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Asymmetric Synthesis of α-Arylglycinols *via* Additions of Lithium Methyl *p*-Tolyl Sulfoxide to *N*-(PMP)arylaldimines Followed by "Non Oxidative" Pummerer Reaction

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Abstract: The results presented in this paper demonstrate that the stereochemical outcome of the reversible additions of lithium (*R*)-methyl *p*-tolyl sulfoxide to *N*-arylidene-*p*-anisidines (*N*-PMP imines) is a function of a) the reaction conditions used and b) the electronic properties of the arylidene moiety on the starting imine. High kinetically controlled (2*S*,*R*S) diastereoselectivity (-70 °C) was achieved for additions of imines bearing relatively electron-rich *N*-arylidene groups, while an electron-deficient nature of this group was found to favor the opposite stereochemical outcome. On the other hand, the reactions run under thermodynamically controlled conditions (0 °C) afforded equimolar mixtures of the diastereomeric products regardless of the pattern of substitution on the starting imines. Enantiopure α-arylglycinols were readily synthesized by "non-oxidative" Pummerer rearrangement of diastereomerically pure β-aryl-β-*N*-(acyl)aminoalkyl sulfoxides, prepared from the corresponding *N*-PMP derivatives.

INTRODUCTION

Chiral sulfoxide-controlled asymmetric reactions represent one of the most developed and reliable methodologies of stereoselective organic synthesis.[1] Application of a sulfoxide group as a chiral auxiliary provides unique synthetic benefits associated with its manifold reactivity. Thus, depending on the architecture of the molecule and the method used to remove the sulfinyl group, it could serve as a chiral equivalent of alkyl (reductive desulfurization),[2] vinyl (*syn*-elimination reaction),[3] hydroxymethyl/hydroxycarbonyl (*Pummerer* rearrangement),[4] and amino (hydrolysis of *N*-sulfinamides) groups.[1h] The use of chiral sulfoxide-stabilized carbanions for asymmetric carbon-carbon bond formation, *via* alkylation or addition reactions to C=O and activated C=C double bonds, is the most synthetically powerful application of this chiral auxiliary and has been extensively studied over the past 15 years.[1f] However, the chiral sulfoxide-controlled additions of nucleophiles to the C=N bond of achiral imines has received much less attention.[5,6] In 1973, Tsuchihashi *et al.* reported

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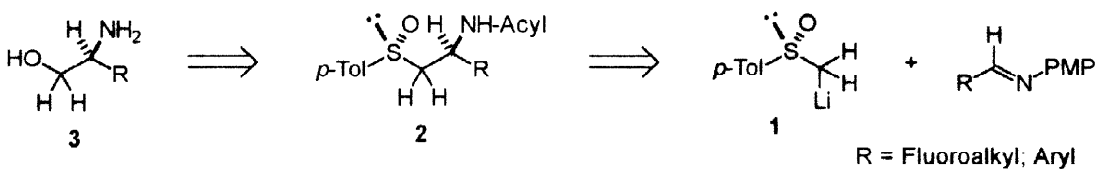
that the reaction between *N*-(benzylidene)aniline and lithium derivative of *p*-tolyl methyl sulfoxide (**1**) occurred with excellent diastereoselectivity to afford the corresponding β-sulfinylethylamine as a sole reaction product.[5a] However, 15 years later, this data was substantially challenged by Kagan *et al.*,[5b] who failed to reproduce the reported diastereoselectivity: under the conditions of Tsuchihashi the diastereomers were observed in a ratio of 75/25. Moreover, these authors found that the stereochemical outcome of the reaction was affected in a surprisingly important manner by the temperature of formation and reaction of **1** with imines. On the other hand, a systematic study conducted by Pyne *et al.* revealed that the diastereoselectivity of the reactions of various chiral sulfoxide-stabilized nucleophiles with imines is subject to kinetic-thermodynamic control.[5c-e] In general, remarkably lower diastereoselection was achieved under equilibrium control. In 1984, Reutrakul *et al.* described the use of α-lithio α-chloro- and α-fluoromethyl phenyl sulfoxide to give the corresponding aziridines in good yields.[5f] Finally, Yamakawa *et al.* described highly diastereoselective reactions between *p*-tolyl 1-chloroalkyl sulfoxides and *N*-(benzylidene)anilines as a general entry to the corresponding *N*-(aryl)aziridines and *N*-(aryl)-1-arylamines.[5g,h]

Retrosynthetic Scheme



As part of our ongoing goal of developing asymmetric methods for preparing selectively fluorinated biologically relevant compounds,[7,8] we have been interested in the addition reactions of lithium methyl *p*-tolyl sulfoxide (**1**) (Retrosynthetic Scheme) to fluorine-containing imines as a general approach to the corresponding amines and amino acids.[9] In particular, we have recently reported some diastereoselective additions of (*R*)-**1** to *N*-(*p*-methoxyphenyl)imines [*N*-(PMP)imines] derived from perfluoroalkyl aldehydes. The mode of reactivity as well as the stereochemical outcome of these reactions were found to be quite different from those described for fluorine-free substrates.[6] The resultant β-sulfinyl amines **2** (R = fluoroalkyl), as their fluorine-free analogues,[10] were found to be synthetically versatile intermediates for preparing a number of biologically relevant amino compounds.[6,9,11] A pleasant bonus from exploration of the reactivity of *N*-acyl-α-fluoroalkyl-β-sulfinylethylamines **2** was the disclosure of a one-pot high yield transformation of these compounds into the corresponding β-fluoroalkyl β-amino alcohols **3**, referred by us as the "non oxidative" *Pummerer* reaction.[11a,b] To demonstrate the general scope and the preparative value of the methodology, we decided to study the additions of lithium methyl *p*-tolyl sulfoxide (**1**) to *N*-(PMP)imines derived from a series of aromatic aldehydes, for preparing the corresponding α-arylglycinols **3** (R = aryl). An additional incentive to undertake this study was the opportunity to shed light upon the discordant data reported on the reactions of chiral sulfoxide-stabilized nucleophiles with imines (*vide supra*)[5a,b] and upon the origin of the stereogenesis in these reactions.

RESULTS AND DISCUSSION

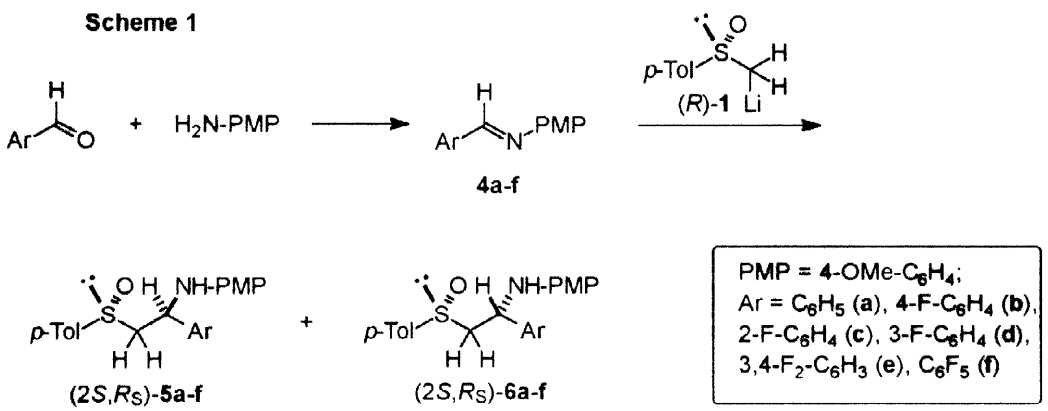
Our experience in the additions of lithium methyl *p*-tolyl sulfoxide (**1**) to fluorinated imines[6,9] suggested that the corresponding *N*-(PMP)imines are the substrates of choice. In fact, the PMP-group can be readily cleaved to afford a free amino function,[12] it provides geometric homogeneity of the imine functionality,[13] it

leaves the C=N double bond electrophilic enough to undergo smooth addition, and it allows the imine nitrogen to form coordinated transition states.[6] Such features are of paramount importance for achieving synthetic efficiency and stereocontrol. A series of *N*-(PMP)arylimines **4a-f**, including unsubstituted *N*-benzylidene-*p*-anisidine (**4a**), monofluoro- **4b-d**, difluoro- **4e** and pentafluoroderivatives **4f** (Scheme 1), was prepared in high chemical yields *via* acid catalyzed condensation of the starting aldehyde and *p*-anisidine. All *N*-(PMP)arylimines **4a-f** were obtained as geometrically (*E*)-homogeneous compounds, according to ^{1}H and ^{19}F NMR spectra.[13]

Addition reactions between *N*-(PMP)arylimines 4a-f and lithium derivative of (*R*)-methyl *p*-tolyl sulfoxide 1 (Table 1).

The stereochemical outcome of reactions between lithium sulfoxide **1** and unsubstituted imine **4a**, as a function of the conditions used (Scheme 1), was studied first. We found that addition of **1** (1.0 equiv), prepared with LDA (1.2 equiv) at -70 °C, to the imine **4a** (1.2 equiv) occurred smoothly at the same temperature to afford, with 70% conversion in 15 min (entry 1), a mixture of the corresponding diastereomers (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** in a ratio of 92.4/7.6, respectively. Prolonged reaction time, 30 min (entry 2), as expected increased conversion of the starting compounds to the products (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** without influencing the stereochemical outcome. Next, we performed a series of reactions varying the temperature of deprotonation of the starting sulfoxide by LDA. Thus, addition of lithium sulfoxide **1**, prepared at -40 °C, to the imine **4a**, at -70 °C, gave a mixture of (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** in the same ratio (92.0/8.0) recorded for the reaction of **1** prepared at -70 °C (entry 2 *vs* entry 3). This result differs from that reported by Kagan *et al.* for the addition of **1** to benzylideneaniline (entry 3 *vs* entry 4).[5b] On the other hand, the reaction of lithium sulfoxide **1**, prepared at 0 °C, and imine **4a** performed at -70 °C (entry 5) gave rise to a mixture of (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** in a ratio of 93.0/7.0, that is markedly higher than the ratio reported by Kagan *et al.* for this reaction (entry 5 *vs* entry 6) and in line with the 92.0/8.0 diastereomeric ratio recorded by the same authors for the reaction of **1** with the benzylideneaniline (entry 5 *vs* entry 7).[5b]

Scheme 1



It is also worth noting that our yield of diastereomeric (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** was much higher than that reported in literature[5b] (entry 5 *vs* entry 6). To better understand the nature of the stereocontrol in these reactions, we performed the addition between lithium sulfoxide **1** and imine **4a** at -70 °C followed by stirring of

Table 1. Addition reactions between imines **4a-f** and lithium (*R*)-methyl *p*-tolyl sulfoxide **1**.

Entry		Ar	T1[a] °C	T2[b] °C	Time min	Yield[c], %	Ratio[d] (2*S*,*R*S)-**5**	(2*R*,*R*S)-**6**
1	**(a)**	C_6H_5	-70	-70	15	69 (70)[e]	92.4[e]	7.6
2	**(a)**	C_6H_5	-70	-70	30	84 (95)[e]	92.0[e]	8.0
3	**(a)**	C_6H_5	-40	-70	15	68 (69)[e]	92.0[e]	8.0
4[f]	**(a)**	C_6H_5[g]	-40	-78	90	88 (-)	77.0	23.0
5	**(a)**	C_6H_5	0	-70	15	73 (73)[e]	93.0[e]	7.0
6[f]	**(a)**	C_6H_5	0	-78	15	32 (-)	86.0	14.0
7[f]	**(a)**	C_6H_5[g]	0	-78	10	99 (-)	92.0	8.0
8	**(a)**	C_6H_5	-70	-70 to 0	120[h]	88 (-)[i]	50.0[e]	50.0
9	**(b)**	4-F-C_6H_4	-70	-70	15	80 (81)[e]	88.2	11.8
10	**(c)**	2-F-C_6H_4	-70	-70	15	84 (91)[e]	87.7	12.3
11	**(c)**	2-F-C_6H_4	0	-70	20	97 (>98)[e]	83.8	16.2
12	**(c)**	2-F-C_6H_4	0	-70 to 0	120[h]	97 (>98)	50.0	50.0
13	**(d)**	3-F-C_6H_4	-70	-70	30	95 (>98)[e]	84.4	15.6
14	**(e)**	3,4-F_2-C_6H_3	-70	-70	25	82 (>98)	79.9	20.1
15	**(e)**	3,4-F_2-C_6H_3	-70	-70	60	77 (>98)	76.0	24.0
16	**(f)**	C_6F_5	-70	-70	60	68 (69)	63.5	36.5
17[f]	**(g)**	4-MeO-C_6H_5	0	-78	40	74 (-)	95.0	5.0
18[f]	**(h)**	4-NO_2-C_6H_5	0	-78	10	95 (-)	76.0	24.0

[a] Temperature at which lithium (*R*)-methyl *p*-tolyl sulfoxide **1** was formed. [b] Temperature of the addition reaction between the corresponding imine (1.2 equiv) and lithium (*R*)-methyl *p*-tolyl sulfoxide **1** (1.0 equiv). [c] Overall isolated yield of both diastereomers (2*S*,*R*S)-**5** and (2*R*,*R*S)-**6**. Conversion (%) of the starting imine, as determined by NMR spectroscopy on the crude reaction mixtures, is given in the parentheses. [d] The ratios were determined by ^1H and ^{19}F NMR [except for (a)] analysis of the crude reaction mixtures. [e] Yields and diastereomer ratios were determined by ^1H NMR and HPLC analyses of the crude reaction mixtures. [f] As reported by Kagan *et al.*, see ref. 5b [g] Reaction of lithium sulfoxide **1** with benzylideneaniline; see ref. 5b. [h] The reaction mixture was stirred for 2 h at 0 °C. [i] Not determined.

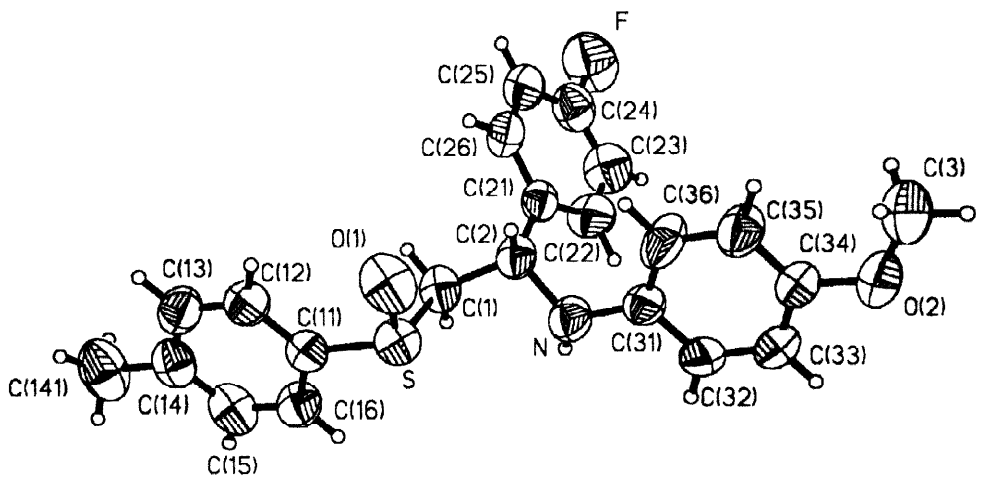
the resultant mixture for 2 h at 0 °C: a virtually 1/1 mixture of diastereomers (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** was obtained (entry 8).

Assuming that the addition is a reversible process and that the diastereomers readily equilibrate at 0 °C we took diastereomerically pure (2*S*,*R*S)-**5a**, which was treated with LDA at -70 °C and the resultant mixture was stirred for 2 h at 0 °C. ^{1}H NMR spectroscopy and HPLC analysis of the crude reaction mixture revealed that a 1/1 ratio of diastereomers (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** was formed, along with minute amounts of the starting compounds. This data indicates that the addition reaction is reversible and its stereochemical outcome can be subject either to kinetic or to thermodynamic control, producing respectively high or low diastereoselectivity. This conclusion is in full agreement with the results reported by Pyne *et al.* on the additions of lithium derivative **1** to benzylideneaniline and related arylimines.[5d]

To assess the ratio of diastereomers **5a** and **6a** both ^{1}H NMR spectroscopy and HPLC analysis were tried. Unfortunately, ^{1}H NMR spectra patterns of diastereomers (2*S*,*R*S)-**5a** and (2*R*,*R*S)-**6a** are extremely similar except for the resonances of the methylene groups. Furthermore, the signal of the minor diastereomer is split into eight lines, the AB part of an ABX system. Therefore, HPLC analysis was used for an accurate determination of the diastereomeric ratios of **5a**/**6a** in the crude reaction mixtures, providing data with an estimated error of ± 0.1 %.

Introduction of just one fluorine atom on the benzylidene site of the starting imine **4** unexpectedly reduced the diastereoselectivity of the condensation. Addition of lithium derivative **1** to the 4-fluoro-imine **4b** afforded a mixture of diastereomers (2*S*,*R*S)-**5b** and (2*R*,*R*S)-**6b** in a ratio of 88.2/11.8 (entry 9). X-ray diffraction of a suitable single crystal grown from a mixture of *n*-hexane/ethyl acetate confirmed the expected (2*S*,*R*S) configuration of the major diastereomer **5b**. In Figure 2 an ORTEP[14a] drawing of (2*S*,*R*S)-**5b** is shown in the absolute configuration and with the appropriate atomic labeling.[14b,c]

Figure 2 - ORTEP[14a] drawing of (2*S*,*R*S)-**5b**. The displacement ellipsoids are shown at the 50% probability level.



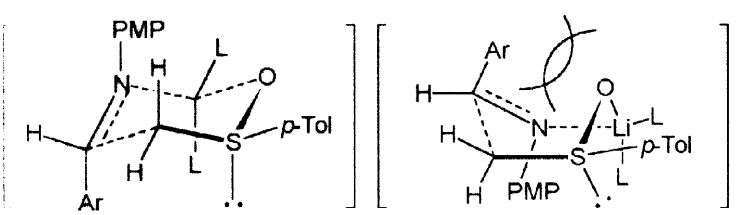
The position of the fluorine atom on the benzylidene site of the starting imine **4** was also found to influence the stereoselectivity of the reaction, albeit to a small extent. Addition of **1** to 2-fluoro-substituted

imine **4c** gave a mixture of diastereomers (2*S*,*R*S)-**5c** and (2*R*,*R*S)-**6c** in a ratio of 87.7/12.3 (entry 10). The influence of the reaction conditions on the stereochemical outcome was checked also in this case. Thus, the reaction of **1**, prepared at 0 °C, with imine **4c** gave rise to a mixture of (2*S*,*R*S)-**5c** and (2*R*,*R*S)-**6c** with a slightly lower diastereoselectivity (83.8/16.2) (entry 11), while equilibration of the diastereomers at 0 °C afforded an equimolar mixture of (2*S*,*R*S)-**5c** and (2*R*,*R*S)-**6c** (entry 12). The reaction between 3-fluoro-substituted imine **4d** and **1** afforded a mixture of the corresponding diastereomers (2*S*,*R*S)-**5d** and (2*R*,*R*S)-**6d** with a ratio of 84.4/15.6 (entry 12), that is the lowest value in the series of the monofluoro-substituted imines.

Addition of an extra fluorine atom to the benzylidene site was found to decrease further the stereocontrol. The reaction of 3,4-difluorosubstituted imine **4e** with lithium sulfoxide **1**, performed under standard conditions, gave a mixture of diastereomers (2*S*,*R*S)-**5e** and (2*R*,*R*S)-**6e** in a 79.9/20.1 ratio, respectively (entry 14). Prolonged reaction time, from 25 min to 1 h, resulted in decreased stereoselectivity (76.0/24.0) (entry 15 *vs* entry 14). Finally, to observe the influence of the extreme case of fluorination on the benzylidene site of the starting imine, we performed the addition of lithium sulfoxide **1** to pentafluorobenzylideneimine **4f**. The reaction followed the expected trend, giving rise to a mixture of diastereomers (2*S*,*R*S)-**5f** and (2*R*,*R*S)-**6f** in a ratio of 63.5/36.5 (entry 16).

Some general conclusions on the nature of stereoselectivity in these reactions can be drawn, on the basis of the data obtained. Firstly, the reactions were shown to proceed in a reversible manner providing an option for kinetic and thermodynamic control of the stereochemical outcome. Taking into account that the time of the reactions conducted at -70 °C did not influence markedly the ratio of diastereomers (2*S*,*R*S)-**5** and (2*R*,*R*S)-**6** (entry 1 *vs* entry 2, and entry 14 *vs* entry 15), we suggest that the stereochemical outcome of the additions carried out at -70 °C reflect kinetic control. On the other hand, one could propose that at temperatures higher than -70 °C, equilibration of the diastereomers might proceed with a higher rate being completed in 2 h at 0 °C (entries 8, 12). Accordingly, to obtain the diastereomers in the kinetically controlled ratio, the reaction should be quenched instantly at -70 °C. In spite of these intricacies, that could affect the recorded diastereomeric ratios, the chemical and stereochemical outcomes of the reactions proved to be remarkably reproducible. This was assessed by performing each addition at least twice. Second, an increase of electron-deficiency of the benzylidene aromatic group of starting imine was found to decrease the kinetically controlled (2*S*,*R*S) diastereoselectivity. This trend, revealed by increasing progressively the fluorine substitution for hydrogen on the benzylidene phenyl ring of **4a-f** (entries 1, 9, 14 and 16), is in good agreement with the data reported by Kagan *et al.* on the reactions of lithium sulfoxide **1** with *N*-(*p*-methoxybenzylidene)- **4g** (entry 17) and *N*-(*p*-nitrobenzylidene)-*p*-anisidines **4h** (entry 18).[5b] According to that study, addition of **1** to imine **4g**, bearing the electron-releasing methoxy substituent, afforded a (2*S*,*R*S) diastereoselectivity even higher (95/5) than that recorded for the reaction of unsubstituted imine **4a** (entry 17 *vs* entries 5, 6). In contrast, addition of **1** to imine **4h**, bearing the electron-withdrawing *p*-nitro substitutent, gave the diastereomeric products with a much lower ratio (76/24) than that of the unsubstituted imine **4a** (entry 18 *vs* entries 5, 6), and comparable with the

Figure 3



TS-A
to give (2*S*,*R*S)-**5a-f**

TS-B
to give (2*S*,*R*S)-**6a-f**

stereochemical outcome recorded by us for the addition of difluoro-substituted imine **4e** (entry 18 *vs* entries 14, 15).

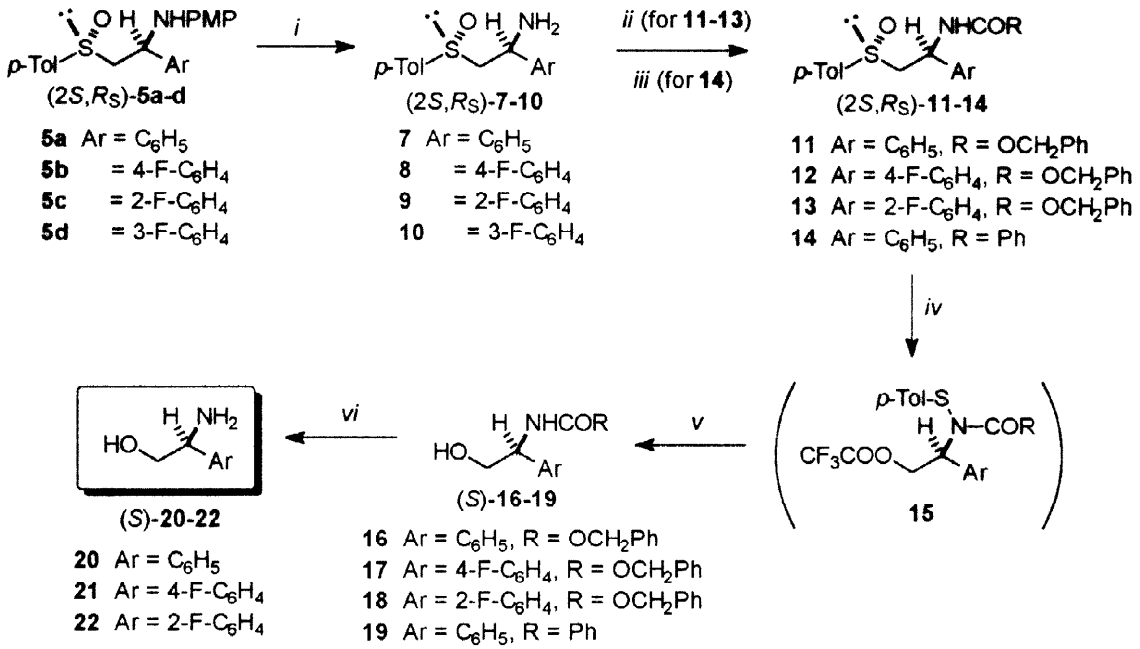
Steric factors are usually dominant in governing the stereochemical outcome in asymmetric reactions. Examples in which electronic, and not steric properties of substituents are of paramount importance in controlling the stereoselectivity are less common. According to Pyne *et al.*,[5c-e] two chelated cyclic transition states (TSs) **A** and **B** might be drawn to account for the formation of diastereomers (2*S*,*R*S)-**5** and (2*R*,*R*S)-**6** (Figure 3). Chair TS-**A** was supposed to be generally more favorable since in the boat TS-**B** the substituent Ar, or any other one, would experience a repulsive steric flagpole interaction with the sulfoxide oxygen. This rationale works nicely to explain the substantial preference for the (2*S*,*R*S) diastereoselectivity in the reaction of unsubstituted imine **4a** with lithium sulfoxide **1**. But how would it help to rationalize both the higher (2*S*,*R*S) preference in the reaction of more electron-rich imine **4g** and, on the other hand, the dramatic erosion of stereoselectivity in favour of the (2*S*,*R*S)-diastereomers in the reactions of the fluoro- and nitro-substituted imines apparent in Table 1? These results are reminiscent of our previous apparently unrelated data on the asymmetric aldol reactions between fluorinated aromatic aldehydes and *iso*-cyanoacetic acid derivatives catalyzed by a gold(I) complex with a chiral *N*,*N*,*N*′,*N*′-tetra-alkylethylenediamino-substituted bis(diphenylphosphino)ferrocene ligand,[15] as well as the results reported by Ojima and Kwon on the phenomenal stereodifferentiation for the aldol reactions of pentafluorophenyl-containing chiral iron acyl complex (PFCHIRAC).[16] In these works an unusual π-p attractive interaction between the electron-deficient fluorinated aromatic ring and the negatively charged enolate oxygen was invoked to explain the stereochemical outcomes. Based on previous experience,[15,16] we suggest that sterically unfavorable transition-state **B**, which leads to the formation of (2*R*,*R*S)-configured products, could be ***stabilized*** by a π-p attractive interaction between the electron-deficient fluorinated benzylidene phenyl ring of the imine and a negatively charged sulfoxide oxygen. The same event might take place in the reaction of *p*-nitro-substituted imine **4h** with lithium sulfoxide **1**. On the other hand, in the reaction of *p*-methoxy-substituted imine **4g**, TS-**B** should be additionally, apart from the sterically unfavorable flagpole interaction, ***destabilized*** by a π-p repulsive interaction between the electron-rich benzylidene phenyl and the sulfoxide oxygen. Our and other's experience in asymmetric reactions is quite rich in examples where a fluorine substituent imposes a unique result on the stereochemical outcome of a reaction to be realized.[17] The present data provide further evidence that a single fluorine atom, even in a position remote to the reaction site, should not be considered as just a substituent but a critically important factor involved in controlling the stereochemical outcome of a reaction.

Elaboration of β-amino sulfoxides 5 to enantiomerically pure α-arylglycinols (Scheme 2).

Based on previous studies on β-perfluoroalkyl-β-*N*-(PMP)aminoalkyl sulfoxides,[6] β-aryl-β-*N*-(PMP)aminoalkyl sulfoxides (2*S*,*R*S)-**5** were not directly submitted to the non-oxidative Pummerer rearrangement, because we suspected them to be unsuitable substrates. Therefore, we first deprotected diastereomerically pure (2*S*,*R*S)-**5a-d** to afford free amino derivatives (2*S*,*R*S)-**7-10**, by treatment with 5 equivalents of CAN, a standard reagent for the removal of the PMP group.[12] Despite the oxidative nature of this reaction and the large excess of CAN, the process was found to be highly site-selective, leaving the sulfoxide group intact. Next, free β-amino sulfoxides **7-10** were acylated to give amides (2*S*,*R*S)-**11-14**, the proper substrates for the "non-oxidative" Pummerer rearrangement. We believe that any *N*-acyl protection would make β-amino sulfoxides suitable for the rearrangement and our choice of *N*-Cbz **11-13** and *N*-benzoyl

derivatives **14** was motivated simply by the opportunity to compare the products obtained in this study with the compounds described in the literature (*vide infra*).

Scheme 2



Key: *i*) CAN, H_2O; *ii*) ClCOOBn, 50% K_2CO_3, dioxane; *iii*) PhCOOH/DCC/DMAP; *iv*) $(CF_3CO)_2O$, *sym*-collidine, MeCN, 0 °C; *v*) K_2CO_3, $NaBH_4$, 0 °C; *vi*) $H_2/Pd(OH)_2/C$

The rearrangements of β-*N*-(acyl)amino sulfoxides (2*S*,*R*S)-**11-14** to (*S*)-**16-19** were studied under the conditions previously developed for the transformations of β-perfluoroalkyl-β-*N*-(acyl)aminoalkyl sulfoxides.[6] We found that such features of substrates (2*S*,*R*S)-**11-14** as stereoelectronic properties of the aryl ring and presence of the benzylic proton in the position β to the sulfoxide group, do not interfere with the normal course of the rearrangement. NMR Spectroscopy analyses allowed us to detect the intermediates **15** in the reaction mixtures, which, upon treatment with aqueous K_2CO_3 followed by $NaBH_4$ (about 5 equiv.), cleanly afforded the target *N*-(acyl)-α-arylglycinols (*S*)-**16-19**. Comparison of the chiroptical and spectral data recorded for compounds (*S*)-**16**, (*S*)-**17** and (*S*)-**19** with those reported in the literature[18] confirmed the assumed structure, absolute configuration and enantiomeric purity of the *N*-(acyl)-α-arylglycinols. Free arylglycinols (*S*)-**20-22** were obtained by hydrogenolysis of the *N*-Cbz group of (*S*)-**16-18**, respectively, using $Pd(OH)_2/C$ as catalyst.

In conclusion, we have demonstrated that the stereochemical outcome of the reversible additions between the lithium derivative of chiral methyl *p*-tolyl sulfoxides and *N*-arylidene-*p*-anisidines (*N*-PMP imines) is a function of: a) the reaction conditions used; b) the electronic properties of the arylidene moiety on the starting imine. High kinetically controlled (2*S*,*R*S) diastereoselectivity (-70 °C) was achieved for the additions of imines bearing relatively electron-rich *N*-arylidene group, while an electron-deficient nature of this group was found to favor formation of the opposite stereochemical outcome. On the other hand, the

thermodynamically controlled conditions (0 °C) were shown to lead to a virtually 1/1 mixture of diastereomeric products regardless of the pattern of substitution on the starting imines. Diastereomerically pure β-aryl-β-*N*-(acyl)aminoalkyl sulfoxides, prepared from the corresponding *N*-PMP derivatives, were shown to undergo non-oxidative Pummerer rearrangement, without any undesirable complications, thus providing a reliable route to target enantiopure α-arylglycinols.

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EXPERIMENTAL SECTION

General Methods. ^{1}H (400 or 250 MHz), ^{19}F (235 Mhz) and ^{13}C (100.6, 62.8 or 50.3 MHz) NMR samples were prepared as dilute solutions in the appropriate deuterated solvent. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F = −162.90) for ^{19}F nuclei. Coupling constants are expressed in Hertz. Anhydrous THF was distilled from sodium and benzophenone. In all other cases commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out under a 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 for flash column chromatography (FC). HPLC analyses were performed on a Waters 600E instrument, using LiChrosorb Si60 (5 μm, Merck) prepacked columns (1.0 mL/min) and *n*-hexane and ethyl acetate HPLC-grade solvents (Merck). Unless otherwise stated, yields refer to isolated products of greater than 95% purity as estimated by ^{1}H and ^{19}F NMR spectroscopy.

X-ray structure determination of (2*S*,*R*S)-5b. A colorless, needle-shape crystal of **5b** (size 0.8 x 0.12 x 0.06), obtained by crystallization from *n*-hexane/ethyl acetate (1:1), was selected for x-ray diffraction analysis. Intensity data were collected on a Siemens P4 diffractometer using graphite-monocromated Cu-Kα radiation (λ = 1.5418Å) in the range $2.76° < \theta < 57.36°$ with the θ/2θ scan technique for a number of 2698 unique reflections (R_{int} = 0.0221, R_{sigma} = 0.0264). Cell parameters were determined by least-square refinement on 2θ values of 24 reflections with $2\theta > 40°$. Three standard reflections were monitored every 97 measured to check crystal orientation and stability and showed no significant decay. Data were corrected for Lorentz and polarization but no absorption correction was applied.

The structure was solved by direct methods using SIR92,[19] and refined by full-matrix least-square on F^2 with anisotropic displacement parameters for all non-hydrogen atoms using SHELXL-97.[20] The amidic hydrogen was located by difference Fourier and refined in the riding mode while all the other hydrogens were included at calculated position with group temperature factors.

The absolute configuration (2*S*,*R*S) was unambiguously determined refining the Flack 'x' parameter[21] (0.02(2)).[14c]

Crystal data: $C_{22}H_{22}NO_2S$, f.w. 383.47, Monoclinic, space group P 2_1, a = 11.031(1)Å, b = 5.627(1)Å, c = 16.927(1)Å, β = 108.75(1)°, V = 994.91Å^3, Z = 2, D_c = 1.28 g/cm^3, μ = 1.66 mm^{-1}, F(000) = 404, restraints = 1, parameters = 254, final R1 = 0.0364, wR2 (all data) = 0.0980, S = 1.043, Flack's parameter = 0.02(2), Extinct. coeff. = 0.0074(8), largest diff. peak and hole 0.149 and -0.148 e.A^{-3}.

General method for preparing *N*-PMP (fluoro)aryl imines 4a-f. The starting aldehyde (35 mmol) was first dissolved in benzene (60 mL) in a round-bottomed flask equipped with a reflux condenser, a Dean-Stark trap and a magnetic stirring bar. *p*-Anisidine (38.5 mmol) and *ca.* 0.5 g of the strongly acidic resin DOWEX 50W X8-400 were added to the reaction flask, and the mixture was stirred at reflux. After the reaction was complete (theoretical amount of water removed, and monitoring by TLC and ^{1}H, ^{19}F NMR spectroscopy), the mixture was allowed to cool at r.t., filtered, the solvent was removed *in vacuo* and imine products were purified by crystallization from *n*-hexane. Imines **4a-f** are solids and could be stored for several months at 4 °C without any deterioration.

4a: 70%; brown-purple crystals; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.89 (m, 2H), 7.46 (m, 3H), 7.24 (m, 2H), 6.94 (m, 2H), 3.83 (s, 3H).

4b: 85%; brown crystals; mp 97-98 °C (*n*-hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.95-6.88 (m, 8H), 3.83 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -109.9 (m). Anal. Calcd for $C_{14}H_{12}NOF$: C, 73.35; H, 5.28; N, 6.11. Found: C, 73.50; H, 5.30; N, 6.05.

4c: 86%; brown crystals; mp 96-97 °C (*n*-hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.22-6.87 (m, 8H), 3.85 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -122.7 (m). Anal. Calcd for $C_{14}H_{12}NOF$: C, 73.35; H, 5.28; N, 6.11. Found: C, 73.55; H, 5.16; N, 6.01.

4d: 89%; brown crystals; mp 65-66 °C (*n*-hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.61 (m, 2H), 7.39 (m, 1H), 7.22 (m, 2H), 7.11 (m, 1H), 6.90 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -113.9 (m); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 163.14 (d, J = 246), 158.59, 156.68 (d, J = 3.7), 144.3, 138.83 (d, J = 7.4), 130.24 (d, J = 7.4), 124.74 (d, J = 3.7), 122.3, 118.1, 114.63, 114.35 (d, J = 9.2), 55.54. Anal. Calcd for $C_{14}H_{12}NOF$: C, 73.35; H, 5.28; N, 6.11. Found: C, 72.99; H, 5.08; N, 5.98.

4e: 96%; brown crystals; mp 70-71 °C (*n*-hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.85-6.88 (m, 7H), 3.83 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -134.5 (m, 1F), -138.0 (m, 1F). Anal. Calcd for $C_{14}H_{11}NOF_2$: C, 68.01; H, 4.48; N, 5.67. Found: C, 68.12; H, 4.42; N, 5.72.

4f: 97%; yellow-brown crystals; mp 128-129 °C (*n*-hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.28 (m, 2H), 6.96 (m, 2H), 3.85 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -143.3 (m, 2F), -151.7 (m, 1F), -162.9 (m, 2F). Anal. Calcd for $C_{14}H_8NOF_5$: C, 55.83; H, 2.68; N, 4.65. Found: C, 56.04; H, 2.78; N, 4.81.

General method for the condensation between α-lithiated methyl *p*-tolyl sulfoxide (*R*)-1 and (fluoro)aryl aldimines 4a-f. To a stirred solution of (*R*)-methyl *p*-tolyl sulfoxide (1.5 mmol) in dry THF (4 mL), cooled at the appropriate temperature T^1 (see Table 1), LDA·THF in *n*-hexane (1.5 M, Aldrich) (1.8 mmol) was added. After stirring for 15 min at the same temperature T^1, the resultant yellow solution was cooled to -70 °C (unless T^1 = -70 °C) and a solution of *N*-PMP fluoroaryl imine **4** (1.8 mmol) in 2 mL of dry THF was added. Progress of the condensation was monitored by TLC and ^{1}H, ^{19}F NMR spectroscopy, and upon completion (see Table 1) the reaction was quenched at -70 °C with aqueous NH_4Cl, extracted with AcOEt, and the collected organic phases dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The diastereoselectivity of the reactions was determined from ^{1}H, ^{19}F NMR spectroscopy and HPLC analyses of the crude reaction mixtures. Crystallization of the crude reaction mixtures, and FC (*n*-hexane/AcOEt) of the mother liquors, afforded the desired *N*-PMP-α-(fluoro)aryl-β-sulfinylamines **5a-f** and **6a-f**. Yields and diastereomeric ratios are summarized in Table 1.

(2*S*,*R*S)-**5a**: white crystals; *Rf* = 0.35 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 166.9 (c 0.82, $CHCl_3$); mp 208-209 °C (*n*-hexane/AcOEt); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.35-7.25 (m, 7H), 6.68 (m, 2H), 6.50 (m, 2H), 4.95 (br signal, 1H), 4.75 (br t, *J* ca. 6.0, 1H), 3.69 (s, 3H), 3.13 (m, 1H), 3.07 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 152.79, 141.73, 140.93, 139.79, 130.08, 128.96, 127.79, 126.52, 124.05, 115.91, 114.64, 63.59, 55.73, 55.62, 21.41.

(2*R*,*R*S)-**6a**: *Rf* = 0.32 (7:3 *n*-hexane/AcOEt); ^1H NMR (250 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.42-7.22 (m, 7H), 6.69 (m, 2H), 6.49 (m, 2H), 4.79 (dd, *J* = 4.8 and 9.6, 1H), 3.69 (s, 3H), 3.27 (m, 1H), 2.94 (m, 1H), 2.40 (s, 3H).

(2*S*,*R*S)-**5b**: white needles; *Rf* = 0.56 (4:6 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 181.8 (c 0.94, $CHCl_3$); mp 176-177 °C (*n*-hexane/AcOEt); ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.36-7.24 (m, 4H), 7.05-6.94 (m, 2H), 6.68 (m, 2H), 6.45 (m, 2H), 5.02 (br signal, 1H), 4.73 (br t, *J* ca. 6, 1H), 3.71 (s, 3H), 3.08 (m, 2H), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -115.9 (m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 162.23 (d, *J* = 246), 152.85, 141.87, 139.76, 139.59, 136.81, 130.16, 128.16 (d, *J* = 8), 124.05, 115.83, 115.82 (d, *J* = 21.6), 114.69, 63.39, 55.66, 55.22, 21.45; FT IR: cm^{-1} 3425, 1510, 1246, 1228, 1034. Anal. Calcd for $C_{22}H_{22}NO_2FS$: C, 68.91; H, 5.78; N, 3.65. Found: C, 68.96; H, 5.81; N, 3.67.

(2*R*,*R*S)-**6b**: *Rf* = 0.46 (4:6 *n*-hexane/AcOEt); ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.40-7.25 (m, 4H), 7.00 (m, 2H), 6.68 (m, 2H), 6.45 (m, 2H), 4.90 (br signal, 1H), 4.78 (dd, *J* = 4.75 and 9.5, 1H), 3.69 (s, 3H), 3.22 (m, 1H), 2.88 (m, 1H), 2.40 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -115.66 (m).

(2*S*,*R*S)-**5c**: yellowish solid; *Rf* = 0.23 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 202.9 (c 0.66, $CHCl_3$); mp 187.5-188 °C (*n*-hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 3H), 7.29 (m, 2H), 7.23 (m, 1H), 7.09-7.00 (m, 2H), 6.78 (br signal, 1H), 6.69 (m, 2H), 6.52 (m, 2H), 5.05 (t, *J* = 6.14, 1H), 3.70 (s, 3H), 3.21 (m, 2H), 2.40 (s, 3H).; ^{19}F NMR ($CDCl_3$) δ -120.7 (ddd, *J* = 5.3, 7.6 and 10.8); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 160.4 (d, *J* = 244.8), 152.48, 141.69, 140.35, 139.84, 130.04, 129.31 (d, *J* = 8.3), 128.73 (d, *J* = 4.3), 127.81 (d, *J* = 12.8), 124.65 (d, *J* = 3.3), 124.04, 115.64 (d, *J* = 21.4), 115.18, 114.7, 61.62, 55.64, 50.53, 21.42; FT IR: cm^{-1} 3439, 1508, 1252, 1220, 1031. Anal. Calcd for $C_{22}H_{22}NO_2FS$: C, 68.91; H, 5.78; N, 3.65. Found: C, 69.09; H, 5.79; N, 3.65.

(2*R*,*R*S)-**6c**: *Rf* = 0.15 (7:3 *n*-hexane/AcOEt); ^1H NMR (250 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.48-7.38 (m, 1H), 7.31 (m, 2H), 7.27-7.17 (m, 1H), 7.10-6.98 (m, 2H), 6.75-6.67 (m, 2H), 6.54-6.46 (m, 2H), 5.05 (dd *J* = 4.5 and 9.5, 1H), 4.90 (br signal, 1H), 3.70 (s, 3H), 3.24 (m, 1H), 3.06 (m, 1H), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -120.95 (m).

(2*S*,*R*S)-**5d**: white solid; *Rf* = 0.35 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 191.0 (c 0.56, $CHCl_3$); mp 190-191 °C (*n*-hexane/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.32-7.25 (m, 3H), 7.15-7.03 (m, 2H), 6.99-6.90 (m, 1H), 6.70 (m, 2H), 6.50 (m, 2H), 5.03 (br signal, 1H), 4.73 (dd, *J* = 3.6 and 9.1, 1H), 3.70 (s, 3H), 3.15 (m, 1H), 3.08 (m, 1H), 2.43 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -113.24 (m); FT IR: cm^{-1} 3441, 1510, 1263, 1239, 1031. Anal. Calcd for $C_{22}H_{22}NO_2FS$: C, 68.91; H, 5.78; N, 3.65. Found: C, 69.14; H, 6.11; N, 3.67.

(2*R*,*R*S)-**6d**: *Rf* = 0.30 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 154.0 (c 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.31 (m, 2H), 7.28 (m, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 6.92 (m, 1H), 6.70 (m, 2H), 6.48 (m, 2H), 4.78 (dd, *J* = 4.5 and 9.8, 1H), 3.70 (s, 3H), 3.27 (m, 1H), 2.93 (m, 1H), 2.42 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -113.12 (m).

(2*S*,*R*$_S$)-**5e**: white solid; *Rf* = 0.19 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 170.2 (c 0.73, $CHCl_3$); mp 160.5-162 °C (*n*-hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.31 (m, 2H), 7.22-7.04 (m, 3H), 6.70 (m, 2H), 6.45 (m, 2H), 5.08 (br signal, 1H), 4.68 (m, 1H), 3.71 (s, 3H), 3.07 (m, 1H), 3.05 (m, 1H), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -137.6 (m, 1F), -140.1 (m, 1F); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 152.59, 150.7 (dd, *J* = 249.3 and 12.8), 149.6 (dd, *J* = 248 and 12.6), 141.96, 140.14, 139.38, 138.81 (*pseudo* t, *J* ca. 4), 130.17, 123.99, 122.26 (dd, *J* = 6.3 and 3.6), 117.8 (d, *J* = 17.3), 115.36 (d, *J* = 17.6), 115.27, 114.7, 63.35, 55.64, 54.68, 21.43; FT IR: cm^{-1} 3438, 1510, 1279, 1242, 1035. Anal. Calcd for $C_{22}H_{21}NO_2F_2S$: C, 65.82; H, 5.27; N, 3.49. Found: C, 65.74; H, 5.18; N, 3.45.

(2*R*,*R*$_S$)-**6e**: *Rf* = 0.13 (7:3 *n*-hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.32 (m, 2H), 7.28-7.08 (m, 3H), 6.70 (m, 2H), 6.43 (m, 2H), 4.77 (dd, *J* = 4.8 and 10.0, 1H), 3.70 (s, 3H), 3.18 (m, 1H), 2.86 (m, 1H), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -137.5 (m, 1F), -139.9 (m, 1F).

(2*S*,*R*$_S$)-**5f**: white solid; *Rf* = 0.50 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 246.8 (c 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.29 (m, 2H), 6.74 (m, 4H), 5.42 (br dd, *J* = 5.0 and 8.2, 1H), 3.72 (s, 3H), 3.42 (m, 1H), 3.18 (m, 1H), 2.41 (s, 3H); ^{19}F NMR ($CDCl_3$) δ - 144.26 (m, 2F), -154.9 (m, 1F), -162 (m, 2F); ^{13}C NMR (62.8 MHz, $CDCl_3$, selected signals) δ 141.95, 139.95, 130.1, 123.92, 117.18, 115.0, 60.51, 55.6, 46.3, 21.4; FT IR: cm^{-1} 3438, 1501, 1240, 1027, 989. Anal. Calcd for $C_{22}H_{18}NO_2F_5S$: C, 58.02; H, 3.98; N, 3.08. Found: C, 57.85; H, 3.68; N, 2.83.

(2*R*,*R*$_S$)-**6f**: *Rf* = 0.40 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 126.5 (c 0.55, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.33 (m, 2H), 6.71 (m, 2H), 6.52 (m, 2H), 5.1 (br t, *J* ca. 7.5, 1H), 3.70 (s, 3H), 3.62 (m, 1H), 3.16 (m, 1H), 2.43 (s, 3H); ^{19}F NMR ($CDCl_3$) δ - 144.9 (m, 2F), -154.8 (m, 1F), -161.95 (m, 2F).

Deprotection of *N*-PMP derivatives 5 to α-(fluoro)aryl-β-sulfinylamines 7-10. A general procedure for removalof the PMP group by CAN. A solution of CAN (2.5 mmol) in 8 mL of water was added at 0 °C to a solution of *N*-PMP derivative **5** in acetonitrile (11 mL). After 30 min at 0 °C (TLC monitoring) a 5% aqueous $NaHCO_3$ solution was added at 0 °C, until almost neutral pH of the mixture was reached. The resultant mixture was allowed to warm up at rt, under stirring, then solid sodium sulfite was added portion-wise, until a brown slurry was formed. AcOEt (*ca.* 10 mL) was added under stirring and the phases were separated. The aqueous layer was washed three times with 5 mL of AcOEt. The collected organic phases were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. The desired free α-(fluoro)aryl-β-sulfinylamines **7-10** were isolated in pure form by FC, for characterization. However, the crude compounds **7-10** were routinely used for the following step, without purification.

(2*S*,*R*$_S$)-**7**: 80%; *Rf* = 0.1 (6:4 *n*-hexane/AcOEt + 2% triethylamine); $[\alpha]_D^{20}$ + 117.3 (c 0.84, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.40-7.20 (m, 7H), 4.56 (m, 1H), 3.01 (m, 1H), 2.98 (m, 1H), 2.40 (s, 3H), 2.16 (br signal, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.3, 141.5, 140.5, 130.05, 128.9, 127.8, 126.2, 124.0, 66.4, 50.85, 21.4.

(2*S*,*R*$_S$)-**8**: 79%; orange solid; *Rf* = 0.1 (6:4 *n*-hexane/AcOEt + 2% triethylamine); $[\alpha]_D^{20}$ + 195.0 (c 0.36, $CHCl_3$); mp 108-110 °C (*n*-hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.35-7.20 (m, 4H), 7.0-6.9 (m, 2H), 4.6 (m, 1H), 3.38 (br signal, 2H), 3.2 (m, 1H), 2.95 (m, 1H), 2.39 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -114.55 (m).

(2*S*,*R*$_S$)-**9**: 71%; white solid; *Rf* = 0.1 (6:4 *n*-hexane/AcOEt + 2% triethylamine); $[\alpha]_D^{20}$ + 193.7 (c 0.56, $CHCl_3$); m.p. 143-145.5 °C (*n*-hex/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.42 (m, 1H), 7.30

(m, 2H), 7.20 (m, 1H), 7.10 (m, 1H), 6.97 (m, 1H), 4.71 (dd, J = 10 and 3.1, 1H), 3.12 (m, 1H), 3.01 (m, 1H), 2.39 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -119.50 (m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.23 (d, J = 246), 141.38, 140.56, 130.56 (d, J = 12.9), 129.92, 129.09 (d, J = 8.3), 127.85 (d, J = 4.6), 124.48 (d, J = 3.5), 123.97, 115.67 (d, J = 21.7), 64.39, 46.3 (d, J = 1.9), 21.28; FT IR: cm^{-1} 3392, 1585, 1487, 1215, 1035. Anal. Calcd for $C_{15}H_{16}NOFS$: C, 64.96; H, 5.81; N, 5.05. Found: C, 65.00; H, 5.75; N, 4.89.

(2*S*,*R*$_S$)-**10**: 90%; yellow-brown needles; Rf = 0.1 (6:4 *n*-hexane/AcOEt + 2% triethylamine); $[\alpha]_D^{20}$ + 198.0 (c 0.69, $CHCl_3$); mp 48-50 °C (*n*-hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.30 (m, 2H), 7.25 (m, 1H), 7.10-7.02 (m, 2H), 6.91 (m, 1H), 4.55 (m, 1H), 3.05 (m, 1H), 2.9 (m, 1H), 2.40 (s, 3H), 2.30 (br signal, 2H); ^{19}F NMR ($CDCl_3$) δ -113 (m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.06 (d, J = 246.9), 146.16 (d, J = 6.5), 141.59, 140.41, 130.32 (d, J = 8.2), 130.06, 123.93, 121.87 (d, J = 2.9), 114.57 (d, J = 21.2), 113.21 (d, J = 21.9), 66.19, 50.5, 21.32; FT IR: cm^{-1} 3375, 1589, 1489, 1231, 1025. Anal. Calcd for $C_{15}H_{16}NOFS$: C, 64.96; H, 5.81; N, 5.05. Found: C, 65.24; H, 5.84; N, 5.00.

Protection of free α-(fluoro)aryl-β-sulfinylamines 7-9 as *N*-Cbz derivatives 11-13. A general procedure. To a solution of starting β-sulfinylamine **7-9** (0.88 mmol) in dioxane (2.5 mL) at rt, 245 μL of 50% aqueous potassium carbonate, followed by neat benzyl chloroformate (0.88 mmol) were added. The mixture was stirred 10 min at rt, filtered, and the solvent was evaporated *in vacuo*. The desired *N*-Cbz derivatives **11-13** were isolated by FC.

(2*S*,*R*$_S$)-**11**: 80%; Rf = 0.4 (4:6 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 147.8 (c 0.18, $CHCl_3$); mp 167-169 °C (AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.42-7.24 (m, 12H), 6.70 (br signal, 1H), 5.21 (m, 1H), 5.12 and 5.05 (AB dd, J = 12.3 Hz, 2H), 3.16 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$) 155.6, 141.9, 139.8, 136.4, 130.1, 128.9, 128.4, 128.0, 127.95, 126.3, 124.0, 66.84, 62.55, 52.55, 21.4. Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.30; H, 5.89; N, 3.60.

(2*S*,*R*$_S$)-**12**: 99%; white solid; Rf = 0.50 (45:55 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 153.0 (c 1.17, $CHCl_3$); foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.40-7.26 (m, 9H), 7.03 (m, 2H), 6.69 (br signal, 1H), 5.18 (m, 1H), 5.11 and 5.01 (AB dd, J = 12.2, 2H), 3.13 (m, 2H), 2.40 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -115.46 (m); ^{13}C NMR (100.6 MHz, $CDCl_3$) 162.3 (d, J = 246.0), 155.5, 142.0, 139.5, 136.25, 130.1, 128.4, 128.0, 124.2, 124.0, 115.7 (d, J = 22.2), 66.9, 63.4, 51.9, 21.4. Anal. Calcd for $C_{23}H_{22}NO_3FS$: C, 67.13; H, 5.39; N, 3.40. Found: C, 67.15; H, 5.42; N, 3.35.

(2*S*,*R*$_S$)-**13**: 86%; yellow-brown solid; Rf = 0.45 (35:65 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 171.0 (c 0.67, $CHCl_3$); mp 139-143 °C (*n*-hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55-7.45 (m, 3H), 7.42-7.00 (m, 10H), 6.60 (br signal, 1H), 5.50 (m, 1H), 5.12 and 5.07 (AB dd, J = 12.3, 2H), 3.25 (m, 1H), 3.20 (m, 1H), 2.39 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -119.55 (m); FT IR: cm^{-1} 3428, 3268, 1702, 1532, 1256, 1030. Anal. Calcd for $C_{23}H_{22}NO_3FS$: C, 67.13; H, 5.39; N, 3.40. Found: C, 66.87; H, 5.40; N, 3.36.

Protection of (2*S*,*R*$_S$)-7 as *N*-benzoyl derivative (2*S*,*R*$_S$)-14. To a solution of **7** (240 mg, 0.9 mmol) in dry CH_2Cl_2 (15 ml) were added solid benzoic acid (122 mg, 1.0 mmol), then DCC (207 mg, 1.0 mmol) and finally a catalytic amount of 4-DMAP (10 mg). The mixture was stirred at rt for 1 h. The solution was diluted with diethyl ether, filtered and the solvent was removed *in vacuo*. The residue was purified by FC.

(2*S*,*R*$_S$)-**14**: 62%; Rf = 0.2 (6:4 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 162.2 (c 0.17, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.85 (d, J = 7.35, 1H), 7.94 (m, 2H), 7.55-7.26 (m, 12H), 5.68 (m, 1H), 3.30 (m, 1H), 3.20 (m, 1H),

2.40 (s, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 166.3, 142.2, 139.6, 139.4, 133.7, 131.7, 130.2, 128.9, 128.6, 127.9, 127.3, 126.3, 124.0, 61.8, 52.2, 21.4. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.95; H, 5.70; N, 3.81.

The "Non-Oxidative Pummerer Reaction". Synthesis of *N*-Cbz Arylglycinols (*S*)-16-19. To a stirred solution of β-aminosulfoxide (2.1 mmol) **11-14** and *sym*-collidine (0.84 mL, 6.3 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere at 0 °C, neat trifluoroacetic anhydride (1.5 mL, 10.5 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C and after 5 min a 20% K_2CO_3 aqueous solution was added until pH 7 was reached. Then, an excess of $NaBH_4$ (about 5 equiv) was added portion-wise at 0 °C, and the mixture was allowed to warm at rt. After 15 min the reaction was quenched with a saturated aqueous ammonium chloride solution, extracted with AcOEt, and the collected organic layers dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. FC of the crude afforded the desired *N*-Cbz 2-arylglycinols (*S*)-**16-19**.

(*S*)-**16**: 79%; Rf = 0.2 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 36.6 (c 0.83, MeOH) (in lit. $[\alpha]_D^{20}$ + 36.2 (c 1.0, MeOH), see Ref. 18a); mp 100-102 °C (*n*-hexane/AcOEt) (in lit. mp 98-99 °C, see Ref. 21c); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H), 5.42 (br signal, 1H), 5.13 and 5.08 (AB dd, 2H, J = 12.2), 4.85 (m, 1H), 3.87 (m, 2H), 2.05 (br signal, 1H).

(*S*)-**17**: 91%; white solid; Rf = 0.15 (75:25 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 27.5 (c 0.5, abs. EtOH) (in lit. $[\alpha]_D^{25}$ + 32.6 (c 0.5, 95% EtOH), see Ref. 18c); mp 106-107 °C (*n*-hexane/AcOEt) (in lit. mp 107-108 °C, see Ref. 21c); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 7H), 7.04 (m, 2H), 5.42 (br signal, 1H), 5.13 and 5.08 (AB dd, J = 12.2, 2H), 4.82 (m, 1H), 3.87 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -115.71 (m); FT IR: cm^{-1} 3411, 3330, 1687, 1540, 1510, 1265. Anal. Calcd for $C_{16}H_{16}NO_3F$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.55; H, 5.58; N, 4.81.

(*S*)-**18**: 98%; white solid; Rf = 0.2 (7:3 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ + 17.9 (c 0.56, $CHCl_3$); mp 101-103 °C (*n*-hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 7H), 7.12 (m, 1H), 7.05 (m, 1H), 5.59 (br d, J = 7.4, 1H), 5.12 (m, 1H), 5.12 and 5.08 (AB dd, J = 12.2, 2H), 3.87 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -119.2 (m); ^{13}C NMR (100.6 MHz, $CDCl_3$) (selected signals) δ 160.4 (d, J = 245.5), 156.2, 136.15, 129.5 (d, J = 9.2), 128.5, 128.2, 124.4, 115.8 (d, J = 22.3), 67.1, 65.15, 52.6; FT IR: cm^{-1} 3330, 1684, 1542, 1283, 1267. Anal. Calcd for $C_{16}H_{16}NO_3F$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.37; H, 6.04; N, 4.60.

(*S*)-**19**: 65%; Rf = 0.25 (6:4 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ - 17.8 (c 0.68, MeOH) (in lit. $[\alpha]_D^{20}$ - 18.0 (c 1.5, MeOH), see Ref. 18b); ^{1}H NMR (250 MHz, $CDCl_3$) δ in full agreement with that reported in the literature.[18b]

Hydrogenolysis of the *N*-Cbz group. Synthesis of the free arylglycinols (*S*)-20-22. A solution of *N*-Cbz arylglycinol (**16-18**) (1.82 mmol) in MeOH (10 mL) was stirred for 15 min in the presence of an excess of $Pd(OH)_2/C$ under a dihydrogen atmosphere. The solution was then filtered on a Celite pad and the solvent removed *in vacuo*. FC of the crude afforded the desired free 2-arylglycinols (*S*)-**20-22**.

(*S*)-**20**: 80%; yellowish solid; $[\alpha]_D^{20}$ + 31.8 (c 0.36, 1*N* HCl) [Commercially available (*S*)-(+)-2-phenylglycinol (Aldrich): $[\alpha]_D^{20}$ + 33 (c 0.75, 1*N* HCl)]; mp 75-77 °C (AcOEt) (Commercially available (*S*)-(+)-2-phenylglycinol (Aldrich): 75-78 °C); ^{1}H NMR (400 MHz, D_2O) δ 7.47-7.33 (m, 5H), 4.01 (t, J = 6.75, 1H), 3.74 and 3.68 (ABX system, m, 2H).

(*S*)-**21**: 87%; white solid; $[\alpha]_D^{20}$ + 47.0 (0.78, $CHCl_3$); mp 94-96 °C (AcOEt); ^1H NMR (400 MHz, D_2O) δ 7.38 (m, 2H), 7.15 (m, 2H), 4.01 (t, *J* = 6.45, 1H), 3.73 and 3.68 (ABX system, m, 2H); ^{19}F NMR (D_2O) δ -113.90 (m); ^{13}C NMR (100.6 MHz, CD_3OD) δ 163.5 (d, *J* = 243.9), 139.1 (d, *J* = 2.6), 129.9 (d, *J* = 6.8), 116.1 (d, *J* = 21.6), 68.5, 58.0; FT IR: cm^{-1} 34363115, 2914, 2846, 1604, 1513, 1224. Anal. Calcd for $C_8H_{10}NOF$: C, 61.92; H, 6.50; N, 9.03. Found: C, 61.36; H, 6.57; N, 8.80.

(*S*)-**22**: 90%; white solid; $[\alpha]_D^{20}$ + 22.2 (c 0.21, MeOH); mp 154-157 °C (*n*-hexane/AcOEt); ^1H NMR (400 MHz, CD_3OD) δ 7.47 (m, 1H), 7.32 (m, 1H), 7.19 (m, 1H), 7.10 (m, 1H), 4.34 (dd, *J* = 4.7 and 7.6, 1H), 3.76 and 3.61 (ABX system, m, 2H); ^{19}F NMR (CD_3OD) δ -117.68 (m); ^{13}C NMR (100.6 MHz) (CD_3OD) δ 161.9 (d, *J* = 244.5), 130.57 (d, *J* = 8.7), 129.65 (d, *J* = 46.5), 129.35 (d, *J* = 4.2), 125.61 (d, *J* = 3.5), 116.4 (d, *J* = 22.5), 66.54, 52.41 (d, *J* = 2.4); FT IR: cm^{-1} 3455, 3054, 2883, 1588, 1516, 1499, 1232. Anal. Calcd for $C_8H_{10}NOF$: C, 61.92; H, 6.50; N, 9.03. Found: C, 62.07; H, 6.40; N, 8.89.

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