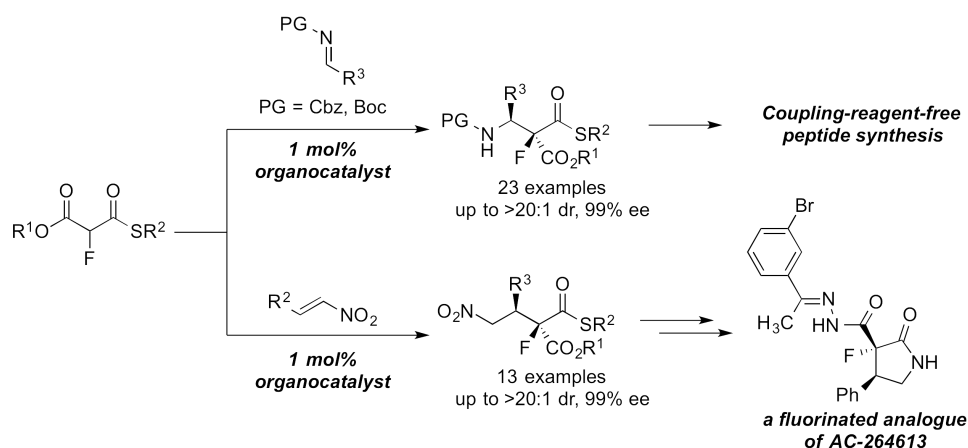


Stereoselective Organocatalyzed Synthesis of α -Fluoro β -Amino and α -Fluoro γ -Nitro Thioesters

E. Cosimi¹, H. Wennemers^{1*}

¹Laboratory 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.