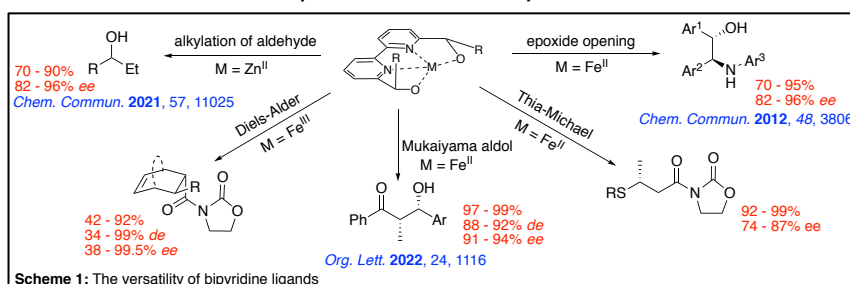


Stereoselective Epoxide Opening Reactions using Grafted Iron-bipyridine Catalysts in Continuous Flow

Context

We are in the midst of a societal awakening in which chemistry has a crucial role to play. Indeed, in the context of sustainable development, we need to design greener reactions using environmentally-friendly elements, freeing ourselves from the rare and often toxic transition metals and rare-earth elements. Another important parameter to consider is the possibility to scale up the processes in order to develop methodologies that can be transferred to industries. For example, low temperature reaction is highly difficult to achieve on batch industrial scale, often prohibiting their consideration in the development of new processes. The sustainability also needs to be addressed in terms of chemical waste and ligand reusability. While catalyst immobilization ensures its recyclability, flow chemistry enables better heat control through more efficient heat transfer, and thus, addressing the issue of sustainability and transferability to industries.



Prof. T. Ollevier has a renowned expertise in asymmetric catalysis using chiral bipyridine ligands (Scheme 1).¹ Noteworthy, he developed iron catalysis. Iron being one of the most abundant metal in the Earth's crust, developing its

chemistry is a strategic choice.² Dr. M. Roy, meanwhile, possesses a know-how in grafting silica particles, having developed chiral solid phases for HPLC separations with Dr. G. Félix before joining Sorbonne Université.³ Dr. Roy is currently working on catalysts immobilization to develop heterogeneous flow chemistry.⁴ Indeed, in addition to better heat transfer, flow chemistry is characterized by a high surface to volume ratio, and allows precise control of reaction time, which in turn influences reaction kinetics and selectivity, sometimes allowing reactions that fail under batch conditions.⁵

The present project is aiming at starting a research collaboration between Prof. T. Ollevier at Université Laval and Dr. M. Roy of the ROCS team at the Institut Parisien de Chimie Moléculaire (IPCM) at Sorbonne Université. It is important to note that numerous Sorbonne Université undergraduates are welcomed to Université Laval for summer internships, with Prof. Ollevier training several of them in his laboratory each year. We now wish to strengthen even more the partnership between the two universities by extending it to academic research through a cotutelle for a joined PhD project.

Scientific objectives

This project is aimed at developing heterogeneous asymmetric catalysis in flow chemistry. Our specific aims are:

- 1) To prepare a family of anchor-bearing bipyridines for immobilization.
- 2) To evaluate their potency in batch and homogeneous flow chemistry.
- 3) To graft them onto a solid support and to assess their potential in flow chemistry.

¹ Lauzon, S.; Schouwey, L.; Ollevier, T. *Org. Lett.* **2022**, *24*, 1116; Lauzon, S.; Ollevier, T. *Chem. Commun.* **2021**, *57*, 11025.

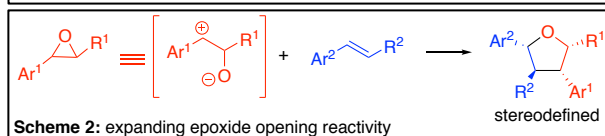
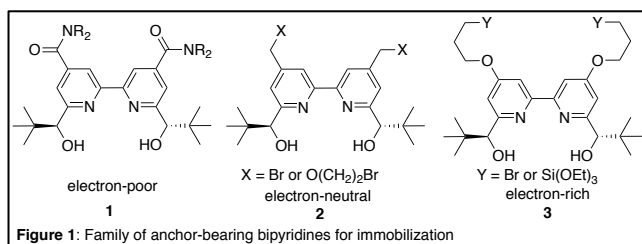
² Fürstner, A. *ACS Cent. Sci.* **2016**, *2*, 778.

³ Pistolozzi, M.; Fortugno, C.; Franchini, C.; Corbo, F.; Muraglia, M.; Roy, M.; Félix, G.; Bertucci, C. *J. Chromatogr. B* **2014**, *968*, 69; Droux, S.; Roy, M.; Félix, G. *J. Chromatogr. B* **2014**, *968*, 22.

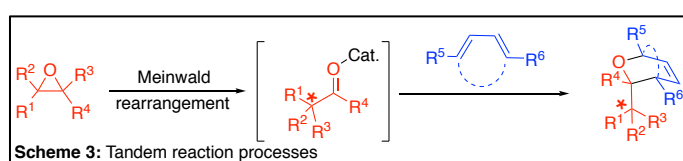
⁴ Kiala Kinkutu, G.; Louis, C.; Roy, M.; Blanchard, J.; Oble J. *Beilstein J. Org. Chem.* **2023**, *19*, 582.

⁵ Munirathinam, R.; Huskens, J.; Verboom, W. *Adv. Synth. Catal.* **2015**, *357*, 1093; Petersen, T. P.; Becker, M. R.; Knochel, P. *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.

Synthetic approach–Methodology



recyclability will be studied. In addition, new nucleophiles like alkenes or silyl enol ethers can be used to generate stereodefined tetrahydrofurans.⁷



functional group upon migration of a substituent.^{8a} Interestingly, the chirality of the bipyridine ligand could dictate which group will migrate, potentially overriding the natural order of group migration. The rearrangement will also be performed in tandem with other reactions,^{8b} such as a tandem Diels-Alder reaction. Reminiscent of epoxides, aziridines will also be considered.

For the last task, the most promising catalysts will be immobilized on silica or polystyrene particles.⁹ Once more, batch and flow conditions will be contemplated and compared.

We are planning a three-year cotutelle, thus, the student will have to meet the requirements of both doctoral schools, including the doctoral exam to become a PhD student in the Canadian university. The PhD proposal will be written during the first year and the oral exam will take place at Université Laval at the end of it. The student will also take two classes at Université Laval, one on each semester he will spend there. The remaining two years, which encompasses the PhD manuscript writing and defense, will be spent at Sorbonne University as described in the following diagram.

Year 1	Synthesis of substituted pyridines	Bipyridine synthesis
		Epoxide opening in batch and flow
Doctoral exam (manuscript PhD proposal writing and oral exam) at Université Laval		
Year 2	Epoxide rearrangement in batch and flow	Bipyridine immobilization
	Work on aziridines	
Year 3	Development of heterogeneous catalysis in batch and flow	Thesis manuscript writing and PhD defense
Sorbonne Université		Université Laval

⁶ Plancq, B.; Ollevier, T. *Chem. Commun.* **2012**, 48, 3806.

⁷ Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, 135, 644; Macias-Villamizar, V. E.; Cuca-Suarez, L.; Rodriguez, S.; Gonzalez, F. V. *Molecules*, **2020**, 25, 692; Langer, P.; Ackardt, T. *Angew. Chem. Int. Ed.* **2000**, 39, 4343.

⁸ a) Izquierdo, J.; Rodriguez, S.; Gonzalez, F. V. *Org. Lett.* **2011**, 13, 3856; b) Mamedova, V. L.; Khikmatova, G. Z. *Chem. Heterocycl. Compd.* **2017**, 53, 976.

⁹ Shabbir, S.; Lee, S.; Lim, M.; Lee, H.; Ko, H.; Lee, Y.; Rhee, H. *J. Organomet. Chem.* **2017**, 846, 296; Zhao, H.; Jiang, Y.; Chen, Q.; Cai, M. *New J. Chem.* **2015**, 39, 2106.