Synthesis of β-hydroxy-α,α-dimethyl carboxylic esters via asymmetric Barbier reaction

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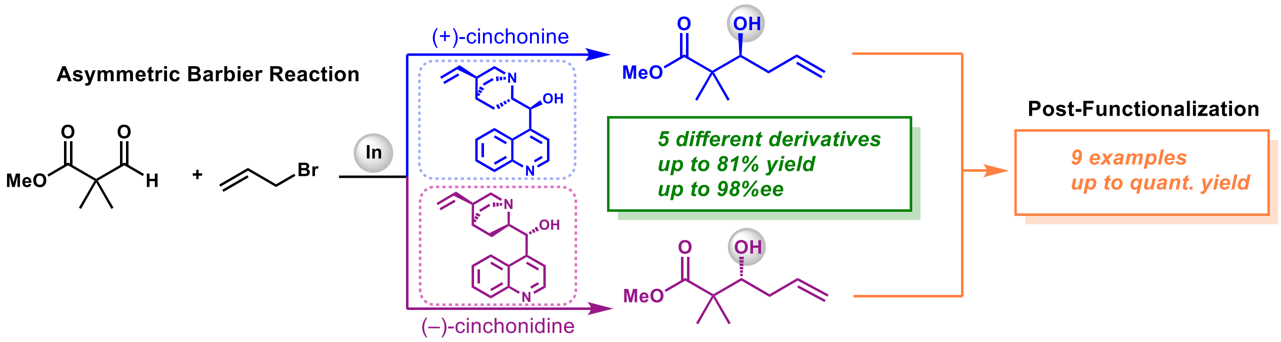

Despite the occurrence of the β-hydroxy-α,α-dimethyl carboxylic ester motif in many natural products[1-4] no attempt was made to synthesize this core structure via a racemic and enantioselective Barbier reaction until now. In this study, the optimized reaction conditions for the achiral Barbier reaction between allyl bromide and a 2,2-dimethyl-3-oxopropanoate were found, yielding the desired β-hydroxy-α,α-dimethyl carboxylic ester in up to 64%. Therefore, different metals, additives, solvents and solvent mixtures were tested. The optimized reaction conditions were then used to expand the substrate scope of the Barbier reaction by using five structurally different allylic and propargylic bromides. By using (+)-cinchonine and (–)-cinchonidine as chiral additives along with indium in a THF / hexane solvent mixture it was possible to obtain five different β-hydroxy-α,α-dimethyl carboxylic esters in an enantioenriched fashion with up to 81% yield and 98%*ee*. Additional post-functionalization provided nine different derivatives in up to quantitative yield.

[1-4] M. A. Rashid, C. L. Cantrell, K. R. Gustafson, M. R. Boyd, *J. Nat. Prod.* **2001**, *64*, 1341; K. C. Nicolaou, D. Schlawe, D. W. Kim, D. A. Longbottom, R. G. De Noronha, D. E. Lizos, R. R. Manam, D. J. Faulkner, *Chem. Eur. J.* **2005**, *11*, 6197; Y. Li, Y.-B. Liu, S.-S. Yu, Phytochem. Rev. 2013, 12, 305; Y. Li, Y.-B. Liu, J.-J. Zhang, Y.-H. Li, J.-D. Jiang, S.-S. Yu, S.-G. Ma, J. Qu, H.-N. Lv, *Org. Lett.* **2013**, *15*, 3074.