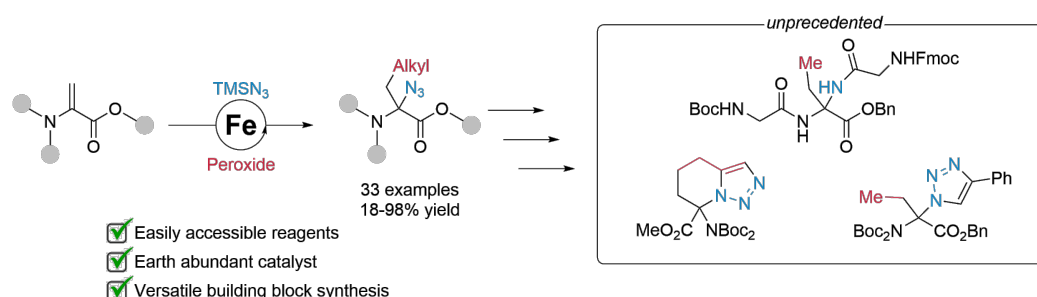


Iron-catalyzed synthesis of α -azido amino acids: an easy access to versatile building blocks

P. Palamini¹, E. M. D. Allouche¹, J. Waser^{1*}

¹École Polytechnique Fédérale de Lausanne, Laboratory of Catalysis and Organic Synthesis

The pharmaceutical industry is interested in the development of new transformations to access diversified amino acids and peptides.¹ Non-proteinogenic amino acids (NPAAs) show great potential for the optimization of various biological properties (half-life, specificity, potency, membrane permeability and conformation) of peptide drugs.² However, the use of α -nitrogen substituted amino acids has been scarce due to their challenging synthesis.^{3,4} To access these underdeveloped scaffolds, we turned ourselves to earth abundant metal catalysis. In the last decades, the use of first-row transition metals such as iron has emerged as an alternative to the well-established transition-metal catalysts such as rhodium, palladium or iridium. In addition to their high availability and reduced cost, they now appear as key catalysts for the development of new radical-mediated synthetic routes.⁵ In this context, we developed an easy access to α -azido amino acids from dehydroamino acids as alkyl radical acceptors using iron catalysis. Various azidated amino acids, both proteinogenic and non-natural analogues, were successfully synthesized. The obtained compounds appear as versatile building blocks that could be transformed into various unprecedented scaffolds including aminal-type peptides, [7,7]-substituted tetrahydro-triazolopyridine and α -alkyl- α -triazole α -amino acids.⁶



[1] Lei Wang, Nanxi Wang, Wenping Zhang, Xurui Cheng, Zhibin Yan, Gang Shao, Xi Wang, Rui Wang, Caiyun Fu. *Signal Transduct. Target. Ther.* **2022**, 7, 48.

[2] Yun Ding, Joey Paolo Ting, Jinsha Liu, Shams Al-Azzam, Priyanka Pandya, Sepideh Afshar. *Amino Acids* **2020**, 52, 1207–1226.

[3] Emmanuelle M. D. Allouche, Raphael Simonet-Davin, Jerome Waser. *Chem. Eur. J.* **2022**, 28, e2022003

[4] Alexandra Bosnidou, Kilian Muñiz. *Angew. Chem. Int. Ed.* **2019**, 58, 7485–7489.

[5] Lie-Jie Cheng, Neal P. Mankad. *Chem. Soc. Rev.* **2020**, 49, 8036–8064.

[6] Manuscript submitted