2025
5(2), 1216

Journal of
Molecular Chemistry

New developments in asymmetric biomimetic transamination for preparation of tetrafluoroethylene-containing amines

Alicja Wzorek[1]*, Nataliya V. Lyutenko[2], Karel D. Klika[3], Taizo Ono[4], Jianlin Han[5]*, Ramin Javahershenas[6]*, Vadim A. Soloshonok[7,8]*

[1]Institute of Chemistry, Jan Kochanowski University in Kielce, Uniwersytecka 7, 25-406 Kielce, Poland. [2]Department of Fine Organic Synthesis, V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, The National Academy of Sciences of Ukraine, 1 Murmanska str., Kyiv 02094, Ukraine. [3]Molecular Structure Analysis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany. [4]National Institute of Advanced Industrial Science and Technology, 463-8560, Nagoya, Japan. [5]Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China. [6]Department of Organic Chemistry, Faculty of Chemistry, Urmia University, Urmia, Iran. [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.

Submitted on: 03-Dec-2024, Accepted and Published on: 03-Jan-2025

Insight-Review

ABSTRACT

Recent advancements in the asymmetric [1,3]-proton shift reaction for the preparation of amino compounds possessing a tetrafluoroethylene moiety have been reported. We critically discuss the observed stereochemical outcomes with respect to the trifluoromethyl and perfluoroalkyl groups traditionally employed in this reaction. The methodological significance of these results is highlighted as well as noting a potential inaccuracy in the reported enantioselectivities due to the self-disproportionation of enantiomers (SDE) phenomenon.

Keywords: biomimetic transamination; [1,3]-proton shift reactions; asymmetric synthesis; fluorine chemistry; tetrafluoroethylene moiety;

INTRODUCTION

The increasing prevalence of fluorine-containing, small-molecule pharmaceuticals is a well-justified phenomenon that capitalizes on the distinctive steric, electrostatic, and chemical properties of fluorine [1]. Despite well-founded health and environmental concerns [2], the integration of fluorine into bioactive molecules has shown no signs of abating [3]. Fluorine-containing drugs literally save lives and contribute significantly to the standards of well-being in Western countries [4]. Nevertheless, projecting future trends, it is plausible to anticipate that well-established substituents in drug design, such as the trifluoromethyl **1** and pentafluoroethyl **2** groups (Figure 1) that degrade into persistent TFA and pentafluoropropionic acid, respectively [5], will likely face increased regulatory scrutiny [6]. On the other hand, fluorinated substituents such as tetrafluoroethylene **3**–**5** [7], which may biodegrade to fluoride and thus align with evolving environmental legislation, are likely to encounter more favorable regulatory prospects.

*Corresponding Author: Vadim A. Soloshonok, Alicja Wzorek, Jianlin Han
Email: vadimsoloshonok@gmail.com (VAS), alicja.wzorek@ujk.edu.pl (AW), hanjl@njfu.edu.cn (JH)

URN:NBN:sciencein.jmc.2025.1216.
DOI: 10.62110/sciencein.jmc.2025.1216
Published by: ScienceIn Publishing https://pubs.thesciencein.org/jmc

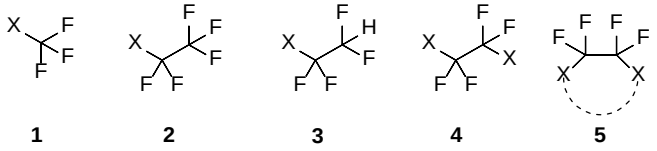


Figure 1. Common fluorine-containing moieties: trifluoromethyl **1**, pentafluoroethyl **2**, tetrafluoroethyl **3**, acyclic tetrafluoroethylene **4**, and cyclic tetrafluoroethylene **5** groups.

The properties and bioactivity of tetrafluoroethylene-containing compounds are generally not well known, apart from reports on the applications of tetrafluoroethylene moieties of types **6** and **7** (Figure 2) in the design of liquid crystals and fluorescent materials [8]. Additionally, compounds **8** and **9** have been reported to exhibit insecticidal and herbicidal activities, respectively [9].

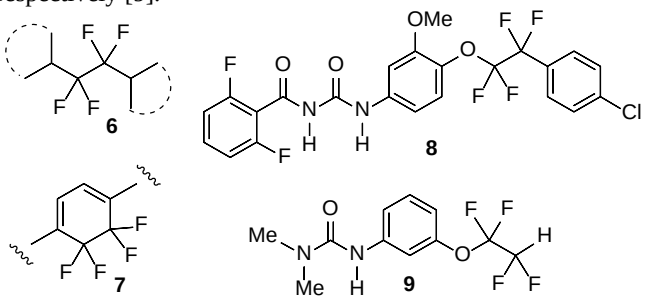
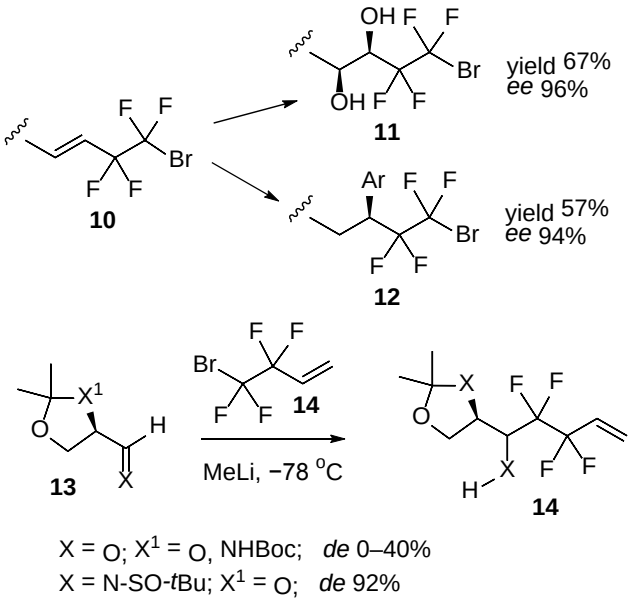


Figure 2. Tetrafluoroethylene-containing compounds **6**–**9** possessing useful properties.

Synthetic approaches for preparing compounds with a tetrafluoroethylene moiety are quite scarce, limited primarily to the elaboration of the double bond in substrates of type **10** or the addition of Li–CF_2CF_2– species to C=O or C=N bonds (Scheme 1).

Sharpless dihydroxylation of the double bond in substrate **10**, conducted under standard conditions, affords diol **11** with excellent enantioselectivity, albeit only in moderate yields [10]. Similarly, the enantioselective conjugate addition of aryl boronic acid to the C=C bond in **10** in the presence of a rhodium/BINAP catalyst provided compound **12** with high enantioselectivity, but again albeit only in 57% yield [11]. It should be noted that low-to-moderate chemical yields coupled with high-to-excellent enantioselectivities can often be an indication of erroneously recorded stereochemical outcomes owing to workers' oversight of the self-disproportionation of enantiomers (SDE) phenomenon [12]. Thus, unless SDE tests [13] are conducted, as required by some journals [14], the true enantioselectivity of these reactions remains unconfirmed and other researchers attempting to replicate such results should be aware of this fact.



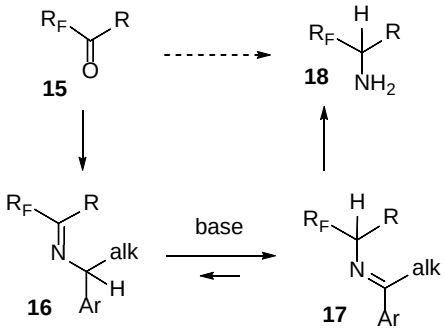
Scheme 1. Examples of asymmetric synthesis of tetrafluoroethylene compounds.

Diastereoselective addition reactions of Li–CF_2CF_2– species to the C=O and C=N bonds of chiral derivatives **13** are conducted under very restrictive and operationally inconvenient conditions, and only yield addition products **14** in moderate yields (61–76%) and variable diastereoselectivity [15].

Considering the high potential interest in tetrafluoroethylene-containing derivatives and the rather limited synthetic access to these compounds, it was exciting to see the report from Tsutomu Konno's laboratory on the asymmetric synthesis of tetrafluoroethylenated amines via the [1,3]-proton shift reaction [16]. In this brief review, we highlight the practical significance and methodological advances of the reported results while at the same time noting potential inaccuracies in the reported enantioselectivities due to the SDE phenomenon.

[1,3]-Proton shift reaction

The [1,3]-proton shift reaction refers to azomethine–azomethine isomerization via base-catalyzed [1,3]-proton transfer, as seen in the transformation of **16** to **17** (Scheme 2) [17]. This isomerization is a crucial step in the overall biomimetic reductive amination [18] of various carbonyl compounds **15** to amines **18** and amino acids [19].

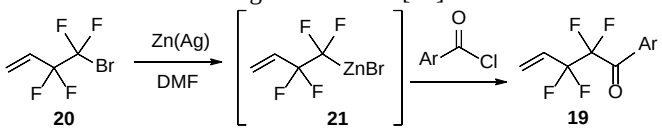


Scheme 2. Azomethine–azomethine isomerization via base-catalyzed [1,3]-proton transfer as a key step in biomimetic reductive amination.

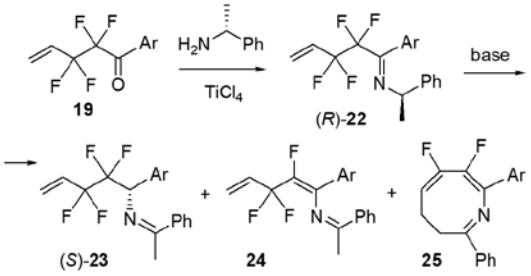
Of particular interest is the asymmetric version of this reaction, which can be conducted using a chiral base [20] and is thus enantioselectively catalyzed or a chiral amine to form the requisite Schiff base **16** [21] and thus utilizes a stoichiometric amount of chiral auxiliary starting from ketone **15**. Base-catalyzed azomethine–azomethine isomerization [22] is a reversible process; therefore, it is only of synthetic value when the equilibrium between **16** and **17** is strongly shifted towards **17**, for example when **17** is present in greater than 95% yield, ultimately leading to the amine **18**. Consequently, all of the parameters, such as the reaction conditions [23] and the nature of the substituents [24], play a critical role in the overall synthetic success. In this regard, the recent reports from Konno's laboratory on the use of tetrafluoroethylene-containing substrates represents a significant methodological advancement and a convenient access route to the corresponding amino compounds possessing valuable properties and potential bioactivity [16].

Asymmetric synthesis of tetrafluoroethylenated amines via [1,3]-proton shift

The starting tetrafluoroethylenated ketones **19** (Scheme 3) were prepared in a single step using commercially available 3,3,4,4-tetrafluoro-1-butene (**20**). These were then converted to organometallic species **21** followed by a reaction with acyl chloride to afford the target ketones **19** [25].



Scheme 3. Synthesis of tetrafluoroethylenated ketones **19**.



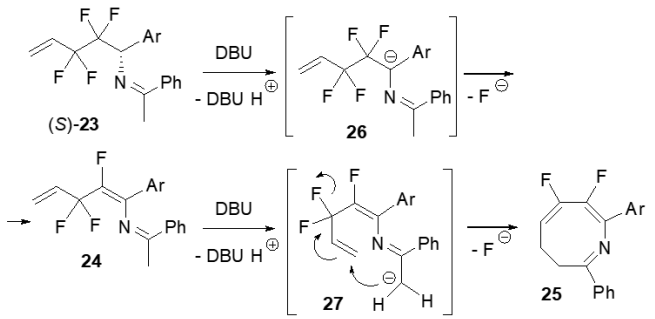
	23	24	25
DBU/1.2, THF	31	16	0
DBU/1.2, CH_3CN	17	0	39
DBU/1.2, Et_2O	38	14	17
DBU/1.2, hexane	26	12	0
DBU/1.2, CH_2Cl_2	36	3	38
DBU/1.2, cyclohexane	32	17	0
DBU/2.4, toluene	50	2	43
DBU/1.2, toluene	33	18	0
DBU/6.8, toluene	31	0	69

Scheme 4. [1,3]-Proton shift reaction of imines **22** with the resulting relative amounts of the products **23**–**25**.

The reaction of ketones **19** with enantiomerically pure 1-phenylethylamine (Scheme 4) were conducted under mild conditions at ambient temperature in diethyl ether using $TiCl_4$ as a dehydrating agent [26]. The procedure yielded the corresponding imines **22** in moderate to excellent isolated yields (60–96%).

The [1,3]-proton shift reaction of tetrafluoroethylenated imines **22** revealed unexpected results. Azomethine–azomethine isomerizations conducted in the presence of a strong base, such as DBU, gave rise to three major products **23**–**25**. Product (*S*)-**23** was the intended and expected compound, while dehydrofluorinated derivative **24** could be anticipated based on literature results [17, 20, 21, 23, 24]. However, the double dehydrofluorinated compound **25** was an entirely unexpected.

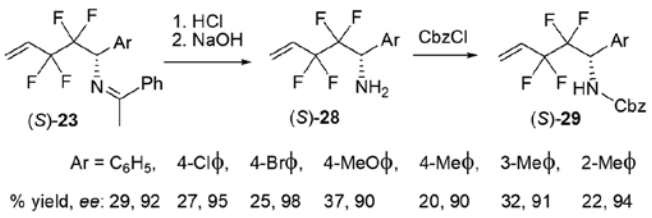
It was demonstrated that the reaction solvent and amount of DBU can profoundly affect the relative ratio of products **23**–**25**. Analysis of the reaction outcomes under various conditions led to the conclusion that imine **23** is the first reaction product, giving rise to intermediate triene **24** via the reaction anionic intermediate **26**. This intermediate then undergoes base-catalyzed cyclization to produce **25** via the reaction anionic intermediate **27**. Cyclic product **25** is likely the final and only product if the reaction is allowed to proceed to completion. The step-by-step sequence of the corresponding reactions and plausible mechanistic details are illustrated in Scheme 5.



Scheme 5. Mechanism of dehydrofluorinated product, **25**formation.

The [1,3]-proton shift products **23** (Scheme 6) were treated with 2*N* HCl aqueous solution in diethyl ether for 2 hours, followed by neutralization with 2*N* NaOH aqueous solution to yield the corresponding free amines **28**. Subsequent treatment of amines **28** with CbzCl and pyridine in dichloromethane afforded the corresponding protected derivatives **29**, which were isolated with high enantiomeric purity and in reasonable yields.

SDE is a ubiquitous and general phenomenon that has been observed and reported for practically all types of chiral compounds under all known physicochemical phase transitions, including achiral gas chromatography [27]. Typical laboratory purification methods such as achiral column chromatography [28] and sublimation [29] are particularly prone to the SDE phenomenon.



Scheme 6. Preparation of the protected target amines **29** from Schiff bases **23**.

Moreover, it has been well established that fluorine is one of the most forceful SDE-phoric groups as a large magnitude of the SDE is often observed for fluorinated compounds when a fluorine atom(s) is(are) located in close proximity to the stereogenic center [30]. Therefore, it should be considered an unfortunate oversight by the authors [16] that they did not perform the required SDE tests [14] relative to their applied purification methods to confirm and validate the reported stereochemical outcome of this novel and fascinating [1,3]-proton shift reaction.

Conclusions

As reported by Konno's group, the [1,3]-proton shift reaction can be successfully extended to the asymmetric synthesis of amines containing a tetrafluoroethylene moiety. However, the corresponding DBU-catalyzed azomethine–azomethine isomerization of tetrafluoroethylene-containing imines is complicated by sequential dehydrofluorination, which leads to the formation of unsaturated byproducts. But by and large the target tetrafluoroethylene imines could be isolated with high enantiomeric purity in moderate yields. However, the true enantioselectivity of these reactions remains unconfirmed in the absence of SDE tests because of the potential for the SDE phenomenon to be in effect during routine purification steps and other workers attempting to replicate the reported results should be aware of this oversight. Nevertheless, the overall procedure provides a simple access to a previously unknown compound with potentially interesting biological activity.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21761132021) and the Qing-Lan Project of Jiangsu Province (for Han) and IKERBASQUE, Basque Foundation for Science (for Soloshonok).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

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

REFERENCES AND NOTES

1. (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.; 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.
2. 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.
3. (a) Han, J.; Wzorek, A.; Dhawan, G.; Zhang, W.; Sorochinsky, A. E.; Ono, T.; Soloshonok, V. A. New drugs appearing on the market in 2023: molecules containing fluorine and fragments of tailor-made amino acids. Ukr. *Bioorg. Acta* **2024**, *19*, 3–20. (b) Wang, Q.; Bian, Y.; Dhawan, G.; Zhang, W.; Sorochinsky, A. E.; Makarem, A.; Soloshonok, V. A.; Han, J. FDA approved fluorine-containing drugs in 2023. *Chin. Chem. Lett.* **2024**, *35*, 109780. (c) 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. (d) 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. (e) 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. (f) 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. (g) 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. *Chin. Chem. Lett.* **2021**, *32*, 3342–3354.
4. (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (b) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. (c) Johnson, B. M.; Shu, Y. Z.; Zhuo, X.; Meanwell, N. A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem.* **2020**, *63*, 6315–6386. (d) Han, J.; Remete, A. M.; Dobson, L. S. Next generation organofluorine containing blockbuster drugs. *J. Fluor. Chem.* **2020**, 239, 109639. (e) 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. (f) 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.
5. (a) Khan, M. F.; Murphy, C. D. Bacterial degradation of the antidepressant drug fluoxetine produces trifluoroacetic acid and fluoride ion. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 9359–9369. (b) Sun, M.; Cui, J.'n.; Guo, J.; Zhai, Z.; Zuo, P.; Zhang, J. Fluorochemicals biodegradation as a potential source of trifluoroacetic acid (TFA) to the environment. *Chemosphere* **2020**, *254*, 126894.
6. (a) Dils, E. *ETC/WMGE Report 9/2021: Fluorinated polymers in a low carbon, circular and toxic-free economy*; European Environment Information and Observation Network, 2021. https://www.eionet.europa.eu/etcs/etc-wmge/products/etc-wmge-reports/fluorinated-polymers-in-a-low-carbon-circular-and-toxic-free-economy. (b) Lohmann, R.; Breivik, K.; Dachs, J.; Muir, D. Global Fate of POPs: Current and Future Research Directions. *Environ. Pollut.* **2007**, *150*, 150–165. (c) Nakayama, S. F., Yoshikane, M.; Onoda, Y. et.al.. Worldwide trends in tracing poly- and perfluoroalkyl substances (PFAS) in the environment. *Trend. Anal. Chem.* **2019**, *121*, 115410. (d) European Chemicals Agency (ECHA), FAS regulation in Europe. https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas. (e) Garnett. K.; Van Calster, G. The Concept of Essential Use: A Novel Approach to Regulating Chemicals in the European Union. *Transnatl. Environ. Law* **2021**, *10*, 159–187.
7. Václavík, J.; Klimánková, I.; Budinská, A.; Beier, P. Advances in the Synthesis and Application of Tetrafluoroethylene- and 1,1,2,2-Tetrafluoroethyl-Containing Compounds. *Eur. J. Org. Chem.* **2018**, *2018*, 3554–3593.
8. (a) Kirsch, P.; Bremer, M.; Huber, F.; Lannert. H; Ruhl, A.; Lieb, M.; Wallmichrath, T. Nematic Liquid Crystals with a Tetrafluoroethylene Bridge in the Mesogenic Core Structure. *J. Am. Chem. Soc.* **2001**, *123*, 5414–5417. (b) Yamada, S.; Tamamoto, K.; Kida, T.; Asai, T.; Ishihara, T.; Konno, T. Rational design and synthesis of a novel laterally-tetrafluorinated tricyclic mesogen with large negative dielectric anisotropy. *Org. Biomol. Chem.* **2017**, *15*, 9442–9454. (c) Yamada, S.; Hashishita, S.; Asai, T. Design, synthesis and evaluation of new fluorinated liquid crystals bearing a CF_2CF_2 fragment with negative dielectric anisotropy. *Org. Biomol. Chem.* **2017**, *15*, 1495–1509. (d) Kajimoto, C.; Yamada, S.; Konno, T. Novel multi-functionalized fluorine-containing organometallics: Preparation and applications of tetrafluoroethylenated zinc reagent. *J. Fluor. Chem.* **2021**, *245*, 109781. (e) Kumon, T.; Hashishita, S.; Kida, T.; Yamada, S.; Ishihara, T.; Konno, T. Gram-scale preparation of negative-type liquid crystals with a CF_2CF_2-carbocycle unit via an improved short-step synthetic protocol. *Beilstein J. Org. Chem.* **2018**, *14*, 148–154. (f) Ohsato, H.; Morita, M.; Yamada, S.; Agou, T.; Fukumoto, H.; Konno, T. Aggregation-induced enhanced fluorescence by hydrogen bonding in π-conjugated tricarbocycles with a CF_2CF_2-containing cyclohexa-1,3-diene skeleton. *Mol. Syst. Des. Eng.* **2022**, *7*, 1129–1137. (g) Ohsato, H.; Kawauchi, K.; Yamada, S.; Konno, T. Diverse Synthetic Transformations Using 4-Bromo-3,3,4,4-tetrafluorobut-1-ene and Its Applications in the Preparation of CF_2CF_2-Containing Sugars, Liquid Crystals, and Light-Emitting Materials. *Chem. Rec.* **2023**, *23*, e202300080.
9. (a) Bianchi, D.; Cesti, P.; Spezia, S.; Garavaglia, C.; Mirenna, L. Chemoenzymatic Synthesis and Biological Activity of Both Enantiomeric Forms of Tetraconazole, a New Antifungal Triazole. *J. Agric. Food Chem.* **1991**, *39*, 197–201. (b) N'Go, I.; Golten, S.; Ardá, A.; Cañada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. Tetrafluorination of Sugars as Strategy for Enhancing Protein–Carbohydrate Affinity: Application to UDP-Gal*p* Mutase Inhibition. *Chem.—Eur. J.* **2014**, *20*, 106–112. (c) Sari, O.; Bassit, L.; Gavegnano, C.; McBrayer, T. R.; McCormick, L.; Cox, B.; Coats, S. J.; Amblard, F.; Schinazi, R. F. Synthesis and antiviral evaluation of 2′,2′,3′,3′-tetrafluoro nucleoside analogs. *Tetrahedron Lett.* **2017**, *58*, 642–644.
10. (a) Boydell, A. J.; Vinader, V.; Linclau, B. Enantioselective Synthesis of Ttetrafluoroethylene-Containing Monosaccharides. *Angew. Chem., Int. Ed.* **2004**, *43*, 5677–5679. (b) Linclau, B.; Boydell, A. J.; Timofte, R. S.; Brown, K. J.; Vinader, V.; Weymouth-Wilson, A. C. Enantioselective synthesis of tetrafluorinated ribose and fructose. *Org. Biomol. Chem.* **2009**, *7*, 803–814.
11. Yamashika, K.; Morishitabara, S.; Yamada, S.; Kubota, T.; Konno, T. An asymmetric tertiary carbon center with a tetrafluoroethylene (–CF_2CF_2–) fragment: Novel construction method and application in a chiral liquid crystalline molecule. *J. Fluor. Chem.* **2018**, *207*, 24–37.
12. (a) Suzuki, Y.; Han, J.; Kitagawa, O.; A. E.; 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. (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) 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.

13. (a) 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. (b) Yasumoto, M.; Ueki, H.; Ono, T.; Katagiri, T.; Soloshonok, V. A. Self-disproportionation of enantiomers of isopropyl 3,3,3-(trifluoro)lactate via sublimation: Sublimation rates vs. enantiomeric composition. *J. Fluor. Chem.* **2010**, *131*, 535–539. (c) Ueki, H.; Yasumoto, M.; Soloshonok V. A. Rational application of self-disproportionation of enantiomers via sublimation—a novel methodological dimension for enantiomeric purifications. *Tetrahedron: Asymmetry* **2010**, *21*, 1396–1400.
14. (a) 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. (b) 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. (c) 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.
15. (a) Fontenelle, C. Q.; Tizzard, G. J.; Linclau, B. The synthesis of tetrafluorinated aminosugars. *J. Fluor. Chem.* **2015**, *174*, 95–101. (b) Konno, T.; Hoshino, T.; Kida, T.; Takano, S.; Ishihara, T. Short synthetic preparation of enantiomerically pure tetrafluoroethylenated sugar derivatives. *J. Fluor. Chem.* **2013**, *152*, 106–113.
16. Kabumoto, Y.; Yoshimoto, E.; Xiaohuan, B.; Yasui, M.; Yamada, S.; Konno, T. Efficient and Convenient Access to Optically Active Tetrafluoroethylenated Amines Based on [1,3]-Proton Shift Reaction. *Beilstein Arch.* **2024**, 202451.
17. (a) 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. (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. (c) 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.
18. Braunshtein, A. E.; Kritsman, M. G. Biological transamination. *Biochemistry* **1937**, *2*, 859–874.
19. (a) Martell, A. E. Vitamin B_6 Catalyzed Reactions of *α*-Aamino and *α*-Keto Acids: Model Ssystems. *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. Mol. Biol. Rev.* **1988**, *52*, 452–484. (d) 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. *Curr. Org. Synth.* **2011**, *8*, 281–294. (e) Wzorek, A.; Han, J.; Lyutenko, N. V.; Koley, M.; Sorochinsky, A. E.; Ono. T.; Soloshonok, V. A. Discovery of biomimetic transamination as a general synthetic method for preparation of fluorine-containing amines and amino acids. *Ukr. Bioorg. Acta* **2023**, *18*, 3–15. (f) Toney, M. D.; Kirsch, J. F. Lysine 258 in Aspartate Aminotransferase Enforcer of the Circe Effect for Amino Acid Substrates and General-Base Catalyst for the 1,3-Prototropic Shift. *Biochemistry* **1993**, *32*, 1471–1479. (g) 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. (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. (c) 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. *Chem. Commun.* **2012**, *48*, 4124–4126.
21. (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.; Ono, T. Highly Enantioselective Transfer of Chirality from a Less to a More Conformationally Unstable Stereogenic Center. A Practical Asymmetric Synthesis of (Fluoroalkyl)amines *via* Biomimetic Transamination. *J. Org. Chem.* **1997**, *62*, 3030–3031. (c) Soloshonok, V.A.; Ohkura, H.; Yasumoto, M. Operationally convenient asymmetric synthesis of (*S*)- and (*R*)-3-amino-4,4,4-trifluorobutanoic 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.
22. Yasumoto, M.; Ueki, H.; Soloshonok, V. A. 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.
23. (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.; 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. (c) 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.
24. (a) Soloshonok, V. A.; Kirilenko, A. G.; Fokina, N. A.; Kukhar, V. P.; Galushko, S. V.; Švedas, 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.; Ono, T. The effect of substituents on the feasibility of azomethine-azomethine isomerization: New synthetic opportunities for biomimetic transamination. *Tetrahedron* **1996**, *52*, 14701–14712. (c) Soloshonok, V. A.; Soloshonok, I. V.; Kukhar, V. P.; Svedas, V. K. Biomimetic Transamination of *α*-Alkyl *β*-Keto Carboxylic Esters. Chemoenzymatic Approach to the Stereochemically Defined *α*-Alkyl *β*-Fluoroalkyl *β*-Amino Acids. *J. Org. Chem.* **1998**, *63*, 1878–1884.
25. Tamamoto, K.; Yamada, S.; Konno, T. Practical tetrafluoroethylene fragment installation through a coupling reaction of (1,1,2,2-tetrafluorobut-3-en-1-yl)zinc bromide with various electrophiles. *Beilstein J. Org. Chem.* **2018**, *14*, 2375–2383.
26. (a) Braconi, E.; Cramer, N. Crossed Regio- and Enantioselective Iron-Catalyzed [4+2]-Cycloadditions of Unactivated Dienes. *Angew. Chem., Int. Ed.* **2022**, *61*, e202112148. (b) Hou, W.; Tang, G. L.; Huang, Z. Thio-imino-tetrahydroacridine Iron Complexes for Ethylene Polymerization. *Organometallics* **2022**, *41*, 3115–3121.
27. Wzorek, A.; Soloshonok, V. A.; Klika, K. D. The Self-Disproportionation of Enantiomers (SDE) of α-Pinene via Evaporation off Silica Gel and Foam Fractionation—Validation of the Plausibility of SDE via Gas Chromatography (GC) for α-Pinene. *Separations* **2023**, *10*, 382.
28. (a) Soloshonok, V. A. Remarkable Amplification of Self-Disproportionation of Enantiomers on Achiral-Phase Chromatography Columns. *Angew. Chem., Int. Ed.* **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.; 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.
29. (a) 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. (b) Soloshonok, V. A; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. Phenomenon of Optical Self-Purification of Chiral Non-Racemic Compounds. *J. Am. Chem. Soc.* **2007**, *129*, 12112–12113. (c) 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. *Curr. Org. Synth.* **2011**, *8*, 310–317.
30. (a) Soloshonok, V. A.; Berbasov, D. O. Self-Disproportionation of Enantiomers on Achiral Phase Chromatography. One More Example of Fluorine's Magic Powers. *Chim. Oggi–Chem. Today* **2006**, *24*, 44–47. (b) 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.