Developments in asymmetric organocatalysis for the synthesis of original enantioenriched heterocyclic compounds

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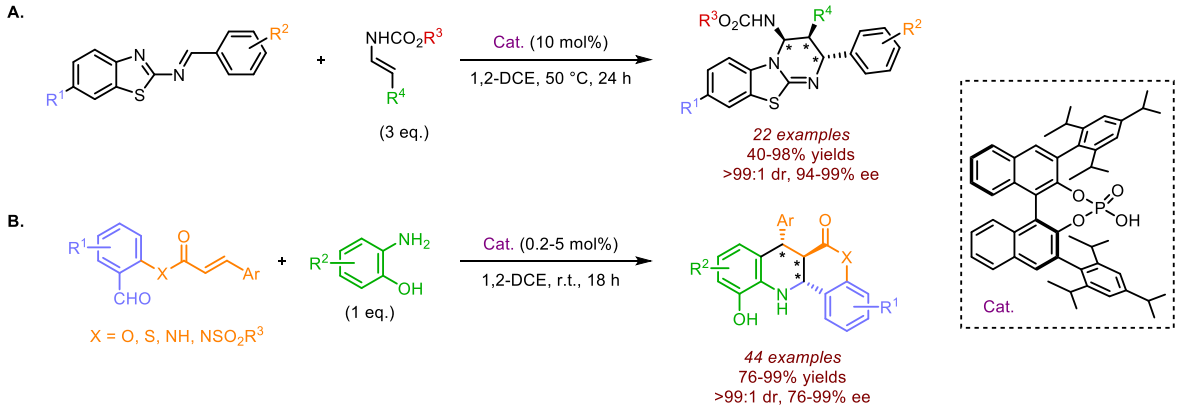
Heterocycles are the key elements of a wide range of natural products as well as drugs currently on the market. They become very attractive structural motifs in pharmaceutical research and their preparation still remains an unfulfilled need with broad perspectives. This work aimed to develop new, efficient and eco-friendly methodologies for the construction of original enantioenriched heterocyclic compounds. For this, asymmetric organocatalysis was selected as method of choice.

The previous expertise of our laboratory guided the selection of the organocatalysts towards the BINOL-based chiral phosphoric acids.[1] With the *green chemistry* concepts in mind, cycloadditions were selected as the best synthetic pathways. Thus, we developed two chiral phosphoric acid-catalyzed enantioselective inverse-electron-demand aza-Diels-Alder reactions which constitute robust, powerful and atom-economic routes to complex optically active heterocycles (Scheme 1).

The first part of this presentation will be devoted to the implementation of an intermolecular inverse-electron-demand aza-Diels-Alder reaction for the preparation of homobenzotetramisole-derived chiral cyclic isothioureas (A., Scheme 1).[2] The envisaged strategy allowed the formation of a large library of compounds, bearing three adjacent stereogenic centers, which were never synthesized before.
In the second part, the development of an intramolecular inverse-electron-demand aza-Diels-Alder reaction will be presented (B., Scheme 1).[3] This strategy provided access to chiral tetrahydrochromanoquinoline type tetracyclic structures with excellent results in terms of yields, enantio- and diastereoselectivities.



Scheme 1. Chiral phosphoric acid-catalyzed enantioselective aza-Diels-Alder reactions

[1] Parmar, D.; Sugiono, E., Raja, S.; Rueping, M. *Chem. Rev.,* **2014**, *114*, 9047; *Chem. Rev.,* **2017**, *117*, 10608.
[2] Jarrige, L.; Glavač, D.; Levitre, G.; Retailleau, P.; Bernadat, G.; Neuville, L.; Masson, G. *Chem. Sci.,* **2019**, *10*, 3765-3769.
[3] Jarrige, L.; Blanchard, F.; Masson, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 10573-10576.; Jarrige, L.; Gandon, V.; Masson, G. *in preparation*.