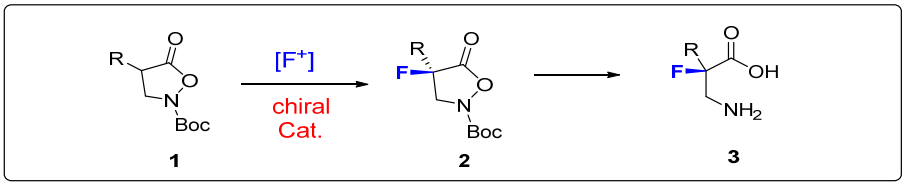
A NEW APPROACH TO PREPARE α-FLUORINATED β-AMINO ACIDS, BEARING A TETRASUBSTITUTED STEREOGENIC CENTER

Isabella Eder, Andreas Eitzinger, and Mario Waser

Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstr. 69, 4040 Linz, Austria

Since no other element is capable of altering the physical and chemical properties of a molecule in such a determined and intriguing way, there are increasing interests for organic chemists, medicinal researchers and pharmacologists to synthesize fluorine containing compounds. The incorporation of fluorine into peptides for example leads to an outstanding high biological activity and a better absorption by the human body, 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 (and subsequent loss of stereoinformation) in case of tertiary fluorinated amino acids. Regarding amino acids, which have already a substituent at the 2-Position of the amino acid, 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 route to prepare substrate 2 with promising *ee* values, which can be converted to the acid 3 for subsequent peptide synthesis. Optimization of reaction conditions and catalyst screening were also conducted to synthesize derivatives of compound 2. Therefore substituted isoxazolidin-5-ones 1 were used as the primary key motif for enantioselective fluorination. 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 agent. Switching of the reducing conditions allowed also the selective synthesis of the protected peptide precursor 3 [3].

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[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]