ISSN 1814-9758. Ukr. Bioorg. Acta, 2023, Vol. 18, N 1
UDC 577.122.34/.345
DOI: https://doi.org/10.15407/bioorganica2023.01.010

UBA
Ukrainica Bioorganica Acta
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REVIEW

Applications of chiral sulfinyl auxiliaries in the asymmetric synthesis of fluorinated amines and amino acids

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Abstract: This review article covers the developments made in collaboration by groups of Professors V.P. Kukhar and P. Bravo to the synthetic applications of sulfinyl compounds as versatile chiral auxiliaries for asymmetric preparation of fluorinated amines and amino acids. The potential of the sulfinyl chiral auxiliaries in the field of stereoselective transformations of fluorinated substrates is demonstrated by diastereoselective methylene transfer from diazomethane to the carbonyl of *β*-keto-*γ*-fluoroalkyl sulfoxides as a general approach for preparation of various fluorinated oxirane derivatives, diastereoselective sulfoxide anions addition to fluorinated imines leading to convenient preparation of *α*-fluoroalkyl *α*-amino acids, hydroxy amines, and amines, diastereoselective Mannich-type reaction between *N-tert*-butanesulfinyl-3,3,3-trifluoroacetaldimine and protected alkyl glycolates furnishing *β*-trifluoromethyl isoserine derivatives and diastereoselective additions of phosphite or *α*-phosphonate anions to *N-tert*-butanesulfinyl-3,3,3-trifluoroacetaldimine using for synthesis of trifluoromethylated *α*- and *β*-aminophosphonic acids. Furthermore, diastereoselective additions of Reformatsky reagent derived from bromodifluoroethyl acetate as well as *α,α*-difluorophosphonate anions to *N-p*-toluenesulfinyl imines allowing convenient preparation of *α,α*-difluoro-*β*-amino acids and *α,α*-difluoro-*β*-amino phosphonates in enantiomerically pure form are described. Effect of fluorine on the mechanism and stereochemical outcome of these reactions is briefly discussed.

Keywords: fluorine and compounds; asymmetric synthesis; sulfoxides; *N*-sulfinyl imines; fluorinated epoxides; *α*-fluoroalkyl amino derivatives; *α*- and *β*-amino acids; *α*- and *β*-aminophosphonates.

Introduction

Sulfinyl compounds such as sulfoxides, *N*-sulfinyl imines, sulfinamides, sulfoximines, and other derivatives (Figure 1), are recognized as powerful chiral auxiliaries that play an important role in the stereoselective preparation of variety of useful compounds [1]. They are also used in catalytic stereoselective reactions, both as ligands for transition metals and as chiral organocatalysts. Recently, the availability of sulfoximines, sulfonimidamides, and sulfonimidates has led to the increased interest in their application in organic synthesis. Due to tetrahedral stereogenic sulfur atom connected to electronegative oxygen atom by a polar, partially dative bond, sulfinyl auxiliaries are capable to provide high levels of stereocontrol in various classes of reactions and can be used as chiral equivalents of alkyl (reductive desulfurization), vinyl (*syn*-elimination reaction), hydroxymethyl (Pummerer rearengement), and amino (hydrolysis of *N*-sulfinyl imines) groups.

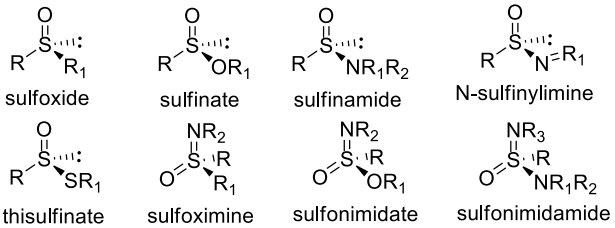

Figure 1. Examples of chiral sulfinyl compounds.

Received: 02.03.2023
Revised: 30.03.2023
Accepted: 20.04.2023
Published online: 30.06.2023

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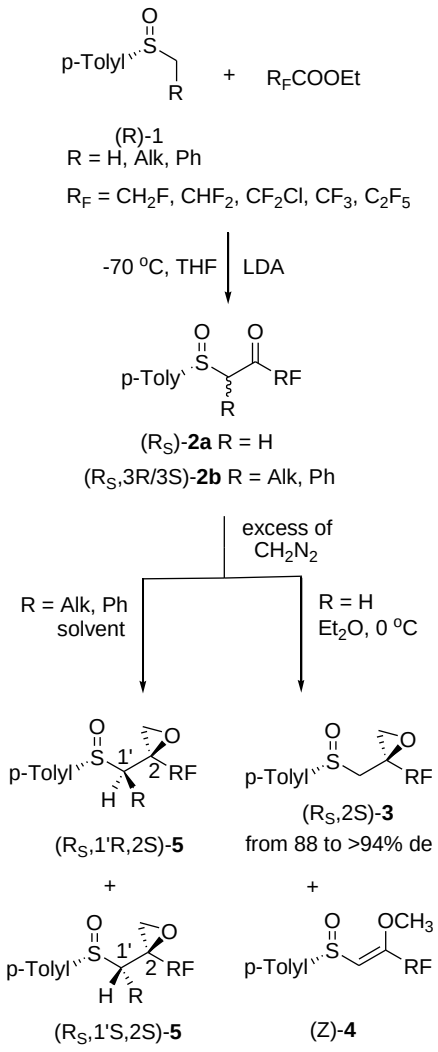
In this review we will discuss the development of sulfinyl auxiliaries methodology achieved in collaboration between groups of Professors V.P. Kukhar [2] and P. Bravo as a part of greater research efforts toward elaboration of convenient methods for asymmetric preparation of fluorinated amines and amino acids and investigation of their biological properties. The transformation of the sulfinyl chiral auxiliaries was featured with good functional group tolerance, and the possibility of modifying complex bioactive scaffolds resulting in augment the diversity and applications of fluorinated amines and amino acids.

Diastereoselective methylene transfer from diazomethane to the carbonyl of β-keto-γ-fluoroalkyl sulfoxides

Our initial investigation in this area was devoted to exploring asymmetric methylene transfer reactions from diazomethane to the carbonyl group of β-keto-γ-fluoroalkyl sulfoxides (*R*)-**2**, available by acylation of the α-lithio derivatives of *p*-tolyl alkyl sulfoxides (*R*)-**1** with fluorinated ethyl acetates, giving rise under mild conditions to the corresponding oxiranes in generally good chemical yields (Scheme 1). The synthetic opportunities associated with the epoxide ring and the sulfinyl group make these products highly promising building blocks for the synthesis of a variety of enantimerically pure open-chain fluorinated compounds containing different functional groups [3]. Thus, reactions of α-unsubstituted β-keto sulfoxides (*R*)-**2a** with diazomethane under optimized conditions in Et_2O at 0 °C led to mixtures of oxiranes (R_S,2*S*)-**3** and enol ethers (*Z*)-**4** ranging from 5:1 to 1:2 [4]. Formation of oxiranes (R_S,2*S*)-**3**, proceeded in good yield and with high diastereomeric excess. The diastereoselectivity in favor of oxiranes (R_S,2*S*)-**3** is consistent with ability of the sulfinyl group to participate in diazomethane coordination resulting in *Re* face attack of β-keto sulfoxides (*R*)-**2a** by approaching reagent. In addition, high diastereoselectivity is also associated with the presence of an electron-withdrawing fluoroalkyl group in β-keto sulfoxides (*R*)-**2a**, since similar results were obtained using the corresponding bromo and chlorine derivatives. This methodology has been expanded to α-alkyl/phenyl substituted β-keto sulfoxides (*R*)-**2b** leading under appropriate conditions to mixture of (R_S,1'*R*,2*S*)-**5** and (R_S,l'*S*,2*S*)-**5** diastereomers in high chemical yields and synthetically useful levels of diastereoselectivity [5]. Predominant role of the sulfinyl group in controlling the configuration of the oxirane ring was generally observed.

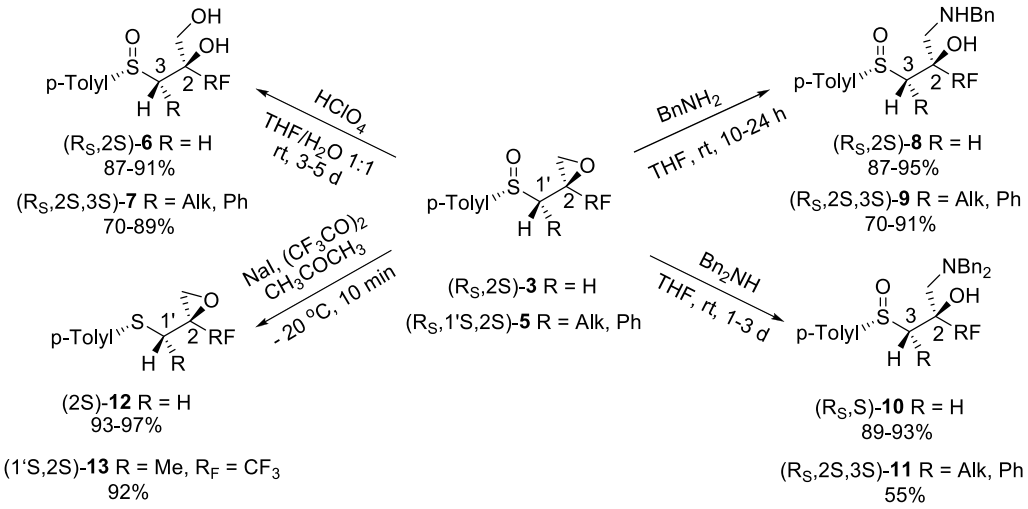
Synthetic application of oxiranes (R_S,2*S*)-**3** and (R_S,l'*S*,2*S*)-**5**, isolated in enantiomerically pure form by fractional crystallization or column chromatography, including ring opening by oxygen, halogen, and nitrogen nucleophiles, reduction and elimination reactions were studied (Scheme 2) [5]. In that context, acid-catalyzed ring-opening of oxiranes (R_S,2*S*)-**3** and (R_S,l'*S*,2*S*)-**5** in THF/water mixture using perchloric acid as the promotor cleanly afforded diols (R_S,2*S*)-**6** and (R_S,2*S*,3*S*)-**7**. Although



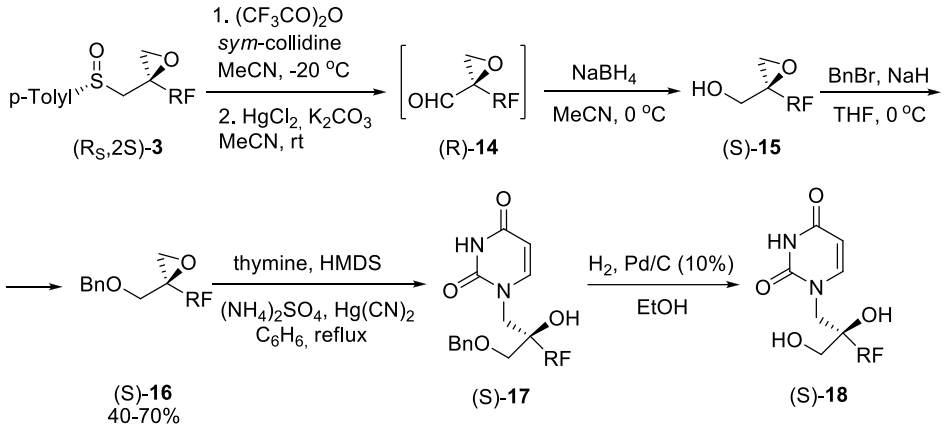
Scheme 1. Reactions of β-keto sulfoxides (*R*)-**2** with diazomethane.

cleanly afforded diols (R_S,2*S*)-**6** and (R_S,2*S*,3*S*)-**7**. Although reactions proceeded at room temperature for 3-5 days, the target products were isolated in high yields (70-91%). Ring opening of oxiranes (R_S,2*S*)-**3** and (R_S,l'*S*,2*S*)-**5** with benzylamine in THF at room temperature proceeded with high rates leading to the selective preparation of amino alcohols (R_S,2*S*)-**8** and (R_S,2*S*,3*S*)-**9** in excellent isolated yields. The reactions of oxiranes (R_S,2*S*)-**3** and (R_S,l'*S*,2*S*)-**5** with dibenzyl amine occurred slowly at room temperature to give *N*,*N*-dibenzyl derivatives (R_S,2*S*)-**10** and (R_S,2*S*,3*S*)-**11**. Treatment of oxiranes (R_S,2*S*)-**3** and (R_S,l'*S*,2*S*)-**5** in acetone solution with NaI and trifluoroacetic anhydride for 10 min at -20 °C gave sulfenyl derivatives (2*S*)-**12** and (1'*S*,2*S*)-**13** without affecting the oxirane ring. It should be noted that ring-opening reactions proceeded with complete regioselectivity involving attack of nucleophile exclusively on the less substituted carbon atom of the epoxide ring and could be explained based on steric and electronic features.

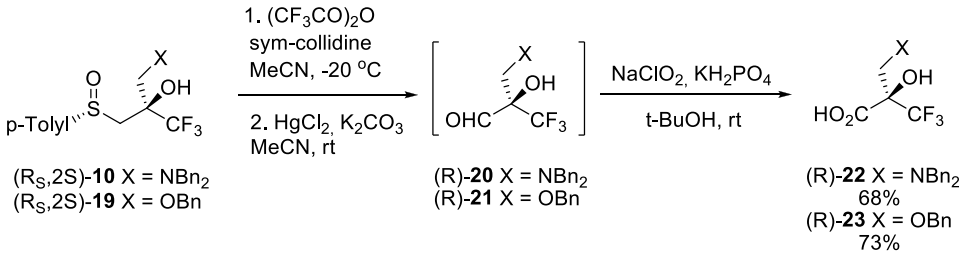
Sulfur-free epoxy alcohols (*S*)-**15** were synthesized by Pummerer rearrangement of oxiranes (R_S,2*S*)-**3** promoted by trifluoroacetic anhydride and *sym*-collidine in



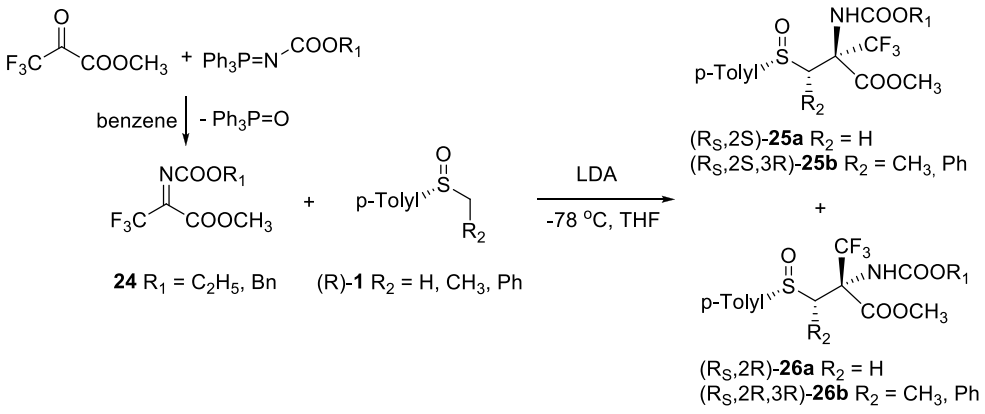
Scheme 2. Ring-opening and reduction reactions of oxiranes (*R*S,2*S*)-**3** and (*R*S,1'*S*,2*S*)-**5**.



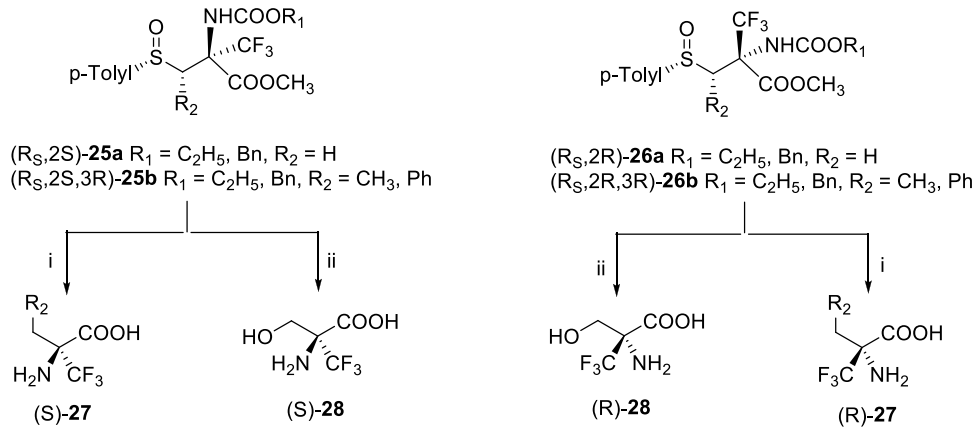
Scheme 3. Ring-opening and reduction reactions of oxiranes (*R*S,2*S*)-**3** and (*R*S,1'*S*,2*S*)-**5**.



Scheme 4. Pummerer rearrangement of acyclic derivatives (*R*S,2*S*)-**10** and (*R*S,2*S*)-**19**.



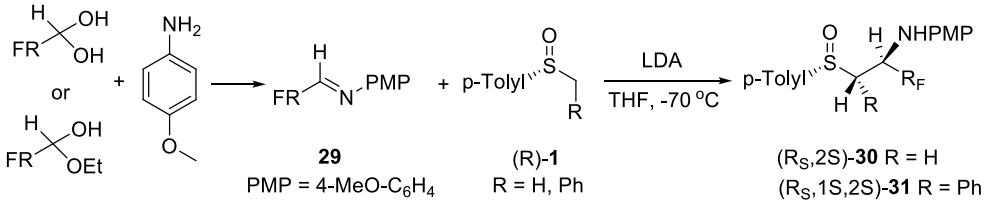
Scheme 5. Addition of *α*-lithiated alkyl *p*-tolyl sulfoxides (*R*)-**1** to *N*-acyl imines of trifluoropyruvate **24**.



Reagents and conditions: i) a) $(CF_3CO)O_2$, NaI, acetone, -20 °C; b) Ni-Raney, ethanol, 80 °C; c) 6N HCl, 100 °C or 0.5 N KOH/CH_3OH, rt; d) DOWEX 50W-8X; ii) a) $(CF_3CO)O_2$, *sym*-collidine, CH_3CN, 0 °C; b) $HgCl_2$, K_2CO_3, 20 °C; c) $NaBH_4$, H_2O, 20 °C; d) Ni-Raney, H_2, Et_2O, 0 °C; e) 0.5 N KOH, MeOH/H_2O, 20 °C; f) DOWEX 50W

Scheme 6. Synthesis of both (*S*)- and (*R*)-enantiomers of α-trifluoromethyl α-amino acids **27** and **28.**

Table 1. Addition of α-lithiated alkyl *p*-tolyl sulfoxides (*R*)-**1** to *N*-PMP aldimines **29**.



Entry	R_F	R	dr	yield (%)
1	CF_3	H	86/14	88(72)
2	CF_2CF_3	H	87/13	87(72)
3	CF_2CF_2H	H	85/15	90(70)
4	CF_3	Ph	86/14	98(59)
5	CF_2CF_3	Ph	87/13	97(60)
6	CF_2CF_2H	Ph	87/13	98(59)

[a] Overall isolated yield. Isolated yield of diastereomerically pure **30** and **31** is given in parentheses.

acetonitrile toward epoxy aldehydes **14** followed by treatment with sodium borohydride (Scheme 3) [4]. Protection of primary alcohols (*S*)-**15** with benzyl bromide in the presence of NaH led to (*S*)-**16** in satisfying overall yield from (R_S,2*S*)-**3**. Subsequent ring opening of (*S*)-**16** with thymine under base conditions in THF at room temperature afforded protected acyclic nucleosides **17** which were isolated by flash chromatography [6]. Finally, reductive debenzylation of **17** employing 10% palladium on carbon in ethanol allowed to obtain enantiomerically pure fluorinated acyclic nucleosides **18** in excellent yield.

The Pummerer rearrangement was used to remove the sulfinyl group in acyclic derivatives (R_S,2*S*)-**10** and (R_S,2*S*)-**19** to yield intermediate aldehydes (*R*)-**20** and (*R*)-**21** which were further transformed into α-hydroxy-α-trifluoromethyl-β-amino acid **22** and α-trifluoromethyl-α,β-dihydroxy acid **23** by oxidation with sodium chlorite (Scheme 4) [4]. It should be noted that chiral trifluorolactic acid derivatives of type **23** are very useful compounds in studying the phenomenon of optical self-purification via preferential sublimation of racemic or enantiomerically pure forms [7].

Chiral sulfoxide anions addition to fluorinated imines

The next aim of our study was the development of diastereoselective addition reactions between sulfoxide stabilized carboanions and fluoroalkylated imines as straightforward approach to corresponding enantiomerically pure α-fluoroalkyl β-sulfinyl amines and then demonstration of their transformation into enantiomerically pure α-amino acids bearing fluoroalkyl substituent on the chiral center. We found that *N*-acyl imines of methyl trifluoropyruvate **24**, derived by the Staudinger reaction of

methyl trifluoropyruvate with triphenylphosphazenes under mild conditions in 70-95% yields [8], were efficient substrates for addition reactions with lithium anion of alkyl *p*-tolyl sulfoxides (*R*)-**1** (Scheme 5) [9]. The nucleophilic addition in THF at -78 ºC preceded regioselectively at the iminic carbon affording corresponding products in good overall yields. However, these reactions were not highly stereoselective and mixtures of all possible diastereoisomers were formed according to ^{1}H and ^{19}F NMR analysis of the crude mixtures. Diastereomerically pure major products **25** and **26** were isolated by flash chromatography and/or fractional crystallization in moderate yields (30-42%). Diastereomeric purity was determined to be >98% *de* for all isomers by HPLC analyses. Configuration assignments of the obtained *β*-amino sulfoxides were made by X-ray crystallography analysis as well as ^{19}F NMR and chemical correlation.

Resulting diastereomers **25b** and **26b** could be transformed into the corresponding free *α*-amino acids (*S*)- and (*R*)-**27** in a three-step reaction sequence (Scheme 6). Well-optimized reduction using sodium iodide and trifluoroacetic anhydride followed by desulfurization with Ni-Raney and further deprotection led to series of *α*-trifluoromethyl *α*-amino acids (*S*)- and (*R*)-**27** with excellent enantiomerical purity.

The Pummerer rearrangement of both diastereomers **25a** and **26a** with trifluoroacetic anhydride and *sym*-collidine followed by hydrolysis of the *α*-trifluoroacetoxy sulfides, in situ reduction of the intermediate aldehydes with sodium borohydride, and subsequent deprotection of amino and carboxylic functions allowed to extend this strategy to the first synthesis of both (*S*)- and (*R*)-enantiomers of *α*-trifluoromethyl serine **28** in enantiomerically pure form (Scheme 6) [10].

We assumed that high electrophilicity of the *N*-acyl imines of methyl trifluoropyruvate [11] resulted in low stereoselectivity of chiral sulfoxide-stabilised carbanions additions. To verify this assumption, we explored nucleophilic additions of chiral sulfoxide-stabilised carbanions to fluoroalkyl *N*-*p*-methoxyphenyl (PMP) aldimines since PMP protective group provided reasonably reactivity the C=N double bond, allowed the imine nitrogen to form coordinated transition states, and was removed by mild and efficient procedures. The starting *N*-PMP aldimines **29** were prepared by direct condensation between *p*-anisidine and perfluoroalkyl aldehydes in their commercially available hydrate or hemi-acetal form exclusively as (*E*)-geometric isomers that is critically important for stereochemical outcome of the addition reactions (Table 1). *N*-PMP aldimines **29** bearing trifluromethyl, pentafluoroethyl and *ω*-hydrotetra-fluoroethyl groups were subjected to addition of lithium anions of Me- and Bn-*p*-tolyl sulfoxides (*R*)-**1** in THF at -70 °C. The reactions proceed with a high reaction rate giving rise to products (R_S,2*S*)-**30** and (R_S,1*S*,2*S*)-**31** in high overall yield [12]. The diastereoselectivities obtained with different *N*-PMP aldimines **29** and sulfoxides (*R*)-**1** were good. Control experiments suggested that additions to *N*-PMP aldimines **29** proceeded irreversibly under kinetic control, which is in sharp contrast to the similar reactions with nonfluorinated substrates. The nature of the fluoroalkyl group of the starting *N*-PMP aldimines **29** had no significant effect on the stereochemical outcome of the addition reactions and diastereoselectivity up to 70% *de* was achieved even in the case of products (R_S,1*S*,2*S*)-**31** when two chiral centers were simultaneously created at the addition stage. *α*-Fluoroalkyl-*β*-sulfinyl amines (R_S,2*S*)-**30** and (R_S,1*S*,2*S*)-**31** were found to be highly crystalline compounds that allowing their purification to enantiomerically pure state by simple crystallization of crude reaction mixtures and determination of absolute configuration by X-ray analysis. The six-membered chair-like transition state where coordination of the metal to the sulfinyl oxygen and imine nitrogen resulting in preferable attack of nucleophile to the *Re* face of the C=N bond in imine and *syn* stereoisomeric form of *α*-carbanion of benzyl *p*-tolyl sulfoxide dictating configuration of the new C-SO stereogenic center explains the stereochemical outcome.

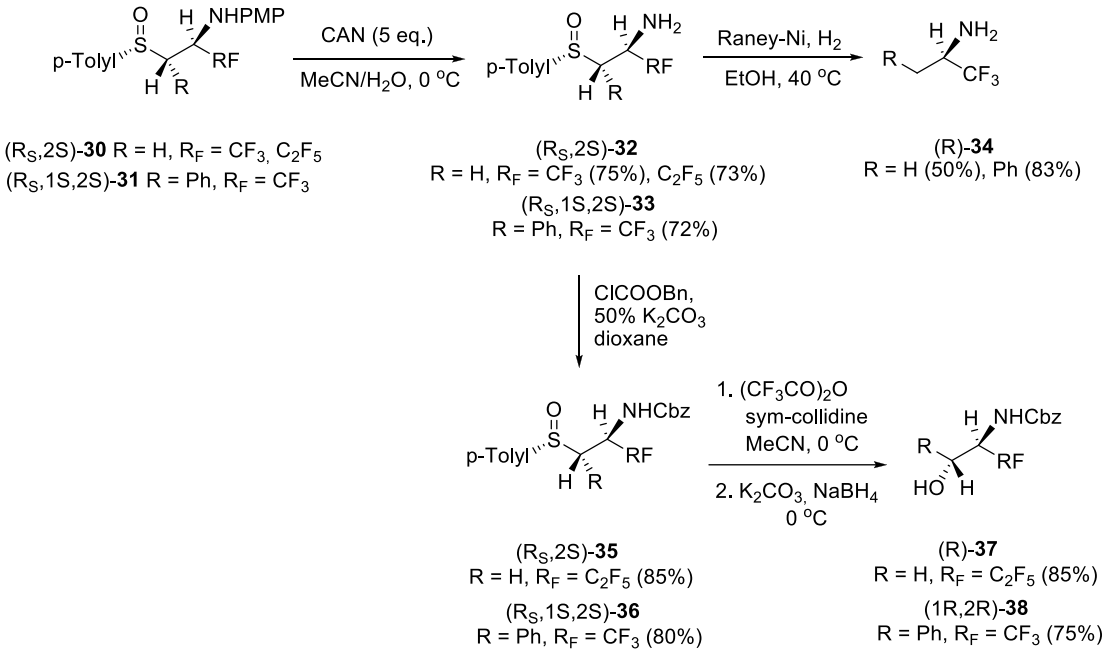
The synthetic application of *N*-PMP protected *α*-fluoroalkyl-*β*-sulfinyl amines (R_S,2*S*)-**30** and (R_S,1*S*,2*S*)-**31** was demonstrated by their conversion into biologically interesting enantiopure *α*-fluoroalkyl amines and amino alcohols without damage to the stereocenters (Scheme 7). Treatment of (R_S,2*S*)-**30** and (R_S,1*S*,2*S*)-**31** with cerium ammonium nitrate (CAN) in acetonitrile at room temperature led to selective cleavage of the *N*-*p*-methoxy-phenyl protective group without oxidation of the sulfinyl moiety even at a larger excess of CAN. This method allowed for preparation of the *N*-unsubstituted *α*-fluoroalkyl-*β*-sulfinyl amines (R_S,2*S*)-**32** and (R_S,1*S*,2*S*)-**33** in moderate to good chemical yields which were further converted into *α*-fluoroalkyl amines (*R*)-**34** by one-pot reductive desulfinylation with Raney-Ni/H_2 in ethanol.

After reprotection of amines (R_S,2*S*)-**32** and (R_S,1*S*,2*S*)-**33** with benzyl chloroformate, the resulting *N*-Cbz derivatives (R_S,2*S*)-**35** and (R_S,1*S*,2*S*)-**36** were subjected to "non-oxidative" Pummerer reaction [13] with trifluoroacetic anhydride and *sym*-collidine followed by treatment with aqueous K_2CO_3 and $NaBH_4$ to give very good yields of the corresponding *β*-amino alcohols (*R*)-**37** and (1*R*,2*R*)-**38**. The asymmetric Pummerer reaction of sulfoxide (R_S,1*S*,2*S*)-**36** is of significant interest since S_N2-type displacement of the sulfinyl by hydroxy group occurred with complete inversion of the absolute configuration at the carbon bearing sulfinyl group yielding *N*-Cbz trifluoronorephedrine (1*R*,2*R*)-**38** with *de* > 99%. The method was extended to *N*-(PMP)-arylimines as an convenient way to prepare enantiopure *α*-arylglycinols [14].

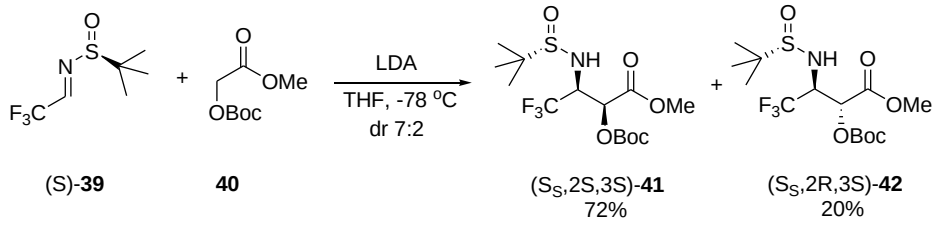
Diastereoselective Mannich-type reaction of *N*-*tert*-butanesulfinyl-3,3,3-trifluoroacetaldimine with protected alkyl glycolates

Chiral fluorinated *N*-*tert*-butanesulfinyl imines are versatile auxiliaries successful employing as electrophiles in a wide range of reactions [15]. As an example, *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine found numerous applications in the asymmetric synthesis of trifluoromethyl-

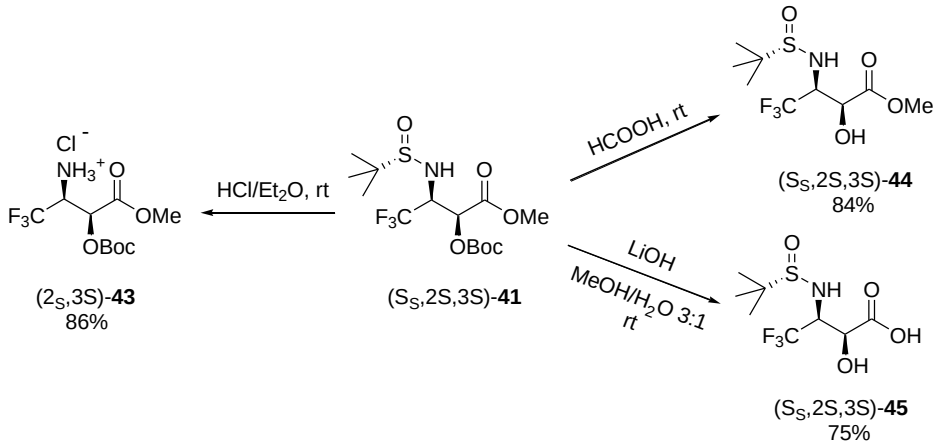
containing amines and amino acids which demonstrated very interesting biological properties. This aldimine exhibited high electrophilicity of the C=N bond facilitating the nucleophilic addition of organometallic compounds to the iminic carbon as well as high level of diastereoselectivity provided by combination of stereo-controlling properties of *tert*-butanesulfinyl and trifluoromethyl groups. In addition, *N-tert*-butylsulfinyl-



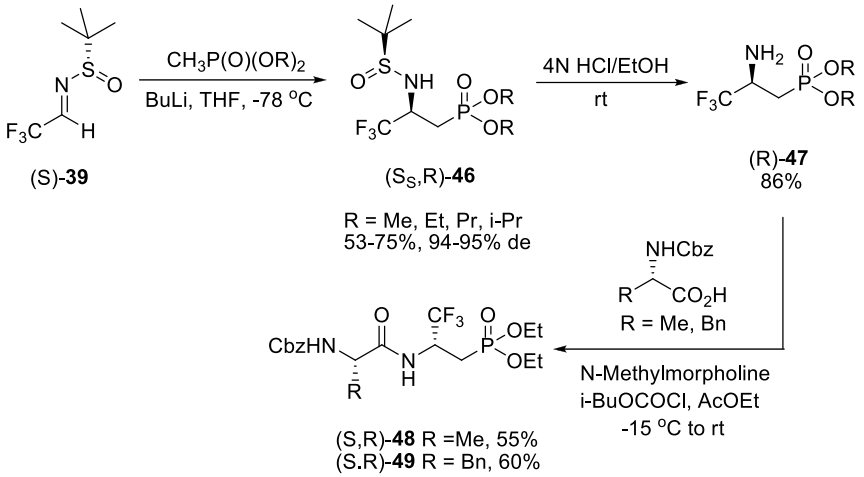
Scheme 7. Synthesis of *α*-fluoroalkyl amines.



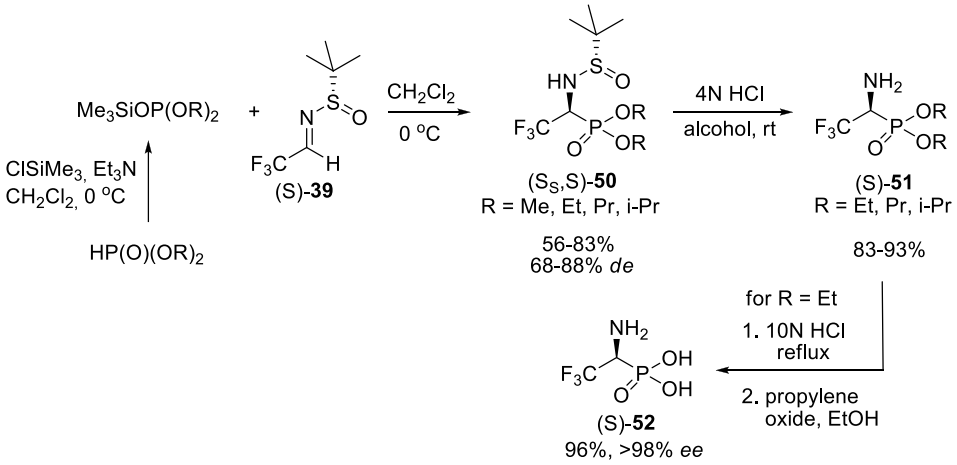
Scheme 8. Mannich-type reaction of imine (*S*)-**39** with lithium enolate derived from Boc-protected methyl glycolate **40**.



Scheme 9. Manipulations with protection groups of *β*-trifluoromethyl isoserine (*S*S,2*S*,3*S*)-**41**.



Scheme 10. Synthesis of *β*-aminophosphonate (*R*)-**47** and *N*-Cbz protected *β*-aminophosphonic dipeptide derivatives (*S,R*)-**48** and (*S,R*)-**49**.



Scheme 11. Addition of dialkyl trimethylsilyl phosphites to imine (*S*)-**39** and deprotection of *N-tert*-butanesulfinyl-*α*-aminophosphonates (*S*S,*S*)-**50**.

3,3,3-trifluoroacetaldimine was readily available in both enantiomeric forms and free amines could be obtained after easy removal of the *tert*-butanesulfinyl group under mild acidic conditions. We used the reactivity and stereocontrolling properties of *N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine (*S*)-**39** in diastereoselective addition with enolates derived from *O*-protected *α*-hydroxyacetates to synthesize *β*-trifluoromethyl isoserine derivatives as structural components of docetaxel analogues (Scheme 8) [16]. After optimization of reaction conditions imine (*S*)-**39** was treated with excess of lithium enolates of Boc-protected methyl glycolate **40** generated with LDA as a base in THF at -78 °C to give mixture of two diastereomeric products (*S*S,2*S*,3*S*)-**41** and (*S*S,2*R*,3*S*)-**42** in moderate ratio of 7:2 with high combined yield although theoretically four isomers could be formed in the addition reaction. It should be noted complete control over the stereogenic C3 by the *tert*-butanesulfinyl/trifluoromethyl groups with no 3*R* stereoisomer being observed in the reaction mixture. Despite the Mannich reaction proceeded with only moderate diastereoselectivity, the mixture of diastereomeric products was easily separated by column chromatography to furnish the enantiomerically pure (*S*s,2*S*,3*S*)-**41** in 72% yield as well as 20% of enantiomerically pure (*S*s,2*R*,3*S*)-**42** and their absolute configuration was established by X-ray analysis. In addition, chemoselective manipulation of the protecting groups in (*S*S,2*S*,3*S*)-**41** provided partially deprotected amino acids (2*S*,3*S*)-**43**, (*S*S,2*S*,3*S*)-**44**, and (*S*S,2*S*,3*S*)-**45** with no loss of diastereomeric purity allowing for incorporation of *β*-trifluoromethyl isoserine residue into more complex products (Scheme 9).

Diastereoselective additions of *α*-phosphonate anions and phosphites to *N-tert*-butanesulfinyl-3,3,3-trifluoroacetaldimine

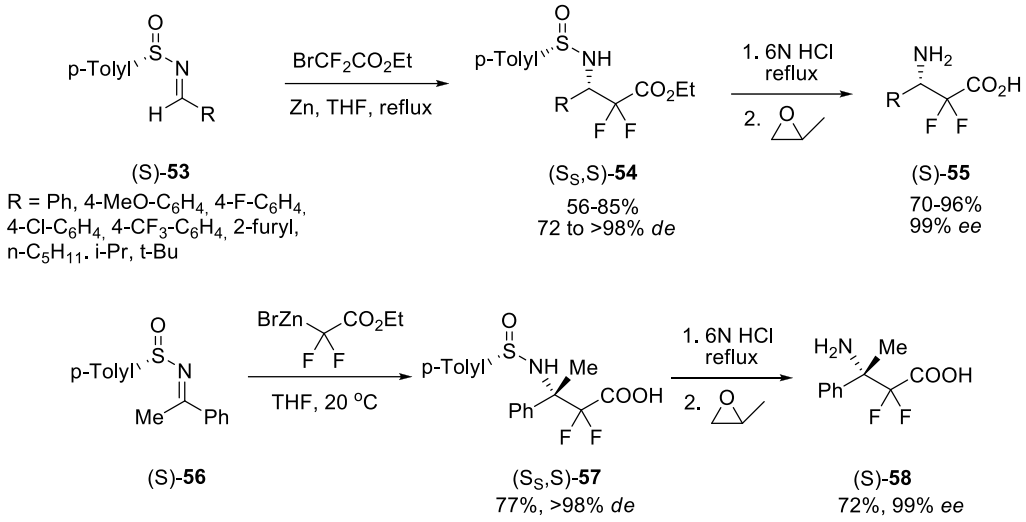
Fluorinated aminophosphonates and aminophosphonic acids belong to important group of natural amino acid mimetics exhibited significant influences on the protease activities with applications ranging from agrochemistry to medicine [17]. They were intensively used in the design and development of potent inhibitors for such enzymes as glutamine synthetase, protein tyrosine phosphatase, HIV

protease, and human collagenase. In addition, fluorinated aminophosphonic acid derivatives also hold great promise as effective starting materials for the preparation of new phosphapeptides [18]. Therefore, basing on our previous results, we devised addition of *α*-phosphonate carbanions to *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine (*S*)-**39** for the asymmetric synthesis of trifluoromethylated *β*-amino-phosphonates (S_S,*R*)-**46** (Scheme 10) [19]. The reactions of imine (*S*)-**39** with excess of dialkyl methylphosphonates were carried out using *n*-BuLi as a base in THF at -78 °C affording corresponding addition adducts (S_S,*R*)-**46** in moderate to good yield with excellent diastereoselectivity 94-95% *de*. The diastereoselectivity of the phosphonate carbanions addition to imine (*S*)-**39** was kinetically controlled and the stereochemical outcome of reaction was consistent with the open transition state model. The major diastereoisomers (*S*s,*R*)-**46** were isolated by column chromatography with diastereomeric purity 96-98% *de*. After selective desulfinylation of addition adducts (*S*s,*R*)-**46**, coupling of *β*-aminophosphonate (*R*)-**47** with *N*-Cbz-L-alanine and *N*-Cbz-L-phenylalanine by using mixed anhydrides method allowed preparing diastereo-isomerically pure *N*-Cbz protected *β*-aminophos-phonic dipeptide derivatives (*S*,*R*)-**48** and (*S*,*R*)-**49** in good yields.

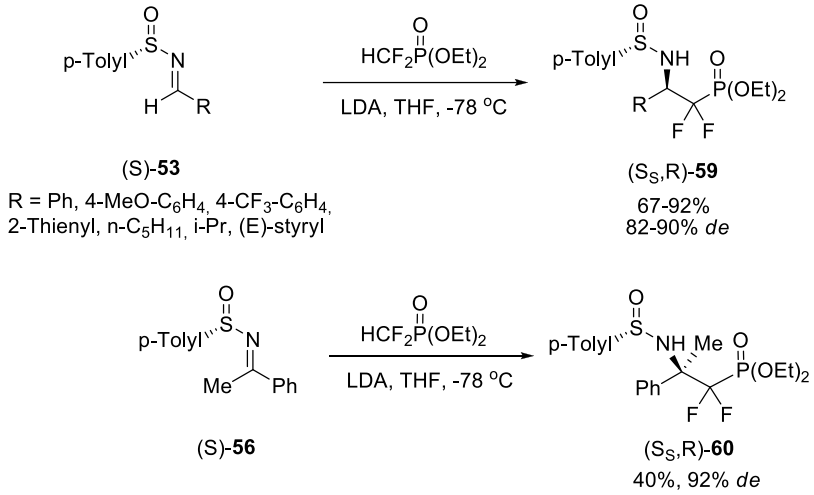
Next, addition reaction of dialkyl trimethylsilyl phosphites as efficient phosphorus nucleophiles to imine (*S*)-**39** was investigated for convenient asymmetric synthesis of phosphonotrifluoroalanine and its derivatives. The dialkyl trimethylsilyl phosphites were generated in situ from corresponding diethyl phosphite in the presence of TMSCl and Et_3N and further reacted with imine (*S*)-**39** in dichloromethane at 0 °C yielding *N*-*tert*-butanesulfinyl *α*-aminophosphonates (S_S,*S*)-**50** in moderate to high yields and diastereoselectivity (Scheme 11) [20]. The best result in term of diastereoselectivity (88% *de*) was achieved with diisopropyl trimethylsilyl phosphite. The major diastereomers were isolated by flash column chromatography or recrystallization in excellent diastereomeric purity and their stereochemistry was determined by X-ray analysis. The formation of the major diastereomers with (S_S,*S*)-configuration was proposed to explain by non-chelated transition state model which provided a rationale for the greater diastereoselectivity observed for the sterically hindered diisopropyl trimethylsilyl phosphite relative to other phosphite derivatives. Partial or complete deprotection of diastereomeric pure *N*-*tert*-butanesulfinyl *α*-aminophos-phonates (S_S,*S*)-**50** under standard conditions led to enantiomerically pure phosphonotrifluoromethyl alanine (*S*)-**52** and its dialkyl esters (*S*)-**51** in excellent yield.

Diastereoselective Reformatsky reaction between *N*-*p*-toluenesulfinyl imines and bromodifluoroethyl acetate

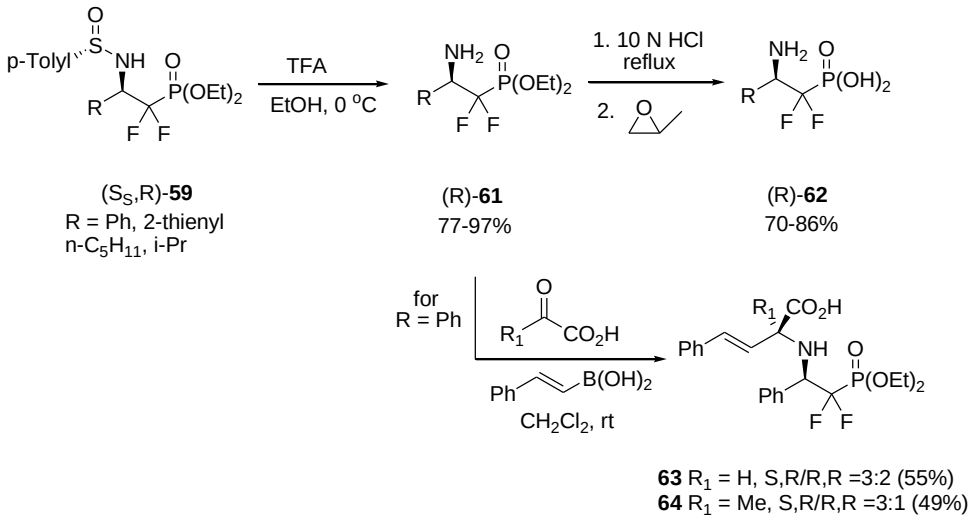
Traditionally, stereoselective nucleophilic addition of difluorinated Reformatsky reagent ($BrZnCF_2CO_2Et$) to imines is considered as the most efficient method for the construction of variety of *α,α*-difluoro-*β*-amino acid derivatives used in the design of peptides and fluoroalkene dipeptide isosteres [21]. *α,α*-Difluoro-*β*-amino acid derivatives are also components of anticancer, and antifungal agents as well as protease inhibitors. We developed stereoselective version of the Reformatsky reaction between ethyl bromodifluoroacetate and *N*-*p*-toluenesulfinyl imines as a generalized and synthetically useful approach to enantiomerically pure *α,α*-difluoro-*β*-amino acids. Treatment of the alkyl and aryl *N*-*p*-toluenesulfinyl aldimines (*S*)-**53** with ethyl bromo-difluoroacetate in the presence of activated Zn powder in boiling THF provided *N*-*p*-toluenesulfinyl protected *α,α*-difluoro-*β*-amino esters **54** with the (S_S,3*S*)-absolute configuration and good to excellent diastereoselectivities (72 to >98 *de*) (Scheme 12) [22]. Optimization experiments shown that 1/2 ratio of aldimines (*S*)-**53** and ethyl bromodifluoroacetate was required for complete transformation of the former to *α,α*-difluoro-*β*-amino esters (S_S,3*S*)-**54** isolated in moderate to good yields (59-85%). The undesired corresponding difluoro-*β*-lactams were not detected in these reactions. The diastereoselectivity of addition to aryl aldimines (*S*)-**53** was noticeably influenced by the electron-donating or withdrawing character of the substituent on the aromatic ring. For example, the very high diastereoselectivity (>98 *de*) was observed in the case of anisaldehyde-derived aldimine (*S*)-**53**. In contrast, the reactions of alkyl aldimines (*S*)-**53** with difluorinated Reformatsky reagent, conducted under the standard conditions, proceeded with similar diastereoselectivity (72-76 *de*) which is lower compared to the aryl aldimines. Finally, Reformatsky reaction of ethyl bromodifluoroacetate with *N*-*p*-toluenesulfinyl ketimine (*S*)-**56** derived from acetophenone was explored to provide the corresponding quaternary carbon-containing chiral *α,α*-difluoro-*β*-amino acid. After optimization of reaction conditions, treatment of ketimine (*S*)-**56** with an excess of difluoroorganozinc reagent freshly preformed from the ethyl bromo-difluoroacetate and zinc in THF at 20 °C gave the addition adduct (S_S,*S*)-**57** in good yield with excellent diastereoselectivity (Scheme 12). The isolation of the *α,α*-difluoro-*β*-amino esters (S_S,3*S*)-**54** and (S_S,*S*)-**57** was effectively achieved either by crystallization or flash chromatography and absolute configuration was determined by X-ray structural analysis. The stereochemical outcome of the described Reformatsky reactions, regarding the absolute configuration of the newly formed carbon stereogenic center, was rationalized by six-membered transition state where the difluoro ester enolate, assumed to exist as C-bound tautomer, attack preferably from the *Re*-face of the (*S*)-configured *N*-*p*-toluenesulfinyl imine. Esters (S_S,3*S*)-**54** and (S_S,3*S*)-**57** were hydrolyzed by refluxing with 6 N HCl to afford, after treatment with propylene oxide, free *α,α*-difluoro-*β*-amino acids (*S*)-**55** and (*S*)-**58** in high isolated yield with excellent enantiomerical purity according to chiral HPLC analysis. The only exception was hydrolysis under standard conditions of the furyl-substituted product (S_S,3*S*)-**54**, when the target amino acid could not be isolated, probably, due to the instability of the furyl ring under strong acidic conditions. It is worth noting that other research groups evaluated the influence of the *N*-*tert*-



Scheme 12. Synthesis and acidic hydrolysis of *N*-*p*-toluenesulfinyl protected *α,α*-difluoro-*β*-amino esters (*S*S,3*S*)-**54** and (*S*S,3*S*)-**57**.



Scheme 13. Reaction of the diethyl lithiodifluoromethylphosphonate with *N*-*p*-toluenesulfinyl imines (*S*)-**53** and (*S*)-**56**.



Scheme 14. Deprotection of *N*-*p*-toluenesulfinyl *α,α*-difluoro-*β*-amino phosphonates (*S*S,*R*)-**59** and utilization of *α,α*-difluoro-*β*-amino phosphonates (*R*)-**61** in the Petasis boronic acid Mannich reaction.

butanesulfinyl group on Reformatsky reaction with ethyl bromodifluoroacetate by examining the addition to corresponding aldimines [23]. Although the *N-tert*-butanesulfinyl protected *α,α*-difluoro-*β*-amino esters were produced with good to excellent diastereoselectivities, separation of the diastereomeric adducts required application of chiral HPLC on preparative scale.

Diastereoselective additions of α,α-difluoro-phosphonate anions to *N-p*-toluenesulfinyl imines

As bioisosteric, non-hydrolyzable analogues of naturally occurring phosphates, *α*-fluorinated phosphonates gained considerable attention in pharmaceutical and agrochemical research [24].

Due to the presence of one or two fluorine atoms at the *α*-position, *α*-fluorinated phosphonates closely mimic the phosphate in terms of pK_{a2} values as well as potential hydrogen bonding interactions like the phosphate oxygen atoms. We explored the use of *N-p*-toluenesulfinyl imines as substrates in reaction with phosphonodifluoromethyl carbanion for stereoselective synthesis of *β*-amino-*α,α*-difluorophosphonates. Structurally diverse enantiomerically pure alkyl and aryl *N-p*-toluenesulfinyl aldimines (*S*)-**53** readily undergo nucleophilic addition with 1.3 equiv of diethyl lithiodifluoromethylphosphonate generated in situ from diethyl difluoromethylphosphonate and LDA in THF at -78 °C affording *N-p*-toluenesulfinyl *α,α*-difluoro-*β*-aminophosphonates (S_S,*R*)-**59** (Scheme 13) [25]. Despite the relatively weak nucleophilicity and poor thermal stability of diethyl lithiodifluoromethylphosphonate, *N-p*-toluenesulfinyl *α,α*-difluoro-*β*-aminophosphonates (S_S,*R*)-**59** were obtained from good to high yields (70-92%). *Additional* experiments showed that the use of different bases and solvents did not improve the selectivity of addition and resulted in incomplete conversion of starting aldimines (*S*)-**53**, as indicated by ^{1}H NMR and TLC analysis of crude reaction mixtures. Under optimized reaction conditions the highest diastereoselectivity (90% *de*) was observed for the addition of diethyl lithio-difluoromethylphosphonate to a benzaldehyde-derived imine (*S*)-**53**. The aryl aldimines (*S*)-**53** containing either an electron-donating group such as methoxy as well as an electron-withdrawing group such as CF_3 at the *para*-position of the phenyl ring were well tolerated under reaction conditions giving the corresponding products (S_S,*R*)-**59** with high diastereoselectivity (88% *de*). At the same time the use of heteroaryl and alkyl aldimines (*S*)-**53** as substrates provided lower stereoselectivity (82-84% *de*). Moreover, *trans*-cinnamaldehyde-derived imine (*S*)-**53** was also compatible affording exclusively 1,2-addition product (S_S,*R*)-**59** with high stereocontrol (88% *de*). Addition of diethyl lithiodifluoromethylphosphonate was expanded to acetophenone-derived *N-p*-toluenesulfinyl imine (*S*)-**56** providing after 1 h adduct (S_S,*R*)-**60** with high diastereoselectivity (92% *de*). However, purification by chromatography allowed the isolation of major diastereomer (S_S,*R*)-**60** in only 40% yield as well as unreacted starting imine (*S*)-**56** in 51% yield. The diastereoselectivity and yield remained essentially unchanged with a longer reaction time. Competitive deprotonation of the imine (*S*)-**56** under base reaction conditions was most likely responsible for the observed moderate yield. The *N-p*-toluenesulfinyl *α,α*-difluoro-*β*-aminophosphonates (S_S,*R*)-**59** and (*SS*,*R*)-**60** were isolated by chromatography or crystallization and their stereochemistry was determined by X-ray analysis. The stereochemical outcome of the reactions is consistent with the open transition state model previously proposed for the addition of dialkyl methylphosphonate carbanions to *N-p*-toluenesulfinyl aldimines (*S*)-**53**.

A two-step deprotection involving *N*-desulfinylation of diastereomerically pure *N-p*-toluenesulfinyl *α,α*-difluoro-*β*-amino phosphonates (S_S,*R*)-**59** with trifluoroacetic acid in EtOH followed by refluxing of resulting *α,α*-difluoro-*β*-amino phosphonates (*R*)-**61** with 10 N HCl afforded, after treatment with propylene oxide, free *α,α*-difluoro-*β*-amino phosphonic acids (*R*)-**62** in good to excellent isolated yields with enantiomerical purity >98% *ee* (Scheme 14). Thus, deprotection of *N-p*-toluenesulfinyl *α,α*-difluoro-*β*-amino-phosphonates (S_S,*R*)-**59** proceeded under described conditions without epimerization at the *β*-position. Employing of phenyl-substituted *α,α*-difluoro-*β*-amino phosphonates (*R*)-**61** as amine component in the Petasis boronic acid Mannich reaction with glyoxylic and pyruvic acids in the presence of styrylboronic acid provided highly functionalized *N*-phosphonomethylglycine analogues **63** and **64** with poor diastereoselectivity [26].

Conclusions

This review highlights several efficient synthetic approaches using chiral sulfinyl auxiliaries for the preparation of biologically relevant fluorinated oxiranes, amines, hydroxy amines, *α*- and *β*-amino acids as well as *α*- and *β*- aminophosphonic acids developed in laboratory of Professor V.P. Kukhar. Currently, the application of chiral sulfinyl auxiliaries in highly selective asymmetric synthesis is a reliable methodology and their synthetic versatility is continuously demonstrated for the preparation of fluorinated amines and amino acids with various types of biological activities. In most cases the existing transition states models facilitate the prediction of the absolute configuration of major diastereoisomers making this methodology attractive for synthetic applications. It should be emphasized that the usefulness of the sulfinyl auxiliaries comes not only from their ability to produce high asymmetric inductions but also from their synthetic versatility allowing construction of enantiopure fluorinated molecules with wide structural and functional diversities. We anticipate that the presented potential of the methodology in which sulfinyl compounds are serving as chirality source in various preparations of fluorinated molecules will encourage developing new asymmetric syntheses of complex natural product analogues for biomedical applications.

Notes

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.

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Застосування хіральних сульфінільних ауксиларів в асиметричному синтезі фторованих амінів і амінокислот

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Резюме: Огляд охоплює розробки, зроблені у співпраці груп професорів В.П. Кухаря та П. Браво щодо синтетичного застосування сульфінільних сполук як універсальних хіральних ауксиларів для асиметричного отримання фторованих амінів та амінокислот. Потенціал сульфінільних хіральних ауксиларів у сфері стереоселективних перетворень фторованих субстратів демонструється діастереоселективним перенесенням метилену від діазометану до карбонілу *β*-кето-*γ*-фторалкілсульфоксидів як загального підходу для отримання різних фторованих похідних оксирану, діастереоселективного сульфоксиду. додавання аніонів до фторованих імінів, що веде до зручного отримання *α*-фторалкіл *α*-амінокислот, гідроксиамінів та амінів, діастереоселективна реакція типу Манніха між *N*-трет-бутансульфінілом-3,3,3-трифторацетальдиміном і захищеними алкілгліколятами, що утворюють *β*-трифторметил використання похідних ізозерину та діастереоселективних приєднань фосфіт- або *α*-фосфонат-аніонів до *N*-трет-бутансульфінілу-3,3,3-трифторацетальдиміну для синтезу трифторметильованих *α*- та *β*-амінофосфонових кислот. Крім того, діастереоселективні додавання реагенту Реформатського, отриманого з бромдифторетилацетату, а також *α,α*-дифторфосфонат-аніонів до *N*-*p*-толуолсульфінілімінів, дозволяють зручно отримувати *α,α*-дифтор-*β*-амінокислоти та *α,α*-дифтор-*β*-амінофосфонати в енантіомерно чистому вигляді описані. Коротко обговорюється вплив фтору на механізм і стереохімічний результат цих реакцій.

Ключові слова: асиметричний синтез; сульфоксиди; *α*-фторалкіламінопохідні; *α*- і β-амінокислоти.