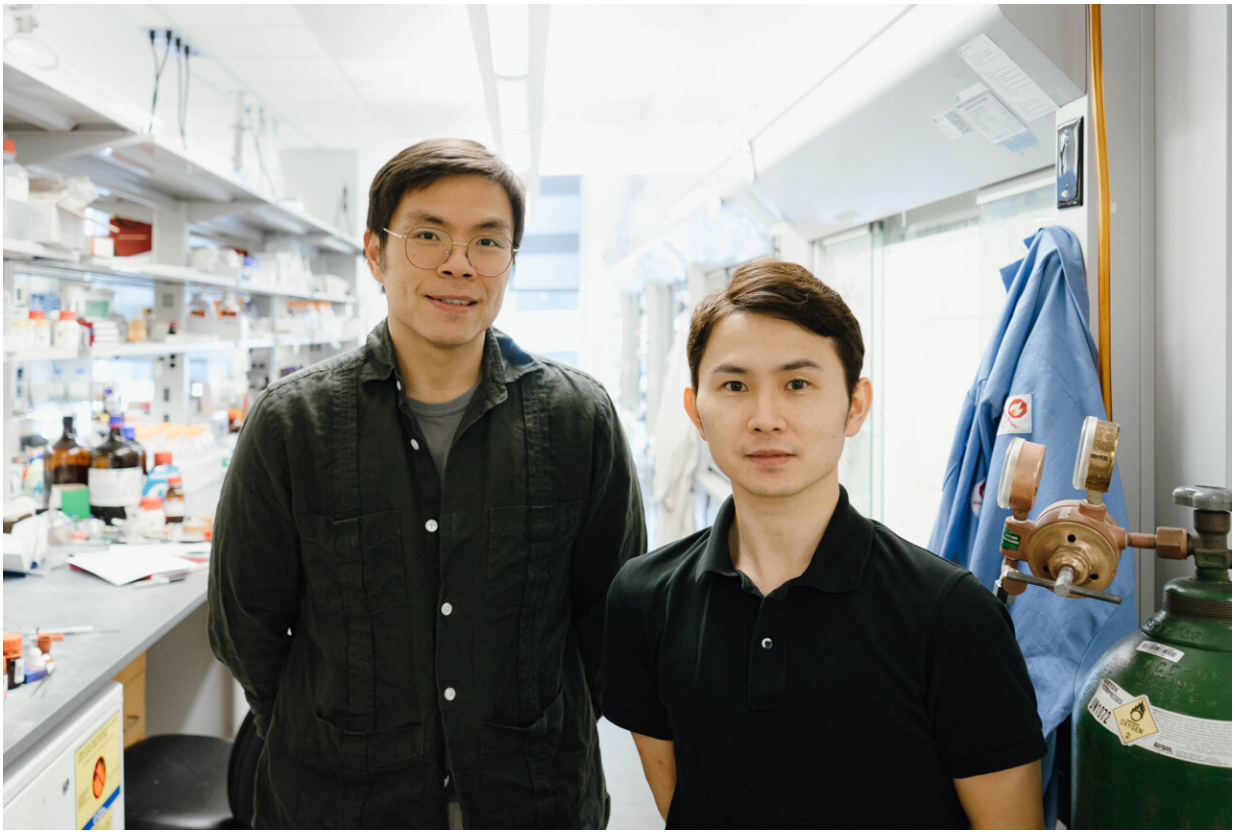
# New synthesis technique cuts drug development time and cost

December 19 2024



Hans Renata and Kenta Yokoi in Renata's lab at Rice. Credit: Alex Becker/Rice University.

A team of chemists from Scripps Research and Rice University has unveiled a novel method to simplify the synthesis of piperidines, a key

structural component in many pharmaceuticals. The study, published in *Science*, combines biocatalytic carbon-hydrogen oxidation and radical cross-coupling, offering a streamlined and cost-effective approach to creating complex, three-dimensional molecules. This innovation could help accelerate drug discovery and enhance the efficiency of medicinal chemistry.

Modern medicinal chemists face increasing challenges as they target complex molecules to address difficult biological targets. Traditional methods for synthesizing flat, two-dimensional molecules, such as pyridines, are well established, but strategies for their 3D counterparts, like piperidines, have been far more elusive.

To bridge this gap, the team introduced a two-stage process to modify piperidines, which are important in many pharmaceuticals. The first step uses biocatalytic carbon-hydrogen oxidation, a method where enzymes selectively add a hydroxyl group to specific sites on piperidine molecules. This process is similar to a common chemical technique called electrophilic aromatic substitution, which works for flat molecules like pyridines, but here it is applied in a 3D structure.

In the second step, these newly functionalized piperidines undergo radical cross-coupling with nickel electrocatalysis. This approach forms new carbon-carbon bonds efficiently by connecting different molecular fragments without the need for extra steps, like adding protective groups that shield parts of the molecule during synthesis or using expensive precious metal catalysts such as palladium. This two-step process dramatically simplifies how complex piperidines are built.

"We've essentially created a modular approach to simplify piperidine synthesis, analogous to how palladium cross-coupling revolutionized pyridine chemistry decades ago," said Hans Renata, study co-author and associate professor of chemistry at Rice. "This represents a powerful

tool to unlock new molecular spaces for drug discovery."

The research demonstrated the streamlined synthesis of numerous high-value piperidines used in natural products and pharmaceuticals, including neurokinin receptor antagonists, anticancer agents and antibiotics. The approach reduced multistep processes from 7-17 steps to just 2-5, drastically improving efficiency and cost.

This achievement is significant for both medicinal and process chemists. By offering a generalizable strategy to rapidly access complex 3D molecules, the method reduces reliance on costly precious metals like palladium and simplifies traditionally challenging synthetic pathways. For pharmaceutical development, this means faster access to life-saving medicines, reduced production costs and a sustainable approach to synthesizing drug candidates.

"This work demonstrates the power of combining enzymatic transformation for selective carbon-hydrogen oxidation and modern cross-couplings for unlocking new molecular spaces for drug discovery," Renata said.

"By combining biocatalytic oxidation and radical cross-coupling, we are enabling access to molecules previously considered inaccessible or prohibitively expensive," said Yu Kawamata, a co-author and institute investigator in the Department of Chemistry at Scripps Research.

The method opens new possibilities for drug design and synthesis, particularly as the industry shifts toward 3D molecular architectures to enhance drug specificity and performance. Patients and health care systems may also benefit from faster, more efficient routes to critical medications, potentially reducing costs and increasing access to new therapies.

**More information:** Jiayan He et al, Biocatalytic C–H oxidation meets radical cross-coupling: Simplifying complex piperidine synthesis, *Science* (2024). DOI: 10.1126/science.adr9368

Provided by Rice University