Keeping it simple—Synthesizing useful organic compounds now made easier and cheaper

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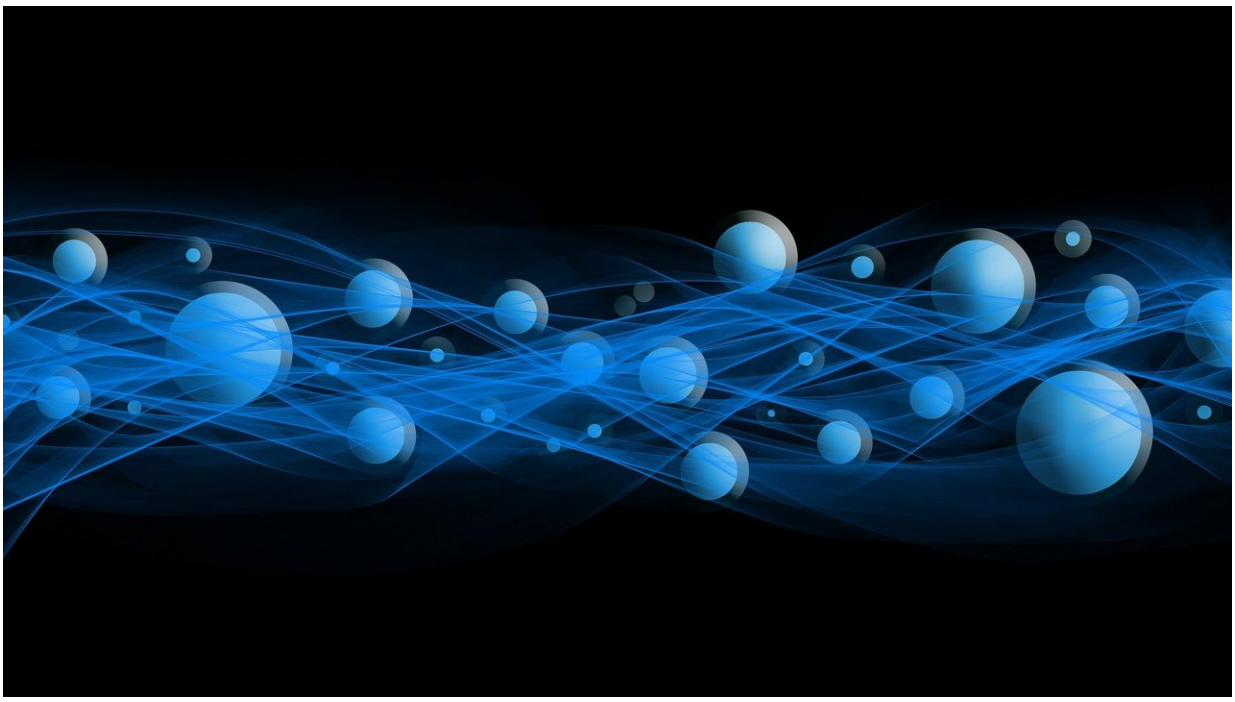

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The Suzuki-Miyaura reaction is a well-known chemical process in which a reaction between organic boronic acids and aryl halides leads to the synthesis of "biaryl" compounds, which are important components of various drugs and chemical products. This is also called cross-coupling,

as two aryl molecules are combined, or cross-coupled, in this process. Because the organic aromatic molecules—which are formed as a result of this reaction—have various applications, such as in solvents and drugs, finding a way of optimizing the existing cross-coupling reactions is crucial. This is why, in a new study published in *ACS Catalysts*, a team of scientists from Japan, including Junior Assoc Prof Yuichiro Mutoh and Prof Shinichi Saito of Tokyo University of Science, wanted to check if this reaction can be made more efficient.

"Protected" organic boronic acid, which is an organic boronic acid with a 'masking group,' is frequently used as a precursor for boronic acid in the Suzuki-Miyaura reaction. Because the reactivity of the protected boronic acid is low, it does not take part in this reaction. Thus, the masking group needs to be removed for the reaction to proceed, which adds another step to the process. This made these scientists wonder: what if the masked molecules were directly used in the reaction? It would lead us to a much faster, cheaper technique!

Prof Saito explains, "Because the removal of the masking group is necessary to provide the latent boronic acids that engage in subsequent Suzuki-Miyaura reactions, the direct use of the protected boronic acid in a Suzuki-Miyaura reaction would be highly desirable in terms number of steps and atom economy. This would help streamline the synthesis of complex molecules." The only challenge was that until now, there was no known way to directly use protected boronic acids without removing the masking group first, and thus, the scientists set out to find ways to do this.

The scientists knew that the process required a palladium catalyst (a molecule or compound that can speed up a reaction), a base, and two starting aryl molecules. They proceeded to check if the reaction takes place with a protected molecule. To begin with, they examined the impact of various bases on the reaction. They saw that when a particular

potassium base, called KOτ-Bu, was used, it resulted in a high yield of products, and this effect as not seen with other bases. Then, they tested various palladium-based catalysts and saw that all catalysts produced a similar yield, indicating that common palladium-based catalyst systems can be used for the cross-coupling. This led them to conclude that the KOτ-Bu base played a crucial role if one was to use protected boronic acid directly.

After over a dozen successful Suzuki-Miyaura reactions with high yield for different biaryl compounds, the team conducted 'control' experiments to check for other variables and to gain insight into the underlying mechanisms of the KOτ-Bu base. Specifically, they checked if the chemical species were present in the reaction mixture before the reaction was complete, which uncovered an intermediate compound involving the KOτ-Bu base and the boronic acid reagent. Using techniques like NMR spectroscopy and single-crystal X-ray diffraction analysis, the scientists confirmed that the key to the success of these cross-coupling reactions is the use of KOτ-Bu as the base, as it enables the formation of an active borate, essential for the reaction.

The methodology discovered in this study provides insight into the Suzuki-Miyaura reaction and proposes a novel way in which the required steps to use protected boronic acids can be minimized. The entire process to obtain biaryl molecules was carried in one single pot, which is advantageous in terms of space and cost. Prof Saito concludes, "We developed a way for the reaction to be step- and pot-economic, features that have received considerable attention in recent years. Thus, this study opens up new possibilities for the use of protected boronic acids in various coupling reactions."

Owing to its novel findings, this study was even selected to be on the cover of the January 2020 issue of *ACS Catalysis*. These findings will hopefully help simplify the synthesis of important complex molecules,

including pharmaceutical drugs, so that more people can benefit from advances in the chemical sciences.

More information: Yuichiro Mutoh et al, Suzuki–Miyaura Cross-Coupling of 1,8-Diaminonaphthalene (dan)-Protected Arylboronic Acids, *ACS Catalysis* (2019). DOI: 10.1021/acscatal.9b03667

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