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Stereoselective synthesis of (*R*)- and (*S*)-α-trifluoromethyl aspartic acid via titanium enolate addition to a sulfinimine of trifluoropyruvate

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Abstract—The reaction of an enantiomerically pure sulfinimine of trifluoropyruvate with several metal enolates is described. The use of $TiCl(O\text{-}iPr)_3$/LDA produced the corresponding sulfinamides with high stereocontrol. The latter could be smoothly transformed into each enantiomer of α-trifluoromethyl aspartic acid with high ee, which has been previously synthesized only in racemic form.

1. Introduction

α-Trifluoromethyl (Tfm) α-amino acids are extremely interesting analogues of natural α-amino acids,[1] owing to the unique properties of the Tfm group, such as high electronegativity, electron density, steric hindrance and hydrophobic character.[2] However, the relatively difficult availability of most Tfm-amino acids in nonracemic form, whose asymmetric synthesis often requires complex experimental protocols and hard to handle starting materials, obstructs a systematic investigation of the biomedicinal and structural features of α-Tfm α-amino acids and their peptidic derivatives. Nonracemic α-Tfm-aspartic acid (Tfm-Asp) is of particular interest, because Asp is a key component of the RGD sequence (Arg-Gly-Asp) that mediates the binding of fibrinogen to its platelet receptor and plays a key role in a variety of human cerebral and cardiovascular diseases. Recently, we have been involved in a project aimed at the synthesis of RGD peptides incorporating Tfm-Asp.[3] Although racemic Tfm-Asp and its derivatives have been reported,[4] to our knowledge Tfm-Asp is hitherto unknown in nonracemic form. Herein we report a practical approach to Tfm-Asp and some derivatives in high ee by exploiting a highly diastereoselective Mannich-type addition of a titanium enolate to a chiral sulfinimine of trifluoropyruvate.

2. Results and discussion

The enantiomerically pure sulfinimine[5] (*S*)-**2** (Scheme 1) was prepared, according to the literature method,[6] by means of a Staudinger (aza-Wittig) reaction of ethyl trifluoropyruvate with the iminophosphorane (*S*)-**1**. The Mannich-type reaction of metal enolates of ethyl and *tert*-butyl acetate **3a** and **b** with (*S*)-**2** was addressed next (Table 1).[7]

The sodium enolates generated in THF by the action of NaHMDS on **3a** and **b**, afforded the target *N*-sulfinyl Tfm-Asp esters **4a** and **b** in low de and modest yields (entries 1 and 3, respectively), whereas the use of diethyl ether proved to be detrimental in terms of yield (entry 2). The use of KHMDS (potassium enolate, entry 4) and LiHMDS (lithium enolate, entry 5) did not produce beneficial effects. Slightly better results were achieved with LDA as base (entry 6), which afforded **4a** in 24% de.[8] Similar results were observed upon transmetallation of the lithium enolate with $TiCl_4$ (entry 7). A remarkable improvement was achieved by performing the transmetallation of lithiated **3b** with $AlCl(Et)_2$, which gave

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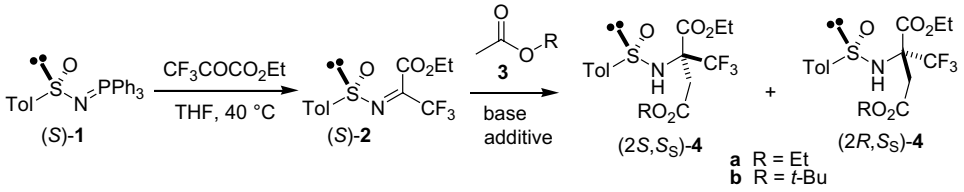


Scheme 1. Addition of enolates of **3** to the sulfinimine (*S*)-**2**.

Table 1. Diastereoselectivity of enolate additions to (*S*)-**2**[a]

Entry	Ester	Base, additive	Solvent	Yield[b] (%)	Ratio 2*S*:2*R*[c]	De
1	**3a**	$NaN(SiMe_3)_2$	THF	48	55:45[d]	10
2	**3a**	$NaN(SiMe_3)_2$	Et_2O	23	55:45[d]	10
3	**3b**	$NaN(SiMe_3)_2$	THF	52	62:38	24
4	**3b**	$KN(SiMe_3)_2$	THF	16	55:45	10
5	**3b**	$LiN(SiMe_3)_2$	THF	37	72:28	44
6	**3a**	LDA	THF	42	62:38[d]	24
7	**3b**	LDA, $TiCl_4$	THF	44	64:36	28
8	**3b**	LDA, $AlCl(Et)_2$	THF	71	83:17	66
9	**3b**	LDA, $TiCl(O\text{-}iPr)_3$	THF	78	96:4	92

[a] The reactions were carried out with a ratio of enolate:imine = 3.0:1.0 at −78 °C (see experimental).
[b] Isolated yields of the two diastereomers.
[c] Determined by HPLC analysis.
[d] The stereochemistry of diastereomers **4a** was not assigned.

(2*S*,S_S)-**4b** in 66% de and 71% overall yield (entry 8). The optimal result was finally obtained with the Ti(O-*i*Pr)$_3$-enolate of **3b** (entry 9), which produced the sulfinamide (2*S*,S_S)-**4b** in very good yield (78%) and excellent diastereocontrol (92% de).

This result, which is in line with the results of Ellman for unfluorinated *N*-*tert*-butylsulfinyl-ketimines[7b] both in terms of degree and direction of the stereocontrol, can be interpreted in terms of a Zimmerman–Traxler-type transition state **TS-1** (Fig. 1), favouring the approach of the enolate from the *re*-face of (*S*)-**2**.[9]

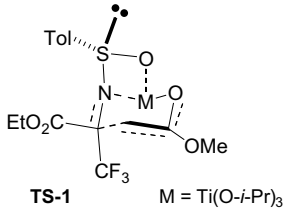


Figure 1. Proposed transition state.

The optimized procedure (Table 1, entry 9) was performed also on the enantiomeric sulfinimine (*R*)-**2**, affording (R_S,2*R*)-**4b** as the major product. The stereochemistry of the latter compound, and therefore of all the compounds derived from **4b**, was unambiguously determined by X-ray diffraction of suitable single crystals (Fig. 2).[10]

Chiral HPLC analysis showed that the major diastereomers **4b** were obtained in 80–84% ee. Apparently, partial

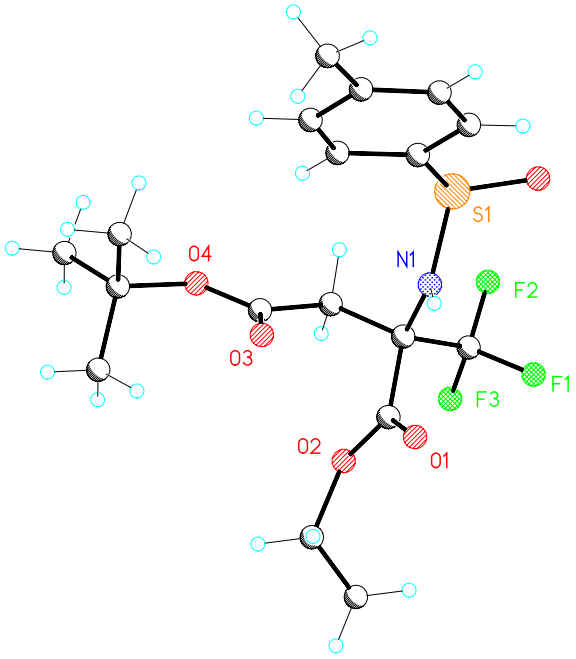


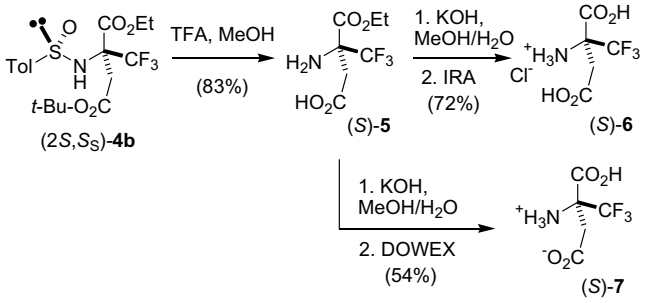
Figure 2. X-ray structure of the sulfinamide (R_S,2*R*)-**4b**.

racemization of the sulfinimine (*S*)-**2** takes place during the enolate addition, as already observed in the reaction with alkyl, benzyl and allyl Grignard reagents.[6] However, the ee of **4b** could be raised to 97% by a single crystallization from diisopropyl ether. This allowed us to continue the synthesis of Tfm-Asp with nearly enantiopure material.

The crystallized major sulfinamide (2*S*,S_S)-**4b** (ee 97%) was next submitted to cleavage of both the *N*-sulfinyl auxiliary and the ester protecting group (Scheme 2). Treatment with TFA in methanol afforded the free amino ester (*S*)-**5**, along with the co-product *p*-Tol-SO_2Me. Saponification with KOH followed by purification either with the ion-exchange resin IRA or DOWEX provided in fair yields the target (*S*)-Tfm-Asp, respectively, as the hydrochloride salt **6** or in its free zwitterionic form **7**. The same protocol was performed on (2*R*,R_S)-**4b** affording the (*R*)-enantiomers of **6** and **7**.

3. Conclusion

In conclusion, we have developed an efficient and stereoselective synthesis of both enantiomers of α-Tfm-



Scheme 2. Elaboration of the major sulfinamide **4b** into α-Tfm-aspartic acid (*S*)-**7** and its hydrochloride (*S*)-**6**.

aspartic acid in high ee exploiting a stereocontrolled Mannich-type reaction of *tert*-butyl acetate titanium enolate with a chiral sulfinimine of trifluoropyruvate.

4. Experimental

4.1. General

Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Coupling constants (J) are reported in hertz. Me_4Si was used as the internal standard (δ_H and $\delta_C = 0.00$) for ^1H and ^{13}C nuclei, while C_6F_6 was used as the external standard ($\delta_F = -162.90$) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; etc. ^1H NMR spectra were recorded at 200 MHz, ^{13}C NMR at 50.3 MHz, ^{19}F NMR at 235.2 MHz. Anhydrous THF was obtained by distillation from sodium. 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. HRMS analyses have been performed by electron spray ionization (ESI) (positive ion mode). 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 chromatography (FC). Diastereoselectivities were determined by HPLC analyses of the corresponding addition products **4** using a Merck LiChroCART® 125-4 LiChrospher® 100 RP-18 (5 μm) column, H_2O/CH_3CN 50:50, 0.8 mL/min. Chiral HPLC analyses were carried out using a Chiralcel OD column, *n*-hex/*iso*-propanol 95:5, 0.8 mL/min. The iminophosphorane (*S*)-**1** was prepared according to the literature.[6]

4.2. Synthesis of 4-*tert*-butyl 1-ethyl *N*-[(4-methylphenyl)sulfinyl]-2-(trifluoromethyl)aspartates (2*S*,S_S)- and (2*R*,S_S)-4

The procedure with ClTi(O-*i*-Pr)$_3$ is described as an example. A solution of 113 μL of (*i*-Pr)$_2$NH (0.795 mmol) in 2 mL of dry THF was cooled to −78 °C. A 2.5 M *n*-hexane solution of *n*-butyllithium (320 μL, 0.795 mmol) was added dropwise via a syringe while stirring. The mixture was allowed to warm to 0 °C and, after 5 min, cooled to −78 °C. Then, 107 μL (0.795 mmol) of *t*-butyl acetate **3b** was added dropwise and the resulting solution stirred for 30 min. Next, ClTi(O*i*-Pr)$_3$ (88 μL, 0.795 mmol) was added dropwise to form the yellow-coloured Ti-enolate, and the solution stirred for 30 min. A solution of sulfinimine (*S*)-**2** (0.265 mmol), prepared in situ as previously described,[6] dissolved in 0.8 mL of THF, was added dropwise and the mixture stirred for 30 min. Upon reaction completion, 1 mL of NH_4Cl (satd) was added at −78 °C and allowed to warm to rt. The mixture was then diluted with ethyl acetate, the aqueous layer separated and extracted with ethyl acetate. The collected organic fractions were washed with brine, dried and concentrated in vacuo. Purification of the crude by FC (*n*-hex/EtOAc 80:20) afforded 3.5 mg of the minor diastereomer (2*R*,S_S)-**4b** ($R_f >$) and 84 mg of the major (2*S*,S_S)-**4b** ($R_f <$) with a 78% overall yield. Sulfinamides **4b** were found to be rather unstable in $CHCl_3$ solution at rt. After one week, almost complete cleavage of the *N*-sulfinyl group was observed.

(2*R*,S_S)-**4b** ($R_f = 0.68$, *n*-hex/EtOAc 70:30): Oil. $[\alpha]_D^{20} = +75.6$ ($c = 0.39$, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.60 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz, 2H), 5.58 (s, 1H), 4.45–4.25 (m, 2H), 3.44 (s, 2H), 2.40 (s, 3H), 1.49 (s, 9H), 1.29 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): 166.6, 166.0, 142.1, 141.8, 129.7, 125.5, 123.7 (q, $J = 286.7$ Hz), 82.8, 64.7 (q, $J = 28.2$ Hz), 63.8, 37.0, 28.0, 21.4, 13.8. ^{19}F NMR ($CDCl_3$): −76.83 (s). HRMS calcd for $C_{18}H_{24}F_3NO_5S$ (MH^+) 424.1405, found 424.1409. HPLC analysis: $t_R = 23.04$ min. Chiral HPLC analysis: $t_R = 7.62$ min, ee 91%.

Enantiomeric (2*S*,R_S)-**4b** showed $[\alpha]_D^{20} = -69.45$ ($c = 0.44$, $CHCl_3$). Chiral HPLC analysis: $t_R = 6.78$ min, ee 84%.

(2*S*,S_S)-**4b** ($R_f = 0.62$, *n*-hex/EtOAc 70/30): Mp (*i*-Pr_2O) = 115 °C. $[\alpha]_D^{20} = +4.3$ ($c = 0.7$, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.65 (d, $J = 8$ Hz, 2H), 7.31 (d, $J = 8$ Hz, 2H), 5.44 (s, 1H), 4.35 (q, $J = 7$ Hz, 2H), 3.45–3.41 (m, 2H), 2.41 (s, 3H), 1.44 (s, 9H), 1.31 (t, $J = 7$ Hz, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 166.0, 142.4, 141.8, 129.8, 125.9, 123.2 (q, $J = 288.2$ Hz), 82.6, 65.2 (q, $J = 28.7$ Hz), 63.6, 34.8, 27.9, 21.4, 13.8. ^{19}F NMR ($CDCl_3$): −77.12 (s). HPLC analysis: $t_R = 16.82$ min. Chiral HPLC analysis: $t_R = 8.15$ min, ee 80%. Anal. Calcd for $C_{18}H_{24}F_3NO_5S$: C, 51.06; H, 5.71; N, 3.31. Found: C, 50.99; H, 5.72; N, 3.73.

Enantiomeric (2*R*,R_S)-**4b** showed $[\alpha]_D^{20} = -5.3$ ($c = 0.43$, $CHCl_3$). Chiral HPLC analysis: $t_R = 6.52$ min, ee 97%.

4.3. Synthesis of α-trifluoromethyl aspartic acid α-carboxy ethyl ester (*S*)-5

To a stirred and cooled (0 °C) solution containing (2*S*,S_S)-**4b** (200 mg, 0.473 mmol, 97% ee) dissolved in 8 mL of methanol, trifluoroacetic acid (73 μL,

0.945 mmol) was added dropwise. The mixture was allowed to warm to 0 °C and stirred for 2 h. After evaporation of the solvent, the crude was diluted with water and diethyl ether and, after separation, the organic layer extracted with a (15%) aqueous solution of HCl. After evaporation of the collected aqueous layers, the residue was loaded onto a Dowex 50 W-X8 column, affording 90 mg of (*S*)-**5** (83%).

(*S*)-**5**: Mp = 155 °C (dec). $[\alpha]_D^{20} = +22.4$ ($c = 0.52$, H_2O). ^1H NMR (D_2O): 4.16 (q, $J = 7.1$ Hz, 2H), 2.78 (ABq, $J = 16.7$ Hz and $\Delta\nu = 96$ Hz, 2H), 1.14 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (D_2O): 178.0, 172.8, 126.6 (q, $J = 284.2$ Hz), 66.7, 65.7 (q, $J = 27.2$ Hz), 41.8, 15.8. ^{19}F NMR (D_2O): −75.02 (s). HRMS calcd for $C_7H_{10}F_3NO_4$ (MH^+) 230.0640, found 230.0635.

Enantiomeric (*R*)-**5** showed $[\alpha]_D^{20} = -21.1$ ($c = 0.53$, H_2O).

4.4. Synthesis of α-trifluoromethyl aspartic acid hydrochloride (*S*)-6

To a solution containing (*S*)-**5** (60 mg, 0.24 mmol) dissolved in 5 mL of a 70:30 methanol/water mixture, 3 mL of a 0.5 M aqueous solution of KOH was added dropwise and the resulting mixture stirred overnight at rt. The reaction solution was acidified to pH = 1 by slowly adding an aqueous solution of HCl (1 M), and the solvent then evaporated. The residue was dissolved in water, and loaded onto an IRA-410 column. Elution with 1 M HCl afforded 41 mg (72%) of hydrochloride (*S*)-**6**.

(*S*)-**6**: Mp = 185 °C (dec). $[\alpha]_D^{20} = +23.5$ ($c = 0.25$, H_2O). ^1H NMR (D_2O): 3.10 (ABq, $J = 18$ Hz and $\Delta\nu = 68$ Hz, 2H). ^{13}C NMR (D_2O): 174.5, 168.8, 125.5 (q, $J = 284.2$ Hz), 65.6 (q, $J = 28.4$ Hz), 37.0. ^{19}F NMR (D_2O): −73.76 (s). HRMS calcd for $C_7H_{10}F_3NO_4$ (MH^+) 230.0640, found 230.0638.

Enantiomeric (*R*)-**6** showed $[\alpha]_D^{20} = -24.3$ ($c = 0.25$, H_2O).

4.5. Synthesis of α-trifluoromethyl aspartic acid (*S*)-7

Working under the same experimental conditions as described above and after the end of reaction, the crude solution was acidified to pH = 1 by adding an aqueous solution of HCl (1 M) and then evaporated. The residue was dissolved in water and loaded onto a Dowex 50 W-X8 column, affording 26 mg of free aminoacid (*S*)-**7** (54% yield) upon elution with a 7.5% aqueous ammonia solution.

(*S*)-**7**: Oil. $[\alpha]_D^{20} = +23.5$ ($c = 0.17$, H_2O). ^1H NMR (D_2O): 2.70 (ABq, $J = 16.7$ Hz and $\Delta\nu = 65$ Hz, 2H). ^{13}C NMR (D_2O): 178.5, 172.9, 126.8 (q, $J = 283.7$ Hz), 66.0 (q, $J = 26.6$ Hz), 40.1. ^{19}F NMR (D_2O): −74.00 (s). Enantiomeric (*R*)-**7** showed $[\alpha]_D^{20} = -18.4$ ($c = 0.19$, H_2O). HRMS calcd for $C_5H_6F_3NO_4$ (MH^+) 202.0327, found: 202.0319.

4.6. X-ray diffraction of (2*R*,R_S)-4b

A suitable crystal (block, colourless, 0.6×0.5×0.2 mm in dimension) was obtained from *i*-Pr_2O. Intensity data were collected on a Siemens P4 diffractometer with graphite monochromated Cu-Kα radiation ($\lambda = 1.54179$ A°), using $\theta/2\theta$ scan technique. Unit cell parameters were determined using 60 reflections in the range $10 \leqslant 2\theta \leqslant 54°$; a total of 2688 reflections were collected up to 136° in 2θ and index range: $-1 \leqslant h \geqslant 23$, $-10 \leqslant k \geqslant 1$, $-13 \leqslant l \geqslant 1$. No crystal decay was observed. Crystal data: $C_{18}H_{24}O_5NF_3S$, $M_r = 423.4$, orthorhombic, space group $P212121$, $a = 19.319(2)$, $b = 9.965(1)$, $c = 10.919(1)$ Å, $V = 2102.1(1)$ Å^3, $Z = 4$, $D_c = 1.338$ g cm^{-3}, $\mu = 1.863$ mm^{-1}, $F(000) = 888$; $\lambda = 1.54179$ Å, room temperature. The structure was solved by direct methods using an SIR97[11] program, which revealed the position of all nonH atoms; H atoms were located at calculated positions and refined in a riding model. The refinement was carried out on F^2 by full-matrix least-squares procedure with SHELXL97[12] for 257 parameters, with anisotropic temperature factors for nonH atoms. The final stage converged to $R = 0.053$ ($R_w = 0.124$) for 2023 observed reflections, with $I \geqslant 2\sigma(I)$, and $R = 0.068$ ($R_w = 0.137$) for all unique reflections after merging. The mean shift/error was 0.003 and the goodness of fit, *S*, was 1.097. The final difference map showed a maximum and minimum residual peaks of 0.26 and −0.24 e Å^{-3}, respectively. The absolute configuration was assigned by the Flack[13] parameter $x = -0.05(4)$ for the (*R*) absolute configuration and $x = 0.96(4)$ for the inverse one, and by an *R*-factor test $R = 0.053$ and $R = 0.059$ for the (*R*) and (*S*) configurations, respectively.

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8. The stereochemistry of diastereomers **4a** was not assigned.
9. (a) It is known that (*S*)-**2** exists in its geometrically homogeneous *E*-form (see Ref. 6). (b) Attempts to prepare *N*-*tert*-butylsulfinylimines of trifluoropyruvate were unsuccessful (see Ref. 6).
10. Full data (excluding structure factors) of the crystal structure have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. 226689. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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