Researchers develop cheap, easy 'kitchen chemistry' to perform formerly complex synthesis

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A team at The Scripps Research Institute has made major strides in solving a problem that has been plaguing chemists for many years: how best to break carbon-hydrogen bonds and then to create new bonds to join molecules together. This problem is of great interest to the pharmaceutical industry, which currently relies on a method to accomplish this feat that is relatively inefficient and sometimes difficult to perform.

The research, led by Scripps Research Associate Professor Jin-Quan Yu, was published November 26, 2009, in *Science Express*, an advance, online edition of the prestigious journal *Science*.

"This paper is a big jump forward," said Yu. "Our reaction is as simple as something you'd do in the kitchen. There are many fewer steps than the conventional method. There's less waste. In addition, everything you need is inexpensive and off-the-shelf—including common table salt."

Because carbon-hydrogen bonds are simple and abundant in naturally occurring organic molecules and in commercially available drugs, they are ideal targets for chemists who want to design and manipulate molecules. An improvement to current methods for working with these bonds has the potential to revolutionize work done in academic and industrial laboratories around the world.

Bread-and-Butter Technology

Currently, to forge carbon-carbon bonds in place of carbon-hydrogen bonds, chemists rely heavily on a method called "Mizoroki-Heck reaction."

In this reaction, chemists first must install a halide in the molecule of interest as a "handle," replacing the existing carbon-hydrogen bonds with carbon-halide bonds. The chemists then join these molecules with other molecules using a metal catalyst, and then remove the "halide handle."

"Once installed, the halide can stick like glue," explained Yu, "so you can join one halogenated molecule with another molecule readily with a metal catalyst. The halide technique is very powerful and many technologies use it, including for the creation of almost any drug. It's a bread-and-butter technology."

But, despite its widespread use, this technique has some downsides. First, there's the waste (both in terms of labor and energy as well as literal waste) of the steps of adding and removing the halide from the molecules. Then, perhaps even more problematic, installing the halide into a molecule of interest isn't always so easy.

"To install a halide, you have to install it at the right position," said Yu. "You can't install it just anywhere. Sometimes that is impossible or difficult, taking many, many steps."

So the question arose: Can chemists develop a new method to manipulate carbon-hydrogen bonds and join together molecules without the intermediate step of installing a halide?

The Search for a Better Way

Over the last several years, many laboratories around the world have taken up this challenge. Early research in this new area of study (including papers by Yu) showed that this goal was possible to achieve under specialized conditions. However, making the reaction economically feasible and practical for the average chemistry laboratory was an elusive goal—until now.

In the new Science Express paper, Yu and colleagues start with a simple and commonly used substrate, a derivative of acetic acid (which gives vinegar it's sour taste).

"This substrate is used daily in the pharmaceutical industry and in natural product synthesis," said Yu. "It's a major class."

The team then designed ligands (molecules that bind to a site on a metal catalyst) out of simple derivatives of amino acids (protein building blocks). Because of their specific shape, these ligands guide the metal to break a carbon-hydrogen bond at a particular position selectively, and carbon-carbon bond formation with another molecule then takes place.

To demonstrate the utility and versatility of the lab's technique, for the study the team synthesized several natural product core structures. These included a complex molecule, a polyketide aromatic, that is an essential component of many antibiotics.

"The *Science* paper is the first demonstration that we can actually take an acetic acid derivative and then make a very complex molecule," said Yu. "And yet in none of the steps do we use anything the layman cannot afford or take off the shelf. We call it 'layman chemistry.' We expect that this reaction and others grounded in this philosophy will find many uses."

Source: The Scripps Research Institute (news : web)