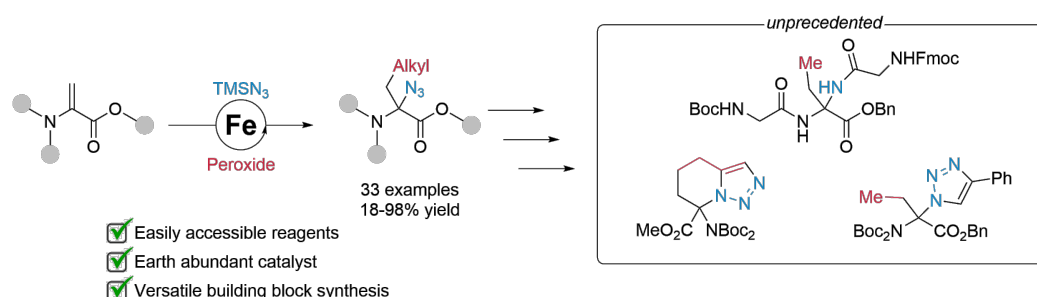


## Iron-catalyzed synthesis of $\alpha$ -azido amino acids: an easy access to versatile building blocks

P. Palamini<sup>1</sup>, E. M. D. Allouche<sup>1</sup>, J. Waser<sup>1\*</sup>

<sup>1</sup>École 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.<sup>1</sup> 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.<sup>2</sup> However, the use of  $\alpha$ -nitrogen substituted amino acids has been scarce due to their challenging synthesis.<sup>3,4</sup> 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.<sup>5</sup> In this context, we developed an easy access to  $\alpha$ -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  $\alpha$ -alkyl- $\alpha$ -triazole  $\alpha$ -amino acids.<sup>6</sup>



[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