

Phase-Transfer Catalysts Shift the Pathway to Transmetalation in Biphasic Suzuki–Miyaura Cross-Couplings

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Since its initial reports in 1979 by Miyaura and Suzuki, the Suzuki–Miyaura coupling (SMC) reaction has become an indispensable tool for carbon–carbon bond formation, earning a share of the 2010 Nobel Prize in Chemistry. Its mild reaction conditions and broad substrate scope have led to widespread applications in pharmaceutical synthesis, medicinal chemistry, natural product synthesis, and polymer synthesis. Despite its broad utility, the dominant mode of transmetalation in SMC reactions remains controversial and highly dependent on the specific reaction conditions employed.

A recent paper published by the group of Professor Jason Hein's group at the University of British Columbia (Vancouver, Canada) represents a significant advancement in the field of SMC reactions. The study explores the mechanistic intricacies of SMC under biphasic conditions and highlights the pivotal role of phase-transfer catalysts (PTCs) in enhancing the reaction rate and shifting the transmetalation pathway and addresses a longstanding controversy in the SMC mechanism, particularly regarding the mode of transmetalation. Traditional studies have proposed two primary pathways: oxo-palladium and boronate-based.

“Our *Nature Communications* paper addresses a longstanding controversy in the SMC mechanism regarding the mode of transmetalation,” said Professor Hein. He explained: “Two major pathways are typically proposed: a Pd–OH based pathway or a boronate-based pathway. Under traditional biphasic reaction conditions, the Pd–OH pathway was found to dominate. This results in sluggish reactivity as the halide byproduct builds up over time and inhibits the catalyst. The introduction of readily available PTCs dramatically improved reactivity under the biphasic conditions. This was found to result from shifting the dominant mode of transmetalation towards a boronate-based system by manipulating the speciation of both the catalyst and nucleophile. Under these conditions, the build-up of the halide salt byproduct benefits the overall reaction. Finally, the impact of organic and aqueous layer proportions was probed. Contrary to typical SMC conditions, minimizing the proportion of the organic layer was found to benefit reactivity.”

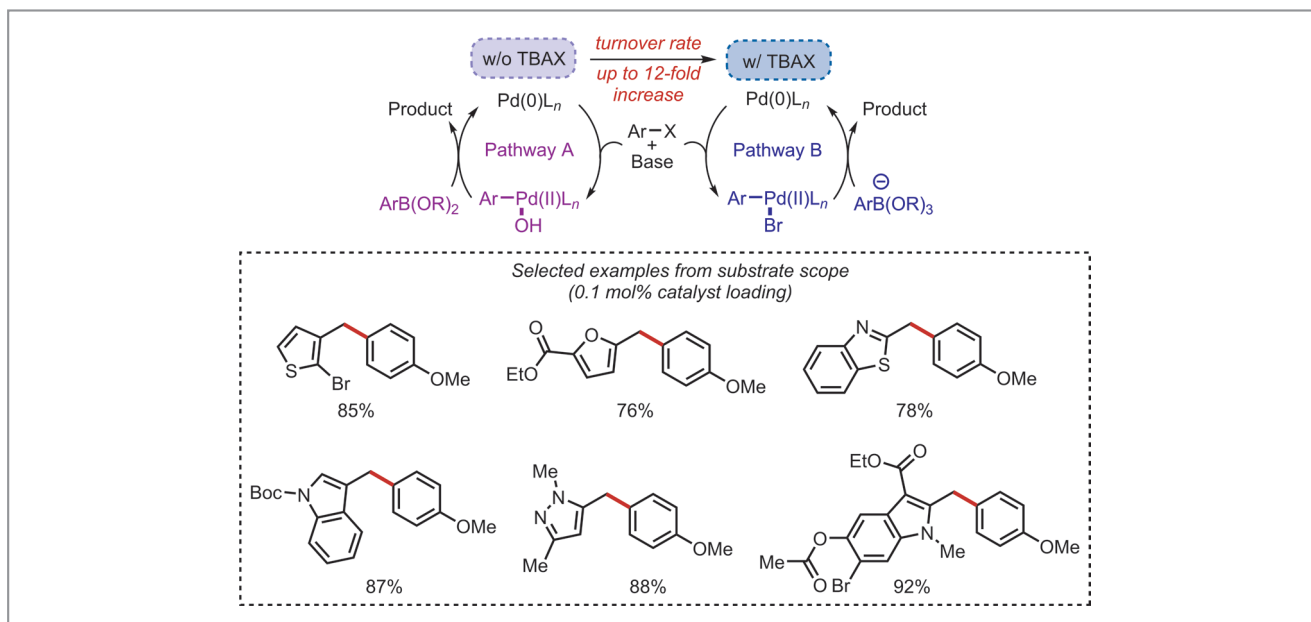
Professor Hein explained that by favoring the boronate pathway, PTCs enhance both catalyst and nucleophile speciation, transforming the halide salt byproduct from an in-

hibitory to a beneficial role, thereby substantially improving reaction rates and efficiency. Professor Hein remarked: “The addition of PTCs not only enhances the reaction rate by a notable 12-fold, but also shifts the transmetalation pathway from the oxo-palladium pathway to the boronate-based pathway. This finding challenges the prevailing emphasis on organo-boron species optimization and highlights the critical influence of water content and PTCs in the reaction medium.”

Studying the mechanism of the SMC is an ongoing effort in the Hein lab. “We hope to shed light on how the specific conditions employed impacts which transmetalation pathway is favored and how that impacts side-product profiles,” said Professor Hein, adding: “This will provide practitioners in the field with a rational approach towards optimization of SMC conditions.”

The success of this project stemmed from the serendipitous combination of technological development with curiosity-driven research. Professor Hein told SYNFORM: “The development of the automated sampling platform leveraged in this study has been a longstanding focus of the Hein lab. Its robust performance under challenging heterogeneous conditions inspired us to explore its potential in one of the most important heterogeneous settings: the SMC under biphasic conditions.”

The practical applications of this research are vast. Professor Hein explained: “The enhanced SMC process can be employed in the synthesis of pharmaceutically relevant compounds, natural products, and polymers.” He concluded: “The demonstrated ability to achieve high yields with low catalyst loadings can lead to more sustainable and economical manufacturing processes in the chemical industry.”



Scheme 1 Addition of a phase-transfer catalyst modifies the catalyst and arylboron speciation, favouring the Ar-Pd(II)X/boronate transmetallation pathway under biphasic conditions. This gives a 12-fold rate enhancement and enables challenging substrates to be accessed while maintaining exceptionally low catalyst loading.

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About the authors



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Yao Shi received her M. Phil. degree in chemistry from the Chinese University of Hong Kong (P. R. of China) under the supervision of Prof. Yeung Ying Yeung. She is currently pursuing her Ph.D. in chemistry under the supervision of Prof. Jason Hein at the University of British Columbia (Canada), focusing on reaction kinetics, employing online monitoring techniques to observe and analyze reactions in real time.



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Joshua S. Derasp began his post-secondary studies at the University of Prince Edward Island (Canada), where he received his B.Sc. in chemistry with honours. He then moved to Ottawa to join the group of Prof. André M. Beauchemin at the University of Ottawa (Canada) receiving his Ph.D in organic chemistry in 2019. He then joined the group of Prof. Jason E. Hein at the University of British Columbia (Canada) as a postdoctoral



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Tristan Maschmeyer-Tombs participated in marine natural products research with Prof. Philip Crews at the University of California, Santa Cruz (USA) and completed a B.Sc. in chemistry with honors in 2018. In 2019, he started his Ph.D studies with Prof. Jason E. Hein at the University of British Columbia (Canada) and completed his degree in 2023. His graduate research focused on the application of benchtop NMR for online reaction monitoring. Currently,



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Jason Hein is a Professor of Chemistry at the University of British Columbia (Canada), and an Adjunct Professor at the University of Bergen, Norway. Prof. Hein was the co-lead of Project ADA; the world's first autonomous discovery platform for thin film materials, supported by Natural Resources Canada, co-PI of the MADNESS team supported by the DARPA Accelerated Molecular Discovery Program and the UBC lead for the Acceleration Consortium CFREF spearheaded by the University of Toronto (Canada). He received his B.Sc. in biochemistry in 2000 and Ph.D. in asymmetric reaction methodology in 2005 from the University of Manitoba, Canada (NSERC PGS-A/B, Prof. Philip G. Hultin). In 2006, he became an NSERC postdoctoral research fellow with Prof. K. Barry Sharpless and Prof. Valery V. Fokin at the Scripps Research Institute in La Jolla, CA (USA). In 2010, he became a senior research associate with Prof. Donna G. Blackmond at the Scripps Research Institute. He began his independent career at the University of California, Merced (USA) in 2011, employing in situ kinetic reaction analysis to rapidly profile and study complex networks of reactions. In 2015, he moved to the University of British Columbia and was promoted to Associate Professor and then full Professor in 2019 and 2024 respectively. His research has resulted in a collection of prototype modular robotic tools and integrated analytical hardware which create the first broadly applicable automated reaction profiling toolkit geared toward enabling autonomous research and discovery.