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Spotlights on Recent *JACS* Publications

BREAKING UP C AND H IS NOW LESS HARD TO DO

Mei Wang, Michael Hall, and colleagues report a new strategy for heterolytically cleaving carbon−hydrogen bonds that may be useful in organic synthesis (DOI: 10.1021/ja5078014).

Many organic syntheses require heterolysis of carbon(sp^3)−hydrogen bonds, in which the carbon atom is activated by removal of a hydrogen ion. So far, chemists have only been able to catalyze such reactions with noble metals such as gold, palladium, or ruthenium, among others. But the harsh conditions these metals often require can threaten to damage sensitive functional groups on the molecule.

Now Wang, Hall, and co-workers offer a milder, iron-mediated approach to carbon−hydrogen bond heterolysis. Inspired by the ability of iron metalloenzyme hydrogenases to carry out the heterolytic cleavage of hydrogen−hydrogen bonds, the team has developed a model of one such catalyst, a diiron complex bearing a diphosphine ligand with a pendant amine base. After a double oxidation of the complex, the iron and amine work together to cleave the carbon−hydrogen bond; the amine takes the proton and the iron takes the carbon and its two electrons. The proposed mechanism is supported by X-ray crystallography and density functional theory calculations.

The work provides an alternative approach to heterolytic carbon−hydrogen bond cleavage that could lead to the design of new catalysts to facilitate future syntheses.

Deirdre Lockwood, Ph.D.

NEW PROBES THAT DETECT AND QUANTIFY PROTEINS INSIDE LIVE CELLS

Researchers continually seek new tools that will help them study the complex workings of proteins, but they sometimes struggle to analyze proteins inside live cells because the tools have trouble penetrating the cell membrane. Additionally, some of the tools may be toxic to live cells.

Now Yousuke Takaoka, Itaru Hamachi, and colleagues have developed a new toolkit of biocompatible probes (DOI: 10.1021/ja508955y). Each probe consists of a protein ligand conjugated to a rhodamine-based dye.

The probe can successfully burrow its way into live cells. In the absence of the probe's target protein, the ligand and rhodamine derivative form an aggregate that is not highly fluorescent. When the target protein is present, this aggregate disassembles—the ligand binds to the protein and the fluorescence of the rhodamine derivative increases. The assembly and disassembly of the aggregate is reversible, and the amount of fluorescence given off quantitatively corresponds to changes in the concentration of the target protein.

The investigators use their probes to detect several different proteins in live mammalian cells. These probes have potential applications in protein sensing and imaging, reversible modulation of cellular processes, and controlled drug release.

Rajendrani Mukhopadhyay, Ph.D.

CATCHING CANCER CELLS WITH LOGIC AND DNA

Weihong Tan and colleagues have developed a DNA-based system that uses Boolean logic gates to profile the expression of multiple cell surface markers. It could be used to identify and deliver therapeutics to cancer cells with high specificity (DOI: 10.1021/ja509263k).

Many cancer cells aberrantly express certain cell surface receptors. To accurately diagnose and treat cancer, researchers want to be able to identify these cells by gauging the expression of multiple cell surface biomarkers simultaneously.

Here, the authors have created a way to achieve this goal using a platform made of multiple DNA aptamers that can be programmed to carry out logic operations. Each aptamer probe has an oligonucleotide tag that binds to a specific cancer biomarker, linked with a reporting fluorophore or therapeutic reagent that signals its expression. Using built-in DNA nanotechnology features including strand displacement reactions, the system can report "OR" for expression of one of several targeted receptors, "AND" for expression of multiple receptors, and "NOT" for lack of expression. By combining these features, the researchers can program higher-order logic operations to screen for cancer cells.

The platform can be used to both image targeted cells and deliver therapeutics to them, potentially leading to more tailored cancer diagnosis and treatment.

Deirdre Lockwood, Ph.D.

FINAL PIECE OF THE MAITOTOXIN JIGSAW PUZZLE

Maitotoxin, produced by the marine plankton species *Gambierdiscus toxicus*, is the largest secondary metabolite known to date as well as the most potent nonprotein neurotoxin ever discovered. For these reasons, the total synthesis of this complicated ladder-like polyether molecule will not only become a classic in modern synthetic chemistry, but it can also help trace the origin of its remarkable toxicity.

After completing the syntheses of five major polycyclic fragments of maitotoxin, K. C. Nicolaou and co-workers finally turned to the QRSTUVWXYZA′ domains and have successfully constructed this last part convergently with the longest linear sequence of 15 steps (DOI: 10.1021/ja509829e). Their synthetic strategy highlights a cascade olefination/ring closing metathesis, followed by a combination of hydroxydithioketal cyclization, and methylation reactions, for the sequential formation of the X and Y rings.

This study showcases a succinct and efficient synthetic design for an extraordinary structural challenge and represents an important step toward the total synthesis of maitotoxin. Moreover, the biological evaluation of the synthesized domains, along with other maitotoxin fragments, reveals interesting structure−activity relationships regarding their inhibitory activity toward maitotoxin-induced Ca^{2+} influx in rat C6 glioma cells.

Xin Su, Ph.D.

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REVEALING THE REACTIVITY OF MYSTERIOUS SILYLONES

First predicted and prepared in 2009 and 2013, respectively, silylones, also known as siladicarbenes, are compounds containing zero-valent silicon coordinated to two carbene ligands. Silylones feature strong Si−C bonds strengthened by a three-center two-electron π-bond, making them much less reactive than carbodicarbenes, their lighter analogues, and the reactivity of silylones therefore remains completely unknown.

Now, Dietmar Stalke, Debasis Koley, and Herbert Roesky, along with co-workers, discover the first reaction of silylones in which they are converted into six-membered cyclic silylenes with tricoordinated silicon through selective tertiary C−H bond activation (DOI: 10.1021/ja510427r). As confirmed by cyclic voltammetry and electron paramagnetic resonance spectroscopy, this transformation proceeds via a highly reactive silylone radical anion intermediate, initiated by substoichiometric potassium.

As a pioneering study on the reactivity of silylones, this work provides solid evidence of key intermediates that may be important for predicting their reaction products under other conditions. In addition, this unique activation mode can be exploited for similar compounds of zero-valent group 14 elements.

Xin Su, Ph.D.

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