

NICOLAS ROTTA-LORIA
BSc Honours (Chemistry), Dalhousie University, 2013

DEPARTMENT OF CHEMISTRY

TITLE OF THESIS: ADVANCES IN LATE-METAL CARBON-NITROGEN BOND FORMATION FOR THE SYNTHESIS OF SUBSTITUTED HETEROCYCLES

TIME/DATE: 9:30am, Wednesday, July 19, 2017

PLACE: Room 3107, The Mona Campbell Building,
1459 LeMarchant Street

EXAMINING COMMITTEE:

Dr. Laurel L. Schafer, Department of Chemistry, University of British Columbia (External Examiner)

Dr. Alison Thompson, Department of Chemistry, Dalhousie University (Reader)

Dr. Alex Speed, Department of Chemistry, Dalhousie University (Reader)

Dr. Laura Turculet, Department of Chemistry, Dalhousie University (Reader)

Dr. Mark Stradiotto, Department of Chemistry, Dalhousie University (Supervisor)

DEPARTMENTAL REPRESENTATIVE: Dr. Erin Johnson, Department of Chemistry, Dalhousie University

CHAIR: Dr. Graham Gagnon, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Late-metal catalyzed cross-couplings have emerged as efficient and selective methodologies for the formation of C-C and C-N bonds. The ability to synthesize complex heterocycles from cheap and abundant starting materials is an invaluable asset to the pharmaceutical industry, given that many pharmaceuticals contain at least one heterocyclic component. This reactivity can be achieved by tuning the steric and electronic properties of ancillary ligands to support metal catalysts in the reaction steps leading to the target substrate.

The Stradiotto group has developed several state-of-the-art methodologies involving ligands for palladium catalysis, for both C-C and C-N bond-forming reactions. These methodologies can be amalgamated into a multicomponent reaction platform to synthesize more complex products from simple materials. Chapter 1 outlines this concept with the application of a Mor-DalPhos/Pd catalyst in the one-pot synthesis of indoles from acetone and simple amines. The robust nature of this method can be extended to include benchtop reaction conditions in a one-step, one-pot synthesis of indoles, thus representing a useful synthetic protocol.

While palladium provides a powerful tool for C-C and C-N bond formation, the general trend in catalysis has shifted toward first row metals as economic alternatives. Nickel complexes have recently emerged as excellent catalysts for amination reactions. The ability to utilize ammonia also represents a sought after reaction, due to the widespread availability and synthetic utility of amino-functionalized products. In this regard, Chapter 2 will focus on the development and application of both commercially available and strategically designed ligand classes for the monoarylation of ammonia with substituted heterocycles.

Hydrazine represents an important synthon in many industrial processes and is synthesized on multi-ton scale every year. Many synthetic challenges arise from utilizing free hydrazine as a reactant in the field of late-metal catalyzed C-N bond-formation. However, gold-catalyzed methodologies have been developed utilizing NHC ligands to allow for the hydrohydrazination of alkynes with parent hydrazine. Chapter 4 examines the development and application of a series of (PR₃) AuCl complexes for use in such transformations, leading to the identification of the first effective phosphine-bound gold complex for use in the hydrohydrazination of alkynes at room temperature.