Beyond Retrosynthetic Analysis: Copper Catalyzed Synthesis of Esters via C–H Functionalization

Submitted by

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October, 2014

DEDICATED TO MY

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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.

October, 2014.
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CERTIFICATE

This is to certify that Saroj Kumar Rout has been working under my supervision since December, 2009 as a regular registered Ph. D. student. His thesis entitled **"Beyond Reterosynthetic Analysis: Copper Catalyzed Synthesis of Esters via C–H Functionalization"** 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.

October, 2014.

Prof. Bhisma K. Patel
(Thesis Supervisor)
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Finally, my Ph. D. endeavor could not have been completed without the endless love, support, tolerance and blessings from my family. Especially my 'Father' whose firm belief in me has given me all the strength to break through all the difficulties in life. I owe my entire life to him. I would like to express my deepest gratitude to my sweet mother for all the unconditional love and sacrifices she has made in her life just for the sake of my upbringing. I am also grateful to my sister, aunties, uncle, cousins and neighbours for their affection and deep concern for my career. They are the main soul and inspiration for each and every step that I achieve in my life.

Still many names are missing whose contribution and help is worth mentioning.

Saroj Kumar Rout

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 the various class of ester synthesis via Cu catalyzed C–H functionalizations using strategies like cross dehydrogenative coupling and functional group directed C–H bond functionalization. Chapter II describes the copper catalyzed oxidative esterification of aldehydes with alkylbenzenes via cross dehydrogenative coupling. Chapter III illustrates directing group assisted copper-catalyzed chemoselective *O*-aroylation of phenols and enols using alkylbenzenes. Chapter IV demonstrates a copper catalyzed esterification of alkylbenzenes with cyclic ethers via C(sp^3)–H activation following cross dehydrogenative coupling (CDC). Chapter V discusses the use of terminal alkynes as the new surrogates for the arylcarboxy group (ArCOO–), which has been employed for the *o*-benzoxylation of 2-phenylpyridine derivatives catalyzed by copper. Each of these chapters comprises of seven subsections which include introduction, previous works, present work, experimental section, references, spectral data and some representative spectra.

CHAPTER I. Transition Metal Catalyzed C–H Functionalizations

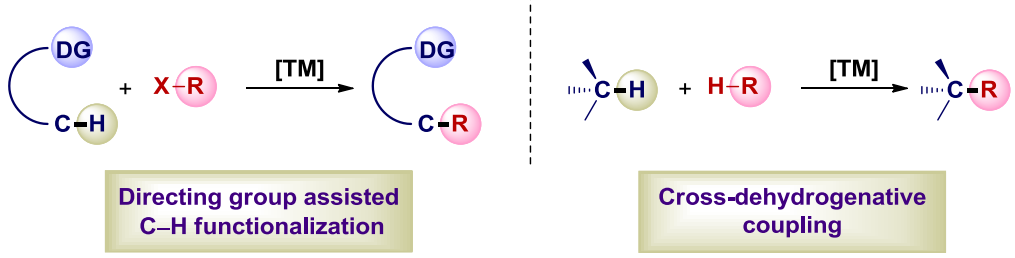
This chapter gives a layout on the history of C–H activation, various strategies adopted in modern days, their advantages, challenges and applications in organic synthesis.

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 could be 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.

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 strategy 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.

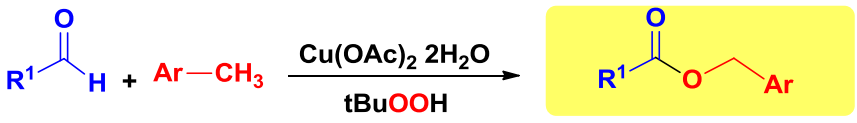


Scheme I.1. *Various C–H functionalization strategies*

CHAPTER II. Copper Catalyzed Oxidative Esterification of Aldehydes With Alkylbenzenes Via Cross Dehydrogenative Coupling

This chapter focuses on the copper catalyzed oxidative esterification of aldehydes with alkylbenzenes via cross dehydrogenative coupling.

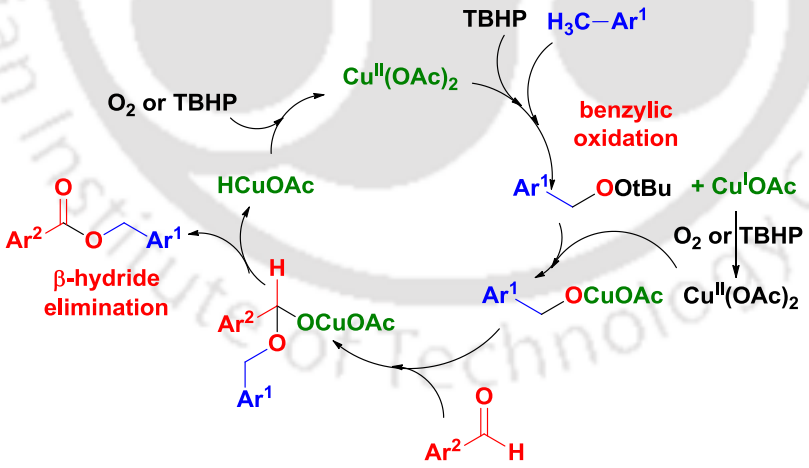
The upsurge in interest in the transition metal catalyzed reactions via the cleavage of ubiquitous C–H bonds has been creating a renaissance in the construction of a diverse array of C–C and C–X (X = hetero atom) bonds. The two most popular approaches are chelation assisted C–H bond functionalization[2] and the cross dehydrogenative coupling (CDC). This field of synthesis has advanced to such an extent that even the otherwise inert sp^3 C–H bonds could now be functionalized. The CDC approach is attractive because it does not require substrate prefunctionalization and is atom economic. As evident from the literature, CDC has been widely investigated for the formation of C–C bonds albeit the concept has rarely been explored regarding C–O bond formation. The relevance of C–O bonds in organic chemistry has resulted in the emergence of various transition metal based methodologies via C–H bond activation. In this regard the ester functionality has been the common target. Some recent metal catalyzed CDC based transformations for the synthesis of esters involve acid and cyclic ethers where the functionalization occurs selectively at the sp^3 carbon atom α to the ethereal oxygen. The use of various copper salts in combination with peroxides as the oxidant is known to work effectively in facilitating functionalizations at the relatively inert sp^3 carbon. However, most of these methodologies concentrate on C–H bond functionalization at the sp^3 carbon atom α to heteroatoms. A direct functionalization at the relatively nonactivated alkylbenzenes has rarely been explored. Herein we developed a copper catalyzed methodology with alkylbenzenes and aldehydes as precursors for the synthesis of benzylic esters via a CDC approach (Scheme II.1).



Scheme II.1. *Benzylic ester synthesis via CDC process*

To attain a suitable reaction condition for the synthesis of benzylic ester various reaction parameters such as catalysts, oxidant and temprature were screened to achieve the maximum possible yield. After a series of experimentation the optimized reaction condition arrived was $Cu(OAc)_2$ $2H_2O$ (10 mol %), *tert* butyl hrdroperoxide (2 equiv) at 100 ^oC. The optimized conditions were applied to the coupling of alkylbenzenes with a set of aromatic aldehydes having both electron-donating and electron-withdrawing substituents. It was observed that, under the present condition, alkylbenzenes smoothly underwent reactions with various aldehydes to afford the desired benzylic esters in good to excellent yields. However, the most appealing outcome in all their reactions were the selective formation monoester with polyalkylated methylarenes *viz p*-xylene, *o*-xylene and mesitylene the other alkyl (methyl) groups remaining intact besides undergoing a smooth reaction with their corresponding coupling aldehyde partners. The reaction of ethylbenzene and isopropylbenzene with a set of aromatic aldehydes proceeded smoothly to form the C–O bond selectively at the 2^o and 3^o benzylic carbon to form the corresponding benzylic esters.

Based on the observationsof controlled experiments a possibly mechanisms has been proposed for this transformation (Scheme II.2).



Scheme II.2. *Proposed mechanism for the synthesis of benzylic ester*

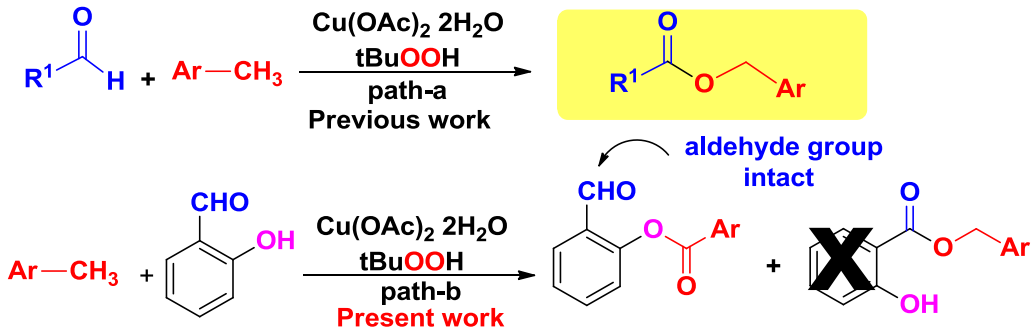
In conclusion we have developed a new and efficient catalytic approach for the synthesis of benzylic ester from aldehydes and alkylbenzenes. This reaction proceeds via benzylic sp^3 C–H bond activation of alkylbenzenes in the presence of an inexpensive

copper catalyst and TBHP combination. Exclusive formation of monoesters was observed for polyalkylated benzenes indicating a high degree of selectivity. This methodology provides an avenue to the synthesis of various unsymmetrical benzylic esters from diverse alkylbenzenes and aldehydes. Hence this protocol is yet another novel addition to the existing methods.

CHAPTER III. Directing Group Assisted Copper-Catalyzed Chemoselective *O*-Aroylation of Phenols and Enols Using Alkylbenzenes

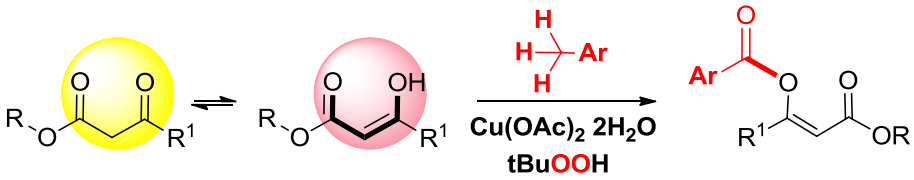
This chapter demonstrates an unprecedented *O*-aroylation of phenols and enols with respect to a directing group via a copper(II) catalyzed CDC approach using alkylbenzene as the synthetic equivalent of an aroyl moiety.

Of late, the construction of C–C and C–X bonds via cross dehydrogenative couplings (CDC) is attractive because it does not require substrate prefunctionalizations and is atom economic. The importance of C–O bonds in synthetic organic chemistry has resulted in the development of a variety of C–H bond functionalization methods mediated by various transition metals. In this context the ester synthesis is in the vanguard. Recent syntheses of esters involve reactions of acids with cyclic ethers where the C–O bond formation takes place at the sp^3 carbon atoms α to the ethereal oxygen. 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. Alkylbenzenes have been excellent aroyl surrogates and are the best alternatives to Friedel-Crafts aroylations. Benzylic esters are obtained by the CDC coupling of aldehydes and alkylbenzenes using the Cu(II) catalyst (path a, Scheme III.1). Thus it would be interesting to see if salicylaldehyde possessing both phenolic –OH and aldehydic functionalities when treated with an alkylbenzene would give benzylic ester or a phenol ester. Phenolic ester (path b, Scheme III.1) was obtained while the aldehydic group survived under the oxidative conditions.



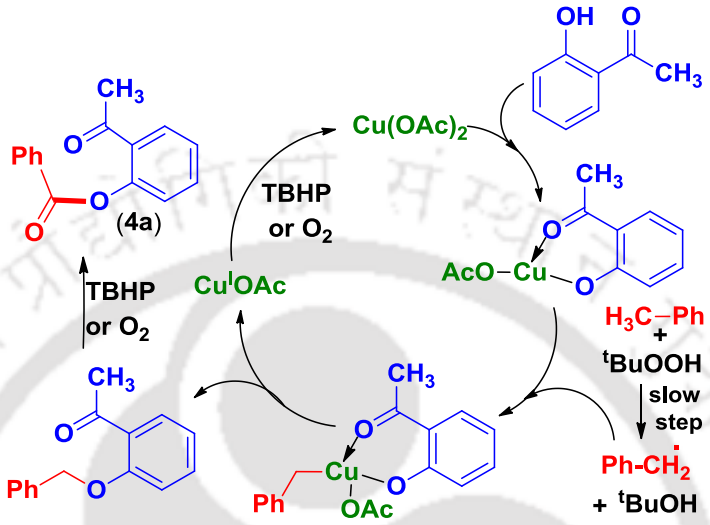
Scheme III.1. *CDC protocols for C–O bond formation via C–H activations*

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 $Cu(OAc)_2$ $2H_2O$ (20 mol %), TBHP (5-6 M in decane) (2 equiv) at 120 ^oC afforded the maximum possible yield of the desired ester. Further reactions were investigated with a set of substituted alkylbenzenes and phenols possessing an ortho –CHO group. All these coupling reactions proceeded smoothly providing their respective *O*-aroylated products in moderate to poor yields. 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 phenols possessing an ortho $–COCH_3$ group. The couplings of these substrates with same set of methylarenes provided their corresponding *O*-aroylated products in the same yield trends as was observed with salicialdehyde. *o*-Hydroxyl carbonyl compounds and the (*Z*)-enol form of 1,3-dicarbonyl compounds have structural analogy so far as the orientation and positioning of carbonyl and hydroxyl groups are concerned. To unravel the potentiality of this approach various 1,3-dicabonyl substrates were reacted with different alkylbenzenes. All these reactions provided highly stereoselective (*Z*)-enol esters (Scheme III.2).

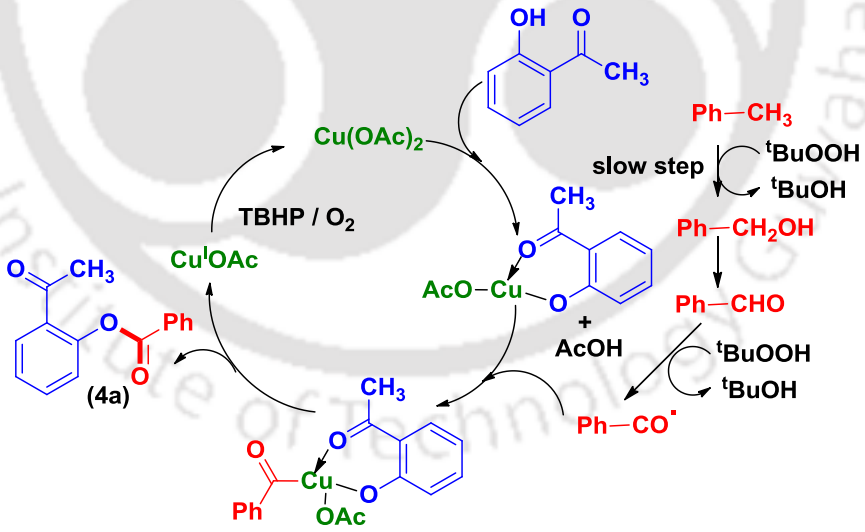


Scheme III.2. *Esterification of enols via C–H functionalization*

Several experimental studies were performed to elucidate the mechanism of this transformation. Based on the observations of these experiments and related literature reports, a dual plausible mechanism operating in tandem has been proposed (Scheme III.3 and Scheme III.4).



Scheme III.3. *Proposed mechanism for O-aroylation via O-benzylated path*



Scheme III.4. *Proposed mechanism for O-aroylation via aldehyde path*

In conclusion, a new, efficient Cu-catalyzed directed *O*-aroylation process (esterification) has been accomplished between alkylbenzenes and *o*-carbonylphenols and β-dicarbonyl compounds using TBHP as the oxidant. A dual mechanism operates in

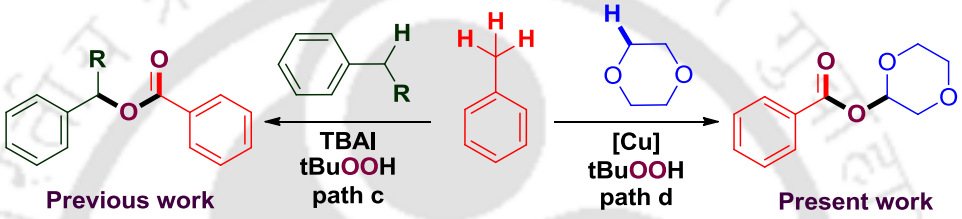
tandem for these transformations. This protocol simultaneously installs two C–O bonds at the expense of three benzylic sp^3 C–H bonds. The phenolic group is selectively aroylated to give esters even in the presence of aldehydic functionality.

CHAPTER IV. A Copper Catalyzed Esterification of Alkylbenzenes with Cyclic Ethers via C(sp^3)–H Activation Following Cross Dehydrogenative Coupling (CDC)

This chapter deals with a copper catalyzed CDC strategy for the synthesis of α-acyloxy ethers by coupling of simple solvents (methylarenes with cyclic ethers) at the expense of four 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 makes 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 c, Scheme IV.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. In pursuit to utilize this "solvent chemistry" in a CDC reaction, cyclic ether (1,4-dioxane) was attempted as a potential coupling partner with alkylbenzenes. Cyclic ethers are widely used as solvents and are also amenable to functionalizations at the sp^3 C–H α to ethereal oxygen. A relatively weak

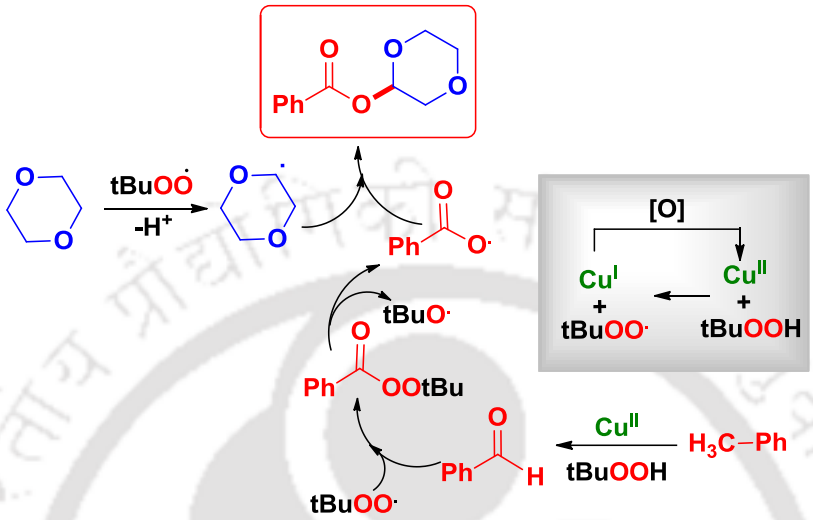
bond dissociation energy of α sp^3 C–H helps to generate a radical center under oxidative conditions thereby allowing a radical / nucleophile to attack at that position. So it would be interesting to see if these two solvents (alkylbenzene and cyclic ether) undergo cross coupling to afford ester under reaction conditions similar to our previous report on benzyl ester synthesis. Although not under metal free conditions, but the use of copper catalyst and a radical initiator led to the formation of the desired α-acyloxy ether (path d, Scheme IV.1). The present methodology on the copper catalyzed solvent-solvent (methylarene-cyclicether) couplings to give α-acyloxy ethers via four sp^3 C–H activations is novel and unique.



Scheme IV.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 %), aqueous TBHP (6 equiv) at 120 ^oC afforded the maximum possible yield of the desired ester. Having established the standard reaction conditions, the present oxidative esterification of cyclic ether were then implemented on cross couplings between 1,4-dioxane and a series of substituted methylarenes. All these coupling reactions proceeded smoothly providing their respective α-acyloxy ethers in moderate to good yields. 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. The successful esterification of 1,4-dioxane with various methylarenes led us to examine the feasibility of this approach with other cyclic ethers possessing single oxygen such as tetrahydropyran and tetrahydrofuran. Unlike in dioxane, the oxidative esterifications of tetrahydropyran with methylbenzenes were not so effective giving α-acyloxy ethers in modest yields. Five membered cyclic ether tetrahydrofuran when reacted with methylbenzene gave negligible amount of α-acyloxy ether.

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 (Scheme IV.2).



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

In conclusion, the present protocol demonstrated a copper catalyzed synthesis of esters from simple solvents. The combination of methylarenes and cyclic ethers result in the formation of α-esterification of ethers via four sp^3 C–H cleavages.

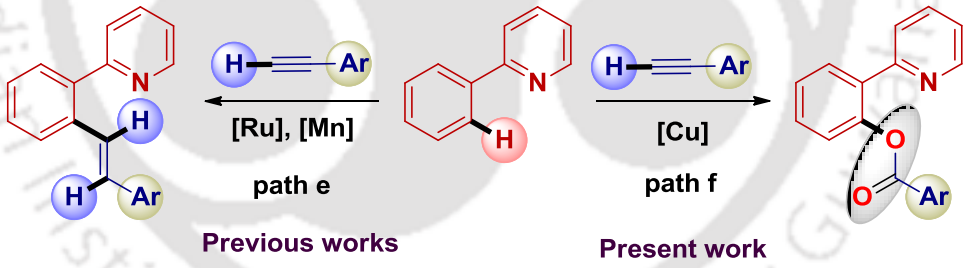
CHAPTER V. Terminal Aryl Alkynes as Arylcarboxy Surrogates Towards *o*-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper

This chapter describes a unique copper catalyzed protocol for the *ortho*-benzoxylation of 2-arylpyridines using terminal alkyne 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 "holy 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.

The C–C bond formations have mostly been directed towards the vinylation of substrates possessing directing groups using expensive metal catalysts such as Ru and Mn (path e, Scheme V.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 uses is so far unfamiliar in this forum. With this motive, when a vinylation of 2-phenylpyridine was attempted with terminal alkyne in presence of a copper catalyst and an oxidant. However, the trial unexpectedly led to *ortho*-benzoxylation exclusively (path f, Scheme V.1). Substrate directed *ortho*-benzoxylation has been achieved previously using carboxylic acid or its derivatives such as benzoate iodonium salts, anhydrides, acid chlorides, acylperoxides, aldehydes and methylarenes. Thus our current observation on *ortho*-benzoxylation using terminal alkyne as ArCOO– surrogate via loss of one carbon atom is unprecedented in the literature.

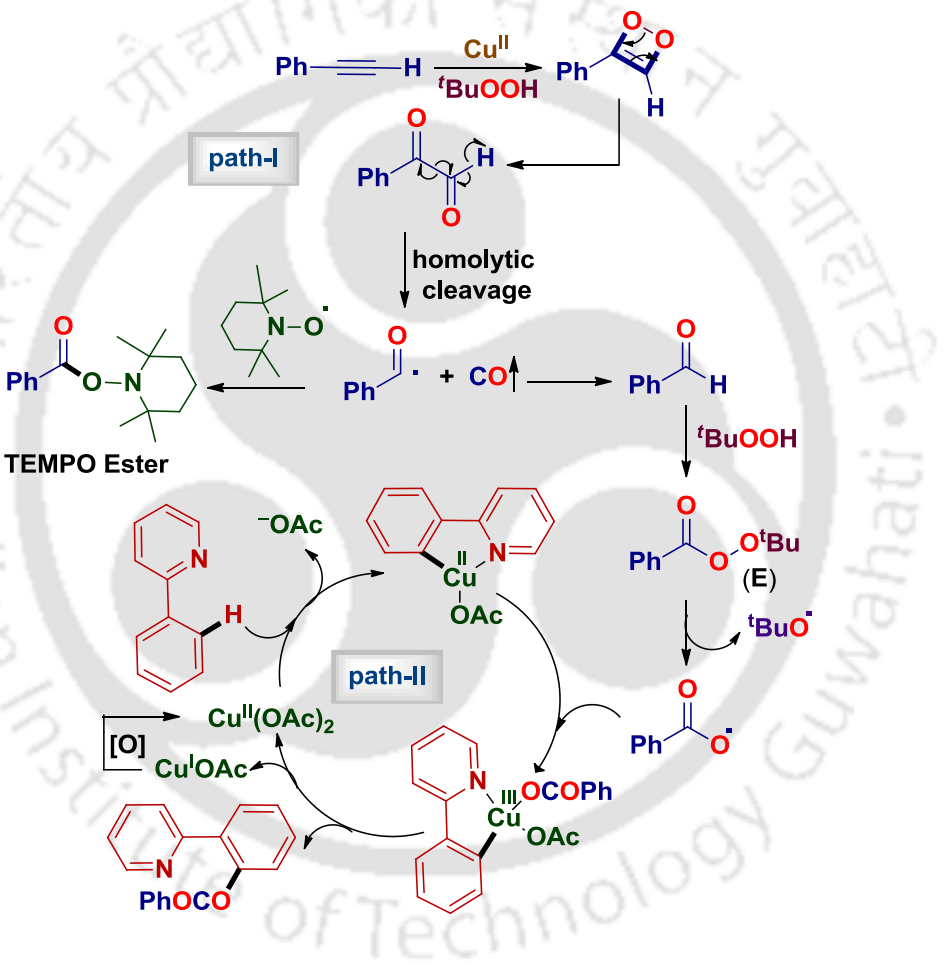


Scheme V.1. *Use of terminal alkenes in C–H activation process*

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 alkynes. All the substituted alkynes 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 alkynes 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 V.2).



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

In conclusion, this methodology illustrates the use of terminal alkynes as the new surrogates for the arylcarboxy group (ArCOO–), which has been employed intriguingly for the *o*-benzoxylation of 2-phenylpyridine derivatives. The formations C–O bond at the expense of one carbon atom form its parent alkynes. 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.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

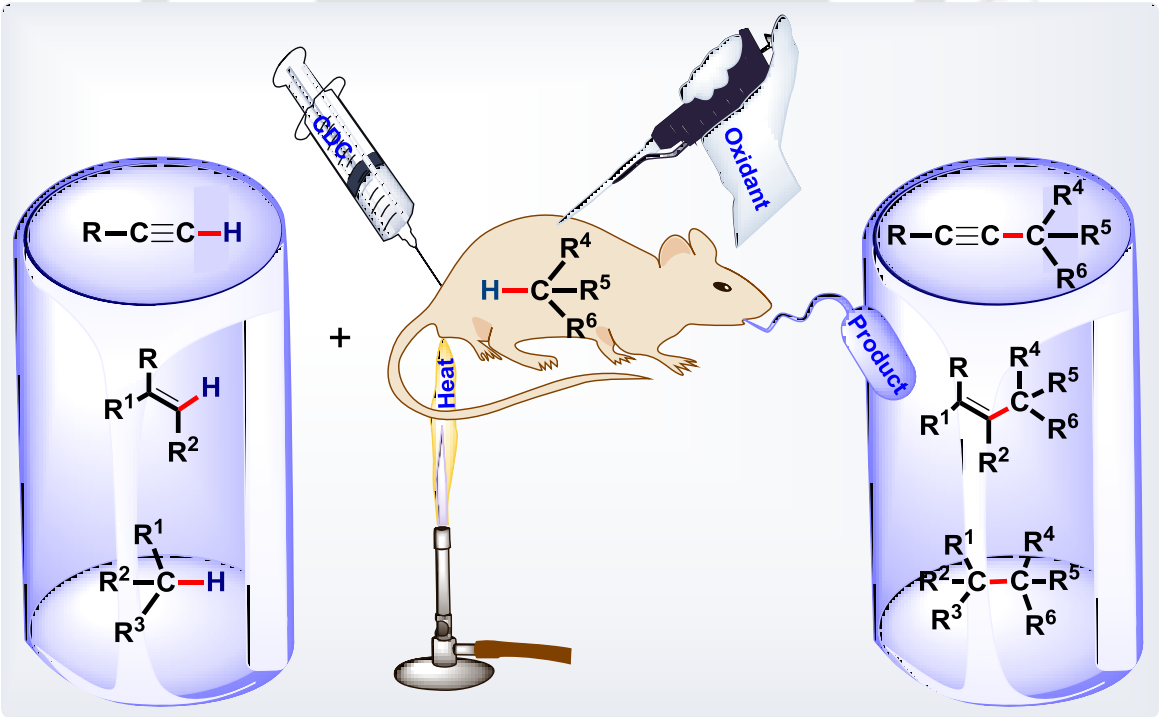
CONTENTS

Chapter V – Terminal Aryl Alkynes as Arylcarboxy Surrogates toward *o*-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Chapter I

Transition Metal Catalyzed C–H Functionalizations

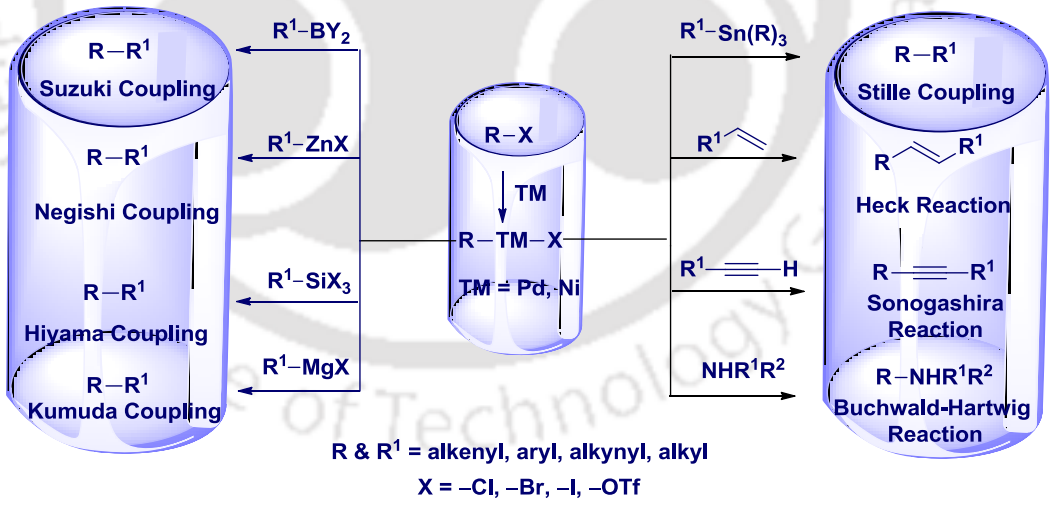


CHAPTER I

I. Transition Metal Catalyzed C–H Functionalizations

I.1. Introduction

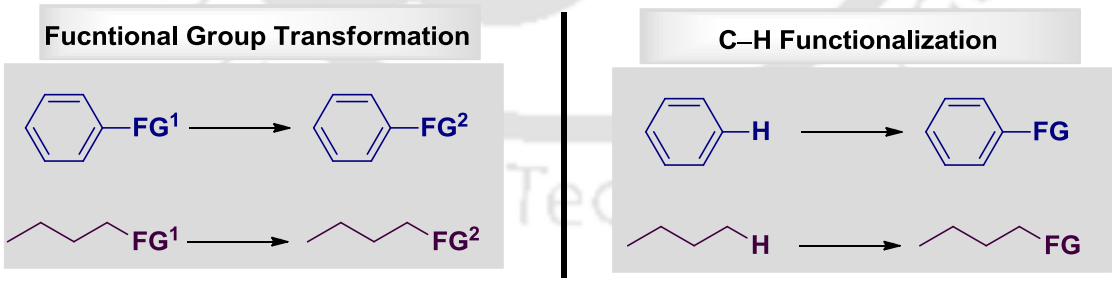
The transition metal catalyzed cross-coupling reactions are very useful tools both in industry as well as in academia for the formation of carbon–carbon and carbon–heteroatom bonds.[1] These methods have gained substantial recognition over the decades and are successfully employed in the synthesis of pharmaceutically active molecules and various commercially important products.[2] Despite the significant progresses made in this area, they are often associated with limitations pertaining to sustainability and step or atom economy. In general, a cross-coupling reaction requires a halide or pseudo halide in the precursor (pre-functionalized starting materials) and also an organometallic nucleophilic reagent (boron, silicon, magnesium, zinc or tin based reagents) (Scheme I.1.1).



Scheme I.1.1. *Representative cross-coupling reactions*

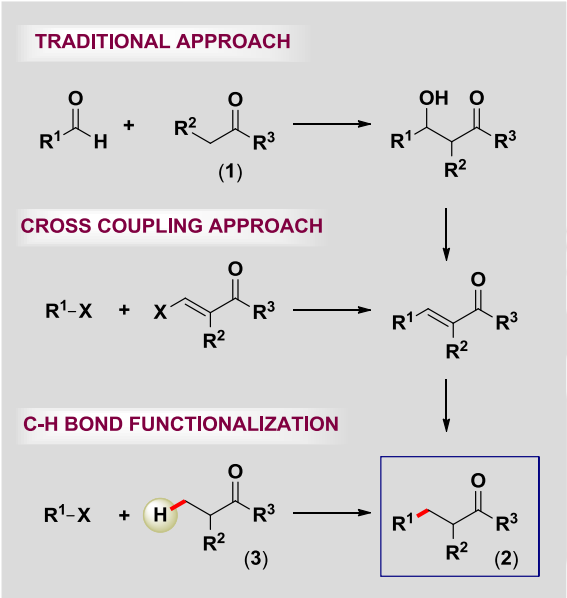
The requirement of pre-functionalized starting materials in these methods leads to additional steps towards the formation of desired chemical bonds. On the other hand, many cross-coupling reactions are associated with generation a stoichiometric amount of metal

salt as waste, for example, Negishi (Zn), Stille (Sn), Kumada (Mg), Fukuyama (Zn), and Suzuki (B) which makes the overall process environmentally unviable. Thus development of alternative strategies, which can circumvent the disadvantages associated with traditional cross-coupling reactions, are always desirable. In addition to these disadvantages use of pre-functionalized starting materials in these methods, leads to additional steps towards the formation of desired chemical bond. The use of unfunctionalized starting materials for the synthesis of C–C and C–hetero atom bonds, that is, via C–H bond activation process, is a more environmentally friendly and atom efficient and if achieved, enantio- or regioselectively can prove as a versatile tool for organic synthesis.[3] The carbon-hydrogen bond is regarded as an the un-functional group in organic chemistry. 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. If such C–H bonds can be perceived as functional groups, it would constitute a faster and more atom-economical synthetic approach (Scheme I.1.2, right) for the construction of complex organic frameworks.[4] This concept is gradually modifying organic chemistry because it provides chemists in both the academic and industrial worlds with new disconnection strategies that give access to molecules with original structures and properties in a more simple, efficient, and ecological manner.

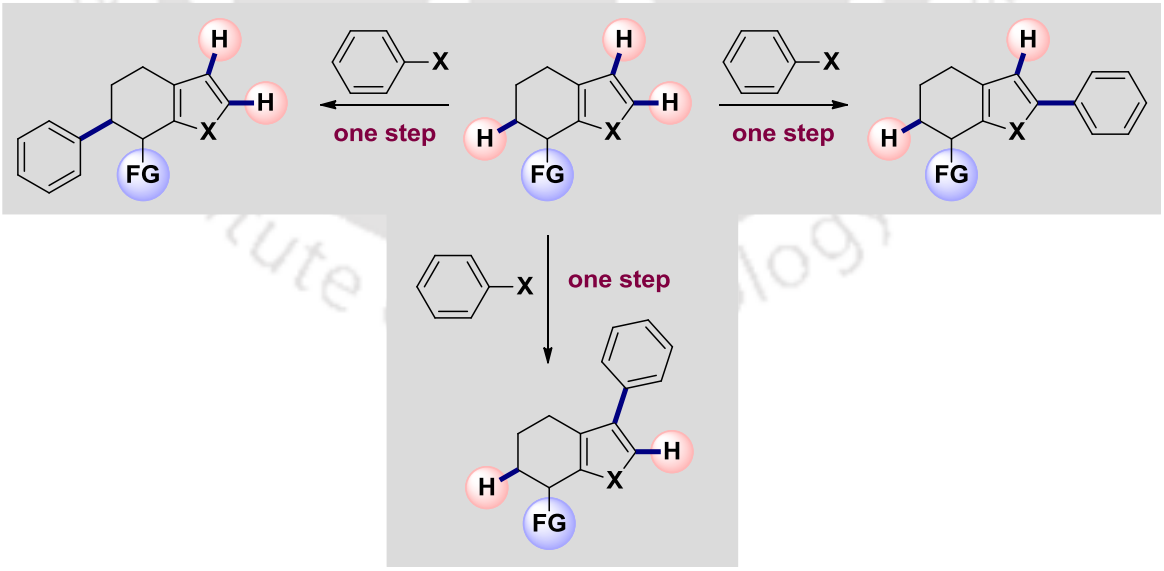


Scheme I.1.2. *Functional group transformation vs. C–H functionalization*

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) whereas to achieve the same via traditional approach or cross-coupling reaction requires several steps. 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.1.2), provides straightforward and concise approach where the topology, or the overall skeletal structure, of the starting material resembles that of the product ("topologically obvious assembly").



Scheme 1.1.2. *Evolving algorithms in organic synthesis.*



Scheme I.1.3. *Structural core diversification by means of C–H bond functionalization*

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.1.3)]. 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.

I.2. Challenges to C–H functionalizations

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

- **Low reactivity:** The pK_a values of the sp^2 or sp^3 hybridized C–H bonds are greater than 30–35. The bond dissociation energy (BDE) required for a direct C–H scission are also high. These intrinsic properties of C–H bonds make them 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.2.1.

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.2.1. *Bond dissociation energy and pKa's of various C–H bonds*

- **Regioselctivity:** A common organic substrate possesses number of similar C–H bonds; thus to selectively activate one desired C–H bond among many is a challenging task. For example, the pharmaceutical Fluoxetine, sold as "Prozac," shown in Figure I.2.1, possesses multiple, unique C–H bonds. Site-selective functionalization of any one of these various

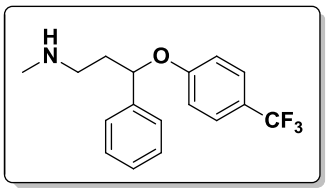
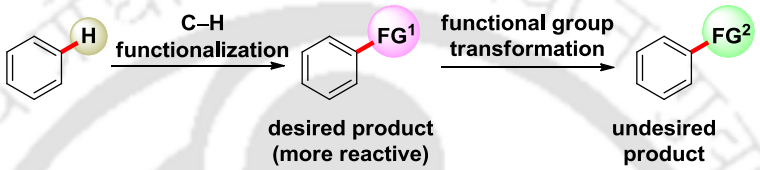


Figure I.2.1. *The pharmaceutical Prozac contains multiple, unique C–H bonds.*

sites could be desirable for structure-activity relationship studies in pursuit of new drug derivatives or to study their pharmacokinetics.

- **Chemoselectivity:** In many cases a C–H functionalization process leads to a product which is more reactive than the starting precursor. In such a case, it is not the starting substrate but the reactive product that undergoes further transformation under the same reaction conditions to give undesirable products; hence deviating from the actual goal (Scheme I.2.1).



Scheme I.2.1. *Chemoselectivity issue in a C–H functionalization process*

A C–H functionalization process are 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.3. Mechanisms of C–H activation

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. Depending on the nature of C–H bonds and the use of transition metal catalysts and ligands the activation of C–H bonds can occur through following ways: (a) oxidative addition, (b) sigma bond metathesis and (c) electrophilic activation.[5] 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.

(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.3.1, complex **A**). This process primarily proceeds through agnostic interaction i.e. distortion of organometallic bringing the appended C–H bond through agnostic interaction. This in turn weakens the C–H bond and can lead to the formation of a new metal-carbon bond (Scheme I.3.1, 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.

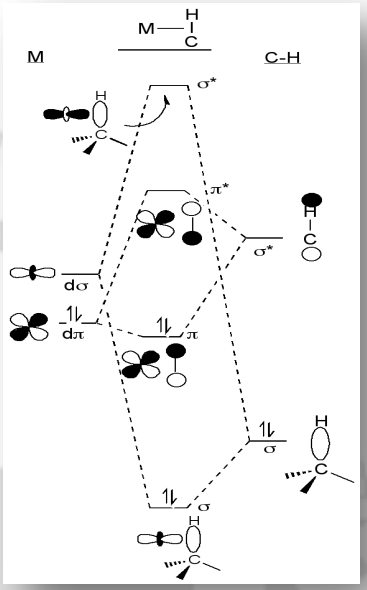
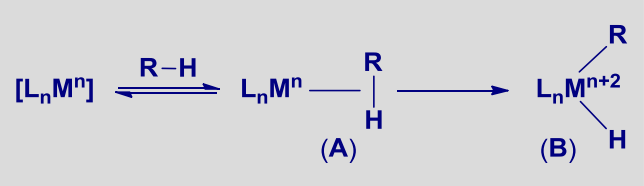


Figure I.3.1. *A qualitative MO diagram for oxidative addition*



Scheme I.3.1. *C–H activation via oxidative addition*

A qualitative molecular orbital diagram showing only the C–H–M π interaction (M = metal) is shown in Figure I.3.1. 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.3.2). 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.3.2).

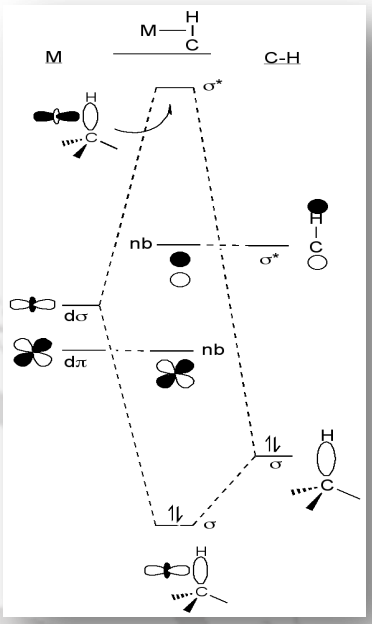
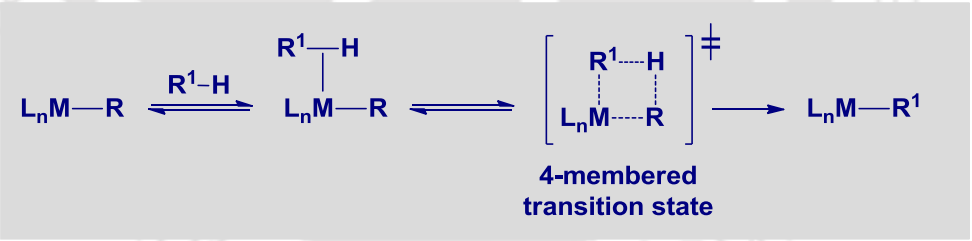


Figure I.3.2. *A qualitative MO diagram for σ-bond metathesis*

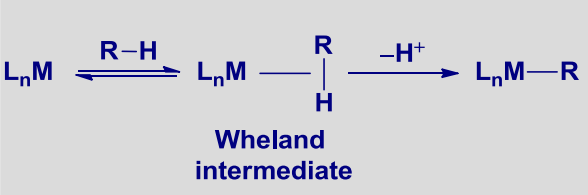


Scheme I.3.2. *C–H activation via σ-bond metathesis*

(c) Electrophilic activation

Late transition metals in a higher oxidation state take part in electrophilic substitutions. Electrophilic metallation 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.3.3). 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.3.3. *C–H activation via electrophilic activation*

A qualitative MO diagram shown in Figure I.3.3 highlights that this mechanism usually involves late transition metals where the d-orbitals have lower in energy.

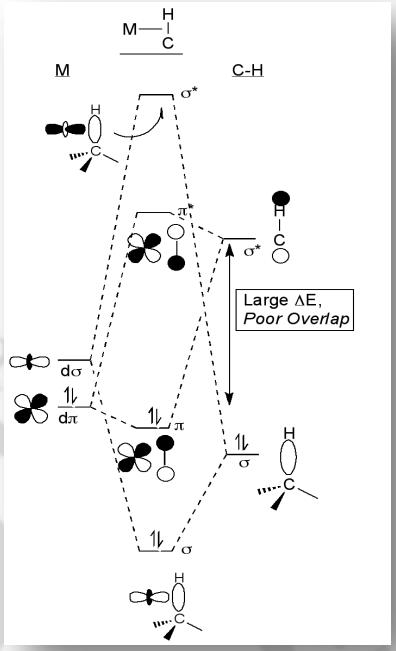
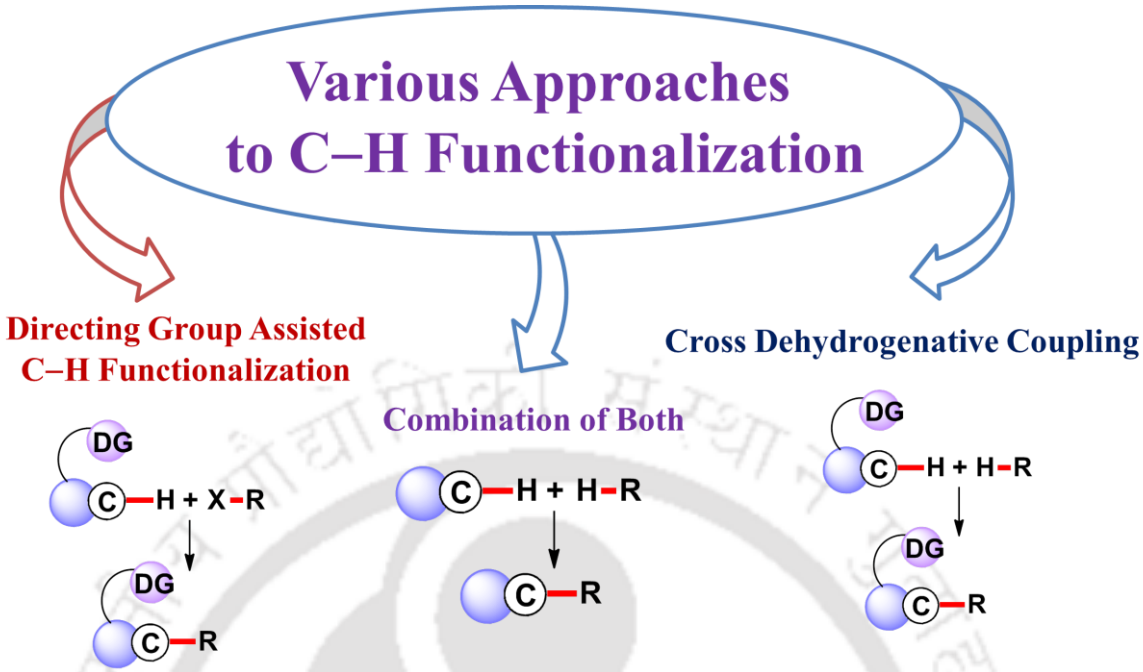


Figure I.3.3. *A qualitative MO diagram for electrophilic activation*

I.4. Various strategies for C–H functionalization

The modern era of 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.4.1). Also there are methodologies which are based on the combination of two aforementioned approaches (Scheme I.4.1).



Scheme I.4.1. *Various approaches to C–H functionalizations*

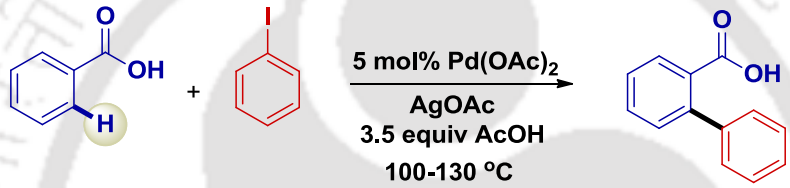
I.4.1 Directing group assisted C–H functionalizations. Directed metallation is one of the powerful approach for selective functionalization of C–H bonds in substrates applicable to a variety of C–H bonds, including those of isolated alkyls.[6] It entails the use of a suitable heteroatomic function in 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.

I.4.1.1. 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**

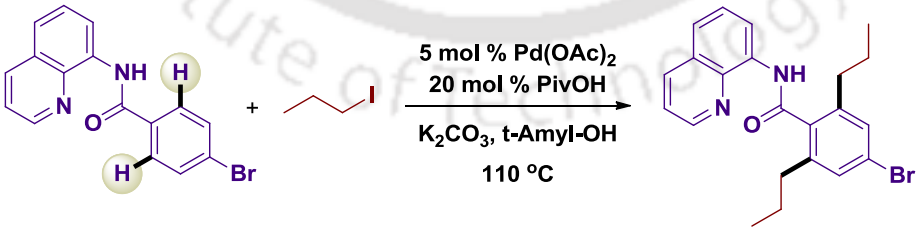
Daugulis and co-workers developed a protocol on Pd(II) catalyzed *ortho*-arylation of benzoic acids in conjunction with stoichiometric silver acetate as the oxidant. (Scheme I.4.1.1.1).[7e] This transformation uses aryl iodides as aryl sources. A related *ortho*-arylation has also been applied to substituted anilides,[9c] benzoxazoles,[7d] and 2-arylpyridines.[7a-b] amides[7f] and oxime ethers[7g] 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,[8a-d] aryl chlorides,[7e] arylboronic acids,[8e-f] arylsilyl ethers[8g-h] and even aryl acyl peroxides[8i] have been used for this purpose very effectively.



Scheme I.4.1.1.1. *Pd-catalyzed ortho-arylation of benzoic acid 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.4.1.1.2).[9a] Directing group assisted alkylation has also been achieved using other alkyl sources that include tetra-alkyl tin reagents,[9b] methylboroxines,[9c] alkylboronic acids[9d] and dicumylperoxide.[9e]

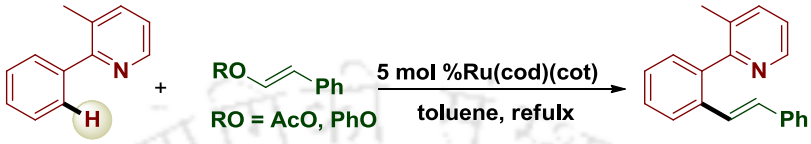


Scheme I.4.1.1.2. *Pd-catalyzed sp^2 C–H alkylation with alkyl halides*

➢ **sp^2 C–H Alkenylation**

Kakiuchi group has shown that alkenyl ethers and esters can be employed for Ru-catalyzed *ortho*-selective alkenylation of 2-arylpyridines and their derivatives (Scheme

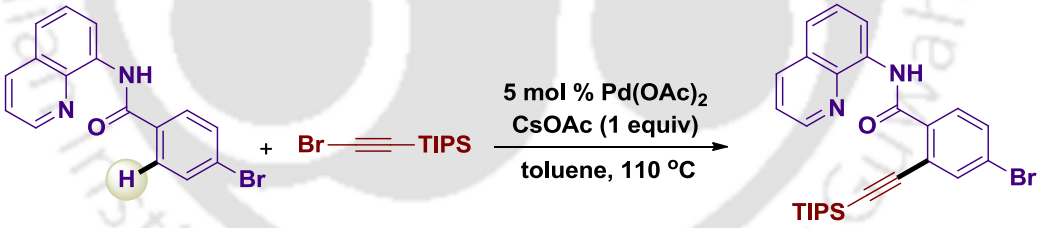
I.4.1.1.3).[10b] In addition to the abovementioned novel discoveries by Daugulis group towards *ortho*-arylation and *ortho*-alkylation, they have demonstrated an intriguing methodology for *ortho*-alkenylation using 3-halo acrylates as alkene substrates.[10a] In one of their independent works, they have also employed 2-bromovinyl benzene as the styrene source for *ortho*-alkenylation of amides.[9a]



Scheme I.4.1.1.3. *Pd-catalyzed coupling of alkenyl ethers with 2-arylpyridines*

- **sp^2 C–H Alkynylation**

The sp^2 C–H alkynylation of substrates possessing various directing groups are limited to few examples only. Chatani group achieved a palladium catalyzed *ortho*-alkynylation of 8-aminoquinolinamide with a TIPS-protected bromoalkyne and CsOAc (Scheme I.4.1.1.4).[11] Other groups reported Ru and Rh catalyzed protocols using pre-activated alkynylating reagents such as alkynyl halides[12] and benziodoxolone-based hypervalent iodine reagents[13] as coupling partners.

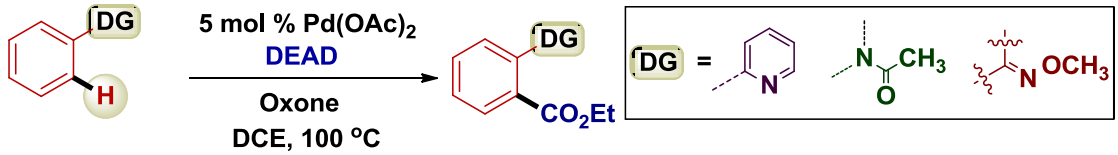


Scheme I.4.1.1.4. *Pd-catalyzed ortho-alkynylation of 8-aminoquinolinamide*

- **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.[14a] $Pd(OAc)_2$ 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.[14b-c] Diethyl azodicarboxylate (DEAD) has been used as a substitute of toxic CO for ethoxycarbonylation of substrates possessing directing groups such as pyridine,

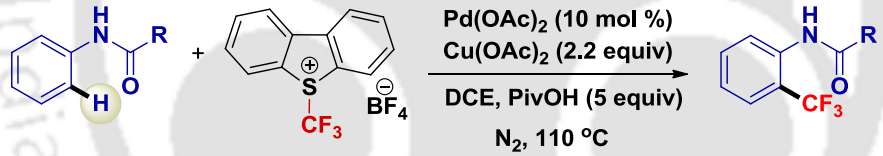
amide and oxime ether in the presence of $Pd(OAc)_2$ as the catalyst and oxone as the terminal oxidant (Scheme I.4.1.1.5).[14d]



Scheme I.4.1.1.5. *Pd-catalyzed ethoxycarbonylation using DEAD*

➢ **sp^2 C–H Trifluoromethylation**

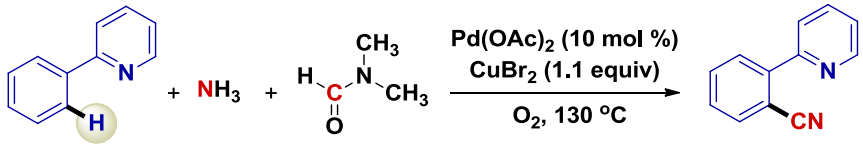
Shi group reported Pd(II)-catalyzed *ortho*-trifluoromethylation of amide or analogous substrates using pivalic acid (PivOH) and $Cu(OAc)_2$ as crucial promoters (Scheme I.4.1.1.6).[15a] Yu group initially demonstrated the Pd(II)-catalyzed trifluoromethylation of 2-arylpyridine using trifluoroacetic acid and $Cu(OAc)_2$ as oxidant.[15b] There has been an evolution of several methods on *ortho*-trifluoromethylation of several other directing group possessing substrates.[15c-d]



Scheme I.4.1.1.6. *Pd-catalyzed ortho-trifluoromethylation of amide*

➢ **sp^2 C–H Cyanation**

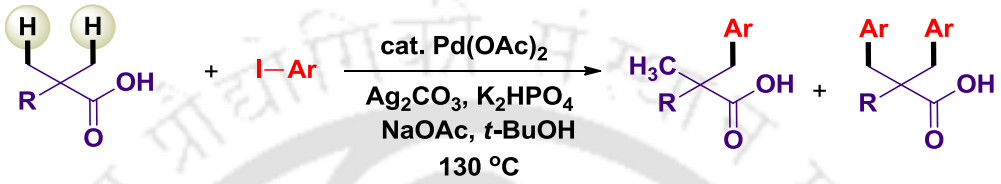
Chang group have reported a Pd catalyzed new protocol for cyanation at arene C–H bonds employing two readily available precursors, NH_3(aq) and DMF as a combined source for the cyano "CN" unit (Scheme I.4.1.1.7).[16a] Other cyano surrogates such as copper(I) cyanide,[16b] potassium ferricyanide,[16c] benzyl nitrile,[16d] acetonitrile,[16e] AIBN[16f] and *tert*-butyl isonitrile[16g] have also been used for the same purpose.



Scheme I.4.1.1.7. *Pd-catalyzed ortho-cyanation of 2-phenylpyridine*

➢ sp^3 C–H Arylation

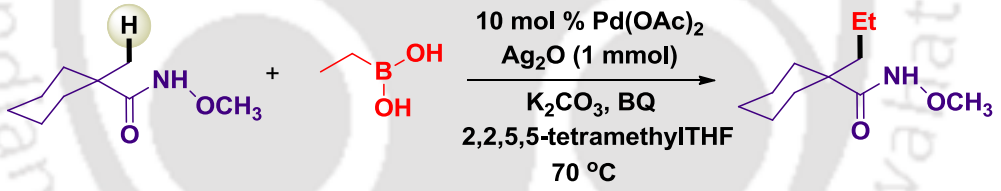
Yu group have developed Pd-catalyzed arylation of unactivated sp^3 C–H in carboxylic acid derivatives with aryl iodides using Ag_2CO_3, 2 equiv of NaOAc and 1 equiv of K_2HPO_4 as additives (Scheme I.4.1.1.8).[17a] Directing groups including pyridines, aminoquinolines, and picolinamides were used, and arylation occurred at both 1° and 2° sp^3 C–H sites.[17b]



Scheme I.4.1.1.8. *Pd-catalyzed sp^3 C–H arylation with aryl iodides*

➢ sp^3 C–H Alkylation

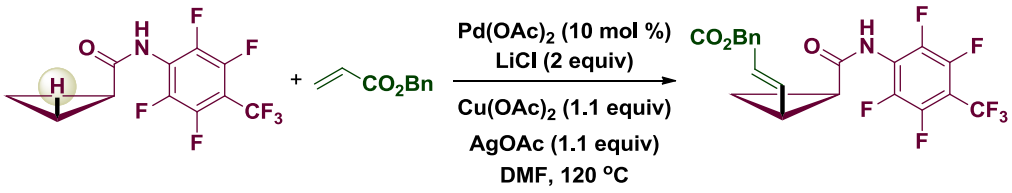
Alkylboronic acids have been employed as alkyl sources for Pd(II) catalyzed alkylation at sp^3 C–H bonds of *N*-methoxy amides as auxillary ligand (Scheme I.4.1.1.9).[18]



Scheme I.4.1.1.9. *Pd-catalyzed sp^3 C–H alkylation with boronic acids*

➢ sp^3 C–H Alkenylation

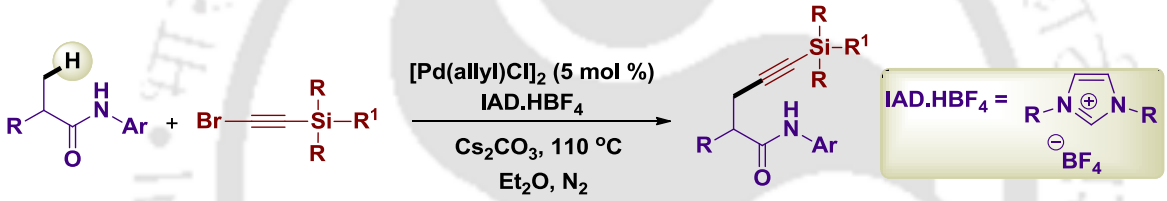
Yu group have developed an amide group assisted Pd(II)-catalyzed reaction protocol for the direct olefination of sp^3 C–H bonds (Scheme I.4.1.1.10).[19a] After β-C–H olefination, the amide products underwent 1,4-conjugate addition to give the corresponding lactams. The same reaction conditions could 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.[19b]



Scheme I.4.1.1.10. *Pd-catalyzed amide directed sp^3 C–H alkenylation*

- **sp^3 C–H Alkynylation**

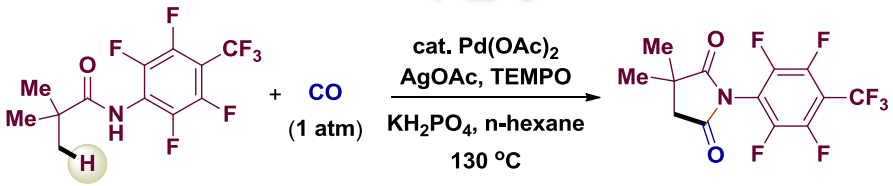
Methods to convert inert C(sp^3)–H bonds to C(sp^3)–alkynyl bonds are rare, with only two precedences in literature. Yu group reported the first example of Pd(0)/NHC and Pd(0)/PR_3-catalyzed alkynylation of β-C(sp^3)–H bonds using an *N*-arylamide auxiliary. (Scheme I.4.1.1.11).[20a] Chatani group illustrated the first Pd(II)-catalyzed coupling of C(sp^3)–H bonds with alkynyl halides via Pd(II)/Pd(IV) catalysis [20b]



Scheme I.4.1.1.11. *Pd-catalyzed sp^3 C–H alkynylation with haloalkynes*

- **sp^3 C–H Carbonylation**

Yu group have achieved a Pd(II)-catalyzed β-C(sp^3)–H carbonylation of *N*-arylamides under an atmosphere of CO (1 atm) for the synthesis of their corresponding succinimides (Scheme I.4.1.1.12).[21] 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.



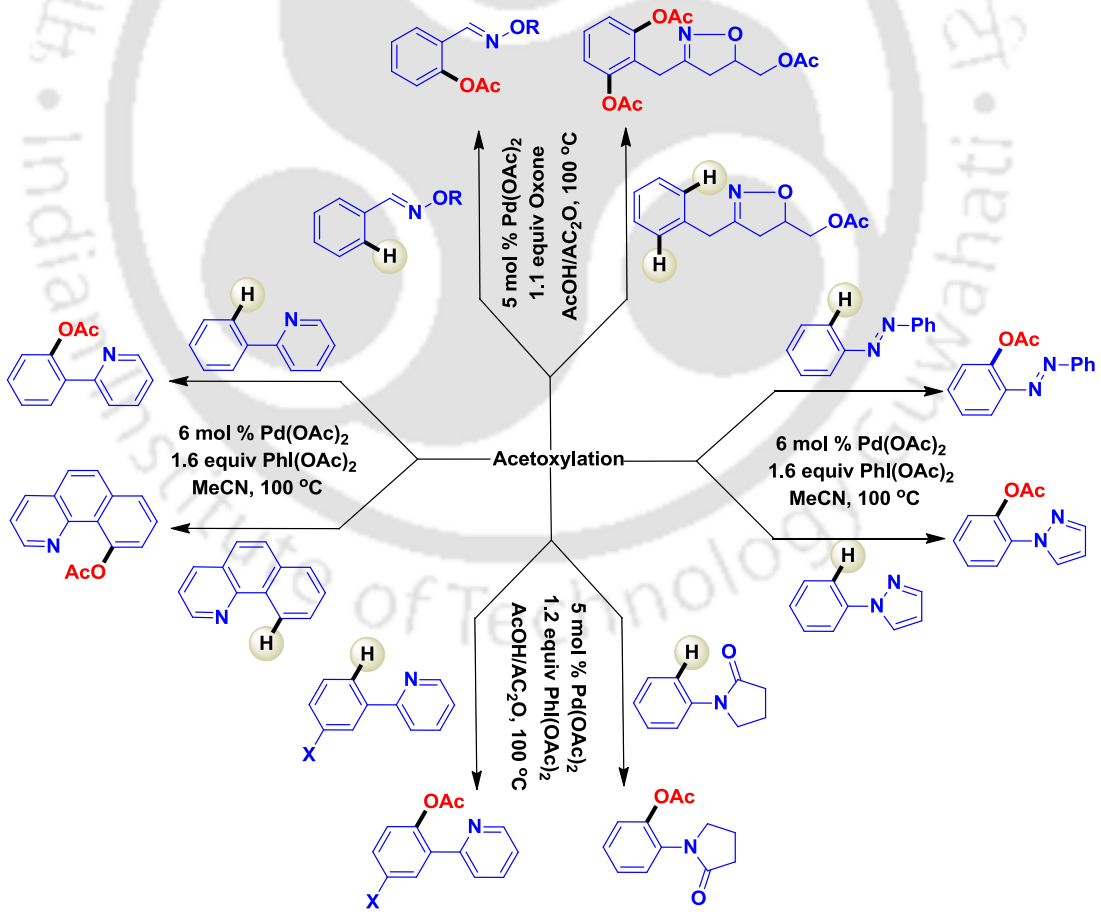
Scheme I.4.1.1.12. *Pd-catalyzed sp^3 C–H carbonylation of amides to synthesize succinimides*

I.4.1.2. 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.

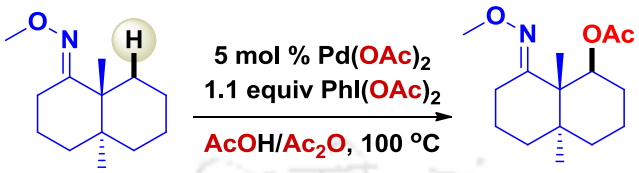
- **C–H Acetoxylation**

Sanford group reported *ortho*-acetoxylated of nitrogen-based directing groups (DG), such as imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles (e.g., pyrazoles and isoxazolines) using $PhI(OAc)_2$ as the oxidant (Scheme I.4.1.2.1).[22]



Scheme I.4.1.2.1. *Pd-catalyzed ortho-acetoxylation of various DG*

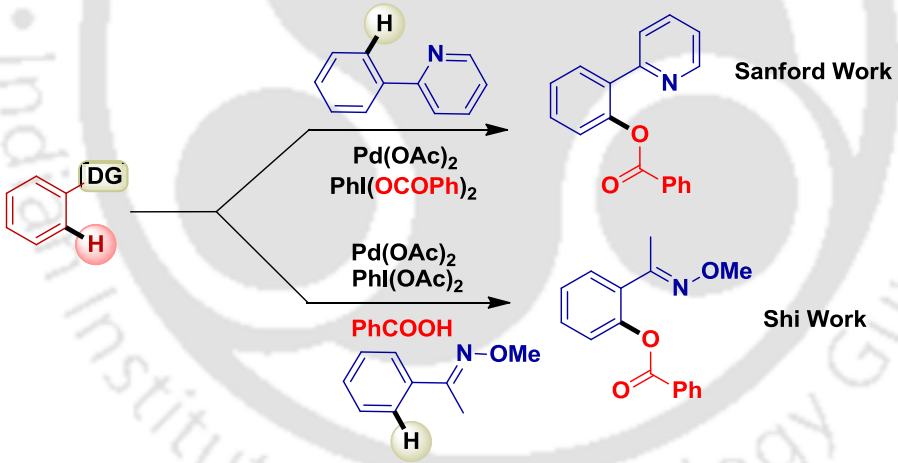
The same group also reported a Pd-catalyzed ligand-directed sp^3 C–H bond oxygenation with $PhI(OAc)_2$ as the terminal oxidant in which both benzylic and unactivated sp^3 C–H bonds were readily converted to acetate group (Scheme I.4.1.2.2).[22a,d]



Scheme I.4.1.2.2. *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 Later, Shi group achieved a similar palladium catalyzed *o*-benzoxylation of ketoxime ether via *in situ* generation of benzoate iodonium salts (Scheme I.4.1.2.3).[23]

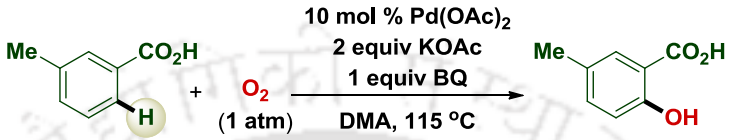


Scheme I.4.1.2.3. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

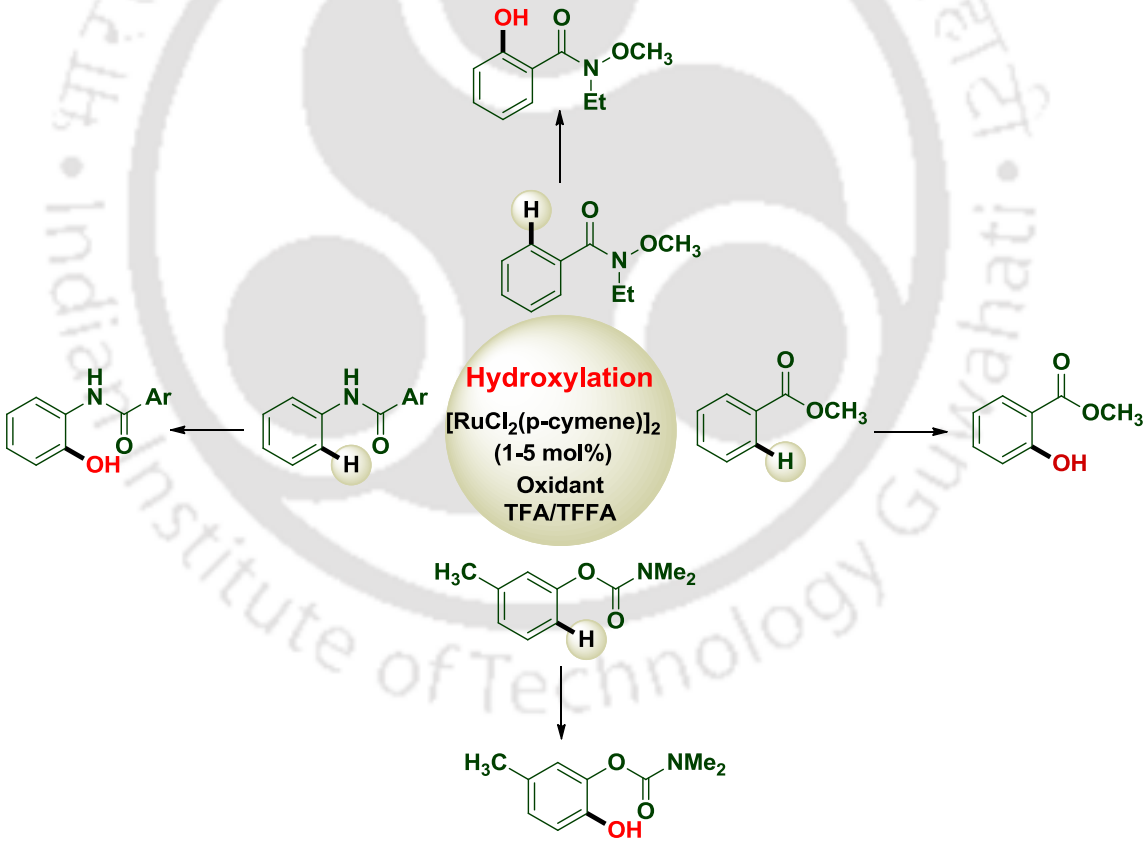
➢ **C–H Hydroxylation**

Yu group have achieved a highly selective Pd-catalyzed *ortho*-hydroxylation of potassium benzoates via activation of dioxygen giving synthetically useful salicyclic acid derivatives (Scheme I.4.1.2.4).[24a] Apart from this, the same group has also described a Cu-catalyzed *ortho*-hydroxylation of 2-arylpyridines that goes via acetoxylation/hydrolysis sequence.[24b] Remarkable recent progress has been accomplished in direct C–H functionalizations for

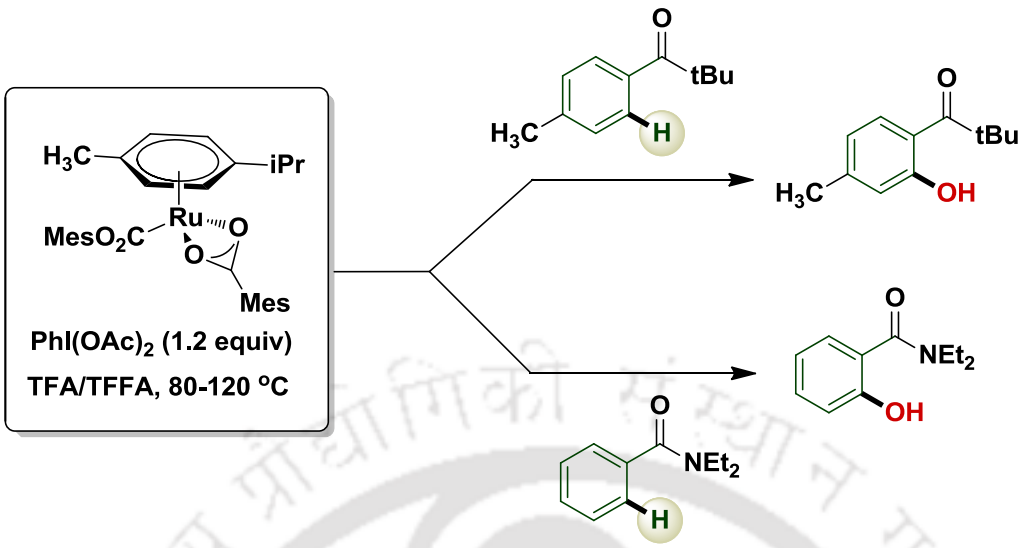
the formation of C–O bonds through the use of readily accessible ruthenium catalysts. Particularly, ruthenium(II) complexes allowed for challenging direct C(sp^2)–H hydroxylation of arenes. These catalysts set the stage for step-economical C–H functionalization with electron-rich as well as electron-deficient (hetero)arenes and, therefore, provided versatile access to diversely decorated phenols (Scheme I.4.1.2.5).[24c]



Scheme I.4.1.2.4. *Pd-catalyzed ortho-hydroxylation of arylcarboxylic acids*



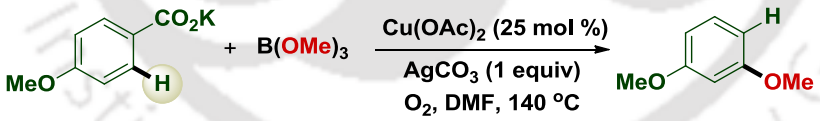
Scheme I.4.1.2.5. *Ru-catalyzed ortho-hydroxylation of various directing group*



Scheme I.4.1.2.5. *Ru-catalyzed ortho-hydroxylation of various directing group*

➢ **C–H Alkoxylation**

Gooβen group demostrated a regiospecific Cu(II) catalyzed *ortho*-alkoxylation of aromatic carboxylates with concomitant decarboxylation (Scheme I.4.1.2.6).[25] 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.



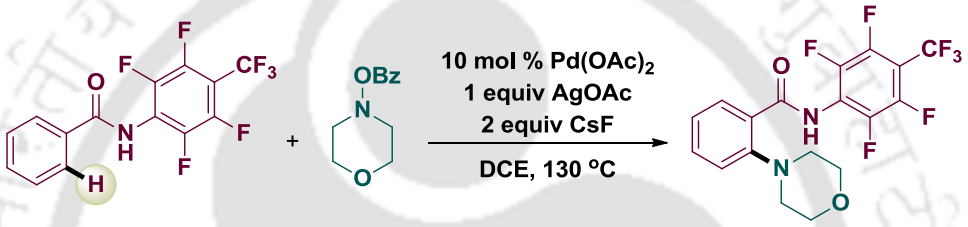
Scheme I.4.1.2.6. *Pd-catalyzed ortho-alkoxylation of arylcarboxylates*

I.4.1.3. 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**

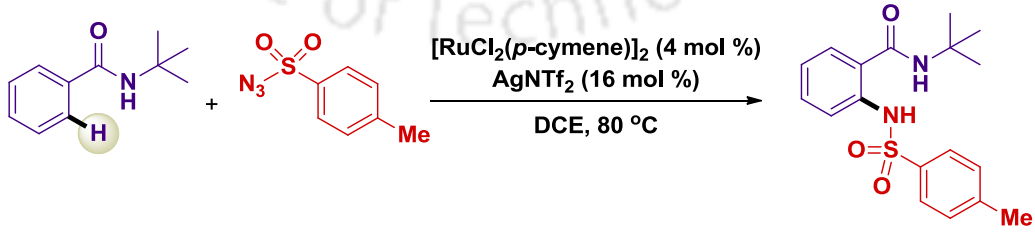
Yu group have further developed a novel protocol to effect C–H amination on a broad range of synthetically useful benzamide substrates with electrophilic *O*-benzoyl hydroxylamines using either Pd(II) or Pd(0) catalysts (Scheme I.4.1.3.1).[26] Additionally, they have shown that a one-pot procedure using 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.4.1.3.1. *Pd-catalyzed intermolecular amination with alkylamines*

➢ **C–H Amidation**

Chang and co-workers have demonstrated a ruthenium-catalyzed C–H bond amidations on arenes bearing synthetically useful directing groups, such as amides or ketones (Scheme I.4.1.3.2).[27] 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.[24c]



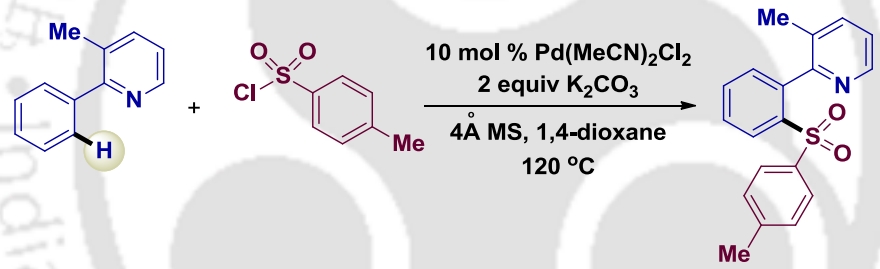
Scheme I.4.1.3.2. *Ru-catalyzed ortho-amidation of benzamides with sulfonyl azides*

I.4.1.4. 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.[28] 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**

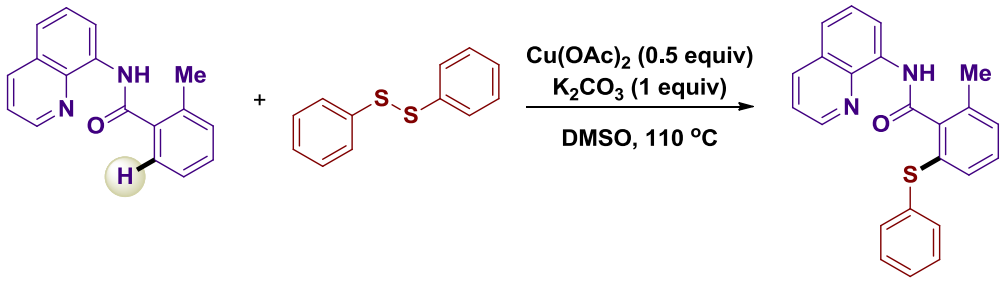
To date, the only example of sulfonylation is the intermolecular Pd-catalyzed C–H activation/C–S bond formation employing $ArSO_2Cl$ as the sulfonating reagent (Scheme I.4.1.4.1).[29] Arylpyridine, arylpyrazole, and aryloxime ether substrates were converted to diarylsulfones using catalytic $Pd(MeCN)_2Cl_2$ and stoichiometric $ArSO_2Cl$.



Scheme I.4.1.4.1. *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.4.1.4.2).[30] The method employs disulfide reagents, copper(II) acetate, and DMSO solvent at 90−130 °C.



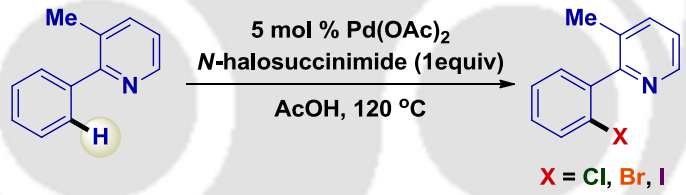
Scheme I.4.1.4.2. *Pd-catalyzed direct sulfenylation of benzoic acid derivatives*

I.4.1.5. 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.

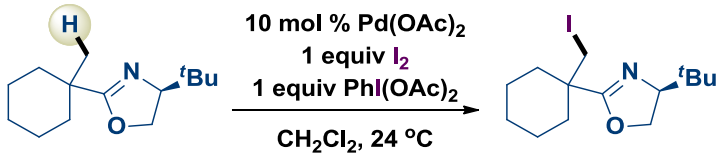
- **C–H Chlorination, bromination and iodination**

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.[31a] 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.4.1.5.1).[31b-c] Apart from the *N*-halo succinimides, other halogenating agents are also used such as CuX_2 (X = Cl, Br),[31c-d] Suárez reagents (XOAc, X = Br, I)[31e-f] and sulfonyl chlorides.[29]



Scheme I.4.1.5.1. *Pd-catalyzed ortho-halogenation of 2-phenylpyridine*

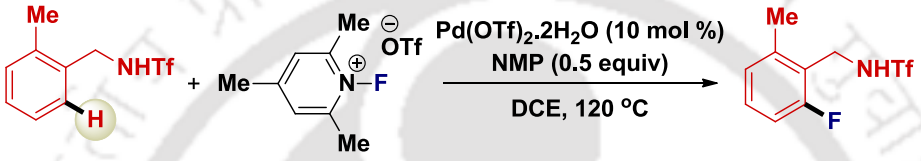
Pertaining to sp^3 halogenation, Pd(II)-catalyzed iodination is reported by Yu group using a combination of $PhI(OAc)_2$ and I_2, to generate in situ IOAc (Scheme I.4.1.5.2).[31e-f] However similar chlorination and bromination is yet to be accomplished.



Scheme I.4.1.5.2. *Pd-catalyzed sp^3 C–H iodination*

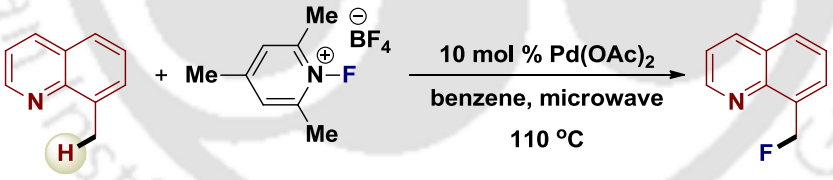
➢ **C–H Fluorination**

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.4.1.5.3).[32a] 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.4.1.5.3. *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.4.1.5.4).[32b] They also showed that microwave heating decreased the reaction time and minimized undesirable side products.



Scheme I.4.1.5.4. *Pd-catalyzed benzylic sp^3 C–H fluorination*

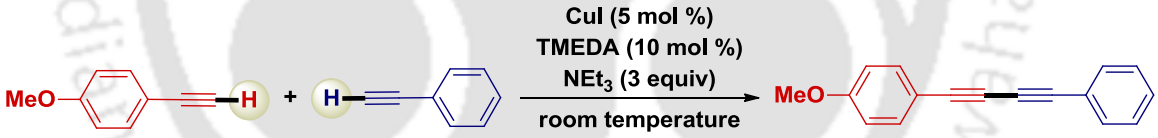
I.4.2. Cross-dehydrogenative coupling (CDC). The cross-dehydrogenative coupling (CDC) reaction generally refers to a cross-coupling reaction between two C–H bonds or C–H and X–H (X = heteroatoms) bonds.[33] In terms of atom economy, this strategy represents one of the most ideal synthetic procedures 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.

I.4.2.1. Representative examples of CDC reactions

- **C(sp)–C(sp) Bond formation**

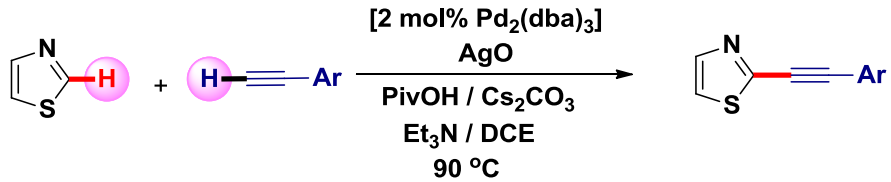
A facile and efficient pathway for the copper iodide and ligand *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA) promoted homo-coupling reaction of terminal alkynes under ambient temperature and air as the oxidant was reported by Zhang group (Scheme I.4.2.1.1).[34] The alkynes, including aromatic alkynes and aliphatic alkynes, could afford the symmetrical as well as unsymmetrical 1,4-disubstituted 1,3-diynes in good to excellent yields.



Scheme I.4.2.1.1 *Copper (I)-catalyzed homo-coupling of terminal alkynes*

- **C(sp)–C(sp^2) Bond formation**

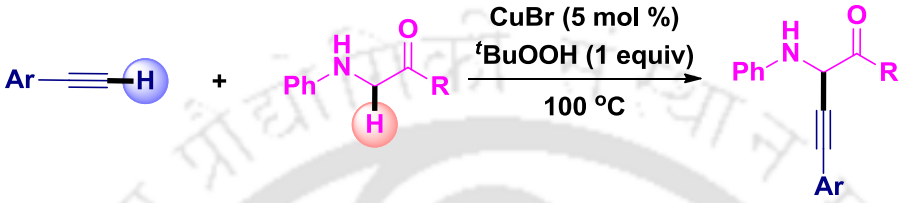
Su group has developed alkynylation of thiazoles and other aromatic heterocycles via oxidative coupling of five-membered heteroarenes and terminal alkynes using the combination of palladium and silver salts (Scheme I.4.2.1.2).[35]



Scheme I.4.2.1.2. *Palladium(II)-catalyzed direct alkynylation of heteroarenes*

➢ **C(sp)–C(sp^3) Bond formation**

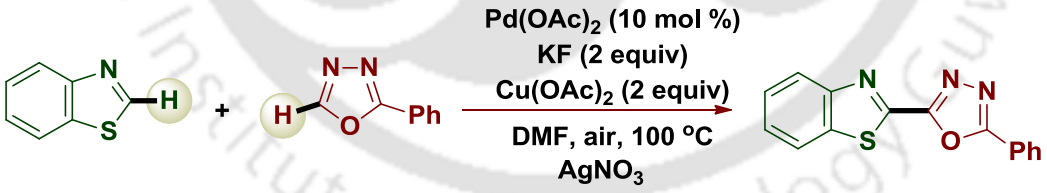
Li group achieved a simple and effective catalytic method to construct propargylamine of various para-methoxyphenyl (PMP)-protected glycine derivatives using copper bromide and *tert*-BuOOH occurring via sp^3 C−H bond and sp C−H bond activations followed by a C−C bond formation (Scheme I.4.2.1.3).[36]



Scheme I.4.2.1.3. *Copper(I)-catalyzed direct alkynylation at sp^3 C–H*

➢ **C(sp^2)–C(sp^2) Bond formation**

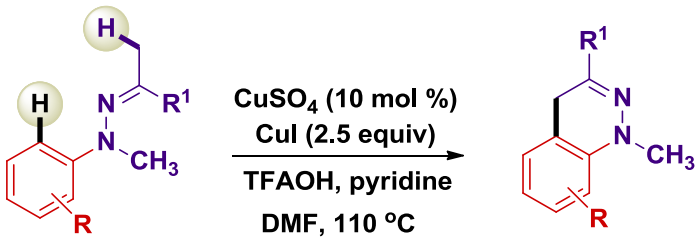
Das and co-workers reported an efficient Pd(II)-catalyzed direct oxidative coupling of benzothiazole with 1,3,4-oxadiazoles that is mediated by co-oxidants $Cu(OAc)_2$ and KF (Scheme I.4.2.1.4).[37] Homocoupling was successfully suppressed such that mixed bisheteroaryls were obtained through the selective cleavage of C–H bonds in both substrates without the requirement of prefunctionalized azoles, designed ligands or a huge excess of one azole over the other.



Scheme I.4.2.1.4. *Palladium(II)-catalyzed oxidative sp^2 C–H/sp^2 C–H coupling*

➢ **C(sp^2)–C(sp^3) Bond formation**

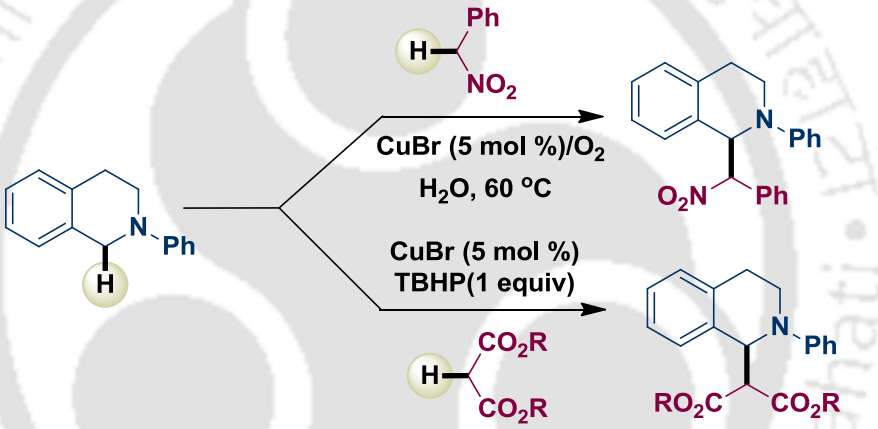
Ge group introduced a Cu-catalyzed aerobic synthesis of functionalized cinnolines via intramolecular (sp^3)C–(sp^2)C bond formation in the presence of a buffer solution of pyridine/trifluoroacetic acid (Scheme I.4.2.1.5).[38] This is an intramolecular version of the dehydrogenative Friedel–Crafts-type arylation.



Scheme I.4.2.1.5. *Cu(II)-catalyzed cinnoline synthesis*

- **C(sp^3)–C(sp^3) Bond formation**

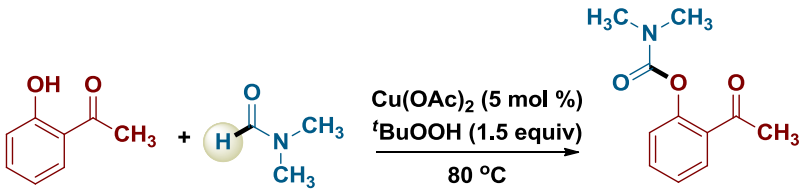
A simple Cu-catalyzed C–C bond formation by Mannich-type reaction in which tetrahydroisoquinolines were successfully coupled with readily available nitroalkane and enolizable malonates was developed by Li group (Scheme I.4.2.1.6).[39]



Scheme I.4.2.1.6. *Cu-catalyzed direct C–C bond formation*

- **C(sp^2)–O Bond formation**

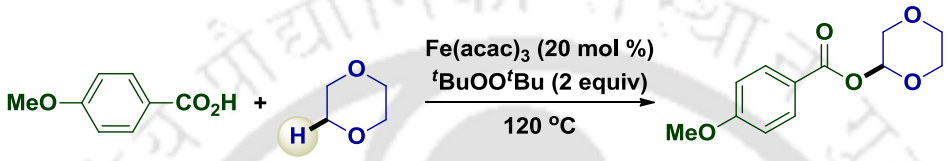
Reddy group developed a novel phosgene-free route to carbamates via copper-catalyzed oxidative C–O bond formation of formamides with phenol and enols (Scheme I.4.2.1.7).[40] A high stereoselectivity was achieved for enol carbamates and the present strategy was also extended to oxidative esterification of carbonyl-substituted phenols.



Scheme I.4.2.1.7. *Copper(II)-catalyzed synthesis of carbamates via C–O bond formation*

➢ **C(sp^3)–O Bond formation**

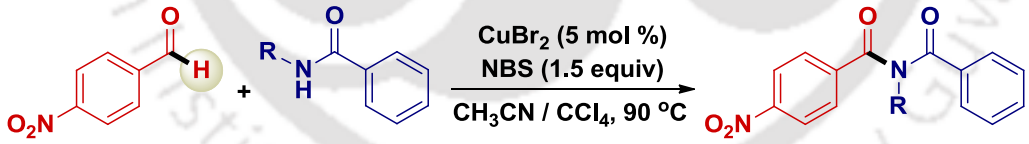
Pan group has recently achieved an iron-catalyzed oxidative esterification of unactivated C(sp^3)−H bonds from symmetric and asymmetric ethers and carboxylic acids using di-*tert*-butyl peroxide (DTBP) as the oxidant via a cross dehydrogenative coupling (CDC) reaction (Scheme I.4.2.1.8).[41] This protocol 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.4.2.1.8. *Iron(III)-catalyzed synthesis of α-acyloxy ethers*

➢ **C(sp^2)–N(amide) Bond formation**

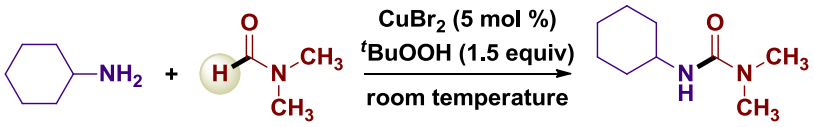
Fu group has developed a hetero-CDC protocol for the synthesis of imides using simple aldehydes and either secondary or tertiary amides as the coupling partners in the presence of copper(II) bromide and NBS (Scheme I.4.2.1.9).[42] The corresponding target products were obtained in good to excellent yields, and an array of functional groups are tolerated under the mild conditions with respect to both amides and aldehydes.



Scheme I.4.2.1.9. *Copper(II)-catalyzed synthesis of imides via sp^2 C–H amidation*

➢ **C(sp^2)–N(amine) Bond formation**

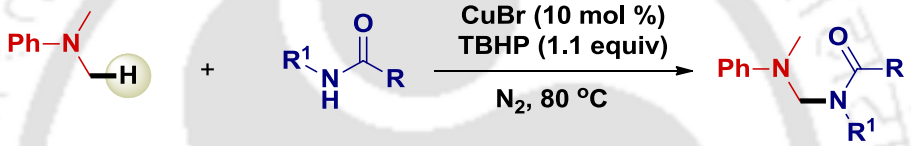
Reddy and co-workers recently reported a copper catalyzed oxidative cross coupling of formamides with amines for the preparation of unsymmetrical urea derivatives at room temperature (Scheme I.4.2.1.10).[43] Noteworthy features of the present work are utilization of *N*-methylformamide as a formamide source and also application towards the synthesis of chiral urea derivatives.



Scheme I.4.2.1.10. *Copper(II)-catalyzed synthesis of ureas via sp^2 C–H amination of N-substituted formamides*

➢ **C(sp^3)–N(amide) Bond formation**

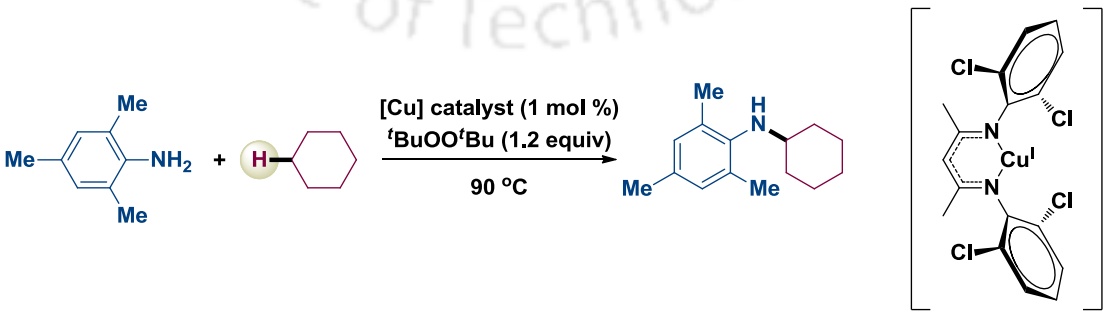
Zhao *et al.* developed an efficient protocol for amidation of (sp^3) C–H bonds, adjacent to a nitrogen atom with amides for the generation of (sp^3) C–N bonds (Scheme I.4.2.1.11).[44] The protocol uses CuBr as the catalyst, TBHP as the oxidant, and decane as the solvent.



Scheme I.4.2.1.11. *Cu-catalyzed direct amidation at sp^3 C–H bonds adjacent to a nitrogen*

➢ **C(sp^3)–N(amine) Bond formation**

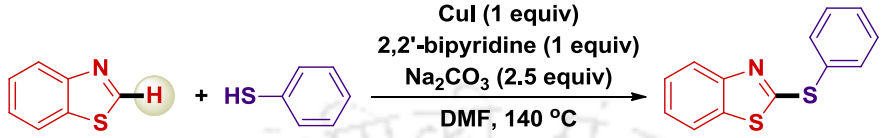
Warren group presented the first general use of anilines in the C–H amination of a range of substrates with Csp^3–H bonds (Scheme I.4.2.1.12).[45] The copper(I) catalyst [{(Cl_2NN)Cu}$_2$(benzene)] in conjunction with the mild oxidant ^{t}BuOO^{t}Bu enables the direct use of a variety of commercially 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.4.2.1.12. *Copper(I)-catalyzed direct amination at inert sp^3 C–H of alkanes*

➢ **C(sp^2)–S Bond formation**

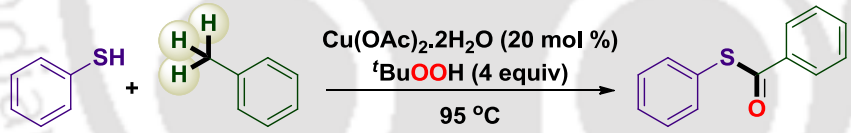
Liu *et al.* reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by the direct thiolation of benzothiazoles with aryl or alkyl thiols in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3 (Scheme I.4.2.1.13).[46]



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

➢ **C(sp^3)–S Bond formation**

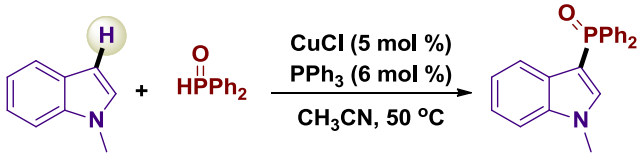
A unique Cu(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes has been recently developed by our group for the synthesis of thioesters in presence of *tert*-butyl hydroperoxide as oxidant as well source of oxygen (Scheme I.4.2.1.14).[47] A thioester moiety is created via 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.4.2.1.14. *Copper(II)-catalyzed synthesis of thioesters*

➢ **C(sp^2)–P Bond formation**

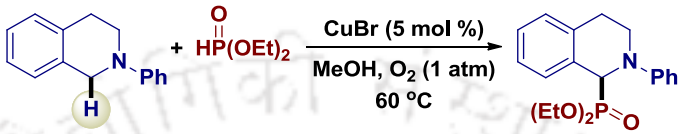
Yang group has recently developed a highly efficient protocol for the preparation of various 3-phosphoindoles via a Cu(I)-catalyzed cross-dehydrogenative coupling between substituted indoles and disubstituted phosphine oxide (Scheme I.4.2.1.15).[48] This is the only precedence for the direct oxidative Csp^2–P bond formation without the assistance of directing groups.



Scheme I.4.2.1.15. *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 has been 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.4.2.1.16).[49]



Scheme I.4.2.1.16. *Copper(I)-catalyzed synthesis of α-aminophosphonates*

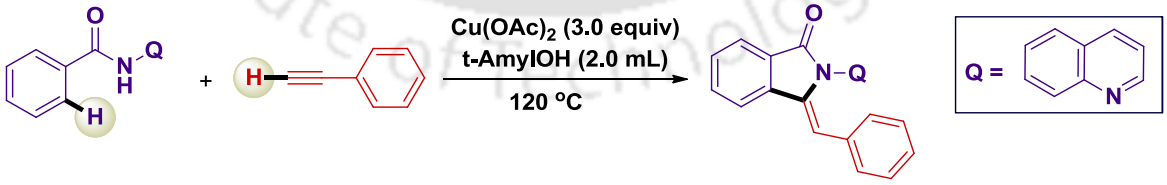
I.4.3. Directing group assisted cross-dehydrogenative coupling:

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 regiselectivity and chemoselectivity and offers a higher degree of C–H bond cleavages.

I.4.3.1. Representative examples of reactions involving directing group assisted cross-dehydrogenative coupling

➢ **C(sp^2)–C(sp) Bond formation**

You group has recently reported a Cu(II)-promoted oxidative C(sp^2)−H/C(sp)−H cross-coupling and intramolecular annulation of arenes with terminal alkynes to prepare 3-methyleneisoindolin-1-one scaffold (Scheme I.4.3.1.1).[50]

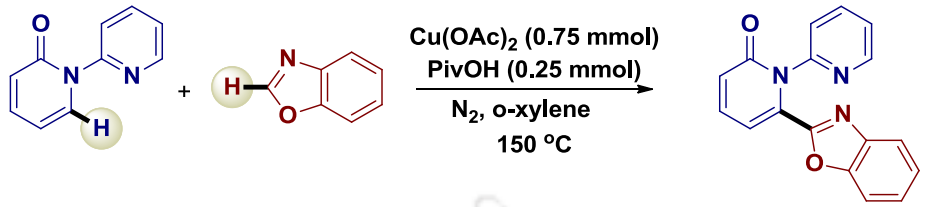


Scheme I.4.3.1.1. *Copper(II)-catalyzed auxillary assisted alkynylation of arenes*

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

Miura group achieved a palladium-free, copper-mediated C6-selective dehydrogenative heteroarylation of 2-pyridones with 1,3-azoles (Scheme I.4.3.1.2).[51] This directing group

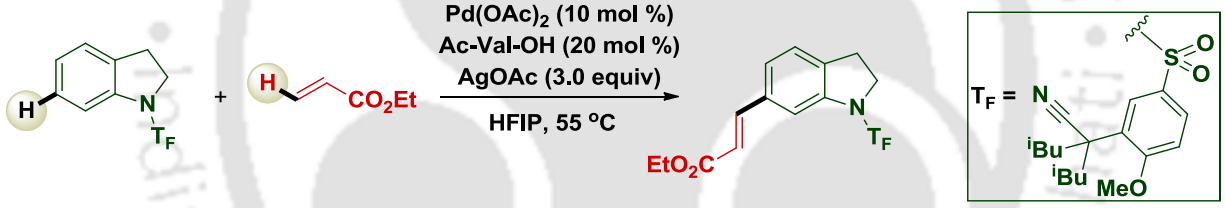
was readily removed after the coupling thus leading to 2- pyridone derivatives with a free N-H group.



Scheme I.4.3.1.2. *Copper(II)-mediated direct biaryl coupling of arylazines and azoles*

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

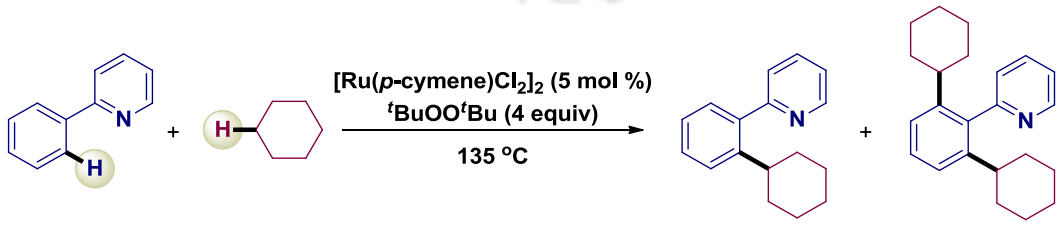
Yu group has developed an improved protocol for aerobic Pd(II)-catalyzed meta-C−H olefination with substrates containing nitrile template attached at the indolinyl nitrogen via a sulfonamide linkage using a novel ligand, Ac-Val-OH, which is capable of accelerating the reaction (Scheme I.4.3.1.3).[52]



Scheme I.4.3.1.3. *Palladium(II)-catalyzed C–H olefination*

- **C(sp^2)–C(sp^3) Bond formation**

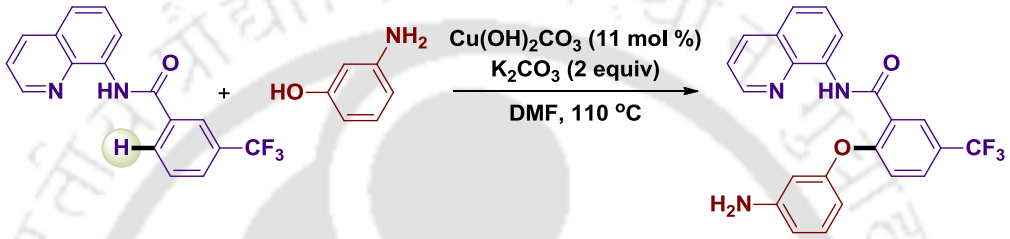
Li group has demonstrated a novel protocol on Ru-catalyzed substrate directed arene–alkane coupling of 2-arylpyridine or analogous substrates using un-reactive cycloalkane as the other coupling partner (Scheme I.4.3.1.4).[53]



Scheme I.4.3.1.4. *Ruthenium(II)-catalyzed C–H cycloalkylation of 2-phenylpyridine*

➢ **C(sp^2)–O Bond formation**

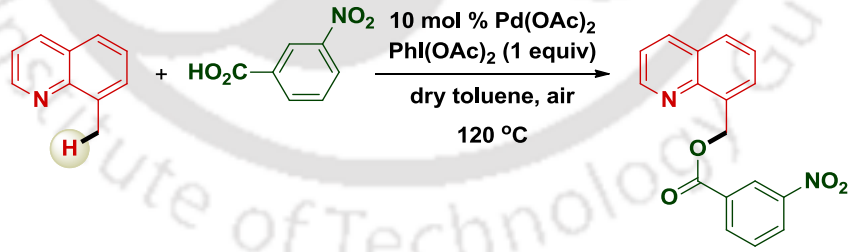
The group of Daugulis has developed a method for direct, auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of amine derivatives (Scheme I.4.3.1.5).[54] The reaction employs $CuCO_3.Cu(OH)_2$ catalyst, air as the oxidant, phenol or alcohol as coupling partners, DMF, pyridine, or DMPU as solvent, and K_2CO_3, tetramethylguanidine, or K_3PO_4 base at 70–130 ^oC.



Scheme I.4.3.1.5. *Copper(II)-catalyzed auxillary assisted C–H alkoxylation*

➢ **C(sp^3)–O Bond formation**

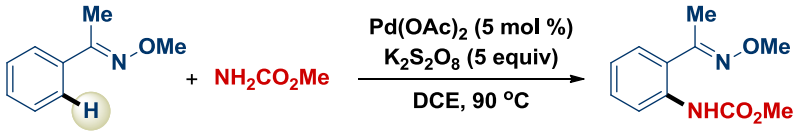
Cheng group has described a chelation-assisted palladium-catalyzed acyloxylation of the sp^3 C–H bond of benzyl group with carboxylic acid employing $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme I.4.3.1.6).[55] The procedure tolerates a series of functional groups, providing the acyloxylated products in moderate to good yields.



Scheme I.4.3.1.6. *Palladium(II)-catalyzed acyloxylation of the benzylic sp^3 C–H bond*

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

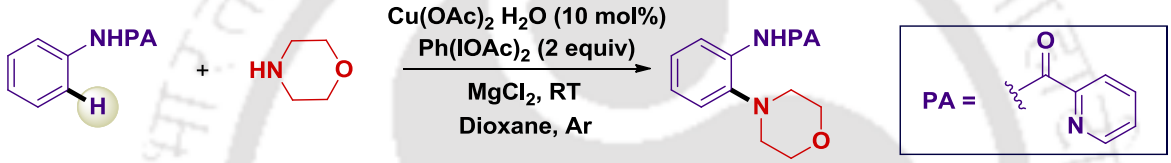
Che group has ilustrated a Pd-catalyzed intermolecular directed C–H amidation via functionalization of sp^2 and sp^3 C–H bonds in pyridine and oxime ether substrates (Scheme I.4.3.1.7).[56] In this system, $Pd(OAc)_2$ served as the catalyst and a combination of $K_2S_2O_8$ and NH_2R was used to introduce the nitrogen functionality.



Scheme I.4.3.1.7. *Ketoxime ether directed palladium(II)-catalyzed amidation of arenes*

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

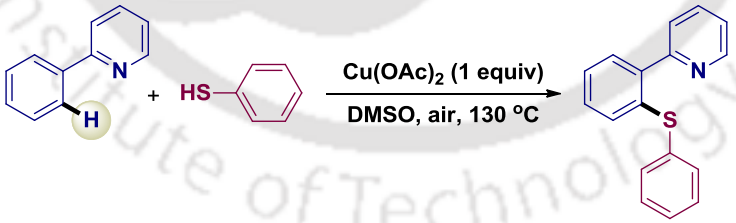
In a recent report, Chen group demonstrated a Cu(II)-mediated carboxamide directed C−H amination with a variety of alkylamines (Scheme I.4.3.1.8).[57] This method offers a practical solution for the rapid synthesis of complex arylamines from simple starting materials and enables new planning strategies for the construction of arylamine-containing pharmacophores.



Scheme I.4.3.1.8. *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.4.3.1.9).[24b]

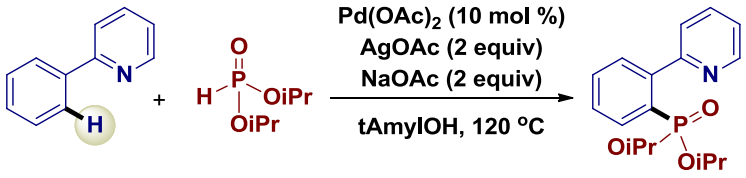


Scheme I.4.3.1.9. *Copper(II)-catalyzed ortho-thiolation of arenes*

➢ **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.4.3.1.10).[58] A variety of heterocyclic substrates were

phosphorylated to give N−P bisdentate compounds that are potentially useful in medicinal chemistry and catalysis.

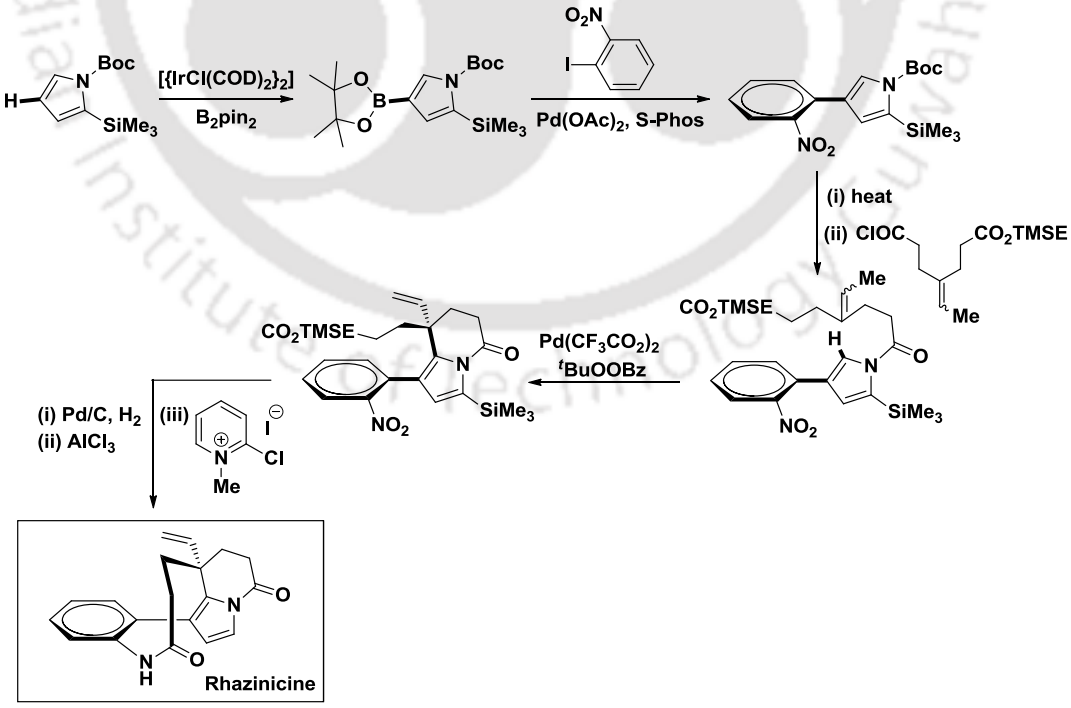


Scheme I.4.3.1.10. *Palladium(II)-catalyzed C−H phosphorylation of 2-phenylpyridine*

I.5. 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.[59] Herein mentioned below is one example of total synthesis 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.5.1. Total synthesis of Rhazinicine



Scheme I.5.1.1. *Total synthesis of Rhazinicine*

Rhazinicine is part of a family of natural products (rhazinilams) that mimic the cellular effects of pacitaxel. Gaunt and co-workers reported the first synthesis of this pyrrole alkaloid rhazinicine by using a short synthetic strategy; demonstrating an iterative and regioselective nature of metal-catalyzed C–H bond functionalizations to influence complex molecule assembly (Scheme I.5.1.1).[60]

I.6. References

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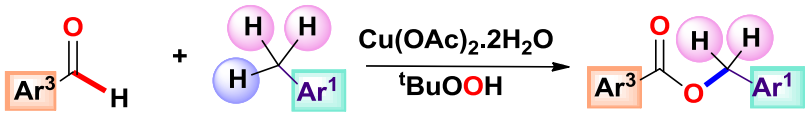
Chapter II

Copper Catalyzed Oxidative Esterification of Aldehydes with Alkylbenzenes via Cross-Dehydrogenative Coupling



***Abstract*: A** *new and efficient catalytic protocol has been developed for the synthesis of benzylic ester from aldehydes and alkylbenzenes. This reaction proceeds via benzylic sp^3 C–H bond activation of alkylbenzenes in the presence of inexpensive copper catalyst and TBHP combination. Exclusive formation of mono-esters was observed for poly alkylatedbenzenes indicating a high degree of selectivity. This methodology provides an avenue to the synthesis of various unsymmetrical benzylic esters from diverse alkylbenzenes and aldehydes. Hence this protocol is yet another novel addition to the existing methods*.

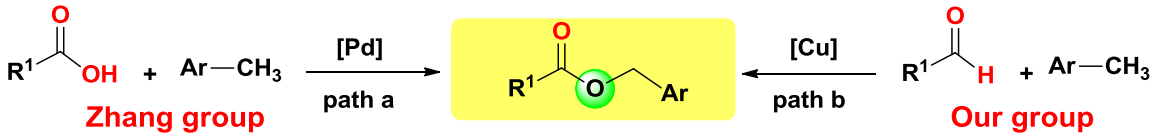
CHAPTER II

II. Copper Catalyzed Oxidative Esterification of Aldehydes with Alkylbenzenes via Cross-Dehydrogenative Coupling

II.1. Introduction

The upsurge in interest in the transition metal catalyzed reactions via the cleavage of ubiquitous C–H bond has been creating renaissance in the construction of a diverse array of C–C and C–X (X = hetero atom) bonds.[1] The two most popular approaches are chelation assisted C–H bond functionalization[2] and the cross-dehydrogenative coupling (CDC).[3] This field of synthesis has advanced to such an extent that even the otherwise inert sp^3 C–H bonds could now be functionalized.[3,4] The CDC approach is attractive because it does not require substrate prefunctionalization and it is atom economic.[1d,5] As evident from the literature, CDC has been widely investigated for the formation of C–C bonds[3a,6] albeit the concept has rarely been explored regarding C–O bond formation. The relevance of C–O bonds in organic chemistry has resulted in the emergence of various transition metal based methodologies via C–H bond activation.[7] In this regard the ester functionality has been the common target. A recent metal catalyzed CDC based transformations for the synthesis of esters involve acid and cyclic ethers where the functionalization occurs selectively at the sp^3 carbon atom α to the ethereal oxygen.[8] The use of various copper salts in combination with peroxides as an oxidant is known to work effectively in facilitating functionalizations at the relatively inert sp^3 carbon.[3a,9] However, most of these methodologies concentrate on C–H bond functionalization at the sp^3 carbon atom α to heteroatoms. A direct functionalization at the relatively non-activated alkylbenzenes has rarely been explored. Herein we developed a copper catalyzed methodology with alkylbenzenes and aldehydes as precursors for the synthesis of benzylic esters via a CDC approach (path b, Scheme II.1.1). After our report a palladium catalyzed oxidative

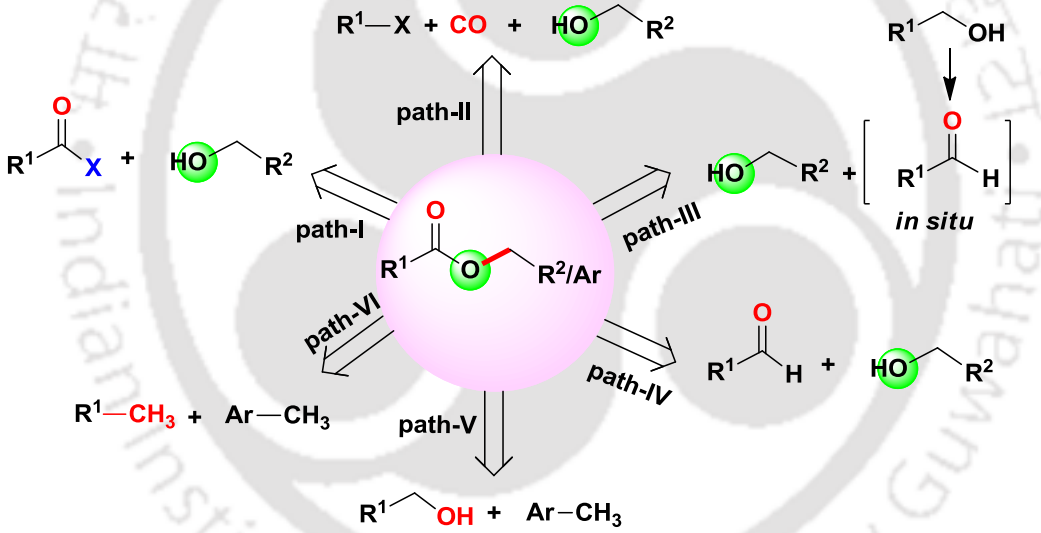
esterification was reported by Zhang group via C–O bond formation at the sp^3 benzylic carbon of various alkylbenzenes with carboxylic acids[10] (path a, Scheme II.1.1).



Scheme II.1.1. *Benzylic ester synthesis via CDC process*

II.2. Strategies for synthesis of benzylic esters

Prior or later to our present report, other groups have achieved similar transition metal catalyzed and metal free protocols for the benzylester synthesis employing either alkylbenzenes, benzyl alcohols, benzaldehydes, acids and acid derivatives.



Scheme II.2.1. *Various routes for the synthesis of benzylic esters*

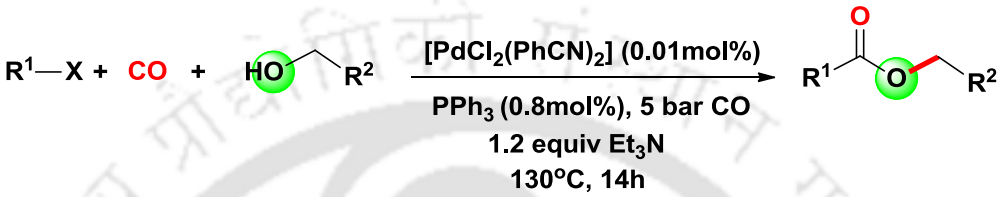
(i) Classical esterification

Traditionally, benzylic esters are prepared by reacting alcohols with carboxylic acids or its derivatives which often require auxiliary chemicals (Scheme II.2.2).[11,12]

Scheme II.2.2. *Benzylic ester synthesis using classical methods*

(ii) Insertion of carbon monoxide

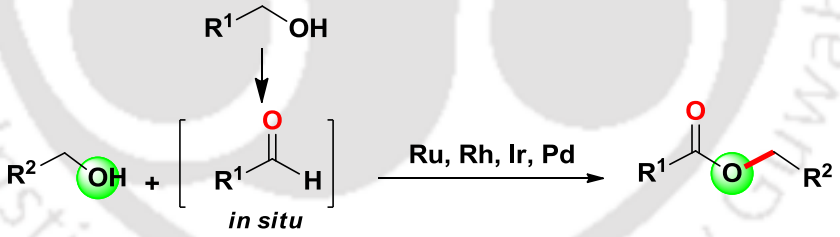
Beller group reported a palladium catalyzed cross-coupling reaction involving carbonylation of aryl halides with subsequent nucleophilic attack of benzyl alcohols to synthesize benzylic esters (Scheme II.2.3).[13] However, the use of carbon monoxide in presence of high temperature and extrusion of halide anions make this reaction environmentally unsustainable.



Scheme II.2.3. *Benzylic ester synthesis using carbon monoxide*

(iii) Metal catalyzed CDC approach for the synthesis of benzylic ester

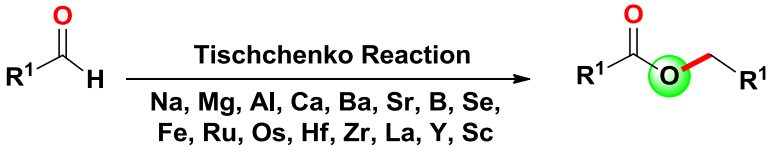
A number of CDC based approaches for the synthesis of benzylic esters have been developed employing metal catalysts such as Ru,[14] Rh,[15] Ir,[16] and Pd.[17] Most of these methods rely on the concept of hydrogen borrowing[18] or hydrogen autotransfer process[19] where benzyl alcohol serves as a precursor.



Scheme II.2.4. *Benzylic ester synthesis using CDC approach*

(iv) Tischchenko Reaction

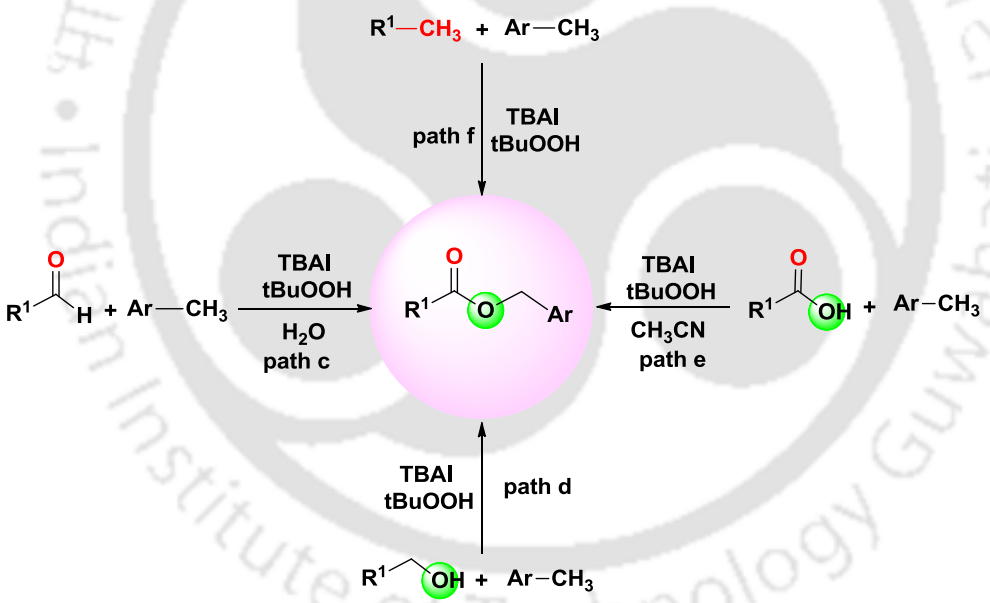
The Tishchenko reaction[20] is the disproportionation of aldehydes (lacking hydrogen atom at α position) where self-coupled ester products are obtained in presence of base and catalyst (Scheme II.2.5).[21-28].



Scheme II.2.5. *Tishchenko reaction*

(v) Metal free approach for synthesis of benzylic ester via CDC

Wang *et al.* reported Bu_4NI-catalyzed benzylic C–H acyloxylation of alkylarenes with readily available aromatic aldehydes using *tert*-butyl hydroperoxide as terminal oxidant (path c, Scheme II.2.6).[29] Fu *et al.* reported direct esterification of alcohols with toluene derivatives using same catalyst and oxidant combination (path d, Scheme II.2.6).[30] Yu group applied a metal-free conditions for the synthesis of benzylic esters via oxidative C–O bond formation at the sp^3 benzylic carbon of various alkylbenzenes with carboxylic acids (path e, Scheme II.2.6).[31] Pushing the ester synthesis to an extreme limit of C–H activation our group very recently developed an efficient metal free (Bu_4NI and TBHP combination) protocol for the synthesis of symmetrical as well as unsymmetrical benzyl esters via a cross-dehydrogenative coupling (CDC) involving alkylbenzene(s) as a self or as a cross coupling partner(s) (path f, Scheme II.2.6).[32]

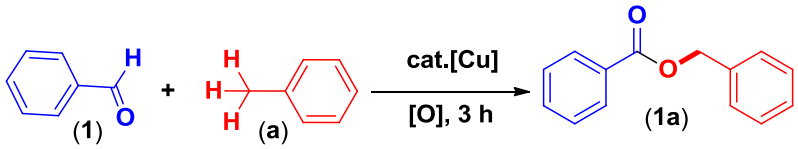


Scheme II.2.6. *Metal free approaches for benzylic ester synthesis*

II.3. Present Work

In continuation to the above protocols for benzylic ester synthesis, herein we illustrate a copper catalyzed synthesis of the same involving aldehydes and alkylbenzenes as the benzyl alcohol surrogates. In this protocol, alkylbenzenes are used as solvent cum reagents for the synthesis of benzylic ester.

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



Entry	Catalyst(mol%)	Oxidant (equiv.)	Temp ^{o}C	Yield(%)[a]
1	CuBr (20)	aq. TBHP (1)	80	22
2	$CuBr_2$ (20)	aq. TBHP (1)	80	32
3	CuCl (20)	aq. TBHP (1)	80	18
4	$CuCl_2$ (20)	aq. TBHP (1)	80	37
5	$Cu(OTf)_2$ (20)	aq. TBHP (1)	80	<10
6	$Cu(OAc)_2$(20)	aq. TBHP (1)	80	38
7	$Cu(OAc)_2.2H_2O$ (20)	aq. TBHP (1)	80	48
8	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (1)	80	60
9	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (2)	80	65
10	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (2)	100	74
11	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (2)	120	74
12	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (3)	100	67
13	$Cu(OAc)_2.2H_2O$ (30)	dec. TBHP (2)	100	75
14	**$Cu(OAc)_2.2H_2O$ (10)**	**dec. TBHP (2)**	**100**	**74**
15	$Cu(OAc)_2.2H_2O$ (5)	dec. TBHP (2)	100	57
16	$Cu(OAc)_2.2H_2O$ (20)	aq. H_2O_2 (2)	100	00
17	Nil	dec. TBHP (2)	100	00
18	$Cu(OAc)_2.2H_2O$ (20)	Nil	100	00

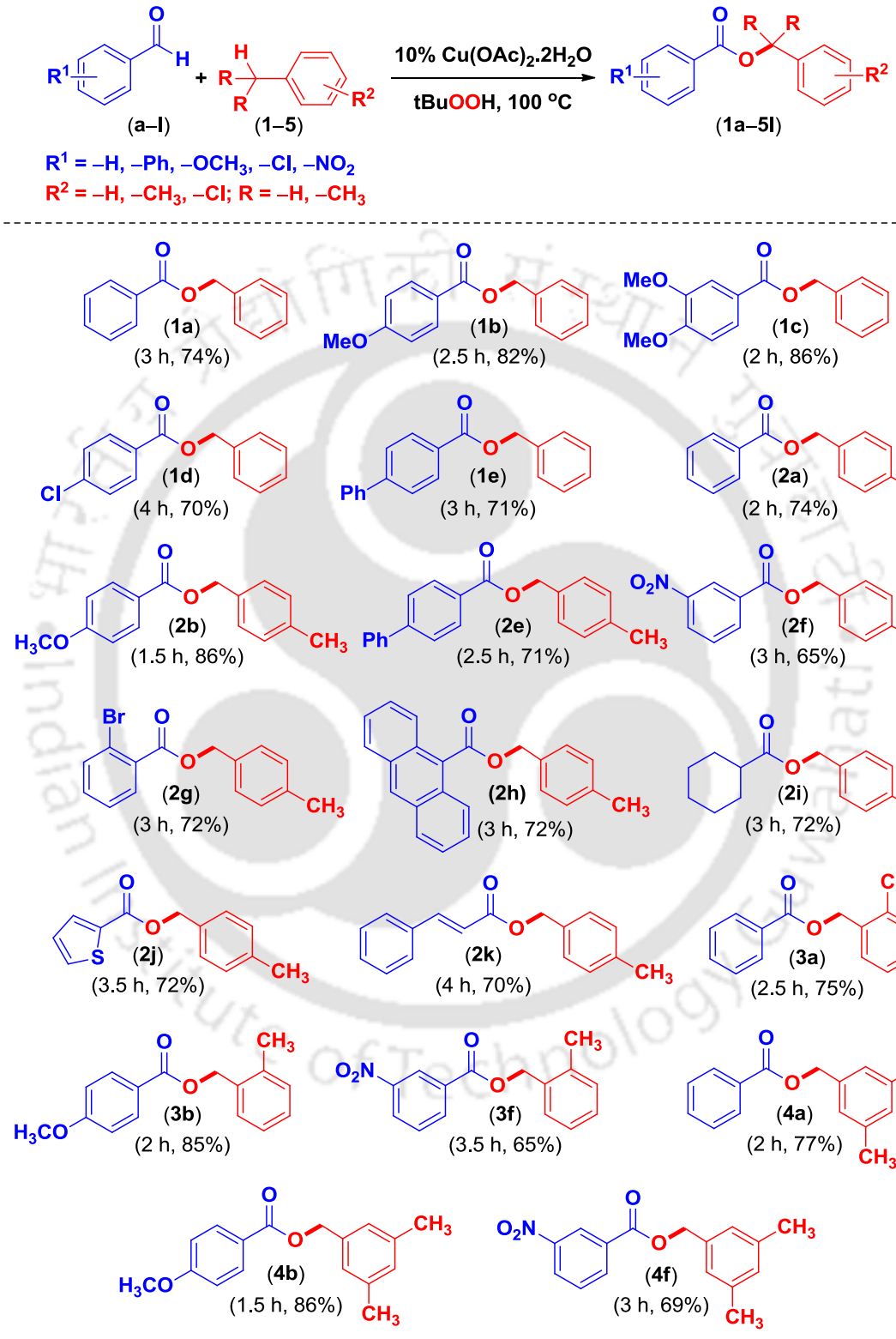
[a]Isolated yield.

Optimization of reaction conditions. Toluene under oxidative conditions particularly in presence of TBHP is known to give benzyl alcohol, benzaldehyde or benzoic acid in the medium via radical oxidation. The benzyl alcohol generated *in situ* can undergo oxidative esterification with aldehyde to give benzylic ester. On the other hand, aldehyde can readily oxidize to carboxylic acid that can couple radically with toluene (benzyl radical) to afford the same. With these possibilities in hand, we initiated our investigation by reacting benzaldehyde (1 equiv) (**a**) with toluene (5 equiv) (**1**) in the presence copper(I) bromide (20 mol %) and aqueous TBHP (1 equiv) at 80 ^{o}C which provided the expected (**1a**) ester but in a mere yield of 22% (Table II.3.1, entry 1). The hydrated copper(II) acetate provided a superior yield (48%) compared to other Cu salts such as $CuBr_2$, CuCl, $CuCl_2$, and $Cu(OTf)_2$ tested (Table II.3.1, entries 2–7). The use of a decane solution of TBHP instead of aqueous TBHP improved the yield up to 60% (Table II.3.1, entry 8) while its two fold

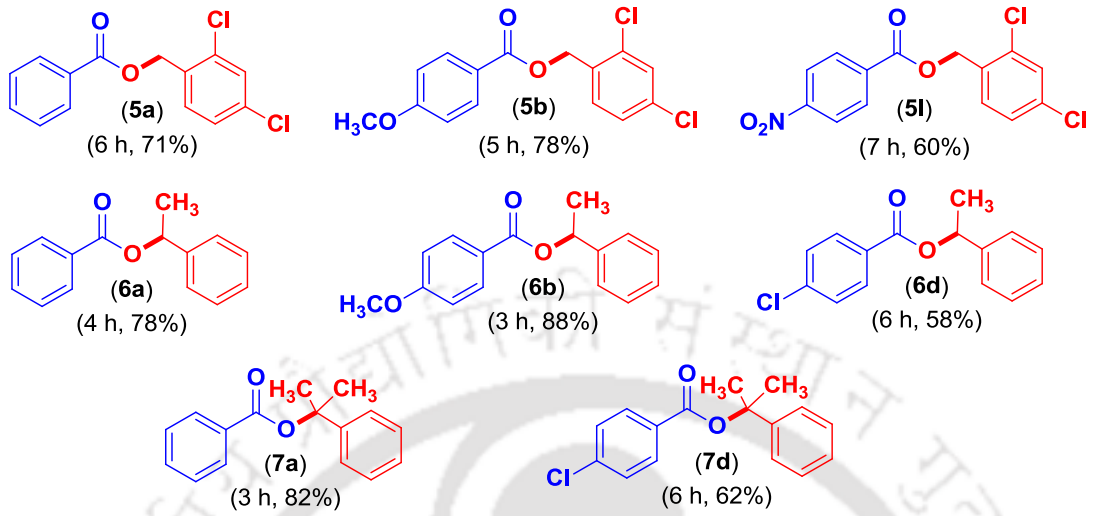
increase improved the yield by further 5% (Table II.3.1, entry 9). An increase in reaction temperature from 80 ^{o}C to 100 ^{o}C resulted in an improved yield of 74% (Table II.3.1, entry 10). Further no change in yield was observed on changing temperature from 100 ^{o}C to 120 ^{o}C (Table II.3.1, entry 11). Even upon increasing the oxidant quantity (3 equiv) or the catalyst quantity (30 mol %) there was no significant improvement in the yield (Table II.3.1, entries 12–13) Interestingly, an identical yield was observed using 10 mol % of the catalyst when TBHP in decane (5–6 M) was used (Table II.3.1, entry 14). Further decrease in catalyst loading (5 mol %) had an adverse effect on product yield (Table II.3.1, entry 15). No desired product was obtained when oxidant aq. H_2O_2 was used instead of TBHP (Table II.3.1, entry 16). The control experiments carried out with either a copper catalyst or TBHP alone did not serve the purpose, as no desired product could be detected (Table II.3.1, entries 17–18).

Substrate scope for benzylic esters. Encouraged by the outcome of the above experiments, the suitability of this protocol was examined toward the synthesis of benzylic esters employing various alkylbenzenes with a set of aldehydes as coupling partners. The optimized conditions were initially applied to the coupling of toluene (**1**) with a set of aromatic aldehydes (**a–e**) having both electron-donating (**b** and **c**) and electron-withdrawing (**d**) substituents as shown in Scheme II.3.1. It was observed that, under the present condition, toluene smoothly underwent reactions with various aldehydes to afford the desired benzylic esters (**1a–1d**) in good to excellent yields as shown in Scheme II.3.1. Reaction with *p*-phenyl benzaldehyde (**e**) gave a fairly good yield of the corresponding benzylic ester (**1e**). As evident from the results in Scheme II.3.1, the electronic effects of the substituent in the aryl ring bearing the aldehyde functionality played a role in controlling the product yields. With electron-donating substituents (**b–c**) high yield of the benzylic esters (**1b–1c**) were obtained in a shorter span while those with electron-withdrawing substituents (**d**) proceeded a bit sluggishly providing moderate yields as shown in Scheme II.3.1. To further unravel potentiality of this approach, other target, alkylbenzenes viz. *p*-xylene (**2**) *o*-xylene (**3**) and mesitylene (**4**) (Scheme II.3.1) were examined, all of which possess more than one benzylic carbon

Scheme II.3.1. *Substrate scope for benzylic esters*[a,b]



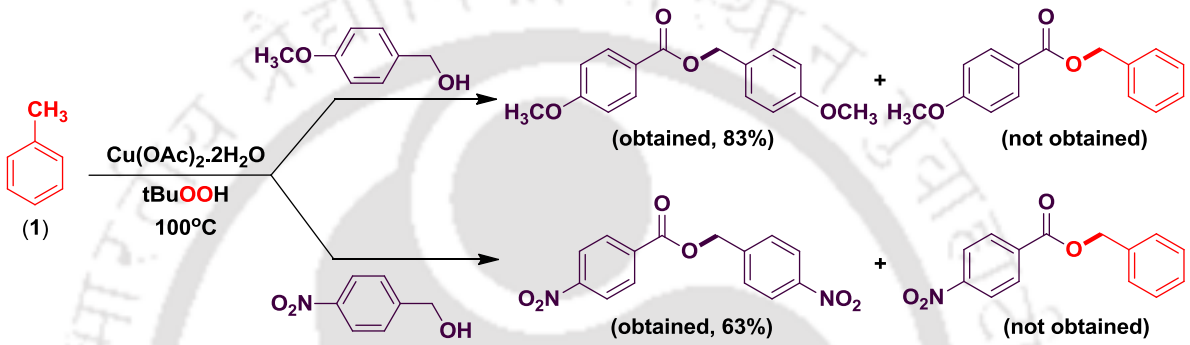
Scheme II.3.1. *Contd.*



[a] Reaction conditions: aldehyde (1 mmol), alkylbenzene (5 mmol), $Cu(OAc)_2.2H_2O$ (0.1 mmol), TBHP (2 mmol), 100 °C, time 1.5–7 h, [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported

A query arises as to whether their reactions would provide mono, bis, or tri esters. However, the most appealing outcome in all their reactions were the selective formation of the corresponding monoester with the other alkyl (methyl) groups remaining intact besides undergoing a smooth reaction with their corresponding coupling aldehyde partners. Specifically, the reaction of *p*-xylene (**2**) when treated with a diverse array of aldehydes, viz. aromatic (**a**–**b**, **e**–**h**), aliphatic (**i**), heteroatomic (**j**), and α–β unsaturated (**k**), provided satisfactory results (Scheme II.3.1). The formations of the benzylic esters (**2a**–**2k**) were unaffected by the influence of any groups present within the aldehydic moiety. This methodology was also equally successful towards mono-esterification of *o*-xylene (**3**) and mesitylene (**4**) with various aldehydes as shown in Scheme II.3.1. Noteworthy, the reactivity trends observed for these di- or tri alkylatedbenzenes with aromatic aldehydes were the same as was observed with toluene (**1**). Next we turned our attention to study the reactivity of benzylic C–H of 2,4-dichloromethylbenzene (**5**) with aromatic aldehydes (**a**, **b**, and **l**). In all these cases the reactions proceeded rather sluggishly to afford the desired products (**5a, 5b** and **5l**) in moderate to good yields depending on the substituent present in the aldehydes (Scheme II.3.1). The slow reactivity of 2,4-dichloromethylbenzene (**5**) could be attributed to the reluctance of the methyl group toward the C–O bond formation with

Cu/TBHP. The reaction of ethylbenzene (**6**) with aromatic aldehydes (**a**, **b**, and **d**) proceeded smoothly to form the C–O bond selectively at the 2° benzylic carbon to form the corresponding benzylic ester (**6a-6d**) (Scheme II.3.1). This observation shows that benzylic carbon is more susceptible toward an oxidative C–O bond formation rather than another alkyl (1°) position. Similar result was observed with isopropylbenzene (**7**) with aldehydes (**a** and **d**) where C–O bond occurred at the 3° benzylic carbon to form the corresponding benzylic esters (**7a** and **7d**) (Scheme II.3.1).

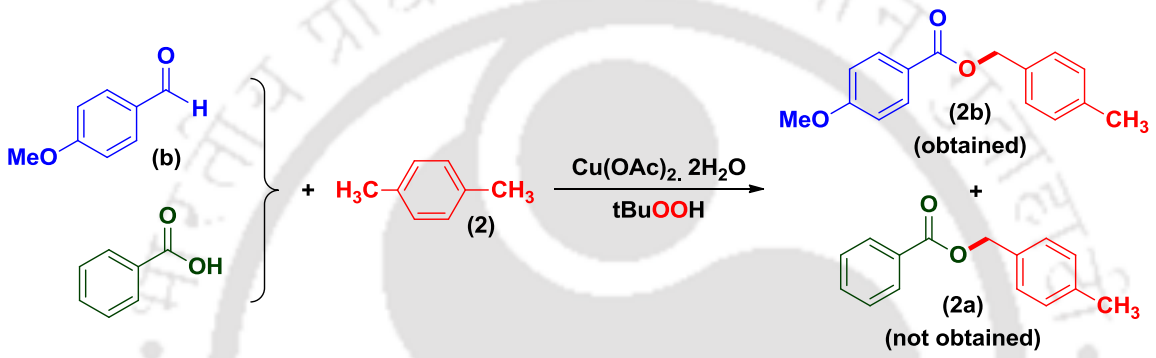


Scheme II.3.2. *Substrate scope for benzylic esters with benzyl alcohols*

The use of benzylic alcohols such as *p*-methoxybenzyl and *p*-nitrobenzyl alcohols (as latent aldehydic functionality) with alkylbenzenes is expected to give the aforementioned unsymmetrical esters. However, when *p*-methoxybenzyl and *p*-nitrobenzyl alcohols were treated separately with toluene (**1**) under the present experimental conditions, only self-coupled symmetrical benzylic esters viz. 4-nitrobenzyl-4-nitrobenzoate and 4-methoxybenzyl-4-methoxybenzoate, were obtained and no traces of unsymmetrical esters benzyl-4-nitrobenzoate and benzyl-4-methoxybenzoate could be found as shown in Scheme II.3.2. Thus, the present methodology is most suitable for the preparation of unsymmetrical esters.

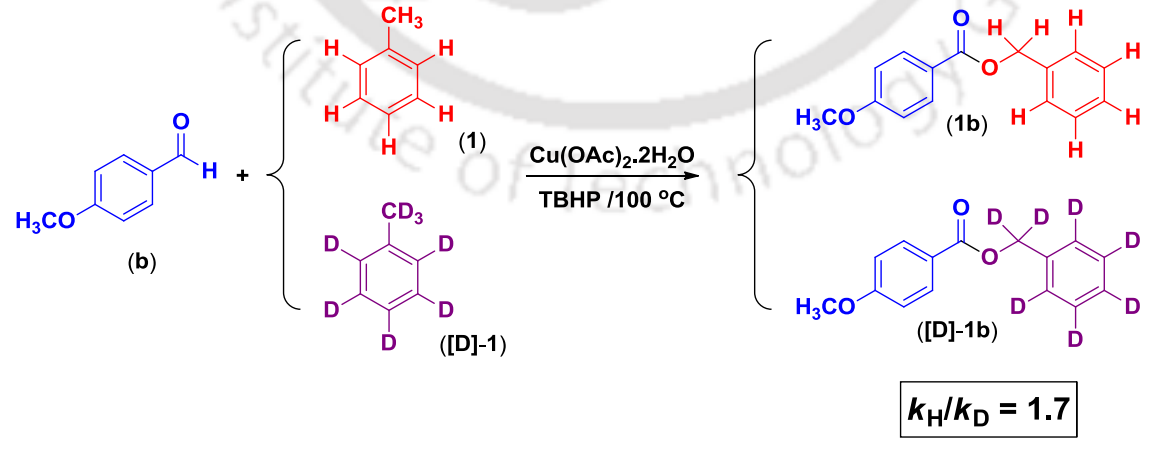
Mechanistic studies. To probe the mechanism of the reaction, several control experiments were performed. During the reaction of benzaldehyde (**a**) with *p*-xylene (**2**), along with the desired product (**2a**), formation of *p*-methylbenzyl alcohol was observed with a trace amount of benzoic acid (oxidation of benzaldehyde). *p*-Methylbenzyl alcohol formed by the oxidation of a combination of *p*-xylene (**2**) with Cu/TBHP.[33] Thus ambiguity appears whether the esterification occurred via a reaction of *in situ* generated benzyl alcohol with

benzaldehyde (**a**) by an oxidative process[34] or by the radical coupling of the *in situ* generated benzoic acid (from benzaldehyde) with *p*-xylene (**2**) as has been reported.[31] To ascertain the exact coupling partners a crossover experiment was performed in which *p*-methoxybenzaldehyde (**b**) and benzoic acid were reacted with *p*-xylene (**2**) under the present experimental conditions (Scheme II.3.3). No formation of 4-methylbenzyl benzoate (**2a**) and exclusive formation of 4-methylbenzyl-4-methoxy benzoate (**2b**) ruled out the usual esterification of acid and alcohol (generated *in situ* from *p*-xylene) or the radical pathway between acid and alkylbenzene.[31]



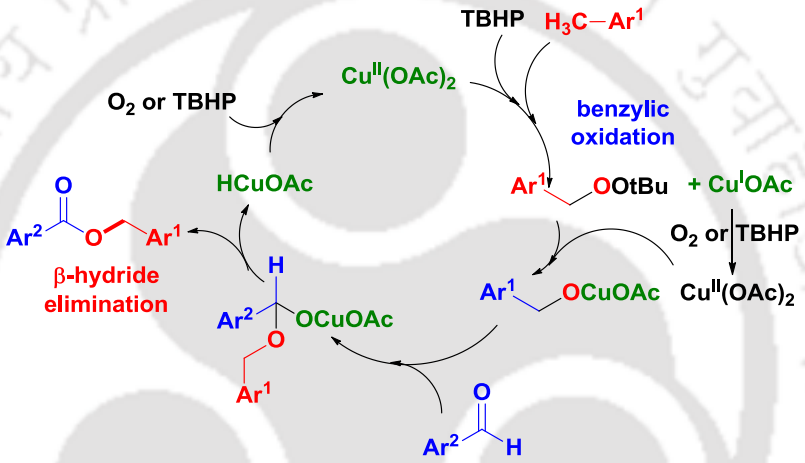
Scheme II.3.3. *Crossover experiment.*

Considerable rate retardation associated with the poor yield of product in the presence of a radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) suggests the radical nature of the reaction path.



Scheme II.3.4. *Kinetic isotope effect studies with deuterated toluene*

No kinetic isotope effect (k_H/k_D ~ 1) was observed when the reaction of deuterated benzaldehyde was carried out with *p*-xylene (**2**) suggesting that hydride transfer is not the rate-determining step. While a kinetic isotope effect (k_H/k_D ~1.7) (see Experimental Section II.4.3) was observed when the reaction of deuterated toluene (d_8 toluene) (**1'**) was carried out with *p*-methoxybenzaldehyde (**b**) suggesting that benzylic C–H bond cleavage to be the rate-determining step (Scheme II.3.4). The results of the above experiments infer that benzylester synthesis occurs via the coupling of aldehyde and the *in situ* generated alcohol (from alkylbenzene) via a hemiacetal intermediate[17,34] as shown in Scheme II.3.5.



Scheme II.3.5. *Proposed mechanism for benzylic ester*

In conclusion we have developed a new and efficient catalytic approach for the synthesis of benzylic ester from aldehydes and alkylbenzenes. This reaction proceeds via benzylic sp^3 C–H bond activation of alkylbenzenes in the presence of an inexpensive copper catalyst and TBHP combination. Exclusive formation of monoesters was observed for polyalkylated benzenes indicating a high degree of selectivity. This methodology provides an avenue to the synthesis of various unsymmetrical benzylic esters from diverse alkylbenzenes and aldehydes. Hence this protocol is yet another novel addition to the existing methods.

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 ^1H NMR (300 MHz and 400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (75 MHz and 100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. Elemental analyses were recorded on CHNS analyzer.

II.4.2. General Procedure for the synthesis of benzyl benzoate (1a). Mixture of [$Cu(OAc)_2.2H_2O$] (21 mg, 10 mol %), benzaldehyde (**a**) (106 mg, 1 mmol), and toluene (**1**) (460 mg, 5 mmol) were taken in an oven dried round bottom flask fitted with a condenser. To this was added TBHP in decane (5-6 M) (400 µL, 2 equiv) and the reaction mixture was heated at 100 ^oC for 3 h. During this period complete disappearance of benzaldehyde (**a**) was observed as judged from TLC. After cooling to room temperature, the reaction mixture was admixed with ethyl acetate (30 mL) which washed with 5% solution of sodium bicarbonate solution (2 x 5 mL). The ethyl acetate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (98: 2, hexane / ethyl acetate) to give **1a** (156 mg, 74% yield).

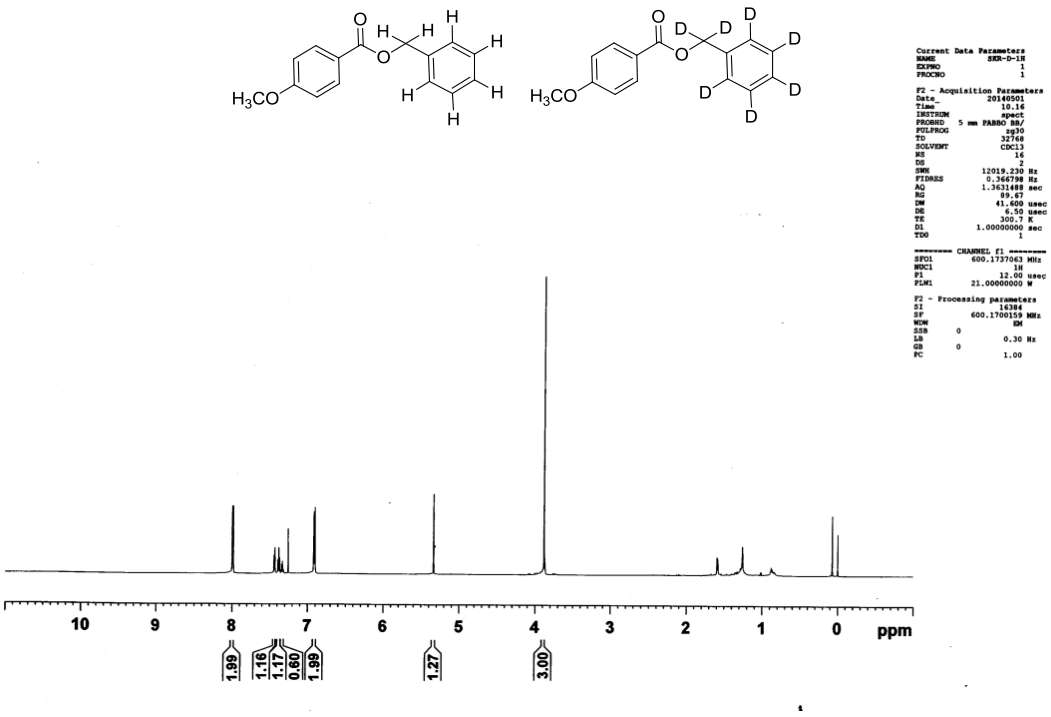
II.4.3. Kinetic isotope effect studies

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

(a) Kinetic isotope effect studies with deuterated benzaldehyde: The kinetic isotope effect on the present transformation was studied taking (**a**) and its corresponding deuterated analogue (*d*-**a**) as the model substrates. During an ongoing reaction of (**a**) 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 $–CH_3$ proton of the product (**2a**) against the $–CH_3$ proton of the substrate (**2**). 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*-**a**) and similarly the ratio of the $–CH_3$ proton of the product (**2a**) against the $–CH_3$ proton of the substrate (*d*-**a**) was calculated. The comparison of the ratio values

obtained from (**a**) and (*d*-**a**) at the same time intervals showed the k_H/k_D~1 i.e. the aldehyde hydrogen abstraction step is not involved in the rate-limiting step.

(b) Kinetic isotope effect studies with deuterated toluene: To a solution of *p*-methoxybenzaldehyde (**b**) (136 mg, 1 mmol) in toluene (**1**) (230 mg, 2.5 mmol) and d_8-toluene (**1′**) (250 mg, 2.5 mmol) was added $Cu(OAc)_2$. $2H_2O$ (21 mg, 0.1 mmol), followed by TBHP in decane (400 µl, 2 mmol) and the resultant mixture was put into a preheated oil bath (100 ^oC) for 3 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate) to give the expected product in 45 % yield. The ratio of the deuterated (**[D]-1b**) and nondeuterated (**1b**) *benzylic ester* product was calculated on the basis of the integration ratio of the benzylic peak at 5.33 (originating from toluene) and $–OCH_3$ proton at 3.85 by adopting the procedure of (Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc*. **2012**, *134*, 9902).



Calculation:

For three methyl protons at 3.85, the integration value is 3.00.

Thus for a single proton the integration corresponds to 3.00 / 3 = 1.0.

Now for the integration value of the protons originating from toluene at 5.33 is 1.27.

Thus the number of protons corresponding to this integration value is 1.27 / 1.00 =1.27.

Upon correlation with the original spectra of (**1b**) the number of proton at 5.33 should be 2.

Hence the proton difference in this region is 2 – 1.27 = 0.73.

Thus the k_H / k_D = 1.27 / 0.73 = 1.739 ~ 1.7

II.5. References

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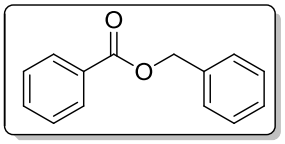
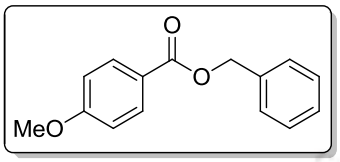
II.6. Spectral data

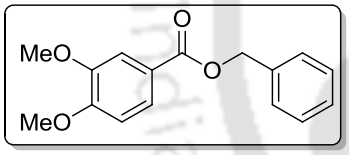


Benzyl benzoate (1a): Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.36 (s, 2H), 7.33–7.46 (m, 7H), 7.53 (t, 1H, *J* = 7.2 Hz), 8.07 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.8, 128.3, 128.4,

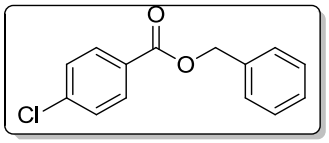
128.5, 128.7, 129.8, 130.3, 133.2, 136.2, 166.6; IR (KBr) 3063, 3032, 2956, 2925, 2856, 1720, 1451, 1269, 1108, 1025, 710 cm^{-1}; Anal. calcd for $C_{14}H_{12}O_2$: C 79.22, H 5.70; found C 79.30, H 5.75.



Benzyl 4-methoxybenzoate (1b): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 5.33 (s, 2H), 6.90 (d, 2H, *J* = 8.8 Hz), 7.32–7.39 (m, 3H), 7.43 (d, 2H, *J* = 7.2 Hz), 8.03 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 66.5, 113.8, 122.7, 128.2, 128.3, 128.7, 131.9, 136.4, 163.6, 166.3; IR (KBr) 2956, 2927, 2850, 1713, 1606, 1511, 1256, 1167, 1099, 1028, 769, 696 cm^{-1}; Anal. calcd for $C_{15}H_{14}O_3$: C 74.36, H 5.82; found C 74.32, H 5.90.

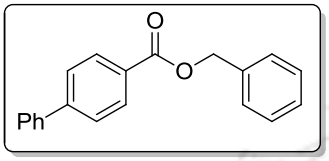


Benzyl 3,4-dimethoxybenzoate (1c): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.90 (s, 3H), 3.91 (s, 3H), 5.33 (s, 2H), 6.86 (d, 1H, *J* = 8.4 Hz), 7.32–7.39 (m, 3H), 7.43 (d, 2H, *J* = 8.0 Hz), 7.56 (m, 1H), 7.69–7.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 56.2, 66.7, 110.4, 112.3, 122.8, 123.9, 128.3, 128.4, 128.8, 136.5, 148.8, 153.3, 166.4; IR (KBr) 2951, 2917, 2849, 1711, 1636, 1270, 1220, 1105, 763 cm^{-1}; Anal. calcd for $C_{16}H_{16}O_4$: C 70.57, H 5.92; found C 70.51, H 5.88.

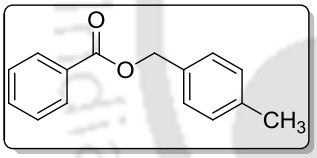


Benzyl 4-chlorobenzoate (1d): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.35 (s, 2H), 7.33–7.43 (m, 7H), 7.99 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 67.1, 128.4, 128.6, 128.8,

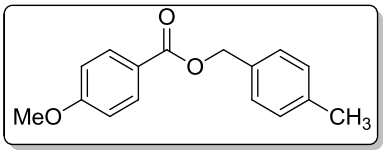
128.9, 129.9, 131,3, 136.0, 139.7, 165.7; IR (KBr) 3032, 2959, 2926, 2852, 1721, 1594, 1487, 1400, 1269, 1092, 1014, 759 cm^{-1}; Anal. calcd for $C_{14}H_{11}ClO_2$: C 68.16, H 4.49; found C 68.24, H 4.53.



Benzyl 4-phenylbenzoate (1e): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.40 (s, 2H), 7.31–7.40 (m, 8H), 7.50–7.60 (m, 4H), 8.12 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.9, 127.3, 127.5, 128.4, 128.5, 128.9, 129.1, 129.9, 130.4, 130.9, 136.3, 140.2, 145.9, 166.5; IR (KBr) 3057, 3031, 2956, 2922, 1715, 1608, 1267, 1100, 746, 696 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_2$ $(M + H)^+$ 289.1223; found 289.1229.

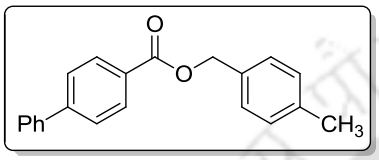


4-Methylbenzyl benzoate (2a): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 5.31 (s, 2H), 7.18 (d, 2H, *J* = 7.6 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 7.40 (t, 2H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 8.06 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 66.8, 128.5, 129.2, 129.4, 129.9, 130.4, 133.1, 133.2, 138.2, 166.6; IR (KBr) 2923, 2858, 1720, 1613, 1515, 1450, 1374, 1314, 1270, 1108, 807, 711 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}O_2$ $(M + H)^+$ 227.1067; found 227.1075.

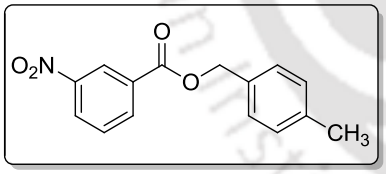


4-Methylbenzyl 4-methoxybenzoate (2b): Yellowish liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 3.75 (s, 3H), 5.21 (s, 2H), 6.81 (d, 2H, *J* = 8.8 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 7.93

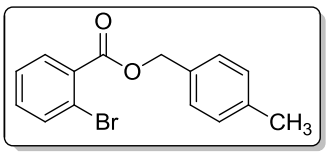
(d, 2H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.6, 66.5, 113.7, 122.8, 128.5, 129.4, 131.9, 133.5, 138.1, 163.6, 166.4; IR (KBr): 2932, 2839, 1711, 1606, 1511, 1460, 1374, 1256, 1167, 1099, 1029, 846, 769, 740 cm^{-1}; Anal. calcd for $C_{16}H_{16}O_3$: C 74.98, H 6.29; found C 75.08, H 6.26.



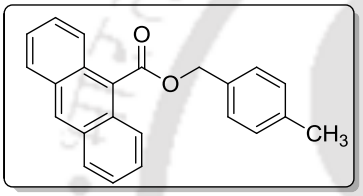
4-Methylbenzyl 4-phenylbenzoate (2e): White liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H), 5.34 (s, 2H), 7.18–7.21 (m, 2H), 7.34–7.38 (m, 2H), 7.42–7.46 (m, 2H), 7.58–7.64 (m, 5H), 8.12 (d, 2H, *J* = 8.8 Hz); ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 66.9, 127.2, 127.4, 128.3, 128.5, 129.1, 129.5, 129.9, 130.4, 133.3, 138.3, 140.2, 145.9, 166.5; IR (KBr): 3057, 3030, 2952, 2922, 1716, 1609, 1271, 1100, 807, 748 cm^{-1}; Anal. calcd for $C_{21}H_{18}O_2$: C 83.42, H 6.00; found C 83.51, H 6.07.



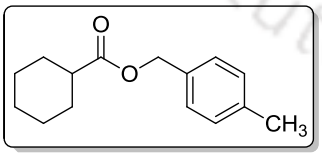
4-Methylbenzyl 3-nitrbenzoate (2f): Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.37 (s, 3H), 5.38 (s, 2H), 7.22 (d, 2H, *J* = 8 Hz), 7.36 (d, 2H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 8.0 Hz), 8.37–8.42 (m, 2H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.4, 68.9, 124.2, 125.4, 127.5, 129.4, 129.6, 131.9, 135.3, 136.5, 141.2, 148.9, 166.2; IR (KBr) 3084, 2910, 2828, 1717, 1605, 1523, 1330, 1262, 1248, 1128, 708 cm^{-1}; Anal. calcd for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16; found C 66.51, H 4.78, N 5.12.



4-Methylbenzyl 2-bromobenzoate (2g): White liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 5.25 (s, 2H), 7.11 (d, 2H, *J* = 8 Hz), 7.21–7.28 (m, 4H), 7.56 (d, 1H, *J* = 8.0 Hz), 7.69 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 67.5, 122.0, 127.3, 128.8, 129.5, 129.9, 131.6, 132.4, 132.7, 134.5, 138.4, 166.2; IR (KBr) 3053, 3026, 2955, 2922, 1731, 1589, 1289, 1248, 1107, 1042, 1027, 808, 744 cm^{-1}; Anal. calcd for $C_{15}H_{13}BrO_2$: C 59.04, H 4.29; found C 59.09, H 4.21.

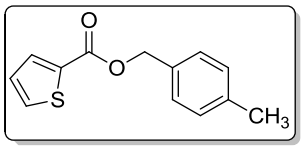


4-Methylbenzyl anthracene-9-carboxylate (2h): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 5.60 (s, 2H), 7.21 (t, 2H, *J* = 8.0 Hz), 7.43–7.50 (m, 6H), 7.94–8.02 (m, 3H), 8.50 (s, 1H), 8.95 (d, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 67.6, 123.7, 125.1, 125.6, 125.8, 127.1, 128.7, 128.9, 129.3, 129.4, 129.5, 131.1, 131.2, 132.3, 132.8, 169.7; IR (KBr) 3053, 2955, 2922, 1719, 1671, 1445, 1197, 1170, 1150, 733 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{18}O_2$ $(M + H)^+$ 327.138; found 327.1375.

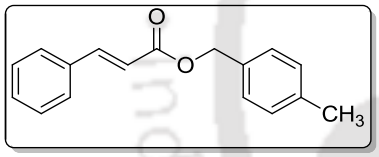


4-Methylbenzyl cyclohexylcarboxylate (2i): White liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19–1.31 (m, 3H), 1.40–1.49 (m, 2H), 1.60–1.64 (m, 1H), 1.72–1.76 (m, 2H), 1.90–1.93 (m, 2H), 2.35 (m, 4H), 5.06 (s, 2H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 25.7, 26.7, 29.3, 43.5, 66.1, 128.4, 129.4, 133.6, 138.1, 176.2; IR (KBr): 2962, 2932, 2905, 2857, 1735, 1450,

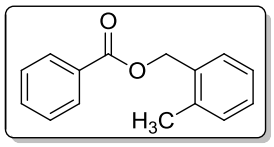
1412, 1260, 1163, 1099, 864, 799 cm^{-1}; Anal. calcd for $C_{15}H_{20}O_2$: C 77.55, H 8.68; found C 77.60, H 8.78.



4-Methylbenzyl thiophene-2-carboxylate (2j): White liquid; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.35 (s, 3H), 5.28 (s, 2H), 7.06–7.08 (m, 1H), 7.18 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 5.2 Hz), 7.81 (d, 1H, *J* = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.4, 66.9, 127.9, 128.5, 129.2, 129.4, 132.6, 133.0, 133.7, 138.3, 162.3; IR (KBr) 3027, 2953, 2923, 1712, 1524, 1417, 1374, 1356, 1273, 1258, 1091, 1075, 806, 753 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{12}O_2S$ $(M + H)^+$ 233.0631; found 233.0637.

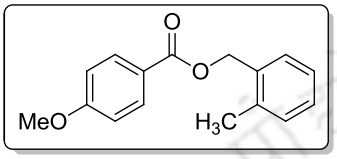


4-Methylbenzyl cinnamate (2k): Yellowish liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 5.21 (s, 2H), 6.47 (d, 1H, *J* = 15.6 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.36–7.38 (m, 3H), 7.50–7.52 (m, 2H), 7.72 (d, 1H, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 66.5, 118.2, 128.3, 128.7, 129.1, 129.5, 130.5, 133.2, 134.6, 138.3, 145.2, 167.0; IR (KBr): 3058, 3027, 2953, 2923, 1712, 1637, 1307, 1269, 1254, 1162, 805, 767 cm^{-1}; Anal. calcd for $C_{17}H_{16}O_2$: C 80.93, H 6.39; found C 80.98, H 6.36.

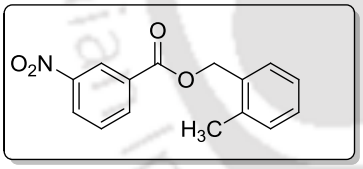


2-Methylbenzyl benzoate (3a): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 5.35 (s, 2H), 7.18-7.24 (m, 3H), 7.36-7.41 (m, 3H), 7.50 (t, 1H, *J* = 7.6 Hz), 8.05 (d, 2H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.1, 65.3, 126.1, 128.5, 128.6, 129.3,

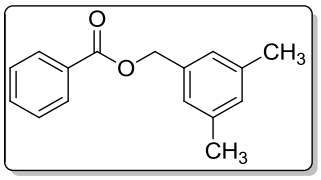
129.7, 130.2, 130.5, 133.1, 134.1, 137.1, 166.4; IR (KBr): 3060, 2958, 2926, 2854, 1733, 1681, 1585, 1486, 1462, 1451, 1424, 1248, 1221, 1059, 1024, 876, 793, 750 cm^{-1}; Anal. calcd for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found C 79.69, H 6.22.



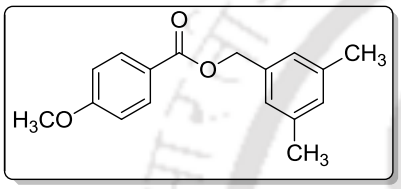
2-Methylbenzyl 4-methoxybenzoate (3b): Yellowish liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 3.82 (s, 3H), 5.33 (s, 2H), 6.89 (d, 2H, *J* = 8.8 Hz), 7.19–7.25 (m, 3H), 7.40 (d, 1H, *J* = 7.2 Hz), 8.01 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.1, 55.5, 65.0, 113.8, 122.7, 126.2, 128.6, 129.3, 130.5, 131.8, 134.4, 137.2, 163.6, 166.3; IR (KBr): 2958, 2934, 2839, 1713, 1606, 1511, 1462, 1373, 1258, 1167, 1098, 1029, 847, 769, 741, 721 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}O_3$ $(M + H)^+$ 257.1172; found 257.1162.



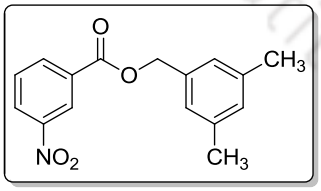
2-Methylbenzyl 3-nitrbenzoate (3f): Yellowish liquid; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.44 (s, 3H), 5.44 (s, 2H), 7.17–7.31 (m, 2H), 7.42 (d, 2H, *J* = 7.6Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 8.37–8.43 (m, 2H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 16.4, 66.9, 123.2, 125.4, 126.3, 127.5, 127.1, 129.5, 129.9, 131.4, 135.3, 136.3, 142.2, 148.9, 166.6; IR (KBr) 3048, 2930, 2848, 1716, 1635, 1543, 1320, 1282, 1255, 1130, 710 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}NO_4$ $(M + H)^+$ 272.0917; found 272.0915.



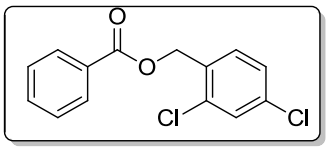
3,5-Dimethylbenzyl benzoate (4a): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 6H), 5.21 (s, 2H), 6.89 (s, 1H), 6.97 (s, 2H), 7.34 (t, 2H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 7.2 Hz), 7.99 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 67.0, 126.3, 128.5, 129.9, 130.1, 130.5, 133.1, 136.1, 138.4, 166.7; IR (KBr): 3035, 2921, 1716, 1635, 1610, 1266, 1209, 1110, 844, 711 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}O_2$ $(M + H)^+$ 241.1223; found 241.1227.



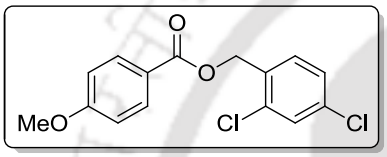
3,5-Dimethylbenzyl 4-methoxybenzoate (4b): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 6H), 3.84 (s, 3H), 5.27 (s, 2H), 6.91 (d, 2H, *J* = 8.8 Hz), 6.97 (s, 1H), 7.06 (s, 2H), 8.04 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.5, 66.7, 113.8, 126.2, 129.4, 130.0, 132.0, 136.3, 138.3, 163.6, 166.4; IR (KBr): 3008, 2959, 2920, 2840, 1713, 1606, 1511, 1301, 1167, 1100, 1029, 846, 769 cm^{-1}; Anal. calcd for $C_{17}H_{18}O_3$: C 75.53, H 6.71; found C 75.60, H 6.66.



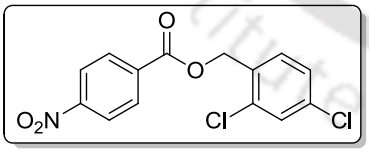
3,5-Dimethylbenzyl 3-nitrbenzoate (4f): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 6H), 5.33 (s, 2H), 6.99 (s, 1H), 7.06 (s, 2H), 7.63 (t, 1H, *J* = 8.0 Hz), 8.37–8.41 (m, 2H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.4, 67.9, 124.9, 125.2, 126.6, 129.6, 129.8, 130.1, 135.6, 135.9, 138.5, 148.5, 164.5; IR (KBr) 3088, 2920, 2868, 1727, 1615, 1533, 1350, 1292, 1258, 1138, 718 cm^{-1}; Anal. calcd for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found C 67.41, H 5.24, N 4.83.



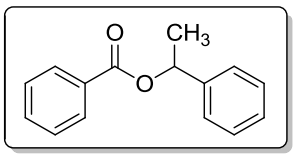
2,4-Dichlorobenzyl benzoate (5a): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.24 (s, 2H), 7.25–2.27 (m, 1H), 7.42–7.46 (m, 4H), 7.57 (t, 1H, *J* = 7.2 Hz), 8.08 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 63.5, 127.4, 128.6, 128.7, 129.6, 129.9, 130.8, 132.6, 133.4, 134.6, 134.8, 166.2; IR (KBr) 3091, 3067, 2956, 2927, 1722, 1589, 1475, 1451, 1270, 1098, 831, 819, 710 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}Cl_2O_2$ $(M + H)^+$ 281.0131; found 281.0137.



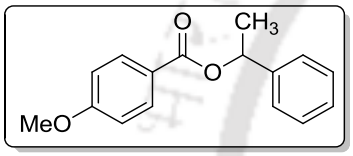
2,4-Dichlorobenzyl 4-methoxybenzoate (5b): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 5.37 (s, 2H), 6.90 (d, 2H, *J* = 9.2 Hz), 7.22–7.24 (m, 1H), 7.38–7.42 (m, 2H), 8.02 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 63.2, 113.8, 122.2, 127.3, 129.5, 130.6, 131.9, 132.8, 134.4, 134.7, 163.7, 165.9; IR (KBr): 3078, 3006, 2960, 2935, 1713, 1606, 1511, 1475, 1368, 1258, 1168, 1098, 1029, 846, 768, 733 cm^{-1}; Anal. calcd for $C_{15}H_{12}Cl_2O_3$: C 57.90, H 3.89; found C 57.83, H 3.92.



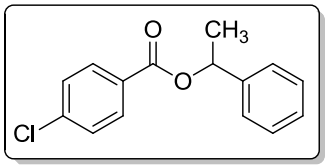
2,4-Dichlorobenzyl 4-nitrobenzoate (5l): Yellow Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.38 (s, 2H), 7.21 (d, 1H, *J* = 8.0 Hz), 7.36–7.38 (m, 2H), 8.14–8.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 64.5, 123.8, 127.6, 129.9, 131.0, 131.4, 131.8, 135.0, 135.3, 135.5, 150.9, 164.5; IR (KBr): 3111, 3076, 3052, 2956, 1728, 1606, 1528, 1347, 1270, 1100, 872, 854, 718 cm^{-1}. Anal. calcd for $C_{14}H_9Cl_2NO_4$: C 51.56, H 2.78, N 4.29; found C 51.61, H 2.70, N 4.18.



1-Phenylethyl benzoate (6a): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.70 (d, 3H, *J* = 6.4 Hz), 6.18 (q, 1H, *J* = 6.4 Hz), 7.30–7.49 (m, 7H), 7.56 (t, 1H, *J* = 7.6 Hz), 8.13 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 72.8, 126.0, 127.8, 128.3, 128.5, 129.5, 130.5, 132.8, 141.8, 165.6; IR (KBr): 3060, 2981, 1717, 1495, 1451, 1315, 1270, 1176, 1109, 1069, 1026, 761, 712, 698 cm^{-1}; Anal. calcd. for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found C 79.69, H 6.17.

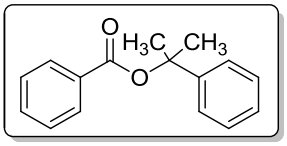


1-Phenylethyl 4-methoxybenzoate (6b): Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.65 (d, 3H, *J* = 6.4 Hz), 3.82 (s, 3H), 6.11 (quart, 1H, *J* = 6.4 Hz), 6.90 (d, 2H, *J* = 7.2 Hz), 7.28 (t, 1H, *J* = 7.6 Hz), 7.35 (t, 2H, *J* = 7.6 Hz), 7.43 (d, 2H, *J* = 8.0 Hz), 8.04 (d, 2H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.6, 55.6, 72.7, 113.7, 123.1, 126.2, 127.9, 128.7, 131.8, 142.2, 163.5, 165.7; IR (KBr): 3063, 3032, 2979, 2934, 2839. 1713, 1606, 1510, 1454, 1258, 1167, 1100, 1029, 847, 769, 698 cm^{-1}; Anal. calcd for $C_{16}H_{16}O_3$: C 74.98, H 6.29; found C 75.06, H 6.33.

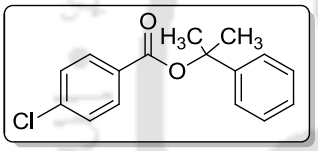


1-Phenylethyl 4-chlorobenzoate (6d): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.67 (d, 3H, *J* = 6.4 Hz), 6.12 (q, 1H, *J* = 6.8 Hz), 7.30–7.44 (m, 7H), 8.00 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 73.2, 126.0, 128.0, 128.5, 128.6, 129.0, 131.0, 139.3, 141.5, 164.8; IR (KBr): 3038, 2981, 2929, 1718, 1594, 1452, 1269, 1103, 1063, 850, 759, 698

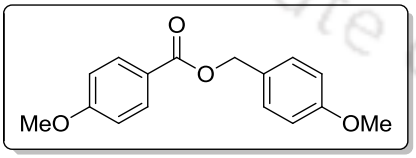
cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}ClO_2$ (MH^+) 261.0677; found 261.0685.



2-Phenylpropan-2-yl benzoate (7a): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.91 (s, 6H), 7.24 (t, 2H, *J* = 7.2 Hz), 7.29–7.34 (m, 2H), 7.39–7.54 (m, 5H), 8.05 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.5, 81.9, 124.0, 126.5, 128.1, 128.8, 129.3, 131.3, 132.4, 145.6, 164.8; IR (KBr): 2981, 2929, 1721, 1450, 1365, 1314, 1281, 1145, 1098, 1070, 1027, 763, 712, 698 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found C 80.03, H 6.77.

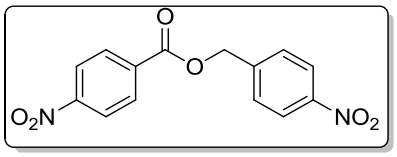


2-Phenylpropan-2-yl 4-chlorobenzoate (7d): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.89 (s, 6H), 7.22–7.42 (m, 7H), 7.96 (d, 2H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.5, 82.4, 124.1, 127.0, 128.2, 128.4, 129.8, 130.8, 138.9, 145.4, 164.0; IR (KBr): 2981, 2931, 1725, 1595, 1449, 1365, 1277, 1145, 1116, 1098, 1015, 853, 761, 698 cm^{-1}; Anal. calcd. for $C_{16}H_{15}ClO_2$: C 69.95, H 5.50; found C 69.87, H 5.54.



4-Methoxybenzyl 4-methoxybenzoate: Yelowish liquid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.79 (s, 3H), 3.82 (s, 3H), 5.25 (s, 2H), 6.87–6.90 (m, 4H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.99 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.4, 55.5, 66.3, 113.7, 114.1, 122.8, 128.6, 130.1, 131.8, 159.7, 163.5, 166.4; IR (KBr): 3002, 2957, 2837, 1707, 1606, 1513, 1255, 1166, 1097, 1029, 823, 769 cm^{-1}; HRMS (ESI) calcd for

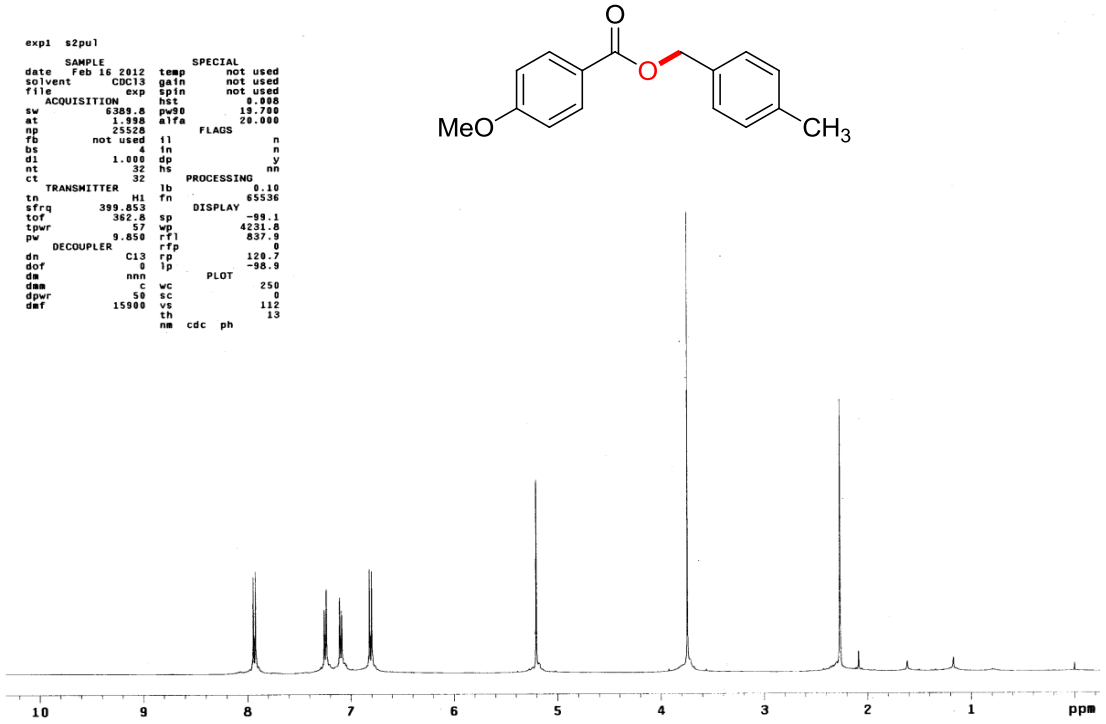
$C_{16}H_{16}O_4$ $(M + H)^+$ 273.1121; found 273.1115.



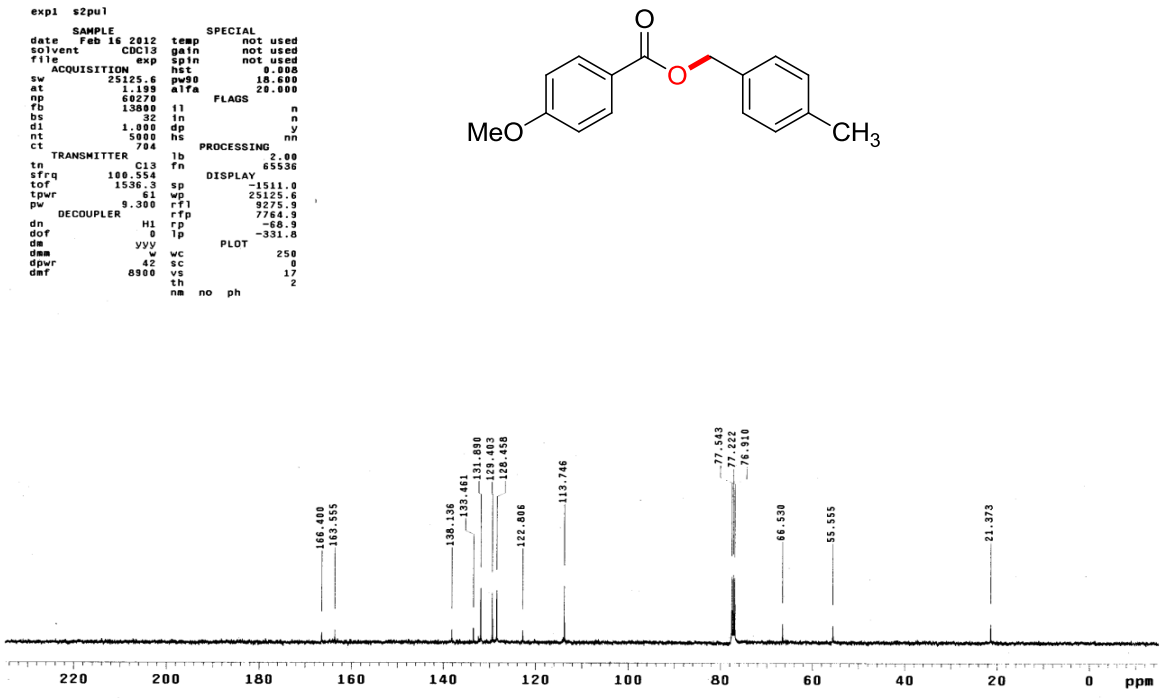
4-Nitrobenzyl 4-nitrobenzoate: Yellowish Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.48 (s, 2H), 7.60 (d, 2H, *J* = 8.8 Hz), 8.22–8.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 68.6, 123.2, 124.4, 128.6, 130.9, 137.5, 146.5, 148.8, 166.7; IR (KBr) 2962, 2923, 2849, 1727, 1645, 1604, 1517, 1347, 1274, 1104, 735, 717 cm^{-1}; Anal. calcd for $C_{14}H_{10}N_2O_6$: C 55.63, H 3.33, N 9.27; found C 55.69, H 3.36, N 9.17

II.7. Spectra

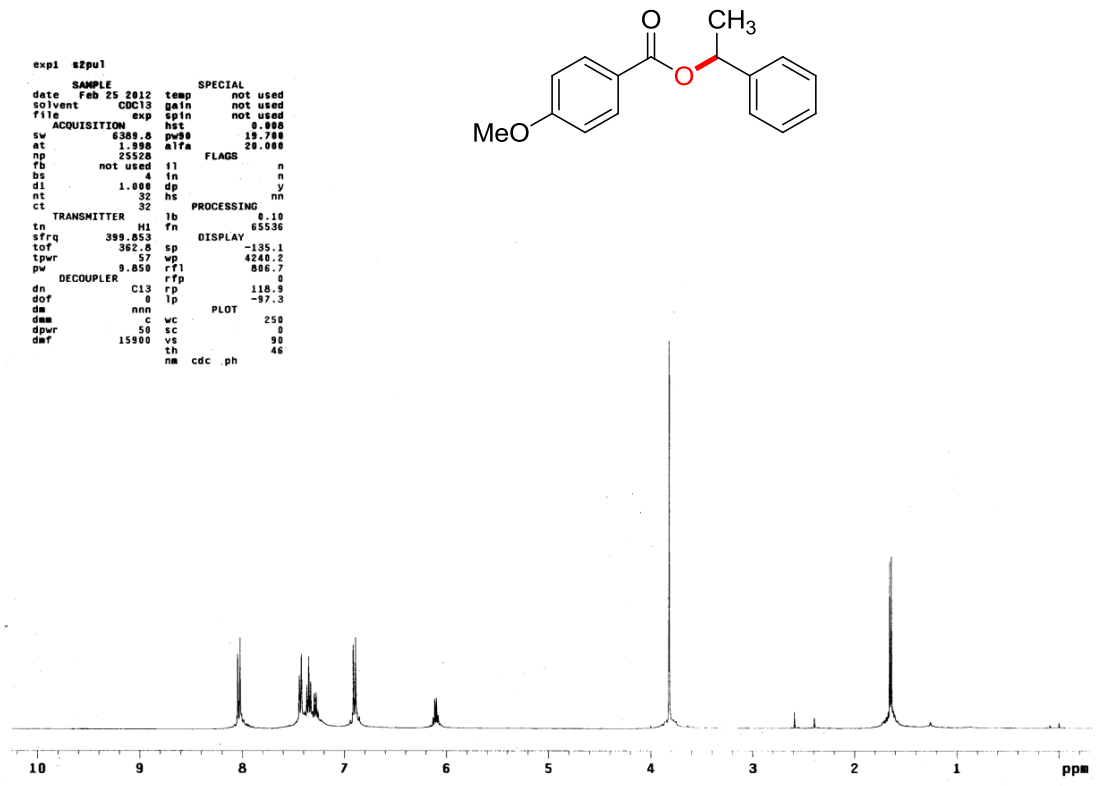
4-Methylbenzyl 4-methoxybenzoate (2b): ^{1}H NMR (400 MHz, $CDCl_3$)



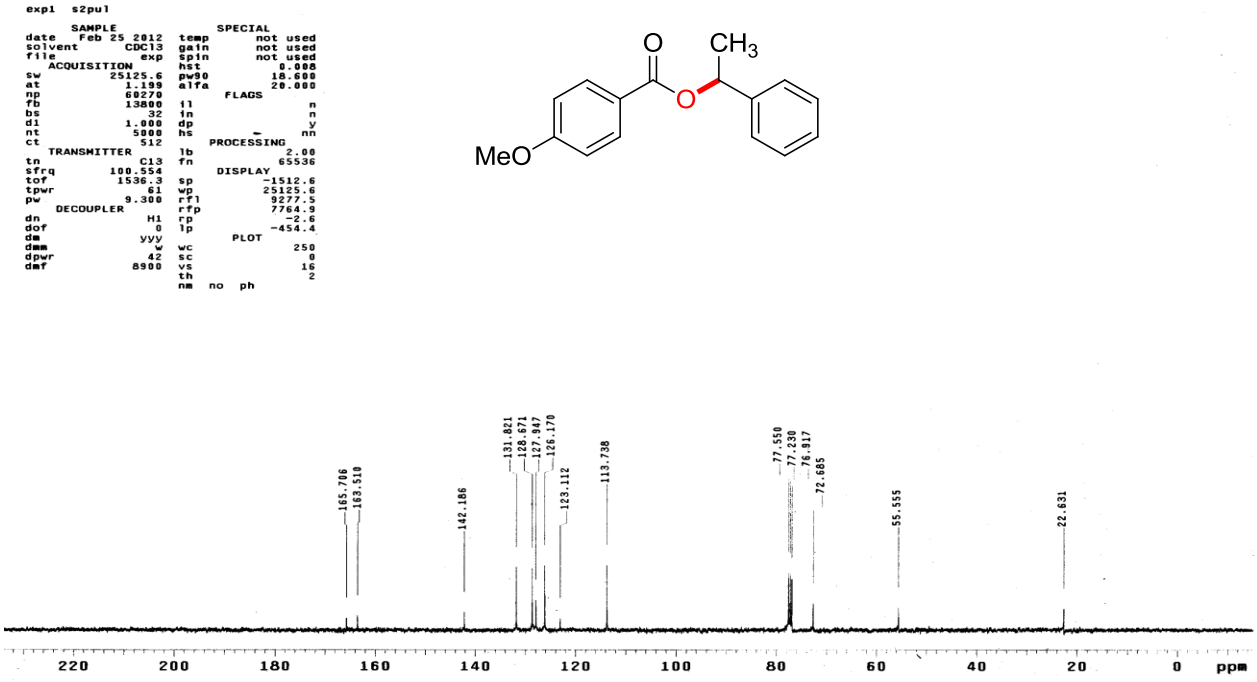
4-Methylbenzyl 4-methoxybenzoate (2b): ^{13}C NMR (100 MHz, $CDCl_3$)



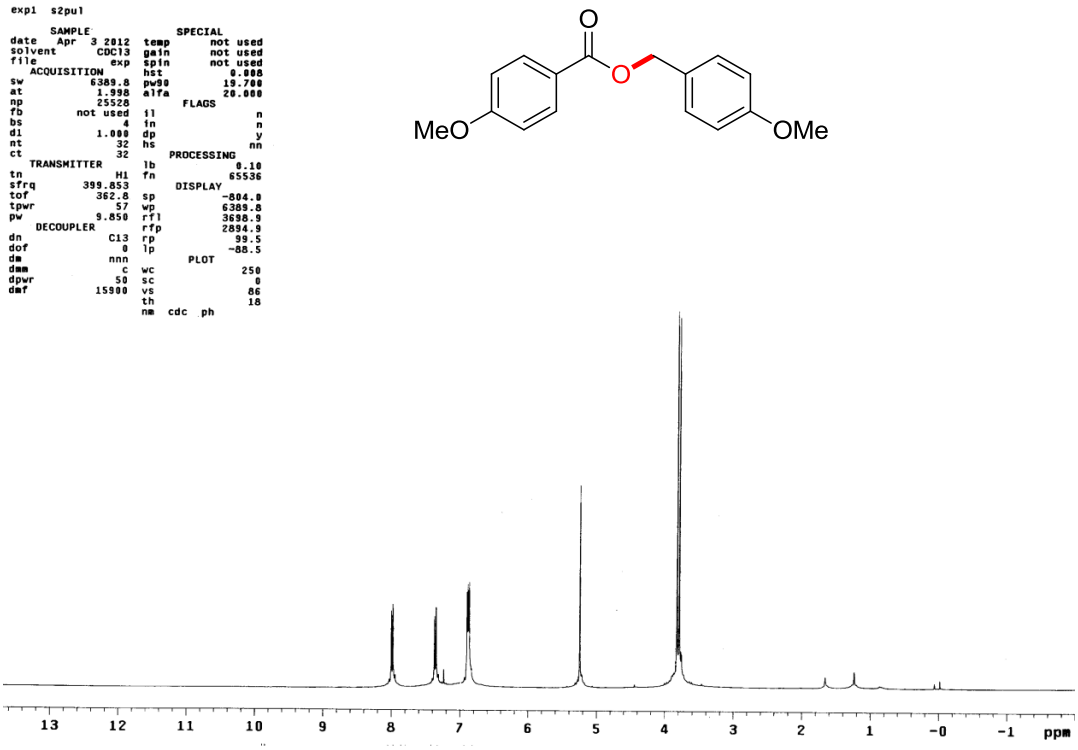
1-Phenylethyl 4-methoxybenzoate (6b): ^{1}H NMR (400 MHz, $CDCl_3$)



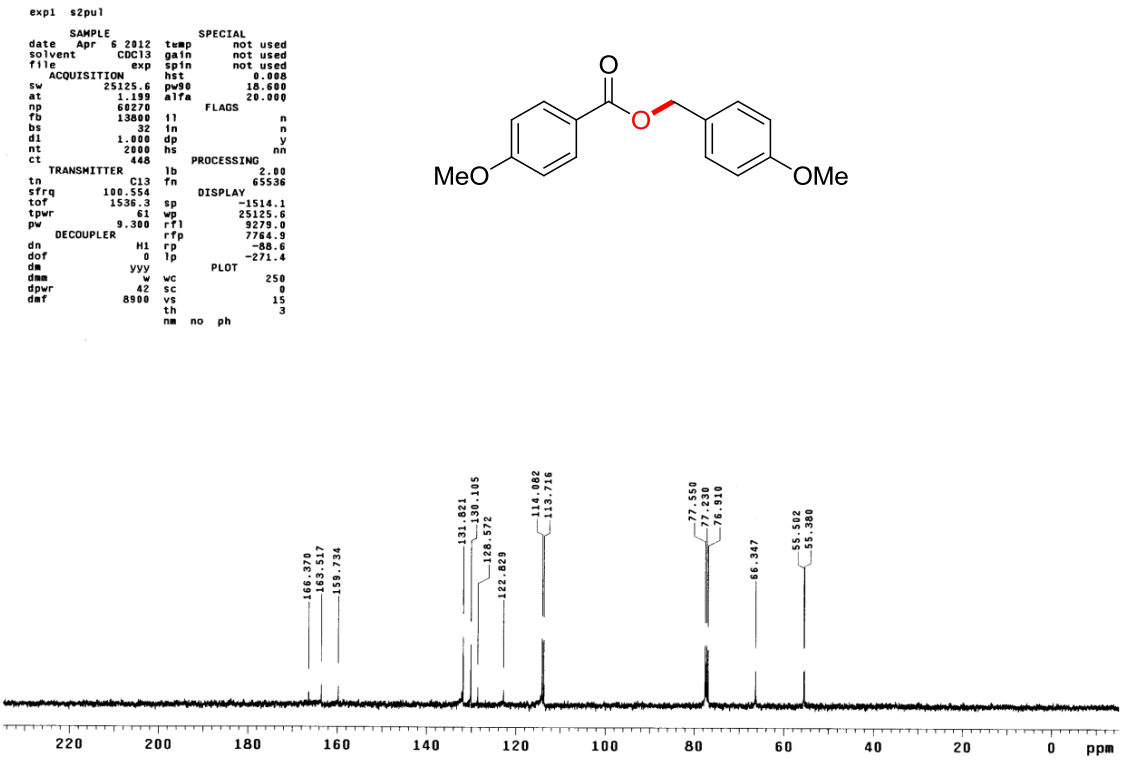
1-Phenylethyl 4-methoxybenzoate (6b): ^{13}C NMR (100 MHz, $CDCl_3$)



4-Methoxybenzyl 4-methoxybenzoate: ^{1}H NMR (400 MHz, $CDCl_3$)



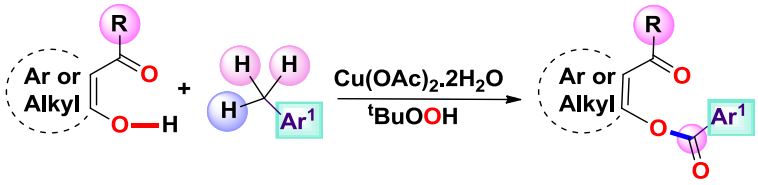
4-Methoxybenzyl 4-methoxybenzoate: ^{13}C NMR (100 MHz, $CDCl_3$)



भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Chapter III

Directing Group Assisted Copper-Catalyzed Chemoselective O-Aroylation of Phenols and Enols Using Alkylbenzenes



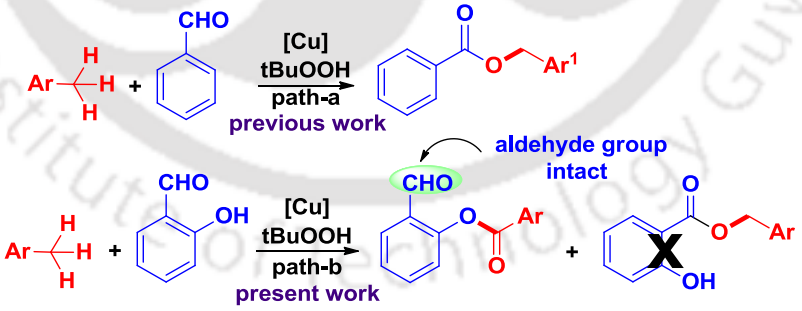
Abstract: ***A new and efficient copper catalyzed directed O-aroylation process (esterification) has been accomplished between alkylbenzenes and o-carbonylphenols and β-dicarbonyl compounds using TBHP as the oxidant. A dual mechanism is operating in tandem for these transformations. This protocol simultaneously installs two C–O bonds at the expense of three benzylic sp^3 C–H bonds. The phenolic group is selectively aroylated (esterified) even in the presence of aldehydic functionality.***

CHAPTER III

III.1. Directing Group Assisted Copper-Catalyzed Chemoselective *O*-Aroylation of Phenols and Enols Using Alkylbenzenes

III.1. Introduction

Of late, the construction of C–C and C–X bonds via cross-dehydrogenative couplings (CDC) is attractive because it does not require substrate prefunctionalizations and is atom economic.[1] The importance of C–O bonds in synthetic organic chemistry has resulted in the development of a variety of C–H bond functionalization methods mediated by various transition metals.[2] In this context the ester synthesis is in the vanguard. Recent synthesis of esters involve reactions of acids with cyclic ethers where the C–O bond formation takes place at the sp^3 carbon atoms α to the ethereal oxygen.[3] 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.[4] Alkylbenzenes have been excellent aroyl surrogates[5] and are the best alternatives to Friedel-Crafts aroylations. Benzylic esters

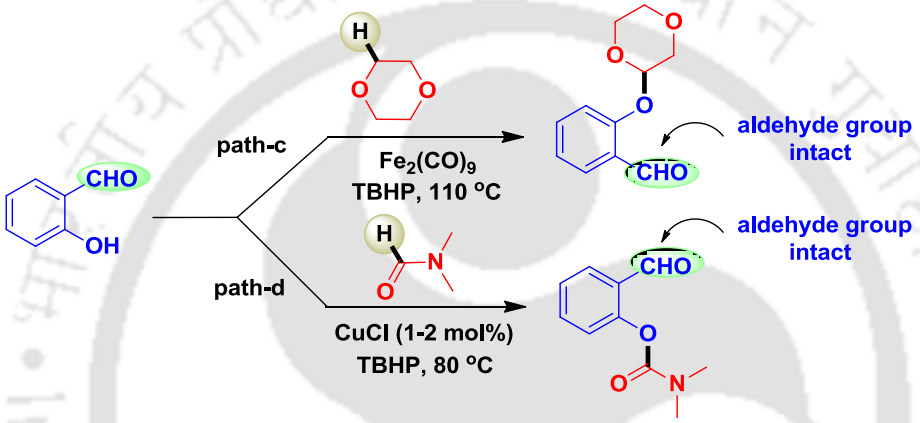


Scheme III.1.1. *CDC Protocols for C–O bond formation via C–H activations*

are obtained by the CDC coupling of aldehydes and alkylbenzenes using the Cu(II) catalyst (path a, Scheme III.1.1).[4a] Thus it would be interesting to see if salicylaldehyde (**1**) possessing both phenolic –OH and aldehydic functionalities when treated with an alkylbenzene would give benzylic ester or a phenol ester (path b, Scheme III.1.1).[4a]

Phenolic ester (path b, Scheme III.1.1) was obtained while the aldehydic function survived under the oxidative conditions.

Pertaining to this report Chang *et al.* have recently developed a novel iron catalyzed protocol for synthesis of ethers involving 2-hydroxybenzaldehyde with cyclic ethers without affecting the sensitive aldehyde group in the presence of an oxidant (path c, Scheme III.1.2).[6] Further same group developed a copper-catalyzed oxidative C−O coupling of formamides with salicylaldehydes where sensitive aldehyde groups remained intact (path d, Scheme III.1.2).[7]

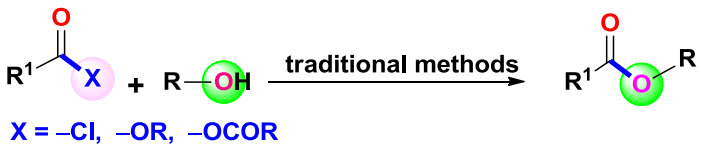


Scheme III.1.2. *C–O bond formation with retention of aldehyde group under oxidative condition via C–H activations*

III.2. Strategies for Esterification

Prior to our present report, esterifications are traditionally achieved by reacting alcohols with carboxylic acids or its derivatives which often require auxiliary chemicals. Besides conventional methods the recently develop methods on esterification are the oxidative esterification of aldehydes and carbonylation of aryl halides which are enlisted below.

(i) Traditional esterification

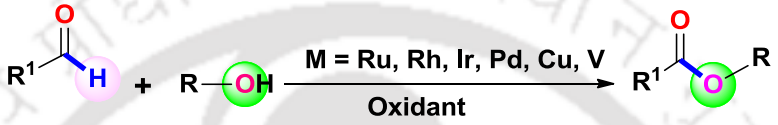


Scheme III.2.1. *Esterification using classical methods*

The traditional methods for the synthesis of ester groups rely on the reaction of preactivated acid derivatives, such as acyl halides, anhydrides, and activated esters, with alcohols in the presence of a stoichiometric amount of base (Scheme III.2.1).[8]

(ii) Oxidative esterification of aldehydes

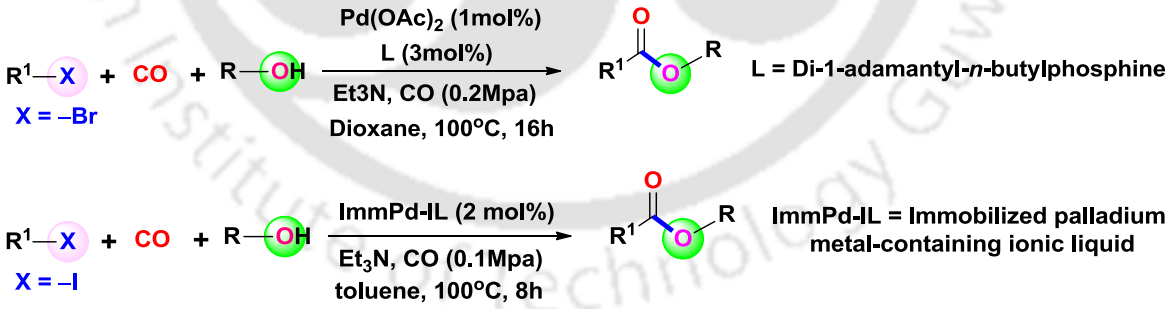
The cross-dehydrogenative coupling (CDC) between aldehydes and alcohols using transition metal catalyst such as Ru,[9] Rh,[10] Ir,[11] Pd,[12] Cu[13] and V[14] represents an economical and sustainable process for the synthesis of esters (Scheme III.2.2).



Scheme III.2.2. *Esterification via CDC approach*

(iii) Esterification using carbon monoxide (CO)

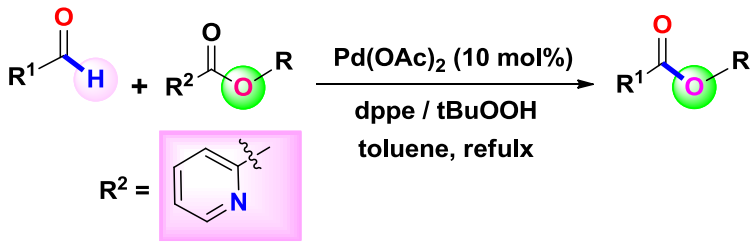
Beller *et al.* reported for the first time the application of palladium/di-1-adamantyl-n-butylphosphine catalysts towards the synthesis of aryl benzoates in the reaction sequence carbonylation of aryl halides followed by esterification with phenols (Scheme III.2.3.).[15] Further Bhanage group developed similar strategy using immobilized palladium metal-containing ionic liquid (ImmPd-IL) recyclable phosphine-free catalyst (Scheme III.2.3.).[16]



Scheme III.2.3. *Esterification using carbnomonoxide (CO)*

(iv) Use of aldehydes in transesterification process

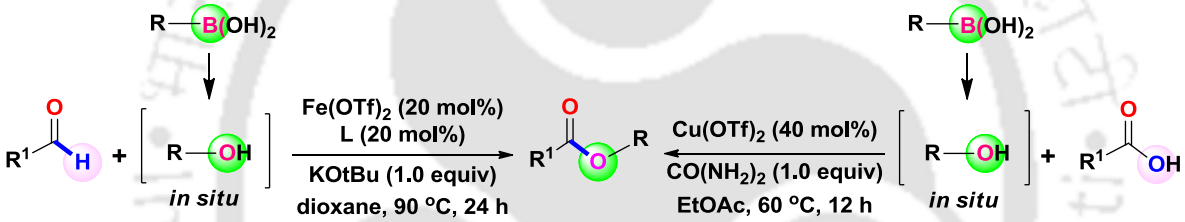
Huang *et al.* reported a palladium catalyzed unique transesterification protocol between pyridine 2-carboxylic esters and various aldehydes by C−H and C−O bond activations (Scheme III.2.4).[17]



Scheme III.2.4. *Transesterification process*

(v) Use of boronic acids in esterification

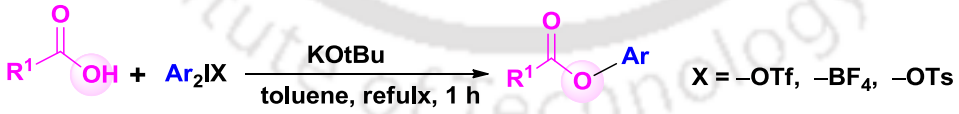
Gois *et al.* developed an efficient NHC-Fe catalyzed methodology to prepare benzoates via aerobic oxidative esterification of aldehydes with boronic acids (Scheme III.2.5).[18] Cheng group developed a $Cu(OTf)_2$-mediated Chan-Lam reaction of carboxylic acid and arylboronic acids, affording the phenolic esters (Scheme III.2.5).[19]



Scheme III.2.5. *Esterification using boronic acids*

(vi) Hypervalent iodine mediated protocol for the synthesis of ester

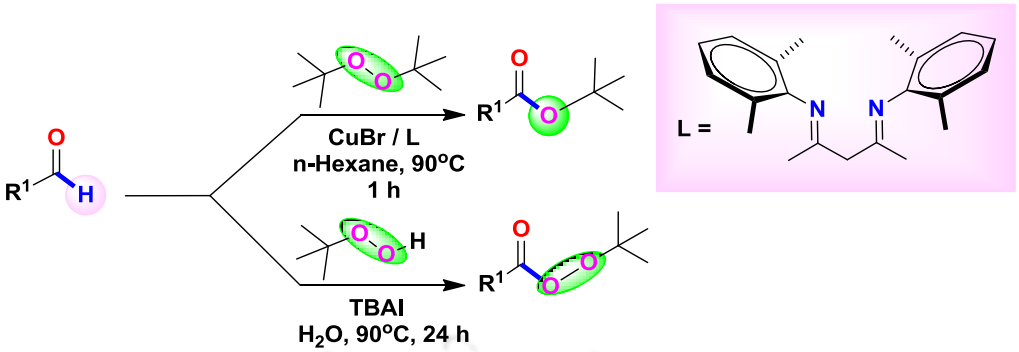
Olofsson *et al.* developed transition-metal-free arylation of carboxylic acids with diaryliodonium salts for the synthesis of aryl esters (Scheme III.2.6)..[20]



Scheme III.2.6. *Esterification using hypervalent iodine*

(vii) Oxidative esterification of aldehyde using TBHP and DTBP

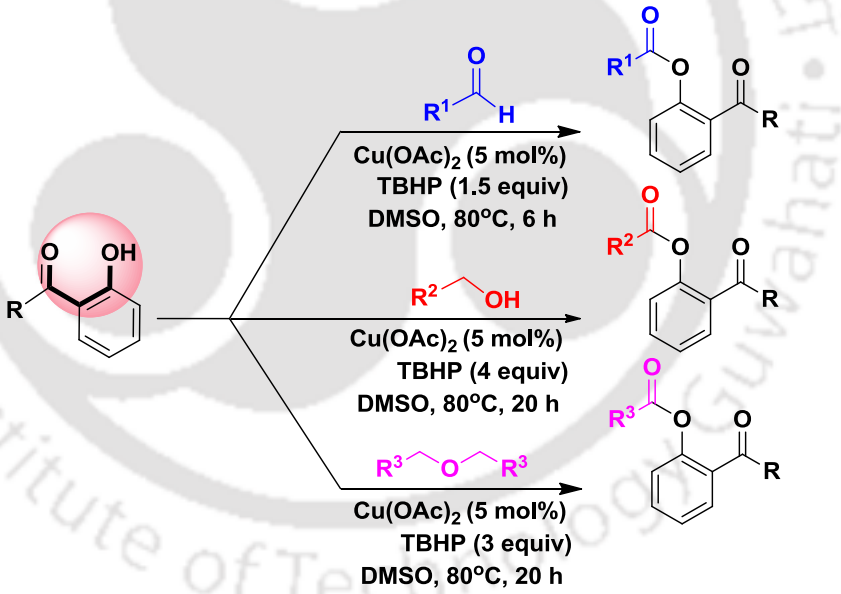
Wei group developed a copper-catalyzed oxidative esterification procedure of aldehydes with *di-tert*-butyl peroxide (DTBP) Scheme III.2.7.[21] Wan *et al.* reported *tert*-butyl perester synthesis directly from aldehydes and *tert*-butyl hydroperoxide (TBHP) via Bu_4NI-catalyzed aldehyde C–H oxidation (Scheme III.2.7).[22]



Scheme III.2.7. *Esterification using TBHP and DTBP*

(viii) Directing group assisted *O*-aroylation

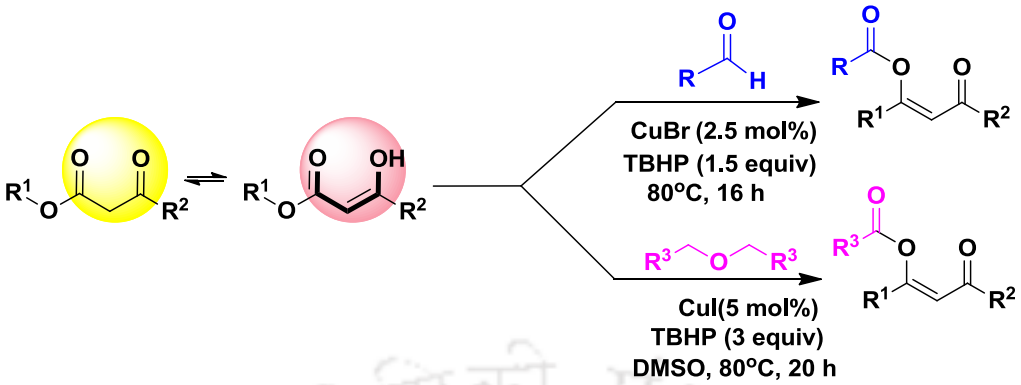
Very specifically regarding the substrate directed coupling for the synthesis of esters via *O*-aroylation processes, a copper catalyzed directed *O*-aroylation of 2-acetylphenols or their analogs has been achieved using various aroyl sources viz. aldehydes,[23] alcohols[13] and ethers[24] as coupling partners (Scheme III.2.8).



Scheme III.2.8. *Directing group assisted approach for esterification*

(viii) Directing group appoarch for *O*-aroylation in β-dicarbonyls

Li *et al.* developed a copper-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds using *tert*-butyl hydroperoxide as an oxidant (Scheme III.2.9).[25] Pertinent to this report Kim group recently developed a similar copper catalyzed strategy with dibenzyl or dialkyl ethers as aroyl surrogates (Scheme III.2.9).[24]



Scheme III.2.9. *Directing group assisted approach for esterification*

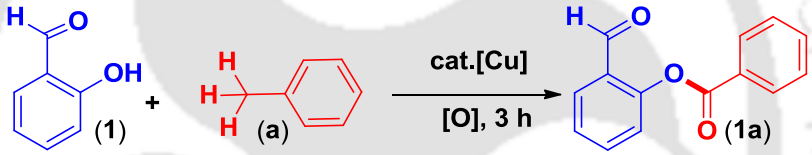
III.3. Present Work

In light of the above-mentioned protocols, the present protocol on *O*-aroylation of phenols and enols with alkylbenzenes demonstrates an unprecedented esterification proceeding via four tandem C–H bond activations (three sp^3 benzylic C–H's and one phenolic –OH / enolic C–H) to selectively install an aroyl moiety at the –OH group present at proximal site of salicylaldehyde (–CHO), 2-acetylphenols ($–COCH_3$) and 1,3-dicarbonyl compounds (–COOR) containing substrates.

Optimization of reaction conditions. Encouraged by this unprecedented result, further optimizations were carried out to achieve a better yield. The use of $Cu(OAc)_2.2H_2O$ provided a superior yield (Table III.3.1, entry 1) compared to other copper salts such as $Cu(OAc)_2$, CuBr, $CuBr_2$, CuCl, $CuCl_2.2H_2O$ and $Cu(OTf)_2$ tested (Table III.3.1, entries 2–7). Increase in the temperature from 100 °C to 120 °C was not that effective as only a marginal improvement in the product yield (40%) was observed (Table III.3.1, entry 8). However, when the reaction was carried out at 120 °C with an increased catalyst loading (20 mol %), the yield improved upto 60% (Table III.3.1, entry 9). No further improvement in the yield could be observed even when the catalyst loading was increased to 30 mol % (Table III.3.1, entry 10). It was observed that either increase (3 equiv) or decrease (1 equiv) in the TBHP (5–6 M) quantity had an adverse effect on the product yield (Table III.3.1, entries 11–12). The decrease in the yield with increase in the oxidant quantity could be due to over oxidation of *O*-aroylated aldehyde to its acid derivative. The use of acid as directing group as in the case of salicylic acid failed to give *O*-aroylated product

suggesting the poor directing ability of –COOH group compared to –CHO group. The nature and their medium of storage of oxidant (TBHP) had a profound influence on the outcome of the product. The use of aqueous TBHP or aqueous H_2O_2 in lieu of TBHP in decane proved to be unsatisfactory (Table III.3.1, entries 13–14). Control experiments carried out with either the Cu salt or TBHP alone failed to yield any coupled product suggesting the interdependency of the catalyst and the oxidant in this coupling reaction (Table III.3.1, entries 15–16). This is the first observation of its kind where alkylbenzene serves as an aroyl source in the *O*-aroylation of the –OH group for a substrate possessing an ortho −CHO group. Yet, under the identical conditions phenol failed to give any trace of ester, confirming the need for of the ortho carbonyl (−CHO) functionality for this esterification.

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



Entry	Catalyst (mol %)	Oxidant (equiv)	Temp ^oC	Yield(%)[a]
1	$Cu(OAc)_2.2H_2O$ (10)	dec. TBHP (2)	100	35
2	CuBr (10)	dec. TBHP (2)	100	15
3	$CuBr_2$ (10)	dec. TBHP (2)	100	22
4	CuCl (10)	dec. TBHP (2)	100	<10
5	$CuCl_2.2H_2O$ (10)	dec. TBHP (2)	100	20
6	$Cu(OTf)_2$ (10)	dec. TBHP (2)	100	5
7	$Cu(OAc)_2$ (10)	dec. TBHP (2)	100	25
8	$Cu(OAc)_2.2H_2O$ (10)	dec. TBHP (2)	120	40
9	**$Cu(OAc)_2.2H_2O$ (20)**	dec. **TBHP (2)**	**120**	**60**
10	$Cu(OAc)_2.2H_2O$ (30)	dec. TBHP (2)	120	60
11	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (3)	120	45
12	$Cu(OAc)_2.2H_2O$ (20)	dec. TBHP (1)	120	30
13	$Cu(OAc)_2.2H_2O$ (20)	aq. TBHP (2)	120	10
14	$Cu(OAc)_2.2H_2O$ (20)	aq. H_2O_2 (2)	120	<5
15	Nil	dec. TBHP (2)	120	00
16	$Cu(OAc)_2.2H_2O$ (20)	Nil	120	00

[a]Isolated yield.

Substrate scope for esters. Further reactions were investigated with a set of substituted alkylbenzenes and phenols possessing an *ortho*–CHO group. The reaction of *p*-xylene (**b**) with 2-hydroxybenzaldehyde (**1**) gave a moderate yield of its mono *O*-aroylated product (**1b**) without affecting the other methyl group (Scheme III.3.1). The structure of the product (**1b**) has been unequivocally confirmed by crystal X-ray crystallography as shown in Figure III.3.1.

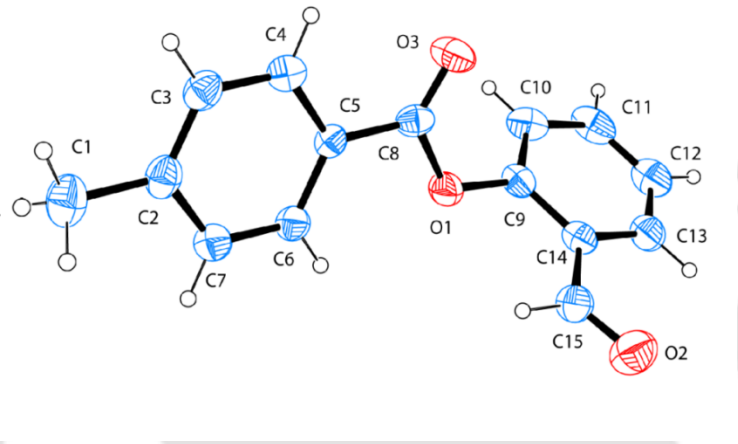
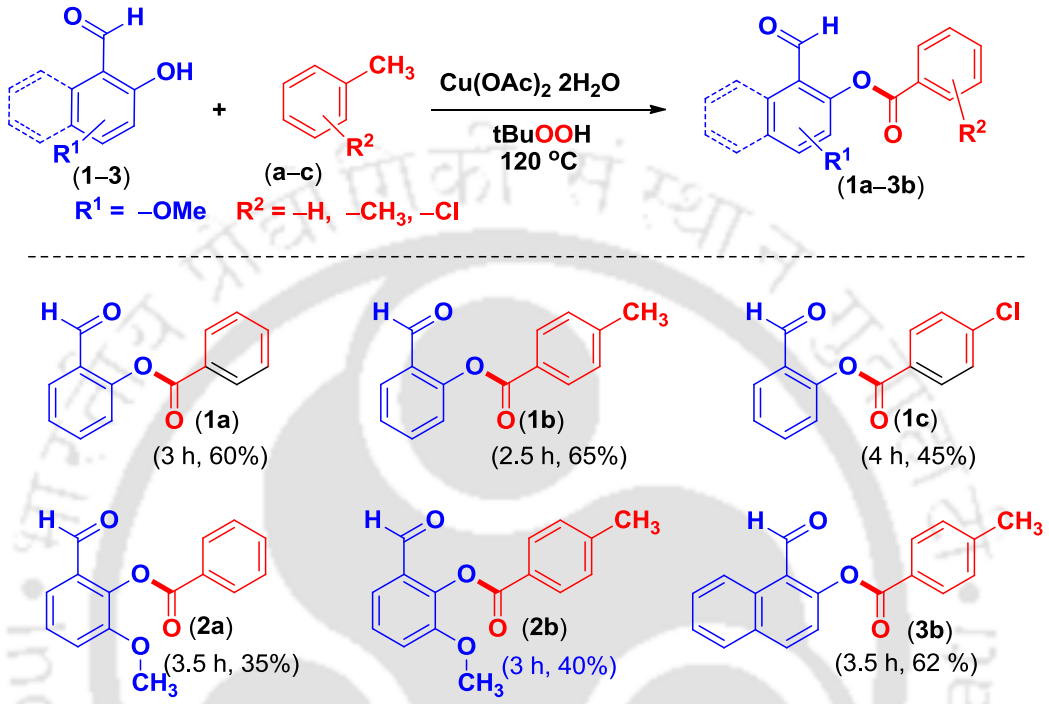


Figure III.3.1. *2-Formylphenyl 4-methylbenzoate (**1b**)*

The survival of the aldehydic group and retention of one of the aryl $–CH_3$ groups in the product (**1b**) can be clearly seen in Figure III.3.1. The reaction of *p*-chlorotoluene (**c**) possessing an electron-withdrawing group (–Cl) with (**1**) proceeded slowly giving product (**1c**) in 45% yield. This suggests a significant electronic effect on the rates of the reactions and hence on the product yields (Scheme III.3.1). Next a sterically hindered phenol, 2-hydroxy-3-methoxybenzaldehyde (**2**), was reacted with toluene (**a**) and *p*-xylene (**b**), and the reaction provided their *O*-aroylated products (**2a** and **2b**) respectively, but in lower yields (Scheme III.3.1). The lesser yields of (**2a** and **2b**) could be attributed to the steric factor imparted by the adjacent methoxy group in (**2**). The naphthoic hyrdoxyl group possessing an aldehydic functionality in its adjacent position as in the case of 2-hydroxy-1-naphthaldehyde (**3**) coupled efficiently with *p*-xylene (**b**) giving *O*-aroylated product (**3b**) in a modest yield (Scheme III.3.1). The use of acid as a directing group as in the case of salicylic acid failed to give phenol ester suggesting the poor directing ability of the –COOH group compared to the –CHO group. While the carboxylic group in salicylic acid

failed to act as a directing group in providing phenol ester, the aldehydic functionality in *o*-hydroxy aldehydes served as an efficient directing group during the *O*-aroylation process.

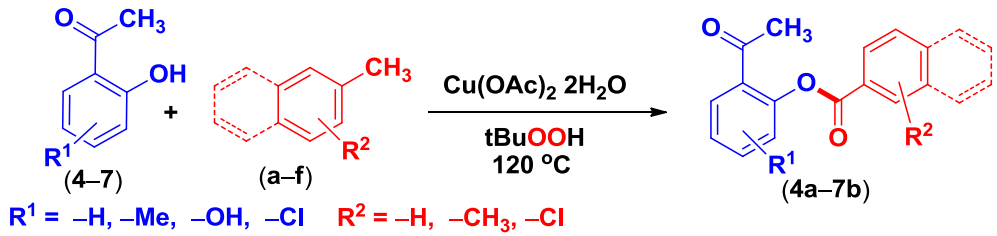
Scheme III.3.1. *Substrate scope for the synthesis of phenol esters*[a,b]

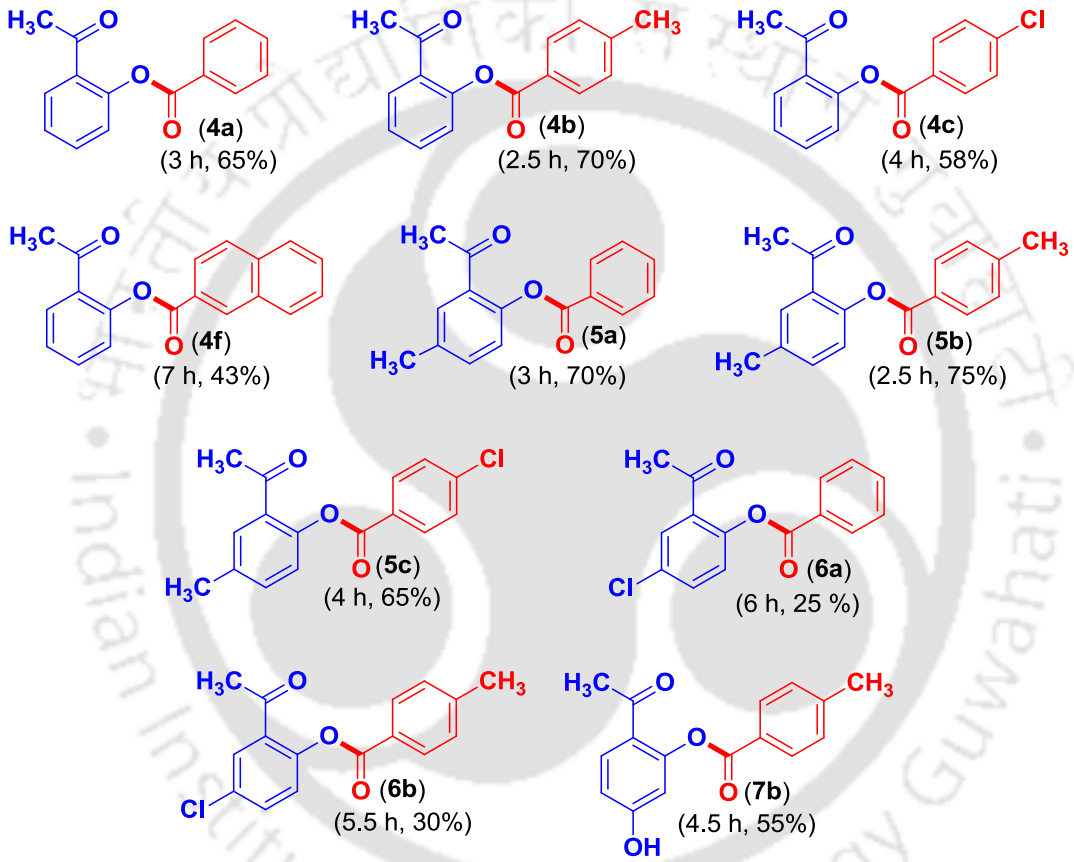


[a]Reaction conditions: phenols (1–3) (1 mmol), alkylbenzenes (a–c) (5 mmol), $Cu(OAc)_2.2H_2O$ (0.2 mmol), TBHP (2 mmol), 120 °C, time 3-4 h. [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

So the obvious query arises whether the *o*-$COCH_3$ group can serve as the directing group in this process. The reaction of 2-hydroxyacetophenone (**4**) with a set of methylarenes viz. toluene (**a**), *p*-xylene (**b**), and *p*-chlorotoluene (**c**) gave moderate yields of their respective *O*-aroylated products, (**4a**, **4b**, and **4c**) (Scheme III.3.2). Besides alkylbenzenes, 2-methylnaphthalene (**f**) could also be employed as an aroyl source in the *O*-aroylation reaction with (**4**) giving corresponding product (**4f**) in modest yield (Scheme III.3.2). The yields of products obtained from substrate (**4**) are better compared to those obtained using substrate (**1**) which is probably due to the better stability of the acetyl group in (**4**) under the oxidative conditions compared to the aldehydic functionality in (**1**) (Scheme III.3.2). The substituent effects present in the aryl ring of 2-hydroxyacetophenone were next investigated. The presence of electron-donating substituents as in the case of 2-

Scheme III.3.2. *Substrate scope for the synthesis of phenol esters*[a,b]





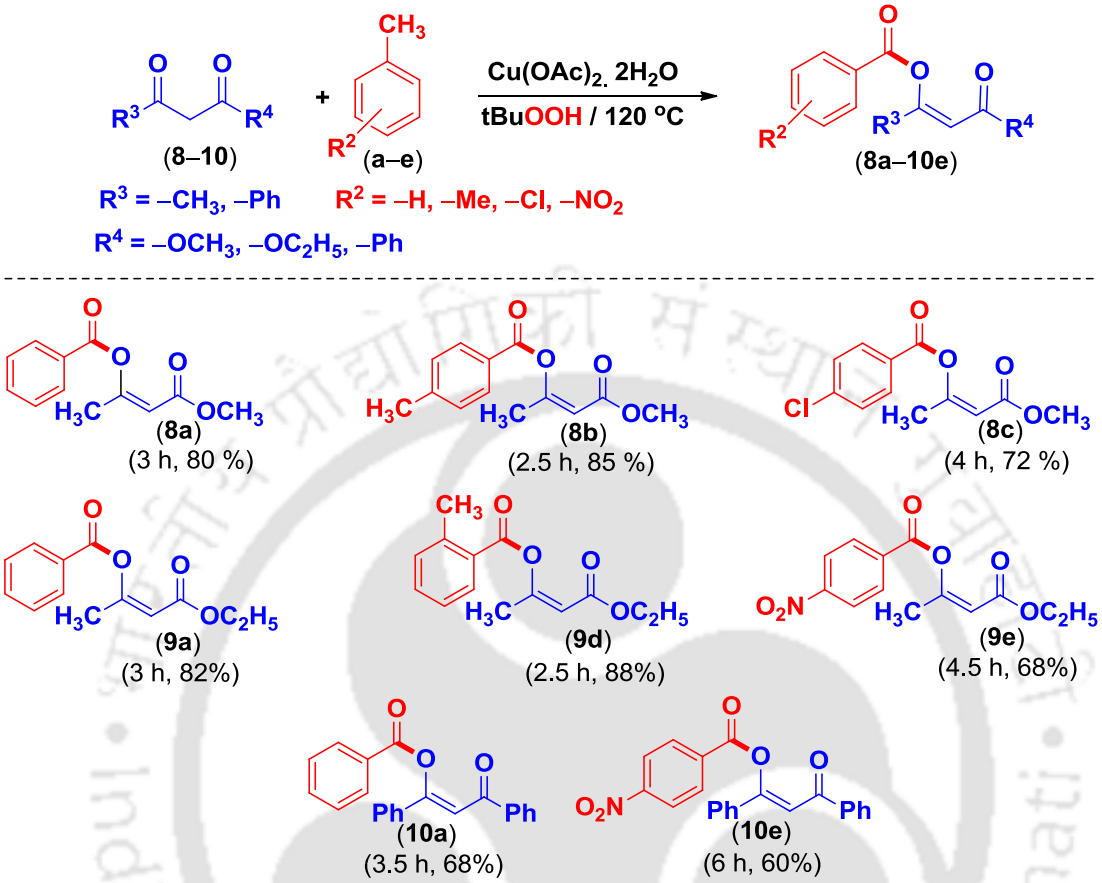
[a]Reaction conditions: phenols (4–7) (1 mmol), alkylbenzenes (a–f) (5 mmol), $Cu(OAc)_2$ $2H_2O$ (0.2 mmol), TBHP (2 mmol), 120 °C, time 3-7 h. [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

hydroxy-5-methylacetophenone (**5**) underwent facile reactions with toluene (**a**), *p*-xylene (**b**) and *p*-chlorotoluene (**c**) giving good to moderate yields of their corresponding *O*-aroylated products (**5a**, **5b**, and **5c**) (Scheme III.3.2). However, substrate possessing an electron-withdrawing group (–Cl) as in the case of 5-chloro-2-hydroxyacetophenone (**6**) coupled with toluene (**a**) and *p*-xylene (**b**) sluggishly providing poorer yields of products

(**6a** and **6b**) respectively (Scheme III.3.2). Due to the presence of $-COCH_3$ directing group in 2,4-dihydroxyacetophenone (**7**), the *o*-hydroxyl group is selectively aroylated without affecting the *p*-hydroxyl group (Scheme III.3.2). Because of the electron-donating *p*-hydroxyl group the yield of the product (**7b**) obtained was better compared to its analogous substrate (**6**) possessing an electron-withdrawing group (–Cl). Thus it is evident that the presence of electron-donating groups in either of the aryl rings (*o*-hydroxy carbonyl compounds and or alkylbenzenes) give better yields while the presence of electron-withdrawing groups result in inferior yields. However, alkyl heteroaryls such as 2-methylpyridine, 3-methylpyridine, and 2-methylimidazole did not serve as aroyl surrogates in *O*-aroylation reactions.

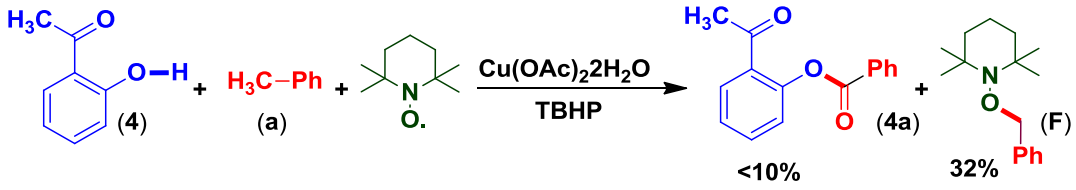
o-Hydroxyl carbonyl compounds and the (*Z*)-enol form of 1,3-dicarbonyl compounds have structural analogy so far as the orientation and positioning of carbonyl and hydroxyl groups are concerned. To unravel the potentiality of this approach various 1,3-dicabonyl substrates were reacted with different alkylbenzenes. β-Carbonyl compounds, methylacetoacetate (**8**) when treated with toluene (**a**), *p*-xylene (**b**), and *p*-chlorotoluene (**c**), all gave their enol esters (**8a**, **8b**, and **8c**) respectively in good yields (Scheme III.3.3). It may be mentioned here that β-carbonyl compounds and C–H bonds adjacent to heteroatoms usually form an $(sp^3)C–(sp^3)C$ bond rather than $(sp^3)C–O$ bond under various metal catalyzed conditions.[1a,1b] Apparently there are few reports on $(sp^3)C–O$ bond formations involving β-carbonyl compounds resulting in enol ethers,[26] enol carbamates,[23] and even enol esters.[25] Moving further, with this strategy other 1,3-dicarbonyl compounds such as ethylacetoacetate (**9**) under the optimized conditions underwent cross dehydrogenative coupling with toluene (**a**), *o*-xylene (**d**), and *p*-nitrotoluene (**e**) giving enol esters (**9a**, **9d**, and **9e**) respectively in good yields (Scheme III.3.3). Alkylbenzenes possessing electron-withdrawing groups gave lesser yields of products compared to those having electron-donating groups, an observation consistent with the results in Scheme III.3.1. Finally, 1,3-diphenyl-1,3-dione (**10**) formed enol esters (**10a**) and (**10e**) in modest yields when treated with toluene (**a**) and *p*-nitrotoluene (**e**) (Scheme III.3.3). All these reactions provided highly stereoselective (*Z*)-enol esters with no loss in stereoselectivity (Scheme III.3.3).

Scheme III.3.3. *Substrate scope for the synthesis enol esters*[a,b]



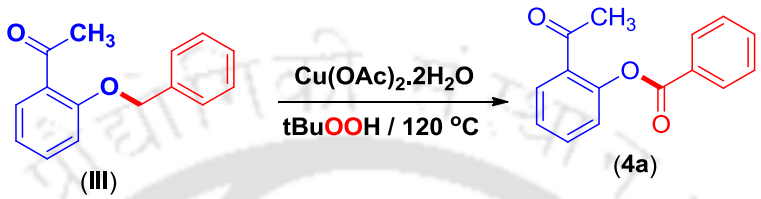
[a]Reaction conditions: 1,3-dicarbonyl (8–10) (1 mmol), alkylbenzenes (a–e) (5 mmol), $Cu(OAc)_2$ $2H_2O$ (0.2 mmol), TBHP (2 mmol), 120 °C, time 3–6 h. [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Mechanistic studies. The presence of a radical quencher (TEMPO) retards the CDC reaction between 2-hydroxyacetophenone (**4**) and toluene (**a**) giving a <10% yield of the product along with a benzyl-TEMPO ether (**F**) (Scheme III.3.4, also see Experimental Section III.4.4) The outcome of this experiment suggest a radical nature of the mechanism and the trapping of benzyl radical by TEMPO indicates benzyl radical insertion path.



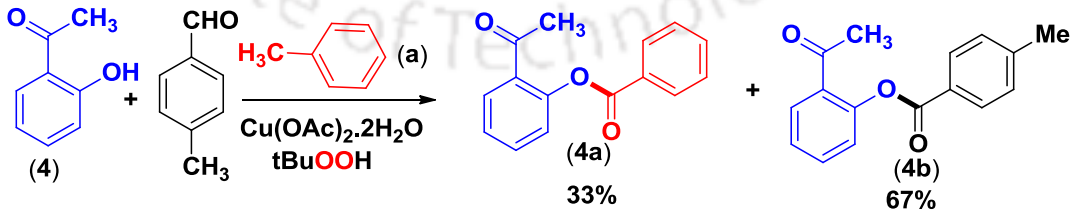
Scheme III.3.4. *Reaction in presence of radical scavenger TEMPO*

To further support the benzyl radical insertion path, when the presynthesized benzyl ether (**III**) was subjected to the present reaction conditions it gave the expected ester product (**4a**) (Scheme III.3.5, also see Experimental section III.4.6). However, the intermediate (**III**) could not be detected during the GC-MS analysis of the reaction mixture which is possibly due to its rapid oxidation to the phenol ester (**4a**).



Scheme III.3.5 *Formation of ester from 1-(2-benzyloxy)phenyl)ethanone*

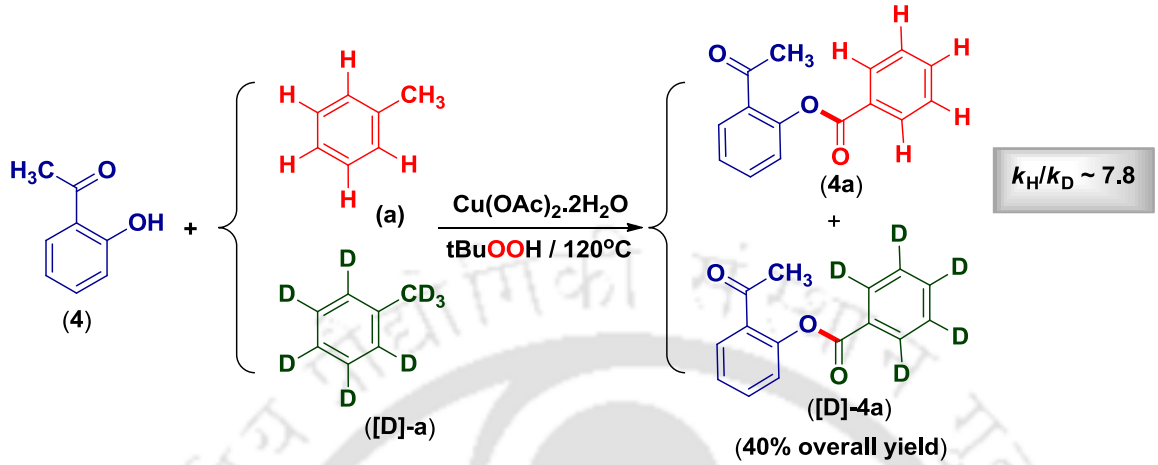
When GC-MS analysis of the reaction between (**4**) and toluene (**a**) was carried out, traces of formation of benzaldehyde and benzylalcohol were detected possibly originating via the radical oxidation of toluene. So in an alternative pathway, the radical coupling of the *in situ* generated benzaldehyde (from toluene) with phenolic O–H cannot be ruled out. Further, the possibility of both mechanisms operating in tandem cannot be ignored. To ascertain the exact nature of the mechanism, a crossover experiment was performed in which an equimolar mixture of 2-hydroxyacetophenone (**4**), *p*-methylbenzaldehyde, and toluene (**a**) were reacted under the present experimental conditions (Scheme III.3.6). Interestingly, both the products (**4a**) and (**4b**) were formed in the ratio 1:2. This experiment supports the dual nature of the mechanism: one involving the benzyl radical path (Scheme III.3.8)[27] and the other via the aroyl radical (Scheme III.3.9).



Scheme III.3.6. *A crossover experiment*

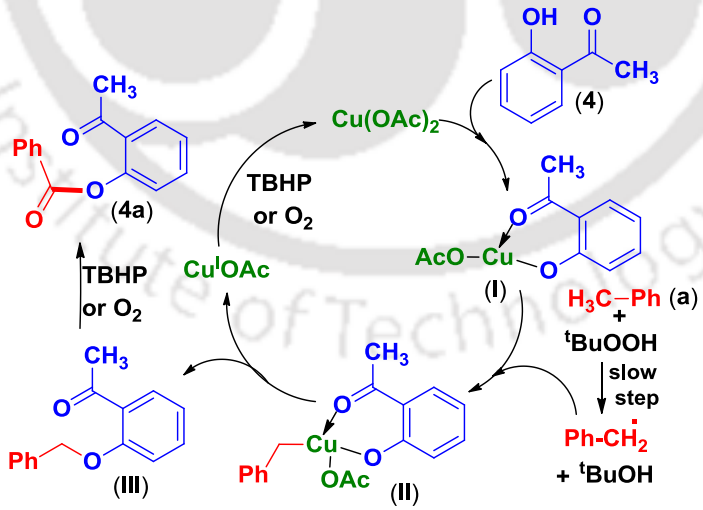
A large kinetic isotope effect (k_H/k_D ~7.8) was observed when the reaction of deuterated toluene (d_8 toluene) was carried out with 2-hydroxyacetophenone (**4**) suggesting

that benzylic C–H bond cleavage to be the rate-determining step (Scheme III.3.7, also see Experimental section III.4.5).



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

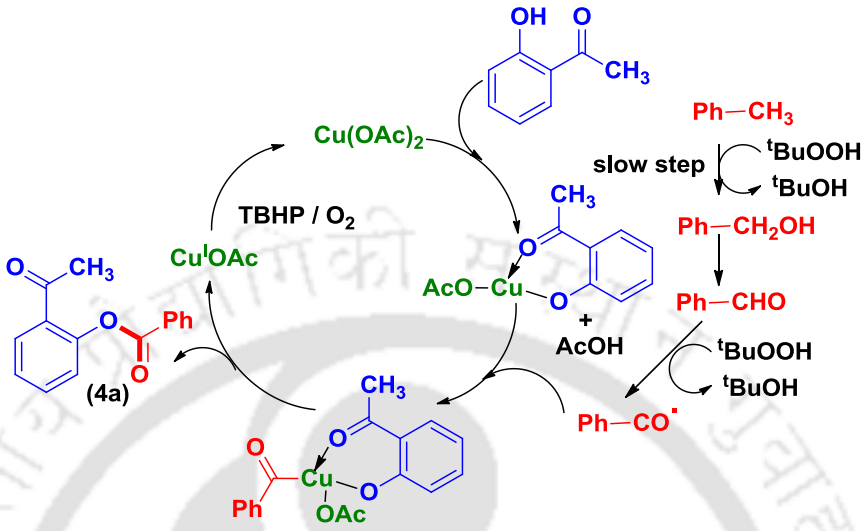
Based on these observations, two possible mechanisms can be envisaged. The first one possibly involves the radical coupling of the benzylic radical and the phenolic –OH via the Cu complexes (**I**) and (**II**) to form *O*-benzylated intermediate (**III**) as depicted in Scheme III.3.8. The *O*-benzylic position of (**III**) perhaps undergoes oxidation to give corresponding phenol ester (**4a**) as shown in Scheme III.3.8.



Scheme III.3.8. *Proposed mechanism for O-aroylation via O-benzylated path*

While in an alternative mechanism toluene first undergoes oxidation to give benzaldehyde which is homolytically cleaved in presence of TBHP to give aroyl radical.

All other steps and proposed intermediates in Scheme III.3.9 are similar to the one proposed by Li *et al*.[25]



Scheme III.3.9. *Proposed mechanism for O-aroylation via aldehyde path*

In conclusion, a new, efficient Cu-catalyzed directed *O*-aroylation process (esterification) has been accomplished between alkylbenzenes and *o*-carbonylphenols and β-dicarbonyl compounds using TBHP as the oxidant. A dual mechanism operates in tandem for these transformations. This protocol simultaneously installs two C–O bonds at the expense of three benzylic sp^3 C–H bonds. The phenolic group is selectively aroylated (esterified) even in the presence of aldehydic functionality.

III.4. Experimental Section

III.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 (300 MHz and 400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (75 MHz and 100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. Elemental analyses were recorded on CHNS analyzer. X-Ray data were collected on SMART APEX equipped with a CCD area

detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany).

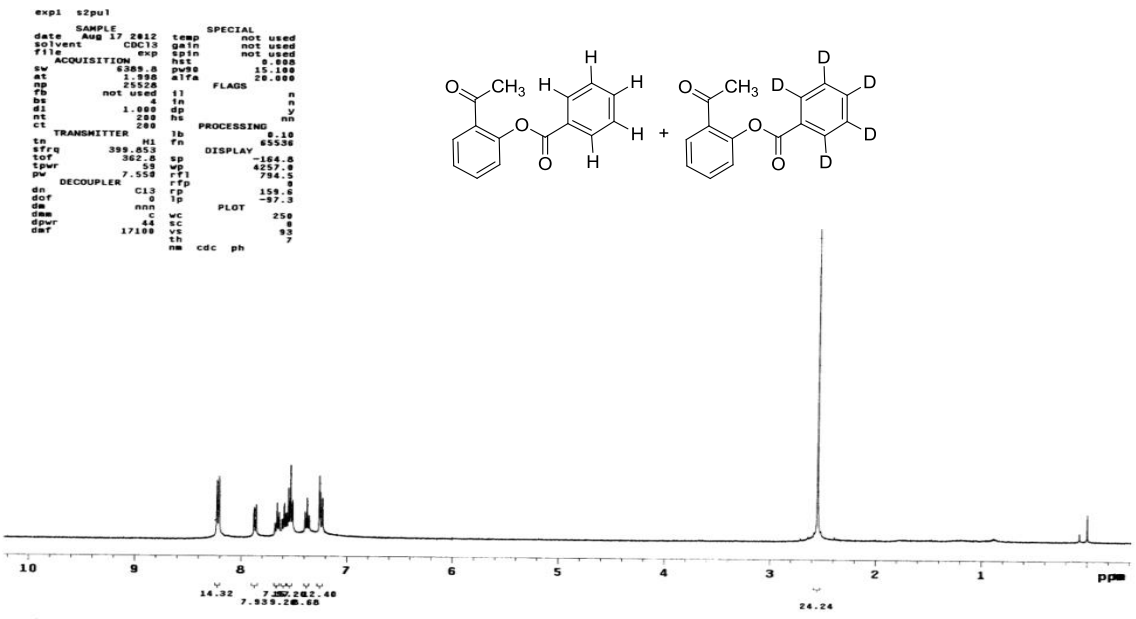
III.4.2. Crystallographic description of 2-formylphenyl 4-methylbenzoate (1b). $C_{15}H_{12}O_3$, crystal dimensions 0.42 x 0.36 x 0.28 mm, M_r = 240.25, Orthorhombic, space group P n a 21, a =22.827(2), b = 4.0137(4), c = 13.1725(12) Å, α = 90 °, β = 90 °, γ = 90 °, V = 1206.87(19) Å^3, Z = 4, ρ_{calcd} = 1.322 mg/m^3, μ = 0.092 mm^{-1}, F(000) = 504.0, reflection collected / unique = 2130 / 1828, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0418, wR_2 = 0.1201, R indices (all data): R_1 = 0.0495, wR_2 = 0.1287, goodness of fit = 0.979. CCDC-944021 for 2-Formylphenyl 4-methylbenzoate (**1b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

III.4.3. General procedure for the synthesis of 2-acetylphenyl benzoate (4a). To a solution of 2-hydroxyacetophenone (**4**) (136 mg, 1 mmol) in toluene (**a**) (460 mg, 5 mmol) was added $Cu(OAc)_2$. $2H_2O$ (42 mg, 0.2 mmol), followed by TBHP in decane (400 µl, 2 mmol) and the resultant mixture was put into a preheated oil bath (120 °C) for 3 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate to give 2-acetylphenyl benzoate (**4a**) (165 mg, 65 % yield).

III.4.4. Mechanistic investigation in the presence of radical scavenger TEMPO. An oven-dried reaction vessel was charged with 2-hydroxyacetophenone (**4**) (136 mg, 1 mmol) in toluene (**a**) (460 mg, 5 mmol) was added $Cu(OAc)_2$. $2H_2O$ (42 mg, 0.2 mmol) and TEMPO (0.312 g, 2 mmol), followed by TBHP in decane (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 °C for 3 h. The reaction after 6 h 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 (<10%) of the desired product (**4a**). This experiment supports the formation of benzyl

radical in the medium from toluene (**a**) induced radically by Cu/TBHP and also the radical nature of the mechanism.

III.4.5. Kinetic isotope effect studies. To a solution of 2-hydroxyacetophenone (**4**) (136 mg, 1 mmol) in toluene (**a**) (230 mg, 2.5 mmol) and d_8-toluene (**[D]-a**) (250 mg, 2.5 mmol) was added $Cu(OAc)_2$. $2H_2O$ (42 mg, 0.2 mmol), followed by TBHP in decane (400 µl, 2 mmol) and the resultant mixture was put into a preheated oil bath (120 ^oC) for 3 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate) to give the expected product in 40 % yield. The ratio of the deuterated (**[D]-4a**) and nondeuterated (**4a**) *O*-aroylated product was calculated on the basis of the integration ratio of the aromatic proton peak at 8.22 (originating from toluene) and $COCH_3$ proton at 2.47 by adopting the procedure of (Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc*. **2012**, *134*, 9902).



Calculation:

For three methyl protons at 2.47, the integration value is 24.24.

Thus for a single proton the integration corresponds to 24.24 / 3 = 8.08.

Now for the integration value of the protons originating from toluene at 8.22 is 14.32.

Thus the number of protons corresponding to this integration value is 14.32 / 8.08 = 1.772. Upon correlation with the original spectra of (**4a**) the number of proton at 8.22 should be 2. Hence the proton difference in this region is 2 – 1.772 = 0.228.

Thus the k_H/k_D = 1.772 / 0.228 = 7.771 ~ 7.8

III.4.6. Control experiment for formation of ester from 1-(2-benzyloxy)phenyl)ethanone. 1-(2-Benzyloxy)phenyl)ethanone (**III**) (57 mg, 0.25 mmol) was treated with $Cu(OAc)_2$. $2H_2O$ (10.5 mg, 0.05 mmol) and TBHP in decane (100 µl, 0.5 mmol) and the reaction mixture was put into a preheated oil bath (120 ^oC) for 2 h. The resultant reaction mixture was admixed with water (2 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate) to give the product 2-acetylphenyl benzoate (**4a**) (45 mg, 75 % yield).

III.5. References

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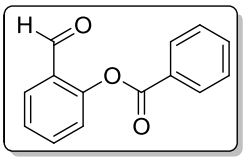
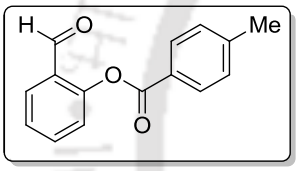
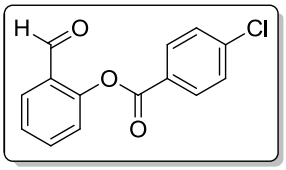
III.6. Spectral data



2-Formylphenyl benzoate (1a): Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 (d, 1H, *J* = 7.6 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.46–7.50 (m, 2H), 7.59–7.63 (m, 2H), 7.90 (d, 1H, *J* = 8.0 Hz), 8.20 (d, 2H, *J* = 8.0 Hz), 10.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.5, 126.4, 128.3, 128.6, 128.7, 130.3, 134.0, 135.3, 152.2, 164.9, 188.4; IR (KBr): 3064, 2856, 2755, 1742, 1700, 1603, 1580, 1452, 1260, 1207, 1177, 1114, 1077, 1058, 1022, 756, 704, 652 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}O_3$ (MH^+) 227.0703; found 227.0709.

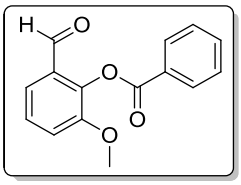


2-Formylphenyl 4-methylbenzoate (1b): White solid; M. P. 73–74 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37, (s, 3H), 7.24–7.27 (m, 3H), 7.32 (t, 1H, *J* = 7.6 Hz), 7.55–7.60 (m, 1H), 7.87 (d, 1H, *J* = 7.6 Hz), 8.07 (d, 2H, *J* = 8.0 Hz), 10.16, (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.6, 123.5, 125.8, 126.3, 128.2, 129.4, 129.9, 130.3, 135.2, 144.9, 152.3, 164.9, 188.4; IR (KBr): 3064, 2856, 2755, 1742, 1700, 1603, 1580, 1452, 1260, 1207, 1177, 1114, 1077, 1058, 1022, 955, 756, 704, 677 cm^{-1}; Anal. calcd for $C_{15}H_{12}O_3$: C 74.99, H 5.03; found C 74.91, H 5.09.

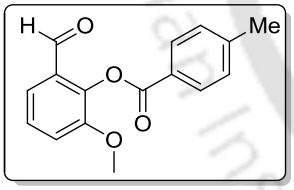


2-Formylphenyl 4-chlorobenzoate (1c): White solid; M. P. 97–99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 (d, 1H, *J* = 4 0 Hz), 7.45 (t, 1H, *J* = 4 0 Hz), 7.50 (d, 2H, *J* = 4 0 Hz), 7.68 (t, 1H, *J* = 8 0 Hz), 7.93 (d, 1H, *J* = 4 0 Hz), 8.15 (d, 2H, *J* = 8 0 Hz), 10.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.5, 126.7, 127.2, 128.2, 128.9,

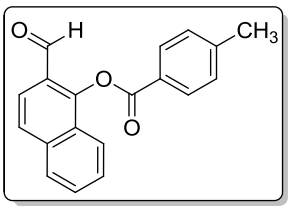
131.0, 131.8, 135.6, 140.7, 151.7, 164.4, 188.5; IR (KBr): 2845, 1741, 1694, 1603, 1592, 1484, 1456, 1398, 1264, 1212, 1171, 1089, 1067, 845, 748 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9ClO_3$ (MH^+) 261.0313; found 261.0301.



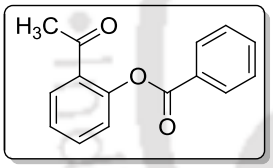
2-Formyl-6-methoxyphenyl benzoate (2a): White solid; M. P. 92–94 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.81 (s, 3H), 7.23 (d, 1H, *J* = 8.0 Hz), 7.35 (t, 1H, *J* = 8.0 Hz), 7.52 (t, 3H, *J* = 8.0 Hz), 7.62–7.67 (m, 1H), 8.23 (d, 2H, *J* = 8.0 Hz), 10.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 56.4, 118.0, 120.6, 126.9, 128.7, 128.8, 129.6, 130.5, 134.0, 142.2, 152.0, 164.5, 188.6; IR (KBr): 3075, 2946, 2845, 2771, 1728, 1697, 1600, 1582, 1482, 1452, 1439, 1318, 1252, 1195, 1172, 1087, 1057, 1023, 829, 786, 727, 706 cm^{-1}; Anal. calcd for $C_{15}H_{12}O_4$: C 70.31, H 4.72; found C 70.36, H 4.65.



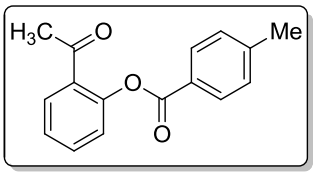
2-Formyl-6-methoxyphenyl 4-metylbenzoate (2b): White solid; M. P. 155–157 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 3.85 (s, 3H), 7.25 (d, 1H, *J* = 8.0 Hz), 7.33–7.38 (m, 3H), 7.52 (d, 1H, *J* = 8.0 Hz), 8.13 (d, 2H, *J* = 8.0 Hz), 10.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 56.5, 118.1, 120.5, 125.9, 126.9, 129.6, 129.7, 130.7, 142.6, 145.0, 152.1, 164.7, 188.7; IR (KBr): 3013, 2944, 2844, 2767, 1730, 1696, 1610, 1583, 1508, 1482, 1459, 1438, 1274, 1261, 1249, 1197, 1174, 1084, 1061, 910, 779, 687 cm^{-1}; Anal. calcd for $C_{16}H_{14}O_4$: C 71.10, H 5.22; found C 71.02, H 5.15.



1-Formylnaphthalen-2yl 4-methylbenzoate (3b): White solid; M. P. 144–146 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.29 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 8.8 Hz), 7.50 (t, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 7.2 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 8.05 (d, 1H, *J* = 8.8 Hz), 8.11 (d, 2H, *J* = 8.4 Hz), 9.20 (d, 1H, *J* = 8.8 Hz), 10.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 121.8, 121.9, 125.5, 125.8, 126.7, 128.5, 129.7, 130.5, 131.1, 131.8, 136.5, 145.4, 155.5, 165.1, 190.3; IR (KBr): 2920, 2869, 2773, 1735, 1686, 1611, 1461, 1373, 1270, 1261, 1205, 1079, 1017, 857, 795, 770, 739, 683 cm^{-1}; Anal. calcd for $C_{19}H_{14}O_3$: C 78.61, H 4.86; found C 78.65, H 4.88.

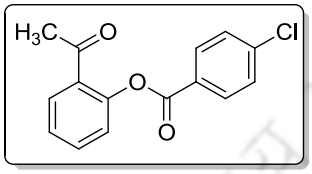


2-Acetylphenyl benzoate (4a): Yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 7.16 (d, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 8.0 Hz), 7.43–7.53 (m, 3H), 7.58 (t, 1H, *J* = 8.0 Hz), 7.78 (d, 1H, *J* = 8.0 Hz), 8.13 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.9, 124.1, 126.4, 128.9, 129.4, 130.4, 130.5, 131.5, 133.6, 134.0, 149.6, 165.3, 197.8; IR (KBr): 2962, 1736, 1687, 1653, 1602, 1481, 1448, 1357, 1267, 1201, 1118, 1060, 1023, 759, 737, 706 cm^{-1}; Anal. calcd for $C_{15}H_{12}O_3$: C 74.99, H 5.03; found C 74.91, H 5.09.

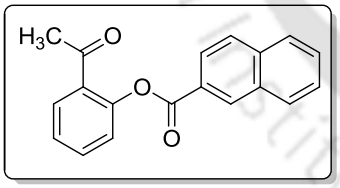


2-Acetylphenyl 4-methylbenzoate (4b): White solid; M. P. 106–108 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 2.51 (s, 3H), 7.20 (d, 1H, *J* = 8.0 Hz), 7.29–7.34 (m, 3H), 7.55 (t, 1H, *J* = 7.6 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 8.09 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):

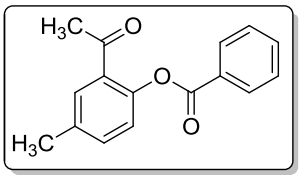
δ (ppm) 21.8, 29.9, 124.0, 126.2, 126.6, 129.5, 130.3, 130.4, 131.5, 133.4, 144.8, 149.6, 165.2, 197.7; IR (KBr): 3063, 3032, 2921, 1738, 1680, 1575, 1484, 1451,1401, 1355, 1314, 1268, 1201, 1176, 1077, 1058, 1023, 898, 876, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}O_3$ (MH^+) 255.1016; found 255.1011.



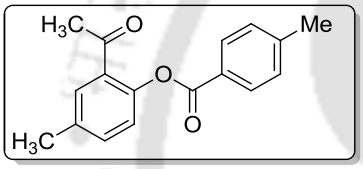
2-Acetylphenyl 4-chlorobenaoate (4c): Gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.54 (s, 3H), 7.25 (t, 1H, *J* = 4 0 Hz), 7.39 (t, 1H, *J* = 4 0 Hz), 7.50 (d, 2H, *J* = 4 0 Hz), 7.60 (t, 1H, *J* = 4 0 Hz), 8.07 (d, 1H, *J* = 4 0 Hz), 8.14 (d, 2H, *J* = 4 0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO d_6): δ (ppm) 28.6, 122.9, 125.5, 126.8, 127.6, 128.1, 128.5, 130.7, 130.9, 139.1, 148.1, 163.3, 196.3; IR (KBr): 3071, 2925, 2851, 1739, 1687, 1593, 1487, 1448, 1400, 1357, 1263, 1199, 1172, 1089, 1069, 1013, 846, 751 cm^{-1}; Anal. calcd for $C_{15}H_{11}ClO_3$: C 65.58, H 4.04; found C 65.51, H 4.09.



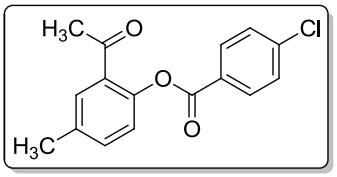
2-Acetylphenyl 2-naphthoate (4f): Gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 7.27 (d, 1H, *J* = 8 4 Hz), 7.35 (t, 1H, *J* = 7 6 Hz), 7.54–7.63 (m, 3H), 7.85–7.95 (m, 4H), 8.19 (d, 1H, *J* = 8 4 Hz), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.9, 124.1, 125.6, 126.3, 126.6, 127.0, 127.9, 128.7, 128.9, 129.7, 130.4, 131.5, 132.4, 132.7, 133.6, 136.1, 149.6, 165.5, 197.8; IR (KBr): 3060, 2925, 2851, 1736, 1687, 1603, 1481, 1447, 1356, 1281, 1227, 1187, 1156, 1128, 1072, 950, 910. 868, 774, 733 cm^{-1}; Anal. calcd for $C_{19}H_{14}O_3$: C 78.61, H 4.86; found C 78.69, H 4.81.



2-Acetyl-4-metylphenyl benzoate (5a): White solid; M. P. 65–67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 2.48 (s, 3H), 7.08 (d, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.47, (t, 2H, *J* = 7.6 Hz), 7.59, (t, 1H, *J* = 7.6 Hz), 7.62 (s, 1H), 8.18 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.7, 29.6, 123.5, 128.6, 129.3, 130.1, 130.5, 130.8, 133.6, 133.9, 135.8, 147.1, 165.2, 197.4; IR (KBr): 3063, 3032, 3007, 2921, 1738, 1680, 1575, 1484, 1451, 1401, 1314, 1268, 1201, 1176, 1077, 1058, 1023, 961, 898, 876, 697 cm^{-1}; Anal. calcd for $C_{16}H_{14}O_3$: C 75.57, H 5.55; found C 75.62, H 5.63.

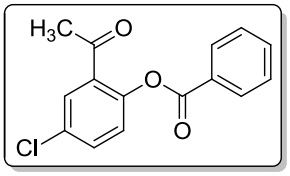


2-Acetyl-4methylphenyl 4-methylbenzoate (5b): Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.39, (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 7.09 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.33–7.36 (m, 1H), 7.62 (s, 1H), 8.08 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.9, 21.9, 30.1, 123.8, 126.7, 129.6, 130.5, 130.7, 131.2, 134.1, 136.0, 144.8, 147.5, 165.5, 197.9; IR (KBr): 3063, 3032, 3007, 2921, 1735, 1682, 1572, 1482, 1454, 1406, 1312, 1262, 1207, 1172, 1075, 1052, 1020, 966, 894, 873, 797 cm^{-1}; Anal. calcd for $C_{17}H_{16}O_3$: C 76.10, H 6.01; found C 76.15, H 6.08.

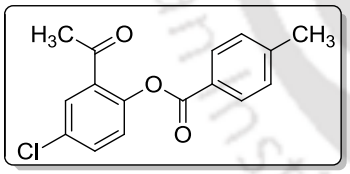


2-Acetyl-4-methylphenyl 4-chlorobenzoate (5c): White solid; M. P. 86–88 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.41 (s, 3H), 2.50 (s, 3H), 7.08 (d, 1H, *J* = 4.0 Hz), 7.35–7.38 (m, 1H), 7.47 (d, 2H, *J* = 4.0 Hz), 7.64 (s, 1H), 8.12 (d, 2H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO d_6): δ (ppm) 20.8, 29.5, 123.6, 128.9, 130.4, 130.7,

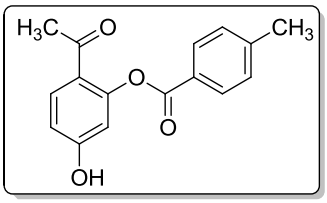
131.2, 131.6, 131.9, 134.1, 140.1, 146.8, 164.5, 197.5; IR (KBr): 2923, 2846, 1735, 1675, 1592, 1491, 1399, 1351, 1264, 1194, 1171, 1072, 1011, 842, 747, cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}ClO_3$ (MH^+) 289.0626; found 289.0622.



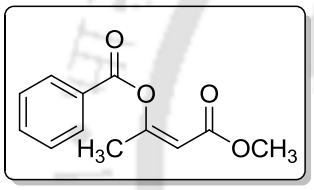
2-Acetyl-4-chlorophenyl benzoate (6a): White solid; M. P. 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.48–7.52 (m, 3H), 7.64 (t, 1H, *J* = 7.6 Hz), 7.79 (d, 1H, *J* = 2.4 Hz), 8.18 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.8, 125.5, 128.8, 128.9, 130.0, 130.4, 131.8, 132.6, 133.1, 134.1, 147.9, 164.9, 196.2; IR (KBr): 3071, 2925, 2859, 1746, 1694, 1599, 1472, 1451, 1395, 1314, 1261, 1203, 1099, 1052, 1022, 1001, 876, 854, 704, 680 cm^{-1}; Anal. calcd for $C_{15}H_{11}ClO_3$: C 65.58, H 4.04; found C 65.52, H 4.01.



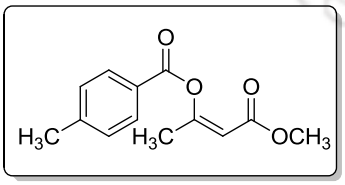
2-Acetyl-4-chlorophenyl 4-methylbenzoate (6b): White solid; M. P. 89–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 2.50 (s, 3H), 7.16 (d, 1H, *J* = 8.8 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.8 Hz), 7.79 (d, 1H, *J* = 2.4 Hz), 8.06 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 30.1, 125.6, 126.3, 129.8, 130.1, 130.6, 131.9, 132.9, 133.3, 145.3, 148.1, 165.1, 196.5; IR (KBr): 3088, 2924, 2854, 1741, 1678, 1654, 1611, 1592, 1493, 1469, 1397, 1355, 1299, 1260, 1194, 1176, 1057, 873, 852, 793, 740,662 cm^{-1}; Anal. calcd for $C_{16}H_{13}ClO_3$: C 66.56, H 4.54; found C 66.51, H 4.62.



2-Acetyl-5-hydroxy 4-methylbenzoate (7b): Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 2.63 (s, 3H), 6.80 (d, 2H, *J* = 7.6 Hz), 6.86 (s, 1H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 8.8 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 12.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 26.9, 111.5, 113.3, 117.9, 126.4, 126.8, 129.4, 129.6, 130.4, 130.5, 132.1, 144.8, 145.1, 157.3, 164.2, 203.8; IR (KBr): 3441, 2923, 2857, 1734, 1639, 1495, 1418, 1363, 1294, 1264, 1248, 1157, 1134, 1075, 982, 740 cm^{-1}; Anal. calcd for $C_{16}H_{14}O_4$: C 71.10, H 5.22; found C 71.15, H 5.28.

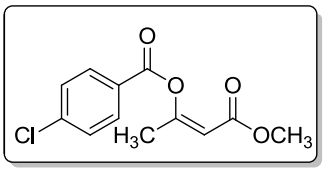


(Z)-4-Methoxy-4-oxobut-2-en-2-yl benzoate (8a): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 2.13 (s, 3H), 3.58 (s, 3H), 5.68 (s, 1H), 7.47 (t, 2H, *J* = 8.0 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 8.1 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 51.4, 108.5, 128.7, 129.5, 130.4, 133.7, 160.6, 163.9, 164.3; IR (KBr): 2951, 1731, 1677, 1612, 1439, 1379, 1271, 1202, 1175, 1145, 1077, 1046, 1019, 922, 832, 743, 685 cm^{-1}; Anal. calcd for $C_{12}H_{12}O_4$: C 65.45, H 5.49; found C 65.37, H 5.39.

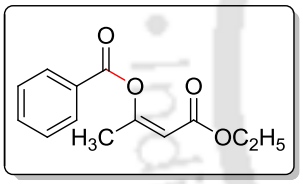


(Z)-4-Methoxy-4-oxobut-2-en-2yl 4-methylbenzoate (8b): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 2.14 (s, 3H), 2.42 (s, 3H), 3.59 (s, 3H), 5.69 (s, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 51.3, 108.3, 126.6, 129.4, 130.4, 144.5, 160.7, 163.8, 164.2; IR (KBr): 2950, 2928, 1727, 1673, 1651, 1437, 1380, 1286, 1251,

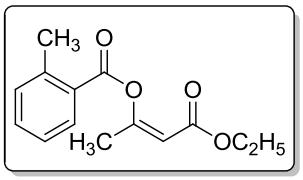
1198, 1141, 1133, 1050, 1042, 736 cm^{-1}; Anal. calcd for $C_{13}H_{14}O_4$: C 66.66, H 6.02; found C 66.73, H 6.09.



(Z)-4-Methoxy-4-oxobut-2-en-2-yl 4-chlorobenzoate (8c): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 2.11 (s, 3H), 3.57 (s, 3H), 5.68 (s, 1H), 7.42 (d, 2H, *J* = 8.8 Hz), 8.02 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 51.4, 108.5, 127.9, 129.1, 131.8, 140.2, 160.5, 163.0, 164.2; IR (KBr): 2952, 2851, 1729, 1680, 1594, 1487, 1441, 1401,1380, 1269, 1203, 1171, 1145, 1077, 1046, 1014, 876, 846, 830, 749, 678 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{11}ClO_4$ (MH^+) 255.0419; found 255.0411.

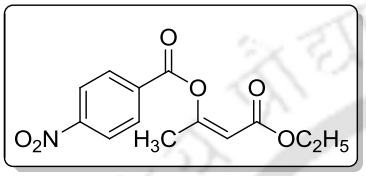


(Z)-4-Ethoxy-4-oxobut-2-en-2-yl benzoate (9a): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 1.07 (t, 3H, *J* = 7.2 Hz), 2.11 (s, 3H), 4.03 (q, 2H, *J* = 7.2 Hz), 5.66 (s, 1H), 7.45 (t, 2H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 8.09 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 21.9, 60.2, 109.1, 128.7, 129.4, 130.4, 133.7, 160.1, 163.8, 163.9; IR (KBr): 2982, 1743, 1722, 1577, 1437, 1382, 1283, 1251, 1193, 1132, 1042, 732, 668 cm^{-1}; Anal. calcd for $C_{13}H_{14}O_4$: C 66.66, H 6.02; found C 66.79, H 6.12.

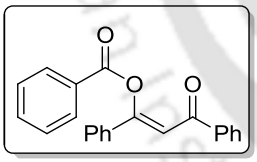


(Z)-4-Ethoxy-4-oxobut-2-en-2-yl 2-methylbenzoate (9d): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15 (t, 3H, *J* = 7.2 Hz), 2.13 (s, 3H), 2.64 (s, 3H), 4.08 (q, 2H, *J* = 7.2 Hz), 5.69 (s, 1H), 7.29 (t, 2H, *J* = 8.0 Hz), 7.43 (t, 1H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 8.0 Hz); ^{13}C

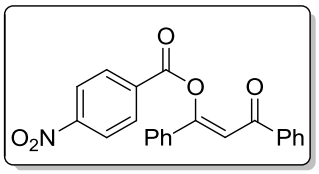
NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 21.9, 22.0, 60.3, 108.9, 126.1, 128.4, 131.6, 131.9, 132.9, 141.5, 160.1, 164.0, 164.2; IR (KBr): 2980, 1741, 1723, 1575, 1439, 1380, 1287, 1252, 1195, 1134, 1044, 735, 666 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}O_4$ (MH^+) 249.1121; found 249.1129.



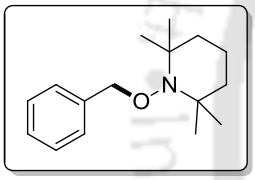
(Z)-4-Ethoxy-4-oxobut-2-en-2-yl 4-nitrobenzoate (9e): Yellow gummy; ^1H NMR (400 MHz, $CDCl_3$):δ (ppm) 1.13 (t, 3H, *J* = 7.2 Hz), 2.15 (s, 3H), 4.04 (q, 1H, *J* = 7.2 Hz), 5.71 (s, 1H), 8.29 (d, 4H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 21.7, 60.4, 109.2, 123.9, 131.6, 135.0, 151.0, 159.7, 162.1, 163.7; IR (KBr): 3113, 2963, 1747, 1719, 1672, 1529, 1440, 1351, 1319, 1266, 1199, 1172, 1143, 1086, 1046, 1014, 870, 799, 740 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{13}NO_6$ (MH^+) 280.0816; found 280.0822.



(Z)-3-Oxo-1,3-diphenylprop-1-en-1-yl benzoate (10a): Colourless liquid; ^1H NMR (400 MHz, $CDCl_3$):δ (ppm) 7.34 (s, 1H), 7.44 (t, 5H, *J* = 7.2Hz), 7.50 (t, 4H, *J* = 7.2 Hz), 7.63 (t, 1H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 7.2 Hz), 7.95 (d, 1H, *J* = 7.2 Hz), 8.18 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 110.1, 126.4, 128.4, 128.7, 128.8, 128.9, 129.1, 129.3, 130.6, 131.3, 132.9, 133.8, 134.1, 157.4, 164.0, 188.5; IR (KBr): 3054, 2923, 1740, 1660, 1600, 1489, 1449, 1355, 1237, 1209, 1174, 1089, 1064, 1037, 1017, 757, 699, 680 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{16}O_3$ (MH^+) 329.1172; found 329.1177.



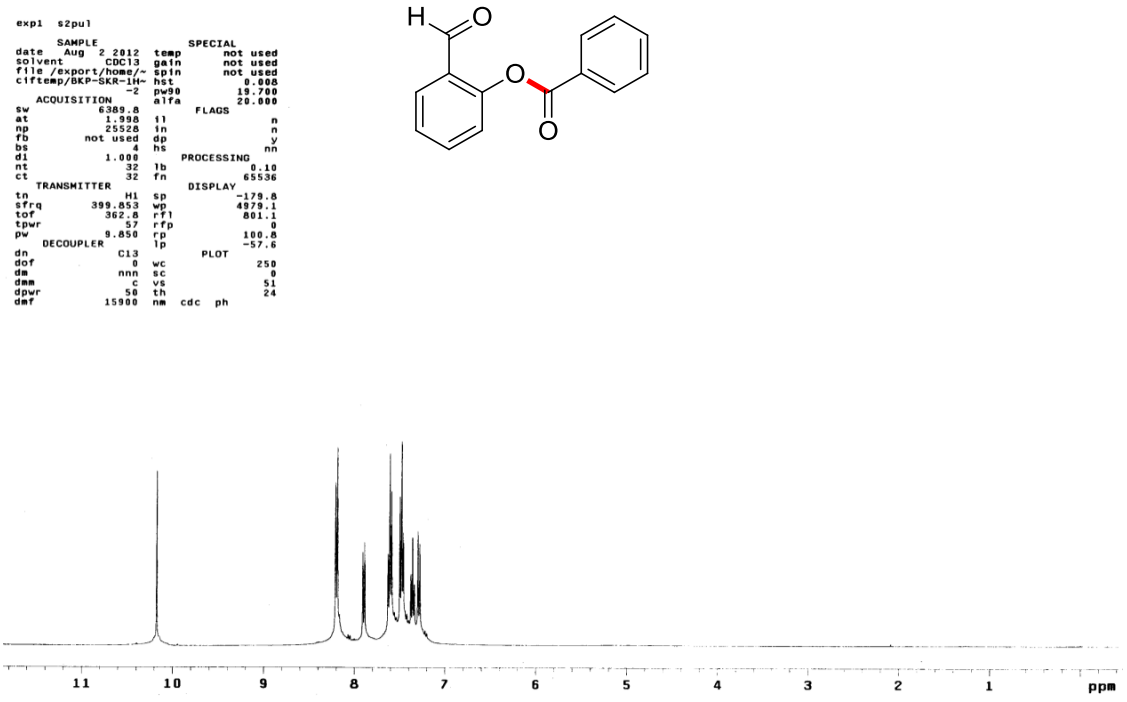
(Z)-3-Oxo-1,3-diphenylprop-1-en-1-yl 4-nitrobenzoate (10e): Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (s, 1H), 7.39-7.51 (m, 6H), 7.61 (t, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 4.8 Hz), 7.95 (d, 2H, *J* = 4.8 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 8.18 (d, 1H, *J* = 7.8 Hz), 8.34 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 110.1, 123.9, 124.4, 126.3, 128.3, 128.7, 129.1, 129.3, 130.5, 130.6, 132.8, 133.8, 150.2, 157.3, 164.0, 190.5; IR (KBr): 3062, 2851, 1744, 1664, 1602, 1575, 1528, 1345, 1233, 1086, 1066, 758, 702 cm^{-1}; Anal. calcd for $C_{22}H_{15}NO_5$: C 70.77, H 4.05, N 3.75; found C 70.79, H 4.12, N 3.68.



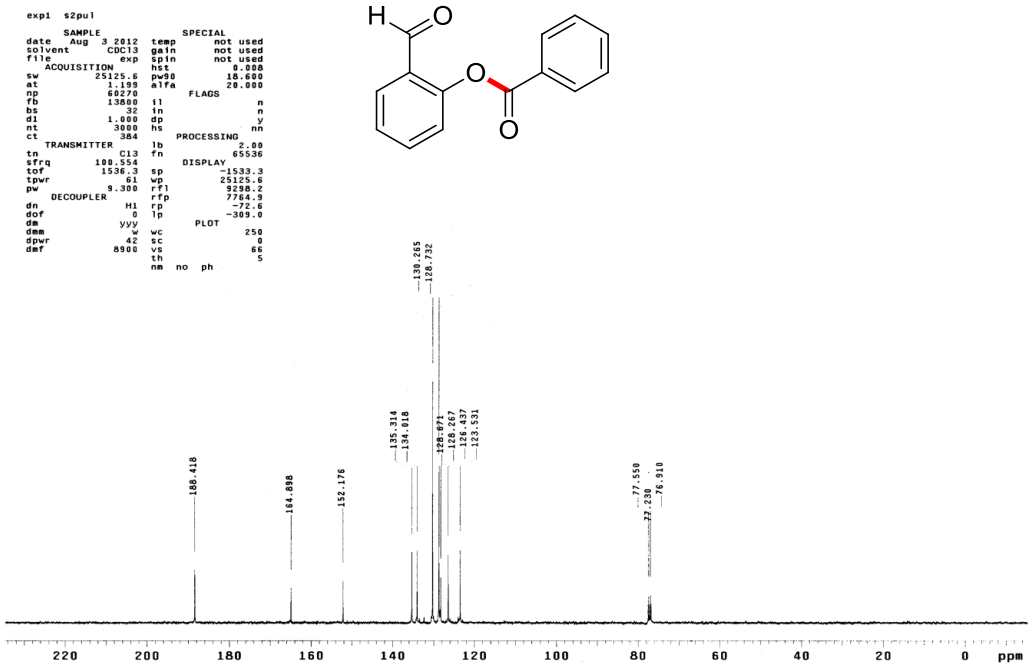
1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (F): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (s, 6H), 1.26 (s, 6H), 1.49–1.70 (m, 6H), 4.87 (s, 2H), 7.27–7.83 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.3, 20.4, 33.2, 39.9, 60.1, 78.9, 127.4, 127.6, 128.3, 138.4; HRMS (ESI): calcd. for $C_{16}H_{25}NO$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

III.7. Spectra

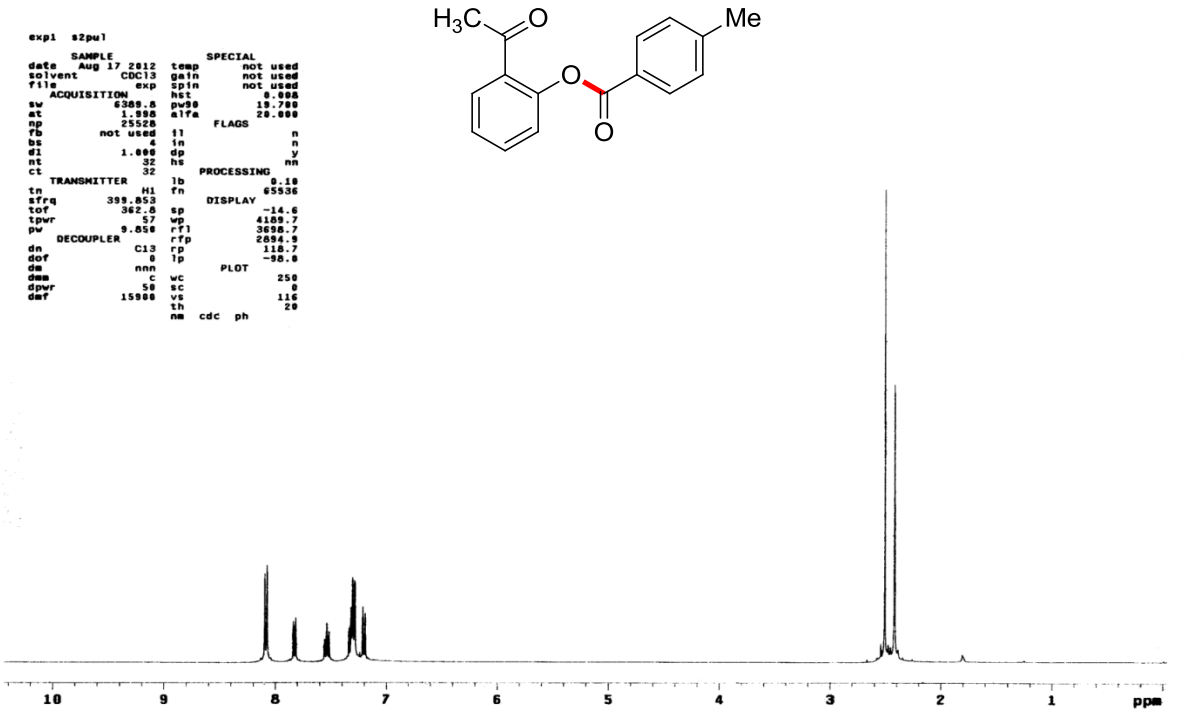
2-Formylphenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



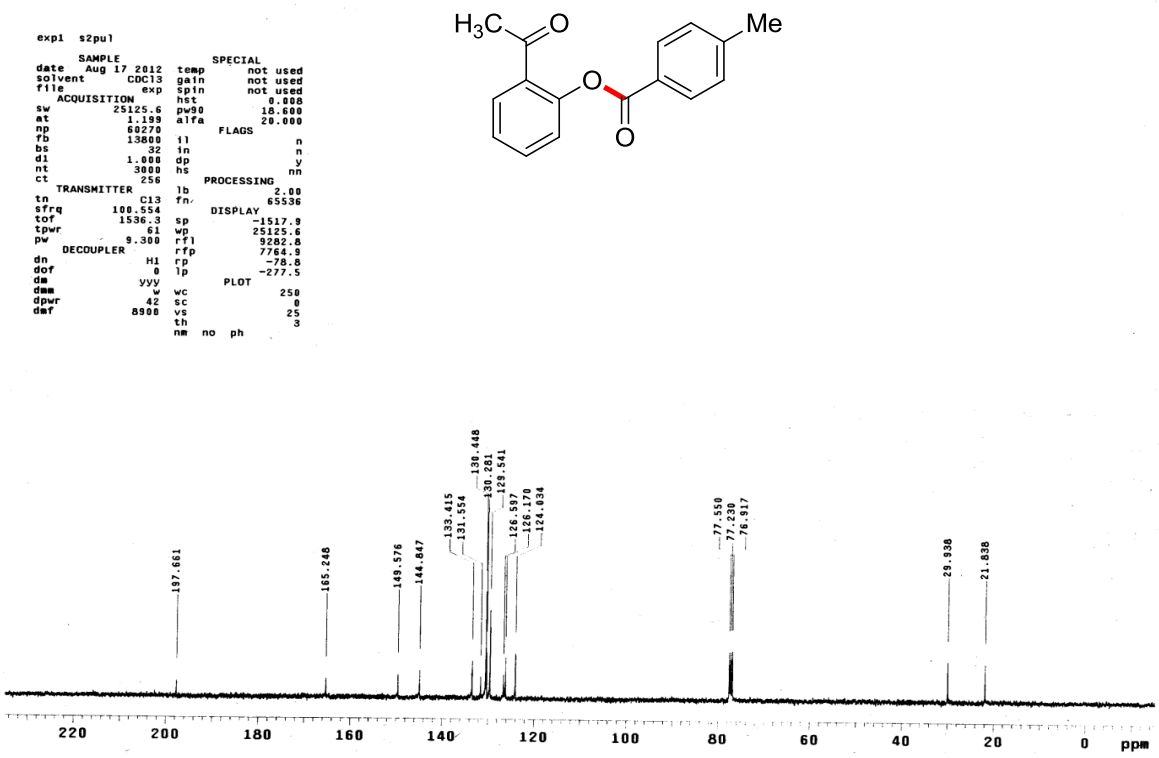
2-Formylphenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



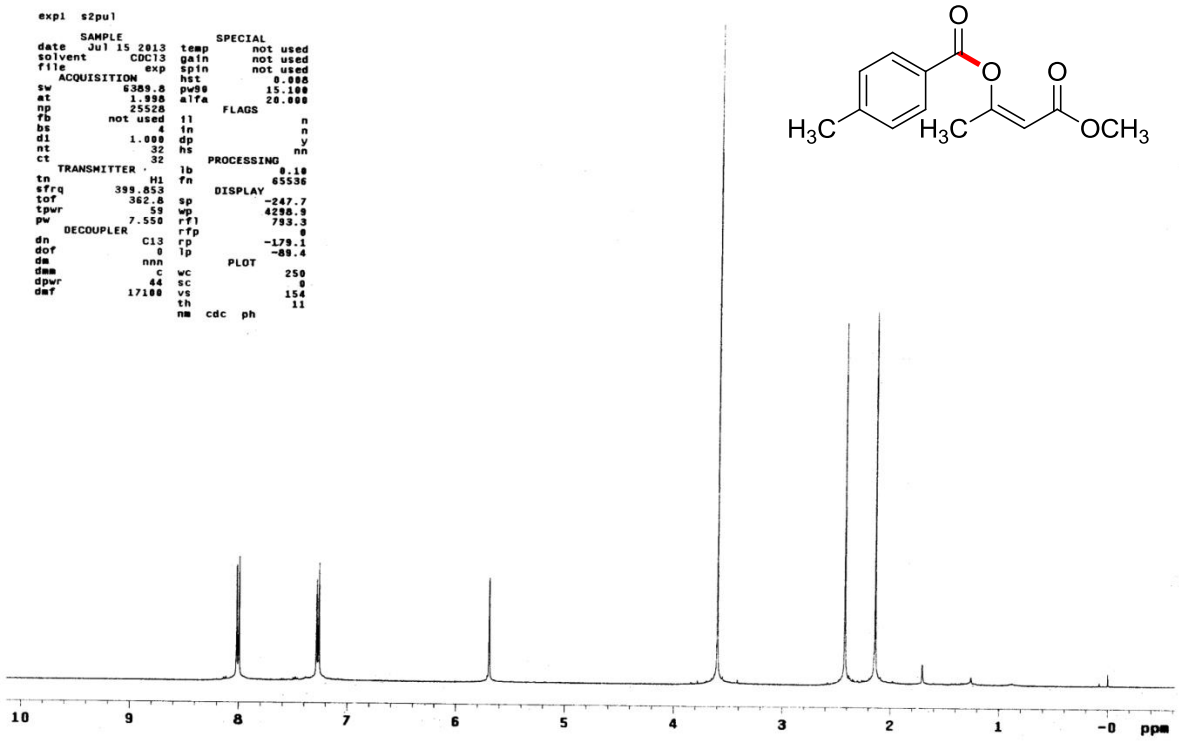
2-Acetylphenyl 4-methylbenzoate (4b): ^{1}H NMR (400 MHz, $CDCl_3$)



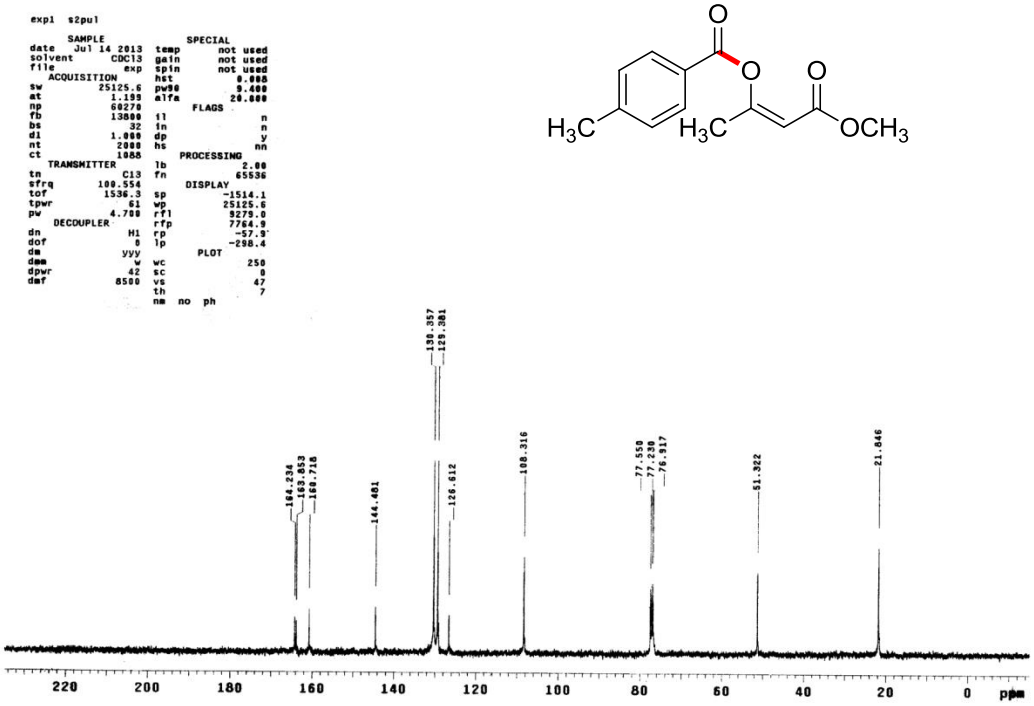
2-Acetylphenyl 4-methylbenzoate (4b): ^{13}C NMR (100 MHz, $CDCl_3$)



(Z)-4-Methoxy-4-oxobut-2-en-2yl 4-methylbenzoate (8b): ^{1}H NMR (400 MHz, $CDCl_3$)



(Z)-4-Methoxy-4-oxobut-2-en-2yl 4-methylbenzoate (8b): ^{13}C NMR (100 MHz, $CDCl_3$)



भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
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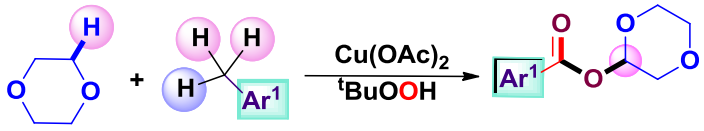
Chapter IV

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



Abstract*: *The present protocol demonstrates a copper catalyzed synthesis of esters from simple solvents. The combination of methylarenes and cyclic ethers result in the formation of α-esterification via four sp^3 C–H cleavages. A regioselective esterification was achieved in case of 1,3-dioxolane. Various mechanistic investigations carried out provide insights into the mechanism for this transformation.

CHAPTER IV

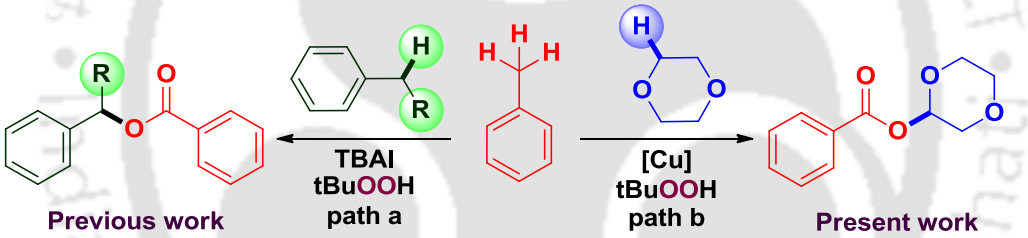
IV. A Copper Catalyzed Esterification of Alkylbenzenes with Cyclic Ethers via C(sp^3)–H Activation Following Cross-Dehydrogenative Coupling (CDC)

IV.1. Introduction

The direct C–H activation path has streamlined the synthesis of functionalized molecules by minimizing the number of synthetic steps and 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.[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 functionalizations via CDC, the alkylbenzenes are found to be useful precursors and have enacted as ArCOO–, ArCO–, $ArCH_2O$– and $ArCH_2$– surrogates;[3] most of which have ultimately led to the synthesis of esters.[3a-d]

Esters are important building blocks in organic synthesis so the most revisited strategies are the one where the installation of ester C–O bond is via C–H activation.[3a-d,4] Hence, synthesis 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 IV.1.1).[3a] In this protocol, one half of alkylbenzene serves as the nucleophile ($ArCOO^-$) while the remaining half behave as electrophile ($ArCH_2^+$) leading to the formation of benzylic ester The most 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. In pursuit to utilize this "solvent chemistry" in a CDC reaction, cyclic ether (1,4-dioxane) was attempted as a potential coupling partner with alkylbenzenes. Cyclic ethers are widely used as solvents and are also amenable to functionalizations at the sp^3 C–H α to ethereal oxygen.[5] A relatively weak bond dissociation energy of α sp^3 C–H helps to generate a radical center under oxidative conditions thereby allowing a radical/nucleophile to attack at that position.[1a,6] So it would be interesting to see if these two solvents (alkylbenzene and cyclic ether) undergo cross coupling to afford ester under reaction conditions similar to our previous report on benzyl ester synthesis (path a, Scheme IV.1.1).[3a] Although not under metal free conditions, but the use of copper catalyst and a radical initiator led to the formation of the desired α-acyloxy ether (path-b, Scheme IV.1.1). Noteworthy to mention the present method on synthesis of α-acyloxy ether with a higher degree of C–H activation (four sp^3 C–H cleavages) from solvents is unprecedented (path b, Scheme IV.1.1).



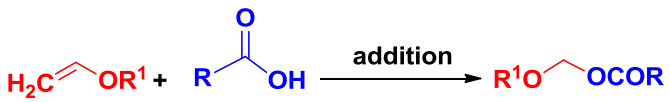
Scheme IV.1.1. *Ester synthesis via solvent-solvent couplings*

IV.2. Strategies for the synthesis of α-acyloxy ether

α-Acyloxy ethers appear frequently as a structural unit[7] in biological and medicinal molecules of interest and are also useful synthetic intermediates[8] in organic synthesis. Existing methods to α-acyloxy ethers can be broadly classified into five main categories; (i) addition of a carboxylic acid to an alkenyl ether, (ii) α-halo substitution of an ether with a carboxylic acid, (iii) treatment of a hemiacetal with an acid or its derivatives, (iv) CDC reaction between a carboxylic acid and an ether and (v) miscellaneous methods comprising of two-step synthesis.

(i) Addition of a carboxylic acid to an alkenyl ether

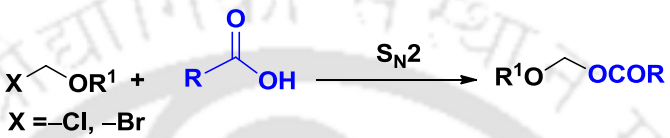
In these process carboxylic acids adds across the double bond of alkenyl ether under heating condition to provide their corresponding α-acyloxy ethers (Scheme IV.2.1).[9]



Scheme IV.2.1. *Classical methods for the synthesis of α-acyloxy ether*

(ii) α-Halo substitution of an ether with a carboxylic acid

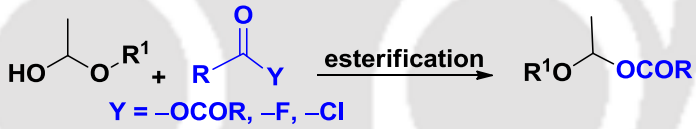
Nucleophlic substitution (via S_N2 path) of the α-halo ether with carboxylic acids in the presence of a suitable base provides α-acyloxy ethers (Scheme IV.2.2).[10]



Scheme IV.2.2. *Synthesis of α-acyloxy ether via S_N2 path*

(iii) Treatment of a hemiacetal with an acid or its derivatives

Traditional synthesis of α-acyloxy ethers can be achieved upon reaction of preactivated acid derivatives, such as acyl halides and esters, with hemiacetals in the presence of a stoichiometric amount of bases (Scheme IV.2.3).[7b,11]

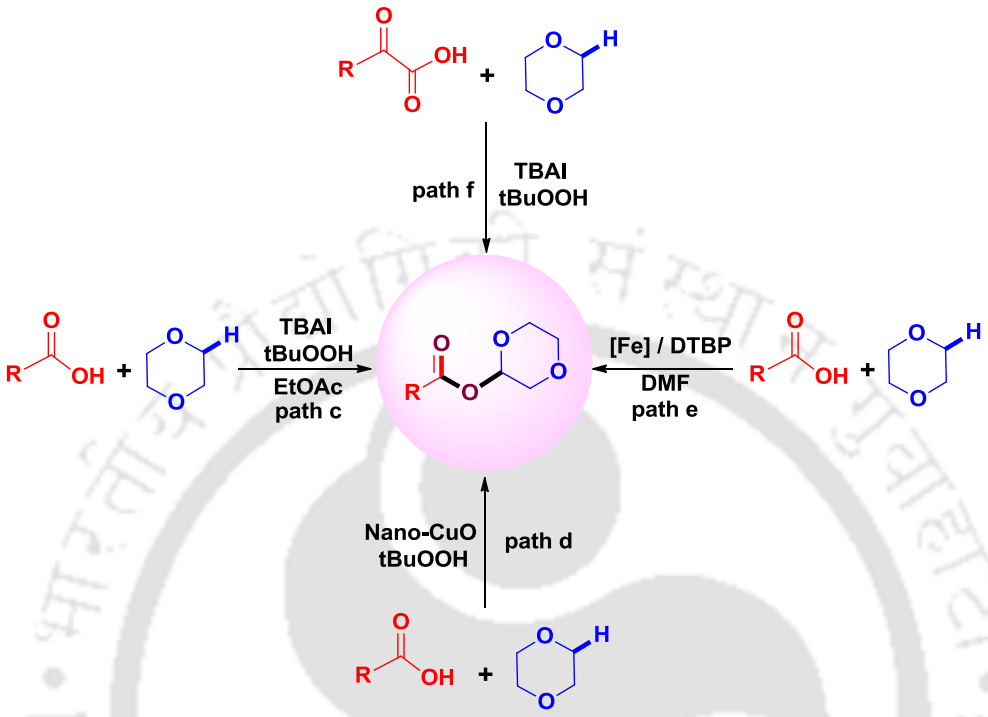


Scheme IV.2.3. *Reaction of hemiacetal with acid derivatives*

(iv) (a) CDC reaction between acids and an ethers

Wan *et al.* reported a simple and efficient method to construct α-acyloxy ethers from ethers and carboxylic acids using Bu_4NI as a catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (path c, Scheme IV.2.4).[12] Lakshmi Kantam group reported a similar protocol for the synthesis of α-acyloxy ethers using combination of CuO nanoparticles and TBHP (path d, Scheme IV.2.4).[13] The same α esterification of cyclic ethers with carboxylic acids via unreactive C(sp^3)–H bond functionalization was achieved by Pan group with an iron salt as catalyst and di-tert-butyl peroxide (DTBP) as the oxidant (path e, Scheme IV.2.4).[14] Recently, Duan group also demonstrated the acyloxylation at the α

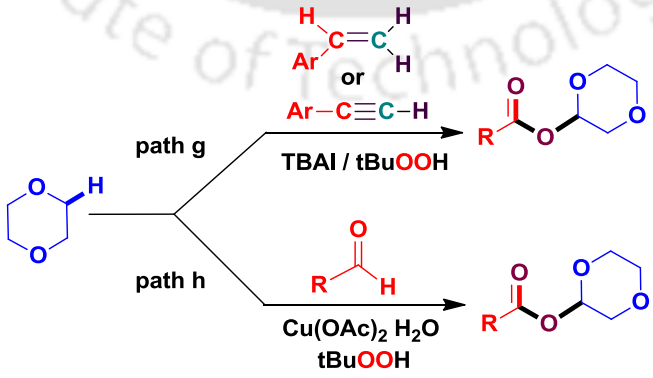
C(sp^3)–H bond of ethers with α-oxocarboxylic acids as the acyloxy source under metal-free conditions (path f, Scheme IV.2.4).[15]



Scheme IV.2.4. *CDC strategy for the synthesis of α-acyloxy ether*

(b) CDC reaction between terminal alkene/alkyne and an ethers

Our group very recently developed an efficient metal free oxidative esterification of sp^3 C–H bonds (adjacent to an oxygen atom) in simple solvents like 1,4-dioxane, tetarhydropyran, tetrahydrofuran using terminal aryl alkenes and alkynes as ArCOO– sources (path g, Scheme IV.2.5).[16]



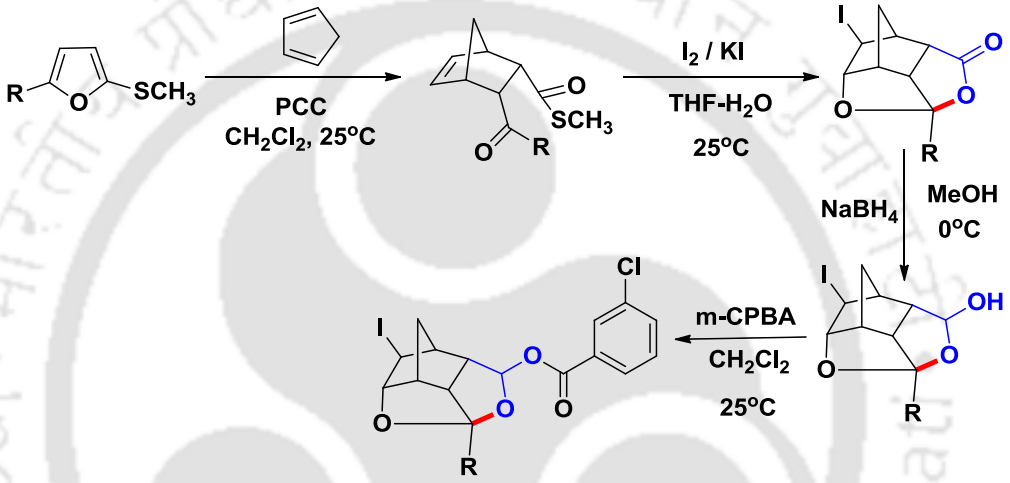
Scheme IV.2.5. *CDC strategy for the synthesis of α-acyloxy ether*

(c) CDC reaction between aldehyde and an ethers

Yuan group developed convenient and efficient protocol for the Cu-catalyzed synthesis of α-acyloxy ethers *via* oxidative cross-coupling reaction of aldehydes and ethers (path h, Scheme IV.2.5).[17]

(v) Miscellaneous methods comprising of two-step synthesis.

Synthesis of diacetal trioxa-cage compounds via a sequential cyclization reaction of norbornene derivatives using known standard reaction conditions (Scheme IV.2.6).[18]



Scheme IV.2.6. *Miscellaneous methods*

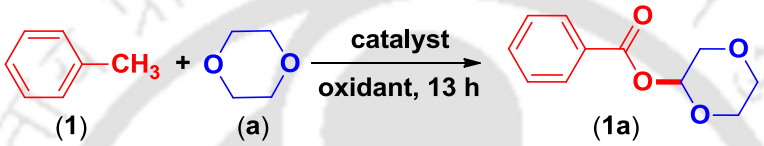
IV.3. Present Work

Although a great number of methodologies appear in literature on the transition metal/metal free catalyzed oxidative esterification of ethers, but the present solvent-solvent (methylarene-dioxane) couplings to give α-acyloxy ether via four sp^3 C–H activations using copper catalyst is novel and unique.

Optimization of reaction conditions. As mentioned above our envisioned route aimed towards the synthesis of α-acyloxy ethers by solvent-solvent coupling in a CDC reaction. To give a practical shape to the above mentioned concept, toluene (**1**) and 1,4-dioxane (**a**) were allowed to react under conditions similar to the coupling between alkylbenzene(s).[3a] However the attempt to achieve the desired cross coupling was not so fruitful as the reaction gave predominantly benzylbenzoate obtained by the self coupling of toluene along

with a trace (<10%) of the desired α-acyloxy ether (**1a**) (Table IV.3.1, entry 1). Hence for the exclusive formation of α-acyloxy ether it was necessary to avoid the competing self coupling between toluene by changing the reaction conditions. During self coupling of alkylbenzene the use of Cu(II)/TBHP combination instead of metal free conditions (Bu_4NI/TBHP) was unproductive. Interestingly, in the present case the use of Cu(II)/TBHP changed the course of the reaction giving the desired cross coupled ester (**1a**) exclusively without any trace of benzylbenzoate (Table IV.3.1, entry 2).

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



(**1**) (**a**) (**1a**)

Entry	Catalyst (mol %)	Oxidant (equiv.)	Temp ^oC	Yield (%)[b]
1	TBAI (10)	aq.TBHP (6)	80	<10
2	$Cu(OAc)_2$ (10)	aq.TBHP (6)	80	63
3	CuBr (10)	aq.TBHP (6)	80	27
4	CuCl (10)	aq.TBHP (6)	80	41
5	CuI (10)	aq.TBHP (6)	80	26
6	$CuBr_2$ (10)	aq.TBHP (6)	80	24
7	$CuCl_2$ (10)	aq.TBHP (6)	80	38
8	$Cu(OTf)_2$ (10)	aq.TBHP (6)	80	00
9	**$Cu(OAc)_2$ (20)**	**aq.TBHP (6)**	**80**	**71**
10	$Cu(OAc)_2$ (30)	aq.TBHP (6)	80	73
11	$Cu(OAc)_2$ (20)	aq.TBHP (7)	80	73
12	$Cu(OAc)_2$ (20)	aq.TBHP (6)	100	63
13	$Cu(OAc)_2$ (20)	dec.TBHP (6)	80	55
14	Nil	aq.TBHP (6)	80	00
15	$Cu(OAc)_2$ (20)	Nil	80	00

[a]Catalyst and oxidants were for 1 mmol of substrates. [b]Isolated yield.

Buoyant by this unique α-esterification of ether originating from solvent-solvent coupling other Cu catalysts were examined in a quest to improve the yield. Among all the other Cu(I) [CuBr, CuCl, and CuI] (Table IV.3.1, entries 3–5) and Cu(II) [$CuBr_2$, $CuCl_2$, and $Cu(OTf)_2$] salts (Table IV.3.1, entries 6–8) tested, $Cu(OAc)_2$ was found to be the best (entry 2, Table IV.3.1). By increasing the $Cu(OAc)_2$ quantity from 10 to 20 mol % the yield improved from 63% to 71% (Table IV.3.1, entry 9). No significant improvement in

the product yield was observed with 30 mol % of the catalyst (Table IV.3.1, entry 10). Even increasing the oxidant quantity from 6 to 7 equiv the yield could not be enhanced further (Table IV.3.1, entry 11). Unexpectedly the yield decreased when the reaction was performed at 100 ^{o}C instead of 80 ^{o}C (Table IV.3.1, entry 12). The use of a decane solution of TBHP (5–6 M) (Table IV.3.1, entry 13) was found to be slightly ineffective compared to its aqueous solution (70%). Control experiments suggest that a catalyst-oxidant combination is indeed essential to bring about the desired transformation (Table IV.3.1, entries 14–15).

Substrate scope for α-acyloxy ethers. Having established the standard reaction conditions, the present oxidative esterification of cyclic ether were then implemented on cross couplings between 1,4-dioxane (**a**) and a series of substituted methylarenes. As can be seen in Scheme IV.3.1, the developed methodology was applicable to a diverse methylarenes irrespective of the nature of their substituents present. In particular, methylarenes possessing electron-donating groups such as *o*-Me (**2**), *m*-Me (**3**), *p*-Me (**4**), 3,5-diMe (**5**), *o*-OMe (**6**), *p*-OMe (**7**) and 2,6-diOMe (**8**) showed higher reactivities compared to methylarene (**1**) giving their respective α-acyloxy ethers (**2a**–**8a**) in moderate to good yields. Lower yields obtained for *o*-subtituted methylarenes (**2**, **6**, **8**) compared to *p*- or *m*- analogues (**3**, **4**, **5**, **7**) could be attributed to steric hindrance imparted by the *o*-substitutents. The structure of α-acyloxy ether (**8a**) has been confirmed by crystal X–ray crystallography as shown in Figure IV.3.1.

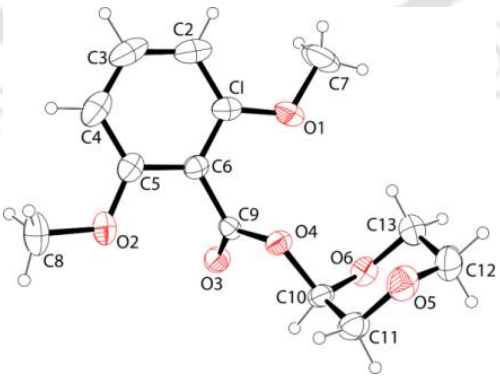
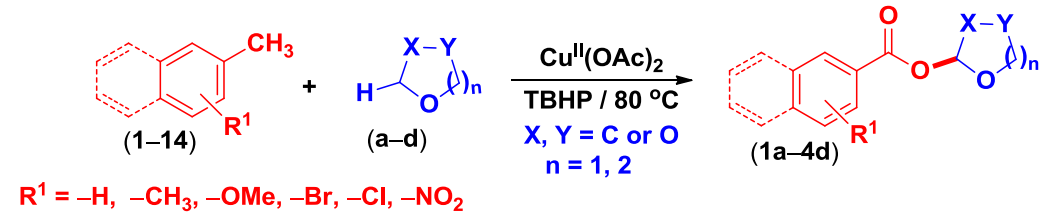
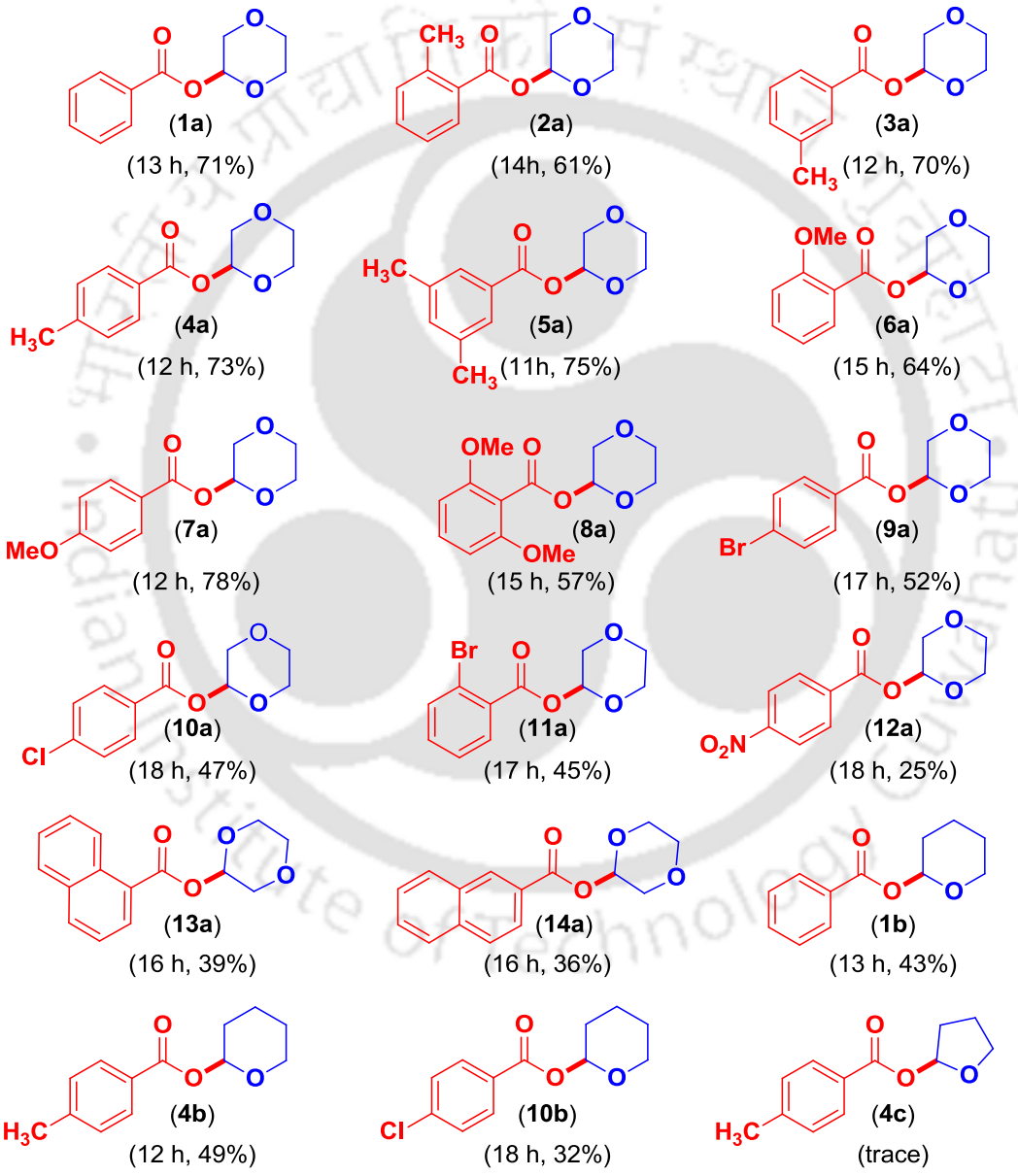


Figure IV.3.1. *1,4-Dioxan-2-yl 2,6-dimethoxybenzoate* ***(8a)***

Scheme IV.3.1. *Substrate scope of α-acyloxy ethers*[a,b,c]





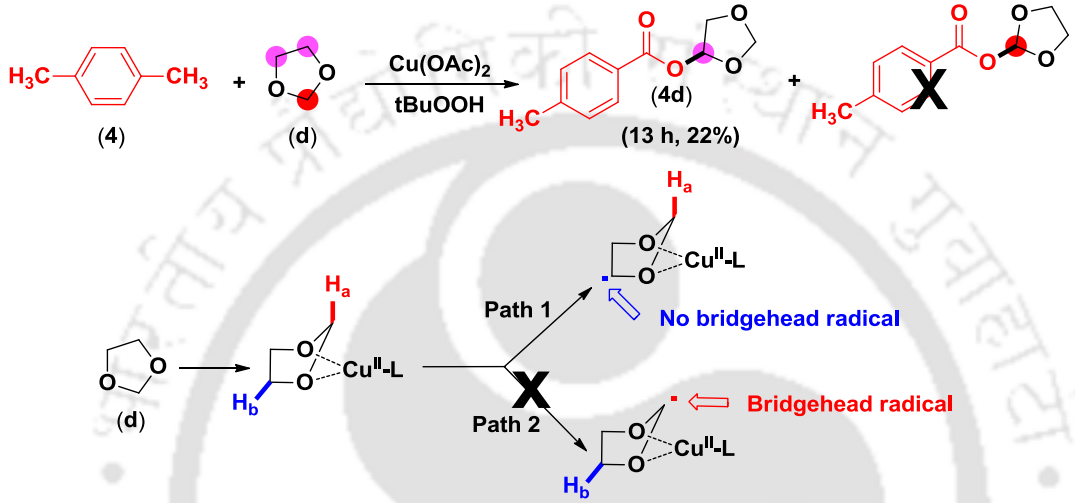
[a]Reaction conditions: **1**−**14** (5 mmol), **a–c** (2 mL), $Cu(OAc)_2$ (0.2 mmol), aq TBHP (6 mmol), temperature 80 °C. [b]Isolated yield. [c]Catalyst and oxidant were for 1 mmol of substrates.

Noteworthy, for polymethylated benzenes (**2**–**5**) one of the –Me group is functionalized while the other –Me group(s) remained intact; consistent with the earlier esterification processes with alkylbenzenes.[3a,c,d] The presence of electron-withdrawing groups in methylbenzenes such as *p*-Br (**9**) and *p*-Cl (**10**) lowered the yields of their corresponding α-acyloxy ethers (**9a**–**10a**). The yield dropped further when the electron-withdrawing substituent –Br (**11**) is present in the *o*-position which is due to steric as well as electronic factors. Alkylbenzene possessing strongly electron-withdrawing group such as *p*–NO_2 (**12**) upon reaction with (**a**) gave poor yield of α-acyloxy ether (**12a**). The fused bicyclic methylarene viz. 1-methylnaphthalene (**13**) and 2-methylnaphthalene (**14**) when coupled with (**a**) provided the desired α-acyloxy ether (**13a**) and (**14a**) in a slightly lesser yield (Scheme IV.3.1).

The successful esterification of 1,4-dioxane (**a**) with various methylarenes led us to examine the feasibility of this approach with other cyclic ethers possessing single oxygen such as tetrahydropyran (**b**) and tetrahydrofuran (**c**). Unlike in dioxane (**a**), the oxidative esterification of tetrahydropyran (**b**) with methylbenzenes (**1**, **4** and **10**) were not so effective giving α-acyloxy ethers (**1b**, **4b** and **10b**) in modest yields. Five membered cyclic ether tetrahydrofuran (**c**) when reacted with methylbenzene (**4**) gave negligible amount of α-acyloxy ether (**4c**). Lower yields obtained using tetrahydropyran (**b**) compared to 1,4-dioxane (**a**) is because in the former there are four equivalent sp^3 C–H's where as in the latter the chances are doubled due to the presence of eight equivalent C–H's. Substantial drop in the yield was observed using tetrahydrofuran (**c**) which could be due to above mentioned statistical factor as well as the instability of the desired radical intermediate. Acylic ether such as dimethoxy ethane (DME) was found to be completely inert under the reaction conditions when treated with *p*-xylene (**4**). Inspite of the favourable statistical possibilities the 18-crown-6 failed to undergo esterification which may be due to steric crowding or its fluxional nature

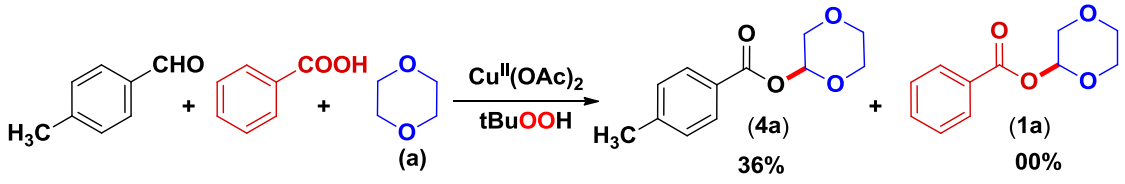
There is a possibility of two kinds of product formation in 1,3-dioxolane (**d**). Esterification can occur at ethereal carbon adjacent to a single oxygen atom or carbon present in between two oxygen atoms. However when a reaction was performed between *p*-xylene (**4**) and 1,3-dioxolane (**d**) under optimized condition exclusive formation of ester (**4d**) was observed with the former possibility (Scheme IV.3.2). The abnormal

regioselectivity of the reaction on the substrate 1,3-dioxolane (**d**) can be explained as follows. If the radical forms at the H_a position (Scheme IV.3.2), it will be a bridgehead radical, which is notoriously very difficult to form.[19] Thus, for the Cu-catalyzed radical reaction of this substrate containing two oxygen atoms, the regioselectivity is abnormal, and the reaction happens selectively at the H_b position and proceeds through path 1 to give the final products (**4d**) (Scheme IV.3.2).



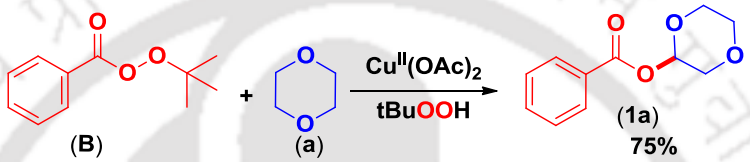
Scheme IV.3.2. *Regioselectivity of the reaction on 1,3-dioxolane*

Mechanistic Studies. Several control experiments were carried out to elucidate the mechanism of these solvent-solvent couplings. Analysis of the reaction mixture between toluene (**1**) and dioxane (**a**) divulged the formation of benzaldehyde and benzoic acid both of which could possibly couple with dioxane (**a**) 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 IV.3.3). Exclusive formation of (**4a**) derived from aldehyde and no trace of (**1a**) (expected from benzoic acid) imply an aldehyde-dioxane coupling.



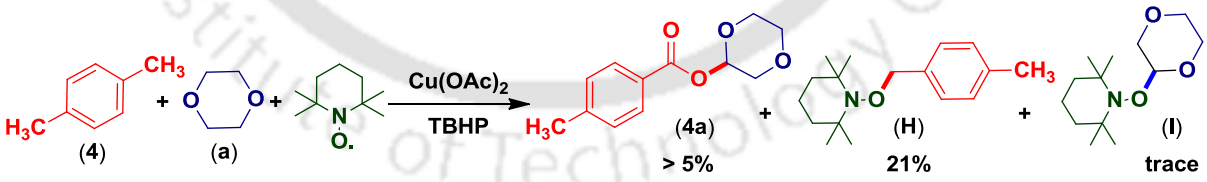
Scheme IV.3.3. *A crossover experiment*

Since benzaldehyde was found to be the coupling partner of dioxane (**a**) rather than benzoic acid, then which intermediate (formed from benzaldehyde) was responsible for the esterification process? It was presumed that excess TBHP and benzaldehyde in the medium might form a perester which could possible act as the benzoxy source like in Kharasch-Sosnovsky reaction.[20] To ascertain this, a reaction was carried out with *tert*-butyl benzoperoxoate (**B**) and dioxane under similar conditions (Scheme IV.3.4). The formation of α-acyloxy ether (**1a**) confirmed our assumption and also indicated a Kharasch-Sosnovsky type path might be operating for the present transformation.



Scheme IV.3.4. *A control experiment*

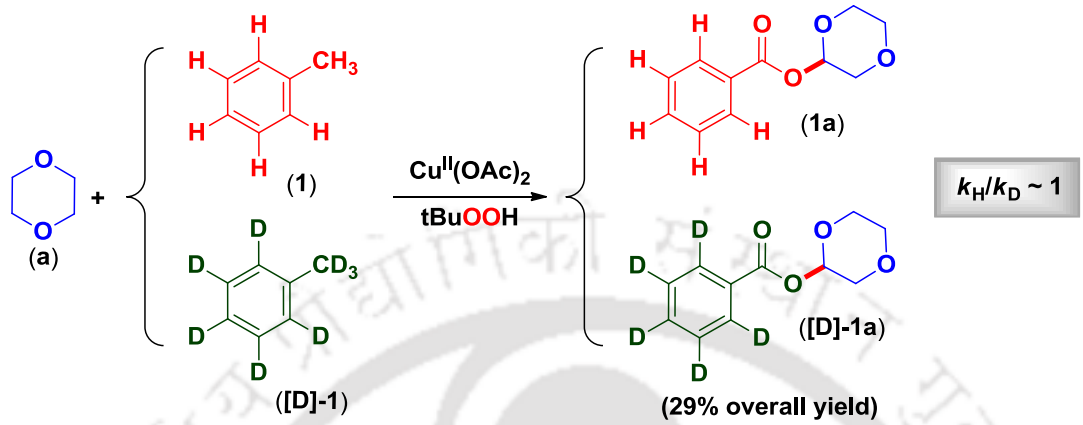
To ascertain the radical nature of the reaction (**4**) and (**a**) were reacted in the presence of radical scavenger 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) under otherwise identical conditions. Along with the formation of traces (< 10%) of (**4a**), a TEMPO ether (**H**) was isolated confirming the formation of benzyl radical intermediate (Scheme IV.3.5). The trapped benzyl radical (**H**) inhibits the formation of key coupling partner *p*-methylbenzaldehyde while the trapped dioxane adduct (**I**) hinders the dioxane radical formation; thereby considerably lowering the yield.



Scheme IV.3.5. *Reaction in presence of radical scavenger TEMPO*

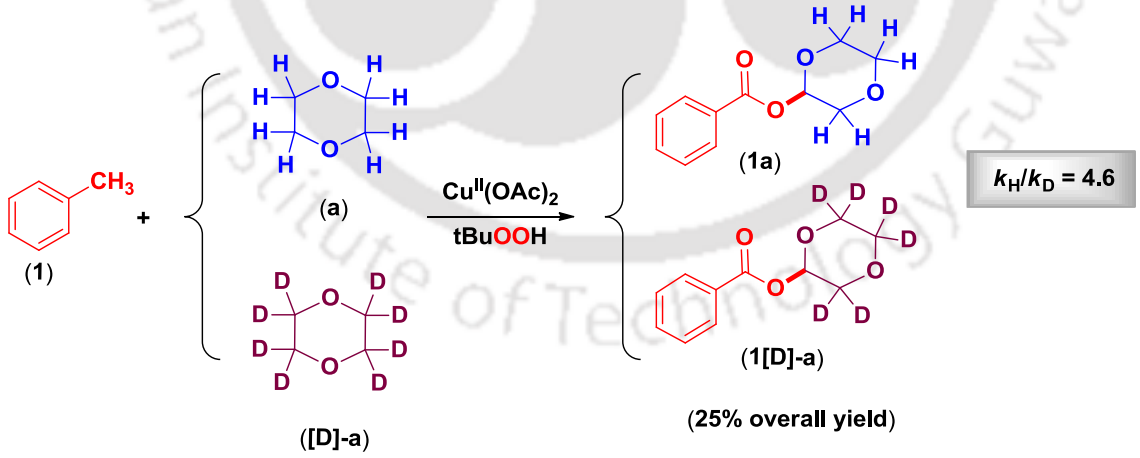
To determine the possible rate limiting step in this reaction two independent intermolecular competing kinetic isotope effect (KIE) experiments were performed. In the first experiment dioxane (**a**) was reacted with an equimolar mixture of toluene (**1**) and d_8-toluene (**[D]-1**) under the standard 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 IV.3.6, also see Experimental section IV.4.5).



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

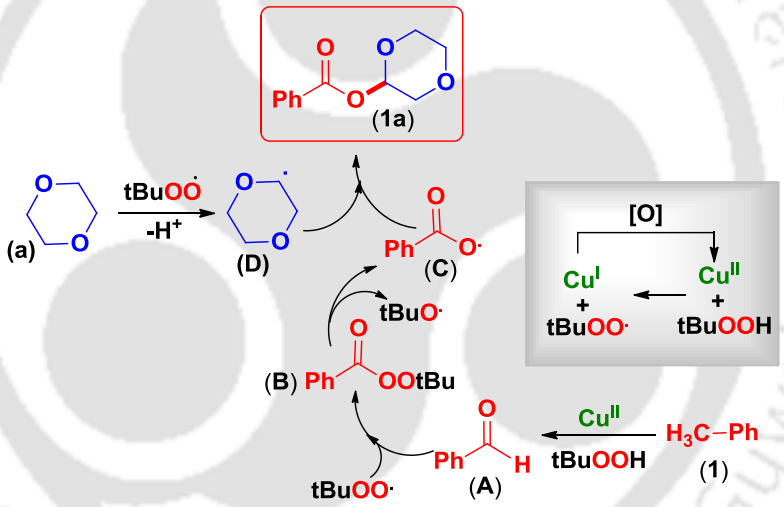
In another intermolecular competing kinetic isotope effect (KIE) experiment, toluene (**1**) was reacted with an equimolar mixture of dioxane (**a**) and d_8-dioxane (**[D]-a**) under identical reaction conditions. A significant KIE was observed in this experiment with k_H / k_D = 5.25. This result indicated that the dioxane sp^3 C–H bond cleavage could be involved in the rate-determining step in this transformation (Scheme IV.3.7, also see Experimental section IV.4.5).



Scheme IV.3.7. *KIE experiment with deuterated dioxane*

The results of the above experiments infer that esterification of cyclic ethers comprise of following steps. Toluene (**1**) gets converted to benzaldehyde (**A**) via the 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 α ethereal hydrogen from dioxane by *tert*-butylperoxy radical gives the radical intermediate (**D**). The radical coupling of (**C**) and (**D**) leads to the formation of ester (**1a**) (Scheme IV.3.8). During the generation of *tert*-butylperoxy radical from TBHP, the Cu(II) gets reduced to Cu(I). Reoxidation of the Cu(I) in the medium regenerates Cu(II) for further reaction (Scheme IV.3.8). The intermediacy of *tert*-butyl benzoperoxate (**B**) in this transformation has been supported from an independent experiment where treatment of presynthesized (**B**) with dioxane (**a**) under similar reaction conditions afforded the α-acyloxy ether (**1a**).



Scheme IV.3.8. *Proposed mechanism for esterification*

In conclusion, the present protocol demonstrated a copper catalyzed synthesis of esters from simple solvents. The combination of methylarenes and cyclic ethers result in the formation of α-esterification via four sp^3 C–H cleavages. A regioselective esterification was achieved in case of 1,3-dioxolane. Various mechanistic investigations carried out provide insights into the mechanism for this transformation.

IV.4. Experimental Section

IV.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 ^1H NMR (300 MHz and 400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (75 MHz and 100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. X-Ray data were collected on SMART APEX equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany).

IV.4.2. Crystallographic description of 1,4-Dioxan-2-yl 2,6-dimethoxybenzoate (8a). $C_{13}H_{13}O_6$, crystal dimensions 0.41 x 0.34 x 0.22 mm, M_r = 268.26, Orthorhombic, space group P b c a, a =11.5879(2), b = 11.6170(2), c = 19.7761(4) Å, α = 90 °, β = 90 °, γ = 90 °, V = 2662.19(8) Å^3, Z = 8, ρ_{calcd} = 1.339 mg/m^3, μ = 0.107 mm^{-1}, F(000) = 1136.0, reflection collected / unique = 2340 / 1594, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0381, wR_2 = 0.0965, R indices (all data): R_1 = 0.0566, wR_2 = 0.1048, goodness of fit = 0.893. CCDC 995330 for 1,4-Dioxan-2-yl 2,6-dimethoxybenzoate (**8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

IV.4.3. General procedure for the synthesis of 1,4-dioxan-2-yl benzoate (**1a**). An oven-dried reaction vessel was charged with toluene (**1**) (460 mg, 5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and aqueous TBHP (70% wt/v) (800 µL, 6 mmol) in 1,4-dioxane (**a**) (2 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 80 °C for 13 h. The 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 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 5% ethyl acetate in hexane to give 1,4-dioxan-2-yl benzoate (**1a**) (147 mg, 71% yield).

IV.4.4. Mechanistic investigation: Trapping of radical intermediates with radical scavenger TEMPO. An oven-dried reaction vessel was charged with *p*-xylene (**4**) (530 mg, 5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol), aq.TBHP (800 µL, 6 mmol), TEMPO (0.312 g, 2 mmol) in dioxnae (**a**) (2 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 80 ^oC for 12 h. The reaction after 12 h afforded the benzyl-TEMPO adduct 2,2,6,6-2,2,6,6-tetramethylpiperidin-1-((4-methylbenzyl)oxy)piperidine (**H**) in 21% yield along with traces (<5%) of the desired product (**4a**). This experiment supports the formation of benzyl radical in the medium from *p*-xylene (**4**) induced radically by Cu/TBHP and also the radical nature of the mechanism.

IV.4.5. Kinetic isotope effect studies.

Two independent intermolecular competing kinetic isotope effect (KIE) experiments were carried out to find out 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**) (233 mg, 2.5 mmol), d_8-toluene (**[D]-1**) (250 mg, 2.5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and aq. TBHP (800 µL, 6 mmol) in dioxane (**a**) (2 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 80 ^oC for 13 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 5% ethyl acetate in hexane to give α-acyloxy ethers (**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 dioxane: An oven-dried reaction vessel was charged with toluene (**1**) (465 mg, 5 mmol), $Cu(OAc)_2$ (36 mg, 0.2 mmol) and aqueous solution of TBHP (5–6 M) (800 µL, 6 mmol) in dioxane (**a**) (1 mL) and d_8-dioxane (**[D]-a**) (1 mL). The flask was fitted to a reflux condenser and the resultant reaction mixture was stirred in a preheated oil bath at 80 ^oC for 13 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 5% ethyl acetate in hexane to give α-acyloxy ethers (**1a** and **1[D]-a**) in 25% 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 = 4.6). This result indicated that the 1,4-dioxane sp^3 C−H bond cleavage should be involved in the rate-determining step of this procedure. The ratio of the deuterated ([D]-1a) and nondeuterated (1a) α-acyloxy ethers product was calculated on the basis of the integration ratio.

Calculation:

For one proton at 7.54, the integration value is 7.34.

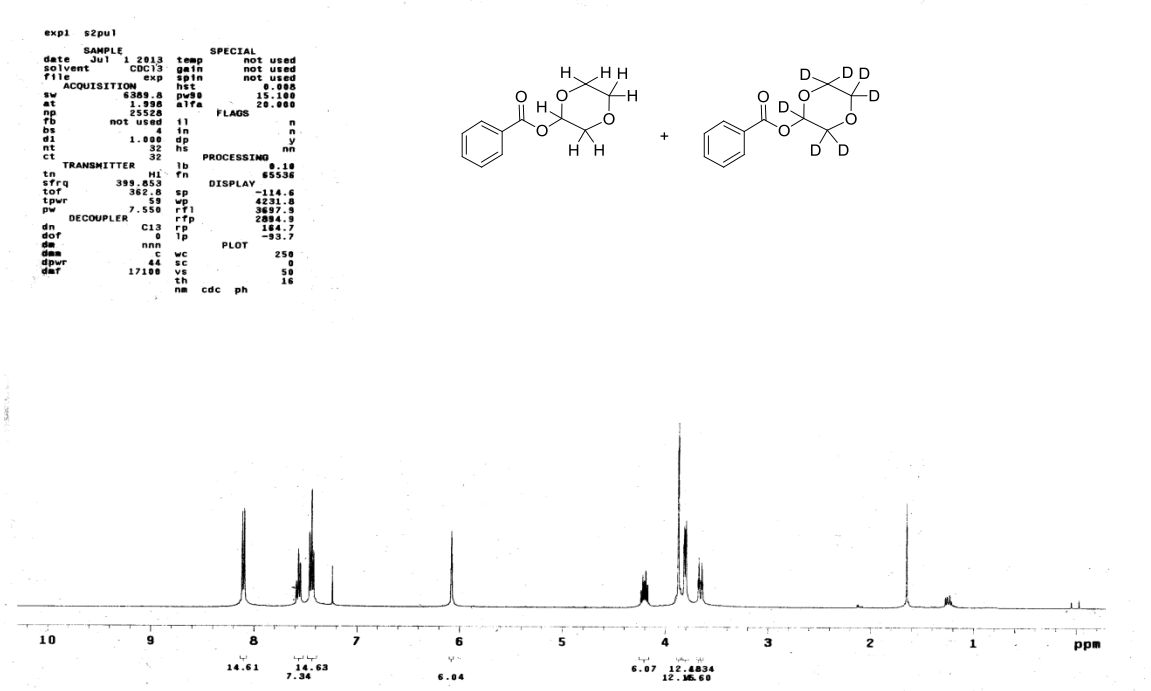
Now for the integration value of the protons originating from dioxane at 6.08 is 6.04.

Thus the number of protons corresponding to this integration value is 6.04 / 7.34 =0.82.

Upon correlation with the original spectra of (**1a**) the number of proton at 6.08 should be 1.

Hence the proton difference in this region is 1 – 0.82 = 0.18

Thus the k_H/k_D = 0.82 / 0.18 = 4.55 ~ 4.6



IV.5. References

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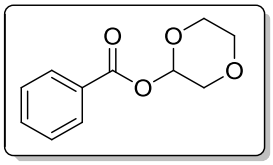
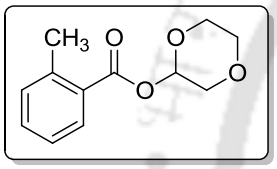
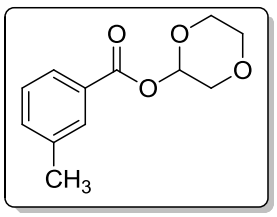
IV.6. Spectral data



1,4-Dioxan-2-yl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.64–3.68 (m, 1H), 3.79–3.82 (m, 2H), 3.85–3.87 (m, 2H), 4.17–4.23 (m, 1H), 6.08 (t, 1H, *J* = 2.0 Hz), 7.42–7.46 (m, 2H), 7.54–7.57 (m, 1H), 8.09–8.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 61.9, 66.3, 68.0, 89.9, 128.6, 129.9, 130.1, 133.6, 165.4; IR (KBr): 3066, 2973, 2858, 1718, 1531, 1452, 1399, 1276, 1015, 912, 880, 712 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{12}O_4$ (MH^+) 209.0808; found 209.0801.

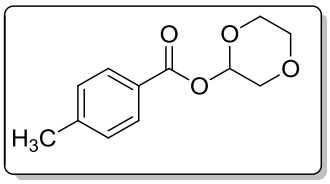


1,4-Dioxan-2-yl 2-methylbenzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.65 (s, 3H), 3.67–3.71 (m, 1H), 3.81–3.84 (m, 2H), 3.86–3.89 (m, 2H), 4.18–4.24 (m, 1H), 6.08 (s, 1H), 7.25–7.29 (m, 2H), 7.41–7.45 (m, 1H), 8.04–8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.1, 62.0, 66.3, 68.1, 89.8, 125.9, 128.9, 131.2, 132.0, 132.7, 141.1, 166.1; IR (KBr): 2972, 2929, 2856, 1724, 1455, 1293, 1250, 1157, 1059, 1016, 911, 881, 739 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_4$ (MH^+) 223.0965; found 223.0969.

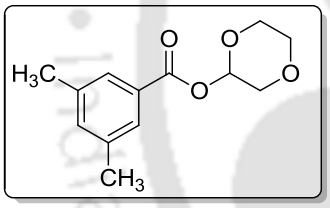


1,4-Dioxan-2-yl 3-methylbenzoate (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.63–3.67 (m, 1H), 3.79–3.83 (m, 2H), 3.86–3.87 (m, 2H), 4.17–4.23 (m, 1H), 6.07 (s, 1H), 7.30–7.38 (m, 2H), 7.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 61.9, 66.3, 68.0, 89.9, 127.3, 128.5, 129.8, 130.5, 134.4, 138.4, 165.6; IR (KBr): 2969, 2924, 2856, 1725, 1454, 1278, 1197, 1152,

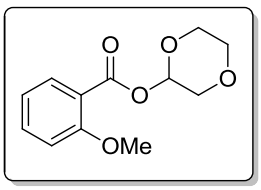
1067, 1017, 919, 880, 745 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_4$ (MH^+) 223.0965; found 223.0962.



1,4-Dioxan-2-yl 4-methylbenzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.56–3.60 (m, 1H), 3.71–3.74 (m, 2H), 3.79–3.80 (m, 2H), 4.10–4.16 (m, 1H), 6.00 (t, 1H, *J* = 2.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.94 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.6, 61.7, 66.0, 67.8, 89.6, 126.9 129.1, 129.9, 144.1, 165.1; IR (KBr): 2973, 2926, 2857, 1725, 1612, 1453, 1276, 1259, 1233, 1178, 1155, 1087, 1066, 1015, 914, 882, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_4$ (MH^+) 223.0965; found 223.0972.

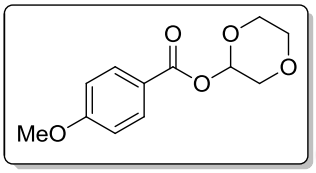


1,4-Dioxan-2-yl 3,5-dimethylbenzoate (5a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 6H), 3.64–3.67 (m, 1H), 3.79–3.82 (m, 2H), 3.86 (s, 2H), 4.17–4.23 (m, 1H), 6.05 (s, 1H), 7.19 (s, 1H), 7.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 61.9, 66.3, 68.0, 89.8, 127.7, 129.7, 135.3, 138.3, 165.7; IR (KBr): 2972, 2916, 2869, 1713, 1609, 1471, 1454, 1383, 1306, 1216, 1151, 1105, 1020, 902, 880, 768 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{16}O_4$ (MH^+) 237.1121; found 237.1128

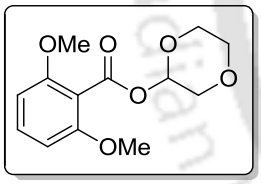


1,4-Dioxan-2-yl 2-methoxybenzoate (6a): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.65–3.69 (m, 1H), 3.80–3.82 (m, 2H), 3.86–3.91 (m, 5H), 4.21–4.27 (m, 1H), 6.08 (t, 1H, *J* = 2.0 Hz), 6.97–7.01 (m, 2H), 7.47–7.51 (m, 1H), 7.88–7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.8, 61.5, 65.9, 67.6, 89.4, 112.0,

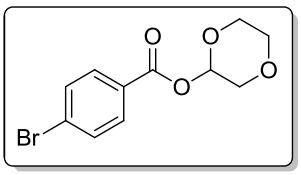
119.3, 119.9, 131.7, 133.9, 159.4, 164.4; IR (KBr) 2971, 2931, 2855, 1733, 1600, 1491, 1462, 1298, 1251, 1157, 1060, 1016, 912, 881, 758 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_5$ (MH^+) 239.0914; found 239.0918..



1,4-Dioxan-2-yl 4-methoxybenzoate (7a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.65–3.69 (m, 1H), 3.81–3.83 (m, 2H), 3.86–3.88 (m, 5H), 4.18–4.24 (m, 1H), 6.07 (s, 1H), 6.93 (d, 2H, *J* = 9.2 Hz), 8.08 (d, 2H, *J* = 9.2 Hz), ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 61.9, 66.3, 68.1, 89.7, 113.9, 122.2, 132.2, 163.9, 165.1; IR (KBr): 2966, 2925, 2853, 1719, 1605, 1510, 1256, 1168, 1114, 1086, 1066, 1019, 911, 880, 769 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_5$ (MH^+) 239.0914; found 239.0919.

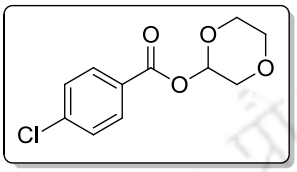


1,4-Dioxan-2-yl 2,6-dimethoxybenzoate (8a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.62–3.66 (m, 1H), 3.77–3.84 (m, 10H), 4.23–4.29 (m, 1H), 6.08 (s, 1H), 6.55 (d, 2H, *J* = 8.8 Hz), 7.29 (t, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.9, 61.2, 65.9, 67.6, 89.7, 103.9, 112.5, 131.3, 157.4, 165.3; IR (KBr): 2970, 2936, 2847, 1739, 1595, 1476, 1295, 1255, 1112, 1060, 1101, 911, 789 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{16}O_6$ (MH^+) 269.1020; found 269.1027.

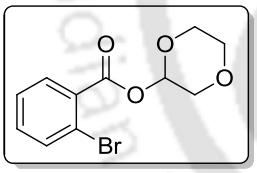


1,4-Dioxan-2-yl 4-bromobenzoate (9a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.63–3.67 (m, 1H), 3.79-3.81 (m, 2H), 3.86 (d, 2H, *J* = 1.6 Hz), 4.14–4.20 (m, 1H), 6.06 (s, 1H), 7.57 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz);

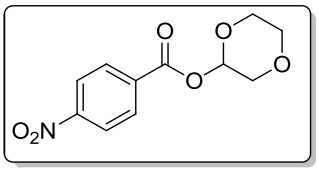
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 62.0, 66.3, 67.9, 90.3, 128.9, 131.6, 132.1, 164.8; IR (KBr) 2972, 2929, 2856, 1729, 1589, 1397, 1274, 1259, 1155, 1090, 1067, 1009, 911, 881, 757 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}BrO_4$ (MH^+) 286.9913; found 286.9909.



1,4-Dioxan-2-yl 4-chlorobenzoate (10a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.64–3.68 (m, 1H), 3.80–3.82 (m, 2H), 3.87 (d, 2H, *J* = 1.6 Hz), 4.15–4.21 (m, 1H), 6.06 (t, 1H, *J* = 2.0 Hz), 7.41 (d, 2H, *J* = 8.8 Hz), 8.03 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 62.0, 63.3, 67.9, 90.3, 129.1, 131.5, 140.2, 164.7; IR (KBr) 2970, 2925, 2855, 1726, 1593, 1259, 1233, 1155, 1090, 1066, 1011, 911, 880, 759 cm^{-1}; HRMS (ESI): calcd. $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0411.

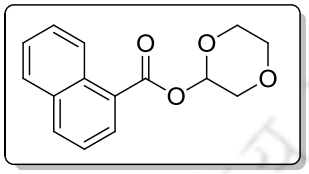


1,4-Dioxan-2-yl 2-bromobenzoate (11a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.63–3.66 (m, 1H), 3.77–3.79 (m, 2H), 3.83–3.88 (m, 2H), 4.19–4.23 (m, 1H), 6.06 (t, 1H, *J* = 1.8 Hz), 7.29–7.35 (m, 2H), 7.63–7.64 (m, 1H), 7.85–7.87 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 61.9, 66.2, 67.8, 90.7, 122.1, 127.4, 131.6, 131.9, 133.1, 134.6, 164.9; IR (KBr): 2971, 2924, 2852, 1734, 1581, 1387, 1276, 1255, 1159, 1093, 1069, 921, 871, 752 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{11}BrO_4$ (MH^+) 286.9913; found 286.9917.

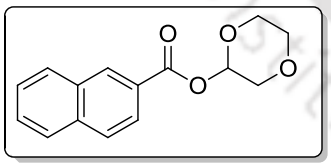


1,4-Dioxan-2-yl 4-nitrobenzoate (12a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.70–3.74 (m, 1H), 3.85–3.88 (m, 2H), 3.93 (d, 2H, *J* = 2.0 Hz), 4.20–4.27 (m, 1H),

6.14 (s, 1H), 8.31 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 61.9, 66.2, 67.7, 90.9, 123.7, 131.1, 135.2, 150.9, 163.5; IR (KBr) 2977, 2929, 2858, 1729, 1595, 1257, 1234, 1157, 1091, 1067, 915, 870, 757 cm^{-1}; HRMS (ESI): calcd. $C_{11}H_{11}NO_6$ (MH^+) 253.2119; found 253.2111.

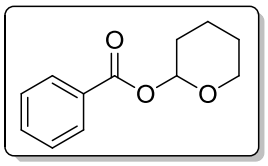


1,4-Dioxan-2-yl 1-naphthoate (13a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.68–3.72 (m, 1H), 3.82–3.85 (m, 2H), 3.93–3.95 (m, 2H), 4.22–4.28 (m, 1H), 6.19 (t, 1H, *J* = 2.0 Hz), 7.48–7.54 (m, 2H), 7.59–7.64 (m, 1H), 7.87 (d, 1H, *J* = 8.0 Hz), 8.03 (d, 1H, *J* = 8.0 Hz), 8.32–8.34 (m, 1H), 9.00 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 61.9, 66.2, 67.9, 89.9, 124.5, 125.8, 126.3, 126.4, 128.1, 128.7, 131.0, 131.6, 133.9, 134.1, 165.9; IR (KBr) 2972, 2927, 2855, 1720, 1593, 1452, 1264, 1232, 1194, 1155, 1130, 1108, 1066, 1018, 933, 911, 882, 814, 782 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_4$ (MH^+) 259.0965; found 259.0961.

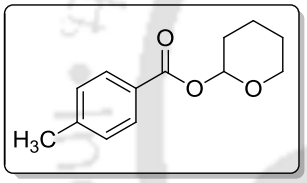


1,4-Dioxan-2-yl 2-naphthoate (14a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.68–3.71 (m, 1H), 3.79–3.86 (m, 2H), 3.91–3.95 (m, 2H), 4.24–4.28 (m, 1H), 6.15 (t, 1H, *J* = 1.8 Hz), 7.52–7.61 (m, 2H), 7.86–7.92 (m, 2H), 7.96–8.00 (m, 1H),8.10–8.14 (m, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 62.1,66.4, 68.2, 90.1, 125.5, 126.9, 127.2, 128.0, 128.1, 128.5, 128.7, 129.7, 131.8, 132.7, 135.9, 165.6; IR (KBr): 2971, 2932, 2851, 1718, 1591, 1446, 1261, 1237, 1196, 1154, 1132, 1102, 1067, 1012, 935, 883, 811, 783 cm^{-1}; HRMS (ESI):

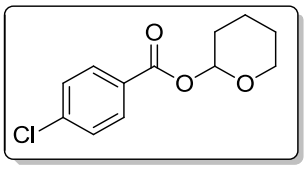
calcd. for $C_{15}H_{14}O_4$ (MH^+) 259.0965; found 259.0961.



Tetrahydro-2*H*-pyran-2-yl benzoate (1b): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.58–1.77 (m, 3H), 1.81–1.99 (m, 3H), 3.72–3.75 (m, 1H), 3.94–4.01 (m, 1H), 6.23 (t, 1H, *J* = 3.2 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 7.54 (t, 1H, *J* = 7.2 Hz), 8.07 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 18.6, 25.0, 29.3, 63.2, 93.1, 128.4, 129.8, 130.3, 133.1, 165.2; IR (KBr) 2924, 2853, 1723, 1607, 1456, 1289, 1121, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_3$ (MH^+) 207.1016; found 207.1011.

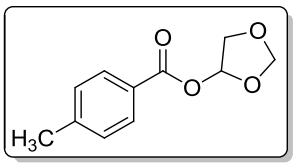


Tetrahydro-2*H*-pyran-2-yl 4-methylbenzoate (4b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.60–1.62 (m, 1H), 1.67–1.71 (m, 2H), 1.80–1.95 (m, 3H), 2.39 (s, 3H), 3.71–3.74 (m, 1H), 3.94–3.98 (m, 1H), 6.21 (t, 1H, *J* = 2.0 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz); ^{13}CNMR (150 MHz, $CDCl_3$): δ (ppm) 18.8, 21.8, 25.2, 29.5, 63.4, 93.1, 127.7, 129.3, 129.9, 143.9, 165.4; IR (KBr): 2945, 2873, 1722, 1611, 1274, 1177, 1206, 1088, 1036, 943, 900, 871, 753 cm^{-1}; HRMS (ESI): calcd.for $C_{13}H_{16}O_3$ (MH^+) 221.1172; found 221.1168.

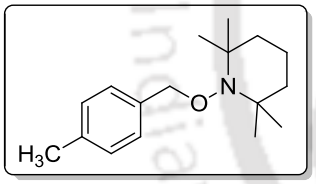


Tetrahydro-2*H*-pyran-2-yl 4-chlorobenzoate (10b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.59–1.67 (m, 1H), 1.72–1.77 (m, 2H), 1.83–1.91 (m, 3H), 3.72–3.75 (m, 1H), 3.92–3.98 (m, 1H), 6.21 (s, 1H), 7.40 (d, 2H, *J* = 8.4 Hz), 8.00 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.8, 25.2, 29.4, 63.5, 93.6, 128.92,

128.97, 131.3, 139.8, 164.6; IR (KBr): 2944, 2871, 1725, 1593, 1272, 1206, 1089, 1016, 940, 898, 868, 758 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{13}ClO_3$ (MH^+) 241.0626; found 241.0620.



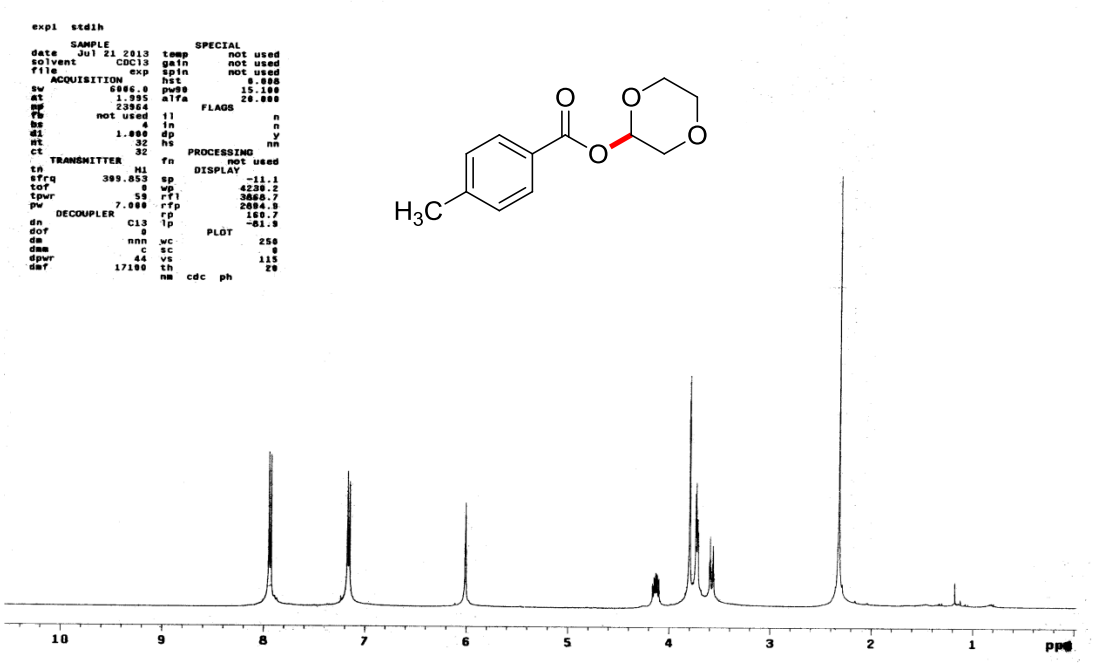
1,3-Dioxolan-4-yl 4-methylbenzoate (4d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 4.10–4.18 (m, 2H), 5.17 (d, 2H, *J* = 15.6 Hz), 6.58 (dd, 2H, *J* = 1.6 Hz, *J* = 2.0 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.93 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 70.9, 94.7, 96.0, 126.9, 129.3, 130.0, 144.5, 166.0; IR (KBr): 2923, 1725, 1693, 1486, 1269, 1197, 1089, 1018, 921, 742 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{13}ClO_3$ (MH^+) 208.2126; found 208.2120.



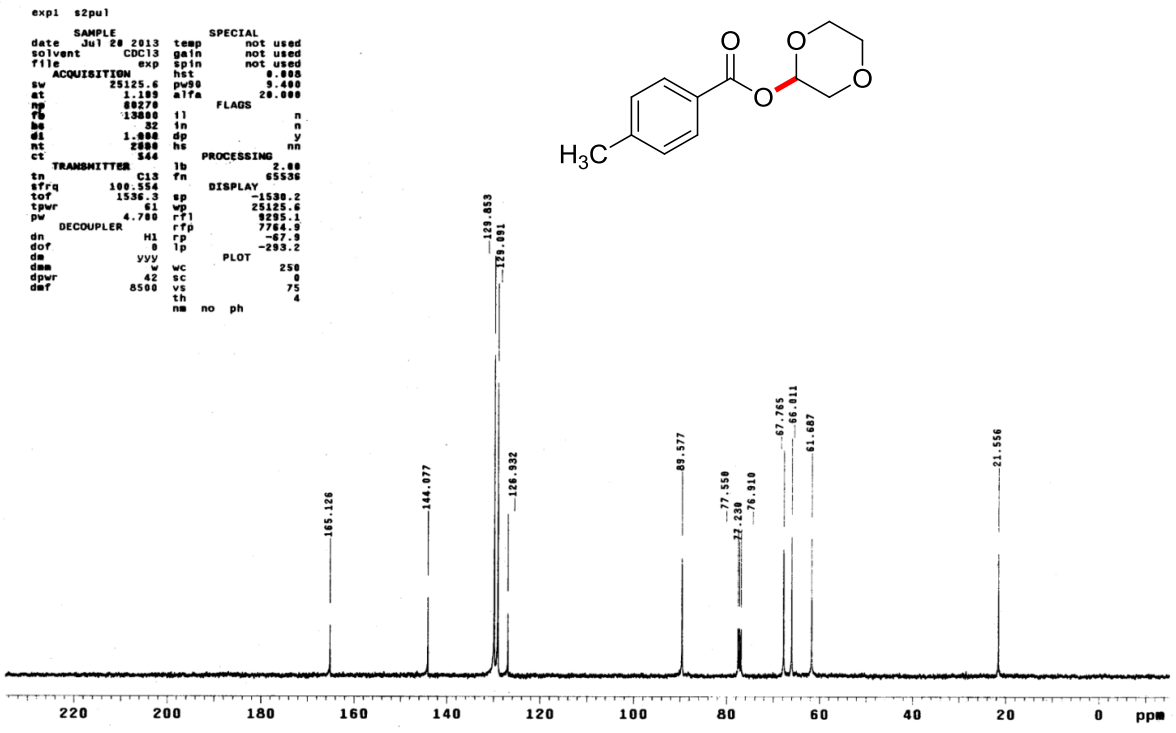
2,2,6,6-Tetramethylpiperidin-1-((4-methylbenzyl)oxy) piperidine (H): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.13 (s, 6H), 1.24–1.25 (m, 7H), 1.32–1.35 (m, 1H), 1.48–1.54 (m, 4H), 2.34 (s, 3H), 4.77 (s, 2H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 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.

IV.7. Spectra

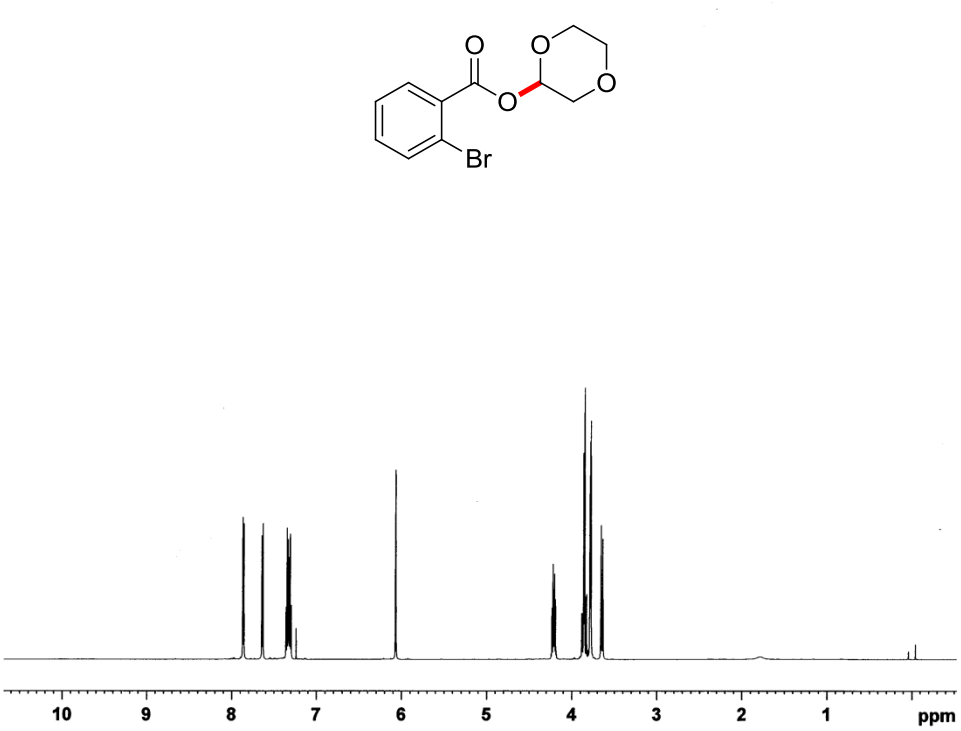
1,4-Dioxan-2-yl 4-methylbenzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$)



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



1,4-Dioxan-2-yl 2-bromobenzoate (11a): ^{1}H NMR (600 MHz, $CDCl_3$)

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Current Data Parameters
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PROCNO                  1

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PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG                22.18
DW               41.600 usec
DE                6.50 usec
TE              298.1 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        600.1737063 MHz
NUC1                   1H
P1                 12.00 usec
PLW1       21.00000000 W

F2 - Processing parameters
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SF          600.1700268 MHz
WDW                   EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
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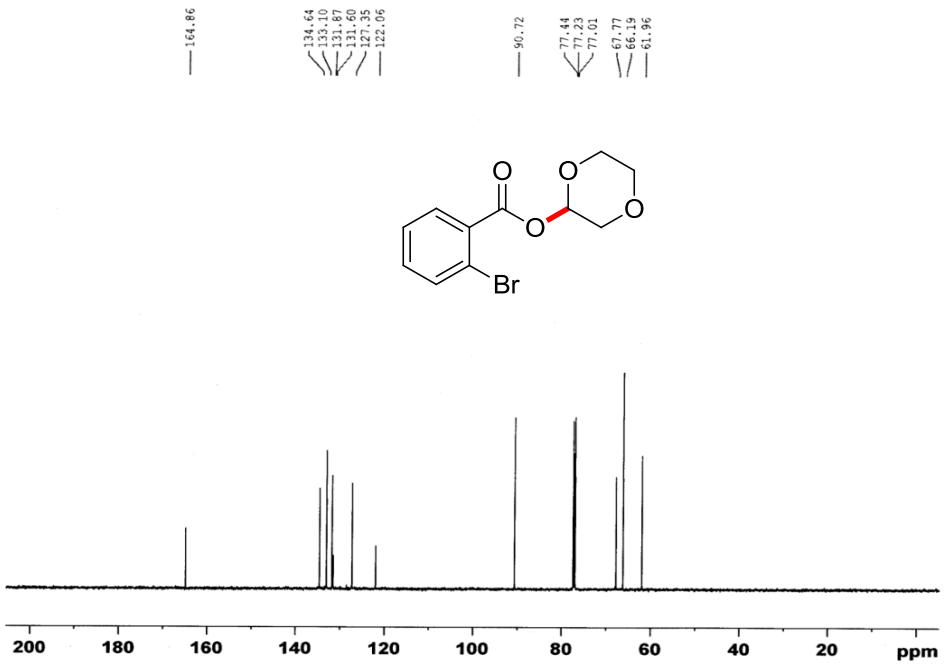
1,4-Dioxan-2-yl 2-bromobenzoate (11a): ^{13}C NMR (150 MHz, $CDCl_3$)

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PROCNO                 1

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D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
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NUC1                  13C
P1                10.50 usec
PLW1       95.00000000 W

======== CHANNEL f2 ========
SFO2        600.1724007 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2             70.00 usec
PLW2       21.00000000 W
PLW12       0.61714000 W
PLW13       0.30239999 W

F2 - Processing parameters
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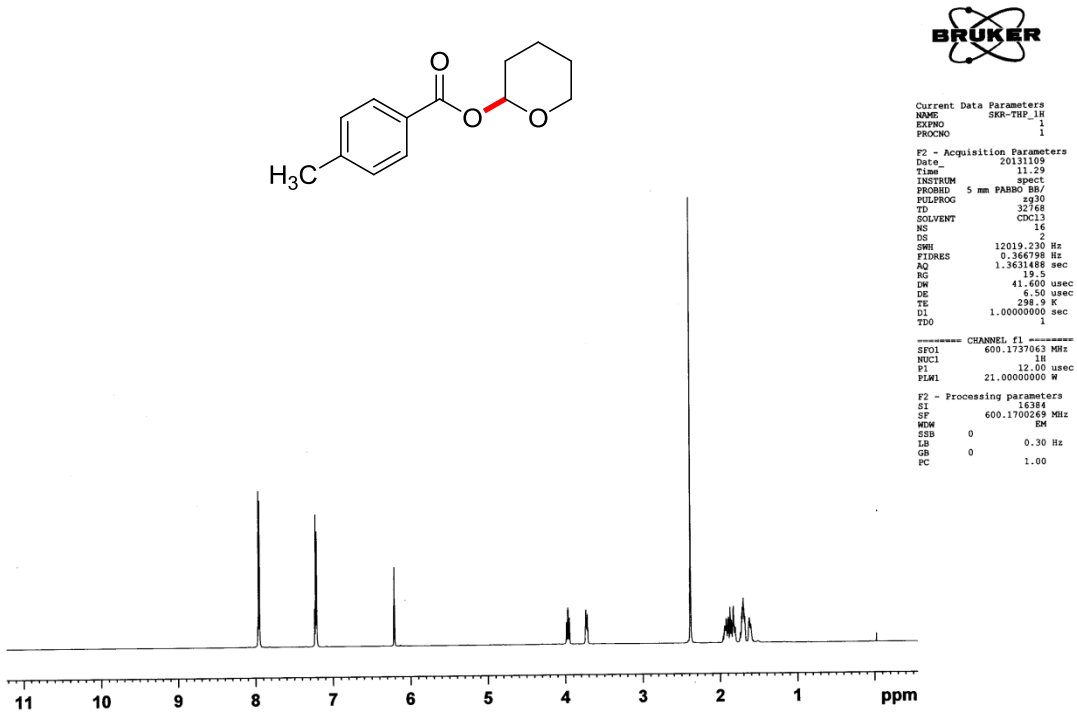
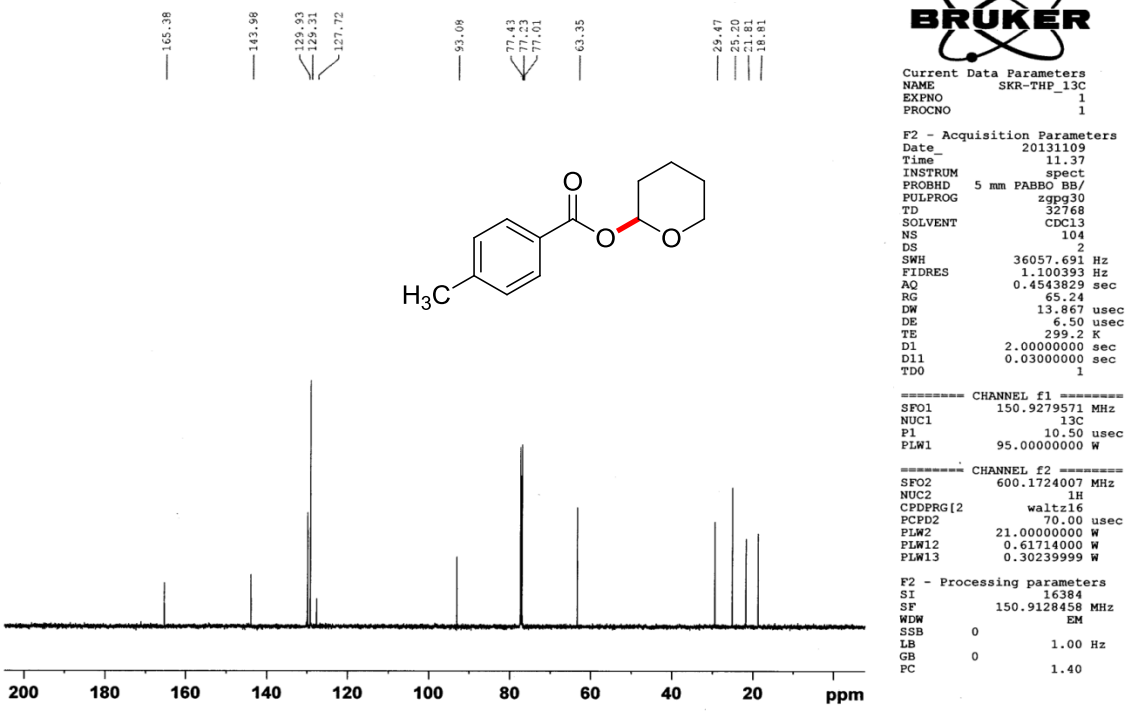
SF          150.9128502 MHz
WDW                   EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

Tetrahydro-2*H*-pyran-2-yl 4-methylbenzoate (4b): ^{1}H NMR (600 MHz, $CDCl_3$)



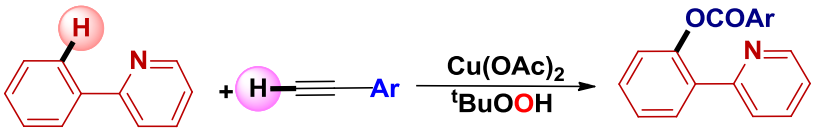
Tetrahydro-2*H*-pyran-2-yl 4-methylbenzoate (4b): ^{13}C NMR (150 MHz, $CDCl_3$)



Indian Institute of Technology Guwahati

Chapter V

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



Abstract: *A variety of alkynes 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.*

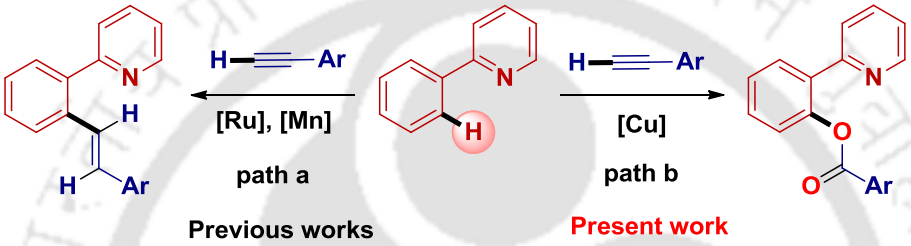
CHAPTER V

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

V.1. Introduction

Metal catalyzed direct transformation of C–H bonds to C–C and C–heteroatom bonds is one of the popular strategy in modern synthetic organic chemistry, providing unprecedented results through selective functionalizations of un-reactive *ortho* C–H bonds.[1] It renders step and atom economic strategy compared to traditional cross-coupling reactions via circuitous use of pre-functionalization starting materials. In this regard, the cross-dehydrogenative coupling (CDC) has played a pivotal role in bringing about transformation of C–H bonds of all types to C–C and C–heteroatom bonds.[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] A fruitful way to achieve this is via the transition metal catalyzed direct alkynylation of sp^2 or sp^3 C–H bonds using terminal alkynes.[3] Not merely this, terminal alkynes have also been explored towards alkenylation of substrates possessing directing groups.[3] Apart from the recently developed C–H activation processes, terminal alkynes are used in classical Sonogashira coupling reaction with arenes containing various leaving groups C–X (X = –I, –Br, –Cl, $–B(OH)_2$, –OTs).[4] They are also an integral part of multi-component reactions (MCR) for the synthesis of a number of important heterocycles.[5] Pertinent to the referred alkenylation involving CDC strategy, the metal catalysts used are expensive Ru and Mn salts (path a, Scheme V.1.1).[3d,e] 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. However the query that exits is whether Cu would favor alkynylation path or the alternative alkenylation path. In pursuit to get an answer to this, a trial reaction was carried out with 2-phenylpyridine (**1**) and phenylacetylene (**a**) in

presence of Cu catalyst and a radical initiator. The result is rather surprising as we did not observe expected *o*-alkenylated product rather the reaction interestingly provided *o*-benzoxylated product (**1a**) exclusively (path b, Scheme V.1.1). Similar to the present oxidation of terminal alkynes, styrenes are reported to undergo Wacker type oxidation to give phenylacetaldehyde[6] while stilbenes are reported to yield 1,2-diketones.[7] Thus the present protocol copper catalyzed *o*-benzoxylation of 2-phenylpyridine from phenylacetylene (ArCOO– source) via loss of one carbon atom is unparallel in the literature (path b, Scheme V.1.1)



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

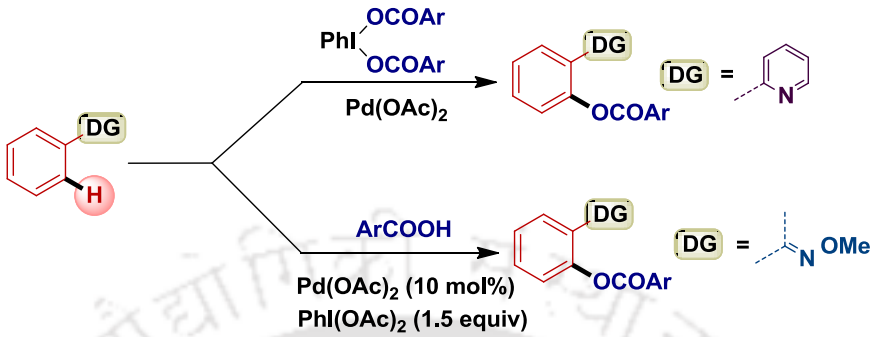
V.2. Strategies for *ortho*-Benzoxylation

The benzoate derivatives are important building blocks in the synthesis of natural and pharmacological compounds.[8,9] Conventional methods of preparation for this esters are Fischer esterification[10] or transesterification reactions,[11] which usually required strong acidic or basic conditions.[12] The Baeyer–Villiger oxidation reaction may suffer from low regioselectivity.[13] In the past few years, oxidative esterification has received significant attention and has become an economical alternative to traditional ester synthesis.[14] An important category of these oxidative esterification reactions is the transition-metal-catalyzed esterification.[14] 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.

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

Sanford group for the first time reported palladium catalyzed *o*-benzoxylation of 2-phenylpyridines using benzoate iodonium salts as ArCOO– surrogates (Scheme V.2.1).[15]

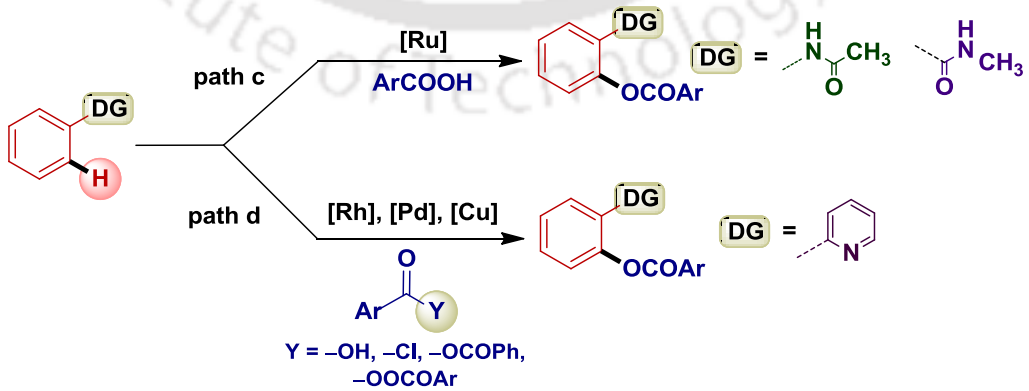
Later, Shi group achieved a similar palladium catalyzed *o*-benzoxylation of ketoxime ethers via *in situ* generation of benzoate iodonium salts (Scheme V.2.1).[16]



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

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

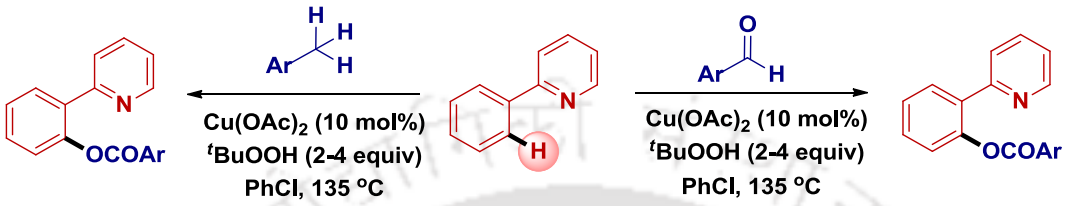
Cheng group has demonstrated *o*-benzoxylation of 2-arylpyridines using either the carboxylic acid/salt[17] or its derivatives such as anhydride[18] and acid chloride[19] as the arylcarboxy sources using various metal catalysts. The use of carboxylic acids for oxidative *o*-benzoxylation of 2-phenylpyridines has also been achieved by Zhong group using palladium catalyst along with copper and silver salts as co-oxidants.[20] A similar palladium catalyzed transformation is reported by Yu group in which aryl acylperoxides[21] has been employed as benzoxy surrogate all these aforesaid report are shown in path d, Scheme V.2.2. Pertinent to the *o*-benzoxylation in substrates possessing other directing groups, very recently Jeganmohan *et al.* have reported ruthenium catalyzed *o*-benzoxylation of acetanilides[22a] and benzamides[22b] using aryl carboxylic acids as coupling partners (path c, Scheme V.2.2).



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

(iii) Aldehyde or alkylbenzenes as ArCOO– source

Huang *et al.* have illustrated that aldehyde (ArCHO) and alkylbenzene ($ArCH_3$) can act as an alternative source of ArCOO– group for *o*-benzoxylation of 2-phenylpyridine catalyzed by copper(II) acetate in presence of TBHP as oxidant (Scheme V.2.3).[23]



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

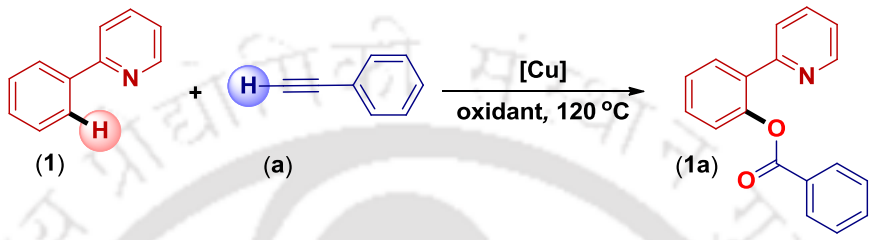
V.3. Present Work

In continuation to the above *o*-benzoxylation protocols, herein a method is reported on copper catalyzed *o*-benzoxylation of 2-arylpyridines using alkynes as the ArCOO– surrogates. This process involve a loss of carbon as carbon monoxide via C–C bond cleavage from the parent alkyne to install a benzoxy group at the proximal site of 2-phenylpyridine.

Optimization of reaction conditions. As has been mentioned earlier, to check the efficacy of a copper catalyst toward *o*-alkynylation or *o*-alkenylation of 2-phenylpyridine (**1**) an initial reaction was performed using phenylacetylene (**a**) in the presence of $Cu(OAc)_2$ (10 mol %) and oxidant cum radical initiator TBHP (3 equiv) in chlorobenzene at 100 °C (Table V.3.1, entry 1). However, the aforesaid reaction unexpectedly provided the *o*-benzoxylated product (**1a**) in a modest yield of 36% (Table V.3.1, entry 1). In pursuit to attain better yield of the ester product, further optimizations were carried out by varying parameters such as catalysts, oxidants, solvents and temperature. Among several catalysts screened, $Cu(OAc)_2$ (Table V.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 V.3.1, entries 2–7). Subsequently by increasing TBHP (5–6 M) quantity from 3 to 4 equivalents enhanced the product yield to 45% (Table V.3.1, entry 8) while a further additional improvement of 7% (Table V.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 (61%, Table V.3.1, entry 10), whilst no significant change in yield occurred with a threefold excess of the catalyst loading (Table V.3.1, entry 11). The yield was bettered by further 6% (Table V.3.1, entry 12) upon perform

Table V.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	36
2	CuBr (10)	TBHP[c] (3)	PhCl	100	17
3	$CuBr_2$ (10)	TBHP[c] (3)	PhCl	100	15
4	CuCl (10)	TBHP[c] (3)	PhCl	100	28
5	$CuCl_2$ (10)	TBHP[c] (3)	PhCl	100	25
6	$Cu(OTf)_2$ (10)	TBHP[c] (3)	PhCl	100	15
7	CuI (10)	TBHP[c] (3)	PhCl	100	23
8	$Cu(OAc)_2$ (10)	TBHP[c] (4)	PhCl	100	45
9	$Cu(OAc)_2$ (10)	TBHP[c] (5)	PhCl	100	52
10	$Cu(OAc)_2$ (20)	TBHP[c] (5)	PhCl	100	61
11	$Cu(OAc)_2$.(30)	TBHP[c] (5)	PhCl	100	62
12	**$Cu(OAc)_2$ (20)**	**TBHP[c] (5)**	**PhCl**	**120**	**67**
13	$Cu(OAc)_2$ (20)	TBHP[c] (5)	toluene	120	58
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

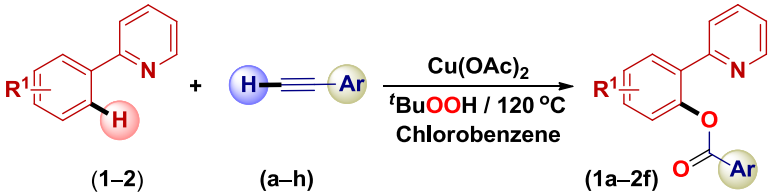
[a]Reaction conditions: 2-phenylpyridine (**1**) (0.5 mmol), phenylacetylene (**a**) (1 mmol), in chlorobenzene (1 mL), time 13 h. [b]Isolated yield. [c]Decane solution (5–6 M). [d]70% aqueous solution.

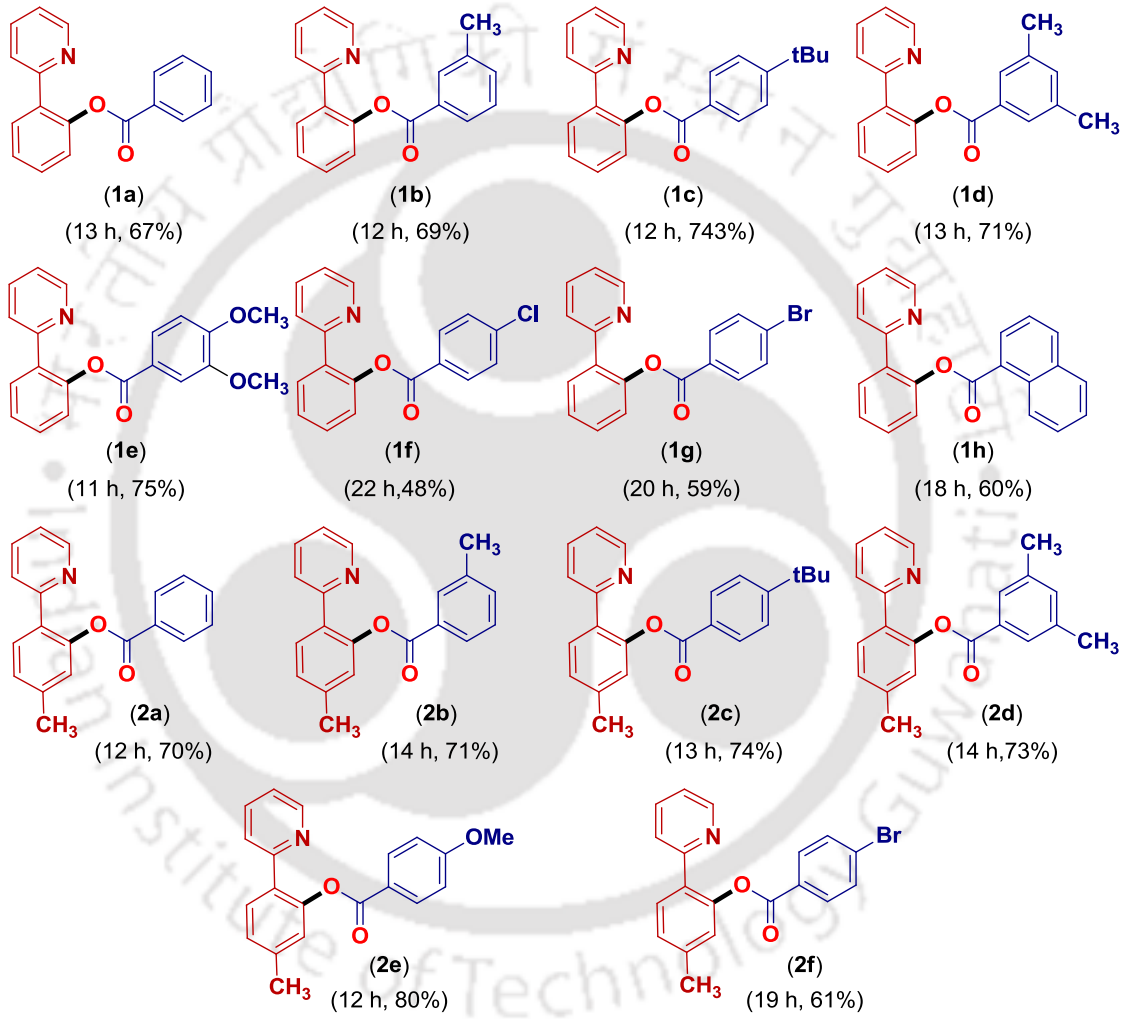
-ing the reaction at 120 °C. Solvents toluene (58%) (Table V.3.1, entry 13) and THF (35%) (Table V.3.1, entry 14) were less efficient compared to the use of chlorobenzene (67%) (Table V.3.1, entry 12), whereas other solvents such as dioxane, DMSO, DMF, DCE were

completely ineffective in bringing about this transformation (Table V.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 27% yield of the desired product under identical reaction conditions (Table V.3.1, entry 19). In absence of either the catalyst or oxidant the reaction failed to proceed giving no traces of the product justifying the decisive role of their combination (Table V.3.1, entry 20–21). Thus the use of $Cu(OAc)_2$ (20 mol%), TBHP (5 equiv) in chlorobenzene at 120 ^oC was found to be the optimized conditions for our 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 arylalkynes. The electron neutral –H (**a**) and electron-donating substituents on phenylacetylenes *viz*. *m*-Me (**b**), *p*-tBu (**c**), 3,5-dimethyl (**d**) and 3,4-diOMe (**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 V.3.1. Moderately electron-withdrawing substituents in phenylacetylenes 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 arylalkynes possessing electro-donating substituents (Scheme V.3.1). However phenylacetylene possessing a strongly electronwithdrawing group such as *m*-NO_2 failed to give any *o*-benzoxylated product with (**1**). The phenylacetylene analogues of naphthalene, 1-naphthylalkyne (**h**) was also effective in bringing about naphthylcarboxylation of (**1**) giving (**1h**) in a moderate yield (Scheme V.3.1). In addition to 2- phenylpyridine (**1**) *o*-benzoxylation of 2-(*p*-tolyl)pyridine (**2**) was also investigated with various arylalkynes and the results are depicted in Scheme V.3.1. The trends in the reactivity of substituted phenylacetylenes were found to be identical as was observed for 2-phenylpyridine (**1**). Nevertheless, the yields of *o*-benzoxylated products (**2a**–**2g**) 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 *o*-tolyl ring in (**2**). Surprisingly, terminal aliphatic alkyne, 1-butyne failed to undergo any *o*-acetoxylation either with (**1**) or (**2**) under the present reaction conditions.

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

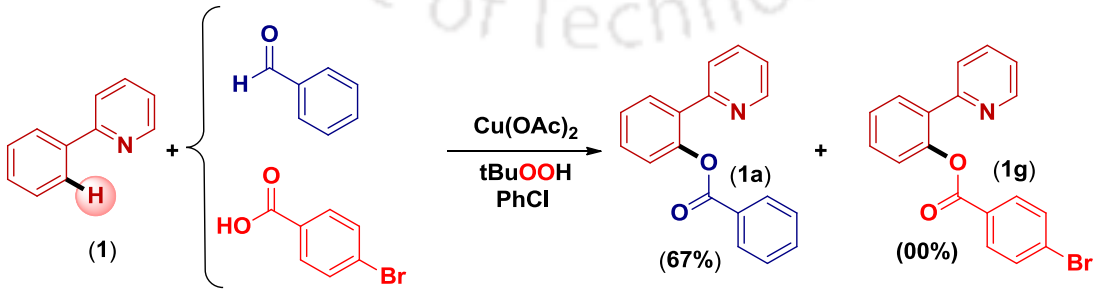




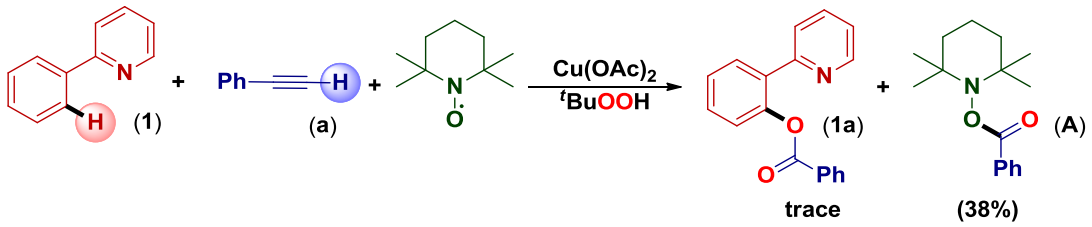
[a]Reaction conditions: arenes (**1–2**) (0.5 mmol), alkynes (**a–h**) (1 mmol), $Cu(OAc)_2$ (0.2 mmol), TBHP (5–6 M) (2.5 mmol), 120 °C, in chlorobenzene (1 mL), time 12–20 h. [b]Yield of isolated pure product.

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. Interestingly instead of phenylacetylene, when phenylglyoxal, benzaldehyde were reacted with 2-phenylpyridine (**1**) independently under otherwise identical conditions, both provided the desired product (**1a**) supporting their intermediacy towards *o*-benzoxylation. While benzoic acid did not provide desired product (**1a**) ruled out involvement acid as intermediate towards *o*-benzoxylation. Since phenylglyoxal is expected to generate from phenylacetylene, related to similar oxidation of alkynes are reported to undergo Wacker type oxidation to give 1,2-diketones.[24] Hence it was envisaged that the formation of phenylglyoxal under oxidative conditions probably occurs via dioxete intermediates as has been proposed by Jiao *et al.* who have shown similar di-keto formation from terminal alkynes for the synthesis of α-ketoamides.[25] Having established the pathway for the phenylglyoxal formation, next we turned our attention towards the formation of benzaldehde 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 (see Experimental Section V.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] To find out the exact coupling partner among aldehyde and acid a control experiment was carried out where an equimolar mixture of benzaldehyde and *p*-bromobenzoic acid were reacted with 2-phenylpyridine (**1**) under identical reaction conditions. Exclusive formation of (**1a**) derived from aldehyde and no trace of (**1g**) (expected from *p*-bromobenzoic acid) imply an aldehyde is the sole coupling partner for this transformation (Scheme V.3.2).

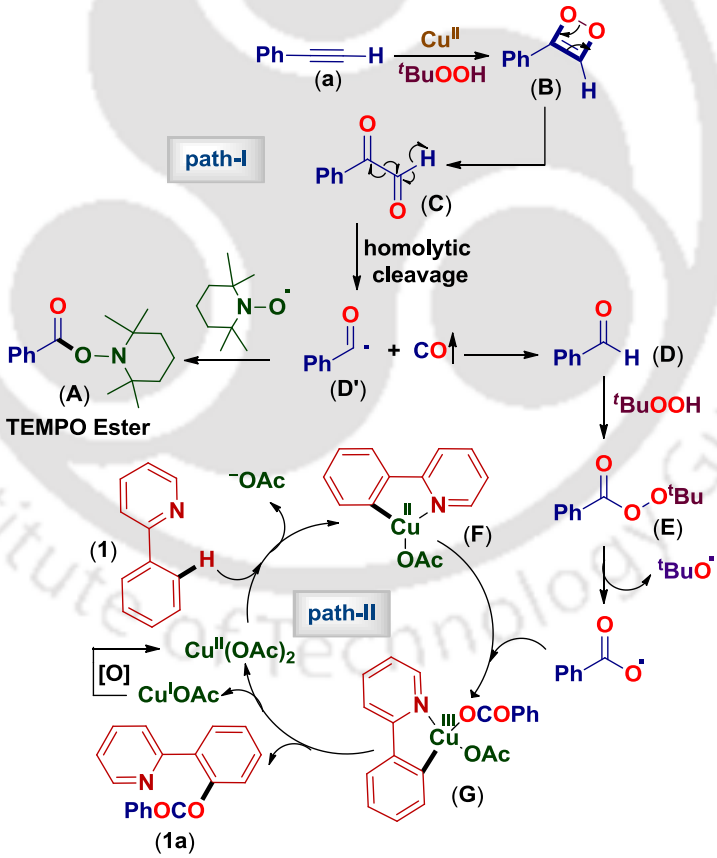


Scheme V.3.2. *A cross over experiment*



Scheme V.3.3. *Reaction in presence of radical scavenger TEMPO*

Also when a standard reaction was performed in the presence of radical quencher 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), substantial rate retardation was observed giving only traces of desired product (**1a**) along with isolation of TEMPO ester (**A**) (Scheme V.3.3) (see Experimental Section V.4.4). This result suggests the radical nature of the mechanism.



Scheme V.3.4. *Proposed mechanism for ortho-benzoxylation*

Parallel to the observations of above experiments a mechanism is proposed composing of three paths as shown in Scheme V.3.4. In path-I, phenylacetylene (**a**) possibly forms a 4-membered cyclic intermediate, 3-phenyl-1,2-dioxete (**B**) upon reaction with TBHP. The ring fragmentation of (**B**) provides phenylglyoxal (**C**) which ultimately heads to the formation of benzaldehyde (**D**) via benzoyl radical (**D′**) through radically induced decarbonylation. The action 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 ^{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 support 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 reoxidized to Cu(II) for next catalytic cycle.

In conclusion, this methodology illustrates the use of phenylacetylenes as the new surrogates for the arylcarboxy group (ArCOO–), which has been employed intriguingly for the *o*-benzoxylation of 2-phenylpyridine derivatives. 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.

V.4. Experimental section

V.4.1. General information. All the reagents were of 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.

V.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), phenylacetylene (**a**) (102 mg, 1 mmol), $Cu(OAc)_2$ (18 mg, 0.2 mmol) and TBHP in decane (5–6 M) (500 µL, 2.5 mmol). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^oC for 13 h. After stipulated time, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate (10 mL). The reaction mixture filtered through a celite bed using ethyl acetate as the eluent (20 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)phenyl 3-methylbenzoate (**1a**) (99 mg, 67% yield).

V.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 V.4.3.1 turned pale blue after 2 hrs of the reaction progress Figure V.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 colouration 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 V.4.3.1
$PdCl_2$-PMA test before reaction

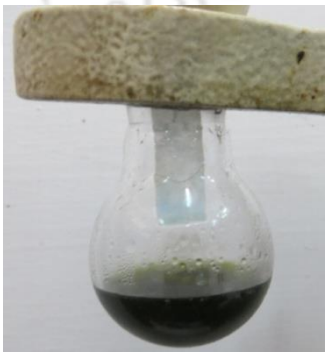


Figure V.4.3.2
$PdCl_2$-PMA test after reaction

V.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), phenylacetylene (**a**) (102 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 (**A**) (38% yield) and traces (<5%) of the desired product (**1a**) was observed. This experiment supports the formation of benzoyl radical (**D´**) in the medium from phenylglyoxal induced radically by Cu/TBHP.

V.5. References

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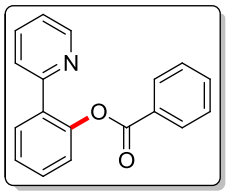
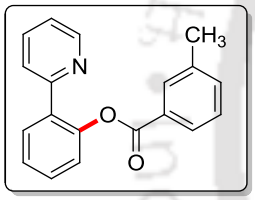
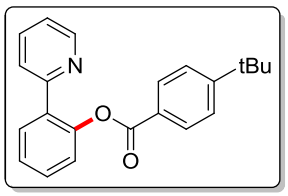
V.6. Spectral data



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.

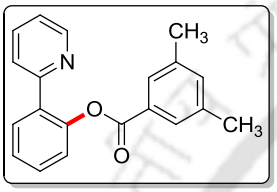


2-(Pyridin-2-yl)phenyl 3-methylbenzoate (1b): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3H), 7.13–7.17 (m, 1H), 7.28–7.34 (m, 2H), 7.37–7.41 (m, 2H), 7.45–7.49 (m, 1H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.59–7.63 (m, 1H), 7.76–7.79 (m, 1H), 7.87 (d, 2H, *J* = 8.0 Hz), 8.60 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.4, 122.3, 123.5, 123.9, 126.5, 127.5, 128.5, 129.5, 129.9, 130.9, 131.1, 133.5, 134.4, 136.3, 138.5, 148.5, 149.8, 155.7, 165.5; IR (KBr) 3051, 2917, 2853, 1734, 1635, 1587, 1462, 1425, 1274, 1182, 1083, 1064, 1024, 989, 902, 871, 751, 738 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1169.

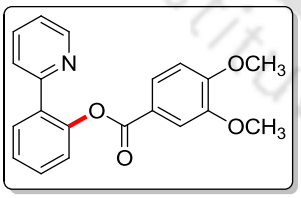


2-(Pyridin-2-yl)phenyl 4-(tert-butyl)benzoate (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (s, 9H), 7.14–7.18 (m, 1H), 7.28 (t, 1H, *J* = 7.6 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.44–7.49 (m, 3H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.60–7.65 (m, 1H), 7.78 (d, 1H, *J* = 7.6 Hz), 8.01 (d, 2H, *J* = 8.8 Hz),

8.62 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.3, 35.3, 122.3, 123.5, 124.0, 125.7, 126.5, 126.8, 129.9, 130.3, 131.1, 133.5, 136.4, 148.5, 149.8, 155.7, 157.4, 165.3; IR (KBr): 3061, 2963, 2869, 1737, 1608, 1586, 1462, 1425, 1408, 1299, 1267, 1185, 1111, 1068, 1014, 853, 792, 769, 757, 748, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{21}NO_2$ (MH^+) 332.1645; found 332.1653.

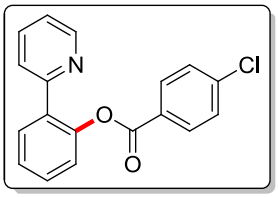


2-(Pyridin-2-yl)phenyl 3,5-dimethylbenzoate (1d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 6H), 7.13–7.16 (m, 1H), 7.20 (s, 1H), 7.25–7.29 (m, 1H), 7.35–7.39 (m, 1H), 7.43–7.47 (m, 1H), 7.54 (t, 2H, *J* = 8.0 Hz), 7.58–7.63 (m, 1H), 7.67 (s, 1H), 7.74–7.77 (m, 1H), 8.59–8.60 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 122.3, 123.4, 123.9, 126.5, 128.0, 129.4, 129.9, 131.1, 133.5, 135.3, 136.3, 138.3, 148.5, 149.7, 155.7, 165.6; IR (KBr): 3060, 3008, 2920, 2854, 1740, 1608, 1585, 1492, 1465, 1425, 1381, 1312, 1186, 1098, 1058, 995, 946, 914, 868, 794, 751, 667 cm^{-1}; HRMS (ESI): calcd.for $C_{20}H_{17}NO_2$ (MH^+) 304.1332; found 304.1333.

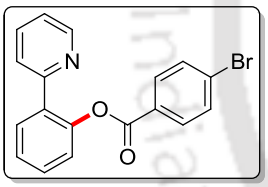


2-(Pyridin-2-yl)phenyl 3,4-dimethoxybenzoate (1e): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.89 (s, 3H), 3.95 (s, 3H), 6.90 (d, 1H, *J* = 8.8 Hz), 7.16–7.19 (m, 1H), 7.26–7.32 (m, 1H), 7.37–7.46 (m, 1H), 7.47–7.50 (m, 1H), 7.54–7.56 (m, 2H), 7.61–7.65 (m, 1H), 7.73–7.78 (m, 2H), 8.61–8.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.2, 110.5, 112.6, 122.0, 122.3, 123.5, 123.9, 124.6, 126.5, 129.9, 131.1, 133.5, 136.4, 148.5, 148.9, 149.8, 153.7, 155.8, 165.1; IR (KBr) 2923, 2852, 1729, 1634,

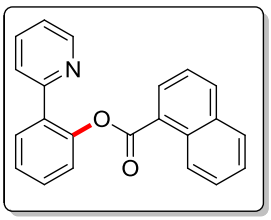
1514, 1462, 1416, 1289, 1271, 1215, 1192, 1172, 1133, 1023, 793, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_4$ (MH^+) 336.1230; found 336.1234.



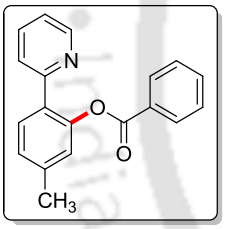
2-(Pyridin-2-yl)phenyl 4-chlorobenzoate (1f): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13–7.17 (m, 1H), 7.28–7.30 (m, 1H), 7.38–7.43 (m, 3H), 7.45–7.53 (m, 3H), 7.60–7.65 (m, 1H), 8.00 (d, 2H, *J* = 8.8 Hz), 8.55–8.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 122.4, 123.4, 123.8, 126.7, 128.1, 129.0, 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.



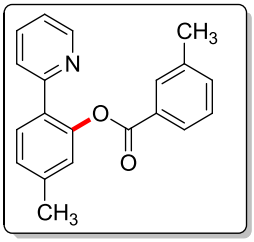
2-(Pyridin-2-yl)phenyl 4-bromobenzoate (1g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 1H), 7.29 (d, 1H, *J* = 8.4 Hz), 7.39–7.43 (m, 1H), 7.46–7.53 (m, 2H), 7.58–7.66 (m, 3H), 7.74–7.76 (m, 1H), 7.93 (d, 2H, *J* = 8.8 Hz), 8.56 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 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 1-naphthoate (1h): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.14–7.15 (m, 1H), 7.37 (d, 1H, *J* = 7.8 Hz), 7.42–7.44 (m, 1H), 7.49–7.55 (m, 3H), 7.56–7.63 (m, 2H), 7.78–7.79 (m, 2H), 7.89 (d, 1H, *J* = 7.6 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 8.30 (d, 1H, *J* = 7.8 Hz), 8.58–8.59 (m, 1H), 8.86 (d, 1H. *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.4, 123.7, 123.9, 124.7, 125.9, 126.2, 126.5, 126.7, 128.2, 128.7, 130.0, 131.1, 131.2, 131.8, 133.8, 134.0, 134.2, 136.5, 148.6, 149.8, 156.1, 165.9; IR (KBr): 3058, 2919, 2846, 1732, 1602, 1586, 1509, 1493, 1471, 1463, 1452, 1425, 1276, 1240, 1186, 1120, 1059, 982, 885, 813, 780, 659, cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}NO_2$ (MH^+) 326.1176; found 326.1179.

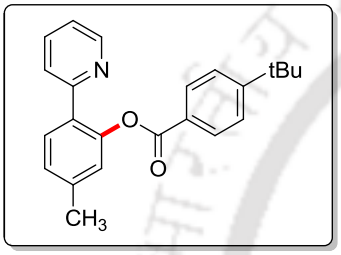


5-Methyl-2-(pyridine-2-yl)phenyl benzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.11–7.14 (m, 2H), 7.19–7.22 (m, 1H), 7.46 (t, 2H, *J* = 8.0 Hz), 7.52–7.61 (m, 3H), 7.67 (d, 1H, *J* = 7.6 Hz), 8.07–8.09 (m, 2H), 8.58 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 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, 708 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ (MH^+) 290.1176; found 290.1172.

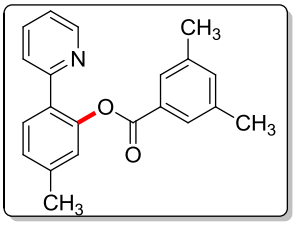


5-Methyl-2-(pyridin-2-yl)phenyl 3-methylbenzoate (2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 2.41 (s, 3H), 7.08–7.12 (m, 2H), 7.17–7.19 (m, 1H), 7.30 (t, 1H, *J* = 7.6 Hz), 7.38 (d, 1H, *J* = 7.6 Hz), 7.51–7.59 (m, 2H),

7.66 (d, 1H, *J* = 8.0 Hz), 7.86–7.89 (m, 2H), 8.57 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 29.8, 122.4, 123.4, 123.9, 126.5, 127.5, 128.5, 129.5, 129.9, 130.9, 131.1, 133.4, 134.4, 136.5, 138.5, 148.5, 149.6, 155.6, 165.5; IR (KBr): 3061, 2924, 2854, 1736, 1591, 1466, 1428, 1274, 1184, 1084, 1063, 1000, 903, 837, 751 cm^{-1}; HRMS (ESI): calcd.for $C_{20}H_{17}NO_2$ (MH^+) 304.1332; found 304.1326.

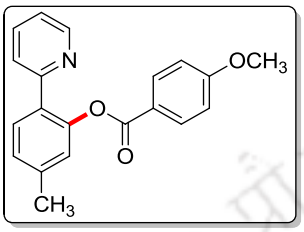


5-Methyl-2-(pyridine-2-yl)phenyl4-(*tert*butyl)benzoate (2c): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.35 (s, 9H), 2.43 (s, 3H), 7.09–7.15 (m, 2H), 7.19 (t, 1H, *J* = 7.2 Hz), 7.44–7.47 (m, 2H), 7.54 (t, 1H, *J* = 7.2 Hz), 7.58–7.61 (m, 1H), 7.67–7.69 (m, 1H), 8.01 (d, 1H, *J* = 8.4 Hz), 8.08 (d, 1H, *J* = 7.8 Hz), 8.57–8.61 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 31.3, 35.4, 122.1, 123.9, 125.7, 126.9, 127.4, 128.7, 129.8, 130.3, 133.6, 136.3, 140.4, 148.4, 149.7, 155.8, 157.4, 165.5; IR (KBr): 3058, 2963, 2868, 1736, 1608, 1587, 1465, 1431, 1408, 1259, 1187, 1152, 1131, 1110, 1064, 1025, 892, 853, 784, 748, 705 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{23}NO_2$ (MH^+) 346.1802; found 346.1809.

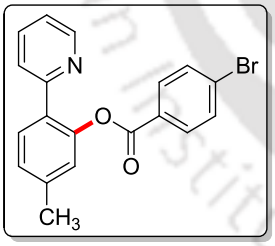


5-Methyl-2-(pyridine-2-yl)phenyl 3,5-dimethylbenzoate (2d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 6H), 2.42 (s, 3H), 7.09–7.15 (m, 2H), 7.18–7.21 (m, 2H), 7.52–7.61 (m, 2H), 7.66–7.70 (m, 3H), 8.58–8.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 21.4, 122.1, 123.8, 123.9, 127.4, 128.1, 129.5, 130.5, 130.8, 135.4, 136.4, 138.3, 140.4, 148.3, 149.7, 155.8, 165.8; IR (KBr):

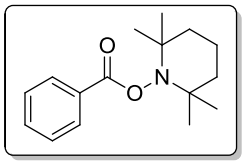
2953, 2921, 2855, 1736, 1611, 1589, 1465, 1432, 1309, 1194, 1154, 1130, 1097, 999, 947, 779, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{19}NO_2$ (MH^+) 318.1489; found 318.1484



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.



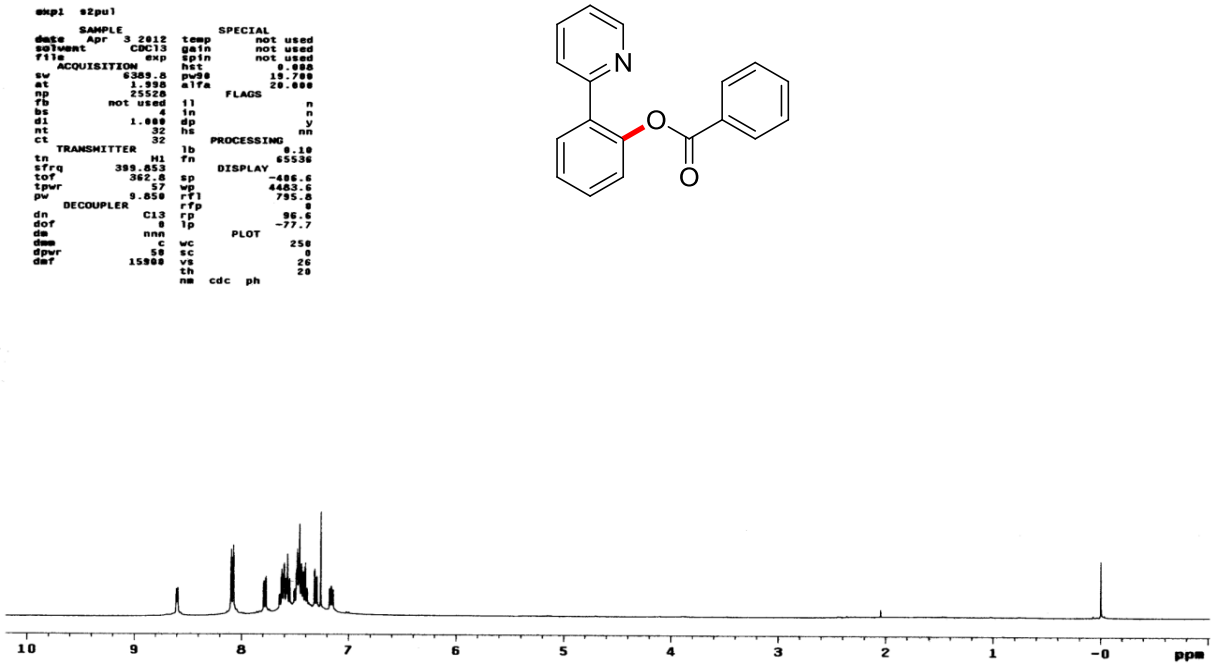
5-Methyl-2-(pyridine-2-yl)phenyl 4-bromobenzoate (2f): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.08–7.13 (m, 2H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 3H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.8 Hz), 8.51–8.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 122.2, 123.6, 123.9, 127.6, 128.7, 128.8, 130.4, 130.8, 131.8, 132.0, 136.4, 140.5, 148.1, 149.7, 155.7, 164.8; IR (KBr): 2955, 2922, 2853, 1737, 1621, 1589, 1465, 1431, 1397, 1258, 1173, 1152, 1131, 1071, 1027, 1010, 783, 747, 678 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO_2$ (MH^+) 368.0281; found 368.0275.



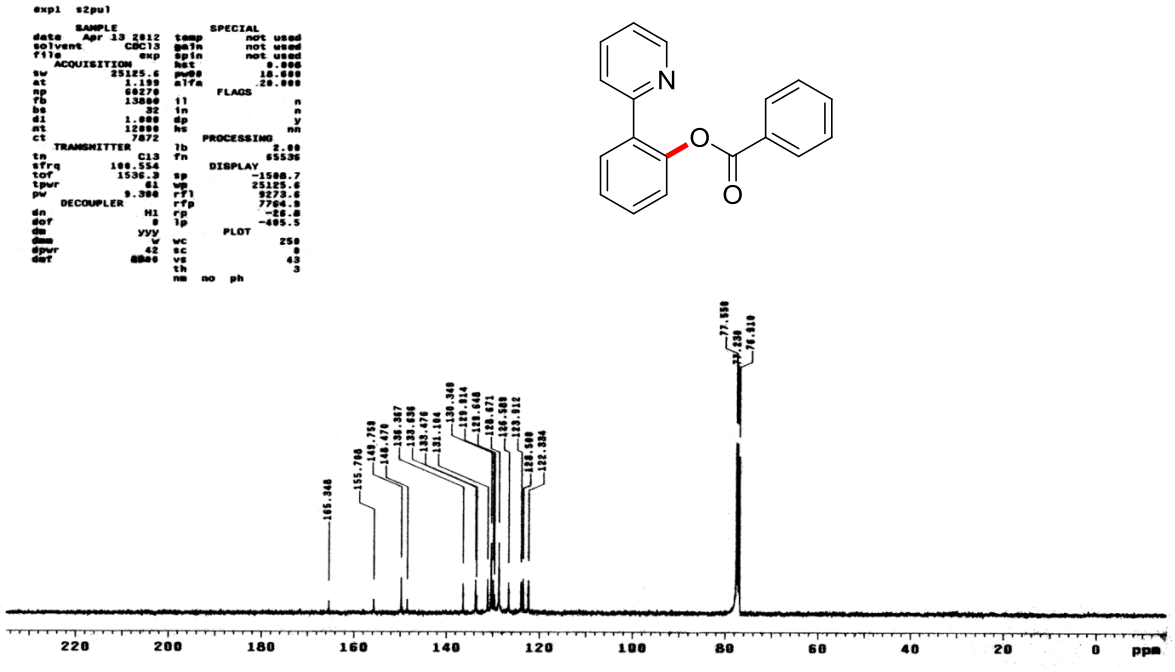
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (A): ^{1}H NMR (600 MHz, $CDCl_3$):δ (ppm) 1.12 (s, 6H), 1.26 (s, 6H), 1.42–1.45 (m, 1H), 1.55–1.58 (m, 2H), 1.66–1.78 (m, 3H), 7.43 (t, 2H, *J* = 7.8 Hz), 7.54 (t, 1H, *J* = 7.8 Hz), 8.03–8.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.2, 21.0, 32.1, 39.2, 60.6, 128.6, 129.7, 129.9, 133.0, 166.6; IR (KBr): 3007, 2973, 2940, 1741, 1641, 1452, 1365, 1253, 1238, 1083, 1062, 1026, 913, 718 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{23}NO_2$ (MH^+) 262.1802; found 262.1801.

V.7. Spectra

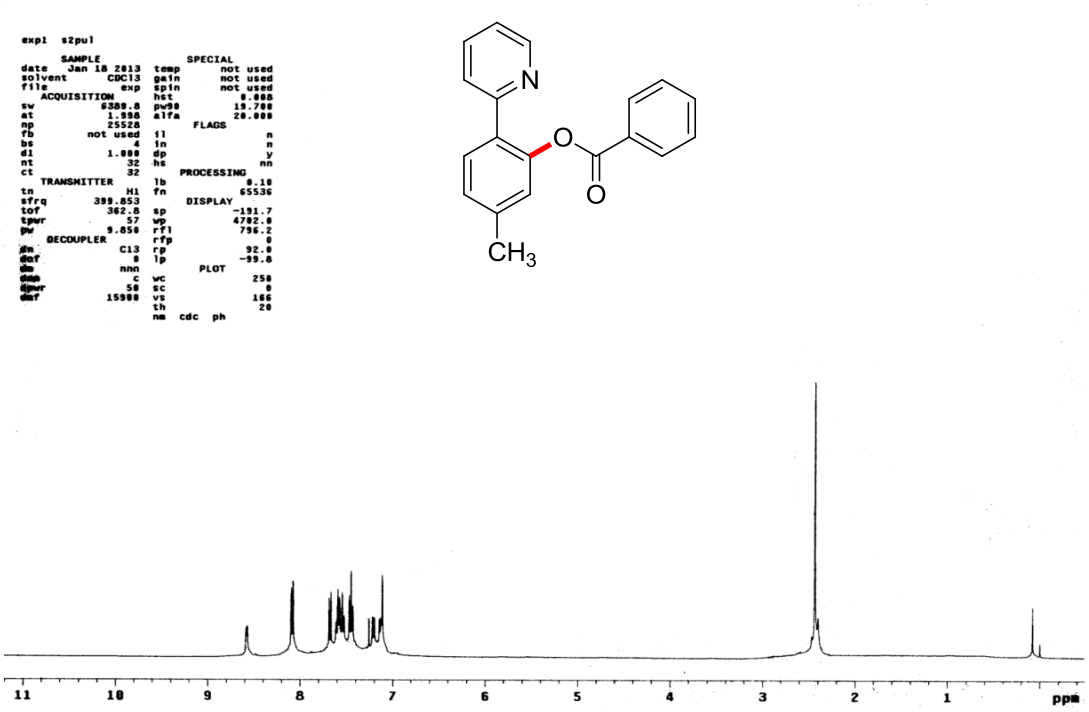
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



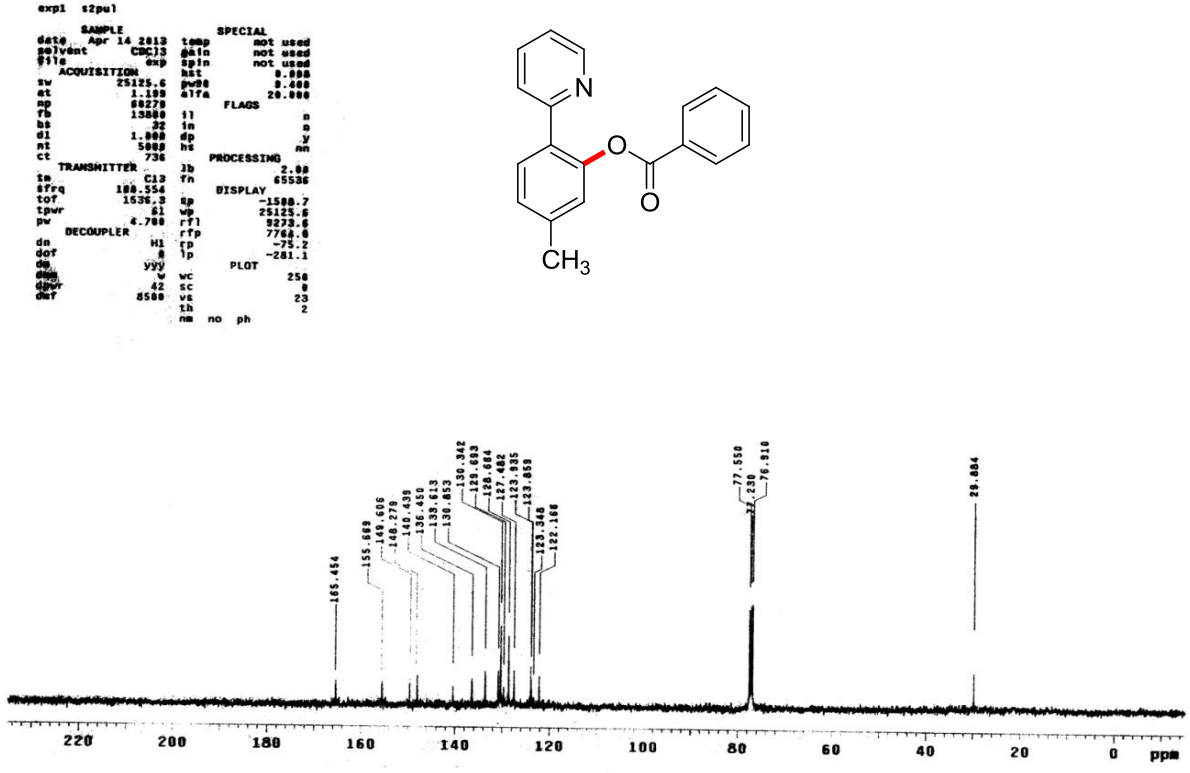
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



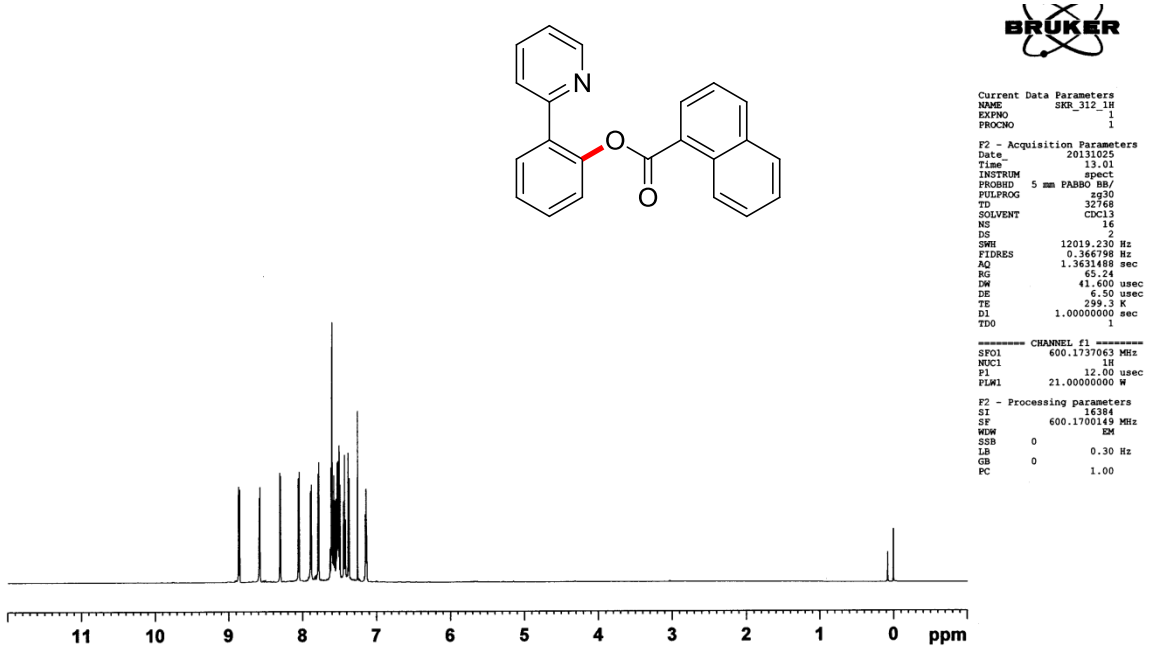
5-Methyl-2-(pyridine-2-yl)phenyl benzoate (2a): ^{1}H NMR (400 MHz, $CDCl_3$)



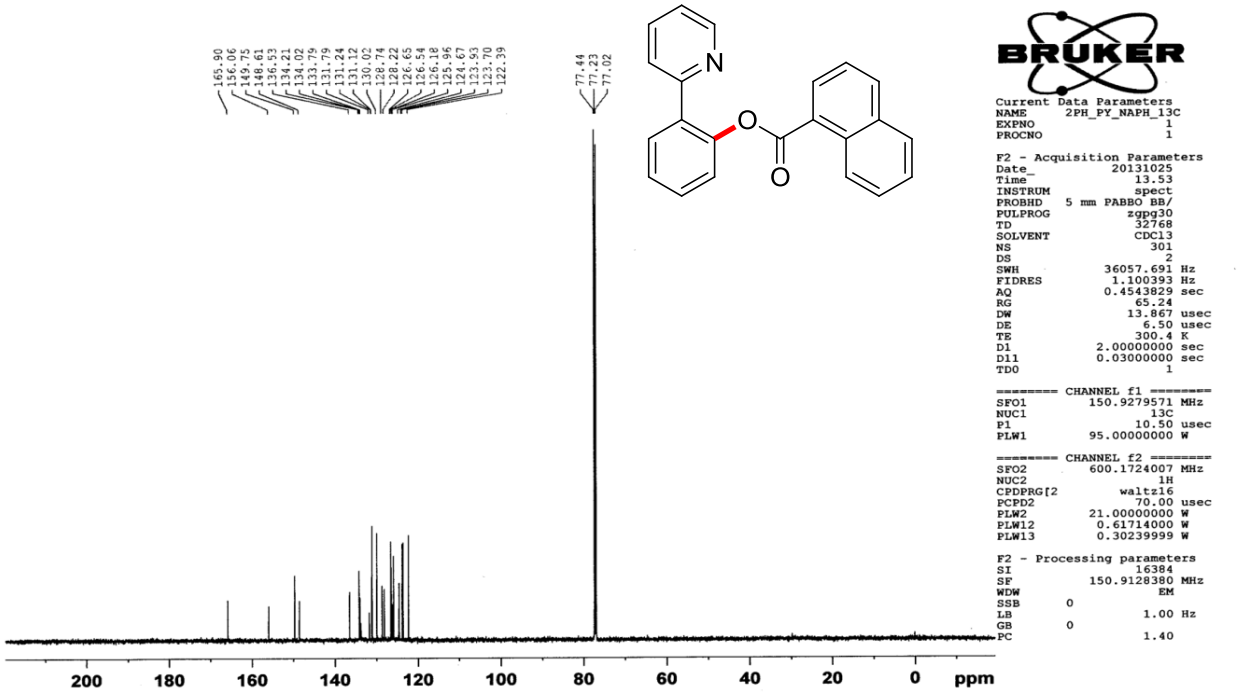
5-Methyl-2-(pyridine-2-yl)phenyl benzoate (2a): ^{13}C NMR (100 MHz, $CDCl_3$)



2-(Pyridin-2-yl)phenyl 1-naphthoate (1h): ^{1}H NMR (600 MHz, $CDCl_3$)



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



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**"
   Majji Ganesh, Srimanta Guin, **Saroj K. Rout**, Ahalya Behera, Bhisma K. Patel* *Chem. Commun.* **2014**, *50*, 12193.
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   Wajid Ali, Srimanta Guin, **Saroj K. Rout**, Anupal Gogoi, Bhisma K. Patel* *Adv. Synth. Catal.* **2014**, DOI: 10.1002/adsc.201400360.
3. "**A metal free domino synthesis of 3-aroylindoles via two sp^3 C–H activation**"
   Anupal Gogoi, Anju Modi, Srimanta Guin, **Saroj K. Rout**, Bhisma K. Patel* *Chem. Commun.* **2014**, *50*, 10445.
4. "**A palladium(II)-catalyzed synthesis of α-ketoamides via chemoselective aroyl addition to cyanamides**"
   Srimanta Guin, **Saroj K. Rout**, Anupal Gogoi, Wajid Ali, Bhisma K. Patel* *Adv. Synth. Catal.* **2014**, *356*, 2559.
5. "**Copper-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**"
   Saroj K. Rout, Srimanta Guin, Wajid Ali, Anupal Gogoi, Bhisma K. Patel* *Org. Lett.* **2014**, *16*, 1614.
7. "**Divergent reactivities of *o*-haloanilides with CuO nanoparticles in water: a green synthesis of benzoxazoles and *o*-hydroxyanilides**"
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9. "**A ligand free copper(II) catalyst is as effective as a ligand assisted Pd(II) catalyst towards intramolecular C–S bond formation via C–H functionalization**"

   Arghya Banerjee, Sourav K. Santra, **Saroj K. Rout,** Bhisma K. Patel* *Tetrahedron* **2013**, *69*, 9096.

10. "**A copper-catalyzed synthesis of 3-aroylindoles via a sp^3 C–H activation followed by C–C and C–O bond formation**"

    Anupal Gogoi, Srimanta Guin, **Saroj K. Rout**, Bhisma K. Patel* *Org. Lett.* **2013**, *15*, 1802.

11. "**Directing group assisted copper-catalyzed chemoselective *O*-aroylation of phenols and enols using alkylbenzenes**"

    Saroj K. Rout, Srimanta Guin, Arghya Banerjee, Nilufa Khatun, Anupal Gogoi, Bhisma K. Patel* *Org. Lett.* **2013**, *15*, 4106.

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    Majji Ganesh, Srimanta Guin, Anupal Gogoi, **Saroj K. Rout**, Bhisma K. Patel* *Chem. Commun.* **2013**, *49*, 3301.

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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19. "**Copper catalyzed oxidative esterification of aldehydes with alkylbenzenes via cross-dehydrogenative coupling**"
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21. "**Copper(II) catalyzed imine C–H functionalization leading to synthesis of 2,5-substituted 1,3,4-oxadiazoles**"
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22. "**Tandem regioselective synthesis of tetrazoles and related heterocycles using iodine**"
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