Swiss Stereoselective Organocatalyzed Synthesis of α-Fluorinated β-Amino Thioesters and their Application in Peptide Synthesis

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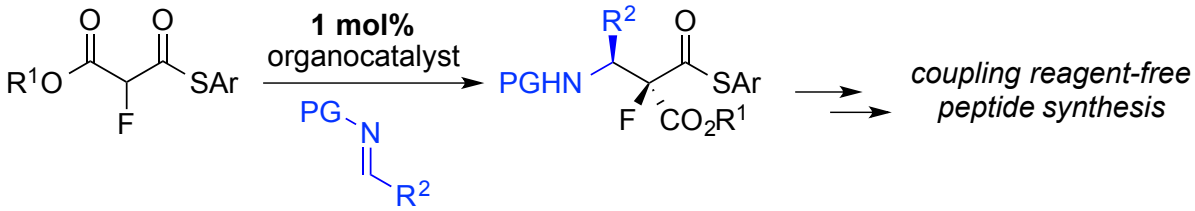
Fluorination and the incorporation of *β*-amino acids into peptides represent powerful strategies to enhance their proteolytic stability and to control their conformation.[1] These features are combined in *α*-fluoro-*β*-amino acids, which influence the conformation of *β*-peptides.[2] However, the stereoselective synthesis of *α*-fluoro-*β*-amino acids is not straightforward.[3] Malonic acid half thioesters (MAHTs) and monothiomalonates (MTMs) have been recognized as valuable thioester enolate equivalents for organocatalyzed addition reactions.[4,5] Recently, our group developed a stereoselective method to access fluorinated aldol products using fluorinated malonic acid half thioesters (F-MAHTs) as building blocks.[6]

Herein we present highly stereoselective organocatalyzed Mannich reactions between fluorinated monothiomalonates (F-MTMs) and *N*-Cbz and *N*-Boc protected imines.[7] The methodology requires only 1 mol% of organocatalyst and provides access to the corresponding *α*-fluoro *β*-amino thioesters, which can be used for coupling reagent-free peptide synthesis in solution and on solid phase.



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[5] For examples with MTMs, see: a) O. D. Engl, S. P. Fritz, H. Wennemers, *Angew. Chem. Int. Ed.* **2015**, *54*, 8193-8197; b) A. Bahlinger, S. P. Fritz, H. Wennemers, *Angew. Chem. Int. Ed.* **2014**, *53*, 8779-8783.

[6] J. Saadi, H. Wennemers, *Nature Chem.* **2016**, *8*, 276–280.

[7] E. Cosimi, O. Engl, J. Saadi, M.-O. Ebert, H. Wennemers, *Angew. Chem. Int. Ed.* **2016**, DOI: 10.1002/ange.201607146.