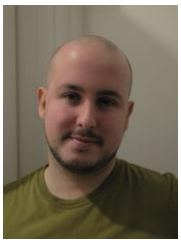
IRON-CATALYZED C(SP^3)-H LACTONIZATION USING HYDROXYLAMINE DERIVATIVES

Hugo Esteves,[1] Tania Xavier,[1] Sonia Lajnef,[1] Fabienne Peyrot,[1,2] Guillaume Lefevre,[3] Guillaume Prestat,[1] Farouk Berhal[1]

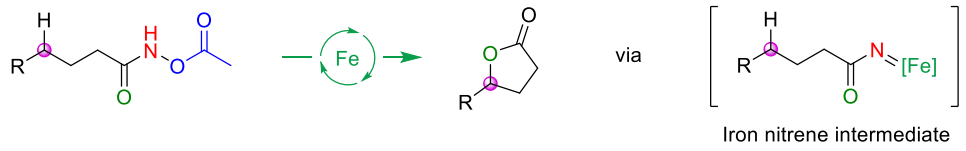


[1] Université Paris Cité, CNRS, Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologiques, F-75006 Paris, France.
[2] Sorbonne-Université, Institut National Supérieur du Professorat et de l'Education (INSPE) de l'Académie de Paris, F-75016 Paris, France.
[3] CNRS, Institute of Chemistry for Life and Health Sciences, CSB2D, Chimie ParisTech, PSL University, 75005 Paris, France.

Lactones are highly valuable intermediates in the synthesis of many natural products, as well as prominent scaffolds in bioactive compounds.[1] Direct functionalization of C-H bonds represents the most straightforward route to these compounds in the context of sustainable chemistry. There has thus been an ongoing effort into the development of efficient and robust methodologies for C-O bond formation.[2] However, most of these developed processes are poorly atom economical, require external oxidants, and are based on the use of rare and expensive transition metals such as palladium.[3]

Nitrenes are well-known for their ability to perform aziridination, alkene difunctionalization and C-H amination.[4] Our group aims to achieve sustainable nitrene transfer processes using iron as the catalyst and hydroxylamines as the nitrogen source.[5] Iron is cheap, abundant, and non-toxic while hydroxylamines are bench-stable, easily accessible, and can form a metallonitrene intermediate in the presence of a transition-metal without the addition of external oxidants.[6] During our investigation on C-H amination, we serendipitously discovered that nitrene chemistry can also allow C-H oxygenation.

In this communication, we will present in detail our recently developed iron-catalyzed lactonization using hydroxylamine derivatives. This sustainable process allows for an efficient access to new C(sp^3)-O bonds, yielding various lactone derivatives in good-to-excellent yields using very mild conditions. A comprehensive mechanistic study has also been carried out to shed light on the mechanism of this transformation.



- Mild conditions
- Various C(sp^3)-H bonds functionalized
- 28 examples
- Up to 88% yield
- Extensive mechanistic study including EPR spectroscopy & DFT calculations

References

[1] Janecki, T. *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*, 1st ed.; Wiley-VCH: Weinheim, **2013**.
[2] Xu, L.-P.; Qian, S.; Zhuang, Z. *et al. Nat Commun.* **2022**, 13, 315.
[3] (a) Liu, B.; Shi, B.-F. *Synlett*. **2016**, 27, 2396-2400. (b) Zhuang, Z.; Yu, J.-Q. *Nature*. **2020**, 577, 656–659.
[4] Wang, Y.-C.; Lai, X.-J.; Huang, K.; Yadav, S.; Qiu, G.; Zhang, L.; Zhou, H. *Org. Chem. Front.* **2021**, 8, 1677-1693.
[5] (a) Manick, A.-D.; Aubert, S.; Yalcouye, B.; Prangé, T.; Berhal, F.; Prestat, G. *Chem. Eur. J.* **2018**, 24, 11485-11492. (b) Abi Fayssal, S.; Giungi, A.; Berhal, F.; Prestat, G. *Org. Process Res. Dev.* **2020**, 24, 695-703. (c) Kirby, G.; Grimaud, L.; Vitale, R., M.; Prestat, G.; Berhal, F. *Green Chem.* **2021**, 23, 9428-9432. (d) Kirby, G.; Prestat, G.; Berhal, F. *J. Org. Chem.* **2023**, 88, 4720-4729.
[6] Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, 127, 14198-14199.