Chapter 1: An overview of Transition-Metal Catalysed Heterocyclic Synthesis

Heterocyclic scaffolds have innate affinity towards protein target owing to their structural resemblance to the amidic bond present in proteins. Thus heterocyclic compounds play a significant role in drug discovery and development. Although, conventionally heterocycles are generated by condensation reaction involving carbonyl compounds and various ring cyclization reactions, here the chemical space by such conventional methods have already been over exploited. In this context, new chemical transformations in synthesis are required for the generation of new chemo-types for searching unexplored region of chemical space. Among various new synthetic pathways reported, transition-metal-catalyzed reactions are some of the most attractive methodologies to access complex and diverse heterocycles from easily available starting materials.

1.1 Transition-metal mediated synthesis of heterocycles

Transition metal catalysed synthesis of heterocycles is carried out by either C-C bond formation or C-Y bond formation processes. For instance, olefin metathesis reaction and cycloisomerization of dienes, diynes and enynes have been efficiently employed for synthesis of heterocycles forging both C-C and C-Y bonds. In contrast, intramolecular Heck, Suzuki and Stille type reaction generally construct heterocycles by C-C bond processes only. Recently, single metal catalytic transformations have expanded the horizons of chemical transformations by coupling to other organic transformations. Such single metal catalysed reactions have been categorized into three major categories: cascade catalysis, tandem catalysis and Domino catalysis.

1.2 One-pot catalysis for the synthesis of heterocycles

Although single metal catalysis have established its place in the synthesis of heterocycles, the combination of two or more transition metals have recently attracted the attention of synthetic organic chemists. Such dual bimetallic catalytic processes have typical advantages: (1) a new and previously unattainable transformation can be achieved by two or more catalytic systems, which cannot be possible by the use of single catalyst alone. (2) An improved stereochemical control is generally observed in dual catalysis. (3) Such processes are efficient and exhibit broaden substrate scope. Typically these bimetallic catalysis are divided into four major groups (Fig 1). The first group is called cooperative
catalysis, where both catalysts share same catalytic cycle (Fig 1A). The second type is called synergistic catalysis, where individual catalyst activates different substrates in a separate catalytic cycle and subsequently they combined to form the product (Fig 1B). The third type is relay catalysis, where both catalysts are present at outset but have distinctly different and consecutive catalytic cycles. In relay catalysis, both substrates react with Cat-1 to generate intermediate, which then enter into second catalytic cycle (Fig 1C). The fourth type is sequential catalysis, which resembles to relay catalysis with one major difference (Fig 1D). Both catalysts and reagents may not be present at outset and can be added after completion of one catalytic cycle. A literature review of last five years will be presented in the thesis.

1.3 Aims and Objectives

1. To design and develop transition metal catalysed new synthetic routes for the synthesis of heterocyclic molecules of biologically significance.
2. To study stereo-, region- and mechanical aspects of the reactions using kinetic spectroscopic studies.
3. To develop eco-friendly routes for pharmaceutical and healthcare sectors for sustainable developments.
4. To scrutinize different forms of energy viz microwave, sono-chemical or ultraviolet radiations and to explore their effect on reactivity.
5. To explore the biological activity of different diversity oriented heterocyclic scaffolds.

Chapter 2: Pd(II)-catalyzed tandem Carboxamidation/ Hydroamidation of 2-bromophenylacetylene for the synthesis of Isoindolin-1-one

2.1 Introduction: Isoindolinone represents an important class of heterocycles with exocyclic double bond. It is found in a range of natural products and exhibit broad range
of pharmacological activity. Owing to its significance, many synthetic methodologies have been reported such as nucleophilic attack of Grignard reagents on phthalimides, electrophilic cyclization of 2-alkynylbenzamides, condensation of 2-halobenzamides with terminal alkynes, transition metal catalyzed directing group assisted C-H activation and various multicomponent methods are widely used. Despite of their utility, these reported methodologies possess some serious drawbacks such as poor yields, limited substrate scope, need of extra-dry conditions and dependency over complex precursors, which are synthesized through mutlistep process. In order to overcome these limitations, we envisaged herein that isocyanide could be effectively utilized as an amide surrogate for the rapid synthesis of 2-alkynylbenzamides 4 from 2-bromoalkynes derivatives (Scheme 1). Later, 2-alkynyls can be cyclized into isoindolin-1-one. Hence a tandem one-pot reaction for the synthesis of isoindolin-1-one from 2-bromoalkynes has been developed.

2.2: Results and Discussion

To test our hypothesis, we embarked our studies by optimizing reaction of 2-bromoalkynes 1 with isocyanides 2 using Pd(OAc)$_2$/Xantphos as a catalyst system. The optimal condition for the tandem reaction was addition of 1 (1.0 equiv) and isocyanide 2 (1.0 equiv) using Pd(OAc)$_2$/Xantphos (3 mol%) and Cs$_2$CO$_3$ (2.0 equiv) at 100 °C in DMF/H$_2$O (9:1) and it afforded 90% of the desired product. The title compound 3 was fully characterized by various spectroscopic techniques such as $^1$H, $^{13}$C NMR, HRMS and X-ray structure analysis. After successful optimization studies, we next investigated the scope and limitation of the tandem
reaction (Fig. 2). All electron withdrawing substituents on alkyl arenes ($R^1$) increased the efficiency of the reactions to produce 3 in good to excellent yield. Both five- and six-membered heterocycles were successfully incorporated at $R^2$. Both $^1$H NMR and X-ray structure analysis confirmed formation of E-isomers as a major product. Interestingly, isocyanides also furnished an additional diversity in the title compound. Interestingly, alkyl substituted terminal alkynes produced 2-alkynylbenzamides and failed to cyclized further under standard reaction conditions. Intermolecular competition experiment with electron deficient and electron rich alkynes further validated that use of electrophilic alkynes is the driving force of cyclization. The tandem reaction also produced quantitative yield in the presence of TEMPO and galvinoxyl, which suggests that reaction follows non-radical path.

**Chapter 3: One-pot synthesis of functionalized 2-pyrones by transesterification and alkenylation of enynoates catalyzed by palladium**

**3.1: Introduction:**

2-Pyrone, a six-membered unsaturated compound containing oxygen atom in the ring, is a part of various natural products and pharmaceutical agents, which display promising range of biological activities. 2-Pyrone has been synthesized by various cyclocondensation reactions, cyclization reaction of $\beta$-halo-$\alpha,\beta$-unsaturated esters, electrophilic cyclization reactions of enynoates, various cycloaddition reactions, carboxylative cyclization and oxidative coupling reaction with alkynes. Here, we envisaged that transesterification of enynoates 5 would produce 5-palladopyrones intermediate 6 which can be easily functionalized by alkenes to generate 5-alkenylpyrones 7 (Scheme 2). 8

**3.2: Results and Discussion**

To test our hypothesis, we began our study by reacting enynoates 5 with styrenes using PdCl$_2$ (10 mol%) and X-phos (20 mol%) as catalyst system, AgOAc (0.5 equiv) as oxidant in acetonitrile (0.5 mL) as solvent at room temperature in the presence of open air...
atmosphere for 24 h proved to be the best optimal choice for this reaction. The methodology involves difunctionalization of internal alkynes by using Pd(II) as a catalyst along with X-Phos as ligand via 6-endo transesterification and subsequent alkenylation pathway. After the optimized reaction conditions in hand, we next investigated the generality of the one-pot reaction (Fig. 3). We found that a broad range of electronically diversified substituents on alkynes and phenyl alkynyl side chain, such as \( p\)-Me, \( p\)-F, \( p\)-OMe etc, were well tolerated. The salient feature of this methodology are simple and easily available starting materials, broader range of unactivated alkenes, reduced synthetic steps, mild reaction conditions and high efficiency.

**Chapter 4: Synthesis of aminotetrazoles by sequential Azide-Isocyanide Coupling/Cyclization Reaction promoted by Pd(0)/Fe(III) dual Catalysis**

**4.1 Introduction:**

5-Aminotetrazoles are nitrogen-rich five-membered aromatic heterocycles with broad range of pharmaceutical applications including non-classical bioisosters, \( cis\)-amide surrogate, antifoggants in photographic materials, propellants and explosives in the field of material science. Besides this, aminotetrazoles also showed promising biological activity like anti-HIV, antiviral and antiallergic activity. Owing to their biological importance, there is a strong demand for the construction of aminotetrazoles. They were traditionally synthesized by diazotization of aminoguanidines, cyclization of carbodiimides or cyanamides with azides, desulfurization of thiourea or selenoureas and nucleophilic substitutions on halo-tetrazoles. Although, these protocols produced aminotetrazoles in fairly good yields, the toxicity of the reagents such as Hg, Pb and their use in stoichiometric amount limited their overall utility.

To overcome these limitations, we envisaged that a cabodiimide 10, generated from azide 8 and isocyanide 9, can be subjected to \([3+2]\) cycloaddition with azides for the synthesis of 5-aminotetrazole (Scheme 3). Our main aim here was to develop a protocol, where toxic reagents can be effectively avoided.
4.2 Results and Discussion:

To develop a sustainable protocol, we first started with method development of azide 8 and isocyanide 9. Here, we found that Pd(PPh₃)₄ (5 mol%) in toluene at room temperature furnished desired carbodiimide 10 in quantitative yield. We, next explored the possibility of [3+2] cyclization of carbodiimide 10 and azide. Among various metal, solvents and azide sources tried, we found that FeCl₃ (10 mol%) and TMSN₃ (1.5 equiv) in toluene at 100 °C worked best. After successfully finding a common solvent for this transformation, we next performed relay protocol, where both catalysts were present at outset. Unfortunately we failed to obtain the desired product due to redox incompatibility of these metals. Thus, we directed our attention to sequential catalysis, where initially 8 and 9 were reacted with Pd-catalyst for 30 min and then TMS-N₃ and FeCl₃ were added, and the reaction was refluxed to 100 °C to furnish the 5-amino-1H-tetrazole 11 in 90% isolated yield (Scheme 3). This simple environmentally benign sequential catalysis exhibited superior features compared to the traditional methods such as no extra additives, tolerates various azides, requires shorter reaction times, exhibited good to excellent yields, employed simple and easily available starting material and showed broader substrate scope and applicability.

With the optimized reaction conditions in hand, we next focused our attention on investigating the substrate scope by employing various electron donating and electron withdrawing substituents (11a-11h) on phenylazides (Figure 4). Both substrates reacted efficiently and produced the title compounds in good yields. The substituents at various position of phenyl azides (ortho, meta and para) were also well tolerated. The diverse range of isocyanides were also tested for this transformation and it was observed that various alkyl, aryl and cycloalkyl isocyanides reacted smoothly. Finally, our bimetallic sequential reaction exhibited excellent and unique regioselectivity, which was characterized by ¹H, ¹³C NMR, mass and X-ray analysis.
Chapter 5: Synthesis of pyrazolo[1,5-c]quinazoline by bimetallic relay Pd(II)/Ag(I) catalysis: Discovery of EGFR inhibitors

5.1 Introduction:

Pyrazolo[1,5-c]quinazoline derivatives are found to be important framework with a broad range of biological activities such as potent phosphodiesterase 10A and Eg5, Gly/NMDA, AMPA and Kainate receptor etc. Conventionally, pyrazolo[1,5-c]quinazolines are synthesized by multistep synthesis involving condensation of 2-pyrazoloanilines or 2-bromopyrazoloanilines with carbonyl compounds and two-component [3+2] cycloaddition reactions of N-aminoquinazoliumylides with olefins. The overall yield of this multistep synthesis is meagre. Owing to its interesting biological activity, the development of one-pot protocol for the synthesis of pyrazolo[1,5-c]quinazolines from simple and easily available starting material is highly desirable. Recent upsurge in the catalytic transformations, involving use of more than one catalyst, enables multiple chemical transformations to access complex molecular constructs. However combining multiple transition metals in a one-pot poses a challenge owing to redox-incompatibilities among various metals. In addition, time resolution of such multicatalytic method is indeed very difficult. In view of their importance, herein, we developed a transition metal catalyzed four component approach for the synthesis of diversified pyrazolo[1,5-c]quinazolines in one-pot methodology (Scheme 4). We envisaged that a carbodiimide A, generated by azide-isocyanide cross coupling reaction of 12 and 13, can react with tosylhydrazide to generate a crucial intermediate azomethine imine B, which can easily cyclize with alkenes to generate complex pyrazolo[1,5-c]quinazolines. As two of these steps are catalyzed by transition metals, the development of a relay protocol is tricky due to incompatibility of metals and time resolution of the individual elementary steps.10

5.2: Results and Discussion:
To test our hypothesis, we embarked our study by reacting 2-azidobenzaldehyde (1.0 equiv), isocyanide (1.2 equiv), tosylhydrazide (1.0 equiv) and methyl acrylate (1.5 equiv) using 7.5 mol% Pd(OAc)$_2$, 10 mol% AgOTf and 3.0 equiv K$_3$PO$_4$ in toluene at room temperature. The use of 4Å MS ensured the synthesis of pyrazolo[1,5-c]quinazolines in quantitative yield. We next directed our efforts to synthesize the library of the pyrazolo[1,5-c]quinazolines by employing various substituents at 2-azidobenzaldehyde 12. The results are summarized in Figure 5. 2-Azidobenzaldehyde 12 demonstrated excellent reactivity under standard reaction conditions. Next we tested various sulphonyl hydrazides which revealed that both electron-donating as well as electron withdrawing substituents were well tolerated affording good to excellent yields. Investigation of substrate tolerance of isocyanide revealed that only tert-butyl and alkyl isocyanides were well compatible. As pyrazolo[1,5-c]quinazoline resemble structurally with erlotinib, we decided to test a focused library of 16 against cancer cell lines of the lung (A549), colon (HCT-116) and human glioblastoma (U-87 MG). We found that pyrazolo[1,5-c]quinazolines exhibited excellent cytotoxicity in all three cancer cell lines. Interestingly, pyrazolo[1,5-c]quinazolines were also selective as they presented negligible toxicity to Human Peripheral Blood Mononuclear Cells (HPBMC). Of these, 16w and 16x were found to inhibit ATP dependent phosphorylation of EGFR in the nanomolar range. In addition, both these compounds increased the ROS level (Fig 6b) and altered mitochondrial membrane potential (Fig 6c) of A549 cancer cell lines leading to reduction of mitochondrial apoptosis and cell death. A substantial increase in the G1 phase of these cells was also observed in the analysis of cell cycle (Fig 6d).
Chapter 6: Pd(II) catalyzed azide-isocyanide coupling/cyclocondensation reaction for the synthesis of quinazoline-3-oxides

6.1 Introduction:
Quinazoline 3-oxides are an important framework found in various natural products and showed promising biological activity including bronchodilators, cardiotonics and fungicides. Generally, quinazoline N-oxides were synthesized using various synthetic approaches such as direct oxidation on parent heterocycles, cyclocondensation reaction of 2-aminooximes with various electrophiles and direct C-H activation methods. However, most of the reported methodologies required prefabricated substrates, which limits its substrate scope and application. Therefore the development of mild and efficient protocol for the synthesis of quinazoline 3-oxides are highly desirable.

6.2 Results and Discussion:
In continuation to our efforts for the synthesis of novel complex heterocyles, we report herein a mild and efficient one-pot three-component synthesis using 2-azidobenzaldehyde 17, isocyanide 18, and hydroxylamine hydrochloride 19 and Pd(OAc)$_2$ (7.5 mol%) as catalyst/4Å MS in toluene at room temperature for 3 h to afford quinazoline 3-oxides in 85% isolated yield (Scheme 6). With the optimized reaction conditions in hand, we next studied the generality and limitations of 3-CR. A broad range of differently substituted 2-azidobenzaldehyde 17a were reacted smoothly to provide the corresponding N-oxides in good to excellent yields. The various halo substituents at para-position were reacted efficiently and furnished excellent yields.

\[ \text{Scheme 6: Synthesis of quinazoline 3-oxides} \]
(20b-20d and 20f-20i). The chemical integrity of various reactive functional groups such as Br, I, Cl, CF$_3$ and ester at various position remained unperturbed under the standard reaction condition providing a chemical handle for further transformation (Fig. 7).

The substrate scope of 3-CR could be elegantly extended to 2-azidoacetophenone (20i) and produced comparable results. To probe the reaction mechanism in more detail, we have also performed the control experiment which concluded that the reaction follows azide-isocyanide denitrogenative coupling/condensation/6-exo-dig cyclization pathway (Fig. 7). The salient feature of our methodology are one-pot process, excellent regioselectivity, broad substrate scope and diversity, mild reaction conditions and short reaction time.

References: