Synthesis of Nonracemic α-Trifluoromethyl α-Amino Acids from Sulfinimines of Trifluoropyruvate

Amparo Asensio,[c] Pierfrancesco Bravo,[a,b] Marcello Crucianelli,*[a] Alessandra Farina,[a] Santos Fustero,[c] Juan García Soler,[c] Stefano V. Meille,[a] Walter Panzeri,[b] Fiorenza Viani,[b] Alessandro Volonterio,[a] and Matteo Zanda*[a]

Keywords: Amino acids / Asymmetric synthesis / Grignard reactions / Sulfinimines / Trifluoromethyl group

We describe a novel and useful method for the synthesis of nonracemic α-trifluoromethyl α-amino acids (α-Tfm-AAs). Key building blocks are the sulfinimines (*S*)-**1a** and (*S*)-**1b**, prepared by Staudinger reaction from trifluoropyruvate esters and the chiral *N*-sulfinyl iminophosphorane (*S*)-**8**, which were treated with benzyl, allyl, and alkylmagnesium halides. The resulting diastereomeric *N*-sulfinyl α-Tfm α-amino esters, **12** and **13**, were produced with moderate to good stereoselectivity and yields. When alkyl Grignard reagents were used, stereocontrol became progressively higher with increasing steric bulk, while reversed, though poor, stereocontrol was achieved with benzyl/allyl Grignard reagents. An explanation for the observed stereochemical outcome is proposed, on the basis of the exclusive *E* geometry (*N*-sulfinyl and CF_3 *trans* about the C=N bond) of the chiral sulfinimines **1**. This assignment is the product of structural correlation and is supported by ab initio calculations and NOE experiments. Sulfinamides **12** and **13** were transformed into a series of nonracemic α-Tfm-AAs **16**–**22**. The sulfinyl auxiliary can be regenerated and recycled.

Introduction

The stereocontrolled synthesis of nonracemic quaternary α,α-disubstituted α-amino acids ($C^{\alpha,\alpha}$-AAs) represents an attractive target in modern organic chemistry, because incorporation of $C^{\alpha,\alpha}$-AAs into peptides imposes significant constraints on their conformational freedom and causes a remarkable proclivity to fold into well defined secondary structures, such as β-bends and α-3_{10} helices.[1] Additional features are increased lipophilicity and higher resistance towards enzymatic hydrolysis.[2] These are all very desirable properties, since some of the major drawbacks in the application of peptides as pharmaceuticals relate to their conformational flexibility, which can result in undesired, nonselective interactions with different receptors, their low bioavailability, and their sensitivity to proteolytic degradation. As a consequence, several methods for the synthesis of chiral nonracemic $C^{\alpha,\alpha}$-AAs have been developed, and the field has recently been reviewed.[3]

α-Trifluoromethyl α-amino acids (α-Tfm AAs) form a special class of manmade $C^{\alpha,\alpha}$-AAs of considerable interest in modern peptide chemistry, in spite of the serious drawback that is the low nucleophilicity of their α-amino function, which makes coupling reactions extremely difficult. This is for several reasons, itemized as follows. (a) The low toxicity of the CF_3 group, in conjunction with its high stability in comparison with CH_2F or CHF_2, make it an attractive substituent for pharmaceutical applications.[4] (b) An α-Tfm-AA incorporated in a peptide sequence exerts relevant polarization effects, which may result in improved metabolic stability with respect to degradation by peptidases, consequently enhancing its bioavailability.[5] (c) The steric requirements of a CF_3 group, which seem to be close to those of an isopropyl residue, introduce severe conformational restrictions and reduce the conformational flexibility, thus minimizing the side effects deriving from low binding affinity.[6] (d) Thanks to its partially lipophilic character, a CF_3 group can give rise to increased lipophilicity in Tfm-substituted peptides, bringing about an enhancement of the in vivo absorption rate and, in general, improvements in permeability through cellular membranes.[4] (e) The high electron density of a CF_3 group, and the implied potential for acting as a weak hydrogen bond acceptor or coordinating site in metal complexes, might produce new modes of interaction with enzymes or receptor subsites.[7] (f) Some α-TFM AAs exhibit anticancer, antibacterial, and antihypertensive properties, as well as the ability to act as potent suicide inhibitors on pyridoxalphosphate-dependent enzymes (transaminases, decarboxylases).[8]

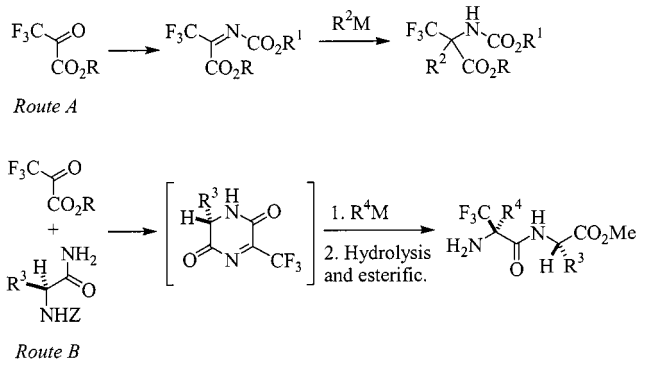
Several synthetic routes to racemic α-Tfm AAs have been developed.[9] The most general approach (Route A, Scheme 1) is represented by the reaction between *N*-protected imines of trifluoropyruvate and a large variety of organometallic nucleophiles R^2M (in which the metal M may be Cd, Mg, Li, Na, Zn).[10]

Besides some chemical and enzymatic resolution processes,[11] the two reported generalized methods currently in

[a] Dipartimento di Chimica del Politecnico,
Via Mancinelli 7, 20131 Milano, Italy
Fax: (internat.) +39−02/2399 3080
E-mail: zanda@dept.chem.polimi.it
[b] C.N.R. − Centro di Studio sulle Sostanze Organiche Naturali, Via Mancinelli 7, 20131 Milano, Italy
[c] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia,
46100-Burjassot, Valencia, Spain

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

  1434−193X/01/0408−1449 $ 17.50+.50/0



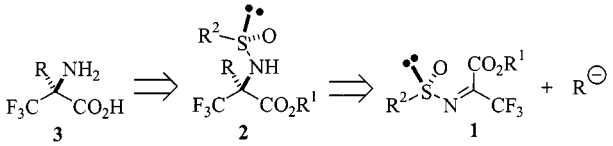
Scheme 1. Routes to α-Tfm α-amino acids

use for the preparation of nonracemic α-Tfm AAs are affected by some drawbacks. Addition of enantiopure lithiated sulfoxides to *N*-alkoxycarbonyl imines of trifluoropyruvate is an asymmetric variant of Route A,[12] suffering from poor stereocontrol in the formation of the stereogenic quaternary center. The stereoselective alkylation of 2,5-diketopiperazines obtained from trifluoropyruvate (Route B, Scheme 1), with organomagnesium and organocadmium reagents is effective for synthesis of the corresponding dipeptide units, but to the best of our knowledge, single α-Tfm-AAs have never been obtained by this route.[13] In this context, the development of a more efficient and general method for the synthesis of chiral, nonracemic α-Tfm-AAs was clearly needed. This issue is successfully addressed in this paper, which presents a full account of the synthesis of a series of nonracemic α-Tfm-AAs.[14]

Results

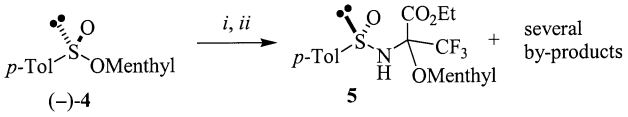
Preparation and Geometry of Sulfinimines of Trifluoropyruvate (S)-1

Our retrosynthetic analysis is shown in Scheme 2. It was intended that treatment of the sulfinimine **1** with R^- nucleophiles should afford the intermediate sulfinamides **2**, and subsequent cleavage of the *N*-sulfinyl auxiliary and hydrolysis of the carboxyl should afford the target α-Tfm-AAs **3**. There was reason to believe that the addition of R^- to **1** would take place stereoselectively, thanks to the proximity of the stereogenic sulfinyl auxiliary to the highly electrophilic iminic carbon.



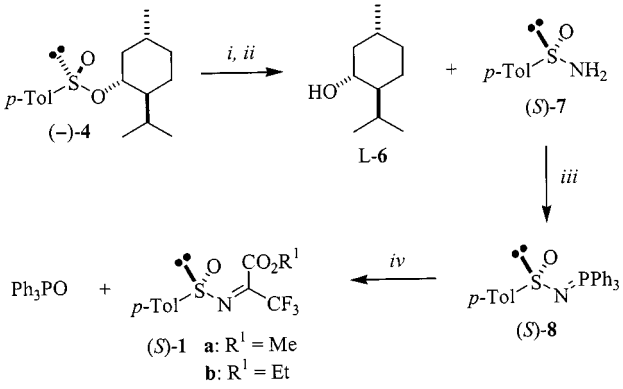
Scheme 2. Retrosynthetic analysis

Enantiopure sulfinimines (thiooxime *S*-oxides) have recently become very popular chiral building blocks, because addition of nucleophiles across their C=N double bond provides *N*-sulfinyl protected amines endowed with a new stereogenic center, often with very good stereocontrol.[15] The breakthrough in the field is probably represented by the work of Davis,[16] who disclosed a very convenient one-pot method for the preparation of enantiopure sulfinimines. Thus, this methodology initially formed the basis for our attempted synthesis of the desired sulfinimine of trifluoropyruvate **1**, but all our efforts met with failure. In fact, treatment of lithium hexamethyldisilazane (LiHMDS) with menthyl sulfinate (−)-**4** (Scheme 3), followed by addition of ethyl trifluoropyruvate (with or without CsF) invariably produced complex mixtures containing a main product that was tentatively identified as the *N*-sulfinyl-*O*-menthyl hemiaminal **5**. No trace of the expected sulfinimine **1** was ever detectable.[17]



Scheme 3. Key: i) $(Me_3Si)_2NLi$, THF; ii) $CF_3COCOOEt$

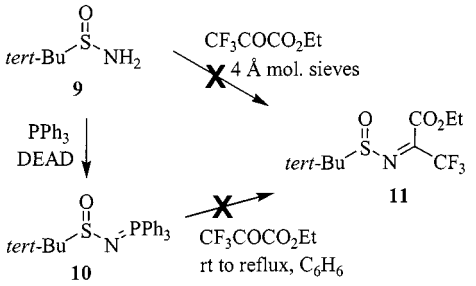
However, it proved possible to prepare the key sulfinimines (*S*)-**1a** and (*S*)-**1b** efficiently by a different pathway; namely by Staudinger (aza-Wittig) reaction,[18] which is known to be an extremely useful tool for preparing imines with a strongly electrophilic character (Scheme 4). Thus, the *p*-tolylsulfinamide (*S*)-**7**, easily obtained as described by Davis,[16] was treated with PPh_3/DEAD in dry THF at room temp.,[19] affording in good yield (92%) the chiral Staudinger reagent (*S*)-**8**, formerly obtained only in racemic form and with low yields from $Ph_3P{=}NH$, *p*-Tol-SOCl, and triethylamine.[20] Enantiomeric (*R*)-**8** was obtained from (*R*)-**7** in identical fashion.



Scheme 4. Key: i) LiHMDS, THF, −70 °C; ii) NH_4Cl/H_2O; ii-i) Ph_3P, DEAD, THF, room temp. (92%); iv) $CF_3COCO_2R^1$, PhH distilled from Na, 40 °C

The following Staudinger reactions between (*S*)-**8** and methyl or ethyl trifluoropyruvate took place cleanly in benzene freshly distilled from Na (ca. 90 min at 40 °C), affording (*S*)-**1a** and (*S*)-**1b**. Inspired by the work of Ellman et al.,[21] we attempted the use of *N*-(*tert*-butanesulfinimines) such as **11** (Scheme 5). To test this approach, we accomplished the synthesis of racemic *tert*-butanesulfinamide **9** by a literature method,[22] and used this compound for the preparation of the racemic Staudinger reagent **10** (PPh_3/DEAD, dry THF, room temp.). Disappointingly and rather surprisingly, the Staudinger reaction between **10** and ethyl trifluoropyruvate did not work at all, either at room temp.

or at reflux in benzene for several days. Similarly negative results were obtained for the reaction between the *tert*-butanesulfinamide **9** and ethyl trifluoropyruvate, in the presence of activated molecular sieves (4 Å).[23] The preparation of **11** was therefore abandoned.



Scheme 5. Attempts to obtain *tert*-butylsulfinylimine **11**

It must be pointed out that, unlike the corresponding *N*-acyl and *N*-alkoxy carbonyl derivatives,[12] sulfinimines (*S*)-**1a** and (*S*)-**1b** can be handled comfortably, because they are much less hygroscopic. Indeed, while the former compounds undergo immediate hydration of the C=N bond in the presence of a stoichiometric amount of water, (*S*)-**1b** did not undergo hydration during 15 min at room temp. in the presence of a large excess of water, as shown by ^{1}H and ^{19}F NMR experiments.

Sulfinimines (*S*)-**1a** and (*S*)-**1b** were used in situ for the next step, without isolation, because purification by flash chromatography (FC) on silica gel gave rise to extended hydrolysis. Nevertheless, (*S*)-**1a** and (*S*)-**1b** were fully characterized as crude products by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. A single set of signals was detected for sulfinimine (*S*)-**1b** from room temp. down to the freezing point of THF. No signals attributable to a second geometric isomer were observed (Table 1), indicating that (*S*)-**1b** exists essentially as a single geometric isomer[24] over a wide range of temperatures. We have recently shown by means of X-ray diffraction and NOE experiments that a wide range of *N*-substituted fluoroalkyl ketimines exist exclusively as (*E*) isomers; that is, with the *N*-substituent and the fluoroalkyl group in *trans* orientation, as a likely consequence of the high steric demand of the latter.[25] On the basis of these arguments, trifluoromethyl sulfinimines (*S*)-**1a** and (*S*)-**1b** are very likely to exist exclusively as (*E*) isomers. This assumption is supported by semiempirical and ab initio calculations.[26] The optimized structures corresponding to both the (*Z*) and (*E*) isomers of **1a** are shown in Figure 1. According to the calculations and independently of the method used, the (*E*) isomer is the most stable one: by 8.3 (RHF//6-31G*), 6.7 (RHF//3-21G), or 7.6 (AM1) kcal mol^{-1}.

Spectroscopic evidence for this point is provided by some NOE experiments on **1b**. Irradiation of the aromatic protons H_a (Figure 2) produced NOE enhancements of 0.25% for ethyl protons H_g and 0.28% for H_h. These values, although rather small if viewed on the normal scale of NOE experiments, are nevertheless of some significance if one considers the distance and the rotational freedom of both the ethyl and the *p*-tolyl groups in (*S*)-**1b**.

Table 1. Selected NMR signals for (*S*)-**1b** (A: $[D_8]$THF; B: $[D_6]$benzene; C: $CDCl_3$)

Groups (see Figure 2)	^{1}H (δ, ppm)	^{19}F (δ, ppm)	^{13}C (δ, ppm)
$(Me)_c$	1.88 (s)[A] 2.39 (s)[B] 2.42 (s)[C]		21.66[A] 21.30[B]
$(CF_3)_d$		−81.35[A] −68.20[B] −70.83[C]	119.23 (q)[A] 118.72 (q)[B]
$(C=N)_e$			152.66 (q)[A] 151.74 (q)[B]
$(CO_2)_f$			161.22[A] 160.50[B]
$(CH_2)_g$	4.17 (m)[A] 4.42 (q)[B] 4.45 (q)[C]		64.40[A] 64.21[B]
$(Me)_h$	1.03 (t)[A] 1.38 (t)[B] 1.42 (t)[C]		14.27[A] 13.95[B]

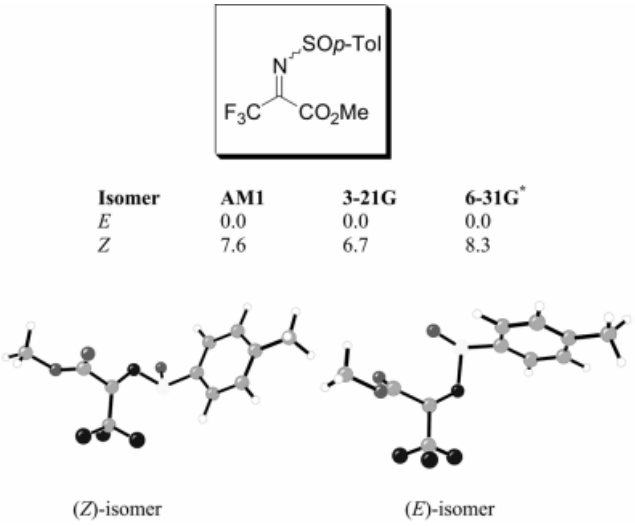


Figure 1. Theoretical calculations on sulfinimine (*S*)-**1a** (energies are in kcal/mol)

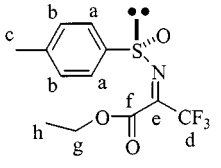
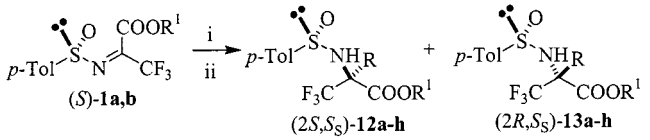


Figure 2. The more stable (*E*) isomer of sulfinimine (*S*)-**1b**

Addition of Grignard Reagents to Sulfinimines (S)-1a and (S)-1b

The key step in our approach to α-Tfm-AAs is the addition of alkylmagnesium reagents across the C=N bond of the sulfinimines (*S*)-**1a** and (*S*)-**1b** (Scheme 6). The optimized reactions were performed (−70 °C, 5 min) in THF distilled from Na/benzophenone. The corresponding diastereomeric sulfinamides **12** and **13a**−**h** were produced with variable stereoselectivities, depending mainly on the nature

of the Grignard reagent, and obtained in diastereomerically and chemically pure form by FC.



Scheme 6. Key: i) RMgX, THF, −70 °C; ii) NH_4Cl/H_2O

Benzylmagnesium chloride reacted with (*S*)-**1a** and (*S*)-**1b** to provide in both cases a mixture of diastereomers **12** and **13a/13b**, in good yields but with low selectivity (30:70) in favor of **13** (entries 1,2, Table 2).

Table 2. Addition of Grignard reagents to the sulfinimines (*S*)-**1a**,**b** prepared in benzene freshly distilled from Na; Grignard reagents were added to (*S*)-**1a** and (*S*)-**1b** in THF freshly distilled from Na/benzophenone

Entry	Product	R	R^1	X	*ee* (%)	Yield (%)[a]	**12/13**
1[b]	**12**,**13a**	benzyl	Me	Cl	92.5[c]	68	30:70
2	**12**,**13b**	benzyl	Et	Cl	92.5[c]	68	30:70
3	**12**,**13c**	allyl	Et	Cl	85	55	34:66
4	**12**,**13d**	isobutyl	Et	Br	88	65	88:12
5	**12**,**13e**	isopropyl	Et	Cl	90.5	72	84:16
6	**12**,**13f**	*n*-butyl	Et	Cl	n.m.	55	74:26
7	**12**,**13g**	ethyl	Et	Br	>96	70	73:27
8	**12**,**13g**	ethyl	Et	Cl	92	55	72:28
9	**12**,**13h**	methyl	Et	Cl	>96	52	55:45

[a] Overall yields from (*S*)-**8**. − [b] Enantiomeric **12** and **13a** were obtained identically from (*R*)-**1a**. − [c] *ee* = 99.9% after crystallization.

Allylmagnesium chloride featured the same sense of diastereoselectivity, providing a mixture of **12/13c** in a modest 34:66 ratio (entry 3). Reversal of diastereoselectivity in favor of diastereomers **12** was observed with alkylmagnesium halides (entries 4−9). The stereocontrol became progressively higher with increasing steric bulk of the Grignard reagent. Good stereoselectivity in favor of **12d** and **12e** was obtained with isobutylmagnesium bromide and isopropylmagnesium chloride, respectively (entries 4 and 5).[27]

In the case of *n*-butylmagnesium chloride (entry 6, Table 2) and ethylmagnesium bromide or chloride (entries 7 and 8, respectively) a modest preference for the corresponding (2*S*,S_S)-diastereoisomers **12f** and **12g** was achieved. We did not observe any meaningful effect of the halogen counterion on the diastereoselectivity. Finally, methylmagnesium chloride produced an almost equimolar mixture of diastereomers **12** and **13h** (entry 9).

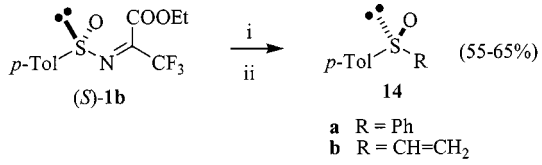
In most cases, a slight racemization of the sulfinyl center of the sulfinimines **1a** and **1b** occurred during the one-pot transformations (*S*)-**8** → (*S*)-**1** → **12/13**, as measured by chiral HPLC analysis (Table 3). Benzyl derivatives **12**, **13a**, and **13b** were obtained in 92.5% *ee*,[28] but crystallization from diisopropyl ether increased the *ee* to 99.9%. In the other cases, the *ee* ranged from 85% (allyl derivatives **12**, **13c**) to >96% (ethyl and methyl derivatives **12**, **13g**, **13h**). It is to be noted that when the reactions were performed in commercially available THF or benzene stored over molecular sieves, without preliminary distillation from sodium, the *N*-sulfinyl α-amino esters **12** and **13d**−**h** obtained from alkylmagnesium halides were isolated in only 20−50% *ee*.[29]

Table 3. Chiral HPLC analysis: t_R for sulfinamides **12**, **13**

Compound	t_R (min)[a] **12** (R_f <)		**13** (R_f >)	
	(2*S*,S_S)	(2*R*,S_S)	(2*R*,S_S)	(2*S*,S_S)
a	n.d.	n.d.	18.0	7.8
b	n.d.	n.d.	17.3	7.6
c	7.3	5.9	10.1	5.4
d	6.9	6.9	10.6	5.3
e	11.0	7.3	10.5	5.3
f	6.3	6.3	6.8	4.0
g	7.8	6.3	8.8	5.7

[a] Chiralcel OD, *n*-hexane/isopropyl alcohol, 85:15, 0.8 mL/min.

Surprisingly, when the sulfinimine (*S*)-**1b** was treated with phenyl- and vinylmagnesium halides under the usual experimental conditions, we observed an anomalous outcome (Scheme 7). In these circumstances, only the corresponding sulfoxides **14**, arising from a nucleophilic attack of Grignard reagent on the sulfur atom, were recovered as the main products, in low *ee*s.[30] The usual products deriving from attack across the C=N bond were neither isolated nor observed in the NMR spectrum of the crude product.[31]



Scheme 7. Key: i) RMgX, THF, −70 °C; ii) NH_4Cl/H_2O

The diastereoselectivity observed with alkylmagnesium halides might be explicable by the chelation model reported in Figure 3, as previously proposed by Wills for related reactions.[32] The carbanion attacks from the *Re* face of the sulfinimine **1b**, which should react in the much more populated (*E*) geometric fashion, through coordination of the sulfinyl oxygen by magnesium. The sulfinimine nitrogen is not likely to be coordinated by Mg, due to its very poor basic character.[25b]

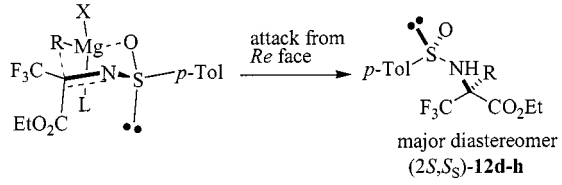


Figure 3. Chelation control (Wills' model)

On the other hand, Fujisawa's non-chelation model[33] (Figure 4) may explain the opposite stereoselectivity displayed by benzylmagnesium and allylmagnesium chloride,

although the reasons for the different behavior are presently unclear.

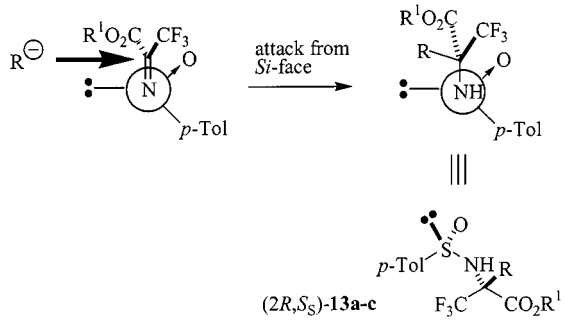
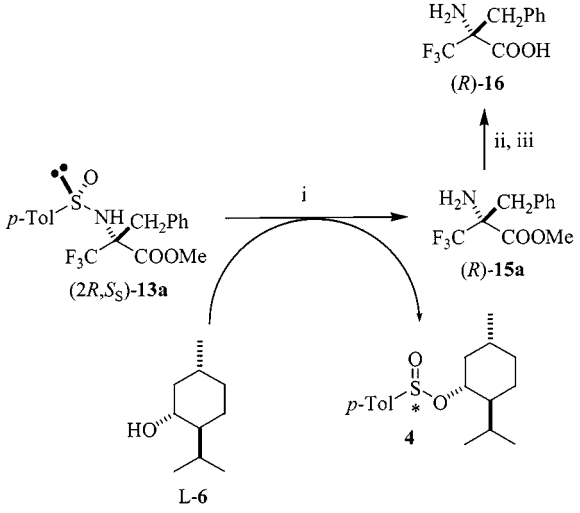


Figure 4. Non-chelation control (Fujisawa's model)

Synthesis of a Series of Nonracemic α-Tfm α-Amino Acids

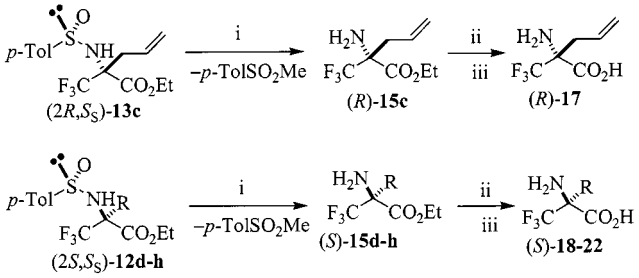
Cleavage of the *N*-sulfinyl group from the intermediate sulfinamides **12** and **13** was next addressed. An attractive feature of this methodology is that the sulfinyl auxiliary can be recovered and recycled, as demonstrated in the preparation of α-Tfm phenylalanine (*R*)-**16** (Scheme 8). Enantiomerically pure **13a** was treated with trifluoroacetic acid (TFA) in the presence of recycled menthol L-**6**.[34] α-Tfm-phenylalanine methyl ester (*R*)-**15a** was formed (90%) together with menthylsulfinate **4** (80%), recovered as a 3:2 mixture of epimers at sulfur; this can be regenerated in diastereomerically pure form (−)-**4** by the method of Posner and Solladié, and hence recycled.[35] This step might be of some importance



Scheme 8. Key: i) TFA, CH_2Cl_2; ii) KOH 0.5 N, MeOH/H_2O 7:3; iii) DOWEX-50 W

from the perspective of scaling up the preparation of α-Tfm-AAs. The methyl ester (*R*)-**15a** can be hydrolyzed according to the literature method,[36] to give the free amino acid (*R*)-**16**. The same sequence repeated on enantiomeric (2*S*,R_S)-**13a** provided (*S*)-**15a** as well.

The other *N*-sulfinyl amino esters (2*S*,S_S)-**12d**−**h** and (2*R*,S_S)-**13c** were treated with TFA in methanol at room



Scheme 9. Key: i) TFA, MeOH; ii) KOH 0.5 N, MeOH/H_2O 7:3; iii) DOWEX-50 W

temp. (Scheme 9), affording the corresponding α-Tfm-AA ethyl esters **15c**−**h**, along with methyl sulfinate, in good yields.[37] These compounds were hydrolyzed, usually without isolation, using 0.5 N KOH in a MeOH/H_2O 7:3 mixture, and then purified with DOWEX-50 W, completing the series of free α-Tfm-AAs **16**−**22** (Table 4).

Stereochemical Assignments

The relative configurations of racemic benzyl and isobutyl sulfinamides **13b** and **12d** were assigned as (2*R*,S_S) and (2*S*,S_S), respectively, by X-ray diffraction analyses of suitable racemic single crystals (Figure 5 and Figure 6).[38]

The stereochemistry of sulfinamides **13a**, **12g**, and **12h** was determined by transformation into the corresponding derivatives methyl α-Tfm-phenylalaninate (*R*)-**15a**, α-Tfm-α-aminobutyric acid (Abu) (*S*)-**21**, and α-Tfm-alanine (*S*)-**22**, the absolute configurations of which were assigned by comparison of their $[\alpha]_D^{20}$ values with literature data.[36,39] In the remaining three cases, the absolute configuration was tentatively assigned by means of the data obtained by chiral HPLC analysis. De facto, the enantiomers (2*S*,S_S)/(2*R*,R_S) of sulfinamides **12b**−**g** showed in all cases a lower Δt_r with respect to their (2*R*,S_S)/(2*S*,R_S)-**13b**−**g** counterparts (see Table 3). Further corroboration of this assignment is provided by comparison between the R_f values of the intermediate sulfinamides **12** and **13**. In fact, in the case of the five

Table 4. List of nonracemic α-Tfm-AAs

Entry	Starting material	R	Product	Yield (%)	$[\alpha]_D^{20}$	ee (%)[a]
1	(2*R*,S_S)-**13a**	Benzyl	(*R*)-**16**	81	+36.9 (*c* = 1.04, H_2O)[36]	> 99
2	(2*R*,S_S)-**13c**	Allyl	(*R*)-**17**	57	+27.0 (*c* = 0.69, H_2O)	85
3	(2*S*,S_S)-**12d**	Isobutyl	(*S*)-**18**	50	+8.20 (*c* = 0.11, H_2O)	88
4	(2*S*,S_S)-**12e**	Isopropyl	(*S*)-**19**	56	−3.05 (*c* = 0.32, H_2O)	90.5
5	(2*S*,S_S)-**12f**	*n*-Butyl	(*S*)-**20**	56	−1.36 (*c* = 2.24, H_2O)	n.d.
6	(2*S*,S_S)-**12g**	Ethyl	(*S*)-**21**	58	−11.0 (*c* = 1.1, EtOH)[36]	> 96
7	(2*S*,S_S)-**12h**	Methyl	(*S*)-**22**	55	−12.6 (*c* = 0.17, H_2O)[39]	> 96

[a] According to the *ee* of the starting material.

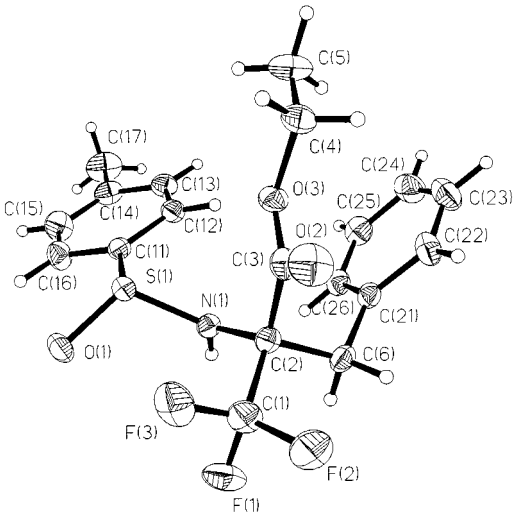


Figure 5. ORTEP diagram of (±)-**13b**

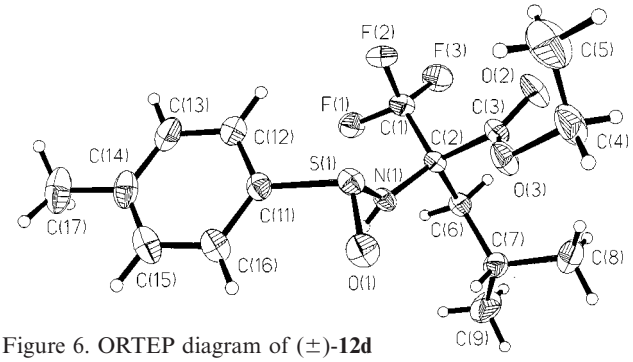


Figure 6. ORTEP diagram of (±)-**12d**

sulfinamides **a**,**b**,**d**,**g**, and **h** with known stereochemistry, the (2*S*,S_S)-diastereomers **12** in all cases displayed a lower R_f than (2*R*,S_S)-**13**, and the same trend was observed for the other diastereomeric sulfinamides identified as **12c**, **12e**, and **12f**.

Conclusions

A series of chiral, nonracemic α-Tfm-AAs was obtained in a straightforward manner, by treatment of a variety of Grignard reagents with the sulfinimines (*S*)-**1**, which are novel, enantiomerically pure, densely functionalized, fluorinated electrophiles offering the potential for further synthetic applications. The intermediate diastereomeric sulfinamides **12** and **13** are readily transformed into the corresponding nonracemic α-Tfm-AAs, providing a means of entry to both enantiomers. Moreover, the source of the chirality − menthyl sulfinate (−)-**4** − can be regenerated and recycled, making this synthetic strategy potentially suitable for multigram scale preparations of chiral, nonracemic α-Tfm-AAs.

Experimental Section

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 internal standard (δ_H and δ_C = 0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F = −162.90) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quadruplet, q; multiplet, m; etc. − Anhydrous solvents were obtained by distillation from sodium (THF, benzene) or from calcium hydride (dichloromethane, diisopropylamine). In all other cases, commercially available, reagent-grade solvents were employed without purification. Grignard reagents were purchased from Sigma/Aldrich/Fluka. Reactions performed in dry solvents were carried out under 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 60 F_{254} silica gel of 0.25 mm thickness were used. Merck 60 silica gel (230−400 ASTM mesh) was employed for flash chromatography (FC). − Chiral HPLC analyses were carried out using a Chiralcel OD column, *n*-hexane/isopropyl alcohol, 85:15, 0.8 mL/min.

Synthesis of *N*-(*p*-Tolylsulfinylimino)triphenylphosphorane [(*S*)-8]: Neat DEAD (1.95 mL, 12.35 mmol) was added dropwise at 0 °C, with stirring, to a solution of (*S*)-**7**[16] (1.93 g, 12.35 mmol) and PPh_3 (3.24 g, 12.35 mmol) in dry THF (50 mL). The resulting dark red mixture was allowed to warm to room temp. over 40 min; the solvent was then removed in vacuo. The iminophosphorane (*S*)-**8** was obtained in pure form by FC (*n*-hexane/AcOEt, 3:7), as a yellowish, sticky oil (4.75 g, 92%): $[\alpha]_D^{20}$ = +7.6 (*c* = 0.83, $CHCl_3$). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.8−7.71 (m, 6 H), 7.67−7.64 (m, 2 H), 7.58−7.53 (m, 3 H), 7.49−7.43 (m, 6 H), 7.2 (d, *J* = 8.3, 2 H), 2.34 (s, 3 H). − ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ = 149.8 (d, *J* = 24), 139.3, 133.0 (d, *J* = 10.2), 132.4 (d, *J* = 2.8), 129.0, 128.7 (d, *J* = 12), 128.6 (d, *J* = 99.8), 125.0, 21.3. ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 27.8 (s) (H_3PO_4 as external standard). − $C_{25}H_{22}NOPS$ (415.5): calcd. C 72.27, H 5.34, N 3.37; found C 72.59, H 4.99, N 3.60. The enantiomeric iminophosphorane (*R*)-**8**, analogously obtained from (*R*)-**7**, had $[\alpha]_D^{20}$ −8.1 (*c* = 0.95, $CHCl_3$).

Synthesis of (±)-*N*-(*tert*-Butylsulfinylimino)triphenylphosphorane (10): Neat DEAD (370 μL, 2.36 mmol) was added dropwise at 0 °C, with stirring, to a solution of (±)-**9**[22] (0.2 g, 1.57 mmol) and PPh_3 (0.61 g, 2.36 mmol) in dry THF (12 mL). The resulting dark red mixture was kept at 0 °C for 1 h, then allowed to warm to room temp., left stirring for 2 hours, and the solvent was removed in vacuo. The iminophosphorane **10** was obtained in pure form by FC (*n*-hexane/AcOEt, 1:3 and AcOEt/MeOH 9:1), as a yellowish, sticky oil (0.36 g, 60%): ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.77−7.68 (m, 6 H), 7.58−7.44 (m, 9 H), 1.18 (s, 9 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 132.6 (d, *J* = 11.1), 132.0 (d, *J* = 3.7), 129.0 (d, *J* = 99.9), 128.3 (d, *J* = 11.1), 55.7 (d, *J* = 18.5), 22.0.

General Procedure for the Synthesis of *N*-(*p*-Tolylsulfinyl) α-Amino Esters 12 and 13: The preparation of sulfinamides **12** and **13a** is described representatively. Neat methyl trifluoropyruvate (188 mg, 1.2 mmol) was added dropwise to a solution of iminophosphorane (*S*)-**8** (0.5 g, 1.2 mmol) in 2 mL of freshly distilled THF. The mixture was warmed at 40 °C for ca. 2 hours; the yellow solution was then cooled to −70 °C. Benzylmagnesium chloride in THF (2.0 M, 0.72 mL, 1.4 mmol) was added dropwise, with stirring. After 15 min, the reaction was quenched at −70 °C with saturated aqueous NH_4Cl solution, then extracted with ethyl acetate, and dried over anhydrous sodium sulfate. Purification by FC (*n*-hexane/AcOEt, 80:20) afforded diastereomerically pure (2*R*,S_S)-**13a** and (2*S*,S_S)-**12a** (0.31 g) in 70:30 ratio and 68% overall yield.

(2*S*,S_S)-12a (R_f <): Oil. − ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.35−7.28 (m, 3 H), 7.2−7.07 (m, 6 H), 5.03 (br signal, 1 H), 3.93

(s, 3 H), 3.81 (d, J = 15.1, 1 H), 3.64 (d, J = 15.1, 1 H), 2.36 (s, 3 H). – ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 166.9, 142.6, 141.6, 132.9, 130.3, 129.6, 128.8, 127.8, 125.8, 123.6 (q, J = 288.4), 68.6 (q, J = 28.0), 54.1, 35.1, 21.2. – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −75.5 (s).

(2*R*,*S*$_S$)-13a (*R*$_f$ >): Solid; $[\alpha]_D^{20}$ = −21.2 (c = 1.2, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.57 (d, J = 8.1, 2 H), 7.38−7.24 (m, 7 H), 4.97 (br signal, 1 H), 3.72 (s, 3 H), 3.61 (d, J = 14.3, 1 H), 3.53 (d, J = 14.3, 1 H), 2.42 (s, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −73.9 (s). – $C_{18}H_{18}F_3NO_3S$ (385.4): calcd. C 56.10, H 4.71, N 3.63; found C 56.33, H 4.55, N 3.39.

Enantiomeric α-amino esters (2*S*,*R*$_S$)-**13a** and (2*R*,*R*$_S$)-**12a**, analogously obtained from (*R*)-**8**, had $[\alpha]_D^{20}$ +22.6 (c = 1.08, $CHCl_3$) and $[\alpha]_D^{20}$ +10.0 (c = 0.24, $CHCl_3$), respectively.

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)phenylalaninate [(2S,S$_S$)-12b] (R$_f$ <): Oil; $[\alpha]_D^{20}$ = −18.0 (c = 0.66, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.33−7.06 (m, 9 H), 5.04 (s, 1 H), 4.45−4.31 (m, 2 H), 3.82 (d, J = 15.1, 1 H), 3.64 (d, J = 15.1, 1 H), 2.35 (s, 3 H), 1.34 (t, J = 7.2, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 75.6 (s).

(2*R*,*S*$_S$)-13b (*R*$_f$ >): Solid; m.p. 105−106 (*i*Pr_2O); $[\alpha]_D^{20}$ = −20.6 (c = 0.72, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.57 (d, J = 8.5, 2 H), 7.38−7.26 (m, 7 H), 5.02 (s, 1 H), 4.26−4.03 (m, 2 H), 3.62 (d, J = 14.4, 1 H), 3.53 (d, J = 14.4, 1 H), 2.47 (s, 3 H), 1.19 (t, J = 7.2, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 74.1 (s). – $C_{19}H_{20}F_3NO_3S$ (399.4): calcd. C 57.13, H 5.05, N 3.51; found C 57.08, H 5.00, N 3.46.

Crystal Data for (±)-13b: $C_{19}H_{20}F_3NO_3S$: M_r = 399.42, colorless crystal (0.5 × 0.3 × 0.1 mm), monoclinic, space group $P21/c$, a = 12.174(1) Å, b = 22.447(1) Å, c = 7.746(1) Å, β =107.25(1)°, V = 2021.5(3) Å^3, Z = 4, ρ_{calcd} = 1.312 g·cm^{-3}, F(000) = 832, λ(Cu-$K\alpha$) = 1.54178 Å, μ = 1.834 mm^{-1}, graphite monochromator, θ-2θ scan, T = 298 K; of 4604 measured reflections (3.8 < θ < 68.0) 3520 were independent (R_{int} = 0.0301). Data were collected with a Siemens P4 diffractometer and corrected for Lorentz, polarization, and decay effects (three standard reflections were measured every 100 reflections).The structure was solved by direct methods (SIR97)[40] and refined on F^2 (SHELXL-97).[41] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were inserted at calculated positions and refined in the riding mode, with the exception of the hydrogen atom bonded to nitrogen; this was located by difference Fourier map and refined isotropically with the constrained distance of 0.86 Å. $wR2$ = 0.1182 and $R1$ = 0.0480 [for 2784 reflections with $I > 2\sigma(I)$], GoF = 1.042 for 250 parameters. A final difference Fourier map showed no residual density below −0.285 or above 0.367 e·Å^{-3}.

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)-α-allylglycinate [(2*S*,*S*$_S$)-12c] (R$_f$ <): Oil; $[\alpha]_D^{20}$ = +4.8 (c = 2.30, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.63 (d, J = 8.0, 2 H), 7.31 (d, J = 8.0, 2 H), 5.71 (m, 1 H), 5.36−5.28 (m, 2 H), 5.02 (br signal, 1 H), 4.34 (q, J = 7.1, 2 H), 3.22−3.04 (m, 2 H), 2.42 (s, 3 H), 1.34 (t, J = 7.1, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 76.0 (s). – HRMS (EI): m/z, calcd. for $C_{15}H_{18}F_3NO_3S$: 349.095950; found 349.096289. – MS (EI): m/z = 349 [M$^+$] (3), 308 (3), 210 (7).

(2*R*,*S*$_S$)-13c (*R*$_f$ >): Oil; $[\alpha]_D^{20}$ = +41.8 (c = 0.94, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (m, 2 H), 7.32 (m, 2 H), 6.09 (m, 1 H), 5.30−5.20 (m, 3 H), 4.30 (m, 2 H), 3.23 (m, 1 H), 3.02 (m, 1 H), 2.40 (s, 3 H), 1.31 (t, J = 7.1, 3 H). – ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 166.2, 142.5, 141.8, 129.8, 129.5, 125.3, 123.9 (q, J = 286.4), 121.2, 67.9 (q, J = 27.5), 63.7, 35.5, 21.3, 13.9. – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −76.0 (s).

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)leucinate [(2*S*,*S*$_S$)-12d] (R$_f$ <): Solid; m.p. 88−90 °C (*i*Pr_2O); $[\alpha]_D^{20}$ = +44.5 (c = 2.40, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.61 (d, J = 8.0, 2 H), 7.32 (d, J = 8.0, 2 H), 5.28 (s, 1 H), 4.42−4.19 (m, 2 H), 2.42 (s, 3 H), 2.40−2.10 (m, 3 H), 1.34 (t, J = 7.2, 3 H), 1.07 (d, J = 6.2, 3 H), 0.85 (d, J = 6.2, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −76.2 (s). – $C_{16}H_{22}F_3NO_3S$ (365.4): calcd. C 52.59, H 6.07, N 3.83; found C 52.50, H 6.11, N 3.90.

Crystal Data for (±)-12d: $C_{16}H_{22}F_3NO_3S$: M_r = 365.41, colorless crystal (0.7 × 0.2 × 0.05 mm), triclinic, space group $P1$(bar), a = 8.999(1) Å, b = 10.769(2) Å, c = 20.030(3) Å, α = 77.91(1)°, β = 84.37(1)°, γ = 80.22(1)°, V=1866.5(5) Å^3, Z = 4, ρ_{calcd} = 1.300 g·cm^{-3}, F(000)=768, λ(Cu-$K\alpha$) = 1.54178 Å, μ = 1.929 mm^{-1}, graphite monochromator, θ-2θ scan, T = 298 K; of 11120 measured reflections (2.3 < θ < 67.5) 6491 were independent (R_{int} = 0.0354). Data were collected with a Siemens P4 diffractometer and corrected for Lorentz, polarization, and decay effects (three standard reflections were measured every 100 reflections).The structure was solved by direct methods (SIR97)[40] and refined on F^2 (SHELXL-97);[41] two molecules are present in the asymmetric unit. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were inserted at calculated positions and refined in the riding mode, with the exception of the hydrogen atoms bonded to nitrogen; this were located by difference Fourier map and refined isotropically with the constrained distance of 0.86 Å. $wR2$ = 0.1194 and $R1$ = 0.0477 [for 4790 reflections with $I > 2\sigma(I)$], GoF = 1.026 for 444 parameters. A final difference Fourier map showed no residual density below −0.250 or above 0.248 e·Å^{-3}.

(2*R*,*S*$_S$)-13d (R$_f$ >): Solid; $[\alpha]_D^{20}$ = +35.2 (c = 1.49, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.64 (d, J = 8.3, 2 H), 7.33 (d, J = 8.3, 2 H), 5.06 (br signal, 1 H), 4.41−4.21 (m, 2 H), 2.43 (s, 3 H), 2.37 (dd, J = 14.7 and 4.3, 1 H), 2.21 (dd, J = 14.7 and 9.1, 1 H), 1.95 (m, 1 H), 1.34 (t, J = 7.0, 3 H), 1.04 (d, J = 6.5, 3 H), 0.91 (d, J = 6.5, 3 H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.1, 143.5, 141.7, 129.8, 125.5, 123.8 (q, J = 288.6), 67.6 (q, J = 27.9), 63.3, 36.8, 24.1, 23.6, 21.5, 21.2, 13.6. – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −76.2 (s).

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)valinate [(2*S*,*S*$_S$)-12e] (R$_f$ <): Oil; $[\alpha]_D^{20}$ = +57.3 (c = 1.05, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.66 (d, J = 8.2, 2 H), 7.32 (d, J = 8.2, 2 H), 4.94 (s, 1 H), 4.39−4.29 (m, 2 H), 2.78 (sept, J = 6.7, 1 H), 2.42 (s, 3 H), 1.34 (t, J = 7.1, 3 H), 1.25 (d, J = 6.7, 3 H), 1.11 (d, J = 6.7, 3 H). – ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 167.1, 143.5, 141.6, 129.7, 125.6, 124.3 (q, J = 287.5), 71.5 (q, J = 26.8), 63.5, 32.5, 21.3, 17.4, 17.2, 13.9. – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −70.4 (s).

(2*R*,*S*$_S$)-13e (R$_f$ >): Oil; $[\alpha]_D^{20}$ = +34.4 (c = 0.55, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.66 (d, J = 8.3, 2 H), 7.32 (d, J = 8.3, 2 H), 4.76 (s, 1 H), 4.36 (q, J = 7.1, 2 H), 2.74 (sept, J = 6.8, 1 H), 2.42 (s, 3 H), 1.36 (t, J = 7.1, 3 H), 1.15 (d, J = 6.8, 3 H), 1.13 (d, J = 6.8, 3 H). – ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −70.1 (s).

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)norleucine [(2*S*,*S*$_S$)-12f] (R$_f$ <): Oil; $[\alpha]_D^{20}$ = +49.5 (c = 1.78, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.6 (d, J = 8.0, 2 H), 7.32 (d, J = 8.0, 2 H), 5.30 (s, 1 H), 4.33 (q, J = 7.0, 2 H), 2.42 (s, 3 H), 2.38−2.3 (m, 2 H), 1.96 (m, 1 H), 1.53−1.34 (m, 2 H), 1.33 (t, J = 7.0, 3 H), 1.10 (m,

1 H), 0.96 (t, J = 7.0, 3 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 166.8, 142.6, 141.7, 129.8, 125.5, 124.2 (q, J = 286.4), 68.4 (q, J = 27.4), 63.6, 30.2, 24.9, 22.6, 21.3, 13.9, 13.6. − ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −76.4 (s).

(2*R*,*S*$_S$)-13f (R$_f$ >): Oil; $[\alpha]_D^{20}$ = +18.1 (c = 0.48, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.64 (d, J = 8.0, 2 H), 7.33 (d, J = 8.0, 2 H), 4.99 (s, 1 H), 4.34 (q, J = 7.0, 2 H), 2.43 (s, 3 H), 2.38−2.29 (m, 2 H), 1.63−1.17 (m, 4 H), 1.33 (t, J = 7.0, 3 H), 0.95 (t, J = 7.0, 3 H). − ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 76.3 (s). − HRMS (EI): m/z, calcd. for $C_{16}H_{22}F_3NO_3S$: 365.127250; found 365.127444. − MS (EI): m/z = 365 [M$^+$] (23), 348 (20), 226 (14).

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)-α-aminobutyrate [(2*S*,*S*$_S$)-12g] (R$_f$ <): Solid; $[\alpha]_D^{20}$ = +77.3 (c = 1.03, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (d, J = 8.0, 2 H), 7.31 (d, J = 8.0, 2 H), 5.27 (s, 1 H), 4.33 (m, 2 H), 2.49−2.32 (m, 2 H), 2.41 (s, 3 H), 1.32 (t, J = 7.1, 3 H), 1.14 (t, J = 7.4, 3 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.7, 142.7, 141.7, 129.8, 125.4, 124.2 (q, J = 286.2), 69.0 (q, J = 27.5), 63.6, 24.0, 21.3, 13.9, 7.7. − ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 76.4 (s). − HRMS (EI): m/z, calcd. for $C_{14}H_{18}F_3NO_3S$: 337.095950; found 337.097008. − MS (EI): m/z = 337 [M$^+$] (10), 264 (7), 139 (100).

(2*R*,*S*$_S$)-13g (*R*$_f$ >): Oil; $[\alpha]_D^{20}$ = +28.2 (c = 0.57, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (m, 2 H), 7.30 (m, 2 H), 5.11 (s, 1 H), 4.30 (q, J = 7.1, 2 H), 2.40 (s, 3 H), 2.35 (q, J = 7.4, 2 H), 1.31 (t, J = 7.1, 3 H), 1.02 (t, J = 7.4, 3 H). − ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −76.2 (s).

Ethyl *N*-(*p*-Tolylsulfinyl)(α-trifluoromethyl)alaninate [(2*S*,*S*$_S$)-12h] (R$_f$ <): Solid; $[\alpha]_D^{20}$ = +43.7 (c = 0.69, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (m, 2 H), 7.30 (m, 2 H), 5.02 (s, 1 H), 4.31 (m, 2 H), 2.42 (s, 3 H), 1.82 (s, 3 H), 1.32 (t, J = 7.1, 3 H). − ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −78.1 (s). − $C_{12}H_{14}F_3NO_3S$ (309.3): calcd. C 46.60, H 4.56, N 4.53; found C 46.90, H 4.57, N 4.80.

(2*R*,*S*$_S$)-13h (R$_f$ >): Oil; $[\alpha]_D^{20}$ = +110.1 (c = 0.80, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (m, 2 H), 7.32 (m, 2 H), 5.26 (s, 1 H), 4.31 (m, 2 H), 2.43 (s, 3 H), 2.02 (s, 3 H), 1.31 (t, J = 7.1, 3 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.7, 141.9, 141.7, 129.8, 125.4, 124 (q, J = 285.0), 64.0 (q, J = 28.8), 63.6, 21.3, 16.1, 13.8. − ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −79.4 (s).

Synthesis of (*R*)-15a with Recovery of the Chiral Auxiliary 4: Trifluoroacetic acid (TFA) (60 μL, 0.78 mmol) was added dropwise to a flask fitted with a stirring bar and containing a cooled (0 °C) solution of (2*R*,*S*$_S$)-**13a** (100 mg, 0.26 mmol) and L-menthol **6** (49 mg, 0.31 mmol) in 1 mL of dry dichloromethane. The solution was stirred for 1 hour at room temp., then concentrated in vacuo. The crude product was purified by FC (*n*-hexane/ethyl acetate from 90:10 to 80:20) affording 58 mg of α-Tfm-α-amino ester (*R*)-**15a** (90% yield) along with 61 mg of menthyl sulfinate **4** (80% yield) as a 3:2 mixture of diastereomers. Compound **4** can be obtained in diastereomerically pure form (−)-**4** by the published method[35] and then recycled.

Methyl α-Tfm-Phenylalaninate [(*R*)-15a]: $[\alpha]_D^{20}$ = +42.4 (c = 1.9, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.35−7.27 (m, 3 H), 7.20−7.15 (m, 2 H), 3.81 (s, 3 H), 3.47 (d, J = 13.7, 1 H), 2.99 (d, J = 13.7, 1 H), 1.80 (br signal, 2 H). − ^{19}F NMR ($CDCl_3$, 235 MHz): δ − 78.1 (s).

Synthesis of α-Trifluoromethyl-α-amino Acids 17−22: Preparation of α-Tfm-α-aminobutyric acid (Abu) (*S*)-**21** is described representatively. Trifluoroacetic acid (TFA) (64 μL, 0.83 mmol) was added dropwise to a flask containing a cooled (0 °C) solution of (2*S*,*S*$_S$)-**12g** (140 mg, 0.42 mmol) in 1 mL of methanol. The solution was stirred for 1 hour at room temp., then concentrated in vacuo. The reaction mixture was diluted with water and, after addition of diethyl ether (1.5 mL) and 10% aqueous HCl (2 mL), vigorously stirred for 1 h. The two layers were then separated; the organic phase was washed with two portions of a 10% solution of HCl, and the collected aqueous phases were concentrated in vacuo. The residue was dissolved in 2 mL of methanol/water 7:3, treated at 0 °C with aq. KOH (0.5 N, 4.7 mL), and then stirred at room temp. for about 4 hours. HCl (3 N) was added until acidic conditions were reached; then the mixture was concentrated in vacuo and loaded onto a Dowex 50 W-X8 column, affording 41 mg (58% overall yield from **12g**) of free α-Tfm-Abu (*S*)-**21.**[36]

α-Tfm-α-Aminobutyric Acid [(*S*)-21]: $[\alpha]_D^{20}$ = −11.0 (c = 1.1, EtOH). The other spectral and chemical-physical data matched those previously reported in the literature.[36]

α-Tfm-α-Allylglycine [(*R*)-17]: (57% from **13c**); $[\alpha]_D^{20}$ = +27.0 (c = 0.69, H_2O); m.p. (white powder from H_2O) > 200 °C (sublim.). − ^{1}H NMR (D_2O, 250 MHz): δ = 5.64 (m, 1 H), 5.23−5.16 (m, 2 H), 2.75 (m, 1 H), 2.43 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 174.5, 132.7, 127.7 (q, J = 283.1), 123.8, 67.0 (q, J = 25.7), 39.3. − ^{19}F NMR (D_2O, 235 MHz): δ −71.6 (s). − MS (EI): m/z = 184 [M$^+$ + 1] (5), 142 (100), 138 (70).

α-Tfm-Leucine [(*S*)-18]: (50% from **12d**); $[\alpha]_D^{20}$ = +8.2 (c = 0.11, H_2O); m.p. (crystals from CH_3CN/CH_3OH) > 200 °C (dec.). − ^{1}H NMR (D_2O, 250 MHz): δ = 1.98 (m, 1 H), 1.80−1.68 (m, 2 H), 0.96 (d, J = 6.3, 3 H), 0.88 (d, J = 6.3, 3 H). − ^{13}C NMR (D_2O, 63 MHz): δ = 173.3, 125.8 (q, J = 283.3), 64.9 (q, J = 25.1), 40.2, 24.1, 23.3, 21.9. − ^{19}F NMR (D_2O, 235 MHz): δ −79.4 (s). − HRMS (EI): m/z, calcd. for $C_7H_{13}F_3NO_2$: 200.089839; found 200.089899. − MS (EI): m/z = 200 [M$^+$ + 1] (5), 154 (100), 112 (56).

α-Tfm-Valine [(*S*)-19]: (56% from **12e**); $[\alpha]_D^{20}$ = −3.0 (c = 0.32, H_2O); m.p. (white powder from H_2O) > 200 °C. − ^{1}H NMR (D_2O, 250 MHz): δ = 2.36 (sept, J = 7.1, 1 H), 0.88 (dd, J = 7.1, 3 H), 0.76 (d, J = 7.1, 3 H). − ^{19}F NMR (D_2O, 235 MHz): δ − 67.8 (s). − HRMS (EI): m/z, calcd. for $C_6H_{11}F_3NO_2$: 186.074188; found 186.073395. − MS (EI): m/z = 186 [M$^+$ + 1] (57), 140 (100), 123 (69).

α-Tfm-Norleucine [(*S*)-20]: (56% from **12f**); $[\alpha]_D^{20}$ = −1.4 (c = 2.24, H_2O); m.p. (white powder from H_2O) > 200 °C. − ^{1}H NMR (D_2O, 250 MHz): δ = 1.95 (m, 1 H), 1.66 (m, 1 H), 1.36−1.17 (m, 3 H), 1.07 (m, 1 H), 0.79 (t, J = 7.1, 3 H). − ^{13}C NMR (D_2O, 63 MHz): δ = 172.5, 127.1 (q, J = 283.0), 68.2 (q, J = 25.7), 33.2, 27.1, 24.4, 15.4. − ^{19}F NMR (D_2O, 235 MHz): δ −72.0 (s). − HRMS (EI): m/z, calcd. for $C_7H_{12}F_3NO_2$: 199.082014; found 199.081223. − MS (EI): m/z = 199 [M$^+$] (26), 154 (100), 98 (28).

α-Tfm-Alanine [(*S*)-22] (55% from **12h**): $[\alpha]_D^{20}$ = −12.6 (c = 0.17, H_2O). (*R*)-**22** (52% from **13h**): +13.2 (c = 0.65, H_2O). The other spectral and chemical-physical data matched those previously reported in the literature.[39]

Crystallographic data (excluding structure factors) for the structures **12d** and **13b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149156 and CCDC-149157. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We thank M.U.R.S.T. COFIN 1998 (Nuove metodologie e strategie di sintesi di composti di interesse biologico), C.N.R. − C.S.S.O.N. and Dirección General de Investigación Científica y Técnica (DGES PB97-0760-C02-01) for financial support. We gratefully acknowledge Dr. Vadim A. Soloshonok (Department of Chemistry, University of Arizona, Tucson) for helpful discussions.

[1] J.-P. Mazaleyrat, M. Wakselman, F. Formaggio, M. Crisma, C. Toniolo, *Tetrahedron Lett.* **1999**, *40*, 6245−6248.

[2] S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1−15 and references therein.

[3] C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599.

[4] R. E. Banks, J. C. Tatlow, B. E. Smart, *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, **1994**.

[5] [5a] B. Koksch, N. Sewald, H.-D. Jakubke, K. Burger, in: *Biomedical Frontiers of Fluorine Chemistry* (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), ACS Series 639: Washington D.C., **1996**, p. 42−58. − [5b] F. Bordusa, C. Dahl, H.-D. Jakubke, K. Burger, B. Koksch, *Tetrahedron: Asymmetry* **1999**, *10*, 307−313. − For our efforts in the synthesis of α-Tfm-AAs containing peptides: [5c] A. Dal Pozzo, L. Muzi, M. Moroni, R. Rondanin, R. de Castiglione, P. Bravo, M. Zanda, *Tetrahedron* **1998**, *54*, 6019−6028. − [5d] A. Dal Pozzo, K. Dikovskaya, M. Moroni, M. Fagnoni, L. Vanini, R. Bergonzi, R. de Castiglione, P. Bravo, M. Zanda, *J. Chem. Res. (S)* **1999**, 468−469.

[6] B. Koksch, N. Sewald, H.-J. Hofmann, K. Burger, H.-D. Jakubke, *J. Peptide Science* **1997**, *3*, 157−167.

[7] See for example: L. R. Scolnick, A. M. Clements, J. Liao, L. Crenshaw, M. Hellberg, J. May, T. R. Dean, D. W. Christianson, *J. Am. Chem. Soc.* **1997**, *119*, 850−851.

[8] [8a] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. − [8b] R. Filler, Y. Kobayashi, L. M. Yagupolskii, *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, **1993**.

[9] N. Sewald, K. Burger, in: *Fluorine-containing Amino Acids: Synthesis and Properties* (Eds.: V. P. Kukhar, V. A. Soloshonok), Wiley: Chichester, **1995**, p. 139−220.

[10] [10a] V. A. Soloshonok, I. I. Gerus, Y. L. Yagupol'skii, *Zh. Org. Khim.* **1986**, *22*, 1335−1337; *Chem. Abstr. 106*: 195861u. − [10b] S. N. Osipov, N. D. Chkanikov, A. F. Kolomiets, A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, 1384−1387; *Chem. Abstr. 106*: 156213q. − [10c] V. A. Soloshonok, I. I. Gerus, Y. L. Yagupol'skii, V. P. Kukhar', *Zh. Org. Khim.* **1987**, *23*, 2308−2313; *Chem. Abstr. 109*: 55185p. − [10d] K. Burger, K. Gaa, *Chem. Ztg.* **1990**, *114*, 101−104. − [10e] K. Burger, N. Sewald, *Synthesis* **1990**, 115−118. − [10f] K. Burger, E. Hoss, K. Gaa, N. Sewald, C. Z. Schierlinger, *Z. Naturforsch., Teil B* **1991**, *46*, 361−384. − [10g] H. Watanabe, Y. Hashizume, K. Uneyama, *Tetrahedron Lett.* **1992**, *33*, 4333−4336. − [10h] S. N. Osipov, A. S. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* **1997**, *38*, 5965−5966. − [10i] H. Amii, Y. Kishikawa, K. Kageyama, K. Uneyama, *J. Org. Chem.* **2000**, *65*, 3404−3408.

[11] [11a] T. Miyazawa, in the book of ref.[9], p. 267−294. − For a review on the asymmetric synthesis of fluoro-amino acids: [11b] K. Uneyama, in: *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemistry, Challenges and Biomedicinal Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**, p. 391−418.

[12] P. Bravo, S. Capelli, S. V. Meille, F. Viani, M. Zanda, V. P. Kukhar, V. A. Soloshonok, *Tetrahedron: Asymmetry* **1994**, *5*, 2009−2018.

[13] N. Sewald, L. C. Seymour, K. Burger, S. N. Osipov, A. F. Kolomiets, A. V. Fokin, *Tetrahedron: Asymmetry* **1994**, *5*, 1051−1060.

[14] For a preliminary communication of this work: P. Bravo, M. Crucianelli, B. Vergani, M. Zanda, *Tetrahedron Lett.* **1998**, *39*, 7771−7774.

[15] [15a] F. A. Davis, R. E. Reddy, "Synthesis of Nonracemic β-Amino Acids via Chiral Sulfinimines" in: *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH: Chichester, **1997**, p. 127−138. − [15b] For a review on the synthesis of amino acids using sulfinimines: F. A. Davis, P. Zhou, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13−18. − See also: [15c] G. Li, S. H. Kim, H.-X. Wei, *Tetrahedron* **2000**, *56*, 719−723 and references therein. − [15d] R. Kawecki, *J. Org. Chem.* **1999**, *64*, 8724−8727. − [15e] J. L. García Ruano, I. Fernández, M. del Prado Catalina, J. A. Hermoso, J. Sanz-Aparicio, M. Martínez-Ripoll, *J. Org. Chem.* **1998**, *63*, 7157−7161 and references therein. − [15f] D. H. Hua, N. Lagneau, H. Wang, J. Chen, *Tetrahedron: Asymmetry* **1995**, *6*, 349−352 and references therein. − [15g] W. Oppolzer, O. Froelich, C. Wiaux-Zamar, G. Bernardinelli, *Tetrahedron Lett.* **1997**, *38*, 2825−2828. − [15h] T. Balasubramanian, A. Hassner, *Tetrahedron Lett.* **1996**, *37*, 5755−5758. − [15i] T.-K. Yang, R.-Y. Chen, D.-S. Lee, W.-S. Peng, Y.-Z. Jiang, A.-Q. Mi, T.-T. Jong, *J. Org. Chem.* **1994**, *59*, 914−921. − [15j] A. Viso, R. Fernández de la Pradilla, C. Guerrero-Strachan, M. Alonso, M. Martínez-Ripoll, I. André, *J. Org. Chem.* **1997**, *62*, 2316−2317. − [15k] M. Mikolajczyk, P. Lizwa, J. Drabowicz, *Tetrahedron: Asymmetry* **1997**, *8*, 3991−3994 and references therein. − [15l] T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12−13.

[16] F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou, P. J. Carroll, *J. Org. Chem.* **1997**, *62*, 2555−2563.

[17] Racemic sulfinimines derived from trifluoromethyl ketones have been described, but those synthetic methodologies are likely to be incompatible with the preparation of nonracemic products, due to the harsh conditions employed: [17a] R. Mews, P. Kricke, I. Stahl, *Z. Naturforsch., Teil B* **1981**, *36*, 1093−1098 and references therein. − [17b] K. Burger, J. Albanbauer, F. Käfig, S. Penninger, *Liebigs. Ann. Chem.* **1977**, 624−633. − [17c] L. N. Markovskii, V. S. Talanov, Yu. G. Shermolovich, *J. Org. Chem. USSR (Engl. Transl.)* **1984**, *20*, 353−362. − [17d] Yu. G. Shermolovich, V. S. Talanov, G. N. Dolenko, L. N. Markovskii, *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 843−849.

[18] [18a] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635−646. − [18b] P. Molina, M. J. Vilaplana, *Synthesis* **1994**, 1197−1218. − [18c] A. W. Johnson, W. C. Kasha, K. A. O. Starzewsky, D. A. Dixon, "Iminophosphoranes and Related Compounds" in: *Ylides and Imines of Phosphorus*; New York: John Wiley & Sons, **1993**, p. 403−483.

[19] S. Bittner, Y. Assaf, P. Krief, M. Pomerantz, B. T. Ziemnicka, C. G. Smith, *J. Org. Chem.* **1985**, *50*, 1712−1718.

[20] A. Senning, P. Kelly, *Naturwissenschaften* **1968**, *55*, 543. *Chem. Abstr. 70*: 47555v.

[21] [21a] B. J. Backes, D. R. Dragoli, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 5472−5478. − [21b] D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 268−269. − [21c] D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883−8904. − [21d] G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278−1284.

[22] D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.

[23] F. A. Davis, W. McCoull, *J. Org. Chem.* **1999**, *64*, 3396−3397.

[24] For a discussion of the configurational and stereochemical properties of ketone-derived sulfinimines, see: [24a] F. A. Davis, E. W. Kluger, *J. Am. Chem. Soc.* **1976**, *98*, 302−303 and references therein. − [24b] P. V. Bharatam, P. Uppal, D. Kaur, *J. Chem. Soc., Perkin Trans. 2* **2000**, 43−50. − [24c] I. M. Lefebvre, S. A. Evans, Jr., *J. Org. Chem.* **1997**, *62*, 7532−7533 and references therein. − [24d] See also ref.[21c].

[25] [25a] S. Fustero, A. Navarro, B. Pina, A. Asensio, P. Bravo, M. Crucianelli, A. Volonterio, M. Zanda, *J. Org. Chem.* **1998**, *63*, 6210−6219. − [25b] P. Bravo, S. Fustero, M. Guidetti, A. Volonterio, M. Zanda, *J. Org. Chem.* **1999**, 64, 8731−8735. − [25c] S. V. Meille, unpublished results. − [25d] A. V. Fokin, A. F. Kolomiets, N. V. Vasil'ev, *Russ. Chem. Rev.* **1984**, *53*, 238−255.

[26] *Gaussian 94, Revision C.3*; M. J. Frisch, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, N. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andrés, E. S. Replogle, R. Gomperts, R. L. Martín, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. J. P. Stewart, M. Head-Gordon, C. González, J. A. Pople, *Gaussian Inc.*, Pittsburgh PA, **1995**.

[27] It is worth noting that isopropylmagnesium chloride did not promote reduction of the C=N bond of (*S*)-**1b**, in sharp con-

trast with the reactions between isopropylmagnesium halides and *N*-alkoxycarbonyl imines of trifluoropyruvate, in which 40% of reduction occurs (see ref. [5a]).

[28] The *ee* values were determined by chiral HPLC analysis of both enantiomers of sulfinamides **12** and **13**, performed with a Chiralcel OD column, using *n*-hexane/isopropyl alcohol, 85:15, as eluent, with a flow rate of 0.8 mL/min.

[29] Attempts to assess the chemical nature and the origin of the racemization by performing the reactions in the presence of small amounts of peroxides, or previously bubbling O_2 through the solvent, or adding traces of water, did not produce any conclusion. However, this undesired event turned out to be useful, because crystallization of sulfinamides **12** and **13** of low *ee* occurs much more effectively, providing diastereomerically pure racemic crystals suitable for X-ray diffraction, while sulfinamides of high *ee* were much less prone to crystallization.

[30] For example, vinyl *p*-tolyl sulfoxide **14b** was recovered with an $[\alpha]_D^{20}$ −52.5 (*c* = 0.54, acetone). Enantiopure (*S*)-**14b** is reported to have $[\alpha]_D^{20}$ −446 (*c* = 1.65, acetone): B. Ronan, H. B. Kagan, *Tetrahedron: Asymmetry* **1991**, *2*, 75−90.

[31] The reasons for this unexpected reactivity are unclear, but a similar event has been recently described in the literature. Methylmagnesium bromide is known to react with *N*-sulfinyl arylidene derivatives to produce the corresponding methyl sulfoxide by S_N2-type displacement at sulfur: P. Moreau, M. Essiz, J. Y. Mérour, D. Bouzard, *Tetrahedron: Asymmetry* **1997**, *8*, 591−598.

[32] D. R. J. Hose, M. F. Mahon, K. C. Molloy, T. Raynham, M. Wills, *J. Chem. Soc., Perkin Trans. 1* **1996**, 691−703.

[33] [33a] T. Fujisawa, Y. Kooriyama, M. Shimizu, *Tetrahedron Lett.* **1996**, *37*, 3881−3884. − [33b] Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, W. Ito, *J. Am. Chem. Soc.* **1986**, *108*, 7778−7786 and references therein.

[34] F. A. Davis, R. E. Reddy, J. M. Szewczyk, *J. Org. Chem.* **1995**, *60*, 7037−7039.

[35] [35a] C. Mioskowski, G. Solladié, *Tetrahedron* **1980**, *36*, 227−236. − [35b] M. Hulce, J. P. Mallamo, L. L. Frye, T. P. Kogan, G. H. Posner, *Org. Synth.* **1986**, *64*, 196−206.

[36] P. Bravo, F. Viani, M. Zanda, V. P. Kukhar, V. A. Soloshonok, N. Fokina, O. V. Shishkin, Yu. T. Struchkov, *Gazz. Chim. Ital.* **1996**, *126*, 645−652.

[37] M. Mikolajczyk, J. Drabowicz, B. Bujnicki, *J. Chem. Soc., Chem. Commun.* **1976**, 568−569.

[38] In both compounds, bond lengths, angles, and torsion angles conform to expectations; the nitrogen atom shows sp^2 hybridization and intermolecular hydrogen bonds involve the amidic hydrogen with the sulfoxide oxygen. The two independent molecules in the crystal of **12d** exhibit only marginal but significant differences (5−10°) in torsion angles, suggesting that the structure determined is close to the minimum energy conformation.

[39] [39a] J. W. Keller, B. J. Hamilton, *Tetrahedron: Asymmetry* **1986**, *27*, 1249−1250. − [39b] See also ref.[12]

[40] A. Altomare, G. Cascarano, A. Guagliardi, *J. Appl. Cryst.* **1993**, *26*, 343−350.

[41] G. M. Sheldrick, *SHELXL97*, *Program for crystal structure refinement*; University of Göttingen; Göttingen, Germany, **1997**.

Received September 13, 2000
[O00474]