

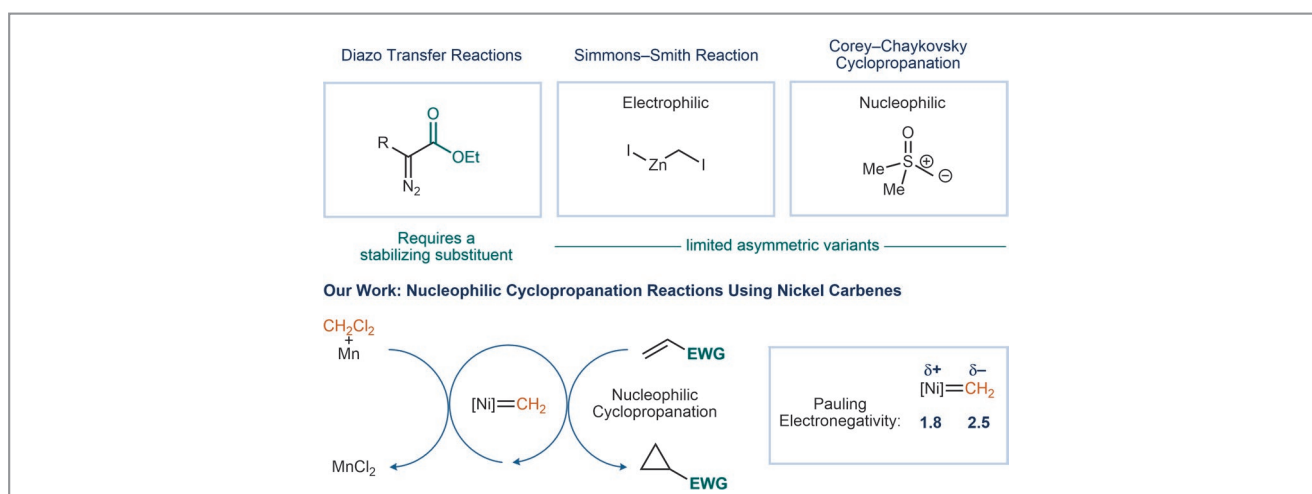
## Nucleophilic Carbenes Derived from Dichloromethane

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The cyclopropyl ring is an important structural motif, featuring high ring strain and reactivity. Its unique properties make it a valuable building block in organic synthesis and drug design. Cyclopropyl rings are found in several pharmaceuticals, as they can introduce desirable properties into drug candidates and therapeutics. Cyclopropyl groups can also serve as bioisosteres for other functional groups, potentially improving drug potency or pharmacokinetics. Among cyclopropyl ring-forming reactions, catalytic alkene cyclopropanation reactions have a long history in organic synthesis, but most methods rely on diazoalkanes, which are energetic molecules that have significant safety concerns when used on commercial scales. For the past five years, the group of Professor Christopher Uyeda at Purdue University (West Lafayette, USA) has been interested in developing catalytic cyclopropanation reactions that can use readily available *gem*-dihaloalkanes as carbene precursors. “Our approach is inspired by a classic cyclopropanation method, the Simmons–Smith reaction,” explained Professor Uyeda. He continued: “However, instead of stoichiometrically generating zinc carbenoids from  $\text{CH}_2\text{I}_2$  and Zn, we are able to catalytically generate nickel carbene intermediates from a variety of *gem*-dihaloalkanes. One advantage of this approach is that the nickel catalyst is much more reactive than Zn metal, which allows us to use dichloro-

methane as the carbene precursor. Another advantage is that we are able to use chiral ligands to carry out highly enantioselective cyclopropanation reactions.” Historically, developing catalytic enantioselective Simmons–Smith reactions has been challenging. Most examples use chiral Lewis acids and are restricted to allylic alcohol substrates. Professor Uyeda and his co-workers are hopeful that their approach using transition-metal catalysis will provide a more general solution to this synthetic problem (Figure 1).

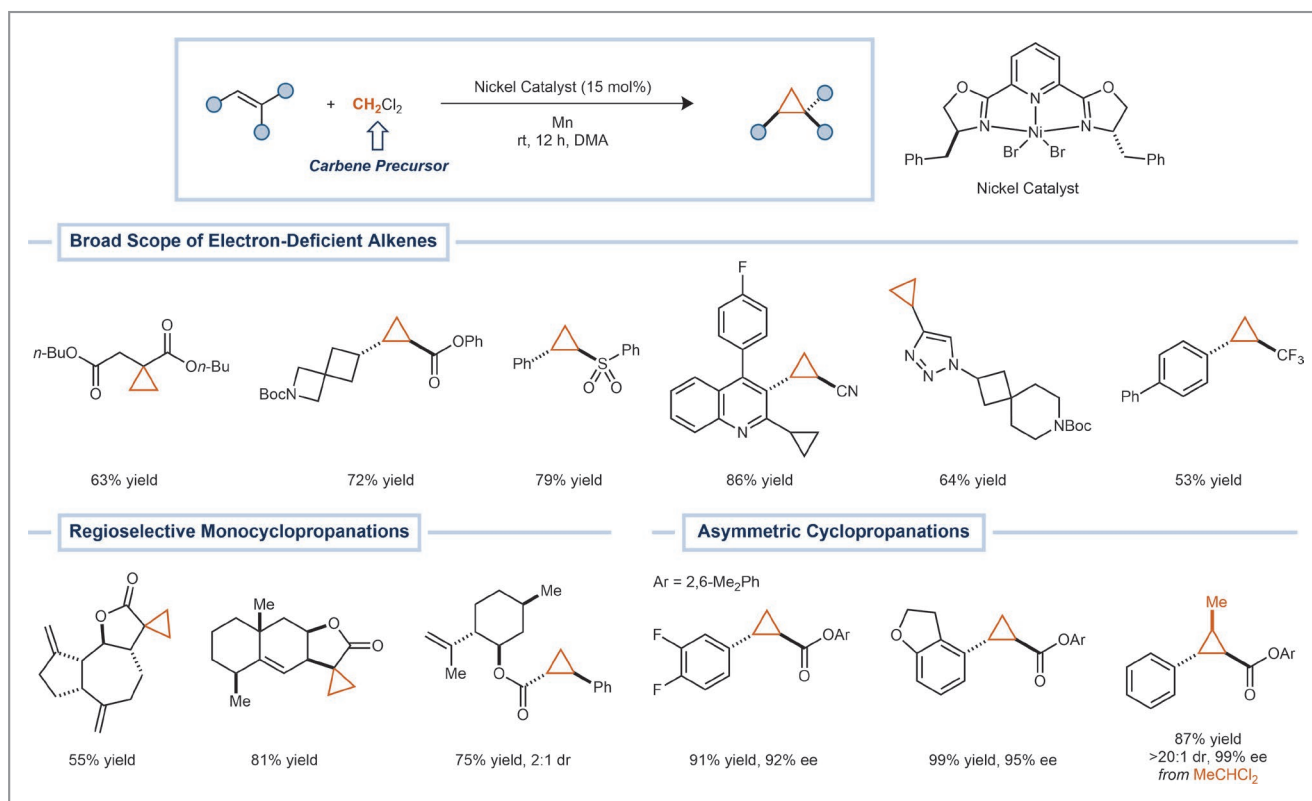
“When we were first thinking about this reaction, we obtained some important clues from the literature,” acknowledged Professor Uyeda. He explained further: “Decades ago, Hiroyoshi Kanai had shown that simple nickel salts enable cyclopropanation reactions of electron-deficient alkenes using typical Simmons–Smith reagents. This finding was intriguing because zinc carbenoids are known to be electrophilic and should be unreactive toward electron-deficient alkenes. Therefore, it was more likely that a nickel carbene of some kind was being generated in the reaction. Our contribution was to show that pyridine–bis(oxazoline) ligands could make the nickel-catalyzed cyclopropanation general across a broad range of substrate classes (Scheme 1). For example, we are able to access cyclopropanes bearing fluoroalkyl groups, sulfones, phosphonate esters, and nitriles, which are difficult



**Figure 1** (Top) Established approaches to cyclopropanation based on diazoalkanes, zinc carbenoids, and sulfur ylides. (Bottom) Nickel-catalyzed cyclopropanation reactions of electron-deficient alkenes (EWG = electron-withdrawing group) using  $\text{CH}_2\text{Cl}_2$  as a carbene precursor. The proposed nickel carbene intermediate has nucleophilic character due to polarization of the Ni–C bond.

to prepare using other methods. For substrates that contain both electron-rich and electron-deficient alkenes, only the electron-deficient alkenes are cyclopropanated, demonstrating the nucleophilic character of the nickel carbene intermediate. Finally, we are able to take simple cinnamate esters and generate 2-aryl cyclopropanes that are found in pharmaceutical compounds.”

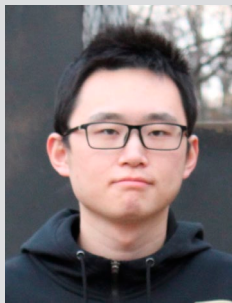
Professor Uyeda concluded: “We hope that these studies will inspire a much broader investigation of transition-metal catalysts for reductive carbene transfer reactions using *gem*-dihaloalkanes. This is an underdeveloped approach to carbene generation, particularly when compared to the large body of literature on diazoalkane chemistry.”



**Scheme 1** A broad scope of electron-deficient alkenes undergo reductive cyclopropanation using a nickel catalyst. For complex polyalkenes, the most electron-deficient alkene is cyclopropanated with high regioselectivity. Chiral nickel catalysts enable highly enantioselective cyclopropanations of cinnamate derivatives.

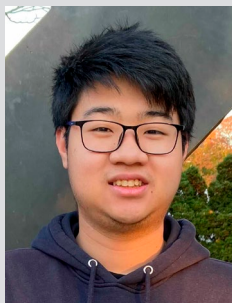
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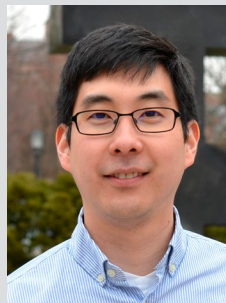
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on nickel-catalyzed carbene transfer reactions and reactivity studies of organonickel complexes.

**Mingxin Liu** received his B.S. in chemistry at Jilin University (P. R. of China) in 2019. During his undergraduate studies, he spent a semester in Prof. Mingji Dai's group at Purdue University (USA) as a visiting student, where he worked on the total synthesis of natural products. Choosing to stay at Purdue University for graduate studies, he is currently a Ph.D. candidate under the guidance of Prof. Uyeda. His graduate research focuses

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**Nguyen Le** received his B.S. in chemistry at Purdue University (USA) in 2023 where he carried out undergraduate research on nickel carbene chemistry in Prof. Christopher Uyeda's group. Currently, he is a Ph.D. student at Cornell University (USA) working under Prof. Song Lin's guidance on electrochemical oxidation catalysis.

*Prof. C. Uyeda*

doctoral research on molecular electrocatalysts for solar fuel production with Prof. Jonas Peters. In 2013, he started his independent program at Purdue University (USA) and is currently the Richard B. Wetherill Professor of Chemistry. His research program focuses on developing catalytic carbene transfer reactions, studying catalytic processes at metal-metal bonds, and studying N=N coupling reactions for the synthesis of azo materials.

**Christopher Uyeda** received his B.S. degree from Columbia University (USA), where he carried out undergraduate research on hydrophobically directed reactions with Prof. Ronald Breslow. He obtained his Ph.D. from Harvard University (USA) under the guidance of Prof. Eric Jacobsen. His thesis described the development of chiral hydrogen-bond donors for enantioselective Claisen rearrangements. He then carried out post-