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REVIEW

Discovery of biomimetic transamination as a general synthetic method for preparation of fluorine-containing amines and amino acids

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Abstract: In this perspective review article, we describe the discovery of azomethine-azomethine isomerization of fluorinated *N*-benzylimines and its further development into one of the most convenient, scalable, and practical synthetic methods for preparation of biologically relevant fluorinated amines and amino acids. Currently referred to as 1,3-Proton Shift Reaction, this method is widely used by organic chemists for synthesis of variety fluorinated amino compounds playing important role in the design of modern pharmaceuticals and agrochemicals.

Keywords: biomimetic reductive amination; fluorinated compounds; amines; α- and β-amino acids; drug design.

Introduction

In 1980s the spectacular future role of fluorine in drug discovery has been far from obvious. Handful of fluorinated pharmaceuticals on the market, such as fludrocortisone **1** [1] and 5-fluorouracil **2** [2] (Figure 1), were considered as a mere curiosity since the extremely poisonous properties of a few naturally occurring fluoroorganic compounds [3] were very well known [4].

On the other hand, amino acids (AAs) are among the most ubiquitous naturally occurring compounds and serve numerous biological functions in living organisms [5]. Traditionally, naturally occurring and tailor-made (synthetic) AAs are being quite frequently used in the modern drug design [6, 7]. Clairvoyant or not, the decision made by Academician V.P. Kukhar in the late 1980s to initiate a new line of research targeting synthesis and bioevaluation of fluorine-containing AAs turn out to be one of the most successful and prolific legacies of the Ukrainian science of chemistry [8]. Nowadays, the introduction of fluorine-containing substituents into the structure of a drug candidate is a rapidly growing trend in the design of modern drugs [9, 10]. Rational, selective fluorination allows for fine-tuning of the targeted bioactivity and pharmacokinetics. Over the last 20 years, fluorine scanning and editing became rather standard steps in the design of new drugs [9, 10]. Tailor-made fluorine-containing AAs are a particularly exciting class of molecules widely used in drug design [11]. Some of the most successful compounds

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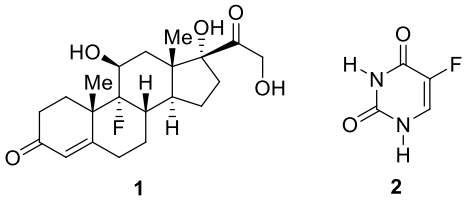
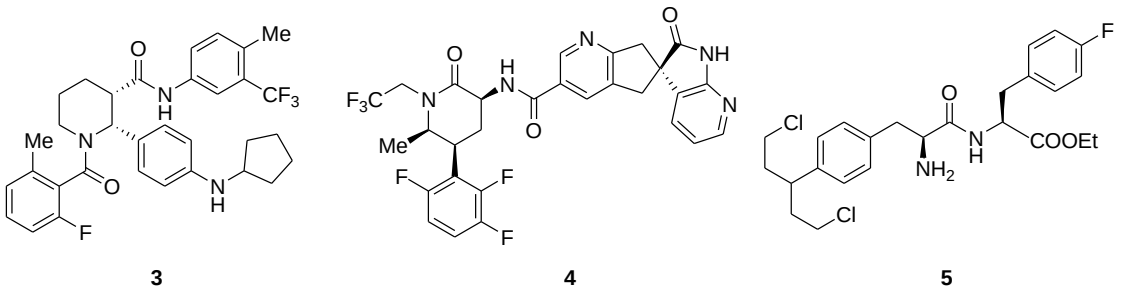


Figure 1. Structures of fludrocortisone **1** and 5-fluorouracil **2**.



3 **4** **5**

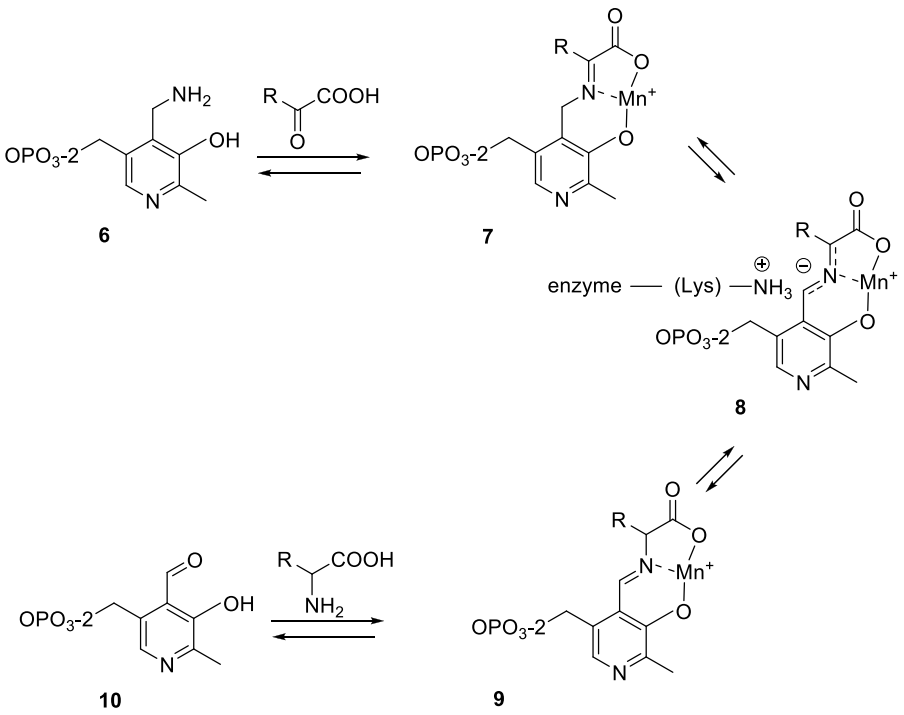
Figure 2. Recently approved drugs Avacopan (Tavneos™) **3**, Atogepant (Qulipta™) **4** and Melflufen (Pepaxto™) **5**.

recently introduced to the market are shown in Figure 2.

Avacopan (Tavneos™) **3** is an orally bioavailable highly selective antagonist of human C5aR1 [12] was introduced by ChemoCentryx. In 2021, Avacopan was approved by the US FDA for the treatment of ANCA-associated vasculitis, a rare form of autoimmune disease [13]. It contains fragments of cyclic *β*-AA and two types of fluorination, aromatic F- and CF_3-groups. Atogepant (Qulipta™) **4** was developed by AbbVie as an orally active and selective antagonist of the calcitonin gene-related peptide (CGRP) receptors [14]. This drug was approved, in 2021, by US FDA for the preventive treatment of episodic migraines in adults [15]. Atogepant contains substituted ornithine, in its lactam form, along with aromatic (F) and aliphatic (CF_3-CH_2) fluorination motifs. Melflufen (Pepaxto™) **5** is a dipeptide composed of two tailor-made AA melphalan [16] and *p*-fluorophenylalanine. It was developed by Oncopeptides for the treatment of multiple myeloma and amyloid light-chain amyloidosis. In 2021 the US FDA approved Melflufen **5** in combination with dexamethasone for the treatment of pre-treated adult patients with relapsed or refractory multiple myeloma [17].

Biological transamination [18], is a primarily important process in living organisms providing metabolic interconversion of *β*-keto and α-amino acids (Scheme 1). Mechanistically, biological transamination consists of a base-catalyzed 1,3-proton transfer across the azaallyllic anion intermediate **8** giving rise to Schiff bases of *α*-keto acids **7** or *α*-amino acids **9** as precursors of *α*-amino acids and pyridoxamine **10**, and correspondingly, *α*-keto carboxylic acids and pyridoxal **6** [19]. In a biological system, the 1,3-proton transfer is catalyzed by the enzymatic lysine omega-amino group which performs enantio-selective proton transfer furnishing either **7** or **9** via the delocalized 2-azaallyl anion **8** [20].

Numerous research groups, in particular, Breslow's [21], Snell's [19e], Martell's [19a], Cram's [22], and Casella's [23] studied the mechanism and stereochemistry of the



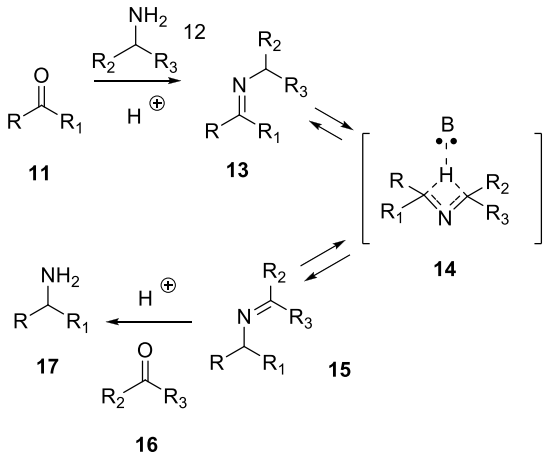
6 **7** **8** **9** **10**

Scheme 1. Biochemical interconversion of *α*-amino and *α*-keto acids.

biological transamination using native as well as model pyridoxal-based systems. They pointed out the importance of the corresponding metal complex formation in controlling the rate and stereochemistry of the transamination process. Furthermore. it was demonstrated that the 1,3-proton shift, in general, requires a strong base for the isomerization to occur at a synthetically useful rate [24]. Moreover, the equilibrium constants measured for the reaction were found to be satisfactorily correlated by the Hammett equation (r = 0.94) suggesting the formation of delocalized azaallylic anion intermediate of type **8**, stabilized by electron-withdrawing and correspondingly, destabilized by electron-releasing substituents [25].

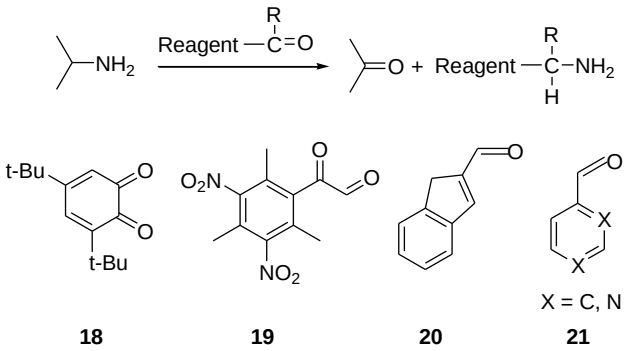
Biomimetic transamination. Non-fluorinated substrates.

From a synthetic point of view, the biological transamination is an intramolecular reduction-oxidation process via base-catalyzed 1,3-proton shift in the azaallylic system of the corresponding imine (Scheme 2). Obviously, if there is a way to control the equilibrium between imines **13** and **15**, then one can realize as biomimetic approach for oxidation of amines **17** to carbonyl compounds **11**, or conversely, reductive amination of carbonyl compounds **11** to amines **17**. To consider this biomimetic approach synthetically useful, the equilibrium between **13** and **15** should show a clear preference for one of the compounds. The obvious methodological advantage of this biomimetic approach over traditional chemical reduction/oxidation methods is that it does not require the use of external oxidative or reducing reagents allowing for the development of an environmentally benign, metal-free reduction or oxidation processes [26].



Scheme 2. Biomimetic transamination of carbonyl compound **11** to amine **17** and vice versa.

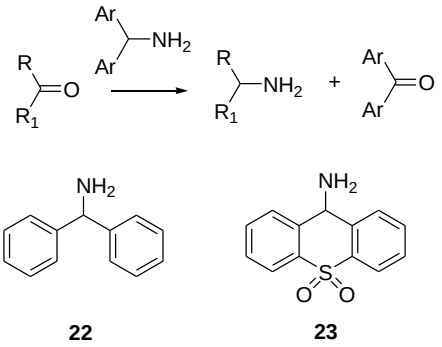
First attempts to mimic the biological transamination were reported by Professor's Corey group who designed highly electrophilic carbonyl compounds **18** and **19** (Scheme 3) and showed their application biomimetic oxidative deamination of primary amines to the corresponding ketones in high yields [26]. Calo *et al.* reported that aldehyde **20** can be efficiently used for oxidative deamination of some amines [27]. Various reagents of type **21**, mimicking natural pyridoxal **6**, were designed by Ohta's [28], Babler's [29] and Rapoport's [30] groups, were shown to be of more general synthetic application as they can be used for preparation of both aldehydes and ketones.



Scheme 3. Synthetically useful reagents for biomimetic transamination.

Examples of biomimetic reductive amination of carbonyl compounds were reported by Cainelli [31], Kuzuhara [32], Breslow [33], Zwanenburg [34], Berg [35], and others [36-39].

In most of cases, benzhydryl aldimines **22**, **23** (Scheme 4), possessing quite an acidic proton as well additional stabilization of the product imine via the resonance, were used as a source of hydrogen and nitrogen atoms. Nevertheless, the application of strong bases, like KOtBu was required to promote the biomimetic 1,3-proton shift transfer. Application of this approach for transamination of ketones was less successful, as compared to aldehydes, except for electrophilic derivatives of *α,β*-dicarbonyl compounds, and *β*-lactams.

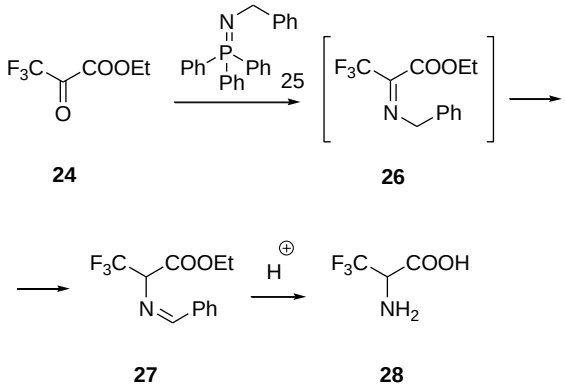


Scheme 4. Application of amines **22** and **23** for biomimetic reductive amination of some carbonyl compounds.

Biomimetic transamination. Fluorinated substrates.

The discovery of biomimetic reductive amination of fluorinated carbonyl compounds dates to 1986 when Kuhar group was trying to perform the Staudinger reaction between keto-ester **24** and phosphazene **25** (Scheme 5) [40]. It was surprising to discover the formation of Schiff base **27** as a sole reaction product. By contrast, the reactions of the

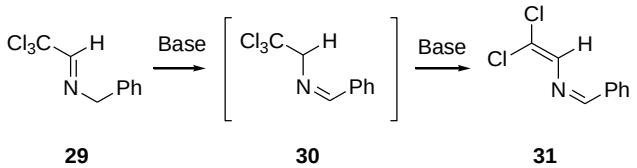
corresponding *N*-alkyl or *N*-aryl phosphazenes in the place of *N*-benzyl **25** gave the expected imine products of type **26** in high isolated yield [40c]. One can assume that the target product **26** underwent in situ irreversible isomerization to imine **27**, catalyzed by the basic reagent **25**. Product **27** was easily hydrolyzed to yield trifluoroalanine **28** in high yield [41].



Scheme 5. Staudinger reaction followed by irreversible isomerization of **26** to **27**.

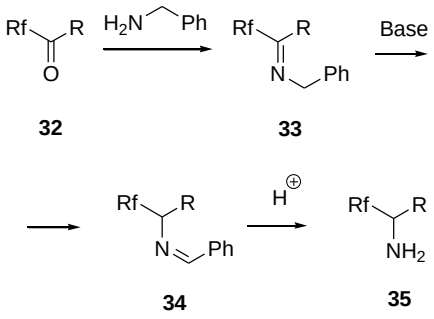
Investigation of possible mechanistic details of the base-catalyzed azomethine-azomethine isomerization of trifluoromethyl containing *N*-benzyl imines pointed to a nonionic character of the corresponding intermediates, similar to **14** (Scheme 2) [42]. The role of a base, even as weak as triethylamine, was suggested to increase the polarization of one of the benzylic protons thus facilitating a concerted 1,3-proton shift transfer within a four-membered ring. [43].

Quite interesting, attempts to use this procedure for chloro- or bromo-containing substrates were not successful. In these cases, the expected dehydrohalogenation was the major outcome of the reactions. For example, the 1,3-proton shift in trichloromethyl imine **29** (Scheme 6) was followed by the dehydrochlorination to yield compound **31** as a sole isolated product [43]. Besides the difference in stability of C-F and C-Cl bonds, this profound difference in the outcome of the reactions of trifluoro- vs. trichloromethyl-containing compounds can be additionally explained by very specific steric [44] and electrostatic [45] effects of trifluoromethyl group repulsing nucleophilic species and thus protecting the imine products from the dehydrochlorination.



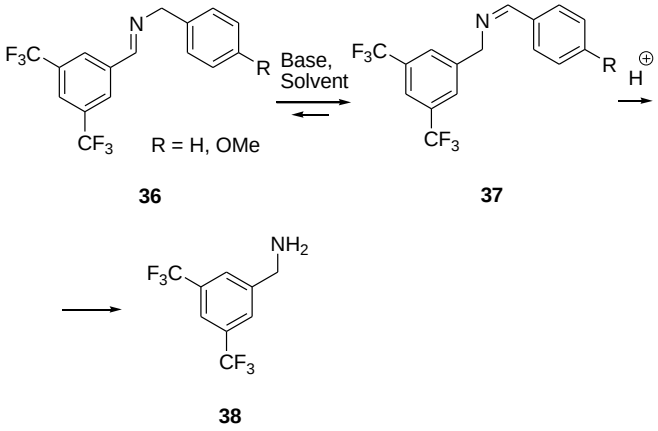
Scheme 6. Attempts to use chlorinated substrates in the biomimetic reductive amination.

The unexpected outcome of the Staudinger reaction (Scheme 5) was followed up by a systematic study of isomerization of *N*-benzyl imines **33** (Scheme 7) derived from various fluorinated aldehydes and ketones **32** [46]. Starting imines **33** can be quantitatively obtained by a direct condensation of benzylamine and the corresponding carbonyl compound using Dean-Stark conditions. It was found that such a relatively weak base as triethylamine is sufficiently active as a catalyst for the isomerization of **33** to Schiff bases **34**. The observed reaction rates were substantially faster for the aldehydes series as compared with that of ketones, which can be rationalized by the lower electrophilicity of the latter due to the electron-donating effect of an alkyl group. In particular, in the case of aldehydes, the isomerization of **33** to **34** takes place at ambient temperature, while in the reaction of keto-derivatives required slightly elevated temperatures (40-50 ºC) for optimal reaction rates. As presented in Scheme 7, carbonyl compounds containing difluoromethyl, trifluoromethyl, perfluoroalkyl, ω-hydro-perfluoroalkyl, and pentafluorophenyl groups were shown to be excellent substrates for biomimetic transamination to the corresponding amines. The triethylamine-catalyzed transformation of **33** to **34** is virtually irreversible providing the latter in high chemical yields (>85%). The resultant product **34** can be easily hydrolyzed (1N HCl) to obtain target amines **35**.



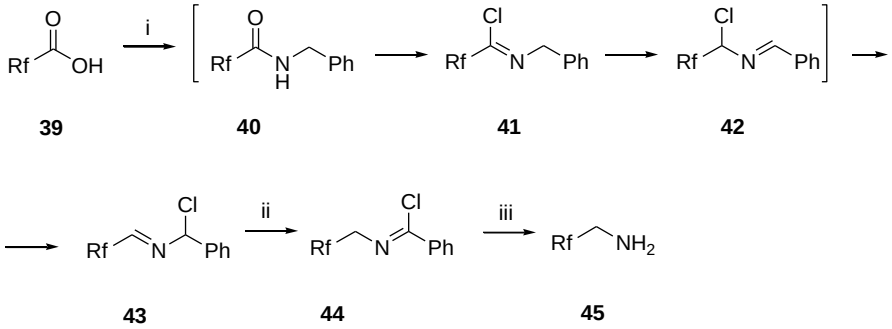
R_f = CHF_2, CF_3, C_2F_5, C_3F_9, C_4F_9, $H(CF_2)_{2\text{-}6}$, C_6F_5
R = H, Alkyl (Me, Et, nPr, Bn), Aryl (Ph, substituted Ph)

Scheme 7. Biomimetic reductive amination of fluorinated aldehydes and ketones.



Scheme 8. Biomimetic transamination approach for preparation 3,5-bis(trifluoromethyl)benzylamine (**38**).

It is interesting to note that in some cases the isomerization of **33** to **34** can take place even without a base, suggesting much greater thermodynamic stability of the latter. Thus, *N*-benzyl imine derived from trifluoro-acetophenone **33** (R_f = CF_3, R = Ph) was quantitatively isomerized to isomerized to Schiff base **34** simply by heating at 200 ºC for



R_f = CF_3 (a); C_2F_5 (b); C_3F_9 (c)

Key: (i) $BnNH_2$ (1 eq.), Ph_3P (4 eq.)/CCl_4 (4 eq.), TEA (1.5 eq.), $CHCl_3$ reflux, 40 min.; (ii) TEA (3 eq.)/H_2O; (iii) MeOH/HCl (conc.), reflux, 24 h

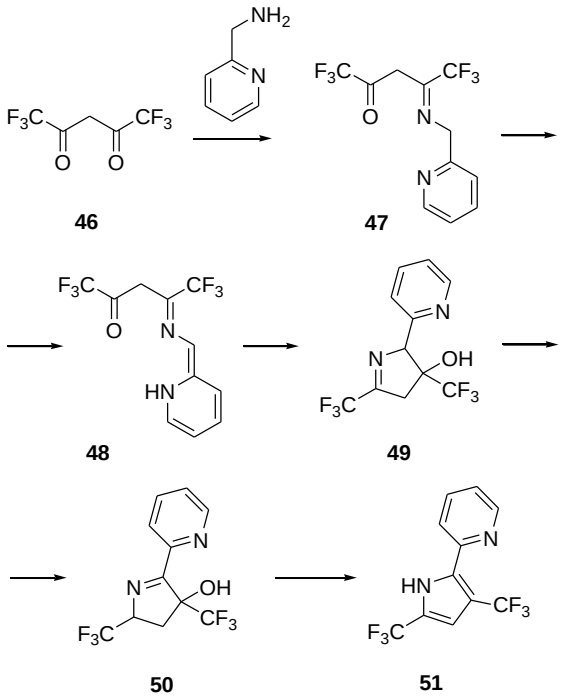
Scheme 9. Application of biomimetic transamination for preparation of amines from the corresponding carboxylic acids.

24 hrs. The target free amine **35** was isolated with excellent (>95%) overall yield [47]. This biomimetic transamination procedure can be easily scaled-up and represents the most advanced preparation of amine **35** (R_f = CF_3, R = Ph), the fluorinated analog of highly biologically important *α*-(phenyl)ethylamine.

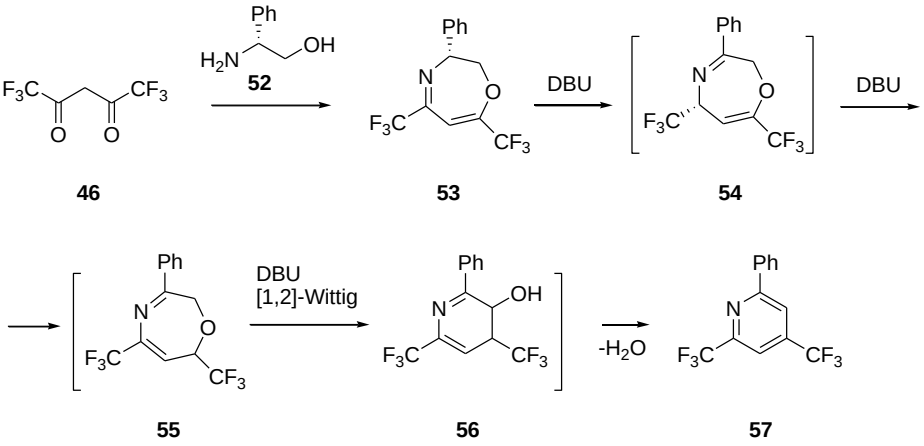
This biomimetic transamination approach can be extended to the derivatives in which trifluoromethyl group is not directly attached to the azaallyllic system. For example, 3,5-bis(trifluoromethyl)benzylamine **38** (Scheme 8), is a key pharmacophore found in numerous biologically active compounds and drug candidates [48]. Therefore, this compound was an exciting target for the biomimetic transamination approach starting from commercially available 3,5-bis(trifluoromethyl) benzaldehyde [49]. Initial attempts to use benzylamine for the transamination of the 3,5-bis(trifluoromethyl) benzaldehyde resulted in a equilibrium shifted towards product **37** (85/15), albeit to a degree of low synthetic application. Further optimization of the reaction conditions (CH_3CN as a solvent and DBU as a base) and application of *p*-(methoxy)benzylamine allowed for a noticeable shift in the equilibrium towards the desired product **37** (95%), which was hydrolyzed to afford the target amine **38** in 75% overall yield.

Of particular importance is the unique application of biomimetic transamination for preparation of amines from the corresponding carboxylic acids. This method involves in situ formation of amides **40**, their transformation to imidoyl chlorides **41**, followed by the first 1,3 proton transfer affording imines **42**. The next reaction step is a chlorotropic shift to yield imines **43**, which undergoes the second 1,3-proton transfer yielding **44**. Imidoyl chlorides **44** can be isolated and via two hydrolytic steps converted to the target amines **45**. Taking into account that the whole transformation involves a sequence of seven reactions, the excellent isolated yields (>90%) of amines **45** were quite remarkable (Scheme 9) [50].

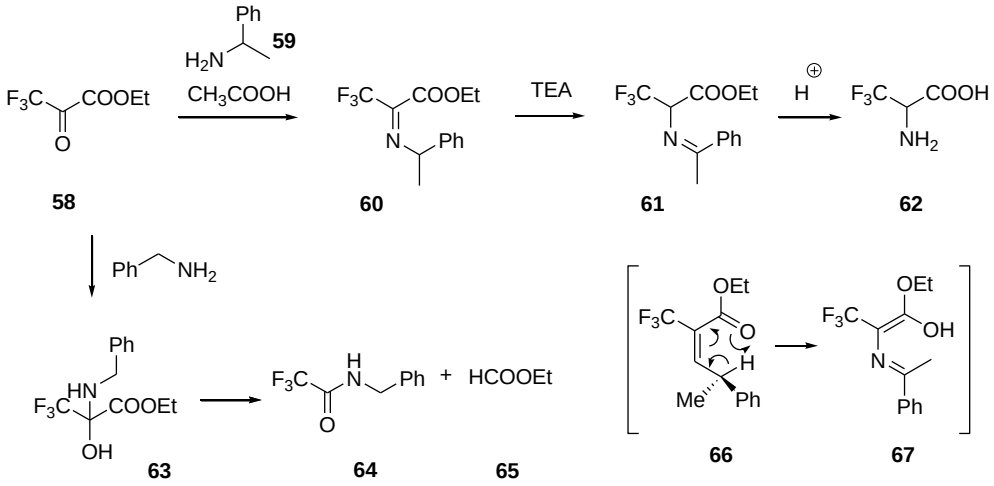
Due to very high reactivity, chemistry of fluorinated dicarbonyl compounds is significantly complicated by the issues of regioselectivity, enolate formation, and structural liability (decomposition) towards nucleophilic reagents. For example, reactions of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione **46** (Scheme 10) with benzylamine gives rise to a mixture of various inseparable products and therefore are of no synthetic value. In sharp contrast to benzylamine, the reaction of 2-picolylamine with dione **46** was found to be a convenient approach of preparation of trifluoromethyl containing myosmines **50**. The whole process includes a series of successive reactions such as formation of the direct condensation product, imine **47**, base-catalyzed 1,3 proton transfer to form highly nucleophilic intermediate **48**, its cyclization to form five-membered 3,4-dihydro-2H-pyrrol-3-ols **49**, followed by the second base-catalyzed 1,3 proton transfer to furnish the target myosmines **50**. Compounds **50** can be isolated or directly dehydrated giving rise to 2-(2-pyridyl)-3,5-bis-(trifluoromethyl)-1H-pyrrole **51** as a sole reaction product [39]. It should be noted that equilibrium



Scheme 10. Biomimetic reductive amination approach of preparation of trifluoromethyl containing myosmines **50**.



Scheme 11. Biomimetic method for preparation of 2,4-bis(tri-fluoromethyl)-6-phenylpyridine.



Scheme 12. Biomimetic synthesis of trifluoro-alanine.

between **47** and **48** significantly favors **47**, however, the irreversible cyclization of **48** to form products **48** followed by biomimetic 1,3 proton shift, drives the reaction to completion with the formation of myosmines **50** [51].

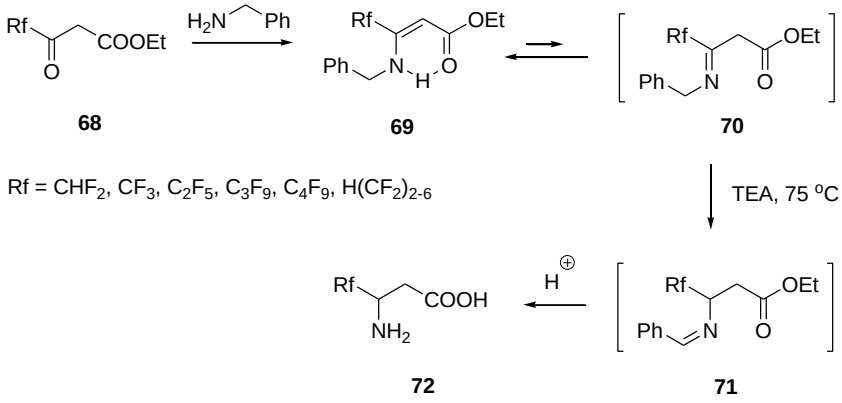
Another synthetically useful reaction of dione **46**, including the biomimetic isomerization step as a key transformation, is presented in Scheme 11. Direct condensation of dione **46** with glycinol **52** gave cyclic product bis(trifluoromethyl)-2,3-dihydro-1,4-oxazepine **53**. Treatment of oxazepine **53** with a DBU initiated the biomimetic 1,3 proton shift affording 1,4-oxazepine **54**. Intermediate **54** cannot be isolated, undergoing in situ yet another DBU-catalyzed 1,3 proton transfer to yield one more isomeric 1,4-oxazepine **55**. Finally, DBU-catalyzed [1, 2] Wittig rearrangement of **55** gave rise to 3,4-dihydro-pyridin-3-ol **56**. Dehydration of compound **56** resulted in the formation of 2,4-bis(trifluoromethyl)-6-phenylpyridine **57** as a final reaction product [52]. One may agree, these multi-step transformations clearly underscore very complex chemistry of fluorinated dicarbonyl compounds. Nevertheless, successful synthesis of interesting fluorine-containing heterocyclic compounds under mild and metal-free conditions bodes well for future application of biomimetic approach in the chemistry of heterocyclic biologically active compounds.

Fluorinated α-keto acids are highly electrophilic compounds. For example, the reaction of keto ester **58** (Scheme 12) with benzylamine gives stable crystalline gem-amino alcohol **63** which can be isolated and fully characterized. However, attempts to dehydrate compound **63** to the corresponding imine under various conditions usually result in the haloformic decomposition giving rise to amide **64** and ester **65**. To overcome the problem of exceptionally high electrophilicity of fluorinated α-keto acids, a special procedure was developed. As shown in Scheme 12, keto ester **58** was reacted with a salts α-(phenyl)ethylamine **59** to form the corresponding gem-amino alcohol which gradually underwent acid-catalyzed dehydration to furnish the target imine **60** in excellent chemical yield (>95%) [53].

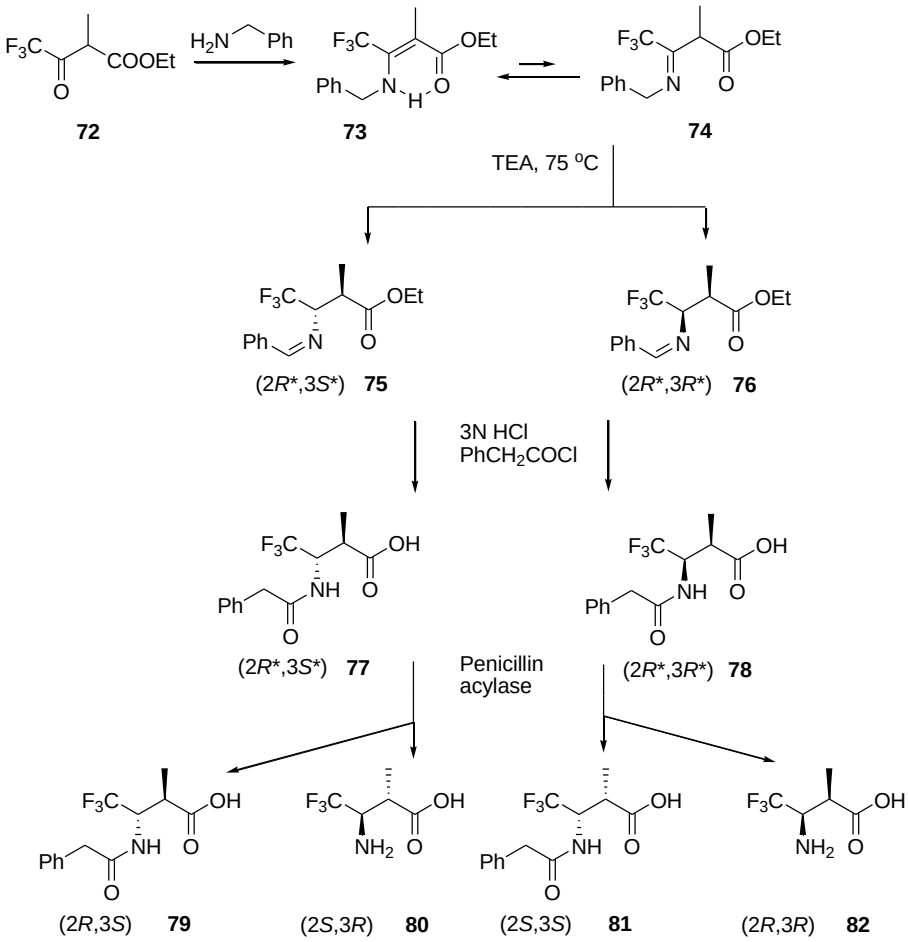
Biomimetic isomerization of Schiff base **60** to imine **61** can be quantitatively conducted at ambient temperature in the presence of triethylamine. Acidic hydrolysis of **61** afforded the target trifluoroalanine **62** [54]. It should be noted that application of enantiomerically pure α-(phenyl)ethylamine allowed preparation of also

enantiomerically pure imine **60**, triethylamine-catalyzed isomerization of which resulted in completely racemic amino acid **62**. To explain this stereochemical outcome one may propose that the proton transfer take place via six-membered transition state **66** leading to achiral intermediate enolate **67**.

Due to the high biological value of fluorinated *β*-amino acids [55] the biomimetic approach for reductive amination of *β*-ketoacids is of great synthetic interest. As presented in Scheme 13, derived from keto esters **68** and benzylamine, imines **70** were cleanly isomerized to Schiff bases **71** on heating at 75 °C in the presence of triethylamine. It should be mentioned that the equilibrium between enamine **69** and imine **70** is nearly completely shifted towards the former. Nevertheless, the very fast and irreversible biomimetic isomerization of **70** affords Schiff bases **71** as the final reaction products [56]. Acidic hydrolysis of imines **71** allows preparation of the target fluorinated *β*-amino acids **72** in high overall yield.



Scheme 13. Biomimetic approach to fluorinated *β*-amino acids.

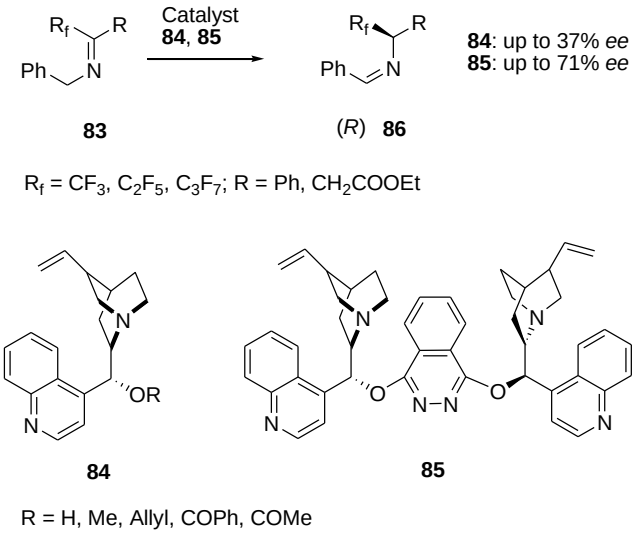


Scheme 14. Chemo-enzymatic approach for synthesis of all four possible stereoisomers of *α*-alkyl-*β*-fluoroalkyl-*β*-amino acids.

This biomimetic approach for the reductive amination of *β*-keto esters **68** is quite general and provides for the most reliable and scalable preparation of biologically important *β*-fluoroalkyl-*β*-amino acids **72**. It should be noted that the amino acids **72** are readily available in enantiomerically pure form via specially developed enzymatic resolution of the corresponding *N*-phenylacetyl derivatives using penicillin acylase [57].

Combination of the biomimetic transamination and the penicillin acylase catalyzed resolution was realized in a chemo-enzymatic approach for synthesis of all four possible stereoisomers of *α*-alkyl-*β*-fluoroalkyl-*β*-amino acids (Scheme 14) [58]. Racemic starting keto ester **72** was transformed into a mixture of enamine **73** and ketimine **74**. Biomimetic isomerization of **74** afforded diastereomers **75** and **76**. Detailed investigation of this isomerization allowed to find that the use of triethylamine as a base favored the (2R*,3S*) diastereomer **75** (40% *de*), while the application of DBU gave (2R*,3R*) diastereomer **76** as the major product (39% *de*).

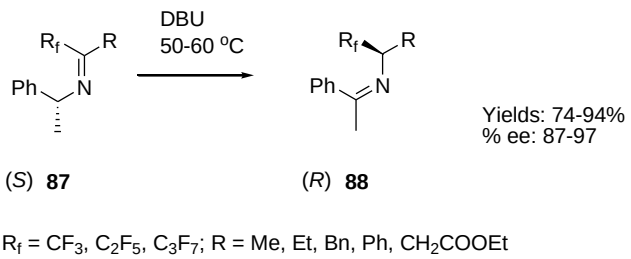
Diastereomerically pure **75** and **76**, obtained by column chromatography, were transformed to *N*-phenylacetyl derivatives **77** and **78** and subjected to kinetic resolution using penicillin acylase. The enzyme-catalyzed hydrolysis of the enantiomers possessing (3R) stereogenic carbon was extremely stereoselective with the rate of higher than 1 to 1000, thus allowing for a complete resolution with excellent chemical yields of both enantiomers. Free (2S,3R)-**80** and (2R,3R)-**82** can be easily separated from the corresponding unhydrolyzed enantiomers (2R,3S)-**79** and (2S,3S)-**81**, which can be hydrolyzed under conventional acidic conditions to produce the corresponding amino acids.



Scheme 15. Asymmetric approaches for biomimetic reductive amination.

Since the interest in fluorinated amines and amino acids is associated with their biological applications in the design of modern pharmaceuticals [59], the development of asymmetric approaches for the biomimetic transamination is particular interest. As shown in Scheme 15, series of cinchonidine derived catalysts **84**, and **85** were used to perform catalytic asymmetric reductive amination of ketimines **83**. Due to relatively low basicity of chiral catalysts **84** the isomerization reactions required high load (50 mol%) of the catalyst and elevated temperatures [60]. The highest enantioselectivity obtained was only in the range of 37% *ee*. A significant advance in this area has been reported recently by J.C. Plaquevent et al. [61]. These authors conduced a systematic study of all factors influencing the enantioselective isomerization step and found that C_2 symmetric catalyst **85** allows the reaction to proceed with up to 71% *ee*.

Another approach to asymmetric biomimetic reductive amination of fluorinated ketones and keto acids can be straightforward application of chiral *α*-(phenyl)ethylamine in the place of benzylamine. It was found that triethylamine is ineffective as a catalyst for the isomerization of ketimines **87**. The reason for such a drastic difference in reactivity of benzylamine and *α*-(phenyl)ethylamine is likely the significantly reduced C-H acidity of the latter [62]. On the other hand, application of a stronger base raised a due concern of the products **88** racemization. It should be noted that this type of asymmetric transformation involves the enantioselective proton transfer from a less to a more C-H acidic product. Thermodynamically, such enantioselective process is forbidden. However, it can be successfully conducted under kinetically controlled conditions, provided that the isomerization step is substantially faster as compared to the racemization of the target product. Moreover, it was also expected that trifluoromethyl group due to its steric bulk [44] and electrostatic features [45] might have some protective role [63] slowing down the undesired racemization process. Detailed investigation of the isomerization of imine **87** to **88** revealed rather unexpected results (Scheme 16). Thus, while racemization was indeed a serious issue at high temperatures, virtually no racemization was observed at ambient-to-60 °C temperature. The discovered DBU-catalyzed reaction conditions were found to be of general synthetic use for asymmetric biomimetic reductive amination of various ketones and *β*-keto acids with good chemical yields and high diastereoselectivity [64, 65].



Scheme 16. Stoichiometric asymmetric reductive amination.

It is interesting to note that the work on asymmetric reductive amination of fluorinated ketones and keto acids led to the discovery of Self-Disproportionation of Enantiomers (SDE) [66] under the conditions of achiral chromatography [67] and sublimation [68]. In particular, fluorinated amines [69], *α*- [70], *β*-amino acids [71], and alcohols [72] usually show very high magnitude of the SDE allowing to use this phenomenon as enantiopurification

method. Nowadays, it is commonly accepted that the SDE is the general phenomenon resulting in enantio-enriched and enantio-depleted fractions anytime a chiral enantiomerically enriched (not racemic or enantiomerically pure) is subjected to physicochemical phase transition. General recognition of the SDE prompted some academic journals to require the SDE-tests as a part of submitted experimental data [73].

Conclusions

In this review, we highlighted major synthetic and methodological ideas which were developed in the area of biomimetic reductive amination of fluorine-containing carbonyl. Some of the methods have rather limited application, while others offer quite practical synthetically efficient solutions. Given the increasing importance of fluorinated amino compounds in health-related research and pharmaceutical industry, the biomimetic transamination may be a method of choice providing the most convenient, generalized, and greener (metal-free) approach to this class of derivatives.

Notes

The authors declare no conflict of interest.

Author contributions. The manuscript was written through contributions of all authors. All authors have approved to the final version of the manuscript.

References

1. (a) Fried, J.; Sabo, E.F. Synthesis of 17α-hydroxycorticosterone and its 9α-halo derivatives from 11-epi-17 α-hydroxycorticosterone. *J. Am. Chem. Soc.* **1953**, *75*, 2273-2274. (b) Fried, J.; Sabo, E.F. 9α-Fluoro derivatives of cortisone and hydrocortisone. *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456.
2. Heidelberger, C.; Chaudhuri, N.K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R.J.; Pleven, E.; Scheiner. J. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature* **1957**, *179*, 663-666.
3. (a) O'Hagan, D.; Harper, D.B. Fluorine-containing natural products. *J. Fluorine Chem*. **1999**, *100*, 127-133. (b) O'Hagan, D.; Schaffrath, C.; Cobb, S.L.; Hamilton, J.T.G.; Cormac, C.D. Biosynthesis of an organofluorine molecule. *Nature* **2002**, *416*, 279. (c) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J.B.; O'Hagan, D.; Naismith, J.H. Crystal structure and mechanism of a bacterial fluorinating enzyme. *Nature* **2004**, *427*, 561-565.
4. Sanada, M.; Miyano, T.; Iwadare, S.; Williamson, J.M.; Arison, B.H.; Smith, J.L.; Douglas, A.W.; Liesch, J.M.; Inamine, E. Biosynthesis of fluorothreonine and fluoroacetic acid by the thienamycin producer, Streptomyces cattleya. *J. Antibiot*. **1986**, *39*, 259-265.
5. (a) Henninot, A.; Collins, J.C.; Nuss, J.M. The current state of peptide drug discovery: Back to the future? *J. Med. Chem.* **2018**, *61*, 1382-1414. (b) Hodgson, D.R.W.; Sanderson, J.M. The synthesis of peptides and proteins containing non-natural amino acids. *Chem. Soc. Rev*. **2004**, *33*, 422-430.
6. (a) Liu, A.; Han, J.; Nakano, A.; Konno, H.; Moriwaki, H.; Abe, H.; Izawa, K.; Soloshonok, V.A. New pharmaceuticals approved by FDA in 2020: Small-molecule drugs derived from amino acids and related compounds, *Chirality*. **2022**, *34*, 86-103. (b) Han, J.; Konno, H.; Sato, T.; Soloshonok, V.A.; Izawa, K. Tailor-Made Amino Acids in the Design of Small-Molecule Blockbuster Drug, *Eur. J. Med. Chem.*, **2021**, *220*, 113448. (c) Han, J.; Konno, H.; Sato, T.; Soloshonok, V.A.; Izawa, K. Peptidomimetics and Peptide-Based Blockbuster Drugs, *Current Organic Chemistry*, **2021**, *25*, 1627-1658. (d) Yin, Z.; Hu, W.; Zhang, W.; Konno, H.; Moriwaki, H.; Izawa, K.; Soloshonok, V.A.; Han, J. Tailor-made amino acid-derived pharmaceuticals approved by the FDA in 2019, *Amino Acids*, **2020**, *52*, 1227-1261.
7. (a) Han, J.; Lyutenko, N.V.; Sorochinsky, A.E.; Okawara, A.; Konno, H.; White, S.; Soloshonok, V.A. Tailor-Made Amino Acids in Pharmaceutical Industry: Synthetic Approaches to Aza-Tryptophan Derivatives, *Chem. Eur. J.* **2021**, *27*, 17510-17528. (b) Han, J., Escorihuela, J., Fustero, S., Landa, A., Soloshonok, V.A., Sorochinsky, A. Asymmetric Michael Addition in Synthesis of β-Substituted GABA Derivatives, *Molecules* **2022**, *27*, 3797. (c) Liu, J.; Han, J.; Izawa, K.; Sato, T.; White, S.; Meanwell, N.A.; Soloshonok, V.A. Cyclic Tailor-Made Amino Acids in the Design of Modern Pharmaceuticals, *Eur. J. Med. Chem.* **2020**, *208*, 112736 (d) Soloshonok, V.A.; Sorochinsky, A.E. Practical Methods for the Synthesis of Symmetrically α,α-Disubstituted-α-Amino Acids, *Synthesis* **2010**, 2319-2344.
8. (a) Lyutenko, N.V.; Sorochinsky, A.E.; Soloshonok, V.A. Applications of chiral sulfinyl auxiliaries in the asymmetric synthesis of fluorinated amines and amino acids. *Ukr. Bioorg. Acta* **2023**, *18*, 10-21. (b) Zou, Y.; Yin Z.; Mei, H.; Konno, H.; Moriwaki, H.; Soloshonok, V.A.; Han, J. Aldol Addition-Cyclization Reaction Cascade on a Platform of Chiral Ni(II) Complex of Glycine Schiff Base, *Ukr. Bioorg. Acta* **2021**, *16*, 3-9. (c) Romanenko, V.D. The Main Directions of Scientific Activity of Academician V.P. Kukhar. *Ukr. Bioorg. Acta* **2022**, *17*, 5-21. (d) Klipkov, A.A.; Gerus, I.I.; Sorochinsky, A.E. Synthesis of Fluorinated Pyrrolizidine, Indolizidine and Quinolizidine Derivatives, *Ukr. Bioorg. Acta* **2022**, *17*, 22-39. (e) Vashchenko, B.V.; Grygorenko, O.O.; Stepaniuk, O.O. Heterocyclizations of β-Alkoxy, β-Diaminoalkyl, and Related β-Functionalized Enones (enals) With NCN-Binucleophiles, *Ukr. Bioorg. Acta* **2022**, *17*, 56-71. (f) Brusnakov, M.Y.; Golovchenko, O.V.; Potikha, L.M.; Brovarets, V.S. 1,3-Oxazoles As Precursors of Phosphorylated Amino Acids and Peptidomimetics, *Ukr. Bioorg. Acta*, **2022**, *17*, 72-80.
9. (a) He, J.; Li, Z.; Dhawan, G.; Zhang, W.; Sorochinsky, A.E.; Butler, G.; Soloshonok, V.A.; Han, J. Fluorine-containing drugs approved by the FDA in 2021, *Chin. Chem. Lett*. **2023**, *34*, 107578. (b) Yu, Y.; Liu, A.; Dhawan, G.; Mei, H.; Zhang, W.; Izawa, K.; Soloshonok, V.A.; Han, J. Fluorine-containing pharmaceuticals approved by the FDA in 2020: synthesis and biological activity, *Chinese Chemical Letters*, **2021**, *32*, 3342-3354. (c) Han, J.; Remete, A.M.; Dobson, L.S.; Kiss, L.; Izawa, K.; Moriwaki, H.; Soloshonok, V.A.; O'Hagan, D. Next generation organofluorine containing blockbuster drugs, *J. Fluor. Chem*. **2020**, *239*, 109639. (d) Mei, H.; Remete, A.M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V.A.; Han, J. Fluorine-containing drugs approved by the FDA in 2019, *Chin. Chem. Lett*. **2020**, *31*, 2401-2413. (e) Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D.M.; Santi, C.; Ruzziconi, R.; Soloshonok, V.A.; Fluorine-Containing Drugs Approved by the FDA in 2018, *Chem. Eur. J.* **2019**, *25*, 11797-11819.
10. (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J.L.; del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001-2011), *Chem. Rev*. **2014**, *114*, 2432-2506. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J.L.; Soloshonok, V.A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas, *Chem. Rev*. **2016**, *116*, 422-518. (c) Zhu, Y.; Han, J.L.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V.A.; Coelho, J.A.S.; Toste, F.D. Modern Approaches for Asymmetric Construction of Carbon-Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs, *Chem. Rev.* **2018**, *118*, 3887-3964. (d) Han, J.; Kiss, L.; Mei, H.; Remete, A.M.; Ponikvar-Svet, M.; Sedgwick, D.M.; Roman, R.; Fustero, S.; Moriwaki, H.; Soloshonok, V.A. Chemical Aspects of Human and Environmental Overload with Fluorine, *Chem. Rev*. **2021**, *121*, 4678-4742. (e) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J.L.; Izawa, K.; Liu, H.; Soloshonok, V.A. Recent advances in the trifluoromethylation methodology and new CF_3-containing drugs, *J. Fluorine Chem.*, **2014**, *167*, 37-54.
11. (a) Wang, N.; Mei, H.; Dhawan, G.; Zhang, W.; Han, J.; Soloshonok, V.A. New Approved Drugs Appearing in the Pharmaceutical Market in 2022, Featuring Fragments of Tailor-Made Amino Acids and Fluorine, *Molecules* **2023**, *28*, 3651. (b) Wang, Q.; Han, J.; Sorochinsky, A.; Landa, A.; Butler, G.; Soloshonok, V.A. The Latest FDA-Approved Pharmaceuticals Containing Fragments of Tailor-

Made Amino Acids and Fluorine, *Pharmaceuticals*, **2022**, *15*, 999. (c) Mei, H.; Han, J.; White, S.; Graham, D.J.; Izawa, K.; Sato, T.; Fustero, S.; Meanwell, N.A.; Soloshonok, V. A. Tailor-Made Amino Acids and Fluorinated Motifs as Prominent Traits in the Modern Pharmaceuticals, *Chem. Eur. J.* **2020**, *26*, 11349-11390. (d) Mei, H.; Han, J.; Klika, K.D.; Izawa, K.; Sato, T.; Meanwell, N.A.; Soloshonok, V.A. Applications of Fluorine-Containing Amino Acids for Drug Design, *Eur. J. Med. Chem.* **2020**, *186*, 111826. (e) Soloshonok, V.A.; Hayashi, T. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Fluorinated Benzaldehydes with a-Isocyanoacetamide, *Tetrahedron: Asymmetry* **1994**, *5*, 1091-1094.

12. (a) Lee, A. Avacopan: First approval. *Drugs* **2022**, *82*, 79-85. (b) Shagdarsuren, G.; Khaidav, G.; Togtokh, A.; Sonomjamts, M.; Shagdarsuren, E. Complement anaphylatoxin C5a, endothelial dysfunction and low-grade inflammation in atherosclerotic vascular diseases. *Cent. Asian J. Med. Sci.* **2018**, *4*, 243-252. (c) Jayne, D.R.W.; Merkel, P.A.; Schall, T.J.; Bekker, P. Avacopan for the treatment of ANCA-associated vasculitis. *N. Engl. J. Med*. **2021**, *384*, 599-609.
13. (a) Osmana, M.; Tervaerta, J.W.C.; Pagnoux, C. Avacopan for the treatment of ANCA-associated vasculitis. *Expert Rev. Clin. Immunol*. **2021**, *17*, 717-726. (b) Thorley, J. FDA approves avacopan for ANCA-associated vasculitis. *Lancet*. **2022**, *4*, e21. (c) WO Patent No 2011/163640 A1. C5AR Antagonists / Greenman, K.L.; Leleti, M.R.; Li, Y.; Powers, J.; Tanaka, H.; Yang, J.; Zeng, Y. Patent appl. No PCT/US2011/041910 24.06.2011. Publ. 29.12.2011. (d) US Patent No 9745268 B2. Processes and intermediates in the preparation of C5AR antagonists / Fan, F.; Kalisiak, J.; Krasinski, A.; Lui, R.; Powers, J.; Punna, S.; Tanaka, H.; Zhang, P. Patent appl. No 14/867669 28.09.2015. Publ. 29.08.2017.
14. (a) Moreno-Ajona, D.; Pérez-Rodríguez, A.; Goadsby, P.J. Small-molecule CGRP receptor antagonists: A new approach to the acute and preventive treatment of migraine. *Med. Drug Discov.* **2020**, *7*, 100053. (b) Wattiez, A.S.; Sowers, L.P.; Russo, A.F. Calcitonin gene-related peptide (CGRP): Role in migraine pathophysiology and therapeutic targeting. *Expert Opin. Ther. Targets* **2020**, *24*, 91-100.
15. (a) Edvinsson, L. The CGRP pathway in migraine as a viable target for therapies. *Headache* **2018**, *58*, 33-47. (b) Dubowchik, G.M.; Conway, C.M.; Xin, A.W. Blocking the CGRP pathway for acute and preventive treatment of migraine: The evolution of success. *J. Med. Chem.* **2020**, *63*, 6600-6623. (c) Deeks, E.D. Atogepant: First approval. *Drugs* **2022**, *82*, 65-70.
16. (a) Miettinen, J.J.; Kumari, R.; Traustadottir, G.A.; Huppunen, M.E.; Sergeev, P.; Majumder, M.M.; Schepsky, A.; Gudjonsson, T.; Lievonen, J.; Bazou, D.; et al. Aminopeptidase expression in multiple myeloma associates with disease progression and sensitivity to melflufen. *Cancers* **2021**, *13*, 1527. (b) Morabito, F.; Tripepi, G.; Martino, E.A.; Vigna, E.; Mendicino, F.; Morabito, L.; Todoerti, K.; Al-Janazreh, H.; D'Arrigo, G.; Canale, F.A.; et al. Spotlight on melphalan flufenamide: An up-and-coming therapy for the treatment of myeloma. *Drug Des. Devel. Ther*. **2021**, *15*, 2969-2978.
17. (a) Gullbo, J.; Tullberg, M.; Våbenø, J.; Ehrsson, H.; Lewensohn, R.; Nygren, P.; Larsson, R.; Luthman, K. Structure-activity relationship for alkylating dipeptide nitrogen mustard derivatives. *Oncol. Res*. **2003**, *14*, 113-132. (b) Dhillon, S. Melphalan Flufenamide (Melflufen): First approval. *Drugs* **2021**, *81*, 963-969.
18. Braunshtein, A.E.; Kritsman, M.G. Biological transamination. *Biochemistry*, **1937**, *2*, 859-874.
19. (a) Martell, A.E. Vitamin B6-catalyzed reactions of alpha-amino and alpha-keto acids: model systems. *Acc. Chem. Res*. **1989**, *22*, 115-124. (b) Tanner, M.E. Understanding nature's strategies for enzyme-catalyzed racemization and epimerization. *Acc. Chem. Res*. **2002**, *35*, 237-246. (c) Wachtershauser, G. Before enzymes and templates: theory of surface metabolism. *Microbiol. Rev*. **1988**, *52*, 452-484. (d) Toney, M.D.; Kirsch, J.F. Lysine 258 in aspartate aminotransferase enforcer of the Circe effect for amino Acid substrates and the general base catalyst for the 1,3-prototropic shift. *Biochemistry* **1993**, *32*, 1471-1479. (e) Longenecker, J.B.; Snell, E.E. The comparative activities of metal ions in promoting pyridoxal-catalyzed reactions of amino Acids. *J. Am. Chem. Soc*. **1957**, *79*, 142-145.
20. Lehninger, A.L.; Nelson, D.L.; Cox, M.M. Principles of Biochemistry, 2nd ed.; Worth Publishers: New York, 1993; pp. 511-514.
21. (a) Liu, L.; Zhou, W.; Chruma, J.; Breslow, R. Transamination reactions with multiple turnovers catalyzed by hydrophobic pyridoxamine cofactors in the presence of polyethylenimine polymers. *J. Am. Chem. Soc*. **2004**, *126*, 8136-8137. (b) Liu, L.; Breslow, R. A new catalytic conjugate addition/aldol strategy that avoids preformed metalated nucleophiles. *J. Am. Chem. Soc*. **2003**, *125*, 12110-12111. (c) Liu, L.; Rozenman, M.; Breslow, R. Hydrophobic effects on rates and substrate selectivities in polymeric transaminase mimics. *J. Am. Chem. Soc*. **2002**, *124*, 12660-12661. (d) Liu, L.; Breslow, R. A potent polymer/pyridoxamine enzyme mimic. *J. Am. Chem. Soc*. **2002**, *124*, 4978-4979.
22. Jaeger, D.A.; Broadhurst, M.D.; Cram, D.J. Electrophilic substitution at saturated carbon. 52. A model for the proton transfer steps of biological transamination and the effect of a 4-pyridyl group on the base-catalyzed racemization of a carbon acid. *J. Am. Chem. Soc*. **1979**, *101*, 717-732.
23. Casella, L.; Gullotti, M. Conformations of pyridoxal Schiff bases of amino acids. A circular dichroism study. *J. Am. Chem. Soc*. **1983**, *105*, 803-809.
24. Layer, R.W. The chemistry of imines. *Chem. Rev*. **1963**, *63*, 489-510.
25. (a) Smith, P.A.S.; Van Dang, C. Prototropic equilibrium of imines. Nbenzylidene benzylamines. *J. Org. Chem*. **1976**, *41*, 2013-2015. (b) Brandenberger, H.; Cohen, P.P. Ein beitrag zum studium des reaktionsmechanismus der biologischen transaminierung. *Helv. Chim. Acta* **1953**, *36*, 549-554.
26. Corey, E.J.; Achiwa, K. Oxidation of primary amines to ketones. *J. Am. Chem. Soc*. **1969**, *91*, 1429-1432.
27. Calo, V.; Lopez, L.; Todesco, P.E. Synthesis of carbonyl compounds via transamination of Schiff bases. *J. Perkin Trans*. *1* **1972**, 1652-1653.
28. Ohta, S.; Okamoto, M. Synthesis of carbonyl compounds via biogenetic-type transamination reaction. *Synthesis* **1982**, 756-758.
29. Babler, J.H.; Invergo, B.J. A facile biomimetic method for oxidative deamination of primary amines to aldehydes via transposition of an imine functionality. *J. Org. Chem*. **1981**, *46*, 1937-1938.
30. Buckley, T.F.; Rapoport, H. Mild and simple biomimetic conversion of amines to carbonyl compounds. *J. Am. Chem. Soc*. **1982**, *104*, 4446-4450.
31. Cainelli, G.; Giacomini, D.; Trere, A.; Boyl, P.P. Efficient transamination under mild conditions: Preparation of primary amine derivatives from carbonyl Compounds via imine isomerization with catalytic amounts of potassium tert-butoxide. *J. Org. Chem*. **1996**, *61*, 5134-5139.
32. Ando, M.; Kuzuhara, H. Asymmetric synthesis of fluoro-phenylalanines and (trifluoromethyl)phenylalanines; the use of chiral pyridoxamine-like pyridinophane-zinc complex as an enzyme mimic. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 1925-1928.
33. Zimmerman, S.; Breslow, R. Asymmetric synthesis of amino acids by pyridoxamine enzyme analogs utilizing general base-acid catalysis. *J. Am. Chem. Soc*. **1984**, *106*, 1490-1491.
34. Willems, J.G.H.; de Vries, J.G.; Nolte, R.J.M.; Zwanenburg, B. Asymmetric imine isomerisation in the enantioselective synthesis of chiral amines from prochiral ketones. *Tetrahedron Lett*. **1995**, *36*, 3917-3920.
35. Hjelmencrantz, A.; Berg, U. New approach to biomimetic transamination using bifunctional [1,3]-proton transfer catalysis in thioxanthenyl dioxide imines. *J. Org. Chem*. **2002**, *67*, 3585-3594.
36. Bachmann, S.; Knudsen, K.R.; Jørgensen, K.A. Mimicking enzymatic transaminations: attempts to understand and develop a catalytic asymmetric approach to chiral a-amino acids. *Org. Biomol. Chem*. **2004**, *2*, 2044-2049.
37. (a) Wu, Y.; Ahlberg, P. Intramolecularity and the function of the side arm base of simple models of transaminases. *J. Org. Chem*. **1992**, *57*, 6324-6327. (b) Wu, Y.; Ahlberg, P. Synthesis of a potential bifunctional mimic of transaminases. *Acta Chem. Scand*. **1992**, *46*, 60-72.
38. (a) Bernauer, K.; Deschenaux, R.; Taura, T. Stereoselectivity in reactions of metal complexes VII. Asymmetric synthesis of amino acids by metal ion-promoted transamination. *Helv. Chim. Acta* **1983**, *66*, 2049-2058. (b) Deschenaux, R.; Bernauer, K. Stereoselectivity in reactions of metal complexes VIII. Asymmetric synthesis of some amino acids by stereoselective transamination of aliphatic keto acids in mixed ligand copper(II)-Schiff-base complexes. *Helv. Chim. Acta* **1984**, *67*, 373-377.
39. Svenson, J.; Zheng, N.; Nicholls, I.A. A molecularly imprinted polymer-based synthetic transaminase. *J. Am. Chem. Soc*. **2004**, *126*, 8554-8560.
40. (a) Soloshonok, V.A.; Gerus, I.I.; Yagupolskii, Y.L. N-(Methoxy-carbonyl) imine of Trifluoropyruvic Acid, *Zh. Org. Khim*. **1986**, *22*, 1335-1337. (b) Soloshonok, V.A.; Gerus, I.I.; Yagupolskii, Y.L.; Kukhar, V.P. Fluorine-Containing amino acids. III. α-Trifluoromethyl- α-Amino Acids, *Zh. Org. Khim*. **1987**, *23*, 2308-2313. (c) Soloshonok, V.A.; Yagupolskii, Y.L.; Kukhar, V.P. Fluorine-Containing Amino Acids. V. Imines of trifluoropyruvic acid in the synthesis of N-Substituted trifluoroalanines. *Zh. Org. Khim*.

1988, *24*, 1638-1644. (d) Shibata, N.; Nishimine, T.; Shibata, N.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Sorochinsky, A.E.; Soloshonok, V.A. Organic base-catalyzed stereodivergent synthesis of (R)- and (S)-3-amino-4,4,4-trifluorobutanoic acids, *Chemical Communications*, **2012**, *48*, 4124-4126. (e) Soloshonok, V.A.; Kacharov, A.D.; Avilov, D.V.; Ishikawa, K.; Nagashima N.; Hayashi, T. Transition Metal/Base-Catalyzed Aldol Reactions of Methyl α-Isocyanoacetate with Prochiral Ketones, a Straightforward Approach to Stereochemically Defined β,β-Disubstituted-β-Hydroxy-α-Amino Acids. Scope and Limitations, *J. Org. Chem.* **1997**, *62*, 3470-3479.

41. (a) Kobzev, S.V.; Soloshonok, V.A.; Galushko, S.V.; Yagupolskii, Y.L.; Kukhar, V.P. Fluorine-Containing amino acids. VI. Acid-Base properties of α-Trifluoromethyl-α-Amino acids. *Zh. Obshch. Khim*. **1989**, *59*, 909-912. (b) Soloshonok, V.A.; Gerus, I.I.; Yagupolskii, Y.L.; Kukhar, V.P. Azomethine-Azomethine isomerization of fluorinated N-Benzylimines. *Zh. Org. Khim*. **1988**, *24*, 993-997.

42. (a) Khotkevich, A.B.; Soloshonok, V.A.; Yagupolskii, Y.L. Kinetics and mechanism of the isomerization of N-(1-Methoxycarbonyl-2,2,2-Trifluoroethylidene)-α-Methylbenzylamine. *Zh. Obshch. Khim*. **1990**, *60*, 1005-1008. (b) Nagy, P.; Ueki, H.; Berbasov, D.O.; Soloshonok, V.A. Kinetics and mechanism of triethylamine-catalyzed 1,3-Proton shift. Optimized and substantially improved reaction conditions for biomimetic reductive amination of Fluorine-Containing carbonyl compounds. *J. Fluor. Chem*. **2008**, *129*, 409-415. (c) Limbach, H.H.; Maennle, F.; Detering, C.; Denisov, G. S. Dynamic NMR studies of base-catalyzed intramolecular single vs. intermolecular double proton transfer of 1,3-bis(4-fluorophenyl)triazene. *Chem. Phys*. **2005**, *319*, 69-92.

43. Ono, T.; Kukhar V.P.; Soloshonok, V.A. Biomimetic reductive amination of Fluoro-Aldehydes and ketones via [1,3]-Proton shift reaction: scope and limitations. *J. Org. Chem.* **1996**, *61*, 6563-6569.

44. (a) Soloshonok, V.A.; Avilov, D.V.; Kukhar, V.P.; Meervelt, L.V.; Mischenko, N. An efficient asymmetric synthesis of (2S,3S)-3-trifluoromethylpyroglutamic acid. *Tetrahedron Lett*. **1997**, *38*, 4903-4904. (b) Bravo, P.; Farina, A.; Kukhar, V.P.; Markovsky, A.L.; Meille, S.V.; Soloshonok, V.A.; Sorochinsky, A.E.; Viani, F.; Zanda, M.; Zappala, C. Stereoselective additions of α-Lithiated Alkyl p-Tolylsulfoxides to N-PMP fluoroalkyl aldimines. An efficient approach to enantiomerically pure Fluoro-Amino compounds. *J. Org. Chem*. **1997**, *62*, 3424-3425. (c) Bravo, P.; Farina, A.; Frigerio, M.; Valdo Meille, S.; Viani, F.; Soloshonok, V.A. New fluorinated chiral synthons. *Tetrahedron Asymmetry* **1994**, *5*, 987-1004.

45. (a) Soloshonok, V.A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. Highly diastereoselective aldol reaction of fluoroalkyl aryl ketones with methyl isocyanoacetate catalyzed by Silver(I)/Triethylamine. *Tetrahedron Lett*. **1994**, *35*, 1055-1058. (b) Soloshonok, V.A.; Avilov, D.V.; Kukhar, V.P. Highly diastereoselective asymmetric aldol reactions of chiral Ni(II)-Complex of glycine with trifluoromethyl ketones. *Tetrahedron Asymmetry* **1996**, *7*, 1547-1550. (c) Soloshonok, V.A.; Avilov, D.V.; Kukhar, V.P.; Meervelt, L.V.; Mischenko, N. Highly diastereoselective aza-Aldol reactions of a chiral Ni(II) complex of glycine with imines. An efficient asymmetric approach to 3-Perfluoroalkyl-2,3-Diamino acids. *Tetrahedron Lett*. **1997**, *38*, 4671-4674. (d) Bravo, P.; Capelli, S.; Guidetti, M.; Meille, S.V.; Viani, F.; Zanda, M.; Markovsky, A.L.; Sorochinsky, A.E.; Soloshonok, V.A. Asymmetric synthesis of α-Arylglycinols via additions of lithium p-Tolyl methyl sulfoxide to N-(PMP)arylaldimines followed by "Non Oxidative" Pummerer reaction. *Tetrahedron* **1999**, *55*, 3025-3040. (e) Yamada, T.; Okada, T.; Sakaguchi, K.; Ohfune, Y.; Ueki, H.; Soloshonok, V.A. Efficient Asymmetric Synthesis of Novel 4-Substituted and Configurationally Stable Analogs of Thalidomide, *Org. Lett*. **2006**, *8*, 5625-5628. (f) Bravo, P.; Capelli, S.; Meille, S.V.; Viani, F.; Zanda, M.; Kukhar, V.P.; Soloshonok, V.A. Synthesis of Optically Pure (*R*)- and (*S*)-α-Trifluoromethyl-Alanine, *Tetrahedron: Asymmetry* **1994**, *5*, 2009-2018. (g) Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A.L.; Sorochinsky, A.E.; Soloshonok I.V.; Soloshonok, V.A. Chiral Sulfoxide Controlled Asymmetric Additions to C,N Double Bond. An Efficient Approach to Stereochemically Defined α-Fluoroalkyl Amino Compounds, *Tetrahedron* **1998**, *54*, 12789-12806.

46. (a) Kukhar, V.P.; Sorochinsky, A.E.; Soloshonok, V.A. Practical synthesis of fluorine-containing α- and β-amino acids. *Future Med. Chem*. **2009**, *1*, 793-819. (b) Soloshonok, V.A.; Kirilenko, A.G.; Kukhar, V.P.; Resnati, G. A practical rout to Fluoroalkyl- and Fluoroarylamines by Base-Catalyzed [1,3]-Proton shift reaction. *Tetrahedron Lett*. **1994**, *35*, 3119-3122.

47. Yasumoto, M.; Ueki, H.; Soloshonok, V.A. Base-Free, Thermal 1,3-Proton shift reaction and its application for operationally convenient and improved synthesis of α-(Trifluoromethyl)benzylamine. *J. Fluor. Chem*. **2007**, *128*, 736-739.

48. (a) Cappelli, A.; Giuliani, G.; Mohr, G.P.; Gallelli, A.; Anzini, M.; Vomero, S.; Cupello, A.; Scarrone, S.; Matarrese, M.; Moresco, R.M.; Fazio, F.; Finetti, F.; Morbidelli, L.; Ziche, M. A non-peptide NK1 receptor agonist showing subpicomolar affinity. *J. Med. Chem*. **2004**, *47*, 1315-1318. (b) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. Design, synthesis, and evaluation of novel 2-substituted-4-aryl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,5]oxazocin-5-ones as NK1 antagonists. *Bioorg. Med. Chem*. **2005**, *13*, 5717-5732.

49. (a) Soloshonok, V.A.; Yasumoto, M. Simple and convenient synthesis of 3,5-bis-(Trifluoromethyl)benzylamine via 1,3-Proton shift reaction. *J. Fluor. Chem*. **2006**, *127*, 889-893. (b) Berbasov, D.O.; Ojemaye, I.D.; Soloshonok, V.A. Synthesis of highly 1,3-Proton-Shift-Transferable N-Benzyl imines of trifluoroacetophenone under the "Low-Basicity" reaction conditions. *J. Fluor. Chem*. **2004**, *125*, 603-607.

50. Soloshonok, V.A.; Ohkura, H.; Uneyama, K. Reducing reagent-free, biomimetic reductive amination of perfluorocarboxylic acids to α,α-dihydroperfluoroamines. *Tetrahedron Lett*. **2002**, *43*, 5449-5452.

51. Ohkura, H.; Berbasov, D.O.; Soloshonok, V.A. Simple and highly diastereoselective synthesis of trifluoromethyl-containing myosmines via reaction between 2-(Aminomethyl)pyridine and 1,1,1,5,5,5-Hexafluoro-2,4- pentanedione. *Tetrahedron Lett*. **2003**, *44*, 2417-2420.

52. Soloshonok, V.A.; Ohkura, H.; Yasumoto, M. Unusual condensation of 1,1,1,5,5,5-Hexafluoro-2,4-pentanedione with (R)-Phenylglycinol. *Mendeleev Commun*. **2006**, 165-167. (b) Soloshonok, V.A.; Ohkura, H.; Yasumoto, M. Novel sequence of two base-catalyzed 1,3 proton shifts and [1,2] wittig rearrangement in the synthesis of 2,4-bis-(Trifluoromethyl)- phenylpyridine. *J. Fluor. Chem*. **2006**, *127*, 708-711.

53. (a) Ohkura, H.; Berbasov, D.O.; Soloshonok, V.A. Chemo- and regioselectivity in the reactions between highly electrophilic fluorine containing dicarbonyl compounds and amines. Improved synthesis of the corresponding imines/enamines. *Tetrahedron* **2003**, *59*, 1647-1656. (b) Soloshonok, V.A.; Ono, T. The Effect of Substituents on the Feasibility of Azomethine-Azomethine Isomerization: New Synthetic Opportunities for Biomimetic Transamination, *Tetrahedron* **1996**, *52*, 14701-14712.

54. Soloshonok, V.A.; Kukhar, V.P. Biomimetic transamination of α-Keto perfluorocarboxylic esters. An efficient preparative synthesis of β,β,β-trifluoroalanine. *Tetrahedron* **1997**, *53*, 8307-8314.

55. Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J.L.; Soloshonok, V.A.; Sorochinsky, A.E. Synthesis of Fluorine Containing β-Amino Acids, *Synthesis* **2011**, 3045-3079.

56. (a) Soloshonok, V.A.; Kirilenko, A.G.; Kukhar, V.P.; Resnati, G. Transamination of fluorinated β-Keto carboxylic esters. A biomimetic approach to β-Polyfluoroalkyl-β-Amino acids. *Tetrahedron Lett*. **1993**, *34*, 3621-3624. (b) Soloshonok, V.A.; Kukhar, V.P. Biomimetic Base-Catalyzed [1,3]-Proton shift reaction. A practical synthesis of β-Fluoroalkyl-β-Amino Acids. *Tetrahedron* **1996**, *52*, 6953-6964.

57. (a) Soloshonok, V.A.; Svedas, V.K.; Kukhar, V.P.; Kirilenko, A.G.; Rybakova, A.V.; Solodenko, V.A.; Fokina, N.A.; Kogut, O.V.; Galaev, I.Y.; Kozlova, E.V.; Shishkina, I.P.; Galushko, S.V. An enzymatic entry to enantiopure β-Amino acids. *Synlett* **1993**, 339-341. (b) Soloshonok, V.A.; Kirilenko, A.G.; Fokina, N.A.; Shishkina, I.P.; Galushko, S.V.; Kukhar, V.P.; Svedas, V.K.; Kozlova, E.V. Biocatalytic resolution of β-Fluoroalkyl-β-amino acids. *Tetrahedron Asymmetry* **1994**, *5*, 1119-1126. (c) Soloshonok, V.A.; Fokina, N.A.; Rybakova, A.V.; Shishkina, I.P.; Galushko, S.V.; Sorochinsky, A.E.; Kukhar, V.P.; Savchenko, M.V.; Svedas, V.K. Biocatalytic approach to enantiomerically pure β-Amino acids. *Tetrahedron Asymmetry* **1995**, *6*, 1601-1610.

58. (a) Soloshonok, V.A.; Kirilenko, A.G.; Fokina, N.A.; Galushko, S.V.; Kukhar, V.P.; Svedas, V.K.; Resnati, G. Chemo-Enzymatic approach to the synthesis of each of the four isomers of α-Alkyl-β-Fluoroalkyl-Substituted β-Amino acids. *Tetrahedron Asymmetry* **1994**, *5*, 1225-1228. (b) Soloshonok, V.A.; Soloshonok, I.V.; Kukhar, V.P.; Svedas, V.K. Biomimetic transamination of α-Alkyl-β-keto carboxylic esters. Chemo-Enzymatic approach to the stereochemically defined α-Alkyl-β-Fluoroalkyl-β-Amino acids. *J. Org. Chem*. **1998**, *63*, 1878-1884.

59. Blaskovich, M.A.T. Unusual amino acids in medicinal chemistry. *J. Med. Chem*. **2016**, *59*, 10807-10836.

60. (a) Soloshonok, V.A.; Kirilenko, A.G.; Galushko, S.V.; Kukhar, V.P. Catalytic asymmetric synthesis of β-Fluoroalkyl-β-Amino acids via

biomimetic [1,3]-Proton shift reaction. *Tetrahedron Lett*. **1994**, *35*, 5063-5064. (b) Soloshonok, V.A.; Yasumoto, M. Catalytic asymmetric synthesis of α-(Trifluoromethyl)benzylamine via cinchonidine derived base-catalyzed biomimetic 1,3-Proton shift reaction. *J. Fluor. Chem*. **2007**, *128*, 170-173.

61. (a) Michaut, V.; Metz, F.; Paris, J.M.; Plaquevent, J.C. Enantioselective organocatalytic route to trifluoromethyl-β-amino acids using chiral bases. *J. Fluorine Chem*. **2007**, *128*, 500-506. (b) Michaut, V.; Metz, F.; Paris, J.M.; Plaquevent, J.C. Ethyl-4,4,4-trifluoroacetoacetate (ETFAA), a powerful building block for enantiopure chirons in trifluoromethyl-β-amino acid series. *J. Fluorine Chem*. **2007**, *128*, 889-895.
62. Kukhar, V.P.; Soloshonok, V.A.; Galushko, S.V.; Rozhenko, A.B. Asymmetric [1,3]-Proton shift in azomethines as a new approach to the synthesis of optically active α-Trifluoromethyl-Containing amines and amino acids. *Dokl. Akad. Nauk SSSR* **1990**, *310*, 886-889.
63. (a) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. Highly regioselective hydrogenolysis of bis(α-methylbenzyl)amine derivatives affected by the trifluoromethyl substituent on the aromatic ring. *Org. Lett*. **2003**, *5*, 1007-1010. (b) Soloshonok, V.A.; Kukhar, V.P.; Galushko, S.V.; Svistunova, N.Y.; Avilov, D.V.; Kuzmina, N.A.; Raevski, N.I.; Struchkov, Y.T.; Pisarevsky, A.P.; Belokon, Y.N. General method for the synthesis of enantiomerically pure β-Hydroxy-α-amino acids, containing fluorine atoms in the side chains. Case of stereochemical distinction between methyl and trifluoromethyl groups. X-Ray crystal and molecular structure of the Nickel(II) complex of (2S,3S)-2- (Trifluoromethyl)threonine. *J. Chem. Soc. Perkin Trans 1* **1993**, 3143-3155. (c) Röschenthaler, G.-V.; Kukhar, V.P.; Kulik, I.B.; Belik, M.Y.; Sorochinsky, A.E.; Rusanov, E.B.; Soloshonok, V.A. Asymmetric synthesis of phosphonotrifluoroalanine and its derivatives using *N-tert*-butanesulfinyl imine derived from fluoral, *Tetrahedron Lett.* **2012**, *53*, 539-542. (d) Soloshonok, V.A.; Hayashi, T. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Methyl Isocyanoacetate with Fluorinated Benzaldehydes, *Tetrahedron Letters* **1994**, *35*, 2713-2716. (e) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D.O.; Soloshonok, V.A. Convenient Asymmetric Synthesis of β-Substituted α,α-Difluoro-β-Amino Acids via Reformatsky Reaction between Davis' *N*-Sulfinylimines and Ethyl Bromodifluoroacetate, *J. Org. Chem*. **2003**, *68*, 7448-7454. (f) Soloshonok, V.A.; Kacharov, A.D.; Hayashi, T. Gold(I)-Catalyzed Asymmetric Aldol Reactions of Isocyanoacetic Acid Derivatives with Fluoroaryl Aldehydes, *Tetrahedron* **1996**, *52*, 245-254.
64. (a) Soloshonok, V.A.; Ono, T. Highly enantioselective transfer of chirality from a less to a more conformationally unstable stereogenic center. A practical asymmetric synthesis of perfluoroalkyl amines. *J. Org. Chem*. **1997**, *62*, 3030-3031. (b) Han, J.; Sorochinsky, A.E.; Ono, T.; Soloshonok, V.A. Biomimetic Transamination - a Metal-Free Alternative to the Reductive Amination. Application for Generalized Preparation of Fluorine-Containing Amines and Amino Acids, *Current Organic Synthesis*, **2011**, *8*, 281-294.
65. (a) Soloshonok, V.A.; Ono T.; Soloshonok, I.V. Enantioselective biomimetic transamination of β-Keto carboxylic acid derivatives. An Efficient asymmetric synthesis of β-Fluoroalkyl-β-Amino acids. *J. Org. Chem*. **1997**, *62*, 7538-7539. (b) Soloshonok, V.A.; Ohkura, H.; Yasumoto, M. Operationally convenient asymmetric synthesis of (S)- and (R)-3-Amino-4,4,4- trifluorobutanoic Acid. Part I: Enantioselective biomimetic transamination of Isopropyl 4,4,4-Trifluoro-3-oxobutanoate. *J. Fluor. Chem*. **2006**, *127*, 924- 929. (c) Soloshonok, V.A.; Ohkura, H.; Yasumoto, M. Operationally Convenient Asymmetric Synthesis of (*S*)- and (*R*)-3-Amino-4,4,4-trifluoro-butanoic Acid. Part II: Enantioselective Biomimetic Transamination of 4,4,4-Trifluoro-3-oxo-*N*-[(*R*)-1-phenylethyl)butanamide, *J. Fluor. Chem*. **2006**, *127*, 930-935. (d) Soloshonok, V.A; Ono, T. First example of continuous-flow reaction conditions for biomimetic reductive amination of fluorine-containing carbonyl compounds. *J. Fluor. Chem*. **2008**, *129*, 785-787. (e) Soloshonok, V.A.; Catt, H. T.; Ono, T. Continuous-Flow asymmetric biomimetic transamination. *J. Fluor. Chem*. **2009**, *130*, 512-515. (f) Soloshonok, V.A.; Catt, H.T.; Ono, T. Biomimetic reductive amination under the continuous-flow reaction conditions. *J. Fluor. Chem*., **2010**, *131*, 261-265.
66. Han, J.; Kitagawa, O.; Wzorek, A.; Klika, K.D.; Soloshonok, V.A. The self-disproportionation of enantiomers (SDE): a menace or an opportunity? *Chem. Sci*., **2018**, *9*, 1718-1739.
67. (a) Soloshonok, V.A. Remarkable amplification of self-disproportionation of enantiomers on achiral-phase chromatography columns. *Angew. Chem. Int. Ed. Engl*. **2006**, *45*, 766-769. (b) Soloshonok, V.A.; Berbasov, D.O. Self-Disproportionation of enantiomers of (R)-Ethyl 3-(3,5-Dinitrobenzamido)- 4,4,4-trifluorobutanoate on achiral silica gel stationary phase. *J. Fluor. Chem*. **2006**, *127*, 597-603. (c) Soloshonok, V.A.; Berbasov, D.O. Self-Disproportionation of enantiomers on achiral phase chromatography. One more example of fluorine's magic powers. *Chimica Oggi/Chem. Today*, **2006**, *24*, 44-47. (d) Soloshonok, V.A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A.E. Self-Disproportionation of Enantiomers via Achiral Chromatography: a Warning and Extra Dimension in Optical Purifications, *Chem. Soc. Rev*. **2012**, *41*, 4180-4188.
68. (a) Soloshonok, V.A; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J.S.; Singleton, D.A. Phenomenon of optical self-purification of chiral nonracemic compounds. *J. Am. Chem. Soc*. **2007**, *129*, 12112-12113. (b) Yasumoto, M.; Ueki, H. Soloshonok, V.A. Self-Disproportionation of enantiomers of trifluoro lactic acid amides via sublimation. *J. Fluor. Chem*., **2010**, *131*, 266-269. (c) Tsuzuki, S.; Orita, H.; Ueki, H.; Soloshonok, V.A. First principle lattice energy calculations for enatiopure and racemic crystals of α-(trifluoromethyl)lactic acid. *J. Fluor. Chem*., **2010**, *131*, 461-466. (d) Albrecht, M.; Soloshonok, V.A.; Schrader, L.; Yasumoto, M.; Suhm, M.A. Chirality-dependent sublimation of α-(trifluoromethyl)-lactic acid: Relative vapor pressures of racemic, eutectic, and enantiomerically pure forms, and vibrational spectroscopy of isolated (S,S) and (S,R) dimmers. *J. Fluor. Chem*., **2010**, *131*, 495-504. (e) Yasumoto, M.; Ueki, H.; Ono, T.; Katagiri, T.; Soloshonok, V.A. Self-Disproportionation of enantiomers via sublimation: Isopropyl 3,3,3-(Trifluoro)lactate. *J. Fluor. Chem*., **2010**, *131*, 535-539. (f) Ueki, H.; Yasumoto, M.; Soloshonok V.A. Rational application of self-disproportionation of enantiomers via sublimation; a novel methodological dimension for optical purifications. *Tetrahedron Asymmetry*, **2010**, *21*, 1396-1400. (g) Han, J.; Nelson, D.J.; Sorochinsky, A.E.; Soloshonok, V.A. Self-Disproportionation of Enantiomers via Sublimation; New and Truly Green Dimension in Optical Purification, *Current Organic Synthesis*, **2011**, *8*, 310-317.
69. (a) Sorochinsky, A.E.; Aceña, J.L.; Soloshonok, V.A. Self-Disproportionation of Enantiomers of Chiral, Non-Racemic Fluoroorganic Compounds: Role of Fluorine as Enabling Element, *Synthesis* **2013**, *45*, 141-152. (b) Nakamura, T.; Tateishi, K.; Tsukagoshi, S.; Hashimoto, S.; Watanabe, S.; Soloshonok, V.A.; Aceña, J.L.; Kitagawa, O. Self-Disproportionation of Enantiomers of Non-racemic Chiral Amine Derivatives Through Achiral Chromatography, *Tetrahedron* **2012**, *68*, 4013-4017. (c) Suzuki, Y.; Han, J.; Kitagawa, O.; Aceña, J.L.; Klika, K.D.; Soloshonok, V.A.A comprehensive examination of the self-disproportionation of enantiomers (SDE) of chiral amides via achiral, laboratory-routine, gravity-driven column chromatography, *RSC Adv.*, **2015**, *5*, 2988-2993.
70. Han, J.; Wzorek, A.; Kwiatkowska, M.; Soloshonok, V.A.; Klika, K.D. The self-disproportionation of enantiomers (SDE) of amino acids and their derivatives, *Amino Acids*, **2019**, *51*, 865-889.
71. Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V.A.; Klika, K.D. Remarkable magnitude of the self-disproportionation of enantiomers (SDE) via achiral chromatography; application to the practical-scale enantiopurification of β-amino acid esters, *Amino Acids*, **2016**, *48*, 605-613.
72. Sorochinsky, A.E.; Katagiri, T.; Ono, T.; Wzorek, A.; Aceña, J.L.; Soloshonok, V.A. Optical purifications via Self-Disproportionation of Enantiomers by achiral chromatography; Case study of a series of α-CF_3-containing secondary alcohols, *Chirality* **2013**, *25*, 365-368.
73. (a) Soloshonok, V.A.; Wzorek, A.; Klika, K.D. A question of policy: should tests for the self-disproportionation of enantiomers (SDE) be mandatory for reports involving scalemates? *Tetrahedron: Asymmetry* **2017**, *28*, 1430-1434. (b) Han, J.; Dembinski, R.; Soloshonok, V.A.; Klika, K.D. A Call for a Change in Policy Regarding the Necessity for SDE Tests to Validate the Veracity of the Outcome of Enantioselective Syntheses, the Inherent Chiral State of Natural Products, and Other Cases Involving Enantioenriched Samples. *Molecules* **2021**, *26*, 3994. (c) Han, J.; Wzorek, A.; Klika, K.D.; Soloshonok, V.A. Recommended Tests for the Self-Disproportionation of Enantiomers (SDE) to Ensure Accurate Reporting of the Stereochemical Outcome of Enantioselective Reactions, *Molecules* **2021**, *26*, 2757.

Біоміметичне трансамінування як загальний підхід до синтезу фторовмісних амінів та амінокислот

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Резюме: Огляд присвячений відкриттю реакції азометин-азометинової ізомеризації фторованих *N*-бензилімінів та її подальшому розвитку в один із найбільш зручних, масштабованих і доступних синтетичних методів отримання біологічно значущих фторованих амінів і амінокислот. Цей метод, який зараз називають реакцією 1,3-протонного зсуву, широко використовується хіміками-органіками для синтезу різноманітних фторованих аміносполук, які відіграють важливу роль у розробці сучасних фармацевтичних препаратів і агрохімікатів.

Ключові слова: біоміметичне відновне амінування; фторовані сполуки; аміни; *α*- і *β*-амінокислоти; раціональне конструювання ліків.