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Novel Approach for Asymmetric Synthesis of Fluorinated β-Amino Sulfones and Allylic Amines

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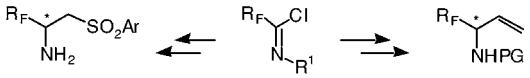
ABSTRACT



Enantiomerically pure γ-fluoroalkyl β-amino sulfones are readily synthesized in three steps starting from fluorinated imidoyl chlorides and arylmethyl sulfones. A complementary two-step sequence starting from chiral fluorinated β-amino sulfoxides has also been developed. To illustrate the application of this procedure, a new method for the synthesis of α-fluoroalkyl allylic amines in optically pure form involving a Julia methylenation–desulfonylation reaction is presented.

Optically pure β-amino sulfones, readily available from serine[1a] and other α-amino acid derivatives,[1b] have demonstrated their utility in asymmetric synthesis. In particular, they are useful in the preparation of cyclic and acyclic nonproteinogenic α-amino acids,[1] peptide isosteres,[1b,2] natural products such as alkaloids[3] and carbohydrate derivatives,[4] and other systems with diverse pharmacological properties.[5] Other procedures involving these compounds, including stereoselective additions of sulfonyl carbanions to chiral *N*-sulfinyl imines[6] and intramolecular[7] and intermolecular[8,9] aza-Michael additions to α,β-unsaturated sulfones, have also appeared in the literature.

The introduction of fluorine in organic molecules has been shown to cause changes in the reactivity and pharmacology of the containing molecules, thus providing new insight into these processes.[10] It is worth noting that although the synthesis of nonfluorinated β-amino sulfones is relatively well-documented in the literature, very little has been published about the corresponding fluorinated derivatives, either in the racemic or in the chiral nonracemic versions.

In this Letter, we report on two simple and complementary methods of synthesis of chiral nonracemic fluorinated β-amino sulfones **5** using imidoyl halides **1** as fluorinated building blocks.[11] Application of this methodology to the asymmetric synthesis of *N*-aryl allylic amines **7** is also described.

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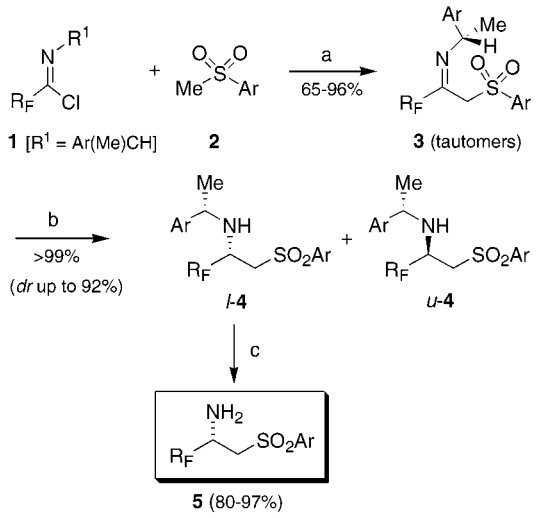
Table 1. Synthesis of Fluorinated β-Imino Sulfones **3** and β-Amino Sulfones **4** and **5**

entry	R_F	Ar	R^1	**3** or **4** yield (%)[a]		reduction conditions[b]	*l*-**4**:*u*-**4**[c]	**5** (%)[a]
1[d]	CF_3	C_6H_5	(*S*)-C_6H_5(Me)CH	**3a** (84)	**4a** (>99)	EtOH, 40 h, 25°C	70:30	(*S*)-**5a** (90)
2	CF_3	C_6H_5	(*S*)-C_6H_5(Me)CH		**4a** (>99)	EtOH, 48 h, −20°C	73:27	
3[e]	CF_3	*p*-MeC_6H_4	(*S*)-C_6H_5(Me)CH	**3b** (82)	**4b** (>99)	THF/MeOH, 72 h, 25°C	76:24	
4[f]	CF_3	*p*-MeC_6H_4	(*S*)-C_6H_5(Me)CH		**4b** (>99)	THF/MeOH, 96 h, −20°C	77:23	
5	CF_3	β-$C_{10}H_7$	(*S*)-C_6H_5(Me)CH	**3c** (90)	**4c** (>99)	THF/MeOH, 72 h, 25°C	77:23	
6	CF_3	β-$C_{10}H_7$	(*S*)-C_6H_5(Me)CH		**4c** (95)	EtOH, 96 h, −20°C	79:21	
7	$CClF_2$	β-$C_{10}H_7$	(*S*)-C_6H_5(Me)CH	**3d** (93)	**4d** (>99)	THF/MeOH, 96 h, 25°C	79:21	
8	$CClF_2$	*p*-MeC_6H_4	(*S*)-C_6H_5(Me)CH	**3e** (88)	**4e** (>99)	THF/MeOH, 96 h, 25°C	81:19	(*R*)-**5b**[g] (92)
9	CF_3	C_6H_5	(±)-α-$C_{10}H_7$(Me)CH	**3f** (72)	**4f** (>99)	THF/MeOH, 72 h, 25°C	83:17	(±)-**5a** (80)
10	CF_3	β-$C_{10}H_7$	(±)-α-$C_{10}H_7$(Me)CH	**3g** (68)	**4g** (>99)	THF/MeOH, 72 h, 25°C	82:18	
11	CF_3	β-$C_{10}H_7$	(±)-α-$C_{10}H_7$(Me)CH		**4g** (93)	EtOH, 96 h, −20°C	85:15	
12[h]	CF_3	α-$C_{10}H_7$	(±)-α-$C_{10}H_7$(Me)CH	**3h** (94)	**4h** (>99)	EtOH, 48 h, 25°C	89:11	(±)-**5c** (97)[i]
13	CF_3	α-$C_{10}H_7$	(±)-α-$C_{10}H_7$(Me)CH		**4h** (94)	EtOH, 72 h, −20°C	93:7	
14	CF_3	α-$C_{10}H_7$	(±)-α-$C_{10}H_7$(Me)CH		**4h** (>99)	EtOH, 240 h, −40°C	96:4	
15	CF_3	C_6H_5	*p*-$MeOC_6H_4$	**3i** (87)	**4i** (>99)	THF/MeOH, 0.5 h, 0°C		
16	CF_2Ph	C_6H_5	*p*-$MeOC_6H_4$	**3j** (77)	**4j** (>99)	THF/MeOH, 0.5 h, 0°C		

[a] Isolated overall yields. [b] $NaBH_4$ (10 equiv) was used as reducing agent except for entries 15 and 16 [$NaBH_4$ (3.0 equiv)]. [c] Determined upon examination of ^{19}F NMR data of the crude reaction mixture. [d] THF/MeOH as solvent, 72 h, 25 °C, *l*-**4a**:*u*-**4a** 70:30, >99%. [e] Similar results have been obtained starting from (*R*)-**3b** [*l*-**4b**:*u*-**4b** 74:26, >99%]. [f] EtOH as solvent, 96 h, −20 °C, *l*-**4b**:*u*-**4b** 78:22, >99%. [g] (*S*)-**5b** was obtained from (2*S*,R_S)-**6b** in two steps (overall yield 45%) (see Scheme 2). [h] THF/MeOH as solvent, 72 h, 25 °C, *l*-**4h**:*u*-**4h** 90:10, >99%. [i] The pure enantiomer (*S*)-**5c** ([α] +11.5 (*c* 0.62, $HCCl_3$)) was also prepared from (2*S*,S_S)-**6a** in two steps (overall yield 65%) (see Table 2 and Scheme 2).

It should be mentioned that, although the diastereoselective reduction of β-imino sulfones[12] represents a simple and direct way to synthesize β-amino sulfones, the correct utilization of this strategy requires the presence of a stereocenter in the imino nitrogen substituent. Our strategy, illustrated in Scheme 1, entails the initial preparation of chiral fluorinated β-imino sulfones **3**, which can be easily carried out via a reaction of fluorinated chiral imidoyl chloride **1**[13] with the appropriate sulfonyl carbanion. The process produces generally high yields (68−94%, Table 1) and results in the isolation of compounds **3** as a tautomeric imino/enamino mixture.[14] In the second step, compounds **3** are then stereoselectively reduced to the corresponding β-amino sulfones **4**. Use of $NaBH_4$ as reducing agent and ethanol or THF/methanol as solvent seems to provide the best diastereocontrol (dr up to 92%, Table 1). Chromatographic separation of the predominant diastereoisomer (*l*-**4** in Scheme 1) followed by hydrogenolysis over palladium on carbon of the chiral amino nitrogen substituent furnishes enantiomerically pure β-amino sulfones **5** in high yields[15] (Scheme 1).

Scheme 1[a]



[a] (a) LDA (2.0 equiv), THF, −78 °C. (b) $NaBH_4$ (10.0 equiv), for solvent, temperature, and reaction time, see Table 1. (c) H_2 (1 atm), Pd/C (10%), MeOH, 25 °C, 48 h for **5a,b** and H_2 (20 bar), Pd/C (10%), HCl/MeOH, 25 °C, 20 days for **5c**.

Table 1 summarizes selected results obtained for the synthesis of β-amino sulfones **4** and **5** under different conditions. The observed selectivity was affected by the size of the aromatic substituents, particularly those on the imino nitrogen grouping. The larger α-naphthyl group in R^1 provided a higher diastereocontrol than the smaller phenyl group (entries 1−14, Table 1). Lowering the reaction temperature improved the diastereoselectivity, albeit only slightly. In the end, **4h** was the compound for which the optimal yield and diastereomeric ratio was obtained (entries 12−14, Table 1).

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(12) Very little about the preparation of such compounds has appeared in the literature. See, for example: (a) Field, L.; Lawson, J. E.; McFarland, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 4389−4394. (b) Muraoka, M.; Yamamoto, T.; Ebisawa, T.; Kobayashi, W.; Takeshima, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1017−1022.

(13) Tamura, K.; Mizukami, H.; Maeda, K. Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−36.

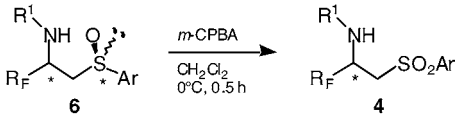
(14) Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210−6219.

(15) More drastic reaction conditions were necessary in the case of **5c** (see Scheme 1).

To test the general applicability of this reaction, we examined the reduction of *N*-aryl *β*-imino sulfones. The reduction took place in minutes and quantitatively afforded the corresponding racemic *N*-aryl *β*-amino sulfones **4i,j** (entries 15 and 16, Table 1).

These same compounds, however, can also be obtained in enantiomerically pure form when chiral *N*-aryl *β*-amino sulfoxides **6** are used as the starting material[16] (see scheme in Table 2). Thus, MCPBA-oxidation of *N*-PMP-protected

Table 2. Fluorinated *N*-Aryl *β*-Amino Sulfones **4** Obtained by Oxidation of *β*-Amino Sulfoxides **6**



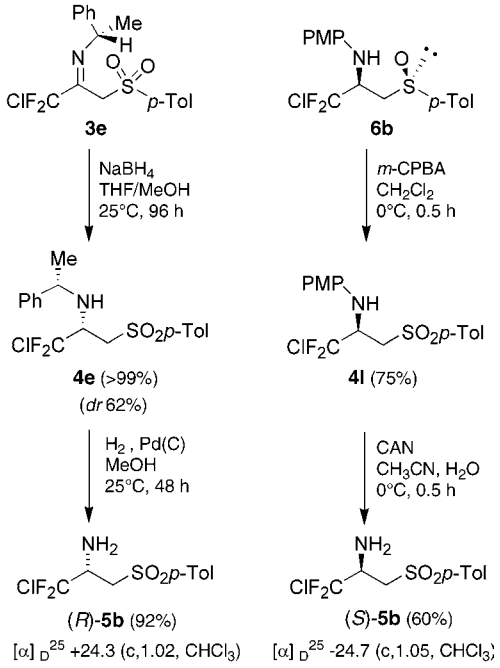
6 **4**

entry	**6**[a]	R_F	Ar	product	yield (%)[b]
1	(2*S*,*S*$_s$)-**6a**	CF_3	α-$C_{10}H_7$	(*S*)-**4k**	83
2	(2*S*,*R*$_s$)-**6b**	$CClF_2$	*p*-MeC_6H_4	(*S*)-**4l**	75
3	(2*S*,*S*$_s$)-**6c**	C_2F_5	α-$C_{10}H_7$	(*S*)-**4m**	45

[a] R^1 = *p*-$MeOC_6H_4$ (PMP) in all cases. [b] Isolated yield.

derivatives **6** cleanly afforded the corresponding *N*-aryl *β*-amino sulfones **4k**−**m** (Table 2), which were then converted into enantiomerically pure *β*-amino sulfones **5** by oxidative cleavage (CAN, 5 equiv) of the PMP group (Scheme 2).

Scheme 2. Determination of Absolute Configuration of **5**



The stereochemical outcome of the C=N bond reduction could not be determined upon simple examination of the spectroscopic data, and unfortunately we were not able to obtain adequate single crystals for X-ray crystallographic analysis of *N*-alkyl *β*-amino sulfones **4** (Scheme 1). Therefore, the configuration of the newly created stereocenter in **4** was determined by means of chemical correlation (Scheme 2). In this fashion, using the chemical methods described above, compound (*S*)-**3e** was easily converted into (*R*)-**5b** in high yield. In a separate process, enantiomerically pure (*S*)-**5b** was prepared in two steps from chiral *β*-amino sulfoxide (2*S*,*R*$_S$)-**6b** via MCPBA-oxidation followed by deprotection of the PMP group (vide supra and Scheme 2). Comparison of the obtained $[\alpha]_D$ values in the two pathways (see Scheme 2) allowed us to assign as *R* (*S* when R_F = CF_3, see Table 1 and Figure 1) the configuration of the newly created center in **4e**, that is, (2*R*,2′*S*)-**4e**.

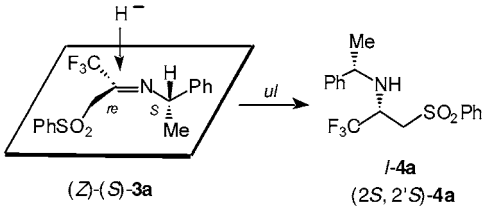


Figure 1.

Taking these results into consideration, we can explain the formation of the major diastereoisomer *l*-**4** [i.e., (2*S*,2′*S*)-**4a**] by assuming that hydride attacks the imino carbon from the opposite side (*re* face) of the α-methyl group (*ul*-1,3-addition),[17] as depicted in Figure 1.

This methodology has remarkable potential for the preparation of fluorine-containing amino derivatives. With this in mind, we applied the strategy described above to the synthesis of enantiomerically pure α-fluoroalkyl allylic amines (Table 3).

Allylic amines are recognized as versatile building blocks for the preparation of a variety of synthetically and biologically important organic derivatives.[18] However, although much effort has been devoted to the study of nonfluorinated allylic amines, very little is known about the synthesis and reactivity of their fluorinated counterparts.[19]

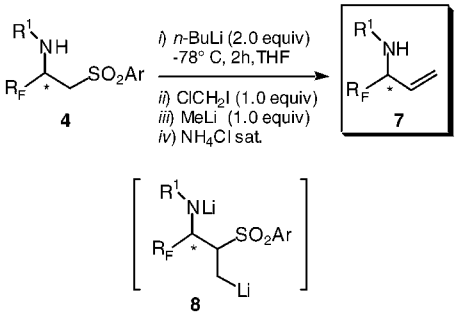
Furthermore, descriptions of the preparation of these derivatives in enantiomerically pure form are rare in the

(16) Compounds **6** were easily prepared, in two steps, from fluorinated imidoyl chlorides and arylmethyl sulfoxides. See: Fustero, S.; Navarro, A.; Pina, B.; García Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621−2624.

(17) Ab initio molecular orbital (MO) calculations (HF/6-31G*) for (*S*)-**3a** predict the (*Z*)-imino geometry as the most stable tautomer [E_{rel} (kcal mol^{-1}): imino (*Z*)-(*S*)-**3a** 0.0; imino (*E*)-(*S*)-**3a** 10.7; enamino (*Z*)-(*S*)-**3a** 9.2].

(18) For reviews, see: (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (b) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685−700. (c) Stütz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320−328. For other recent examples, see: (d) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761−6762. (e) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005. (f) Katritzky, A. R.; Cheng, D.; Li, J. *J. Org. Chem.* **1998**, *63*, 3438−3444.

Table 3. Fluorinated Allylic Amines **7** Obtained from Amino Sulfones **4**



entry	compound	R_F	Ar	product	yield[b]
1	(±)-**4i**	CF_3	C_6H_5	(±)-**7a**	73
2	(*S*)-**4k**	CF_3	α-$C_{10}H_7$	(*R*)-**7a**	70
3	(*R*)-**4l**	$CClF_2$	*p*-MeC_6H_4	(*S*)-**7b**	70
4	(*S*)-**4m**	C_2F_5	α-$C_{10}H_7$	(*R*)-**7c**	45
5	(±)-**4j**	CF_2Ph	C_6H_5	(±)-**7d**	47[c]

[a] R^1 = *p*-$MeOC_6H_4$ (PMP) in all cases. [b] Isolated yield (%). [c] Not optimized. Starting material (35%) was recovered.

literature. In fact, to the best of our knowledge only two examples have been reported: one in 2001, when Prakash, Olah, et al. reported the first asymmetric synthesis of α-trifluoromethylated allylic amines via nucleophilic trifluoromethylation of chiral α,β-unsaturated sulfinimines,[20a] and more recently, when Konno developed a new synthesis of γ-fluoroalkyl allylic amines by means of enantiospecific Pd-catalyzed allylic substitution of nonracemic mesylates.[20b]

Our approach consists of a Julia-type methylenation−desulfonylation reaction[21] of β-amino sulfones **4** (R^1 = PMP). Treatment of compounds **4** with 2 equiv of *n*-butyllithium at −78 °C followed by consecutive addition of $ClCH_2I$ (1.0 equiv) and methyllithium (1.0 equiv) thus furnished the organolithium intermediate **8**, which underwent spontaneous β-elimination to afford the corresponding fluorinated allylic amines **7**. The process, which appears in general to be independent of the R_F substituent, works well and generally takes place with good yields (45−73%). Table 3 summarizes the obtained results.

In conclusion, we have developed a new and very simple enantioselective approach to fluorinated β-amino sulfones **5** based on the unprecedented diastereoselective reduction of chiral β-imino sulfones. An alternative and complementary two-step strategy to **5** has been accomplished from chiral β-amino sulfoxides. In addition, the synthetic utility of β-amino sulfones has been demonstrated in the synthesis of enantiomerically pure α-fluoroalkyl allylic amines.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data for compounds **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For racemic synthesis, see: (a) Weygand, F.; Steglich, W.; Oettmeir, W.; Maierhofer, A.; Loy, R. S. *Angew. Chem.* **1966**, *78*, 640−640; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 600−600. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *Synlett* **1995**, 659−660. (c) Xu, Y.; Dolbier, W. R. *J. Org. Chem.* **2000**, *65*, 2134−2137. (d) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77−78. (e) Sergeeva, N. N.; Golubev, A. S.; Hennig, L.; Findeisen, M.; Paetzold, E.; Oehme, G.; Burger, K. *J. Fluorine Chem.* **2001**, *111*, 41−44. (f) Palacios, F.; Pascual, S.; Oyarzabal, J.; Ochoa de Retana, A. M. *Org. Lett.* **2002**, *4*, 769−772.

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