

# 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](http://www.nature.com/ncomms/2015/150...full/ncomms6943.html)

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