

***Copper based Catalyst Design and Methodology Development  
for Cyanation and Chan–Lam Cross–Coupling Reactions***

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***Doctor of Philosophy***

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## Chapter 6

*Conclusion*

*&*

*Future scope*

## Chapter 6

### 6.1 General Conclusion

This thesis mainly focuses on the use of Cu-metal catalysis in cyanation reaction and Chan-Lam cross-coupling reaction. It comprises of **four** experimental works (chapters) and **six** chapters in total. A schematic representation of the experimental works is shown in Figure 6.1.

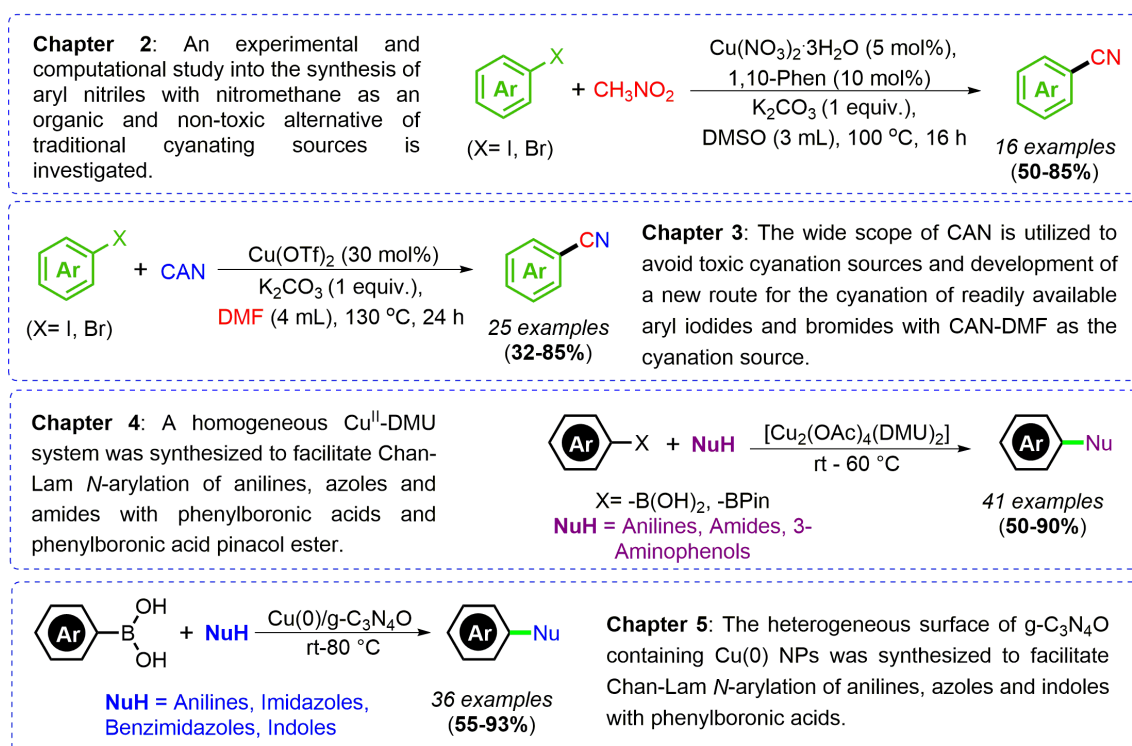


Figure 6.1 Brief representations of experimental works

#### 6.1.1 Significant findings of the performed cyanation reactions

Two non-toxic, cheap and easily available cyanating sources are introduced. The first cyanating source, **Nitromethane** is an organic nitrile alternative source; while the second cyanating source is a combination of carbon source and nitrogen source i.e. **CAN-DMF**, where CAN is the nitrogen source and DMF is the carbon source and also the solvent. Both the cyanating sources were utilized for the cyanation of aryl iodides and aryl bromides under homogeneous Cu-catalysis. The two methodologies presented a broad substrate scope of the corresponding nitriles with simple Cu-salts in catalytic

amounts; without the requirement of fancy ligands. The mechanism of cyanation in both the protocols were thoroughly studied and discussed in detail in the thesis.

### **6.1.2 Significant findings of the performed Chan–Lam cross–coupling reactions**

Two Cu–based catalytic systems were developed to achieve efficient Chan–Lam cross–couplings encompassing a broad range of nitrogen nucleophiles. The first catalytic system is a **Cu–*N,N'*-dimethylurea** (Cu–DMU) “homogeneous” catalytic system which is developed to obtain Chan–Lam arylation of amines, 3-Aminophenols and primary amides with phenylboronic acid and phenylboronic acid pinacol ester as the arylating partner. The catalyst was characterized through single crystal structure elucidation. It was cheap and chemoselective. The synthetic utility of the catalytic system was demonstrated through a site–selective post–modification of two active pharmaceutical ingredients (APIs).

The second catalytic system is a Cu(0)–based heterogeneous catalytic system where Cu(0) nanoparticles (NPs) are dispersed and stabilized on a graphitic carbon nitride oxide (**Cu(0)/g-C<sub>3</sub>N<sub>4</sub>O**) surface. The  $\pi$ –bonded layered configuration of g-C<sub>3</sub>N<sub>4</sub>O was utilized to anchor a high loading of desired Cu(0) NPs and stabilize them for up to five catalytic cycles. The formation of the catalytic system was confirmed by UV–vis spectroscopy, FT–IR spectroscopy,  $p$ –XRD pattern analysis, BET surface area analysis, TEM–EDX analysis, XPS and Auger electron spectroscopy. It could be easily prepared in water and the preparation methodology involved a mild reducing agent, ascorbic acid. The heterogeneous catalytic system was employed in the Chan–Lam arylation of three types of *N*–nucleophiles i.e. anilines, azoles and indoles with phenylboronic acids as the arylating agent. Substrate-dependent limitations of the developed protocols are very few and all of them were characteristic of Chan–Lam cross–coupling reactions.

Both the developed catalysts boost the applicability of Chan–Lam cross–coupling reaction in synthetic organic chemistry with simple Cu–based catalytic systems.

### **6.2 Future Scope of the work**

The current work described in this thesis has the potential to be extended to useful transformations. Accordingly, the future scope of the work is described below:

- i) Aryl nitriles are a gateway to biologically active azaheterocycles. The future scope of this work therefore, lies in modulation of these nitriles into useful azaheterocycles. One such convenient synthetic route to heterocycles is through the formation of nitrilium ions from nitriles (Figure 6.2).

Nitrilium ions are usually generated by the alkylation/arylation/protonation of nitriles. They are principle reactive intermediates of breakthrough protocols like the Beckmann rearrangement, Ritter reaction, von Braun reaction and the Bischler–Napieralski reaction. They are stable, generated *in situ* and leads to a variety of attractive heterocycles on attack by a suitable nucleophile; followed by intramolecular cyclization through an electrophilic attack of the nitrilium nitrogen atom or its neighbouring iminium carbon on olefinic (heterocyclic) or aromatic (hetero) groups. Moreover, reactions involving *N*-Phenylnitrilium ion (**1**, Figure 6.2) show a high degree of specificity.

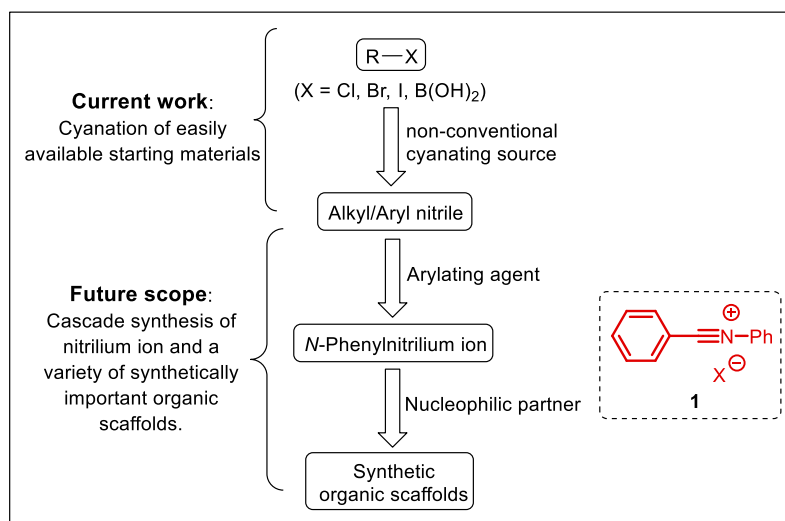


Figure 6.2 Schematic representation of future scope with aryl nitriles

- ii) Although the current work utilizes the *N*-rich Lewis basic sites on the surface of  $g\text{-C}_3\text{N}_4$  to promote Chan–Lam cross–coupling reactions, Graphitic carbon-nitride ( $g\text{-C}_3\text{N}_4$ ) is also a well-known metal-free photo-catalyst on account of its stability, suitable band-gap and effortless syntheses from simple *N*-precursors. Therefore, its photo-catalytic activity can be tested for Chan–Lam reactions to establish a broader substrate scope, specifically for substrates that are sluggish under normal

reaction conditions like substrates with electron-withdrawing groups and bulky substituents.

- iii) As already discussed, ureas are small useful ligands that are virtually unexplored in Cu-catalysis. Just as they could serve as efficient ligands in Chan–Lam cross-coupling reaction, these will also be useful auxiliaries for other important C–N bond formation reactions with Cu-catalysis.