

PhD Position at ENS de Lyon (starting sept 2022) – ED 206

Synthesis and applications of a highly preorganised bifunctionalised chiral platform

Synthèse et applications d'une plateforme chirale bifonctionnalisée rigide et fortement pré-organisée

Under the supervision of

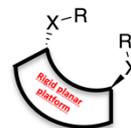
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Summary: Synthesis, characterisation and applications of a new class of highly preorganised chiral compounds with chelating properties supported by a rigid planar platform for various applications. The project will include development and evaluation of the performances of derivatives with potential applications in domains such as

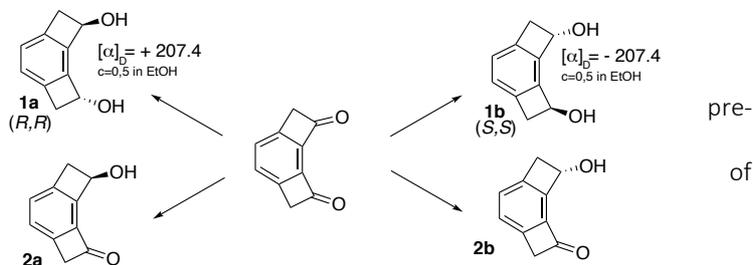
- New chiral catalysts
- « chiral building blocks » with axial chirality
- Access to helicoidal compounds with control of the helicity
- Templates for introducing chirality in material synthesis



Introduction

1,4-Diols are key intermediates because of their applications in the food and cosmetics industry, but also as precursors of plastics, pharmaceuticals, fibers, solvents or biologically active lactones. Their optically active versions also constitute structural units of a large number of biologically active compounds (pharmaceuticals, flavors or fragrances) but have also been used as ligands and chiral auxiliaries in asymmetric synthesis.¹ In particular, they are found as precursors of intermediates such as disubstituted pyrrolidines or phosphine derivatives used as ligands in asymmetric hydrogenations. For these reasons, the preparation of enantiopure 1,4-diols using efficient and selective methodologies is an area of interest in organic chemistry.

Preliminary Results: This project is the continuation of a first series of results allowing access to enantiomerically pure families of chiral compounds based on an unprecedented highly organized planar rigid platform. Synthetic pathway to enantiomerically pure **1a** and to one the keto-alcohols **2a**, **2b** have already been developed by our team from corresponding diketone via different enzymatic reduction conditions carried out in water. The starting diketone synthesis is well mastered by our team and can be obtained at gram scale (2-3g per batch) in two steps.



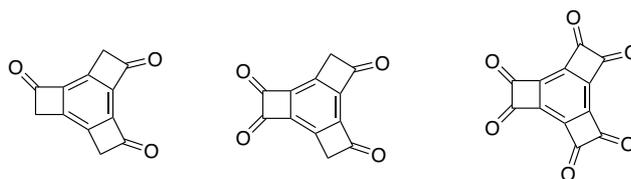
¹ a) Seebach, D.; Beck, A.K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138 b) Denmark, S.E.; Chang, W.-T.T.; Houk, K.N.; Liu, P. *J. Org. Chem.* **2015**, *80*, 313-366.

To date, our approach uses raw fruits or vegetables in water. That makes it low cost, green and very easy to implement. Raw carrots² led to enantiopure **1a** with complete reduction of the two ketones whereas horseradish led to an enantioselective monoreduction. If full characterization of **1a** and **1b**³ and absolute configuration assignment have already been performed through chiroptical techniques, the experimental conditions to access enantiomerically pure **1b**, **2a,b** still have to be further explored and optimized.

Project : A first objective of this PhD work will consist in screening a pre-selected set of enzymatic conditions to identify and optimize conditions to obtain all four enantiopure compounds **1** and **2**, and fully characterize them. We will include in our study the large family of isolated and commercially available Keto Reductases (KRED)⁴ as well as more conventional chiral hydride donors. Some keto-reductases are indeed known to give rather mono-reduction products on diketones while others lead preferentially to di-reduction products. In a second time, synthesis of diamino chiral analogues will be also investigated through the reduction of corresponding diimines using iminoreductases⁵.

Developing a route to the chiral keto-alcohols **2a, b** is also of great interest for us as it will induce differentiation of the two substitution moieties, allowing further functionalization reactions. We aim specifically to access to chiral amino alcohols to take advantage of the difference of affinity between N and O with silicon to explore how this platform could induce chirality into the array of siliceous framework of nanomaterials (imprint a chiral pattern to the pore wall surface of mesoporous silica nanospheres). This project will be performed in collaboration with the team of Pr Laurent Bonnevot at ENS de Lyon.

Evaluation of the conditions for stereoselective reduction on more complex known platforms (see below) will also be performed.



The originality of the project consists in the easy and convenient access to an unprecedented series of rigid planar platform with very strong preorganisation (elbow shaped) and bearing one or two chiral centers with heteroatoms pointing in two different half-spaces. Those building blocks may find applications in various fields such as asymmetric catalysis (chelating properties), materials for optic, chiral recognition and chiral helicoidal compounds or interactions. Some of them will be explored in the course of the PhD (at least starting on **1a** and **1b** being already available) in parallel of the development of the other targets.

Profile of the candidate

We are looking for a highly motivated candidate with a Master diploma in Organic chemistry. The applicant must have a strong background in organic chemistry and in spectroscopic techniques aimed for characterizing organic compounds (NMR, UV-visible, IR...). The synthetic part and the characterization of the compounds made by the applicant will constitute a large part of the work. Thus, a strong personal investment by the candidate is required to complete the subject of this PhD. It will also allow the applicant to develop its skills in enzymatic reaction, organic synthesis, spectroscopic characterization (NMR, HPLC, UV-Vis) and in chiroptical techniques (ECD, VCD and ROA).

A CV, a letter of motivation, a transcript of record of the Master and the e-mail coordinates of two persons that can recommend the applicant have to be sent to philippe.maurin@ens-lyon.fr

² Lacheretz R., Pardo D.G., Cossy J., *Org. Lett.*, **2009**, *11*, 1245-1248.

³ Compound **1b** was isolated by preparative chiral chromatography from a racemic mixture for characterization purpose

⁴ a) Kambourakis, S. *et al.*, *Adv. Synth. Catal.* **2006**, *348*, 1958 – 1969 b) Wells, A., S. *et al* *Org. Process Res. Dev.* **2020**, *24*, 6, 1131–1140

⁵ Turner, N. J. *et al.*, *Curr Opin Chem Biol*, **2017**, *37*, 19-25