

Practical Methods for the Stereoselective Synthesis of Bioactive Amines

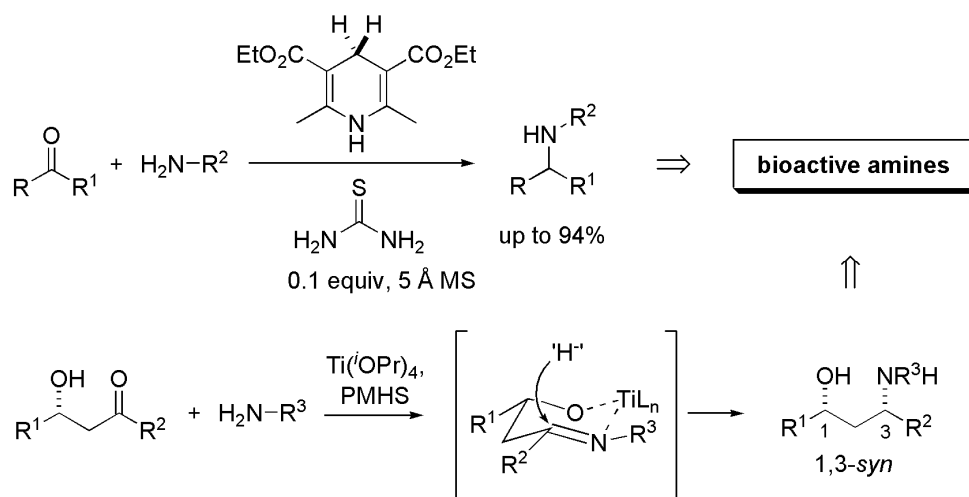
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Chiral amines are key structural elements in bioactive natural products and pharmaceuticals rendering their synthesis an objective of high priority from the perspective of natural product chemistry and drug discovery.^[1] Our research programmes are directed towards the development of novel - in comparison to known procedures more direct and effective - methods to synthesize chiral amines in only one chemical, *stereoselective* transformation from ketones as readily available building blocks ('direct asymmetric reductive amination').

Based on an innovative biomimetic approach, we have recently developed a novel strategy method for the direct reductive amination of ketones and aldehydes, which relies on selective formation of hydrogen bonds.^[2,3] It requires only catalytic amounts of thiourea as hydrogen bond donor and utilizes the Hantzsch ester for transfer hydrogenation. The efficiency of this method for the synthesis of bioactive amines was demonstrated. The mild and nonacidic conditions together with the high chemoselectivity of this protocol enable applications also to complex and/or acid-sensitive structures, as well as sterically hindered substrates.^[4] Furthermore, the underlying catalytic cycle and the modular structure of the organocatalyst allows the development of asymmetric variants.

In addition, we have devised a efficient procedures for the highly diastereoselective directed reductive amination β -hydroxy-amines for the preparation of 1,3-*syn* amino alcohols as key synthons in bioactive structures.^[1,5] The operationally simple protocol uses $\text{Ti}(\text{OPr})_4$ for coordination of the intermediate imino-alcohol and PMHS as reducing agent. Furthermore, the method was expanded to an asymmetric aldol-reductive amination sequence to allow a highly convergent synthesis of the hydroxy-amine core of the HIV-protease inhibitors ritonavir and lopinavir, presenting the shortest synthesis of these key pharmaceutical building blocks reported so far.



[1] F. Sasse, D. Menche, *Nature Chemical Biology*, in press.

[2] D. Menche, F. Arikian, *Synlett* **2006**, 841-844.

[3] D. Menche, J. Hassfeld, J. Li, G. Menche, S. Rudolph, A. Ritter, *Org. Lett.* **2006**, 8, 741-744.

[4] D. Menche, S. Böhm, J. Li, S. Rudolph, W. Zander, *Tetrahedron Lett.* **2007**, 48, 365-369.

[5] D. Menche, F. Arikian, J. Li, S. Rudolph, *Org. Lett.*, in press.