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Spotlights on Recent *JACS* Publications

GIVING DIRECTION FROM ACROSS THE RING

Debabrata Maiti and co-workers report the selective functionalization of a carbon−hydrogen bond on an aromatic ring. C−H bond activation is an important tool in the synthesis of complex molecules; here the authors have expanded the toolbox by demonstrating bond functionalization directed by a substituent on the opposite side of the aromatic ring (DOI: 10.1021/jacs.5b06793).

The so-called directing group forms a complex with an organometallic catalyst involved in the reaction, and the size and structure of the directing group dictate which position on a molecule becomes modified. *Ortho-* and, more recently, *meta-*functionalization of simple aromatics is well-known, but *para-*functionalization has remained a significant challenge. With the new strategy, the researchers achieve selective functionalization—with product ratios of up to 20:1 for desired vs undesired isomers—of the carbon−hydrogen bond *para* to the directing group.

In the reaction, the substrate and catalyst form a relatively rigid 17-membered metallacycle that aligns the reactants in a configuration to generate product in yields of up to 82%. A silicon atom in the metallacycle is another feature that improves outcomes for this bond functionalization reaction. The authors demonstrate the utility of this new carbon−hydrogen bond activation method via the formation of both carbon−carbon and carbon−oxygen bonds.

Sonja Krane, Ph.D.

CHEMOENZYMATIC APPROACH TO GLYCAN SYNTHESIS

Glycobiology is a notoriously challenging field of study. One obstacle is that glycans are difficult to generate uniformly in vitro, complicating structure−function studies. Now, Barbara Imperiali and colleagues describe a chemoenzymatic strategy for synthesizing specific azide-modified heptasaccharides from the pathogen *Campylobacter jejuni* (DOI: 10.1021/jacs.5b07146).

C. jejuni glycoproteins contain a common seven-sugar glycan, produced by enzymes in the N-linked protein glycosylation (Pgl) pathway. First, Imperiali and her team confirm that the Pgl enzymes that add the first three sugars in the glycan core can use azide-modified substrates. By combining different substrates and Pgl enzymes, they then synthesize specific trisaccharides and a complete heptasaccharide, all of which incorporate azide functional groups, and subsequently they transfer those saccharide structures from their lipid carriers to a peptide substrate. Finally, the researchers use "click chemistry" to couple fluorophores and biotin tags to azide-modified sugar chains, demonstrating the research utility of these modifications.

Given the power of bioinformatics to identify similar gene clusters in other organisms, "we anticipate that this study will provide a guide for the application of parallel approaches for the preparation of glycoconjugate targets from other pathogenic and symbiotic bacteria," the authors write.

Jeffrey M. Perkel

SIMPLE AMINO ACID SWITCH STRENGTHENS TIES THAT HELP COLLAGEN BIND

Collagen could be called "The Force" of biology: it is the most abundant animal protein, supporting skin, bones, muscles, and other connective tissue with its triple-helical structure. In medicine, collagen is used to help heal wounds, regenerate tissues, and graft bones, among other applications. But some patients' immune response to the protein, and its potential for instability when isolated, can complicate these solutions.

As a result, researchers have tried to modify the protein to produce more durable versions. Now David Chenoweth and colleagues report a simple substitution with the most stabilizing effect on this protein observed to date (DOI: 10.1021/jacs.5b04590). The authors replace the glycine residues in collagen's peptide backbone with the synthetic amino acid aza-glycine, which has a nitrogen atom in place of the natural residue's α-carbon. On the basis of modeling studies, the researchers suggest that the aza-glycine modification stabilizes the protein by increasing hydrogen bonding across collagen's three strands.

The refashioned collagen could be used to design new biomimetic materials and expand the protein's utility in biomedical applications that may benefit from improved stability.

Deirdre Lockwood, Ph.D.

SELF-ASSEMBLY: NOT AS SIMPLE AS IT SEEMS

Self-assembly processes can be exploited to construct a variety of nanomaterials, including one-dimensional supramolecular polymers made from small molecules. While these self-assembly processes are often simple and straightforward—like a basic nucleation mechanism, for example—recent studies on natural protein-based fibrils suggest that aggregation can involve multiple concurrent pathways.

In a new study, Tom F. A. de Greef, E. W. Meijer, and their co-workers show that elucidating these complex self-assembly mechanisms requires an equally complex method that combines experimental data with thermodynamic and kinetic modeling (DOI: 10.1021/jacs.5b08138). The researchers characterize the self-assembly using various spectroscopic techniques. The results highlight two possible mechanisms in which these polymers aggregate: a single nucleation−elongation pathway, or two parallel pathways in which shorter disordered aggregates compete with longer structured fibers for free monomers.

When the correct mechanism cannot be distinguished by thermodynamic modeling, the researchers turn to kinetic modeling using data from temperature-jump spectroscopy. The results show that the two parallel, competing pathways is in fact the correct aggregation mechanism. The authors suggest that combining multiple spectroscopic techniques with modeling can be used to gain a better understanding of other self-assembly mechanisms, providing opportunities to direct assembly toward more desired morphologies.

Christen Brownlee

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