New chemical reaction holds promise for drug development

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The extensive suite of robotics in the Caltech Center for Catalysis and Chemical Synthesis enabled Brian Stoltz and his colleagues to discover the new alkylation reaction. Credit: Caltech

A team of researchers at the California Institute of Technology (Caltech) has devised a new method for making complex molecules. The reaction they have come up with should enable chemists to synthesize new varieties of a whole subclass of organic compounds called nitrogen-containing heterocycles, thus opening up new avenues for the development of novel pharmaceuticals and natural products ranging from chemotherapeutic compounds to bioactive plant materials such as morphine.

The team -- led by Brian Stoltz, the Ethel Wilson Bowles and Robert

Bowles Professor of Chemistry, and Doug Behenna, a scientific researcher -- used a suite of specialized robotic tools in the Caltech Center for Catalysis and Chemical Synthesis to find the optimal conditions and an appropriate catalyst to drive this particular type of reaction, known as an alkylation, because it adds an alkyl group (a group of carbon and hydrogen atoms) to the compound. The researchers describe the reaction in a recent advance online publication of a paper in *Nature Chemistry*.

"We think it's going to be a highly enabling reaction, not only for preparing complex natural products, but also for making pharmaceutical substances that include components that were previously very challenging to make," Stoltz says. "This has suddenly made them quite easy to make, and it should allow medicinal chemists to access levels of complexity they couldn't previously access."

The reaction creates compounds called heterocycles, which involve cyclic groups of carbon and nitrogen atoms. Such nitrogen-containing heterocycles are found in many natural products and pharmaceuticals, as well as in many synthetic polymers. In addition, the reaction manages to form carbon-carbon bonds at sites where some of the carbon atoms are essentially hidden, or blocked, by larger nearby components.

"Making carbon-carbon bonds is hard, but that's what we need to make the complicated structures we're after," Stoltz says. "We're taking that up another notch by making carbon-carbon bonds in really challenging scenarios. We're making carbon centers that have four other carbon groups around them, and that's very hard to do."

The vast majority of pharmaceuticals being made today do not include such congested carbon centers, Stoltz says—not so much because they would not be effective compounds, but because they have been so difficult to make. "But now," he says, "we've made it very easy to make

those very hindered centers, even in compounds that contain nitrogen. And that should give pharmaceutical companies new possibilities that they previously couldn't consider."

Perhaps the most important feature of the reaction is that it yields almost 100 percent of just one version of its product. This is significant because many organic compounds exist in two distinct versions, or enantiomers, each having the same chemical formula and bond structure as the other, but with functional groups in opposite positions in space, making them mirror images of each other. One version can be thought of as right-handed, the other as left-handed.

The problem is that there is often a lock-and-key interaction between our bodies and the compounds that act upon them—only one of the two possible hands of a compound can "shake hands" and fit appropriately. In fact, one version will often have a beneficial effect on the body while the other will have a completely different and sometimes detrimental effect. Therefore, it is important to be able to selectively produce the compound with the desired handedness. For this reason, the FDA has increasingly required that the molecules in a particular drug be present in just one form.

"So not only are we making tricky carbon-carbon bonds, we're also making them such that the resulting products have a particular, desired handedness," Stoltz says. "This was the culmination of six years of work. There was essentially no way to make these compounds before, so to all of a sudden be able to do it and with perfect selectivity… that's pretty awesome."

More information: "Enantioselective construction of quaternary N-heterocycles by palladium-catalysed decarboxylative allylic alkylation of lactams," *Nature Chemistry*.

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