Synthesis of α-Fluorinated β-amino acids, bearing a tetrasubstituted stereogenic center

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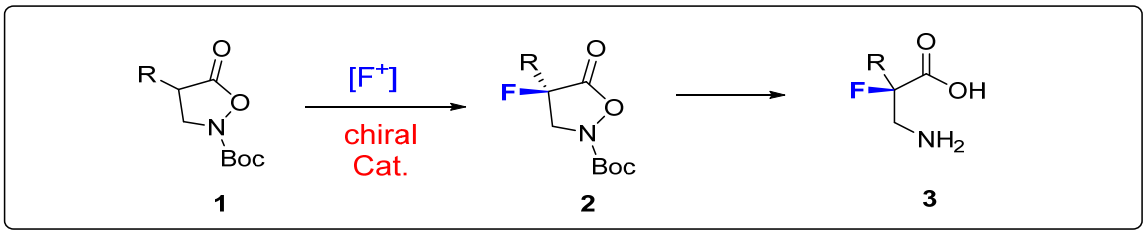
Fluorine has the unique property to alter the physical and chemical property of a molecule. Therefore there are increasing interests for organic chemists and medicinal researchers to synthesize fluorine containing compounds. The incorporation of fluorine into peptides for example leads to an outstanding high biological activity, which is extremely useful for new medicinal products [1].

However, the number of synthetic routes for the preparation of enantiopure α-Fluorinated β-amino acids is still limited. This is mainly due to racemization in case of tertiary fluorinated amino acids and for amino acids, which have already a substituent at the 2-Position, the main synthetic challenge is the direct fluorination at the already crowded tertiary substituted C-2 center [2].



The methology represented here, provides a facile and enantioselective route to prepare substrate **2**, which can be converted to the acid **3** for further use in peptide synthesis. Substituted isoxazolidin-5-ones **1** were used as the primary key motif for optimizing the reaction conditions and for catalyst screening. Both electron-withdrawing and electron-donating groups afforded the desired products **2** with good yields and a high level of selectivity. The fluorinated products were readily converted into various $\beta^{2,2}$ amino acids by removal of the protecting group, followed by reductive N-O cleavage using different reducing agents. Switching of the reducing conditions allowed also the selective synthesis of the protected peptide precursor **3** [3].

[1] F. Mansour, and L. Hunter, Synthesis and applications of backbone-fluorinated amino acids, *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, eds. G. Haufe, and F. R. Leroux, Vol. 1 (Elsevier Inc., 2018), chap. 9

[2] J. Annibaletto, S. Qudeyer, V. Levacher, and J. F. Briére, Catalytic Enantioselective Synthesis of Isoxazolidin-5-ones, *Synthesis*, **2017**, 49, 2117-2128

[3] I. Eder, A. Eitzinger, and M. Waser, Synthesis of α-Fluorinated β-amino acids [unpublished results]