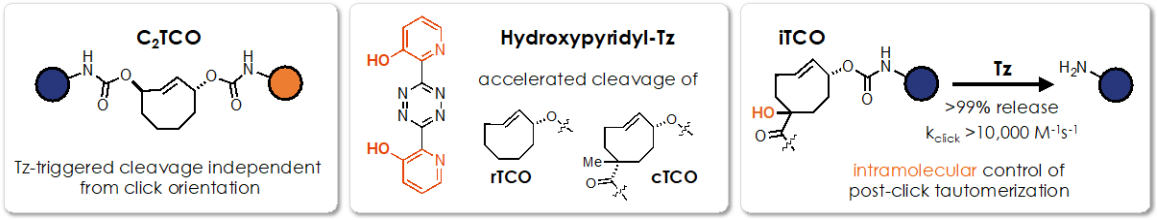
Unlocking Chemistry: Next-Level Bioorthogonal Click-To-Release

Hannes Mikula
Institute of Applied Synthetic Chemistry, TU Wien, Vienna, Austria

Bioorthogonal chemistry provides powerful tools for selective ligation and bond-cleavage in complex biological environments. Among these, the tetrazine/*trans*-cyclooctene (Tz/TCO) click-to-release reaction enables controlled molecular disassembly, advancing targeted drug delivery and prodrug activation, with first clinical trials now underway. However, conventional Tz/TCO systems suffered from incomplete or slow click-to-release.[1] We developed next-level molecular tools with exceptional kinetics and precision: a C_2-symmetric TCO (C_2TCO) that enables near-instantaneous cleavage,[2] hydroxypyridyl-tetrazines that achieve complete and accelerated release,[3] and the intramolecularly controlled iTCO that allows highly reactive tetrazines to function as efficient molecular scissors, elevating click-to-release chemistry to the performance level required for efficient *in vivo* application.[4] Together, these tools enable fast and near-quantitative bioorthogonal bond-cleavage and cascade reactions with ON/OFF control at molecular precision. This presentation will highlight the molecular designs and mechanistic insights that led us to redefine the performance limits of Tz/TCO click-to-release chemistry.



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