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Asymmetric synthesis of β,β-difluoroamino acids via cross-coupling and Strecker reactions

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Abstract

β,β-Difluoroamino acids were synthesized from commercially available ethyl bromodifluoroacetate using cross-coupling and Strecker reactions as key steps. The coupling reaction of aryl iodides with ethyl bromodifluoroacetate gave the corresponding coupling products, which were transformed to 2-difluoromethyl-1,3-oxazolidines in two steps. Boron trifluoride etherate promoted Strecker reaction of 2-difluoromethyl-1,3-oxazolidines gave α-amino nitriles in good yields and diastereoselectivities. After removal of chiral auxiliary and hydrolysis of the nitrile group, β,β-difluorophenylalanine was obtained with 73% ee. Partial racemization occurred during the hydrolysis of nitrile group.

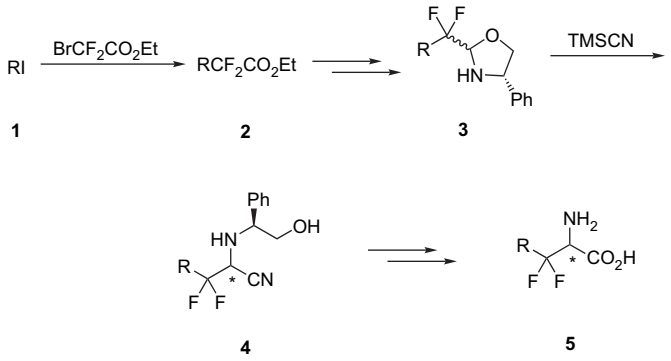
Keywords: Fluorinated amino acid; Bromodifluoroacetate; Cross-coupling reaction; Strecker reaction

1. Introduction

Fluorinated amino acids have gained an important position in the synthesis of compounds exhibiting interesting properties for bioorganic application.[1] Among them, *gem*-difluoroamino acids and their derivatives have been the subject of considerable research because the CF_2/CH_2 transposition has been recognized as a valuable tool in the blockage of metabolic process. β,β-Difluorophenylalanine is an attractive unnatural amino acid target because of its biological and pharmacological properties.[2] Two synthetic methods for this fluorinated amino acid have been developed by direct fluorination. One utilized the ring-opening reaction of 2-carboxyl-1-phenyl-1-azirine with hydrogen fluoride pyridine and optically active isomers were prepared by enzymatic hydrolysis.[3] The other employed a lengthy route containing twice *vic*-bromofluorination at the beginning and there was no stereoselectivity during the construction of the chiral center.[4] Therefore it is necessary to develop more efficient strategies for the synthesis of β,β-difluorophenylalanine and its derivatives. In this paper we report a convenient asymmetric synthesis of β,β-difluoroamino acids starting from ethyl bromodifluoroacetate and aryl iodides.

2. Results and discussion

The synthetic route is shown in Scheme 1. The crossing-coupling reaction of aryl halides **1** with ethyl bromodifluoroacetate



Scheme 1.

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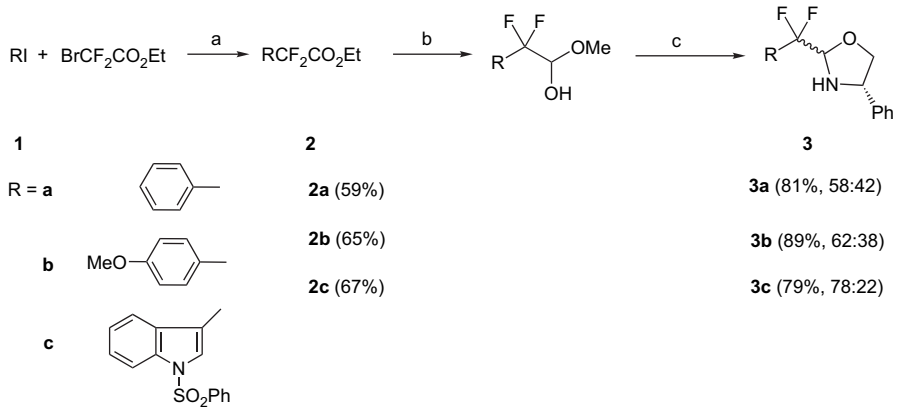


Scheme 2. (a) Cu, DMSO, 55 °C. (b) $NaBH_4$, MeOH, −55 °C. (c) (*S*)-phenylglycinol, PPTS, toluene, Dean Stark distillation.

was used to prepare α,α-difluoroesters **2**,[5] which was next transformed to oxazolidines **3**. Strecker reaction of **3** afforded the corresponding amino nitriles **4**. Removal of the chiral auxiliary of **4** followed by hydrolysis gave title compound **5**.

Iodobenzene (**1a**), 4-iodoanisole (**1b**), and 3-iodo-1–phenylsulfonyl-1*H*-indole (**1c**) were chosen as starting materials, which may finally be converted to difluorinated analogs of important natural phenylalanine, tyrosine, and tryptophan (Scheme 2). In the presence of copper powder, the cross-coupling reaction of **1** and ethyl bromodifluoroacetate took place readily in DMSO under mild conditions to give α,α-difluoroesters **2** in good yields. Reduction of **2** with $NaBH_4$ in methanol gave the corresponding methyl hemiacetals, which were not stable enough for purification by column chromatography and were condensed with (*S*)-phenylglycinol directly to give oxazolidines **3**, the stable equivalents of the corresponding imines.[6,7]

A stereoselective approach to α-amino nitriles was developed by Brigaud et al. using Lewis acid promoted Strecker reaction of 2-trifluoromethyl-1,3-oxazolidines.[7] Under similar conditions, diastereomeric mixture of oxazolidines **3** was allowed to react with trimethylsilyl cyanide in the presence of $BF_3\cdot OEt_2$ and α-amino nitriles **4** were obtained in high yields with good diastereoselectivities (Scheme 3). The absolute configuration of the major product was determined by X-ray crystallographic studies (Fig. 1).[8] The formation of an iminium ion intermediate has been proposed for the good diastereoselectivity of the above Strecker reaction.[7] The existence of the intermediate in our reaction was partially proved by a simple NMR experiment. When $BF_3\cdot OEt_2$ was added to a $CDCl_3$ solution of **3a**, new signals appeared for protons of imine in its ^1H NMR spectrum. Therefore the nucleophilic attack took place mainly from the *Si* face to give major diastereomer with (*S*,*S*) configuration due to the hindering effect of phenyl in the iminium ion intermediate (Fig. 2).[9]

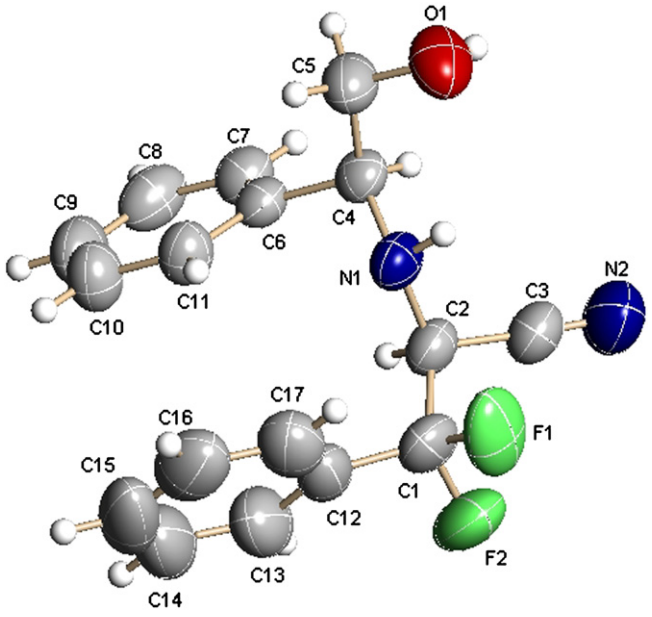
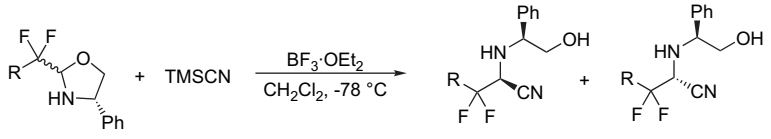


Figure 1. ORTEP of the crystal structure of **4a** (major isomer).

Compound **4a** was chosen as an example for the following transformations. The chiral auxiliary of **4a** was removed by reacting with lead tetraacetate in a mixed solvent of dichloromethane and methanol. After hydrolysis of the nitrile group with



Scheme 3. Strecker reaction of **3** and TMSCN.