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

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Development of 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, advances in the selective activation of amide bonds by destabilization-controlled metal insertion into the N–C(O) bond as well as the design of new, highly active NHC catalysts will be presented. The amide bond activation reactions are enabled by rationally-tuned decrease of amidic resonance and ground-state-destabilization, which is a leading theme of this thriving cross-coupling manifold. The transition-metal-catalyzed cross-coupling of 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. 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. The ligands discussed represent several classes of 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, encompassing imidazol-2-ylidenes, imidazo[1,5-a]pyridine-3-ylidenes, thiazol-2-ylidenes and cyclic (alkyl)(amino)carbenes.