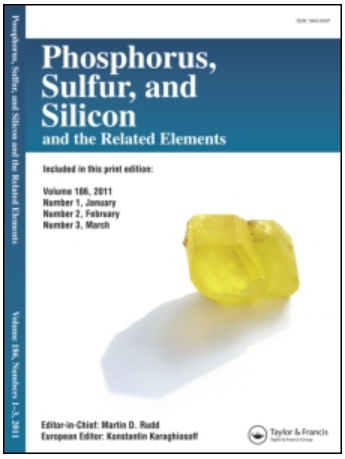

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First Method for the Preparation of Strongly Electrophilic Chiral Sulfinimines, and Applications in Asymmetric Synthesis

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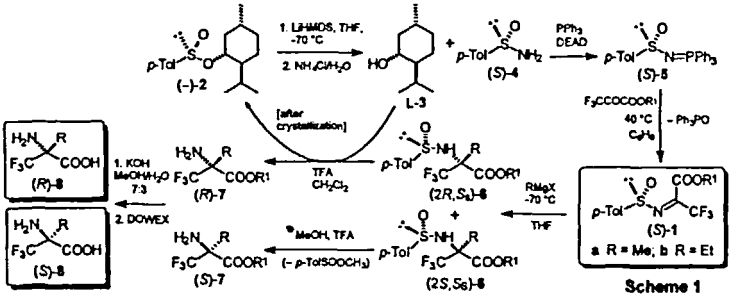
A new and preparatively useful method for the synthesis of non racemic α-trifluoromethyl α-amino acids is presented, using chiral sulfinimines of trifluoropyruvate as key-building blocks.

Keywords: sulfinimines; trifluoromethyl; amino acids; Grignard

α-Trifluoromethyl α-amino acids (α-Tfm-AAs) are synthetic analogues of naturally occurring amino acids (AAs)[1]. The great interest in α-Tfm-AAs arises from the fact that some of them exhibit attractive biological activity, and that some peptides containing α-Tfm-AAs have increased metabolic stability and biological activity[2]. Further interest arises from the synthetic challenge connected with the stereocontrolled formation of the trifluoromethylated quaternary amino acidic centre. This paper describes a new method for the preparation of non racemic α-Tfm-AAs.

The key sulfinimines (*S*)-**1a,b** were synthesized *via* Staudinger reaction between the chiral iminophosphorane (*S*)-**5** (Scheme 1), prepared by reaction of DEAD/PPh_3 with the sulfinamide (*S*)-**4** (92%), and methyl/ethyl trifluoropyruvate in benzene (90 min at 40 °C). Addition of several Grignard reagents (THF, -70 °C), provided the corresponding diastereomeric sulfinamides **6a-g** with moderate to good yields and diastereoselectivity (Scheme 1 and Table 1).



Scheme 1

Scheme 1 and Table 1. Addition of Grignard reagents to (*S*)-**1a,b**.

Product	R	X	Yields from $CF_3COCOOR^1$	Diast. ratio $(2S,S_S)/(2R,S_S)$-**6**
6a	CH_2Ph (R^1 = Me)	Cl	65%	30/70
6b	CH_2Ph (R^1 = Et)	Cl	68%	30/70
6c	$CH_2CH(CH_3)_2$	Br	65%	87/13
6d	$CH(CH_3)_2$	Cl	72%	84/16
6e	$(CH_2)_3CH_3$	Cl	55%	74/26
6f	CH_2CH_3	Br	70%	73/27
6f	CH_2CH_3	Cl	55%	72/28
6g	CH_3	Cl	52%	55/45

Alcoholysis of the sulfinamides **6** was efficiently and mildly accomplished with trifluoroacetic acid and methanol or recycled menthol, providing the amino esters **7**. In the latter case menthyl sulfinate can be recovered and recycled. Alkaline hydrolysis of several amino esters **7** afforded the α-Tfm-AAs (**8**): (*R*)-α-Tfm-phenylalanine, (*S*)-α-Tfm-leucine, (*S*)-α-Tfm-butyrine and (*S*)-α-Tfm-alanine.

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