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Straightforward Synthesis of (*S*)- and (*R*)-α-Trifluoromethyl Proline from Chiral Oxazolidines Derived from Ethyl Trifluoropyruvate

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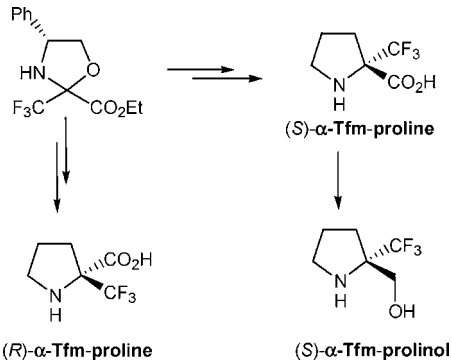
ABSTRACT



A concise synthesis of both enantiomers of α-Tfm-proline and (*S*)-α-Tfm-prolinol from ethyl trifluoropyruvate is reported. The key step is a diastereoselective allylation reaction of ethyl trifluoropyruvate and (*R*)-phenylglycinol-based oxazolidines or imine. The lactone obtained by cyclization of the resulting hydroxy ester proved to be a valuable intermediate for the synthesis of (*S*)-α-Tfm-allylglycine and (*S*)-α-Tfm-norvaline in enantiopure form.

Substituted prolines have gained considerable interest in recent years. These conformationally constrained amino acids constitute one of the most powerful tools to control the conformation of the peptide backbone for investigating structure−activity relationships.[1]

Particularly, fluorinated analogues of proline have attracted special interest to control the cis−trans isomerization of the prolyl bonds[2] and, very recently, for the design enzyme inhibitors.[3] There are a number of methods describing the synthesis of fluoro-substituted prolines in various positions of the pyrrolidine ring,[4] but very little is known about the

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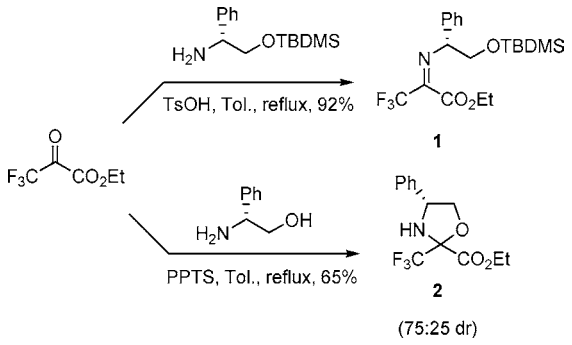
Scheme 1. Synthesis of Ethyl Trifluoropyruvate Based Imine **1** and Oxazolidines **2**

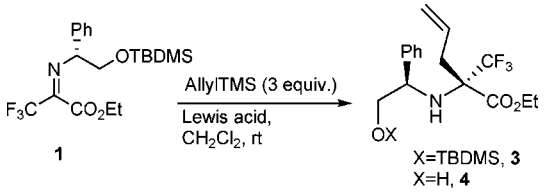


introduction of a fluorinated group in the α-position.[5] The formation of racemic ethyl α-difluoromethylproline ester was recently reported.[6]

However, despite their potential interest, the α-Tfm-proline and the corresponding α-Tfm-prolinol have never been reported even in the racemic series. We present here the synthesis of these promising compounds in enantiopure form.

Among the various methods reported in the literature,[7] the addition of organometallic species to trifluoropyruvate-based chiral imines proved to be a valuable approach for the synthesis of α-trifluoromethyl α-amino acids (α-Tfm AAs).[8] In the course of our studies, we recently reported their stereoselective synthesis using a Strecker-type reaction on chiral CF_3-oxazolines or imines as the key step.[9] We now report a complementary strategy involving the allylation reaction of trifluoropyruvate and (*R*)-phenylglycinol-based imines and oxazolidines which would constitute a straightforward route to α-Tfm-proline. The (*R*)-phenylglycinol chiral auxiliary was chosen because of its versatility. It can be removed either by hydrogenolysis or $Pb(OAc)_4$ treatment. Moreover, both diastereomers of phenylglycinol are commercially available. The starting imine **1** was very conveniently prepared from ethyl trifluoropyruvate and *O*-TBDMS (*R*)-phenylglycinol (Scheme 1). The oxazolidines **2** were obtained as a 75:25 diastereomeric mixture from (*R*)-phenylglycinol under PPTS catalysis in 65% yield.[10] Both oxazolidine diastereomers could be easily separated by chromatography on silica gel.

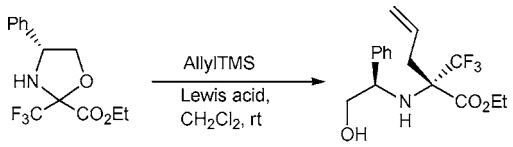
Table 1. Allylation Reaction of Imine **1**



entry	Lewis acid	product	yield (%)[a]	dr[b]
1	$Yb(OTf)_3$ (0.1 equiv)	no reaction		
2	$BF_3{\cdot}OEt_2$ (2 equiv)	**3** + **4**	38 (3)	85:15
			40 (4)	84:16
3	$SnCl_4$ (1.25 equiv)	**3**	72	77:23

[a] Isolated yield. [b] Measured by ^{19}F NMR. The (*S*,*R*) configuration of the major diastereomer was assigned by correlation with the coresponding amino acid configuration (vide infra).

Table 2. Allylation Reaction of Oxazolidines **2**



entry	dr of **2**[a]	Lewis acid	yield (%)[b] of **4**	dr[c]
1	60:40	TMSOTf (0.1 equiv)	no reaction	
2	65:35	TiCl4 (2 equiv)	87	63:37
3[d]	65:35	$BF_3{\cdot}OEt_2$ (2 equiv)	86	73:27
4	100:0	$BF_3{\cdot}OEt_2$ (2 equiv)	92	69:31
5[e]	75:25	$BF_3{\cdot}OEt_2$ (2 equiv)	91	75:25

[a] Measured by ^{19}F NMR after chromatographic separation. [b] Isolated yield. [c] Measured by ^{19}F NMR of the crude reaction mixture. [d] A low conversion of the oxazolidine **2** occurred when $SnCl_4$ was used as the Lewis acid. [e] Reaction performed on 5.79 g scale with 2 equiv of allylTMS.

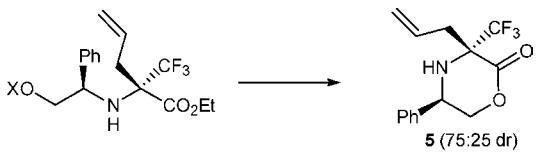
The allylation reaction with allyltrimethylsilane under Lewis acid activation was first investigated starting from the imine **1** (Table 1).

Conversely to the Strecker-type reaction,[9] no reaction occurred in the presence of a catalytic amount of $Yb(OTf)_3$. However, the allylation reaction was efficiently promoted by 2 equiv of $BF_3{\cdot}Et_2O$ to give the expected silylated allylic amino ester **3** in 38% yield (85:15 dr) along with unprotected product **4** in 40% yield (84:16 dr) (Table 1, entry 2). The protected compound **3** was obtained in 72% yield (77:23 dr) when the reaction was carried out in the presence of 1.25 equiv of $SnCl_4$ (Table 1, entry 3).

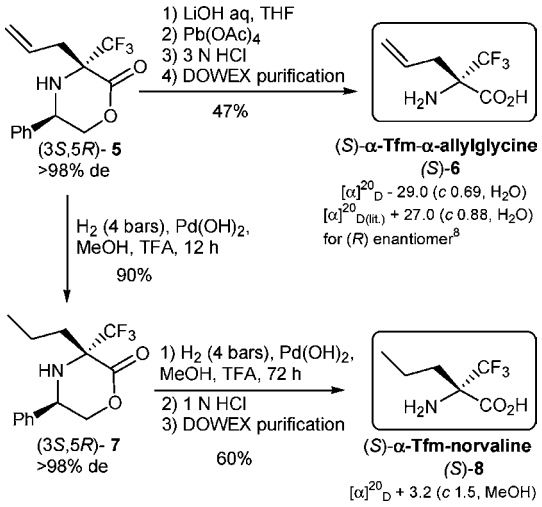
In a similar manner, the allylation reaction was performed starting from the oxazolidines **2** (Table 2).

In opposition to the Strecker-type reaction, no allylation occurred in the presence of a catalytic amount of TMSOTf (Table 2, entry 1). However, the allylation reaction from the oxazolidine diastereomeric mixture **2** proceeded smoothly at room temperature when $TiCl_4$ or $BF_3{\cdot}Et_2O$ was used as the Lewis acid. The expected allylic amino esters **4** were obtained in 87−92% yield (Table 2, entries 2−5). It should be noticed that almost the same diastereomeric mixture of compounds **4** was achieved whatever the initial oxazolidine

Scheme 2. Cyclization of **3** and **4** into Lactone **5**



Scheme 3. Configurationnal Assignments and Synthesis of (*S*)-α-Tfm-α-allylglycine and (*S*)-α-Tfm-norvaline in Enantiopure Form



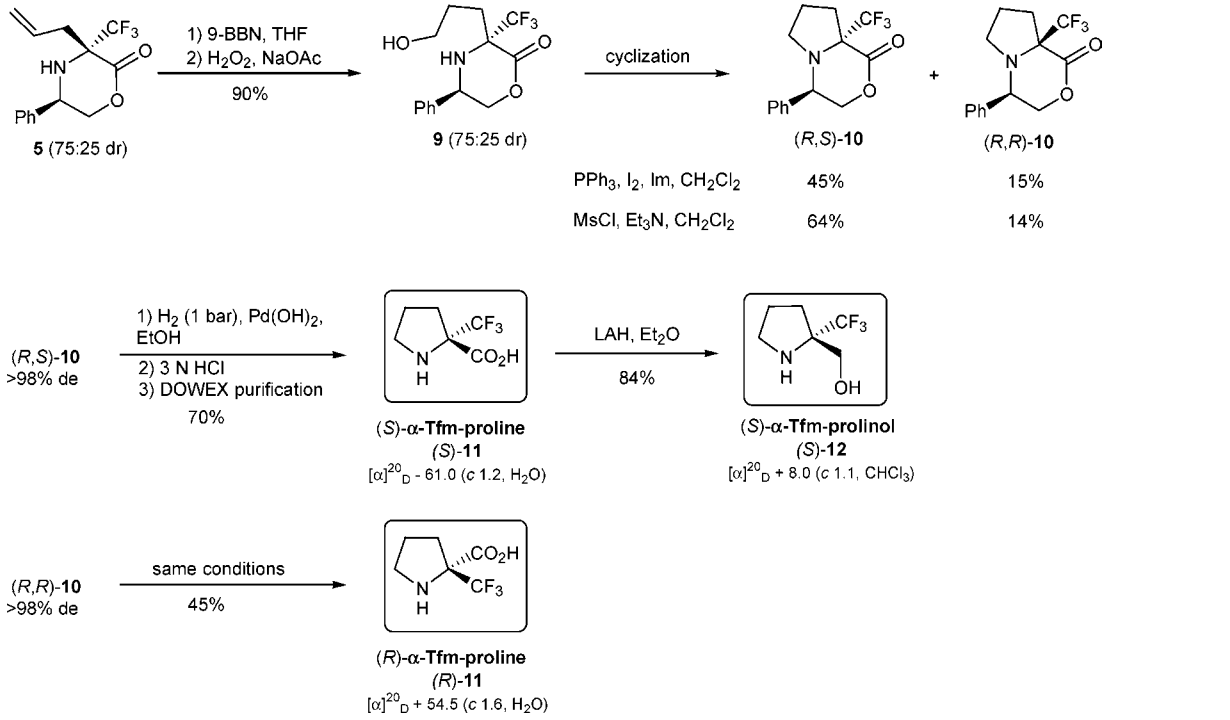
2 ratio was. This observation strongly suggests that the same iminium is formed starting from both oxazolidine and, consequently, their separation is useless. The (*R*,*S*) configuration assignment of the major diastereomer (vide infra) is in agreement with the less hindered *re* face attack of the intermediate iminium we already proposed.[11] At this point the chromatographic separation of (*R*,*S*)-**4** and (*R*,*R*)-**4** was quite difficult. Fortunately this separation was easier after cyclization into morpholinones **5** (Scheme 2).

The (*R*,*S*) configuration of the pure major **5** diastereomer was assigned by correlation with the corresponding (*S*)-Tfm-α-allylglycine (*S*)-**6** obtained after saponification and removal of the (*R*)-phenylglycinol side chain (Scheme 3). The optical rotation of (*S*)-**6** was consistent with the literature data reported for the (*R*)-enantiomer.[8] Additionally, the hydrogenolysis of (*S*,*R*)-**5** provided a very convenient access to the novel (*S*)-Tfm-norvaline (*S*)-**8** in enantiopure form (Scheme 3). To our knowledge, this constrained α-trifluoromethyl amino acid has never been reported before in nonracemic form.

With the chiral allyl morpholinone **5** in hand, we then investigated its transformation into our synthetic targets α-Tfm-prolines and α-Tfm-prolinol in a few steps. The morpholinone **5** was first subjected to a 9-BBN hydroboration reaction to give the alcohol **9** in 90% yield (Scheme 4). The cyclization of **9** building the pyrrolidine five-membered ring was conveniently achieved by means of iodine substitution or mesylate activation of the hydroxy group. It should be noticed that, at this stage, the two bicyclic diastereomers **10** were very conveniently separated by silica gel chromatography[12] to give (*R*,*S*)-**10** in 64% isolated yield and (*R*,*R*)-**10** in 14% isolated yield.

The clean removal of the (*R*)-phenylglycinol chiral auxiliary of diastereomerically pure (*R*,*S*)-**10** with standard hydrogenolysis conditions[13] furnished the expected enantiopure (*S*)-α-Tfm-proline (*S*)-**11** in 70% yield. Following the same procedure, enantiopure (*R*)-α-Tfm-proline (*R*)-**11** was obtained from the diastereomerically pure (*R*,*R*)-**10**. As (*S*)-phenylglycinol is also commercially available, (*R*)-**11** could be alternatively prepared from the corresponding (*S*) imine or oxazolidine. Furthermore, the enantiomerically pure (*S*)-α-Tfm-prolinol (*S*)-**12** was efficiently obtained in 84%

Scheme 4. Concise Synthesis of Both Enantiomers of α-Tfm-proline and (*S*)-α-Tfm-prolinol in Enantiopure Form from **5**



yield from the lithium aluminum hydride reduction of the (*S*)-α-Tfm-proline (*S*)-**11**.

In conclusion, we have successfully developed a straightforward synthetic route for the synthesis of novel highly constrained α-trifluoromethyl α-amino acids in enantiopure form from chiral trifluoropyruvate-based imine or oxazolidines. Further investigations about synthetic applications of enantiopure α-Tfm-proline and α-Tfm-prolinol are underway and will be reported in due course.

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Supporting Information Available: General experimental methods, complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The yield was raised to 93% when decarboxylation of ethyl trifluoropyruvate did not occur.

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(12) With petroleum ether/ethyl ether 90:10 eluent system: R_f for (*R*,*R*)-**10** = 0.43 and R_f for (*R*,*S*)-**10** = 0.13.

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