

Chemoenzymatic synthesis of optically active α -cyclopropylpyruvates and cyclobutenoates via enzyme-catalyzed carbene transfer with diazopyruvate



Raphaël Dollet,^{a,†} Juan D. Villada,^{b,†} Thomas Poisson,^a

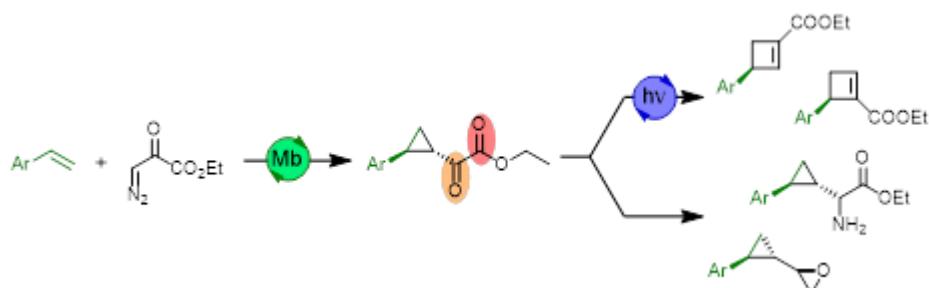
Rudi Fasan^{b,*} and Philippe Jubault^{a,*}

^aINSA Rouen Normandie, Univ Rouen Normandie, CNRS, Normandie Univ, COBRA UMR 6014, INC3M FR 3038, F-76000 Rouen, France, E-mail : philippe.jubault@insa-rouen.fr

^bDepartment of Chemistry and Biochemistry, University of Texas at Dallas, 800 W. Campbell Road, Richardson, TX 75080 (USA), E-mail: rudi.fasan@utdallas.edu

Cyclopropanes are very interesting scaffolds as they are present in the structure of many natural compounds and drugs. In recent years, many efforts have been made to develop diastereoselective and enantioselective cyclopropanation reactions, using mostly metallo-catalyzed reaction (Rh, Ru, Co for example).¹ During The last decade, biocatalytic strategies appeared very powerful approaches for stereoselective cyclopropanation reactions using engineered hemoproteins such as myoglobin and cytochrome P450s.² This strategy has proved a large substrate tolerance and also a high diastero- and enantio-selectivity. Using this method, we developed a highly biocatalytic enantioselective cyclopropanation using ethyl diazopyruvate (EDPv) as an original carbene source and compatible with a biocatalytic strategy.³

Moreover, to highlight the synthetic potential of our enantiopure cyclopropanes, we demonstrated their easily transformation into cyclobuteanoates through a photochemical ring expansion reaction, leading to product with a total transfer of chirality.



Scheme 1. Access to α -cyclopropyl pyruvates by biocatalysis and pyruvate pattern diversification.

References

- (a) H. Wang, D. M. Guptill, A. Varela-Alvarez, D. G. Musaev and H. M. L. Davies *Chem. Sci.* **2013**, 4, 2844–2850. (b) M. Bos, W.S. Huang, W, T. Poisson, X. Panneccoucke, A. B. Charette and P. Jubault *Angew. Chem. Int. Ed.* **2017**, 56, 13319–13323. (c) H. Inoue, N. Phan Thi Thanh, I. Fujisawa and S. Iwasa, *Org. Lett.* **2020**, 22, 1475–1479.
- (a) M. Bordeaux, V. Tyagi and R. Fasan *Angew. Chem. Int. Ed.* **2015**, 54, 1744–1748. (b) K. E. Hernandez, H. Renata, R. D. Lewis, S. B. J. Kan, C. Zhang, J. Forte, D. Rozzell, J. A. McIntosh and F. H. Arnold *ACS Catal.* **2016**, 6, 7810–7813. (c) D. Nam, V. Steck, R. J. Potenzino and R. Fasan *J. Am. Chem. Soc.* **2021**, 143, 2221–2231. (d) R. Mao, D. J. Wackelin, C. S. Jamieson, T. Rogge, S. Gao, A. Das, D. M. Taylor, K. N. Houk and F. H. Arnold *J. Am. Chem. Soc.* **2023**, 145, 16176–16185.
- R. Dollet, J. D. Villada, T. Poisson, R. Fasan, P. Jubaut *Org. Chem. Front.*, **2024**, DOI: 10.1039/D3QO01987J