Cross-Coupling of Amides by N–C Activation and N-Heterocyclic Carbene Ligand Development

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Development of new strategies encompassing activation of inert bonds has revolutionized organic synthesis. N-Heterocyclic carbenes (NHCs) represent a tremendously important and versatile class of ligands in organometallic chemistry and catalysis. In this lecture, recent developments in the the selective activation of amide bonds by destabilization-controlled metal insertion into the N–C(O) bond as well as in the design of new, highly active NHC catalysts for cross-coupling reactions will be presented. The ligands discussed represent several new classes of recently commercialized NHCs and NHC-metal complexes that enable steric and electronic tuning of the metal center by complementary strategies relying on (1) backbone, (2) wingtip, and (3) ancillary ligand development. Steric and electronic tuning of the carbene center is a recurring theme of this class of ligands, encompassing imidazol-2-ylidenes, imidazo[1,5-a]pyridine-3-ylidenes, thiazol-2-ylidenes and cyclic (alkyl)(amino)carbenes. The amide bond activation reactions are enabled by rationally-tuned decreased amidic resonance, ground-state-destabilization, which is an emerging theme of this thriving cross-coupling manifold. This transition-metal-catalyzed cross-coupling of amide N–C(O) bonds holds a potential for widespread synthetic and biological applications. The selectivity in amide bond cross-coupling will be discussed. Representative examples to be discussed include Pd-, Ni- and Rh-catalyzed (1) acyl, and (2) aryl cross-couplings. Furthermore, recent advances in decarbonylative cross-coupling of carboxylic acids by selective generation of acyl-to-aryl metal intermediates for cross-coupling reactions of general carboxylic acid electrophiles will be presented.

"Too close to close? The biradical is the answer"

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ABSTRACT:

The stereoselective synthesis of cyclobutanes that possess an array of stereocenters in a contiguous fashion has attracted the wide interest of the synthetic community. Cyclobutanes can be generated from the contraction of pyrrolidines through the formation of 1,4-biradical intermediates. Little else is known about the reaction mechanism of this reaction. Here, we unveil the mechanism for this stereospecific synthesis of cyclobutanes by means of DFT calculations [1]. The rate-determining step of this transformation corresponds to the release of N_2 from the 1,1-diazene intermediate to form an open-shell singlet 1,4-biradical. The formation of the stereoretentive product is explained by the barrierless collapse of this open-shell singlet 1,4-biradical. The knowledge of the reaction mechanism is used to predict that the methodology could be amenable to the synthesis of [2]-ladderanes and bicyclic cyclobutanes.

[1] R. Monreal-Corona, M. Solà, A. Pla-Quintana, A. Poater, Stereoretentive Formation of Cyclobutanes from Pyrrolidines: Lessons Learned from DFT Studies of the Reaction Mechanism. *J. Org. Chem.* **2023**, *88*, 4619–4626.