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N-Cbz-Trifluoropyruvaldehyde *N,S*-Ketal: Absolute Stereochemistry and Addition of Grignard Reagents. Highly Stereoselective Entry to Trifluoro Analogues of *Ephedra* Alkaloids

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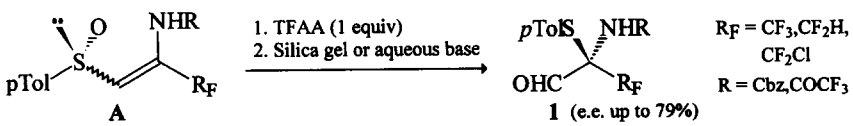
Abstract: The chiral non racemic *N*-Cbz-trifluoropyruvaldehyde-*N,S*-ketal **1a** (enantiomeric excess up to 74%) is a new trifluoro 3-C building block, which has been reacted with several Grignard reagents, stereoselectively affording the corresponding secondary carbinols **2**. The *N,S*-ketal stereocentre, whose absolute stereochemistry has been determined by X-ray analysis of the α-phenylpropionate **3**, is able to provide excellent stereocontrol. Highly stereoselective *p*-tolylthio group displacement afforded the *N*-Cbz-phenyl derivative **2d**, transformed into trifluoro-norephedrine (*S,S*)-**5** and -ephedrine (*S,S*)-**6**.

The biomedicinal relevance and the increasing range of application of fluoroorganic chemicals is urging chemists to the exploration of new synthetic routes to chiral non racemic selectively fluorinated organic molecules.[1] The "fluorination approach" is straightforward but often suffers from low selectivity and yields, particularly with complex substrates. The "building block approach" is very attractive, but the limited number of readily available fluorine containing starting materials is still an obstacle to the strategy.[2]

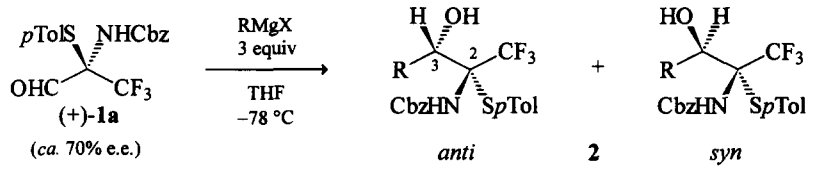
As a result of ongoing studies directed to finding new fluorinated building blocks and stereoselective approaches to fluoroorganic fine chemicals, we have recently reported the stereospecific synthesis of chiral non racemic fluoropyruvaldehyde-*N,S*-ketals **1** through a self-immolative Pummerer-type rearrangement of enantiopure α-fluoroalkyl-β-sulfinylenamines **A** (Scheme 1).[3] To the best of our knowledge fluoropyruvaldehyde-*N,S*-ketals **1** are the first examples reported in literature of non enolizable aldehydes simoultaneously bearing a sulfur, a nitrogen and a carbon atom in α-position.[4] Therefore, the properties and the reactivity of this unprecedented class of molecules represent a new exciting area of chemistry.



Scheme 1

In this paper we describe the determination of the absolute configuration of the *N*-Cbz-trifluoropyruvaldehyde-*N,S*-ketal **1a**, its stereoselective reaction with Grignard reagents and the exploitation of this strategy in the highly stereoselective approach to trifluoro-norephedrine (*S,S*)-**5** and -ephedrine (*S,S*)-**6**.

We were greatly gratified to see that Grignard reagents (3 equiv) smoothly reacted (2 min.) with the aldehyde **1a** (samples with *c.a.* 70% e.e. were used) affording the corresponding secondary carbinols **2** with yields and stereoselections ranging from good to excellent (Scheme 2 and Table 1).



2

Scheme 2

Scheme 2 and Table 1. Addition of Grignard reagents to the trifluoropyruvaldehyde *N,S*-ketal (+)-**1a**.

Product	X	R	*anti/syn*	Yield	^{19}F NMR *anti* **2**	^{19}F NMR *syn* **2**
2a	Cl	CH_3	17 : 1	72 %	– 72.0	– 72.5
2b	Br	CH_2CH_3	4 : 1	72 %	– 71.1	– 72.4
2c	Br	$CH{=}CH_2$	36 : 1	94 %	– 69.2	– 71.1
2d	Cl	Ph	7 : 1	90 %	– 71.3	– 72.2

The best yields were achieved by dropwise addition of a THF solution of aldehyde to a cooled (–78 °C) THF solution of Grignard reagent.[5] The *anti*-isomers[6] **2a-d** are the main reaction products with the tested alkyl, vinyl and phenyl Grignard reagents. The enantiomeric excesses of all major diastereoisomers **2**, checked by esterification with both enantiomers of α-phenylpropionic acid (PPA) and subsequent NMR analysis of the crude mixtures, resulted to be identical (70%) to those of the starting aldehyde **1a**.

The remarkable stereoselectivity of these reactions could be explained as follows.

The addition to **1a** does not take place at all using 1 equiv. of Grignard reagent. Therefore, it appears more than reasonable to hypothesize the addition of a second molecule of Grignard reagent to the preformed intermediate chelated magnesium derivative **B** (Figure 1), which is widely accepted for the reactions of known *N*-monoprotected α-aminoaldehydes with organomagnesium reagents.[4a] On this basis, the "Cram's cyclic model" can rationalize the observed stereoselection. Thus, the major *anti*-products **2** should arise from an attack of a molecule of Grignard reagent from the trifluoromethyl group side of **B**, away from the *p*-tolylthio group, which plays the role of "large" substituent.[7]

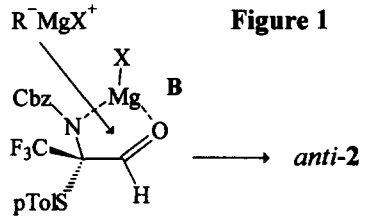
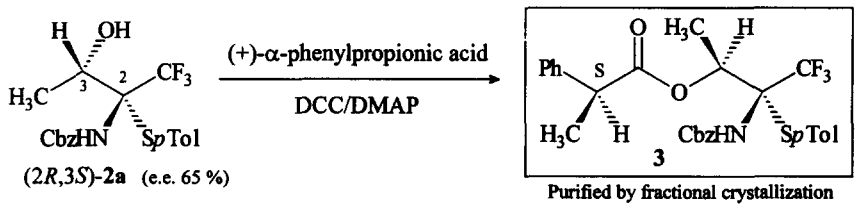


Figure 1

The absolute stereochemistry of the carbinolic centre C-3 was determined by NMR analysis of the α-phenylpropionic esters of methyl, ethyl and vinyl derivatives **2a-c**.[8]



Scheme 3

Scheme 3. Synthesis of the α-phenylpropionic ester **3** for X-ray analysis.

Single crystal X-ray diffraction of **3**, the (*S*)-α-phenylpropionic ester of *anti*-(2*R*,3*S*)-**2a** (Fig. 2),[9] confirmed the C-3 configuration and allowed to determine unambiguously the absolute stereochemistry of the ketal stereocentre C-2 (Scheme 3), thus assessing that the *N*-Cbz-trifluoropyruvaldehyde-ketal (+)-**1a** has (*R*) stereochemistry.

Anti-(2*R*,3*S*) stereochemistry was confidently assigned to the major diastereoisomer of the phenyl derivative **2d** by ^{19}F NMR, and later confirmed by chemical correlation (see below).

In fact, it can be easily seen from Table 1 that the signals of the trifluoromethyl groups of the *anti*-diastereoisomers are always observed at lower fields than those in the *syn* series. A similar trend has been already described for the ^{19}F NMR spectra of a closely related series of γ-trifluoro-β-aminoalcohols.[11]

We next turned our attention to the removal of the *p*-tolylthio group from **2**, in order to exploit the methodology for the synthesis of chiral non racemic γ-trifluorosubstituted β-aminoalcohols, for example analogues of *ephedra* alkaloids.

A screening of several reductive conditions revealed that treatment of the phenyl derivative (2*R*,3*S*)-**2d** with $NaBH_4$ (5 equiv) in pyridine[12] at 0 °C produces a clean and highly diastereoselective desulfenylation (d.s. > 90%), occurring with retention of configuration at the amine stereocentre. Formation of the *anti* product *N*-Cbz trifluoronorephedrine (*S*,*S*)-**4** (70% yield, Scheme 4) can be interpreted in terms of a pyridine promoted elimination of *p*-thiocresol from **2d**, leading to formation of the corresponding transient chiral α-hydroxy-*N*-Cbz-imine, which is stereoselectively reduced by $NaBH_4$.

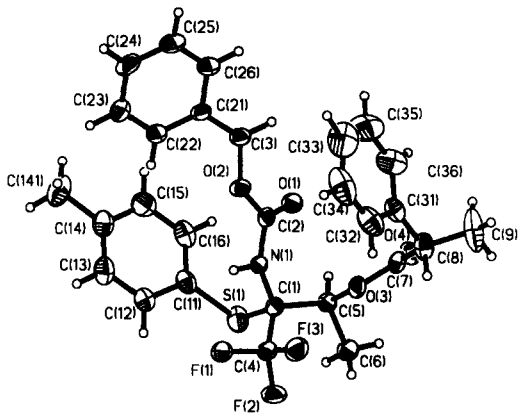
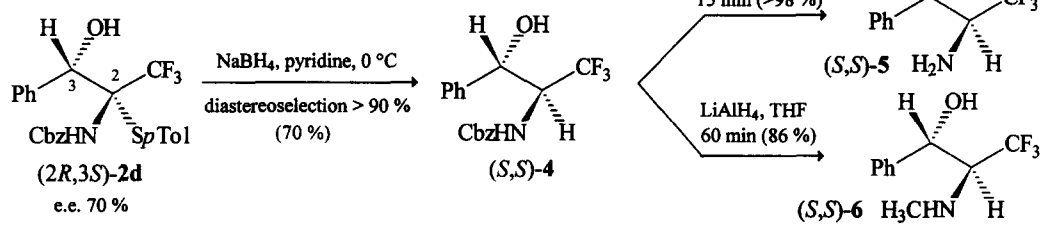


Figure 2. ORTEP[10] view of **3**.

Scheme 4



Scheme 4. Synthesis of trifluoro-norephedrine (*S*,*S*)-**5** and -ephedrine (*S*,*S*)-**6**.

Finally, hydrogenolysis of (*S*,*S*)-**4** with $Pd(OH)_2$ (15 min, rt) quantitatively provided trifluoronorephedrine (*S*,*S*)-**5** (70% e.e.). The spectral properties of (*S*,*S*)-**5**, which is a white solid with $[\alpha]^{20}_D$ + 11.5 (c 1.05, $CHCl_3$),[13] match those recently reported in literature for racemic trifluoronorephedrine.[11]

On the other hand, trifluoroephedrine (*S*,*S*)-**6**, having $[\alpha]^{20}_D$ + 9.0 (c 0.80, $CHCl_3$) and *ca.* 70% e.e., was obtained in high yield by reduction of the *N*-Cbz group of (*S*,*S*)-**4** with $LiAlH_4$ in refluxing THF.

It is noteworthy that the stereoselective synthesis of compounds **1-6** can be equally applied to the synthesis of their enantiomers by simply switching the starting β-sulfinylenamine **A** to **ent-A**.

The chemistry of the new promising fluorinated 3-C building blocks fluoropyruvaldehyde-*N*,*S*-ketals **1**, as well as further applications in the stereoselective synthesis of biomedicinally interesting chiral molecules endowed with a γ-fluorosubstituted-β-aminoalcohol framework, are currently under investigation.

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* E-mail: zanda@dept.chem.polimi.it; fax number 39-2-2399-3080.

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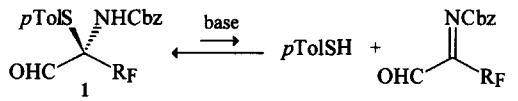
4. (a) For *N*-monoprotected α-amino aldehydes see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149-164. Devant, R. M.; Radunz, H.-E. In *Houben-Weyl: Methods in Organic Synthesis*; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1995; Vol. E21b, p. 1151. (b) For chiral α-trifluoromethylated aldehydes: Konno, T.; Yamazaki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 199-208. (c) For α-sulfenyl aldehydes: Eames, J.; de las Heras, M. A.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4077-4080. Eames, J.; Jones, R. V. H.; Warren, S. *Ibid.* **1996**, *37*, 4823-4826. Sato, T.; Otera, J. *Synlett* **1995**, 351-352.
5. Inverse addition generally led to incomplete reactions and partial racemization of unreacted **1a**. Elimination-addition of *p*-thiocresol through a transient achiral imine should be the reason for this racemization, as assessed by treatment of aldehydes **1** with bases, even weak, like triethylamine and $NaHCO_3$.



6. *Syn* and *anti* descriptors refer to the relative position of the amino and the hydroxy groups with respect to the molecular carbon backbone.
7. The tendency of an arylthio group to behave as "large" ligand is well recognized. See for example: Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484-489. Annunziata, R.; Cinquini, M.; Cozzi, F.; Fuchicello, A. *Tetrahedron* **1991**, *47*, 3853-3868. The high level of discrimination between the *p*-tolylthio and the CF_3 group, the latter of which has been proposed to be of similar size as the isopropyl group (see ref. 4b), is not surprising. In fact, arylthio ligands have been reported to be remarkably "larger" than the isopropyl group. See for example: Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775-4778. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456-461.
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9. Crystal data: $C_{28}H_{28}F_3NO_4S$, f.w. 531.57, Monoclinic, space group $P2_1$, a = 7.630(1)Å, b = 15.096(1)Å, c = 11.744(1)Å, β = 90.20(1)°, V = 1352.7(2)Å^3, Z = 2, D_c = 1.305 g/cm^3, μ = 1.536mm^{-1}, F(000) = 556, final R1 = 0.0464, wR2(all data) = 0.1276, S = 1.060, Flack's parameter (Flack, H.D. *Acta Cryst.* **1983**, *A 39*, 876-880) = -0.01(3), Extinct. coeff. = 0.0071(7), largest peak and hole 0.176 and -0.210eÅ^{-3}. X-ray diffraction data were collected from a colorless crystal platelet of **3** (size 0.05 x 0.2 x 1.2mm), with graphite monochromated Cu-K_α radiation (λ = 1.5418Å). The structure was solved by direct methods using SIR92 (Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi A. *J.Appl.Cryst.* **1993**, *26*, 343-350) and refined by full-matrix least squares on F^2 using SHELXL93 (Sheldrick, G.M. **1993**, *SHELXL93, Program for the Refinement of Crystal structures,* University of Göttingen, Germany). Non-hydrogen atoms were refined anisotropically. The amide hydrogen has been located by difference-Fourier technique and refined while the others have been included at calculated positions and refined with group temperature factors. Molecular dimensions fall in the expected ranges.
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12. Ogura, K.; Yoshimura, I.; Katoh, N.; Tsuchihashi, G. *Chem. Lett.* **1975**, 803-804.
13. Enantiopure (*R,R*)-**5**, having $[\alpha]^{20}_D$ – 14.0 (c 1.24, $CHCl_3$), has been recently synthesized in these laboratories by a completely different strategy. The related manuscript is in preparation.

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