Chemists introduce new copper-catalyzed C-H activation strategy

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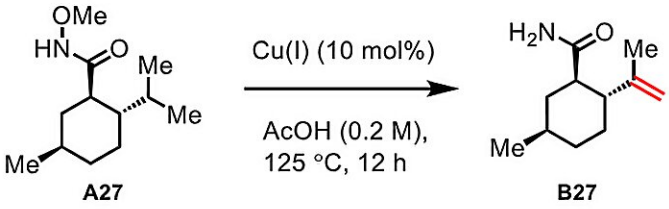

entry	Catalyst (10 mol%)	Yield of **B27** (%)
1	CuOAc	0
2	CuCl	0
3	CuBr	5
4	CuI	0
5	Cu(TC)	0
6	Cu_2O	0
7	$[(CH_3CN)_4Cu]PF_6$	6
8	$[(CH_3CN)_4Cu]BF_4$	**18**
9	$(CF_3SO_3Cu)_2{\bullet}C_6H_6$	0
10	$[(CH_3CN)_4Cu]BF_4$	18*

Investigation of Cu(I) salts for γ-dehydrogenation. Reaction conditions: catalyst (10 mol%), AcOH (0.2 M), 125 °C, 12 h. Isolated yields are reported. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07341-z

Inspired by what human liver enzymes can do, Scripps Research chemists have developed a new set of copper-catalyzed organic synthesis reactions for building and modifying pharmaceuticals and other molecules. The new reactions are expected to be widely used in drug discovery and optimization, as well as in other chemistry-based industries.

In their study, published in *Nature*, the chemists showed that their new methods can be used to perform two modifications—called dehydrogenations and lactonizations—on a broad class of inexpensive starting compounds. The reactions require only a simple copper-based catalyst, whereas related reactions typically require much more cumbersome and expensive methods—though this specific type of reaction was previously inaccessible by any organic synthesis method.

"This new two-mode approach could be particularly useful for late-stage modifications and diversifications of natural products and drug molecules," says study senior author Jin-Quan Yu, Ph.D., Frank and Bertha Hupp Professor of Chemistry and Bristol Myers Squibb Endowed Chair in Chemistry at Scripps Research.

The study's first authors were postdoctoral research associate Shupeng Zhou, Ph.D., and doctoral student Annabel Zhang, Ph.D., both of the Yu lab during the study.

The initial goal of the research was to find a new and better method for what chemists call carbon-hydrogen (CH) activation, in which a hydrogen atom on the carbon backbone of an organic compound is detached and replaced with something else—a valuable tool for drug synthesis.

In this case, the Yu lab—which has a history of innovations in CH activation chemistry—sought a better way to do CH activations that

replace the hydrogen with an oxygen atom. This is a common transformation in the construction or modification of biologically active molecules, though chemists haven't had laboratory methods for doing it that are as simple, direct and broadly useful as they would like.

Yu and his team looked to nature for inspiration, in particular to cytochrome P450 enzymes, which are found in most living organisms, and help clear potentially toxic molecules in the human liver. Cytochrome P450 enzymes perform oxygen-for-hydrogen reactions very efficiently.

Some of these enzymes have the additional ability to catalyze a different hydrogen-removal process called dehydrogenation, which can be used to strip hydrogens from two carbons simultaneously, allowing other atoms—or clusters of atoms—to replace them. The chemists set themselves the ambitious goal of finding a general organic synthesis method for doing either the oxygenation or dehydrogenation reaction, as these versatile "bimodal" enzymes do in living cells.

After months of experimentation, Yu's team found that, through chemical transformations similar to those done by the bimodal cytochrome P450 enzymes, they could efficiently make compounds called unsaturated primary amides—a class that includes many drug molecules—by dehydrogenating inexpensive starting compounds called methoxyamides. For the catalyst, they needed only copper fluoride—also inexpensive and easy to use.

As the chemists explored the breadth of their new dehydrogenation method using different specific starting compounds, they observed trace amounts of a type of molecule called a lactone, indicating that an oxygenation reaction had occurred. Ultimately, they were able to determine the reaction conditions that favored this oxygenation or "lactonization" over the dehydrogenation. In other words, like the

bimodal enzymes that had inspired them, they were able to control whether their approach led down one reaction path or the other.

The team demonstrated the remarkable versatility of this set of reactions by using it to modify—via dehydrogenation or lactonization, or both—a wide variety of starting compounds, including the neurological drug valproic acid and the cholesterol-lowering drug gemfibrozil. (Modifications of existing complex molecules to create potentially better variants are a common drug discovery and optimization technique.)

Yu and his group are currently developing a similar approach for making and modifying lactone- and amide-related compounds called lactams, which include some antibiotics.

"We've already had a lot of interest in this new approach from pharma industry chemists," Yu says.

"Copper-catalyzed dehydrogenation or lactonization of C(sp3)–H bonds" was co-authored by Shupeng Zhou, Zi-Jun Zhang and Jin-Quan Yu.

More information: Shupeng Zhou et al, Copper-catalyzed dehydrogenation or lactonization of C(sp3)–H bonds, *Nature* (2024). DOI: 10.1038/s41586-024-07341-z

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