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Spotlights on Recent *JACS* Publications

CHIRAL CARBON CENTERS VIA TANDEM CATALYSIS

The construction of acyclic all-carbon quaternary stereogenic centers is an ongoing challenge for synthetic chemists. One of the most common strategies is the chiral α-alkylation of carbonyl compounds, usually entailing coupling between electron-rich enolate or enamine-based intermediates and electrophiles, but this strategy has disadvantages that must be overcome.

Now, Sanzhong Luo and co-authors report a creative modification to this approach by combining organocatalysis with radical addition, instead of conventional nucleophilic substitution (DOI: 10.1021/ja508605a). The transformation proceeds via a tandem primary amine-photoredox catalytic process where photogenerated open-shell acyl radicals are added to β-ketocarbonyl-derived chiral enamine intermediates with high stereoselectivity. Even more impressively, spiro-γ-lactams with two well-defined nonadjacent quaternary stereocenters can be synthesized from appropriate substrates in single operations.

As a facile and powerful path to asymmetric α-alkylation, this method expands the tools available for the construction of chiral carbon centers. By facilitating access to molecular motifs that are otherwise intractable, it demonstrates potential utility in overcoming some of the challenges facing pharmaceutical and natural product chemistry.

Xin Su, Ph.D.

A RARE EXAMPLE OF STEREOCHEMICAL RETENTION

Nucleophilic substitution is a fundamental transformation of organic chemistry that involves the replacement of one ligand with another. For such reactions involving saturated carbon atoms in solution, the process typically results in scrambled absolute stereochemistry or stereochemical inversion. Nature is known to be able to avoid these otherwise inevitable outcomes with the help of enzymes that contain sterically constrictive binding pockets capable of stabilizing reactive intermediates and catalyzing the reaction with in a selective manner.

In a recent report, Chen Zhao, F. Dean Toste, Kenneth Raymond, and Robert Bergman describe the first synthetic supramolecular complex capable of driving a nucleophilic substitution reaction that leaves the original stereochemistry intact (DOI: 10.1021/ja508799p). The researchers find that the host complex—a tetrahedral nanovessel that presents metal ions at each vertex and naphthalene-based bridging ligands along each edge—contains a well-defined hydrophobic internal cavity that enables it to stabilize carbocation intermediates through cation–π interactions. These stabilizing interactions, coupled with the ability of the bridging ligands to block the back side of the intermediate carbocation, enable the nucleophilic addition to occur asymmetrically, yielding a product with the same absolute stereochemistry as the starting material.

Christine Herman, Ph.D.

SETTLING THE DEBATE OVER THE MECHANISM OF AROMATASE

Francis K. Yoshimoto and F. Peter Guengerich settle a long-time debate over the mechanism of aromatase, a member of the cytochrome P450 family of oxidative enzymes and a key drug target for hormone-dependent breast cancers (DOI: 10.1021/ja508185d). Aromatase converts androgens, the male sex hormones, into estrogens, the female sex hormones, via a three-step process. However, the mechanism of the third step has been a source of considerable controversy, with no fewer than five pathways proposed and dissension over the exact iron species involved.

The authors use a deuterated androgen substrate and $^{18}O_2$ to distinguish between possible mechanisms. They also use a novel diazo compound to facilitate detection of formic acid, one of the products of the reaction. Analysis of the products by high resolution mass spectrometry reveals a lack of incorporation of ^{18}O incorporation into formic acid, pointing to the utilization of Compound I, or FeO^{3+}, as the active iron species in the reaction.

Cytochrome P450 enzymes have been identified in all forms of life and are key players in biosynthesis of steroids and fatty acids as well as in the metabolism of drugs and toxins. The approach used here can be applied to investigate the mechanisms of other members of this important enzyme superfamily.

Eva J. Gordon, Ph.D.

NEW GENERATION OF RHODIUM COMPOUNDS COULD BOOST CHEMOTHERAPY

In an advance that could lead to more effective cancer treatment, Alexis Komor and Jacqueline Barton have developed a new set of rhodium complexes that target DNA mismatches and thus cancerous cells deficient in DNA mismatch repair (DOI: 10.1021/ja5072064).

To treat cancer more efficiently, researchers want to design chemotherapeutics that specifically target cancer cells. Compounds called rhodium metalloinsertors are promising in this regard. They specifically bind mismatched base pairs in DNA, which are in higher frequency in some cancer cells, and selectively promote the death of these cells.

Now Komor and Barton have made a group of new rhodium metalloinsertors that are more selective than their precursors and more potent than the common chemotherapy drug cisplatin. The team attributes these improved properties to a new ligand coordination with a rhodium–oxygen bond. The effective dose of the new compounds is as much as twenty times lower than that of earlier rhodium metalloinsertors. The complexes could spur on the development of a class of more sensitive and cell-selective chemotherapeutic agents.

Deirdre Lockwood, Ph.D.

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NEW LABEL FOR THREE-DIMENSIONAL SUPER-RESOLUTION MICROSCOPY OF LIVE CELLS

Scientists have used optical microscopy for centuries to study living organisms. But until recently, optical microscopy's resolution was restricted by the diffraction limit, which prevents two dots of light, separated by a distance of 200 nm or less, from being distinguished from one another. Over the past 20 years, researchers have been developing special fluorescent labels that allow them to overcome the diffraction limit to carry out super-resolution microscopy.

Now Marissa K. Lee, W. E. Moerner, and colleagues describe a new fluorescent label, a small molecule called rhodamine spirolactam (DOI: 10.1021/ja508028h). The investigators can control when it fluoresces, since the label turns on only when hit with a 405 nm laser pulse. This blue control pulse operates in the visible light region of the electromagnetic spectrum, thereby reducing damage of live cells during imaging.

With their new label, the researchers carry out super-resolution microscopy in three dimensions of live bacterial cell surfaces. The non-toxic label allows bacteria to grow normally. Because the label permits the investigators to distinguish structures as close as 10−20 nm apart, it also allows investigators to see cell-surface details that are not visible by standard optical microscopy. The combination of super-resolution, non-toxicity, and operation in the visible spectrum means that this label will be useful in the future for detailed analyses of living cell surfaces.

Rajendrani Mukhopadhyay, Ph.D.