SYNOPSIS

The contents of this thesis have 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 on different aspects of C–H functionalization and cascade reactions: advantages, challenges and solutions of them. All the other chapters emphasize on C–C, C–O, C–S and C–N bond forming reactions via metal-catalyzed/mediated C–H functionalization using strategies like cross-dehydrogenative coupling, functional group directed C–H bond functionalization and cascade reactions involving isocyanides, 2-alkynylanilines and aryl isothiocyanates.

Chapter II illustrates a protocol for copper-catalyzed synthesis of phenol carbamates from dialkylformamides and phenols possessing benzothiazole, quinoline and formyl as directing groups at their *ortho*-position.

Chapter III describes the use of methylarenes as aroyl surrogates toward *S*-aroylation of thiols and regiospecific acylation of *N*-heterocycles catalyzed by copper and aluminum salts respectively.

Chapter IV demonstrates a cascade synthesis of dihydrobenzofurans and Aurones via palladium-catalyzed insertion of isocyanides into 2-halophenoxy acrylates.

Chapter V describes about the cascade reactions involving internal alkynes for the synthesis of benzofuran [3,2-*c*] quinolin-6[*5*-*H*]ones using Cs_2CO_3 as carbonyl as well as oxygen source and indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates in the presence of copper and silver salts respectively.

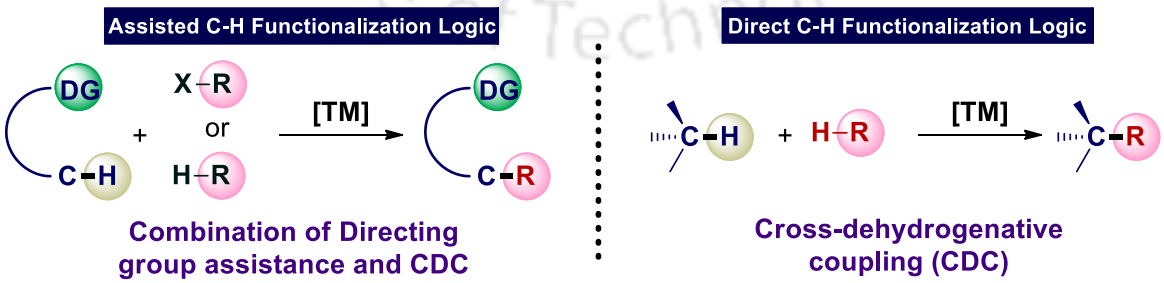
Each of these chapters comprises of introduction, previous work, present work, experimental section, references, spectral data and few representative spectra.

CHAPTER I. An Overview of Metal-Catalyzed C–H Functionalization and Cascade Reactions

First part of this chapter gives a layout on the history of C–H activation, various strategies adopted in modern days, their advantages, challenges and applications in organic synthesis.

Coupling chemistry is an important synthetic strategy, widely used in both industry and academia for the formation of carbon–carbon and carbon–heteroatom bonds. The traditional coupling procedures involve either the use of stoichiometric organometallic reagents or the transition metal-catalyzed coupling of functionalized hydrocarbons. There has been substantial progress in these methods over the last few decades and they are successfully applied in the synthesis of commercially important products. However, the use of pre-functionalized starting materials in these methods adds extra step towards the formation of desired chemical bond, is a major concern for the modern day synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize un-functionalized starting materials by the direct functionalization of C–H bonds.

The carbon–hydrogen bond is regarded as the un-functional group. Its unique position in organic chemistry is well illustrated by the standard representation of organic molecules: the presence of C–H bonds is indicated simply by the absence of any other bond. This "invisibility" of C–H bonds reflects both their ubiquitous nature and their lack of reactivity. With these characteristics in mind it is clear that if the ability to selectively functionalize C–H bonds are well developed, it could potentially constitute the most broadly applicable and powerful class of transformations in organic synthesis.



Scheme I.1.*Various C–H functionalization strategies*

With the motive of broadening this revolutionary aspect of organic synthesis, in modern times more systematic and concerted efforts have been made in C–H bond activation and its application in coupling chemistry. As a result exceptionally useful methods for organic synthesis have been developed and one such way is the transition metal catalyzed C–H bond functionalization to achieve C–C and C–X bonds. Most of these methodologies stand on the two pillars of the C–H bond activation: (a) cross-dehydrogenative coupling and (b) substrate directed C–H bond functionalization (Scheme I.1). In this context our group has been involved in the development of new disconnection approach and generation of various functionalities by cleaving the inert C–H bonds.

The second part of this chapter provides an overview about the cascade reactions especially transition metal-catalyzed/mediated reactions of isocyanide insertion, 2-alkynylaniline, and aryl isothiocyanates towards heterocycles synthesis.

Increasing a molecular complexity has long been a dream of chemists as it resembles the nature, where very complicated molecules could be synthesized, in terms of creating many bonds, rings, and stereocenters in a single transformation. Most of the complex compound found in the nature can be synthesized by a linear total synthesis applying advance version of chemical synthetic process. Therefore the main challenge in future is to produce these molecules in a more efficient and economical way which will enable the use of more sophisticated structures in industry and academia. Since accessibility highly depends upon the number of steps required to achieve the desired compound, step economy is an important factor to be addressed. In this regards sequential reaction involving several distinct transformations into a single step are one of the most powerful synthetic tools in modern organic chemistry. Compared to traditional stepwise reaction, sequential transformation (e.g. cascade, domino and tandem reaction) possess unique atom economy feature and significant advantages. 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 formed under the reaction conditions. L. F. Tietze, defines domino/cascade reactions as;

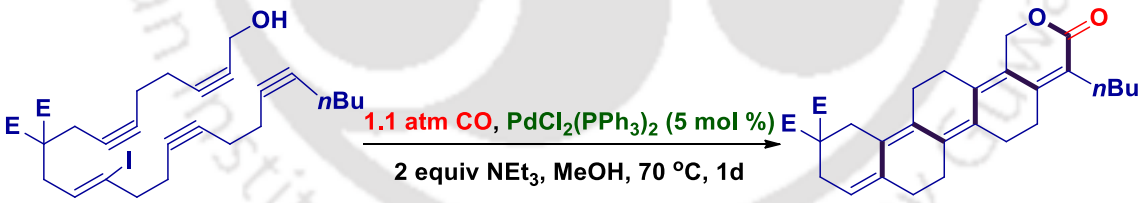
"*A process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*"

Cascade reactions are also considered to contribute to green chemistry because of the reduced waste production and increased atom efficiency. Cascade reactions require a combination of highly selective transformations compatible with different functional groups, which can be challenging to engineer. Consequently, a good understanding of the combined processes is required in order to develop such combinations.

Domino reactions can be classified based on the nature of transformations involves during the cascade mechanisms.

1. Cationic 2. Anionic 3. Radical 4. Pericyclic 5. Photochemical 6. Transition metal-catalyzed 7. Oxidation or Reduction initiated 8. 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 utilized 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. In 1994 Negishi developed a Pd(II)-catalyzed enetetraynes cyclization that display a good example of metal-catalyzed cascade reaction (Scheme I.2).



Scheme I.2. *Pd-catalyzed cascade annulation of enetetraynes*

CHAPTER II. Copper(II)-Catalyzed Cross-Dehydrogenative Coupling of *N,N*-Disubstituted Formamides and Phenols: A Direct Access to Carbamates

This chapter focuses on the copper(II)-catalyzed synthesis of phenol carbamates from cross-dehydrogenative coupling of *N,N*-Disubstituted Formamides and Phenols having moiety like benzothiazole, quinoline and formyl group as directing groups at their *ortho* position.

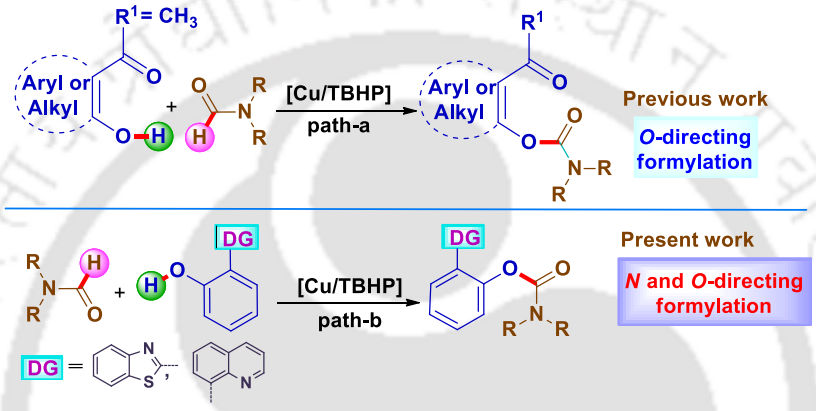
Organic carbamates are useful agrochemicals, pharmaceuticals and are also present in a wide range of biologically active natural products. In addition, carbamates play an important role as intermediates in organic synthesis and serve as a protecting group during peptide synthesis. The general methods for the carbamates synthesis require intermediates such as chloroformates or isocyanates which, in turn are prepared from phosgene or its derivatives. Thus, a phosgene-free synthesis of carbamates is most appreciable from the environmental point of view. This motive has led to the synthesis of carbamates by other methods such as (i) oxidative and reductive carbonylation of amines and nitro aromatics, (ii) reaction of amines with CO_2, (iii) metal-catalyzed cross coupling of isocyanate with alcohols and (iv) via C–H functionalizations.

The drawbacks of traditional cross coupling reactions have been very much sought out with the emergence of the direct C–H bond activation as an alternative route in organic synthesis. First method for the synthesis of carbamates via sp^2 C–H bond activation of dialkylformamides was reported by the Reddy and co-workers in 2011. They achieved this novel strategy by using *ortho* acetyl as directing group with the help of Cu(II) salt as the catalyst and *tert*-butylhydroperoxide (TBHP) as terminal oxidant. Since this early work, a number of other protocols were already developed by the different other groups using directing group assistance as well as without directing group.

N,N–Dialkylformamides have attracted much attention because of their polygonal utility in C–H functionalizations. They have been reported as surrogates of various functional groups depending upon the reaction conditions. For example *N,N*-dimethylformamide (DMF) is known to act as the source of –Me, –CO, $–NMe_2$, $–CONMe_2$, –CHO and –CN groups in various synthetic protocols. Among these groups, the synthetic utility of dialkylformamides as an aminocarbonyl ($–CONR_2$) group is well documented in the literature. All of the aforementioned reactions proceed via oxidative C–C or C–N bond formations. In the C–O bond forming segment, the use of dialkylformamides as an aminocarbonyl surrogate has been utilized for the synthesis of carbamates by reacting them with phenols and enols possessing *ortho* carbonyl directing groups.

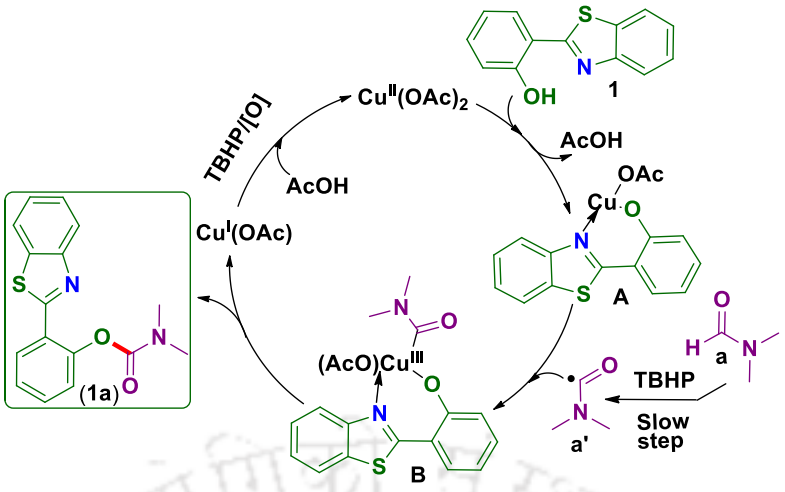
Our motive to choose benzothiazole as directing group present *ortho* to the –OH group because of the biological and pharmaceutical importance of it, as well as the co-ordination ability of *N*-atom to the transition metal. The functionalizations of benzothiazole would provide pathways for the synthesis of intermediates that may find

potential applications in various other fields. This has been realized through some of our recent achievements on transition metal-catalyzed directing group-assisted (*N*-atom) functionalizations of *ortho* C–H bond of 2-aryl moiety in benzothiazole. Where *N*-atom of benzothiazole co-ordinate with transition metal and direct it for functionalization of *ortho* C–H bond of 2-aryl moiety. Thus, we envisaged that the directing *N*-atom of benzothiazole could facilitate a metal-catalyzed aminocarbonylation of the hydroxyl group present at the proximal carbon atom. Such aminocarbonylation would lead to the formation of a hybrid benzothiazole–carbamate moiety (Scheme II.1).



Scheme II.1. *Methods of carbamates synthesis from phenols and formamides*

To reach the suitable reaction condition for the synthesis of phenol carbamates various reaction parameters such as catalyst, oxidant, solvent and temperature were scrutinized. After a series of optimization experiments it was found that the use of 5 mol % of $Cu(OAc)_2$ in the presence of aqueous TBHP (3 equiv) at 80 ^{o}C were the best condition. With this optimized conditions in hand, we investigated the scope of this transformation with different formamides and phenols possessing *N*-directing groups. It was found that various formamide including cyclic as well as acyclic were reacted with 2-(benzo[*d*]thiazol-2-yl)phenol and its derivatives to give good to excellent yield. However, acyclic formamides gives slightly better yield as compare to cyclic one. Apart from the benzothiazole, the *N*-atom in 8-hydroxyquinoline provided a similar chelation assistance towards *O*-formamidation. As we previously explore that the formyl group of salicylaldehyde acts as a direction group toward *O*-aroylation. In a similar way different salicylaldehyde reacts with formamides to afford the corresponding carbamates in good yields.



Scheme II.2. *Plausible mechanism for Cu(II)-catalyzed C–O bond formation*

Based on our results, experimental observations and literature precedents a radical mechanism for this transformation was predicted that involves formation of aminoacyl radical as the crucial step (Scheme II.2).

In conclusion, we have developed an efficient protocol for the synthesis of phenol carbamates from dialkylformamides and phenols possessing benzothiazole, quinoline and formyl as directing groups at their *ortho*-position. This directing group-assisted cross-dehydrogenative coupling (CDC) occurs between the formyl C–H of dialkylformamides and the phenolic O–H bond in the presence of the Cu(II) catalyst and oxidant aqueous TBHP. A plausible radical mechanism has been proposed for the reaction.

CHAPTER III.

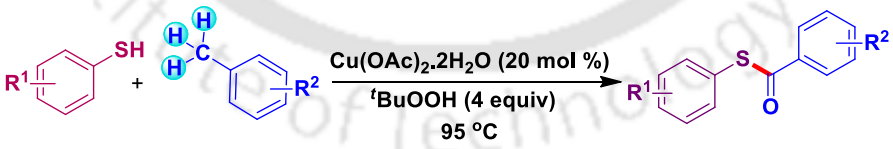
This chapter has been divided in to two sections. Section A describes the copper(II)-catalyzed *S*-aroylation of thiols with alkylbenzenes under oxidative condition, whereas Section B highlights $AlCl_3$-catalyzed regiospecific acylation of electron deficient *N*-heterocycles with methylarenes under oxidative condition.

SECTION IIIA: Thioesterification of Alkylbenzenes with Thiols via Copper-Catalyzed Cross Dehydrogenative Coupling without a Directing Group

This chapter deals with the thioesterification of alkylbenzene with the thiols catalyzed by copper(II) under oxidative condition through cross-dehydrogenative coupling.

In spite of reaching great advances, the vast majority of functionalization processes at sp^3 C–H bonds via CDC have been achieved by the sp^3 C–C bond forming reactions. The sp^3 C–heteroatom bond formation by CDC strategy is mostly confined to the construction of C–N and C–O bonds with only few examples of C–S bond formations. Thus, it is imperative to develop protocols for the later bonds since sulfur-containing compounds find potential uses in the pharmaceutical and agrochemical industries. One of the problems associated with the use of thiols as coupling partner during C–S bond formation is its propensity to undergo oxidative self-dimerization which inhibits the desired C–S bond formation. To combat this disadvantage of thiols, they are mostly employed in the form of their disulfides, sulfonylhydrazides or sulfonylchlorides that generate *in situ* reactive free radical or cationic intermediates essential for CDC reactions. Few direct thiolations using thiols or their derivatives have been demonstrated at sp^3 C–H bonds α to a heteroatom or a carbonyl group under metal free conditions, but no such relevant examples at the relatively un-activated benzylic sp^3 C–H have been reported in the literature.

Thioesters have been synthesized previously by applying various strategies. These include (i) thioesterfication or trans-thioesterification of carboxylic acids or its derivatives, (ii) thiocarbonylation of iodoarenes with thiols and carbon monoxide using Pd catalyst, (iii) recently developed oxidative coupling of aldehydes or benzyl alcohols with thiols in the presence of *N*-heterocyclic carbene (NHC) or (iv) via a radical path. In this context, the present CDC approach using simple alkylbenzene and thiol to afford thioester is distinctive (Scheme IIIA.1).



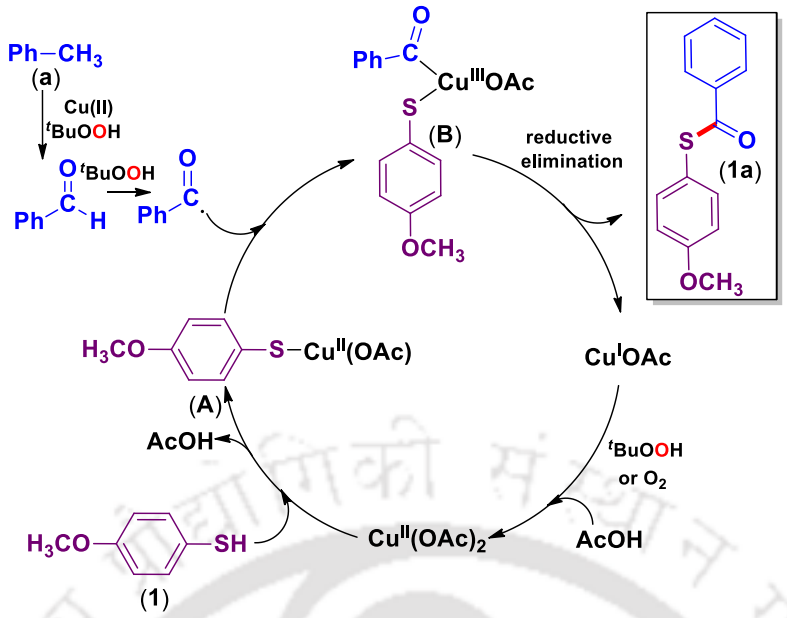
Scheme IIIA.1. *Thioesterification of alkylbenzenes*

Our recent success on substrate directed *O*-aroylation of phenol using alkylbenzene as the aroyl source prompted us to investigate how alkylbenzene would react with thiol under similar conditions. Ideally, a radical CDC between thiol and alkylbenzene should result in the formation of an *S*-benzyl thioether via C–S bond formation. A benzylic oxidation of *S*-benzyl ether at the expense of two benzylic C–H bonds would give the

thioester as was observed in our earlier report with phenol. To initiate the envisaged strategy *p*-methoxybenzenethiol and toluene were reacted in the presence of catalyst $Cu(OAc)_2$ (20 mol %) and oxidant TBHP (4 equiv) at 95 ^oC. To our delight the reaction afforded the corresponding thioester in 67% yield after 6 h. It may be noted here that a similar *O*-aroylation required the assistance of *o*-carbonyl as the directing group. The non-requirement of directing group in this case is possibly because of the efficient binding of soft Cu with soft thiol nucleophile.

Various reaction parameters such as catalysts, oxidants and temperature were screened to obtain the optimal conditions for this reaction and it was found that the use of $Cu(OAc)_2.2H_2O$ (20 mol %), oxidant TBHP 5–6 M in decane (4 equiv) at a reaction temperature of 95 ^oC under air atmosphere is the most suitable conditions for our further exploration to extend the scope of this transformation. The optimized condition then implemented for the *S*-aroylation of thiols with different alkylbenzens. Irrespective to their electronic environments both on thiols and alkylbenzenes coupled efficiently to give the desired thioesters in moderate to good yield. Aliphatic thiols such as propane, butane and dodecane thiols also underwent *S*-aroylation when coupled with *p*-xylene under the present reaction conditions affording their corresponding thioester in moderate yield. One of the interesting features of this protocol is that in case of polyalkylated benzene only one of them reacts while other remains as such.

Several experimental studies were performed to clarify the mechanism of this transformation. Based on the observations of these experiments and previous related literature reports, a plausible mechanism has been proposed. In this thioesterification the reagent TBHP serves the twin role of an oxidant and a radical initiator (Scheme IIIA.2).



Scheme IIIA.2. *Proposed mechanism for thioesterification*

In conclusion a CDC protocol has been developed for the *S*-aroylation of thiols using alkylbenzenes as aroyl surrogates in the presence of Cu/TBHP. In this reaction, simultaneously C–S and C–O bonds are installed at the expense of three sp^3 C–H bonds of alkylbenzene and an sp^3 S–H bond of thiol.

SECTION IIIB: Regiospecific Benzoylation of Electron-Deficient *N*-Heterocycles with Methylbenzenes via a Minisci-Type Reaction

This chapter demonstrates the regiospecific acylation of electron deficient *N*-heterocycles catalyzed by $AlCl_3$ through CDC reaction using alkylbenzene as synthetic equivalent of aroyl moiety under oxidative condition.

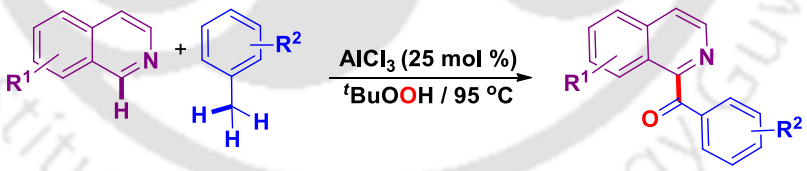
Of significant interest are methods that provide access to molecules in step- and atom-economic fashion from readily available precursors. In the past few decades, the construction of C–C bonds through C–H bond activation is a rapidly expanding field of research as it provides an atom-economical and shorter route for the synthesis of organic compounds and offers substantial benefits.

Nitrogenous heterocycles are widely distributed in nature and present in large proportion in commercial drugs. These heterocycles also have enormous applications in both chemistry and biology. Heterocyclic moieties bearing an acyl group have been found

in drugs which are important in pharmacological studies. Until now, a number of methods have been developed for the synthesis of electron-deficient heterocycles, but their functionalization using cross-dehydrogenative coupling is far less visited.

In contrast to electron-rich heterocycles, acylation of electron-deficient heterocycles is much more challenging and only a few reports are available. Among these, the Minisci reaction is the most commonly used approach, which involves the addition of an *in situ* generated nucleophilic acyl radical from aldehyde to an electron-deficient heterocycles. Although it represents a straightforward strategy but suffers from certain drawbacks such as harsh reaction conditions, poor site selectivity, limited substrate scope and the use of transition-metal salts up to stoichiometric amounts. To overcome these aspects, the Antonchick and Prabhu groups independently reported metal-free analogues of the Minisci reaction under ambient conditions.

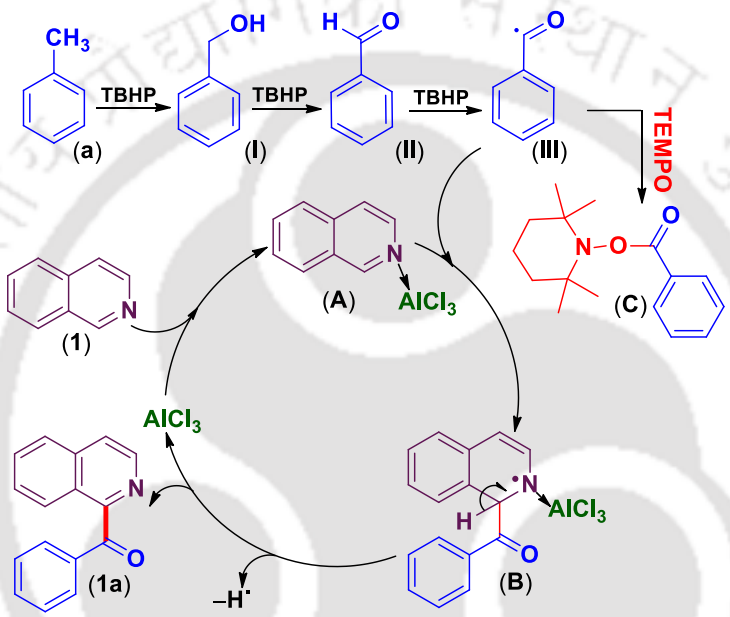
In continuation to our efforts in utilizing alkylbenzenes as different surrogates via metal and metal-free C–H functionalization strategies, we envisaged that an acyl radical (generated *in situ* from methylarenes under oxidative conditions) could be utilized for the direct acylation of *N*-heterocycles. Intrigued by the key mechanistic feature of Antonchick report; we anticipated that the direct use of CF_3COOH could generate a similar protonated intermediate. On the other hand, employing TBHP as the oxidant is expected to afford the other coupling counterpart to the acyl radical from methylarenes (Scheme IIIB.1).



Scheme IIIB.1. *Our strategy for acylation of N-heterocycle*

A number of screening experiments were carried out to reach the optimum reaction condition. It was found that the use of $AlCl_3$ (25 mol %) and TBHP (5–6 M in decane) (3 equiv) at 95 ^oC under N_2 atmosphere is the best optimized condition to explore the substrate scope of present protocol. With this optimized conditions in hand, we examined the scope of this cross-dehydrogenative couplings by reacting isoquinoline with a set of alkylbenzenes possessing both electron-donating as well as electron-withdrawing substituents. Under the present conditions, isoquinolines were smoothly acylated with

various alkylbenzenes to afford the corresponding coupled products in moderate to good yields. In case of isoquinoline we got exclusively C1-acylated product. Similarly quinoline also underwent cross-dehydrogenative coupling with different alkylbenzenes to give exclusive C2-monoacylated products. It is to be noted that in case of quinolines the acylation took place regioselectively at its C2 position only with no traces of other regioisomers. No C4-aroylation product was observed even when the C2 position was blocked with a methyl or a *tert*-butyl group, suggesting the strong regioselective nature of the present transformation.



Scheme IIIB.2. *Plausible mechanism for C1 acylation*

On the basis of the experimental observations and literature precedence, a plausible mechanism is proposed (Scheme IIIB.2). Generation of acyl radical is the key step in the present transformation.

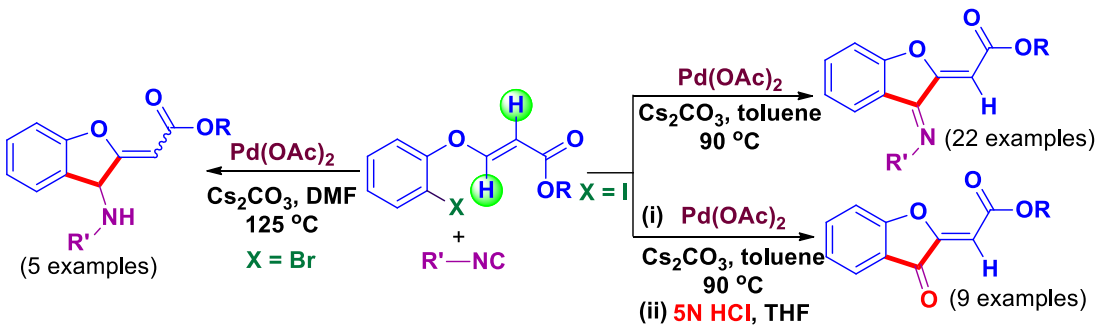
In conclusion, we have developed an efficient, mild and cost-effective method for the regiospecific acylation of electron-deficient *N*-heterocycles using methylbenzenes. In this transformation, Lewis acid $AlCl_3$ is used as catalyst and TBHP as oxidant. The reaction serves as complement to classical Minisci reaction.

CHAPTER IV. Cascade Synthesis of Dihydrobenzofurans and Aurones via Palladium-Catalyzed Isocyanides Insertion into 2-Halophenoxy Acrylates

This chapter describes about palladium(II)-catalyzed synthesis of 2,3-disubstituted benzofurans and aurones using isocyanides as C1 building block.

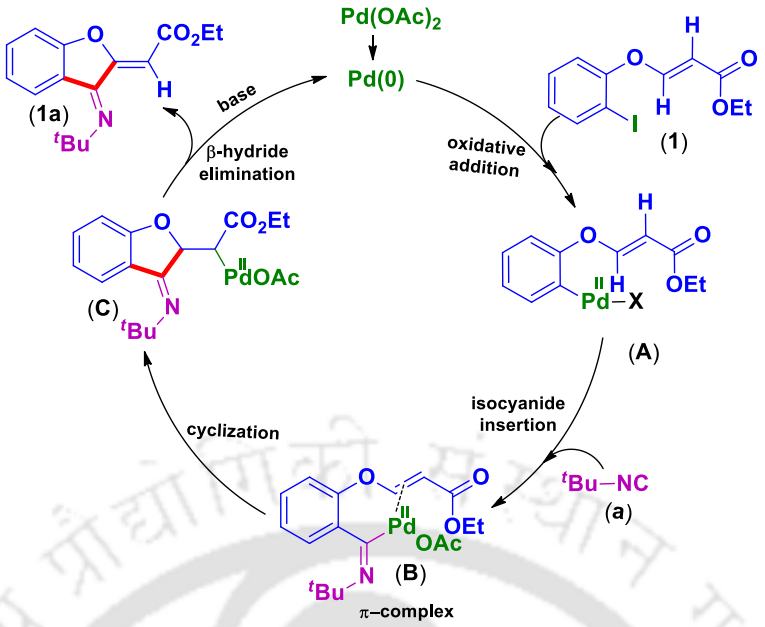
Dihydrobenzofurans are important building blocks in organic synthesis and also key structural motif of numerous natural products with biological activities. Aurones have been described as antifungal agents, as inhibitors of tyrosinase and as antioxidants. Similarly, dihydrobenzofuran moiety have been reported to present in a vast array of natural products and numerous synthetic compounds with useful biological activities. Numerous efforts have been reported for the synthesis of dihydrobenzofuran skeleton including intramolecular Friedel-Craft reaction and Wittig reaction. With advancement of transition metal-catalyzed C–C and C–O bond formation reactions, 2,3-disubstituted benzofurans can be synthesized from *o*-functionalized phenols and their derivatives through palladium-, copper-, platinum- and silver-catalyzed reactions. Dihydrobenzofurans and aurones can also be synthesized by the Rh-catalyzed intramolecular carbene insertion and Heck reaction of salicylaldehydes with acrylates respectively. In the past few years palladium-catalyzed cascade reactions have emerged as an attractive strategy to avoid the requirement of decorated precursors and therefore enhance the efficiency to achieve the target molecules.

Migratory insertions of isocyanides during palladium-catalyzed reactions have appeared as powerful methods for the preparation of carbo and heterocyclic products. Both the electro- and nucleophilic nature of isocyanides have established them as powerful and versatile C1 building blocks in organic synthesis. Apart from participating in multicomponent reaction palladium-catalyzed isocyanide insertion offer great potential for the synthesis of oxygen containing heterocycles. In light of these aspects herein we wish to report the synthesis of 2,3-disubstituted benzofurans and aurones via palladium-catalyzed isocyanides insertion reaction with 2-iodophenoxy acrylate (Scheme IV.1).



Scheme IV.1. *Pd-catalyzed synthesis of dihydrobenzofurans and aurones*

To attain the suitable reaction condition for the synthesis of 2,3-disubstituted benzofurans various reaction parameters such as catalyst, base, solvent and reaction temperature were screened to achieve the maximum product yield. After a series of screening experiments, the optimized reaction condition was found as $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (3 equiv) at 90 ^oC in toluene. Once optimized condition was achieved, we examined the scope of this palladium-catalyzed cascade process. It was found that both electron-donating and electron-withdrawing substituents are well tolerated under the present reaction conditions. The compound formed bearing two interesting exocyclic double bonds that can be utilized for rapid construction of molecuclar complexity. Approaches to synthesize such a skeleton were quite limited so far. The compound formed contains exocyclic imine functionality that can be hydrolyzed by refluxing it with 5N HCl in THF to give the various substituted aurones. Interestingly when iodo was replaced with bromo the product formed with reduced exocyclic imine. Based on our observation and literature precedence plausible mechanism has been proposed (Scheme IV.2).



Scheme IV.2. *Plausible mechanism for the synthesis of 2,3-dihydrobenzofurans*

In summary, we have developed a palladium-catalyzed cascade process involving isocyanide insertion and $C_{sp}{}^2$–H cross coupling for the synthesis of 2,3-disubstitued benzofurans. The advantage of this work includes the synthesis of oxygen heterocycle from simple and commercially available starting material, phosphine-ligand free condition, and formation of two new C–C bond.

CHAPTER V.

This chapter has been divided in to two sections. Section A illustrates the use of Cs_2CO_3 as carbonyl and oxygen in copper(II)-catalyzed cascade synthesis of benzofuran[3,2-*c*] quinolin-6[5-*H*]ones, whereas Section B highlights Ag_2CO_3-mediated cascade synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocynates.

SECTION VA. Cs_2CO_3 as a Source of Carbonyl and Ethereal Oxygen in a Cu-Catalyzed Cascade Synthesis of Benzofuran[3,2-*c*] quinolin-6[5-*H*]ones

This chapter highlights about copper(II)-catalyzed synthesis of benzofuran[3,2-*c*] quinolin-6[5-*H*]ones using Cs_2CO_3 as the source of carbonyl and ethereal oxygen.

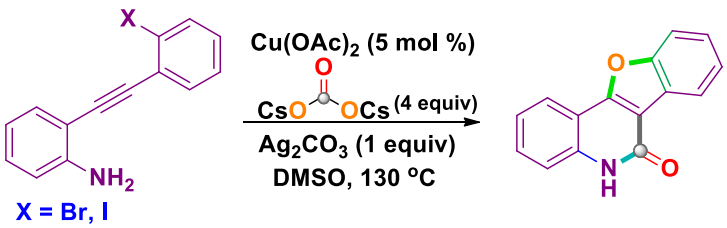
In the modern era of organic chemistry, the synthesis of highly functionalized and structurally diverse heterocycles is a challenging task. In this regard, domino reactions are

a most promising approach for the synthesis of complex organic molecules. Formation of multiple C–C and C–heteroatom bonds for rapid access to fused and complex polycyclic skeletons is an attractive feature of any domino reaction. Recently, the strategy has emerged as a powerful "Synthetic Avenue" for the conversion of internal alkynes into biologically interesting polycycles or spiro heterocycles.

Benzofuro[3,2-*c*]quinolin-6(*5H*)-one derivatives are reported to show activity against osteoporosis and malaria. Surprisingly, the literature contains only a few reports describing the synthesis of benzofuro[3,2-*c*]quinolin-6(*5H*)-ones.

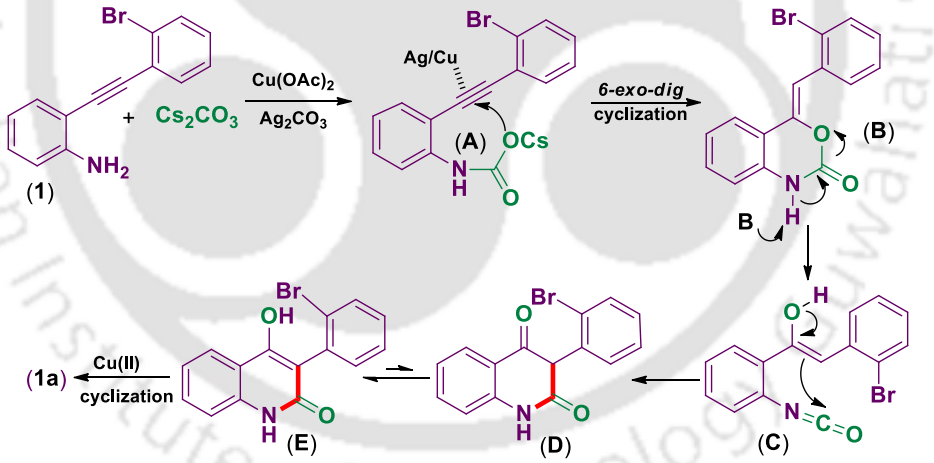
In continuation of our effort towards copper-catalyzed synthesis of heterocycles, when 2-((2-bromophenyl)ethynyl)aniline was treated with L-alanine in the presence of $Cu(OAc)_2$ and Cs_2CO_3 in DMSO at 130 ^oC a product was isolated in 57% yield. Spectroscopic analysis (NMR, IR and HRMS) and subsequent crystal structure determination of one of its derivative confirms its structure to be benzofuro[3,2-*c*]quinolin-6(*5H*)-one. The product structure demonstrates a few interesting facets of this transformation *viz.* the incorporation of carbonyl as well as an ethereal oxygen functionality in the resultant heterocycle and their origin. The unique feature of this heterocycle is the simultaneous formation of three types of bonds *viz.* two C–O and both one C–C and one C–N bond.

It is well established that metal carbonates and bicarbonates act as CO_2 source. It has been reported that Cs_2CO_3 serves as a CO_2 source for the synthesis of cyclic or acyclic carbonates. Recently, Cs_2CO_3 as an oxygen source for the synthesis of ester by the coupling of acid chloride and alkyl halide has been reported. So far, the synthesis of biologically active heterocycles using CO_2 generated from metal carbonates is unfamiliar. On the other hand, gaseous CO_2 has been extensively utilized for the synthesis of carbonates, acid, ester and lactone. Silver-catalyzed incorporation of gaseous CO_2 in a variety of internal and terminal alkynes, allenes, *o*-alkynylacetophenone, and allylsilane as well as carboxylation of terminal alkynes are summarized by Yamada *et al*. The inserted CO_2 undergo various kinds of rearrangements to afford various heterocycles. Similarily, Cu(II)-catalyzed incorporation of CO_2 into alkene, alkyne, allene and other systems has been reported by other groups. To the best of our knowledge the cascade synthesis of benzofuro[3,2-*c*]quinolin-6(*5H*)-ones is being reported for the first time utilizing CO_2 from Cs_2CO_3 (Scheme VA.1).



Scheme VA.1. *Cs_2CO_3 as carbonyl and oxygen source in heterocycle synthesis*

To find out the appropriate optimized condition a series of experiment have been carried out and it was found that the use of $Cu(OAc)_2$ (5 mol %), Cs_2CO_3 (4 equiv), Ag_2CO_3 (1 equiv) in DMSO (3 mL) at 130 ^oC is best condition for the present transformation. With the this optimized conditions in hand, we explore the generality and scope of this protocol and the experimental results suggest that irrespective of the substituent on the either ring, underwent efficient cascade cyclization to afford their corresponding cyclized product in moderate to good yield. When the bromo substituent was replaced with an iodo group the yields of products were marginally better than their bromo analogues.



Scheme VA.2. *Plausible mechanism for the synthesis of benzofuro[3,2-c]quinolinones*

To understand the nature of this unprecedented carbonylation-etherification process and to gain insight into the reaction mechanism, a number of experiments have been carried out. On the basis of the results obtained from control experiment and literature precedence a plausible mechanism has been proposed that proceeds through the isocyanate type of intermediate (Scheme VA.2).

In conclusion, we have developed a novel protocol for the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives catalyzed by Cu(II). Concomitant installation of three types of bonds *viz.* two C–O and both one C–C and one C–N achieved in a tandem process. In this carbonylation-etherification cascade process both carbonyl and ethereal oxygen originates from Cs_2CO_3.

SECTION VB: Microwave-Assisted Cascade Strategy for the Synthesis of Indolo[2,3-*b*]quinolines from 2-(Phenylethynyl)anilines and Aryl Isothiocyanates

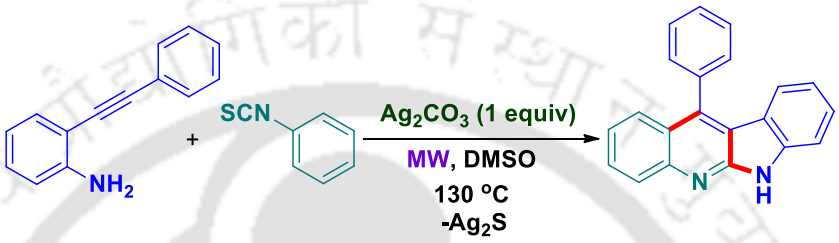
This chapter describes Ag_2CO_3-mediated synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates.

There has been continuous interest in the synthesis of natural product like compounds with privileged scaffolds that are likely to have potential biological activities. Among these privilege scaffolds, indoloquinoline alkaloids represent one of the important classess of heterocycles due to their immense biological activity including the ability to interact with DNA as an intercalator to inhibit topoisomerase II activity. Recent results reveals that some new indolo[2,3-*b*]quinoline (norcryptotackieine) types of natural products isolated from the leaves of *Justicia betonica* exhibit exceptional pharmacological properties such as potent antiplasmodial, antiproliferative, and antitumor activity. Therefore, developing strategies for the synthesis of indolo-fused quinolines that are more efficient, cost-effective, atom-economical and practical are sought-after.

Currently, cascade reactions are one of the most promising approaches in organic synthesis due to their high atom economy, better efficiency and easy handling during the assembly of complex molecular structures. Furthermore, microwave assisted organic synthesis have the advantage of greater reactivity, mild reaction conditions, high selectivity and shorter reaction times. Therefore, cascade reaction carried out under a microwave conditions are further advantageous to conventional heating.

Most of the available synthetic strategies for the synthesis of indolo[2,3-*b*]quinolines rely on the use of indole and its derivative as one of the coupling partners. The indoloquinoline system has also been assembled through a thermal cyclization of an enyne-carbodiimide. In 2003 Curran *et al.* reported the synthesis of indolo[2,3-*b*]quinoline via a cascade radical annulation of *o*-alkynyl thiourea that involves irradiation of UV light (with medium pressure Hg lamp) in a pyrex glass tube requiring a large

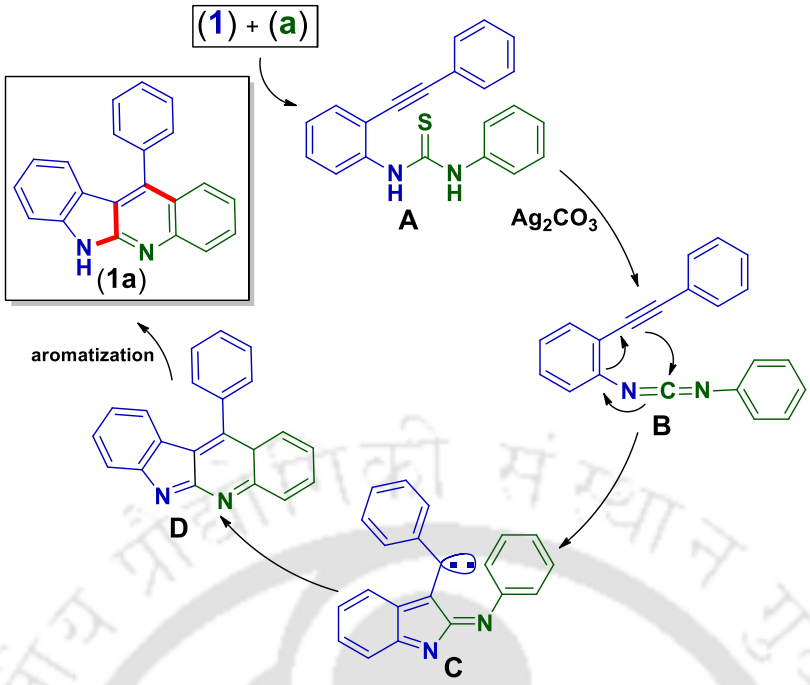
excess of *tris*(trimethylsilyl) silane (TTMSH) (4 equiv), AIBN (1 equiv) in anhydrous benzene. Although this method provides fruitful access to indoloquinolines, the use of certain carcinogens (benzene) and expensive and excess amounts of reagents and the requirements of a specialized setup to give moderate yields and lower substrate scope limit their applications. Thus in an attempt to obliterate the limitations of the earlier methods, we developed a straightforward and versatile protocol for the synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates (Scheme VB.1).



Scheme VB.1. *Indoloquinoline synthesis from o-alkynyl aniline and phenyl isothiocyanate*

Various reaction parameters were scrutinized to reach the optimum reaction condition and it was use of 1 equiv of Ag_2CO_3 in DMSO at 130 ^oC under microwave heating (MW 150W) for 30 minutes. Under the optimized conditions various 2-(phenylethynyl)anilines and aryl isothiocyanates were subjected to the reaction conditions to explore the scope of this cascade protocol. Phenyl isothiocyanates possessing electron-donating (EDG) substituents at their *para* position afforded the corresponding products in better yields compared to un-substituted and electron-withdrawing (EWG) substituents. Effect of substituent present on the other phenyl ring found similar to the substituent on phenyl isothiocyanates.

To understand the mechanism of this process, control experiments were conducted. The formation of Ag_2S in the reaction medium has been confirmed by powder XRD and EDX analysis. On the basis of our experimental findings and previous literature, a plausible reaction mechanism has been proposed (Scheme VB.2).



Scheme VB.2. *Proposed mechanistic pathway*

In conclusion, we have developed an elegant cascade approach for the synthesis of indoloquinolines. This protocol allows the practical synthesis of many valuable indolquinoline alkaloids through Ag_2CO_3-mediated cascade annulation of internal alkynes under microwave heating.