New Versatile Fluorinated Chiral Building Blocks: Synthesis and Reactivity of Optically Pure α-(Fluoroalkyl)-β-sulfinylenamines

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Efficient synthesis of optically pure α-(fluoroalkyl)-β-sulfinyl enamines has been achieved by aza-Wittig reaction of triphenyliminophosphoranes with the corresponding α-fluorinated-α′-sulfinyl ketones. The title compounds **3**,**4** showed an overwhelming preference for the *Z* stereochemistry of the enamine form. Their general reactivity has been studied. The reaction with some electrophiles (*i.e.* benzyl chloroformate and benzyl and allyl bromide) occurs at the nitrogen atom providing the corresponding *N*,*N*-disubstituted enamines. Nucleophiles add smoothly to C-2: heteroatom-centered nucleophiles like methanol, ammonia, and thiophenol afford *gem*-disubstituted derivatives under thermodynamic control, while a *C*-centered nucleophile like nitromethane adds in irreversible fashion. The hydride- and deuteride-promoted reduction of **3**,**4** to the *N*-Cbz-protected (**14**) and *N*-unprotected (**15**) α-fluorinated-α′-sulfinyl amines has been studied. Hydride addition was stereoselective, while low stereoselection was obtained with the other tested nucleophiles. Desulfurization of the optically pure 1,1,1-trifluoro-3-sulfinyl amine **15a** afforded (*R*)-1-(trifluoromethyl)ethylamine **17**. The Pummerer rearrangement of **14** occurs in an unusual nonoxidative way affording the sulfenamide **24**, that readily provided (*R*)-(2-H)- and -(2-D)-3,3,3-trifluoroalaninol (**19**) and (*R*)-3,3,3-trifluoroalanine (**22**).

Introduction

One of the continuing goals of our laboratories is to develop new synthetic routes to optically pure and selectively fluorinated organic molecules of biological significance. Chiral sulfoxides are important building blocks in organic synthesis:[1] the preparation and reaction of their α-lithium derivatives has been an active area of research leading to numerous applications.[2] They have been key starting materials in our chemical developments, since upon acylation by fluorinated esters they afford α-fluoro-substituted-α′-sulfinyl ketones,[3] important intermediates in many synthetic routes to complex fluorinated molecules.

In previous contributions from our laboratories α-fluoro-substituted-α′-sulfinyl ketones have been utilized mainly in the construction of substances possessing oxygen functionalities while much less attention has been paid, by us and others, to the synthesis and use of the corresponding nitrogen-substituted derivatives.[4] Given the synthetic versatility associated with sulfinyl moieties, the ever increasing interest in fluoro-substituted compounds in biochemistry and medicinal chemistry,[5] and the large variety of nitrogen-containing biologically active compounds, it appeared that a new and general approach to γ-fluoro-β-nitrogen substituted sulfoxides would be an important and interesting matter. This paper outlines an experimental procedure for obtaining the title compounds in high yield and in pure form from the corresponding α-fluoro-substituted-α′-sulfinyl ketones and the results of studies devoted to clarify their reactivity pattern.

Among the different approaches that could be envisaged and have been used for the synthesis of α-fluoroimine derivatives, i.e. the addition of primary and secondary amines to acetylenic sulfoxides,[6a] the addition of amines to allenic sulfoxides,[6b] the reaction of metalated sulfoxides with nitriles,[6c] the addition of lithio enamines to sulfinic esters,[6d] and more recently the acid-catalyzed condensation between aliphatic amines and α-sulfinyl ketones,[6e] the last one seemed to us the most useful for the synthesis of the title compounds, since starting α′-sulfinyl ketones are available at any grade of fluorosub-

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(2) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961 and references therein quoted.

(3) Bravo, P.; Piovosi, E.; Resnati, G. *Synthesis* **1986**, 579.

(4) For the synthesis of chiral fluorinated cyclic alcohols: Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459. For fluorinated nucleosides: Bravo, P.; Mele, A.; Salani, G.; Viani, F.; La Colla, P. *Gazz. Chim. Ital.* **1995**, *125*, 295. For fluoro-oxiranes: Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F.; Zappalà, C. Cavicchio, G.; Crucianelli, M. *Tetrahedron* **1995**, *51*, 8289. For the synthesis of optically pure α-trifluoromethyl amino acids: Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2009.

(5) (a) Resnati, G. *Tetrahedron* **1993**, *49*, 9385−9445. (b) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Son Inc.: New York, 1991. (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993. (e) Kukhar, V. P.; Soloshonok, V. A. In *Fluorine Containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Son Inc.: New York, 1994.

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stitution (in α position and far away) and in optically pure form, by the method we have already reported.[3]

However, the condensation of amines on α-fluoro or α-perfluorinated ketones usually leads to *gem*-hydroxy-amino compounds (hemiaminals) because of the high stabilization of sp^3 hybridized carbon induced by α-fluoro-substitution; they can be dehydrated to the corresponding imines with increasing difficulty as fluorosubstitution increases: this can be incompatible with the presence of the stereogenic sulfinyl moiety. Moreover, perfluorinated imines are not easy to obtain in pure form because during the isolation or purification procedures the excess of amine, the solvent, or water can add to the reactive C═N double bond forming undesired byproducts.[7] Finally, because of the presence of the electron-withdrawing sulfinyl group, these molecules could exist both in imine and enamine form, each one giving rise to two geometrical isomers.

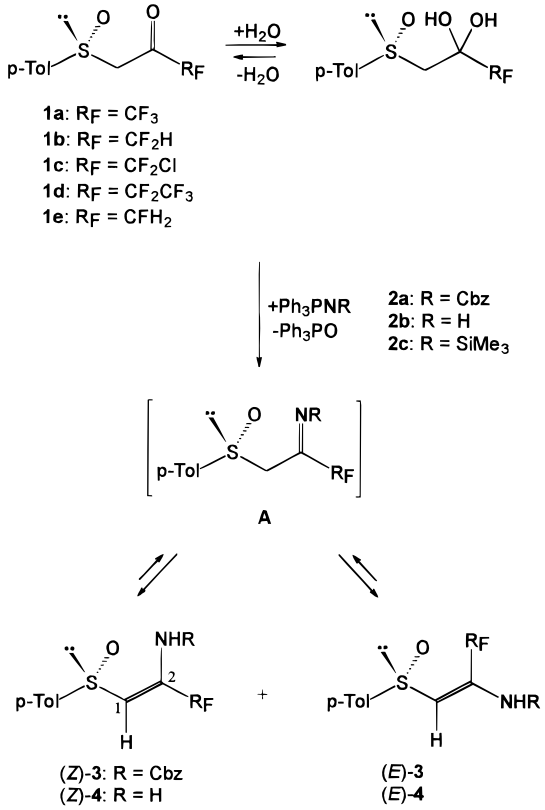
For these reasons, in order to obtain title compounds in optically pure form, we turned our attention on the aza-Wittig reaction, which can be performed in neutral conditions, in non nucleophilic solvents, with equimolar amounts of reagents. Though a number of iminophosphoranes have been reacted with fluorinated aldehydes, ketones, and α-keto esters, this reaction does not belong to the arsenal of reactions routinely used for the synthesis of imines. In fact, a strong activation of the C═O moiety by electron-withdrawing groups is generally required. This is mainly due to the lower reactivity of iminophosphoranes with respect to the corresponding carbon−phosphorus ylides,[8] although the ρ values for the aza-Wittig reactions of various carbonyl compounds are reported to be similar, in many cases, to those of the corresponding Wittig reactions.[9]

Herein we wish to report a full account of the synthesis of the title compounds by means of the aza-Wittig reaction, and of their reactivity and their use in the stereoselective synthesis of fluorinated analogues of amines, amino alcohols, and amino acids.

Results and Discussion

Synthesis of Title Compounds.[10] We were delighted to see that the aza-Wittig reaction of stabilized *N*-(benzyloxycarbonyl)iminophosphorane (*N*-Cbz iminophosphorane) **2a**[11] with α-fluorinated-α′-sulfinyl ketones **1a**−**d**, mainly or totally existing in *gem*-diolic form (Scheme 1), was efficient in benzene at reflux temperature. The reaction was quite slow (about 20 h), but purification by flash chromatography (FC) afforded in good yields the desired products **3a**−**d** in optically pure form. Conversions ranged from 70% to 86.5% (Table 1), and the unreacted iminophosphorane **2a** can be almost quantitatively recovered in the same chromatographic conditions.

Scheme 1



In the case of the monofluorinated molecule **1e** the reaction was sluggish: after 60 h only a 10% yield was reached, though the conversion was high (95%). When the non-fluorinated α-sulfinyl ketone (*R*)-[(4-methylphenyl)sulfinyl]propan-2-one was reacted in the same conditions, after 16 h the unchanged starting materials were recovered, while the α-substituted sulfinyl ketone (*R*)-3-[(4-methylphenyl)sulfinyl]-3-phenyl-1,1,1-trifluoropropan-2-one rapidly decomposed upon heating.

Primary enamines **4a** and **4c** were obtained in high yields (91% and 85%, respectively) after 16 h at rt from the reaction of the trifluoro and the difluorochloro *gem*-diols **1a** and **1c** with the *N*-$SiMe_3$ iminophosphorane **2c**, that was prepared *in situ* and cleanly reacted with or without *in situ* desilylation to the more reactive **2b** (R = H).[12] In both cases only *N*-desilylated enamines were recovered after FC. Finally, primary enamine **4b** was obtained in 85% yield (calculated from ^{1}H NMR spectrum of the crude reaction mixture), but hydrolysis occurred during FC. Anyway, **4b** may be employed for *in situ* reactions.

As expected, the above described results show a clear-cut increase of reactivity of the α-fluorinated-α′-sulfinyl

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(7) Osipov, S. N.; Kolomiets, A. F.; Fokin, A. V. *Russ. Chem. Rev.* **1992**, *61* (8), 798. For a recent report on the preparation of α-(fluoro- and -perfluoroalkyl) imines from the corresponding fluorinated ketones and aldehydes and benzylamine see: Soloshonok, V. A.; Kirilenko, A. G.; Kukhar, V. P.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 3119. In our hands, attempts to obtain the title compounds directly from acid catalyzed condensation of benzylamine and α-(fluoroalkyl)-α′-sulfinyl ketones did not gave satisfactory results.

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(9) Johnson, A. W.; Wong, S. C. K. *Can J. Chem.*, **1966**, *44*, 2793. For some reviews on the aza-Wittig reaction see: Johnson, A. W.; Kasha, W. C.; Starzewsky, K. A. O.; Dixon, D. A. *Ylides and Imines of Phosphorus*; John Wiley: New York, 1993; Chapt. 13. Molina, P.; Vilaplana, M. J. *Synthesis*, **1994**, 1197 and references cited therein.

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Table 1. NOE and selected ^{1}H NMR values of enamines (see Schemes 1 and 2)

compound	R_F	R	R′	yield % (conv)	NOE %[a] {R_F}/H-1	δ_{H-1}	δ_{NH}	δ_{H-3} (R_F)
(*Z*)-**3a**	CF_3	Cbz	H	78 (85)	10.5	6.42	7.28	–
(*Z*)-**3b**	CF_2H	Cbz	H	48	11.5	5.70	9.95	7.06
(*E*)-**3b**	CF_2H	Cbz	H	32 (86.5)[b]	4.5	7.30	6.80	7.25
(*Z*)-**3c**	CF_2C_l	Cbz	H	72 (78)	13.8	6.54	6.76	–
(*Z*)-**3d**	CF_2CF_3	Cbz	H	58 (70)	14.5	6.60	6.45	–
(*Z*)-**3e**	CFH_2	Cbz	H	10 (95)	12.5	5.33	10.24	5.42
(*Z*)-**4a**	CF_3	H	H	91	16.0	5.30	5.35	–
(*Z*)-**4b**	CF_2H	H	H	85[c]	h	5.12	5.28	5.95
(*Z*)-**4c**	CF_2C_l	H	H	85	h	5.32	5.38	–
(*Z*)-**6a**	CF_3	Cbz	Cbz	80	9.4	6.92	–	–
(*Z*)-6b	CF_2H	Cbz	Cbz	54 (75)	9.5	6.77	–	6.08
(*Z*)-**7a**	CF_3	Cbz	benzyl	70,[d] 65[e]	h	6.80	–	–
(*Z*)-**7b**	CF_2H	Cbz	benzyl	~73[f]	8.6[g]	6.61	–	5.89
(*E*)-**7b**	CF_2H	Cbz	benzyl	~62.6 (85)[f]	h	6.08	–	6.78
(*Z*)-**8a**	CF_3	Cbz	allyl	76	h	6.9	–	–
(*Z*)-**8b**	CF_2H	Cbz	allyl	56 (68.5),[d] 69 (73)[e]	h	6.69	–	6.09
(*E*)-**8b**	CF_2H	Cbz	allyl	~35 (63)[f]	h	6.38	–	6.78

[a] Heteronuclear NOE. [b] Calculated from **1b** recovered ((*Z*)- and (*E*)-**3b** were obtained in the same reaction). [c] Calculated from ^{1}H NMR spectrum of the crude. [d] Method A (see Experimental Section). [e] Method B (see Experimental Section). [f] Obtained as mixture with *Z* (*E*) isomer (method B see Experimental Section). [g] Homonuclear NOE. [h] Not measured.

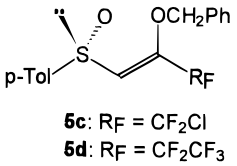
ketones **1** toward iminophosphoranes **2** with increasing α-halogenation.

The only relevant byproducts we have detected in the aza-Wittig reaction have been the enol ethers **5c** and **5d**[13] (Figure 1), obtained in the reaction of the *gem*-diols **1c** and **1d** with the phospha-azene **2a**. The enol ether **5d** was independently synthesized by a reported method.[14]

Structure Determination. The *N*-Cbz-β-sulfinyl enamines **3a**–**d** are stable crystalline compounds that can be stored for indefinite time at rt, while the primary enamines **4a,c** are oily compounds which can be purified by FC and stored at 0 °C for long time.

The products of the aza-Wittig were entirely in enamine form: imine products **A** have never been detected by ^{1}H and ^{19}F NMR analyses of the crude. Solid phase IR spectra of **3a**–**c**, purified by FC and crystallized, confirmed the absence of a C=N band, while the strong bands of N–H stretching were always clearly detectable (see supporting information). The β-sulfinyl enamines **3** may exist as (*E*)- and (*Z*)-geometric isomers or as an equilibrium mixture: however, for the **3a**,**c**–**e**, **4a**–**c** derivatives, obtained as pure compounds by FC, we have been able to detect only the *Z* geometric isomer, both in the solid state and in solution. Only the difluoro derivative **3b** was obtained from the reaction as a *Z*:*E* = 3:2 mixture of isomers, easily separable in pure form by FC. Equilibration between the isomeric enamines (*E*)- and (*Z*)-**3b** was experimentally observed: interconversion occurred at very low rate in solution at rt and at neutral pH, but starting from pure (*Z*)-**3b** a ratio of (*Z*)-**3b**:(*E*)-**3b** = 3:2 was reached after one night at 50 °C in benzene solution.

The most significant NMR data of compounds **3a**–**e**, **4a**–**c** are reported in Table 1. The stereochemistry at the double bond of the enamines **3a**–**e**, **4a** was established from the heteronuclear NOE effect measured on H-1 by irradiating the fluorine atoms. In the case of the *Z* isomers the NOE for H-1 is very large, ranging from 10.5 to 16.0%. For the (*E*)-**3b** isomer, as expected, this



5c: $R_F = CF_2Cl$
5d: $R_F = CF_2CF_3$

Figure 1.

effect is much smaller (4.5%). The *Z* stereochemistry at the double bond of the primary enamines **4b** and **4c** was confidently assigned, given the similarity of their NMR spectra with those of (*Z*)-**4a** (see Experimental Section). The chemical shift of the carbamic proton shows strong variations within the examined compounds. In the spectra of (*Z*)-**3a**, (*Z*)-**3c**, (*Z*)-**3d**, and (*E*)-**3b** a broad signal, that resonates in the range 6.4–7.3 ppm and is shifted upfield with dilution, can be certainly assigned to the NH proton. For compounds (*Z*)-**3b** and (*Z*)-**3e**, bearing the difluoro- and monofluoromethyl substituent, respectively, the NH resonance falls at ca. 10 ppm., and no appreciable shift was observed upon dilution. These data suggest the presence in solution of an intramolecular hydrogen bond between the carbamic proton and the sulfinyl oxygen for (*Z*)-**3b** and (*Z*)-**3e**, but not for (*Z*)-**3a**, (*Z*)-**3c**, (*Z*)-**3d** (and obviously for (*E*)-**3b**).

The absence of intramolecular hydrogen bond between the NH and the sulfinyl oxygen in the latter compounds means that the driving force for the overwhelming preference of the *N*-Cbz enamines **3a,c,d** for the *cis* stereochemistry at the double bond must be searched elsewhere.[15] Moreover, also the *N*,*N*-disubstituted enamines **6**–**8a** show the same stereochemical behavior. A possible explanation could be given by invoking a repulsive nonbonded interaction between the R_F and the oxygen atom of the sulfinyl group. On the other hand a favorable nonbonded interaction between the sulfinyl group and the nitrogen atom, possibly implying a hypervalent sulfur, may also be considered.[16]

The *N*-monosubstituted (**3b**) and *N*,*N*-disubstituted (**6b**, **7b**, **8b**) enamines bearing the CF_2H group were

(13) In the preliminary report[10] the enol ethers **5c,d** were mistaken for *E* isomers of **3c** and **3d**. Probably these byproducts do not arise from the corresponding β-sulfinyl enamines, because under aza-Wittig reaction conditions they did not afford the enol ethers **5**. It is likely that they are directly produced by reaction of the *gem*-diols **1c**,**d** with the iminophosphorane **2a**.

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(15) For a conformational study on β-sulfinyl enamines and α-sulfinylimines see: Kozersky, L.; Kawecki, R.; Hanson, P. E. *Magn. Reson. Chem.*, **1994**, *32*, 517. For a discussion about the intramolecular hydrogen bonding in β-sulfinyl enamines see ref 6d.

(16) Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*, CRC Press: Boca Raton, 1991; pp 21–26.

obtained as mixtures of (*E*)- and (*Z*)-geometric isomers, thus showing only slight preference for the *cis* geometry. This feature, unique in the variety of enamines synthesized in the present work, may be attributed to the presence in solution of an intramolecular hydrogen bond between the sulfinyl oxygen and the hydrogen of the CF_2H group.[17] ^1H NMR Chemical shifts of H-1 and H-3 seem also to agree with this explanation.

Further investigations on these phenomena are presently underway by means of X-ray crystallographic analysis of the *N*-Cbz-*β*-sulfinyl enamines **3**, NMR studies of their properties in solution, and calculations. The results of these efforts will be published in due time.

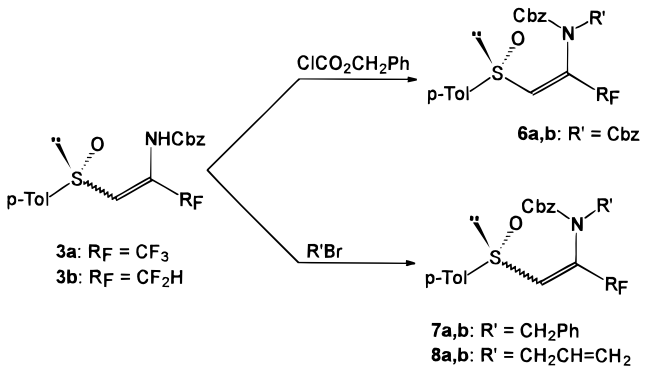
Reactivity of Title Compounds: General Considerations. We have studied the general reactivity of the *N*-Cbz trifluoro derivative **3a** and, for sake of comparison, that of the difluoro enamine **3b**, with the view of assessing the employment of the α-(fluoroalkyl)-*β*-sulfinyl enamines in the synthesis of sulfur-free fluorinated analogues of naturally occurring molecules having biological interest. Title compounds show a complex reactivity pattern. They possess at least four contiguous sites which can enter into reaction: the sulfinyl group, the two C-1 and C-2 sp^2 atoms of the carbon−carbon double bond, and the nitrogen atom. Because of the presence of the fluoro-substituted alkyl group at the C-2 and of the Cbz protecting group at the nitrogen atom, compounds **3** should be electron-poor systems when compared with known α-sulfinyl imines and α-imino ketones and esters. Therefore one should expect they will show a high reactivity toward species having nucleophilic character.

Reactions with Electrophiles. The primary trifluoro enamine **4a**, upon treatment with *n*-BuLi in tetrahydrofuran (THF) at −78 °C, followed by $ClCOOCH_2Ph$, smoothly afforded the *N*-Cbz protected derivative **3a**. However, under these conditions the yield did not exceed 50%, and a reversed addition (the lithium derivative of **4a** to a cooled solution of $ClCOOCH_2Ph$) did not change the situation. Presumably, since the *N*-Cbz product **3a** is more acidic than **4a**, a half quantity of the former is consumed, forming the lithium derivative of **3a**, that is not reactive in these conditions toward the excess of chloroformate. Unreacted starting enamine **4a** can be quantitatively recovered by FC purification of the crude.

The nitrogen atom was found to be the reactive site of the difluoro and trifluoro *N*-Cbz enamines **3a**,**b**, when they were treated with the tested electrophiles in presence of bases, while in absence of the latter no reaction was detected. The reactions of the *N*-Cbz-*β*-sulfinyl enamines **3a** and **3b** with electrophiles are outlined in Scheme 2. The *N*-Cbz trifluoro enamine **3a** reacted with benzyl chloroformate in dioxane/50% aqueous K_2CO_3 at rt (method A), affording the (*Z*)-*N*,*N*-bis-Cbz derivative **6a** (80%). The original *cis* double bond stereochemistry was retained, as shown by NOE difference experiments. The same enamine **3a** reacted with benzyl and allyl bromides both according to method A and in dimethylformamide (DMF)/NaH from 0 °C to rt (method B) giving, in moderate to good yields, the corresponding *N*-benzyl and *N*-allyl derivatives **7a** and **8a**. Slightly better yields were obtained by following method A.

Only one geometric isomer was always detected, to which a *Z* stereochemistry was confidently assigned in analogy with **6a**.

Scheme 2



Both the (*E*)- and (*Z*)-geometric isomers of the difluoro enamine **3b** were separately submitted to the above described reactions with electrophiles. As clearly detected by thin layer chromatography (TLC), (*E*)- and (*Z*)-**3b** are prone to interconversion when treated with bases (method A or B).

Method B was found to be considerably more efficient but less diastereoselective than method A in the reaction of (*Z*)- and (*E*)-**3b** with allyl and benzyl bromide. In fact only (*Z*)-*N*,*N*-diprotected enamines were obtained with method A starting separately from (*Z*)- or (*E*)-**3b**, while when method B was adopted, mixtures of (*E*)- and (*Z*)-*N*,*N*-diprotected enamines **7b** and **8b** were obtained, as clearly detected by ^1H and ^{19}F NMR. The ratio of the isomers **7b**,**8b** produced with method B reflected the geometry of the starting enamine. The stereochemistry at the double bonds was unequivocally established by means of homonuclear NOE experiments performed on **7b**, while the stereochemistry of the two isomers of **8b** was assigned by comparison with the NMR spectra of **7b**. Interestingly, upon treatment with benzyl chloroformate, the (*Z*)-**3b** isomer afforded only the corresponding *cis*-*N*,*N*-bis-Cbz-enamine (*Z*)-**6b**, as shown by NOE experiments. Moreover, (*Z*)-**3b** was found to react better than (*E*)-**3b** with the tested electrophiles. The former afforded the difluoro *N*,*N*-disubstituted enamines **6b**−**8b** in yields ranging from 54% to 94%, while for the latter the yields were much lower (see Experimental Section).

The (*Z*)-*N*,*N*-disubstituted enamines are easily distinguishable from the (*E*)- isomers by means of their ^1H and ^{19}F NMR spectra. In fact, the signals of the (*Z*)- isomers in $CDCl_3$ at rt were very broad, while those of the (*E*)-isomers in the same conditions were perfectly sharp. The broad signals displayed by the (*Z*)-*N*,*N*-disubstituted enamines **6**−**8** at rt should be due to the hindered rotation around some C−N bond (most probably around the enamine C=C−N bond); sufficiently sharp signals can be obtained just by increasing the temperature of the sample to 306−318 K.

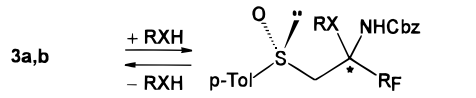
It is noteworthy that the attack of all tested electrophilic species described herein[18] does not occur on carbon C-1, the usual reactive site for "normal" metalated enamines.[19] The low reactivity of C-1 as nucleophilic site is probably due to the presence of fluorine atoms, which make the enamine *π* system electron-poor.

(17) Erickson, J. A.; Mc Loughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626−1631.

(18) The reactions of the *β*-sulfinyl enamines **3** with acyl halides and anhydrides have a completely different and much more complex outcome, presently not well understood and under active investigation. The results will be reported in due course.

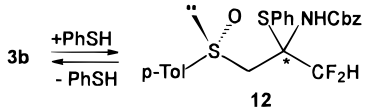
(19) Whitesell, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Academic Press: Oxford, 1991; Vol. 6, pp 703-732. Martin, S. F. *Ibid.*, Vol. 2, pp 475−502. Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517. Hickmott, P. W. *Tetrahedron* **1986**, *40*, 2989.

Scheme 3

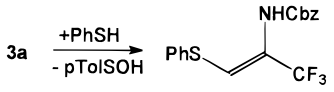


9a,b: X = O; R = CH_3
10a,b: X = N; R = H_2
11a,b: X = CH_2; R = NO_2

Scheme 4



12



13

Reactions with Nucleophiles. Carbon C-2 is highly reactive toward nucleophiles (Scheme 3) and a new stereogenic center is formed in this reaction. α-(Trifluoromethyl)- and α-(difluoromethyl)-*N*-Cbz-β-sulfinyl enamines **3a** and **3b** reacted efficiently and under very mild conditions with *O*, *N*, *C*, and *S*-centered nucleophiles.

Methanol (used as reagent and solvent in the presence of a catalytic amount of conjugate base) added at rt in 12 h to the enamines **3a** and **3b** afforded good yields of the diastereoisomeric *N*,*O*-disubstituted hemiaminals **9a,b**.

Ammonia (30% aqueous solution) reacted in 15 min with THF solutions of **3a** and **3b** at rt giving, in almost quantitative yield, diastereomeric mixtures of aminals **10a,b**. These compounds are quite stable and can be easily purified by FC.

Also, carbon-centered nucleophiles like nitromethane added to the β-sulfinyl enamines **3a,b** producing the nitro-compounds **11a,b**. This modified Henry (nitroaldol) reaction was carried out at rt for 24−48 h, using nitromethane as solvent, with a catalytic amount of base. The trifluoro derivative **11a** was obtained in 80% yield; the difluoro derivative **11b** in 93% yield starting from (*Z*)-**3b**.

The reaction of the enamines **3a,b** with a sulfur nucleophile such as thiophenol was found to be highly sensitive to the fluorination degree, which modulates the reactivity of the substrate. When the trifluoro enamine **3a** was reacted with 4 equiv of thiophenol and a catalytic amount of base, only the vinyl sulfide **13** was surprisingly obtained. On the other hand, the difluoro enamines (*Z*)- and (*E*)-**3b** reacted in the expected fashion: the *N*,*S*-disubstituted derivative **12** was obtained after 16 h in 70% and 63% yield, respectively (Scheme 4). Probably **13** arises from an *anti*-Michael addition of phenyl sulfide ion to **3a** and subsequent β-elimination of the *p*-toluenesulfenate ion.[20]

Concerning the diastereoselectivity of the reactions of the *N*-Cbz β-sulfinyl enamines **3a,b** with nucleophiles, almost equimolar mixtures of addition products **9a**, **10a**, and **11a**, arising, respectively, from the addition of *O*, *N*, and *C* centered nucleophiles, were obtained from the trifluoro enamine **3a**. Both the (*Z*)- and (*E*)-isomers of the difluoroenamine **3b** were separately reacted with the reported nucleophiles, but no significant differences in the diastereomeric ratio of the resulting products **9b**, **10b**, **11b**, and **12** was observed. The difluoro hemiaminal **9b**, the trifluoro aminal **10a**, the trifluoro nitro derivative **11a**, and the difluoro phenylthio derivative **12** were obtained in diastereomerically pure form by FC.[23]

With the above described results in hand, we were not surprised to find that the addition reactions of heteroatom centered nucleophiles on the enamines **3a,b** run under thermodynamic control. In fact, after a few days in chloroform solution at rt, the *N*,*O*-derivative **9** and the *N*,*N*-derivative **10** partially or completely reconverted into the corresponding starting enamine **3**; moreover, when the diastereomerically pure disubstituted derivatives **9b**, **10a**, and **12** were submitted to the conditions under which they were obtained from **3**, the original diastereomeric ratio was smoothly achieved. On the other hand, in the case of nitromethane the reaction probably occurs under kinetic control. In fact, no reequilibration was observed when diastereomerically pure **11b** was left in nitromethane at rt in presence of a catalytic amount of base for one week.

The high reactivity of the α-(fluoroalkyl)-β-sulfinyl enamines **3** toward nucleophiles can be attributed to the known stabilizing effect for quaternary species (hydrates, hemiacetals, etc.) of perfluoroalkyl groups α to carbonyls or imines, and to the fact that during the addition of anions a negative charge evolving in reaction intermediates on carbon C-1 will be stabilized by the adjacent sulfinyl group.

Reactions with Hydride Reducing Agents. Chiral β-sulfinyl amines are molecules of remarkable usefulness for the stereoselective synthesis of natural and biologically active compounds.[24] For this reason the efficient and stereoselective reduction of the α-(fluoroalkyl)-β-sulfinyl enamines **3**,**4** is a fundamental step with the view of the synthesis of chiral fluorinated molecules of biological interest. The hydride-promoted reduction of cyclic and acyclic α-sulfinylimines has been extensively studied,[4d,e,25,26] but we have found that the fluorosubstitution changes the usual reactivity of the title compounds toward hydrides.

The reduction of the primary and *N*-Cbz α-(fluoroalkyl)-β-sulfinyl enamines to the corresponding β-sulfinyl amines **14** and **15** (Scheme 5) was systematically studied on **3a** and **4a** (a full account on the hydride-promoted reduction of the β-sulfinyl enamines **3a**, **4a**, and **4c** can be found in supporting information).

(20) Only few examples of *anti*-Michael additions are known, but this unusual outcome has been already reported in the additions of PhS^- to 4,4,4-trifluoro-1-phenylbut-2-yn-1-one[21] and β,β-bis(trifluoromethyl)acrylic esters.[22] For a recent example of *anti*-Michael additions of heteroatom nucleophiles see: Back, T. G.; Wehrli, D. *Tetrahedron Lett.* **1995**, *36*, 4737 and references therein quoted.

(21) Bumgardner, C. L.; Bunch, J. E.; Whangbo, M.-H., *J. Org. Chem.* **1986**, *51*, 4082.

(22) Martin, V.; Molines, H.; Wakselman, C. *J. Org. Chem.*, **1992**, *57*, 5530.

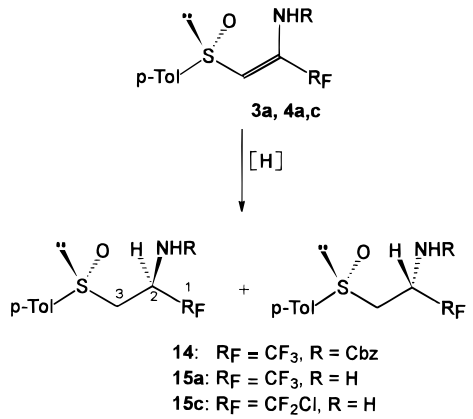
(23) There is only one precedent of optically pure aminals like **10**, as stated by: Matsumura, Y.; Tomita, T. *Tetrahedron Lett.*, **1994**, *35*, 3737.

(24) For the use of β-sulfinyl amines in the synthesis of alkaloids see Hua and co-workers, ref 6d; see also Pyne, S. G.; Dikic, B. *J. Org. Chem.*, **1990**, *55*, 1932 and references cited therein. For their use as ligands of transition metals see the works of Kagan, ref 6e. See also: Lim, C. C.; Leung, P. H.; Sim, K. Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1883.

(25) Carreno, M. C.; Dominguez, E.; Garcia Ruano J. L.; Pedregal, C.; Rodriguez, J. H. *Tetrahedron* **1991**, *47*, 10035. Hua, D. H. Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998.

(26) Ogura, K.; Tomori, H.; Fujita, M. *Chem. Lett.* **1991**, 1407.

Scheme 5



The *N*-Cbz enamine **3a** was reduced upon treatment with $NaBH_4$ in a 4:1 THF/H_2O mixture at rt, affording the diastereoisomeric amines **14** with low diastereoselection (68% yield). Surprisingly, using methanol as solvent, upon treatment with $NaBH_4$, **3a** afforded the *N*,*O*-disubstituted ketal **9a**, while no appreciable reduction was detected. In our hands $HB(OAc)_3$, $BH_3{\cdot}SMe_2$, L-Selectride, $NaBH_3CN$, and diisobutylaluminum hydride (DIBALH) were not effective in the reduction of **3a** to the corresponding amine **14**.

The primary α-(trifluoromethyl)-*β*-sulfinyl enamine **4a** was reduced to the diastereomeric amines **15a** in the same conditions and with the same low diastereoselection already described for **3a**. However, the reaction was found to occur also in dry THF (the *N*-Cbz enamine **3a** was practically unreactive in dry THF toward $NaBH_4$), and even though the reaction rate was low (40 h at rt) the diastereoselection was remarkably higher (60% de) than that obtained in the presence of water, delivering the diastereoisomeric *β*-sulfinyl amines **15a** in 83% yield.

The K- or L-Selectride promoted reduction of the primary trifluoro enamine **4a** proved to be highly stereoselective affording **15a** with a $(2S,R_S)/(2R,R_S) = 90:10$ diastereomeric ratio in CH_2Cl_2 and 93:7 in THF. The reduction was very fast, but required the use of a *one-pot* stepwise procedure to reach a satisfying yield. When a small excess of K- or L-Selectride was added to the primary enamine at −20 °C, only about 40% of **15a** formed after the first addition. In fact, as already reported,[26] the reducing agent, acting as a strong base, is able to remove an NH proton producing the corresponding azaenolate, which proved to be unreactive toward the hydride. The addition of a small excess of ethanol can regenerate the unreacted enamine. Careful removal of the excess of ethanol and further addition of Selectride produces further reduction. Repeating this procedure twice a yield of 75% was reached using CH_2Cl_2 as solvent (unreacted **4a** was almost quantitatively recovered).

Also the primary difluorochloro enamine **4c** was stereoselectively reduced with L-Selectride in CH_2Cl_2 at −20 °C, affording the amines **15c** in $(2S,R_S)/(2R,R_S) = 5:95$ diastereomeric ratio. The reduction was performed as already described for **4a**.

In our hands no reaction occurred with DIBALH (even in the presence of $ZnBr_2$ or ZnI_2) and $BH_3{\cdot}$THF.

It is likely that the low reactivity of the tested α-(fluoroalkyl)-*β*-sulfinyl enamines **3** toward electrophilic reducing agents is due to the fluorosubstitution that makes the enamine framework electron poor.

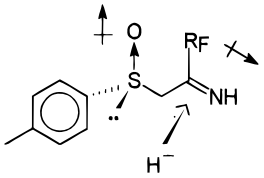


Figure 2.

The $(2S,R_S)$ absolute stereochemistry of **15a** was assigned by X-ray crystallographic analysis (see supporting information) of the major diastereoisomer obtained in the L-Selectride promoted reduction of **4a**. In the ORTEP view of compound **15a** it can be seen the all *trans* conformation of the sulfoxide chain implying a *gauche* value for the dihedral angle S(1)−C(1)−C(2)−N(1) and consequently a possible interaction between the lone-pair of N and the S atom.

The stereochemistry of **14** was assigned by chemical correlation. In fact, treatment of $(2S,R_S)$-**15a** with benzyl chloroformate and 50% K_2CO_3 in dioxane afforded the major diastereoisomer of **14** obtained in the $NaBH_4$/−20 °C reduction of the *N*-Cbz enamine **3a**. The stereochemistry of the difluorochloro amine **15c** was assigned by comparison of the ^1H NMR spectra, since the two pairs of major and minor diastereoisomers of the L-Selectride-promoted reduction of **4a** and **4c** showed great similarity (see Experimental Section).

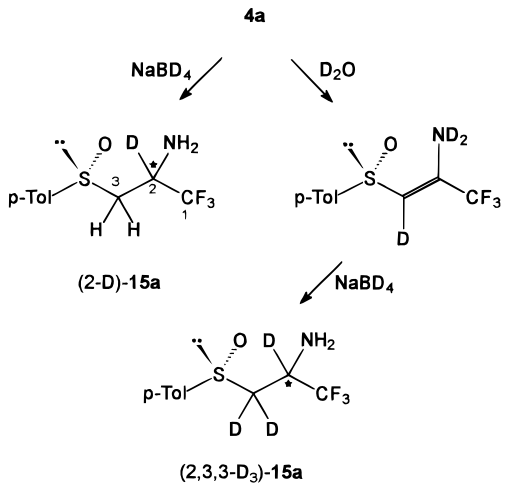
As already hypothesized, a rationale for the high diastereoselectivity showed by K- and L-Selectride in the reduction of **4a,c** could be given considering that such reducing agents are highly sterically demanding: so, the attack of the hydride is expected to be much more easy from the *re* face of the transient tautomeric imine form of **4a,c** in the conformation in which the dipole−dipole interactions between the C=N and the S=O groups are minimized (Figure 2).[27]

Deuterium-substituted molecules are important and useful tools for investigations on metabolism, on mechanism of action of enzymes, and on mechanism of reactions. By means of the above described methods of reduction of the enamines **3**, we were able to synthesize regio- and stereoselectively deuterium substituted *β*-sulfinyl amines **15a**. Selective deuterium substitution at C-2 was achieved by reduction of **4a** to (2-D)-**15a** with $NaBD_4$ in dry THF (Scheme 6). The diastereoselection was similar to that obtained in the reduction of **4a** with $NaBH_4$ in dry THF. Exhaustive deuterium substitution was obtained upon preliminary exchange of **4a** with D_2O, that afforded the corresponding (*N*,*N*,3-D_3)-enamine, which was treated, without isolation, with $NaBD_4$ in dry THF. After aqueous workup the *β*-sulfinyl amine (2,3,3-D_3)-**15a** was cleanly obtained, the substitution degree being >95% both in the C-2 and C-3 positions.

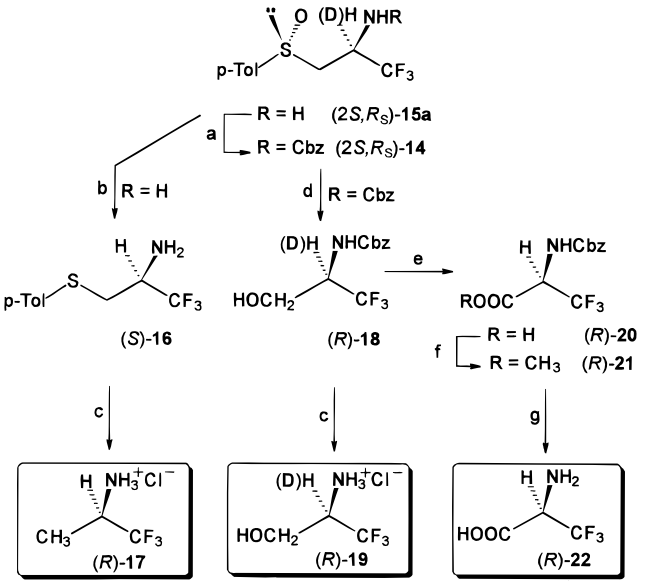
Reactions at the Sulfinyl Moiety: (a) Synthesis of Amines and Amino Acids. For a suitable use of the title compounds **3** in the synthesis of chiral fluorinated analogues of naturally occurring or fluoro-substituted biologically active compounds, it is necessary to have at disposal efficient procedures for the removal of the stereogenic auxiliary group. Herein we report the application of two classical reactions for sulfur removal, examined closely on the trifluoro-*β*-sulfinyl amines $(2S,R_S)$-**15a** and $(2S,R_S)$-**14** (Scheme 7).

(27) Solladiè, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.*, **1985**, *26*, 435. Pyne, S. G.; Hajipour, A. R. *Tetrahedron*, **1994**, *50*, 13501 and references cited therein.

Scheme 6



Scheme 7[a]



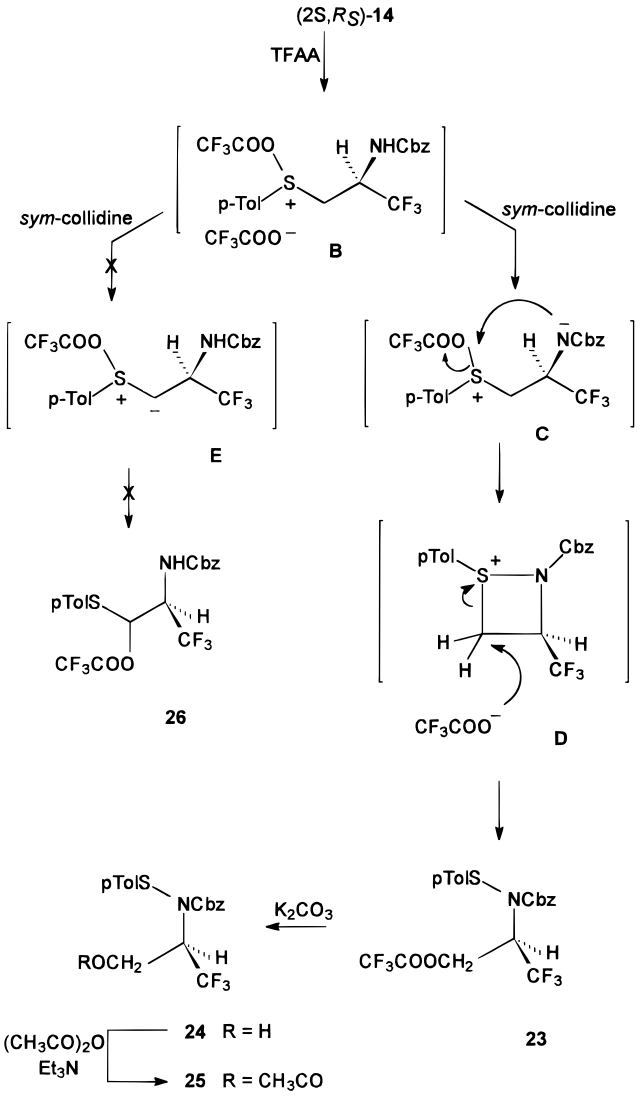
[a] (a) $ClCO_2CH_2Ph$, 50% aqueous K_2CO_3, dioxane, rt (100%); (b) TMSCl, NaI, 0 °C, CH_3CN; (c) (i) H_2, Ra-Ni, EtOH, rt; (ii) 1 N HCl; (d) (i) trifluoroacetic anhydride, sym-collidine, CH_3CN, 0 °C; (ii) aqueous K_2CO_3; (iii) $NaBH_4$; (e) $RuO_2{\cdot}xH_2O$ (cat.), $NaIO_4$, 3:2 acetone/water, rt, 1 h (65%); (f) CH_2N_2/Et_2O (65%); (g) H_2, $Pd(OH)_2$, EtOH, rt, 1 h (65%).

Specifically, the reduction of (2*S*,R_S)-**15a** to the corresponding sulfide **16** was smoothly achieved with TMSCl and NaI in acetonitrile at 0 °C. Standard desulfurization of (*S*)-**16** with Raney Ni and H_2 cleanly afforded (*R*)-1-(trifluoromethyl)ethylamine that was isolated as hydrochloride (*R*)-**17**.

The Pummerer rearrangement performed on (2-H)- and (2-D)-(2*S*,R_S)-**14**, as expected, produced the removal of the sulfinyl auxiliary group with the introduction of an oxygen functionality in its place.

When (2-H)- and (2-D)-**14** were treated first with trifluoroacetic anhydride (TFAA) and *sym*-collidine at 0 °C and then with aqueous K_2CO_3 and finally with $NaBH_4$ at rt, the (2-H)- and (2-D)-*N*-Cbz-amino alcohols (*R*)-**18** were, respectively, obtained in *one-pot* in 86% yield. As expected, no loss of deuterium was observed for (2-D)-(*R*)-**18**. Deprotection of **18** by hydrogenolysis with Raney Ni in H_2 atmosphere afforded, after treatment with 1 N aqueous HCl, the (2-H)- and (2-D)-3,3,3-trifluoroalaninol hydrochlorides (*R*)-**19**.

Scheme 8



The direct oxidation of (*R*)-**18** to the *N*-Cbz-3,3,3-trifluoroalanine **20** was achieved by the Sharpless method with catalytic $RuO_2{\cdot}xH_2O$ and $NaIO_4$ at rt.[28] The resulting product (*R*)-**20** was isolated and characterized or *in situ* transformed, upon treatment with ethereal diazomethane, into the corresponding methyl ester (*R*)-**21** (65%), known in the literature, though only in racemic form.[29] Hydrogenolysis of the Cbz protection of (*R*)-**21** with $Pd(OH)_2$ in ethanol at rt cleanly afforded (*R*)-3,3,3-trifluoroalanine **22** in 64% yield.[30]

(b) Nonoxidative Pummerer Rearrangement of 1,1,1-Trifluoro-3-sulfinyl Amine 14. Intensive efforts to isolate the expected intermediate derivative **26** (Scheme 8), or the corresponding α-amino aldehyde, from the Pummerer rearrangement of **14** were unsuccessful. Moreover, we observed that the $NaBH_4$ reduction of the intermediate product of the Pummerer rearrangement to the alcohol **18** did not require, as usual and above reported, a preliminary hydrolysis of the expected inter-

(28) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. See also: Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 6523.

(29) Burger, K.; Hoss, E.; Gaa, K.; Sewald, N.; Schierlinger, C. *Z. Naturforsch.* **1991**, *B46*, 361.

(30) The yields of RuO_2-catalyzed oxidation and of hydrogenolysis have not been optimized.

mediate **26**. Apparently, **26** was not formed at all and the reaction followed a completely different course. So we decided to further investigate this intriguing matter.

As outlined in Scheme 8, when (2*S*,R_S)-**14** was treated with TFAA and *sym*-collidine in acetonitrile at 0 °C, the α-sulfenamido trifluoroacetate **23** was surprisingly recovered as the only product. Upon treatment with aqueous K_2CO_3, **23** smoothly provided the sulfenamido alcohol **24**, whose structure was confirmed by *O*-acetylation to **25**. The sulfenamide **23** is clearly the product of an abnormal Pummerer rearrangement. In the most likely reaction path the *sym*-collidine, acting as a proton scavenger on **B** (the normal acylated intermediate), produces the zwitterionic intermediate **C** by preferential removal of the carbamic proton. Probably, the fluoro-substitution plays an important role making the abstraction of the NH proton more competitive with respect to the protons in α to the sulfinyl moiety. Nitrogen atom binding to the positively charged sulfur atom and S−O bond breaking leads to the four-membered ring intermediate **D**.[31] Attack of the trifluoroacetate ion on the CH_2, which occurs with cleavage of the S−C bond, gives the α-sulfenamido trifluoroacetate **23**.[32,33]

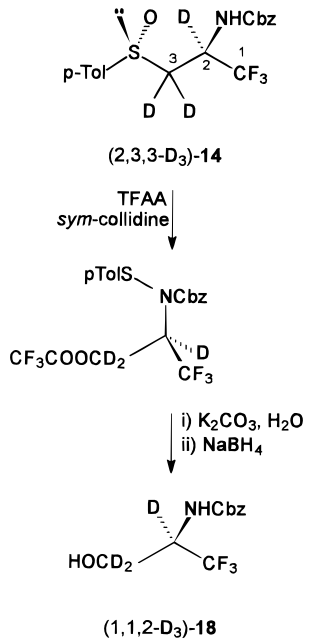
The formation of a σ-sulfurane intermediate (tetracoordinate sulfur), stabilized by the presence of two electron-withdrawing ligands on sulfur (the trifluoroacetoxy group and the carbamic nitrogen), may also be conceived as an alternative pathway.[34]

As a proof that the reaction does not involve the normal H-1 removal, (2,3,3-D_3)-(R_S,2*S*)-**14** was submitted to the Pummerer rearrangement (Scheme 9).[35] The sulfenamide intermediate, reduced *in situ* with $NaBH_4$ to the *N*-Cbz-amino alcohol (1,1,2-D_3)-**18**, was found to have retained the original deuterium in C-2.

Conclusions. In the present paper we have reported the aza-Wittig reaction of iminophosphoranes **2a**−**c** with α-fluoro-substituted-α′-sulfinyl ketones **1a**−**e** for the preparation of enantiomerically pure primary and *N*-Cbz protected α-(fluoroalkyl)-β-sulfinyl enamines. Structural studies showed an overwhelming preference for the enamine form with a *cis* configuration between the amino and the sulfinyl groups.

The title compounds **3a**−**e**, **4a**−**c** are new and versatile fluorinated chiral building blocks as shown by their manifold reactivity. The addition of *O*, *N*, *C*, and *S*-centered nucleophiles gives rise to substituted α-(fluoroalkyl)-β-sulfinyl amines with a quaternary carbon atom,

Scheme 9



and, though the diastereoselection was found to be modest, the process is efficient and occurs under mild conditions.

The introduction of hydride species has been examined in detail. β-Sulfinylamines have been obtained by this route in good yields and with high diastereoselection, also in deuterium-substituted form.

The removal of the chiral auxiliary sulfinyl group was achieved by reductive desulfurization or by introduction of an oxygen function in its place. The latter transformation was obtained by Pummerer rearrangement of the *N*-Cbz-1,1,1-trifluoro-3-[(4-methylphenyl)sulfinyl] amine **14**, a reaction that proceeds through a sequence of unusual intermediates.

The usefulness of the title compounds as fluorinated nitrogen-substituted templates for the synthesis of fluorinated molecules of biological interest has been demonstrated. (*R*)-1-(Trifluoromethyl)ethylamine (**17**), a small chiral fluorinated amine, which has already been employed as a key constituent of molecules with herbicide, insecticide, nematocide, and acaricide properties,[36] has been stereoselectively obtained starting from the primary trifluoro sulfinyl amine **15a**. Accordingly, the *N*-Cbz derivative **14** delivered (*R*)-(2-H)- and (2-D)-(*R*)-3,3,3-trifluoroalaninol (to our knowledge not reported in literature)[37] and (*R*)-3,3,3-trifluoroalanine (until now not described in optically pure form),[38] that is reported to be a potent mechanism-based inhibitor of a number of pyridoxal phosphate-dependent enzymes.[39]

Experimental Section

General Procedure. ^1H, ^{19}F, and ^{13}C nuclear magnetic resonance samples were prepared as dilute solutions in $CDCl_3$ or D_2O. Chemical shifts (δ) are reported in parts per million

(31) The formation of acylaminosulfonium ions as intermediates of Pummerer rearrangement has been already proposed: Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K.; Fujima, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405, and references cited therein. For a four membered acylaminosulfonium ion see: Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukazawa, Y. *J. Org. Chem.* **1987**, *52*, 5239.

(32) This unusual nonoxidative pathway is probably general for TFAA-promoted Pummerer rearrangement of *N*-Cbz 1,1,1-trifluoro-3-sulfinyl amines as shown in the preliminary report: Arnone, A.; Bravo, P.; Bruché, L.; Crucianelli, M.; Vichi, L.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 7301.

(33) A similar outcome was reported for various alkyl *o*-carbamoylphenyl sulfoxides, which afforded 1,2-benzisothiazole derivatives upon treatment with Lewis acids: Uchida, Y.; Oae, S. *Gazz. Chim. Ital.*, **1987**, *117*, 649. See also: Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, L. L. *Tetrahedron Lett.* **1992**, *33*, 153. For a nonoxidative Pummerer rearrangement producing β-lactams see: Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490.

(34) See ref 16, pp 18−21.

(35) In this case, the deuteration degree in the 3 position was kept at 75%, in order to better detect any change in the labeling degree during the process.

(36) For optically pure 1-(trifluoromethyl)ethylamine see: (a) Tarnow, H.; Baasner, B.; Luerssen, K.; Santel, H. J.; Schmidt, R. R. Ger. Offen. DE 3900300 A1 900712, 1990, *Chem. Abstr. 113*, 212024. (b) Tarnow, H.; Baasner, B.; Homeyer, B.; Hartwig, J. Eur. Pat. Appl., EP 323637 A1 890712, 1990, *Chem. Abstr. 112*, 98219.

(37) The unfluorinated naturally occurring analogue is contained in ergonovine (D-lysergic acid L-1-hydroxy-2-propylamide), an important ergot alkaloid with therapeutic applications.

(38) Very recently Uneyama and co-workers reported an interesting approach to enantioenriched (*R*)-3,3,3-trifluoroalanine (ee 62%) by enantioselective reduction of *N*-aryl imines of 3,3,3-trifluoropyruvic esters: Sakai, T.; Yan, F.; Uneyama, K. *Synlett* **1995**, 753.

(ppm) of the applied field. Me_4Si was used as internal standard (δ_H and $\delta_C = 0.00$) for ^1H and ^{13}C nuclei, while C_6F_6 was used as external standard ($\delta_F = -162.90$) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. Coupling constants (J) are reported in hertz (Hz). The ^1H homonuclear and the $^1H-^{19}F$ heteronuclear NOE difference experiments were performed with the decoupler on resonance and then subtracted from a control spectrum with the decoupler off resonance. The irradiation time was 4 s and the relaxation delay 8 s. The signals of the aromatic protons and of the methyl protons on the tolyl group have not been tabulated, but were always consistent with the proposed structures. $[\alpha]_D$ and $[\alpha]_{365}$ values were taken on a Jasco-Dip polarimeter. Anhydrous solvents were obtained by distillation from sodium (ethyl ether, benzene) or from CaH_2 (diisopropylamine). Anhydrous THF was distilled from sodium and benzophenone. In all other cases commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out under nitrogen. A routine workup of the reaction means that the quenched reaction mixture was extracted with ethyl acetate, the collected organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical TLC was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230−400 ASTM mesh) was employed for column chromatography. HPLC analyses were performed on a LiChrosorb Si60 (5 μm, Merck) prepacked column, and hexane and ethyl acetate HPLC-grade solvents (Merck) were used. Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Synthesis of compounds **1a**−**e** has been already described.[3]

Synthesis of [(Benzyloxycarbonyl)imino]triphenylphosphorane (2a). To a solution of trimethylsilyl azide (1.0 g, 8.7 mmol) and benzyl chloroformate (0.48 mL, 6.2 mmol) in dry benzene (10 mL) under nitrogen were added three drops of pyridine, and the solution was heated for 30 min at reflux temperature and then diluted with benzene (10 mL) and cooled to 0 °C. To the solution was slowly added a solution of triphenylphosphine (1.6 g, 6.2 mmol) in benzene (15 mL). When nitrogen evolution ceased, the mixture was stirred for 30 min at rt, and then the solvent was removed under reduced pressure. Crystallization of the residue (ethyl acetate) afforded **2a** as white crystals (2.5 g, 98% yield): R_f (1:1 hexane/ethyl acetate) 0.43; mp 101−103 °C (ethyl acetate); ^1H NMR ($CDCl_3$) 5.05 (2H, s).

Synthesis of Sulfinylenamines 3a−e. General Procedure. The synthesis of **3b** is described as example. To a stirred solution of sulfinyl ketone **1b** (0.80 g, 3.4 mmol) in dry benzene (14 mL) was added iminophosphorane **2a** (1.39 g, 3.4 mmol) under nitrogen. The mixture was refluxed for 18 h, and then the solvent was removed under reduced pressure. The residue was purified by FC (hexane/ethyl acetate from 7:3 to 3:2), giving 0.99 g of a 3:2 mixture of sulfinyl enamines (*Z*)-**3b** and (*E*)-**3b** (80% overall yield, 86.5% conversion) and 72 mg of unreacted starting material **1b** (9%).

Following the same procedure the sulfinyl enamines **3a,c**−**e** were obtained as (*Z*)-isomers (Table 1). Yields, % (conversions %) were the following: **3a**, 78 (85); **3c**, 72 (78); **3d**, 58 (70); **3e**, 10 (95).

(*Z*)-**3a**: R_f (3:1 hexane/ethyl acetate) 0.35; mp 145−147 °C (ethyl acetate); $[\alpha]^{20}_D$ 12.9 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.28 (1H, br s), 6.42 (1H, s), 5.25 (1H, d, $J = 12$ Hz), 5.19 (1H, d, $J = 12$ Hz); ^{13}C NMR ($CDCl_3$) 153.2, 142.5, 138.8, 135.0, 130.3, 129.7, 128.7, 128.6, 128.4, 125.3, 128.1 (q, $J = 3.6$ Hz), 119.7 (q, $J = 276$ Hz), 68.6, 21.5; ^{19}F NMR ($CDCl_3$) 70.5 (3F, s). Anal. Calcd for $C_{18}H_{16}F_3NO_3S$: C, 56.33; H, 4.21; N, 3.65. Found: C, 56.07; H, 4.19; N,3.69.

(*Z*)-**3b**: R_f (3:1 hexane/ethyl acetate) 0.40; mp 119−121 °C (ethyl acetate); $[\alpha]^{20}_D$ 536.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) 9.95 (1H, s), 7.06 (1H, t, $J = 55$ Hz), 5.7 (1H, s), 5.15 (2H, s); ^{13}C NMR ($CDCl_3$) 152.3, 142.8, 139.8 (t, $J = 23.8$Hz), 139.4, 135.2, 130.4, 128.6, 128.5, 128.3, 125.1, 109.5 (t, $J = 9.1$ Hz), 108.3 (t, $J = 242.7$ Hz), 67.8, 21.4; ^{19}F NMR ($CDCl_3$) 122.3 (2F, d, $J = 55$ Hz). Anal. Calcd for $C_{18}H_{17}F_2NO_3S$: C, 59.17; H, 4.69; N, 3.83. Found: C, 59.29; H, 4.73; N, 3.80.

(*E*)-**3b**: R_f (3:1 hexane/ethyl acetate) 0.20; mp 117−119 °C (ethyl acetate); $[\alpha]^{20}_D$ 70.1 (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.25 (1H, t, $J = 56$ Hz), 6.8 (1H, br s), 5.13 (2H, s); ^{13}C NMR ($CDCl_3$) 152.3, 141.8, 140.5, 135.8 (t, $J = 23$ Hz), 134.8, 130.2, 128.8, 128.7, 128.5, 124.3, 121.8 (t, $J = 6.92$ Hz), 108.4 (t, $J = 242.2$ Hz), 68.0, 21.4; ^{19}F NMR ($CDCl_3$) 120.2 (2F, m, $J = 308$, 56 and 8 Hz).

(*Z*)-**3c**: R_f (3:1 hexane/ethyl acetate) 0.30; mp 162−163 °C (ethyl acetate); $[\alpha]^{20}_D$ 156.4 (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$) 6.76 (1H, br s), 6.54 (1H, s), 5.28 (1H, d, $J = 12$ Hz), 5.22 (1H, d, $J = 12$ Hz); ^{13}C NMR ($CDCl_3$) 153.7, 142.3, 139, 135, 132.9 (t, $J = 29.2$ Hz), 130.2, 129.9 (t, $J = 3.1$ Hz), 128.8, 128.7, 128.4, 125.3, 122.3 (t, $J = 292.5$ Hz), 68.7, 21.5; ^{19}F NMR ($CDCl_3$) 59.3 (1F, d, J = 170 Hz), 60.4 (1F, d, J = 170 Hz). Anal. Calcd for $C_{18}H_{16}ClF_2NO_3S$: C, 54.07; H, 4.03; N, 3.50. Found: C, 53.21; H, 4.09; N, 3.38.

The enol ether (*Z*)-**5c** was obtained as byproduct in 4% yield: R_f (3:1 hexane/ethyl acetate) 0.35; ^1H NMR ($CDCl_3$) 6.25 (1H, s), 5.46 (1H, d, $J = 12$ Hz), 5.40 (1H, d, $J = 12$ Hz); ^{19}F NMR ($CDCl_3$) 57.9 (1F, d, $J = 170$ Hz), 58.8 (1F, d, $J = 170$ Hz).

(*Z*)-**3d**: R_f (3:1 hexane/ethyl acetate) 0.45; mp 122−125 °C (ethyl acetate); $[\alpha]^{20}_D$ 149.6 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) 6.60 (1H, s), 6.45 (1H, br s), 5.22 (1H, d, $J = 12$ Hz), 5.28 (1H, d, $J = 12$ Hz); ^{13}C NMR ($CDCl_3$) 153.5, 142.3, 138.9, 134.9, 134.8 (t, $J = 3.65$ Hz), 130.2, 128.8, 128.7, 128.3, 125.3, 118.2 (qt, $J = 287.1$ and 37.2 Hz), 68.8, 21.5; ^{19}F NMR ($CDCl_3$) 119.7 (1F, d, $J = 270$ Hz), 122.6 (1F, d, $J = 270$ Hz), 84.6 (3F, s); MS (CI, 70 eV) *m*/*z* (%) 433 (M^+, 100); Anal. Calcd for $C_{19}H_{16}F_5NO_3S$: C, 52.66; H, 3.72; N, 3.23. Found: C, 52.52; H, 3.71; N, 3.17.

The enol ether (*Z*)-**5d** was obtained as byproduct in 14% yield: R_f (3:1 hexane/ethyl acetate) 0.50; oily compound; $[\alpha]^{20}_D$ 204.2 (*c* 1.39, $CHCl_3$); ^1H NMR ($CDCl_3$) 6.30 (1H, s), 5.48 (1H, d, $J = 12$ Hz), 5.42 (1H, d, $J = 12$ Hz); ^{13}C NMR ($CDCl_3$) 148.4 (t, $J = 25$ Hz), 142.1, 140.5, 134.2, 130.4, 129.1, 128.8, 128.0, 124.1, 121.4, 77.5, 21.4; ^{19}F NMR ($CDCl_3$) 83.7 (3F, s), 119.2 (2F, s); MS (CI, 70 eV) *m*/*z* (%) 390 (M^+, 100).

(*Z*)-**3e**: R_f (3:1 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ 284.9 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) 10.24 (1H, br s), 5.42 (2H, m, $J = 46$ and 2 Hz), 5.33 (1H, s), 5.10 (2H, s); ^{19}F NMR ($CDCl_3$) 221.65 (1F, t, $J = 46$ Hz). Anal. Calcd for $C_{18}H_{18}FNO_3S$: C, 62.23; H, 5.22; N, 4.03. Found: C, 62.41; H, 5.33; N, 3.92.

Synthesis of Sulfinylenamines 4a−c. General Procedure. The synthesis of **4a** is described as example. For the synthesis of iminophosphorane **2c**, a modified Kloek−Leschinsky procedure[12] was used: a solution of trimethylsilyl azide (133 μL, 1.0 mmol) and triphenylphosphine (262 mg, 1.0 mmol) in toluene (0.5 mL) was refluxed for 4 h under nitrogen. The mixture was cooled to rt. The crude [(trimethylsilyl)imino]-triphenylphosphorane **2c** solution was added *via cannula* to a dry benzene (1.5 mL) solution of sulfinyl ketone **1a** (250 mg, 1.0 mmol). The solution was kept for 14 h at rt under nitrogen, and then the solvent was removed under reduced pressure. FC of the residue (1:1 hexane/ethyl acetate) afforded 227 mg of (*Z*)-**4a** (91% yield). Following the Kloek−Leschinsky procedure, where the iminophosphorane **2b** is generated *in situ* from **2c**, comparable results were obtained.

(*Z*)-**4a**: R_f (3:1 hexane/ethyl acetate) 0.25; $[\alpha]^{20}_D$ 458.9 (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.35 (2H, br s), 5.31 (1H, s); ^{13}C NMR ($CDCl_3$) 141.7, 141.6 (q, $J = 33.2$ Hz), 140.8, 130, 124.7, 119.9 (q, $J = 276.2$ Hz), 98 (q, $J = 3.97$ Hz), 21.23; ^{19}F NMR ($CDCl_3$) 73.0 (3F, s).

(*Z*)-**4b** (85% yield, calculated by ^1H and ^{19}F NMR of the crude): R_f (1:1 hexane/ethyl acetate) 0.31; ^1H NMR ($CDCl_3$)

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5.95 (1H, t, J = 55 Hz), 5.28 (2H, br s), 5.12 (1H, s); ^{13}C NMR ($CDCl_3$) 146.2 (t, J = 22.5 Hz), 111.0 (t, J = 243.8 Hz), 96.9 (t, J = 6.9 Hz), 20.8; ^{19}F NMR ($CDCl_3$) 123.1 (2F, dd, J = 55 and 15 Hz).

(*Z*)-**4c** (85% yield): R_f (3:1 hexane/ethyl acetate) 0.20; $[\alpha]^{20}_D$ +200.3 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 5.38 (2H, br s), 5.32 (1H, s); ^{13}C NMR ($CDCl_3$) 145.9 (t, J = 27.7 Hz), 142, 140.9, 130.2, 124.9, 122.2 (t, J = 292.3 Hz), 96.7 (t, J = 4.9 Hz), 21.4; ^{19}F NMR ($CDCl_3$) 59.7 (1F, d, J = 167 Hz), 60.9 (1F, d, J = 167 Hz).

Synthesis of the Enol Ether 5d. To a solution of sulfinyl ketone **1d** (100 mg, 0.33 mmol) in DMF (1.5 mL) were added benzyl bromide (158 L, 1.33 mmol) and K_2CO_3 (46 mg, 0.33 mmol). After stirring the mixture at rt for 24 h, water (2 mL) was added and the reaction was routinely worked-up. The residue was purified by FC (3:1 hexane/ethyl acetate), affording 39 mg of the enol ether (*Z*)-**5d** (30%).

Reaction of Primary Sulfinylenamine 4a with Benzyl Chloroformate. Synthesis of 3a. To a solution of primary β-sulfinyl enamine **4a** (100 mg, 0.4 mmol) in dry THF (3.0 mL), cooled at 78 °C was added 160 L of a 2.5 M solution of *n*-butyllithium in hexane dropwise. After 15 min at 78 °C neat benzyl chloroformate (68 mg, 0.4 mmol) was added. The resulting solution was stirred at 78 °C for 5 min, quenched at the same temperature with a saturated aqueous solution of NH_4Cl, and routinely worked-up. Purification by FC of the crude (hexane/ethyl acetate from 3:1 to 7:3) afforded 77 mg (50% yield) of *N*-Cbz β-sulfinyl enamine **3a** and 49 mg (49%) of the starting primary enamine **4a**.

Reaction of Sulfinylenamines 3a,b with Benzyl Chloroformate. Synthesis of 6a,b. **Method A**. To a solution of **3a** (160 mg, 0.42 mmol) in dioxane (1.0 mL) were added 160 L of 50% aqueous K_2CO_3 and benzyl chloroformate (150 L, 1.05 mmol). The solution was stirred at rt for 2 d (separation of KCl was observed). After evaporation of the organic solvent the residue was diluted with water (5 mL) and routinely worked-up. The crude was submitted to FC, and 167 mg of (*Z*)-**6a** (80% yield) was obtained. Under the same conditions, (*Z*)- and (*E*)-**3b** gave very poor yields of **6b** after 4 days.

Method B. To a solution of (*Z*)-**3b** (150 mg, 0.41 mmol) in DMF (1.0 mL) at 0 °C are added oil-free NaH (11 mg, 0.45 mmol) and, dropwise, after 5 min (a suspension formed), a solution of benzyl chloroformate (117 L, 0.82 mmol) in DMF (0.5 mL). The mixture was warmed to rt in 30 min and, after 40 min, the workup and purification already described for method A gave 107 mg of (*Z*)-**6b** (54% yield, 75% conversion). Under the same conditions, (*E*)-**3b** gave a partial equilibration into the (*Z*)-**3b** isomer and only traces of the expected product after several hours.

(*Z*)-**6a**: R_f (3:1 hexane/ethyl acetate) 0.4; mp 80−82 °C (ethyl acetate); $[\alpha]^{20}_D$ 3.6 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.92 (1H, s), 5.36−5.16 (4H, br m); ^{13}C NMR ($CDCl_3$) 143.3, 142.8 (q, J = 2.53 Hz), 137.9, 134.2, 130.4, 128.7, 128.6, 128.3, 125, 119.7 (q, J = 276.7 Hz), 69.9, 21.5; ^{19}F NMR ($CDCl_3$) 69.4 (3F, s). Anal. Calcd for $C_{26}H_{22}F_3NO_5S$: C, 60.34; H, 4.28; N, 2.71. Found: C, 60.18; H, 4.31; N, 2.69.

(*Z*)-**6b**: R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ 34.56 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.77 (1H, s), 6.08 (1H, t, J = 55 Hz), 5.26 (4H, s); ^{13}C NMR ($CDCl_3$) 150.6, 142.6, 139.9 (t, J = 4.5 Hz), 138.6, 135.2 (t, J = 25.3 Hz), 134.3, 130.3, 128.7, 128.6, 128.3, 124.7, 109.9 (t, J = 246 Hz), 69.7, 21.5; ^{19}F NMR ($CDCl_3$) 123.0 (d, 2F, J = 55 Hz).

Reaction of Sulfinylenamines 3a,b with Benzyl Bromide. Synthesis of 7a,b. **Method A**. To a solution of sulfinyl enamine **3a** (150 mg, 0.39 mmol) in dioxane (1.0 mL) were added 150 L of a 50% aqueous solution of K_2CO_3 and then benzyl bromide (116 L, 0.98 mmol). The resulting biphasic system was vigorously stirred at rt for 2 d (slow separation of KBr was observed). After evaporation of the organic solvent the residue was diluted with water and routinely worked-up. The crude was submitted to FC, giving pure (*Z*)-**7a** (70% yield).

(*Z*)-**7a**: R_f (3:1 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ 128.8 (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.80 (1H, s), 5.40−4.60 (4H, br m); ^{13}C NMR ($CDCl_3$) 154.0, 142.4, 138.6, 135.2, 133.2 (q, J = 35.2 Hz), 130.2, 129.6, 128.8, 128.5, 128.5, 128.4, 128.1, 124.5, 120.5 (q, J = 278.7 Hz), 68.9, 52.7, 21.4; ^{19}F NMR ($CDCl_3$) 67.6 (3F, s). Anal. Calcd for $C_{25}H_{22}F_3NO_3S$: C, 63.41; H, 4.68; N, 2.96. Found: C, 63.65; H, 4.84; N, 2.89.

Method B. To a solution of enamino sulfoxide (*Z*)-**3a** (150 mg, 0.39 mmol) in DMF (1.0 mL) were added oil-free NaH (12 mg, 0.5 mmol) and, after 5 min, benzyl bromide (116 mL, 0.98 mmol) at 0 °C. The mixture was vigorously stirred for 2 h at rt, and then the solvent was evaporated under reduced pressure. The residue was treated with water and routinely worked-up. The residue was purified by FC, giving pure benzyl derivative **7a** (65% yield).

The same A and B methods were separately performed on both (*Z*)- and (*E*)-**3b**. The method A gave (*Z*)-**7b** as single product with 64% yield (71% conversion) starting from (*Z*)-**3b**, and 41% (62%) starting from (*E*)-**3b**. The method B gave a mixture of (*Z*)- and (*E*)-**7b** (not separable by FC) with an about 3.5:1 *Z*/*E* ratio and 94% yield starting from (*Z*)-**3b**, and about 6:1 *E*/*Z* ratio, 73% yield (85% conversion) starting from (*E*)-**3b**.

(*Z*)-**7b**: R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ 107.8 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.61 (1H, s), 5.89 (1H, t, J = 55 Hz), 5.20 (2H, s), 4.95 (1H, d, J = 15 Hz), 4.73 (1H, d, J = 15 Hz); ^{13}C NMR ($CDCl_3$) 154.7, 142.1, 139.6, 139.5, 138.7 (t, J = 24 Hz), 135.8, 135.5, 130.1, 129.1, 128.8, 128.6, 128.4, 128.3, 128.1, 124.6, 110.9 (t, J = 246 Hz), 68.6, 53.3, 21.3; ^{19}F NMR ($CDCl_3$) 119.5 (2F, br signal).

(*E*)-**7b**: R_f 0.35; ^{1}H NMR ($CDCl_3$) 6.78 (1H, t, J = 54 Hz), 6.08 (1H, s), 5.18 (1H, d, J = 12 Hz), 5.10 (1H, d, J = 12 Hz), 4.74 (1H, d, J = 15 Hz), 4.58 (1H, d, J = 15 Hz); ^{13}C NMR ($CDCl_3$) 154.5, 142.0, 141.0, 139.1, 138.4 (t, J = 24.3 Hz), 136, 135.4, 130.2, 128.6, 128.5, 128.38, 128.1, 127.9, 124.5, 110.3 (t, J = 243 Hz), 68.5, 53.1, 21.4; ^{19}F NMR ($CDCl_3$) 112.9 (1F, dd, J = 56 and 307 Hz), 120.5 (1F, dd, J = 56 and 307 Hz). ^{1}H NMR spectra of compounds (*Z*)- and (*E*)-**7b** were recorded at 318 K.

Reaction of Sulfinylenamines 3a,b with Allyl Bromide. Synthesis of 8a,b. **Method A**. To a solution of enamino sulfoxide (Z)-**3b** (160 mg, 0.44 mmol) in dioxane (1.2 mL) were added 50% aqueous K_2CO_3 (160 L) and allyl bromide (160 L, 1.32 mmol). Then the above described method A was followed. Purification of the crude gave (*Z*)-**8b** in 56% yield (68.5% conversion). The same method A was performed on (*Z*)-**3a**, giving (*Z*)-**8a** in 76% yield.

Method B. To a solution of (Z)-**3b** (0.44 mmol) in DMF (1.0 mL) at 0 °C was added oil-free NaH (0.53 mmol). After 5 min the suspension was treated with allyl bromide (1.32 mmol). After 40 min at rt the reaction mixture was worked-up as described above (method B), giving (*Z*)-**8b**: 69% (73% conversion). The same method B performed on (*E*)-**3b** gave a mixture of (*E*)- and (*Z*)-**8b** (about 2:1 *E*/*Z* ratio) not separable by FC in 52% yield (63% conversion).

(*Z*)-**8a**: R_f (3:1 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ 130.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.9 (1H, s), 6.1−5.9 (1H, m), 5.35 (2H, s), 5.3−5.1 (2H, m), 4.5−4 (2H, m); ^{13}C NMR ($CDCl_3$) 142.7, 133.6 (q, J = 35.7 Hz), 131.3, 130.3, 128.6, 128.4, 128.1, 124.8, 120.8, 120.3 (q, J = 278 Hz), 68.7, 52.4, 21.5; ^{19}F NMR ($CDCl_3$) 68.6 (3F, br signal).

(*Z*)-**8b**: R_f (65:35 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ 120.35 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.69 (1H, dd, J = 0.95 and 0.91 Hz), 6.09 (1H, t, J = 55 Hz), 6.05−5.87 (1H, m), 5.4−5.1 (4H, m), 4.35−4.09 (2H, m); ^{13}C NMR ($CDCl_3$) 142.3, 139.1, 135.4, 132, 130.2, 128.6, 128.4, 128.1, 124.6, 120, 110.6 (t, J = 245.7 Hz), 68.5, 52.9, 21.4; ^{19}F NMR ($CDCl_3$) 120.5−121.5 (2F, br signal). ^{1}H NMR spectra were recorded at 306 K for (*Z*)-**8a** and 308 K for (*Z*)-**8b**.

(*E*)-**8b**: R_f 0.35; ^{1}H NMR ($CDCl_3$) 6.78 (1H, t, J = 56 Hz), 6.38 (1H, br signal), 5.83−5.6 (1H, m), 5.34−4.98 (4H, m), 4.2−4.0 (2H, m); ^{13}C NMR ($CDCl_3$) 154.0, 142.1, 139.7, 135.3, 132.1, 130.3, 128.6, 128.4, 128.2, 124.5, 119.1, 110.3 (t, J = 243.3 Hz), 68.4, 52.8, 21.4.^{19}F NMR ($CDCl_3$) 112.8 (1F, dd, J = 56 and 307 Hz), 121.2 (1F, dd, J = 56 and 307 Hz).

Reaction of Sulfinylenamines 3a,b with Methanol. Synthesis of 9a,b. To a solution of (*Z*)-**3b** (0.36 mmol) in methanol (1.2 mL) was added a catalytic amount of oil-free NaH, and the mixture was left at rt for 12 h. After evaporation

of the solvent under reduced pressure, FC of the crude (7:3 hexane/ethyl acetate) gave a 87.5% overall yield of a 1.5:1.0 mixture of the methoxy derivatives **9b**.

Under the same conditions (*Z*)-**3a** gave a 81% overall yield of about 1:1 mixture of the methoxy derivatives **9a** not separable by FC.

9a: R_f (3:1 hexane/ethyl acetate) 0.30: ^{1}H NMR ($CDCl_3$) of the mixture 6.16 and 6.13 (1H, br s), 5.14 and 5.16 (2H, s), [3.67 (1H, d, J = 14 Hz), 3.35 (1H, d, J = 14 Hz)] and 3.59 (2H, s), 3.52 and 3.50 (3H, s); ^{19}F NMR ($CDCl_3$) of the mixture 79.45 and 79.6 (3F, s). Anal. Calcd for $C_{19}H_{20}F_3NO_4S$: C, 54.93; H, 4.85; N, 3.37. Found: C, 54.26; H, 4.88; N, 2.93.

9b (major diastereoisomer): R_f (7:3 hexane/ethyl acetate) 0.41; oily compound; $[\alpha]^{20}_D$ 235.9 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.96 (1H, dd, J = 57.5 and 54 Hz), 5.13 (2H, s), 3.58 (3H, s), 3.14 (1H, d, J = 14 Hz), 3.06 (1H, d, J = 14 Hz); ^{13}C NMR ($CDCl_3$) 155, 142.5, 139.7, 135.7, 130.3, 128.6, 128.3, 128.1, 123.9, 110.5 (dd, J = 247.4 Hz), 85.8 (t, J = 25.2 Hz), 67.2, 58.2, 52.3, 21.5; ^{19}F NMR ($CDCl_3$) 135.0 (1F, dd, J = 281 and 54 Hz), 135.4 (1F, dd, J = 281 and 57.5 Hz).

9b (minor diastereoisomer): R_f 0.35; oily compound; $[\alpha]^{20}_D$ 122.5 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.72 (1H, br s), 6.59 (1H, t, J = 55.6 Hz), 5.16 (1H, J = 12.2 Hz), 5.08 (1H, J = 12.2 Hz), 3.43 (1H, J = 14 Hz), 3.32 (3H, s), 3.02 (1H, J = 14 Hz); ^{13}C NMR ($CDCl_3$) 154.2, 142.3, 140.2, 135.7, 130.3, 128.6, 128.4, 128.1, 123.8, 113.5 (t, J = 250.5 Hz), 85.5 (t, J = 24.4 Hz) 67.2, 56.9, 50.0, 21.5; ^{19}F NMR ($CDCl_3$) 132.9 (1F, dd, J = 281 and 55.6 Hz), 131.1 (1F, dd, J = 281 and 55.6 Hz).

Reaction of Sulfinylenamines 3a,b with Ammonia. Synthesis of 10a,b. To a solution of (*Z*)-**3b** (140 mg, 0.38 mmol) in THF (1 mL) was added an excess of 30% aqueous solution of ammonia (two drops). The solution was left at rt. After 15 min the solvent was removed under reduced pressure, and the residue was purified by FC (3:2 hexane/ethyl acetate), giving 134 mg of an about 1:1 mixture of the diastereoisomeric aminal derivatives **10b** (92% overall yield) not separable by FC.

Under the same conditions (*Z*)-**3a** gave a 90% overall yield of a 1:1 mixture of the aminals **10a**.

10a (first diastereoisomer): R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ 117.6 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.17 (1H, br s), 5.12 (1H, d, J = 12 Hz), 5.18 (1H, d, J = 12 Hz), 3.73 (1H, J = 13 Hz), 3.03 (1H, J = 13 Hz), 2.87 (2H, br s); ^{13}C NMR ($CDCl_3$) 154.2, 142.3, 139.4, 135.7, 130.2, 128.6, 128.4, 128.2, 123.9 (q, J = 287.3 Hz), 123.9, 70.7 (q, J = 31.2 Hz), 67.2, 59.6, 21.5; ^{19}F NMR ($CDCl_3$) 84.1 (3F, s).

10a (second diastereoisomer): R_f 0.30: $[\alpha]^{20}_D$ 159.6 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.48 (1H, br s), 5.16 (1H, d, J = 12 Hz), 5.10 (1H, d, J = 12 Hz), 3.17 (1H, J = 14 Hz), 3.06 (2H, br s), 2.97 (1H, J = 14 Hz); ^{19}F NMR ($CDCl_3$) 82.75 (3F, s).

10b: R_f 0.35: ^{1}H NMR ($CDCl_3$) of the mixture 6.98 and 6.32 (1H, br s), 6.38 and 6.14 (1H, t, J = 56 Hz), 5.11 (2H, s) and 5.13 (1H, d, J = 12 Hz), 5.05 (1H, d, J = 12 Hz), 3.48 (1H, d, J = 13.8 Hz), 3.0 (1H, d, J = 13.8 Hz), and 3.14 (1H, d, J = 14 Hz), 2.92 (1H, d, J = 14 Hz), 2.64 (only one signal, 2H, br s); ^{13}C NMR ($CDCl_3$) of the mixture 155.4 and 154.9, 142.3 and 142.0, 139.9 and 139.7, 135.8 and 135.7, 130.2 and 130.1, 128.5 and 128.5, 128.3 and 128.2, 128.0 and 128.0, 123.9 and 123.9, 113.3 (t, J = 249.4 Hz) and 112.9 (dd, J = 246 Hz), 69.8 (t, J = 22.4 Hz) and 69.7 (dd, J = 22.6 Hz), 67.0, 60.4 and 59.9, 21.4; ^{19}F NMR ($CDCl_3$) of the mixture [136.6 (1F, dd, J = 279 and 56 Hz), 134.3 (1F, dd, J = 279 and 56 Hz)] and [136.6 (1F, dd, J = 275 and 56 Hz), 131.1 (1F, dd, J = 275 and 56 Hz)].

Reaction of Sulfinylenamines 3a,b with Nitromethane. Synthesis of 11a,b. To a solution of (*Z*)-**3b** (125 mg, 0.34 mmol) in nitromethane (1 mL) was added a catalytic amount of oil-free NaH, and the mixture was kept at rt for 36 h. After evaporation of the solvent under reduced pressure, the residue was purified by FC (from 7:3 to 3:2 hexane/ethyl acetate), giving 135 mg of an about 2:1 mixture of the derivatives **11b** not separable by FC (93% overall yield).

The same reaction was performed on (*E*)-**3b** giving, after longer reaction time (48 h), about 2.7:1 ratio of the same mixture of derivatives **11b** (44% yield, 68% conversion), and on (*Z*)-**3a**, giving a 1:1 mixture of derivatives **11a** (80% overall yield) after shorter reaction time (24 h).

11a (first diastereoisomer): R_f (3:1 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ 107.2 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.23 (1H, br s), 5.48 (1H, d, J = 14 Hz), 5.24 (1H, d, J = 12 Hz), 5.16 (1H, d, J = 12 Hz), 5.00 (1H, d, J = 14 Hz), 4.04 (1H, d, J = 14 Hz), 2.82 (1H, d, J = 14 Hz); ^{13}C NMR ($CDCl_3$) 154.4, 142.7, 138.9, 135.5, 130.4, 128.7, 128.5, 128.2, 124 (q, J = 288.4 Hz), 123.9, 75, 67.8, 60.5 (q, J = 30.14 Hz), 58.1, 21.5; ^{19}F NMR ($CDCl_3$) 76.9 (3F, s).

11a (second diastereoisomer): R_f (3:1 hexane/ethyl acetate) 0.40; $[\alpha]^{20}_D$ 122.3 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.54 (1H, br s), 5.58 (1H, d, J = 13 Hz), 5.49 (1H, d, J = 13 Hz), 5.17 (1H, d, J = 12 Hz), 5.10 (1H, d, J = 12 Hz), 3.37 (1H, d, J = 14 Hz), 3.26 (1H, d, J = 14 Hz); ^{19}F NMR ($CDCl_3$) 76.4 (3F, s).

11b (major diastereoisomer): R_f (7:3 hexane/ethyl acetate) 0.36; ^{1}H NMR ($CDCl_3$) 7.17 (1H, br s), 6.36 (1H, t, J = 55.4 Hz), 5.3−5.0 (4H, m), 3.52 (1H, J = 14 Hz), 2.87 (1H, J = 14 Hz); ^{13}C NMR ($CDCl_3$) 155, 142.6, 139.2, 135.5, 130.3, 128.6, 128.4, 128.0, 123.8, 113.4 (t, J = 252 Hz), 74, 67.6, 59.3 (t, J = 23 Hz), 57.4, 21.4; ^{19}F NMR ($CDCl_3$) 128.8 (2F, d, J = 55.4 Hz); MS (EI, 70 eV) *m*/*z* (%) 426 (M^+, 18), 319 (20), 139 (16), 91 (100).

11b (minor diastereoisomer): R_f 0.36; ^{1}H NMR ($CDCl_3$) 6.72 (1H, br s), 6.71 (1H, t, J = 55.4 Hz), 5.3−5.0 (4H, m), 3.42 (1H, d, J = 14 Hz), 3.14 (1H, d, J = 14 Hz); ^{19}F NMR ($CDCl_3$) 131.6 (1F, dd, J = 288 and 55.4 Hz), 133.1 (1F, dd, J = 288 and 55.4 Hz).

Reaction of Sulfinylenamines 3a,b with Thiophenol. Synthesis of 12 and 13. To a solution of (*Z*)-**3b** (145 mg, 0.397 mmol) in THF (1.2 mL) were added thiophenol (163 mL, 1.59 mmol) and a catalytic amount of oil-free NaH. The mixture was kept at rt for 16 h, then solvent was evaporated under reduced pressure. The crude was purified by FC (from 8:2 to 65:35 hexane/ethyl acetate) giving 132 mg of an about 2:1 mixture (70% overall yield) of thiophenyl derivatives **12**.

Under the same conditions (*E*)-**3b** gave a 63% overall yield of about 2.5:1 ratio of the same mixture of derivatives **12**, while (*Z*)-**3a**, after 1 h, gave a 70% yield of vinyl sulfide **13** as the main product.

12 (major diastereoisomer): R_f (7:3 hexane/ethyl acetate) 0.62; $[\alpha]^{20}_D$ 166.1 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.15 (1H, br s), 6.96 (1H, t, J = 56 Hz), 4.96 (1H, d, J = 10 Hz), 4.86 (1H, d, J = 10 Hz), 3.28 (1H, d, J = 14 Hz), 3.19 (1H, d, J = 14 Hz); ^{13}C NMR ($CDCl_3$) 154.1, 142.3, 139.5, 138.5, 135.5, 130.2, 130.1, 128.9, 128.5, 128.3, 128.2, 123.9, 113.1 (dd, J = 256 Hz), 69.6 (dd, J = 25.6 Hz), 67.2, 58.6 (d, J = 4.9 Hz), 21.4; ^{19}F NMR ($CDCl_3$) 125.5 (1F, dd, J = 290 and 65 Hz), 132.9 (1F, dd, J = 290 and 65 Hz), MS (EI, 70 eV) *m*/*z* (%) 335 (M^+, 8), 200 (5), 149 (16), 91 (100).

12 (minor diastereoisomer): R_f (7:3 hexane/ethyl acetate) 0.53; $[\alpha]^{20}_D$ 123 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.91 (1H, t, J = 56 Hz), 6.54 (1H, br s), 5.20 (1H, d, J = 12 Hz), 5.00 (1H, d, J = 12 Hz), 3.47 (1H, d, J = 14 Hz), 3.03 (1H, d, J = 14 Hz); $_{13}$C NMR ($CDCl_3$) 153.9, 142.4, 138.0, 135.8, 131.4, 130.4, 130.3, 129.6, 129.2, 128.6, 128.4, 123.8, 114.3 (dd, J = 255.4 Hz), 69.3 (dd, J = 24.69 Hz), 67.2, 61.0, 21.5; ^{19}F NMR ($CDCl_3$) 123.3 (1F, dd, J = 290 and 65 Hz), 128.4 (1F, dd, J = 290 and 65 Hz). Anal. Calcd for $C_{24}H_{23}F_2NO_3S_2$: C, 60.61; H, 4.87; N, 2.95. Found: C, 60.62; H, 4.87; N, 2.89.

13: R_f (9:1 hexane/ethyl acetate) 0.35; ^{1}H NMR ($CDCl_3$) 7.08 (1H, s), 5.98 (1H, br s), 5.23 (2H, s); ^{13}C NMR ($CDCl_3$) 153.1, 135.6, 133.8, 132.9, 131.3, 129.5, 128.6, 128.5, 128.4, 128.3, 121.0 (q, J = 272.6 Hz), 118.7 (q, J = 35.21 Hz), 68; ^{19}F NMR ($CDCl_3$) 70.3 (s, 3F). Anal. Calcd for $C_{17}H_{14}F_3NO_2S$: C, 57.78; H, 3.99; N, 3.96. Found: C, 57.35; H, 4.28; N, 3.57.

Reductions with $NaBH_4$ and $NaBD_4$. General Procedure. To a solution of trifluoro *N*-Cbz-β-sulfinyl enamine **3a** (77 mg, 0.2 mmol) in a THF/H_2O = 4:1 mixture, cooled at 0 °C, was added $NaBH_4$ (2 equiv) portionwise and the mixture was kept under stirring for 30 min, then heated to rt and stirred for 3 h. The reaction was quenched with 1 N HCl and routinely worked up. FC of the crude (7:3 hexane/ethyl acetate) afforded 20 mg (27%) of (2*S*,R_S)-**14** and 32 mg (41%) of (2*R*,R_S)-**14**. When methanol was used as solvent an about

equimolar mixture of the diastereoisomeric *N*,*O*-disubstituted hemiaminals **9a** was recovered in almost quantitative yield after FC.

The same procedure was applied for the reduction of the primary trifluoro enamine **4a** (100 mg, 0.4 mmol); in this case the reaction was quenched with a saturated aqueous NH_4Cl solution, giving after FC (2:3 hexane/ethyl acetate 1% NEt_3), the unprotected diastereoisomeric β-sulfinyl amines **15a**. When a THF/H_2O = 4:1 mixture was used as solvent 40 mg (40%) of (2*S*,R_S)-**15a** and 40 mg (40%) of (2*R*,R_S)-**15a** were obtained. When dry THF was used as solvent, 66 mg (66%) of (2*S*,R_S)-**15a** and 17 mg (17%) of (2*R*,R_S)-**15a** were obtained.

When $NaBD_4$ was used as reducing agent with the primary trifluoro enamine **4a**, the reaction was performed in dry THF, strictly following the above described procedure: the diasteroisomeric (2-D)-1,1,1-trifluoro-3-sulfinyl amines **15a** were recovered in a (2*S*,R_S):(2*R*,R_S) = 4:1 ratio, with a substitution degree >95%.

The preparation of the perdeuterated derivative (2,3,3-D_3)-**15a** was accomplished by repeated addition and evaporation at reduced pressure (60 °C) of D_2O to the primary β-sulfinyl enamines **4a** and subsequent treatment with $NaBD_4$ in dry THF according to the previously reported procedure. Generally, after five additions and evaporations of D_2O the substitution degree in position 3 of the products **15a** was found to be >95%, while a lower 3-deuteration degree was obtained with a less intensive exchange with D_2O.

(2*S*,R_S)-**14**: R_f (7:3 hexane/ethyl acetate) 0.30; $[\alpha]^{20}_D$ 159.8 (*c* 0.92, $CHCl_3$); mp 155−157 °C (AcOEt); ^{1}H NMR ($CDCl_3$) 6.13 (1H, br d, *J* = 10 Hz), 5.15 (2H, s), 4.78 (1H, m), 3.04 (2H, m), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) 155.4, 142.4, 139.5, 135.7, 130.3, 128.6, 128.3, 128.2, 124.4 (q, *J* = 282.9 Hz), 123.9, 67.7, 55.3, 49.8 (q, *J* =32.2 Hz), 21.4; ^{19}F NMR ($CDCl_3$) 76.15 (3F, d, *J* = 7 Hz). Anal. Calcd for $C_{18}H_{18}F_3NO_3S$: C, 56.10; H, 4.71; N, 3.63. Found: C, 56.14; H, 4.74; N, 3.59.

(2*R*,R_S)-**14**: R_f (7:3 hexane/ethyl acetate) 0.25; we were not able to obtain this product sufficiently pure for a polarimetric analysis; ^{1}H NMR ($CDCl_3$) 5.52 (1H, br d, *J* = 10 Hz), 5.12 (2H, s), 4.66 (1H, m), 3.15 (2H, m), 2.38 (3H, s); ^{19}F NMR ($CDCl_3$) 77.55 (3F, d, *J* = 7 Hz).

(2*S*,R_S)-**15a**:[40] R_f (2:3 hexane/ethyl acetate, 1% NEt_3) 0.35; $[\alpha]^{20}_D$ 263.8 (*c* 0.23, $CHCl_3$); mp 126−127 °C (iPr_2O); ^{1}H NMR ($CDCl_3$) 3.81 (1H, ddd, *J* = 11.5, 7.1 and 2.6 Hz), 2.98 (1H, dd, *J* = 13.1 and 2.6 Hz), 2.71 (1H, dd, *J* = 13.1 and 11.5 Hz), 2.43 (3H, s), 1.73 (2H, br s); ^{13}C NMR ($CDCl_3$) 142.1, 140.0, 130.2, 125.7 (q, *J* = 281.4 Hz), 123.9, 58.0, 49.7 (q, *J* = 30.8 Hz), 21.4; ^{19}F NMR ($CDCl_3$) 79.38 (3F, d, *J* = 7.1 Hz). 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*R*,R_S)-**15a**: R_f (2:3 hexane/ethyl acetate 1% NEt_3) 0.30; ^{1}H NMR ($CDCl_3$) 3.67 (1H, m), 3.07−2.95 (2H, m), 2.43 (3H, s), 1.72 (2H, br signal); ^{19}F NMR ($CDCl_3$) 79.9 (3F, d, *J* = 7.2 Hz).

Reductions with Selectride. General Procedure. To a solution of the primary α-(trifluoromethyl)-β-sulfinyl enamine **4a** (250 mg, 1.0 mmol) in dry CH_2Cl_2 cooled at −20 °C was added 1 mL of a 1 M THF solution of L- or K-Selectride (1 equiv). After 5 min at −20 °C the reaction was quenched with a small excess of ethanol. The mixture was heated to rt, and the solvent was carefully removed. The procedure was repeated twice. The reaction was finally quenched with saturated aqueous NH_4Cl and routinely worked up. FC gave 150 mg (60%) of the β-sulfinyl amine (2*S*,R_S)-**15a** and 37 mg (15%) of about an equimolar mixture of the same product (2*S*,R_S)-**15a** with (2*R*,R_S)-**15a**. The same procedure was applied on the primary α-(difluorochloromethyl)-β-sulfinyl enamine **4c** (268 mg, 1.0 mmol), and after FC were obtained 170 mg (63%) of β-sulfinyl amine (2*S*,R_S)-**15c** and 30 mg (11%) of an about equimolar mixture of the same product (2*S*,R_S)-**15c** and of (2*R*,R_S)-**15c**.

(2*S*,R_S)-**15c**: R_f (2:3 hexane/ethyl acetate, 1% NEt_3) 0.40; $[\alpha]^{20}_D$ 236.9 (*c* 0.68, $CHCl_3$); mp 133−136 °C (AcOEt); ^{1}H NMR ($CDCl_3$) 3.88 (1H, m), 3.07 (1H, dd, *J* = 13.2 and 2.5 Hz), 2.67 (1H, dd, *J* = 13.2 and 11.5 Hz), 2.43 (3H, s), 1.80 (2H, br s); ^{13}C NMR ($CDCl_3$) 142.1, 140.2, 130.7 (t, *J* = 296.7 Hz), 130.2, 124.0, 59.0 (d, *J* = 1.16 Hz), 55.2 (t, *J* = 26.4 Hz), 21.4; ^{19}F NMR ($CDCl_3$) 63.75 (1F, br d, *J* = 165 Hz), 64.35 (1F, br d, *J* = 165 Hz); Anal. Calcd for $C_{10}H_{12}F_2ClNOS$: C, 44.86; H, 4.52; N, 5.23. Found: C, 45.71; H, 4.50; N, 5.24.

(2*R*,R_S)-**15c**: R_f (2:3 hexane/ethyl acetate, 1% NEt_3) 0.35; we were not able to obtain this product sufficiently pure for a polarimetric analysis; ^{1}H NMR ($CDCl_3$) 3.63 (1H, m), 3.04 (2H, m), 2.43 (3H, s), 1.77 (2H, br signal); ^{19}F NMR ($CDCl_3$) 63.8 (1F, br d, *J* = 128 Hz), 65.1 (1F, br d, *J* = 128 Hz).

Deoxygenation of (2*S*,R_S)-15a: Synthesis of (*S*)-16. Neat trimethylsilyl chloride (0.30 mL, 2.38 mmol) was added to a stirred, cooled (0 °C) solution of sulfoxide (2*S*,R_S)-**15a** (200 mg, 0.80 mmol) in acetonitrile (6 mL). After 5 min at 0 °C, NaI (0.59 g, 3.95 mmol) was added portionwise. In 5 min at the same temperature the reaction mixture became dark red. The reaction was quenched at 0 °C with an excess of saturated aqueous Na_2SO_3. A routine workup afforded a residue, which, upon FC (9:1 hexane/ethyl acetate) gave 138 mg (74%) of the β-thio amine (*S*)-**16**.

(*S*)-**16**: R_f (9:1 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ 97.36 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 3.31 (1H, dd, *J* = 14 and 3 Hz), 3.28 (1H, ddd, *J* = 10.5, 7 and 3 Hz), 2.77 (1H, dd, *J* = 14 and 10.5 Hz), 2.33 (3H, s), 1.61 (2H, br signal); ^{19}F NMR ($CDCl_3$) 78.84 (3F, d, *J* = 7 Hz). Anal. Calcd for $C_{10}H_{12}F_3NS$: C, 51.05; H, 5.14; N, 5.96. Found: C, 50.97; H, 5.12; N, 5.91.

Synthesis of (*R*)-17. To a stirred solution of the thio amine (*S*)-**16** (134 mg, 0.57 mmol) in absolute ethanol (5.0 mL) was added Raney Ni (ca. 0.5 g), and the slurry was vigorously stirred overnight under hydrogen. Raney Ni was removed by filtration on a Celite pad, and a 1 N HCl solution (1.2 mL) was added to the resulting solution. The solvent was removed under reduced pressure, affording 71 mg (86%) of the hydrochloride (*R*)-**17** as a white powder.

(*R*)-**17**: $[\alpha]^{20}_D$ 2.29 (*c* 1.06, CH_3OH), (in lit.[37a] the (*S*) enantiomer is reported to have a negative value of $[\alpha]^{20}_D$); mp > 195 °C dec; ^{1}H NMR (MeOD) 4.22 (1H, m), 1.49 (3H, d, *J* = 7 Hz); ^{13}C NMR (D_2O) 126.6 (q, *J* = 279.3 Hz), 51.3 (q, *J* = 32.9 Hz), 14.1; ^{19}F NMR (MeOD) 75.3 (3F, d, *J* = 7 Hz).

Pummerer Reaction on 14: Synthesis of (2-H)- and (2-D)-N-Cbz-3,3,3-Trifluoroalaninol (*R*)-18. All the reactions used for the synthesis of *N*-Cbz-3,3,3-trifluoroalaninol **18**, described below, were performed, without any modification, also on the corresponding deuterium substituted compound (2,3,3-D_3)-**14**. The synthesis of the latter was performed as described above for perdeuterated **15a**. Loss of deuterium was never detected during the above mentioned procedures.

To a stirred solution of (2*S*,R_S)-**14** (0.52 g, 1.4 mmol) and *sym*-collidine (0.54 mL, 4.1 mmol) in acetonitrile (10 mL) under nitrogen at 0 °C was added TFAA (0.96 mL, 6.8 mmol) was added dropwise. The reaction mixture was stirred at 0 °C and after 10 min 0.5 mL of water was added, followed by solid K_2CO_3 until pH 7 was reached. The reaction was warmed up to rt and after 15 min an excess of $NaBH_4$ (about 3 equiv) was added portionwise. After 5 min the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with AcOEt. The collected organic layers were treated twice with a 1 N HCl solution (5 mL) to remove the excess of *sym*-collidine and then washed with aqueous $NaHCO_3$. After a routine workup the residue was submitted to FC (65:35 hexane/ethyl acetate), affording 0.31 g (86%) of (*R*)-**18** as a white solid.

(*R*)-**18**: R_f (7:3 hexane/ethyl acetate) 0.25; $[\alpha]^{20}_D$ 10.9 (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 5.54 (1H, br d, *J* = 9.5 Hz), 5.14 (2H, s), 4.37 (1H, m), 3.94 (1H, br dd, *J* = 12.0 and 4.1 Hz), 3.84 (1H, br dd, *J* = 12.0 and 4.3 Hz), 2.12 (1H, br signal); ^{19}F NMR ($CDCl_3$) 75.18 (3F, d, *J* = 9 Hz); MS (EI, 70 ev) m/z (%) 263 (M^+, 15), 108 (90), 91 (100).

3,3,3-Trifluoroalaninol hydrochloride (*R*)-19. To a stirred solution of (*R*)-**18** (132 mg, 0.5 mmol) in absolute ethanol (4.0 mL), was added Raney Ni (ca. 0.4 g) and the slurry was vigorously stirred overnight at rt under hydrogen. Raney

(40) The authors have deposited atomic coordinates for compound (2*S*,R_S)-**15a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Ni was removed by filtration through a Celite pad, and a 1 N HCl solution (1.2 mL) was added to the resulting solution. The solvent was removed under reduced pressure affording 76 mg (93%) of the hydrochloride (*R*)-**19** as a white powder.

(*R*)-**19**: $[\alpha]^{20}_D$ 7.86 (*c* 0.70, EtOH); mp >145 °C dec; ^{1}H NMR (CD_3OD) 4.22−4.08 (1H, m), 4.00−3.86 (2H, m). ^{13}C NMR (CD_3COCD_3) 125.9 (q, J = 279.5 Hz), 58.8 (d, J = 2.18 Hz), 55.7 (q, J = 30.3 Hz). ^{19}F NMR (CD_3OD) 71.3 (3F, d, J = 8 Hz).

Synthesis of *N*-Cbz-3,3,3-Trifluoroalanine (*R*)-20. To a solution of *N*-Cbz-amino alcohol (*R*)-**18** (263 mg, 1.0 mmol) in 5.0 mL of a 3:2 acetone/H_2O mixture was added solid $NaIO_4$ (0.34 g, 1.6 mmol), followed by $RuO_2 \cdot xH_2O$ (30 mg, 0.22 mmol). The mixture was stirred at rt for 1 h and then quenched by addition of 5 mL of *i*-PrOH. The suspension was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The crude was dissolved in ethyl acetate (5 mL) and extracted three times with 5 mL of a 5% aqueous $NaHCO_3$ solution. The collected aqueous phases were treated with 1 N HCl until an acidic pH was reached. The milky mixture was then extracted with ethyl acetate until it became clear. The residue was purified by FC (2:3 hexane/ethyl acetate), affording 180 mg (65%) of (*R*)-**20**, as a white solid.

(*R*)-**20**: $[\alpha]^{20}_D$ −6.98 (*c* 0.83, MeOH); mp 103−105 °C (AcOEt); ^{1}H NMR (CD_3OD) 5.16 (2H, s), 4.99 (1H, q, J = 8 Hz); ^{19}F NMR(CD_3OD) 72.7 (d, J = 8 Hz).

Synthesis of *N*-Cbz-Methyl Ester 21 of 3,3,3-Trifluoroalanine 20. The crude reaction mixture of the above described $RuO_2 \cdot xH_2O$-catalyzed oxidation was dissolved in ether and treated at 0 °C with a freshly prepared ethereal diazomethane solution. The resulting solution was kept 5 min at 0 °C and then concentrated under reduced pressure. The residue was purified by FC (85:15 hexane/ethyl acetate) giving the pure methyl ester (*R*)-**21** in 65% yield, starting from the amino alcohol (*R*)-**18** (quantitative yield was obtained in the esterification step).[29]

(*R*)-**21**: $[\alpha]^{20}_D$ 8.00 (*c* 0.52, $CHCl_3$); mp 101−103 °C (AcOEt); ^{1}H NMR ($CDCl_3$) 5.63 (1H, br d, J = 7 Hz), 5.16 (2H, s), 5.06 (1H, m), 3.87 (3H, s); ^{19}F NMR ($CDCl_3$) 74.2 (d, J = 7 Hz); MS (EI, 70 ev) m/z (%) 291 (M^+, 8), 108 (90), 91 (100).

Synthesis of 3,3,3-Trifluoroalanine (*R*)-22. To a stirred solution of *N*-Cbz-3,3,3-trifluoroalanine (*R*)-**20** (75 mg, 0.27 mmol) in absolute ethanol (4.0 mL) was added about 30 mg of $Pd(OH)_2$ (Pd 20%), and the slurry was vigorously stirred for 1 h at rt under hydrogen. $Pd(OH)_2$ was removed by filtration on a Celite pad, and the solvent was evaporated under reduced pressure affording 25 mg (64%) of 3,3,3-trifluoroalanine (*R*)-**22** as a white powder.

(*R*)-**22**: $[\alpha]^{20}_D$ 15.42 (*c* 0.78, MeOH), (lit.[38] value for $[\alpha]^{20}_D$ (*c* 0.76, MeOH) of enantioenriched (*R*)-**22** (ee 62%) has been reported = +6.8); mp 205−207 °C (sublimate: lit.[29] sublimation T > 205 °C) (EtOH); ^{1}H NMR (D_2O) 4.32 (1H, q, J = 9.0 Hz); ^{13}C NMR (D_2O) 164.7, 122.1 (q, J = 280 Hz), 54.9 (q, J = 30 Hz); ^{19}F NMR (D_2O) 69.1 (3F, d, J = 9.0 Hz).

Synthesis of Trifluoroacetate Sulfenamide 23. The above described procedure of the Pummerer reaction performed on (2*S*,R_S)-**14** is followed to the point where TFAA was added. After 5 min the solvent was removed at reduced pressure and the crude submitted to FC (hexane/ethyl acetate 9:1), affording (*R*)-**23** as a yellowish oil.

(*R*)-**23**: R_f (8:2 hexane/ethyl acetate) 0.85; ^{1}H NMR ($CDCl_3$) 5.41 (1H, m), 5.35 and 5.31 (2H, br d, J = 12.2 Hz), 4.79 (1H, br dd, J = 11.6 and 9.3 Hz), 4.60 (1H, br dd, J = 11.6 and 3.9 Hz), 2.31 (3H, br s); ^{19}F NMR ($CDCl_3$) 72.11 (3F, br signal) and 75.94 (3H, br s). A partial hydrolysis to (*R*)-**24** (ca. 10%) was observed during the FC.

Synthesis of Sulfenamido Alcohol 24. The above described procedure of the Pummerer reaction performed on (2*S*,R_S)-**14** is followed to the point where solid K_2CO_3 was added. To the reaction mixture was added H_2O (5 mL) and then routinely worked-up. The residue was submitted to FC (3:1 hexane/ethyl acetate), giving (*R*)-**24** in 90% yield.

(*R*)-**24**: R_f (4:1 hexane/ethyl acetate) 0.40; $[\alpha]^{20}_D$ 34.4 (*c* 0.56, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) 5.28 (2H, br s), 5.16 (1H, ddq, J = 8.7, 8.5 and 4.6 Hz), 4.33 (1H, br dd, J = 5.8 and 5.2 Hz), 4.13 (1H, br ddd, J = 11.6, 8.7 and 5.8 Hz), 4.00 (1H, ddd, J = 11.6, 5.2 and 4.6 Hz), 2.3 (3H, br s); ^{13}C NMR ($CDCl_3$) 158.2, 132.8, 135.2, 133.6, 130.1, 128.6, 128.5, 128.2, 128.2, 124.0 (q, J = 283.5 Hz), 69.7 (t, J = 149 Hz), 62.0 (dq, J = 142 and 29 Hz), 57.9 (t, J = 145.5 Hz), 21.2 (q, J = 126.5 Hz); ^{19}F NMR (CD_3COCD_3) 67.47 (3F, br d, J = 8.5 Hz); MS (EI, 70 eV) m/z (%) 385 (M^+, 100), 341 (20), 250 (40), 123 (90), 91 (100).

Synthesis of Acetyl Derivative (25) of Sulfenamido Alcohol 24. To a THF (0.5 mL) solution of the sulfenamido alcohol (*R*)-**24** (38 mg, 0.1 mmol) were added neat acetic anhydride (22 μL, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) at rt. After 10 h at the same temperature the solvent was removed at reduced pressure. FC (4:1 hexane/ethyl acetate) of the crude afforded 38 mg (90%) of the acetyl sulfenamide (*R*)-**25**.

(*R*)-**25**: R_f (4:1 hexane/ethyl acetate) 0.50; ^{1}H NMR ($CDCl_3$) 5.32 (2H, br s), 5.28 (1H, m), 4.54 (1H, br dd, J = 11.9 and 9.6 Hz), 4.39 (1H, br dd, J = 11.9 and 4.2 Hz), 2.32 (3H, br s), 1.8 (3H, br signal); ^{13}C NMR ($CDCl_3$) 170.0, 157.8, 138.5, 135.3, 133.4, 129.7, 128.6, 128.5, 128.3, 128.2 (q, J = 281.2 Hz), 128.2, 69.7, 58.9 (q, J = 30 Hz), 58.8, 21.1, 20.3; ^{19}F NMR ($CDCl_3$) 72.46 (3F, br signal); MS (EI, 70 eV) m/z (%) 427 (M^+, 65), 383 (25), 232 (70), 91 (100).

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Supporting Information Available: Crystal data and ORTEP drawing of (2*S*,R_S)-**15a**; copies of the following spectra: ^{1}H NMR of compound (*R*)-**18**, ^{1}H and ^{19}F NMR of (*R*)-**20**, ^{13}C NMR of (*R*)-**22**, ^{1}H and ^{13}C NMR of (*R*)-**24**, (*R*)-**25**; reductions of sulfinyl enamines **3a**, **4a,c** by some hydride reducing agents are discussed and the results are reported in Table 2; selected IR characteristic bands of several compounds are collected in Table 3 (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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