CHAPTER 5

Conclusions

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5.1 General Conclusions

Across the world, synthetic chemist always plays pivotal role in design and synthesis of biologically potent fused heterocyclic molecules due to its wide applications in agrochemical, pharmaceuticals and their ubiquity in various natural products. However, to achieve these complex bioactive organic molecules with not only minimization of synthetic steps and with high atom economy but also easily from available precursors are the major concern. In this regards, synthesis of the complex heterocyclic frameworks in a single step utilizing tandem or domino approach and one-pot sequential protocol is always on high priority. Besides, transition metal-catalyzed C–H activation attracted great attention over traditional methods for the construction of fused heterocyclic moieties without pre-functionalization of starting materials.

In the recent years, C–H functionalization and cross-dehydrogenative coupling received great attention for the C–C and C–X (X = N, O, S, halogen etc.) bond formation. These methodologies provide high molecular complexity, excellent regioselectivity and exhibit high functional group tolerance. In the thesis entitled **"Synthesis and Functionalization of Heterocyclic Compounds *via* Palladium/Rhodium-Catalyzed Cross-Dehydrogenative Coupling Reactions"** synthesis and functionalization of various heterocyclic compounds have been achieved through palladium or rhodium catalyzed oxidative cross-dehydrogenative coupling reactions.

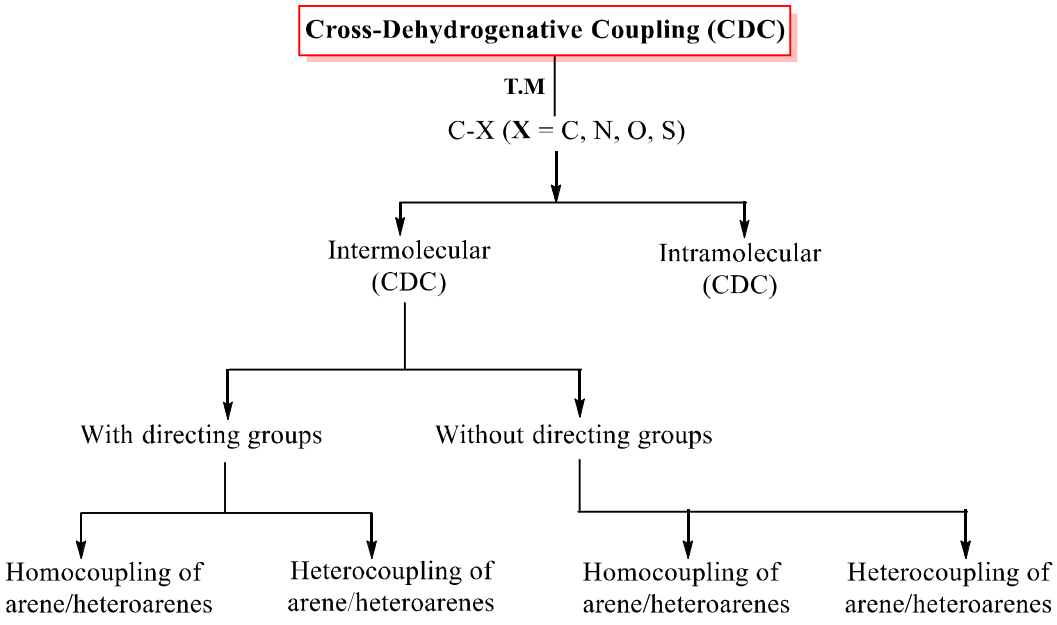
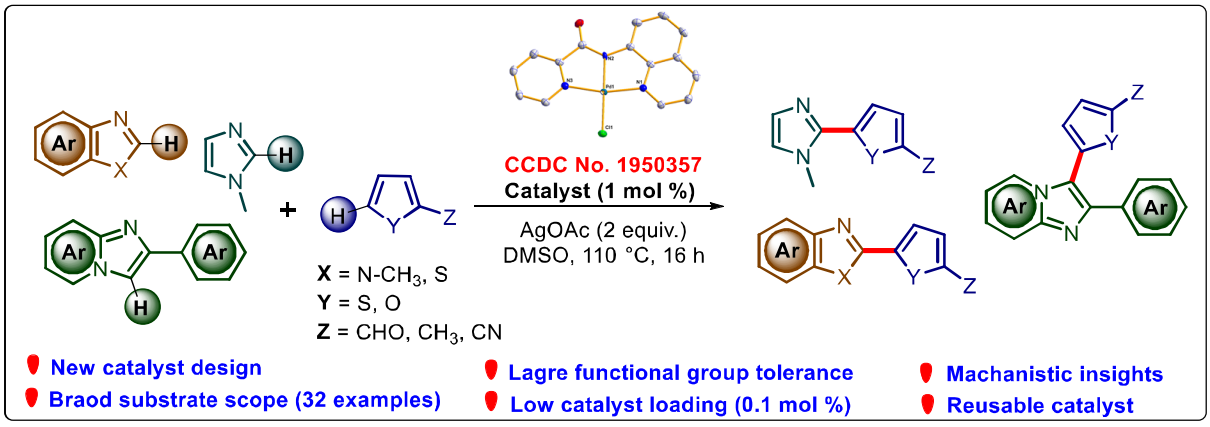


Figure 5.1 Flow chart presentation of cross-dehydrogenative coupling reactions

Chapter 5

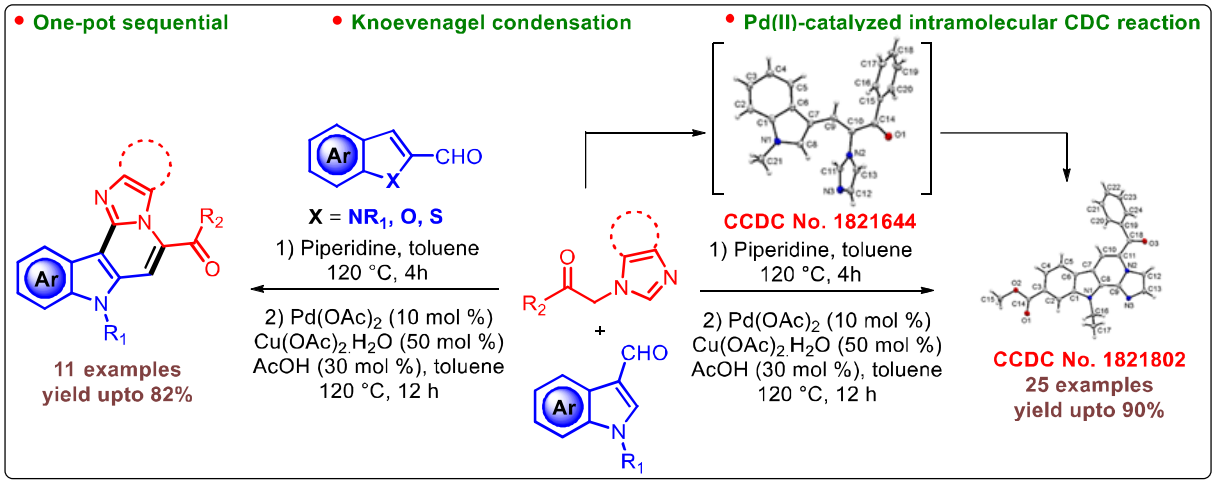
Chapter 1 of the thesis describes the concise overview of literature reports on C–H functionalization and oxidative C–H/C–H coupling reactions. The plenty of reports of CDC reactions provide a valuable opportunity for the synthesis of aza fused heterocycles and exploit their wide applications in the field of optoelectronic and pharmaceuticals.

Further, synthesis of new class of palladium complexes of NNN/CNN pincer ligands is described. The synthesized palladium complexes were well characterized by NMR, mass, and IR spectroscopy. Moreover, all complexes unambiguously characterized by single-crystal X-ray studies, which help in identification of structures of the complexes and bonding of palladium with ligands. These complexes were found to be very efficient catalysts for the hetero cross dehydrogenative coupling reaction of thiophene, furan, and benzothiazole derivatives with a wide range of heteroarenes such as *N*-methyl benzimidazole, *N*-methylimidazole, benzothiazole, and imidazo[1,2-*a*]pyridines and homo cross-dehydrogenative coupling reactions of thiophenes and benzothiazole. The catalyst showed high functional group tolerance, and only 1.0 mol % of the catalyst loading is required to achieve good yields (up to 77%) in short reaction time. The efficiency of the catalyst was proven by reusability experiments. The results revealed that, catalyst can be reused efficiently up to four reaction cycles for the homocoupling of 2-formylthiophene. The mechanism of the reaction proposed on the basis of some control experiments. Interestingly, acetate analogue of the palladium catalyst (C5) intermediate of this reaction generated *in situ* is an active catalyst.



Scheme 5.1 Pd(II)-pincer catalyzed cross dehydrogenative coupling of (hetero)arenes

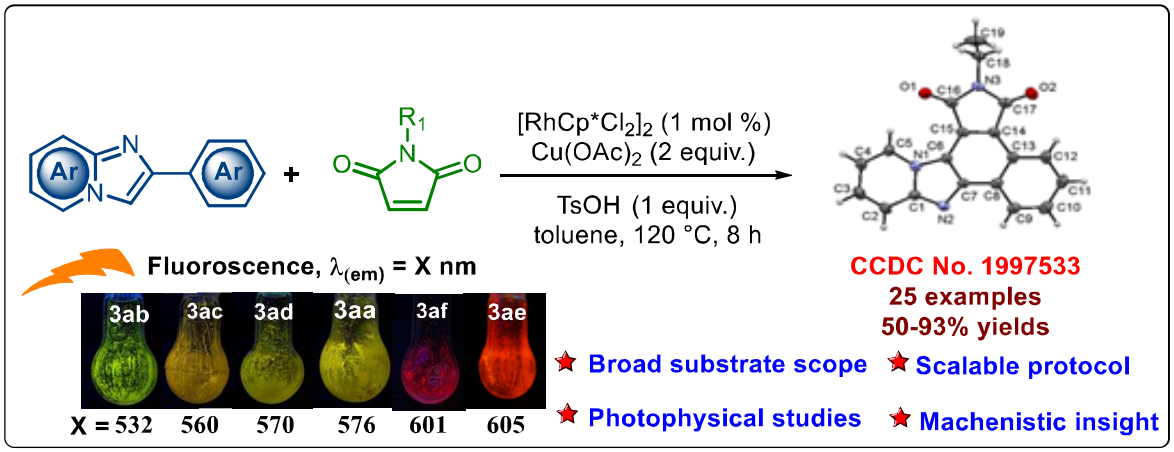
Chapter 2 deals with the synthesis of imidazopyridine-fused indoles derivatives. A one-pot sequential Knoevenagel condensation followed by Pd(II)-catalyzed intramolecular oxidative C C coupling has been applied for the synthesis of imidazopyridine fused indoles using readily obtainable starting materials. The structure of product was confirmed by various spectral data such as ^{1}H, ^{13}C, IR, HRMS and single crystal X-ray analysis. A series of 36 analogous was synthesized in moderate to excellent yields with tolerance of various functional groups and gram scaled reaction also underwent smoothly without problem. Pleasingly, the current protocol utilized for the benzofuran-3-carbaldehyde as well as thiophene-2-carboxaldehyde derivatives. A tentative mechanism of the reaction was proposed on the basis of control experiments. The intermediate of the reaction and its site selectivity toward palladium catalyst was exclusively explored. This developed one-sequential protocol opens new route to construct aroyl functionalized imidazopyridine-fused indoles which could provide a new series of medicinally relevant indole based imidazopyridines.



Scheme 5.2 Synthesis of Pd(II)-catalyzed imidazopyridine indoles derivatives

Chapter 3 describes significance of oxidative cross-dehydrogenative coupling for the synthesis of diverse extended π-conjugated polyheterocycles. The current chapter demonstrated, rhodium-catalyzed oxidative annulation reactions of 2-arylimidazopyridine and 2-arylindoles with maleimides. The chapter is divided in two parts. In **part A**, rhodium-catalyzed oxidative dual C–H functionalization has been reported for the annulation of 2-arylimidazopyridines with maleimides. The reaction of 2-arylimidazopyridines with maleimides in the presence

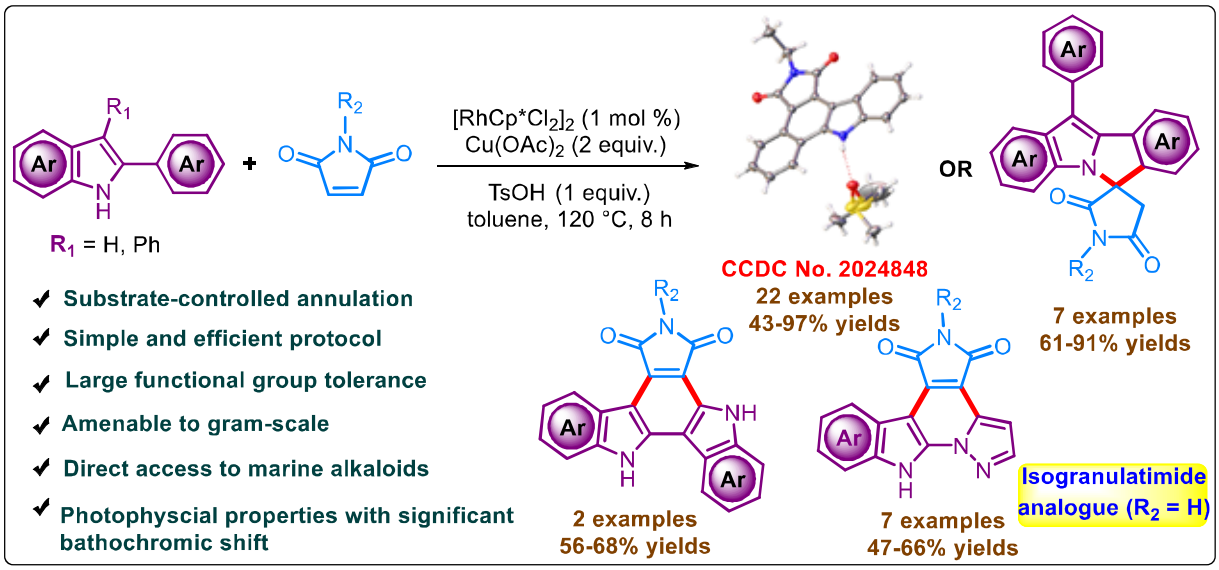
$[RhCp^*Cl_2]_2$ (1 mol %), $Cu(OAc)_2$ (2 equiv.) and *p*-toluenesulfonic acid (TsOH, 1 equiv.) in toluene at 120 °C for 8 h gave desired annulated products 1*H*-benzo[*e*]pyrido[1',2':1,2]imidazo[4,5-*g*]isoindole-1,3(2*H*)-diones in good to excellent yields. To gain insight into the mechanism, i*n situ* generated rhodacycle was successfully trapped and analyzed by HRMS. After synthesis and characterization of all products, they were evaluated for the photophysical studies. Firstly, UV-vis absorption and fluorescence spectra of all annulated products were recorded in $CHCl_3$. Likewise, solvent study and acid sensing experiment were also performed. The transition between annulated products was fully defined by time-dependent density functional theory (TD-DFT) **(Scheme 5.3)**.



Scheme 5.3 Rhodium(II)-catalyzed oxidative annulation of 2-aryl imidazo[1,2-*a*]pyridines with maleimides

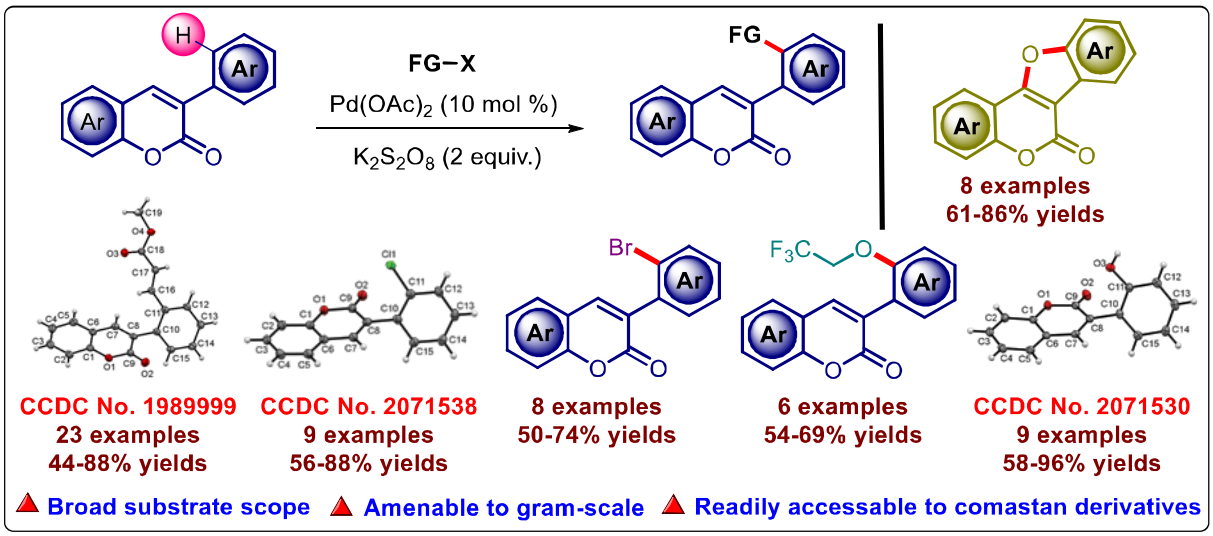
In **part B**, Rh(III)-catalyzed dehydrogenative annulation and spirocyclization of 2-arylindoles and 2-(1*H*-pyrazol-1-yl)-1*H*-indole with maleimides has been described. The reaction of 2-arylindoles with maleimides afforded the desired annulated products in good to excellent yields. Moreover, 2-(1*H*-pyrazol-1-yl)-1*H*-indoles and 2,3-bisindoles also reacted smoothly to access the desired cyclized products in moderate to good yields. Interestingly, the annulation of 2-(1*H*-pyrazol-1-yl)-1*H*-indoles with maleimides under the optimal reaction conditions afforded isogranulatimide alkaloid analogues in moderate yields. However, 3-phenylindoles reacted with maleimides under standard condition to afford the spiro products in good to excellent (76-91%) yields. On the basis of control experiments and HRMS reports, a putative reaction mechanism has been described. The

synthesized annulated products were well investigated towards the absorption and fluorescence properties **(Scheme 5.4)**.



Scheme 5.4 Rhodium(II)-catalyzed oxidative annulation of 2-aryl indoles with maleimides

Chapter 4 elaborates palladium(II)-catalyzed C–H functionalization of 3-arylcoumarins for the synthesis of functionalized coumarins. In this chapter palladium-catalyzed, weakly coordinating lactone directed C–H bond functionalization of 3-arylcoumarins has been summarized. The versatility of the protocol was highlighted by prototypical methods for alkenylation, halogenation, fluoroalkoxylation, and hydroxylation. The derived strategy showed broad substrate scope furnished good to excellent yields of coumarin derivatives. The functionalized coumarin derivatives were well characterized by ^{1}H NMR, ^{13}C NMR and HRMS analysis as well as single X-ray crystal analysis. Pleasingly, synthesized hydroxy coumarin derivatives were utilized for the construction of coumestan derivatives in good yields. After the scalability experiment, the synthesized functionalized coumarins were used for the synthetic manipulations to other functionalized moieties. Based on several control experiments, the putative mechanism has been described and followed the concerted metalation deprotonation (CMD) pathway.



Scheme 5.5 Pd(II)-catalyzed C(sp^2)–H bond functionalization of 3-arylcoumarins

5.2 Future Scope of the Research Work

Nitrogen containing fused heterocyclic compounds have significant role in organic synthesis due to their wide range of applications in natural products, pharmaceuticals, medicinal chemistry, and material science. The major concern for the access of these potent heterocyclic compounds is the requirement of pre-functionalized starting materials, ultimate multistep synthesis causes low atom and step economy. Thus, transition metal-catalyzed C–H functionalization and oxidative annulation engrossed more attention in chemical transformations to afford the *N*-fused heterocycles in one step synthesis from readily available substrate.

Although the thesis is primarily focused on the C–H functionalization and cross-dehydrogenative coupling reactions, still, there is broad scope for the synthesis of fused aza-heterocycles and their C–H activation. In particular, biologically important 2-arylimidazo[1,2-*a*]pyridines, 2-arylindoles and 3-arylcoumarins were exclusively explored and used for further C–H functionalization. Some of the target molecules are demonstrated below which can be prepared by minor modification of the reaction condition developed for the C–H bond functionalization and annulation reactions. Furthermore, it would be very interesting to explore synthesis of the target molecules using 3d-transtion metal catalysts which are cheaper and environment friendly (**Figure 5.2**).

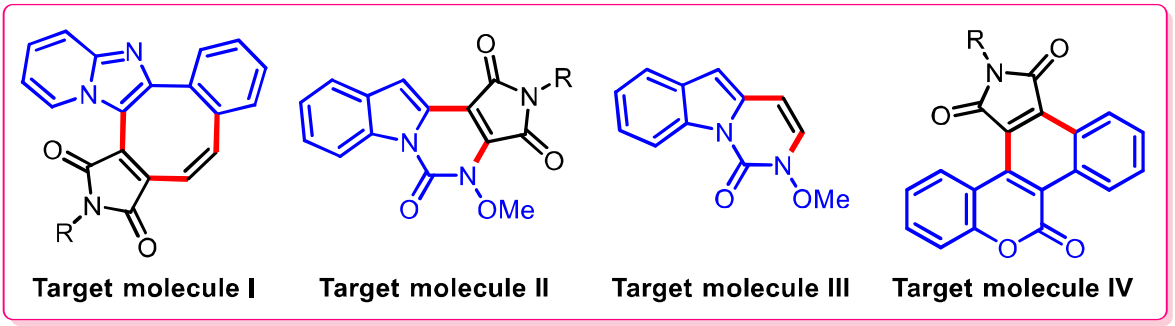


Figure 5.2 Transition metal-catalyzed synthesis of fused heterocycles