

C-H ACTIVATION ENABLES A CONCISE AND STEREOSELECTIVE TOTAL SYNTHESIS OF QUININE AND ANALOGUES

Martin Berger,^a Daniel H. O'Donovan,^a Paul Aillard,^a Aurélien de la Torre,^a Desislava Petkova,^a Danny Geerdink,^a Christian Knittl-Frank,^a Marcel Kaiser^b and Nuno Maulide^{a,*}

^aInstitute of Organic Chemistry, University of Vienna, Vienna, 1090, Austria

^bSwiss Tropical and Public Health Institute, Basel, 4002, Switzerland

Quinine is undoubtedly one of the most famous molecules in organic synthesis [1]. Besides its application as last resort drug in the treatment of malaria [2], it is a privileged structure in asymmetric catalysis with excellent asymmetric induction [3].

Previously reported stereoselective total syntheses of Quinine share as common feature the late-stage construction of the quinuclidine moiety, which represents the central core of this natural product [4]. In this presentation, we will discuss how the use of catalytic C-H activation leads to a fundamentally different approach to this classic target [5-6], allowing the synthesis of this legendary natural product in only 10 steps [7]. Our strategy leads not only to Quinine itself but also enables the preparation of novel C-3 arylated analogues, one of which possesses significantly improved antimalarial activity when compared to the natural product *in vivo*.

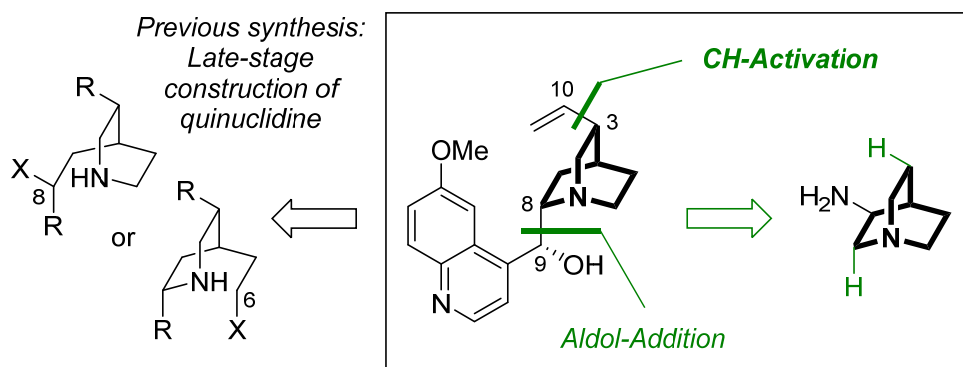


Figure 1. Synthesis of Quinine by C-H activation of an aminoquinoline precursor.

[1] J. I. Seeman, *Angew. Chem. Int. Ed.* **2007**, *46*, 1378-1413.

[2] J. Achan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J. Rosenthal, U. D'Allessandro, *Malar. J.* **2011**, *10*:144.

[3] S.-K. Tian, Y. Chen, J. Hang, P. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621-631.

[4] T. S. Kaufman, E. A. Ruveda, *Angew. Chem. Int. Ed.* **2005**, *44*, 854-885.

[5] J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754-8786.

[6] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.

[7] D. H. O'Donovan, P. Aillard, M. Berger, A. de la Torre, D. Petkova, C. Knittl-Frank, D. Geerdink, M. Kaiser, N. Maulide, *Angew. Chem. Int. Ed.* **2018**, *57*, 10737-10741.