Copper (**Cu**) is one of the most abundant of all transition metals. A suitable alternative to indispensable but toxic and expensive palladium (Pd), Cu first gained recognition in the chemical industry as catalysts with the independent efforts of Ullmann [1] and Goldberg [2] in biaryl synthesis. Although the metal was employed in stoichiometric amounts to stitch carbon-carbon (C–C) bonds, latter works demonstrated an equivalent efficacy of Cu in catalytic amounts too [3]. Since the discovery of Gilman's reagent, the understanding of organometallic chemistry of Cu is slightly underdeveloped due to lack of fundamental insights into the reactivity of organocuprates in the oxidation states of Cu(I) or Cu(III) [4]. Inspite of that, diverse reactions are designed and executed with Cu-catalysis, showcasing the benefit both from the environmental and an economical point of view.

Of several transition metals that are utilized to mediate the process of cyanation, Cu gets the lion's share. The exploration of novel methodologies for the introduction of a nitrile group into an aromatic framework is a much desired endeavour. Its appearance in a number of heterocyclic natural products and its ease to transform into a plethora of useful functionalities such as aromatic acids, esters, amines, amides, aldehydes and nitrogen heterocycles accounts for its versatility and applications [5]. According to a report published in 2010, around 30 nitrile-containing pharmaceuticals have been suggested in a variety of medications with an additional 20, being considered as leads for clinical development. The lethal effects, caused by the stoichiometric use of metal cyanides and high temperature (approx. 150-250 °C) employed in the classical approaches of cyanation by Sandmeyer [6] and Rosenmund-von Braun [7], prompted the utilization of either indirect cyanide sources or *in situ* generated cyanide. Apart from the recently established indirect cyanation sources like acetone cyanohydrin, DMF, *t*-BuNC, NaN_3, dimethylmalononitrile, $K_4[Fe(CN)_6]$ and AIBN, the extensive utilization of combination of sources of carbon and nitrogen to generate aryl nitriles are gaining increasing importance. The combination of NH_3(aq)-DMF, NH_4I-DMF, NH_4HCO_3-DMSO and NH_4HCO_3-DMF are some standout examples [8].

From one domain of Cu-catalysis to another, carbon-nitrogen (C–N) bond formations remain to enthrall synthetic chemists for its appearance in molecules with notable biological activities. Credited for a universal demand for more than 100 years, the three most influential C-N bond forming strategies available to a synthetic chemist at present

are the Buchwald-Hartwig reaction [9], the Ullmann-Goldberg reaction and the Chan-Lam cross-coupling reaction [10]. The pioneering discovery of a mild Cu-mediated cross-coupling between arylboronic acids and nitrogen nucleophiles, independently by Chan [11] and Lam [12] led to the rapid growth in such transformation. This powerful nucleophile-nucleophile (oxidative) cross-coupling employs "air stable" arylboronic acids as the arylating partner and displays wide substrate scope with a much easier "open-flask" approach (ambient temperature, mild base and run in air). However, the reaction suffers from long reaction time, use of excess arylboronic acids, need for additives (molecular oxygen, pyridine-*N*-oxide, TEMPO), possibility of a number of side reactions and difficulty with boronic acids bearing electron withdrawing groups. Therefore, design of efficient Chan-Lam cross-coupling methodologies is essential to obtain desirable C−N bond transformations.

The Thesis

The thesis comprises a total of **six chapters**. Chapters **2** and **3** of the thesis deal with two Cu−catalyzed methodologies for cyanation of aryl halides, while the subsequent chapters (Chapter **4** and **5**) discusses methodologies of Chan-Lam cross-coupling reaction developed using a homogeneous Cu−catalyst and a heterogeneous Cu-based catalyst respectively. To bring clarity in expression, each work is systematically organized and discussed in the thesis.

Chapter 1: The first chapter provides a general introduction in which "Cu" metal in catalysis and its organometallic chemistry is discussed. Various cyanation processes developed with Cu-catalysts are shown along with discussions of their merits and demerits. Further, a literature review of Cu-catalysis in C−N bond formation reactions, particularly Chan-Lam cross-coupling reaction is also addressed in detail. The objectives of the thesis are also outlined towards the end.

Chapter 2: This chapter discusses a simple Cu^I−mediated protocol for the synthesis of aryl nitriles with inexpensive and readily available nitromethane as the cyanating source (Scheme **1**). The method involves simple reaction conditions and is additive free with low catalyst loading. Exhibiting a wide substrate scope, various *o-*, *m-* and *p*-substituted aryl iodides and bromides (**1**) react with nitromethane (**2**) under the optimized
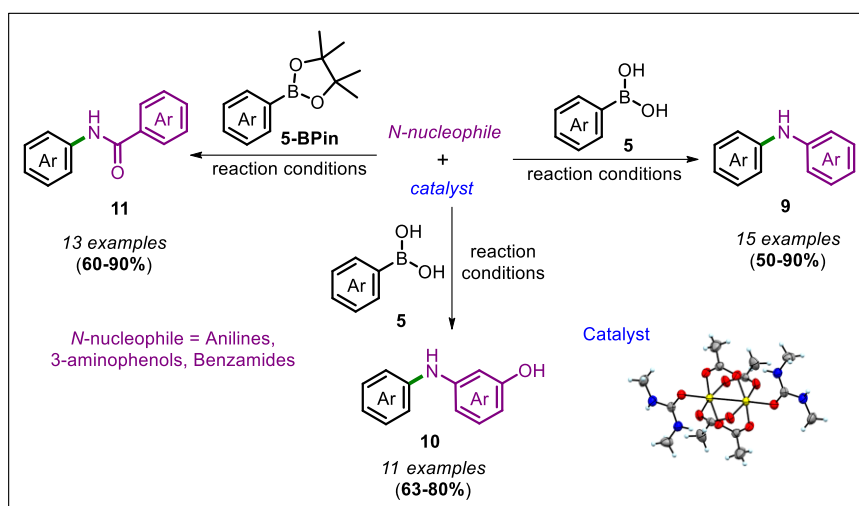
condition to give the respective cyanated product (**3**) in moderate to good yields (50-85%). The developed protocol is driven by an unusual *in situ* reduction of Cu^{II} and highlights an unprecedented, dual role played by nitromethane in the reaction medium. In addition to being the cyanating source, nitromethane also helps in the *in situ* generation of active Cu^{I} species by reduction of the parent Cu(NO$_3$)$_2$·3H$_2$O salt. The formation of Cu^{I} in the reaction medium is confirmed by UV−Vis spectroscopy, cyclic voltammetry and EPR spectroscopy. The mechanism of cyanation of aryl halides is elucidated by a congregation of three cycles, namely the *in situ* reduction of Cu^{II} species by nitromethane, generation of HCN species from nitromethane and a regular organometallic pathway which releases the nitrile derivative. The mechanism of generation of CN⁻ from nitromethane is also computationally validated. This method holds the distinction of involving a rarely encountered Cu^{I} catalytic species as well as facile *in situ* generation of nucleophilic CN⁻ to yield synthetically useful aromatic nitriles.
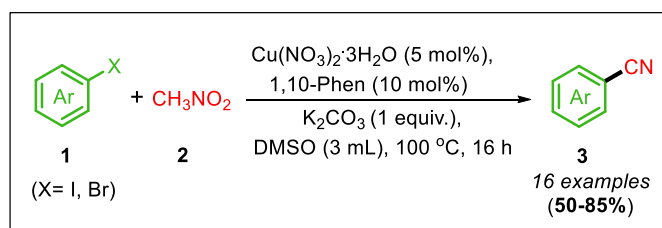
Scheme **1**. Synthesis of aryl nitriles with nitromethane as the cyanating source

Chapter 3: Facilitated by the dual role of Ceric Ammonium Nitrate (CAN), this chapter discusses a cost-effective approach for the cyanation of aryl iodides and bromides with the combination of Ceric Ammonium Nitrate (CAN)−Dimethylformamide (DMF) as an addition to the existing pool of combined cyanation sources (Scheme **2**). The reaction is catalyzed by a readily available Cu(OTf)$_2$ salt. Variously substituted aryl iodides and bromides (**1**) reacted smoothly, producing the desired aryl nitriles (**3**) in moderate to good yields (32-85%). In addition to being an oxidant, CAN also acts as a source of nitrogen in the protocol. Mechanistic study suggests that CAN acts as a nitrogen-atom donor through the NH$_4^+$ ions. The generation of CN⁻ in the reaction medium is supported by the picrate paper test. Labeling studies strongly suggests that it is the methyl carbon and not the carbonyl carbon of DMF that contributes to the formation of

the cyanated product. The oxidizing behaviour of CAN in the reaction medium is further supported by XPS analyses of cerium ions before and after the reaction. The wide scope of CAN is utilized in this work to avoid toxic cyanation sources and additional employment of a nitrogen source, ligand, or other additives.

Scheme **2**. Synthesis of aryl nitriles with CAN−DMF as the combined cyanide source

Chapter 4: This chapter explores and discusses *N,N'*−dimethylurea (DMU) as a ligand aid to Chan-Lam *N*−arylation of primary amides, anilines and 3−aminophenols with arylboronic acids (**5**) and its ester derivative (**5-Bpin**) as the arylating agents (Scheme **3**). Urea and its derivatives are small inexpensive ligands that serve as important raw materials in organic synthesis. They are excellent hydrogen bonding molecules [13], possess long shelf-life and are credited for their ability to coordinate to the metal centre in both neutral and ionic states. They were useful as ligands to Pd to achieve Suzuki−Miyaura cross-couplings, phosphine ligand−free Heck couplings and as alternative green ligands to reprotoxic NMP for alkylations. Despite their tested robustness with Pd−catalysis, ureas and their derivatives are practically unexplored in Cu−catalysis.

The developed reaction is catalyzed by Cu and its *in-situ* complexation with DMU brings about efficient synthesis of *N*-arylated anilines (**9**), 3-aminophenols (**10**) and primary amides (**11**) in good to very good yields (50-90%). The developed [$Cu_2(OAc)_4(DMU)_2$] catalyst is cheap, free from prior synthesis of the metal-complex, is chemoselective and suitable for mono-arylation of primary amides. The crystal structure of the catalyst is also studied. Substrate-dependent limitations of the developed protocol are few and all of them are characteristic of Chan-Lam cross-coupling reactions. The methodology is further applied in a selective post-modification of two active pharmaceutical ingredients (APIs). The developed catalyst extends the scope of *N,N'*−dimethylurea as an auxiliary in inexpensive and versatile Cu-catalysis.

Scheme 3. Chan-Lam *N*-arylation with Cu^II–DMU

Chapter 5: This chapter discusses about the synthesis of a heterogeneous catalyst (Cu(0)/g-C$_3$N$_4$O) which is employed in the Chan-Lam *N*−arylation of anilines, azoles and indoles with arylboronic acids as the arylating agent. In recent times, polymeric graphitic carbon nitride (simply, g-C$_3$N$_4$) has attracted much attention as catalytic materials on account of its suitability in sustainable chemistry [14]. The most thermally (up to 600 °C in air) and chemically stable (resistant to acids, bases and organic solvents) of all carbon nitrides, g-C$_3$N$_4$ is expected to be a conjugated two−dimensional polymer of carbon, nitrogen and some hydrogen and tends to form π−conjugated planar layers similar to that in graphite. Due to lack of experimental evidence, the probable building block of g-C$_3$N$_4$ swings between a triazine unit (C$_3$N$_3$) and a tri-*s*-triazine (heptazine) unit. The presence of oxygen within the polymeric matrix of g-C$_3$N$_4$ imparts Brønsted acidic property in addition to the inherent Lewis basic properties of the surface [15]. It also generates additional active sites and imparts a good dispersion of the material in water, which is otherwise insoluble in most organic solvents.

Integrating all the properties of g-C$_3$N$_4$O, Cu(0) nanoparticles (NPs) with an average size of 7-8 nm are immobilized on a template-free carbon-nitride oxide surface (g-C$_3$N$_4$O). The heterogeneous surface of g-C$_3$N$_4$O containing Cu(0) NPs and offering Lewis basic sites can effectively facilitate base-free Chan-Lam *N*−arylation of anilines and azoles with arylboronic acids (**5**) (Scheme **4**). The *N*-arylation of indoles, however, requires a mild base. The g-C$_3$N$_4$O surface is obtained through microwave irradiation of guanidine hydrochloride and polyethylene glycol (PEG) 400 in water, without the use of additional

oxidizing agents; and Cu(0) NPs are dispersed on its surface using an aqueous solution of L−ascorbic acid to obtain Cu(0)/g-C$_3$N$_4$O. The bulk morphology of the synthesized catalyst is studied by TEM-EDX analysis and the catalyst is characterized by UV-Vis spectroscopy, p-XRD analysis, FT−IR spectroscopy, BET surface area analysis, XPS and auger electron spectroscopy. Good to moderate yields (55-93%) of synthetically important *N*−arylanilines (**6**), *N*−aryl−1*H*−azoles (**7**) and *N*−aryl−1*H*−indoles (**8**) are obtained, all of which have wide pharmaceutical applications. A plausible mechanism of Cu(0)−catalyzed Chan-Lam *N*−arylation is also proposed in this work. The reaction proceeds under heterogeneous catalysis and the catalyst can be reused up to five catalytic cycles without significant oxidation of the Cu(0) NPs. The stability of Cu(0) on the g-C$_3$N$_4$O surface is confirmed by XPS and auger experiments. This work extends the scope of Chan−Lam cross-coupling reaction through the introduction of Cu(0) NPs as the pre-catalyst.
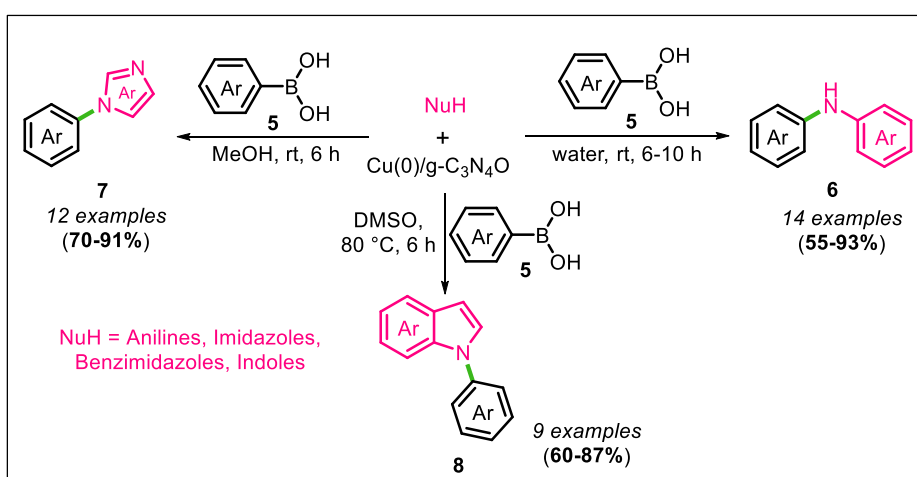
Scheme **4**. Chan-Lam *N*-arylation with Cu(0)/g-C$_3$N$_4$O

Chapter 6: This chapter represents a summary of the significant findings of all the above works. This chapter also provides a future prospect to extend and improve the current works.