Chemists show proof of concept for new method of accelerating drug discovery research

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Chemists have made a significant advancement to directly functionalize C-H bonds in natural products by selectively installing new carbon-carbon bonds into highly complex alkaloids and nitrogen-containing drug molecules. C-H functionalization is a much more streamlined process than traditional organic chemistry, holding the potential to greatly reduce the time and number of steps needed to create derivatives of natural products.

Nature Communications published the findings, emerging from a collaboration with Novartis Institutes for BioMedical Research and Emory University. The collaboration was fostered by the National Science Foundation's Center for Selective C-H Functionalization (CCHF), headquartered at Emory.

"This paper is essentially a proof of concept," says co-author Huw Davies, an organic chemist at Emory and director of the CCHF. "We've shown that C-H functionalization has reached the stage where it can readily be applied to derivatization of nitrogen-containing compounds, ubiquitous in the discovery and development of new medicines."

Co-authors are Novartis chemists Rohan Beckwith, Jing He and Lawrence Hamann.

The CCHF is at the forefront of a major paradigm shift in organic

chemistry. The center brings together scientists from leading research universities across the United States, Asia and Europe - as well as from private industry - with the aim of making organic synthesis faster, simpler and greener.

Traditionally, organic chemistry has focused on the division between reactive, or functional, molecular bonds and the inert, or non-functional bonds carbon-carbon (C-C) and carbon-hydrogen (C-H). The inert bonds provide a strong, stable scaffold for performing chemical synthesis on the reactive groups.

C-H functionalization flips this model on its head: It bypasses the reactive groups and does synthesis at the inert C-H sites.

"We had already demonstrated that we have a tool box of reagents and catalysts that allow us to control which sites in a molecule will undergo C-H functionalization," Davies says. "Novartis wanted to explore whether this chemistry was robust enough to be carried out on really complex compounds like alkaloids."

Alkaloids are a family of natural products produced by plants that have biological properties important to medicine. Morphine, codeine and opioids are examples of alkaloids.

A key part of the drug development process is creating libraries of derivatives from such natural products: Groups of chemical compounds with small molecular differences. "These small differences could determine whether a compound is toxic or carries other liabilities, or has the right mix of properties to become a safe and effective therapeutic agent," Davies says.

The results outlined in the paper demonstrate the efficiency of rhodium catalysts to selectively install a new carbon-carbon bond into complex

alkaloids in a highly controlled manner.

The research also demonstrates the ability of the CHHF to pioneer new ways of chemists working together: Breaking through the traditional boundaries of individual labs, academic institutions, countries and corporations to create a global collaboration of chemists taking different approaches to similar problems.

"Novartis sees great potential in C-H functionalization," Davies says. "It has been an early and enthusiastic supporter of the CCFH through collaborative research of scientists at Novartis and in CCHF academic labs."

More information: *Nature Communications*, www.nature.com/ncomms/2015/150 … full/ncomms6943.html

Provided by Emory University

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