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Diastereodivergent Synthesis of Fluorinated Cyclic β^3-Amino Acid Derivatives

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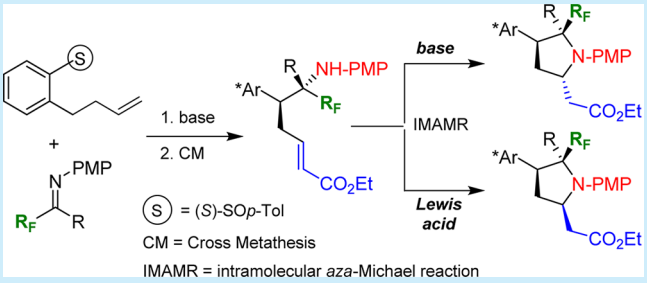
Supporting Information

ABSTRACT: The ability of 2-*p*-tolylbenzyl carbanions to behave as a source of chiral benzylic nucleophiles has been shown in its reaction with fluorinated imines. The process takes place with high levels of stereocontrol, rendering the corresponding amines as single diastereoisomers. Subsequent cross-metathesis followed by intramolecular aza-Michael reaction makes the synthesis of fluorinated homoproline derivatives bearing three stereogenic centers possible. Furthermore, the selectivity of the cyclization process can easily be tuned up in a diastereodivergent manner simply by changing the reaction conditions.



The synthesis of enantiomerically pure β-amino acid derivatives is an area of intense research activity.[1] This structural motif is present in a wide variety of natural products and biologically active compounds.[2] Perhaps the most relevant feature is that β-amino acids constitute the structural units of β-peptides, compounds with high relevance in medicinal chemistry.[3] They fold into highly stable secondary structures and show greater stability and resistance against degradation by protease-type hydrolases as these enzymes only identify α-amino acids.[4] Despite their significance and the well-known benefits that fluorine atoms often confer to organic molecules modulating their biological properties,[5] synthetic approaches to access fluorinated β-amino acids in enantiomerically pure form lag behind their α counterparts. Furthermore, most reported examples focus on the synthesis of acyclic compounds.[6]

In general, fluorinated cyclic β-amino acids (β-aa) can be classified into three constitutional isomers (β^2-, β^3-, and $\beta^{2,3}$-aa) with different structural features as shown in Figure 1.

The most frequent synthetic targets are $\beta^{2,3}$-aa derivatives, also known as 2-aminocycloalkanecarboxylic acids (2-ACACs), probably due to their analogy with the naturally occurring antifungal agent cispentacin.[7] The first report dealing with the synthesis of this class of β-amino acids in enantiomerically pure form was developed by our research group, involving the use of fluorinated imidoyl chlorides as starting materials.[8] The sequence cross-metathesis (CM) with (−)-8-phenylmenthyl acrylate followed by Dieckmann condensation and stereoselective imine reduction gave rise to the desired products. Probably the most commonly employed strategy to prepare these derivatives to date involves the late-stage nucleophilic fluorination of adequately functionalized enantiomerically pure cyclohexane- and cyclopentanecarboxylic acids.[9] Very recently, the synthesis of *cis*-2-amino-1-fluorocyclobutane-1-carboxylic acid was accomplished by chemical resolution.[10]

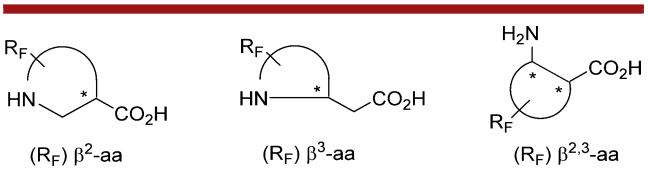


Figure 1. Classification of fluorinated cyclic β-amino acids (β-aa).

To the best of our knowledge, no reports on the preparation of enantiomerically pure fluorinated cyclic β^2-aa have been described to date,[11] although two different strategies were devised to access fluorine-containing β^3-aa derivatives. The first one involved a tandem nucleophilic addition−intramolecular aza-Michael reaction (IMAMR) of aromatic sulfinyl imines bearing a conjugated ester moiety at the *ortho* position.[12] The second one combined, in a tandem fashion, a CM reaction and an IMAMR of fluorinated amides bearing a chiral conjugated ester.[13]

The enantioselective formation of C−C bonds at the benzylic positions has been of great interest for many research groups since benzylic stereogenic carbon atoms very often appear in the framework of important organic molecules.[14] The use of benzyllithium carbanions stabilized by enantiopure *o*-sulfinyl groups provided a facile solution to the creation of benzylic stereocenters, facilitating diastereoselective reactions with electrophiles by a 1,4-induction process.[15]

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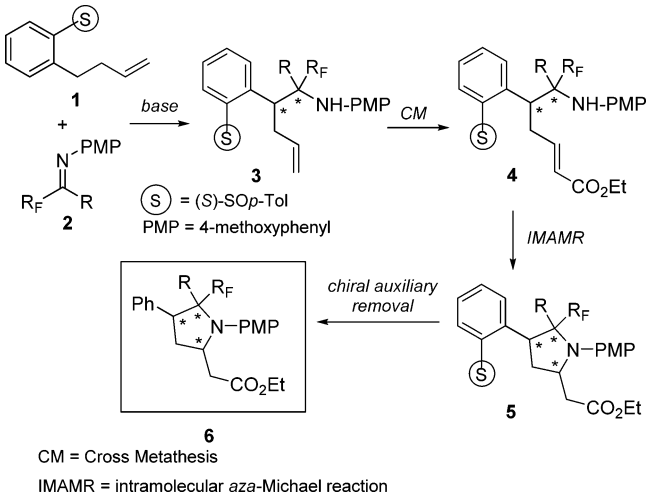
Herein, we describe the stereoselective synthesis of fluorinated homoproline derivatives containing three chiral centers. The synthetic strategy to prepare these β^3-aa derivatives involved the reaction of 2-*p*-tolylsulfinyl benzyl carbanions, generated in situ from sulfoxide **1**, with fluorinated imines **2**. Previous work by our research group showed that related processes take place with complete control of the configuration at the two simultaneously created stereogenic centers.[16] The subsequent sequence CM, IMAMR, and sulfoxide removal rendered the desired cyclic products **6** with high levels of stereocontrol at the three generated stereocenters (Scheme 1).

Scheme 1. Synthetic Strategy for the Synthesis of Cyclic Fluorinated β^3-aa Derivatives

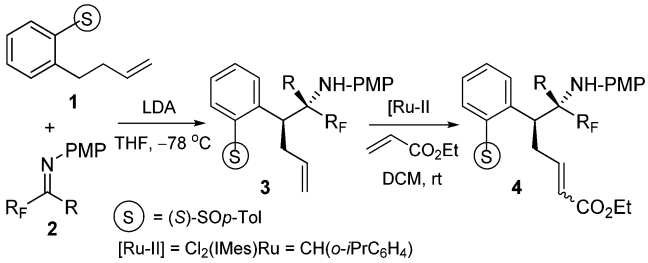


Deprotonation of sulfoxide (*S*)-**1** at the benzylic position with LDA at −78 °C and subsequent treatment with trifluoromethyl aldimine **2a** leads to the exclusive formation of amine **3a** in a highly selective manner in 71% yield when the reaction is hydrolyzed at −78 °C.[16c] These optimized conditions were extended to other fluorinated imines **2**, giving rise to the corresponding fluorinated amines **3** in moderate yields as single diastereoisomers (Table 1).

While metathesis reactions involving sulfinyl amines are very scarce in the literature, probably due to their basicity,[17] in our case, the CM reaction of substrates **3** with ethyl acrylate took place in DCM at room temperature to render conjugated esters **4** in moderate to good yields as separable mixtures of *E*/*Z* diastereoisomers (Table 1). The attenuated basicity of amines **3** due to the presence of the fluorinated substituents would explain the success of the CM process under mild conditions.[18]

With conjugated esters **4** in hand, the next step in our study was the evaluation of the IMAMR.[19] Initially, the cyclization was performed under basic conditions with compound **4a** as the model substrate. After several bases (TBAF, DBU, *t*-BuOK, $LiN(SiMe_3)_3$, $KN(SiMe_3)_3$, NaH), temperatures (−78 °C, 0 °C, room temperature), and solvents (CH_2Cl_2, THF, toluene) were tested, the best conditions to effect the cyclization entailed the use of TBAF (tetrabutylammonium fluoride) as base in THF at room temperature. Under these conditions, the corresponding pyrrolidine **5a** was achieved in good yield (78%) and diastereoisomeric ratio (5:1), the *anti* isomer being the major product (Table 2, entry 1). These conditions were further extended to substrates **4**, giving rise to the desired

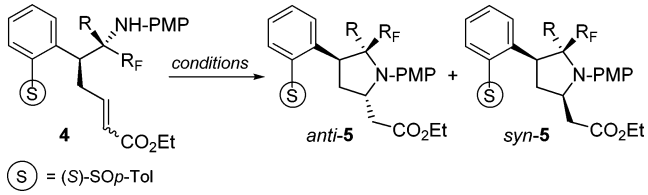
Table 1. Preparation of Enantiomerically Pure Fluorinated Amines 3 and 4



entry	2	R_F	R	3 (% yield)[a]	4 (%,[a] *E*/*Z*)[b]
1	**2a**	CF_3	H	**3a** (71)	**4a** (74, 8:1)
2	**2b**	CF_3	Me	**3b** (56)	**4b** (76, 6:1)
3	**2c**	CF_2Cl	H	**3c** (45)	**4c** (52, 5:1)
4	**2d**	CF_3	2-furyl	**3d** (62)	**4d** (50, 5:1)
5	**2e**	CF_2H	Me	**3e** (57)	**4e** (58, 7:1)

[a]Isolated yields after flash column chromatography. [b]Diastereoisomeric ratios were determined by ^{1}H NMR integration.

Table 2. IMAMR of Conjugated Esters 4



entry	4	conditions[a]	5 (% yield)[b]	ratio[c] *anti*-5/*syn*-5
1	**4a**	A	**5a** (78)	5:1
2	**4a**	B	**5a** (88)	>1:99
3	**4b**	A	**5b** (70)	7:1
4	**4b**	B	**5b** (78)	>1:99
5	**4c**	A	**5c** (82)	7:1
6	**4c**	B	**5c** (72)	>1:99
7	**4d**	A	**5d** (73)	>99:1
8	**4d**	B	**5d** (63)	>1:99
9	**4e**	A	**5e** (90)	1.5:1
10	**4e**	B	**5e** (86)	1:11

[a]Conditions A: **4** (1 equiv), TBAF (1 equiv) in THF (0.1 M) for 1h at rt. Conditions B: **4** (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv) in DCM (0.1 M) for 1 h at rt. [b]Isolated yields after flash column chromatography. [c]Diastereoisomeric ratios were determined by ^{1}H NMR integration.

fluorinated homoproline derivatives **5** (Table 2, entries 3, 5, and 7) in good yields (70−82%) and diastereoselectivities, except for substrate **4e** containing a CF_2H moiety that led to an almost equimolecular mixture of both isomers (Table 1, entry 9). The IMAMR was also evaluated in the presence of a Lewis acid. When compound **4a** was treated with $BF_3{\cdot}OEt_2$, the exclusive formation of the *syn*-**5a** isomer (88% yield) was observed (Table 2, entry 2). This means that it is possible to perform a diastereodivergent synthesis of both diastereoisomers merely by changing the reaction conditions. Thus, these acidic conditions for the IMAMR were applied to the rest of substrates **4**, and a highly diastereoselective cyclization took place, giving fluorinated pyrrolidines *syn*-**5** in good yields (63−86%) (Table 2, entries 4, 6, 8, and 10).

Finally, the last step of our synthetic sequence was the removal of the chiral auxiliary. Exposure of compounds **5** to Raney Ni in THF for 15 min gave rise to the fluorinated

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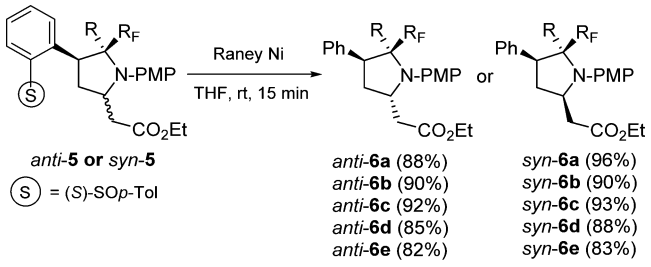
homoproline derivatives **6** in good yields as single isomers (Scheme 2).

Scheme 2. Chiral Auxiliary Removal on Compounds 5



The high selectivity achieved in the Lewis acid environment could be attributed to the formation of a chelate with the boron atom, with the participation of ester carbonyl, the sulfoxide, and the nitrogen atom (Figure 2). This tight arrangement would

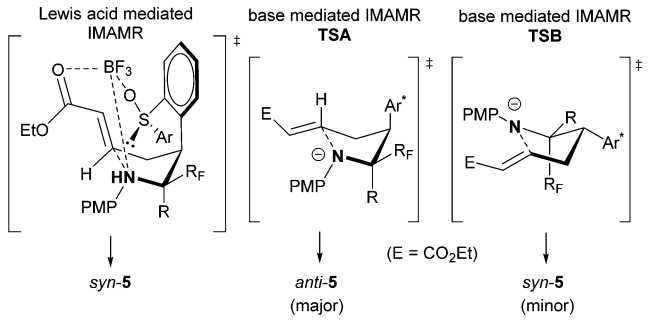
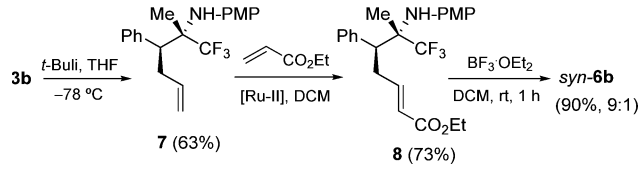


Figure 2. Rationalization of the stereochemical outcome in the IMAMR.

guide the addition of the nucleophile to the *Re* face of the conjugated ester, leading to the formation of the *syn* product under these conditions. On the other hand, the formation of the *anti* product was implemented in basic medium. Under these conditions, the nucleophilic addition would be controlled by the steric requirements of the CF_3 moiety, located in a pseudoequatorial arrangement (Figure 2, **TSA**). In the particular case of substrate **4e**, the less sterically demanding CF_2H group enables the contribution of a competitive transition state (Figure 2, **TSB**) with the chiral sulfoxide in the pseudoequatorial position. This scenario would explain the formation of an almost equimolecular amounts of diastereoisomers *syn*- and *anti*-**5e** (Table 2, entry 9).

In order to verify the role of the sulfoxide moiety in the diastereoselectivity of the process, an additional experiment was designed. We envisioned that the removal of the chiral auxiliary before cyclization would provide valuable information concerning this point. To this end, compound **3b** was treated with *t*-Buli in order to remove the sulfoxide group. Then, the resulting trifluoromethylamine **7** was reacted with ethyl acrylate under the standard CM conditions and the corresponding unsaturated ester **8** was cyclized in the presence of $BF_3{\cdot}OEt_2$ to render compound **6b** (90% yield) as a 9:1 mixture of diastereoisomers, with *syn*-**6b** being the major diastereomer (Scheme 3). This drop in selectivity indicates that the presence of the sulfoxide, which offers an additional coordination site to the Lewis acid, probably plays an important role in the stereochemical outcome of the cyclization process.

Scheme 3. Role of Sulfoxide in the IMAMR



The relative stereochemistry of final products **6** was determined in both diastereoisomers *anti*-**6b** and *syn*-**6b** by NOESY experiments. Thus, compound *anti*-**6b** showed two NOE correlations: one between H_a and one H_c (Figure 3) and

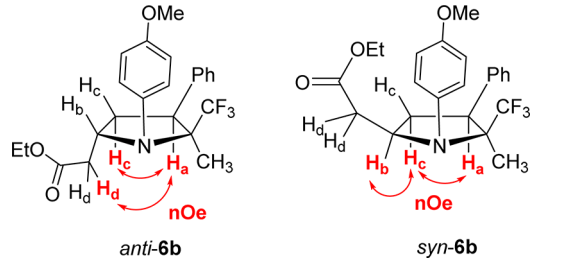


Figure 3. Determination of the relative stereochemistry of compounds **6**.

another one between H_a and H_d, which indicates the *cis* relative disposition of these H atoms and the ester group. On the other hand, compound *syn*-**6b** also showed two NOE correlations: one between H_a and H_c and a second one between H_c and H_b, indicating the *cis* relative disposition between the three protons (Figure 3). For the rest of compounds **6** an analogous stereochemical assignment was assumed.

In summary, stereocontrolled access to fluorinated homoproline derivatives has been achieved by taking advantage of the ability of *p*-tolylbenzyl sulfinyl carbanions to undergo stereoselective addition to fluorinated imines. The chiral amines obtained were then efficiently transformed into cyclic β^3-amino acid derivatives following the sequence CM-IMAMR. Interestingly, a stereodivergent cyclization was performed by changing the reaction conditions of the IMAMR. The role of the sulfoxide auxiliary in the stereochemical outcome of the process was also evaluated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02759.

Experimental procedures, characterization data of all new compounds, and NMR charts (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. José Luis García Ruano on the occasion of his retirement.

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