

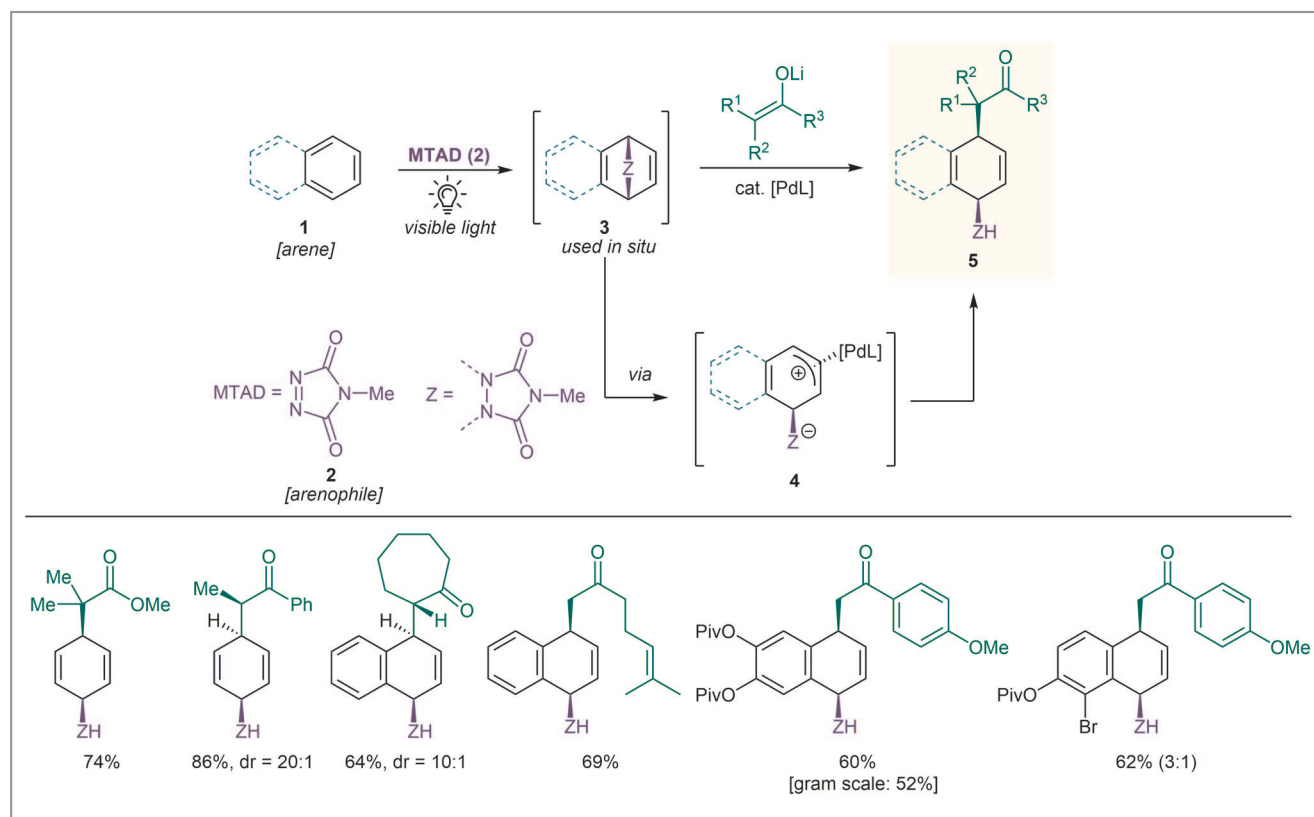
# Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination

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Arenes constitute one of the most abundant classes of compounds, and are often associated with structural planarity, exceptional stability, and chemical inertness. While most of the reactions involving arenes as substrates result in net conservation of aromaticity, there are several reactions that result in loss of aromaticity, known as dearomatizations. Such transformations play an important role in synthetic organic chemistry as they present a direct link between readily available arenes and high-value-added synthetic intermediates. However, many dearomatization reactions do not introduce functionalities, and further transformations are often required to install desired reactive groups or molecular handles. Thus, the development of novel dearomative functionalizations continues to be an active area of research as it could expand the synthetic utility of arenes and provide more direct access to valuable building blocks.

In a recent *JACS* paper from Professor David Sarlah's group at the University of Illinois at Urbana-Champaign (USA) a novel palladium-catalyzed transformation was devised to perform a net *syn*-1,4-carboamination with enolates as nucleophilic counterparts (see Scheme 1). "In a two-step, one-pot process we were able to introduce two functionalities on a wide range of conveniently accessible arenes, in a highly diastereo- and enantioselective fashion," commented Professor Sarlah. "Our approach features an addition of enolates, derived from either ketones or esters, to the proposed electrophilic intermediate **4** that was generated from compound **3** and catalytic amounts of a Pd catalyst. Catalyst loadings could be as low as 2.5 mol%."

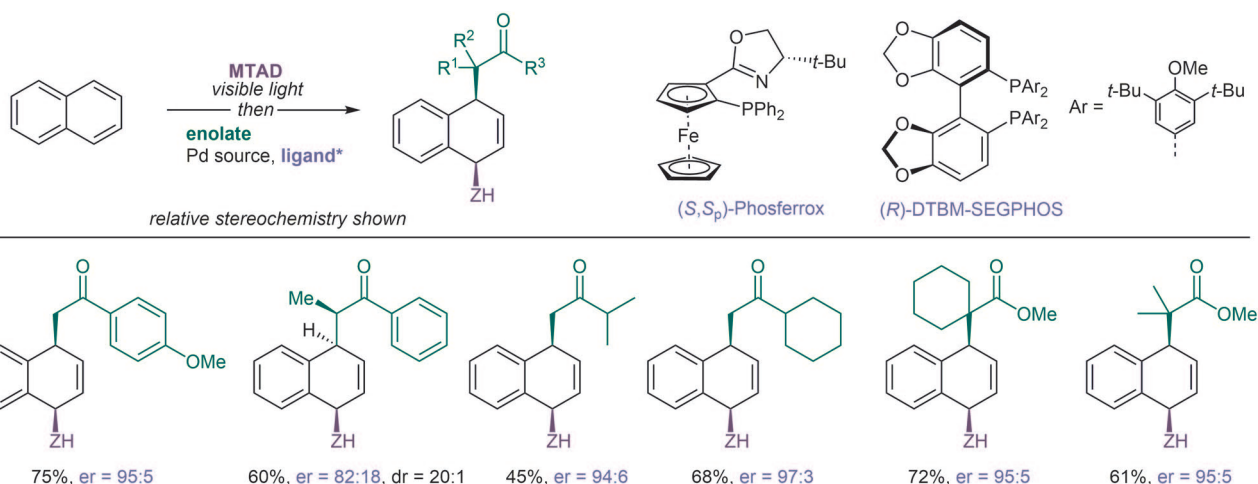
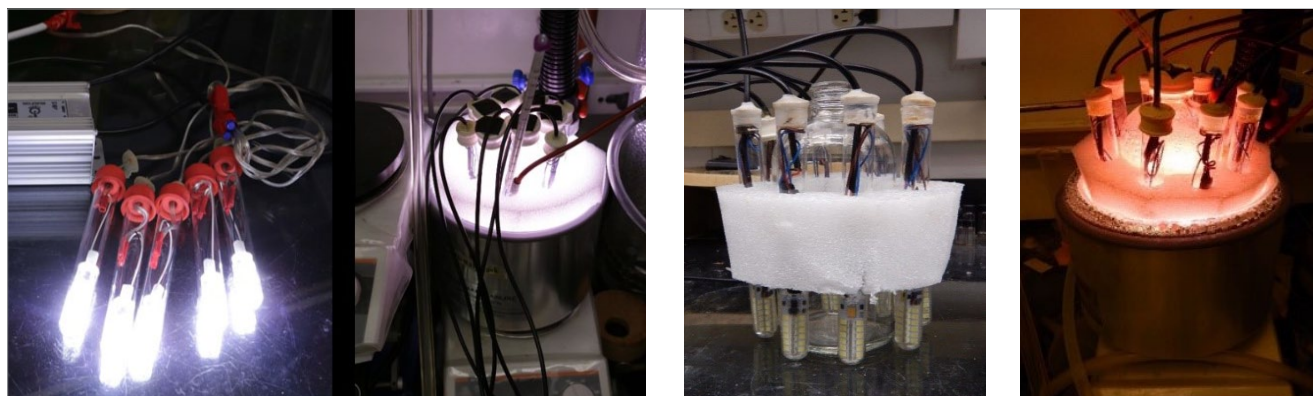
It has recently been shown by Professor Sarlah and co-workers (see the references in the original paper for more information) that MTAD (4-methyl-1,2,4-triazoline-3,5-dione, **2**) underwent a cycloaddition reaction with a range of arenes



**Scheme 1** Net *syn*-1,4-carboamination of arenes, proposed intermediate and selected products

The resulting cycloadducts **3**, common intermediates in Professor Sarlah's transformations, were unstable and, except in some cases, could not be isolated. "Several compounds of type **3** have been previously reported by Sheridan. We were surprised that no one had transformed this early finding into a synthetic methodology," explained Professor Sarlah. "It was later found that there were more molecules of similar structures that were also able to undergo these reactions. Analogously to the Diels–Alder reaction where TAD derivatives are

The reactivity of intermediates **3** is being thoroughly studied in Professor Sarlah's laboratory. "When we just started establishing the arenophile-mediated chemistry, we focused on derivatization of the double bond. However, it was also important to explore different modes of reactivity," said Professor Sarlah. "It was interesting to find out that somewhat analogous to Tsuji–Trost allylations, our intermediate can undergo oxidative addition to Pd(0) complexes that results in the formation of electrophilic allyl species **4**. We assume their formation happens primarily because of the regioselectivity and exceptional diastereoselectivity of the process. *syn*-Selectivity



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arises from a classical double-inversion pathway. The process is exceptionally well controlled inherently, as we never observed any other constitutional isomers.”

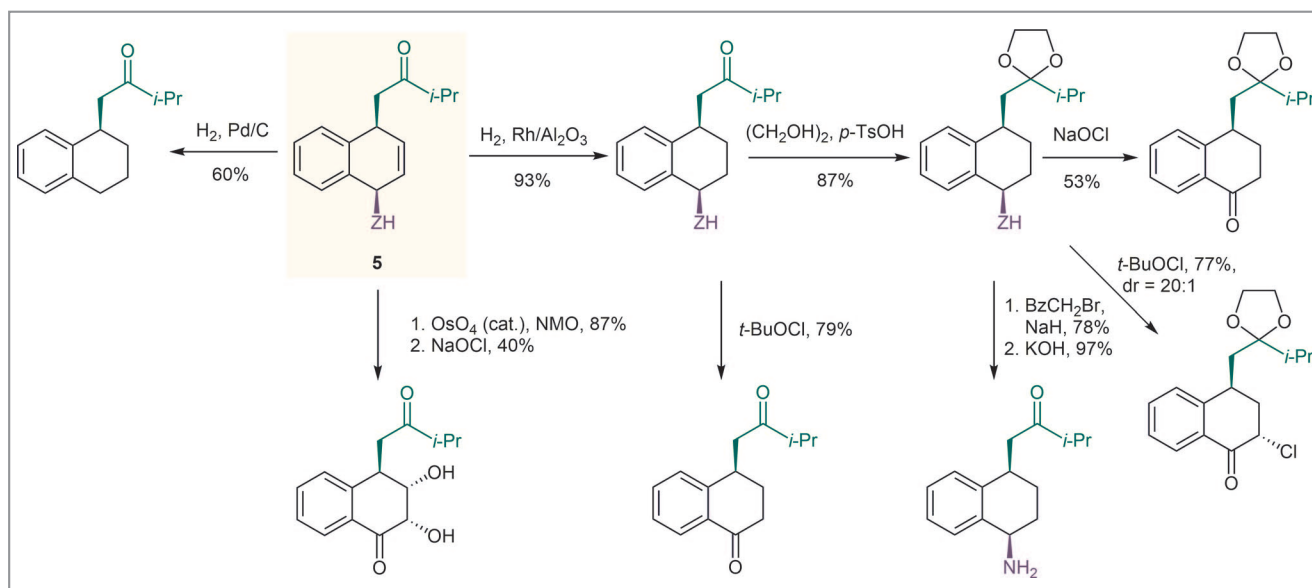
Having the substrate scope in hand, the authors sought to develop an enantioselective process (see Scheme 2). Professor Sarlah remarked: “It was quite unexpected that the (*S,S*)<sub>p</sub>-*t*-Bu-Phosferrox ligand turned out to be the optimal one for the reaction with ketone enolates. Previously, we established a different nickel-catalyzed carboamination with Grignard reagents as nucleophilic counterparts that featured the same ligand scaffold. As for the ester enolates, additional optimization of conditions resulted in changing the metal source to allylpalladium chloride and using DTBM-SEGPHOS as a ligand.”

Apart from establishing a selective dearomative difunctionalization, the authors also managed to perform a series of derivatizations of the product **5** (see Scheme 3), demonstrating the broader utility of this method.

Concerning future directions, Professor Sarlah remarked: “Despite having made a good start with the palladium-catalyzed reactions of the arene–arenophile cycloadducts, there is still plenty of work that needs to be done. First, we will explore a range of different nucleophiles. Second, we are working to get a more comprehensive picture of the mechanism behind these transformations. Last, but not less important, this methodology still has to be tested in a synthesis to demonstrate its true potential.” He then concluded: “Arenes are among the most abundant and cheapest materials in organic chemistry, yet their full synthetic potential is still underexplored. For the

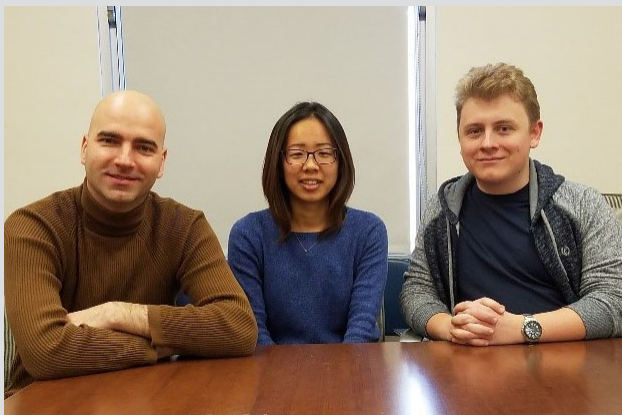
first time we have demonstrated that it is possible to transform a wide variety of aromatic systems without substrate-dependent methods or stoichiometric amounts of transition metals, by using a small organic molecule as the key mediator. We hope that this method will be recognized as a useful synthetic tool in both academic and industrial environments.”

*Matthew Fensle*



**Scheme 3** Further derivatizations of product **5**

## About the authors



*From left: Prof. D. Sarlah, M. Okumura, A. Shved*

**David Sarlah** is an assistant professor in the Department of Chemistry at the University of Illinois at Urbana-Champaign (UIUC, USA). He was born in Slovenia, where he earned his B.S. degree from the University of Ljubljana. He obtained his Ph.D. in 2011 with Professor K. C. Nicolaou at The Scripps Research Institute (USA), and then joined the laboratory of Professor Erick M. Carriera at ETH Zürich (Switzerland). In 2014, David returned to the USA to start his own laboratory at the University of Illinois, which explores both chemical synthesis of biologically active natural products and methods development.

**Mikiko Okumura** was born and raised in Japan. She received her B.S. (2012) and M.S. (2014) in chemistry at the University of Tokyo (Japan) working with Professor Shū Kobayashi. She began her graduate studies in the Sarlah group at UIUC (USA) in the fall of 2014, and is currently working on developing new dearomatization strategies.

**Alexander Shved** was born and raised in Moscow (Russia). He obtained his M.S. degree in 2016 from the Moscow University of Chemical Technology of Russia, Higher Chemical College of the Russian Academy of Sciences (RAS). Before graduation, he worked in Professor Sema L. Ioffe's group at the Zelinsky Institute of Organic Chemistry RAS (Russia) where he studied the chemistry of nitronates. In autumn 2016, Alex joined Professor David Sarlah's group at the UIUC (USA) as a research assistant working on dearomative methodologies. In the beginning of 2018 he joined the group again, this time as a graduate student. His current research interests involve in-depth studies of reaction mechanisms, computational chemistry and development of new methodologies. In his spare time Alex enjoys cooking, fishing and travelling.