Go meta: New technique expands possibilities for molecular designers

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Chemists at The Scripps Research Institute (TSRI) have developed a broadly useful technique for building new drug molecules and other chemical products.

The technique, reported March 9, 2015 as an Advance Online paper by the journal *Nature*, is an improved, easier method for "meta-C-H activation," the attachment of a desired group of atoms to a particularly hard-to-reach position on the carbon backbone of an organic molecule.

"This method can be used for the synthesis of small quantities, for example to discover potential new drug compounds, and also for bulk manufacturing," said Jin-Quan Yu, the Frank and Bertha Hupp Professor of Chemistry at TSRI.

Yu's laboratory specializes in finding better ways to build organic molecules and has now published five such innovations in *Nature* or *Science* over the past year. These highly technical methods generally pass under the radar of popular science news, but academic and professional chemists have been adopting them enthusiastically, using them to develop next-generation drugs and other novel chemical products.

A better method for meta-C-H activation should be especially welcome, given the traditional difficulty of that feat.

Challenges for Molecule Builders

C-H activation means breaking a bond between a carbon and a hydrogen atom—hydrogen atoms being the default attachments to carbons in simple hydrocarbon molecules—and replacing the hydrogen with something else. Usually that something else is a more reactive cluster of atoms called a functional group, which helps give the resulting molecule its desired properties.

Chemists who build molecules using C-H activations often use an existing functional group on a hydrocarbon to facilitate the breaking of a nearby C-H bond and attachment of a second functional group. Just where that new C-H activation will occur, on a standard hexagonal hydrocarbon structure, depends largely on the properties of the existing group. But in general, it is easier to achieve C-H activation at the next carbon on the hydrocarbon ring, at what is called the ortho position, or at the location one carbon farther away, at the meta position.

Breaking a C-H bond and attaching a new functional group at this meta position, farther away from the existing substituent, tends to be trickier—in some cases it can be done with a small number of specific substrates, in other cases it is effectively out of reach.

In 2012 in *Nature*, Yu and his team reported developing a set of flexible, U-shaped helper molecules that could arch outwards from an existing functional group and swing a C-H-bond-breaking palladium atom onto the meta position, enabling a functional group to attach there.

That invention was quickly adopted by pharmaceutical chemists. But for the new study, Yu and his laboratory sought a more streamlined meta-C-H activation method, one that would not require pre-installing this U-shaped template.

New Avenues for Drugs, Plastics and Industrial

Chemicals

The new method the team invented was inspired in part by the Catellani reaction, named for Italian chemist Marta Catellani. This reaction uses a palladium C-H-bond-breaker and a uniquely reactive compound called norbornene to selectively attach a functional group at the ortho position to an aryl iodide. Yu's team, including first author Xiao-Chen Wang, a postdoctoral fellow, found a way to modify the Catellani method for the attachment of functional groups at the meta position to an existing functional group instead.

In the new method, a palladium atom is directed to the ortho position by an already-attached, common type of functional group. Norbornene is added and has the effect of flipping the palladium atom from the ortho to the meta position—enabling a new functional group to attach at that point.

The reaction also includes a newly designed helper molecule, a pyridine ligand, which facilitates norbornene's activity as well as the eventual attachment of a new functional group.

"The key to the success of this reaction is our tailor-made pyridine ligand, which beautifully orchestrates many elementary steps in the catalytic cycle, avoiding the formation of unwanted side products," said Yu. "This project has been seven years in the making, and we are happy to finally find the solution."

One bonus is that the same setup can be used to attach a functional group at the ortho position if norbornene is not added. Another feature is that the pyridine and norbornene interact only transiently with the compound and don't require extra steps to remove at the end of the reaction. In addition, these reagents can be fully recycled after the reaction.

As the team showed in their study, the new technique and its variations can be applied to classes of compounds that are frequently used to make drugs, plastics and other industrial chemicals, allowing modifications that were previously much harder to achieve—including double additions of functional groups at both the meta position and the ortho position.

"The blood thinner Plavix and the ADHD drug Concerta are just two examples of common compounds that could be readily diversified in this way," Yu said.

More information: Ligand-Enabled meta-C-H Activation Using a Transient Mediator, DOI: 10.1038/nature14214

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