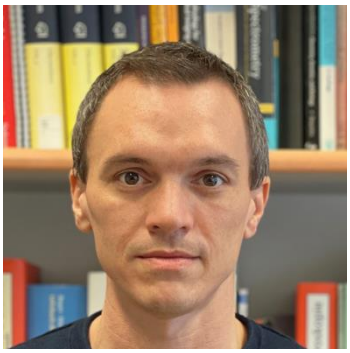
# Exit the Cube: Next-Level Molecular Tools for Click-Triggered Bioorthogonal Bond-Cleavage

**Hannes Mikula**
TU Vienna

Getreidemarkt 9/163, 1060 Vienna, Austria
Email: hannes.mikula@tuwien.ac.at | Tel: +43-1-58801-163721 |
Web: https://www.mikulalab.com

**Abstract**
Bioorthogonal chemistry is bridging the divide between static chemical connectivity and the dynamic physiologic regulation of molecular state, enabling transformations that drive multiple technologies. The toolbox of bioorthogonal reactions has expanded substantially in the past decade, providing chemists with highly selective methods to achieve efficient ligation in complex biological environments, even in living systems. In parallel, the concept of bioorthogonal bond-cleavage has further expanded the repertoire of *in vivo* chemical methods, with the reactions of tetrazines (Tz) and *trans*-cyclooctenes (TCO) standing out due to exceptional reaction kinetics and structural versatility. This emerging class of molecular transformations has enabled a variety of applications, including new concepts for drug delivery and activation, as well as methods to spatiotemporally control the function of molecules in biological environments. However, despite significant advances in the field, existing chemical tools have fundamentally lacked the performance characteristics needed to make more advanced strategies plausible. Based on our rigorous pursuit of mechanistic understanding, we have developed molecular tools with exceptional chemical performance and unique capabilities. Our $C_2$-symmetric TCO-linker ($C_2$TCO) can be cleaved efficiently within minutes or even seconds, which allowed us to introduce bioorthogonal turn-off as a new concept. Based on these insights and the unexpected discovery of a new release mechanism, we were able to develop next-level molecular tools, including Tz scissors and the click-cleavable linker iTCO, finally enabling nearly instantaneous bioorthogonal bond-cleavage under physiological conditions.

**Bio**



Hannes Mikula is Associate Professor of Chemical Biology at the Institute of Applied Synthetic Chemistry at TU Vienna, Austria. His research focuses on the development of biocompatible transformations with unmatched chemical performance and unique capabilities. One of the main goals of his group is to design new chemical tools for ultrafast bioorthogonal bond-cleavage and application of this concept in chemical biology and molecular targeting. Hannes trained as a synthetic chemist, finishing his studies in 2008 and, following a 1-year career break (parental leave), received his Ph.D. in 2014. Fascinated by the development of bioorthogonal chemistry, he then joined the group of Prof. Ralph Weissleder at the Massachusetts General Hospital & Harvard Medical School as a postdoctoral fellow supported by the Austrian Science Fund (FWF). He returned to TU Vienna in 2016 as a young principal investigator and became a research group leader in 2018. Hannes was awarded a START grant by the FWF (the highest award for young scientists in Austria) in 2021 and received an ERC Starting Grant from the European Research Council in 2022, aiming for the development of bioorthogonal strategies to control and navigate molecules in cellular environments.