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# SYNTHESIS OF TAILOR-MADE AMINO ACIDS CONTAINING C($sp^2$)–F BONDS.

***Alicja Wzorek[1], Jianlin Han[2], Taizo Ono[3], Karel D. Klika[4], Daniel Baecker[5], Wei Zhang[6], Vadim A. Soloshonok[7,8*]***

*[1] Institute of Chemistry, Jan Kochanowski University in Kielce, Uniwersytecka 7, 25-406 Kielce, Poland;*
*[2] Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China;*
*[3] National Institute of Advanced Industrial Science and Technology (AIST), 2266-98, Anagahora, Shimoshidami, Moriyama-ku, Nagoya, 463-8560, Japan;*
*[4] Research & Development Center, Archer Daniels Midland, 1001 N Brush College Rd., Decatur, IL 62521, USA;*
*[5] Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Freie Universität Berlin, Königin-Luise-Straße 2+4, 14195 Berlin, Germany;*
*[6] Department of Chemistry, University of Massachusetts Boston, Boston MA 02125, USA;*
*[7] Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain;*
*[8] IKERBASQUE, Basque Foundation for Science, María Díaz de Haro 3, Plaza Bizkaia, 48013 Bilbao, Spain.*
*e-mail: vadimsoloshonok@gmail.com*

Amino acids are fundamental to virtually every aspect of biological science and healthcare serving as the cornerstone of molecular structure and function. Research has now expanded beyond naturally occurring amino acids to tailor-made derivatives enabling precise control over biological processes and unlocking new functionalities unattainable with standard amino acids and peptides. One of the most exciting advancements is the development of fluorine-containing amino acids which integrate the powerful pharmacological effects of fluorine with the structural adaptability of amino acid frameworks. This review explores the synthesis of fluorinated amino acids bearing unsaturated residues—a highly valuable and distinct subgroup within the broader class of fluorinated amino acids. These specialized molecules feature fluorine directly bonded to $sp^2$-hybridized carbon atoms, effectively replicating the electronic properties of aromatic substitution without relying on an aromatic system. The olefinic placement of fluorine enhances molecular stability and imparts specific steric, geometric, chemical, and biological characteristics critical for drug design and bioactive compound development. The synthetic strategies presented herein are organized around key transformations, including α alkylation of amino acids, side chain elaboration, introduction of amino and/or carboxylic functionalities, and the generation of unsaturation within fluoro-amino acid cores. By compiling these methodologies we aim to provide a comprehensive resource and a source of inspiration for researchers engaged in synthetic and medicinal chemistry, drug discovery, and organofluorine chemistry.

**Key words**: Fluorine, Amino Acids, Fluorinated Pharmaceuticals, Unsaturated/Olefinic Groups, Synthesis, Nucleophilic and Electrophilic Glycine Equivalents.

*INTRODUCTION*. Amino acids, the fundamental building blocks of proteins, have played a crucial role in medicine and drug development for centuries. Their significance was first recognized in the 19th century when scientists began isolating and identifying individual amino acids from natural sources. The discovery of essential amino acids, those that the human body cannot synthesize, highlighted their importance in nutrition and metabolic health [1–5].

Early pharmaceutical applications of amino acids revolved around dietary supplements and medical nutrition therapy for conditions such as malnutrition and metabolic disorders. As biochemical research advanced in the 20th century, amino acids became central to developing hormonal therapies, such as insulin synthesis, which revolutionized diabetes treatment. Additionally, peptide-based drugs derived from amino acids, such as exenatide for diabetes, enfuvirtide for AIDS, and goserelin for breast cancer among many others, have paved the way for new antibiotics, enzyme inhibitors, and vaccines [6–9].

In modern pharmaceutical science, amino acids play a pivotal role in biotechnologically produced drugs (biopharmaceuticals), targeted therapies, and synthetic medicinal compounds (small molecule pharmaceuticals). A significant breakthrough—a paradigm shift in drug design – has emerged with the strategic use of modified tailor-made amino acids [10–17] instead of their natural counterparts. These custom engineered amino acids can be rationally designed to enhance drug stability, solubility, and absorption thereby optimizing biological efficacy and enabling more precise targeted delivery [18–22].

The unique combination of fluorine's beneficial properties [23–30] with the inherent structural versatility of amino acids [31–36] underscores the significant value of fluorine-containing amino acids in drug design. These tailor-made amino acid derivatives allow for the precise fine tuning of drug activity and pharmacokinetic profiles leading to the development of more targeted and efficient treatments. As a result, the selective synthesis of fluorinated α [37–46] and β amino acids [47–56] has been an area of intense research activity in the past two decades [57–77]. The strategic introduction of fluorine into bioactive molecules has evolved into a well-established strategy in drug development culminating in the approval of numerous fluorinated pharmaceuticals by the US Food and Drug Administration (FDA) [78–80]. Ultimately, the combined incorporation of fluorine and amino acid scaffolds into drug design represents a substantial advancement in medicinal chemistry opening new possibilities for the development of more effective and safer therapeutic interventions.

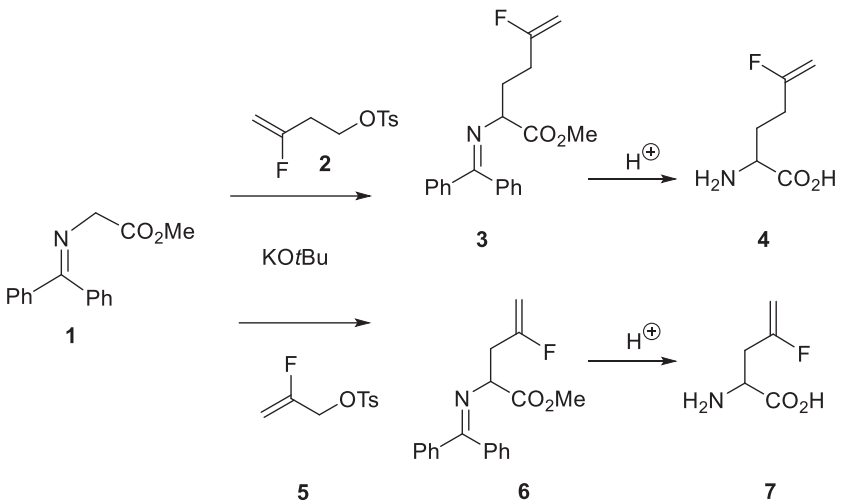
This review covers the synthesis of tailor-made amino acids bearing fluorine-containing unsaturated residues, a distinct and valuable subgroup within the broader class of fluorinated amino acids. These unique amino acids feature fluorine directly bonded to $sp^2$-hybridized carbon atoms mimicking the electronic effects of aromatic substitution but without the aromatic framework. The olefinic positioning of fluorine enhances its stability and imparts specific steric, geometric, chemical, and biological properties. The synthetic strategies discussed herein are organized by key transformations: α-alkylation of amino acids, elaboration of amino acid side chains, introduction of amino and/or carboxylic functionalities, and the generation of unsaturation on pre-existing fluoro-amino acid cores. We

anticipate that this compilation will serve as a valuable resource and source of inspiration for researchers and practitioners across synthetic and medicinal chemistry, drug design, and the wider field of organofluorine chemistry.

*EXPERIMENT AND DISCUSSION OF THE RESULTS.*

**α-Alkylation of glycine and higher α amino acids.**

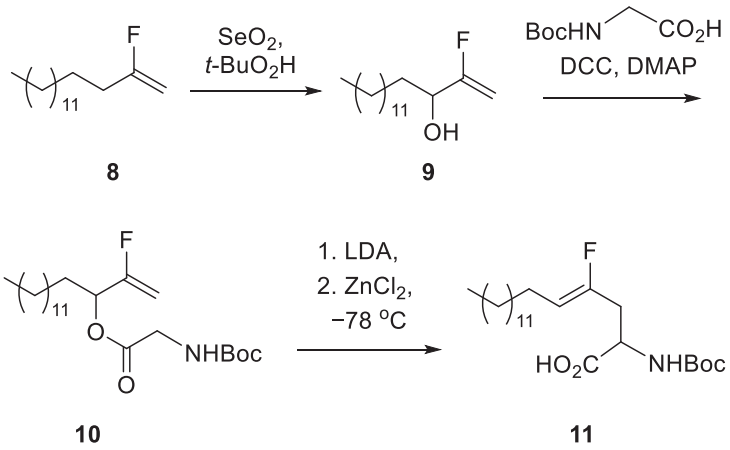
The alkylation of nucleophilic glycine, alanine, and other α amino acids represents one of the most versatile and widely employed methods for synthesizing tailor-made amino acids with novel side chains [81–83]. This approach, applied to the synthesis of fluoro-olefinic amino acids is illustrated in Scheme 1. The benzophenone Schiff base of glycine ester **1**, introduced by G. Stork [84] and further refined by M. O'Donnell [85], was alkylated with 2-fluorobut-1-ene **2** yielding product **3** in moderate yield. Hydrolysis of intermediate **3** produced 2-amino-5-fluorohex-5-enoic acid (**4**) in an overall yield of ca. 20% [86].




Scheme 1. Synthesis of unsaturated fluoro-amino acids **4** and **7** via alkyl halide alkylation.

Under identical conditions, the 2-fluoro-allyl alkylating reagent fluoro-allyl tosylate **5** (Scheme 1) was employed to synthesize 2-amino-4-fluoropent-4-enoic acid (**7**) in a significantly improved yield of 80–90% [86].

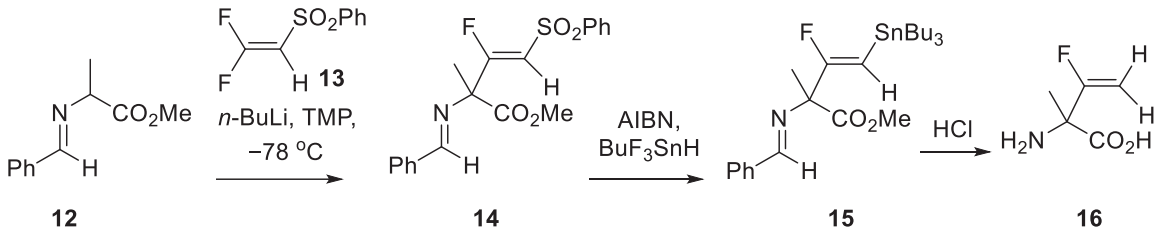
The same research group led by G. Haufe [87] reported the synthesis of lipophilic amino acid **11** (Scheme 2) featuring a fluorovinyl group as part of a $C_{16}$ side chain. The reaction sequence begins with commercially available fluoro-olefin **8**, which is hydroxylated to alcohol **9** under oxidative conditions using $SeO_2$ and *tert*-butyl hydroperoxide. Subsequently, alcohol **9** is coupled with N-Boc glycine forming ester **10** using condensation reagents *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminophenol (DMAP). Finally, ester **10** undergoes treatment with lithium diisopropylamide (LDA) to initiate the Claisen rearrangement yielding amino acid **11** in an impressive 86% yield.




Scheme 2. Synthesis of fluorovinyl amino acid **11** via Claisen rearrangement.

It is worth noting that fluorovinyl-containing amino acids **4**, **7**, and **11** could serve as suitable substrates for dynamic kinetic resolution (DKR) through the direct formation of chiral Ni(II) complexes [88–90] enabling their preparation in both enantiomeric forms.

The synthesis of quaternary amino acids through the alkylation of alanine or higher amino acids presents a significantly greater challenge compared to the alkylation of their glycine derivatives.

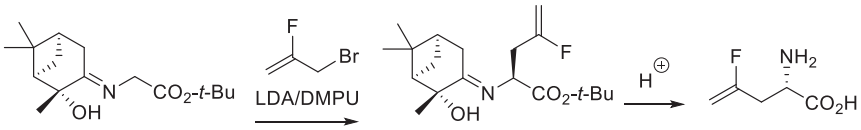



Scheme 3. Synthesis of α-(1'-fluoro)vinyl amino acid **16**.

This is due to the combined impact of steric and electronic factors which necessitate much more rigorous reaction conditions [91–93]. The vinylation variant of this process closely parallels alkylation, similarly requiring strong bases and highly controlled reaction environments [94]. For instance, the benzophenone-derived Schiff base of glycine ester **1** (Scheme 1) is unsuitable for the synthesis of quaternary amino acids due to its significant steric bulk. Instead, the less sterically demanding benzaldehyde-derived Schiff base **12** (Scheme 3) is typically employed for quaternization of alanine and higher amino acids. The process begins with aldimine **12** which is treated with *n*-BuLi and 2,2,6,6-tetramethylpiperidine (TMP) to generate the corresponding enolate. This enolate is then reacted with 1-(2,2-difluorovinylsulfonyl)benzene (**13**) yielding the vinylated product **14** in up to 91% yield. Subsequently, the sulfonyl group in

**14** is displaced using $Bu_3SnH$ in the presence of azobisisobutyronitrile (AIBN) producing tributylstannane **15** in an excellent yield exceeding >90%. Finally, intermediate **15** is treated with HCl to remove the $SnBu_3$ group and to hydrolyze both the Schiff base and ester functional groups resulting in α-(1'-fluoro)vinyl amino acid **16**. This method demonstrates high generality as alanine can be substituted by various other amino acids featuring aliphatic, aromatic, or side chains containing appropriately protected carboxylic or amino functionalities [95].

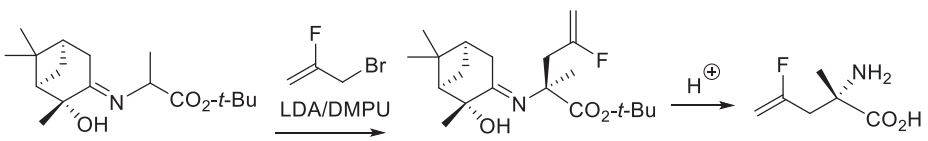
The asymmetric synthesis of (*S*)-2-amino-4-fluoropent-4-enoic acid (**19**) is achieved through the fluoro-allylation of the chiral Schiff base (*R*)-**17** (Scheme 4) [96]. The chiral nucleophilic glycine equivalent (*R*)-**17**, derived from 2-hydroxy-3-pinanone, is reacted with 3-bromo-2-fluoropropene at –78 °C in the presence of LDA and *N*,*N*'-dimethylpropyleneurea (DMPU) yielding the fluoro-allylated product (*S*)-**18** in 73% yield and diastereoselectivity exceeding 97%. Subsequent acidic hydrolysis of the Schiff base and deprotection of the carboxylic group results in the formation of amino acid (*S*)-**19**.




(*R*)-**17** (*S*)-**18** (*S*)-**19**

Scheme 4. Asymmetric synthesis of amino acid (*S*)-**19**.

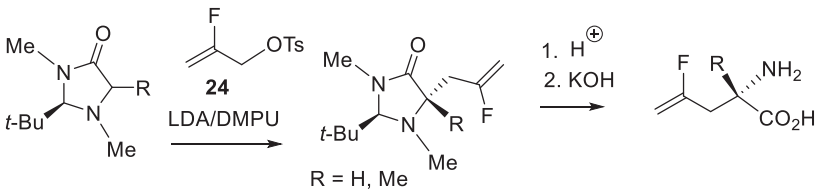
As shown in Scheme 5, this approach can be employed for the synthesis of the fluorinated quaternary amino acid (*S*)-**22**. The necessary Schiff base **20** is derived from (*R*,*R*,*R*)-2-hydroxy-3-pinanone and racemic alanine or either of its enantiomers. Since the fluoro-allylation reaction proceeds via the formation of the corresponding enolate, the initial configuration of the alanine residue does not influence the stereochemical outcome. Under strongly basic conditions, Schiff base (*R*)-**20** undergoes allylation to yield the product (*S*)-**21** in a moderate yield of 64% but with high diastereoselectivity that exceeds 97%. Subsequent hydrolytic deprotection of both the amino and carboxylic functional groups results in the formation of the fluorinated quaternary amino acid (*S*)-**22** [97]. It should be noted that the sense of asymmetric induction observed was consistent with that seen in similar transformations of glycine-derived compounds (Scheme 4).




(*R*)-**20** (*S*)-**21** (*S*)-**22**

Scheme 5. Asymmetric synthesis of quaternary amino acid (*S*)-**22**.

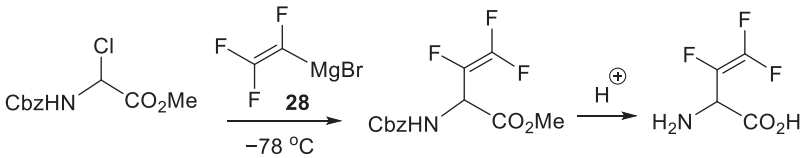
The same research group led by G. Haufe [98] investigated the application of the chiral glycine equivalent imidazolidinone (*R*)-Boc-BMI **23**, introduced by D. Seebach [99], for the asymmetric synthesis of fluoro-amino acids **26** (Scheme 6). The fluoro-allylation of imidazolidinone (*R*)-**23**, derived from glycine (R = H) or alanine (R = Me), was carried out using fluorovinyl tosylate **24** in the presence of LDA/DMPU. This reaction yielded products **25** in 89% and 84% yields for R = H and Me, respectively, along with excellent diastereoselectivities exceeding >97%. Functional group deprotection was performed in two stages: first, the *tert*-butyl group was removed under acidic conditions and then subsequently the N-methyl amide group was cleaved using KOH. However, the latter step caused partial racemization in the case of glycine-derived products due to the presence of a relatively acidic α hydrogen.




Scheme 6. Asymmetric synthesis of fluoro-amino acid **26**.

In all the methods reported above for the asymmetric synthesis of fluoro-allyl amino acids, the fluorine atom on the allylating reagents was found to exert virtually no influence on the chemical or stereochemical outcome of the reactions. It can be postulated that utilizing these reagents for the fluoro-allylation of other, more effective and practical nucleophilic glycine and alanine equivalents [100–105] may offer a significantly improved pathway for the efficient synthesis of this class of fluoro-olefinic amino acids.

Finally, application of the electrophilic glycine equivalent **27** (Scheme 7) to the synthesis of trifluorovinyl amino acid **30** [106] leverages the unique reactivity of electrophilic reagent **27** enabling efficient nucleophilic substitution of the chlorine with various Grignard reagents. Specifically, the reaction of **27** with the Mg-trifluorovinyl reagent **28** proceeds cleanly in tetrahydrofuran (THF) at −78 °C providing product **29** in good yield. Subsequent acidic hydrolysis of **29** yields trifluorovinyl amino acid **30**.

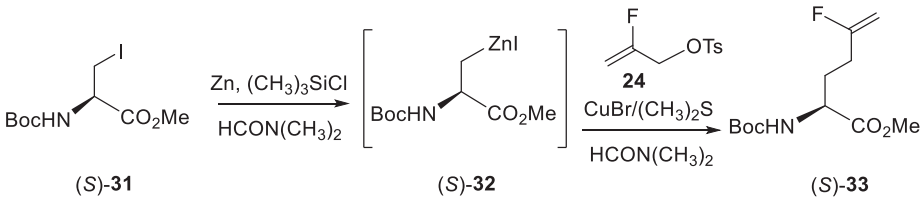



Scheme 7. Synthesis of trifluorovinyl amino acid **30**.

*Elaboration of amino acid side chains.*

The elaboration of amino acid side chains involves modifying their structures to introduce new groups or functional groups, thereby

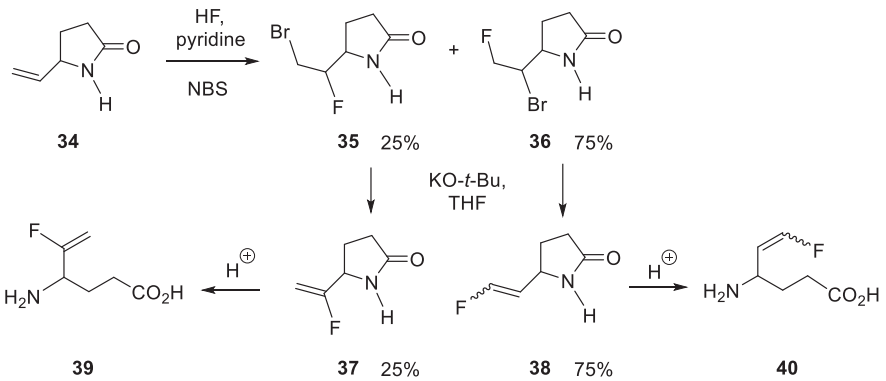
expanding their chemical versatility and functionality. The process typically starts with protecting reactive groups such as amino or carboxylic groups to prevent unwanted reactions. The side chain can then be selectively transformed using techniques such as alkylation, acylation, or coupling reactions. These modifications can introduce fluorine atoms, aromatic groups, hydroxyls, or other functionalities enabling the synthesis of tailor-made amino acids. Such elaboration is crucial for designing bioactive molecules, catalysts, or advanced materials as it allows fine tuning of structural and functional properties for specific applications. A representative transformation of this type is illustrated in Scheme 8.




Scheme 8. Synthesis of amino acid (*S*)-**33**.

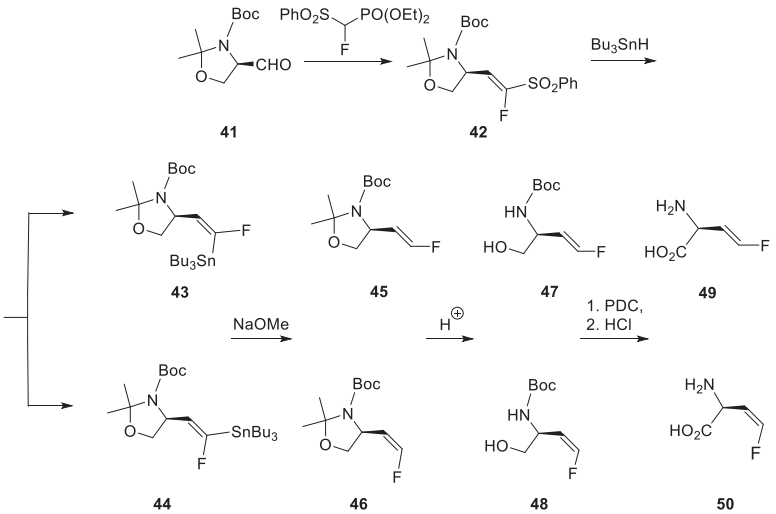
Methyl *N*-Boc-(*S*)-2-amino-5-fluorohex-5-enoate {(*S*)-**33**} was synthesized starting from the alanine iododerivative (*S*)-**31**. The reaction, carried out in the presence of activated zinc, results in the formation of intermediate (*S*)-**32**. Subsequent treatment of intermediate (*S*)-**32** with CuBr, followed by allylation using tosylate **24**, yielded product (*S*)-**33** in 61% yield [107]. Notably, the optical integrity of the compound remains intact throughout this process enabling the preparation of enantiopure (*S*)-**33**.

The preparation of fluorinated γ amino acids **39** and **40** is illustrated in Scheme 9 [108, 109]. The synthesis begins with vinyl pyrrolidone **34** which undergoes fluorination–bromination of the double bond using a combination of HF/pyridine and *N*-bromosuccinimide (NBS) yielding a mixture of products **35** and **36** in a 25:75 ratio, respectively. The elimination of HBr under strongly basic conditions produces the unsaturated compounds **37** and **38**. Following the separation of isomers **37** and **38**, hydrolysis of the amide bond results in γ-fluorovinyl-γ-amino acids **39** and **40**.



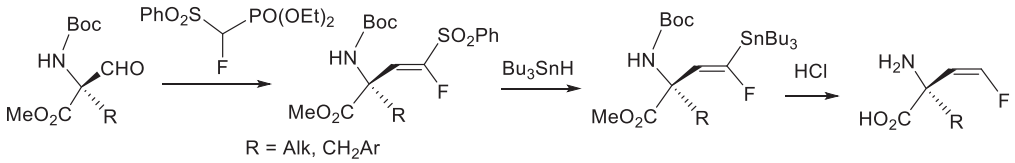

Scheme 9. Preparation of γ amino acids **39** and **40**.

Enantiopure 4-formyl-oxazolidine **41** (Scheme 10), derived from natural serine, is extensively used in organic synthesis as a masked equivalent of generic amino acids featuring an α formyl group ready for functional elaboration [110]. Compound **41** has been successfully applied in the preparation of isomeric fluorovinyl amino acids **49** and **50**. In the initial step, the formyl group in **41** reacts with diethyl fluoro(phenylsulfonyl)methylphosphonate yielding the corresponding vinyl sulfone **42**. Vinyl sulfone **42** is then treated with $Bu_3SnH$ resulting in the formation of isomeric products **43** and **44**. Following separation via column chromatography, each isomer is treated with strong base to produce the respective fluorovinyl derivatives **45** and **46**. Subsequent hydrolytic opening of the oxazolidine ring in **45** and **46**, combined with oxidation of the alcohol functionality in **47** and **48** using pyridinium dichromate (PDC), and final N-Boc deprotection yields the fluorovinyl amino acids **49** and **50** in overall yields of ca. 10% [111].



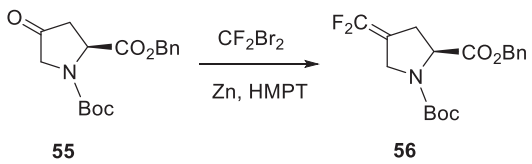

Scheme 10. Synthesis of amino acids **49** and **50**.

The reaction sequence described in Scheme 10 can be effectively utilized for the preparation of fluorovinyl quaternary amino acids [112]. The process begins with compounds **51** (Scheme 11), which feature appropriately protected amino and carboxyl groups. Compounds **51** react with α-fluoro-α-(phenylsulfonyl)methyl phosphonate to yield α-fluorovinyl sulfones **52**. These reactions are performed in the presence of lithium hexamethyldisilazide (LiHMDS) as a strong base at –78 °C depending on the nature of the side chains. Moreover, each compound **52** is obtained as a single *E* geometric isomer. The sulfone group in compounds **52** is subsequently converted to stannane derivative **53**. In the final step, acidic hydrolysis leads to the formation of (*Z*)-α-(2'-fluoro)vinyl amino acids **54** in yields ranging from 52–93%. This method demonstrates broad tolerance for diverse substituents, accommodating both natural and tailor-made amino acids including simple alkyl or benzyl-type groups as well as substituents containing appropriately protected functional groups.



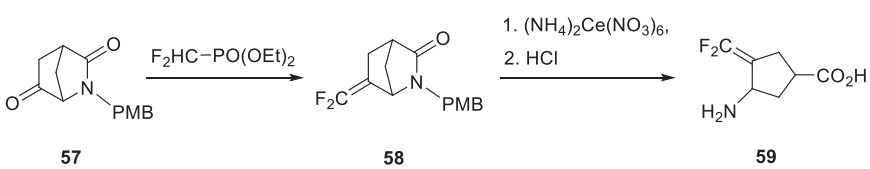

Scheme 11. Synthesis of (*Z*)-α-(2'fluoro)vinyl amino acids **54**.

Sterically constrained prolines are highly valued by chemical biologists, molecular biophysicists, and medicinal chemists for their ability to modulate the conformational landscape of peptides and drug candidates during the discovery stage [113–116]. An example of the synthesis of such conformationally constrained prolines is presented in Scheme 12. The procedure involves the addition of $CF_2Br_2$ to the carbonyl group of keto derivative **55**, facilitated by zinc and hexamethylphosphoramide (HMPT), to yield 4-difluoromethyleneproline **56** in 48% yield. Compound **56** was subsequently utilized for the preparation of the corresponding saturated 4-difluoromethyl-L-proline or, with orthogonal protection, employed in peptide synthesis [117].




Scheme 12. Synthesis of conformationally constrained 4-difluoromethyleneproline **56**.

Considering the remarkable biological significance of γ aminobutyric acid (GABA) and its derivatives, conformationally constrained GABA analogs are highly sought after in biochemistry and drug design [118–120]. For instance, amino acid **59** (Scheme 13) features two distinct steric/conformational constraints: a five-membered ring and a C=C double bond. The addition of two fluorine atoms to the double bond introduces particular effects such as enhanced polarity and increased lipophilicity, both of which are crucial for interactions with biological receptors. The synthesis of amino acid **59** begins with the reaction of cyclic amidoketone **57** with diethyl difluoromethylphosphonate, yielding difluoromethylene derivative **58** [121]. Subsequent deprotection of the amide nitrogen in **58**, followed by hydrolytic cleavage of the amide bond, completes the reaction sequence producing the cyclic difluoromethylene GABA analog **59**.

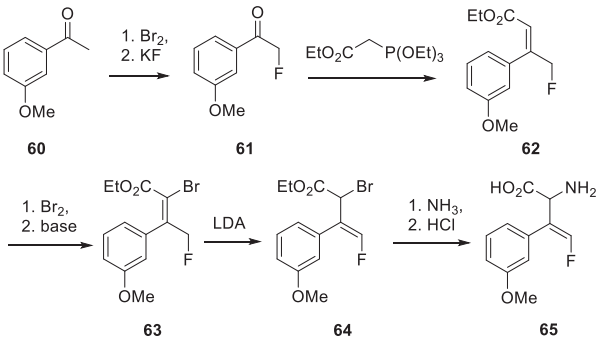



Scheme 13. Preparation of conformationally constrained cyclic γ amino acid **59**.

*The introduction of carboxyl and/or amino groups onto a fluoro-olefinic framework.*

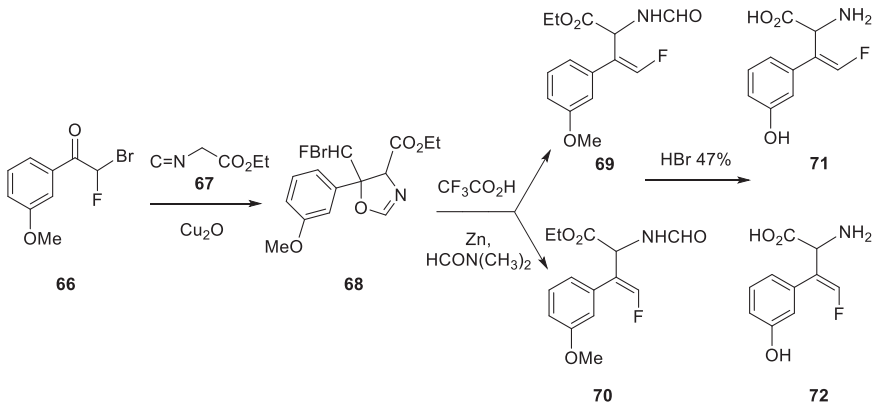
The incorporation of carboxyl or amino functionalities onto an existing organic framework combines standard and well established approaches from organofluorine and amino acid chemistry. Due to the stability of the C($sp^2$)–F bond, fluoro-olefinic organic compounds typically exhibit resistance to nucleophilic substitution reactions which are commonly employed to introduce carboxyl or amino groups [122].

A representative example of this approach (Scheme 14) is the synthesis of (*E*)-β-(fluoromethylene)-*m*-tyrosine (**65**) [123, 124] which begins with the bromination of commercially available methoxy-substituted acetophenone **60** followed by substitution of the bromine with fluorine using potassium fluoride to yield fluoro-acyl **61** in 54% yield. Compound **61** is then treated with triethyl phosphonoacetate in the presence of NaH producing the unsaturated intermediate **62** as a mixture of *Z* and *E* isomers in a ratio of 8:1 in 80% yield. Subsequent bromination of intermediate **62** followed by the elimination of HBr using piperidine generates the bromo derivative **63**. The key step in this synthesis is the LDA-assisted isomerization of **63** into the thermodynamically more stable compound **64** which possesses a more acidic hydrogen at the α position relative to the ester group. The final steps include the introduction of an amino group through treatment of **64** with ammonia, neutralization, and hydrolytic deprotection of the carboxylic group ultimately affording compound (*E*)-β-(fluoromethylene)-*m*-tyrosine (**65**).




Scheme 14. Synthesis of (*E*)-β-(fluoromethylene)-*m*-tyrosine (**65**).

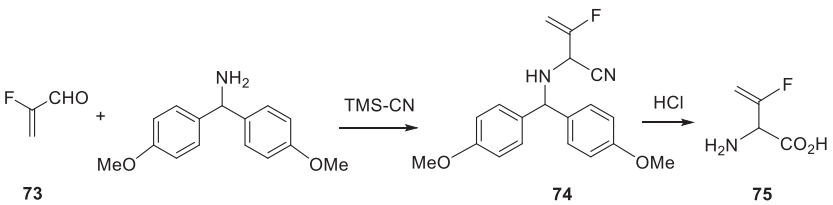
The reactions of isocyanoacetates with fluorinated carbonyl compounds represent a well established method for the preparation of fluorinated α-amino-β-hydroxy acids [125–127]. An intriguing application of this approach for the synthesis of unsaturated derivatives is outlined in Scheme 15 [123, 124]. The cyclization of bromofluoroacetophenone **66** with isocyanoacetate **67** catalyzed by $Cu_2O$ efficiently produces oxazoline intermediate **68** in an excellent 90% yield. Subsequent treatment of the heterocyclic product **68** with trifluoroacetic acid and activated zinc results in oxazoline ring opening forming a mixture of geometric isomers **69** and **70** which are separable by column chromatography. Finally, refluxing **69** and **70** in 47% aqueous HBr removes all protecting groups yielding the geometric isomers **71** (*Z*) and **72** (*E*) of β-(fluoromethylene)-*m*-tyrosine in ca. overall yields of 25%.




Scheme 15. Synthesis of the geometric isomers **71** (*Z*) and **72** (*E*) of β-(fluoromethylene)-*m*-tyrosine.

During the enzymatic enantioresolution of the geometric isomers **71** (*Z*) and **72** (*E*) of β-(fluoromethylene)-*m*-tyrosine, it was found [128] that only the *E* isomer **72** exhibited biological activity undergoing reactions with α-chymotrypsin, facilitating the preparation of the *R* and *S* enantiomers of (*E*)-β-(fluoromethylene)-*m*-tyrosine (**72**). While it is surprising that the enantiomers of **71** were unreactive, as a result, enzymatic treatment provides a useful method for separating both the geometric and optical isomers [128]. Additionally, a compelling avenue for further investigation would involve chemical deracemization via DKR processes [129–131] to examine the influence of geometric configuration on the stereochemical outcome.

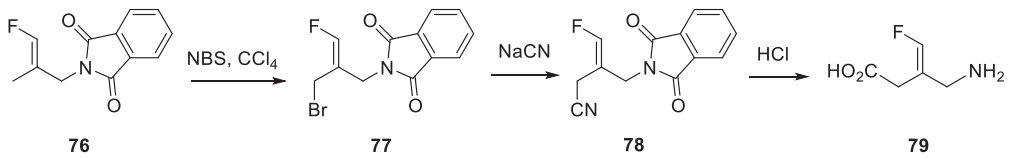
The Strecker synthesis of amino acids is one of the oldest and most classical chemical reactions [132]. An example of its application in the synthesis of fluoro-olefinic amino acids is depicted in Scheme 16 [133]. In this process, 2-fluoroacrolein (**73**) reacts with *bis*(4-methoxyphenyl)methanamine as the amino group source and trimethylsilylcyanide (TMS-CN) as the carboxylic group source to form intermediate **74**. This intermediate is subsequently hydrolyzed to yield 2-amino-3-fluorobutenoic acid (monofluorovinyl glycine, **75**) in an overall yield of ca. 30%.




Scheme 16. Synthesis of 2-amino-3-fluorobutenoic acid (**75**).

In addition to α amino acids, the introduction of amino acid functionalities can also be applied to the preparation of fluoro-olefinic GABA derivatives which not only imparts fluorine effects, but also strategically restricts the number of accessible conformations. As

illustrated in Scheme 17 [123, 124], phthalimide **76** undergoes bromination at the methyl group to yield bromo derivative **77** in high yield. The bromide in **77** is subsequently substituted with a cyanide group via reaction with sodium cyanide in dimethyl sulfoxide producing nitrile **78**. Finally, treatment of compound **78** with 6 *N* hydrochloric acid under reflux conditions results in the hydrolysis of the nitrile group and the removal of the phthalimide protection leading to the formation of γ amino acid **79**.



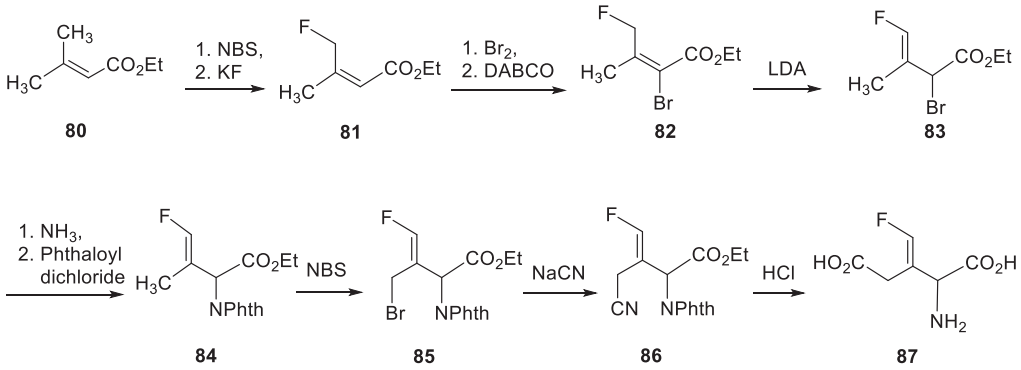

Scheme 17. Preparation of fluoromethylene GABA derivative **79**.

Glutamic acid is a crucial amino acid involved in protein synthesis and nitrogen metabolism. It supports immune function, provides energy for immune cells, and serves as a precursor to amino acids such as glutamine. Additionally, as glutamate it acts as the primary excitatory neurotransmitter in the brain playing an essential role in synaptic transmission, learning, and memory [134–138]. The remarkable biological versatility of glutamic acid and its derivatives has inspired significant synthetic efforts to develop various tailor-made derivatives [139–142].

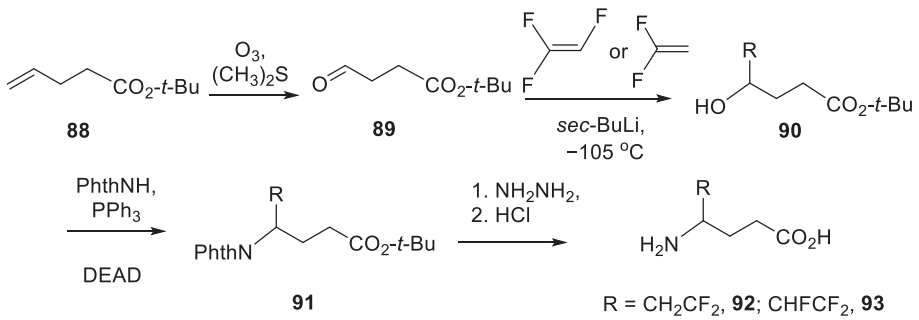
The synthesis of glutamic acid **87** featuring a fluorine-containing unsaturated moiety is illustrated in Scheme 18 [123, 124]. The procedure begins with the electrophilic bromination of inexpensive and commercially available ethyl 3,3-dimethylacrylate (**80**) using NBS followed by substitution of the bromine with fluorine via potassium fluoride yielding fluoro-acrylate **81**. Compound **81** is then subjected to radical bromination with bromine followed by dehydrobromination using 1,4-diazabicyclo[2.2.2]octane (DABCO) producing α-bromofluoro-acrylate **82**. The subsequent isomerization of **82** to **83**, facilitated by LDA, is driven by the greater thermodynamic stability of **83** due to the higher acidity of the proton at the α position relative to the ester functional group. The bromine in **83** is replaced by an amino group through treatment with ammonia and the amino group is then protected using phthaloyl dichloride yielding protected amino acid **84**. A second carboxylic function is introduced via electrophilic bromination of **84** with NBS producing bromo derivative **85**. Substitution of bromine with a CN group is achieved using sodium cyanide generating nitrile **86**. The final step involves hydrolysis and deprotection of compound **86** under acidic conditions to yield (*E*)-β-fluoromethyleneglutamic acid (**87**).

The general method for preparing GABA derivatives featuring di- and trifluorovinyl groups is outlined in Scheme 19 [108]. The process begins with the oxidation of unsaturated ester **88** to aldehyde **89** via standard ozonolysis. The addition of 1,1-difluoroethene or 1,1,2-trifluoroethene to the carbonyl group of **89** is conducted under strictly controlled conditions at −105 °C using *sec*-BuLi as base. The resulting

alcohols **90** are then reacted with phthalimide in the presence of $PPh_3$ and diethyl azodicarboxylate (DEAD) yielding protected amino acids **91**. The final steps involve deprotection of the amino group using hydrazine followed by acidic hydrolysis of the ester group. This procedure yields 4-amino-6,6-difluoro-5-hexenoic acid (**92**) and 4-amino-5,6,6-trifluoro-5-hexenoic acid (**93**), both of which are GABA analogs presenting a wide range of opportunities for exploration in biochemistry and medicinal chemistry.



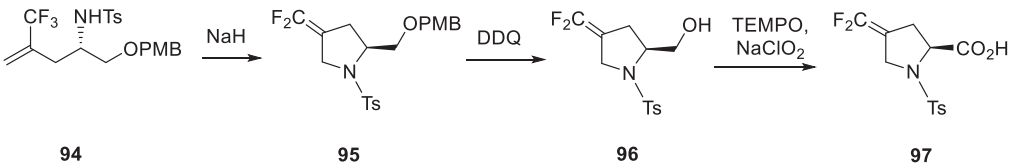

Scheme 18. Synthesis of (*E*)-β-fluoromethyleneglutamic acid (**87**).




Scheme 19. Synthesis of GABA analogs 4-amino-6,6-difluoro-5-hexenoic acid (**92**) and 4-amino-5,6,6-trifluoro-5-hexenoic acid (**93**).

As shown in Scheme 12, (*S*)-3-(difluoromethylene)proline can be synthesized from (*S*)-3-oxoproline **55** using $CF_2Br_2$/Zn [117]. An alternative method for preparing this highly intriguing conformationally constrained and fluorine-containing proline analog is outlined in Scheme 20 [143]. This approach begins with the cyclization of a trifluoromethyl-containing and appropriately protected amino alcohol **94**. The reaction requires strong base to deprotonate the NH group and is conducted in dimethylformamide at 120 °C for 4 hours. Cyclic compound **95** is then treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to remove the *p*-methoxybenzyl (PMB) protecting group. This reaction occurs in a $CH_2Cl_2$–MeOH solvent mixture at ambient temperature but requires ca. two days to

complete. The deprotected alcohol **96** is oxidized to a carboxylic acid using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/$NaClO_2$ under mild conditions in acetonitrile at ambient temperature. However, this step progresses only slowly, taking ca. seven days. Despite the extended reaction times, the mild conditions result in excellent yields exceeding 90% at every step of the process. This method ultimately provides NTs-protected (*S*)-3-(difluoromethylene)proline (**97**) making it a synthetically appealing approach.

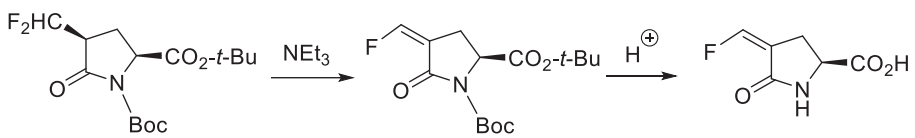



**94** **95** **96** **97**

Scheme 20. Synthesis of (*S*)-3-(difluoromethylene)proline **97**.

**Generation of unsaturation on pre-existing fluoro-amino acid cores.**

Sterically and conformationally constrained pyroglutamic acids are vital in medicinal chemistry due to their distinct ability to modulate protein structure and function. These derivatives enable the targeted restriction of peptide backbone flexibility, stabilizing specific conformations that enhance binding affinity and selectivity for biological targets. Consequently, the synthesis of substituted pyroglutamic acids has garnered considerable attention [144–146]. The synthesis of (*S*)-4-monofluoromethylenylpyroglutamic acid (**100**) is outlined in Scheme 21 [147]. The process begins with 4-difluoromethylpyroglutamate (**98**), derived from naturally occurring 4-hydroxyproline [123, 124]. Treatment of **98** with triethylamine in acetonitrile induces dehydrofluorination providing compound **99** in yields of up to 90%. The final step involves standard acidic deprotection of the N-Boc and *tert*-butyl ester groups under mild conditions affording free (*S*)-4-monofluoromethylenylpyroglutamic acid (**100**).



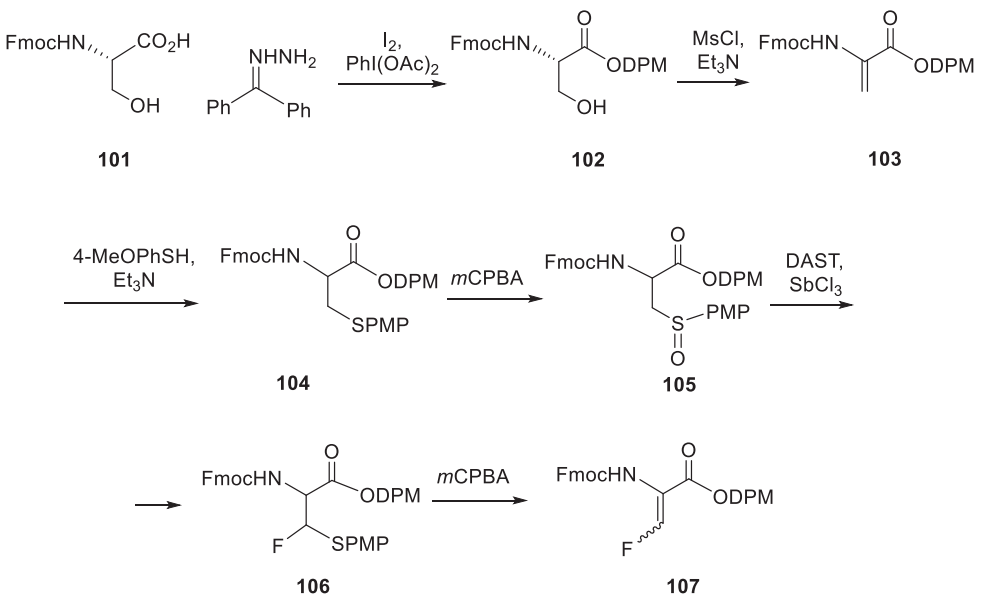

**98** **99** **100**

Scheme 21. Preparation of (*S*)-4-monofluoromethylenylpyroglutamic acid (**100**).

The fluoro–Pummerer rearrangement is a variant of the classic Pummerer rearrangement [148] in which sulfur-containing compounds undergo structural reorganization via an electrophilic activation process. In this modified reaction, the introduction of fluorine enhances the electrophilicity of the sulfonium intermediate leading to regioselective rearrangement and functionalization of adjacent carbon centers [149, 150]. The reaction is valuable in

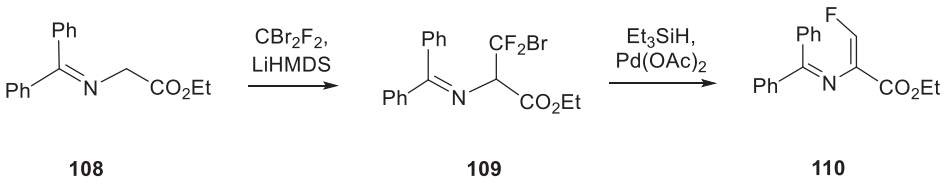
synthetic chemistry, particularly for constructing fluorinated heterocycles and bioactive molecules with tailored electronic and steric properties.

An example of the application of the fluoro–Pummerer rearrangement as a key step in the synthesis of β-fluorodehydroalanine **107** is illustrated in Scheme 22 [151]. The process begins with the reaction of N-Fmoc-protected serine **101** with 1-(diphenylmethylene)hydrazine in the presence of iodine and (diacetoxyiodo)benzene yielding compound **102** in 90% yield while installing the ester protective group. Compound **102** is then converted into the corresponding ester via reaction with mesyl chloride followed by elimination of methanesulfonic acid using triethylamine affording dehydroalanine **103** in 82% yield. Addition of 4-methoxybenzenethiol to the double bond in **103** produces derivative **104** in 70% yield which is subsequently oxidized to sulfoxide **105** using *m*-chloroperoxybenzoic acid (*m*CPBA) in 95% yield. The key fluoro–Pummerer rearrangement step is performed by treating **105** with diethylaminosulfur trifluoride (DAST) in the presence of $SbCl_3$ resulting in fluoro derivative **106** in 70% yield. The final two steps involve oxidation of the sulfur atom in **106** followed by thermal elimination to regenerate the double bond ultimately producing fluorodehydroalanine **107** as a 1:1 mixture of *Z* and *E* isomers in 47% combined yield.



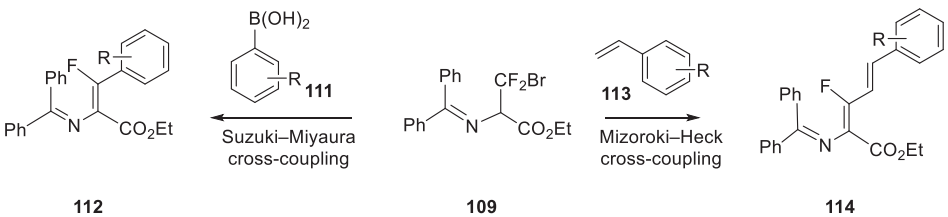

Scheme 22. Synthesis of β-fluorodehydroalanine **107**.

An improved strategy for the preparation of (*Z*)-β-fluorodehydroalanine (**110**) is outlined in Scheme 23 [152]. The synthesis begins with the alkylation of glycine Schiff base **108** using $CBr_2F_2$ and LiHMDS as base yielding bromodifluoro alanine **109**. Compound **109** is then subjected to selective reduction with $Et_3SiH$ in the presence of $Pd(OAc)_2$ resulting in the stereoselective formation of (*Z*)-β-fluorodehydroalanine (**110**) in 60% yield from **108**.




Scheme 23. Synthesis of (*Z*)-β-fluorodehydroalanine (**110**).

Bromodifluoro alanine **109** has proven to be a highly versatile starting material for the generalized synthesis of various β-substituted derivatives of β-fluorodehydroalanine via Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions (Scheme 24) [152]. For instance, Schiff base **109** undergoes cross-coupling with *p*-methoxyphenylboronic acid (**111**) in the presence of potassium carbonate, water (150 μL), $PdCl_2$ (5 mol%), and $PPh_3$ (10 mol%) in 1,4-dioxane at 100 °C for 2 hours yielding fluorinated dehydroamino acid **112** in 65% yield. Alternative phosphine ligands, such as 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)-biphenyl (Davephos), 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthen (Xantphos), 1,1'-bis(diphenylphosphino)ferrocene (dppf), or 1,2-bis(diphenylphosphino)ethane (dppe), as well as bases such as $K_3PO_4$, $KHCO_3$, KOH, $Et_3N$, or $Cs_2CO_3$, can be used to optimize the reaction conditions for different substituents R on boronic acid **111**. Using this method, over 50 distinct derivatives of **112** have been synthesized in yields ranging from 49–93%.




Scheme 24. Synthesis of β-substituted (*Z*)-β-fluorodehydroalanine derivatives **112** and **114** via Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions.

In the Mizoroki–Heck cross-coupling reaction, Schiff base **109** and styrene **113** are treated in THF at 100 °C with $Pd(PPh_3)Cl_2$ (5 mol%), NaI (3 eq.), and $Et_3N$ (5 eq.) yielding diene amino acids **114**. Styrenes bearing both electron-donating and electron-withdrawing substituents were well tolerated (12 examples) affording the desired products in moderate-to-good yields of 45–82%. Notably, the stereoselectivity was excellent, consistently favoring the (2*Z*,4*E*)-isomer irrespective of the substituents [152].

*CONCLUSIONS.* As discussed, the current wealth of synthetic methodologies enables access to a diverse range of tailor-made amino acids featuring mono-, di-, and trifluorovinyl groups as well as mono- and difluoromethylene functionalities. These fluorinated substituents can be introduced into both linear and cyclic α amino acids as well as their γ amino

acid counterparts. While some approaches in this review are of primarily historical significance, others represent cutting-edge advancements in modern synthetic methodology. Despite these developments, fluorine-containing olefinic amino acids remain comparatively underexplored, particularly when contrasted with amino acids bearing aromatic or fully aliphatic fluorination. This underdevelopment likely stems from the inherent challenges of aliphatic fluorination which often results in highly polar fluorinated unsaturated bonds prone to unwanted addition and isomerization reactions. Consequently, aliphatic fluorination is largely absent in approved pharmaceutical drugs and agrochemicals. However, this landscape is poised to change with the growing scientific recognition of dehydroalanine's role in naturally occurring peptides. Post-translational modifications of peptides and proteins not only drive new therapeutic discoveries, but also serve as a catalyst for innovations in synthetic organic chemistry and chemical biology. Notably, in the past five years, remarkable progress has been achieved in visible light-driven radical conjugate addition to dehydroalanine enabling site-selective functionalization of peptides and proteins. These advancements have significantly expanded the scope of tailor-made amino acid synthesis while furthering the frontiers of bioconjugation and bioorthogonal chemistry [153–157]. As a result, renewed interest in fluorinated derivatives of dehydroalanine and other fluoro-olefinic amino acids is expected. Beyond their promising biological activities, fluorine-containing olefinic amino acids also offer unique opportunities for investigating the self-disproportionation of enantiomers (SDE) phenomenon [158–160]. Amino acids are known to exhibit a strong tendency for SDE in achiral chromatography, and due to their elevated volatility conferred by fluorinated unsaturated groups, these derivatives are particularly well suited for SDE via sublimation studies [161–163]. Given the regulatory significance of chiral drug characterization, examining SDE behavior in biologically active compounds [164–167] plays a crucial role in fulfilling US FDA requirements for chiral drug submissions [168–170]. With fluorinated compounds continuing to serve as essential tools across the pharmaceutical, agrochemical, and materials industries, and with increasing recognition of the benefits of unsaturated fluorine-containing motifs, research in this field is expected to grow substantially in the coming years.

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## СИНТЕЗ СПЕЦІАЛЬНО РОЗРОБЛЕНИХ АМІНОКИСЛОТ, ЩО МІСТЯТЬ ЗВ'ЯЗКИ C(sp²)–F

***Аліція Взорек[1], Цзяньлінь Хань[2], Тайзо Оно[3], Карел Д. Кліка[4], Даніель Беккер5, Вей Чжан[6], Вадим А. Солошонюк[7,8]****

*[1] Інститут хімії, Університет імені Яна Кохановського в Кельцях, вул. Університецька 7, 25–406 Кельце, Польща;*

[2] *Цзянсуський центр спільного інноваційного ефективного перероблення та використання лісових ресурсів, Хіміко-технологічний коледж, Нанкінський лісотехнічний університет, Нанкін 210037, Китай;*
[3] *Національний інститут передових промислових наук і технологій (AIST), 2266–98, Анагахора, Шимошідамі, Моріяма-ку, Нагоя, 463–8560, Японія;*
[4] *Науково-дослідний центр, Archer Daniels Midland, 1001 N Brush College Rd., Декейтер, Іллінойс 62521, США;*
[5] *Відділ фармацевтичної та лікарської хімії, Фармацевтичний інститут, Вільний університет Берліна, Кьонігін-Луїзе-Штрасе 2+4, 14195 Берлін, Німеччина;*
[6] *Хімічний факультет, Університет Массачусетса в Бостоні, Бостон, Массачусетс 02125, Сполучені Штати Америки;*
[7] *Відділ органічної хімії I, Хімічний факультет, Університет Країни Басків UPV/EHU, Пасео Мануель Лардізабаль 3, 20018 Сан-Себастьян, Іспанія;*
[8] *ІКЕРБАСКЕ, Баскська наукова фундація, вул. Марія Діас де Харо 3, Площа Бізкая, 48013 Більбао, Іспанія.*
*email: vadimsoloshonok@gmail.com*

Амінокислоти є фундаментальними практично для кожного аспекту біологічної науки та охорони здоров'я, слугуючи наріжним каменем молекулярної структури та функції. Дослідження тепер розширилися за межі природних амінокислот до спеціально розроблених похідних, що дало змогу точно контролювати біологічні процеси та відкривати нові функціональні можливості, недосяжні зі стандартними амінокислотами та пептидами. Одним із найцікавіших досягнень є розроблення фторвмісних амінокислот, які поєднують потужні фармакологічні ефекти фтору зі структурною адаптивністю амінокислотних каркасів. Цей огляд досліджує синтез фторованих амінокислот, що містять ненасичені залишки – надзвичайно цінну та окрему підгрупу в ширшому класі фторованих амінокислот. Ці спеціалізовані молекули характеризуються безпосереднім зв'язком фтору з $sp^2$-гібридизованими атомами вуглецю, ефективно відтворюючи електронні властивості ароматичного заміщення без використання ароматичної системи. Олефінове розташування фтору підвищує стабільність молекули та надає специфічних стеричних, геометричних, хімічних і біологічних характеристик, критично важливих для розроблення лікарських засобів та біологічно активних сполук. Представлені тут стратегії синтезу організовано навколо ключових перетворень, включаючи α-алкілування амінокислот, нарощування бічних ланцюгів, введення аміно- та/або карбоксильних функціональних груп і створення ненасиченості в межах фтороамінокислотних ядер. Збираючи ці методології, ми прагнемо надати вичерпний ресурс та джерело натхнення для дослідників, які працюють у галузях синтетичної та медичної хімії, розроблення лікарських засобів та органофторної хімії.

**Ключові слова**: фтор, амінокислоти, фторовані фармацевтичні препарати, ненасичені/олефінові групи, синтез, нуклеофільні та електрофільні еквіваленти гліцину.

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