Leveraging One- and Two-Electron Mechanisms in Nickel-Catalyzed Cross-Coupling

Tianning Diao
New York University

While palladium-catalyzed cross-coupling reactions have revolutionized the construction of multi-aryl scaffolds in pharmaceutical synthesis, the reactivity of nickel in mediating radical pathways has expanded the scope of cross-coupling to include a variety of alkyl motifs. Through mechanistic investigations and understanding the ligand effects, we have established that strong σ-donor and π-acceptor ligands exhibit redox-activity, facilitating nickel catalysts to initiate radical formation, capture radicals, and direct bond formation from open-shell intermediates. The orthogonal reactivity of radicals with polar functional groups in biomolecules has opened new avenues for synthesizing non-canonical peptides and carbohydrates, which are important for drug discovery. In contrast, two-electron pathways are crucial for nickel-catalyzed bi-aryl coupling. Building on this insight, we have developed a novel ligand that enhances the reactivity of nickel-catalyzed Suzuki-Miyaura couplings, paving the way for the application of nickel catalysts in pharmaceutical process synthesis.