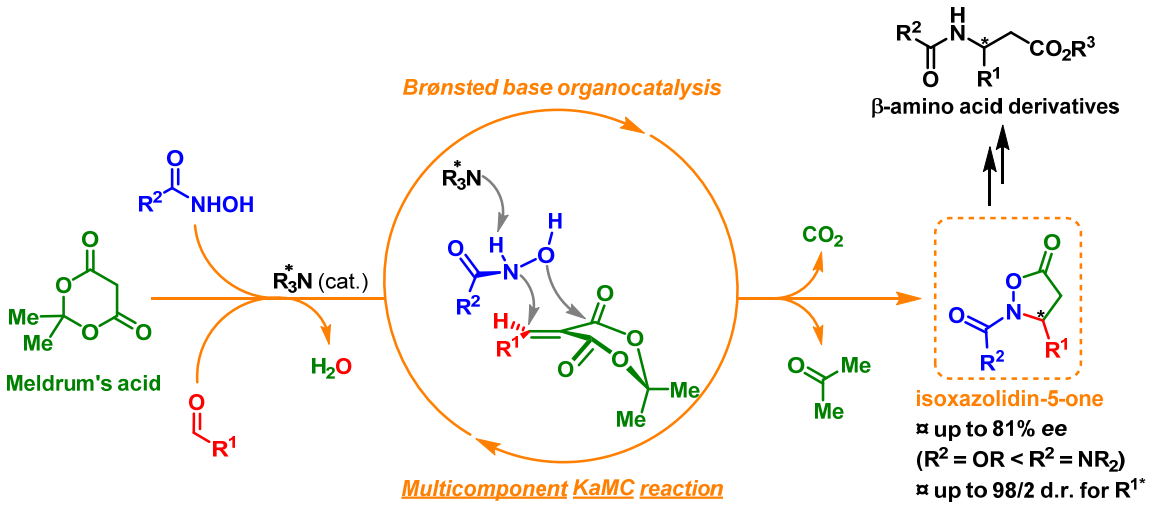
MULTICOMPONENT ORGANOCATALYTIC SYNTHESIS OF ISOXAZOLIDIN-5-ONES

Julien Annibaletto, Christophe Berini, Vincent Levacher, Sylvain Oudeyer, Jean-François Brière

Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France

Isoxazolidin-5-one derivatives are important heterocyclic building blocks in organic synthesis.[1] This heterocyclic ring has been used for the elaboration of bioactive compounds such as nucleoside analogues or steroidal compounds.[2] Moreover, isoxazolidin-5-ones are useful precursors of β-amino acids after reductive cleavage of the *N-O* bond[1] or by making use of the KAHA ligation process, developed by the Bode group.[3]



Our team have developed an efficient racemic and diastereoselective multicomponent reaction (MCR) involving Meldrum's acid, various aldehydes and *N*-acylhydroxylamines upon a Knoevenagel-azaMichael-cyclocondensation (KaMC) domino process.[4] In the context of more recent development, we tackled an organocatalytic enantioselective synthesis of isoxazolidin-5-one derivatives through the multicomponent KaMC reaction.[5] Thanks to an original chiral Brønsted base catalyst (R_3N^*), a series of chiral isoxazolidin-5-one derivatives were obtained in moderate to high yields and up to 81% *ee*. We are pleased to describe herewith the development of a stereoselective KaMC reaction together with the use of isoxazolidin-5-one derivatives as precursors of β-amino acid derivatives.

---

[1] Annibaletto, J.; Oudeyer, S.; Levacher, V.; Brière, J.-F. *Synthesis* **2017**, *49*, 2117.

[2] Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337.

[3] (a) Juarez-Garcia, M. E.; Yu, S.; Bode, J. W. *Tetrahedron*, **2010**, *66*, 4841. (b) Yu, J.-S.; Hidetoshi, N.; Shibasaki, M. *Angew. Chem. Int. Ed.*, **2018**, *57*, 818.

[4] Berini, C.; Sebban, M.; Oulyadi, H.; Sanselme, M.; Levacher, V.; Brière, J.-F. *Org. Lett.* **2015**, *17*, 5408.

[5] Unpublished results.