Stereoselective Additions of α-Lithiated Alkyl-*p*-tolylsulfoxides to *N*-PMP(fluoroalkyl)aldimines. An Efficient Approach to Enantiomerically Pure Fluoro Amino Compounds

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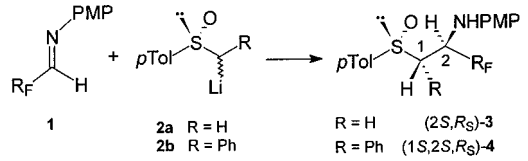
We have recently reported the use of enantiopure α-(fluoroalkyl) *β*-sulfinyl amines (FSAs) as starting building blocks for the asymmetric synthesis of fluorinated amino compounds of biomedicinal interest. Further, we have found that, apart from conventional removal of the sulfinyl auxiliary by substitution with hydrogen, this group can be displaced, in a highly stereospecific S_N2 fashion, by a hydroxy group.[2] This disclosure gave us additional impetus in developing FSAs as versatile intermediates in the enantiocontrolled synthesis of structurally varied fluorinated amines, amino alcohols, amino acids, and hydroxy amino acids.[3]

In this paper, we report our initial studies on the asymmetric additions of α-lithiated alkylarylsulfoxides to (fluoroalkyl)aldimines, which provide an efficient, generalized synthesis of the targeted FSAs. The effectiveness of this strategy is illustrated in the practical and highly stereoselective synthesis of (*R*,*R*)-trifluoronorephedrine, hitherto unavailable in ep form.

Stereoselective additions to C=N double bonds belong to one of the less developed classes of asymmetric reactions. In particular, for the addition of chiral sulfoxide-stabilized nucleophiles to achiral imines, only a handful of reports have appeared in the literature.[4] It was shown that the stereochemical outcome of these additions heavily depends on both the reaction conditions applied and the nature of the substrates and could be subject to kinetic or thermodynamic control. Moreover,

Scheme 1



while for the reactions of imines derived from aromatic aldehydes high values of stereoselectivity could be achieved, aliphatic imines were found to be less suitable substrates for these additions. Considering our design, the use of fluorinated imines might produce additional limitations, arising from the strong electron-withdrawing nature and steric demands of the fluoroalkyl group in the starting electrophiles **1**.[5]

For preliminary evaluation of the viability of this approach, we undertook the investigation of the additions of Me- and Bn-*p*-tolylsulfoxides (*R*)-**2a**,**b** to the imines bearing CF_3, CF_2CF_3, and CF_2CF_2H groups **1a**−**c** (Scheme 1). The choice of the *N*-protecting group was of paramount importance. In fact, it was shown that the substituent on nitrogen has a critical influence in determining the stereochemical outcome of the reactions of imines with nucleophiles because it strongly affects the imine geometry, the reactivity of the C=N bond, and the coordinative ability of the nitrogen atom.[6]

After achieving only limited success with the additions of α-lithiated alkyl-*p*-tolylsulfoxides to *N*-(alkoxycarbonyl)ketimines,[7] we turned our attention to the *N*-(*p*-methoxyphenyl) (PMP) derivatives **1**.[8] Imines **1a**−**c** were easily prepared by a direct condensation between *p*-anisidine and the appropriate aldehyde in presence of an acidic catalyst.[9] An important feature of these substrates is that they are geometrically *anti*-homogeneous.[10]

The condensations between imines **1a**−**c** and α-lithium derivatives of Me-*p*-tolylsulfoxide **2a** were run in THF at −70 °C (Table 1).[11] We have found that the additions occurred with a high reaction rate (15 min) to afford cleanly the desired FSAs (2*S*,R_S)-**3** in an excellent overall yield (96−98%). Determination of the stereoselection of the condensation by ^{19}F NMR of the crude reaction mixture also gave very encouraging results. Thus, regardless of the nature of the imine fluoroalkyl group,

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(10) According to NMR analyses (^1H, ^{19}F) imines **1a**−**c** exist as single geometrical isomers. The *anti* conformation was confidently assigned by analogy with the parent unfluorinated derivatives; see ref 8b.

(11) **General Procedure.** To a stirred solution of LDA (1.8 mmol) in dry THF (4 mL) cooled at −60 °C was added a solution of (*R*)-Me-*p*-tolylsulfoxide (1.5 mmol) in 2 mL of dry THF. After 5 min at the same temperature, the yellow solution was cooled to −70 °C. Then, a solution of *N*-PMP(fluoroalkyl)imine **1** (1.8 mmol) in 2 mL of dry THF was added. After 15 min, the reaction was quenched at −70 °C with aqueous NH_4Cl and routinely worked up. Crystallization of the crude reaction mixtures and flash chromatography of the mother liquors (hexane/ethyl acetate) afforded the desired *N*-PMP-FSAs **3** and **4**.

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Table 1. Addition of Enantiopure α-Lithiated Alkyl-*p*-tolylsulfoxides 2 to α-(Fluoroalkyl)aldimines 1[a,b]

imine/ product[c]	R_F	R	major/ minor dr	yield (%) (major diast)[d]
1a/**3a**	CF_3	H	92/8	>98 (74)
1b/**3b**	CF_2CF_3	H	94/6	96 (72)
1c/**3c**	CF_2CF_2H	H	92/8	97 (70)
1a/**4a**	CF_3	Ph	85/15[e]	98 (59)
1b/**4b**	CF_2CF_3	Ph	88/12[e]	97 (60)
1c/**4c**	CF_2CF_2H	Ph	83/17[e]	>98 (59)

[a] Only the major diastereoisomeric products are depicted, for clarity. [b] Imines **1** were added at −70 °C. [c] α-Lithium sulfoxide formed at −60 °C, reaction time 15 min. [d] Overall yield determined by ^{19}F NMR of the crude. The isolated yield of the *major* diastereoisomer is reported in parentheses. [e] Ratio of major diastereoisomer/sum of the three minor diastereoisomers.

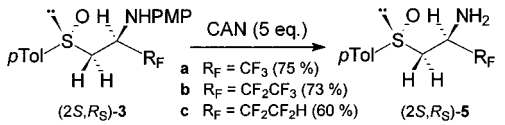
all reactions proceeded with high diastereoselectivity, providing the major diastereoisomers (2*S*,R_S)-**3** in 84−88% de. Further purification of the products (2*S*,R_S)-**3** to diastereoisomerically pure state was easily achieved by crystallization of the crude mixtures.

It is worth noting that the stereoselectivity of the condensations was not markedly influenced by an increase of the reaction time, suggesting that the additions occur irreversibly and the stereochemical outcome is therefore kinetically controlled. Further evidence was obtained by submitting enantiomerically and chemically pure minor diasteroisomer (2*R*,R_S)-**3a** to the exact reaction conditions (LDA, −70 °C) for 90 min, which revealed neither decomposition of **3a** to the starting materials nor its epimerization to the major diastereoisomer. The (2*S*,R_S)-absolute configuration of the trifluoromethyl-containing product **3a** was determined by X-ray analysis of the *N*-unprotected derivative (2*S*,R_S)-**5a**, previously described by us (see below).[1]

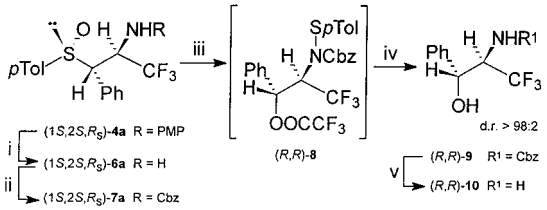
The condensations between imines **1a**−**c** and the lithium derivative of Bn-*p*-tolylsulfoxide ((*R*)-**2b**) were quite intriguing due to the more complex mechanism of stereochemical discrimination involved in the simultaneous formation of two new stereogenic centers. Despite steric shielding and additional stabilization of (*R*)-**2b**, these reactions were found to be fast even at −70 °C in THF (15 min). The corresponding diastereoisomeric FSAs (1*S*,2*S*,R_S)-**4** formed in very good yields and, to our great satisfaction, with a high and synthetically useful level of stereoselectivity, affording with overwhelming preference one out of four possible diastereoisomers, as revealed by ^{19}F NMR of the raw reaction mixtures. Also in this case, the purification of the main diastereoisomer to diastereoisomerically pure state could be achieved merely by crystallization of the crude mixture. Determination of the absolute configuration of **4a** by X-ray analysis gave rather surprising results.[14] In fact, the (1*S*,2*S*,R_S)-absolute configuration of the main diastereoisomer **4a** was found to be opposite to the stereochemistry of the β-sulfinylamine stereoselectively formed in the condensation between *N*-phenylbenzaldimine and the α-lithium derivative of (*R*)-Bn-*t*-Bu-sulfoxide.[4c] While the direct comparison of the factors influencing the stereochemical preferences in our study and in the previously reported reactions is not possible, we assume that in the condensations studied herein the fluoroalkyl group might play a key role in determining the observed stereochemical outcome.

The chemoselective oxidative deprotection of the *N*-PMP derivatives **3** and **4** to the corresponding compounds having a free amino function has also been addressed.[12]

Scheme 2



Scheme 3[a]



[a] Key: (i) CAN (72%); (ii) $ClCOOCH_2Ph$, K_2CO_3 50%, dioxane, 60 °C (80%); (iii) $(CF_3CO)_2O$, *sym*-collidine, CH_3CN, 0 °C; (iv) $NaBH_4$, THF/H_2O, 0 °C (75% from **7a**); (v) H_2/$Pd(OH)_2$−C (100%).

A series of experiments revealed that treatment of (2*S*,R_S)-**3** with 5 equiv of CAN in acetonitrile at rt are the conditions of choice to obtain the desired free amino derivatives (2*S*,R_S)-**5** in good chemical yield (Scheme 2). Oxidation of the sulfinyl to sulfonyl moiety was never observed, even with a larger excess of CAN.

A wide range of synthetic applications can be readily envisaged for the present approach. For example, reductive desulfinylation of the FSAs can produce the corresponding fluoroamines.[1] More intriguing is the preparation of the trifluoro analog of norephedrine (*R*,*R*)-**10** (Scheme 3), which serves to illustrate the efficient and straightforward elaboration of the enantiopure FSAs in a biologically important amino alcohol derivative. This protocol features an absolute economy and the full exploitation of the carbon stereocenters formed by action of the sulfinyl group.

The *N*-PMP group of (1*S*,2*S*,R_S)-**4a** was cleaved with CAN, the amino group of the free FSA (1*S*,2*S*,R_S)-**6a** was reprotected, affording the *N*-Cbz derivative (1*S*,2*S*,R_S)-**7a**, which was submitted to the stereoselective "non-oxidative" Pummerer reaction, recently reported from these laboratories.[1,2] Treatment of (1*S*,2*S*,R_S)-**7a** with TFAA and *sym*-collidine produced a clean S_N2-type displacement of the sulfinyl by a trifluoroacetoxy group, stereospecifically affording the α-trifluoroacetoxy sulfenamide (*R*,*R*)-**8**. $NaBH_4$ reduction of the crude (*R*,*R*)-**8** delivered the *N*-Cbz trifluoro norephedrine (*R*,*R*)-**9** with diastereoselection >98:2 (the other diastereoisomer was not detected in the crude reaction mixture). Hydrogenolysis of the *N*-Cbz protection afforded in quantitative yield the ep trifluoronorephedrine (*R*,*R*)-**10**, previously described in racemic form.[13]

The extension of the methodology to the preparation of more complex targets is under active investigation.

Supporting Information Available: Experimental procedures and spectral data of major diastereoisomers **3**−**5** and of compounds **6**, **7**, **9**, **10**, including a table of spectroscopic data and copies of ^1H, ^{19}F, and ^{13}C NMR, low-resolution mass spectra; crystal data and ORTEP drawing of (1*S*,2*S*,R_S)-**4a** (48 pages).

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(14) The author has deposited atomic coordinates for **4a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.