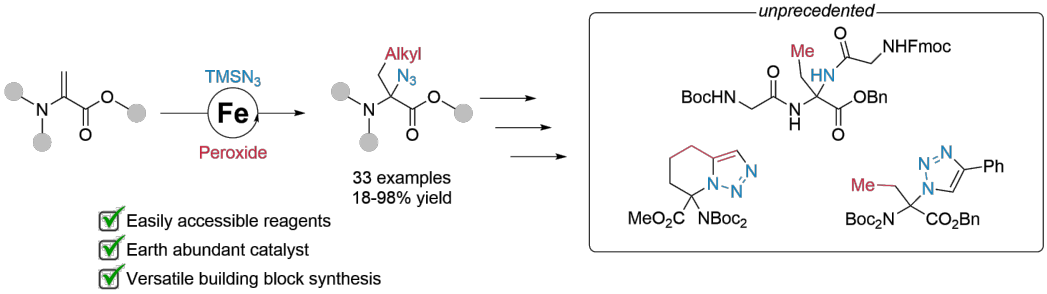
Iron-catalyzed synthesis of alpha-azido amino acids: an easy access to versatile building blocks

P. Palamini[1], E. M. D. Allouche[1], J. Waser[1]*

[1]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.[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