Vers la synthèse d'aza-hétérocycles saturés chiraux par Auto-Transfert d'Hydrogène (ATH)

Toward the synthesis of chiral saturated *N*-heterocycles *via* Borrowing Hydrogen approach (BH)

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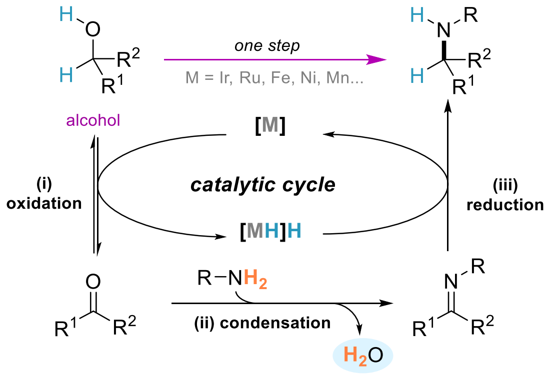
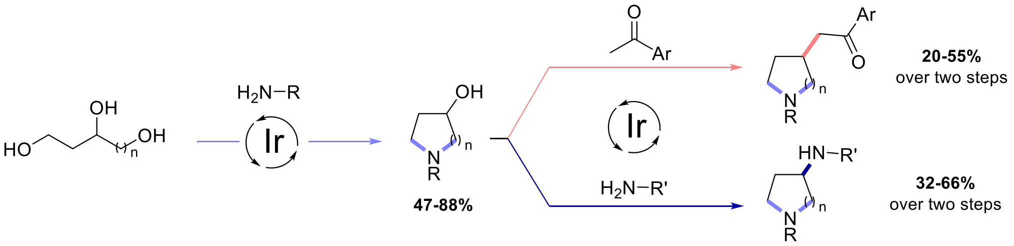
Over the last decades, the borrowing hydrogen (BH) methodology has emerged as an attractive strategy for the construction of novel CN bonds from an alcohol and an amine. This one-pot process involves a catalytic reduction of an unreactive alcohol into a carbonyl, followed by *in situ* imine formation and subsequent reduction. Metals such as Ir, Ru, Fe and Mn enable this transformation with water as the sole by-product (Scheme 1).[1] In recent years, our group has applied this strategy for the valorization of bio-based alcohols, such as isohexides and 1,4-D-sorbitan, to access chiral amines and amino alcohols.[2]



Scheme 1. Generalized BH catalytic cycle for CN bonds formation

More recently, we reported the use of this methodology for the construction of *N*-heterocycles, such piperidines and pyrrolidines (Scheme 2).[3] These valuable compounds occur in many natural alkaloids and rank as the most prevalent saturated heterocycles in drugs approved by the U.S. Food and Drug Administration.[4] The advantage of our approach lies in the use of triols, which provide access to pyrrolidinols and piperidinols that can be further post-functionalized through novel C–N[3] or C–C[5] bond formation.



Scheme 2. Previous work on Ir-catalyzed synthesis of pyrrolidinols and piperidinols[3b,5]

Despite significant advances reported in the literature,[3a,6,7] access to chiral saturated *N*-heterocycles *via* the BH methodology remains a major synthetic challenge. **The first objective of this PhD project will focus on the**

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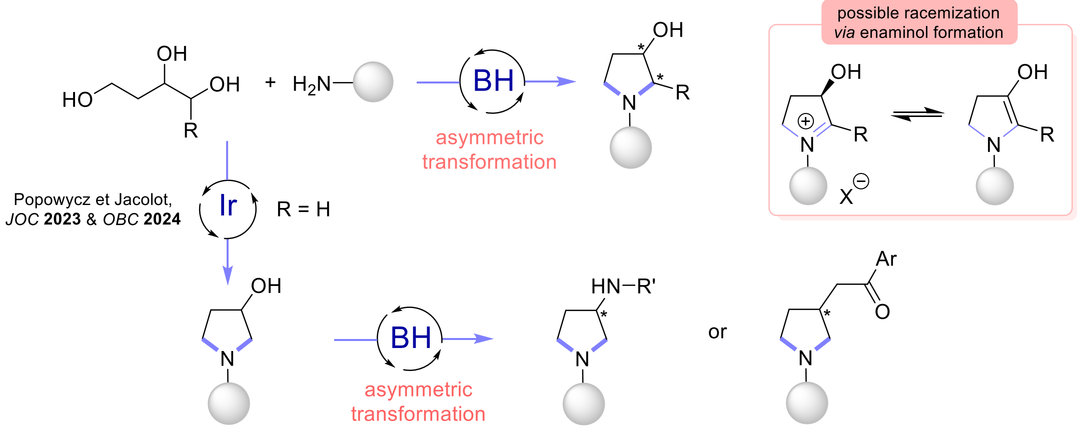
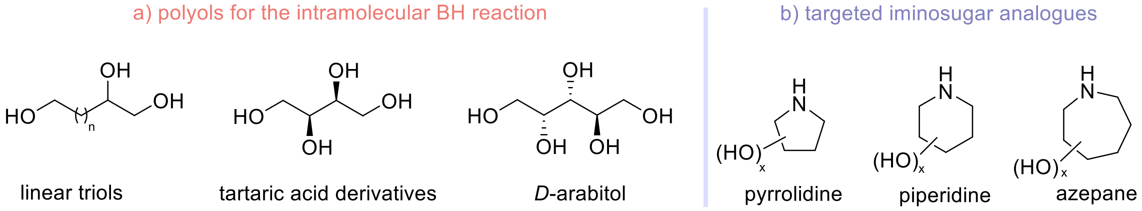
synthesis of chiral substituted piperidines and pyrrolidines directly from racemic triols. We have recently shown that the use of chiral 1,2,4-butanetriol results in a loss of chirality, most likely due to racemization *via* an enaminol intermediate (Scheme 3). Therefore, the reduction step appears to be enantiodetermining. To address this issue, two strategies will be investigated for the synthesis of chiral piperidinol and pyrrolidinol: (i) the use of chiral amines as chiral auxiliaries,[6] or (ii) cooperative catalysis combining a chiral phosphoric acid with a metal catalyst.[7] Taking advantage of our expertise on preparation and functionalization of saturated *N*-heterocycles, we also envision to tackle the preparation of chiral 3-substituted pyrrolidines and 4-substituted piperidines *via* asymmetric *N*[8] or *C*[9]-alkylation using racemic 3-pyrrolidinol and 4-piperidinol.



Scheme 3. Preparation of chiral saturated *N*-heterocycles *via* the BH methodology

The second objective of the project will exploit the BH process for the preparation of polyhydroxy-pyrrolidines and piperidines from biomass-derived polyols (pentoses such as ribose, arabinose, xylose, or tartaric acid derivatives - Scheme 4). These molecules, also known as iminosugars are known for their strong inhibitory potential against glucosidases, representing an interesting source for the development of new therapeutic agents (antiviral agents, diabetes treatment, etc.).[10] In addition to the synthetic challenges involving two fundamental issues: regioselectivity and stereoselectivity, these molecules may be subject to biological screening in collaboration with the university of Florence (Italy).



Scheme 4. a) polyols to be tested in BH amination reaction and b) structures of the targeted molecules

The PhD student will develop strong expertise in synthetic methodology and the structural characterization of chiral molecules. Although in full charge of the operational part, he or she will benefit from a participatory, reliable and guiding management from a close-knit team, with common processes and attached with the same care for quality. This constant support to autonomy and innovation will be reinforced by written and oral communication competencies. A solid background in synthetic organic chemistry and experience in NMR (^{1}H, ^{13}C and 2D) structural characterization will be appreciated. Overall, we are seeking a motivated, reliable and well-organized candidate who values teamwork.

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