Scientists use cooperative action of a ligand-counterion system for sustainable ether production

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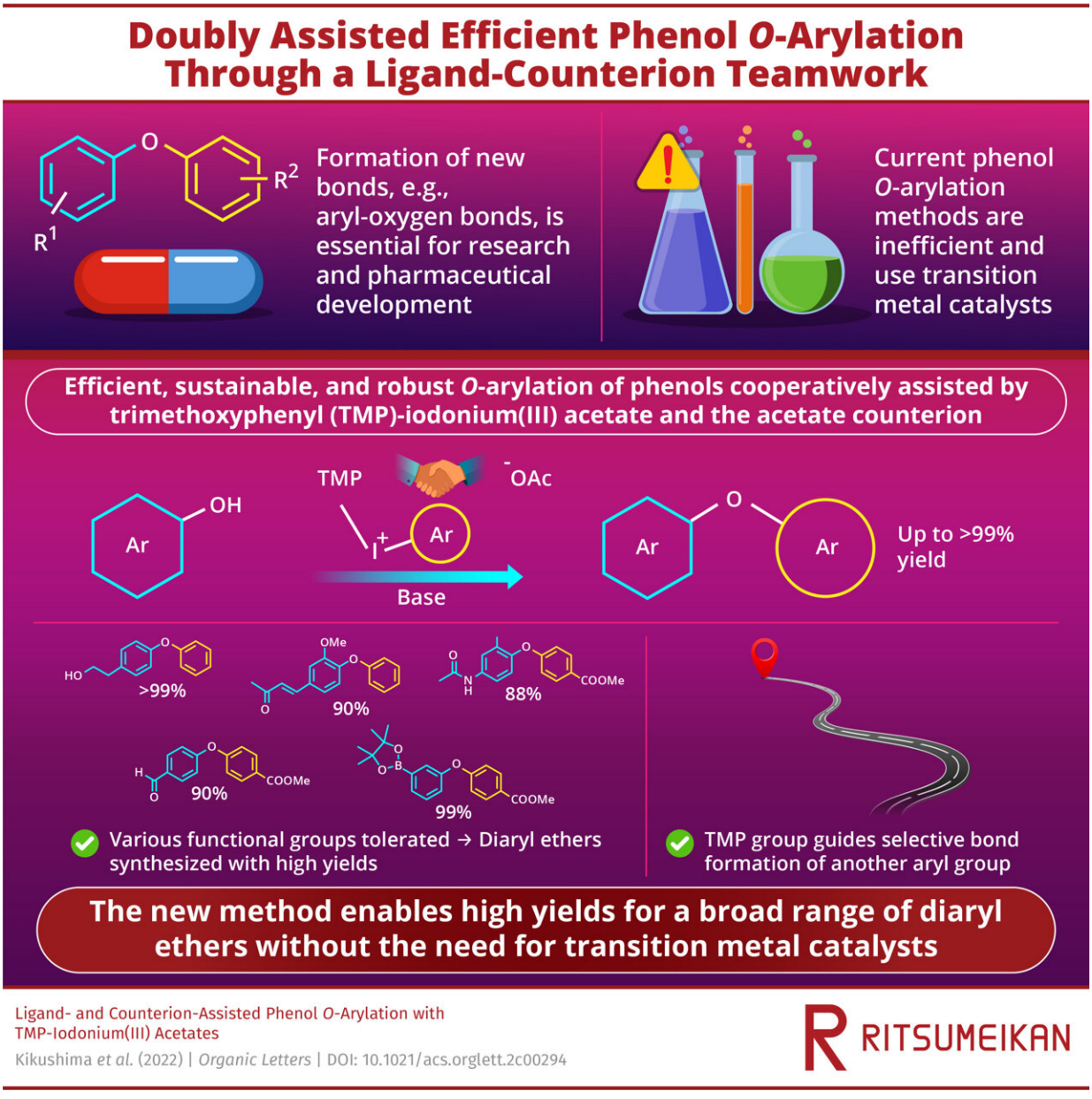

Scientists use cooperative action of a ligand-counterion system for sustainable ether production necessary for pharmaceutical applications. Credit: Ritsumeikan University

The continued development of pharmaceuticals depends on the ability to form a wide range of chemical bonds. Diaryl ethers, characterized by the presence of an oxygen atom connected to two aryl groups, are a class of organic compounds with a broad range of applications, notably as a refrigerant and an antiseptic for preventing infections. In particular, diaryl ethers have been a topic of research interest as their organic synthesis has proved difficult. They can be formed from aryl-alcohols, or phenols, when a second aryl group replaces the alcoholic hydrogen. But current phenol O-arylation methods are inefficient and makes use of rare transition metal catalysts (notably the palladium catalyzed cross-coupling reaction won the 2010 Nobel Prize in Chemistry). In addition, they are unselective, meaning many different side products are generated, reducing the efficiency and final yield of the desired organic compound.

Now, a more sustainable alternative to transition metal catalysts has been proposed by a team of researchers from Ritsumeikan University, Japan. In this work, the transition metal is replaced with a readily available and easily synthesized starting material, trimethoxyphenyl (TMP)-iodonium(III) acetate. "This iodonium salt contains two key structures, namely the TMP ligand and the acetate counterion, that work together to increase the reactivity of the O-arylation reaction and, in turn, enhance the ether bond formation, leading to significantly higher yields of diaryl ethers than has been reported in the past. It is a perfect teamwork," explains Assistant Professor Kotaro Kikushima, the lead

author of the study. This paper was made available online on March 7, 2022 and was published in Volume 24 Issue 10 of the journal *Organic Letters* on March 18, 2022.

Based on the structural features of phenyl(TMP)iodonium acetate, the researchers predicted that the diaryliodonium salt would have high reactivity. Accordingly, the combination of the trimethoxyphenyl group and acetate anion working together to enhance the reactivity of the phenol oxygen atom was determined for the first time in their study.

The variety and diversity of compounds is an important factor when designing methods for a green, sustainable chemistry future. To test the general nature of this method, the team tested and used various organic functional groups for O-arylation. To their delight, they found that the method was extremely robust and tolerant to a variety of functional groups, leading to a broad range of ethers synthesized with significantly higher yields than other reported techniques, an important consideration for industrial applications. The potential for scaling-up this process to industrial needs has also been demonstrated by performing the reaction on a gram-scale, retaining high efficiency. In addition to high yields and sustainable starting materials the method presented one more advantage compared to present techniques: increased selectivity. The TMP group guided the selective arylation of the other functional group, allowing for more control, and no unwanted side products.

"The present method would provide a cost-effective and robust access to a wide range of useful organic molecules under green sustainable conditions without the need for transition metal catalysts. Our next goal is to recycle and re-use the iodine-containing waste, which is formed as a side product during the arylation. Electrochemical or photochemical methods could then be used to sustainably restore the hypervalent iodine(III) which could then be used in another arylation," explains Professor Toshifumi Dohi, the co-author of the study.

Adding these green recycling strategies to the presented arylation reaction would provide the ideal sustainable synthetic methodology for transition-metal-free bond formations without dangerous chemical waste, a seismic shift in the sustainability of organic synthesis. With impressive teamwork between ligands and counterions demonstrated, the future of organic chemistry has never looked so green.

More information: Kotaro Kikushima et al, Ligand- and Counterion-Assisted Phenol O-Arylation with TMP-Iodonium(III) Acetates, *Organic Letters* (2022). DOI: 10.1021/acs.orglett.2c00294

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