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Asymmetric synthesis of β-trifluoromethyl-β-amino acids, including highly sterically constrained α,α-dialkyl derivatives

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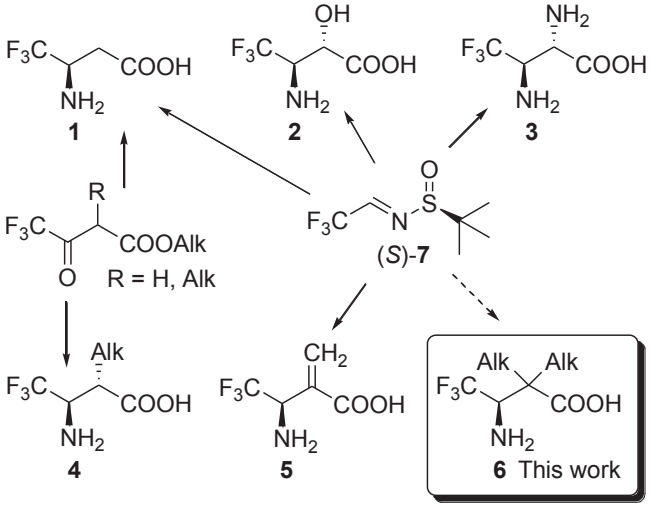
ABSTRACT

Reported herein is asymmetric synthesis of β-trifluoromethyl-β-amino acids via Mannich addition reactions between (S_s)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine and lithium enolates of alkyl acetates. In particular, the scope of this approach allows for preparation of the previously illusive, highly sterically constrained α,α-dialkyl-β-trifluoromethyl-β-amino acids. The method affords the target products with good to excellent chemical yields and diastereoselectivities.

1. Introduction

Due to the essential role of fluorine containing compounds in numerous modern industries, synthesis of this class of organic derivatives continues to attract considerable attention.[1] In fact, the interest in development of new methods for preparation of selectively fluorinated compounds is at an all-time high,[2] because of the rapidly growing number of pharmaceutical products bearing fluorine.[3] Taking into account the general biological importance of amino acids in biological evolution and sustenance of human health, preparation of the corresponding fluorinated derivatives is particularly motivating.[4] For example, the family of β-trifluoromethyl-β-alanines **1**–**5** (Scheme 1) has received significant attention due to high pharmaceutical value of these β-amino acids.[4a]



Scheme 1. Known **1**–**5** and unknown **6** types of β-trifluoromethyl-β-alanines.

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Synthesis of β-alanines of type **1**[5] and **4**[6] in enantiomerically pure form,[7] can be conveniently achieved via biomimetic transamination of the corresponding β-keto acid derivatives. However, like in the case of non-fluorinated β-amino acids,[8] more general approach is provided by Mannich addition reactions. Thus, the reactions of (S_s)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine **7**[9,10] (Scheme 1) or its analogs[11] with malonic or acetic acid derivatives allows for stereodivergent synthesis of (*R*)- and (*S*)-β-trifluoromethyl-β-alanines **1**[12] or β-trifluoromethyl isoserines **2**.[13] The additions of imine **7** with glycine Schiff bases affords α,β-diamino acids **3**[14] and aza-Baylis–Hillman reactions gives rise to α-methylene-β-trifluoromethyl-β-amino acids **5**.[15]

However, despite an extensive research in this area, α,α-dialkyl-β-trifluoromethyl-β-alanines **6** still remains synthetically unknown and biologically unexplored. β-Amino acids of type **6** embody quite a challenging structural class of sterically constrained β-amino acids, but, by analogy with α-amino counterparts,[16] hold an exciting potential in the de novo peptide design. The major synthetic hurtle associated with the preparation of amino acids **6**, is not only their extreme sterically congested nature, but rather the fact that all previously developed methods for preparation of β-amino acids of types **1**–**5** cannot be directly used for the synthesis of derivatives **6**. Consequently, building on our success in the application of chiral imine **7** for synthesis of sterically difficult targets,[17] we were highly motivated to develop a general synthesis of β-trifluoromethyl-β-amino acids, including this unknown type of sterically constrained derivatives **6**.

2. Results and discussion

Our research strategy was based on the assumption that synthesis of the target compounds would require in situ generation of metal enolates using strong bases and controlled conditions. Therefore, we decided to study first the reactions of simple acetates to gage the general reactivity and stereoselectivity. As a model substrate we selected benzyl acetate **8a** (Table 1), which itself and its products are traceable by TLC analysis. Substrate **8a** reacted with imine **7** under variety of conditions to optimize the base, solvent and reaction temperature (Table 1).

Analysis of the data presented in Table 1, allows to make several unexpected, interesting conclusions. First, the diastereoselectivity of these additions was excellent, as in all successful reactions only a single diastereomeric product was detected in the crude reaction mixtures (entries 1–3, 7, 9. 11–13). Second, the choice of base had a dramatic impact on the reaction progress, rendering the Li-derived bases generally better performing as compared to bases derived from Na or K; among which the LDA was the best. Third, quite unexpectedly, toluene, used as a solvent, allowed for better chemical yields as compared to THF, which is usually used for generation of Li-enolates. Finally, initiating the reactions at low −78 °C, followed by a gradual warm-up to ambient temperature, resulted in shorter reaction time as well as the best range of chemical yields (entries 12 and 13).

One may agree that complete (>99% dr) diastereomeric control in these reactions was quite unexpected and presents a rare example of perfect stereochemical outcome. Therefore, we decided to investigate these reactions further, as a function of the ester substituent on starting acetate **8**. To this end, we performed a series of reactions presented in Scheme 2.

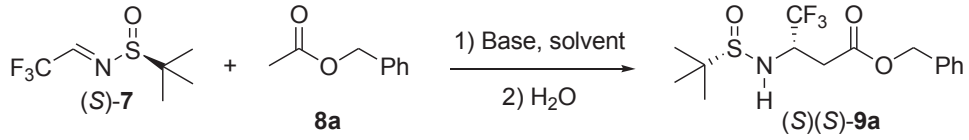
As shown in Scheme 2, the perfect stereochemical outcome was constantly maintained regardless of the ester substituents. In some cases the chemical yields were lower than expected, which rather reflects differences in physicochemical properties of particular products **9a**–**l**, influencing the isolation procedure. Most importantly, all products **9a**–**l** were isolated as pure diastereomers, presenting no need for any additional purification.

Taking advantage of high crystallinity of product **9b**, we performed its crystallographic analysis which revealed the (*S*) absolute configuration of the newly created stereogenic carbon (Fig. 1). Considering close similarity of spectral and chiroptical properties between products **9a**–**l**, all compounds **9a**–**l** have the same (*S*) configuration of the β-amino acid moiety.

Drawing from these results, we then focused on preparation of the target α,α-dialkyl-β-trifluoromethyl-β-amino acids **6**. Using the optimized reaction conditions, we studied the addition reactions of six types of α,α-di-substituted acetates **10a**–**f** presented in Scheme 3.

Once again, the results obtained were rather unexpected and interesting. To our delight, the α,α-(dimethyl)acetate **10a** gave truly

Table 1
Optimization of the reaction conditions between chiral imine (*S*)-**7** and benzyl acetate **8a**[a]



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	dr[c]
1	LDA	THF	−78	12	66	>99:1
2	LiHMDS	THF	−78	12	60	>99:1
3	NaHMDS	THF	−78	12	58	>99:1
4	KHMDS	THF	−78	12	Trace	ND[e]
5	$(CH_3)_3COLi$	THF	−78	12	Trace	ND
6	$(CH_3)_3COK$	THF	−78	12	NR[d]	—
7	LDA	Toluene	−78	12	79	>99:1
8	LDA	DCM	−78	12	NR	—
9	LDA	Toluene	−40	12	<20	>99:1
10	LDA	Toluene	−20	12	Trace	ND
11	LDA	Toluene	−78 to 0	12	81	>99:1
12	LDA	Toluene	−78 to rt	12	84	>99:1
13	LDA	Toluene	−78 to rt	2	83	>99:1

[a] Reaction conditions: imine **7** (0.5 mmol), **8a** (1.2 equiv of **7**), base (1.2 equiv of **8a**) and solvent (5 mL).
[b] Isolated yield.
[c] Determined by crude ^{19}F NMR analysis.
[d] Not reaction.
[e] Not determined.