SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

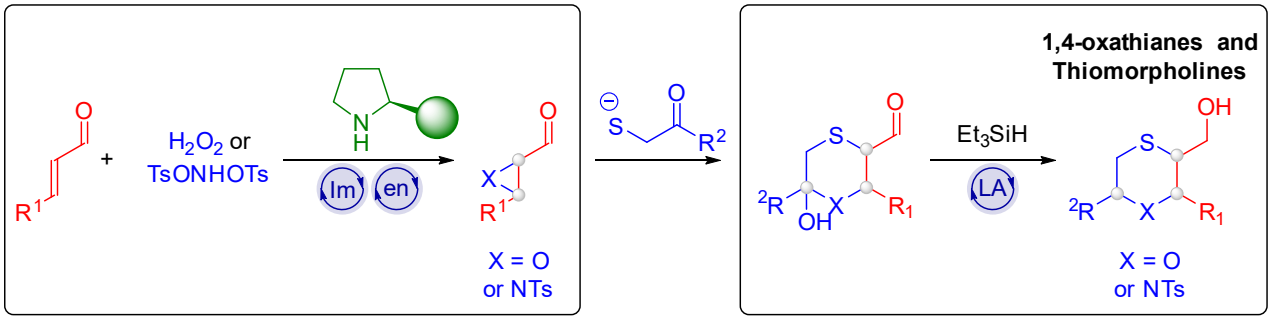
Asymmetric Synthesis of 1,4-Oxachalcogenanes and 1,4-Azochalcogenanes

Pedro Jorge Hauy,[1*] Natalia Takata,[1] Alcindo Aparecido dos Santos[1] and Bruno Matos Paz[1]
1) Chemistry Institute, University of São Paulo, IQ-USP
**e-mail: pedro.hauy@usp.br*

Keywords: *Catalysis, stereoselective synthesis, 1,4-oxachalcogenane*

ABSTRACT

Morpholine is a heterocyclic compound present in a wide range of commercial drugs as well as drug candidates. Its prominent in medicinal chemistry due to it's great pharmacological potential, as well synthetic feasibility.[1] 1,4-Oxathianes and thiomorpholines have the potential to serve as bioisosteres for 1,4-dioxanes and morpholines,[2] allowing them to imitate their pharmacological effects while potentially presenting improved or altered biological activity. This attribute renders them advantageous in drug discovery programs, facilitating the generation of analogs of current medications with potential enhancements of effectiveness and bioavailability. We were able to synthetize 1,4-oxathianes and thiomorpholines enantioselectively via organocatalysis. By reacting chiral *α*,*β*-epoxy **1**[3] or *α*,*β*-*N*-Tosyl-aziridine aldehydes **2**[4] with *in situ* generated *α*-keto thiolates **3**,[5] a ring opening driven by ring-strain followed by a hemiacetalization/hemiamination afforded the key heterocyclic aldehyde **4**. Reduction with a mild reducing agent in the presence of Lewis acids afforded de desired 1,4-Oxathianes and thiomorpholines.



ACKNOWLEDGEMENTS

We would like to acknowledge the financial support granted by the São Paulo State Research Foundation (Processo FAPESP Grant 2022/14310-0), the Brazilian National Council for Scientific and Technological Development (CNPq Scholarship 161543/2021-9) and the University of São Paulo (USP Grant 2022.1.9345.1.2).

REFERENCES

(1) *Morpholine as a Privileged Structure: A Review on the Medicinal Chemistry and Pharmacological Activity of Morpholine Containing Bioactive Molecules*. Kourounakis, A. P.; Xanthopoulos, D.; Tzara, A. *Med. Res. Rev.* **2020**, *40*, 709–752.
(2) *Investigation of chalcogen bioisosteric replacement in a series of heterocyclic inhibitors of tryptophan 2,3-dioxygenase.* Kozlova, A., Thabault, L., Dauguet, N., Deskeuvre, M., Stroobant, V., Pilotte, L., Liberelle, M., Van den Eynde, B., & Frédérick, R. *Eur. J. Med. Chem.* **2022**, *227*, 113892.
(3) *Asymmetric Organocatalytic Epoxidation of α,β-Unsaturated Aldehydes with Hydrogen Peroxide.* Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965.
(4) *Organocatalytic Preparation of Simple β-Hydroxy and β-Amino Esters: Low Catalyst Loadings and Gram-Scale Synthesis* Jiang, H.; Gschwend, B.; Albrecht, Ł.; Anker Jørgensen, K. *Org. Lett.* **2010**, *12*, 5052–5055.
(5) *The Preparation of 1,4-Dithienes.* Baker, R. H.; Barkenbus, C. *J. Am. Chem. Soc.* **1936**, *58*, 262–264.