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Synthesis of (2*S*,3*S*)-β-(trifluoromethyl)-α,β-diamino acid by Mannich addition of glycine Schiff base Ni(II) complexes to *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine

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ABSTRACT

A convenient access to (2*S*,3*S*)-β-(trifluoromethyl)-α,β-diamino acid is reported by using highly diastereoselective Mannich addition reactions of either chiral or achiral Ni(II) complexes derived from glycine Schiff bases to a chiral sulfinimine, *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine. Disassembly of the resultant Ni(II) complexes affords the target amino acid which was, for the first time, isolated in enantiomerically pure form and fully characterized.

1. Introduction

The design and synthesis of fluorine-containing amino acids and peptides [1] is a very active research field with major implications in chemistry and biology as well as the discovery of new drug candidates [2]. Thus, it is well-known that the selective fluorination of peptidic compounds usually contributes to an improvement of their chemical and thermal stabilities, and hence to their bioavailability. In particular, introduction of trifluoromethyl groups into amino acids is a common strategy in the quest for new bioactive compounds because of the unique characteristics of the CF_3 moiety. In recent years there has been a tremendous upsurge of synthetic methodologies for the convenient trifluoromethylation of organic compounds, especially on late stages of the synthetic processes without affecting sensitive functional groups [3]. Nonetheless, using CF_3-bearing building blocks as starting materials is still a valuable approach, provided that these small molecules are readily available, and preferably chiral [4].

Among amino acids, α,β-diamino acids constitute an important group of compounds widely found in nature as structural motifs of biologically relevant molecules [5]. However, the preparation of their fluorinated analogues is surprisingly a much underdeveloped area. In this context, it should be mentioned that the synthetic access to β-(trifluoromethyl)-α,β-diamino acid (2*S*,3*S*)-**5** was reported through the Mannich addition to PMP-protected imine **2** using Ni(II) complex (*S*)-**1** as a nucleophilic glycine equivalent (NGE) [6] (Scheme 1). Thus, when the reaction was conducted under conditions of kinetic control, the process took place with moderate diastereoselectivity to afford adduct (*S*)(2*S*,3*S*)-**3** as the major isomer. It should be emphasized that synthetic access to (*S*)-**1** is very straightforward from *N*-benzylproline, 2-aminobenzophenone, glycine and a Ni(II) salt [7]. Furthermore, its hydrolytic disassembly rendered the target compound (2*S*,3*S*)-**5** with quantitative recovery of the corresponding ligand (*S*)-**6**, that can be conveniently recycled in the production of complex (*S*)-**1**.

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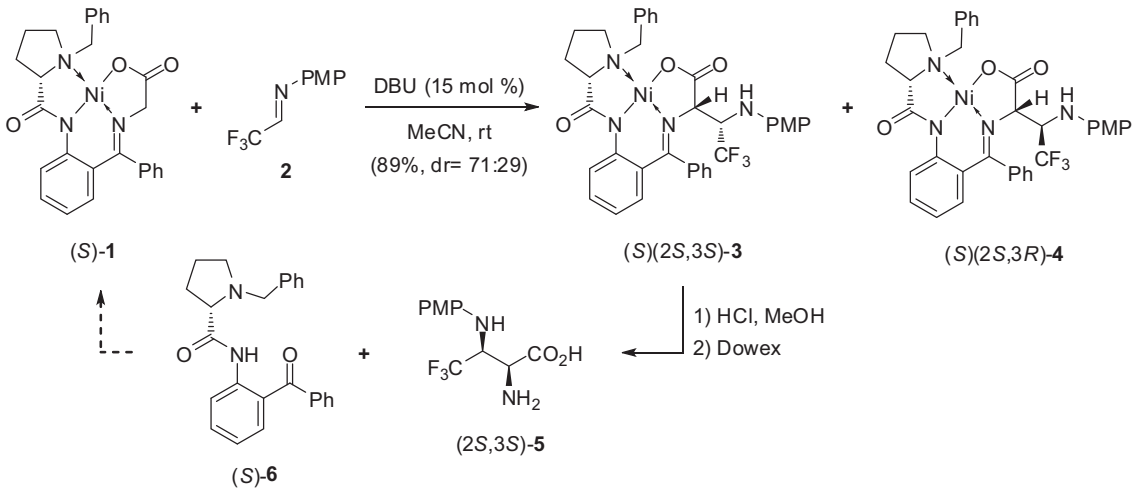


Scheme 1. Synthesis of CF_3-diamino acid (2*S*,3*S*)-**5** from chiral Ni(II) complex (*S*)-**1**.

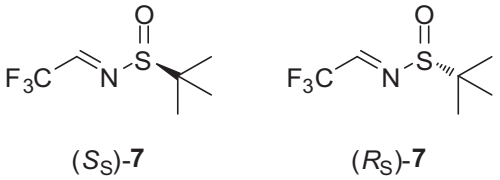


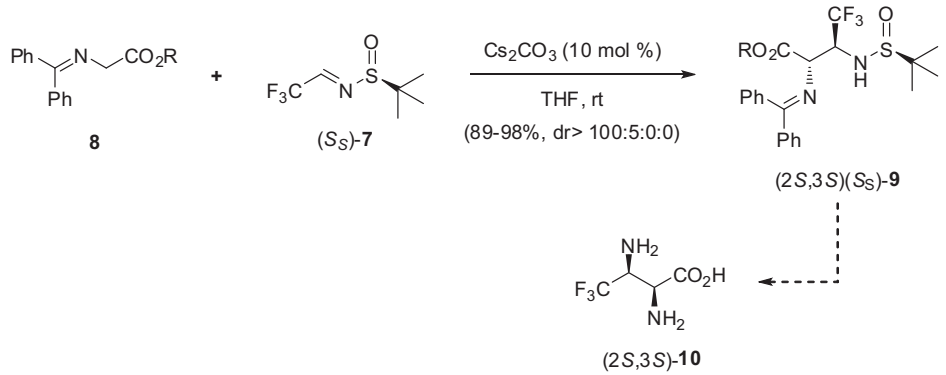
Fig. 1. Structures of sulfinimines (S_S)- and (R_S)-**7**.

Alternatively, *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine **7** is a chiral sulfinimine derived from trifluoroacetaldehyde (fluoral) and accessible in both enantiomeric forms [8] (Fig. 1). This compound has been employed for the expedient synthesis of a wide variety of α-(trifluoromethyl)amines [9]. For instance, several Mannich-type processes have been performed with (S_S)- or (R_S)-**7** by reaction with enolates derived from α-hydroxyesters [10], malonates [11] or indanones [12], as well as with other nucleophiles such as phosphites [13], lithium anions derived from phosphonates [14] or heterocycles [15].

Recently, it was found that Mannich adducts (2*S*,3*S*)(S_S)-**9** were formed in very good yield and excellent diastereoselectivity upon reactions of sulfinimine (S_S)-**7** with benzophenone imines of glycine esters **8** [16] (Scheme 2). Nevertheless, implementation of this approach for the preparation of the corresponding free α,β-diamino acid (2*S*,3*S*)-**10** may not be feasible on a large scale due to the relative instability of NGEs **8**. It would be also desirable to take advantage of alternative types of NGEs which could be recovered and recycled after releasing the target amino acid molecule. As previously stated, these drawbacks can be circumvented by employing Ni(II) complexes derived from glycine Schiff bases such as (*S*)-**1**. Consistent with our interest in the synthesis of fluorine-containing biological relevant compounds in general [17] and in particular amino acids using the numerous applications of this class of NGEs [18–20], the aim of the current work is to explore the reactivity of different chiral and achiral Ni(II) complexes towards sulfinimine **7**, with the ultimate goal of accessing the previously unreported α,β-diamino acid (2*S*,3*S*)-**10** on a relatively large scale.

2. Results and discussion

Our investigation began with the Mannich reaction of chiral Ni(II) complex (*S*)-**1** and chiral sulfinimines (S_S)- or (R_S)-**7**. It would be anticipated that a pair of matched and mismatched reactions would emerge, according to the stereodirecting bias of both reactants. Thus, it is well established that kinetic control in the alkylation reactions of Ni(II) complex (*S*)-**1** usually affords up to 85:15 diastereoselectivity, favoring the corresponding (*S*) configuration at the α-carbon [21], and that was also the case in the previously shown example of a Mannich reaction with an achiral imine [6] (Scheme 1). On the other hand, the high facial selectivity displayed by chiral sulfinimine **7** was also demonstrated [9–15]. Therefore, the reaction of complex (*S*)-**1** with sulfinimine (S_S)-**7** constituted a perfectly matched case since essentially only one diastereomer (*S*)(2*S*,3*S*)(S_S)-**11** was observed (Scheme 3). In contrast, the analogous reaction using the enantiomeric sulfinimine (R_S)-**7** produced a mixture of two major diastereomers



Scheme 2. Mannich reaction between NGEs **8** and sulfinimine (S_S)-**7**.