STEREOSELECTIVE CATALYTIC SYNTHETIC STRATEGIES FOR ACTIVE PHARMACEUTICAL INGREDIENTS (API) PRECURSORS

Margherita Pirola[1], Maurizio Benaglia[1]

[1]*Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, 20133 Milano Italy*

In the field of APIs (Active Pharmaceutical Ingredients), the industry is gradually progressing towards enantiopure formulations. In this context, chiral amines are unanimously considered a class of paramount importance, due to their widespread diffusion in a plethora of compounds. In the present study it is reported a catalytic, metal-free approach to the synthesis of chiral amines, direct precursors of two important APIs: Letermovir (**a**), a drug that shows great promise for the next-generation treatment of HCMV (human Cytomegalovirus) infection; fluorinated Retro-thiorphan peptide mimetic (**b**), a potent and selective inhibitor of the metalloproteinase NEP (neutral endopeptidase). The key step in both synthesis is the stereoselective catalytic reduction of an enamine moiety; we decided to perform this transformation using a metal-free reducing agent, trichlorosilane ($HSiCl_3$),[1] in combination with a catalytic amount of a chiral Lewis base (LB) as organocatalyst.[2] (Figure 1)

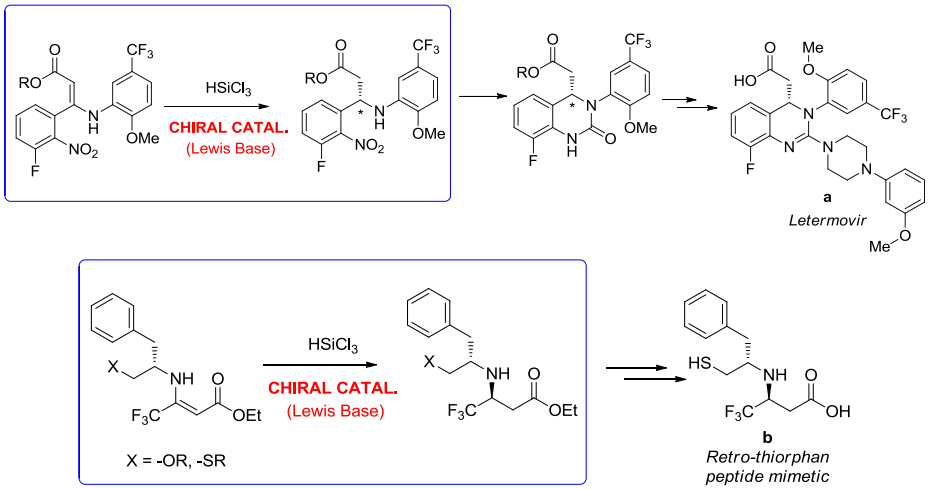

Figure 1

The use of $HSiCl_3$ in the presence of catalytic amounts of a chiral LB is a well-established methodology to perform enantioselective reduction of carbon-nitrogen double bonds, also exploiting micro- and mesoreactors to perform the synthesis of chiral APIs under continuous flow conditions.[3]

References:

[1] For some recent examples on the use of trichlorosilane for the synthesis of APIs see: Brenna, D.; Benaglia, M.; Porta, R.; Fernandes, S.D.; Burke, A.J. *Eur. J. Org. Chem*, **2016**, 39-44; Brenna, D.; Pirola, M.; Raimondi, L.; Burke, A.J.; Benaglia, M. *Bioorg. & Med. Chem.*, **2017**, doi: http://dx.doi.org/10.1016/j.bmc.2017.01.023.

[2] Brenna, D.; Porta, R.; Massolo, E.; Raimondi, L.; Benaglia, M. *Chem. Cat. Chem.* **2017**, 941 –945;

[3] Pirola, M.; Compostella, M.E.; Raimondi, L.; Puglisi, A.; Benaglia, M. *Synthesis*, **2018**, doi: 10.1055/s-0036-1591911.