Preparation of (*R*)-Fluoropyruvaldehyde *N,S*-Ketals by Highly Stereospecific Tandem Pummerer Rearrangement/1,2-*p*-Tolylthio Group Migration of (*R*)-α-(Fluoroalkyl)-*β*-sulfinylenamines†

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Fluoropyruvaldehyde *N,S*-ketals (*R*)-**2** have been prepared in good yields (up to 88%) and ee (up to 79%) from α-(fluoroalkyl)-*β*-sulfinylenamines (*R*)-(*Z*)-**1**, through a new self-immolative tandem sequential process, consisting of a Pummerer reaction, promoted by trifluoroacetic anhydride, followed by a 1,2-migration of the *p*-tolylthio group, triggered by addition of silica gel or aqueous base. Each transfer of stereogenic center, from sulfur to the α-carbon and then to the *β*-carbon, occurs with an average degree of enantioselectivity up to 94:6. *Cis* geometry between the sulfinyl and the amino groups of the starting enamine (*R*)-**1** is necessary for achieving high level of stereocontrol, since neighboring group participation by the *N*-Cbz amino group prevents the sulfinyl center from racemization promoted by trifluoroacetic anhydride. NMR studies have shown that imines **3** are intermediate products of the Pummerer rearrangement, which are stable in the reaction environment.

Introduction

Molecular recognition, which is the basis of biological activity, arises from the interactions of the substrate (drug) with the receptor site.[1] Many factors contribute to this phenomenon, like steric hindrance, dipole interactions, lipophilicity, and others, which are always closely related to the tridimensional structure of the two counterparts. For this reason the relative and absolute stereochemistry of a molecule plays a key-role in determining its biological properties, as witnessed by the dramatic difference of activity featured by two diastereoisomers and even by two enantiomers of a chiral substance.[2] On the other hand, the introduction of trifluoromethyl groups or the substitution of hydrogens or hydroxyl groups with fluorine atoms in biologically active molecules has become an important strategy for increasing the biological activity of a molecule, since fluorine substituents may assist drug absorption, modify its tissue distribution, and significantly change preferred molecular conformations.[3] Fluoro-substitution may provide excellent protection against oxidation or acid hydrolysis of sensitive groups and provide hydrogen acceptor ability.[3d,e] Furthermore, a large array of mechanism-based inhibitors show increased activity thanks to fluoro-substitution; among them, α-fluoromethyl- and *β*-fluoro-α-amino acids have been widely used as selective inhibitors of pyridoxal-dependent enzymes.[4] The application of fluorine-containing molecules as drugs, as medical diagnostics or as probes for the investigation of methabolic pathways is therefore of great interest for the scientific community. Since fluoro-compounds are practically xenobiotic, considerable efforts are directed toward the discovery of highly efficient routes to single enantiomers of selectively fluorinated molecules.[5]

A few years ago we undertook a study for finding new strategies for the stereoselective synthesis of biologically relevant chiral nonracemic fluoro-amino compounds, based on the use of the sulfinyl group as a stereocontrolling agent.[6] In a recent preliminary report we have described a new class of three-carbon chiral nonracemic fluorinated building blocks, namely fluoropyruvaldehyde-*N,S*-ketals (F-PAKs) (*R*)-**2**,[7] synthesized from α-(fluoroalkyl)-*β*-sulfinylenamines (F-SEs) (*R*)-**1** (Scheme 1), flu-

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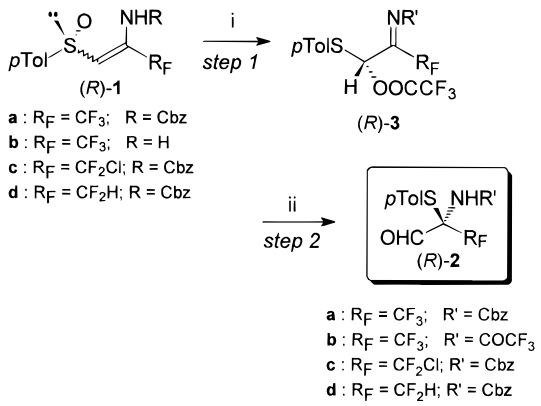
Scheme 1[a]



[a] Key: (i) TFAA, THF; (ii) procedure A: $NaHCO_3$ up to pH 7; procedure B: (1) SiO_2, (2) H_2O.

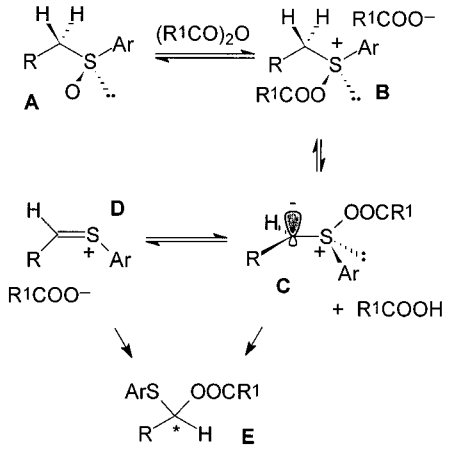
orinated templates available in enantiomerically pure form from fluoroacetic esters[8] or acids[9] as fluorine sources. The absolute stereochemistry of (+)-(*R*)-triF-PAK **2a** has been determined by X-ray analysis and its use for the stereoselective synthesis of trifluoro analogues of *Ephedra* alkaloids has been also reported in a communication.[10] It is worth noting that, to the best of our knowledge, F-PAKs (*R*)-**2** are the first examples of nonenolizable aldehydes simultaneously bearing a sulfur, a nitrogen, and a carbon atom in the α-position.[11]

An investigation of the scope, limits, and mechanism of the tandem process leading to the F-PAKs (*R*)-**2** is addressed in this study.

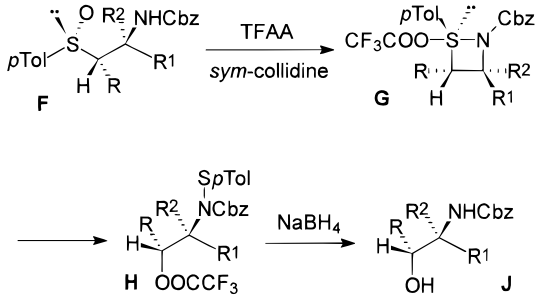
Results

The Pummerer reaction (PR) is a well-known method for the synthesis of α-substituted sulfides from the corresponding sulfoxides.[12] The "traditional" PR involves an anhydride-promoted transformation of the sulfinyl group of **A** into a trivalent sulfonium cation **B** (Scheme 2), followed by base removal of a labilized α-sulfur proton and consecutive formation of the chiral ylide **C**. This intermediate can afford directly the chiral α-substituted sulfide **E**, which is a masked aldehyde, through migration

Scheme 2. "Traditional" Pummerer Reaction



Scheme 3. "Nonoxidative" Pummerer Reaction



of the R^1COO residue, or indirectly through the achiral sulfonium cation **D**, which produces **E** by reassembling with the R^1COO^- anion.

We have recently reported that α-(fluoroalkyl)-β-sulfinylamines **F** (Scheme 3) submitted to Pummerer conditions (TFAA, *sym*-collidine) follow the so-called "nonoxidative"[13] or "interrupted"[14] pathway. The trivalent sulfonium cation formed from **F** undergoes intramolecular trapping by the nucleophilic β-nitrogen, leading to the sulfurane intermediate **G**, which spontaneously gives rise to a S_N2-type displacement of the sulfinyl residue by the trifluoroacetoxy group, with formation of the trifluoroacetoxy sulfenamide **H** (diastereoselectivity > 98:2), easily transformed into the corresponding γ-fluoro-β-amino alcohol **J**.

The unsaturated counterparts of **F**, namely F-SEs (*R*)-**1**, upon treatment with 1 equiv of TFAA in dry THF at 0 °C immediately provide an intermediate compound (Scheme 1, step 1), which, without isolation, further reacts with diluted aqueous $NaHCO_3$, or with SiO_2 at the same temperature (step 2, procedure A and B, respectively), affording the F-PAKs (*R*)-**2** as unique reaction products. These new and structurally stable molecules are produced with variable degree of enantiomeric purity depending on the experimental conditions applied. The same process occurs for F-SEs (*R*)-**1** having diverse α-fluoroalkyl residues, like CF_3, CF_2Cl, CF_2H.

In view of the potential interest in the differently fluoro-substituted F-PAKs (*R*)-**2** as chiral nonracemic building blocks for the synthesis of organofluorine compounds, we explored a large set of starting F-SEs (*R*)-**1**,

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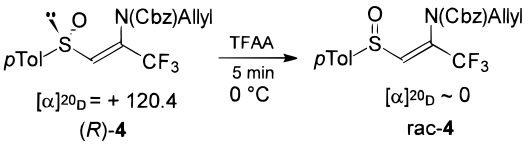
Table 1. Synthesis of β-Fluoropyruvaldehydes *N*,*S*-Ketals (*R*)-2 from α-(Fluoroalkyl)-β-sulfinylenamines (*R*)-1[a]

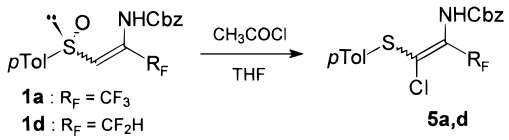
				procedure A[b]				procedure B[c]			
entry	enamine	R_f	product	$[\alpha]^{20}_D$ ($CHCl_3$)	ee (%)	yield (%)	[**1**], M	$[\alpha]^{20}_D$ ($CHCl_3$)	ee (%)	yield (%)	[**1**], M
1	(*R*)-(*Z*)-**1a**	CF_3	(+)-(*R*)-**2a**	+136.2 (*c* 0.65)	67	85	0.15	+138.6 (*c* 0.89)	69	57	0.10
2	(*S*)-(*Z*)-**1a**	CF_3	(−)-(*S*)-**2a**	−134.9 (*c* 0.68)	67	85	0.15	np	np	np	np
3[d]	(*R*)-(*Z*)-**1b**	CF_3	(+)-(*R*)-**2b**	+173.8 (*c* 0.52)	44	88	0.15	+199.9 (*c* 1.23)	52	71	0.10
4	(*R*)-(*Z*)-**1c**	CF_2Cl	(+)-(*R*)-**2c**	np	np	np	np	+185.0 (*c* 0.60)	79	70	0.10
5	(*R*)-(*Z*)-**1d**	CF_2H	(+)-(*R*)-**2d**	+193.0 (*c* 0.64)	42	86	0.25	+280.8 (*c* 0.64)	62	58	0.10
6	(*R*)-*E*-**1d**	CF_2H	(+)-(*R*)-**2d**	+23.6 (*c* 0.66)	6	86	0.30	+36.7 (*c* 0.67)	8	56	0.10

[a] Step 1 performed adding 1 equiv of TFAA to a solution of F-SE (*R*)-**1** in THF cooled at 0 °C. [b] Step 2 performed by treating the reaction mixture with 5% aqueous $NaHCO_3$ for 5 min at 0 °C. [c] Step 2 performed by treating the reaction mixture with ca. 50 mg of SiO_2 for 5 min at 0 °C. [d] 2 equiv of TFAA were used. np = not performed.

Scheme 4



Scheme 5



reaction promoters, and conditions, the most significant experiments being reported in Table 1. In all cases tested, the best yields of (*R*)-**2** were obtained when 5% aqueous $NaHCO_3$ was used in step 2, whereas better ees were obtained with SiO_2/water.

The *N*-Cbz triF-SE (*R*)-(*Z*)-**1a** provided the (+)-(*R*) enantiomer of the corresponding triF-PAK **2a** with ee up to 67% and 69% (Table 1, entry 1, procedures A and B, respectively). Obviously, the enantiomeric F-SE (*S*)-(*Z*)-**1a** afforded the triF-PAK (−)-(*S*)-**2a** (entry 2).

Reaction of the *N*-unprotected triF-SE (*R*)-(*Z*)-**1b** required 2 equiv of TFAA to reach completion, affording the *N*-trifluoroacetyl triF-PAK (*R*)-**2b** with ee up to 52% (Table 1, entry 3, procedure B). It is clear that the first equivalent of TFAA should trifluoroacetylate the unprotected nitrogen of (*R*)-(*Z*)-**1b**, and the second one should promote the rearrangement.

The highest enantioselectivity was obtained for the chlorodiF-PAK (+)-(*R*)-**2c** (79% ee), obtained in 70% yield from the *N*-Cbz chlorodiF-SE (*R*)-(*Z*)-**1c** (Table 1, entry 4, procedure B).

The diF-SE (*R*)-**1d** was available also in pure *E* form, namely with the sulfinyl and the amino groups in trans configuration, thus allowing us to check the influence of the double bond geometry on the reaction. In analogy with the other cis F-SEs, the *N*-Cbz diF-SE (*R*)-(*Z*)-**1d** produced the corresponding diF-PAK (+)-(*R*)-**2d** with good yields and ees (Table 1, entry 5, 42% procedure A, 62% procedure B).

In contrast, the trans diF-SE (*R*)-*E*-**1d** produced the diF-PAK (+)-(*R*)-**2d** with very low stereospecifity (ee 6−8%, Table 1, entry 6), although the reaction was smooth as usual.

Scale-up of these reactions (up to ca. 3 g of (*R*)-(*Z*)-**1a**) was possible, affecting neither the enantioselectivity nor the yield.

N,*N*-Diprotected F-SEs[8] (*R*)-**4** proved to be unreactive toward TFAA, under the same conditions, but were recovered completely racemized after 5 min, as witnessed by the lack of optical activity (Scheme 4).

The use of TFAA as promoter of the PR (step 1) was found to be of paramount importance for achieving an efficient formation of the F-PAKs (*R*)-**2**. Under standard conditions, other Pummerer promoters such as acetic anhydride or trimethylsilyl triflate led to recovery of starting material, or to the formation of completely different products, as observed when F-SEs (*R*)-**1a**,**d** were treated with acetyl chloride in THF (Scheme 5). By this procedure the achiral α-chlorovinyl sulfides **5a**,**d** were produced as single geometric isomers after 4 h at rt. The stereochemistries of **5** were not investigated.

To (1) gain information on the reaction mechanism,[15] (2) check the chemical and optical stability of F-PAKs (*R*)-**2**, (3) find out the best conditions to accomplish the title reaction, and (4) establish its scope and limits, further investigations, described in the following sections, were performed.

NMR Experiments for the Elucidation of the Reaction Pathway. With the goal of elucidating the reaction pathway, the F-SEs (*R*)-**1a** and (*R*)-**1d** were treated with TFAA in a NMR tube, monitoring the evolution of the system by ^1H, ^{13}C, and ^{19}F NMR. As an example we describe the results obtained for the reaction of the diF-SE (*R*)-(*Z*)-**1d**. The compound (0.1 mmol) was dissolved directly in the NMR tube in THF-d_8 and its ^1H and ^{19}F NMR spectra were recorded (Figure 1a and 2a). Then 1 equiv of neat TFAA was added to the solution via syringe at rt and new ^1H and ^{19}F NMR spectra were immediately acquired (Figure 1b and 2b). The reaction was found to be very fast, since the signals of the starting (*R*)-(*Z*)-**1d** had already completely disappeared, but, to our great delight, a product different from the final diF-PAK **2d** was detected. In the ^1H spectrum the signal of the amide proton at 9.9 ppm had disappeared, and the resonances of the methyl and aromatic hydrogens of the *p*-tolyl group shifted upfield (Figure 1b), characteristic of the sulfoxide → sulfide transformation. On these bases, the structure of the imine (*R*)-**3d** was assigned to the reaction intermediate.[16] Accordingly, the ^{19}F spectrum (Figure 2b) showed the signal of a new trifluoroacetyl group at −73.4 ppm, besides that of TFA at −74.6 ppm and the resonances of the CF_2H group at −120.7 and −123.2 ppm (broad signals due probably to the occurrence of some exchange phenomena, as the syn/anti equilibrium of the imine bond or the hindered rotation

(15) Tsuchihashi and Ogura reported a rearrangement of racemic *N*-unprotected β-methylthio β-sulfinylenamines **K** (Scheme 6), promoted by acetic anhydride in the presence of pyridine, producing the thiolesters **L**. To our knowledge no details have appeared on the mechanism of that process, which presents several analogies with the title reaction. (a) Ogura, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 1960. See also: (b) Ogura, K.; Ito, Y.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2013.

(16) The absolute stereochemistries of the intermediate imines (*R*)-**3** are confidently assigned on the basis of the mechanistic rationale discussed onward.

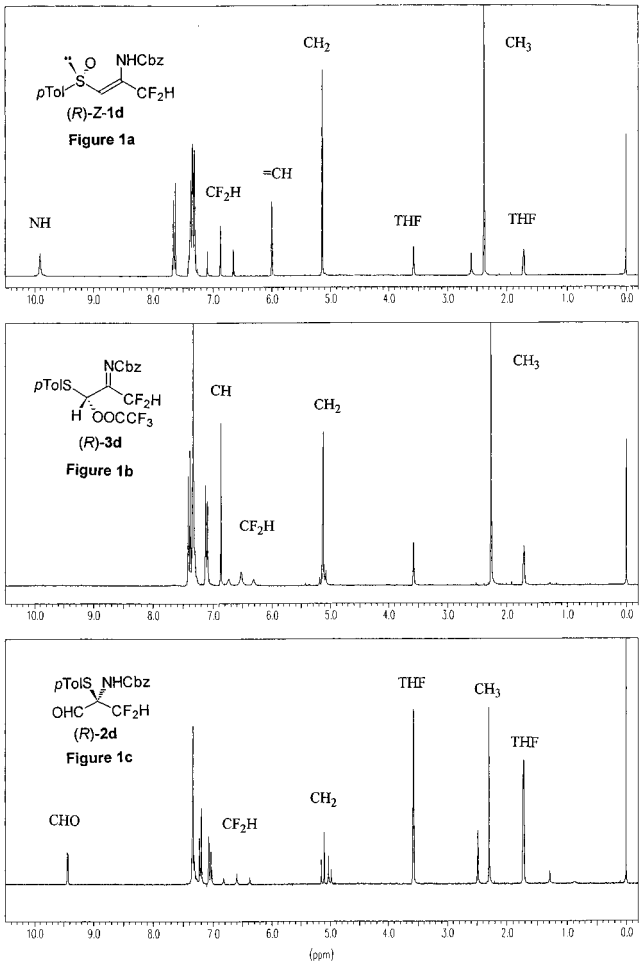


Figure 1.

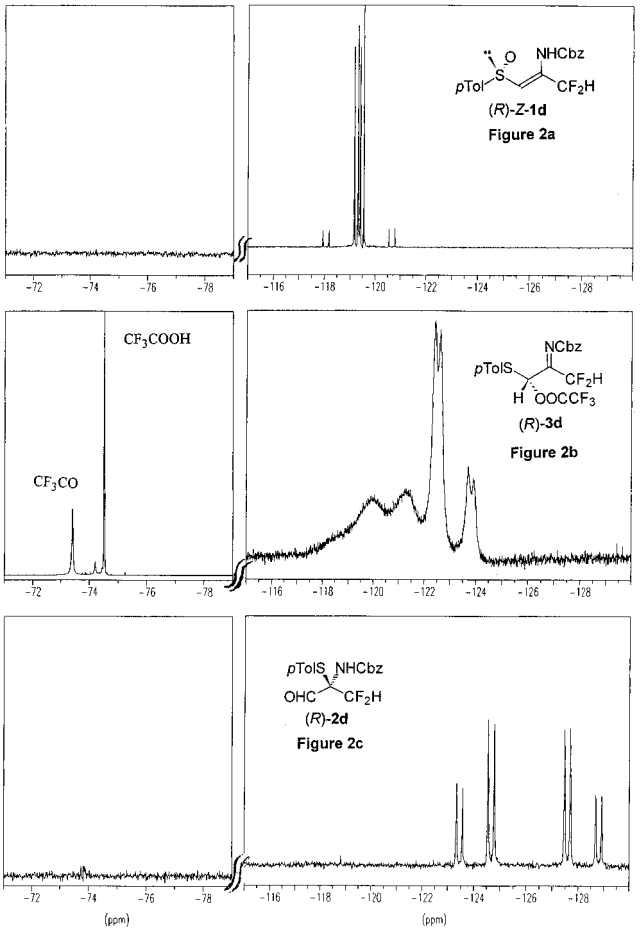


Figure 2.

around the carbamate bond, which was slow on the NMR time scale). It was also possible to obtain the carbon spectrum of (*R*)-**3d**, displaying a significant resonance at δ 80.4, which can be assigned to the methine carbon O−CH−S.

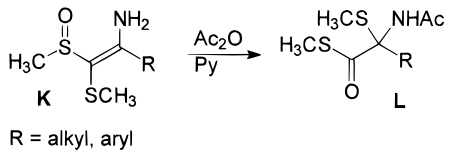
The intermediate (*R*)-**3d** was found to be stable overnight in the NMR tube at rt. Subsequently, the reaction mixture was poured in a flask, silica gel was added, followed by water, and finally the mixture was routinely worked up. ^{1}H and ^{19}F NMR spectra of the crude product in THF-d_8 were recorded (Figure 1c and 2c). The resonance of the trifluoroacetyl group was found to be absent, while the aldehyde signal at 9.45 ppm was present, confirming the expected formation of the diF-PAK (*R*)-**2d**.

An identical pathway, involving the formation of the same intermediate difluoroimine (*R*)-**3d**, was observed by monitoring by ^{1}H and ^{19}F NMR the reaction of the trans diF-SE (*R*)-*E*-**1d** with TFAA. After one night (*R*)-**3d** produced from (*R*)-*E*-**1d** was submitted to step 2, as described above, and the diF-PAK (*R*)-**2d** was obtained in ca. 60% yield. A very low ee value (ca. 8%) was measured for the isolated sample.

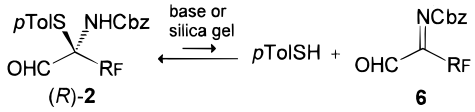
Finally, NMR monitoring of the reaction involving the triF-SE (*R*)-(*Z*)-**1a** showed the clean formation of the corresponding intermediate trifluoroimine (*R*)-**3a**, in THF-d_8 solution (see Experimental Section), and of the final triF-PAK (*R*)-**2a**, after quenching.

Chemical and Optical Stability of the Fluoropyruvaldehyde *N,S*-Ketals (*R*)-2. Despite their highly unusual molecular array, F-PAKs (*R*)-**2** are considerably stable and can be stored neat for several months at 4 °C without any decomposition or racemization, with the exception of the *N*-trifluoroacetyl triF-PAK (*R*)-**2b**, which requires lower temperature of storage. However, a strong decrease of the ee of the isolated F-PAKs (*R*)-**2**, accompanied by formation of *p*-thiocresol, was evidenced by simply increasing a few minutes the time of exposure of the reaction mixture to the aqueous $NaHCO_3$ solution (step 2), when using procedure A. In light of this observation, investigation of the chemical and optical stability of the molecules (*R*)-**2** was undertaken. Substantial optical stability was detected toward acids. For example the $[\alpha]^{20}_D$ of (*R*)-**2a** in chloroform, treated with TFA, did not change significantly after 3 d at rt. The optical stability toward silica gel is only moderate, and the extent of racemization strongly depends on the time and the way of exposure. When SiO_2 was added to a chloroform solution of (*R*)-**2a** and kept under magnetic stirring for several hours, a substantial optical stability was detected. A fast elution on a short silica gel flash chromatographic column did not remarkably affect the ee of the F-PAKs (*R*)-**2**, but a 30-min stay in the column produced ca. 50% of racemization. The optical stability of (*R*)-**2** toward bases was found to be higher in the absence of water, whereas treatment with an aqueous base, even weak, proved to have a dramatic effect. Triethylamine produced complete racemization of (*R*)-**2a** in chloroform after 3 d at rt, but the same compound in THF was completely racemized by 5% aqueous $NaHCO_3$ after ca. 30 min under stirring at rt. The proclivity of F-PAKs (*R*)-**2** to undergo racemization promoted by bases

Scheme 6



Scheme 7



or silica gel can be interpreted in terms of an elimination−addition of *p*-thiocresol, probably through the corresponding achiral imine form **6** (Scheme 7).[17] This hypothesis should account for the formation of *p*-thiocresol observed under racemization conditions.

Determination of the Ees and Assignment of the Absolute Stereochemistries. Attempts to obtain separation of the enantiomers of the F-PAKs (*R*)-**2** by using a chiral phase HPLC column (Chiralcel OB and OD) were unsuccessful, because of extended decomposition. However, ^{1}H and ^{19}F NMR analysis of pure samples of (*R*)-**2**, using the chiral shift reagent (+)-[Eu(hfc)$_3$], allowed us to assess their enantiomeric ratio.

The addition of (+)-[Eu(hfc)$_3$] to the $CDCl_3$ solution of the samples **2a**−**d** caused an extensive broadening of the whole ^{1}H spectrum, except for the signals of the *p*-tolyl protons *ortho* to the methyl group. In the case of compound (*R*)-**2a**, whose stereochemistry has been previously determined,[10] we observed that the signals of the (−)-(*S*)-enantiomer were shifted to low fields slightly more than the signals of the (+)-(*R*)-enantiomer. This behavior is common for all compounds **2a**−**d**, strongly suggesting that F-PAKs (+)-**2b**−**d** should have (*R*), while the (−)-enantiomers should have (*S*)-configuration.

Influence of Solvent, Temperature, and Concentration. Further experiments were performed in order to probe the influence of solvent, temperature, and concentration of the starting F-PAKs (*R*)-**2** on yield and enantioselectivity of the process. Since F-PAKs (*R*)-**2**, as described above, are rather stable both chemically and optically toward silica gel in the reaction environment, whereas extended racemization can be promoted by aqueous $NaHCO_3$, the following conditions were used: a solution of triF-SE (*R*)-(*Z*)-**1a** in the appropriate solvent was treated with 1 equiv of TFAA (step 1); after 1 min, silica gel was added, and the resulting mixture was stirred for 5 min (step 2); water was added, and 1 min later the reaction was routinely worked up and the product purified by flash chromatography. Each experiment was repeated at least twice, to assess its reproducibility and to achieve reliable data.

It can be seen from the data reported in Table 2 that the solvent is of paramount importance, THF being by far the best choice (entry 1). CH_2Cl_2, acetonitrile, and acetone (entries 2−4, respectively) provided much worse yields and enantioselectivity. Only acetone produced a degree of enantiocontrol comparable with that obtained in THF. Chloroform gave disappointing results, because the desired triF-PAK (*R*)-**2a** was produced only in traces, along with several unidentified byproducts. The diF-SE

(17) An alternative racemization path involves the equilibrium between the F-PAKs **2** and the α-hydroxy imine form **11** (Scheme 12).

Table 2. Influence of the Solvent on the Conversion of the *N*-Cbz α-(Trifluoromethyl)-*β*-sulfinylenamine (*R*)-1a to (*R*)-2a

entry	solvent	ee	yield, %	$[\alpha]^{20}_D$
1	THF	68%	57	+138.6 (*c* 0.89)
2	CH_2Cl_2	32%	44	+70.5 (*c* 0.22)
3	CH_3CN	59%	39	+123.0 (*c* 0.15)
4	acetone	67%	44	+135.8 (*c* 0.22)

Scheme 8. Reaction of α-(Difluoromethyl)-*β*-sulfinylenamine (*R*)-(*Z*)-1d in $CDCl_3$

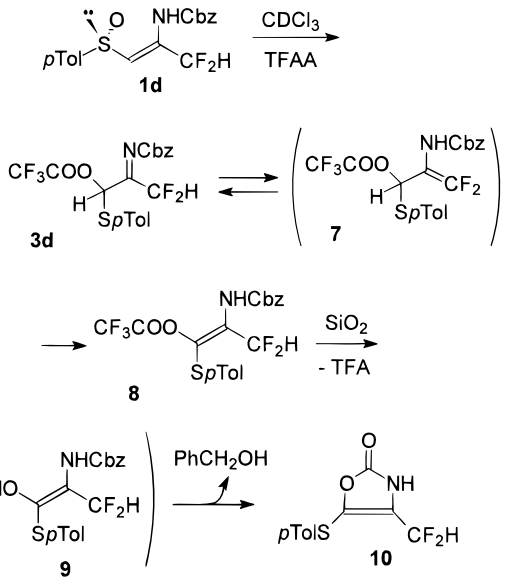


Table 3. Influence of Temperature on the Conversion of the *N*-Cbz α-(Trifluoromethyl)-*β*-sulfinylenamine (*R*)-(*Z*)-1a to (*R*)-2a in THF

entry	T (step 1 and 2), °C	ee, %	yield, %	$[\alpha]^{20}_D$
1	−30	60	61	+123.9 (*c* 0.53)
2	0	62	64	+128.6 (*c* 0.62)
3	10	63	59	+128.7 (*c* 0.73)
4	20	69	64	+141.8 (*c* 0.72)

(*R*)-(*Z*)-**1d** showed a quite similar behavior under standard conditions in the same solvents, but overnight treatment with TFAA in chloroform at rt, followed by the usual addition of silica gel, workup, and purification, produced the unexpected achiral 4-(difluoromethyl)-Δ-4-oxazol-2-one **10** (Scheme 8). The experiment was repeated in a NMR tube by dissolving 0.1 mmol of (*R*)-(*Z*)-**1d** in $CDCl_3$ and adding 1.1 equiv of neat TFAA to the solution at rt.

The intermediate imine **3d** immediately formed, in a mixture with a second compound, probably the chiral tautomeric enamine form **7**. However, the structure of **7** was not unequivocally determined, because of the complexity of the spectra. After one night at rt, **3d** was found to be completely transformed into the corresponding achiral enamine tautomer **8** (see Experimental Section). After solvent evaporation, the crude was charged in a flash chromatographic column. By action of silica gel, the trifluoroacetyl group was cleaved and the resulting intermediate **9** produced the 4-(difluoromethyl)-Δ-4-oxazol-2-one **10** and benzyl alcohol through spontaneous intramolecular cyclization.

The effect of temperature was investigated by means of some experiments performed on the conversion of triF-SE (*R*)-(*Z*)-**1a** to (*R*)-**2a** between −30 °C and rt (Table 3), using THF as solvent and keeping constant all the other

Table 4. Influence of Concentration of *N*-Cbz α-(Trifluoromethyl)-*β*-sulfinylenamine (*R*)-(*Z*)-1a on the Conversion to (*R*)-2a in THF

entry	concn, M	ee, %	yield, %	$[\alpha]^{20}_D$
1	0.02	65	64	+131.1 (*c* 0.73)
2	0.1	62	64	+128.6 (*c* 0.62)
3	0.2	55	52	+112.2 (*c* 0.62)

experimental factors (amount of reagents, concentration of the starting F-SE, purification procedure). The best result both in terms of ee and yield was obtained at rt (entry 4), while the first three entries show that the enantioselectivity decreased proportionally with decreasing temperature.

An investigation of the influence of the concentration of the starting F-SEs (*R*)-(*Z*)-**1a** was addressed next, using THF as solvent under the same conditions described above (Table 4). A remarkably favorable "dilution effect" was experienced, and a clear-cut decrease of both yield and ee occurred when the concentration of (*R*)-(*Z*)-**1** was increased from 0.02 M (entry 1) to 0.2 M (entry 3).

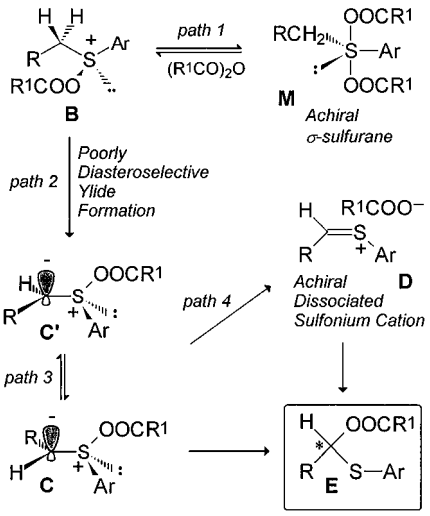
Discussion

From the above-described experiments it clearly appears that the F-PAKs (*R*)-**2** are produced from the corresponding F-SEs (*R*)-**1** through an unprecedented self-immolative tandem sequential process (Scheme 1),[18] consisting of a PR promoted by TFAA which produces the imine (*R*)-**3** (step 1), followed by a 1,2-migration of the *p*-tolylthio group, triggered by addition of aqueous $NaHCO_3$ or silica gel (step 2). This reaction occurs with an unusually high level of stereoselection, given the acyclic nature of the substrates. In fact, though we have not been able to determine the enantioselectivity of the single steps, it can be calculated that each transfer of a stereocenter features an average degree of stereoselectivity up to 94:6, as observed for the chlorodiF-PAK (*R*)-**2c**, obtained with 79% ee. With the current state of knowledge, the influence of solvent and temperature (Tables 2 and 3) is not easy to rationalize, but the improvement of both yield and enantioselectivity (Table 4) obtained upon dilution of the starting F-SEs (*R*)-(*Z*)-**1** strongly suggests that the whole process should have an intramolecular character. To get a clear picture of the reaction, it can be useful to focus the attention on the stereochemical aspects of each step.

Step 1: the Pummerer rearrangement. In the PR the stereogenic sulfinyl group is reduced to sulfenyl and the stereocenter shifts to the vicinal α-carbon (Scheme 9). When an anhydride $(R^1CO)_2O$ is used as a promoter, the degree of stereoselectivity depends on the stereospecifity of the migration of the R^1COO group. Despite their widespread use in synthesis, only a few examples of stereoselective Pummerer-type reactions have been reported so far.[19] Four distinct "racemization paths" can be held responsible for the loss of stereochemical information.

The first cause, in the order of events but probably also for importance, is the racemization of the sulfinyl stereocenter (*path 1*). It is generally believed that epimerization occurs via formation of an achiral *σ*-sulfurane (**M**),[20] this problem being particularly serious with highly reactive anhydrides, like TFAA.[21]

Scheme 9. General Paths for the Loss of Stereochemical Information in the Pummerer Reaction



Stereoselective deprotonation of the α-hydrogen atom of the chiral trivalent sulfonium cation **B**, formed from the starting sulfoxide **A** and TFAA (Scheme 2), plays a key role in determining the stereoselection of the PR.[22] Formation of the ylide **C** having a trans relationship between the most sterically demanding R and Ar groups, through removal of the *pro-S* proton, is favored over the cis ylide **C′**. A nonstereoselective deprotonation (*path 2*) or interconversion between the acyclic chiral ylides **C** and **C′** (*path 3*)[23] should produce a nonstereoselective PR. Finally, the formation of a free achiral sulfonium cation **D** from the sulfonium ylide **C** through S−O bond breaking, followed by random recombination, should afford a racemic final product **E** (*path 4*).[12]

To understand the reasons for the uncommonly high stereocontrol of our reaction, three items should be kept in mind: (1) *N*,*N*-diprotected F-SEs such as (*R*)-**4** (Scheme 4) do not give rise to the rearrangement when treated

(18) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 137. (b) Tietze, L. F. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 115.

(19) (a) Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 303 and references therein. (b) Harwood, L. M.; Lilley, I. A. *Synlett* **1996**, 1010. (c) Abe, H.; Itani, J.; Masunari, C.; Kashino, S.; Harayama, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1197. (d) Craig, D.; Daniels, K.; MacKenzie, A. *Tetrahedron* **1993**, *49*, 11263. (e) Ikeda, M.; Kosaka, K.; Sakakibara, M.; Okano, M. *Heterocycles* **1993**, *35*, 81. (f) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Ohishi, H. *J. Am. Chem. Soc.* **1994**, *116*, 5116. (g) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935. (h) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641 and references therein. (i) Wolfe, S.; Kazmaier, P. M.; Auksi, H. *Can. J. Chem.* **1979**, *57*, 2404. (j) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518. (k) Masuda, T.; Numata, T.; Furukawa, N.; Oae, S. *Chem. Lett.* **1977**, 903. (l) McCormick, J. E.; McElhinney, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 93 and references therein.

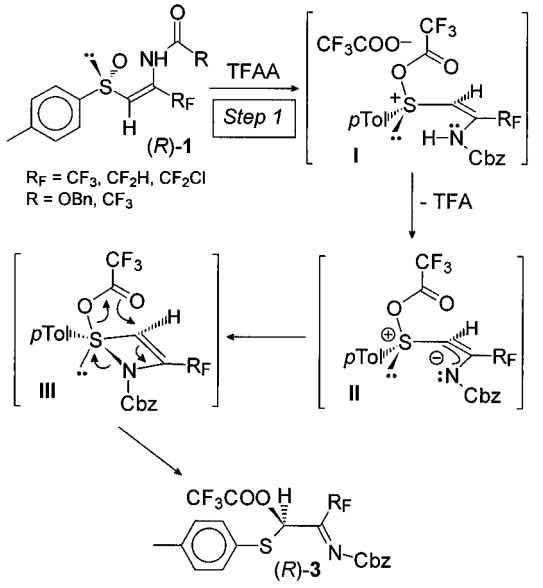
(20) See ref 19a and references therein. See also: (a) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, *18*, 1337.

(21) DCC has been used as a scavenger of acyloxy anions, sometimes producing a remarkable improvement of stereoselection, but also a dramatic lowering of yields: (a) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1976**, *B30*, 219. (b) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, *20*, 1869. (c) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257. (d) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266. (e) Oae, S., Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 270.

(22) The deprotonation step of the PR has been elegantly studied by Kita and Shibata, who used *O*-silylated ketene acetals for achieving excellent stereocontrol: Kita, Y.; Shibata, N. *Synlett* **1996**, 289 and references therein.

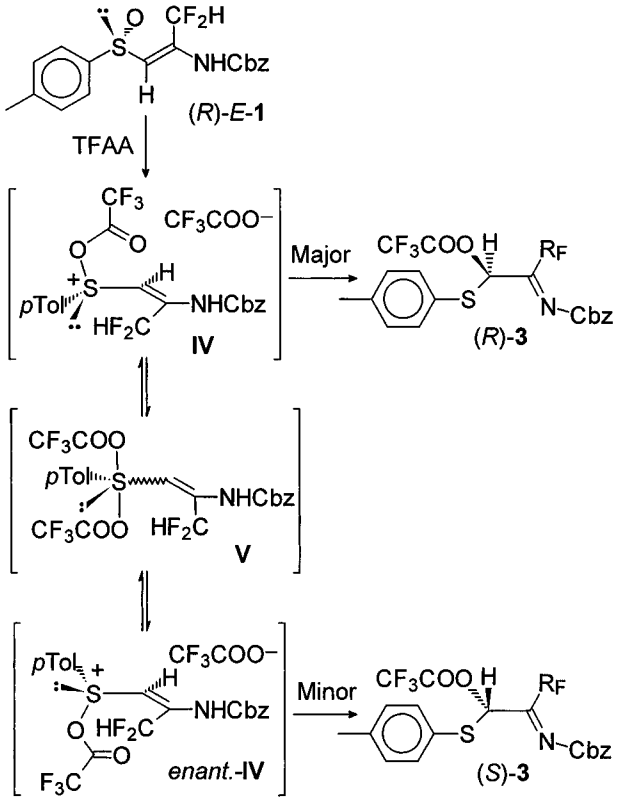
(23) For a discussion on this eventuality see: Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* **1994**, *35*, 9733 and references therein.

Scheme 10. Step 1, the Pummerer Reaction of *cis* F-SEs (*R*)-(*Z*)-1



with TFAA, but racemize completely within a few minutes; (2) the same intermediate difluoroimine **3d** (Scheme 1) is cleanly produced from both the diF-SEs *E*- and *Z*-(*R*)-**1d**, as clearly shown by the NMR experiments described above, but (3) cis geometry of the enamine double bond is strictly necessary for achieving high stereoselectivity. All this evidence points to the fact that the NHCbz group plays a key role in the step 1 of the tandem process, namely the PR, preventing TFAA-promoted racemization of the sulfinyl stereocenter,[24] as well as allowing an efficient transfer of the stereochemical information from the sulfinyl group to the α-stereogenic center. In the mechanism proposed (Scheme 10) the "usual" trivalent trifluoroacetoxysulfonium salt **I** should forms by action of TFAA on the F-SEs (*R*)-(*Z*)-**1**. Loss of TFA from **I** produces the chiral ylide **II**. An attractive interaction between the positive sulfur and the negatively charged nitrogen atom immediately locks the conformation of **II**, which might be also conceived as a highly reactive four-membered sulfurane **III**,[25] thus preventing the formation of an achiral sulfurane like **M** (Scheme 9, *path 1*), that would occur through addition of a second trifluoroacetoxy anion to the sulfonium cation **I**.[26] The electron-poor character of **II** and **III**, due to the electron-withdrawing effect of the CF_3 and NCbz groups, and the stabilizing delocalization of the negative charge of the ylide **II**, should strongly disfavor the formation of the corresponding achiral sulfonium cation (see compound **D**, Scheme 9, *path 4*),[27] leading to a highly stereospecific migration of the trifluoroacetoxy group from the sulfur to the *si* face of the C-1 position.

Scheme 11. Step 1, the Pummerer Reaction of *trans* diF-SEs (*R*)-*E*-1d



On the contrary, the sulfur and the nitrogen atoms of the diF-SE (*R*)-*E*-**1d** are far away and cannot interact (Scheme 11). For this reason all racemization paths described in Scheme 9 can be in principle operating, though in the light of the discussion above, racemization of the sulfinyl stereocenter through formation of the achiral sulfurane **V** (*path 1*) should be the main event.

Step 2: the 1,2-*p*-tolylthio group migration. The intermediate imines (*R*)-**3** formed in step 1 (Scheme 1) are perfectly stable in the reaction environment (THF, 1 equiv of TFA), as clearly demonstrated by the NMR experiments. Formation of the F-PAKs (*R*)-**2** is triggered by the addition of SiO_2 or aqueous $NaHCO_3$ which are able to cleave the trifluoroacetyl group,[28] leading to the formation of the transient α-hydroxy α-*p*-tolylthio imine (*R*)-**11** (Scheme 12). The latter should immediately undergo 1,2-migration of the *p*-tolylthio group, which should occur in suprafacial fashion through the five-membered cyclic conformation having a hydrogen bond between the hydroxy and the imino functions, as already proposed for cyclic analogues of (*R*)-**11**.[29] Step 2 can be formally considered an α-hydroxy-imine/α-amino-aldehyde rearrangement, which is known to be an equilibrium process, usually requiring high temperature and prolonged heating to reach a satisfactory advancement toward the aldehyde form. In this case the equilibrium is strongly shifted toward the α-amino-aldehyde form (*R*)-**2** even at low temperature, probably because of the strong stabilization of the sp^3 *N*,*S*-ketal carbon induced by the electron-withdrawing fluoroalkyl group.[30]

(24) For some examples of neighboring group participation by amino functions under Pummerer conditions see: (a) Sharma, A. K.; Ku, T.; Dawson, A. D.; Swern, D. *J. Org. Chem.* **1975**, *40*, 2758. (b) Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukuzawa, Y. *J. Org. Chem.* **1987**, *52*, 5239. (c) Uchida, Y.; Oae, S. *Gazz. Chim. Ital.* **1987**, *117*, 649. (d) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405. See also ref 19i.

(25) For stable four-membered cycles such as **III** see: Tornus, I.; Schaumann, E.; Mayer, R.; Adiwidjaja, G. *Liebigs Ann.* **1995**, 1795.

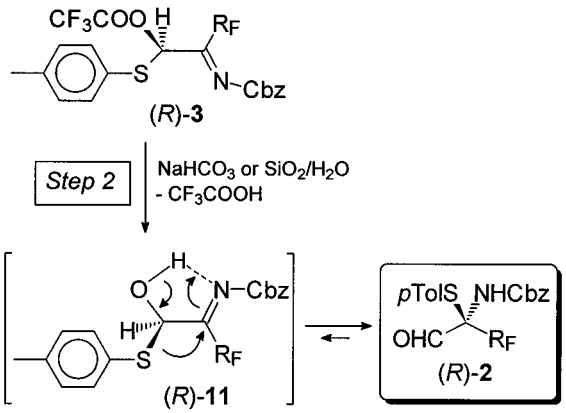
(26) We thank Prof. Józef Drabowicz (Polish Academy of Sciences, Lodz, Poland) who suggested to us that the low enantioselectivity featured by the diF-PAK (*R*)-*E*-**1d** could have been due to racemization of the sulfinyl stereocenter by action of TFAA.

(27) See ref 12b, p 388.

(28) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: London: 1991.

(29) (a) Stevens, C. L.; Hanson, H. T.; Taylor, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2769. (b) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 6647 and references therein.

Scheme 12. Step 2, the 1,2-*p*-Tolylthio Group Migration



Conclusions

In summary, we have presented the synthesis of fluoropyruvaldehyde *N*,*S*-ketals (*R*)-**2**, new fluorinated chiral nonracemic building blocks, through an unprecedented highly stereoselective tandem sequential PR/1,2-*p*-tolylthio group migration. The reaction pathway has been now elucidated and further improvements could be achieved through a careful screening and choice of reagents and conditions. The work currently in progress by means of chemometric methods should hopefully lead to a fully optimized protocol in the next future. Furthermore, the highly efficient transfer of stereochemical information here described, and similar results regarding the stereospecific "nonoxidative" PR of α-(fluoroalkyl)-*β*-sulfinylamines **F** (Scheme 3),[13] suggest a new strategy for useful applications of the PR in asymmetric synthesis: a properly located NHCbz function can prevent a sulfinyl group, submitted to Pummerer conditions, from racemization and produce a highly stereoselective process via stereospecific formation of a chiral sulfurane intermediate. Further studies on the exploitation of this methodology are currently in progress.

Experimental Section

General Procedure. ^{1}H, ^{19}F, and ^{13}C nuclear magnetic resonance samples were prepared as dilute solutions in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and $\delta_C = 0.00$) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard ($\delta_F = -162.90$) for ^{19}F nuclei. Ees have been determined by ^{1}H and ^{19}F NMR analysis of pure samples of F-PAKs (*R*)-**2**, by using the chiral shift reagent (+)-[Eu(hfc)$_3$] in $CDCl_3$ solution. 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 in nitrogen atmosphere. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (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 as a reagent (step 2, procedure B) and for flash column chromatography (FC). Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano).

Preparation of the α-(Fluoroalkyl)-*β*-sulfinylenamines (F-SEs) (*R*)-1.

Compounds (*R*)-**1a**−**d** were prepared according to the procedure described in the literature.[8]

(*R*)-(*Z*)-**1a**: R_f (3:1 hexane/ethyl acetate) 0.35; mp 145−147 °C (ethyl acetate); $[\alpha]^{20}_D$ −12.9 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 153.18, 142.5, 138.77, 135.04, 130.3, 129.7, 128.7, 128.6, 128.38, 125.3, 128.15 (q, J = 3.6 Hz), 119.74 (q, J = 276 Hz), 68.6, 21.5; ^{19}F NMR ($CDCl_3$) δ −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.

(*R*)-(*Z*)-**1b**: R_f (3:1 hexane/ ethyl acetate) 0.25; $[\alpha]^{20}_D$ +458.9 (*c* 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.35 (2H, br s), 5.31 (1H, s); ^{13}C NMR ($CDCl_3$) δ 141.75, 141.56 (q, J = 33.2 Hz), 140.8, 130, 124.7, 119.94 (q, J = 276.2 Hz), 98 (q, J = 3.97 Hz), 21.23; ^{19}F NMR ($CDCl_3$) δ −73.0 (3F, s).

(*R*)-(*Z*)-**1c**: R_f (3:1 hexane/ethyl acetate) 0.30; mp 162−163 °C (ethyl acetate); $[\alpha]^{20}_D$ −156.4 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 153.7, 142.3, 139, 135, 132.9 (t, J = 29.2 Hz), 130.2, 129.86 (t, J = 3.1 Hz), 128.76, 128.74, 128.36, 125.3, 122.35 (t, J = 292.5 Hz), 68.74, 21.5; ^{19}F NMR ($CDCl_3$) δ −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.

(*R*)-(*Z*)-**1d**: R_f (3:1 hexane/ethyl acetate) 0.40; mp 119−121 °C (ethyl acetate); $[\alpha]^{20}_D$ +536.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.95 (1H, s), 7.06 (1H, t, J = 55 Hz), 5.7 (1H, s), 5.15 (2H, s); ^{13}C NMR ($CDCl_3$) δ 152.34, 142.77, 139.8 (t, J = 23.8 Hz), 139.41, 135.25, 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 ($CDCl_3$) δ −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.

(*R*)-*E*-**1d**: R_f (3:1 hexane/ethyl acetate) 0.20; mp 117−119 °C (ethyl acetate); $[\alpha]^{20}_D$ +70.1 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, t, J = 56 Hz), 6.8 (1H, br s), 5.13 (2H, s); ^{13}C NMR δ ($CDCl_3$) 152.29, 141.8, 140.5, 135.76 (t, J = 23 Hz), 134.8, 130.25, 128.77, 128.72, 128.5, 124.32, 121.78 (t, J = 6.92 Hz), 108.4 (t, J = 242.2 Hz), 68.05, 21.4; ^{19}F NMR ($CDCl_3$) δ −120.2 (2F, m, J = 308, 56 and 8 Hz).

Synthesis of the Fluoropyruvaldehyde *N*,*S*-Ketals (*R*)-2. Procedure A. Step 1. To a stirred 0.15 M solution of *N*-Cbz triF-SE (*R*)-(*Z*)-**1a** (0.38 g, 1 mmol) in dry THF, cooled at 0 °C, was added neat TFAA (1 mmol, 0.14 mL) via syringe and left 1 min under stirring. TLC monitoring showed the immediate disappearance of (*R*)-**1**, with the formation of a unique spot at much higher R_f (0.45 in *n*-hexane/AcOEt 85:15).

Step 2. A 5% $NaHCO_3$ aqueous solution was added at 0 °C, until neutral pH was reached, and the resulting solution was left 5 min under stirring. The aqueous layer was extracted with AcOEt. The collected organic phases dried over anhydrous sodium sulfate were filtered, and the solvent was removed under reduced pressure. FC of the crude reaction mixture on a short silica gel column afforded 0.32 g (85%) of triF-PAK (*R*)-**2a**, having $[\alpha]^{20}_D$ +136.2 (*c* 0.65, $CHCl_3$) and ee 67%.

Procedure B. Step 1. A 0.1 M solution of (*R*)-(*Z*)-**1a** (0.38 g, 1 mmol) was used, following the same protocol described for procedure A.

Step 2. Silica gel (ca. 0.4 g) was added in one portion at 0 °C, and the resulting mixture was vigorously stirred for 5 min at the same temperature. Then water (ca. 10 mL) was added at 0 °C, and the phases were immediately separated. The aqueous layer was extracted with AcOEt. The collected organic phases dried over anhydrous sodium sulfate were filtered, and the solvent was removed under reduced pressure. FC of the crude reaction mixture on a short silica gel column afforded 0.22 g (57%) of triF-PAK (*R*)-**2a**, having $[\alpha]^{20}_D$ +138.6 (*c* 0.89, $CHCl_3$) and ee 69%.

(*R*)-**2a**: yellowish oil; R_f 0.45 (85:15 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.37 (1H, q, J_{FH} = 1.7 Hz), 7.43−7.32 (5H, m), 7.20 (2H, d, J = 8 Hz), 7.01 (2H, d, J = 8 Hz), 5.53 (1H, br s), 5.20 (1H, d, J = 12 Hz), 5.07 (1H, d, J = 12 Hz), 2.32 (3H, s); ^{19}F NMR ($CDCl_3$) δ − 70.45 (q, J_{HF} = 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 183.0 (q, J_{CF} = 1.8 Hz), 153.3, 141.7, 138.1, 135.3, 130.3,

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128.8, 128.7, 122.7 (q, J_{CF} = 287 Hz), 120.7, 72.8 (q, J_{CF} = 28.9 Hz), 67.9, 21.4; MS (EI, 70 eV) *m*/*z* (%) 383 (M^+, 8), 124 (35), 91 (100). Anal. Calcd for $C_{18}H_{16}NO_3F_3S$: C, 56.39; H, 4.21; N, 3.65. Found: C, 56.49; H, 4.30; N, 3.50.

(*R*)-**2b**: for yields, $[\alpha]^{20}_D$, and ees see Table 1; yellowish oil; R_f 0.63 (80:20 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.39 (1H, q, J_{HF} = 1.2 Hz), 7.25 (2H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 6.99 (1H, br signal), 2.37 (3H, s); ^{19}F NMR ($CDCl_3$) δ −68.9 (3F, d, J_{HF} = 1.2 Hz), −76.8 (3F, d, J_{HF} = 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 181.9 (q, J_{CF} = 2.5 Hz), 155.3 (q, J_{CF} = 38.5 Hz), 142.7, 137.9, 130.8, 128.7, 122.3 (q, J_{CF} = 287.1 Hz), 115.1 (q, J_{CF} = 289.2 Hz), 72.1 (q, J_{CF} = 30.2 Hz), 21.4; MS (EI, 70 eV) *m*/*z* (%) 345 (M^+, 13), 317 (18), 316 (10), 123 (100), 91 (35); FT IR (cm^{-1}) 3344, 1755, 1728, 1523, 1275, 1170. Anal. Calcd for $C_{12}H_9NO_2F_6S$: C, 41.75; H, 2.63; N, 4.06. Found: C, 41.60; H, 2.77; N, 3.98.

(*R*)-**2c**: for yields, $[\alpha]^{20}_D$, and ees see Table 1; solid; R_f 0.46 (80:20 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.40 (1H, s), 7.44−7.32 (5H, m), 7.22 (2H, d, J = 8 Hz), 7.01 (2H, d, J = 8 Hz), 5.65 (1H, br s), 5.22 (1H, d, J = 12 Hz), 5.08 (1H, d, J = 12 Hz), 2.32 (3H, s); ^{19}F NMR ($CDCl_3$) δ −54.6 (1F, d, J_{FF} = 168 Hz), −58.2 (1F, d, J_{FF} = 168 Hz); ^{13}C NMR ($CDCl_3$) δ 183.1, 153.3, 141.6, 138.2, 135.5, 130.3, 128.8, 128.7, 128.6, 127.9, (dd, J_{CF} = 299 and 306 Hz), 121.7, 68.1, 21.3; MS (EI, 70 eV) *m*/*z* (%) 399 (M^+, 4), 371 (4), 262 (12), 244 (18), 124 (100), 91 (100); FT IR (cm^{-1}) 3372 (br), 1721, 1494, 1245. Anal. Calcd for $C_{18}H_{16}NO_3F_2ClS$: C, 54.07; H, 4.03; N, 3.50. Found: C, 54.15; H, 4.05; N, 3.47.

(*R*)-**2d**: for yields, $[\alpha]^{20}_D$, and ees see Table 1; white solid, the racemate could be crystallized from diisopropyl ether: mp 81−82 °C; R_f 0.67 (80:20 *n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 9.49 (1H, s), 7.48−7.32 (5H, m), 7.07 (2H, d, J = 8 Hz), 6.95 (2H, d, J = 8 Hz), 6.90 (1H, t, J_{HF} = 55 Hz), 5.64 (1H, br s), 5.22 (1H, d, J = 12 Hz), 4.98 (1H, d, J = 12 Hz), 2.30 (3H, s); ^{19}F NMR ($CDCl_3$) δ −132.6 (1F, dd, J_{HF} = 55 Hz and J_{FF} = 290 Hz), −122.1 (1F, dd, J_{HF} = 56 Hz and J_{FF} = 290 Hz); ^{13}C NMR ($CDCl_3$) δ 183.2 (t, J_{CF} = 4 Hz), 153.7, 141.3, 137.9, 135.5, 130.2, 128.9, 121.2, 113.4 (dd, J_{CF} = 247.6 and 252.4 Hz), 73.2 (t, J_{CF} = 23 Hz), 67.6, 21.4; MS (EI, 70 eV) *m*/*z* (%) 365 (M^+, 4), 124 (35), 91 (100); FT IR (cm^{-1}) 3372 (br), 1721 (br), 1494, 1245. Anal. Calcd for $C_{18}H_{17}NO_3F_2S$: C, 59.17; H, 4.69; N, 3.83. Found: C, 59.48; H, 4.85; N, 3.58.

When step 1 was performed in a NMR tube, the intermediate imines (*R*)-**3** formed immediately after addition of TFAA to a THF-d_8 solution of (*R*)-(*Z*)-**1a**,**d** and (*R*)-*E*-**1d** (ca. 0.1 M), at rt. These compounds are substantially stable after 48 h at rt in the reaction environment.

(*R*)-**3a**: ^{1}H NMR (THF-d_8) δ 7.39 (2H, d, J = 8 Hz), 7.38−7.28 (5H, m), 7.15 (2H, d, J = 8 Hz), 6.91 (1H, s), 5.20 (1H, d, J = 12 Hz), 5.10 (1H, d, J = 12 Hz), 2.27 (3H, s); ^{19}F NMR (THF-d_8) δ −67.0 (3F, br s), −73.4 (3F, s); ^{13}C NMR (THF-d_8) δ 157.8, 155.5 (q, J_{CF} = 45.8 Hz), 152.2 (br signal), 141.9, 136.5, 135.7, 130.9, 129.3, 129.1, 124.5 (br signal), 118.4 (q, J_{CF} = 281 Hz), 115.0 (q, J_{CF} = 285 Hz), 80.3, 69.5, 21.0.

(*R*)-**3d**: ^{1}H NMR (THF-d_8) δ 7.40 (2H, d, J = 8 Hz), 7.38−7.30 (5H, m), 7.12 (2H, d, J = 8 Hz), 6.87 (1H, s), 6.53 (1H, t, J_{HF} = 53.5 Hz), 5.17 (1H, d, J = 12.3 Hz), 5.11 (1H, d, J = 12.3 Hz), 2.28 (3H, s); ^{19}F NMR (THF-d_8) δ −73.4 (3F, s), −120.7 (1F, br signal), −123.2 (1F, dd, J_{HF} = 53.5 Hz and J_{FF} = 305.8 Hz); ^{13}C NMR (THF-d_8) δ 159.3, 158.2 (t, J_{CF} = 23.6 Hz), 156.3 (q, J_{CF} = 42.4 Hz), 141.7, 136.6, 136.2, 131.0, 129.3, 129.2, 124.6, 116.0 (q, J_{CF} = 284 Hz), 80.4, 69.3, 21.4.

Influence of Solvent, Concentration, and Temperature. General Procedure for the Experiments of Tables 2−4. The procedure B described for the synthesis of the F-PAKs (*R*)-**2** was carried out on a 0.1 mmol scale (38 mg) of triF-SE (*R*)-**1a**, using the appropriate solvent (Table 2), temperature (Table 3), and concentration (Table 4). Experiments reported in Tables 2 and 3 were carried out with [(*R*)-**1a**] = 0.1 M. Experiments described in Tables 2 and 4 were carried out at 0 °C. Dry THF was used as solvent for the experiments reported in Tables 3 and 4. Purifications were performed on a flash chromatographic column having 1 cm of inside diameter, charged with 13 cm of silica gel, using a mixture 85:15 *n*-hexane/AcOEt as eluant, with 5 min of elution time for all the experiments reported in Tables 2−4.

Chemical and Optical Stability of the Fluoropyruvaldehyde *N*,*S*-Ketals (*R*)-2. Toward TFA. A chloroform solution (1 mL) of triF-PAK (*R*)-**2a** (6 mg) having $[\alpha]^{20}_D$ +136.2 (*c* 0.65, $CHCl_3$) was treated with 1 drop of TFA. After 3 d at rt, neither significant change of the $[\alpha]^{20}_D$ value nor decomposition were detected. The same chemical and optical stability toward TFA was detected for a sample of diF-PAK (*R*)-**2d** having $[\alpha]^{20}_D$ +193.0 (*c* 0.64, $CHCl_3$).

Toward Silica Gel. A chloroform solution (1 mL) of triF-PAK (*R*)-**2a** (8 mg) having $[\alpha]^{20}_D$ +136.2 (*c* 0.65, $CHCl_3$) was treated with 20 mg of silica gel. The slurry was vigorously stirred at rt for 8 h and then filtered. Neither significant change of the $[\alpha]^{20}_D$ value nor decomposition were detected. Under the same conditions, chemical and optical stability toward silica gel were detected for a sample of diF-PAK (*R*)-**2d** having $[\alpha]^{20}_D$ +193.0 (*c* 0.64, $CHCl_3$).

A sample of triF-PAK (*R*)-**2a** (40 mg) having $[\alpha]^{20}_D$ +136.2 (*c* 0.65, $CHCl_3$) and ee 67% was charged in a silica gel chromatographic column. After 30 min at rt the sample was eluted with a 85:15 *n*-hexane/AcOEt mixture. Evaporation of the solvent at reduced pressure afforded 35 mg of (*R*)-**2a** having $[\alpha]^{20}_D$ +64.8 (*c* 0.68, $CHCl_3$) and 37% ee.

Toward Triethylamine. A chloroform solution of diF-PAK (*R*)-**2d** (8 mg) having $[\alpha]^{20}_D$ +191.4 (*c* 0.81, $CHCl_3$) was treated with one drop of triethylamine. After 60 h a polarimetric analysis of the sample was carried out: $[\alpha]^{20}_D$ +40.1 (*c* 0.81, $CHCl_3$). After 12 h more at rt no optical activity was detected. The solvent was evaporated, and ^{1}H and ^{19}F NMR analysis of the sample confirmed its substantial chemical stability. A sample of triF-PAK (*R*)-**2a** with $[\alpha]^{20}_D$ +136.4 (*c* 0.72, $CHCl_3$), under the same conditions, was racemized after 3 d.

Toward Aqueous $NaHCO_3$. A THF solution (1 mL) of triF-PAK (*R*)-**2a** (30 mg) having $[\alpha]^{20}_D$ +136.4 (*c* 0.72, $CHCl_3$) was treated with 0.5 mL of an aqueous $NaHCO_3$ solution, and vigorously stirred for 30 min at rt. After standard workup, the residue was flash chromatographed on a short silica gel column, affording 22 mg of pure (*R*)-**2a** having no optical activity.

Pummerer Reaction Promoted by Acetyl Chloride. A 0.1 M solution of F-SE (*R*)-**1** in dry THF (1 mL) was treated at rt with 2 equiv of acetyl chloride (16 μL). The mixture was stirred for 4 h at rt. The solvent was removed at reduced pressure, and the crude mixture was submitted to FC, affording the corresponding α-chloro sulfides **5** as white solids.

5a: yield 95%; R_f 0.46 (85:15 *n*-hexane/AcOEt); mp 119−121 °C (*n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.36 (2H, d, J = 8 Hz), 7.34 (5H, m), 7.17 (2H, d, J = 8 Hz), 6.07 (1H, br s), 5.18 (2H, s), 2.36 (3H, s); ^{19}F NMR ($CDCl_3$) δ −61.1 (s); ^{13}C NMR ($CDCl_3$) δ 153.4, 140.0, 135.6, 135.5, 133.7, 130.3, 128.7, 128.5, 128.2, 126.4, 121.1 (q, J_{HF} = 267 Hz), 68.2, 21.3; MS (EI, 70 eV) *m*/*z* (%) 403 (M^+ + 2, 22), 401 (M^+, 66), 367 (10), 322 (6), 91 (100); FT IR (cm^{-1}) 3433, 3260, 1707, 1503, 1333, 1258, 1119. Anal. Calcd for $C_{18}H_{15}NO_2F_3SCl$: C, 53.80; H, 3.76; N, 3.49. Found: C, 53.90; H, 3.80; N, 3.45.

5d: yield 90%; R_f 0.46 (85:15 *n*-hexane/AcOEt); mp 94−96 °C (*n*-hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 7.35 (5H, m), 7.30 (2H, d, J = 8 Hz), 7.15 (2H, d, J = 8 Hz), 7.02 (1H, t, J_{HF} = 54.3 Hz), 6.17 (1H, s), 5.18 (2H, s), 2.35 (3H, s); ^{19}F NMR ($CDCl_3$) δ −117.05 (d, J_{HF} = 54.5 Hz); ^{13}C NMR ($CDCl_3$) δ 152.7, 139.2, 135.6, 134.4, 131.7, 130.3, 130.0, 128.6, 128.4, 128.2, 127.0, 110.3 (t, J_{HF} = 238.9 Hz), 68.0, 21.2; MS (EI, 70 eV) *m*/*z* (%) 385 (M^+ + 2, 5), 383 (M^+, 15), 339 (4), 304 (34), 212 (29), 124 (26), 91 (100); FT IR (cm^{-1}) 3400, 3273, 1719, 1524, 1234, 1110, 1032. Anal. Calcd for $C_{18}H_{16}NO_2F_2SCl$: C, 56.32; H, 4.20; N, 3.65. Found: C, 56.50; H, 4.34; N, 3.45.

Synthesis of the 4-(Difluoromethyl)-Δ-4-oxazol-2-one (10). The general procedure described for the step 1 of the preparation of F-PAKs (*R*)-**2** was followed, running the reaction in a NMR tube, with a 0.1 M solution of (*R*)-**1d** in $CDCl_3$. The imine **3d** formed immediately after addition of TFAA at rt, in equilibrium with a second compound, probably the chiral enamine tautomer **7**. Due to the complexity of the related NMR spectra, we have been not able to unambigously determine the structure of **7**. After one night at rt the achiral enamine **8** was present as a unique product.

8: ^{1}H NMR ($CDCl_3$) δ 9.47 (1H, br s) 7.46−7.36 (5H, m), 7.35 (2H, d, J = 8 Hz), 7.18 (2H, d, J = 8 Hz), 6.75 (1H, t, J_{HF} = 53.4 Hz), 5.36 (2H, s), 2.36 (3H, s); ^{19}F NMR ($CDCl_3$) δ −76.2 (3F, s), −116.7 (2F, d, J_{HF} = 53.4 Hz); ^{13}C NMR ($CDCl_3$) δ 160.4 (q, J_{CF} = 42.7 Hz), 156.8, 139.8, 133.2, 131.5, 130.7, 129.7, 129.3, 128.7, 126.3, 124.8 (t, J_{CF} = 26.4 Hz), 114.5 (q, J_{CF} = 284.9 Hz), 106.7 (t, J_{CF} = 235.8 Hz), 69.8, 21.1.

The solvent was then removed at reduced pressure, and the crude mixture was submitted to FC. The oxazolone **10** was obtained in 62% yield as a white solid, together with benzyl alcohol.

10: R_f 0.28 (85:15 *n*-hexane/AcOEt); mp 147−150 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, br s), 7.31 (2H, d, J = 8 Hz), 7.16 (2H, d, J = 8 Hz), 6.72 (1H, t, J_{HF} = 52 Hz), 2.34 (3H, s). ^{19}F NMR ($CDCl_3$) δ −116.55 (d, J_{HF} = 52 Hz). ^{13}C NMR ($CDCl_3$) δ 155.2, 139.2, 133.9 (t, J_{CF} = 10.0 Hz), 130.9, 130.4, 128.7, 125.0, (t, J_{CF} = 25.7 Hz), 106.9 (t, J_{CF} = 235.9 Hz), 21.1; MS (EI, 70 eV) m/z (%) 257 (M^+, 72), 237 (45), 91 (28), 45 (100). Anal. Calcd for $C_{11}H_9NO_2F_2S$: C, 51.36; H, 3.53; N, 5.44. Found: C, 51.66; H, 3.59; N, 5.33.

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