SYNOPSIS

The contents of this thesis has been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview of cascade reactions for heterocycle synthesis, different aspect of C–H functionalization and the oxirane chemistry for the construction of C–C and C–heteroatom bonds. All other chapters' highlight on C–C, C–N, C–O, and C–S bond forming reactions via cascade strategy involving reactions of 2-halobenzamides with (aryl)methanamines and *o*-alkynylanilines with aroyl isothiocyanates, C–H functionalization strategies like directing-group assisted C–H activation followed by annulation and cross-dehydrogenative coupling and lastly oxirane ring opening with aroyl/acyl isothiocyanates.

Chapter II demonstrates a CuO nano particle catalyzed domino synthesis of 2,3-disubstituted quinazolinones from 2-halobenzamides and (aryl)methanamines.

Chapter III describes a base promoted cascade synthesis of quinoline-4(1*H*)-thiones via an in situ generated *o*-alkynylthiourea obtained by reacting *o*-alkynylanilines with aroyl/acyl isothiocyanates.

Chapter IV illustrates a Ru(II)-catalyzed regiospecific C–H/S–H annulation of quinoline-4(1*H*)-thiones with alkynes leading to the synthesis of thiopyrano[2,3,4-*de*]quinolines.

Chapter V elucidates a Cu(II)-catalyzed oxidative methylene-bridged dimerization of two analogous imidazo[1,2-*a*]pyridine using *N*,*N*-dimethylacetamide (DMA) as solvent cum methylene source.

Chapter VI describes a regioselective and concomitant transfer of thiocyanate (–SCN) and aroyl/acyl (–COR) group from aroyl/acyl isothiocyanate onto oxiranes giving thiocyanato benzoates.

Each of these chapters comprises of introduction, previous work, present work, experimental section, references, spectral data and few representative spectra.

CHAPTER I: An Overview of Cascade Reactions, Metal-Catalyzed C–H Functionalization and Oxirane Chemistry for the Construction of C–C and C–Heteroatom Bonds

First part of this chapter gives an overview about the cascade reactions towards the synthesis of heterocyclic molecule.

Molecules containing heterocyclic substructures have always attracted the synthetic chemists since they often exhibit diverse and important biological properties. Consequently, developing novel methods for the stereoselective synthesis of hetero-polycyclic ring systems have gained considerable attention in the field of synthetic organic chemistry. The efficiency with which the heterocyclic molecules can be constructed is more important from the economic and ecological point of view. The increase in molecular complexity as one progresses from simple starting material to the final product can give a measure of the competency of reaction. The number of steps required to achieve the desired target, avoidance of toxic reagents, reduction of waste and responsible treatment of resources is also crucial. In this regard, sequential reactions have evolved as powerful synthetic tool in modern organic chemistry. In comparison to traditional stepwise reaction, sequential reactions (such as cascade, domino and tandem reaction) are characterized by their great elegance, high stereoselectivity, few steps and reduction in the amount of undesired by-products. Cascade reactions are sequence of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process repeats until a stable product is formed under the same reaction condition. L. F. Tietze, defines domino/cascade reactions as:

"*A process where two or more bond-forming transformations occur under the same reaction conditions, without the addition of auxiliary reagents or catalysts and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.*"

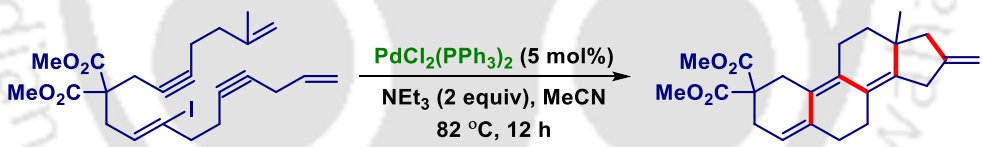
Cascade reactions can be considered to fall under the banner of 'green chemistry' because single reaction solvent, workup procedure, and purification step may be required to provide a desired product that would otherwise be synthesized over the course of several individual steps. Cascade reactions require a combination of highly selective transformations compatible with different functional groups, which can be challenging to

chemists. Consequently, a good understanding of the combined processes is required in order to develop such combinations.

Domino/cascade reactions can be classified based on the nature of the mechanism involved in each step as:

1. Cationic 2. Anionic 3. Radical 4. Pericyclic 5. Photochemical 6. Transition metal-catalyzed 7. Nucleophilic/electrophilic initiated. 8. Oxidation or Reduction initiated. 9. Enzyme assisted.

During cascade reactions preserving the functional group in a molecule is one of the challenging tasks for synthetic organic chemists. As a result, to address such issue a good synthetic combination is required. In last few decades use of transition metals in organic transformation has increased tremendously. Transition metals have been found as of immense importance in cascade reactions. Various transition metals such as Cu, Pd, Ru, Rh, Ir, Mn, Fe, Ag, Co, and Au have been employed in the cascade reactions. However, the chemistry of palladium, silver and copper are versatile and quite well understood. Therefore, there are numerous reports on palladium, silver and copper-catalyzed cascade reactions in recent time. Negishi developed a Pd(II)-catalyzed formation of a polycyclic compound that display a good example of metal-catalyzed cascade reaction (Scheme I.1).



Scheme I.1. *Formation of polycyclic compound*

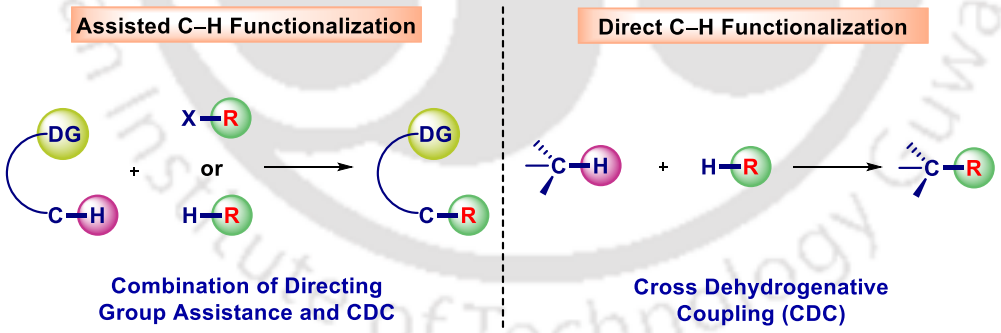
The second part of this chapter gives an outline on the history of C–H activation, various tactics implemented in modern days, their advantages, challenges and application in organic synthesis.

Coupling chemistry is an important synthetic approach towards the construction of C–C and C–heteroatom bonds that has been widely explored in industry and academia. The traditional coupling reactions involves the use of pre-functionalized starting materials and stoichiometric organometallic reagents. Over the past few decades there has been extensive progress in this area of research and this methodology has been successfully implemented for the synthesis of many commercially important molecules. Conversely, the use of pre-functionalized substrates adds extra steps to the overall method and is a major concern for the synthetic chemists from an atom-economic and environmental

perspective. This issues can be addressed by using un-functionalized starting materials and direct functionalization of C–H bonds.

The C–H bonds are considered as dormant functional groups. They are highly stable and resistant to reaction with acids and bases or electrophiles and nucleophiles. Due to the ubiquitous nature of C–H bonds in an organic molecule, selective functionalization of a desired C–H bond and preserving the existing functionality in the molecule is quiet challenging. With this features in mind, it is clear that if the balance between the reactivity and selectivity is achieved it could potentially constitute the most broadly relevant and powerful class of transformations in organic synthesis.

With the aim to enhance this revolutionary field of organic synthesis, more systematic and concerted efforts have been made towards C–H activation and its application in coupling chemistry in recent years. As a consequence, remarkably useful methods have been developed and transition-metal catalyzed C–H bond functionalization is one such tactic to achieve C–C and C–X (X = heteroatom) bond formation. The two most common approach towards C–H activation are: (i) chelation assisted C–H bond functionalization and (ii) cross dehydrogenative coupling (Scheme I.2). In this regard, our group has been involved in the development of new methodologies towards the functionalization of inert C–H bonds.



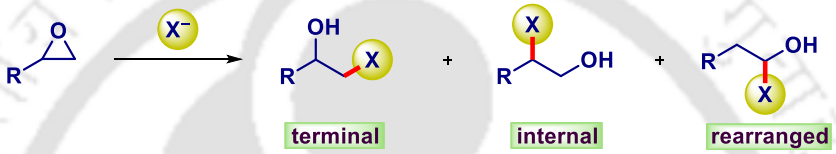
Scheme I.2. *Diverse C–H functionalization route*

The third section of this chapter gives a brief account on exploring the chemistry of oxirane towards the formation of C–C and C–heteroatom bonds.

The oxirane ring, one of the simplest heterocycle, is a vital functional group in organic chemistry. Due to their ease of formation they are widely utilized as versatile starting material and synthetic intermediates in organic synthesis. The inherent ring strain along with the polarization of the carbon–oxygen bonds generates a significant reactivity profile

for oxiranes. The ring-opening reactions of oxiranes with a variety of nucleophilic reagents (such as acids, bases, reducing and oxidizing agents) can be attributed to the electrophilic nature of this heterocycle leading to the synthesis of multi-functionalized organic compounds. Generally, the ring-opening of epoxides is an atom-economical process, generating highly regio- and stereoselective products under suitable reaction conditions.

The stereoselectivity of oxirane ring opening is usually *anti* and the regioselectivity depends on the oxirane structure and reaction conditions. The three major possibilities for nucleophilic substitution is depicted in Scheme I.3 under suitable reaction conditions. With these characteristic features of oxirane in mind we set to explore its reactivity towards the construction of C–C and C–heteroatom bonds.



Scheme I.3. *Three major possibilities of nucleophilic attack*

CHAPTER II: CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential *N*-Arylation and Oxidative C–H Amidation

This chapter focuses on CuO nanoparticle catalyzed synthesis of 2,3-disubstituted quinazolinones from 2-halobenzamides and (aryl)methanamines under an air atmosphere. This cascade synthesis involves Ullmann coupling between 2-halobenzamide and (aryl)methanamine, oxidation of the *in situ* generated secondary amine to imine followed by an intramolecular nucleophilic attack of the amidic N–H on to the imine carbon (C–N bond formation) resulting in the synthesis of 2,3-disubstitued quinazolinones.

In last few decades, synthesis of nitrogen containing polyheterocycles via domino approach and the reaction involving the direct C–H bond functionalization has emerged as one of the powerful tools for their synthesis. A significant attention has been paid to nitrogen bearing heterocycles, as they are the integral part of many natural products and biologically and pharmaceutically active molecules. Among nitrogen containing heterocycles, quinazolinones represent a class of very important structural motifs as they form the core skeleton of many natural products like luotonine A, rutaecarpine, bouchardatine. They are also the major building blocks of many drugs having anti-

hypertensive, anti-inflamatory, anti-bacterial, anti-cancer and anti-tuberculosis activities. Therefore, there is substantial interest to develop novel, efficient and practical approach for their synthesis. Since quinazolinones are assigned as privileged structure in drug development, a number of methods have been developed for their synthesis. The conventional synthesis of quinazolinones involves coupling of *o*-aminobenzamides or *o*-nitrobenzamides with aldehydes, alcohols and other coupling reagents. However, benzoic acid derivatives bearing *o*-amino or *o*-nitro groups are not readily available and are difficult to prepare. With the advancement of Cu catalyzed *N*–arylation strategies for the synthesis of *N*–heterocycles Fu group reported the synthesis of quinazolinones using 2-halobenzamide and benzylamine using copper(I) in an air atmosphere. So far many methods have been reported using various transition metal catalysts. However, due to homogeneous nature of the reaction mixture further use of the catalyst for the next catalytic cycle is rarely studied as the separation of catalyst and product is often difficult. Heterogeneous catalytic systems have several advantages in terms of good dispersion of their active site, easy separation of reaction mixture and catalyst recyclability over homogeneous systems.

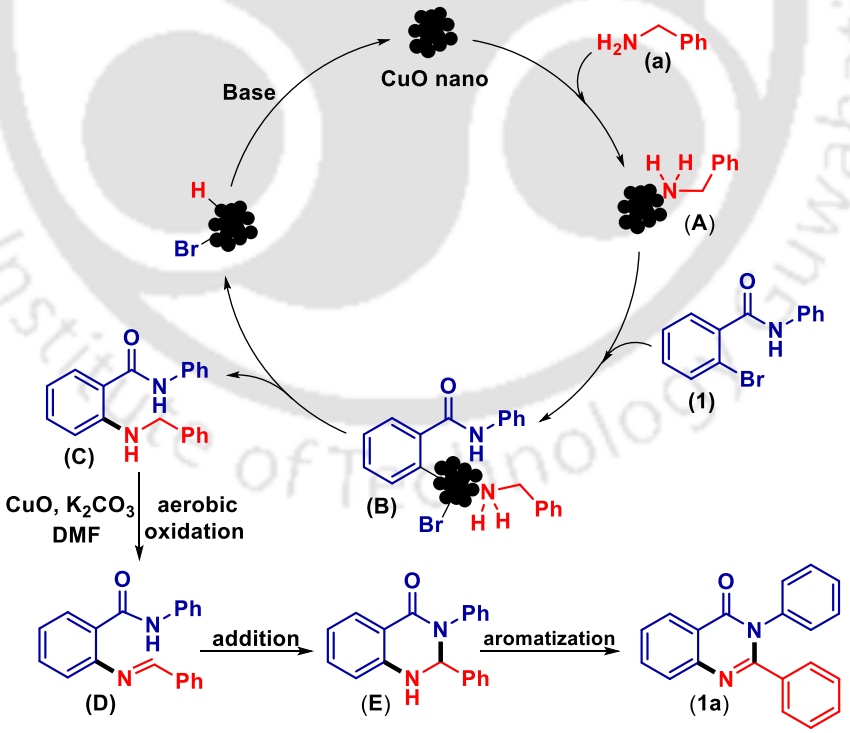
In modern era of organic synthesis, nanoparticle catalyzed reactions has been one of the most progressive research areas. Owing to the advantage of heterogeneous catalyst, nano-crystalline metal oxides have always tempted the synthetic chemists. They are advantageous over conventional metal catalyst in terms of large surface area, high reactivity, high thermal resistance giving higher yields with better atom economy. Several *N, O* and *S*-arylation reactions using CuO nano particle are already reported. To the best of our knowledge, nano CuO catalyzed domino reaction for the synthesis of quinazolinones have not been explored. Herein, we report a simple and efficient method for the synthesis of a diverse array of quinazolinones via the Ullmann coupling of various *o*-halobenzamides and (aryl)methanamines followed by an intramolecular aerobic oxidative C–H amidation.

To reach the suitable reaction condition for the synthesis of quinazolinones various reaction parameters such as catalyst, base, solvent and temperature were scrutinized. After a series of optimization, it was found that the use of 5 mol% CuO nano, 3 equiv K_2CO_3 in DMF at 120 ^oC to be the optimal reaction condition. With this optimized conditions in hand, we investigated the scope of this transformation with various 2-halobenzamides and (aryl)methanamines. Most of the substrates provided good to moderate yields of products

regardless of their electronic environment. Maximum yields were obtained when the substituents in the aryl ring of benzylamine and *N*-aryl ring of benzamides were both electron-donating. Slightly lower yields were obtained when any one of the ring is substituted with electron-donating groups and the other ring with electron-neutral and electron-withdrawing groups. The reaction also went efficiently with heterocyclic analogues of benzylamines and *N*-aryl benzamides.

Several control experiments were performed to understand the possible reaction mechanism. Based on the observation of these experiments and previous related literature reports, a plausible reaction mechanism has been proposed (Scheme II.1).

To check the efficacy of the catalyst for the next catalytic cycle, the catalyst was recovered. The catalytic efficiency of the recovered catalyst was examined upto three cycles. It was found that the catalytic activity of the recovered CuO was slightly lower in subsequent cycles. After third cycle the reaction mixture containing the catalyst was centrifuged and its surface morphology was analyzed and compared with that of fresh catalyst using TEM, which shows agglomeration of the catalyst during the course of the reaction.



Scheme II.1. *Plausible mechanism for CuO nanoparticle catalyzed synthesis of quinazolinones*

In conclusion, we have developed a CuO nanoparticle catalyzed simple and efficient method for the synthesis of 2,3-disubstituted quinazolinones by coupling of 2-halobenzamides and (aryl)methanamines. This reaction operates through sequential C–N bond formation, aerobic oxidation and intramolecular cyclization without the requirement of ligand and additives. The method is advantageous as it offers low catalyst loading, high yield, and recyclability of the catalyst and tolerance of a wide range of functional groups.

CHAPTER III: Base-Promoted Synthesis of Quinoline-4(1*H*)-thiones from *o*-Alkynylanilines and Aroyl Isothiocyanates

This chapter demonstrate a base-promoted synthesis of quinoline-4(1*H*)-thiones from the *in situ* generated *o*-alkynylthiourea, obtained by reacting *o*-alkynylanilines with aroyl/acyl isothiocyanates. A 6-*exo*-dig *S*-cyclization of the *in situ* generated thiourea is followed by a rearrangement to give quinoline-4(1*H*)-thiones.

Construction of heterocycles with privileged scaffolds, which exhibit various biological activities, is in great demand in the field of chemical genetics. Among numerous efforts devoted towards the development of these compounds, cascade reactions have emerged as a powerful synthetic tool in modern synthetic organic chemistry. Compared to the traditional stepwise synthesis, cascade reactions have the advantage of sequential incorporation of multiple C–C and C–hetero atom bonds in one-pot, thereby increasing the overall synthetic efficiency. Taking advantage of this strategy, several alkyne-based substrates, possessing internal nucleophiles at appropriate positions, are often utilized for the construction of interesting heterocycles. Among various alkynes, *o*-alkynylanilines have been extensively employed for the construction of molecular frameworks such as indole, quinoline, quinazolinone, benzoxazine, 4*H*-benzo[*d*][1,3]thiazine using various metal salts such as palladium, copper and silver.

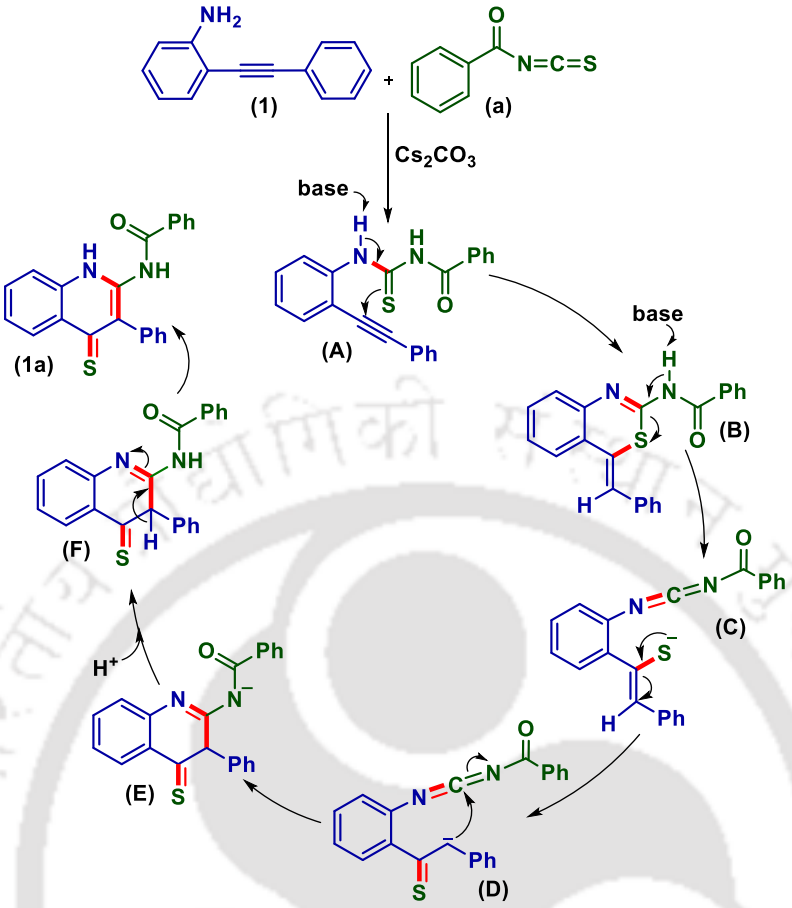
Recently, our group reported the synthesis of indolo[2,3-*b*]quinolines from *o*-alkynylanilines and aryl isothiocyantes in presence of Ag_2CO_3 under microwave heating. Interestingly, replacement of aryl isothiocyante with an aroyl isothiocyante completely changed the course of reaction and the product outcome, giving a quinoline-4(1*H*)-thione. We carried out an initial investigations by reacting 2-(phenylethynyl)aniline and benzoyl isothiocyanate in the presence of CuI (10 mol %) and K_2CO_3 (4 equiv) in 1,4-dioxane at 110 ^oC. The reaction gave a completely new product i.e. *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide which was analyzed by spectroscopic methods and

further confirmed by single-crystal X-ray diffraction of one of its derivative. Interestingly, the benzoyl thiourea generated *in situ* underwent a 6-*exo*-dig *S*-attack onto the internal alkyne, followed by rearrangement giving thequinoline-4(1*H*)-thione moiety in 100% atom economy.

Based on recent studies, quinoline-4(1*H*)-thione derivatives are found to be inhibitors of virulence factor elastase of the human pathogen *Pseudomonas aeruginosa*. Some of the quinoline-4(1*H*)-thione derivatives are reported to form oxovanadium complexes with $VO(acac)_2$, exhibiting cytotoxic activity and apoptosis in human malignant cell lines. Despite the importance of the quinoline-4(1*H*)-thione framework, there are only a few reports of their synthesis which mainly involve thioketolization of the preformed quinolin-4(1*H*)-ones with phosphorus pentasulfide (P_4S_{10}) or with Lawesson's reagent. To the best of our knowledge, there is no report at this date for the synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate in the presence of base.

Various reaction parameters such as catalysts, base, solvent and temperature were screened to obtain the optimal conditions for this reaction and it was found that the reaction in the absence of any catalyst and merely in the presence of Cs_2CO_3 (2 equiv) and CH_3CN solvent at 80 ^oC under air is the most suitable conditions. With this optimized condition the scope of this transformation was extended to a variety of *o*-alkynylanilines and aroyl isothiocyanates. Aroyl isothiocyanates having electron-donating (EDG) or electron-withdrawing (EWG) substituents and acyclic as well as heterocyclic carbonyl isothiocyanates all reacted competently giving good yields of their respective products. The presence of different substituents on the phenyl rings of *o*-alkynylanilines also gave good to excellent yields of the product on reaction with various aroyl isothiocyanates.

Based on the literature reports, a plausible pathway has been proposed for the base-promoted cascade reaction (Scheme III.1).



Scheme III.1. *Plausible mechanism for the synthesis of quinoline-4(1H)-thiones*

In conclusion, we have demonstrated a metal-free approach for the synthesis of quinoline-4(1*H*)-thione derivatives. This is the first example of a base promoted synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate. Through the cascade process, simultaneous formation of three C–C, C–N and C–S bonds has been accomplished. This protocol shows wide functional group tolerance with good to excellent yields of the product in 100% atom economy.

CHAPTER IV: A Thiocarbonyl Directed Regiospecific C–H/S–H Annulation of Quinoline-4(1*H*)-thiones with Alkynes

This chapter gives a unique illustration of regiospecific C–H/S–H annulation of quinoline-4(1*H*)-thiones with alkynes directed via a C=S group using a Ru(II)-catalyst. Here, preferential annulation takes place at the sterically hindered position even in the presence of three other competing sites *viz.* two C–H/N–H and one C–H/O–H leading to the synthesis of thiopyrano[2,3,4-*de*]quinolines.

The evolution of C–H bond activation is emerging as one of the most powerful tools in synthetic chemistry and has streamlined the construction and functionalization of complex molecules in the past decade. Among various transition metals, ruthenium catalyzed chelation directed C–H bond activation, followed by annulation with alkynes, has led to the synthesis of a wide range of fused polyheterocycles. To accomplish this, diverse N- and O- based directing groups such as amines, anilides, imines, amides, ketones, esters, carboxylic acids, and alcohols have been well studied. The coordination of heteroatom to the metal centre is assumed to be the key step in these transformations, thereby directing the metal centre to the proximal C–H bond and thus achieving the desired functionalization. In the midst of several directing groups, sulfur containing compounds such as thiols, thioethers, sulfoxides have not been utilized for any metal directed annulations. Nevertheless, arylation, alkenylation and heterocycle synthesis have been reported. Remarkably, organosulfur compounds are important chemical entities because of its occurrence in many biological systems, synthetic drugs and functional materials. However, the susceptibility of sulfur to easy oxidation and its affinity towards metal ions poisons the catalyst thereby hampering its usage in C–H activation reactions. Any sulfur directed annulation is hitherto unprecedented and thus developing novel routes for the synthesis of complex molecules with concurrent sulphur incorporation is highly desirable.

Quinoline-4(1*H*)-thione i.e., *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide moiety reported in our previous chapter have four directing sites *viz.* two C–H/N–H, and one each of C–H/S–H and C–H/O–H susceptible for possible annulation with alkyne. Previously our group reported a Ru(II)-catalyzed oxidative C–H/O–H annulation of 2-arylquinolinone with internal alkynes wherein, annulation is via the more favourable phenolic form of quinone over other possible pathways (C–H/N–H and C–H/C–H). In this case, the metal coordinates to the weaker carbonyl oxygen in the presence of stronger nitrogen-directing group giving a regiospecific annulated product. Thus, we were inquisitive to see whether annulation reaction in quinoline-4(1*H*)-thione will proceed via the thiophenolic form (C–H/S–H) or other competing sites (C–H/N–H or C–H/O–H) will dictate?

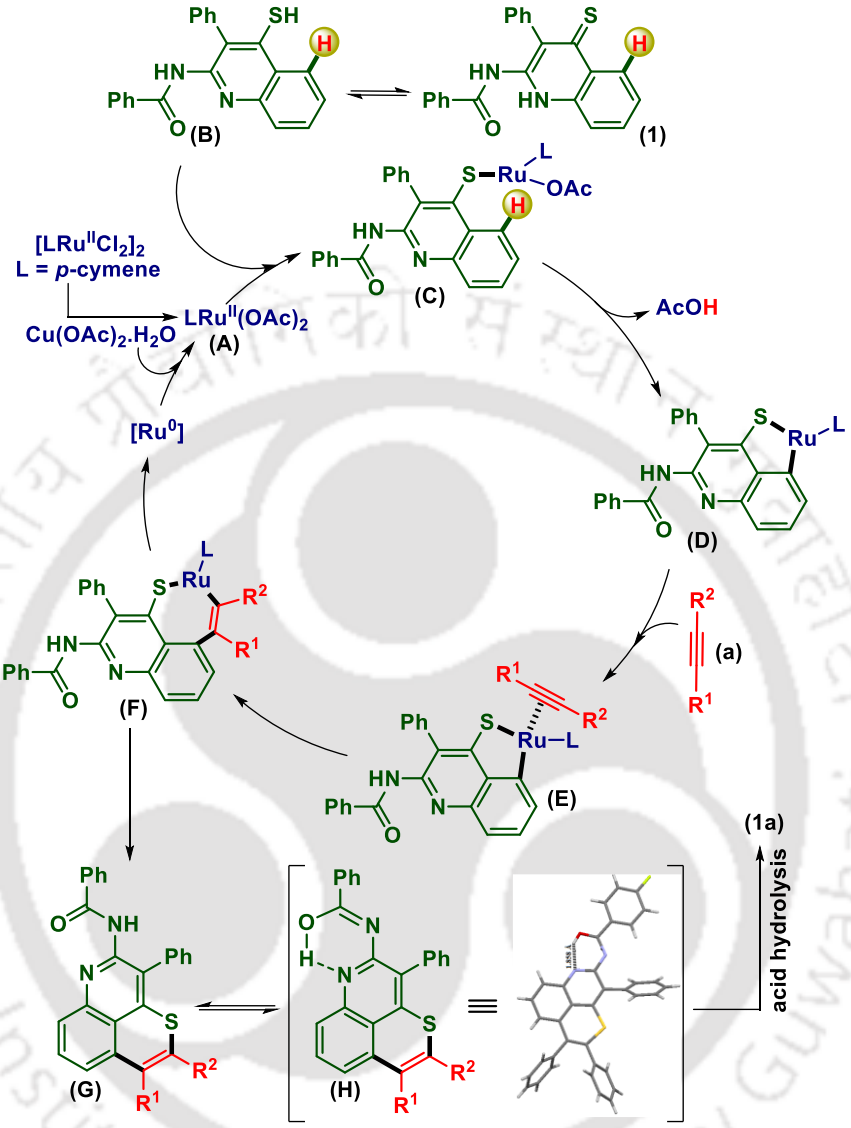
With this motivation, we commenced our exploration by reacting *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide and diphenylacetylene with the well investigated catalyst $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), AgOAc (1 equiv) as the oxidant in

AcOH under air at 110 ^{o}C. A new product was isolated in 55% yield after 12 h. Spectroscopic analysis (^{1}H NMR and ^{13}C NMR) revealed its structure to be 3,5,6-triphenylthiopyrano[2,3,4-*de*]quinolin-2-amine, which was reconfirmed by single crystal X-ray diffraction. The analysis of the product confirms a [4 + 2] annulation of alkyne via oxidative C–H/S–H bond cleavage over other competing annulations (C–H/N–H or C–H/O–H). This process is however associated with the loss of –COPh group possibly via a hydrolytic path. Thus the question arises, whether the amide bond cleavage takes place before the annulation or after? Subsequently, crystal structure of one of the isolated intermediate (after 30 minutes) confirms that the annulation precedes over the amidic bond cleavage. It is worthy to mention that, the alkyne annulations reported till date often involves C–H/N–H, C–H/O–H, and C–H/N–O bond cleavages. To the best of our knowledge, this is the only example of alkyne annulation via C–H/S–H bond functionalization leading to the first synthesis of thiopyrano[2,3,4-*de*]quinolines.

Quinoline and quinoline-fused polyheterocycles are important building blocks in natural products, agrochemicals, material chemistry, and also useful as chiral ligands. Among various quinoline derivatives, thiopyranoquinoline are of considerable interest as they exhibit significant pharmaceutical activities. Molecules having thiopyranoquinoline framework are reported to function as inhibitors of telomerase and are valuable for the treatment of cellular proliferation disorders. Considering the importance of quinoline-fused thiopyran ring system, the present synthetic protocol would render the generation of thiopyrano[2,3,4-*de*]quinoline moiety with potential application in diverse field of research.

To find out the appropriate optimized condition a series of experiments have been carried out and it was found that the use of $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), $Cu(OAc)_2.H_2O$ (2 equiv) in AcOH under air at 110 ^{o}C is the best condition for the present transformation. After establishing the optimized annulation strategy, we probed the diversity of this oxidative annulation by employing various decorated quinoline-4(1*H*)-thiones with variety of symmetrical internal alkynes. Gratifyingly, the present protocol proceeded well with a variety of *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamides derivative giving good to excellent yields of the product. Interestingly, the reaction with asymmetric alkynes as well as terminal alkynes gave a single regioisomeric product.

Based on literature reports a plausible reaction mechanism has been proposed as depicted in Scheme IV.1.



Scheme IV.1. *Plausible mechanism for annulation of quinoline-4(1H)-thiones*

In summary, we have demonstrated the first thiocarbonyl directed regiospecific annulation of alkynes with quinoline-4(1*H*)-thiones. In a multi-directed sites *viz.* C–H/N–H and C–H/O–H, the C–H/S–H annulation is preferred even under a constraint environment. Terminal and unsymmetrical alkynes, gave single regioisomeric product. Thus, thiopyrano[2,3,4-*de*]quinolines could be conveniently synthesized via the coupling of quinoline-4(1*H*)-thiones with internal or terminal alkynes.

CHAPTER V: *N,N*-Dimethylacetamide (DMA) as a Methylene Synthon for Regioselective Linkage of Imidazo[1,2-*a*]pyridine

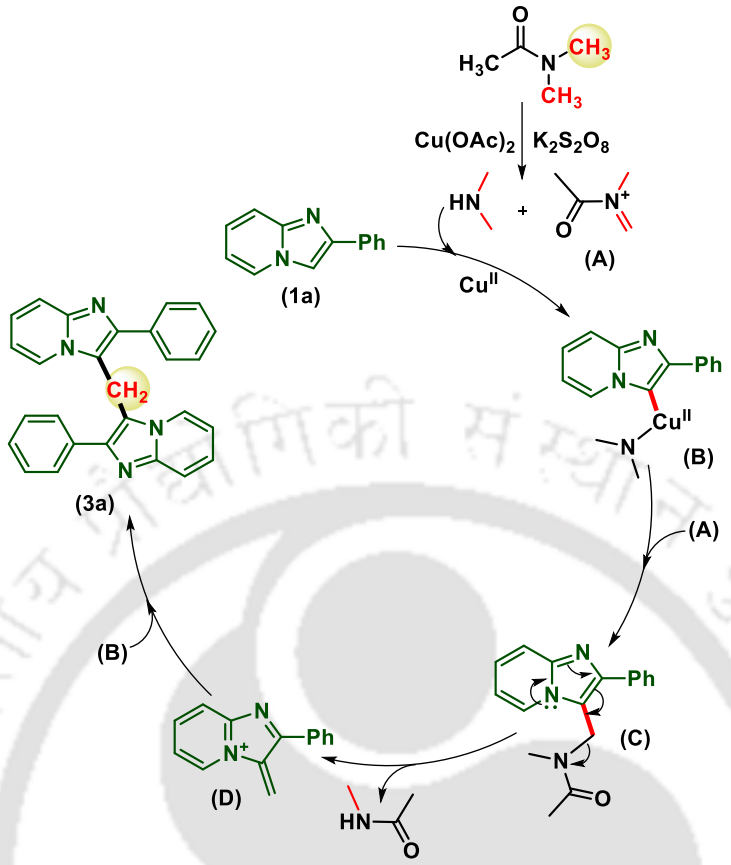
This chapter demonstrates a Cu(II)-catalyzed oxidative methylene-bridged dimerization of two analogous imidazo[1,2-*a*]pyridine using *N,N*-dimethylacetamide (DMA) as solvent cum methylene source.

Cross-dehydrogenative coupling (CDC) under oxidative conditions is one of the most efficient and straightforward tools for the construction of C–C bonds. This strategy is now so powerful that, even the commonly used organic solvents such as formamides and sulfoxides are utilized as the source of various functional groups. *N,N*-dimethylformamide (DMF), a well-known solvent, has turned out to be a multipurpose reagent widely used in organic chemistry as building block of various units such as -O, -CO, -NMe_2, -$CONMe_2$, -Me, -CHO, etc. Similarly, dimethyl sulfoxide (DMSO) is also utilized as the source of -SMe, -CN, -CHO, -Me, etc. *N,N*-dimethylacetamide (DMA), although chemically inert compared to DMF, has been successfully explored as a one-carbon synthon for the synthesis of terminal alkenes and heterocycles *via* sp^3–sp^3 and sp^2–sp^3 C–H couplings, respectively. However, the use of DMA as the source of a one-carbon linker between two analogous imidazo[1,2-*a*]pyridines *via* cross-dehydrogenative coupling of sp^2 C−H of arene and sp^3 C−H bond of DMA is unfamiliar so far.

Among the *N*-heterocycles, imidazo[1,2-*a*]pyridines represent an important structural motif because of their prevalence in the field of medicinal and material chemistry. The derivatives are reported to have a diverse array of biological activities such as antiviral, antibacterial, antifungal, antiulcer, and antihelminthics. They also form the core skeleton of many pharmaceutically important drugs such as necopidem, saripidem, alpidem, zolpidem and zolimidine. Owing to the ubiquity of imidazo[1,2-*a*]pyridine framework in various fields, substantial attention has been paid to their synthesis and further functionalizations. Of late, many methods have been explored for the C-3 functionalization of imidazo[1,2-*a*]pyridines, *viz*. trifluoromethylation, sulfenylation, fluorination, cyanation, thiocyanation, dicarbonylation, aminomethylation as well as oxidative homocoupling of two imidazo[1,2-*a*]pyridine moieties. Although there have been significant developments toward the regioselective functionalization at the C-3 carbon, the quest for the further derivatizations is still ongoing.

With the aim to functionalize the C-3 position of imidazo[1,2-*a*]pyridine, it was treated with DMA (solvent cum reagent) in the presence of catalyst CuI (20 mol%) and oxidant $K_2S_2O_8$ (1 equiv.). Formation of an unexpected product was observed in 50% yield. The product showed a singlet at 4.99 ppm in its ^{1}HNMR and a peak at 19.9 ppm in its ^{13}CNMR spectra, which may be due to the presence of a methylene carbon in the product. Furthermore, from the single crystal X-ray diffraction study of one of its derivative, its structure was established to be a C-3 methylene bridge bis-heterocycle. To ascertain the source of the methylene carbon in the product, a similar reaction was carried out separately with *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylacetamide (DEA) in lieu of DMA under otherwise identical conditions. Formation of product was observed only with DMF (and not with DEA), thereby suggesting that the methylene carbon possibly originates from the *N*-methyl group of DMA/DMF and not from the acetyl group of DMA. When the reaction was carried out with DMF-d_7, insertion of a deuterated methylene group was observed, which was confirmed from the HR-MS analysis of the reaction mixture. This result unequivocally confirms that the *N*-Me group of DMA/DMF is the source of methylene carbon in the product. There are reports where the *N*-methyl of DMA served as a one-carbon surrogate for the synthesis of terminal alkenes. The group of Xu and Wang have independently reported vinylation of 2-methylazaarenes using iron(III) catalyst. Recently, Miura *et al.* have developed a copper(II) catalyzed α-methylenation of benzylpyridines. Lately, DMF and DMA both were employed as a one-carbon source by Lei and Li using copper(II) and iron(III) catalysts respectively. Herein, we report DMA as a one-carbon source, i.e. as a methylene linker for coupling of two imidazo[1,2-*a*]pyridines.

Encouraged by the above unprecedented result, further optimizations of the reaction parameters such as catalysts, oxidants and reaction temperature were screened to find the optimal reaction condition to achieve the maximum yield of the product. After a series of experiments, the best condition was found as $Cu(OAc)_2$ (20 mol%), $K_2S_2O_8$ (2 equiv) in DMA under air at 120 ^{o}C. The scope and generality of this methodology was then extended to a range of imidazo[1,2-*a*]pyridines. Irrespective of the nature of the substituent on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridine moiety and substituents on the pyridine ring of imidazo[1,2-*a*]pyridine moiety all gave moderate to good yields of the products.



Scheme V.1. *Plausible mechanistic pathway*

To gain an insight into the reaction mechanism, a number of control experiments were carried out. On the basis of the results obtained from these experiments and literature precedence a plausible reaction mechanism has been proposed as shown in Scheme V.1.

In conclusion, we have developed a copper(II)-catalyzed dimerization of two imidazo[1,2-*a*]pyridine moieties with a methylene linkage in the presence of an external oxidant. Use of cheaper reagents, regioselectivity, and broad substrate scope are the notable features of this methodology. The synthesized methylene bridged dimeric imidazo[1,2-*a*]pyridine derivatives may find applications in the field of medicinal and material chemistry.

CHAPTER VI: Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxiranes Using Aroyl Isothiocyanates

This chapter describes a regioselective and concomitant transfer of thiocyanate (–SCN) and aroyl/acyl (–COR) groups from aroyl/acyl isothiocyanates onto oxiranes,

giving thiocyanato benzoates in 100% atom economy. In this biomimetic organocatalytic process, one part (–SCN) of aroyl/acyl isothiocyanates acts as the nucleophile whereas the other half (–COR) serves as an electrophilc partner.

The desire to develop newer methodology for the construction of C–C and C–X (X = heteroatom) bonds has brought about many appealing results in the field of synthetic chemistry. Compared to the traditional electrophiles, epoxides have emerged as attractive coupling partners. The ring strain in epoxides makes them susceptible to ring opening with a range of nucleophiles such as alcohols, amines, thiols and other strong nucleophilic organometallic reagents like Grignard or organolithium. Recently, there have been many reports on transition-metal-catalyzed coupling of epoxides with aryl halides, arenes, alkenes, alkynes and boronic acids, resulting in the construction of a variety of alcohols. However, these transition-metal-catalyzed reactions are not universally acceptable due to their high cost and toxicity.

From our previous work on biomimetic thiocyanate group transfer from aroyl isothiocyanate onto α-haloketones, a nucleophilic substitution product was observed in the absence of any real nucleophile. In this process, the α-haloketone serves as an electrophile and the aroyl isothiocyanate as the source of nucleophile (–SCN). Thus, it will be interesting to see if an oxirane can act as the electrophilic partner for this nucleophile-less nucleophilic substitution. Furthermore, if the ring opens up, what will be the fate of the resultant alkoxy ion? Will it form an alcohol (via protonation), or will it undergo further nucleophilic attack onto a suitable electrophile?

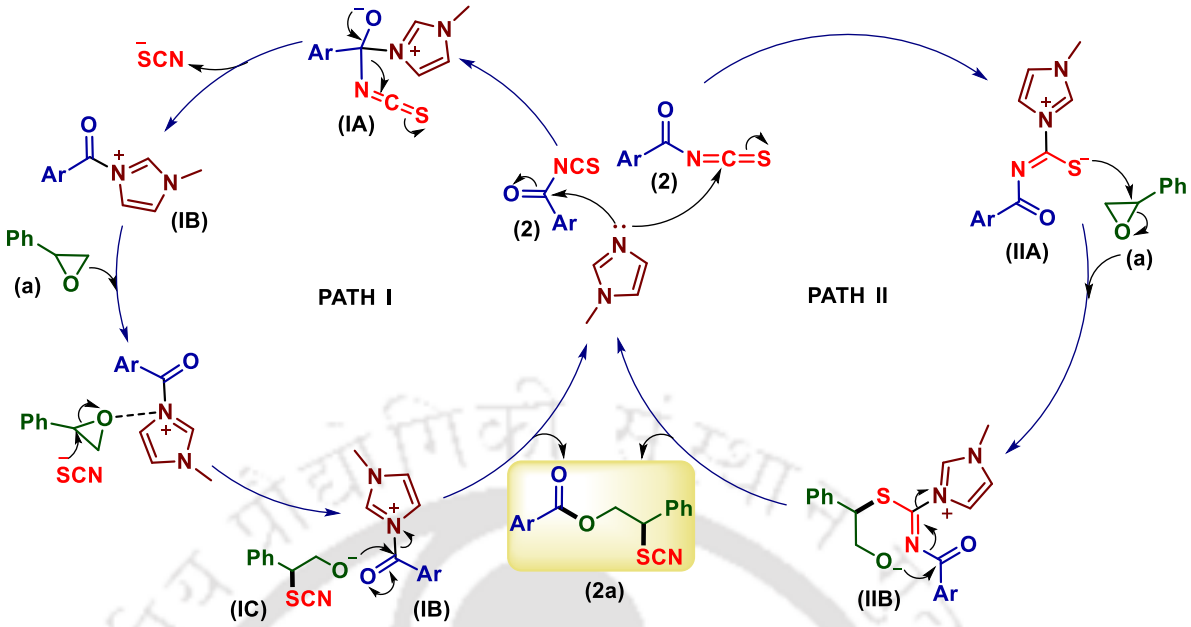
To find answers to the above queries, a reaction was carried out with benzoyl isothiocyanate (1 equiv) and 2-phenyloxirane (1 equiv) in the presence of *N*-methylimidazole (NMI) (1 equiv) in acetonitrile (2 mL) at room temperature, under a reaction condition identical to that reported in our previous work. Both reactants were completely consumed (as indicated by TLC) giving a new product. The IR spectra of newly formed product showed a characteristic peak at 2154 cm^{-1} suggesting the incorporation of a –SCN group. Another peak at 1705 cm^{-1} may be due to the presence of a carbonyl group in the resultant product. Further, ^{1}H and ^{13}C NMR of the isolated product revealed the presence of an ester functionality. Finally, the structure of the product was confirmed by single-crystal X-ray diffraction study of one of its derivative, which revealed the presence of a thiocyanate as well as an ester functionality. As anticipated, the thiocyanate acts as a

nucleophile and attacks at the Aα position of the epoxide. The resultant alkoxy species obtained by the ring opening of epoxide possibly undergoes benzoylation, giving 2-phenyl-2-thiocyanatoethyl benzoate. Here, the reaction gave a single regioisomeric product in 67% isolated yield. In the absence of NMI, the reaction did not proceed at all, suggesting its definite involvement during this simultaneous electrophilc-nucleophilic process. This unprecedented outcome showing the transfer of both halves (i.e., thiocyanate (–SCN) and the acyl (–COPh) group from aroyl/acyl isothiocyanate to oxirane) results in the formation of a product having new C–S and C–O bonds in 100% atom economy.

Organic thiocyanates are prevalent subunits in bioactive compounds possessing antimicrobial and antiproliferative activity and are versatile precursors for the synthesis of many sulfur-containing heterocycles. Aryl esters are also a ubiquitous functionality found in pharmaceuticals, agrochemicals and polymers and are important building blocks for organic synthesis. The presence of both of these important functionalities, viz. thiocyanate and ester, in a single molecule derived from readily available starting material is a boon to synthetic chemists.

Encouraged by this double functional group transfer, further optimizations were carried out to improve the yield of the *bis*-functionalized product. Various other organic bases, solvents and temperature were scrutinized and it was found that the reaction gave the best yield with 20 mol% of NMI at room temperature in the absence of any solvent. The scope of this methodology was further extended to a range of aroyl/acyl isothiocyanates and oxirane derivatives. The presence of electron donating substituent on the phenyl ring of aroyl isothiocyanate gave better yield with 2-phenyloxirane derivatives compared to electron withdrawing substituents. In the case of glycidic epoxide, the –SCN attack takes place at the Aα (benzylic carbon) site, giving single regioisomeric products. In the case of non-benzylic oxiranes the attack of –SCN takes place at the less sterically hindered carbon (Aβ).

To ascertain the nucleophilic (S_N2) path of oxirane ring opening in glycidic epoxide systems reactions were conducted with chiral epoxides and the isolated products were found to be optically active. Based on our previous work and from literature reports a plausible reaction mechanism has been proposed (Scheme VI.1).



Scheme VI.1. *Plausible reaction mechanism*

In conclusion, we have demonstrated a biomimetic organocatalytic bis-functionalization of oxiranes from aroyl/acyl isothiocyanates in the presence of NMI. In this simultaneous electrophilic–nucleophilic reaction, the thiocyanate (–SCN) of aroyl/acyl serves as the nucleophile, whereas the aroyl part acts as the electrophilic partners, giving products in 100% atom economy. In this metal free process, C–S and C–O bonds are simultaneously constructed in the presence of NMI under solvent free conditions.