Transition Metal-Catalyzed Synthesis of Anhydrides, Ketones, Esters and 2*H*-Benzotriazoles via C–H Bond Functionalization

Submitted by

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March 2016

Dedicated to my
Mother Ushiman Bibi
&
Father (Late) Sk. Taher Ali

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Bhisma K. Patel.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Nilufa Khatun has been working under my supervision since July, 2010 as a regular registered Ph. D student. I am forwarding this thesis entitled "**Transition Metal-Catalyzed Synthesis of Anhydrides, Ketones, Esters and *2H*-Benzotriazoles via C–H Bond Functionalization"** being submitted for the Ph. D (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

March, 2016
IIT Guwahati

Prof. Bhisma K. Patel
Supervisor
Department of Chemistry
IIT Guwahati

Preface

During the past several decades, the field of C–H functionalization has flourished the synthetic organic chemistry. An extensive investigation of metal-catalyzed transformation of inert C–H bond to C–C and C–X (X = heteroatoms) bonds unlocks the golden opportunities in the synthesis of small molecules. Compared to classical cross-coupling reactions, the exploitation of C–H bond as one of the coupling partner would be greener and advantageous in terms of reduced waste generation, operational simplicity, avoidance of preparation of starting materials and shorten synthetic route. As a consequence, transition metal-catalyzed C–H bond strategy has been adopted as the powerful working tool for the synthesis of various small molecules at present. The contents of this thesis have been divided into five main chapters based on the experimental results carried out during the complete course of research period. The chapter I is the introductory chapter of this thesis which presents a brief overview of transition metal-catalyzed C–H bond functionalization processes: advantages, challenges, solutions and applications of them. The remaining four chapters describe the experimental works emphasizing on palladium or copper catalyzed C–C, C–N and C–O bond forming reactions *via* either empoying cross dehydrogenative coupling (CDC) or substrate directed C–H bond functionalization strategies. Chapter II describes a CuO nano catalyzed, unique CDC protocol for the synthesis of carboxylic acid anhydrides *via* double sp^2 C–H activation of arylaldehydes using TBHP as the oxidant. Chapter III demonstrates a Pd(II)-catalyzed unprecedented protocol for the ketone synthesis using terminal aryl alkenes and alkynes as new aroyl surrogates *via* a substrate directed sp^2 C–H functionalization. Chapter IV illustrates the use of benzylic ethers as the alternative source of arylcarboxy surrogates for ester synthesis *via* a copper-catalyzed substrate directed sp^2 C–H functionalization of 2-phenylpyridine derivatives. Chapter V describes a palladium-catalyzed elegant protocol for the synthesis of 2-aryl-*2H*-benzotriazoles from azoarenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant through substrate directed C–H functionalization strategies.

Acknowledgement

At the very outset, I take this great opportunity to express my best regards, sincere gratitude from the deepest chord of my heart profound to my research guide Prof. Bhisma Kumar Patel for providing me the lab facilities and a higher learning environment. His brilliant suggestions, proficient guidance, inspiration, encouragement, positive-criticism and creative-scientific ideas helped me a lot to enhance my knowledge in my presonal as well as professional life. Apart from these 'subjective' criterias, his affectionate nature and caring attitude to each and every student especially towards me also needs a separate mention.

Besides my guide, I like to acknowledge my sincere thanks to all my doctoral committee members, Prof. Biplab Mondal, Dr. Chandan K. Jana, Prof. Vikash K. Dubey, Dr. Dipankar Srimani and Dr. Akshai Kumar A. S. for their valuable suggestion, insigtful comments, advices and periodic evaluation of my thesis work.

Being a master-graduate alumnus of this department, I am extending my sincere thanks to all the faculties of Department of Chemistry, IIT Guwahati for their help, encouragement, guidance and suggestions through out the entire M.Sc and Ph.D course. I also wish to thank all the staff memebers of Chemistry department especially Nilotpal da, Diganta da, Aniruddha da, Imdadul da and Abhilasha di for their kind help throughout the Ph. D. couse. A special thank to Dr. Babulal Das, for his continuous help whatever I needed.

I wish to convey my sincere gratitude to IIT Guwahati for all the facilities that were made available to me, the Council of Scientific and Industrial Research (CSIR), India for financial support.

I like to thank my lab super-seniors Hari da, Ramesh da, Santosh da and Ali di for their unending help, valuable suggestion and continuous encouragement at the initial stage of my Ph. D career. I also feel lucky to mention the name of my other two seniors Saroj da, Srimanta da, M.Sc-Ph.D batch-mate Arghya, lab-mate Anupal, Ganesh, sweet-juniors Sourav, Wajid, Ahalya, Anju, Suresh, Prakash, Bilal, Prasenjit, Dipti, Research Associate Joy da and Sutapa di in my thesis. There may be some misunderstanding amongst us due to our "very own characteristic features", but we worked as an individual unit in every aspect and shared very light moments together. I wish to convey a special thank to all of you for maintaining a friendly atmosphere in the lab. I also had the opportunity to work with some dedicated summer and M. Sc trainees like, Sudipta, Pallabita, Swavalina, Soumya, Praveen, Tulika (Agrawal), Nasrin and Tulika (Dutta).

I wish to acknowledge my sincere gratitude to Mr. Chinmoy Sinha for his kind help, valuable suggestions which inspired me a lot to take a new step in my life and wish him a very happy and peaceful long life. I will keep repeating those words till my last breath.

I also take this opportunity to express my sincere thanks to all of my IITG friends, seniors and juniors: Satyapriya, Tuhin, Najbul, Sukhamoy, Muthu, Radha, Rama, Ajaz, Satavisha, Ravi da, Ashif da, Somu da, Pankaj da, Palash da, Raihana di, Sameer, Akhtar, Shaad, Adil, Sabera, Sahnawaz, Soumendra, Buddhadeb, Afsana, Mahmuda, Subho, Sayan, Sourav, Utpal, Arvin, Shilaj and many more whom I met in different time in IITG. A special owe to Sumana, Debarchana and Poulomi di for their love, help and unfailing support which makes my hostel-stay 'a home away from home'.

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I also take this opportunity to convey my best regards to all of my teachers who made me 'not me, but me' from an ordinary poor village girl belonging from a reserved, backward society to a 'modified' one. Ratan master-moshay, Chobbi aunti, Shoroshi master-moshay, Gopal master-moshay, Sanjay sir, Ashis da, Sujit da, Narayan sir, Pathik Sir, Mainul sir, Mahadev sir, Jayashree mam, AKM sir and all of my school teachers, who are my educational-back bone from my childhood.

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Finally I am honestly grateful to my family members for their endless love, unending support and blessing. A great thanks to my babu (father) for his silent contribution in my life and be in peace wherever he is. After my father's tragic demise at early stage of my life, it is my 'mother' who upbrings me up like a 'princess' inspite of having utter proverty and sacrifices a lot in her life. I owe my entire life to her. At the same time, I am grateful to my younger sister, Julefa Khatun for her unconditional love, support and uncountable sacrifices. I am also thankful to my brothers, sister-in-laws, sisters, brother-in-laws, nieces, nephews, uncles, aunties, in-laws family and neighbours for their affection and unending blessing.

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Chapter I: Introduction: A Brief Overview of Transition Metal-Catalyzed C–H Functionalization

This chapter presents a brief overview of the revolutionary aspect of C–H functionalizations, their advantages compare to traditional cross coupling reaction, challenges and solutions, different types of implemented strategies for methodologies and a myriad of applications in synthetic organic chemistry.

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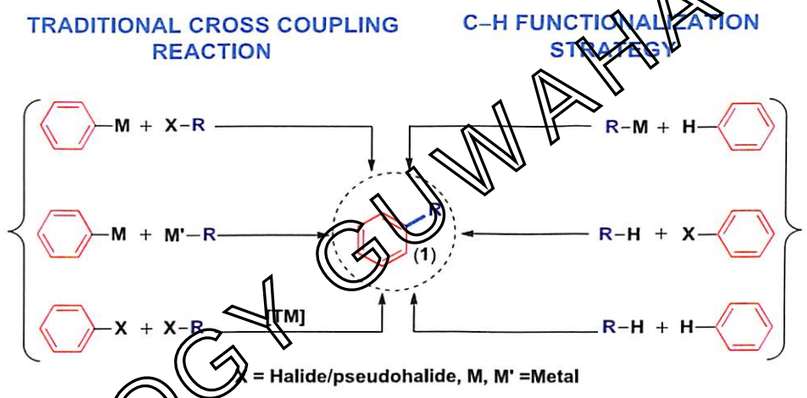
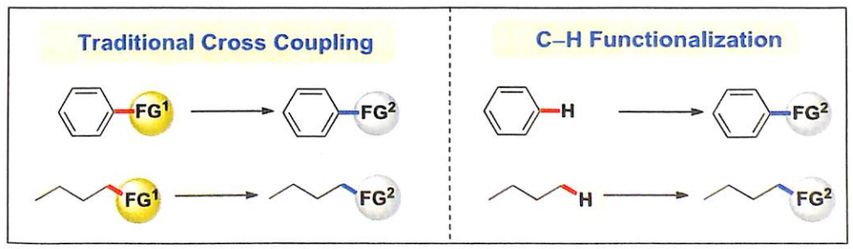
those strategies, carbon-carbon and carbon heteroatom bond forming reactions *via* cross coupling, widely used in both academic and industrial worlds have emerged as the most reliable one. The traditional approach for the cross-coupling reactions involves transformation of a pre-existing functional group with another one to obtain the desired chemical function. The classical cross coupling reactions typically involve either the coupling reaction of an organometallic reagent with an aryl halide or another organometallic reagent for the synthesis targeted bi-aryl compound (**1**) as shown in Scheme 1, left side. Alternatively, the compound (**1**) can be obtained by metal mediated homo coupling reaction of two aryl halides/pseudohalides (Scheme 1, left side). The use of such pre-functionalized substrates provided the new and versatile synthetic tools to the synthetic chemists achieving the selective preparation of novel molecules. Thus, those strategies unleashed a fast and relevant progress over the past decades. The well known cross coupling reactions include Suzuki, Sonogashira, Stille, Kumada, Himaya or Negishi and others has been prevalent for many decades and allowed the use of pre-functionalized precursors over non-functionalized one. However, the use of those expensive and pre-elaborated molecules in those methods requires paying extra 'price' to achieve such degree of selectivity. In particular, the obligation to use activated pre-functionalized coupling partner is wasteful since it needs installation and subsequent disposal of waste agents. Furthermore, preparation and isolation of those expensive and pre-elaborated independent coupling partners added extra steps towards the formation of desired chemical bonds. Thus, those problems associated with pre-installation processes caused a major concern to the synthetic chemists in terms of atom-economic and environmental point of view. Due to those unavoidable reasons, over the last decades, the modern research has been directed in a quest to develop new processes aiming to achieve identical final molecules with the same selectivity, but in a greener and more sustainable way. In this aspect, probably the best and most possible sustainable way to fulfill the mentioned demands is the direct functionalization of C–H bonds utilizing non-functionalized precursors.



Scheme 1. Different approximations of the cross coupling reactions

The C–H bonds are ubiquitous in organic molecules, from small molecule backbone to the more elaborated natural products with comparable dissociation energies and regarded as the non-functional group. Due to small difference in electro negativities between carbon and hydrogen, the C–H bonds are regarded as being non-polar. In structural formula of molecules, the hydrogen bonds are often omitted for clarity which indicated the ubiquitous nature and lack of reactivity i.e. 'inertness' of it towards the chemical reaction. So, it is easy to envisage that the selective and direct functionalization of C–H bonds would bring a faster and more atom-economical synthetic approach (Scheme 1, right side). The use of C–H bonds as a reactive coupling partner similar to C–X bonds (X = metal/halide/pseudohalide) would provide a powerful and straightforward strategies for the formation of complex organic structures. Furthermore, use of C–H bonds as one of the functional groups in coupling reaction would be profitable in terms of operational simplicity, avoidance of pre-installation of starting materials, reduced waste generation and shorten the synthetic route.



Scheme 2. Different adopted strategies for C–H functionalization

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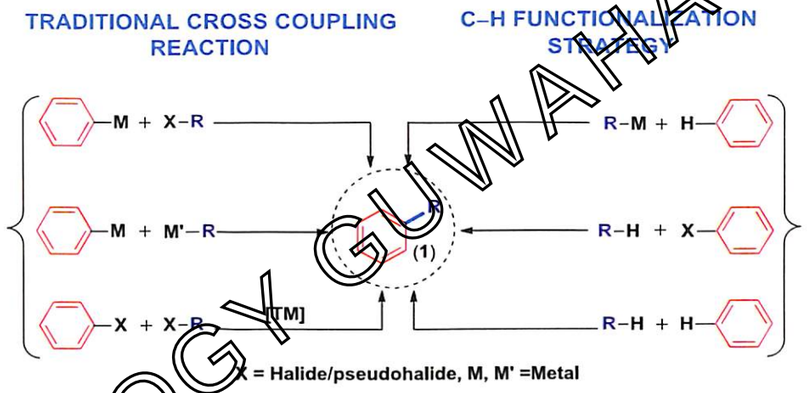

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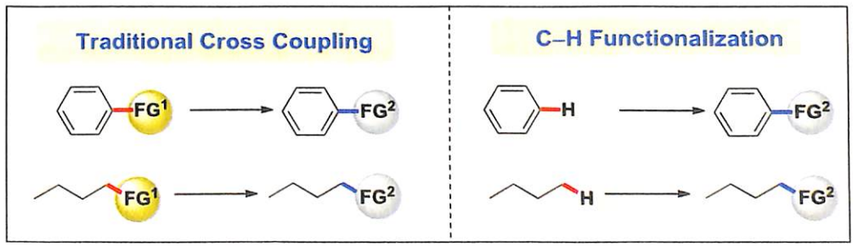


Scheme 2. Different adopted strategies for C–H functionalization

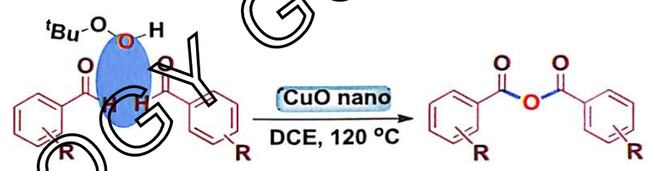
The revolutionary aspect of this concept is gradually renovating organic chemistry and brings a renaissance with newer disconnection approaches giving opportunity to access desired molecules with original structures in a more simple, efficient, cost effective and ecological manner. As a consequence, the last decade has seen an unprecedented growth of interest to develop synthetic methods utilizing C–H bonds activation strategies in coupling chemistry. The one of the best way is the metal-catalyzed C–H bonds functionalization to achieve C–C, C–N, C–O and C–X bonds as shown in scheme 2. Most of the metal mediated selective C–H functionalization strategies rely on two elegant approaches including (a) Ligand directed C–H functionalization (b) cross dehydrogenative coupling. In this aspect, our group has been engaged last few years to develop methodologies to achieve the desired C–C and C–X bonds (X = heterto atom/halide) *via* above mentioned protocols and produced a myriad of organic compounds.

Chapter II: Nano CuO Catalyzed Cross Dehydrogenative Coupling (CDC) of Aldehydes to Anhydrides

This chapter demonstrates the elegant synthesis of carboxylic acid anhydrides directly from arylaldehydes using CuO nanoparticles as the catalyst and *tert*-butyl hydropeoxide (TBHP) as the oxidant *via* Cross Dehydrogenative Coupling (CDC).

The essence of transition metal-catalyzed C–H bond functionalizations is an important ongoing theme in organic chemistry. Directing group-assisted C–H bond functionalization and cross dehydrogenative coupling (CDC) reactions are preferred in this field because of their atom- and step-economy. To date, although several CDC methodologies have been reported for the formation of C–C bonds, less effort has been directed toward C–O bond-forming reactions. Carboxylic acid anhydrides, an important organic compound, are generally used in the preparation of amides and esters and they have found applications in the synthesis of peptides and drugs. The literatures demonstrated a number of methodologies for the synthesis of anhydrides including dehydration of carboxylic acids in the presence of dehydrating reagents, classical substitution reaction between acyl halides/anhydrides with carboxylates, palladium-catalyzed carbonylation of aryl halide with metal carboxylate, functionalization of carboxylic acid C–O bond with a photoredox catalyst or a 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) catalyzed direct oxidation of aldehyde and palladium catalyzed direct conversion of aryl iodides

into the corresponding anhydrides under CO atmosphere. Although transitional metal-catalyzed aldehydic C–H functionalizations are known, double aldehydic C–H functionalization using nano CuO resulting in the formation of carboxylic acid anhydride is unprecedented. Herein, we developed a protocol in which both inter- and intra- molecular double aldehydic sp^2 C–H functionalization, leading to anhydrides using nano CuO and TBHP.



Scheme 3. Synthesis of anhydrides from aldehydes *via* CDC process

During optimization, various reaction parameters such as catalyst, oxidant, solvent, time and temperature were screened to attain the best possible yield. After a series of several reactions, a combination of aldehyde (1.0 equiv.), CuO nano (5 mol%) and portionwise addition of TBHP in decane (2 equiv.) at 120 °C in DCE was chosen as the optimized conditions for the self coupling of aldehydes. The present conditions of this unique oxidative coupling reaction were applied to a range of other aldehydes. Aromatic aldehydes bearing electron-rich substituents, irrespective of their position(s) in aromatic ring, underwent the CDC reaction smoothly to afford the corresponding symmetrical carboxylic acid anhydrides in modest to good yields. One setback of this interesting transformation is that whereas aromatic aldehydes possessing weakly electron-withdrawing groups gave negligible amounts of product, substrates possessing strongly electron-withdrawing groups completely failed to give their desired anhydrides.

Based on the results of the controlled experiments and trapped intermediates, the mechanism presented in Scheme 4 has been suggested for this transformation.

The revolutionary aspect of this concept is gradually renovating organic chemistry and brings a renaissance with newer disconnection approaches giving opportunity to access desired molecules with original structures in a more simple, efficient, cost effective and ecological manner. As a consequence, the last decade has seen an unprecedented growth of interest to develop synthetic methods utilizing C–H bonds activation strategies in coupling chemistry. The one of the best way is the metal-catalyzed C–H bonds functionalization to achieve C–C, C–N, C–O and C–X bonds as shown in scheme 2. Most of the metal mediated selective C–H functionalization strategies rely on two elegant approaches including (a) Ligand directed C–H functionalization (b) cross dehydrogenative coupling. In this aspect, our group has been engaged last few years to develop methodologies to achieve the desired C–C and C–X bonds (X = heterto atom/halide) *via* above mentioned protocols and produced a myriad of organic compounds.

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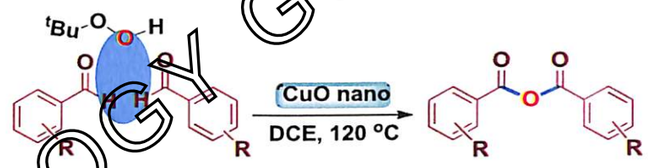

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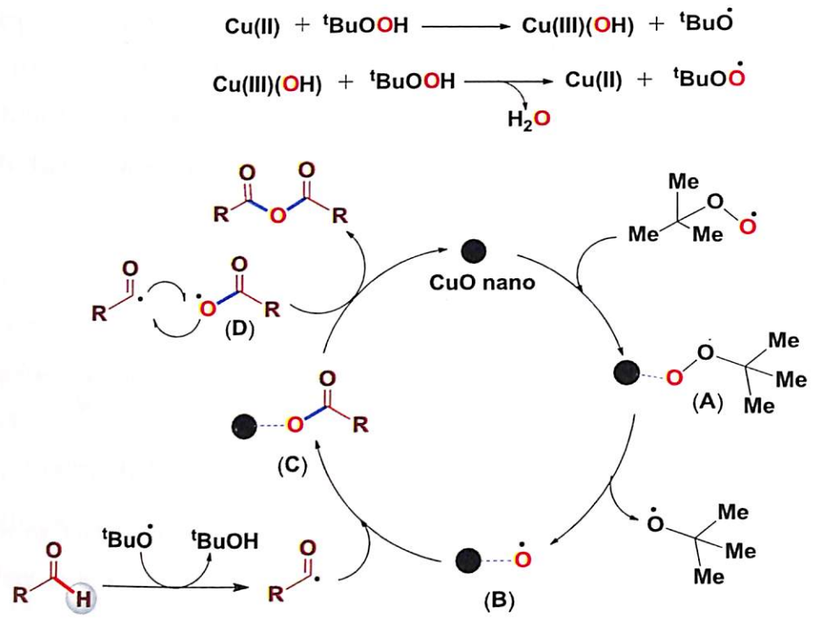


Scheme 4. Plausible reaction mechanism for anhydride formation

In conclusion, a convenient method has been developed for the synthesis of carboxylic acid anhydrides from aromatic aldehydes. This method follows a unique double sp^2 C–H functionalization of aldehydes in the presence of nano CuO catalyst and oxidant TBHP.

Chapter III: Pd(II)-Catalyzed *O*-Aroylation of Directing Arenes using Terminal Aryl Alkenes and Alkynes: Synthesis of Ketones

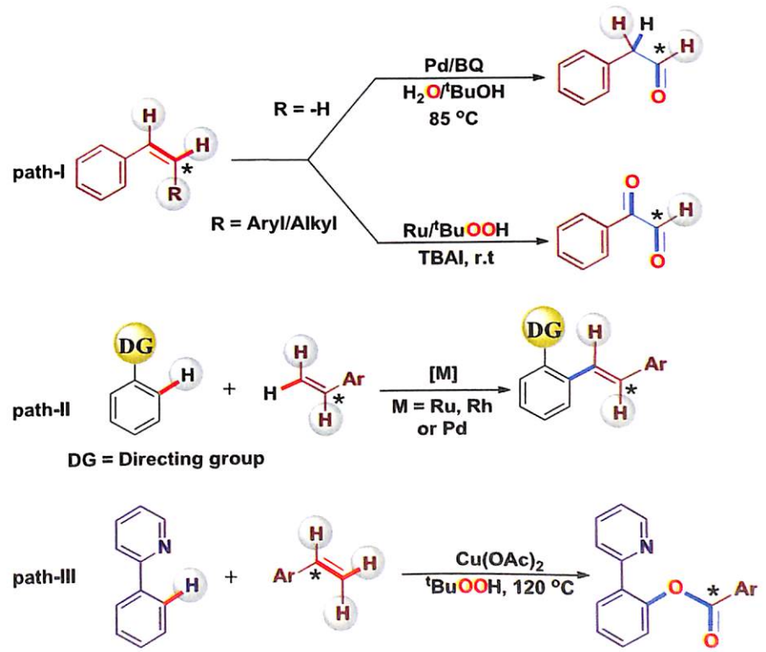
This chapter demonstrates a substrate-directed Pd-catalyzed unprecedented *o*-aroylation strategy using new aroyl surrogates *viz.* terminal aryl alkenes and alkynes in the presence of TBHP.

The development of efficient and newer strategies for the construction of carbon-carbon (C–C) bonds is of immense interest to synthetic chemists. An extensive investigation on transition metals catalyzed C–H bond activation strategies have greatly revolutionalized the C–C bond forming processes. The direct use of C–H bonds to generate C–C bonds is highly desirable since it has the potential to streamline synthetic schemes by shortening the number of synthetic steps and thus maintaining better atom economy of the processes. In particular, most C–H bond

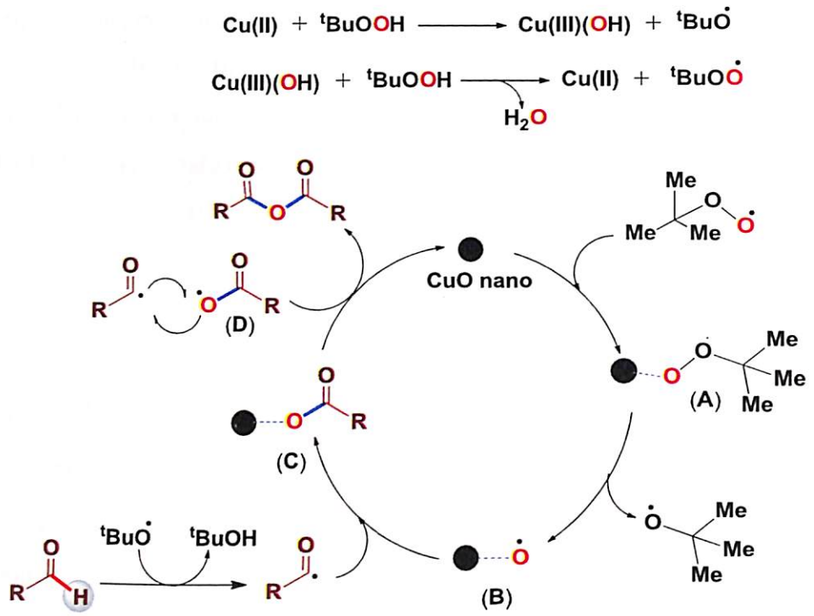
functionalizations processes based on two ingenious approaches *viz.* directing-group assisted C–H functionalization or cross-dehydrogenative coupling (CDC).

Aryl alkenes are susceptible to undergo Wacker type oxidation to give phenylacetaldehyde (Scheme 5, path-I(a)) while diarylethenes are reported to form 1,2-diketones (Scheme 5, path-I(b)) using Pd and Ru catalysts respectively. In a separate study, terminal aryl alkenes are reported to introduce a vinyl moiety at the *ortho* site of ligand directed substrates using various metal catalysts such as Rh, Ru and even Pd as shown in Scheme 5, path-II. Very recently our group have demonstrated a Cu(II)-catalyzed *o*-benzoxylation of 2-phenylpyridine using both terminal aryl alkenes and alkynes as arylcarboxy (ArCOO-) surrogates as shown in Scheme 5, path-III.

To check the product probability, we thought to implement Pd catalyst during the reaction between 2-phenylbenzothiazole, a directed substrate and terminal aryl alkenes. Now the query arises whether this catalytic condition provides *o*-vinylation as reported with catalysts like Ru, Rh and Pd or *o*-benzoxylation as has been demonstrated with Cu catalyst or all together a differential reactivity leading to a new product may be observed.



Scheme 5. Catalyst-controlled selectivity of alkenes oxidation.



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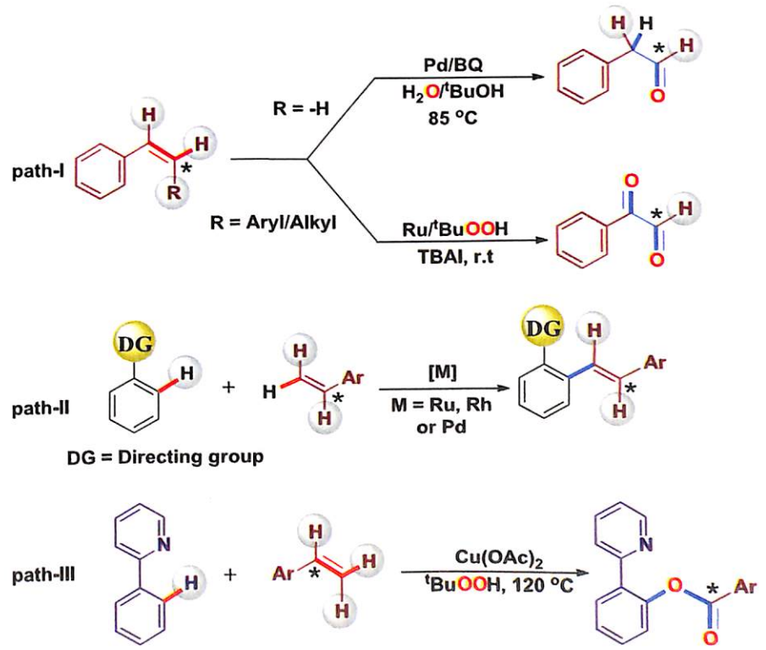

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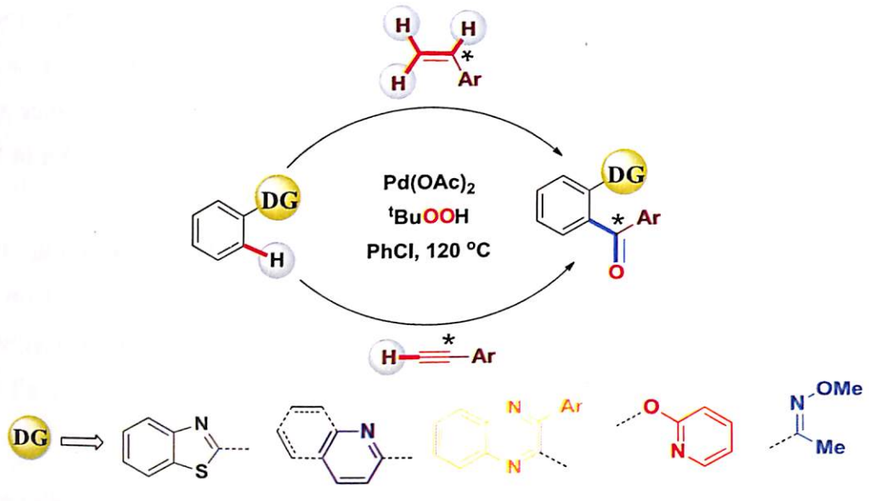


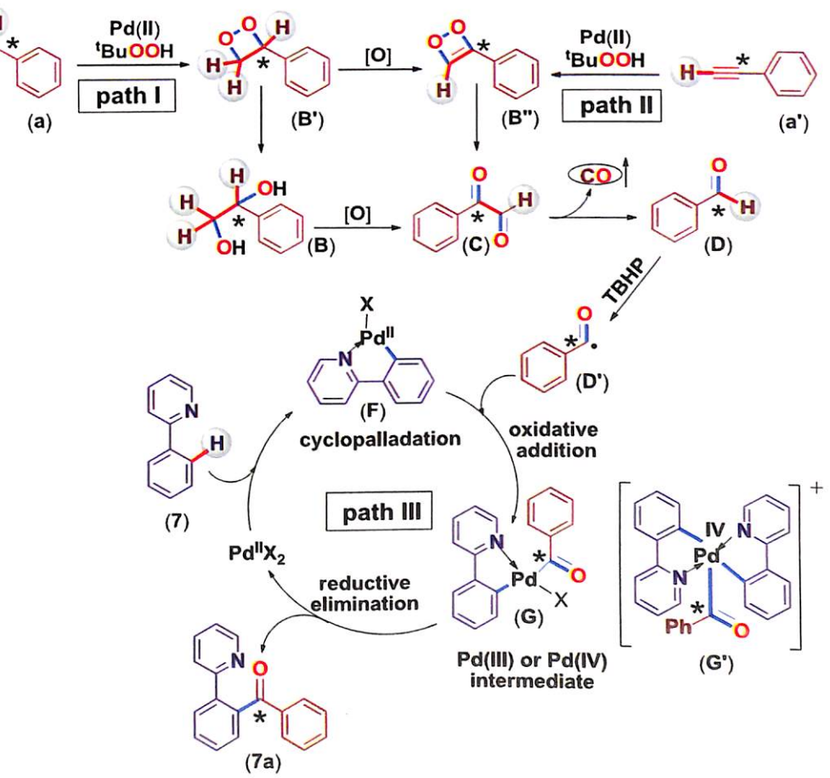
Scheme 6. *O*-aroylation of directed arenes using alkenes and alkynes as the aroyl (ArCO–) surrogates

Various reaction parameters such as catalyst, solvent and oxidant were screened to attain the best possible yield of the desired ketone. Finally, a mixture of 2-phenylbenzothiazole (1 equiv.) and styrene (2.5 equiv.), $Pd(OAc)_2$ (10 mol%) and TBHP in decane (5 equiv.) in chlorobenzene at 120 °C was chosen as the best optimized reaction conditions. The present methodology was then implemented on 2-phenylbenzothiazole and its derivatives with a variety of terminal alkenes. Terminal aryl alkenes possessing both electron donating and electron-withdrawing substituents coupled efficiently with the directing substrate to give their corresponding ketones in modest to good yield. Aryl alkenes having electron withdrawing substituents provided higher yield of desired ketones than those bearing electron donating substituents. In addition, directing substrates bearing electron donating substituents furnished better yield compared to those having electron withdrawing substituents. The present optimized conditions were equally applicable to a set of other directed substrates *viz.* 2-phenyl pyridine, 2,3-diphenylquinoxaline, benzoquinoline,

2-aroyloxypyridine and acetophenone *O*-methyl ketoxime and provided their corresponding *o*-aroylated *i.e* ketone products.

Likewise aryl alkenes, aryl alkynes *viz.* phenyl acetelene was also found to serve as the aroyl (ArCO–) surrogates under the optimized conditions but provided a poor yield of expected ketone because of unavoidable homo-coupling reaction of phenyl acetelene. Ultimately, a modified condition with a high catalytic loading (20 mol%) along with the use of increased amount of TBHP (10 equiv.) was chosen for the further reaction. In a similar way, 2-phenylbenzothiazole, 2-phenyl pyridine, benzoquinoline, 2-aroyloxypyridines were also subjected to this modified reaction conditions and provided poor to modest yields of their corresponding ketone products.

Based on results obtained from controlled experiments and taking cues from the related literatures, a plausible mechanism has been proposed as shown in scheme 7.



Scheme 7. Plausible mechanism for *o*-aroylation.

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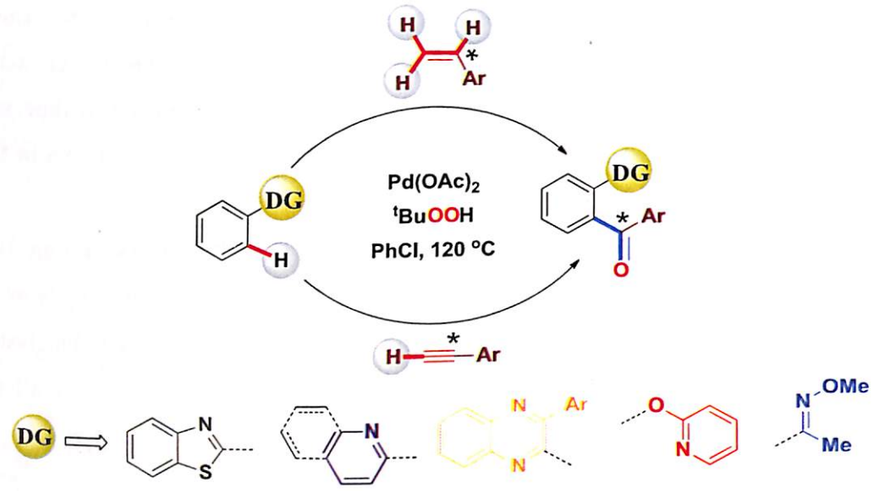

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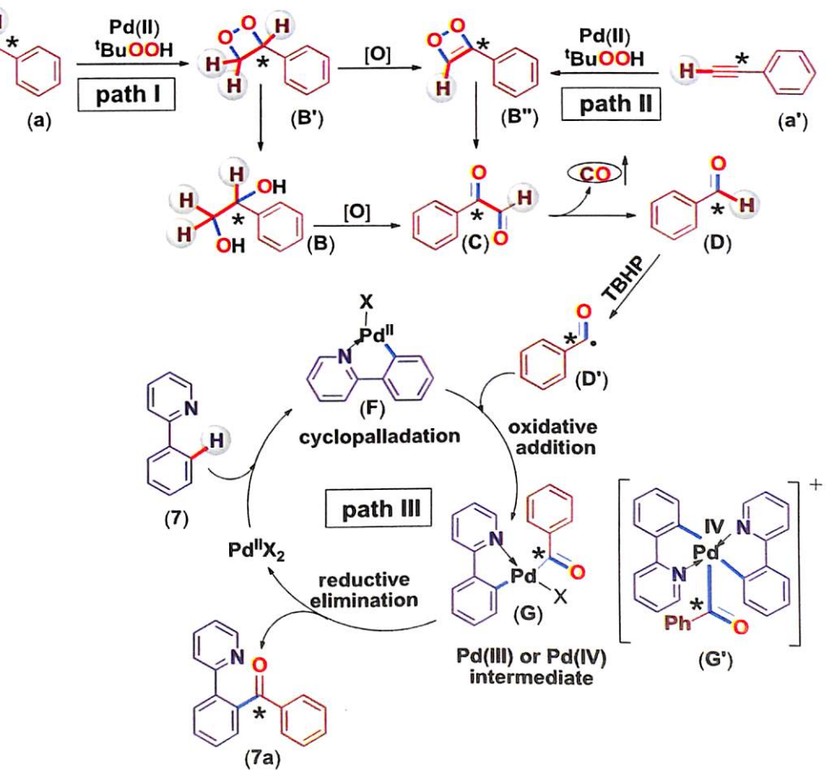

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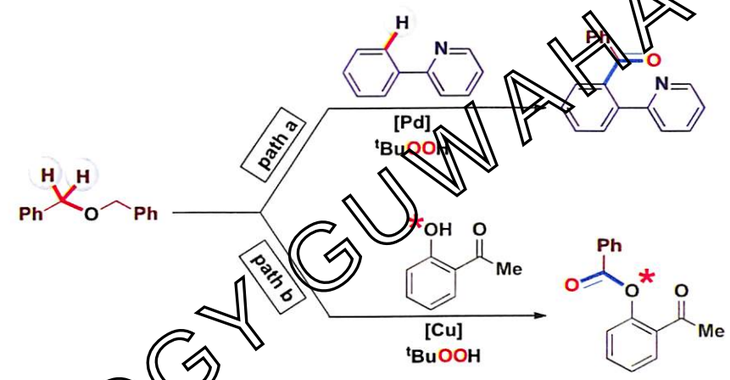
In conclusion, we have developed a new, efficient Pd-catalyzed directing group-assisted aroylation of arenes using terminal alkenes and alkynes as the new aroyl surrogate giving ketone products. This strategy have been implemented to a wide range of ligand directed substrates and afforded modest to good yields with a good tolerance of functional groups. Differential selectivities of Cu and Pd have been demonstrated; while Cu/TBHP combination installs an *o*-aryloxy (ArCOO–) the use of Pd/TBHP incorporate an *o*-aroyl (ArCO–) group using both alkenes and alkynes.

Chapter IV: Benzylic Ethers as Arylcarboxy Surrogates in Substrate Directed *ortho* C–H Functionalization Catalyzed by Copper: Synthesis of Esters

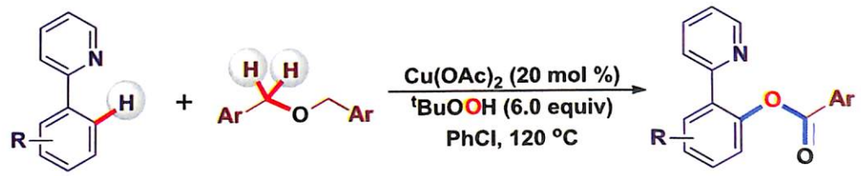
This chapter portrays an *ortho*-benzoxylation of 2-arylpyridines using benzylic ethers as the alternative arylcarboxy sources (ArCOO–) *via* sp^2 C–H bond activation.

Recently considerable efforts have been devoted for the *ortho* selective direct functionalization of unreactive C–H bonds for the construction of C–C and C–X (X = heteroatom) bonds using transition metals such as Pd, Cu, Ru, Rh and Ir. Among *ortho* C–C and C–X bond making processes, the C–O bond forming processes are difficult to promote due to the binding of electronegative oxygen atom with transition metals thereby making it inactive for further reactions. Direct functionalization of C–H bonds has become the most attractive approach in recent organic synthesis as it obviates prefunctionalization of substrates. On the other hand, benzylic ethers are commonly used as protecting groups for alcohols that can be easily cleaved under suitable oxidizing or reducing conditions. It has also served as the dormant synthetic equivalents of aldehydes, carboxylic acids or esters depending upon the reaction conditions. Benzyl ether served as aroyl (ArCO–) equivalent both under Palladium (II) or Copper (I/II) catalyzed reactions utilizing TBHP as the oxidant as illustrated in scheme 8. But under Cu catalyzed reaction conditions, it resulted in O-aroylation and not C-aroylation.



Scheme 8. Metal dependent reactivities of dibenzyl ethers

To test whether benzyl ether serves as an aroyl (ArCO–) equivalent or as an arylcarboxy (ArCOO–) source during Cu-catalyzed substrate-directed C–H functionalization, 2-phenyl pyridine and dibenzylic ether were reacted in presence of TBHP in decane in DCE solvent. The reaction ended up giving an ester, 2-(pyridin-2-yl)phenyl benzoate (*i.e* an ester product) as shown in scheme 9. This result illustrates that dibenzyl ether serves as a carboxy (ArCOO–) source in the presence of Cu catalyst. This Cu-catalyzed reaction showed differential reactivity to that of Palladium (II) and even with Copper (I/II) where benzyl ether acted only as an aroyl (ArCO–) group (scheme 8).



Scheme 9. *o*-benzoxylation of 2-arylpyridines using benzylic ethers as (ArCOO–) source

To attain a suitable reaction condition for the synthesis of ester various reaction parameters *viz.* catalyst, solvent and oxidant were varied in a quest to achieve the best possible yield of ester. Finally, the optimized reaction condition utilized for further reaction was the use of 2-phenylpyridine (0.5 mmol), dibenzyl ethers (0.75 mmol), $Cu(OAc)_2$ (20 mol%), TBHP (aq. 70%) (6 equiv.) in chlorobenzene (0.5 mL) at 120 °C. The scope of this strategy was implemented to the reaction between 2-phenylpyridine, substituted 2-phenylpyridines and various substituted

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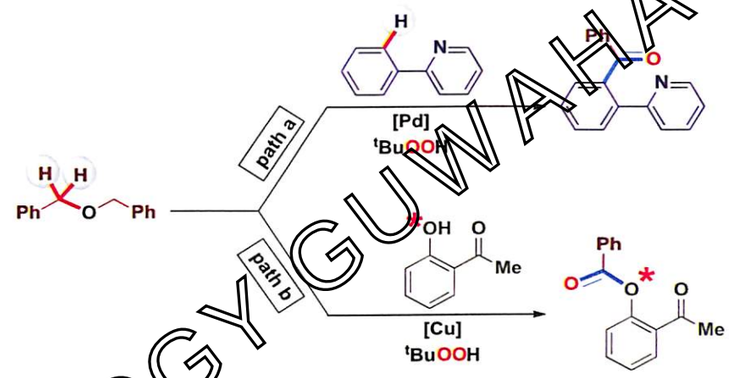

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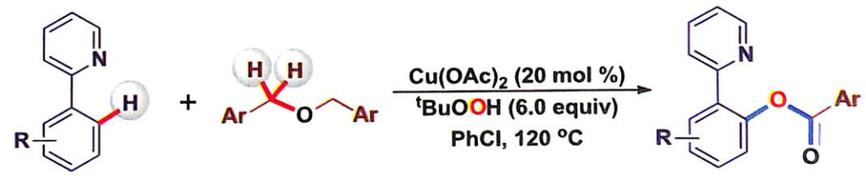

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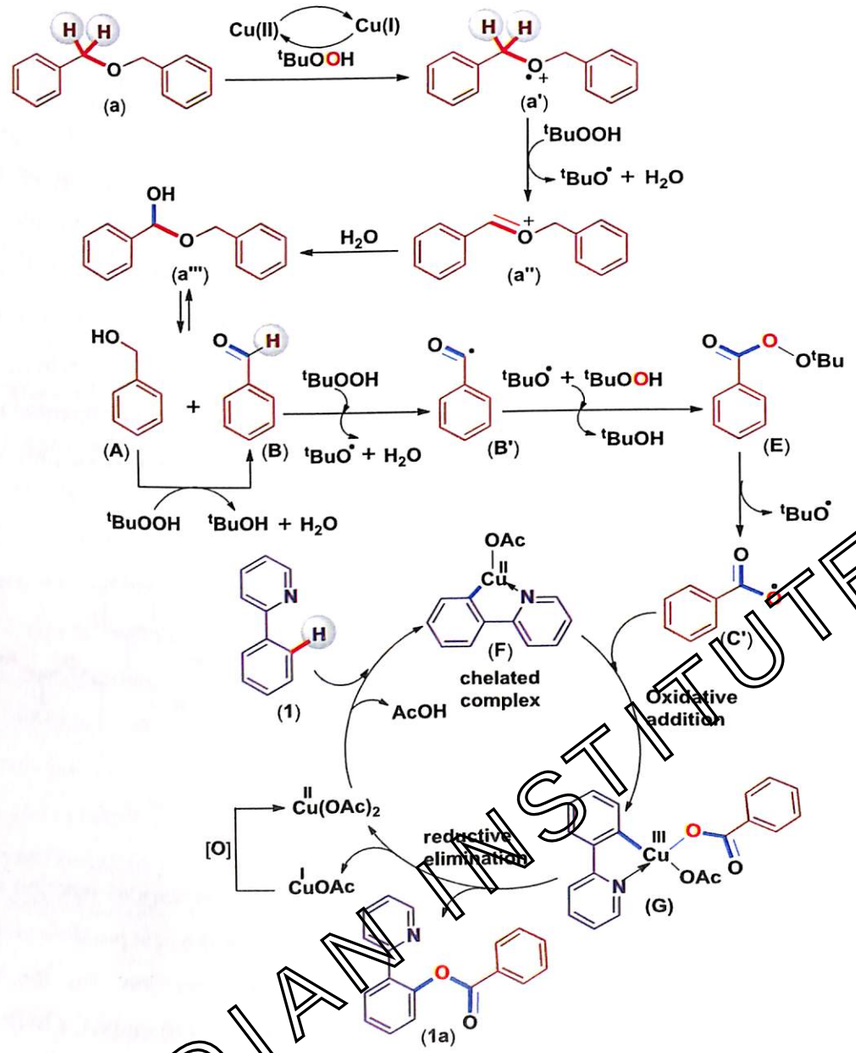

Scheme 10. Plausible mechanism for *o*-benzoxylation of 2-phenylpyridine

Based on results/observation of controlled experiments performed and taking cues from the related literatures, a plausible reaction mechanism has been postulated as shown in Scheme 10.

In Conclusion, an efficient Cu^{II}-catalyzed protocol for the *o*-benzoxylation of 2-phenylpyridine derivatives has been demonstrated utilizing benzyl ethers as the new arylcarboxy surrogates. The reaction shows a broad substrates scope and good tolerance toward the various functional groups using inexpensive copper catalyst. A mechanistic investigation reveals that the reaction is going *via* radical pathways. In addition, this reaction demonstrates the differential reactivity of Cu catalyst to that of Pd catalyst.

Chapter V: Palladium-Catalyzed Synthesis of 2-Aryl-*2H* Benzotriazoles from Azoarenes and $TMSN_3$

This chapter focuses on the palladium (II) catalyzed synyhesis of 2-aryl-*2H*-benzotriazoles from azobenzenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant *via* intermolecular azidation (C–N bond formation) through *ortho* sp^2 C–H functionalization of azobenzenes and sequential intramolecular cyclization (N–N bond formation)

2-Aryl-*2H*-benzotriazoles, are important nitrogen containing heterocylcles which are found extensively in pharmaceuticals and structural component in many UV stabilizers and organic electronic materials. Compounds having 2-aryl-*2H*-benzotriazole scaffold as privileged skeleton include a seratonine/dopamine receptor ligand, Tinuvin-P (an ultraviolate light absorber), human growth hormone upregulator and monomer of PCDTPBt (an electron acceptor in solar cell) etc.

Existences of three isomeric benzotriazoles based on N^1, N^2 and N^3 substitutions make the selective synthetic strategies challenging. Because of the thermodynamic stability of N^1 isomer, compared to its N^2-isomer more synthetic methods have been reported for the former. Several mathodologies are documented in the literature for the synthesis of 2-aryl-*2H*-benzotriazoles include: (i) thermal decomposition of 2-azidoazoarenes, (ii) reduction of 2-[2-nitrophenylazo] derivatives by thiourea and Zn/NH_4Cl, (iii) oxidative coupling of *ortho* substituted azoaniline by metal catalysts such as SmI_2, Zn or Cu, (iv) metal-catalyzed arylation of unsubstituted benzotriazoles leading to the formation of a regioisomeric mixture of N^1-and N^2-benzotriazoles (iv) cross coupling of 2-haloaryltriazenes and NaN_3 (v) Rh-catalyzed *ortho* C–H activation of azobenzenes utilizing *N*-sulphonyl azide (TsN_3) as the aminating source. Although this latest

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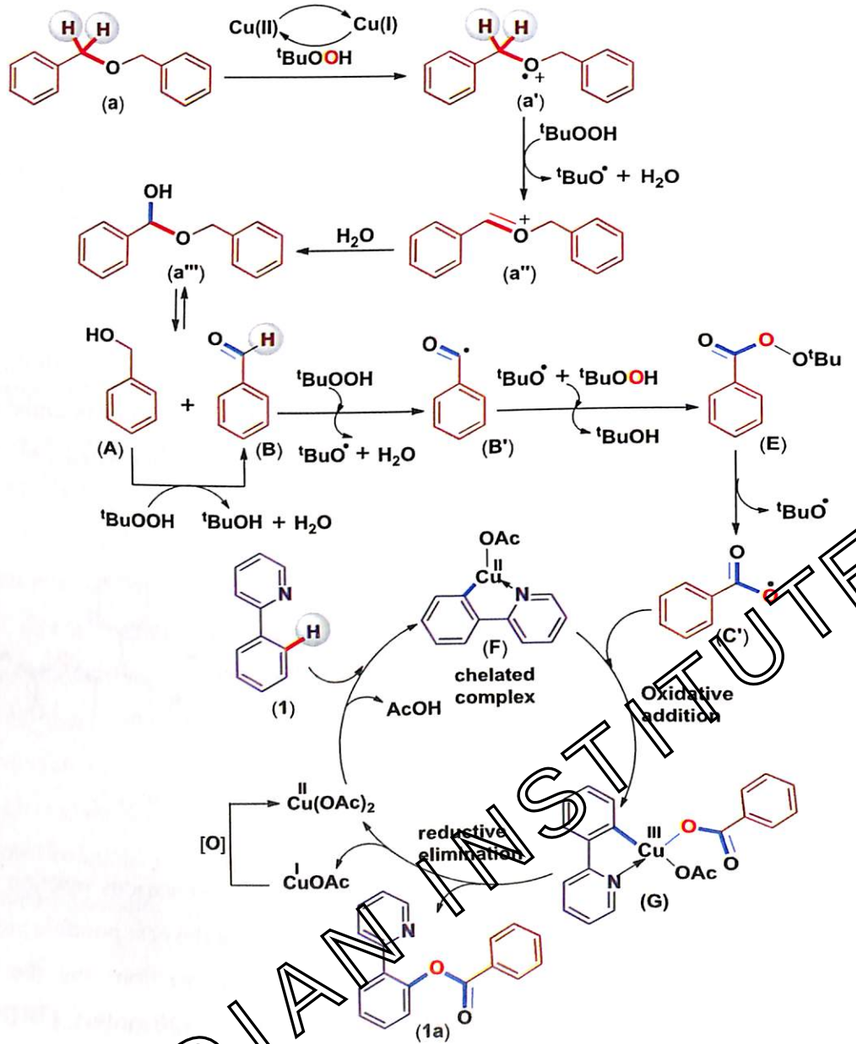

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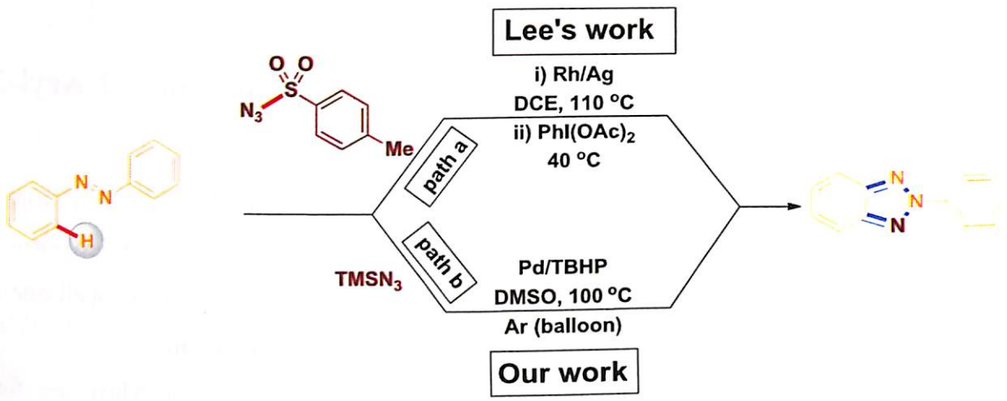
protocol as in Scheme 11, path a described by Lee group *via ortho* C–H activation of azobenzenes is elegant one, the use of an expensive combinations of catalyst $[Cp^*RhCl_2]_2$, co-catalyst $AgNTf_2$ and oxidant $PhI(OAc)_2$ make this method economically unviable. Thus, the development of an efficient, cost effective and atom-economic protocol is very much in need.

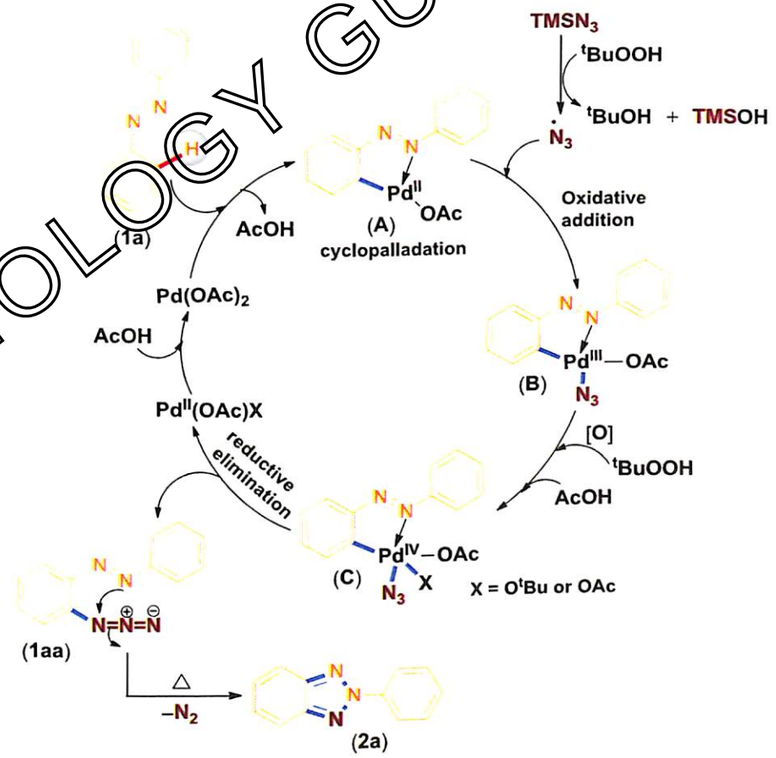
Herein we developed a palladium catalyzed methodology for the synthesis of 2-aryl-*2H*-benzotriazoles from azoarenes through *ortho* sp^2 C–H functionalization using $TMSN_3$ and TBHP as in Scheme 11, path b.



Scheme 11. Metal-catalyzed synthesis of 2-aryl-*2H*-benzotriazoles *via o-C-H activation*

Various reaction parameters such as catalyst, oxidant, additives, solvent and temperature were screened to obtain the optimal conditions for this reaction in a quest to attain the best possible yield. Finally it was found that the use of azobenzene (0.5 equiv.), $TMSN_3$ (2 equiv.), TBHP-decane (2 equiv.) in DMSO (1.0 mL) at 100 °C under argon atmosphere was used to be the best suitable conditions for the subsequent transformation. The optimized conditions were then applied to a range of substituted azoarenes to afford their corresponding *2H*-benzotriazoles. This protocol is found to be compatible with several functional groups having electron donating as well as electron-withdrawing substituents in aromatic ring of azoarenes. In general, azoarenes bearing electron-donating substituents provided better yields of their products compared to those bearing electron-withdrawing substituents. The higher yields obtained for electron-donating azoarenes could be attributed because of their better chelating ability with electrophilic Pd (II) catalyst.

Some controlled reactions were performed to deduce the plausible reaction mechanism for this transformation. Based on these results/observations of these experiments and taking cues from the recent literature precedent, a plausible mechanism has been proposed as shown in Scheme 12.

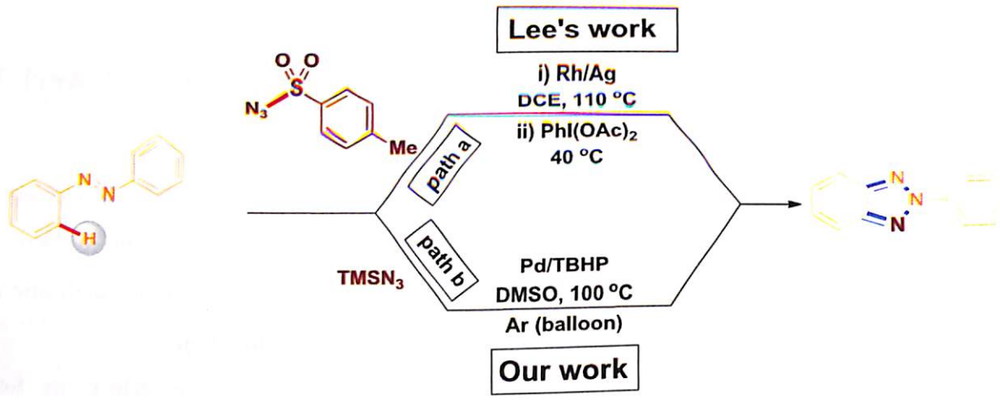


Scheme 12. Plausible mechanism for *ortho* aminative heterocyclyzation of azobenzenes

In summary, we have developed an efficient and regioselective protocol for the synthesis of 2-aryl-*2H*-benzotriazoles *via* Pd(II)-catalyzed *ortho* sp^2 C–H activation of azoarenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant. The ligand directed intermolecular azidation (C–N bond formation) through *ortho* sp^2 C–H functionalization of azobenzenes and sequential intramolecular cyclization (N–N bond formation) leads to the formation of 2-aryl-*2H*-benzotriazoles. For unsymmetrical azoarenes the heterocyclization is preferred at the aromatic ring rich in electron compared to electron neutral (-H) or electron-deficient aromatic rings. A wide range of substrate makes this method a suitable alternative to the existing alternative.

protocol as in Scheme 11, path a described by Lee group *via ortho* C–H activation of azobenzenes is elegant one, the use of an expensive combinations of catalyst $[Cp^*RhCl_2]_2$, co-catalyst $AgNTf_2$ and oxidant $PhI(OAc)_2$ make this method economically unviable. Thus, the development of an efficient, cost effective and atom-economic protocol is very much in need.

Herein we developed a palladium catalyzed methodology for the synthesis of 2-aryl-*2H*-benzotriazoles from azoarenes through *ortho* sp^2 C–H functionalization using $TMSN_3$ and TBHP as in Scheme 11, path b.



Scheme 11. Metal-catalyzed synthesis of 2-aryl-*2H*-benzotriazoles *via o-C-H activation*

Various reaction parameters such as catalyst, oxidant, additives, solvent and temperature were screened to obtain the optimal conditions for this reaction in a quest to attain the best possible yield. Finally it was found that the use of azobenzene (0.5 equiv.), $TMSN_3$ (2 equiv.), TBHP-decane (2 equiv.) in DMSO (1.0 mL) at 100 °C under argon atmosphere was used to be the best suitable conditions for the subsequent transformation. The optimized conditions were then applied to a range of substituted azoarenes to afford their corresponding *2H*-benzotriazoles. This protocol is found to be compatible with several functional groups having electron donating as well as electron-withdrawing substituents in aromatic ring of azoarenes. In general, azoarenes bearing electron-donating substituents provided better yields of their products compared to those bearing electron-withdrawing substituents. The higher yields obtained for electron-donating azoarenes could be attributed because of their better chelating ability with electrophilic Pd (II) catalyst.

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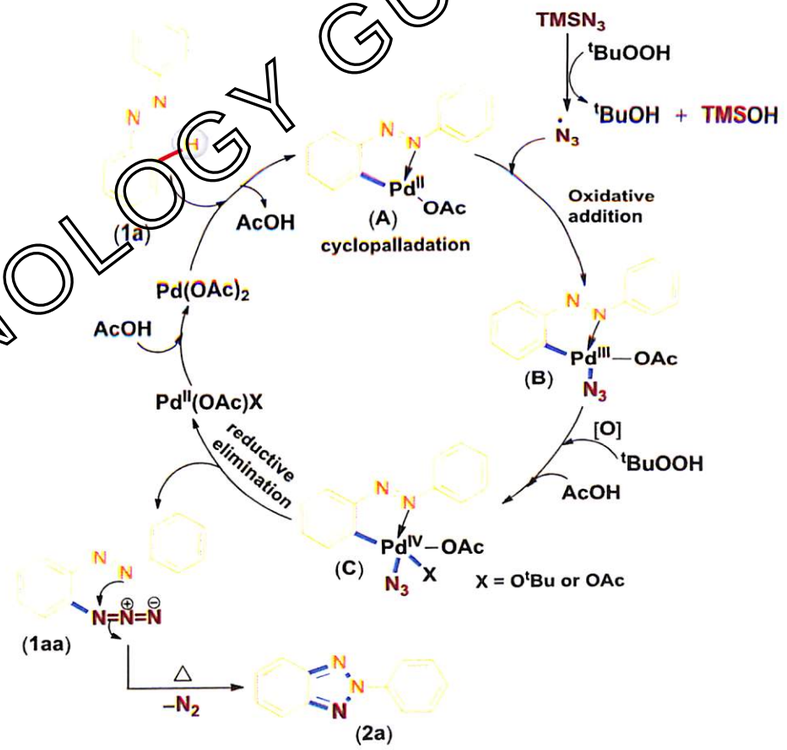

Scheme 12. Plausible mechanism for *ortho* aminative heterocyclyzation of azobenzenes

In summary, we have developed an efficient and regioselective protocol for the synthesis of 2-aryl-*2H*-benzotriazoles *via* Pd(II)-catalyzed *ortho* sp^2 C–H activation of azoarenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant. The ligand directed intermolecular azidation (C–N bond formation) through *ortho* sp^2 C–H functionalization of azobenzenes and sequential intramolecular cyclization (N–N bond formation) leads to the formation of 2-aryl-*2H*-benzotriazoles. For unsymmetrical azoarenes the heterocyclization is preferred at the aromatic ring rich in electron compared to electron neutral (-H) or electron-deficient aromatic rings. A wide range of substrate makes this method a suitable alternative to the existing alternative.

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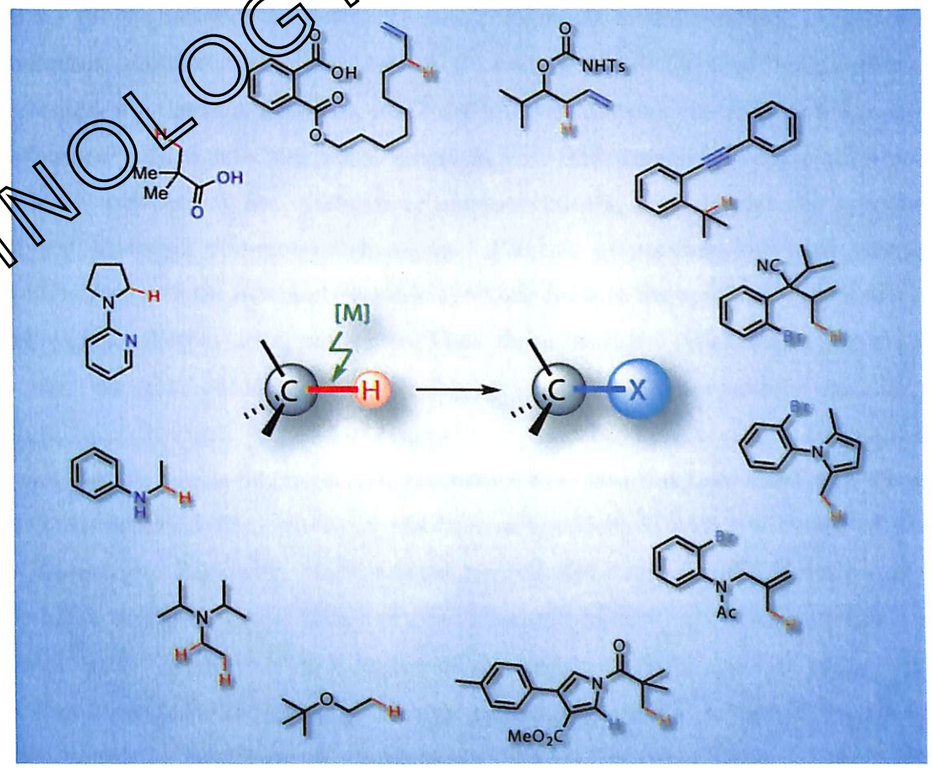
Chapter I

Introduction: A Brief Overview of Transition Metals-Catalyzed C–H Bond Functionalization



''C–H activation is at the center of organic chemistry''

Albert Eschenmoser, 2010

Chapter I

I. A Brief Overview of Transition Metal-Catalyzed C–H Bond Functionalization

I.1. Introduction

Metal-catalyzed organic synthesis has revolutionized the way to design retro-synthetic strategies for the synthesis of unachievable new compounds to the synthetic chemists. Among those strategies, carbon-carbon and carbon-heteroatom bond forming reactions *via* cross coupling, widely used in both academic and industrial worlds have emerged as the most reliable one.[1] Undoubtedly, such selective transformations will find widespread application across the chemical field, including in the synthesis of pharmaceuticals, natural products, agrochemicals, polymers and feedstock commodity chemicals.[2] The use of pre-functionalized substrates[3] in these methods provided the new and versatile synthetic tools to the synthetic chemists achieving the selective preparation of novel molecules. Thus, those strategies unleashed a fast and relevant progress over the past decades. The well known cross coupling reactions include Suzuki, Sonogashira, Stille, Kumada, Himaya or Negishi and others has been prevalent for many decades and allowed the use of pre-functionalized precursors over non-functionalized one. Recently, in 2010, the importance of these strategies has been acknowledged with the award of the Nobel Prize in Chemistry to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki. However, the use of those expensive and pre-functionalized or pre-elaborated molecules in those methods requires paying extra 'price' to achieve such degree of selectivity. In particular, the obligation to use activated pre-functionalized coupling partner is wasteful since it needs installation and subsequent disposal of waste agents. Furthermore, preparation and isolation of these expensive and pre-elaborated independent coupling partners added extra steps towards the formation of desired chemical bonds. Thus, those problems associated with pre-installation processes caused a major concern to the synthetic chemists in terms of atom-economic and environmental point of view. Due to these unavoidable reasons, over the last decades, the modern research has been directed in a quest to develop new processes aiming to achieve identical final molecules with the same selectivity, but in a greener and more sustainable way. In this aspect, probably the best and

most possible sustainable way to fulfill the mentioned demands is the direct functionalization of C–H bond utilizing non-functionalized precursors.[4]

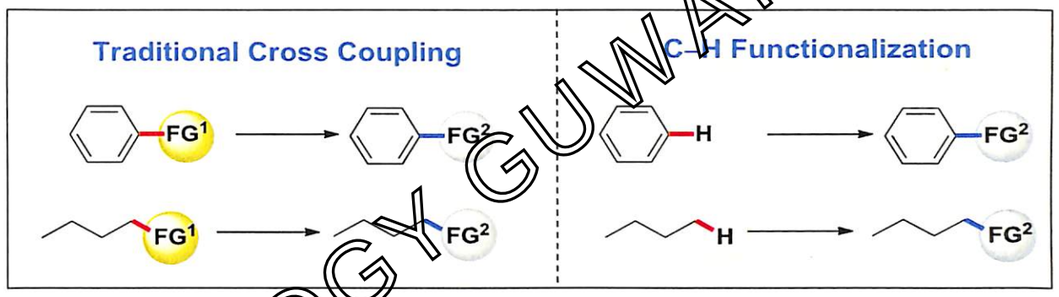
The C–H bonds are ubiquitous in organic molecules, from small molecule backbone to the more elaborated natural products with comparable dissociation energies and regarded as the non-functional group. Due to small difference in electro negativities between carbon and hydrogen, the C–H bonds are regarded as being non-polar. In structural formula of molecules, the hydrogen bonds are often omitted for clarity which indicates the ubiquitous nature and lack of reactivity *i.e.* 'inertness' of it towards the chemical reaction. So, it is easy to envisage that the selective and direct functionalization of C–H bond would bring a faster and more atom-economical synthetic approach. The use of C–H bond as a reactive coupling partner similar to C–M (M = metal) or C–X bond (X = halide/pseudohalide) would provide a powerful and straightforward strategies for the formation of complex organic structures. According to G. B. Shul'pin and A. E. Shilov, as reported in *Chemical Reviews*, 1997 "When we refer to 'the activation' of a molecule, we mean that the reactivity of this molecule increases due to some action.... It is reasonable to propose that to activate a σ-bond such as a C–H bond is to increase the reactivity of this bond toward a reagent".[5] This insight is expected to bring an incredible alteration in the blueprints of future synthetic routes to complex molecules since it provides a novel disconnection in retro-synthetic analysis. Furthermore, use of C–H bond as one of the functional groups in coupling reactions would be profitable in terms of operational simplicity, avoidance of pre-installation of starting materials, reduced waste generation and shorten the synthetic route.

I.2. Difference of Traditional Cross Coupling and C–H Functionalization

The traditional approach for the cross coupling reactions involves transformation of a pre-existing functional group with another one to obtain the desired chemical function as in Scheme I.2.1. Those functional groups *i.e.* reactive coupling partners are mainly introduced into the organic molecules by means of multi-step transformations.

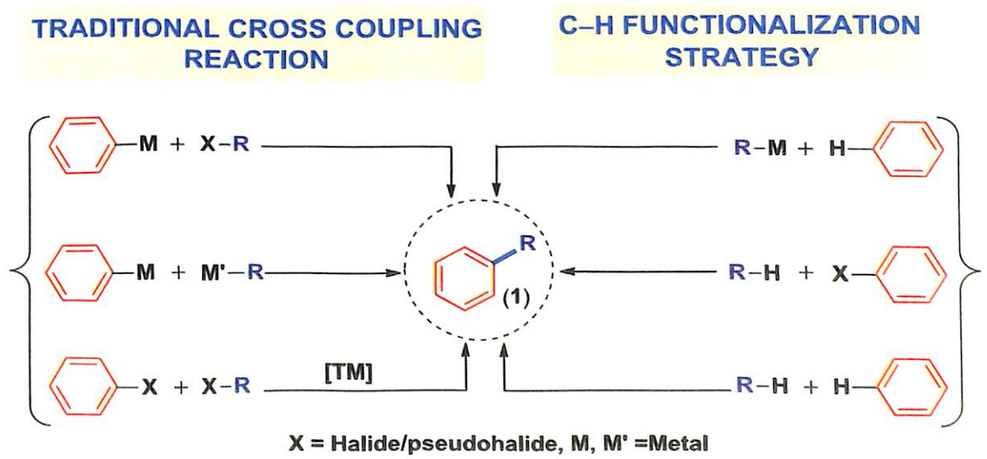
The classical cross coupling reactions typically involve either the coupling of an organometallic reagent with an aryl halide or another organometallic reagent for the synthesis of targeted bi-aryl compound (**1**) as shown in Scheme I.2.2, left side. Alternatively, the compound

(**1**) can be obtained by metal mediated homo coupling reaction of two aryl halides/pseudohalides (Scheme I.2.2, left side).



Scheme I.2.1. *Traditional cross coupling vs. C–H functionalization*

The requirements of those expensive and pre-elaborated functionalized substrates added extra steps in synthetic route. Moreover, many cross coupling reactions ended up with the generation of a stoichiometric amount of waste materials. While the same bi-aryl compound (**1**) may be accessed by utilizing unactivated C–H bond as one of the coupling partners (Scheme I.2.2, right side). As a substitute of reactive C–X and C–M bonds, the most precise one-step direct coupling of two carbon-hydrogen (C–H) bonds to form one C–C bond without disturbing the molecular environment brings a significant appeal for chemical synthesis. Although this process is unfavorable from a thermodynamic point of view due to the high bond strength of an aryl C–H bond. The homocoupling reaction of two benzene rings to give corresponding biphenyl compound and hydrogen is thermodynamically disfavored by 13.8 kJ/mol.[6]



Scheme I.2.2. *Different approximations of the cross coupling reactions (Traditional vs. Modern)*

From the above comparison study between traditional cross coupling and C–H functionalization strategy, it can be conclude that the C–H functionalization should be very advantageous because of the following reasons:

✓ The C–H bonds are ubiquitous in organic species, from natural feedstock to the more elaborated natural products

✓ No need of pre-functionalization of the starting materials, usually prepared in tedious multi-step process.

✓ Step, time and atom economical

✓ Cost effective and energy saving

✓ Considerable reduction in waste generation

I.3. Challenges in C–H Functionalization

In spite of all the advantages, the use of C–H bond as the coupling partner has few drawbacks due to its "own special properties". These reasons can be documented as-

❖ **Inherent low reactivity:** The reason of this chemical "inertness" arises from the constituent atoms in which all being held together by strong and localized C–C and C–H bonds. The strength of typical C–H bonds represents a first and very significant challenge in this area. Most of the cases involved C–H bonds are either sp^2 or sp^3 hybridized whose pK_a values are in the range of 30–35.[7c,8] Moreover, cleavage of those bonds involves energies of dissociation about 100 Kcal/mol.[7c,8] This 'intrinsic' high pK_a values and high bond dissociation energies (BDE) as well as their "paraffin" nature (as they possess neither low lying HOMOs nor high lying LUMOs), make C–H bonds completely inert to chemical reactions. The BDE and the pK_a values of various C–H bonds are given in Table I. 3.1.

Chemical bonds	Nature	BDE (Kcal/mol)	pK_a (water)
H_3C–H	Methyl C–H	105	48
C_2H_5–H	Ethyl C–H	101	50
CH_2=CH–H	Vinylic C–H	111	44
HC≡C–H	Acetylenic C–H	133	25
C_6H_5–H	Phenylic C–H	113	43
CH_2=$CHCH_2$–H	Allylic C–H	89	43
C_6H_5–CH_2–H	Benzylic C–H	90	41

Table I.3.1. *Bond dissociation energy and pK_a values of various C–H bonds*

❖ **Regioselctivity:** The own ubiquity of the C–H bonds can be a problem if several C–H bonds are amenable to activation at the same time.[7a] Therefore, designing a strategy that selectively functionalize a single C–H bond keeping all others C–H bonds as intact within a complex molecule remains a second critical challenge in this field. For example, the indol derivative as shown in Figure I.3.1 contains two different types of C–H bonds (H_a and H_b) in its fused five-membered ring. A site selective strategy for the activation of one of them leads to the higher degree of selectivity.

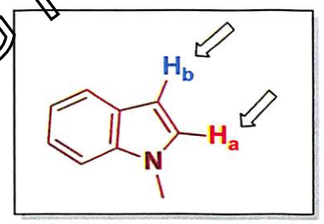
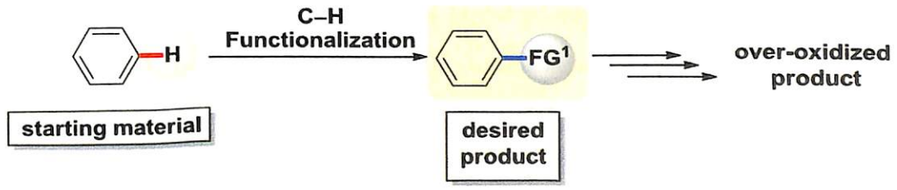


Figure I.3.1. *Indole molecules with multiple numbers of different types of C–H bonds*

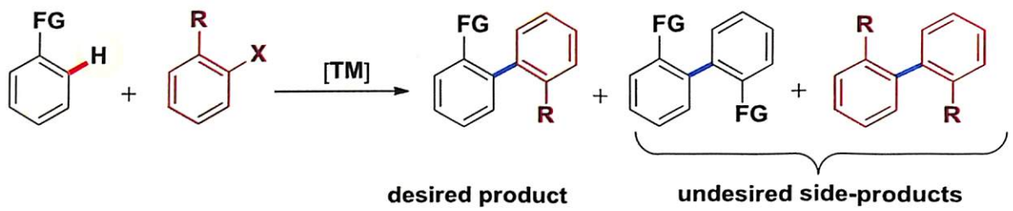
❖ **Chemoselectivity:** The inability to stop functionalization process at required oxidation state to obtain the desired functionalized product represents third major challenge in this area.[7a] This problem arises due to the formation of more reactive functionalized product than the starting material. In such cases, the functionalized product may prone to undergo further oxidation (Scheme I.3.1). This fact leads to the formation of undesirable product or mixture of products and hence diverges from the actual goal. Though the over-oxidation of starting precursor or desired products is often highly thermodynamically unfavourable.



Scheme I.3.1. *Chemoselectivity problem arises in C–H bond functionalization process*

❖ **Stereoselectivity:** The functionalization of C–H bond of a molecule in a highly diastereoselective and/or enantioselective way for the construction of new stereogenic centre creates a fourth challenge in this field.[7a]

❖ **Homo-coupling reaction of active partners:** A minor issue arises due to the self-coupling reaction of the reactive coupling partners present in a metal-catalyzed C–H functionalization strategy. As a result, the desired product obtained in a lower yield because of such homo-coupling reaction which make the coupling partners unavailable for desired transformation (Scheme I.3.2).



Scheme I.3.2. *Homo-coupling issues in C–H bond functionalization process*

In spite of those challenges, a C–H functionalization strategy also suffers from a minor issue which arises due to the preservation of the certain existing functional moieties in starting precursors. However, the fundamental challenges in C–H functionalization that need to be addressed are: (i) increase of **reactivity** of inert C–H bonds; (ii) the requirement to control **site selectivity** in molecules that contain diverse C–H bond amenable to functionalization; (iii) **chemoselectivity** and (iv) **stereoselectivity.**

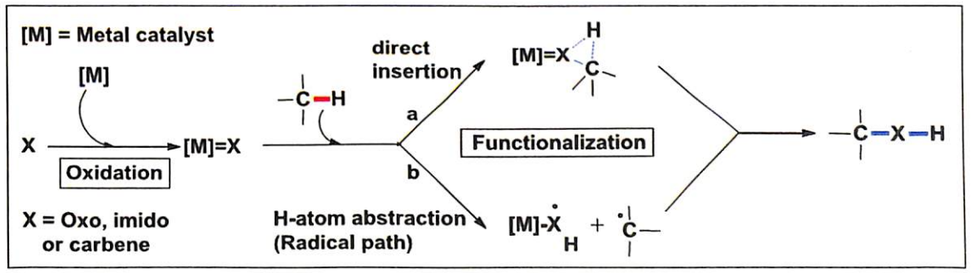
I.4. Solution to the Challenges in C–H Functionalization

- **I.4.1. Solution to inherent low reactivity of C–H bond:** The first challenge *i.e.* "inertness" of C–H bonds due to their high bond dissociation energy has been addressed and settled by the use of transition metals catalyst.[7a] A multitude of studies demonstrates that metals catalyst can react with C–H bonds and help to lower the activation energy for bond dissociation. The high bond dissociation energy of C–H bonds most probably is compensated by metal-organic bond interactions.

Depending on the different types of interactions, the transition metal-catalyzed C–H functionalization can be classified into two different categories: (A) Outer sphere mechanism or coordination chemisty and (B) Inner sphere mechanism or organometallic chemistry.[7]

(A) Outer sphere mechanism/coordination chemisty

The 'outer-sphere' mechanism for C–H bonds functionalization follows the mimic strategy of biological oxidation reactions catalyzed by enzymes such as cytochrome P450 and methane monooxygenase (MMO). This mechanism proceeds *via* formation of a metal complex with high oxidation state which possessing an activated ligand X. This X is typically a metal oxo-, imido- or carbene species. In the next step, this complex then interacts with a C–H bond through ligand X (Scheme I.4.1.1). The latter step can proceed by either direct insertion of C–H bond (Scheme I.4.1.1a) or an independent H-atom abstraction (radical path) by the metal complex (Scheme I.4.1.1b). The main characteristic feature of such type of mechanism is that the C–H bond of substrate does not involve in direct interaction with the transition metal center, instead reacts with a coordinated ligand. As can be seen from the Scheme I.4.1.1, these transformations produce radical and/or cationic character at carbon, and therefore particularly show high selectivity for weaker C–H bonds such as C_{sp^3}–H bonds.

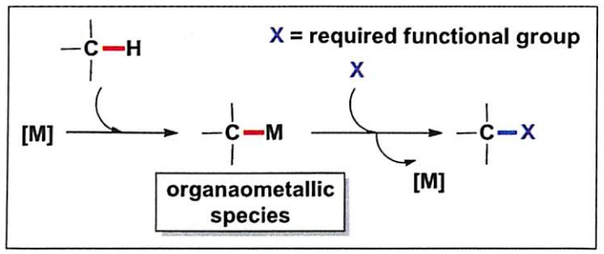


Scheme I.4.1.1. *C–H functionalization through outer sphere mechanism*

(B) Inner-sphere mechanism/organometallic chemistry

The 'inner-sphere' C–H bond functionalization mechanism follows two discrete steps: (i) the first step involve cleavage of a C–H bond to form a transition metal alkyl/aryl species *i.e.* organometallic species and (ii) in the next step, this *in situ* generated organometallic species can be converted to a new functional groups by reaction with either an external reagent or an organyl ligand attached to the metal center (Scheme I.4.1.2). The main characteristic feature of this mechanism is the construction of a distinct organometallic intermediate. The high bond

dissociation energy of C–H bond is most probably compensated by the formation of organometallic intermediate *i.e.* formation of C–M bond and more often this species is far more reactive than their initial counterpart. The structural and electronic parameters of this active intermediate further dictate the regio- and stereoselectivity of functionalization. More often these transformations showed strong influence to activate the less sterically hindered C–H bonds of a molecule, thus maintaining a high selectivity. Apart from these factors, the ligand environment at the metal center and the concerned mechanism involved in the C–H bond cleavage step also help to control selectivity in these systems.



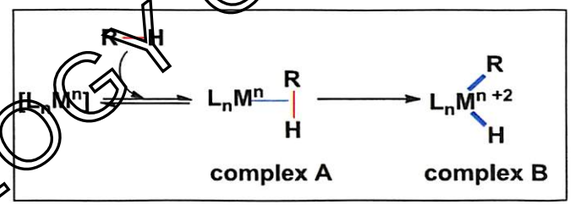
Scheme I.4.1.2. *C–H functionalization through inner sphere mechanism*

Depending on the nature of C–H bonds, transition metal catalyst, ligand sphere (L_n) at the metal center, solvent and additives, the inner sphere mechanism can be sub-classified in five catagories,[8] including (a) oxidative addition, (b) sigma bond metathesis, (c) electrophilic activation, (d) metalloradical activation and (e) 1,2-addition. Among these, first three are quite common while remaining two is rare in C–H functionalization strategy. All the sub-classified mechanisms involve a "true" activation of C–H bond due to the close proximity and direct interaction of the metal ion and the C–H bond, resulting in a discrete organometallic species in a form of "true" σ C–M bond. In this activation process, a C–H bond directly penetrates the coordination region of the metal centre as a σ-organyl ligand.

(a) Oxidative addition

In organometallic chemistry, the 'oxidative' addition is the addition of a X–Y bond to a metal centre. This addition is usually facilitated by the higher electron dense metal centre attached to the σ donar ligand such as R_3P. oxidative addition is typical for late transition metal complexes generally found in the right side of the periodic table such as Re, Fe, Ru, Os, Rh, Ir and Pt. In this mechanism, electron rich and the low valent metal complexes can easily

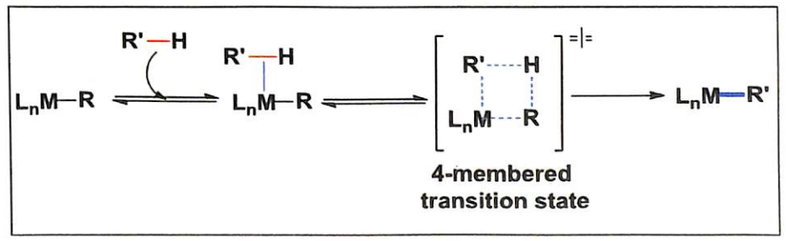
coordinate to a σ C–H bond by donating its electron density to the vacant σ* orbital (Scheme I.4.1.3, complex A). Such interactions thus weaken the σ C–H bond and lead to the formation of new σ C–M bond (*i.e* formation of an organometallic species) by cleaving the original C–H bond (Scheme I.4.1.3, complex B). Since the two previously non-bonding electron of metal are being used for the formation of new bond, the oxidation state of metal centre formally increased by two units. This process is comparable to the formation of Grignard reagents from alkyl halide and Mg



Scheme I.4.1.3. *C–H functionalization through oxidative addition*

(b) Sigma bond metathesis

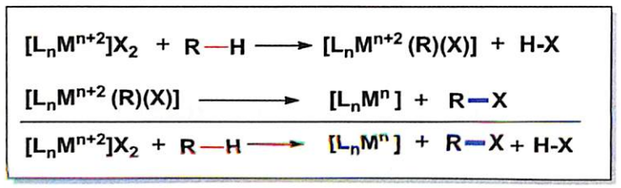
Such reversible reaction is typical for "early" transition metal complexes with d^0 electronic configuration. Transition metal complexes which fail to attain oxidative addition due to lack of accessible (n + 2) oxidation state are suitable for such reactions. These metals are most commonly found in group 3 of the periodic table such as scandium, lanthanides and actinides, but some typical examples involving metals of groups 4 and 5 are also being reported. This activation mechanism allows the formation of an organometallic species as intermeadiate having a σ C–M bond. This reaction occurs via a concerted σ C–H bond cleavage and involves a four-membered transition state as shown in Scheme I.4.1.4.



Scheme I.4.1.4. *C–H functionalization through* σ-bond metathesis

(c) Electrophilic activation

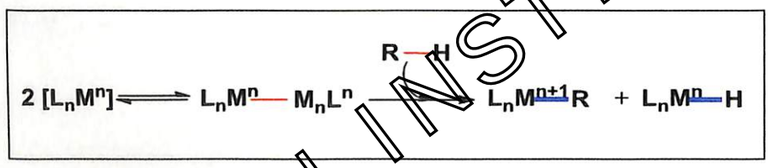
Late transition-metal in higher oxidation state such as Pd^{+2}, Pt^{+2} and/or Pt^{+4}, Hg^{+2} and Tl^{+3} complexes can take part in such reaction. Electrophilic activation of an aromatic nucleus can occur through an Electrophilic Aromatic Substitution reaction which proceeds in two stages. In the first stage, the addition of the electrophilic species to the arene leads to the formation of a Wheland intermediate (an arenium intermediate) while in the next step there is a loss of proton. Alteratively, the same activation can occur through deprotonation of a C–H sigma complex, similar to sigma bond metathesis when the base is halide but not when the base is –OAc, as it then occurs through a six membered transition state.



Scheme I.4.1.5. *C–H functionalization through electrophilic addition*

(d) Metalloradical activation

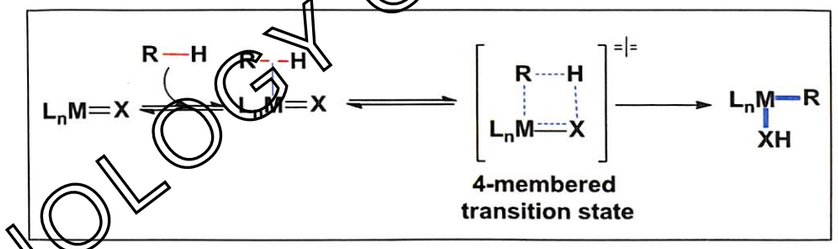
This mechanism is typical for the activation of σ C–H bond of saturated hydrocarbon (alkane) only. Transition metal complexes existing in monomer–dimer equilibrium in a reaction can reversibly break alkane C–H bond and form two separate halves of metal complexes attached to the two fragments of C–H bond. As shown in Scheme I.4.1.6, the cleavage of metal-metal bond during the reaction leads to the formation of one σ-organyl complex and one metal hydride. Methane is the most reactive hydrocarbon for this class of reaction. Usually rhodium and ruthenium complexes are utilized for such activation reactions.



Scheme I.4.1.6. *C–H functionalization through metalloradical activation*

(e) 1,2-Addition

1,2-Addition reactions involve the addition of a σ C–H bond to a metal-nonmetal double bond. In a typical example, addition of a σ C–H bond across the M=X double bonds leads to the formation of a true σ-organyl complex *via* a four-membered transition state (Scheme I.4.1.7). Usually early and middle transition metals meet these criteria, though the scope of the reaction and its potential application for alkane C–H bond functionalization remains unclear.



Scheme I.4.1.7. *C–H functionalization through 1,2-addition*

I.4.2. Solution to regioselectivity in C–H functionalization: This problem arises due to the presence of a multiple and unique C–H bonds in a molecule. A number of approaches have been developed by synthetic chemists to address this problem including (a) the use of "innate" functionality of a molecule and (b) the use of covalently or fleetingly bound coordinating (chelating) ligands within a substrate as directing groups, (c) the use of substrates possessing comparatively weaker or activated C–H bonds such as 3° or benzylic/allylic systems, (d) carrying out intramolecular functionalization *via* thermodynamically favourable five- or six-membered transition states, (e) utilization of supramolecular chemistry to dictate a specific C–H bond close to the catalyst active site and (f) the use of the different transition metal catalysts or ligands to control the differential selectivity. Among those approaches mentioned above, first two are the most important and popular in this field, which are elaborated below:

✓ **I.4.2a. "Innate" functionality of a molecule:** In principle, every molecule possesses a natural reactivity based on its steric and electronic biases, which dictates the C–H functionalization to a specific position in the absence of other directing forces. The functionalizations of various heterocycles and substituted arenes in a selective way due to the different distribution of electron density in molecular cores are the archetype example of this "innate" property.[9] The specific positions of regioselective C–H functionalization by the attack

of nucleophiles (Nu) or electrohiles (E) of some representative molecules are shown in Figure I.4.2.1, indicated by arrow sign. For instances, C-2 position of pyrrole and C-3 position of indole are the susceptible sites.

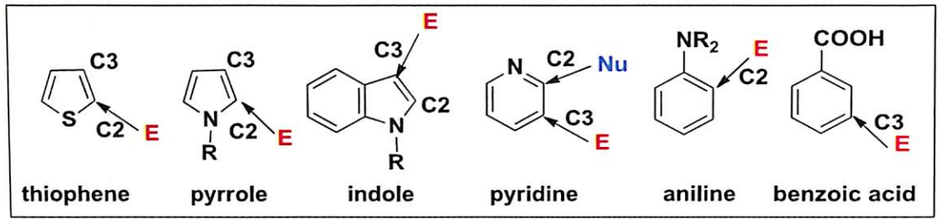


Figure I.4.2.1. *Regioselective C–H functionalization via "innate" functionality*

✓ **I.4.2b. Influence of the directing groups**: The selective functionalization of C-3 position of pyrrole or C-2 position of indole (as shown in Figure I.4.2.1) have to be "directed" or "guided" by some external forces, because these positions of those molecules are not accessible due to above mentioned inherent property *i.e* "innate" reactivity. This "directed" approach must be considered as a complementary task to that of natural positions, since in this way all targeted positions of a given molecule could be functionalized. A number of strategies have been developed to achieve a directed functionalization utilizing different functional groups with active donar atoms such as *N*, *O*, *P*, *S*, *Se* and *Si* etc. These donar atoms are capable enough to coordinate even weakly[10] with the metal centre. Such interaction assists the substrate to penetrate into the coordination sphere of metals and leads to the formation of a coordinated complex. The substrate that is functionalized serves as one of the organyl ligand. In this way, once the substrate is coordinate to the metal centre, instead of whole molecule, only few distinct positions of the substrate fall in the close vicinity of the metal and hence only selected C–H bonds would be activated. The resulting cyclometallated complex,[11] usually a five- or six-membered ring, serves as versatile intermediate to afford functionalized product bearing new C–X (X = C or heteroatoms) bonds. As these functional groups dictate the metal to bind at the specific position of the substrate, they are properly called as "directing groups" (DG) and whole strategy is known as "coordination-directed metallation" or "directing group-assisted C–H functionalization".[12] This strategy drastically restricts the number of C–H bonds could be functionalized and the final products obtained with a high degree of selectivity. This protocol is compatible well with a variety of transition metals with a combination of different oxidants or even under oxidant free

condition. However, most widely used transition metals for directed functionalization are Pd, Ru, Rh and Cu; though the other transition metals such as Mn, Fe, Co, Ni, Re, Ir, Pt, Ag and Au are also frequently used. Some typical directing groups generally employed for the directed functionalization are as shown in Figure I.4.2.2.

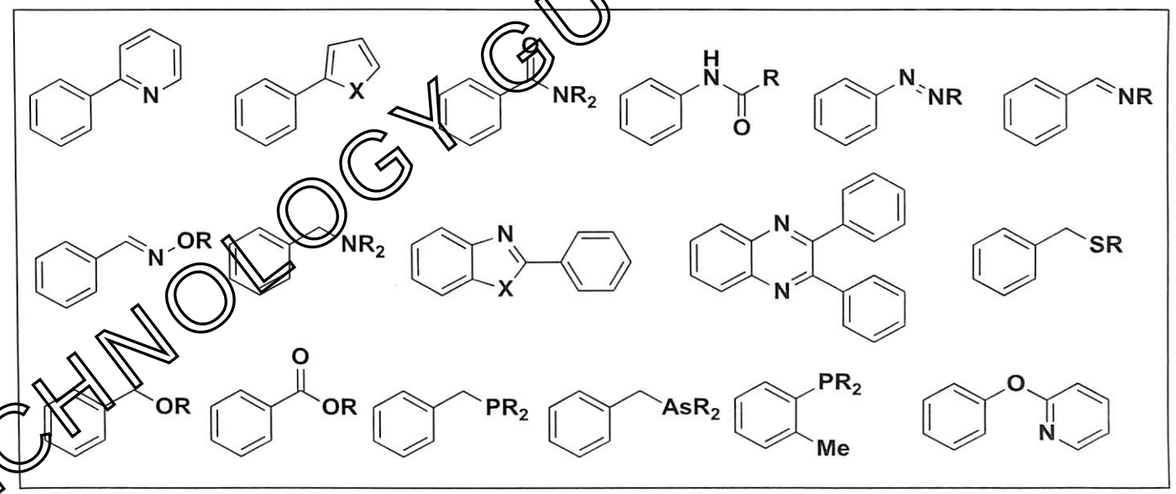


Figure I.4.2.2. *Selected functional moieties used as potential directing groups*

❖ **Advantages, limitations and corresponding solutions of utilizing directing groups:**

Advantages:

✓ Dictate the transition metal to bind at the specific position of the substrate to be functionalized

✓ Higher degree of regioselectivity achieved in functionalized product

Limitations:

- In most of the cases, the functionalizations are restricted to *ortho* position with respect to directing groups. For instance, an unlimited number of functional moieties which are shown in Figure I.4.2.2, typically utilized as the *ortho* directing groups in the presence of transition metals catalyst.
- In most cases, an external oxidant is generally required to regenerate the catalyst
- Some typical good directing groups such as pyridines or other chelating cores need additional synthetic steps for their pre-installation as well as their removal, once the selective C–H bond functionalizations were done. It is easy to envisage that these chelating cores are no longer

necessary after the functionalizations. However, in many cases these efficient cores cannot be removed easily and continued to remain as the integral part of the substrates. Moreover, they are resistance to undergo further functionalization.

Solution to above limitations:

✓ Over the past three decades, a number of elegant principles and tactics have been established for achieving *ortho* selective C–H functionalization. But when the targeted C–H bond maintains a specific distant from existing functional groups brings a significant challenge to the synthetic chemists. In logical sense, the functionalizations of such C–H bonds will lead to a distinct structural diversity. The formation of a thermodynamically favourable five- or six membered cyclometalled complex permits competent *ortho* C–H functionalization reactions. However, development of remote C–H functionalization reactions suffers from the difficulty in attaining a cyclometalled complex larger than six-membered rings. Yet, a number of especially designed (template-based) functional moieties which permit *meta* C–H functionalization reactions are developed in recent years as shown in Figure I.4.2.3.[13]

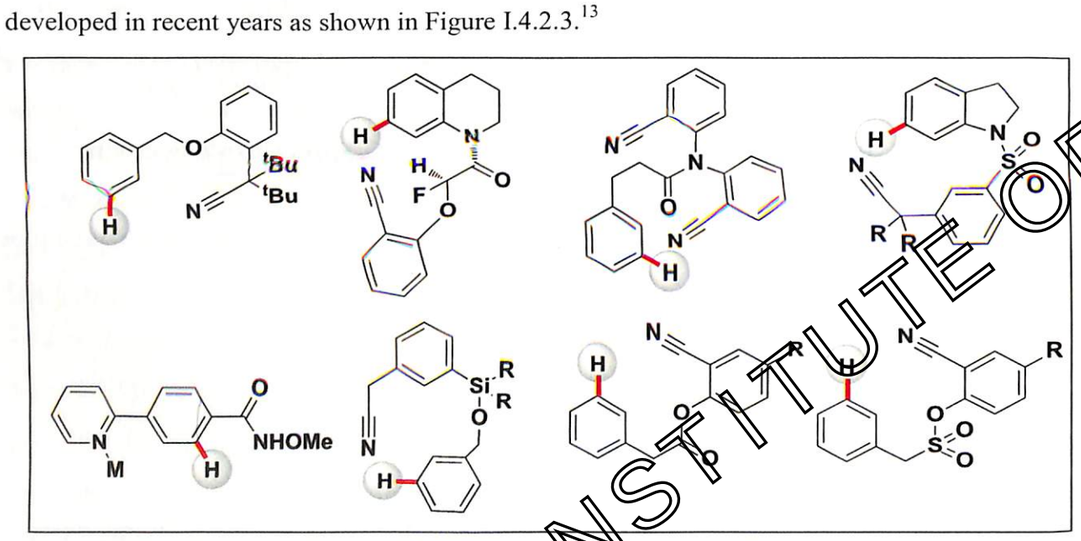


Figure I.4.2.3. *Template based potential meta directing groups*

✓ To avoid the use of non-convertible functional groups and to achieve a high level of atom economy by minimizing waste generation, some multi-functional directing groups have been developed. Those directing groups execute additional role along with their directing/guiding ability such as "built-in oxidant". Those directing groups contain a covalent bond which is

responsible for the oxidation of metals centre and thus circumvent the exploitation of external oxidants in those C–H functionalization processes. In literature, typically N–O bonds[14] in keto oxime, *N*-alkoxybenzamide and pyridine-*N*-oxide have been employed to function as internal oxidants which are shown in Figure I.4.2.4.

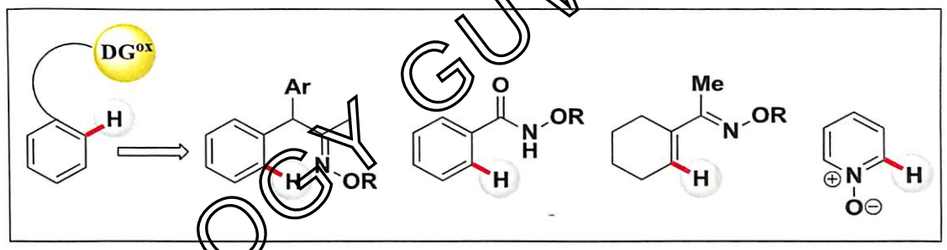


Figure I.4.2.4. *Potential directing groups with internal oxidants*

✓ The use of "traceless" functional groups as potential directing moieties in C–H functionalization processes fulfils another multi-tasking character of directing groups. In this case, the total functional group or part of it, is removed from the rest of the molecule by treating with other external reagents, once the desired orientation/functionalizations were achieved. For instance, a cutting-edge advance have been achieved by utilizing silanols,[15a] ketooxime ether,[15b] 2-pyridylsulfonyl,[15c] carboxylates,[15d,e] and aminated boron compounds[15f] as traceless directing groups in this field as shown in Figure I.4.2.5.

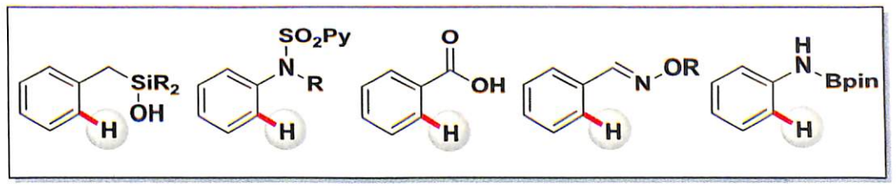


Figure I.4.2.5. *Example of some traceless directing groups*

✓ Apart from those, some multi-tasking functional groups are also designed which have capabilities of guided/directed C–H functionalizations as well as the insertion abilities into the final molecules at the end of the reactions. Thus, such protocols represent the most excellent example of atom economy as nothing or almost nothing fragment is lost during the reactions.[16]

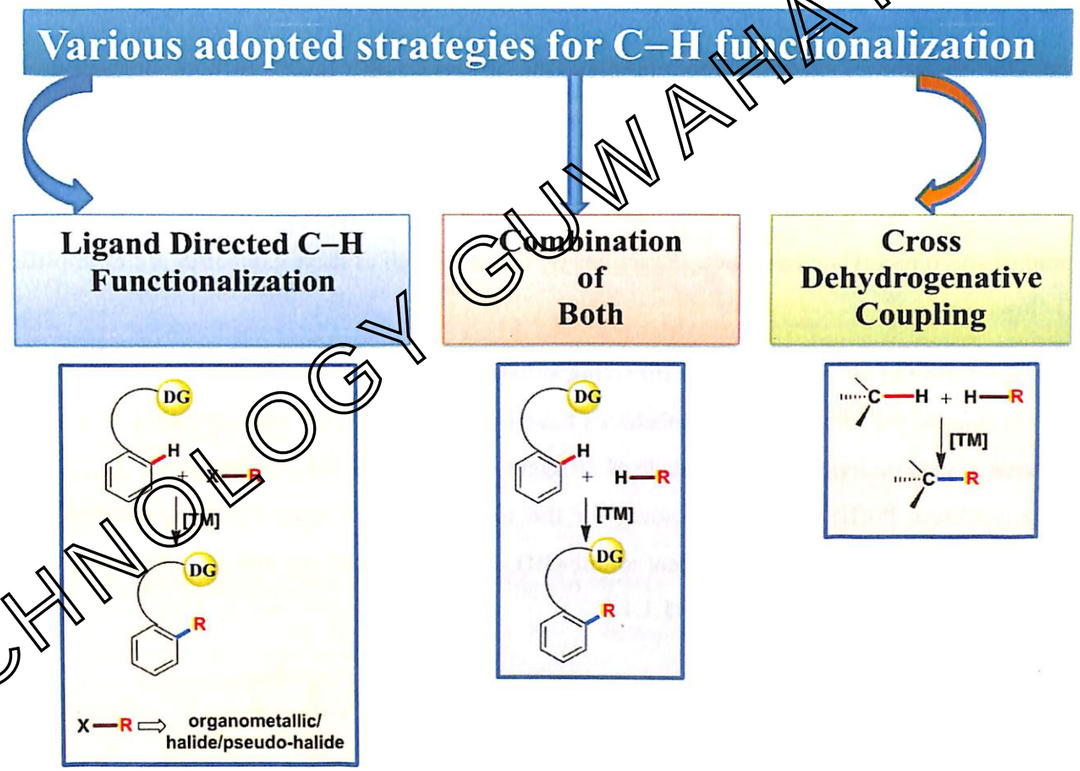
➢ **I.4.3. Solution to chemoselectivity in C–H functionalization:** A number of strategies have been developed to overcome the problems associated with chemoselectivity,[7a] including: (i) running the reactions for shorter time, (ii) using large excesses of substrate with respect to oxidant, (iii) preferences for intra- molecular functionalization rather than intermolecular, (iv) kinetically blocking the over-oxidation by pre-installing a deactivating functional groups and (v) catalyst selection and design.

➢ **I.4.4. Solution to stereoselectivity in C–H functionalization:** This problem has been least explored till date. Though the use of substrates possessing pre-installed stereocenters or chiral auxiliaries (substrate-based approach) as well as the use of chiral transition metal complexes (catalyst-based approach) has been developed recently to address this issue.[7a] Apart from those, a stereospecific oxidative functionalization of C–H bonds at existing stereo-centers leads to the formation of new chiral molecules and provides an additional attractive approach in this field.

I.5. An Array of C–H Functionalization

Though several enzymes such as cytochrome P450 and methane monooxygenase have been performing C–H functionalization for the several billion years, laboratory bench-work for C–H functionalization started as early as the end of nineteenth century. Early 1990's can be assigned as the 'golden era' of C–H functionalization because from that time onwards an unstoppable rush has been started in metal-catalyzed direct C–H functionalizations.

A number of metal salts and complexes were found to activate the inert C–H bonds and leading to the formation of a myriad of new organic compounds. Such achievement in this field may be regarded as the major advances in synthetic organic chemistry in the first decades of 21st century. The discovery of the new and efficient catalytic protocols boosted this field day by day. Based on strategies utilized for the C–H functionalization, it can be classified into two major categories including (i) directing group-assisted C–H functionalization/coordination metallation and (ii) cross-dehydrogenative coupling (CDC). In addition, the combined protocol of these two aforementioned approaches also utilized in many cases.



Scheme I.5.1. *Various adopted strategies for C–H functionalization*

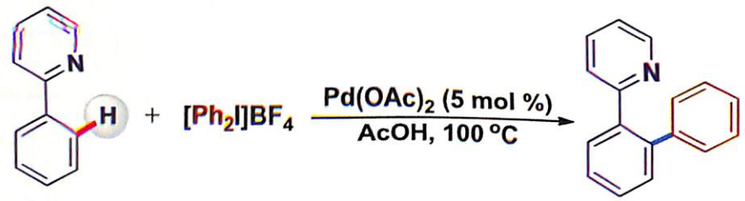
I.5.1. Directing group-assisted C–H functionalization: Directing group-assisted metallation[17] is one of the powerful tools for C–H functionalization which removes the regioselectivity problems by drastically reducing the number of amenable C–H bonds present in a molecule. The revolutionary aspect of this concept is gradually renovating organic chemistry and brings a renaissance with newer disconnection approaches giving opportunity to access desired molecules. As a consequence, the last decade has seen an unprecedented growth of interest to develop synthetic methods utilizing C–H bonds activation strategies in coupling chemistry. This is one of the best ways to activate C–H bonds by metal catalyst for the construction of C–C, C–N, C–O and C–X (X = halogen/boron/silicon/phosphorous) bonds.

I.5.1.1. Representative example of C–C bond forming reactions

Construction of carbon-carbon (C–C) bonds provides the most essential linkage in the organic precursors. Thus, transition metal-catalyzed formation of C–C bonds *via* ligand directed C–H activation has become the most striking area in this field. Typically such reactions were performed to afford *ortho*-arylated, alkylated, alkenylated, alkynylated, carbonylated, cyanated and trifluoro methylated products. Reactions pertinent to each of these categories are exemplified below:

✓ **Arylation of sp^2 C–H bond of directing substrates**

A number of robust directed substrates have been *ortho* arylated successfully with a proper source of aryl moieties in the presence of different oxidants. In 2005, Sanford group developed a regioselective Pd(II)-catalyzed protocol for the sp^2 C–H arylation of 2-phenylpyridines using stoichiometric amount of hypervalent iodine-(III) reagent $[Ph_2I]BF_4$ as aryl source as well as the oxidants[18a,b] as shown in Scheme I.5.1.1.1.



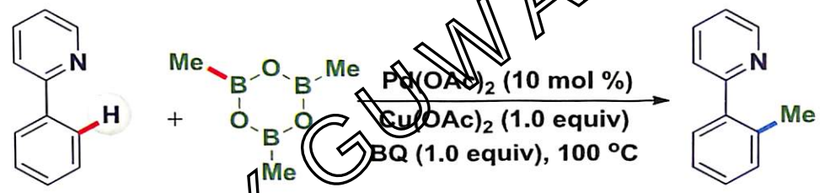
Scheme I.5.1.1.1. *Pd-catalyzed arylation of 2-phenylpyridine using $[Ph_2I]BF_4$*

While Wu[18c] and Daugulis[18d] group independently utilized aryl iodides in Pd(II)-catalyzed arylation of the same directed substrate. A similar *ortho* arylation strategy utilizing aryl iodide has also been successfully applied to other directing substrates such as benzamides,[19a] anilides,[19b] carboxylic acids,[19c] benzyl amines,[19d] benzoxazoles,[19e] amides[19f] and oxime ether.[19g] Other reagents such as aryl chlorides,[19c] arylboronic acids,[20a,b] aromatic acyl peroxides,[20c] organo tin,[20d] and aromatic sillyl ethers[20e,f] also served as effective aryl sources for sp^2 C–H arylation.

✓ **Alkylation of sp^2 C–H bond of directing substrates**

As early as 1984, Tremont group disclosed a Pd(II)-catalyzed efficient protocol for the *ortho* alkylation of acetanilide with alkyl iodides.[21a] In 2006, Yu Group developed a palladium-catalyzed alkylation protocol for 2-phenylpyridine with methylboroxine.[21b] The combination of

$Pd(OAc)_2$, $Cu(OAc)_2$ and benzoquinone provided a promising solution for the alkylation of sp^2 C–H bonds as in Scheme I.5.1.1.2.

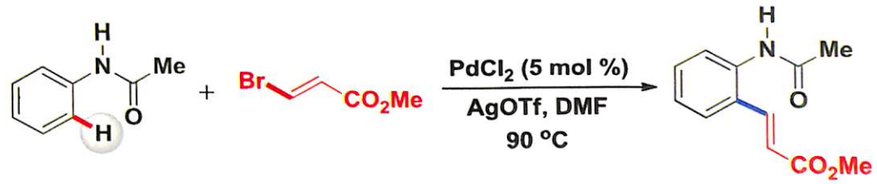


Scheme I.5.1.1.2. *Pd-catalyzed alkylation of 2-phenylpyridine with methylboroxine*

Apart from those, tetra alkyl organotin,[21c] alkylboronic acids,[21d] alkyl iodides or bromomides[21e] and dicumylperoxide[21f] were used successfully as active alkylating precursors for the alkylation of directing substrates.

✓ **Alkenylation of sp^2 C–H bond of directing substrates**

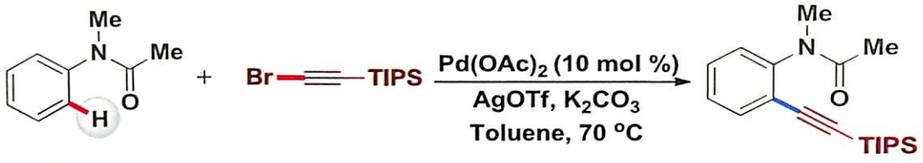
Daugulish and co-workers described a Pd(II)-catalyzed interesting protocol for *ortho* alkenylation of *N*-acylated or *N*-pivaloylated anilines using 3-bromo acrylates as the alkene/vinyl sources (Scheme I.5.1.1.3).[22a] In another work, alkenyl ethers and esters were also used as efficient vinyl source in Ru-catalyzed *ortho* C–H functionalization of 2-phenylpyridines.[22b]



Scheme I.5.1.1.3. *Pd-catalyzed alkenylation of amides with 3-bromo acrylates*

✓ **Alkynylation of sp^2 C–H bond of directing substrates**

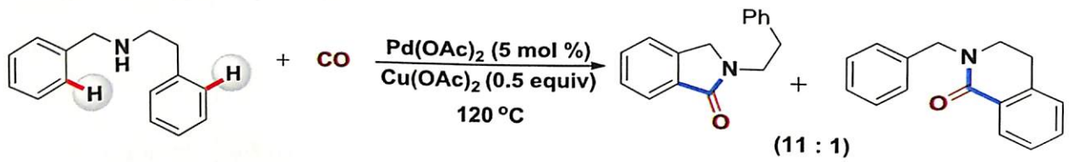
Palladium-catalyzed sp^2 C–H alkynylation of directed substrates are limited, only a handful of reports have been documented in literature. In a work, Chatani group demonstrated a Pd(II)-catalyzed *ortho*-alkynylation of anilide using pre-activated silyl-protected (TIPS) bromoalkynes as the coupling partners (Scheme I.5.1.1.4).[23a] Almost similar protocols have been developed for the *ortho* alkynylation of amides containing 8-aminoquinolines as auxiliary[23b] and 2-phenylpyridines using Pd and Ru catalyst respectively.[23c]



Scheme I.5.1.1.4. *Pd-catalyzed alkynylation of amides with TIPS-bromoalkynes*

✓ **Carbonylation of sp^2 C–H bond of directing substrates**

In 2004, Orito group developed a $Pd(OAc)_2$ catalyzed intriguing protocol for the carbonylation of *N*-alkyl-ω-arylalkylamines under CO atmosphere affording the corresponding benzolactum under mild conditions (Scheme I.5.1.1.5).[24a]

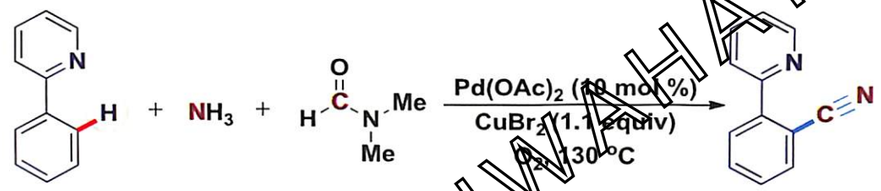


Scheme I.5.1.1.5. *Ortho carbonylation of benzylated amine with carbonmonoxide*

Ortho carboxylation of the other directed substrates using CO as carbonyl sources also have been achieved by several groups leading to the formation of *ortho*-amides,[24b] acids[24c] or esters[24d] derivatives. In a recent work, diethyl azodicarboxylate (DEAD) has been utilized as the carbonyl source in lieu of obnoxious and toxic CO for ethoxycarbonylation of 2-phenylpyridines, amides and oxime erthers using $Pd(OAc)_2$/oxone catalytic system.[24e]

✓ **Cyanation of sp^2 C–H bond of directing substrates**

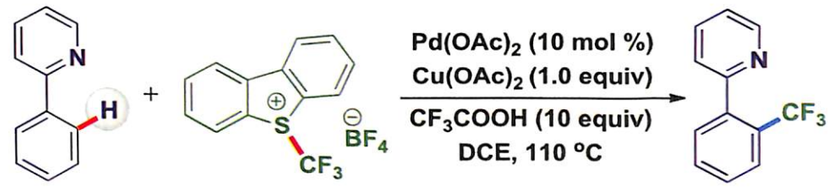
Chang group recently demonstrated that a combination of *N*,*N*-dimethylformamide and ammonia under Pd/Cu catalytic condition can serve as "cyano" (CN) unit for the cyanation of *ortho* C–H of 2-phenylpyridine derivatives in an oxygen atmosphere as in Scheme I.5.1.1.6.[25a] A variety of other cyanating reagents such as copper cyanide (I),[25b] potassium ferricyanide[25c] benzyl nitrile,[25d] acetonitrile,[25e] AIBN,[25f] *tert*-butyl isonirile[25g,h] and *N*-cyano-*N*-phenyl-*p*-methyl-benzenesulfonamide (NCTS)[25i] have also been employed successfully in various metal-catalyzed directed cyanation reactions.



Scheme I.5.1.1.6. *Pd-catalyzed ortho cyanation of 2-phenylpyridine*

✓ **Trifluoromethylation of sp^2 C–H bond of directing substrates**

The introduction of a trifluoromethyl group into an organic scaffold *via* C–H functionalization is a hot research area in recent time. In 2010, Yu and co-workers first disclosed an intriguing protocol for *ortho* trifluoromethylation of *N*-directed substrates including 2-phenylpyridines, pyrimidines, imidazoles or thiazoles using highly reactive sulfonium salts in presence of $Pd(OAc)_2$ as the catalyst (Scheme I.5.1.1.7).[26a]

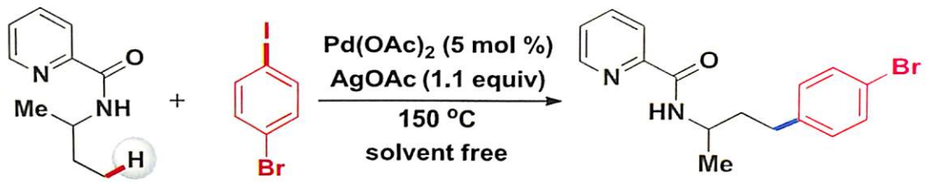


Scheme I.5.1.1.7. *Ortho trifluoromethylation of 2-phenylpyridine with sulfonium salt*

Later on, the *ortho* trifluoromethylation of different directed substrates *viz* benzamides,[26b] benzylamines[26c] and anilides[26d] were performed in a slight modified conditions by same group and others. Hypervalent iodine reagents were also successfully utilized for *ortho*-trifuloromethylation of benzo[*h*] quinoline compounds by Sanford group.[26e]

✓ **Arylation of sp^3 C–H bond of directing substrates**

In a report Daugulish group showed that a combination of $Pd(OAc)_2$ and AgOAc efficiently activate the sp^3 C–H bonds of *N*-directed substrates utilizing aryl iodides as the aryl precursor. This strategy demonstrates a highly regioselective *β*-arylation of 8-aminoquinolines and γ-arylation of picolinamides derivatives (Scheme I.5.1.1.8).[27a]

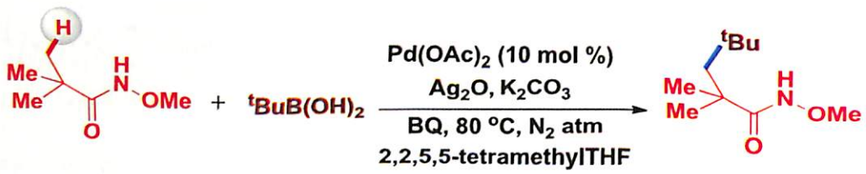


Scheme I.5.1.1.8. *Pd-catalyzed sp^3 C–H arylation of picolinamide*

In their independent works, Yu group utilized aryl iodides or boronic acids as the coupling partner for the β-sp^3 C–H arylation of *o*-directed substrates *viz.* carboxylic acid[27b] and its amide derivatives[27c,d] in presence of Pd catalyst and suitable oxidants and ligands.

✓ **Alkylation of sp^3 C–H bond of directing substrates**

The first Pd-catalyzed β-sp^3 C–H alkylation of amide derivatives (*o*-Methyl hydroxamic acids) using alkyl boronic acid as the coupling partner and air as the terminal oxidant was developed by Yu group in 2008 (Scheme I.5.1.1.9).[28a]

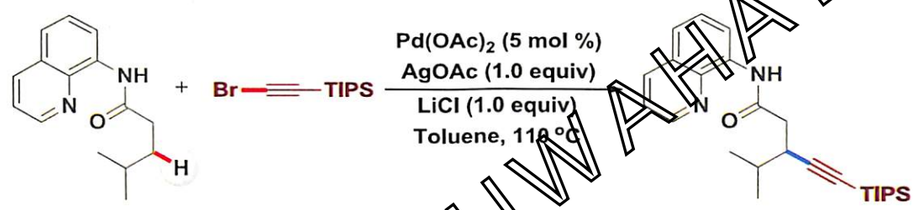


Scheme I.5.1.1.9. *Pd-catalyzed sp^3 C–H alkylation of amides using boronic acid*

Most recently a Pd-catalyzed sp^3 C–H alkylation of amide derivatives using alkyl halides as the coupling partners were also demonstrated by Yu[28b] and Daugulis groups.[28c]

✓ **Alkynylation of sp^3 C–H bond of directing substrates**

Chatani group first disclosed an intriguing protocol for the sp^3 C–H alkynylation of amide derivatives bearing 8-aminoquinoline as auxiliary using sillyl protected bromo-alkynes as the coupling partner *via* Pd(II)/Pd(IV) catalytic system in 2011 (Scheme I.5.1.1.10).[29a]

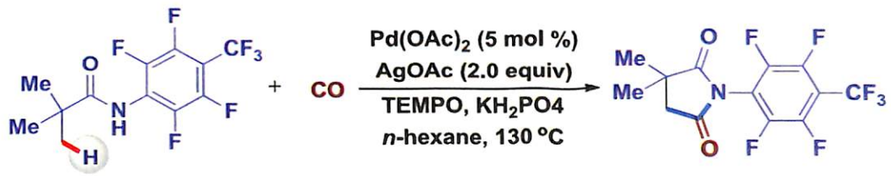


Scheme I.5.1.1.10. *Pd-catalyzed sp^3 C–H Alkynylation via Pd(II)/Pd(IV) system*

While in 2013, Yu group developed a ligand mediated protocol for the β-sp^3 C–H alkynylation of amide derivatives by coupling it with alkynyl iodides or bromides *via* a Pd(0)/Pd(II) catalytic system.[29b]

✓ **Carbonylation of sp^3 C–H bond of directing substrates**

Transition metal-catalyzed carbonylation of sp^3 C–H bond is rare, only few precedents are available in literature. Murai group first demonstrated a pyridine-moiety directed carbonylation of sp^3 C–H bonds adjacent to nitrogen atom in the presence of Rh catalyst.[30a] In 2010, Yu group developed a Pd(II)-catalyzed sp^3 C–H carbonylation at the *β*-position of *N*-arylamides using CO as the carbonyl surrogate. Amide directed cleavage of sp^3 C–H bonds, insertion of CO and intramolecular C–N bond formation gave the corresponding succinamide derivatives (Scheme I.5.1.1.11).[30b]



Scheme I.5.1.1.11. *Pd-catalyzed sp^3 C–H carbonylation of amide*

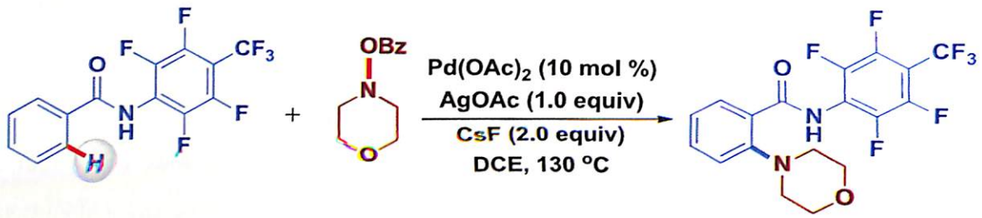
I.5.1.2. Representative example of C–N bond forming reactions

The carbon-nitrogen (C–N) bonds are the ubiquitous and primary linkage in most of the organic compounds. The frequent encounter of nitrogen-bearing compounds as functional materials, natural products and important pharmaceutical agents motivated synthetic chemists in developing selective and efficient protocols for the facile construction of C–N bonds. Transition metal-catalyzed directed C–N bond formation is one of the powerful tools to achieve this goal. Reactions involving C–N bonds formation can be classified in four categories depending on the

nature of the final products such as amination, amidation, azidation and nitration. Reactions pertinent to each of these categories are exemplified below:

✓ **Amination of sp^2 C–H bond of directed substrates**

In 2011, Yu group achieved a sp^2 C–H amination of *N*-aryl benzamides using *o*-benzoyl hydroxylamines as aminating source with either Pd(II) or Pd(0) catalysts (Scheme I.5.1.2.1).[31a] Apart from this, aryl azides[31b] and benzyl azides[31c] have been utilized as the aminating surrogates in transition metal-catalyzed *ortho* amination reactions using almost similar conditions.



Scheme I.5.1.2.1. *Pd-catalyzed sp^2 C–H amination of benzamide*

✓ **Amidation of sp^2 C–H bond of directed substrates**

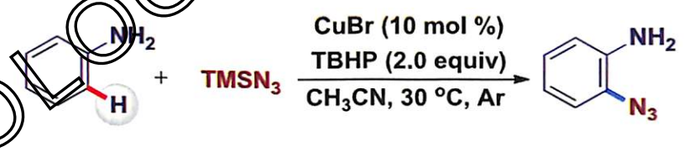
For the first time Zhang group decoded an amide directed, palladium-catalyzed intermolecular protocol for the installation of an *ortho* C–N bond with the non-nitrene-based nitrogen source *N*-fluorobenzenesulfonimide (NFSI) as in Scheme I.5.1.2.2.[32a]

Scheme I.5.1.2.2. *Pd-catalyzed sp^2 C–H amidation of amides with NFSI*

A number of other amidating reagents such as *N*-tosyloxycarbamates[32b] and organic azides[32c] have been utilized as the effective coupling partners with various directed substrates to serve the same purpose.

✓ **Azidation of sp^2 C–H bond of directed substrates**

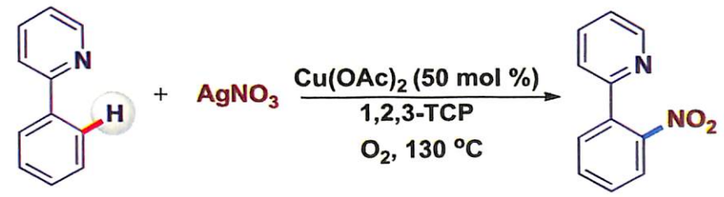
Transition metal-catalyzed direct azidation of sp^2 C–H bonds are relatively rare and only two precedents are available in literature. Jiao group developed a novel and efficient copper-catalyzed azidation of anilines *via* C–H activation in which the primary amine acts as a directing group. A combination of CuBr, trimethylsilyl azide ($TMSN_3$) and oxidant TBHP successfully installs an azide moiety at the *ortho* site of primary anilines (Scheme I.5.1.2.3).[33a] Li group first demonstrated a Rh-catalyzed *ortho* azidation of various *N*-directed substrates including 2-phenylpyridines, pyrimidines and pyrazoles utilizing NaN_3 as the coupling partner.[33b]



Scheme I.5.1.2.3. *Cu-catalyzed sp^2 C–H azidation of aniline*

✓ **Nitration of sp^2 C–H bond of directed substrates**

Liu and Bi group decoded first time a novel copper mediated protocol for the installation of a nitro-group at the *ortho* position of directed substrate 2-phenyl pyridines using $AgNO_3$ as the source of 'NO_2' group. In this reaction, O_2 is used as the terminal oxidant (Scheme I.5.1.2.4).[34]



Scheme I.5.1.2.4. *Cu-catalyzed sp^2 C–H nitration of 2-phenylpyridine*

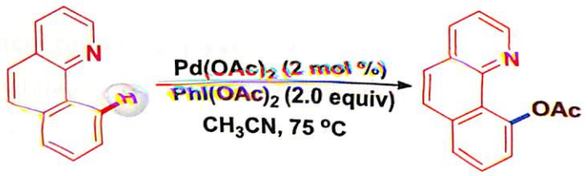
I.5.1.3. Representative example of C–O bond forming reactions

Like C–C and C–N bonds, C–O bond is also one of the primary linkages in chemical compounds. Oxygenated compounds found their applications extensively in natural products, pharmaceuticals, polymers and agrochemical industries. Owing to prevalence of C–O bonds, a number of strategies have been developed. Among them, transition metal-catalyzed directed C–O bond forming reactions *via* cleavage of sp^2 or sp^3 C–H bonds represent a potential approach

to serve the purpose. Though a number of reports are available on substrate directed *ortho* C–C and C–N bonds making processes, relatively less attention has been paid to the C–O bond forming reactions. Because of the strong affinity of electronegative oxygen atom towards transition metals makes it inactive for further transformation. Based on the literature documented strategies, the ligand directed *ortho* C–O bonds forming reactions can be classified in following categories and representative examples pertinent to each category are given below:

✓ **Acetoxylation of sp^2 C–H bond of directed substrates**

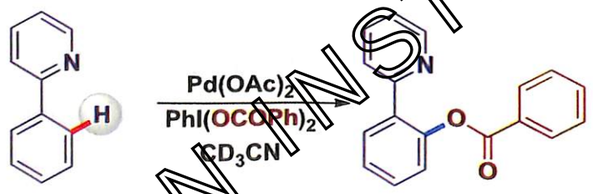
In 2004, Sanford and co-workers first reported a Pd(II)-catalyzed efficient and highly regio- and chemoselective protocol for the ligand directed oxidative C–O bond forming reaction using stoichiometric amount of $PhI(OAc)_2$ as the oxidant. A variety of *N*-directed substrates including benzo[*h*]quinoline, 2-phenylpyridines, azobenzenes, pyrazoles, imines, oxime ethers and pyrrolidinones used as the excellent directing groups and provided their corresponding *ortho* acetoxylated products in good yields (Scheme I.5.1.3.1).[35]



Scheme I.5.1.3.1. *Pd-catalyzed sp^2 C–H acetoxylation of benzo[h]quinoline*

✓ **Benzoxylation of sp^2 C–H bond of directed substrates**

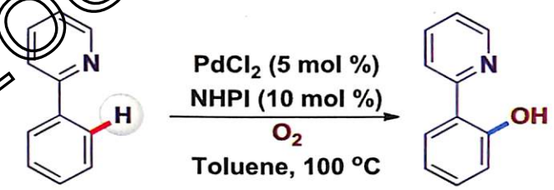
Sanford group disclosed the first example of Pd(II)-catalyzed *ortho* benzoxylation of 2-phenylpyridines using hypervalent iodine as the source of $PhCOO^-$ group (Scheme I.5.1.3.2).[36]



Scheme I.5.1.3.2. *Pd-catalyzed sp^2 C–H benzoxylation of 2-phenylpyridine*

✓ **Hydroxylation of sp^2 C–H bonds of directed substrates**

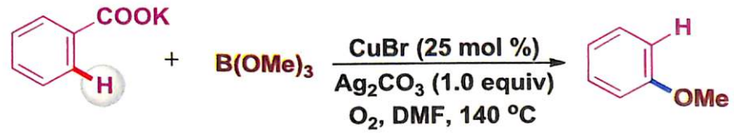
Jiao group demonstrated a highly selective direct *ortho* sp^2 C–H hydroxylation of 2-phenylpyridines using a combination of $PdCl_2$, NHPI and molecular oxygen. In this transformation, Oxygen is employed as reagents and the sole oxidant (Scheme I.5.1.3.3).[37a] Yu group also reported *ortho* hydroxylation of same substrate using $Cu(OAc)_2$ as the catalyst as well as oxygen source of the newly installed C–O bond.[37b] Other directing substrates such as potassium benzoates,[37c] aromatic ketones[37d] esters and amides[37e] were successfully hydrolyzed utilizing suitable metals catalyst and oxidants.



Scheme I.5.1.3.3. *Pd-catalyzed sp^2 C–H hydroxylation of 2-phenylpyridine*

✓ **Alkoxylation of sp^2 C–H bond of directed substrates**

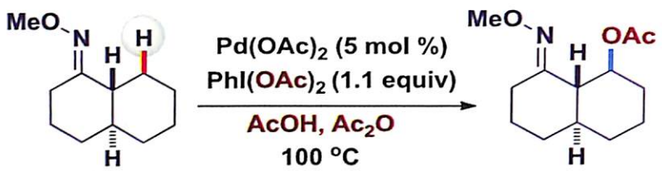
A Cu(II)-catalyzed regiospecific *ortho* alkoxylation of aromatic carboxylates with trimethylborate was developed by Gooßen group. The concomitant decarboxylation after installation of an *ortho* alkoxy moiety provided access to the aromatic ethers from widely available carboxylic acids (Scheme I.5.1.3.4).[38]



Scheme I.5.1.3.4. *Cu-catalyzed sp^2 C–H alkoxylation of carboxylate*

✓ **Acetoxylation of sp^3 C–H bond of directed substrates**

Sanford group disclosed an efficient Pd(II)-catalyzed ligand directed unactivated sp^3 C–H acetoxylation reaction using $PhI(OAc)_2$ as the suitable oxidant. Oxime ethers and pyridine derivatives were effectively acetoxylated in moderate to good yields involving a Pd(II)/Pd(IV) catalytic system (Scheme I.5.1.3.5).[39]



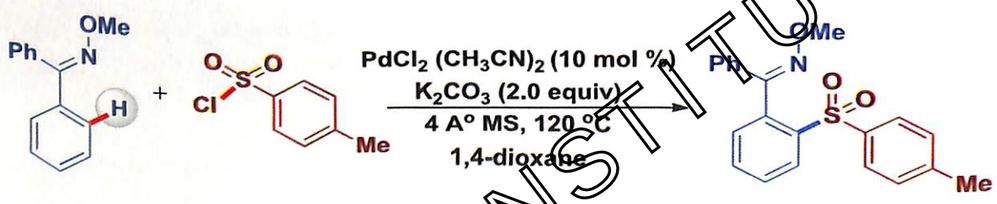
Scheme I.5.1.3.5. *Pd-catalyzed sp^3 C–H acetoxylation of oxime ether*

I.5.1.4. Representative example of C–S bond forming reactions

Sulphur compounds have long been recognized as the essential components of life as it is an important unit of many amino acids, hormones, proteins and enzymes. They are widely used in pharmaceuticals, agrochemical, material and biological sciences. Despite of their potent utilities, only a handful of report using transition metal-catalyzed ligand directed C–S bond forming processes are available in literature. This is due to easy and competing oxidation of sulphur compounds under oxidative conditions, distracting from the actual goal. Reactions pertinent to each category are exemplified below:

✓ **Sulfonylation of sp^2 C–H bond of directed substrates**

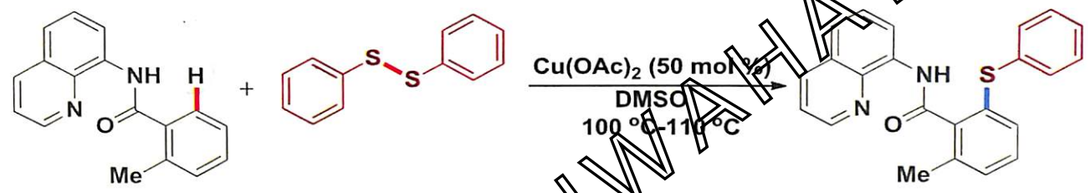
In 2009, Dong group reported the first example of *N*-directed Pd(II)-catalyzed direct *ortho* C–S bond formation at the expense of sp^2 C–H bond, utilizing arylsulfonyl chlorides as remarkably flexible coupling partner. The reactions of arylsulfonyl chlorides with 2-phenylpyridines, pyrazoles, keto-oxime ethers, catalyzed by $Pd(CH_3CN)_2Cl_2$, furnished their corresponding *ortho* aryl-sulphonated products (Scheme I.5.1.4.1).[40]



Scheme I.5.1.4.1. *Pd-catalyzed sp^2 C–H sulfonylation of 2-phenylpyridine*

✓ **Sulfenylation of sp^2 C–H bond of directed substrates**

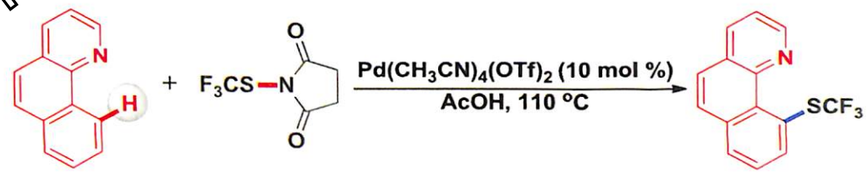
A copper-catalyzed direct thiolation of aryl C–H bonds of auxiliary assisted benzamide derivatives was described by Daugulis group, employing disulfides as effective coupling partners (Scheme I.5.1.4.2).[41]



Scheme I.5.1.4.2. *Cu-catalyzed sp^2 C–H sulfenylation of benzamide*

✓ **Trifluoromethylthiolation of sp^2 C–H bond of directed substrates**

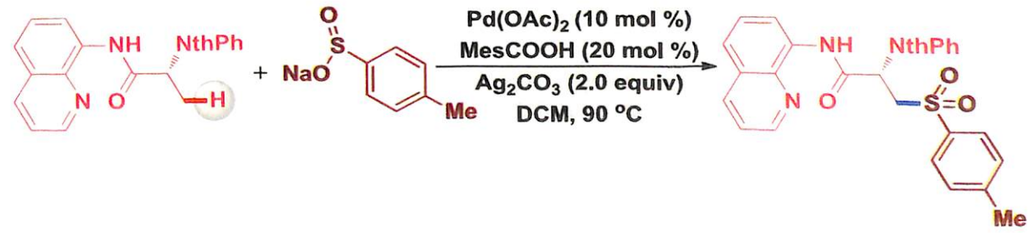
Shen group demonstrated an intermolecular highly selective Pd(II)-catalyzed efficient protocol for the trifluoromethylthiolation of sp^2 C–H bond of benzo[*h*]quinoline utilizing an electrophilic trifluoromethylthio substituted succinamide reagent as the active coupling partner. The reaction was compatible with a variey of substituted 2-phenylpyridines and benzo[*h*]quinoline derivatives containing various functional groups (Scheme I.5.1.4.3).[42]



Scheme I.5.1.4.3. *Pd-catalyzed sp^2 C–H trifluoromethylthiolation of benzo[h]quinoline*

✓ **Sulfonylation of sp^3 C–H bond of directed substrates**

Shi and co-workers demonstrated a Pd(II)-catalyzed intriguing protocol for the sulfonylation of unactivated sp^3 C–H bonds of amides containing 8-aminoquinoline as an auxiliary, employing sodium arylsulfinates as the potential sulfonylating agent. This reaction showed good functional group tolerance and provided a broad range of aryl alkyl sulfones (Scheme I.5.1.4.4).[43]



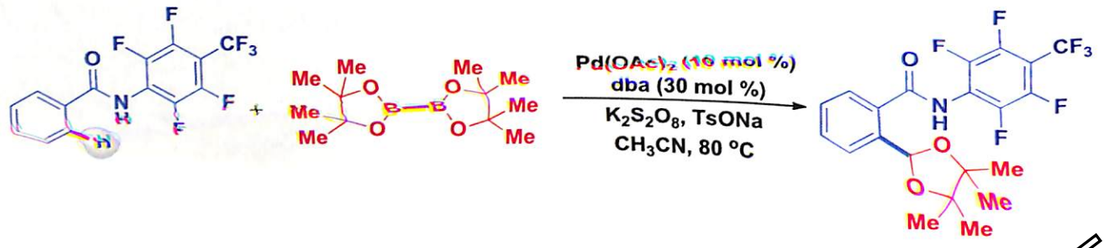
Scheme I.5.1.4.4. *Pd-catalyzed sp^3 C–H sulfonylation of amide*

I.5.1.5. Representative example of C–B, C–P, C–Si and C–Se bond forming reactions

Transition metal-catalyzed ligand directed *ortho* C–B, C–P, C–Si and C–Se bond forming reactions are restricted, but not rare in literature. Reactions pertinent to each of these categories are exemplified below:

✓ **Borylation of sp^2 C–H bond of directed substrates**

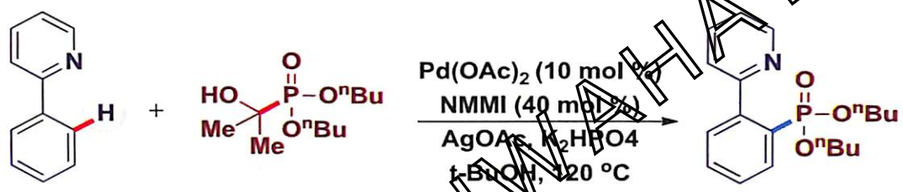
The first Pd-catalyzed *ortho* C–H borylation of amide derivatives was reported by Yu group employing diboron reagents (B_2Pin_2) as coupling partners. The use of electron deficient dibenzylideneacetone (dba) ligand, weak base TsONa and a strong oxidant $K_2S_2O_8$ were found crucial for affording good yield of the corresponding *ortho* boraylated products (Scheme I.5.1.5.1).[44]



Scheme I.5.1.5.1. Pd-catalyzed sp^2 C–H borylation of benzamide

✓ **Phosphorylation of sp^2 C–H bond of directed substrates**

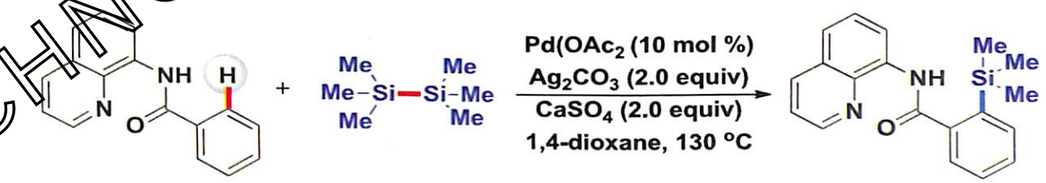
The construction of *ortho* C–P bonds *via* Pd-catalyzed C–H functionalization of *N*-directed substrates demonstrated by Murakami group using α-hydroxyalkylphosphonates as the efficient coupling partners. A variety of *N*-directed substrates including 2-phenylpyridines, quinolines, isoquinolines, benzo[*h*]quinolines and pyrimidines were phosphorylated to afford corresponding N–P bi-dentated compounds which are potentially valuable in medicinal chemistry and catalysis (Scheme I.5.1.5.2).[45]



Scheme I.5.1.5.2. Pd-catalyzed sp^2 C–H phosphorylation of 2-phenylpyridine

✓ **Silylation of sp^2 C–H bond of directed substrates**

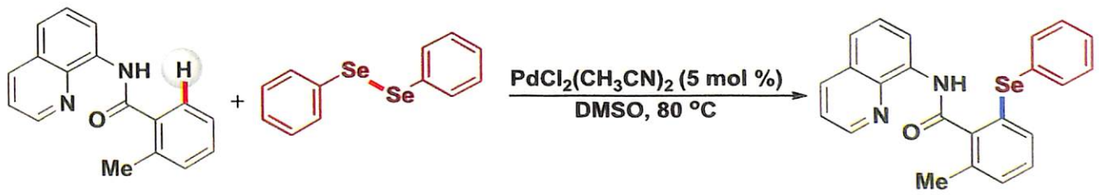
Kanai group developed a Pd-catalyzed regioselective *ortho* silylation of benzamides containing 8-aminoquinoline as the auxiliary ligands with hexamethyldisilane as the silicon source. In this transformation, silver salts and calcium sulphate are used as the optimal oxidant and additive respectively (Scheme I.5.1.5.3).[46]



Scheme I.5.1.5.3. Pd-catalyzed sp^2 C–H silylation of benzamide

✓ **Selenation of sp^2 C–H bond of directed substrates**

A direct selenation of inert C–H bonds of directed substrates *viz.* benzamides, benzylamines 2-arylpyridines and benzo[*h*]quinolines was achieved by Nishihara group utilizing diselenides as the coupling partners with Pd(II) catalyst. The reaction showed a good compatible with a variety of functional groups and provided their corresponding *ortho* selenated products in good yields (Scheme I.5.1.5.4).[47]



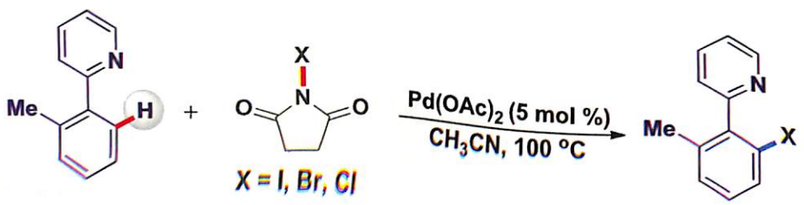
Scheme I.5.1.5.4. Pd-catalyzed sp^2 C–H selenation of benzamide

I.5.1.6. Representative example of C–X (X = Halogen) bond forming reactions

Halogenated organic compounds are indispensably important scaffolds in natural products, pharmaceutical and medicinal chemistry. Transition metal-catalyzed construction of carbon-halogen bonds (C–X) *via* ligand directed C–H functionalizations have emerged as a powerful tools to synthesis such aryl halides in the last decade. Reactions pertinent to each of these categories are exemplified below:

✓ **Iodination, Bromination and Chlorination of sp^2 C–H bond of directed substrates**

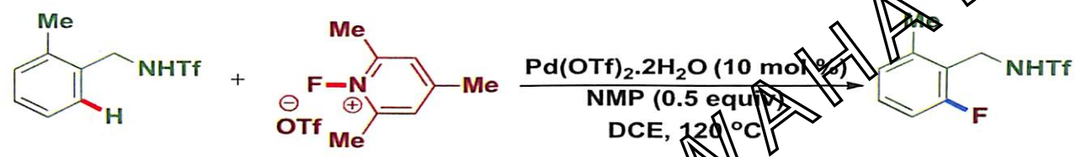
In 2001, Kodama group first demonstrated an highly efficient Pd(II)-catalyzed intriguing protocol for the installation of an *ortho* iodo moitety to carboxylic acid derivatives employing *N*-iodosuccinamide as the source of iodine.[48a] Later on, Sanford and co-workers applied same protocol for the selective iodination, bromination and chlorination of sp^2 C–H bonds of various directed substrates using corresponding *N*-halosuccinamides as the coupling reagents and oxidants.[48b,c] Both *N*-directed substrates (Pyridines, isoquinolines, isoxazolines and oxime ethers) as well as *O*-directed substrates (amides) were successfully halogenated and provided their corresponding products in good yields (Scheme I.5.1.6.1).



Scheme I.5.1.6.1. *Pd-catalyzed sp^2 C–H halogenation of 2-phenylpyridine*

✓ **Fluorination of sp^2 C–H bond of directed substrates**

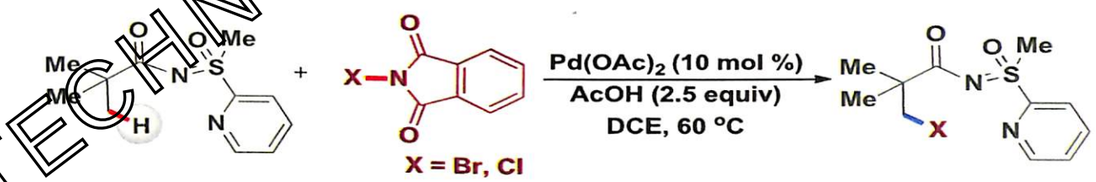
Yu group demonestrated an example of Pd(II)-catalyzed *ortho* sp^2 C–H fluorination of triflamide-protected benzylamines as the directing substrates. The use of *N*-fluoro-2,4,6-trimethylpyridinium triflate as the F^+ source, $Pd(OTf)_2{\cdot}2H_2O$ as the catalyst and NMP as the promoter are decisive for the competent *ortho* fluorination to afford synthetically useful yields. (Scheme I.5.1.6.2).[49]



Scheme I.5.1.6.2. *Pd-catalyzed sp^2 C–H fluorination of protected amine*

✓ **Iodination, Bromination and Chlorination of sp^3 C–H bond of directed substrates**

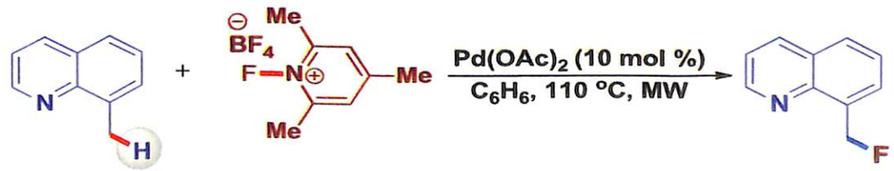
Sahoo group first demonstrated a Pd(II)-catalyzed, *S*-Methyl-*S*-2-pyridyl-sulfoximine (MPyS) assisted bromination and chlorination at β-sp^3 C–H bonds employing corresponding *N*-halophthalimides as the coupling partners. The unprecedented halogenations (Br/Cl) at β-sp^3 C–H bonds of acid derivatives provided an easy access of highly functionalized quaternary carbon centers (Scheme I.5.1.6.3).[50]



Scheme I.5.1.6.3. *Pd-catalyzed sp^3 C–H halogenations (Br/Cl) of sulfoximine*

✓ **Fluorination of sp^3 C–H bond of directed substrates**

A Pd(II)-catalyzed construction of C–F bonds *via* cleavage of sp^3 C–H bonds of 8-methylquinoline using highly effective electrophilic reagent, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoborate as the F^+ source was first described by Sanford group. The reaction might entail a Pd(II)/Pd(IV) catalytic system (Scheme I.5.1.6.4).[51]



Scheme I.5.1.6.4. *Pd-catalyzed sp^3 C–H fluorination of 8-methylquinoline*

I.5.2 Cross Dehydrogenative Coupling (CDC): The cross dehydrogenative coupling reaction can be defined as one type of cross-coupling reaction between two or more C–H bonds (formation of C–C bond) or C–H and X–H bonds (formation of C–X bond; X = heteroatom).[52] Despite being termed cross dehydrogenative coupling (CDC), hydrogen gas is not usually evolved as the byproduct of these transformations. Typically construction of a bond with the loss of H_2 is thermodynamically unfavorable and thus demands an external driving force, namely, a suitable sacrificial oxidant. These oxidants act as hydrogen acceptor in the form of oxygen, peroxides *viz*. hydrogen peroxide, *tert*-butyl hydrogen peroxide (TBHP), di-*tert*-butyl peroxide (DTBP), *N*-halosuccinamides and $K_2S_2O_8$ etc and most of the cases the H_2O is recognized as the byproduct for these transformations. Oxidative formations of different bonds through this protocol have been accomplished using various catalysts. Reactions pertinent to C–C and C–X (X = N, O and S) involving CDC strategies are exemplified below:

Advantages:

- ✓ Use of non-prefunctionalized starting material, hence step economic and greener approach
- ✓ Free from stoichiometric amounts of halogenated or organometallic by-products
- ✓ Maintains a high atom economy and the simplest strategy so far
- ✓ Except use of sacrificial oxidant, free from use of other driving forces such as directing substrates
- ✓ Achievement of a high degree of C–H functionalization

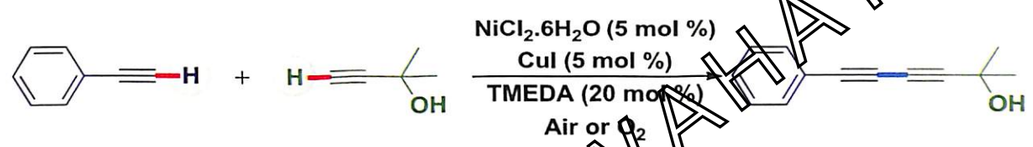
Limitations

- ✓ Due to lack of directing force, fuctionalization can happen at any C–H bonds, leading to regioselectivity problems
- ✓ Multiple functionalization at the different carbon centres leading to chemoselectivities issues

I.5.2.1 Representative example of C–C bond forming reactions

✓ **C_{sp}–H and C_{sp}–H Coupling**

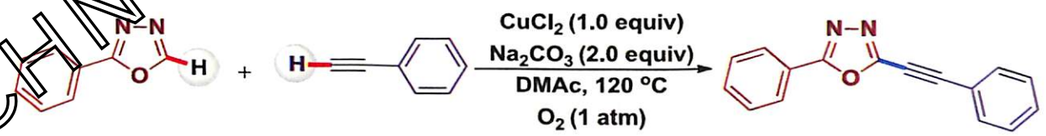
Lei group first demonstrated an efficient Ni/Cu-cocatalyzed, ligand TMEDA promoted protocol for the synthesis of a variety of unsymmetrical conjugated dyenes in excellent yields from two different terminal alkynes *via* C_{sp}–C_{sp} coupling (Scheme I.5.2.1.1).[53]



Scheme I.5.2.1.1. *Ni/Cu-cocatalyzed C_{sp}–C_{sp} heterocoupling of two terminal alkynes*

✓ **C_{sp}–H and C_{sp2}–H Coupling**

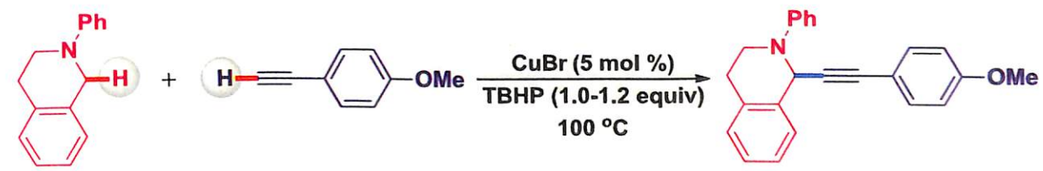
An efficient Cu-catalyzed or promoted protocol for the intermolecular direct coupling of sp C–H of terminal alkynes and sp^2 C–H of heterocycles *viz.* oxadiazoles and oxazoles under O_2 atmosphere leading to the formation of C_{sp}–C_{sp2} bond was reported by Miura group. A range of terminal alkynes and heterocycles underwent smoothly to afford their corresponding products in moderate to good yields under the reaction conditions (Scheme I.5.2.1.2).[54]



Scheme I.5.2.1.2. *Cu-catalyzed direct alkynylation via C_{sp}–C_{sp2} coupling*

✓ **C_{sp}–H and C_{sp3}–H Coupling**

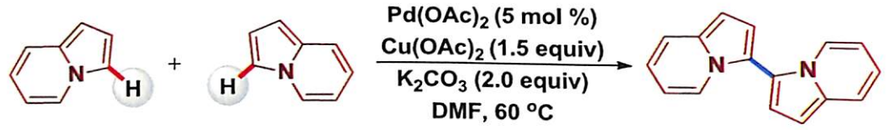
In 2004, Li group first disclosed a simple and effective catalytic method for the synthesis of propargylamine derivatives by using a combination of CuBr/TBHP system. This protocol demonstrates a direct intermolecular coupling of sp^3 C–H bond adjacent to nitrogen atom and sp C–H bond of terminal alkynes (Scheme I.5.2.1.3).[55]



Scheme I.5.2.1.3. *Cu-catalyzed direct alkynylation via C_{sp}–C_{sp3} coupling*

✓ **C_{sp2}–H and C_{sp2}–H Coupling**

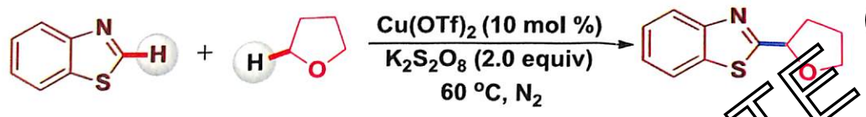
You group achieved a Pd(II)-catalyzed highly regioselective homocoupling of indolizines using $Cu(OAc)_2$ as oxidant and K_2CO_3 as base through double C–H activation. A wide range of indolizine substrates with different substituents underwent smooth coupling to afford corresponding bi-indolizines in good to excellent yields (Scheme I.5.2.1.4).[56]



Scheme I.5.2.1.4. *Pd-catalyzed oxidative homocoupling via double C_{sp2}–H activation*

✓ **C_{sp2}–H and C_{sp3}–H Coupling**

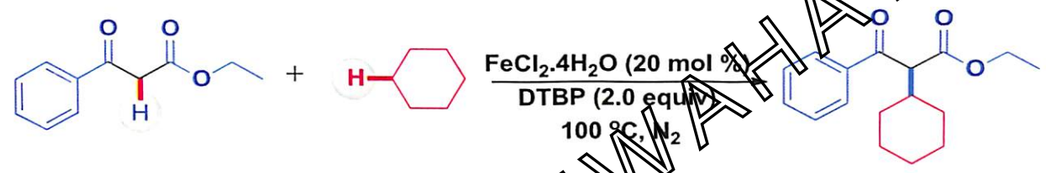
In 2013, Pan group developed an efficient and widely applicable Cu-catalyzed reaction of (benzo)thiazoles with cyclic ethers under mild conditions. The combination of $Cu/K_2S_2O_8$ system promotes the direct coupling of a sp^2 C–H bond of azole derivatives and sp^3 C–H bond of inactive ethers (tetrahudrofuran or dioxane) leading to the formation corresponding desired products in good yields (Scheme I.5.2.1.5).[57]



Scheme I.5.2.1.5. *Cu-catalyzed C_{sp2}–C_{sp3} Coupling of benzothiazole and THF*

✓ **C_{sp3}–H and C_{sp3}–H Coupling**

Li group developed $FeCl_2$-catalyzed highly efficient alkylation of active methylene compounds with simple cyclic alkanes using DTBP (*di-tert* butylperoxide) as the terminal oxidant. In this reaction one C–C bond is formed at the expense of two sp^3 hybridized C–H bonds (Scheme I.5.2.1.6).[58]

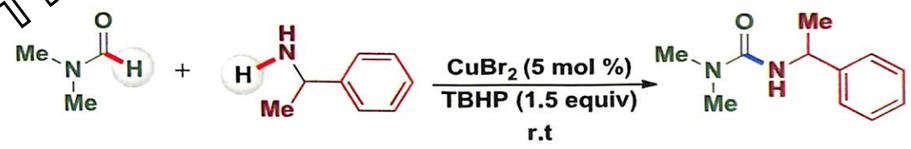


Scheme I.5.2.1.6. *Fe-catalyzed C_{sp3}–C_{sp3} Coupling of β-ketoester and cyclohexane*

I.5.2.2. Representative example of C–N bond forming reactions

✓ **C_{sp2}–H and N_{sp3}–H (amine) Coupling**

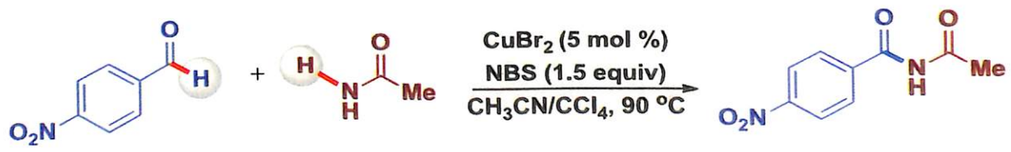
A highly efficient Cu-catalyzed protocol for the synthesis of unsymmetrical ureas through cross dehydrogenative coupling of sp^2 C–H bonds of formamides and sp^3 N–H bonds of primary amines was developed by Reddy groups (Scheme I.5.2.2.1).[59] This reaction was found suitable to a variety of formamides as well as primary and secondary amines.



Scheme I.5.2.2.1. *Cu-catalyzed coupling of C_{sp2}–H of amide and N_{sp3}–H of amine*

✓ **C_{sp2}–H and N_{sp3}–H (amide) Coupling**

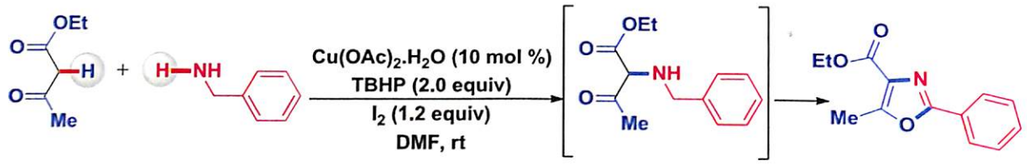
As shown in above Scheme I.5.2.2.1, not only sp^3 N–H bonds of primary amines, but also the amidic sp^3 N–H bonds has been activated using combination of CuBr/NBS involving a CDC strategy as demonstrated by Fu group. In this reaction, sp^2 C–H bonds of aromatic aldehydes couples with sp^3 N–H bonds of amides as shown in Scheme I.5.2.2.2. This reaction tolerates a wide range of functional groups with respect to both amides and aldehydes, providing their corresponding products in good to excellent yields.[60]



Scheme I.5.2.2.2. *Cu-catalyzed coupling of C_{sp2}–H of aldehyde and N_{sp3}–H of amide*

✓ **C_{sp3}–H and N_{sp3}–H (amine) Coupling**

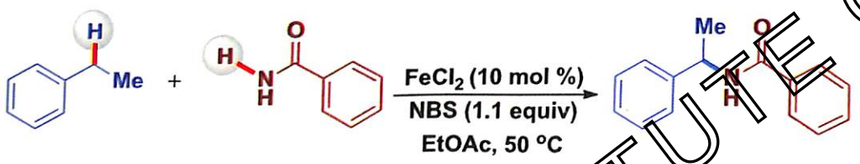
In 2010, Wang group developed a Cu(II)-catalyzed, I_2 and TBHP mediated efficient protocol for the synthesis of poly substituted oxazoles from benzylamines and β-diketo derivatives *via* CDC protocol. In this reaction, free sp^3 N–H bond of benzyl amines efficiently coupled with sp^3 C–H of β-diketo esters and a concurrent tandem cyclization led to the formation of polysubstituted oxazoles (Scheme I.5.2.2.3).[61]



Scheme I.5.2.2.3. *Cu-catalyzed coupling of C_{sp3}–H of* β*-diketo ester and N_{sp3}–H of amine*

✓ **C_{sp3}–H and N_{sp3}–H (amide) Coupling**

Fu group demonstrated an efficient protocol where sp^3 N–H bond of amide was utilized as the coupling partner for the amidation of benzylic sp^3 C–H bond under mild conditions. The inexpensive and readily available catalyst-oxidant ($FeCl_2$/NBS) combination efficiently promoted amidation of the unactivated C–H bonds and provided their corresponding products in moderate to good yields (Scheme I.5.2.2.4).[62]



Scheme I.5.2.2.4. *Fe-catalyzed coupling of benzylic C_{sp3}–H and N_{sp3}–H of amide*

✓ **C_{sp3}–H and N_{sp2}–H (imine) Coupling**

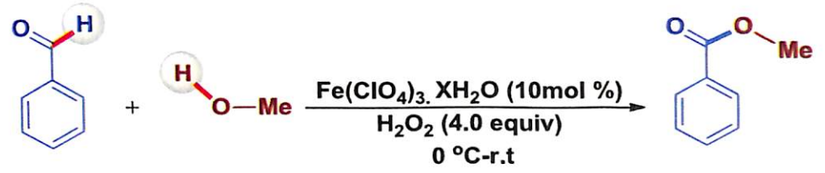
Bolm and co-workers reported a Fe-catalyzed intriguing protocol for the direct coupling of N_{sp2}–H bond of sulfoximines and C_{sp3}–H bond of diarylmethanes through hetero-cross-dehydrogenative coupling (CDC). This intermolecular C–N bond formation strategy showed a good functional group tolerance and provided *N*-alkylated sulfoximines with α-branched substituents in moderate to good yields (Scheme I.5.2.2.5).[63]

Scheme I.5.2.2.5. *Fe-catalyzed coupling of benzylic C_{sp3}–H and N_{sp2}–H of imine*

I.5.2.3. Representative example of C–O bond forming reactions

✓ **C_{sp2}–H and O_{sp3}–H (alcohol) Coupling**

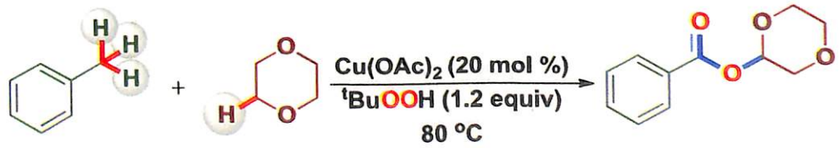
Darcel group reported a Fe(III)-catalyzed, hydroperoxide (H_2O_2) mediated highly efficient protocol for the synthesis of esters *via* oxidative couling beween C_{sp2}–H of aldehydes and O_{sp3}–H of alcohols under mild conditions.[64] Both aliphatic and aromatic aldehydes are compatible with this reaction. The operational simplicity, environmental acceptability and use of inexpensive catalyst are main attribute of this protocol (Scheme I.5.2.3.1).



Scheme I.5.2.3.1. *Fe-catalyzed direct coupling of C_{sp2}–H and O_{sp3}–H of alcohol*

✓ **C_{sp3}–H and O_{sp3}–H Coupling**

Recently our group demonstrated a highly selective Cu(II)-catalyzed CDC strategy for the synthesis of esters from simple solvents employing TBHP as the terminal oxidant as well as the oxygen source.[65] The *in situ* generated benzoxy radical, obtained by the cleavage of three C_{sp3}–H bonds of alkylbenzenes, efficiently coupled with the α-C_{sp3}–H of cyclic ether and led to the formation of new C–O bond (Scheme I.5.2.3.2).

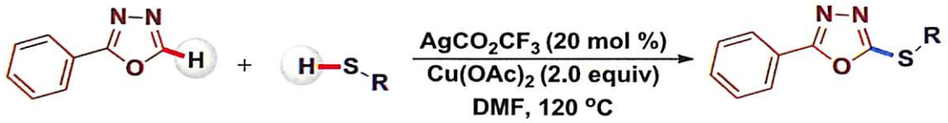


Scheme I.5.2.3.2. *Cu-catalyzed direct coupling of C_{sp3}–H of and O_{sp3}–H bond*

I.5.2.4. Representative example of C–S bond forming reactions

✓ **C_{sp2}–H (aryl) and S_{sp3}–H (thiol) Coupling**

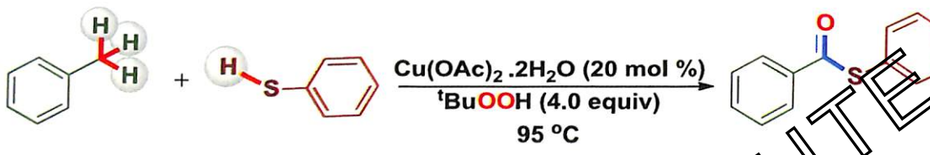
Gao and co-workers reported a Lewis acid catalyzed, Cu(II) mediated direct thiolation between C_{sp2}–H bond of azole derivative and sp^3 hybridized free S–H bond of aliphatic or aromatic thiol under base free condition.[66] This protocol showed a good tolerance towards broad range of substrates and functional groups (Scheme I.5.2.4.1).



Scheme I.5.2.4.1. *Ag-catalyzed thiolation of sp^2 C–H of azoles and free S–H bond*

✓ **C_{sp3}–H (alkyl)** and **S_{sp3}–H (thiol) Coupling**

Recently our group developed a Cu(II)-catalyzed, TBHP mediated efficient CDC protocol for the direct coupling of thiols and alkylbenzenes for the synthesis of thioesters.[67] The *in situ* generated aromatic aldehydes, obtained at the expense of two C_{sp3}–H bonds of alkylbenzenes, efficiently coupled with the sp^3 S–H bond of thiol and led to the formation of thioesters (Scheme I.5.2.4.2).



Scheme I.5.2.4.2. *Cu-catalyzed thiolation of sp^3 C–H of alkylbenzene and free S–H bond*

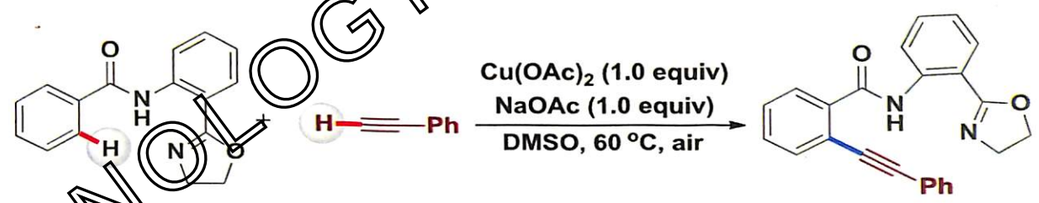
I.5.3. Combination strategy: Directing group-assisted cross dehydrogenative coupling:

The regio- and chemoselectivity issues due to multiple numbers of unique protons in a molecule are main barrier in cross dehydrogenative coupling reaction (CDC). Introduction of a directing group in CDC coupling reaction overcomes such problems and brings higher degree of selectivity for the construction of C–C and C–X bond (X = heteroatom). Thus, the combination strategy represents a most powerful technique in C–H functionalization. Reactions pertinent to this category for the formation of C–C and C–X (X = N, O and S) are exemplified below:

I.5.3.1. Representative example of C–C bond forming reactions

✓ **C_{sp2}–H (aryl) and C_{sp}–H (alkynyl) Coupling**

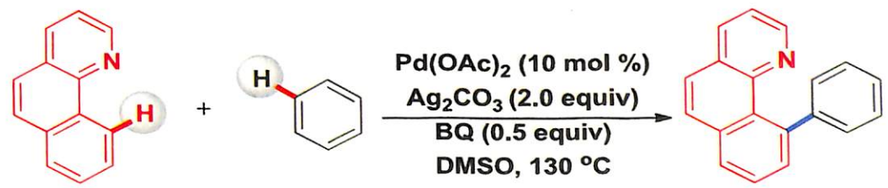
Recently Yu group achieved Cu(II)-promoted an intriguing protocol for the *ortho* alkynylation of amide derivatives using oxazoline as the directing group with terminal alkynes.[68] A wide variety of directed arenes/heteroarenes and terminal alkynes having different substituents are compatible under the reaction conditions and provided corresponding *ortho* alkynylated products in moderate to good yields (Scheme I.5.3.1.1).



Scheme I.5.3.1.1. *C–C bond formation by C_{sp2}–H and C_{sp}–H coupling*

✓ **C_{sp2}–H (aryl) and C_{sp2}–H (aryl) Coupling**

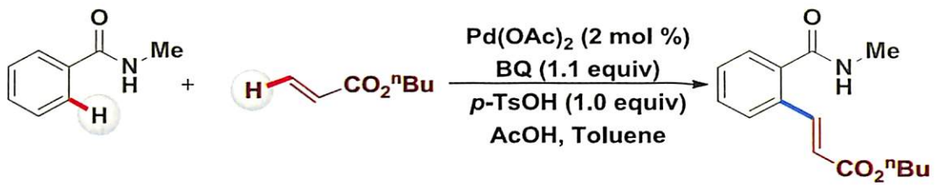
In 2007, Sanford group first reported a Pd(II)-catalyzed oxidative cross coupling between two sp^2 C–H bonds of aryl moieties where benzo[*h*]quinolines act as the directing substrates and simple arenes are used as the coupling partner (Scheme I.5.3.1.2).[69]



Scheme I.5.3.1.2. *C–C bond formation by C_{sp2}–H (aryl) and C_{sp2}–H (aryl) coupling*

✓ **C_{sp2}–H (aryl) and C_{sp2}–H (alkenyl) Coupling**

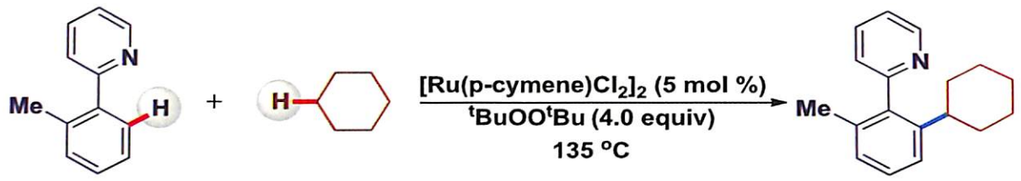
de Vries and de Leeuwen group reported an electrophilic Pd complex catalyzed highly selective and mild oxidative coupling between anilide derivatives and acrylates through *ortho* C–H bond activation. The reaction occurs even at room temperature using a cheap oxidant benzoquinone in high yields up to 91% (Scheme I.5.3.1.3).[70]



Scheme I.5.3.1.3. *C–C bond formation by C_{sp2}–H (aryl) and C_{sp2}–H (alkenyl) coupling*

✓ **C_{sp2}–H (aryl) and C_{sp3}–H (alkyl) Coupling**

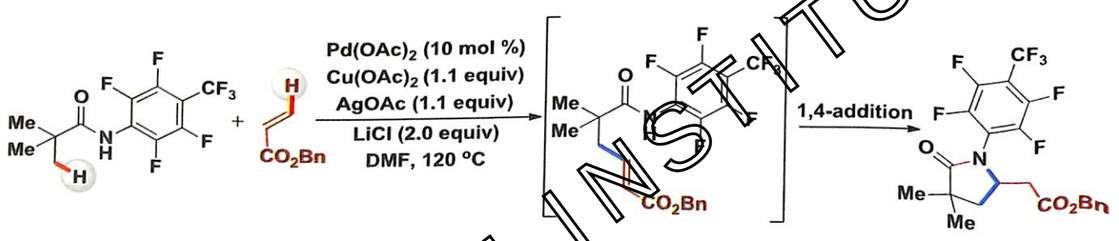
In 2008, Li group first disclosed a ligand directed Ru-catalyzed and DTBP mediated novel C–C bond forming strategy utilizing 2-phenylpyridine derivatives as the directing ligand and unactivated cycloalkane as the coupling partner (Scheme I.5.3.1.4).[71]



Scheme I.5.3.1.4. *C–C bond formation by C_{sp2}–H (aryl) and C_{sp3}–H (alkyl) coupling*

✓ **C_{sp3}–H (alkyl) and C_{sp2}–H (alkenyl) Coupling**

In 2004, Yu group first developed a methodology for the β-sp^3 C–H olefination of an amide directed substrate in the presence of palladium catalyst using acrylate as the efficient coupling partner. The *in situ* generated olifinated amide products further underwent a 1,4-conjugate addition to furnish corresponding five membered lactum derivatives (Scheme I.5.3.1.5).[72]

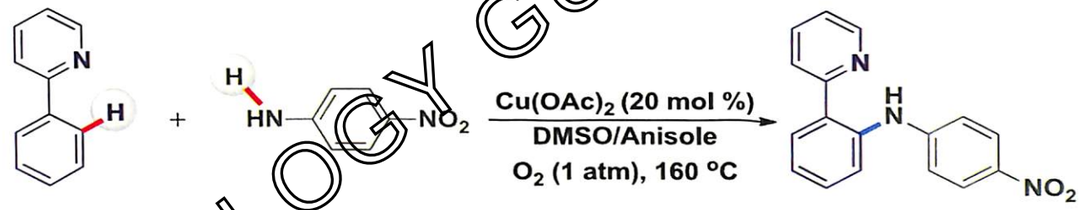


Scheme I.5.3.1.5. *C–C bond formation by C_{sp3}–H (alkyl) and C_{sp2}–H (alkenyl) coupling*

I.5.3.2. Representative example of C–N bond forming reactions

✓ **C_{sp2}–H (aryl) and N_{sp3}–H (amine) Coupling**

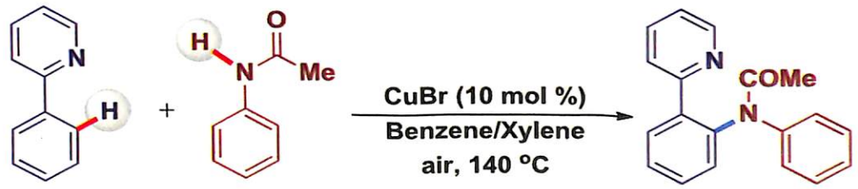
Nicholas and co-workers reported a simple and efficient $Cu(OAc)_2$-catalyzed, O_2-mediated *ortho* amination of 2-phenylpyridine derivatives employing electron-deficient anilines as the coupling partner (Scheme I.5.3.2.1).[73]



Scheme I.5.3.2.1. *C–N bond formation by C_{sp2}–H (aryl) and N_{sp3}–H (amine) coupling*

✓ **C_{sp2}–H (aryl) and N_{sp3}–H (amide) Coupling**

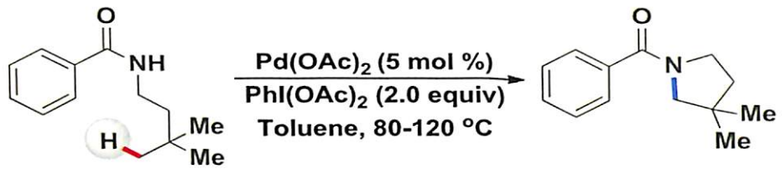
Li and Chen group achieved an intermolecular dehydrogenative amidation of arenes assisted by chelating groups such as 2-pyridyl or 1-pyrazolyl utilizing amides as the coupling partners in the presence of CuBr as a catalyst and air as the terminal oxidant (Scheme I.5.3.2.2).[74]



Scheme I.5.3.2.2. *C–N bond formation by C_{sp2}–H (aryl) and N_{sp3}–H (amide) coupling*

✓ **C_{sp3}–H (alkyl) and N_{sp3}–H (amide) Coupling**

Daugulis group developed Pd(II)-catalyzed an intriguing protocol for the construction of pyrrolidine, indoline and isoindoline derivatives *via* intramolecular sp^3 C–H/N–H coupling. This palladium-catalyzed method employed a picolinamide directing group and $PhI(OAc)_2$ as oxidant in toluene at 80–120 °C (Scheme I.5.3.2.3).[75]

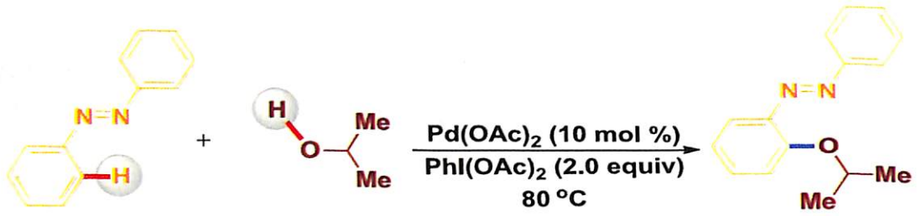


Scheme I.5.3.2.3. *C–N bond formation by C_{sp3}–H (alkyl) and N_{sp3}–H (amide) coupling*

I.5.3.3. Representative example of C–O bond forming reactions

✓ **C_{sp2}–H (aryl) and O_{sp3}–H (alcohol) Coupling**

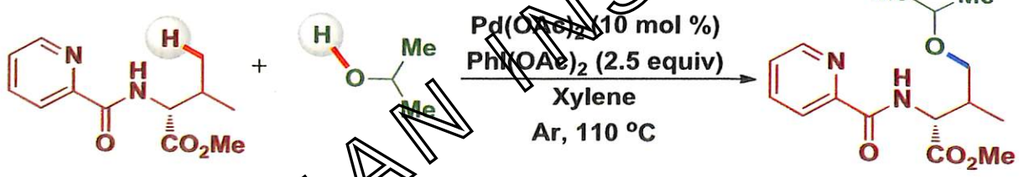
Sun and co-workers demonstrated an efficient and highly regioselective protocol for the *ortho* alkoxylation of aromatic azo compounds employing both primary and secondary alcohols as the coupling partners and $PhI(OAc)_2$ as the oxidant *via* Pd(II)/Pd(IV) catalytic system (Scheme I.5.3.3.1).[76]



Scheme I.5.3.3.1. *C–O bond formation by C_{sp2}–H (aryl) and O_{sp3}–H (alcohol) coupling*

✓ **C_{sp3}–H (aryl) and O_{sp3}–H (alcohol) Coupling**

Chen group reported $Pd(OAc)_2$-catalyzed, $PhI(OAc)_2$-mediated an intriguing protocol for the synthesis of alkyl ethers by the functionalization of unactivated sp^3 hybridized C–H bonds at γ or δ positions of picolinamide-protected amines with a range of alcohols (Scheme I.5.3.3.2).[77]

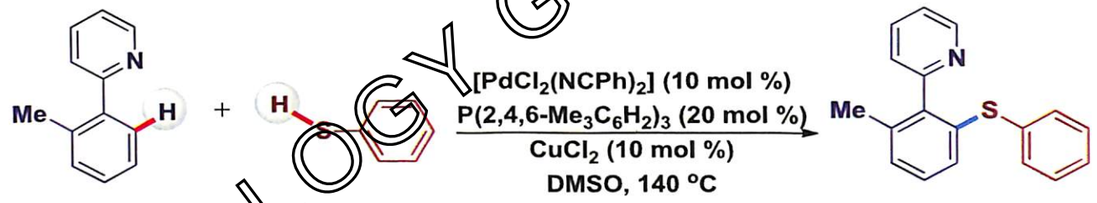


Scheme I.5.3.3.2. *C–O bond formation by C_{sp3}–H (alkyl) and O_{sp3}–H (alcohol) coupling*

I.5.3.4. Representative example of C–S bond forming reactions

✓ **C_{sp2}–H (aryl) and S_{sp3}–H (thiol) Coupling**

Most recently, Nishihara group achieved a ligand mediated Pd and Cu co-catalyzed direct *ortho* sulfenylation of 2-phenylpyridines using thiol as the efficient coupling partner through Pd(II)/Pd(IV) catalytic system (Scheme I.5.3.4.1).[78]

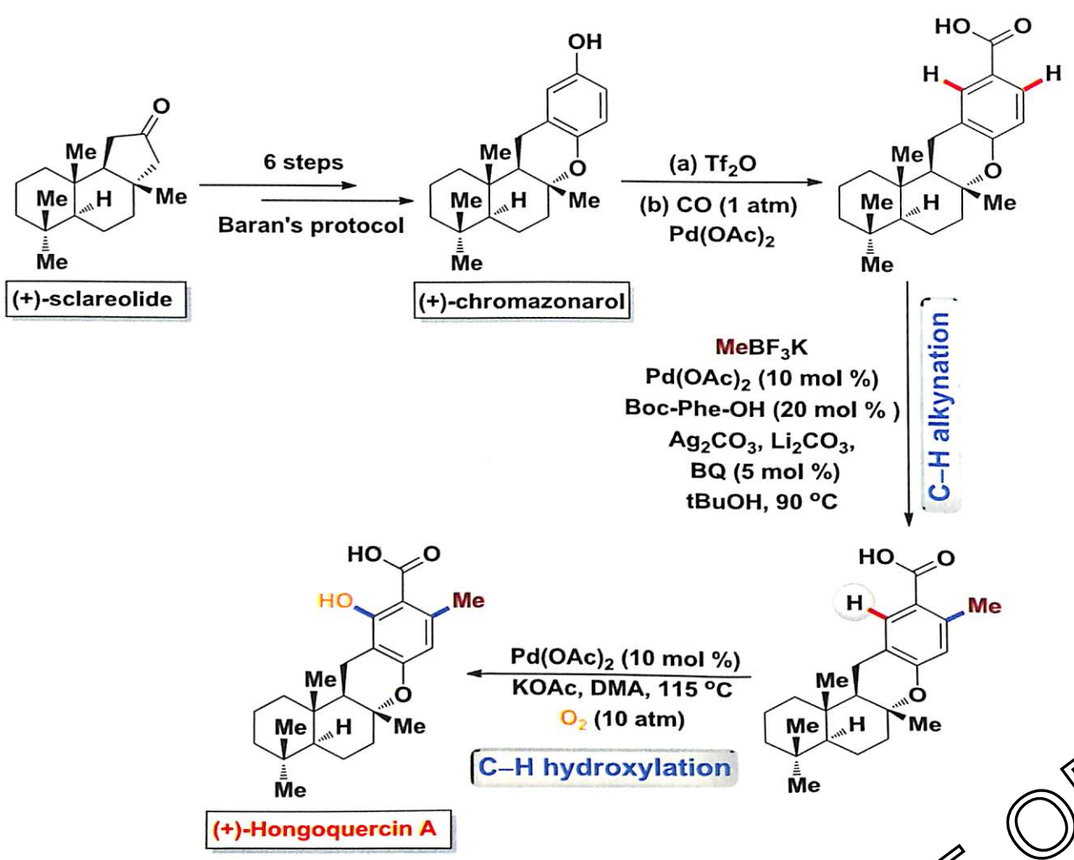


Scheme I.5.3.4.1. *C–S bond formation by C_{sp2}–H (aryl) and S_{sp3}–H (thiol) coupling*

I.6. C–H functionalization Logic in Total Synthesis: A New Tool

The essence of C–H functionalization strategy is not only limited to synthesize small molecules, rather it spread its branches towards the synthesis of complex natural products.[79] Translating the methodological developments to its use in the assembly of complex natural products now becomes an important challenge to the synthetic chemists. The continued advancement and relevance of ''economy'' in the design and execution of such complex natural products synthesis has arguably boosted up the area of C–H functionalization beyond curiosity. Herein one example is shown in scheme I.6.1.

Very recenly (2013), Yu and Baran group reoprted a concise total synthesis of (+)-Hongoquercin A, an important sesquiterpenoid antibiotic of fungal origin.[80a] The use of two successive C–H disconnections strategy to build C–C and C–O bonds in a controlled, site-specific fashion is a unique maneuver in synthesis planning of (+)-Hongoquercin A from (+)-chromazonarol.[80b] A Pd(II)-catalyzed, ligand-accelerated, benzoic-acid directed intermolecular *ortho* C–H alkylation method had been adopted for the construction of new C(aryl)–C(alkyl) bond. In the next step, *ortho* C–H hydroxylation protocol had been employed for the construction of *ortho* C–O bond (Scheme I.6.1).



Scheme I.6.1. *Total synthesis of (+)-Hongoquercin A*

I.7. References and Notes

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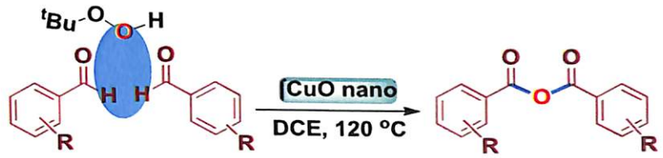
Chapter II

Nano CuO-Catalyzed Cross Dehydrogenative Coupling (CDC) of Aldehydes to Anhydrides



II. Abstract: *An elegant synthesis of carboxylic acid anhydrides has been developed directly from arylaldehydes using CuO nanoparticles as the catalyst and tert-butyl hydropeoxide (TBHP) as the oxidant. During anhydride formation the reaction proceed through a double sp^2 C–H functionalization of aldehydes to generate two consecutive C–O bonds.*

Chapter II

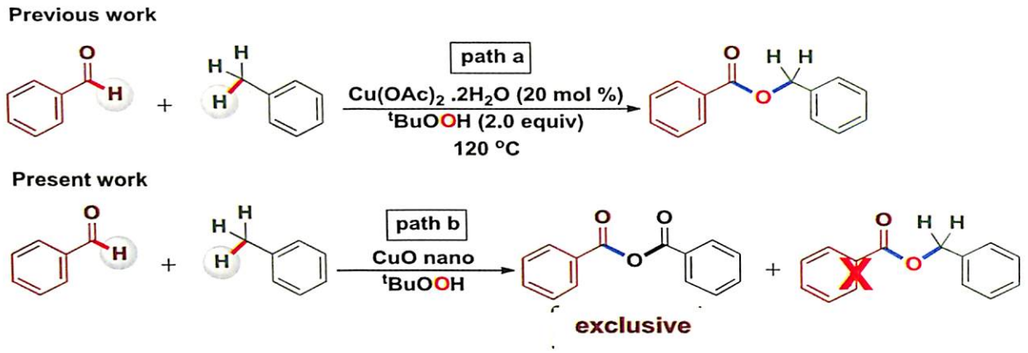
II. Nano CuO-Catalyzed Cross Dehydrogenative Coupling (CDC) of Aldehydes to Anhydrides

II.1. Introduction

The essence of transition metal-catalyzed C–H bond functionalization is an important ongoing theme in organic chemistry.[1] Directing group-assisted C–H bond functionalization[2] and cross dehydrogenative coupling (CDC)[3] reactions are preferred in this field because of their atom and step-economy. To date, although several CDC methodologies have been reported for the formation of C–C bonds,[3a,4] less effort has been directed toward C–O bond forming reactions. Development of various transition metal-catalyzed C–H functionalization methodologies for the construction of C–O bonds have been emerged as relevant topic recently in this regard.[5]

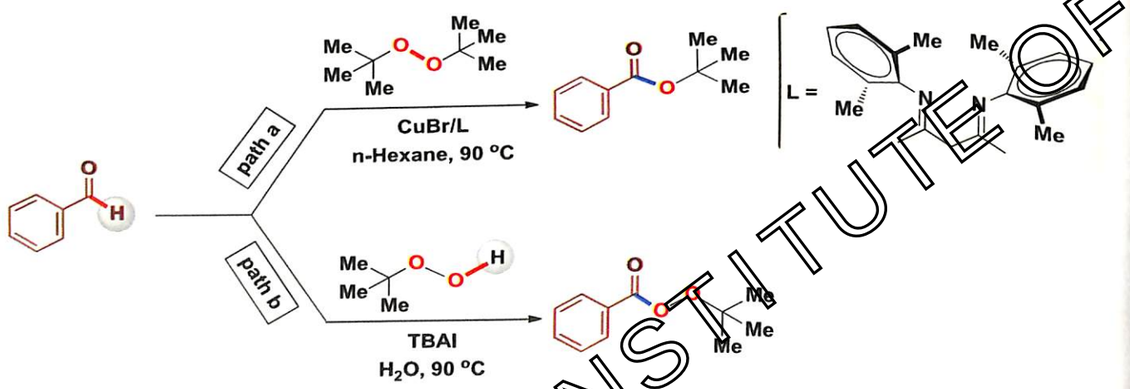
Nano CuO is one of the most extensively employed materials used in catalysis because of its high thermal resistance, surface effect, superior quantum size, high reactivity and peculiar physical and chemical properties compared with ordinary CuO. Besides working at low catalyst loading, the particles are recoverable because of their insolubility in most solvents, which thereby facilitates recycling. To date, CuO nanoparticles have been used for cross coupling reactions in the construction of C–N, C–O, C–S and N–N bonds.[6] Only in one instance, synthesized CuO nanospindle has been utilized for the arylation of azole derivatives *via* sp^2 C–H functionalization employing aryl iodides as the coupling partner.[7]

Recently our group developed a $Cu(OAc)_2{\cdot}2H_2O$-catalyzed highly efficient intriguing protocol for the synthesis of benzylic esters by the CDC reaction of aldehydes and alkylbenzenes in presence of *tert*-butyl hydroperoxide (TBHP) as oxidant as well as source of oxygen (path a, Scheme II.1.1).[5e] In this CDC reaction, the *in situ* generated benzyl alcohol, obtained by the sp^3 C–H oxidation of toluene (alkylbenzene), efficiently coupled with aldehydic sp^2 C–H bond and led to the formation of benzyl benzoate.



Scheme II.1.1. *Divergent reactivity of ordinary copper salt and CuO nano catalyst*

Thus, it would be interesting to see whether copper oxide nano catalyst could activate the sp^3 C–H bond of unactivated alkylbezenes for the synthesis of same (benzylic ester). With this curiosity in mind, when reaction performed with benzaldehyde using CuO nano as catalyst in toluene in the presence of TBHP, benzoic anhydride was obtained as the exclusive product instead of expected benzyl benzoate (path b, Scheme II.1.1). Thus, copper oxide (CuO) nano catalyst exhibits a divergent reactivity to that of ordinary copper salts $Cu(OAc)_2{\cdot}2H_2O$.



Scheme II.1.2. *Differential reactivity of catalyst for aldehydic sp^2 C–H functionalization*

Differential reactivities of catalysts including organocatalyst were observed during aldehydic sp^2 C–H functionalization in presence of different peroxide. Wei group recently demonstrated a Cu(I)-catalyzed, ligand promoted oxidative esterification (C–O bond formation) of aldehydes

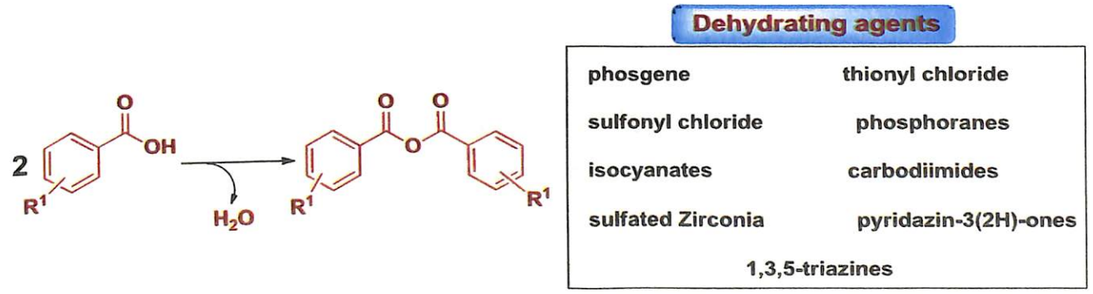
with di-*tert*-butyl peroxide (DTBP) which provided corresponding *tert*-butyl esters as shown in path a, Scheme II.1.2.[8] Wan and co-workers reported an organo-catalytic procedure for the synthesis of *tert*-butyl-perester directly from aldehyde and TBHP *via* sp^2 C–H oxidation of aldehyde using tetra-butylammonium iodide (TBAI) as the catalyst (path b, Scheme II.1.2).[9] It may be noteworthy to mention here that though various transition metals catalyst have been employed for the aldehydic C–H functionalizations,[10] the use of copper oxide (CuO) nano as catalyst for such reactions are rarely been reported in literature.

II.2. Reported Strategies for the Synthesis of Carboxylic acid Anhydrides

Carboxylic acid anhydrides are used in the preparation of a range of carboxylic acid derivatives such as amides and esters[11a,b] and they have found applications in the synthesis of peptides and drugs.[11c] Such applications of anhydride scaffolds have often driven the synthetic chemists for the development of new protocols to meet their demand. Literature enumerates a number of protocols for their synthesis which can be categorized into five main classes: (i) dehydration of carboxylic acid derivatives; (ii) classical nucleophilic reactions; (iii) cross coupling reactions; (iv) carbonylation reaction and (v) cross dehydrogenative coupling (CDC).

(i) Dehydration of carboxylic acid derivatives

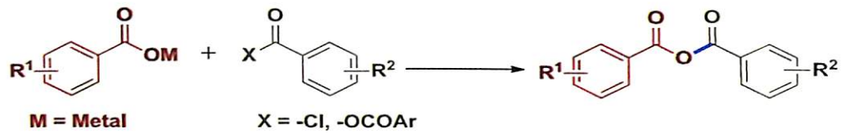
The traditional methodologies for the synthesis of anhydrides rely on dehydration of carboxylic acids in the presence of various dehydrating reagents such as phosgene,[12a] thionyl and sulfonyl chlorides,[12b,c,d] phosphoranes,[12e] isocyanates[12f] carbodiimides,[12g] sulfated zirconia,[12h] pyridazin-3(2*H*)-ones[12i] and 1,3,5-triazines[12j] (Scheme II.2.1). However, the use of stoichiometric amount of those reagents, longer reaction time, use of toxic and corrosive reagents and harsh reaction condition are the major setbacks of these methodologies.



Scheme II.2.1. *Synthesis of anhydrides through dehydration of carboxylic acids*

(ii) Classical nucleophilic reaction

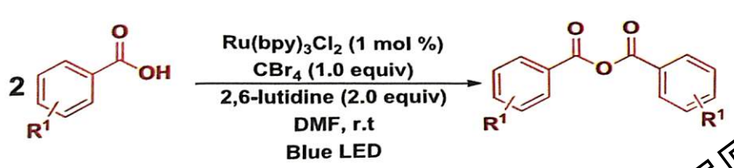
In another traditional way, anhydrides can be prepared by reacting acylating agents such as acyl halides and another anhydrides (as reactant) with carboxylates salt *via* simple nucleophilic substitution reactions (Scheme II.2.2).[13]



Scheme II.2.2. *Synthesis of anhydrides via nucleophilic substitution*

(iii) Cross coupling reaction

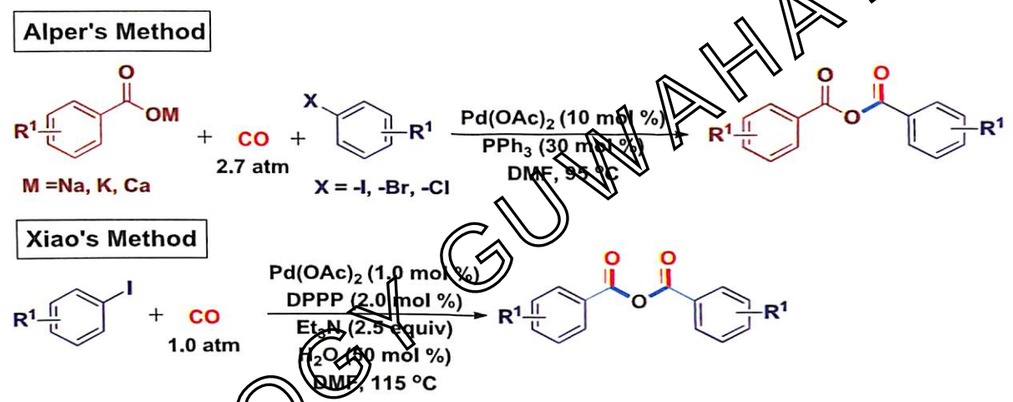
Stephenson group reported a new class of cross coupling approach for the formation of symmetrical anhydrides *via* photochemical activation of C–O bond of carboxylic acids.[14] The *in situ* generated Vilsmeier–Haack reagent, obtained by the reaction of photoredox catalyst $Ru(bpy)_3Cl_2$ and CBr_4 in DMF successfully converted various aryl and alkyl carboxylic acids into their corresponding anhydrides in excellent yields at room temperature (Scheme II.2.3).



Scheme II.2.3. *Synthesis of anhydrides via photocatalytic cross coupling reaction*

(iv) Carbonylation reaction

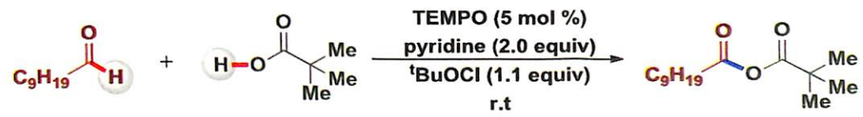
In 1989, for the first time Alper group reported homogeneous Pd(II)-catalyzed an efficient protocol for the synthesis of symmetrical anhydrides *via* carbonylated cross coupling reaction of metal (Na, K and Ca) carboxylates and aryl halides under a CO atmosphere (2.7 atm) as shown in Scheme II.2.4.[15a] Furthermore, Xiao and co-workers demonstrated a modified and highly improved palladium-catalyzed protocol for the direct conversion of aryl iodides into corresponding anhydrides through an atmospheric carbonylation process (Scheme II.2.4).[15b] In this modified carbonylation reaction, CO and H_2O have been employed as the sources of carbonyl moieties and anhydric oxygen respectively in resultant anhydrides.



Scheme II.2.4. *Synthesis of anhydrides through carbonylation process*

(v) Cross dehydrogenative coupling (CDC) reaction

There is only one instance where a metal free CDC protocol has been employed for the synthesis of anhydrides documented in literature. In 2012, Szpilman and co-workers demonstrated an organocatalyst TEMPO mediated direct aldehydic sp^2 C–H oxidation of aldehydes to mixed anhydrides utilizing pivalic acid as efficient coupling partner (Scheme II.2.5).[16] The *in situ* formed mixed anhydrides can be converted to esters, secondary, tertiary or Weinreb amides in high yields under mild conditions.



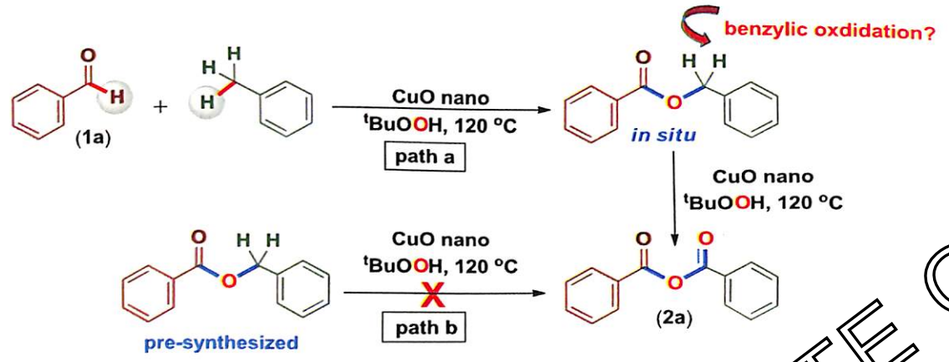
Scheme II.2.5. *Synthesis of anhydrides through CDC reaction*

II.3. Present Work

In continuation to the above mentioned strategies for the synthesis of carboxylic acid anhydrides, herein a CuO nano-catalyzed protocol for the synthesis of the same *via* a CDC reaction was reported. An initial investigation was started with benzaldehyde (**1a**) (1 mmol) as the protypical substrate with nano CuO (5 mol %) and TBHP in decane (5–6 M, 1 equiv) in toluene at 120 °C. Interestingly, the reaction of the aforementioned combinations resulted in the formation of benzoic anhydride (**2a**) in 23% isolated yield (Table II.3.1, entry 1). This unique

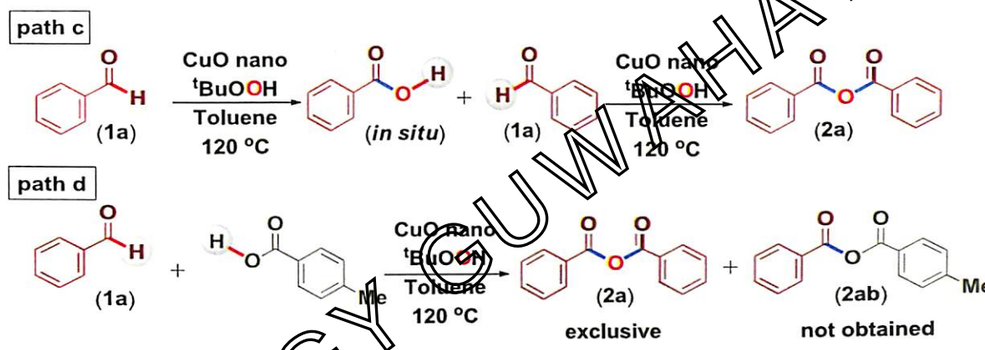
and unprecedented formation of benzoic anhydride raises query about the source of 2nd benzoyl moiety (PhCO–) in it and hence some preliminary investigations were performed.

Preliminary investigation: It was envisioned that benzoic anhydride (**2a**) might originate from benzylic oxidation of the resultant benzyl benzoate, generated by the nano CuO-catalyzed CDC coupling reaction of benzaldehyde (**1a**) and toluene as shown in path a, Scheme II.3.1 like our previous work[5e] (path a, Scheme II.1.1). The possibility of such double oxidations of alkylbenzene (toluene) seemed quite possible due to high reactivity of nano CuO catalyst. However, when a pre-synthesized benzyl benzoate was treated under the same reaction conditions, formation of benzoic anhydride (**2a**) was not observed at all (path b, Scheme II.3.1). This experiment thus ruled out the involvement of the solvent (toluene) in benzoic anhydride (**2a**) as benzoyl (PhCO–) surrogate.



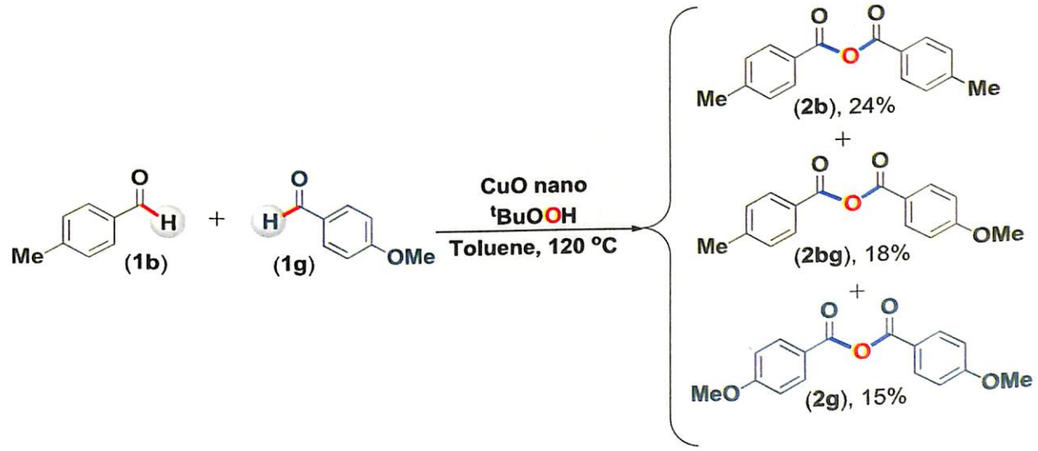
Scheme II.3.1. *A control experiment to check solvent (toluene) involvement*

Alternatively, benzoic anhydride (**2a**) might originate *via* the CDC coupling of benzaldehyde (**1a**) and benzoic acid generated *in situ* under the oxidative conditions (path c, Scheme II.3.2). However, when an equimolar mixture of benzaldehyde (**1a**) and *p*-methylbenzoic acid were reacted, symmetrical anhydride (**2a**) was obtained exclusively, with no trace of unsymmetrical anhydride (**2ab**) as shown in path d, Scheme II.3.2. This result ruled out the possibility of CDC coupling of acid and aldehyde.



Scheme II.3.2. *A control experiment to verify aldehyde-acid CDC coupling*

To confirm the exact coupling partner(s) an equimolar mixture of two different aldehydes, *p*-methylbenzaldehyde (**1b**) and *p*-methoxybenzaldehyde (**1g**) were treated under the reaction conditions. Analysis of the reaction mixture revealed the formation of two symmetrical anhydrides **2b** (24%) and **2g** (15%) and an unsymmetrical anhydride **2bg** (18%) (Scheme II.3.3). From these experiments it is evident that the coupling partners are aldehyde itself and the symmetrical anhydrides (**2b**) and (**2g**) are obtained by the self coupling of respective aldehydes (**1b**) and (**1g**), whereas the unsymmetrical anhydride (**2bg**) is formed by cross-coupling of two different aldehydes.

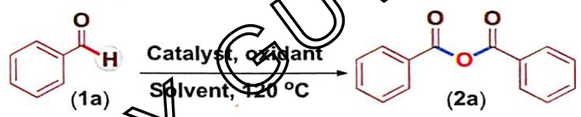


Scheme II.3.3. *A control experiment to verify aldehyde-aldehyde CDC coupling*

Optimization of reaction condition: Encouraged by this unique protocol of anhydride formation from aldehyde by self coupling, further optimizations were performed by varying the reaction parameters. Instead of nano catalyst, the use of conventional Cu salts such as $Cu(OAc)_2$, $CuBr_2$, CuCl and $Cu(OTf)_2$ in toluene failed to give the expected anhydride (**2a**); instead, formation of benzyl benzoate was observed (Table II.3.1, entries 2–5). The formation of benzyl benzoate is consistent with our recent results.[5e] These results suggest the differential reactivity of nano CuO compared with that of other Cu salts. To ascertain the special attribute of nano CuO (> 50 nm) an identical reaction was performed with ordinary CuO and it was found that the later behave more like typical Cu-salts giving > 10% yield of the anhydride (**2a**) (Table II.3.1, entry 6). This experiment demonstrates the peculiar chemical properties of nano CuO compared with ordinary copper oxide. Proceeding further towards optimization, for the conversion of benzaldehyde (**1a**) into benzoic anhydride (**2a**), solvent 1,2-dichloroethane (DCE) gave the best yield (31%) compared with other solvents such as DMF (2%), DMSO (3%), CH_3CN (16%) and chlorobenzene (22%) (Table II.3.1, entries 7–11). The product yield improved substantially (52%) when the quantity of TBHP was increased to two fold (Table II.3.1, entry 12). Extending the reaction time was not beneficial because the anhydride generated decomposed with time, which may be due to the presence of excess TBHP. Sequential addition of TBHP in four equal lots in a time interval of 30 minutes obviates the problem and the yield improved up to 61% after 5 h (Table II.3.1, entry 13). The use of an equivalent quantity of aqueous TBHP in lieu of a decane solution of TBHP (5–6 M) was not so satisfactory and the yield dropped to 45% (Table II.3.1, entry 14). A range of other oxidants such as di-*tert*-butyl peroxide (DTBP), H_2O_2, *m*-chloroperbenzoic acid (*m*-CPBA), $K_2S_2O_8$ and Oxone were tested; however, all were found to be ineffective for this transformation (Table II.3.1, entries 15–19). Either a decrease in the catalyst loading to 2.5 mol % or a reduction in the reaction temperature to 80 °C had adverse effects on product yields. Furthermore, the reaction failed to proceed in the absence of either nano CuO or TBHP, giving no traces of benzoic anhydride (**2a**), confirming the essential requirement for both reagents in this transformation (Table II.3.1, entries 20–21). The question then arises whether the central oxygen in anhydride originates from the TBHP or from atmospheric oxygen. To investigate the later possibility, the reaction was performed in an argon atmosphere. Identical yield of the product under these conditions confirmed that atmospheric oxygen is not the source of oxygen in the anhydride; rather, it must originates from TBHP. Thus, a combination of

aldehyde (**1a**, 1 equiv), CuO nano (5 mol %) and portionwise addition of TBHP in decane (2 equiv) at 120 °C in DCE was chosen as the optimized conditions for the self coupling of aldehydes.

Table II.3.1. Screening of reaction condition



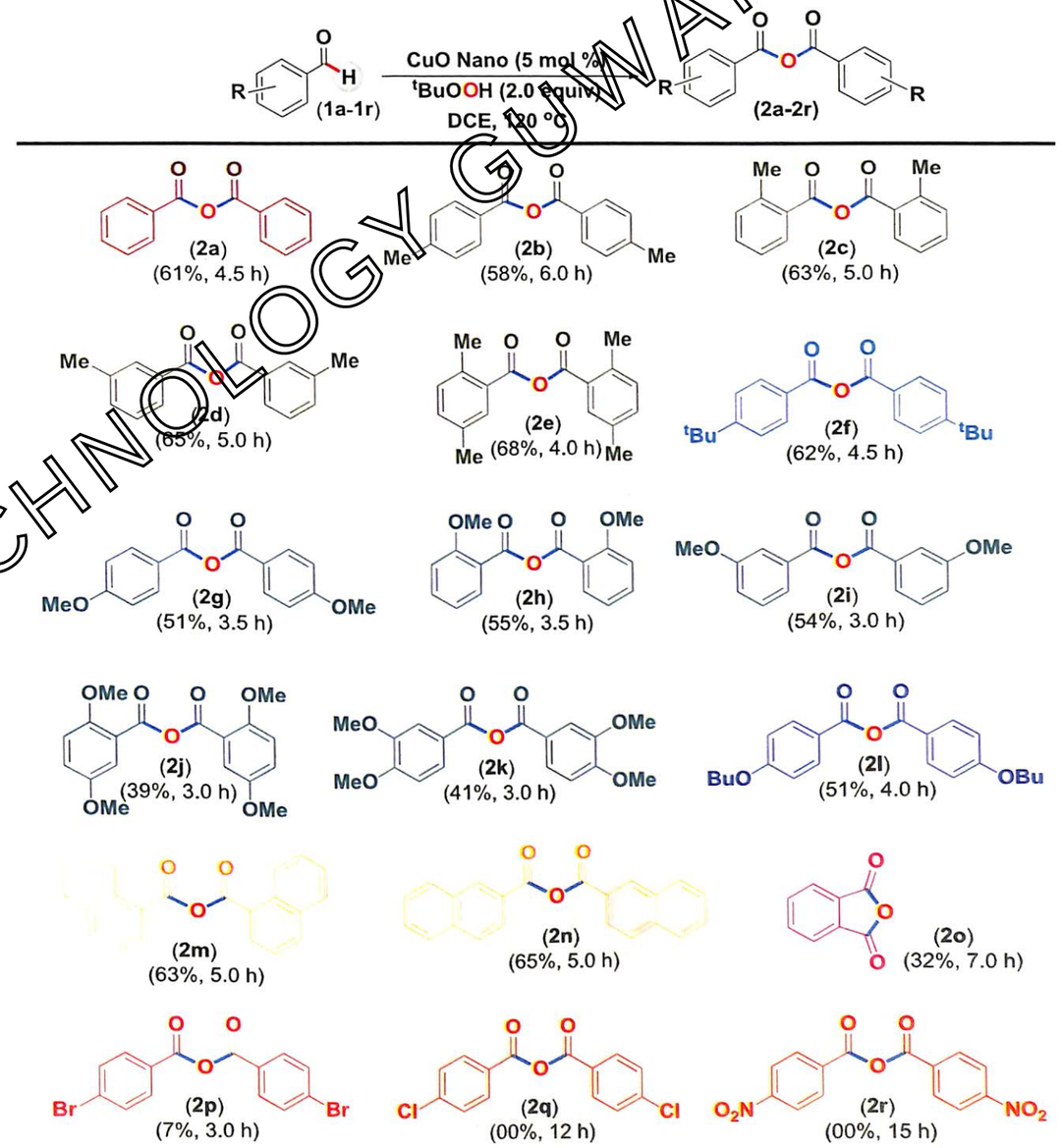
Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	Yield (%)[a]
1	CuO nano (5)	TBHP (1)	Toluene	23
2	$Cu(OAc)_2$ (5)	TBHP (1)	Toluene	0[b]
3	$CuBr_2$ (5)	TBHP (1)	Toluene	0[b]
4	CuCl (5)	TBHP (1)	Toluene	0[b]
5	$Cu(OTf)_2$ (5)	TBHP (1)	Toluene	0[b]
6	CuO (5)	TBHP (1)	Toluene	< 10
7	CuO nano (5)	TBHP (1)	DCE	31
8	CuO nano (5)	TBHP (1)	DMF	2
9	CuO nano (5)	TBHP (1)	DMSO	3
10	CuO nano (5)	TBHP (1)	CH_3CN	16
11	CuO nano (5)	TBHP (1)	PhCl	22
12	CuO nano (5)	TBHP (2)	DCE	52
13	**CuO nano (5)**	**TBHP (2)**	**DCE**	**61**[c]
14	CuO nano (5)	TBHP (2) (aq)	DCE	45
15	CuO nano (5)	DTBP (2)	DCE	0[d]
16	CuO nano (5)	H_2O_2 (2)	DCE	0[d]
17	CuO nano (5)	*m*-CPBA (2)	DCE	0[d]
18	CuO nano (5)	$K_2S_2O_8$ (2)	DCE	0[d]
19	CuO nano (5)	Oxone (2)	DCE	0[d]
20	CuO nano (5)	-	DCE	0[d]
21	-	TBHP (2)	DCE	0[e]

[a]Isolated yield after 4.5 h. [b]Benzyl benzoate was observed (32–45%). [c]TBHP (2 equiv) was added in 4 portions at 30 minutes intervals. [d]Recover of starting material. [e]Converted to benzoic acid.

Substrate scope for anhydride synthesis: To extend the substrates scope of this unique oxidative coupling reaction, the present conditions were applied to a range of other aldehydes. As summarized in Scheme II.3.4, aromatic aldehydes bearing electron-rich substituents, irrespective of their position(s) in aromatic ring, underwent the CDC reaction smoothly to afford the corresponding symmetrical carboxylic acid anhydrides in modest to good yields. Aromatic aldehydes containing weakly activating substituents such as *p*-methyl (**1b**) coupled efficiently under the reaction conditions, providing (**2b**) in 58% yield (Scheme II.3.4). Similarly, other

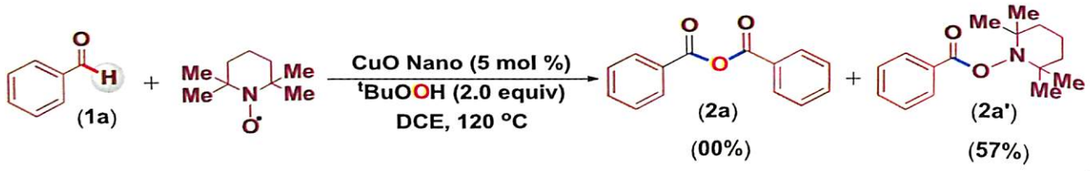
isomeric aldehydes including *o*-methyl (**1c**) and *m*-methyl (**1d**) reacted efficiently to furnish their corresponding anhydrides (**2c**) and (**2d**), respectively in 63% and 65% yields (Scheme II.3.4). 2,5-Dimethyl benzaldehyde (**1e**), when reacted under the identical conditions, gave a good yield (68%) of corresponding anhydride (**2e**). The CDC coupling reaction of *p*-*tert*-butyl benzaldehyde (**1f**) afforded 62% yield of symmetric anhydride (**2f**). However, for *p*-methoxybenzaldehyde (**1g**), although the reaction proceeded rapidly, giving the corresponding anhydride (**2g**), the product decomposed giving only 51% isolated yield. Likewise, when other aromatic aldehydes bearing one or more methoxy substituents in the aryl ring such as *o*-methoxy (**1h**), *m*-methoxy (**1i**), 2,5-dimethoxy (**1j**), and 3,4-dimethoxy (**1k**) underwent oxidative homocoupling, modest yields (41–55%) of the respective anhydrides (**2h**), (**2i**), (**2j**) and (**2k**) were obtained (Scheme II.3.4). Other aromatic aldehyde bearing an activating substituent such as *p*-butoxy benzaldehyde (**1l**) provided 51% yield of (**2l**). Although the CDC reactions were found faster for aromatic aldehydes bearing methoxy substituents, the final isolated yields were lower due to concurrent decomposition of resultant anhydrides to carboxylic acids. The present protocol was found to be equally effective for polycyclic aromatic aldehydes such as 1-napthyldehyde (**1m**) and 2-napthyldehyde (**1n**) which produced their corresponding anhydrides (**2m**) and (**2n**) in 63% and 65% yields, respectively. Intramolecular CDC of an aromatic 1,2-dicarbaldehyde [*i.e.* *o*-phthaldehyde (**1o**)] led to the formation of phthalic anhydride (**2o**) in 32% yield. One setback of this interesting transformation is that whereas aromatic aldehydes possessing weakly electron-withdrawing groups gave negligible amounts of product, substrates possessing strongly electron-withdrawing groups completely failed to give their desired anhydrides. When *p*-bromobenzaldehyde (**1p**) was subjected to the reaction, a trace of product (**2p**, 7%) was detected by GC and IR, as shown in Scheme II.3.4. Other aldehydes possessing deactivating substituents such as *p*-Cl (**1q**) and *p*-NO_2 (**1r**) failed to yield any traces of the desired anhydrides (**2q**) and (**2r**) respectively. Aliphatic aldehydes such as acetaldehyde, cyclohexylcarbaldehyde and glutaraldehyde failed to undergo intermolecular and intramolecular CDC reaction.

Scheme II.3.4. Substrate scope for nano CuO-catalyzed synthesis of anhydrides from aldehydes through CDC[a,b]



[a]Reaction conditions: aroylaldehyde (1 mmol), CuO (5 mol %) and TBHP in decane (2 equiv, 400 μL) at 120 °C.
[b]Yield of the isolated pure product.

Mechanistic studies: To deduce a possible mechanistic path, a reaction was performed in the presence of one equivalent of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). Isolation of TEMPO-ester (**2a′**) along with complete inhibition of anhydride product formation (**2a**) suggests the formation of an acyl radical in reaction medium and radical nature of the reaction mechanism (Scheme II.3.5).



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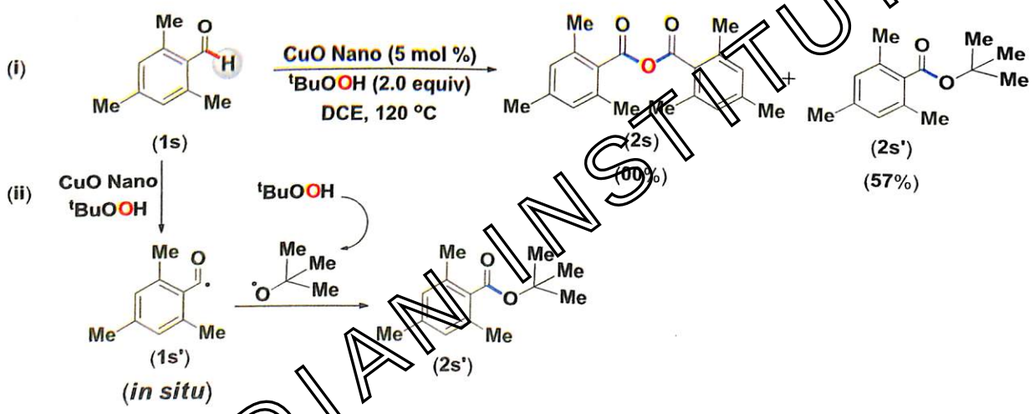
Scheme II.3.5. *Reaction performed in presence of radical inhibitor TEMPO*

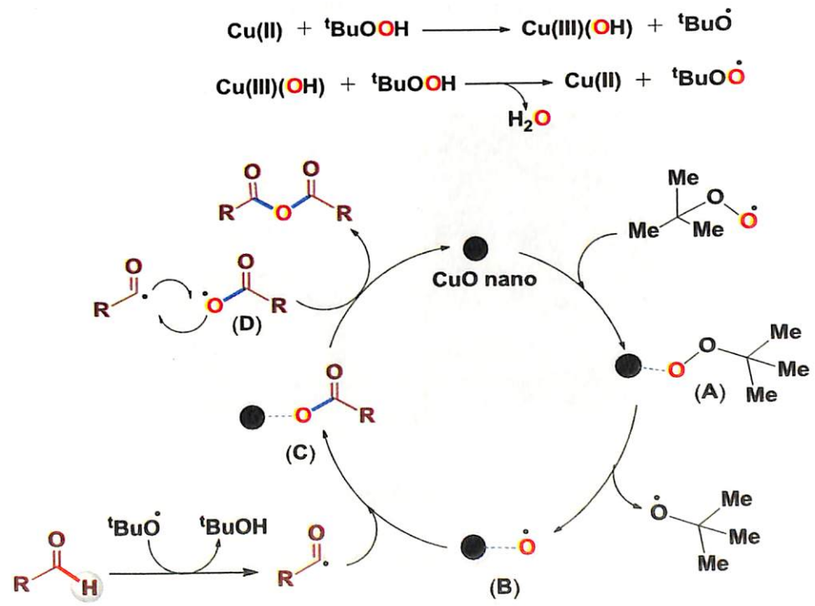
Furthermore, during the reaction of 2,4,6-trimethyl benzaldehyde (**1s**), formation of only *tert*-butyl 2,4,6-trimethylbenzoate (**2s′**) (57%) was observed, rather than the expected anhydride (**2s**) as shown in Scheme II.3.6(i). Formation of a *tert*-butoxy radical could take place by radical coupling of the corresponding acyl radical intermediate (**1s′**) obtained by the reaction of aldehyde (**1s**) and TBHP with *tert*-butoxy radical.[9] Thus, one half of the anhydride originates from the intermediate acyl radical. In this reaction, no trace of corresponding anhydride (**2s**) was observed, which ruled out the possible formation of (**2s′**) by the nucleophilic attack of *tert*-butanol on the corresponding anhydride (**2s**) generated *in situ*, suggesting it originates through coupling of acyl radical (**1s′**) and *tert*-butoxy radical as shown in Scheme II.3.6(ii).



Scheme II.3.6. *Reaction with 2,4,6-trimethyl benzaldehyde (1s)*

The product (**2s′**) is a dead end product and does not react further even in the presence of another aldehyde to give any mixed anhydride. From Scheme II.3.2 it is evident that carboxylic acid is not the other coupling partner but the other half must be an equivalent radical species obtained in the medium.

Based on the results of the controlled experiments, from the isolation of trapped intermediate (**2s′**), and from recent reports,[17a,b] the mechanism presented in Scheme II.3.7 has been suggested. Initially, reaction of Cu^{II} and *tert*-butylhydroperoxide (TBHP) generates a *tert*-butoxy radical and Cu^{III} species in the medium. The Cu^{III} species is reduced to Cu^{II} by the action of a second equivalent of TBHP and produces $^{t}BuOO^{\bullet}$ radical. This $^{t}BuOO^{\bullet}$ radical generated *in situ* then forms *tert*-butyl nano-CuO peroxidase species (**A**), similar to the nano-Au peroxidase species proposed by Shaiano *et al.*[17b] Homolytic cleavage of intermediate (**A**) generates a reactive metal oxide radical (**B**) on the surface of the nanoparticles. The acyl radical formed *in situ* by the action of TBHP and aldehyde produces CuO-acylate species (**C**). Further, homolytic cleavage of (**C**) gives acyloxy radical (**D**), which couples with an acyl radical to produce carboxylic anhydride with concurrent regeneration of CuO nano catalyst for next catalytic cycle.



Scheme II.3.7. *Plausible reaction mechanism for anhydride formation*

The nano CuO catalyst was recovered from reaction mixture after one cycle by centrifugation which was washed successively with ethyl acetate, water and acetone and dried. As evident from the powder XRD of nano CuO before and after one cycle, the composition of the catalyst remains unchanged (Figure II.3.1). However, a substantial drop in the isolated yield (61% to 45%) was observed when the catalyst was recycled, which is due to agglomeration leading to inheterogenity in the particle size, as evident from the TEM image of CuO nanoparticles before and after 1st cycle (Figure II.3.2).

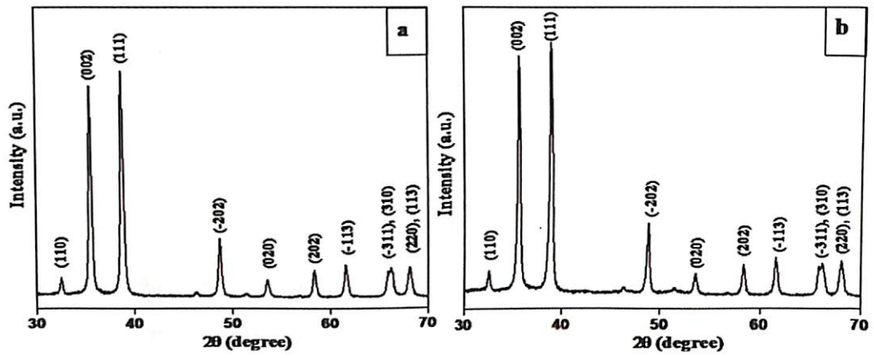


Figure II.3.1. Powder X-ray diffraction pattern of nano CuO: (a) fresh (b) after 1st cycle

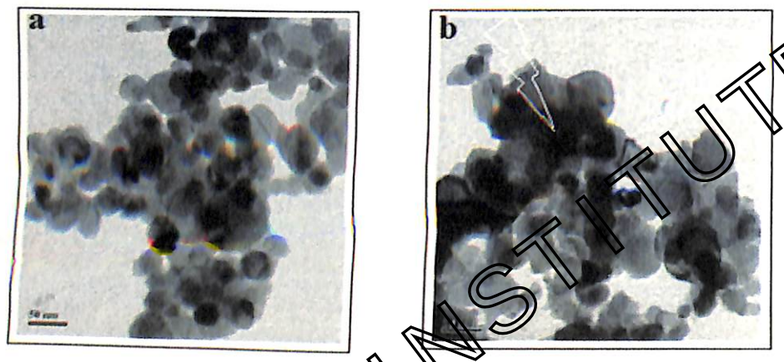


Figure II.3.2. TEM images of (a) fresh nano CuO and (b) nano CuO after 1st cycle

In conclusion, a convenient method has been developed for the synthesis of carboxylic acid anhydrides from aromatic aldehydes in modest to good yields. This method follows a unique double sp^2 C–H functionalization of aldehydes in the presence of nano CuO catalyst. This is the

first example where CuO nano catalyst has been utilized for the synthesis of carboxylic acid anhydrides *via* CDC coupling reaction of aromatic aldehydes. Moreover, this protocol also shows a differential reactivity to that of organocatalytic system (TBAI/TBHP) during sp^2 C–H functionalization of aldehydes. While the present protocol (nano CuO/TBHP) furnished carboxylic acid anhydrides as the exclusive product, the organocatalytic system yielded corresponding *tert*-butyl-perester as the main product. TBHP serves as oxidant as well as anhydric oxygen donar in this reaction. Instead of its uniqueness, this protocol suffered from major drawbacks as it failed to give corresponding anhydrides from aliphatic aldehydes and aromatic aldehydes containing electron-withdrawing substituents. This limitation of this methodology has to address in near future.

II.4. Experimental Section

II.4.1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Elemental analysis was performed with a Perkin Elmer 2400 elemental analyzer. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. Commercially available CuO nano (<50 nm) were purchased from Sigma-Aldrich.

II.4.2. General procedure for the synthesis of benzoic anhydride (2a) from benzaldehyde (1a) utilizing CuO oxide nano catalyst and TBHP:

To a solution of benzaldehyde (**1a**, 106 mg, 1 mmol) in DCE (3 mL) was added CuO nano catalyst (5 mol %, 4 mg) and 100 μL (0.5 mmol) of TBHP in decane (5–6 M) and the resultant mixture was placed in a preheated oil bath (120 °C). Second, third and fourth portions of TBHP (3 x 100 μL) were added at time intervals of 30 minutes. The progress of the reaction was monitored by TLC. After 5 h, the total conversion of the starting material and the appearance of

a new spot were observed by TLC. The crude product obtain by evaporation of DCE, was extracted with ethyl acetate (2 x 20 mL) and 10% saturated $NaHCO_3$ solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified over a column on silica gel (hexane/ethyl acetate = 9:1) to give benzoic anhydride (**2a**) in 61% yield (69 mg).

II.4.3. Mechanistic investigation in presence of radical inhibitor TEMPO:

An oven-dried 25 mL round bottle flask was charged with benzaldehyde (**1a**, 106 mg, 1 mmol) in DCE (3 mL) was added CuO nano catalyst (5 mol %, 4 mg), TEMPO (156 mg, 1 mmol) and 100 μL (0.5 mmol) of TBHP in decane (5–6 M) and the resultant mixture was placed in a preheated oil bath (120 ^{o}C). Second, third and fourth portions of TBHP (3 x 100 μL) were added at time intervals of 30 minutes. The progress of the reaction was monitored by TLC. The reaction after 5 h afforded the TEMPO-ester (**2a'**) in 63% (164 mg) yield along with complete inhibition of anhydride formation (**2a**). This reaction supports the formation of acyl radical in the reaction medium and the radical nature of the mechanism.

II.5. References and Notes

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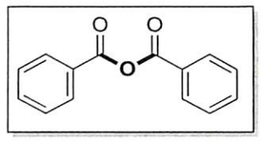
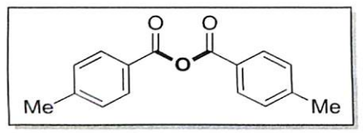
II.6. Spectral data

Benzoic anhydride (2a):



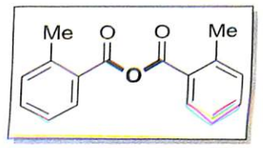
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.53 (t, 4H, J = 7.8 Hz), 7.67 (t, 2H, J = 7.8 Hz), 8.16 (d, 4H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 129.0, 130.7, 134.7, 162.5; IR (KBr): 3064, 2925, 1789, 1727, 1694, 1599, 1451, 1316, 1278, 1173, 1039, 1017, 996, 800, 778, 703 cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{10}O_3$ (226.227): C 74.33, H 4.46; found C 74.45, H 4.42.

4-Methylbenzoic anhydride (2b):



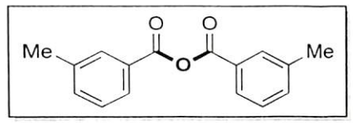
White solid; M.p. 83–86 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 6H), 7.30 (d, 4H, J = 8.4 Hz), 8.03 (d, 4H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.9, 126.4, 129.7, 130.8, 145.7, 162.7; IR (KBr): 2954, 2923, 1774, 1713, 1609, 1223, 1209, 1172, 1039, 1003, 838, 823 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55; found C 75.67, H 5.57.

2-Methylbenzoic anhydride (2c):



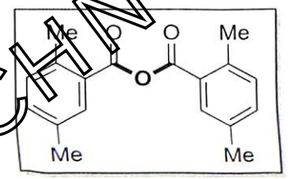
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.71 (s, 6H), 7.30–7.34 (m, 4H), 7.51 (t, 2H, J = 7.2 Hz), 8.06 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 22.2, 126.3, 127.9, 131.6, 132.4, 133.8, 142.7, 163.1; IR (KBr): 3069, 2975, 2930, 1784, 1723, 1602, 1574, 1487, 1458, 1338, 1255, 1126, 977 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55; found C 75.65, H 5.57.

3-Methylbenzoic anhydride (2d):



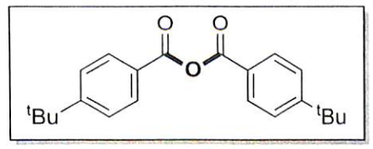
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 6H), 7.41 (t, 2H, J = 7.8 Hz), 7.48 (d, 2H, J = 7.8 Hz), 7.94–7.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.4, 127.9, 128.9, 131.2, 135.5, 138.9, 162.8; IR (KBr): 3068, 2923, 1786, 1723, 1607, 1589, 1486, 1456, 1381, 1251, 1154, 1031, 997, 892, 793 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55; found C 75.67, H 5.52.

2,5-Dimethylbenzoic anhydride (2e):



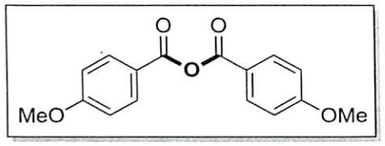
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.37 (s, 6H), 2.65 (s, 6H), 7.22 (d, 2H, J = 7.2 Hz), 7.32 (d, 2H, J = 7.2 Hz), 7.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 20.9, 21.7, 127.7, 132.0, 132.3, 134.6, 135.9, 139.6, 163.4; IR (KBr): 2927, 2861, 1782, 1723, 1614, 1571, 1499, 1449, 1382, 1303, 1242, 1163, 1137, 1004, 977, 819, 770 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{18}O_3$ (282.333): C 76.57, H 6.43; found C 76.70, H 6.49.

4-(*tert*-butyl)Benzoic anhydride (2f):



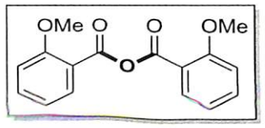
Colourless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 1.36 (s, 18H), 7.53 (d, 4H, J = 8.4 Hz), 8.08 (d, 4H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 31.2, 35.4, 126.0, 126.3, 130.7, 158.6, 162.7; IR (KBr): 2963, 2871, 1789, 1731, 1607, 1574, 1463, 1410, 1366, 1224, 1178, 1107, 1045, 852, 764 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{26}O_3$ (338.439): C 78.07, H 7.74; found C 78.15, H 7.77

4-Methoxybenzoic anhydride (2g):



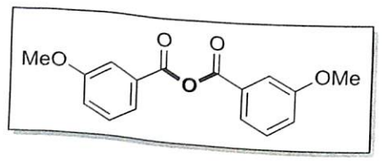
White solid; M.p. 95.5–97.5 °C (reported 94–96 °C)[14]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.89 (s, 6H), 6.98 (d, 4H, J = 8.8 Hz), 8.09 (d, 4H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.8, 114.3, 121.4, 133.0, 162.5, 164.7; IR (KBr): 2946, 1790, 1712, 1634, 1608, 1510, 1465, 1331, 1264, 1221, 1159, 1041, 1014, 1001, 838, 760 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_5$ (286.2788): C 67.13, H 4.93; found C 67.25, H 4.90.

2-Methoxybenzoic anhydride (2h):



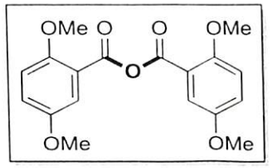
Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.83 (s, 6H), 6.96–7.03 (m, 4H), 7.54 (t, 2H, J = 6.8 Hz), 7.99 (d, 2H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 56.1, 112.3, 120.5, 133.3, 135.4, 160.3, 162.1; IR (KBr): 2925, 2841, 1782, 1731, 1600, 1579, 1489, 1465, 1436, 1288, 1256, 1200, 1165, 1117, 1020, 755 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_5$ (286.2788): C 67.13, H 4.93; found C 67.23, H 4.93.

3-Methoxybenzoic anhydride (2i):



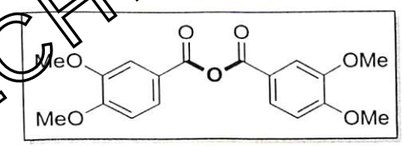
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.86 (s, 6H), 7.21 (dd, 2H, J_1 = 2.4 Hz, J_2 = 7.8 Hz), 7.24 (t, 2H, J = 8.4 Hz), 7.645–7.652 (m, 2H), 7.74 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.6, 115.1, 121.3, 123.1, 130.08, 130.25, 160.1, 162.4; IR (KBr): 2940, 2837, 1788, 1724, 1600, 1585, 1487, 1465, 1453, 1431, 1289, 1262, 1194, 1153, 1022, 991, 896, 749 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{14}O_5$ (286.2788): C 67.13, H 4.93; found C 67.27, H 4.95.

2,5-Dimethoxybenzoic anhydride (2j):



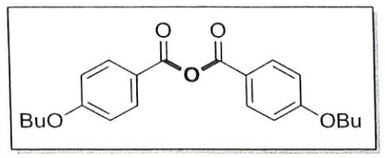
Yellowish solid; M.p. 87–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.82 (s, 12H), 6.95 (d, 2H, J = 8.8 Hz), 7.13 (dd, 2H, J_1 = 3.2 Hz, J_2 = 9.2 Hz), 7.55 (d, 2H, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 56.1, 56.7, 113.9, 117.0, 118.6, 121.9, 153.3, 154.7, 162.1; IR (KBr): 2933, 1784, 1731, 1581, 1500, 1464, 1418, 1281, 1232, 1180, 1164, 1021, 815 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{18}O_7$ (346.3306): C 62.42, H 5.24; found C 62.50, H 5.21.

3,4-Dimethoxybenzoic anhydride (2k):



Yellowish solid; M.p. 122–124 °C (reported[18] 124–125 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.95 (s, 6H), 3.97 (s, 6H), 6.94 (d, 2H, J = 8.4 Hz), 7.62 (s, 2H), 7.78 (dd, 2H, J_1 = 1.8 Hz, J_2 = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 56.19, 56.25, 110.6, 112.7, 121.4, 125.2, 149.2, 154.5, 162.6; IR (KBr): 2925, 2852, 1762, 1711, 1676, 1518, 1467, 1419, 1351, 1270, 1238, 1198, 1162, 1134, 1065, 1019, 911, 868 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{18}O_7$ (346.3306): C 62.42, H 5.24; found C 62.65, H 5.23.

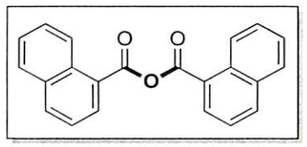
4-Butoxybenzoic anhydride (2l):



^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.97 (t, 6H, J = 7.6 Hz), 1.46–1.52 (m, 4H), 1.76–1.82 (m, 4H), 4.03 (t, 4H, J = 6.8 Hz), 6.94 (d, 4H, J = 9.2 Hz), 8.06 (d, 4H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.9, 19.3, 31.2, 68.2, 114.7, 121.1, 132.9, 162.5, 164.3; IR (KBr): 3073, 2959, 2872, 1756, 1719, 1605, 1576, 1509, 1467,

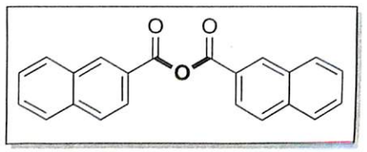
1422, 1317, 1264, 1223, 1162, 1052, 964, 836 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{26}O_5$ (370.4378): C 71.33, H 7.07; found C 71.45, H 7.11.

1-Naphthoic anhydride (2m):



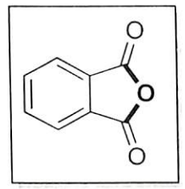
Yellow solid; M.p. 140–142 °C (reported 142–144 °C)[15b]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.56 (t, 2H, J = 8.0 Hz), 7.61 (t, 2H, J = 7.6 Hz), 7.72 (t, 2H, J = 7.6 Hz), 7.94 (d, 2H, J = 8.4 Hz), 8.15 (d, 2H, J = 8.0 Hz), 8.44 (d, 2H, J = 6.8 Hz), 9.16 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 124.6, 125.0, 125.8, 126.9, 129.0, 132.0, 132.3, 134.1, 135.7, 163.1; IR (KBr): 3052, 2922, 1770, 1708, 1592, 1568, 1510, 1441, 1348, 1262, 1224, 1170, 1145, 1058, 961, 771 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{14}O_3$ (326.328): C 80.97, H 4.32; found C 81.08, H 4.35.

2-Naphthoic anhydride (2n):



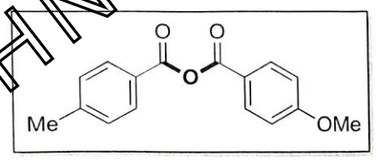
Off-white solid; M.p. 115–117 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.59 (t, 2H, J = 7.8 Hz), 7.65 (t, 2H, J = 7.8 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 9 Hz), 8.00 (d, 2H, J = 7.8 Hz), 8.17 (dd, 2H, J_1 = 1.2 Hz, J_2 = 10.2 Hz), 8.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 125.6, 126.3, 127.4, 128.1, 129.1, 129.5, 129.9, 132.7, 133.0, 136.5, 162.9; IR (KBr): 3056, 2924, 2853, 1786, 1723, 1629, 1596, 1504, 1460, 1355, 1263, 1216, 1179, 1130, 1086, 1032, 949, 863 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{14}O_3$ (326.328): C 80.97, H 4.32; found C 80.05, H 4.30.

Isobenzofuran-1,3-dione (2o):



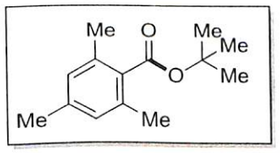
White Solid; M.p. 132–134 °C (reported 130–132 °C)[14]; ^{1}H NMR ($CDCl_3$ + DMSO-d_6 (1-2 drop), 400 MHz): δ (ppm) 7.79–7.82 (m, 2H), 7.88–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6 (1-2 drop), 100 MHz): δ (ppm) 125.6, 131.1, 136.1, 162.7; IR (KBr): 2932, 2013, 1852, 1791, 1762, 1691, 1469, 1403, 1358, 1258, 1108, 1070, 906, 738 cm^{-1}; elemental analysis calcd. (%) for $C_8H_4O_3$ (148.1154): C 64.87, H 2.72; found C 64.96, H 2.70.

4-Methoxybenzoic-4-methylbenzoic anhydride (2bg):



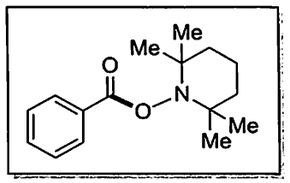
Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.43 (s, 3H), 3.88 (s, 3H), 6.96 (d, 2H, J = 9.2 Hz), 7.29 (d, 2H, J = 8.4 Hz), 8.02 (d, 2H, J = 8.4 Hz), 8.08 (d, 2H, J = 8.8 Hz); IR (KBr): 2924, 2851, 1780, 1718, 1606, 1629, 1510, 1460, 1263, 1222, 1162, 1037, 1013, 997, 841 cm^{-1}; elemental analysis calcd. (%) for $C_{13}H_{10}N_2$ (194.2315): C 71.10, H 5.22; found C 71.19, H 5.25.

***Tert*-butyl 2,4,6-trimethylbenzoate (2s′):**



Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.59 (s, 9H), 2.27 (s, 3H), 2.31 (s, 6H), 6.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 19.7, 21.3, 28.5, 81.6, 128.5, 132.8, 134.6, 138.8, 169.7; IR (KBr): 2977, 2926, 1721, 1612, 1471, 1456, 1367, 1282, 1258, 1162, 1089, 858, 843 cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{20}O_2$ (220.3066): C 76.33, H 9.15; found C 76.45, H 9.18.

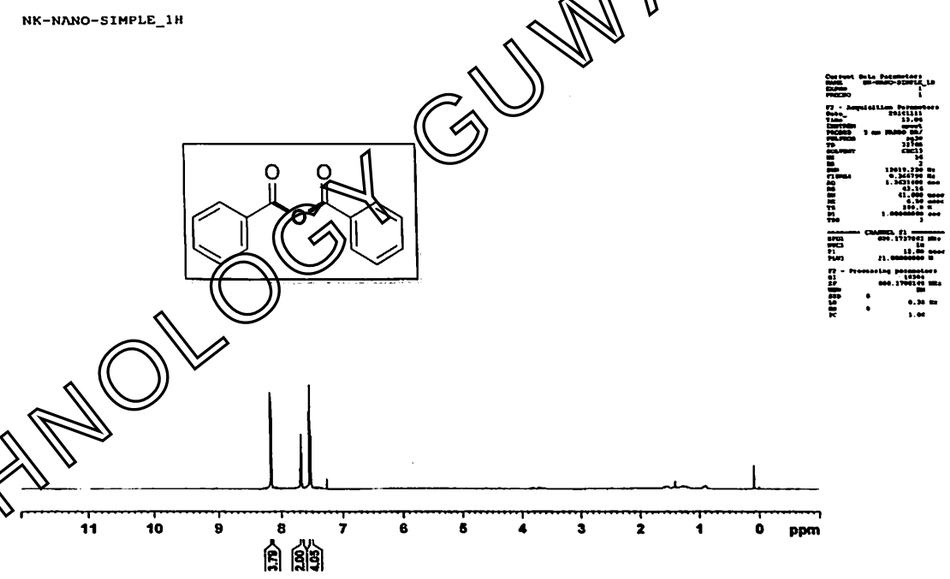
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (2a′):



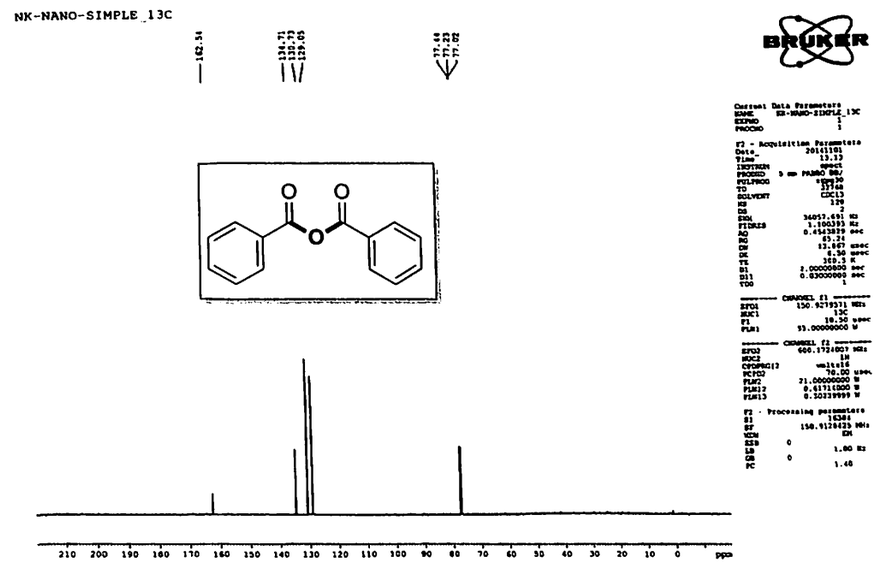
Reddish solid; M.p. 83–85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.17 (s, 6H), 1.32 (s, 6H), 1.49–1.52 (m, 1H), 1.62–1.65 (m, 2H), 1.72–1.86 (m, 3H), 7.51 (t, 2H, J = 7.6 Hz), 7.62 (t, 1H, J = 7.2 Hz), 8.13 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 15.9, 19.7, 37.9, 59.2, 127.3, 128.4, 128.5, 131.6, 165.2; IR (KBr): 3069, 2977, 2925, 1744, 1597, 1448, 1380, 1363, 1251, 1236, 1132, 1082, 1064, 992, 905 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{23}NO_2$ (261.3584): C 73.53, H 8.87, N 5.36; found C 73.66, H 8.90, N 5.31.

II.7. Selected Spectra

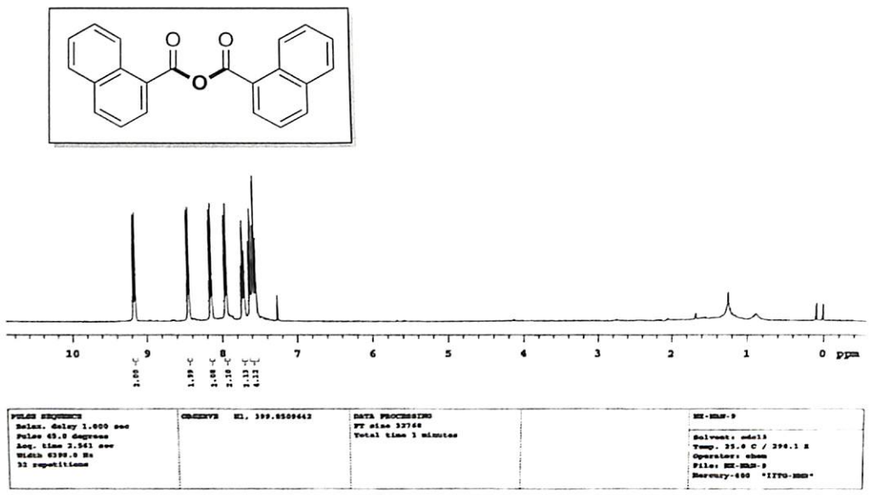
Benzoic anhydride (2a): ^{1}H NMR (600 MHz, $CDCl_3$)



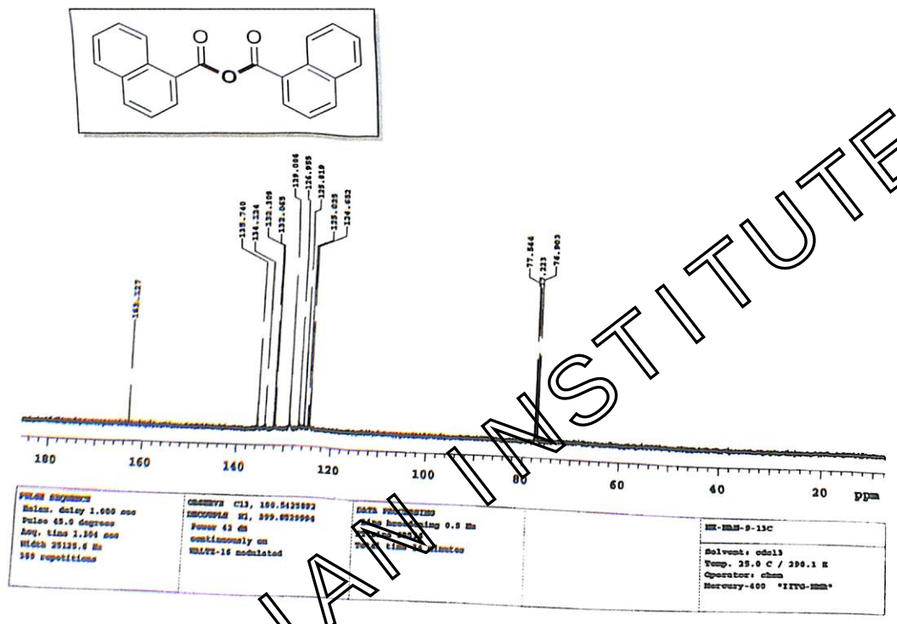
Benzoic anhydride (2a): ^{13}C NMR (150 MHz, $CDCl_3$)



1-Naphthoic anhydride (2m): ^{1}H NMR (400 MHz, $CDCl_3$)

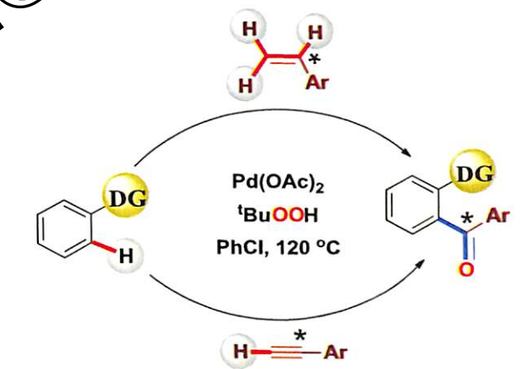


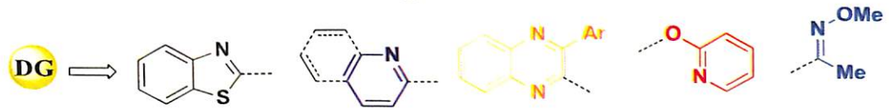
1-Naphthoic anhydride (2m): ^{13}C NMR (100 MHz, $CDCl_3$)



Chapter III

Pd(II)-Catalyzed *o*-Aroylation of Directing Arenes using Terminal Aryl Alkenes and Alkynes: Synthesis of Ketones





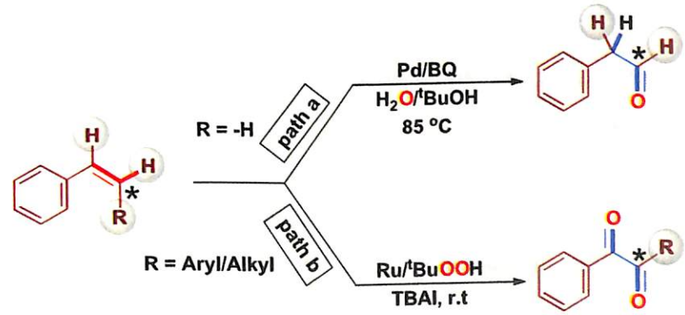
III. Abstract: *A substrate-directed Pd-catalysed o-aroylation strategy has been demonstrated using new aroyl surrogates viz. terminal aryl alkenes and alkynes in the presence of TBHP. By a subtle change in catalyst from Cu to Pd, a differential selectivity is observed. While terminal aryl alkenes/alkynes in the presence of Cu/TBHP is reported to act as o-aryloxy (ArCOO-) source, the use of Pd/TBHP installs an aroyl (ArCO-) group at ortho position with respect to the directing arenes. This strategy have been implemented to a wide range of ligand directed substrates and afforded modest to good yields.*

Chapter III

III. Pd(II)-Catalyzed *o*-Aroylation of Directing Arenes using Terminal Aryl Alkenes and Alkynes: Synthesis of Ketones

III.1. Introduction

The development of efficient and newer strategies for the construction of carbon-carbon (C–C) bonds is of immense interest to synthetic chemists. Formation of complex molecular architectures starting from simple molecules have been earlier achieved *via* various classical approaches like nucleophilic additions, substitutions, Friedel-Craft type reactions, pericyclic reactions and even transition metal-catalyzed cross coupling approaches. Of late extensive investigation on transition metal-catalyzed C–H bond activation strategies have greatly revolutionized the C–C bond forming processes, as C–C bond formation is considered as the "holey grail" of organic chemistry.[1] The direct use of C–H bonds to generate C–C bonds is highly desirable since it has the potential to streamline synthetic schemes by shortening the number of synthetic steps and thus maintaining better atom economy of the processes. In particular, most C–H bond functionalizations processes rely on two elegant approaches *viz.* directing group-assisted C–H functionalization[2] or cross dehydrogenative coupling (CDC).[3]

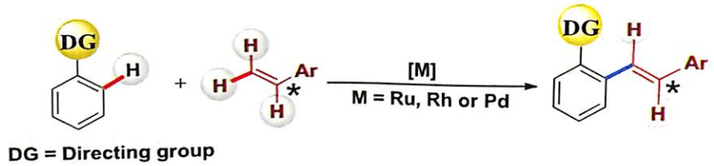


Scheme III.1.1. *Differential oxidation of alkene derivatives under different metal catalysts*

Aryl alkenes are susceptible to undergo Wacker type oxidation to give phenylacetaldehyde (Scheme III.1.1, path a) using a combination of palladium (II) as the catalyst and *p*-benzoquinone as the oxidant as reported by Grubbs group.[4] In an independent work, Wan group

demonstrated that a combination of oxidant TBHP and catalyst Ru, oxidized diarylethenes to 1,2-diketones[5] as shown in Scheme III.1.1, path b).

In a separate study, terminal aryl alkenes are reported to introduce a vinyl moiety at the *ortho* site of ligand directed substrates including imines, ketones, anilides, benzamides, carboxylic acids, benzyl amines, *N*-pyridine oxides and indole derivatives using various transition metal catalysts such as Rh, Ru and even Pd as in Scheme III.1.2.[6]

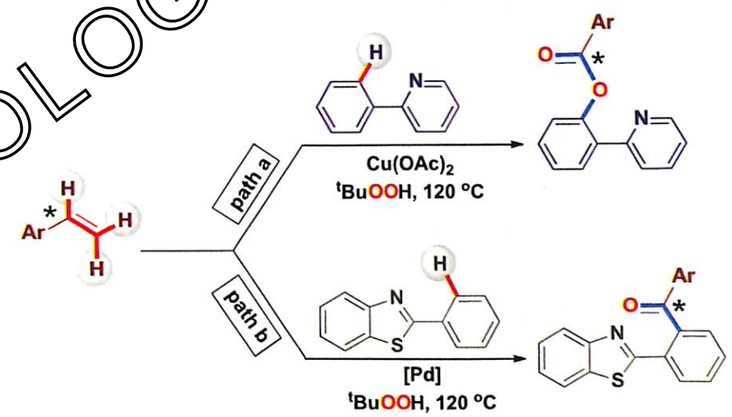


Scheme III.1.2. *Ortho vinylation of directing substrates under different metal catalysis*

Very recently our group have demonstrated a Cu(II)-catalyzed highly efficient protocol for *ortho* benzoxylation of 2-phenylpyridine using terminal aryl alkenes as arylcarboxy (ArCOO–) surrogates utilizing TBHP as oxidant as well as oxygen source as in Scheme III.1.3, path a.[7] In this reaction, terminal alkenes are converted to arylcarboxy surrogates by the action of TBHP and Cu catalyst and subsequently installed a arylcarboxy (ArCOO–) moiety at the *ortho* position of 2-phenylpyridines. The reaction proceeded through sequential C–O bond formations at the expense of four sp^2 hydrogen atom and loss of one carbon atom as CO.

Catalyst-controlled selectivity during directed or non-directed C–C or C–heteroatom bond formation is not unprecedented in literature. In one of our recent report during the synthesis of 2-aminobenzothiazoles from 2-halothioureas, Cu preferred dehalogenative path while Pd followed C–H activation path.[8] Differential reactivity is also observed during directed *o*-functionalization of 2-phenylpyridine with alkylbenzenes; while Pd catalyst is reported to give *o*-aroylated (ArCO–) product,[9a] Cu catalyst installs an arylcarboxy (ArCOO–) group at the *ortho* site.[10] Taking cues from these literature reports on catalyst-controlled selectivities and from our recent success on transition metal-catalyzed *ortho* C–H functionalizations,[8,9] implementation of Pd catalyst during the reaction between 2-phenylbenzothiazole (as directing substrate) and terminal aryl alkene such as styrene was thought. Now the query arises whether this catalytic condition provides *o*-vinylation as reported with catalysts like Ru, Rh and Pd or *o*-benzoxylation as has

been demonstrated with Cu catalyst or all together a differential reactivity leading to a new product may be observed. Instead of formation of *o*-vinylated product or *o*-benzoxylated product (ester formation), the reaction ended up with the exclusive formation of *o*-benzoylated product *i.e.* a ketone (Scheme III.1.3, path b). In this reaction, in the presence of Pd/TBHP system styrene served as the synthetic equivalent of benzoyl (PhCO–) group and subsequent functionalization of *ortho* C–H of 2-phenylbenzothiazole led to the formation of new C–C bond. This result is contrary to the previous substrate directed *o*-vinylation using Pd catalyst, of course a different combinations of oxidants are used.[6d]

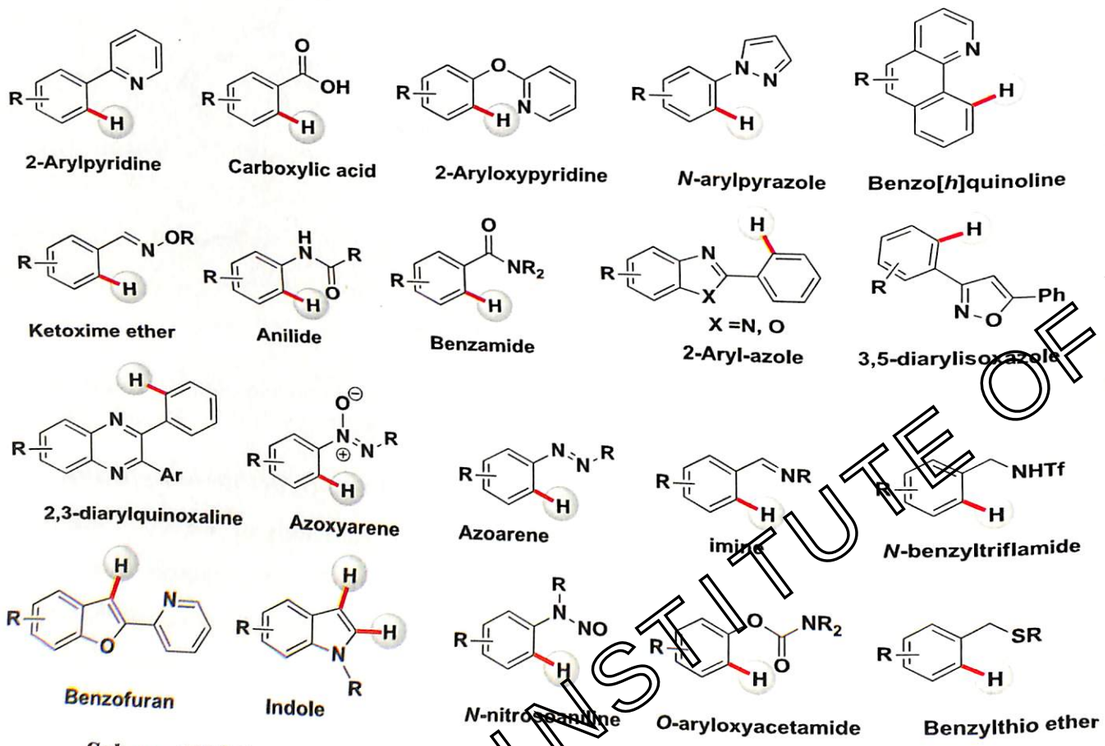


Scheme III.1.3. *Differential reactivity of Cu and Pd catalyst during olefinic oxidation*

III.2. Available Strategies for Ketone Synthesis through *ortho*-Aroylation

Ketones, chemically known as alkanone, constitute a broad family of 'carbonyl' chemistry. They are extensively used in pharmaceutical, natural products, agrochemicals and material chemistry.[11] Traditionally they are synthesized by oxidation of secondary alocohols utilizing stoichiometric amount of various oxidizing agents such as CrO_3, $K_2Cr_2O_7$, PCC (pyridinum chlorochromate) and PDC (pyridinum dichromate) etc.[12] Modified Fridel Craft acylation method, involving the use of stoichiometric amount of Lewis acid is a powerful tool in this field to access corresponding ketones.[13] The metal-catalyzed (lithium, magnesium or aluminium) reduction of various carboxylic acid derivatives such as nitriles, Weinreb amides, anhydrides and acid chlorides is also one of the reliable approach for their synthesis.[14] Though those above mentioned strategies good enough to meet their demand, use of strong nucleophiles, strong basic

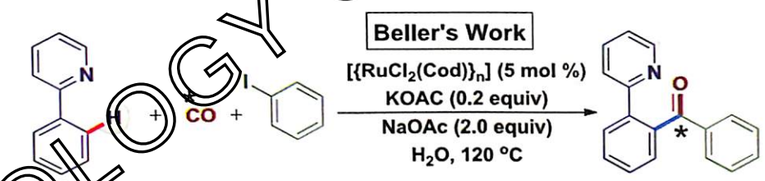
or acidic conditions, use of stoichiometric amount of reagents, harsh reaction conditions, low functional group tolerance and untunable regioselectivity most often bring difficulties to those existing methodologies. To overcome such associated problems in ketone synthesis, recently a number of alternative protocols have been postulated in literature. Among them, transition metals- catalyzed aroylation/acylation of aromatic compounds through C–H functionalization is considered as one of the most promising approach to access ketones. A number of directed substrates as shown in Scheme III.2.1, possessing *N* or *O* even *S* as the chelating atoms have been successfully *ortho* acylated employing various aroyl surrogates. These well-developed strategies can be categorized based on the source of utilized aroyl surrogates as depicted below:



Scheme III.2.1. *Commonly investigated directed substrates for ortho aroylation*

(i) Carbon monoxide (CO) as aroyl surrogate through carbonylative coupling

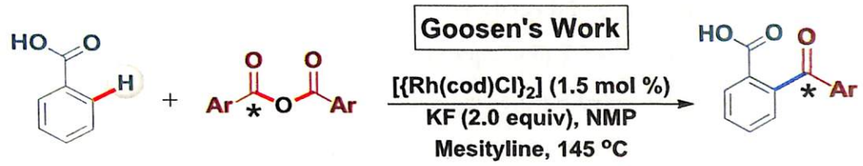
There is only one instance where carbon monoxide (CO) employed as the aroyl surrogate for the metal-catalyzed ligand directed C–H functionalization process. In 2013, Beller and co-workers first demonstrated a ruthenium-catalyzed unique carbonylation protocol for the synthesis of ketones *via* C–H activation of 2-phenylpyridine and its derivatives, pyrazoles and pyrimidines under CO atmosphere as in Scheme III.2.2.[15]



Scheme III.2.2. *Ortho aroylation thorough Carbonylation process*

(ii) Carboxylic acids and its derivatives as aroyl (ArCO–) surrogate

In 2013, Fu group reported a Pd(II)-catalyzed highly efficient and novel protocol for the *ortho* acylation of 2-arylpyridine derivatives employing carboxylic acids as the active aroyl (ArCO–) surrogates.[16a] In their independent work, Kakiuchi and Gooβen group employed acyl chlorides[16b] and carboxylic acid anhydrides[16c] (as shown in Scheme III.2.3), as the efficient coupling partners for the *ortho* acylation of 2-arylpyridines and carboxylic acids respectively under different metal catalysis.

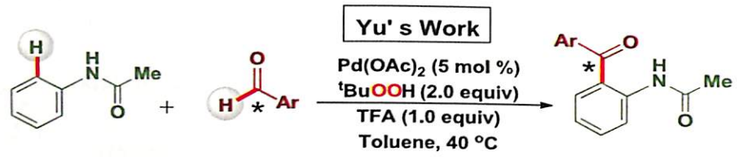


Scheme III.2.3. *Ortho aroylation of carboxylic acid using carboxylic acid anhydrides*

(iii) Aldehyde as aroyl surrogate through CDC reaction

Aldehydes are being regarded as the potent functional moieties to install an aroyl/acyl group at the *ortho* site of various *N*-directed or *O*-directed substrates. In 2009, Cheng group reported the first example of Pd-catalyzed *ortho* acylation of 2-arylpyridines and related compounds.[17a] A number of other directing substrates *viz.* 2-aryloxypyridines, *N*-phenyl pyrazoles, benzo[*h*]quinoline, ketoxime ethers, anilides, benzamides, azoxyarenes, azoarenes, *N*-

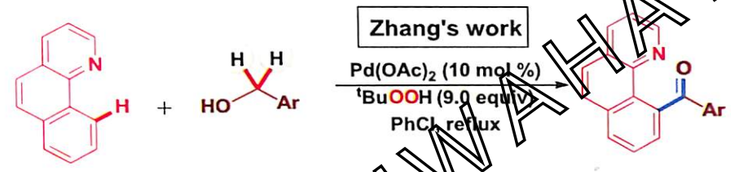
benzyltriflamides, benzofuran, indoles (at C2 or C3 acylation), 2-arylbenzothiazoles, 2-arylbenzoxazoles, 3,5-diarylisoxazoles and 2,3-diarylquinoxazolines derivatives have been subjected for *ortho* acylation employing aldehydes as the aroyl (ArCO–) surrogates.[17b] Palladium salts and TBHP are most often used as catalyst and terminal oxidant respectively in these above mentioned strategies. Though Rh-catalyzed protocols for the *ortho* acylation of benzamides,[17c] ketoxime ether[17d] and C2 acylation of indole[17e] derivatives are also known in literature. This elegant strategy can be categorized as the directing group-assisted cross dehydrogenative coupling reaction. One representative example of this category using anilide as the directing substrate is shown in Scheme III.2.4.



Scheme III.2.4. *Ortho aroylation using aldehyde as an aroyl surrogate*

(iv) Alcohol as aroyl surrogate through CDC reaction

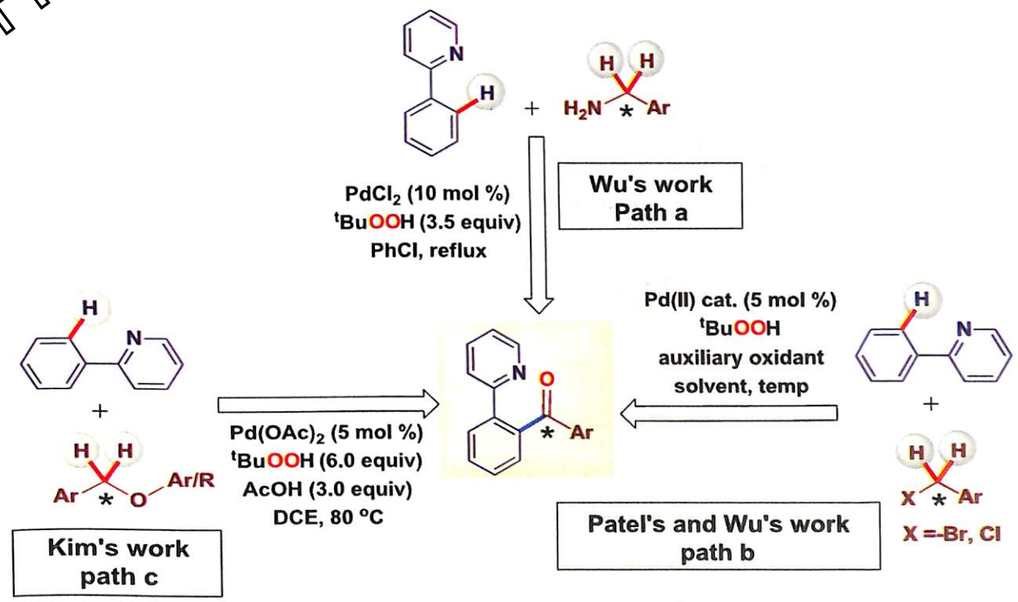
Primary alcohol, especially benzyl alcohol derivative, can be oxidized into the corresponding aldehyde under oxidative conditions and this *in situ* generated aldehyde can serve as active aroyl (ArCO–) source in metal-catalyzed acylation strategies. Due to this property of alcohols, the use of them as the efficient aroyl (ArCO–) surrogates has also been explored in literature. Li and co-workers first demonstrated a Pd-catalyzed TBHP mediated intriguing protocol for the regioselective *ortho* acylation of 2-phenylpyridines utilizing benzyl alcohols.[18] Almost similar strategies have been implemented for the competent *ortho* acylation of other directing substrates such as anilides, 2-arylbenzothiazoles, 2-arylbenzoxazoles, benzo[*h*]quinoline, *N*-benzyltriflamides, 2-aryloxypyridines, ketoxime ethers, azoxyarenes and azoarenes employing benzyl alcohols under Pd/TBHP catalytic system.[17b] One representative example of this category using benzo[*h*]quinoline as the directing substrate is shown in Scheme III.2.5.



Scheme III.2.5. *Ortho aroylation using benzyl alcohol as an aroyl surrogate*

(v) Benzylic system (benzyl amines, benzyl bromides and benzylic ethers) as aroyl surrogates through CDC reaction

In 2013, Wu group achieved a Pd(II)-catalyzed efficient protocol for the *ortho* aroylation of 2-phenylpyridines utilizing benzyl amines as the aroyl sources (Scheme III.2.6, path a).[19a] Very recently, benzyl bromides and chlorides have been utilized as the active aroyl sources for the *ortho* aroylation of the same substrates in a Pd-catalyzed reaction as demonstrated by our group and Wu group respectively (Scheme III.2.6, path b).[19b-c]



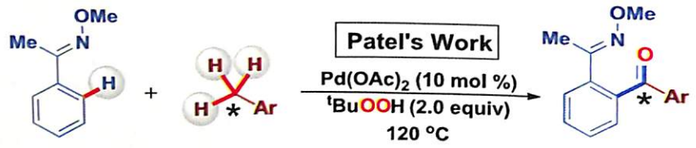
Scheme III.2.6. *Ortho aroylation using benzylic species as aroyl surrogates*

Apart from these reports, in 2014, Kim group has also shown that benzylic ethers can act as the synthetic equivalent of aroyl moieties (ArCO–) in Pd-catalyzed reaction to achieve *ortho* acylated products of corresponding directed sunstrates such as 2-arylpyridines, ketoxime ethers,

pyrazoles, 2-aryloxypyridines and benzo[*h*]quinoline derivatives. In these strategies, TBHP is employed as the terminal oxidant as well as oxygen source of acyl moieties (Scheme III.2.6, path c).[19d]

(vi) Alkylarenes as aroyl surrogate through CDC reaction

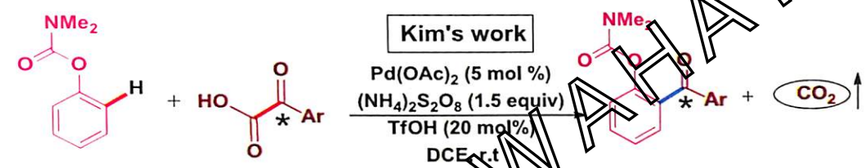
Our group decoded the first example of Pd(II)-catalyzed *ortho* acylation of directed substrates including 2-arylpyridines, 2-aryloxypyridines and ketoxime ethers utilizing alkylarenes as the efficient aroyl (ArCO–) equivalent in the presence of TBHP as oxidant as well as source of oxygen of aroyl moiety (Scheme III.2.7).[9a] Later on, arylarenes have also been utilized as the aroyl source to access the corresponding *ortho* acylated products of various directing substrates such as anilides, azoarenes, *N*-nitrosoaniline, 2-arylbenzothiazoles and 2-arylbenzoxazoles employing almost similar reaction conditions.[17b]



Scheme III.2.7. *Ortho aroylation using alkylarenes as aroyl surrogates*

(vii) α-Oxoacid as aroyl surrogate through decarboxylative CDC reaction

The use of α-oxoacids as the aroyl sources in transition metal-catalyzed acylation strategy of directed arenes follows the decarboxylative cross dehydrogenative coupling pathway. The *in situ* generated acyl radical, obtained by the loss of one molecule of CO_2 from α-oxoacids in the presence of transition metals catalyst and suitable oxidants/additives, efficiently couples with the directed arenes. Ge group first demonstrated a novel approach for the *ortho* acylation of 2-arylpyridines utilizing α-oxoacids under Pd/Ag catalytic system.[20a] Later on, the same group reported similar *ortho* acylation protocol for the synthesis of corresponding ketones of acetanilides[20b] and carboxylic acids.[20c] This decarboxylative CDC strategy have also been successfully applied for the *ortho* acylation of other directing substrates including ketoxime ethers, *o*-aryl carbamates, indolines, azoarenes, 2-aryl-azole derivatives, isoxazoles, benzylated thioethers and indole derivatives (C2 acylation) etc.[17b] One representative example in this category employing *o*-aryl carbamates as the directing substrate is shown in Scheme III.2.8.



Scheme III.2.8. *Ortho aroylation using α-oxoacids as aroyl surrogates*

(viii) Other aroyl (ArCO–) sources

In 2012, α-diketones were successfully implemented as the aroyl equivalents in Pd/TBHP mediated acylation of 2-arylpyridines derivatives by Wang group.[21a] Very recently Liu and co-workers had shown that mandelic acids can serve as the efficient aroyl sources under almost similar conditions for the *ortho* aroylation of same substrates.[21b] Additionally, in 2015, α-hydroxyketones were also explored as aroyl sources and applied in the acylation of azoarenes by Ranu and co-workers.[21c]

Scheme III.2.9. *Ortho aroylation using α-diketones, mandelic acids and α-hydroxy ketones as aroyl surrogates*

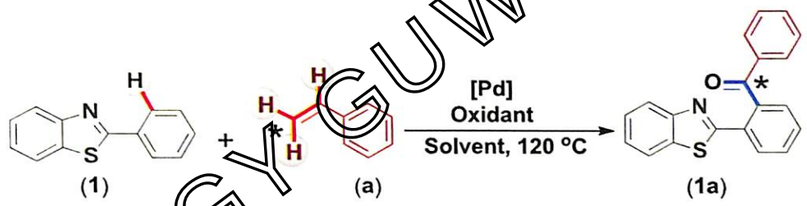
III.3. Present Work

In continuation to the above mentioned protocols for ketone synthesis *via* C–H functionalization of directed substrates, herein the development of a novel and versatile Pd(II)-catalyzed protocol for synthesis of same utilizing terminal alkenes/alkynes as the aroyl (ArCO–) surrogates was reported. The reaction proceeds through sequential C–O and C–C bonds formation along with the loss of one carbon atom as CO from the parent alkenes/alkynes and subsequently installs an aroyl (ArCO–) source at the *ortho* site of various directed substrates.

Optimization of reaction conditions: An initial trial reaction was performed with 2-phenylbenzothiazole (**1**) (1 equiv) and styrene (**a**) (2.5 equiv) in the presence of catalyst $Pd(OAc)_2$ (5 mol %) and TBHP in decane (5–6 M) (2 equiv) in chlorobenzene at 120 °C. The reaction gave an *o*-aroylated product (2-(benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (**1a**) in a mere yield of 25%. The use of terminal aryl alkenes as aroyl surrogate using Pd-catalyst substrate directed processes is not reported till date.[22] Encouraged by this unprecedented result, a set of reactions were performed by varying reaction parameters to achieve the best possible yield of *o*-aroylated product (**1a**). Among the various Pd catalysts screened, $Pd(OAc)_2$ (Table III.3.1, entry 1) was found to be superior (25%) over other catalysts such as $PdCl_2$ (17%), Pd(TFA)$_2$ (9%), $PdCl_2(PPh_3)_2$ (12%) as shown in Table III.3.1, entries 1–4. An increase in the catalyst loading from 5 to 10 mol %, the product yield improved from 25% to 42% (Table III.3.1, entry 5). Interestingly, when the oxidant quantity (TBHP in decane) was increased by two fold, the yield improved upto 57% (Table III.3.1, entry 6). A further improvement in the yield (63%) was observed when the reaction was performed with 5 equiv. of oxidant (Table III.3.1, entry 7). The use of an excess (beyond 5 equiv) of TBHP has no substantial effect on the product yield. The nature of oxidant and their medium of storage have profound effect on the product yield. For instance, when an aqueous TBHP was used in lieu of a decane TBHP the yield dropped to 29% whereas aqueous H_2O_2 failed to produce the expected product (Table III.3.1, entries 8–9). The reaction failed to afford any desired product either in the absence of catalyst or the oxidant. In a quest to improve the yield further various solvents *viz.* THF, DMF, DMSO, 1,4-dioxane and DCE were screened (Table III.3.1, entries 10–14) but all were found inferior to chlorobenzene. A decrease in reaction temperature from 120 °C to 100 °C had an adverse effect on the product yield (53%). Finally, a mixture of 2-phenylbenzothiazole (**1**) (1 equiv) and styrene (**a**) (2.5

equiv), $Pd(OAc)_2$ (10 mol %) and TBHP in decane (5 equiv) in chlorobenzene at 120 °C was chosen as the best optimized reaction conditions (Table III.3.1, entries 3).

***Table III.3.1**. Screening of reaction conditions*[a,b]

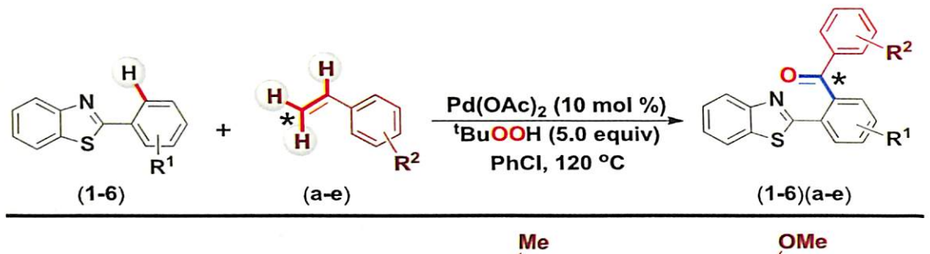


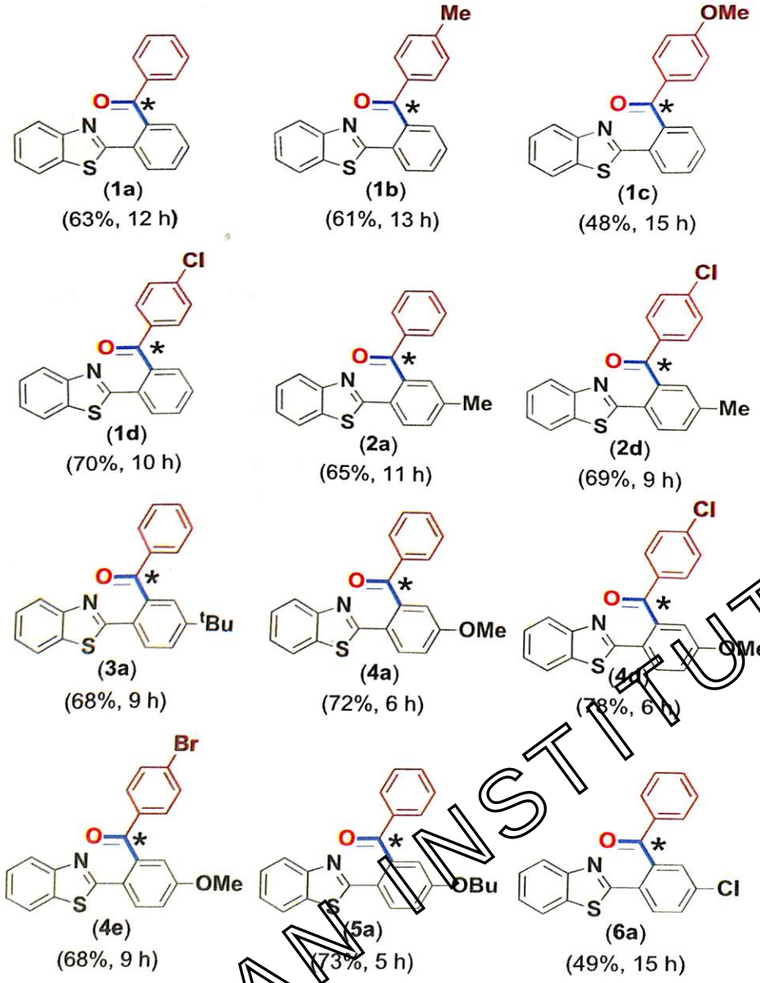
Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	Yield (%)
1	$Pd(OAc)_2$ (5)	TBHP (2)	PhCl	25
2	$PdCl_2$ (5)	TBHP (2)	PhCl	17
3	$Pd(TFA)_2$ (5)	TBHP (2)	PhCl	9
4	$PdCl_2(PPh_3)_2$ (5)	TBHP (2)	PhCl	12
5	$Pd(OAc)_2$ (10)	TBHP (2)	PhCl	42
6	$Pd(OAc)_2$ (10)	TBHP (4)	PhCl	57
7	**$Pd(OAc)_2$ (10)**	**TBHP (5)**	**PhCl**	**63**
8	$Pd(OAc)_2$ (10)	TBHP (5)[c]	PhCl	29
9	$Pd(OAc)_2$ (10)	H_2O_2 (5)	PhCl	00
10	$Pd(OAc)_2$ (10)	TBHP (5)	THF	<9
11	$Pd(OAc)_2$ (10)	TBHP (5)	Dioxane	43
12	$Pd(OAc)_2$ (10)	TBHP (5)	DMF	27
13	$Pd(OAc)_2$ (10)	TBHP (5)	DMSO	33
14	$Pd(OAc)_2$ (10)	TBHP (5)	DCE	52

[a]Reaction conditions: 2-phenylbenzothiazole (**1**), (1 equiv, 0.5 mmol), styrene (**a**) (2.5 equiv, 1.25 mmol) and TBHP in decane (5–6 M) (5 equiv, 500 μL) in chlorobenzene (1.0 mL), 12 h. [b]Isolated yield. [c]aq.TBHP.

Substrate scope for *ortho* aroylation with terminal alkenes: After establishing the optimized conditions, the present methodology was then implemented on 2-phenylbenzothiazole (**1**) with a variety of terminal alkenes. Terminal aryl alkenes possessing both electron-donating and electron-withdrawing substituents coupled efficiently with the directing substrate (**1**). Terminal aryl alkenes having weekly activating substituent *p*-Me (**b**) efficiently reacted with (**1**) giving 61% yield of (**1b**) while strongly activating substituent *p*-OMe (**c**) provided lower yield (48%) of the corresponding product (**1c**) as shown in Scheme III.3.1. Alkene having weekly electron-withdrawing substituent *p*-Cl (**d**) showed smooth conversion with 2-phenylbenzothiazole (**1**) providing 70% yield of (**1d**).

Scheme III.3.1. *Scope of ortho aroylation of 2-arylbezthiazoles with terminal alkenes*[a,b]



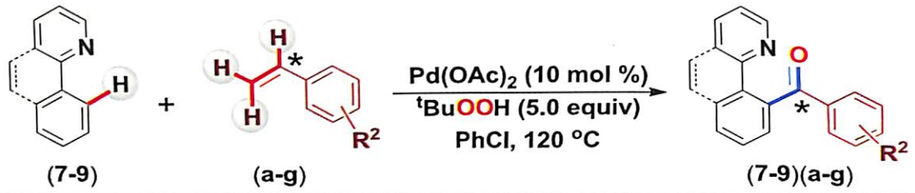


[a]Reaction conditions: 2-arylbenzothiazole (**1–6**), (0.5 mmol), alkenes (**a–e**) (1.25 mmol) and TBHP in decane (5–6 M) (500 μL) in chlorobenzene (1.0 mL), 130 °C, 5–15 h. [b]Yields of isolated product.

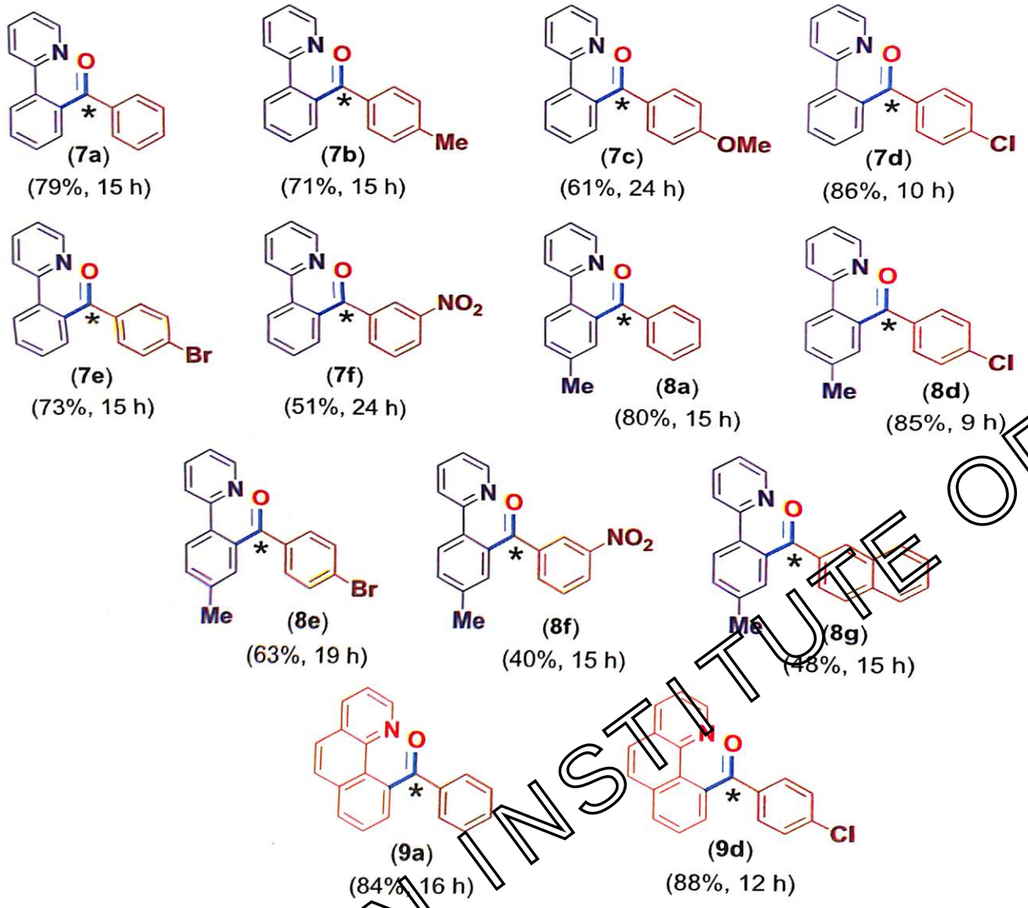
Further, this selective *o*-aroylation protocol was extended to substituted 2-phenylbenzothiazole containing both electron-donating and electron-withdrawing substituents. 2-Aryl substituted benzothiazoles with mild activating substituents in 2-phenyl ring such as *p*-Me (**2**) when treated with styrene (**a**) and *p*-Cl styrene (**d**) gave (**2a**) and (**2d**) in 65% and 69% yields respectively. Similarly, *p*-^{t}Bu (**3**) efficiently reacted with styrene (**a**) providing 68% yield of (**3a**) as shown in Scheme III.3.1. Styrene containing electro-neutral –H (**a**), *p*-Cl (**d**) and *p*-Br (**e**) when treated with directing substrate (**4**) possessing a strongly electron-donating substituent *p*-OMe under the optimized conditions, all provided corresponding *o*-aroylated products (**4a**), (**4d**) and (**4e**) in good yields (Scheme III.3.1). Substrate (**5**) possessing *p*-OBu group when treated with styrene (**a**), a good yield (73%) of corresponding product (**5a**) was obtained. Next, 2-phenylbenzothiazole having a weekly deactivating substituent such as *p*-Cl (**6**) when treated with styrene (**a**), a moderate yield (49%) of (**6a**) was obtained.

After successfully achieving *o*-aroylation of benzothiazoles (Scheme III.3.1) using terminal alkenes as aroyl surrogates the protocol was then extended to other substrate directed arenes. At first, commonly investigated *N*-directed arene, 2-phenylpyridine (**7**) when reacted with styrene (**a**) under the identical conditions, a good yield (79%) of (**7a**) was obtained after 15 h. As demonstrated in Scheme III.3.2, styrenes bearing both activated substituents such as *p*-Me (**b**), *p*-OMe (**c**) and deactivated substituents *p*-Cl (**d**), *p*-Br (**e**) and *m*-NO_2 (**f**) when treated with 2-phenylpyridine (**7**), all provided modest to good yields of their corresponding *o*-aroylated products (**7b–7f**) respectively. Similarly, *p*-methyl-2-phenylpyridine (**8**) also reacted with styrene (**a**) and substituted styrenes such as *p*-Cl (**d**), *p*-Br (**e**), *m*-NO_2 (**f**) and even 2-napthylstyrene (**g**) providing their desired *o*-aroylated products (**8a**), (**8d**), (**8e**), (**8f**) and (**8g**) as shown in Scheme III.3.2. Use of styrenes (**a**) and (**d**) as *o*-aroyl equivalents have been demonstrated through successful aroylation of benzo[*h*]quinoline (**9**) giving products (**9a**) and (**9d**) respectively as shown in Scheme III.3.2.

Scheme III.3.2. *Scope of ortho aroylation of 2-phenylpyridines and benzo[h]quinoline with terminal alkenes*[a,b]



(7-9) (a-g) (7-9)(a-g)

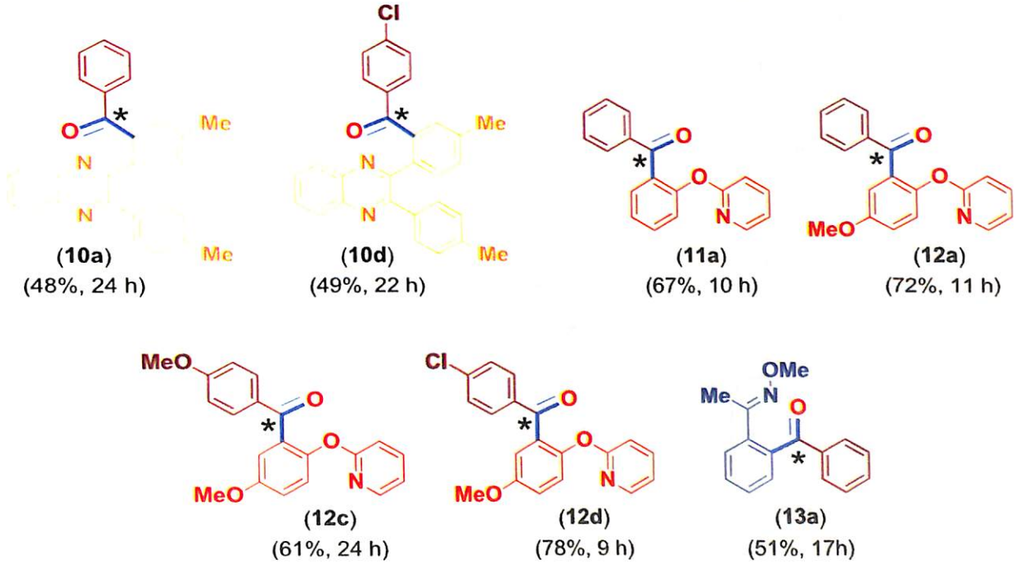


[a]Reaction conditions: directing arenes (**7–9**), (0.5 mmol), alkenes (**a–g**) (1.25 mmol) and TBHP in decane (5–6 M) (500 μL) in chlorobenzene (1.0 mL), 120 °C, 9–24 h. [b]Yields of isolated product.

This strategy was found to be successful with another directing arene 2,3-diphenylquinoxaline containing *p*-Me substituent (**10**) at its 2,3-aryl rings providing their desired o-aroylated products (**10a**) and (**10d**) respectively, when treated with styrene (**a**) and its *p*-Cl derivative (**d**) as shown in Scheme III.3.3. Interestingly, arenes possessing removable directing groups such as 2-aroyloxypyridine (**11–12**) and acetophenone *o*-methyl oxime (**13**) were successfully *o*-aroylated under the present optimized conditions. 2-Aroyloxypyridine containing electron neutral –H (**11**) and electron donating *p*-OMe (**12**) substituents reacted with styrene derivatives (**a**), (**c**) and (**d**) providing their corresponding *o*-aroylated products (**11a**), (**12a**), (**12c-d**) respectively (Scheme III.3.3). Similarly, acetophenone *o*-methyl ketoxime (**13**) when reacted with styrene (**1**) gave decent yield of the *o*-aroylated product (**13a**) as in Scheme III.3.3.

Scheme III.3.3. *Scope of ortho aroylation of different directed arenes with terminal alkenes*[a,b]

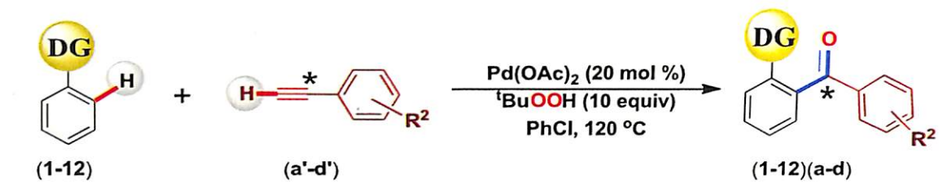
(10-13) (a, c-d) (10-13)(a, c-d)

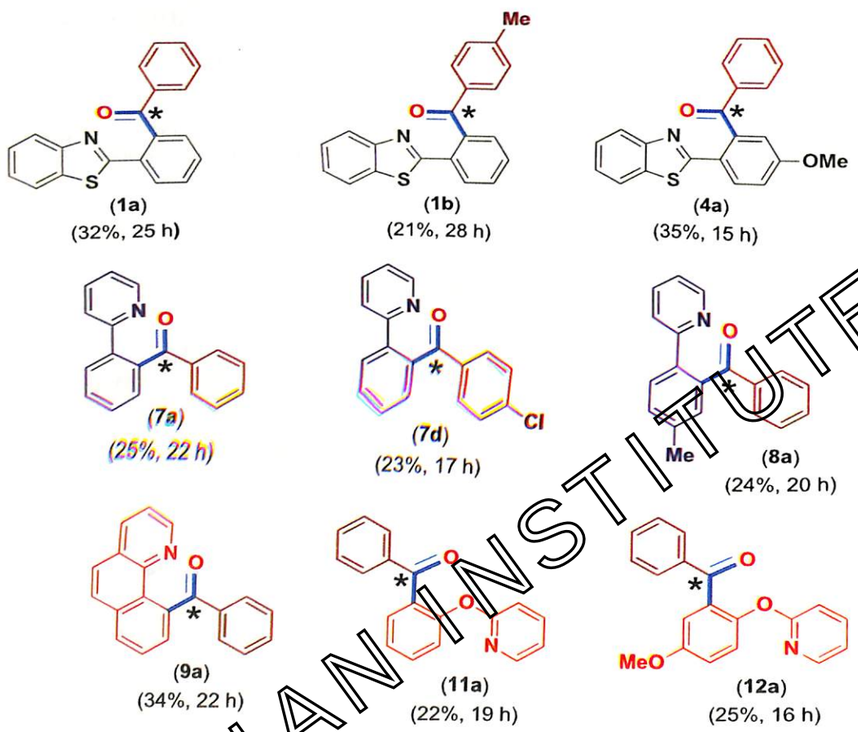


[a]Reaction conditions: directing arenes (**10–13**), (0.5 mmol), alkenes (**a, c–d**) (1.25 mmol) and TBHP in decane (5–6 M) (500 μL) in chlorobenzene (1.0 mL), 120 °C, 10–24 h. [b]Yields of isolated product.

Alkynylation of sp^2 and sp^3 C–H bonds using terminal alkynes by metal-catalyzed cross coupling reactions are well investigated.[23-24] Specially, phenylacetylenes are used as *o*-alkenylated partner in the chelation assisted C–H activation process.[24c] Besides terminal alkenes, terminal alkynes are found to be the efficient source of carboxy group under Cu/TBHP system.[7] So in next approach, to see if phenyl acetylene can act as a benzoxy source (PhCOO–) or it will be a source of aroyl group (PhCO–) similar to styrene as discussed above was thought.

Scheme III.3.4. *Scope of ortho aroylation of different directed arenes with terminal alkynes*[a,b]

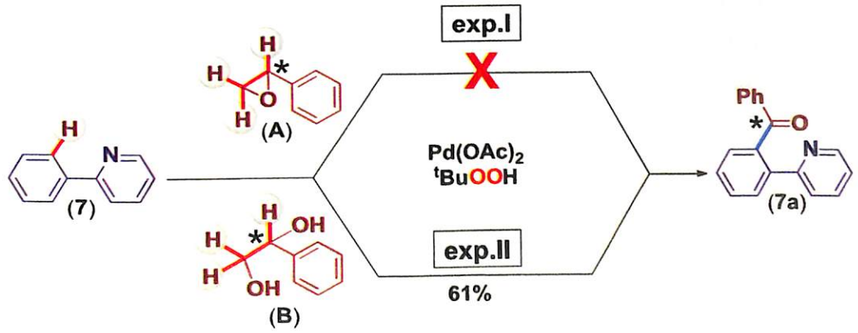




[a]Reaction conditions: directing arenes (**1–12**), (0.5 mmol), alkynes (**a′–d′**) (1.25 mmol) and TBHP in decane (5–6 M) (500 μL) in chlorobenzene (1.0 mL), 120 °C, 15–28 h. [b]Yields of isolated product.

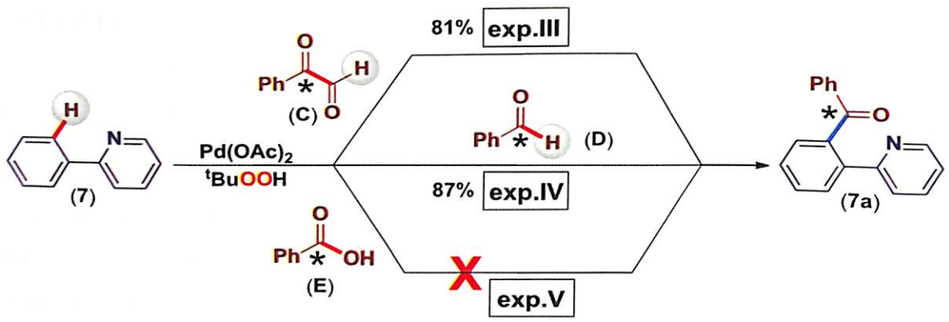
Thus when (**1**) and phenyl acetylene (**a′**) were reacted under the identical conditions to that of styrene (**a**), surprisingly *o*-aroylated product (**1a**) was again obtained but in a poor yield of 25%. Hence, further optimization reactions were performed to get an improved yield. Even by increasing the catalyst quantity 20 mol % and TBHP (10 equiv), the yield did not improve beyond 32%. Thus high catalytic loading (20 mol %) condition was chosen and was applied for all aryl acetylenes towards substrate directed *o*-aroylation. Subsequently substrate 2-phenyl benzothiazole (**1**) when treated with *p*-Me phenyl acetylene (**b′**) under the modified optimized conditions, gave (**1b**) in 21% yield. Other directed arenes such as 4-OMe substituted 2-phenyl benzothiazole (**4**), 2-phenylpyridine derivatives (**7**) and (**8**), benzo[*h*]quinoline (**9**), 2-aroyloxypyridines (**11**) and (**12**) when treated with various terminal alkynes (**a′**) **and** (**d′**), **yielded** their corresponding aroylated products in the range of 21–35% yields as shown in Scheme III.3.4. Alkynes provided much lower yields than alkenes because of possible homo-coupling which make the aroyl sources unavailable for further *o*-aroylation.

Mechanistic studies: Several control reactions were carried out to illustrate a plausible mechanistic path for this unprecedented Pd-catalyzed *o*-aroylation. Styrene in the presence of peroxide oxidant TBHP may form styrene oxide (**A**) or 1-phenyl-1,2-ethane diol (**B**) by hydrolysis of styrene oxide (**A**) in the reaction medium. To ascertain which one of this (**A** or **B**) intermediate is involved, both were reacted separately with 2-phenylpyridine (**7**) under otherwise identical conditions. In the former case (Scheme III.3.5, exp. I) no desired product was obtained whereas the later (Scheme III.3.5, exp. II) provided 61% yield of the desired product (**7a**) suggesting (**B**) as one of the possible active intermediates in the reaction.



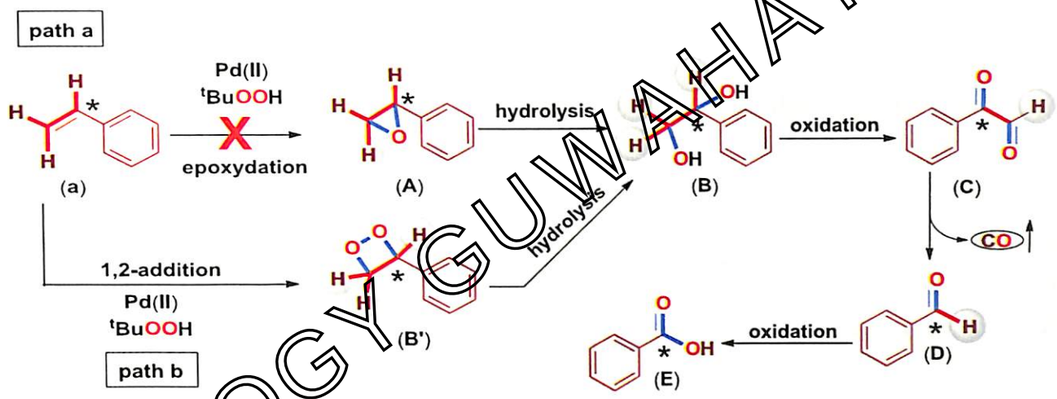
Scheme III.3.5. *Control reactions with styrene oxide (A) and or 1-phenyl-1,2-ethane diol (B)*

Analysis of the crude reaction mixture between styrene, TBHP and Pd after one hour divulged the presence of phenylglyoxal (**C**), benzaldehdye (**D**) and benzoic acid (**E**) in the medium. Therefore (**C**), (**D**) and (**E**) are other possible intermediates (in addition to (**B**)) which may lead to *o*-aroylation of (**7**), an observation consistent with our recent result.[7,25] To confirm the other possible active intermediates, 2-phenylpyridine (**7**) was treated separately with (**C**), (**D**) and (**E**) under identical conditions. While reaction with (**C**) (Scheme III.3.6, exp. III) and (**D**) (Scheme III.3.6, exp. IV) provided product (**7a**) in 81% and 87% yields respectively, benzoic acid (**E**) (Scheme III.3.6, exp. V) failed to give any trace of (**7a**).



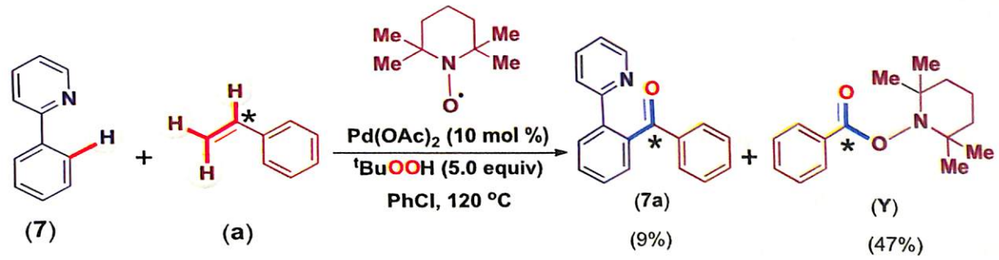
Scheme III.3.6. *Control reactions with phenylglyoxal (**C**), benzaldehyde (**D**) and benzoic acid (**E**)*

A possible pathway for the formation of phenylglyoxal (**C**), benzaldehyde (**D**) and benzoic acid (**E**) from styrene has been recently demonstrated by us[7,25] which is shown in Scheme III.3.7. As shown in Scheme III.3.5, exp. I, styrene oxide (**A**) failed to give product (**7a**), there by ruling out the involvement of it in this reaction.

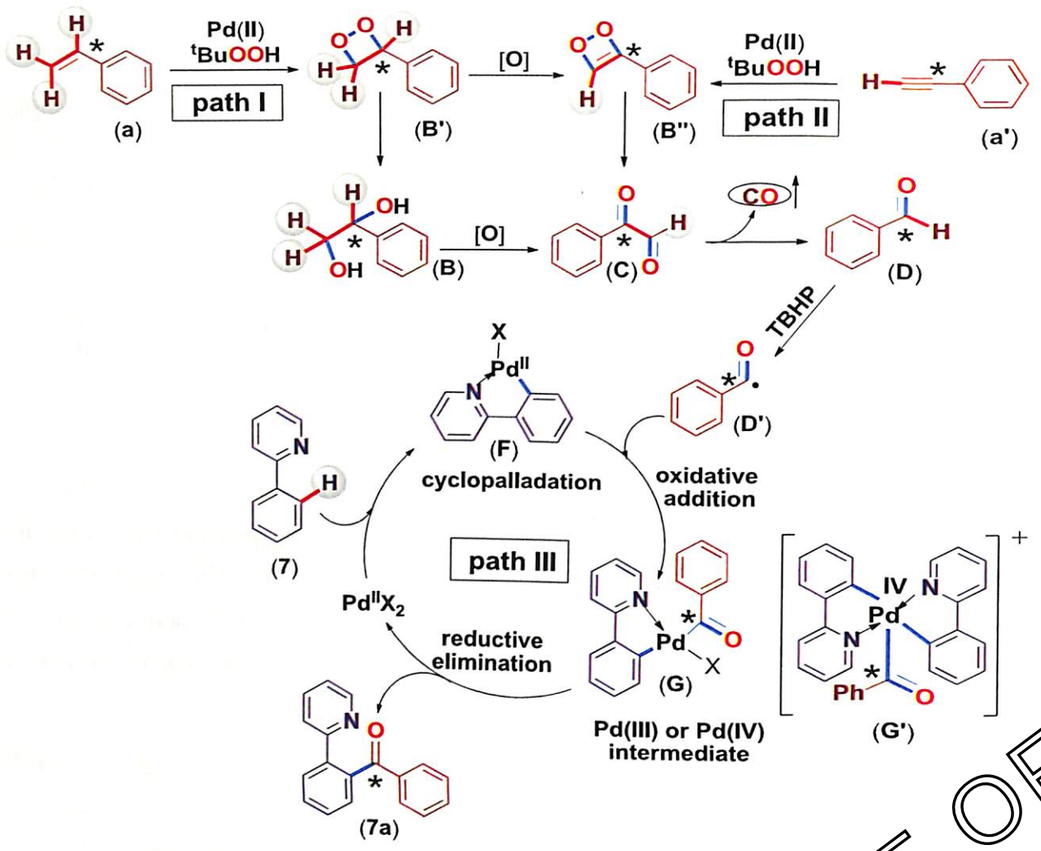


Scheme III.3.7. *Tentative path for formation of various oxidized species from styrene*

Furthermore, to deduce the nature of the reaction, a standard reaction was carried out in the presence of a radical quencher TEMPO (2.5 equiv) keeping other reaction parameters intact. Detection of TEMPO-ester (**Y**) (47%) along with substantial drop in product yield (9%) of (**7a**) suggests the radical nature of the reaction (Scheme III.3.8). In fact all the active intermediates (**B**), (**C**) and (**D**) are capable of generating aroyl radical under the reaction conditions toward *o*-aroylation.



Scheme III.3.8. *Control reaction in presence of radical inhibitor TEMPO*



Scheme III.3.9. *Plausible mechanism for ortho aroylation*

Based on results obtained from controlled experiments and recent literature,[7,26-27] a plausible mechanism has been proposed for this transformation as shown in Scheme III.3.9. In path-I, styrene possibly form a four-membered dioxetane intermediate (**B′**) by the action of Pd/TBHP.[7,25] A 1,2-type addition of σ O–O bond of TBHP across the C=C double bond of styrene lead to the formation of such 4- membered intermeadiate (**B'**). The ring opening of the intermediate (**B′**) may give 1-phenyl-1,2-ethanediol (**B**), which readily oxidized to give phenylglyoxal (**C**) under the oxidative reaction condition. Alternatively, cyclic intermediate (**B′**) may undergo oxidation to generate another cyclic intermediate (**B″**) which may also be directly obtained from phenylacetylene (**a′**) (Scheme III.3.9, path II). Formation of intermediate (**B″**) from (**a′**) has been reported by Jiao *et al.* in their pioneer work during the synthesis of α-

ketoamides from terminal alkynes.[28] The ring fragmentation of intermediate (**B″**), may provide phenylglyoxal (**C**). Intermediate (**C**) in presence of TBHP leads to the formation of benzyldehyde (**D**) with the extrusion of CO. Further benzaldehyde (**D**) in presence of TBHP leads to the formation of benzoyl radical (**D′**). In path-III, cyclopalladation of the directing arene (**7**) leads to the formation of Pd-substrate complex (**F**). In the next step, the oxidative addition of *in situ* generated benzoyl radical (**D′**) to Pd-substrate complex (**F**) leads to the formation of a Pd(IV)[26] or a dimeric Pd(III)[29] intermediate (**G**). During the course of this reaction, the formations of the cationic Pd (IV) intermediate (**G′**) has been detected by the ESI/MS analysis of reaction aliquot. Finally, a reductive elimination of the Pd from (**G**) leads to C–C bond formation to afford *o*-aroylated product (**7a**) along with the regeneration of the Pd (II) catalyst for the next cycle.

In conclusion, a new and efficient Pd-catalyzed directing group-assisted aroylation of arenes using terminal alkenes and alkynes as the new aroyl surrogate has been developed. Though the literature enumerates a number of aroyl surrogates for the synthesis of such ketones, use of terminal alkenes and alkynes as the aroyl surrogate is unique and unprecedented in literature. Mostly terminal alkenes and alkynes used as *o*-vinylated/*o*-alkenylated partner in transition metal-catalyzed directed C–H functionalization process. This process involves a sequential formation of C–O and C–C bond/(s) at the expense of four sp^2 C–H and one carbon atom as CO when terminal alkenes used as the aroyl surrogate. In case of terminal alkynes, this protocol installs an acyl group at the proximal site of directed substrates *via* extrution of one molecule of CO and two hydrogen atoms (one sp^2 C–H bond of directed arene and one sp C–H bond of terminal alkyne). Based on the detection of reaction intermediates and taking cues from the literature a radical mechanism has been proposed. This strategy has been implemented to a wide range of ligand directed substrates and afforded modest to good yields. This protocol showed a good tolerance of functional groups. Differential selectivities of Cu and Pd have been demonstrated; while Cu/TBHP combination installs an *o*-aryloxy (ArCOO–), the use of Pd/TBHP incorporate an *o*-aroyl (ArCO–) group using both alkenes and alkynes.

III.4. Experimental Section

III.4.1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Mass spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1.Elemental analysis was performed with a Perkin Elmer 2400 elemental analyzer. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

III.4.2A. General procedure for the synthesis of (2-(benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a) from 2-phenylbenzo[*d*]thiazole (1) and styrene (a):

An oven-dried flask was charged with 2-phenylbenzo[*d*]thiazole (**1**), (0.5 mmol, 0.105 g), styrene (**a**) (1.25 mmol, 0.13 g), $Pd(OAc)_2$ (10 mol %, 0.011 g), TBHP in decane (5–6 M) (500 μL) in chlorobenzene (1 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 °C for 12 h. After stipulated time, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate (1 x 10 mL). This diluted reaction mixture passed through a Celite bed and subsequently washed with additional (2 x 10 mL) ethyl acetate. The combined organic layer then washed with 10% aq. saturated solution of $NaHCO_3$ (2 x 5 mL) followed by water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using (Heane/ethylacetate = 19:1) as eluent to yield pure [2-(benzo[*d*]thiazol-2-yl)phenyl](phenyl)methanone (**1a**, 0.198 g, 63%) as a gummy material.

III.4.2B. General procedure for the synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone (7a) from 2-phenylpyridine (7) and phenylacetylene (a′):

An oven-dried flask was charged with phenyl acetylene (a′), (0.125 mmol, 0.128g), 2-phenylpyridine (7), (0.5 mmol, 0.078 g), $Pd(OAc)_2$ (10 mol %, 0.022 g), TBHP in decane (5–6 M) (1.0 mL) in chlorobenzene (1 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 °C for 25 h. After stipulated time, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate (1 x 10 mL). This diluted reaction mixture passed through a Celite bed and subsequently washed with additional (2 x 10 mL) ethyl acetate. The combined organic layer then washed with 10% aq. saturated solution of $NaHCO_3$ (2 x 5 mL) followed by water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using Heane/ethylacetate = 9:1) as eluent to yield pure phenyl(2-(pyridin-2-yl)phenyl)methanone (**7a**, 0.083g, 32%) as brown solid.

III.5. References and Notes

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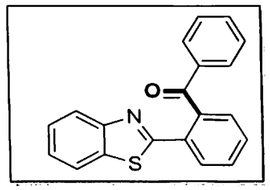
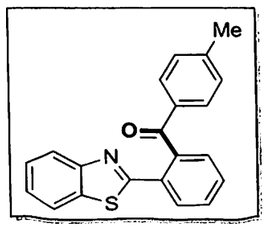
III.6. Spectral data

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a):



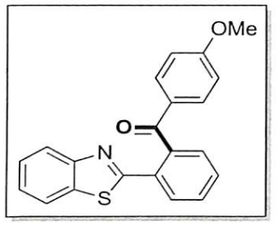
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.28–7.31 (m, 3H), 7.34–7.39 (m, 2H), 7.54 (d, 1H, J = 7.2 Hz), 7.59–7.65 (m, 2H), 7.76 (d, 2H, J = 7.8 Hz), 7.78 (d, 2H, J = 8.4 Hz), 7.94 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 121.6, 123.6, 125.5, 126.3, 128.4, 129.0, 129.4, 129.8, 130.4, 130.5, 132.2, 132.8, 135.4, 137.9, 139.9, 153.5, 165.5, 197.7; IR (KBr): 3060, 2922, 2848, 2554, 1686, 1668, 1596, 1581, 1451, 1426, 1315, 1283, 1258, 1176, 1054, 1026, 969, 923, 761 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}NOS^+$ (M + H$^+$) 316.0791; found 316.0793.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(*p*-tolyl)methanone (1b):



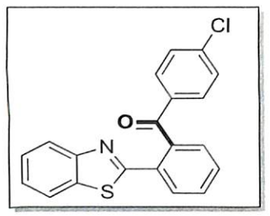
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.29 (s, 3H), 7.10 (d, 2H, J = 8.0 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.36 (t, 1H, J = 7.6 Hz), 7.49 (d, 1H, J = 7.6 Hz), 7.56–7.63 (m, 2H), 7.67 (d, 2H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.81 (d, 1H, J = 8.2 Hz), 7.94 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.8, 121.6, 123.7, 125.4, 126.3, 128.9, 129.2, 129.7, 129.9, 130.2, 130.4, 132.2, 135.4, 135.6, 140.2, 143.8, 153.7, 165.6, 197.5; IR (KBr): 2967, 2850, 2772, 1638, 1510, 1479, 1458, 1432, 1313, 1224, 1071, 964, 766 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{16}NOS^+$ (M + H$^+$) 330.0947, found 330.0943.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(4-methoxyphenyl)methanone (1c):



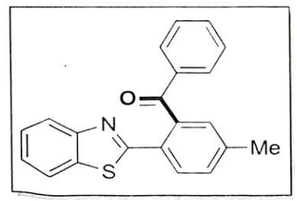
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.76 (s, 3H), 6.78 (d, 2H, J = 8.0 Hz), 7.26–7.31 (m, 1H), 7.36 (t, 1H, J = 7.6 Hz), 7.48 (d, 1H, J = 7.6 Hz), 7.55–7.62 (m, 2H), 7.76 (t, 3H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.0 Hz), 7. 95 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.5, 113.8, 121.6, 123.7, 125.4, 126.3, 128.7, 129.9, 130.1, 130.3, 130.9, 131.9, 132.1, 135.7, 140.2, 153.7, 163.5, 165.6, 196.4; IR (KBr): 3063, 2931, 2838, 1660, 1600, 1510, 1456, 1433, 1314, 1256, 1175, 1150, 1029, 966, 929, 843, 762, 729 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}NO_2S^+$ ($M + H^+$) 346.0896; found 346.0900.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(4-chlorophenyl)methanone (1d):



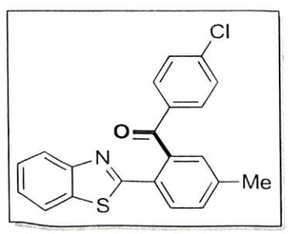
White solid; M.p. 134–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.24–7.27 (m, 2H), 7.29–7.34 (m, 1H), 7.35–7.39 (m, 1H), 7.51 (d, 1H, J = 6.8 Hz), 7.59–7.64 (m, 2H), 7.66–7.70 (m, 2H), 7.75–7.77 (m, 1H), 7.79–7.82 (m, 1H), 7.93 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 121.6, 123.6, 125.7, 126.5, 128.8, 128.9, 129.8, 130.5, 130.7, 132.1, 135.4, 136.5, 139.1, 139.4, 153.6, 165.2, 196.5; IR (KBr): 3055, 2957, 2923, 2845, 1670, 1585, 1571, 1482, 1427, 1400, 1305, 1289, 1263, 1241, 1185, 1150, 1096, 969, 936, 924, 845, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}ClNOS^+$ ($M + H^+$) 350.0401; found 350.0410.

(2-(Benzo[*d*]thiazol-2-yl)-5-methylphenyl)(phenyl)methanone (2a):



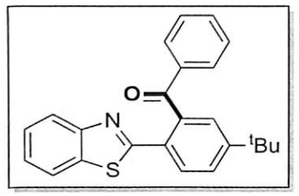
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.46 (s, 3H), 7.24–7.30 (m, 3H), 7.33–7.38 (m, 3H), 7.41 (d, 1H, J = 8.0 Hz), 7.71–7.76 (m, 4H), 7.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.5, 121.4, 123.3, 125.2, 126.2, 128.3, 129.3, 129.4, 129.7, 130.9, 132.7, 133.7, 135.2, 137.9, 139.7, 141.0, 153.5, 165.6, 197.9; IR (KBr): 3052, 3022, 2928, 2855, 1668, 1597, 1563, 1511, 1479, 1452, 1432, 1401, 1315, 1289, 1258, 1208, 1179, 1116, 1075, 975, 854, 826, 789, 757 cm^{-1}; elemental analysis calcd. (%) for $C_{21}H_{15}NOS$ (329.4143): C 76.57, H 4.59, N 4.25; found C 76.65, H 4.65, N 4.20.

(2-(Benzo[*d*]thiazol-2-yl)-5-methylphenyl)(4-chlorophenyl)methanone (2d):



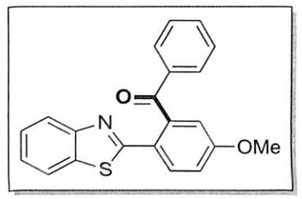
Yellow solid; M.p. 162–164 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.46 (s, 3H), 7.27 (d, 2H, J = 7.8 Hz), 7.30–7.35 (m, 2H), 7.37 (t, 1H, J = 3.6 Hz), 7.41 (d, 1H, J = 7.8 Hz), 7.69 (d, 2H, J = 9.6 Hz), 7.73 (d, 1H, J = 7.8 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.81 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.6, 121.6, 123.4, 125.5, 126.3, 128.7, 129.1, 129.4, 129.7, 130.6, 131.2, 135.2, 136.6, 139.0, 139.3, 141.3, 153.6, 165.3, 196.7; IR (KBr): 3056, 2958, 2924, 1661, 1637, 1606, 1585, 1572, 1482, 1426, 1398, 1311, 1287, 1259, 1182, 1151, 1091, 1010, 924, 826, 758 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}ClNOS^+$ ($M + H^+$) 364.0557; found 364.0561.

(2-(Benzo[*d*]thiazol-2-yl)-5-(*tert*-butyl)phenyl)(phenyl)methanone (3a):



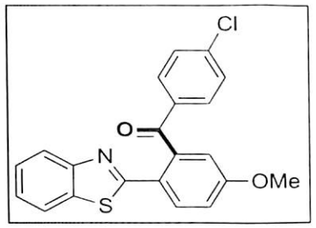
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.38 (s, 9H), 7.24–7.31 (m, 4H), 7.33–7.38 (m, 2H), 7.53 (s, 1H), 7.63 (d, 1H, J = 8.4 Hz), 7.74–7.78 (m, 3H), 7.86 (d, 1H, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 31.3, 35.3, 121.5, 123.4, 125.3, 125.9, 126.2, 127.4, 128.3, 129.4, 129.6, 132.7, 135.3, 138.1, 139.5, 153.7, 154.2, 165.5, 198.3; IR (KBr): 3068, 3028, 2967, 1670, 1596, 1560, 1515, 1485, 1449, 1431, 1395, 1368, 1314, 1255, 1162, 1105, 1023, 972, 902, 857, 805, 759 cm^{-1}; elemental analysis calcd. (%) for $C_{24}H_{21}NOS$ (371.4938): C 77.59, H 5.70, N 3.77; found C 77.67, H 5.76, N 3.71.

(2-(Benzo[*d*]thiazol-2-yl)-5-methoxyphenyl)(phenyl)methanone (4a):



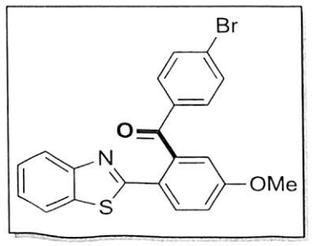
Brown solid; M.p. 147–149 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.89 (s, 3H), 7.02 (d, 1H, J = 2.4 Hz), 7.12 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.0 Hz), 7.23–7.26 (m, 1H), 7.27–7.33 (m, 3H), 7.36–7.38 (m, 1H), 7.73 (t, 2H, J = 9.0 Hz), 7.77 (d, 2H, J = 6.6 Hz), 7.86 (d, 1H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.9, 114.1, 116.1, 121.4, 123.3, 124.7, 125.1, 126.2, 128.4, 129.4, 131.3, 132.9, 135.2, 137.8, 141.5, 153.7, 161.3, 165.2, 197.4; IR (KBr): 3052, 2926, 2848, 1668, 1599, 1485, 1465, 1448, 1437, 1399, 1331, 1247, 1231, 1178, 1105, 1029, 965, 839, 762, 729, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}NO_2S^+$ ($M + H^+$) 346.0896; found 346.0901.

(2-(Benzo[*d*]thiazol-2-yl)-5-methoxyphenyl)(4-chlorophenyl)methanone (4d):



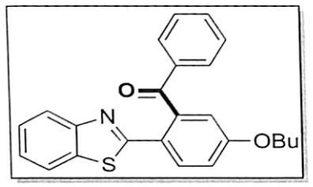
Yellow solid; M.p. 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.89 (s, 3H), 6.97 (d, 1H, J = 2.8 Hz), 7.12 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.4 Hz), 7.25–7.29 (m, 3H), 7.34 (t, 1H, J = 7.4 Hz), 7.71 (d, 3H, J = 8.4 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.9, 114.1, 116.2, 121.5, 123.2, 124.6, 125.3, 126.3, 128.8, 130.6, 131.4, 135.1, 136.4, 139.2, 140.9, 153.7, 161.5, 165.0, 196.2; IR (KBr): 3094, 2926, 2852, 1672, 1603, 1585, 1568, 1482, 1436, 1408, 1294, 1266, 1176, 1089, 1038, 970, 950, 828, 816, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}ClNO_2S^+$ ($M + H^+$) 380.0507; found 380.0512.

(2-(Benzo[*d*]thiazol-2-yl)-5-methoxyphenyl)(4-bromophenyl)methanone (4e):



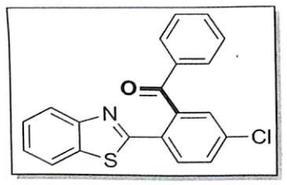
Yellow solid; M.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.89 (s, 3H), 6.99 (d, 1H, J = 2.4 Hz), 7.11 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.27 (t, 1H, J = 7.2 Hz), 7.33 (t, 1H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.69 (d, 1H, J = 7.8 Hz), 7.76 (d, 1H, J = 8.4 Hz), 7.85 (d, 1H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.9, 114.0, 116.2, 121.5, 123.2, 124.5, 125.3, 126.3, 127.9, 130.7, 131.3, 131.7, 135.1, 136.8, 140.9, 153.6, 161.4, 164.9, 196.3; IR (KBr): 3082, 2925, 2852, 1671, 1602, 1585, 1567, 1483, 1435, 1402, 1290, 1228, 1106, 1068, 969, 830, 758 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}BrNO_2S^+$ ($M + H^+$) 425.9982; found 425.9985.

(2-(Benzo[*d*]thiazol-2-yl)-5-butoxyphenyl)(phenyl)methanone (5a):



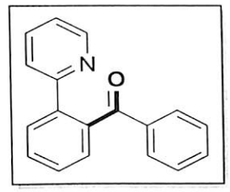
White solid; M.p. 131–133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.98 (t, 3H, *J* = 7.6 Hz), 1.48–1.53 (m, 2H), 1.77–1.82 (m, 2H), 4.05 (t, 2H, *J* = 6.4 Hz), 7.01 (s, 1H), 7.11 (d, 1H, *J* = 8.6 Hz), 7.23–7.34 (m, 4H), 7.38 (t, 1H, *J* = 7.2 Hz), 7.73 (t, 2H, *J* = 7.2 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.85 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.9, 19.3, 31.3, 68.4, 114.6, 116.4, 121.4, 123.2, 124.4, 125.0, 126.1, 128.4, 129.4, 131.3, 132.8, 135.2, 137.8, 141.4, 153.7, 160.9, 165.3, 197.5; IR (KBr): 3058, 2961, 2928, 2870, 1674, 1607, 1568, 1511, 1485, 1437, 1410, 1294, 1227, 1111, 1076, 1043, 972, 953, 856, 823, 810, 762 cm^{-1}; elemental analysis calcd. (%) for $C_{24}H_{21}NO_2S$ (387.4932): C 74.39, H 5.46, N 3.61; found C 74.48, H 5.51, N 3.52.

(2-(Benzo[*d*]thiazol-2-yl)-5-chlorophenyl)(phenyl)methanone (6a):



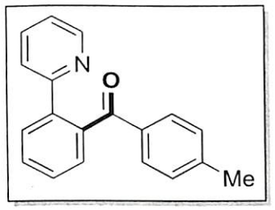
White solid; M.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26–7.36 (m, 4H), 7.38–7.43 (m, 2H), 7.51 (s, 1H), 7.60 (d, 1H, *J* = 8.4 Hz), 7.75–7.78 (m, 3H), 7.87 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 121.6, 123.6, 125.7, 126.5, 128.5, 129.0, 129.4, 130.4, 130.7, 130.9, 132.2, 135.4, 136.9, 137.4, 141.3, 153.5, 164.1, 196.1; IR (KBr): 3065, 3022, 2925, 2848, 1672, 1595, 1581, 1560, 1509, 1474, 1452, 1433, 1378, 1313, 1291, 1265, 1185, 1158, 1129, 1100, 1021, 1005, 968, 947, 877, 817, 782, 755 cm^{-1}; elemental analysis calcd. (%) for $C_{20}H_{12}ClNOS$ (349.8329): C 68.67, H 3.46, N 4.00; found C 68.75, H 3.52, N 3.90.

Phenyl(2-(pyridin-2-yl)phenyl)methanone (7a):



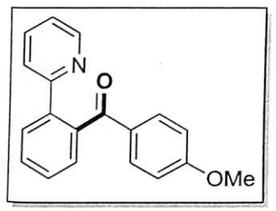
Brown solid; M.p. 101–103 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 6.99–7.01 (m, 1H), 7.25 (t, 1H, *J* = 7.2 Hz), 7.35–7.38 (m, 1H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.50–7.56 (m, 4H), 7.58–7.61 (m, 1H), 7.68 (d, 2H, *J* = 7.8 Hz), 7.76 (d, 1H, *J* = 7.8 Hz), 8.36–8.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 122.1, 122.9, 128.2, 128.7, 129.0, 129.3, 129.7, 130.4, 132.5, 136.5, 138.1, 139.6, 139.8, 149.2, 156.9, 198.4; IR (KBr): 3061, 2926, 2854, 1666, 1587, 1469, 1452, 1438, 1426, 1283, 1247, 1151, 935, 755, 700 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{14}NO^+$ (M + H^+) 260.1070; found 260.1072.

(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone (7b):



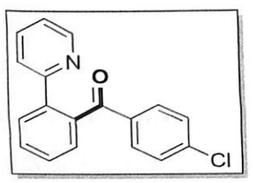
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.30 (s, 3H), 7.02–7.04 (m, 1H), 7.07 (d, 2H, *J* = 7.8 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.49–7.52 (m, 2H), 7.54–7.61 (m, 4H), 7.76 (d, 1H, *J* = 7.8 Hz), 8.41–8.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.8, 122.1, 123.2, 128.6, 128.9, 129.1, 129.2, 129.3, 129.9, 130.2, 130.3, 135.4, 136.5, 143.4, 149.2, 157.1, 198.1; IR (KBr): 3055, 2926, 1666, 1606, 1469, 1442, 1438, 1426, 1281, 1265, 1151, 935, 742 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO^+$ (M + H^+) 274.1226; found 274.1229 .

(4-Methoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone (7c):



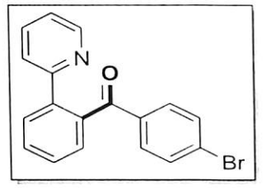
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.79 (s, 3H), 6.76 (d, 2H, J = 9.0 Hz), 7.03–7.05 (m, 1H), 7.46 (d, 1H, J = 7.8 Hz), 7.50 (d, 2H, J = 4.2 Hz), 7.54–7.59 (m, 2H), 7.68 (d, 2H, J = 8.4 Hz), 7.76 (d, 1H, J = 7.8 Hz), 8.41–8.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.5, 113.5, 122.1, 123.2, 128.6, 129.0, 129.2, 130.1, 130.9, 132.2, 136.4, 139.7, 139.9, 149.4, 157.3, 163.2, 197.2; IR (KBr): 3061, 2930, 2855, 1658, 1598, 1509, 1468, 1439, 1426, 1304, 1285, 1256, 1176, 1148, 1024, 930, 844, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H$^+$) 290.1176; found 290.1180.

(4-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone (7d):



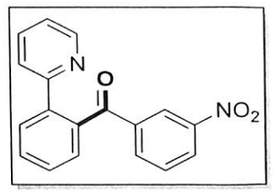
Brown solid; M.p. 84–86 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 6.99–7.01 (m, 1H), 7.21 (d, 2H, J = 8.4 Hz), 7.49–7.51 (m, 3H), 7.55–7.59 (m, 2H), 7.60 (d, 2H, J = 8.4 Hz), 7.75 (d, 1H, J = 7.8 Hz), 8.31–8.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.2, 122.5, 128.4, 128.7, 128.8, 129.1, 130.5, 130.8, 136.5, 136.6, 138.6, 139.1, 139.5, 149.0, 156.5, 197.1; IR (KBr): 2926, 2856, 1663, 1587, 1487, 1468, 1437, 1401, 1303, 1265, 1013, 928, 796, 753, 742 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}ClNO^+$ (M + H$^+$) 294.0680; found 294.0685.

(4-Bromophenyl)(2-(pyridin-2-yl)phenyl)methanone (7e):



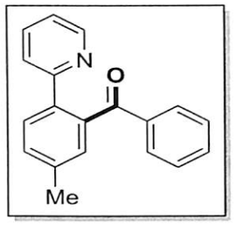
Yellowish solid; M.p. 94–96 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.01–7.03 (m, 1H), 7.39 (d, 2H, J = 8.4 Hz), 7.49–7.55 (m, 5H), 7.57–7.61 (m, 2H), 7.76 (d, 1H, J = 7.8 Hz), 8.32–8.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.3, 122.5, 127.4, 128.76, 128.82, 129.1, 130.5, 130.9, 131.5, 136.6, 137.0, 139.2, 139.6, 149.1, 156.5, 197.3; IR (KBr): 3049, 2926, 2856, 1664, 1584, 1482, 1468, 1437, 1397, 1302, 1282, 1264, 1176, 1151, 1068, 1010, 927, 795, 741 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}BrNO^+$ (M + H$^+$) 338.0175; found 338.0183.

(3-Nitrophenyl)(2-(pyridin-2-yl)phenyl)methanone (7f):



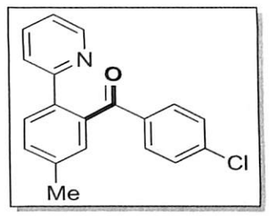
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 6.97–6.99 (m, 1H), 7.44 (t, 1H, J = 7.8 Hz), 7.55–7.56 (m, 2H), 7.60–7.61 (m, 1H), 7.63–7.66 (m, 2H), 7.79 (d, 1H, J = 7.8 Hz), 7.99 (d, 1H, J = 7.8 Hz), 8.19 (d, 1H, J = 7.8 Hz), 8.23 (d, 1H, J = 4.8 Hz), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.2, 122.4, 123.8, 126.4, 128.6, 129.2, 129.4, 131.0, 134.6, 136.9, 138.4, 139.5, 140.0, 148.1, 148.8, 156.0, 195.7; IR (KBr): 3082, 2926, 2856, 1674, 1612, 1586, 1530, 1470, 1440, 1348, 1298, 1281, 1252, 1087, 972, 754, 708 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}N_2O_3^+$ (M + H$^+$) 305.0921; found 305.0924.

(5-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone (8a):



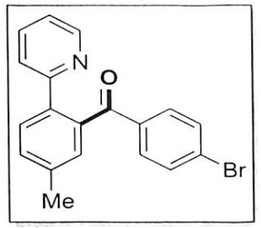
Brown solid; M.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 6.94–6.96 (m, 1H), 7.24 (t, 2H, J = 7.8 Hz), 7.33–7.36 (m, 2H), 7.39 (d, 1H, J = 7.8 Hz), 7.45 (d, 1H, J = 7.8 Hz), 7.49–7.52 (m, 1H), 7.65–7.68 (m, 3H), 8.31–8.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.3, 121.8, 122.6, 128.1, 128.7, 129.6, 129.8, 131.0, 132.4, 136.3, 136.9, 138.2, 138.8, 139.6, 149.1, 156.9, 198.6; IR (KBr): 2923, 2854, 1668, 1588, 1469, 1428, 1317, 1300, 1286, 1248, 1210, 837, 790, 750, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO^+$ ($M + H^+$) 274.1226; found 274.1233.

(4-Chlorophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (8d):



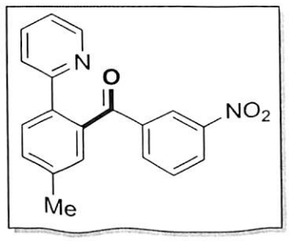
Brown solid; M.p. 95–97 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.43 (s, 3H), 6.96–6.98 (m, 1H), 7.20 (d, 2H, J = 8.4 Hz), 7.31 (s, 1H), 7.39 (d, 1H, J = 8.4 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.52–7.55 (m, 1H), 7.60 (d, 2H, J = 8.4 Hz), 7.65 (d, 1H, J = 7.8 Hz), 8.28–8.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.2, 121.9, 122.2, 128.4, 128.5, 129.6, 130.7, 131.1, 136.5, 136.6, 136.7, 138.5, 138.9, 139.1, 148.9, 156.4, 197.2; IR (KBr): 3057, 2921, 2856, 1664, 1587, 1470, 1431, 1402, 1307, 1287, 1250, 1211, 1089, 1013, 967, 847, 835, 823, 788, 762 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}ClNO^+$ ($M + H^+$) 308.0837; found 308.0844.

(4-Bromophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (8e):



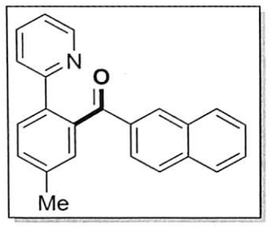
Yellow solid; M.p. 90–92 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 6.98–7.00 (m, 1H), 7.31 (s, 1H), 7.37–7.41 (m, 3H), 7.49 (d, 1H, J = 7.2 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.55–7.58 (m, 1H), 7.66 (d, 1H, J = 7.8 Hz), 8.30–8.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 122.0, 122.3, 127.3, 128.6, 129.7, 130.9, 131.2, 131.5, 136.6, 136.8, 137.2, 139.1, 139.2, 149.1, 156.5, 197.6; IR (KBr): 3057, 2921, 2852, 1666, 1585, 1470, 1431, 1396, 1304, 1285, 1250, 1208, 1172, 1067, 1008, 967, 845, 787, 759 cm^{-1}; HRMS (ESI): calcd. For $C_{19}H_{15}BrNO^+$ ($M + H^+$) 352.0332; found 352.0322.

(5-Methyl-2-(pyridin-2-yl)phenyl)(3-nitrophenyl)methanone (8f):



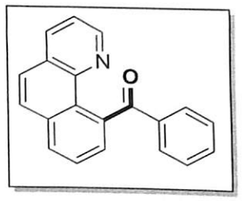
Liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.47 (s, 3H), 6.94–6.97 (m, 1H), 7.36 (s, 1H), 7.44–7.46 (m, 2H), 7.56–7.59 (m, 2H), 7.70 (d, 1H, J = 7.8 Hz), 8.01 (d, 1H, J = 7.2 Hz), 8.18 (d, 1H, J = 7.8 Hz), 8.21 (d, 1H, J = 4.2 Hz), 8.41–8.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 121.9, 122.2, 123.8, 126.3, 128.4, 129.3, 129.9, 131.7, 134.6, 136.7, 136.9, 138.4, 139.6, 140.2, 148.2, 148.8, 155.9, 195.9; IR (KBr): 3082, 2926, 2856, 1673, 1611, 1588, 1531, 1468, 1430, 1349, 1303, 1250, 1209, 1086, 990, 830, 789, 774, 733 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}N_2O_3^+$ ($M + H^+$) 319.1077; found 319.1074.

(5-Methyl-2-(pyridin-2-yl)phenyl)(naphthalen-2-yl)methanone (8g):



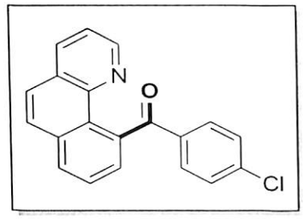
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.13 (s, 3H), 6.88–6.90 (m, 1H), 7.39 (s, 1H), 7.43 (d, 2H, J = 7.8 Hz), 7.46–7.53 (m, 3H), 7.71–7.79 (m, 4H), 7.90–7.93 (m, 1H), 8.07 (s, 1H), 8.28–8.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 121.8, 122.5, 125.2, 126.6, 127.8, 128.3, 128.5, 128.9, 129.7, 129.9, 131.1, 131.6, 132.5, 135.4, 135.7, 136.4, 137.1, 138.9, 139.8, 149.1, 156.9, 198.7; IR (KBr): 3054, 2923, 2852, 1662, 1625, 1587, 1466, 1428, 1351, 1289, 1232, 1187, 1111, 827, 778, 763 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}NO^+$ (M + H$^+$) 324.1383; found 324.1388.

Benzo[*h*]quinolin-10-yl(phenyl)methanone (9a):



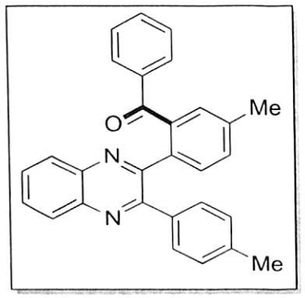
Yellowish solid; M.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.28–7.32 (m, 3H), 7.40 (t, 1H, J = 7.8 Hz), 7.63 (d, 1H, J = 7.2 Hz), 7.72 (d, 1H, J = 8.4 Hz), 7.72–7.79 (m, 3H), 7.88 (d, 1H, J = 8.4 Hz), 8.04 (d, 1H, J = 8.4 Hz), 8.07–8.08 (m, 1H), 8.49–8.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 121.8, 126.3, 126.6, 127.1, 127.87, 127.94, 128.2, 128.9, 129.1, 129.3, 131.9, 133.9, 135.4, 139.1, 139.4, 144.8, 147.2, 198.7; IR (KBr): 3059, 2928, 2854, 1672, 1578, 1510, 1448, 1421, 1314, 1273, 1212, 1175, 890, 840, 759, 731, 705 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}NO^+$ (M + H$^+$) 284.1070; found 284.1076.

Benzo[*h*]quinolin-10-yl(4-chlorophenyl)methanone (9d):



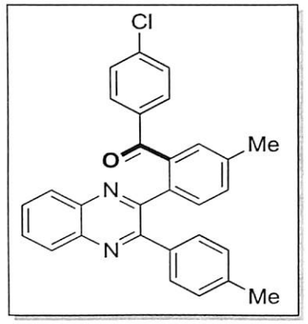
Yellowish solid; M.p. 155–157 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.24 (d, 2H, J = 8.4 Hz), 7.30–7.32 (m, 1H), 7.59 (d, 1H, J = 7.2 Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.70–7.72 (m, 1H), 7.75–7.77 (m, 1H), 7.86–7.87 (m, 1H), 8.02 (d, 1H, J = 8.4 Hz), 8.07 (d, 1H, J = 7.8 Hz), 8.468–8.473 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 121.9, 126.3, 126.5, 127.2, 127.9, 128.5, 129.2, 129.4, 130.1, 133.9, 135.5, 137.9, 138.0, 138.5, 144.6, 147.2, 197.4; IR (KBr): 3059, 2928, 2854, 1668, 1587, 1510, 1483, 1422, 1395, 1302, 1267, 1207, 1169, 1088, 1002, 894, 835, 765, 748 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}ClNO^+$ (M + H$^+$) 318.068; found 318.064.

(5-Methyl-2-(3-(*p*-tolyl)quinoxalin-2-yl)phenyl)(phenyl)methanone (10a):



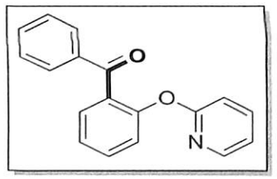
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.27 (s, 3H), 2.39 (s, 3H), 6.93 (d, 2H, J = 8.0 Hz), 7.22 (s, 1H), 7.25–7.29 (m, 4H), 7.38–7.44 (m, 4H), 7.55 (d, 1H, J = 7.6 Hz), 7.64–7.71 (m, 2H), 7.98 (d, 1H, J = 7.2 Hz), 8.07 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.1, 21.3, 127.8, 128.9, 129.1, 129.2, 129.5, 129.7, 130.0, 130.3, 130.6, 131.5, 131.9, 132.4, 135.7, 137.1, 137.9, 138.2, 138.7, 138.8, 140.9, 141.3, 153.5, 153.7, 196.5; IR (KBr): 3036, 2924, 2858, 1716, 1660, 1587, 1449, 1400, 1343, 1316, 1271, 1211, 1177, 1121, 1050, 979, 824, 762, 704 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{23}N_2O^+$ (M + H$^+$) 415.1805; found 415.1811.

(4-Chlorophenyl)(5-methyl-2-(3-(*p*-tolyl)quinoxalin-2-yl)phenyl)methanone (10d):



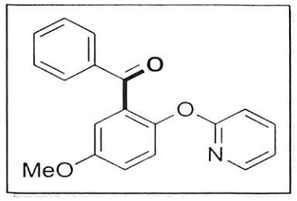
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.29 (s, 3H), 2.41 (s, 3H), 6.95 (d, 2H, J = 7.6 Hz), 7.18 (s, 1H), 7.26 (t, 3H, J = 8.8 Hz), 7.31–7.33 (m, 2H), 7.35 (s, 1H), 7.42 (d, 1H, J = 7.6 Hz), 7.59 (d, 1H, J = 8.0 Hz), 7.68–7.73 (m, 2H), 7.98–8.00 (m, 1H), 8.09–8.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 21.5, 127.6, 128.2, 129.0, 129.1, 129.2, 129.4, 129.7, 129.9, 130.4, 131.5, 131.8, 132.3, 135.5, 135.8, 138.3, 138.5, 138.9, 141.1, 141.4, 153.5, 153.6, 195.4; IR (KBr): 2985, 2923, 2856, 1660, 1606, 1588, 1456, 1400, 1343, 1285, 1267, 1180, 1121, 1089, 1048, 1014, 997, 824, 761 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{22}ClN_2O^+$ ($M + H^+$) 449.1415; found 449.1415.

Phenyl(2-(pyridin-2-yloxy)phenyl)methanone (11a):



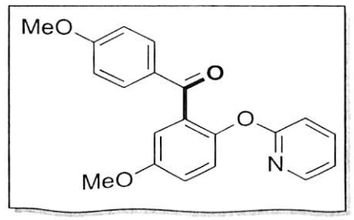
Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.59 (d, 1H, J = 8.0 Hz), 6.84–6.87 (m, 1H), 7.26 (d, 1H, J = 7.6 Hz), 7.32 (t, 3H, J = 8.0 Hz), 7.44–7.51 (m, 2H), 7.55 (d, 2H, J = 7.2 Hz), 7.75 (d, 2H, J = 7.2 Hz), 7.99–8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 111.6, 118.6, 122.9, 124.8, 128.2, 129.87, 129.95, 130.4, 132.4, 132.9, 137.7, 139.5, 147.1, 151.8, 163.1, 195.5; IR (KBr): 3063, 2924, 2854, 1666, 1596, 1572, 1466, 1448, 1427, 1290, 1265, 1206, 1145, 1103, 1026, 989, 931, 885, 760, 700 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{14}NO_2^+$ ($M + H^+$) 276.1019; found 276.1027.

(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (12a):



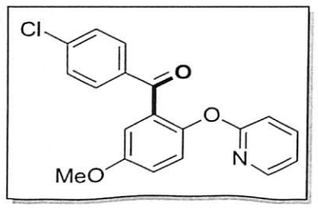
Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.83 (s, 3H), 6.51 (d, 1H, J = 8.4 Hz), 6.82–6.85 (m, 1H), 7.07–7.12 (m, 2H), 7.19 (d, 1H, J = 8.8 Hz), 7.31 (t, 2H, J = 7.6 Hz), 7.44–7.49 (m, 2H), 7.74 (d, 2H, J = 8.4 Hz), 7.99–8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.9, 111.3, 114.6, 118.3, 118.4, 124.3, 128.2, 129.9, 132.9, 133.1, 137.6, 139.3, 145.0, 147.1, 156.5, 163.5, 195.2; IR (KBr): 3059, 2929, 2854, 1667, 1595, 1492, 1428, 1286, 1268, 1201, 1142, 1036, 878, 779, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_3^+$ ($M + H^+$) 306.1125; found 306.1125.

(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(4-methoxyphenyl)methanone (12c):



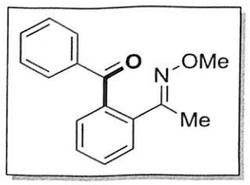
Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.81 (s, 3H), 3.82 (s, 3H), 6.59 (d, 1H, J = 8.8 Hz), 6.81 (d, 2H, J = 9.2 Hz), 6.94 (d, 1H, J = 8.8 Hz), 7.01–7.02 (m, 1H), 7.06–7.09 (m, 1H), 7.18 (d, 1H, J = 8.8 Hz), 7.49 (t, 1H, J = 8.6 Hz), 7.76 (d, 2H, J = 8.8 Hz), 8.02–8.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.6, 55.9, 113.3, 113.5, 114.4, 117.7, 118.4, 124.1, 130.3, 132.5, 133.6, 139.4, 144.7, 147.2, 156.5, 163.6, 163.7, 193.8; IR (KBr): 3061, 2934, 2838, 1659, 1598, 1572, 1510, 1492, 1465, 1427, 1258, 1201, 1169, 1031, 847, 775 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_4^+$ ($M + H^+$) 336.1230; found 306.1235.

(4-Chlorophenyl)(5-methoxy-2-(pyridin-2-yloxy)phenyl)methanone (12d):



Liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.83 (s, 3H), 6.54 (d, 1H, J = 8.4 Hz), 6.85–6.88 (m, 1H), 7.05 (d, 1H, J = 3.2 Hz), 7.09–7.12 (m, 1H), 7.18 (d, 1H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.48–7.52 (m, 1H), 7.68 (d, 2H, J = 8.4 Hz), 7.99–8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.9, 111.2, 114.5, 114.9, 118.5, 124.3, 128.5, 131.3, 132.7, 135.9, 139.4, 139.5, 144.9, 147.1, 156.6, 163.3, 194.1; IR (KBr): 3063, 2931, 2838, 1669, 1592, 1488, 1465, 1428, 1268, 1233, 1201, 1142, 1090, 1036, 1014, 966, 882, 849, 775 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}ClNO_3^+$ ($M + H^+$) 340.0735; found 340.0741.

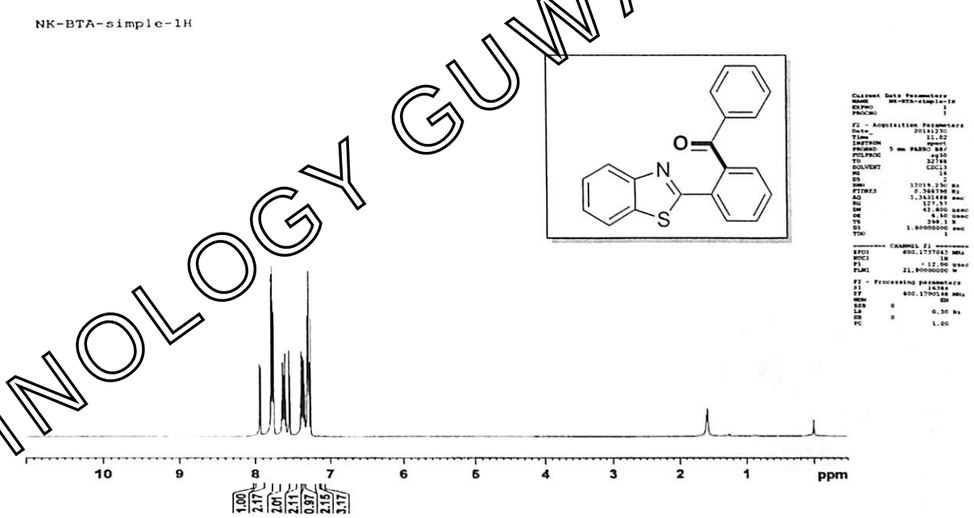
(E)-(2-(1-(Methoxyimino)ethyl)phenyl)(phenyl)methanone (13a):



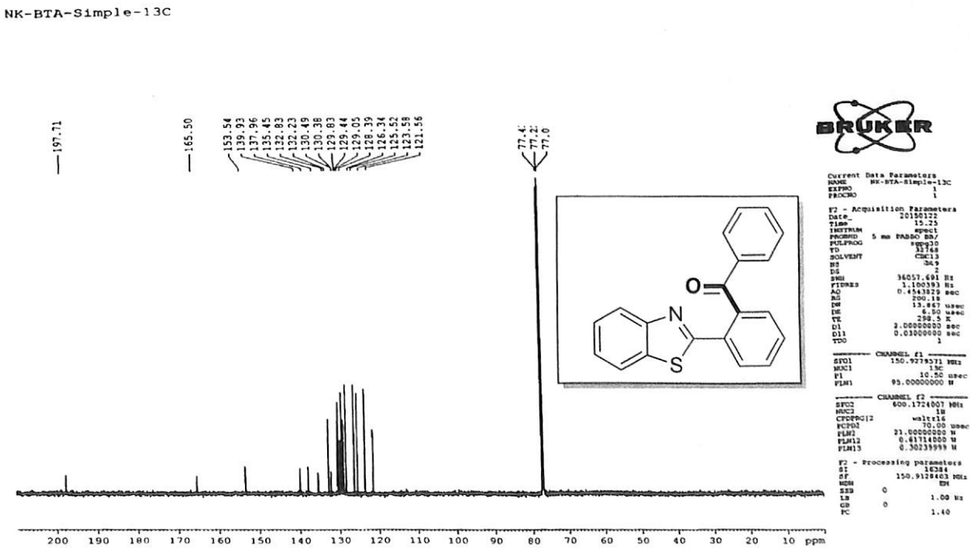
Yellow solid; M.p. 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.01 (s, 3H), 3.65 (s, 3H), 7.38 (t, 2H, J = 7.6 Hz), 7.44–7.47 (m, 2H), 7.48–7.53 (m, 3H), 7.69 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.6, 61.8, 127.9, 128.4, 128.8, 129.2, 129.5, 130.4, 132.7, 136.6, 138.4, 139.1, 154.2, 197.8; IR (KBr): 3060, 2979, 2934, 2927, 1666, 1597, 1448, 1356, 1313, 1285, 1249, 1046, 927, 896, 762, 701, 644 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}NO_2^+$ ($M + H^+$) 254.1176; found 254.1184.

III.7. Selected Spectra

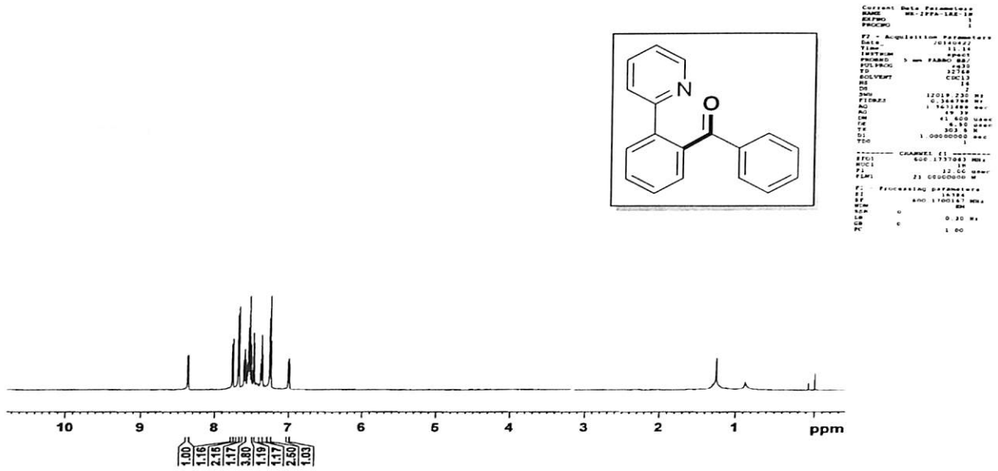
(2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a): ^{1}H NMR ($CDCl_3$, 600 MHz)



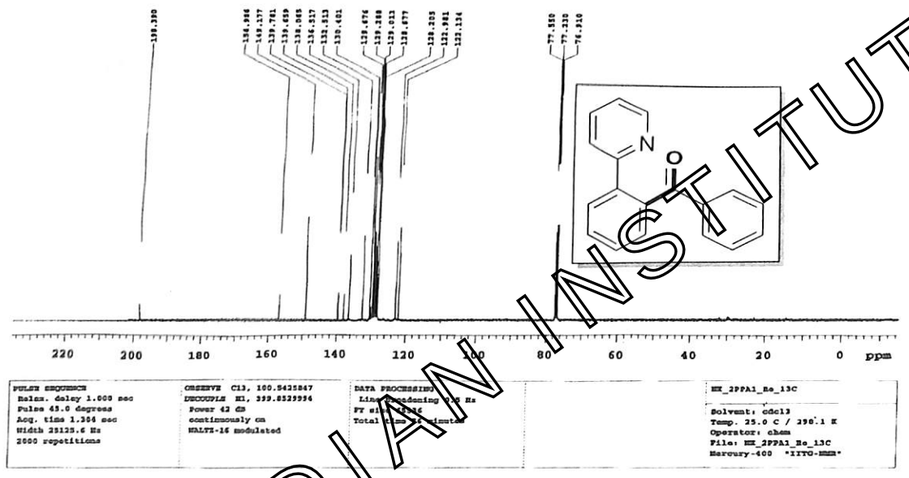
2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a): ^{13}C NMR ($CDCl_3$, 150 MHz)



Phenyl(2-(pyridin-2-yl)phenyl)methanone (7a): ^{1}H NMR ($CDCl_3$, 600 MHz)

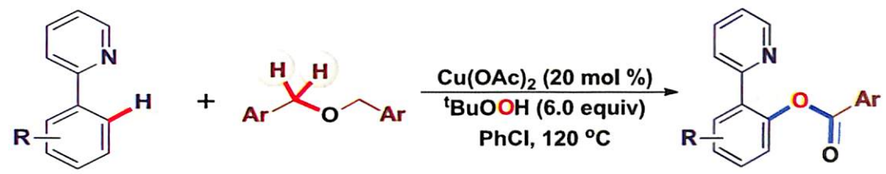


Phenyl(2-(pyridin-2-yl)phenyl)methanone (7a): ^{13}C NMR ($CDCl_3$, 100 MHz)



Chapter IV

Benzylic Ethers as Arylcarboxy Surrogates in Substrate Directed *ortho* C–H Functionalization Catalyzed by Copper: Synthesis of Esters



IV. Abstract: *A copper catalyzed ortho-benzoxylation of 2-arylpyridines has been accomplished using benzylic ethers as the alternative arylcarboxy sources (ArCOO–) via sp^2 C–H bond activation. The use of Pd/TBHP catalytic system is reported to install an o-aroyl (ArCO–) moiety at the 2-arylpyridine while the Cu/TBHP combinations fixes a benzoxy (ArCOO–) group at the ortho site. The reaction shows a broad substrates scope and good tolerance toward the various functional groups using inexpensive copper catalyst. A mechanistic investigation reveals that the reaction is going via radical pathways.*

Chapter IV

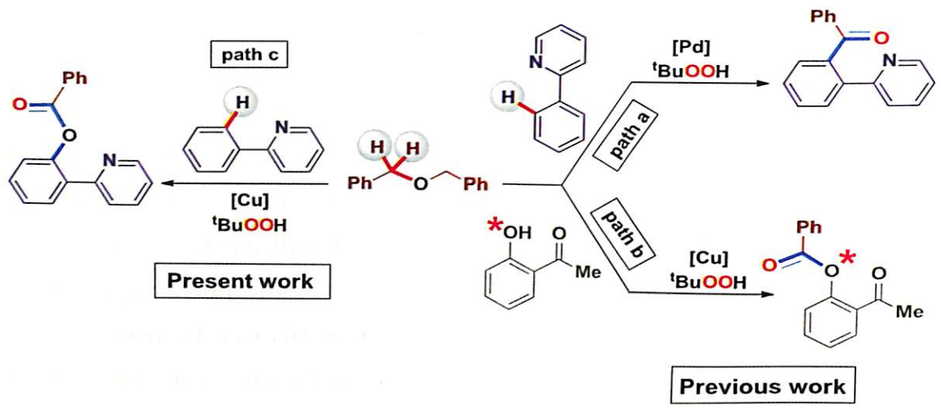
IV. Benzylic Ethers as Arylcarboxy Surrogates in Substrate Directed *ortho* C–H Functionalization Catalyzed by Copper: Synthesis of Esters

IV.1. Introduction

Recently considerable efforts have been devoted for the *ortho* selective direct functionalization of unreactive C–H bonds for the construction of C–C and C–X (X = heteroatom) bonds using transition metals such as Pd, Cu, Ru, Rh and Ir.[1] Among *ortho* C–C and C–X bond making processes, the C–O bond forming processes are difficult to promote due to the binding of electronegative oxygen atom with transition metals thereby making it inactive for further reactions.[2] Direct functionalization of C–H bond has become the most attractive approach in recent organic synthesis as it obviates prefunctionalization of substrates. In this context, our group has made ample contributions in the development of several unconventional coupling partners. Alkylbenzenes,[3] terminal alkenes/alkynes[4] and benzyl amines[5a] have been employed as the synthetic equivalents of $ArCH_2O$–,[3a] ArCO–,[3b-c,4c] and ArCOO–[3d,4a-b,5a] in directed and non-directed C–H functionalizations. In continuation to these developments, developing alternative synthetic precursors of arylcarboxy group (ArCOO–) was taken into consideration.

Benzylic ethers are commonly used as protecting groups for alcohols that can be easily cleaved under suitable oxidizing or reducing conditions.[6] It has also served as the dormant synthetic equivalents of aldehydes, carboxylic acids or esters depending upon the reaction conditions.[7] Benzyl ether served as aroyl (ArCO–) equivalent both under palladium (II)[8a] (Scheme IV.1.1, path a) or copper (I/II)[8b] (Scheme IV.1.1, path b) catalyzed reactions utilizing TBHP as the oxidant. But under Cu-catalyzed reaction condition, it resulted in *O*-aroylation and not *C*-aroylation.[8b] To test whether benzyl ether serves as an aroyl (ArCO–) equivalent or as an arylcarboxy (ArCOO–) source during Cu-catalyzed substrate-directed C–H functionalization, 2-phenylpyridine and dibenzylic ether were reacted using a combination of $Cu(OAc)_2$ and TBHP. To our delight, the reaction ended up giving 2-(pyridin-2-yl)phenyl benzoate, an ester as shown

in Scheme IV.1.1, path c. This result illustrates that dibenzyl ether serves as a carboxy (ArCOO–) source in the presence of Cu catalyst. This Cu-catalyzed reaction showed differential reactivity to that of palladium (II)[8a] and even with copper (I/II)[8b] where benzyl ether acted only as an aroyl (ArCO–) group.



Scheme IV.1.1. *Metal dependent reactivities of dibenzyl ethers*

Pertinent to this report, catalyst dependent selectivity is not uncommon in literature. In our earlier works, during the synthesis of 2-aminobenzothiazoles from 2-halothioureas, catalyst CuI followed C–X (X =-halogen) bond breaking path while Pd^{II}-preferred the C–H activation path.[3a] Further, divergent reactivity was observed using alkyl benzenes,[3b] terminal alkenes,[4b] arylureas,[4c] and benzyl amines.[10] They all serve as aroyl (ArCO–) surrogates for substrate-directed *ortho*-aroylation when the catalyst used was Pd^{II}, while the use of Cu^{II} catalyst preferred installing aryl carboxy (ArCOO–) groups at the *ortho* site of directing arenes.[4a,5,11]

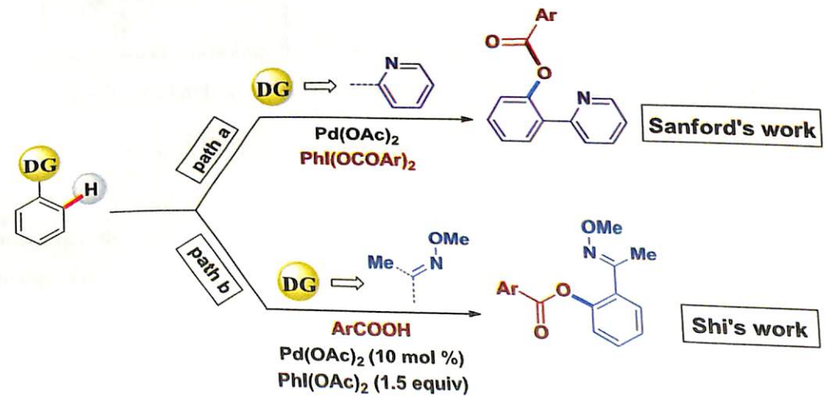
IV.2. Available Strategies for Ester Synthesis through *ortho*-Benzoxylation

The esters functionality, especially the benzoate moieties are omnipresent structural unit in many natural products and pharmacologically active compounds of medicinal interest.[12-13] The traditional strategies for the synthesis of ester derivatives rely on the base mediated classical nucleophilic reaction of preactivated carboxylic acid derivatives, namely acyl halides, anhydrides and another activated esters (as reactant) with alcohols.[12b] The Fischer esterification,[14] transesterification process[15] and Baeyer-Villiger oxidation,[16] which generally involve the use of

strong acid/base or peroxide respectively are the elegant tools to meet their demands. Most recently, a number of 'oxidative' approaches for esterification have gained a tremendous attention and serving as alternative protocols to the existing traditional methods.[17] Among them, transition metal-catalyzed substrate directed oxidative esterification through *ortho* C–H bond activation occupies the central area in this field.[17] Though directed substrates such as acetanilide, benzamide and ketoxime ether have been investigated recently for *ortho* benzoxylation, but 2-phenylpyridine is the mostly employed directed substrates for such esters synthesis. Existing methods for *ortho* benzoxylation of various directing substrates can be broadly classified into following categories based on the source of arylcarboxy surrogates (ArCOO–) as depicted below:

(i) Hypervalent iodonium benzoate salts as arylcarboxy (ArCOO–) source

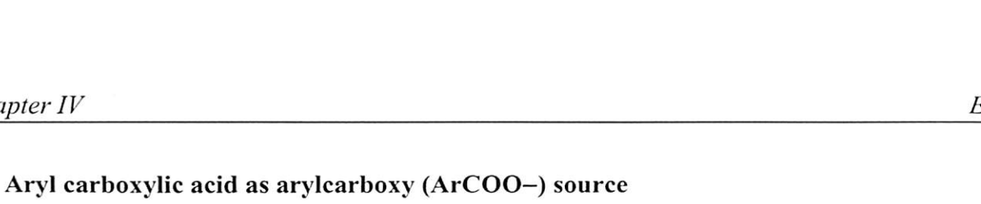
In 2005, Sanford and co-workers developed a regioselective Pd(II)-catalyzed *ortho* benzoxylation of 2-phenylpyridines employing hypervalent iodonium benzoate salts which served as the source of arylcarboxy as well as the oxidant. This protocol successfully installed a benzoxy (PhCOO–) moiety at the *ortho* site of 2-phenylpyridines through sp^2 C–H functionalization *via* Pd(II)/Pd(IV) catalytic system (Scheme IV.2.1, path a).[18a] Later on, in 2011, Shi group developed a similar palladium-catalyzed, $PhI(OAc)_2$ mediated protocol for synthesis of corresponding ester derivatives of ketoxime ethers, a removable directing substrate, using *in situ* generated benzoate iodonium salts as shown in Scheme IV.2.1, path b.[18b]



Scheme IV.2.1. *Ortho benzoxylation using hypervalent iodonium salt as ArCOO– source*

(ii) Aryl carboxylic acid as arylcarboxy (ArCOO–) source

The direct use of carboxylic acids as the ArCOO– sources in metal-catalyzed *ortho* benzoxylation process is limited due to rapid formation of metal-carboxylic acid complex through direct coupling of involved species. Such complexation process thereby makes the metal catalyst inactive for further progress of the reaction. Though few reports are available in literature in which carboxylic acids itself are being used as the ArCOO– surrogate. Cheng *et al.* utilized aromatic carboxylic acids as the direct sources of ArCOO– group in a rhodium-catalyzed synthesis of *ortho* esters of 2-phenylpyridines.[19] Later, Zhong and co-workers achieved a Pd-catalyzed, Cu/Ag co-catayzed oxidative *o*-benzoxylation of same substrates employing aromatic carboxylic acids as the efficient coupling partner.[20] Other directing substrates such as acetanilides[21a] and benzamides[21b] were successfully employed for competent *ortho* benzoxylation using aryl carboxylic acids in a ruthenium-catalyzed reaction as demonstrated by Jeganmohan *et al.* Very recently, our group demonstrated a Pd(II)-catalyzed highly efficient intriguing protocol for the synthesis of corresponding esters of various directing substrates including 2-phenylbenzothiazoles and 2-phenylpyridines etc using carboxylic acids. In this protocol, ceric ammonium nitrate (CAN) is employed as the efficient terminal oxidant.[22]

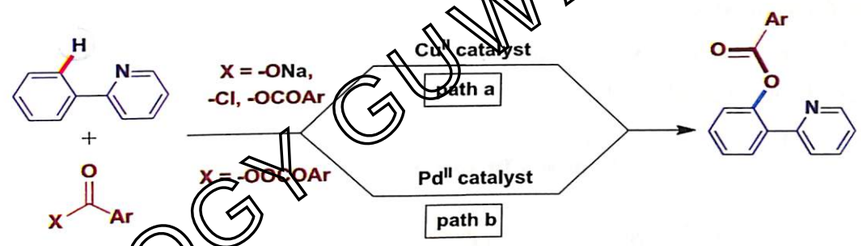


Scheme IV.2.2. Ortho benzoxylation using carboxylic acid as ArCOO– source

(iii) Aryl carboxylic acid derivatives as arylcarboxy (ArCOO–) source

The problems associated in transition metal-catalyzed benzoxylation could be overcome by employing a surrogate of the carboxylic acid *in lieu* of carboxylic acids. The use of a carboxylic acid surrogates can minimize the competitive complex formation by producing the corresponding carboxylic acid in the reaction medium in a slow and step-wise manner. Cheng *et al.* demonstrated that various carboxylic acid derivatives such as carboxylic acid salts,[23a] anhydrides[23b] and acid chlorides[23c] could be employed as the efficient surrogates of ArCOO– groups for the *ortho* benzoxylation of 2-phenylpyridines in the presence of copper catalyst as

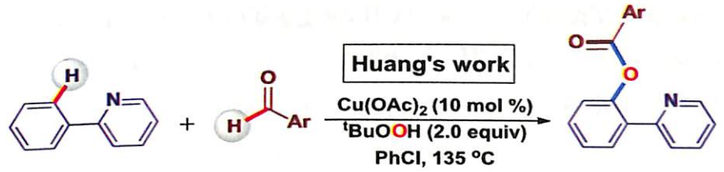
shown in Scheme IV.2.3, path a. Apart from these reports, Yu group has shown that aryl carboxy peroxides can act as an effective benzoxy surrogates for the synthesis of corresponding esters of 2-phenylpyridines in the presence of Pd catalyst (Scheme IV.2.3, path b).[23d]



Scheme IV.2.3. Ortho benzoxylation using carboxylic acid derivatives as ArCOO– source

(iv) Aromatic aldehyde as arylcarboxy (ArCOO–) source

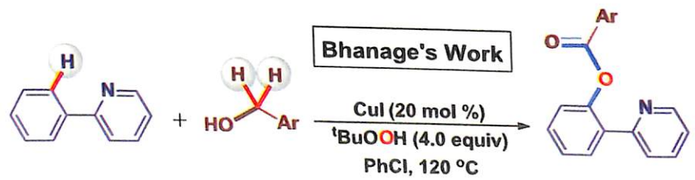
Huang and co-workers developed a Cu(II)-catalyzed, TBHP mediated protocol for *ortho* benzoxylation of 2-phenylpyridines using aromatic aldehydes as the coupling partner[11] as shown in Scheme IV.2.4.



Scheme IV.2.4. Ortho benzoxylation using aldehyde as ArCOO– source

(v) Benzyl alcohol as arylcarboxy (ArCOO–) source

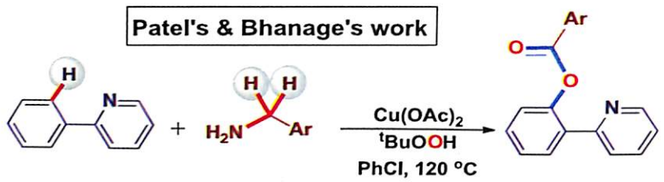
Benyl alcohols can be easily oxidized to corresponding aldehydes under oxidative reaction conditions. These *in situ* generated aldehydes can serve as the effective coupling partners for metal-catalyzed reactions. Very recently Bhanage *et al.* utilized benzyl alcohols for the *ortho* benzoxylation of 2-phenylpyridines in a copper-catalyzed reaction (Scheme IV.2.5).[5b]



Scheme IV.2.5. Ortho benzoxylation using alcohol as ArCOO– source

(vi) Benzyl amine as arylcarboxy (ArCOO–) source

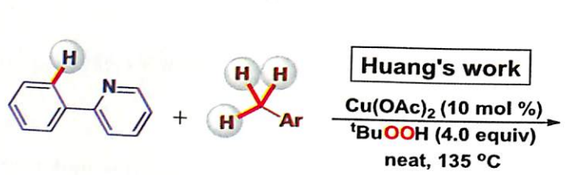
Benzyl amines have been found as an efficient arylcarboxy (ArCOO–) surrogates in substrate directed copper-catalyzed, TBHP mediated reaction as demonstrated by Bhanage group[5b] and our group[5a] at the same time. The *in situ* generated benzoxy radicals, obtained by the action of TBHP on benzyl amines, coupled with 2-phenylpyridines at the *ortho* site to produce corresponding esters in moderate to good yield as illustrated in Scheme IV.2.6.



Scheme IV.2.6. *Ortho benzoxylation using alcohol as ArCOO– source*

(vii) Alkyl benzene as arylcarboxy (ArCOO–) source

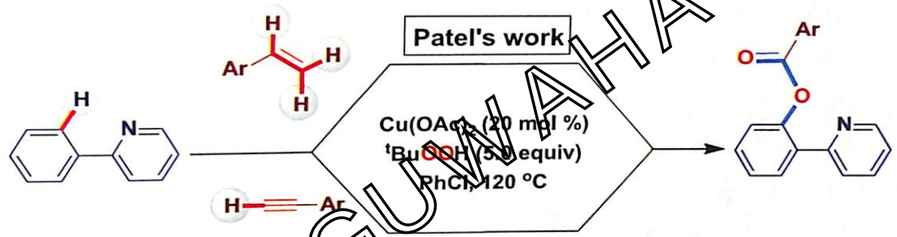
Alkyl benzenes were utilized as the efficient aryl carboxy surrogates (ArCOO–) for the *ortho* benzoxylation of 2-phenylpyridines in a Cu(II)-catalyzed reaction as reported by Huang *et al.* In this domino oxidation reaction, TBHP is utilized as the oxidant as well as oxygen source of ArCOO– moiety as in Scheme IV.2.7.[11]



Scheme IV.2.7. *Ortho benzoxylation using alkyl benzene as ArCOO– source*

(viii) Terminal aryl alkenes and alkynes as arylcarboxy (ArCOO–) source

Most recently, our group demonstrated a Cu(II)-catalyzed, TBHP mediated novel protocol for the synthesis of *ortho* ester of 2-phenylpyridine derivatives utilizing terminal alkenes and alkynes as the efficient benzoxy source. This reaction proceeds though a sequential formation of C–O bonds and loss of one carbon atom as CO *via* cleavage of C–C bond as in Scheme IV.2.8.[4a]



Scheme IV.2.8. *Ortho benzoxylation using terminal alkene and alkyne as ArCOO– source*

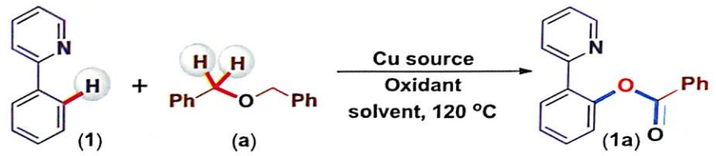
IV.3. Present Work

In the light of above mentioned protocols, herein a copper-catalyzed synthesis of *ortho* ester derivatives of 2-phenylpyridines *via* C–H functionalization using benzyl ethers as alternative surrogates of ArCOO– source is illustrated. This reaction proceeds through a sequential formation and cleavage of C–O bonds *via* loss of four sp^3 C–H bonds from both halves of benzyl ether and installs a benzoxy moiety at the proximal site of 2-phenylpyridine.

Optimization of reaction conditions: As has been mentioned earlier, initially a reaction was carried out between 2-phenylpyridine (**1**) and dibenzyl ether (**a**) in the presence of CuI (10 mol %) as the catalyst, TBHP in decane (5–6 M) (3 equiv) as the oxidant in 1,2-dichloroethane (DCE) solvent (Table IV.3.1, entry 1). The reaction ended up giving 2-(pyridin-2-yl)phenyl benzoate (**1a**), an ester, in 23% yield along with the recovery of both the starting materials (**1**) and (**a**). Encouraged by the finding of benzyl ethers serving as the alternative surrogate of ArCOO–, a series of reactions were carried out by varying catalysts, oxidants and solvents to arrive at the best possible yield. At first, the efficacies of various copper salts were screened keeping all other parameters constant. Among the catalysts tested (Table IV.3.1, entries 2–9) such as CuCl (17%), CuBr (18%), $Cu(OTf)_2$ (18%), $CuCl_2$ (11%), $CuBr_2$ (9%), CuO (11%) and $CuSO_4{\cdot}5H_2O$ (8%) in DCE solvent, $Cu(OAc)_2$ (26%) (Table IV.3.1, entry 4) was found to be the ideal. The yield of the desired product (**1a**) marginally improved (37%) when the amount of $Cu(OAc)_2$ was increased to 20 mol % (Table IV.3.1, entry 10). Furthermore, the use of excess $Cu(OAc)_2$ (upto 30 mol %) did not improve the yield (41%) significantly (Table IV.3.1, entry 11). Polar aprotic solvents such as DMSO, DMF and CH_3CN were found to be less effective for this transformation as illustrated in Table IV.3.1, entries 12–14. The use of chlorobenzene as the

solvent provided better yield (41%) with lesser side products (Table IV.3.1, entry 15) than DCE (Table IV.3.1, entry 10).

Table IV.3.1. *Screening of the reaction conditions*[a,b]



Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	Yield (%)
1	CuI (10)	TBHP (3)	DCE	23
2	CuCl (10)	TBHP (3)	DCE	17
3	CuBr (10)	TBHP (3)	DCE	18
4	$Cu(OAc)_2$ (10)	TBHP (3)	DCE	26
5	$Cu(OTf)_2$ (10)	TBHP (3)	DCE	18
6	$CuCl_2$ (10)	TBHP (3)	DCE	11
7	$CuBr_2$ (10)	TBHP (3)	DCE	9
8	CuO (10)	TBHP (3)	DCE	11
9	$CuSO_4.5H_2O$ (10)	TBHP (3)	DCE	8
10	$Cu(OAc)_2$ (20)	TBHP (3)	DCE	37
11	$Cu(OAc)_2$ (30)	TBHP (3)	DCE	41
12	$Cu(OAc)_2$ (20)	TBHP (3)	DMSO	6
13	$Cu(OAc)_2$ (20)	TBHP (3)	DMF	5
14	$Cu(OAc)_2$ (20)	TBHP (3)	CH_3CN	13
15	$Cu(OAc)_2$ (20)	TBHP (3)	PhCl	41
16	$Cu(OAc)_2$ (20)	Aq.TBHP (3)	PhCl	47
17	**$Cu(OAc)_2$ (20)**	**Aq.TBHP (6)**	**PhCl**	**58**
18	$Cu(OAc)_2$ (20)	H_2O_2 (6)	PhCl	00
19	$Cu(OAc)_2$ (20)	DTBP (6)	PhCl	00
20	$Cu(OAc)_2$ (20)	*m*-CPBA (6)	PhCl	00
21	$Cu(OAc)_2$ (20)	Oxone (6)	PhCl	00
22	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (6)	PhCl	00
23	-	Aq.TBHP (6)	PhCl	00
24	$Cu(OAc)_2$ (20)	-	PhCl	00
25	$Cu(OAc)_2$ (20)	Aq.TBHP (6)	PhCl	47[c]

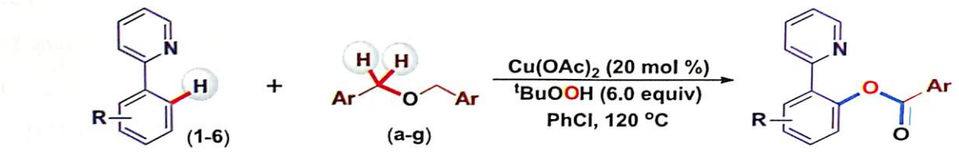
[a]Reaction conditions: 2-phenylpyridine (**1**), (0.5 mmol), dibenzyl ether (**a**), (0.75 mmol), PhCl (0.5 mL), 22 h. [b]Isolated yield. [c]Reaction carried out at 100 °C.

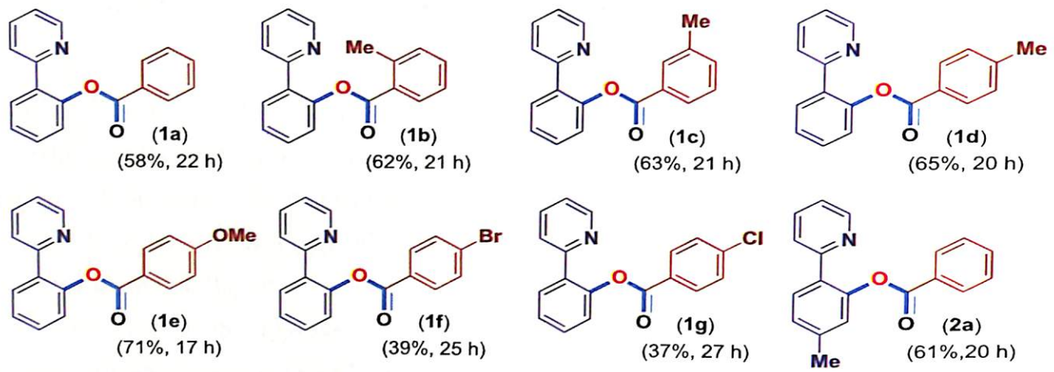
The use of 70% aqueous solution of TBHP in lieu of decane TBHP was found to be better (47%) for this transformation as shown in Table IV.3.1, entry 16. A further improvement in the yield (upto 58%) of (**1a**) was observed when the aq. TBHP quantity was increased to two fold (6 equiv) (Table IV.3.1, entry 17). Instead of using TBHP, other oxidants such as H_2O_2, di-*tert*-

butyl peroxide (DTBP), *m*-chloroperbenzoic zcid (*m*-CPBA), Oxone and $K_2S_2O_8$ were also tested during the screening of the reaction. As shown in Table IV.3.1, entries 18–22, all these oxidants are found to be ineffective for this transformation. Notably, either in the absence of copper salt or TBHP, the reaction failed to yield the desired product (**1a**). The yield of product (**1a**) dropped to 47% when the reaction temperature was decreased from 120 °C to 100 °C. Finally, the optimized reaction condition was, the use of 2-phenylpyridine (**1**) (0.5 mmol), dibenzyl ethers (**a**) (0.75 mmol), $Cu(OAc)_2$ (20 mol %), TBHP (aq. 70%) (6 equiv) in chlorobenzene (0.5 mL) at 120 °C.

With the above optimized conditions in hand, the scope of this strategy was then implemented to the reaction between 2-phenylpyridine (**1**) and various substituted dibenzyl ethers and the results are summarized in Scheme IV.3.1. Dibenzyl ethers having electron neutral –H (**a**) and electron-donating groups such as *o*-Me (**b**), *m*-Me (**c**), *p*-Me (**d**) and *p*-OMe (**e**) as well as electron-withdrawing *p*-Br (**f**) and *p*-Cl (**g**) substituents were all found to serve as ArCOO– sources and gave good to moderate yields of corresponding products of (**1a–1g**). The presence of electron-donating substituents in the aryl ring of dibenzyl ethers irrespective of their position of attachments (**b–e**) provided better yields than those possessing electron-withdrawing substituents (**f** and **g**) as shown in Scheme IV.3.1. The efficacy of this coupling reaction was further executed with substituted 2-phenylpyridines such as 2-*p*-tolylpyridine (**2**). Reaction of (**2**) with various substituted dibenzyl ethers (**a–g**) were then carried out and all provided good to moderate yields of their respective products (**2a–2g**) as shown in Scheme IV.3.1. Similarly, 2-*m*-tolylpyridine (**3**) when treated with dibenzyl ether (**a**) under the reaction conditions gave a good yield of the desired product (**3a**). Further 2-(4-methoxyphenyl)pyridine (**4**), another activated substrate when treated with dibenzyl ethers possessing electron neutral –H (**a**) and electron-withdrawing *p*-Cl (**g**) under the present reaction conditions, provided (**4a**) and (**4g**) in 75% and 54% yields respectively as shown in Scheme IV.3.1. Dibenzyl ether (**a**) also served as ArCOO– surrogate with other 2-phenylpyridine derivatives possessing electron-withdrawing substituents such as *p*-Br (**5**) and *p*-Cl (**6**), giving *o*-benzoxylated products (**5a**) and (**6a**) respectively in moderate yields.

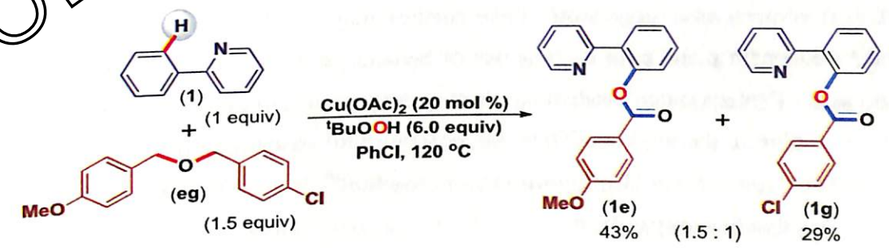
Scheme IV.3.1. *Substrate scope for ortho benzoxylation using dibenzyl ethers*[a,b]





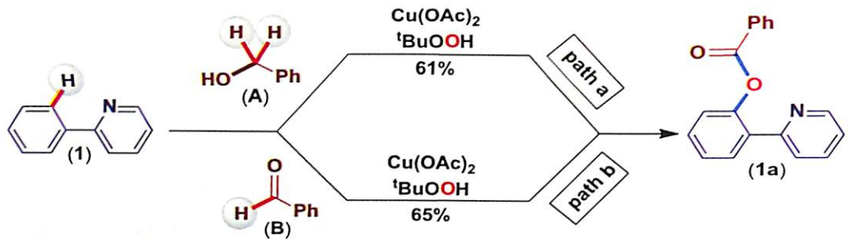
[a]Reaction condition: 2-arylpyridine (0.5 mmol), dibenzyl ether (0.75 mmol) and aq. TBHP (70%) (6 equiv) at 120 °C in chlorobenzene (0.5 mL). [b]Yield of isolated product.

However, directed arenes bearing activated substituents such as *p*-Me (**2**), *m*-Me (**3**) and *p*-OMe (**4**) gave better yields compare to those possessing electron-withdrawing substituents such as *p*-Br (**5**) and *p*-Cl (**6**) (Scheme IV.3.1). This is because of the better electrophilic metallation of Cu(II) catalyst with activated 2-aryl rings of 2-arylpyridine. To check whether both the halves of a dibenzyl ether acted as the arylcarboxy source or not, an unsymmetrical dibenzyl ether (**eg**) was treated with 2-phenylpyridine (**1**). Under the present reaction conditions, the unsymmetrical dibenzyl ether (**eg**) provided a separable mixture of (**1e**) and (**1g**) in a ratio of 1.5:1 as shown in Scheme IV.3.2. This result reconfirms that both the halves served as aryl carboxy source but the activated aryl ring acts as a better *o*-benzoxy source compare to its deactivated counterpart (Scheme IV.3.2).



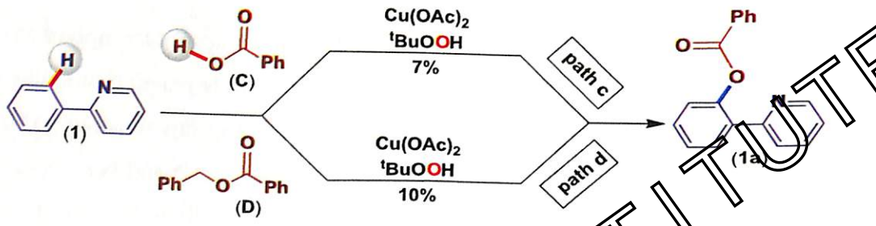
Scheme IV.3.2. *Reaction performed with 2-phenylpyridine (1) and unsymmetrical ether (eg)*

A set of control reactions were performed to gather the evidences to support the postulated reaction mechanism for this transformation. Analysis of the crude reaction products of dibenzyl ether (**a**) under the optimized conditions in the absence of directing substrate (**1**) revealed the presence of benzyl alcohol (**A**), benzaldehyde (**B**), benzoic acid (**C**) and benzylbenzoate (**D**) as detected by HRMS, which is consistent with previous observations.[8b] Thus, to find out the possible active intermediates, at first reactions of benzyl alcohol (**A**) and benzaldehyde (**B**) with (**1**) were carried out separately under otherwise identical conditions. Interestingly benzyl alcohol (**A**) and benzaldehyde (**B**) when reacted with (**1**), provided the corresponding product (**1a**) in 61% and 65% yields respectively (Scheme IV.3.3, path a and path b). These results strongly support their intermediacy during this transformation.



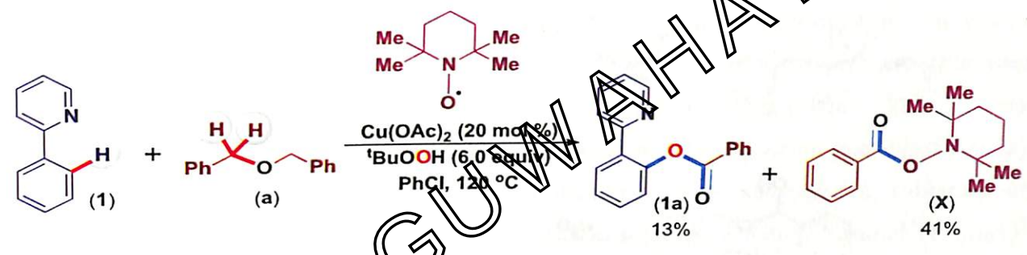
Scheme IV.3.3. *Control reactions performed with benzyl alcohol (**A**) and benzaldehyde (**B**)*

Later on, reactions of other two remaining indentified species (by HRMS) *viz.* benzoic acid (**C**) and benzylbenzoate (**D**) with (**1**) were again carried out separately under otherwise identical conditions. In these reactions, benzoic acid (**C**) and benzylbenzoate (**D**) yielded only 7% and 10% of (**1a**) respectively, suggesting those species may not be the active coupling partners (Scheme IV.3.4, path c and path d). The use of benzoic acid in lieu of dibenzyl ether provided only a trace of *o*-benzoxylated product supporting the presence of active benzoxy radical and not the benzoate anion in the medium. Thus, the possibility of oxidation of the ligand chelated Cu^{II} species to Cu^{III} species *via* disproportionation reaction[24] is less feasible as compared to its oxidation *via* active benzoxy radical.



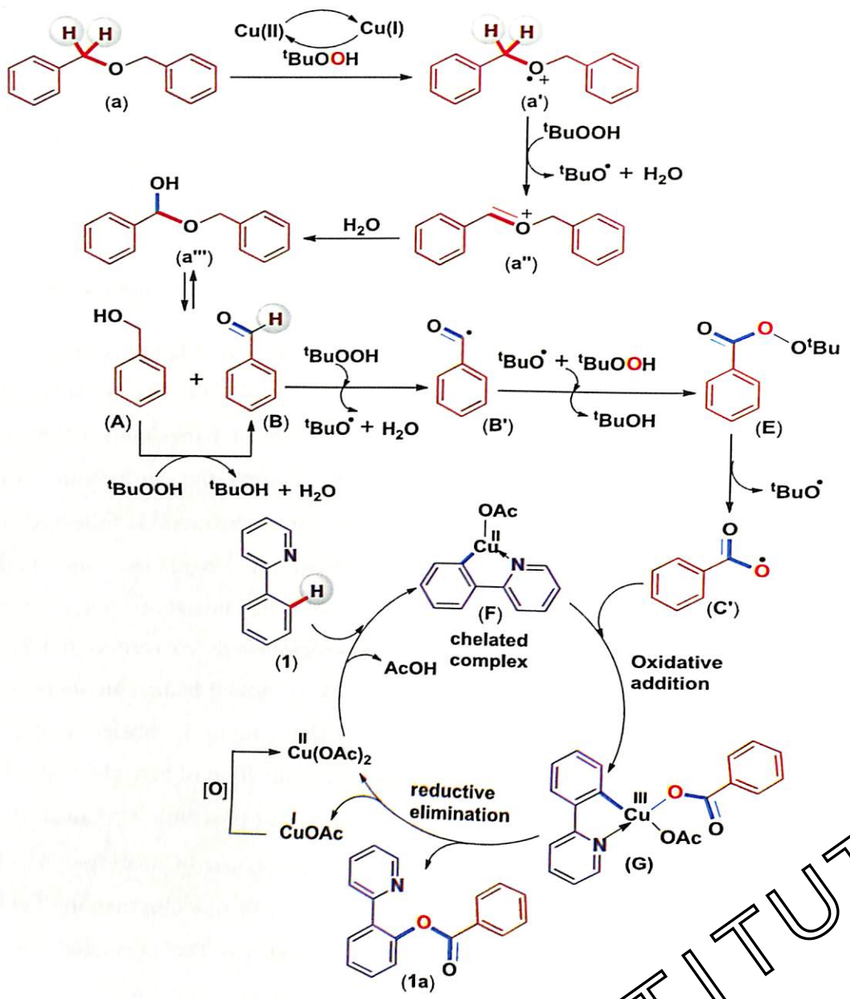
Scheme IV.3.4. *Control reactions performed with benzoic acid (**C**) and benzylbenzoate (**D**)*

Furthermore, to support the radical nature of the coupling, a reaction was conducted in the presence of a radical quencher TEMPO (3.0 equiv) keeping other reaction parameters constant. A substantial drop in the yield of (**1a**) (13%) along with the formation of TEMPO-ester (**X**) confirms the radical nature of the reaction as illustrated in Scheme IV.3.5.



Scheme IV.3.5. *Control reaction performed with radical inhibitor TEMPO*

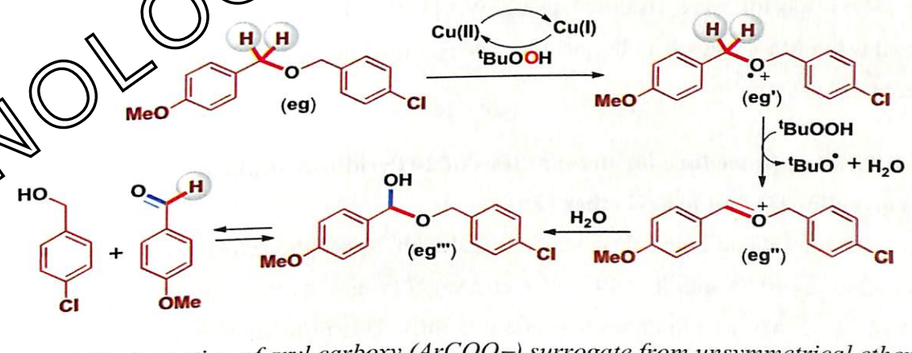
Results obtained from controlled experiments and from our recent reports[4a,5a] a plausible reaction mechanism has been postulated as shown in Scheme IV.3.6. Presumably, TBHP in the presence of copper catalyst produces species (**a′**) *via* an initial SET mechanism. The intermediate species (**a′**) undergo proton abstraction of α–sp^3 C–H bond to give an oxonium species (**a″**). However, alternative path involving α–sp^3 C–H proton abstraction followed by a SET mechanism to form oxonium species (**a″**) cannot be ruled out.[25] A nucleophilic attack of water on oxonium species leads to the formation of an unstable hemi-acetal species (benzyloxy)(phenyl)methanol (**a‴**). This hemi-acetal species easily cleaved to give an equimolar mixture of benzyl alcohol (**A**) and benzaldehyde (**B**). Thus formed benzyl alcohol (**A**) generated is further oxidized to the corresponding benzaldehyde (**B**). Due to the presence of an excess of TBHP, the *in situ* generated (**B′**) obtained by the proton abstraction of benzaldehyde (**B**), forms a perester species (**E**). Homolytic cleavage of this perester (**E**) forms carboxy radical (**C′**). Further oxidative addition of this carboxy radical (**C′**) with cyclometallated Cu complex (**F**) lead to the formation of an unstable Cu^{III} intermediate (**G**). Finally, a reductive elimination of (**G**) installs a benzoxy moiety at the *ortho* site of (**1**) forming Cu^{I} species. The generated Cu^{I} catalyst is oxidized to Cu^{II} for subsequent catalytic cycle as shown in Scheme IV.3.6.



Scheme IV.3.6. *Plausible mechanism for o-benzoxylation of 2-phenylpyridine (1)*

In case of unsymmetrical dibenzyl ether (**eg**) provided (**1e**) as the major product. This is due to the formation of a more stable oxonium species by the α–sp^3 C–H proton abstraction from activated ring side (**eg′′**). The *in situ* generated hemi-acetal intermediate (**eg′′′**) cleaved to equimolar mixture of 4-methoxybenzaldehyde and 4-chlorobenzyl alcohol as shown in Scheme IV.3.7. The *in situ* generated 4-methoxybenzaldehyde then undergo preferential coupling with 2-phenylpyridine (**1**), while *in situ* formed 4-chlorobenzyl alcohol needed an extra oxidizing step to

get corresponding aldehyde. This favoured coupling of electron-donating substituent is true even when an equimolar mixture of 4-methoxybenzaldehyde and 4-chlorobenzaldehyde were reacted with (**1**) under the optimized conditions. The ratio of corresponding *o*-benzoxylated products (**1e**) and (**1g**) obtained were 7:3 confirming our assumption. The higher propensity of formation of *o*-benzoxylated product derived from electron-donating part of unsymmetrical dibenzylether (**eg**) has been ascertained even when the reaction was performed with 0.5 mmol (1 equiv) of unsymmetrical ether (**eg**). The ratio of products (**1e**) and (**1g**) (1.45:1) obtained were almost identical (1.50:1) using 0.75 mmol (1.5 equiv) of (**eg**) supporting our presumption.



Scheme IV.3.7. *Formation of aryl carboxy (ArCOO–) surrogate from unsymmetrical ether (**eg**)*

In conclusion, an efficient Cu^{II}-catalyzed protocol for the *o*-benzoxylation of 2-arylpyridine derivatives has been demonstrated utilizing benzyl ethers as the new arylcarboxy surrogates. The reaction shows a broad substrates scope and good tolerance toward the various functional groups using inexpensive copper catalyst. A mechanistic investigation reveals that the reaction is going *via* radical pathways. In addition, this reaction demonstrates the differential reactivity of Cu catalyst to that of Pd catalyst. It is true that benzyl alcohols and benzaldehydes also serve as the *o*-benzoxy source, however aldehydes on storage easily oxidizes to their corresponding acids. Similarly, alcohols are also prone to oxidative conditions. The use of dibenzylether is advantageous because they are not only stable to areal oxidation but also releases two equivalents of aroylcarboxy group per molecule. The reaction proceeds through sequential formation of C–O bonds involving overall cleavages of five C–H bonds (four benzylic sp^3 C–H's and one sp^2 arene C–H) and one C–O bond to selectively install an arylcarboxy moiety at the *ortho* site of 2-arylpyridine derivatives.

IV.4. Experimental Section

IV.4. 1. General information:

All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Mass spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

IV.4. 2. General procedure for the synthesis of 2-(Pyridin-2-yl)phenyl benzoate (1a) from 2-phenylpyridine (1) and benzyl ether (a):

A oven-dried round bottle flask was charged with 2-phenylpyridine (**1**), (0.5 mmol, 0.078 g), benzyl ether (**a**) (0.75 mmol, 0.149 g), $Cu(OAc)_2$ (20 mol %, 0.018 g), 70% aqueous solution TBHP (6 equiv, 430 μL) in chlorobenzene (0.5 mL). This resultant reaction mixture was stirred in a preheated oil bath at 120 °C for 22 h and the progress of the reaction was monitored by TLC. The reaction mixture was cooled down to room temperature, residual solvent evaporated under reduced pressure and diluted with ethyl acetate (1 x 10 mL). This diluted reaction mixture was passed through a Celite bed and subsequently washed with ethyl acetate (2 x 10 mL). The combined organic layer was then washed with 10% aq. saturated solution of $NaHCO_3$ (2 x 5 mL) followed by water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using (heane/ethylacetate = 9:1) as the eluent to give pure compound (2-(pyridin-2-yl)phenyl benzoate) (**1a**, 0.08 g, 58%) as a brownish oil material.

IV.5. References and Notes

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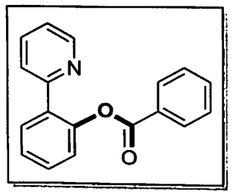
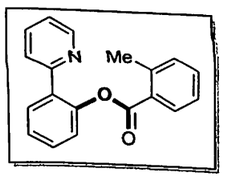
IV.6. Spectral data

2-(Pyridin-2-yl)phenyl benzoate (1a):



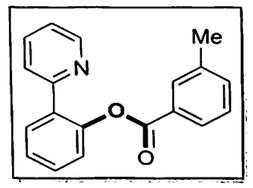
Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.14–7.17 (m, 1H), 7.31 (d, 1H, J = 8.4 Hz), 7.38–7.44 (m, 2H), 7.46–7.51 (m, 2H), 7.55–7.65 (m, 3H), 7.77–7.79 (m, 1H), 8.09 (d, 2H, J = 7.6 Hz), 8.59–8.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.3, 123.5, 123.9, 126.6, 128.7, 129.7, 129.9, 130.4, 131.1, 133.5, 133.6, 136.4, 148.5, 149.8, 155.8, 165.4; IR (KBr): 3062, 2924, 2854, 1737, 1585, 1564, 1493, 1463, 1451, 1426, 1262, 1195, 1177, 1116, 1080, 1062, 1023, 754, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{14}NO_2^+$ (M + H$^+$) 276.1019; found 276.1019.

2-(Pyridin-2-yl)phenyl 2-methylbenzoate (1b):



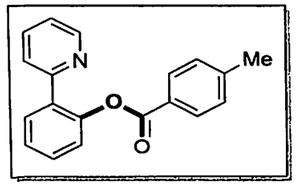
Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.53 (s, 3H), 7.16–7.19 (m, 1H), 7.24–7.29 (m, 3H), 7.30–7.45 (m, 2H), 7.47–7.51 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.63–7.67 (m, 1H), 7.76 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.6 Hz), 7.99–8.01 (m, 1H), 8.61–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.8, 122.3, 123.6, 123.9, 125.9, 126.5, 128.8, 129.9, 131.1, 131.3, 131.9, 132.7, 133.7, 136.4, 141.4, 148.5, 149.7, 156.0, 165.9; IR (KBr): 3064, 2926, 2853, 1738, 1603, 1585, 1492, 1462, 1425, 1289, 1246, 1190, 1135, 1046, 1022, 793, 752, 736, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H$^+$) 290.1176; found 290.1182.

2-(Pyridin-2-yl)phenyl 3-methylbenzoate (1c):



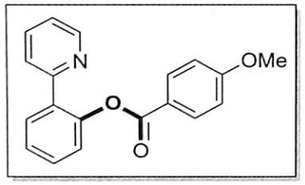
Yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.39 (s, 3H), 7.16–7.17 (m, 1H), 7.30 (d, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.38–7.41 (m, 2H), 7.46–7.49 (m, 1H), 7.56 (d, 1H, J = 7.8 Hz), 7.61–7.63 (m, 1H), 7.78 (dd, 1H, J_1 = 1.8 Hz, J_2 = 7.8 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.90 (s, 1H), 8.60–8.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 122.3, 123.5, 123.9, 126.5, 127.5, 128.6, 129.6, 129.9, 130.9, 131.1, 133.5, 134.4, 136.3, 138.5, 148.5, 149.8, 155.8, 165.5; IR (KBr): 3062, 2923, 2856, 1731, 1608, 1565, 1587, 1493, 1463, 1426, 1275, 1184, 1115, 1064, 1025, 990, 903, 793, 739 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H$^+$) 290.1176; found 290.1180.

2-(Pyridin-2-yl)phenyl 4-methylbenzoate (1d):



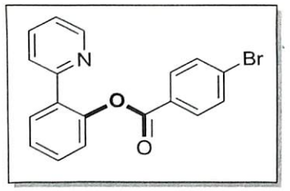
Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.43 (s, 3H), 7.14–7.18 (m, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.29–7.31 (m, 1H), 7.38–7.42 (m, 1H), 7.46–7.50 (m, 1H), 7.54–7.57 (m, 1H), 7.59–7.64 (m, 1H), 7.78 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.97 (d, 2H, J = 8.0 Hz), 8.59–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.9, 122.3, 123.6, 123.9, 126.5, 126.9, 129.4, 129.8, 130.4, 131.1, 133.6, 136.3, 144.5, 148.6, 149.8, 155.8, 165.4; IR (KBr): 3063, 2923, 2853, 1738, 1610, 1585, 1571, 1442, 1425, 1263, 1223, 1177, 1066, 1018, 836, 746, 767 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H$^+$) 290.1176; found 290.1173.

2-(Pyridin-2-yl)phenyl 4-methoxybenzoate (1e):



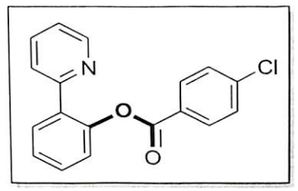
Brownish gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.87 (s, 3H), 6.93 (d, 2H, J = 8.8 Hz), 7.14–7.17 (m, 1H), 7.29 (d, 1H, J = 8.4 Hz), 7.37–7.41 (m, 1H), 7.45–7.49 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.59–7.64 (m, 1H), 7.77–7.79 (m, 1H), 8.04 (d, 2H, J = 8.8 Hz), 8.61–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.7, 113.9, 121.9, 122.3, 123.6, 123.9, 126.4, 129.8, 131.1, 132.5, 133.5, 136.3, 148.6, 149.8, 155.8, 163.9, 165.0; IR (KBr): 3063, 3010, 2933, 2842, 1730, 1606, 1582, 1510, 1462, 1424, 1317, 1255, 1195, 1166, 1114, 1068, 1024, 847, 752 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_3^+$ (M + H$^+$) 306.1125; found 306.1134.

2-(Pyridin-2-yl)phenyl 4-bromobenzoate (1f):



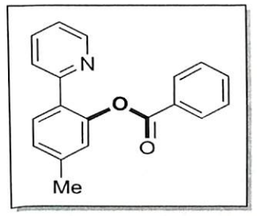
Pale yellow gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.15–7.18 (m, 1H), 7.29 (d, 1H, J = 8.0 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.62–7.66 (m, 1H), 7.75 (d, 1H, J = 6.8 Hz), 7.93 (d, 2H, J = 8.8 Hz), 8.56–8.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.4, 123.5, 123.8, 126.8, 128.7, 128.9, 130.0, 131.1, 131.9, 132.1, 133.5, 136.5, 148.3, 149.8, 155.8, 164.7; IR (KBr): 3062, 2924, 2852, 1738, 1606, 1589, 1484, 1463, 1426, 1397, 1261, 1193, 1173, 1116, 1071, 1010, 846, 792, 749 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}BrNO_2^+$ (M + H$^+$) 354.0124; found 354.0124.

2-(Pyridin-2-yl)phenyl 4-chlorobenzoate (1g):



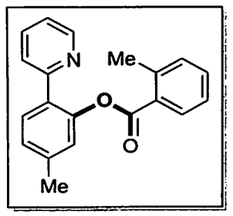
Colourless gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.16–7.18 (m, 1H), 7.30 (d, 1H, J = 8.4 Hz), 7.39–7.44 (m, 3H), 7.47–7.50 (m, 1H), 7.52 (d, 1H, J = 7.8 Hz), 7.62–7.65 (m, 1H), 7.76 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.2 Hz), 8.01 (d, 2H, J = 8.4 Hz), 8.56–8.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.4, 123.5, 123.8, 126.8, 128.2, 129.1, 129.9, 131.1, 131.8, 133.5, 136.4, 140.2, 148.3, 149.8, 155.8, 164.6; IR (KBr): 3065, 2924, 2853, 1739, 1592, 1492, 1463, 1426, 1401, 1261, 1194, 1172, 1116, 1091, 1071, 1014, 848, 750 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}ClNO_2^+$ (M + H$^+$) 310.0629; found 310.0631.

5-Methyl-2-(pyridin-2-yl)phenyl benzoate (2a):



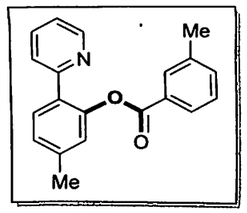
Reddish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 7.12–7.13 (m, 2H), 7.21 (d, 1H, J = 7.8 Hz), 7.45 (t, 2H, J = 7.8 Hz), 7.54 (d, 1H, J = 7.2 Hz), 7.58–7.61 (m, 2H), 7.69 (d, 1H, J = 7.8 Hz), 8.09 (d, 2H, J = 7.8 Hz), 8.57–8.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 122.1, 123.7, 123.9, 127.5, 128.7, 129.8, 130.3, 130.6, 130.8, 133.6, 136.3, 140.4, 148.3, 149.7, 155.8, 165.5; IR (KBr): 3061, 2924, 2854, 1732, 1666, 1621, 1587, 1467, 1451, 1432, 1257, 1177, 1152, 1081, 1063, 1025, 826, 784, 750, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H$^+$) 290.1176; found 290.1178.

5-Methyl-2-(pyridin-2-yl)phenyl 2-methylbenzoate (2b):



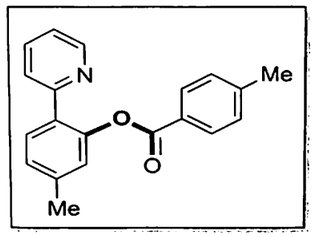
Yellowish gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.44 (s, 3H), 2.54 (s, 3H), 7.09 (s, 1H), 7.13–7.17 (m, 1H), 7.20 (d, 1H, J = 7.6 Hz), 7.23–7.27 (m, 2H), 7.41–7.45 (m, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.61 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.65 (d, 1H, J = 8.4 Hz), 7.99–8.02 (m, 1H), 8.59–8.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.4, 21.8, 122.1, 123.8, 124.0, 125.9, 127.4, 128.9, 130.78, 130.80, 131.3, 131.9, 132.6, 136.3, 140.4, 141.3, 148.3, 149.7, 150.1, 166.0; IR (KBr): 3058, 2925, 2853, 1738, 1621, 1587, 1574, 1465, 1431, 1288, 1245, 1151, 1136, 1045, 782, 736 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_2^+$ ($M + H^+$) 304.1332; found 304.1332.

5-Methyl-2-(pyridin-2-yl)phenyl 3-methylbenzoate (2c):



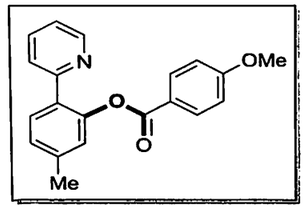
Yellowish oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.40 (s, 3H), 2.44 (s, 3H), 7.11 (s, 1H), 7.12–7.14 (m, 1H), 7.21 (d, 1H, J = 7.2 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.40 (d, 1H, J = 7.8 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.58–7.61 (m, 1H), 7.68 (d, 1H, J = 7.8 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.90 (s, 1H), 8.58–8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.4, 21.8, 122.1, 123.8, 124.0, 125.9, 127.4, 128.9, 130.78, 130.80, 131.3, 131.9, 132.6, 136.3, 140.4, 141.3, 148.3, 149.7, 150.1, 166.0; IR (KBr): 3058, 2925, 2853, 1738, 1621, 1587, 1574, 1465, 1431, 1288, 1245, 1151, 1136, 1045, 782, 736 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_2^+$ ($M + H^+$) 304.1332; found 304.1328.

5-Methyl-2-(pyridin-2-yl)phenyl 4-methylbenzoate (2d):



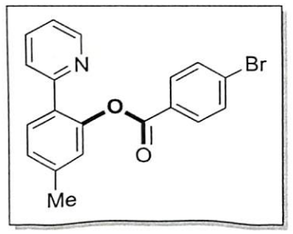
Brownish gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.42 (s, 3H), 2.43 (s, 3H), 7.11–7.14 (m, 2H), 7.20 (d, 1H, J = 8.0 Hz), 7.24–7.26 (m, 2H), 7.52–7.54 (m, 1H), 7.56–7.61 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz), 7.97 (d, 2H, J = 8.4 Hz), 8.58–8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.4, 21.9, 122.0, 123.8, 123.9, 127.0, 127.4, 129.4, 130.4, 130.6, 130.8, 136.2, 140.3, 144.4, 148.4, 149.7, 155.8, 165.5; IR (KBr): 3052, 2922, 2852, 1735, 1611, 1586, 1465, 1431, 1258, 1171, 1151, 1130, 1070, 1019, 835, 781, 746, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_2^+$ ($M + H^+$) 304.1332; found 304.1337.

5-Methyl-2-(pyridin-2-yl)phenyl 4-methoxybenzoate (2e):



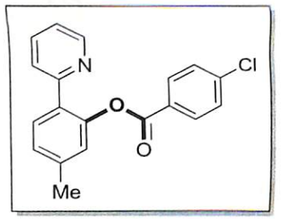
Brownish gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.43 (s, 3H), 3.87 (s, 3H), 6.93 (d, 2H, J = 8.8 Hz), 7.10–7.11 (m, 1H), 7.13 (d, 1H, J = 6.0 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 7.6 Hz), 7.57–7.61 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz), 8.04 (d, 2H, J = 8.8 Hz), 8.58–8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.4, 55.7, 113.9, 122.0, 122.1, 123.8, 124.0, 127.3, 130.6, 130.8, 132.5, 136.2, 140.3, 148.4, 149.7, 155.8, 163.9, 165.2; IR (KBr): 3059, 2924, 2853, 1731, 1606, 1586, 1511, 1464, 1432, 1254, 1167, 1130, 1071, 1027, 846, 782, 763, 692 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_3^+$ ($M + H^+$) 320.1281; found 320.1289.

5-Methyl-2-(pyridin-2-yl)phenyl 4-bromobenzoate (2f):



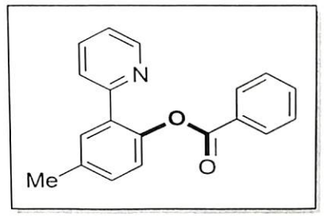
Light yellow thik gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 7.10 (s, 1H), 7.13–7.15 (m, 1H), 7.21 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.59–7.63 (m, 3H), 7.65 (d, 1H, J = 8.4 Hz), 7.94 (d, 2H, J = 8.8 Hz), 8.54–8.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 122.2, 123.7, 123.9, 127.6, 128.75, 128.84, 130.5, 130.8, 131.9, 132.1, 136.4, 140.5, 148.2, 149.7, 155.8, 164.9; IR (KBr): 3061, 2924, 2853, 1738, 1621, 1589, 1511, 1484, 1466, 1432, 1397, 1258, 1173, 1152, 1131, 1072, 1011, 784, 748 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}BrNO_2^+$ (M + H^+) 368.0281; found 368.0281.

5-Methyl-2-(pyridin-2-yl)phenyl 4-chlorobenzoate (2g):



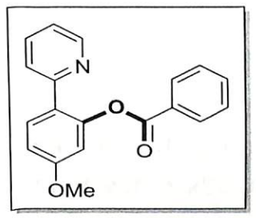
Brownish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 7.11 (s, 1H), 7.12–7.14 (m, 1H), 7.21 (d, 1H, J = 7.8 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.59–7.62 (m, 1H), 7.65 (d, 1H, J = 7.8 Hz), 8.01 (d, 2H, J = 7.8 Hz), 8.54–8.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.4, 122.2, 123.6, 123.9, 127.6, 128.3, 129.1, 130.5, 130.8, 131.7, 136.4, 140.1, 140.5, 148.2, 149.7, 155.8, 164.7; IR (KBr): 3053, 2923, 2853, 1738, 1621, 1590, 1487, 1466, 1431, 1400, 1258, 1172, 1152, 1131, 1090, 1072, 1052, 848, 784, 750 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}ClNO_2^+$ (M + H^+) 324.0786; found 324.0786.

4-Methyl-2-(pyridin-2-yl)phenyl benzoate (3a):



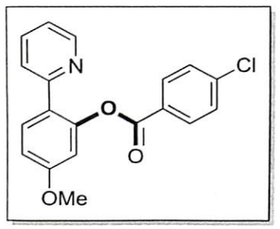
Light yellow gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.44 (s, 3H), 7.14–7.16 (m, 1H), 7.18 (d, 1H, J = 8.4 Hz), 7.27–7.29 (m, 1H), 7.45 (t, 2H, J = 7.8 Hz), 7.55 (d, 1H, J = 7.2 Hz), 7.58–7.62 (m, 3H), 8.08 (d, 2H, J = 7.8 Hz), 8.60–8.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.1, 122.3, 123.2, 123.9, 128.6, 129.8, 129.9, 130.4, 130.6, 131.5, 133.0, 133.6, 136.3, 146.3, 149.8, 155.8, 165.5; IR (KBr): 3061, 2923, 2852, 1731, 1586, 1566, 1499, 1462, 1452, 1436, 1428, 1314, 1264, 1195, 1177, 1131, 1080, 1062, 1024, 991, 871, 799, 773, 747, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2^+$ (M + H^+) 290.1176; found 290.1182.

5-Methoxy-2-(pyridin-2-yl)phenyl benzoate (4a):



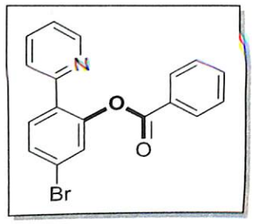
Brown gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.87 (s, 3H), 6.83–6.84 (m, 1H), 6.96 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.09–7.13 (m, 1H), 7.46 (t, 2H, J = 8.0 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.57–7.62 (m, 2H), 7.74 (d, 1H, J = 8.4 Hz), 8.10 (d, 2H, J = 7.2 Hz), 8.56–8.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.8, 108.9, 112.8, 121.9, 123.6, 125.9, 128.7, 129.7, 130.4, 131.8, 133.7, 136.4, 149.4, 149.7, 155.6, 160.9, 164.4; IR (KBr): 3050, 2925, 2852, 1737, 1617, 1587, 1510, 1465, 1433, 1314, 1260, 1189, 1154, 1124, 1061, 1079, 1023, 881, 784, 706 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}NO_3^+$ (M + H^+) 306.1125; found 306.1130.

5-Methoxy-2-(pyridin-2-yl)phenyl 4-chlorobenzoate (4g):



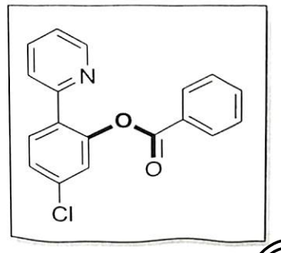
Brown gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.87 (s, 3H), 6.83–6.84 (m, 1H), 6.96 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.4 Hz), 7.10–7.12 (m, 1H), 7.44 (d, 2H, J = 8.4 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.58–7.61 (m, 1H), 7.71 (d, 1H, J = 8.4 Hz), 8.03 (d, 2H, J = 8.4 Hz), 8.52–8.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 55.8, 108.9, 112.9, 121.9, 123.4, 125.9, 128.2, 129.1, 131.7, 136.4, 140.2, 140.8, 149.3, 149.7, 155.6, 160.9, 164.5; IR (KBr): 3049, 2925, 2851, 1739, 1617, 1593, 1509, 1465, 1433, 1400, 1283, 1259, 1190, 1154, 1124, 1090, 1014, 846, 783, 749 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}ClNO_3^+$ (M + H$^+$) 340.0735; found 340.0745.

5-Bromo-2-(pyridin-2-yl)phenyl benzoate (5a):



Light brown gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.14–7.17 (m, 1H), 7.43–7.48 (m, 3H), 7.51–7.53 (m, 2H), 7.57–7.63 (m, 2H), 7.66 (d, 1H, J = 8.8 Hz), 8.03–8.06 (m, 2H), 8.56–8.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.6, 122.9, 123.8, 126.9, 128.8, 129.2, 129.8, 130.4, 132.2, 132.6, 133.9, 136.5, 148.9, 149.9, 154.8, 164.9; IR (KBr): 3051, 2924, 2851, 1741, 1640, 1590, 1463, 1252, 1195, 1055, 868, 746, 706 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}BrNO_2^+$ (M + H$^+$) 354.0124; found 354.0128.

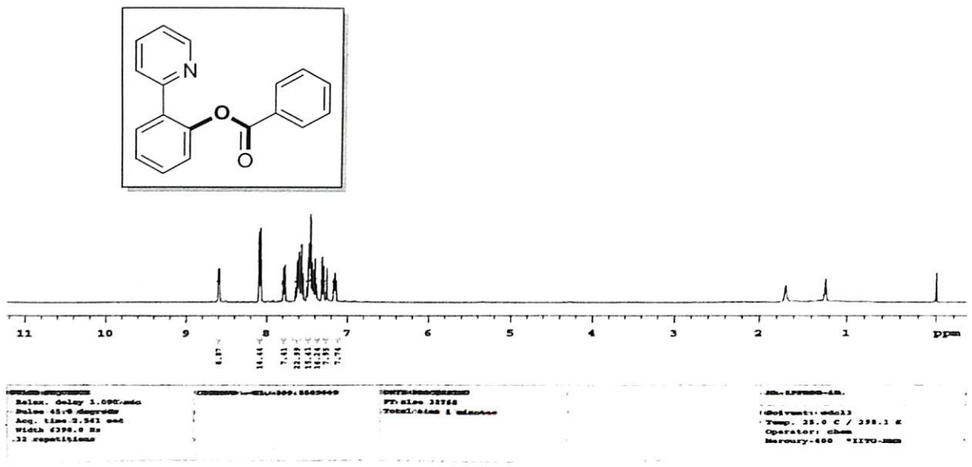
5-Chloro-2-(pyridin-2-yl)phenyl benzoate (6a):



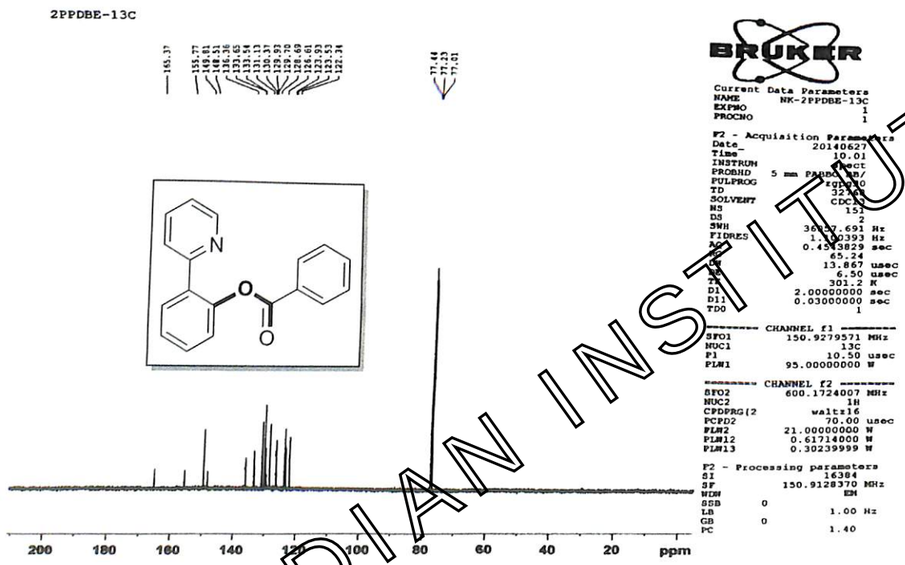
Light yellowish gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.16–7.18 (m, 1H), 7.348–7.352 (m, 1H), 7.38 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.0 Hz), 7.47 (t, 2H, J = 7.8 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.59–7.64 (m, 2H), 7.75 (d, 1H, J = 8.4 Hz), 8.07 (d, 2H, J = 9 Hz), 8.58–8.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 122.6, 123.8, 124.0, 126.9, 128.8, 129.2, 130.4, 131.9, 132.1, 133.91, 135.1, 136.5, 148.9, 149.9, 154.8, 164.9; IR (KBr): 3065, 2924, 2852, 1742, 1601, 1585, 1491, 1462, 1433, 1395, 1275, 1195, 1126, 1086, 1058, 1023, 892, 783, 747, 706 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}ClNO_2^+$ (M + H$^+$) 310.0629; found 310.063.

IV.7. Selected Spectra

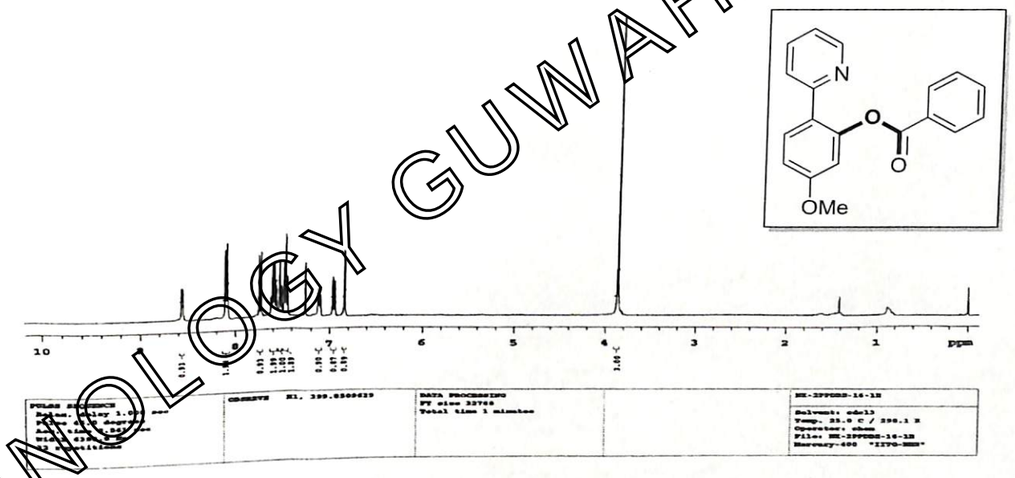
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{1}H NMR ($CDCl_3$, 400 MHz)



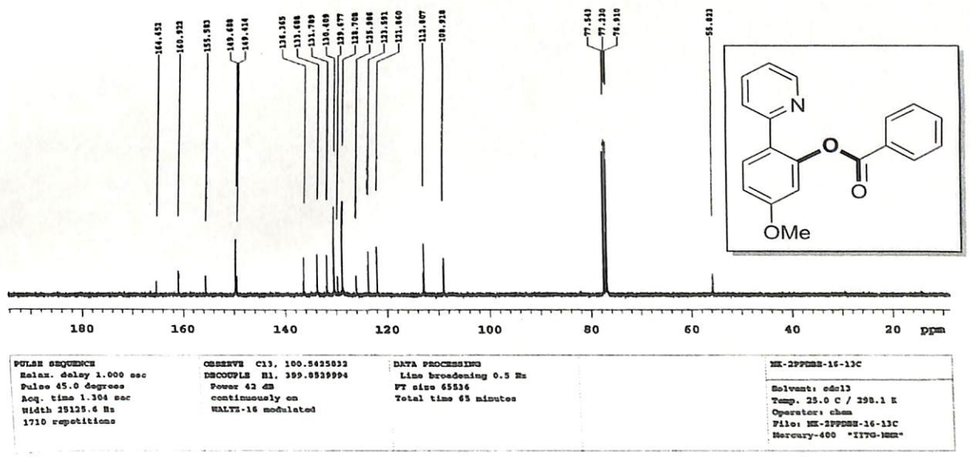
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{13}C NMR ($CDCl_3$, 150 MHz)



5-Methoxy-2-(pyridin-2-yl)phenyl benzoate (4a): ^{1}H NMR ($CDCl_3$, 400 MHz)

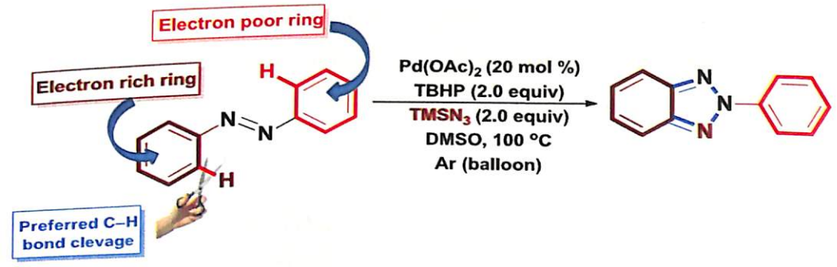


5-Methoxy-2-(pyridin-2-yl)phenyl benzoate (4a): ^{13}C NMR ($CDCl_3$, 100 MHz)



Chapter V

Palladium-Catalyzed Synthesis of 2-Aryl-*2H*-Benzotriazoles from Azoarenes and $TMSN_3$



V. Abstract: *Substrate directed ortho C–H amination of azoarenes using $TMSN_3$ as the source of nitrogen leading to the synthesis of 2-aryl-2H-benzotriazoles has been accomplished with the help of Pd/TBHP combinations. An intermolecular o-azidation (C–N bond formation) followed by an intramolecular N–N bond formation via nucleophilic attack of one of the azo nitrogen onto the o-azide nitrogen leads to cyclization with the expulsion of N_2.*

Chapter V

V. Palladium-Catalyzed Synthesis of 2-Aryl-2*H*-Benzotriazoles from Azoarenes and $TMSN_3$

V.1. Introduction

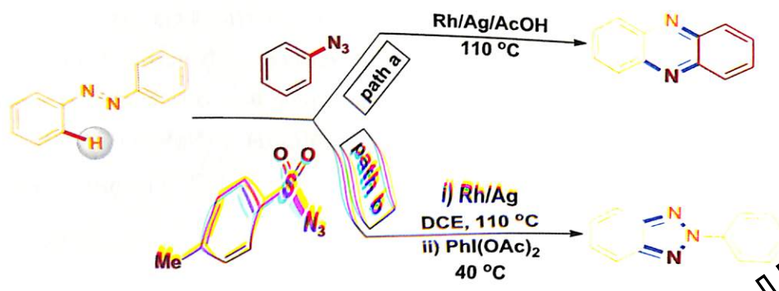
Direct C–H bond functionalization by transition metal catalysts has opened a plethora of methods in the construction of C–C, C–N and C–heteroatom bonds.[1-4] Strategies involving inert C–H bond activation are important and significant due to their step and atom economy which circumvent pre-fuctionalization of starting materials. In particular, directed C–H bond amination strategies have received a great attention recently.[5-7] A range of preactivated aminating reagents such as *N*-carboxylates,[8a] *N*-fluorobenzenesulfonimide (NFSI),[8b] *N*-tosylates,[8c] *N*-halides,[8d] benzoyl hydroxylamines[8e] and highly active nitrene precursors, especially azides derivatives[8f-8h] have been explored as the potential aminating reagents under different metal catalysis.

Organic azides are important building blocks in synthetic chemistry and have found wide applications in medicinal chemistry, material science, polymer and biological science.[9] Generally, azide moiety is introduced into organic molecules *via* Sandmeyer reaction,[10a,b] Cu-catalyzed coupling of aryl halides/boronic acids with azides (NaN_3 or $TMSN_3$),[10c,d] coupling between organometallics and TfN_3[10e] and metal free[10f-h] or metal mediated C–H functionalization.[10i,j] As a nitrene precursor, *ortho* azido group can participate in intramolecular cyclization after releasing a molecule of N_2. Taking advantage of this, a number of metal-catalyzed protocols have been developed for the synthesis of nitrogen containing heterocycles. Prefunctionalized 2-azido substrates or the *in situ* generated *ortho* azido moiety introduced *via* cross coupling reactions or C–H functionalization often undergo intramolecular cyclizations leading to various heterocycles.[11]

Aromatic azoarenes constitute an important class of conjugated molecules because they exhibit a diverse array of spectral properties. They find applications as industrial dyes, food additives, photochemical molecular switches, host-guest recognition, liquid crystal assemblies, biomedical image analysis, molecular motor design, materials and protein probes.[12] From a synthetic point of view, in 1971, azoarenes as the directing group were first introduced by Fahey

for the *o*-halogenation *via* a C–H activation strategy.[13] However, its synthetic utility was dormant until very recently when a series of transition metal-catalyzed reactions involving azoarenes as the directing substrates were exploited. Examples include Pd-catalyzed *ortho*-aroylation,[14] *o*-nitration,[15,16a] *o*-alkoxylation,[16b] *o*-halogenation,[16c] Rh-catalyzed alkyne annulations,[16d] allylation,[16e] *o*-acylation and its transformation to indazoles[16f] and *o*-amination.[16g,h] In addition, Re and Rh-catalyzed syntheses of nitrogenous heterocycles using aldehyde,[17a] α-diazo esters[17b] and diazotized Meldrum's acid[17c] have been reported.

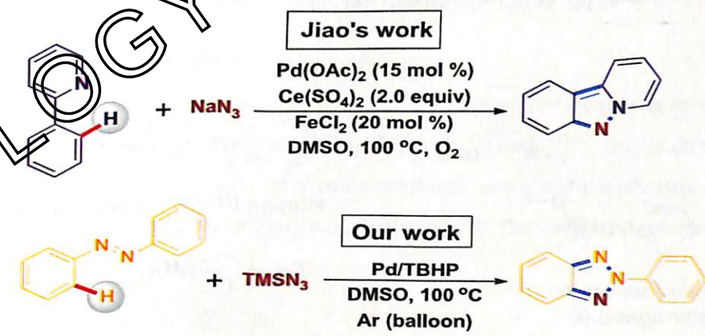
With azo as the directing group, depending upon the nature of azides (as the source of nitrogen) either a six or a five member heterocycle is formed using Rh catalyst. In 2013, Ellman group showed that the use of aryl azide (ArN_3) as coupling partner for sp^2 C–H functionalization of azoarenes provided phenazines as the sole product (Scheme V.1.1, path a).[18] While in 2014, Lee and co-workers demonstrated that use of tosyl azide employing the same directed substrates (azoarenes) led to the exclusive formation of *2H*-benzotriazole derivatives as shown in Scheme V.1.1, path b.[19]



Scheme V.1.1. *Differential reactivities of azide derivatives with azobenzene under Rh catalysis*

Pertaining these works, Jiao group showed that when 2-phenylpyridines, a *N*-directed substrate, was treated with inorganic azide NaN_3 as the coupling partner under a Pd-catalyzed condition gave fused heterocycle pyrido[1,2–*b*]indazoles as shown in Scheme V.1.2.[11d] Although an elegant transformation of azoarenes to *2H*-benzotriazoles has been described by the Lee group, the use of expensive combinations of catalyst $[Cp^*RhCl_2]_2$, co-catalyst $AgNTf_2$ and oxidant $PhI(OAc)_2$ makes this method economically unviable (Scheme V.1.1, path b).[19] Thus, the development of an efficient, cost-effective and atom-economic protocol is very much in need. With our continuing efforts to establish newer strategies for the synthesis of heterocycles

through C–H activation,[20] and taking cues from the recent reports,[11d,18,19] our investigation started. The main objective was to check whether other commercially available metal catalyst and cheaper oxidant could be a replacement for the synthesis of *2H*-benzotriazoles following *o*-C–H activation of azoarenes. With this curiosity in mind, when a reaction was carried out using azobenzene as the starting material in the presence of Pd/TBHP combination and $TMSN_3$ as the nitrogen source, the reaction gave 2-phenyl-*2H*-benzotriazoles as the exclusive product (Scheme V.1.2).



Scheme V.1.2. *Synthesis of nirogenious heterocycles from directed substrates employing azides*

V.2. Available Strategies for Synthesis of 2-Aryl-2*H*-Benzotriazole

Benzotriazole is a fused heterocyclic compound having three vicinal nitrogen atoms in its five member ring. This ring can exist in two tautomeric forms *viz.* N^1 (N^3) or 1*H* isomer and N^2 or 2*H*-isomer due to the presence of one labile proton as shown in Figure V.2.1.

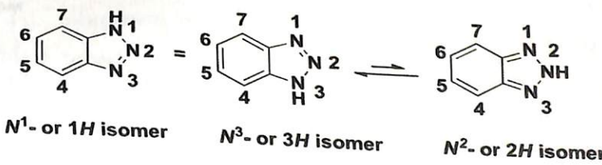
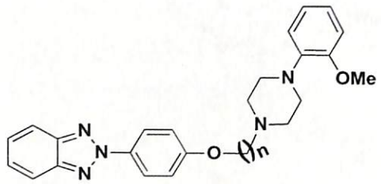


Figure V.2.1. *Different tautomeric structures of benzotriazole*

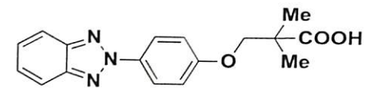
The N^1 and N^3 isomers are identical due to their structural similarity. The N^1 (1*H*) isomer is predominantly present in equilibrium with N^2 (2*H*) isomer at room temperature due to its

thermodynamical stability. The greater aromaticity of benzoid structure in N^1 (1*H*) isomer is the source of its stability compared to the quinoid-like structure in N^2 (2*H*) isomer.

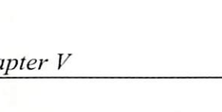
2-Aryl-*2H*-benzotriazoles are important heterocycles which are found extensively in pharmaceuticals and are structural components of many UV stabilizers and organic electronic materials.[21] Compounds having 2-aryl-*2H*-benzotriazole scaffold as primary skeleton include a seratonine/dopamine receptor ligand (**I**), human PPAR-α activator (**II**), Tinuvin-P (**III**) an ultraviolet light absorber, PCDTPBt (**IV**) an electron acceptor in organic solar cell, an ultraviolet light stabilizer (**V**) and an antiviral agent (**VI**) against ssRNA positive viruses are shown in Figure V.2.2.



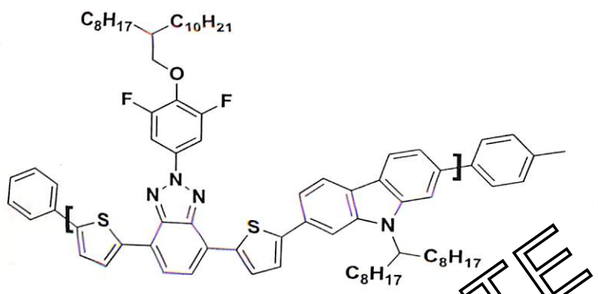
Seratonine/dopamine receptor ligand (**I**)



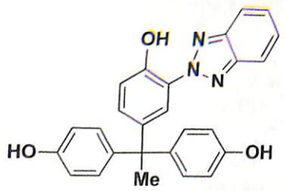
Human PPAR α activator (**II**)



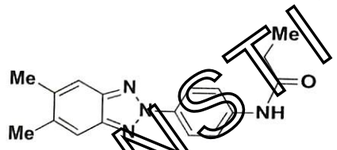
Tinuvin-P
UV lihgt absorber (**III**)



PCDTPBt
electron acceptor in organic solar cell (**IV**)



UV light stabilizer (**V**)



Antiviral activity (**VI**)

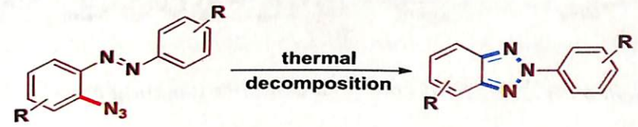
Figure V.2.2. *Important compounds having 2-aryl-2H-benzotriazole cores*

Existence of two isomeric benzotriazoles based on N^1 (N^3) and N^2 substitutions makes the selective synthetic strategies challenging. Because of the thermodynamic stability of N^1 or 1*H* isomer compared to its N^2 or 2*H* isomer as stated earlier, more synthetic methods have been reported for the former.[22]

A multitude application of 2-aryl-*2H*-benzotriazoles along with their frequently encountered structural units in biologically active molecules and in material chemistry (as shown in Figure V.2.2), have resulted the development of various protocols for their synthesis. The literature documented methodologies for their synthesis can be categorized as follows:

(i) Thermal decomposition of *ortho* azidoazoarenes

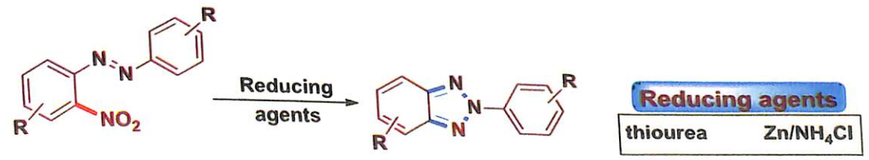
The Traditional methods for direct synthesis of 2-aryl-*2H*-benzotriazoles *via* thermal decomposition of *ortho* azidoazoarenes were developed by Zincke[23a,b] and Hall[23c] groups many years ago as shown in Scheme V.2.1. The main problem associated with this protocol is the difficulty in synthesizing o-aminoazobenzenes, from which the o-azidoazobenzenes could be prepared.



Scheme V.2.1. *Thermal decomposition of ortho azidoazoarenes*

(ii) Reduction of *ortho* nitroazoarenes

Tanimoto group demonstrated that an *in situ* reduction of *ortho* substituted nitroazoarenes using thiourea led to the facile synthesis of *2H*-benzotriazoles in 1986.[24] Later on, in 2014, Sun group showed that a combination of Zn and NH_4Cl[15] is quite effective for the competent reduction of *ortho* nitro moiety of nitroazoarenes for the synthesis of same molecule as in Scheme V.2.2.



Scheme V.2.2. *Reduction of ortho nitroazoarenes*

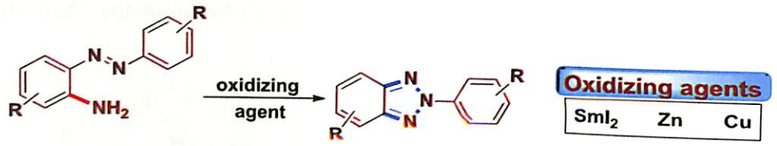
(iii)Aromatic nucleophilic substitution (SNAr) reaction

In a patented work, Bore group demonstrated that an aromatic nucleophilic displacement of nitro group of corresponding *ortho* substituted azoarenes with sodium azide (NaN_3) and a subsequent thermal decomposition led to the formation of *2H*-benzotriazoles[25] (Scheme V.2.3).

Scheme V.2.3. *SNAr reaction of ortho nitroazoarenes with sodium azide*

(iv)Oxidative cyclization of *ortho* azoanilines

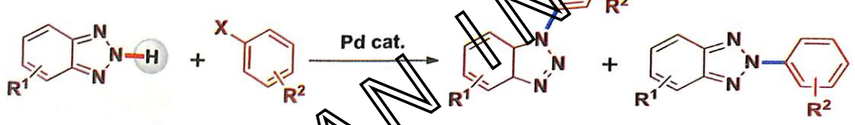
An oxidative cyclization of *ortho* substituted azoanilines to *2H*-benzotriazoles is typically mediated by various metal catalysts such as SmI_2,[26a] Zn[26b] or Cu[26c] as shown in Scheme V.2.4.



Scheme V.2.4. *Metal-catalyzed oxidative coupling of ortho azoanilines*

(v) Cross coupling reaction of benzotriazoles

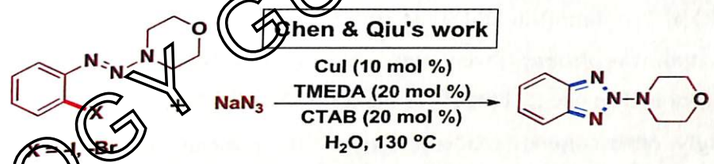
Metal-catalyzed cross coupling arylation of unsubstituted benzotriazoles with various arylating agents such as aryl iodides/bromides led to the formation of *2H*-benzotriazoles derivatives (Scheme V.2.5).[27a,b] Though those methodologies are quite effective for their synthesis, but most often they are associated with the formation of a regio-isomeric mixture of N^1- and N^2-benzotriazoles.



Scheme V.2.5. *Metal-catalyzed cross coupling reaction of unsubstituted benzotriazoles*

(vi)Cross coupling reaction of *ortho* haloaryltriazenes

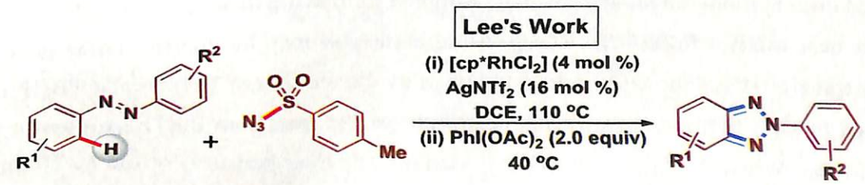
Chen and Qiu group described a copper(I)-catalyzed, TMEDA mediated highly efficient cascade cross coupling reaction between 2-haloaryltriazenes (halo = -I, -Br) and sodium azide in water which gave corresponding 2-alkyl- and 2-aryl- benzotriazoles in moderate to excellent yields as shown in Scheme V.2.6.[28]



Scheme V.2.6. *Copper-catalyzed cross coupling reaction of ortho haloaryltriazenes*

(vii) C–H activation of azoarenes

There is only one instance where sp^2 C–H bond of azoarenes has been activated utilizing metal catalyst for the synthesis of 2-aryl-*2H*-benzotriazoles derivatives. In 2014, Lee group developed a Rh-catalyzed, $PhI(OAC)_2$ mediated highly regioselective synthetic methodology for the synthesis of 2-aryl-2*H*-benzotriazoles from non-prefunctionalized azoarenes employing sulfonyl azides as the efficient coupling partner as shown in Scheme V.2.7.[19]



Scheme V.2.7. *Rh-catalyzed ortho sp^2 C–H activation of azoarenes*

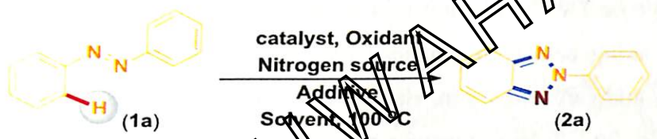
V.3. Present Work

The disadvantages associated with the above mentioned strategies include synthesis of prefunctionalized strating materials such as *ortho* azido, nitro and anino azoarenes, use of expensive catalyst/co-catalyst and untunable regioselectivity restrict their synthetic utility. Herein a straightforward and versatile Pd(II)-catalyzed, TBHP mediated protocol for the synthesis of 2-aryl-2*H*-benzotriazoles through sp^2 C–H functionalization of non-functionalized

azoarenes employing organic azides $TMSN_3$ as the effective nitrogen source is illustrated. This reaction proceeded through consequitive formation of intermolecular C–N and intramolecular N–N bonds *via* the cleavage of *ortho* C–H bond of azoarenes.

Optimization of reaction condition: Initially, a trial experiment was performed by treating azobenzene (**1a**) (0.5 mmol) with NaN_3 (1.0 mmol), in the presence of $Pd(OAc)_2$ (10 mol %) and oxidant $Ce(SO_4)_2$ (1.0 mmol) in DMSO at 100 °C by taking cues from the previous report.[11d] No product formation was observed even after 72 h, only starting material (**1a**) was recovered at the end of the reaction. The use of $TMSN_3$ in lieu of NaN_3 also failed to produce any positive result. Disappointingly, other common oxidants used mostly in metal-catalyzed C–H functionalizations such as CAN, DDQ, $Cu(OAc)_2$, Ag_2O, $K_2S_2O_8$, Oxone and O_2 were completely unproductive (Table V.3.1, entry 3). Interestingly, keeping all other parameters constant the use of TBHP as oxidant (1 equiv) provided 2-phenyl-*2H*-benzotriazole (**2a**) in 42% yield (Table V.3.1, entry 4). Encouraged by this preliminary success a series of reactions were performed by varying other reaction parameters to obtain the best possible yield of (**2a**). At first, the catalytic efficacy of various Pd-catalysts [$Pd(OAc)_2$ (42%), $PdCl_2$ (28%), $PdBr_2$ (33%), $Pd(CH_3CN)_2Cl_2$ (21%)] were tested among which $Pd(TFA)_2$ (49%) was found to be better as shown in Table V.3.1, entries 4–8. Although $Pd(TFA)_2$ gave superior yield, on a couple of occasions the reaction flask exploded even at room temperature which prompted us to avoid its use, and therefore switched to the next best catalyst $Pd(OAc)_2$. The possible explosion may be due to *in situ* generation of highly explosive HN_3. The azide radical obtained by the reaction of $TMSN_3$ and TBHP is rapidly converted to HN_3 by the *in situ* generated trifluoroacetic acid from $Pd(TFA)_2$ possibly causing the explosion. When the catalyst $Pd(OAc)_2$ loading was increased to two fold *i.e* 20 mol %, the yield of the expected product improved up to 62% (Table V.3.1, entry 9). No further significant improvement in the yield (65%) was observed even when the catalyst loading was increased up to three fold (30 mol %). Other solvents such as THF (<5%), dioxane (<5%), PhCl (41%) and DMF (48%) (Table V.3.1, entries 11–14) tested under otherwise identical conditions were all found to be inferior to DMSO. The oxidant TBHP (in decane) was superior to other peroxide oxidants such as 70% aqueous TBHP (42%) and 30% aqueous H_2O_2 (00%) (Table V.3.1, entries 15–16) in terms of yields. A further improvement in the product yield (70%) was observed when the oxidant (decane-TBHP) amount was increased from 1 to 2 equiv (Table V.3.1, entry 17).

Table V.3.1. *Screening of reaction conditions*[a]



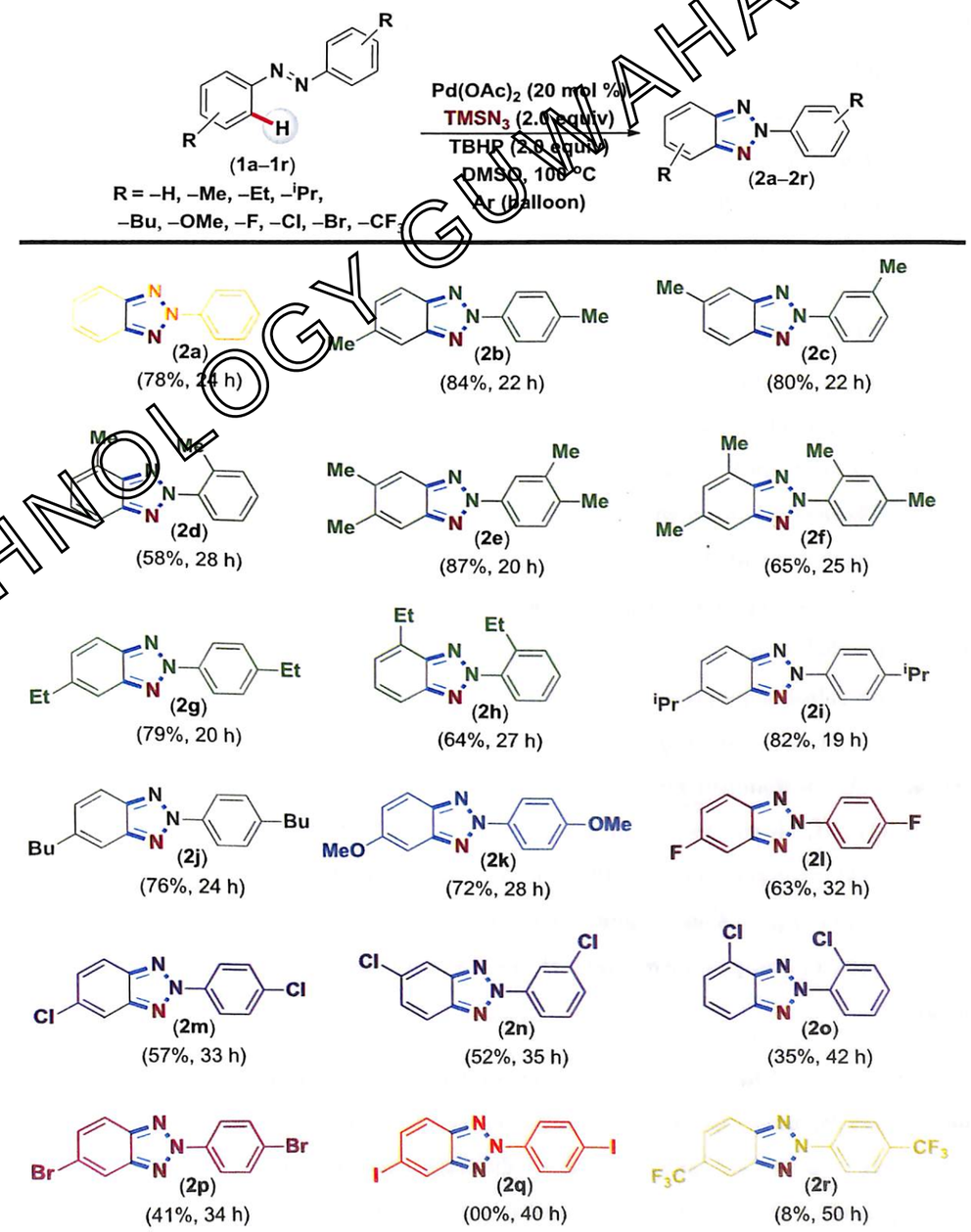
Entry	Catalyst (mol %)	Azide (equiv)	Oxidant (equiv)	Solvent	Additive	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	NaN_3 (2)	$Ce(SO_4)_2$ (1)	DMSO	–	00
2	$Pd(OAc)_2$ (10)	$TMSN_3$ (2)	$Ce(SO_4)_2$ (1)	DMSO	–	00
3	$Pd(OAc)_2$ (10)	$TMSN_3$ (2)	V.O[c,d] (1)	DMSO	–	00
4	$Pd(OAc)_2$ (10)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	42
5	$PdCl_2$ (10)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	28
6	$PdBr_2$ (10)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	33
7	$Pd(CH_3CN)_2Cl_2$ (10)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	21
8	$Pd(TFA)_2$ (10)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	49
9	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	62
10	$Pd(OAc)_2$ (30)	$TMSN_3$ (2)	TBHP (1)	DMSO	–	65
11	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (1)	THF	–	< 5
12	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (1)	Dioxane	–	< 5
13	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (1)	PhCl	–	41
14	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (1)	DMF	–	48
15	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	Aq.TBHP (1)	DMSO	–	42
16	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	Aq.H_2O_2 (1)	DMSO	–	00
17	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	–	70
18	$Pd(OAc)_2$ (20)	$TMSN_3$ (3)	TBHP (2)	DMSO	–	71
19	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (3)	DMSO	–	73
20	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	O_2	61
21	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	$PhI(OAc)_2$[e]	63
22	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	$FeCl_2$[e]	61
23	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	$Cu(OAc)_2$[e]	65
24	**$Pd(OAc)_2$ (20)**	**$TMSN_3$ (2)**	**TBHP (2)**	**DMSO**	–	**78**[f]
25	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	TBHP (2)	DMSO	–	65[g]
26	-	$TMSN_3$ (2)	TBHP (2)	DMSO	–	00
27	$Pd(OAc)_2$ (20)	$TMSN_3$ (2)	-	DMSO	–	00

[a]Reaction condition: azobenzene (**1a**, 0.5 mmol), in solvent (1.0 mL) at 100 °C for 24 h. [b]Isolated yield. [c]V.O = CAN (1 equiv), DDQ (1 equiv), $Cu(OAc)_2$ (1 equiv), Ag_2O (1 equiv), $K_2S_2O_8$ (1 equiv) and Oxone (1 equiv) used under air. [d]O_2 balloon. [e]20 mol % under air. [f]Reaction with argon balloon. [g]Reaction was carried out for 36 h at 80 °C.

No further significant enhancement in the yield was observed either by increasing the amount of aminating source *i.e* $TMSN_3$ (3 equiv) (71%) or oxidant TBHP (3 equiv) (73%) (Table V.3.1, entries 18–19). Taking cues from previous reports,[19,11d] the effects of additives such as O_2, $PhI(OAc)_2$, $FeCl_2$ and $Cu(OAc)_2$ were also examined along with decane-TBHP as illustrated in Table V.3.1, entries 20–23. Unfortunately, none of the additives had any positive effects on the product yield. Interestingly, when this reaction was carried out in an argon atmosphere, the yield of the product improved up to (78%) as shown in Table V.3.1, entry 24. By performing the reaction at lower temperature (80 °C) led to a sluggish (36 h) reaction giving a lower yield (65%) of the product (Table 1, entry 25). It is not surprising that the reaction did not proceed in the absence of either $Pd(OAc)_2$ or TBHP suggesting the essential requirements of both (Table V.3.1, entries 26–27). Optimally, the desired product (**2a**) was obtained in a best possible yield of 78% when the reaction was carried out using azobenzene (**1a**) (0.5 mmol), $TMSN_3$ (2 equiv) and decane-TBHP (2 equiv) in DMSO (1.0 mL) at 100 °C under an atmosphere of argon. It may be mentioned here that both catalyst $Pd(OAc)_2$ and oxidant TBHP are not only commercially available but are also cheaper compared to catalyst $[Cp^*RhCl_2]_2$, co-catalyst $AgNTf_2$ and oxidant $PhI(OAc)_2$ combinations.

After establishing the optimized parameters, this protocol was subsequently applied to a range of substituted azoarenes to afford their corresponding *2H*-benzotriazoles. This protocol is found to be compatible with several functional groups such as electron-donating alkyl [–Me (**1b–1f**), –Et (**1g** and **1h**), –^{i}Pr (**1i**) and –Bu (**1j**)], methoxy (–OMe) (**1k**), moderately electron-withdrawing halogens [–F(**1l**), –Cl (**1m–1o**) and –Br (**1p**)] and strongly electron-withdrawing ($-CF_3$) (**1r**) substituents in aromatic ring of azoarenes. All the substrates in Scheme V.3.1 (**1a–1r**) are symmetrically substituted azoarenes. Azoarenes possessing weakly activating substituents such as *p*-Me (**1b**), *m*-Me (**1c**) and *o*-Me (**1d**) underwent *o*-aminative-heterocyclization smoothly giving their corresponding *2H*-benzotriazoles (**2b–2d**) in moderate to good yields as shown in Scheme V.3.1. Symmetrically substituted di-methylated azoarenes such as 3,4-dimethyl (**1e**) and 2,4-dimethyl (**1f**) under the optimized reaction conditions furnished their corresponding *2H*-benzotriazoles (**2e**) and (**2f**) respectively, in 87% and 65% yields (Scheme V.3.1).

Scheme V.3.1. *Substrate scope for symmetrical azoarenes*[a,b]



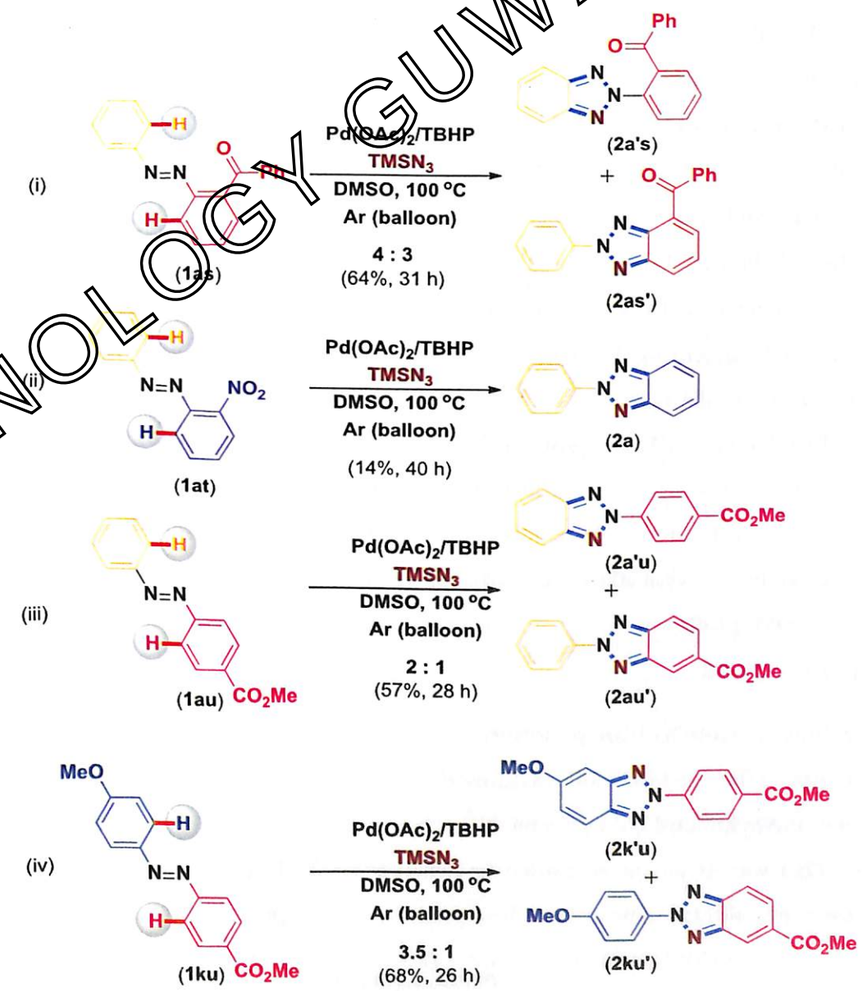
[a]Reaction condition: symmetrical azobenzene (0.5 mmol), $TMSN_3$ (2 equiv) and TBHP-decane (2 equiv) in DMSO (1.0 mL) at 100 °C for 19–50 h. [b]Isolated yields of pure product.

Azoarenes possessing other weakly activating substituents such as 4-ethyl (**1g**) and 2-ethyl (**1h**) reacted under identical conditions to give (**2g**) and (**2h**) respectively, in 79% and 64% yields. Similarly, the reaction of 4-*iso*propyl (**1i**) and 4-butyl (**1j**) substituted symmetrical azoarenes under standard conditions afforded 82% and 76% yields of their corresponding products (**2i** and **2j**) respectively. A moderate yield (72%) of (**2k**) was obtained when both the aryl rings are electron rich due to the presence of methoxy (–OMe) (**1k**) substituent as in Scheme V.3.1. However, the azoarenes possessing weakly deactivating substituents, irrespective of their positions in the aryl ring such as *p*-F (**1l**), *p*-Cl (**1m**), *m*-Cl (**1n**) and *o*-Cl (**1o**), provided their respective *2H*-benzotriazoles (**2l–2o**) in moderate to poor yields (in the range of 63–35%). Other weakly electron-withdrawing substituents such as *p*-bromo (**1p**) under the standard conditions gave only 41% yield of (**2p**), while *p*-iodo (**1q**) failed to react which is mainly because of the electronic effect of substituents and partly due to their insolubility in DMSO. Similarly, strongly electron-withdrawing substituents such as *p*-CF_3 (**1r**) furnished only low yield (8%) of (**2r**) even after 50 h which is mainly because of the electronic effect of $-CF_3$ substituent. As can be seen in Scheme V.3.1, barring one exception (**1k**) azoarenes bearing electron-donating substituents (**1b–1j**) provided better yields of their products (**2b–2j**) compared to those bearing electron-withdrawing substituents (**1l–1r**). The higher yields obtained for electron-donating azoarenes could be attributed to their better chelating ability with electrophilic Pd (II) catalyst. The electronic-effect is dominated by the steric factor when the substituents are present at their *ortho* positions (**1d**, **1f**, **1h** and **1o**) giving lower yields of products (**2d**, **2f**, **2h** and **2o**) compared to their *para* and *meta* analogues as shown in Scheme V.3.1. All the *meta* substituted azoarenes (**1c**), (**1e**) and (**1n**) gave single regioisomeric products (**2c**), (**2e**) and (**2n**) respectively. In these cases the less sterically hindered *o*-C–H (*i.e. para* to the *meta* substituents) is exclusively functionalized.

After the successful synthesis of a series of *2H*-benzotriazoles from symmetrical azoarenes (Scheme V.3.1), unsymmetrical azoarenes were taken into consideration.* A query arises whether this protocol will be applicable for the regioselective *o*-aminative-heterocyclization or would it provide a mixture of constitutional isomeric products? Keeping the substrate reactivity trends from Scheme V.3.1 in mind, some azoarenes were especially designed for this. These designed azoarenes possess either electron-neutral (–H) or electron-donating (–OMe)

substituents in one of the aromatic rings while the other ring contains electron-withdrawing substituents such as *o*-COPh, *o*-NO_2 and *p*-CO_2Me.

Scheme V.3.2. *Regioselectivity in unsymmetrical azoarenes*[a,b]

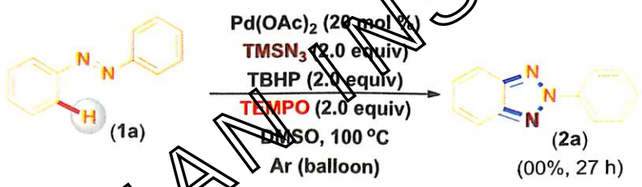


[a]Reaction condition: unsymmetrical azoarene (0.5 mmol), $TMSN_3$ (2 equiv) and TBHP-decane (2 equiv) in DMSO (1 mL) at 100 °C for 26–40h. [b]Isolated yields of product(s).

Substrate (**1as**) has an electron-withdrawing *o*-COPh group in one of the aromatic rings and an electron neutral (–H) substituent in the other ring, but when subjected to the present reaction conditions, an inseparable constitutional isomeric mixture of *2H*-benzotriazoles (**2a's**) and (**2as'**)

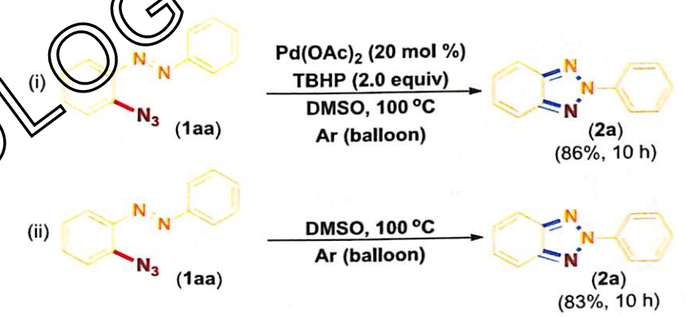
were obtained in the ratio of 4 : 3 (as judged from ^{1}H NMR) in 64% yield as illustrated in Scheme V.3.2(i). (*E*)-1-(2-Nitrophenyl)-2-phenyldiazene (**1at**), another unsymmetrical azoarene, under the present reaction conditions gave a product (**2a**) [Scheme V.3.2(ii)] having no intact nitro group. This unexpected formation of product (**2a**) from unsymmetrical azoarene (**1at**) can be explained by the intermolecular nucleophilic attack (SNAr) of the *in situ* generated *o*-azido group on to the carbon attached to the nitro group. The product (**2a**) was obtained in a mere yield of 14% and the rest was unreacted starting material. Nevertheless this reaction supports the intermediacy of *o*-azido species. The failure to obtain a nitrophenyl-substituted benzotriazole from (**1at**) is possibly due to the presence of a strong deactivating *ortho* $-NO_2$ substituent which reduces the chelating ability of the "azo moiety" toward electrophilic Pd (II). Another unsymmetrical substrate (**1au**) containing *p*-CO_2Me substituent in one aromatic ring and electron neutral (–H) in the other ring, furnished a mixture of inseparable constitutional isomeric products (**2a′u**) and (**2au′**) in the ratio of 2 : 1 in 57% yield as shown in Scheme V.3.2(iii). Similarly, substrate (**1ku**) having *p*-CO_2Me group in one ring and *p*-OMe group in the other ring underwent *o*-aminative-heterocyclization giving inseparable products (**2k′u** and **2ku′**) in the ratio of 3.5 : 1 [Scheme V.3.2(iv)]. From the above reactions [Scheme V.3.2(i), (iii) and (iv)] it is evident that the *o*-aminative-heterocyclization is preferred at the aromatic rings possessing electron-donating substituent (–OMe) followed by electron neutral (–H), and the electron-withdrawing substituents *p*-CO_2Me and *o*-COPh.

Some control reactions were performed to deduce the plausible reaction mechanism for this transformation. When this reaction was carried out in the presence of a radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidinooxy) keeping other reaction parameters constant, no product formation (**2a**) was observed as shown in Scheme V.3.3. Thus complete suppression of the product formation of (**2a**) indicates a radical pathway for this process.



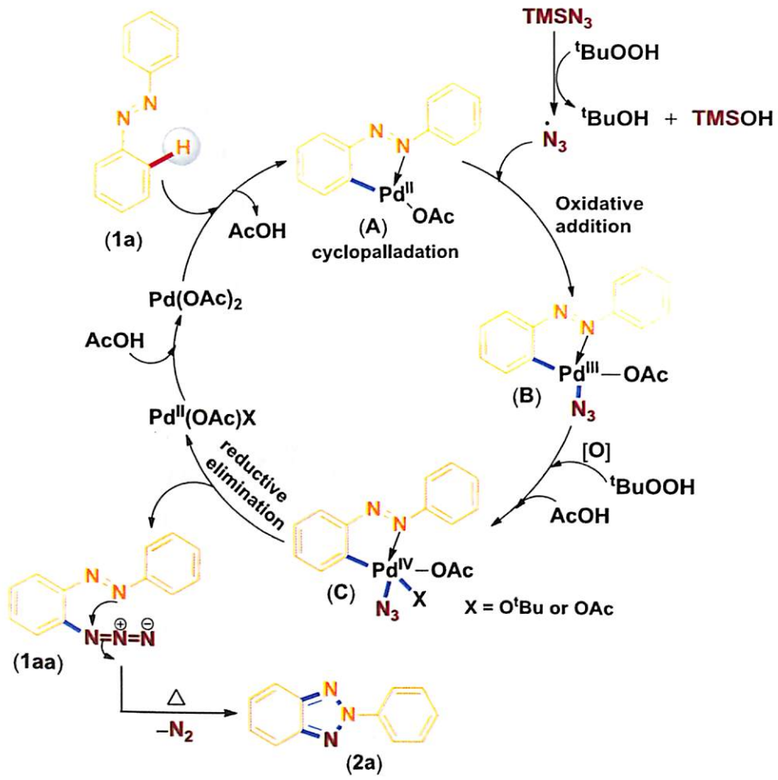
Scheme V.3.3. *Control reactions performed in presence of radical inhibitor TEMPO*

Furthermore, formation of product (**2a**) from unsymmetrical azoarenes bearing *o*-nitro group (**1at**) [Scheme V.3.2(ii)] can be explained if there is formation of an *o*-azido species which is possibly the intermediate in these reactions. When a pre-synthesized *ortho* azido azobenzene (**1aa**) was treated under the present reaction conditions, formation of corresponding product 2-phenyl-*2H*-benzotriazole (**2a**) was obtained in 86% yield as in Scheme V.3.4(i). This further supports the intermediacy of *ortho* azido species for these reactions. The thermal decomposition of (**1aa**) at 100 °C to (**2a**) in 83% yield suggests the non-involvement of Pd-catalyst and oxidant (TBHP) in the final step [Scheme V.3.4(ii)].



Scheme V.3.4. *Control reactions performed*

Based on these experimental results and taking cues from the recent literature precedent,[14-16,29-30] a plausible mechanism has been proposed as shown in Scheme V.3.5. Presumably, an initial cyclopalladation between "azo moiety" of azobenzene and Pd(II) catalyst leads to the formation of intermediate complex (**A**). The *in situ* generated azide radical,[31] obtained by the reaction of $TMSN_3$ and TBHP, then reacts with Pd-complex (**A**), which is oxidized to give a Pd(III)[29] intermediate (**B**) (Scheme V.3.5). A further oxidation of intermediate (**B**) by TBHP leads to the formation of a Pd(IV)[30] intermediate (**C**). Thus TBHP is playing the dual role of an oxidant as well as a radical generator. Apart from this, the ^{t}BuO moiety generated from TBHP may act as one of the ligand for Pd^{IV} as in intermediate (**C**). A reductive elimination of intermediate (**C**) leads to the formation of an *ortho* azido azobenzene (**1aa**) and regenerating palladium (II) catalyst for the next cycle. In the final stage, attack of one of the azo nitrogen onto the *o*-azide nitrogen of the *in situ* generated *ortho* azido substrate (**1aa**) leads to cyclization giving (**2a**), with the expulsion of a molecule of N_2.



Scheme V.3.5. *Plausible mechanism for ortho-aminative heterocyclyzation*

In summary, an efficient and regioselective protocol for the synthesis of 2-aryl-*2H*-benzotriazoles *via* Pd(II)-catalyzed *ortho* sp^2 C–H activation of symmetrical azoarenes using $TMSN_3$ as the nitrogen source and TBHP as the oxidant has been developed. The ligand directed intermolecular azidation (C–N bond formation) through *ortho* sp^2 C–H functionalization of azobenzenes followed by intramolecular cyclization (N–N bond formation) leads to the construction of 2-aryl-*2H*-benzotriazoles. For unsymmetrical azoarenes the heterocyclization is preferred at the aromatic ring rich in electron compared to electron neutral (–H) or electron-deficient aromatic rings. A wide range of substrates scope with tolerance of various functional groups makes this method a suitable alternative to the existing methods for the synthesis of 2-aryl-*2H*-benzotriazoles. Use of non-prefunctionalized strating materials, inexpensive metal catalyst, cheaper oxidant and compactability with a wide range of substrates is the main attribute

of this present strategy. Instead of its potentiality, the unturnable regioselectivity for unsymmetriacal azoarenes yielding constitutional isomeric mixtures still remains as challenging task for this task which needs to be addressed in near future.

V.4. Experimental Section

V.4. 1. General information:

All the compounds were commercial grade and were used without further purification. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for proton NMR (600 MHz) and for ^{13}C NMR (150 MHz). HRMS spectra were recorded using ESI mode (Q-TOF type Mass Analyzer). IR spectra were recorded in KBr or neat.

V.4. 2. General Procedure for the Synthesis of 2-Phenyl-2*H*-benzo[d][1,2,3]triazole (2a):

Azobenzene (**1a**, 91 mg, 0.5 mmol), $Pd(OAc)_2$ (22 mg, 20 mol %), $TMSN_3$ (115 mg, 1 mmol), TBHP in decane (5–6 M) (200 μL, 1 mmol) and DMSO (1 mL) were sequentially added to a 25 mL oven dried round-bottle flask containing a magnetic needle. Through a steady flow of argon gas the flask was sealed with a rubber septum. To maintain a positive pressure of argon, the flask was fitted with an argon balloon and the resultant reaction mixture was stirred in a preheated oil bath at 100 °C. The progress of the reaction was monitored by TLC. After the completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a small bed of Celite and washed with an additional amount of ethyl acetate (20 mL). This combined organic layer of ethyl acetate (30 mL) then washed with water (2 x 5 mL). The aqueous layer was separated using a separating funnel and the organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with (hexane/ethyl acetate = 95.5:0.5) to give 2-phenyl-*2H*-benzo[*d*][1,2,3]triazole (**2a**) in 78%.yield (76 mg) as yellowish solid.

***V.4. 3. A general note for compounds designation:**

A typical symmetrical azoarene (starting material) is designated as (**1a**) while its product is referred as (**2a**). The numerical number (**1**) stands for starting material while (**2**) is for product and (**a**) for a particular substituent. For unsymmetrical azoarenes, both a numbering and two letters have been used. For instance, in (**1as**) the number (**1**) is for the starting material while the double letter (**as**) indicates the presence of two different aryl rings. The alphabet (**a**) signifies simple phenyl ring while (**s**) signifies an aryl ring having *o*-COPh substituent. The numbering (**2a's**) suggests that the *ortho*-aminative heterocyclization is taking place at the phenyl ring, while (**2as'**) indicates the *ortho*-aminative heterocyclization is at the aryl ring having *o*-COPh substituent. Similar nomenclature is followed for other symmetrical and unsymmetrical azoarenes and their products.

V.5. References and Notes

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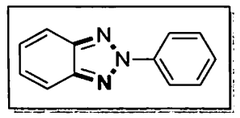
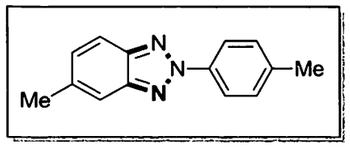
V.6. Spectral data

2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole (2a):



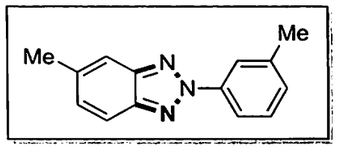
Yellowish solid; M.p. 98–100 °C (Reported[19] 101–103 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.42–7.44 (m, 2H), 7.45 (t, 1H, J = 7.8 Hz), 7.56 (t, 2H, J = 8.4 Hz), 7.93–7.95 (m, 2H), 8.36 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 118.5, 120.8, 127.3, 129.1, 129.6, 140.5, 145.2; IR (KBr): 3063, 2924, 2854, 1643, 1594, 1564, 1488, 1460, 1445, 1412, 1339, 1318, 1288, 1221, 1070, 1020, 963, 917, 809, 760 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{10}N_3^+$ (M + H$^+$) 196.0869; found 196.0871.

5-Methyl-2-(*p*-tolyl)-2*H*-benzo[*d*][1,2,3]triazole (2b):



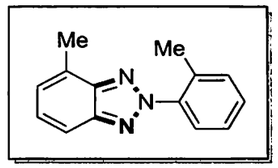
Yellowish solid; M.p. 113–115 °C (Reported[19] 121–124 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.43 (s, 3H), 2.51 (s, 3H), 7.23–7.26 (m, 1H), 7.33 (d, 2H, J = 8.4 Hz), 7.66 (s, 1H), 7.80 (d, 1H, J = 9 Hz), 8.20 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.3, 22.4, 116.7, 117.8, 120.5, 130.1, 137.3, 138.4, 139.0, 143.8, 145.6; IR (KBr): 3059, 2922, 2853, 1627, 1562, 1508, 1449, 1351, 1311, 1275, 1220, 1175, 1166, 1115, 1104, 1040, 973, 841, 764 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}N_3^+$ (M + H$^+$) 224.1182; found 224.1179.

5-Methyl-2-(*m*-tolyl)-2*H*-benzo[*d*][1,2,3]triazole (2c):



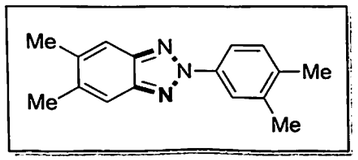
Yellowish solid; M.p. 77–79 °C (Reported[19] 77–80 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.48 (s, 3H), 2.51 (s, 3H), 7.24–7.26 (m, 2H), 7.42 (t, 1H, J = 8.0 Hz), 7.66 (s, 1H), 7.82 (d, 1H, J = 8.8 Hz), 8.12 (d, 1H, J = 8.4 Hz), 8.16 (s, 1H), ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 21.6, 22.4, 116.7, 117.8, 117.9, 121.2, 129.4, 129.7, 130.3, 137.5, 139.7, 140.6, 143.9, 145.7; IR (KBr): 3027, 2922, 2852, 1625, 1613, 1590, 1562, 1554, 1491, 1466, 1422, 1352, 1299, 1275, 1222, 1156, 1144, 1090, 1011, 972, 901, 879, 798, 780 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}N_3^+$ (M + H$^+$) 224.1182; found 224.1185.

4-Methyl-2-(*o*-tolyl)-2*H*-benzo[*d*][1,2,3]triazole (2d):



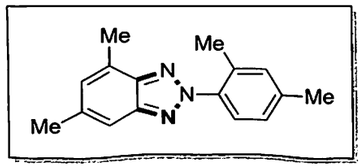
Red liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.41 (s, 3H), 2.73 (s, 3H), 7.19 (d, 1H, J = 6.8 Hz), 7.33–7.43 (m, 4H), 7.69 (d, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 17.4, 18.9, 115.8, 126.0, 126.3, 126.8, 127.3, 129.3, 129.7, 131.8, 133.7, 140.6, 144.9, 145.5; IR (KBr): 3058, 2924, 2852, 1608, 1583, 1512, 1497, 1463, 1433, 1382, 1337, 1289, 1281, 1264, 1156, 1131, 1095, 1038, 969, 874, 792, 753, 711 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}N_3^+$ (M + H$^+$) 224.1182; found 224.1187.

2-(3,4-Dimethylphenyl)-5,6-dimethyl-2*H*-benzo[*d*][1,2,3]triazole (2e):



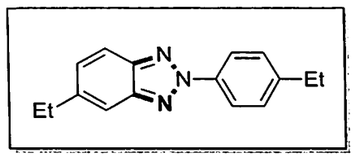
Yellow solid; M.p. 193–195 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.33 (s, 3H), 2.38 (s, 3H), 2.41 (s, 6H), 7.26–7.28 (m, 1H), 7.64 (s, 2H), 8.01 (d, 1H, J = 5.4 Hz), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 19.7, 20.1, 21.2, 116.8, 117.9, 121.5, 130.6, 137.5, 137.7, 138.1, 138.6, 144.5; IR (KBr): 3034, 2921, 2852, 1610, 1552, 1499, 1447, 1416, 1376, 1358, 1280, 1219, 1167, 1125, 1081, 1026, 1003, 971, 901, 880, 818, 720 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}N_3^+$ (M + H$^+$) 252.1495; found 252.1497.

2-(2,4-Dimethylphenyl)-4,6-dimethyl-2*H*-benzo[*d*][1,2,3]triazole (2f):



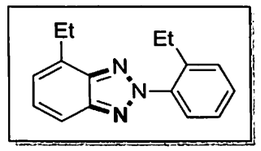
Red Solid; M.p. 49–51 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 2.35 (s, 3H), 2.41 (s, 3H), 2.48 (s, 3H), 2.68 (s, 3H), 7.02 (s, 1H), 7.15 (d, 1H, J = 7.8 Hz), 7.18 (s, 1H), 7.52 (s, 1H), 7.55 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 17.3, 18.8, 21.3, 22.3, 113.9, 126.0, 127.4, 128.5, 128.9, 132.3, 133.2, 137.2, 138.3, 139.8, 144.1, 145.3; IR (KBr): 2947, 2921, 2854, 1697, 1623, 1579, 1510, 1498, 1447, 1380, 1335, 1286, 1264, 1248, 1237, 1158, 1141, 1041, 972, 876, 838, 775 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}N_3^+$ (M + H$^+$) 252.1495; found 252.1492.

5-Ethyl-2-(4-ethylphenyl)-2*H*-benzo[*d*][1,2,3]triazole (2g):



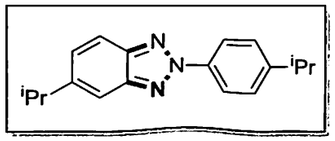
Red liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 1.30 (t, 3H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.8 Hz), 2.74 (q, 2H, J = 7.2 Hz), 2.81 (q, 2H, J = 7.8 Hz), 7.28 (dd, 1H, J_1 = 1.2 Hz, J_2 = 9.0 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.68 (s, 1H), 7.83 (d, 1H, J = 9.0 Hz), 8.23 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 15.5, 15.6, 28.7, 29.6, 115.3, 118.0, 120.6, 128.9, 129.3, 138.6, 143.7, 144.0, 145.4, 145.7; IR (KBr): 2964, 2925, 2853, 1629, 1561, 1512, 1455, 1376, 1310, 1284, 1266, 1241, 1218, 1175, 1113, 1052, 975, 965, 863, 838 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}N_3^+$ (M + H$^+$) 252.1495; found 252.1498.

4-Ethyl-2-(2-ethylphenyl)-2*H*-benzo[*d*][1,2,3]triazole (2h):



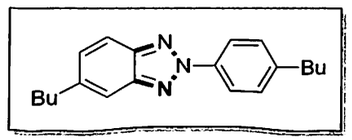
Pale Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.11 (t, 3H, J = 7.6 Hz), 1.42 (t, 3H, J = 7.6 Hz), 2.71 (q, 2H, J = 7.2 Hz), 3.12 (q, 2H, J = 7.6 Hz), 7.20 (d, 1H, J = 7.2 Hz), 7.36 (t, 2H, J = 8.0 Hz), 7.41–7.47 (m, 2H), 7.63 (d, 1H, J = 8.4 Hz), 7.77 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 14.3, 15.1, 25.2, 115.9, 124.1, 126.6, 126.8, 127.3, 130.0, 130.3, 135.4, 139.8, 140.2, 144.8, 145.1; IR (KBr): 3056, 2968, 2933, 2874, 1607, 1583, 1494, 1457, 1372, 1345, 1286, 1264, 1221, 1157, 1134, 1054, 971, 948, 872, 805, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}N_3^+$ (M + H$^+$) 252.1495; found 252.1491.

5-Isopropyl-2-(4- isopropylphenyl)-2*H*-benzo[*d*][1,2,3]triazole (2i):



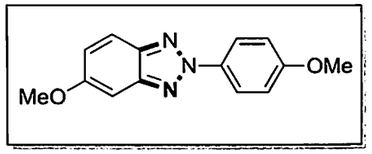
Light red Solid; M.p. 58–60 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 1.30 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.35 (s, 3H), 2.96–3.02 (m, 1H), 3.03–3.09 (m, 1H), 7.33 (d, 1H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.73 (s, 1H), 7.85 (d, 1H, J = 9.0 Hz), 8.25 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 23.9, 24.1, 34.0, 34.7, 113.8, 118.1, 120.6, 127.5, 128.1, 138.6, 144.1, 145.6, 148.3, 149.9; IR (KBr): 2956, 2925, 2866, 1562, 1513, 1463, 1453, 1430, 1383, 1362, 1354, 1307, 1276, 1253, 1216, 1146, 1106, 1052, 1032, 969, 947, 864, 840, 818, 731 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{22}N_3^+$ (M + H$^+$) 280.1808; found 280.1812.

5-Butyl-2-(4- butylphenyl)-2*H*-benzo[*d*][1,2,3]triazole (2j):



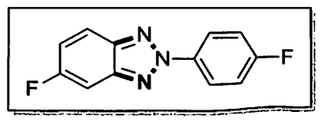
Reddish liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.93–0.97 (m, 6H), 1.32–1.44 (m, 4H), 1.61–1.72 (m, 4H), 2.69 (t, 2H, J = 8.0 Hz), 2.76 (t, 2H, J = 8.0 Hz), 7.25–7.27 (m, 1H), 7.34 (d, 2H, J = 8.4 Hz), 7.66 (s, 1H), 7.82 (d, 1H, J = 8.8 Hz), 8.21 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.14, 14.16, 22.49, 22.52, 33.4, 33.7, 35.5, 36.3, 116.1, 117.9, 120.5, 129.5, 129.6, 138.6, 142.3, 144.0, 144.1, 145.6; IR (KBr): 2955, 2932, 2857, 1629, 1608, 1561, 1512, 1465, 1427, 1378, 1352, 1277, 1257, 1234, 1141, 1114, 1081, 1017, 970, 953, 930, 836, 808 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{26}N_3^+$ (M + H$^+$) 308.2121; found 308.2125.

5-Methoxy-2-(4- methoxyphenyl)-2*H*-benzo[*d*][1,2,3]triazole (2k):



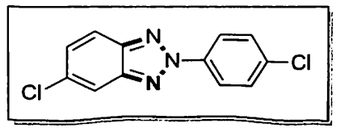
Yellowish solid; M.p. 140–142 °C (Reported[19] 147–150 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.89 (s, 3H), 3.91 (s, 3H), 7.04 (d, 2H, J = 9.6 Hz), 7.09 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.12–7.13 (m, 1H), 7.78 (d, 1H, J = 9.2 Hz), 8.21 (d, 2H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 55.7, 55.8, 94.9, 114.7, 119.1, 121.7, 122.1, 134.3, 141.2, 146.0, 159.3, 159.9; IR (KBr): 3002, 2972, 2924, 2840, 1630, 1610, 1566, 1453, 1439, 1405, 1359, 1289, 1256, 1225, 1207, 1190, 1169, 1133, 1108, 1087, 1025, 970, 852, 837, 827 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}N_3O_2^+$ (M + H$^+$) 256.1081; found 256.1080.

5-Fluoro-2-(4- fluorophenyl)-2*H*-benzo[*d*][1,2,3]triazole (2l):



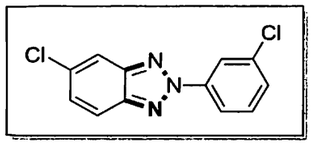
Brownish solid; M.p. 169–171 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.26–7.29 (m, 3H), 7.55 (d, 1H, J_1 = 2.4 Hz, J_2 = 9.0 Hz), 7.94–7.96 (m, 1H), 8.34–8.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 116.6 (d, J = 24 Hz), 119.1 (d, J = 28.5 Hz), 120.3 (d, J = 10.5 Hz), 122.6 (d, J = 9 Hz), 136.7, 142.5, 145.2 (d, J = 15 Hz), 161.1, 162.7, 163.1 (d, J = 249 Hz); ^{19}F NMR ($CDCl_3$, 564.7 MHz): δ −112.4, −111.9; IR (KBr): 2958, 2923, 2853, 1663, 1614, 1603, 1568, 1509, 1429, 1409, 1353, 1303, 1279, 1222, 1158, 1121, 1096, 1085, 972, 956, 832, 803 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8F_2N_3^+$ (M + H$^+$) 232.0681; found 232.0682.

5-Chloro-2-(4- chlorophenyl)-2*H*-benzo[*d*][1,2,3]triazole (2m):



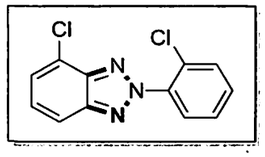
White solid; M.p. 177–179 °C (Reported[19] 185–187 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.38 (dd, 1H, J_1 = 1.8 Hz, J_2 = 9.0 Hz), 7.53 (d, 2H, J = 9.0 Hz), 7.86 (d, 1H, J = 9.0 Hz), 7.91 (s, 1H), 8.28 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 117.6, 119.8, 122.0, 129.3, 129.9, 133.5, 135.4, 138.8, 143.9, 145.6; IR (KBr): 3062, 2922, 2851, 1617, 1589, 1557, 1491, 1482, 1415, 1397, 1319, 1304, 1267, 1244, 1218, 1171, 1139, 1112, 1092, 965, 938, 861, 828, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8Cl_2N_3^+$ (M + H^+) 264.0090; found 264.0092.

5-Chloro-2-(3- chlorophenyl)-2*H*-benzo[*d*][1,2,3]triazole (2n):



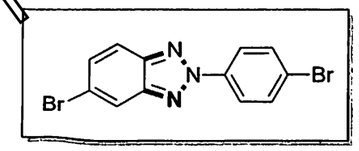
White solid; M.p. 157–159 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.38 (dd, 1H, J_1 = 1.2 Hz, J_2 = 9.0 Hz), 7.45 (d, 1H, J = 7.8 Hz), 7.49 (t, 1H, J = 7.8 Hz), 7.87 (d, 1H, J = 9.0 Hz), 7.92 (s, 1H), 8.24 (d, 1H, J = 7.8 Hz), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 117.6, 118.8, 119.9, 121.1, 129.4, 129.5, 130.8, 133.6, 135.6, 141.1, 143.8, 145.6; IR (KBr): 2955, 2923, 2852, 1594, 1586, 1556, 1483, 1453, 1437, 1280, 1266, 1243, 1218, 1109, 1071, 1049, 962, 938, 880, 862, 783, 762 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8Cl_2N_3^+$ (M + H^+) 264.0090; found 264.0092.

4-Chloro-2-(2- chlorophenyl)-2*H*-benzo[*d*][1,2,3]triazole (2o):



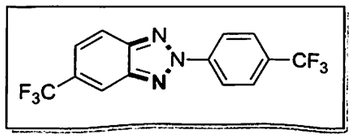
Colourless gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.41 (t, 1H, J = 7.8 Hz), 7.47–7.54 (m, 3H), 7.64 (d, 1H, J = 8.4 Hz), 7.75 (d, 1H, J = 6.6 Hz), 7.91 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 117.5, 118.8, 123.7, 126.9, 127.7, 127.8, 128.6, 131.2, 131.4, 138.7, 143.6, 145.8; IR (KBr): 2958, 2924, 2852, 1735, 1582, 1555, 1485, 1448, 1346, 1293, 1261, 1203, 1144, 1113, 1050, 1032, 979, 962, 870, 793, 704 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8Cl_2N_3^+$ (M + H^+) 264.0090; found 264.0095.

5-Bromo-2-(4- bromophenyl)-2*H*-benzo[*d*][1,2,3]triazole (2p):



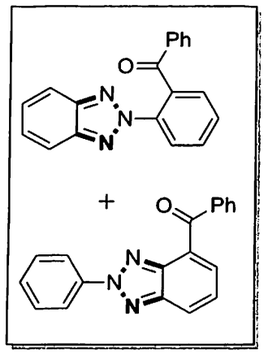
Brown solid; M.p. 160–162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.50 (dd, 1H, J_1 = 1.2 Hz, J_2 = 9.0 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 9.0 Hz), 8.10 (s, 1H), 8.22 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 119.9, 120.9, 121.4, 122.2, 123.4, 131.6, 132.8, 139.2, 143.9, 146.1; IR (KBr): 2953, 2852, 1614, 1554, 1487, 1477, 1411, 1348, 1318, 1302, 1264, 1240, 1215, 1141, 1095, 1070, 1032, 1008, 964, 927, 824, 800 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8Br_2N_3^+$ (M + H^+) 351.9079; found 351.9083.

5-(Trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*d*][1,2,3]triazole (2r):



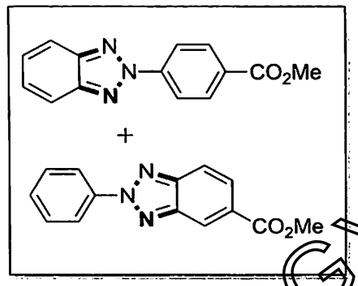
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.63 (d, 1H, J = 8.4 Hz), 7.86 (d, 2H, J = 9.0 Hz), 8.07 (d, 1H, J = 9.0 Hz), 8.30 (s, 1H), 8.53 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 117.6 (t, J = 4.5 Hz), 120.2, 121.3, 123.3, 124.0, 125.9, 127.1 (t, J = 4.5 Hz), 130.1 (q, J = 33 Hz), 131.8 (q, J = 33 Hz), 142.5, 144.3, 146.2; ^{19}F NMR ($CDCl_3$, 564.7 MHz): δ −63.5, −63.3; IR (KBr): 2956, 2924, 2853, 1639, 1614, 1569, 1510, 1471, 1429, 1360, 1321, 1265, 1244, 1168, 1134, 1107, 1065, 1045, 967, 945, 886, 847 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_8N_3F_6^+$ (M + H$^+$) 332.0617; found 332.0620.

Phenyl (2-Phenyl-2*H*-benzo[*d*][1,2,3]triazol-4-yl)methanone + (2-(2*H*-Benzo[*d*][1,2,3]triazol-2-yl)phenyl)(phenyl)methanone (2a′s + 2as′):



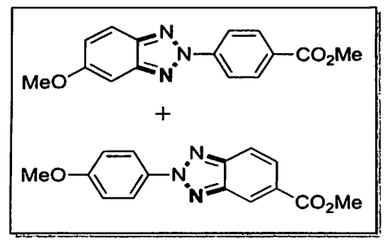
Yellowish solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.18 (t, 2H, J = 7.8 Hz), 7.26–7.27 (m, 3H), 7.37 (t, 1H, J = 3.6 Hz), 7.43–7.52 (m, 5H), 7.61–7.67 (m, 6H), 7.69–7.72 (m, 2H), 7.75 (d, 1H, J = 7.2 Hz), 7.92 (d, 2H, J = 7.8 Hz), 8.16 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 7.8 Hz), 8.32 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 118.4, 121.0, 122.7, 123.0, 123.6, 126.4, 127.3, 128.2, 128.4, 128.7, 128.9, 129.47, 129.55, 130.0, 130.2, 130.5, 131.3, 132.8, 133.1, 134.2, 137.2, 137.9, 138.5, 140.2, 143.2, 145.2, 145.8, 194.3, 195.2; IR (KBr): 3038, 2923, 2852, 1668, 1654, 1596, 1578, 1566, 1489, 1462, 1448, 1446, 1438, 1347, 1331, 1321, 1308, 1288, 1233, 1218, 1181, 1156, 1061, 998, 962, 937, 849, 773 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}N_3O^+$ (M + H$^+$) 300.1131; found 300.1130.

Methyl 2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole-5-carboxylate + Methyl 4-(2*H*-Benzo[*d*][1,2,3]triazol-2-yl)benzoate (2a′u + 2au′):



Light red solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.95 (s, 3H), 3.99 (s, 3H), 7.44 (dd, 2H, J_1 = 3.0 Hz, J_2 = 6.6 Hz), 7.48–7.50 (m, 1H), 7.57 (t, 2H, J = 7.8 Hz), 7.93 (dd, 2H, J_1 = 3.0 Hz, J_2 = 6.6 Hz), 7.96 (d, 1H, J = 9.0 Hz), 8.06 (d, 1H, J = 9.0 Hz), 8.23 (d, 2H, J = 8.4 Hz), 8.37 (d, 2H, J = 7.8 Hz), 8.44 (d, 2H, J = 8.4 Hz), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 52.6, 52.7, 118.5, 118.7, 120.5, 121.0, 122.3, 122.8, 123.3, 127.3, 127.9, 129.2, 129.7, 129.8, 130.5, 130.8, 131.2, 140.3, 143.5, 144.6, 145.5, 146.9, 166.4, 166.9; IR (KBr): 2949, 2916, 2842, 1718, 1605, 1560, 1504, 1441, 1422, 1345, 1381, 1279, 1219, 1194, 1150, 1136, 1011, 962, 855, 831, 807, 767, 747 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{12}N_3O_2^+$ (M + H$^+$) 254.0924; found 254.0923.

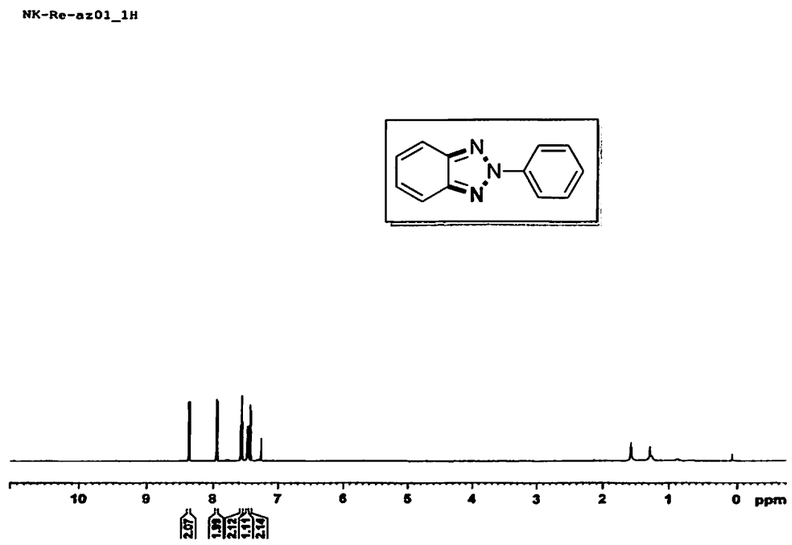
Methyl 2-(4-Methoxyphenyl)-2*H*-benzo[*d*][1,2,3]triazole-5-carboxylate + Methyl 4-(5-Methoxy-2*H*-benzo[*d*][1,2,3]triazol-2-yl)benzoate (2k′u + 2ku′):



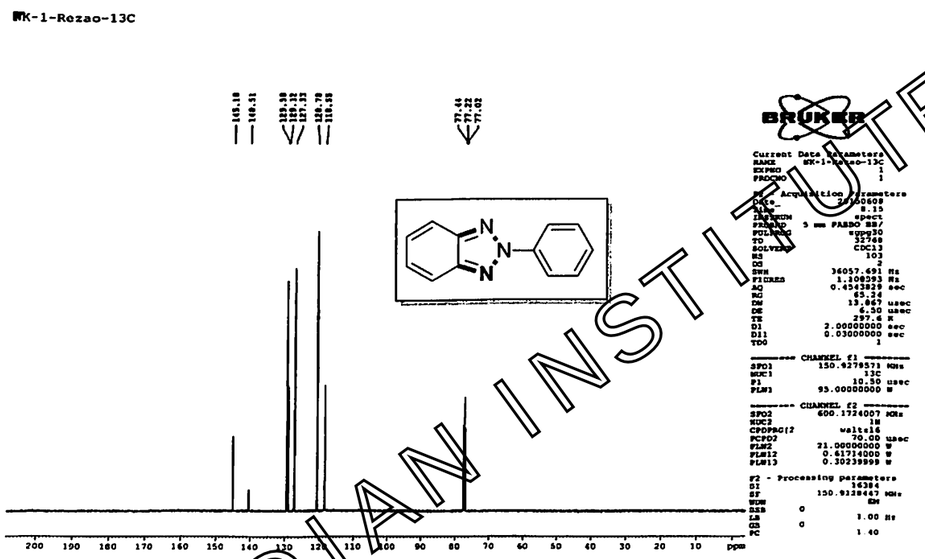
Yellowish solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 3.89 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 7.06 (d, 2H, J = 9.0 Hz), 7.09–7.12 (m, 2H), 7.78 (d, 1H, J = 9.6 Hz), 8.01–8.04 (m, 2H), 8.20 (d, 2H, J = 9.0 Hz), 8.29 (d, 2H, J = 9.0 Hz), 8.37 (d, 2H, J = 9.0 Hz), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 52.5, 55.8, 94.7, 114.5, 114.7, 118.2, 119.4, 119.9, 122.0, 122.4, 122.5, 123.6, 125.4, 127.0, 129.9, 130.8, 131.2, 141.9, 143.5, 146.6, 159.9, 160.8, 166.4, 166.9; IR (KBr): 2954, 2924, 2852, 1715, 1630, 1606, 1563, 1509, 1455, 1439, 1299, 1282, 1251, 1228, 1184, 1171, 1143, 1129, 1108, 1082, 1022, 967, 950, 855, 828, 802, 766 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}N_3O_3^+$ (M + H$^+$) 284.1030; found 284.1030.

V.7. Selected Spectra

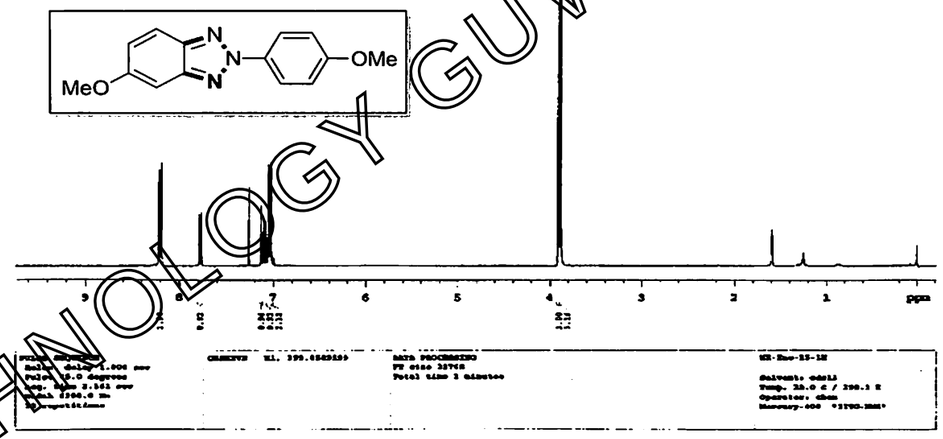
2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole (1a): ^{1}H NMR ($CDCl_3$, 600 MHz)



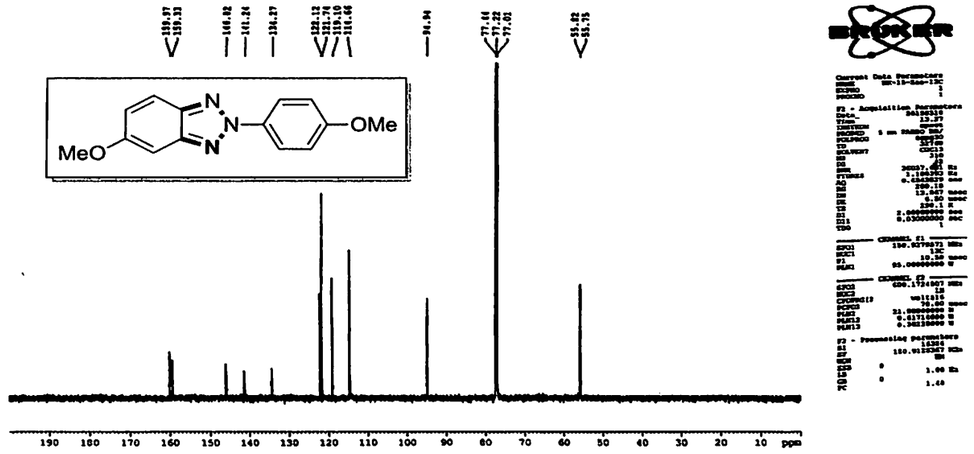
2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole (1a): ^{13}C NMR ($CDCl_3$, 150 MHz)



5-Methoxy-2-(4- methoxyphenyl)-2*H*-benzo[*d*][1,2,3]triazole (1k): ^{1}H NMR ($CDCl_3$, 400 MHz)



5-Methoxy-2-(4- methoxyphenyl)-2*H*-benzo[*d*][1,2,3]triazole (1k): ^{13}C NMR ($CDCl_3$, 150 MHz)



Publications

(1) Palladium-Catalyzed Synthesis of *2H*-Benzotriazoles from Azoarenes and $TMSN_3$
Khatun, N.; Modi, A.; Ali, W.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 9662.

(2) Benzylic ethers as arylcarboxy surrogates in substrate directed *ortho* C–H functionalisation catalysed by copper
Khatun, N.; Banerjee, A.; Santra, S. K.; Ali, W.; Patel, B. K. *RSC Adv.* **2015**, *5*, 36461.

(3) Pd(II)-catalysed *o*-aroylation of directing arenes using terminal aryl alkenes and alkynes
Khatun, N.; Banerjee, A.; Santra, S. K.; Behera, A.; Patel, B. K. *RSC Adv.* **2014**, *4*, 54533.

(4) Nano CuO Catalyzed Cross Dehydrogenative Coupling (CDC) of Aldehydes to Anhydrides
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(5) A one-pot strategy for the synthesis of 2-aminobenzothiazole in water by copper catalysis
Khatun, N.; Jamir, L.; Ganesh, M.; Patel, B. K. *RSC Adv.* **2012**, *2*, 11557.

(6) Divergent reactivities of *o*-halo anilides with CuO nanoparticle in water: A green synthesis of benzoxazoles and *o*-hydroxy anilide
Khatun, N.; Guin, S.; Rout, S. K.; Patel, B. K. *RSC Adv.* **2014**, *4*, 10770.

(7) CuO nanoparticle catalysed synthesis of *2H*-indazoles under ligand free conditions
Khatun, N.; Gogoi, A. Basu, P.; Das, P.; Patel, B. K. *RSC Adv.* **2014**, *4*, 4080.

(8) Tandem regioselective synthesis of tetrazoles and related heterocycles using iodine
Yella, R.; **Khatun**, N.; Rout, S. K.; Patel, B. K. *Org. Biomol.Chem.* **2011**, *9*, 3235.

(9) A one pot synthesis of [1,3,4]-oxadiazoles mediated by molecular iodine
Guin, S.; Rout, S. K.; Ghosh, T.; **Khatun, N.**; Patel, B. K. *RSC Adv.* **2012**, *2*, 3180.

(10) Tandem synthesis of [1,2,4]-triazoles mediated by iodine-a regioselective approach
Guin, S.; Rout, S. K.; **Khatun, N.**; Ghosh, T.; Patel, B. K. *Tetrahedron* **2012**, *68*, 5066.

(11) The oxidative cleavage of an anti-Hugerschoff product: a mild environmentally benign one pot synthesis of ureas from isothiocyanates
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(12) Cu(II) catalysed chemoselective oxidative transformation of thiourea to thioamidoguanidine/2- aminobenzothiazole
Sahoo, S. K.; **Khatun**, **N.**; Gogoi, A.; Deb, A.; Patel, B. K. *RSC Adv.* **2013**, *3*, 438.

(13) Stable Cu(I) Complexes with Thioamidoguanidine Possessing Halide-Bridge Structure.
Sahoo, S. K.; **Khatun**, **N.**; Jena, H. S.; Patel, B. K. *Inorg. Chem.* **2012**, *51*, 10800.

(14) Directing group sssisted copper-catalyzed chemoselective O-Aroylation of phenols and enols using alkylbenzenes
Rout, S. K.; Guin, S.; Banerjee, A.; **Khatun**, **N.**; Gogoi, A.; Patel, B. K. *Org. Lett.* **2013**, *15*, 4106.

(15) Ceric Ammonium Nitrate (CAN): An Efficient Oxidant for Pd(II)-Catalyzed Substrate Directed o-Benzoxylation and o-Aroylation
Santra, S. K.; Banerjee, A.; **Khatun**, **N.**; Patel, B. K. *Eur. J. Org. Chem.* **2015**, 350.

(16) Palladium catalyzed *ortho*-halogenation of 2-arylbenzothiazole and 2,3-diarylquinoxaline
Santra, S. K.; Banerjee, A.; **Khatun**, **N.**; Samanta, A.; Patel, B. K. *RSC Adv.* **2015**, *5*, 11960.

(17) Benzyl bromides as aroyl surrogates in substrate directed Pd catalysed *o*-aroylation
Behera, A.; Ali, W.; Guin, S.; **Khatun, N.**; Mohanta, P. R.; Patel, B. K. *RSC Adv.* **2015**, *5*, 33334.

(18) Copper(I)-promoted cycloalkylation–peroxidation of unactivated alkenes *via* sp^3 C–H functionalisation
Banerjee, A.; Santra, S. K.; Mishra, A.; **Khatun**, **N.**; Patel, B. K. *Org. Biomol.Chem.* **2015**, *13*, 1307.

(19) Generation of bis-Acyl Ketals from Esters and Benzyl Amines Under Oxidative Conditions
Ganesh, M.; Rajamanickam, S.; **Khatun, N.**; Santra, S. K.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 3440.

(20) Oxidant controlled regioselective mono- and di-functionalizations of coumarins
Banerjee, A.; Santra, S. K.; **Khatun, N.**; Ali, W.; Patel, B. K. *Chem. Commun.* **2015**, *51*, 15422.

(21) CuO Nanoparticle Catalyzed Synthesis of 2,3-Disubstituted Quinazolinones via Sequential *N*-Arylation and Oxidative C–H Amidation
Modi, A.; Ali, W.; Mohanta, P. R.; **Khatun, N.**; Patel, B. K. *ACS Sustainable Chem. Eng.* **2015**, *3*, 2528.

(22) Copper Catalysed Cascade Synthesis of Imidazolidine-benzothiazole and Imidazolidine-tetrazole Hybrid Heterocycles from *bis*-Thioureas *via* Desulfurisation Strategy.
Majji, G.; Sahoo, S. K.; **Khatun, N.**; Patel, B. K. *Eur. J. Org. Chem.* **2015**, *Eur. J. Org. Chem.* **2015**, 7534.

(23) PdII/$CuBr_2$ catalysed keto α-Csp^3-H benzoxylation of *N,N*-dialkylamides directed by *o*-hydroxy group
Santra, S. K.; Banerjee, A.; Rajamanickam, S.; **Khatun, N.**; Patel, B. K. *Chem. Commun.* **2016**, DOI: 10.1039/C6CC00971A.