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WHEN IT TAKES THREE TO TANGO: A COMBINATION CATALYST FOR PROTEIN POST-TRANSLATIONAL MODIFICATIONS

In nature, a single genome can encode for multiple proteins, giving rise to the over 25 thousand proteins currently identified as part of the human proteome. This staggering array of proteins is achieved via natural processes within cells that can direct protein post-translational modifications or PTMs. PTMs are chemical modifications that can regulate interactions between nucleic acids, proteins, and other cellular molecules, and thereby control protein expression. By installing non-natural PTMs within cells, researchers have sought to understand and control enzyme activity, signal transduction, and transcriptional processes.

Abiotic catalysis is one such methodology that can alter protein behavior via chemical reactions driven by non-natural PTMs within cells. However, for this approach to be successful, PTMs must alter a targeted site on the selected protein while bypassing other highly reactive molecules present in cells. By introducing a three-component catalyst system that consists of a protein ligand, a hydroxamic acid Lewis base, and a diol moiety, Shigehiro Kawashima, Kenzo Yamatsugu, Motomu Kanai, and co-workers have demonstrated the ability to enable highly specific acetylation reactions to install PTMs (DOI: 10.1021/jacs.1c07060). The high specificity of this reaction within living cells improves the translation potential for technologies such as Proteolysis TArgeting Chimeras (PROTACs) that are aimed at degrading proteins, thereby providing a mechanism by which therapeutic challenges such as drug resistance toward cancer treatments and bacterial infections can be overcome. Targeted in-cell catalysis will expand mechanisms by which the pathogenesis of diseases such as cancer, neurodegenerative disorders, heart diseases, and diabetes are currently studied, thereby paving the way for novel treatment modalities and disease prevention.

Devatha P. Nair Ph.D.

EFFICIENT CATALYTIC ACCESS TOWARD α-CHIRAL SECONDARY ALKYL AMINES

Chiral amines are ubiquitous in a vast array of essential scaffolds, including pharmaceuticals, agrochemicals, bioactive compounds, and ligands used in the asymmetric synthesis of chiral molecules. However, their synthesis is often tricky and is faced with numerous challenges when traditional methods of alkylating nitrogen-containing motifs are employed. Furthermore, in cases where reactivity is possible, obtaining higher levels of enantioselectivity often comes up as a significant layered challenge. Therefore, a general catalytic approach toward synthesizing α-chiral secondary alkyl amines has enormous potential to impact the broader field of synthetic organic chemistry.

Xin-Yuan Liu and co-workers have now reported a copper-catalyzed method to access α-chiral secondary alkyl amines (DOI: 10.1021/jacs.1c07726). Specifically, the authors have developed an enantioconvergent N-alkylation of sulfoximines with racemic secondary alkyl halides. Using this method, the authors enable access to enantioenriched primary amines using an ammonia surrogate. With this method's overall efficiency, operational simplicity, and practicality, this newly disclosed strategy is expected to find general use in the large-scale synthesis of chiral amines in drug discovery and development endeavors.

Suman Chakrabarty Ph.D.

A SPOONFUL OF THIOL MAKES THE REACTION GO FASTER

Hydrogen gas is attractive for multiple applications, from rocket to car fuel, but, as the famous example of the Hindenburg showed, it is also highly flammable. Because of this, safely storing the gas is a challenge. One way to meet this challenge is to store hydrogen gas precursors, like methanol, rather than hydrogen gas itself. Hydrogen gas would then be released from a methanol and water mixture through the reforming process. But there are downsides to this method: it needs elevated temperatures, high pressures for heterogeneous catalysis methods, or the addition of a strong base for homogeneous catalysis methods, all of which limit the range of applications such a storage system can be used for.

Now, David Milstein and co-workers share a way to reform methanol without the use of a base using a ruthenium pincer complex (DOI: 10.1021/jacs.1c09007). Initially, the reaction without the base was pretty sluggish. But the addition of thiol, 1 equiv per catalyst, improved the catalytic activity by 2 orders of magnitude and resulted in a turnover of over 130,000—a record for a homogeneously catalyzed methanol-reforming reaction that is base-free. This highly efficient and speedy reaction not only could bring hydrogen storage to a wider range of applications but also, utilizing its acceleration effect by

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thiol, could be used to tackle other challenging transformations as well like C−H activation.

Attabey Rodríguez Benítez

A FORMAL AFFAIR: RATIONALLY DESIGNED TIED AND LINKED PROTEINS

Proteins are chains of amino acids that form distinct three-dimensional conformations to achieve biological functionality. From highly ordered beta sheets to alpha helices, the intricacies of protein folding is a biological marvel. A subset of proteins harbor an additional layer of complexity, having self-entangled or "knotted" backbones with complex topologies whose assembly is ill-defined by fundamental local contact properties, and presents complications for characterizing these curious structures.

Though a puzzling mechanism in the protein folding paradigm, self-entangled protein structures are ubiquitous in biology, albeit, lesser explored. In part this is because it is sterically and energetically unfavorable for long peptides to fold into highly knotted structures. To overcome these limitations, Yuuki Inomata, Tomohisa Sawada, and Makoto Fujita designed a synthetic strategy to rationally design self-entangled nanostructures via short-chain peptide folding, and assembly triggered by metal coordination, generating highly complex synthetic torus knot and link structures (DOI: 10.1021/jacs.1c08094). The authors describe, for the first time, generating torus knots with nine or more crossings and characterize a novel ring-opening oligomerization which facilitates the reaction. The approach is incredibly versatile and stereoselective, ultimately enabling the rational design of diverse topological structures. Moreover, this synthetic approach is apt to help clarify the properties of knotted proteins to further deconstruct this mysterious element of protein biology and perhaps shed light on how these intricate topologies might support or sustain biological functions.

Kelly Montgomery

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