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Review

Asymmetric synthesis of fluorine-containing amines, amino alcohols, α- and β-amino acids mediated by chiral sulfinyl group☆

Alexander E. Sorochinsky [a,*], Vadim A. Soloshonok [a,b]

[a] Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of the Ukraine, Murmanska Street 1, Kyiv 94 02660, Ukraine
[b] Department of Chemistry and Biochemistry, The University of Oklahoma, 620 Parrington Oval, Room 208, Norman, OK 73019-3051, USA

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ABSTRACT

This review article provides a critical overview of several different synthetic approaches developed for asymmetric preparation of fluorine-containing amines, amino alcohols, α- and β-amino acids. The common feature of these methods is the application of sulfinyl group as a chiral auxiliary to control the stereochemical outcome of the reactions under study. In particular, the following general methods are critically discussed: diastereoselective methylene transfer from diazomethane to the carbonyl of β-keto-γ-fluoroalkyl sulfoxides as a general approach for preparation of various α-fluoroalkyl α-sulfinylalkyl oxiranes. The resulting compounds were used as true chiral synthons for their further elaboration via oxidative or reductive desulfurization, to numerous fluorine-containing and biologically relevant amino- and hydroxy-containing derivatives. Another general approaches discussed here are asymmetric additions to C=N double bond. One of them is addition of chiral sulfoxide stabilized carbon nucleophiles to fluorine-containing imines, leading to convenient preparation of alpha-fluoroalkyl derivatives of alpha amino acids and amines. Another approach is asymmetric Reformatsky reaction between *N*-sulfinyl imines and ethyl bromodifluoroacetate allowing operationally convenient preparation of α,α-difluoro-β-amino acids in enantiomerically pure form. Finally, structurally similar but mechanistically different addition reactions of diethyl difluoromethylphosphonate to *N*-sulfinyl imines, as a general approach to asymmetric synthesis of α,α-difluoro-β-aminophosphonates and phosphonic acids, are discussed. Effect of fluorine on the mechanism and stereochemical outcome of these reactions is discussed in detail and compared, where it is possible, with that of the analogous reactions of fluorine-free substrates.

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Contents

1. Introduction

Over recent decade organic compounds possessing both nitrogen and fluorine atoms and especially fluorinated amines and amino acids have received noticeable attention from the bioorganic and medicinal chemistry practitioners due to profound change of their overall reactivity and functional properties, such as

☆ Dedicated to the memory of our friend and colleague Dr. Andreii L. Markovsky.

* Corresponding author. Tel.: +380 44 5732531; fax: +380 44 5732552.
E-mail addresses: sorochinsky@bpci.kiev.ua (A.E. Sorochinsky), vadim@ou.edu (V.A. Soloshonok).

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acidity and basicity [1]. Introduction of fluorine affects nearly all physical, adsorption and distribution properties of amines and amino acids. On the biological level these changes can lead to significant alteration of the original biological activity or even to completely new mode "substrate-receptor" interactions relative to the hydrocarbon analogue [2]. Moreover Seebach's work on fluorinated β-amino acids has recognized them as powerful tool to modify the structure and properties of β-peptides [3]. Therefore the development of synthetic methods allowing reliable, convenient access to such compounds on the relatively large scale, and desirably in enantiomerically pure form, to satisfy the need for systematic biological studies, is currently in focus of research activity of many groups having expertise in organic, fluoroorganic chemistry as well as asymmetric synthesis.

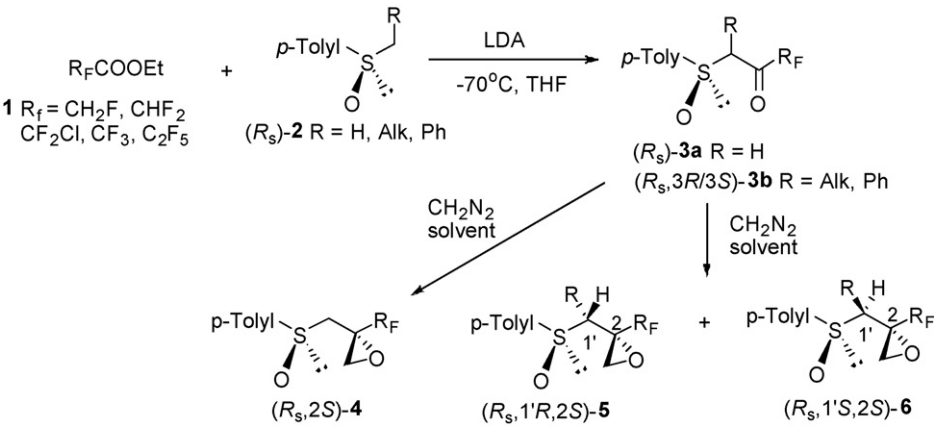
Among the numerous currently available asymmetric methodologies, stoichiometric approach with application of chiral sulfinyl auxiliaries (sulfoxides and *N*-sulfinyl imines) is probably the most well studied and successfully applied in asymmetric synthesis of fluorine-containing amino compounds. Due to the electronic and stereochemical properties sulfinyl group based auxiliaries provide high levels of stereocontrol in various classes of reactions and can serve as chiral equivalent of alkyl (reductive desulfurization), vinyl (*syn*-elimination reaction), hydroxymethyl/hydroxycarbonyl (Pummerer rearrangement), and amino (hydrolysis of N-sulfinamides) groups [4]. Before discussing the work conducted by our group, here we give a brief overview of the relevant literature results, allowing the readers to appreciate the synthetic wealth of sulfinyl group based asymmetric methodology. In early reports the efficiency of the chiral sulfinyl group in stereoselective transformations of fluorinated substrates has been demonstrated by hydride reduction of fluorinated β-iminosulfoxides [5] and N-sulfinyl imines [6]. The stereochemical outcome and stereoselectivity of the reduction can be controlled by variation of steric bulk and electronic properties of reducing reagent. Later it has been shown that fluorinated *N*-sulfinyl imines are excellent substrates for the 1,2-addition of organometallic [7] and arylboronic [8] reagents yielding the desired adducts in high diastereoselectivities. *N*-*tert*-butylsulfinyl imines are preferred substrates for reactions with organometallic reagents due to undesirable displacement of the sulfinyl auxiliary observed for *N*-*p*-toluenesulfinyl imines. A highly diastereoselective trifluoromethylation of chiral *N*-sulfinyl imines has been achieved by means of Ruppert–Prakash reagent in the presence of fluoride source [9] or Lewis base [10]. Nucleophilic trifluoromethylation of *N*-sulfinyl aldimines was also carried out with CF_3^- reagent derived from CF_3I/TDAE [11]. Di- and mono-fluoromethyl phenyl sulfones $PhSO_2CF_2H$ and $PhSO_2CH_2F$ have been successfully applied for highly diastereoselective fluoroalkylation of *N*-sulfinyl imines [12].

The goal of this review is to describe contributions to the synthetic applications of sulfoxides and *N*-sulfinyl imines for the asymmetric synthesis of biologically relevant, fluorine-containing amines, amino alcohols, α- and β-amino acids made by the Kiev's school of bioorganic chemistry. Our interest in this area was inspired by the innovative work of Professor P. Bravo and most of our results were obtained in collaboration with his group. Our initial investigations were devoted to development of highly regio- and diastereoselective methylene transfer from diazomethane to the carbonyl of β-keto-γ-fluoroalkyl sulfoxides. α-Fluoroalkyl epoxides obtained are true fluorinated synthons for generalized asymmetric synthesis of various biologically relevant compounds by means of regioselective ring opening with different nucleophiles as well as chemical elaboration of the sulfinyl group. Then we studied diastereoselective addition reactions between chiral sulfoxide stabilized carboanions and fluoroalkylated imines to afford corresponding enantiomerically pure α-fluoroalkyl β-sulfinyl amines and demonstrated their transformation into series enantiomerically pure α-fluoroalkyl amines, hydroxy amines and amino acids. We found that *N*-(*p*-methoxyphenyl)aldimines bearing fluoroalkyl or electron-rich aryl group were very efficient substrates in addition reactions to provide corresponding β-sulfinyl amines in excellent yields and good diastereoselectivity. Following that, the efficient synthesis of α,α-difluoro-β-amino acids derivatives as well as α,α-difluoro-β-aminophosphonates based on addition of difluoro Reformatsky reagent and difluoromethylphosphonate carbanion to enantiomerically pure *N*-*p*-toluenesulfinyl imines as chiral auxiliaries was also achieved. We developed optimal reaction conditions allowing the preparation a wide variety of α,α,-difluoro-β-aminophosphonates and phosphonic acids in enantiomerically pure form.

2. Diastereoselective methylene transfer from diazomethane to the carbonyl of β-keto-γ-fluoroalkyl sulfoxides. Synthesis and further chemical elaboration of α-fluoroalkyl α-sulfinylalkyl oxiranes

The first aim of our study was to develop a new synthesis of enantiomerically pure α-fluoroalkyl epoxides as valuable intermediates for the construction of the α-fluoroalkyl tertiary alcohols *via* nucleophilic opening of the oxirane ring. Stereocontrolled synthesis of the α-fluoroalkyl epoxides remains a difficult task in organic chemistry because classical routs to non-fluorinated epoxides, despite advances in the development of effective catalytic asymmetric epoxidation, could not be applied to the fluorinated compounds due to the unique electronic and stereochemical properties of fluoroalkyl substituents and new practical synthetic methods for preparation of α-fluoroalkyl epoxide have still to be explored [13]. In the course of developing a new access to chiral fluorinated epoxides possessing stereogenic quaternary carbon we investigated chiral auxiliary-controlled asymmetric methylene transfer reactions from diazomethane to the carbonyl of (R_s)-β-keto-γ-fluoroalkyl sulfoxides **3** available from fluorinated ethyl acetates **1** and α-lithio derivatives of (*R*)-*p*-tolyl alkyl sulfoxides **2** (Scheme 1). Previously β-keto-γ-fluoroalkyl sulfoxides **3** were used mainly through stereoselective reduction processes for preparation of chiral fluorinated oxygen compounds of synthetic and biological interest [14]. Reactions of α-unsubstituted β-keto sulfoxides (R_s)-**3a** with diazomethane gave rise to sulfinylmethyl epoxides **4** with good to excellent regio- and stereoselectivities [15]. A screening of solvents showed that the best diastereoselectivity was obtained in diethyl ether, while methanol and ethanol led to decrease in the diastereoselectivity with higher yield of epoxides **4**. The stereochemical outcome of these transformations is in agreement with coordination of diazomethane to the sulfinyl oxygen, resulting in *Re* face attack of β-keto sulfoxides (R_s)-**3a**. When α-alkyl/aryl substituted β-keto sulfoxides (R_s)-**3b**, as mixture of (3*S*/3*R*)-diastereomers, were treated with diazomethane, the corresponding oxiranes were formed in good chemical yields [16].[1] Diastereoisomers **5** and **6**, the major products in these reactions, had identical absolute configuration of the oxirane ring. This fact indicates that stereogenic sulfur center present in molecule effectively controlled the stereochemistry of oxirane ring formation affording (*S*) configured epoxides with moderate to high diastereoselectivity from the (R_s)-sulfoxides. Increase in the fluorine substitution for hydrogen on the starting sulfoxides (R_s)-**3b** (R_f = CH_2F, CHF_2, CF_3) facilitated the addition reactions giving rise to epoxides **5** and **6** with a substantially enhanced diastereoselectivity of the epoxide ring formation and did not influence the stereochemical preference. The stereoselec-

[1] Isolation of (R_s,3*S*/3*R*)-**3b** by flash chromatography did not allow separation of the diastereomers.



Scheme 1.

tivity at the α-center to sulfinyl group was usually lower regardless the reaction conditions and could be modulated with the solvent polarity. For example, reaction of α-alkyl β-keto sulfoxides (R_s)-**3b** gave rise to epoxides **6** as a major product in methanol, while diethyl ether favored the formation of diastereomers **5**. At the same time α-aryl β-keto sulfoxides (R_s)-**3b** in both methanol and diethyl ether afforded diastereomers **5** with 70–80% de. However the stereogenic α-center to sulfinyl group has no particular importance from a synthetic point of view, since it is lost upon elaboration of the sulfinyl epoxides to sulfur free compounds. Nevertheless diastereomerically pure epoxides **5** and **6** were isolated by silica gel column chromatography for further structural and chiroptical investigations. The stereochemical outcome for the reactions of α-alkyl/aryl substituted β-keto sulfoxides (R_s)-**3b** can be rationalized in terms of a six-membered chair-like transition states **A**–**C** with diazomethane coordinating to the sulfinyl oxygen as shown in Fig. 1. The reactions of (R_s,3*R*)-**3b** diastereomers with diazomethane could proceed *via* favorable transition state **A** in which steric interactions between substituents are minimized. In contrast, for (R_s,3*S*)-**3b** diastereomers transition states **B** and **C** are destabilized since substituent R must occupy a sterically unfavorable position. Thus, the stereochemical outcome of the reactions of (R_s,3*S*/3*R*)-**3b** diastereomers might be a function of (a) the starting diastereomeric composition, (b) the epimerization rates of diastereomers and (c) relative thermodynamic stability of transition states **B** and **C** as a function of the nature of the substitution on the β-keto sulfoxide.

We have studied synthetic opportunity associated with the epoxide ring and the sulfinyl group including epoxide ring-opening with oxygen and nitrogen nucleophiles, reduction and elimination reactions to afford synthetically and biologically interesting compounds (Scheme 2). Since epoxide **4** having acidic CH_2 group is prone to rearrangement under basic conditions with aqueous solution of potassium hydroxide or with LDA in THF to give open-chained allylic alcohols **7** we developed acid-catalyzed ring-opening protocol using $HClO_4$ as a promoter and THF as the solvent. Under these reaction conditions fluorinated epoxides **4**–**6** were cleanly transformed to diols **8**–**10**. The reactions proceeded at room temperature for five days, however the target products were isolated in high yield (80–90%). On treatment of **4**–**6** with a slight excess of benzyl amine in tetrahydrofurane, the epoxides is smoothly opened with relatively high rates, as compared with the acid-catalyzed opening by water and afforded amino alcohols **11**–**13** in excellent isolated yields (90%). The reactions of the epoxides **4** and **6** with dibenzyl amine occurred at room temperature for three days to give *N*,*N*-dibenzyl derivatives **14** and **15** in reasonable yield (55–60%). It is necessary to emphasize that all ring-opening reactions, in particular acid-catalyzed, proceeded with complete regioselectivity involving attack of nucleophile exclusively on the less substituted carbon atom of the epoxide ring and can be explained based on steric and electronic features. Standard reduction of sulfinyl group to the thio group with NaI and trifluoroacetic anhydride in acetone followed by desulfenylation promoted by Raney Ni under hydrogen atmosphere as well as thermal elimination of the sulfinyl group were conducted to demonstrate the methods for preparation of the enantiomerically pure diols **17**–**19** and amino alcohols **16** and **20** with the fluoroalkylated quaternary centers that can be used as ligands or chiral auxiliaries in asymmetric synthesis [17].

The transformation of α-fluoroalkyl epoxide **4** to fluoroalkyl acyclic analogues of nucleoside **25** as well as α-trifluoromethyl-α-hydroxy acids **29** and **30** using Pummerer rearrangement as key step in the reaction sequences was considered to be an interesting application of fluorinated synthon strategy and results are shown in Scheme 3 [14,18]. Displacement of the sulfinyl auxiliary in epoxide **4** by hydroxyl group through Pummerer rearrangement

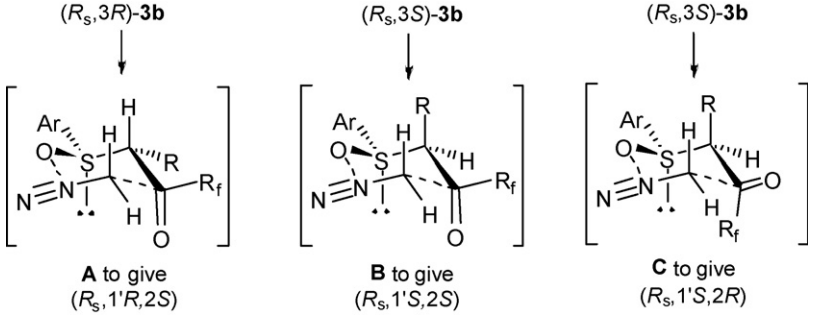
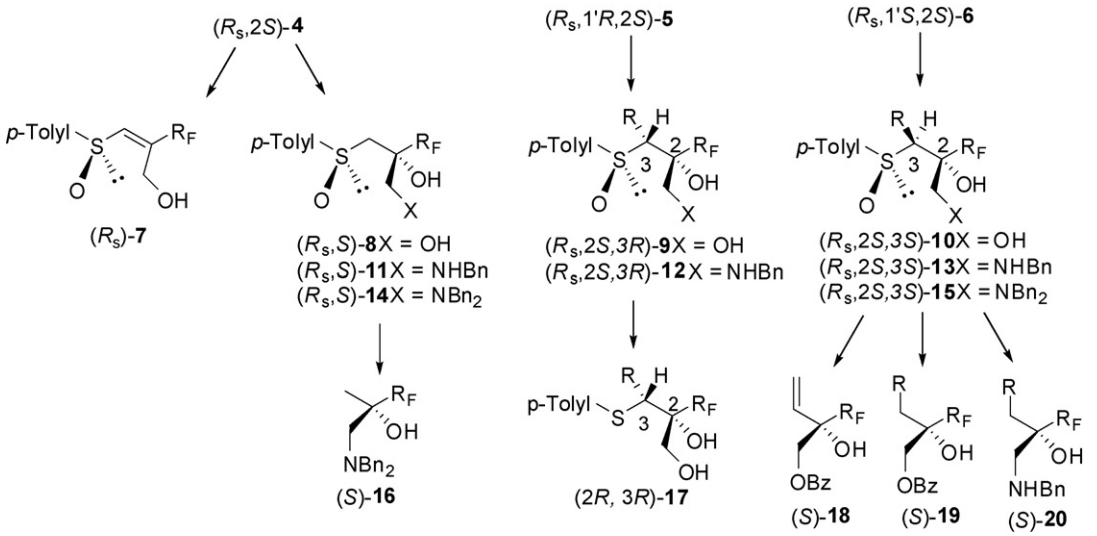


Fig. 1.

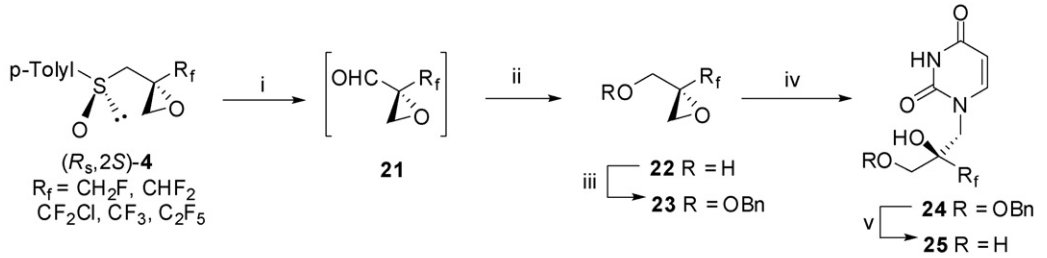


Scheme 2.

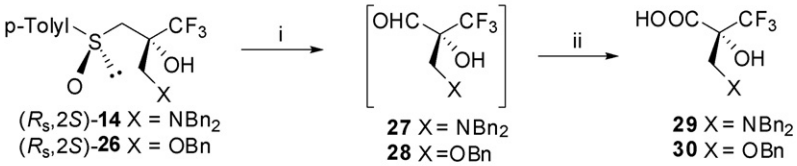
promoted by trifluoroacetic anhydride and *sym*-collidine in acetonitrile, followed by hydrolysis of the labile thiotrifluoroacetoxy intermediate and $NaBH_4$ reduction of aldehyde **21** afforded primary alcohol **22** without affecting the oxirane ring. Protection of primary alcohol **22** with benzyl bromide in the presence of NaH led to **23** in 60% overall yield from **4**. Regioselective oxirane opening was achieved by treatment of **23** with thymine under base conditions, affording protected acyclic nucleosides **24** in 70% isolated yield. Finally, removal of the protective group was achieved by hydrogenation employing 10% palladium on carbon in ethanol, giving polyfluoroalkylated acyclic nucleosides **25** in high purity. Pummerer rearrangement of acyclic derivatives **14** and **26** followed by mild oxidation of intermediate aldehydes **27** and **28** allowed the synthesis α-hydroxy-α-trifluoromethyl-β-amino acid **29** and α-trifluoromethyl-α,β-dihydroxy acid **30**. It is interesting to note that chiral derivatives of trifluorolacetic acid of type **30** are very useful compounds in studying the phenomenon of optical self-purification via preferential sublimation of racemic or enantiomerically pure forms [19].

3. Chiral sulfoxide controlled asymmetric additions to C=N double bond. Synthesis of α-fluoroalkyl α-amino acids, hydroxy amines and amines

Nucleophilic addition of various organometallic reagents to C=N double bond of imines proved to be very convenient approach to amine derivatives in the racemic or optically active form. Taking into account biological and synthetic application of enantiomerically pure amines and α-amino acids bearing fluoroalkyl substituent on the chiral center our group studied diastereoselective additions of α-lithiated alkyl *p*-tolyl sulfoxides to fluoroalkylated imines as the most straightforward approach to these classes of compounds in an asymmetric manner. From earlier research it was known that high stereoselectivity could be achieved for addition of chiral sulfoxide-stabilized carbanions to imines derived from aromatic aldehydes under conditions of kinetic control [20]. On the other hand, enolizable *N*-aryl and *N*-alkyl imines were less suitable substrates for these additions, presumably, due to their lower reactivity and enolization side-



Reagents and conditions: i) a) $(CF_3CO)_2O$, *sym*-collidine, CH_3CN, -20°C, b) $HgCl_2$, K_2CO_3, CH_3CN, 20°C; ii) $NaBH_4$, 0°C; iii) NaH, BnBr, DMF; iv) a) thymine, HMDS, $(NH_4)_2SO_4$, $Hg(CN)_2$, C_6H_6, reflux; v) H_2, Pd/C (10%), EtOH, 3 atm.



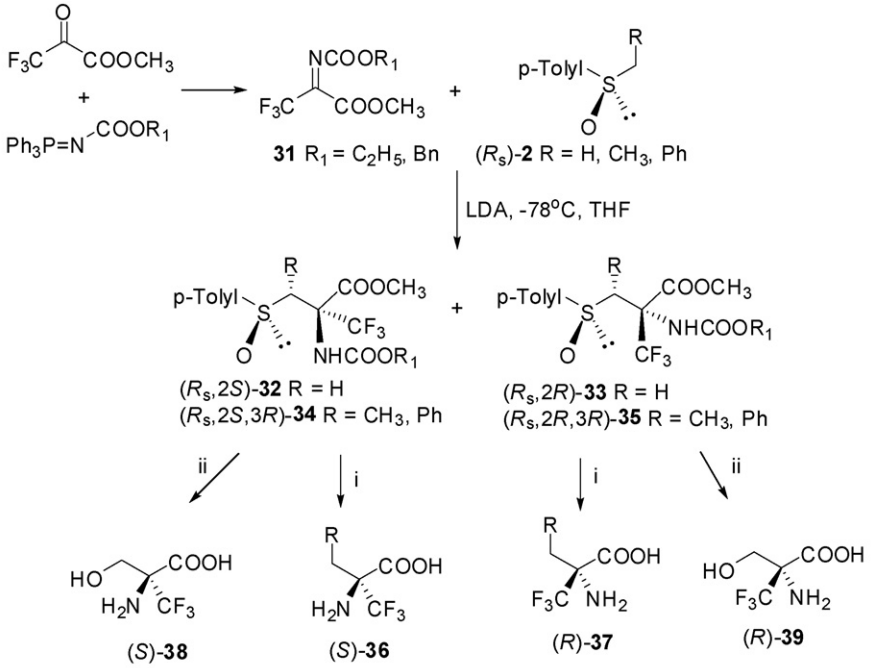
Reagents and conditions: i) a) $(CF_3CO)_2O$, *sym*-collidine, CH_3CN, -20°C, b) $HgCl_2$, K_2CO_3, CH_3CN, 20°C; ii) $NaClO_2$, KH_2PO_4, $(CH_3)_3COH$, 2-methyl-2-butene, H_2O, 20°C.

Scheme 3.

processes. Later it has been identified that even under optimal conditions only moderate diastereoselectivity of β-amino sulfoxide formation was observed in the addition of anion of methyl *p*-tolyl sulfoxide to *N*-sulfonyl imine derived from cinnamaldehyde [21]. At the same time, the addition of the lithium anions derived from (*R*)-methyl and ethyl *p*-tolyl sulfoxides to *N*-arylsulfinyl imines took place in a highly stereoselective manner providing an access to enantiomerically pure β-(*N*-sulfinyl)amino sulfoxides even in the case in which two new stereogenic centers are created [22]. Thus, for the addition of sulfoxide- stabilized carbanions the nature of imines, the reaction conditions, and the substituent on imine nitrogen are critically important in controlling the stereochemical outcome. The *N*-protected group not only affected the reactivity of C=N double bond but also its geometry and coordination ability of the imine nitrogen. However, it was not obvious what stereochemical outcome we would observe in the proposed asymmetric addition to fluoroalkyl imines because of special electronic properties and steric demands of the fluoroalkyl group [23].

Initially we identified imines of trifluoropyruvate as convenient and readily available synthon for preparation of α-trifluoromethyl-α-amino acids. The effective method to synthesize desired imines is the Staudinger reaction of trifluoropyruvate with triphenylphosphazenes [24]. The reaction proceeds under mild conditions giving rise to imines in 70–95% yields. We found that the reaction of lithium anion of alkyl *p*-tolyl sulfoxides (R_s)-**2** with *N*-acyl imines of methyl trifluoropyruvate **31** in THF at −78 °C regioselectively afforded the addition products at the imine carbon in good overall yields (Scheme 4) [25]. 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 **32**–**35**, the major products in these reactions, were isolated by flash chromatography and/or fractional crystallization in moderate yields (30–42%). The optical 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. Conversion of each separated diastereomers **32**–**35** to the corresponding free α-amino acids was then accomplished in a three-step reaction sequence. Well-optimized reduction using sodium iodide and trifluoroacetic anhydride in acetone followed by desulfurization with Ni-Raney in refluxing ethanol and further deprotection provided a series of α-trifluoromethyl α-amino acids **36** and **37** with excellent ee's in all cases. Pummerer rearrangement of both *N*-Cbz diastereomers **32** and **33** with trifluoroacetic anhydride and *sym*-collidine followed by reduction of the intermediate aldehydes with sodium borohydride and deprotection of amino and carboxylic functions allowed us to extend this strategy to the first synthesis of both enantiomers of α-trifluoromethyl serines **38** and **39** in optically pure form [26].

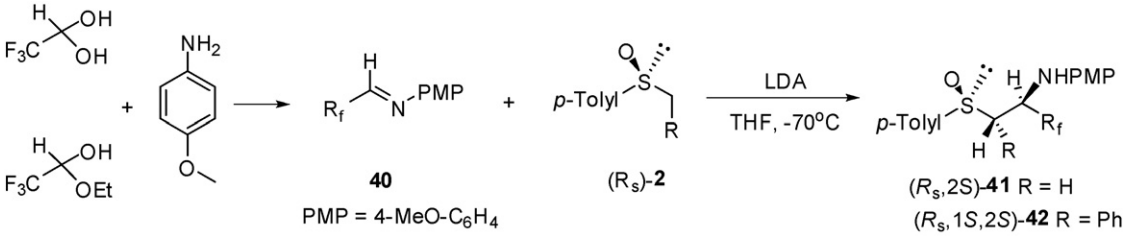
The exceptionally high reactivity of the *N*-acyl imines of trifluoropyruvate may be responsible for the poor stereoselectivity of sulfoxide-stabilized carbanions additions. In order to decrease the reactivity of the starting imines we turned our attention to such electrophilic substrates as fluoroalkyl *N*-(*p*-methoxyphenyl)aldimines. The *N*-*p*-methoxyphenyl protective group was chosen because of its synthetic versatility. It can be readily cleaved to afford a free amine function, provides geometric homogeneity of the imine functionality, induces reasonably high electrophilicity to the C=N double bond, and allows the imine nitrogen to form coordinated transition states. According to the ^{1}H, ^{13}C and ^{19}F NMR data the starting *N*-(*p*-methoxyphenyl)aldimines **40**, easily prepared by direct condensation between *p*-anisidine and perfluoroalkyl aldehydes in their commercially available hydrate or hemiacetal form, exist exclusively as (*E*)-geometric isomers that is critically important considering stereochemical outcome of the addition reactions. Condensation of lithium anion of alkyl *p*-tolyl sulfoxides (R_s)-**2** with *N*-(*p*-methoxyphenyl)aldimines **40** proceeded with high rate at −70 °C giving rise to addition products



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 4.

Table 1
Addition of α-lithiated alkyl p-tolyl sulfoxides (R_s)-**2** to fluoroalkylaldimines **40**.[a]



Entry	R_f	R	Dr (major/minor)[b]	Yield (%)[c]
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] Imines **40** were added at −70 °C to a THF solution of lithium anion of alkyl p-tolyl sulfoxides (R_s)-**2**.
[b] Values dr were determined by ^{19}F NMR analysis of the crude reaction mixtures.
[c] Overall isolated yield. Isolated yield of diastereomerically pure **41** and **42** is given in parentheses.

(R_s,2*S*)-**41** and (R_s,1*S*,2*S*)-**42** in excellent yields (Table 1) [27]. The nature of the fluoroalkyl group on the starting imines **40** had no particular influence on the stereochemical outcome of the addition reactions. Generally high diastereoselectivity, more than 70% de, was achieved even for the case of **42** when two chiral centers were simultaneously created in the single addition step (Table 1, entries 4–6). Previously it has been shown that the temperature, during generation of α-lithio derivatives of alkyl *p*-tolyl sulfoxides (R_s)-**2** and its reaction with non-fluorinated imines, strongly affect the diastereoselectivity of β-amino sulfoxide formation [20a]. However variation of experimental parameters (temperature and order of the addition) of the reactions under study did not show major influence on the stereochemical outcome. At the same time these experiments revealed that the addition reactions to polyfluoroalkyl imines occur irreversibly and the observed diastereoselectivity is kinetically controlled. α-Fluoroalkyl-β-sulfinyl amines **41** and **42** were found to be highly crystalline compounds and major diastereomers were readily obtained in enantiomerically pure state through a simple crystallization of the crude product mixtures.

Unexpectedly the absolute configuration of **42** was found to be opposite of that obtained in reactions of α-lithium derivative of benzyl *t*-butyl sulfoxide with non-fluorinated imines [20b]. To rationalize this observation four possible for the condensation of lithium anion of benzyl *p*-tolyl sulfoxide (R_s)-**2** with *N*-(*p*-methoxyphenyl)aldimines **40** six-membered cyclic transition states **A**–**D** should be considered (Fig. 2). The chair like TS-**B**, leading to the (R_s,1*S*,2*S*)-configured products is clearly favored with respect to other transition states, because in the boat TS-**C** and TS-**D** the fluoroalkyl group experiences repulsive steric and electrostatic interactions with sulfoxide oxygen, while in the chair TS-**A** the fluoroalkyl substituent and the phenyl of the sulfoxide moiety are in sterically unfavorable gauche disposition to each other. It is interesting that high stereoselectivity was observed during the formation of C–SO stereogenic center, indicating that during the reaction there is a kinetic preference for less thermodynamically favorable *syn* stereoisomeric form of α-carbanion of benzyl *p*-tolyl sulfoxide. Thus, stereoelectronically demanding fluoroalkyl group on starting imines was demonstrated to be the reason for this unusual stereochemical outcome.

To demonstrate the general synthetic application of *N*-(*p*-methoxyphenyl)aldimines we studied additions of lithium derivatives of methyl *p*-tolyl sulfoxide (R_s)-**2** to imines **43** derived from a series of aromatic aldehydes (Table 2) [28]. It turned out that addition reactions preceded in a reversible manner and the stereochemical outcome was shown to be a function of the reaction conditions and electronic properties of the arylidene moiety on the starting imine. High (2*S*) diastereoselectivity of 84–90% de could be obtained under condition of kinetic control (short reaction time, low temperature) for imines **43** bearing relatively electron rich *N*-arylidene group (Table 2, entries 1 and 3). Progressive introduction of fluorine atoms on the benzyliden phenyl ring decreases the kinetically controlled diastereoselectivity and in the case of pentafluorobenzylideneimine **43** a mixture of corresponding diastereomers (R_s,2*S*)-**44** and (R_s,2*R*)-**45** was obtained in a ratio of 64/36 (Table 2, entries 4, 6–9). It is interesting to note that very similar effect of fluorination on the stereochemical outcome was observed also in the gold(I)-catalyzed asymmetric aldol reaction of fluorinated benzaldehydes with α-isocyanoacetamide [29]. The introduction of electron withdrawing *p*-nitro substituent also led to diastereomeric products with much lower ratio than that of the unsubstituted imine **43** (Table 2, entries 1 and 10). The proposed explanation for observed stereochemical preferences was based on the attractive electrostatic interactions between electron-deficient

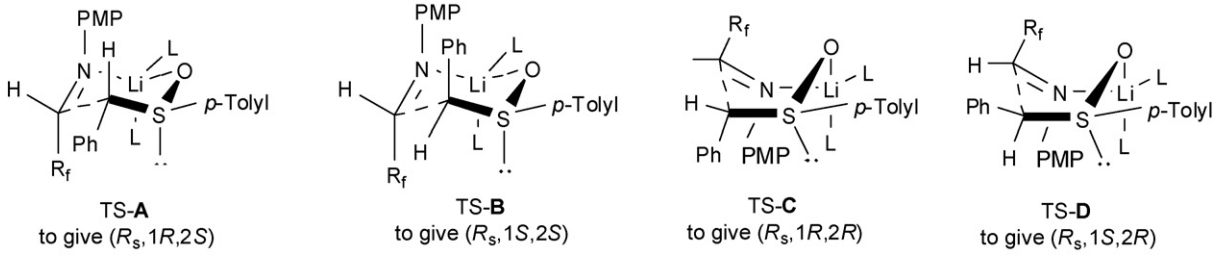
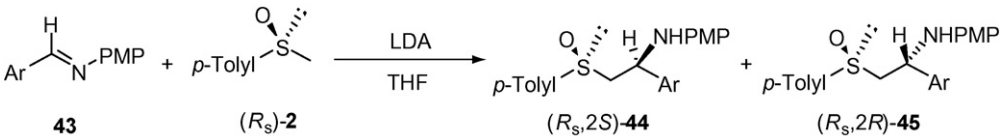


Fig. 2.

Table 2
Addition of α-lithiated methyl *p*-tolyl sulfoxide (*R*)-**2** to arylaldimines **43**.



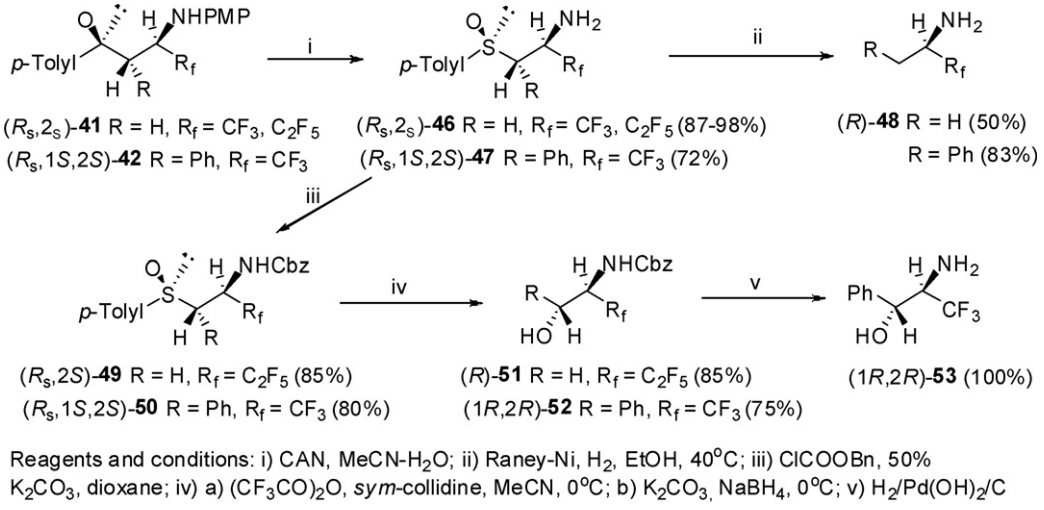
43 (*R*$_s$)-**2** (*R*$_s$,2*S*)-**44** (*R*$_s$,2*R*)-**45**

Entry	Ar	Temperature (°C)	Yield[a]	Ratio[b]	
			%	(2*S*,*R*$_s$)	(2*R*,*R*$_s$)
1	C_6H_5	−78	99	92.0	8.0
2	C_6H_5	−70 to 0	88	50.0	50.0
3	4-MeO-C_6H_4	−78	74	95.0	5.0
4	2-F-C_6H_4	−70	84	87.7	12.3
5	2-F-C_6H_4	−70 to 0	97	50.0	50.0
6	4-F-C_6H_4	−70	80	88.2	11.8
7	3-F-C_6H_4	−70	95	84.4	15.6
8	3,4-F_2-C_6H_4	−70	82	79.9	20.1
9	C_6F_5	−70	68	63.5	36.5
10	4-NO_2-C_6H_4	−70	95	76	24

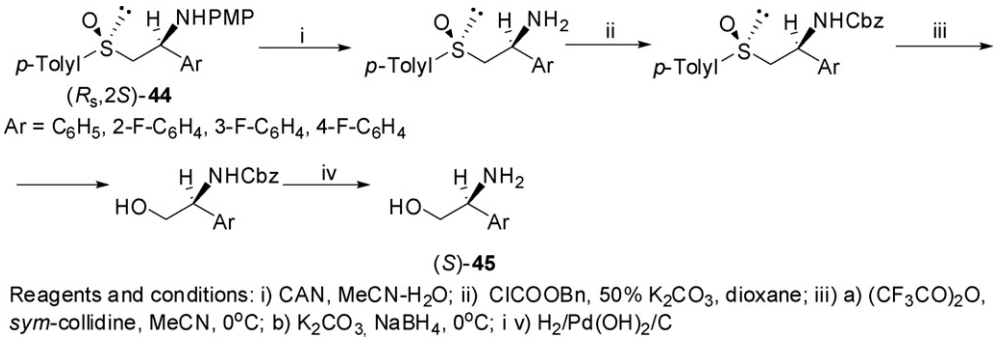
[a] Overall isolated yield of both diastereomers (*R*$_s$,2*S*)-**44** and (*R*$_s$,2*R*)-**45**.
[b] The ratios were determined by ^{1}H and ^{19}F NMR analysis of the crude reaction mixtures.

benzylidene phenyl ring of the fluoro- and *p*-nitro-substituted imines and negatively charged sulfoxide oxygen, which could stabilize the sterically unfavorable transition state leading to formation of (*R*$_s$,2*R*)-configured products. It is necessary to note that reactions under thermodynamically controlled conditions (0 °C) afforded 1/1 mixture of diastereomeric products regardless of the substitution on the starting imines (Table 2, entries 2 and 5).

Preparation of biologically interesting enantiomerically pure α-fluoroalkyl-containing amines and hydroxy amines from α-fluoroalkyl-β-sulfinyl amines **41** and **42** are depicted in Scheme 5. Treatment of α-fluoroalkyl-β-sulfinyl amines **41** and **42** with cerium ammonium nitrate (CAN) in acetonitrile at room temperature leads to selective cleavage of the *N*-*p*-methoxyphenyl protective group without oxidation of the sulfinyl moiety, which is necessary for further synthetic elaboration. This method allows for preparation of the *N*-unsubstituted β-sulfinyl amines **46** and **47** in high chemical yields. Transformation of α-fluoroalkyl-β-sulfinylamines **46** and **47** to fluorinated amines **48** could be accomplished by one-pot reductive desulfinylation with Raney-Ni/H_2 in ethanol. When amines **46** and **47** after temporary re-protection as *N*-Cbz derivatives **49** and **50** were submitted to non-oxidative Pummerer conditions (trifluoroacetic anhydride and *sym*-collidine), the trifluoroacetoxy group displaced the sulfinyl group in an S_N2 manner to afford a sulfenamide intermediate [30]. One-pot treatment of this intermediate with aqueous K_2CO_3 and $NaBH_4$ provided very good yields of the corresponding β-amino alcohols **51** and **52**. The asymmetric Pummerer reaction of sulfoxide **50** is of significant interest, since it takes place with complete inversion of the absolute configuration at the carbon bearing sulfinyl group, yielding *N*-Cbz trifluoronorephedrine **52** with de >99%. The Cbz-group was removed with Pd(OH)$_2$/H_2 providing trifluoronorephedrine **53**, which optical rotation and spectral properties confirmed the inversion of the configuration in the course of non-oxidative Pummerer reaction. We next demonstrated the utility of the diastereochemically pure β-aryl-β-*N*-(*p*-methoxyphenyl)aminoalkyl sulfoxides **44** for the synthesis of enantiomerically pure α-arylglycinol **54** as outlined in Scheme 6.



Scheme 5.



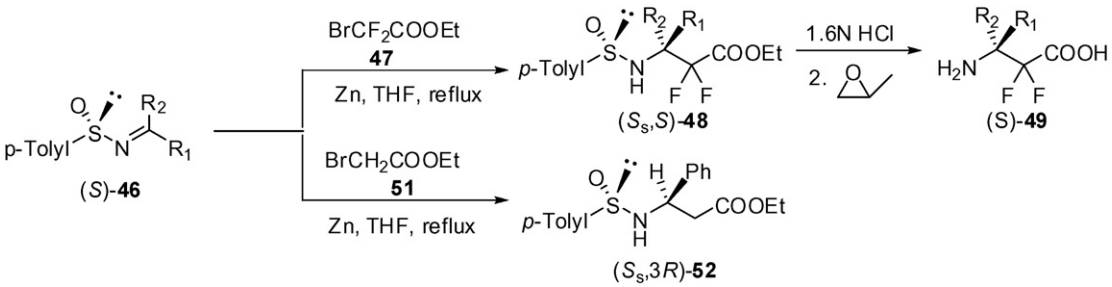
Scheme 6.

4. Reformatsky reaction between *N*-sulfinyl imines and ethyl bromodifluoroacetate. Asymmetric synthesis of α,α-difluoro-β-amino acids

Recently fluorinated β-amino acids have received extensive attention, owing to their role in peptidomimetic and medicinal chemistry. Therefore several general approaches for introducing either fluorine atoms or fluoroalkyl group into β-amino acids have been reported in the literature [31]. Among fluorinated β-amino acids CF_2-containing derivatives have been regarded as one of the most interesting types: they have been used in the design of peptides [32], fluoroalkene dipeptide isosteres [33] as well as side chain of docetaxel analogue [34]. Most recently these derivatives were shown to be important compounds in investigation of the phenomenon of self-disproportionation of enantiomers under the conditions of achiral chromatography [35]. Reformatsky-type and Rh-catalyzed Reformatsky-Honda reactions of bromodifluoroacetates with various 1,3-oxazolidinones and aldimines derived from chiral β-aminoalcohols has been recognized as the most useful method for the formation a variety of α,α-difluoro-β-amino acid derivatives [33a,36]. In many cases, reactions took place with good level of stereoselectivity giving rise to α,α-difluoro-β-amino acid derivatives and/or difluoro-β-lactams depending on structure of substrates and reaction conditions. When these methods produced difluoro-β-lactams the additional ring-opening step was required to prepare the desired α,α-difluoro-β-amino acids. We have focused our attention on exploring the enantiomerically pure *N*-*p*-toluenesulfinyl imines developed by Davis et al. in the reactions with Reformatsky reagent derived from ethyl bromodifluoroacetate, since very high diastereoselectivity was observed for the addition of metal enolate of methyl acetate to *N*-*p*-toluenesulfinyl imines [37]. These results suggested the practical efficiency of the *N*-sulfinyl group in controlling the stereoselectivity of addition reactions of stabilized carbon nucleophiles to imines. Moreover, the sulfinyl group serves as versatile amine protecting group that enables the incorporation of amino derivatives into a series of more complex structures and can be easily removed under mild acid conditions without any extent of undesirable epimerization.

With a goal in mind, we prepared a variety of structurally diverse chiral *N*-*p*-toluenesulfinyl imines by condensation of commercially available (*S*)-*p*-toluenesulfinamide with the appropriate carbonyl compounds in the presence of $Ti(OEt)_4$ according to Davis' method [38]. When the enantiomerically pure aryl *N*-*p*-toluenesulfinyl imines (*S*)-**46** were treated with ethyl bromodifluoroacetate **47** in the presence of activated Zn dust under high temperature, the desired *p*-toluenesulfinamides **48** were obtained with the (*Ss,3S*)-absolute configuration of the major diastereomers and in highly diastereoselective manner (Table 3, entries 1–5) [39]. In a series of experiments designed to optimize chemical yield of addition products **48**, we found that a 1/2 ratio of aryl *N*-sulfinyl aldimines (*S*)-**46** and ethyl bromodifluoroacetate **47** was required for complete transformation of the former to sulfinamides **48**, isolated with over 80% yield. The undesired corresponding difluoro-β-lactams were not detected in these reactions. We demonstrated that the diastereoselectivity of these addition reactions of aromatic aldehyde-derived (*S*)-**46** was noticeably influenced by the electron-donating or withdrawing character of the substituent on the aromatic ring in (*S*)-**46**. The very high diastereoselectivity was observed in the case of anisaldehyde-derived *N*-sulfinyl imine (*S*)-**46** (Table 3, entry 2). On the other hand, the reactions of *p*-fluoro- and *p*-chloro- substituted (*S*)-**46** gave the corresponding products **48** with % de comparable with that observed in the addition to unsubstituted *N*-benzylidene derivative (*S*)-**46** (Table 3, entries 1, 3 and 4). In contrast, the reaction of *p*-trifluoromethyl- and 2-furyl-conaining sulfinimines (*S*)-**46** showed lower stereochemical outcome as compared with the diastereoselectivity observed in the reactions of *N*-benzylidene derivative (Table 3, entries 1, 5 and 6). When substituents were an aliphatic group, even bulky, all reactions proceeded with the same efficiency as with the aromatic series but with lower diastereoselectivity. Thus the products **48** bearing *n*-alkyl and *i*-propyl group were obtained with 72% de, while a bit higher, 76% de, selectivity was observed in the reaction of the *t*-butyl-containing derivative (Table 3, entries 7–9). The isolation of the major products **48** was effectively achieved either by crystallization or flash chromatography. Finally, we examined the Reformatsky reaction of *N*-sulfinyl ketimine (*S*)-**46** derived from acetophenone to produce the corresponding quaternary carbon-containing chiral α,α-difluoro-β-amino acid. In general, the Reformatsky reactions of bromodifluoroacetates with ketimines have been substantially much less studied, probably due to the lower reactivity of ketimines and their tendency to enolization. To our satisfaction, the acetophenone-derived ketimine (*S*)-**46** reacted well giving rise to the expected addition product **48** in moderate yield, however, with excellent diastereoselectivity (Table 3, entry 10). Further optimization of the reaction conditions revealed that the yield of **48** could be raised to a more satisfactory level by performing the Reformatsky-type reaction at room temperature with organozinc reagent, generated in THF according to the literature procedure [40] (Table 3, entry 11). Since the excellent diastereoselectivity in these high-temperature Reformatsky reactions was rather unexpected, we assumed that the presence of the fluorine atoms in the reagent **47** might have some effect on the stereochemical outcome. Therefore, we decided to conduct the reaction between benzaldehyde-derived imine (S)-**46** and fluorine-free ethyl bromoacetate **51** using our standard reaction conditions. Surprisingly, the reaction with ethyl bromoacetate **51** proceeded with similar to the fluorinated analog **47** rate affording the product **52** in 94% de. This result suggested that the fluorine atoms in the reagent **47** have no effect on the stereochemical outcome of the Reformatsky reactions and the operationally convenient conditions used by us might be of general application for preparing fluorinated as well as non-fluorinated β-amino acids.

Table 3
Reformatsky reactions between *N*-*p*-toluenesulfinyl imines (*S*)-**46** and ethyl bromodifluoroacetate **47**.[a]



Entry	*N*-sulfinyl imines (*S*)-**46**		Products (*Ss,3S*)-**48**		Products (*S*)-**49**
	R_1	R_2	Yield[b] (%)	de[c] (%)	Yield[d] (%)
1	C_6H_5	H	82	92	88
2	4-MeO-C_6H_4	H	82	>98	96
3	4-F-C_6H_4	H	83	94	82
4	4-Cl-C_6H_4	H	85	93	78
5	4-CF_3-C_6H_5	H	85	80	94
6	2-Furyl	H	77	86	–
7	*n*-C_5H_{11}	H	59	72	56
8	*i*-Pr	H	65	72	63
9	*t*-Bu	H	60	76	70
10	C_6H_5	CH_3	56	>98	72
11[e]	C_6H_5	CH_3	77	>98	

[a] All reactions were conducted by slow addition of solution of 2 eq. of ethyl bromodifluoroacetate **47** and 1 eq. of imine (S)-**40** in THF to a refluxing suspension of 2 eq. of activated Zn powder in THF.
[b] Isolated yields of pure products after column chromatography.
[c] Determined by ^{19}F and ^{1}H NMR analysis of the crude reaction mixtures.
[d] Isolated yields of pure products.
[e] Reaction was conducted by addition of 1 eq. of imine (S)-**40** in THF to 3 eq. of $BrZnCF_2COOEt$ in THF at 20 °C.

The stereochemical outcome of the described Reformatsky reactions, regarding the absolute configuration of the newly formed carbon stereogenic center, is similar to the stereochemical preferences generally observed for additions of organometallic reagents including enolates, Grignard reagents, metallo phosphite and ethylaluminum cyanoisopropoxide to *N*-sulfinyl imines and can be explained by six-membered chair-like transition states where coordination of the metal to the sulfinyl oxygen directs addition of the incoming nucleophile on the *Re* face of the *N*-sulfinyl imine.

Hydrolysis of diastereomerically pure sulfinamides **48** was affected by refluxing with 6*N* HCl. Extraction with ether to remove the sulfinic acids, removal of the aqueous solvent, and treatment of the residue with propylene oxide/*i*-PrOH afforded the corresponding α,α-difluoro-β-amino acids **49** in good to excellent yields. The chiral HPLC analysis [41] indicated that free α,α,-difluoro-β-amino acids **49** were obtained with excellent ee's.

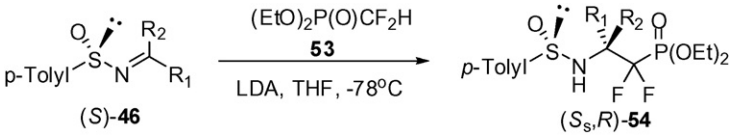
It should be mentioned that influence of *tert*-butylsulfinyl group as an imine substituent on the addition of the Reformatsky reagent derived from ethyl bromodifluoroacetate at the same time has been reported by Staas et al. [32c]. In their studies, addition of Reformatsky reagent to (*R*)-*N*-*tert*-butylsulfinyl aldimines at room temperature afforded the sulfinamide adducts in 51–82% yield and diastereoselectivity ranged from 80:20 for alkyl side chains such as propyl, to 95:5 for the 2-thiazolyl case. However application of chiral HPLC was required for isolation of the diastereomerically pure products.

5. Addition of diethyl difluoromethylphosphonate to *N*-sulfinyl imines. Asymmetric synthesis of α,α-difluoro-β-aminophosphonates and phosphonic acids

Encouraged by the success of using the *N*-sulfinyl group as a chiral auxiliary in the Reformatsky reaction of imines with ethyl bromodifluoroacetate, we turned our attention to addition of difluoromethylphosphonate carbanion to *N*-sulfinyl imines. Aminophosphonic acids containing a difluoromethylene group bonded to a phosphorus atom recently received significant attention as hydrolytically stable isosteric and isopolar phosphoamino acids mimetic [42]. Furthermore, fluorine-containing aminophosphonates and aminophosphonic acids display a broad range of biological properties such as antiviral, antifungal and antitumor effects, as well as enzyme-inhibitory activity [43]. Our investigation was based on reported asymmetric addition of alkyl- [44] and halomethylphosphonate carbanions [45] to *N*-sulfinyl imines. Addition of a methylphosphonate carbanion to aldehyde-derived (*S*)-*N*-sulfinyl imines afforded *N*-sulfinyl β-aminophosphonates with the (*R*)-absolute configuration at the newly generated stereogenic center of the major diastereomers. Stereoselectivity ranged between 66 and 82% de depending on the nature of the imine and the reaction conditions. In the analogous reactions of aldehyde-derived (*S*)-*N*-sulfinyl imines with chloromethylphosphonate carbanions, the corresponding α-chloro-β-amino adducts were isolated with the exclusive (*R*)-absolute configuration at the β-carbon atom. The (*R*) absolute configuration at the β-carbon atom in the major diastereomers is opposite to that obtained in reaction of sulfinimines with metal enolate. This difference may reflect the greater steric bulk of α-phosphonates carbanions as well as their non-planar tetrahedral structure.

We have found that phosphonodifluoromethyl carbanion, generated in situ from diethyl difluoromethylphosphonate **53** and LDA in THF at −78 °C, could readily undergo nucleophilic addition with a variety of structurally diverse enantiomerically pure *N*-sulfinyl aldimines (*S*)-**46** giving the corresponding *N*-sulfinyl α,α-difluoro-β-aminophosphonates **54** with 82–90% de (Table 4) [46]. In spite of the relatively weak nucleophilicity and thermal instability of diethyl lithiodifluoromethylphosphonate, *N*-

Table 4
Reaction of the diethyl difluoromethylphosphonate **53** with *N*-sulfinyl imines (*S*)-**46**.[a]



Entry	*N*-Sulfinyl imine (*S*)-**46**		Product (*Ss*,*R*)-**54**	
	R_1	R_2	de (%)[b]	Yield (%)[c]
1	Ph	H	90	74
2	*p*-MeO-C_6H_4	H	88	92[d]
3	*p*-CF_3-C_6H_4	H	88	70
4	2-thienyl	H	84	67
5	*n*-C_5H_{11}	H	84	72
6	*i*-Pr	H	82	75
7	*E*-PhCH=CH	H	88	76
8	Ph	CH3	92	40

[a] Reactions were performed using 1 equiv of *N*-sulfinyl imine (*S*)-**46** and 1.3 equiv of diethyl difluoromethylphosphonate **53**.
[b] Determined by ^{1}H and ^{19}F NMR analysis of the crude reaction mixtures
[c] Isolated yield of major diastereoisomer.
[d] Combined yield of diastereoisomers.

sulfinyl α,α-difluoro-β-aminophosphonates **54** were obtained in good yields. Variation of the bases, solvents and additives did not improve the selectivity of addition and resulted in incomplete conversion of starting (*S*)-**46**, as indicated by ^{1}H NMR and TLC analysis of crude reaction mixtures. The diastereoselectivity of reactions with aryl aldimines was independent of electronic factors and substrates (*S*)-**46** containing either electron- withdrawing or electron-donating groups, such as *p*-trifluoromethylphenyl and *p*-methoxyphenyl reacted to produce the corresponding adducts **54** with the stereochemical outcome compared to that observed for *N*-benzylidene derivative (*S*)-**46** (Table 4, entries 1–3). However, the use of heteroaromatic and alkylsubstituted *N*-sulfinyl aldimines (S)-**46** as substrates provided lower stereoselectivity. The size of the alkyl group has no effect on the diastereoselectivity of the addition as illustrated by *N*-sulfinyl aldimines (S)-**46** bearing *n*-pentyl and *i*-propyl groups (Table 4, entries 5 and 6). When *trans*-cinnamaldehyde-derived (*S*)-**46** was subjected to our reaction conditions, the 1,2-addition product **54** was obtained exclusively in good yield and with high diastereoselectivity (Table 4, entry 7). Attempts to extend the scope of the reaction by employing imines derived from ketones have met with limited success. Deprotonation of **53** with LDA in THF at −78 °C, followed by addition of acetophenone-derived *N*-sulfinyl imine (*S*)-**46** led to formation of adduct **46** with a 92% de and in only moderate yield after 1 h of the reaction (Table 1, entry 8). The diastereoselectivity and yield remained essentially unchanged with a longer reaction time. Competitive deprotonation of the acetophenone-derived *N*-sulfinyl imine (*S*)-**46** was likely responsible for the moderate yield observed in the addition reaction. It was anticipated that the effect of a cerium salt on the reactivity of dialkyl lithiodifluoromethylphosphonate [47] might favor addition to acetophenone-derived sulfinimine (*S*)-**46** over deprotonation. However, conducting the reaction in the presence of one equivalent of cerium (III) chloride did not significantly change both the yield and stereoselectivity in this case. It should be noted that crystallization or chromatographic purification afforded the diastereomerically pure products **54**.

The (*R*) absolute configuration of the newly formed stereogenic center in the major diastereomers **54** corresponds to that observed for the addition of methylphosphonate carbanions to *N*-sulfinyl aldimines (*S*)-**46**. Thus, the stereochemical outcome is consistent with the open transition state **A** proposed in the non-fluorinated series [44a,b]: the lithium cation coordinates to both the phosphonate oxygen of **53** and the sulfinyl oxygen of the substrate (*S*)-**46** in an *s-cis* conformation, and addition to the C=N bond occurs from the least hindered face that is opposite to the *p*-tolyl group (Fig. 3).

A significant advantage of the sulfinyl methodology is that *N*-sulfinyl β-aminophosphonates have the potential to undergo further synthetic transformations. The diastereomerically pure **54** were converted to α,α-difluoro-β-aminophosphonates **55** by trifluoroacetic acid catalyzed methanolysis, which allowed to deprotect selectively the amino function (Scheme 7). Subsequent hydrolysis of **55** in refluxing 10*N* HCl provided, after treatment with propylene oxide, crystalline α,α-difluoro-β-aminophosphonic acids **56** in good to excellent isolated yields. The enantiomeric purity of α,α-difluoro-β-aminophosphonic acids **56** thus obtained was >98% ee. After re-protection of **55** as *N*-Cbz derivative **57** by treatment with benzyloxycarbonyl chloride/potassium carbonate, the corresponding β-aminophosphonic acid **58** and β-aminophosphonate monoester **59** were obtained according to standard methods. The *N*-Cbz-protected difluorophosphonate monoester **59** was converted into the sodium salt of difluorophosphonamidic acid **61** after coupling with benzylamine followed by deprotection with sodium iodide in methyl ethyl ketone. Characterization of sodium salt **61** involved the examination of the hydrolytic stability of the phosphonamide linkage. It was found that at 21 °C difluorophosphonoamidic acid was stable at pH above 5, that is quite opposite to that of nonfluorinated compounds. However, partial slow hydrolysis was observed at pH 2.18 (half life was 36 h). Difluorophosphonamides, hydrolytically stable at physiological pH, may find biochemical applications as potent inhibitors of metallo-proteases [48].

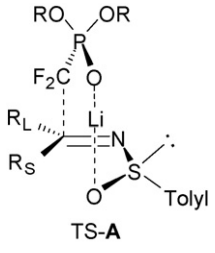
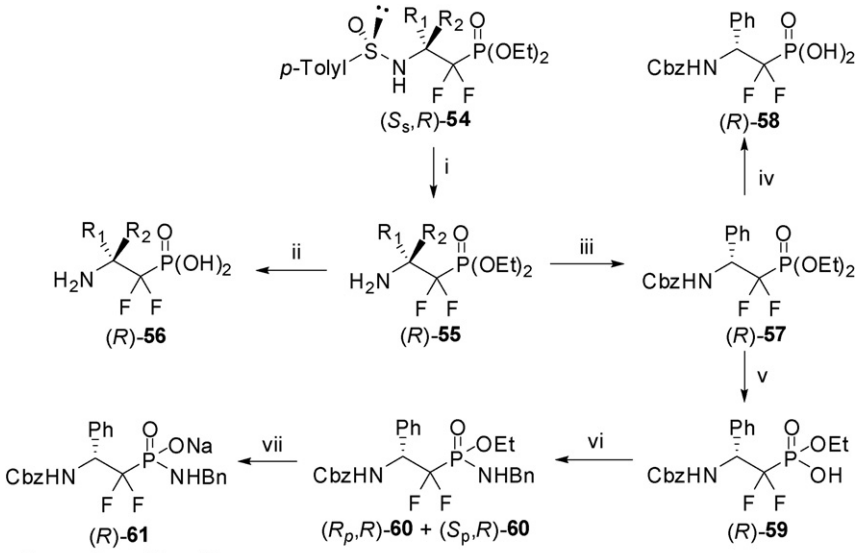


Fig. 3.



Reagents and Conditions:
i) CF_3COOH, EtOH, 20°C; ii) a) 10N HCl, reflux, b) propylene oxide, EtOH, 20°C; iii) CbzCl, K_2CO_3, THF, 20°C; iv) Me_3SiBr, CH_2Cl_2, 20°C; v) NaI, acetone, reflux; vi) a) EtONa, EtOH, 20°C, b) $(COCl)_2$, DMF, CH_2Cl_2, 0°C, c) $BnNH_2$, Et_3N, CH_2Cl_2, 20°C; vii) NaI, methyl ethyl ketone, reflux.

Scheme 7.

6. Conclusion

We have developed several new efficient methodologies using sulfinyl auxiliaries for the preparation of biologically relevant fluorine-containing amino compounds. Highly diastereoselective methylene transfer from diazomethane to fluoroalkyl β-keto sulfoxides provide an efficient approach to the α-fluoroalkyl epoxides as chiral building blocks for rational design of enantiomerically pure diols, amino alcohols, α-hydroxy-β-amino and α,β-dihydroxy acids as well as acyclic analogues of nucleosides with the fluoroalkylated quaternary centers. Enantiomerically pure α-fluoroalkyl β-sulfinyl amines, precursors of α-fluoroalkyl amines, hydroxy amines and amino acids, can be prepared by addition of alkyl *p*-tolyl sulfoxide anion to *N*-(*p*-methoxyphenyl)aldimines bearing fluoroalkyl group in excellent yields and good diastereoselectivity. These reactions can be used to introduce two chiral centers in one step by using the α-carbanion of benzyl *p*-tolyl sulfoxide as the nucleophile. The enantiomerically pure *N*-sulfinyl imines were found to be efficient substrates in the high temperature Reformatsky-type additions with ethyl bromodifluoroacetate providing for reliable approach to the enantiomerically pure α,α-difluoro-βamino acids. The efficient route to diastereomerically pure *N*-sufinyl-α,α-difluoro-β-aminophosphonates by addition of difluoromethylphosphonate carbanion to enantiomerically pure *N*-sulfinyl imines opened new opportunities for asymmetric synthesis of enantiomerically pure α,α-difluoro-β-aminophosphonates, α,α-difluoro-β-aminophosphonic acids and their derivatives.

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