

PhD Proposal - ADR Ecole Doctorale de Chimie 2020

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Dual catalysed enantioselective C-C bond formation as a new approach to the desymmetrisation of diols.

La formation énantioselective de liaison C-C par catalyse duale comme nouvelle approche en désymétrisation de diols.

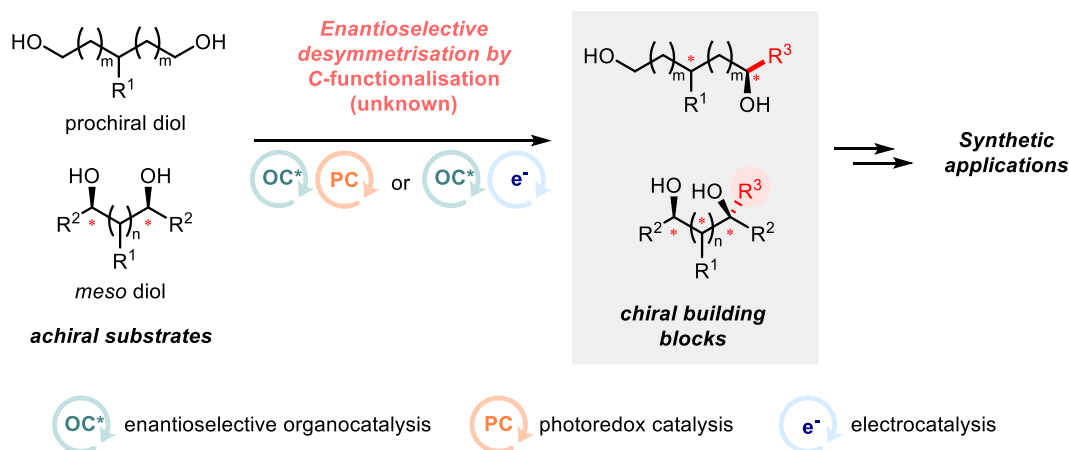
Key-words: *organic synthesis, diols, desymmetrisation, enantioselective organocatalysis, photoredox catalysis, electrosynthesis.*

CONTEXT: The enantioselective desymmetrisation of prochiral and *meso* diols is a powerful strategy to quickly access enantioenriched building blocks from readily accessible substrates.¹ The desymmetrisation of diols then constitute a key step in several total syntheses.² In the last few decades, the increasing interest to such transformations have resulted in the multiplication of innovative catalytic methodologies allowing the desymmetrisation of a broad range of symmetric diols. In view, pioneering enzymatic approaches have been competed by metal catalysed and above, organocatalytic approaches.³ From a chemical point of view, the differentiation of the two hydroxyl groups relies on the reactivity of the oxygen atom and results in acylation, oxidation, sulfonylation, etherification, phosphorylation and silylation reactions. In one respect, this general strategy can be considered as an enantioselective protection allowing the creation (or the revelation) of stereogenic centres but poorly increasing the molecular complexity. In this framework, **the desymmetrisation of diols by enantioselective C-C bond formation would be of tremendous interest in total synthesis.** However, this strategy remains highly challenging due to the difficulty to functionalise unreactive carbon atoms from alcohols and the lack of chiral catalysts able to ensure a good stereocontrol in such transformations.

¹ For selected reviews on this topic, see : a) M. D. Díaz-de-Villegas, K. A. Gálvez, R. Badorrey, M. P. López-Ramde-Víu, *Chem. Eur. J.* **2012**, *18*, 13920; b) A. Enriquez-García, E. P. Kündig, *Chem. Soc. Rev.* **2012**, *41*, 7803.

² For reviews partially addressing this topic, see: a) M. Wang; M. Feng; B. Tang; X. Jiang, *Tetrahedron Lett.* 2014, *55*, 7147; b) J. Merad, M. Candy, J.-M. Pons, C. Bressy, *Synthesis* **2017**, *49*, 1938.

³ For a review on this topic, see : A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson, D. J. Dixon, *Chem.Soc.Rev.* **2016**, *45*, 5474.



PhD PROJECT: From recently, our research group attempts to merge electron-transfer driven transformations⁴ and asymmetric organocatalysis to set up new efficient and innovative chemical reactions. In this context, the present project aims to develop a new synthetic methodology allowing the desymmetrisation of diols thanks to catalytic enantioselective C-C bond formations. Based on recent studies,⁵ we expect that this transformation could be achieved by combining visible-light photoredox catalysis or electrocatalysis and a finely designed chiral organocatalyst. In that case, the redox conditions should promote the generation of α -hydroxy radicals participating in the formation of new C-C bonds through Giese-type reactions. On the other hand, the chiral organocatalyst should ensure the enantiocontrol of the transformation. This exploratory and interdisciplinary project will require, the **design and the synthesis of new chiral organocatalysts** able to control the enantioselectivity of the process, the **optimization of the photocatalytic system**, extensive **mechanistic investigations** (NMR, cyclic voltammetry, luminescence experiments...). Alternative **electrochemical approaches** will be explored. Ultimately, **synthetic applications** will be investigated by targeting advanced polyol intermediates in the synthesis of polyketides.

Candidate profile: the candidate should demonstrate solid competences in organic synthesis and an experience in catalysis or multi-steps synthesis will be appreciated. Moreover, the candidate should be highly self-motivated, dynamic and appreciate to work as a team.

⁴ For recent examples, see : a) C. Adouama, R. Keyrouz, G. Pilet, C. Monnereau, D. Gueyrard, T. Noël and M. Médebielle. *Chem. Commun.* **2017**, 53, 5653; b) C. Adouama, M. E. Buden, W. D. Guerra, M. Puiatti, B. Joseph, S. M. Barolo, R. A. Rossi and M. Médebielle. *Org. Lett.* **2019**, 21, 320.

⁵ a) J. L. Jeffrey, J. A. Terrett, D. W. C. MacMillan, *Science* **2015**, 349, 1532; b) I. C. Wan, M. D. Witte, A. J. Minnaard, *Chem. Commun.* **2017**, 53, 4926; c) V. Dimakos, H. Y. Su, G. E. Garrett, M. S. Taylor, *J. Am. Chem. Soc.* **2019**, 141, 5149; d) K. Sakai, K. Oisaki, M. Kanai, *Adv. Synth. Catal.* **2020**, 362, 337.