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Spotlights on Recent *JACS* Publications

REDEFINING PROTEINS AS NEW MATERIAL FOR NANOPARTICLES

For drug delivery and other biomedical applications, crafting nanoparticles from proteins can have numerous advantages, such as biodegradability, stability, low immunogenicity and toxicity, and easy functionalization. However, the methods used to synthesize protein nanoparticles thus far have involved the dissolution or denaturation of the native protein structure into hydrophobic materials or a stabilizing cross-linking step using toxic compounds, and these modifications could compromise the proteins' safety *in vivo*. Peter Wich and co-workers develop a new method for creating stable protein nanoparticles able to carry pharmaceutical cargo that requires no denaturation, cross-linking, or additional surfactants (DOI: 10.1021/jacs.6b06243).

The new method instead involves PEGylating the protein's surface, rendering it fully soluble in an organic solvent while preserving the initial structure of the protein. After evaporation of the solvent, nanoparticles composed of tightly packed proteins remain. Lysozyme-based nanoparticles prepared using this technique can successfully trap the cancer drug doxorubicin and ferry it into cells with controlled cellular uptake. The researchers demonstrate the utility of this technique on several different proteins as well, including β-lactoglobulin, ovalbumin, and human serum albumin. This method offers a novel and versatile way to form protein nanoparticles for technological and pharmaceutical innovations.

Christen Brownlee

CLEAVE THE SINGLES TO MINGLE

Organic reactivity generally originates from unsaturated π-bonds and polar σ-bonds, forming the basis for most common transformations of synthetic value. On the other hand, nonpolar σ-bonds, in particular C−C bonds, are thermodynamically stable and therefore very difficult to activate, making them less attractive for organic synthesis.

However, in certain cases, C−C bonds can be selectively cleaved by transition metal complexes, opening new synthetic opportunities. In a recent Perspective, Masahiro Murakami and Naoki Ishida present an overview of transition-metal-catalyzed C−C bond cleavage reactions in both historical and modern contexts, demonstrating their potential as innovative and useful tools for synthetic chemistry (DOI: 10.1021/jacs.6b01656). In particular, the scientists point out that photochemical activation can be a convenient approach to energetically disfavored intermediates.

Although current C−C bond activation examples involve special strained bonding scenarios in most cases, the synergistic combination of light and conventional metal catalysts may be applicable to more general situations, thereby expanding the scope of substrates. Successful C−C bond functionalization will help eliminate the need for many steps and provide new inspiration for simpler and more straightforward synthetic designs.

Xin Su, Ph.D.

FOR A THERAPEUTIC TRIP, PACK A NANOSUITCASE

Building nanostructures from DNA has been a boon for a multitude of applications, offering particular promise in biomedical fields such as drug delivery. DNA cages and scaffolds have already proven their worth in delivering oligonucleotide drugs and small-molecule pharmaceuticals and could potentially form the basis for vaccines. However, precisely targeting cell types of interest with these nanostructures remains a challenge. Hanadi Sleiman and co-workers report a new way to release cargo in the right place: by packaging it in DNA "nanosuitcases", minimal cages that open with a messenger RNA or microRNA trigger (DOI: 10.1021/jacs.6b08369).

The prism-shaped cages contain two gating strands that unwind by strand displacement when they encounter selected oligonucleotide triggers, allowing them to retain their siRNA cargo until they meet the appropriate cytoplasmic genetic markers. Tests show that these structures assemble in nearly quantitative yield and maintain their integrity under biological conditions, including elevated temperatures, reduced magnesium concentrations, and the presence of nucleases. Assessing the effectiveness against two targets, luciferase and fatty acid synthase, the researchers find that these "nanosuitcases" readily release their cargo on demand. The authors suggest that the ability to tailor to these constructs could give them wide applicability in a number of different biological systems.

Christen Brownlee

C−C CROSS-COUPLING WITH ALCOHOLS

Transition-metal-catalyzed cross-coupling reactions, usually between electrophilic halides and organometallic-based nucleophilic partners, play a central role in modern synthetic organic chemistry. Common nucleophilic reagents, such as boronic acids, organozincs, and organostannanes, however, require preformation and can be expensive.

To pursue the direct use of simple and widely available molecules as nucleophilic partners, David MacMillan and Xiaheng Zhang develop a general route for efficiently activating readily available alcohols to form nucleophilic partners for C_{sp^3}−C_{sp^2} cross-coupling by the merger of nickel and photoredox catalysis, so-called metallaphotoredox catalysis (DOI: 10.1021/jacs.6b09533).

The authors demonstrate the preparation of a diverse range of alkyl-aryl products from simple alcohols using this method, and they test the method's efficiency in several coupling reactions, where some of the boronic acid equivalents of alcohols are not readily available. This protocol is applied successfully for the facile modification of a steroid natural product and quick access to an anti-tuberculosis drug candidate. The reported strategy provides an expedient solution for late-stage functionalization and drug development and is likely to be widely adopted throughout the pharmaceutical and academic community.

Xin Su, Ph.D.

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