INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: **Exploration of Newer Strategies for the Construction of C-C and C-Heteroatom Bonds under Metal and Metal-free Conditions**

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SHORT ABSTRACT

The contents of the thesis have been divided into six chapters based on the results of experimental works performed during the complete course of the research period.

The *Chapter I* / introductory chapter of the thesis presents an overview of the newer methodologies such as C–H bond functionalisation, cross-dehydrogenative coupling and other newer strategies leading to the formation of C–C and C–heteroatom bonds under metal and metal-free conditions. *Chapter II* describes a copper (II) catalysed *o*-benzoxylation of 2-phenylpyridines using benzylamines as the arylcarboxy (ArCOO-) surrogates. Differential reactivities and selectivities of Cu and Pd catalysts have been demonstrated in the reactions of benzylamines with 2-phenylpyridines. Various benzylamines were utilized as the new arylcarboxy (ArCOO-) surrogate in the presence of $Cu(OAc)_2$ as the catalyst and TBHP as the oxidant. *Chapter III* illustrates the use of benzyl bromides as the new aroyl (ArCO-) surrogates towards substrate directed *o*-aroylation *via* C-H bond activation. An oxidative cross-coupling between directing substrates (2-aryl pyridines / benzo[*h*]quinoline) and benzyl bromides *via* the combined effect of oxidants TBHP and NMO, catalysed by Pd(II) has been described. The in situ generated benzaldehyde originating from benzyl bromide is the active aroylating source for this

carbo-acylation process. A radical pathway has been proposed for this *o*-aroylation process. *Chapter IV* describes a transition metal-free synthesis of α-ketoamides from aryl methyl ketones and alkylphosphoramides in the presence of tetrabutylammoniun iodide ($^{n}Bu_4NI$) and aqueous *tert*-butyl hydroperoxide (TBHP). Here alkylphosphoramides acts as the new dialkylaminyl (-NR_2) source. A series of aryl methyl ketones having both electron-donating as well as electron-withdrawing groups were successfully employed for the synthesis of their corresponding α-ketoamides using hexamethylphosphoramide and other alkylphosphoramides. *Chapter V* demonstrates a new one-pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides from benzo[*d*]thiazol-2-amines, iodoarenes and carboxylic acids (RCOOH) *via* ring opening rearrangement functionalisation (RORF). Here, the ring opening is associated with the loss of carbon and nitrogen atoms with concurrent S-arylation and *N*-acylation leading to *ortho*-bifunctionalised products. A further sequential addition of *tert*-butyl hydroperoxide (TBHP) results in the formation of a sulfur oxidised product, *N*-(2-(phenylsulfinyl)phenyl)acetamide. Various aliphatic as well as aromatic carboxylic acids are utilized in this telescopic synthesis. Based on the experimental findings and literature reports, a plausible reaction mechanism has been proposed for this unprecedented ring opening rearrangement functionalisation (RORF). *Chapter VI* illustrates a cyano (-CN) sacrificial regioselective (arylthio)-arylamination of quinoline and isoquinoline *N*-oxides using *N*-(2-(arylthio)aryl)cyanamides as the new arylthio-arylaminating agent in the presence of CuI. This reductive amination proceeds in one pot at 80 ^{o}C in the absence of any additives. This is a unique demonstration of aryl cyanamides serving as the new arylaminating agents on quinoline/isoquinoline *N*-oxides with concurrent auto-reduction of *N*-oxides.

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

SYNOPSIS

The contents of this thesis have been divided into six 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 the newer methodologies such C–H functionalisation, cross dehydrogenative coupling and other newer strategies leading to the formation of C–C and C–heteroatom bonds under metal and metal-free conditions. All the other chapters emphasise on C–C, C–O and C–N bond forming reactions under metal and metal-free conditions using strategies like C–H functionalisations, cross dehydrogenative coupling, one pot sequential and rearrangement reactions.

Chapter II demonstrates a copper catalysed *o*-benzoxylation of 2-phenylpyridines using benzyl amines as the arylcarboxy surrogate.

Chapter III illustrates the use of benzyl bromides as the aroyl source towards substrate directed *o*-aroylation catalysed by palladium salts.

Chapter IV describes the synthesis of α-ketoamides from arylmethyl ketones under a metal free condition using alkylphosphoramides as the aminyl source.

Chapter V demonstrates a one-pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides and *N*-(2-(phenylsulfinyl)phenyl)acetamides from 2-amino benzothiazole, aryl iodide and carboxylic acids *via* ring opening rearrangement functionalisation.

Chapter VI illustrates a cyano sacrificial (arylthio)-arylamination of quinoline and isoquinoline *N*-oxides using *N*-(2-(arylthio)aryl)cyanamides.

CHAPTER I. An Overview of C–H Functionalisation, Cross Dehydrogenative Coupling and Other Newer Aspects of C–C and C–Heteroatom Bond Formations

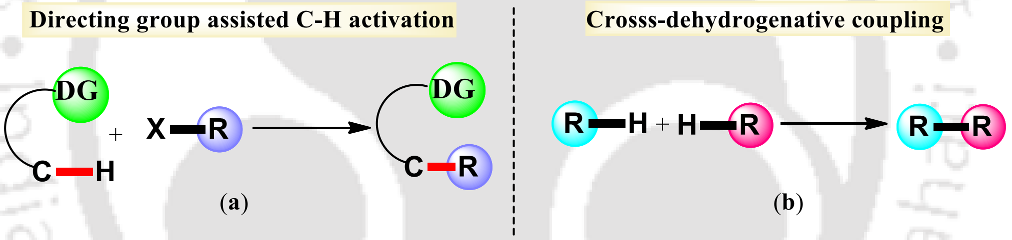
This chapter includes the history of C–H functionalisation, their advantages, challenges and applications in organic synthesis. It also involves other strategies such as cross dehydrogenative coupling, transition metal catalysed one pot sequential and rearrangement reactions for the construction of carbon-carbon and carbon-heteroatom bonds.

Coupling chemistry is an important synthetic strategy, extensively used in both industry and academics for the formation of C–C and C–heteroatom bonds. The traditional coupling procedures involve either the use of stoichiometric organometallic reagents, or the transition metal catalysed coupling of functionalised hydrocarbons. There has been substantial development of these methods over the last few decades, and they are successfully applied in the synthesis of commercially important products. However, the requirement of pre-functionalised starting materials in these methods, adds additional steps towards the formation of desired product, is a major concern along with atom-economic and environmental concerns. The best way to address this issue is to utilise un-functionalised starting materials *via* the direct functionalisation of C–H bonds.

On the other hand, direct C–H bond functionalisation reactions are limited by two fundamental challenges (i) the inert nature of carbon-hydrogen bonds and (ii) the requirement to control site selectivity in molecules that contain diverse C–H groups. However, the first challenge can be overcome by the use of a transition metals which can react with C–H bonds to form reactive C–M bonds. The second major challenge *i.e.* selectivity can be achieved by the use of substrates that contain co-ordinating ligands *viz.* the directing groups. These directing groups have a heteroatom which can co-ordinate with the metal and bring it to the close proximity of the desired C–H bond which is the subject of functionalisation. The process so developed is termed as directing group assisted C–H activation [Scheme I, (a)].

However, one more aspect to construct C–C and C–heteroatom bond is the oxidative coupling in the presence or absence of a metal catalyst is cross-dehydrogenative coupling (CDC) strategy (Scheme I, (b)). It generally refers to a cross-coupling reaction between two C–H bonds. In terms of atom economy, this synthetic method represents one of the most ideal synthetic procedures for selective C–C and C–heteroatom bond forming reactions.

With the motive of broadening the revolutionary aspect of organic synthesis, sometimes chemists use the combination of these two strategies: (a) substrate directed C–H bond functionalisation and (b) cross dehydrogenative coupling for the transformation of C–H bonds to C–C and C–heteroatom bonds. In this context, our group has developed a number of new disconnection approaches and generation of various functionalities *via* cleavage of inert C–H bonds.



Scheme I.1. *(a) Substrate directed C–H bond functionalisation; (b) cross dehydrogenative coupling*

Other than the above two strategies, the reactions like one pot sequential reactions and rearrangement reactions are also utilised tremendously for the construction C–C and C–heteroatom bonds. Among the C–heteroatom bonds, the construction of the C–N bond is of significant importance as it opens avenues for the introduction of nitrogen into organic molecules. Despite significant achievements in this field, the construction of the C–N bond is still a major challenge for organic chemists, due to the involvement of harsh reaction conditions or the use of expensive catalysts in many cases. Thus, it is a challenge to develop alternative, milder and cheaper methodologies for the construction of C–N bonds in one pot. In view of this aspect, the techniques to achieve newer methods for the construction of C–N bonds are the use of transition metals which can increase the reactivity of the substrate so that it can undergo a rearrangement process. The traditional rearrangement reactions which are mainly based on the electrophillic and nucleophillic nature of the substrates, can be further extended by using transition metal catalysts.

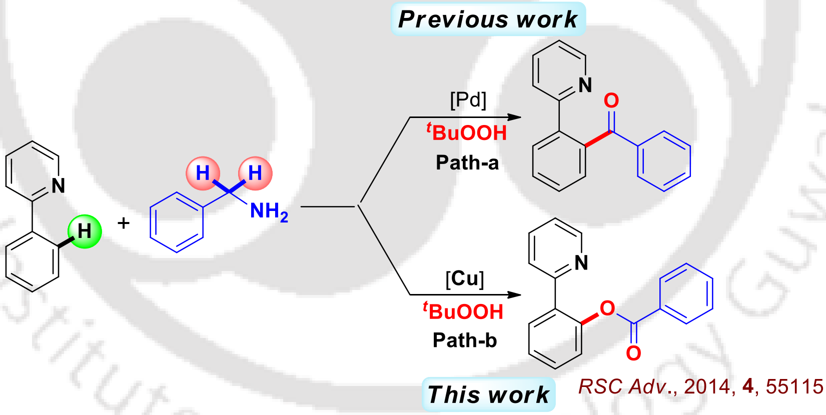
CHAPTER II. Benzylamine as Arylcarboxy Surrogate: A Copper Catalysed *o*-Benzoxylation of 2-Phenylpyridines using Benzyl amines

This chapter describes a copper(II) catalysed *o*-benzoxylation of 2-arylpyridines using arylmethylamines as the arylcarboxy- surrogate in the presence of oxidant.

Metal catalysed direct transformation of C–H bonds into C–C or C–heteroatom bonds is one of the reliable and facile tools in current organic chemistry. It renders step and atom economic strategy compared to traditional cross-coupling reactions *via* circuitous use of pre-functionalised starting materials. Even more attractive is the new disconnection approach, which would greatly enhance the number of retrosynthetic steps to build complex molecular scaffolds. Pertinent to this, the directing group assisted C–O bond formation mostly concentrated on acetoxylation and hydroxylation *via* C–H bond activation. However, reports on benzoxylation *via* same strategy are comparatively fewer inspite of their importance in the synthesis of natural products and pharmacological compounds. Previously, the *o*-benzoxylation of 2-phenylpyridine has been achieved using benzoate iodonium salts, carboxylic acids/salts or its derivatives such as acid chlorides, anhydrides or peroxides, aldehydes, alkylbenzenes, terminal alkenes and alkynes as the benzoxy surrogates. Similar *o*-benzoxylation has been achieved with other directing groups such as ketoxime ether, acetanilides and benzamides using carboxylic acids in the presence of Pd and Ru catalysts. In continuation of the search for a suitable precursor that can serve as an unorthodox surrogate of various functionalities, in the present case we took up benzyl amine as the potential candidate. Benzyl amines are highly susceptible to imine formation under an oxidative condition which can be further manipulated in various ways to achieve C–C and C–N bonds.

In 2013, Wu group developed a Pd catalysed protocol for *ortho*-aroylation of 2-phenylpyridine using benzyl amines as ArCO– surrogates (Scheme II.1, path-a). Although Pd and Cu show similar reactivities in coupling reactions, there are instances where they behave differently for the same reaction. But there are few reports available for the differential reactivity of Pd and Cu catalyst. For example, in the synthesis of 2-aminobenzothiazoles from 2-halothioureas, it was observed that copper prefers dehalogenative path where as palladium favours C–H activation strategy. Moreover, copper and palladium behave differently in the reaction between alkylbenzenes and 2-phenylpyridines giving *o*-benzoxylated (–OCOAr) and *o*-aroylated (–COAr) products respectively. Thus it would be interesting to see how copper catalyst influences the reaction between 2-phenylpyridine and benzyl amine.

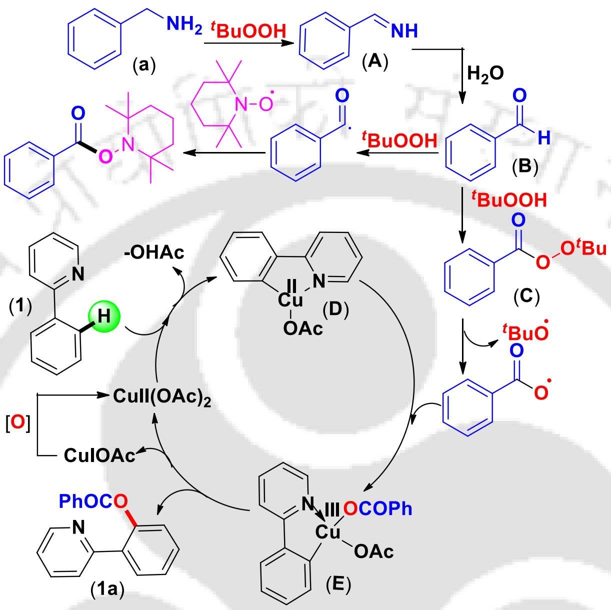
For achieving the goal, an initial trial was performed by reacting 2-phenylpyridine (**1**) and *p*-methylbenzyl amine (**c**) in the presence of $Cu(OAc)_2$ (20 mol %) and oxidant TBHP (5–6 M in decane) (5 equiv) in chlorobenzene at 120 °C. The reaction led to an exclusive formation of *o*-benzoxylated (–OCOAr) product (**1c**) rather than an *o*-aroylated (–COAr) product (Scheme II.1, path-b) which was observed using Pd catalyst (path-a, Scheme II.1). This observation highlights the divergence in the selectivity achieved with the change of transition metal catalyst.



Scheme II.1. *Selectivity achieved in the presence of different transition metal catalysts*

To arrive at the best possible yield of the o-benzoxylation of 2-phenylpyridine, various reaction parameters such as catalyst, oxidant, solvent and temperature were scrutinised. After a series of optimisations, the use of $Cu(OAc)_2$ (20 mol %), TBHP (5-6 M in decane) (6 equiv.) and chlorobenzene (2 mL) at 120 °C was found to be the best condition for this transformation. The optimised conditions were then implemented for o-benzoxylation of 2-arylpyridines using various substituted benzylamines. It was found that both the 2-phenylpyridines as well as benzylamines possessing electron-donating substituents gave the desired products in a better yield as compared to those possessing electron-withdrawing substituents.

From the experimental observations, a tentative mechanism has been proposed for the copper catalysed *o*-benzoxylation of 2-arylpyridines as depicted in Scheme II.2.



Scheme II.2. *Proposed mechanism for ortho-benzoxylation of 2-phenylpyridine*

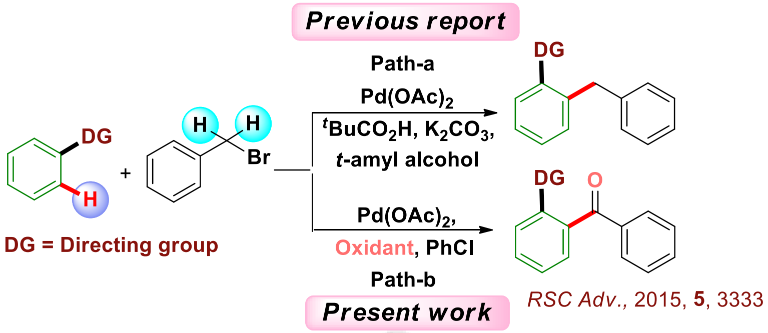
In conclusion we have developed an *o*-benzoxylation reaction of 2-phenylpyridine using benzyl amines as an unconventional synthetic equivalent of arylcarboxy groups (ArCOO–). A plausible reaction mechanism involving an *in situ* generation of intermediates such as imine and aldehyde from arylmethylamine has been proposed. The radical nature of the reaction has been established by isolation of TEMPO ester. This protocol shows the differential selectivities and reactivities of Cu and Pd catalysts for the same reaction.

CHAPTER III: Benzyl Bromides as Aroyl Surrogates in Substrate Directed Pd Catalysed *o*-Aroylation

This chapter explains an oxidative cross-coupling between directing substrates and benzyl bromides *via* the directing group assisted C–H functionalisation. The combined effect of catalyst and oxidants resulted in the *o*-aroylation of directing substrates using benzyl bromides as the efficient aroyl surrogates.

In last two decades, an extensive exploration of Pd-catalysed regioselective C–H functionalisation has been investigated to transform simple precursors into products of significant importance, particularly for the synthesis of complex molecules and natural products. Most of these Pd-catalysed reactions have been intended for the C–C bond forming processes involving sp, sp^2 or sp^3 hybridised C–H's as a mutual or a cross-coupling partners. The classical synthesis of aryl ketones mainly rely on the Friedel-Crafts acylation of aromatics in the presence of corrosive $AlCl_3$ or by the oxidation of corresponding secondary alcohols. Compared to the classical Friedel-Crafts acylation, the direct introduction of carbonyl functionality into aromatic motifs *via* C–H bond cleavage is more eco-friendly alternative. The acylation of 2-phenylpyridines *via ortho*-C–H bond activation has been previously reported by our group and others using aldehydes, α-oxocarboxylic acids, alcohols, α-diketones, toluenes, benzylamines and alkenes / alkynes as aroyl surrogates. The process of aroylation is of significant importance because aryl ketones are useful in pharmaceuticals, fragrance, dye and agrochemical industries. However, the cross-dehydrogenative coupling (CDC) strategy of converting sp^2 C–H bonds of aryl moiety into C–C bonds are challenging. Generally, most of the developed approaches on regioselective C–H activation involve suitable catalysts, functionalised partners and oxidants.

In search of an alternative aroyl source, we envisaged that benzyl bromides which under an oxidative condition can be converted into benzaldehyde may serve as the aroylating source. With this in mind, an initial trial reaction was performed between 2-phenylpyridine (**1**) (0.5 mmol) and benzyl bromide (**a**) (1 mmol) in the presence of $Pd(OAc)_2$ (5 mol%) and oxidant TBHP (5–6 M in decane) (4 equiv.) in chlorobenzene (2 mL) at 120 ^{o}C and formation of an *o*-aroylated product was observed (Scheme III.1, path-b). It may be mentioned here that in an auxillary assisted Pd catalysed C–C bond forming reaction benzyl bromide served as the benzylating agent for the sp^2 and sp^3 C–H bonds. Herein we disclose the first report on the use of benzyl bromides as aroylating agent in Pd-catalysed substrate directed process (Scheme III.1, path-a).

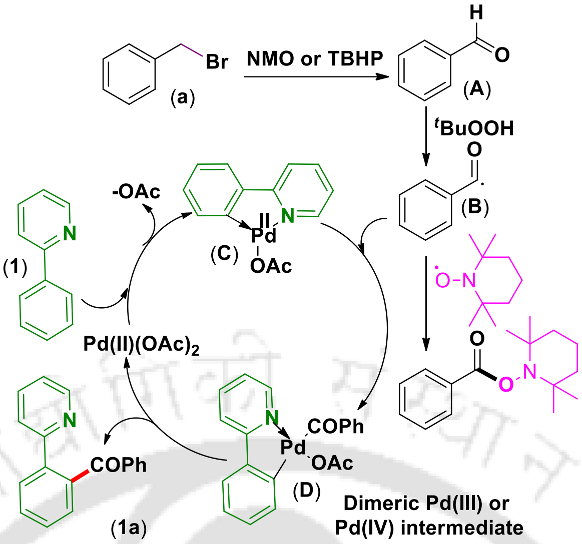


Scheme III.1. *Differential reactivities of benzyl bromides towards directing substrates*

As the initial yield (37%) of the product is very low, we probed the effect of aroylating agent, catalysts, oxidants, additives, and solvents to obtain the best yield of the *o*-aroylated product. The oxidant *N*-methyl morpholine *N*-oxide (NMO) is reported to be quite effective in converting benzyl halides to their corresponding aldehydes, which we presume to be the active aroylating agent. Again it was assumed that the catalytic activity of Pd may be hampered in acidic medium. Since an equivalent amount of HBr is liberated in the medium during the conversion of benzyl bromide to active aroylating species, it was decided to perform the reaction in the presence of a mild base. After screening of all the reagents, catalyst, oxidants and bases, the final optimum condition was found to be the use of 2-phenyl pyridine (**1**) (0.5 mmol), benzyl bromides (**a**) (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (2 equiv.), *N*-methyl morpholine *N*-oxide (2 equiv.), K_2CO_3 (1.5 equiv.) in chlorobenzene (2 mL) at 120 °C.

The optimised condition was then implemented for the *o*-aroylation of 2-phenylpyridines using various substituted benzyl bromides. It was observed that both the 2-phenylpyridines as well as benzylamines possessing electron-donating substituents yielded their desired products in a good yield as compared to their electron-withdrawing analogue. Besides the 2-phenylpyridines, benzo[*h*]quinoline, a rigid directing system has similar structural frame to that of 2-phenylpyridine (**1**) was employed to the present *o*-aroylation process. A moderate to good yield of the aroylated product was obtained from the oxidative coupling of benzo[*h*]quinoline and substituted benzyl bromides.

Based on the literature reports and experimental findings, a plausible mechanism for this palladium catalysed carbo-acylation reaction of 2-phenyl pyridine (**1**) with benzyl bromide (**a**) *via* directed C–H bond activation is depicted in Scheme III.2.



Scheme III.2. *Proposed mechanism for o-aroylated product from benzyl bromide and 2-phenylpyridine*

In summary, the present protocol demonstrates a convenient and efficient synthesis of aryl ketones *via* Pd-catalysed *ortho*-C–H activation of 2-phenylpyridines and benzo[*h*]quinoline using commercially available benzyl bromides as unconventional synthetic equivalents of aroyl group (ArCO–). All the benzyl bromides having activating or deactivating groups efficiently gave the desired product with 2-aryl pyridines and benzo[*h*]quinoline.

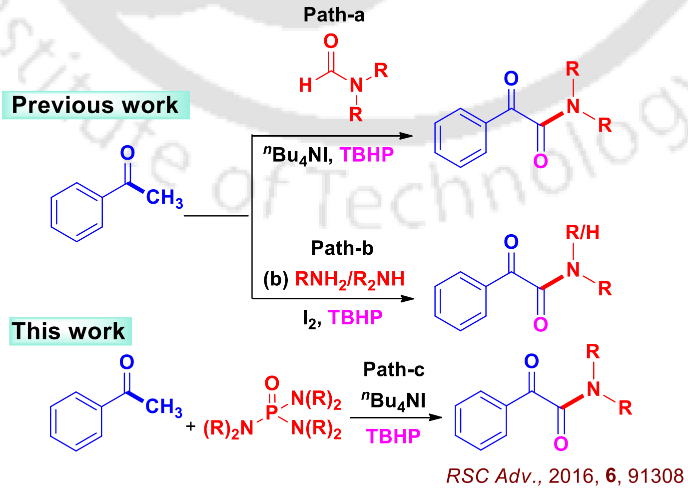
CHAPTER IV: Transition Metal-free Synthesis of α-Ketoamides from Arylmethyl Ketones and Alkylphosphoramides

This chapter deals with a cross dehydrogenative coupling reaction (CDC) leading to the synthesis of α-ketoamides from aryl methyl ketones and alkylphosphoramides under a metal–free oxidative condition. Here, alkylphosphoramides has been utilised as the synthetic equivalent of dialkyl amine source (-NR$_2$).

Cross-dehydrogenative coupling (CDC) has contributed tremendously in the development of atom and step-economic process for the synthesis of complex molecular architectures from simple precursors. The CDC process plays a pivotal role in bringing about the transformation of C–H bonds of all types (sp, sp^2 and sp^3) to C–C and C–heteroatom bonds. Of various C–heteroatom bonds, the construction of C–N bond is one of the most fundamental challenge in the synthesis of biologically important molecules, natural products, pharmaceuticals and other functional materials.

On the other hand, α-ketoamide constitutes the basic subunits of many synthetically and biologically important molecules. These motifs are used in the designing of peptidase inhibitors, histone deacetylases and human cytosolic phospholipase A_2, which is applicable for inhibiting several classes of proteases such as serine, cysteine and HIV. Because of the wide applicability of α-ketoamides, a number of synthetic routes have been developed for their synthesis.

Previously, arylmethylketones have been employed for the synthesis of α-ketoamide by coupling it with dialkylformamides (Path-a, Scheme IV.1) and primary/secondary amines (Path-b, Scheme IV.1). Arylmethylketone can be converted into phenylglyoxal in the presence of an appropriate oxidant that may serve as a α-ketyl (ArCOCO−) surrogate. This α-ketyl group may couple with the *in situ* generated amines from phosphoramides (which is used as a solvent in organic reactions) under an oxidative condition to afford a α-ketoamide. Keeping this in mind, when acetophenone (**a**) (0.5 mmol) was treated with hexamethylphosphoramide (HMPA) (**1**) (1.5 mmol) in the presence of *tetra*-butylammonium iodide (^{n}Bu$_4$NI) (20 mol%), chlorobenzene (PhCl) (2 mL) and a decane solution of *tert*-butylhydroperoxide (TBHP) (4 equiv.) at 130 °C, formation of *N,N*-dimethyl-2-oxo-2-phenylacetamide (**1a**) was observed in 61% isolated yield.

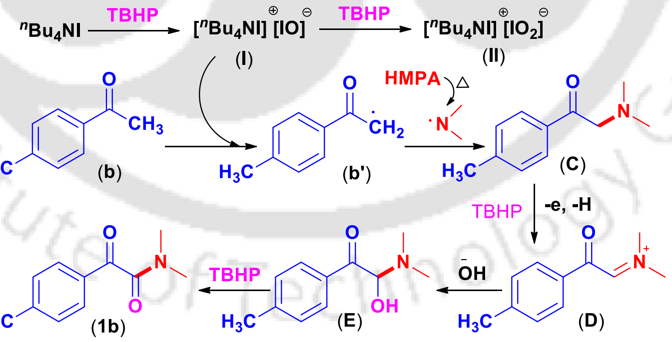


Scheme IV.1. *Synthesis of α-ketoamides from arylmethylketones*

Getting a new route to synthesise α-ketoamides, various reaction parameters such as iodine source, solvent, oxidant, temperature and time were screened for the reaction to further improve the yield. Finally, the optimised condition for this transformation is the use of acetophenone (0.5 mmol), hexamethylphosphoramide (1.5 mmol), $^{n}Bu_4NI$ (20 mol%), chlorobenzene (2 mL) and aq. TBHP (70 wt% in H_2O) (3 mmol) at 130 °C for 45 minutes.

With this optimised condition in hand, different arylmethylketones bearing both electron-donating and electron-withdrawing groups were subjected to the current reaction condition with hexamethylphosphoramide. It was noticed that arylmethylketones bearing electron-donating groups gave superior yields of the product than their electron-withdrawing partner. Adopting the same optimised condition, a library of α-ketoamides were also synthesised using different arylmethylketones and hexalkylphosphoramides. All the cyclic as well as long chain acyclic alkylphosphoramides are well tolerated the present strategy and furnishing the corresponding α-ketoamides in good yield.

By summing up all the experimental results and from the literature precedences, a plausible mechanism is proposed for the formation α-ketoamide from arylmethylketone and alkylphosphoramide (Scheme IV.2).



Scheme IV.2. *Plausible mechanism for the synthesis of α-ketoamides*

In conclusion, we have developed a novel and efficient metal-free protocol for the synthesis of α-ketoamides from arylmethyl ketones and different alkylphosphoramides in the presence of TBAI as the catalyst and TBHP as the oxidant in a short period of time. A series of alkylphosphoramide having different functional groups have been utilised for the synthesis of corresponding α-ketoamide. This process tolerates a variety of functional groups and allows the synthesis of α-ketoamide derivatives in moderate to good yields. Based on the experimental findings, a plausible radical mechanism has been proposed for this transformation.

CHAPTER V. One Pot Sequential Synthesis of *N*-(2-(Phenylsulfinyl)phenyl)acetamides: A Ring Opening Rearrangement Functionalisation (RORF)

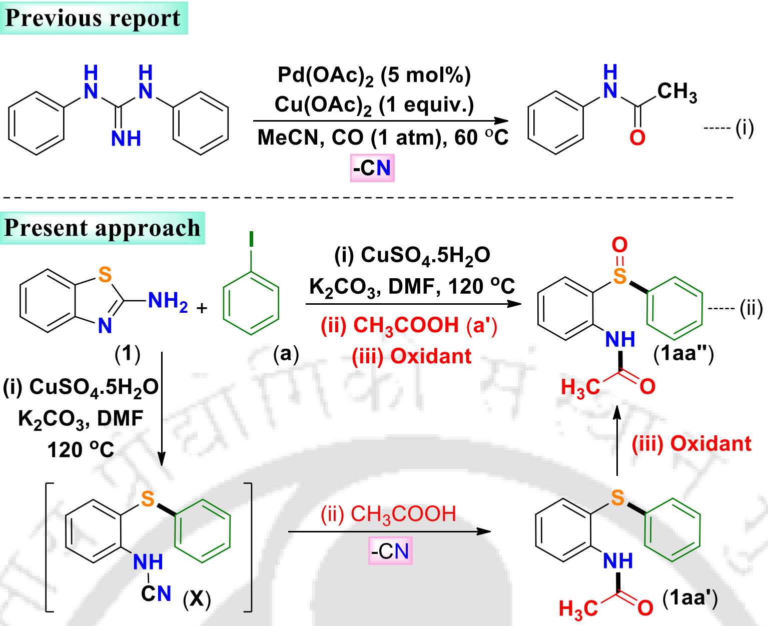
This chapter describes a new one pot synthesis of *N*-(2-(phenylthio)phenyl)acetamides from readily available benzo[*d*]thiazol-2-amine and iodobenzene involving a sequential copper-catalysed intermolecular C−S coupling followed by an intermolecular C–N bond formation with carboxylic acids *via* a rearrangement process. The further sequential addition of an oxidant resulted in the formation of sulfur-oxidised product *N*-(2-(phenylsulfinyl)phenyl)acetamide.

The effectiveness of one pot sequential reactions are important due to several synthetic transformations and bond-forming steps can be carried out in a single pot, while circumventing several purification procedures at the same time. A one pot procedure can thus minimise chemical waste, save time, and simplify practical aspects. In recent years transition metal catalysts are particularly effective reagents in achieving this one pot and multi-step synthesis. This is evidenced by a dramatic increase of impressive syntheses over the past decades. In particular, the copper-mediated C−N bond forming reaction is of high demand due to the use of low cost catalyst.

On the other hand, due to the associated ring strains in three and four membered carbo- and heterocycles, they often undergo ring opening in the presence of appropriate nucleophiles. Although five membered heterocycles such as thiazole, imidazole, oxazole and some of their benzo fused heterocycles *viz.* benzothiazole, benzoimidazole, benzoxazole and benzoisothiazole are more stable in terms of ring strain but are susceptible to ring opening. This type of ring opening is not only restricted to simple benzothiazoles and 1,3-azoles but also observed in 2-aminobenzothiazoles. A coupling reaction between 2-aminobenzothiazole and terminal alkyne resulted in the formation of benzo[*b*][1,4]thiazine-4-carbonitrile. Here, the ring opening is followed by an oxidative coupling with an alkyne and finally the reaction terminates *via* an intermolecular cyclisation process. In yet another method, the synthesis of 2-

(phenylthio)phenylcyanamide from 2-halothiourea and iodobenzene in the presence of $CuSO_4.5H_2O$ or CuI/ligand has been established *via* the intermediacy of 2-aminobenzothiazole. In 2015, a non-enzymatic decomposition of guanidine derivatives into anilides with the loss of a –CN moiety has been developed by Shi group [Scheme V.1, (i)]. Here, a combination of catalyst $Pd(OAc)_2$, an equivalent of $Cu(OAc)_2$ and CO were utilised for the transformation of 1,3-diarylguanidines to acetanilides *via* the cleavage of C–N bond. Taking cues from literature reports, we have designed a telescopic protocol for the synthesis of *N*-(2-(phenylthio)phenyl)acetamides [Scheme V.1, (ii)]. 2-(Phenylthio)phenylcyanamide (**A**) can be obtained from 2-aminobenzothiazole (**1**) and iodobenzene (**a**) in the presence of $CuSO_4.5H_2O$ *via* a ring opening intermolecular C–S cross coupling reaction (Scheme V.1). We anticipated that the *in situ* generated cyanamide (**X**) possesses an electrophilic carbon and a fragile N–CN bond which may undergo a similar cyano sacrificial acetolysis to that of 1,3-diarylguanidine to generate an acetamide (Scheme V.1). The *N*-(2-(phenylthio)phenyl)acetamide (**1aa′**) having a diarylsulfide moiety can be further oxidised to its sulfoxide (**1aa′′**) analogue in the presence of a suitable oxidant [Scheme V.1, (ii)].

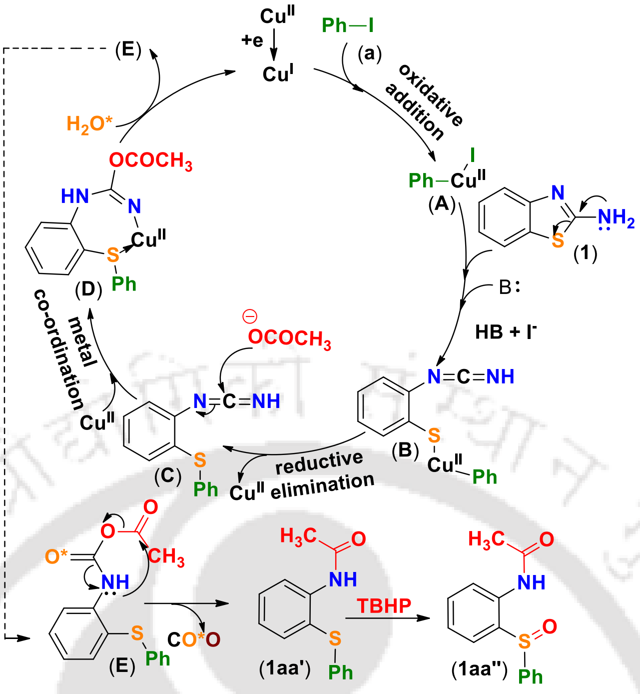
An initial experiment was carried out using 2-aminobenzothiazole (**1**) and iodobenzene (**a**) in the presence of $CuSO_4.5H_2O$ and Cs_2CO_3. The exclusive formation of cyanamide (**X**) was observed after 4 h, which is consistent with the previous literature reports. To check whether the envisioned cyano sacrificial acetolysis could be accomplished in one pot, AcOH (5 equiv.) was added to the same reaction mixture after the initial formation of cyanamide (**X**) and heating was continued further. To our delight, the expected *N*-acetylated product 2-(phenylthio)phenylacetamide (**1aa′**, 29%) was obtained *via* the loss of a cyano (-CN) group. The structure of the product (**1aa′**) was further confirmed by X-ray crystallographic analysis.



Scheme V.1. *Cyano sacrificial functionalisation strategies*

Inspired by the positive outcome, the reaction parameters are again scrutinised to achieve a better yield of the product. The investigation was commenced by using benzo[*d*]thiazol-2-amine (**1**) and 4-methyliodobenzene (**d**) as the reacting partners. Finally, a two-step optimised process was developed for the synthesis of *N*-(2-(*p*-tolylthio)phenyl)acetamide (**1da′**). In the first step the combination of $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.) and DMF (1 mL) at 120 °C for 4 h and in the second step addition of AcOH (20 equiv., 0.6 mL) at 120 °C for 5 h was found to be the best optimal condition for the *N*-acetylation. Further the addition of TBHP (6 equiv.) to the same reaction was found to be the *in situ* oxidation of sulfide (**1da′**) to sulfoxide (**1da″**). Adopting the optimised condition, a series of *N*-(2-(phenylthio)phenyl)acetamides and *N*-(2-(phenylsulfinyl)phenyl)acetamide were synthesised by using several aryliodides, 2-aminobenzothiazoles and both the aliphatic and aromatic carboxylic acids.

Based on the experimental findings and literature reports, a plausible mechanism has been proposed (Scheme V.2).



***Scheme V.2.** Proposed mechanism for the one pot synthesis of N-(2-(phenylsulfinyl)phenyl)acetamide*

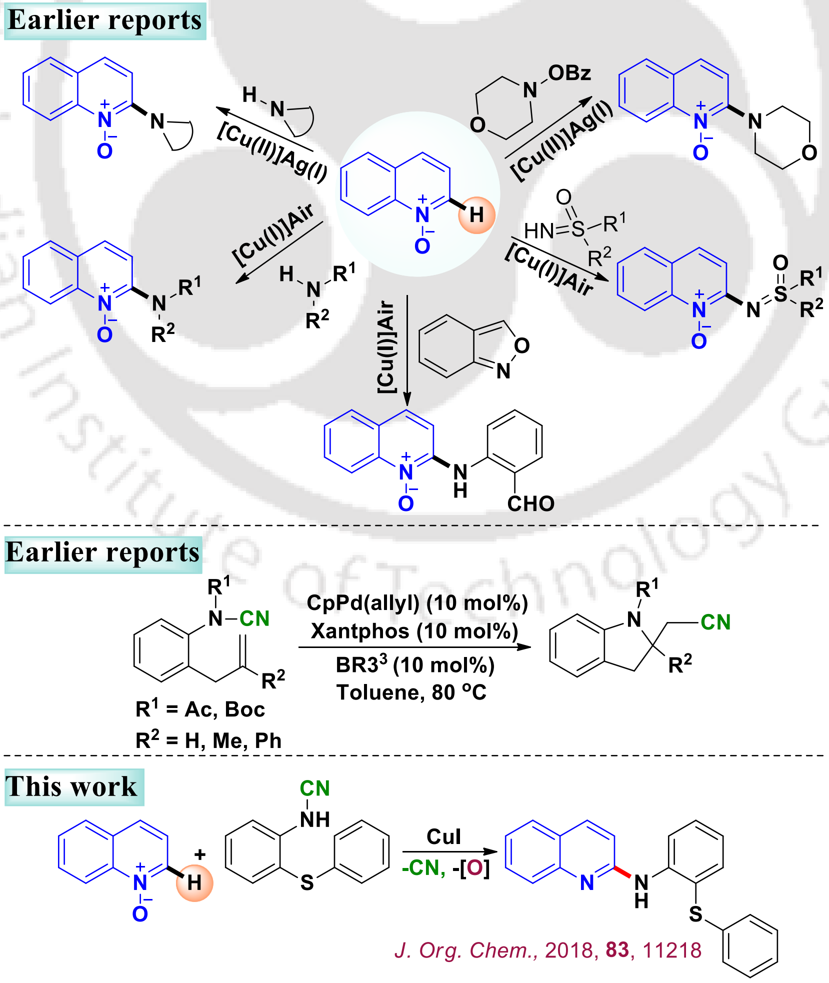
In conclusion, a one pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides has been accomplished by using benzo[*d*]thiazol-2-amine, aryl iodide and carboxylic acids in presence of Cu catalysts and base. The corresponding oxidised products can be obtained in the presence of TBHP. The process is accompanied with the loss of C and N atoms with concurrent *S*-arylation and *N*-acylation leading to a bi-functionalised amidic product *N*-(2-(phenylsulfinyl)phenyl)acetamide

CHAPTER VI. Cyano Sacrificial (Arylthio)-arylamination of Quinoline and Isoquinoline *N*-Oxides using *N*-(2-(Arylthio)aryl)cyanamides

This chapter describes a copper(I) catalysed regioselective arylthio-arylamination of quinoline and isoquinoline *N*-oxides at the expense of a cyano (-CN) group from *N*-(2-(arylthio)aryl)cyanamides. This is a unique illustration of aryl cyanamides serving as arylaminating agents on quinoline/isoquinoline *N*-oxides without any additional *N*-oxide removal step.

Recent advances in transition-metal catalysis have led to the development of effective methods for regioselective C−C and C−heteroatom bond formations. The construction of C−N bonds has attracted considerable attention since nitrogen containing motifs have found significant applications in biological and medicinal chemistry. Among various nitrogen bearing scaffolds, functionalised quinolines are reported to have antimalarial, antibacterial, antifungal and antimicrobial activities.

Various transition metal catalysed C2 selective functionalisations such as arylation, heteroarylation, alkylation, alkenylation and C−O or C−S bond formations on quinoline *N*-oxide moiety have been successfully accomplished. Undoubtedly, the regioselective C−N bond formation of these heterocyclic *N*-oxides have emerged as powerful tools in organic synthesis. Nevertheless few specialised synthetic methods are available to achieve this in a step-economic way (Scheme VI.1). The C2 selective amination of quinoline *N*-oxides have been achieved by using mostly secondary aliphatic amines in presence of Cu^{I} and Cu^{II} catalysts. However, the use of anthranil is the sole example of an arylamination of quinoline *N*-oxides (Scheme VI.1).



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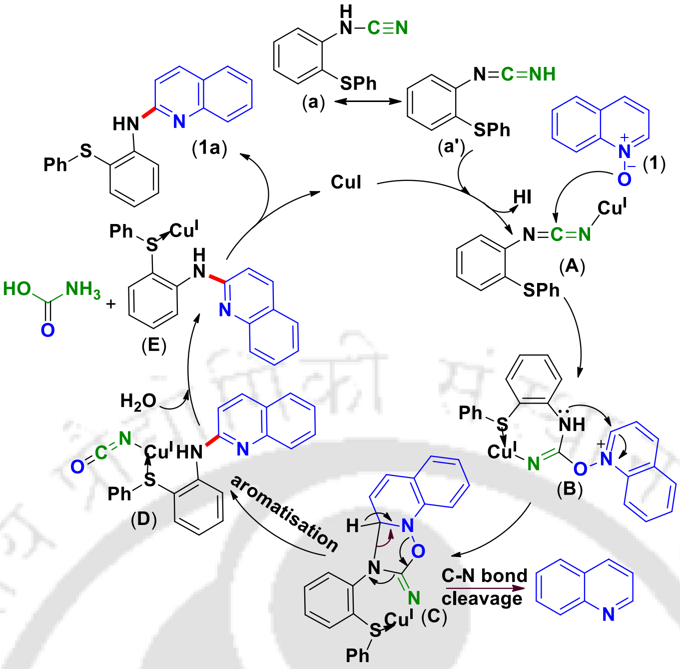
Scheme VI.1. *Differential reactivity of quinoline N-oxides and cyanamides*

Arylcyanamides are previously used for the aminocyanation of alkene. An organic cyanamide possesses a nucleophilic N–H site, an electrophilic cyanamide carbon and a fragile N–CN bond. On the other hand, because of the nucleophilic nature of quinoline *N*-oxide (**1**) and the presence of an electrophilic C2 site, we envisaged that the *N*-(2-(arylthio)aryl)cyanamide (**a**) might serve as an C2-arylthio-arylaminating agent on (**1**). This may be accomplished by the initial nucleophilic attack of the quinoline *N*-oxide (**1**) onto the electrophilic carbon of cyanamide (**a**) followed by an intramolecular nucleophilic attack at the C2 position of (**1**). Here, the sulfur atom of *S*-phenyl ring may further facilitate the reactivity of the cyanamide *via* co-ordination with a Cu-salt. The above anticipated reaction was initially executed using a *N*-(2-(phenylthio)phenyl)cyanamide (**a**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.25 mmol) and CuI (20 mol%) in 1,4-dioxane (2 mL) at 110 ºC. Formation of a new product (**1a**) (43%) was observed along with the isolation of quinoline (23%) and unreacted quinoline *N*-oxide (15%). The spectroscopic analysis of the isolated product revealed its structure to be *N*-(2-(phenylthio)phenyl)quinolin-2-amine (**1a**).

Encouraged by this C2 selective cyano sacrificial arylthio-arylamination, various other reaction parameters were further evaluated to achieve better yield of the product. After a series of experimentation, the ideal optimised condition for this arylamination is the use of *N*-(2-(*p*-tolylthio)phenyl)cyanamide (**b**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.5 mmol) and CuI (15 mol%) in CH_3CN (2 mL) at 80 ºC for 18 h.

The above optimised condition was then implemented to explore the scope and generality of the process. It was found that both the quinoline and isoquinoline *N*-oxide dervatives are successfully coupled with a series arylthio-arylcyanamides and afforded their corresponding products.

Based on the control experiments and the literature reports a possible mechanism for this regioselective arylthio-arylamination is depicted in Scheme VI.2.



Scheme VI.2. *Plausible mechanism for the arylthio-arylamination of quinoline N-oxide by using arylthio-arylcyanamide*

In conclusion, for the first time we have utilised arylcyanamides as an aminating agents towards regioselective C2-arylamination and C1-arylamination of quinoline and isoquinoline respectively. In many aminations of quinoline and isoquinoline *N*-oxides, the *N*-oxide moiety remained intact after the amination thereby requiring additional removal step. Currently the present arylthio-arylamination of quinoline and isoquinoline using *N*-(2-(phenylthio)phenyl)cyanamide as the aminating agent works best.