

## Multimetallic Catalyzed Cross-Coupling of Aryl Bromides with Aryl Triflates

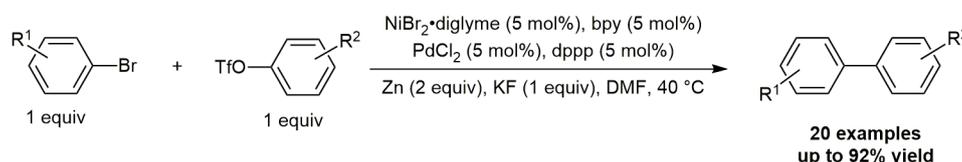
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The ‘classical’ Ullmann reaction is the copper-catalyzed synthesis of symmetric biaryls from aryl halides. Variants of this reaction based on a single metal catalyst have been the object of intensive studies as a means of producing more complex and non-symmetrical biaryls. “The multimetallic catalyzed cross-Ullmann reaction provides two major contributions to the synthetic community: the first, a general method to access unsymmetrical biaryls from widely available starting materials, and second, a guiding principle for the cooperation of two metal catalysts in coupling reactions,” said Professor Daniel Weix at the University of Rochester, New York (USA). While the synthesis of biaryls from arylboron, aryltin, arylzinc, and arylsilicon reagents is well established, in many cases the corresponding aryl halide or aryl pseudohalide would be a more convenient starting material, allowing for increased substrate diversity. The new cross-Ullmann method recently identified by the group of Professor Weix enables the cross-coupling of aryl bromides with aryl triflates with high selectivity and functional group tolerance. Professor Weix explained: “Unsymmetrical biaryls can be isolated in up to 92% yield and both electron-rich and electron-deficient arenes can be employed. These results are promising for the development of other multimetallic catalyzed cross-coupling methods, especially when the substrates may be structurally or electronically similar, as in the formation of dienes ( $sp^2$ – $sp^2$  coupling) and alkanes ( $sp^3$ – $sp^3$  coupling).”

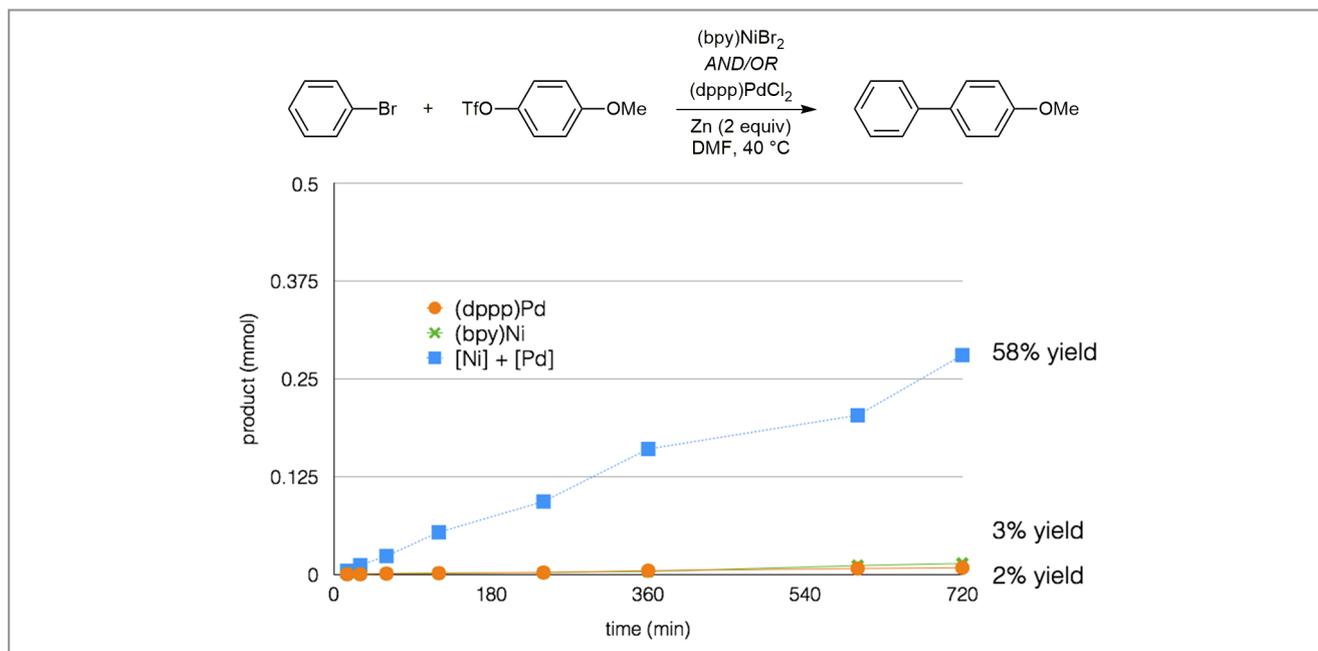
Multimetallic catalysis is represented in several well-known synthetic methods, such as the Wacker oxidation and the Sonogashira coupling. Although it holds great promise, it remains a nascent area in organic chemistry due to the complexity of integrating the reactivity of two metals. Professor Weix said: “Since the founding years of our research program,

we have been interested in multimetallic catalysis and how it could be applied to a reductive cross-electrophile coupling.” He continued: “Also, because of our success in developing methods for the coupling of aryl halides with alkyl halides, we were frequently asked about the potential for a cross-Ullmann reaction. We believed that a cross-Ullmann reaction would be a great vehicle to explore multimetallic catalysis because a general cross-coupling between two aryl halides had not yet been achieved, and the reaction would provide a route to valuable products.” Laura Ackerman – one of the authors of this study – had already spent a year synthesizing and studying the reactivity of various aryl metal complexes and the group knew that in order to design a successful multimetallic reaction, they would need selective activation of each aryl substrate and facile transmetalation between the two catalysts. Professor Weix said: “We hypothesized that the pairing of two reactive catalysts might result in rapid byproduct formation, and conversely, very stable catalysts might not promote any reaction at all. We decided that at least one catalyst should be relatively reactive in comparison to the other.” Due to the group’s experience with nickel catalysis and the myriad of literature on palladium-catalyzed cross-coupling reactions, the authors immediately focused on the combination of two catalysts that they knew possessed orthogonal selectivities for aryl bromides and aryl triflates.

The first nickel- and palladium-catalyzed cross-Ullmann reaction was very promising: Professor Weix and co-workers obtained greater than statistical selectivity; however, the overall product yield and reaction times were not ideal for the practicing synthetic chemist. Professor Weix explained: “Aiming to improve the yields of the reaction, Laura decided to investigate the use of KF as an additive, which had litera-



**Scheme 1**



Scheme 2

ture precedence for enhancing selectivity in metal-catalyzed cross-coupling reactions.” The third author of this study, Matt Lovell, helped Laura explore the effect of other additives on the multimetallic reaction, and extended the conditions to heteroaryl halides. “While the origin of the cooperation between nickel and palladium warrants further study, it is already apparent that the reaction does not proceed selectively with only one of the two catalysts,” said Professor Weix. “The nickel catalyst rapidly dimerizes aryl bromides before consuming any aryl triflate, while the palladium catalyst is selective for the addition of aryl triflates and is slow to dimerize materials. It appears that throughout the reaction, the arylpalladium intermediate is present in high concentration, while the arylnickel intermediate immediately reacts with the persistent palladium complex once formed.” Professor Weix concluded: “The elucidation of the mechanism of this reaction is an alluring challenge that we are now investigating in our lab. One could imagine that the conditions discovered for this cross-Ullmann reaction could be extended far beyond reductive cross-coupling to other exciting areas, such as cross-dehydrogenative coupling.”

*Matt Lovell*

### About the authors



M. M. Lovell

**Matthew Lovell** was born and raised in Munroe Falls, Ohio (USA). He graduated from the University of Rochester (USA) in 2014, majoring in chemistry and psychology. Matt worked in the Weix group for two years (2012–2014), studying nickel- and palladium-catalyzed reactions, and volunteering his time as an emergency medical technician. He is currently starting the first year of his Master’s program at Case Western Reserve University (USA) in medical physiology.

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*L. K. G. Ackerman*

**Laura Ackerman** was born and raised in Honolulu, Hawai'i (USA). After attending Punahou School, she attended Claremont McKenna College (USA) and majored in chemistry and religious studies while investigating asymmetric reactions under the supervision of Professor Anna G. Wenzel. After graduation in 2009, Laura returned to Hawai'i to conduct research under Professor David A. Vicic at the University of Hawai'i

at Mānoa on copper-promoted trifluoromethylation reactions. In 2010 Laura began researching in the Weix group at the University of Rochester as an NSF graduate fellow, exploring multi-metallic catalytic reactions and nickel-catalyzed cross-electrophile couplings.

*Prof. D. J. Weix*

**Daniel Weix** was born in Milwaukee, Wisconsin (USA) in 1978. He received a BA in chemistry at Columbia University (USA) in 2000 while working on helicenes with Professor Thomas Katz. After graduation, Daniel joined the group of Professor Jonathan Ellman at UC-Berkeley (USA) as an NSF graduate fellow in the area of sulfinamide chemistry. He received his PhD in 2005 and moved to Yale University (USA) as an NIH Postdoctoral Scholar under Professor John Hartwig from 2005–2008.

He was appointed Assistant Professor at the University of Rochester (USA) in 2008 and was promoted to Associate Professor in 2014. He has received several awards, including the Thieme Chemistry Journal Award, the Alfred P. Sloan Research Fellowship, the Camille Dreyfus Teacher-Scholar Award, and the Novartis Early Career Award. His research interests are in the development of new mechanisms in catalysis and their application in useful chemical reactions, especially in the area of cross-electrophile coupling.