The stereoselective synthesis of α-Tfm-amino acids from chiral CF₃ building blocks

ABSTRACT
In this mini-review, we report recent advances in the stereoselective synthesis of α-Tfm-amino acids starting from chiral CF₃-containing building blocks.

INTRODUCTION
α-Trifluoromethyl amino acids (α-Tfm Aas) are very attractive target molecules for the design of biologically active compounds (1). Several methods reported for their synthesis employ racemic resolutions (2) or enantioselective reduction of a prochiral imine-type precursor (3). In this mini-review we will focus on different strategies developed for the stereoselective synthesis of α-Tfm-amino acids involving chiral CF₃-containing building blocks.

THE DIPEPTIDE APPROACH
The strategy first initiated by Burger and co-workers (4) was to take advantage of the chiral centre of an amino acid to create a new chiral centre in α-position of the CF₃ group of a trifluoropyruvate-based imine 1 (Scheme 1). The moderate diastereoselectivity was significantly increased by organometallics addition to a cyclic chiral trifluoromethyl-2,5-diketopiperazine 2 (5) (Scheme 1). This route is particularly well adapted for the synthesis of α-Tfm Aas dipeptides. Very recently, Uneyama and co-workers (6) reported the synthesis of a similar kind of α-Tfm alanine dipeptide 4 starting from a prochiral 2-aminoperfluoropropane 3 (Scheme 1).

CHIRAL β-SULFINYLENAMINES AND β-IMINOSULFOXIDES
The chiral β-sulfinylamine 6 obtained from the chiral α-sulfinyl ketone 5 by an aza-Wittig reaction proved to be an interesting building block for the synthesis of 3,3,3-trifluoroalanine through hydrides reductions and nonoxidative Pummerer rearrangement (7) (Scheme 2). The diastereoselectivity of the reduction was significantly increased by using β-iminosulfoxides (8) and especially the naphtyliminosulfoxide 7 because of a π-stacking interaction as a source of stereocontrol (9).

REACTIONS FROM TRIFLUOROPYRUVATE IMINES
Several complementary strategies were adopted for the stereoselective synthesis of α-Tfm Aas such as α-Tfm-alanine (10) or α-Tfm-β-hydroxyaspartic acid (11) by addition of a chiral α-lithio sulfoxide or a chiral enolate to a non chiral trifluoropyruvate imine (Scheme 3). The target enantiopure amino acids were obtained in several steps from the diastereomerically pure intermediate addition products 8 and 9. In a similar manner than Tfm-alanines, enantiopure L-α-Tfm-threoninate and D-α-Tfm-allo-threoninate were synthesized starting from (R)-ethyl p-tolylsulfoxide as chiral-α-hydroxyethyl anion equivalent (12).

The other strategy for the synthesis of nonracemic α-Tfm Aas also reported by Zanda and co-workers consisting in the addition of organometallic species to a chiral trifluoropyruvate sulfinylimine proved to be very productive for the synthesis of various α-Tfm Aas (13) (Scheme 4). The hydride reduction of the chiral sulfinylamine 10 provided a route to the non-racemic (R)-3,3,3-trifluoroalanine (14). Likewise, the highly diastereoselective α-
ethenylation of 10 offered an access to enantiomerically pure α-ethenyl, α-vinyl and α-ethyl 3,3,3-trifluoroalaninates (15).

Moreover, functionalized side chains could be conveniently introduced by means of Mannich-type reaction or titanium enolate addition to give (R)- and (S)-α-Tfm aspartic acid (16).

CHIRAL TRIFLUOROMETHYL IMINES AND OXAZOLIDINES BUILDING BLOCKS

More recently, we developed in our group a new strategy for the stereoselective synthesis of enantiopure α-Tfm Aas based on the Strecker-type reaction from chiral α-CF₃-imines and iminiums (17).

The reaction from chiral CF₃-imines was efficiently promoted in mild conditions with a catalytic amount of Yb(OTf)₃ to give the corresponding α-CF₃-amino nitriles as diastereomeric mixtures (Scheme 5). The Strecker-type reaction was also efficiently carried out from 2-trifluoromethyl oxazolidines derived from fluoral or CF₃-ketones and (R)-phenylglycinol. Thanks to this chiral amino alcohol side chain, the two amino nitrile diastereomers were generally easily separated by silica gel chromatography.

The major diastereomer was resulting from a re face attack of the intermediate iminium. The diastereomerically pure α-amino nitriles were then conveniently transformed into the corresponding α-Tfm Aas in a few steps (Scheme 6). According to the same approach, Lu and co-workers (18) reported recently the synthesis of the (S)-trifluoromethylphenylglycine by means of a highly diastereoselective Strecker reaction on a chiral α-CF₃-sulfinylimine (Scheme 6).

Starting from the chiral imine 11 or the oxazolidines 12 obtained from ethyl trifluoropyruvate and (R)-phenylglycinol, we recently reported a straightforward synthesis of several α-Tfm Aas in enantiopure form.
involving a diastereoselective allylation as the key step (19) (Scheme 7). The lactone 13 obtained by cyclization of the resulting hydroxyster proved to be a valuable building block for the synthesis of (S)-, (R)-α-Tfm prolines, (S)-α-Tfm allylglycine and (S)-α-Tfm norvaline in enantiopure form.

In conclusion, chiral sulfinyl groups, amino acids and amino alcohols such as (R)-phenylglycinol are playing a central role as chiral auxiliaries in the design of new synthetic methods for the preparation of non racemic α-Tfm amino acids in enantiopure form remains a challenge. Moreover there is still a need for new methodologies adapted to their large scale synthesis. Until the discovery of completely enantioselective catalytic methods, the use of chiral fluorinated building blocks constitute an efficient strategy.

REFERENCES AND NOTES