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IMPROVING ON NATURE FOR ENZYMATIC NITROGEN INSERTION

Biological systems use various classes of enzymes to catalyze C−H functionalization reactions. The most studied of these enzymes are the cytochrome P450 heme monooxygenases, which use a reactive Fe-oxo species to selectively hydroxylate substrates using molecular oxygen. Analogous reactions that functionalize substrates with nitrogen would ease access to a plethora of different aminated products; however, enzymatic heteroatom C−H functionalization in biological systems is restricted to oxygen and halogen introduction.

Frances Arnold, Jennifer Hirschi, Soumitra Athavale, and their colleagues sought to end this disparity by developing new-to-nature heme-containing nitrene transferases for enzymatic nitrogen insertion into unactivated C−H bonds (DOI: 10.1021/jacs.2c08285). The researchers used directed evolution to develop two different lineages of enzymes for animation and amidation. Both of these lineages showed high promiscuity toward a wide array of substrates. Computational studies and kinetic isotope effects suggest that the enzymes catalyze these reactions using a stepwise radical pathway involving an irreversible, enantiodetermining hydrogen atom transfer, followed by a lower-barrier diastereoselectivity-determining radical rebound step. In-enzyme molecular dynamics simulations revealed a predominantly hydrophobic pocket in these enzymes with favorable dispersion interactions with the substrate. These enzymes offer a new biochemical path for accessing nitrogen-containing compounds.

Christen Brownlee

TWIST ON, TWIST OFF: A NEW STRATEGY FOR THE DESIGN OF FLUORESCENT PROBES

Fluorescence imaging is a key technique for studying the behavior of biomolecules. To make biomolecules visible by spectroscopy, fluorogenic probes—typically small molecules that undergo a fluorescence on/off change in response to a target biomolecule—must be used to dye the biomolecule. A fundamental understanding of the mechanisms responsible for fluorescence on/off control is required to improve the field and develop new fluorogenic dyes using rational molecular design strategies. Previously, strategies such as photon-induced electron transfer, Förster resonance energy transfer, and spirocyclization have been established based on analysis of the quenching mechanism of non-fluorescent derivatives of fluorophores.

Now, Yasuteru Urano and co-workers have established a new strategy to rationally develop new fluorogenic probes by controlling the twisted intramolecular charge transfer (TICT) process (DOI: 10.1021/jacs.2c06397). The fluorescence quenching mechanism of *N*-phenyl rhodamine dyes was investigated via time-dependent density functional theory calculations and photophysical evaluation of derivatives. Using the TCIT-based design strategy, a new set of fluorogenic probes were designed, synthesized, and utilized for fluorescence imaging of biosamples. This new strategy for rational design of fluorogenic probes promises important applications in improving the way we study biomolecules in the life sciences and medicinal research.

Jenna N. Humke

A NEW APPROACH TO THE BIOSYNTHESIS OF NON-NATURAL DEPSIPEPTIDES BY SITE-SPECIFIC INSERTION OF HYDROXY ACIDS

Depsipeptides are bicyclic peptides in which amide bonds are replaced with CO_2 ester bonds. They are of great interest because of their microbial and anticancer properties.

A team of researchers led by Donald Hilvert now report the development of a directed strategy to convert natural α-amino acid-accepting non-ribosomal peptide synthetase domains into α-hydroxy acid-accepting variants (DOI: 10.1021/jacs.2c07013). These variants open up the possibility to probe and tune the activities of diverse peptide (molecules consisting of 2−50 amino acids) in a simple and predictable way.

The researchers based their research on an earlier developed high-throughput yeast display assay that they used to reprogram a covalent amino-acid-specific A domain for the recognition of an α-hydroxy acid. This research opens the door to tailored synthetases for sustainable production of a wide range of non-natural depsipetides.

Alexander Hellemans

A RADICAL APPROACH TO ALKENE DIFUNCTIONALIZATION

Alkenes are ubiquitous feedstock chemicals routinely employed as synthons for the organic synthesis of valuable complex molecules in academia and industry. In particular, carboamination of alkenes has emerged as a powerful approach

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toward synthesizing amine-containing scaffolds. However, this transformation is primarily executed using catalysts from rare-earth transition metals featuring polar mechanistic paradigms. As the synthetic community moves toward developing greener and more sustainable chemical transformations, the quest to develop powerful catalysts using more abundant first-row transition metals is seeing a new resurgence.

Now Zong-Liang Li, Xin-Yuan Liu, and co-workers report the development of a radical alkene carboamination with sulfoximines (DOI: 10.1021/jacs.2c08035). The team designed a copper catalysis featuring unique counterion and ligand effects to promote the reaction of alkenes with alkyl halides and sulfoximines. A net three-component enantioselective coupling enables the formation of chiral C−N bonds. The method developed is general and demonstrates tolerance of a variety of non-participating functional groups, and it is expected to be of general interest to academic and industrial organic chemists.

Suman Chakrabarty Ph.D.

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