Chemoselective and site-selective peptide and native protein modification enabled by aldehyde auto-oxidation and multi-component approach

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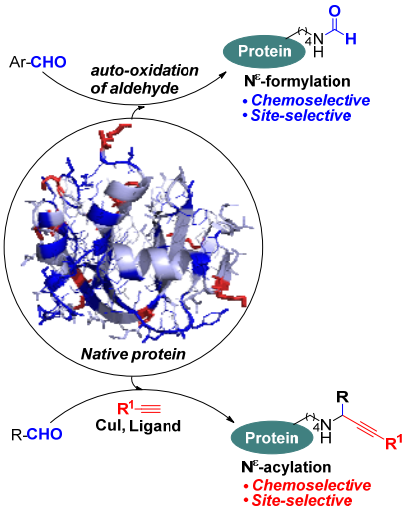
Absract: Attachment of tags to the proteins provides utility platforms for biologics, biomaterials, and biophysics.[1] A chemical technology that can deliver single-site labeling of endogenous proteins would be ideal to meet these requirements. The challenge in the identification of a site with unique reactivity emerges from the abundance of functional groups with similar reactivity. This is complicated further by the presence of multiple copies of each residue. We have developed chemical approaches that offer single-site installation of formyl[2] and propargyl[3] groups to ε-amine of native proteins in physiological conditions. The formylation methodology is enabled by aldehyde auto-oxidation re-routing for regulated formate generation and reversible N-terminus protection. Partial interception of the formylation route delivers site-selective acylation. On the other hand, propargylation is enabled by a multicomponent transformation in the presence of protein, aldehyde, acetylene, and Cu-ligand complex. In both the methodologies, single ε-amine is labeled in a pool of nucleophilic residues, α-amine and several copies of ε-amine. These results validate that subtle difference in reactivity of protein backbone residues can be distinguished through a chemical transformation. The multi-dimensional roles played by the aldehyde drives the selectivity.



[1] (a) Krall, N.; da Cruz, F. P.; Boutureira, O.; Bernardes, G. J. L. *Nat. Chem.* **2016**, *8*, 103-113. (b) Walsh, G.; Jefferis, R. *Nat. Biotechnol.* **2006**, *24*, 1241-1252.
[2] Landa, P.; Adusumalli, S. R.; Chilamari, M.; Rai, V. *Chem. Commun.***2016**, **DOI**: 10.1039/C6CC09555K.
[3] Chilamari, M.; Landa, P.; Rai, V. *Patent application 201621030484,* **2016**.