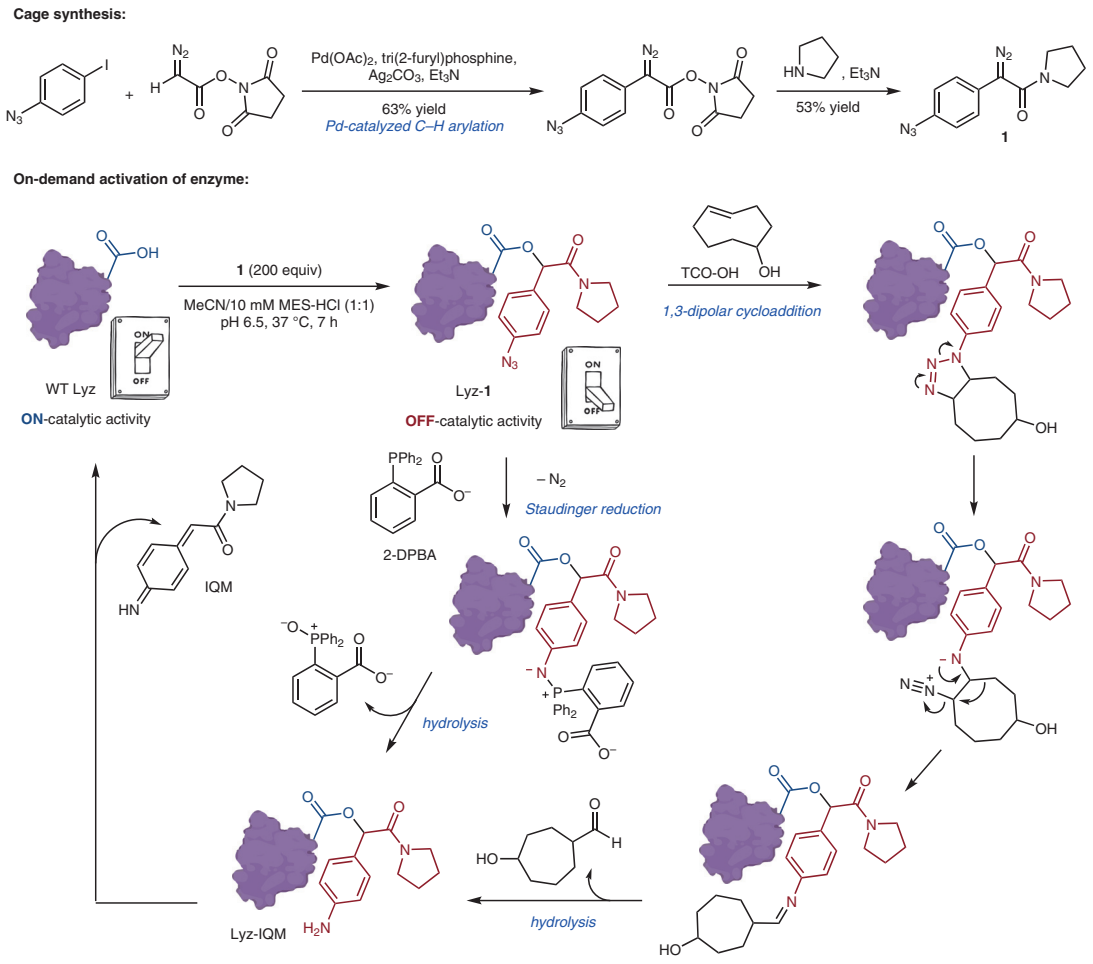
Y. D. PETRI, C. S. GUTIERREZ, R. T. RAINES* (MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, USA)

Chemoselective Caging of Carboxyl Groups for On-Demand Protein Activation with Small Molecules
*Angew. Chem. Int. Ed.* **2023**, *62*, e202215614 DOI: 10.1002/anie.202215614.

# Controlling Protein Activity with a Carboxyl Group Cage




**Significance:** Amino acid cages are valuable chemical tools for controlling the activity and interactions of proteins. Protein cages have been primarily designed for Lys, Tyr, and Sec amino acids. In this study, the authors expand this toolbox by developing diazo-based compound **1** that can selectively cage solvent-exposed amino acids containing carboxyl groups. The caged residues can be released, in a traceless fashion, with two small-molecule triggers.

**Comment:** To demonstrate the utility of their tool, the authors caged lysozyme (Lyz), which has a catalytic Glu35 with elevated p$K_a$. Lyz-**1** shows severely reduced catalytic activity, which can be recovered through the addition of commercially available 2-DPBA and TCO-OH. The addition of these two small-molecule triggers leads to uncaging to the wild-type Lyz enzyme.

**SYNFACTS Contributors:** Dirk Trauner, Tongil Ko
Synfacts 2023, 19(07), 0721 Published online: 16.06.2023
**DOI:** 10.1055/s-0042-1751934; **Reg-No.:** T05323SF



**Category**
Innovative Drug Discovery and Development

**Key words**
cage
1,3-dipolar cycloaddition
Staudinger reduction

Synfact of the Month