## Category

Innovative Drug
Discovery and
Development

## Controlling Protein Activity with a Carboxyl Group Cage

Cage synthesis:

On-demand activation of enzyme:




$-\mathrm{N}_{2}$






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 $\mathbf{1}$ 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 Glu 35 with elevated $\mathrm{p} K_{\mathrm{a}}$. Lyz- $\mathbf{1}$ 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.

