# Crossing the ring: New method enables C-H activation across saturated carbocycles

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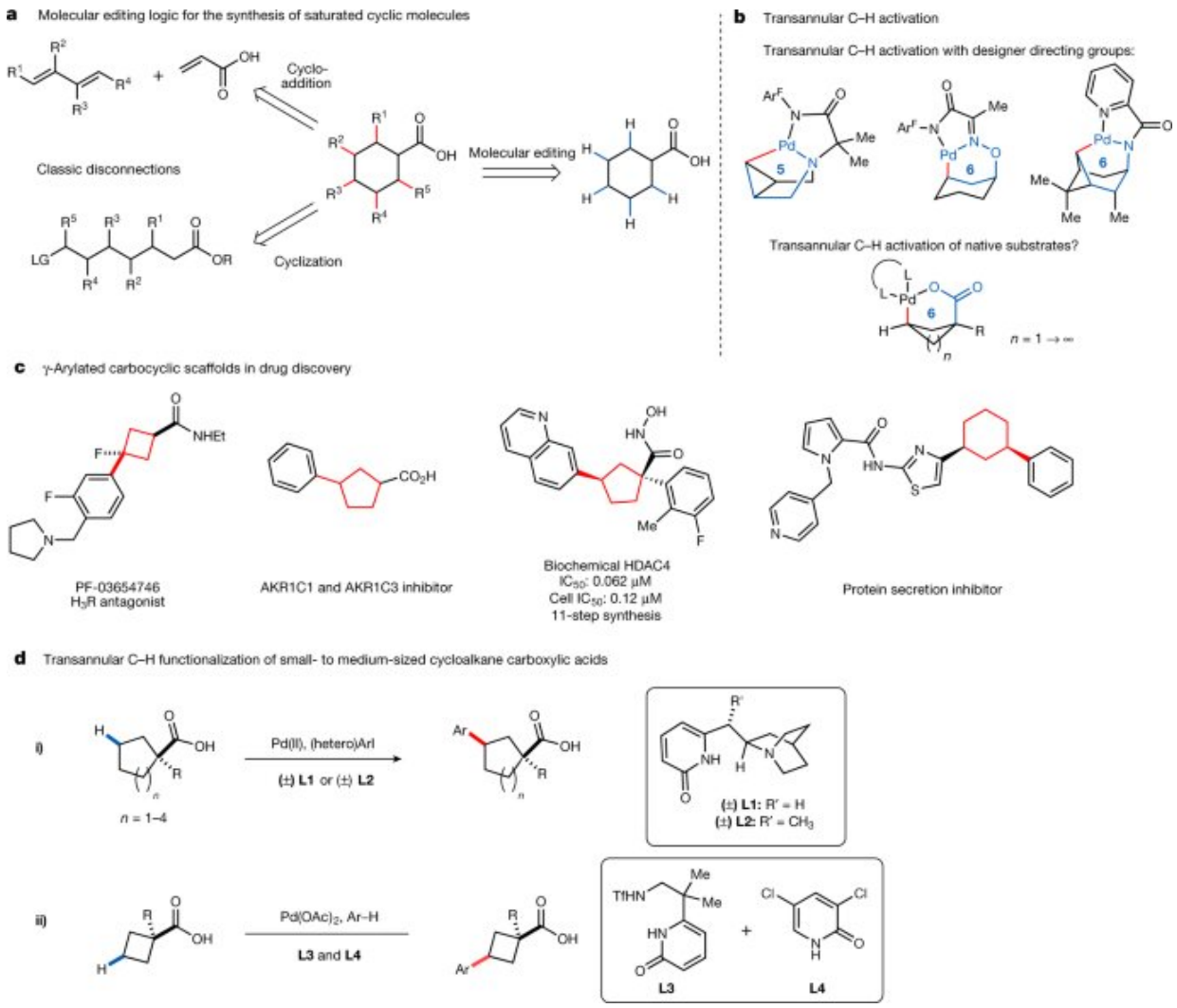


Transannular C–H arylation via activation of methylene C–H bonds. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-06000-z

A new "molecular editing" technique from Scripps Research enables chemists to add new elements to organic molecules at locations that were previously out of reach.

The researchers described their new method in *Nature*. The method uses a designer molecule called a ligand that helps a palladium-atom catalyst reach from one side of a carbon-atom ring to break a carbon-hydrogen bond on the other side, allowing a new set of molecules to join at that site. This molecule-building feat was previously impossible for so-called "saturated" rings of carbon atoms, which are common features in drug molecules.

"Previously, to achieve the same result, one would have to undertake a de novo approach —what we call a cyclization reaction—involving the formation of a new ring structure from an acyclic chain, using this new method, we can directly modify an existing ring to avoid a cyclization process that can often prove challenging," says study senior author Jin-Quan Yu, Ph.D., the Bristol Myers Squibb Endowed Chair in Chemistry and the Frank and Bertha Hupp Professor in the Department of Chemistry at Scripps Research.

"In addition to saving steps, this unprecedented synthetic strategy can introduce new chemical space for drug discovery as structurally distinct substrates are incorporated into the ring."

Yu and his laboratory are already renowned for their innovations in C-H functionalization, which is a powerful way of building complex organic molecules to make new pharmaceuticals and other valuable commercial compounds. In this approach, chemists use ligands and catalysts to disconnect a hydrogen (H) atom from a carbon (C) atom at a desired position on an organic molecule. This disconnection allows a new cluster of molecules, known as a functional group, to bond where the hydrogen atom had been.

Most molecules that are used to build new drugs include rings of carbon atoms, also called carbocycles. Thanks in part to Yu's group, the C-H functionalizations of carbon atoms on these rings have become relatively easy in many cases. This approach is often not applicable, though, in cases where the existing functional group needed to anchor the ligand and catalyst is directly across the ring from the desired C-H functionalization site.

"We call this scenario 'crossing the river,' and it has been extremely challenging because the palladium catalyst must form a strained 'bridge' connecting the existing functional group and the desired carbon site on the other side of the ring," Yu says.

The most challenging cases are those in which the carbon-ring structures are "saturated," which means their carbons are connected only with single carbon-carbon bonds. Saturated carbon rings are common in pharmaceutical chemistry, but are harder targets for C-H functionalization, in part because the C-H bonds have less affinity for metal catalysts, compared to the double C-C bonds of unsaturated carbon rings.

The Yu lab has achieved C-H functionalization across unsaturated rings, but there has been no way to do this across a saturated ring—until now.

In the study, Yu and his team, including co-first authors Guowei Kang, Ph.D., Daniel Strassfeld, Ph.D., and Tao Sheng, Ph.D., all postdoctoral research associates in the Yu lab, were able—after months of trial and error—to develop quinuclidine-pyridone and sulfonamide-pyridone ligands enabling cross-ring functionalization with saturated carbon rings. They showed that the approach can work for rings containing from four to eight carbon atoms, within a wide variety of molecules.

The researchers demonstrated the new technique by easily

functionalizing molecules that are being used to develop future drugs, including compounds called histone deacetylase inhibitors, which are under investigation as potential cancer treatments.

"We anticipate that this new tool will greatly simplify the synthesis of a large class of carbocyclic molecules used in pharmaceutical chemistry, expanding chemical space for the discovery of new and better drugs," Yu says.

**More information:** Jin-Quan Yu, Transannular C–H functionalization of cycloalkane carboxylic acids, *Nature* (2023). DOI: 10.1038/s41586-023-06000-z.
www.nature.com/articles/s41586-023-06000-z

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