SUJET DE THESE :

Fonctionnalisation d'alcools biosourcés par auto-transfert d'hydrogène

PHD PROPOSAL :

Functionalization of biobased alcohols *via* borrowing hydrogen methodology

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Keywords: bio-based alcohols, organometallic catalysis, synthetic methodology

Laboratory: Organic and Bioorganic Chemistry (COB), Institute for Molecular and Supramolecular Chemistry (ICBMS)

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Scientific content: The synthetic valorization of biomass-derived chemicals produced from carbohydrates has received great attention from the chemistry community to extend the wide applications of these so-called bio-based platforms. In parallel with the comprehensive efforts made for increasing the efficiency and sustainability of their production, research for finding them original applications *via* the development of innovative and modern methodologies has been also intensified. In that approach, we have been involved in the development of synthetic methodologies to transform bio-based platforms such as **isohexides**[1] and 5-HMF[2] into more complex molecules with high-added value such as amines. The advent of green chemistry has also promoted innovative methodologies such as borrowing hydrogen transformations for the construction of novel C-N (and C-C) bonds. A first step of catalytic dehydrogenation converts an unreactive alcohol into the corresponding carbonyl compound. Subsequent reaction with an amine leads to the imine *in situ*, which upon hydrogenation affords the desired product and water as sole by-product.[3] In this context, we have been interested to use this methodology to functionalize the bio-based isohexides in a more direct way, with a step economy, allowing also a lean in terms of procedure, time and waste.

We recently reported the first direct regio- and diastereoselective amination of isohexides (isosorbide and isomannide) through borrowing hydrogen methodology (BH) using a cooperative catalysis between an iridium catalyst and a Brønsted acid (Scheme 1).[4] The access to chiral amino-alcohol (NH_2-OH) and diamine (NH_2-NH_2) as interesting optically pure bio-based monomers was also proposed using the BH strategy as a sustainable route for their preparation.

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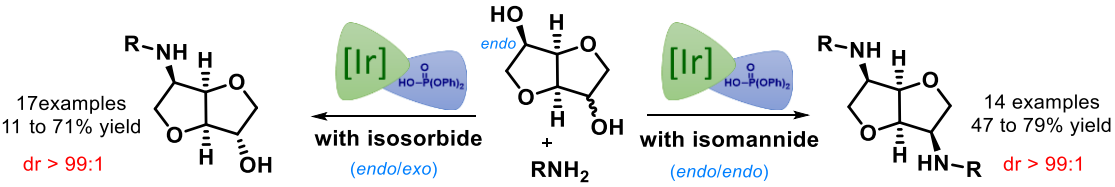
[1] Janvier, M.; Moebs-Sanchez, S.; Popowycz, F. *Chimia* **2016**, *70*, 77; Janvier, M.; Moebs-Sanchez, S. ; Popowycz, F. *Eur. J. Org. Chem*. **2016**, 2308.

[2] Fan, W. ; Verrier, C. ; Queneau, Y. ; Popowycz, F. *Curr. Org. Synth.* **2019**, *16*, 583 ; Fan, W.; Queneau, Y.; Popowycz, F. *Green Chem*. **2018**, *20*, 485

[3] Corma, A.; Navas, J.; Sabater, M. J. *Chem. Rev.* **2018**, *118*, 1410-1459

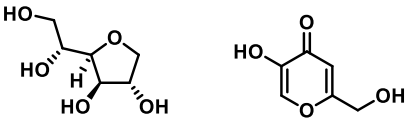
[4] Jacolot, M.; Moebs-Sanchez, S.; Popowycz, F. *J. Org. Chem.* **2018**, *83*, 9456; Bahé, F.; Grand, L.; Cartier, E.; Jacolot, M.; Moebs-Sanchez, S.; Portinha, D.; Fleury E.; Popowycz, F. *Eur. J. Org. Chem.* doi.org/10.1002/ejoc.201901661



Scheme 1 Direct regio- and diastereoselective amination of isohexides

The first part of the PhD project will be devoted to the more challenging direct C-alkylation with isohexides using the BH methodology. New functionalized isohexides could be obtained by **two-carbon elongation of isosorbide** using activated nucleophiles such as α-methyl ketones, acetonitrile or nitromethane. To our knowledge, a sole patent reported the access to C-alkylated isosorbide in 3 steps: i) secondary alcohol oxidation ii) HWE Reaction iii) olefin reduction[5] but no direct C-alkylation has been reported with isohexide derivatives. Valorization of those novel functionalized isohexides, promising bio-based monomers, will also be undertaken in collaboration with the IMP-INSA laboratory.

The second aspect of the research project will consist in extending our methodology to the direct functionalization (C-N and C-C bonds formation) of novel bio-based alcohols such as **1,4-D-sorbitan**, a chiral tetraol obtained by dehydration of sorbitol and precursor of isosorbide, and **kojic acid**, a by-product in the fermentation process of malting rice (Figure 1).



1,4-D-sorbitan Kojic acid

Figure 1 Bio-based alcohols

Required Background: We are looking for a highly motivated person with a strong background in organic chemistry (Master degree). Appropriate education profile should include experience in multi-step organic synthesis and associated analytical skills (NMR, MS, IR). Experience in organometallic chemistry and/or in asymmetric synthesis will be appreciated but are not mandatory. A good motivation to learn, communication skills, curiosity, and agreeable team spirit are also among important qualities.

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[5] Apgar, J. M. ; Arasappan, A.; Biftu, T.; Chen, P.; Feng, D.; Guidry, E.; Hicks, J.; Kekec, A.; Leavitt, K.; Li, B.; McCracken, T.; Sebhat, I. ; Qian, X. ; Wei, L. ; Wilkening, R. ; Wu, Z. PCT Int. Appl. (2014), WO 2014031515