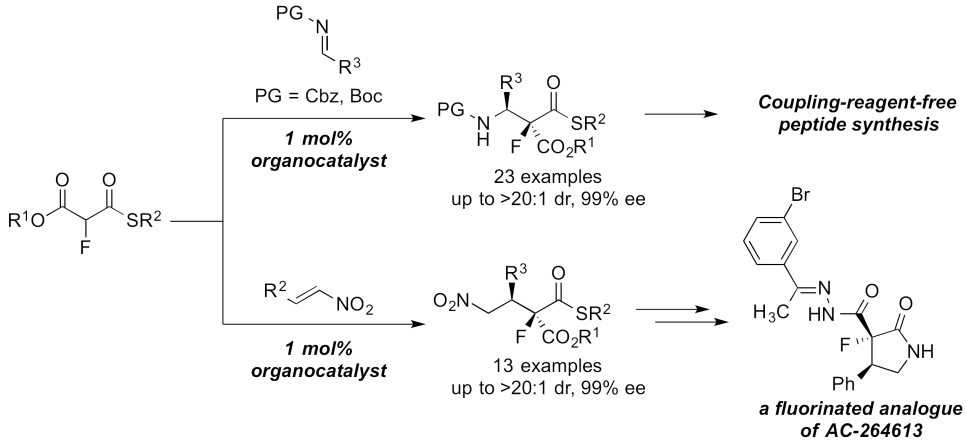
Stereoselective Organocatalyzed Synthesis of α-Fluoro β-Amino and α-Fluoro γ-Nitro Thioesters

E. Cosimi[1], H. Wennemers[1]*

[1]Laboratory for Organic Chemistry, D-CHAB, Switzerland

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] Recently, our group developed a stereoselective method to access fluorinated aldol products using fluorinated malonic acid half thioesters (F-MAHTs) as building blocks.[3] Herein we present highly stereoselective organocatalyzed Mannich reactions between fluorinated monothiomalonates (F-MTMs) and N-Cbz and N-Boc protected imines as well as Michael reactions between F-MTMs and nitroolefins.[4] These reactions require only 1 mol% of organocatalyst and provide access to the corresponding α-fluoro β-amino thioesters and α-fluoro γ-nitro thioesters, respectively. α-fluoro β-amino thioesters can be directly used for peptide synthesis in solution and on solid phase, whereas α-fluoro γ-nitro thioesters can be transformed into the corresponding fluorinated lactams, as showcased in the synthesis of a fluorinated analogue of AC-264613.[5]



[1] D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366–1375.
[2] T. L. March, M. R. Johnston, P. J. Duggan, J. Gardiner, *Chem. Biodiv.* **2012**, *9*, 2410–2441.
[3] J. Saadi, H. Wennemers, *Nature Chem.* **2016**, *8*, 276–280.
[4] a) E. Cosimi, O. Engl, J. Saadi, M.-O. Ebert, H. Wennemers, *Angew. Chem. Int. Ed.* **2016**, *55*, 13127-13131; b) E. Cosimi, J. Saadi, H. Wennemers, *Org. Lett.* **2016**, *18*, 6014-6017.
[5] Seitzberg, J. G.; Knapp, A. E.; Lund, B. W.; Bertozzi, S. M.; Currier, E. A.; Ma, J.-N.; Sherbukhin, V.; Burstein, E. S.; Olsson, R. *J. Med. Chem.* **2008**, *51*, 5490–5493.