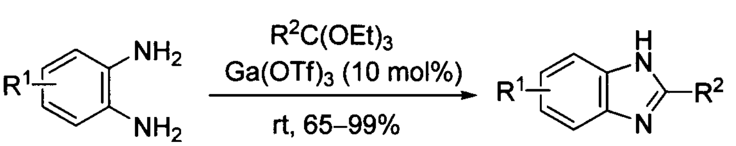
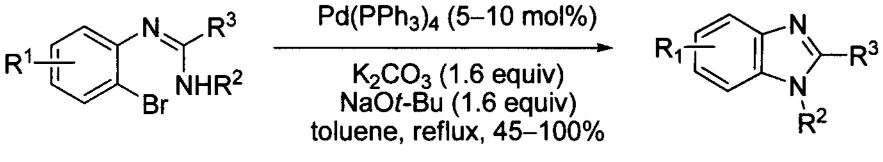


8.8 Construction of the Benzimidazole Core Using Transition Metal-Mediated Approaches

8.8.1 C–N Bond Formation from Aryl Halide

In recent years, significant research effort has been directed toward identification of new methods for benzimidazole synthesis.[53] Recent advances, particularly in transition metal-mediated reactions, have ushered in novel synthetic approaches for the construction and functionalization of this useful ring system. The present overview of new transition metal-mediated synthetic approaches focuses primarily on methodologies reported from 2008 to early 2012 that may soon find broader application in drug synthesis.

Brain and Brunton reported one of the early palladium-catalyzed cyclizations, which provided benzimidazoles in moderate to high yield.[54] In this study, $Pd(PPh_3)_4$ was used to catalyze the intramolecular *N*-arylation of *o*-bromoamidines to afford variously substituted 1-alkyl or 1-phenyl-benzimidazoles. This report set the stage for additional investigations of transition-metal mediated *N*-arylation as a tactic for benzimidazole synthesis.



In more recent adaptations of metal-catalyzed benzimidazole construction, copper catalysts have gained preeminence for mediating either intermolecular or intramolecular C–N bond formation with aryl bromides or iodides. The utility of copper catalysis in intermolecular amidations was highlighted by Zheng and Buchwald in their report of the stepwise formation of *N*-alkyl benzimidazoles using intermolecular amidation as a key step.[55] Copper-catalyzed amidation of *o*-iodo- or *o*-bromo-*N*-alkylanilines is achieved using CuI (5 mol%), diamine ligand (L), and Cs_2CO_3 in 1,4-dioxane. The resultant anilide is then subjected to dehydrative conditions in analogy to the classical Phillips approach.