Beyond Traditional Coupling: Transition Metal Catalyzed C–C and C–O Bond Formations via C–H Activation

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August, 2014

IN MEMORY OF MY

GRANDFATHER

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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 Srimanta Guin has been working under my supervision since July, 2009 as a regular registered Ph. D. student. His thesis entitled **"Beyond Traditional Coupling: Transition Metal Catalyzed C–C and C–O Bond Formations via C–H Activation"** is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis to submit for the Ph. D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

August, 2014.

Prof. Bhisma K. Patel
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Srimanta Guin

SYNOPSIS

The contents of this thesis have been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview on different aspects of C–H functionalization processes: advantages, challenges and solutions of them. All the other chapters emphasize on C–C and C–O bond forming reactions via palladium or copper catalyzed C–H functionalizations using strategies like cross dehydrogenative coupling and functional group directed C–H bond functionalization. Chapter II describes a protocol for copper catalyzed syntheses of 2,5-disubstitued-1,3,4-oxadiazoles from *N*-aryl-*N*-arylidinehydrazines via an intramolecular C–O bond formation at the imine C–H bond. Chapter III illustrates the use of styrenes as the new arylcarboxy surrogates toward *o*-benzoxylation of 2-phenylpyridine derivatives catalyzed by copper. Chapter IV demonstrates a palladium catalyzed aroylation protocol at the *ortho* C–H bond of substrates possessing various directing groups with methylarenes as the synthetic equivalent of aroyl group. Chapter V deals with a protocol for allyl esters synthesis via copper catalyzed solvent-solvent (methylarenes-cycloalkane) couplings. Except chapter I, all other chapters comprise of seven subsections which include introduction, literature reports, present work, experimental section, references, spectral data and some selected spectra.

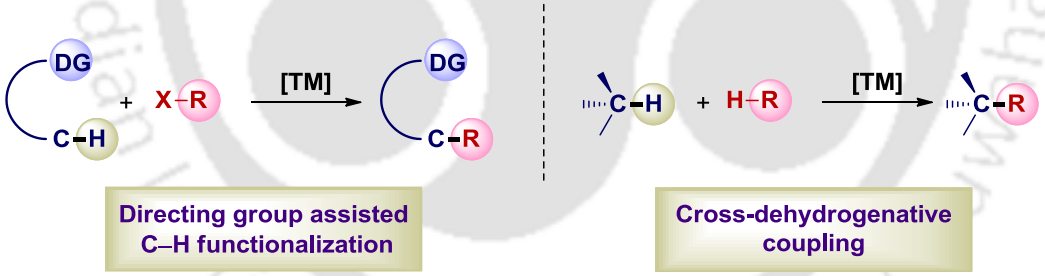
CHAPTER I. An Overview of Transition Metal Catalyzed C–H Functionalizations

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

Coupling chemistry is an important synthetic strategy, widely used in both industry and academia for the formation of carbon-carbon and carbon-heteroatom bonds. The traditional coupling procedures involve either the use of stoichiometric organometallic reagents, such as Grignard and organolithium reagents, or the transition metal catalyzed coupling of

functionalized hydrocarbons. There has been substantial progress in these methods over the last few decades, and they are successfully applied in the synthesis of commercially important products. However, the use of prefunctionalized starting materials in these methods, thus adding steps towards the formation of desired chemical bond, is a major concern for the synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize unfunctionalized starting materials by the direct activation of C–H bonds.

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



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

With the motive of broadening this revolutionary aspect of organic synthesis, in modern times more systematic and concerted efforts have been made in C–H bond activation and its application in coupling chemistry. As a result exceptionally useful methods for organic synthesis have been developed, and one such way is the transition metal catalyzed C–H bond functionalization to achieve C–C and C–X bonds. Most of these methodologies stand on the two pillars of the C–H bond activation: (a) cross dehydrogenative coupling and (b) substrate directed C–H bond functionalization (Scheme

I.1). In this context our group has been involved in the development of new disconnection approach and generation of various functionalities cleaving the inert C–H bonds.

CHAPTER II. Copper(II) Catalyzed Imine C–H Functionalization Leading to Synthesis of 2,5-Substituted-1,3,4-Oxadiazoles

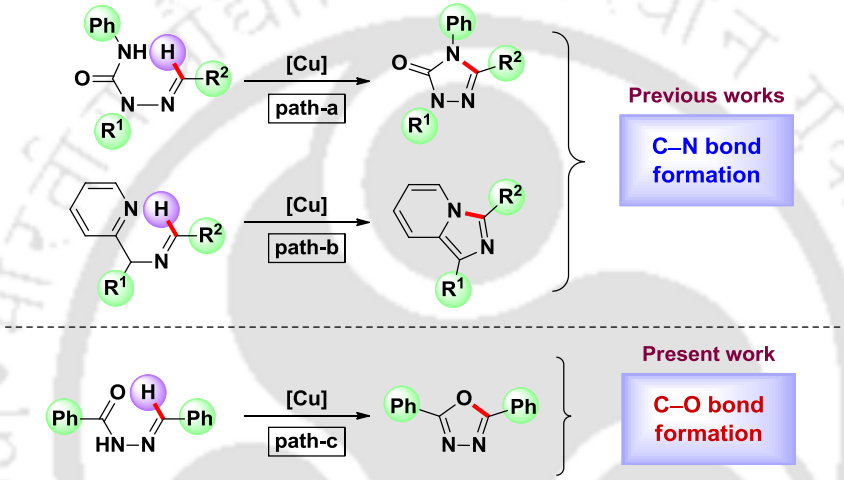
This chapter focuses on the copper catalyzed synthesis of 2,5-disubstitued-1,3,4-oxadiazoles from *N*-aryl-*N*-arylidinehydrazines via an intramolecular C–O bond formation at the imine C–H bond.

The π-conjugated heterocycles comprise an important structures class as they find applications in the field of material science and pharmaceutical chemistry. Amongst them, the 2,5-disubstituted-1,3,4-oxadiazole motifs are of considerable importance primarily due to their unique optoelectronic properties that are being exploited in the development of organic light emitting diodes (OLEDS) and utilized in energy efficient, full-color, flat-panel displays. Certain suitably conjugated oxadiazoles are also known to perform as multi-photon absorbing systems. Beside their electronic properties, these scaffolds encompass a wide range of biological properties that make them particularly attractive in the field of organic synthesis.

A myriad of applications of the 1,3,4-oxadiazole motif have resulted to they being encountered through the development of various protocols. Several methodologies are documented in the literature for their synthesis, which can be generalized into four main strategies as follows: (i) oxidative cyclization of *N*-acylhydrazones; (ii) cyclo-dehydration of 1,2-diacylhydrazines; and (iii) C–H activation strategies. In most of the methodologies, the former two strategies are employed, while there is only a single precedence for the latter strategy. However, the disadvantages associated with the aforementioned methodologies, owing to the use of expensive, hazardous materials or cumbersome multi-stepped processes bind them to limited synthetic scope.

Thus in an attempt to obliterate the limitations of the earlier methods, we developed a straight forward and versatile protocol for the copper(II) catalyzed oxidative C–H bond functionalization / C–O bond formation of imines from *N*-arylidenearoylhydrazide derivatives to afford various 2,5-disubstituted-1,3,4-oxadiazoles (Scheme II.1).

Noteworthy to mention, that functionalizations of unreactive C–H bonds are more advantageous in terms of atom and step economy. Although they have been focused towards the transition metal catalyzed functionalization of the sp^2 C–H bonds of arenes and heteroarenes; in contrast the functionalization of imine C(sp^2)–H bond are relatively rare. Pertinent to imine C(sp^2)–H functionalizations only C–C and C–N bond formations (path-a and b, Scheme II.1) were known but there was no report on similar C–O bond formation until this report (path-c, Scheme II.1).

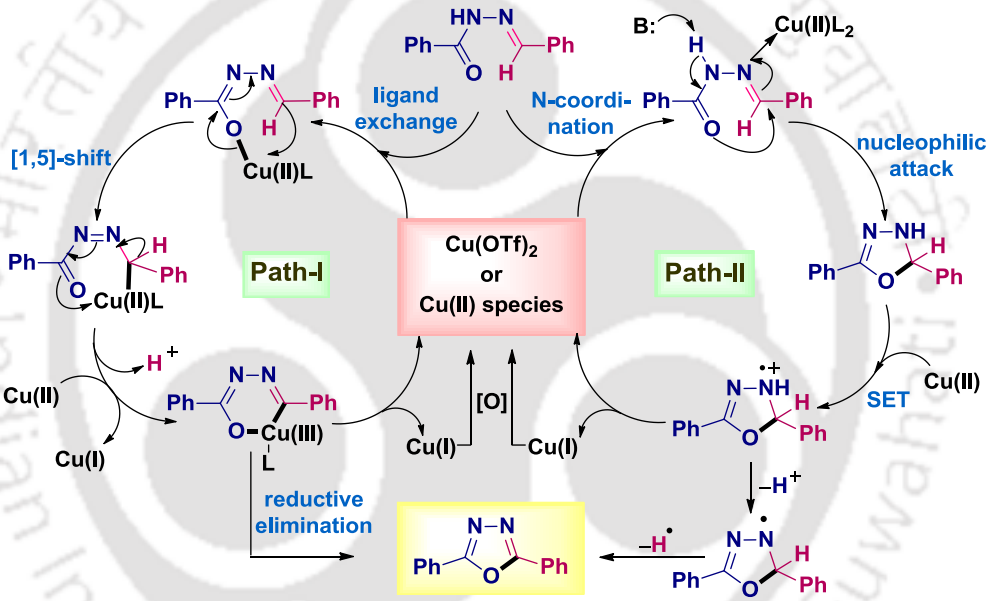


Scheme II.1. *Copper catalyzed imine C–H bond functionalizations*

To attain a suitable reaction condition for the synthesis of 2,5-substituted-1,3,4-oxadiazoles various reaction parameters such as catalysts, base, solvents were screened to achieve the maximum possible yield. After a series of experimentation the optimized reaction condition arrived was $Cu(OTf)_2$ (10 mol %), Cs_2CO_3 (1 equiv) at 110 ^oC in DMF under an air atmosphere (O_2 as the terminal oxidant). *N*-benzoylhydrazones derived from benzohydrazide and various aryl aldehydes were subjected to the optimized reaction conditions. This methodology was found to be compatible with a variety of electron donating and electron-withdrawing groups in aryl aldehydes giving good to excellent yields of their corresponding 2,5-substituted-1,3,4-oxadiazoles. However, compared to substrates bearing electron donating groups, electron withdrawing substituents gave better yields in shorter reaction times. *N*-benzoylhydrazones substrates originating from heterocyclic aldehydes provided moderate yields of their respective 1,3,4-oxadiazoles.

Besides benzohydrazide, other substituted hydrazides could also be employed in this methodology.

Based on the results / observations of mechanistic investigations and literature reports two alternative mechanisms were proposed for this transformation (Scheme II.2). The first mechanism is based on an electrophilic metalation at the imine C–H followed by an intramolecular C–O bond formation (Path I, Scheme II.2). The alternative mechanism features the Lewis acidic property of Cu(II) which leads to an intramolecular nucleophilic attack by amidic oxygen onto the imine carbon resulting in an oxidative heterocyclization (Path II, Scheme II.2).



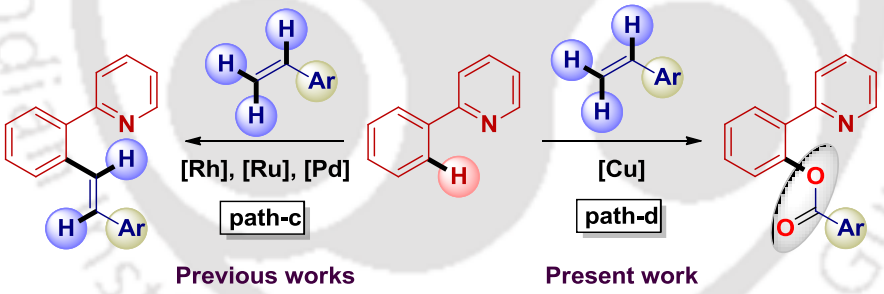
Scheme II.2. *Plausible mechanism for the formation 2,5-substituted-1,3,4-oxadiazoles*

In conclusion, we have for the first time developed a catalytic method for the synthesis of 2,5-disubstituted [1,3,4]-oxadiazoles via imine C–H functionalization of *N*-benzylidenebenzohydrazide. Low catalyst loading under ligand free condition, inexpensive metal catalyst, performance under ordinary atmospheric conditions and compatibility of a wide range of substrates makes this method a suitable alternative to the existing protocols.

CHAPTER III. Terminal Aryl Alkenes as Arylcarboxy Surrogates Toward *o*-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper

This chapter describes a unique copper catalyzed protocol for the *ortho*-benzoxylation of 2-arylpyridines using terminal alkene as a new surrogate of carboxylic acid.

The combination of transition metal catalysts and chelation-assisted groups has brought about renaissance in organic chemistry providing unprecedented results through selective functionalizations of un-reactive *ortho* C–H bonds particularly for the construction of C–C and C–heteroatom bonds. Pertinent to these seminal achievements, protocols for the direct conversion of C–H bonds to C–C bonds stands out to be the key pillar in providing a great impetus to modern synthetic chemistry as C–C bond formation is regarded as the "holey grail" of organic chemistry. Oxidative C–H bond functionalizations have been successfully applied to construct C–C bonds involving either sp, sp^2 or sp^3 hybridized carbons as mutual cross-coupling partners.



Scheme III.1. *Use of terminal alkenes in C–H activation processes*

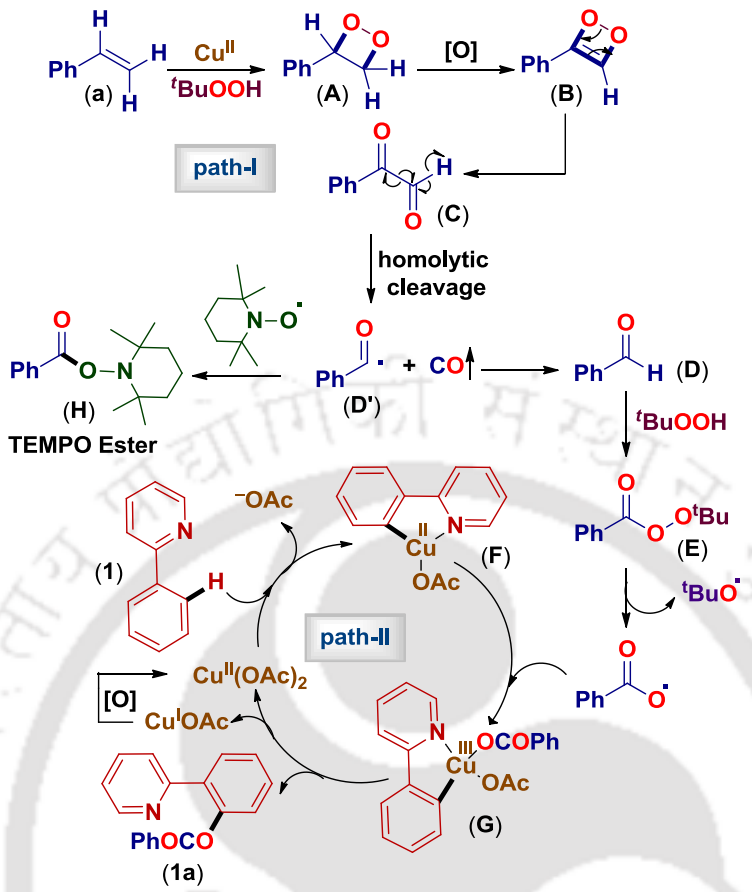
The C–C bond formations have mostly been directed towards the vinylation of substrates possessing directing groups using expensive metal catalysts such as Rh, Ru and Pd (path-c, Scheme III.1). Thus, it would be desirable and appreciable if the same can be achieved using less expensive and more environmentally benign metals such as Cu, albeit its use is so far unfamiliar in this forum. With this motive, when a vinylation of 2-phenylpyridine was attempted with styrene in presence of a copper catalyst and an oxidant. However, the trial unexpectedly led to *ortho*-benzoxylation exclusively (path-d, Scheme

III.1). Substrate directed *ortho*-benzoxylation has been achieved previously using carboxylic acid or its surrogates such as benzoate iodonium salts, anhydrides, acid chlorides, acylperoxides, aldehydes and methylarenes. Thus our current observation on *ortho*-benzoxylation using styrene as ArCOO– surrogate via four sp^2 C–H cleavages and loss of one carbon atom is unprecedented in the literature.

Various reaction parameters such as catalysts, oxidants, solvents and temperature were screened to obtain the optimal conditions for this reaction and it was found that the use of $Cu(OAc)_2$ (20 mol%), TBHP (5 equiv) in chlorobenzene at 120 ^oC was found to be the suitable conditions for our subsequent exploration to extend the scope of this transformation. The optimized conditions were then executed for *o*-benzoxylation of 2-phenylpyridine and 2-(*p*-tolyl)pyridine using various substituted styrenes. All the substituted styrenes served as excellent benzoxy surrogates toward *o*-benzoxylation of arenes. In particular those bearing electron donating groups gave higher yields of their respective esters, while the yields were moderate with styrenes possessing electron withdrawing groups.

This elegant and unprecedented transformation is a mechanistic enigma to us and hence systematic investigations were carried out. On the basis of the results obtained from these control experiments as well as the literature reports, a plausible mechanism has been proposed that comprises of two paths (Scheme III.2). As depicted in the mechanism, alkene gets converted to glyoxal through the intermediacy of four-membered oxetane and dioxete. The glyoxal is then homolytically cleaved to give the corresponding aldehyde along with the loss of carbon monoxide. This in situ generated aldehyde serves as the feedstock of the benzoxy group in this transformation.

In conclusion, this methodology illustrates the use of styrenes as the new surrogates for the arylcarboxy group (ArCOO–), which has been employed intriguingly for the *o*-benzoxylation of 2-phenylpyridine derivatives. The reaction proceeds through sequential C–O bond formations at the expense of four sp^2 C–H and one carbon atom. Based on the reaction intermediates detected a plausible mechanism has been proposed which accounts for most of the experimental observations. Thus the present methodology provides a new avenue for the synthesis of benzoate esters.



Scheme III.2. *Proposed mechanism for ortho-benzoxylation*

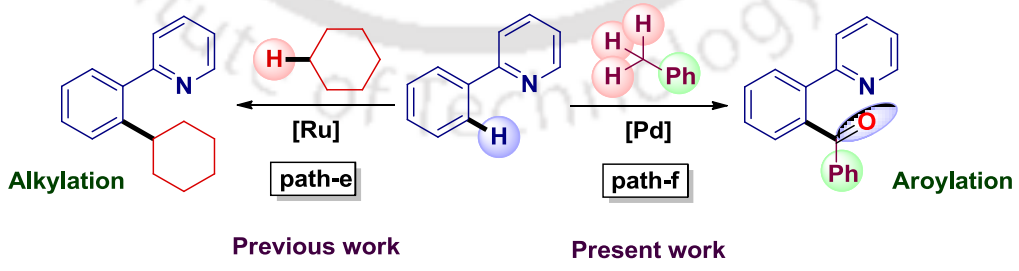
CHAPTER IV. Four Tandem C–H Activations: A Sequential C–C and C–O Bond Making via Pd-Catalyzed Cross Dehydrogenative Coupling (CDC) Approach

This chapter demonstrates an unprecedented aroylation at the *ortho* C–H bond with respect to a directing group via a palladium(II) catalyzed CDC approach using alkylbenzene as the synthetic equivalent of an aroyl moiety.

The modern era of organic chemistry has brought about many appealing results pertaining to transition metal catalyzed C–H bond activations with subsequent functionalizations. Foundations to most C–H activation processes generally rely on the strategies of directing group assisted C–H bond functionalization and cross dehydrogenative coupling (CDC). These two techniques are highly appreciable due to

being atom and step economic. Despite the significant progress made in this area the more challenging arene–alkane couplings remain scarce which is due to the inertness of sp^3 C–H bonds; thus much of it is yet to be explored.

Pertaining to the substrate directed arene–alkane coupling there is only a single precedence where 2-aryllpyridine or analogous substrates have undergone direct C–H alkylation using un-reactive cycloalkanes as the other coupling partner (path-e, Scheme IV.1). However a direct coupling approach to achieve *ortho*-benzylation of substrates possessing *N* or *O* donor atoms cleaving the sp^3 benzylic C–H bond is yet to be accomplished. With the motive of exploring this unexplored, we attempted benzylation of 2-phenylpyridine with toluene. However instead of *ortho*-benzylation of 2-phenylpyridine it led to an unexpected *ortho*-benzoylation of 2-phenylpyridine (i.e. ketone formation) (path-f, Scheme IV.1). Similar directing group assisted aroylation of arenes via C–H bond cleavage have been achieved using various surrogates of acyl group. Depending on the strategies adopted, these methods can be classified into four heads as follows, (i) *ortho*-selective Friedel-Crafts acylation; (ii) carbonylative processes; (iii) cross dehydrogenative couplings and (iv) decarboxylative couplings of α-oxoacids. However, the present protocol on *o*-acylation of arenes with alkylbenzenes demonstrates an unprecedented arene–alkane coupling (C–C bond formation) with a subsequent C–O bond formation proceeding via four tandem C–H bond activations (three sp^3 benzylic C–H's and one sp^2 arene C–H) to selectively install an aroyl moiety at the proximal site of directing group containing substrates.

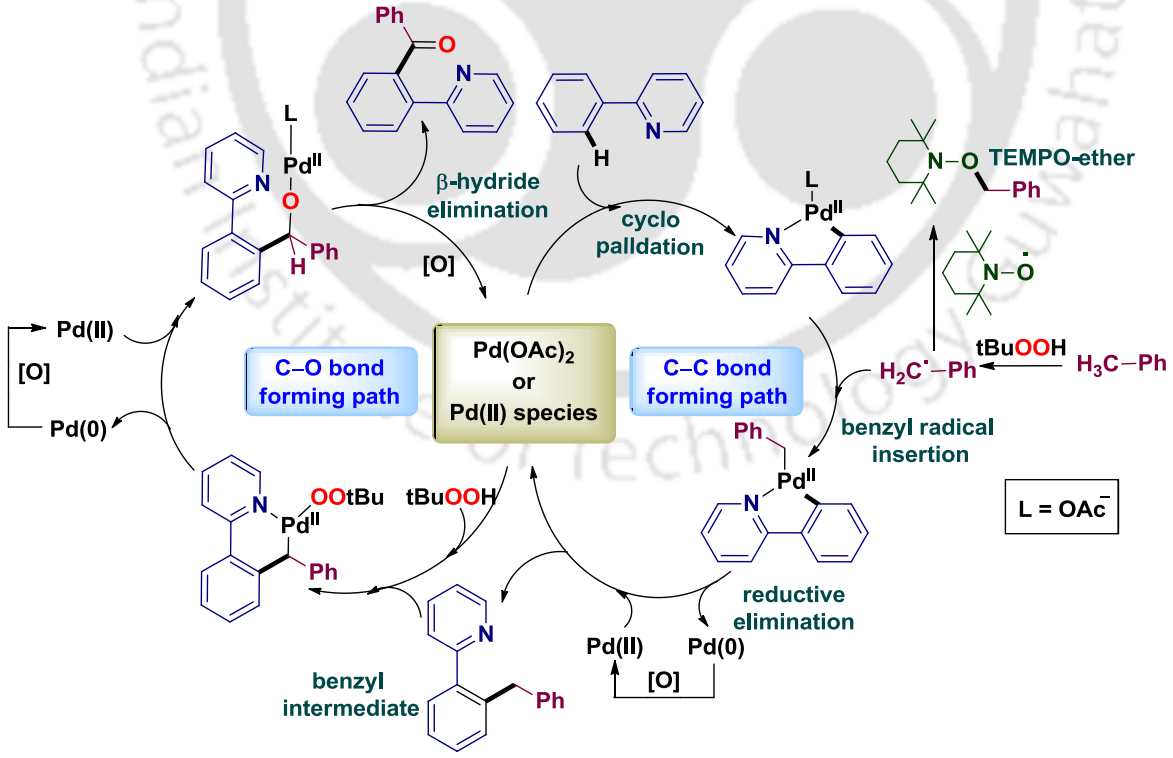


Scheme IV.1. *CDC approaches on arene-alkane couplings*

Reaction parameters such as catalysts, oxidants and temperature were varied to obtain the optimal conditions for this reaction and it was found that the use of $Pd(OAc)_2$ (10

mol%), TBHP (5-6 M in decane) (2 equiv) at 120 ^{o}C afforded the maximum possible yield of the desired ketone. The optimized conditions were then implemented in the coupling reactions between 2-phenylpyridine and a set of methylarenes. All these coupling reactions proceeded smoothly providing their respective *o*-aroylated products in good to excellent yields. Methylarenes possessing electron donating substituents provided higher yields of aroylated products in shorter reaction time than those bearing electron withdrawing substituents. An interesting feature of the reactions with polymethylated benzenes was the exclusive formation of monoaroylated products, with the other methyl group(s) remaining intact. Furthermore, the same optimized reaction conditions were equally applicable to the 2-aryloxypyridine and aryl ketoxime ethers. The couplings of these substrates with same set of methylarenes provided their corresponding *o*-aroylated products and the yield follow a similar trend as was observed with 2-phenylpyridine.

Several experimental studies were performed to elucidate the mechanism of this transformation. Based on the observations of these experiments and related literature reports, a plausible mechanism has been proposed which comprise of two paths operating in tandem (Scheme IV.2).



Scheme IV.2. *Proposed mechanism for o-aroylation*

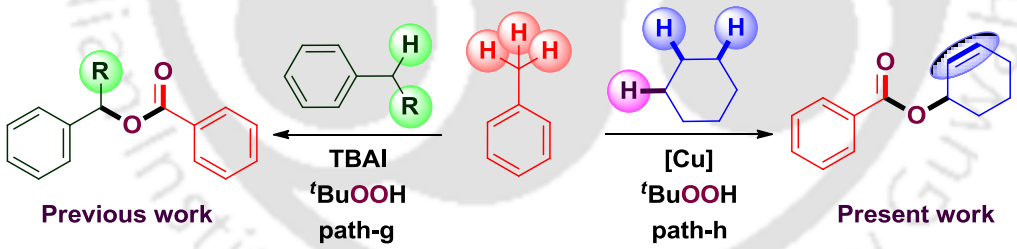
In conclusion, an aroylation protocol at the *ortho* C–H bond has been accomplished via sequential C–C / C–O bond formations involving four C–H bond activations. This is the first illustration of an arene–alkane coupling giving an *o*-aroylated product involving activations of a nonreactive benzylic sp^3 C–H of methylarenes and sp^2 C–H bonds of arenes facilitated by the directing groups. With polymethylated arenes, selective monoaroylated products were formed without affecting the other methyl groups. Hence by judging the practicality of the present protocol, it can be an additional alternative to the existing acylation reactions.

CHAPTER V. Copper Catalyzed Esterification of Alkylbenzenes with Cycloalkanes via C(sp^3)–H Activation Following Cross Dehydrogenative Coupling (CDC)

This chapter deals with a copper catalyzed CDC strategy for the synthesis of allyl esters by coupling of simple solvents (methylarenes with cycloalkanes) at the expense of six consecutive sp^3 C–H bonds.

The direct C–H activation path has streamlined the synthesis of functionalized molecules by minimizing the number of synthetic steps and making the processes more atom economic. One such strategy, the cross dehydrogenative coupling (CDC) has played a vital role by providing synthetic values to such methodologies. The CDC protocols have been employed to access a diverse array of C–C and C–heteroatom bonds, by functionalizing C–H bonds of all types (sp, sp^2, sp^3). The extreme reluctance of sp^3 C–H bonds to enter into the periphery of chemical reactions make their selective functionalization a formidable challenge. The solutions to these problems have resulted in some appealing results on sp^3 C–H functionalizations. Among these results ester C–O bond formation at the sp^3 C–H have attracted significant interest in recent times. Pertinent to oxidative esterification functionalizing sp^3 C–H bond, a protocol has been developed for the synthesis of benzylic esters involving only alkylbenzene(s) as a self or cross coupling partners under a metal free conditions (path-g, Scheme V.1). In this protocol, one half of alkylbenzene serves as the nucleophile ($ArCOO^-$) while the remaining half behaves as

electrophile ($ArCH_2^+$) leading to the formation of benzylic ester. A remarkable outcome that has emerged out of this ester synthesis is the involvement of solvents (methylarenes) as substrates for sp^3 C–H functionalizations via CDC. The curiosity that arose was whether cycloalkane behave similarly as a cross coupling partner with alkylbenzenes to give cycloalkyl benzoate under favorable conditions. In pursuit of this, cyclohexane was attempted as a potential coupling partner with toluene. Although not under metal free conditions, but the use of copper catalyst and a radical initiator unexpectedly led to the formation of an allyl ester via a dehydrogenative-olefination followed by oxidative esterification at the allylic C–H (path-h, Scheme V.1). This process formally involves six sp^3 C–H bond cleavages; (three each from either of the coupling partners) which is high for any single process. Prior to this present report, allylic esters have been synthesized via transition metal catalyzed allylic C–H bond oxidation. Among the various processes developed, the copper catalyzed allylic oxidation of olefins with peresters, known as Kharasch–Sosnovsky reaction is of particular interest. Nevertheless, the present methodology on the copper catalyzed solvent-solvent (methylarene-cycloalkane) couplings to give cycloallyl benzoates via six sp^3 C–H activations is novel and unique.

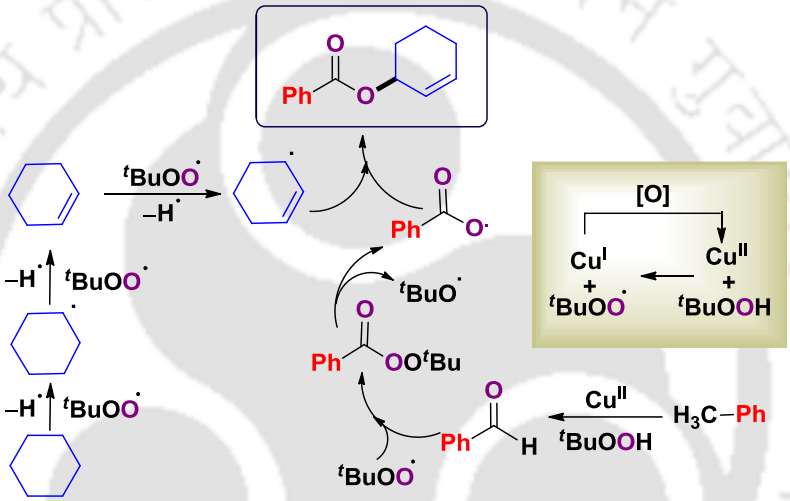


Scheme V.1. *Ester synthesis via solvent-solvent couplings*

Rigorous optimizations were carried out to establish the suitable conditions for this transformation. The use of $Cu(OAc)_2$ (20 mol%), TBHP (5–6 M in decane) (8 equiv) at 120 ^oC gave a modest yield, which was the maximum that could be attained. The yield could not be improved further because of intrinsic low reactivity of the sp^3 C–H bonds in cyclohexane. Having established the optimal reaction conditions, the present oxidative esterification of cycloalkanes were then implemented on cross couplings between cycloalkanes and a series of substituted methylarenes. The developed methodology was

applicable to a diverse methylarenes irrespective of the nature of their substituents present; however the yields were modest in all the cases. The most appealing outcome in all the reactions of the polymethylated benzenes were the selective formation of the corresponding monoester functionalizing one of the –Me group with the other –Me group(s) remaining intact.

Based on the extensive experimental data, a plausible mechanism similar to Kharasch-Sosnovsky reaction has been proposed, which includes dehydrogenation-olefination of cycloalkanes followed by an oxidative esterification at the allylic position (Scheme V.2).



Scheme V.2. *Proposed mechanism for oxidative esterification*

In conclusion, this work describes the first example of the Cu-catalyzed dehydrogenation-olefination of cycloalkanes and subsequent esterification of the allylic C(sp^3)–H bond with methylbenzenes in the presence of TBHP as the oxidant. This reaction involves six consecutive sp^3 C–H bond cleavages. An appreciable range of methylarenes can be used in this reaction with cycloalkanes allowing a direct preparation of the corresponding cycloallyl esters.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
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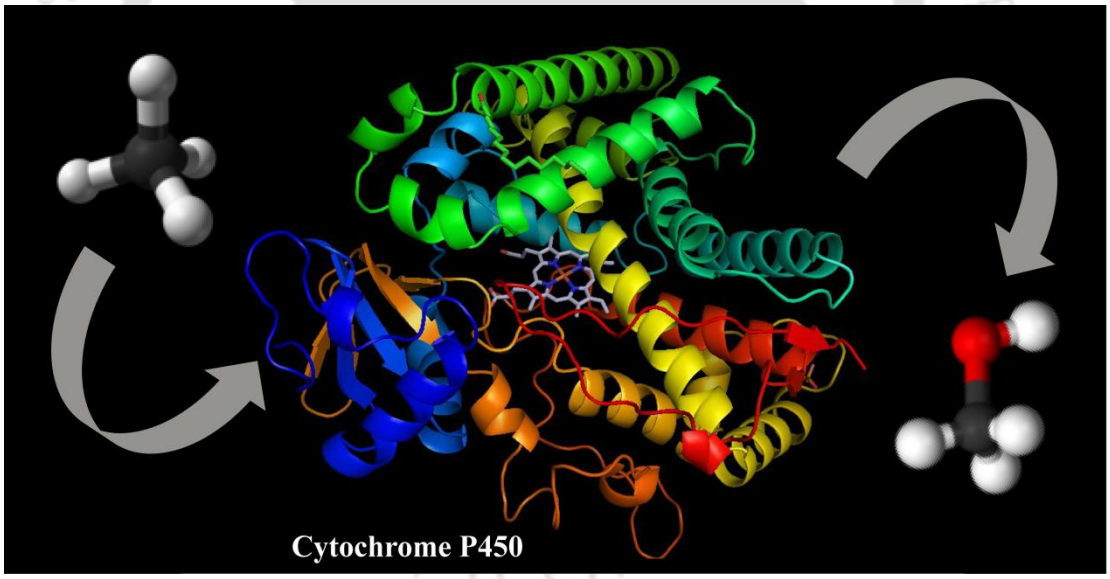
Chapter I

An Overview of Transition Metal Catalyzed C–H Functionalizations



CHAPTER I

I. An Overview of Transition Metal Catalyzed C–H Functionalizations

I.1. Introduction

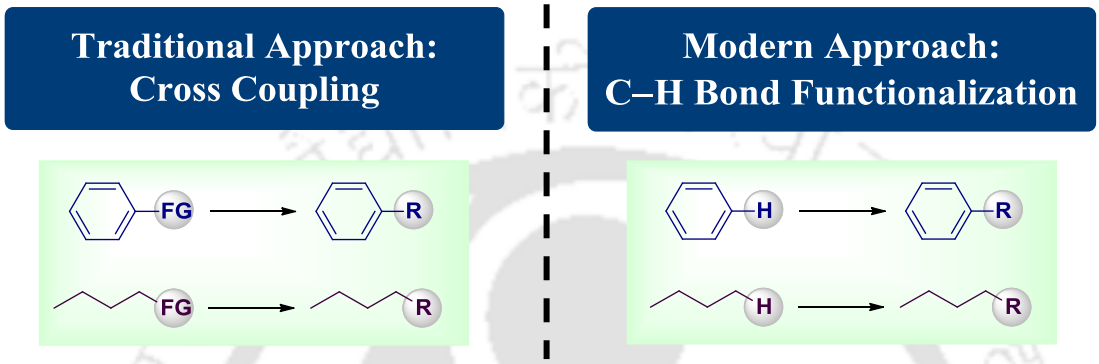
Coupling chemistry is an important synthetic strategy; widely used in both industry and academia for the formation of carbon–carbon and carbon–heteroatom bonds.[1] The traditional coupling procedures involve either the use of stoichiometric organometallic reagents, or the transition metal catalyzed coupling of functionalized hydrocarbons. There has been substantial progress in these methods over the decades, and are successfully applied in the synthesis of commercially important products.[2] However, the use of pre-functionalized starting materials in these methods, thus adding steps towards the formation of desired chemical bond, is a major concern for the synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize un-functionalized starting materials by the direct activation of carbon-hydrogen bonds.[3]

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

I.2. Comparison between traditional and modern coupling

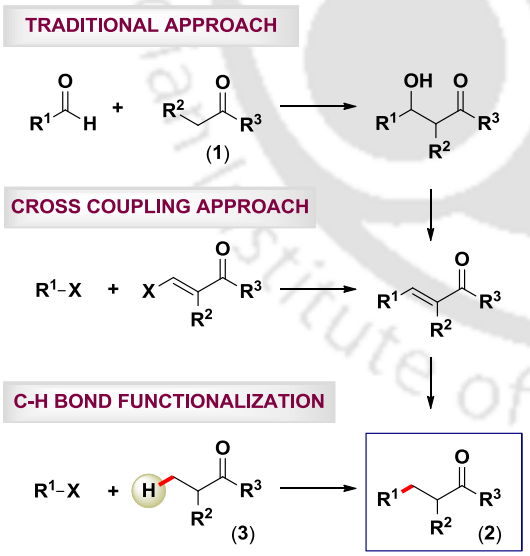
Organic synthesis relies on the transformation of functional groups, or structural features exhibiting relatively high chemical reactivity. Thus, installment of a new bond

requires the presence of either a heteroatom, such as oxygen or a halogen, or unsaturation (i.e., absence of hydrogens) in the carbon backbone (Scheme I.2.1). This logic underpins the process of synthetic planning or synthetic strategy. The reactive sites or functional groups are typically incorporated by means of multiple transformations; consequently, the starting materials are often rather dissimilar from the final products.



Scheme I.2.1. *Traditional approach vs. modern approach*

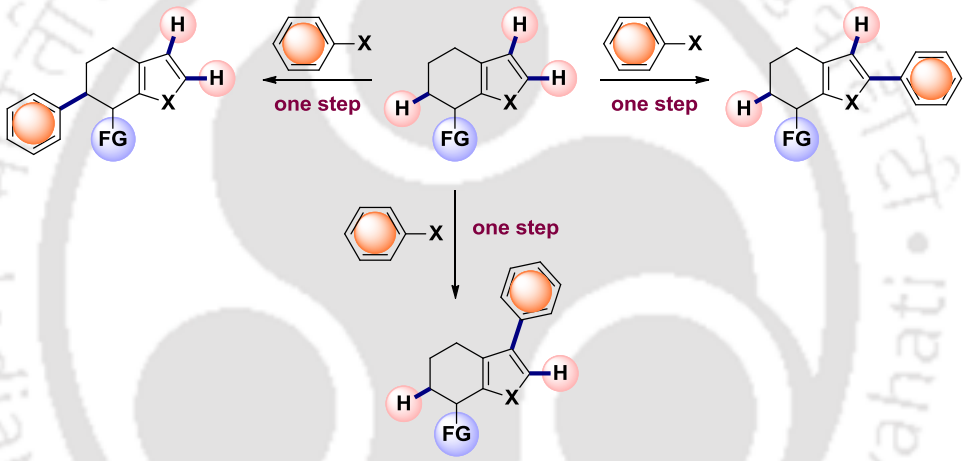
This is illustrated by the sequence of several steps that converts compound (**1**) to product (**2**) (Scheme I.2.2). In this light, it becomes clear that the introduction of new functionality directly through transformation of C–H bonds unlocks opportunities for markedly different synthetic strategies. For example, the same target molecule (**2**) may be accessed in a single step by displacement of a hydrogen atom (Scheme I.2.2). Considering the high abundance of C–H bonds, precise one-step substitution of carbon-hydrogen bonds with C–C or C–X bonds (where X is a heteroatom), without disruption of the surrounding molecular structure, carries considerable appeal for synthesis. Thus, selective C–H bond functionalization, as exemplified by the direct conversion of compound (**3**) to product (**2**) (Scheme I.2.2), provides straightforward and concise approach where the topology, or the



Scheme 1.2.2. *Evolving algorithms in organic synthesis.*

overall skeletal structure, of the starting material resembles that of the product ("topologically obvious assembly").

In addition to the assembly of specific target molecules, C–H bond functionalization also reshapes synthetic strategies for the preparation of series of compounds ["structural core diversification" (Scheme I.2.3)]. The ability to selectively target a number of different C–H bonds in a complex substrate permits direct access to multiple analogues from a common structural predecessor. This sharply contrasts with traditional approaches, wherein multistep, and often distinct, de novo sequences are required for each derivative. Thus, by viewing C–H bonds as "ubiquitous functionality", a new chapter is being opened in organic synthesis with many exciting opportunities.



Scheme I.2.3. *Structural core diversification by means of C–H bond functionalization.*

Taking into consideration all the aforementioned features of C–H functionalization processes, it can be said that they are advantageous over the traditional coupling procedures because of the following reasons:

- C–H bonds are ubiquitous / could provide new disconnections
- Step and atom economical
- Cost effective

I.3. Challenges to C–H functionalizations

Although C–H functionalizations are advantageous, however to execute them is challenging due to following reasons:

- **Intrinsic low reactivity:** Most of the C–H bonds are either sp^2 or sp^3 hybridized; whose pK_a values are greater than 30–35. These bonds are also associated with high bond dissociation energy (BDE). Hence they are notoriously inert to both homolytic and heterolytic cleavage. The bond strength and pK_a values of various C-H bonds are shown in Table I.3.1.

Bond	BDE (Kcal/mol)	pK_a (water)
CH_3–H	103	48
CH_2=CH–H	112	50
C_6H_5–H	110	43
CH_2=$CHCH_2$–H	88	43
$C_6H_5CH_2$–H	85	41

Table I.3.1. *Bond dissociation energy and pKa's of various C-H bonds*

- **Regioselctivity:** C–H bonds are ubiquitous in organic molecules; therefore to fine tune a process to selectively target a desired C–H bond leaving all others intact is difficult. For example, the pharmaceutical Fluoxetine, sold as "Prozac," shown in Figure I.3.1, possesses multiple, unique C–H bonds. Site-selective functionalization of any one of these various sites could be desirable for structure-activity relationship studies in the pursuit of new drug derivatives or to study pharmacokinetics.

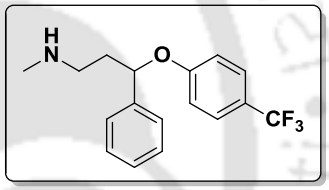
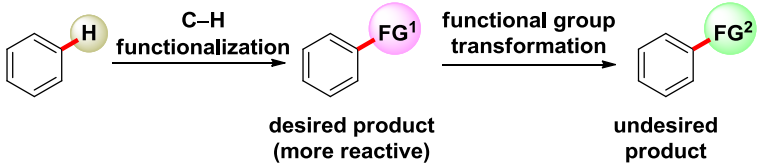


Figure I.3.1. *The pharmaceutical Prozac contains multiple, unique C–H bonds.*

- **Chemoselectivity:** In a C–H functionalization process the product formed may be more reactive than the starting precursor. In such a case, the product is susceptible to undergo further functional group transformation or functionalization under the same reaction conditions to give undesirable products; hence deviating from the actual goal (Scheme I.3.1).



Scheme I.3.1. *Chemoselectivity issue in a C–H functionalization process*

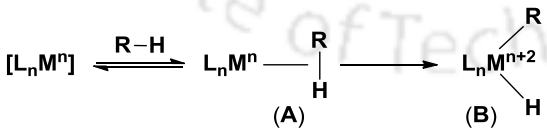
Apart from these three vital challenges, a C–H functionalization process is also associated with certain minor issues such as preservation of the existing functional group(s) in the starting precursor and controlling of competing side reactions such as homo- and hetero-coupling. Hence the two major issues that crop out of these points and that need to be resolved are *reactivity* and *selectivity*.

I.4. Classification of reactions

An attractive strategy for overcoming these challenges is the use of a transition metal catalyst. A catalyst is defined as a reagent which lowers the activation barrier of a given reaction without being consumed during that transformation. In the case of C–H functionalization, a transition metal catalyst can be used to "activate" the C–H bond by lowering the activation energy for bond scission. There are five distinct mechanisms for these reactions by which stable organometallic species are formed; three of these are quite common, while the other two are rare.[4]

(a) Oxidative addition

In this mechanism, a transition metal catalyst can coordinate to a C–H σ-bond, donating electron density into the σ* orbital (Scheme I.4.1, complex **A**). This in turn weakens the C–H bond and can lead to the formation of a new metal-carbon bond (Scheme I.4.1, complex **B**). The cleavage of the C–H bond by direct participation of a transition metal ion proceeds with an increase in the oxidation state of the transition metal.



Scheme I.4.1. *C–H activation via oxidative addition*

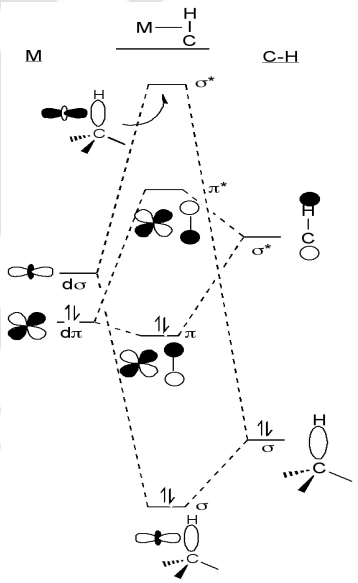


Figure I.4.1. *A qualitative MO diagram for oxidative addition*

A qualitative molecular orbital diagram showing only the C–H–M π interaction (M = metal) is shown in Figure I.4.1. The resulting organometallic intermediate can then be further manipulated to release different carbon–X

bonds, where X is halogen, oxygen, nitrogen, carbon, etc. Oxidative addition reactions are typical for electron-rich, low-valent complexes of the 'late' transition metals found towards the right side of the periodic table such as Re, Fe, Ru, Os, Rh, Ir, Pt.

(b) Sigma-bond metathesis

This activation mechanism consists of the formation of an organometallic derivative, i.e., a compound containing an M–C σ-bond (M = metal) as an intermediate. The reaction occurs via a concerted σ-bond cleavage and formation involving a four-membered transition state (Scheme I.4.2). These reactions are mediated typically by early and late transition metal complexes that do not have an accessible (n+2) oxidation state i.e. for which the oxidative addition is forbidden. Many transition metals with d^0 electronic configurations meet these criteria. These metals are most commonly from group 3 of the periodic table (Sc, lanthanides and actinides), but some examples involving metals of groups 4 and 5 are also known. A qualitative molecular orbital diagram for this type of reaction indicates that there is no π interaction because there are no d-electrons (Figure I.4.2).

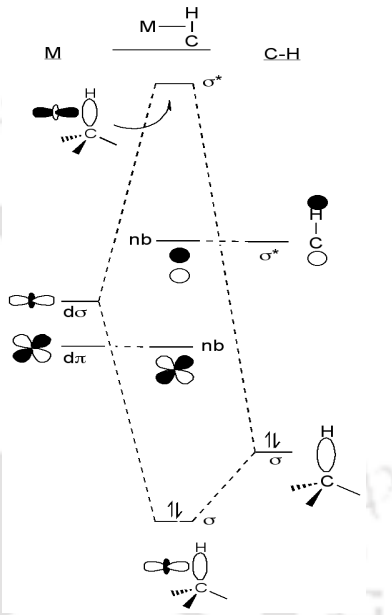
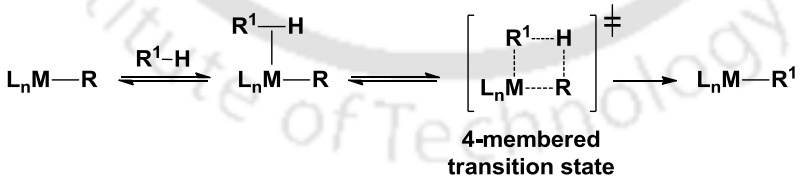


Figure I.4.2. *A qualitative MO diagram for σ-bond metathesis*

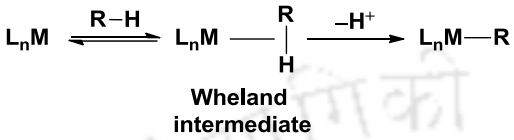


Scheme I.4.2. *C–H activation via σ-bond metathesis*

(c) Electrophilic activation

Late transition metals in a higher oxidation state take part in electrophilic substitutions. Electrophilic metalation of an aromatic nucleus proceeds in two stages; the electrophilic species first adds to the arene with the formation of a Wheland intermediate while in the

second step there is a loss of proton to give a distinct σ-organyl complex (Scheme I.4.3). An analogous intermediate might be formed during the interaction of a saturated hydrocarbon with an electrophilic metal-containing species, but should be much less stable.



Scheme I.4.3. *C–H activation via electrophilic activation*

A very qualitative MO diagram shown in Figure I.4.3 highlights that this mechanism usually involves later transition metals where the d orbitals have dropped in energy.

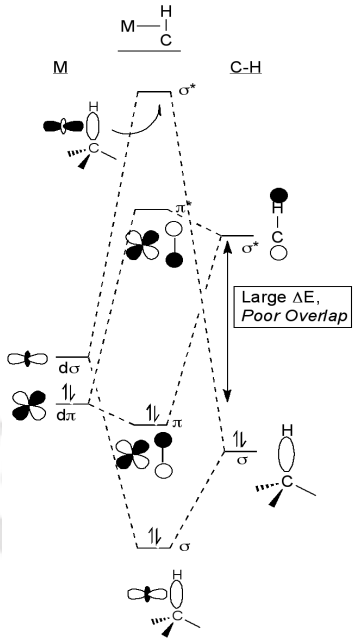
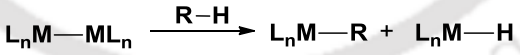


Figure I.4.3. *A qualitative MO diagram for electrophilic activation*

(d) Metalloradical activation

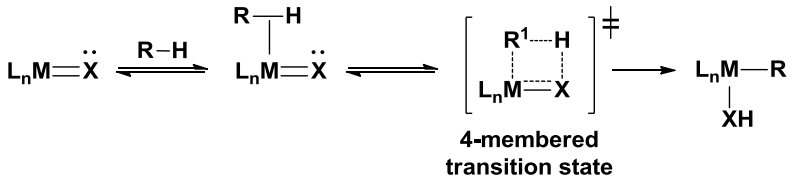
This type of mechanism is known for alkane C–H activation only. A transition metal complex existing in monomer–dimer equilibrium can reversibly break alkane C–H bonds, with the attachment of two fragments to two separate halves of the metal complex (Scheme I.4.4). Methane is the most reactive hydrocarbon for this class of reaction. Usually complexes of rhodium and ruthenium are employed for this activation reaction.



Scheme I.4.4. *C–H activation via metalloradical mechanism*

(e) 1,2-Addition

1,2-Addition reactions involve the addition of a C–H bond to a metal-nonmetal double bond (Scheme I.4.5). A typical example of this type consist of alkane additions across M=N and M=C double bonds of early and middle transition-metal centres, however the scope of this type of reaction and its potential for alkane functionalization remain unclear. The occurrence of a 1,2-addition mechanism is not known with sp^2 C–H bonds.



Scheme I.4.5. *C–H activation via 1,2-addition mechanism*

As shown above, all the classified mechanisms involve "true" metal complex activation of the C–H bond. This type of activation is called "true" because it is only in this case that the closest contact between a metal ion and the C–H bond (i.e., a normal σ-bond between M and C) is realized. In the "true" activation, a C–H-containing compound enters the coordination sphere of the metal complex in the form of an σ-organyl ligand.

I.5. Early stage of C–H activation: A historical survey

The activation of C–H bonds by transition metal-based systems has a long history. Bacteria have been practicing it for several billion years! In human body cytochrome P450 enzymes typically catalyze the conversion of C–H bonds to C–O bonds in organic compounds. These enzymes are involved in making cholesterol, steroids and other lipids; they also metabolize drugs, converting them to highly oxidized compounds that can be excreted by the body. The active sites of these enzymes contain iron atoms that play a crucial role in the C–H activation process. Another striking example of a C–H activating enzyme is methane monooxygenase, which was discovered in a class of bacterium, that lives at the interface of aerobic and anaerobic environments. This enzyme converts methane to methanol, although it can also oxidize several other organic compounds.

On a more conscious level, in the context of "modern" chemistry, the renaissance of inorganic/organometallic chemistry dates back to early 1900's. The first metal-containing systems which were capable of reacting with hydrocarbons and other C–H compounds, such as Fenton's reagent (hydroxylation) and mercury salts (direct mercuration), were discovered as early as the end of nineteenth century. During the 1930s, the electrophilic auration of arenes was described,[5a] a radical-chain auto-oxidation of hydrocarbons initiated by metal derivatives was developed,[5b] and a method for the metal-oxo complex promoted oxidation of alkenes and arenes by hydrogen peroxide was

proposed.[5c] A second spurt in pioneering research occurred in this field in the 1960s. Reactions involving the cyclometalation (i.e., the cleavage of a C–H bond in a metal-coordinated phosphine or amine ligand) of aromatic[5d] and sp^3-hybridized carbon atoms[5e] were found. It was demonstrated that palladium(II) derivatives induce the oxidative coupling of arenes[5f] and the arylation of alkenes (the Fujiwara reaction),[5g] while platinum-(II) salts catalyze H–D exchange between benzene and D_2O.[5h] In 1969, the first activation reactions of C–H bonds in alkanes were discovered.[5i] It was found that (i) platinum(II) salts catalyze the H–D exchange between methane or its analogues and D_2O at 100 °C, and (ii) the complex $CoH_3(PPh_3)_3$ induces the deuteration of methane by D_2 at room temperature. It has now become evident that organometallic derivatives are formed as intermediates in all these instances. In the 1970s it was shown that alkanes are oxidized by platinum(IV),[6a] palladium(II),[6b] ruthenium(IV),[6c] and cobalt(III)[6d-e] compounds and that complexes of iridium(III)[6f] and titanium(II)[6g] catalyze the H–D exchange. The next decade was marked by vigorous development of the activation of alkanes and arenes by low-valent metal complexes. These reactions proceed via an oxidative addition mechanism to form either alkyl or aryl derivatives of metals or alkenes.[6h-n]

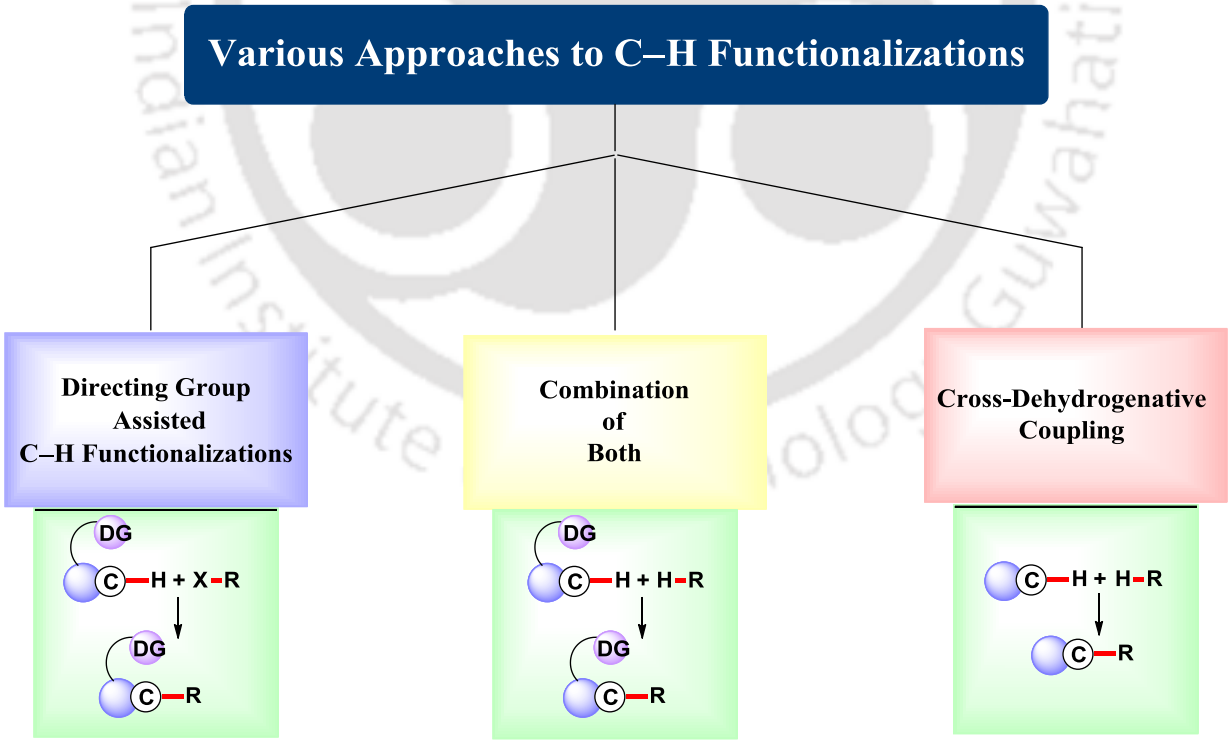
In contrast to the numerous publications devoted to C–H bond activation by low-valent metal complexes, far fewer examples of C–H bond activation bond by high oxidation state metal complexes are known which proceed by formation of organometallic compounds. For example, the ion $PtCl_6^{2-}$ metalates arenes in a manner similar to palladium(II). However, σ-aryl complexes of Pt(IV) are stable compounds and have been isolated,[7a] while σ-aryl complexes of palladium(II) are not stable and continue to react. The $PtCl_6^{2-}$ ion easily platinates arenes when irradiated with light[7b] or γ-irradiation.[7c] This platination is the first example of a photoelectrophilic substitution on an arene. Another example of C–H bond activation by a high-valent metal complex is provided by the exchange reaction between a methyllutetium σ-complex and $^{13}CH_4$.[7d]

At the end of the 1980s, the intensity of investigations into C–H bond activation by low-valent metal complexes began to diminish and interest gradually shifted to the oxidation of hydrocarbons by high-valent metal-oxo compounds and oxygen. Thereafter attention was being focused on biological and biomimetic oxidations. Cytochrome P450

model studies were propelled by the use of iodosyl benzene as an oxygen atom donor in catalytic oxidation reactions and by the use of metalloporphyrins as models for the active center of the enzyme.[7e] The more recent Gif systems used for the selective oxidation of alkanes are of considerable interest because of their unusual selectivity and mechanisms.[7f]

I.6. Modern era of C–H functionalizations

The modern era of the transition metal catalyzed C–H functionalization processes took off in early 1990's when there was a dramatic increase in the number of metal salts and complexes that were found to initiate C–H activation. Since then there has been a tremendous growth in this area of synthetic organic chemistry. The strategies generally adopted in these reactions can be classified into two major heads namely (i) directing group assisted C–H functionalizations and (ii) cross-dehydrogenative coupling (CDC) (Scheme I.6.1). Also there are methodologies which are based on the combination of two aforementioned approaches (Scheme I.6.1).



Scheme I.6.1. *Various approaches to C–H functionalizations*

I.6.1 Directing group assisted C–H functionalizations. Directed metallation is a powerful approach for selective functionalization of C–H bonds in substrates applicable to a variety of C–H bonds; including those of isolated alkyls.[8] It entails the use of a suitable heteroatomic function in the substrate to direct a metal complex to the vicinity of a distant C–H bond. The resulting metallacycle, usually a five- or six-membered ring, serves as a versatile intermediate en-route to products containing new C–C or C–X bonds. This strategy is known to function well with variety of transition metals in combination with oxidants or even without them. However, the most widely used transition metals are Ru, Rh, Pd and Cu. Besides these other transition metals viz. Mn, Fe, Co, Ni, Re, Ir, Pt, Ag, Au are also employed.

Advantages:

- Direct the transition metal into close proximity to the C–H bond to be activated.
- Higher effective concentration of the catalyst at the site of interest.
- High levels of regioselectivity and increased reactivity.

Limitations:

- In most cases, functionalizations are limited to *ortho* C–H bond of the directing groups.
- Additional synthetic steps involving installation and removal of directing groups. (In many cases the directing group is an integral part of the substrate).

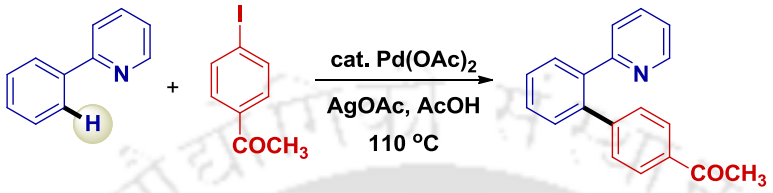
I.6.1.1. Representative examples of carbon-carbon bond formation

C–C Bond formation provides the requisite connectivity for the synthesis of large and complex molecular structure from simple precursors. Thus, the most widely studied area in this field is transition metal catalyzed ligand-directed C–H activation followed by C–C coupling to afford *ortho*-aryl, alkyl, alkenyl, alkynyl, carbonyl, trifluoromethyl and cyano products. Reactions pertinent to each of these categories are exemplified below.

- **sp^2 C–H Arylation**

Daugulis and co-workers developed a protocol on Pd(II) catalyzed sp^2 C–H arylation of 2-arylpyridines in conjunction with AgOAc as the oxidant and AcOH as additive (Scheme I.6.1.1.1).[9a-b] These transformation uses aryl iodides as aryl sources. A related *ortho*-arylation has also been applied to substituted anilides,[9c] benzoxazoles,[9d] and benzoic acid derivatives.[9e] Amide[9f] and oxime ether[9g] directed versions have also been used as the

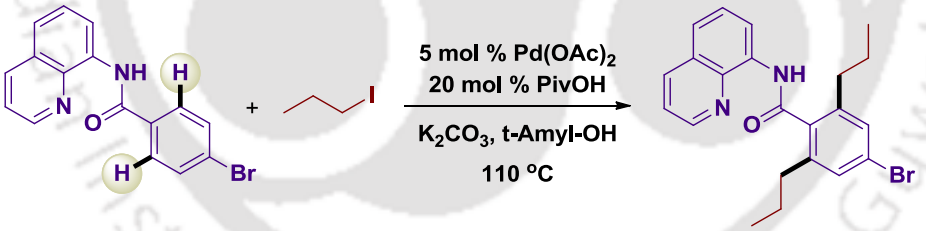
first step in tandem sequences to generate fluorenones. All of these transformations show broad scope and functional group compatibility. Apart from aryl iodides a variety of other arylating agents such as diphenyliodonium salts,[10a-d] aryl chlorides,[9e] arylboronic acids,[10e-f] arylsilyl ethers[10g-h] and even aryl acyl peroxides[10i] have been used for this purpose very effectively.



Scheme I.6.1.1.1. *Pd-catalyzed ortho-arylation of 2-phenylpyridine with aryl iodides*

➢ **sp^2 C–H Alkylation**

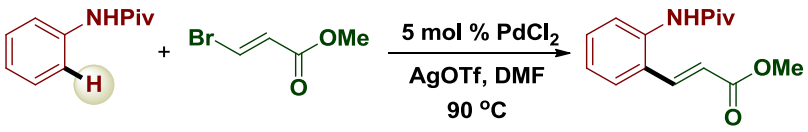
Daugulis group also reported a Pd(II)-catalyzed alkylation of arenes bearing aminoquinolines as directing group with alkyl iodides or bromides (Scheme I.6.1.1.2).[11a] Directing group assisted alkylation has also been achieved using other alkyl sources that include tetra-alkyl tin reagents,[11b] methylboroxines,[11c] alkylboronic acids[11d] and dicumylperoxide.[11e]



Scheme I.6.1.1.2. *Pd-catalyzed sp^2 C–H alkylation with alkyl halides*

➢ **sp^2 C–H Alkenylation**

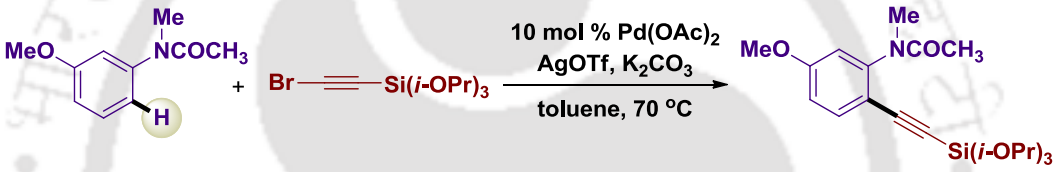
In addition to the abovementioned novel discoveries by Daugulis group towards *ortho*-arylation and *ortho*-alkylation, they have demonstrated an intriguing methodology for *ortho*-alkenylation using 3-halo acrylates as alkene substrates (Scheme I.6.1.1.3).[12a] In one of their independent works, they have also employed 2-bromovinyl benzene as the styrene source for *ortho*-alkenylation of amides.[11a] In a recent work, Kakiuchi group has shown that alkenyl ethers and esters can be employed for Ru-catalyzed *ortho*-selective alkenylation of aromatic compounds.[12b]



Scheme I.6.1.1.3. *Pd-catalyzed coupling of haloolefins with anilides*

- **sp^2 C–H Alkynylation**

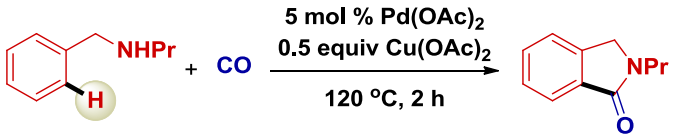
The sp^2 C–H alkynylation of substrates possessing various directing groups are limited to few examples only. One of the early reports was by the Chatani group who achieved a palladium catalyzed *ortho*-alkynylation of anilides with a silyl-protected bromoalkyne, AgOTf, and K_2CO_3 (Scheme I.6.1.1.4).[13] Other Ru and Rh catalyzed protocols are also reported using pre-activated alkynylating reagents such as alkynyl halides[14] and benziodoxolone-based hypervalent iodine reagents[15] as coupling partners.



Scheme I.6.1.1.4. *Pd-catalyzed ortho-alkynylation of anilides with haloalkynes*

- **sp^2 C–H Carbonylation**

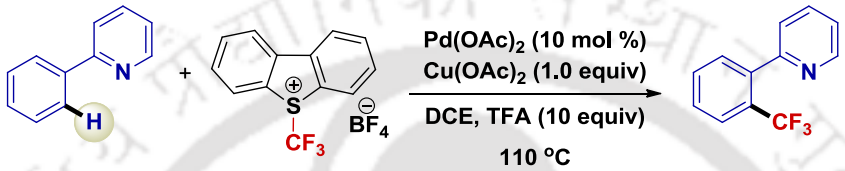
An early example of Pd-catalyzed directed C–H carbonylation involved the formation of benzolactam derivatives from benzylamines under an atmosphere of CO (Scheme I.6.1.1.5).[16a] $Pd(OAc)_2$ was used as the catalyst, and $Cu(OAc)_2$ and O_2 served as co-oxidants. *Ortho*-carbonylation of other directing groups is reported using CO as the carbonyl source for the synthesis of *ortho*-esters.[16b-c] Diethyl azodicarboxylate (DEAD) has been used as a substitute of toxic CO for ethoxycarbonylation of substrates possessing directing groups such as pyridine-, amide-, and oxime ether in the presence of $Pd(OAc)_2$ as the catalyst and oxone as the terminal oxidant.[16d]



Scheme I.6.1.1.5. *Pd-catalyzed ortho-carbonylation of benzylamines*

➢ **sp^2 C–H Trifluoromethylation**

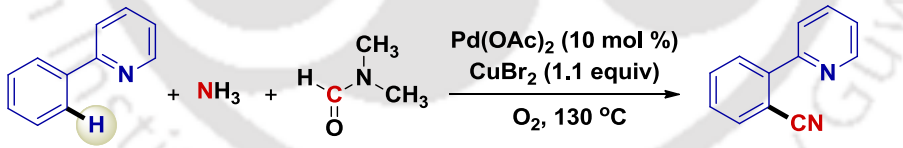
Yu group reported the first example of Pd(II)-catalyzed *ortho*-trifluoromethylation of 2-arylpyridines or analogous substrates using trifluoroacetic acid (TFA) and $Cu(OAc)_2$ as crucial promoters (Scheme I.6.1.1.6).[17a] Later the same group also demonstrated the Pd(II)-catalyzed trifluoromethylation of benzamides using *N*-alkylformamide as a crucial promoter.[17b] There has been an evolution of several methods on *ortho*-trifluoromethylation of several other directing group possessing substrates.[17c-d]



Scheme I.6.1.1.6. *Pd-catalyzed ortho-trifluoromethylation of 2-phenylpyridine*

➢ **sp^2 C–H Cyanation**

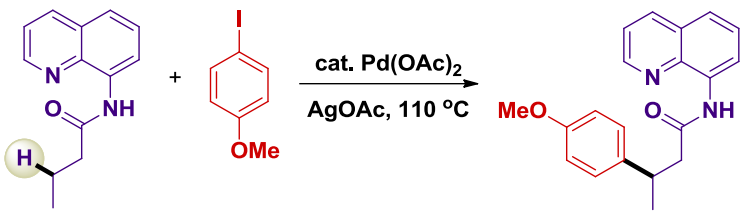
Chang group developed an intriguing protocol for cyanation at arene C–H bonds employing *N*,*N*-dimethylformamide and ammonia as a combined source for the cyano "CN" unit (Scheme I.6.1.1.7).[18a] Other cyano surrogates such as copper(I) cyanide,[18b] potassium ferricyanide,[18c] benzyl nitrile,[18d] acetonitrile,[18e] AIBN[18f] and *tert*-butyl isonitrile[18g] have also been used for the same purpose.



Scheme I.6.1.1.7. *Pd-catalyzed ortho-cyanation of 2-phenylpyridine*

➢ **sp^3 C–H Arylation**

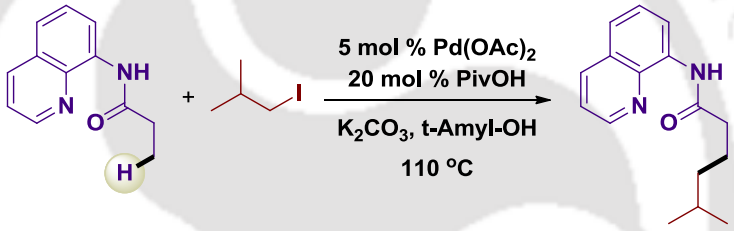
The combination of AgOAc and Ar-I has been utilized for the Pd-catalyzed arylation of unactivated sp^3 C–H bonds (Scheme I.6.1.1.8).[19a] Directing groups including pyridines, aminoquinolines, and picolinamides were used, and arylation occurred at both 1° and 2° sp^3 C–H sites.[19a] The coupling of aryl iodides with sp^3 C–H bonds in carboxylic acid derivatives has also been achieved using a slight modification of the above conditions. This system used Ag_2CO_3, 2 equiv of NaOAc and 1 equiv of K_2HPO_4.[19b]



Scheme I.6.1.1.8. *Pd-catalyzed sp^3 C–H arylation with aryl iodides*

➢ **sp^3 C–H Alkylation**

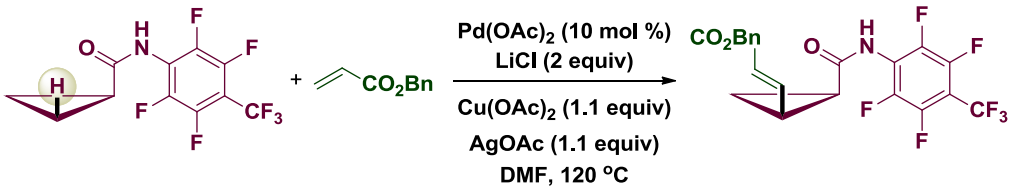
Alkyl iodides or bromides have been employed as alkyl sources for Pd(II) catalyzed alkylation at sp^3 C–H bonds of amides bearing aminoquinolines as auxillary ligand (Scheme I.6.1.1.9).[11a] Yu group also developed a similar alkylation protocol cleaving sp^3 C–H of *N*-methoxy amides using Pd(II) catalyst and alkylboronic acids as alkyl sources.[20]



Scheme I.6.1.1.9. *Pd-catalyzed sp^3 C–H alkylation with alkyl iodides*

➢ **sp^3 C–H Alkenylation**

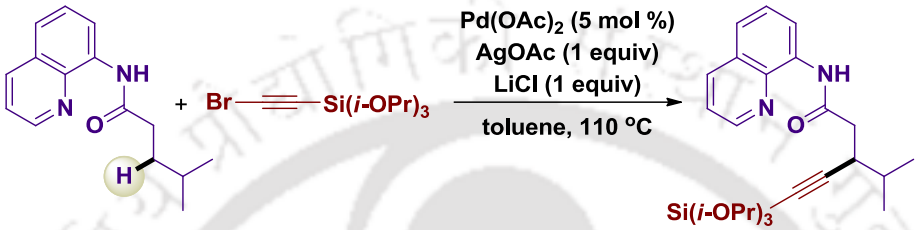
Yu group developed an amide group assisted Pd(II)-catalyzed reaction protocol for the direct olefination of sp^3 C–H bonds (Scheme I.6.1.1.10).[21a] After β-C–H olefination, the amide products underwent 1,4-conjugate addition to give the corresponding lactam compounds. The reaction conditions could also be applied to promote olefination of cyclopropyl methylene C–H bonds and substrates containing α-hydrogen atoms. Later, the same group applied the same method for the generation of β-quaternary carbon centers.[21b]



Scheme I.6.1.1.10. *Pd-catalyzed amide directed sp^3 C–H alkenylation*

➢ **sp^3 C–H Alkynylation**

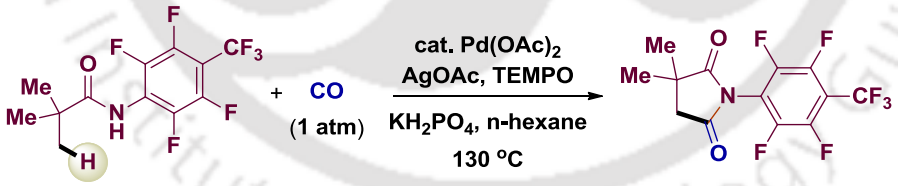
Methods to convert inert C(sp^3)−H bonds to C(sp^3)−alkynyl bonds are rare, with only two precedences in literature. Chatani group illustrated the first Pd(II)-catalyzed coupling of C(sp^3)−H bonds with alkynyl halides via Pd(II)/Pd(IV) catalysis (Scheme I.6.1.1.11).[22a] While Yu group reported the first example of Pd(0)/NHC and Pd(0)/PR_3-catalyzed alkynylation of β-C(sp^3)−H bonds using an *N*-arylamide auxiliary.[22b]



Scheme I.6.1.1.11. *Pd-catalyzed sp^3 C–H alkynylation with haloalkynes*

➢ **sp^3 C–H Carbonylation**

Yu group achieved a Pd(II)-catalyzed β-C(sp^3)–H carbonylation of *N*-arylamides under CO (1 atm) for the synthesis of their corresponding succinimides (Scheme I.6.1.1.12).[23] These products could be readily converted to 1,4-dicarbonyl compounds by hydrolysis. This method was equally effective towards methylene C(sp^3) –H carbonylation of cyclopropanes.



Scheme I.6.1.1.12. *Pd-catalyzed sp^3 C–H carbonylation of amides to synthesize succinimides*

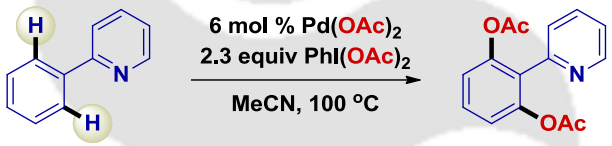
I.6.1.2. Representative examples of carbon-oxygen bond formation

Oxygenated molecules are key intermediates in organic synthesis and constitute important structural motifs of useful pharmaceuticals, agrochemicals, polymers, and biologically active compounds. Thus C–O bond forming reactions have gained prime importance since years. The C–O bond installations via C(sp^2)–H or C(sp^3)–H cleavage

occur in several ways; the common forms being acetoxylation, benzoxylation, hydroxylation and alkoxylation. Representative examples pertaining to various forms of C–O bond formations are shown below.

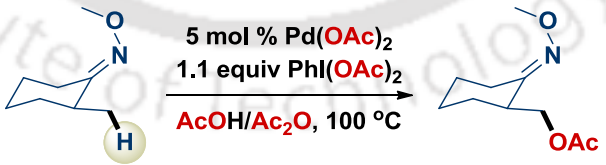
➢ **C–H Acetoxylation**

Sanford group reported the first example of ligand-directed sp^2 C–H bond oxygenation using $PhI(OAc)_2$ as a stoichiometric oxidant in conjunction with catalytic $Pd(OAc)_2$ (Scheme I.6.1.2.1).[24a] A variety of pyridine derivatives served as excellent directing groups, affording their respective *ortho*-acetoxylated products. Other nitrogen-based directing groups, including imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles (e.g., pyrazoles and isoxazolines) were also effective. Furthermore, amides, which contain relatively basic oxygen atoms, could be used to direct these reactions. Other iodine oxidants or peroxides have been utilized towards acetoxylation reactions.[24b-c]



Scheme I.6.1.2.1. *Pd-catalyzed ortho-acetoxylation of 2-phenylpyridine*

The same group also reported a Pd-catalyzed ligand-directed sp^3 C–H bond oxygenation also used $PhI(OAc)_2$ as the terminal oxidant in which both benzylic and unactivated sp^3 C–H bonds were readily converted to OAc groups (Scheme I.6.1.2.2).[24a,d] Oxime ether and pyridine directing groups could be utilized for these transformations.[24a,d]

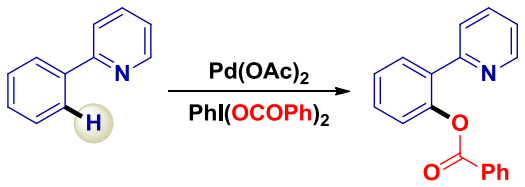


Scheme I.6.1.2.2. *Pd-catalyzed sp^3 C–H acetoxylation of ketoxime ethers*

➢ **C–H Benzoxylation**

Sanford *et al.* reported palladium catalyzed *o*-benzoxylation of 2-phenylpyridines using benzoate iodonium salts as the ArCOO– surrogates for the first time (Scheme I.6.1.2.3).[25a]

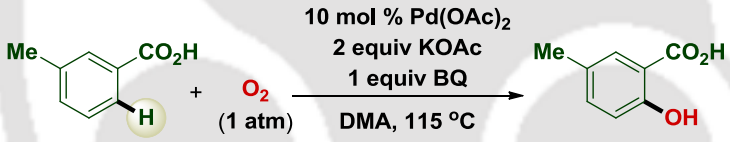
Later, Shi group achieved a similar palladium catalyzed *o*-benzoxylation of ketoxime ether via *in situ* generation of benzoate iodonium salts.[25b]



Scheme I.6.1.2.3. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

➢ **C–H Hydroxylation**

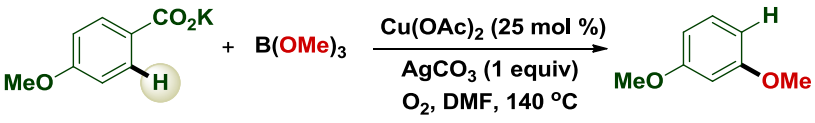
Yu group achieved a highly selective Pd-catalyzed *ortho*-hydroxylation of potassium benzoates via activation of dioxygen giving synthetically useful salicyclic acid derivatives (Scheme I.6.1.2.4).[26a] Apart from this, the same group has also described a Cu-catalyzed *ortho*-hydroxylation of 2-arylpyridines that goes via acetoxylation/hydrolysis sequence.[26b] Many Ru-catalyzed hydroxylation of arenes bearing various directing groups also prevail in literature.[26c]



Scheme I.6.1.2.4. *Pd-catalyzed ortho-hydroxylation of arylcarboxylic acids*

➢ **C–H Alkoxylation**

Gooβen group demonstrated a regiospecific Cu(II) catalyzed *ortho*-alkoxylation of aromatic carboxylates with concomitant decarboxylation (Scheme I.6.1.2.5).[27] This protocol gives access to the important substrate class of aromatic ethers from widely available carboxylic acids. This process, in which the carboxylate substituent serves as a cleavable directing group, represents a rare example of an aromatic substitution reaction in which the original substitution pattern is altered in a defined way.



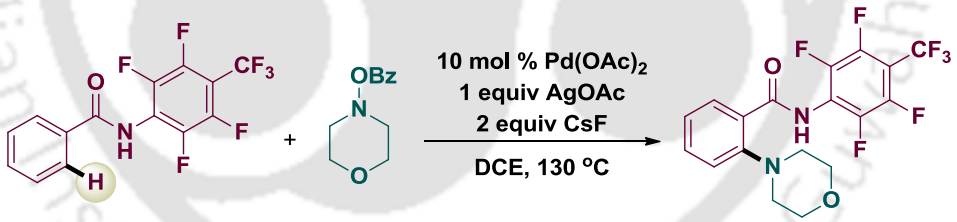
Scheme I.6.1.2.5. *Pd-catalyzed ortho-alkoxylation of arylcarboxylates*

I.6.1.3. Representative examples of carbon-nitrogen bond formation

Transition metal catalyzed ligand-directed C–H functionalization has also been utilized for the construction of C–N bonds, which are important structural motifs found in various pharmaceuticals, agrochemicals, polymers and many biologically active molecules. Reactions resulting in C–N bond formation consist of two classes' viz. amination and amidation. Some examples where the nitrogen group is delivered from an external reagent (intermolecular reaction) are illustrated below.

- **C–H Amination**

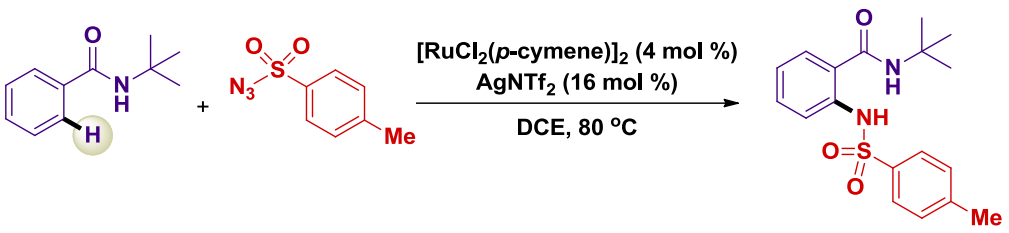
Yu group developed a novel protocol to effect C–H amination on a broad range of synthetically useful benzamide substrates with electrophilic *O*-benzoyl hydroxylamines using either Pd(II) or Pd(0) catalysts (Scheme I.6.1.3.1).[28] Additionally, they have shown that a one-pot procedure using secondary amines directly in the presence of benzoyl peroxide is also possible. The compatibility of this amination reaction with several different *O*-benzoyl hydroxylamine reagents derived from simple dialkylamines allows for the convergent synthesis of an important class of tertiary and secondary aryl-alkyl amines starting from benzoic acids.



Scheme I.6.1.3.1. *Pd-catalyzed intermolecular amination with alkylamines*

- **C–H Amidation**

Chang and co-workers demonstrated a ruthenium-catalyzed C–H bond amidations on arenes bearing synthetically useful directing groups, such as amides or ketones (Scheme I.6.1.3.2).[29] A wide range of benzamides and aryl ketones were readily amidated at the *ortho*-position using sulfonyl azides with excellent catalytic efficacy and selectivity. The practical importance of the products was showcased by the preparation of a wide range of heterocycles with potential biological activities. Analogous amidation reactions using sulfonyl azides as precursors are illustrated with other directing groups as well.[26c]



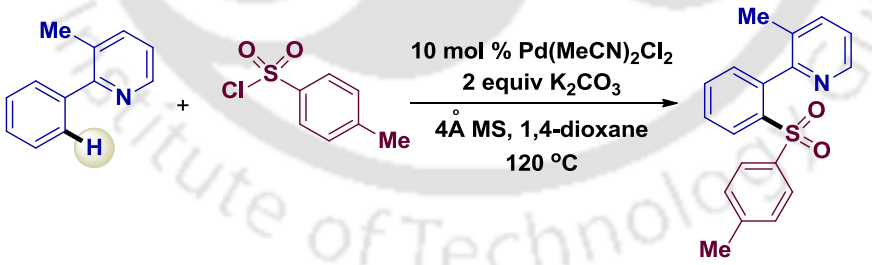
Scheme I.6.1.3.2. *Ru-catalyzed ortho-amidation of benzamides with sulfonyl azides*

I.6.1.4. Representative examples of carbon-sulfur bond formation

Despite the potential uses of sulfur- containing compounds in the pharmaceutical and agrochemical industries etc., the latest developments on transition metal catalyzed ligand-directed formation of carbon-sulfur bonds remains relatively rare. Most examples involve intramolecular reactions to generate the C–S linkage.[30] One reason for difficulties in the development of C–S bond-forming reactions could be competing oxidation of sulfur under oxidative conditions, diminishing the reactivity to give the desired products.

- **C–H Sulfonylation**

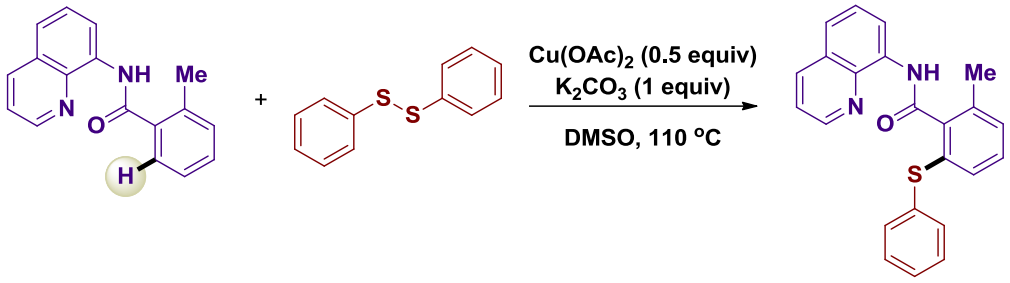
To date, the only example of sulfonylation is the intermolecular Pd-catalyzed C–H activation/C–S bond formation employing $ArSO_2Cl$ as the sulfonating reagent (Scheme I.6.1.4.1).[31] Arylpyridine, arylpyrazole, and aryloxime ether substrates were converted to diarylsulfones using catalytic $Pd(MeCN)_2Cl_2$ and stoichiometric $ArSO_2Cl$.



Scheme I.6.1.4.1. *Pd-catalyzed ortho-sulfonylation of 2-phenylpyridine*

- **C–H Sulfenylation**

Daugulis group has developed an auxiliary-assisted, copper catalyzed or promoted sulfenylation of benzoic acid derivative β-C−H bonds and benzylamine derivative γ-C−H bonds (Scheme I.6.1.4.2).[32] The method employs disulfide reagents, copper(II) acetate, and DMSO solvent at 90−130 °C.



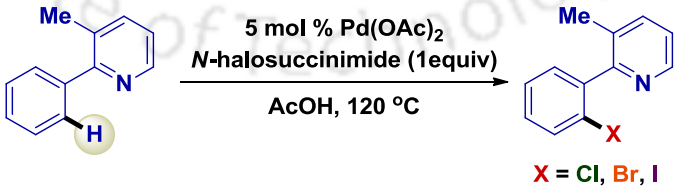
Scheme I.6.1.4.2. *Pd-catalyzed direct sulfenylation of benzoic acid derivatives*

I.6.1.5. Representative examples of carbon-halogen bond formation

The installation of a C–X (X = Cl, Br, I) bond via C–H activation has got high synthetic importance from the perspective of their use in coupling chemistry for further functionalizations. Although C–F bonds are not useful in this respect, however fluoroaromatic compounds possess inertness; high chemical, thermal, and metabolic stability; and unique electronic properties. They are widely used as pharmaceuticals, agrochemicals, and imaging materials.

- **C–H Chlorination, bromination and iodination**

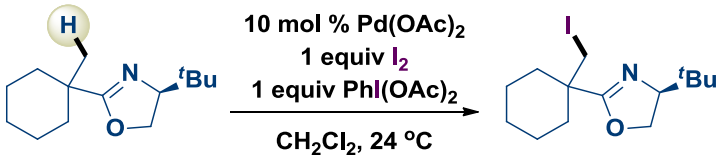
A patent by Kodama and co-workers demonstrated that the combination of $Pd(OAc)_2$ and *N*-iodosuccinimide promotes the *ortho*-iodination of benzoic acids.[33a] Sanford group applied similar conditions to the directed chlorination, bromination and iodination of arenes with a wider variety of directing groups, including pyridines, oxime ethers, isoquinolines, amides, and isoxazolines (Scheme I.6.1.5.1).[33b-c] Apart from the *N*-halo succinimides, other halogenating agents are also used such as CuX_2 (X = Cl, Br),[33c-d] Suárez reagents (XOAc, X = Br, I)[33e-f] and sulfonyl chlorides.[31]



Scheme I.6.1.5.1. *Pd-catalyzed ortho-halogenation of 2-phenylpyridine*

Pertaining to sp^3 halogenation, Pd(II)-catalyzed iodination is reported by Yu group using a combination of $PhI(OAc)_2$ and I_2, to generate in situ IOAc (Scheme I.6.1.5.2).[33e-f]

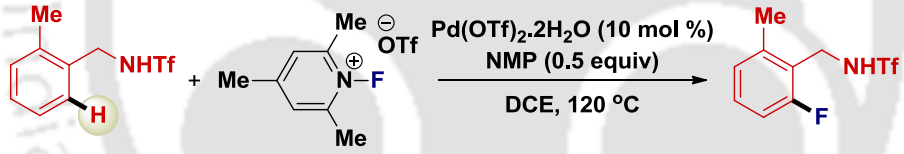
However similar chlorination and bromination is yet to be accomplished.



Scheme I.6.1.5.2. *Pd-catalyzed sp^3 C–H iodination*

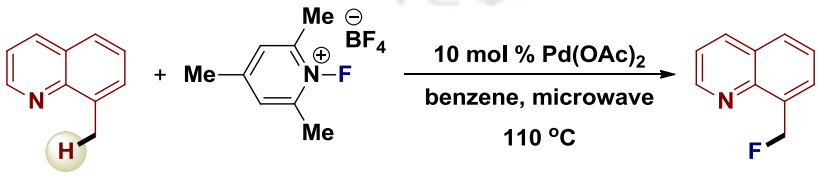
➢ **C–H Fluorination**

Yu group achieved a catalytic C–H fluorination to benzylamine-based substrates. *N*-Fluoro-2,4,6-trimethylpyridinium triflate was used as the "F^+" source along with *N*-methylpyrrolidinone (NMP) as a key promoter for the $Pd(OTf)_2$-catalyzed fluorination of triflamide-protected benzylamines (Scheme I.6.1.5.3).[34a] This is a valuable development because triflamides can be converted to a broad range of synthetically useful functional groups including benzaldehydes, benzylamines, nitriles, and benzylmalonates, thereby providing access to a variety of functionalized aryl fluoride containing products.



Scheme I.6.1.5.3. *Pd-catalyzed ortho fluorination of benzylamine derivatives*

Sanford group first demonstrated the Pd-catalyzed benzylic fluorination of benzylic sp^3 C–H using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the electrophilic fluorinating reagent for this transformation (Scheme I.6.1.5.4).[34b] They also showed that microwave heating decreased the reaction time and minimized undesirable side products.



Scheme I.6.1.5.4. *Pd-catalyzed benzylic sp^3 C–H fluorination*

I.6.2. Cross-dehydrogenative coupling (CDC). The cross-dehydrogenative coupling (CDC) reaction generally refers to a cross-coupling reaction between two C–H bonds or C–H and X–H (X = heteroatoms) bonds.[35] In terms of atom economy, this strategy represents one of the most ideal synthetic procedures for selective C–C and C–X bond forming reactions. The reaction require a hydrogen acceptor which can take the form of oxygen, hydrogen peroxide, organic peroxides, for example, *tert*-butyl hydrogen peroxide (TBHP) or *tert*-butyl peroxide (TBP), and *N*-halosuccinimides, for example, *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS). CDCs have been shown to function well in the presence of a variety of metal catalysts, such as Cu, Fe, and Pd, which serve to activate the electrophilic coupling partner. There are also examples that function without the use of metal catalysts. Interestingly, there are some examples of CDCs that have been successfully applied in water, consequently, further enhancing their environmental friendliness. A few enantioselective examples of CDCs have been reported, however, there is a significant amount of work to be realized in this area.

Advantages:

- Non-requirement of any directing groups or pre-functionalization in starting materials.
- Ambient reaction conditions and simple starting materials
- High degree of C–H bond activation.

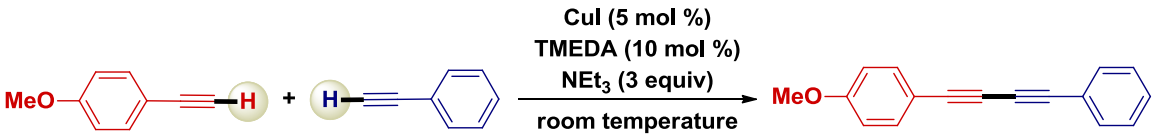
Limitations:

- Regioselectivity issues; functionalization can occur at any of the C–H's.
- Lacking of chemoselectivity due to over-functionalization.

I.6.2.1. Representative examples of CDC reactions

- **C(sp)–C(sp) Bond formation**

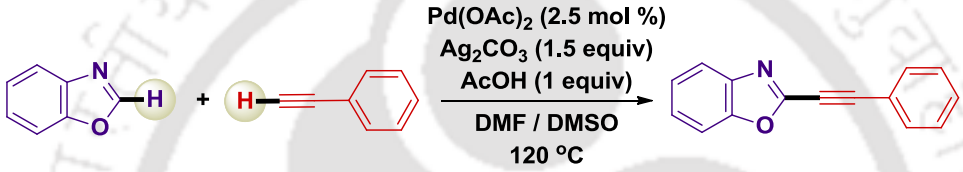
A facile and efficient pathway for the copper iodide and ligand *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA) promoted homo-coupling reaction of terminal alkynes under ambient temperature and air as the oxidant was reported by Zhang group (Scheme I.6.2.1.1).[36] The alkynes, including aromatic alkynes and aliphatic alkynes, could afford the symmetrical as well as unsymmetrical 1,4-disubstituted 1,3-diynes in good to excellent yields.



Scheme I.6.2.1.1 *Copper (I)-catalyzed homo-coupling of terminal alkynes*

➢ **C(sp)–C(sp^2) Bond formation**

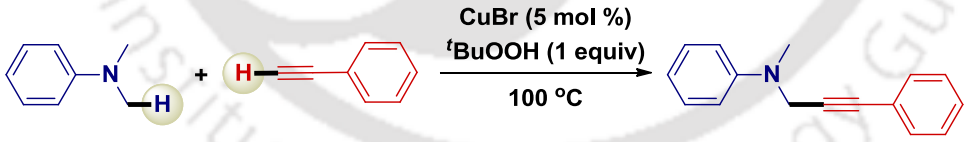
Murai group developed a widely applicable oxidative coupling of five-membered heteroarenes and terminal alkynes that uses a combination of palladium and silver salts (Scheme I.6.2.1.2).[37] Under suitable conditions, imidazole, benzimidazole, imidazo[1,5-*a*]pyridines, oxazole, benzoxazole, thiazole, and benzothiazole could be alkynylated.



Scheme I.6.2.1.2. *Palladium(II)-catalyzed direct alkynylation of heteroarenes*

➢ **C(sp)–C(sp^3) Bond formation**

Li group achieved a simple and effective catalytic method to construct propargylamine using copper bromide and *tert*-BuOOH via a combination of sp^3 C−H bond and sp C−H bond activations followed by a C−C bond formation (Scheme I.6.2.1.3).[38]

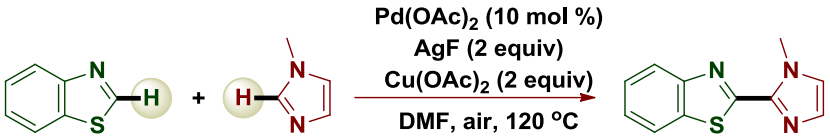


Scheme I.6.2.1.3. *Copper(I)-catalyzed direct alkynylation at sp^2 C–H*

➢ **C(sp^2)–C(sp^2) Bond formation**

Ofial and co-workers reported an efficient Pd(II)-catalyzed method for the direct C2 heteroarylation of benzazoles with N–, O–, and S– containing azoles that is mediated by co-oxidants $Cu(OAc)_2$ and AgF (Scheme I.6.2.1.4).[39] Homocoupling was successfully suppressed such that mixed bisheteroaryls were obtained through the selective cleavage of C–H bonds in both substrates without the requirement of prefunctionalized azoles, design-

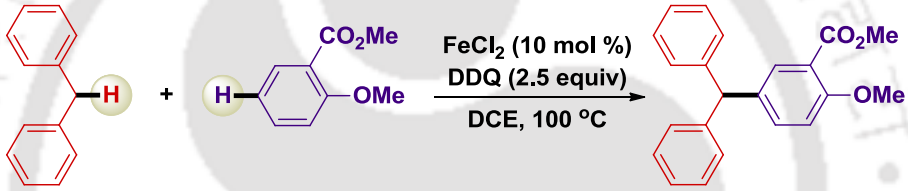
ed ligands, or a huge excess of one azole over the other.



Scheme I.6.2.1.4. *Palladium(II)-catalyzed oxidative sp^2 C–H/sp^2 C–H coupling*

➢ **C(sp^2)–C(sp^3) Bond formation**

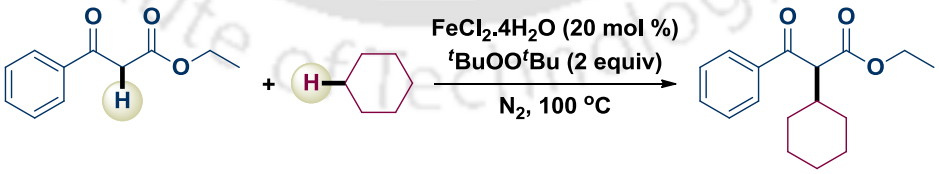
The group of Shi introduced a $FeCl_2$-catalyzed oxidative cross-coupling between compounds containing benzylic sp^3 C–H and arene sp^2 C–H in presence of DDQ as oxidant (Scheme I.6.2.1.5).[40] This is a useful method for the synthesis of di- or tri-phenylmethane derivatives using simple starting materials.



Scheme I.6.2.1.5. *Iron(II)-catalyzed direct arylation at benzylic sp^3 C–H*

➢ **C(sp^3)–C(sp^3) Bond formation**

A simple $FeCl_2$-catalyzed C–C bond formation by direct alkylation of activated methylene using simple cycloalkanes was developed by Li group (Scheme I.6.2.1.6).[41] Several kinds of alkanes were found to react with phenyl β-ketoester and diketone compounds to afford alkylated 1,3-dicarbonyl compounds.

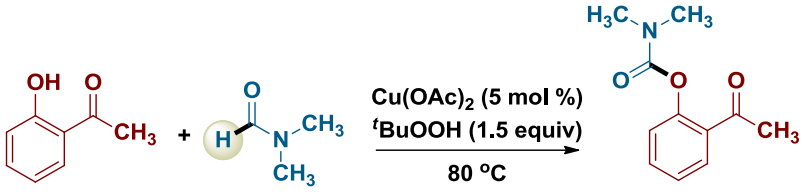


Scheme I.6.2.1.6. *Iron(II)-catalyzed direct cycloalkylation of β-dicarbonyl compounds*

➢ **C(sp^2)–O Bond formation**

Reddy group developed a novel phosgene-free route to carbamates via copper-catalyzed oxidative C–O bond formation of formamides with phenol and enols (Scheme

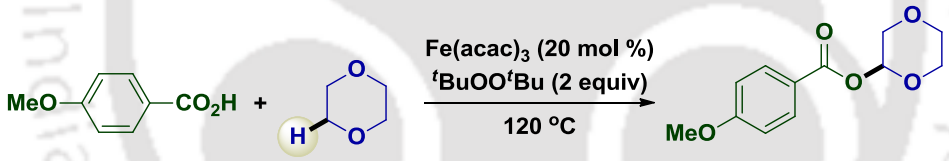
I.6.2.1.7).[42] A high stereoselectivity was achieved for enol carbamates and the present strategy was also extended to oxidative esterification of carbonyl-substituted phenols.



Scheme I.6.2.1.7. *Copper(II)-catalyzed synthesis of carbamates via C–O bond formation*

- **C(sp^3)–O Bond formation**

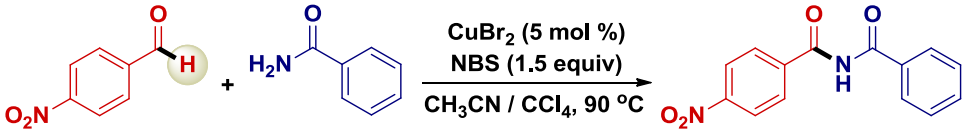
Pan group has recently achieved an iron-catalyzed oxidative esterification of unactivated C(sp^3)–H bonds from symmetric and asymmetric ethers and carboxylic acids using di-*tert*-butyl peroxide (DTBP) as the oxidant via a cross dehydrogenative coupling (CDC) reaction (Scheme I.6.2.1.8).[43] This protocol tolerates a wide range of cyclic ethers to react with aromatic acids and phenylacetic acid, providing an efficient method for the preparation of α-acyloxy ethers with good to excellent yields.



Scheme I.6.2.1.8. *Iron(III)-catalyzed synthesis of α-acyloxy ethers*

- **C(sp^2)–N(amide) Bond formation**

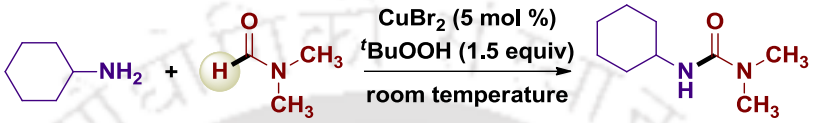
Fu group developed a hetero-CDC protocol for the synthesis of imides using simple aldehydes and either secondary or tertiary amides as the coupling partners in the presence of copper(II) bromide and NBS (Scheme I.6.2.1.9).[44] The corresponding target products were obtained in good to excellent yields, and an array of functional groups are tolerated under the mild conditions with respect to both amides and aldehydes.



Scheme I.6.2.1.9. *Copper(II)-catalyzed synthesis of imides via sp^2 C–H amidation*

➢ **C(sp^2)–N(amine) Bond formation**

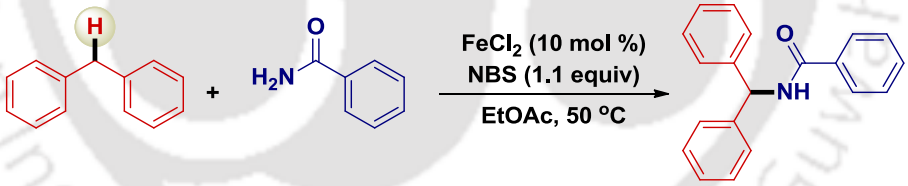
Reddy and co-workers recently reported a copper catalyzed oxidative cross coupling of formamides with amines for the preparation of unsymmetrical urea derivatives at room temperature (Scheme I.6.2.1.10).[45] Noteworthy features of the present work are utilization of *N*-methylformamide as a formamide source and also application towards the synthesis of chiral urea derivatives.



Scheme I.6.2.1.10. *Copper(II)-catalyzed synthesis of ureas via sp^2 C–H amination of N-substituted formamides*

➢ **C(sp^3)–N(amide) Bond formation**

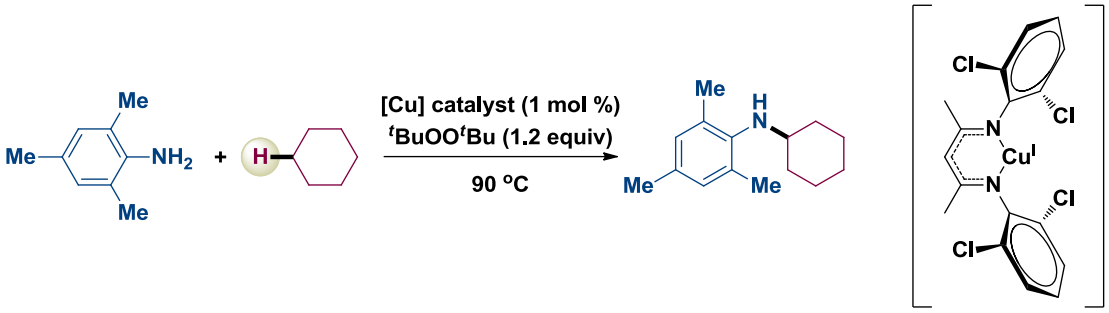
Fu *et al.* developed an efficient protocol for amidation of benzylic sp^3 C–H bonds providing reasonable yields of corresponding products under mild conditions (Scheme I.6.2.1.11).[46] The protocol uses $FeCl_2$ as the catalyst, NBS as the oxidant, and ethyl acetate as the solvent.



Scheme I.6.2.1.11. *Iron(II)-catalyzed direct amidation at benzylic sp^3 C–H*

➢ **C(sp^3)–N(amine) Bond formation**

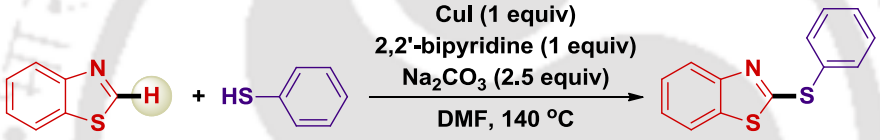
Warren group presented the first general use of anilines in the C–H amination of a range of substrates with Csp^3–H bonds (Scheme I.6.2.1.12).[47] The copper(I) catalyst [{(Cl_2NN)Cu}$_2$(benzene)] in conjunction with the mild oxidant ^{t}BuOO^{t}Bu enables the direct use of a variety of commercially available anilines in C–H amination. Even strong, unactivated C(sp^3)–H bonds could be efficiently functionalized by using low catalyst loadings and electron-poor anilines which suppress diazene formation.



Scheme I.6.2.1.12. *Copper(I)-catalyzed direct amination at inert sp^3 C–H of alkanes*

➢ **C(sp^2)–S Bond formation**

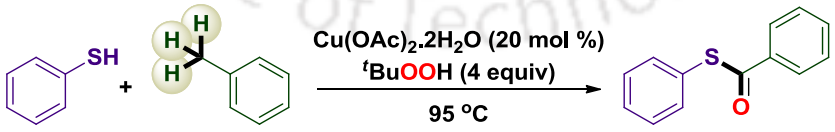
Liu *et al.* reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by the direct thiolation of benzothiazoles with aryl or alkyl thiols in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3 (Scheme I.6.2.1.13).[48]



Scheme I.6.2.1.13. *Copper(I)-catalyzed direct thiolation of benzothiazole*

➢ **C(sp^3)–S Bond formation**

A unique Cu(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes has been recently developed by our group for the synthesis of thioesters in presence of *tert*-butyl hydroperoxide as oxidant as well oxygen source (Scheme I.6.2.1.14).[49] A thioester moiety is created via successive C–S and C–O bond formation at the expense of three sp^3 C–H bonds of the alkylbenzene and one sp^3 S–H bond of the thiol.

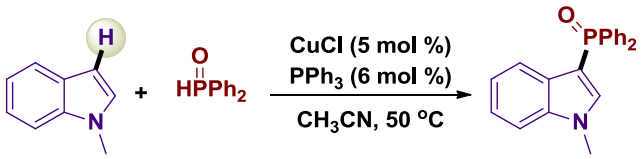


Scheme I.6.2.1.14. *Copper(II)-catalyzed synthesis of thioesters*

➢ **C(sp^2)–P Bond formation**

Yang group has recently developed a highly efficient protocol for the preparation of various 3-phosphoindoles via a Cu(I)-catalyzed cross-dehydrogenative coupling between

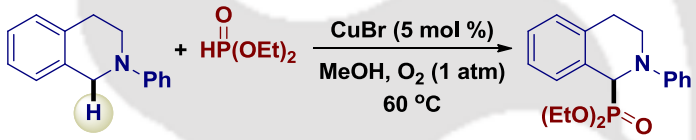
substituted indoles and disubstituted phosphine oxide (Scheme I.6.2.1.15).[50] This is the only precedence for the direct oxidative Csp^2–P bond formation without the assistance of directing groups.



Scheme I.6.2.1.15. *Copper(I)-catalyzed direct phosphorylation of indoles*

➢ **C(sp^3)–P Bond formation**

An efficient cross-dehydrogenative coupling (CDC) between sp^3 C–H and H–P bonds was developed by Li group using copper salt as catalyst and molecular oxygen as the terminal oxidant; this methodology provides an easy access to biologically important α-aminophosphonates (Scheme I.6.2.1.16).[51]



Scheme I.6.2.1.16. *Copper(I)-catalyzed synthesis of α-aminophosphonates via CDC between sp^3 C–H and P–H bonds*

I.6.3. Directing group assisted cross-dehydrogenative coupling: This combination represents the most powerful approach to selectively functionalize *ortho* C–H bonds to form C–C or C–X (X = hetero atom) bonds. This strategy has the advantages of both the regioselectivity and chemoselectivity and offers a higher degree of C–H bond cleavages.

I.6.3.1. Representative examples of reactions involving directing group assisted cross-dehydrogenative coupling

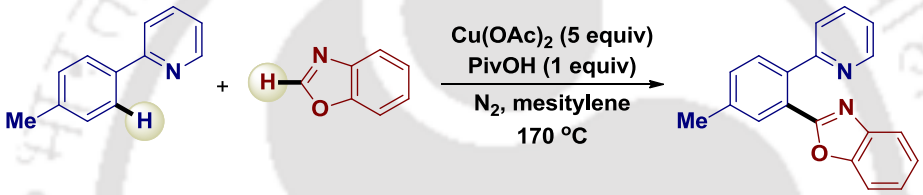
➢ **C(sp^2)–C(sp) Bond formation**

Yu group recently reported a Cu(II)-promoted *ortho*-alkynylation of arenes and heteroarenes with terminal alkynes to prepare aryl alkynes (Scheme I.6.3.1.1).[52] A variety of arenes and terminal alkynes bearing different substituents are compatible with this reaction, thus providing an alternative disconnection to Sonogashira coupling.

Scheme I.6.3.1.1. *Copper(II)-catalyzed auxillary assisted alkynylation of arenes*

➢ **C(sp^2)–C(sp^2)-(aryl) Bond formation**

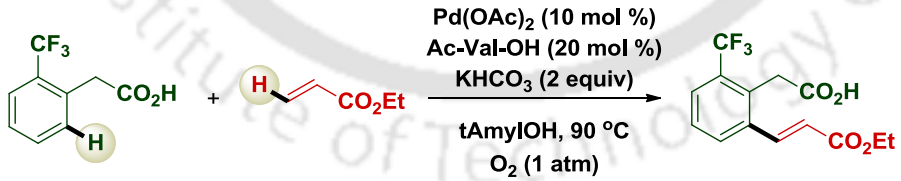
Miura group achieved a palladium-free, copper-mediated intermolecular direct biaryl coupling of arylazines and azoles (Scheme I.6.3.1.2).[53] The process provides a concise access to heteroarene containing biaryl structures of substantial utility in the areas of pharmaceuticals and functional materials.



Scheme I.6.3.1.2. *Copper(II)-mediated direct biaryl coupling of arylazines and azoles*

➢ **C(sp^2)–C(sp^2)-(alkenyl) Bond formation**

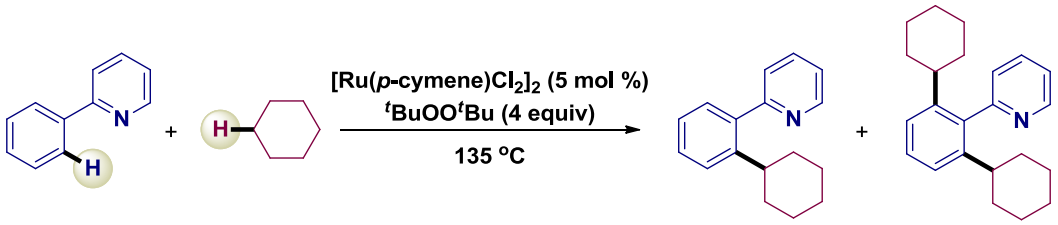
Yu group developed an improved protocol for aerobic Pd(II)-catalyzed C–H olefination of phenylacetic acid substrates using a novel ligand, Ac-Val-OH, which is capable of accelerating the reaction (Scheme I.6.3.1.3).[54]



Scheme I.6.3.1.3. *Palladium(II)-catalyzed C–H olefination of phenylacetic acid*

➢ **C(sp^2)–C(sp^3) Bond formation**

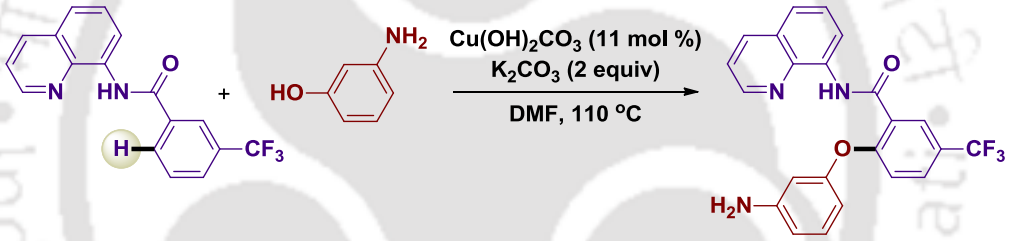
Li group demonstrated a novel protocol on Ru-catalyzed substrate directed arene–alkane coupling of 2-arylpyridine or analogous substrates by using un-reactive cycloalkane as the other coupling (Scheme I.6.3.1.4).[55]



Scheme I.6.3.1.4. *Ruthenium(II)-catalyzed C–H cycloalkylation of 2-phenylpyridine*

- **C(sp^2)–O Bond formation**

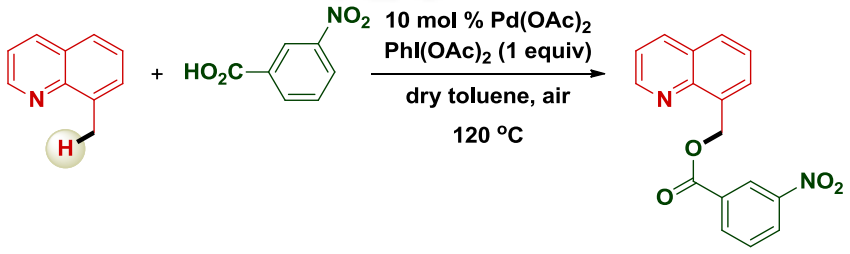
Daugulis group developed a method for direct, auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of amine derivatives (Scheme I.6.3.1.5).[56] The reaction employs $CuCO_3.Cu(OH)_2$ catalyst, air as the oxidant, phenol or alcohol as coupling partners, DMF, pyridine, or DMPU as solvent, and K_2CO_3, tetramethylguanidine, or K_3PO_4 base at 70–130 °C.



Scheme I.6.3.1.5. *Copper(II)-catalyzed auxillary assisted C–H alkoxylation*

- **C(sp^3)–O Bond formation**

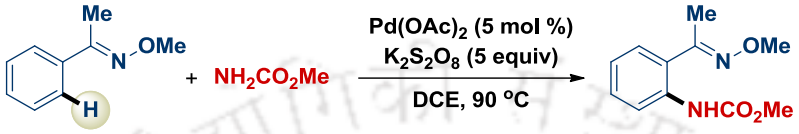
Cheng group described a chelation-assisted palladium-catalyzed acyloxylation of the sp^3 C–H bond of benzyl group with carboxylic acid employing $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme I.6.3.1.6).[57] The procedure tolerates a series of functional groups, providing the acyloxylated products in moderate to good yields.



Scheme I.6.3.1.6. *Palladium(II)-catalyzed acyloxylation of the benzylic sp^3 C–H bond*

➢ **C(sp^2)/C(sp^3)–N(amide) Bond formation**

Che group illustrated a Pd-catalyzed intermolecular directed C–H amidation via functionalization of sp^2 and sp^3 C–H bonds in pyridine and oxime ether substrates (Scheme I.6.3.1.7).[58] In this system, $Pd(OAc)_2$ served as the catalyst and a combination of $K_2S_2O_8$ and NH_2R was used to introduce the nitrogen functionality.



Scheme I.6.3.1.7. *Ketoxime ether directed palladium(II)-catalyzed amidation of arenes*

➢ **C(sp^2)–N-(amine) Bond formation**

In a recent report, Yu group demonstrated a Cu(II)-mediated C−H amination of arenes with a variety of anilines (Scheme I.6.3.1.8).[59] The exceptional compatibility of this amination with multiple heteroatoms present in both reactants renders this reaction highly valuable.

Scheme I.6.3.1.8. *Copper(II)-catalyzed amide directed amination of arenes*

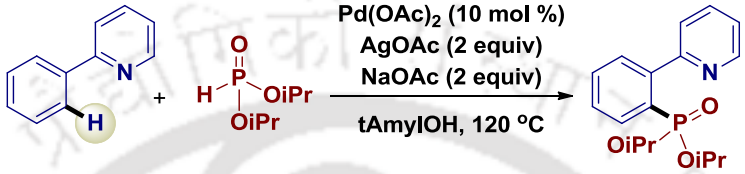
➢ **C(sp^2)–S Bond formation**

Yu group has accomplished a Cu(II)-catalyzed direct sulfenylation at sp^2 C–H of 2-arylpyridine using benzene thiol as the coupling partner (Scheme I.6.3.1.9).[26b]

Scheme I.6.3.1.9. *Copper(II)-catalyzed ortho-thiolation of arenes*

➢ **C(sp^2)–P Bond formation**

Yu group has also reported a Pd(II)-catalyzed C−H phosphorylation of 2-arylpyridines with both H-phosphonates and diaryl phosphine oxides as suitable coupling partners for this reaction (Scheme I.6.3.1.10).[60] A variety of heterocyclic substrates were phosphorylated to give N−P bisdentate compounds that are potentially useful in medicinal chemistry and catalysis.



Scheme I.6.3.1.10. *Palladium(II)-catalyzed C−H phosphorylation of 2-phenylpyridine*

I.7. C–H Activation: A new paradigm for total synthesis

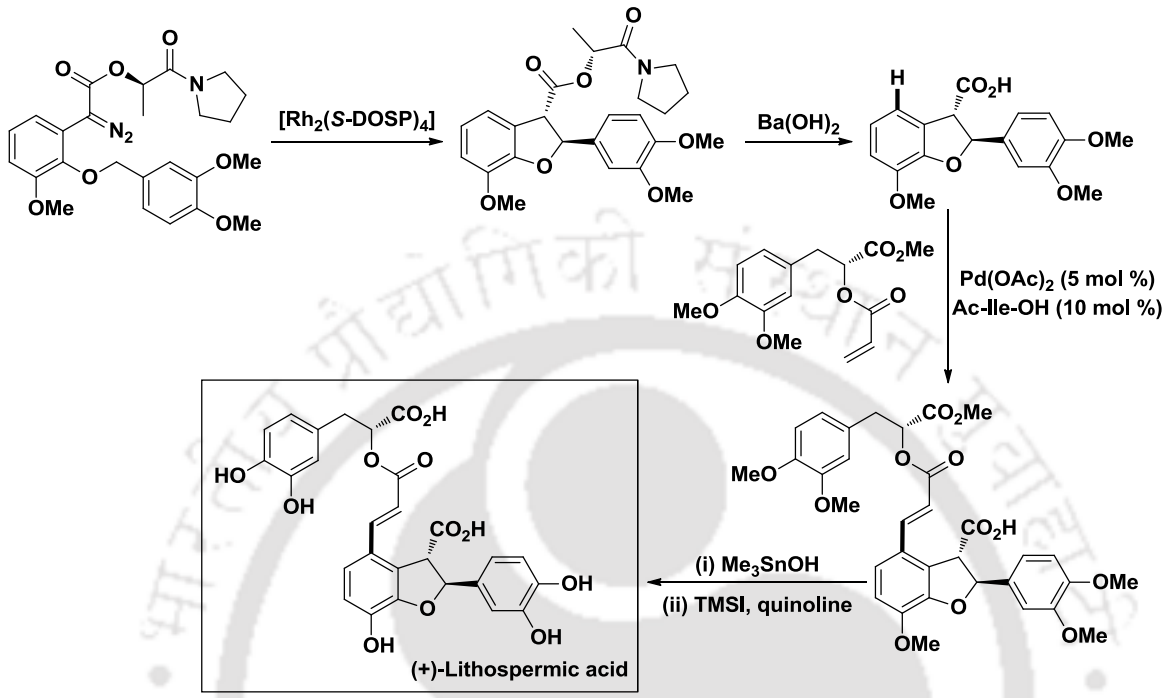
As a powerful testament of this emerging synthetic tool, applications of C–H activation in the context of total synthesis of complex natural products are beginning to blossom.[61] Herein mentioned below are two examples of total syntheses showcasing creative and ingenious incorporation of C–H activation as a strategic maneuver compared to the traditional methods, illuminating a new paradigm in strategic synthetic design.

I.7.1. Total synthesis of (+)-lithospermic acid

Lithospermic acid has been implicated as an active component in Danshen, one of the most popular traditional herbs used in the treatment of cardiovascular disorders, cerebrovascular diseases, various types of hepatitis, chronic renal failure, and dysmenorrheal. Recent studies have shown that (+)-lithospermic acid has potent and nontoxic anti-HIV activity.

Yu group reported a total synthesis of this important natural product which exploits two successive C–H activation reactions as key steps. Rh-catalyzed carbene C–H insertion reaction utilizing Davies's catalyst to forge dihydrobenzofuran core, and a late-stage Pd-catalyzed intermolecular C–H olefination coupled the olefin unit with the dihydrobenzofuran core to construct the molecule in a highly convergent manner (Scheme

I.7.1.1).[62] The intermolecular C–H olefination reaction was accelerated by the amino acid ligand Ac-Ile-OH, the most sophisticated application to date of arene C–H olefination.

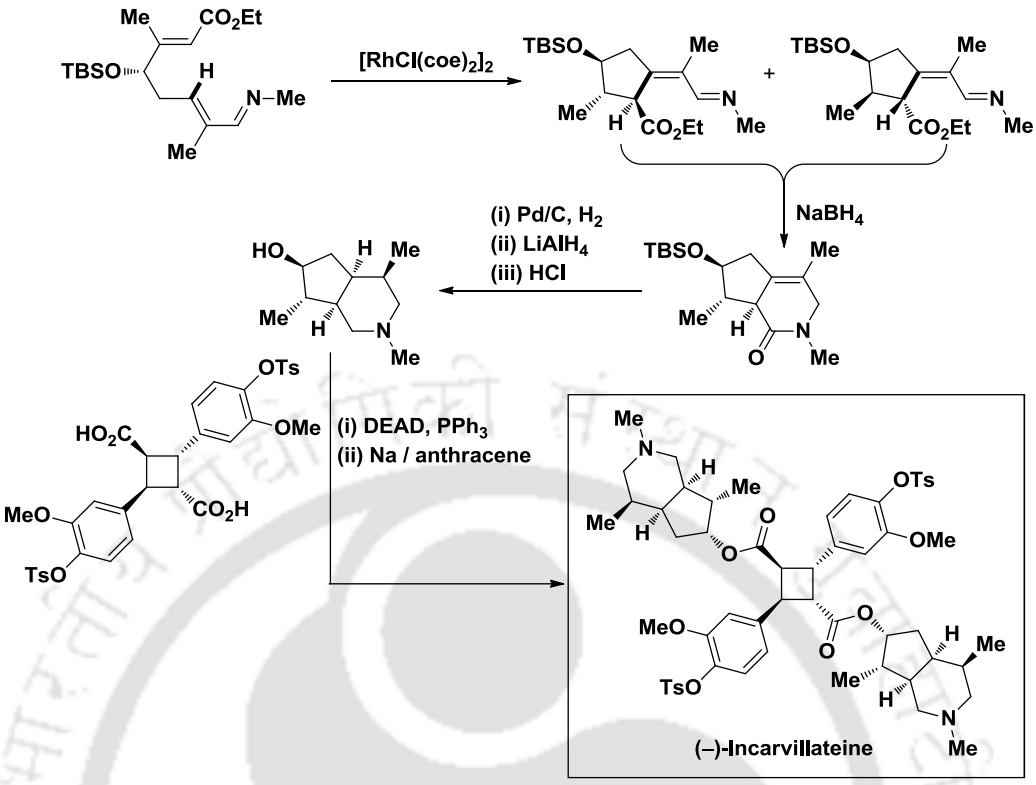


Scheme I.7.1.1. *Total synthesis of (+)-lithospermic acid*

I.7.2. Total synthesis of (–)-incarvillateine

(–)-Incarvillateine is a structurally unusual cyclobutane containing monoterpene alkaloid found to exhibit potent analgesic properties. The antinociceptive property of incarvillateine observed in formalin-induced pain model in mice indicated a partial interaction with the opioid receptor, and the cyclobutane moiety was suggested to be an important pharmacophore.

Bergman and Ellman reported a concise asymmetric synthesis of (–)-incarvillateine employing an intramolecular alkylation of an olefinic C–H bond to set two of the stereocenters with simultaneous stereospecific introduction of an exocyclic, tetrasubstituted alkene framework upon which the bicyclic piperidine could rapidly be assembled (Scheme I.7.2.1).[63] Mechanistically, α,β-unsaturated imine first undergoes a Rh-catalyzed C–H activation under a set of carefully defined reaction conditions to afford the intermediate metallocycle which proceeds to give the exocyclic compound.



Scheme I.7.2.1. *Total synthesis of (–)-incarvillateine*

I.8. References

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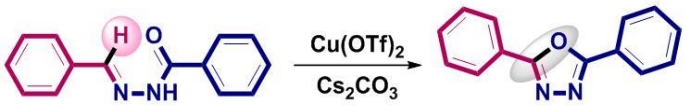
Chapter II

Copper(II) Catalyzed Imine C–H Functionalization Leading to Synthesis of 2,5-Substituted-1,3,4-Oxadiazoles



- one C–H bond cleavage
- intramolecular C–O bond formation
- mild reaction conditions

Abstract: *A direct access to symmetrical and unsymmetrical 2,5-disubstituted [1,3,4]-oxadiazoles has been accomplished through an imine C–H functionalization of N-arylidenearoylhydrazide using a catalytic quantity of $Cu(OTf)_2$. This is the first example of amidic oxygen functioning as a nucleophile in a Cu-catalyzed oxidative coupling of an imine C–H bond. These reactions can be performed in air atmosphere and moisture making it exceptionally practical for application in organic synthesis.*

CHAPTER II

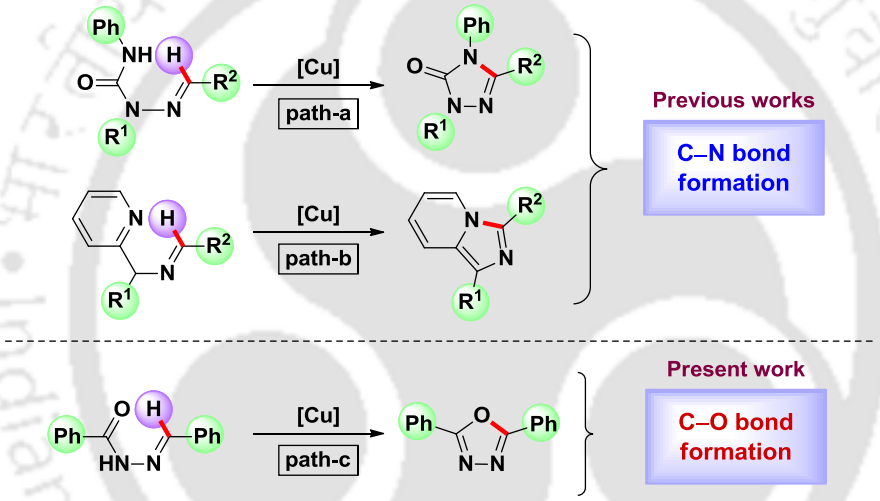
II. Copper(II) Catalyzed Imine C–H Functionalization Leading to Synthesis of 2,5-Substituted-1,3,4-Oxadiazoles

II.1. Introduction

Of late the transition metal catalyzed direct functionalizations of ubiquitous C–H bonds have attracted much attention due to operational simplicity and avoidance of the arduous substrate pre-activation steps.[1] These advantages have brought about atom and step-economy by streamlining the overall processes. In fact the great advances made in this field have led to the organic C–H bonds viewed as dormant synthetic equivalents of many reactive functional groups. In this context, however the vast majority of the focuses has been directed toward the transition metal catalyzed functionalization of the sp^2 C–H bonds of arenes and heteroarenes;[1] in contrast the functionalization of an imine C(sp^2)–H bond is relatively rare.[2] The imine containing precursors have mostly been utilized toward transition metal catalyzed addition reactions across a polar imine C–N bond. Some examples pertaining to addition reactions are, a Pd catalyzed addition of 2-methyl aza-arenes to imines,[3a] benzyl nitriles with sulfonylimines,[3b,c] rhodium catalyzed oxidative coupling of aromatic imines with alkynes,[3d] and 2-arylpyridines.[3e] In other cases substrates possessing imine functionality have been observed to undergo skeletal rearrangement[4a-c] or utilize the proximate effect of coordination to the metal centre which serves as a directing group toward sp^2 and sp^3 C–H bond activation.[4d-f]

Pertinent to imine C(sp^2)–H functionalizations, Ellman group has demonstrated a copper catalyzed arylation (C–C bond formation) at the imine C(sp^2)–H bond of benzotriazepines.[5] Noto *et al.* described a copper catalyzed synthesis of 1,2,4-triazoles from benzaldehyde semicarbazones via an oxidative C–N bond formation at the imine C(sp^2)–H (path-a, Scheme II.1.1).[6] An analogous copper catalyzed oxidative C–N bond forming protocol was subsequently reported by Döring and co-workers for the synthesis of heterobicycles from various Schiff bases (path-b, Scheme II.1.1).[7] Barring these examples

on C–C and C–N bond formations via functionalizations of C(sp^2)–H of imine there was no report on similar C–O bond formation. Inspired by these developments on imine C(sp^2)–H bond functionalizations particularly using copper catalyst, we anticipated that a copper based strategy could be applied to construct 2,5-disubstitued-1,3,4-oxadiazole from *N*-aryl-*N*-arylidinehydrazines via intramolecular C–O bond formation at the imine C–H bond (path-c, Scheme II.1.1). It may be mentioned here that there are few examples of amidic oxygen functioning as nucleophile in copper catalyzed oxidative C–O bond formation at sp^2 C–H of arenes,[8] but no precedence of it in catalytic oxidative coupling reactions involving imine C–H bonds.



Scheme II.1.1. *Copper catalyzed heterocyclization via imine C–H bond functionalizations*

II.2. Strategies for the synthesis of 2,5-substituted-1,3,4-oxadiazoles

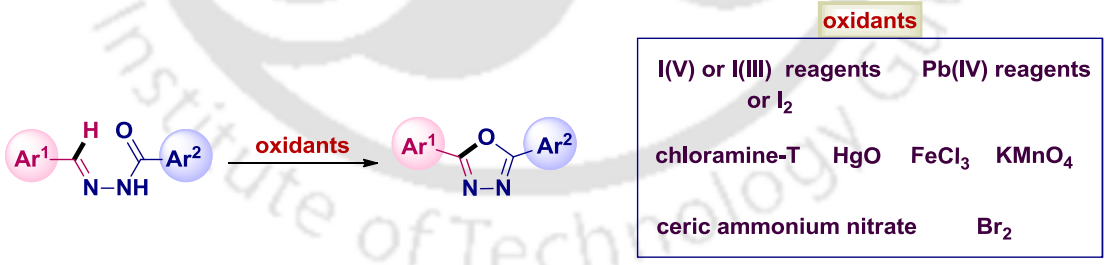
The π-conjugated heterocycles comprise an important structures class as they find applications in the field of material science and pharmaceutical chemistry. Amongst them, the 2,5-disubstituted-1,3,4-oxadiazole motifs are of considerable importance primarily due to their unique optoelectronic properties that are being exploited in the development of organic light emitting diodes (OLEDS) and utilized in energy efficient, full-color, flat-panel displays.[9] Certain suitably conjugated oxadiazoles are also known to perform as multiphoton absorbing systems.[9b] Besides their electronic properties, these scaffolds

encompass a wide range of biological properties that make them particularly attractive in the field of organic synthesis.[10]

A myriad of applications of the 1,3,4-oxadiazole motif have resulted to them being encountered through the development of various protocols. Several methodologies are documented in the literature for their synthesis, which can be categorized into three main strategies: (i) oxidative cyclization of *N*-acylhydrazones; (ii) cyclo-dehydration of 1,2-diacylhydrazines; and (iii) C–H activation. In most of the methodologies, the former two strategies are employed, while there is only a single precedence of the latter strategy.

(i) Oxidative cyclization of *N*-acylhydrazones

Oxidative cyclization of *N*-acylhydrazones to 2,5-disubstituted-1,3,4-oxadiazoles are carried out with various oxidizing agents such as hypervalent iodines,[11a-e] chloramine T,[11f] ceric ammonium nitrate (CAN),[11g] $FeCl_3$,[11h] tetravalent lead reagents,[11i,j] Br_2,[11k] $KMnO_4$,[11l] or HgO[11m] (Scheme II.2.1). However most of them suffer a major setback from the standpoint of environmental concerns as they involve the use of stoichiometric amount of oxidants, harsh conditions and the use of toxic and corrosive reagents. Recently our group has developed a more sustainable synthesis of 2,5-disubstituted-1,3,4-oxadiazoles that uses a catalytic quantity of molecular iodine and oxidant aqueous hydrogen peroxide to promote the oxidative cyclization.[11n] A similar methodology has also been reported by Chang's group where they have used iodine in stoichiometric quantity.[11o]

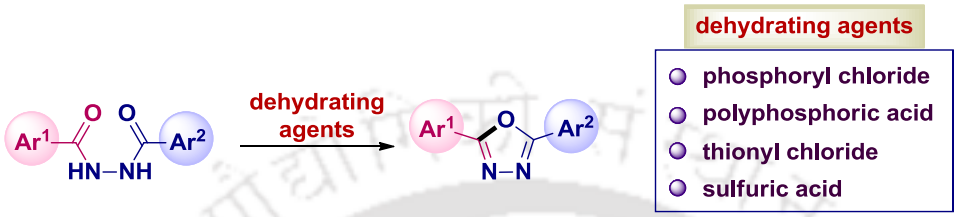


Scheme II.2.1. *Synthesis of 1,3,4-oxadiazoles by oxidative cyclization*

(ii) Cyclo-dehydration of 1,2-diacylhydrazines

A dehydrative cyclization of 1,2-diacylhydrazines to 2,5-disubstituted-1,3,4-oxadiazoles is mediated typically by dehydrating agents such as thionyl chloride, polyphosphoric acid, phosphorus oxychloride or sulfuric acid (Scheme II.2.2).[12] The use of strong acidic conditions and toxic reagents make these protocols incompatible with various

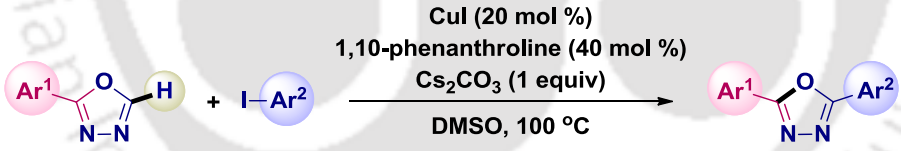
functional groups and thus impedes the substrate scope. In certain processes, instead of using presynthesized 1,2-diacylhydrazines, it is generated *in situ* in the reaction medium by direct reaction of carboxylic acids or acyl chlorides with acid hydrazides or hydrazines which subsequently undergo cyclo-dehydration promoted by various reagents to afford 2,5-disubstituted-1,3,4-oxadiazoles.[13]



Scheme II.2.2. *Synthesis of 1,3,4-oxadiazoles via cyclo-dehydration*

(iii) C–H activation

Miura's group has developed a Cu(I) promoted C–H arylation of a preformed 2-substituted-1,3,4-oxadiazoles with aryl iodides for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (Scheme II.2.3).[14] Although this strategy via copper catalyzed C–H activation seems advantageous, but it uses preformed 2-substituted-1,3,4-oxadiazoles as precursors which in turn is difficult to prepare.

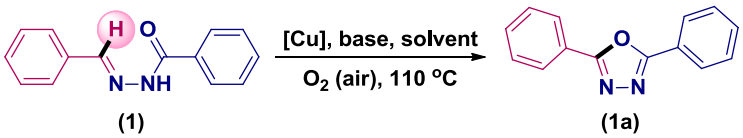


Scheme II.2.3. *Synthesis of 1,3,4-oxadiazoles via C–H activation*

II.3. Present work

The disadvantages associated with the aforementioned methodologies, owing to the use of expensive, hazardous materials or cumbersome multi-stepped processes bind them to limited synthetic scope. Thus in an attempt to obliterate the limitations of these methods, herein, we report the development of a straightforward and versatile protocol for the Cu(II) catalyzed oxidative C–H bond functionalization/C–O bond formation of imines from *N*-arylidenearoylhydrazide derivatives to afford various 2,5-disubstituted-1,3,4-oxadiazoles.

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



(1) (1a)

Entry	Catalyst (mol %)	Base	Solvent	Time (h)	Yield (%)
1	$Cu(OTf)_2$ (10)	Cs_2CO_3	DMSO	36	20
2	$Cu(OTf)_2$ (10)	Cs_2CO_3	Toluene	36	12
3	$Cu(OTf)_2$ (10)	Cs_2CO_3	Dioxane	36	30
4	$Cu(OTf)_2$ (10)	Cs_2CO_3	CH_3CN	36	10
5	**$Cu(OTf)_2$ (10)**	**Cs_2CO_3**	**DMF**	**16**	**85**
6	$Cu(OTf)_2$ (10)	K_2CO_3	DMF	16	63
7	$CuSO_4.5H_2O$ (10)	Cs_2CO_3	DMF	16	55
8	$Cu(OAc)_2$ (10)	Cs_2CO_3	DMF	16	40
9	$CuCl_2$.(10)	Cs_2CO_3	DMF	16	65
10	$CuBr_2$.(10)	Cs_2CO_3	DMF	16	68
11	CuCl (10)	Cs_2CO_3	DMF	16	32
12	CuBr (10)	Cs_2CO_3	DMF	16	25
13	CuI.(10)	Cs_2CO_3	DMF	16	08
14	$Cu(OTf)_2$ (5)	Cs_2CO_3	DMF	16	71
15	$Cu(OTf)_2$ (20)	Cs_2CO_3	DMF	16	87
16	$Cu(OTf)_2$ (10)	Nil	DMF	16	00
17	Nil	Cs_2CO_3	DMF	16	00

[a]Reaction conditions: *N*-benzylidenebenzohydrazide (**1**) (1 mmol), base (1 equiv), solvent (2 mL) at 110 °C in an air atmosphere. [b]Isolated yield.

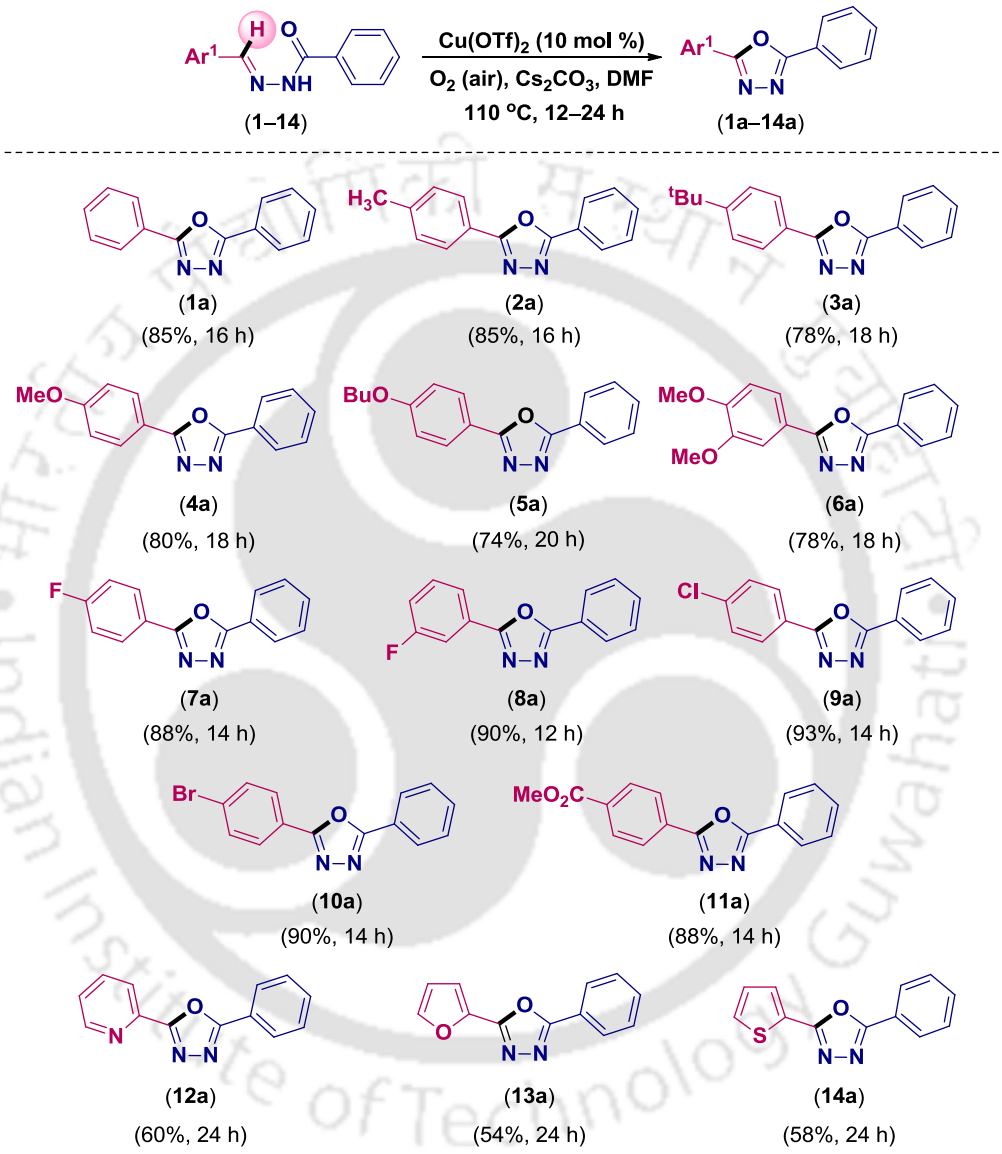
Optimization of reaction conditions. To develop the idea of intramolecular C–O bond formation, an initial reaction was attempted for the cyclization of *N*-benzylidenebenzohydrazide (**1**) as the model substrate in the presence of catalytic quantity of $Cu(OTf)_2$ (10 mol %) and Cs_2CO_3 (1 equiv) as the base at 110 °C in DMSO solvent. The reaction afforded the desired cyclized product, 2,5-diphenyl-1,3,4-oxadiazole (**1a**) in a mere yield of 20% after 36 h (Table II.3.1, entry 1). In pursuit to attain a suitable reaction condition for this transformation various reaction parameters such as solvents, base and reaction temperature were screened. When the reaction was performed in other solvents such as toluene, dioxane and acetonitrile the yield of the product (**1a**) was unsatisfactory even after 36 h (Table II.3.1, entries 2–4). However when the same reaction was carried out in DMF solvent, a vast improvement in the yield (85%) of (**1a**) was observed in a shorter reaction time of 16 h (Table II.3.1, entry 5). With DMF as the solvent of choice, variations in bases and catalysts were made to achieve the maximum possible yield. The

use of K_2CO_3 in replacement of Cs_2CO_3 was not that effective as the yield of (**1a**) dropped by 22% (Table II.3.1, entry 6). Other copper(II) [$CuSO_4.5H_2O$, $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$] (Table II.3.1, entries 7–10) and copper(I) [CuCl, CuBr, CuI] (Table II.3.1, entries 11–13) sources tested afforded inferior results revealing $Cu(OTf)_2$ (Table II.3.1, entry 5) as the most effective catalyst for the present transformation. A decrease in the catalyst loading (5 mol %) had an adverse effect on the product yield while its increase (20 mol %) provided a marginal improvement by 2% (Table II.3.1, entries 14–15). No product was obtained either in the absence of catalyst or base which suggests that metal/base combination is required for the reaction to occur (Table II.3.1, entries 16–17). After a series of experimentation the optimized reaction condition arrived was $Cu(OTf)_2$ (10 mol%), Cs_2CO_3 (1 equiv) at 110 ^oC in DMF solvent under an air atmosphere (O_2 as the terminal oxidant). Under all other conditions either substantial decomposition or multitudes of side products were observed.

Substrate scope for 2,5-substituted-1,3,4-oxadiazoles. Having the above optimized conditions in hand various *N*-arylidenebenzohydrazides, derived by condensation of benzohydrazide and substituted aldehydes, were subjected to the present reaction conditions. As the results shown in Scheme II.3.1 attests, this methodology is compatible with a variety of electron-donating and electron-withdrawing groups. *N*-Arylidenebenzohydrazides derived from arylaldehydes possessing electron-donating groups such as –Me, –^{t}Bu, –OMe, –OBu, *di*-OMe all gave substituted 1,3,4-oxadiazoles (**2a**), (**3a**), (**4a**), (**5a**) and (**6a**) in good yields (Scheme II.3.1). Similarly substrates possessing electron-withdrawing groups such as –F, –Cl, –Br, –CO_2Me underwent C–H functionalization to give 1,3,4-oxadiazoles (**7a**), (**8a**), (**9a**), (**10a**), and (**11a**) in excellent yields. As can be seen from Scheme II.3.1, compared to substrates bearing electron-donating groups, electron-withdrawing substrates gave better yields. Benzohydrazide substrates originating from heterocyclic aldehydes such as pyridine, furan and thiophene gave poorer yields of the products (**12a**), (**13a**) and (**14a**). However, *N*-benzoylhydrazone derived from aliphatic aldehydes such as butyraldehyde failed to give any traces of the desired product. The substrate decomposed to aldehyde along with several other inseparable products. The failure of this reaction could be attributed to two factors; (i) it is possible that the imine bond can enolize; thus converting *N*-benzoylhydrazone to its corresponding enamine under the reaction conditions which inhibits the oxidative

cyclization and (ii) the lesser acidic character of the imine C–H bonds could be another possible reason judging from the reactivity trends for substituted aromatics.

Scheme II.3.1. *Substrate scope for 1,3,4-oxadiazoles varying aldehydes*[a,b]

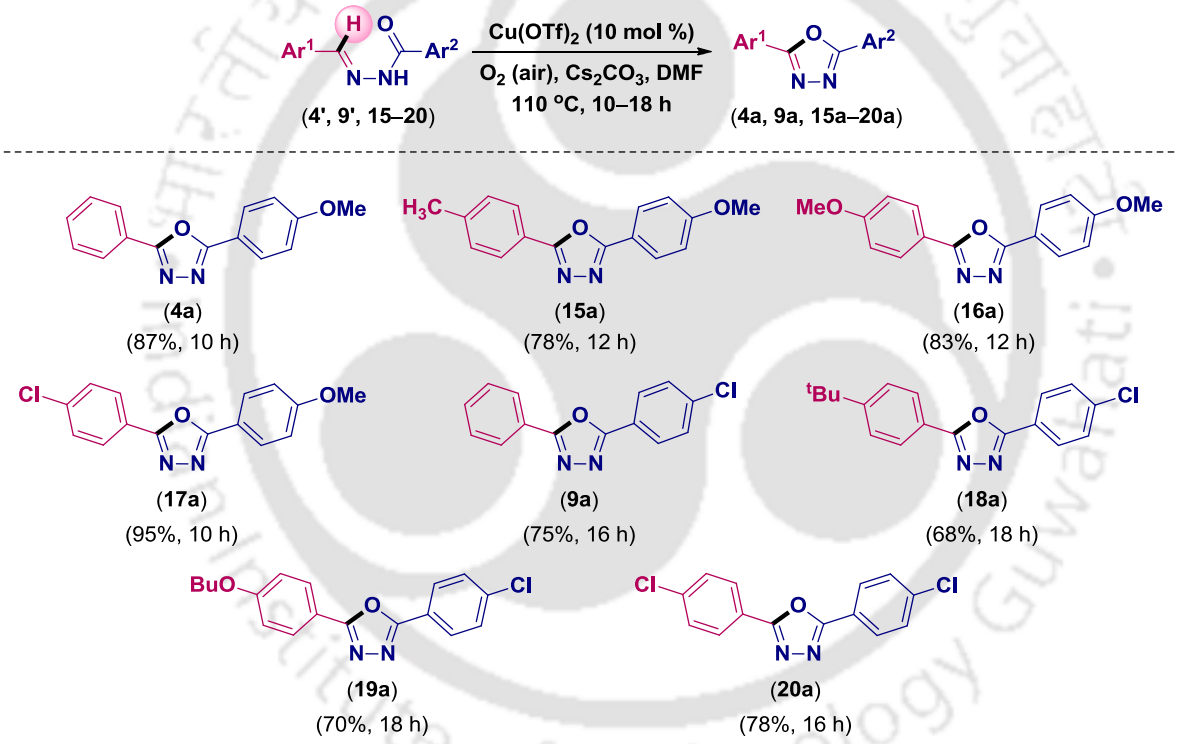


[a]Reaction conditions: *N*-arylidenebenzohydrazide (**1**–**14**) (1 mmol), $Cu(OTf)_2$ (10 mol %), Cs_2CO_3 (1 equiv), DMF (2 mL) at 110 °C in an air atmosphere. [b]Isolated yield.

Besides *N*-arylidenebenzohydrazides, other hydrazides such as *N′*-arylidene-4-methoxybenzohydrazides reacted with equal efficiency giving substituted oxadiazoles (**4a**), (**15a**), (**16a**) and (**17a**) in good to excellent yields (Scheme II.3.2). Similarly *N′*-arylidene-4-chlorobenzohydrazides underwent reaction smoothly to afford the corresponding

symmetrical and unsymmetrical oxadiazoles (**9a**), (**18a**), (**19a**) and (**20a**) (Scheme II.3.2) but in a slightly moderate yields compared to the methoxy analogue. A comparative study of the unsubstituted (**1a**), 4–OMe (**4a**) and 4–Cl (**9a**) substrates on the aroylhydrazide part suggest the reaction to be superior for the methoxy substrate (**4a)** (Scheme II.3.2) followed by unsubstituted (**1a**) (Scheme II.3.1) and chloro (**9a**) analogues (Scheme II.3.2) in terms of yields and enhanced reaction rates. Also it was observed that electron-withdrawing substituents on the arylaldehydes improved the yields as in the case (**7a**–**11a**) (Scheme II.3.1) probably through an increment in the acidity of the imine proton.

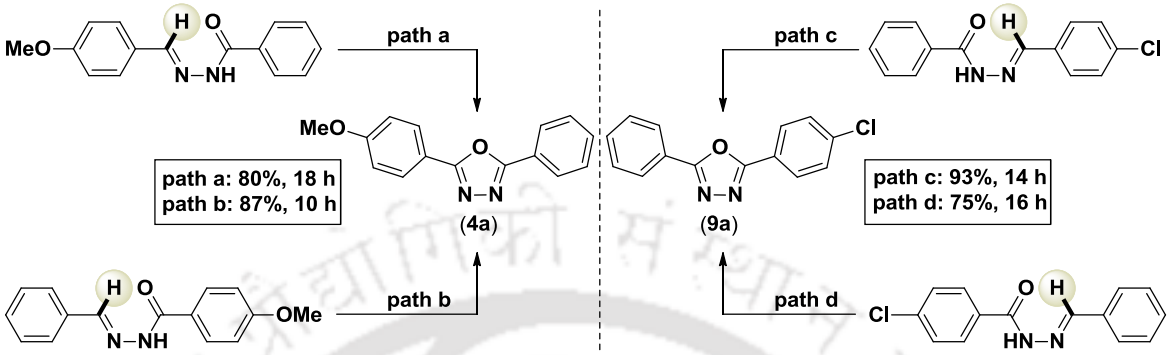
Scheme II.3.2. *Substrate scope for 1,3,4-oxadiazoles varying hydrazides*[a,b]



[a]Reaction conditions: *N*-arylidenebenzohydrazide (**15**–**20**) (1 mmol), $Cu(OTf)_2$ (10 mol %), Cs_2CO_3 (1 equiv), DMF (2 mL) at 110 °C in an air atmosphere. [b]Isolated yield.

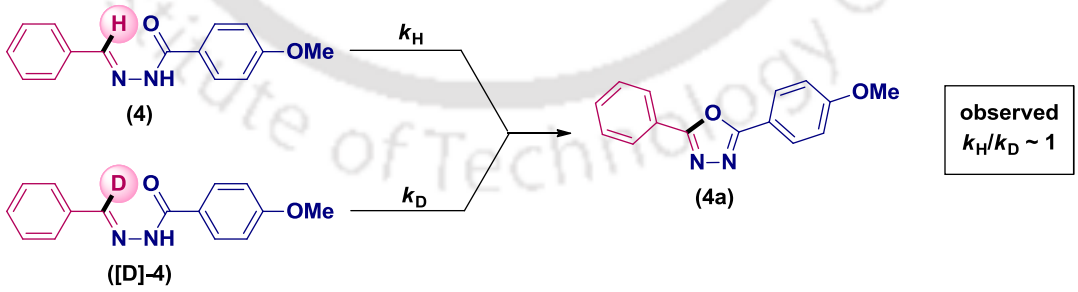
It is interesting to mention here that both *N′*-(4-methoxybenzylidene)benzohydrazide (path-a, Scheme II.3.3) and *N′*-benzylidene-4-methoxybenzohydrazide (path-b, Scheme II.3.3) gave 2-(4-methoxyphenyl)-5-phenyl-1,3,5-oxadiazole (**4a**). The yield was superior by the later approach. Similarly, product (**9a**) can be obtained from either *N′*-4-chlorobenzylidene)benzohydrazide (path-c, Scheme II.3.3) or *N′*-benzylidene-4-

chlorobenzohydrazide (path-d, Scheme II.3.3) but for this the former approach is better in terms of yield and reaction time.



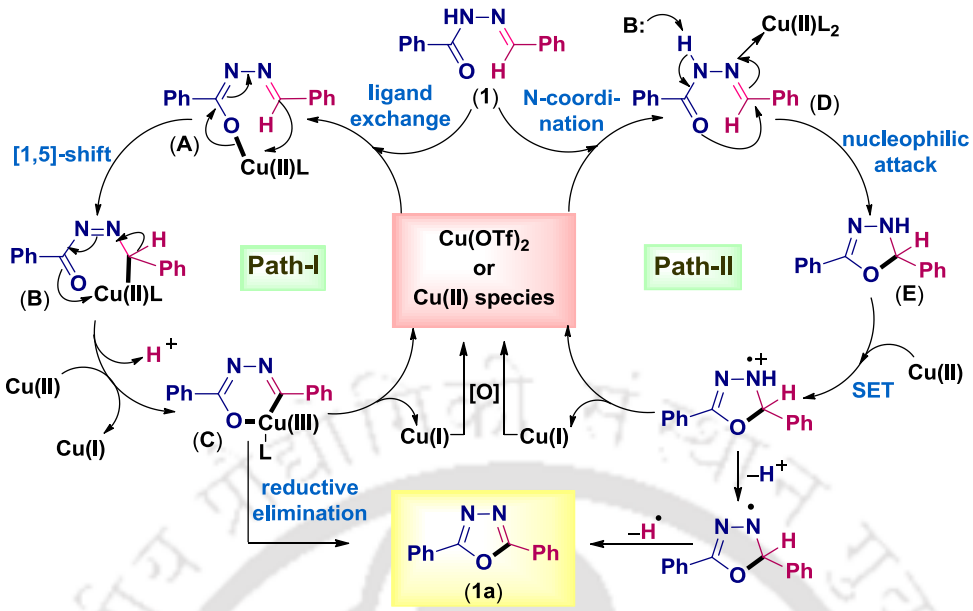
Scheme II.3.3. *Dual routes for the formation of 1,3,4-oxadiazoles (**4a**) and (**9a**)*

Mechanistic Studies. It can be noticed from the reactivity trends of the substrates that an electron-donating substituent in the hydrazide part and an electron-withdrawing substituent in the aldehyde part gave higher yields of the products in shorter reaction time. These observations entail that the electronic effects of the substituents in the hydrazide part and the acidity of the imine hydrogen, which in turn depends on the nature of the substituents in the aldehyde part, govern the yields as well as the reaction times for this transformation. Also the result of kinetic isotope effect (KIE) studies (see Experimental Section II.4.3) suggests that the imine hydrogen abstraction step is not involved in the rate-limiting step (observed k_H/k_D~1) (Scheme II.3.4).



Scheme II.3.4. *Kinetic isotope effect studies*

Keeping in view the above observations and related literature reports, two kinds of mechanisms either of which might operate in this transformation. The first mechanism (Path-I, Scheme II.3.5) is similar to Nagasawa's synthesis of benzoxazoles via C–H functi-



Scheme II.3.5. *Plausible mechanism for Cu(II) catalyzed formation 2,5-substituted-1,3,4-oxadiazoles*

onalization,[8] where an electrophilic metalation process might be involved in the oxidative C–O coupling reaction. In the first step, copper center undergoes a complexation with the amidic oxygen of (**1**) giving rise to the intermediate (**A**). A possible [1,5]-shift of the copper center in second step results in the intermediate (**B**) where a C–Cu bond is formed. The oxidation of Cu(II) center in (**B**) to a Cu(III) species leads to the formation of a six-membered metallacycle (**C**). The loss of an electron from Cu(II) in (**B**) is probably taken up by another Cu(II) species in the medium, which in turn get reduced to Cu(I).[15] In the final step, the reductive elimination of Cu(III) from (**C**) and subsequent C–O bond formation gives the desired 2,5-diphenyl-1,3,4-oxadiazole (**1a**). The Cu(I) species generated in the reaction medium is re-oxidized in the presence of atmospheric oxygen to Cu(II) for the next catalytic cycle. The alternative mechanism for this transformation is based on the earlier works where analogous substrates had undergone copper catalyzed oxidative heterocyclization.[6,7] In this mechanism (Path-II, Scheme II.3.5), copper(II) first acts as a Lewis acid to coordinate with the imine nitrogen of (**1**) giving rise to intermediate (**D**). Such coordination facilitates a nucleophilic attack by amidic oxygen onto the imine carbon forming the amine intermediate (**E**). As copper(II) is an efficient oxidant of aliphatic amines,[16] it then serves to oxidize the resulting amine intermediate (**E**) through

either a one or two-electron process,[17] thereby providing 2,5-diphenyl-1,3,4-oxadiazole (**1a**). The fate of the Cu(I) species formed is the same as in the former mechanism.

In conclusion, we have for the first time developed a catalytic method for the synthesis of 2,5-disubstituted [1,3,4]-oxadiazoles via imine C–H functionalization of *N*-benzylidenebenzohydrazide. Low catalyst loading, ligand free conditions, inexpensive metal catalyst, performance under ordinary atmospheric conditions and compatibility with a wide range of substrates make this method a suitable alternative to the existing protocols.

II.4. Experimental section

II.4.1. General information. All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulphate. 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 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. The arylidenearoylhydrazides were prepared by the condensation of one equivalent of corresponding hydrazides and aldehydes in ethanolic medium under reflux condition for 2–6 h.

II.4.2. General procedure for the synthesis of 2,5-diphenyl-1,3,4-oxadiazole (1a). An oven-dried flask was charged with $Cu(OTf)_2$ (0.0362g, 0.10 mmol), Cs_2CO_3 (0.326 g, 1 mmol), *N*-benzylidenebenzohydrazide (**1**) (0.224 g, 1 mmol) and solvent DMF (2 mL). The flask was kept in a pre-heated oil bath at 110 ^oC. Heating was continued for 16 h, during which the consumption of the starting material was confirmed by TLC analysis. The reaction mixture was then cooled and admixed with water (5 mL). The mixture was extracted with ethyl acetate (2 x 15 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. Concentration in vacuo followed by silica gel column purification (EtOAc: Hexane as eluents) gave 2,5-diphenyl-1,3,4-oxadiazole (0.190 g, .85 mmol) in 85% yield. The identity and purity of the product were confirmed by spectroscopic

analysis. The same procedure was also followed for the synthesis of other 1,3,4-oxadiazoles.

II.4.3. Kinetic isotope effect studies. The kinetic isotope effect of the present transformation was studied taking (**4**) and its corresponding deuterated analogue (**[D]-4**) as the model substrates. During an ongoing cyclization reaction of (**4**) under the standard conditions, an aliquot from the reaction mixture was taken after 10 min and worked up in the usual procedure. The reaction mixture was then dried properly, and ^{1}HNMR was studied to get the ratio of –OC**H**$_3$ proton of the product (**4a**) against the –OCH$_3$ proton of the substrate (**4**). This process was repeated at an interval of 10 min for a total of 2 h of the reaction to get the ratio values at all time intervals. The same procedure was then applied to (*d*-**4**) and similarly the ratio of the –OCH$_3$ proton of the product (**4a**) against the –OCH$_3$ proton of the substrate (**[D]-4**) was calculated. The comparison of the ratio values obtained from (**4**) and (**[D]-4**) at the same time intervals showed the k_H/k_D~1 suggesting that the imine hydrogen abstraction step is not involved in the rate-limiting step.

II.5. References

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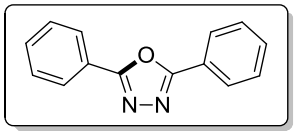
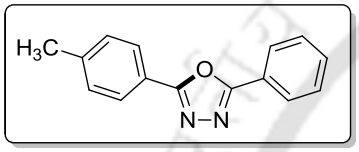
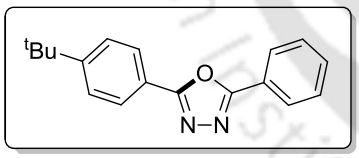
II.6. Spectral data



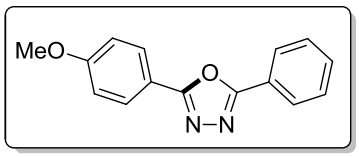
2,5-Diphenyl-1,3,4-oxadiazole (1a): M.p. 136–138 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53–7.55 (m, 6H), 8.13–8.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 124.1, 127.1, 129.3, 131.9, 164.8; IR (KBr): 3058, 2919, 1547, 1484, 1445, 1268, 1155, 1068, 1019, 964, 922, 782, 710, 686 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}N_2O$ (MH^+) 223.0866; found 223.0863.



2-Phenyl-5-*p*-tolyl-1,3,4-oxadiazole (2a): M.p. 121–122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 7.34 (d, 2H, *J* = 8.0 Hz), 7.53–7.56 (m, 3H), 8.04 (d, 2H, *J* = 8.0 Hz), 8.13–8.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 121.3, 124.2, 127.0, 129.2, 129.9, 131.8, 142.5, 164.5, 164.9; IR (KBr): 3060, 2919, 2852, 1610, 1581, 1550, 1496, 1486, 1445, 1271, 1173, 1076, 822, 728, 702, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}N_2O$ (MH^+) 237.1022; found 237.1020.

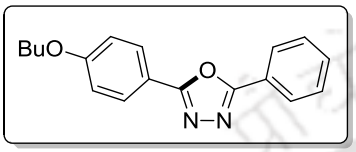


2-(4-*tert*-Butylphenyl)-5-phenyl-1,3,4-oxadiazole (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 9H), 7.50–7.54 (m, 5H), 8.05 (d, 2H, *J* = 8.4 Hz), 8.11–8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.2, 35.2, 121.2, 124.2, 126.1, 126.9, 127.0, 129.1, 131.7, 155.4, 164.5, 164.8; IR (KBr): 3066, 2962, 2869, 1615, 1550, 1494, 1449, 1363, 1269, 1066, 1016, 842, 714, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{18}N_2O$ (MH^+) 279.1492; found 279.1487.

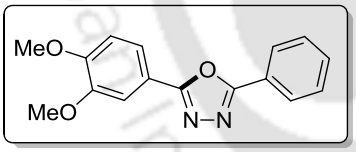


2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (4a): M.p. 149–150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 3H), 7.02 (d, 2H, *J* = 8.4 Hz), 7.52–7.53 (m, 3H),

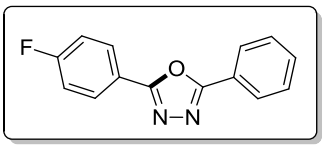
8.07 (d, 2H, *J* = 8.4 Hz), 8.11–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 114.7, 116.6, 124.2, 127.0, 128.9, 129.2, 131.7, 162.5, 164.3, 164.7; IR (KBr): 2956, 2923, 2848, 1616, 1503, 1262, 1066, 1017, 831, 737, 706, 684 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}N_2O_2$ (MH^+) 253.0972; found 253.0970.



2-(4-Butoxyphenyl)-5-phenyl-1,3,4-oxadiazole (5a) M.p. 111–112°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.99 (t, 3H, *J* = 7.2 Hz), 1.51 (sextet, 2H, *J* = 7.2 Hz), 1.80 (quin, 2H, *J* = 7.2 Hz), 4.03 (t, 2H, *J* = 6.4 Hz), 7.01 (d, 2H, *J* = 8.8 Hz), 7.51–7.53 (m, 3H), 8.05 (d, 2H, *J* = 8.8 Hz), 8.10–8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0, 19.4, 31.3, 68.1, 115.2, 116.3, 124.3, 127.0, 128.8, 129.2, 131.7, 162.2, 164.3, 164.8; IR (KBr): 3065, 2953, 2867, 1609, 1497, 1475, 1300, 1253, 1175, 1004, 837, 704, 686 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{18}N_2O_2$ (MH^+) 295.1441; found 295.1445.

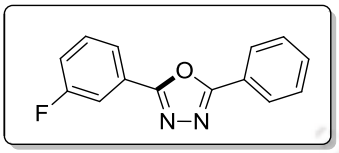


2-(3,4-Dimethoxyphenyl)-5-phenyl-1,3,4-oxadiazole (6a): M.p. 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.96 (s, 3H), 4.00 (s, 3H), 6.99 (d, 1H, *J* = 8.4 Hz), 7.53–7.55 (m, 3H), 7.65–7.71 (m, 2H), 8.12–8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 56.1, 56.2, 109.5, 111.2, 116.5, 120.5, 124.1, 126.9, 129.1, 131.7, 149.4, 152.1, 164.3, 164.6; IR (KBr): 3070, 2963, 2934, 2829, 1596, 1497, 1468, 1270, 1248, 1229, 1140, 1104, 1026, 802, 730, 719, 701, 688 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_3$ (MH^+) 283.1077; found 283.1077.

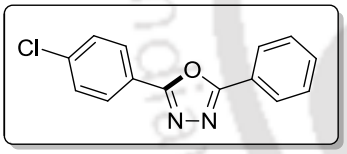


2-(4-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (7a): M.p. 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22–7.27 (m, 2H), 7.54–7.57 (m, 3H), 8.13–8.18 (m, 4H);

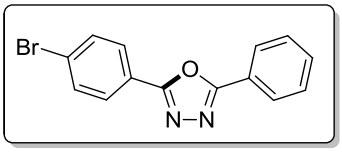
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 116.5, 116.7, 120.5, 124.0, 127.1, 129.28, 129.33, 129.4, 132.0, 163.7, 164.0, 164.8, 166.2; IR (KBr): 3061, 2921, 1606, 1549, 1496, 1221, 1149, 1069, 841, 733, 703, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9N_2OF$ (MH^+) 241.0772; found 241.0770.



2-(3-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (8a): M.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24–7.29 (m, 1H), 7.52–7.58 (m, 4H), 7.85 (d, 1H, *J* = 7.6 Hz), 7.95 (d, 1H, *J* = 7.6 Hz), 8.14–8.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 114.0, 114.2, 118.9, 119.1, 122.9, 123.8, 125.9, 126.0, 127.2, 129.3, 131.1, 131.2, 132.1, 161.8, 163.8, 164.3, 165.0; IR (KBr): 3081, 2928, 1547, 1465, 1454, 1445, 1272, 1204, 1068, 866, 804, 726, 688 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9N_2OF$ (MH^+) 241.0772; found 241.0772.

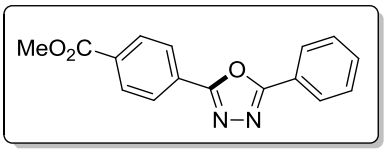


2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (9a): M.p. 161–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49–7.53 (m, 5H), 8.06 (d, 2H, *J* = 8.0 Hz), 8.11 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.6, 123.9, 127.2, 128.4, 129.3, 129.7, 132.1, 138.2, 164.0, 164.9; IR (KBr): 3061, 2920, 1605, 1550, 1478, 1406, 1086, 1074, 839, 730, 702, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9N_2OCl$ (MH^+) 257.0476; found: 257.0471.

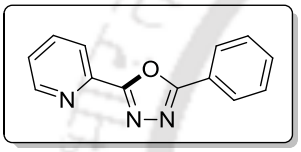


2-(4-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (10a): M.p. 169–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40–7.44 (m, 3H), 7.56 (d, 2H, *J* = 8.8 Hz), 7.88 (d, 2H, *J* = 8.8 Hz), 8.01 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.9, 123.8, 126.5, 127.1, 128.4, 129.2, 132.0, 132.5, 163.9, 164.8; IR (KBr): 3062, 2923, 2853, 1602, 1544, 1473, 1447, 1402, 1072, 1009, 728, 704, 689

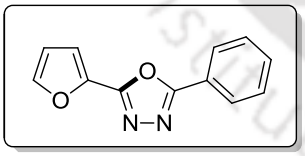
cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9N_2OBr$ (MH^+) 300.9971; found 300.9965.



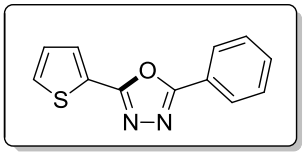
Methyl-4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzoate (11a): M.p. 161–162 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.97 (s, 3H), 7.55–7.57 (m, 2H), 8.15–8.17 (m, 2H), 8.21 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 52.7, 123.9, 127.0, 127.3, 127.9, 129.4, 130.5, 132.2, 133.0, 164.0, 165.3, 166.3; IR (KBr): 3063, 2923, 2852, 1719, 1546, 1278, 1104, 1015, 717, 686 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O_3$ (MH^+) 281.0921; found 281.0920.



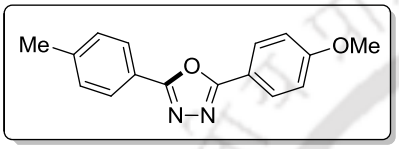
2-Phenyl-5-(pyridine-2-yl)-1,3,4-oxadiazole (12a): M.p. 110–112 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44–7.54 (m, 4H), 7.90 (t, 1H, *J* = 10.4), 8.21 (d, 2H, *J* = 8.8 Hz), 8.31 (d, 1H, *J* = 10.4 Hz), 8.81 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.5, 123.8, 126.0, 127.5, 129.2, 132.2, 137.4, 143.9, 150.5, 164.1, 165.8; IR (KBr): 3053, 2963, 2917, 1585, 1547, 1449, 1261, 1091, 1070, 1024, 795, 715, 686 cm^{-1}; Anal calcd. for $C_{13}H_9N_3O$: C 69.95, H 4.06, N 18.82; found C 69.91, H 4.08, N 18.76.



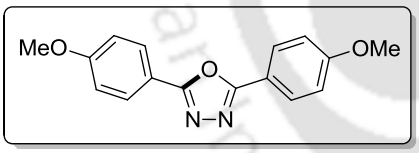
2-(Furan-2-yl)-5-phenyl-1,3,4-oxadiazole (13a): M.p. 98–100 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.63–6.64 (m, 1H), 7.24 (d, 1H, *J* = 3.6 Hz), 7.53–7.55 (m, 3H), 7.68 (s, 1H), 8.13 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 112.4, 114.3, 123.7, 127.2, 129.3, 132.1, 139.7, 145.9, 157.1, 164.3; IR (KBr): 3142, 2962, 2924, 1633, 1555, 1519, 1490, 1450, 1290, 1173, 1083, 1014, 898, 777, 764, 724, 688 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_8N_2O_2$ (MH^+) 213.0659; found 213.0653.



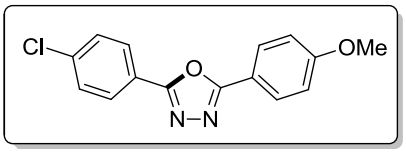
2-Phenyl-5-(thiophen-2-yl)-1,3,4-oxadiazole (14a): M.p. 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21 (m, 1H), 7.55–7.59 (m, 4H), 7.85 (m, 1H), 8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.9, 125.4, 127.2, 128.4, 129.3, 130.0, 130.4, 132.0, 161.1, 164.2; IR (KBr): 3101, 2923, 2852, 1584, 1550, 1485, 1447, 1058, 1023, 852, 776, 718, 687 cm^{-1}; Anal calcd. for $C_{12}H_8N_2OS$: C 63.14, H 3.53, N 12.27; found C 63.19, H 3.46, N 12.20.



2-(4-Methoxyphenyl)-5-*p*-tolyl-1,3,4-oxadiazole (15a): M.p. 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.87 (s, 3H), 7.01 (d, 2H, *J* = 11.6 Hz), 7.31 (d, 2H, *J* = 10.4 Hz), 7.98–8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 55.6, 114.7, 116.7, 121.5, 127.0, 128.8, 129.9, 142.2, 162.4, 164.5; IR (KBr): 2928, 2829, 1612, 1492, 1304, 1254, 1170, 1033, 835, 822, 744 cm^{-1}; Anal calcd. for $C_{16}H_{14}N_2O_2$: C 72.16, H 5.30, N 10.52; found C 72.24, H 5.33, N 10.47.

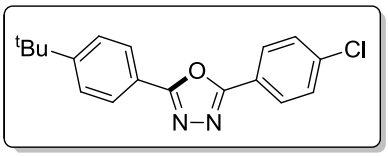


2,5-Bis(4-methoxyphenyl)-1,3,4-oxadiazole (16a): M.p. 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.85 (s, 6H), 6.99 (d, 4H, *J* = 11.6 Hz), 8.02 (d, 4H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 114.5, 116.6, 128.6, 162.3, 164.1; IR (KBr): 2939, 2833, 1611, 1492, 1303, 1255, 1170, 1021, 834, 745 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_3$ (MH^+) 283.1077; found:283.1074.

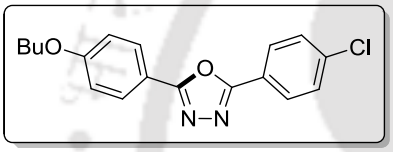


2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (17a): M.p. 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.85 (s, 3H), 6.99 (d, 2H, *J* = 11.6 Hz), 7.46 (d, 2H, *J* = 11.2 Hz), 8.01 (d, 4H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 114.7, 116.3, 122.6, 128.2, 128.8, 129.5, 137.9, 162.6, 163.4, 164.8; IR

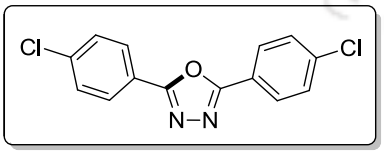
(KBr): 2929, 2829, 1611, 1495, 1479, 1305, 1252, 1170, 1089, 1028, 834, 743 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{11}N_2O_2Cl$ (MH^+) 287.0582; found 287.0582.



2-(4-*tert*-Butylphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (18a): M.p. 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.29 (s, 9H), 7.49–7.56 (m, 4H), 8.03–8.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.3, 35.3, 121.1, 122.7, 126.3, 127.0, 128.3, 129.6, 138.1, 155.7, 163.7, 165.0; IR (KBr): 3085, 2960, 2865, 1604, 1496, 1482, 1268, 1091, 843, 831, 727 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}N_2OCl$ (MH^+) 313.7934; found 313.7940.



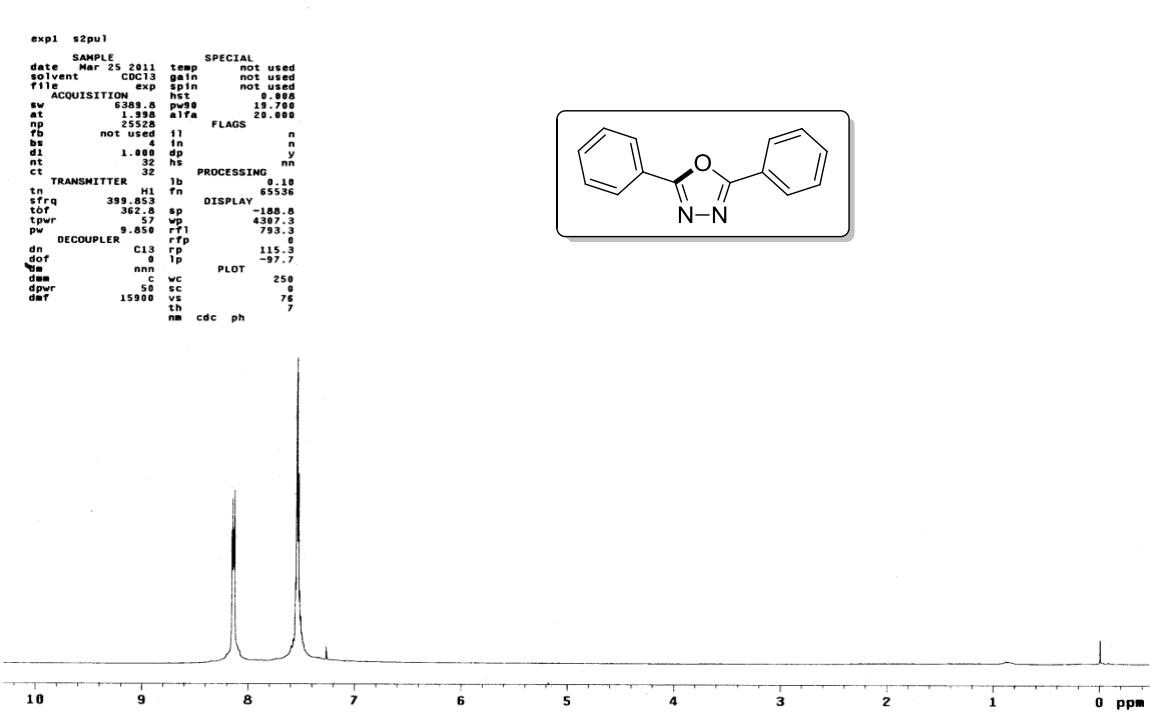
2-(4-Butoxyphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (19a): M.p. 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.00 (t, 3H, *J* = 9.6 Hz), 1.50–1.56 (m, 2H), 1.78–1.83 (m, 2H), 4.04 (t, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 11.6 Hz), 7.50 (d, 2H, *J* = 11.2 Hz), 8.03–8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0, 19.4, 31.3, 68.2, 115.2, 116.1, 122.8, 128.2, 128.9, 129.6, 137.9, 162.3, 163.4, 164.9; IR (KBr): 3082, 2957, 2872, 1612, 1492, 1483, 1254, 1177, 1088, 1008, 839, 740 cm^{-1}; Anal calcd. for $C_{18}H_{17}N_2O_2Cl$: C 65.75, H 5.21, N 8.52; found C 65.79, H 5.23, N 8.48.



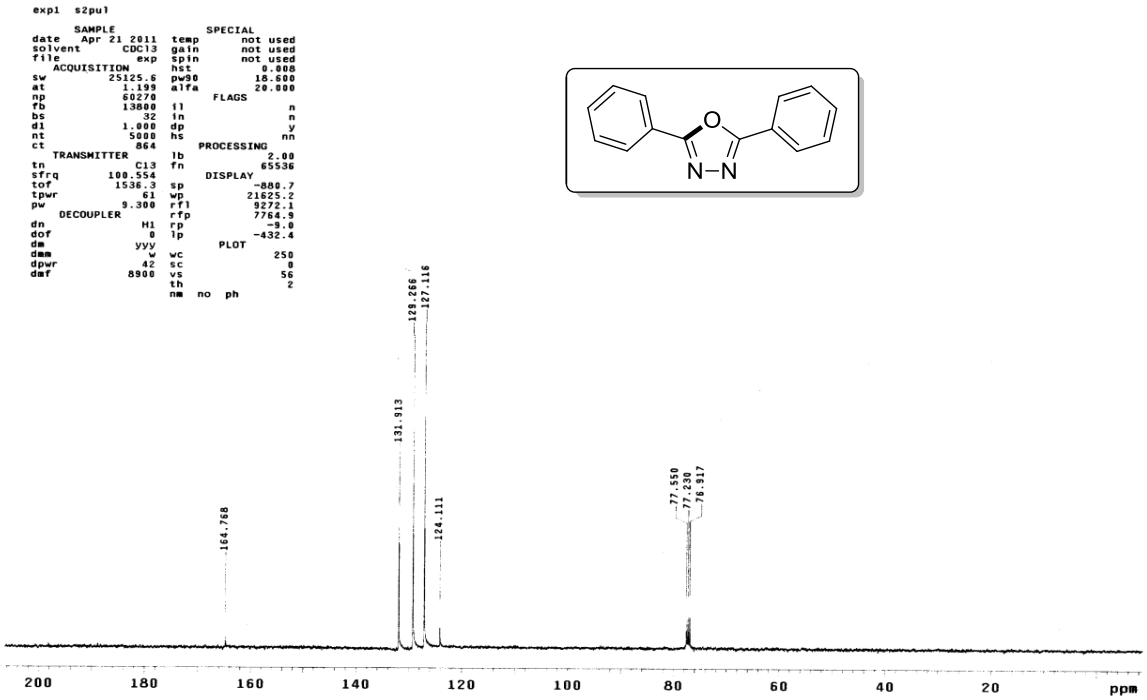
2,5-Bis(4-chlorophenyl)-1,3,4-oxadiazole (20a): M.p. 250–251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, 4H, *J* = 11.2 Hz), 8.07 (d, 4H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.4, 128.4, 129.7, 138.4, 164.2; IR (KBr): 3084, 2956, 2924, 2853, 1605, 1478, 1461, 1261, 1091, 1073, 1011, 838, 738 cm^{-1}; Anal calcd. for $C_{14}H_8N_2OCl_2$: C 57.76, H 2.77, N 9.62; found C 57.79, H 2.80, N 9.57.

II.7. Spectra

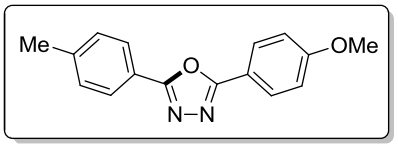
2,5-Diphenyl-1,3,4-oxadiazole (1a): ^{1}H NMR (400 MHz, $CDCl_3$)

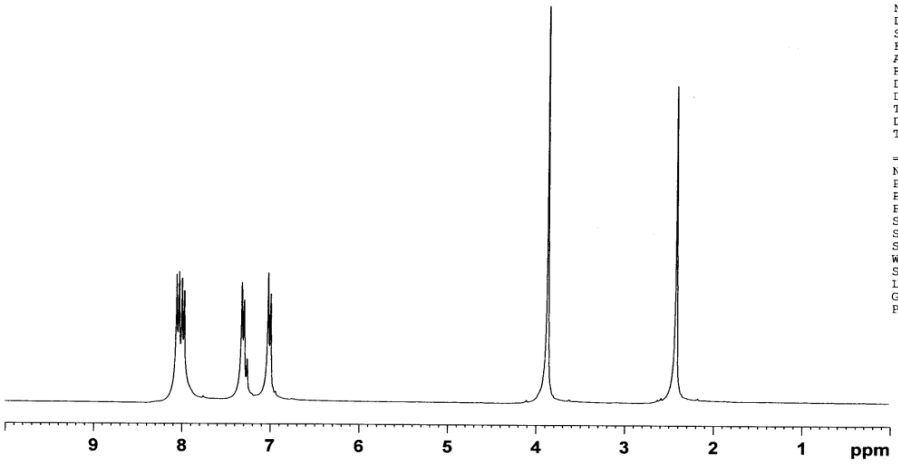


2,5-Diphenyl-1,3,4-oxadiazole (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



2-(4-Methoxyphenyl)-5-*p*-tolyl-1,3,4-oxadiazole (15a): ^{1}H NMR (400 MHz, $CDCl_3$)



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2-(4-Methoxyphenyl)-5-*p*-tolyl-1,3,4-oxadiazole (15a): ^{13}C NMR (100 MHz, $CDCl_3$)

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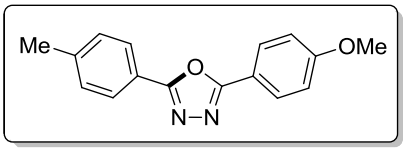
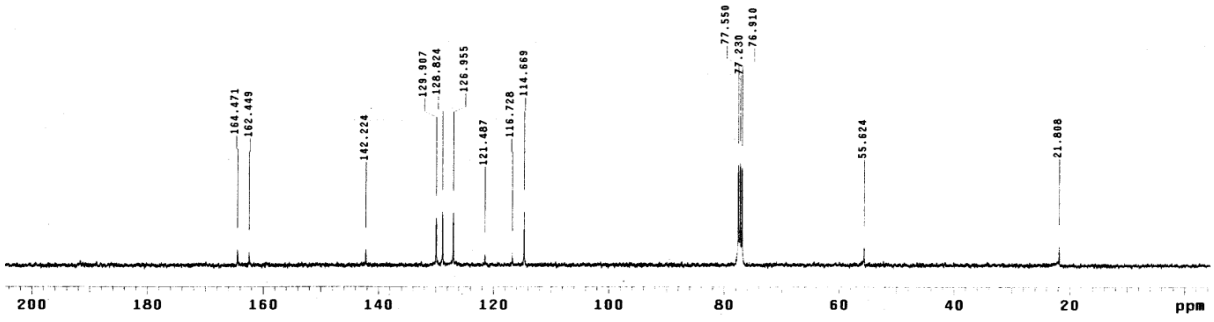
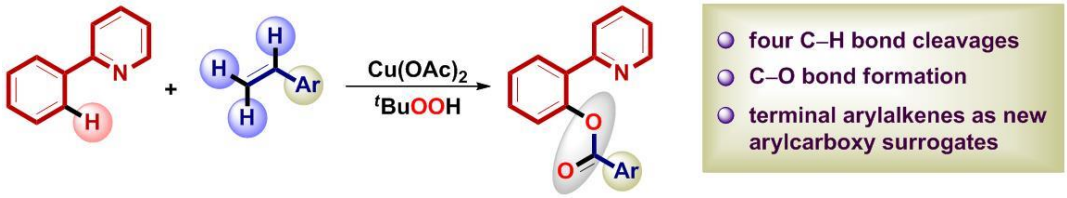




Indian Institute of Technology Guwahati

Chapter III

Terminal Aryl Alkenes as Arylcarboxy Surrogates toward o-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper



Abstract: *A variety of styrenes serve as excellent arylcarboxy sources in bringing about substrate directed o-benzoxylation of 2-phenylpyridine derivatives catalyzed by Cu(II) in the presence of TBHP. This reaction proceeds via formation of phenylglyoxal followed by decarbonylation to benzoyl radical / benzaldehyde which acts as the arylcarboxy source.*

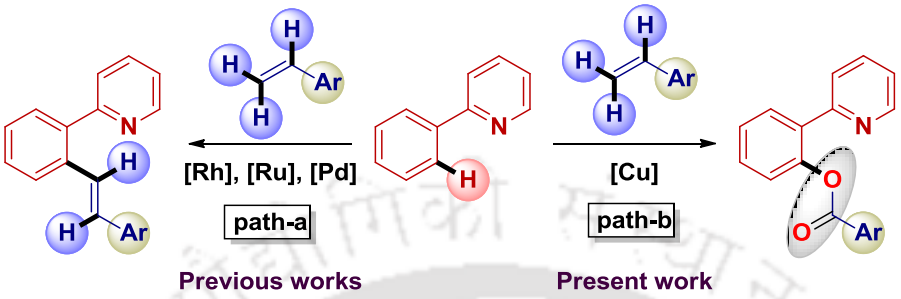
CHAPTER III

III. Terminal Aryl Alkenes as Arylcarboxy Surrogates toward *o*-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper

III.1. Introduction

The transition metal catalyzed selective functionalizations of un-reactive C–H bonds have brought about renaissance in modern synthetic organic chemistry.[1] In fact C–H bond activation is one of the most alluring approaches in organic synthesis that obviates substrate pre-functionalization, thereby reducing the number of synthetic steps and making the method atom economic. Among the many C–H bond activation protocols which have been developed over the past few years, catalytic cross-dehydrogenative coupling (CDC) reactions with the assistance of a directing group have been found to be particularly useful for various C–C and C–heteroatom bond formations.[2] In fact, the CDC has mostly been directed towards C–C bond formation as it provides the requisite connectivity to build larger and complex structures.[2] One of the extensively studied C–C bond forming reactions is the vinylation of substrates possessing directing groups using expensive metal catalysts such as Rh, Ru, and Pd (path-a, Scheme III.1.1).[3] Thus, it would be desirable and appreciable if the same can be achieved using less expensive and more environmentally benign metals such as Cu, albeit its use is so far unfamiliar in this forum. Some of the protocols related to Cu-catalyzed vinylation of sp^2 C–H and sp^3 C–H require a radical initiator to promote the reactions.[4] Taking cues from these reported methods, a trial reaction was attempted toward radically induced *ortho*-alkenylation of 2-phenylpyridine using styrene as vinyl source and copper as catalyst. Instead of the expected *o*-alkenylated product the reaction interestingly provided *o*-benzoxylated product exclusively. This result is rather surprising as styrene is not known to be the synthetic equivalent for the benzoxy (ArCOO−) group. Related to similar oxidation of alkenes, styrenes are reported to undergo Wacker type oxidation to give phenylacetaldehyde[5] while stilbenes are reported to yield

1,2-diketones.[6] Thus the current copper catalyzed *o*-benzoxylation (C–O bond formation) of 2-phenylpyridine from styrene which is serving as ArCOO– surrogate via loss of one carbon atom is unprecedented in the literature (path-b, Scheme III.1.1).



Scheme III.1.1. *Use of terminal alkenes in C–H activation process*

Noteworthy to mention that construction of a C–O bond via C–H activation is quite difficult which is most probably due to high electronegativity of oxygen atom and the metal–ligand bond strength.[7] Despite these challenges the relevance of C–O bonds in organic chemistry have resulted in pioneering discoveries on various transition metal based methodologies via directing group assisted C–H bond activation. But most of the reactions on substrate directed C–O bond formations are concerned on *ortho*-hydroxylation,[8] *ortho*-alkoxylation[8a,9] and *ortho*-acetoxylation;[10] albeit similar reports on *ortho*-benzoxylation are relatively fewer in numbers. The problem associated with transition metal catalyzed *ortho*-benzoxylation by direct coupling of carboxylic acid and aromatics is the rapid metal-carboxylic acid complex formation; thereby rendering the metal catalysts inactive and inhibit further progress of the reaction. One way of overcoming this problem is to employ a surrogate of the carboxylic acid that can inhibit the competitive complex formation via slow and stepwise generation of carboxylic acid in the reaction medium. Thus our present finding on the use of terminal alkenes as a potential synthetic equivalent of benzoxy (ArCOO–) group for *ortho*-benzoxylation of 2-phenylpyridines blends well with the aforementioned concept.

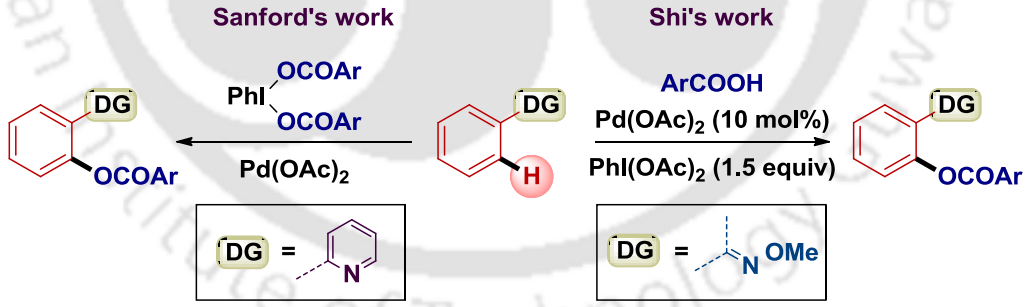
III.2. Strategies for *ortho*-benzoxylation

The ester functionality is ubiquitous as the structure of important natural and synthetic molecules and the need for ester compounds will never lessen.[11] Benzoate derivatives are

important building blocks in the synthesis of natural and pharmacological compounds.[12] Usually, these compounds are prepared via Fischer esterification[13] or transesterification reactions,[14] which normally involve strong acidic or basic conditions limiting the reaction scope.[15] The Baeyer–Villiger oxidation reaction may suffer from low regioselectivity.[16] In the past few years, oxidative esterification has received significant attention and has become an economical alternative to traditional ester synthesis.[17] An important category of these oxidative esterification reactions is the transition-metal-catalyzed esterification.[17] Not merely our present observation exemplify this reaction type, but other groups have also achieved similar transition metal catalyzed *o*-benzoxylation of substrates possessing various directing groups employing either carboxylic acid directly or various surrogates of carboxylic acid which have enacted as ArCOO– source. Some of the recent protocols on oxidative esterification are enlisted below.

(i) Benzoate iodonium salts [PhI(OCOAr)$_2$] as ArCOO– source

Sanford *et al.* reported palladium catalyzed *o*-benzoxylation of 2-phenylpyridines using benzoate iodonium salts as ArCOO– surrogates for the first time.[18] Later, Shi group achieved a similar palladium catalyzed *o*-benzoxylation of ketoxime ethers via *in situ* generation of benzoate iodonium salts.[19]

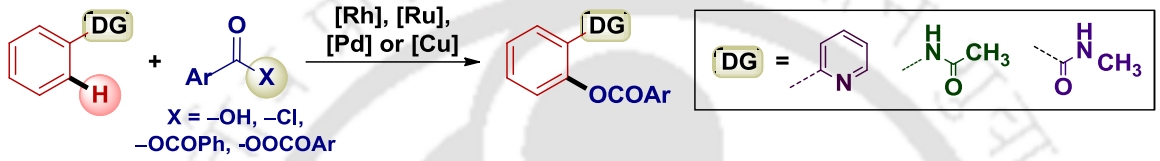


Scheme III.2.1. *o-Benzoxylation using benzoate iodonium salts*

(ii) Aryl carboxylic acids or its derivatives as ArCOO– source

Cheng group has demonstrated the use of aromatic carboxylic acids directly as the ArCOO– source for *o*-benzoxylation of 2-arylpyridines using rhodium catalyst.[20a] The same group has shown that acid derivatives in the form of carboxylic acid salt,[20b] anhydride[20c] and acid chloride[20d] could be used for the same purpose. Zhong group has also

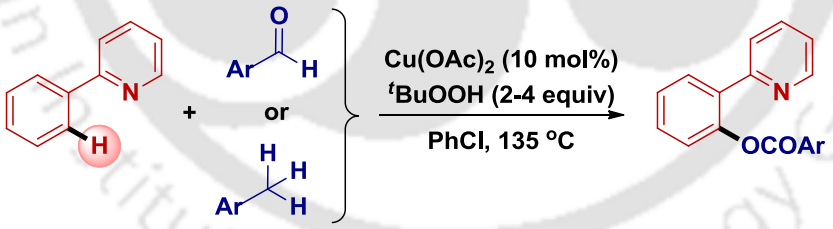
achieved an oxidative *o*-benzoxylation of 2-phenylpyridines with aromatic carboxylic acids under ligand-free conditions using palladium catalyst along with copper and silver salts as additives.[21] Aryl acylperoxides has also been found to be an effective benzoxy surrogate as illustrated by Yu group in a palladium catalyzed *o*-benzoxylation of 2-phenylpyridines.[22] Pertinent to the *o*-benzoxylation in substrates possessing other directing groups, very recently Jeganmohan *et al.* have reported ruthenium catalyzed *o*-benzoxylation of acetanildes[23a] and benzamides[23b] using aryl carboxylic acids as coupling partners.



Scheme III.2.2. *o-Benzoxylation using carboxylic acids or its derivatives*

(iii) Aldehyde or alkylbenzenes as ArCOO– source

Huang *et al.* have shown that aldehyde (ArCHO) and alkylbenzene ($ArCH_3$) can also be used as alternative sources of ArCOO– group for *o*-benzoxylation of 2-phenylpyridine.[24]

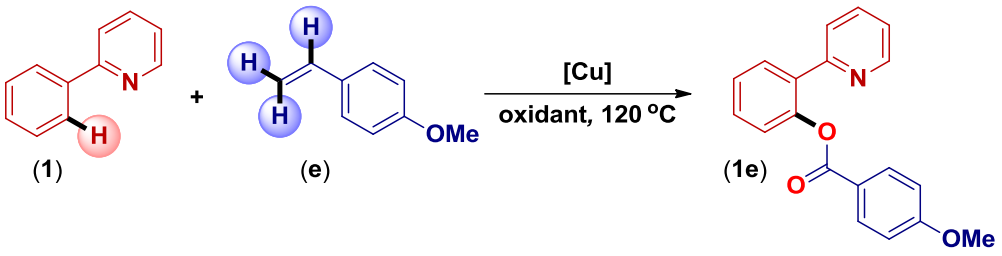


Scheme III.2.3. *o-Benzoxylation using aldehydes or alkylbenzenes*

III.3. Present work

In continuation to the above *o*-benzoxylation protocols, herein a method is reported on copper catalyzed *o*-benzoxylation of 2-arylpyridines using styrenes as the ArCOO– surrogates. This process involve overall cleavages of four sp^2 C–H's and also a loss of a carbon atom via C–C bond breakage from the parent alkene to install a benzoxy group at the proximal site of 2-phenylpyridine.

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



Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	Temp °C	Yield (%)
1	$Cu(OAc)_2$ (10)	TBHP[c] (3)	PhCl	100	46
2	CuBr (10)	TBHP[c] (3)	PhCl	100	27
3	$CuBr_2$ (10)	TBHP[c] (3)	PhCl	100	21
4	CuCl (10)	TBHP[c] (3)	PhCl	100	28
5	$CuCl_2$ (10)	TBHP[c] (3)	PhCl	100	35
6	$Cu(OTf)_2$ (10)	TBHP[c] (3)	PhCl	100	15
7	CuI (10)	TBHP[c] (3)	PhCl	100	33
8	$Cu(OAc)_2$ (10)	TBHP[c] (4)	PhCl	100	55
9	$Cu(OAc)_2$ (10)	TBHP[c] (5)	PhCl	100	62
10	$Cu(OAc)_2$ (20)	TBHP[c] (5)	PhCl	100	71
11	$Cu(OAc)_2$.(30)	TBHP[c] (5)	PhCl	100	72
12	**$Cu(OAc)_2$ (20)**	**TBHP[c] (5)**	**PhCl**	**120**	**78**
13	$Cu(OAc)_2$ (20)	TBHP[c] (5)	toluene	120	68
14	$Cu(OAc)_2$ (20)	TBHP[c] (5)	THF	120	35
15	$Cu(OAc)_2$ (20)	TBHP[c] (5)	dioxane	120	00
16	$Cu(OAc)_2$ (20)	TBHP[c] (5)	DMSO	120	00
17	$Cu(OAc)_2$ (20)	TBHP[c] (5)	DMF	120	00
18	$Cu(OAc)_2$ (20)	TBHP[c] (5)	DCE	120	00
19	$Cu(OAc)_2$ (20)	TBHP[d] (5)	PhCl	120	27
20	$Cu(OAc)_2$ (20)	Nil	PhCl	120	00
21	Nil	TBHP (5)	PhCl	120	00

[a]Reaction conditions: 2-phenylpyridine (**1**) (0.5 mmol), *p*-methoxy styrene (**e**) (1 mmol), time 10 h. [b]Isolated yield. [c]Decane solution (5–6 M). [d]70% aqueous solution.

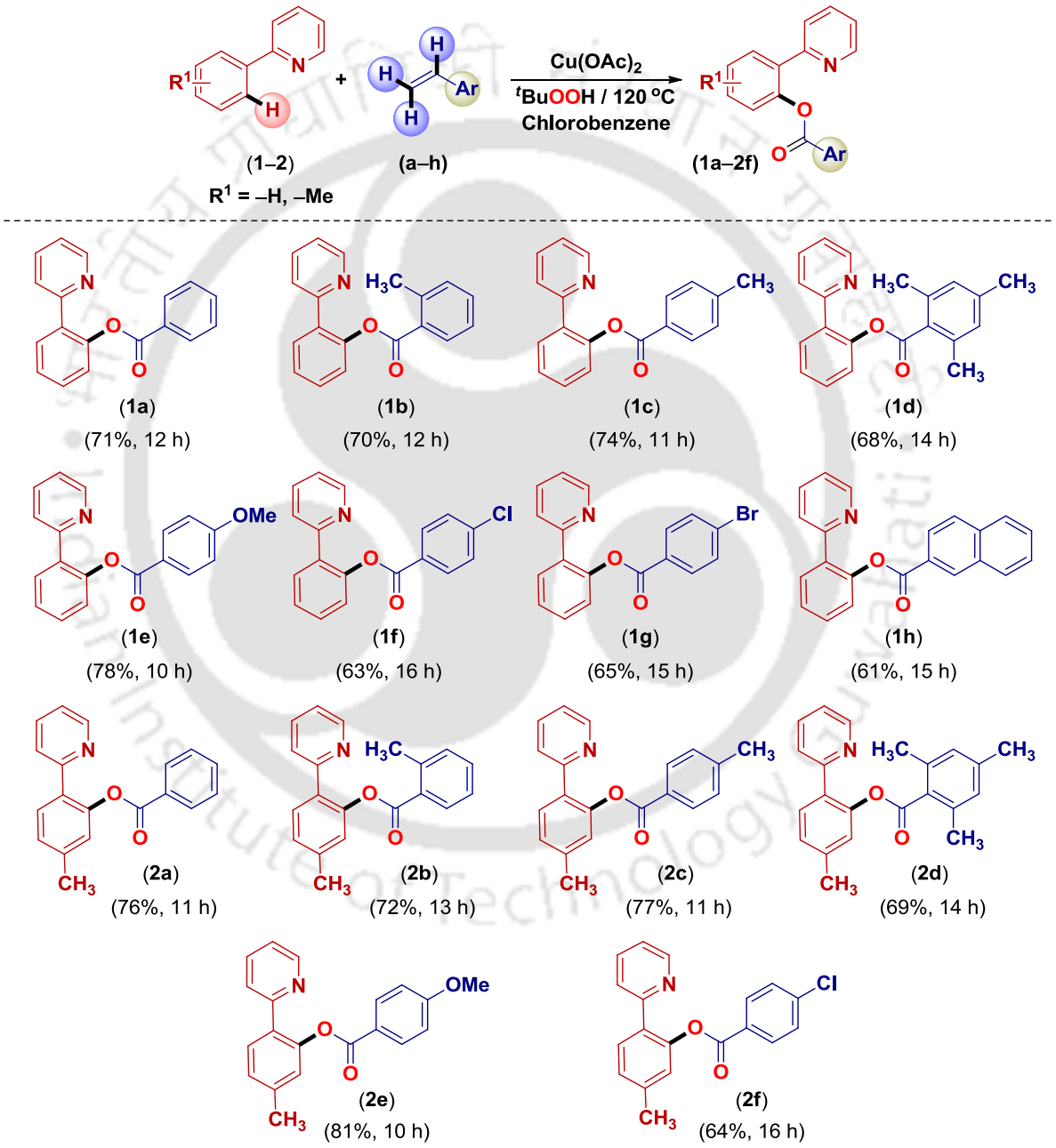
Optimization of reaction conditions. As has been mentioned earlier, to check the efficacy of a copper catalyst toward *o*-alkenylation of 2-phenylpyridine (1) an initial reaction was performed using *p*-methoxy styrene (e) as the alkenyl source in the presence of $Cu(OAc)_2$(10 mol %) and oxidant cum radical initiator TBHP (3 equiv) in chlorobenzene at 100 °C (Table III.3.1, entry 1). However, the aforesaid reaction surprisingly provided an *o*-benzoxylated product (**1e**) in a modest yield of 46% (Table III.3.1, entry 1). Encouraged by this unique result, further optimizations were carried out to attain better yield of the *o*-benzoxylated product by screening various reaction parameters such as catalyst, oxidant,

solvent and temperature. Among several catalysts screened, $Cu(OAc)_2$ (Table III.3.1, entry 1) was found to be the superior to various Cu(I) [CuBr, CuCl and CuI] and Cu(II) [$CuBr_2$, $CuCl_2$, $Cu(OTf)_2$] salts (Table III.3.1, entries 2–7). Subsequently by increasing the TBHP (5–6 M) quantity from 3 to 4 equivalents, the product yield was enhanced to 55% (Table III.3.1, entry 8) while a further improvement of 7% (Table III.3.1, entry 9) was observed using 5 equiv of the same. The use of 6 equiv of TBHP did not make any further augmentation in the yield. A two-fold increase in the catalyst loading led to a better yield (71%, Table III.3.1, entry 10), whilst no significant change in yield occurred with a three-fold excess of the catalyst loading. The yield was increased by an additional 7% (Table III.3.1, entry 12) upon performing the reaction at 120 ^oC. Solvents toluene (68%) (Table III.3.1, entry 13) and THF (35%) (Table III.3.1, entry 14) were less efficient compared to the use of chlorobenzene (78%) (Table III.3.1, entry 12), whereas other solvents such as dioxane, DMSO, DMF, DCE were completely ineffective in bringing about this transformation (Table III.3.1, entries 15–18). The use of aq. TBHP in lieu of a decane solution of TBHP (5–6 M) was found to be far less effective giving only a 27% yield of the desired product under identical reaction conditions (Table III.3.1, entry 19). The reaction failed to proceed in the absence of either the catalyst or the oxidant the reaction suggesting their combination as an essential requirement (Table III.3.1, entry 20–21). Thus the use of $Cu(OAc)_2$ (20 mol%) and TBHP (5 equiv) in chlorobenzene at 120 ^oC was found to be the optimized conditions for subsequent exploration to extend the scope of this transformation.

Substrate scope for *o*-benzoxylation. The above optimized conditions were then executed for *o*-benzoxylation of 2-phenylpyridine (**1**) using various substituted styrenes. The electron neutral –H (**a**) and electron-donating substituents on styrenes *viz*. *o*-Me (**b**), *p*-Me (**c**), 2,4,6-trimethyl (**d**) and *p*-OMe (**e**) served as excellent benzoxy surrogates toward *o*-benzoxylation of 2-phenylpyridine (**1**) providing their respective products (**1a**–**1e**) in moderate yields as shown in Scheme III.3.1. Moderately electron-withdrawing substituents in styrenes such as *p*-Cl (**f**) and *p*-Br (**g**) also acted as their respective benzoxy sources yielding corresponding *o*-benzoxylated products (**1f** and **1g**) but in slightly lesser yields compared to styrenes possessing electro-donating substituents (Scheme III.3.1). However styrene possessing a strongly electron-withdrawing group such as *m*-NO_2 failed to give an

o-benzoxylated product with (**1**).The styrene analogue of naphthalene, 2-vinylnaphthalene (**h**) was also effective in bringing about naphthylcarboxylation of (**1**) giving (**1h**) in a moderate yield (Scheme III.3.1). In addition to 2- phenylpyridine (**1**), *o*-benzoxylation of 2-(*p*-tolyl)pyridine (**2**) was also investigated with various styrenes and the results are

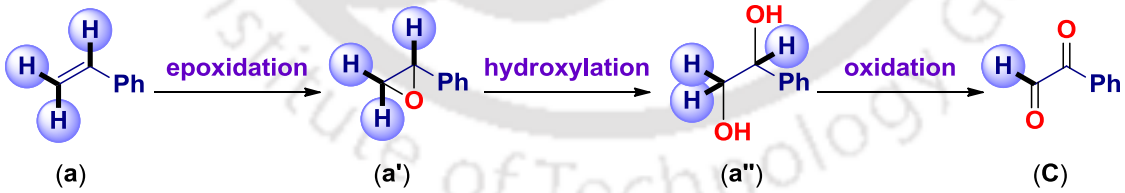
Scheme III.3.1. *Substrate scope for o-benzoxylation*[a,b]



[a]Reaction conditions: arenes (**1–2**) (0.5 mmol), alkenes (**a–h**) (1 mmol), $Cu(OAc)_2$ (0.2 mmol), TBHP (5–6 M) (2.5 mmol), 120 °C, in chlorobenzene (1 mL), time 10–16 h. [b]Yield of isolated pure product.

depicted in Scheme III.3.1. The trends in the reactivity of substituted styrenes were found to be identical to those observed for 2-phenylpyridine (**1**). Nevertheless, the yields of *o*-benzoxylated products (**2a**–**2f**) obtained were marginally better with 2-(*p*-tolyl)pyridine (**2**) than 2-phenylpyridine (**1**), which is perhaps due to better chelation of the metal catalyst with the electron rich *p*-tolyl ring in (**2**). Surprisingly, terminal aliphatic alkene 1-methyl 4-butene failed to undergo any *o*-acetoxylation either with (**1**) or (**2**) under the present reaction conditions.

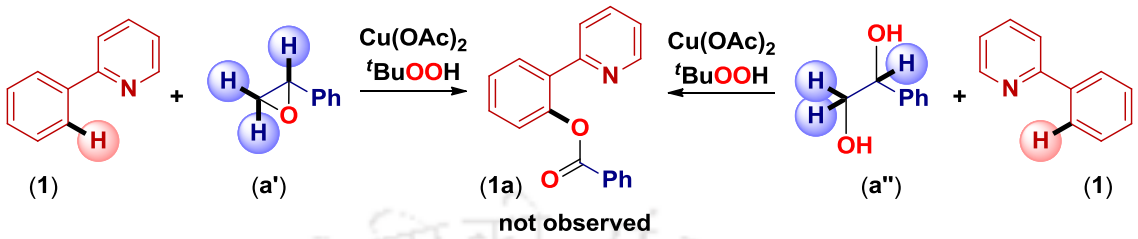
Mechanistic studies. This elegant and unprecedented transformation is a mechanistic enigma to us and hence systematic investigations were carried out to depict a plausible mechanism. A careful examination of the reaction mixture obtained by reacting (**1**) with (**a**) divulges the presence of intermediates such as phenylglyoxal, benzaldehyde and benzoic acid in the medium along with other intermediates. Surprisingly instead of styrene, when phenylglyoxal and benzaldehyde were reacted with (**1**) independently under otherwise identical conditions, both provided the desired product (**1a**) supporting their intermediacy in this transformation. Since phenylglyoxal is expected to be generated from styrene, it was envisaged that its formation in the medium possibly occurs via the intermediacy of styrene epoxide (**a´**) and 1-phenyl-1,2-ethanediol (**a"**) in the reaction sequence epoxidation followed by epoxide ring opening to give diol and subsequent oxidation of diol to give phenylglyoxal (Scheme III.3.2).



Scheme III.3.2. *Tentative path for phenylglyoxal formation*

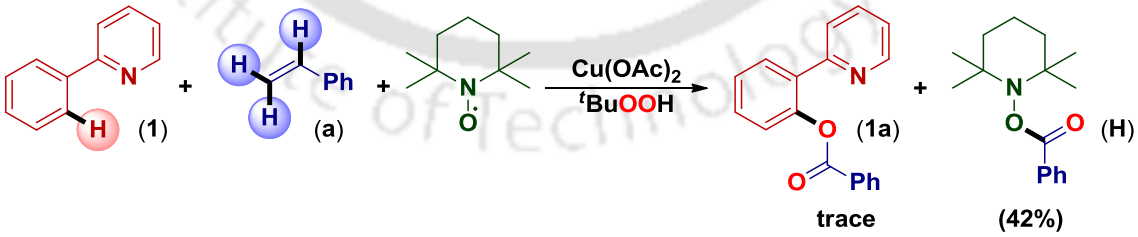
If this is the path for the formation of phenylglyoxal, then the treatment of both these intermediates with 2-phenylpyridine (**1**) under similar reaction conditions are likely to give the desired *o*-benzoxylated product (**1a**). So in lieu of styrene two independent reactions were performed; one with styrene epoxide (**a´**) and the other using 1-phenyl-1,2-ethanediol

(**a"**) but both reactions failed to offer the expected product (**1a**), thus ruling out the involvement of either of them as possible intermediates (Scheme III.3.3).



Scheme III.3.3. *Control experiments*

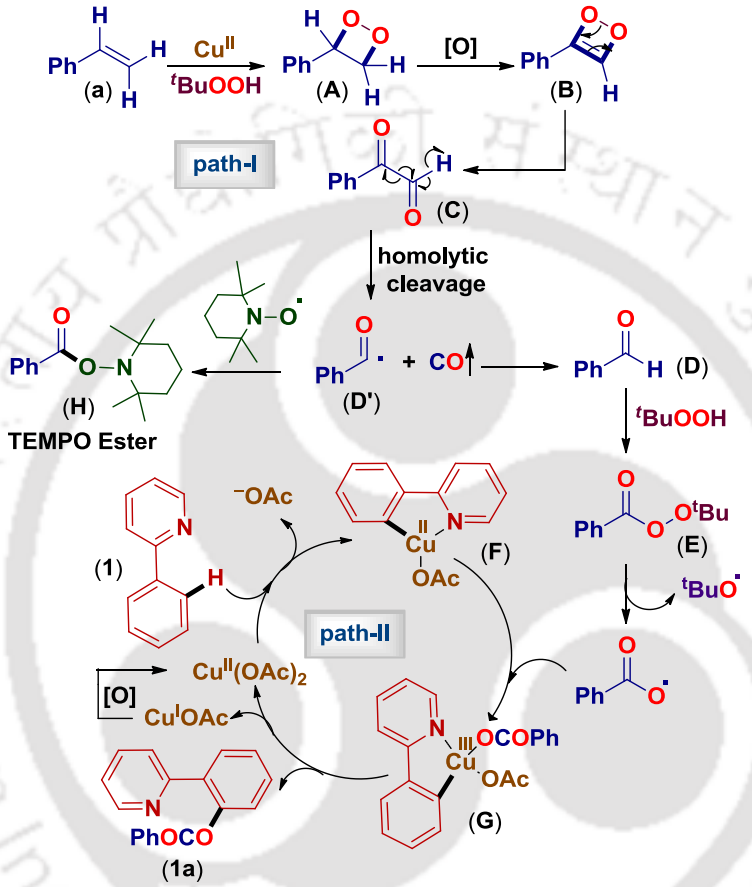
Hence it was reasoned that the formation of phenylglyoxal under oxidative conditions probably occurs via dioxetane and dioxete intermediates as has been proposed by Jiao *et.al* who have proposed similar di-keto formation from terminal alkynes during the synthesis of α-ketoamides.[25] Having established the pathway for the phenylglyoxal formation, next we turned our attention towards the formation of benzaldehyde and benzoic acid in the medium. Under the oxidative condition conversion of benzaldehyde to benzoic acid is not surprising but formation of benzaldehyde (possibly from phenylglyoxal) was rather puzzling. The detection of CO in the reaction mixture accounts for the loss of one carbon possibly from phenylglyoxal (Scheme III.3.4, also see Experimental Section III.4.3). In a control experiment when phenylglyoxal was treated under the identical reaction conditions detection of CO and formation of benzaldehyde was observed reconfirming our assumption.[26]



Scheme III.3.4. *Reaction in presence of radical scavenger TEMPO*

Also when a standard reaction was performed in the presence of radical quencher 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO), substantial rate retardation was observed giving only traces of desired product (**1a**) along with isolation of TEMPO ester (**H**)

(Scheme III.3.4, also see Experimental Section III.4.4). This result suggests the radical nature of the mechanism where TBHP is playing the role of radical initiator as well as the oxygen source in the reaction. It also entails that benzaldehyde is the key intermediate in this transformation.



Scheme III.3.5. *Proposed mechanism for ortho-benzoxylation*

Parallel to the observations of above experiments a mechanism is proposed composing of three paths as shown in Scheme III.3.5. In path-I, styrene (**a**) possibly forms a 4-membered cyclic intermediate, 3-phenyl-1,2-dioxetane (**A**) upon reaction with TBHP. Intermediate (**A**) then undergoes oxidative dehydrogenation to generate intermediate 3-phenyl-1,2-dioxete (**B**). The ring fragmentation of (**B**) provides phenylglyoxal (**C**) which ultimately heads to the formation of benzaldehyde (**D**) via a benzoyl radical (**D′**) through radically induced decarbonylation. The effect of TBHP on (**D**) or (**D′**) forms *tert*-butyl benzoperoxate (**E**). In path-II, Cu(II) undergoes chelation with (**1**) to give the complex (**F**).

Loss of the ^{t}BuO radical from (**E**) with subsequent ligation of the benzoxy radical with (**F**) gives the Cu(III) intermediate (**G**). Successful benzoxylation of (**1**) using either (**D**) or presynthesized (**E**) under identical reaction conditions supports their intermediacy in this transformation. The reductive elimination in the final step leads to the *o*-benzoxylated product (**1a**) while the Cu(I) generated is re-oxidized to Cu(II) for the next catalytic cycle.

In conclusion, this methodology provides a new avenue for the synthesis of benzoate esters using styrenes as the new surrogates for the arylcarboxy group (ArCOO–), toward *o*-benzoxylation of 2-phenylpyridine derivatives. The reaction proceeds through sequential C–O bond formations at the expense of four sp^2 C–H and one carbon atom. Based on the reaction intermediates detected and results of the control experiments a plausible mechanism has been proposed which accounts for most of the experimental observations.

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 sulphate. 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 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using ESI mode. FT-IR spectra were recorded in KBr or neat.

III.4.2. General procedure for the synthesis of 2-(pyridin-2-yl)phenylbenzoate (1a). An oven-dried flask was charged with 2-phenylpyridine (**1**) (78 mg, 0.5 mmol), styrene (**a**) (105 mg, 1 mmol), $Cu(OAc)_2$ (18 mg, 0.2 mmol), TBHP in decane (5–6 M) (500 µL, 2.5 mmol) and solvent chlorobenzene (1 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^{o}C for 12 h. After stipulated time, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate (10 mL). The reaction mixture was filtered through a celite bed and washed with an additional amount of ethyl acetate (2 x 10 mL). The combined organic

layer was subsequently washed with 5% solution of sodium bicarbonate solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed in vacuo. The residue was purified over a column of silica gel and eluted with (9:1, hexane/ethyl acetate) to give 2-(pyridin-2-yl)phenylbenzoate (**1a**) (97 mg, 71% yield). The same procedure was also followed for o-benzoxylation of (**1**) and (**2**) with other styrenes (**a**–**h**).

III.4.3. Detection of CO. For the detection of extrusion of carbon monoxide, a strip containing $PdCl_2$ and PMA (phosphomolybdic acid) was hanged from the neck of the reaction flask as shown in the figure below. The initial yellow colour of the strip before the reaction (Figure III.4.3.1) turned pale blue after 2 hrs of the reaction progress (Figure III.4.3.2). This colour change confirms the extrusion of CO from the reaction. The same detection technique was performed independently with phenylglyoxal and similar blue coloration was observed (within 10 minutes) along with the formation of benzaldehyde (**D**). The blue coloration of the strip is of molybdenum blue formed by the reduction of phosphomolybdic acid by carbon monoxide.[26]

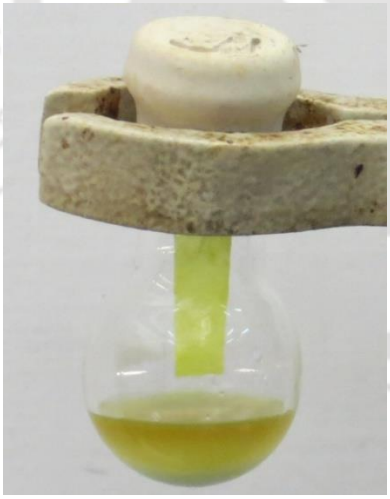


Figure III.4.3.1
$PdCl_2$-PMA test strip before reaction

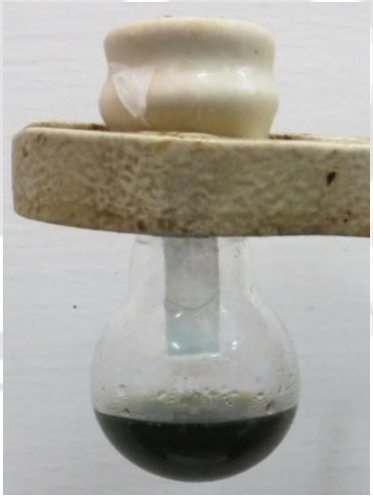


Figure III.4.3.2
$PdCl_2$-PMA test strip after reaction

III.4.4. Mechanistic investigation in the presence of radical scavenger TEMPO. An oven-dried reaction vessel was charged with 2-phenylpyridine (**1**) (78 mg, 0.5 mmol),

styrene (**a**) (105 mg, 1 mmol), $Cu(OAc)_2$ (18 mg, 0.2 mmol), TBHP in decane (5–6 M) (500 µL, 2.5 mmol) TEMPO (0.156 g, 1 mmol) and solvent chlorobenzene (1 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^{o}C for 12 h. The reaction after 12 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**H**) (42% yield) along with traces (<5%) of the desired product (**1a**). This experiment supports the formation of benzoyl radical (**D´**) in the medium generated by homolytic cleavage of phenylglyoxal in the presence of $Cu(OAc)_2$ and TBHP.

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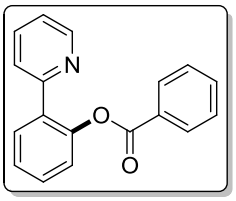
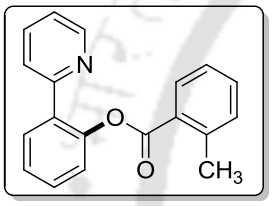
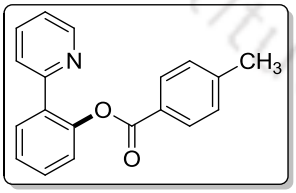
III.6. Spectral data



2-(Pyridin-2-yl)phenylbenzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 1H), 7.29–7.32 (m, 1H), 7.39–7.51 (m, 4H), 7.55–7.65 (m, 3H), 7.78–7.79 (m, 1H), 8.07–8.10 (m, 2H), 8.59–8.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.3, 123.5, 123.9, 126.7, 128.7, 129.7, 130.0, 130.4, 131.1, 133.5, 133.7, 136.4, 148.5, 149.8, 155.8, 165.4; IR (KBr): 3062, 2927, 2858, 1737, 1592, 1458, 1260, 1190, 1067, 1020, 842, 751, 749, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}NO_2$ (MH^+) 276.1019; found 276.1014.

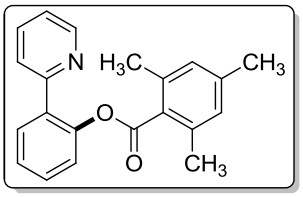


2-(Pyridin-2-yl)phenyl 2-methylbenzoate (1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.53 (s, 3H), 7.17–7.20 (m, 1H), 7.25–7.30 (m, 3H), 7.38–7.51 (m, 3H), 7.54–7.57 (m, 1H), 7.60–7.67 (m, 1H), 7.74–7.77 (m, 1H), 7.98–8.02 (m, 1H), 8.61–8.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 122.3, 123.6, 123.9, 125.9, 126.5, 128.7, 129.9, 131.0, 131.2, 131.9, 132.7, 133.6, 136.4, 141.3, 148.5, 149.6, 155.9, 165.8; IR (KBr): 3062, 2962, 2928, 2856, 1743, 1585, 1492, 1467, 1426, 1289, 1250, 1197, 1155, 1115, 1040, 1021, 884, 794, 736, 693, 616 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1171.

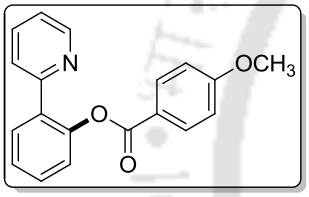


2-(Pyridin-2-yl)phenyl 4-methylbenzoate (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.14–7.17 (m, 1H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.29–7.31 (m, 1H), 7.38–7.42 (m, 1H), 7.46–7.49 (m, 1H), 7.55–7.57 (m, 1H), 7.59–7.63 (m, 1H), 7.77–7.79 (m, 1H), 7.97 (d, 2H, *J* = 8.0 Hz), 8.59–8.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 122.3, 123.5, 123.9, 126.5, 126.9, 129.4, 129.9, 130.4, 131.1, 133.5, 136.3, 144.5, 148.5, 149.8, 155.7, 165.4; IR (KBr): 3043, 2999, 2919, 2846, 1732, 1608, 1582, 1491, 1455, 1424, 1265, 1193, 1174, 1114, 1066, 1014, 834, 744 cm^{-1}; HRMS

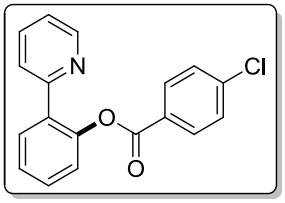
(ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1173.



2-(Pyridin-2-yl)phenyl 2,4,6-trimethylbenzoate (1d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.20 (s, 6H), 2.27 (s, 3H), 6.83 (s, 2H), 7.20–7.24 (m, 1H), 7.32–7.34 (m, 1H), 7.37–7.41 (m, 1H), 7.47–7.51 (m, 1H), 7.56 (d, 1H, *J* = 7.6 Hz), 7.63–7.67 (m, 1H), 7.70–7.75 (m, 1H), 8.66 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0, 21.3, 122.4, 123.2, 124.6, 126.6, 128.9, 129.9, 131.3, 134.2, 136.1, 136.4, 140.1, 148.4, 149.8, 156.0, 168.4; IR (KBr): 2924, 2856, 1742, 1611, 1585, 1493, 1463, 1425, 1379, 1243, 1187, 1163, 1051, 1022, 852, 752, 613 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{19}NO_2$ (MH^+) 318.1489; found 318.1481.

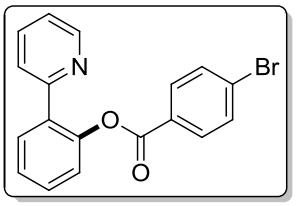


2-(Pyridin-2-yl)phenyl 4-methoxybenzoate (1e): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.90 (s, 3H), 6.92 (d, 2H, *J* = 8.8 Hz), 7.14–7.17 (m, 1H), 7.28–7.30 (m, 1H), 7.36–7.40 (m, 1H), 7.44–7.49 (m, 1H), 7.53–7.56 (m, 1H), 7.59–7.62 (m, 1H), 7.77–7.79 (m, 1H), 8.03 (d, 2H, *J* = 8.8 Hz), 8.60–8.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 113.9, 121.8, 122.2, 123.5, 123.8, 126.3, 129.8, 130.9, 132.4, 133.4, 136.2, 148.5, 149.7, 155.6, 163.9, 164.9; IR (KBr): 3061, 3007, 2964, 2953, 2840, 1731, 1606, 1583, 1511, 1463, 1423, 1253, 1195, 1166, 1114, 1067, 1025, 848, 793, 753, 692, 636 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_3$ (MH^+) 306.1125; found 306.1133.

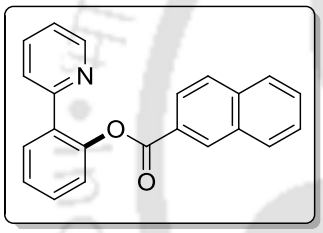


2-(Pyridin-2-yl)phenyl 4-chlorobenzoate (1f): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13–7.17 (m, 1H), 7.28–7.30 (m, 1H), 7.38–7.43 (m, 3H), 7.45–7.53 (m, 3H), 7.60–7.65 (m, 1H), 8.00 (d, 2H, *J* = 8.8 Hz), 8.55–8.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 122.4, 123.4, 123.8, 126.7, 128.1, 129.0, 129.9, 131.1, 131.7, 133.4, 136.4, 140.1, 148.3, 149.7, 155.7, 164.5; IR (KBr) 2924, 2853, 1738, 1593, 1478, 1429, 1400, 1263, 1191, 1090, 1073, 1014, 966, 795, 752, 627 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}ClNO_2$

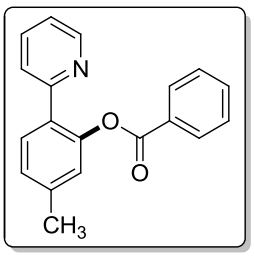
(MH^+) 310.0629; found 310.0635.



2-(Pyridin-2-yl)phenyl 4-bromobenzoate (1g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 1H), 7.29 (d, 1H, *J* = 8.4 Hz), 7.39–7.43 (m, 1H), 7.46–7.53 (m, 2H), 7.58–7.66 (m, 3H), 7.74–7.76 (m, 1H), 7.93 (d, 2H, *J* = 8.8 Hz), 8.56 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.4, 123.4, 123.8, 126.7, 128.6, 128.7, 128.9, 130.3, 131.1, 131.8, 132.0, 136.4, 148.3, 149.7, 155.7, 164.7; IR (KBr): 3052, 2925, 2850, 1733, 1587, 1492, 1482, 1465, 1450, 1423, 1395, 1261, 1186, 1166, 1068, 1058, 1023, 1008, 849, 795, 761, 749 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}BrNO_2$ (MH^+) 354.0124; found 354.0117.

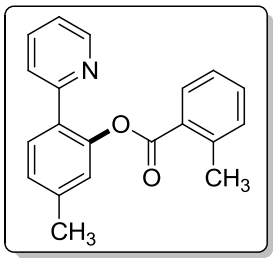


2-(Pyridin-2-yl)phenyl 2-naphthoate (1h): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09–7.13 (m, 1H), 7.34 (d, 1H, *J* = 8.0 Hz), 7.38–7.44 (m, 1H), 7.47–7.61 (m, 5H), 7.77–7.79 (m, 1H), 7.87 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 2H, *J* = 8.8 Hz), 8.05–8.07 (m, 1H), 8.56 (d, 1H, *J* = 8.8 Hz), 8.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.3, 123.5, 123.9, 125.7, 126.6, 126.8, 126.9, 127.9, 128.5, 128.8, 129.7, 129.9, 131.1, 132.1, 132.7, 133.6, 135.9, 136.4, 148.6, 149.8, 155.8, 165.5; IR (KBr): 3057, 2923, 2850, 1733, 1629, 1585, 1492, 1463, 1425, 1281, 1222, 1187, 1127, 1063, 1024, 951, 867, 774, 750 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}NO_2$ (MH^+) 326.1176; found 326.1167.

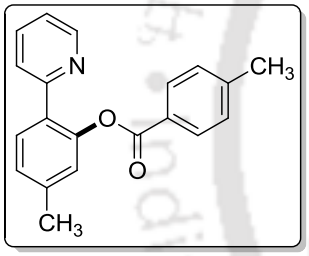


5-Methyl-2-(pyridine-2-yl)phenyl benzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.11–7.14 (m, 2H), 7.19–7.22 (m, 1H), 7.46 (t, 2H, *J* = 8.0 Hz), 7.52–7.61 (m, 3H), 7.67 (d, 1H, *J* = 7.6 Hz), 8.07–8.09 (m, 2H), 8.58 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.8, 122.2, 123.3, 123.85, 123.93, 127.5, 128.7, 129.7, 130.3, 130.9, 133.6, 136.5, 140.4, 148.3, 149.7, 155.7, 165.4; IR (KBr): 2924, 2853, 1735, 1623, 1596, 1467, 1382,

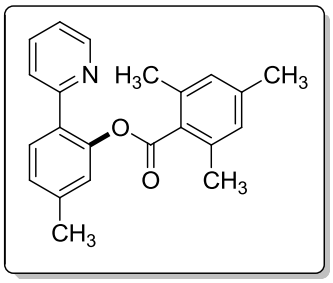
1259, 1175, 1155, 1131, 1079, 1062, 1024, 780, 740, cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1172.



5-Methyl-2-(pyridine-2-yl)phenyl 2-methylbenzoate (2b): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 2.53 (s, 3H), 7.09 (s, 1H), 7.11–7.15 (m, 1H), 7.18–7.25 (m, 3H), 7.40 (t, 1H, *J* = 7.6 Hz), 7.51–7.53 (m, 1H), 7.58–7.66 (m, 2H), 8.01 (d, 1H, *J* = 7.6 Hz), 8.57–8.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 21.8, 122.1, 123.8, 124.0, 125.9, 127.4, 128.9, 130.8, 131.2, 131.9, 132.6, 136.3, 140.4, 141.3, 148.3, 149.7, 156.0, 166.0; IR (KBr) 3062, 2961, 2926, 1737, 1623, 1586, 1573, 1466, 1431, 1288, 1245, 1151, 1135, 1045, 893, 782, 736, 691 cm^{-1}; HRMS (ESI): calcd.for $C_{20}H_{17}NO_2$ (MH^+) 304.1332; found 304.1335.

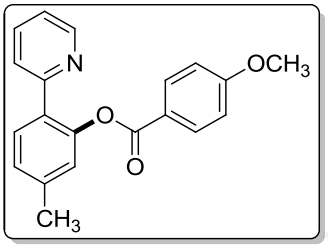


5-Methyl-2-(pyridine-2-yl)phenyl 4-methylbenzoate (2c): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 2.42 (s, 3H), 7.09–7.12 (m, 2H), 7.18–7.20 (m, 1H), 7.23–7.25 (m, 2H), 7.52–7.59 (m, 2H), 7.68 (d, 1H, *J* = 7.6 Hz), 7.97 (d, 2H, *J* = 8.4 Hz), 8.57–8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 21.9, 122.0, 123.8, 123.9, 126.9, 127.4, 129.4, 130.4, 130.5, 130.8, 136.3, 140.3, 144.4, 148.3, 149.7, 155.7, 165.5; IR (KBr) 3056, 2953, 2922, 2852, 1735, 1612, 1586, 1465, 1431, 1258, 1177, 1152, 1130, 1070, 1019, 892, 781, 746, 687 cm^{-1}; HRMS (ESI): calcd.for $C_{20}H_{17}NO_2$ (MH^+) 304.1332; found 304.1338.

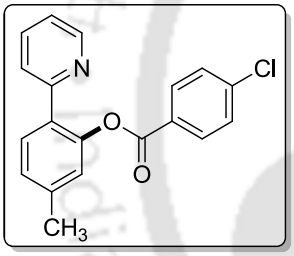


5-Methyl-2-(pyridine-2-yl)phenyl 2,4,6-trimethylbenzoate (2d): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.20 (s, 6H), 2.27 (s, 3H), 2.46 (s, 3H), 6.84 (s, 2H) 7.13 (s, 1H), 7.19–7.21 (m, 2H), 7.54 (d, 1H, *J* = 7.6 Hz), 7.61–7.64 (m, 2H), 8.66 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 21.1, 24.7, 122.1, 123.4, 124.4, 127.3, 128.3, 128.7, 129.6, 130.9, 135.9, 136.3, 139.9, 140.3, 147.9, 149.4, 155.7, 168.3; IR (KBr) 2953, 2923, 2854, 1742, 1611, 1587, 1466, 1431, 1379, 1253, 1243, 1163, 1127, 1094, 1052, 954,

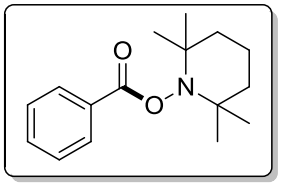
825, 784, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{21}NO_2$ (MH^+) 332.1645; found 332.1649.



5-Methyl-2-(pyridine-2-yl)phenyl 4-methoxybenzoate (2e): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 3.85 (s, 3H), 6.89–6.92 (m, 2H), 7.07–7.12 (m, 2H), 7.16–7.18 (m, 1H), 7.49–7.52 (m, 1H), 7.55–7.59 (m, 1H), 7.65 (d, 1H, *J* = 8.0 Hz), 8.00–8.03 (m, 2H), 8.56–8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.7, 113.9, 122.0, 122.1, 123.9, 124.0, 127.3, 130.6, 130.9, 132.5, 136.3, 140.4, 148.4, 149.7, 155.8, 163.9, 165.2; IR (KBr) 2961, 2924, 2845, 1737, 1606, 1510, 1465, 1432, 1254, 1167, 1130, 1069, 1026, 846, 782 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_3$ (MH^+) 320.1281; found 320.1284.



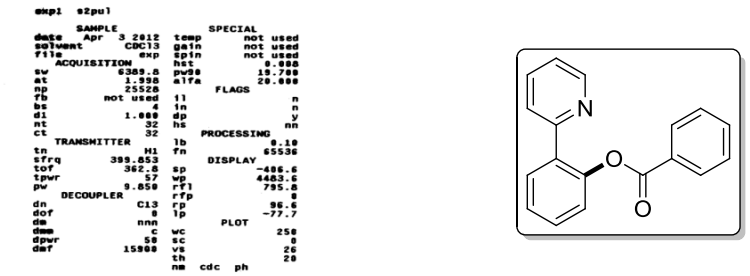
5-Methyl-2-(pyridin-2-yl)phenyl 4-chlorobenzoate (2f): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.10–7.15 (m, 2H), 7.20–7.22 (m, 1H), 7.43 (d, 2H, *J* = 8.8 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.59–7.66 (m, 2H), 8.01 (d, 2H, *J* = 8.8 Hz), 8,55 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 122.2, 123.6, 123.9, 127.6, 128.2, 129.0, 130.4, 130.8, 131.7, 136.4, 140.1, 140.5, 148.1, 149.7, 155.8, 164.7; IR (KBr): 3057, 2923, 2847, 1739, 1620, 1590, 1507, 1487, 1465, 1431, 1400, 1258, 1227, 1172, 1152, 1131, 1090, 1071, 1013, 847, 826, 748, 750, 680 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}ClNO_2$ (MH^+) 324.0786; found 324.0781.

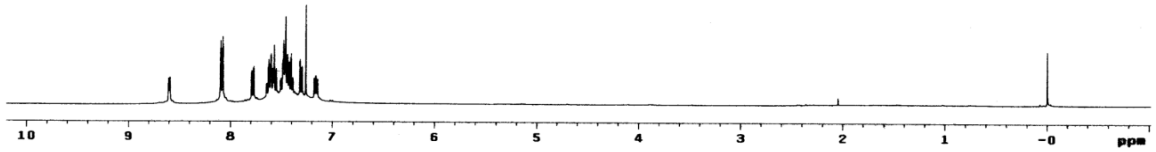


2,2,6,6-Tetramethylpiperidin-1-yl benzoate (H): ^1H NMR (600 MHz, $CDCl_3$):δ (ppm) 1.12 (s, 6H), 1.26 (s, 6H), 1.42–1.45 (m, 1H), 1.55–1.58 (m, 2H), 1.66–1.78 (m, 3H), 7.43 (t, 2H, *J* = 7.8 Hz), 7.54 (t, 1H, *J* = 7.8 Hz), 8.03–8.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.2, 21.0, 32.1, 39.2, 60.6, 128.6, 129.7, 129.9, 133.0, 166.6; HRMS (ESI): calcd. for $C_{16}H_{23}NO_2$ (MH^+) 262.1802; found 262.1801.

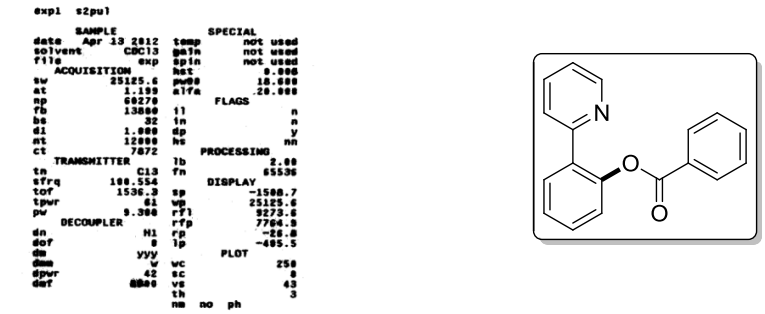
III.7. Spectra

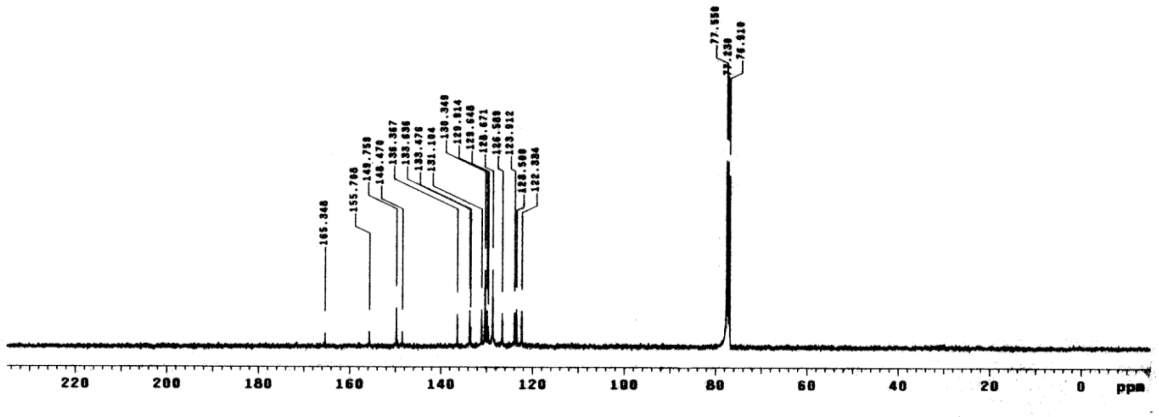
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



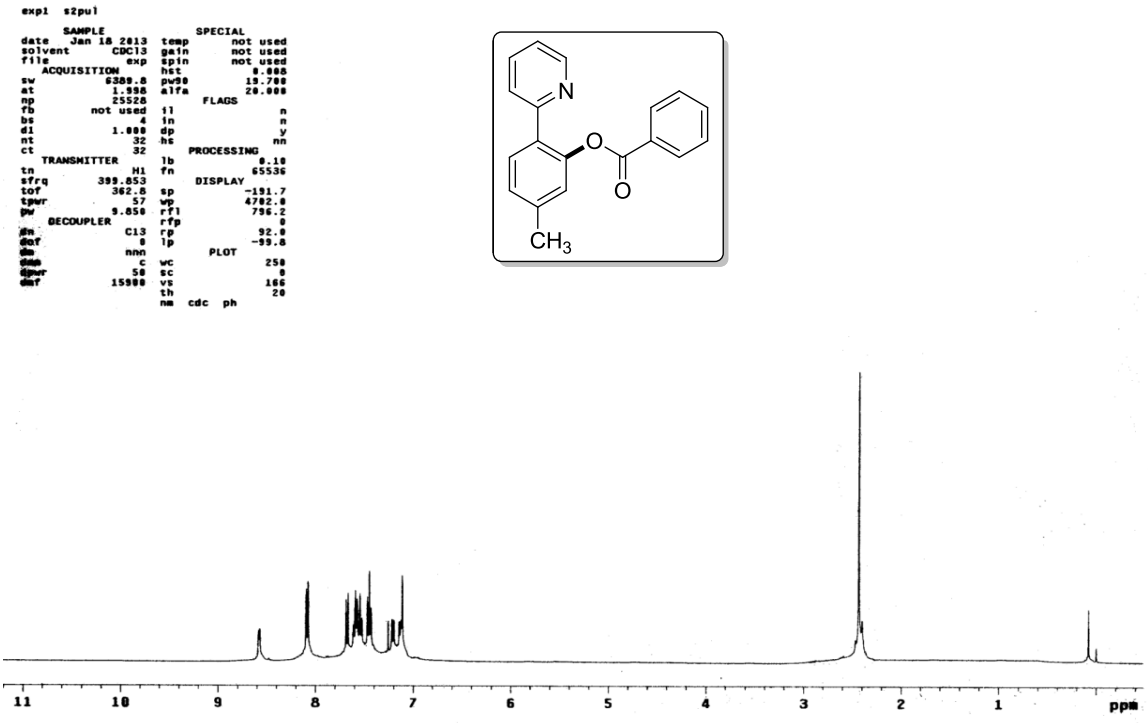


2-(Pyridin-2-yl)phenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)

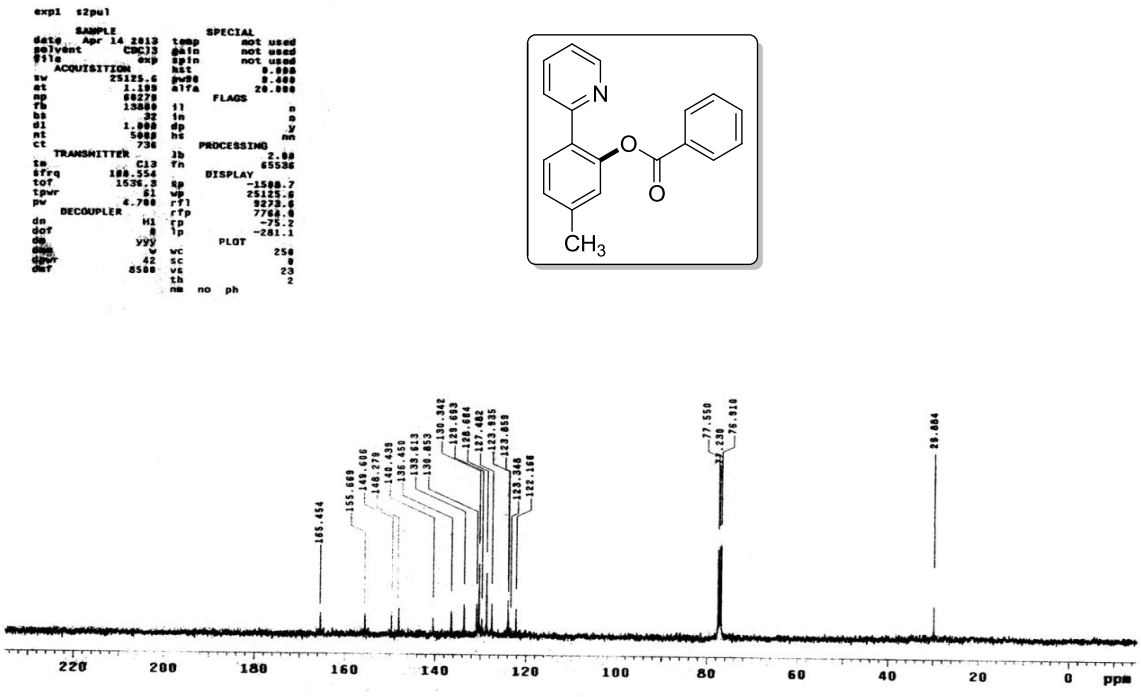




5-Methyl-2-(pyridine-2-yl)phenyl benzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$)



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



भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
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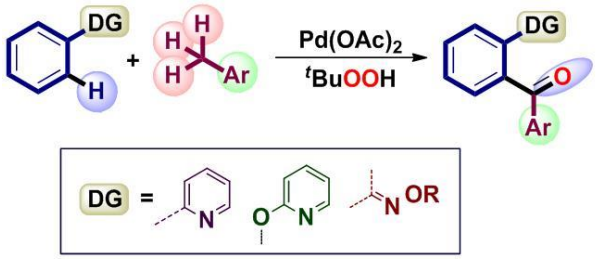
Chapter IV

Four Tandem C–H Activations: A Sequential C–C and C–O Bond Making via Pd-Catalyzed Cross-Dehydrogenative Coupling (CDC) Approach



Abstract: *An unprecedented palladium(II) catalyzed aroylation at the ortho C–H bond has been accomplished via a CDC approach using alkylbenzenes as the synthetic equivalent of an aroyl moiety. The reaction proceeds at the expense of four consecutive C–H bond cleavages (three sp^3 benzylic C–H's and one sp^2 arene C–H).*

CHAPTER IV

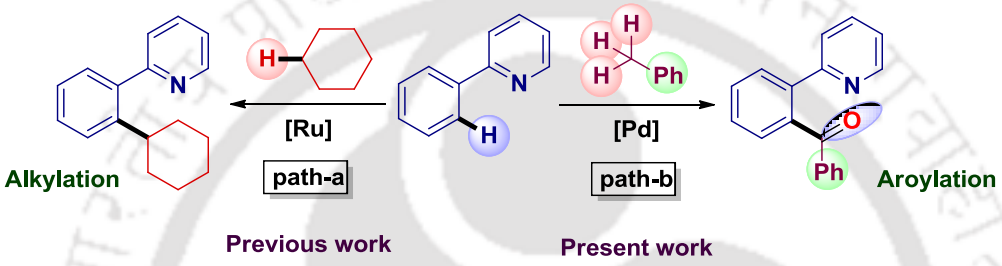
IV. Four Tandem C–H Activations: A Sequential C–C and C–O Bond Making via Pd-Catalyzed Cross-Dehydrogenative Coupling (CDC) Approach

IV.1. Introduction

The modern era of organic chemistry has brought about many appealing results pertaining to transition metal catalyzed C–H bond activations with subsequent functionalizations.[1] Foundations to most C–H activation processes generally rely on the strategies of directing group assisted C–H bond functionalization[2] and cross dehydrogenative coupling (CDC).[3] These two techniques are highly appreciable due to being atom and step economic. Pertinent to these seminal achievements, protocols for the direct conversion of C–H bonds to C–C bonds stand out to be the key pillar in providing a great impetus to modern synthetic chemistry, as C–C bond formation is regarded as the "holey grail" of organic chemistry.[4] Oxidative C–H bond functionalizations have been successfully applied to construct C–C bonds involving sp, sp^2 or sp^3 hybridized carbons as mutual cross-coupling partners.[5] Despite the significant progress made in this area the more challenging arene–alkane couplings remain scarce which is due to the inertness of sp^3 C–H bonds.[6]

A survey of the literature entails that pertaining to the substrate directed arene–alkane coupling there is only a single precedence where 2-arylpyridine or analogous substrates have undergone direct C–H alkylation using un-reactive cycloalkane as the other coupling partner (path a, Scheme IV.1.1).[6a] However, a similar coupling approach to achieve *ortho*-benzylation of substrates possessing *N* or *O* donor atoms cleaving the sp^3 benzylic C–H bond is yet to be accomplished. The reports on *ortho*-benzylation that exist use benzyl bromide as the source of benzyl group.[7] With the motive of exploring this unachieved, we envisaged that can alkylbenzenes like cycloalkanes be used to the same effect to achieve *ortho*-benzylation of 2-arylpyridine under similar conditions to the previous report on

arene–alkane coupling. However, the attempt to attain *ortho*-benzylation of 2-phenylpyridine with toluene using a palladium catalyst and a radical initiator surprisingly led to the *ortho*-benzoylation (i.e. ketone formation). This particular observation was the origin to the present endeavor on palladium catalyzed *ortho*-aroylation of substrates possessing various directing groups with alkylbenzenes as new synthetic equivalent of the benzoyl functionality (path b, Scheme IV.1.1). In this case, incorporation of a benzoyl functionality occurs is at the expense of four consecutive C–H bond (three sp^3 benzylic C–H bonds and one sp^2 arene C–H bond) cleavages.



Scheme IV.1.1. *CDC approaches on arene-alkane couplings*

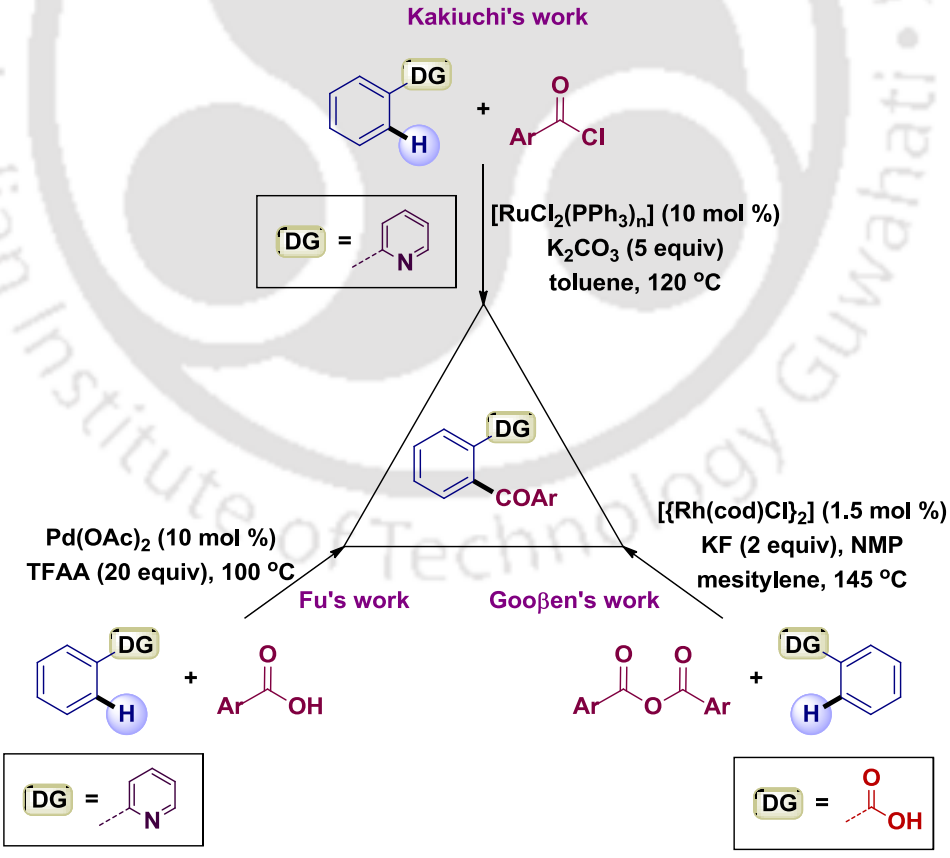
IV.2. Strategies for *ortho*-aroylation

Diaryl and aryl alkyl ketones are fundamental intermediates in the synthesis of pharmaceutical, natural products, functional materials and agrochemicals.[8] They are usually synthesized by Friedel–Crafts acylation, which involves the use of a stoichiometric amount of Lewis acid and has poor functional group compatibility and untunable regioselectivity.[9] The oxidation of secondary alcohols is also a powerful tool to access ketones, but stoichiometric amount of oxidants are generally required.[10] The reactions of carboxylic acid derivatives, such as nitriles, Weinreb amides, anhydrides, or acid chlorides with lithium, magnesium, or aluminum reagents are also important methods for the synthesis of the corresponding ketones.[11] However, these transformations require either highly basic and nucleophilic or acidic conditions, resulting in low compatibility with most functional groups. Thus, the construction of elaborated ketones generally involves further functionalization steps that are time-consuming and have low yields. To circumvent these drawbacks, in recent years, various alternative methods have been developed. Among these methods, transition metal catalyzed acylation of arenes via C–H bond cleavage represents a

direct and promising approach to access ketones.[12] The various methods that have been employed can be classified into four heads as follows, (i) *ortho*-selective Friedel-Crafts acylation using carboxylic acids or its derivatives; (ii) the carbonylative processes; (iii) cross-dehydrogenative coupling with various acyl surrogates (iv) decarboxylative couplings of α-oxoacids and (v) miscellaneous methods

(i) *ortho*-Selective Friedel-Crafts aroylation using carboxylic acids or its derivatives

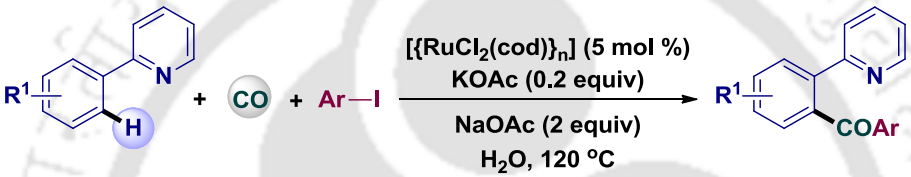
The direct use of carboxylic acids or its derivatives for *ortho*-acylation of arenes are rare in literature (Scheme IV.2.1). Kakiuchi and co-workers achieved a ruthenium catalyzed *ortho*-selective acylation of arylpyridines with acyl chlorides via C–H bond cleavage under oxidant-free conditions.[13a] An analogous palladium catalyzed *ortho*-selective aromatic C–H bond acylation with readily available carboxylic acids was reported by Fu *et. al.*[13b] Very recently, Gooβen group demonstrated a rhodium catalyzed method for the *ortho*-acylation of arylcarboxylic acids with carboxylic anhydrides.[13c]



Scheme IV.2.1. *o-Aroylation using carboxylic acid or its derivatives*

(ii) The carbonylative processes

There exists only a single precedence on the carbonylative process to achieve *ortho*-acylation. Beller group has reported ketone synthesis by carbonylative coupling reactions of aryl halides via ruthenium catalyzed directed C–H bond activation (Scheme IV.2.2).[14a] Apart from this directed *ortho*-acylation, similar non-directed carbonylative coupling reaction between aryl iodide and heterocycle has also been achieved by the same group in the presence of palladium and copper salts.[14b] While Lei *et al.* recently presented an elegant palladium catalyzed process for the double C–H oxidative carbonylation of diphenyl ether derivatives to obtain xanthones.[14c]



Scheme IV.2.2. *o-Aroylation via carbonyl insertion*

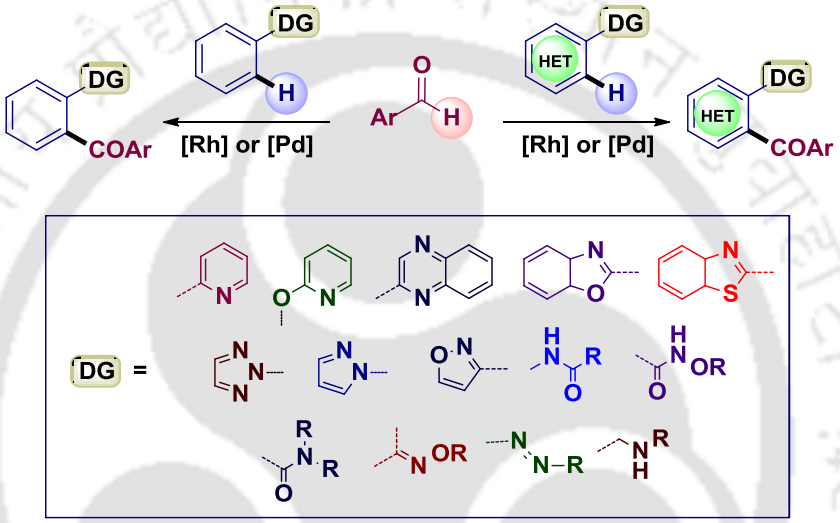
(iii) The cross-dehydrogenative coupling approach with various aroyl surrogates

Of late a number of CDC based protocols on the *ortho*-acylation of substrates possessing various directing groups have been achieved. These protocols can be further classified into four categories depending on the acyl surrogates that have been employed.

(a) Aldehyde as aroyl source

The use of aldehyde as the latent functionality of an aroyl group has been extensively studied with various substrates possessing *N* and *O* donor atoms (Scheme IV.2.3). Cheng and co-workers pioneered in developing a Pd-catalyzed coupling of 2-arylpyridines with benzaldehydes to give aromatic ketones using dioxygen as the oxidant.[15a] They have shown the same is applicable to substrates such 2-aryloxypyridines and *N*-phenyl pyrazoles.[15a] Li and co-workers also reported a similar oxidative coupling of 2-arylpyridines with aliphatic aldehydes using a Pd/TBHP combination.[15b] Since these early works, a number of other *ortho*-chelating groups such as ketoxime ether,[15c-d] anilide,[15d-h] benzamide,[15i-j] oxazole,[15k] triazole[15l] and even azobenzene[15m] have been studied toward similar *ortho*-acylation using aldehydes as the ArCO– source. Very recently our group has

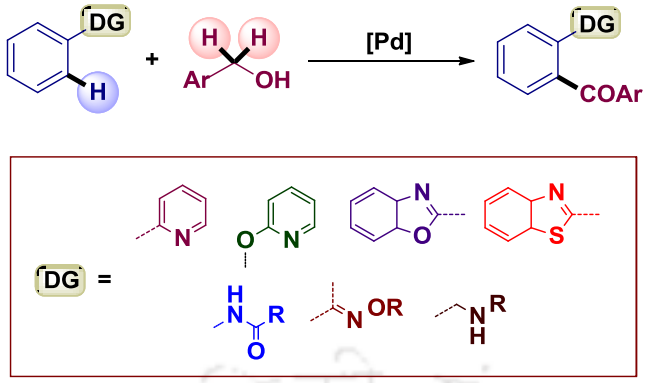
also achieved the same using thiazole,[15n] isoxazole[15o] and quinoxazoline[15p] as the directing groups. Most of these protocols have been catalyzed by Pd salts in the presence of TBHP as the oxidant. Where the oxidative couplings between arenes and aldehydes have been studied to quite an extent, analogous reports on *ortho*-acylation of heteroarenes remain scarce. The two precedence that exist are rhodium-catalyzed oxidative C2-acylation of indoles with aryl and alkyl aldehydes developed by Li group[15q] and a palladium catalyzed C3-acylation of benzofurans and bezothiophenes reported recently by Pan group.[15r]



Scheme IV.2.3. *o-Aroylation using aldehyde as an aroyl source*

(b) Benzyl alcohol as aroyl source

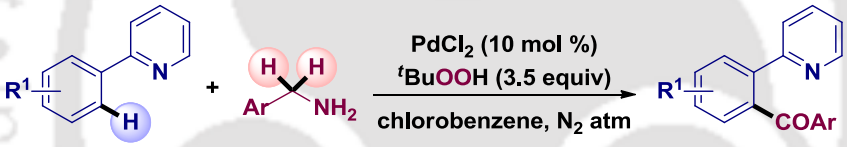
As mentioned above, aldehydes have served as an efficient acyl sources for the synthesis of ketones via oxidative coupling. Since primary alcohols have the ability to generate in situ aldehydes under oxidative conditions, they have also been used intriguingly in various *ortho*-acylation protocols. Li group first reported a palladium catalyzed regioselective acylation of aromatic C–H bonds using alcohols in the presence of peroxide as the oxidant.[16a] Later alcohols have been utilized for acylation of substrates possessing various other directing groups viz. 2-aryloxypyridines,[16b] ketoxime ether,[16c] anilide,[16d-e] oxazole[16f] and thiazole.[16f-g] Likewise in aldehydes, herein as well the protocols are catalyzed by Pd salts in the presence of TBHP as the oxidant. The directing groups employed for achieving *ortho*-acylation of arenes are shown in Scheme IV.2.4.



Scheme IV.2.4. *o-Aroylation using benzyl alcohol as an aroyl source*

(c) Benzylamine as aroyl source

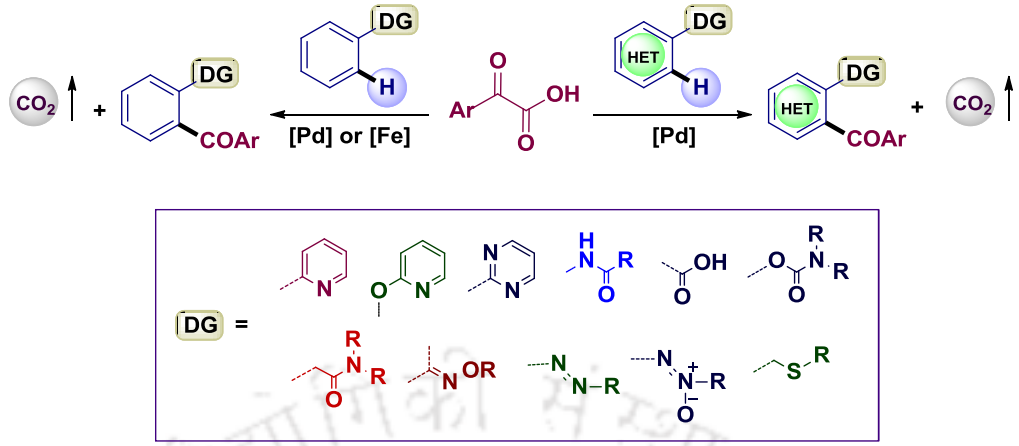
Wu group has recently developed a facile and efficient protocol for palladium-catalyzed *ortho*-acylation of 2-arylpyridines employing arylmethyl amine as an efficient aroyl source (Scheme IV.2.5).[17]



Scheme IV.2.5. *o-Aroylation using benzylamine as aroyl source*

(iv) Decarboxylative coupling of α-oxoacid

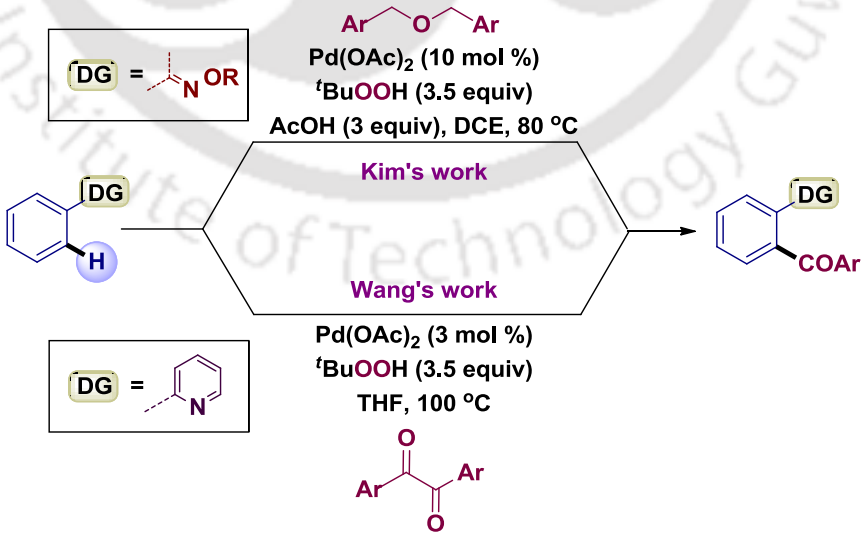
α-Oxoacids are susceptible to undergo decarboxylation under oxidative conditions which is why they are used as aroyl sources in various transition metal catalyzed ketone synthesis (Scheme IV.2.6). Pertaining to directed *ortho*-acylation, Ge group has demonstrated a novel Pd-catalyzed protocol to access *o*-acyl acetanilides via decarboxylative coupling of α-oxoacids with acetanilides at room temperature.[18a] Later the same group achieved similar protocols on *ortho*-acylation of 2-arylpyridines[18b] and carboxylic acids.[18c] The decarboxylative coupling of α-oxoacids for ketone synthesis has also been implemented on substrates bearing other directing groups such as 2-aryloxypyridines,[18d] ketoxime ether,[18e-f] cyclic enamides,[18g] carbamates,[18h] acetamide,[18i] azobenzene,[18j-k] azoxybenzene[18l] and even thioether.[18m] Pertinent to application of such strategy on heteroarenes, C-2 acylation in indoles has been reported by Zhu group.[18n]



Scheme IV.2.6. *o-Aroylation via decarboxylative coupling*

(v) Miscellaneous methods

This class comprise of protocols in which the aroyl species is generated in situ in the reaction medium by C–C or C–X bond scission of the starting precursor (Scheme IV.2.7). Wang group has achieved an efficient carbo-acylation reaction of 2-arylpyridines with α-diketones via Pd-catalyzed C–H bond activation and C–C bond cleavage in the presence of TBHP as the radical initiator.[19a] Very recently, Kim and co-workers have shown that ethers can also act as the acyl surrogate to afford ketones via C–O bond cleavage and C–C bond formation.[19b]



Scheme IV.2.7. *o-Aroylation using benzil or ether as an aroyl source*

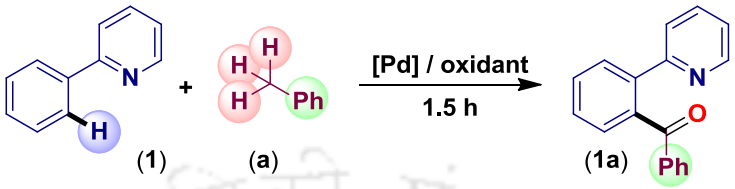
IV.3. Present work

In light of the above-mentioned protocols, the present protocol on *o*-aroylation of arenes with alkylbenzenes demonstrates an unprecedented arene–alkane coupling (C–C bond formation) with a subsequent C–O bond formation involving four tandem C–H bond activations (three sp^3 benzylic C–H's and one sp^2 arene C–H) to selectively install an aroyl moiety at the proximal site of directing group containing substrates.[20]

Optimization of reaction conditions. As mentioned above our initial intention was to achieve *ortho*-benzylation of 2-phenylpyridine and accordingly an initial foray was attempted by reacting 2-phenylpyridine (**1**) (1 equiv) and toluene (**a**) (10 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) and TBHP in decane (5–6 M) (1 equiv) at 120 ^oC. Interestingly, the reaction of the aforementioned combinations resulted in the formation of phenyl(2-(pyridine-2-yl)phenyl)methanone (**1a**), an aroylated product (53%) instead of the expected benzylated product (Table IV.3.1, entry 1). Further optimizations were carried out by varying the reaction parameters in a quest to improve the overall yield. Other potential Pd catalysts such as $Pd(TFA)_2$, $PdCl_2$, and $PdBr_2$ were evaluated (Table IV.3.1, entries 2–4), and $Pd(OAc)_2$ was the most effective catalyst giving superior results (Table IV.3.1, entry 1). The use of $Pd(TFA)_2$ gave poor conversion (15%) along with the formation of multitudes of side products (Table IV.3.1, entry 2). Although the reactions with $PdCl_2$ and $PdBr_2$ (Table IV.3.1, entries 3–4) were clean and smooth, the yields were modest as compared to that for $Pd(OAc)_2$ (Table IV.3.1, entry 1). An increase in the catalyst loading to 10 mol % and in the TBHP quantity by two-fold provided substantial improvement in the isolated yield (85%) (Table IV.3.1, entry 6). The nature of peroxides and their medium of storage had a marked influence on the product yield. For instance the use of either aqueous TBHP or aqueous H_2O_2 as the oxidants proved to be ineffective (Table IV.3.1, entries 7–8). A decrease in the reaction temperature (100 ^oC) reduced the product yield to 77% (Table IV.3.1, entry 9). Control experiments carried out in the absence of either $Pd(OAc)_2$ or TBHP failed to give the desired product (Table IV.3.1, entries 10–11) suggesting the requirement of both the metal catalyst and the oxidant. Solvent optimizations were not carried out as the methylarenes used were liquids which

served the purpose of both reactants and the reaction medium for these oxidative aroylations. The results for various trial reactions are summarized in Table IV.3.1.

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



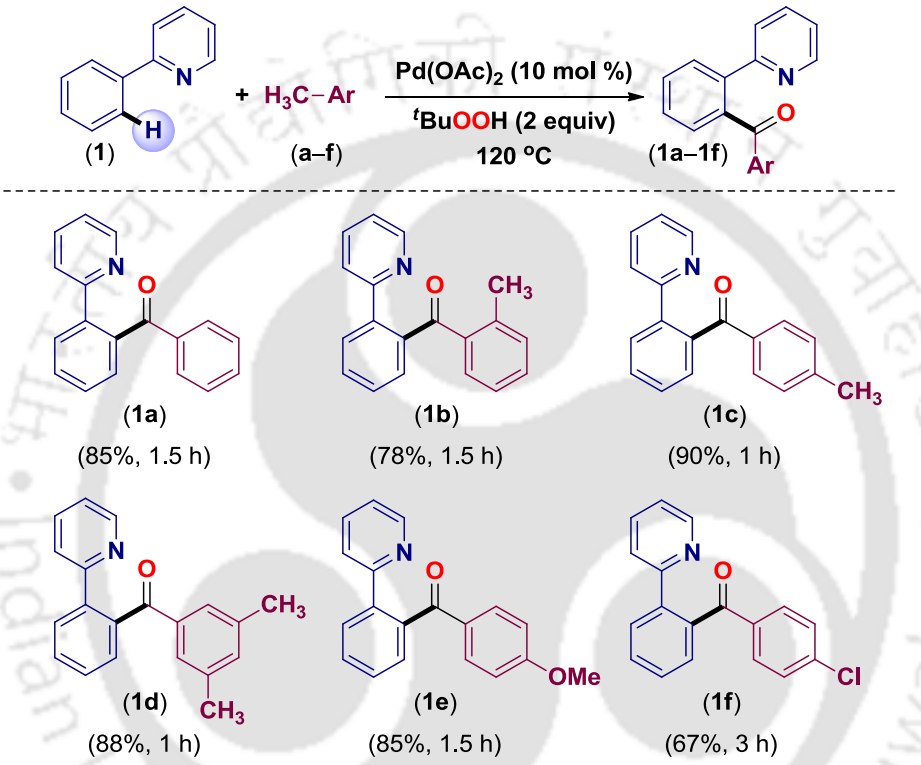
Entry	Catalyst (mol %)	Oxidant (equiv)	Temp ^{o}C	Yield (%)
1	$Pd(OAc)_2$(5)	TBHP[c] (1)	120	53
2	$Pd(TFA)_2$(5)	TBHP[c] (1)	120	15
3	$PdCl_2$ (5)	TBHP[c] (1)	120	30
4	$PdBr_2$ (5)	TBHP[c] (1)	120	42
5	$Pd(OAc)_2$(10)	TBHP[c] (1)	120	73
6	**$Pd(OAc)_2$(10)**	**TBHP[c] (2)**	**120**	**85**
7	$Pd(OAc)_2$(10)	TBHP[d] (2)	120	20
8	$Pd(OAc)_2$(10)	H_2O_2[e] (2)	120	00
9	$Pd(OAc)_2$(10)	TBHP[c] (2)	100	77
10	$Pd(OAc)_2$(10)	Nil	120	00
11	Nil	TBHP[c] (2)	120	00

[a]Reaction conditions: 2-phenylpyridine (**1**) (1 equiv), toluene (**a**) (10 equiv), time 1.5 h. [b]Isolated yield. [c]Decane solution (5–6 M). [d]70% aqueous solution. [e]30% aqueous solution.

Substrate scope for *o*-aroylation. Encouraged by this unique arene–alkane coupling, the optimized conditions were implemented in the coupling reactions between a set of substituted alkylbenzenes with arenes possessing directing groups such as 2-pyridyl, 2-oxopyridyl, and ketoxime ether. The initial investigations were focused on the reactions of 2-phenylpyridine (**1**) with polymethylated benzenes, viz. *o*-xylene (**b**), *p*-xylene (**c**), and mesitylene (**d**). All these coupling reactions proceeded smoothly providing their respective *ortho*-aroylated products (**1b**–**1d**) in excellent yields (Scheme IV.3.1). The lesser yield observed in the case of *o*-xylene (**b**) compared to its para (**c**) or meta (**d**) analogues is possibly due to the steric hindrance of the *ortho* methyl group in *o*-xylene (**b**). The main features of these reactions were the exclusive formation of mono-aroylated products, with the other methyl group(s) remaining intact. The reaction with *p*-methoxytoluene (**e**) afforded the expected product (**1e**) in an excellent yield (Scheme IV.3.1). However, when *p*-chlorotoluene (**f**), was used as the coupling partner the product (**1f**) yield dropped

considerably (67%) (Scheme IV.3.1). These results imply that the electronic effects of the substituents in the methylarenes affect the reaction rates and the product yields. Substituted toluenes possessing electron-donating groups undergo more facile coupling with arenes than the substrate having an electron-withdrawing group.

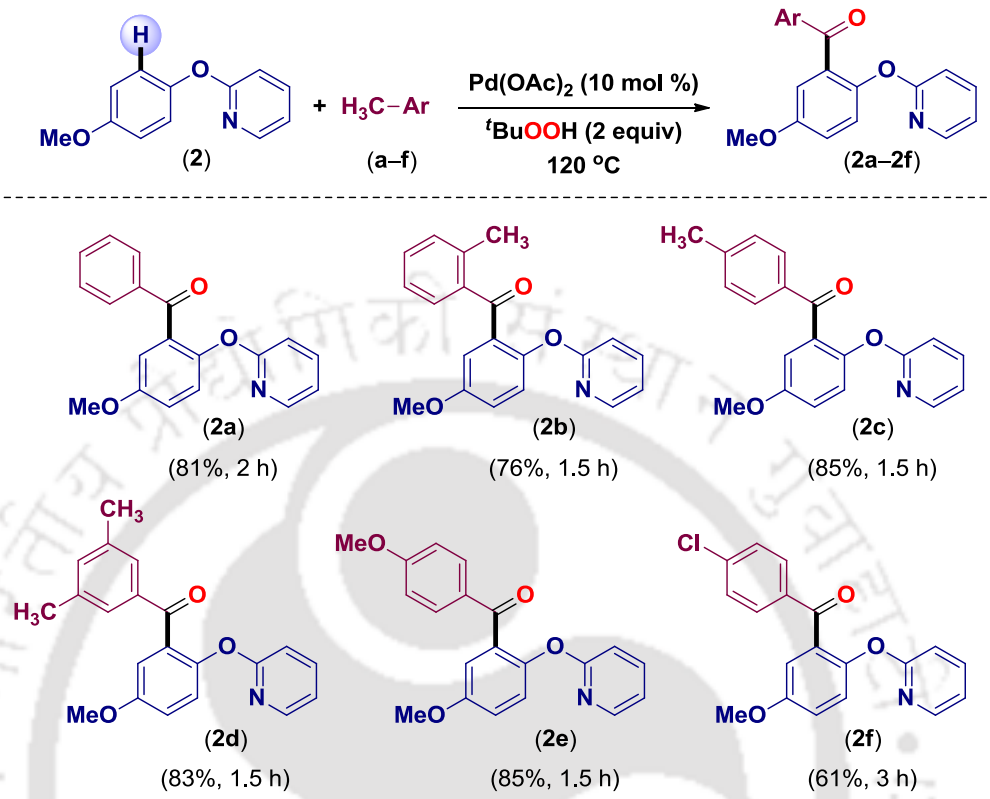
Scheme IV.3.1. *Substrate scope for o-aroylation of 2-phenylpyridine*[a,b]



[a] Reaction conditions: 2-phenylpyridine (**1**) (1 mmol), methylbenzenes (**a–f**) (10 mmol), $Pd(OAc)_2$ (0.1 mmol), TBHP in decane (5–6 M) (2 mmol), 120 °C, time 1–3 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Furthermore, the same optimized reaction conditions were equally applicable to the 2-aryloxypyridine substrate, such as 2-(4-methoxyphenoxy)pyridine (**2**) possessing an additional *O*-linker between the pyridyl and the aryl ring. The reaction of 2-(4-methoxyphenoxy)pyridine (**2**) with the same set of methylarenes gave moderate to high yields of their respective monoaroylated products (**2a**–**2f**) (Scheme IV.3.2). Herein, a similar trend in reactivity and selectivity were observed for methylarenes when coupled with 2-(4-methoxyphenoxy)pyridine (**2**) as was the case with substrate 2-phenylpyridine (**1**).

Scheme IV.3.2. *Substrate scope for o-aroylation of 2-aryloxypyridine*[a,b]

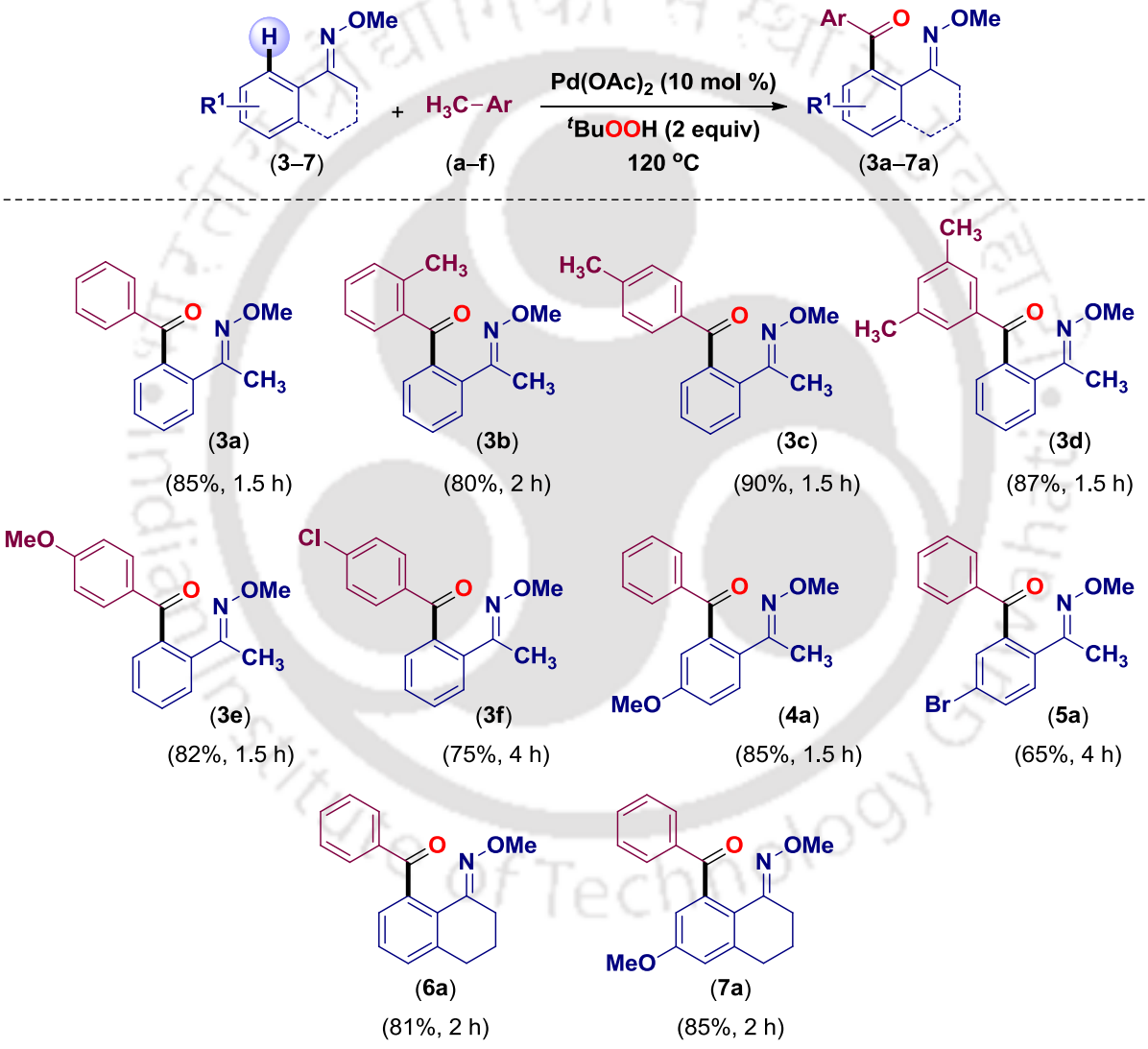


[a] Reaction conditions: 2-aryloxypyridine (**2**) (1 mmol), methylbenzenes (**a–f**) (10 mmol), $Pd(OAc)_2$ (0.1 mmol), TBHP in decane (5–6 M) (2 mmol), 120 °C, time 1.5–3 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

So far as the *ortho*-aroylation is concerned, the aryl ketone oxime ethers as the substrates have significant prospects. The 1,2-diacylarenes generated upon deprotection of oxime ether are useful precursors to a number of biologically important scaffolds such as isoindoles, isoquinolines, *N*-arylpthalimidines, and pthalazines.[21] Thus, a similar aroylation reaction was attempted with the acetophenone *O*-methyl oxime (**3**) and toluene (**a**) employing the above optimized conditions. Encouragingly, the reaction provided an excellent yield of the *o*-aroylated product (**3a**) (Scheme IV.3.3). Subsequent reactions were carried out with acetophenone *O*-methyl oxime (**3**) and other methylarenes as the coupling partners. The yields of coupled products (**3b**–**3e**) were relatively higher with *p*-chlorotoluene being the lone exception giving a modest yield of the product (**3f**) (Scheme IV.3.3). The effects of substituents present in the acetophenone *O*-methyl oxime were investigated. *p*-Methoxyacetophenone *O*-methyl oxime (**4**) underwent a facile aroylation

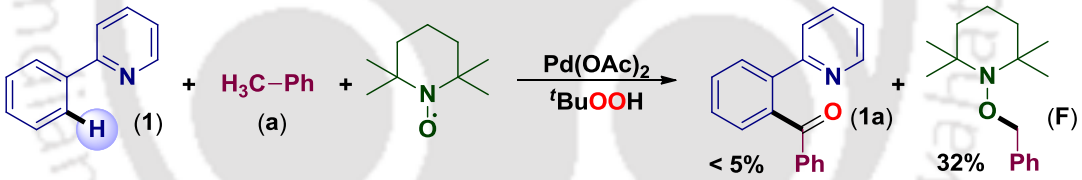
with toluene affording a high yield of the desired product (**4a**) (Scheme IV.3.3). However with *p*-bromoacetophenone *O*-methyl oxime (**5**), the product (**5a**) yield was moderate (Scheme IV.3.3). The *O*-methyl oxime of bicyclic ketones, viz. α-tetralone analogues (**6**–**7**) underwent smooth reactions with toluene furnishing their corresponding aryl ketones (**6a**–**7a**) in excellent yields (Scheme IV.3.3).

Scheme IV.3.3. *Substrate scope for o-aroylation of ketoxime ether*[a,b]



[a] Reaction conditions: ketoxime ether (**3–7**) (1 mmol), methylbenzenes (**a–f**) (10 mmol), $Pd(OAc)_2$ (0.1 mmol), TBHP in decane (5–6 M) (2 mmol), 120 °C, time 1.5–4 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

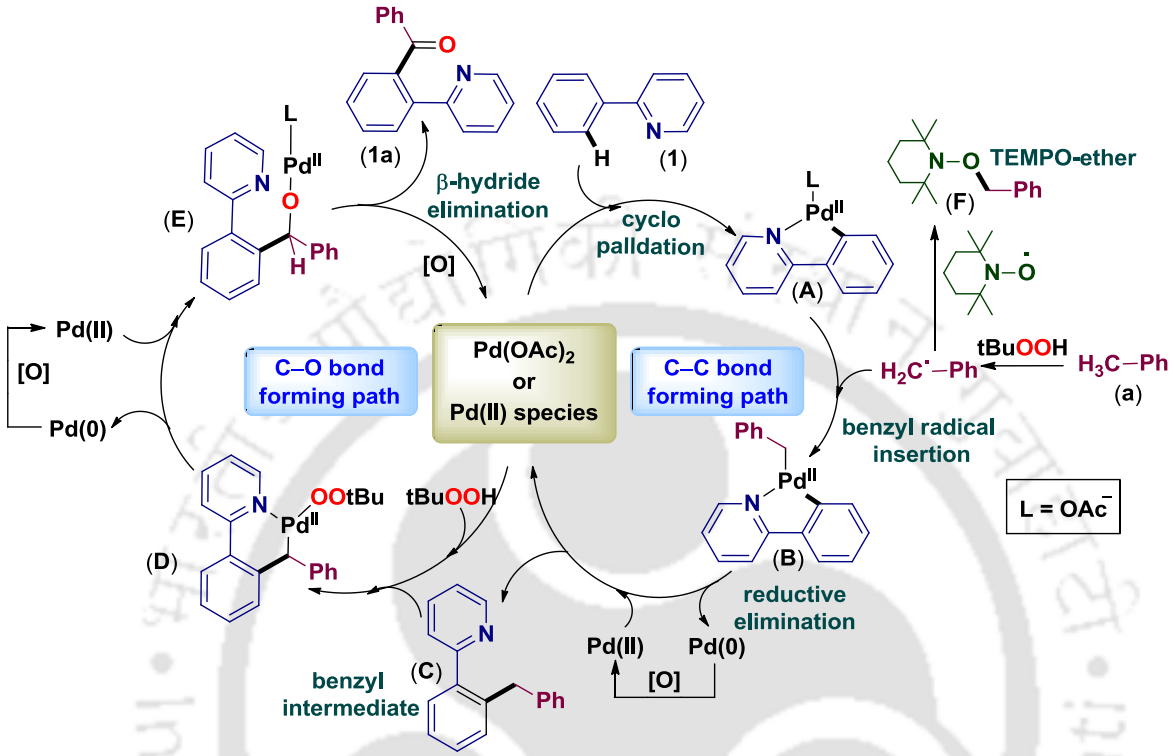
Mechanistic studies. There are two possible mechanisms that can operate for this transformation. In the first possible route, the oxidation of methylarenes to corresponding aldehydes (i.e. C–O bond formation) might occur initially followed by aroylation at the *ortho* C–H bond of arenes (i.e. C–C bond formation) to give the expected product.[14] In an alternative route, first benzylation (i.e. C–C bond formation) might take place to give *ortho*-benzylated intermediate which on subsequent oxidation at the benzylic position (i.e. C–O bond formation) can lead to the desired product. To probe which path is prevalent several experimental studies were performed. GC-MS analysis of the aliquots taken during an ongoing reaction of 2-phenylpyridine (**1**) with toluene (**a**) showed no presence of either benzaldehyde or benzyl alcohol in the reaction medium that could possibly form via a radical oxidation of toluene (**a**). In another experiment when 2-phenylpyridine (**1**) and toluene (**a**) were reacted under standard conditions in presence of radical scavenger 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO), there was a considerable quenching of the reaction giving < 5% yield of the expected product (**1a**) along with a benzyl-TEMPO ether (**F**) (Scheme IV.3.4).



Scheme IV.3.4. *Reaction in presence of radical scavenger TEMPO*

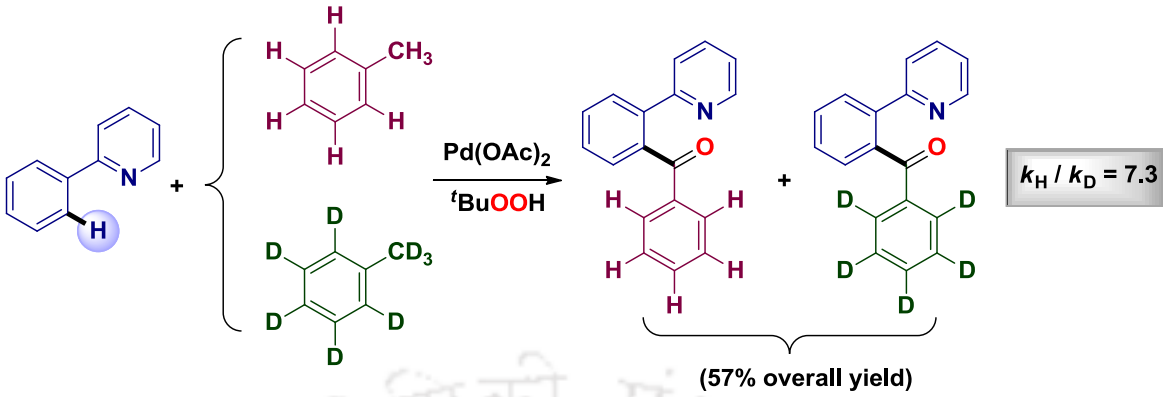
The outcome of the above experiment suggests two things; (i) the mechanism is radical in nature where TBHP is possibly playing the role of both an oxidant and a radical initiator and (ii) the trapping of benzyl radical with TEMPO and not observing any aldehyde formation indicates the benzylation is followed by benzylic oxidation. Based on these observations and literature reports,[6a,22] a plausible mechanism has been proposed for this transformation (Scheme IV.3.5). The mechanism comprises of two paths; C–C bond formation and C–O bond formation. In C–C bond forming path, presumably TBHP generates a radical at the benzylic carbon of alkylbenzene (**a**) that undergoes addition to the Pd-substrate complex (**A**) to form the intermediate (**B**). Reductive elimination of the Pd catalyst from (**B**) affords the benzylic product (**C**). While in the C–O bond forming path,

Pd/TBHP facilitate rapid oxidation at the benzylic position of intermediate (**C**) to generate the keto functionality (**1a**) via intermediacy of (**D**) and (**E**).[21h]



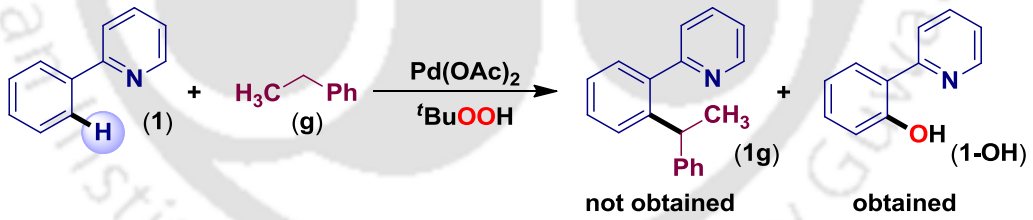
Scheme IV.3.5. *Proposed mechanism for o-aroylation*

All our attempts to trap the benzylated product failed due to the fast oxidation kinetics. In other words, either the cleavage of benzylic C–H bond or arene sp^2 C–H bond might be involved in the rate-determining step. To ascertain this presumption, an intermolecular competing kinetic isotope effect (KIE) experiment was performed by reacting 2-phenylpyridine (**1**) with an equimolar mixture of toluene (**a**) and d_8-toluene (**[D]-a**) under the standard reaction conditions. A high kinetic isotope effect (k_H/k_D = 7.3) observed in this experiment suggests it is the not the arene sp^2 C–H bond but the benzylic C–H bond cleavage that is involved in the rate-determining step for this transformation (Scheme IV.3.6, also see Experimental section IV.4.4). This fact can be further rationalized from the observations that the reactions worked better with methylarenes possessing electron-donating groups for which the initial benzyl radical formation i.e. oxidation is more facile compared to those having electron-withdrawing substituents.



Scheme IV.3.6. *KIE experiment with deuterated toluene*

In an attempt to isolate the benzylated intermediate and prevent further oxidation, (**1**) was reacted with ethylbenzene (**g**) instead of methylarenes under the standard conditions (Scheme IV.3.7). However, the reaction yielded an *o*-hydroxylated product (**1-OH**) in 20% yield instead of the expected benzylated product (**1g**) leaving a major amount of unreacted starting material (**1**) even after 24 h (Scheme IV.3.7). Although we have isolated the reactive intermediates to unravel the mechanism, however failure to obtain or observe the *ortho*-benzylated intermediate makes the mechanistic picture currently unclear. Thus a detailed mechanism of each elementary step is still to be illuminated.



Scheme IV.3.7. *Reaction of 2-phenylpyridine with ethylbenzene*

In conclusion, an aroylation protocol at the *ortho* C–H bond has been accomplished via sequential C–C/C–O bond formations involving four C–H bond activations. This is the first illustration of an arene–alkane coupling giving an *o*-aroylated product involving activations of nonreactive benzylic sp^3 C–H of methylarenes and sp^2 C–H bonds of arenes facilitated by the directing groups. With polymethylated arenes, selective monoaroylated products were formed without affecting the other methyl groups. Hence by judging the

practicality of the present protocol, it can be an additional alternative to the existing acylation reactions.

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 sulphate. 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 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. FT-IR spectra were recorded in KBr or neat. HRMS spectra were recorded using ESI mode. Elemental analyses were recorded on CHNS analyzer.

IV.4.2. General procedure for the synthesis of phenyl(2-(pyridine-2-yl)phenyl)methanone (1a). An oven-dried reaction vessel was charged with 2-phenylpyridine (**1**) (155 mg, 1 mmol), toluene (**a**) (920 mg, 10 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol) and TBHP in decane (5–6 M) (400 µL, 2 mmol). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 1.5 h. The reaction mixture was cooled down to room temperature and then filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with 5% solution of sodium bicarbonate solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed in vacuo. The residue was purified over a column of silica gel and eluted with (9:1, hexane/ethyl acetate) to give phenyl(2-(pyridine-2-yl)phenyl)methanone (**1a**) (220 mg, 85% yield). The same procedure was also followed for *o*-aroylation of other arenes (**2**–**7**) with alkylbenzenes (**a**–**f**).

IV.4.3. Mechanistic investigation in the presence of radical scavenger TEMPO. An oven-dried reaction vessel was charged with 2-phenylpyridine (**1**) (155 mg, 1 mmol),

toluene (**a**) (920 mg, 10 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), TBHP in decane (5–6 M) (400 µL, 2 mmol) and TEMPO (0.312 g, 2 mmol). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 1.5 h. The reaction mixture after usual work up and purification by column chromatography afforded the benzyl-TEMPO adduct 2,2,6,6-2,2,6,6-tetramethylpiperidin-1-((4-methylbenzyl)oxy) piperidine (**F**) in 32% yield along with traces (< 5%) of the desired product (**1a**). This experiment suggests the formation of benzyl radical in the medium from toluene (**1**) and also the radical nature of the mechanism.

IV.4.4. Intermolecular competing kinetic isotope effect (KIE) experiment with deuterated toluene. An oven-dried reaction vessel was charged with 2-phenylpyridine (**1**) (78 mg, 0.5 mmol), toluene (**a**) (230 mg, 2.5 mmol), d_8-toluene ([**D**]-**a**) (250 mg, 2.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol) and TBHP in decane (5–6 M) (200 µL, 1 mmol). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 1.5 h. The reaction mixture was then worked up in usual procedure and the crude product was purified over a column of silica gel eluted with (9:1, hexane/ethyl acetate) to give ketone products (**1a** and [**D**]-**1a**) in 57% overall yield. The k_H/k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed a significant KIE (k_H/k_D = 7.3). This result suggests that the benzylic sp^3 C−H bond cleavage is involved in the rate-determining step of this transformation.

Calculation:

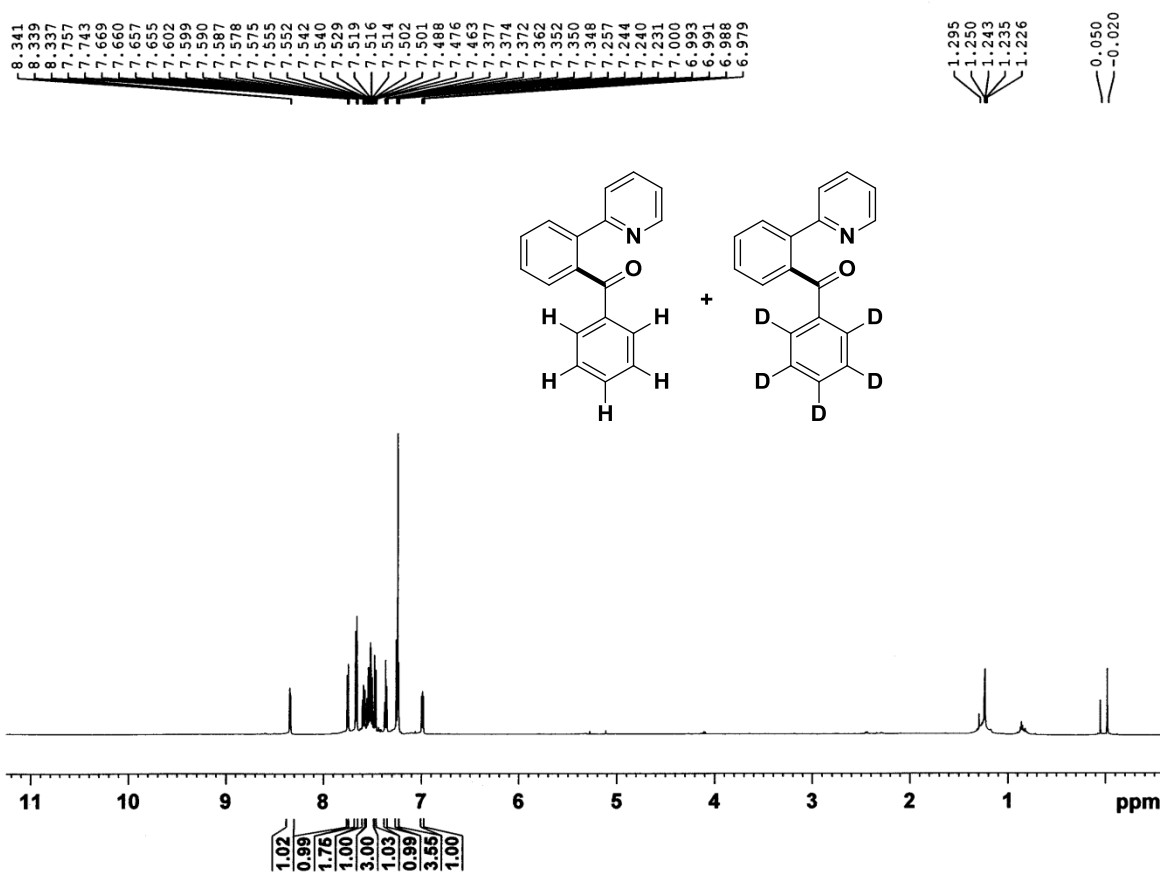
The integration value of protons originating from 2-phenylpyridine at 8.34 ppm and 6.99 ppm is 1.02 and 1.00 respectively.

Upon correlation with the original spectra of (**1a**) the number of protons that is originating from toluene at 7.66 should be 2.

However the integration value at this region is 1.76.

Hence the proton difference in this region is 2 – 1.76 = 0.24.

Thus the k_H/k_D = 1.76 / 0.24 = 7.33 ~ 7.3



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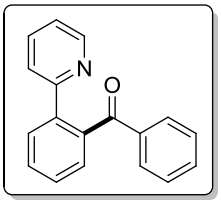
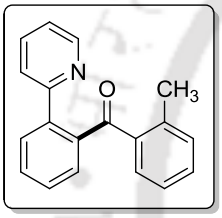
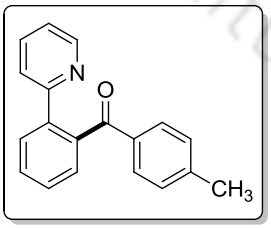
IV.6. Spectral data



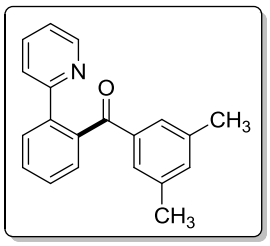
Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.02 (t, 1H, *J* = 6.8 Hz), 7.25–7.29 (m, 1H), 7.39 (t, 1H, *J* = 7.2 Hz), 7.48–7.63 (m, 6H), 7.69 (d, 2H, *J* = 7.6 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 8.36–8.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.1, 122.8, 128.2, 128.6, 128.9, 129.2, 129.6, 130.3, 132.5, 136.5, 138.0, 139.6, 139.8, 149.1, 156.9, 198.3; IR (KBr): 3065, 2919, 2851, 1665, 1586, 1283, 1247, 925, 755, 700 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}NO$ (MH^+) 260.1070; found 260.1072.



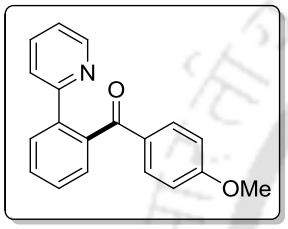
(2-(Pyridin-2-yl)phenyl)(*o*-tolyl)methanone (1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.57 (s, 3H), 6.93 (t, 1H, *J* = 7.6 Hz), 6.99–7.02 (m, 1H), 7.08 (d, 1H, *J* = 7.6 Hz), 7.14–7.18 (m, 2H), 7.40 (d, 1H, *J* = 8.0 Hz), 7.49–7.66 (m, 5H), 8.42–8.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 122.0, 122.8, 125.0, 128.6, 129.3, 130.0, 130.6, 130.7, 131.1, 131.4, 136.4, 138.2, 139.3, 140.3, 140.8, 148.9, 157.6, 200.0; IR (KBr): 3062, 3021, 2961, 2926, 1661, 1588, 1486, 1456, 1437, 1426, 1297, 1273, 927, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO$ (MH^+) 274.1226; found 274.1223.



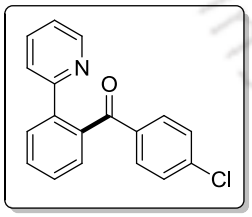
(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 7.02–7.09 (m, 3H), 7.46–7.61 (m, 7H), 7.77 (d, 1H, *J* = 7.6 Hz), 8.40–8.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 122.2, 123.2, 128.6, 129.0, 129.1, 129.2, 129.3, 130.0, 130.3, 135.4, 136.6, 143.4, 149.2, 157.1, 198.2; IR (KBr): 3054, 2923, 1661, 1607, 1467, 1440, 1426, 1281, 1264, 929, 739 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO$ (MH^+) 274.1226; found 274.1230.



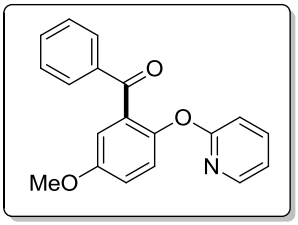
(3,5-Dimethylphenyl)(2-(pyridin-2-yl)phenyl)methanone (1d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 6H), 7.01–7.04 (m, 2H), 7.32 (s, 2H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.50–7.61 (m, 4H), 7.75 (d, 1H, *J* = 7.6 Hz), 8.40–8.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 122.2, 123.3, 127.7, 127.9, 128.5, 129.3, 130.3, 134.4, 135.1, 136.5, 137.8, 138.1, 139.8, 149.1, 157.3, 198.6; IR (KBr): 3054, 3005, 2919, 1667, 1605, 1440, 1426, 1310, 1225, 866, 821, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO$ (MH^+) 288.1383; found 288.1388.



(4-Methoxyphenyl)(2-(pyridin-2-yl)phenyl)methanone (1e): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.77 (s, 3H), 6.75 (d, 2H, *J* = 8.8 Hz), 7.02–7.05 (m, 1H), 7.46 (d, 1H, *J* = 8.0 Hz), 7.49–7.60 (m, 4H), 7.68 (d, 2H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 7.6 Hz), 8.41–8.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.3, 113.3, 121.9, 122.9, 128.3, 128.7, 129.0, 129.9, 130.6, 131.8, 136.3, 139.3, 139.6, 149.0, 156.9, 163.0, 196.9; IR (KBr): 3065, 2917, 1651, 1602, 1465, 1440, 1256, 1023, 930, 844, 752 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1181.

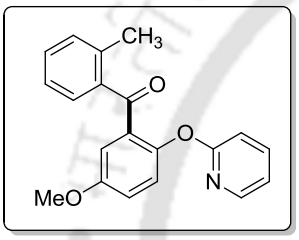


(4-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1f): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.00–7.03 (m, 1H), 7.22 (d, 2H, *J* = 8.8 Hz), 7.50–7.52 (m, 3H), 7.55–7.62 (m, 4H), 7.76 (d, 1H, *J* = 8.0 Hz), 8.31–8.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.2, 122.5, 128.4, 128.68, 128.72, 129.1, 130.4, 130.7, 136.6, 138.6, 139.1, 139.5, 149.0, 156.5, 197.0; IR (KBr): 3061, 3010, 2928, 1667, 1587, 1485, 1470, 1439, 1427, 1398, 1283, 1090, 928, 844, 749 cm^{-1}; Anal calcd. for $C_{18}H_{12}ClNO$: C 73.60, H 4.12, N 4.77; found C 73.66, H 4.10, N 4.70.



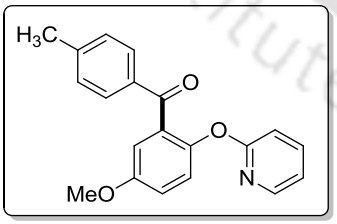
(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone

(2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.83 (s, 3H), 6.52 (d, 1H, *J* = 8.0 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* = 8.0 Hz), 7.46 (t, 2H, *J* = 8.4 Hz), 7.74 (d, 2H, *J* = 8.0 Hz), 8.00–8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.9, 111.2, 114.6, 118.2, 118.3, 124.3, 128.2, 129.9, 133.0, 133.1, 137.5, 139.3, 145.0, 147.1, 156.5, 163.5, 195.2; IR (KBr): 3061, 3005, 2956, 2936, 1667, 1596, 1489, 1465, 1428, 1266, 1201, 1036, 779, 736, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_3$ (MH^+) 306.1225; found 306.1226.



(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(*o*-tolyl)methanone

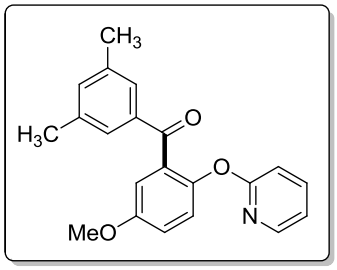
(2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 3.85 (s, 3H), 6.38 (d, 1H, *J* = 8.4 Hz), 6.82–6.85 (m, 1H), 7.03 (t, 1H, *J* = 7.6 Hz), 7.09 (d, 1H, *J* = 8.0 Hz), 7.125–7.130 (m, 2H), 7.20–7.24 (m, 2H), 7.31 (d, 1H, *J* = 7.6 Hz), 7.42–7.46 (m, 1H), 8.00–8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3, 55.9, 111.0, 114.9, 118.2, 119.4, 124.7, 125.1, 130.0, 130.9, 131.0, 133.8, 137.8, 138.7, 139.2, 145.6, 147.0, 156.8, 163.5, 196.9; IR (KBr): 3064, 2960, 2927, 1661, 1594, 1489, 1465, 1427, 1269, 1231, 1200, 1036, 733 cm^{-1}; Anal calcd. for $C_{20}H_{17}NO_3$: C 75.22, H 5.37, N 4.39; found C 75.29, H 5.39, N 4.31.



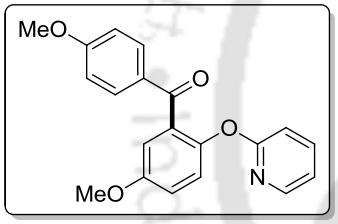
(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(*p*-tolyl)methanone

(2c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 3.83 (s, 3H), 6.57 (d, 1H, *J* = 8.0 Hz), 6.84–6.88 (m, 1H), 7.03 (d, 1H, *J* = 3.2 Hz), 7.07–7.14 (m, 3H), 7.19 (d, 1H, *J* = 8.8 Hz), 7.47–7.51 (m, 1H), 7.66 (d, 2H, *J* = 8.4 Hz), 8.02–8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 55.9, 111.3, 114.5, 117.9, 118.3, 124.2, 128.9, 130.2, 133.4, 134.9, 139.3, 143.9, 144.9, 147.1, 156.5, 163.6, 194.8; IR (KBr) 3057, 3005, 2939, 1661, 1605, 1489, 1465, 1266, 1035, cm^{-1}; Anal calcd. for $C_{20}H_{17}NO_3$: C

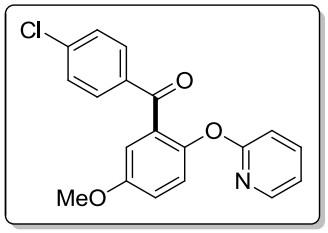
75.22, H 5.37, N 4.39; found C 75.17, H 5.45, N 4.28.



(5-Methoxy-2-(pyridine-2-yloxy)phenyl)(3,5-dimethylphenyl) methanone (2d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 6H), 3.84 (s, 3H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.84–6.87 (m, 1H), 7.04–7.12 (m, 3H), 7.19 (d, 1H, *J* = 8.8 Hz), 7.36 (s, 2H), 7.47–7.51 (m, 1H), 8.04–8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 55.9, 111.4, 114.5, 118.0, 118.3, 124.3, 127.7, 133.4, 134.6, 137.6, 137.8, 139.3, 145.0, 147.1, 156.4, 163.5, 195.7; IR (KBr) 3055, 3005, 2920, 1661, 1606, 1488, 1464, 1428, 1305, 1265, 1201, 1035, 871, 776, 735 cm^{-1}; Anal calcd. for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20; found C 75.72, H 5.83, N 4.12.

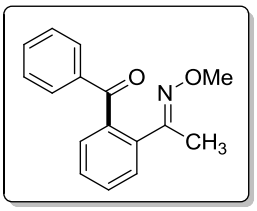


(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(4-methoxyphenyl) methanone (2e): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.825 (s, 3H), 3.833 (s, 3H), 6.59 (d, 1H, *J* = 8.4 Hz), 6.80–6.87 (m, 3H), 7.02–7.03 (m, 1H), 7.06–7.09 (m, 1H), 7.18 (d, 1H, *J* = 8.8 Hz), 7.47–7.52 (m, 1H), 7.76 (d, 2H, *J* = 8.8 Hz), 8.01–8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 55.9, 111.3, 113.5, 114.3, 117.7, 118.3, 124.1, 130.3, 132.5, 133.6, 139.3, 144.7, 147.2, 156.5, 163.6, 163.7, 193.7; IR (KBr): 3057, 3009, 2937, 2839, 1660, 1598, 1464, 1427, 1261, 1032, 847, 775 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_4$ (MH^+) 336.1230; found 336.1230.

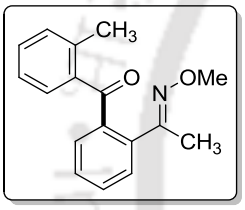


(4-Chlorophenyl)(5-methoxy-2-yloxy)phenyl)methanone (2f): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.84 (s, 3H), 6.54 (d, 1H, *J* = 8.4 Hz), 6.85–6.88 (m, 1H), 7.05 (d, 1H, *J* = 2.8 Hz), 7.09–7.12 (m, 1H), 7.18 (d, 1H, *J* = 8.8 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 7.48–7.52 (m, 1H), 7.68 (d, 2H, *J* = 8.8 Hz), 7.99–8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.9, 111.2, 114.4, 118.4, 118.5, 124.2, 128.4, 131.2, 132.6, 135.8, 139.3, 139.4, 144.8,

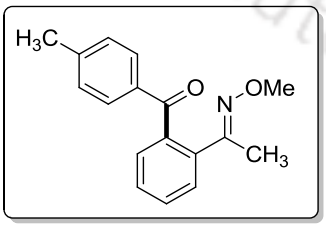
147.0, 156.5, 163.2, 193.9; IR (KBr) 3065, 3011, 2934, 1667, 1593, 1488, 1089, 1037, 774 cm^{-1}; Anal calcd. for $C_{19}H_{14}ClNO_3$: C 67.16, H 4.15, N 4.12; found C 67.11, H 4.19, N 4.04.



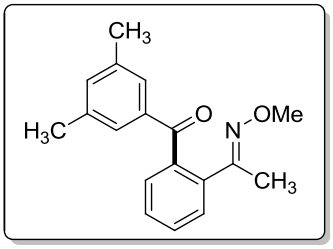
(2-(1-Methoxyiminoethyl)phenyl)(phenyl)methanone (3a): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.00 (s, 3H), 3.65 (s, 3H), 7.38 (t, 2H, *J* = 8.0 Hz), 7.44–7.52 (m, 5H), 7.69 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.6, 61.8, 127.8, 128.4, 128.7, 129.1, 129.4, 130.4, 132.7, 136.6, 138.3, 139.0, 154.2, 197.8; IR (KBr): 3061, 2979, 2934, 1669, 1595, 1448, 1313, 1284, 1249, 1044, 925, 899, 758, 707 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{15}NO_2$ (MH^+) 254.1176; found 254.1172.



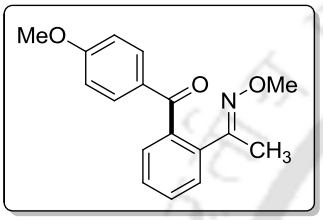
(2-(1-Methoxyiminoethyl)phenyl)(*o*-tolyl)methanone (3b): ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.94 (s, 3H), 2.55 (s, 3H), 3.80 (s, 3H), 7.12 (t, 1H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 7.6 Hz), 7.27 (d, 1H, *J* = 7.6 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.41–7.46 (m, 2H), 7.51–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 15.5, 21.2, 61.8, 125.2, 128.4, 128.6, 130.0, 130.4, 130.9, 131.4, 131.7, 137.6, 138.2, 139.2, 140.0, 155.9, 199.2; IR (KBr) 3062, 2963, 2935, 1666, 1596, 1455, 1300, 1276, 1246, 1048, 927, 892, 757, 732 cm^{-1}; Anal calcd. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found C 76.43, H 6.47, N 5.18.



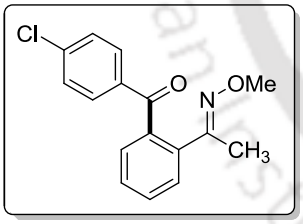
(2-(1-Methoxyiminoethyl)phenyl)(*p*-tolyl)methanone (3c): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H), 2.40 (s, 3H), 3.69 (s, 3H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.44–7.45 (m, 2H), 7.50–7.52 (m, 2H), 7.62 (d, 2H, *J* = 8.0 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 14.7, 21.8, 61.8, 127.8, 128.6, 129.0, 129.1, 129.6, 130.2, 135.7, 136.5, 139.2, 143.4, 154.2, 197.4; IR (KBr): 3060, 2962, 2936, 1666, 1606, 1311, 1286, 1047, 929, 896, 761 cm^{-1}; Anal calcd. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found C 76.35, H 6.48, N 5.15.



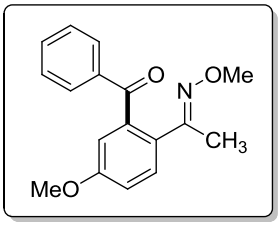
(2-(1-Methoxyiminoethyl)phenyl)(3,5-dimethylphenyl) methanone (3d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.99 (s, 3H), 2.30 (s, 6H), 3.69 (s, 3H), 7.14 (s, 1H), 7.30 (s, 2H), 7.43–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.9, 21.3, 61.8, 127.3, 127.9, 128.6, 129.3, 130.3, 134.4, 136.8, 138.0, 138.3, 139.2, 154.5, 198.0; IR (KBr): 3059, 2935, 2898, 1666, 1605, 1311, 1225, 1048, 895, 761 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}NO_2$ (MH^+) 282.1489; found 282.1488.



(2-(1-Methoxyiminoethyl)phenyl)(4-methoxyphenyl) methanone (3e): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.04 (s, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 6.88 (d, 2H, *J* = 7.2 Hz), 7.43 (m, 2H), 7.49 (m, 2H), 7.71 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.8, 55.6, 61.8, 113.6, 127.9, 128.6, 128.9, 130.0, 131.1, 131.9, 136.5, 139.3, 154.4, 163.3, 196.5; IR (KBr) 3062, 2963, 2936, 1659, 1600, 1508, 1462, 1441, 1314, 1289, 1256, 1176, 1150, 1046, 930, 895, 845, 762 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{17}NO_3$ (MH^+) 284.1281; found 284.1284.

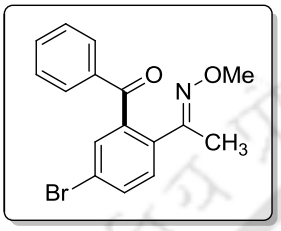


(4-Chlorophenyl)(2-(1-methoxyiminoethyl)phenyl)methanone (3f): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.05 (s, 3H), 3.67 (s, 3H), 7.37 (d, 2H, *J* = 8.8 Hz), 7.43–7.57 (m, 4H), 7.65 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.2, 61.8, 127.7, 128.7, 128.8, 128.9, 130.4, 130.6, 136.2, 136.7, 138.5, 138.9, 153.7, 196.4; IR (KBr) 3068, 2974, 2935, 1670, 1592, 1484, 1397, 1369, 1285, 1088, 1037, 928, 894, 764 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}ClNO_2$ (MH^+) 288.0786; found 288.0782.

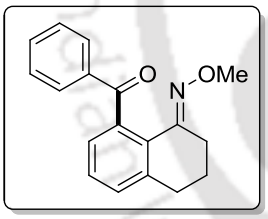


(5-Methoxy-2-(1-methoxyiminoethyl)phenyl)(phenyl) methanone (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.99 (s, 3H), 3.63 (s, 3H), 3.85 (s, 3H), 6.99 (d, 1H, *J* = 2.8 Hz), 7.03–7.06 (m, 1H), 7.38–7.44 (m, 3H), 7.51 (t, 1H, *J* = 7.2 Hz), 7.71 (d, 2H,

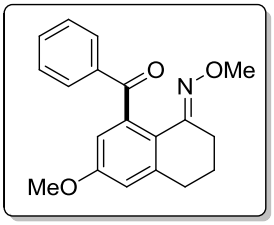
J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 55.6, 61.6, 114.2, 115.9, 128.3, 128.7, 129.0, 129.3, 132.6, 138.2, 140.4, 153.4, 159.9, 197.4; IR (KBr): 3060, 2962, 2936, 1667, 1600, 1564, 1496, 1449, 1287, 1234, 1046, 965, 895, 839, 748, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{17}NO_3$ (MH^+) 284.1281; found 284.1277.



(5-Bromo-2-(1-methoxyiminoethyl)phenyl)(phenyl)methanone (5a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.99 (s, 3H), 3.62 (s, 3H), 7.34–7.41 (m, 3H), 7.52 (t, 1H, *J* = 7.6 Hz), 7.57 (d, 1H, *J* = 2.0 Hz), 7.62–7.64 (m, 1H), 7.66–7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 61.9, 123.0, 128.5, 129.3, 129.4, 131.8, 133.0, 133.2, 135.2, 137.7, 140.7, 153.0, 196.0; IR (KBr): 3060, 2963, 2936, 1669, 1596, 1582, 1448, 1315, 1281, 1046, 898, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}BrNO_2$ (MH^+) 332.0281; found 332.0287.

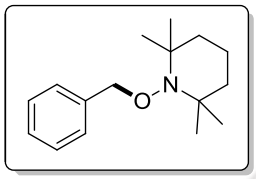


1,2,3,4-Tetrahydro-1-methoxyiminonaphthalen-8-yl)(phenyl) methanone (6a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.85 (quin, 2H, *J* = 6.4 Hz), 2.57 (t, 2H, *J* = 6.4 Hz), 2.80 (t, 2H, *J* = 6.0 Hz), 3.54 (s, 3H), 7.20 (d, 1H, *J* = 7.2 Hz), 7.27 (d, 1H, *J* = 8.0 Hz), 7.33–7.39 (m, 3H), 7.48 (t, 1H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 24.4, 30.5, 61.7, 126.5, 128.3, 128.6, 129.0, 129.1, 129.7, 132.3, 138.4, 138.8, 140.7, 151.9, 198.1; IR (KBr): 3059, 2936, 1669, 1597, 1581, 1448, 1313, 1280, 11049, 879, 714 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_2$ (MH^+) 280.1332; found 280.1331.



1,2,3,4-Tetrahydro-6-methoxy-1-methoxyiminonaphthalen-8-yl) (phenyl)methanone (7a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.84 (quin, 2H, *J* = 6.4 Hz), 2.54 (t, 2H, *J* = 6.8 Hz), 2.76 (t, 2H, *J* = 6.0 Hz), 3.51 (s, 3H), 3.83 (s, 3H), 6.75 (d, 1H, *J* = 2.8 Hz), 6.79 (d, 1H, *J* = 2.8 Hz), 7.37 (t, 2H, *J* = 8.0 Hz), 7.49 (t, 1H,

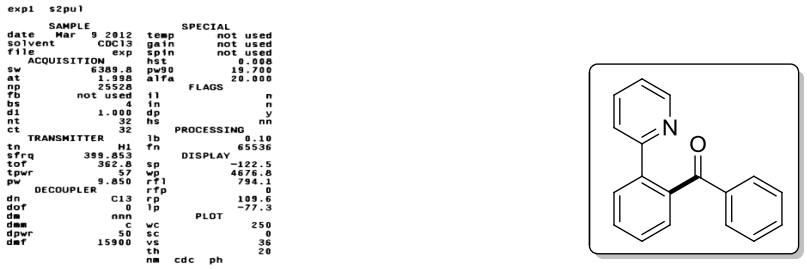
J = 7.6 Hz), 7.71–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 24.3, 30.8, 55.6, 61.6, 112.3, 114.9, 128.3, 129.1, 132.3, 138.3, 140.4, 142.6, 151.6, 159.8, 197.7; IR (KBr): 3059, 2936, 1669, 1595, 1470, 1449, 1353, 1316, 1288, 1150, 1043, 878, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{19}NO_3$ (MH^+) 310.1438; found 310.1435.

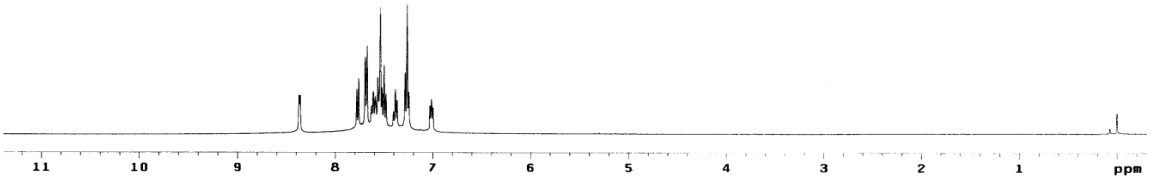


1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (F): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (s, 6H), 1.26 (s, 6H), 1.49–1.70 (m, 6H), 4.87 (s, 2H), 7.27–7.83 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.3, 20.4, 33.2, 39.9, 60.1, 78.9, 127.4, 127.6, 128.3, 138.4; HRMS (ESI): calcd. for $C_{16}H_{25}NO$ (MH^+) 248.2009; found 248.2002.

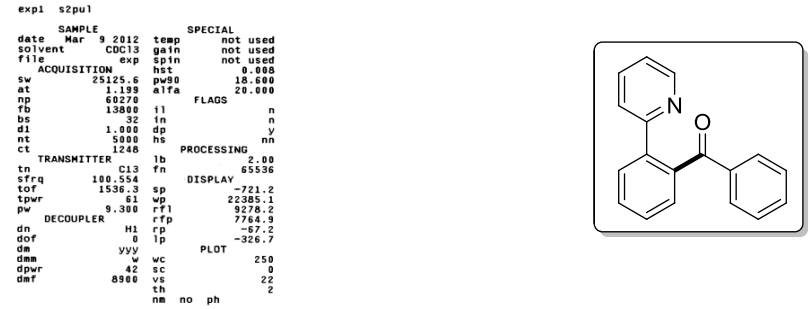
IV.7. Spectra

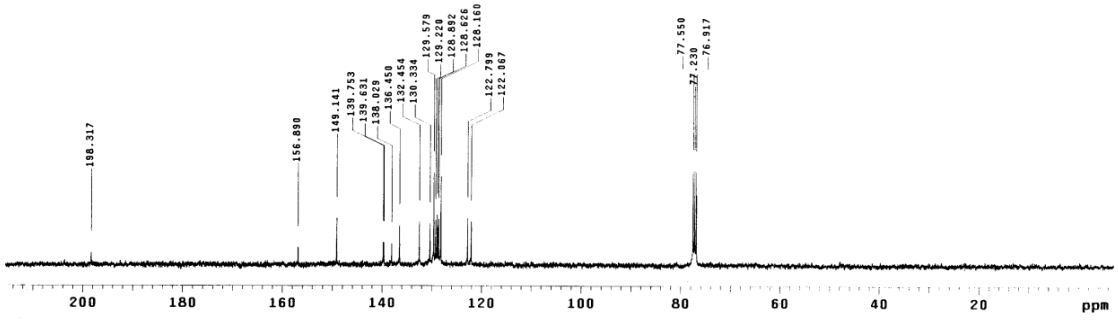
Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



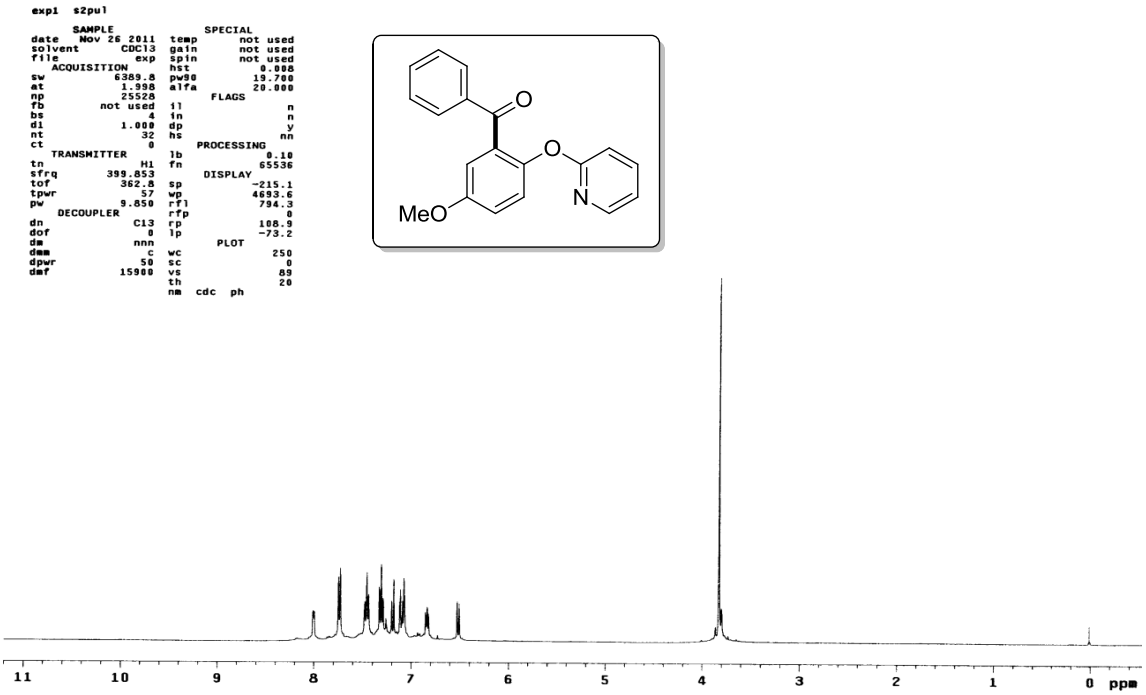


Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{13}C NMR (100 MHz, $CDCl_3$)

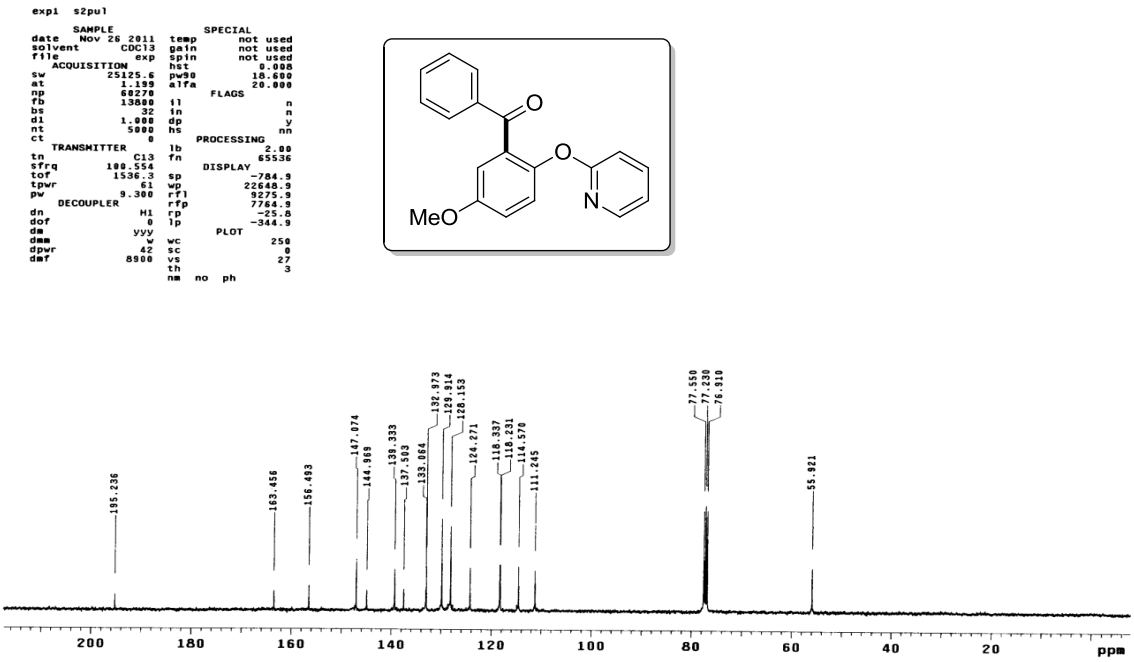




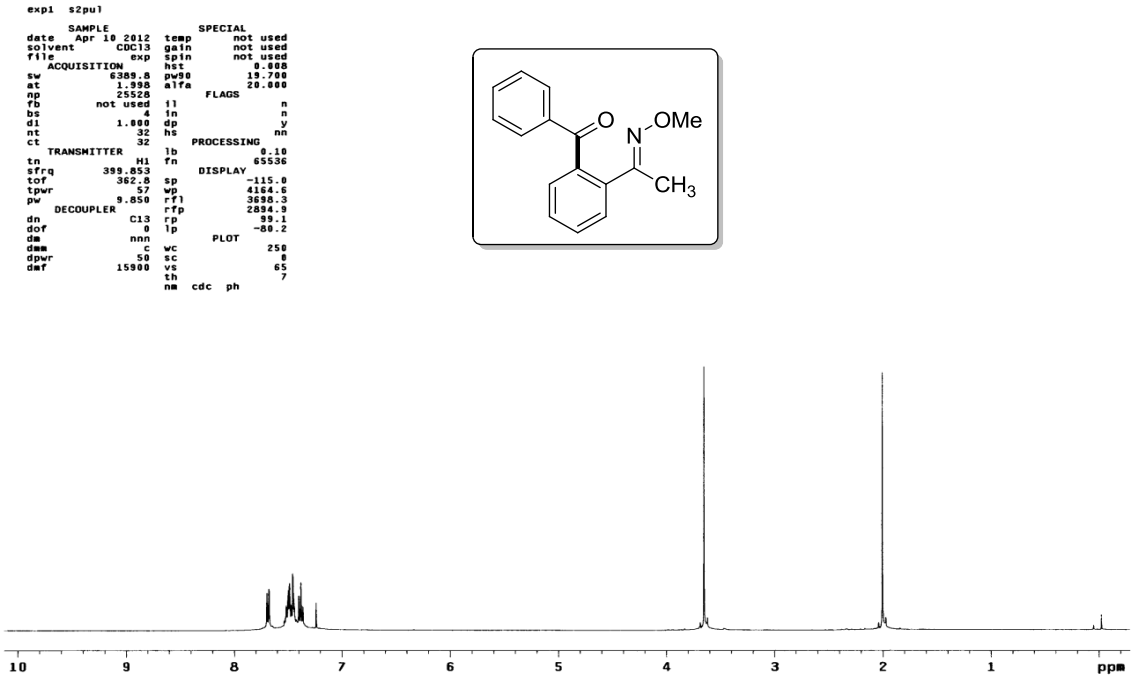
(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (2a): ^{1}H NMR (400 MHz, $CDCl_3$)



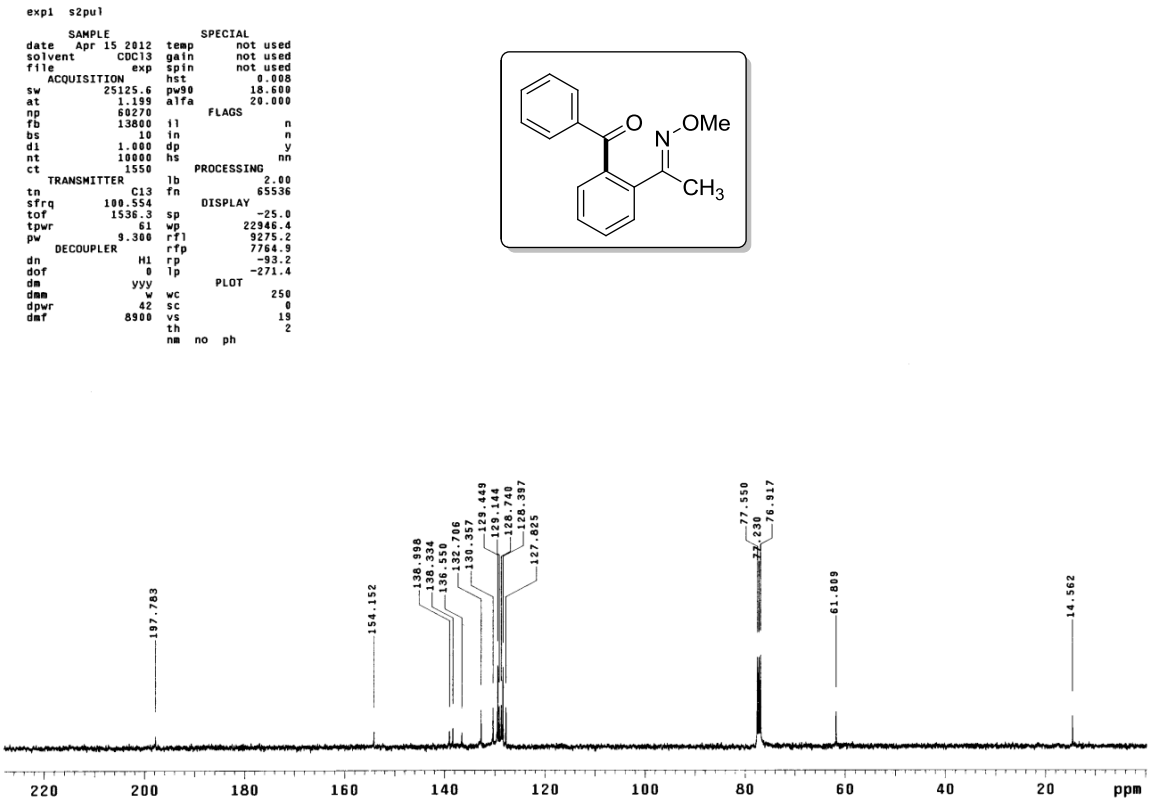
(5-Methoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (2a): ^{13}C NMR (100 MHz, $CDCl_3$)



(2-(1-Methoxyiminoethyl)phenyl)(phenyl)methanone (3a): ^{1}H NMR (400 MHz, $CDCl_3$)



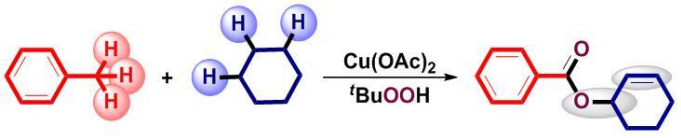
(2-(1-Methoxyiminoethyl)phenyl)(phenyl)methanone (3a): ^{13}C NMR (100 MHz, $CDCl_3$)



भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Chapter V

Copper-Catalyzed Esterification of Alkylbenzenes with Cycloalkanes via C(sp^3)–H Activation Following Cross-Dehydrogenative Coupling (CDC)



- six C–H bond cleavages
- solvent-solvent couplings
- unexpected dehydrogenative-olefination of cycloalkanes

Abstract: *This protocol describes a Cu-catalyzed dehydrogenation-olefination and esterification of the C(sp^3)–H bond of cycloalkanes with alkylbenzenes in presence of TBHP as the oxidant. This reaction involves six consecutive sp^3 C–H bond cleavages. An appreciable range of methylarenes can be used in this reaction with cycloalkanes allowing a direct preparation of the corresponding cycloallyl esters.*

CHAPTER V

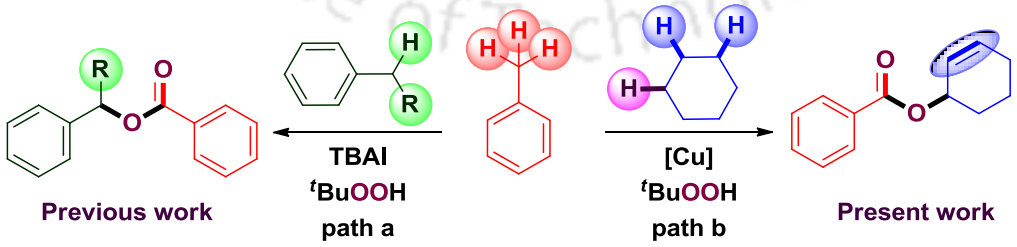
V. Copper-Catalyzed Esterification of Alkylbenzenes with Cycloalkanes via C(sp^3)–H Activation Following Cross-Dehydrogenative Coupling (CDC)

V.1. Introduction

The direct C–H activation path has streamlined the synthesis of functionalized molecules by minimizing the number of synthetic steps and making the processes more atom economic. One such strategy, the cross dehydrogenative coupling (CDC) has played a pivotal role by providing synthetic values to such methodologies.[1] The CDC protocols have been employed to access a diverse array of C–C and C–heteroatom bonds, by functionalizing C–H bonds of all types (sp, sp^2, sp^3).[2] The extreme reluctance of sp^3 C–H bonds to enter into the periphery of chemical reactions make their selective functionalization a formidable challenge. The solutions to these problems have resulted in some appealing results on sp^3 C–H functionalizations.[1a,b] In a limited hemisphere of sp^3 C–H bond functionalizations via CDC, the alkylbenzenes (methylarenes) are found to be useful precursors and have significant prospects in organic synthesis. In various protocols, they have enacted as ArCOO–, ArCO–, $ArCH_2O$– and $ArCH_2$– surrogates depending on the reaction conditions;[3] most of which have ultimately led to the synthesis of esters.[3a-d]

The formation of C−O bonds is a fundamental transformation in synthetic organic chemistry.[4] In particular; C−O bond construction through C−H activation is of great current interest. Pertinent to the abovementioned the ester functionality has been the common target and so the most revisited strategies are the one where the installation of ester C−O bond is via C−H activation.[3a-d,5] Esters are important building blocks in organic synthesis; hence syntheses of different classes of esters by unconventional approaches are always appreciable, particularly through functionalizations of inert C–H bonds. In this regard, our group has developed a protocol for the synthesis of benzylic esters involving only alkylbenzene(s) as the self or cross coupling partners under metal free conditions

(path a, Scheme V.1.1).[3a] In this protocol, one half of the alkylbenzene serves as the nucleophile ($ArCOO^-$) while the remaining half behaves as electrophile ($ArCH_2^+$) leading to the formation of benzylic ester. A remarkable outcome that has emerged out of this ester synthesis is the involvement of solvents (methylarenes) as substrates for sp^3 C–H functionalizations via CDC. The curiosity that arose was whether cycloalkanes behave similarly as mutual cross coupling partners with alkylbenzenes to give cycloalkyl benzoate under favorable conditions. Cycloalkanes are known to be widely used as solvents; however direct functionalization of them has been virtually unexplored owing to the high bond dissociation energy (BDE) of their sp^3 C–H bonds. Some reports that exist in literature are concerned on C–C,[1a-b,6] C–N[7] and C–S[8] bond formations involving cleavage of inert sp^3 C–H bonds, albeit a direct construction of ester C–O bond is unfamiliar. In pursuit to construct an ester C–O bond via sp^3 C–H activation of cycloalkane utilizing this "solvent chemistry" in a CDC reaction, cycloalkane (cyclohexane) was attempted as a potential coupling partner with alkylbenzenes. Although not under metal free conditions, but the use of copper catalyst and a radical initiator unexpectedly led to the formation of an allyl ester (path b, Scheme V.1.1). We envisaged the formation of an ester C–O bond at cyclohexane with PhCOO– derived from toluene. But the generation of an olefinic system and further formation of C–O bond at its allylic position leading to an allyl ester is unprecedented (path b, Scheme V.1.1). The present expedition toward the synthesis of allyl esters originated from this particular observation. Noteworthy to mention that this process formally involves six sp^3 C–H bond cleavages; (three each from either of the coupling partners) which is high for any single process.



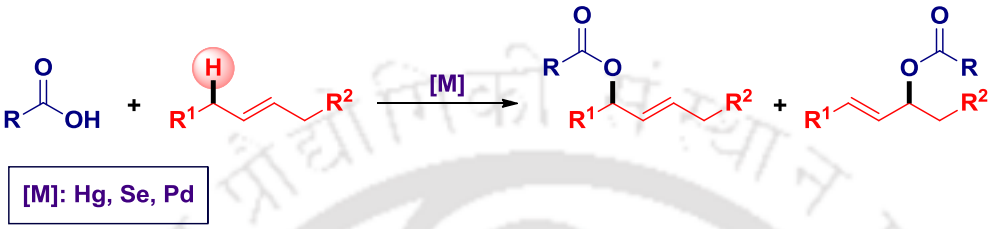
Scheme V.1.1. *Ester synthesis via solvent-solvent couplings*

The catalytic dehydrogenative olefination of alkanes observed during this process might have a great impact on chemical industries in the following decades, due to the abundance of alkanes and increasing use of olefins as raw materials. In recent years, catalytic dehydrogenation of alkanes to alkenes has witnessed remarkable progress.[9] Among the known examples of catalytic dehydrogenation of cyclohexane described to date, the catalytic systems based on Ir,[10] Pt,[11] and Re[12] complexes are the most studied. Recently, Pérez and co-workers discovered that the dehydrogenation of cycloalkanes to cycloalkenes can be accomplished by the reaction between hydrocarbons and hydrogen peroxide with copper complexes as a catalyst.[13] Although the chemical yields of the these conversions into cycloalkenes were only 4%, the potential of copper-based catalysts could not be underappreciated as it is much more economical compared to the Ir, Pt, and Re derived catalysts. Therefore, Cu-catalyzed dehydrogenation−olefination of cycloalkanes is a research area of great scientific significance.

V.2. Strategies for the synthesis of allyl esters

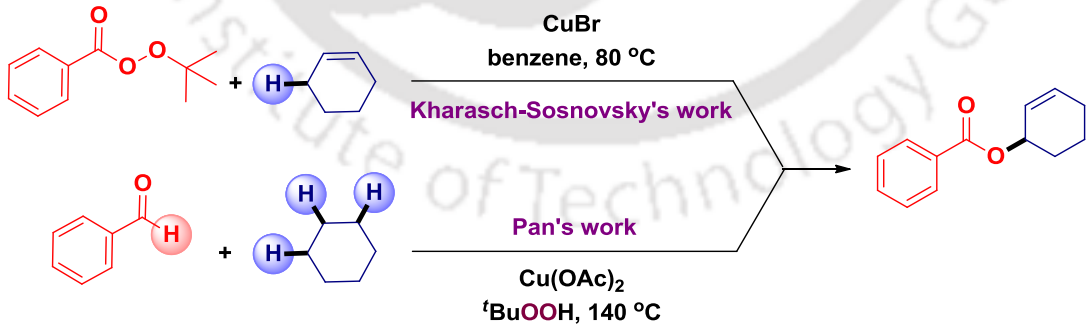
Allyl esters and their derivatives are valuable building blocks for the synthesis of complex molecules and key intermediates in the productions of many fine chemicals.[14] Also with various transformations available for olefin, they can be further modified into various other functionalities which can also have useful synthetic applications.[15] Allyl esters have also been employed as an efficient protecting group of the carboxyl group in the synthesis of peptides.[16] Allyl esters are traditionally achieved by reacting allyl alcohols with carboxylic acids or their derivatives which often require auxiliary chemicals. Apart from these conventional methods, they can also be synthesized by transition-metal-catalyzed nucleophilic substitution at the allylic position by carboxylates.[17] Although these methods afford a direct approach to allyl esters, but they often suffer from regioselectivity problems owing to the double bond isomerization in the allylic systems. Besides these, the formation of allyl esters via C–H bond oxidation has attracted considerable interest and has emerged as a viable approach for the synthesis of complex targets. Various reactions mediated by mercury,[18] selenium[19] or palladium[20] salts in stoichiometric amounts were developed at initial stages to bring about allylic C–H bond oxidation (Scheme V.2.1).

Shortly afterwards a re-oxidation of the catalysts with oxygen or other oxidizing agents such as manganese dioxide, quinone and benzoyl peroxide were employed to facilitate the development of the first catalytic variants of this reaction.[21] However most of the methodologies are concerned on the synthesis of allylic acetates, hence a generalized method with wide substrate scope is lacking.



Scheme V.2.1. *Preparation of allyl carboxylates from alkenes*

Developed in late 1950's, the copper-catalyzed allylic oxidation of olefins with peresters, known as Kharasch–Sosnovsky reaction, represents a powerful tool for direct C–H bond functionalization at the allylic position of olefins (Scheme V.2.2).[22] In fact it remains the most practical approach for the synthesis of allyl benzoates and acetates in terms of regio as well as stereoselectivity. A great deal of research efforts has been invested to improve the efficiency of this copper-catalyzed allylic oxidation of olefins due to its potential utility in organic synthesis.[23] Also efforts have been made towards attaining an asymmetric version of this method.[23c-d]



Scheme V.2.2. *Synthesis of allyl benzoates using copper salt*

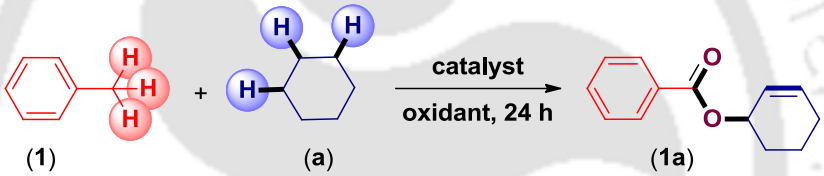
Very recently Pan group has developed an interesting modification of Kharasch–Sosnovsky reaction, where they have shown that arylaldehydes and cycloalkanes in

presence of copper acetate and *tert*-butyl hydroperoxide have afforded the corresponding allyl esters in the sequence dehydrogenation−olefination of cycloalkanes followed by a cross dehydrogenative coupling (Scheme V.2.2).[24] This reaction involves four C−H bond activations (one sp^2 aldehydic C–H and three sp^3 cycloalkane C–H's).

V.3. Present work

Although a great number of methodologies appear in literature on the copper catalyzed oxidative esterification of alkenes and even alkanes, but the present methodology on the copper catalyzed solvent-solvent (methylarene-cycloalkane) couplings to give cycloallyl benzoates via six sp^3 C–H cleavage is unique.

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



Entry	Catalyst (mol %)	Oxidant (equiv)	Temp ^oC	Yield (%)[c]
1	TBAI (20)	TBHP[d] (6)	80	00
2	$Cu(OAc)_2$ (20)	TBHP[d] (6)	80	00
3	$Cu(OAc)_2$ (20)	TBHP[d] (6)	120	21
4	**$Cu(OAc)_2$ (20)**	**TBHP[d] (8)**	**120**	**33**
5	$Cu(OAc)_2$ (20)	TBHP[d] (10)	120	35
6	$Cu(OAc)_2$ (20)	TBHP[e] (8)	120	10
7	$Cu(OAc)_2$ (20)	DTBP (8)	120	00
8	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (8)	120	00
9	$Cu(OAc)_2$ (20)	H_2O_2[f] (8)	120	00
10	CuCl (20)	TBHP[d] (8)	120	12
11	CuBr (20)	TBHP[d] (8)	120	18
12	CuI(20)	TBHP[d] (8)	120	23
13	$CuCl_2$ (20)	TBHP[d] (8)	120	<5%
14	$CuBr_2$ (20)	TBHP[d] (8)	120	<5%
15	$Cu(OTf)_2$ (20)	TBHP[d] (8)	120	00
16	$Cu(OAc)_2$ (30)	TBHP[d] (8)	120	33
17	$Cu(OAc)_2$ (20)	Nil	120	00
18	Nil	TBHP[d] (8)	120	00

[a]Reaction conditions: toluene (2.5 mmol), cyclohexane (4 ml), time 24 h. [b]Catalyst and oxidants were for 1 mmol of substrates. [c]Isolated yield. [d]Decane solution (5–6 M). [e]70% aqueous solution. [f]30% aqueous solution.

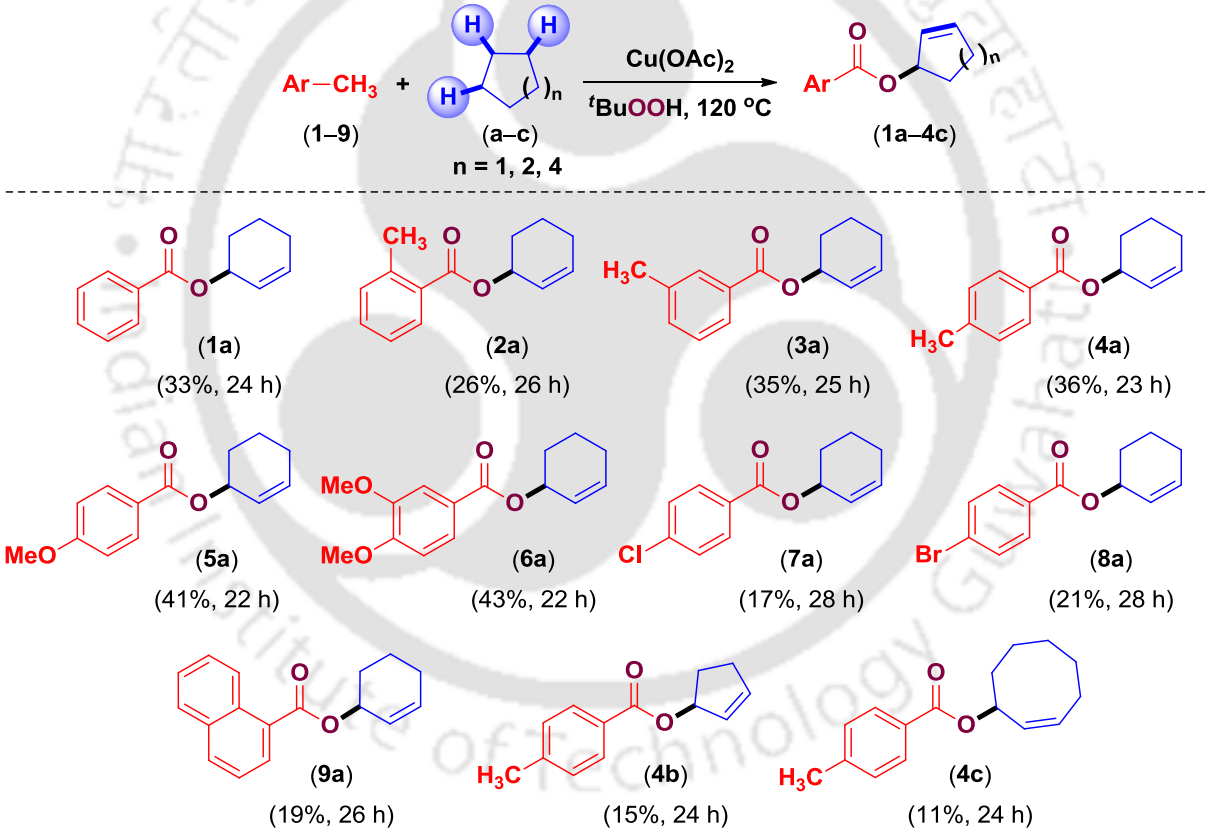
Optimization of reaction conditions. As mentioned above our envisioned route aimed towards the synthesis of cycloalkyl benzoate by solvent-solvent coupling in a CDC reaction. To give a practical shape to the above mentioned concept, toluene (**1**) and cyclohexane (**a**) were allowed to react in the presence of tetrabutylammonium iodide (TBAI) (10 mol %) and TBHP (5–6 M in decane) (6 equiv) at 80 ^{o}C; a condition similar to the coupling between alkylbenzene(s) (entry 1, Table V.3.1).[3a] However the attempt to achieve the desired cross coupling was not fruitful as the reaction gave predominantly benzyl benzoate obtained by the self coupling of toluene without any traces of desired cyclohexyl benzoate (entry 1, Table V.3.1). Hence for the exclusive formation of the desired cross coupled ester, it was necessary to avoid the competing self coupling between toluene by changing the reaction conditions. During self coupling of alkylbenzene it was observed that the combination of Cu(II)/TBHP instead of metal free conditions (Bu_4NI/TBHP) was unproductive. Hence to curb the formation of benzyl benzoate, the same reaction was attempted using $Cu(OAc)_2$ (20 mol %) as the catalyst (entry 2, Table V.3.1) keeping other conditions constant. Unfortunately other than the detection of benzaldehyde originating from toluene (**1**) oxidation no desired coupling product was observed. However, when the same reaction was performed at 120 ^{o}C surprisingly formation of an allyl ester (**1a**) was observed in a mere yield of 21% (entry 3, Table V.3.1). Thus in the present case the use of Cu(II)/TBHP is conducive to the formation of allyl ester (**1a**) exclusively without any trace of benzyl benzoate. Inspired by this unique formation of allyl ester (**1a**) originating from dehydrogenative-olefination of cyclohexane and subsequent esterification with toluene (**1**), other reaction parameters were examined in a quest to improve the yield. Increasing the oxidant quantity from 6 to 8 equiv the yield enhanced from 21 to 33% (entry 4, Table V.3.1). Further increase in TBHP quantity (10 equiv) did not lead to any noticeable increase in the desired product (entry 5, Table V.3.1). The medium of storage of oxidant TBHP was found to be quite influential for the present transformation. While a decane solution of TBHP provided 33% yield (entry 4, Table V.3.1), the use of an aqueous solution of TBHP (70%) proved to be less effective giving only 10% yield of the allyl ester (**1a**) (entry 6, Table V.3.1). The use of other oxidants such as di-*tert*-butyl peroxide (DTBP), $K_2S_2O_8$ and H_2O_2 (30% aqueous solution) were completely ineffective in the present case (entries 7–9, Table V.3.1). Among all the other

Cu(I) [CuCl, CuBr, and CuI] (entries 10–12, Table V.3.1) and Cu(II) [$CuCl_2$, $CuBr_2$, and $Cu(OTf)_2$] salts (entries 13–15, Table V.3.1) tested, $Cu(OAc)_2$ was found to be the superior (entry 4, Table V.3.1). No significant improvement in the product yield was observed even with 30 mol % of the catalyst (entry 16, Table V.3.1). Control experiments suggest that a catalyst-oxidant combination is indeed essential to bring about the desired transformation (entries 17–18, Table V.3.1). After rigorous optimizations it was found that the use of $Cu(OAc)_2$ (20 mol %), TBHP (5–6 M in decane) (8 equiv) at 120 ^oC gave the maximum possible yield of 33%. Even with this level of optimizations the yield could not be improved beyond 33%. This is possibly because of the existence of these two solvents in their vapor phase which limits their opportunity to react at the interface containing the catalyst and oxidant. To prevent the escape of vapors from the flask a reaction was performed in a teflon lined stainless steel autoclave under otherwise similar conditions. However the strategy did not work and benzaldehyde was the major product detected along with a trace (<5%) of (**1a**). Thus, it seems the poor yield obtained in this esterification protocol is due to the intrinsic low reactivity of the sp^3 C–H bonds in cyclohexane.

Substrate scope for allyl esters. Having established the optimal reaction conditions, the present oxidative esterification of cycloalkanes were then implemented on cross couplings between cyclohexane (**a**) and a series of substituted methylarenes (**1**–**12**). As can be seen in Scheme V.3.1, the developed methodology was applicable to a diverse methylarenes irrespective of the nature of the substituents present. For methylbenzenes possessing electron-donating substituents such as *o*-Me (**2**), *m*-Me (**3**), *p*-Me (**4**), *p*-OMe (**5**) and 3,4-di-OMe (**6**) the yields of the corresponding allyl esters (**2a**–**6a**) ranged from 26% to 43% (Scheme V.3.1). Lower yield obtained for *o*-substituted methylarenes (**2**) compared to their *p*- or *m*- analogues (**3** and **4**) could be attributed to steric hindrance imparted by the *ortho*-substitutent. The most appealing outcome in all the reactions of the polymethylated benzenes (**2**–**4**) were the selective formation of the corresponding monoester functionalizing one of the –Me group with the other –Me group remaining intact. The yields of allyl esters (**7a** and **8a**) derived from methylbenzenes having moderately electron-withdrawing substituents such as *p*-Cl (**7**) and *p*-Br (**8**) were 17% and 21% respectively (Scheme V.3.1). Thus the presence of moderately electron-withdrawing groups in

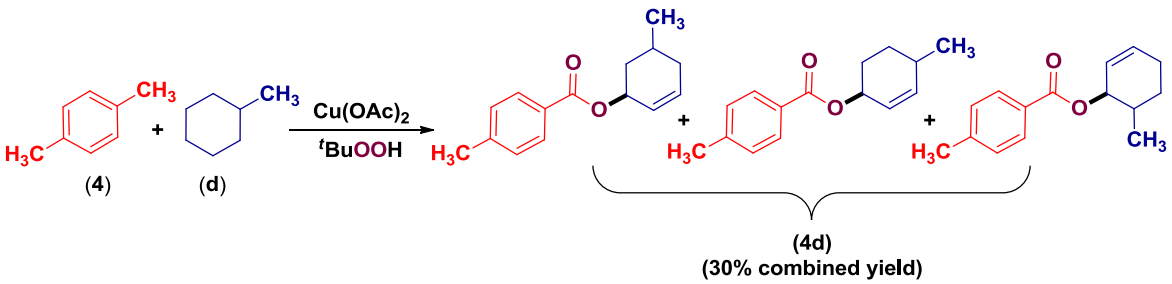
methylbenzene lowered the yields of their corresponding allyl esters in comparison to those possessing electron-donating substituents. Bicyclic methylarene, 1-methylnaphthalene (**9**) upon coupling with (**a**) afforded its allyl ester (**9a**) in a poor yield of 19% (Scheme V.3.1). Other cycloalkanes viz. cyclopentane (**b**) and cyclooctane (**c**) when reacted with (**4**) gave their corresponding allyl esters (**4b** and **4c**) however in poor yields (Scheme V.3.1). The lower yields obtained in five and eight membered cycloalkanes are in part due to their radical instability and unfavorable strain of their corresponding cyclo-alkenes.

Scheme V.3.1. *Substrate scope for allyl esters*[a,b]



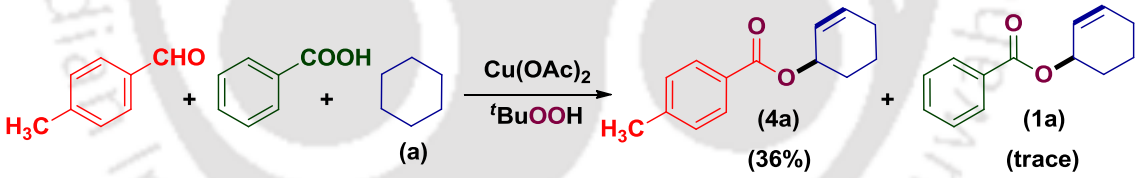
[a]Reaction conditions: methylarenes (**1**−**12**) (2.5 mmol), cycloalkanes (**a**−**c**) (4 mL), $Cu(OAc)_2$ (0.2 mmol), TBHP (5−6 M) (8 mmol) at 120 °C. [b]Isolated yield. [c]Catalyst and oxidant were for 1 mmol of substrates.

To see if a regioselective esterification could be achieved methylcyclohexane (**d**) was reacted with (**4**) under the present reaction conditions. ^{1}H and ^{13}C NMR analysis revealed the formation of at least three regioisomeric esters obtained in a combined yield of 30% (Scheme V.3.2).



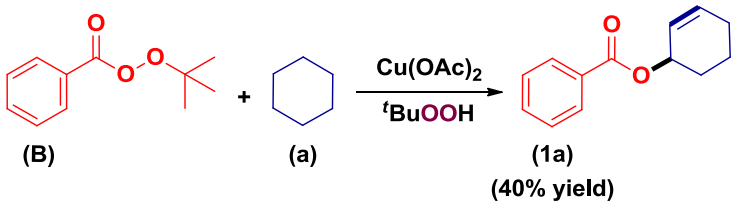
Scheme V.3.2. *Formation of three regioisomeric allyl esters (**4d**)*

Mechanistic studies. Several control experiments were carried out to elucidate the mechanism of these solvent-solvent couplings. Analysis of the reaction mixture between (**1**) and (**a**) divulged the formation of benzaldehyde and benzoic acid in the medium, both of which could possibly couple with cyclohexane to give (**1a**). To find out the exact coupling partner among aldehyde and acid a control experiment was carried out where an equimolar mixture of *p*-methylbenzaldehyde and benzoic acid were reacted with dioxane (**a**) under identical reaction conditions (Scheme V.3.3). Formation of (**4a**) (derived from benzaldehyde) as major product and only traces of (**1a**) (expected from benzoic acid) imply an aldehyde-cyclohexane coupling to be predominant.

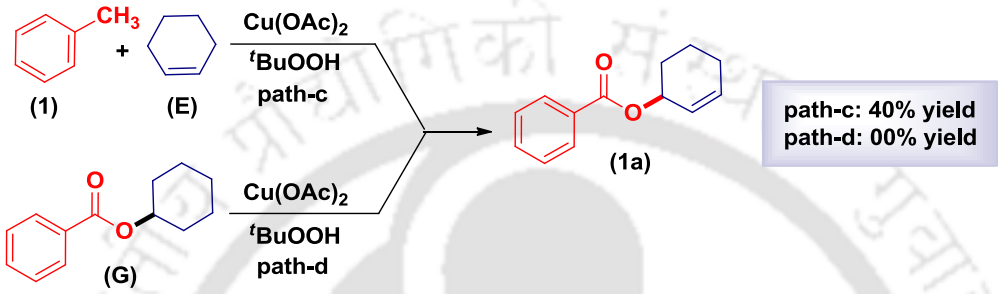


Scheme V.3.3. *A crossover experiment*

Since benzaldehyde was found to be the main coupling partner of cyclohexane rather than benzoic acid, then which intermediate (formed from benzaldehyde) was responsible for the esterification process? It was presumed that excess TBHP and benzaldehyde (generated in situ) might form a perester which could possibly act as the benzoxy source like in Kharasch-Sosnovsky reaction.[22] To ascertain this, a reaction was carried out with *tert*-butyl benzoperoxoate (**B**) and cyclohexane under similar conditions (Scheme V.3.4). The formation of allyl ester (**1a**) confirmed our assumption and also indicates a Kharasch-Sosnovsky type path for the present transformation.

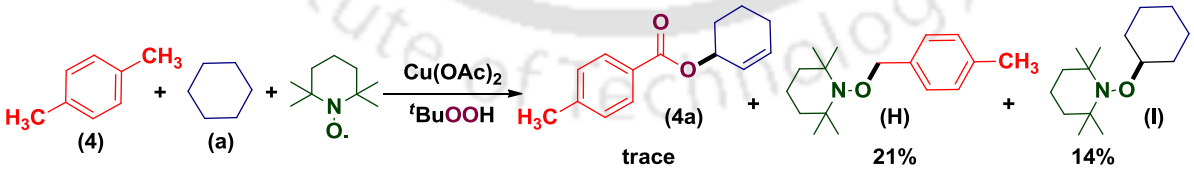


Scheme V.3.4. *A control experiment*



Scheme V.3.5. *Control experiments*

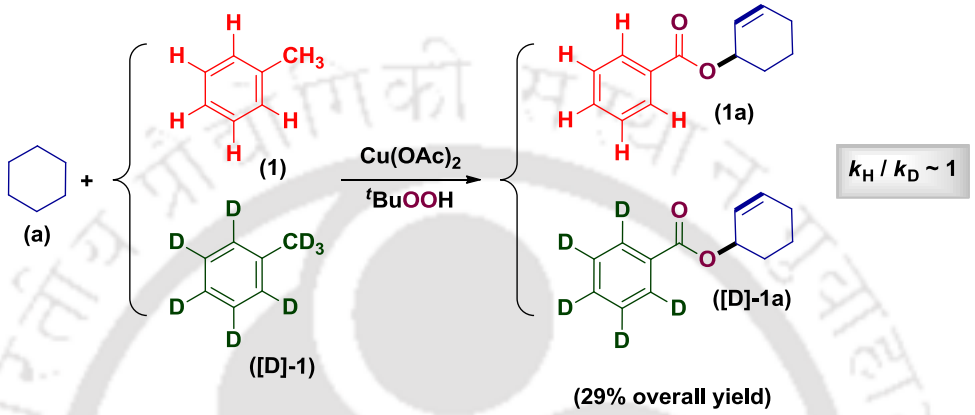
Another query that arose was whether the dehydrogenative olefination of cyclohexane occurs first; followed by the construction of an ester C–O bond at the allylic position or a reverse sequence operates. To reveal the exact sequence, two independent reactions were performed. In the first reaction, toluene and cyclohexene (**E**) were reacted (path-c, Scheme V.3.5) while in the second a pre-synthesized cyclohexyl benzoate (**G**) was treated under the standard reaction conditions (path-d, Scheme V.3.5). The formation of allyl ester (**1a**) in the former and failure in the latter suggests that dehydrogenative olefination precedes the ester C–O bond formation.



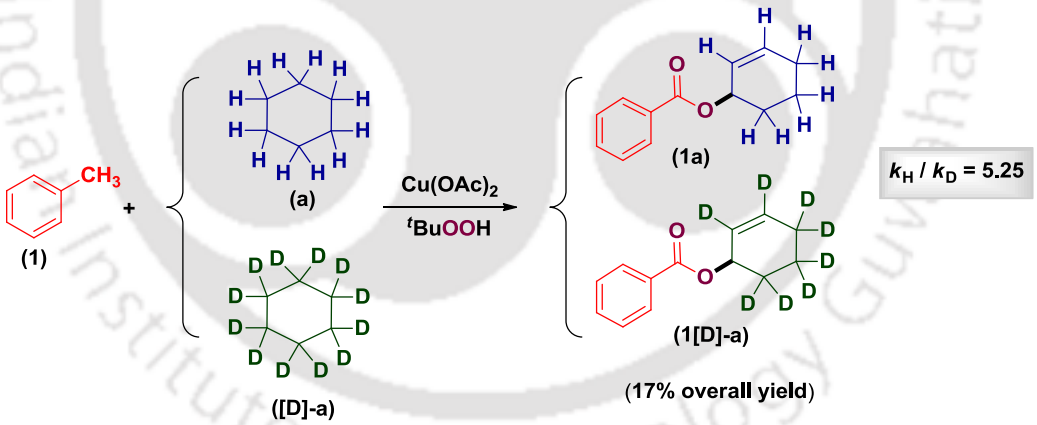
Scheme V.3.6. *Reaction in presence of radical scavenger TEMPO*

To ascertain the radical nature of the reaction (**4**) and (**a**) were reacted in the presence of radical scavenger 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) under otherwise identical conditions. Along with the formation of traces of (**4a**), TEMPO ethers (**H**) and (**I**)

were isolated confirming the formation of benzyl radical and cyclohexyl radical in the reaction medium (Scheme V.3.6, also see Experimental section V.4.3). The trapped benzyl radical (**H**) inhibits the formation of key coupling partner *p*-methylbenzaldehyde while the trapped cyclohexyl radical (**I**) hinders the cyclohexene formation; thereby considerably lowering the yield.



Scheme V.3.7. *KIE experiment with deuterated toluene*

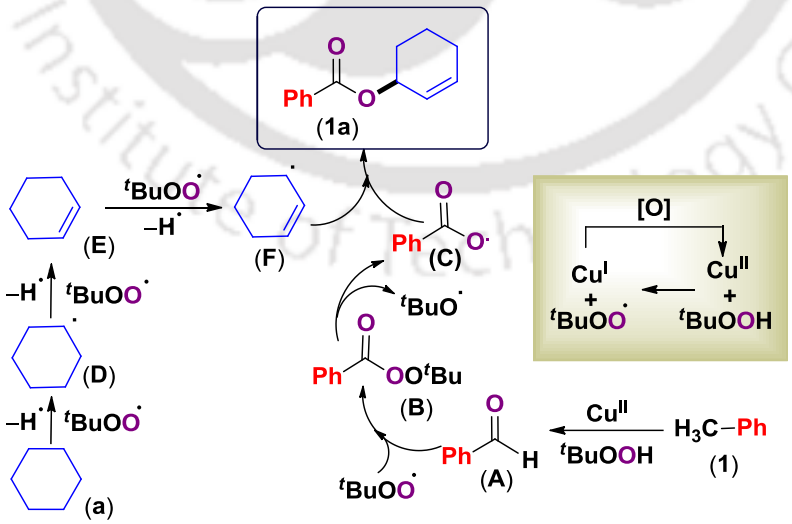


Scheme V.3.8. *KIE experiment with deuterated cyclohexane*

To determine the possible rate limiting step in this reaction two independent intermolecular competing kinetic isotope effect (KIE) experiments were performed. In the first experiment cyclohexane (**a**) was reacted with an equimolar mixture of toluene (**1**) and d_8-toluene ([**D**]-**1**) under the standard reaction conditions. A kinetic isotope effect (k_H/k_D ~ 1) ruled out the involvement of a benzylic C–H cleavage as the rate determining step

(Scheme V.3.7, also see Experimental section V.4.4). In another experiment, toluene (**1**) was reacted with an equimolar mixture of cyclohexane (**a**) and d_{12}-cyclohexane ([**D**]-**a**) under identical reaction conditions. A significant KIE was observed in this experiment with k_H/k_D = 5.25. This result indicates that the cyclohexane's sp^3 C−H bond cleavage is involved in the rate-determining step of this transformation (Scheme V.3.8, also see Experimental section V.4.4).

The results of the above experiments infer that this oxidative esterification process comprise of following steps. Toluene (**1**) gets converted to benzaldehyde (**A**) via a radical oxidation in the presence of Cu/TBHP. The *tert*-butylperoxy radical generated from TBHP adds to benzaldehyde (**A**) providing *tert*-butyl benzoperoxate (**B**). Homolytic cleavage of peroxy species (**B**) affords benzoxy radical (**C**) along with *tert*-butoxyl radical. On the other hand abstraction of a hydrogen radical from cyclohexane by *tert*-butylperoxy radical gives the cyclohexyl radical intermediate (**D**), which then undergoes dehydrogenation to cyclohexene (**E**) according to the process described by Pérez and co-workers.[13] A further hydrogen radical abstraction from the allylic position in the presence of *tert*-butylperoxy radical forms the allyl radical species (**F**). In the final step, a radical coupling of (**C**) and (**F**) leads to the formation of allyl ester (**1a**) (Scheme V.3.8). During the generation of *tert*-butylperoxy radical from TBHP, the Cu(II) gets reduced to Cu(I). Re-oxidation of the Cu(I) species in the medium regenerates Cu(II) for further reaction (Scheme V.3.9).



Scheme V.3.9. *Proposed mechanism for oxidative esterification*

In conclusion, this work describes the first example of a Cu-catalyzed dehydrogenation-olefination and esterification of the C(sp^3)−H bond of cycloalkanes with alkylbenzenes in presence of TBHP as the oxidant. This reaction involves six consecutive sp^3 C–H bond cleavages. An appreciable range of methylarenes can be used in this reaction with cycloalkanes allowing a direct preparation of the corresponding cycloallyl esters. Based on the extensive experimentation, a plausible mechanism is proposed which includes dehydrogenation-olefination of cycloalkanes followed by an oxidative esterification at the allylic position similar to Kharasch-Sosnovsky reaction.

V.4. Experimental section

V.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. 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 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using ESI mode. FT-IR spectra were recorded in KBr or neat.

V.4.2. General procedure for the synthesis of cyclohex-2en-1-yl benzoate (**1a**). An oven-dried reaction vessel was charged with toluene (**1**) (230 mg, 2.5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and decane solution of TBHP (5–6 M) (1600 µL, 8 mmol) in cyclohexane (**a**) (4 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 24 h. The mixture was cooled down to room temperature and diluted with 10 mL of ethyl acetate. The reaction mixture was filtered through a celite bed and washed with additional amount of ethyl acetate (2 x 10 mL). The combined organic layer was subsequently washed with 5% solution of sodium bicarbonate solution (2 x 10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatile organics were removed in vacuo. The residue was purified over a column of silica gel and eluted with 2% ethyl acetate in hexane to give

cyclohex-2en-1-yl benzoate (**1a**) (66 mg, 33% yield). The same procedure was also followed for the synthesis of other allyl esters (**2a**–**4d**).

V.4.3. Trapping of radical intermediates with radical scavenger TEMPO. An oven-dried reaction vessel was charged with *p*-xylene (**4**) (265 mg, 2.55 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol), decane solution of TBHP (5–6 M) (1600 µL, 8 mmol), TEMPO (0.312 g, 2 mmol) in cyclohexane (**a**) (4 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 24 h. The reaction mixture after usual work up and purification by column chromatography afforded the benzyl-TEMPO adduct (**H**) (21% yield) and cyclohexyl-TEMPO adduct (**I**) (14%) along with traces of the allyl ester (**4a**). Both the benzyl-TEMPO ether and cyclohexyl-TEMPO ether were characterized by various spectroscopic studies and ESI-MS analysis. This experiment confirms the formation of benzyl radical and cyclohexyl radical in the reaction medium which are key intermediates in this transformation. Also quenching in the yield of allyl ester (**4a**) suggests a radical nature of the mechanism.

V.4.4. Kinetic isotope effect studies.

Two independent intermolecular competing kinetic isotope effect (KIE) experiments were carried out to find the possible rate determining step in this transformation.

(a) Kinetic isotope effect studies with deuterated toluene. An oven-dried reaction vessel was charged with toluene (**1**) (115 mg, 1.25 mmol), d_8-toluene ([**D**]-**1**) (125 mg, 1.25 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and decane solution of TBHP (5–6 M) (1600 µL, 8 mmol) in cyclohexane (**a**) (4 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 24 h. The reaction mixture was then worked up in usual procedure and the crude product was purified over a column of silica gel eluting with 2% ethyl acetate in hexane to give allyl esters (**1a** and [**D**]-**1a**) in 29% overall yield. The k_H/k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed that it was nearly equal to one ($k_H/k_D \sim 1$). This result ruled out the involvement of benzylic sp^3 C–H cleavage as the rate determining step.

(b) Kinetic isotope effect studies with deuterated cyclohexane. An oven-dried reaction vessel was charged with toluene (**1**) (230 mg, 2.5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and

decane solution of TBHP (5–6 M) (1600 µL, 8 mmol) in cyclohexane (**a**) (2 mL) and d_{12}-cyclohexane ([**D**]-**a**) (2 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^{o}C for 24 h. The reaction mixture was then worked up in usual procedure and the crude product was purified over a column of silica gel eluting with 2% ethyl acetate in hexane to give allyl esters (**1a** and **1**[**D**]-**a**) in 17% overall yield. The k_H/k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed a significant KIE (k_H/k_D = 5.25). This result indicates that the cyclohexane's sp^3 C−H bond cleavage should be involved in the rate-determining step of this protocol.

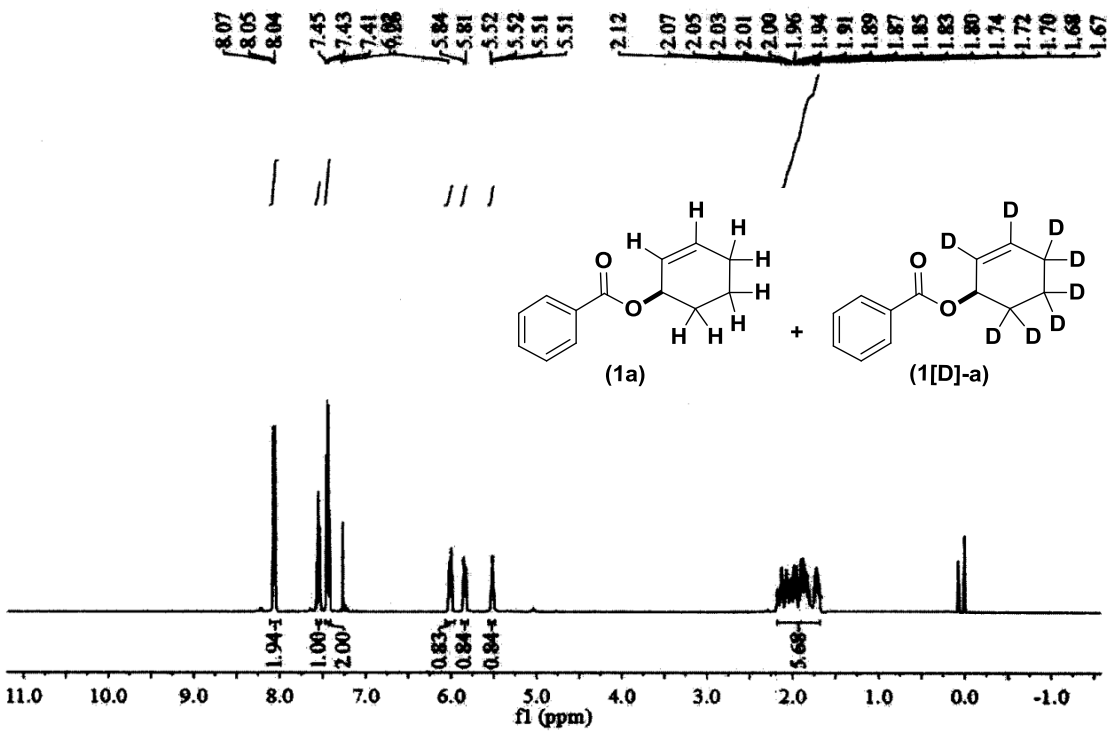
Calculation:

The integration value of protons originating from cyclohexane at 5.51–5.52 ppm is 0.84.

Upon correlation with the original spectra of (**1a**) the number of proton that is originating from cyclohexane at the same region should be 1.

Hence the proton difference in this region is 1 – 0.84 = 0.16.

Thus the k_H/k_D = 0.84 / 0.16 = 5.25



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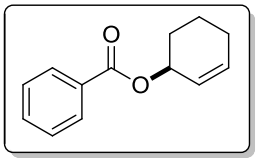
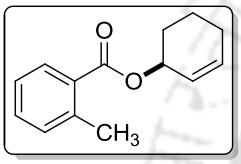
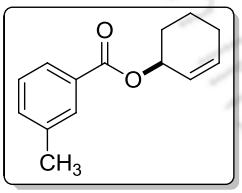
V.6. Spectral Data



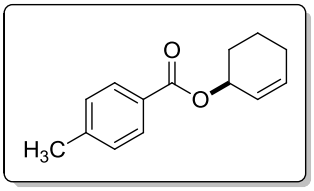
Cyclohex-2en-1-yl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60–2.15 (m, 6H), 5.47–5.48 (m, 1H), 5.78–5.82 (m, 1H), 5.95–5.99 (m, 1H), 7.40 (t, 2H, *J* = 7.6 Hz), 7.52 (t, 1H, *J* = 7.2 Hz), 8.02 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.2, 25.2, 28.7, 68.8, 125.9, 128.5, 129.8, 131.0, 132.9, 133.1, 166.5; IR (KBr): 2926, 2855, 1713, 1450, 1269, 1110, 918, 710 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{14}O_2$ (MH^+) 203.1067; found 203.1061.



Cyclohex-2en-1-yl 2-methylbenzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.66–2.18 (m, 6H), 2.60 (s, 3H), 5.48–5.51 (m, 1H), 5.82–5.86 (m, 1H), 5.98–6.02 (m, 1H), 7.23 (t, 2H, *J* = 7.2 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.90 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.2, 21.9, 25.2, 28.7, 68.6, 125.8, 125.9, 130.5, 130.8, 131.8, 131.9, 132.9, 140.1, 167.6; IR (KBr): 2930, 2863, 1714, 1455, 1253, 1136, 1077, 919, 738 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}O_2$ (MH^+) 217.1223; found 217.1227.

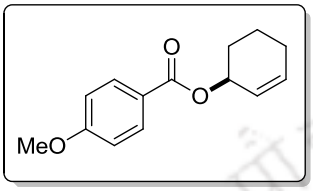


Cyclohex-2en-1-yl 3-methylbenzoate (3a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.68–2.13 (m, 6H), 2.38 (s, 3H), 5.49–5.51 (m, 1H), 5.81–5.84 (m, 1H), 5.98–6.02 (m, 1H), 7.30–7.35 (m, 2H), 7.84–7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.2, 21.5, 25.2, 28.7, 68.8, 126.1, 127.0, 128.4, 130.3, 130.9, 132.9, 133.7, 138.3, 166.6; IR (KBr): 2925, 2853, 1711, 1452, 1273, 1197, 1104, 1018, 801, 744 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}O_2$ (MH^+) 217.1223; found 217.1218.

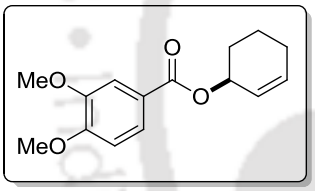


Cyclohex-2en-1-yl 4-methylbenzoate (4a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.66–2.13 (m, 6H), 2.38 (s, 3H), 5.47–5.48 (m, 1H), 5.79–5.82 (m, 1H), 5.96–5.98 (m, 1H), 7.20 (d, 2H, *J* = 8.4

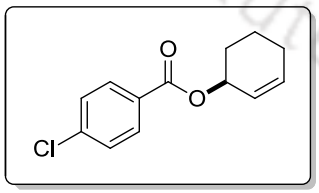
Hz), 7.91 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4, 19.1, 22.4, 25.9, 65.8, 123.3, 125.5, 126.5, 127.1, 130.1, 140.8, 163.7; IR (KBr): 2929, 2863, 1712, 1270, 1106, 1013, 919, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}O_2$ (MH^+) 217.1223; found 217.1225.



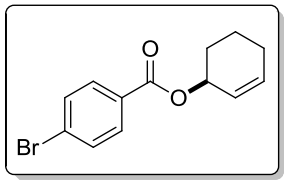
Cyclohex-2en-1-yl 4-methoxybenzoate (5a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.62–2.15 (m, 6H), 3.83 (s, 3H), 5.45–5.46 (m, 1H), 5.78–5.81 (m, 1H), 5.95–5.99 (m, 1H), 6.88 (d, 2H, *J* = 8.8 Hz), 7.98 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.2, 25.2, 28.7, 55.6, 68.5, 113.7, 123.5, 126.2, 131.8, 132.8, 163.4, 166.2; IR (KBr): 2932, 2848, 1707, 1258, 1167, 1104, 1029, 919, 8484, 771 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}O_3$ (MH^+) 233.1172; found 233.1177.



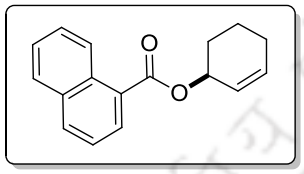
Cyclohex-2en-1-yl 3,4-dimethoxybenzoate (6a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38–2.21 (m, 6H), 3.76 (s, 3H), 3.77 (s, 3H), 5.18–5.22 (m, 1H), 5.61–5.69 (m, 1H), 5.81–5.85 (m, 1H), 6.65–6.79 (m, 1H), 7.41 (s, 1H), 7.54 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.6, 24.5, 28.0, 55.5, 68.0, 109.8, 111.6, 122.8, 123.1, 125.6, 132.1, 148.1, 152.4, 165.4; IR (KBr): 3032, 2942, 1710, 1590, 1336, 1042, 928, 767 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{18}O_4$ (MH^+) 263.1205; found 263.1203.



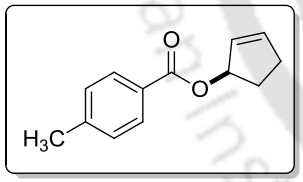
Cyclohex-2en-1-yl 4-chlorobenzoate (7a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.70–2.13 (m, 6H), 5.48-5.50 (m, 1H), 5.81-5.84 (m, 1H), 6.00-6.03 (m, 1H), 7.40 (d, 2H, J = 8.4 Hz), 7.90 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.1, 25.2, 28.6, 69.2, 125.7, 128.8, 129.5, 131.2, 133.3, 139.4, 165.6; IR (KBr): 3033, 2940, 1718, 1575, 1420, 1259, 1129, 1074, 915, 750 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{13}ClO_2$ (MH^+) 237.0604; found 237.0612.



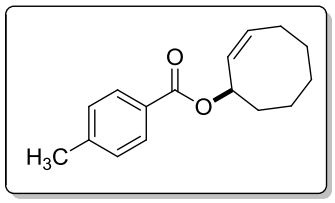
Cyclohex-2en-1-yl 4-bromobenzoate (8a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.63–2.15 (m, 6H), 5.46–5.47 (m, 1H), 5.77–5.81 (m, 1H), 5.96–6.01 (m, 1H), 7.54 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.1, 25.1, 28.6, 69.2, 125.7, 128.0, 129.9, 131.4, 131.8, 133.3, 165.7; IR (KBr): 2929, 2858, 1716, 1268, 1107, 1010, 916, 756 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{13}BrO_2$ (MH^+) 281.0172; found 281.0166.



Cyclohex-2en-1-yl 1-naphthoate (9a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.69–2.17 (m, 6H), 5.60–5.61 (m, 1H), 5.89–5.92 (m, 1H), 6.01–6.05 (m, 1H), 7.45–7.53 (m, 2H), 7.57–7.62 (m, 1H), 7.86 (d, 1H, *J* = 8.0 Hz), 7.98 (d, 1H, *J* = 8.0 Hz), 8.15–8.18 (m, 1H), 8.89 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.2, 25.2, 28.7, 68.9, 126.1, 126.3, 126.4, 127.8, 127.9, 128.7, 130.3, 130.4, 131.6, 133.2, 133.3, 134.1, 167.6; IR (KBr): 2930, 2858, 1711, 1441, 1243, 1197, 1135, 1010, 916, 782 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{16}O_2$ (MH^+) 253.1223; found 253.1226.

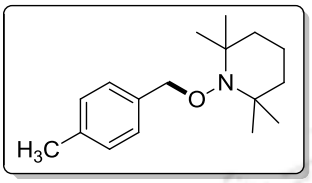


Cyclopent-2en-1-yl 4-methylbenzoate (4b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.91–1.97 (m, 1H), 2.31–2.42 (m, 5H), 2.53–2.59 (m, 1H), 5.90–5.92 (m, 2H), 6.12–6.13 (m, 1H), 7.19 (d, 2H, *J* = 8.0 Hz), 7.89 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 30.1, 31.4, 81.1, 128.2, 129.2, 129.7, 129.8, 137.7, 143.6, 166.9; IR (KBr): 2926, 2855, 1712, 1271, 1176, 1027, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{14}O_2$ (MH^+) 203.1067; found 203.1069.

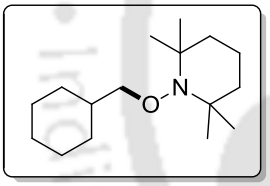


(Z)-Cyclooct-2en-1-yl 4-methylbenzoate (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.55–2.33 (m, 10H), 2.38 (s, 3H), 5.56–5.61 (m, 1H), 5.65–5.72 (m, 1H), 5.83–5.87 (m, 1H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$): δ (ppm) 21.9, 23.6, 26.1, 26.6, 29.1, 35.4, 72.9, 128.3, 129.3, 129.6, 129.7, 131.0, 143.6, 166.3; IR (KBr): 2926, 2858, 1714, 1273, 1107, 1020, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{20}O_2$ (MH^+) 245.1536; found 245.1533.



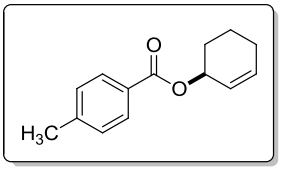
2,2,6,6-Tetramethylpiperidin-1-((4-methylbenzyl)oxy) piperidine (H): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.13 (s, 6H), 1.24–1.25 (m, 7H), 1.32–1.35 (m, 1H), 1.48–1.54 (m, 4H), 2.34 (s, 3H), 4.77 (s, 2H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.2, 20.3, 21.2, 33.1, 39.8, 60.0, 78.7, 127.7, 128.9, 135.2, 137.0; IR (KBr): 2974, 2928, 2873, 1516, 1469, 1359, 1261, 1132, 1047, 802 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{27}NO$ (MH^+) 262.2165; found 262.2165.

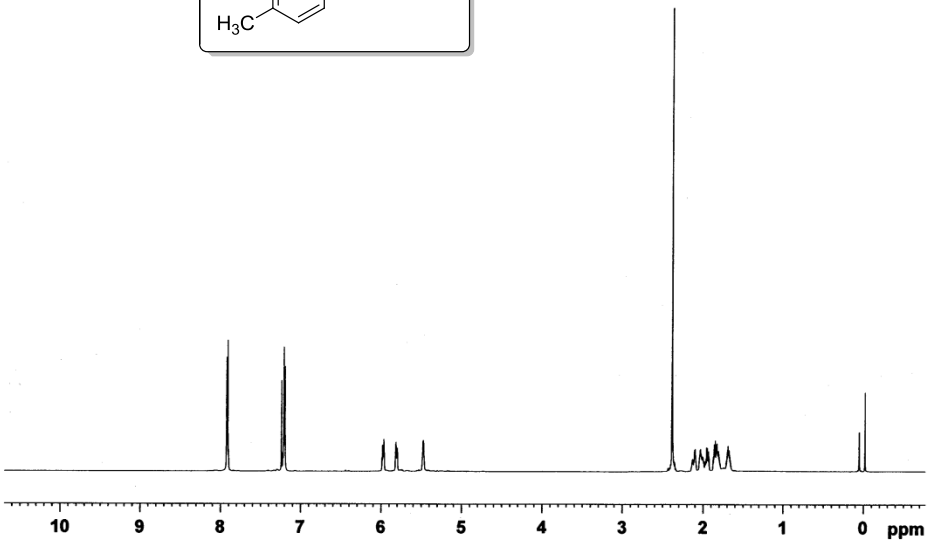


1-(Cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (I): ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H), 1.14 (s, 6H), 1.31–1.19 (m, 6H), 1.54–1.46 (m, 6H), 1.74 (bs, 2H), 2.04 (bs, 2H), 3.58 (bs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 17.6, 25.3, 26.2, 33.1, 34.7, 40.5, 59.8, 81.9; IR (KBr): 2967, 2932, 2855, 1467, 1452, 1374, 1348, 1257, 1242, 1208, 1181, 1151, 1132, 1092, 1058, 1044, 1021, 993, 966, 913, 710 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{29}NO$ (MH^+) 240.2329; found 240.2332.

V.7. Spectra

Cyclohex-2en-1-yl 4-methylbenzoate (4a): ^{1}H NMR (600 MHz, $CDCl_3$)



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PROCNO                   1

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DE                  6.50 usec
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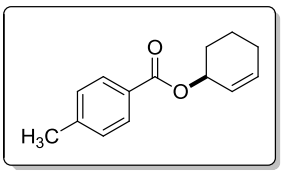
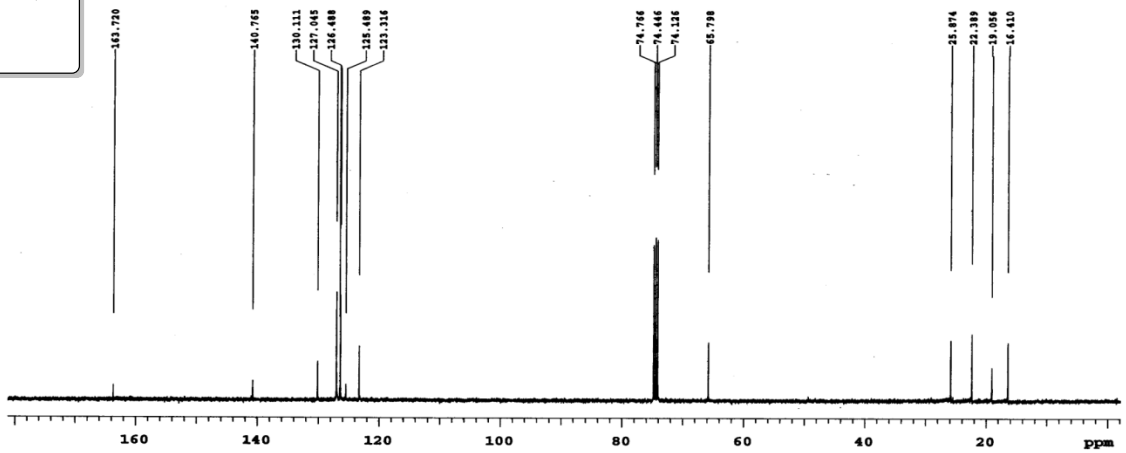
Cyclohex-2en-1-yl 4-methylbenzoate (4a): ^{13}C NMR (100 MHz, $CDCl_3$)



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 Pulse 45.0 degrees             Power 42 dB
 Acq. time 1.304 sec            continuously on
 Width 25125.6 Hz               WALTZ-16 modulated
 12 repetitions

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 1 minute

p-Me-Cyclo

Solvent: D2O
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
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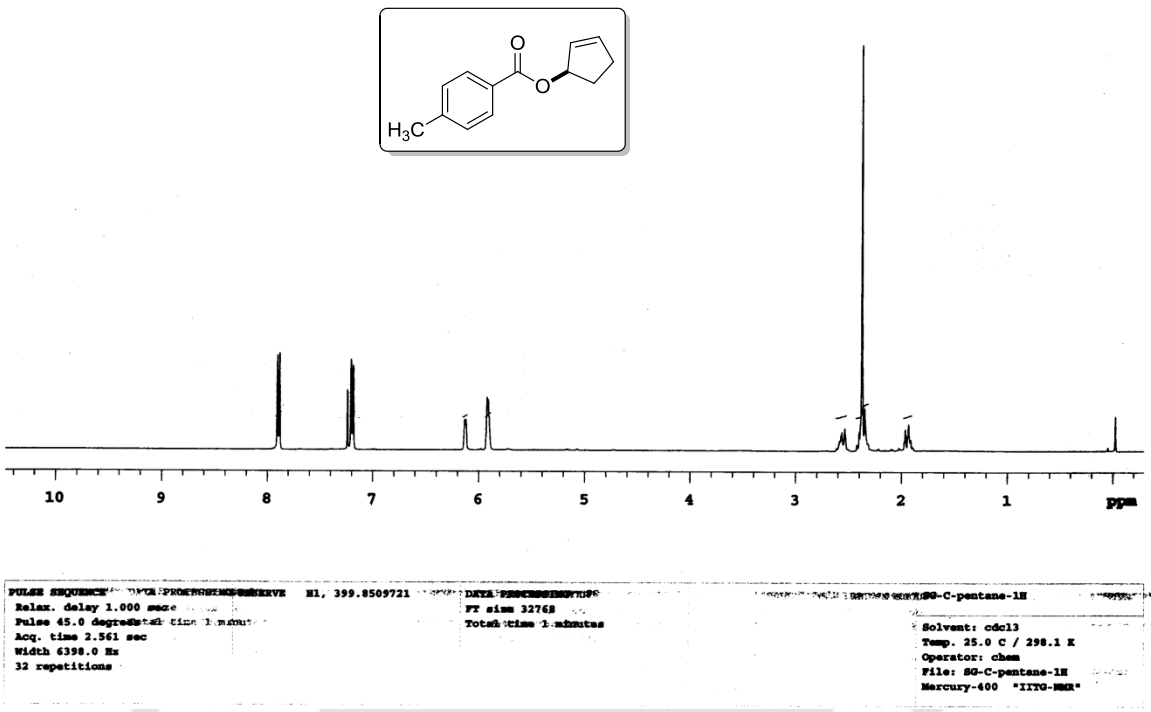
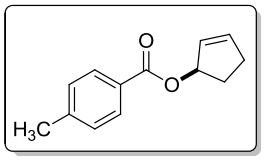
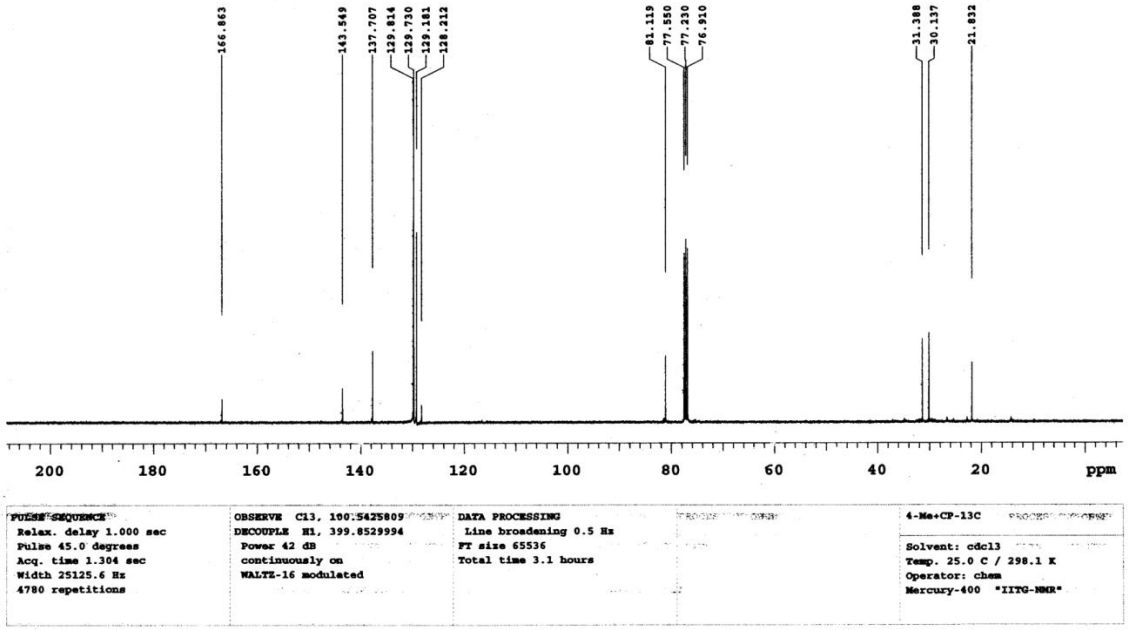
Cyclopent-2en-1-yl 4-methylbenzoate (4b): ^{1}H NMR (400 MHz, $CDCl_3$)



Cyclopent-2en-1-yl 4-methylbenzoate (4b): ^{13}C NMR (100 MHz, $CDCl_3$)





भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

PUBLICATIONS

1. "**Cyclic ethers to esters and mono-esters to bis-esters with unconventional coupling partners under metal free conditions via sp^3 C–H functionalisation**"
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2. "**Thioesterification of alkylbenzenes with thiols via copper-catalyzed cross-dehydrogenative coupling without directing group**"
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3. "**A metal free domino synthesis of 3-aroylindoles via two sp^3 C–H activation**"
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4. "**A palladium(II)-catalyzed synthesis of α-ketoamides via chemoselective aroyl addition to cyanamides**"
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5. "C**opper-catalyzed esterification of alkylbenzenes with cyclic ethers and cycloalkanes via C(sp^3)–H activation following cross-dehydrogenative coupling**"
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6. "**Terminal aryl alkenes and alkynes as arylcarboxy surrogates toward *o*-benzoxylation of 2-phenylpyridine catalyzed by copper**"
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11. "**Directing group assisted copper-catalyzed chemoselective *O*-aroylation of phenols and enols using alkylbenzenes**"
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13. "**Palladium catalyzed *ortho*-aroylation of 2-arylbenzothiazoles and 2-arylbenzoxazoles with aldehydes**"
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17. "**Tandem synthesis of [1,2,4]-triazoles mediated by iodine-a regioselective approach**"
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