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Spotlights on Recent *JACS* Publications

THREE COMPONENTS, TWO CATALYSTS, ONE ENANTIOMERIC ALLYLBORATION PRODUCT

Organoboranes are versatile synthetic building blocks, and direct access to their multifunctional and enantioenriched derivatives is highly desirable. As one of the most straightforward routes to this class of compounds, stereoselective carboboration of alkenes is often pursued but rarely achieved.

Now, Jian Liao and co-workers develop a facile strategy for enantioselective borylallylation of styrenes through a cooperative copper/palladium catalytic cascade, where copper-catalyzed asymmetric borylation seamlessly couples with palladium-catalyzed allylation (DOI: 10.1021/jacs.5b09146). This approach efficiently assembles chiral β-allylboronic esters in a single step from simple and readily available achiral reactants such as bis(pinacolato)diboron and allylic carbonates. Previously such a synthesis would be a costly and laborious task.

As the first example of asymmetric catalysis for intermolecular 1,2-carboboration of alkenes, the current study adds a valuable entry to the toolbox of stereospecific alkene difunctionalization. Meanwhile, the successful demonstration of copper/palladium transmetalation provides useful insights into the design of catalytic systems with multiple active species for complex and well-choreographed transformations.

Xin Su, Ph.D.

MULTIPRONGED ATTACK ON MYOTONIC DYSTROPHY TYPE I

Some diseases wreak havoc through complicated molecular mechanisms. Seeking a single therapeutic target—one protein or enzyme within that complicated cellular machinery—that can be treated with a single drug is often ineffective. Now Steven Zimmerman and colleagues describe a multipronged approach to tackle myotonic dystrophy type I, one example of a complex disease (DOI: 10.1021/jacs.5b09266).

The disorder, which is caused by a mutation in a gene called DMPK, affects many systems in the body including skeletal and smooth muscle, the endocrine system, and the central nervous system. RNA transcribed from the mutated DMPK gene is toxic because it binds to other critical proteins, gets translated into protein more often than necessary, and potentially disrupts the regulation of another important class of RNA molecules called microRNAs. The researchers create small-molecule drug candidates that multi-task in three distinct ways: they stop the DNA from being transcribed into the toxic RNA, but if some slips through, they inhibit its binding to critical proteins and chew it up, thereby preventing its translation into protein.

The investigators successfully test three drug candidates in model cells for myotonic dystrophy type I. The investigators believe that one of the molecules that works well in a fruit-fly model of the disease is the first small molecule to control the level of the toxic RNA in an animal model of this complex disorder.

Rajendrani Mukhopadhyay, Ph.D.

MAGNESIUM PLAYS CRITICAL ROLE IN BACTERIAL RIBOSWITCH FOLDING

Bacterial messenger RNAs—the genetic code that is translated into proteins—usually contain a stretch of RNA that does not encode protein. In some cases, this RNA stretch, known then as a riboswitch, binds to small molecules to change the messenger RNA conformation and regulate the quantity of encoded protein expressed in the cell. Because riboswitches influence messenger RNA function, they are viewed as potential drug targets. However, researchers have been puzzled by the mechanisms that underpin the binding of small molecules to riboswitches.

Now Nils Walter and colleagues show that magnesium ions play an under-appreciated role in riboswitch folding (DOI: 10.1021/jacs.5b09740). The investigators use a single-molecule fluorescence microscopy technique to study the binding of three small molecules of varying affinities to a model bacterial riboswitch. When magnesium is absent, the small molecules bind to the open riboswitch and induce the RNA to fold around them. But when small—even micromolar—concentrations of magnesium are present, a different mechanism comes into play where the riboswitch first takes on a stable, folded conformation with a preformed binding pocket into which the small molecules slide.

"We anticipate that [our single molecule approach] will pave the way for deciphering the coupled ligand binding and folding pathways of many riboswitch RNAs, which will render them attractive antibiotic drug targets," conclude the authors.

Rajendrani Mukhopadhyay, Ph.D.

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