472; 1992, *62*, 1760**

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.[20] 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 aminophosphonate chemistry is illustrated by the method developed by Lazukina and Kukhar to synthesize β-aminoethylphosphonic acid starting from tris(trimethylsilyl)phosphite and functionalized aziridines.[21]

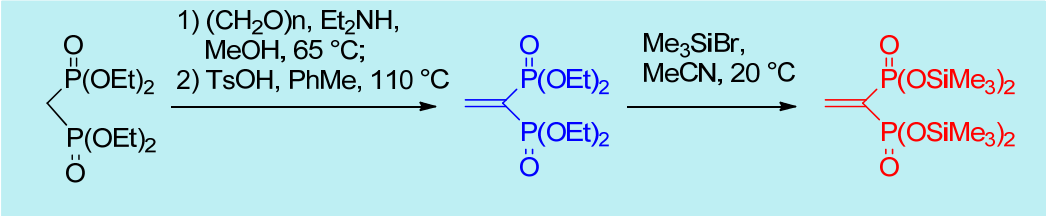


70-80%

PG = CO_2Me, CO_2Et, $P(O)(OEt)_2$

***Zh. Obshch. Khim.* 1988, *58*, 939**

Over the course of the next years, Kukhar and his co-workers extended the silicon methodology to develop preparative methods for a wide range of α- and β-aminophosphonates and their derivatives, including acyclic, cyclic, and heterocyclic compounds.[22] Thus, this approach was successfully used in a straightforward synthesis of highly functionalized 2-aminoethylidene-1,1-bisphosphonic acids via the Michael addition of amines to easily available tetrakis(trimethylsilyl) ethenylidene-1,1-bisphosphonate. DFT calculations (in collaboration with J.-M. Sotiropoulos and Karinne Miqueu from Université de Pau, France) allowed getting insight on peculiarities of the electronic structure of molecules $H_2C{=}C[P(O)(OR)_2]_2$.[23]



Phosphorus, Sulfur Silicon Relat. Elem., 2011, 799. Synlett, 2011, 1370

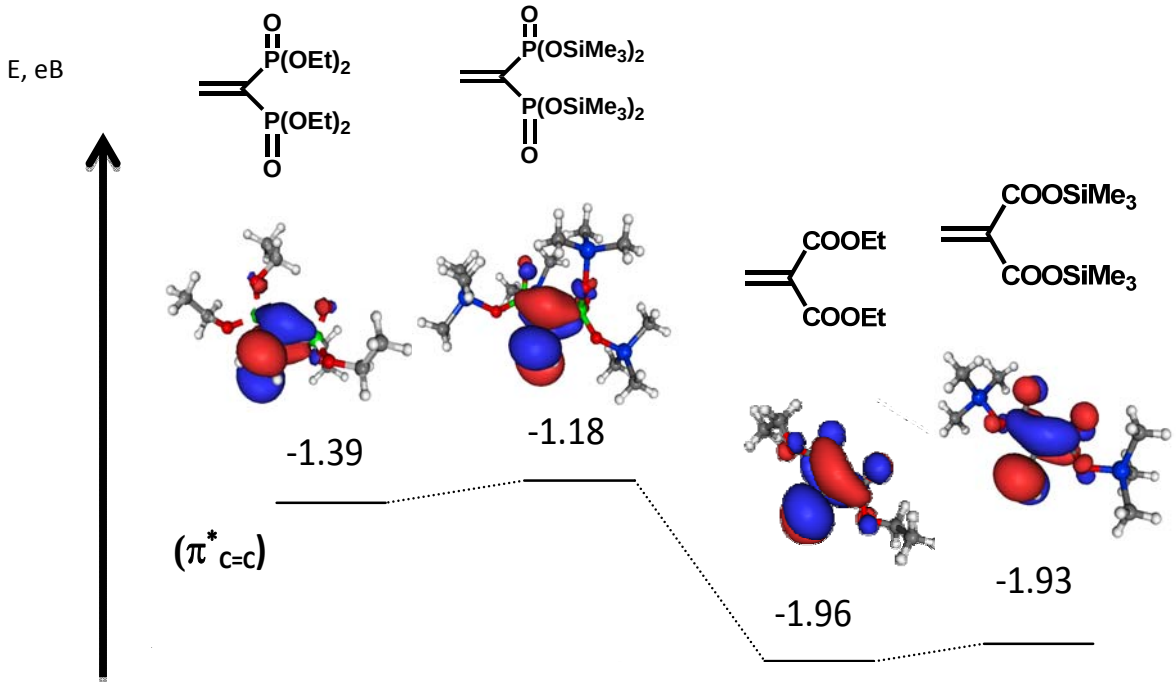
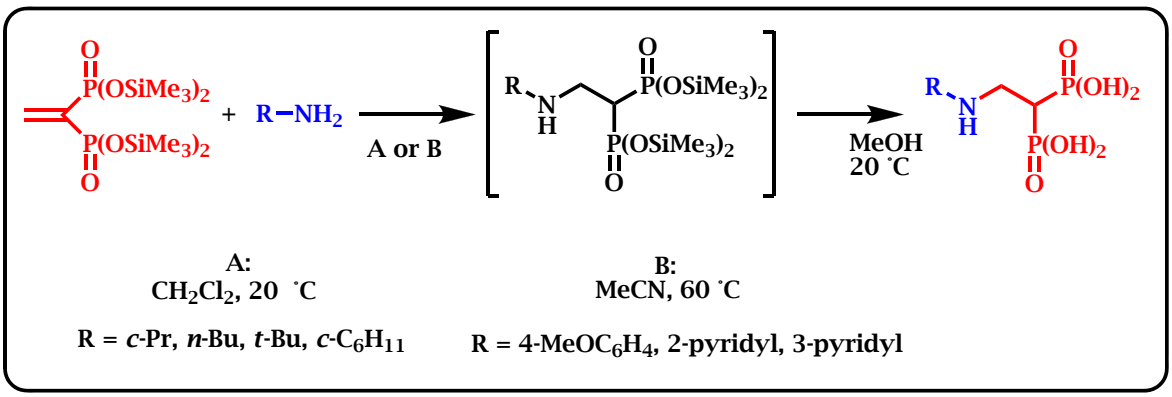
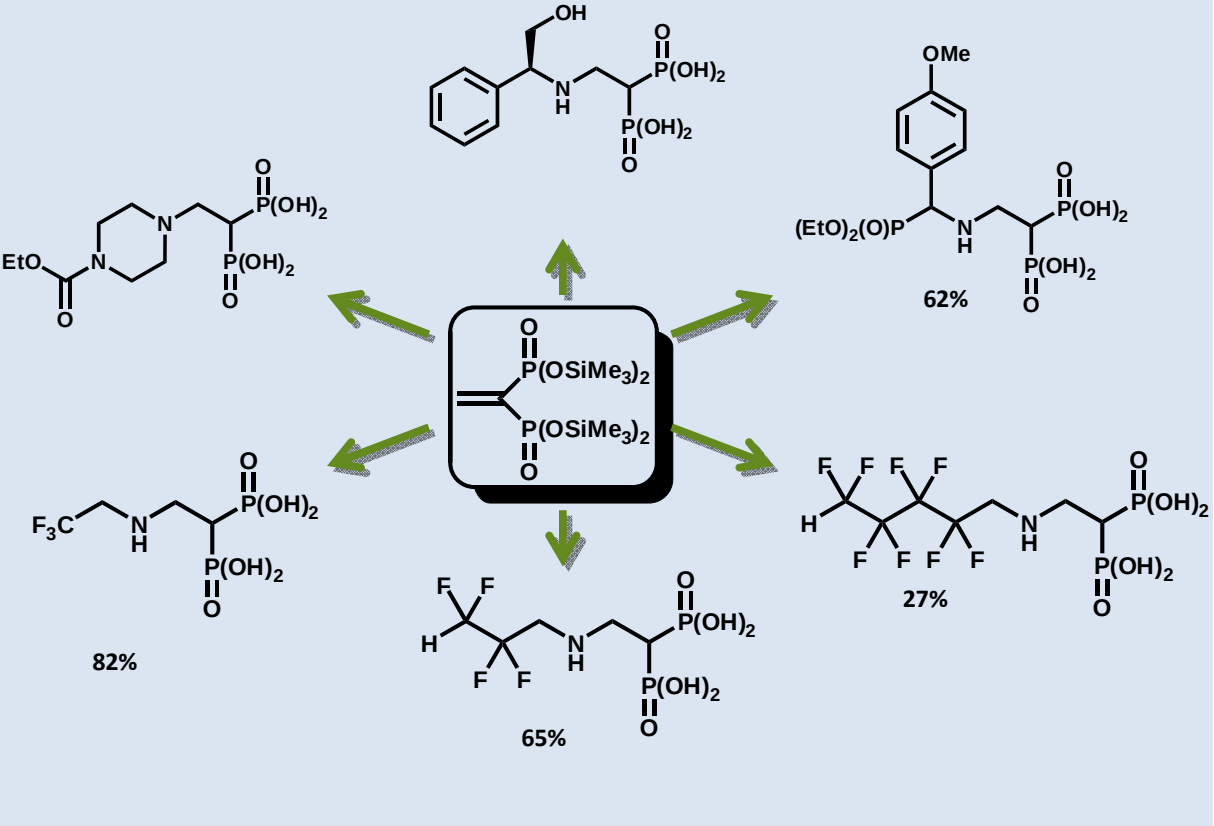


Figure 5. Plot and energetic positions Kohn-Sham energies of the $\pi_{C=C}$ and $\pi^*_{C=C}$ for ethyl and silyl esters of 1,1-substituted alkenes

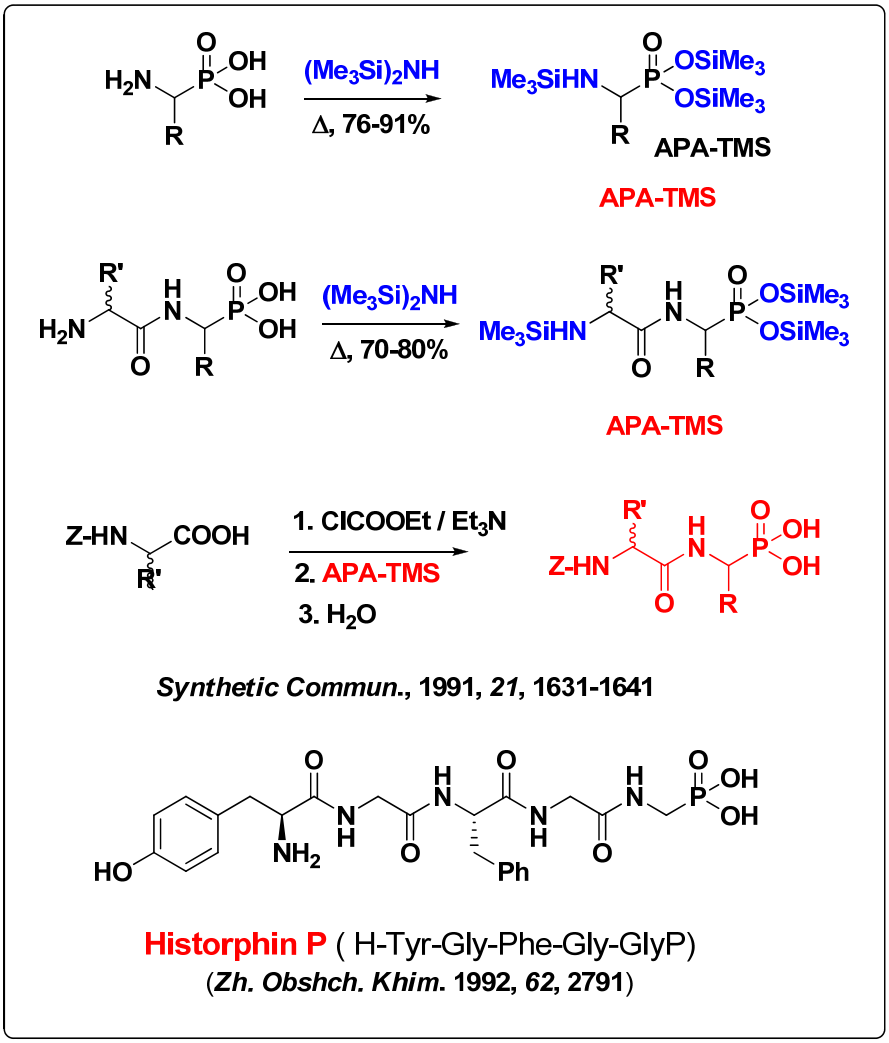
Treatment of the silyl esters with methanol at room temperature smoothly yielded the corresponding 2-aminoethylidene-1,1-bisphosphonic acids. The biological activity of these compounds as immunomodulatory agents was a subject of special investigation.



Interestingly, the addition reactions of tetrakis(trimethylsilyl) ethenylidene-1,1-bisphosphonate tolerate base- and acid-sensitive functional groups. Furthermore, potassium salts of 2-aminoethylidene-1,1-bisphosphonic acids could be easily prepared directly from the corresponding Michael adducts and KF.[23]

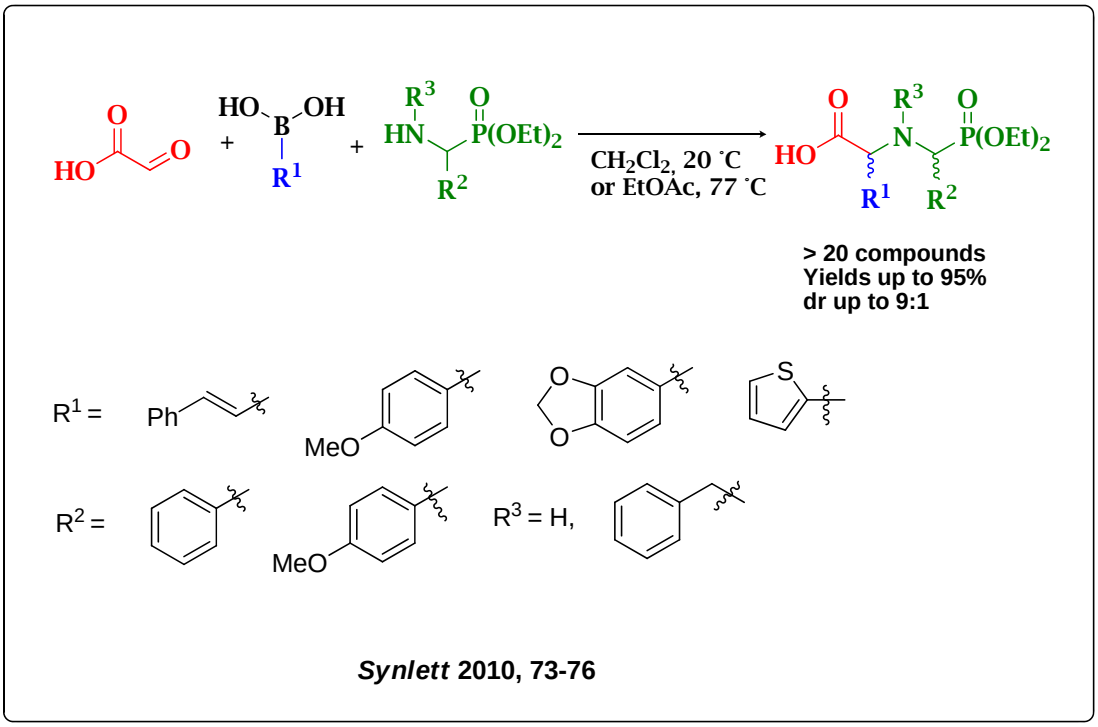


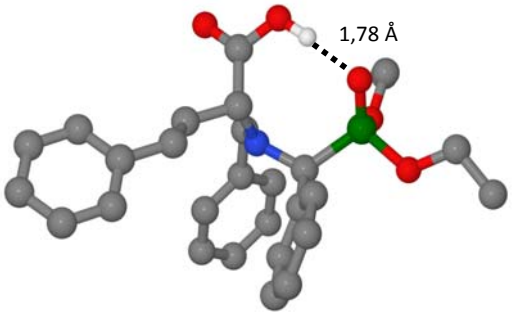
It is well known that the use of aminophosphonic acid esters for peptide synthesis is complicated by their instability, and the condensations with free aminophosphonic acids often yield low yields. To overcome such difficulties, Kukhar and co-workers used trimethylsilyl derivatives in the synthesis of unprotected phosphonopeptides with a *P*-terminal aminophosphonate residue. Heating of free aminophosphonic acids with an excess of hexamethyldisilazane gives TMS-protected aminophosphonates 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}).[24,25]

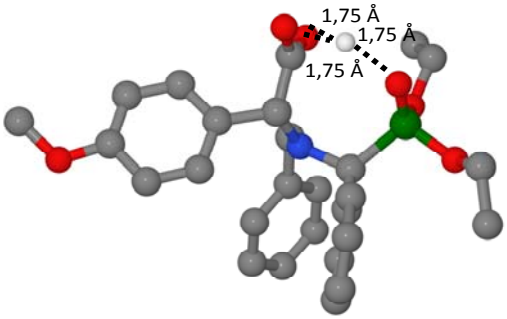


Kukhar and co-workers appear to be one of the pioneers in utilization of aminophosphonates as amine components in the Petasis boronic acid Mannich reaction.[26-28] Among multicomponent reactions, the Petasis three-component reaction has been focus of attention in the last decades due to a number of advantages. 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

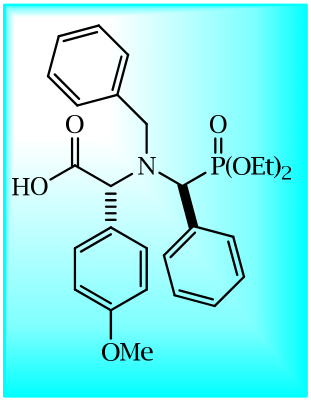
reaction products, made on the basis of theoretical calculations and X-ray diffraction studies, completely coincide.[26]





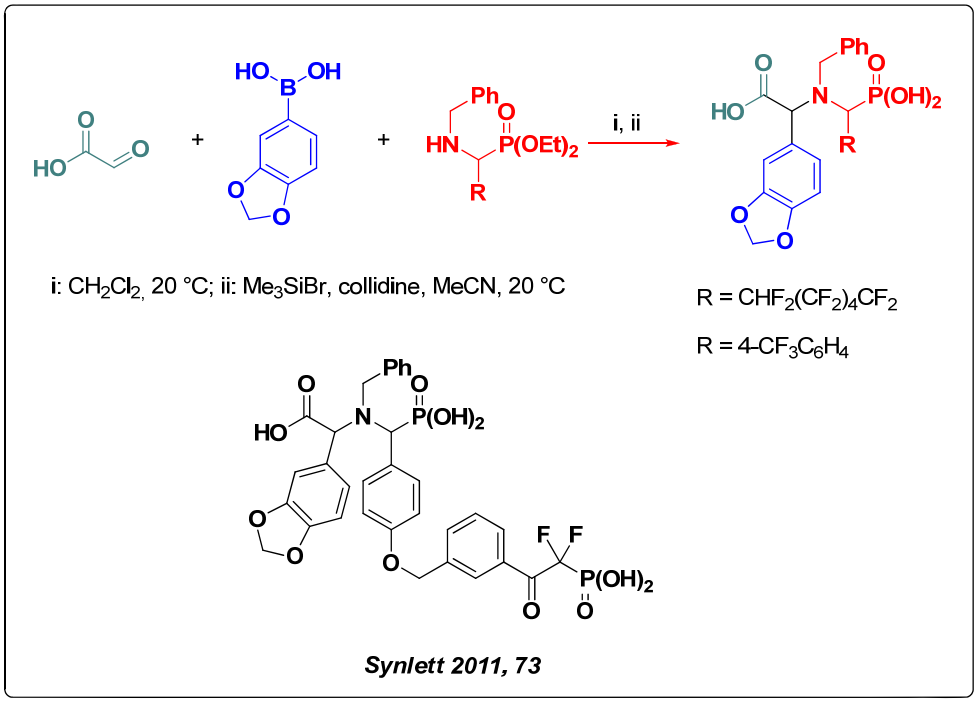


DFT NMR calculations: pseudo-"trans" diastereomer should be the major one, carboxyl and phosphoryl groups should be in close proximity and involved in hydrogen bonding

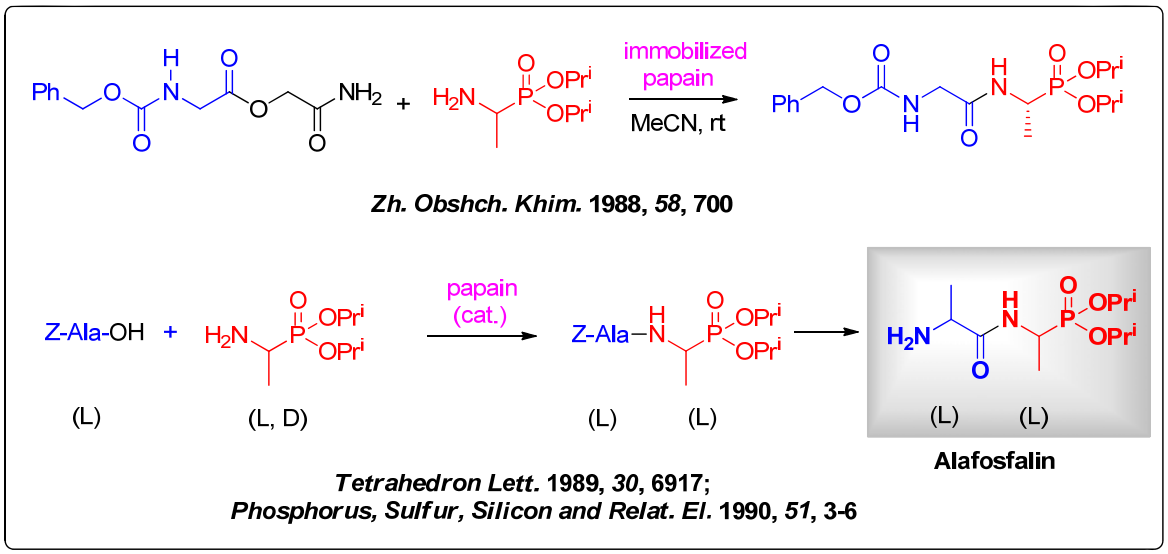


X-Ray analysis: the major diastereomer possesses pseudo-"trans" configuration carboxyl anf phosphoryl groups are in close proximity, possibility due to hydrogen bonding

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.[27,28]



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 V. Solodenko and V. Kukhar on the example of synthesis of diisopropyl ester of 1-(*N*-benzyloxycarbonylglycilamino)ethylphosphonic acid.[29] Thus, racemic diisopropyl ester of 1-aminoethylphosphonic 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-aminophosphonate 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*.[30,31]



In 1991, V. Solodenko, T. Kasheva, V. Kukhar et al. reported effective method for the preparation of optically active α-aminophosphonic acids by means of Penicillin Acylase-catalyzed resolution of their racemic derivatives.[32] It turned out that Penicillin Acylase is capable of stereoselectively hydrolyzing the phenacyl derivatives of 1-aminophosphonates, preferentially choosing *R*-enantiomers from the racemic mixture. For example, for 1-(*N*-phenacetylamino)ethyl phosphonic acid the ratio of the bimolecular rate constants of hydrolysis of the *R* and *S* enantiomers is about $6 \cdot 10^4$. Optimization of the conditions of enzymatic separation made it possible to propose this process as a preparative method. After biocatalytic hydrolysis of the racemic phenacylaminophosphonate by chromatography, *R*-aminophosphonic acid was separated from the unaffected *S*-enantiomer. The latter is converted to free *S*-aminophosphonic acid by an acidic hydrolysis. Thus, in one process both enantiomers of aminophosphonate analogs of alanine, leucine, phenylglycine and phenylalanine were obtained. An increase in the enzyme concentration also causes the hydrolysis of the phenacetyl derivative of D-amino acid. Using this, a two-step separation method was developed in which a low enzyme concentration is first used to produce the L-enantiomer and then it is increased to produce the D-amino acid. Enzymatic hydrolysis with penicillin acylase was also used to separate the enantiomers of phenacyl derivatives of aminophosphonate diesters and ethylphosphonous acid.[33-35]

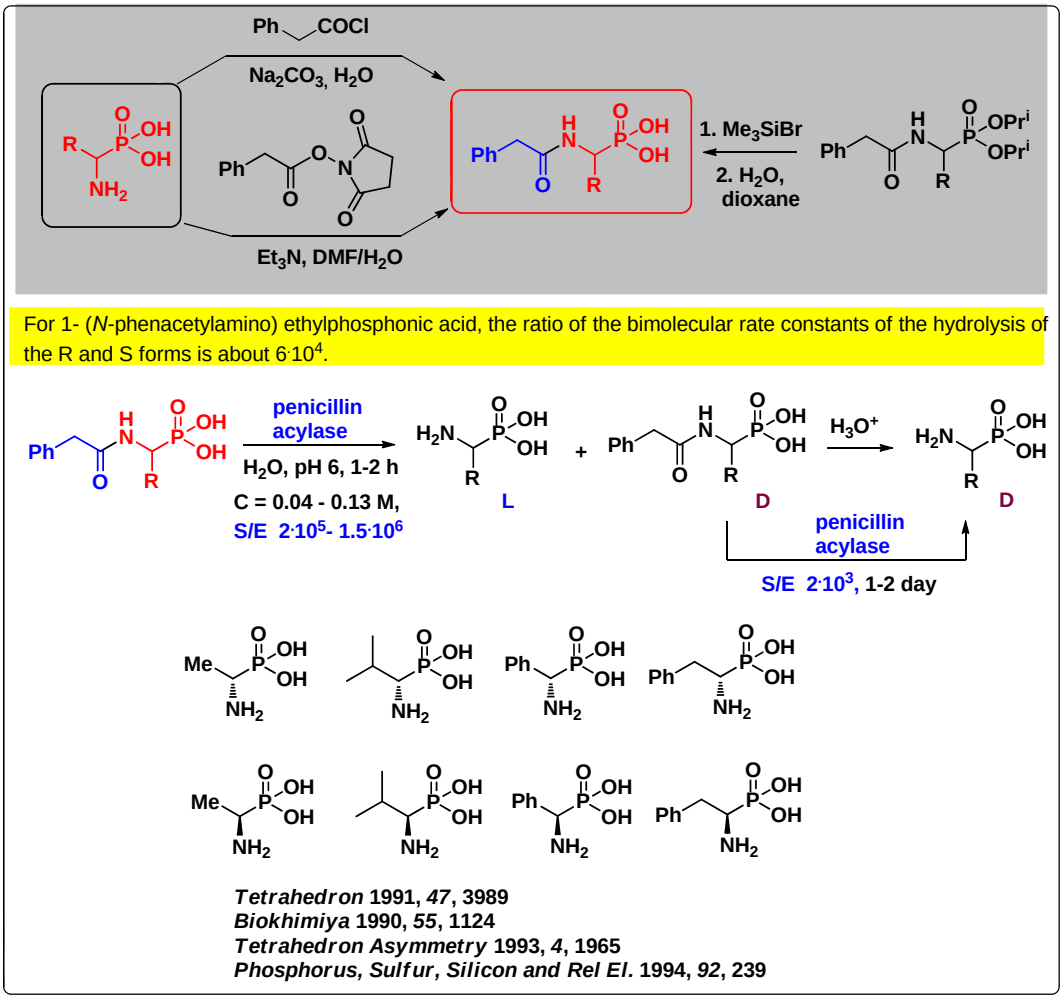
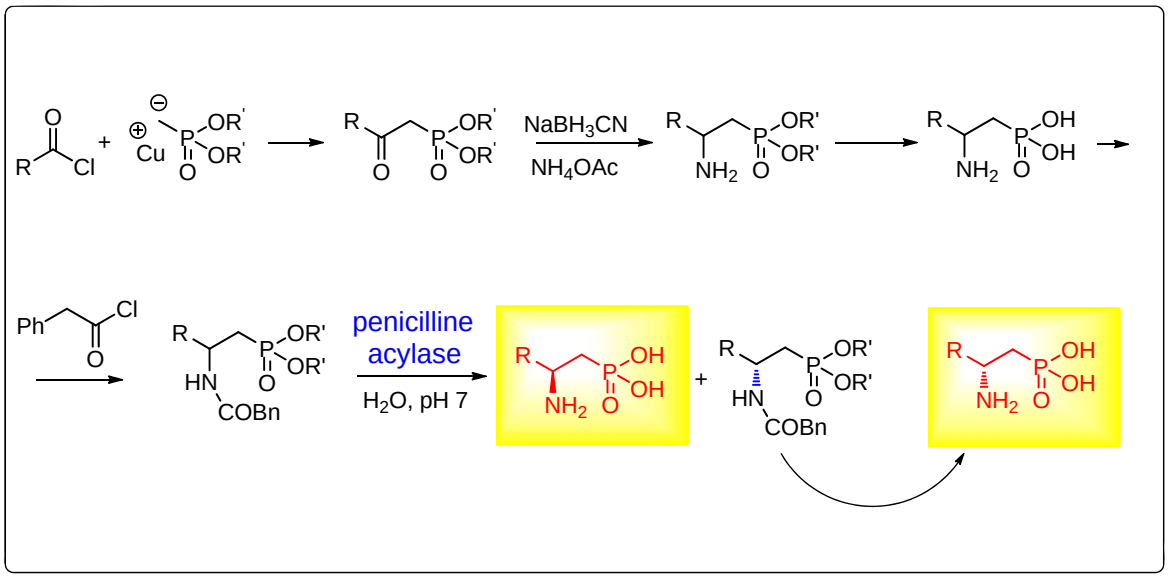
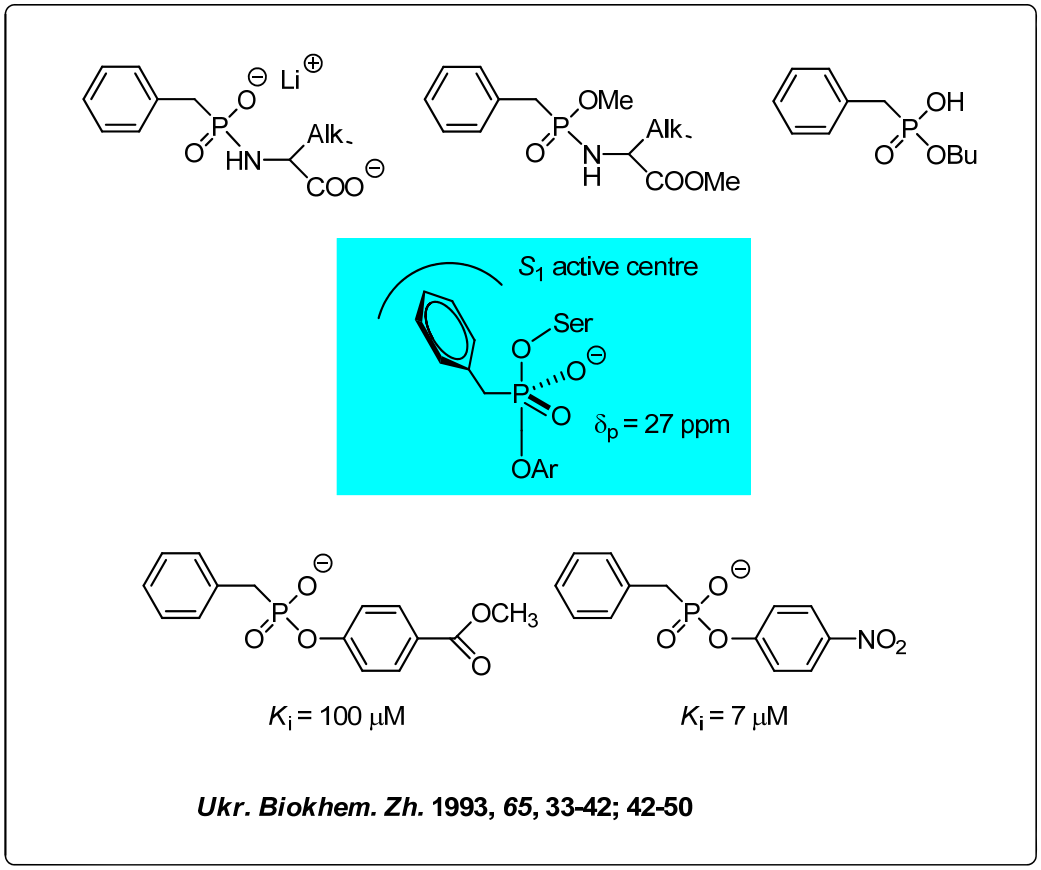


Figure 6. Dr.V. Solodenko (in the foreground), Dr. A. Sorochinsky and eng. M. Furmanova

The broad substrate specificity of Penicillin Acylase also makes it possible to use its catalytic properties for the separation of β-aminophosphonates. It turned out that in the case of *N*-phenylacetyl derivatives of β-aminophosphonates, the rate and enantioselectivity of hydrolysis depends 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.[36]

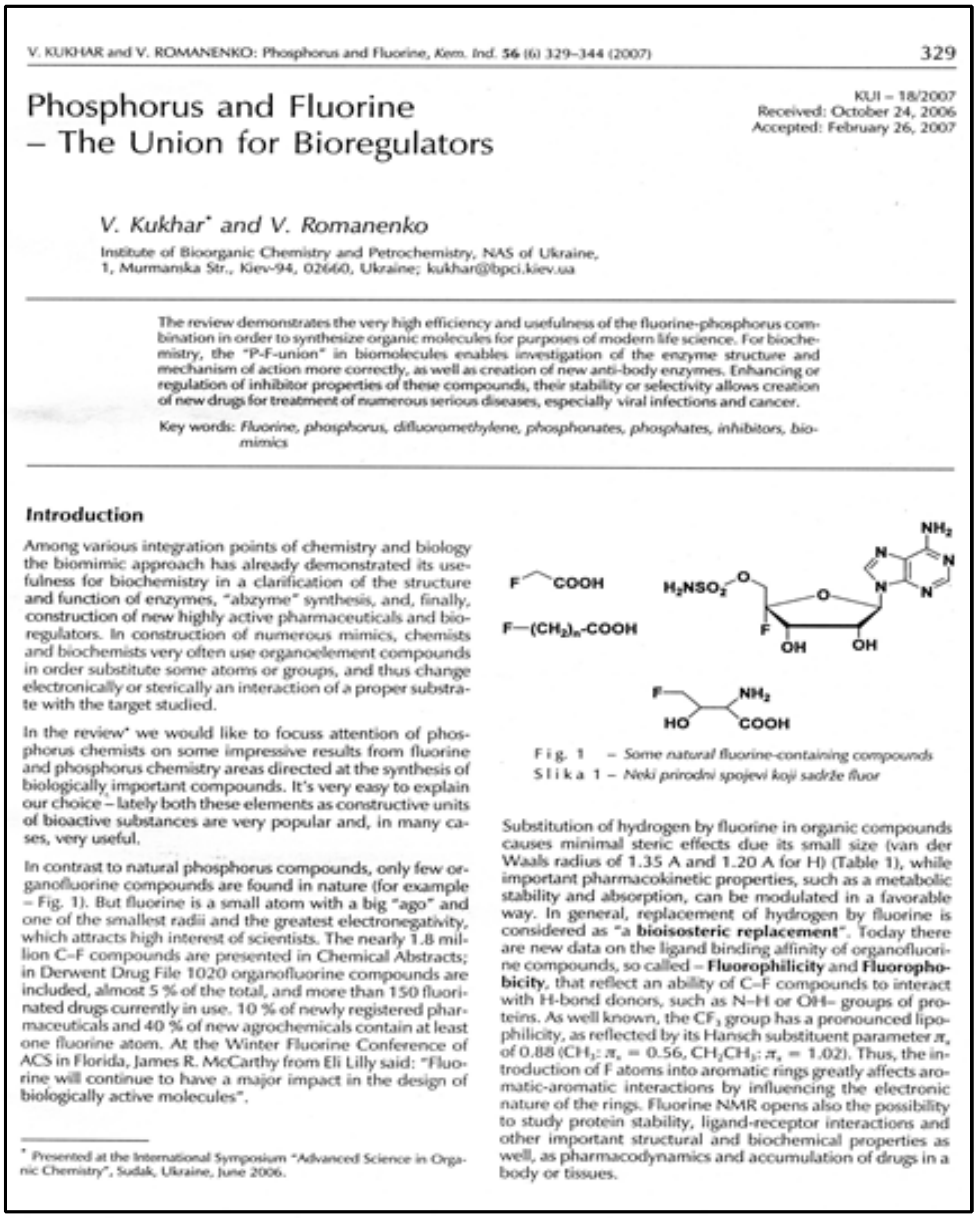


Further studies performed in Kukhar's laboratory showed that organophosphorus compounds can act not only as substrates but also as inhibitors in relation to Penicillin Acylase. In particular, it has been found that aryl esters and amides of benzylphosphonic acid are selective reversible competitive inhibitors 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.[37,38]



***Ukr. Biokhem. Zh.* 1993, *65*, 33-42; 42-50**

In the 1980s, the search for his own path in chemistry by Prof. Kukhar led to the development of research in various, at first glance, little related, areas of organic synthesis. Among them, mention should be made of the synthesis and study of the properties of dicoordinated phosphorus compounds (O.I. Kolodiaznyi, I.V. Shevchenko), research in the field of phosphorus ylides (O.I. Kolodiazhnyi), the chemistry of leukotrienes (A.E. Sorochinsky, A.M. Kornilov), halogenated pyridines (S.D. Moshchitsky) and halogen-containing polyhedranes (A.M. Aleksandrov, V.F. Baklan, A.N. Khil'chevsky). Considerable efforts were also undertaken to develop methods for chromatographic separation of diastereomeric compounds and racemic mixtures (S.V. Galushko). Synthetic possibilities opened up by these works led to the formulation of the main task of further investigations: **practical synthesis and investigation of properties of biomolecules with fluorine and phosphorus in racemic and enantiomeric forms.** [39]



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The review demonstrates the very high efficiency and usefulness of the fluorine-phosphorus combination in order to synthesize organic molecules for purposes of modern life science. For biochemistry, the "P-F-union" in biomolecules enables investigation of the enzyme structure and mechanism of action more correctly, as well as creation of new anti-body enzymes. Enhancing or regulation of inhibitor properties of these compounds, their stability or selectivity allows creation of new drugs for treatment of numerous serious diseases, especially viral infections and cancer.

Key words: *Fluorine, phosphorus, difluoromethylene, phosphonates, phosphates, inhibitors, biomimics*

Introduction

Among various integration points of chemistry and biology the biomimic approach has already demonstrated its usefulness for biochemistry in a clarification of the structure and function of enzymes, "abzyme" synthesis, and, finally, construction of new highly active pharmaceuticals and bioregulators. In construction of numerous mimics, chemists and biochemists very often use organoelement compounds in order substitute some atoms or groups, and thus change electronically or sterically an interaction of a proper substrate with the target studied.

In the review* we would like to focuss attention of phosphorus chemists on some impressive results from fluorine and phosphorus chemistry areas directed at the synthesis of biologically important compounds. It's very easy to explain our choice – lately both these elements as constructive units of bioactive substances are very popular and, in many cases, very useful.

In contrast to natural phosphorus compounds, only few organofluorine compounds are found in nature (for example – Fig. 1). But fluorine is a small atom with a big "ago" and one of the smallest radii and the greatest electronegativity, which attracts high interest of scientists. The nearly 1.8 million C–F compounds are presented in Chemical Abstracts; in Derwent Drug File 1020 organofluorine compounds are included, almost 5 % of the total, and more than 150 fluorinated drugs currently in use. 10 % of newly registered pharmaceuticals and 40 % of new agrochemicals contain at least one fluorine atom. At the Winter Fluorine Conference of ACS in Florida, James R. McCarthy from Eli Lilly said: "Fluorine will continue to have a major impact in the design of biologically active molecules".

* Presented at the International Symposium "Advanced Science in Organic Chemistry", Sudak, Ukraine, June 2006.

Fig. 1 – *Some natural fluorine-containing compounds*
Slika 1 – *Neki prirodni spojevi koji sadrže fluor*

Substitution of hydrogen by fluorine in organic compounds causes minimal steric effects due its small size (van der Waals radius of 1.35 A and 1.20 A for H) (Table 1), while important pharmacokinetic properties, such as a metabolic stability and absorption, can be modulated in a favorable way. In general, replacement of hydrogen by fluorine is considered as "a **bioisosteric replacement**". Today there are new data on the ligand binding affinity of organofluorine compounds, so called – **Fluorophilicity** and **Fluorophobicity**, that reflect an ability of C–F compounds to interact with H-bond donors, such as N–H or OH– groups of proteins. As well known, the CF_3 group has a pronounced lipophilicity, as reflected by its Hansch substituent parameter π_x of 0.88 (CH_3: π_x = 0.56, CH_2CH_3: π_x = 1.02). Thus, the introduction of F atoms into aromatic rings greatly affects aromatic-aromatic interactions by influencing the electronic nature of the rings. Fluorine NMR opens also the possibility to study protein stability, ligand-receptor interactions and other important structural and biochemical properties as well, as pharmacodynamics and accumulation of drugs in a body or tissues.

Figure 7. First page of the article "*Phosphorus and Fluorine – The Union for Bioregulators*" published in Journal "**Chemistry in Industry**" (2007)

The beginning of this story 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.[1-3,15,36,39-44]

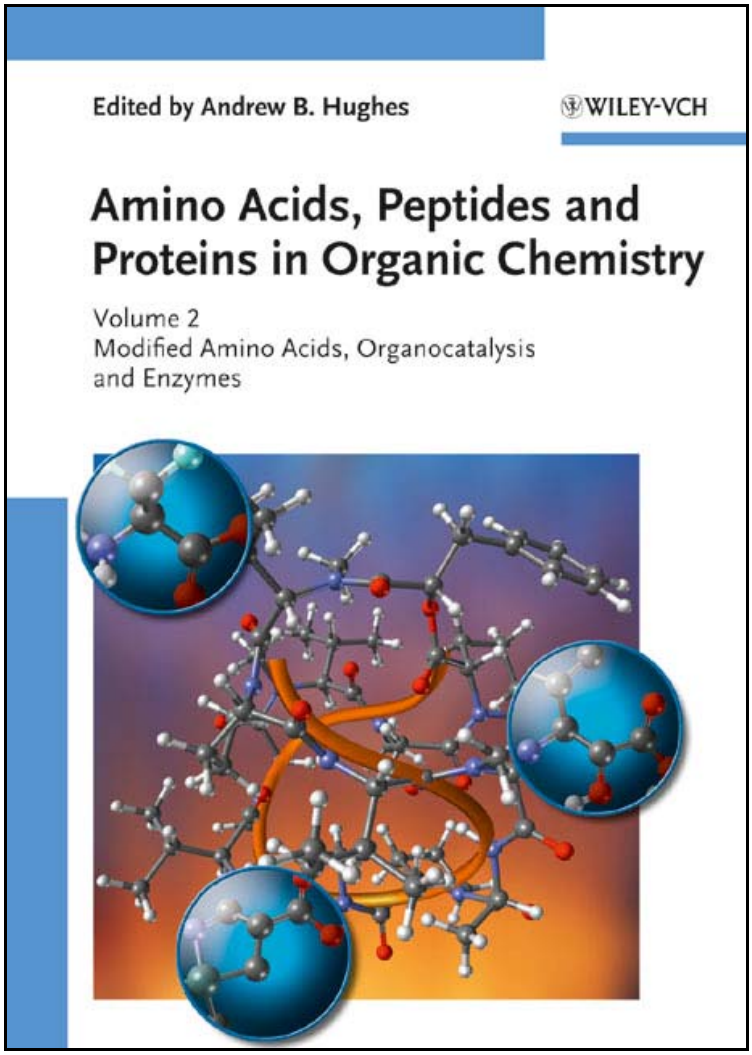
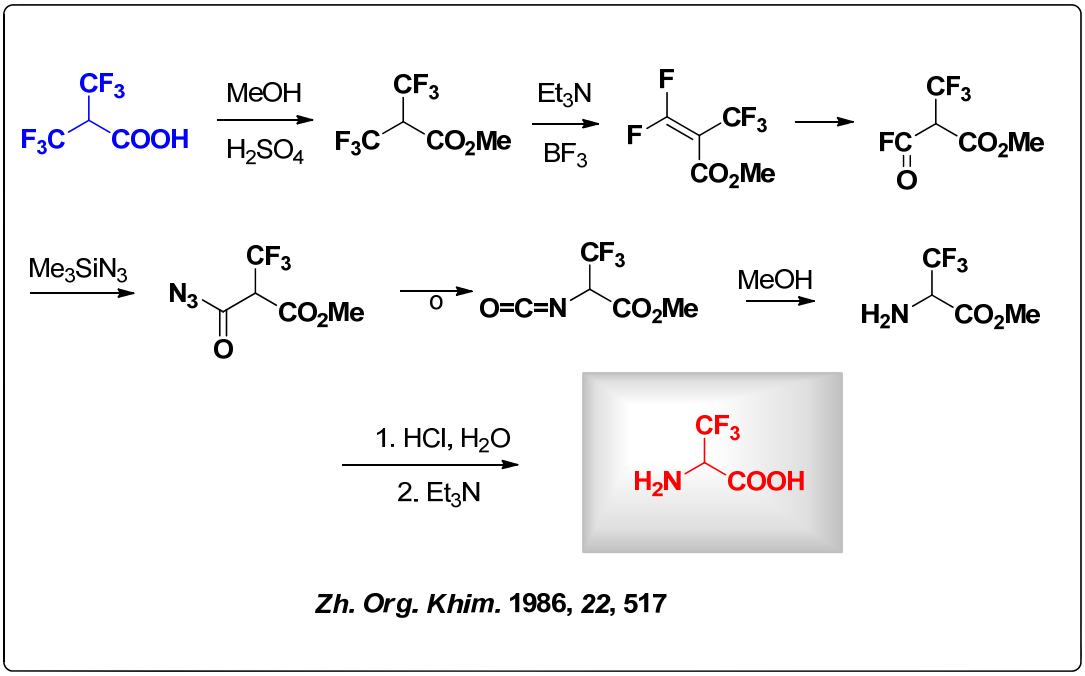


Figure 8. Book Chapter: V.P. Kukhar and V.D. Romanenko. *Chemistry Aminophosphonic Acids and Phosphonopeptides*. In **Amino Acids, Peptides and Proteins in organic Chemistry**. Ed. Andrew B. Hughes. Vol. 2 pp. 189-249. Wiley-VCH. Weinheim. 2009

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

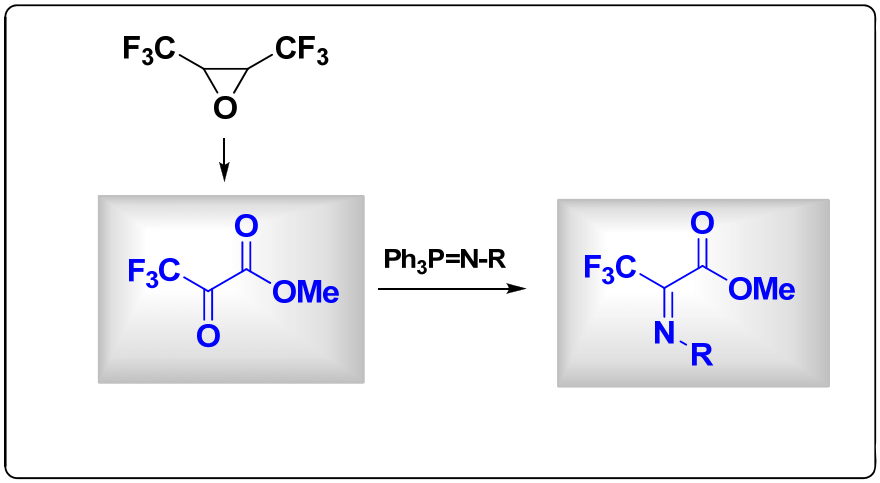
natural molecules is that the presence of fluorine atoms and fluoroalkyl groups in an organic compound increase substantially their lipophilicity facilitating membrane permeability and hydrophobic binding. The fluorine substitution for hydrogen can also be efficiently used for quite unique tagging of 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.

The first fluorine-containing amino acid in Kuhar's laboratory was β,β,β-trifluoroalanine. To synthesize this compounds methyl α-hydroperfluoro-*iso*-butyrate was converted into methyl 3,3,3-trifluoro-2-(fluorocarbonyl)propanoate and then into azido derivative by reaction with Me_3SiN_3. Obtained azide was transformed into isocyanate by Curtius rearrangement be heating at 60 ^oC in 88 % yield. Isocyanate easily reacted with alcohols or phenol to give *N*-alkoxycarbonyl-3,3,3-trifluroalanines in high yields. The latter were hydrolysed with conc. HCl affording methyl trifluoroalanine hydrochloride in 90 % yield.[45]

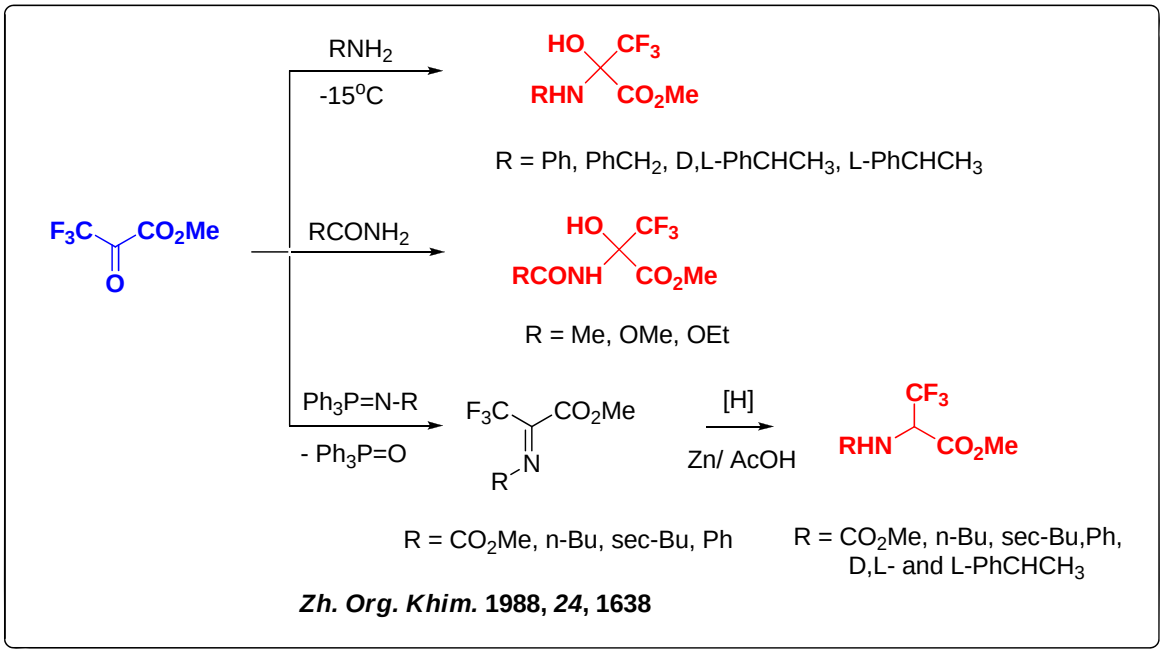


***Zh. Org. Khim.* 1986, *22*, 517**

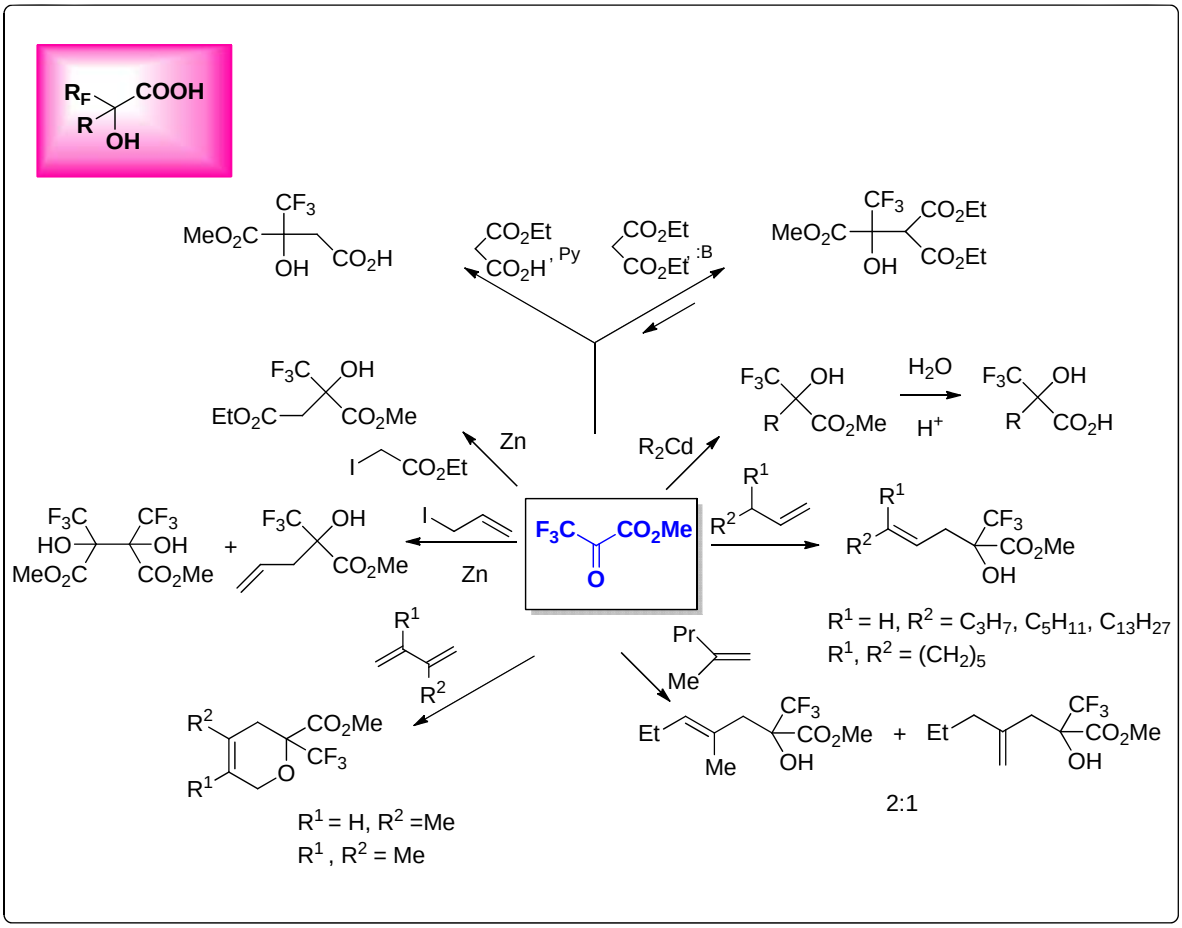
In order to synthesize a family of *N*- and *C*-substituted (trifluoro)alanines trifluoropyruvic acid was selected as convenient and readily available starting material.



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 (trifluoro)alanines.[46]

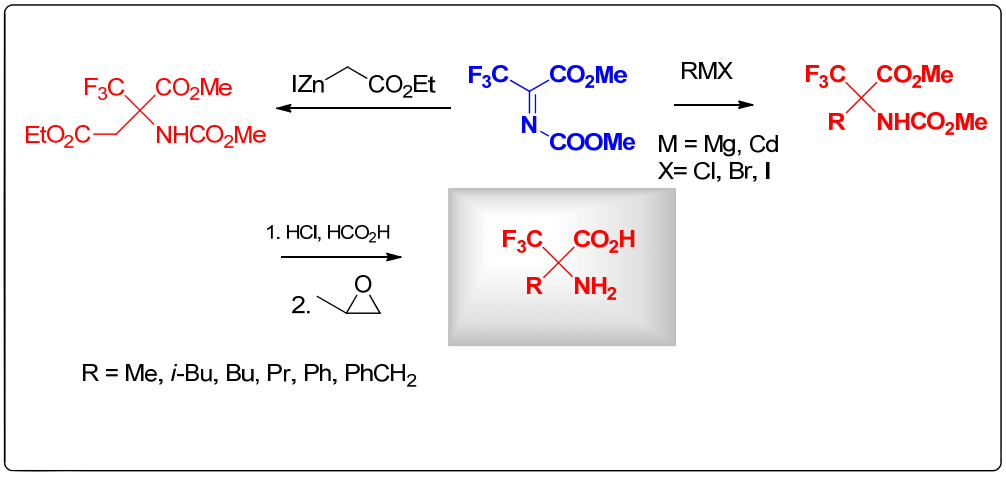


Besides the amino acids synthesis, the trifluoropyruvic acid was found to be also attractive starting compound for preparation of α-trifluoromethyl α-hydroxy acids.[47,48] The latter still remain overlooked as potentially promising class of compounds for bioorganic and medicinal chemistry research. Kukhar 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.[49,50]

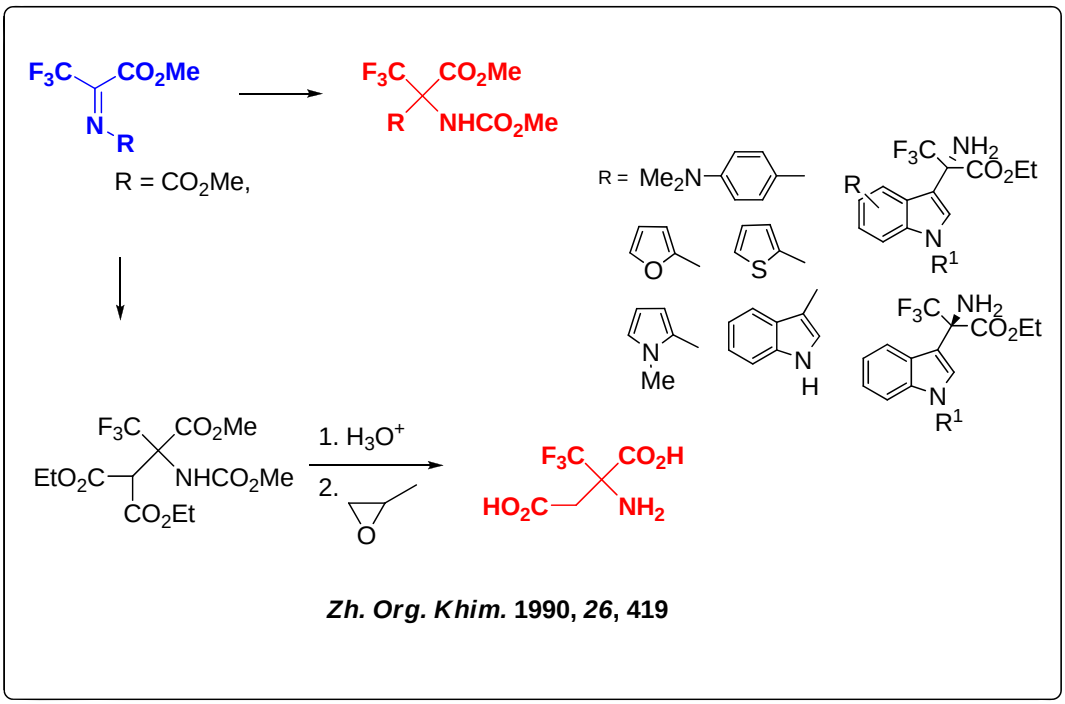


Reactivity of methyl trifluoropyruvate imines towards nucleophilic addition was strongly connected by nature of the corresponding *N*-substituents. Thus, *N*-alkyl and *N*-phenyl derivatives were inert in reactions with alcohols, water, Zn- and Mg-organometallic reagents. In sharp contrast *N*-methoxycarbonylimine (R = CO_2Me) due to presence of three strongly electron-withdrawing substituents reacted easily with various nucleophilic reagents to yield α-trifluoromethyl amino acids. For example, a reaction of the imine with Mg- and Cd-organometallic reagents at low temperature has been successfully used for synthesis of various α-trifluorimethyl containing amino acids such as alanine, leucine, norleucine,

norvaline, phenylglycine and phenylalanine. Reformatsky reaction of the imine with ethyl iodoacetate resulted in 2-trifluoromethylasparaginic acid derivative.[51,52]

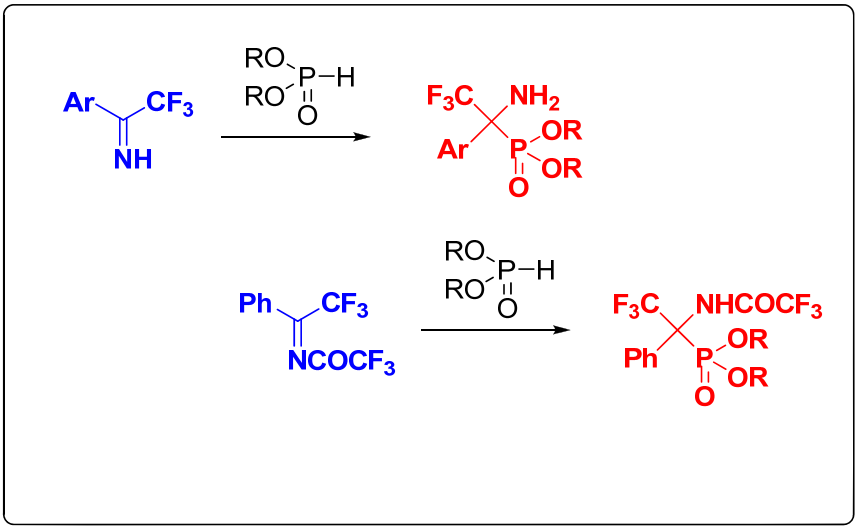


It has been established that the imines of methyl trifluoropyruvate are also very useful substrates for preparation of various trifluoromethyl substituted amino acids via *C*-alkylation or cycloaddition reactions. For instance, *N*-acylimines with highly electrophilic C=N bond (R = CO_2Me, SO_2Ph) can be converted into 2-aryl- and 2-hetaryl-3,3,3-trifluoroalanines by action of activated aromatic and heterocyclic compounds. [52]

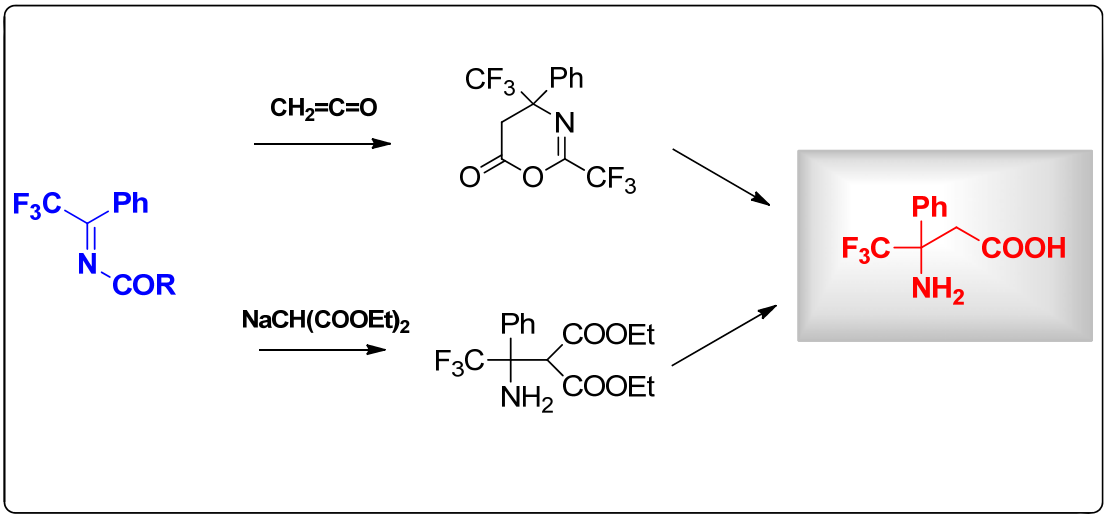


***Zh. Org. Khim.* 1990, *26*, 419**

Addition of dialkyl phosphite to imines derived from the corresponding trifluoromethyl ketones presents very simple approach to CF_3-containing α-amino phosphonic acids and can be conducted without any catalyst or even solvent. [53]

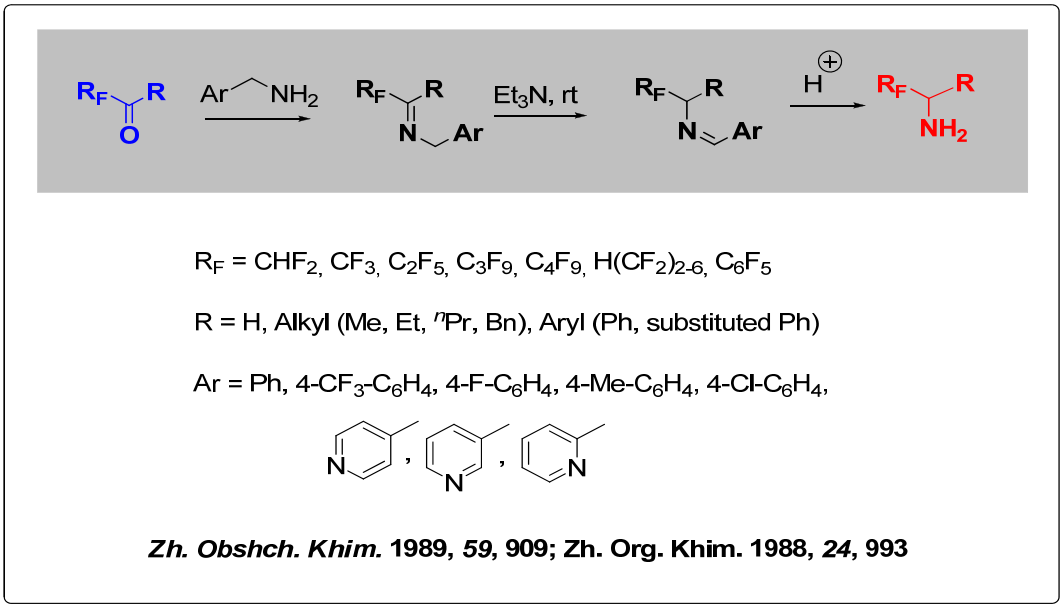


The useful properties associated with imines of trifluoromethylketones resulted in the development of new methods for the synthesis of CF_3-containing β-amino acids.

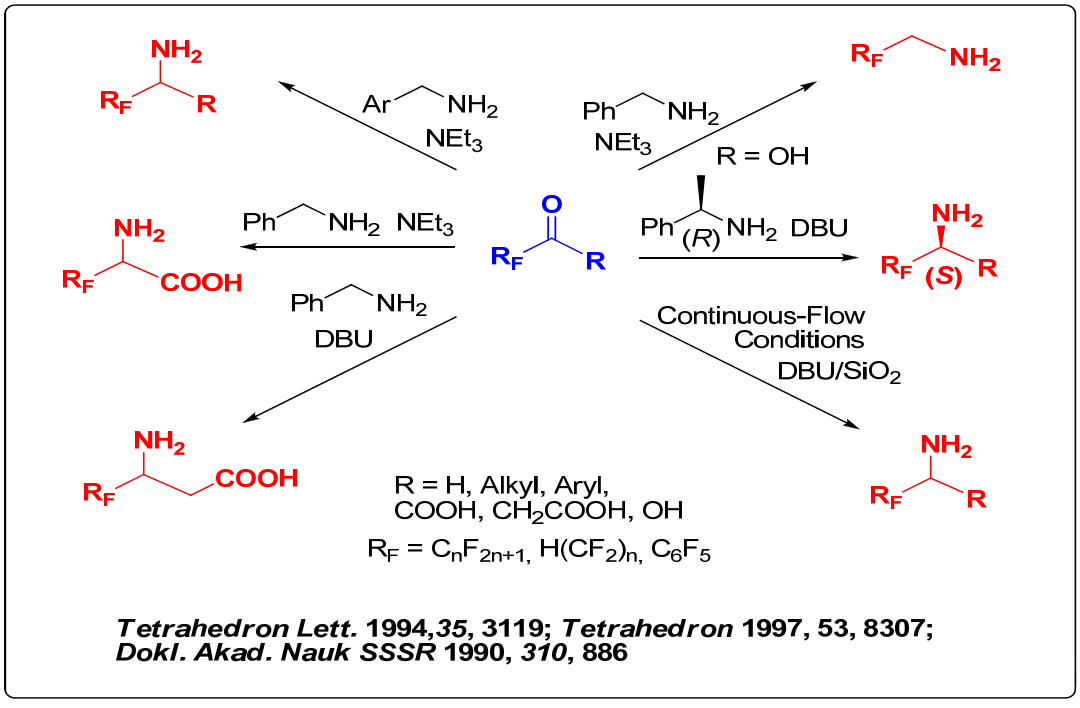


In the late 1980s, Soloshonok and Kukhar found a new effective approach to fluoroalkyl-amino acids, based on biomimetic base-catalyzed [1,3]-proton shift reaction. It was demonstrated that base-catalyzed isomerization of α-fluoro *N*-(benzyl) imines, in particular substrates containing trifluoromethyl 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.[54-56] This finding made authors to conclude that they found a new synthetic

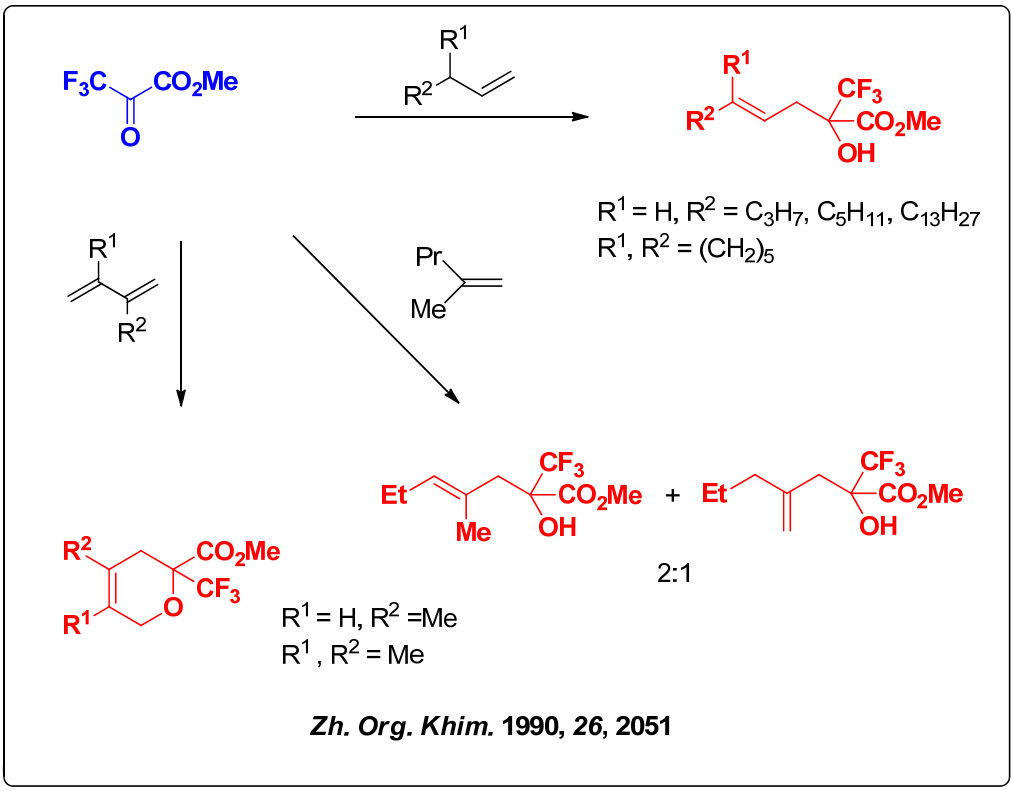
procedure for reductive amination allowing in elegant biomimetic regime to dispense with the normally required hydrogenation step.



Further research has demonstrated remarkable generality of this biomimetic approach for transamination of various fluorinated carbonyl compounds to amino derivatives.[56] 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.[57-60]



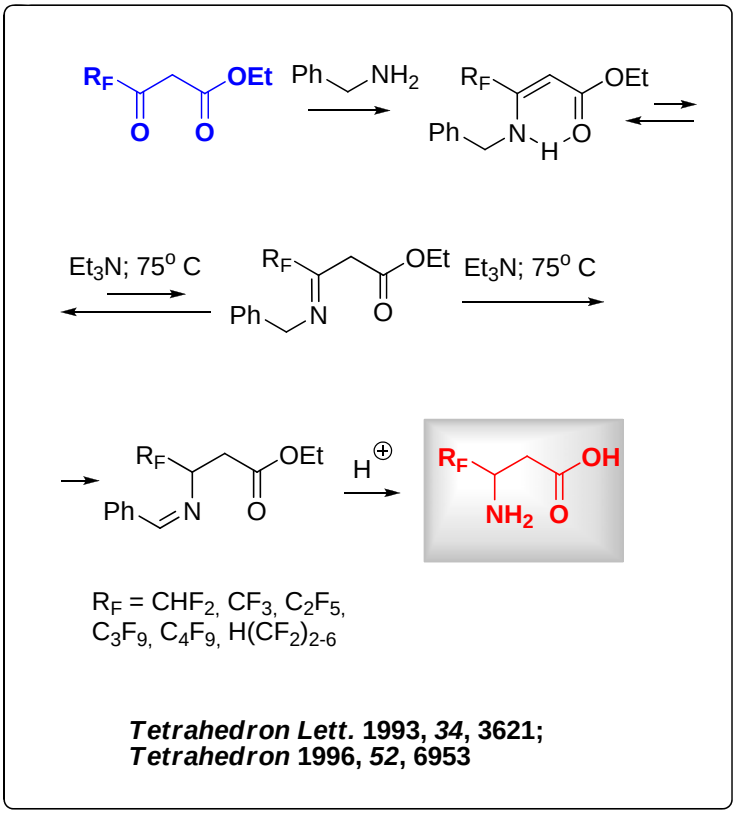
Methyl trifluoropyruvate was also found to be highly reactive in "ene" reaction with 1-alkenes. Due to its exceptionally high electrophilicity these reactions can be conducted without any catalyst (usually Lewis acid is required) at ambient temperatures or moderate heating yielding α-allyl derivatives 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.[61]



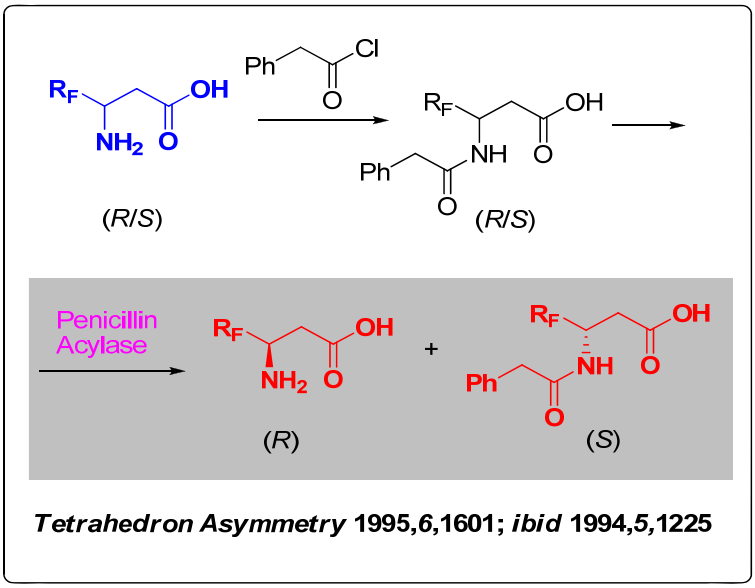
***Zh. Org. Khim.* 1990, *26*, 2051**

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

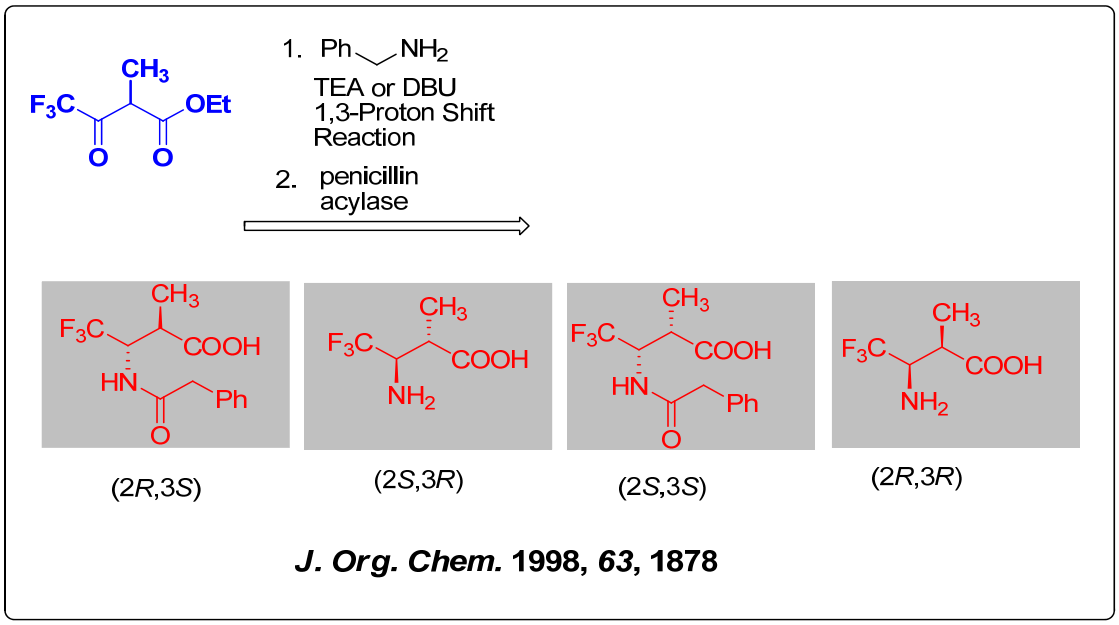
yield. The reason for the dramatic difference in reactivity between the fluorinated and non-fluorinated β-keto acid esters is that the presence of fluorinated group in imines renders the α-C-H proton substantially more acidic as compared with the acidity of the corresponding benzylic protons. [62,63]



Racemic β-amino acids can be efficiently resolved to enantiomerically pure forms using biocatalytic methods.[64,65] In particular, as shown in Scheme below, amino acids were converted to 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). [66,67]



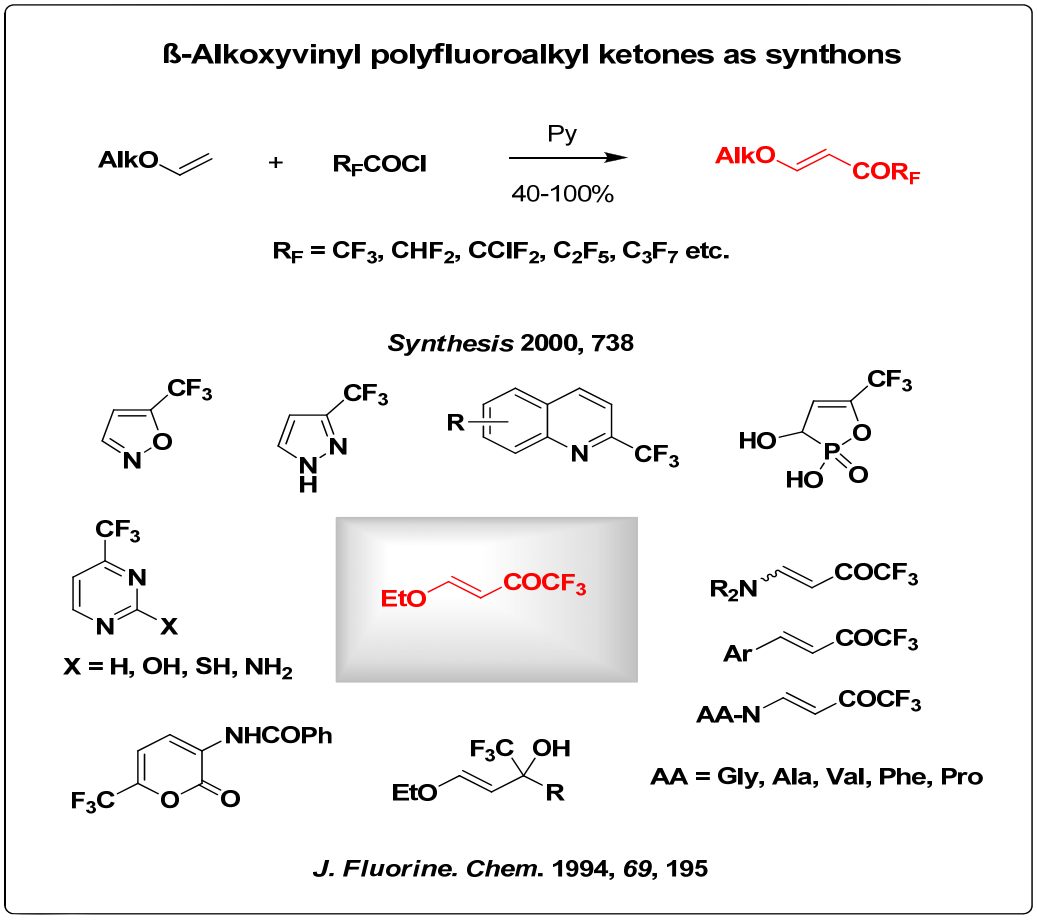
Interesting combination of the biomimetic transamination and Penicillin Acylase catalyzed resolution was used in the development of chemo-enzymatic protocol for preparation of enantiomerically pure fluorinated β-amino acids. Thus, starting from keto ester all four stereoisomers of α-alkyl-β-fluoroalkyl-β-amino acids were prepared in enantiomerically pure form and reasonable chemical yields.[68] 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. [69,70]



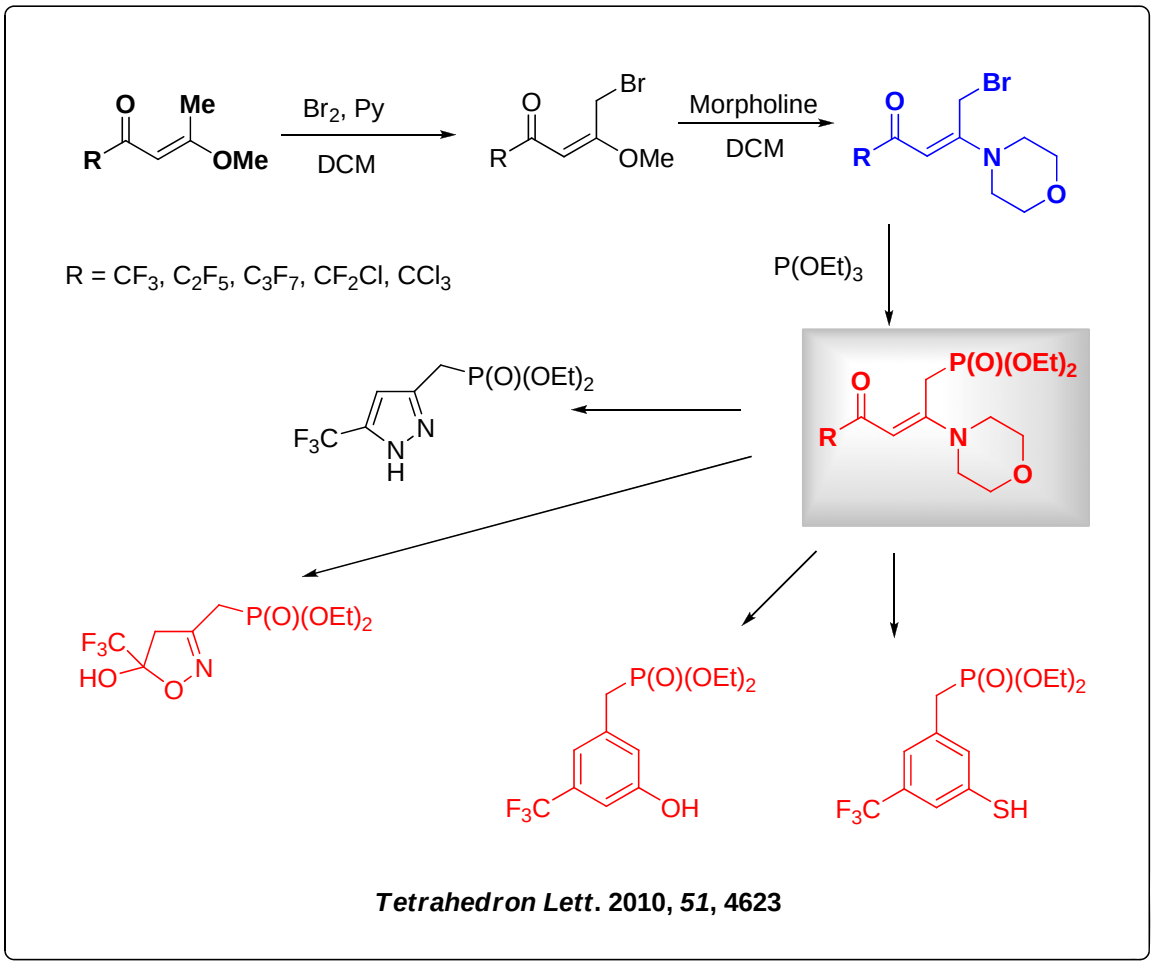
Different approaches have been applied to the synthesis of fluorinated unsaturated compounds; none of them seems to have general applicability and difficulties were, generally,

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 Valery Kuhar, his favorite approach for the synthesis of fluorine-containing biologically active compounds was the application of the synthon strategy. 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 and unsaturated polyfunctional compounds with fluorine atom or fluorine containing groups.

Dr. I. 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.[71-73] 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 group 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. [74-76]

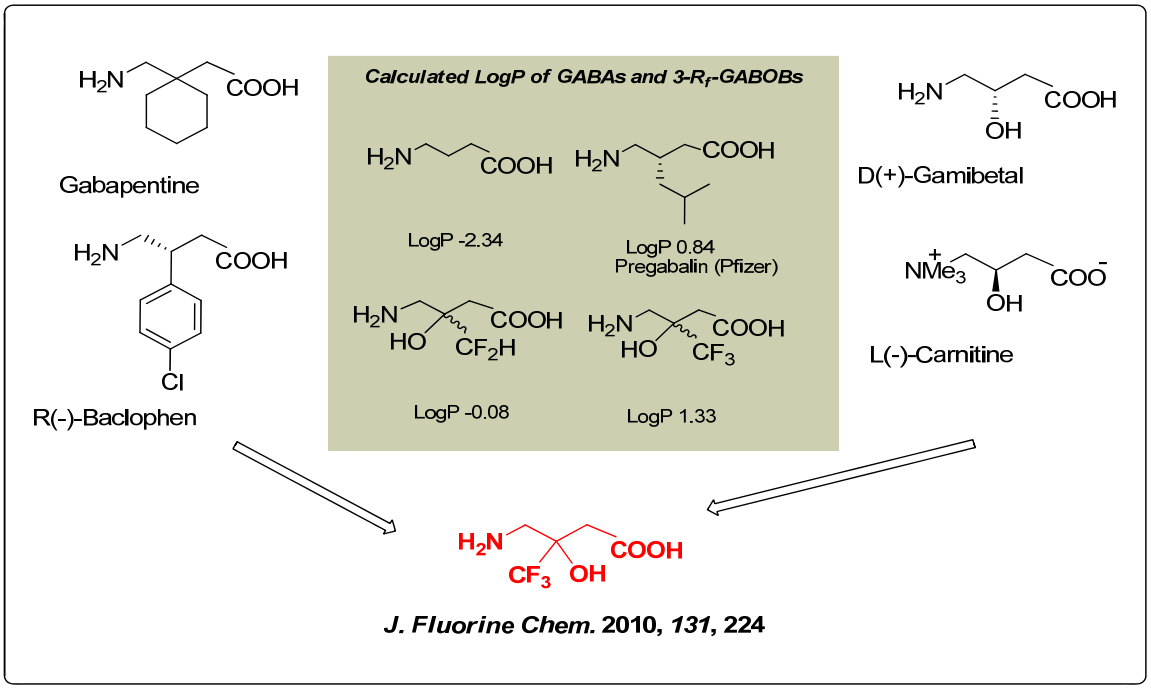


A number of polyhalogenoalkyl-containing phosphonates with an enaminone core were synthesized from readily available β-alkoxyvinyl polyhalogenoalkyl ketones by successive bromination, amination, and Arbuzov reaction. The new phosphonates were used for the synthesis of five- and six-membered heterocycles bearing both trifluoromethyl and methylenephosphonate groups. [77]

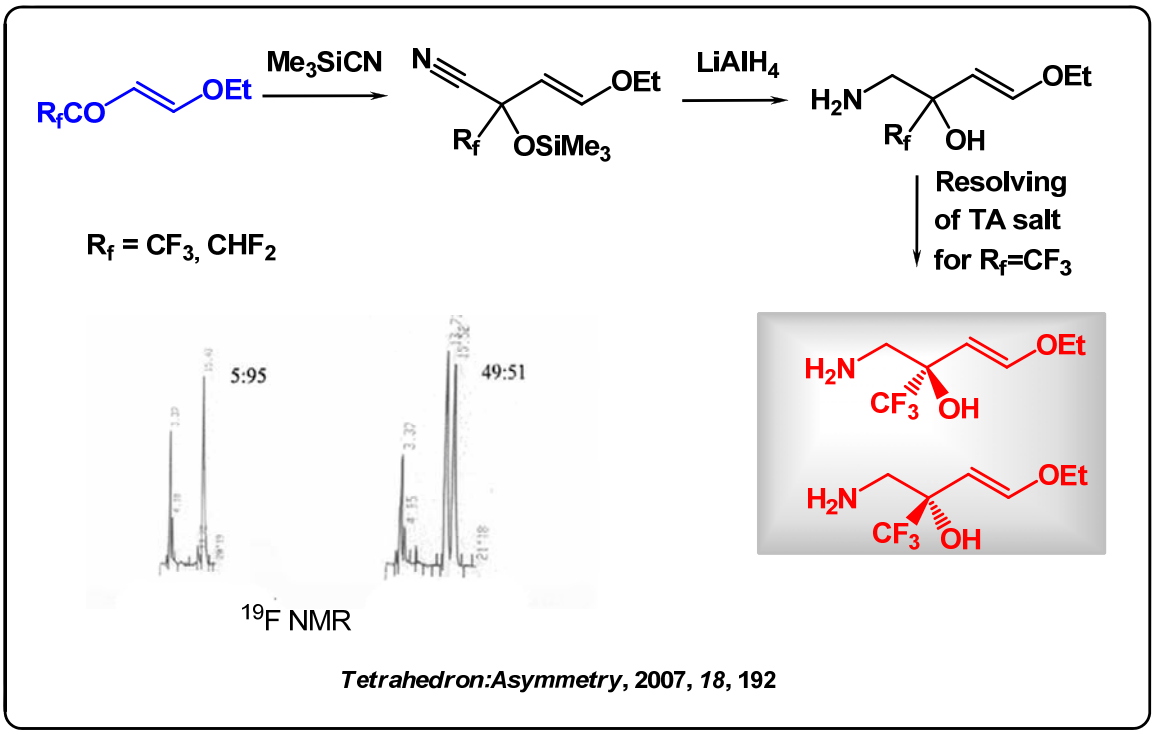


***Tetrahedron Lett*. 2010, *51*, 4623**

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.



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. [78-80]



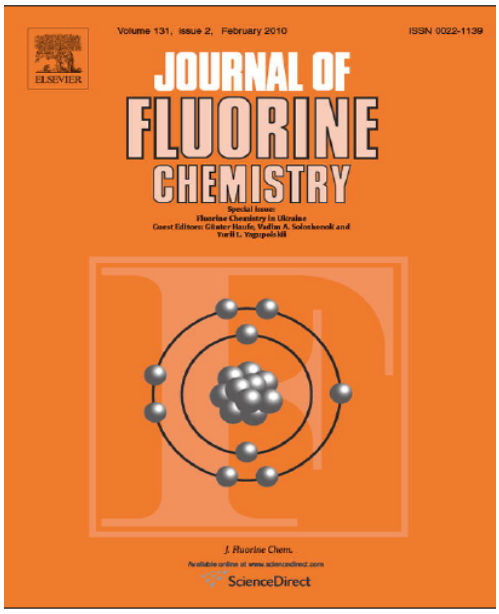
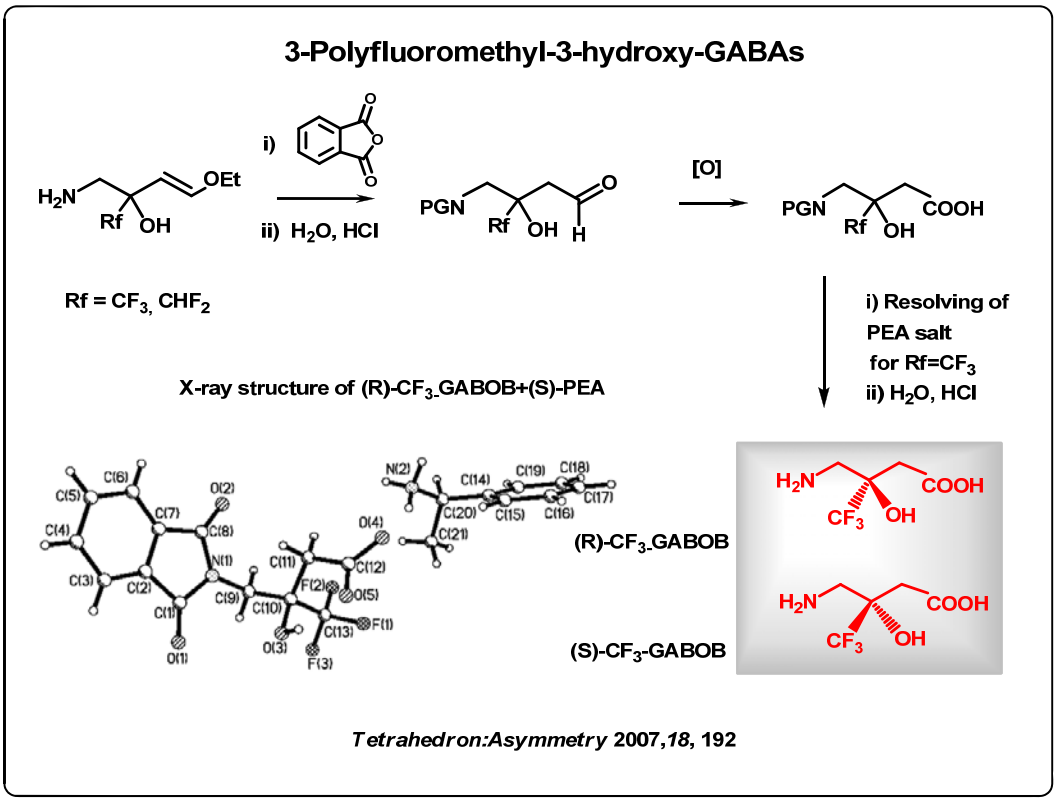
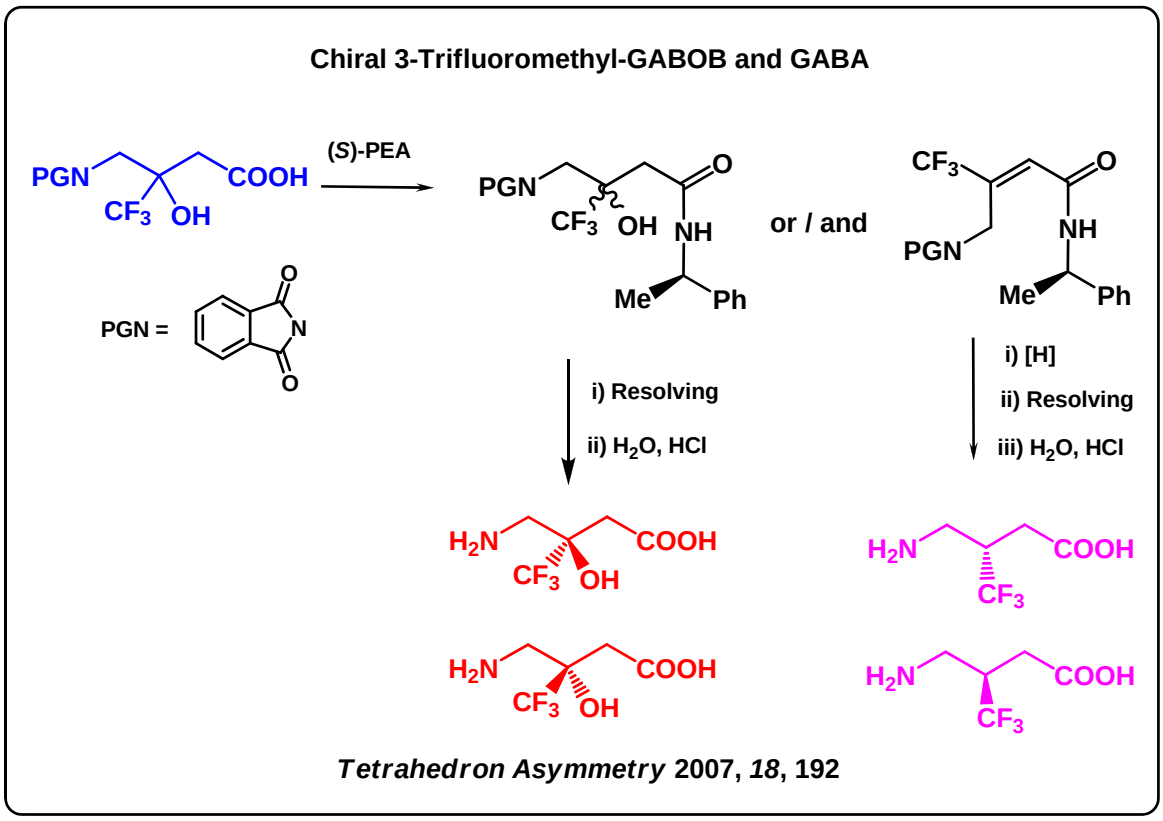


Figure 9. The article "*Synthesis of new β-trifluoromethyl containing GABA and β-fluoromethyl containing N-benzylpyrrolidinones*" appeared in a **Journal of Fluorine Chemistry** (2010) published by ELSEVIER

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.[81]



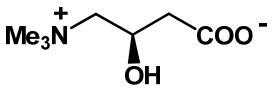
Another possibility to obtain optically pure β-trifluoromethyl GABOB was performed by transformation of protected GABOB in diastereomeric amides which can be resolved by column chromatography giving after hydrolysis optically pure CF_3-GABOB. [81]



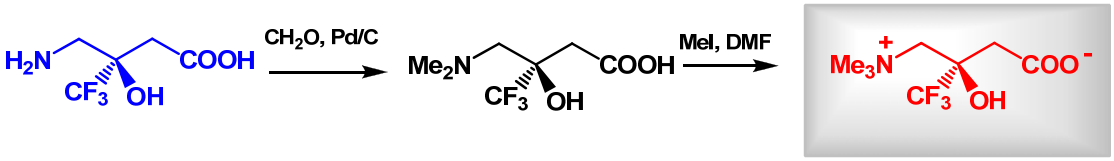
Kukhar and co-worker also described the first synthesis of a fluorinated carnitine. L-Carnitine (3-hydroxy-4-trimethylammonium butyrate) is a small molecule to be found in almost all cells. The increase of the lypophilicity of carnitine molecule was achieved thanks to the introduction of the trifluoromethyl 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. [82]

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. [83]

Synthesis of 3-Trifluoromethyl-L-carnitine

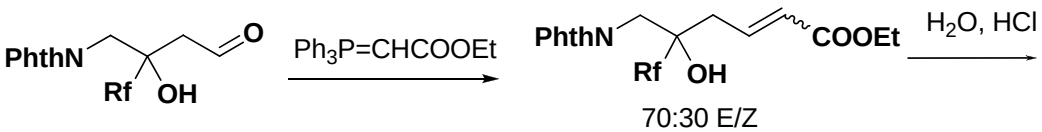


(L)-Carnitine



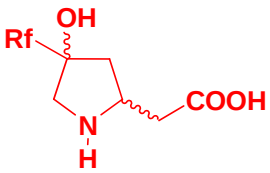
Ukrainica Bioorganica Acta, 2007, *1*, 43

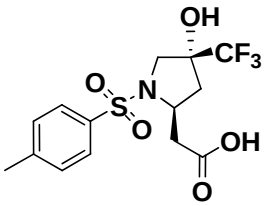
4-Polyfluoromethyl-4-hydroxy-homoproline

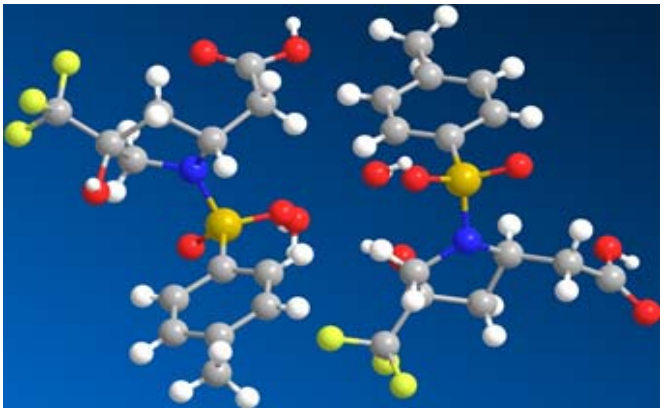


70:30 E/Z

Rf = CF_3, CHF_2







X-ray structure of *N*-Tos-(4*S*,2*R*)-Homo-Pro

Derivatives of 4-hydroxy-homoprolines are potent GABA-uptake inhibitors of both GAT-1 and GAT-3

Taking into account the fact that glutamic acid and glutamine play a key role in various biological processes, Kukhar and co-workers have developed an efficient synthesis of 6-polyfluoroalkyl-pyranones by the condensation of enones and *N*-acylglycines.. The reaction of pyranones with amines gives easily corresponding pyridones. Both heterocycles have been

used in the synthesis of fluorinated amino acids. Thus, the reduction of pyranones in methanol with $PdCl_2$ in the presence of trimethylamine gives 5-polyfluoralkyl-5-hydroxy-norleucines as diastereomeric mixture. [84]

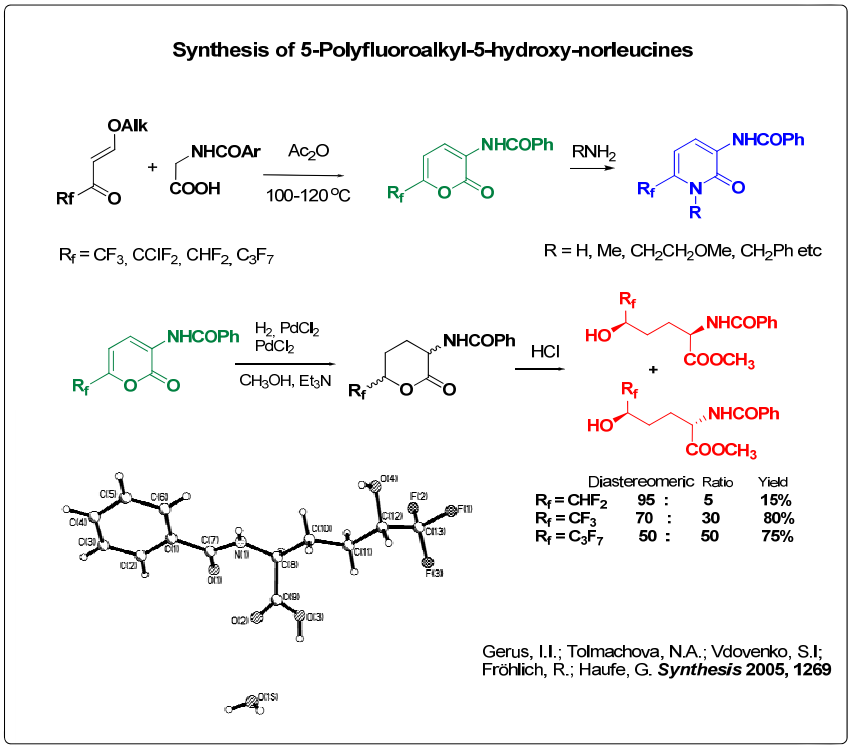
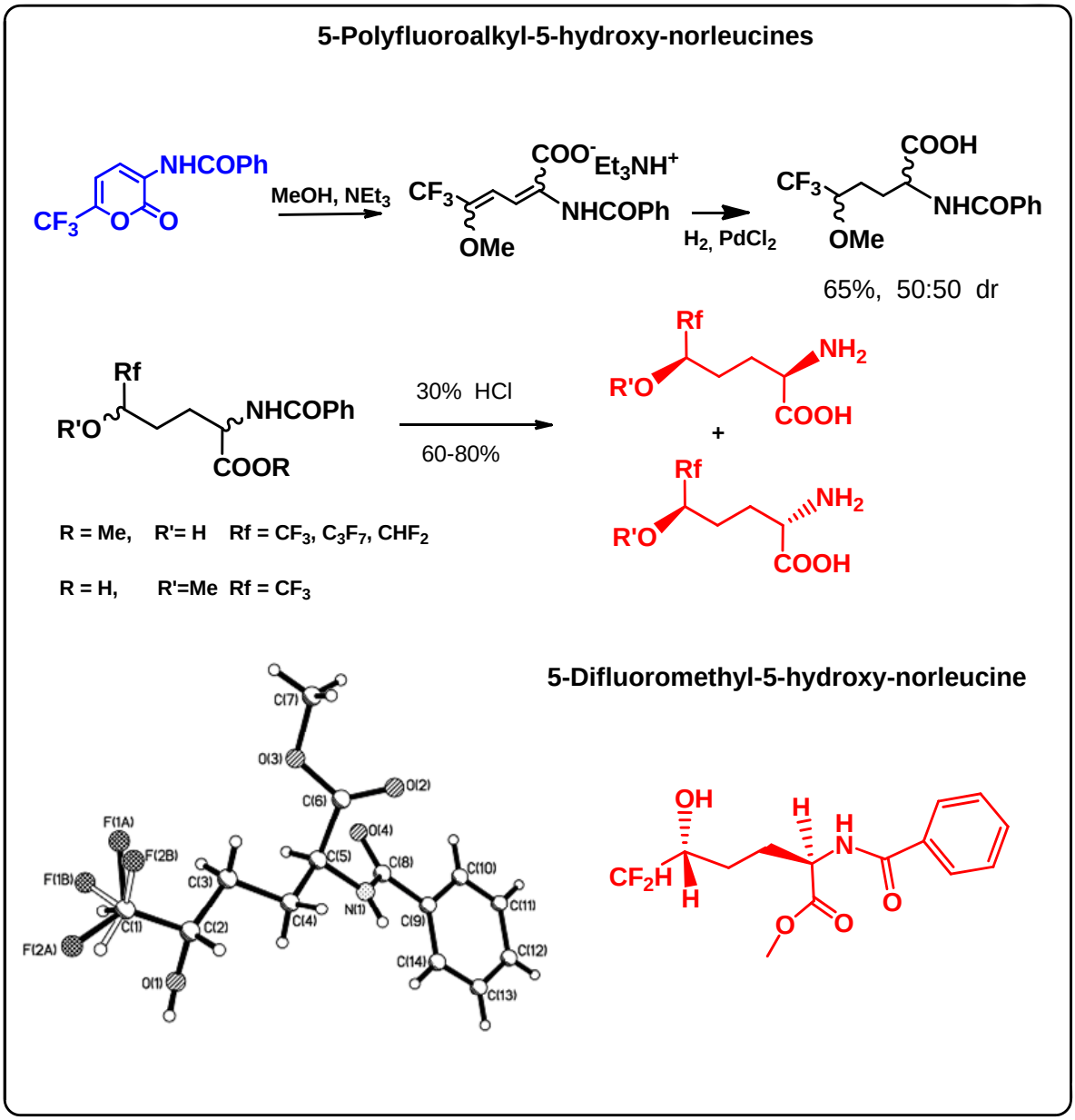
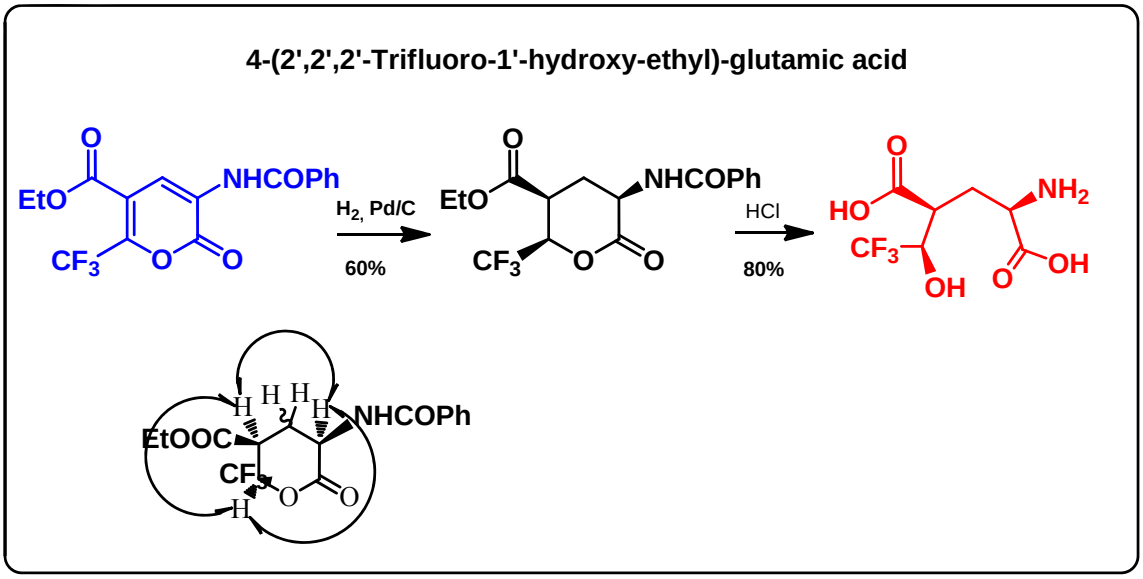


Figure 10. Dr. Igor Gerus, Dr. Marina Gorbunova (Derkach) and Dr. Maria Kolycheva (from right to left; about 1990)

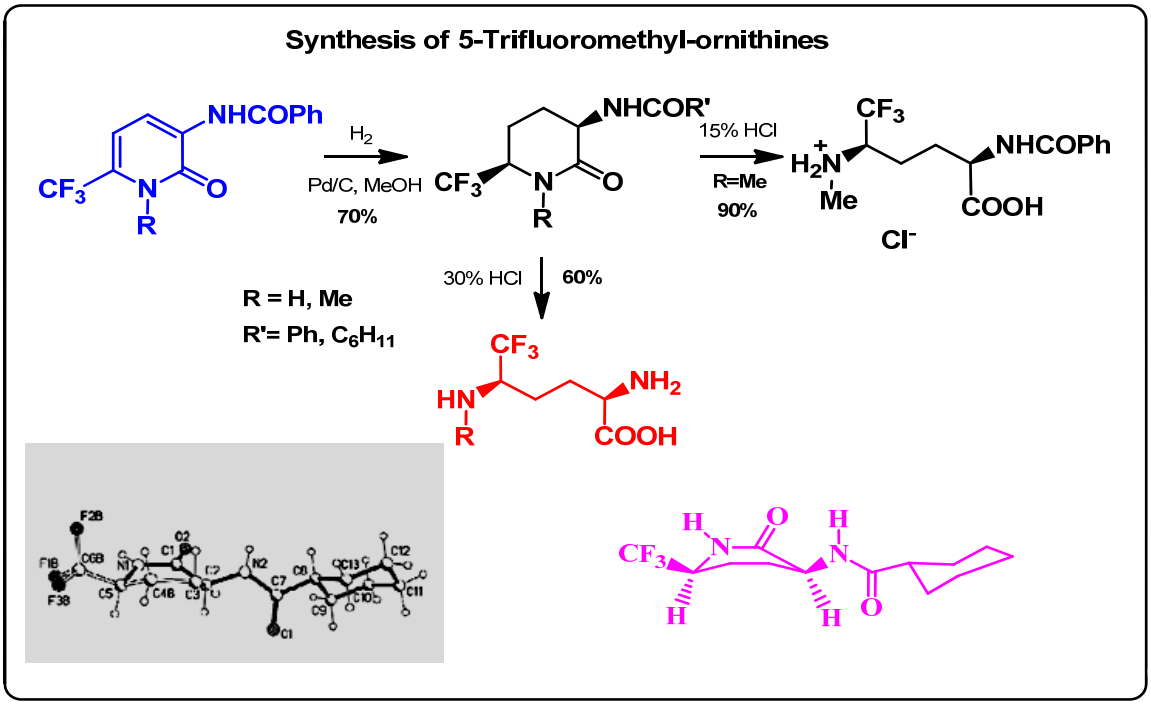
6-Trifluoromethyl-pyranone can be also easily transformed into *N*-benzoyl amino acid as diastereoisomeric mixture in ratio 50:50 after the addition of methanol and subsequent reduction.



Pyranone with trifluoromethyl and ester groups at 6 and 5 positions correspondingly was used as a synthon to synthesize trifluorohydroxyethyl derivate of glutamic acid. All three substituents in this compound are positioned in *cis* configuration to each other as it was established by NOE experiment.

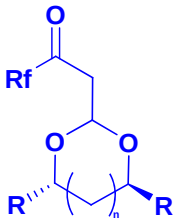


6-Trifluoromethylpyridones were obtained from the pyranone and corresponding amines. The reduction of the pyridones gave diastereoisomerically pure *cis*-piperidinones (established by NOE and X-ray analysis) which were successfully hydrolyzed to corresponding 5-trifluoromethylornithines. In this way Kukhar and co-workers synthesized a number of polyfluoroalkyl containing amino acids in various forms: racemate, optically or diastereomeric pure, or as mixture of diastereomers. The biological tests of some of them on rats demonstrated their immunomodulatory activity.[82]

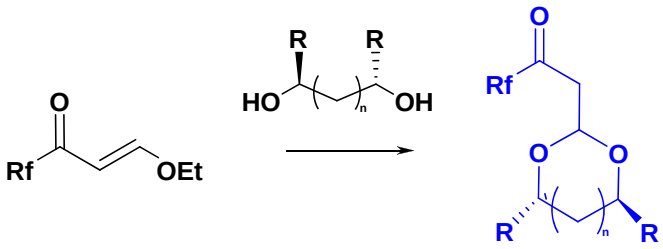


Another class of fluorinated acetyl acetaldehyde derivatives are fluorinated β-ketoacetales which can be easily prepared by the reaction of corresponding β-alkoxy enone with 1,2 or 1,3-diol. The peculiarity of these derivatives is that they do not have reactive β-position for nucleophilic attack as in the case of β-alkoxy enones. These compounds were used as the starting materials for the fluoromevalonate synthesis.[85]

Fluorinated Acetylacetaldehyde Derivatives (Starting Materials)



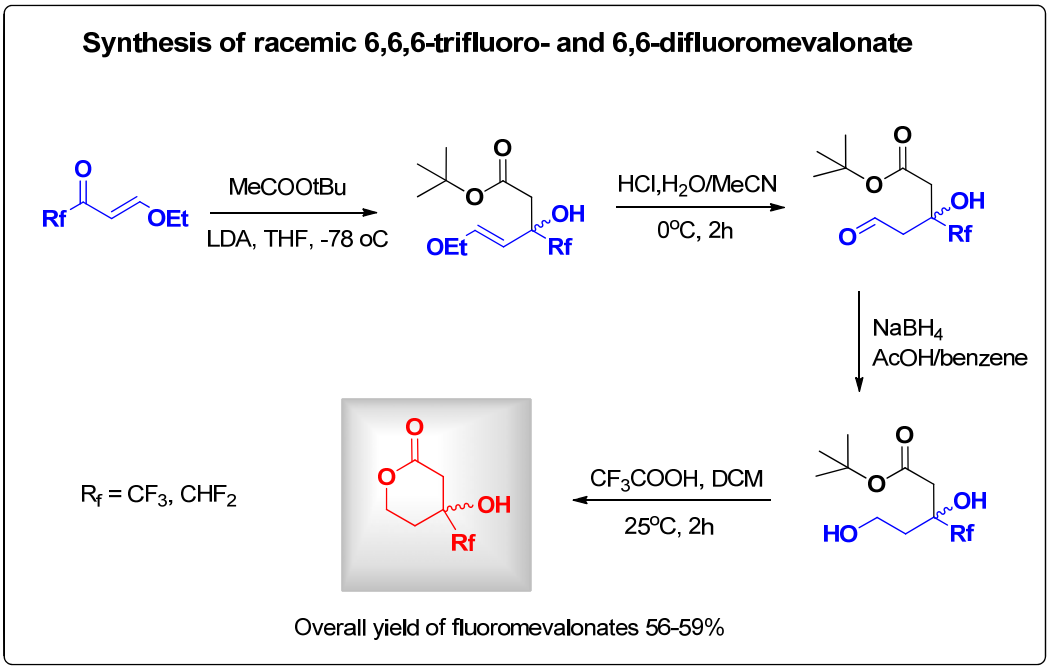
ß-Ketoacetales



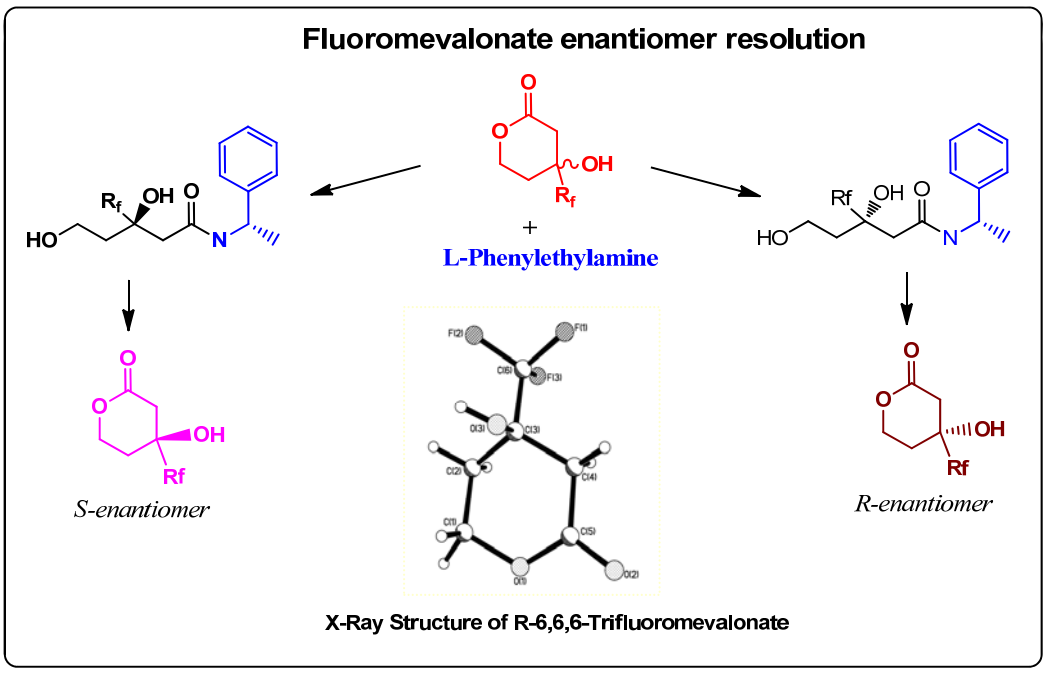
n = 0; R = H; R_f = CF_3, CHF_2, CF_2Cl
n = 0; R = CO_2Et; R_f = CF_3
n = 1; R = H; R_f = CF_3

***J. Fluor. Chem.*, 2005, *126*, 543**

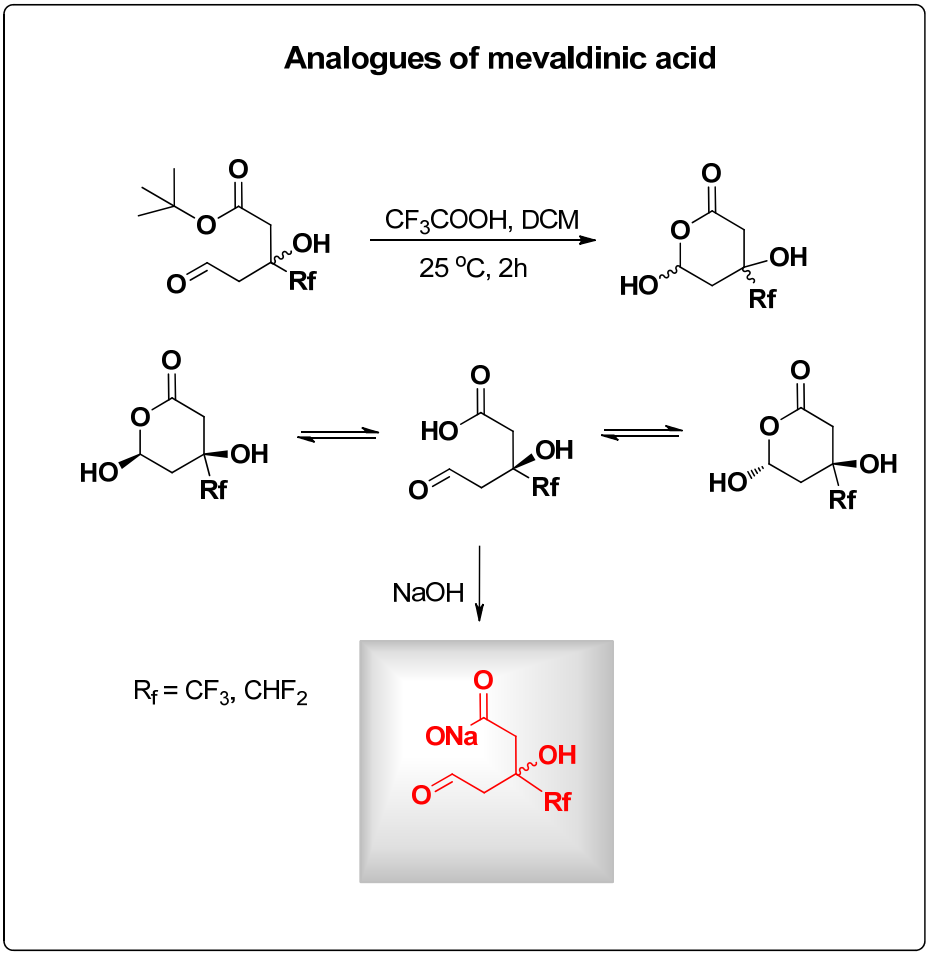
Synthesis of 6,6,6-trifluoro- and 6,6-difluoromevalonates starts from aldol condensation of β-alkoxy enone with *t*-butyl acetate. The next step is a mild hydrolysis of ethoxy vinyl group. *t*-Butyl group does not hydrolyze in the condition of the reaction. The aldehyde thus obtained can be easily reduced by sodium triacetoxyborohydride giving corresponding diol**.** The last stage of the synthesis is removal of protective *t*-butyl group by dry trifluoroacetic acid in dichloromethane.



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-(-)-phenylethylamine 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.

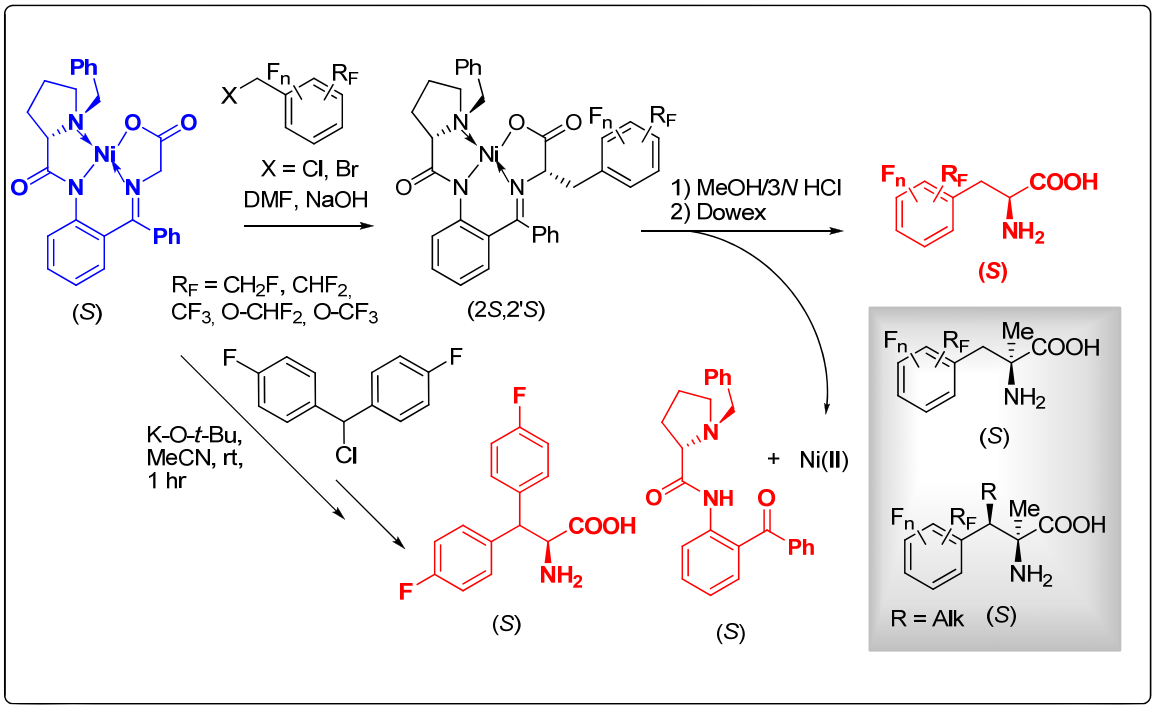


The proposed scheme can also be used for synthesis of racemic difluoromethyl- and trifluoromethyl analogues of mevaldinic acid. On the basis of NMR-spectra it was shown that trifluoromevaldinic acid exists in solution as an equilibrium mixture of two diastereomeric lactoles and an acyclic form. Sodium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

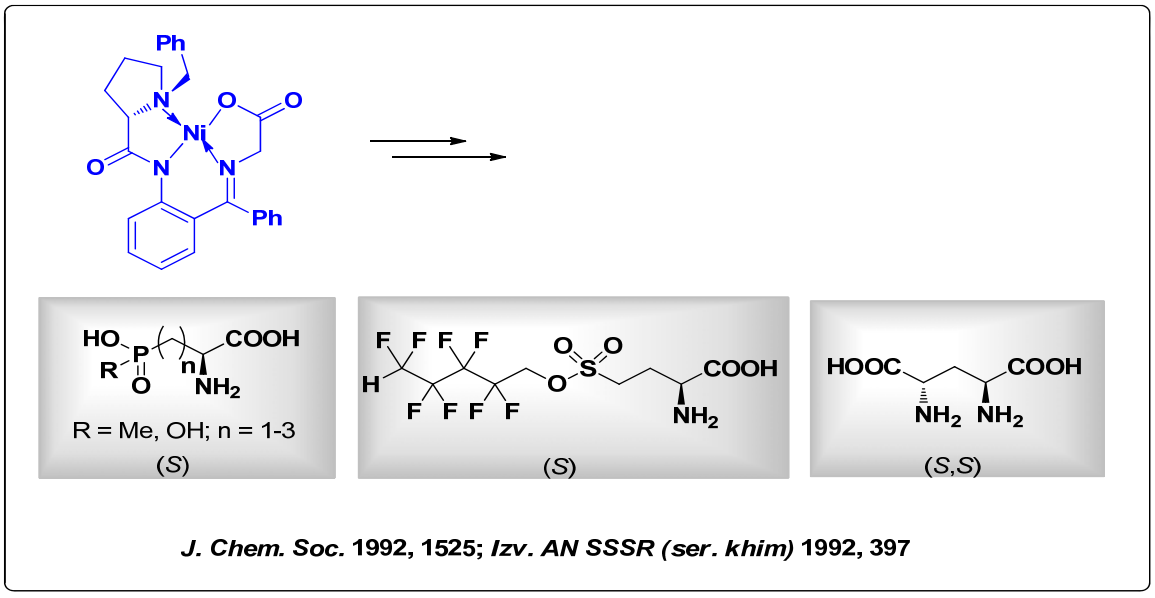


One of the most interesting projects of Kukhar's laboratory is the asymmetric synthesis of various fluorine-containing α-amino acids via homologation of the chiral Ni(II) Schiff's base complex of glycine with (*S*)-*o*-[*N*-(*N*′-benzylprolyl)amino]-benzophenone. This area of research was initiated in collaboration with Professor Yuriy Belokon' and was developed by Dr. Vadim 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*) stereochemistry of the newly formed stereogenic center of amino acids. The process of disassembly of alkylated complex includes a treatment of their solution in MeOH with 3 *N* HCl followed by isolation of the target amino acids via ion-exchange chromatography. This disassembly procedure also

allows for virtually complete recovery of the chiral ligand which can be reused to make starting glycine derivative. [86,87]



Taking into account the biological importance of phosphorus and sulfur containing analogues of α-amino acids, this asymmetric methodology was applied for preparation of ω-phosphino- and phosphono- derivatives of dicarboxylic amino acids, as well as polyfluorinated ester of homocysteic acid. [88,89]

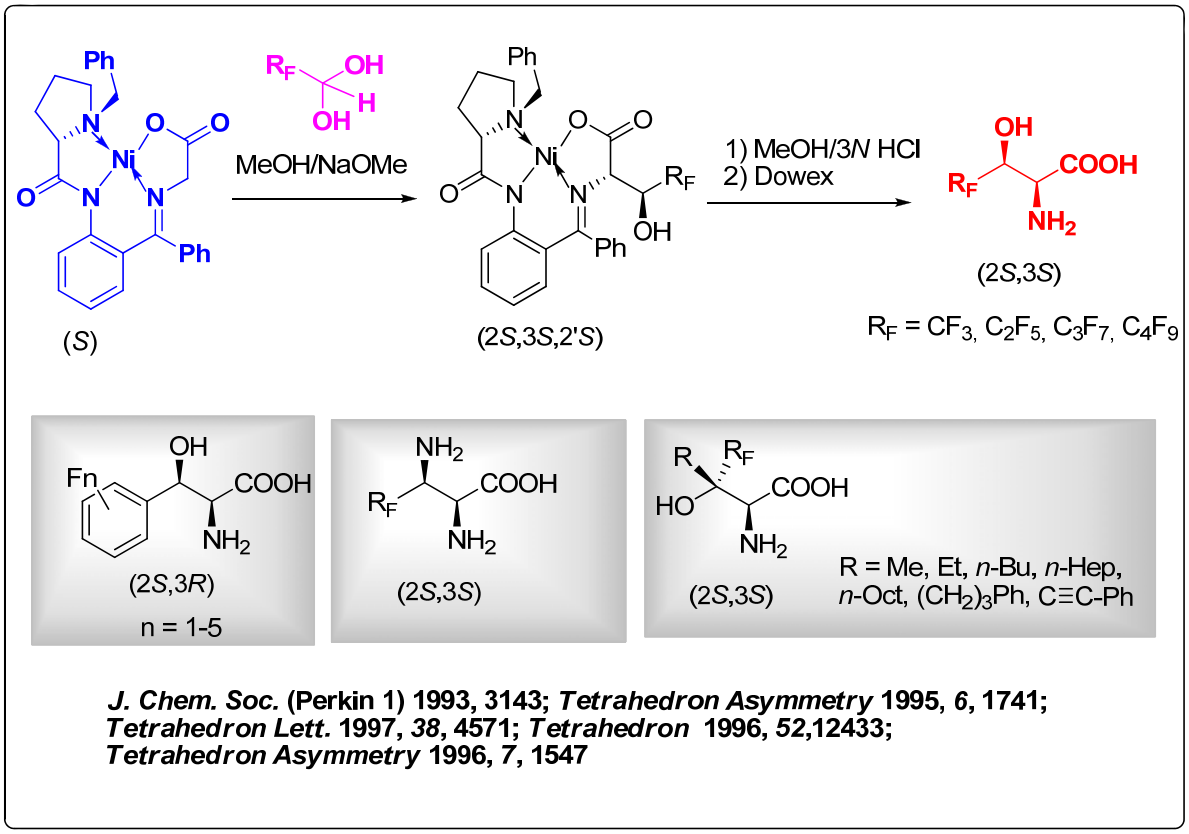


J. Chem. Soc. 1992, 1525; *Izv. AN SSSR (ser. khim)* 1992, 397

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.[90] 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.[91] 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.

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.[91]

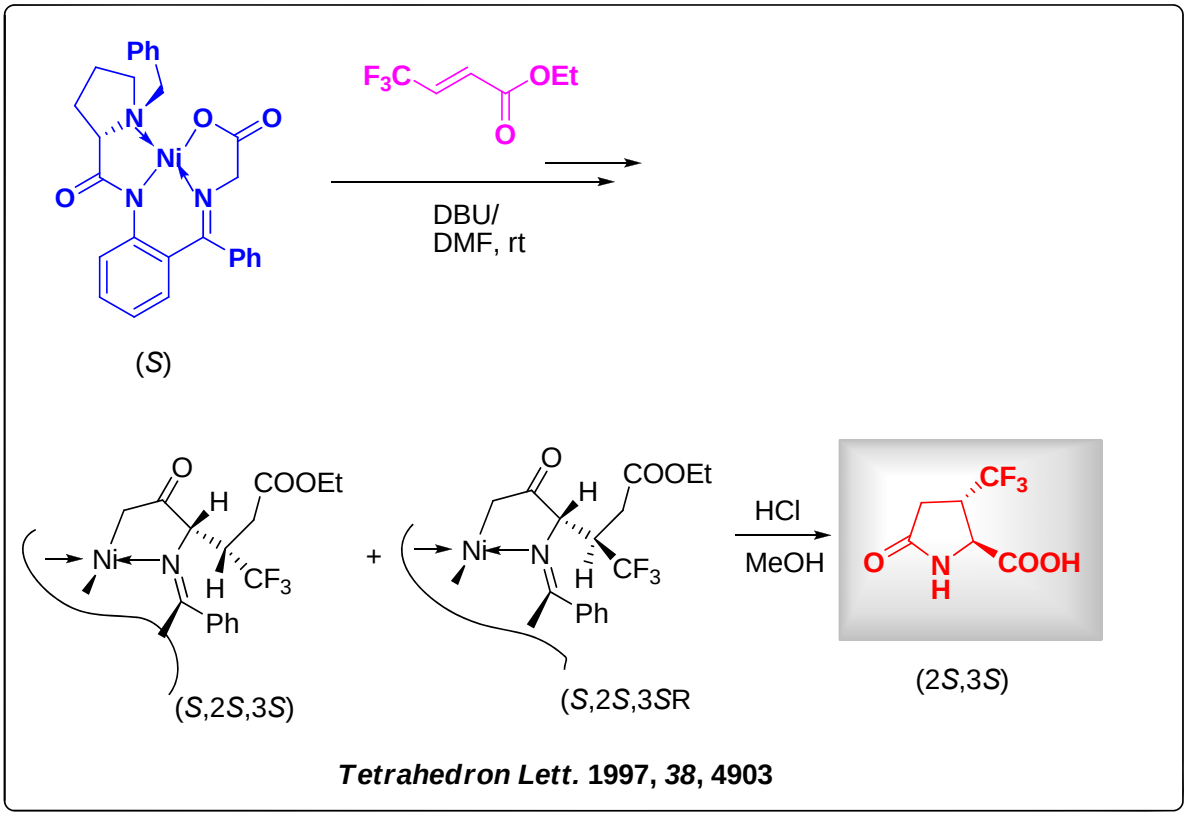
Application of imines derived from perfluoroalkyl aldehydes allowed to prepare quite a unique class of α,β-di-amino-β-perfluoroalkyl carboxylic acids (2*S*,3*S*).[92]



***J. Chem. Soc.* (Perkin 1) 1993, 3143; *Tetrahedron Asymmetry* 1995, *6*, 1741; *Tetrahedron Lett.* 1997, *38*, 4571; *Tetrahedron* 1996, *52*,12433; *Tetrahedron Asymmetry* 1996, *7*, 1547**

Aldol addition reactions of "normal", fluorine-free, ketones with Schiff base are generally unpractical due to the unfavorable electronic as well as steric characteristics. In sharp contrast, alkyl perfluoroalkyl ketones was found to react easily with glycine derivative providing straightforward access to the family of α-amino-β-hydroxy-β-alkyl-β-perfluoroalkyl carboxylic acids (2*S*,3*S*), unavailable by other methods.[93] Again, and quite remarkably, the perfluoroalkyl group in these reactions played the role of the stereo-controlling substituent favoring the predominant formation of the (2*S*,3*S*) configured products.[94]

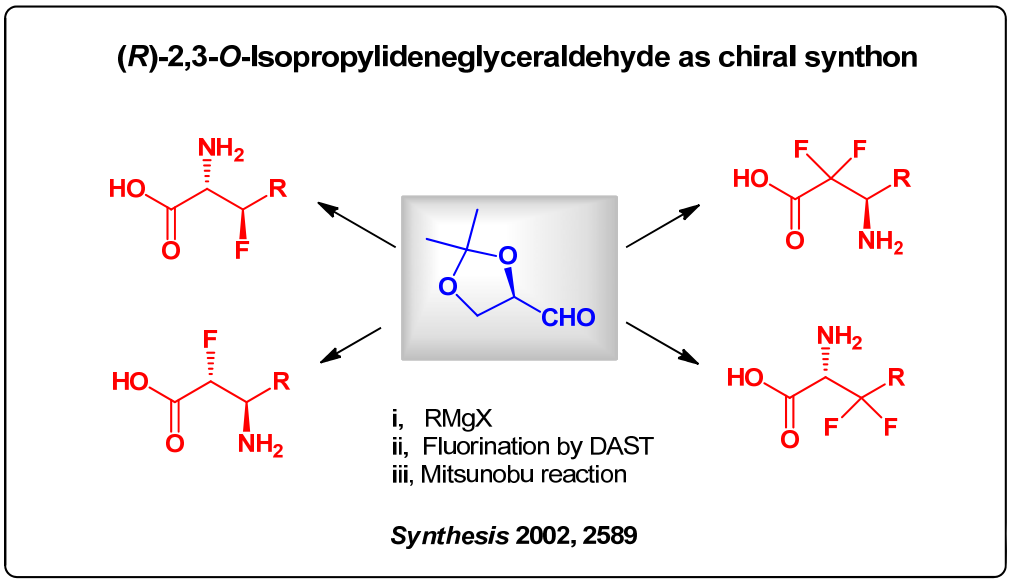
Ni(II) complex of the Schiff base of glycine with (*S*)-o-[*N*-(*N*-benzylpropyl)amino] benzophenone readily reacts with ethyl 4,4,4-trifluorocrotonate in ethanol solution in the presence of DBU to afford a mixture of two diastereomers in ratio of 81:19, isolated with an excellent yield. The absolute 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. [95]



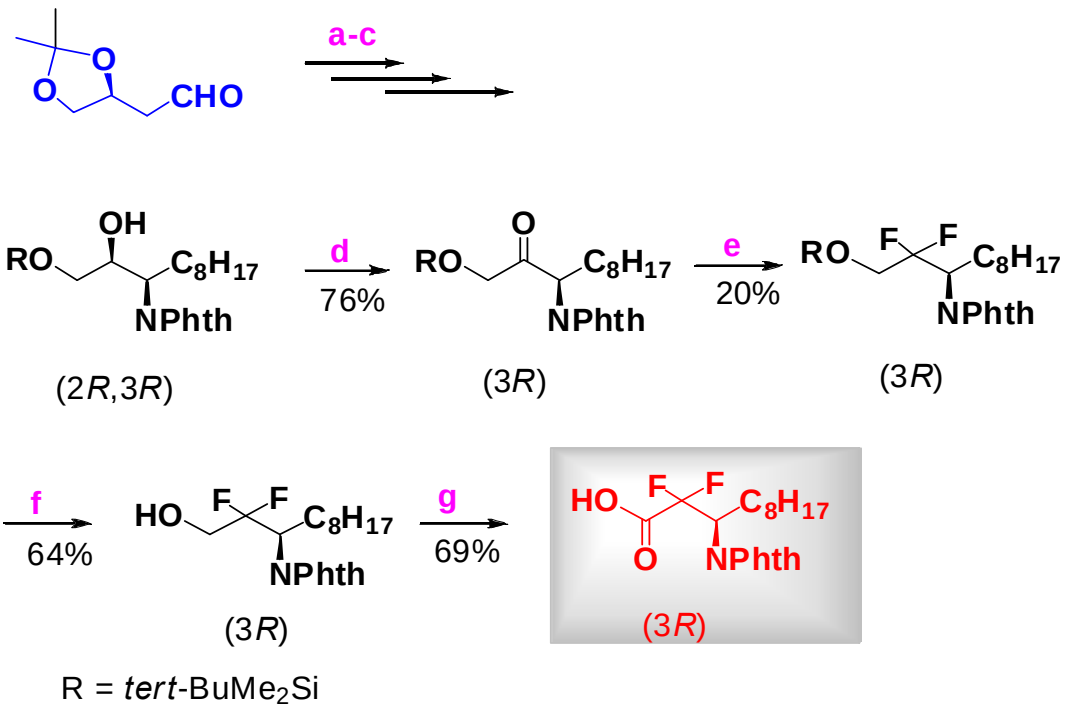
***Tetrahedron Lett.* 1997, *38*, 4903**

Figure 11. Prof. Dr. Vadim Soloshonok (on the right) and Prof. Dr. Diether Seebach (on the left). Photograph taken in 2013 at the University Basque Country, San Sebastian (Spain)

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.[96]



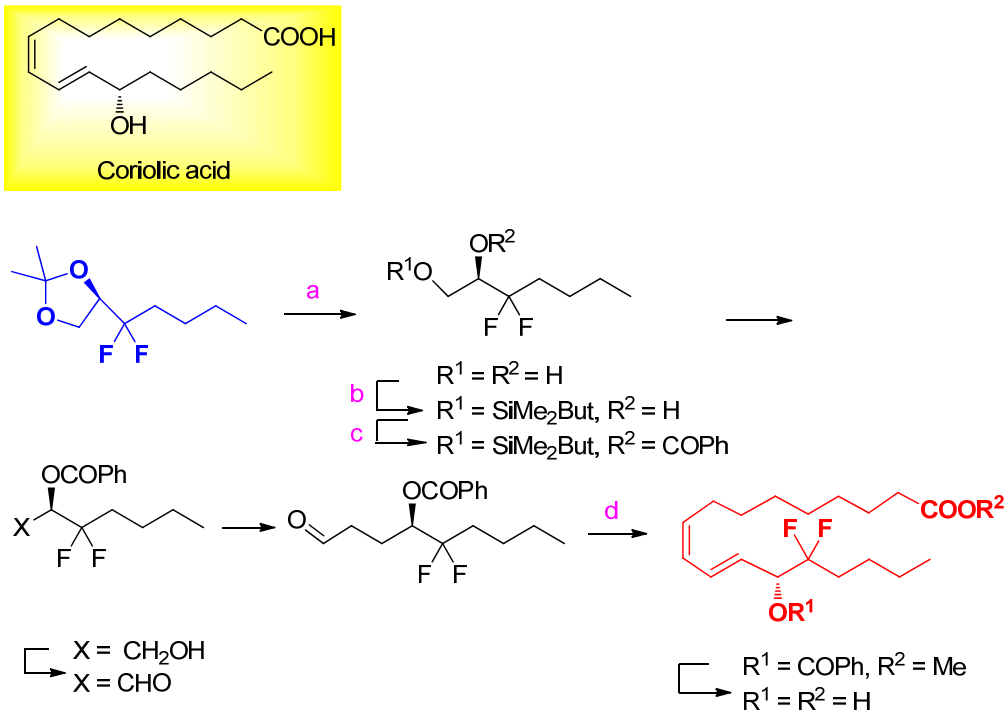
The stereocontrolled synthesis of *N*-protected (3*R*)-3-amino-2,2-difluoroundecanoic acids is a representative example.[96]



Reagents and conditions: a) *n*-$C_8H_{17}MgBr$, THF, -30 °C; b) PhthNH, DEAD, Ph_3P, toluene, 0 °C; c) 4N HCl; d) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, 1 h; e) Morpho-DAST, CH_2Cl_2, 30 °C, 45 h; f) dioxane/HCl/H_2O (93:5:2), 35-40 °C, 25 h; g) $NaIO_4$,$RuCl_3 \cdot H_2O$, CCl_4/MeCN/H_2O, r.t., 24 h

***Synthesis* 2002, 2589**

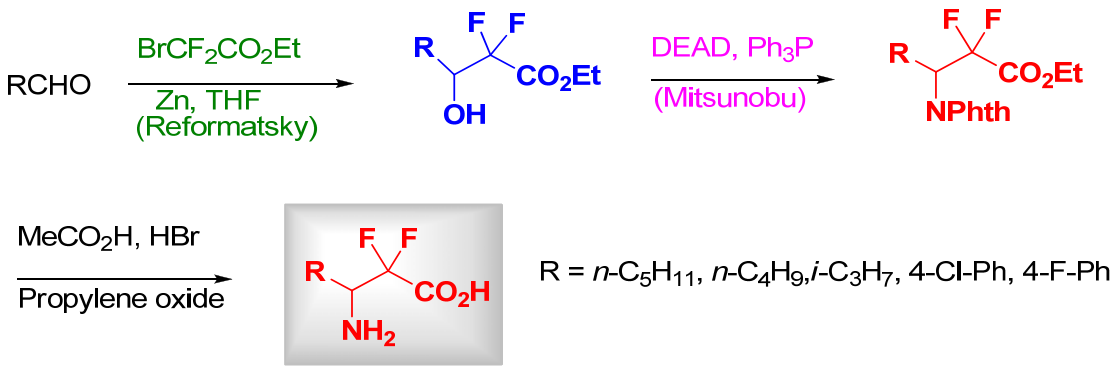
Another example including the efficient, stereoselective synthesis of (*R*)-14,14-difluorocoriolic acid starting from (*R*)-2,3-O-isopropylideneglyceraldehyde via the key intermediate (*R*)-3,3-difluoro-1,2-dihydroxyheptane has been reported by Andrei Kornilov and Alexander Sorochinsky.[97] The fluorinated 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.



Reagents and conditions: a) 4N HCl-THF (1:4), 20 ° C, 78%; b) *t*-$BuMe_2SiCl$, 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=$CH(CH_2)_7COOMe$, 85%; h) LiOH, THF-H_2O (4:1), 20 °C, 45%

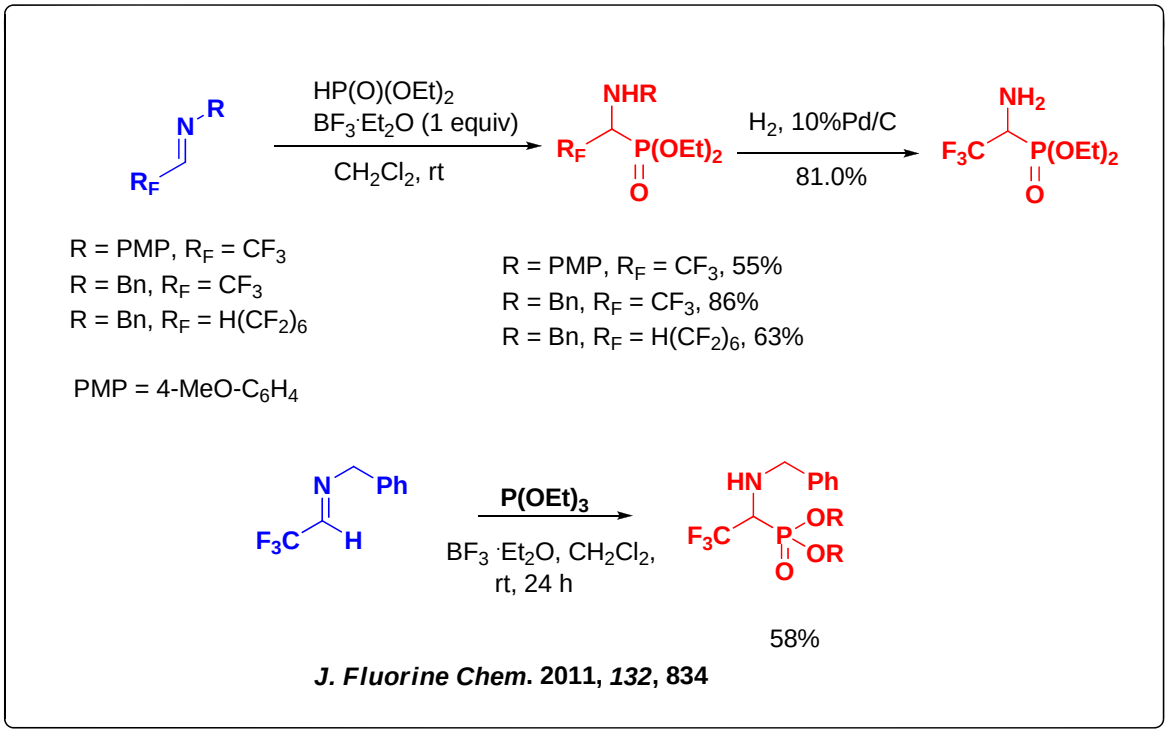
***Tetrahedron Asymmetry* 1994, *5*, 1015**

A three-stage synthesis of the fluorinated amino acids from aliphatic and aromatic aldehydes and ethyl bromodifluoroacetate has been carried out by Natalie Fokina and Andrei Kornilov using a combination of the Mitsunobu and Reformatsky procedures.[98]



***J. Fluorine Chem.* 2001, *111*, 69**

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.[100]

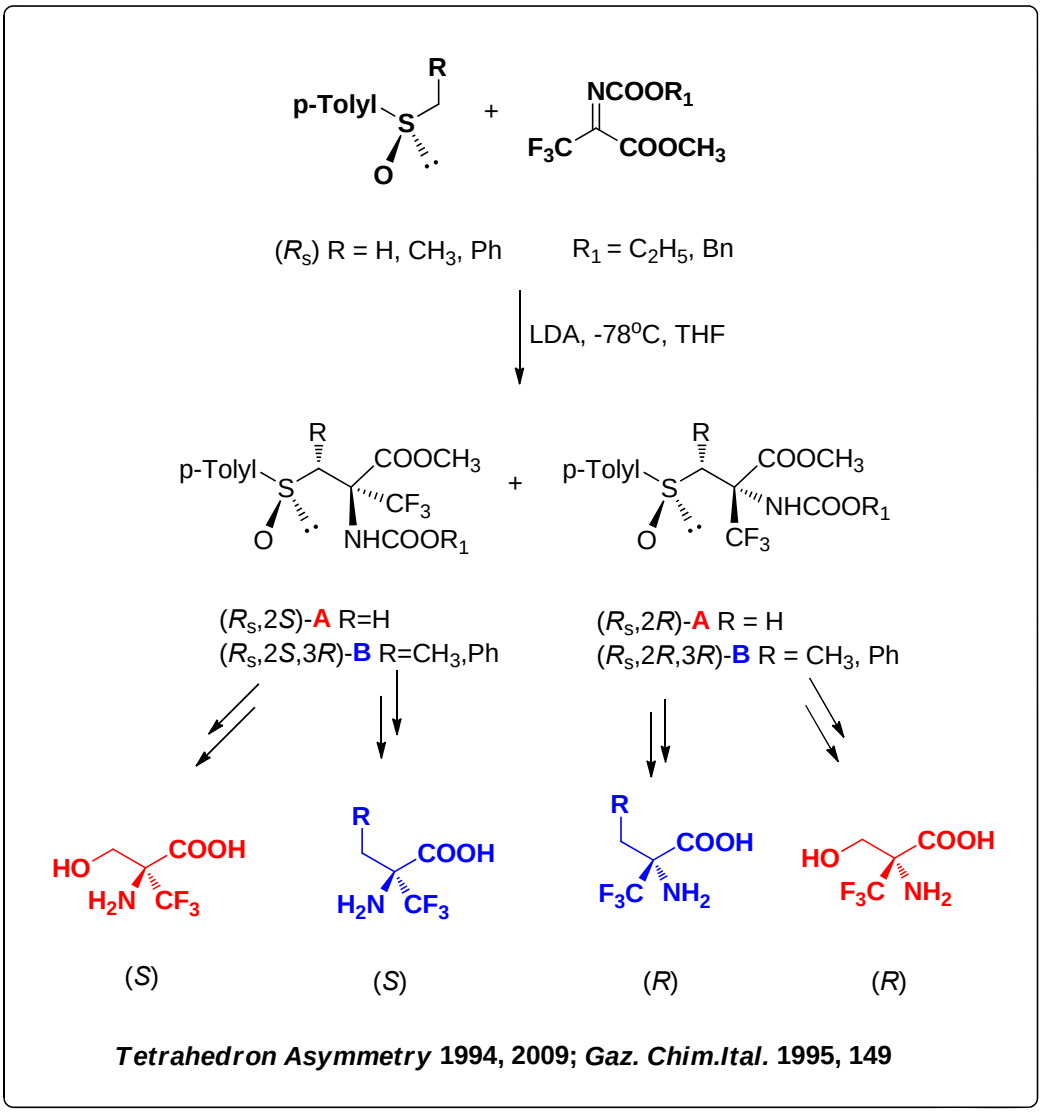


***J. Fluorine Chem.* 2011, *132*, 834**

Figure 12. The article "*Fluorinated Phosphonic Acids: Synthesis and Biomedical Application*", reflecting one of the modern concepts of bioorganic chemistry of phosphorus, appeared in a journal ***Chemical Reviews*** published by American Chemical Society (2006).[41]

Sulfinyl group mediated asymmetric synthesis of fluorine-containing amines, amino alcohols and amino acids is another important area of scientific research of Prof. Kukhar and co-workers.[101] 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 -78 ^{o}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-trifluoromethyl serines.

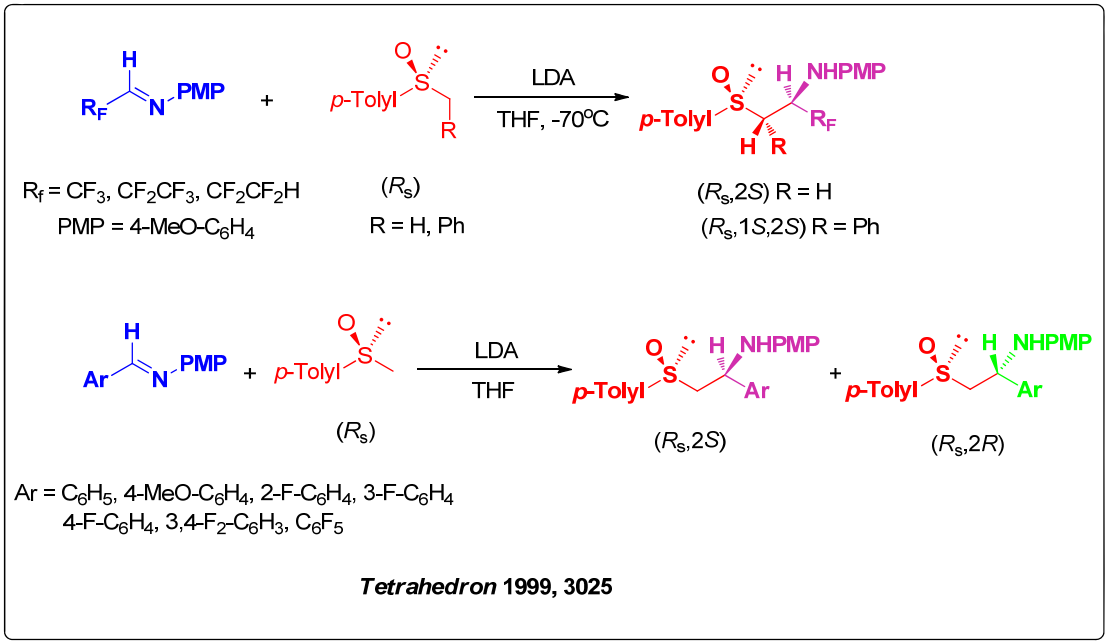
Each of separated diastereomers **B** after well-optimized reduction, desulfurization and deprotection procedures provided a series of α-trifluoromethyl α-amino acids. [103,104]



***Tetrahedron Asymmetry* 1994, 2009; *Gaz. Chim.Ital.* 1995, 149**

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 <1997JOC3424, 1998T12789>.[104,105] Condensation of the lithium anion of alkyl *p*-

tolyl sulfoxides (R_s) with *N*-(*p*-methoxyphenyl)aldimines proceeded with high rate at -70 °C 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-MeO-C_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 pentafluorobenzylidene imine a mixture of corresponding diastereomers (R_s,2*S*) and (R_s,2*R*) was obtained in a ratio of 64:36. 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 C-SO stereogenic center.[106]

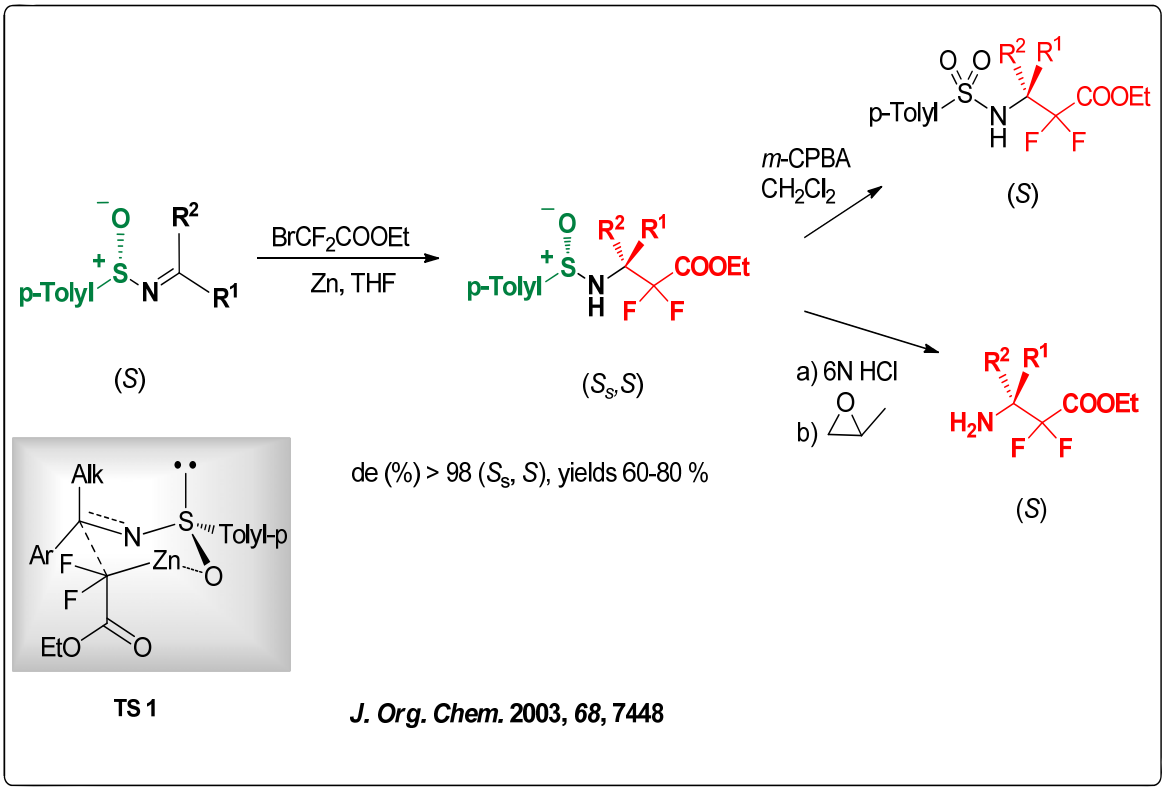


The direct asymmetric synthesis of α,α-difluoro-β-amino acids has been realized by Alexander Sorochinsky et al. via Reformatsky reaction of ethyl bromodifluoroacetate with enantiomerically pure *N*-*p*-toluenesulfinyl imines. The enantiomerically pure *N*-*p*-toluenesulfinyl imines were treated with ethyl bromodifluoroacetate in the presence of activated Zn dust under high temperature to provide the desired *p*-toluenesulfinamides with the (*S*$_s$,*3S*)-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).[107]

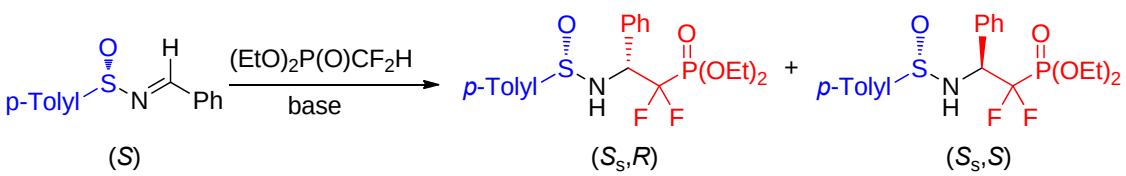
Figure 13. Dr. Alexander Sorichinsky (on the left) and Dr. Igor Shchevchenko (on the right)

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 bromodifluoroacetate 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.

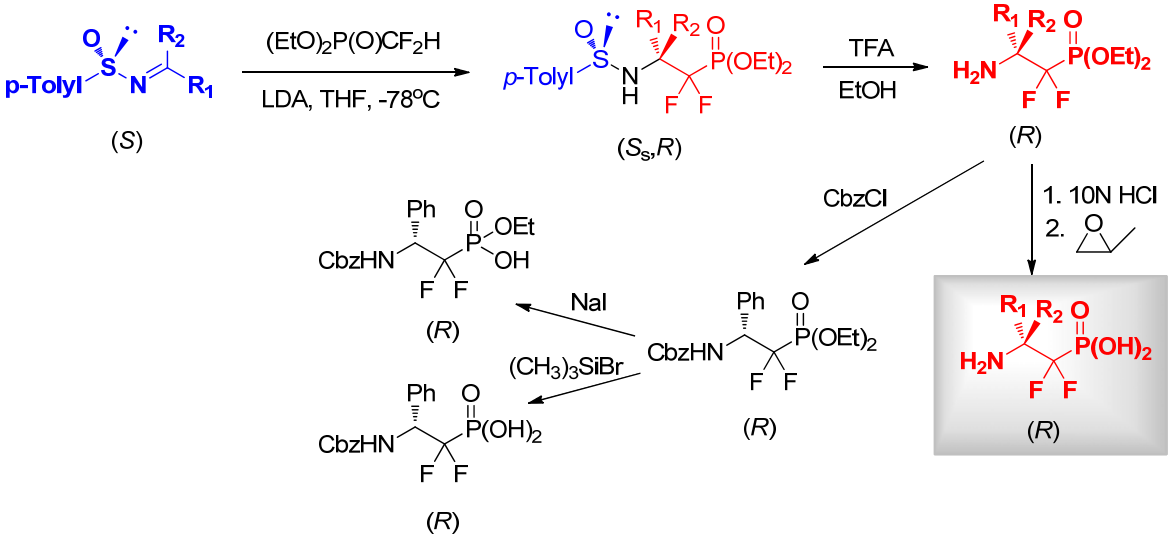


Addition of phosphonodifluoromethyl carbanion obtained by deprotonation of diethyl difluoromethylphosphonate with LDA in THF at –78 °C to enantiomerically pure sulfinimine (*S*) proceeded smoothly to afford corresponding *N*-sulfinyl α,α-difluoro-β-amino phosphonate after mild acidic work up. In spite 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.[108,109]



***Tetrahedron Lett.* 2004, 6665**

In accordance with previous experiments, addition of diethyl difluoromethylphosphonate to other *N*-sulfinylaldimines in THF using LDA as a base proceeds in excellent diastereoselectivity. The *N*-sulfinyl α,α-difluoro-β-aminophosphonate diastereomers were separated by chromatography or crystallization to give the major pure diastereomers (S_s, *R*).



R_1 = Ph, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 2-thienyl, *n*-C_5H_{11}, *i*-Pr, (*E*)-PhCH=CH
R_2 = H, CH_3

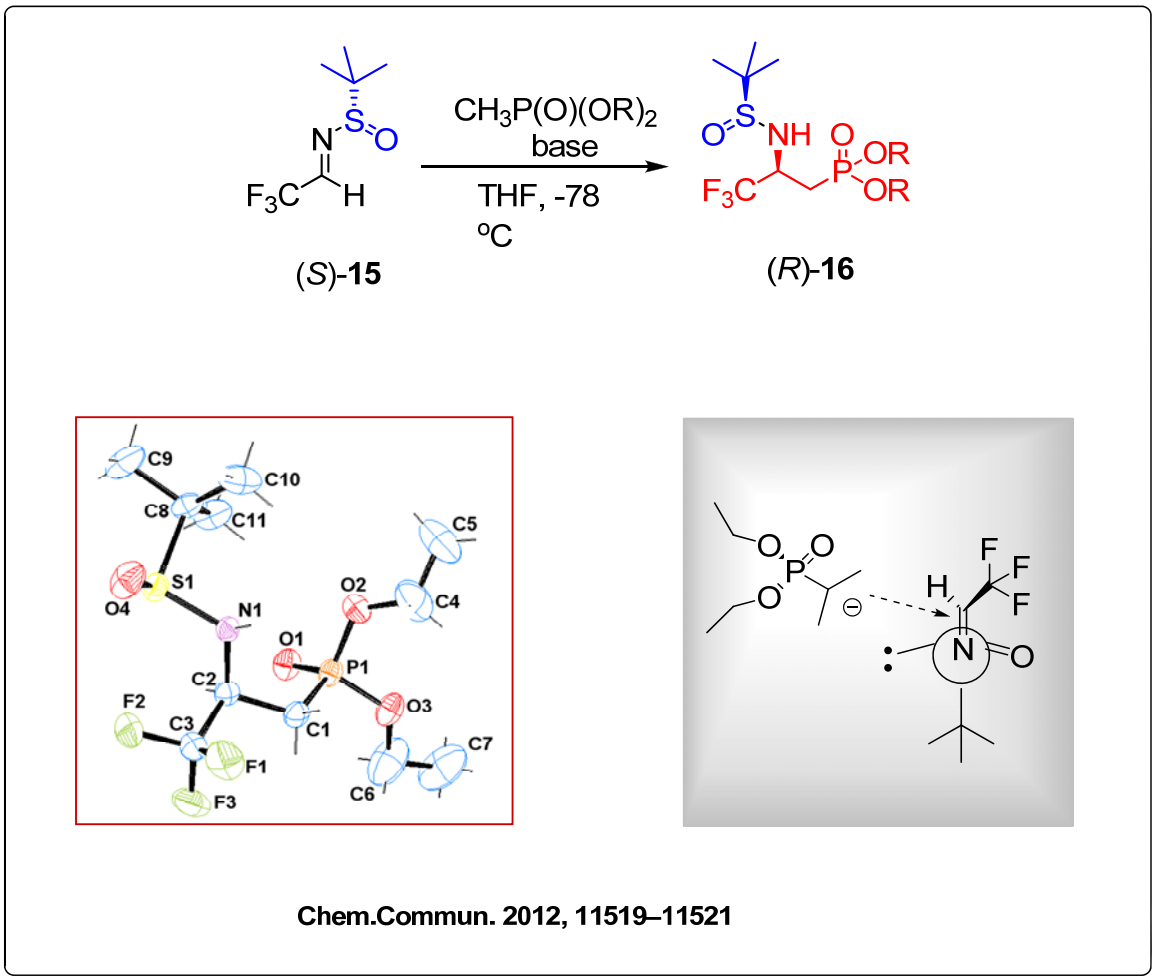
The attractive feature of sulfinyl methodology is that the sulfinyl auxiliary can be both stereodirecting and NH_2 protecting group

***Tetrahedron* 2006, 9902**

Figure 14. The article *"Diastereoselective addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines: synthesis of α,α-difluoro-β-aminophosphonates, phosphonic acids, and phosphonamidic acids"* appeared in a Journal **Tetrahedron** (2006) published by ELSEVIER

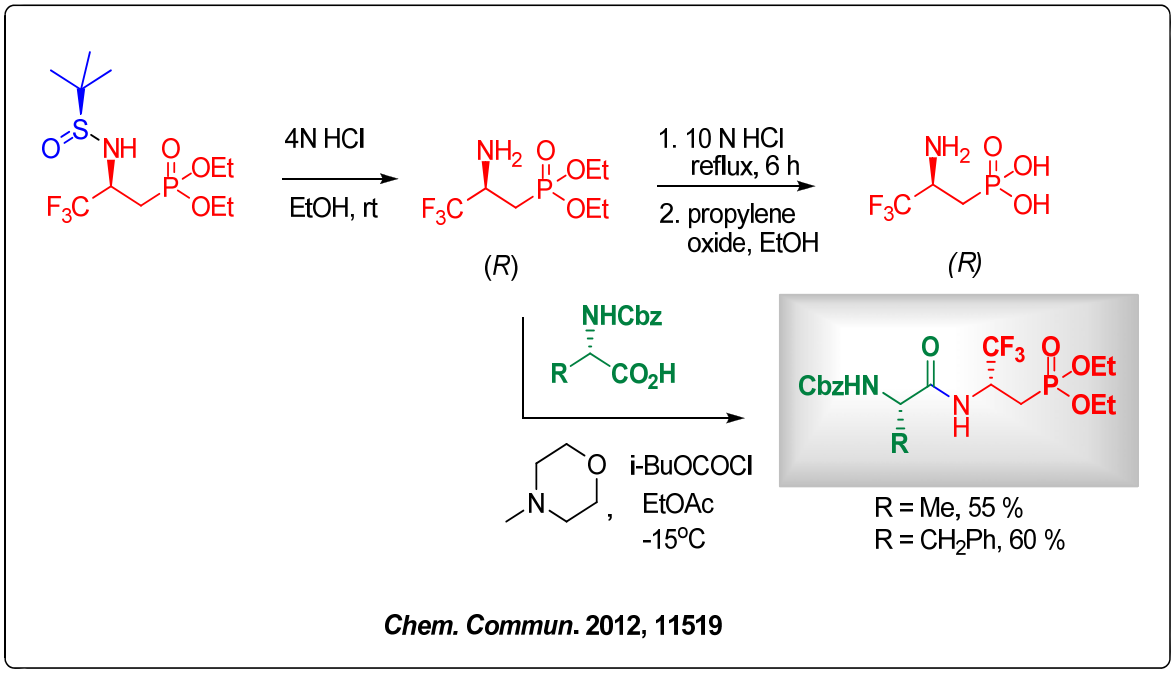
Subsequent studies have demonstrated that *N-tert*-butanesulfinyl imine derived from fluoral is extremely useful building block for the asymmetric synthesis of fluorinated amines and related molecules due to excellent diastereoselectivity of nucleophilic addition reactions across C=N double bond and mild conditions for cleavage. Kukhar and co-workers applied this available chiral reagent as straightforward approach for 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-trifluoroacetaldimine with dialkyl methylphosphonates employing *n*-BuLi, LDA and LHMDS as deprotonating reagents provides the convenient stereoselective approach to β-trifluoromethyl-β-aminophosphonic acids. 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.[110]



Chem.Commun. 2012, 11519–11521

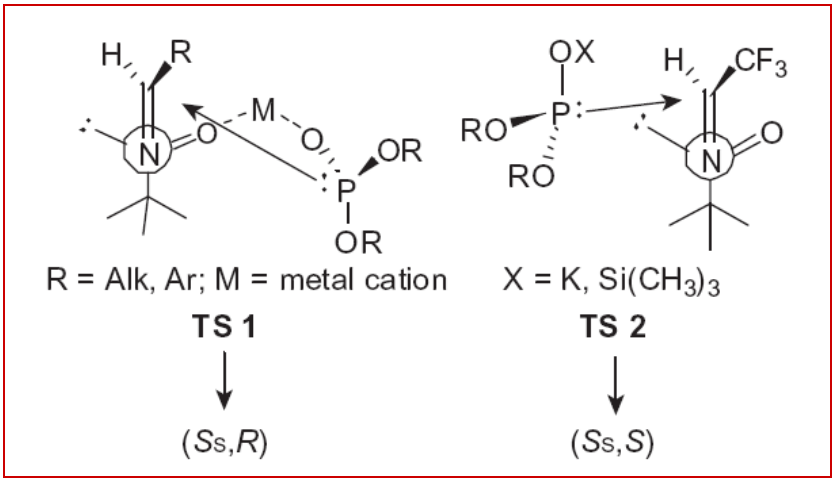
An important advantage of using the *tert*-butanesulfinyl group in aminophosphonate syntheses was that it can be removed under mild acidic conditions without effecting phosphonate ester group. By performing the desulfinylation reaction, the β-trifluoromethyl-β-aminophosphonates could be isolated in excellent yield. Enantiopure trifluoromethylated β-aminophosphonate (*R*) has been incorporated into peptide chains by coupling with *N*-Cbz-L-alanine and *N*-Cbz-L-phenylalanine. According to ^{19}F NMR as well as ^{31}P NMR analysis the diastereoisomerically pure *N*-Cbz protected β-aminophosphonic dipeptide derivatives (*S*, *R*) were conveniently obtained in good yield by this procedure. [110,111]

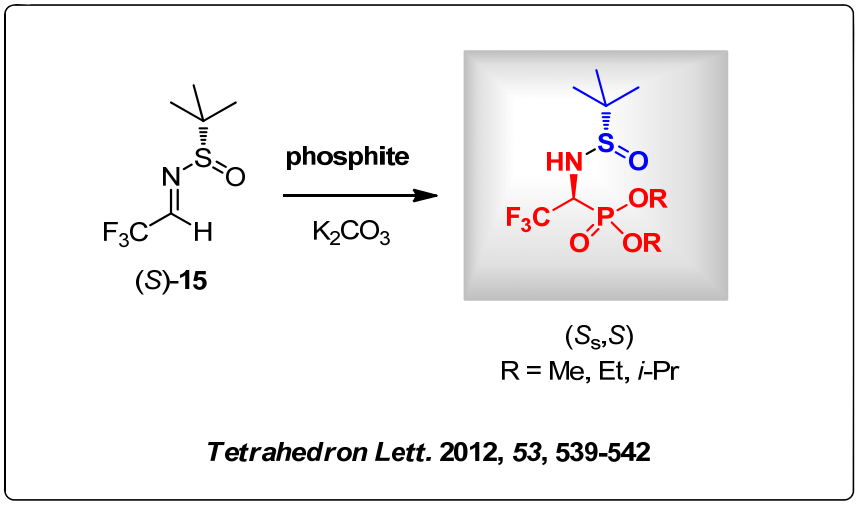


***Chem. Commun.* 2012, 11519**

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 trimethylsilyl phosphite 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. 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.

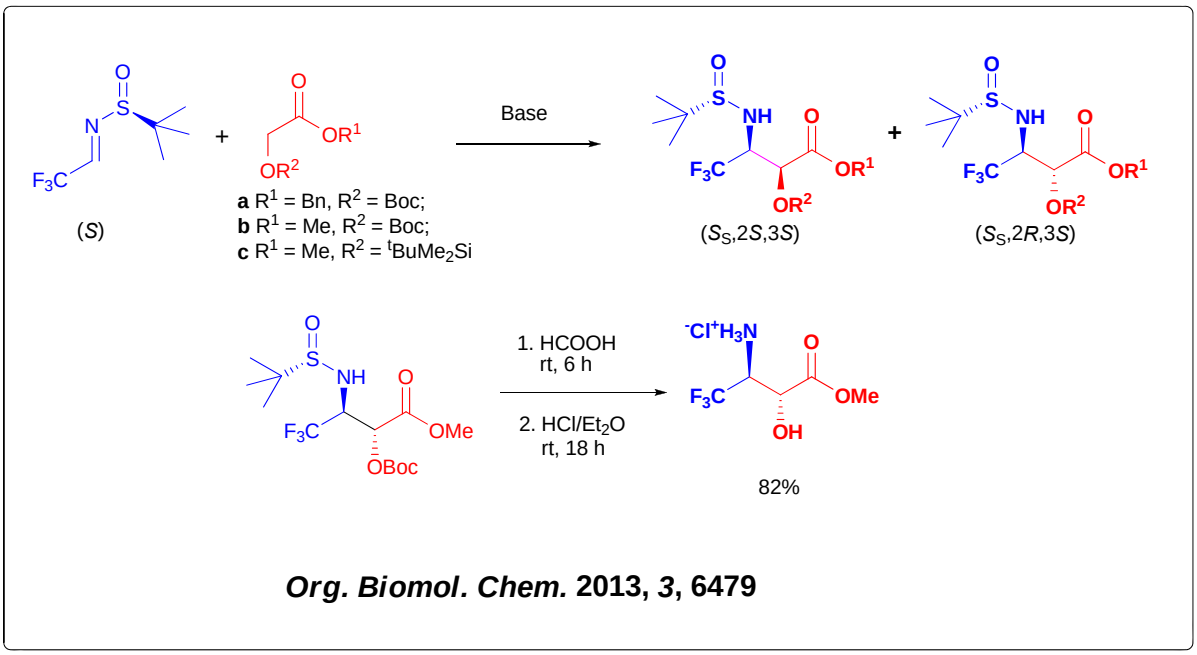




From the beginning of the 2000s, the scientific interests of the Prof. Kukhar focused on the development of regio- and stereoselective methods for the design of *polyfunctional phosphate mimetics* and their subsequent use as synthons in the targeted synthesis of biologically active compounds. A profound understanding of the trends in the development of scientific research in the field of organophosphorus and organofluorine chemistry was manifested in the relevance of the studies conducted by Prof. Kukhar. In particular, practical approaches to the design of fluorine-containing bioactive compounds have been reviewed in the highly acclaimed articles "*Fluorinated phosphonates: synthetic and biomedical*

applications" (***Chemical Rewiews***),[41] "*Advances in the synthesis of fluorinated aminophosphonates and aminophosphonic acid* " (**Royal Society of Chemistry Advances**),[44] "*Application of Silicon Methodologies for the Synthesis of Mono- and Bisphosphonic Acids*" (**Current Organic Synthesis**),[20] "*Progress in the Development of Pyrophosphate Bioisosteres: Synthesis and Biomedical Potential of 1-Fluoro- and 1,1-Difluoromethylene-1,1-bis-phosphonates*" (***Current Organic Chemistry***)[42], "*1-Amino-1,1-bisphosphonates. Fundamental syntheses and new developments*" (***Arkivoc***)[43], "*Fluorinated organophosphates for biomedical purposes*" (***Tetrahedron***)[112].

Among the achievements of this period, it should be noted new asymmetric approach to β-trifluoromethyl isoserines. The enantiopure (2*S*,3*S*)- and (2*R*,3*S*)-β-trifluoromethyl isoserine 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-trifluoromethyl isoserines thus obtained are useful intermediates for synthesis of corresponding *N*,*O*-protected and partially deprotected aminoacids.[113]

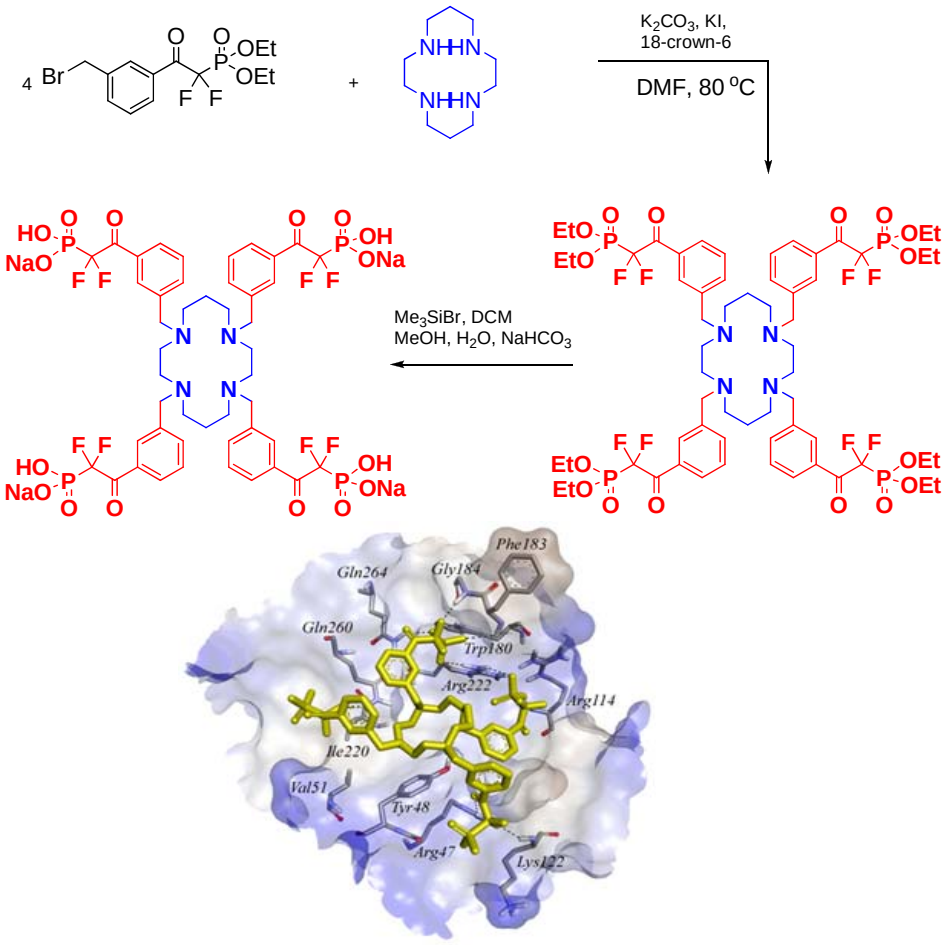


***Org. Biomol. Chem.* 2013, *3*, 6479**

The Kukhar's research group in cooperation with Prof. I. Beletskaya and her co-workers (RAN) also worked out the synthesis of previously hard-to-reach phosphonates and bisphosphonates on the platform of tetraazamacrocycles (cyclames and cyclenes). Studies of the biological activity of these compounds performed in the laboratory of Prof. A. I. Vovk showed that cyclam bearing four benzyl-linked α,α-difluoro-β-ketophosphonate substituents can strongly inhibit activity of TC-PTP with IC_{50} value of 75 nM. 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 signaling pathways in living cells.[114,115]

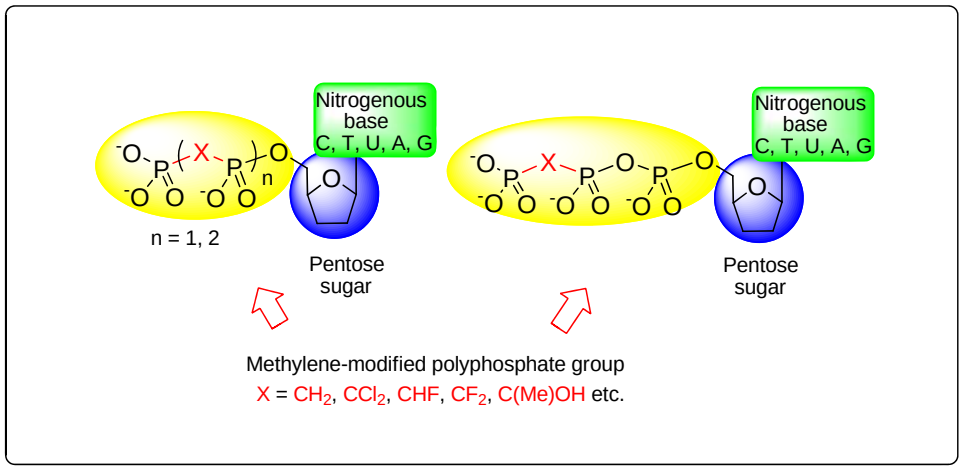
Synthesis of benzyl-linked α,α-difluoro-β-ketophosphonate derivatives of cyclam



Possible binding mode of cyclam-based derivative at the active site of TC-PTP

***Org. Biomol Chem.* 2015, 7437**

The last publication of Prof. Kukhar was entitled "*Phosphonate analogues of nucleoside polyphosphates*" (***Arkivoc*, 2018**).[116] This work suggested the further development of the bioisosteric concept in application to new types of element-substituted phosphonates of nucleotide nature, but suddenly were interrupted… Valery Kukhar became seriously ill in November 2016, and he died within a few months.



* * *

Professor Valery Kukhar did not hide his concern about the prospects for the development of Ukrainian bioorganic chemistry. He was skeptical about authoritarian methods of managing science. Confirmation of this can be found in his numerous interviews with the media. But he was a great optimist about the prospects for the development of the world bioorganic and biochemical science on the achievements of which depends the further progress of many vital areas of human activity such as pharmaceutical science, medicine, ecology and agriculture. Valery Kukhar believed that we are still at the beginning of the more in-depth study and use of chemistry and biochemistry fluorine-phosphorus compounds as a powerful instrument of cognition of biological processes and the creation of new highly effective drugs, particularly for viral and oncological diseases. He believed that there is still a large room for chemical creativity in approaching new and effective peptide mimics, haptens of catalytic antibodies, enzyme inhibitors, antibiotics, and other pharmacological agents. He thought that more comprehensive studies on individual stereoisomers are clearly warranted to establish the nature of host-guest complexes since the CHF and P stereochemistry may influence such factors as unfavorable steric effects, favorable van der Waals interactions, dipole-dipole and ion-dipole interactions, and fluorine hydrogen bonding. Today these effects remain controversial and difficult to evaluate. He was sure that the “artificial” introduction of the fluorine into biological systems inspired by biochemical processes will continue to generate new efficient drugs and pharmaceuticals.

Getting pleasure from teaching, Valery Kukhar tried to instill a love for scientific research to his students. He believed that "*knowledge is power*" and that "*you are what you know*". He had a fine sense of humor, liked jazz music, painting, comics, and jokes. His report at the award ceremony of Arbuzov's Prize ended with the words: *The purpose of the game is the same for cells as for the people working in the laboratory.*

Distinguished in chemistry, administration, and public service, as well as in personality and character, Valery Kukhar was a key figure in the growth of the bioorganic science in Ukraine.

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