Electrochemical Homo- and Cross- Annulation of Alkynes and Nitriles for the Regioselective Synthesis of 3,6-Diarylpyridines

M.Lepori[a], M. Ghosh[a], T. Mandal[a], J.P. Barham[a] and O.Reiser[a]

[a] *Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany*
e-mail: Mattia.Lepori@chemie.uni-regensburg.de

The pyridine moiety is among the most extensively used heterocycles in the field of drug design[1] as well as has agrochemical applications. [2] Given this importance and ubiquity, different pathways were developed for the synthesis of substituted pyridine-containing scaffolds. Besides classic strategies (*e.g.* Pd-catalyzed Suzuki cross coupling), one of the most promising approaches consists of a [2+2+2] intramolecular annulation of alkynes and nitriles. However, the methods reported so far relies on the use of transition metals or are mainly limited to the coupling of two identical alkynes.[3-4] Herein, we report an electrochemical strategy for a metal- and oxidant- free, green regioselective synthesis of 3,6-diarylpyridines (**Figure 1**).[5] Harvesting electrochemical energy and catalytic amounts of triphenylamine (**TPA**), two identical or two different alkynes can be coupled with a nitrile, resulting in a broad applicability in both homo- and cross- coupling to generate disubstituted pyridines. The method is also applicable for late-stage functionalization of pharmaceutical and bioactive molecules. Notably, the reaction demonstrated to be scalable up to gram scale in both batch and continuous flow, utilizing a cutting-edge electrochemical continuous flow reactor (FAVO^{TM} CreaFlow reactor).[6]

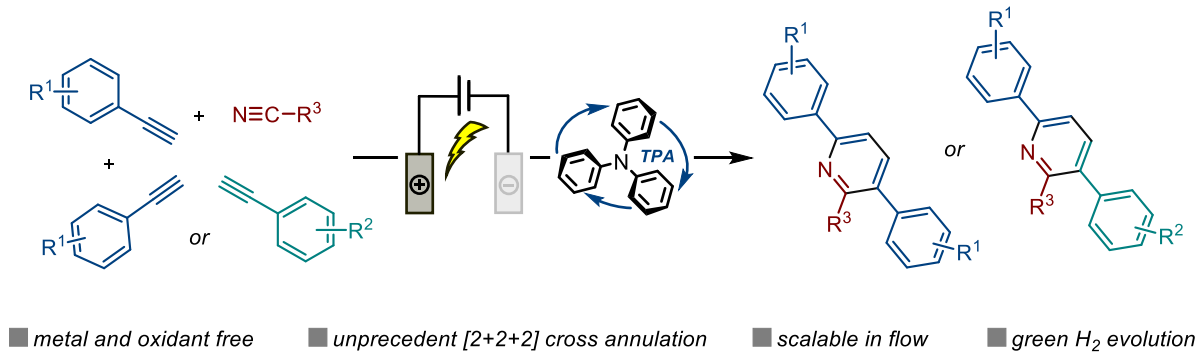

***Figure 1**: Electrochemical [2+2+2] annulation of alkynes and nitriles.*

[1] S. De, A. Kumar, S.K. Shah, S. Kazi, N. Sarkar, S. Banerjee, S. Dey, *RSC Adv.* **2022**, *12*, 15835.
[2] A.Y. Guan, C.L. Liu, X.F. Sun, Y. Xie, M.A. Wang, *Bioorg. Med. Chem.* **2016**, *24*,342.
[3] I. Thiel, H. Jiao, A. Spannenber, M. Hapke, *Eur. J. Org. Chem.* **2013**, *19*, 2548.
[4] . K. Wang, L.G. Meng, L. Wang, *Org. Lett.* **2017**, *19*, 1958.
[5] *Manuscript in preparation*.
[6] https://www.creaflow.be/favotm-5-flow-reactor.