Two Practical and Efficient Approaches to Fluorinated and Nonfluorinated Chiral β-Imino Sulfoxides

Santos Fustero,* Antonio Navarro, Belén Pina, and Amparo Asensio

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46100-Burjassot (Valencia), Spain

Pierfrancesco Bravo, Marcello Crucianelli, Alessandro Volonterio, and Matteo Zanda*

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

Received February 23, 1998

Reaction of fluorinated and nonfluorinated *N*-substituted imidoyl chlorides **1** with lithium derivatives of enantiopure methyl *p*-tolyl sulfoxide **2a** (or racemic methyl phenyl sulfoxide **2b**) gave a wide variety of chiral *N*-substituted β-imino sulfoxides **4** in good to excellent yields. The title compounds (*R*)-**4** were also prepared by aza-Wittig reaction of γ-fluoro-β-keto sulfoxides (*R*)-**5** and *N*-aryl iminophosphoranes **6**. The imino−enamino equilibrium was studied, showing, in all instances, the imino form as the predominant tautomer independent of the nature of the *N*-substituent. The configuration of the C=N double bond was found to be *Z* for both *N*-alkyl and *N*-aryl derivatives on the basis of ^{1}H NMR NOE difference experiments performed over several compounds. Ab initio calculations (HF/6-31G*) carried out on several representative examples of **1** and **4** are, in general, consistent with the experimental results.

Introduction

The development of new and efficient methods for the regio- and stereoselective approach to compounds of high synthetic and pharmacological interest is one of the most active areas of research in modern organic chemistry.[1] In the search for new strategies for the preparation of biologically active molecules, we focused our attention on fluorine-containing acyclic nitrogen compounds.

Organofluorine chemicals are finding increasing utility in various fields including medicinal, biological, agricultural, and analytical chemistry.[2] Although most applications involve fluorinated oxygen derivatives,[2,3] the synthesis and reactivity of fluorine-containing amino compounds have received a great deal of attention in recent years owing to their peculiar biological behavior, arising mainly from the fact that fluorine substituents weaken the basicity, in turn modifying solubility, desolvation, and binding properties. In particular, fluorine-containing amino acids[4a−e] and amino alcohols[4f] are compounds which exhibit unique biological properties.[2,4]

Among the easily accessible fluoro-amino building blocks, perfluoroalkyl imidoyl halides,[5] particularly the trifluoromethyl derivative, have recently emerged as promising and valuable synthetic intermediates that can be converted into a variety of useful nitrogen heterocycles[5b,6] and other functionalized acyclic compounds including trifluoromethyl ketimines,[5b] α,β-unsaturated trifluoromethyl ketones,[7] amidines, and imidates.[6b,8] Following an efficient modification of the methodology previously developed by Appel,[9] perfluoroalkyl imidoyl halides have recently been synthesized in a high-yielding

(1) Helmchen, G.; Hoffmann, R. W., Mulzer, J.; Schaumann, E. *Stereoselective Synthesis*; Houben-Weyl Methods of Organic Chemistry; Georg Thieme Verlag: Stuttgart, 1996, Workbench Edition E21, Vols. 1−10.

(2) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993. (c) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (d) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. (e) For a review see also: Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (f) Resnati, G.; Soloshonok, V. A. Tetrahedron Symposia-in Print-no. 58. *Tetrahedron* **1996**, *52*, 1, 319.

(3) See for example: (a) Arnone, A.; Bravo, P.; Frigerio, M.; Viani. F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459. (b) Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani. F.; Zappalà, C.; Cavicchio, G.; Crucianelli, M. *Tetrahedron* **1995**, *51*, 8289. (c) Hui-Ping, G.; Chang-Ming, H. *Synthesis* **1996**, 1363.

(4) A number of fluorine-containing amino acids have been synthesized and studied as potential enzyme inhibitors. Amino acids containing the trifluoromethyl group are also potential antimetabolites because of the relatively nontoxic and stable nature of this group. See for example: (a) *Fluorine-containig Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (b) Sakai, T.; Yan, F.; Kashino, S.; Uneyama, K. *Tetrahedron* **1996**, *52*, 233. (c) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521. (d) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2009. (e) Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1995**, *7*, 1601. (f) Bégué, J.-P.; Bonnet-Delpon, D. Trifluoromethylated Amino Alcohols: New Synthetic Approaches and Medicinal Targets. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; pp 59−72.

(5) (a) Kantlehner, W.; Mergen, W. W. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: 1995; Vol. 5, Chapter 17. (b) Uneyama, K.; Morimoto, O.; Yamashita, F. *Tetrahedron Lett.* **1989**, *30*, 4821.

(6) (a) Uneyama, K.; Yamashita, F.; Sugimoto, K.; Morimoto, O. *Tetrahedron Lett.* **1990**, *31*, 2717. (b) Uneyama, K.; Kobayashi, M. *Tetrahedron Lett.* **1991**, *32*, 5981. (c) Uneyama, K.; Sugimoto, K. *J. Org. Chem.* **1992**, *57*, 6014. (d) Kobayashi, M.; Sadamune, K.; Mizukami, H.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 1909. (e) Watanabe, H.; Yan, F.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758. (f) Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **1994**, *59*, 929.

(7) Huang, W. S.; Yuan, C. Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 741.

(8) Uneyama, K.; Kobayashi, M. *J. Org. Chem.* **1994**, *59*, 3003.

(9) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801 and references therein.

S0022-3263(98)00336-3 CCC: $15.00
Published on Web 08/11/1998

one-pot procedure by Uneyama[10] starting from perfluoroalkyl carboxylic acids and primary amines. In this context we have studied the reactivity of imidoyl chlorides toward azaenolates derived from 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines and report a simple route to masked *N*-substituted β-enamino acid derivatives.[11] These compounds can be regarded as precursors of β-amino acids.

Chiral sulfoxides and, particularly, β-keto sulfoxides, are very interesting compounds widely used in asymmetric synthesis.[12,13] These reagents are usually obtained by simple acylation of α-metalated chiral sulfoxides with esters.[14] The fluorinated version was developed in a similar way, in the laboratories of Politecnico of Milan,[15] and the utility of γ-fluoro-β-keto sulfoxides has been demonstrated in the preparation of several chiral fluorinated oxygen compounds of synthetic and biological interest.[16]

In contrast with β-keto sulfoxides, the corresponding imino derivatives have received relatively little attention. Although β-imino sulfoxides and their enamine tautomers, including a few containing fluorine examples,[17] have been known for a reasonable time, their utility in asymmetric synthesis had not been demonstrated until recently.[17,18] These compounds were used, mainly through selective reduction processes, for preparing analogues of biologically active molecules such as optically active amines,[17b,19] amino alcohols,[17b] amino acids,[17b] and alkaloid precursors.[20] A limited number of synthetic methods have been developed in recent years for preparing β-imino sulfoxides using approaches which can be classified into the following four categories:

(i) The condensation between β-keto sulfoxides and amines,[18a,21] which is the most, a priori, simple synthetic strategy. However, this reaction is not satisfactory for the preparation of γ-fluoro-β-imino sulfoxides and is progressively less efficient with increasing fluorination level.[17] For these reasons we have developed an alternative route to some α-(fluoroalkyl)-β-sulfinyl enamines **4** (R^2 = Cbz or H and $R^1 = R_F$) based on an aza-Wittig reaction of imino phosphoranes (Ph_3PNR^2, R^2 = Cbz or $SiMe_3$) with fluorinated β-keto sulfoxides[17] (see retrosynthetic scheme, eq 1). A similar methodology had been applied to the synthesis of β-enamino esters.[22,23]

(ii) Andersen-type syntheses,[24] which involve the reaction of metalated alkyl imines with chiral sulfinic esters. This procedure has been applied with success to acyclic,[21d,25] endocyclic,[20] and exocyclic imines.[18b] The major limitation of this procedure is the need to keep a strict control of the reaction conditions in order to avoid undesired competing reactions such as epimerization of the sulfinyl stereocenter.[21d]

(iii) Michael-type addition of primary and secondary amines to either allenyl[25a,26] or alkynyl chiral sulfoxides.[27,28] Owing to their relative inaccessibility, allenyl sulfoxides have been used only for specific cases when the aforementioned strategies (i and ii) have failed.[25a]

(iv) Reaction of sulfinyl carbanions with nitriles of which only a few examples have been described, the best results being obtained with aromatic nitriles.[19,29]

Since all the existing approaches to β-imino sulfoxides possess several limitations in their general applicability, the development of new and general methodologies for the synthesis of these useful derivatives is highly desirable. In this paper we report in detail two practical and efficient strategies for the synthesis of fluorinated and nonfluorinated β-imino sulfoxides (**4**) (retrosynthetic scheme, eq 1): the reaction of chiral lithiated aryl methyl sulfoxides (**2**) with imidoyl chlorides (**1**) (route A)[30] and the extension of the "aza-Wittig approach" to the synthesis of *N*-aryl γ-fluoro-β-imino sulfoxides (*R*)-**4** (route

(10) Uneyama, K.; Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H. *J. Org. Chem.* **1993**, *58*, 32.

(11) Fustero, S.; Navarro, A.; Díaz, D.; de la Torre, M. G.; Asensio, A.; Sanz, F.; Liu González, M. *J. Org. Chem.* **1996**, *61*, 8849.

(12) (a) Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: New York, 1988. (b) Solladié, G. *Synthesis* **1981**, 185. (c) Solladié, G. *Pure Appl. Chem.* **1988**, *60*, 1699. (d) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. (d) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961. (e) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.

(13) See for example: Solladié, G.; Colobert, F. In *Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 5, pp 3606 and 3235 and references therein.

(14) (a) Solladié, G.; Fréchou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912. (b) Carreño, M. C.; García Ruano, J. L.; Rubio, A. *Tetrahedron Lett.* **1987**, *28*, 4861. (c) Solladié, G.; Ghiatou, N. *Tetrahedron: Asymmetry* **1992**, *3*, 33.

(15) (a) Bravo, P.; Piovosi, E.; Resnati, G. *Synthesis* **1986**, 579. (b) Bravo, P.; Zanda, M. Asymmetric Synthesis of Fluoro-Organic Compounds via Chiral Sulfoxide Chemistry. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemistry, Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, in press.

(16) See for example: (a) Bravo, P.; Frigerio, M.; Resnati, G. *J. Org. Chem.* **1990**, *55*, 4216. (b) Bravo, P.; Pregnolato, M.; Resnati, G. *J. Org. Chem.* **1992**, *57*, 2726.

(17) (a) Bravo, P.; Crucianelli, M.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 3043. (b) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375. Corrigenda: *J. Org. Chem.* **1996**, *61*, 9635. (c) Arnone, A.; Bravo, P.; Bruché, L.; Crucianelli, M.; Vichi, L.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 7301.

(18) (a) Kawecki, R.; Kozerski, L.; Urbanczyk-Lipkowska, Z.; Bocelli, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2255. (b) Carreño, M. C.; Dominguez, E.; García Ruano, J. L.; Pedregal, C.; Rodriguez, J. H. *Tetrahedron* **1991**, *47*, 10035. (c) Bravo, P.; Crucianelli, M.; Fronza, G.; Zanda, M. *Synlett* **1996**, 249. (d) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, *62*, 8031.

(19) Tsuchihashi, G.-I.; Iriuchijima, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, *14*, 3389.

(20) (a) Hua, D. H.; Bharathi, S. N.; Takusagawa, F.; Tsujimoto, A.; Panangadan, J. A. K.; Hung, M.-H.; Bravo, A. A.; Erpelding, A. M. *J. Org. Chem.* **1989**, *54*, 5659. (b) Hua, D. H.; Bharathi, S. N.; Robinson, P. D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128. (c) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (d) Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144. (e) Bravo, P.; Crucianelli, M.; Farina, A.; Meille, S. V.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **1998**, *435*.

(21) (a) Kawecki, R.; Kozerski, L. *Tetrahedron* **1986**, *42* 1469. (b) Ogura, K.; Ishida, M.; Tomori, H.; Fujita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3531. (c) Baldenius, K.-U.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 597. (d) García Ruano, J. L.; Lorente, A.; Rodriguez, J. H. *Tetrahedron Lett.* **1992**, *33*, 5637. (e) Ogura, K.; Tomori, H.; Fujita, M. *Chem. Lett.* **1991**, 1407.

(22) Kloeck, J. A.; Leschinsky, K. L. *J. Org. Chem.* **1978**, *43*, 1460.

(23) Shen, Y.; Gao, S. *J. Fluorine Chem.* **1996**, *76*, 37.

(24) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.

(25) (a) Annunziata, R.; Cinquini, M.; Restelli, A.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1183. (b) See ref 18a and references therein.

(26) Truce, W. E.; Markley, L. D. *J. Org. Chem.* **1970**, *35*, 3275.

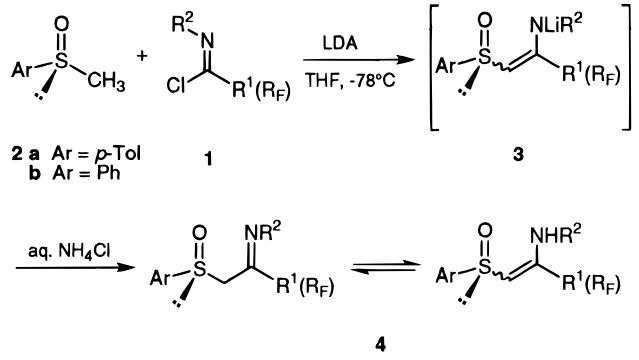
(27) (a) McMullen, C. H.; Stirling, C. J. M. *J. Chem. Soc. B* **1966**, 1217. (b) Lee, A. W. M.; Chan, W. H.; Lee, Y.-K. *Tetrahedron Lett.* **1991**, *32*, 6861. (c) Lee, A. W. M.; Chan, W. H.; Tao, Y.; Lee, Y. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 477. (d) Chan, W.; Lee, A. W. M.; Jiang, L. *Tetrahedron Lett.* **1995**, *36*, 715.

(28) For synthesis of chiral alkynyl sulfoxides, see: (a) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078. (b) See ref 27b.

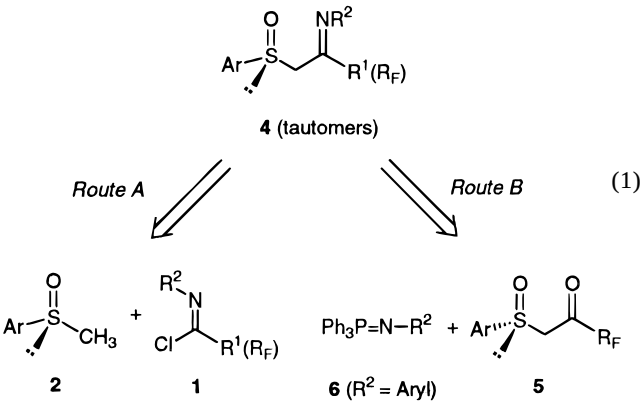
(29) (a) Yokoyama, M.; Takeshima, T. *Tetrahedron Lett.* **1978**, *19*, 147. (b) Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 614. (c) Alternatively, fluorinated *N*-unsubstituted β-enamino sulfoxides have been prepared by using *N*-trimethylsilyl iminophosphoranes as already indicated (see ref 17b).

(30) For preliminary communications, see: (a) Bravo, P.; Cavicchio, G.; Crucianelli, M.; Markovsky, A. L.; Volonterio, A.; Zanda, M. *Synlett* **1996**, 887. (b) Fustero, S.; Navarro, A.; Asensio, A. *Tetrahedron Lett.* **1997**, *38*, 4891. Corrigenda: *Tetrahedron Lett.* **1997**, *38*, 6477.

Scheme 1



B).[30a] The results of an ab initio (HF/6-31G*) study carried out in order to establish, or predict, the configurational stability of tautomers and geometric isomers of β-imino sulfoxides (**4**), as well as of imidoyl chlorides (**1**), are also presented, and comparisons are made, wherever possible, with the accompanying experimental evidence.



(1)

Results and Discussion

Route A. The synthesis of β-imino sulfoxides **4** via imidoyl chlorides **1** is outlined in Scheme 1. Commercially available (+)-(*R*)- and (−)-(*S*)-methyl *p*-tolyl sulfoxides **2a**[24,31] and (±)-methyl phenyl sulfoxide **2b** were lithiated with LDA in THF. Subsequently, the appropriate *N*-alkyl or *N*-aryl imidoyl chloride **1**[10] was slowly added at −78 °C, affording the corresponding β-imino sulfoxides **4** in high yields (Table 1). The reactions were accomplished either by using 1.0 equiv of sulfoxide **2** and 2 equiv of LDA, mixed at −40 °C (method 1), or by using 2.0 equiv of lithiated methyl *p*-tolyl sulfoxide (*R*)-**2a** prepared at −70 °C (method 2).[32a] In almost all instances (method 1 or 2) the reactions proceeded to completion,[32b] as indicated by TLC (for details see Experimental Section).

Most of the cases reported in Table 1 relate to imidoyl chlorides (**1**) bearing *p*-methoxyphenyl and α-phenylethyl groups as R^2 substituents. This choice was made because both these R^2 groups can be readily cleaved at a later stage, ultimately furnishing the corresponding *N*-unsubstituted derivative by standard procedures.[4b,33]

Although the reaction between imidoyl chlorides **1** and lithiated sulfoxides **2** (route A) has rather general applicability, its particular importance is in the synthesis of fluorinated derivatives ($R^1 = R_F$).[34] In fact, fluorinated *N*-alkyl (Table 1, entries 4, 6, 9, 12, 17, 18, and 19) as well as *N*-aryl (Table 1, entries 1, 2, 3, 5, 7, 8, 10, 11, 13, 14, 15, and 16) β-imino sulfoxides (**4**) were always obtained in good to excellent yields. All these reactions were very fast (less than 20 min) and proceeded well under mild conditions (−78 to −50 °C) (see Experimental Section).[35]

Fluorine-free β-imino sulfoxides **4b,c,p** (Table 1, entries 2, 3, and 16) were obtained by employing imidoyl chlorides (**1**) derived from aromatic amines (R^2 = aryl) and bulky aliphatic, aromatic, and heteroaromatic carboxylic acids (R^1 = *tert*-butyl, phenyl, and pyridyl). In these cases the protocol also worked well, although higher temperatures (−78 to 0 °C) and longer reaction times (∼3−5 h) were required. In general, results were better when fluorinated *N*-aryl imidoyl chlorides (**1**) ($R^1 = R_F$) were used, a feature ascribed to the higher electrophilicity of the iminic carbon in these derivatives. Moreover, it must be noted that, in contrast with those examples described in the literature,[36] this method also produced high yields when it was applied to the synthesis of derivatives **4b,c,n,p** (Table 1, entries 2, 3, 14, and 16), which are not activated by fluoroalkyl residues.

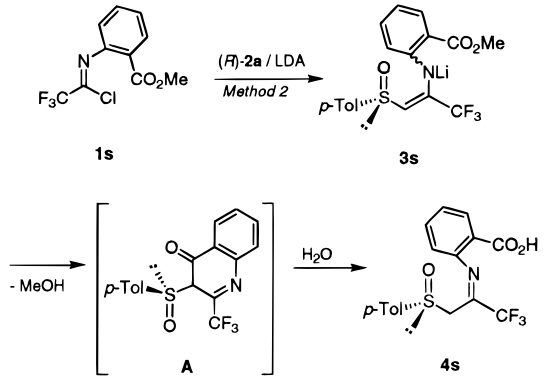
(31) These compounds can also be synthesized on a large scale by using the DAG methodology. See for example: (a) Guerrero de la Rosa, V.; Ordoñez, M.; Llera, J. M.; Alcudia, F. *Synthesis* **1995**, 761. (b) El Ouazzani, H.; Khiar, N.; Fernández, I.; Alcudia, F. *J. Org. Chem.* **1997**, *62*, 287.

(32) (a) When method 2 was employed, the excess of sulfoxide (*R*)-**2** could be recovered quantitatively by flash chromatography (FC). (b) The use of only 1 equiv of LDA (or, alternatively, lithiated sulfoxide **2**) led, in all cases, to yields lower than 50%. See also ref 11 and literature cited therein.

(33) See for example: Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557. Of particular synthetic interest is the chemoselective cleavage of the *N*-PMP group of β-aminosulfoxides, obtained by hydride-promoted reduction of β-iminosulfoxides **4** with ceric ammonium nitrate, which does not affect the stereogenic sulfinyl group. See ref 30a.

(34) We have not applied this methodology to the synthesis of fluorine-free β-imino sulfoxides **4** where R^1 and R^2 are aliphatic groups. The thermal instability of the *N*-alkyl imidoyl chlorides **1** derived from aliphatic carboxylic acids (see refs 9 and 10) and their, in general, lower reactivity coupled with the fact that these systems have already been successfully prepared by condensation or Andersen-type reactions, as described by García Ruano et al. (see ref 21d), are some of the reasons for our choice.

(35) In one case this reaction was accompanied by an unexpected side reaction. Addition of (2-methoxycarbonylphenyl)imino trifluoroacetimidoyl chloride **1s** to lithiated (*R*)-(+)-**2a** produced the *N*-(2-hydroxycarbonyl-phenyl)imino derivative **4s**, as a nearly unique product. Hydrolysis of the methyl ester functionality may be explained by postulating that the intermediate lithiated β-sulfinyl enamine **3s** undergoes an intramolecular Dieckmann-type cyclization, producing the unstable cyclic derivative **A**. Under aqueous workup conditions, the final product **4s** can be produced by retro-condensation. Nevertheless, it cannot be ruled out that the carboxylic acid might also emerge by simple hydrolysis of the ester under alkaline conditions as suggested by one of the referees.



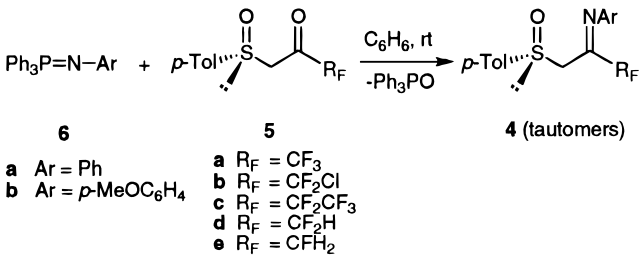
(36) Very poor yields were always obtained for these derivatives (0−30%) (refs 21a,c and 25a).

Table 1. *N*-Substituted β-Imino Sulfoxides 4 Obtained from Aryl Methyl Sulfoxides 2 and Imidoyl Chlorides 1 (Route A)

		Imidoyl chlorides (**1**)				
entry	**2**[a]	R^1	R^2	product	yield (%)[b]	method
1	(+)-**2a**	CF_3	*p*-$MeOC_6H_4$	(R_S)-**4a**	85 (>99)	1 (2)
2	(+)-**2a**	*t*-Bu	*p*-MeC_6H_4	(R_S)-**4b**	65	1
3	(+)-**2a**	Ph	Ph	(R_S)-**4c**	93	1
4	(+)-**2a**	CF_3	(*R*)-(+)-C_6H_5(Me)CH	(*R*,R_S)-**4d**	82	1
5	(+)-**2a**	CF_3CF_2	*p*-$MeOC_6H_4$	(R_S)-**4e**	82	1
6	(+)-**2a**	CF_3CF_2	(*R*)-(+)-C_6H_5(Me)CH	(*R*,R_S)-**4f**	80	1
7	(+)-**2a**	CF_3	Ph	(R_S)-**4g**	90	2
8	(+)-**2a**	CF_3	*m*-$MeOC_6H_4$	(R_S)-**4h**	>99	2
9	(+)-**2a**	CF_3	*n*-hexyl	(R_S)-**4i**	80	2
10	(+)-**2a**	CF_2Cl	Ph	(R_S)-**4j**	74	2
11	(+)-**2a**	CF_2Cl	*m*-$MeOC_6H_4$	(R_S)-**4k**	76	2
12	(−)-**2a**	CF_3	(*S*)-(+)-*c*-C_6H_{11}(Me)CH	(*S*,S_S)-**4l**	97	1
13	(−)-**2a**	$CF_3(CF_2)_6$	*p*-$MeOC_6H_4$	(S_S)-**4m**	92	1
14	(−)-**2a**	*p*-FC_6H_4	*p*-MeC_6H_4	(S_S)-**4n**	87	1
15	(−)-**2a**	CF_2Cl	*p*-$MeOC_6H_4$	(S_S)-**4o**	72	1
16	(−)-**2a**	3-Pyridyl	*p*-$MeOC_6H_4$	(S_S)-**4p**	80	1
17	(−)-**2a**	CF_3	*c*-C_6H_{11}	(S_S)-**4q**	72	1
18	(−)-**2a**	CF_3	(*R*)-(+)-C_6H_5(Me)CH	(*R*,S_S)-**4d**	83	1
19	(±)-**2b**	CF_3	(*S*)-(+)-*c*-C_6H_{11}(Me)CH	(*S*,*R*/S_S)-**4r**	85	1

[a] **2a**: (*R*)-(+)-methyl *p*-tolyl sulfoxide and (*S*)-(−)-methyl *p*-tolyl sulfoxide. **2b**: (±)-methyl phenyl sulfoxide. [b] Yield after purification.

Scheme 2



Route B. The synthesis of some *N*-aryl β-imino sulfoxides (*R*)-**4** via aza-Wittig reaction[37] of γ-fluoro-β-keto sulfoxides (*R*)-**5** with *N*-aryl imino triphenylphosphoranes **6** is reported in Scheme 2. The starting *N*-phenyl imino phosphorane **6a** was prepared by reaction of Ph_3PBr_2 and aniline with triethylamine as base (Kirsanov reaction).[38a,b] The *N*-*p*-methoxyphenyl imino phosphorane **6b** was prepared by reaction of *p*-methoxyphenyl azide with triphenylphosphine (Staudinger reaction).[37,38c]

An equimolar amount of *N*-aryl iminophosphorane **6** and γ-fluoro-β-keto sulfoxide [(R_S)-**5a**−**d**], in dry benzene, was reacted overnight at room temperature affording the corresponding *N*-aryl γ-fluoro β-imino sulfoxides [(R_S)-**4a**,**g**,**j**,**o**,**t**,**u**,**v**], in high yield (Table 2).

Table 2. *N*-Aryl γ-Fluoro β-Imino Sulfoxides (R_S)-4 Obtained via Aza-Wittig (Route B)

entry	R_F	Ar	product	yield (%)
1	CF_3	*p*-$MeOC_6H_4$	(R_S)-**4a**	93
2	CF_3	Ph	(R_S)-**4g**	85
3	CF_2Cl	Ph	(R_S)-**4j**	82
4	CF_2Cl	*p*-$MeOC_6H_4$	(R_S)-**4o**	97
5	CF_2CF_3	Ph	(R_S)-**4t**	76
6	CF_2H	Ph	(R_S)-**4u**	90
7	CFH_2	Ph	(R_S)-**4v**	ca. 30

The "aza-Wittig method" is particularly useful for the preparation of β-imino sulfoxides (**4**) bearing an activating group in the β-position. In fact β-keto sulfoxides (**5**) which have a fluorine-free alkyl chain in the β-position (for example, a methyl group) are unreactive at room temperature toward *N*-aryl iminophosphoranes (**6**). Monofluorinated β-keto sulfoxide (R_S)-**5e** is poorly reactive, demonstrated by the fact that after 30 h at 50 °C only ca. 30% of (R_S)-**5e** was transformed into the desired product (R_S)-**4v**. In contrast, difluoro β-keto sulfoxide (R_S)-**5d** and β-perhaloalkylated β-keto sulfoxides (R_S)-**5a**−**c** are very reactive, even at room temperature. This finding correlates well with our previous studies on the behavior of β-keto sulfoxides as substrates of the aza-Wittig reaction with *N*-Cbz and *N*-$SiMe_3$ imino triphenylphosphoranes.[17a,b]

There was no evidence of racemization in either synthetic route. Reaction of chiral *N*-(*S*)-[1-cyclohexylethyl]-2,2,2-trifluoroacetimidoyl chloride **1l** with enantiopure (*S*)-methyl *p*-tolyl sulfoxide **2a** provided only one diastereoisomer (*S*,S_S)-**4l** (entry 12, Table 1), based on NMR analysis (^1H and ^{19}F) of the crude reaction mixture. As expected, reaction of (*S*)-**1l** with racemic (±)-methyl phenyl sulfoxide provided equal diastereomeric quantities of the β-imino sulfoxide **4r** (entry 19, Table 1), again estimated on the basis of NMR experiments.[39]

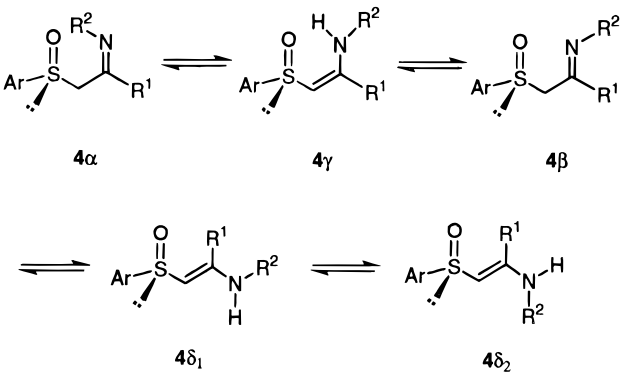
Purification of β-Imino Sulfoxides. Purification of β-imino sulfoxides (**4**) was carried out in most cases by flash chromatography (FC) or, alternatively, by medium-pressure liquid chromatography (MPLC) on silica gel.

(37) The term "aza-Wittig reaction" is adopted in this paper for reasons of clarity, due to its widespread use in the literature. The name "aza-Wittig" arises from the similarity between this reaction, involving iminophosphoranes, and the true Wittig reaction, which makes use of carbon−phosphorus ylides. However, it must be recognized that the former reaction was discovered by Staudinger: (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861. We thank Dr. Vadim A. Soloshonok, National Industrial Research Institute of Nagoya, Japan, for pointing this out. The fact that "Staudinger reaction", which would be more appropriate, is the well-established name for two other important processes, namely, the reaction between azides and triphenylphosphine, as well as the reaction between ketenes and imines, leading to β-lactams, led us to use the term "aza-Wittig reaction" to avoid confusion. For recent reviews see: (c) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (d) Johnson, A. W.; Kasha, W. C.; Starzewsky, K. A. O.; Dixon, D. A. *Ylides and Imines of Phosphorus*; John Wiley: New York, 1993; Chapter 13.

(38) (a) Kirsanov, A. V. *Izv. Akad. Nauk SSSR* **1950**, 426; *Chem. Abstr.* **1951**, *45*, 1503. (b) Horner, L.; Oediger, H. *Liebigs Ann. Chem.* **1959**, *627*, 142. (c) Leffler, J. E.; Temple, R. D. *J. Am. Chem. Soc.* **1967**, *89*, 5235.

(39) To date we have not been able to obtain the pure single diastereoisomers by chromatography (FC or MPLC).

Chart 1



Some partial hydrolysis to the corresponding β-keto sulfoxides was occasionally observed, but this could be avoided by pre-elution with a 2% triethylamine/hexanes solution.[40] Chemically pure fluorinated β-imino sulfoxides (**4**) are stable compounds which can be stored at 0 °C for a long time and handled at room temperature without any deterioration.

Tautomerism of β-Imino Sulfoxides. Almost all the β-imino sulfoxides **4** obtained by either route were single iminic tautomers (Chart 1).[41] However, the exact tautomeric composition appeared to be sensitive to the structural features of the β-imino sulfoxides. NMR analysis (^{1}H, ^{19}F, and ^{13}C) in $CDCl_3$ at room temperature showed that fluorinated *N*-aryl derivatives **4** exist only as the *Z* iminic tautomers (**4**α) (Chart 1) (see below).[42] However, fluorinated *N*-alkyl and fluorine-free derivatives (**4**) contain detectable amounts (10−20%) of the other three tautomeric forms shown (**4**β,γ,δ). Under the same conditions, a significant amount of the *E* iminic form was observed only in the case of **4b** (R^1 = *t*-Bu) (Table 1, entry 2) (78/22 *Z*/*E*). Monofluorinated β-imino sulfoxide (R_S)-**4v** (Table 2, entry 7) was produced via route B as an almost equimolar mixture of *Z* (**4**α) and *E* (**4**β) iminic tautomers although, in this case, we were not able to obtain chemically pure samples, only mixtures of (R_S)-**4v** with the corresponding starting β-keto sulfoxide (R_S)-**5e** (see Experimental Section).

A study of the thermal stability of these derivatives was addressed next. When fluoroalkyl *N*-aryl derivatives, for example, compound **4a** (entry 1, Table 1), were heated at 50 °C in a $CDCl_3$ solution for 5 days their original homogeneous *Z* iminic structure (see below) was completely preserved, as confirmed by NMR. The same stability was observed for *N*-aryl β-imino sulfoxides not bearing a fluoroalkyl residue,[43] such as **4c**[44] and **4n** (both obtained via route A as a 9:1 mixture of *Z*/*E* iminic tautomers) (entries 3 and 14, Table 1). In contrast, for fluoroalkyl *N*-alkyl derivatives, such as **4d** (entries 4 and 18, Table 1), the freshly prepared homogeneous *Z* iminic tautomer underwent slow isomerization upon standing neat at room temperature, to form the corresponding enamino tautomer.[45] The original situation was restored when the enaminic tautomers were redissolved in $CDCl_3$ and allowed to stand in solution for a few hours.

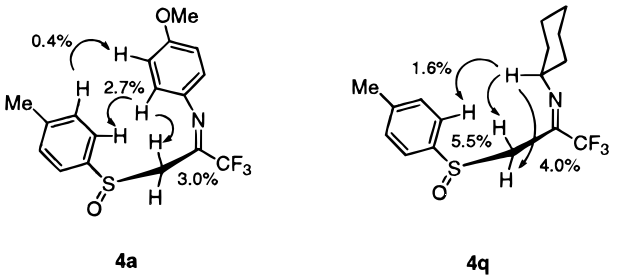


Figure 1. Representative NOE results.

All this experimental evidence, in conjuntion with the computational studies (see below), point to the fact that the *Z* iminic configuration is the thermodynamically more stable tautomeric form for β-imino sulfoxides.

Structure Determination. The structure and stereochemistry of the β-imino sulfoxides (**4**) prepared by routes A and B were deduced on the basis of their NMR (^{1}H, ^{13}C, and ^{19}F) spectra and elemental and HRMS analyses. Thus, for instance, the ^{1}H NMR spectrum of the chlorodifluoro derivative **4o** (entry 15, Table 1) displays characteristic signals at δ 3.71 (d, J = 12.7 Hz, 1H) and 4.03 (d, J = 12.7 Hz, 1H) corresponding to the AB system of CH_2S*O. In the ^{19}F NMR spectrum the CClF_2 group resonates at δ −59.2 (d_{AB}, $^2J_{FF}$ = 163.5 Hz, 1F) and −60.0 (d_{AB}, $^2J_{FF}$ = 163.5 Hz, 1F). Finally, the three main features of the ^{13}C NMR spectrum are the signals corresponding to the *C*H_2S*O, *C*ClF_2, and *C*═N groups which appear at δ 55.7, 123.2 (t, $^1J_{CF}$ = 292.8 Hz), and 152.3 (t, $^2J_{CF}$ = 28.5 Hz), respectively. These data confirm unequivocally the iminic structure proposed for **4o**.

Further corroboration for the correct configuration assignment to the tautomers **4**α and **4**β[41] was obtained by ^{1}H NMR NOE difference experiments performed on **4a** (entry 1, Table 1 and Figure 1), as well as by ab initio calculations (see below). These studies showed that β-imino sulfoxides **4** exist mainly in the *Z* iminic configuration. Thus, irradiation of the singlet at δ 6.87 (4H) of the aromatic ring of the *p*-anisidine group of **4a** led to a 3.0% and 2.7% enhancement of the signals corresponding to CH*H*S*O (δ 4.09, d) and *ortho* hydrogens of the *p*-tolyl sulfinyl (δ 7.28, d) groups, respectively. Correspondingly, irradiation of the signal at δ 7.28 showed only a small interaction (0.4%) with the hydrogens (δ 6.87) of the *p*-anisidine ring. Unfortunately, the proximity and overlapping of some of the aromatic signals of compounds **4c** (entry 3, Table 1) and **4n** (entry 14, Table

(40) Meyers, A. I.; Novachek, K. A. *Tetrahedron Lett.* **1996**, *37*, 1747.

(41) **4**α: *Z* imino configuration. **4**β: *E* imino configuration. **4**γ: *Z* enamino configuration. **4**δ: *E* enamino configuration.

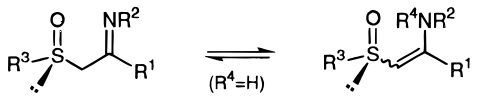
(42) On one occasion, for compound **4n** (entry 14, Table 1), small amounts of other tautomers were observed by ^{19}F NMR spectroscopy.

(43) Only compound **4p** (entry 16, Table 1) underwent a very slow *Z* → *E* imine isomerization by heating in $CDCl_3$ solution at 50 °C for 3 weeks. The peculiar behavior of **4p** may be explained by assuming the presence of a charge-transfer interaction between the π−electron-deficient pyridine and the π-electron-rich *p*-anisidine aromatic rings, which should stabilize the *E* iminic isomer.

(44) In contrast with this result, it has been reported in the literature (see ref 25a) that compound **4c**, initially obtained *only* as an *Z* imino tautomer, undergoes a complete *Z* → *E* imine isomerization by standing at room temperature for several days. For comparison, we have also used the methodology described in ref 25a for preparing **4c** (29%). We found that both methods afforded the same 9:1 mixture of *Z*/*E* imino tautomers. In any case we could not observe *Z* → *E* imine isomerization.

(45) This could be observed by ^{1}H and ^{19}F NMR since the initial AB system of the CH_2S*O group in (*R*,S_S)-**4d** (entry 18, Table 1) was slowly converted to a *singlet* corresponding to the ═C*H*S*O group of the *Z* enaminic structure and the *quartet* of the NC*H*CH_3 group appeared as a multiplet due to the additional coupling with the N*H* of the enaminic form. Moreover, the CF_3 group signal moved upfield from δ_F −72.1 to −62.1 ppm. Similar isomerizations have also been observed for related compounds (see ref 17b).

Chart 2



4 (tautomers)

4	R^1	R^2	R^3	R^4
4A	Me	Bn	*p*-Tol	H
4B	Me	*p*-Anis	*p*-Tol	H
4C	Me	Bn	Me	H
4D	Me	Me	Me	H
4E	Me	Me	Me	Me

1) made selective irradiation difficult; therefore observed NOE values were not meaningful.

Similarly, *N*-alkyl derivatives such as compound **4q** (entry 17, Table 1 and Figure 1) showed an NOE enhancement (5.5 and 4.0%) for the diastereotopic hydrogens (CH_2SO) at δ 3.69 and 3.92 respectively through irradiation of the multiplet at 3.21 ppm corresponding to the methine cyclohexyl moiety proton. An additional NOE (1.6%) was observed with the *ortho*-hydrogens of the *p*-tolyl ring at δ 7.51.[46]

Computational Studies. To gain further insight into the relative stabilities of the *Z* and *E* iminic and enaminic tautomers of compounds **4** (Chart 1) we have carried out semiempirical (AM1) and ab initio (HF/3-21G and HF/6-31G*) molecular orbital calculations involving full optimizations using the Gaussian94 series of programs.[47] Representative compounds synthesized in this work, such as **4a**, **4c**, **4d**, and **4v** were first examined. Next, the study was extended to other selected examples taken from the literature, for instance **4A**,[21d] **4B**,[48] **4C**,[21a] and **4E**,[21a] as well as the simple derivative **4D** (Chart 2), considered as a model. The HF/6-31G* optimized geometries of the most stable tautomer for some representative compounds **4** are shown in Figure 2, while their total and relative energies at the HF/6-31G* level of theory are summarized in Table 3.[49] Preliminary examination of these data reveals that calculations closely match the experimental results.

By comparing the relative energies of the *N*-aryl derivatives **4a**, **4c**, and **4v** (Table 3) for the several tautomers shown in Chart 1, it can be seen that the *Z* imino tautomer (**4**α) is predicted to be more stable than the other three tautomeric forms (**4***β*, **4***γ*, and **4**δ), in agreement with the experimental evidence.[48,50]

The situation is somewhat more complicated for *N*-alkyl derivatives. Thus, for example, for the fluorine-free *N*-alkyl *β*-imino sulfoxide **4A**,[21d] the *Z* enamino tautomer is known to be preferred. According to our calculations, the energy difference between the *Z* enamino form (**4***γ*) and the *Z* and *E* imino structures (**4**α and **4***β*) (1.3 and 0.8 kcal/mol, respectively) is in clear accordance with the experimental results.[21d] Subsequently, we performed the calculations on derivatives **4C**[21a] and **4D** producing energy differences of only 0.9 and 0.5 kcal/mol in favor of the *E* imine form (**4***β*). This suggests that compounds **4C** and **4D** should exist as an imino−enamino mixture, in agreement with experimental findings.[21a] In the case of *N*-alkyl fluoroalkyl derivatives, such as **4d**, the *Z* iminic tautomer is 1.8 and 1.9 kcal/mol more stable than the *E* imino and *Z* enamino isomers, respectively, in accord with *N*-aryl fluoroalkyl derivatives. This tendency has also been observed for all fluorinated *N*-alkyl derivatives synthesized in this work (see Table 1).

Finally, from the data listed in Table 3, it can also be inferred that for the *N*,*N*′-disubstituted fluorine-free derivatives the *E* enamino configuration is found to be more stable than the corresponding *Z* enamino configuration, as expected.[21a,51]

Furthermore, we performed a computational study on the relative stabilities of the *Z* and *E* geometries of the starting fluorinated imidoyl chlorides **1**, for example, **1a** ($R^1 = CF_3$; $R^2 = p$-$MeOC_6H_4$, entry 1, Table 1) and **1q** ($R^1 = CF_3$; $R^2 = c$-C_6H_{11}, entry 17, Table 1) (Scheme 3). It must be pointed out that, although these compounds were always obtained as a single isomer,[5b,6d] to our knowledge the exact geometry of the C=N double bond has not yet been established.

Semiempirical (AM1) and ab initio (HF/3-21G and HF/6-31G*) results for fluorinated imidoyl chlorides **1** were in good agreement with the experimental results. Thus, these derivatives appear to exist exclusively in the *Z* geometry, **1a** being 5.6 kcal mol^{-1} (4.1 at AM1 and 5.3 at 3-21-G) more stable than the *E* geometry at HF/6-31G* level, and **1q** being 5.9 kcal mol^{-1} (3.0 at AM1 and 4.1 at HF/3-21G) more stable than the *E* geometry at HF/6-31G* level.

In conclusion, two new and efficient approaches (routes A and B) to fluorinated chiral *β*-imino sulfoxides **4** have been developed. The first methodology (route A) has also been extended to nonfluorinated *N*-aryl *β*-imino sulfoxides. The "aza-Wittig method" (route B) is an alternative and complementary approach, particularly attractive for the preparation of *β*-imino sulfoxides bearing perhaloge-

(46) It must be emphasized that certain ambiguities exist in the literature regarding the stereochemistry of the double bond of the iminic and enaminic tautomers of derivatives **4** (see ref 21). Thus, for example, Ogura assigned an *E* enamino configuration to *N*-alkyl *β*-enamino sulfoxides resulting from condensations of *β*-ketosulfoxides with aliphatic amines (see ref 21e), while the same author proposed the opposite *Z* enamino configuration for related compounds obtained in a similar manner (see ref 21b). This, and other contradictory results (see refs 21a,c), can be explained by assuming that the reaction conditions, as well as the methodology used to prepare the target *β*-imino sulfoxides, are critical in obtaining one or the other tautomer.

(47) *Gaussian 94, Revision C.3*; Frisch, M. J.; Schlegel, Trucks, G. W.; H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, N.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martín, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; González, C.; Pople, J. A.; Gaussian Inc., Pittsburgh, PA, 1995.

(48) Lorente, A., Ph.D. Thesis, Universidad Autónoma de Madrid, 1997. See also ref 21d.

(49) It must be pointed out that good agreement between theory and experimental exists only for the highest level of theory (HF/6-31G*// HF/6-31G*).

(50) A different result was found in the case of the *N*-aryl fluorine-free derivative **4B** (Chart 2 and Table 3). HF/6-31G* calculations for **4B** predict the *E* imino (**4***β*) configuration as the most stable tautomer. Accordingly, this compound has been obtained by García Ruano et al. (see ref 48) as an *E* imino/*Z* imino/*Z* enamino (50/10/40) mixture from the *N*-PMP imine of acetone, following an Andersen-like method.

(51) Kozerski, L.; Kawecki, R.; Bednarek, E. *Magn. Reson. Chem.* **1987**, *25*, 712.

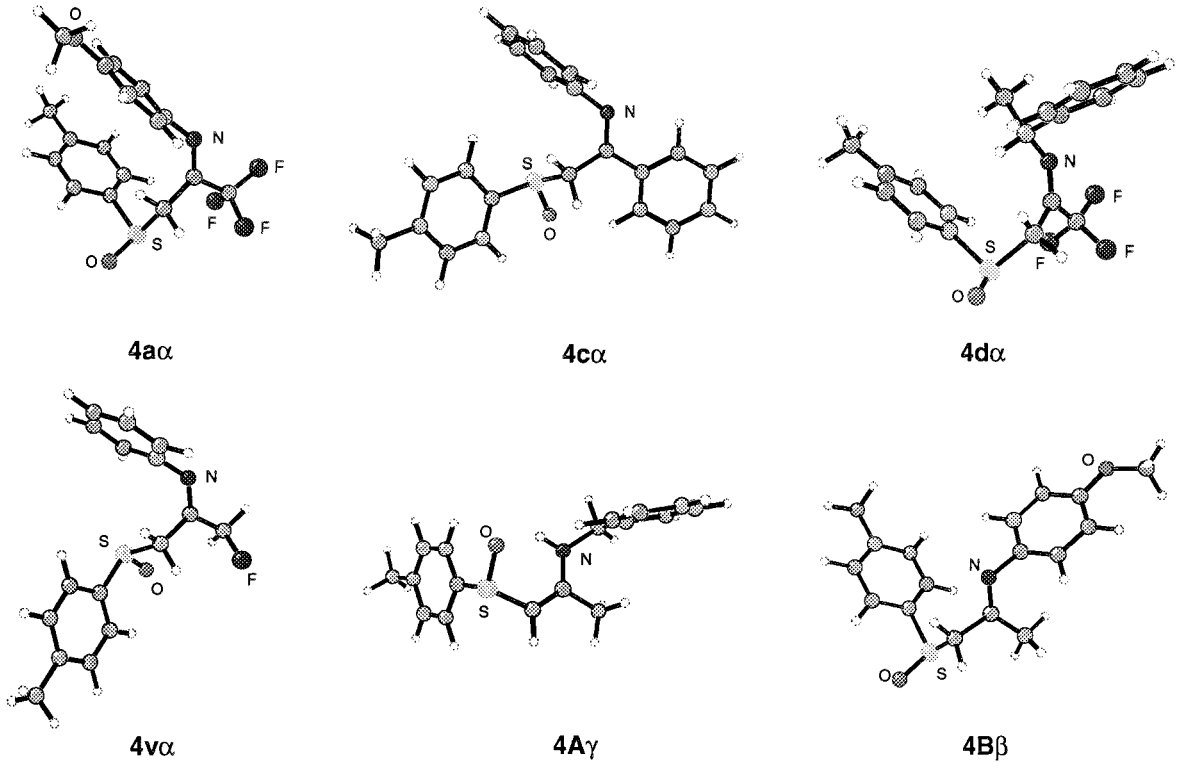


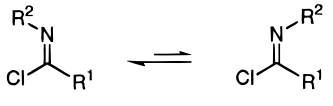
Figure 2. HF/6-31G* optimized structures of compounds **4a**α, **4c**α, **4d**α, **4v**α, **4A**γ, and **4B**β.

Table 3. Calculated Total (hartree) and Relative Energies (kcal mol^{-1}) of the Optimized Structures 4a, 4c, 4d, 4v, and 4A−E Using Molecular Orbital Calculations (HF/6-31G*//6-31G*)

compd	tautmr	E_{tot}	E_{rel}
4a	α	−1553.000 11	0.0
	β	−1552.997 22	1.8
	γ	−1552.995 99	2.6
	δ_1	−1552.984 29	9.9
4c	α	−1333.059 95	0.0
	β	−1333.055 79	2.6
	γ	−1333.053 94	3.8
	δ_2	−1333.049 38	6.6
4d	α	−1517.187 40	0.0
	β	−1517.190 19	1.8
	γ	−1517.187 16	1.9
	δ_1	−1517.173 43	10.5
4v	α	−1241.394 11	0.0
	β	−1241.387 16	4.4
	γ	−1241.383 54	6.6
	δ_2	−1241.384 06	6.3
4A	α	−1181.575 43	1.3
	β	−1181.576 26	0.8
	γ	−1181.577 54	0.0
	δ_1	−1181.565 54	7.5
4B	α	−1256.423 36	1.3
	β	−1256.425 47	0.0
	γ	−1256.423 48	1.2
	δ_1	−1256.413 22	7.7
	δ_2	−1256.416 05	5.9
4C	α	−952.027 35	2.9
	β	−952.031 89	0.0
	γ	−952.030 45	0.9
	δ_1	−952.019 71	7.6
	δ_2	−952.023 40	4.4
4D	α	−722.480 53	2.8
	β	−722.484 94	0.0
	γ	−722.484 12	0.5
	δ_1	−722.474 80	6.4
4E	*E*	−761.498 15	0.0
	Z	−761.490 71	4.7

nated and *gem*-difluorinated β-alkyl residues, the latter being difficult to synthesize via imidoyl halides. Furthermore, the imino−enamino equilibrium of β-imino

Scheme 3



sulfoxides **4** has been studied on the basis of their spectral properties (NOE experiments) and additionally by ab initio calculations at the HF/6-31G* level of theory. The results of this study have allowed us to predict that fluorinated derivatives appear, almost independent of their structural nature, in the *Z* imino configuration predominantly, while, for the fluorine free derivatives, either a *Z* enamino or an *E* imino/*Z* enamino mixture is preferred. This study has also permitted us to establish that the starting imidoyl chlorides **1** should exist in a *Z* configuration. Further studies on the reduction of the C=N bond of **4**, as well as the exploitation of β-imino sulfoxides for the stereoselective synthesis of biologically important fluoro-amino compounds, are in progress.

Experimental Section

General Methods. All reactions were performed on a dual manifold vacuum/argon system. General details concerning the treatment of solvents and reagents are provided in the Experimental Section of our earlier publications.[11,18d] (+)-(*R*)- and (−)-(*S*)-methyl *p*-tolyl sulfoxide and (±)-methyl phenyl sulfoxide were purchased from Aldrich Co. and used without further purification. Alternatively, (+)-(*R*)-methyl *p*-tolyl sulfoxide was prepared by the Andersen protocol from (−)-menthyl sulfinate and methylmagnesium iodide.[24] Imidoyl chlorides were prepared according to the methods described in the literature.[9,10] *N*-Phenyl iminotriphenylphosphorane **6a** was prepared by Kirsanov reaction of aniline with Ph_3PBr_2.[38a,b] *N*-*p*-Methoxyphenyl iminotriphenylphosphorane **6b** was prepared by Staudinger reaction of *p*-methoxyphenyl azide with

triphenylphosphine.[37,38c] All other reagents were of the best commercial grade available and were used without further purification. Reaction progress was monitored by analytical thin-layer chromatography (TLC) on UV active silica gel 60 F_{254} and visualization was achieved using UV illumination and iodine. Column chromatography methods, flash chromatography, and medium pressure liquid chromatography (MPLC) were carried out as previously reported.[11,17b] Melting points are uncorrected. All NMR spectra were recorded in $CDCl_3$ solution. ^1H and ^{13}C nuclei were determined using TMS (0 ppm) and the center line of the chloroform-*d* triplet (77.0 ppm) as internal standard, while $CFCl_3$ (0 ppm) (compounds prepared by route A, method 1) or C_6F_6 (compounds prepared by route A, method 2, and route B) were used as external standards for ^{19}F nuclei. *J* values are reported in hertz. Composition of tautomeric mixtures was quantitatively established on the basis of ^{19}F NMR analysis. Infrared spectra are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained at 70 eV by electron impact. FAB mass spectra were obtained using Cs^+ as reagent ions with a *m*-nitrobenzyl alcohol (NOBA) matrix. Elemental analyses were performed by the Microanalytical Service of the University of Zaragoza and by Redox SNC, Cologno M. (Milano).

Computational Methods. Ab Initio molecular orbital calculations were performed with the GAUSSIAN 94 package of programs.[47] For further details regarding instrumentation and others see ref 11.

General Procedure for the Synthesis of *N*-Substituted β-Imino Sulfoxides 4 via Imidoyl Chlorides (Route A). Route A. Method 1. To a stirred solution of diisopropylamine (0.6 mL, 4 mmol) in THF (10 mL) at −40 °C was added *n*-butyllithium (2.5 M in hexanes, 1.6 mL, 4 mmol) dropwise. After stirring for 30 min, (*R*)- or (*S*)-methyl-*p*-tolylsulfoxide **2** (0.31 g, 2 mmol) in THF (10 mL) was slowly added. The yellow solution was slowly warmed (20 min) to 0 °C and was then cooled to −78 °C. A solution of the desired imidoyl chloride **1** (2 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was monitored by TLC analysis. After the total disappearance of the starting material the reaction was quenched by addition of methanol (0.5 mL) and the solution was allowed to reach rt. The solvents were removed under reduced pressure. Methylene chloride (50 mL) was poured onto the crude mixture, and the solution was washed with brine. Drying ($MgSO_4$), filtration, and evaporation furnished the crude product **4**.

Method 2. In this case 2 equiv of (*R*)-methyl *p*-tolyl sulfoxide **2** was lithiated by 2 equiv of LDA at −70 °C for 10 min, following the procedure described above. The reactions were quenched with an excess of a saturated aqueous solution of ammonium chloride at −78 °C. The resulting mixture was allowed to warm to room temperature under stirring. The unreacted equivalent of (*R*)-methyl *p*-tolyl sulfoxide **2** was always recovered almost quantitatively by flash chromatography.

General Procedure for the Synthesis of *N*-Aryl β-Imino Sulfoxides (*R*)-4 via Aza-Wittig (Route B). To a stirred mixture of β-keto sulfoxide (*R*)-**5a**−**d** (1 equiv) in dry benzene (5 mL) at room temperature, solid iminophosphorane **6** (1 equiv) was added in one portion. The resulting solution was stirred overnight at room temperature, and the solvent was removed under reduced pressure. In the case of monofluorinated derivative (*R*)-**5e** the reaction mixture was stirred for 30 h at 50 °C.

Purification was carried out as indicated in each case.

(R_S)-2-(*Z*)-*p*-Anisylimino-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4a). Recrystallization [*n*-hexane−CCl_4 (5:1) or *i*-Pr_2O] gave a pale-yellow solid, which soon became orange upon standing in the presence of air (route A, 85% with method 1, quantitative yield with method 2; route B, 93%): R_f = 0.4 (*n*-hexanes−EtOAc 8:2); $[\alpha]^{25}_D$ −327.7 (*c* 0.50, $CHCl_3$); mp 97−99 °C [from *n*-hexane−CCl_4 (5:1)], 92−93 °C (from *i*-Pr_2O); ^1H NMR (250 MHz) 2.41 (s, 3H), 3.75 (d, *J* = 12.6, 1H), 3.82 (s, 3H), 4.09 (d, *J* = 12.6, 1H), 6.87 (s, 4H), 7.28 (d, *J* = 8.0, 2H), 7.45 (d, *J* = 8.0, 2H); ^{13}C NMR (62.8 MHz) 21.4, 55.4, 55.9,-114.2, 119.1 (q, $^1J_{CF}$ = 277.2), 121.4, 123.8, 130.2, 138.9, 140.1, 142.7, 149.0 (q, $^2J_{CF}$ = 34.7), 158.3; ^{19}F NMR (235 MHz) −71.2 ($CFCl_3$ as standard) or −72.1 (C_6F_6 as standard); IR (KBr) 1502, 1250, 1053; HRMS (FAB) calcd for ($M^+ + 1$) $C_{17}H_{17}NO_2SF_3$ 356.0932, found 356.0930. Anal. Calcd for $C_{17}H_{16}NO_2SF_3$: C, 57.46; H, 4.54; N, 3.94; S, 9.02. Found: C, 57.55; H, 4.38; N, 3.92; S, 8.95.

(R_S)-2-(*Z*)-*p*-Tolylimino-3,3-dimethylbuthyl-1-*p*-tolylsulfoxide (4b). MPLC [*n*-hexanes−EtOAc (20:1)] on silica gel (R_f = 0.4) gave **4b** (65%; route A, method 1) as an orange oil: $[\alpha]^{25}_D$ +4.8 (*c* 0.56, $CHCl_3$); ^1H NMR (250 MHz) (major tautomer) 1.30 (s, 9H), 2.34 (s, 3H), 2.35 (s, 3H), 3.69−3.65 (m, 2H), 6.60 (d, *J* = 8.2, 2H), 7.03−7.19 (m, 6H); (minor tautomer) 1.18 (s, 9H), 1.29 (s, 3H), 3.70 (m, 2H), 6.47 (d, *J* = 8.2, 2H); ^{13}C NMR (75 MHz) (major tautomer) 21.2 (q), 28.1 (q), 28.7 (q), 40.4 (s), 58.1 (t), 118.9 (d), 123.3 (d), 129.5 (d), 129.6 (d), 132.7 (s), 141.6 (s), 148.0 (s), 171.1 (s), 176.8 (s); (minor tautomer) 20.7 (q), 20.6 (q), 21.2 (q), 57.9 (t), 118.4 (d), 123.2 (d), 129.1 (d), 129.1 (d), 131.8 (s), 140.9 (s), 142.4 (s), 148.6 (s), 171.0 (s), 176.8 (s); IR (KBr) 1636, 1514, 1500, 1042; HRMS calcd for (M^+) $C_{20}H_{25}NOS$ 327.1657, found 327.1651. Anal. Calcd for $C_{20}H_{25}NOS$: C, 73.35; H, 7.69; N, 4.28; S, 9.79. Found: C, 73.50; H, 7.48, N, 4.22; S, 9.70.

(R_S)-2-(*Z*)-Phenylimino-2-phenylethyl-1-*p*-tolylsulfoxide (4c). Recrystallization (*n*-hexanes−EtOAc (1:10)) afforded a white solid (93%; route A, method 1): $[\alpha]^{25}_D$ −78.8 (*c* 0.65, $CHCl_3$); mp 110−112 °C; ^1H NMR (250 MHz) (major tautomer) 2.37 (s, 3H), 4.05 (d, *J* = 12.7, 1H), 4.32 (d, *J* = 12.7, 1H), 6.56 (d, *J* = 8.0, 2H), 7.05−7.41 (m, 10H), 7.98 (d, *J* = 8.0, 2H); (minor tautomer) 4.26 (d, *J* = 12.7, 1H), 4.47 (d, *J* = 12.7, 1H), 6.58 (d, *J* = 8.0, 2H), 7.20−7.70 (m, 10H), 7.89 (d, *J* = 8.0, 2H); ^{13}C NMR (62.8 MHz) (major tautomer) 21.3 (q), 58.0 (t), 119.6 (d), 123.8 (d), 123.9 (d), 128.0 (d), 128.5 (d), 129.3 (d), 129.8 (d), 131.1 (d), 137.4 (s), 139.9 (s), 142.1 (s), 149.9 (s), 158.8 (s); (minor tautomer) 68.0 (t); IR (KBr) 1623, 1588, 1294, 1041; HRMS calcd for (M^+) $C_{21}H_{19}NOS$ 333.1187 found, 333.1177. Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.65; H, 5.75; N, 4.20; S, 9.60. Found: C, 75.95; H, 5.70; N, 4.11; S, 9.43.

(R,R_S)-2-(*Z*)-(*N*-1-Phenylethylimino)-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4d). Flash chromatography (*n*-hexanes−EtOAc (3:1)) on silica gel (R_f = 0.3) furnished **4d** (82%; route A, method 1) as a clear yellow oil: $[\alpha]^{25}_D$ +206.1 (*c* 0.68, $CHCl_3$); ^1H NMR (250 MHz) 1.33 (d, *J* = 6.5, 3H), 2.41 (s, 3H), 3.79 (d, *J* = 13.0, 1H), 4.03 (d, *J* = 13.0, 1H), 4.81 (q, *J* = 6.5, 1H), 7.25−7.38 (m, 7H), 7.50 (d, *J* = 8.1, 2H); ^{13}C NMR (62.8 MHz) 21.4, 24.2, 54.5, 61.2, 119.2 (q, $^1J_{CF}$ = 261.9), 123.9, 126.6, 127.4, 128.6, 129.8, 130.2, 139.5, 142.9, 147.3 (q, $^2J_{CF}$ = 40.3); ^{19}F NMR (235 MHz) −72.1; IR (neat) 1608, 1533, 1186, 1149, 1028; HRMS (FAB) calcd for ($M^+ + 1$) $C_{18}H_{19}NOSF_3$ 354.1139, found 354.1143. Anal. Calcd for $C_{18}H_{18}NOSF_3$: C, 61.18; H, 5.13; N, 3.97; S, 9.07. Found: C, 61.25; H, 5.05; N, 3.83; S, 8.98.

(R,S_S)-2-(*Z*)-(*N*-1-Phenylethylimino)-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4d). Flash chromatography [*n*-hexanes−EtOAc (3:1)] on silica gel (R_f = 0.4) furnished (R,S_S)-**4d** (83%; route A, method 1) as a clear yellow solid: $[\alpha]^{25}_D$ +169.4 (*c* 1.08, $CHCl_3$); mp 138−140 °C; ^1H NMR (250 MHz) 1.46 (d, *J* = 6.5, 3H), 2.28 (s, 3H), 3.57 (d, *J* = 13.0, 1H), 4.00 (d, *J* = 13.0, 1H), 4.74 (q, *J* = 6.5, 1H), 7.11−7.28 (m, 7H), 7.46 (d, *J* = 8.1, 2H); ^{13}C NMR (62.8 MHz) 21.4, 25.2, 54.9, 60.9, 119.3 (q, $^1J_{CF}$ = 261.9), 123.6, 126.2, 127.2, 128.5, 130.3, 139.9, 142.7, 143.1, 147.5 (q, $^2J_{CF}$ = 40.3); ^{19}F NMR (235 MHz) −71.9; IR (neat) 1608, 1533, 1186, 1149, 1028; HRMS (FAB) calcd for ($M^+ + 1$) $C_{18}H_{19}NOSF_3$ 354.1139, found 354.1131. Anal. Calcd for $C_{18}H_{18}NOSF_3$: C, 61.18; H, 5.13; N, 3.97; S, 9.07. Found: C, 61.32; H, 5.11; N, 3.92; S, 9.02.

(R_S)-2-(*Z*)-(*p*-Anisylimino)-4,4,4,3,3-pentafluorobutyl-1-*p*-tolylsulfoxide (4e). Flash chromatography (*n*-hexanes−EtOAc (3:1)) on silica gel (R_f = 0.5) furnished **4e** (82%; route A, method 1) as a clear yellow solid: $[\alpha]^{25}_D$ −398.52 (*c* 0.81, $CHCl_3$); mp 58−60 °C; ^1H NMR (250 MHz) 2.41 (s, 3H), 3.76 (d, *J* = 12.7, 1H), 3.82 (s, 3H), 4.11 (d, *J* = 12.7, 1H), 6.90 (m, 4H), 7.29 (d, *J* = 8.2, 2H), 7.45 (d, *J* = 8.2, 2H); ^{13}C NMR (62.8 MHz) 21.4, 55.5, 56.2, 110.2 (tq, $^1J_{CF}$ = 260.5, $^2J_{CF}$ = 36.9), 114.2, 118.4 (qt, $^1J_{CF}$ = 286.4, $^2J_{CF}$ = 40.5), 121.5, 123.8, 130.2, 139.0, 140.2, 142.7, 150.0 (t, $^2J_{CF}$ = 27.7), 158.4; ^{19}F NMR (235

MHz) −50.6 (s, 3F), −83.8 (d, $^2J_{FF}$ = 286.3, 1F), −85.3 (d, $^2J_{FF}$ = 286.3, 1F); IR (KBr) 1500, 1242, 1054; HRMS (FAB) calcd for (M^+) $C_{18}H_{16}NO_2SF_5$ 405.0822, found 405.0825. Anal. Calcd for $C_{18}H_{16}NO_2SF_5$: C, 53.32; H, 3.98; N, 3.46; S, 7.91. Found: C, 53.10; H, 3.45; N, 3.46; S, 8.38.

(*R*,*R*$_S$)-2-(*Z*)-(*N*-1-Phenylethylimino)-4,4,4,3,3-pentafluorobutyl-1-*p*-tolylsulfoxide (4f). Flash chromatography (*n*-hexanes−EtOAc (3:1)) on silica gel (two spots were detected by TLC, R_f = 0.4, 0.1) furnished **4f** (80%; route A, method 1) as a yellow oil: $[\alpha]^{25}_D$ +2.75 (*c* 0.87, $CHCl_3$); ^{1}H NMR (200 MHz) 1.52 (d, *J* = 6.4, 3H), 2.35 (s, 3H), 3.67 (d, *J* = 13.0, 1H), 4.07 (d, *J* = 13.0, 1H), 4.84 (q, *J* = 6.4, 1H), 7.19−7.36 (m, 7H), 7.53 (d, *J* = 8.1, 2H); ^{1}H NMR (400 MHz) a small amount of the minor tautomer is observed 5.18 (s); ^{13}C NMR (62.8 MHz) 21.4, 25.6, 54.9, 61.4, 110.0 (tq, $^1J_{CF}$ = 255.8, $^2J_{CF}$ = 36.4), 118.4 (qt, $^1J_{CF}$ = 283.6, $^2J_{CF}$ = 40.5), 123.6, 126.0, 127.2, 128.5, 130.3, 139.7, 142.8, 143.2, 148.3 (t, $^2J_{CF}$ = 27.7); ^{19}F NMR (235 MHz) −81.1, −115.8; IR (neat) 1669, 1491, 1222, 1058; HRMS (FAB) calcd for (M^+ + 1) $C_{19}H_{19}NOSF_5$ 404.1108, found 404.1093. Anal. Calcd for $C_{19}H_{18}NOSF_5$: C, 56.57; H, 4.50; N, 3.47; S, 7.95. Found: C, 56.30; H, 4.42; N, 3.41; S, 7.83.

(*R*$_S$)-2-(*Z*)-Phenylimino-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4g). Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel (R_f = 0.55, *n*-hexane/EtOAc 7:3), gave **4g** (route A, 90% with method 2; route B, 85%) as a yellow oil: $[\alpha]^{25}_D$ −72.7 (*c* 0.33, $CHCl_3$); ^{1}H NMR (250 MHz) *δ* 2.40 (s, 3H), 3.74 (d, *J* = 12.6, 1H), 4.01 (d, *J* = 12.6, 1H), 6.75 (m, 2H), 7.17−7.40 (m, 7H); ^{13}C NMR (50.3 MHz) *δ* 21.3, 55.9, 119.0, 119.1 (q, $^1J_{CF}$ = 280.0), 123.9, 125.9, 129.0, 130.2, 139.9, 142.7, 145.9, 150.4 (q, $^2J_{CF}$ = 34.9); ^{19}F NMR (235 MHz) −72.4 (s); IR (NaCl) 1670, 1590, 1485, 1480, 1330, 1220, 1175, 1130; HRMS calcd for (M^+) $C_{16}H_{14}NOSF_3$ 325.0748, found 325.0740. Anal. Calcd for $C_{16}H_{14}NOSF_3$: C, 59.07; H, 4.34; N, 4.31. Found: C, 58.82; H, 4.71; N, 4.22.

(*R*$_S$)-2-(*Z*)-*m*-Anisylimino-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4h). Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel (R_f = 0.50, *n*-hexane/EtOAc 7:3), gave **4h** (quantitative; route A, method 2) as a yellow oil: $[\alpha]^{25}_D$ −76.2 (*c* 0.46, $CHCl_3$); ^{1}H NMR (250 MHz) *δ* 2.40 (s, 3H), 3.76 (d, *J* = 12.6, 1H), 3.80 (s, 3H), 4.03 (d, *J* = 12.6, 1H), 6.34 (m, 2H), 6.74 (m, 1H), 7.19−7.32 (m, 3H), 7.40 (d, *J* = 8.3, 2H); ^{13}C NMR (50.3 MHz) *δ* 21.4, 55.3, 56.0, 104.8, 111.0, 111.7, 119.1 (q, $^1J_{CF}$ = 279.2), 123.8, 129.9, 130.2, 139.9, 142.8, 147.0, 150.5 (q, $^2J_{CF}$ = 35.0), 160.2; ^{19}F NMR (235 MHz) −72.3 (s); IR (NaCl) 1665, 1590, 1575, 1475, 1325, 1270, 1255, 1195, 1175, 1130 (br); HRMS calcd for (M^+) $C_{17}H_{16}NO_2SF_3$ 355.0854, found 355.0840. Anal. Calcd for $C_{17}H_{16}NO_2SF_3$: C, 57.46; H, 4.54; N, 3.94. Found: C, 57.72; H, 4.54; N, 3.77.

(*R*$_S$)-2-(*Z*)-*n*-Hexylimino-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4i). Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel (three spots were detected by TLC, R_f = 0.60, 0.55, 0.25, *n*-hexane/EtOAc 7:3), gave **4i** (80%; route A, method 2) as a yellow oil: $[\alpha]^{25}_D$ +75.53 (*c* 0.17, $CHCl_3$); major imine isomer (ca. 90% of the mixture) ^{1}H NMR (250 MHz) *δ* 0.88 (m, 3H), 1.20−1.40 (m, 6H), 1.49−1.69 (m, 2H), 2.44 (s, 3H), 3.15−3.28 (m, 1H), 3.34−3.54 (m, 1H), 3.71 (d, *J* = 13.1, 1H), 4.04 (d, *J* = 13.1, 1H), 7.36 (d, *J* = 8.0, 2H), 7.56 (d, *J* = 8.0, 2H); ^{13}C NMR (50.3 MHz) *δ* 13.8, 21.2, 22.3, 26.7, 29.8, 31.3, 52.7, 54.3, 119.0 (q, $^1J_{CF}$ = 278.8), 123.7, 130.1, 139.7, 142.6, 148.6 (q, $^2J_{CF}$ = 34.2); ^{19}F NMR (235 MHz) *δ* −73.1 (s); minor enamine isomers (both ca. 5% of the mixture) ^{1}H NMR (250 MHz) *δ* 5.16 and 5.41 (s, SC*H*=C); ^{19}F NMR (235 MHz) *δ* −69.1 and −62.9 (s); IR (NaCl) 3300, 1690, 1620, 1550, 1510, 1470 (br), 1350, 1210, 1150 (br); HRMS calcd for (M^+) $C_{16}H_{22}NOSF_3$ 333.1374, found 333.1376. Anal. Calcd for $C_{16}H_{22}NOSF_3$: C, 57.64; H, 6.65; N, 4.20. Found: C, 58.01; H, 6.43; N, 3.65.

(*R*$_S$)-2-(*Z*)-Phenylimino-3-chloro-3,3-difluoropropyl-1-*p*-tolylsulfoxide (4j). Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel (R_f = 0.55, *n*-hexane/EtOAc 7:3) gave **4j** (route A, 74% with method 2; route B, 82%), which was recrystallized (*n*-hexane) to give a white solid: mp 63−65 °C; $[\alpha]^{20}_D$ −146.7 (*c* 0.21, $CHCl_3$); ^{1}H NMR (250 MHz) *δ* 2.41 (s, 3H), 3.78 (d, *J* = 12.8, 1H), 4.05 (d, *J* = 12.8, 1H), 6.79 (m, 2H), 7.15−7.40 (m, 7H); ^{13}C NMR (50.3 MHz) *δ* 21.4, 55.9, 119.0, 123.0 (t, $^1J_{CF}$ = 294.6), 123.8, 125.8, 129.0, 130.2, 140.2, 142.6, 146.0, 153.4 (t, $^2J_{CF}$ = 29.3); ^{19}F NMR (235 MHz) *δ* −60.0 (s); IR (NaCl) 1670, 1590, 1480, 1390, 1285, 1150, 1120, 1075, 1050, 1035. Anal. Calcd for $C_{16}H_{14}NOSF_2Cl$: C, 56.22; H, 4.13; N, 4.10. Found: C, 56.12; H, 4.18; N, 4.06.

(*R*$_S$)-2-(*Z*)-*m*-Anisylimino-3-chloro-3,3-difluoropropyl-1-*p*-tolylsulfoxide (4k). Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel (R_f = 0.50, *n*-hexane/EtOAc 7:3), gave **4k** (76%; route A, method 2), which was recrystallized (*n*-hexane/*i*-Pr_2O) to give a white solid: mp 68−69 °C; $[\alpha]^{25}_D$ −168.2 (*c* 0.40, $CHCl_3$); ^{1}H NMR (250 MHz) *δ* 2.41 (s, 3H), 3.80 (d, *J* = 12.9, 1H), 3.83 (s, 3H), 4.06 (d, *J* = 12.9, 1H), 6.39 (m, 2H), 6.72 (m, 1H), 7.25−7.35 (m, 3H), 7.38 (d, *J* = 8.2, 2H); ^{13}C NMR (50.3 MHz) *δ* 21.3, 55.3, 56.0, 104.8, 111.0, 111.7, 122.9 (t, $^1J_{CF}$ = 294.7), 123.7, 129.9, 130.2, 140.2, 142.7, 147.1, 153.5 (t, $^2J_{CF}$ = 29.2), 160.2; ^{19}F NMR (235 MHz) *δ* −60.0 (s); IR (NaCl) 1660, 1590, 1475, 1375, 1350, 1130; HRMS calcd for (M^+) $C_{17}H_{16}NO_2SF_2Cl$ 371.0558, found 371.0568. Anal. Calcd for $C_{17}H_{16}NO_2SF_2Cl$: C, 54.98; H, 4.35; N, 3.77. Found: C, 54.75; H, 4.20; N, 3.44.

(*S*,*S*$_S$)-2-(*Z*)-(*N*-1-Cyclohexylethylimino)-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4l). Flash chromatography (CH_2Cl_2) on silica gel (two spots were detected by TLC, R_f = 0.5, 0.2) gave **4l** (97%; route A, method 1) as a clear yellow oil: $[\alpha]^{25}_D$ −129.2 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz) 0.85−1.83 (m, 13H), 2.44 (s, 3H), 3.47 (m, 1H), 3.73 (t, *J* = 12.3, 1H), 3.96 (d, *J* = 12.3, 1H), 7.38 (d, *J* = 8.0, 2H), 7.59 (d, *J* = 8.0, 2H); ^{13}C NMR (62.8 MHz) 17.9, 21.4, 26.1, 26.2, 26.3, 29.0, 29.4, 43.8, 54.6, 62.2, 119.1 (q, $^1J_{CF}$ = 277.7), 123.9, 130.2, 140.1, 142.7, 147.0 (q, $^2J_{CF}$ = 33.9); ^{19}F NMR (235 MHz) four tautomers, −71.7 (87%), −67.2 (4%), −63.7 (3%), −61.8 (6%); IR (neat) 1449, 1338, 1140; HRMS (FAB) calcd for (M^+ + 1) $C_{18}F_{25}NOSF_3$ 360.1609, found 360.1601. Anal. Calcd for $C_{18}F_{24}NOSF_3$: C, 60.15; H, 6.73; N, 3.90; S, 8.92. Found: C, 59.95; H, 6.57; N, 3.80; S, 9.10.

(*S*$_S$)-2-(*Z*)-(*p*-Anisylimino)-(2-perfluoroheptyl)ethyl-1-*p*-tolylsulfoxide (4m). Flash chromatography [*n*-hexanes−EtOAc (3:1)] on silica gel (R_f = 0.5) afforded **4m** (92%; route A, method 1) as a clear yellow solid: $[\alpha]^{25}_D$ +269.4 (*c* 1.00, $CHCl_3$); mp 62−64 °C; ^{1}H NMR (200 MHz) 2.33 (s, 3H), 3.68 (d, *J* = 12.5, 1H), 3.74 (s, 3H), 4.04 (d, *J* = 12.5, 1H), 6.83 (s, 4H), 7.21 (d, *J* = 8.2, 2H), 7.37 (d, *J* = 8.2, 2H); ^{13}C NMR (62.8 MHz) 21.4, 55.5, 56.9, 106.0−116.1 (m, C_7F_{15}), 114.3, 121.4, 123.8, 130.3, 139.3, 140.3, 142.7, 150.5 (t, $^2J_{CF}$ = 26.7), 158.5; ^{19}F NMR (235 MHz) −81.1 (t, $^3J_{FF}$ = 9.8, 3F), −111.6 (dt, $^2J_{FF}$ = 280.5, $^3J_{FF}$ = 12.3, 1F), −113.2 (d, $^2J_{FF}$ = 280.5, $^3J_{FF}$ = 12.3, 1F), −120.9 (m, 4F), −122.3 (m, 2F), −123.0 (m, 2F), −126.4 (m, 2F); IR (neat) 1604, 1508, 1242, 1057; HRMS (FAB) calcd for (M^+) $C_{23}H_{16}NO_2SF_{15}$ 656.0741, found 656.0732. Anal. Calcd for $C_{23}H_{16}NO_2SF_{15}$: C, 42.13; H, 2.46; N, 2.14; S, 4.88. Found: 42.04; H, 1.99; N, 2.12; S, 4.76.

(*S*$_S$)-2-(*Z*)-(*p*-Tolylimino)-2-(*p*-fluorophenyl)ethyl-1-*p*-tolylsulfoxide (4n). Recrystallization (*n*-hexanes−EtOAc (5:1)) gave **4n** as a white solid (87%; route A, method 1): $[\alpha]^{25}_D$ +62.0 (*c* 0.71, $CHCl_3$); mp 241−243 °C; ^{1}H NMR (250 MHz) 2.34 (s, 3H), 2.39 (s, 3H), 4.05 (d, *J* = 12.8, 1H), 4.29 (d, *J* = 12.8, 1H), 6.50 (d, *J* = 8.0, 2H), 7.09−7.26 (m, 8H), 7.97 (dd, J_1 = 8.6, J_2 = 5.4, 2H); ^{13}C NMR (62.8 MHz) 20.8, 21.4, 57.7, 115.3, 115.7, 119.2, 124.2, 129.3, 129.6, 130.1, 133.5, 139.8, 142.2, 155.2, 162.5, 166.5; ^{19}F NMR (235 MHz) −109.3 (m, 1F); IR (KBr) 1635, 1514, 1224, 1043; HRMS calcd for (M^+ + 1) $C_{22}H_{21}NOSF$ 366.1328, found 366.1325. Anal. Calcd for $C_{22}H_{20}NOSF$: C, 72.30; H, 5.52; N, 3.83; S, 8.77. Found: C, 72.11; H, 5.42; N, 3.85; S, 8.50.

(*S*$_S$)-2-(*Z*)-(*p*-Anisylimino)-3-chloro-3,3-difluoropropyl-1-*p*-tolylsulfoxide (4o). Flash chromatography [*n*-hexanes−EtOAc (3:1)] on silica gel (R_f = 0.6) gave **4o** (72%; route A, method 1) as a brown solid: $[\alpha]^{25}_D$ +391.5 (*c* 1.02, $CHCl_3$); mp 59−61 °C; ^{1}H NMR (250 MHz) 2.32 (s, 3H), 3.71 (d, *J* = 12.7, 1H), 3.74 (s, 3H), 4.03 (d, *J* = 12.7, 1H), 6.80−6.83 (m, 4H), 7.20 (d, *J* = 8.2, 2H), 7.36 (d, *J* = 8.2, 2H); ^{13}C NMR (62.8 MHz) 21.4, 55.4, 55.7, 114.2, 121.4, 123.2 (t, $^1J_{CF}$ = 292.8), 123.8, 130.2, 138.9, 140.3, 142.6, 152.3 (t, $^2J_{CF}$ = 28.5), 158.2; ^{19}F NMR (235 MHz) −59.2 (d, $^2J_{FF}$ = 163.5, 1F), −60.0 (d, $^2J_{FF}$ = 163.5, 1F) ($CFCl_3$ as standard) or −59.2 (d, $^2J_{FF}$ = 163.5,

1F), −59.9 (d, $^2J_{FF}$ = 163.5, 1F) (C_6F_6 as standard); IR (neat) 1603, 1503, 1251, 1047; HRMS (FAB) calcd for (M^+ + 1) $C_{17}H_{17}NOSF_2Cl$ 372.0637, found 372.0624. Anal. Calcd for $C_{17}H_{16}NOSF_2Cl$: C, 54.98; H, 4.35; N, 3.77; S, 8.62. Found: 54.48; H, 4.15; N, 3.78; S, 8.94. The enantiomer **(R_S)-(*Z*)-4o** was obtained by aza-Wittig reaction in 97% yield (route B): $[\alpha]^{25}_D$ −344.6 (*c* 0.95, $CHCl_3$); R_f and ^{1}H, ^{13}C, and ^{19}F spectra were identical to those of enantiomeric compound **(S_S)-(*Z*)-4o**.

(S_S)-2-(*Z*)-(*p*-Anisylimino)-2-(3-pyridyl)ethyl-1-*p*-tolylsulfoxide (4p). Flash chromatography (EtOAc) on silica gel (R_f = 0.3) gave **4p** (80%; route A, method 1) as a dense yellow oil: $[\alpha]^{25}_D$ +21.3 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz) (major isomer) 2.28 (s, 3H), 3.72 (s, 3H), 3.98 (d, *J* = 13.0, 1H), 4.00 (d, *J* = 13.0, 1H), 6.60 (d, *J* = 8.8, 2H), 6.79 (d, *J* = 8.8, 2H), 7.05−7.32 (m, 5H), 8.15 (m, 1H), 8.54 (m, 1H), 9.06 (m, 1H); ^{13}C NMR (75 MHz) 22.2 (q), 56.4 (q), 57.9 (t), 115.1 (d), 121.6 (d), 124.2 (d) 124.8 (d), 130.9 (d), 134.2 (s), 136.2 (d), 140.5 (s), 143.3 (d), 149.7 (s), 152.2 (d), 157.6 (s), 157.8 (s), 179.7 (s); IR (neat) 1634, 1585, 1241, 1035; HRMS (FAB) calcd for (M^+ + 1) $C_{21}H_{21}N_2O_2S$ 365.1324, found 365.1334. Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69; S, 8.80. Found: 69.05; H, 5.22; N, 7.55; S, 8.68.

(S_S)-2-(*Z*)-Cyclohexylimino-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4q). Flash chromatography [*n*-hexanes−EtOAc (5:1)] on silica gel (R_f = 0.2) gave **4q** (72%; route A, method 1) as a clear yellow oil: $[\alpha]^{25}_D$ −158.2 (*c* 1.15, $CHCl_3$); ^{1}H NMR (250 MHz) 1.09−1.79 (m, 10H), 2.35 (s, 3H), 3.21 (m, 1H), 3.69 (d, *J* = 12.6, 1H), 3.92 (d, *J* = 12.6, 1H), 7.30 (d, *J* = 8.0, 2H), 7.51 (d, *J* = 8.0, 2H); ^{13}C NMR (62.8 MHz) 21.2 (q), 23.7 (t), 23.8 (t), 25.0 (t), 32.5 (t), 32.7 (t), 54.2 (t), 61.0 (d), 119.0 (CF_3, q, $^1J_{CF}$ = 277.5), 123.8 (d), 130.1 (d), 139.6 (s), 142.7 (s), 146.0 (C=N, q, $^2J_{CF}$ = 34.7); ^{19}F NMR (235 MHz) −72.0 (81.0%), −68.1 (8.0%), −64.2 (1.5%), −61.8 (9.5%); IR (KBr) 1669, 1595, 1198, 1056; HRMS (FAB) calcd for (M^+ + 1) $C_{16}H_{21}NOSF_3$ 332.1296, found 332.1293. Anal. Calcd for $C_{16}H_{20}NOSF_3$: C, 57.99; H, 6.08; N, 4.23; S, 9.67. Found: C, 57.72; H, 5.87; N, 4.19; S, 9.58.

(±)-(*S*,*R*/S_S)-2-(*Z*)-(*N*-1-Cyclohexylethylimino)-3,3,3-trifluoropropyl-1-phenylsulfoxide (4r). MPLC [*n*-hexanes−EtOAc (3:1)] on silica gel (two spots were detected by TLC, R_f = 0.7, 0.3) gave **4r** (85%; route A, method 1) as a clear yellow oil: diastereomeric mixture (ca. 1:1) ^{1}H NMR (250 MHz) (*S*,S_S), 0.85−1.83 (m, 13H), 3.34−3.48 (m, 1H), 3.71 (t, *J* = 12.3, 1H), 3.89 (d, *J* = 12.3, 1H), 7.45−7.69 (m,4H); (*S*,R_S), 0.85−1.83 (m, 13H), 3.34−3.48 (m, 1H), 3.57 (t, *J* = 12.3, 1H), 3.99 (d, *J* = 12.3, 1H), 7.45−7.69 (m, 4H); ^{13}C NMR (50 MHz) (both diastereomers) 17.7 (q), 18.7 (q), 25.9 (t), 26.0 (t), 26.1 (t), 26.2 (t), 29.2 (t), 29.3 (t), 43.3 (d), 43.7 (d), 54.3 (t), 54.5 (t), 62.1 (d), 62.5 (d), 119.4 (CF_3, q, $^1J_{CF}$ = 274.2), 123.6 (d), 123.7 (d), 129.5 (d), 131.9 (d), 131.9 (d), 143.2 (s), 143.4 (s), 146.8 (C=N, q, $^2J_{CF}$ = 33.9); ^{19}F NMR (235 MHz) four isomers each diastereoisomer, −71.8 (85.3%), −67.2 (3.9%), −63.7 (2.3%), −61.8 (8.5%); −71.6 (87.0%), −67.4 (4.3%), −63.5 (2.2%), −61.8 (6.5%); IR (neat) 1669, 1443, 1334, 1139, 1086, 1049; HRMS (FAB) calcd for (M^+ + 1) $C_{17}H_{23}NOSF_3$ 346.1452, found 346.1446. Anal. Calcd for $C_{17}H_{22}NOSF_3$: C, 59.11; H, 6.42; N, 4.05; S, 9.28. Found: C, 58.95; H, 6.34; N, 4.08; S, 9.22.

(R_S)-(*Z*)-2-(2-hydroxycarbonylphenylimino)-3,3,3-trifluoropropyl-1-*p*-tolylsulfoxide (4s). The reaction between 2-methoxycarbonylphenyltrifluoroacetimidoyl chloride **1s** and lithiated methyl *p*-tolyl sulfoxide (*R*)-**2a**, according to the general procedure, directly provided **4s** (71%, route A, method 2), purified by flash chromatography [*n*-hexanes−EtOAc (1:1)] on silica gel (R_f = 0.45) and recrystallized (*i*-Pr_2O) to give a white solid: $[\alpha]^{25}_D$ +125.9 (*c* 0.068, $CHCl_3$); mp 152−155 °C; ^{1}H NMR (250 MHz) 2.40 (s, 3H), 4.33 (d, *J* = 13.5, 1H), 4.56 (d, *J* = 13.5, 1H), 7.26−7.34 (m, 3H), 7.50 (d, *J* = 7.7, 2H), 7.69 (m, 1H), 7.90 (d, *J* = 8.1, 1H), 8.66 (d, *J* = 8.5, 1H), 10.25 (br s, 1H); ^{13}C NMR (50.3 MHz) 21.3, 66.6, 115.4 (q, $^1J_{CF}$ = 288.6), 121.0, 122.4, 124.0, 124.8, 130.0, 132.5, 136.3, 138.4, 138.9, 142.6, 155.4 (q, $^2J_{CF}$ = 37.7), 195.8; ^{19}F NMR (235 MHz) −77.44 (s); HRMS calcd for (M^+) $C_{17}H_{14}NO_3SF_3$ 369.0647, found 369.0651. Anal. Calcd for $C_{17}H_{14}NO_3SF_3$: C, 55.28; H, 3.82; N, 3.79. Found: C, 55.34; H, 3.90; N, 3.78.

(R_S)-2-(*Z*)-(Phenylimino)-4,4,4,3,3-pentafluorobutyl-1-*p*-tolylsulfoxide (4t). Flash chromatography [*n*-hexanes−EtOAc (3:1)] on silica gel (R_f = 0.60, *n*-hexanes−EtOAc 7:3) furnished **4t** (76%; route B), which was recrystallized (*i*-Pr_2O) to give a white solid: $[\alpha]^{25}_D$ −133.4 (*c* 1.0, $CHCl_3$); mp 96−98 °C; ^{1}H NMR (250 MHz) 2.41 (s, 3H), 3.76 (d, *J* = 12.6, 1H), 4.03 (d, *J* = 12.6, 1H), 6.78 (m, 2H), 7.15−7.43 (m, 7H); ^{13}C NMR (100.6 MHz) 21.5, 56.4, 109.9 (tq, *J* = 258.3 and 37.1), 118.4 (qt, *J* = 286.8 and 35.7), 119.0, 123.8, 126.05, 129.05, 130.2, 140.1, 142.7, 146.0, 151.5 (t, $^2J_{CF}$ = 28.1); ^{19}F NMR (235 MHz) −117.3 (d, $^2J_{FF}$ = 313, 1F), −116.0 (d, $^2J_{FF}$ = 313, 1F), −82.3 (s, 3F); HRMS calcd for (M^+) $C_{17}H_{14}NOSF_5$ 375.0716, found 375.0704. Anal. Calcd for $C_{17}H_{14}NOSF_5$: C, 54.40; H, 3.76; N, 3.73. Found: C, 54.53; H, 3.77; N, 3.72.

(R_S)-2-(*Z*)-(Phenylimino)-3,3-difluoropropyl-1-*p*-tolylsulfoxide (4u). Flash chromatography [cyclohexanes−EtOAc (7:3)] on silica gel (R_f = 0.35) furnished **4u** (90%; route B), as a red oil: $[\alpha]^{25}_D$ +76.34 (*c* 0.87, $CHCl_3$). Imine tautomer (ca. 90% of the mixture): ^{1}H NMR (250 MHz) 2.41 (s, 3H), 3.74 (d, *J* = 12.4, 1H), 3.96 (d, *J* = 12.4, 1H), 6.23 (t, J_{CF} = 54.8, 1H), 6.67 (m, 2H), 7.22−7.42 (m, 7H); ^{13}C NMR (62.8 MHz) 21.5, 54.95, 113.95 (t, $^1J_{CF}$ = 244.6), 119.1, 123.9, 125.5, 129.0, 130.2, 140.3, 142.5, 146.8, 155.6 (t, $^2J_{CF}$ = 27.7); ^{19}F NMR (235 MHz) −121.8 (dd, $^2J_{FF}$ = 317 and $^2J_{FH}$ = 54.9, 1F), −120.4 (dd, $^2J_{FF}$ = 317 and $^2J_{FH}$ = 54.9, 1F). Enamine tautomer (ca. 10% of the mixture): ^{1}H NMR (250 MHz) 2.39 (s, 3H), 5.83 (d, *J* = 3, 1H), 6.21 (br signal, 1H), 7.13 (d, *J* = 8, 2H), 7.23 (t, *J* = 54, 1H), 7.16−7.34 (m, 5H), 7.47 (d, *J* = 8, 2H); ^{19}F NMR (235 MHz) −114.9 (dd, $^2J_{HF}$ = 54 and $^2J_{FF}$ = 305), −125.7 (dd, $^2J_{HF}$ = 54 and $^2J_{FF}$ = 305); HRMS calcd for (M^+) $C_{16}H_{15}NOSF_2$ 307.0842, found 307.0844.

(R_S)-2-(*Z*)-(Phenylimino)-3-fluoropropyl-1-*p*-tolylsulfoxide (4v). The aza-Wittig reaction was carried out at 50 °C for 30 h. Flash chromatography [*n*-hexanes−EtOAc (7:3)] on silica gel (R_f = 0.25) furnished **4v** (ca. 30%; route B), as a red oil, and as a mixture with ca. 30% of starting monofluoro β-ketosulfoxide (*R*)-**5a**. (*R*)-**4v** in an almost equimolar ratio of two iminic tautomers. Overall yield ca. 30%: ^{1}H NMR (250 MHz) 2.41 (s, 3H) and 2.43 (s, 3H), 3.66 (dd, *J* = 2.1 and 12.5, 1H) and 3.82 (dd, *J* = 2.1 and 12.5, 1H), 4.07 (d, *J* = 1.1, 1H), 4.08 (d, *J* = 1.1, 1H), 4.77 (d, *J* = 46.6, 2H), 4.79 (d, *J* = 46.6, 2H), 5.12 (dd, J_{HH} = 13.4 and J_{HF} = 46.6, 1H) and 5.19 (dd, J_{HH} = 13.4 and J_{HF} = 46.6, 1H); ^{19}F NMR (235 MHz) −225.25 (t, *J* = 46.6), −224.3 (t, *J* = 46.6).

Acknowledgment. The authors are grateful to the Dirección General de Investigación Científica y Técnica for their financial support of this research (DGICYT, PB94-1313-C02-02 and PB97-0760-C02-01) and also the CIEMAT (Ministerio de Industria y Energía) for computer time. A predoctoral fellowship from the Universidad de Valencia to A.N. and from the Generalitat Valenciana to B.P. are also gratefully acknowledged.

Supporting Information Available: Calculated relative energies (kcal mol^{-1}) at semiempirical (AM1) and ab initio (HF/3-21G) calculations (Table 4) and copies of optimized structures at the HF/6-31G* level corresponding to compounds **1a**, **1q**, **4a**, **4c**, **4d**, **4v**, and **4A**−**E** (41 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.

JO980336F