

Spotlights on Recent JACS Publications

■ SIMPLICITY IN MAKING COMPLEX FUSED N-HETEROCYCLES

As anyone who has watched a child construct a block tower can attest, it seems to be human nature to build complex targets from simple materials with minimal efforts, and chemists are no exception. Specifically, synthetic organic chemists have gone to great lengths to build intricate polycyclic frameworks in natural products using reactive cationic species.

As part of their studies on the chemistry of ynamides—key synthetic intermediates and excellent substrates for important organic reactions—Sébastien Thibaudeau, Gwilherm Evano, and colleagues reveal an unprecedented cascade polycyclization promoted by Brønsted acids (DOI: 10.1021/ja504818p). Keteniminium ions, simply generated upon the protonation of ynamides, are converted into fused ring systems with well-defined stereochemistry through a hydrogen shift and two cyclizations within a single operation.

The researchers present an elegant transformation that enables the formation of up to three contiguous chiral centers and seven fused rings in one step, demonstrating extreme simplicity in constructing complex molecular motifs. The convenient access to the core of alkaloid haouamine A based on this method underscores its potential utility in medicinal chemistry and natural product synthesis.

Xin Su, Ph.D.

■ NEGISHI COUPLING GOES ASYMMETRIC ON SULFONAMIDES AND SULFONES

Enantioconvergent synthesis—in other words, the conversion of a racemic substrate into one enantiomeric product—is a straightforward approach to a diverse variety of chiral molecular motifs. However, there is no general method for applying this strategy to control the chirality of carbon centers attached to sulfur, such as in sulfonamides and sulfones, two types of useful synthetic intermediates or biologically active molecules.

The gap is now bridged by a new highly stereoselective catalytic Negishi cross-coupling reaction developed by Gregory C. Fu and colleagues (DOI: 10.1021/ja506885s). In the presence of a chiral nickel catalyst, racemic α -bromosulfonamides and -sulfones couple with organozinc and organozirconium reagents to yield enantioenriched aryl- or alkenyl-substituted products through a radical pathway.

This research expands the scope of nickel-catalyzed enantioselective cross-couplings and also adds an example to the small collection of stereoconvergent reactions of unactivated alkyl electrophiles. Its wide substrate scope and compatibility facilitates easy access to a number of chiral sulfonamide and sulfone targets.

Xin Su, Ph.D.

■ MESSENGER RNA: IT'S IN THE DELIVERY

Kazunori Kataoka and co-workers report an effective new approach for transporting messenger RNA (mRNA), the intermediary between genes and proteins, into cells (DOI: 10.1021/ja506194z). Cellular delivery of RNA has promising

therapeutic applications, especially in the area of gene therapy, but challenges associated with effective delivery of these negatively charged, labile biomolecules has hindered development on this front.

Polyplexes—positively charged molecular carriers that can escort mRNA across cell membranes—are composed of a polymer of aspartamide residues containing varying lengths of side chain aminoethylene repeats. The authors discover that polyplexes with an odd number of repeats are more effective mRNA delivery agents than those with an even number of repeats. Interestingly, these findings with mRNA are opposite those found with polyplexes that deliver DNA into cells in which polyplexes with an even number of repeats are superior. This observation suggests that both carrier and nucleic acid structure contribute to the cell delivery process.

More effective mRNA delivery into cells is needed to realize the promise of mRNA-based therapies. The findings reported here enable the continued refinement of polyplexes as mRNA delivery vehicles and potential therapeutic agents.

Eva J. Gordon, Ph.D.

■ POSSIBLE LINK BETWEEN BIOLOGICAL AND INDUSTRIAL NITROGEN FIXATION

Nitrogen is an essential nutrient that is abundantly available in Earth's atmosphere in the form of the dinitrogen (N_2) molecule, which cannot be assimilated by plants and animals. Instead, living things must obtain their nitrogen through “nitrogen fixation”, a process in which the very strong and nonpolar $N\equiv N$ triple bond is cleaved to generate two ammonia (NH_3) molecules. This biological process occurs through the action of the enzyme nitrogenase, found only in a select group of microorganisms. In industry, nitrogen fixation is achieved through the Haber–Bosch process, which celebrated its centenary last year. Now Jeremy Smith, Martin Kirk, Brian Hoffman, and co-workers have characterized a new iron–nitride complex that provides a possible link between these two processes (DOI: 10.1021/ja505403j).

The team combines advanced electron-nuclear double resonance (ENDOR) spectroscopic measurements with quantum chemical calculations to characterize a Jahn–Teller distortion in which the iron–nitride complex decreases its energy by lowering its symmetry. Surprisingly, the investigation further reveals an essentially spherical nitride trianion bound to iron. The results suggest an orbital selection mechanism for proton or H-atom transfer with significant implications for the catalytic conversion of N_2 to NH_3 by nitrogenase and industrial catalysts.

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