Synthesis of α-trisubstituted β-functionalised Amines from Thioimidates

Clara Bouvet[1], Lorène Crespin, Thi Minh Thi Le, Jean-François Poisson*, Sébastien Carret*

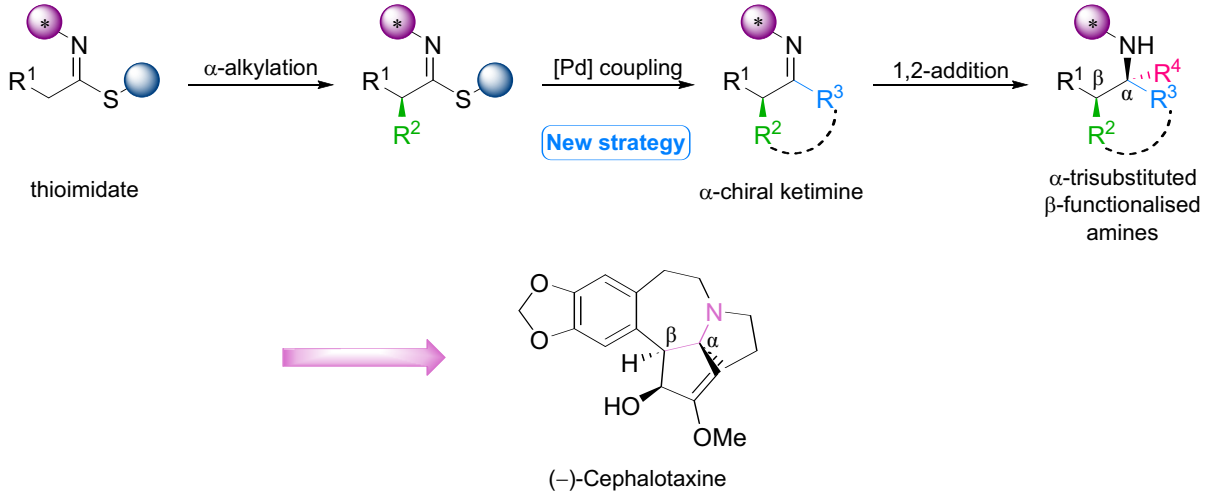
[1]*Département de Chimie Moléculaire, Equipe SeRCO, UGA – UMR 5250, 301 rue de la Chimie – 38610 Grenoble – France*

E-mail: clara.bouvet1@univ-grenoble-alpes.fr

α-trisubstituted β-functionalised amine is a key structural motif in many natural products, particularly in alkaloids. Due to its presence in biologically active compounds, such as (–)-Homoharringtonine, an FDA approved medicine used to treat chronic myeloid leukemia,[1] and for the synthetic challenge it represents, its synthesis is of great interest for chemists.

Lately, the group developed an access to α-trisubstituted β-functionalised amines from an innovative chiral thioimidate intermediate (*Scheme 1*). This strategy allowed the total synthesis of 4 alkaloids from the Lycorine family, including (+)-Kirkine.[2]

However, the coupling step leading to the desired ketimine remains a big challenge as well as the formation of the tetrasubstituted α-carbon bearing the nitrogen. Indeed, depending on the R^2 group, a stoichiometric amount of palladium is sometimes required to perform the coupling reaction. That is why we recently developed a complementary strategy that allows the introduction of a broad range of R^3 groups on the ketimine, while preserving the α-chirality. Followed by a 1,2-addition, this method will lead to the desired α-trisubstituted β-functionalised amines. This innovative procedure will then be used to envision the total synthesis of (–)-Cephalotaxine (*Scheme 1*).



Scheme 1: synthesis of α-trisubstituted β-functionalised amines from thioimidates

References

[0] DeAngelo, D. J. et Al. *Oncol Ther* **2018**, *6*, 9–20

[2] (a) Lorène Crespin, Thèse de doctorat, Université Grenoble Alpes **2015** ; (b) Thi Minh Thi Le, Thèse de doctorat, Université Grenoble Alpes **2018**