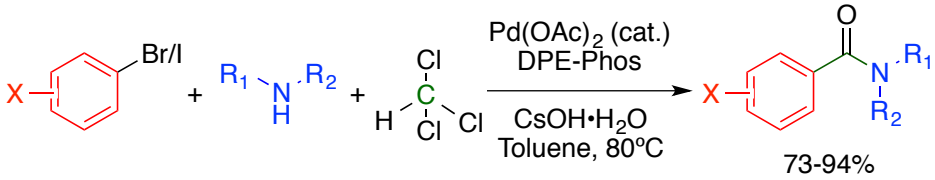
Palladium Catalyzed CO-Free Aminocarbonylation of Aryl Halides

Samuel N. Gockel and Kami L. Hull

The amide is an important functional group often found in biologically active compounds or in key intermediates towards the total synthesis of these compounds. With the advent of transition metal catalysis, the carbonylation of aryl halides with CO and amines has become a powerful approach towards amide formation. These methodologies suffer a drawback in the use of superstoichiometric and, in some cases, high pressures of highly toxic CO. Specialized reactors, storage procedures, and laboratory equipment are all required for the execution of this chemistry. Therefore, significant efforts have been put into developing CO-free aminocarbonylation protocols. Herein, we report the discovery and development of a CO-free aminocarbonylation reaction using $CsOH \bullet H_2O$ and reagent quantities of chloroform as the carbonyl source. The reaction is highly functional group tolerant, allowing for the coupling of a wide variety of aryl iodides and bromides with primary and secondary amines to furnish amides in good chemical yield. By harnessing the divergent mechanism by which the amide carbonyl is formed, we aim to realize new transformations and structures that are not accessible by traditional carbonylation.



Understanding How Imperfect Small Molecule Mimics of Missing Proteins Restore Physiology

Jennifer Hou and Martin D. Burke

Diseases caused by an excess of protein function can be treated by small molecule inhibitors. However, in the case of diseases caused by dysfunctional or missing proteins, this approach is typically ineffective. Several strategies to try to address the latter include gene therapy or direct replacement of the missing protein (e.g. insulin to treat diabetes). However, despite important progress, to date more than 30 human diseases caused by dysfunctional or missing ion channel proteins remain incurable, demonstrating the need for new therapeutic strategies. We demonstrated that the ion channel forming small molecule Amphotericin B (AmB) was able to vigorously and sustainably restore physiology in a growth deficient strain of yeast *Saccharomyces cerevisiae* (*S. cerevisiae*) lacking potassium transporter proteins Trk1p and Trk2p. We hypothesize that ion channel forming small molecules work in collaboration with cellular networks of contributing proteins, involved in promoting physiological transmembrane ion gradients, to restore physiology in *S. cerevisiae*. Our findings will lay the foundation for the utilization of imperfect small molecule mimics as a viable new strategy for the treatment of diseases cause by missing or dysfunctional proteins and will guide the rational design of derivatives with enhanced therapeutic effectiveness for the betterment of human health.