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Chiral Sulfoxide Controlled Asymmetric Additions to C-N Double Bond. An Efficient Approach to Stereochemically Defined α-Fluoroalkyl Amino Compounds

Pierfrancesco Bravo,* Maurizia Guidetti, Fiorenza Viani and Matteo Zanda*

C.N.R. - Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Andrey L. Markovsky and Alexander E. Sorochinsky

The Ukrainian Academy of Sciences, Institute of Bioorganic Chemistry and Petrochemistry, Murmanskaya 1, Kiev - 94, 253660, Ukraine

Irina V. Soloshonok and Vadim A. Soloshonok*

National Industrial Research Institute of Nagoya, Hirate-cho 1-1, Kita-ku, Nagoya City, Aichi Prefecture 462, Japan

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Abstract: This paper presents a full account of studies into the asymmetric addition reactions between α-lithium derivatives of enantiomerically pure methyl and benzyl *p*-tolyl sulfoxides and the *N*-(*p*-methoxyphenyl)aldimines, bearing trifluoromethyl, pentafluoroethyl and ω-hydrotetrafluoroethyl groups, to afford the corresponding α-fluoroalkyl β-sulfinylamines, synthetically versatile precursors of a series of enantiomerically pure biomedicinally important α-fluoroalkylalkylamines and α-fluoroalkyl-β-hydroxyalkylamines. The addition reactions were found to proceed under mild conditions allowing for convenient preparation of the corresponding α-fluoroalkyl β-sulfinylamines in excellent yields and good enantiomeric purity. The stereochemical outcomes of these reactions were shown to be subject to kinetic control, that is in sharp contrast to the corresponding reactions of fluorine-free imines. The absolute configurations of the addition products suggest that the fluoroalkyl group on starting imines plays a role of enantiodirecting, sterically larger substituent causing realization of an unusual for this type of reactions transition states.

INTRODUCTION

Amino compounds, in which a nitrogen is bound to a stereogenic carbon, make up a large body of naturally occurring and medicinally important molecules. Therefore, the development of asymmetric methodology allowing for the synthesis of stereochemically defined and structurally varied amino compounds has been an ongoing goal of organic chemists in recent years.[1] Among the biologically relevant targets, chiral and enantiomerically pure fluorine-containing amino compounds are of particular interest. It has been well-demonstrated that a selective substitution of fluorine for hydrogen offers a unique approach to the rational

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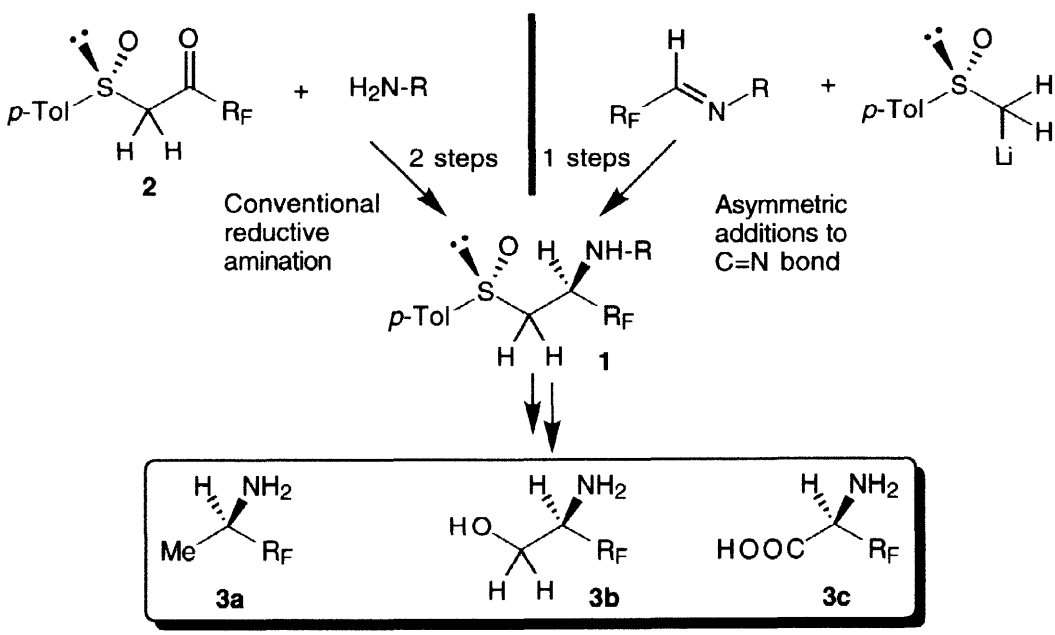
modification of biological and physical properties of organic molecules.[2] However, the enantiocontrolled preparation of fluorinated compounds is a synthetically challenging endeavor, due to the unique properties of fluorine substituents and, in particular, their controversial stereochemical behavior.[3,4] Thus, despite several generalized methods for preparing racemic fluorine-containing amino acids and amines has been developed,[2,5] there are only a limited number of synthetically meaningful approaches to the asymmetric synthesis of these highly biologically interesting compounds.[3,6,7]

Recently we have reported on the synthesis of enantiomerically pure α-fluoroalkyl-β-sulfinylethylamines **1** and demonstrated their efficient transformation into a series of α-fluoroalkyl substituted amines, aminoalcohols and amino acids (Figure 1). In particular, α-fluoroalkyl substituted amines **3a** were obtained by the reductive desulfinylation, which allows for a substitution of the sulfinyl group with a hydrogen atom. Of remarkable synthetic interest was the finding that *N*-Cbz α-fluoroalkyl β-sulfinylamines **1** could be transformed one-pot, in high yields, into α-fluoroalkyl β-amino alcohols **3b**, by means of the "non oxidative *Pummerer* reaction".[8a] Moreover, for compounds **1** having a stereogenic center in the position alpha to the sulfinyl group, the substitution of the latter by a hydroxyl could be performed with an excellent S_N2-type stereocontrol.[8b] Finally, enantiopure α-fluoroalkyl α-amino acids **3c** were obtained by oxidation of β-amino alcohols **3b**.[7b] Given the synthetic versatility associated with sulfinyl moieties[9,10] one can readily envisage an exciting potential of α-fluoroalkyl β-sulfinylamines **1** for preparing structurally varied and stereochemically defined fluoro-amino compounds of biomedicinal importance, provided, however, ready access to the optically pure β-sulfinylethylamines **1**. The reported reductive amination approach to the targeted compounds **1** has several synthetic drawbacks such as a necessity to employ the *N*-Cbz or *N*-$SiMe_3$ iminophosphoranes for the reaction with β-keto sulfoxides **2** to afford the corresponding imines/enamines, and their quite complicated and generally low-yield reduction to β-sulfinylamines **1**.[7b] Obviously, the most straightforward, an atom economy[11] approach to the α-fluoroalkyl β-sulfinylamines **1** would be the direct assembling of the alkyl aryl sulfoxide residue with the fluoroalkylimine framework by C-C bond forming. Moreover, this approach could allow for preparing β-substituted β-sulfinylalkylamines **1**, unavailable by the reductive amination method, that would significantly

Figure 1



increase the synthetic versatility of the β-sulfinyl amines **1**. On the other hand, the enantioselective additions to C-N double bonds belong to the least developed classes of asymmetric reactions. In particular, for the addition of chiral sulfoxide-stabilized carbon nucleophiles to achiral imines, only a handful of reports are extant.[12] It has been shown that the stereochemical outcome of these additions heavily depends on both the reaction condition applied and the nature of the substrates,[12b] and could be subject to kinetic or thermodynamic control.[12d] Moreover, while for the reactions of the imines derived from aromatic aldehydes high values of stereoselectivity and chemical yields could be achieved, aliphatic imines were found to be less suitable substrates for these additions, presumably, due to their lower reactivity. Furthermore, considering our design, there may be additional limitations imposed by the strong electron-withdrawing nature and steric demands of the fluoroalkyl group in the starting imines.[4]

In this paper we present a full account[13] of our studies of the asymmetric addition reactions between the α-lithium derivatives of enantiomerically pure methyl and benzyl *p*-tolyl sulfoxides and the *N*-(*p*-methoxyphenyl)aldimines (*N*-PMP imines), bearing trifluoromethyl, pentafluoroethyl and ω-hydrotetrafluoroethyl groups, to afford the α-fluoroalkyl β-sulfinyl amines **1** (Figure 1). Efficient elaboration of **1** to the series of enantiomerically pure biomedicinally important α-fluoroalkylalkylamines **3a**, α-fluoroalkyl-β-hydroxyalkylamines **3b**, in particular, the trifluoronorephedrine hitherto unavailable in optically pure form, is also presented.

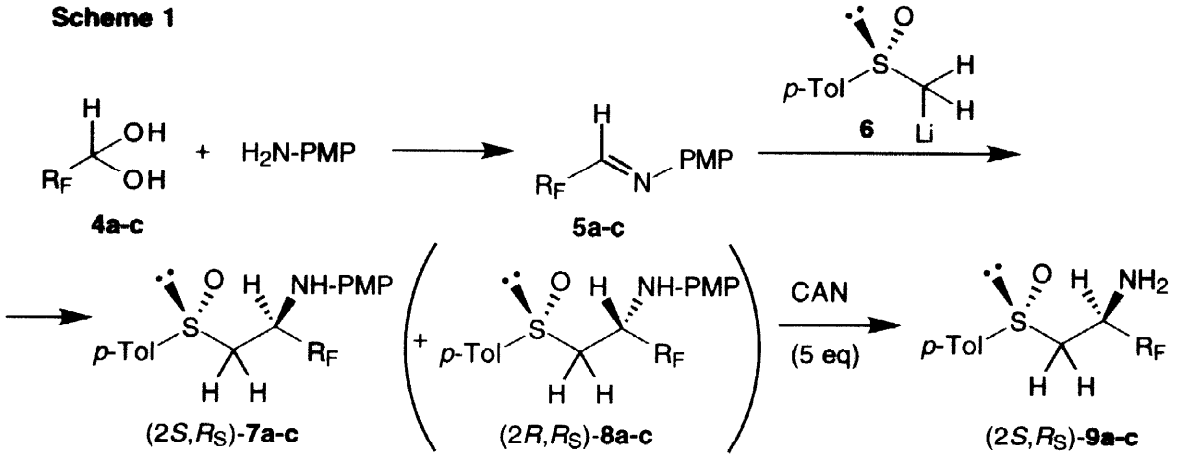
RESULTS AND DISCUSSION

For the addition reactions of imines with nucleophiles the substituent on the imine nitrogen was shown to be critically important in controlling the chemical and stereochemical outcomes of these condensations.[1] Thus, the *N*-protective group crucially affects the reactivity of C-N double bond, its geometry and the coordinative ability of the imine nitrogen. Moreover, from a synthetic point of view, the *N*-protective group should be efficiently removed to afford a free amino function. Therefore, the correct choice of the *N*-protective group for the starting imines was of paramount importance. After achieving only a limited success in the additions of α-lithiated alkyl aryl sulfoxides to *N*-acyl imines,[7c,14] we turned our attention to the *N*-*p*-methoxyphenyl (PMP) derivatives **5**.[15] The advantage of a PMP protective group is that it provides geometric homogeneity of the imine functionality[16] and induces reasonably high electrophilicity to the C-N double bond, while leaving alive lone electron pair on the nitrogen.

We have found that the desired *N*-PMP imines of fluoroalkyl aldehydes **5a-c** could be easily prepared by the direct condensation between *p*-anisidine and an appropriate aldehyde **4a-c**, taken in its commercially available hydrate form, in the presence of an acidic catalyst (Scheme 1). According to the ^{1}H, ^{19}F and ^{13}C NMR data, imines **5a-c** are geometrically (*E*)-homogeneous,[16] that is critically important considering the stereochemical outcome of their addition reactions.

Addition reactions between imines 5a-c and α-lithium derivative of (*R*)-methyl *p*-tolyl sulfoxide 6. The addition reactions between lithium derivatives of chiral sulfoxides and *N*-alkylideneamines are virtually unstudied. The only example we found in the literature is the condensation of *N*-*n*-propylideneaniline with (*R*)-**6**. This reaction was shown to proceed in a tetrahydrofuran (THF) solution at -45 °C for 2 h to afford a mixture of the corresponding diastereomeric β-amino sulfoxides in 85% yield and with 60% de of the (2*S*,R_S)-configured isomer.[12d] In contrast to this, the condensations between fluorinated aldimines **5a-c** and **6** (Scheme 1) were found to occur almost instantly in a THF solution at -70 °C to give cleanly a mixture of the

Scheme 1



PMP = 4-OMe-C_6H_4; R_F = CF_3 (**a**), C_2F_5 (**b**), CF_2CHF_2 (**c**)

desired products **7a-c** and **8a-c** in an excellent overall chemical yield (Table 1, entries 1-3). Determination of the stereochemical outcome of the condensations by ^{19}F NMR on the crude reaction mixture revealed that, regardless of the nature of fluoroalkyl group on starting imines **5a-c**, all reactions proceeded in highly diastereoselective manner giving rise to the major diastereomers **7a-c** in 70-71% de. β-Amino sulfoxides **7a-c** were found to be highly crystalline compounds thus allowing their facile purification to enantiomerically pure state by simple crystallization of the crude reaction mixtures.[17] To establish the absolute configurations of the resultant products **7a-c** and **8a-c**, trifluoromethyl-containing **7a** was deprotected to give free β-amino sulfoxide **9a** (*vide infra*) which has shown identical NMR patterns and optical rotation to the previously described derivative of (2*S*,R_S) configuration, determined by X-ray analysis.[7b] Accordingly, the diastereoisomers **7a-c** and **8a-c** were assigned (2*S*,R_S) and (2*R*,R_S) absolute configurations, respectively.

Aiming to improve the diastereoselectivity of the reactions, we noticed the data reported by *Kagan et al.* on

Table 1. Addition reactions of (*R*)-**6** to aldimines **5a-c**[a]

entry	R_F	Method[b]	Yield,[c] %	Dr (**7**/**8**)[d]
1	CF_3 (**a**)	A	88 (74)	86/14
2	C_2F_5 (**b**)	A	87 (72)	87/13
3	CF_2CHF_2 (**c**)	A	90 (70)	85/15
4	CF_3 (**a**)	B	88	86/14
5	CF_3 (**a**)	C	87	86/14

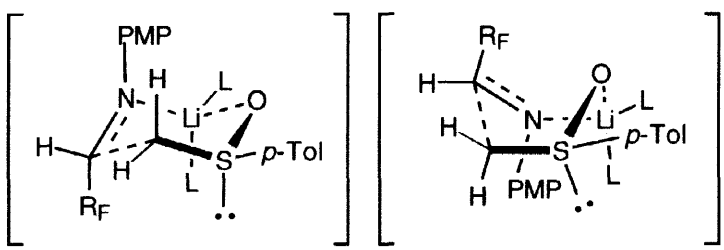
[a] All reactions were run in THF under nitrogen atmosphere. Imines **5a-c** were added at -70 °C to a THF solution of (*R*)-**6**; reaction time 15 min. [b] A = Solution of (*R*)-methyl *p*-tolyl sulfoxide was added to a LDA solution. B = The metallation of (*R*)-methyl *p*-tolyl sulfoxide to afford (*R*)-**6** was carried out at 0 °C. C = LDA solution was added to a solution of (*R*)-methyl *p*-tolyl sulfoxide. [c] Overall isolated yield of **7** and **8**. Isolated yield of diastereomerically pure **7** is given in the parentheses. [d] Values dr were determined by ^{19}F NMR analysis on the crude reaction mixtures.

the remarkable effect of the temperature of lithium derivative **6** formation on the stereochemical outcome of the corresponding addition reactions with benzylidenamines.[12b] According to *Kagan's* recipe for highest diastereoselectivity, we performed the condensation (at -70 °C) of trifluoromethyl-containing imine **5a** with lithium derivative (*R*)-**6**, prepared by the metallation of the (*R*)-methyl *p*-tolyl sulfoxide at 0 °C. Unfortunately, the products **7a** and **8a** were obtained in the same diastereomeric ratio (entry 4). Similarly, the opposite order of addition of LDA and the (*R*)-methyl *p*-tolyl sulfoxide to afford (*R*)-**6** (entry 5), had no influence on the stereochemical outcome. Finally, we investigated reversibility of the reactions under study. The metallation of diastereomerically pure (2*S*,R_S)-**7a** under the exact reaction conditions (LDA, -70 °C), followed by stirring of the resultant mixture for 2h at 0 °C, gave no signs of (2*S*,R_S)-**7a** epimerization to (2*R*,R_S)-**8a** or formation of starting imine **5a**; product (2*S*,R_S)-**7a** was isolated chemically and stereochemically intact. These data clearly suggest that the addition reactions of fluorinated imines **5a-c** with lithium derivative (*R*)-**6** occur irreversibly and the observed regio- and diastereoselectivities are kinetically controlled. These results are in sharp contrast with the data reported by *Pyne et al.*,[12d] on the reactions between lithium derivative **6** and the imines of general formula R-CH=N-R' (R = Ph, 2-furyl, Et; R' = Ph, Me). The corresponding addition products were shown to readily undergo interconversion (a thermodynamic control), presumably *via* a retro-addition reaction, at 0 °C.

Since the starting imines **5a-c** are assumed to be (*E*)-geometrically homogeneous, two chelated cyclic transition states (TSs) **A** and **B** (Fig. 2) could be envisioned to account for the stereochemical preferences observed. In the chair TS-**A** the fluoroalkyl group R_F points down away from the rest of the substituents, minimizing any non-bonding interaction. By contrast, in the boat TS-**B** the fluoroalkyl group is up and interacts unfavorably with the sulfoxide oxygen. Besides the steric, non-bonding interactions, the boat TS-**B** might be additionally destabilized by the electrostatic repulsive interaction between the fluoroalkyl group and partially negatively charged sulfoxide oxygen.[4d-g] Thus, TS-**A** should be favored relative to TS-**B** leading to the (2*S*,R_S)-configurated diastereomers as dominant products.

In fact, in contrast to *N*-Cbz β-aminosulfoxides, *N*-PMP derivatives of type **7** do not undergo direct displacement of the sulfinyl by a hydroxy group under "non oxidative" *Pummerer* rearrangement conditions.[8d] Therefore it was necessary to find out a practical and high yielding method for the chemoselective cleavage of the PMP group in the presence of a stereogenic sulfinyl moiety. A series of experiments revealed that treatment of *N*-PMP derivatives **7a-c** with 5 equiv of CAN[15] in acetonitrile at 0 °C are the conditions of choice. Another critical point was a work-up procedure. We found that the resultant mixture should be treated first with aqueous $NaHCO_3$, up to almost neutral pH, and then left under stirring for a few minutes, to reduce the excess of CAN with Na_2SO_3. This protocol allows for preparing of the target free amino derivatives **9a-c** in high chemical yields and virtually without oxidation of the sulfinyl moiety, which is necessary for further synthetic elaboration.

Figure 2

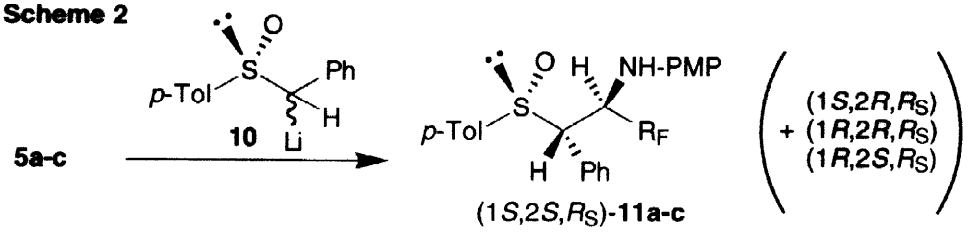


TS-**A** to give (2*S*,R_S)-**7a-c**

TS-**B** to give (2*R*,R_S)-**8a-c**

Addition reactions between imines 5a-c and α-lithium derivative of (*R*)-benzyl *p*-tolyl sulfoxide 10. The condensations between imines **5a-c** and the lithium derivative of benzyl *p*-tolyl sulfoxide **10** were quite intriguing due to the more complex mechanism of stereochemical discrimination might be involved in the simultaneous formation of two new

Scheme 2



R_F = CF_3 (**a**), C_2F_5 (**b**), CF_2CHF_2 (**c**)

stereogenic centers. However, the steric shielding and additional stabilization of the carbanion **10** rose questions on its reactivity towards imines **5a-c**. Thus, for example, it was reported that *N*-propylidene- and *N-iso*-butylideneanilines[12c,18] give no addition products in the reaction with the corresponding lithium derivative of benzyl *t*-butyl sulfoxide. In contrast to these worrisome expectations, we found that condensations of (*R*)-**10** with imines **5a-c** proceed with high reaction rate (15 min) at -70 °C in THF giving rise to a mixture of diastereomeric products in excellent chemical yield (Scheme 2; Table 2, entries 1-3). However, the most exciting finding was the stereochemical outcome of the reactions. Determination of the diastereomeric composition of the crude reaction mixtures by ^{19}F NMR revealed that one out of four possible diastereomers was formed with overwhelming preference. Also in this case the nature of the fluoroalkyl group on the starting imines **5a-c** had no particular influence on the stereochemical result of the addition reactions providing in all cases the major diastereomers **11a-c** in more than 70% de. Similarly to the condensations of (*R*)-**6** discussed above, lithiation of the (*R*)-benzyl *p*-tolyl sulfoxide at 0 °C, to give (*R*)-**10**, did not improve the stereochemical result of the reactions of the latter with imines **5a-c** (entry 4). Purification of the dominant diastereomers **11a-c** to the enantiomerically pure state was easily accomplished merely by crystallizing the crude reaction mixtures.

Determination of the absolute configuration of **11a** by X-ray analysis gave totally unexpected result. Thus, the revealed (1*S*,2*S*,R_S) configuration of **11a** was found to be opposite to the (1*R**,2*R**,R^*_S)[19] stereochemistry of the β-sulfinylamines obtained stereoselectively in the corresponding reaction between the α-lithium derivative

Table 2. Addition reactions of (*R*)-**10** to aldimines **5a-c**[a]

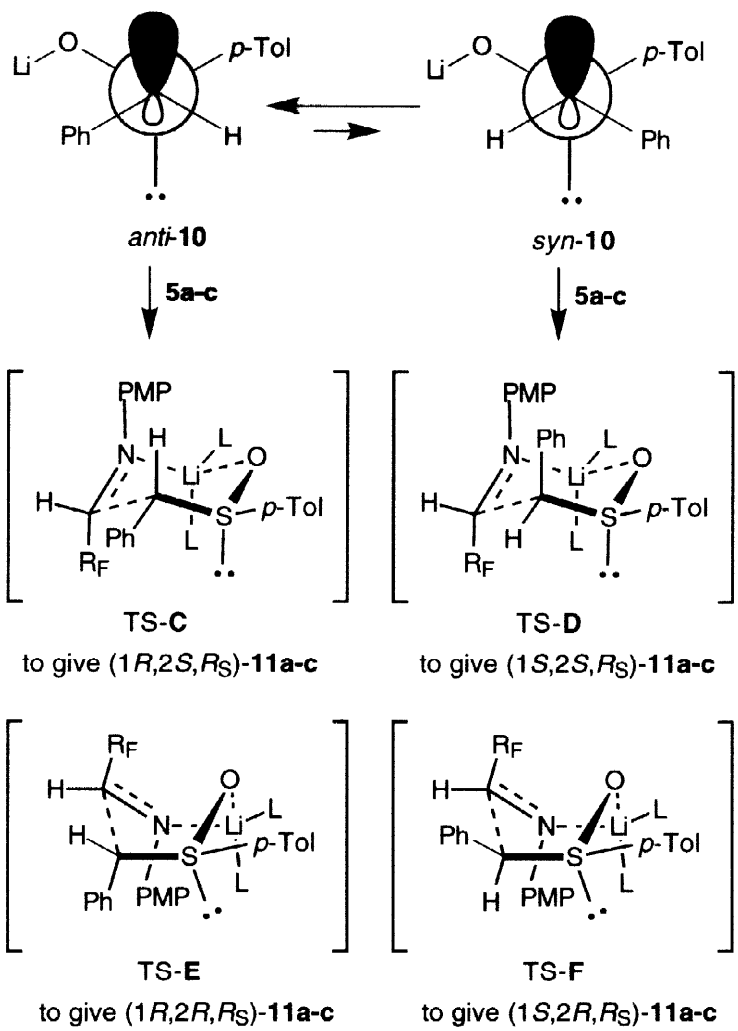
entry	R_F	Method[b]	Yield,[c] %	Dr[d] (**11**/3 minor)
1	CF_3 (**a**)	A	98 (59)	86/14
2	C_2F_5 (**b**)	A	97 (60)	87/13
3	CF_2CHF_2 (**c**)	A	98 (59)	87/13
4	CF_3 (**a**)	B	-	78/22

[a] All reactions were run in THF under nitrogen atmosphere. Imines **5a-c** were added at -70 °C to a THF solution of (*R*)-**10**; reaction time 15 min. [b] A = Solution of (*R*)-methyl *p*-tolyl sulfoxide was added to a LDA solution. B = The metallation of (*R*)-methyl *p*-tolyl sulfoxide to afford (*R*)-**10** was carried out at 0 °C. [c] Overall yield (^{19}F NMR) of (1*S*,2*S*,R_S)-**11** and minor diastereomers. Isolated yield of diastereomerically pure is given in the parentheses. [d] Values dr were determined by ^{19}F NMR analysis on the crude reaction mixtures.

of benzyl *t*-butyl sulfoxide and the imines of general formula R-CH=N-R' [R = Ph, (*E*)-PhCH=CH, 2-furyl, Et; R' = Ph, Me].[12c]

To account for this surprising difference in the stereochemical preferences, an opposite absolute configuration at both newly formed stereogenic centers, four available for the condensations under study chelated cyclic TS-**C**-**F** should be considered (Fig. 3). According to *Pyne et al.*,[12c] only the chair and boat TS, of type **C** and **E**, respectively, should be considered for the reactions of α-lithium derivative of benzyl *t*-butyl sulfoxide with the imines R-CH=N-R' (*vide versa*), due to the great thermodynamic preference of *anti* stereochemistry of the former over the *syn* counterpart. The authors reasonably assumed that the boat TS might be favored over the chair TS since in the latter the phenyl of the sulfoxide moiety and the substituent at the imine carbon experience a sterically unfavorable *gauche* interaction. Noteworthy that high diastereoselectivity in these reactions was observed for the imines bearing at the imine carbon flat aromatic or unsaturated substituents, capable of minimizing a flagpole interaction with the sulfoxide oxygen in the boat TS. Since the stereocontrolling ability of the *p*-tolyl group is much less effective, as compared with the *t*-butyl, the anion (*R*)-**10** is assumed to exist in a solution as a mixture of the corresponding *anti* and *syn* forms, obviously, with a substantial domination of the former.[20] Moreover, the detection of more than two diastereomeric products in the all reaction mixtures, clearly suggests that (*R*)-**10** reacts with imines **5a-c** in both stereoisomeric forms. Considering the TS-**C**-**F** one could assume that TS-**D**, leading to the (1*S*,2*S*,*R*$_S$)-configurated products **11a-c**, might be strongly favored over the rest of possible intermediates. In fact, in the boat TS-**E** and TS-**F** the fluoroalkyl group experiences repulsive steric and electrostatic interactions with the sulfoxide oxygen (*vide versa*), while in the chair TS-**C** the fluoroalkyl substituent and the phenyl of the sulfoxide moiety are in sterically unfavorable *gauche* disposition to each other. If our arguments are correct and the reactions proceed through the chair TS-**D**, these would be the first example when due to the unique properties of the fluorine containing substrates **5a-c**, lithium derivative of benzyl *p*-tolyl sulfoxide **10** reacts with imines predominantly in its less thermodynamically favorable *syn* stereoisomeric form.[20,21] Thus, the results obtained suggest that in the reactions of lithium derivative (*R*)-**10** with imines **5a-c** the fluoroalkyl group plays the role of stereocontrolling factor and its position as a sterically larger substituent might be of

Figure 3

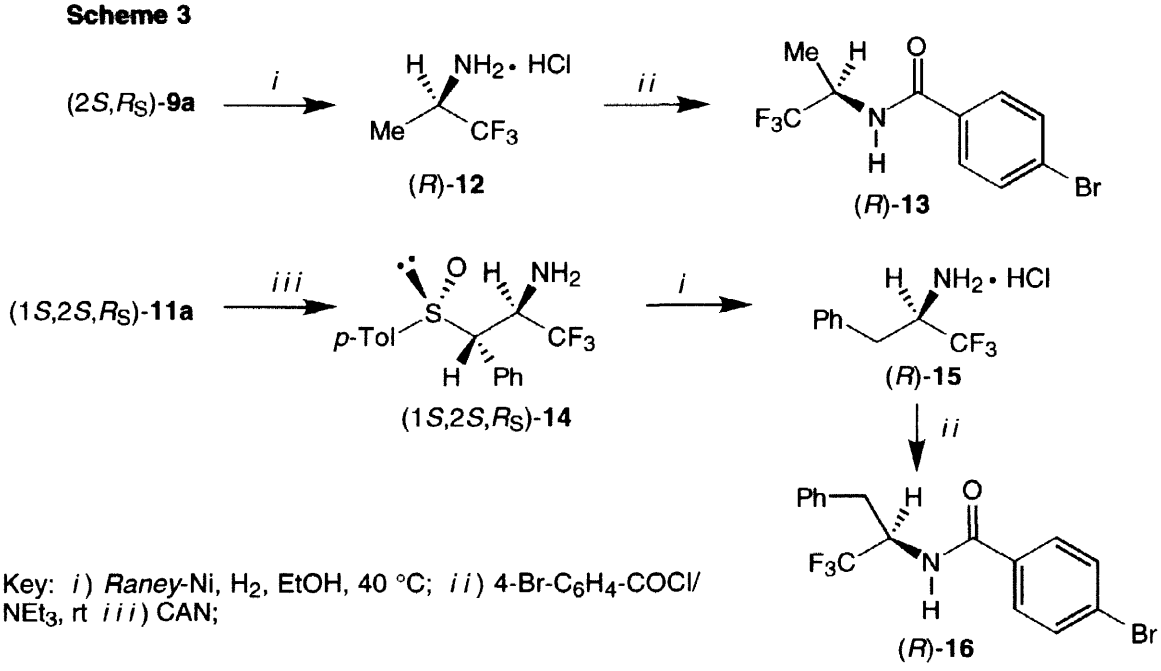


paramount importance in determining the corresponding TS.

Elaboration of β-amino sulfoxides 9 and 11 to enantiomerically pure fluoroalkyl-amino derivatives. Preparation of biologically interesting enantiopure α-fluoroalkyl-containing amines and amino-alcohols starting from β-amino sulfoxides (2*S*,*R*S)-**9** and (1*S*,2*S*,*R*S)-**11** are depicted in Schemes 3 and 4. Recently we have reported that transformation of β-amino sulfoxide (2*S*,*R*S)-**9a** to fluorinated *iso*-propylamine (*R*)-**12** could be accomplished *via* two-stages procedure with a respectable overall yield (80%), including the deoxygenation of sulfoxide **9a** to the corresponding sulfide and the desulfurization of the latter to afford amine (*R*)-**12**.[7b] Since both stages are of reductive nature we attempted to prepare the amine (*R*)-**12** *via* one-pot procedure, through reductive desulfinylation of (2*S*,*R*S)-**9a** with Raney-Ni/H_2 in ethanol. Unfortunately, yield of amine (*R*)-**12** was lower (50%) with respect to the two-steps procedure, presumably due to a partial loss of the volatile amine (*R*)-**12** under a moderate heating (40 °C) required by the hydrogenolysis of the sulfoxide group. The amine (*R*)-**12** thus prepared, showed the opposite sign optical rotation, as compared with the sample synthesized *via* two-steps procedure (*vide versa*).[7b] Furthermore, we have found that both the sign and magnitude of optical rotation of amine (*R*)-**12** markedly depend on the solvent used and degree of a solvent purity, for instance, a percentage of water in methanol. To put to rest this controversy, we prepared the corresponding *p*-bromobenzoyl derivatives (*R*)-**13** of both samples and purified them *via* chromatography on silica gel. To our satisfaction, the *p*-bromobenzoyl derivatives obtained showed exactly the same sign and magnitude of optical rotation.[22] Since the magnitude of optical rotation of amine (*R*)-**12** is quite small and its sign depends on the recording conditions, we would suggest to use derivatives of type **13**, which are more suitable for proper chiroptical characterization than hydrochloride **12**.

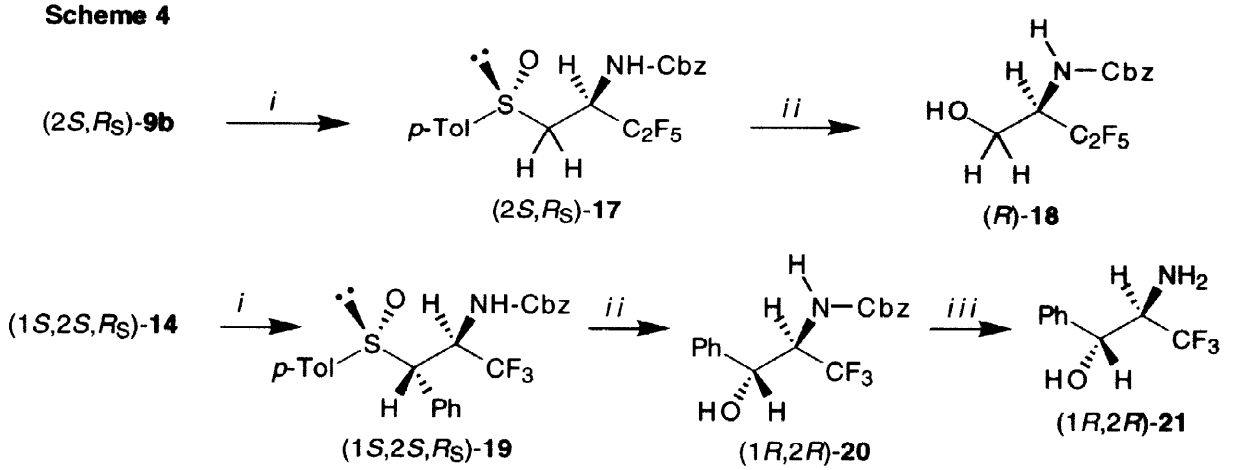
By the same one-pot reductive desulfinylation protocol we prepared (*R*)-α-trifluoromethyl-β-phenylethylamine **15** from the *N*-PMP β-aminosulfoxide (1*S*,2*S*,*R*S)-**11a**. Compound **11a** was first treated with CAN, to afford the unprotected derivative (1*S*,2*S*,*R*S)-**14** (72%) which was directly submitted to hydrogenolysis with Raney-Ni/H_2 for 18 h at 40 °C in ethanol, to give (*R*)-**15**, isolated as hydrochloride in 83%

Scheme 3



Key: *i*) *Raney*-Ni, H_2, EtOH, 40 °C; *ii*) 4-Br-C_6H_4-COCl/ NEt_3, rt *iii*) CAN;

Scheme 4



Key: *i*) ClCOOBn, 50% K_2CO_3, dioxane; *ii*) a: $(CF_3CO)_2O$, *sym*-collidine, MeCN, 0 °C; b: K_2CO_3, $NaBH_4$, 0 °C; *iii*) $H_2/Pd(OH)_2/C$

yield. Similarly to amine **12**, (*R*)-**15** was transformed into the corresponding *p*-bromobenzoyl amide (*R*)-**16**, for proper characterization and comparison with the literature data.[6a]

The non-oxidative *Pummerer* rearrangement, which allows for one-pot S_N2-type substitution of a hydroxy group for a sulfoxide functionality, was applied for transformation of (2*S*,R_S)-**9b** to the β-hydroxy amino derivative bearing pentafluoroethyl group (*R*)-**18**. First, β-amino sulfoxide (2*S*,R_S)-**9b** was protected to give *N*-benzyloxycarbonyl derivative (2*S*,R_S)-**17** in high chemical yield (86%). Next, (2*S*,R_S)-**17** was treated with 5 equiv of TFAA and 3 equiv of *sym*-collidine, at 0 °C. After 5 min the pH was raised to 8 by addition of aqueous K_2CO_3 (10%), then an excess of $NaBH_4$ was added to the mixture. The β-amino alcohol (*R*)-**18** was obtained in 85% yield by flash chromatography. Synthetically more challenging was the stereocontrolled transformation of β-aminosulfoxides **11**, having a stereogenic center in α position to the sulfinyl group, into the enantiopure fluorinated analogs of *ephedra* alkaloids. β-Aminosulfoxide (1*S*,2*S*,R_S)-**14** was protected with $ClCOOBn/K_2CO_3$, affording (1*S*,2*S*,R_S)-**19** (80%), which was submitted to the "non oxidative" *Pummerer* protocol. Thus, treatment of (1*S*,2*S*,R_S)-**19** with TFAA (5 equiv) and *sym*-collidine (3 equiv) afforded the expected rearrangement product. The reaction mixture was concentrated, the residue was dissolved in THF/H_2O (4:1), then treated with an excess of $NaBH_4$ (*ca* 6 equiv). The desired *N*-Cbz trifluoronorephedrine (1*R*,2*R*)-**20** was obtained with de >99% and isolated in pure form by flash chromatography (75%). Finally, the Cbz group was hydrogenolyzed with $Pd(OH)_2/H_2$, smoothly providing trifluoronorephedrine (1*R*,2*R*)-**21**, whose spectral properties matched those previously reported in literature.[10d,e]

In conclusion, we have demonstrated that the addition reactions between the lithium derivatives of chiral alkyl *p*-tolyl sulfoxides (*R*)-**6**, (*R*)-**10** to *N*-PMP fluoroalkylaldimines **5a-c** proceed under mild conditions allowing for convenient preparation of the corresponding α-fluoroalkyl β-sulfinylamines in excellent yields and enantiomeric purity. The stereochemical outcome of these reactions was shown to be subject to kinetic control, that is in sharp contrast to the corresponding reactions of the fluorine-free imines. The absolute configuration of the addition products suggests that the fluoroalkyl group on the starting imines **5a-c** plays the role of enantiodirecting, sterically larger substituent causing realization of the unusual for this type of reactions transition state. The demonstrated versatility of the α-fluoroalkyl β-sulfinylamines as precursors to numerous fluorinated and polyfunctional biologically interesting compounds render the developed approach an useful synthetic method.

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EXPERIMENTAL SECTION

General. For standard laboratory praxis and techniques see related paper, ref. 7b.

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and/or ^1H and ^{19}F NMR spectrometry. All new compounds were characterized by ^1H, ^{19}F, ^{13}C NMR and by mass spectrometry or elemental analysis.

X-ray structure determination of (1*S*,2*S*,*R*S)-**11a**. Colorless crystals of **11a** suitable for X-ray analysis were obtained by crystallization from *n*-hexane/ethyl acetate (1:1). Diffraction data were collected on a Siemens P4 diffractometer, with monochromated Cu-Kα radiation (λ=1.5418). The selected crystal had dimensions of 0.3 x 0.15 x 0.02 mm. Cell constants were obtained by least squares refinement on 2θ values of 20 reflections with 27<2θ<40. Crystal data are: $C_{22}H_{22}O_2F_3NS$, f.w. 433.48, orthorhombic, space group $P2_12_12_1$, a = 5.7288(9) Å, b = 17.734(2) Å, c = 21.183(2) Å, V = 2152.1(5) $Å^3$, Z = 4, D_c = 1.338 Mg/m^3, μ = 1.734 mm^{-1}, F(000) = 904. Intensity data were collected using the θ-2θ scan technique, in the range 3<θ<57°. Two octants (+h, +k, +l) and (-h, -k, -l) corresponding to 2909 independent reflections were collected. Three standard reflections were measured every 100 reflections and showed no significant decay. The data were corrected for Lorentz and polarization effects, but no absorption correction was applied. The structure was solved using the SIR92[23] program and refined by full-matrix least squares on F^2 values with SHELXL-93.[24] Non-hydrogen atoms were refined with anisotropic temperature factors, hydrogens were included at calculated positions and refined in the riding mode. The final value of the residuals R and wR2 were 0.0666 and 0.1031 for 1666 reflections with I>2σ(I). The highest and lowest residual peaks in final difference-Fourier map were respectively 0.181 and -0.188 $eÅ^{-3}$.

Determination of the absolute configuration by X-ray diffraction data was based on the refinement of Flack's *x* parameter.[25] The resulting value of -0.01(5) unambiguously determines the absolute configuration as C1(S),C2(S),S1(R). Atomic coordinates for the structure have been deposited with the Cambridge Crystallographic Data Centre, at the time of short communication[13] submission, and can be obtained on request from: The Director, Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

General Method for Preparing *N*-PMP fluoroalkyl imines 5a-c. The starting fluoroalkyl aldehyde hydrate **4a-c** (35 mmol) was first dissolved in benzene (70 mL) in a round-bottomed flask equipped with a reflux condenser, a *Dean-Stark* trap and a magnetic stirring bar. *p*-Anisidine (38.5 mmol) and *ca.* 0.5 g of the strongly acidic resin DOWEX 50W X8-400 were added to the reaction flask, and the mixture was stirred at reflux. After the reaction was complete (theoretical amount of water removed, and monitoring by GLC, TLC and ^1H, ^{19}F NMR), the solvent was removed *in vacuo* and imine products were purified by distillation. Imines **5a-c** are colorless oils and could be stored neat without any deterioration for *ca* 1 month under nitrogen atmosphere at 4 °C. Decomposition can be easily detected from the darkening of the oil, due to the formation of *p*-anisidine.

***N*-(2,2,2-Trifluoroethylidene)-*p*-methoxyaniline (5a)**: 93%, bp 55-56 °C (*ca.* 0.3 mm Hg). ^1H NMR ($CDCl_3$) δ 7.82 (q, 1H, *J* = 3.6 Hz), 7.32-7.25 (m, 2H), 6.97-6-90 (m, 2H), 3.85 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -71.8 (d, *J* = 3.6 Hz). ^{13}C NMR ($CDCl_3$) δ 160.5 (s), 144.1 (q, *J* = 38.8 Hz), 140.0 (s), 119.5 (q,

J = 273.3 Hz), 123.2 (s), 114.0 (s), 55.6 (s). Anal. Calcd for $C_9H_8F_3NO$: C, 53.21; H, 3.97; N, 6.89; F, 28.05. Found: C, 53.27; H, 4.00; N, 6.73; F, 27.95.

***N*-(3,3,3,2,2-Pentafluoropropylidene)-*p*-methoxyaniline (5b)**: 87%, bp 50-51 °C (*ca.* 0.2 mm Hg). ^{1}H NMR ($CDCl_3$) δ 7.88 (tq, 1H, J = 1.4 and 6.0 Hz), 7.35-7.25 (m, 2H), 6.98-6.90 (m, 2H), 3.84 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -84.1 (d, 3F, J = 1.4 Hz), -120.5 (d, 2F, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$) δ 160.6 (s), 144.4 (q, J = 28.6 Hz), 140.3 (s), 123.2 (s), 114.6 (s), 55.5 (s); the corresponding resonances of CF_3CF_2 group are obscured due to their low intensity. Anal. Calcd for $C_{10}H_8F_5NO$: C, 47.44; H, 3.19; N, 5.53; F, 37.52. Found: C, 47.53; H, 3.21; N, 5.44; F, 37.39.

***N*-(3,3,2,2-Tetrafluoropropylidene)-*p*-methoxyaniline (5c)**: 83%, bp 61-62 (*ca.* 0.3 mm Hg); ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 1H), 7.30-7.22 (m, 2H), 6.96-6.89 (m, 2H), 6.22 (tt, 1H, J = 4.9 and 53.2 Hz), 3.82 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -120.45 (m, 2F), -139.20 (m, 2F). ^{13}C NMR ($CDCl_3$) δ 160.4 (s), 147.6 (t, J = 31.4 Hz), 140.6 (s), 123.1 (s), 110.3 (tt, J = 249.8 Hz and 33.3 Hz), 114.6 (s), 55.5 (s); the corresponding resonance of CF_2 group is obscured due to its low intensity. Anal. Calcd for $C_{10}H_9F_4NO$: C, 51.07; H, 3.86; N, 5.96; F, 32.31. Found: C, 51.13; H, 3.88; N, 5.91; F, 32.23.

Condensation between α-lithiated methyl *p*-tolyl sulfoxide (*R*)-6 and fluorinated aldimines 5a-c: A General Procedure. To a stirred solution of LDA (1.8 mmol) in dry THF (4 mL) cooled at -60 °C, a solution of (*R*)-*p*-tolyl sulfoxide **6** (1,5 mmol) in 2 mL of dry THF was added. After stirring for 5 min at the same temperature, the resultant yellow solution was cooled to -70 °C and a solution of *N*-PMP fluoroalkyl imine **5** (1.8 mmol) in 2 mL of dry THF was added. Progress of the condensation was monitored by TLC and upon completion (15 min), the reaction was quenched at -70 °C with aqueous NH_4Cl, extracted with ethyl acetate, and the collected organic phases dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The diastereoselectivity of the reactions was determined from ^{1}H and ^{19}F NMR analysis of the crude reaction product. Crystallization of the crude reaction mixtures (*n*-hexane/ethyl acetate), and flash chromatography (*n*-hexane/ethyl acetate) of the mother liquors, afforded the targeted *N*-PMP-α-fluoroalkyl-β-sulfinylamines **7a-c** and **8a-c**. Melting points were determined on the samples crystallized (*n*-hexane/ethyl acetate) at least twice.

(2*S*,*R*$_S$)-*n*-3,3,3-Trifluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (7a). 74 %; R_f = 0.39 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +168.6 (*c* 0.63, $CHCl_3$); mp 192-193 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 2H, J = 8.1 Hz), 7.34 (d, 2H, J = 8.1 Hz), 6.80 (s, 4H), 4.42 (br.m, 1H), 3.77 (br.s, 1H), 3.76 (s, 3H), 3.13 (dd, 1H, J = 3.1 and 13.1 Hz), 2.84 (dd, 1H, J = 10.8 and 13.1 Hz), 2.42 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -76.1 (d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 154.1 (s), 142.2 (s), 140.4 (s), 139.6 (s), 130.3 (s), 124.0 (s), 116.8 (s), 115.1 (s), 58.0 (s), 55.8 (s), 54.2 (q, J = 30.4 Hz), 21.4 (s); the quartet of CF_3 group is obscured due to its low intensity. MS (EI, 70 eV) m/z (%) 357 (M^+, 25), 217 (100), 148 (39), 122 (76). Anal. Calcd for $C_{17}H_{18}F_3NO_2S$: C, 57.13; H, 5.08; N, 3.92. Found: C, 57.24; H, 5.11; N, 3.87.

(2*R*,*R*$_S$)-*n*-3,3,3-Trifluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (8a). R_f = 0.30 (7/3 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 6.80-6.74 (m, 2H), 6.60-6.54 (m, 2H), 4.18 (br.m, 1H), 3.75 (s, 3H), 3.67 (br.d, 1H, J = 8.9 Hz), 3.19-3.13 (m, 2H), 2,40 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -76.8 (d, J = 6.0 Hz).

(2*S*,*R*$_S$)-*n*-4,4,4,3,3-Pentafluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (7b). 72%; R_f = 0.34 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +132.5 (*c* 0.75, $CHCl_3$); mp 171-172 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 6.80 (s, 4H), 4.61 (br.m, 1H), 3.76

(s, 3H), 3.75 (br.d, 1H, J = 8.5 Hz), 3.17 (m, 1H), 2.85 (dd, 1H, J = 10.8 and 13.5 Hz), 2.43 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -82.4 (s, 3F), -119.9 (dd, 1F, J = 6.8 Hz, J = 272.9 Hz), -126.2 (dd, 1F, J = 21.0 and 272.9 Hz); ^{13}C NMR ($CDCl_3$) δ 153.7 (s), 142.2 (s), 140.2 (s), 139.0 (s), 130.3 (s), 123.9 (s), 116.0 (s), 114.9 (s), 58.3 (s), 55.6 (s), 52.2 (t, J = 22.4 Hz), 21.5 (s); the resonances of CF_3CF_2 group are obscured due to their low intensity. MS (EI, 70 eV) m/z (%) 407 (M^+, 100), 267 (79), 122 (36). Anal. Calcd for $C_{18}H_{18}F_5NO_2S$: C, 53.07; H, 4.45; N, 3.44. Found: C, 53.15; H, 4.51; N, 3.39.

(2*R*,*R*S)-*n*-4,4,4,3,3-Pentafluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (8b). R_f = 0.26 (7/3 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 2H, J = 8.6 Hz), 7.26 (d, 2H, J = 8.6 Hz), 6.81-6.75 (m, 2H), 6.60-6.55 (m, 2H), 4.41 (br.m, 1H), 3.76 (s, 3H), 3.26 (dd, 1H, J = 6.0 and 13.8 Hz), 3.15 (dd, 1H, J = 7.7 and 13.8 Hz), 2.39 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -82.2 (s, 3F), -120.0 (dd, 1F, J = 7.6 and 275.0 Hz), -126.4 (dd, 1F, J = 15.2 and 275.0 Hz).

(2*S*,*R*S)-*n*-4,4,3,3-Tetrafluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (7c). 70 %; R_f = 0.26 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +123.6 (*c* 0.73, $CHCl_3$); mp 164-165 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 2H, J = 8.2 Hz), 7.33 (d, 2H, J = 8.2 Hz), 6.83-6.73 (m, 4H), 5.96 (dt, 1H, J = 10.0 and 54.5 Hz), 4.44 (m, 1H), 3.76 (s, 3H), 3.75 (m, 1H), 3.23 (m, 1H), 2.84 (dd, 1H, J = 9.7 and 12.9 Hz), 2.43 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -125.5 (m, 1F), -128.7 (m, 1F), -135.6 (m, 1F), -143.7 (m, 1F); ^{13}C NMR ($CDCl_3$) δ 153.8 (s), 142.1 (s), 140.3 (s), 138.8 (s), 130.2 (s), 123.9 (s), 116.2 (s), 115.0 (s), 57.3 (s), 55.6 (s), 52.0 (t, J = 23.2 Hz), 21.4 (s); the resonances of CHF_2CF_2 group are obscured due to their low intensity. MS (EI, 70 eV) m/z (%) 389 (M^+, 33), 249 (100), 148 (26), 122 (34). Anal. Calcd for $C_{18}H_{19}F_4NO_2S$: C, 55.52; H, 4.92; N, 3.60. Found: C, 55.55; H, 4.97; N, 3.58.

(2*R*,*R*S)-*n*-4,4,3,3-Tetrafluoro-2-(*N*-*p*-methoxyphenyl)aminopropyl *p*-tolyl sulfoxide (8c). R_f = 0.19 (7/3 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 6.84-6.75 (m, 2H), 6.66-6.57 (m, 2H), 6.00 (dt, 1H, J = 10.0 and 47.2 Hz), 4.30 (br.m, 1H), 3.77 (s, 3H), 3.50 (br.s, 1H), 3.26 (dd, 1H, J = 5.2 and 14.0 Hz), 3.13 (dd, 1H, J = 8.2 and 14.0 Hz), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -126.4 (m, 1F), -129.8 (m, 1F), -136.2 (m, 1F), -144.1 (m, 1F).

Condensation Between α-Lithiated Benzyl *p*-tolyl Sulfoxide 10 and Fluorinated Aldimines 5a-c. The general procedure described for the condensation between α-lithiated methyl *p*-tolyl sulfoxide **6** and fluorinated aldimines **5a-c** was followed, except for the solution of LDA in THF was added to a suspension of benzyl *p*-tolyl sulfoxide **10** in the same solvent.

(1*S*,2*S*,*R*S)-*n*-3,3,3-Trifluoro-2-(*N*-*p*-methoxyphenyl)amino-1-phenylpropyl *p*-tolyl sulfoxide (11a). 59%; R_f = 0.45 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +283.6 (*c* 0.87, $CHCl_3$); mp 167-168 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.26-6.82 (m, 13H), 4.65 (m, 1H), 4.12 (br.d, 1H, J = 10.8 Hz), 3.79 (s, 3H), 3.64 (d, 1H, J = 10.0 Hz), 2.30 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -72.6 (d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 153.9 (s), 141.2 (s), 139.9 (s), 137.4 (s), 129.4 (s), 129.3 (s), 129.2 (s), 128.5 (s), 127.7 (s), 125.7 (q, J = 286.5 Hz), 124.3 (s), 116.7 (s), 114.9 (s), 70.4 (s), 59.2 (q, J = 27.9 Hz), 55.7 (s), 21.4 (s). MS (EI, 70 eV) m/z (%) 433 (M^+, 17), 294 (100), 216 (27), 139 (30), 122 (91). Anal. Calcd for $C_{23}H_{22}F_3NO_2S$: C, 63.73; H, 5.11; N, 3.23. Found: C, 63.77; H, 5.14; N, 3.20.

In the ^{19}F NMR ($CDCl_3$) spectrum of the crude reaction mixture the following resonances could be reasonably assigned to the minor diastereomers: δ -72.55 (d, J = 6.4 Hz); -73.44 (d, J = 6.4 Hz), -73.48 (d, J = 6.4 Hz).

(1*S*,2*S*,*R*S)-*n*-4,4,4,3,3-Pentafluoro-2-(*N*-*p*-methoxyphenyl)amino-1-phenylpropyl *p*-tolyl sulfoxide (11b). 60%; R_f = 0.41 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +250.9 (*c* 0.65, $CHCl_3$); mp 160-161 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.27-6.88 (m, 9H), 6.85 (s, 4H), 4.78 (br.m, 1H), 4.10 (d, 1H, *J* = 10.8 Hz), 3.79 (d, 1H, *J* = 8.0 Hz), 3.77 (s, 3H), 2.31 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -82.2 (s, 3F), -113.3 (d, 1F, *J* = 274.7 Hz), -126.9 (dd, 1F, *J* = 22.9 and *J* = 274.7 Hz); ^{13}C NMR ($CDCl_3$) δ 153.5 (s), 141.3 (s), 138.9 (s), 137.5 (s), 129.6 (dd, *J* = 2.5 and 1.1 Hz), 129.3 (s), 128.4 (s), 127.6 (s), 124.3 (s), 115.6 (s), 114.9 (s), 71.0 (s), 56.8 (t, *J* = 22.3 Hz), 55.6 (s), 21.4 (s); the resonances of CF_3CF_2 group are obscured due to their low intensity. MS (EI, 70 eV) m/z (%) 483 (M^+, 100), 344 (66), 139 (12), 122 (51). Anal. Calcd for $C_{24}H_{22}F_5NO_2S$: C, 59.62; H, 4.58; N, 2.90. Found: C, 59.62; H, 4.59; N, 2.88.

In the ^{19}F NMR ($CDCl_3$) spectrum of the crude reaction mixture the following resonances could be reasonably assigned to the minor diastereomers: δ (CF_3) -82.64 (s, 3F), (CF_2) -116.4 (d, 1F, *J* = 274.6 Hz) and -125.8 (dd, 1F, *J* = 20.4 and 274.6 Hz); (CF_3) -82.54 (s, 3F), (CF_2) -116.9 (dd, 1F, *J* = 3.8 and 275.0 Hz) and -127.3 (dd, 1F, *J* = 22.8 and 275.0 Hz); (CF_3) -81.45 (s, 3F), (CF_2) -110.3 (m, 1F) and -122.4 (dd, 1F, *J* = 24.0 and 281.2 Hz).

(1*S*,2*S*,*R*S)-*n*-4,4,3,3-Tetrafluoro-2-(*N*-*p*-methoxyphenyl)amino-1-phenylpropyl *p*-tolyl sulfoxide (11c). 59%; R_f = 0.43 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +268.4 (*c* 0.98, $CHCl_3$); mp 160-161 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.26-6.92 (m, 9H), 6.85 (s, 4H), 5.62 (ddt, 1H, *J* = 2.7, 8.5 and 53.3 Hz), 4.65 (m, 1H), 4.13 (br.d, 1H, *J* = 10.8 Hz), 3.78 (s, 3H), 3.76 (d, 1H, *J* = 9.2 Hz), 2.31 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -122.8 (m, 1F), -127.6 (m, 1F), -136.3 (m, 1F), -142,7 (m, 1F); ^{13}C NMR ($CDCl_3$) δ 153.7 (s), 141.3 (s), 139.1 (s), 137.5 (s), 129.8 (s), 129.5 (s), 129.2 (s), 128.5 (s), 127.8 (s), 124.3 (s), 115.9 (s), 115.1 (s), 70.5 (s), 56.6 (dd, *J* = 23.5 and 21.7 Hz), 55.7 (s), 21.4 (s); the resonances of CHF_2CF_2 group are obscured due to their low intensity. MS (EI, 70 eV) m/z (%) 465 (M^+, 17), 326 (100), 248 (16), 139 (36), 122 (63). Anal. Calcd for $C_{24}H_{23}F_4NO_2S$: C, 61.92; H, 4.98; N, 3.01. Found: C, 61.94; H, 5.01; N, 2.97.

In the ^{19}F NMR ($CDCl_3$) spectrum of the crude reaction mixture the following resonances could be reasonably assigned to the minor diastereomers: δ (CF_2) -124.0 (m, 1F) and -127.2 (m, 1F); (CHF_2) -135.0 (m, 1F) and -144.6 (m, 1F); (CF_2) -126.2 (m, 1F) and -128.7 (m, 1F); (CHF_2) -136.0 (m, 1F) and -145.3 (m, 1F); (CF_2) -124.5 (m, 1F) and -129.2 (m, 1F); (CHF_2) -136.0 (m, 1F) and -145.1 (m, 1F).

Deprotection of *N*-PMP Derivatives 7a-c to α-Fluoroalkyl-β-sulfinylamines 9a-c and 14; A General Procedure for Removal of the PMP Group by CAN. A solution of CAN (2.5 mmol) in 8 mL of water was added at 0 °C to a solution of *N*-PMP derivative (2*S*,*R*S)-**7a-c** or (1*S*,2*S*,*R*S)- **11a** (0.5 mmol) in acetonitrile (11 mL). After 30 min at 0 °C (TLC monitoring) a 5% aqueous $NaHCO_3$ solution was added at 0 °C, until almost neutral pH of the mixture was reached. The resultant mixture was allowed to warm up at rt, under stirring, then solid sodium sulfite was added portion-wise, until a brown slurry was formed. AcOEt (*ca* 10 mL) was added under stirring and the phases were separated. The aqueous layer was washed three times with 5 mL of AcOEt. The collected organic phases were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The target free α-fluoroalkyl-β-sulfinylamines (2*S*,*R*S)-**9a-c** and (1*S*,2*S*,*R*S)-**14** were isolated by flash chromatography (*n*-hexane/AcOEt).

(2*S*,*R*S)-*n*-3,3,3-Trifluoro-2-aminopropyl *p*-tolyl sulfoxide (9a). 98 %; R_f = 0.35 (2/3 *n*-hexane/ethyl acetate + 1% NEt_3); $[\alpha]_D^{20}$ +263.8 (*c* 0.23, $CHCl_3$); mp 126-127 °C (*i*-Pr_2O). ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, *J* = 8.2 Hz), 7.36 (d, 2H, *J* = 8.2 Hz), 3.81 (ddd, 1H, *J* = 11.5, 7.1 and 2.6 Hz), 2.98 (dd, 1H, *J* = 13.1 and 2.6 Hz), 2.71 (dd, 1H, *J* = 13.1 and 11.5 Hz), 2.43 (s, 3H), 1.73 (br.s, 2H); ^{19}F NMR ($CDCl_3$)

δ -79.38 (d, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 142.09 (s), 139.95 (s), 130.23 (s), 125.67 (q, J = 281.4 Hz), 123.91 (s), 58.04 (s), 49.66 (q, J = 30.8 Hz), 21.4 (s). Anal. Calcd for $C_{10}H_{12}F_3NOS$: C, 47.80; H, 4.81; N, 5.57. Found: C, 47.67; H, 4.80; N, 5.53.

(2*S*,*R*$_S$)-*n*-4,4,4,3,3-Pentafluoro-2-aminopropyl *p*-tolyl sulfoxide (9b). 87%; R_f = 0.38 (6/4 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +219.9 (*c* 0.64, $CHCl_3$); mp 109-111 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 2H, J = 8.2 Hz), 7.36 (d, 2H, J = 8.2 Hz), 3.96 (m, 1H), 3.03 (m, 1H), 2.72 (dd, 1H, J = 11.4 and 12.8 Hz), 2.44 (s, 3H), 1.70 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -81.9 (s, 3F), -123.1 (dd, 1F, J = 8.3 and 270.0 Hz), -128.2 (dd, 1F, J = 16.0 and 270.0 Hz); ^{13}C NMR ($CDCl_3$) δ 142.1 (s), 139.9 (s), 131.4 (s), 123.9 (s), 121.9-109.3 (m, CF_2CF_3), 57.9 (s), 48.3 (t, J = 24.0 Hz), 21.3 (s). Anal. Calcd for $C_{11}H_{12}F_5NOS$: C, 43.85; H, 4.01; N, 4.65. Found: C, 43.88; H, 4.10; N, 4.63.

(2*S*,*R*$_S$)-*n*-4,4,3,3-Tetrafluoro-2-aminopropyl *p*-tolyl sulfoxide (9c). 90%; R_f = 0.31 (1/1 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +216.6 (*c* 0.98, $CHCl_3$); mp 85-86 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2H, J = 8.2 Hz), 7.36 (d, 2H, J = 8.2 Hz), 6.12 (dddd, 1H, J = 1.9, 7.7, 52.9 and 54.8 Hz), 3.85 (m, 1H), 3.05 (m, 1H), 2.80 (dd, 1H, J = 10.8 and 13.5 Hz), 2.44 (s, 3H), 1.73 (br.s, 2H); ^{19}F NMR ($CDCl_3$) δ -126.5 (m, 1F), -130.4 (m, 1F), -136.8 (m, 1F),-141.7 (m, 1F); ^{13}C NMR ($CDCl_3$) δ 141.95 (s), 139.6 (s), 130.2 (s), 123.8 (s), 121.0-105.0 (m, CF_2CF_2H), 57.7 (s), 47.9 (dd, J = 22.2 and 25.8 Hz), 21.25 (s). MS (EI, 70 eV) m/z (%) 567 ($2M^+$ +1, 35), 284 (M^+ +1, 100), 144 (76), 139 (67). Anal. Calcd for $C_{11}H_{13}F_4NOS$: C, 46.64; H, 4.62; N, 4.95. Found: C, 46.65; H, 4.64; N, 4.92.

(1*S*,2*S*,*R*$_S$)-3,3,3-Trifluoro-2-amino-1-phenylpropyl *p*-tolyl sulfoxide 14. 72 %; R_f = 0.26 (6/4 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +309.2 (*c* 0.65, $CHCl_3$); mp 151-152 °C (*n*-Hex/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.25-6.82 (m, 9H), 4.13 (m, 1H), 3.46 (d, 1H, J = 10.8 Hz), 2.29 (s, 3H), 2.02 (d, 2H, J = 7.7 Hz); ^{19}F NMR ($CDCl_3$) δ –73.37 (d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 141.2 (s), 129.7 (s), 129.3 (s), 129.2 (s), 128.4 (s), 128.1 (s), 127.6 (s), 124.4 (s), 117.1 (s), 116.4 (s), 71.0 (s), 54.5 (q, J = 30.4 Hz), 21.4 (s), resonance of the CF_3 group is obscured; MS (EI, 70 eV) m/z (%) 328 (M^+ +1, 19), 188 (100), 91 (33).

Reductive Desulfinylation of β-sulfinylamines (2*S*,*R*$_S$)-9a and (1*S*,2*S*,*R*$_S$)-14. Synthesis of amine hydrochlorides (*R*)-12 and (*R*)-15. To a solution of β-sulfinylamine (2*S*,*R*$_S$)-**9a** or (1*S*,2*S*,*R*$_S$)-**14** (0.29 mmol) in absolute ethanol (4 mL) *ca* 0.5 g of *Raney*-Ni were added. The resultant mixture was vigorously stirred for 24 h under hydrogen atmosphere at 40 °C, cooled and filtered on a Celite pad. Aqueous 1*N* HCl (1 mL) was added and the solvent was removed *in vacuo* to yield the desired hydrochloride (*R*)-**12** or (*R*)-**15** as a white solid.

(*R*)-1,1,1-Trifluoro-*iso*-propylamine hydrochloride (12): 50%; $[\alpha]_D^{20}$ -1.0 (*c* 0.75, MeOH), [literature data (ref. 6a): $[\alpha]_D^{25}$ -2.94 (*c* 1, MeOH); $[\alpha]_D^{25}$ -4.24 (*c* 1, EtOH)]; t.sub >100 °C; ^{1}H NMR (methanol-d_4) δ 4.22 (m, 1H), 1.49 (d, 3H, J = 7.0 Hz); ^{13}C NMR (methanol-d_4) δ 126.6 (q, J = 279.3 Hz), 51.3 (q, J_{CF} = 32.9 Hz), 14.1 (s); ^{19}F NMR (methanol-d_4) δ -75.3 (d, J = 7.0 Hz).

(*R*)-1,1,1-Trifluoro-3-phenyl-*iso*-propylamine hydrochloride (15): 83%; $[\alpha]_D^{20}$ +21.4 (*c* 0.9, EtOH), [literature data (ref. 6a): $[\alpha]_D^{25}$ +22.19 (*c* 1, EtOH)]. t.sub >100 °C; ^{1}H NMR (CD_3CN) δ 7.44-7.28 (m, 5H), 4.19 (m, 1H), 3.39 (dd, 1H, J = 7.0 and 14.5 Hz), 3.25 (dd, 1H, J = 7.0 and 14.5 Hz); ^{19}F NMR (CD_3CN) δ -71.39 (d, J = 7.0 Hz).

(2*S*,*R*$_S$)-*n*-4,4,4,3,3-Pentafluoro-2-(*N*-carbobenzoxy)aminopropyl *p*-tolyl sulfoxide (17). To a solution of starting β-sulfinylamine (2*S*,*R*$_S$)-**9b** (0.28 mmol) in dioxane (4 mL) at rt, 86 μL of 50% aqueous potassium carbonate, followed by neat benzyl chloroformate (40 μL, 0.28 mmol) were added. The

mixture was stirred for 2 h at rt, filtered, and the solvent was evaporated *in vacuo*. The targeted *N*-Cbz derivative (2*S*,*R*S)-**17** was isolated by flash chromatography (*n*-hexane/ethyl acetate 7:3). Yield 86%; R_f = 0.42 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +135.2 (*c* 0.66, $CHCl_3$); mp 143.5-144.5 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 2H, *J* = 8.2 Hz), 7.41-7.35 (m, 5H), 7.34 (d, 2H, *J* = 8.2 Hz), 5.79 (d, 1H, *J* = 9.7 Hz), 5.21 (d, 1H, *J* = 12.0 Hz), 5.14 (d, 1H, *J* = 12.0 Hz), 4.97 (m, 1H), 3.15-2.96 (m, 2H), 2.42 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -83.2 (br.s, 3F), -120.3 (dd, 1F, *J* = 7.0 and 275.0 Hz), -125.7 (dd, 1F, *J* = 19.0 and 275.0 Hz). Anal. Calcd for $C_{19}H_{18}F_5NO_3S$: C, 52.41; H, 4.17; N, 3.22. Found: C, 52.43; H, 4.18; N, 3.21.

(1*S*,2*S*,*R*S)-*n*-3,3,3-Trifluoro-2-(*N*-*p*-carbobenzoxy)amino-1-phenylpropyl *p*-tolyl sulfoxide (19). To a solution of starting β-sulfinylamine (1*S*,2*S*,*R*S)-**14** (0.93 mmol) in dioxane (15 mL) at rt, 0.5 mL of 50% aqueous potassium carbonate, followed by neat benzyl chloroformate (0.39 mL, 2.8 mmol) were added. The mixture was heated at 70 °C for 4 h, then cooled to rt, filtered, and the solvent evaporated *in vacuo*. The targeted *N*-Cbz derivative (1*S*,2*S*,*R*S)-**19** was isolated by flash chromatography (*n*-hexane/AcOEt 7/3). Yield 80%; R_f = 0.36 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +121.3 (*c* 0.32, $CHCl_3$); mp 157-159 °C (*n*-Hex/AcOEt). ^{1}H NMR ($CDCl_3$) δ 7.44-6.80 (m, 14H), 6.27 (d, 1H, *J* = 8.8 Hz), 5.23 (s, 2H), 5.02 (m, 1H), 3.86 (d, 1H, *J* = 8.1 Hz), 2.30 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -73.0 (br.s); ^{13}C NMR ($CDCl_3$) δ 155.6 (s), 141.6 (s), 136.7 (s), 135.9 (s), 129.5 (s), 129.3 (s), 129.0 (s), 128.8 (s), 128.6 (s), 128.4 (s), 128.3 (s), 127.9 (s), 124.6 (q, *J* = 284.9 Hz), 124.3 (s), 67.8 (s), 66.9 (s), 55.5 (q, *J* = 29.6 Hz), 21.4 (s). MS (EI, 70 eV) m/z (%) 462 (M^+ +1, 13), 322 (25), 139 (6), 91 (100). Anal. Calcd for $C_{24}H_{22}F_3NO_3S$: C, 62.46; H, 4.80; N, 3.04. Found: C, 62.45; H, 4.78; N, 3.05.

The "Non-Oxidative *Pummerer* Reaction". Synthesis of (*R*)-*n*-2-(*N*-carbobenzoxy)amino-3,3,4,4,4-pentafluorobutanol (18). To a stirred solution of *N*-Cbz derivative (2*S*,*R*S)-**17** (0.2 mmol) and *sym*-collidine (80 μL, 0.6 mmol) in acetonitrile (4 mL) under a nitrogen atmosphere at 0 °C, neat trifluoroacetic anhydride (0.14 mL, 1.0 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C and after 5 min a 10% K_2CO_3 aqueous solution was added until pH 7 was reached. Then, an excess of $NaBH_4$ (about 5 eq) was added portion-wise at 0 °C, and the mixture was allowed to warm at rt. After 15 min the reaction was quenched with a saturated aqueous ammonium chloride solution, extracted with AcOEt, and the collected organic layers dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Flash chromatography (hexane/AcOEt 8/2) of the crude product afforded the desired hydroxy derivative (*R*)-**18**. Yield 85%; R_f = 0.38 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ -8.1 (*c* 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.43-7.29 (m, 5H), 5.40 (m, 1H), 5.15 (s, 2H), 4.51 (m, 1H), 4.03 (dd, 1H, *J* = 12.0 and 4.4 Hz), 3.89 (br.dd, 1H, *J* = 12.0 Hz); ^{19}F NMR ($CDCl_3$) δ -84.0 (s, 3F), -121.8 (dd, 1F, *J* = 278.0 and 7.5 Hz), -125.5 (dd, 1F, *J* = 278.0 and *J* = 19.5 Hz). Anal. Calcd for $C_{12}H_{12}F_5NO_3$: C, 46.02; H, 3.86; N, 4.47. Found: C, 46.37; H, 3.80; N, 4.53.

The "Non-Oxidative *Pummerer* Reaction". Synthesis of (1*R*,2*R*)-*n*-1-Phenyl-2-(*N*-carbobenzoxy)amino-3,3,3-trifluoropropanol (20). To a stirred solution of *N*-Cbz derivative (1*S*,2*S*,*R*S)-**19** (0.5 mmol) and *sym*-collidine (0.2 mL, 1.5 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere at 0 °C, neat trifluoroacetic anhydride (0.35 mL, 2.5 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C and after 10 min water was added, and the mixture was extracted with ethyl acetate. The solvent was evaporated *in vacuo* and the residue was dissolved in 10 mL of a THF/water (4/1) mixture and cooled at 0 °C. An excess of $NaBH_4$ (about 3 eq) was added portion-wise. After 10 min the reaction was warmed to rt and other *ca* 3 eq of $NaBH_4$ were added. After 15 min the reaction was quenched with a saturated

aqueous ammonium chloride, extracted with ethyl acetate, and the collected organic layers dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Flash chromatography (hexane/ethyl acetate 8/2) of the crude product afforded the desired hydroxy derivative (1*R*,2*R*)-**20**. Yield 75%; R_f = 0.50 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ -54.1 (*c* 0.28, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ 7.10-7.65 (m, 10H), 6.79 (d, 1H, *J* = 10.0 Hz), 5.00 (d, 1H, *J* = 12.6 Hz), 4.93 (d, 1H, *J* = 12.6 Hz), 5.02 (d, 1H, *J* = 8.4 Hz), 4.60 (m, 1H); ^{19}F NMR (acetone-d_6) δ -67.4 (d, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 156.0 (s), 138.1 (s), 135.7 (s), 128.8 (s), 128.7 (s), 128.6 (s), 128.4 (s), 128.1 (s), 126.7 (s), 124.3 (q, *J* = 282.5 Hz), 72.2 (s), 67.6 (s), 57.5 (q, *J* = 28.3 Hz); FT-IR (cm^{-1}) 3420, 3310, 1695, 1549, 1249, 1176, 1120. MS (EI, 70 eV) m/z (%) 340 (M^+ +1, 6), 319 (8), 233 (28), 197 (28), 172 (20), 107 (72), 91 (100). Anal. Calcd for $C_{17}H_{16}F_3NO_3$: C, 60.17; H, 4.75; N, 4.13. Found: C, 60.19; H, 4.74; N, 4.11.

Synthesis of Trifluoronorephedrine (1*R*,2*R*)-21. A solution of *N*-Cbz trifluoronorephedrine (1*R*,2*R*)-**20** (80 mg, 0.24 mmol) in 5 mL of MeOH was vigorously stirred at rt under H_2 atmosphere, in presence of $Pd(OH)_2$-C (50% Pd) for 15 min. The resultant mixture was filtrated on a Celite pad and the solvent removed *in vacuo*. Flash chromatography (*n*-hexane/ethyl acetate 7/3) of the crude product afforded the desired trifluoronorephedrine (1*R*,2*R*)-**21** in quantitative yield. R_f = 0.22 (7/3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ -14.0 (*c* 1.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.2-7.6 (m, 5H), 4.93 (d, 1H, *J* = 5.6 Hz), 3.60 (dq, 1H, *J* = 5.5 and 7.4 Hz), 2.72 (br.s, 2H); ^{19}F NMR ($CDCl_3$) δ -74.69 (d, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 138.8 (s), 128.6 (s), 128.5 (s), 127.0 (s), 72.1 (s), 58.5 (q, *J* = 26.0 Hz), the corresponding resonance of the CF_3 group is obscured. FT-IR (cm^{-1}): 3380 (broad), 1261, 1154, 1124. MS (EI, 70 eV) m/z (%) 206 (M^+ +1, 10), 188 (17), 185 (9), 174 (31), 107 (71), 79 (100).

Synthesis of *N*-(*p*-Bromobenzoyl) Derivatives (*R*)-13 and (*R*)-16. A General Method. To a stirred suspension of chlorohydrate (*R*)-**12** or (*R*)-**15** (1 mmol) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere at 0 °C, triethylamine (2.5 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C and after 10 min *p*-bromobenzoyl chloride (1 mmol) was added drop-wise. The resultant mixture was stirred at 0 °C for 30 min and then 1 h at rt. Upon completion of the reaction (monitoring by TLC) water (5 mL) was added, and the organic phase was separated washed with water and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded crystalline and analytically pure amides (*R*)-**13** or (*R*)-**16**.

(*R*)-*N*-(*p*-Bromobenzoyl)-1,1,1-trifluoro-*iso*-propylamine (13): 94%; $[\alpha]_D^{24}$ +14.20 (*c* 0.83, $CDCl_3$), t. sub. >100 °C; ^{1}H NMR (acetone-d_6) δ 8.12 (br.s, 1H), 7.88-7.85 (m, 2H), 7.70-7.66 (m, 2H), 4.95 (qq, 1 H, *J* = 6.9 and 8.5 Hz), 1.44 (d, 3H, *J* = 6.9 Hz); ^{19}F NMR (acetone-d_6) δ -77.8 (d, *J* = 8.5 Hz). ^{13}C NMR (acetone-d_6) δ 166.47 (s), 134.01 (s), 132.44 (s), 130.33 (s), 126.93 (q, *J* = 280.9 Hz), 126.64 (s), 47.41 (q, *J* = 31.4 Hz), 14.00 (q, *J* = 2.3 Hz). Anal. Calcd for $C_{10}H_9BrF_3NO$: C, 40.57; H, 3.06; N, 4.73; F, 19.25. Found: C, 40.55; H, 3.09; N, 4.69; F, 19.22.

(*R*)-*N*-(*p*-Bromobenzoyl)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (16): 95%; $[\alpha]_D^{24}$ +60.37 (*c* 0.35, $CDCl_3$); t. sub. >150 °C; ^{1}H NMR (acetone-d_6) δ 8.20 (br.d, 1H, *J* = 12.0 Hz), 7.74-7.70 (m, 2H), 7.64-7.61 (m, 2H), 7.40-7.37 (m, 2H), 7.30-7.20 (m, 3H), 5.15 (dddq, 1 H, *J* = 3.9, 11.7, 12.0 and 8.5 Hz), 3.30, 3.07 (ABX, 1H, *J* = 3.9, 11.7 and 14.1 Hz); ^{19}F NMR (acetone-d_6) δ -76.23 (d, *J* = 8.5 Hz). ^{13}C NMR (acetone-d_6) δ 166.78 (s), 137.09 (s), 133.88 (s), 132.40 (s), 130.15 (s), 130.04 (s), 129.29 (s), 127.71 (s), 126.60 (q, *J* = 281.7 Hz), 126.59 (s), 53.00 (q, *J* = 29.9 Hz), 34.22 (q, *J* = 1.7 Hz). Anal. Calcd for $C_{16}H_{13}BrF_3NO$: C, 51.63; H, 3.52; N, 3.76; F, 15.31. Found: C, 51.71; H, 3.57; N, 3.69; F, 15.25.

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17 On the other hand, this beneficial property of **7a-c** could create some problems in determining the stereochemical outcome of small scale reactions, as it was in our initial study. Thus, the diastereomeric ratios reported in the preliminary communication (ref. 13) should be corrected.

18 In the original text of ref. 12c compound Et-CH=N-Ph is named as *N*-ethylideneaniline.

19 In the experimental part of ref. 12c the configuration of the dominant isomers is given as (R^*_S,1*S**,2*R**), however, as it follows from the discussion and depicted in the schemes and transition states, the configuration of the main product is (R^*_S,1*R**,2*R**).

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