One-step synthesis of pharmaceutical building blocks: New method for anti-Michael reaction

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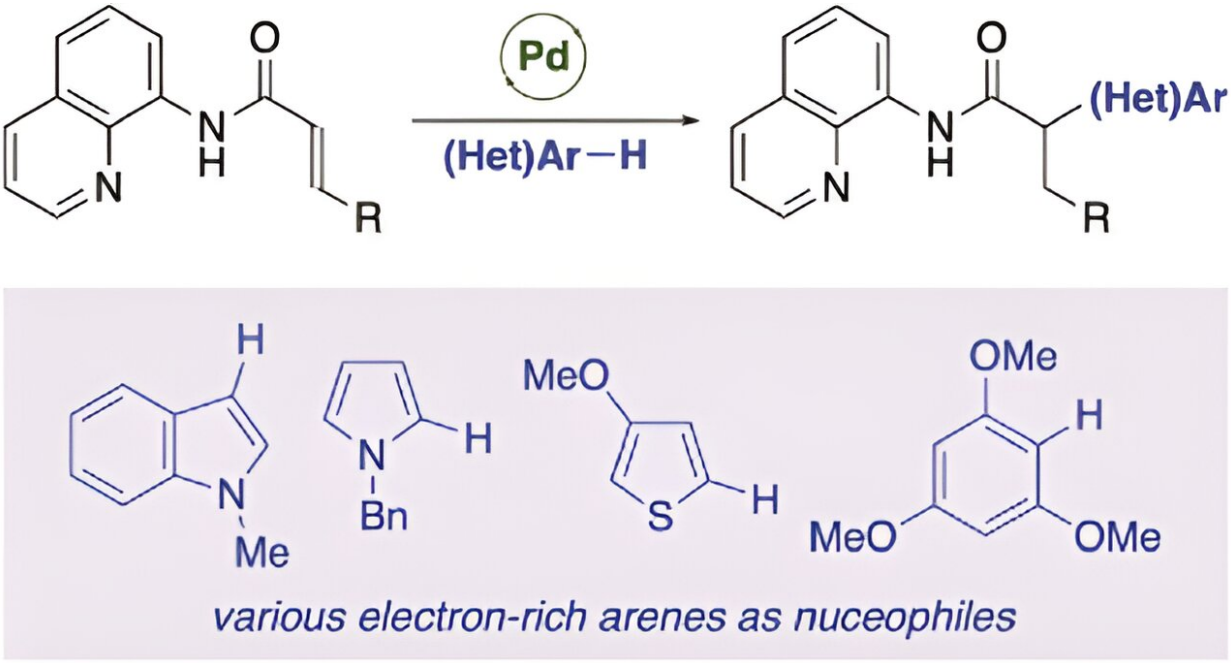

Credit: *Journal of the American Chemical Society* (2024). DOI: 10.1021/jacs.4c00841

In 1887, chemist Sir Arthur Michael reported a nucleophilic addition reaction to the β-position of α,β- unsaturated carbonyl compounds. These reactions, named Michael addition reactions, have been extensively studied to date. In contrast, the anti-Michael addition

reaction, referring to the nucleophilic addition reaction to the α-position, has been difficult to achieve. This is due to the higher electrophilicity of the β-position compared to the α-position.

Previous attempts to overcome these difficulties have involved two main methods. The first is restricting the addition position via intramolecular reactions, while the second method involves introducing a strong-electron withdrawing group at the β-position. However, these methods are not ideal for synthesizing complex molecules via the anti-Michael reaction.

In a new study, a global team of researchers, led by Professor Takanori Matsuda and including Ryota Moro, both from the Department of Applied Chemistry at Tokyo University of Science, Japan, as well as including Assistant Professor Hirotsugu Suzuki from the Tenure-Track Program for Innovative Research at the University of Fukui, Japan, successfully achieved palladium-catalyzed anti-Michael addition reaction of acrylamides. This represents the first example of an anti-Michael-type addition reaction.

"We found that the presence of a catalytic amount of palladium(II) trifluoroacetate $Pd(TFA)_2$ is capable of facilitating the anti-Michael addition of indole to acrylamide with an aminoquinoline group as a directing group, producing the addition product in high-yield," explains Prof. Matsuda.

The research is published in the *Journal of the American Chemical Society*.

The team reasoned introducing a directing group into an α,β-unsaturated carbonyl compound could facilitate an anti-Michael type addition reaction by stabilizing the reaction intermediate. To test this, the researchers first used an acrylamide having an aminoquinoline-directing

group, and a nucleophile, 1-methylindole, as model substrates to investigate the anti-Michael type addition reaction in the presence of the palladium catalyst.

This reaction produced the desired product with a 90% yield. At a reaction scale of 2 millimoles, there was no yield loss, signifying the practicality of the reaction.

This reaction was also carried out with β-substituted cinnamamide derivatives and crotonamide derivatives with an alkyl group. Moreover, the reaction proceeded smoothly with a wide range of nucleophiles, including many indoles, heterocyclic compounds such as pyrroles and thiophenes, and electron-rich aromatic compounds.

Additionally, the aminoquinoline-directing group used in this reaction can be converted to carboxylic acids and other amides, signifying the usefulness of the reaction.

The researchers also investigated the mechanism for this reaction through labeling experiments. They found that initially, the acrylamide coordinates to $Pd(TFA)_2$ to form a five-membered ring palladacyle intermediate. The reaction then proceeds with the nucleophilic attack by indole on the intermediate, producing alkylpalladium species. Finally, an acid removes palladium and regenerates $Pd(TFA)_2$, producing the desired α-substituted carbonyl compound.

Highlighting the potential applications of this study, Dr. Suzuki says, "The anti-Michael type addition is expected to become an ideal one-step reaction with 100% atomic efficiency for the synthesis of α-substituted carbonyl compounds, which are often used in pharmaceuticals. Our method will enable the widespread application of this reaction."

Overall, this novel method can lead to efficient and sustainable synthesis

of α-substituted carbonyl compounds and consequently pharmaceuticals, among other organic compounds.

More information: Hirotsugu Suzuki et al, Palladium-Catalyzed anti-Michael-Type (Hetero)arylation of Acrylamides, *Journal of the American Chemical Society* (2024). DOI: 10.1021/jacs.4c00841

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