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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/PPh₃ 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 and Table 1. Addition of Grignard reagents to (S)-1a,b.

Product	R	Х	Yields from CF ₃ COCOOR ¹	Diast. ratio (2S,S _S)/(2R,S _S)-6
6a	$CH_2Ph(R^1 = Me)$	CI	65%	30/70
6Ъ	$CH_2Ph(R^1=Et)$	Cl	68%	30/70
6c	CH ₂ CH(CH ₃) ₂	Br	65%	87/13
6d	CH(CH ₁) ₂	Cl	72%	84/16
6e	(CH ₂) ₃ CH ₃	Cl	55%	74/26
6f	,CH₂CH₃	Br	70%	73/27
6f	CH₂CH₃	Cl	55%	72/28
6g	СН,	CI	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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