

Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

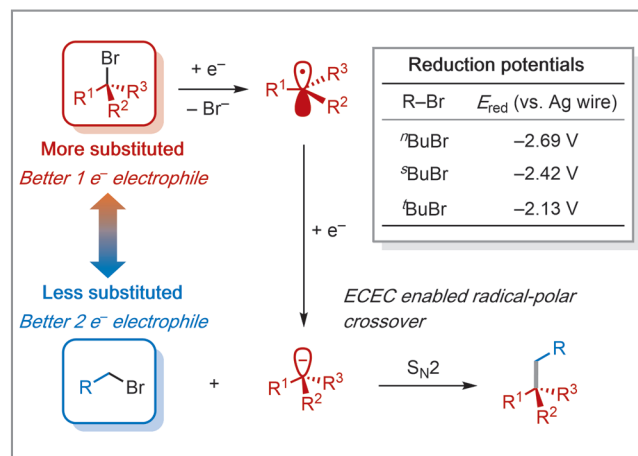
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Carbon–carbon bonds are key structural units in organic molecules. Thus, a tremendous effort has been dedicated to studying their formation. Transition-metal-catalyzed cross-coupling reactions are among the most reliable approaches for the formation of C–C bonds in organic synthesis. To avoid synthetic steps to preform organometallic reagents as well as stability and functional-group-tolerance issues that are commonly associated with these nucleophiles, cross-electrophile coupling (XEC) of organic halides has drawn substantial attention in the last decade as a methodology for achieving C–C bond formations.¹ However, despite great advances in this area, the selective XEC of two alkyl halides to construct C(sp³)–C(sp³) bonds has remained elusive.^{2,3}

Harnessing electrochemistry to solve challenging problems in organic synthesis has been an overarching goal of Professor Song Lin's research program at Cornell University (Ithaca, New York, USA). Professor Lin told SYNFORM: "In the past several years, we have advanced various electrocatalytic methods for the oxidative difunctionalization of alkenes.⁴ Recently, we turned our attention toward electroreductive chemistry. Employing electrochemical reduction of chlorosilanes and alkyl bromides, we have, for example, achieved intermolecular disilylation⁵ and carbo-functionalization of alkenes.^{6"}

Inspired by the S_N2 reaction, which is commonly used to forge C(sp³)–C(sp³) bonds, the group envisioned a new approach to cross-couple two alkyl halides by exploiting their disparate electronic and steric properties (Scheme 1). "Specifically, tertiary alkyl halides preferentially undergo two consecutive single-electron reductions over less substituted primary halides to generate the corresponding carbanions, which then selectively react with primary halides owing to their smaller steric profiles," remarked Professor Lin.

Dr. Wen Zhang, the lead author of the *Nature* paper and a postdoctoral associate in the Lin laboratory, explained: "This work is innovative and significant for the following reasons: (1) The mechanism of our e-XEC process is fundamentally different from previously reported Ni-catalyzed methods as it does not require the generation of metal-alkyl intermediates, which can often lead to unselective electrophile activation or various other side reactions. (2) The e-XEC shows improved cross-coupling selectivity (vs. homocoupling) compared with known methods for C(sp³)–C(sp³) XEC. (3) Guided by cyclic voltammetry and DFT calculations, a broad scope of

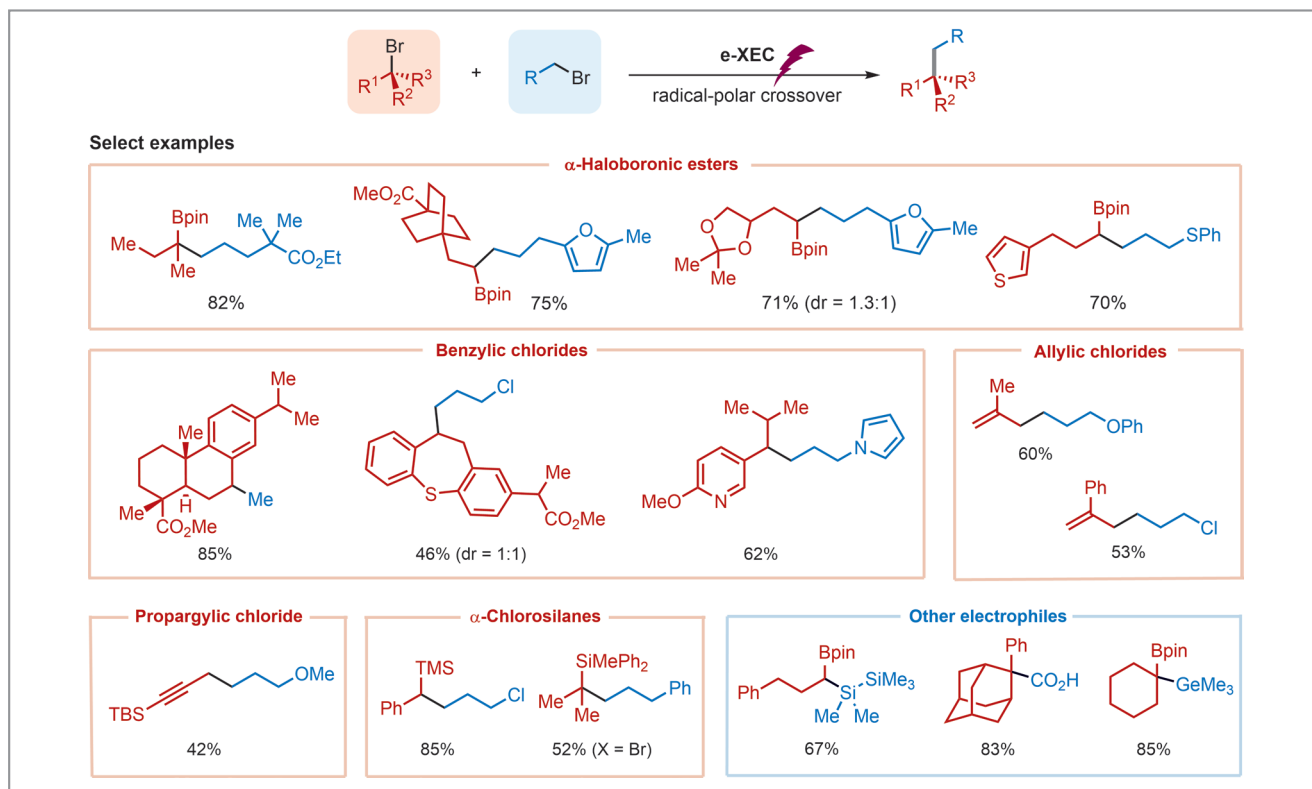


Scheme 1 Reaction design for e-XEC reaction; ECEC = electrochemical–chemical–electrochemical–chemical.

alkyl halides was shown to be compatible with the process, including α-haloboronic esters, α-halosilanes, benzylic chlorides, and allylic/propargylic halides, giving rise to a diverse panel of synthetically valuable intermediates (Scheme 2). (4) Mechanistic studies using electroanalytical and spectroscopic tools addressed issues connected to electrode passivation and informed the development of a more practical and scalable procedure."

Highlighting the future directions of the research described in this article, Professor Lin pointed out that an anion-stabilizing substituent was introduced on one of the alkyl halide electrophiles to improve reaction selectivity. "To broaden the scope of e-XEC, we will continue to explore selective reactions of two unactivated alkyl halides," said Professor Lin, continuing: "In addition, we hope to further improve the scalability of this reaction beyond laboratory scale by identifying a homogeneous reductant to replace the Mg sacrificial anode in combination with the use of a flow reactor. Besides alkyl halides, there are many other types of electrophiles that are interesting to explore using this electroreductive strategy."

The completion of this project was the result of a highly synergistic collaboration among the Lin group at Cornell, the See group at Caltech, and the Process Chemistry group at Merck. "The synthetic work carried out at Cornell benefited tremendously from the feedback and guidance from collaborators at Merck," acknowledged Professor Lin. He concluded:



Scheme 2 Selected substrate scope

“Also, the See group studied electrode passivation using electroanalytical and spectroscopic tools, and their expertise in Mg battery research brought about a simple solution to the troubling electrode fouling by using a metal-coordinating co-solvent.”

Mattes female

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About the authors

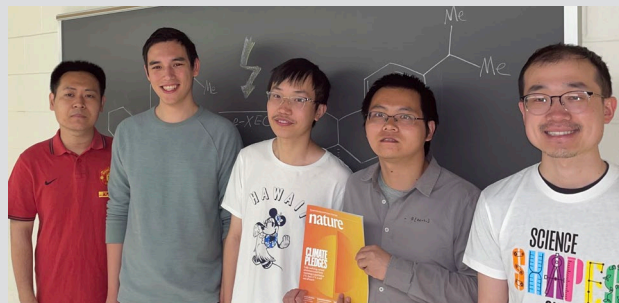


From left: W. Zhang, Prof. K. See and S. Ware

Wendy Zhang was born and raised in Changchun (P. R. of China). She completed her B.S. and M.S. at The College of William and Mary (USA) under Professor William McNamara in iron polypyridyl catalyst for photocatalytic hydrogen evolution. She later joined Professor Kimberley See's lab at Caltech (USA), focusing on improving the performance of Mg sacrificial anodes for organic electrosynthesis.

Kimberly See is an Assistant Professor of Chemistry in the Division of Chemistry and Chemical Engineering at Caltech (USA). She was born and raised in Colorado and received her B.S. in chemistry from the Colorado School of Mines (USA). Kim pursued her Ph.D. in chemistry at the University of California, Santa Barbara (USA) where she worked with Profs. Ram Seshadri and Galen Stucky. Kim was awarded the St. Elmo Brady Future Faculty Postdoctoral Fellowship at the University of Illinois at Urbana-Champaign (USA) and worked with Prof. Andrew Gewirth in the Department of Chemistry. Now, her group at Caltech studies the electrochemistry of Earth abundant, inexpensive materials with a focus on next-generation energy storage.

Skyler Ware was born and raised in Cincinnati, OH (USA). She completed her B.S. at The Ohio State University in 2018, where she conducted undergraduate research with Professor Robert Baker in electrochemical CO₂ reduction. In autumn 2018, she joined Professor Kim See's research group as a graduate student at Caltech (USA). Her research focuses on electrolyte development for electrocatalysis and energy storage devices.



From left: Dr. Y. Wang, J. Rein, L. Lu, Dr. W. Zhang and Prof. S. Lin

Yi Wang was born in Zhejiang (P. R. of China). He received his B.S. degrees in chemistry and economics from Peking University (P. R. of China). Then, he pursued graduate studies under the supervision of Professor Zhi-Xiang Yu at Peking University. His doctoral research was focused on mechanistic studies of catalytic reactions and carbon-to-carbon proton transfers. In September 2021, he joined the Lin research group at Cornell University (USA) as a postdoctoral associate. His current research is focused on developing and understanding electrochemical reactions.

Jonas Rein was born in Dudweiler (Germany) in 1999 and grew up in Mainz (Germany). He received his B.Sc. degree in 2019 from the Johannes-Gutenberg University in Mainz (Germany) working under the supervision of Prof. Waldvogel on electrochemical C–H functionalizations. Since then, he has been with Prof. Lin's group at Cornell University (USA) for his Ph.D. studies focusing on the development of high-throughput experimentation for electrochemistry and novel scaffolds for asymmetric organocatalysis.

Lingxiang Lu was born and raised in P. R. of China. He received his B.S. degree in chemistry from Wuhan University under the supervision of Prof. Hexiang Deng and Fusheng Ke, working on metal–organic frameworks and lithium sulfur batteries. In 2017, he joined Prof. Song Lin's research group at Cornell (USA) for Ph.D. studies on electrosynthesis. He is currently working on developing electroreductive transformations for organic synthesis.

Wen Zhang was born and raised in Anhui (P. R. of China). He obtained his B.S. from Sichuan University (P. R. of China) in 2013. Then, he pursued graduate studies under the guidance of Prof. Guosheng Liu at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (P. R. of China). His doctoral research was focused on asymmetric C–H bond functionalization.

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zation via copper-catalyzed radical relay. In December 2018, he started his postdoctoral studies with Prof. Song Lin at Cornell University (USA) where his research is focused on the development of novel electrochemical methods for organic synthesis.

Song Lin was born and raised in Tianjin (P. R. of China). After earning his B.S. from Peking University (P. R. of China) in 2008, he pursued graduate studies at Harvard University (USA) working under the direction of Prof. Eric Jacobsen. His doctoral research was focused on the development and mechanistic understanding of enantioselective organocatalysis. He then carried out postdoctoral studies with Prof. Chris Chang at UC Berkeley (USA) on electrocatalytic reduction of CO₂ using covalent organic frameworks. In the summer of 2016, Prof. Song Lin joined the Cornell faculty (USA). His research focuses on the discovery of new catalytic strategies for organic synthesis using fundamental principles of electrochemistry and radical chemistry.



J. Mondragon

Wolczanski, working with strained molecules to generate novel alkylidenes.

Jose Mondragon was born in Peru, in the city of Lima, and moved to New Jersey (USA) at the age of 7 where he grew up. He joined Professor Song Lin's lab at Cornell University (USA) in the summer of 2019 as a rising sophomore, where he worked on titanium radical redox relay cyclization cascades, and will graduate with an A.B. in chemistry in the spring of 2022. His current research is in the field of organometallics with Professor Peter



Dr. N. Strotman

doctoral fellow with Professor Gregory C. Fu, where he developed Ni-mediated methods for asymmetric Hiyama couplings of α -bromoesters. Over the last 15 years, Neil has leveraged his

Neil Strotman is the Director of Catalysis, Labeled Compound Synthesis, and Particle Engineering in Process Research and Development at Merck & Co. in Rahway, NJ (USA). Neil obtained his Ph.D. under the direction of Professor Charles P. Casey at the University of Wisconsin-Madison (USA) studying reactivity and mechanisms of organometallic processes with Ti, Zr, Ru, and Re. He next moved to MIT (USA) as a post-

skills in physical organic chemistry and catalysis in the enabling technologies space and has gained experience in process development, plant scale implementation, project leadership, PAT, and flow chemistry. In his free time, Neil enjoys hiking, woodworking, and traveling with his family.



Dr. D. Lehnher

University (USA) with Prof. William Dichtel researching nanographenes and ortho-arylene-based foldamers. In 2016 he joined the Catalysis Group within Process Research and Development at Merck & Co., Inc. in Rahway, NJ (USA). His research interests are at the intersection of reaction discovery, physical organic chemistry, computational chemistry, and new capabilities to enable the development of medicines.

Dan Lehnher received his B.Sc. from the University of Victoria (Canada). He pursued his graduate studies under the mentorship of Prof. Rik Tykwinski (Chemistry) and Prof. Frank Hegmann (Physics) developing organic materials for optoelectronic applications. He carried out postdoctoral research at Harvard University (USA) with Prof. Eric Jacobsen focused on organocatalysis and reaction mechanism elucidation, and subsequently at Cornell