Oxidative C–O Bond Formation via C–H Functionalization under Metal Free Conditions

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted by

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October, 2015

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Dedicated to My Teachers

Mr. B. P. Naidu

Dr. S. Sattibabu

Mr. M. Srinivasa Rao

Prof. Bhisma K. Patel

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

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

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

October, 2015
IIT Guwahati.

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CERTIFICATE

This is to certify that Majji Ganesh has been working under my supervision since December, 2010 as a regular registered Ph. D. student. His thesis entitled "**Oxidative C–O Bond Formation via C–H Functionalization under Metal Free Conditions**" is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, 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, 2015.

Prof. Bhisma K. Patel
(Thesis Supervisor)
Department of Chemistry
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Majji Ganesh

Abstract

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 chapter I of the thesis presents introduction to metal free catalyzed C–H functionalizations, their advantages, challenges and applications in organic synthesis. All the other chapters emphasize on the oxidative C–O bond formation via C–H functionalization and oxidative cyclization under metal free conditions. Chapter II describes the syntheses of benzylic esters from alkylbenzenes as the only precursor via a cross dehydrogenative coupling (CDC) under a metal free condition involving four sp^3 C–H bond activations. A method for cyclic ethers to esters and monoesters to diesters (*gem*-diacylates) under metal free conditions via cleaving sp^3 C–H bonds in simple solvents like 1,4-dioxane, tetrahydropyran, tetrahydrofuran and ethyl acetate with terminal aryl alkenes and alkynes illustrated in chapter III. Chapter IV demonstrates the treatment of benzylamines with esters possessing α-sp^3 C–H bond in the presence of TBAI/TBHP provided *bis*-acyl ketals rather than amides. Benzylamines under the same oxidative conditions generate α-acyloxy ethers with cyclic ethers. Chapter V describes the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from *N*-aroylhydrazones and *N*-acetylhydrazones via oxidative cyclization using catalytic quantity of iodine in the presence of an aqueous hydrogen peroxide oxidant. Each of these chapters comprises of seven subsections which include introduction, literature reports, present work, experimental section, references, spectral data and some selected spectra.

CHAPTER I. Introduction to Metal Free Catalyzed C–H Functionalizations

This chapter gives a layout on metal free catalyzed C–H functionalizations, their advantages, challenges and applications in organic synthesis.

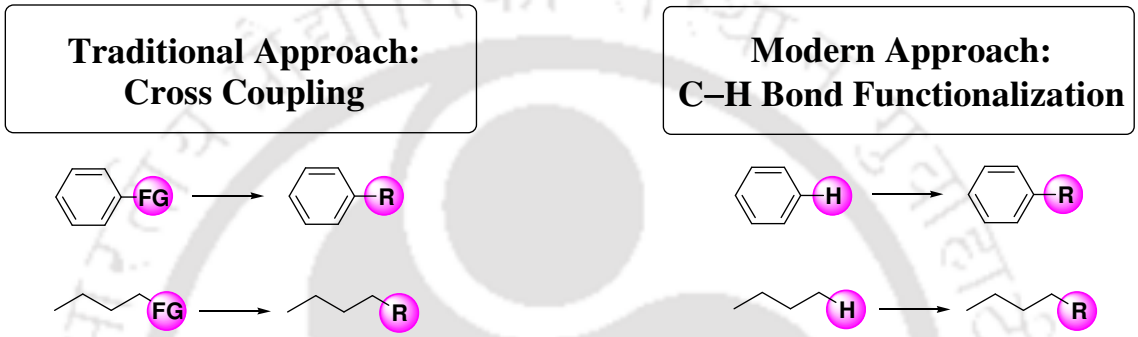
Coupling chemistry is a vital tool for synthetic chemist, which is widely used in both academia and industry. It is useful for the synthesis of various organic compounds, especially important natural products and biologically active molecules via carbon–carbon and carbon–heteroatom bond formation. Transition metal catalyzed

oxidative coupling reactions have become attractive and the topic of significant research efforts over the last few decades. However, transition metal catalyzed oxidative coupling reactions are still limited in applications and confront challenges to some extent, owing to the instinctive drawbacks of the catalytic systems. Most of the transition metal catalysts are normally expensive, toxic and sensitive to moisture. Furthermore removal of trace amounts of transition metal residues from desired products is quite costly and challenging, while crucial, especially in the pharmaceutical industry. Last but not the least, the large consumption of transition metals does not indeed meet the requirement of sustainable development. Obviously, alternative pathways to construct C–C and C–X bonds under transition metal free conditions to fulfill the transition metal catalyzed oxidative coupling reactions are highly appealing. Thus, studies on transition metal free oxidative coupling reactions are of great significance to provide a better understanding of how the reactions work with or without transition metals.

The transition metal free coupling procedures involve the use of functionalized starting materials and stoichiometric reagents via base promoted homolytic aromatic substitution (HAS), photo induced pathway, electrophilic aromatic substitution (Friedel-Crafts reaction), nucleophilic aromatic substitution, aryne intermediate pathway. There has been substantial progress in these methods over the last few years 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 prefunctionalized starting materials by the direct functionalization of C–H bonds.

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

systematic and concerted efforts have been made in C–H bond functionalization and its application in coupling chemistry. As a result exceptionally useful methods for organic synthesis have been developed, and one such strategy is the metal free catalyzed C–H bond functionalization to achieve C–C and C–X bonds (Scheme I.1). Most of these metal free methodologies stand on the cross dehydrogenative coupling (CDC). 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. *Traditional approach vs. modern approach*

The intramolecular C–C and C–X (X= heteroatom) bond formation via the intramolecular cross dehydrogenative coupling (CDC) of two carbon–hydrogen (C–H) bonds or C–H and X–H (X= heteroatom) bonds has become a very useful tool for the construction of organic compounds mainly heterocycles, which resulted in the discovery of numerous novel synthetic strategies. Compared with the coupling cyclization, this oxidative cyclization (i.e., intramolecular cross dehydrogenative coupling) strategy makes the substrates more accessible and allows more efficient synthesis of structurally diverse products since it does not require prefunctionalization of the reaction center (Scheme I.2).

Scheme I.2 *Coupling cyclization vs. oxidative cyclization*

However, the oxidative cyclization strategies involve either the use of transition metal or metal free conditions. Here, we illustrated some of metal free catalyzed oxidative cyclization reactions for C–C and C–X (X= heteroatom) bond formation.

CHAPTER II. Easy Access to Benzylic Esters Directly from AlkylBenzenes under Metal Free Conditions

This chapter focuses on the the syntheses of benzylic esters from alkylbenzenes as the only precursor via a cross dehydrogenative coupling (CDC) under a metal free condition involving four sp^3 C–H bond activations.

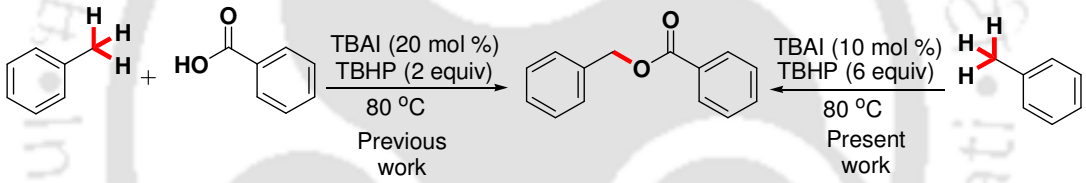
The selective oxidative cleavage of sp^3 C–H bond is of paramount interest to both academic and industrial research. The two most common strategies adopted for the C–H bond activation processes rely on the concept of chelation assisted C–H bond functionalization and cross dehydrogenative coupling (CDC). CDC based methodologies are highly appreciable because it does not require substrate prefunctionalization. Besides being atom and step economic, these reactions are often air and moisture insensitive, and thereby can be performed in an aqueous environments or an air atmosphere. The CDC approach has been mainly exploited towards the C–C bond formations, but of late the numbers of C–O bond forming reactions are also increasing.

The CDC based protocols in the construction of C–O bond have been achieved using transition metal catalysts such as Cu, Fe, Ru, Rh, Ir, and Pd in combination with various oxidants. However, the disadvantages associated with these methodologies, owing to the use of expensive metal catalysts, elevated reaction temperature and the problems associated with the removal of metal residues limit their practical applicability. Therefore, increasing interest has been focused on metal free catalysts particularly towards the formation of a C–O bond.

Selective to the C–O bond formation, the ester functionalities particularly, the benzylic esters are common target because of their applications in synthetic organic and medicinal chemistry. Besides the traditional esterification reactions involving alcohols and acids (or their equivalents), several elegant protocols have been developed lately. Catalysts such as Ru, Rh, Ir, Pd and V have been employed for the cross dehydrogenative coupling (CDC) between aldehydes or the *in situ* generated aldehydes

and alcohols for the synthesis of benzylic esters. Most of these processes rely on the concept of either hydrogen borrowing or a hydrogen auto transfer process.

Recently a CDC based approach has been developed by our group for the synthesis of benzylic esters from aryl aldehydes and alkylbenzenes using Cu(II) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant. Efficient coupling of carboxylic acids or the *in situ* generated carboxylic acids and alkylbenzenes have also been reported under a metal free conditions using tetra *n*-butylammonium iodide (Bu_4NI) as the catalyst and TBHP as the oxidant (Scheme II.1). Here, we developed a metal free protocol for the synthesis of benzylic esters via a cross dehydrogenative coupling (CDC) involving alkylbenzene(s) as a self or as a cross coupling partner(s) via the intermediacy of (Ar-COOH) and the benzylic carbocation obtained from the other half of the alkylbenzene; both symmetrical as well as unsymmetrical esters can be prepared using Bu_4NI and TBHP (Scheme II.1).

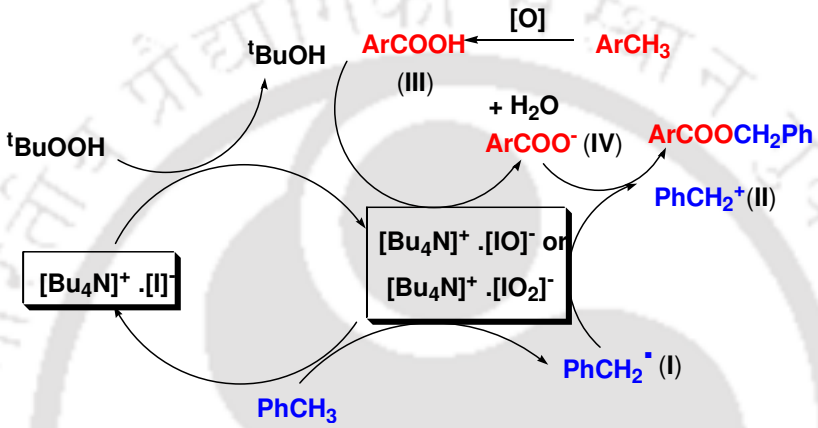


Scheme II.1. *Bu_4NI-catalyzed synthesis of benzylic esters*

To attain a suitable reaction condition for the synthesis of benzylic esters various reaction parameters such as catalysts, oxidants were screened to achieve the maximum possible yield. After a series of experimentation the optimized reaction condition arrived was Toluene (1 mL), Bu_4NI (10 mol %), aqueous TBHP (70% in water) (6 equiv) at 80 ^oC. In light of these novel observations the optimized conditions were subsequently applied to various toluenes towards self oxidative esterification. It was observed that, under the present conditions, toluene with electron-donating substituents, the reactions proceeded smoothly to afford the desired self coupled benzylic esters in excellent yields. For toluenes possessing electron-withdrawing substituents, the reaction provided the desired benzylic esters in good yields but the reactions were a bit sluggish. With this motivation the present methodology was next sought towards the cross dehydrogenative coupling (CDC) between ethylbenzene and various substituted toluenes. In all their reactions, the corresponding benzylic esters were obtained in moderate to high yields via

a selective C–O bond formation at the more stable 2° benzylic carbon of the ethylbenzene. This methodology is also equally successful for CDC between isopropylbenzene and alkyl benzenes giving modest yield of unsymmetrical esters. However, the yields obtained were lower than expected which could be due to steric factor imparted by the isopropyl group.

Taking cues from the literature and the controlled experiments carried out, a plausible mechanism has been proposed for this transformation (Scheme II.2).



Scheme II.2. *Proposed mechanism of the oxidative esterification*

In conclusion, for the first time benzylic esters have been prepared from alkylbenzenes as the only precursor via a cross dehydrogenative coupling (CDC) under a metal free condition involving four sp^3 C–H bond activations. This method gives self coupled product for mono or poly methylatedbenzenes. The cross coupled product can be prepared from ethylbenzene and methylbenzene where acid part is derived from methylbenzene and the benzyl cation is derived from ethylbenzene. A various functional groups are tolerated under the present reaction conditions. Thus this approach has great academic and industrial significance.

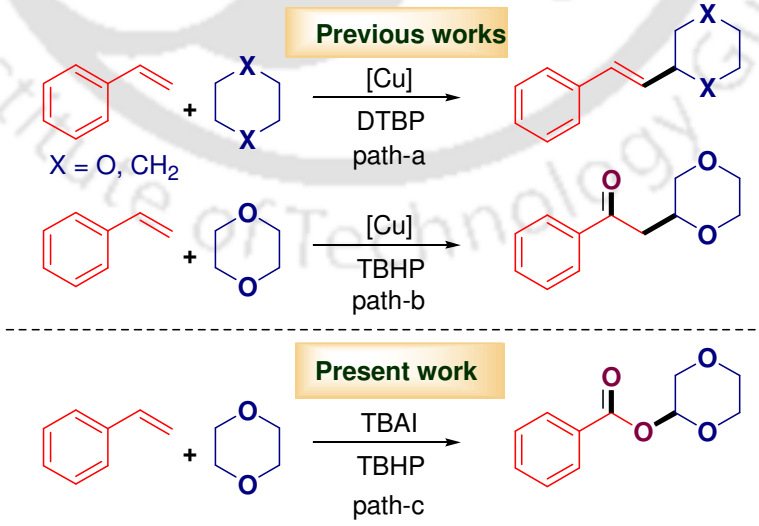
CHAPTER III. Cyclic Ethers to Esters and Monoesters to *bis*-Esters with Unconventional Coupling Partners under Metal Free Conditions via sp^3 C–H Functionalization

This chapter describes a metal free oxidative esterification of sp^3 C–H bonds (adjacent to an oxygen atom) in simple solvents like 1,4-dioxane, tetarhydropyran,

tetrahydrofuran and ethyl acetate with terminal aryl alkenes and alkynes as ArCOO– sources.

Organic chemists continue to strive towards the development of atom and step economic process for the synthesis of complex molecular structures from simple precursors. What better way to achieve this than to manipulate ubiquitous C–H bonds? In this regard, 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. 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. One of the extensively studied approaches in this forum is the substrate directed alkenylations using Rh, Ru and Pd catalysts. However, scrutiny entails that most of these transformations are for sp^2 C–H bonds facilitated by a multitude of directing groups. In contrast, due to their intrinsically low reactivity (high p*K*a and bond energy) similar alkenylation at sp^3 C–H bonds remain virtually unexplored.

The recently developed radically induced vinylation of the sp^3 C–H bonds of cyclic ethers and cycloalkanes using a copper catalyst are the only two reports to date (Scheme III.1, path-a). The current trend in organic synthesis is to use and encourage metal-free catalysts such as iodine, iodide salts and organoammonium iodides, which are often appropriate substitutes to transition metals.



Scheme III.1. *Differential reactivity of alkenylbenzene with cyclic ethers*

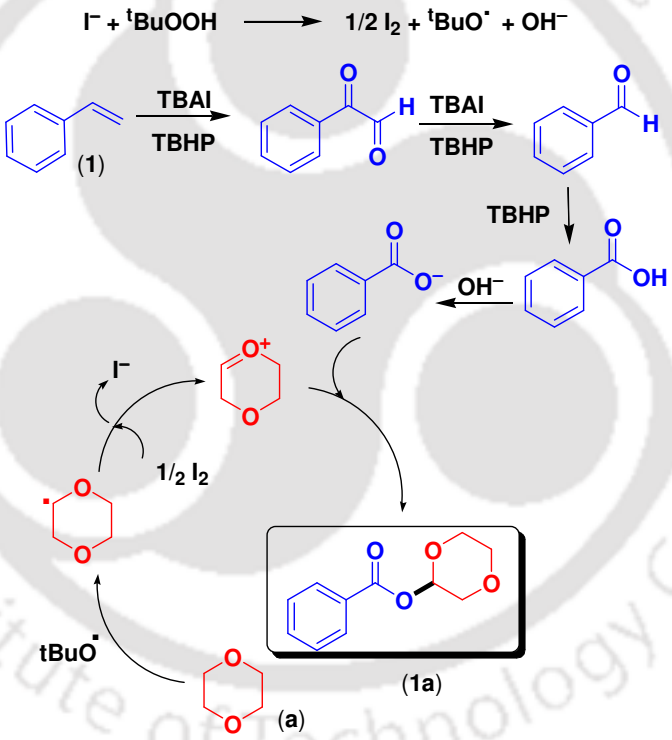
These metal free catalysts (in combination with oxidant) either complement or show similar reactivity to that of transition metals in bringing about requisite transformations. In addition, their use is highly advantageous from an enviroeconomic point of view for a sustainable future. In order to achieve the same, we attempted similar alkenylation of dioxane with styrene under metal free conditions. However, instead of alkenylation of dioxane it led to an unexpected α-esterification of dioxane (i.e. α-acyloxy ether formation) (Scheme III.1, path-c). Notably, the coupling of styrene with cyclic ether in presence of CuBr/TBHP is reported to undergo oxyalkylation i.e. ketone formation (Scheme III.1, path-b). Thus the divergence in selectivities achieved with various catalyst/oxidant combinations further highlights the significance of the present finding.

Various reaction parameters such as catalysts, oxidants and temperature were screened to obtain the optimal conditions for this reaction and it was found that the ideal conditions are the use of Bu_4NI (20 mol %), decane solution of TBHP (5−6 M) (6 equiv) and a reaction temperature of 80 ^oC. The optimized conditions were then executed for oxidative esterification of sp^3 C−H bonds (adjacent to an oxygen atom) in 1,4-dioxane, tetarhydropyran, tetrahydrofuran with various styrenes and phenylacetylenes. It was observed that, substituted styrenes containing electron-donating groups provided the corresponding products in higher yields than those bearing electron-withdrawing groups. The lower yields of products obtained with phenylacetylenes compared to styrenes is due to the competitive homocoupling of terminal alkynes to diynes under the reaction conditions.

Ethyl acetate (bearing sp^3 C−H α to oxygen) is predominantly used as a solvent and a diluent. The oxidative α C−H functionalization of ethyl acetate is a very exigent task because it is prone to hydrolysis and *trans*-esterification. Thus selective functionalizations of ethyl acetate would not only be a challenging task but also exciting if achieved. To explore this, the above optimized conditions were implemented on ethyl acetate by treating it with styrene. Interestingly, the product obtained was found to be a double ester formed via functionalization at the α-sp^3 C−H of ethyl acetate without affecting the existing ester functionality. This double esterification of ethyl acetate was then tested with various styrenes and phenylacetylenes; all provided unsymmetrical *gem*-diacylates in moderate yields.

Several control experiments were carried out to depict a plausible mechanism for these coupling reactions (Scheme III.2). A similar mechanism can be proposed involving ethyl acetate instead of cyclic ether.

In conclusion, we have developed a method for cyclic ethers to esters and monoesters to diesters (*gem*-diacylates) under metal free conditions cleaving sp^3 C–H bonds in simple solvents like 1,4-dioxane, tetrahydropyran, tetrahydrofuran and ethyl acetate with terminal aryl alkenes and alkynes. The coupling partners are the *in situ* generated $ArCOO^-$ from styrenes and phenylacetylenes and the solvents (cyclic ethers and ethyl acetate). Conceptually C=C bond cleavage of styrene to generate benzaldehyde can be considered as substitute of ozonolysis.



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

CHAPTER IV. Generation of *bis*-Acyl Ketals from Esters and Benzyl Amines under Oxidative Conditions

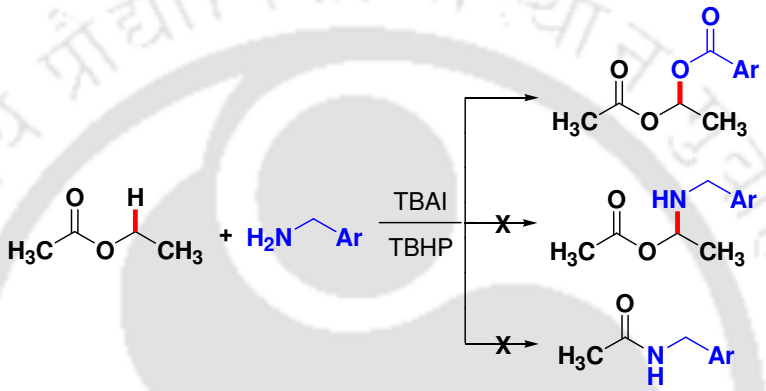
This chapter demonstrates the treatment of benzylamines with esters and cyclic ethers possessing α-sp^3 C–H bond in the presence of TBAI/TBHP provided *bis*-acyl ketals and α-acyloxy ethers respectively.

In the modern era of organic chemistry, the atom and step economical synthesis of complex target molecules from simple precursors via direct C(sp^3)–H bond functionalization is of paramount interest to both academia and industrial research. Thus, synthetic chemists continue to strive toward the development of "ideal synthetic procedures" to directly transform C–H bonds into other functional groups, which could eventually be applied to the synthesis of natural products. In this perspective, cross dehydrogenative coupling (CDC) has played a vital role in the construction of a diverse array of C–C and C–heteroatom bonds, by functionalizing C–H bonds of all types. One of the extensively studied approaches in this forum is the CDC strategy involving simple solvents (i.e., alkylbenzenes, cyclic ethers, and cycloalkanes with various coupling partners), most of which have ultimately lead to the synthesis of esters via C(sp^3)–H functionalization.

Barring one example from our group, functionalization of α-sp^3 C–H bond in ethyl acetate (ester) has been virtually unexplored. Ethyl acetate is predominantly used as a solvent and diluents because it is inexpensive and less toxic. Due to its reactive nature toward various nucleophiles and its susceptibility to hydrolysis, selective functionalization of esters in general and ethyl acetate in particular is a challenging task. Pertinent to this "solvent chemistry" in CDC reactions, recently our group has developed a protocol for the synthesis of esters via oxidative esterification of α-sp^3 C–H bond in ethyl acetate with terminal alkenes and alkynes under metal-free conditions, where alkenes and alkynes served as ArCOO- surrogates. It would be exciting if one can explore the selective α-sp^3 C–H functionalization of ethyl acetate as uncharted so far.

Benzylamines are latent sources to aroyl (ArCO–) and aryl carboxy (ArCOO–) groups. The Wu group has reported a Pd catalyzed *ortho*-acylation of 2-phenylpyridine using benzylamines, where it serves as ArCO- surrogates. Very recently our group has developed a copper-catalyzed protocol for the *o*-benzoxylation of 2-phenylpyridines using benzylamines as the arylcarboxy (ArCOO–) equivalents. Recently, alkenes and alkynes are also found to be the surrogates of the ArCOO- group and have been utilized for the *bis*-esterification of ethyl acetate. Further, when Pd is used as the catalyst, benzylamine act as an aroyl (ArCO–) source, while the use of Cu installs an aryl carboxy (ArCOO–) group into *ortho*-directing substrates. Of late, metal free combinations, *viz.,*

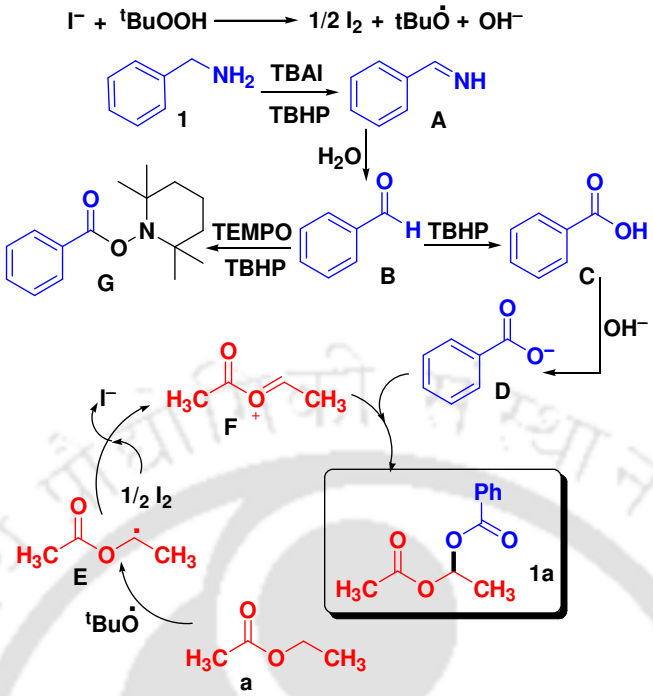
tetrabutylammonium iodide (TBAI) / TBHP, are an efficient substitute to transition metals/oxidant combinations. Thus, the reaction of benzylamine and ethyl acetate under a metal-free oxidative condition is expected to yield an amide or a *bis*-ester of ethyl acetate. When we treated benzylamine with ethyl acetate under metal free conditions, outcome of the reaction observed was not amidation, rather it was further esterification of ethyl acetate (Scheme IV.1). This observation suggests incorporation of the ArCOO-group into an ester where benzylamine serves as a source to the aryl carboxy (ArCOO–) group.



Scheme IV.1. *Selectivity achieved with benzylamine and ethyl acetate*

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 Bu_4NI (20 mol %), and aqueous TBHP (70% in water) (6 equiv) at a temperature of 80 ^oC afforded the maximum possible yield of the desired product.

The optimized conditions were then implemented for the oxidative esterification of ethyl acetate, *n*-propyl acetate and *n*-butyl acetate using various substituted benzylamines. It was observed that substituted benzylamines possessing electron-withdrawing groups provided the corresponding products in lower yields than those bearing electron-donating groups. This approach was subsequently applied to cyclic ethers such as 1,4-dioxane, tetrahydropyran and tetrahydrofuran. Unlike in 1,4-dioxane, the oxidative esterification of tetrahydropyran and tetrahydrofuran with benzylamines were not so effective in terms of yields, and they afforded α-acyloxy ethers in lower yields. Taking cues from the control experiments that were carried out and from the literature reports, a possible mechanism has been proposed (Scheme IV.2).



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

In conclusion, treatment of benzylamines with esters possessing α-sp^3 C–H bond in the presence of TBAI/TBHP provided *bis*-acyl ketals rather than amides. Symmetrical cyclic ethers afforded a monoester; however, unsymmetrical cyclic ether provided a single regioisomeric ester via sp^3 C–H bond functionalization. Benzylamine under oxidative condition provided aryl carboxylic ion which is one of the coupling partners in this solvent chemistry. A plausible reaction mechanism involving radical pathways has been suggested for this CDC coupling.

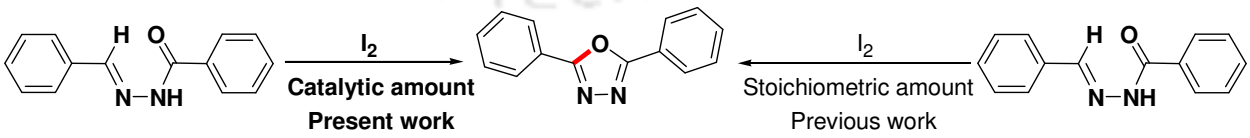
CHAPTER V. Iodine–Catalyzed Oxidative Cyclization of Acylhydrazones to 2,5-Substituted 1,3,4-Oxadiazoles

This chapter deals with an iodine catalyzed synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from *N*-aroylhydrazones and *N*-acetylhydrazones via oxidative cyclization.

1,3,4-Oxadiazoles, a π-conjugated heterocycle are an interesting class of compound since molecule possessing this skeleton has been widely used in materials science and medicinal chemistry. Due to myriad of applications of 1,3,4-oxadiazole motif several methodologies are described in the literature for their synthesis. These

scaffolds are synthesized by the electrophilic substitution of 2-substituted-5-trimethylsilyl-1,3,4-oxadiazole toward various electrophiles such as Cl_2, Br_2, acyl chlorides or isocyanates. An alternative route to 2,5-disubstituted 1,3,4-oxadiazoles is via the dehydrative cyclization of 1,2-diacylhydrazines. Typically, a dehydrative cyclization is carried out using reagents such as phosphorus oxychloride, sulphuric acid, thionyl chloride, PPA or $[Et_2NSF_2]BF_4$. Besides the traditional synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, involving acyl chlorides or carboxylic acids with acid hydrazines or hydrazides, some elegant protocols have also been developed.

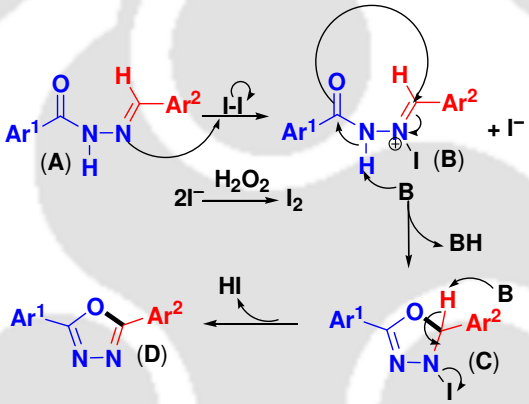
Miura group has developed a copper mediated C–H arylation of a preformed 2-substituted 1,3,4-oxadiazole with an aryl halide. Recently we have achieved direct access to the synthesis of both symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles via the imine C–H bond functionalization of *N*-arylidenearoylhydrazides or aroylhydrazone using catalytic quantity of $Cu(OTf)_2$. However, the disadvantages associated with the aforementioned methodologies, owing to the use of expensive, hazardous materials or cumbersome multi-stepped processes bind them to limited synthetic scope. Usually iodine mediated reactions are preferred over metal catalyzed oxidation in pharmaceutical industries due to avoiding the need for removal of metal impurities, low cost, being environmental benign and operational simplicity. Oxidative cyclization of *N*-acylhydrazones with iodine is another convenient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. Chang group reported oxidative cyclization of acylhydrazones into 1,3,4-oxadiazoles by employing stoichiometric molecular iodine (Scheme V.1). Here, we developed an iodine catalyzed oxidative cyclization of acylhydrazones for the synthesis of 2,5-substituted 1,3,4-oxadiazoles (Scheme V.1).



Scheme V.1. *Synthesis of 2,5-substituted 1,3,4-oxadiazoles via oxidative cyclization*

Rigorous optimizations were carried out to establish the suitable conditions for this transformation. The use of iodine (10 mol %), aq. H_2O_2 (4 equiv) and K_2CO_3 (2 equiv) in DMSO at room temperature gave the maximum yield of the desired 2,5-

substituted 1,3,4-oxadiazole. Having the above optimized conditions in hand various *N*-benzoylhydrazones derived from benzoylhydrazide and various aldehydes were subjected to the present reaction conditions. This methodology gave better yields of the products for substrates possessing electron donating groups in the aryl ring of the precursor aldehyde. The present reaction conditions when applied to various *N*-acetylhydrazone failed to give good yields of the products. Interestingly upon increasing the reaction temperature to 50 ^{o}C and the use of the stronger base Cs_2CO_3 gave satisfactory yields of various 2,5-substituted 1,3,4-oxadiazoles. Based on literature reports and the control experiments carried out a possible mechanism has been proposed for the formation of 2,5-substituted 1,3,4-oxadiazoles (Scheme V.2).



Scheme V.2. *Proposed mechanism for the formation of 2,5-substituted 1,3,4-oxadiazoles*

In conclusion, we have developed an oxidative cyclization method using I_2/ H_2O_2 catalytic system for the synthesis of 2,5-substituted 1,3,4-oxadiazoles. An inexpensive, environmental friendly catalyst, mild reaction conditions and compatibility with a wide range of substrates make this method superior to all methods documented in literature.

Contents

CHAPTER I

Metal Free Catalyzed C–H Functionalizations

CHAPTER I

I. Introduction to Metal Free Catalyzed C–H Functionalizations

I.1. Introduction

Coupling chemistry is a vital tool for synthetic chemist, which is used widely in both academia and industry for the synthesis of various organic compounds, especially important natural products and biologically active molecules via carbon–carbon and carbon–heteroatom bond formation.[1]

Transition metal catalyzed oxidative coupling reactions have become attractive and the topic of significant research efforts over the last few decades.[2] However, transition metal catalyzed oxidative coupling reactions are still limited in applications and confront challenges to some extent, owing to the inherent drawbacks of the catalytic systems. Most of the transition metal catalysts are normally expensive, toxic and sensitive to moisture. Furthermore, removal of trace amounts of transition metal residues from desired products is quite expensive and challenging, while crucial, especially in the pharmaceutical industry.[3] In many of these reactions, special additives and co catalysts are also critical to promote the efficiency and selectivity of transformations.[4] Last but not the least, the large consumption of transition metals does not indeed meet the requirement of sustainable development.[5] Obviously, alternative pathways to construct C–C and C–X bonds under transition metal free conditions to fulfil the transition metal catalyzed oxidative coupling reactions are highly appealing. Thus, studies on transition metal free oxidative coupling reactions are of great significance to provide a better understanding of how the reactions work with or without transition metals.

The transition metal free coupling procedures involve the use of functionalized starting materials and stoichiometric reagents via base promoted homolytic aromatic substitution (HAS), photo induced pathway, electrophilic aromatic substitution (Friedel-Crafts reaction), nucleophilic aromatic substitution, aryne intermediate pathway. There has been substantial progress in these methods over the last few years and they are successfully applied in the synthesis of commercially important products.[6] However, the

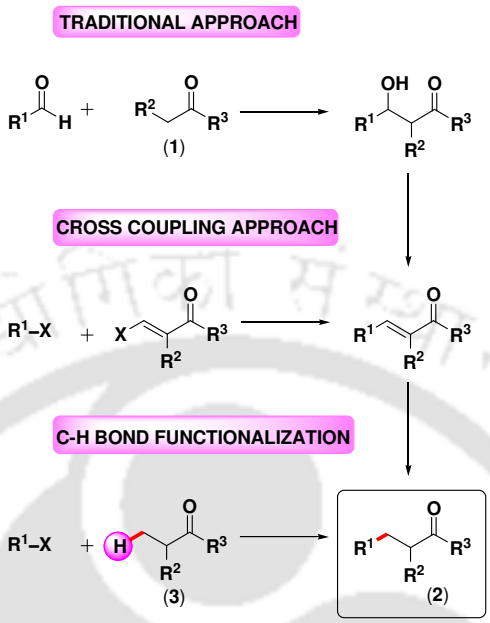
use of prefunctionalized starting materials in these methods, thus adding steps towards the formation of desired chemical bond, is a major concern for the synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize un-functionalized starting materials by the direct functionalization of C–H bonds.[7]

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

I.2. Comparison between Traditional Coupling and C–H Functionalization

The introduction of new functionality directly through transformation of C–H bonds unlocks opportunities for different synthetic strategies. For example, traditional approach involves several steps that converts compound (**1**) to product (**2**) as shown in Scheme I.2.1. The same target molecule (**2**) may be accessed in a single step by displacement of a hydrogen atom (Scheme I.2.1). Considering the high abundance of C–H bonds, precise one-step substitution of C–H 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. As exemplified in Scheme I.2.1, selective C–H bond

functionalization provides a straightforward approach for the synthesis product (**2**) from compound (**3**).



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

From the above comparison study between traditional cross coupling and C–H functionalization strategy, it can be conclude that the C–H functionalization is very beneficial due to the following reasons:

- ❖ C–H bonds are ubiquitous/ could provide new disconnections
- ❖ No need of pre-functionalization of the starting materials
- ❖ Step and atom economical
- ❖ Cost effective and energy saving process
- ❖ Waste generation reduced considerably

I.3. Challenges to C–H Functionalizations

Although C–H functionalizations are advantageous, the use of C–H bond as the coupling partner is challenging due to following reasons:

- ➢ **Inherent low reactivity:** C–H bonds are extremely inert to both homolytic and heterolytic cleavage due to their high bond dissociation energy (BDE) and pK_a values. The bond strength and pK_a values of various C–H bonds are shown in Table I.3.1.

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

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

- **Regioselectivity:** C–H bonds are ubiquitous in organic molecules; therefore, designing a strategy that selectively functionalizes a single C–H bond keeping all others as intact within a complex molecule is difficult. For example, the pharmaceutical compound Prozac possesses multiple, unique C–H bonds. Regioselective functionalization of any one of these sites could be desirable to study pharmacokinetics (Figure I.3.1).

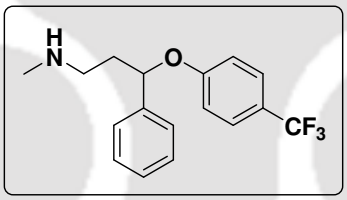
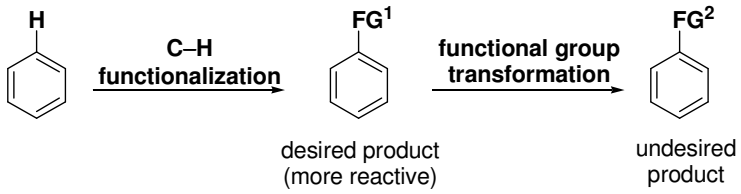


Figure I.3.1. *The pharmaceutical compound having multiple, unique C–H bonds*

- **Chemoselectivity:** The failure to stop functionalization process at required stage to obtain the desired product represents another challenge in this area. If the product formed is more reactive than the starting precursor, the functionalized product may participate in further functional group transformation under the same reaction conditions; therefore deviating from the actual goal (Scheme I.3.1).



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

Apart from the above three fundamental challenges, a C–H functionalization process is also associated with certain minor issues i.e., controlling of competing side reactions such as homo-and hetero-coupling and preservation of the certain existing functional moieties in starting precursors.

I.4. Metal Free Catalyzed C–H Bond Functionalization via Cross Dehydrogenative Coupling (CDC) Approach

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.[2a,8] This CDC reaction is a step and atom-economic process for the generation of pharmaceuticals and diverse other materials. In terms of atom economy, CDC strategy represents one of the most ideal synthetic procedures for selective C–C and C–X bond forming reactions. This strategy is becoming more attractive due to high degree of C–H bond functionalization, non-requirement of any directing groups, requirement of ambient reaction conditions and simple starting materials, formation of environmentally acceptable by-products.

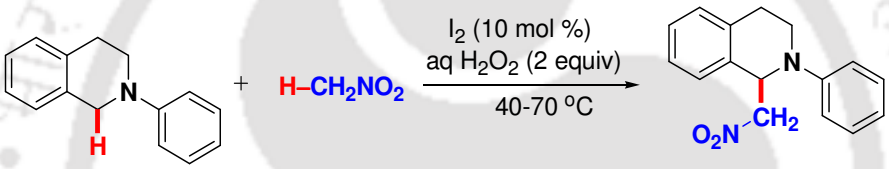
Inspired by this green and sustainable chemistry, synthetic chemists have developed numerous CDC protocols. Interestingly, there are some examples of CDCs that have been successfully applied in water, consequently, further enhancing their environmental friendliness.[2a,8] But many of these methods are based on transition metal catalysis, which is not universally acceptable in terms either cost or toxicity and the other limitations such as regioselectivity, chemoselectivity and the necessity for additional oxidants such as hydrogen peroxide, organic peroxides i.e., *tert*-butyl hydrogen peroxide (TBHP) or *tert*-butyl peroxide (TBP), and *N*-halosuccinimides i.e., *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS).

As an alternative to transition metal catalyzed reactions, metal free versions have become more important due to low cost and environmental acceptability. Substantial advancement in metal free oxidative C–C and C–X (X= heteroatoms) bond forming reactions via C–H functionalization has recently taken place.[8d,9]

I.4.1. Representative Examples of Carbon-Carbon Bond Formation

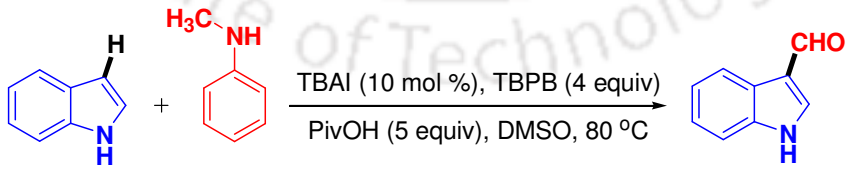
C–C Bond formation provides the requisite connectivity for the synthesis of a large and complex molecular structure from simple precursors. Recently developed protocol in this field is metal free catalyzed C–H bond functionalization via cross dehydrogenative coupling (CDC). Representative examples pertaining to various forms of C–C bond formations are discussed below.

Itoh and co-workers developed a protocol for the C–C bond formation between tertiary amines and carbon nucleophiles (nitroalkanes and carbonyl compounds) using iodine and hydrogen peroxide catalytic system (Scheme I.4.1.1).[10] This is the first molecular iodine catalyzed cross dehydrogenative coupling (CDC) reaction involving two sp^3 C–H bonds.



Scheme I.4.1.1. *Iodine-catalyzed cross dehydrogenative coupling (CDC) of tertiary amines and carbon nucleophiles*

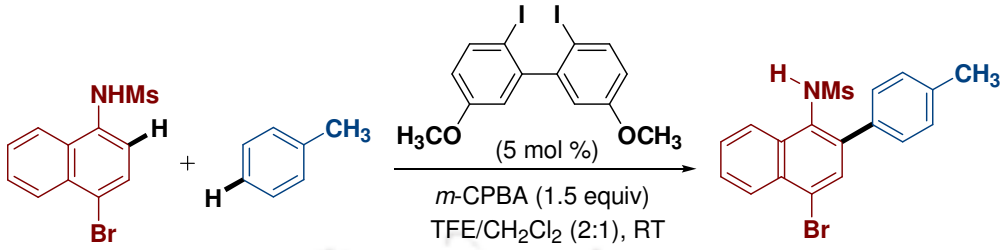
Wang group illustrated a tetrabutylammonium iodide (TBAI)-catalyzed C3-formylation of indoles using *N*-methylaniline as a formylating reagent (Scheme I.4.1.2).[11] Various N–H and *N*-substituted indoles were tolerated under reaction conditions and afforded corresponding formylated indoles in good yields, without need of toxic phosphorus oxychloride and transition metal catalyst.



Scheme I.4.1.2. *TBAI-catalyzed C3-formylation of indoles*

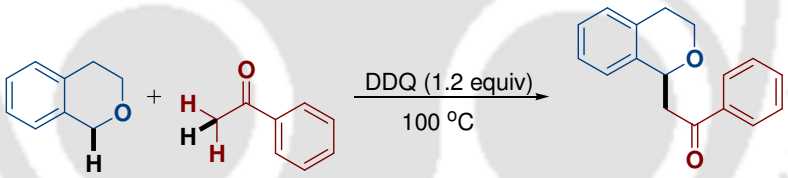
Kita *et al.* reported an organocatalytic oxidative C–C bond formation via biaryl cross coupling between *N*-methanesulfonyl anilides and aromatic hydrocarbons (Scheme I.4.1.3).[12] In this method, the desired products were obtained in good to excellent yields

under metal free (substituted 2,2'-diiodobiphenyls/*meta*-chloroperbenzoic acid) conditions.



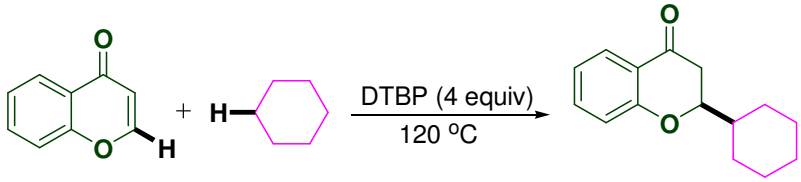
Scheme I.4.1.3. *Organocatalytic oxidative C–C bond formation via biaryl cross coupling*

DDQ-mediated direct cross dehydrogenative coupling (CDC) of benzyl ethers with simple ketones via C–C bond formation was developed by Li group (Scheme I.4.1.4).[13] The less reactive nucleophiles i.e., methyl ketones, even coupled smoothly in this method, which were unreactive under transition metal catalyzed conditions. Due to no requirement of any additional transition metals, solvent and additives makes this procedure as an ideal example of "green chemistry".



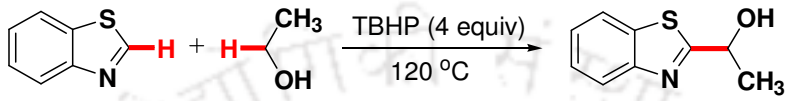
Scheme I.4.1.4. *DDQ-mediated CDC reaction between benzyl ethers and simple ketones*

Han group reported a protocol for the oxidative C–C bond formation from chromones and alkanes via C(sp^3)–H bond functionalization and subsequent conjugate addition using di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme I.4.1.5).[14] Different alkanes and substituted chromones were tolerated, giving corresponding 2-alkylchromanones in moderate to good yields. This method provided a atom-economic route for the syntheses of 2-alkylchromanones via C(sp^3)–H functionalization of alkanes.



Scheme I.4.1.5. *Synthesis of 2-alkylchromanones via sp^3 C–H functionalization*

Wang and co-workers described the direct C2-alkylation of azoles with alcohols and ethers via oxidative C–H activation under metal/base free conditions (Scheme I.4.1.6).[15] The cross dehydrogenative coupling between α-sp^3 C–H in alcohols/ethers and 2-position sp^2 C–H in azoles proceeded smoothly in the presence of *tert*-butyl hydroperoxide (TBHP). Various useful azoles derivatives were prepared in good yields by this mild method.

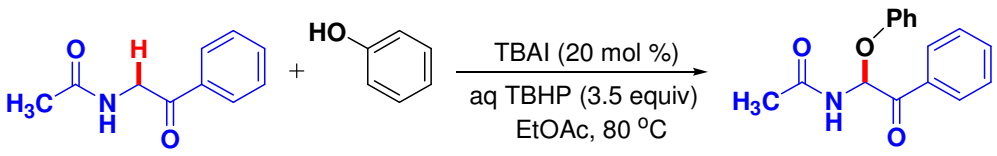


Scheme I.4.1.6. *Direct C2-alkylation of azoles via dehydrogenative cross coupling*

I.4.2. Representative Examples of Carbon-Oxygen Bond Formation

Oxygenated molecules are key intermediates in organic synthesis and constitute an important structural motif of useful pharmaceuticals, agrochemicals, polymers and biologically active compounds. Thus C–O bond forming reactions have gained prime importance since years. Representative examples pertaining to various forms of C–O bond formations are covered in the introduction section of respective chapters and selected few examples are discussed below.

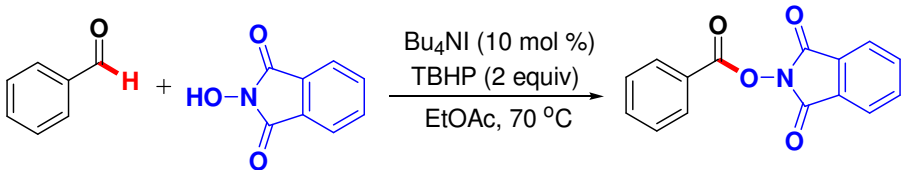
Nachtsheim group illustrated a convenient method for the direct oxidative coupling between phenols and α-aminoacetophenones using tetrabutylammoniumiodide (TBAI) and *tert*-butyl hydroperoxide (TBHP) (Scheme I.4.2.1).[16] In this protocol coupling of diverse phenols and α-aminoacetophenones, resulted in various α-phenoxylated 2-aminoacetophenones yields up to 92% within short reaction times (20 min). This method is a rare example for oxidative coupling between an oxidatively labile phenol and a α-enolic carbon atom under metal free conditions.



Scheme I.4.2.1. *TBAI-catalyzed direct phenoxylation of 2-aminoacetophenones*

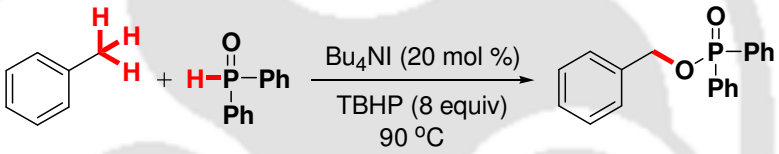
Barbas group reported a protocol for the cross coupling of aldehydes with *N*-hydroxyimides in the presence of Bu_4NI and TBHP (Scheme I.4.2.2).[17] Except aliphatic

aldehydes, a wide range of aromatic aldehydes were efficiently coupled with *N*-hydroxyimides under these reaction conditions.



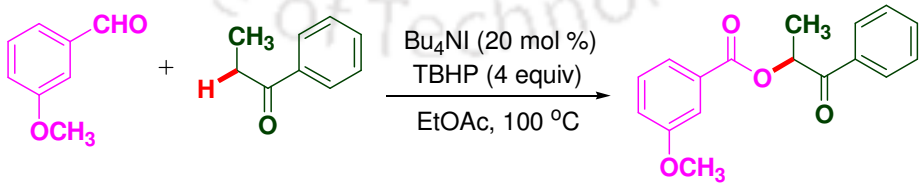
Scheme I.4.2.2. *Organocatalytic cross coupling of aldehydes with N-hydroxyimides*

Tang *et al.* described an efficient metal free approach for the phosphorylation of benzyl C–H bonds in alkylbenzenes using tetrabutylammonium iodide (Bu_4NI) as a catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant (Scheme I.4.2.3).[18] A number of toluene derivatives and phosphorus nucleophiles are tolerated in this transformation, affording their corresponding phosphate esters in moderate to good yields. Furthermore, all the starting materials are simple and commercially available.



Scheme I.4.2.3. *Bu_4NI-catalyzed phosphorylation of benzyl C–H bonds*

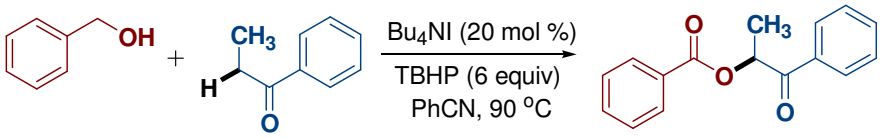
Wang and co-workers demonstrated Bu_4NI-catalyzed α-acyloxylation of ketones with aldehydes (Scheme I.4.2.4).[19] A broad number of substrates tolerated under reacton conditions, for instance (hetero) aromatic aldehydes or cyclohexanecarbaldehyde with arylalkyl ketones in the presence of Bu_4NI and TBHP generated corresponding α-acyloxy ketones in good yields.



Scheme I.4.2.4. *Bu_4NI-catalyzed α-acyloxylation of ketones with aldehydes*

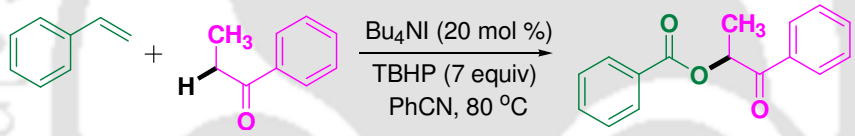
Bu_4NI-catalyzed α-acyloxylation of ketones with benzyl alcohols has been achieved by Cheng's group (Scheme I.4.2.5).[20] The reaction of alcohols and ketones proceeded smoothly to generate the desired α-acyloxycarbonyl compounds in moderate

to good yields. In this transformation, the *in situ* generated hypervalent iodide species could oxidize ketones to give carbocation α– to carbonyl group, which served as key intermediates in this reaction.



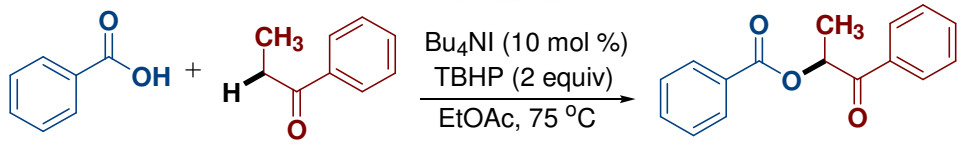
Scheme I.4.2.5. *Bu_4NI-catalyzed α-acyloxylation of ketones with benzyl alcohols*

Pan and co-workers developed a protocol for the α-benzoxylation of ketones using terminal aryl alkenes under metal free conditions (Scheme I.4.2.6).[21] Under these reaction conditions, the aryl alkenes served as an arylcarboxy surrogate and coupled with several propiophenones and acetophenones to give desired products in good yields. This method can be considered as a substitute to an ozonolysis reaction in which the C=C bond cleavage of terminal alkene affords aldehyde.



Scheme I.4.2.6. *Bu_4NI-catalyzed α-benzoxylation of ketones with aryl alkenes*

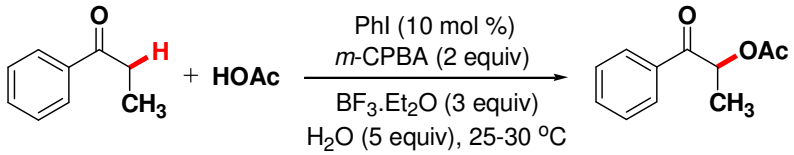
Ishihara *et al.* reported oxidative coupling of ketones, aldehydes and 1,3-dicarbonyl compounds with carboxylic acids in the presence of Bu_4NI and TBHP (Scheme I.4.2.7).[22] Various ketones, aldehydes and 1,3-dicarbonyl compounds were coupled with carboxylic acids to generate their corresponding *α*-acyloxycarbonyl compounds in good to excellent yields. Noteworthy, in the case of aldehydes, piperidine was needed as an additive to direct α-oxyacylation under milder conditions.



Scheme I.4.2.7. *Bu_4NI-catalyzed α-oxyacylation of ketones with benzoic acids*

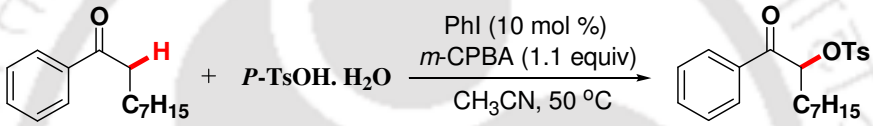
Ochiai's group developed a protocol for oxidative α-acetoxylation of ketones using iodobenzene as the catalyst and *m*-CPBA as a oxidant (Scheme I.4.2.8).[23] The *in*

situ generated hypervalent species (diacyloxyiodo)benzene from iodobenzene and *m*-CPBA was the active catalyst in this transformation.



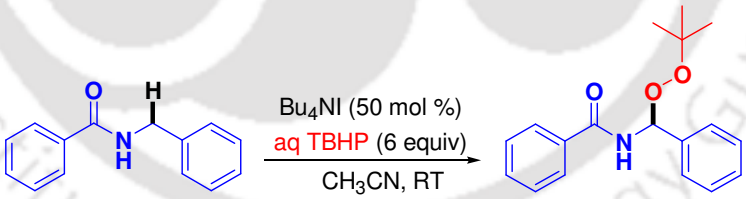
Scheme I.4.2.8. *Iodobenzene-catalyzed α-acetoxylation of ketones*

Togo *et al.* illustrated an iodobenzene-catalyzed α-tosyloxylation of ketones with *p*-toluenesulfonic acid (Scheme I.4.2.9).[24] Various ketones, including aliphatic ketones were tolerated and afforded the desired tosyloxylated ketones in good yields under the reaction conditions.



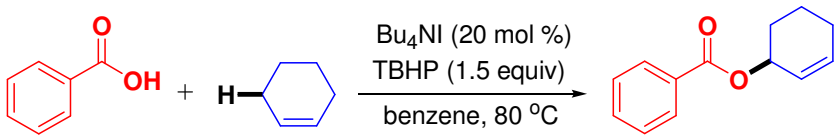
Scheme I.4.2.9. *Iodobenzene-catalyzed α-tosyloxylation of ketones*

Yu and co-workers developed a Bu_4NI-catalyzed peroxidation of C–H bonds adjacent to an amide nitrogen atom (Scheme I.4.2.10).[25] Different peroxides were obtained in good yields via C–O coupling under mild reaction conditions.



Scheme I.4.2.10. *Bu_4NI-catalyzed peroxidation of C–H bonds adjacent to an amide nitrogen*

Bu_4NI-catalyzed synthesis of allylic esters from oxidative coupling of carboxylic acids and allylic C–H nucleophiles was achieved by Wan's group (Scheme I.4.2.11).[26] Various carboxylic acids such as aryl, heteroaryl and alkyl carboxylic acids cross coupled with diverse allylic C–H nucleophiles to produce their corresponding allylic esters in good to excellent yields.

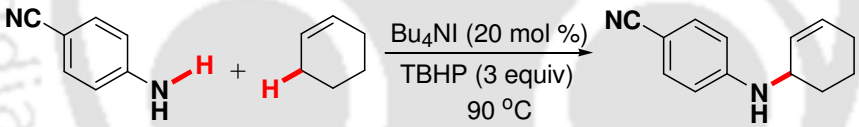


Scheme I.4.2.11. *Bu_4NI-catalyzed synthesis of allylic esters*

I.4.3. Representative Examples of Carbon-Nitrogen Bond Formation

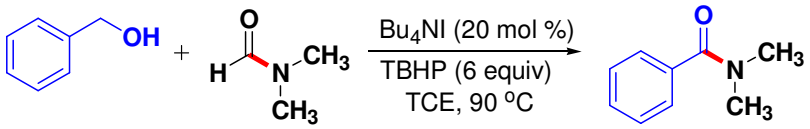
C–N bond-forming methods are of immense importance since nitrogen-containing core units are widely found in natural products and materials science. In recent years, C–N bond forming reactions under metal free conditions attract immediate attention from the academic and industrial communities. Representative examples pertaining to various C–N bond formations are shown below.

Wang and co-workers developed a Bu_4NI-catalyzed synthesis of *N*-substituted anilines from cyclohexene, cyclopentene and alkylbenzenes via direct C–H amination of allylic and benzylic C(sp^3)–H bonds using aromatic anilines as the nitrogen source (Scheme I.4.3.1).[27] This protocol was a practical straightforward route to a variety of *N*-substituted anilines under metal free conditions.



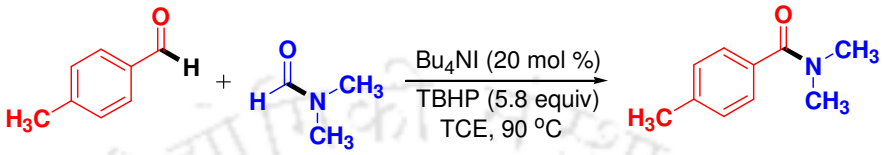
Scheme I.4.3.1. Bu_4NI-*catalyzed direct C–H amination of allylic C(sp^3)–H bonds with anilines*

Zhu's group illustrated the synthesis of amides from alcohols and dialkylformamides under Bu_4NI/TBHP catalytic system (Scheme I.4.3.2).[28] Various alcohols and *N*,*N*-disubstituted formamides were scrutinized to provide the desired amides in good yields. This method was resourceful for future applications due to mild reaction conditions, short reaction time and operational simplicity.



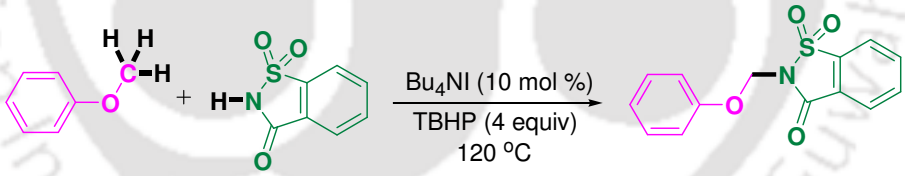
Scheme I.4.3.2. *Bu_4NI-catalyzed synthesis of amides from alcohols and dialkylformamides*

Wan *et al.* reported a Bu_4NI-catalyzed C–N bond formation via oxidative coupling of aldehydes and dialkylformamides (Scheme I.4.3.3).[29] Variety of aldehydes and formamides were tolerated in this reaction and afforded corresponding amides. In this transformation, the C–N bond formations occur by cross coupling of acyl and aminyl radicals originated from aldehydes and formamides respectively.



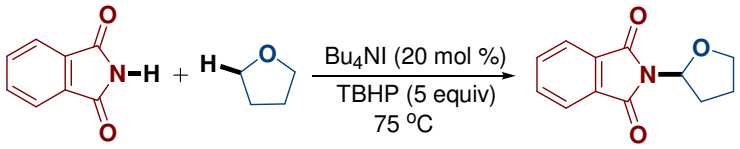
Scheme I.4.3.3. *Bu_4NI-catalyzed oxidative coupling of aldehydes and dialkylformamides*

Sun group developed an intermolecular oxidative C–N bond formation from cross dehydrogenative coupling of aryl ethers and saccharins under Bu_4NI/TBHP condition (Scheme I.4.3.4).[30] Increasing interest on functionalization of sp^3 C–H bond in aryl ethers is to understand the intrinsic characteristics between $C(sp^2)$–O bonds and $C(sp^3)$–H of aryl ethers. Desired imidation products were obtained in good yields from aryl ethers, cyclic and chain alkyl ethers via C–N bond formation under metal free conditions.



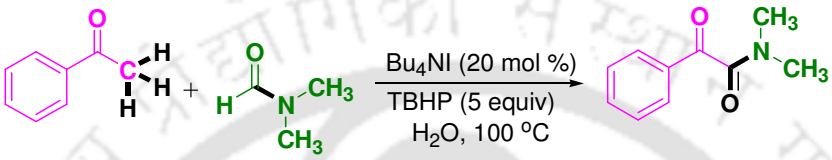
Scheme I.4.3.4. *Bu_4NI-catalyzed imidation of α–sp^3 C–H bonds in aryl ethers*

Du group reported a Bu_4NI-catalyzed synthesis of hemiaminal ethers from alkyl ethers and amines via direct $C(sp^3)$–H bond amination (Scheme I.4.3.5).[31]. The use of metal free and mild reaction conditions are beneficial features of this protocol.



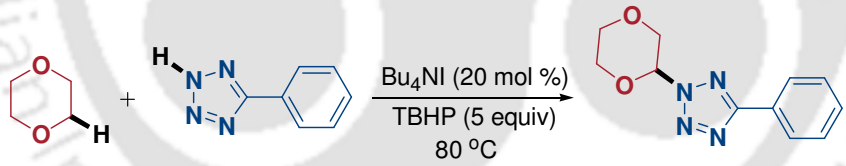
Scheme I.4.3.5. *Organocatalytic amination of alkyl ethers through oxidative $C(sp^3)$–N bond formation*

Qu and co-workers described the direct synthesis of α-ketoamides from aryl methyl ketones and dialkylformamides without use of transition metals in water (Scheme I.4.3.6).[32] Different ketones and dialkylformamides i.e., DMF, *N*,*N*-diethylformamide, piperidine-1-carbaldehyde, morpholine-4-carbaldehyde, 4- methylpiperazine-1-carbaldehyde were tested and the corresponding products were obtained in good yields. The use of metal free catalyst in water as well as cheap and easily available starting materials makes this method environmentally friendly.



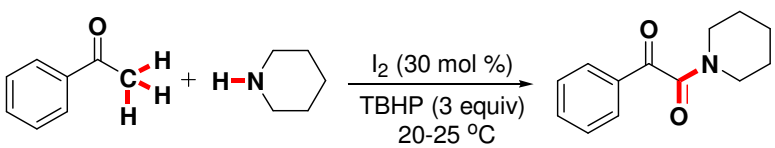
Scheme I.4.3.6. *Bu$_4$NI-catalyzed synthesis of α-ketoamides from aryl methyl ketones and dialkylformamides*

Wang group illustrated a Bu$_4$NI-catalyzed oxidative C–N bond formation via cross dehydrogenative coupling of alkyl ethers and aryl tetrazoles (Scheme I.4.3.7).[33] Notably, the present protocol is useful for the synthesis of triazoles bearing a hemiaminal ether structure.



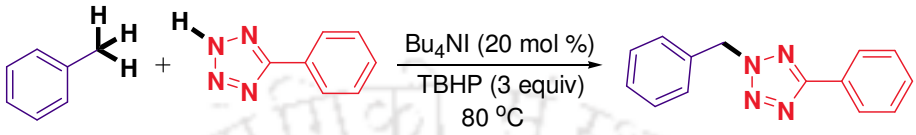
Scheme I.4.3.7. *Bu$_4$NI-catalyzed direct oxidative coupling of alkyl ethers with aryl tetrazoles*

Wang and co-workers demonstrated an iodine-catalyzed synthesis of α-ketoamides from oxidative coupling of acetophenones and amines (Scheme I.4.3.8).[34] Different kinds of ketoamides were synthesized in good yields using metal free and solvent free conditions at room temperature.



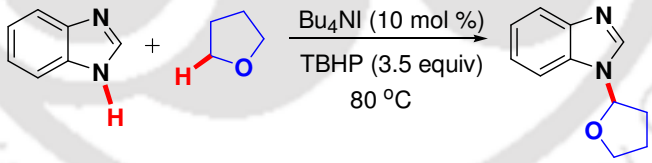
Scheme I.4.3.8. *Iodine-catalyzed oxidative coupling of acetophenones with amines*

Wang group reported the direct oxidative coupling of methylarenes with aryl tetrazoles for constructing alkylated aryl tetrazoles under metal free conditions (Scheme I.4.3.9).[35] This transformation involves the direct C–N bond formation via sp^3 C–H functionalization. Various benzylic C–H substrates and aryl tetrazoles tolerated smoothly to deliver the corresponding products in good yields.



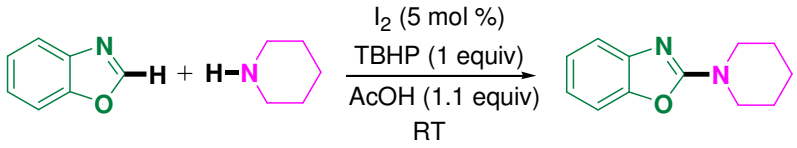
Scheme I.4.3.9. *Bu_4NI-catalyzed oxidative coupling of methylarenes with aryl tetrazoles*

Singh *et al.* described a Bu_4NI-catalyzed synthesis of *N*-substituted azoles from the cross dehydrogenative coupling of azoles with ethers and thioethers via α-C(sp^3)–H functionalization (Scheme I.4.3.10).[36] A diverse range of azoles such as 1*H*-benzimidazole, 9*H*-purine, 1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole and 1*H*-pyrazole were successfully coupled with various ethers and thioethers such as tetrahydrofuran, tetrahydropyran, 1,4-dioxane, diethyl ether, tetrahydrothiophene and 1,3-dithiolane under the optimized conditions. Furthermore, *N*-substituted azoles which can be used as synthons/intermediates in organic chemistry were synthesized in this method.



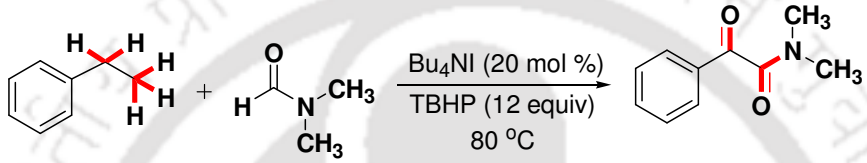
Scheme I.4.3.10. *Metal free catalyzed cross dehydrogenative coupling of azoles with ethers*

A facile metal free approach for the oxidative amination of benzoxazole with secondary or primary amines via C–H bond functionalization has been achieved by Prabhu group (Scheme I.4.3.11).[37] This is user friendly method to make C–N bonds since it produces tertiary butanol and water as the by-product, which are environmentally benign. A wide range of benzoxazole derivatives containing electron-donating and electron-withdrawing groups were coupled with both primary and secondary amines to give therapeutically active aminated benzoxazoles in high yields.



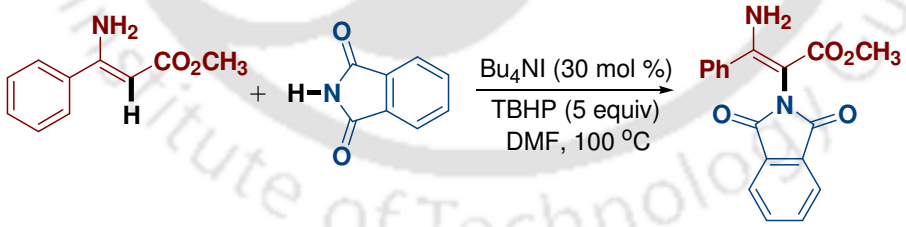
Scheme I.4.3.11. *Iodine-catalyzed amination of benzoxazoles*

Sun and co-workers developed a Bu_4NI-catalyzed synthesis of α-ketoamides from ethylarenes and *N*,*N*-dialkylformamide via multiple sp^3 C–H bond activation (Scheme I.4.3.12).[38] It is the first example for the sequential C–O and C–N bonds formation through multiple inert sp^3 C–H bond activation in alkylbenzenes.



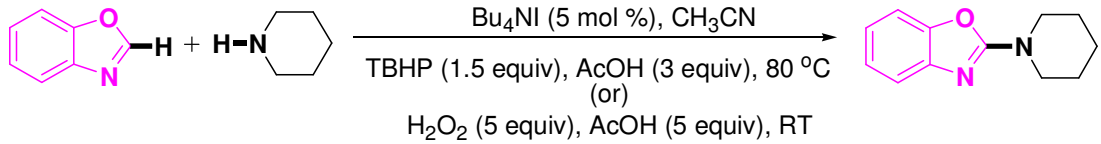
Scheme I.4.3.12. *Bu_4NI-catalyzed sequential C–O and C–N bond formation via sp^3 C–H bond functionalization of ethylarenes*

Du *et al.* reported metal free oxidative C(sp^2)–N bond formation by cross coupling of enamines and electron-deficient amines such as phthalimides, succinimide using Bu_4NI as a catalyst and TBHP as the oxidant (Scheme I.4.3.13).[39] This strategy is highlighted by appealing features such as use of readily available starting materials, wide substrate scope and transition metal free conditions.



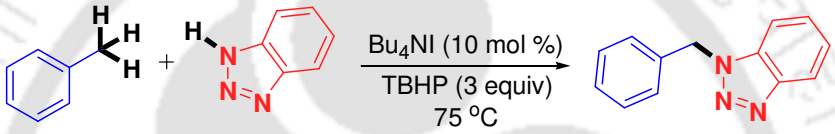
Scheme I.4.3.13. *Metal free cross coupling of enamines and electron-deficient amines*

Nachtsheim's group developed a Bu_4NI-catalyzed oxidative C–H amination of benzoxazoles using either H_2O_2 or TBHP (Scheme I.4.3.14).[40] Various benzoxazoles and amines were tolerated and afforded resultant substituted 2-aminobenzoxazoles in good yields.



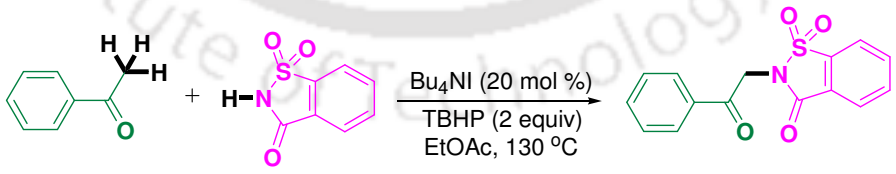
Scheme I.4.3.14. *Bu_4NI-catalyzed oxidative C–H amination of benzoxazoles*

Zhu *et al.* illustrated a Bu_4NI-catalyzed oxidative C–H amination of benzylic C–H bonds by empolying various nitrogen heterocycles as the amine sources and TBHP as oxidant (Scheme I.4.3.15).[41] A variety of alkylbenzenes could be transformed into the desired amination products in good to excellent yields under optimized conditions. This method is useful for the synthesis of imidazole and purine nucleoside derivatives and also been easily scaled-up to the gram scale.



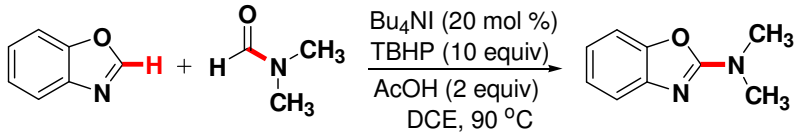
Scheme I.4.3.15. *Bu_4NI-catalyzed amination of alkylbenzenes*

Zhang and co-workers developed a protocol for the synthesis of α-amino ketones via Bu_4NI-catalyzed oxidative imidation of ketones with imides (Scheme I.4.3.16).[42] Different ketones were coupled smoothly with various imides such as phthalimide, saccharin and succinimide to generate their corresponding α-amino ketones in good yields. This is the first example for C–N bond formation via cross coupling of sp^3 C–H bonds in simple ketones and N–H bonds in imides under Bu_4NI/TBHP catalytic condition.



Scheme I.4.3.16. *Bu_4NI-catalyzed oxidative imidation of ketones with imides*

A metal free and simple protocol for the amination of benzoxazoles using formamides as nitrogen sources was achieved by Wang's group (Scheme I.4.3.17).[43] A number of substituted benzoxazoles coupled smoothly with a series of formamides to furnish the desired amination products in high yields.

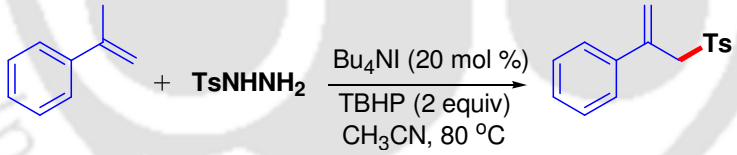


Scheme I.4.3.17. *Metal free direct amination of benzoxazoles using formamides as nitrogen sources*

I.4.4. Representative Examples of Carbon-Sulfur Bond Formation

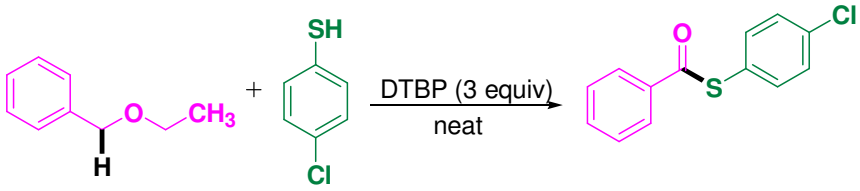
Despite the potential uses of sulfur containing compounds in the pharmaceutical and agrochemical industries. The latest developments on metal free catalyzed CDC protocols for carbon-sulfur bond forming reactions remains relatively rare. One reason for difficulties in the development of C–S bond forming reactions could be competing oxidation of sulfur under oxidative conditions, diminishing the reactivity to give the desired products.

Li group developed a Bu_4NI-catalyzed C–S bond formation through oxidative allylic sulfonylation of α-methyl styrene derivatives with sulfonyl hydrazides (Scheme I.4.4.1).[44] Diverse functional groups such as methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl and naphthyl were well tolerated and afforded the corresponding sulfones in good yields.



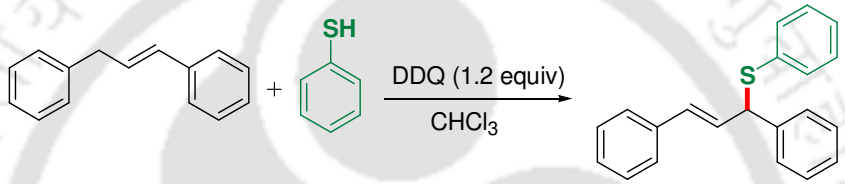
Scheme I.4.4.1. *Bu_4NI-catalyzed oxidative allylic sulfonylation of α-methyl styrene*

Cai and co-workers demonstrated a unprecedented method for the synthesis of thioesters by the direct oxidative cross couplings of benzylic ethers with thiophenols or thiols under metal free conditions (Scheme I.4.4.2).[45] This coupling reaction involves the direct oxidative C(sp^3)–H bond functionalization and C–O cleavage of benzylic ethers. Moreover, this method provides alternative routes for the synthesis of biologically active thioester derivatives.



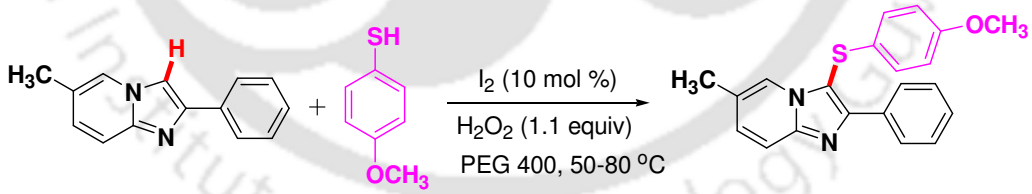
Scheme I.4.4.2. *Direct oxidative coupling of thiols and benzylic ethers*

Bao *et al.* illustrated a DDQ-promoted C–S bond formatin via oxidative coupling of allylic/propargylic sp^3 C–H with various nucleophiles (Scheme I.4.4.3).[46] Aromatic thiophenols, 1,3-dicarbonyl compounds, aliphatic alcohols and oximes nucleophiles were tolerated under optimized conditions and corresponding products were obtained in good yields.



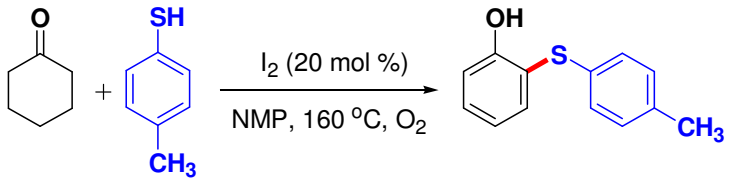
Scheme I.4.4.3. *DDQ-promoted oxidative coupling between allylic sp^3 C–H and thiols*

Hiebel group developed an iodine-catalyzed regioselective sulfenylation of imidazoheterocycles in polyethylene glycol 400 (PEG400) (Scheme I.4.4.4).[47] A variety of 3-arylthioimidazoheterocycles were obtained in moderate to good yields using I_2 as the catalyst and H_2O_2 as an oxidant.



Scheme I.4.4.4. *Iodine-catalyzed sulfenylation of imidazoheterocycles*

Deng's group described Iodine catalyzed synthesis of 2-arylsulfanylphenols from thiols and cyclohexanones in the presence of O_2 (Scheme I.4.4.5).[48] Thiols reacted efficiently with cyclohexanones and produced the desired products in moderate to good yields. A wide range of functional groups such as halo, hydroxyl and ester groups were compatible. However, the steric hindrance on the cyclohexanones drastically affects the efficiency of this transformation.



Scheme I.4.4.5. *Iodine-catalyzed synthesis of 2-arylsulfanylphenol from thiols and cyclohexanones*

I.5. Metal Free Catalyzed C–C and C–X (X= heteroatom) Bond Formation via Oxidative Cyclization

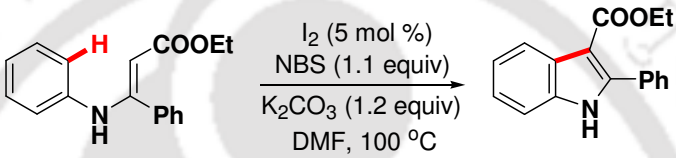
The intramolecular C–C and C–X (X= heteroatom) bond formation via the intramolecular cross dehydrogenative coupling (CDC) of two carbon–hydrogen (C–H) bonds or C–H and X–H (X= heteroatom) bonds has become a very useful tool for the construction of heterocycles, which resulted in the discovery of numerous novel synthetic methods.[49] Compared with the coupling cyclization, this oxidative cyclization (i.e., intramolecular cross dehydrogenative coupling) strategy does not require prefunctionalization of the reaction center, which makes the substrates more accessible and allows more efficient synthesis of structurally diverse products (Scheme I.5.1).

Scheme I.5.1. *Coupling cyclization vs. oxidative cyclization*

However, the oxidative cyclization strategies involve either the use of transition metal or metal free conditions. Here, we illustrated some metal free catalyzed oxidative cyclizations for C–C and C–X (X= heteroatom) bond formation.

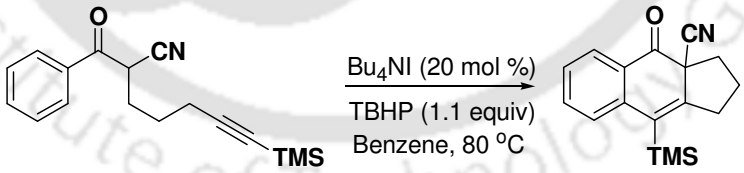
I.5.1. Representative Examples of Oxidative Cyclizations

Li and co-workers developed an I_2-catalyzed protocol for the synthesis of indole skeleton via oxidative cyclization of *N*-aryl enamines (Scheme I.5.1.1).[50] *N*-phenyl enamines with electron-donating and electron-withdrawing groups at *para* position undergo an intramolecular oxidative cyclization to give their resultant indoles in excellent yields. *Ortho*-substituted enamines afforded corresponding products in low yields, which might be due to steric hindrance. Enamines with *meta*-substitution furnished two regioisomers with excellent combined yields under the standard reaction conditions.



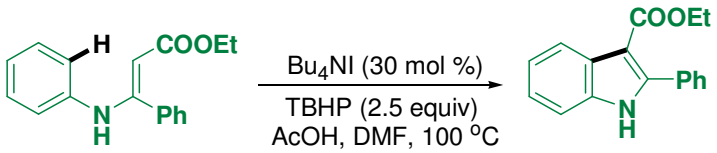
Scheme I.5.1.1. *Iodine-catalyzed indole formation via oxidative cyclization of N-aryl enamines*

Shia *et al.* reported an intramolecular cyclization of the α-cyano-TMS (TMS- = Me_3Si-)/aryl-capped alkynyl aryl alkyl ketones using Bu_4NI as a catalyst and TBHP as the oxidant (Scheme I.5.1.2).[51] In this radical mediated reaction a high level of functionalization containing [6,6,5] tricyclic frameworks were constructed under metal free conditions.



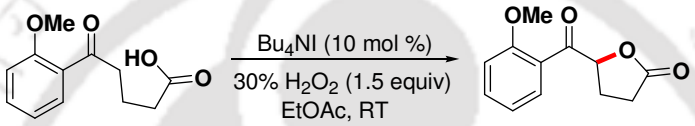
Scheme I.5.1.2. *Bu_4NI-catalyzed intramolecular cyclization of the α-cyano-TMS/aryl-capped alkynyl aryl alkyl ketones*

Li group demonstrated a Bu_4NI-catalyzed synthesis of 1*H*-indole derivatives via intramolecular cross dehydrogenative coupling (CDC) path (Scheme I.5.1.3).[52] *N*-arylenamines undergo intramolecular oxidative coupling in the presence of Bu_4NI/TBHP condition and provided theier corresponding 1*H*-indoles in good to excellent yields.



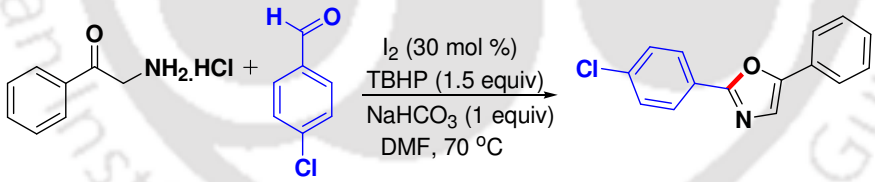
Scheme I.5.1.3. *Bu_4NI-catalyzed intramolecular oxidative coupling of N-arylenamines*

Ishihara and co-workers developed a tetrabutylammonium iodide (Bu_4NI) catalyzed oxylactonization of 5-oxo-5-phenylpentanoic acid derivatives using aq H_2O_2 at room temperature (Scheme I.5.1.4).[53] Noteworthy, both γ-aryl- and γ-heteroarylcarbonyl-γ-butyrolactones were obtained in excellent yields. But, γ-alkylcarbonyl-γ-butyrolactone and δ-benzoyl-δ-valerolactone were resulted in moderate yields.



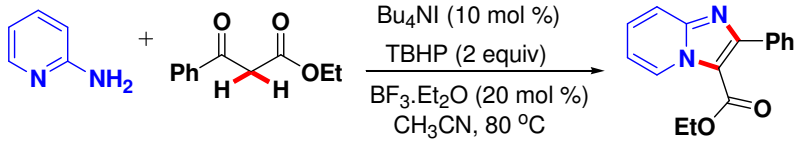
Scheme I.5.1.4. *Bu_4NI-catalyzed oxylactonization of oxocarboxylic acids*

Wang's group illustrated a practical and simple synthesis of 2,5-disubstituted oxazoles from 2-amino acetophenones salts and aldehydes via an iodine-catalyzed tandem oxidative cyclization (Scheme I.5.1.5).[54] A wide range of functional groups were compatible in this reaction and afforded the desired products in good yields.



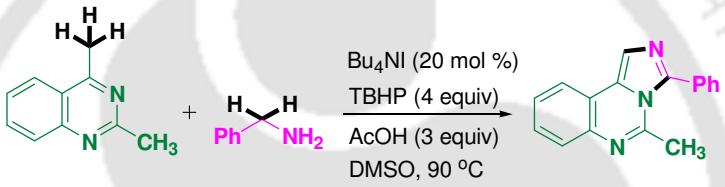
Scheme I.5.1.5. *Iodine-catalyzed synthesis of 2,5-disubstituted oxazoles via an tandem oxidative cyclization*

Yu *et al.* described the synthesis of imidazo[1,2-α]pyridines by the oxidative coupling of 2-aminopyridines with *β*-keto esters and 1,3-diones via C–N bond formation (Scheme I.5.1.6).[55] This protocol represents a simple and economical approach for the synthesis of imidazo[1,2-a]pyridines. Moreover, 2-alkyl substituted imidazo[1,2-α]pyridine-3-carboxylates and 2-alkyl-3-acyl imidazo[1,2-α]pyridines were synthesized through this method.



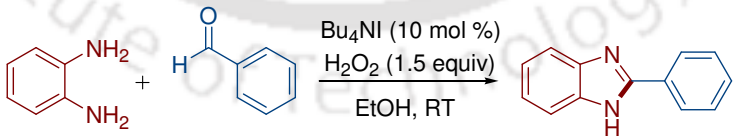
Scheme I.5.1.6. *Bu_4NI-catalyzed oxidative coupling of 2-aminopyridines with β-ketoesters*

A Bu_4NI-catalyzed oxidative domino synthesis of imidazo[1,5-c]quinazolines from 4-methylquinazolines and benzylamines via a tandem reaction following sp^3 C–H functionalization has been achieved by Li group (Scheme I.5.1.7).[56] Notably, under the optimized conditions only the 4-methyl group of quinazolines were selectively aminated and gave the corresponding products in good yields. Furthermore, the same products could be obtained using α-amino acids as the amine source via a decarboxylative path.



Scheme I.5.1.7. *Bu_4NI-catalyzed selective dual amination of sp^3 C–H bonds*

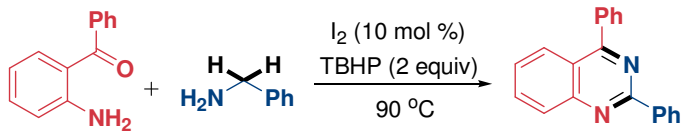
Wei and co-workers reported an efficient synthesis of benzimidazoles from *o*-phenylenediamines and benzaldehydes using Bu_4NI as the catalyst and hydrogen peroxide as oxidant (Scheme I.5.1.8).[57] Heteroaryl, benzylic, allylic and aliphatic aldehydes were all tolerated to generate the desired benzimidazoles in good to excellent yields at ambient temperature. In addition, the present method was then extended for the synthesis of imidazolines, benzoxazoles and benzothiazoles.



Scheme I.5.1.8. *Bu_4NI-catalyzed synthesis of benzimidazoles from o-phenylenediamines and benzaldehydes*

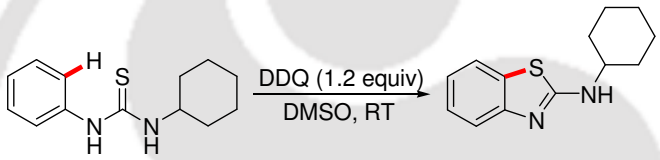
Wang's group developed a molecular iodine catalyzed synthesis of 2-phenylquinazolines via a tandem reaction following sp^3 C–H functionalization (Scheme I.5.1.9).[58] Various 2-phenylquinazolines were synthesized from 2-aminobenzophenones and benzylic amines through a tandem reaction process. Inspired by this work, the same

group then achieved the efficient synthesis of quinazolines from 2-aminobenzophenones using α-amino acids and ammonia as the source of nitrogen.



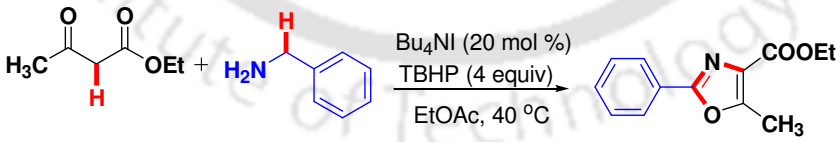
Scheme I.5.1.9. *Iodine-catalyzed synthesis of 2-phenylquinazolines via a tandem reaction following sp^3 C–H functionalization*

Wang and co-workers described a DDQ-mediated synthesis of 2-aminobenzothiazoles from diarylthioureas via C(sp^2)–S bond formation (Scheme I.5.1.10).[59] 2-Alkylaminobenzothiazoles were isolated in excellent yield from aryl-alkyl thiourea under optimized conditions.



Scheme I.5.1.10. *DDQ-promoted oxidative C–S bond formation*

Zhu *et al.* illustrated Bu_4NI-catalyzed synthesis of oxazole derivatives via dual sp^3 C–H activation under mild conditions (Scheme I.5.1.11).[60] Oxidative cascade C–N/C–O bond formations takes place in this protocol. Different 1,3-dicarbonyl compounds and benzylamines coupled efficiently to give their desired oxazoles in good yields.



Scheme I.5.1.11. *Bu_4NI-catalyzed synthesis of oxazole via oxidative cascade C–N/C–O bond formation*

I.6. References:

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CHAPTER II

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Easy access to benzylic esters directly from alkyl benzenes under metal-free conditions†‡

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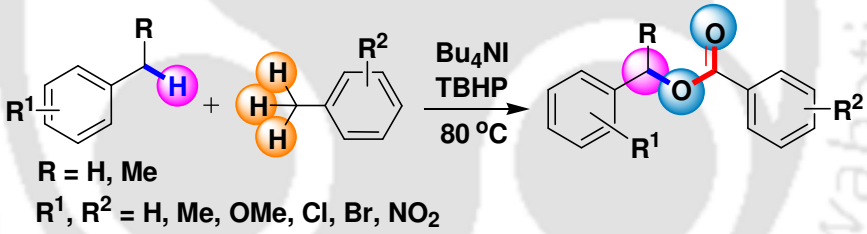


Abstract: **An efficient metal free protocol has been developed for the synthesis of benzylic esters via a cross dehydrogenative coupling (CDC) involving alkylbenzene(s) as a self or as a cross coupling partner(s) via the intermediacy of (Ar-COOH) and the benzylic carbocation obtained from the other half of the alkylbenzene; both symmetrical as well as unsymmetrical esters can be prepared using Bu_4NI and TBHP.**

CHAPTER II

II. Easy Access to Benzylic Esters Directly from Alkylbenzenes under Metal Free Conditions

II.1. Introduction

The selective oxidative cleavage of sp^3 C–H bond is of paramount interest to both academic and industrial research.[1] The two most common strategies adopted for the C–H bond activation processes rely on the concept of chelation assisted C–H bond functionalization[2] and cross dehydrogenative coupling (CDC).[3] CDC based methodologies are highly appreciable because it does not require substrate prefunctionalization. Besides being atom and step economic, these reactions are often air and moisture insensitive, and thereby can be performed in an aqueous environments or an air atmosphere.[4] The CDC approach has been mainly exploited towards the C–C bond formations,[3a,5] but of late the number of C–O bond forming reactions are also increasing.[3e,6]

The CDC based protocols in the construction of C–O bond have been achieved using transition metal catalysts such as Cu, Fe, Ru, Rh, Ir and Pd in combination with various oxidants.[7] However, the disadvantages associated with these methodologies, owing to the use of expensive metal catalysts and the problems associated with the removal of metal residues limit their practical applicability. Therefore, increasing interest has been focused on metal free catalysts particularly towards the formation of a C–O bond.[6a-c,8]

Selective to the C–O bond formation, the ester functionalities particularly, the benzylic esters are common target because of their applications in synthetic organic and medicinal chemistry.[9]

II.2. Strategies for the Synthesis of Benzylic Esters

Barring our present work, the synthesis of benzylic esters have been achieved using alcohols, aldehydes, acids, acid derivatives and alkylbenzenes under either transition metal or metal free conditions.

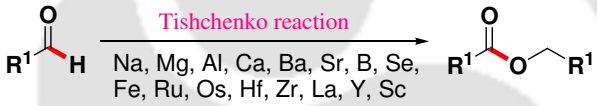
(i) Traditional esterification

The traditional esterification methods are often require auxiliary reagents to afford benzylic esters by the treatment of alcohols with acids or acid derivatives (Scheme II.2.1).[10]

Scheme II.2.1. *Benzylic esters synthesis using traditional methods*

(ii) Tishchenko reaction path

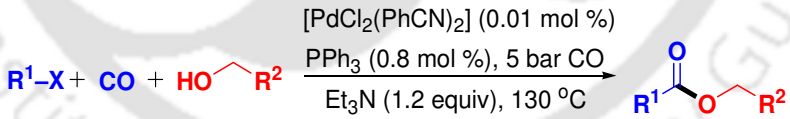
In this method, the symmetrical benzylic esters are synthesized from aldehydes (lacking hydrogen atom at α position) in presence of base and catalyst (Scheme II.2.2).[11]



Scheme II.2.2. *Tishchenko reaction path*

(iii) Insertion of carbon monoxide

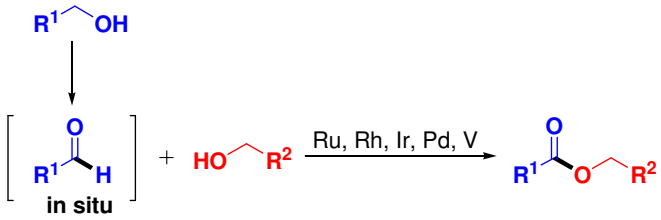
Beller and co-workers reported a palladium catalyzed cross coupling reaction involving carbonylation of aryl halides with subsequent nucleophilic attack of benzyl alcohols to synthesize benzylic esters (Scheme II.2.3).[12]



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

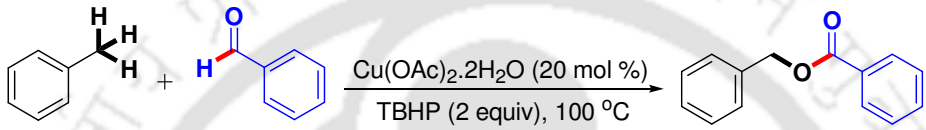
(iv) Transition metal catalyzed CDC approach for the synthesis of benzylic esters

Besides the traditional esterification reactions, several elegant CDC protocols have been developed lately for the synthesis of benzylic esters. Pertinent to this, catalysts such as Ru, Rh, Ir, Pd and V have been employed for the cross dehydrogenative coupling (CDC) between aldehydes or the *in situ* generated aldehydes and alcohols to obtain desired products (Scheme II.2.4.1).[13] Most of these processes rely on the concept of either hydrogen borrowing[14] or a hydrogen auto transfer process[15] where benzyl alcohols serves as a precursor.



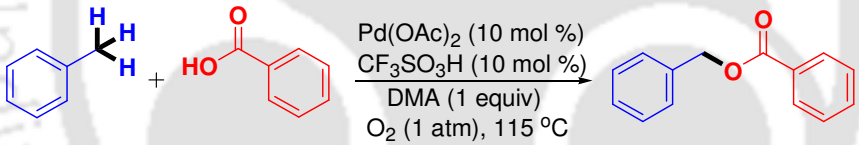
Scheme II.2.4.1. *Transition metal catalyzed CDC approach*

Our group have developed a CDC based approach for the synthesis of benzylic esters from aryl aldehydes and alkylbenzenes using Cu(II) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme II.2.4.2).[6e]



Scheme II.2.4.2. *Cu(II)-catalyzed synthesis of benzylic esters via CDC approach*

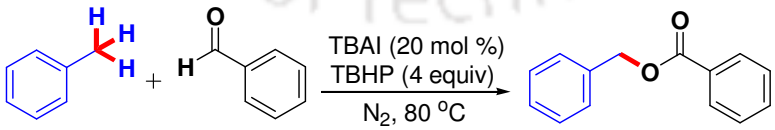
Zhang and co-workers reported a palladium catalyzed oxidative esterification of carboxylic acids with alkylbenzenes via benzylic C–H activation (Scheme II.2.4.3).[16]



Scheme II.2.4.3. *Palladium-catalyzed synthesis of benzylic esters via C–H activation*

(v) CDC approach for the synthesis of benzylic esters under metal free conditions

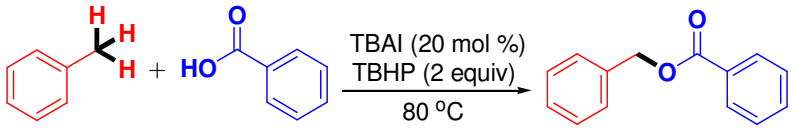
Wang et al. demonstrated a TBAI-catalyzed benzylic C–H acyloxylation of alkylarenes with aromatic aldehydes using *tert*-butyl hydroperoxide as terminal oxidant (Scheme II.2.5.1).[8d]



Scheme II.2.5.1. *TBAI-catalyzed benzylic C–H acyloxylation of alkylarenes*

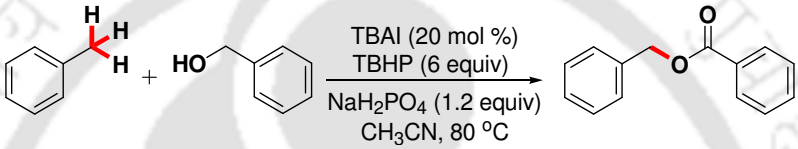
Yu group reported a metal-free oxidative esterification of benzylic C–H bonds via oxidative C–O bond formation at the sp^3 benzylic carbon of various alkylbenzenes

with carboxylic acids (Scheme II.2.5.2).[8c] In this method benzylic substrates could react smoothly with various carboxylic acids to give esters in good to excellent yields.



Scheme II.2.5.2. *Oxidative esterification of benzylic C–H bonds under metal free condition*

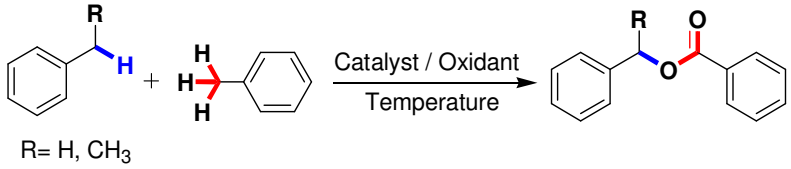
TBAI-catalyzed protocol for the synthesis of benzyl esters directly from alcohols and toluene derivatives was reported by Fu group (Scheme II.2.5.3).[17]



Scheme II.2.5.3. *TBAI-catalyzed benzylic C–H acyloxylation of alkylarenes with alcohols*

II.3. Present Work

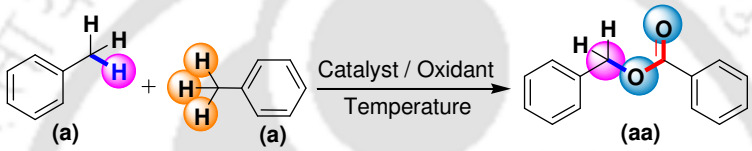
During the course of our investigations[6e] on CDC coupling between benzaldehyde and *p*-methoxy toluene the formation of benzoic acid and *p*-methoxybenzyl alcohol originating respectively from benzaldehyde and *p*-methoxytoluene was observed. The *in situ* generated *p*-methoxybenzyl alcohol can be further converted to its aldehyde and subsequently to carboxylic acid under the oxidative reaction conditions. Thus, the *in situ* formed aldehyde or acid can in turn couple with the unreacted alkylbenzene in the medium to give an ester via a CDC approach.[6e,8c-d] Hence, we envisaged a self coupling of an alkylbenzene or a cross coupling between two different alkylbenzenes to obtain a symmetrical or an unsymmetrical ester (Scheme II.3.1).



Scheme II.3.1. *Synthesis of benzylic esters directly from alkylbenzenes*

Optimization of reaction conditions. In pursuit of the above objective when toluene (**a**) was treated with $Cu(OAc)_2.2H_2O$ (0.1 equiv) and TBHP (4 equiv) a condition similar to our previous report,[6e] only a trace (< 3%) of benzylbenzoate (**aa**) was formed (Table II.3.1, entry 1) along with the substantial formation of benzoic acid. Inspite of the presence of significant amount of benzoic acid in the medium the amount of ester (**aa**) formed was negligible as the Cu(II)/TBHP condition is perhaps not conducive for the coupling between an acid and an alkylbenzene.[6e] Traces of the ester (**aa**) formed is possibly due to the less concentration of benzaldehyde and benzyl alcohol present in the medium, while most of the benzaldehyde gets rapidly oxidised to benzoic acid.[6e]

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



Entry	Catalyst (mol %)	Oxidant (equiv)	Temp (^oC)	Yield %[b]
1	$Cu(OAc)_2.2H_2O$ (10)	TBHP in decane (4)	100	3
2	Bu_4NI (10)	TBHP in decane (4)	25	30
3	Bu_4NI (10)	TBHP in decane (6)	80	90
4	**Bu_4NI (10)**	**aq TBHP (6)**	**80**	**95**
5	Bu_4NI (10)	aq TBHP (6)	100	95
6	Bu_4NI (20)	aq TBHP (6)	80	95
7	Bu_4NI (5)	aq TBHP (6)	80	60
8	Bu_4NI (10)	aq TBHP (5)	80	50
9	Bu_4NI (10)	aq H_2O_2 (6)	80	00
10	Bu_4NI (10)	DDQ (6)	80	00
11	Bu_4NI (10)	$PhI(OAc)_2$ (6)	80	00
12	Bu_4NBr (10)	aq TBHP (6)	80	00
13	KI (10)	aq TBHP (6)	80	00
14	I_2 (10)	aq TBHP (6)	80	00
15	nil	aq TBHP (6)	80	00
16	Bu_4NI (10)	nil	80	00

[a]Toluene (1mL), Reaction time: 6 h, [b]Isolated yield.

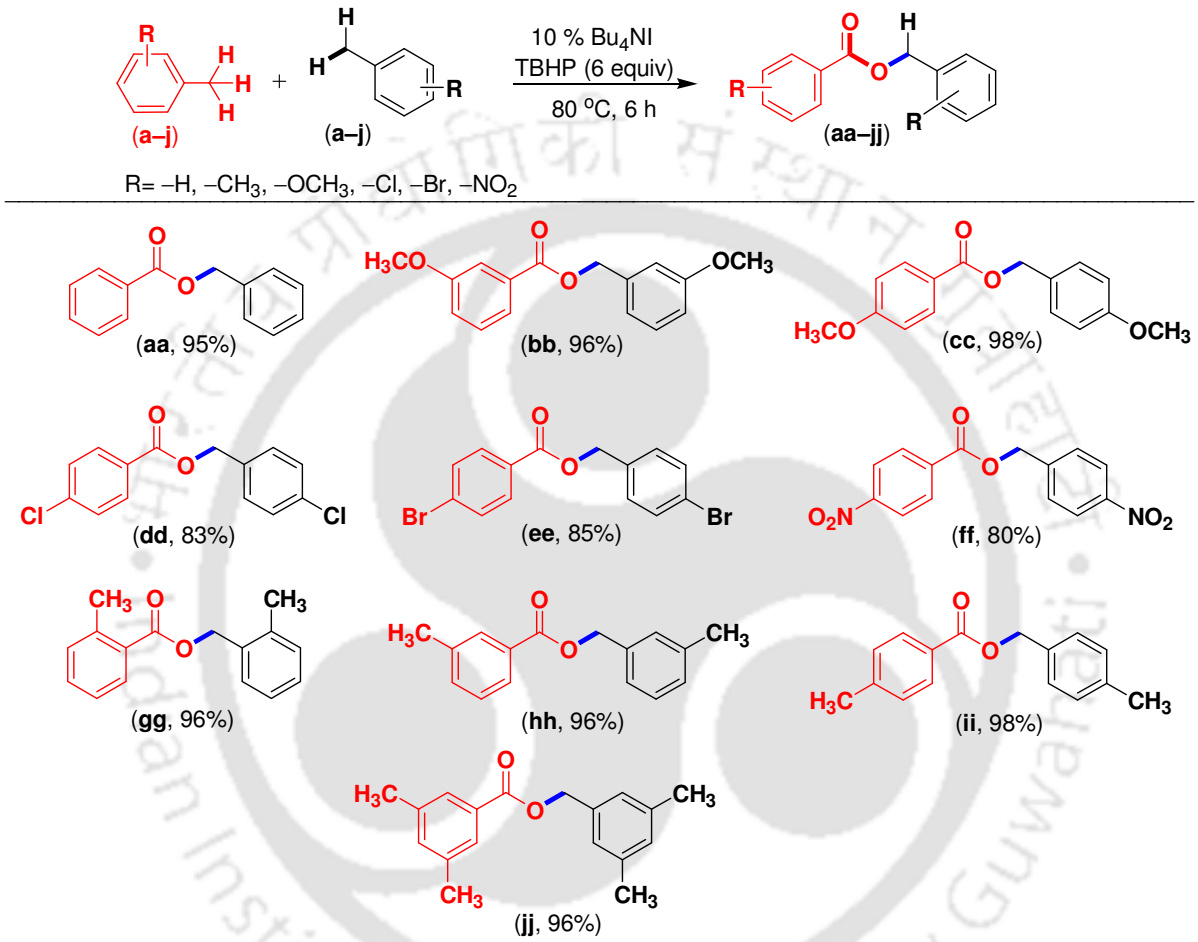
Metal free catalyst Bu_4NI in combination with oxidant TBHP is not only an efficient reagent for the oxidation of alkylbenzenes to acids but is also equally effective towards cross dehydrogenative coupling between acids and alkylbenzenes.[8c-d] With this inspiration, further optimization was undertaken towards a metal free sp^3 C–H bond oxidative esterification using toluene (**a**) as the self coupling partner. Toluene (**a**) (1 mL) was treated with 10 mol % of Bu_4NI and TBHP (5-6 M in decane) (4 equiv) at room

temperature which afforded benzylbenzoate (**aa**) in 30% isolated yield (Table II.3.1, entry 2). Here the alkylbenzene (toluene) acts as reactant(s) i.e., self coupling partners as well as a solvent. When the same reaction was performed using 6 equivalents of TBHP at 80 ^{o}C the yield improved upto 90% (Table II.3.1, entry 3). Gratifyingly, the use of aqueous TBHP (70%) instead of a decane solution of TBHP (5-6 M) improved the yield upto 95% (Table II.3.1, entry 4). Increasing the reaction temperature to 100 ^{o}C or increase in the catalyst quantity to 20 mol % no further improvement in the yield was observed (Table II.3.1, entries 5-6). However a decrease in the catalyst loading (5 mol %) and oxidant quantity (5 equiv) reduced the product yield (Table II.3.1, entries 7-8). No desired product could be obtained when oxidants H_2O_2, DDQ, $PhI(OAc)_2$ (Table II.3.1, entries 9-11) were used instead of TBHP. Other halogen species such as Bu_4NBr, KI and I_2 (Table II.3.1, entries 12-14) were found to be completely ineffective. Control experiments carried out in the absence of either the catalyst ($Bu_4N^+I^-$) or the oxidant (TBHP) (Table II.3.1, entries 15-16) failed to bring about the desired transformation suggesting the requirement of this particular combination.

Substrate scope for symmetrical benzylic esters. In light of these novel observations the optimized conditions were subsequently applied to *m*-methoxy (**b**), *p*-methoxy (**c**), *p*-chloro (**d**), *p*-bromo (**e**) and *p*-nitro (**f**) toluenes towards self oxidative esterification. It was observed that, under the present conditions, toluene with electron-donating substituents (**b** and **c**), the reactions proceeded smoothly to afford the desired self coupled benzylic esters (**bb**, **cc**) in excellent yields (Scheme II.3.2). For toluenes possessing electron-withdrawing substituents (**d** and **e**), the reaction provided the desired benzylic esters (**dd** and **ee**) in good yields but the reactions were a bit sluggish (Scheme II.3.2). The sluggishness was quite pronounced with substrate bearing strongly electron withdrawing -NO_2 (**f**) in toluene under the present reaction conditions giving poor yield of (25%) of the desired ester (**ff**). For such deactivated substrate, an improved yield (80%) was obtained when the reaction was performed at 110 ^{o}C (Scheme II.3.2). These results imply that the electronic effects of the substituents in the methyl benzene affect the reaction rates and the product yields. The synthetic utility of this approach was then applied to various di-alkylatedbenzenes such as *o*-xylene (**g**), *m*-xylene (**h**), *p*-xylene (**i**) all of which gave self coupled monoesters (**gg**), (**hh**) and (**ii**) in excellent yields (Scheme II.3.2). Only monoesters were obtained in these cases and no traces of diesters were

detected. Symmetrical trialkylatedbenzene such as mesitylene (**j**) yielded the corresponding self coupled monoester (**jj**) (Scheme II.3.2).

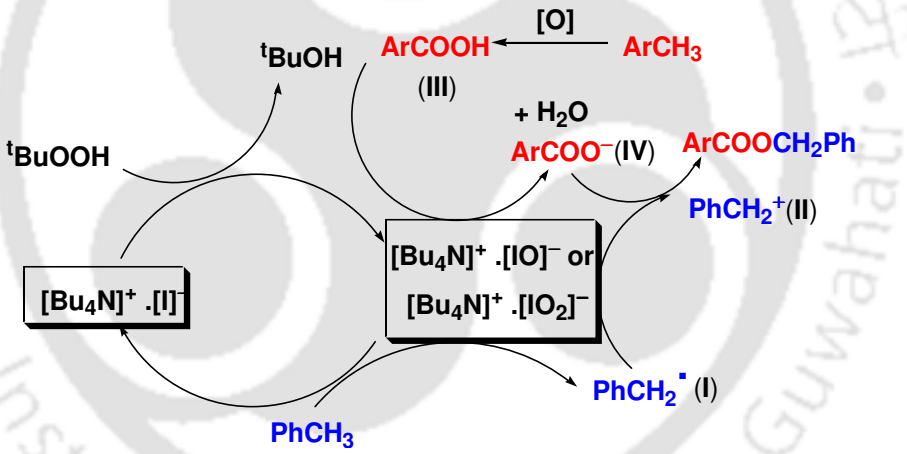
Scheme II.3.2. *Substrate scope for the synthesis of symmetrical benzylic esters via metal free C–H functionalization*[a,b]



[a]Reaction conditions: alkylbenzene (1 mL), $Bu_4N^+I^-$ (0.1 mmol), TBHP (6 mmol), 80 °C, time 6 h. [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Mechanistic studies. Taking cues from the literature and the controlled experiments carried out, a mechanism similar to the one proposed by Yu *et.al.*[8c] and Wang *et.al.*[8d] could be suggested for this transformation as well. The oxidant TBHP is known to oxidize the catalyst $Bu_4N^+I^-$ to either $[Bu_4N^+][IO]^-$ or $[Bu_4N^+][IO_2]^-$.[18] However we have observed the formation of $[IO]^-$ *i.e* $[Bu_4N^+][IO]^-$ by ESI mass analysis of the reaction mixture. This active hypoiodite $[Bu_4N^+][IO]^-$ species would initiate a homolytic cleavage at the benzylic C–H bond of the toluene to give a benzyl radical (**I**).[8c-d,19]

Formation of benzyl radical (**I**) could be the rate determining step in the entire reaction. The benzylic radical (**I**) is further oxidised by the hypoiodite species $[Bu_4N^+][IO]^-$ to a benzyl cation (**II**). Alternatively, some of the alkylbenzene could be converted to its alcohol via a radical oxidation path and subsequently to corresponding acid (**III**) via an aldehyde intermediate (Scheme II.3.3). After the formation of the acid (**III**) the oxygen atom of hypoiodite species $[IO]^-$ removes the acidic proton from the benzoic acid giving a benzoate ion (**IV**). Finally, the coupling between the *in situ* generated benzoate ion (**IV**) and the benzyl cation (**II**) would give the desired ester as shown in (Scheme II.3.3). As per the mechanism, four equivalents of oxidant (TBHP) get consumed forming an equivalent of benzoate ion (**IV**) and further two equivalents are required for the formation of benzyl cation (**II**) from alkylbenzene. Thus, a total of six equivalents of TBHP is essential for the coupling of two equivalents of alkylbenzene giving an equivalent of ester.



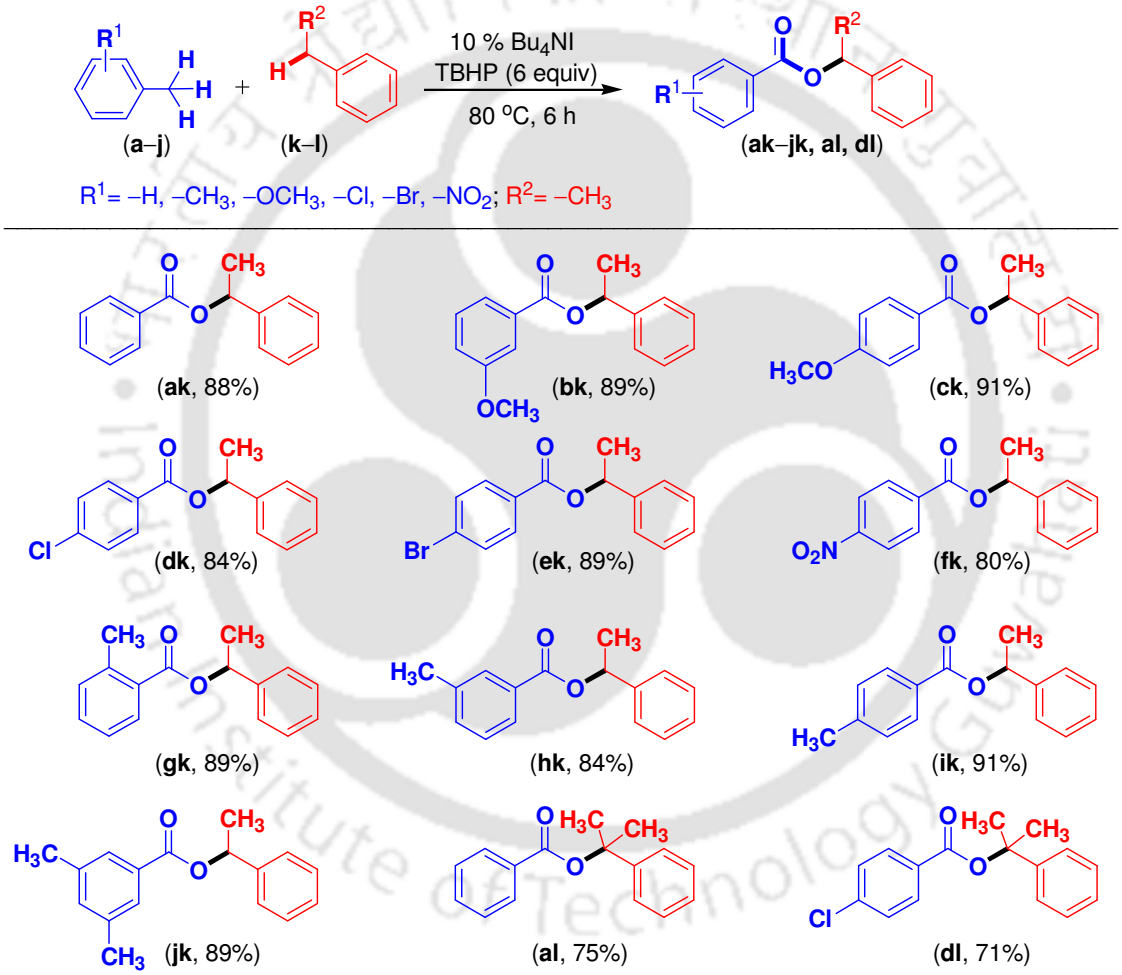
Scheme II.3.3. *Proposed mechanism of the oxidative esterification.*

As depicted in the mechanism (Scheme II.3.3), during the formation of a symmetrical ester, one half of the alkylbenzene is transformed to acid which couples with the *in situ* generated benzyl cation derived from the other half of the alkylbenzene. Ethylbenzene is expected to form more stable carbocation than the methylbenzene and the latter is more susceptible to oxidation giving acid. Thus, if an equimolar mixture of ethyl and methylbenzene is treated under the present reaction conditions, synthesis of unsymmetrical esters could be feasible.

Substrate scope for unsymmetrical benzylic esters. With the above motivation the present methodology was next sought towards the cross dehydrogenative coupling

(CDC) between ethylbenzene (**k**) and various substituted toluenes bearing electron-neutral (**a**), electron-donating (**b-c**) and electron-withdrawing substituents (**d-f**). In all their reactions, the corresponding benzylic esters (**ak-fk**) were obtained in moderate to high yields via a selective C–O bond formation at the more stable 2° benzylic carbon of the ethylbenzene as has been envisaged earlier (Scheme II.3.4).

Scheme II.3.4. *Substrate scope for the synthesis of unsymmetrical benzylic esters via metal free C–H functionalization*[a,b]



[a]Reaction conditions: alkylbenzene (1 mL), $Bu_4N^+I^-$ (0.1 mmol), TBHP (6 mmol), 80 °C, time 6 h. [b]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

This methodology was also equally successful towards the reactions of di and tri-alkylatedbenzenes (**g-j**) with ethylbenzene (**k**) as shown in Scheme II.3.4. Herein as well the monoester formations (**gk-jk**) took place selectively as have been observed during the self coupling of (**g-j**). However, trace amount (2-5%) of self coupled esters (**aa-jj**)

were also obtained in the entire cross coupling cases along with the predominant formation of cross coupled esters (**ak-jk**). This methodology is also equally successful for CDC between isopropylbenzene (**l**) and alkyl benzenes such as toluene (**a**) and *p*-chlorotoluene (**d**) giving modest yield of unsymmetrical esters (**al**) and (**dl**) respectively (Scheme II.3.4). However, the yields obtained were lower than expected which could be due to steric factor imparted by the isopropyl group.

Conclusions. In conclusion, for the first time benzylic esters have been prepared from alkylbenzenes as the only precursor via a cross dehydrogenative coupling (CDC) under a metal free condition involving four sp^3 C–H bond activations. This method gives self coupled product for mono or poly methylatedbenzenes. The cross coupled product can be prepared from ethylbenzene and methylbenzene where acid part is derived from methylbenzene and the benzyl cation is derived from ethylbenzene. A various functional groups are tolerated under the present reaction conditions. Thus this approach has great academic and industrial significance.

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 (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.

II.4.2. General procedure for the synthesis of benzyl benzoate (aa). A mixture of Bu_4NI (36.9 mg, 10 mol %) and toluene (**a**) (1 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture an aqueous solution of TBHP (70% in H_2O) (857 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^oC for 6 h. During this period formation of benzyl benzoate (**aa**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL).

The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (98: 2, hexane / ethyl acetate) to afford benzyl benzoate (**aa**) (201 mg, 95% yield).

II.4.3. General procedure for the synthesis of 1-phenylethyl benzoate (ak). A mixture of Bu_4NI (36.9 mg, 10 mol %), toluene (**a**) (0.5 mL) and ethylbenzene (**k**) (0.5 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture an aqueous solution of TBHP (70% in H_2O) (857 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^oC for 6 h. During this period formation of 1-phenylethyl benzoate (**ak**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (98: 2, hexane / ethyl acetate) to afford 1-phenylethyl benzoate (**ak**) (198 mg, 88% yield).

II.4.4. General procedure for the synthesis of 2-phenylpropan-2-yl benzoate (al). A mixture of Bu_4NI (36.9 mg, 10 mol %), toluene (**a**) (0.5 mL) and isopropylbenzene (**l**) (0.5 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture an aqueous solution of TBHP (70% in H_2O) (857 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^oC for 6 h. During this period formation of 1-phenylethyl benzoate (**al**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (98: 2, hexane / ethyl acetate) to afford 2-phenylpropan-2-yl benzoate (**al**) (180 mg, 75% yield).

II.5. References

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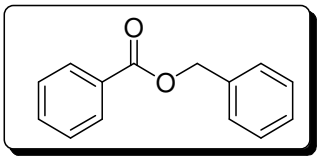
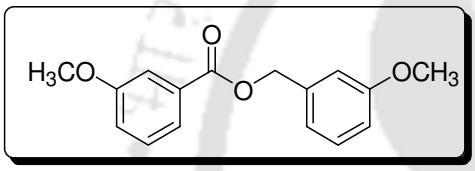
II.6. Spectral Data

Benzyl benzoate (aa):



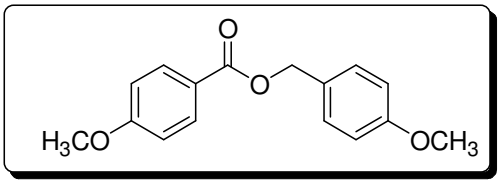
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.36 (s, 2H), 7.33–7.45 (m, 7H), 7.54 (t, 1H, *J* = 7.6 Hz), 8.08 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.7, 128.2, 128.3, 128.4, 128.6, 129.7, 130.2, 133.0, 136.1, 166.4; IR (KBr): 3066, 3033, 2923, 1718, 1451, 1314, 1271, 1109, 1070, 1026, 711 cm^{-1}; Anal. calcd. for $C_{14}H_{12}O_2$: C 79.22, H 5.70; found C 79.20, H 5.78.

3-Methoxybenzyl 3-methoxybenzoate (bb):



Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.81 (s, 3H), 3.83 (s, 3H), 5.33 (s, 2H), 6.88 (d, 1H, *J* = 8.4 Hz), 6.98 (s, 1H), 7.02 (d, 1H, *J* = 7.6 Hz), 7.08–7.11 (m, 1H), 7.28–7.35 (m, 2H), 7.60 (s, 1H), 7.68 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.4, 55.6, 66.8, 113.8, 114.4, 119.6, 120.5, 122.3, 129.6, 129.8, 131.6, 137.7, 159.8, 159.9, 166.4; IR (KBr): 2938, 2837, 1717, 1602, 1587, 1489, 1456, 1275, 1225, 1104, 1043, 756 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_4$: C 70.57, H 5.92; found C 70.62, H 5.84.

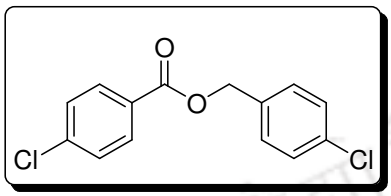
4-Methoxybenzyl 4-methoxybenzoate (cc):



Yellowish liquid; ^{1}H 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,

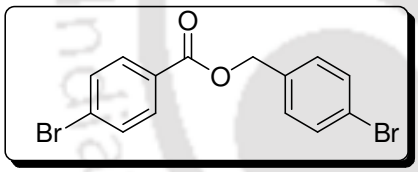
159.7, 163.5, 166.4; IR (KBr): 3002, 2957, 2837, 1707, 1606, 1513, 1255, 1166, 1097, 1029, 823, 769 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}O_4$ (MH^+) 273.1121; found 273.1115.

4-Chlorobenzyl 4-chlorobenzoate (dd):



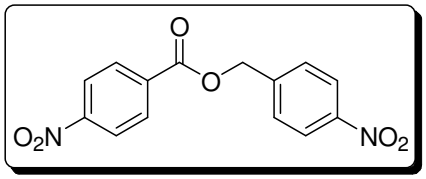
White solid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.31 (s, 2H), 7.37–7.42 (m, 6H), 7.99 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 66.1, 128.3, 128.8, 128.9, 129.7, 131.0, 131.1, 134.3, 139.6, 165.4; IR (KBr): 3049, 2927, 2852, 1715, 1592, 1488, 1400, 1307, 1274, 1172, 1123, 1091, 1014, 848, 810, 756 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}Cl_2O_2$ (MH^+) 281.0131; found 281.0124.

4-Bromobenzyl 4-bromobenzoate (ee):



White solid; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.30 (s, 2H), 7.31 (d, 2H, *J* = 8 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 66.2, 122.5, 128.4, 128.8, 130.0, 131.3, 131.9, 134.8, 165.6; IR (KBr): 2928, 2852, 1713, 1588, 1483, 1397, 1271, 1172, 1121, 1105, 1067, 1011, 803, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}Br_2O_2$ (MH^+) 368.9120; found 368.9123.

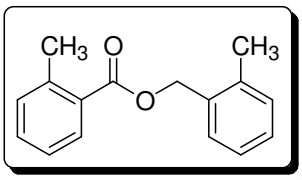
4-Nitrobenzyl 4-nitrobenzoate (ff):



Yellowish gum; ^1H 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,

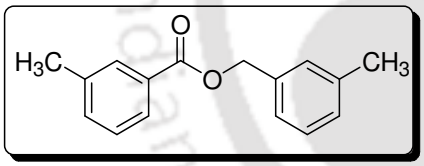
128.6, 130.9, 137.5, 146.5, 148.8, 166.7; IR (KBr): 2962, 2923, 2849, 1727, 1645, 1604, 1517, 1347, 1274, 1104, 735, 717 cm^{-1}; Anal. calcd. for $C_{14}H_{10}N_2O_6$: C 55.63, H 3.33, N 9.27; found C 55.69, H 3.36, N 9.17.

2-Methylbenzyl 2-methylbenzoate (gg):



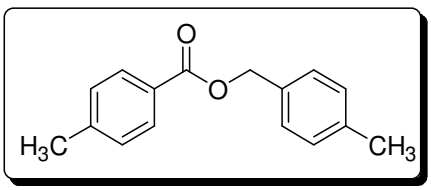
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.60 (s, 3H), 5.34 (s, 2H), 7.18–7.24 (m, 5H), 7.34–7.42 (m, 2H), 7.93 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.9, 21.7, 64.8, 125.7, 126.0, 128.4, 129.2, 129.4, 130.3, 130.6, 131.7, 131.9, 134.1, 136.8, 140.3, 167.0; IR (KBr): 3066, 3022, 2929, 1717, 1605, 1457, 1290, 1250, 1141, 1075, 738 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}O_2$ (MH^+) 241.1223; found 241.1219.

3-Methylbenzyl 3-methylbenzoate (hh):



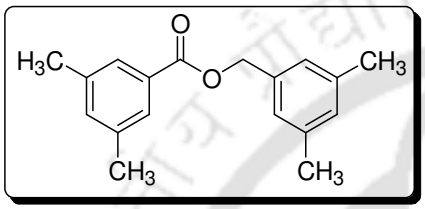
Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37(s, 3H), 2.38 (s, 3H), 5.31 (s, 2H), 7.14 (d, 1H, *J* = 6.4 Hz), 7.23–7.34 (m, 5H), 7.88 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 21.4, 66.7, 125.3, 126.9, 128.3, 128.5, 129.0, 130.1, 130.2, 133.7, 136.1, 138.1, 138.2, 166.5; IR (KBr): 3027, 2922, 1721, 1610, 1455, 1372, 1276, 1197, 1106, 1081, 781, 746 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found C 79.82, H 6.94.

4-Methylbenzyl 4-methylbenzoate (ii):



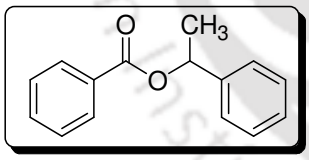
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 2.35 (s, 3H), 5.28 (s, 2H), 7.16 (t, 4H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8 Hz), 7.94 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.9, 21.4, 66.2, 127.5, 128.2, 128.9, 129.1, 129.6, 133.2, 137.7, 143.4, 166.2; IR (KBr): 2923, 2857, 1718, 1613, 1451, 1372, 1271, 1177, 1103, 1018, 807, 754 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found C 79.82, H 6.84.

3,5-Dimethylbenzyl 3,5-dimethylbenzoate (jj):



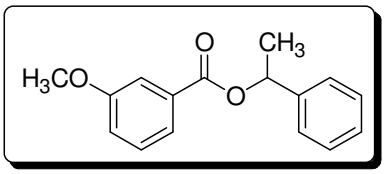
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 6H), 2.32 (s, 6H), 5.26 (s, 2H), 6.95 (s, 1H), 7.04 (s, 2H), 7.15 (s, 1H), 7.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 21.3, 66.8, 126.2, 127.5, 129.9, 130.2, 134.7, 136.1, 138.0, 138.2, 166.8; IR (KBr): 3011, 2920, 2863, 1717, 1609, 1456, 1382, 1310, 1209, 1163, 1115, 846, 768 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{20}O_2$ (MH^+) 269.1536; found 269.1534.

1-Phenylethyl benzoate (ak):



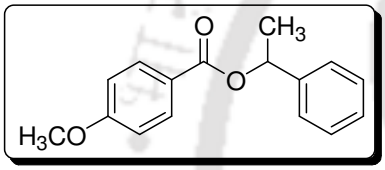
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.70 (d, 3H, *J* = 6.4 Hz), 6.18 (q, 1H, *J* = 6.4 Hz), 7.30–7.49 (m, 7H), 7.56 (t, 1H, *J* = 7.6 Hz), 8.13 (d, 2H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 72.8, 126.0, 127.8, 128.3, 128.5, 129.5, 130.5, 132.8, 141.8, 165.6; 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 3-methoxybenzoate (bk):



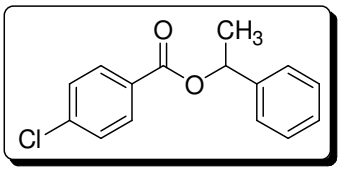
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.68 (d, 3H, *J* = 6.8 Hz), 3.79 (s, 3H), 6.15 (q, 1H, *J* = 6.4 Hz), 7.41–7.46 (m, 5H), 7.52–7.56 (m, 2H), 7.94 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.2, 55.4, 75.0, 113.8, 120.5, 126.4, 128.5, 129.0, 129.9, 130.1, 135.0, 140.5, 163.5, 166.6; IR (KBr): 2929, 2846, 1717, 1635, 1587, 1266, 1199, 757, 699 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_3$: C 74.98, H 6.29; found C 74.92, H 6.35.

1-Phenylethyl 4-methoxybenzoate (ck):



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 (q, 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 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.

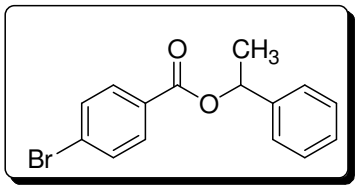
1-Phenylethyl 4-chlorobenzoate (dk):



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,

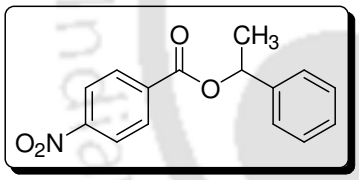
164.8; IR (KBr): 3038, 2981, 2929, 1718, 1594, 1452, 1269, 1103, 1063, 850, 759, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}ClO_2$ (MH^+) 261.0677; found 261.0685.

1-Phenylethyl 4-bromobenzoate (ek):



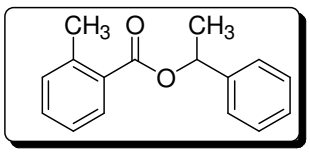
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.66 (d, 3H, *J* = 6.4 Hz), 6.11 (q, 1H, *J* = 6.4 Hz), 7.29–7.43 (m, 6H), 7.56 (d, 2H, *J* = 8.8 Hz), 7.92 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.2, 73.2, 126.0, 126.6, 127.9, 128.5, 129.4, 131.1, 131.6, 141.5, 164.8; IR (KBr): 3034, 2980, 2931, 1719, 1590, 1269, 1102, 1065, 1012, 848, 756, 698 cm^{-1}; Anal. calcd for $C_{15}H_{13}BrO_2$: C 59.04, H 4.29; found C 59.11, H 4.33.

1-Phenylethyl 4-nitrobenzoate (fk):



Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.71 (d, 3H, *J* = 6.4 Hz), 6.16 (q, 1H, *J* = 6.8 Hz), 7.32–7.46 (m, 5H), 8.21–8.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 73.8, 123.1, 125.8, 127.9, 128.4, 130.3, 135.5, 140.9, 150.1, 163.4; IR (KBr): 3035, 2984, 2934, 1724, 1689, 1607, 1527, 1452, 1351, 1271, 1199, 1103, 1061, 874, 762, 720, 699 cm^{-1}; Anal. calcd. for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16; found C 66.46, H 4.79, N 5.12.

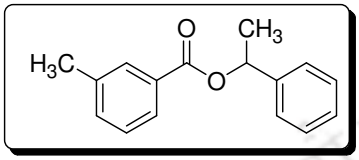
1-Phenylethyl 2-methylbenzoate (gk):



Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.66 (d, 3H, *J* = 6.8 Hz), 2.58 (s, 3H), 6.11 (q, 1H, *J* = 6.4Hz), 7.18–7.36 (m, 6H), 7.43 (d, 2H, *J* = 7.6 Hz), 7.96 (d,

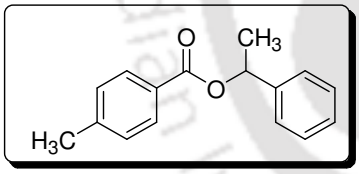
1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 22.3, 72.6, 125.6, 126.0, 127.8, 128.5, 129.9, 130.5, 131.6, 131.8, 140.1, 141.8, 166.5; IR (KBr): 3066, 3033, 2980, 2929, 1717, 1456, 1290, 1254, 1143, 1077, 1029, 738, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}O_2$ (MH^+) 241.1223; found 241.1216.

1-Phenylethyl 3-methylbenzoate (hk):



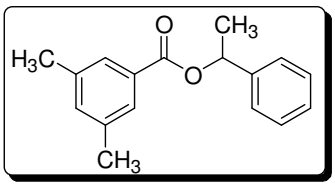
Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.71 (d, 3H, *J* = 6.4 Hz), 2.61 (s, 3H), 6.17 (q, 1H, *J* = 6.8 Hz), 7.33–7.49 (m, 7H), 7.91 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.5, 22.3, 75.0, 126.4, 126.8, 128.5, 128.9, 129.0, 130.1, 132.7, 133.3, 135.0, 140.5, 163.5; IR (KBr): 2984, 2931, 1738, 1693, 1597, 1452, 1199, 1176, 1059, 983, 761, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}O_2$ (MH^+) 241.1223; found 241.1221.

1-Phenylethyl 4-methylbenzoate (ik):



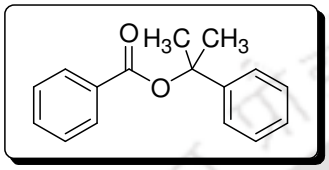
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.64 (d, 3H, *J* = 6.8 Hz), 2.58 (s, 3H), 6.11 (q, 1H, *J* = 6.4 Hz), 7.17–7.35 (m, 6H), 7.43 (d, 2H, *J* = 8 Hz), 7.96 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 22.3, 72.6, 125.6, 126.0, 127.8, 128.5, 130.5, 131.6, 140.1, 141.8, 166.5; IR (KBr): 3066, 3027, 2979, 2923, 1717, 1455, 1255, 1077, 1029, 738, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}O_2$ Anal. calcd. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found C 79.85, H 6.67.

1-Phenylethyl 3,5-dimethylbenzoate (jk):



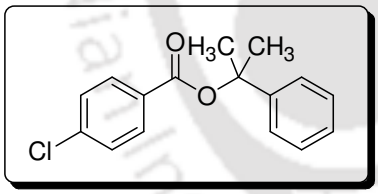
Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.68 (d, 3H, *J* = 6.4 Hz), 2.58 (s, 6H), 6.15 (q, 1H, *J* = 6.8 Hz), 7.31–7.46 (m, 6H), 7.94 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 22.2, 75.0, 126.4, 128.4, 129.0, 130.0, 133.2, 134.9, 137.2, 140.4, 163.4; IR (KBr): 2923, 2852, 1734, 1635, 1449, 1198, 1177, 979, 760, 744, 698 cm^{-1}; Anal. calcd. for $C_{17}H_{18}O_2$: C 80.28, H 7.13; found C 80.37, H 7.09.

2-Phenylpropan-2-yl benzoate (al):



Colourless liquid; ^{1}H 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 (dl):

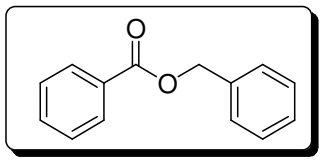


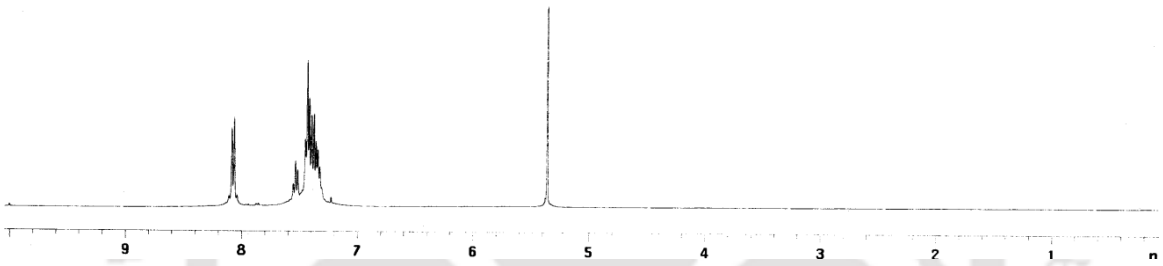
Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.89 (s, 6H), 7.22–7.42 (m, 7H), 7.96 (d, 2H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.5, 82.4, 124.1, 127.0, 128.2, 128.4, 129.8, 130.8, 138.9, 145.4, 164.0; IR (KBr): 2981, 2931, 1725, 1595, 1449, 1365, 1277, 1145, 1116, 1098, 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.

II.7. Selected Spectra

Benzyl benzoate (aa): ^{1}H NMR (400 MHz, $CDCl_3$)

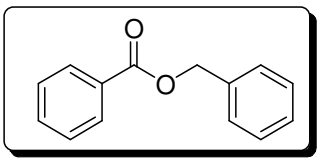
SAMPLE		SPECIAL	
date	Aug 28 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	10010.0	pw90	19.700
at	1.996	alfa	20.000
np	39952	FLAGS	
fb	not used	il	n
bs	4	in	n
d1	1.000	dp	y
nt	32	hs	nn
ct	32	PROCESSING	
TRANSMITTER		lb	0.10
tn	H1	fn	65536
sfrq	399.853	DISPLAY	
tof	362.8	sp	-54.4
tpwr	57	wp	4071.3
pw	9.850	rfl	2617.4
DECOUPLER		rfp	0
dn	C13	rp	132.1
dof	0	lp	-137.7
dm	nnn	PLOT	
dmm	c	wc	250
dpwr	50	sc	0
dmf	15900	vs	43
		th	20
		nm	cdc ph

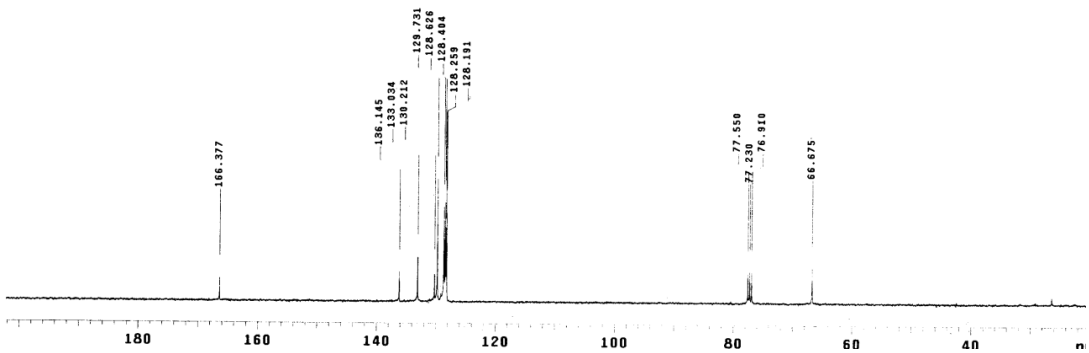




Benzyl benzoate (aa): ^{13}C NMR (100 MHz, $CDCl_3$)

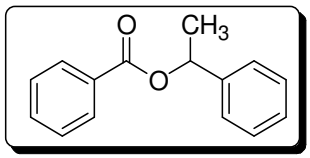
SAMPLE		SPECIAL	
date	Sep 1 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	25125.6	pw90	18.600
at	1.199	alfa	20.000
np	60270	FLAGS	
fb	13800	il	n
bs	32	in	n
d1	1.000	dp	y
nt	12000	hs	nn
ct	928	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	65536
sfrq	100.554	DISPLAY	
tof	1536.3	sp	1705.7
tpwr	61	wp	18620.9
pw	9.300	rfl	9294.3
DECOUPLER		rfp	7764.9
dn	H1	rp	-59.1
dof	0	lp	-332.0
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	42	sc	0
dmf	8900	vs	28
		th	3
		nm	no ph

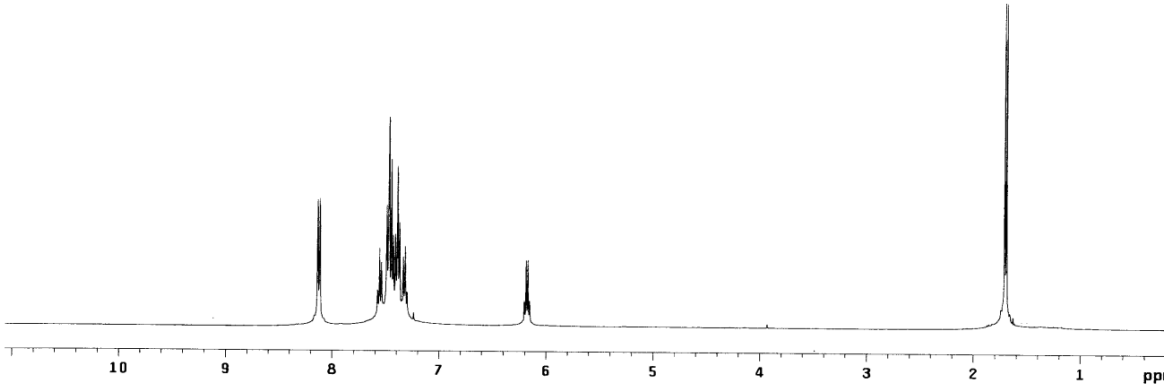




1-Phenylethyl benzoate (ak): ^{1}H NMR (400 MHz, $CDCl_3$)

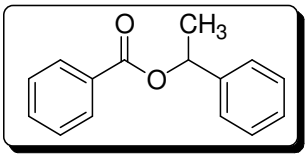
date	Sep 27 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	6006.0	pw90	19.700
at	1.995	alfa	20.000
np	23964	FLAGS	
fb	not used	il	n
bs	4	in	n
d1	1.000	dp	y
nt	32	hs	nn
ct	32	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	399.853	sp	36.5
tof	0	wp	4387.8
tpwr	57	rfl	3868.4
pw	7.000	rfp	2894.9
DECOUPLER		rp	115.5
dn	C13	lp	-87.4
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	50	vs	70
dmf	15900	th	14
		nm	cdc ph

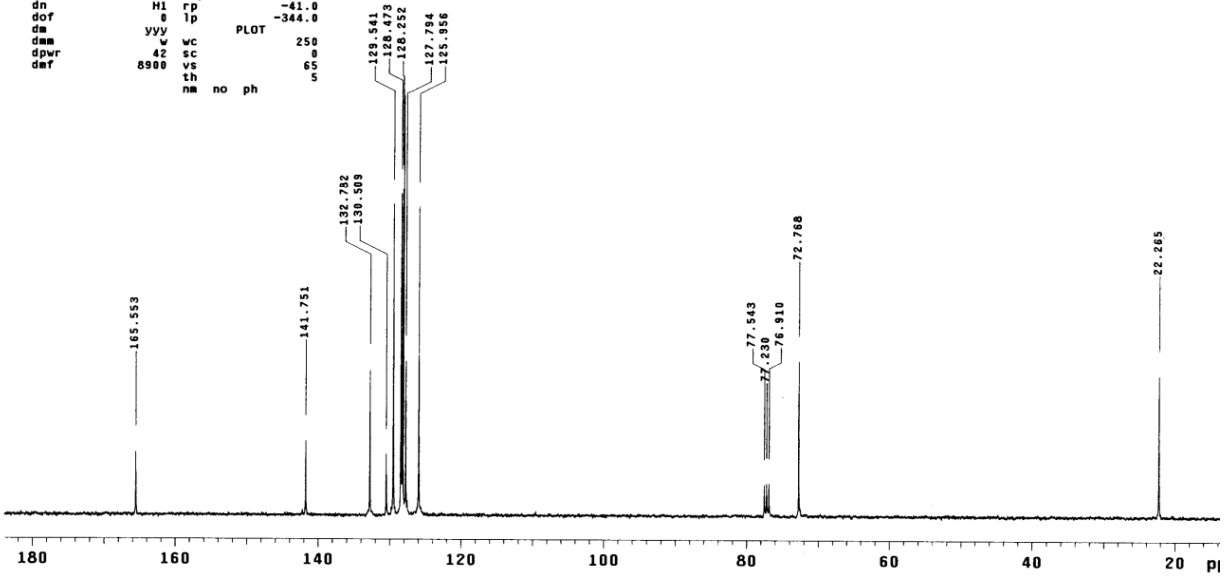




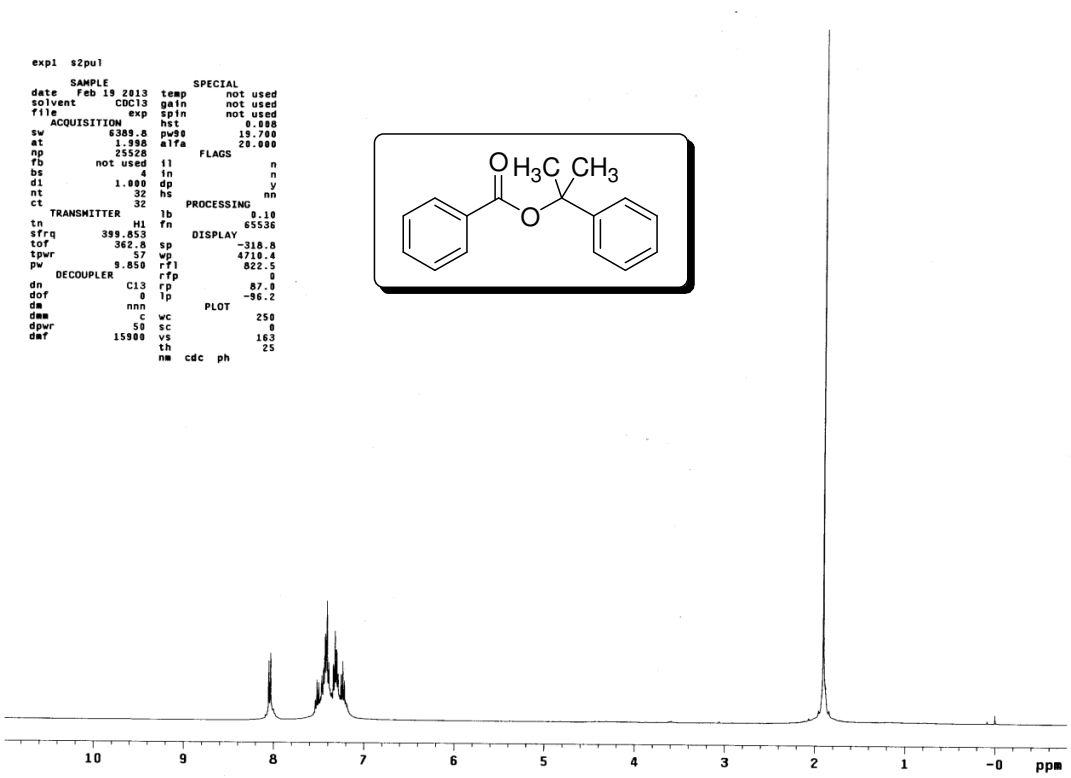
1-Phenylethyl benzoate (ak): ^{13}C NMR (100 MHz, $CDCl_3$)

date	Sep 30 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	25125.6	pw90	18.600
at	1.199	alfa	20.000
np	60270	FLAGS	
fb	13800	il	n
bs	10	in	n
d1	1.000	dp	y
nt	5000	hs	nn
ct	340	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	65536
sfrq	100.554	DISPLAY	
tof	1536.3	sp	1058.5
tpwr	61	wp	17432.4
pw	9.300	rfl	9314.3
DECOUPLER		rfp	7764.9
dn	H1	rp	-41.0
dof	0	lp	-344.0
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	42	sc	0
dmf	8900	vs	65
		th	5
		nm	no ph

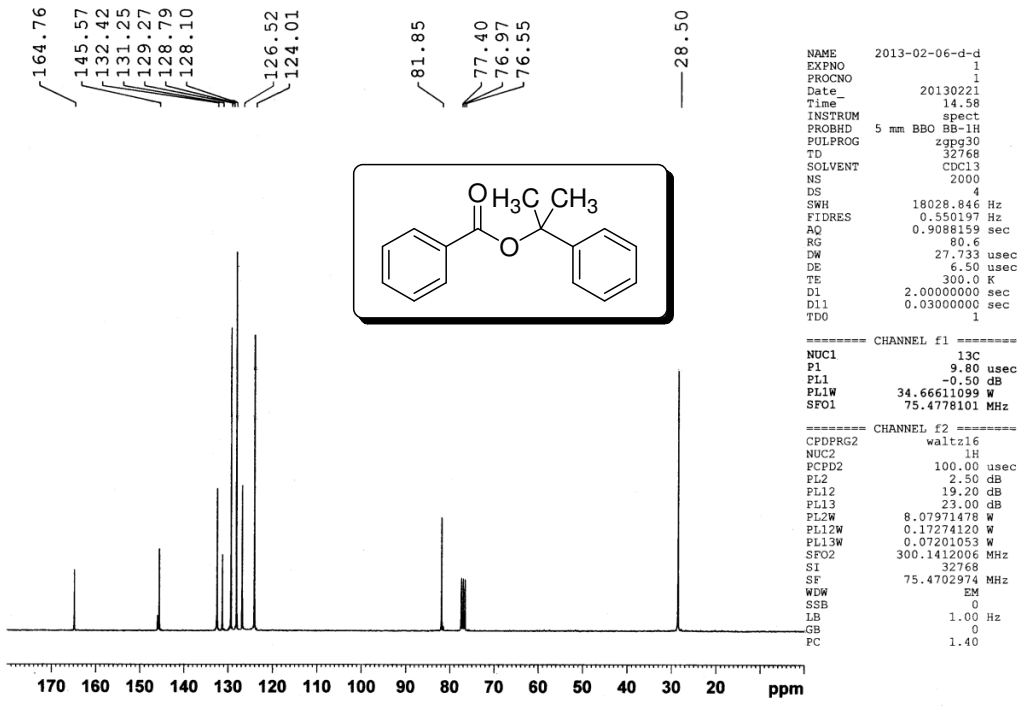




2-Phenylpropan-2-yl benzoate (al): ^{1}H NMR (400 MHz, $CDCl_3$)



2-Phenylpropan-2-yl benzoate (al): ^{13}C NMR (75 MHz, $CDCl_3$)



CHAPTER III

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Cyclic ethers to esters and monoesters to bis-esters with unconventional coupling partners under metal free conditions *via* sp^3 C–H functionalisation†‡

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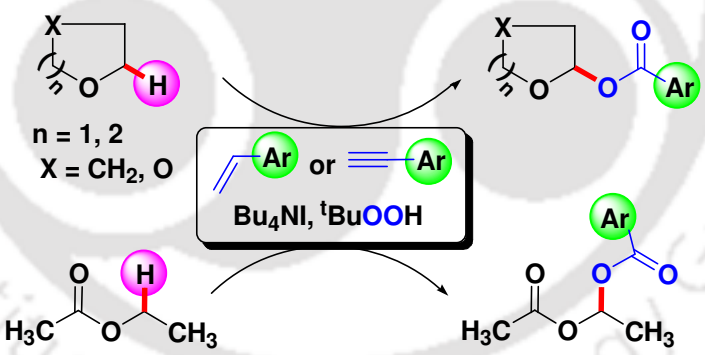


Abstract: **An efficient metal free oxidative esterification of sp^3 C–H bonds (adjacent to an oxygen atom) in simple solvents like 1,4-dioxane, tetarhydropyran, tetrahydrofuran and ethyl acetate has been achieved using terminal aryl alkenes and alkynes as ArCOO– sources.**

CHAPTER III

III. Cyclic Ethers to Esters and Monoesters to *bis*-Esters with Unconventional Coupling Partners under Metal Free Conditions via sp^3 C–H Functionalization

III.1. Introduction

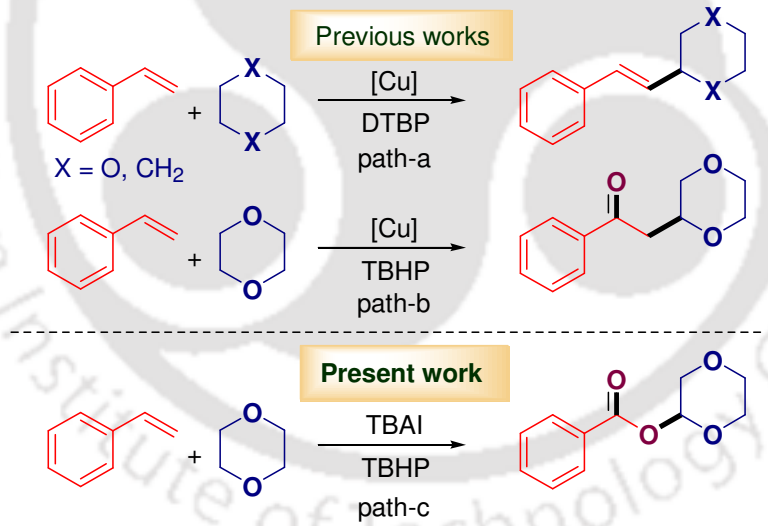
Organic chemists continue to strive towards the development of atom and step economic process for the synthesis of complex molecular structures from simple precursors. What better way to achieve this than to manipulate ubiquitous C–H bonds?[1] In this regard, cross dehydrogenative coupling (CDC) has 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.[2a,2b,2g] One of the extensively studied approaches in this forum is the substrate directed alkenylations using Rh, Ru and Pd catalysts.[1h,3] However, scrutiny entails that most of these transformations are for sp^2 C–H bonds facilitated by a multitude of directing groups.[4]

In contrast, due to their intrinsically low reactivity (high p*K*a and bond energy) similar alkenylation at sp^3 C–H bonds remain virtually unexplored. In this regard, recently two independent groups developed radically induced vinylation of the sp^3 C–H bonds of cyclic ethers and cycloalkanes using a copper catalyst (Scheme III.1.1, path-a).[5] Initially, Lei *et al.* reported a copper-catalyzed oxidative alkenylation of ethers with olefins (Scheme III.1.1, path-a).[5a] In this protocol various ethers and olefins coupled well and gave the corresponding alkenylation products in good to excellent yields. Subsequently, a method for the direct alkenylation of simple alkanes with styrenes using $Cu(OTf)_2$ as the catalyst was illustrated by Wei group (Scheme III.1.1, path-a).[5b]

The current trend in organic synthesis is to use and encourage metal free catalysts such as iodine, iodide salts and organoammonium iodides, which are often appropriate substitutes to transition metals.[2e,2f,6] These metal free catalysts (in combination with oxidant) either complement or show similar reactivity to that of transition metals in bringing about requisite transformations. In addition, their use is highly advantageous from an enviroeconomic point of view for a sustainable future. In order to achieve the

same, when we attempted similar alkenylation of cyclic ether 1,4-dioxane with styrene using tetrabutylammonium iodide (TBAI)/TBHP, surprisingly the α-esterification of dioxane i.e., formation of α-acyloxy ether was observed (Scheme III.1.1, path-c).

This observation clearly indicates that the reactivity of TBAI/TBHP combination is in sharp contrast to a Cu salts/oxidant combination which results in α-acyloxy ether (Scheme III.1.1, path-c) as the sole product rather than the expected vinylation (Scheme III.1.1, path-a). The *in situ* generation of another coupling partner, *viz.* the benzoxy group ($PhCOO^-$) derived from styrene is not surprising, as the same was recently generated under similar conditions (Cu/TBHP).[7] Thus the TBAI/TBHP combination is also expected to generate $PhCOO^-$ from styrene under identical conditions. Notably, the coupling of styrene with cyclic ether in the presence of CuBr/TBHP is reported to undergo oxyalkylation i.e., ketone formation (Scheme III.1.1, path-b).[8] Thus the divergence in selectivities achieved with various catalyst/oxidant combinations further highlights the significance of the present finding.



Scheme III.1.1. *Differential reactivity of alkenylbenzene with cyclic ethers.*

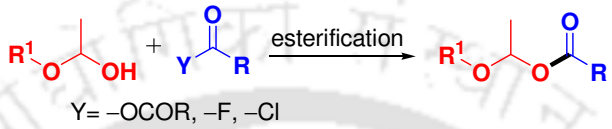
III.2. Strategies for the Synthesis of α-Acyloxy Ethers

α-Acyloxy ethers are valuable synthetic intermediates[9] in organic synthesis and are part of biological molecules.[10] Synthesis of α-acyloxy ethers has been achieved by other strategies that can be classified into five main categories: (i) esterification of hemiacetals with acids or its derivatives,[11] (ii) addition of carboxylic acids to alkenyl ethers,[12] (iii) complex routes comprising of two-step synthesis,[13] (iv) α-halo substitution

of ethers with carboxylic acids[14] and (v) CDC transformations under either transition metal or metal free catalysts in combination with various oxidants.[15]

(i) Esterification of hemiacetals with acids or its derivatives

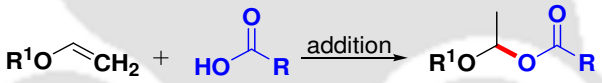
Treatment of hemiacetals with acyl halides and anhydrides in the presence of a stoichiometric amount of bases lead to the formation of α-acyloxy ethers (Scheme III.2.1).[11]



Scheme III.2.1. *Reaction of hemiacetals with acyl halides and esters*

(ii) Addition of carboxylic acids to alkenyl ethers

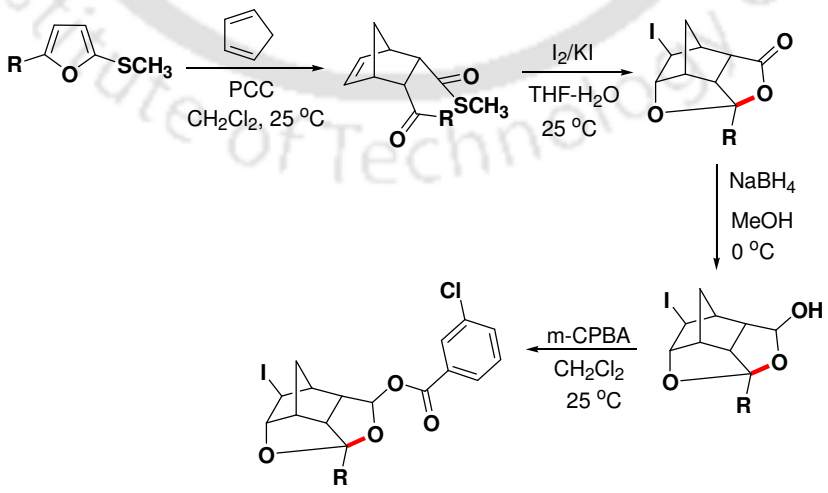
In this method the synthesis of α-acyloxy ethers can be achieved by the addition of carboxylic acids across the double bond of alkenyl ethers under heating condition (Scheme III.2.2).[12]



Scheme III.2.2. *Synthesis of α-acyloxy ethers from alkenyl ethers*

(iii) Complex routes comprising of two-step synthesis

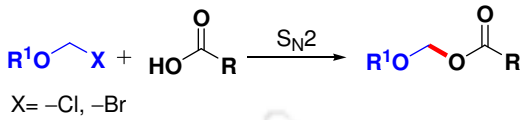
Sequential cyclization of norbornene derivatives under standard reaction conditions affords diacetal trioxa-cage compounds (Scheme III.2.3).[13]



Scheme III.2.3. *Miscellaneous methods*

(iv) α-Halo substitution of ethers with carboxylic acids

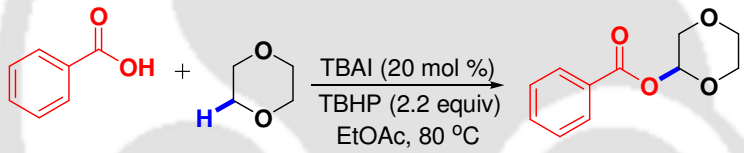
In this process the α-acyloxy ethers are synthesized by nucleophilic substitution (S_N2 path) of α-halo ethers with carboxylic acids in the presence of a suitable base (Scheme III.2.4).[14]



Scheme III.2.4. *Synthesis of α-acyloxy ethers via S_N2 path*

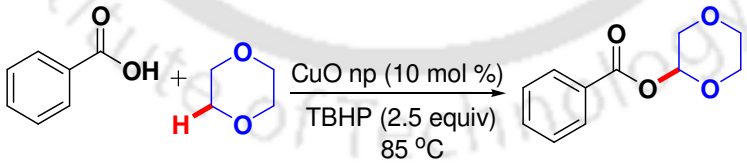
(v) Transition metal or metal free catalyzed CDC transformations

Wan group developed a simple and efficient method to construct α-acyloxy ethers from ethers and carboxylic acids using TBAI and TBHP combination. This protocol involves the CDC reaction of C–H bond in dioxane and the carboxylic O–H group under metal free conditions (Scheme III.2.5.1).[15a]



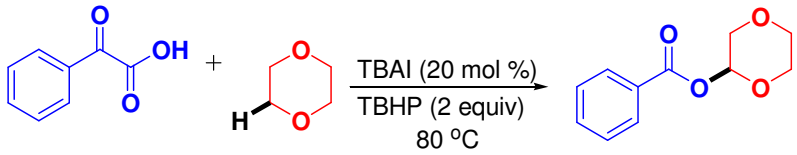
Scheme III.2.5.1. *TBAI-catalyzed cross dehydrogenative coupling of acids with ethers*

Lakshmi Kantam and co-workers illustrated a similar cross coupling reaction of carboxylic acids with cyclic ethers for the synthesis α-acyloxy ethers using CuO nanoparticles as catalyst and TBHP as an oxidant (Scheme III.2.5.2).[15b]



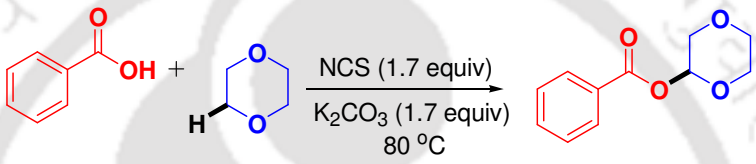
Scheme III.2.5.2. *Copper-catalyzed cross coupling reaction of acids with cyclic ethers*

A TBAI-catalyzed protocol for the decarboxylative acyloxylation of α-sp^3 C–H bonds in ethers with α-oxocarboxylic acids was reported by Duan *et al.* (Scheme III.2.5.3).[15c] In this method variety of α-acyloxy ethers were constructed by the decarboxylative coupling of α-oxocarboxylic acids with ethers using an inexpensive catalyst–oxidant system.



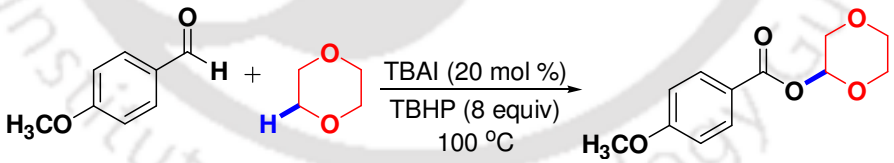
Scheme III.2.5.3. *TBAI-catalyzed decarboxylative acyloxylation of sp^3 C–H bond in ethers*

Xu group reported *N*-chlorosuccinimide mediated oxidative C–H bond functionalization/esterification of α-alkoxy alkanes with acids. In this transformation alkyl-, aryl-, alkenyl- and alkynyl-carboxylic acids are all well tolerated and gave corresponding α-acyloxy ethers in good yields (Scheme III.2.5.4).[15d]



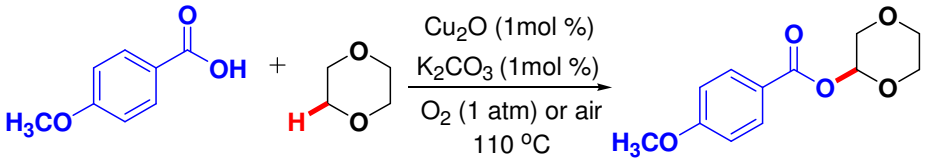
Scheme III.2.5.4. *N-Chlorosuccinimide-mediated CDC of carboxylic acids with cyclic ethers*

Wang *et al.* demonstrated a TBAI-catalyzed α-acyloxylation of ethers with aldehydes using TBHP as the oxidant. This method exhibit a broad substrates scope, including aromatic/heteroaromatic aldehydes and cyclic, acyclic diethers, crown ethers (Scheme III.2.5.5).[15e]



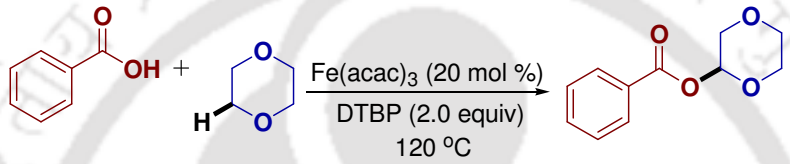
Scheme III.2.5.5. *TBAI-catalyzed α-acyloxylation of ethers with aldehydes*

Liu and co-workers developed a Cu catalyzed oxidative coupling of carboxylic acids and aldehydes with ethers (Scheme III.2.5.6).[15f] A range of α-acyloxy ethers and formates of 1,2-ethanediol are synthesized in this method by direct coupling of carboxylic acids and aldehydes with glycol ethers. Furthermore, large-scale synthesis of valuable pharmaceuticals containing a α-acyloxy ether subunit could provide under reaction conditions.



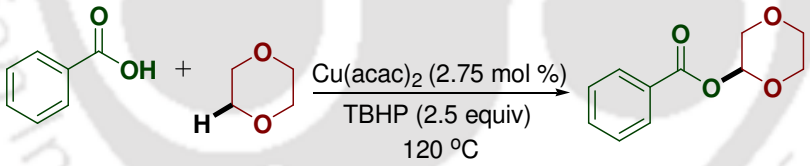
Scheme III.2.5.6. *Cu-catalyzed oxidative coupling of acids with ethers*

Han group described an iron-catalyzed cross dehydrogenative coupling of C(sp^3)–H bonds in cyclic ethers with carboxylic acids for the synthesis of α–acyloxy ethers (Scheme III.2.5.7).[15g] A wide range of cyclic ethers are coupled with phenylacetic acids and aromatic acids, providing corresponding α-acyloxy ethers in good to excellent yields.



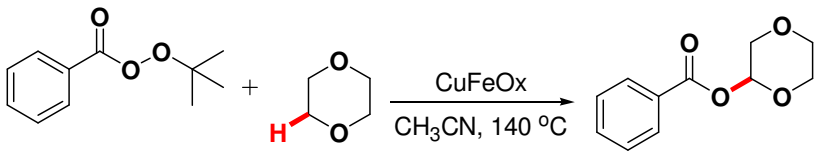
Scheme III.2.5.7. *Iron-catalyzed oxidative esterification of C(sp^3)–H bonds in ethers*

A copper(II)-catalyzed protocol for the synthesis of α-acyloxy ethers via cross dehydrogenative coupling of carboxylic acids and cyclic ethers using TBHP as the oxidant has been developed by Chaudhuri and co-workers (Scheme III.2.5.8).[15h]



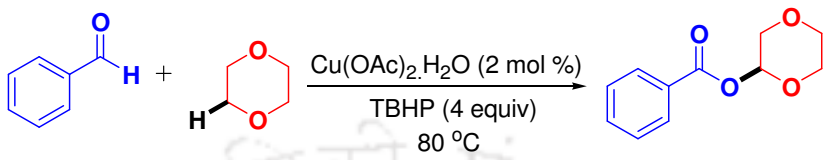
Scheme III.2.5.8. *Copper(II)-catalyzed synthesis of α-acyloxy ethers*

Guerra *et al.* developed a copper–iron mixed oxide catalyst for the synthesis of α-acyloxy-1,4-dioxanes and 1,4-dithianes employing *t*-butyl peroxyesters. The acyloxylation of α-sp^3 C–H bonds in ethers and thioethers can be performed in an efficient and clean way using copper–iron mixed oxides (Scheme III.2.5.9).[15i]



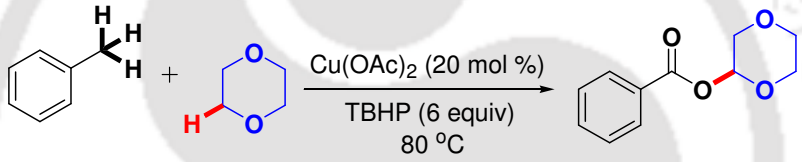
Scheme III.2.5.9. *Copper-iron mixed oxide-catalyzed synthesis of α-acyloxy-1,4-dioxanes*

An efficient CDC protocol for the construction of C–O bonds from aldehydes and ethers using copper catalyst has been demonstrated by Yuan group (Scheme III.2.5.10).[15j] Various α-acyloxy ethers were obtained with excellent yields via oxidative cross coupling of aldehydes and ethers under reaction conditions.



Scheme III.2.5.10. *Copper-catalyzed C–O bond formation from aldehydes and ethers*

Following the CDC strategy, our group has developed a protocol for the synthesis of α-acyloxy ethers via a Cu mediated solvent-solvent coupling between alkylbenzenes and cyclic ethers (Scheme III.2.5.11).[16]



Scheme III.2.5.11. *Copper-catalyzed esterification of alkylbenzenes with cyclic ethers*

Apart from these results there are other oxidative C–O bond forming reactions most of which are for acetoxylation and hydroxylation.[17]

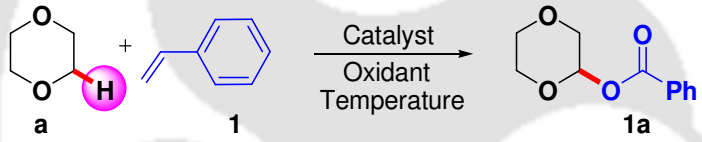
III.3. Present Work

The query that arose was whether the radically induced vinylation at the inert α-sp^3 C–H bonds of cyclic ethers using copper salts/oxidant[5] can similarly be accomplished with tetrabutylammonium iodide (TBAI) and TBHP combination.

Optimization of reaction conditions. The above query encouraged a trial reaction between cyclic ether 1,4-dioxane (**a**) and styrene (**1**) in the presence of TBAI (10 mol %) and aqueous TBHP (4 equiv) at 80 °C. The surprising outcome of this reaction was the unexpected α-esterification of dioxane resulting in the product (**1a**) in 20% yield (Table III.3.1, entry 1). After the preliminary success on unusual esterification further attempts were made to improve the yield of (**1a**) by varying the reaction parameters. When the above coupling reaction was performed with a decane solution of TBHP (5-6 M) (4 equiv) instead of an aqueous TBHP (70% in water) the yield increased up to 45% (Table

III.3.1, entry 2). By increasing the TBHP quantity from 4 to 6 equiv and Bu_4NI from 10 to 20 mol % the yield increased from 45% to 70% (Table III.3.1, entries 3–5). Furthermore, no enhancement in the yield was observed with increase in the catalyst Bu_4NI (30 mol %), oxidant TBHP (7 equiv) and reaction temperature (100 ^oC) (Table III.3.1, entries 6–8). Other oxidants such as di-*tert* butyl peroxide (DTBP), aq H_2O_2, oxone, $K_2S_2O_8$ and benzoylperoxide were completely ineffective for this transformation (Table III.3.1, entries 9–13). Instead of Bu_4NI other halogen species such as Bu_4NBr, KI and I_2 (Table III.3.1, entries 14–16) were completely unproductive. The control experiments carried out with either TBHP or catalyst (Bu_4NI) alone were ineffective towards this CDC coupling (Table III.3.1, entries 17–18). Thus, the ideal conditions are the use of styrene (1 mmol), 1,4-dioxane (1 mL), Bu_4NI (20 mol %), decane solution of TBHP (5–6 M) (6 equiv) and a reaction temperature of 80 ^oC.

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

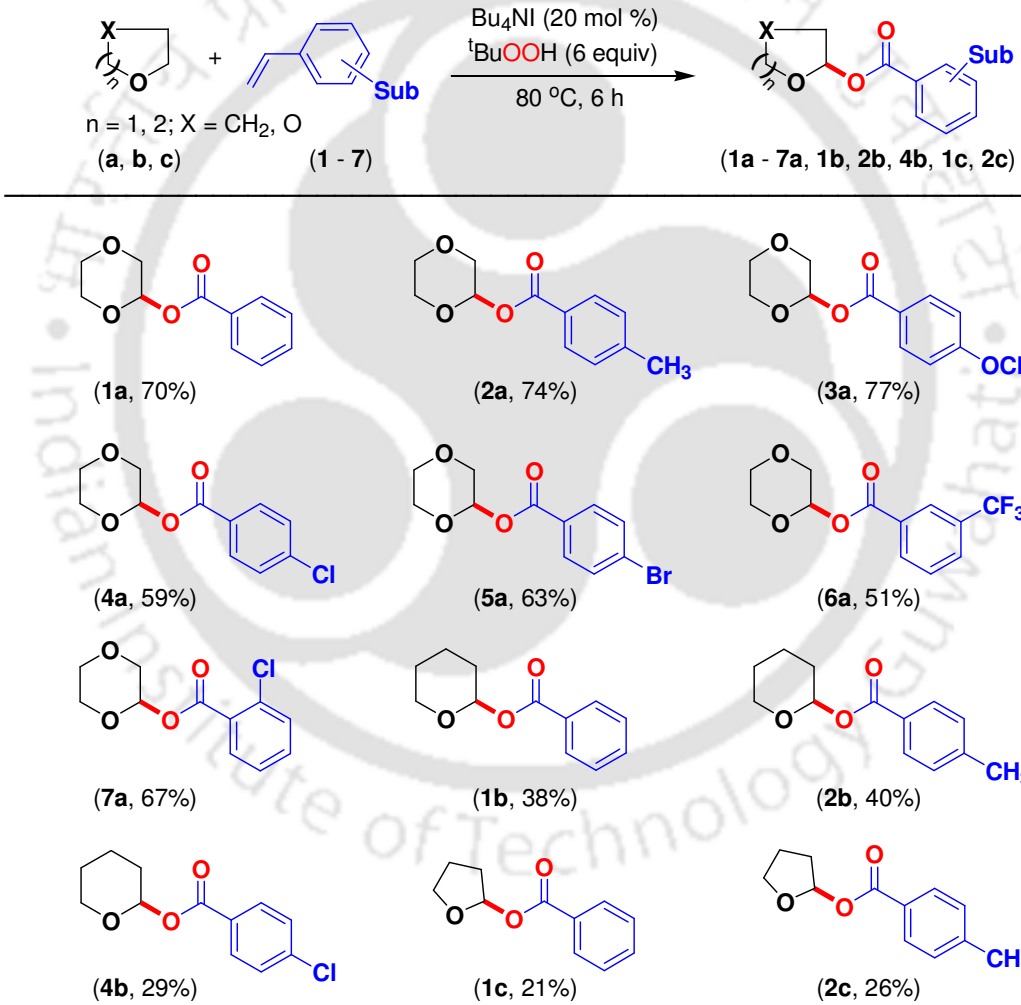


Entry	Catalyst (mol %)	Oxidant (equiv)	Temp (^oC)	Yield[b] (%)
1	Bu_4NI (10)	aq TBHP (4)	80	20
2	Bu_4NI (10)	TBHP in decane (4)	80	45
3	Bu_4NI (10)	TBHP in decane (5)	80	52
4	Bu_4NI (10)	TBHP in decane (6)	80	60
5	**Bu_4NI (20)**	**TBHP in decane (6)**	**80**	**70**
6	Bu_4NI (30)	TBHP in decane (6)	80	69
7	Bu_4NI (20)	TBHP in decane (7)	80	66
8	Bu_4NI (20)	TBHP in decane (6)	100	65
9	Bu_4NI (20)	DTBP (6)	80	00
10	Bu_4NI (20)	aq H_2O_2 (6)	80	00
11	Bu_4NI (20)	Oxone (6)	80	00
12	Bu_4NI (20)	$K_2S_2O_8$ (6)	80	00
13	Bu_4NI (20)	PhCOOCOPh (6)	80	00
14	Bu_4NBr (20)	TBHP in decane (6)	80	00
15	KI (20)	TBHP in decane (6)	80	00
16	I_2 (20)	TBHP in decane (6)	80	00
17	nil	TBHP in decane (6)	80	00
18	Bu_4NI (20)	nil	80	00

[a]1,4-Dioxane (1mL), styrene (1 mmol), Reaction time: 6 h, [b]Isolated yield.

Substrate scope for α-acyloxy ethers. Having established the optimized parameters, the oxidative esterifications of 1,4-dioxane (**a**) with various substituted styrenes were tested and the results are summarized in Scheme III.3.1. Under the optimized conditions, electron neutral styrene –H (**1**) and styrenes possessing either electron-donating substituents such as *p*-Me (**2**), *p*-OMe (**3**) or electron-withdrawing substituents such as *p*-Cl (**4**), *p*-Br (**5**), *m*-CF_3 (**6**) and *o*-Cl (**7**) were found to serve as ArCOO– surrogates providing the desired α-acyloxy ethers (**1a–7a**) in good yields (Scheme III.3.1).

Scheme III.3.1. *Substrate scope for α-acyloxy ethers*[a,b]



[a]Reaction conditions: styrene (1 mmol), cyclic ethers (1 mL), TBAI (0.2 mmol), TBHP (6 mmol) at 80 °C. [b]Isolated yields.

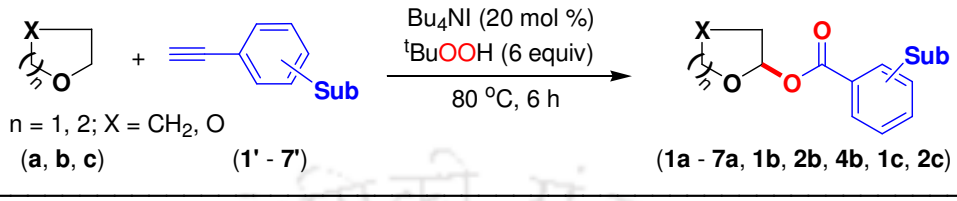
It was observed that, substituted styrenes containing electron-donating groups provided the corresponding products in higher yields than those bearing electron-

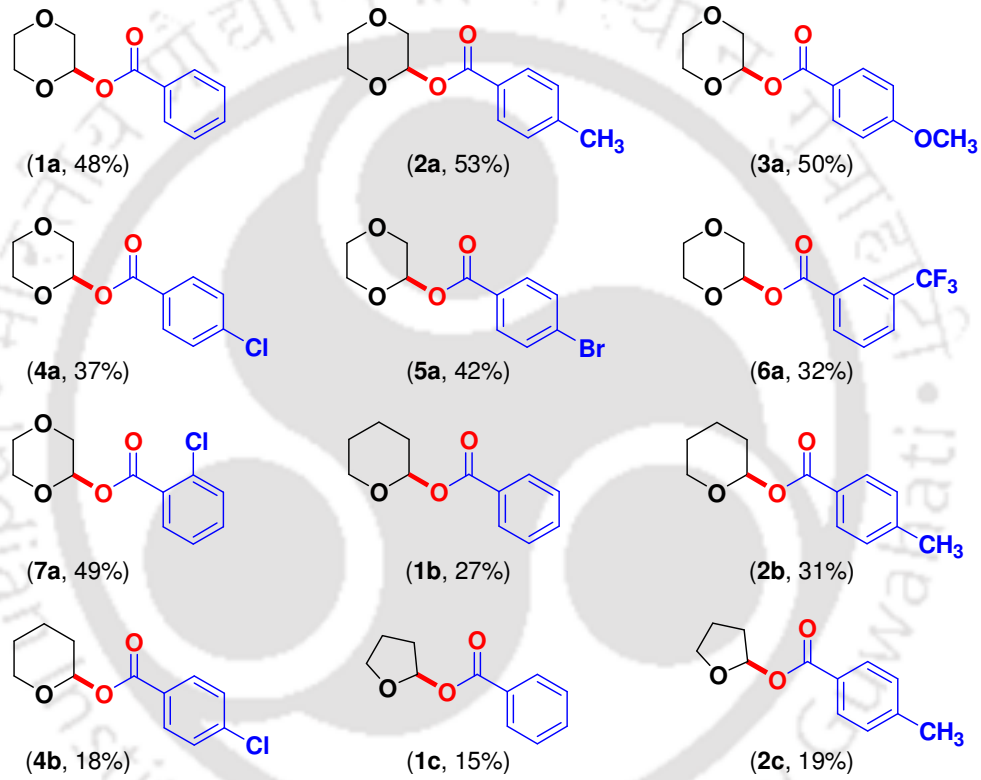
withdrawing groups. These results imply that the electronic factor of substituents on the phenyl ring of styrenes affects the reaction rates as well as the product yields. This reactivity trend is consistent with our recent *o*-benzoxylation of 2-phenylpyridine using styrenes as aryl carboxy source.[7] This approach was further examined with other cyclic ethers possessing single oxygen i.e., tetrahydropyran (**b**) and tetrahydrofuran (**c**). The oxidative esterification of tetrahydropyran (**b**) with styrenes (**1**, **2** and **4**) was not so effective in terms of yields as compared to 1,4-dioxane and it afforded α-acyloxy ethers (**1b**, **2b** and **4b**) in lower yields (Scheme III.3.1). Tetrahydrofuran (**c**) with styrenes (**1** and **2**) provided much lower yields of α-acyloxyethers (**1c** and **2c**) (Scheme III.3.1). In the case of 1,4-dioxane (**a**) there are eight equivalent sp^3 C–H's where as in tetrahydropyran (**b**) and tetrahydrofuran (**c**) there are only four such sp^3 C–H's, thus the yield obtained in the later two are lower compared to the former due to statistical factor.

Substrate scope for α-acyloxy ethers. Beside styrenes, phenylacetylenes are efficient arylcarboxy source under Cu(II)/TBHP conditions.[7] We were therefore curious to see whether under the present metal free conditions phenylacetylenes could generate an arylcarboxy group and couple with cyclic ethers, similar to styrenes. With this objective phenylacetylene (**1′**) was treated with 1,4-dioxane (**a**) under the previously optimized conditions. It was heartening to observe that the product α-acyloxyethers (**1a**) was obtained in 48% yield. Thus similarly to styrene the benzoxy group ($PhCOO^-$) can be generated from phenylacetylene under metal free condition which is unprecedented. In order to generalise this methodology, 1,4-dioxane (**a**) was treated with various phenylacetylenes (**2′–7′**) and the results are summarized in Scheme III.3.2. Phenylacetylenes having either electron-donating groups such as *p*-Me (**2′**), *p*-OMe (**3′**) or electron-withdrawing groups such as *p*-Cl (**4′**), *p*-Br (**5′**), *m*-CF_3 (**6′**) and *o*-Cl (**7′**) served as ArCOO– surrogates under the present conditions providing their desired esters (**2a–7a**) in moderate yields (Scheme III.3.2). Additionally, the oxidative esterification of tetrahydropyran (**b**) with various phenylacetylenes (**1′**, **2′** and **4′**) gave α-acyloxy THP ethers (**1b**, **2b** and **4b**) in lower yields (Scheme III.3.2). Tetrahydrofuran (**c**) with phenylacetylenes (**1′** and **2′**) provided much lower yields of α-acyloxy THF ethers (**1c** and **2c**) (Scheme III.3.2). The lower yields of products obtained with phenylacetylenes

compared to styrenes is due to the competitive homocoupling of terminal alkynes to diynes under the reaction conditions.

Scheme III.3.2. *Substrate scope for α-acyloxy ethers*[a,b]



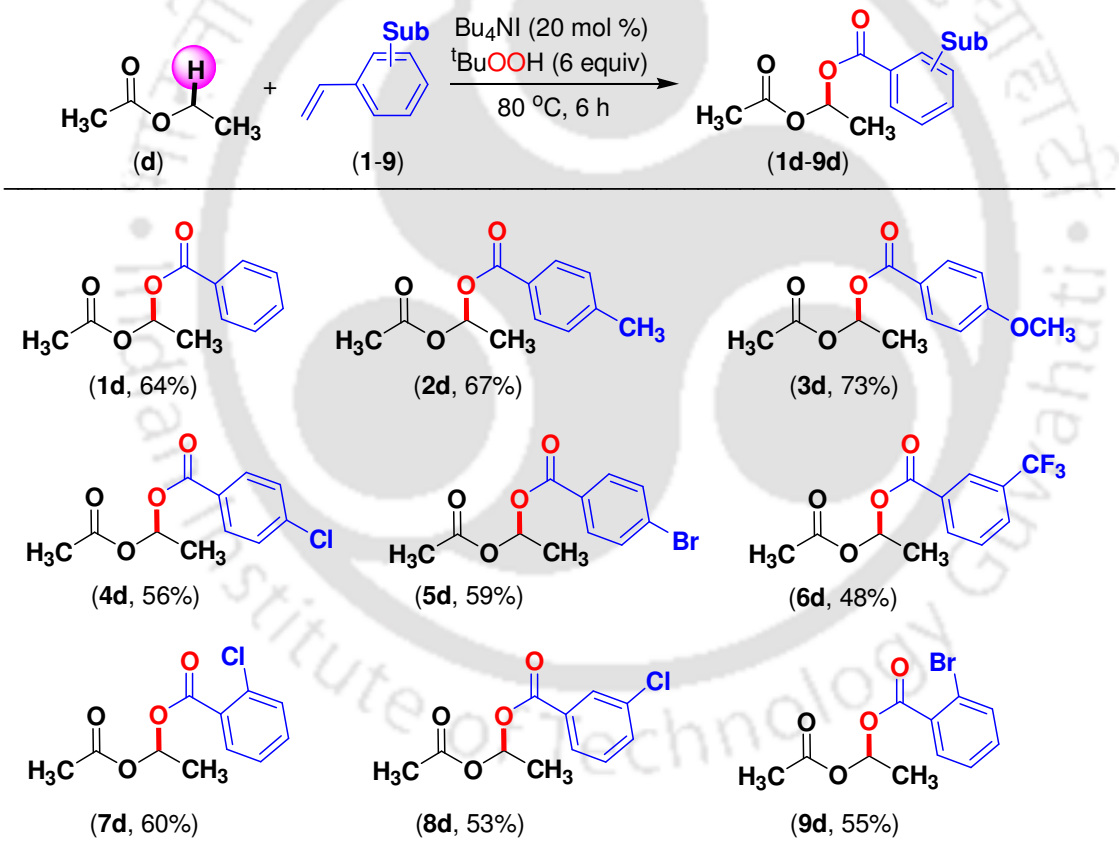


[a]Reaction conditions: phenylacetylene (1 mmol), cyclic ethers (1 mL), TBAI (0.2 mmol), TBHP (6 mmol) at 80 °C.
[b]Isolated yields.

Cyclic ethers such as 1,4-dioxane, tetrahydrofuran and tetrahydropyran are the only common solvents utilised for α C–H functionalizations.[15,16] Ethyl acetate (bearing sp^3 C–H α to oxygen) is predominantly used as a solvent and a diluent. The oxidative α C–H functionalization of ethyl acetate (**d**) is a very exigent task because it is prone to hydrolysis and *trans*-esterification. Thus selective functionalizations of ethyl acetate would not only be a challenging task but also exciting if achieved.

Substrate scope for esterification of ethyl acetate. To explore this, the above optimized conditions were implemented on ethyl acetate (**d**) by treating it with styrene (**1**). Interestingly, the product obtained was found to be a double ester (**1d**) formed via functionalization at the α-sp^3 C–H of ethyl acetate without affecting the existing ester functionality. The double ester is nothing but an unsymmetrical *gem*-diacylates.[18] This double esterification of ethyl acetate was then tested with other styrenes that had electron-donating groups such as *p*-Me (**2**), *p*-OMe (**3**) and electron-withdrawing groups such as *p*-Cl (**4**), *p*-Br (**5**), *m*-CF_3 (**6**), *o*-Cl (**7**), *m*-Cl (**8**) and *o*-Br (**9**) all provided unsymmetrical *gem*-diacylates (**2d–9d**) in moderate yields as shown in Scheme III.3.3.

Scheme III.3.3. *Substrate scope for esterification of ethyl acetate*[a,b]



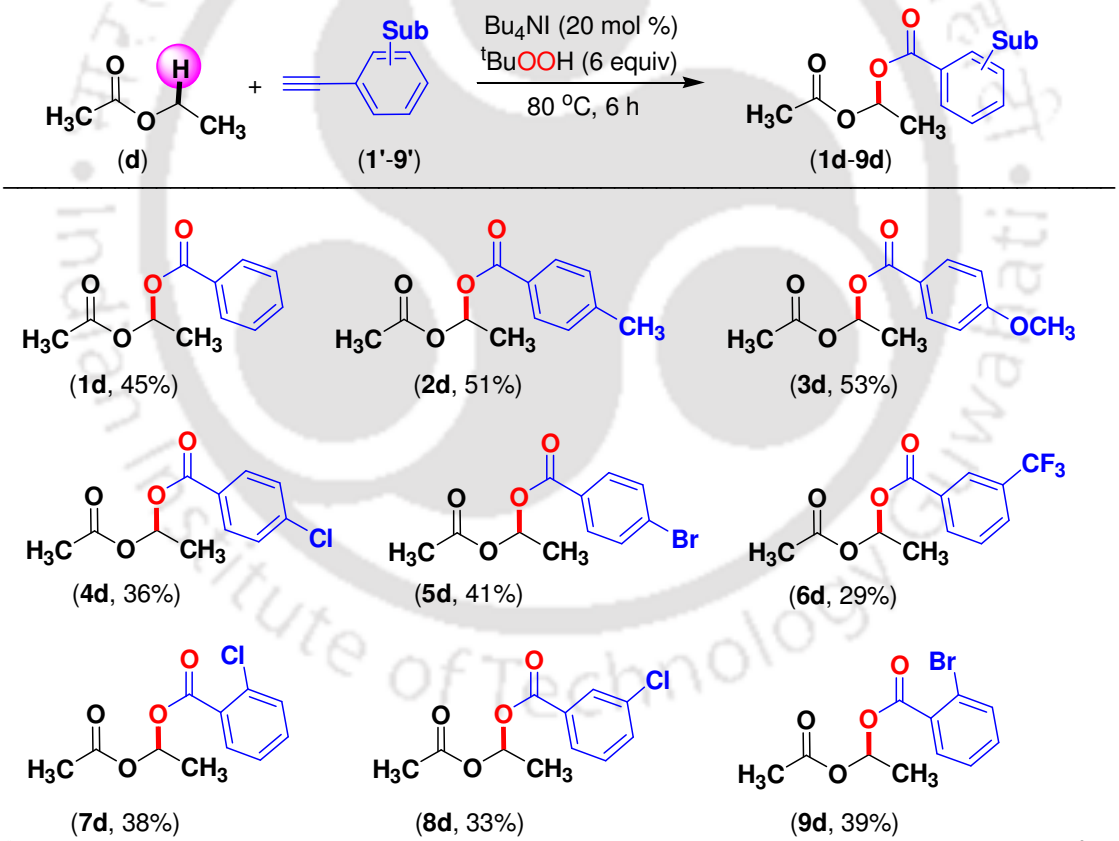
[a]Reaction conditions: styrene (1 mmol), ethylacetate (2 mL), TBAI (0.2 mmol), TBHP (6 mmol) at 80 °C. [b]Isolated yields.

In these cases also the benzoxy groups originated from respective styrenes.[7] It may be noted here that active methylene compounds possessing sp^3 C–H α to oxygen

upon the reaction with carboxylic acids under similar conditions give double esters via oxidative esterification at the active methylene C–H.[19]

Substrate scope for esterification of ethyl acetate. As phenylacetylenes are also potential benzoxy surrogates as observed during the esterification of cyclic ethers, they were utilised for the double esterification of ethyl acetate. Various substituted phenylacetylenes with electron neutral –H (**1′**), electron-donating groups such as *p*-Me (**2′**), *p*-OMe (**3′**) and electron-withdrawing groups such as *p*-Cl (**4′**), *p*-Br (**5′**), *m*-CF_3 (**6′**), *o*-Cl (**7′**), *m*-Cl (**8′**) and *o*-Br (**9′**) enacted as corresponding arylcarboxy surrogates for the formation of unsymmetrical *gem*-diacylates (**1d–9d**) but in relatively lower yields (Scheme III.3.4).

Scheme III.3.4. *Substrate scope for esterification of ethyl acetate*[a,b]

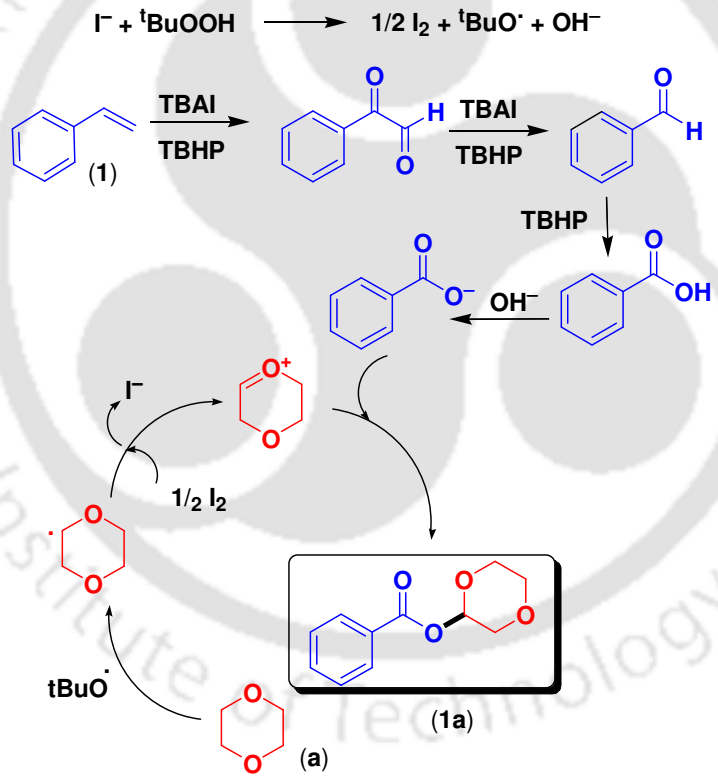


[a]Reaction conditions: phenylacetylene (1 mmol), ethylacetate (2 mL), TBAI (0.2 mmol), TBHP (6 mmol) at 80 °C.

[b]Isolated yields.

Mechanistic studies. Several control experiments were carried out to depict a plausible mechanism for these coupling reactions. Analysis of the reaction mixture obtained by

reacting 1,4-dioxane (**a**) with styrene (**1**) revealed the presence of intermediate benzaldehyde and benzoic acid in the medium (Scheme III.3.5). Formation of benzaldehyde from styrene is expected to occur via decarbonylation of the *in situ* generated phenylglyoxal intermediate.[7] Under oxidative reaction conditions, benzaldehyde is converted to benzoic acid which could be the possible source of carboxy group in these reactions.[6a] When benzoic acid was treated with 1,4-dioxane (**a**) under the present reaction condition exclusive formation of (**1a**) was observed (90%) implying the coupling partners are carboxylic acid and dioxane.[15a] Apart from benzoic acid when phenylglyoxal and benzaldehyde were reacted independently with 1,4-dioxane (**a**), the desired ester (**1a**) was obtained in 84 and 87% yields respectively; thus confirming their intermediacy in this transformation.



Scheme III.3.5. *Proposed mechanism for oxidative esterification*

A standard reaction performed between (**a**) and (**1**) in the presence of radical quencher 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) led to drastic quenching of the product (**1a**) yield; suggesting a radical pathway for this transformation. The results of the above experiments and related literature reports[7,15a] convey the operation of following paths for the oxidative esterification. Styrene (**1**) in the presence of

TBAI/TBHP is converted to benzoic acid via the intermediacy of phenylglyoxal and benzaldehyde (Scheme III.3.5). To rule out the source of oxygen from molecular oxygen, esterifications of 1,4-dioxane (**a**) with styrene (**1**) were carried out in an argon atmosphere under anhydrous conditions. The reaction proceeded smoothly giving product (**1a**) in identical yield suggesting that the oxygen atom in ester/carboxylic acid thus indeed originating from TBHP only.[20] The generated benzoic acid is deprotonated to give an anionic benzoate. In another path, radical abstraction of sp^3 C–H α to ethereal oxygen in dioxane gives the radical intermediate (Scheme III.3.5). This species then undergoes a further one electron oxidation (SET) with iodine forming the oxonium species. In the ultimate step, nucleophilic attack of benzoate ion on the α carbon of oxonium species gives α-acyloxy ether (**1a**) (Scheme III.3.5). A similar mechanism can be proposed involving ethyl acetate instead of cyclic ether.

Conclusions. In conclusion, we have developed a method for cyclic ethers to esters and monoesters to diesters (*gem*-diacylates) under metal free conditions cleaving sp^3 C–H bonds in simple solvents like 1,4-dioxane, tetrahydropyran, tetrahydrofuran and ethyl acetate with terminal aryl alkenes and alkynes. The coupling partners are the *in situ* generated $ArCOO^-$ from styrenes and phenylacetylenes and the solvents (cyclic ethers and ethyl acetate). Conceptually C=C bond cleavage of styrene to generate benzaldehyde can be considered as the substitute of ozonolysis.

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 ^1H NMR (400 MHz and 600 MHz), $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

III.4.2. General procedure for the synthesis of 1,4-dioxan-2-yl benzoate (1a). A mixture of Bu_4NI (73.8 mg, 20 mol %), styrene (**1**) (104 mg, 1 mmol) and 1,4-dioxane (**a**) (1 mL) were taken in an oven dried round bottom flask fitted with a condenser. To

this mixture a decane solution of TBHP (5-6 M) (1200 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^{o}C for 6 h. During this period formation of 1,4-dioxan-2-yl benzoate (**1a**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and elutedwith (96: 4, hexane / ethyl acetate) to afford 1,4-dioxan-2-yl benzoate (**1a**) (146 mg, 70% yield).

III.4.3. General procedure for the synthesis of 1,4-dioxan-2-yl benzoate (**1a**)**.** A mixture of Bu_4NI (73.8 mg, 20 mol %), phenyl acetylene (**1′**) (102 mg, 1 mmol) and 1,4-dioxane (**a**) (1 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture a decane solution of TBHP (5-6 M) (1200 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^{o}C for 6 h. During this period formation of 1,4-dioxan-2-yl benzoate (**1a**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and elutedwith (96: 4, hexane / ethyl acetate) to afford 1,4-dioxan-2-yl benzoate (**1a**) (100 mg, 48% yield).

III.4.4. General procedure for the synthesis of 1-acetoxyethyl benzoate (**1d**)**.** A mixture of Bu_4NI (73.8 mg, 20 mol %), styrene (**1**) (104 mg, 1 mmol) and ethyl acetate (**d**) (2 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture a decane solution of TBHP (5-6 M) (1200 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^{o}C for 6 h. During this period formation of 1-acetoxyethyl benzoate (**1d**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude

product was purified over a column of silica gel and eluted with (97: 3, hexane / ethyl acetate) to afford 1-acetoxyethyl benzoate (**1d**) (133 mg, 64% yield).

III.4.5. General procedure for the synthesis of 1-acetoxyethyl benzoate (1d). A mixture of Bu_4NI (73.8 mg, 20 mol %), phenyl acetylene (**1′**) (102 mg, 1 mmol) and ethyl acetate (**d**) (2 mL) were taken in an oven dried round bottom flask fitted with a condenser. To this mixture a decane solution of TBHP (5-6 M) (1200 µL, 6 equiv) was added and the reaction mixture was heated at 80 ^oC for 6 h. During this period formation of 1-acetoxyethyl benzoate (**1d**) was observed as judged from TLC. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 x 5 mL) and a 5% solution of sodium thiosulphate (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (97: 3, hexane / ethyl acetate) to afford 1-acetoxyethyl benzoate (**1d**) (94 mg, 45% yield).

III.4.6. Determine the extrusion of CO from the reaction. For the detection of evolution 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.

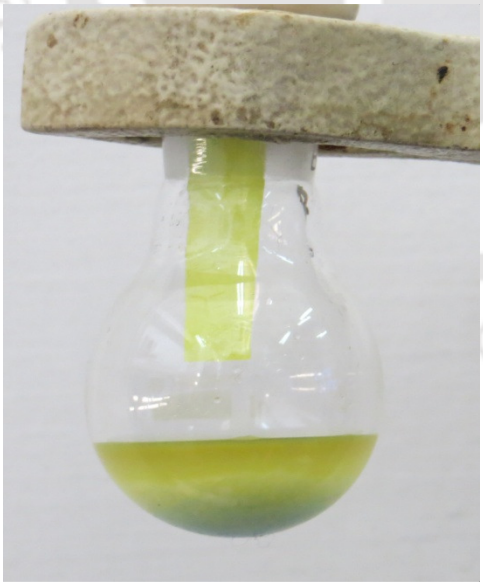


Fig 1

$PdCl_2$-PMA test strip before reaction

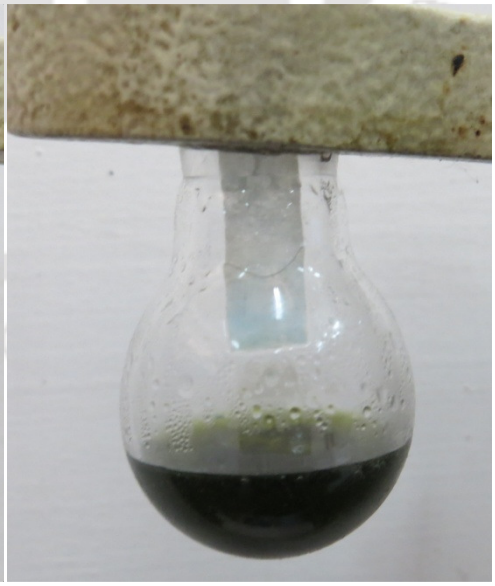


Fig 2

$PdCl_2$-PMA test strip after reaction

The initial yellow colour of the strip before the reaction (Figure 1) turned pale blue after 1.5 h of the reaction progress (Figure 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 15 minutes) with the formation of benzaldehyde.[21]

III.5. References

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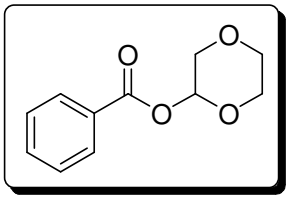
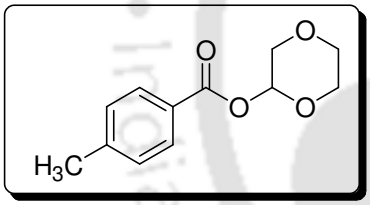
III.6. Spectral Data

1,4-Dioxan-2-yl benzoate (**1a**):



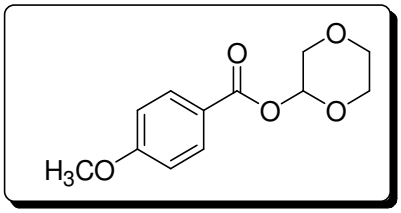
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.64–3.68 (m, 1H), 3.80–3.82 (m, 2H), 3.83–3.88 (m, 2H), 4.18–4.24 (m, 1H), 6.08 (s, 1H), 7.44 (t, 2H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 8.11 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 61.8, 66.1, 67.8, 89.8, 128.5, 129.8, 129.9, 133.4, 165.2; IR (KBr): 2971, 2925, 2856, 1726, 1602, 1452, 1258, 1155, 1065, 1018, 912, 880, 713 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{12}O_4$ (MH^+) 209.0808; found 209.0802.

1,4-Dioxan-2-yl 4-methylbenzoate (**2a**):



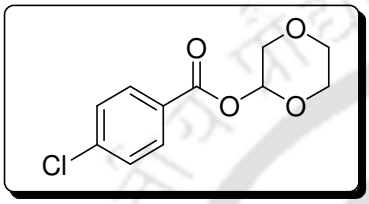
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.66–3.69 (m, 1H), 3.82–3.83 (m, 2H), 3.88–3.89 (m, 2H), 4.20–4.24 (m, 1H), 6.08 (t, 1H, *J* = 1.8 Hz), 7.26 (d, 2H, *J* = 10.2 Hz), 8.02 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 61.8, 66.1, 67.9, 89.7, 127.0 129.2, 130.0, 144.2, 165.2; IR (KBr): 2974, 2926, 2857, 1726, 1612, 1453, 1355, 1156, 1016, 912, 882, 755, 691, 577 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_4$ (MH^+) 223.0965; found 223.0969.

1,4-Dioxan-2-yl 4-methoxybenzoate (**3a**):



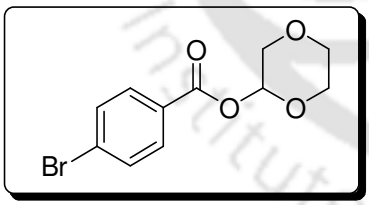
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.65–3.69 (m, 1H), 3.81–3.83 (m, 2H), 3.86–3.88 (m, 5H), 4.18–4.24 (m, 1H), 6.07 (s, 1H), 6.93 (d, 2H, *J* = 9.2 Hz), 8.08 (d, 2H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.1, 61.5, 65.8, 67.6, 89.3, 113.5, 121.8, 131.7, 163.5, 164.6; IR (KBr): 2971, 2929, 2855, 1723, 1607, 1511, 1458, 1421, 1257, 1168, 1087, 1021, 912, 881, 852, 771 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_5$ (MH^+) 239.0914; found 239.0921.

1,4-Dioxan-2-yl 4-chlorobenzoate (**4a**):



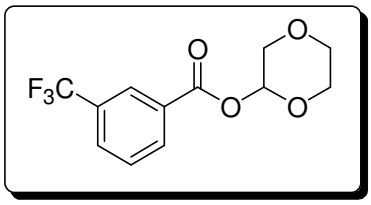
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.67–3.71 (m, 1H), 3.83–3.85 (m, 2H), 3.89–3.90 (m, 2H), 4.18–4.24 (m, 1H), 6.09 (t, 1H, *J* = 1.6 Hz), 7.44 (d, 2H, *J* = 8.4 Hz), 8.07 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 62.0, 66.3, 68.0, 90.2, 128.4, 129.0, 131.5, 140.1, 164.6; IR (KBr) 2924, 2855, 1726, 1594, 1260, 1155, 1090, 1012, 912, 881, 756 cm^{-1}; HRMS (ESI): calcd. $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0413.

1,4-Dioxan-2-yl 4-bromobenzoate (**5a**):



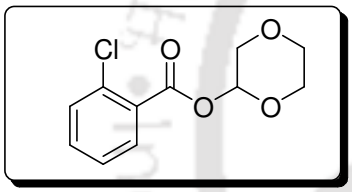
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.63–3.67 (m, 1H), 3.79–3.81 (m, 2H), 3.86 (d, 2H, *J* = 1.6 Hz), 4.14–4.20 (m, 1H), 6.06 (s, 1H), 7.57 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 62.0, 66.3, 67.9, 90.3, 128.9, 131.6, 132.1, 164.8; IR (KBr) 2972, 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 286.9921.

1,4-Dioxan-2-yl 3-(trifluoromethyl)benzoate (**6a**):



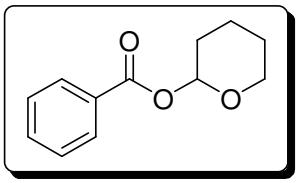
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.67–3.70 (m, 1H), 3.82–3.84 (m, 2H), 3.89–3.90 (m, 2H), 4.17–4.24 (m, 1H), 6.10 (s, 1H), 7.60 (t, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 8.29 (d, 1H, *J* = 8.4 Hz), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 62.1, 66.3, 67.9, 90.7, 126.9, 127.0, 129.4, 130.1, 130.2, 130.9, 131.6, 133.3, 164.2; IR (KBr) 2924, 1730, 1636, 1449, 1333, 1251, 1166, 1128, 1071, 1016, 914, 879, 695 cm^{-1}; HRMS (ESI): calcd.for $C_{12}H_{11}F_3O_4$ (MH^+) 277.0682; found 277.0678.

1,4-Dioxan-2-yl 2chlorobenzoate (**7a**):



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.61–3.64 (m, 1H), 3.76–3.77 (m, 2H), 3.83–3.84 (m, 2H), 4.16–4.22 (m, 1H), 6.06 (s, 1H), 7.26–7.30 (m, 1H), 7.37–7.42 (m, 2H), 7.88 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 61.9, 66.1, 67.7, 90.5, 126.7, 129.5, 131.3, 131.9, 133.1, 134.1, 164.4; IR (KBr) 2975, 2857, 2717, 1731, 1633, 1593, 1438, 1353, 1292, 1159, 1108, 1066, 1044, 1012, 911, 880, 749, 581 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0427.

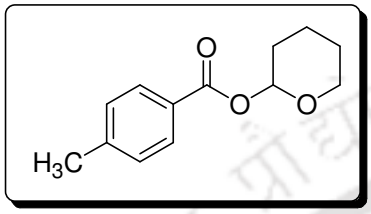
Tetrahydro-2*H*-pyran-2-yl benzoate (**1b**):



^{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,

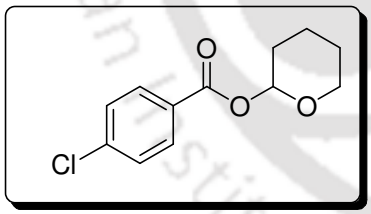
1H, *J* = 7.2 Hz), 8.07 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 18.6, 25.0, 29.3, 63.2, 93.1, 128.4, 129.8, 130.3, 133.1, 165.2; IR (KBr) 2924, 2853, 1723, 1607, 1456, 1289, 1121, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_3$ (MH^+) 207.1016; found 207.1009.

Tetrahydro-2*H*-pyran-2-yl 4-methylbenzoate (**2b**):



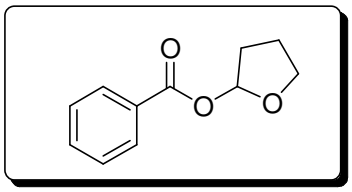
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.60–1.62 (m, 1H), 1.67–1.71 (m, 2H), 1.80–1.95 (m, 3H), 2.39 (s, 3H), 3.71–3.74 (m, 1H), 3.94–3.98 (m, 1H), 6.21 (t, 1H, *J* = 2.0 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.8, 21.8, 25.2, 29.5, 63.4, 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 221.1165.

Tetrahydro-2*H*-pyran-2-yl 4-chlorobenzoate (**4b**):



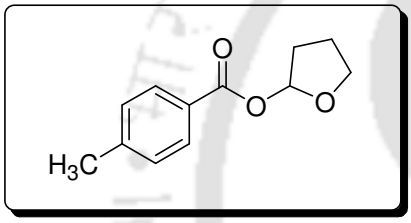
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.59–1.67 (m, 1H), 1.72–1.77 (m, 2H), 1.83–1.91 (m, 3H), 3.72–3.75 (m, 1H), 3.92–3.98 (m, 1H), 6.21 (s, 1H), 7.40 (d, 2H, *J* = 8.4 Hz), 8.00 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.8, 25.2, 29.4, 63.5, 93.6, 128.92, 128.97, 131.3, 139.8, 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 241.0631.

Tetrahydrofuran-2-yl benzoate (**1c**):



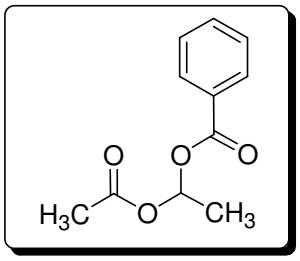
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.05–2.12 (m, 2H), 2.45–2.54 (m, 2H), 4.10–4.22 (m, 2H), 5.52 (s, 1H), 7.39–7.43 (m, 2H), 7.52–7.56 (m, 1H), 7.98–8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.7, 29.7, 67.1, 100.7, 128.6, 129.88, 129.93, 133.5, 166.2; IR (KBr): 2901, 1720, 1637, 1489, 1450, 1349, 1317, 1277, 1117, 1069, 1028, 958, 909, 713 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{12}O_3$ (MH^+) 193.0859; found 193.0863.

Tetrahydrofuran-2-yl 4-methylbenzoate (**2c**):



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.03–2.09 (m, 2H), 2.36 (s, 3H), 2.43–2.52 (m, 2H), 4.08–4.21 (m, 2H), 5.51 (s, 1H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 28.6, 29.7, 67.0, 100.6, 127.1, 129.2, 129.9, 144.1, 166.3; IR (KBr): 2901, 2127, 1717, 1613, 1445, 1349, 1278, 1179, 1112, 1029, 958, 909, 842, 755, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}O_3$ (MH^+) 207.1016; found 207.1014.

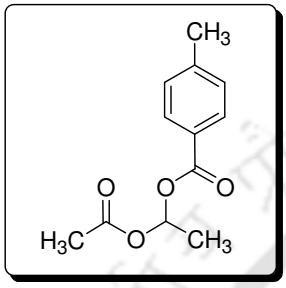
1-Acetoxyethyl benzoate (**1d**):



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.61 (d, 3H, *J* = 5.2 Hz), 2.09 (s, 3H), 7.12 (q, 1H, *J* = 5.2 Hz), 7.44 (t, 2H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz); 8.05 (d, 2H, *J* = 6.8 Hz);

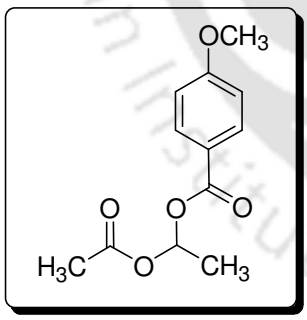
^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 21.1, 89.2, 128.6, 129.5, 130.1, 133.6, 164.8, 169.2; IR (KBr) 2929, 2851, 1768, 1731, 1602, 1446, 1375, 1278, 1228, 1064, 1011, 945, 713 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{12}O_4$ (MH^+) 209.0808; found 209.0812.

1-Acetoxyethyl 4-methylbenzoate (**2d**):



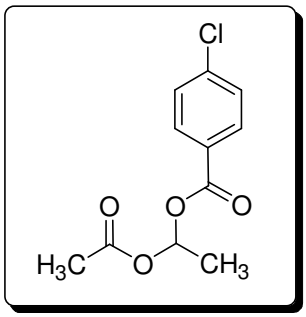
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60 (d, 3H, *J* = 5.6 Hz), 2.09 (s, 3H), 2.41 (s, 3H), 7.10 (q, 1H, *J* = 5.6 Hz), 7.25 (d, 2H, *J* = 3.6 Hz), 7.93 (d, 2H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8, 21.1, 21.9, 89.1, 129.3, 130.1, 130.1, 144.4, 164.7, 169.1; IR (KBr) 2926, 2856, 1758, 1729, 1613, 1446, 1371, 1276, 1228, 1183, 1065, 1012, 945, 752, 699 cm^{-1}; HRMS (ESI): calcd.for $C_{12}H_{14}O_4$ (MH^+) 223.0965; found 223.0967.

1-Acetoxyethyl 4-methoxybenzoate (**3d**):



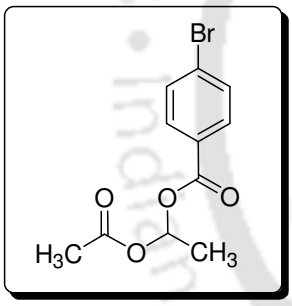
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.59 (d, 3H, *J* = 5.2 Hz), 2.09 (s, 3H), 3.86 (s, 3H), 6.91 (d, 2H, *J* = 9.2 Hz), 7.09 (q, 1H, *J* = 5.6 Hz), 8.00 (d, 2H, *J* = 9.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 21.1, 55.7, 89.1, 113.9, 121.9, 132.2, 164.0, 164.5, 169.2; IR (KBr) 2931, 2845, 1759, 1725, 1607, 1512, 1460, 1421, 1375, 1260, 1169, 945,848, 769 cm^{-1}; HRMS (ESI): calcd.for $C_{12}H_{14}O_5$ (MH^+) 239.0914; found 239.0908.

1-Acetoxyethyl 4-chlorobenzoate (**4d**):



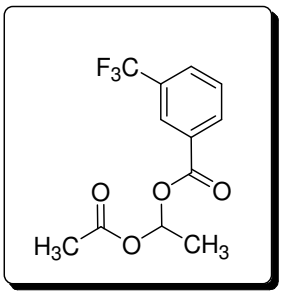
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60 (d, 3H, *J* = 5.6 Hz), 2.09 (s, 3H), 7.09 (q, 1H, *J* = 5.6 Hz), 7.41 (d, 2H, *J* = 8.8 Hz), 7.97 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8, 21.0, 89.2, 127.9, 128.9, 131.4, 140.1, 163.8, 169.1; IR (KBr) 2924, 2854, 1759, 1732, 1595, 1488, 1376, 1275, 1227, 1067, 1012, 945, 759 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0421.

1-Acetoxyethyl 4-bromobenzoate (**5d**):



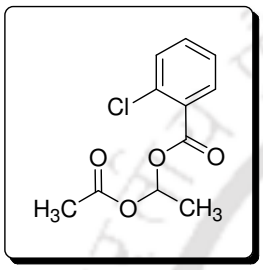
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.60 (d, 3H, *J* = 4.8 Hz), 2.09 (s, 3H), 7.09 (q, 1H, *J* = 5.4 Hz), 7.58 (d, 2H, *J* = 7.8 Hz), 7.89 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.8, 21.0, 89.3, 128.4, 128.8, 131.5, 132.0, 164.0, 169.0; IR (KBr) 2996, 2935, 1759, 1732, 1590, 1484, 1397, 1374, 1275, 1226, 1068, 1009, 945, 847, 756 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}BrO_4$ (MH^+) 286.9913; found 286.9924.

1-Acetoxyethyl 3-(trifluoromethyl)benzoate (**6d**):



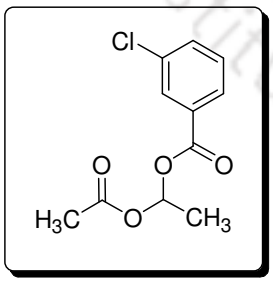
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.64 (d, 3H, *J* = 5.2 Hz), 2.12 (s, 3H), 7.14 (q, 1H, *J* = 5.2 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 8.24 (d, 1H, *J* = 7.6 Hz), 8.30 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.8, 21.0, 89.6, 126.9, 127.0, 129.4, 130.1, 130.5, 131.3, 133.3, 163.5, 169.1; IR (KBr) 2926, 1762, 1620, 1445, 1375, 1335, 1260, 1223, 1171, 1130, 1071, 1011, 946, 756, 695 cm^{-1}; HRMS (ESI): calcd.for $C_{12}H_{11}F_3O_4$ (MH^+) 277.0682; found 277.0690.

1-Acetoxyethyl 2-chlorobenzoate (**7d**):



^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.61 (d, 3H, *J* = 6.0 Hz), 2.10 (s, 3H), 7.09 (q, 1H, *J* = 5.4 Hz), 7.31 (t, 1H, *J* = 7.2 Hz), 7.41–7.46 (m, 2H), 7.83 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.7, 21.0, 89.6, 126.8, 129.3, 131.4, 131.8, 133.2, 134.3, 163.7, 169.1; IR (KBr) 2927, 1760, 1635, 1599, 1438, 1374, 1294, 1253, 1224, 1077, 1041, 1010, 945, 867, 749 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0429.

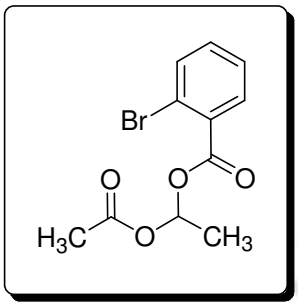
1-Acetoxyethyl 3-chlorobenzoate (**8d**):



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.59 (d, 3H, *J* = 5.6 Hz), 2.08 (s, 3H), 7.07 (q, 1H, *J* = 5.6 Hz), 7.35–7.40 (m, 1H), 7.51–7.55 (m, 1H), 7.91 (d, 1H, *J* = 8.0 Hz), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8, 21.0, 89.4, 128.2, 130.1, 130.2, 131.3, 133.7, 134.8, 163.6, 169.1; IR (KBr) 2923, 2081, 1760, 1735, 1635, 1426, 1374, 1290,

1259, 1223, 1068, 1010, 947, 746 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}ClO_4$ (MH^+) 243.0419; found 243.0425.

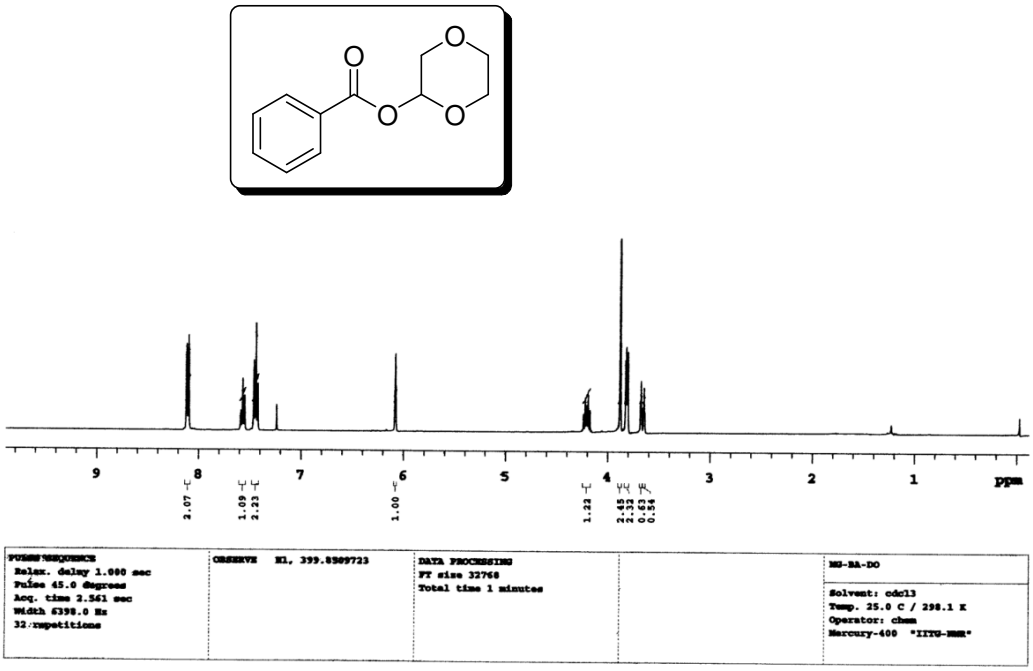
1-Acetoxyethyl 2-bromobenzoate (**9d**):



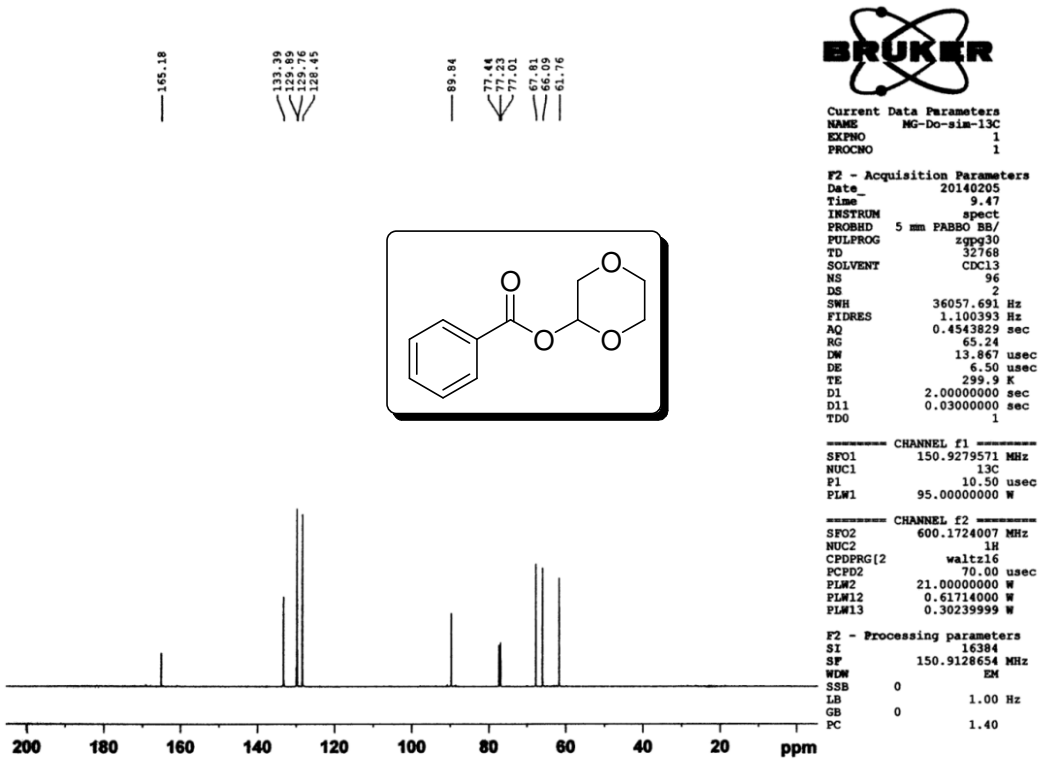
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.63 (d, 3H, *J* = 5.2 Hz), 2.12 (s, 3H), 7.09 (q, 1H, *J* = 5.2 Hz), 7.33–7.39 (m, 2H), 7.67 (d, 1H, *J* = 7.2 Hz), 7.81 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.7, 21.0, 89.7, 122.2, 127.4, 131.4, 131.8, 133.2, 134.7, 164.1, 169.1; IR (KBr) 2922, 1760, 1638, 1433, 1374, 1293, 1223, 1073, 1010, 945, 746, 699 cm^{-1}; HRMS (ESI): calcd.for $C_{11}H_{11}BrO_4$ (MH^+) 286.9913; found 286.9907.

III.7. Selected Spectra

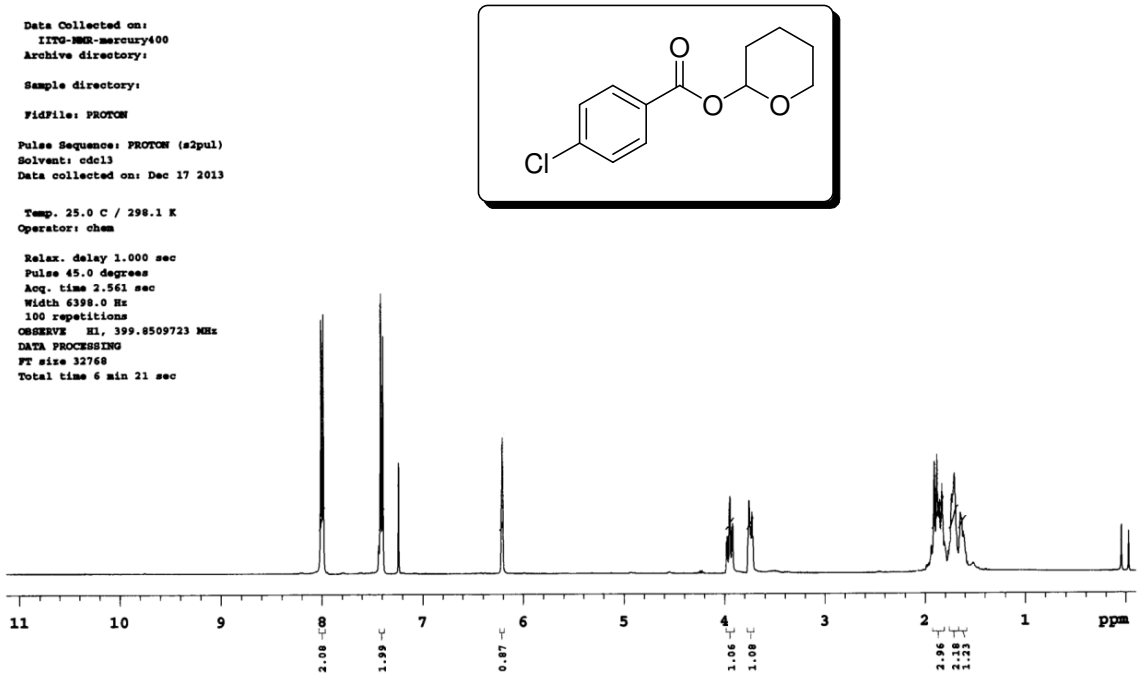
1,4-Dioxan-2-yl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



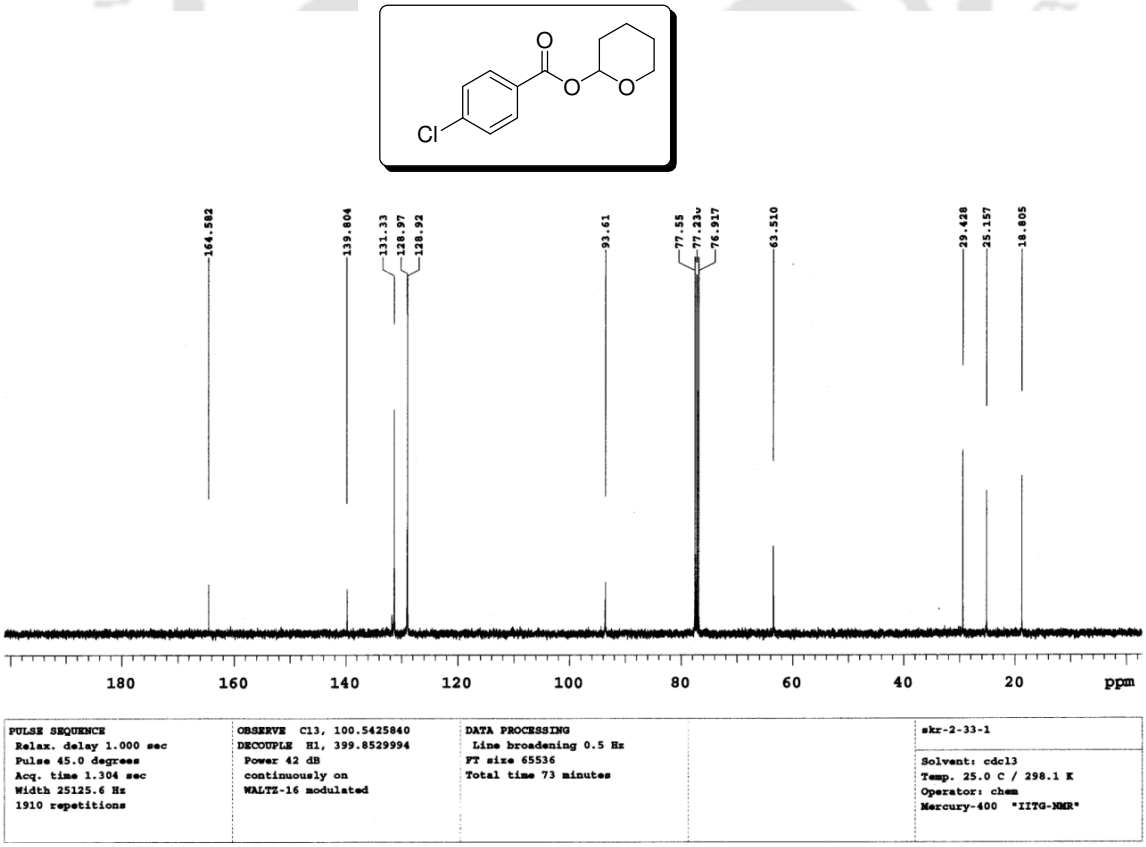
1,4-Dioxan-2-yl benzoate (1a): ^{13}C NMR (150 MHz, $CDCl_3$)



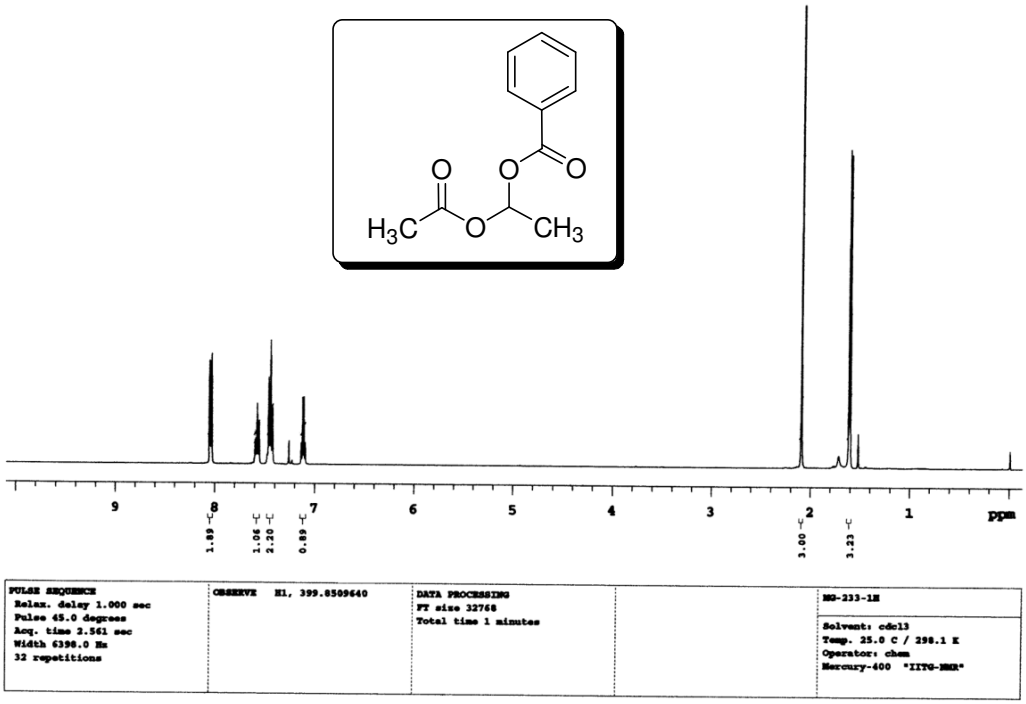
Tetrahydro-2*H*-pyran-2-yl 4-chlorobenzoate (4b): ^{1}H NMR (400 MHz, $CDCl_3$)



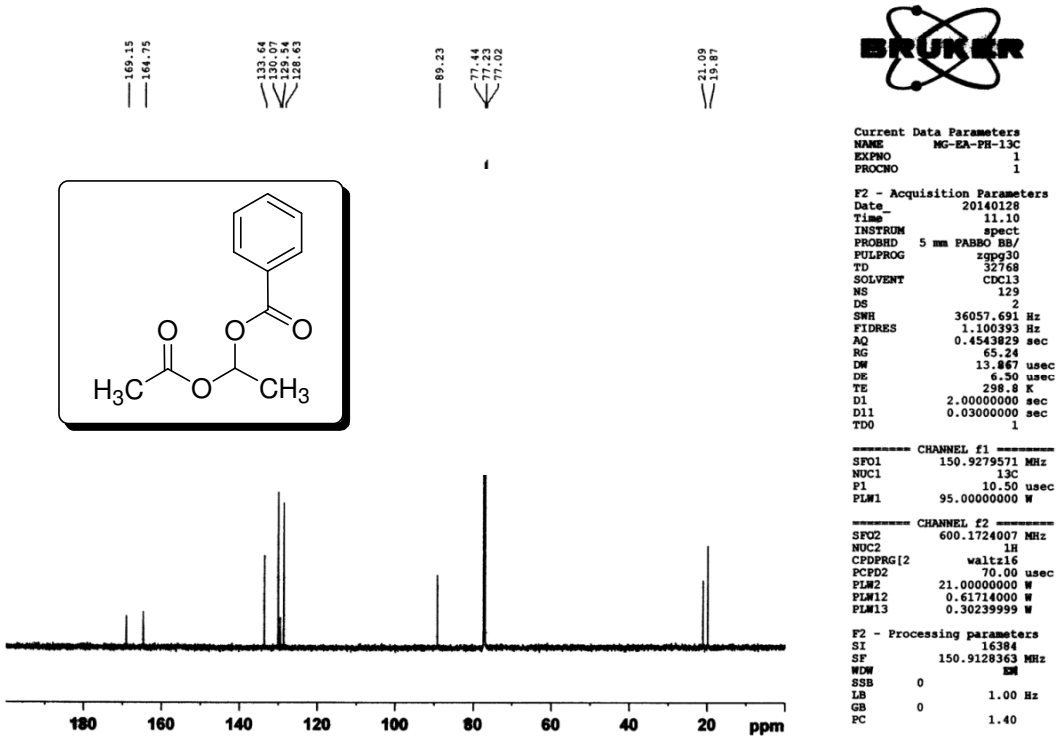
Tetrahydro-2*H*-pyran-2-yl 4-chlorobenzoate (4b): ^{13}C NMR (100 MHz, $CDCl_3$)



1-Acetoxyethyl benzoate (1d): ^{1}H NMR (400 MHz, $CDCl_3$)



1-Acetoxyethyl benzoate (1d): ^{13}C NMR (150 MHz, $CDCl_3$)



CHAPTER IV

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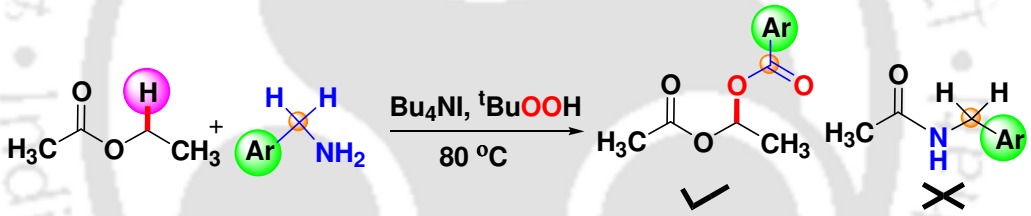
Generation of bis-Acyl Ketals from Esters and Benzyl Amines Under Oxidative Conditions

Ganesh Majji, Suresh Rajamanickam, Nilufa Khatun, Sourav Kumar Santra, and Bhisma K. Patel*

J. Org. Chem. 2015, 80, 3440−3446



Abstract: **Treatment of benzylamines with esters at an elevated temperature are expected to give amides. However, in the presence of TBAI/TBHP, esters possessing a methylene carbon α-to oxygen with benzylamines provide *bis*-esters rather than the expected amides. Benzylamines under oxidative conditions generate less nucleophilic carboxylates, which couples at the sp^3 C–H bonds of esters and cyclic ethers to give *bis*-acyl ketals and α-acyloxy ethers, respectively.**

CHAPTER IV

IV. Generation of *bis*-Acyl Ketals from Esters and Benzylamines under Oxidative Conditions

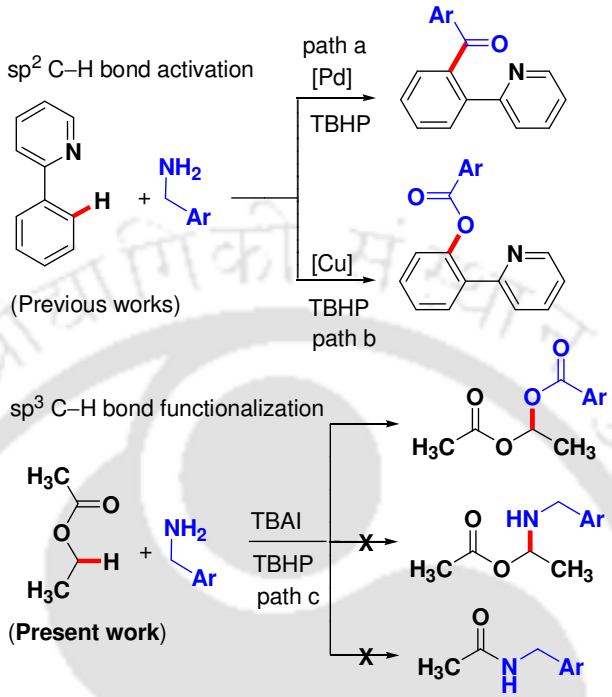
IV.1. Introduction

In the modern era of organic chemistry, the atom and step economical synthesis of complex target molecules from simple precursors via direct C(sp^3)–H bond functionalization is of paramount interest to both academia and industrial research.[1] Thus, synthetic chemists continue to strive toward the development of "ideal synthetic procedures" to directly transform C–H bonds into other functional groups, which could eventually be applied to the synthesis of natural products.[2] In this perspective, cross dehydrogenative coupling (CDC) has played a vital role in the construction of a diverse array of C–C and C–heteroatom bonds, by functionalizing C–H bonds of all types.[3] One of the extensively studied approaches in this forum is the CDC strategy involving simple solvents (i.e., alkylbenzenes, cyclic ethers and cycloalkanes with various coupling partners), most of which have ultimately lead to the synthesis of esters via C(sp^3)–H functionalization.[4]

Barring one example from our group, functionalization of α-sp^3 C–H bond in ethyl acetate (ester) has been virtually unexplored.[5] Ethyl acetate is predominantly used as a solvent and diluents because it is inexpensive and less toxic. Due to its reactive nature toward various nucleophiles and its susceptibility to hydrolysis, selective functionalization of esters in general and ethyl acetate in particular is a challenging task. Pertinent to this "solvent chemistry" in CDC reactions, recently our group has developed a protocol for the synthesis of esters via oxidative esterification of α-sp^3 C–H bond in ethyl acetate with terminal alkenes and alkynes under metal free conditions, where alkenes and alkynes served as ArCOO- surrogates.[5] It would be exciting if one can explore the selective α-sp^3 C–H functionalization of ethyl acetate as uncharted so far.

Benzylamines are latent sources to aroyl (ArCO–) and aryl carboxy (ArCOO–) groups.[6,7] The Wu group has reported a Pd catalyzed *ortho*-acylation of 2-phenylpyridine using benzylamines, where it serve as ArCO- surrogates (path a, Scheme IV.1.1).[6a] Very

recently our group has developed a copper-catalyzed protocol for the *o*-benzoxylation of 2-phenylpyridines using benzylamines as the arylcarboxy (ArCOO–) equivalents (path b, Scheme IV.1.1).[7]



Scheme IV.1.1. *Selectivity achieved with various catalysts in the reactions of benzylamine*

Recently, alkenes and alkynes are also found to be the surrogates of the ArCOO- group and have been utilized for the *bis*-esterification of ethyl acetate.[5] Further, when Pd is used as the catalyst, benzylamine act as an aroyl (ArCO–) source, while the use of Cu installs an aryl carboxy (ArCOO–) group into *ortho*-directing substrates.

Of late, metal free combinations, *viz.,* tetrabutylammonium iodide (TBAI) / TBHP, are an efficient substitute to transition metals/oxidant combinations. Thus, the reaction of benzylamine and ethyl acetate under a metal free oxidative condition is expected to yield an amide or a *bis*-ester of ethyl acetate.[5,8] To seek an answer to the above possibilities, when we performed a reaction by treating ethyl acetate with benzylamine under TBAI / TBHP condition, the outcome of this reaction was not amidation, rather it was further esterification of ethyl acetate that is formation of *bis*-ester of ethyl acetate (path c, Scheme IV.1.1). This observation suggests incorporation of the ArCOO- group into an ester where benzylamine serves as a source to the aryl

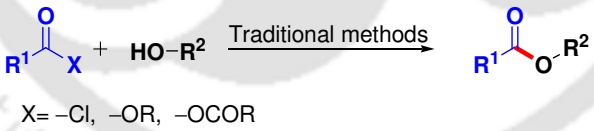
carboxy (ArCOO–) group. It may be mentioned here that Wang et al. have reported a direct amidation of benzylamine with *N*-substituted formamide via oxidative coupling in the presence of I_2 / TBHP, where benzylamine is the aroyl (ArCO–) equivalent.[6b] It has been observed earlier that the same precursor may operate either as an aryl carboxy (ArCOO–) or an aroyl (ArCO–) equivalent, depending upon the nature of the metal catalyst used. For example, benzylamine and alkylbenzene are both surrogates to ArCOO- and ArCO- groups.[6,7,9] Thus, generation of ArCOO- from $ArCH_2NH_2$ and its subsequent incorporation into an ester under a metal free condition (TBAI) shows identical reactivity to that of the Cu catalyst.[7] Therefore, the present protocol for the formation of a double ester via the α-sp^3 C–H bond functionalization of ethyl acetate without affecting the existing ester functionality is unexplored.

IV.2. Strategies for Esterification

Esterifications are traditionally achieved by reacting alcohols with carboxylic acids or its derivatives under auxiliary chemicals environment. Besides classical methods recently oxidative esterification methods are developed in this regard.

(i) Traditional esterification

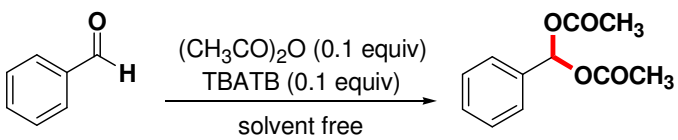
The traditional esterification strategies rely on the treatment of alcohols with acid and preactivated acid derivatives such as acyl halides, anhydrides and activated esters in the presence of a stoichiometric amount of base (Scheme IV.2.1).[10]



Scheme IV.2.1. *Conventional esterification methods*

(ii) Synthesis of *gem*-diacylates

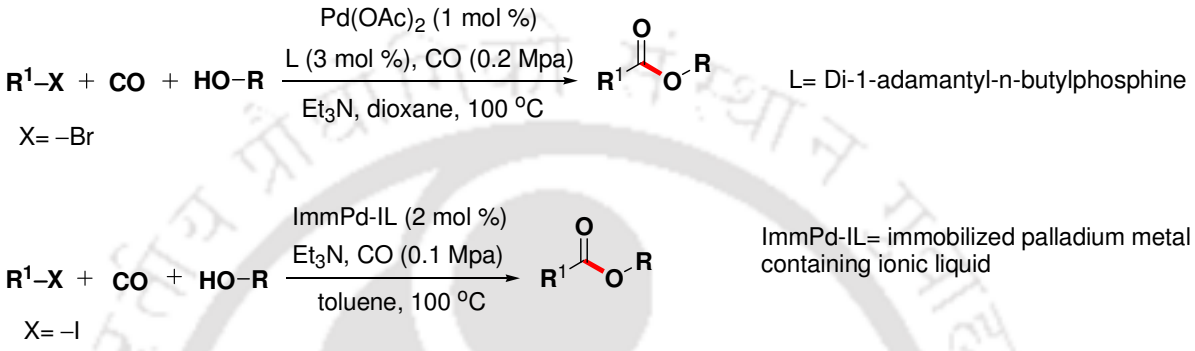
Our group developed a protocol for the chemoselective conversion of aldehydes to *gem*-diacylates. Various aliphatic and aromatic aldehydes are tolerated under the reaction conditions (Scheme IV.2.2).[8]



Scheme IV.2.2. *TBATB-catalyzed synthesis of gem-diacylates from aldehydes*

(iii) Esterification using carbon monoxide

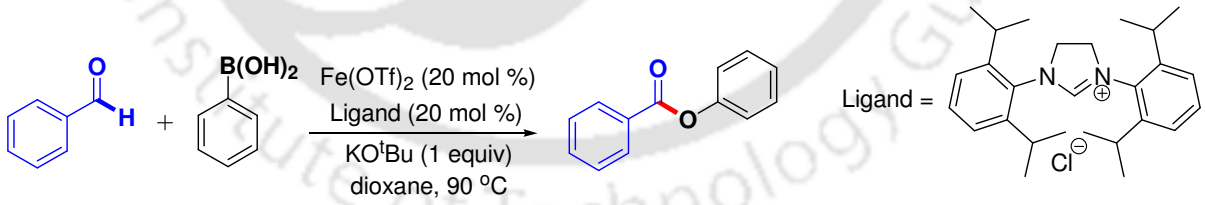
Beller and co-workers illustrated the synthesis of aryl benzoates via carbonylation of aryl halides followed by esterification with phenols using palladium/di-1-adamantyl-*n*-butylphosphine catalytic system (Scheme IV.2.3).[11a] Further, similar strategy using immobilized palladium metal containing ionic liquid (ImmPd-IL) catalyst was reported by Bhanage *et al.* (Scheme IV.2.3).[11b]



Scheme IV.2.3. *Esterification using carbon monoxide*

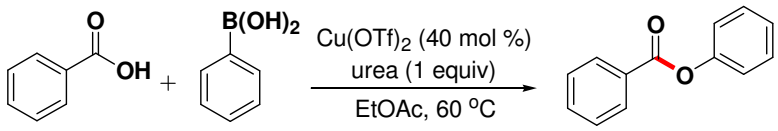
(iv) Esterification using boronic acid

Gois's group developed a method for the aerobic oxidative esterification of aldehydes with boronic acids using NHC-Iron-catalytic system (Scheme IV.2.4.1).[12a] In this method authors prepared various benzoates using equimolar amounts of both the aldehydes and boronic acids under reaction conditions.



Scheme IV.2.4.1. *Aerobic oxidative esterification of aldehydes*

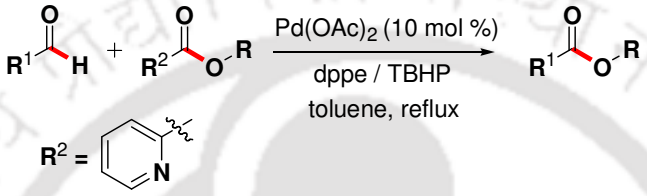
A $Cu(OTf)_2$-mediated Chan-Lam reaction of carboxylic acids with aryl boronic acids has been demonstrated by Cheng group. A series of functional groups such as methoxycarbonyl, acetoxy, free phenolic hydroxyl, vinyl, nitro, trifluoromethyl, methoxyl, bromo, chloro, iodo and acetyl groups are tolerated under reaction conditions to access phenolic esters in moderate to good yields (Scheme IV.2.4.2).[12b]



Scheme IV.2.4.2. *$Cu(OTf)_2$-mediated Chan-Lam reaction of carboxylic acids*

(v) Transesterification using aldehydes

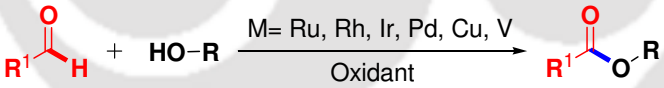
Huang and co-workers reported a palladium catalyzed transesterification of pyridine 2-carboxylic esters with aldehydes via C–H and C–O bond activations (Scheme IV.2.5).[13]



Scheme IV.2.5. *Transesterification process*

(vi) Oxidative esterification of aldehydes via cross dehydrogenative coupling approach

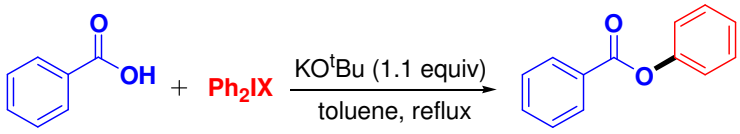
An atom and step economical protocols for the synthesis of esters from aldehydes and alcohols via cross dehydrogenative coupling (CDC) using transition metal catalyst such as Ru, Rh, Ir, Pd, Cu and V have been developed by several groups (Scheme IV.2.6).[14]



Scheme IV.2.6. *Esterification via CDC approach*

(vii) Esters synthesis using hypervalent iodine

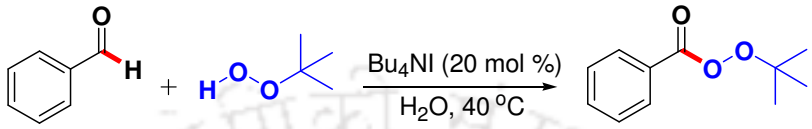
Olofsson group reported a metal free strategy for the synthesis of aryl esters from carboxylic acids and diaryliodonium salts (Scheme IV.2.7).[15] This method is compatible with wide range of aromatic and aliphatic carboxylic acids, affording aryl esters in good yields within short reaction times. Moreover, good chemoselectivity is observed with unsymmetrical diaryliodonium salts under metal free conditions.



Scheme IV.2.7. *Metal free synthesis of aryl esters*

(viii) Oxidative esterification of aldhyde using TBHP

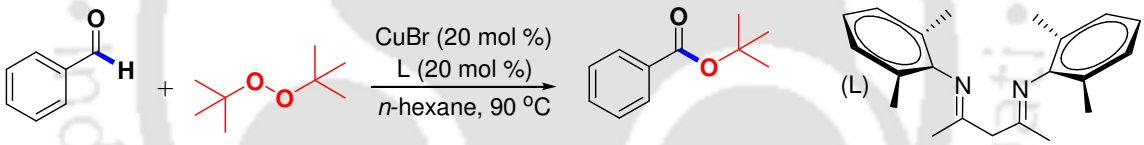
Wan and co-workers demonstrated a Bu_4NI-catalyzed protocol for the synthesis of *tert*-butyl peresters from aldehydes and TBHP (Scheme IV.2.8).[16] This is a practical and sustainable method for the synthesis of allylic esters from simple aldehydes and alkenes, which is analogous to the Kharasch-Sosnovsky reaction.



Scheme IV.2.8. *Bu_4NI-catalyzed synthesis of tert-butyl peresters from aldehydes*

(ix) Oxidative esterification of aldhyde using DTBP

Wei *et al.* reported copper catalyzed synthesis of carboxylic esters from aldehydes and dialkyl peroxides via oxidative esterification (Scheme IV.2.9).[17] This protocol gives a novel approach for the synthesis of various esters in good to excellent yields under mild conditions.



Scheme IV.2.9. *Copper-catalyzed oxidative esterification of aldehydes with dialkyl peroxides*

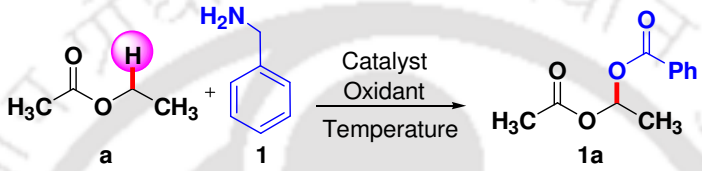
IV.3. Present Work

Treatment of benzylamines with esters at an elevated temperature is expected to give amides. However, in the presence of Bu_4NI / TBHP, esters possessing a methylene carbon α-to oxygen with benzylamines provided *bis*-esters rather than the expected amides. Benzylamines under oxidative conditions generate less nucleophilic carboxylates, which couples at the sp^3 C–H bonds of esters to give *bis*-acyl ketals.

Optimization of reaction conditions. An initial reaction was performed by reacting ethyl acetate (2 mL) and benzylamine (1 mmol) in the presence of Bu_4NI (20 mol %) and oxidant TBHP (5–6 M in decane) (6 equiv) at 80 °C (Table IV.3.1, entry 1). The outcome of this reaction was not amidation, rather it was further esterification of ethyl acetate obtained (**1a**) in 32% yield. Encouraged by this unique esterification of ester,

further optimization reactions were performed by varying reaction parameters to attain the best yield of the product. Gratifyingly, when the above reaction was performed using an aqueous TBHP (70% in water) (6 equiv) in lieu of a decane solution of the TBHP (5–6 M) product yield improved up to 69% (Table IV.3.1, entry 2). Keeping all other parameters constant but decreasing the quantity of TBHP from 6 to 5 equiv or the Bu_4NI quantity from 20 to 10 mol %, a reduction in the product yields (62% and 58%, respectively) (Table IV.3.1, entries 3–4) were found.

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



a 1 1a

Entry	Catalyst (mol %)	Oxidant (equiv)	Temp (^oC)	Yield (%)[b]
1	Bu_4NI (20)	TBHP (dec.) (6)	80	32
2	**Bu_4NI (20)**	**aq TBHP (6)**	**80**	**69**
3	Bu_4NI (20)	aq TBHP (5)	80	62
4	Bu_4NI (10)	aq TBHP (6)	80	58
5	Bu_4NI (30)	aq TBHP (6)	80	68
6	Bu_4NI (20)	aq TBHP (7)	80	65
7	Bu_4NI (20)	aq TBHP (6)	100	64
8	Bu_4NI (20)	aq H_2O_2 (6)	80	nd
9	Bu_4NI (20)	DTBP (6)	80	nd
10	Bu_4NI (20)	PhCOOCOPh (6)	80	nd
11	Bu_4NI (20)	Oxone (6)	80	nd
12	Bu_4NI (20)	$K_2S_2O_8$ (6)	80	nd
13	Bu_4NI (20)	DDQ (6)	80	nd
14	Bu_4NBr (20)	aq TBHP (6)	80	nd
15	I_2 (20)	aq TBHP (6)	80	nd
16	KI (20)	aq TBHP (6)	80	nd
17	–	aq TBHP (6)	80	nd
18	Bu_4NI (20)	–	80	nd

[a]Reaction condition: ethyl acetate (2 mL), benzylamine (1 mmol), time 8 h. [b]Isolated yield. nd = not detected.

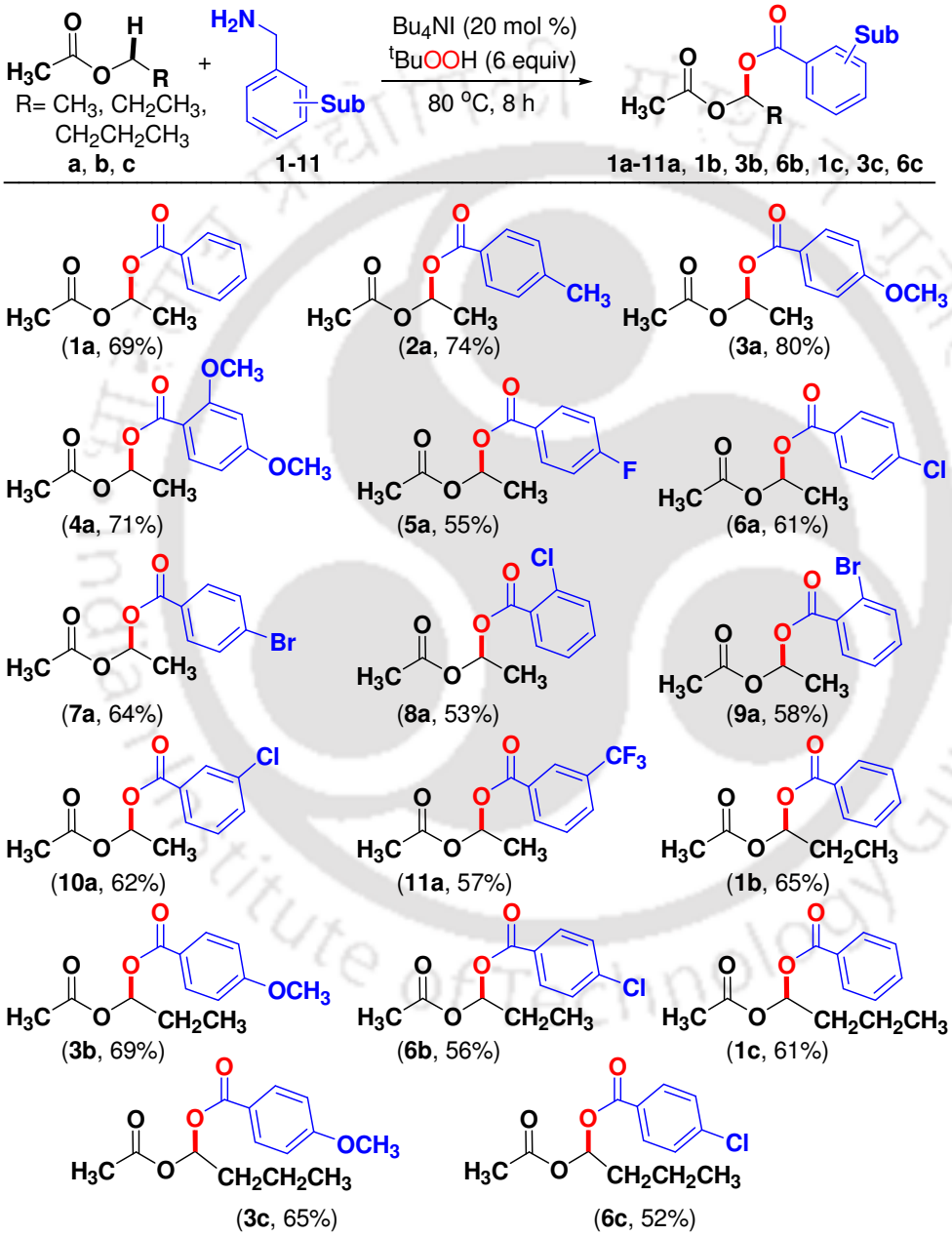
No further improvement in the yield was observed by either increasing the catalyst Bu_4NI (30 mol %), oxidant TBHP (7 equiv), or reaction temperature (100 ^oC) (Table IV.3.1, entries 5–7). Other oxidants such as aq H_2O_2, di-*tert* butyl peroxide

(DTBP), benzoylperoxide, oxone, $K_2S_2O_8$ and DDQ were completely unproductive (Table IV.3.1, entries 8−13). Surprisingly, no desired product could be obtained when other halogen species such as Bu_4NBr, I_2 and KI (Table IV.3.1, entries 14−16) were used instead of Bu_4NI. Control experiments performed in the absence of either oxidant (TBHP) or catalyst (Bu_4NI) failed to achieve the desired transformation (Table IV.3.1, entries 17−18). The by-products formed in these reactions (Table IV.3.1, entries 8, 10−12 and 14−17) are benzaldehyde and benzoic acid only. However, using oxidants such as DTBP (Table IV.3.1, entry 9), DDQ (Table IV.3.1, entry 13) and in the absence of any oxidant (Table IV.3.1, entry 18), benzylamine remained intact. Benzaldehyde is generated *in situ* from benzylamine under oxidative condition via the intermediacy of phenylmethanimine and benzoic acid by the oxidation of performed benzaldehyde. Therefore, the use of benzylamine (1 mmol), ethyl acetate (2 mL), Bu_4NI (20 mol %) and aqueous TBHP (70% in water) (6 equiv) at a temperature of 80 ^oC gave the best conversion after 8 h (Table IV.3.1, entry 2).

The above optimized condition was then implemented for the oxidative esterification of ethyl acetate (**a**) using various substituted benzylamines. The electron neutral –H (**1**) and electron-donating substituents, *viz., p*-Me (**2**), *p*-OMe (**3**), 2,4-di-OMe (**4**), as well as electron-withdrawing substituents, *viz., p*-F (**5**), *p*-Cl (**6**), *p*-Br (**7**), *o*-Cl (**8**), *o*-Br (**9**), *m*-Cl (**10**) and *m*-CF_3 (**11**) present in the phenyl ring of benzylamines were all found to serve as ArCOO- surrogates providing the desired double esters i.e., unsymmetrical *gem*-diacylates (**1a−11a**) in good to moderate yields as shown in Scheme IV.3.1. It was observed that substituted benzylamines possessing electron-withdrawing groups provided the corresponding products in lower yields than those bearing electron-donating groups. These results imply that the electronic effect of substituents on the phenyl ring of benzylamines played a role in controlling the product yields. This trend in reactivity is similar to our recent *o*-benzoxylation of 2-phenylpyridine using benzylamines as ArCOO- sources.[7] The synthetic utility of this double esterification strategy was further examined with another ester, *n*-propyl acetate (**b**) having a methylene carbon α- to oxygen. When various benzylamines (**1**), (**3**) and (**6**) were reacted with *n*-propyl acetate (**b**) under identical reaction conditions, the desired double esters (**1b**), (**3b**) and (**6b**) were obtained in similar yields to that using ethyl acetate (**a**) (Scheme IV.3.1). Yet another analogous ester *n*-butyl acetate (**c**) upon treatment with a

set of benzylamines (**1**), (**3**) and (**6**) produced their respective desired double esters (**1c**), (**3c**) and (**6c**) in modest yields (Scheme IV.3.1). Here again, the trends in the reactivity of substituted benzylamines were found to be identical to those observed for ethyl acetate (**a**).

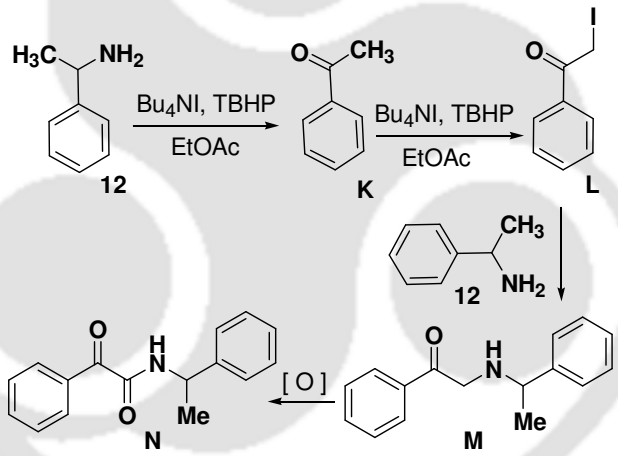
Scheme IV.3.1. *Substrate scope for esterification of esters*[a,b]



[a]Reaction conditions: benzylamine (1 mmol), ester (2 mL), TBAI (0.2 mmol), and TBHP (6 mmol) at 80 °C.
[b]Isolated yields.

The use of allylamine in lieu of benzylamine was not successful. Neither amidation nor ester formation was observed when allyl amine was subjected under the present reaction conditions with ethyl acetate as the allyl amine remain intact. Interestingly, when α-methyl benzylamine (**12**) was treated with ethyl acetate (**a**) under the present reaction condition, no amidation was observed. The reaction gave a complex mixture from which two major products, viz., acetophenone (**K**) (15%) and 2-oxo-2-phenyl-*N*-(1-phenylethyl)acetamide (**N**) (40%), could be isolated (Scheme IV.3.2). Under the reaction conditions, α-methyl benzylamine (**12**) is converted to acetophenone (**K**). Further reaction of acetophenone with the *in situ* generated iodine gave α-iodoacetophenone (**L**). Reaction of α-iodoacetophenone (**L**) with α-methyl benzylamine (**12**) provided intermediate product (**M**), which is rapidly oxidized to 2-oxo-2-phenyl-*N*-(1-phenylethyl)acetamide (**N**) as shown in Scheme IV.3.2.

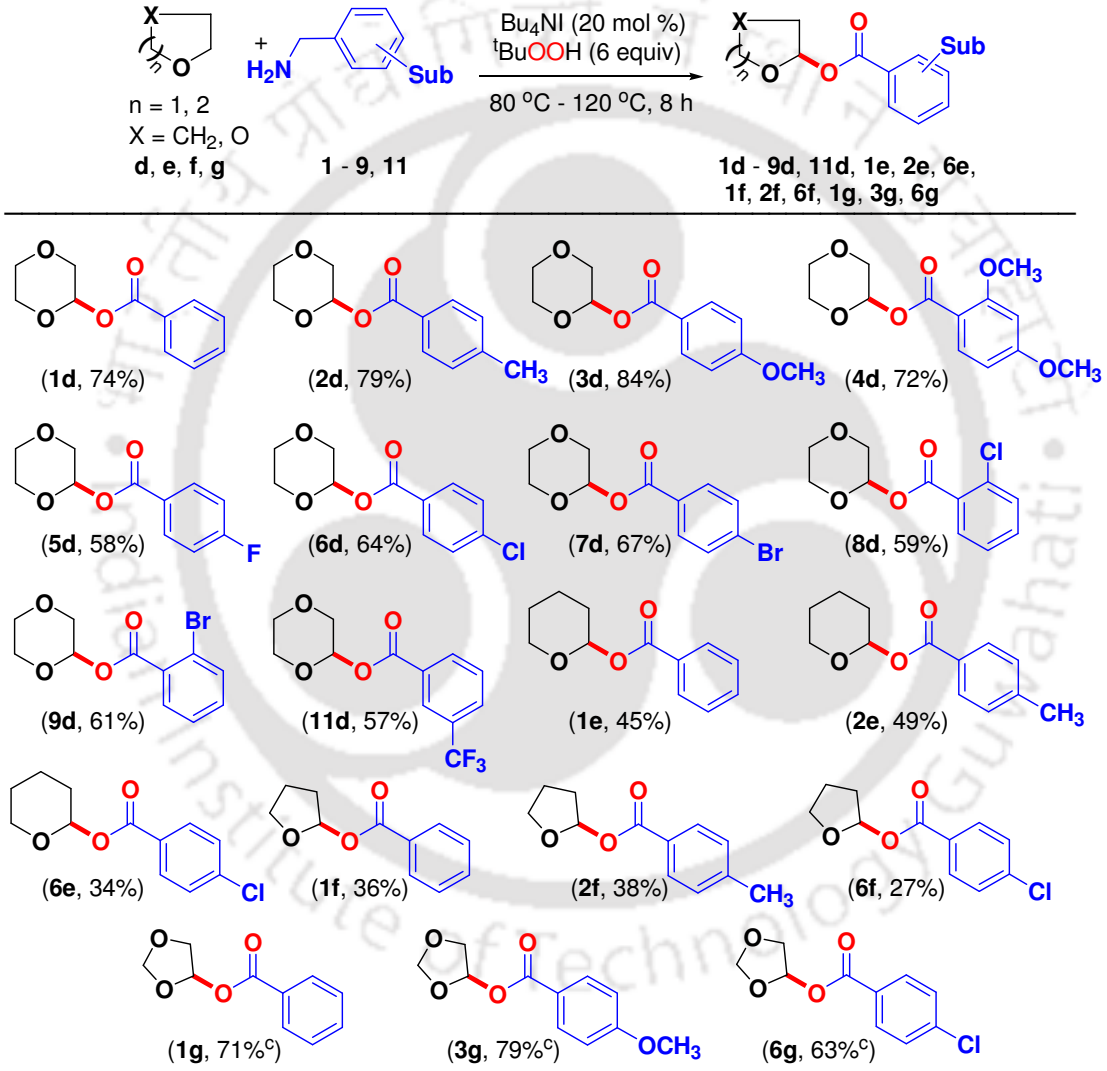
Scheme IV.3.2. *Fate of α-methyl benzylamine*



The successful oxidative esterifications of sp^3 C–H bonds α- to an oxygen atom in esters with benzylamines led us to scrutinize the feasibility of this protocol with cyclic ether (i.e., 1,4-dioxane (**d**) having sp^3 C–H bonds α- to an oxygen atom). To demonstrate the practical utility of the above-mentioned concept, benzylamine (**1**) was treated with 1,4-dioxane (**d**) under the above optimized conditions. To our delight, the product was found to be α-acyloxyether (**1d**) obtained in good yield (74%). For the synthesis of α-acyloxyethers, in addition to the traditional methods such as (i) addition of carboxylic acids to alkenyl ethers,[18] (ii) α-halo substitution of ethers with carboxylic acids,[19] (iii) esterification of hemiacetals with acids or its derivatives[20] and (iv) complex routes

comprising of a two-step synthesis,[21] several elegant CDC protocols have been developed lately.[22] Recently, our group has also developed two CDC protocols, one involving a Cu-mediated solvent–solvent coupling between alkylbenzenes and cyclic ethers,[9a] and the other a metal free oxidative esterification of α-sp^3 C–H bonds in cyclic ethers with terminal alkenes and alkynes.[5]

Scheme IV.3.3. *Substrate scope for α-acyloxy ethers*[a,b]



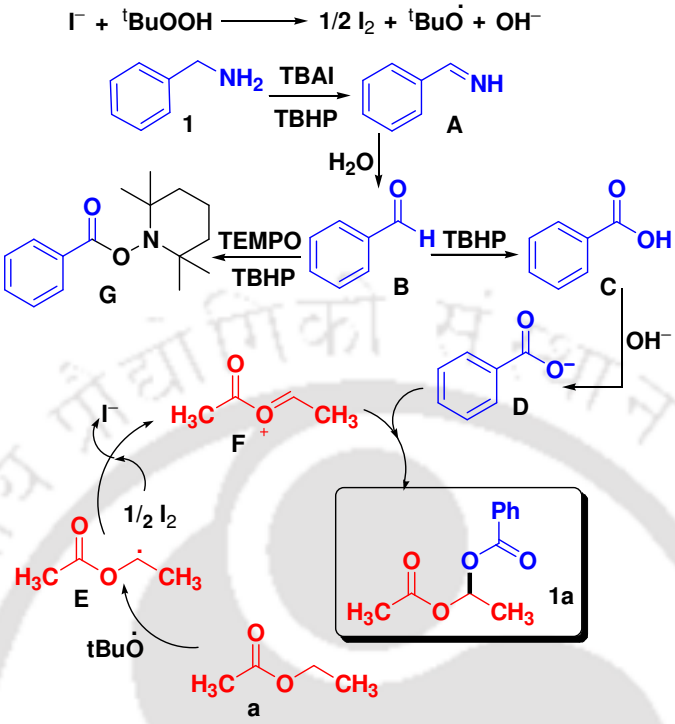
[a]Reaction conditions: benzylamine (1 mmol), cyclic ethers (1 mL), TBAI (0.2 mmol), TBHP (6 mmol) at 80 °C.
[b]Isolated yields. [c]Reaction performed at 120 °C.

Proceeding further toward the substrate exploration, 1,4-dioxane (**d**) was reacted with a set of benzylamines having electron-donating substituents such as *p*-Me (**2**), *p*-

OMe (**3**), 2,4-di-OMe (**4**), and electron-withdrawing substituents such as *p*-F (**5**), *p*-Cl (**6**), *p*-Br (**7**), *o*-Cl (**8**), *o*-Br (**9**) and *m*-CF_3 (**11**) all of which provided the desired α-acyloxyethers (**2d–9d** and **11d**) in good-to-moderate yields (Scheme IV.3.3). This approach was subsequently applied to other cyclic ethers possessing single oxygen [i.e., tetrahydropyran (**e**) and tetrahydrofuran (**f**)]. Unlike in 1,4-dioxane (**d**), the oxidative esterification of tetrahydropyran (**e**) and tetrahydrofuran (**f**) with benzylamines (**1**), (**2**) and (**6**) were not so effective in terms of yields, and they afforded α-acyloxy ethers (**1e**), (**2e**), (**6e**), (**1f**), (**2f**) and (**6f**) in lower yields as shown in Scheme IV.3.3. Due to the presence of eight equivalent sp^3 C–H's in 1,4-dioxane (**d**), it gave better yields of product compared to four such sp^3 C–H's containing substrates, tetrahydropyran (**e**) and tetrahydrofuran (**f**), which may be possibly due to the statistical reason. The oxidative esterification of 1,3-dioxolane with benzylamines (**1**), (**3**) and (**6**) provided single regioisomer (**1g**), (**3g**) and (**6g**) respectively, in good yields when the reaction was performed at 120 ^oC (Scheme IV.3.3). Here the esterification is taking place at the less acidic sp^3 C–H bond rather than at the more acidic sp^3 C–H, which is possibly due to the radical formed is so stable that it can't react further.

Mechanistic studies. To elucidate a plausible mechanism for this coupling reaction, several control experiments were carried out. Analysis of the reaction mixture between 1,4-dioxane (**d**) and benzylamine (**1**) along with the formation of the desired product, revealed the presence of benzaldehyde and benzoic acid in the medium, suggesting their intermediacy (Scheme IV.3.4). Formation of benzaldehyde from benzylamine is expected to go via the hydrolysis of the *in situ* generated imine, which in turn, is obtained by the oxidation of benzylamine.[6b] The benzaldehyde so generated gets converted to benzoic acid under oxidative conditions, which could be the possible source of the ArCOO- group in these reactions.[4a] Product (**1a**) was obtained in 90% yield when benzoic acid was reacted with ethyl acetate (**a**) under the present reaction conditions, implying the coupling partners are carboxylic acid and ethyl acetate.[14a] The presence of a radical scavenger 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) considerably quenches the coupling reaction between benzylamine (**1**) and ethyl acetate (**a**) giving < 4% yield of the expected product, indicating the radical nature of the mechanism. The trapped TEMPO-ester (**G**) has been isolated and characterized.

Scheme IV.3.4. *Proposed mechanism for oxidative esterification*



Taking cues from the control experiments that were carried out and from the literature reports,[7,14a] a possible mechanism as shown in Scheme IV.3.4 has been proposed. Initially, benzylamine (**1**) in the presence of TBAI / TBHP is converted to benzoic acid (**C**) via the intermediacy of phenylmethanimine (**A**) and benzaldehyde (**B**) (Scheme IV.3.4). Benzamide from possible oxidation of the aminal formed between aldehyde (**B**) and amine was not isolated from the reaction mixture. Furthermore, subjection of the benzamide to the reaction conditions with ethyl acetate gave rise to no coupling, ruling out the intervention of a benzamide intermediate. Though benzaldehyde is generated in the reaction mixture, formation of benzylschiff base adduct under these conditions was not detected. If at all formed, it can possibly be hydrolyzed rapidly back to corresponding aldehyde and amine. Subsequently, less nucleophilic benzoate (**D**) is generated by the deprotonation of benzoic acid (**C**). On the other hand, radical abstraction of α-sp^3 C–H bond in ethyl acetate gives the radical intermediate (**E**), which then undergoes a further single electron transformation (SET) with iodine to give an oxonium species (**F**) (Scheme IV.3.4). Finally, nucleophilic attack of benzoate ion (**D**)

on the α carbon of oxonium species (**F**) provided the double ester (**1a**) (Scheme IV.3.4). A similar mechanism can be proposed involving 1,4-dioxane instead of ester.

Conclusions. In conclusion, treatment of benzylamines with esters possessing α-sp^3 C–H bond in the presence of TBAI / TBHP provided *bis*-acyl ketals rather than amides. Symmetrical cyclic ethers afforded a monoester; however, unsymmetrical cyclic ether provided a single regioisomeric ester via sp^3 C–H bond functionalization. Benzylamine under oxidative condition provided aryl carboxylic ion which is one of the coupling partners in this solvent chemistry. A plausible reaction mechanism involving radical pathways has been suggested for this CDC coupling.

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 sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 and 600 MHz), and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). ^{19}F NMR spectra were recorded in $CDCl_3$ with CF_3COOH as the internal standard (564.7 MHz). HRMS spectra were recorded using the ESI mode (Q-TOF MS Analyzer). IR spectra were recorded in KBr or neat.

IV.4.2. General procedure for the synthesis of 1-acetoxyethyl benzoate (1a). A mixture of Bu_4NI (73.8 mg, 20 mol %), benzylamine (**1**) (107 mg, 1 mmol) and ethyl acetate (**a**) (2 mL) were taken in an oven-dried round-bottom flask fitted with a refluxed condenser. To this mixture, an aqueous solution of TBHP (70% in H_2O) (857 μL, 6 equiv) was added, and the reaction mixture was heated at 80 ^oC for 8 h. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 × 5 mL) and a 5% solution of sodium thiosulfate (2 × 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with 97: 3 hexane:ethyl acetate to afford 1-acetoxyethyl benzoate (**1a**) (143.5 mg, 69% yield).

IV.4.3. General procedure for the synthesis of 1,4-dioxan-2-yl benzoate (1d). A mixture of Bu_4NI (73.8 mg, 20 mol %), benzylamine (**1**) (107 mg, 1 mmol) and 1,4-dioxane (**d**) (1 mL) were taken in an oven dried round bottom flask fitted with a refluxed condenser. To this mixture, an aqueous solution of TBHP (70% in H_2O) (857 μL, 6 equiv) was added and the reaction mixture was heated at 80 ^oC for 8 h. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed successively with a 5% solution of sodium bicarbonate (2 × 5 mL) and a 5% solution of sodium thiosulfate (2 × 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (96:4, hexane / ethyl acetate) to afford 1,4-dioxan-2-yl benzoate (**1d**) (154 mg, 74% yield).

IV.5. References

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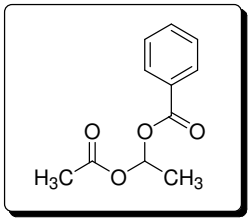
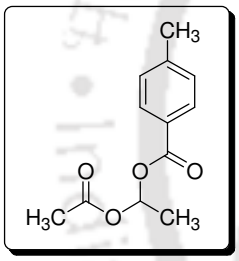
IV.6. Spectral Data

1-Acetoxyethyl benzoate (1a):



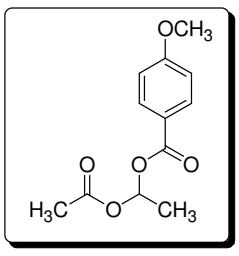
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, 3H, *J* = 5.2 Hz), 2.09 (s, 3H), 7.12 (q, 1H, *J* = 5.2 Hz), 7.44 (t, 2H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 8.05 (d, 2H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.9, 21.1, 89.2, 128.6, 129.5, 130.1, 133.6, 164.8, 169.2. IR (KBr): 2929, 2851, 1768, 1731, 1602, 1446, 1375, 1278, 1228, 1064, 1011, 945, 713 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{12}O_4$ $(M+Na)^+$, 231.0634; found, 231.0640.

1-Acetoxyethyl 4-methylbenzoate (2a):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, 3H, *J* = 5.6 Hz), 2.09 (s, 3H), 2.41 (s, 3H), 7.10 (q, 1H, *J* = 5.6 Hz), 7.25 (d, 2H, *J* = 3.6 Hz), 7.93 (d, 2H, *J* = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 21.1, 21.9, 89.1, 129.3, 130.1, 130.1, 144.4, 164.7, 169.1. IR (KBr): 2926, 2856, 1758, 1729, 1613, 1446, 1371, 1276, 1228, 1183, 1065, 1012, 945, 752, 699 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{14}O_4$ $(M+Na)^+$, 245.0790; found, 245.0783.

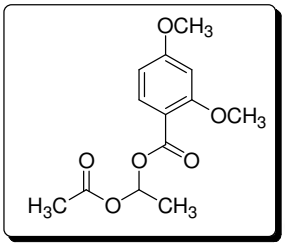
1-Acetoxyethyl 4-methoxybenzoate (3a):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, 3H, *J* = 5.2 Hz), 2.06 (s, 3H), 3.83 (s, 3H), 6.89 (d, 2H, *J* = 8.8 Hz), 7.07 (q, 1H, *J* = 5.2 Hz), 7.97 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100

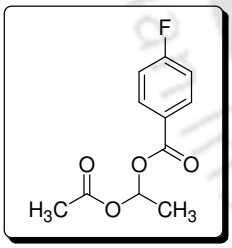
MHz, $CDCl_3$): δ 19.9, 21.1, 55.7, 89.1, 113.9, 121.9, 132.2, 164.0, 164.5, 169.2. IR (KBr): 2931, 2845, 1759, 1725, 1607, 1512, 1460, 1421, 1375, 1260, 1169, 945, 848, 769 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{14}O_5$ $(M+Na)^+$, 261.0739; found, 261.0731.

1-Acetoxyethyl 2,4-dimethoxybenzoate (4a):



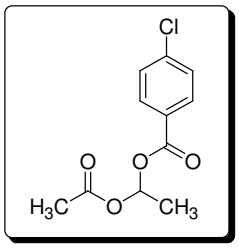
^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, *J* = 5.6 Hz), 2.08 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.48–6.50 (m, 2H), 7.06 (q, 1H, *J* = 5.6 Hz), 7.88 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.9, 21.1, 55.7, 56.2, 88.9, 99.1, 104.9, 111.2, 134.3, 162.4, 163.2, 165.0, 169.2. IR (KBr): 2943, 2843, 1744, 1723, 1609, 1577, 1506, 1421, 1253, 1031, 945, 836, 770 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{16}O_6$ $(M+Na)^+$, 291.0845; found, 291.0840.

1-Acetoxyethyl 4-fluorobenzoate (5a):



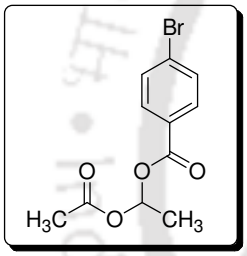
^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, 3H, *J* = 5.6 Hz), 2.10 (s, 3H), 7.08–7.16 (m, 3H), 8.05–8.09 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.9, 21.1, 89.3, 115.8 (d, *J* = 22.1 Hz), 125.8, 132.6, 132.7 (d, *J* = 9.0 Hz), 163.8, 166.3 (d, *J* = 252 Hz), 169.1. ^{19}F NMR (564.7 MHz, $CDCl_3$) δ −105.5. IR (KBr): 2994, 2941, 1759, 1732, 1605, 1508, 1414, 1376, 1279, 1231, 1064, 1011, 946, 854, 767 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{11}FO_4$ $(M+Na)^+$, 249.0539; found, 249.0546.

1-Acetoxyethyl 4-chlorobenzoate (6a):



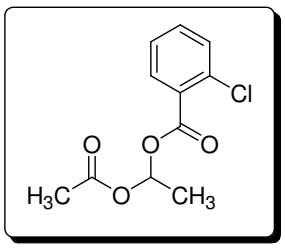
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, 3H, *J* = 5.6 Hz), 2.09 (s, 3H), 7.09 (q, 1H, *J* = 5.6 Hz), 7.41 (d, 2H, *J* = 8.8 Hz), 7.97 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 21.0, 89.2, 127.9, 128.9, 131.4, 140.1, 163.8, 169.1. IR (KBr): 2924, 2854, 1759, 1732, 1595, 1488, 1376, 1275, 1227, 1067, 1012, 945, 759 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{11}ClO_4$ $(M+Na)^+$, 265.0244; found, 265.0250.

1-Acetoxyethyl 4-bromobenzoate (7a):



^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60 (d, 3H, *J* = 4.8 Hz), 2.09 (s, 3H), 7.09 (q, 1H, *J* = 5.4 Hz), 7.58 (d, 2H, *J* = 7.8 Hz), 7.89 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.8, 21.0, 89.3, 128.4, 128.8, 131.5, 132.0, 164.0, 169.0. IR (KBr): 2996, 2935, 1759, 1732, 1590, 1484, 1397, 1374, 1275, 1226, 1068, 1009, 945, 847, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{11}BrO_4$ $(M+Na)^+$, 308.9739; found, 308.9748.

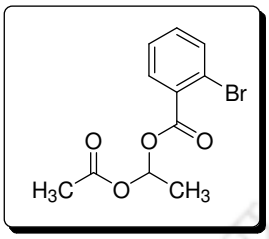
1-Acetoxyethyl 2-chlorobenzoate (8a):



^{1}H NMR (600 MHz, $CDCl_3$): δ 1.61 (d, 3H, *J* = 6.0 Hz), 2.10 (s, 3H), 7.09 (q, 1H, *J* = 5.4 Hz), 7.31 (t, 1H, *J* = 7.2 Hz), 7.41–7.46 (m, 2H), 7.83 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR

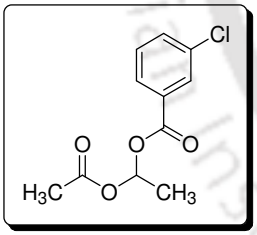
(150 MHz, $CDCl_3$): δ 19.7, 21.0, 89.6, 126.8, 129.3, 131.4, 131.8, 133.2, 134.3, 163.7, 169.1. IR (KBr): 2927, 1760, 1635, 1599, 1438, 1374, 1294, 1253, 1224, 1077, 1041, 1010, 945, 867, 749 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{11}ClO_4$ $(M+Na)^+$, 265.0244; found, 265.0240.

1-Acetoxyethyl 2-bromobenzoate (9a):



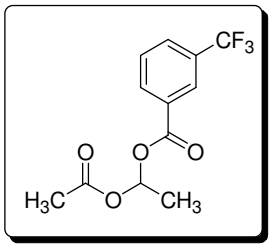
^1H NMR (400 MHz, $CDCl_3$): δ 1.63 (d, 3H, *J* = 5.2 Hz), 2.12 (s, 3H), 7.09 (q, 1H, *J* = 5.2 Hz), 7.33–7.39 (m, 2H), 7.67 (d, 1H, *J* = 7.2 Hz), 7.81 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 21.0, 89.7, 122.2, 127.4, 131.4, 131.8, 133.2, 134.7, 164.1, 169.1. IR (KBr): 2922, 1760, 1638, 1433, 1374, 1293, 1223, 1073, 1010, 945, 746, 699 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{11}BrO_4$ $(M+Na)^+$, 308.9739; found, 308.9743.

1-Acetoxyethyl 3-chlorobenzoate (10a):



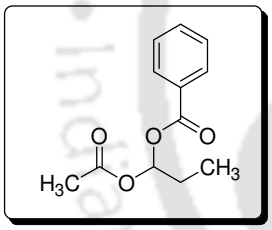
^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (d, 3H, *J* = 5.6 Hz), 2.08 (s, 3H), 7.07 (q, 1H, *J* = 5.6 Hz), 7.35–7.40 (m, 1H), 7.51–7.55 (m, 1H), 7.91 (d, 1H, *J* = 8.0 Hz), 8.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 21.0, 89.4, 128.2, 130.1, 130.2, 131.3, 133.7, 134.8, 163.6, 169.1. IR (KBr): 2923, 2081, 1760, 1735, 1635, 1426, 1374, 1290, 1259, 1223, 1068, 1010, 947, 746 cm^{-1}, HRMS (ESI): calcd for $C_{11}H_{11}ClO_4$ $(M+Na)^+$, 265.0244; found, 265.0238.

1-Acetoxyethyl 3-(trifluoromethyl)benzoate (11a):



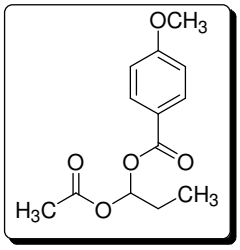
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (d, 3H, *J* = 5.2 Hz), 2.12 (s, 3H), 7.14 (q, 1H, *J* = 5.2 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 8.24 (d, 1H, *J* = 7.6 Hz), 8.30 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.8, 21.1, 89.6, 122.9, 124.7, 127.0 (t, *J* = 5.3 Hz), 129.4, 130.2 (t, *J* = 5.3 Hz), 130.5, 131.4 (q, *J* = 33.0 Hz), 133.3, 163.5, 169.1. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ −63.6. IR (KBr): 2926, 1762, 1620, 1445, 1375, 1335, 1260, 1223, 1171, 1130, 1071, 1011, 946, 756, 695 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{11}F_3O_4$ $(M+Na)^+$, 299.0507; found, 299.0512.

1-Acetoxypropyl benzoate (1b):



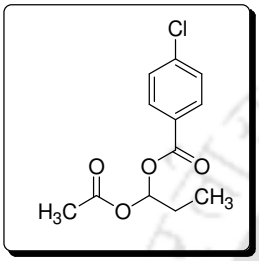
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, 3H, *J* = 7.6 Hz), 1.91−1.98 (m, 2H), 2.10 (s, 3H), 7.01 (t, 1H, *J* = 8.4 Hz), 7.43−7.48 (m, 2H), 7.56−7.60 (m, 1H); 8.05 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 7.9, 21.1, 26.8, 91.9, 128.7, 129.6, 130.1, 133.6, 164.9, 169.3. IR (KBr): 2978, 2939, 1760, 1732, 1602, 1452, 1373, 1276, 1222, 1117, 1018, 961, 711 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{14}O_4$ $(M+Na)^+$, 245.0790; found, 245.0783.

1-Acetoxypropyl 4-methoxybenzoate (3b):



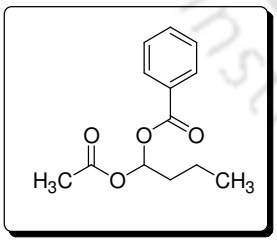
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (t, 3H, *J* = 7.2 Hz), 1.91–1.93 (m, 2H), 2.09 (s, 3H), 3.86 (s, 3H), 6.92 (d, 2H, *J* = 9.0 Hz), 6.98 (t, 1H, *J* = 5.4 Hz), 8.00 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 7.9, 21.1, 26.9, 55.7, 91.7, 113.9, 121.9, 132.2, 164.0, 164.6, 169.3. IR (KBr): 2976, 2939, 2843, 1759, 1726, 1607, 1512, 1422, 1318, 1224, 1168, 1021, 961, 848, 769 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{16}O_5$ $(M+Na)^+$, 275.0896; found, 275.0902.

1-Acetoxypropyl 4-chlorobenzoate (6b):



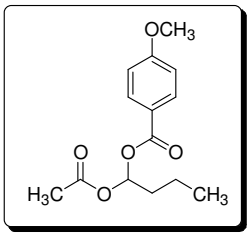
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (t, 3H, *J* = 7.2 Hz), 1.92–1.94 (m, 2H), 2.10 (s, 3H), 6.98 (t, 1H, *J* = 4.8 Hz), 7.42 (d, 2H, *J* = 6.6 Hz), 7.98 (d, 2H, *J* = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 7.9, 21.0, 26.8, 92.0, 128.1, 129.0, 131.5, 140.2, 164.0, 169.3. IR (KBr): 2978, 2939, 1760, 1733, 1595, 1489, 1372, 1274, 1221, 1092, 1013, 850, 758 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{13}ClO_4$ $(M+Na)^+$, 279.0400; found, 279.0409.

1-Acetoxybutyl benzoate (1c):



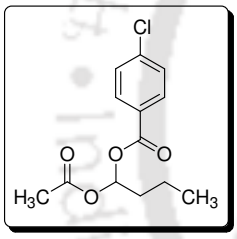
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.97 (t, 3H, *J* = 7.2 Hz), 1.46–1.51 (m, 2H), 1.86–1.90 (m, 2H), 2.07 (s, 3H), 7.04 (t, 1H, *J* = 5.4 Hz), 7.41–7.45 (m, 2H), 7.56 (t, 1H, *J* = 7.2 Hz), 8.03 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 17.1, 21.1, 35.6, 91.1, 128.7, 129.6, 130.1, 133.6, 164.9, 169.3. IR (KBr): 2963, 2933, 2876, 1761, 1732, 1602, 1453, 1374, 1272, 1219, 1117, 1015, 802, 712 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{16}O_4$ $(M+Na)^+$, 259.0947; found, 259.0941.

1-Acetoxybutyl 4-methoxybenzoate (3c):



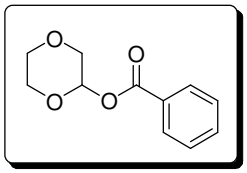
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J* = 7.2 Hz), 1.47–1.51 (m, 2H), 1.87–1.89 (m, 2H), 2.09 (s, 3H), 3.86 (s, 3H), 6.91–6.94 (m, 2H), 7.04 (t, 1H, *J* = 5.4 Hz), 8.00 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 17.1, 21.1, 35.6, 55.7, 90.9, 113.9, 122.0, 132.2, 164.0, 164.6, 169.3. IR (KBr): 2962, 2934, 2875, 1759, 1725, 1607, 1512, 1464, 1373, 1260, 1168, 1028, 847, 769 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{18}O_5$ $(M+Na)^+$, 289.1052; found, 289.1045.

1-Acetoxybutyl 4-chlorobenzoate (6c):



^{1}H NMR (600 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J* = 7.2 Hz), 1.46–1.51 (m, 2H), 1.88–1.89 (m, 2H), 2.09 (s, 3H), 7.03 (t, 1H, *J* = 5.4 Hz), 7.41–7.44 (m, 2H), 7.96 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.9, 17.1, 21.0, 35.5, 91.2, 128.1, 129.0, 131.5, 140.2, 164.0, 169.2. IR (KBr): 2963, 2933, 2876, 1760, 1732, 1595, 1488, 1372, 1219, 1173, 1013, 849, 685 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{15}ClO_4$ $(M+Na)^+$, 293.0557; found, 293.0549.

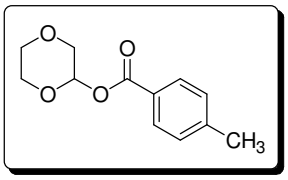
1,4-Dioxan-2-yl benzoate (1d)[14e]:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64–3.68 (m, 1H), 3.80–3.82 (m, 2H), 3.83–3.88 (m, 2H), 4.18–4.24 (m, 1H), 6.08 (s, 1H), 7.44 (t, 2H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.2 Hz),

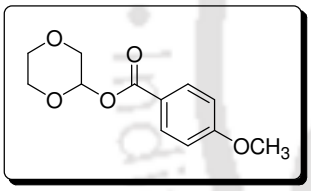
8.11 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.8, 66.1, 67.8, 89.8, 128.5, 129.8, 129.9, 133.4, 165.2. IR (KBr): 2971, 2925, 2856, 1726, 1602, 1452, 1258, 1155, 1065, 1018, 912, 880, 713 cm^{-1}.

1,4-Dioxan-2-yl 4-methylbenzoate (2d)[14f]**:**



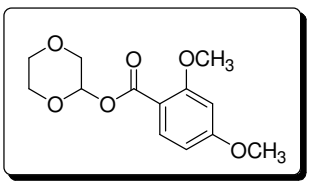
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.66–3.69 (m, 1H), 3.82–3.83 (m, 2H), 3.88–3.89 (m, 2H), 4.20–4.24 (m, 1H), 6.08 (s, 1H), 7.26 (d, 2H, *J* = 10.2 Hz), 8.02 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.7, 61.8, 66.1, 67.9, 89.7, 127.0 129.2, 130.0, 144.2, 165.2. IR (KBr): 2974, 2926, 2857, 1726, 1612, 1453, 1355, 1156, 1016, 912, 882, 755, 691, 577 cm^{-1}.

1,4-Dioxan-2-yl 4-methoxybenzoate (3d)[14f]**:**



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63–3.66 (m, 1H), 3.78–3.80 (m, 2H), 3.84–3.89 (m, 5H), 4.15–4.21 (m, 1H), 6.04 (s, 1H), 6.91 (d, 2H, *J* = 7.6 Hz), 8.05 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 62.0, 66.3, 68.1, 89.7, 113.9, 122.2, 132.2, 164.0, 165.1. IR (KBr): 2971, 2929, 2855, 1723, 1607, 1511, 1458, 1421, 1257, 1168, 1087, 1021, 912, 881, 852, 771 cm^{-1}.

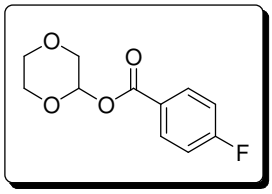
1,4-Dioxan-2-yl 2,4-dimethoxybenzoate (4d)[14e]**:**



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62–3.65 (m, 2H), 3.76–3.78 (m, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.16–4.22 (m, 2H), 6.02 (s, 1H), 6.45–6.48 (m, 2H), 7.93 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 56.1, 62.0, 66.3, 68.1, 89.4, 99.1, 104.8, 111.7,

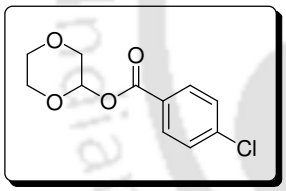
134.3, 162.1, 164.0, 164.9. IR (KBr): 2971, 2937, 2853, 1725, 1609, 1576, 1505, 1459, 1213, 1163, 1019, 911, 882, 770 cm^{-1}.

1,4-Dioxan-2-yl 4-fluorobenzoate (5d)[14a]:



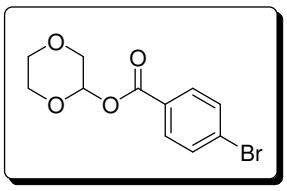
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.67–3.69 (m, 1H), 3.82–3.83 (m, 2H), 3.88–3.89 (m, 2H), 4.19–4.23 (m, 1H), 6.09 (s, 1H), 7.12–7.15 (m, 2H), 8.13–8.15 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 61.8, 66.1, 67.8, 90.0, 115.7 (d, J = 21.8 Hz), 126.1, 132.5 (d, J = 9.3 Hz), 164.7 (d, J = 144 Hz), 166.9. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ −105.5. IR (KBr): 2977, 2951, 2870, 1725, 1606, 1509, 1453, 1362, 1284, 1148, 1092, 1067, 912, 884 cm^{-1}.

1,4-Dioxan-2-yl 4-chlorobenzoate (6d)[14a]**:**



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67–3.71 (m, 1H), 3.83–3.85 (m, 2H), 3.89–3.90 (m, 2H), 4.18–4.24 (m, 1H), 6.09 (t, 1H, J = 1.6 Hz), 7.44 (d, 2H, J = 8.4 Hz), 8.07 (d, 2H, J = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 62.0, 66.3, 68.0, 90.2, 128.4, 129.0, 131.5, 140.1, 164.6. IR (KBr): 2924, 2855, 1726, 1594, 1260, 1155, 1090, 1012, 912, 881, 756 cm^{-1}.

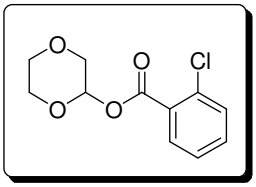
1,4-Dioxan-2-yl 4-bromobenzoate (7d)[14a]**:**



^{1}H NMR (400 MHz, $CDCl_3$): δ 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

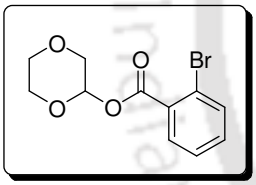
Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.0, 66.3, 67.9, 90.3, 128.9, 131.6, 132.1, 164.8. IR (KBr): 2972, 2929, 2856, 1729, 1589, 1397, 1274, 1259, 1155, 1090, 1067, 1009, 911, 881, 757 cm^{-1}.

1,4-Dioxan-2-yl 2-chlorobenzoate (8d)[14c]:



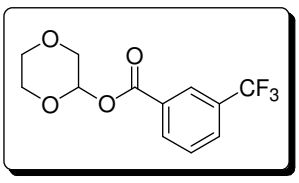
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61–3.64 (m, 1H), 3.76–3.77 (m, 2H), 3.83–3.84 (m, 2H), 4.16–4.22 (m, 1H), 6.06 (s, 1H), 7.26–7.30 (m, 1H), 7.37–7.42 (m, 2H), 7.88 (d, 1H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.9, 66.1, 67.7, 90.5, 126.7, 129.5, 131.3, 131.9, 133.1, 134.1, 164.4. IR (KBr): 2975, 2857, 2717, 1731, 1633, 1593, 1438, 1353, 1292, 1159, 1108, 1066, 1044, 1012, 911, 880 cm^{-1}.

1,4-Dioxan-2-yl 2-bromobenzoate (9d)[9a]**:**



^{1}H NMR (600 MHz, $CDCl_3$): δ 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 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}.

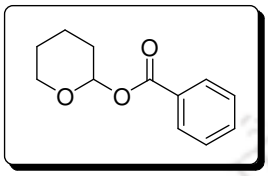
1,4-Dioxan-2-yl 3-(trifluoromethyl)benzoate (11d):



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67–3.70 (m, 1H), 3.82–3.84 (m, 2H), 3.89–3.90 (m, 2H), 4.17–4.24 (m, 1H), 6.10 (s, 1H), 7.60 (t, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz),

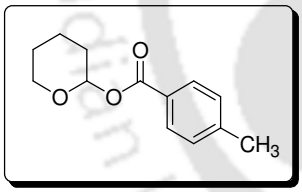
8.29 (d, 1H, *J* = 8.4 Hz), 8.34 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 62.1, 66.3, 67.9, 90.7, 122.9, 124.7, 127.0 (t, *J* = 4.2 Hz), 129.4, 130.2 (d, *J* = 6.0 Hz), 130.9, 131.4 (q, *J* = 32.7 Hz), 133.3, 164.2. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ −63.4. IR (KBr): 2924, 1730, 1636, 1449, 1333, 1251, 1166, 1128, 1071, 1016, 914, 879, 695 cm^{-1}.; HRMS (ESI): calcd for $C_{12}H_{11}F_3O_4$ $(M+Na)^+$, 299.0507; found, 299.0501.

Tetrahydro-2H-pyran-2-yl benzoate (1e)[14a]:



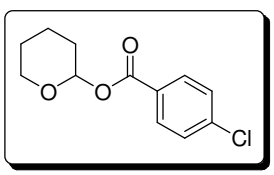
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58−1.77 (m, 3H), 1.81−1.99 (m, 3H), 3.72−3.75 (m, 1H), 3.94−4.01 (m, 1H), 6.23 (t, 1H, *J* = 3.2 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 7.54 (t, 1H, *J* = 7.2 Hz), 8.07 (d, 2H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 25.0, 29.3, 63.2, 93.1, 128.4, 129.8, 130.3, 133.1, 165.2. IR (KBr): 2924, 2853, 1723, 1607, 1456, 1289, 1121, 709 cm^{-1}.

Tetrahydro-2H-pyran-2-yl 4-methylbenzoate (2e)[14f]:



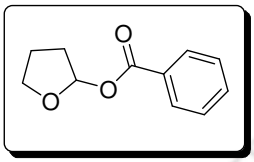
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60−1.62 (m, 1H), 1.67−1.71 (m, 2H), 1.80−1.95 (m, 3H), 2.39 (s, 3H), 3.71−3.74 (m, 1H), 3.94−3.98 (m, 1H), 6.21 (t, 1H, *J* = 2.0 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.8, 21.8, 25.2, 29.5, 63.4, 93.1, 127.7, 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}.

Tetrahydro-2H-pyran-2-yl 4-chlorobenzoate (6e)[9a]:



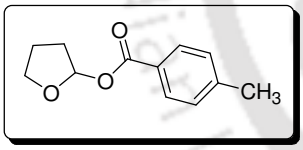
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59–1.67 (m, 1H), 1.72–1.77 (m, 2H), 1.83–1.91 (m, 3H), 3.72–3.75 (m, 1H), 3.92–3.98 (m, 1H), 6.21 (s, 1H), 7.40 (d, 2H, *J* = 8.4 Hz), 8.00 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 25.2, 29.4, 63.5, 93.6, 128.92, 128.97, 131.3, 139.8, 164.6. IR (KBr): 2944, 2871, 1725, 1593, 1272, 1206, 1089, 1016, 940, 898, 868, 758 cm^{-1}.

Tetrahydrofuran-2-yl benzoate (1f)[14a]:



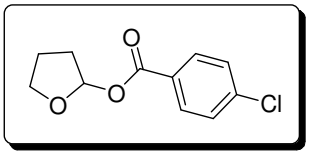
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05–2.12 (m, 2H), 2.45–2.54 (m, 2H), 4.10–4.22 (m, 2H), 5.52 (s, 1H), 7.39–7.43 (m, 2H), 7.52–7.56 (m, 1H), 7.98–8.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 29.7, 67.1, 100.7, 128.6, 129.88, 129.93, 133.5, 166.2. IR (KBr): 2901, 1720, 1637, 1489, 1450, 1349, 1317, 1277, 1117, 1069, 1028, 958, 909, 713 cm^{-1}.

Tetrahydrofuran-2-yl 4-methylbenzoate (2f)[14f]:



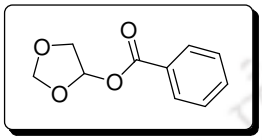
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03–2.09 (m, 2H), 2.36 (s, 3H), 2.43–2.52 (m, 2H), 4.08–4.21 (m, 2H), 5.51 (s, 1H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 28.6, 29.7, 67.0, 100.6, 127.1, 129.2, 129.9, 144.1, 166.3. IR (KBr): 2901, 2127, 1717, 1613, 1445, 1349, 1278, 1179, 1112, 1029, 958, 909, 842, 755, 691 cm^{-1}.

Tetrahydrofuran-2-yl 4-chlorobenzoate (6f):



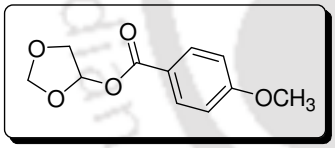
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99–2.10 (m, 2H), 2.45–2.54 (m, 2H), 4.09–4.23 (m, 2H), 5.51 (s, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 29.6, 67.0, 100.6, 128.3, 128.9, 131.2, 140.0, 165.3. IR (KBr): 2943, 2906, 1718, 1593, 1486, 1402, 1344, 1276, 1107, 1032, 943, 889, 760 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{11}ClO_3$ $(M+Na)^+$, 249.0295; found, 249.0300.

1,3-Dioxolan-4-yl benzoate (1g):



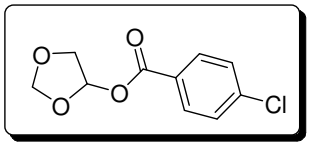
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.12–4.19 (m, 2H), 5.16 (s, 1H), 5.21(s, 1H), 6.59–6.60 (m, 1H), 7.45 (t, 2H, *J* = 7.8 Hz), 7.59 (t, 1H, *J* = 7.2 Hz), 8.05 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 71.0, 94.9, 96.2, 128.7, 129.7, 130.0, 133.7, 166.1. IR (KBr): 2926, 2881, 1729, 1602, 1452, 1316, 1269, 1167, 1069, 1024, 990, 870, 711 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{10}O_4$ $(M+Na)^+$, 217.0477; found, 217.0470.

1,3-Dioxolan-4-yl 4-methoxybenzoate (3g)[14e]:



^{1}H NMR (600 MHz, $CDCl_3$): δ 3.83 (s, 3H), 4.07–4.14 (m, 2H), 5.12 (s, 1H), 5.16 (s, 1H), 6.53–6.54 (m, 1H), 6.89 (d, 2H, *J* = 9.0 Hz), 7.97 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.5, 70.8, 94.5, 95.9, 113.8, 121.9, 132.0, 163.9, 165.6. IR (KBr): 2970, 2882, 1719, 1607, 1512, 1422, 1318, 1260, 1169, 1028, 1087, 922, 769 cm^{-1}.

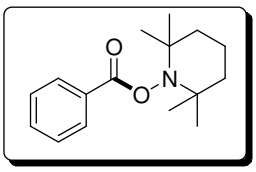
1,3-Dioxolan-4-yl 4-chlorobenzoate (6g):



^{1}H NMR (600 MHz, $CDCl_3$): δ 4.10–4.17 (m, 2H), 5.14 (s, 1H), 5.19 (s, 1H), 6.56–6.57 (m, 1H), 7.41 (d, 2H, *J* = 6.6 Hz), 7.97 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 70.9, 95.0, 96.2, 128.1, 129.0, 131.3, 140.2, 165.1. IR (KBr): 2975, 2881, 2782, 1731,

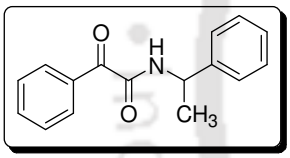
1594, 1488, 1402, 1269, 1169, 1038, 1014, 921, 851, 759 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_9ClO_4$ $(M+Na)^+$, 251.0087; found, 251.0095.

2,2,6,6-Tetramethylpiperidin-1-yl benzoate (G):



^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.31 (s, 6H), 1.48−1.52 (broad singlet, 1H), 1.61−1.64 (broad singlet, 2H), 1.71 (m, 3H), 7.50 (t, 2H, J = 7.6 Hz), 7.61 (t, 1H, J = 6.8 Hz), 8.11 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 21.0, 32.1, 39.2, 60.5, 128.6, 129.7, 133.0, 166.5. IR (KBr): 2974, 2934, 1749, 1540, 1378, 1255, 1176, 1081 cm^{-1}, HRMS (ESI): calcd for $C_{16}H_{23}NO_2$ (MH^+), 262.1807; found, 262.1812.

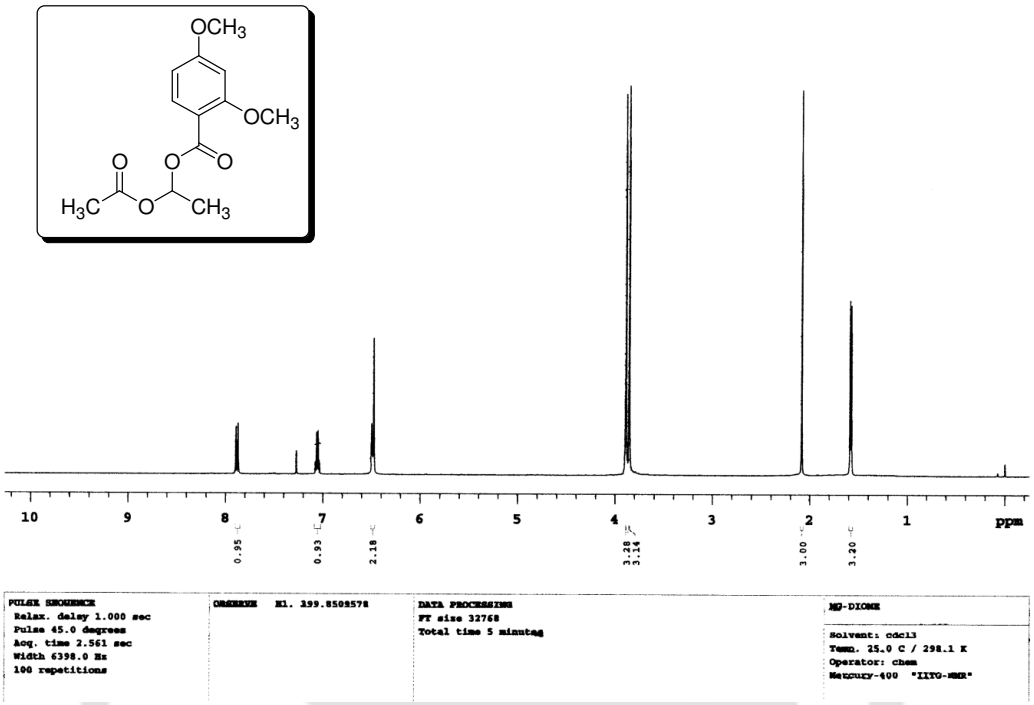
2-Oxo-2-phenyl-*N*-(1-phenylethyl)acetamide (N):



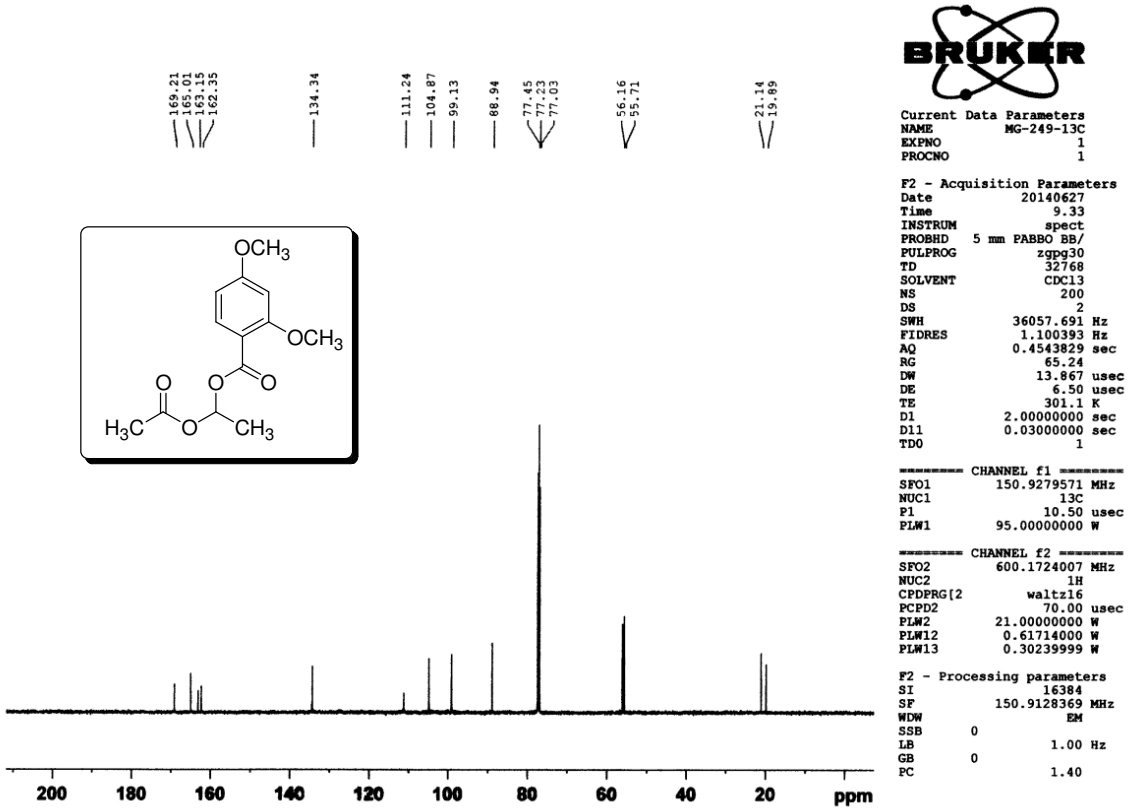
^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, J = 6.8 Hz), 5.13-5.20 (m, 1H), 7.35-7.36 (m, 5H), 7.45 (t, 2H, J = 8.4 Hz), 7.60 (t, 1H, J = 7.6 Hz), 8.32 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 49.3, 126.4, 127.9, 128.7, 129.0, 131.5, 133.5, 134.6, 142.4, 160.9, 187.8. IR (KBr): 3451, 2962, 2925, 2851, 1662, 1596, 1449, 1218, 1178, 1021, 744, 698 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{15}NO_2$ (MH^+), 254.1176; found, 254.1185.

IV.7. Selected Spectra

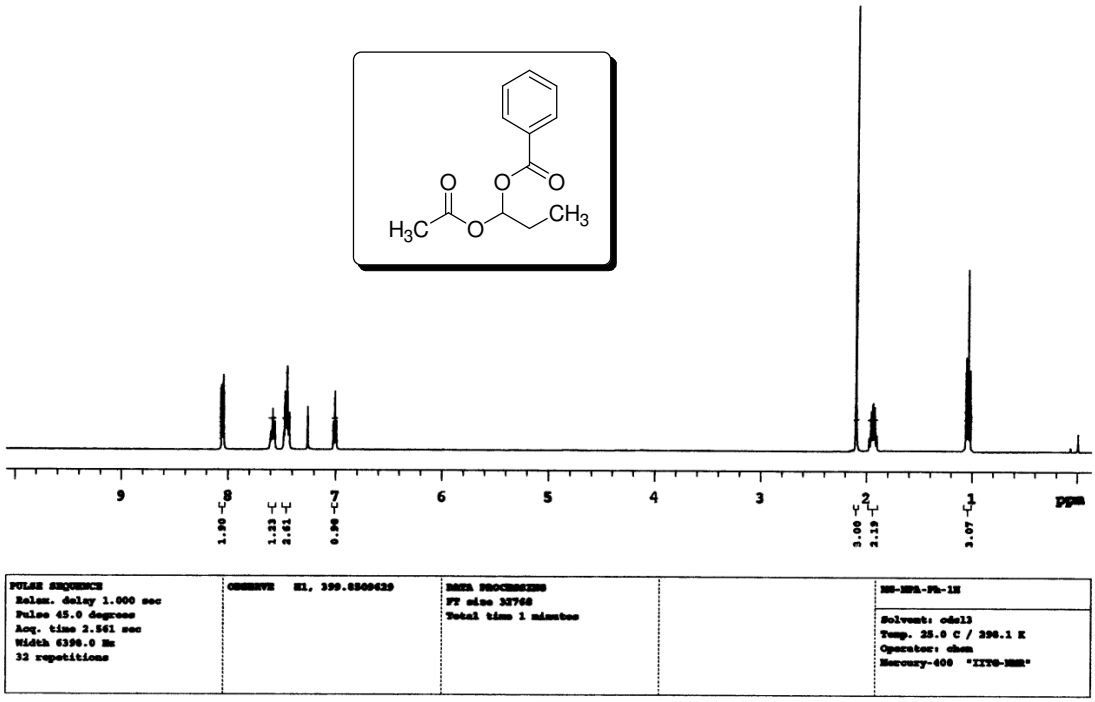
1-Acetoxyethyl 2,4-dimethoxybenzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$)



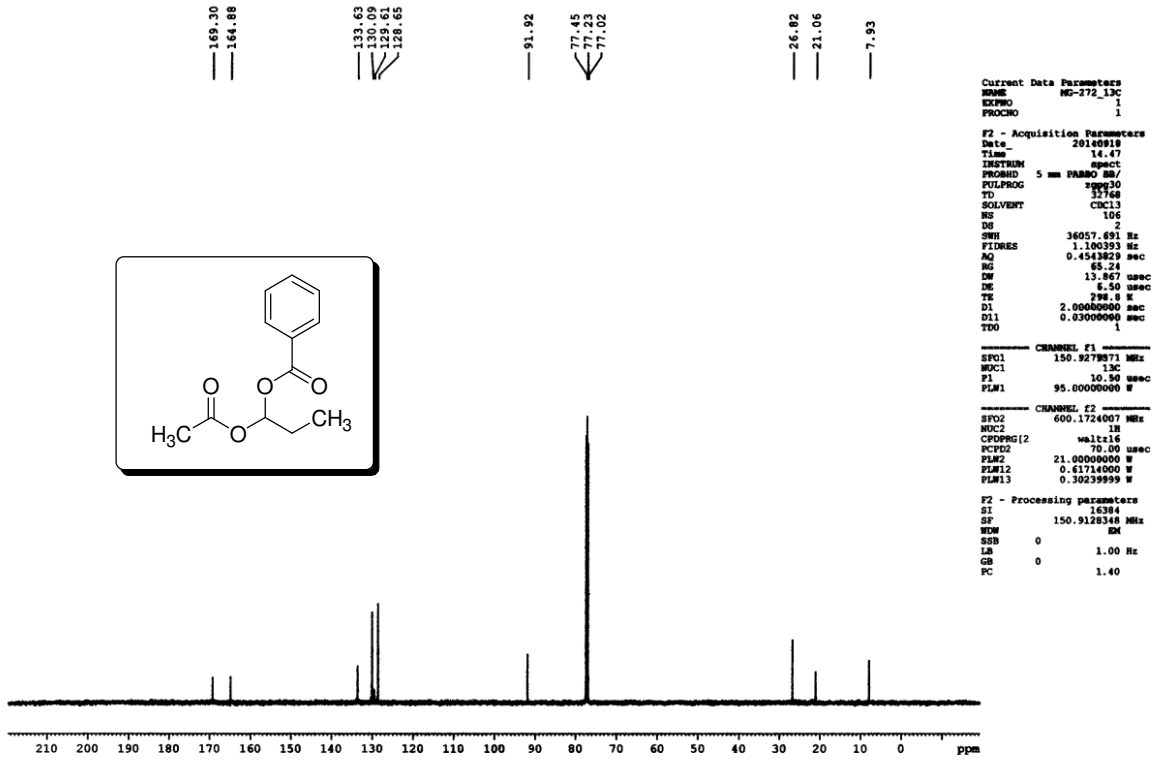
1-Acetoxyethyl 2,4-dimethoxybenzoate (4a): ^{13}C NMR (150 MHz, $CDCl_3$)



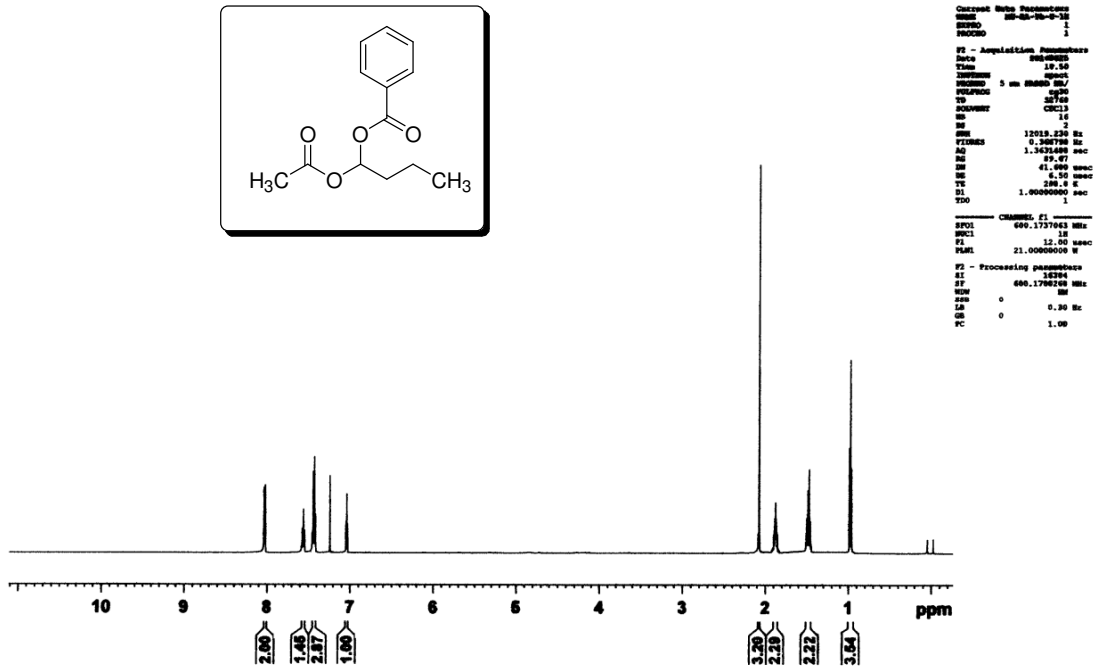
1-Acetoxypropyl benzoate (1b): ^{1}H NMR (400 MHz, $CDCl_3$)



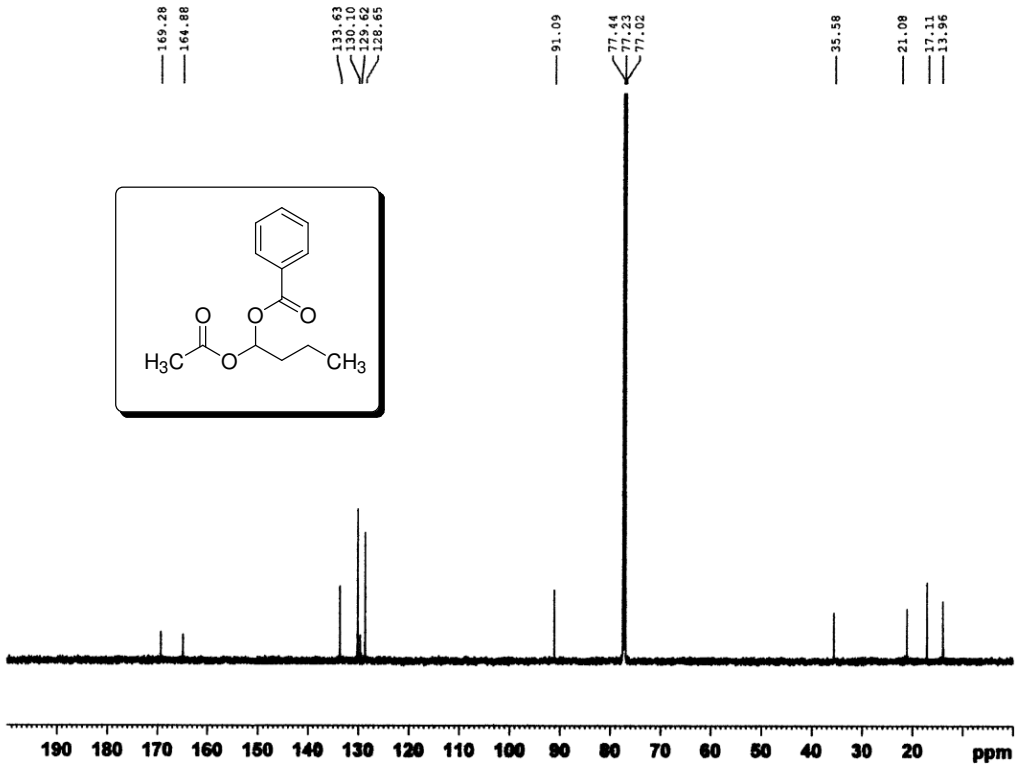
1-Acetoxypropyl benzoate (1b): ^{13}C NMR (150 MHz, $CDCl_3$)



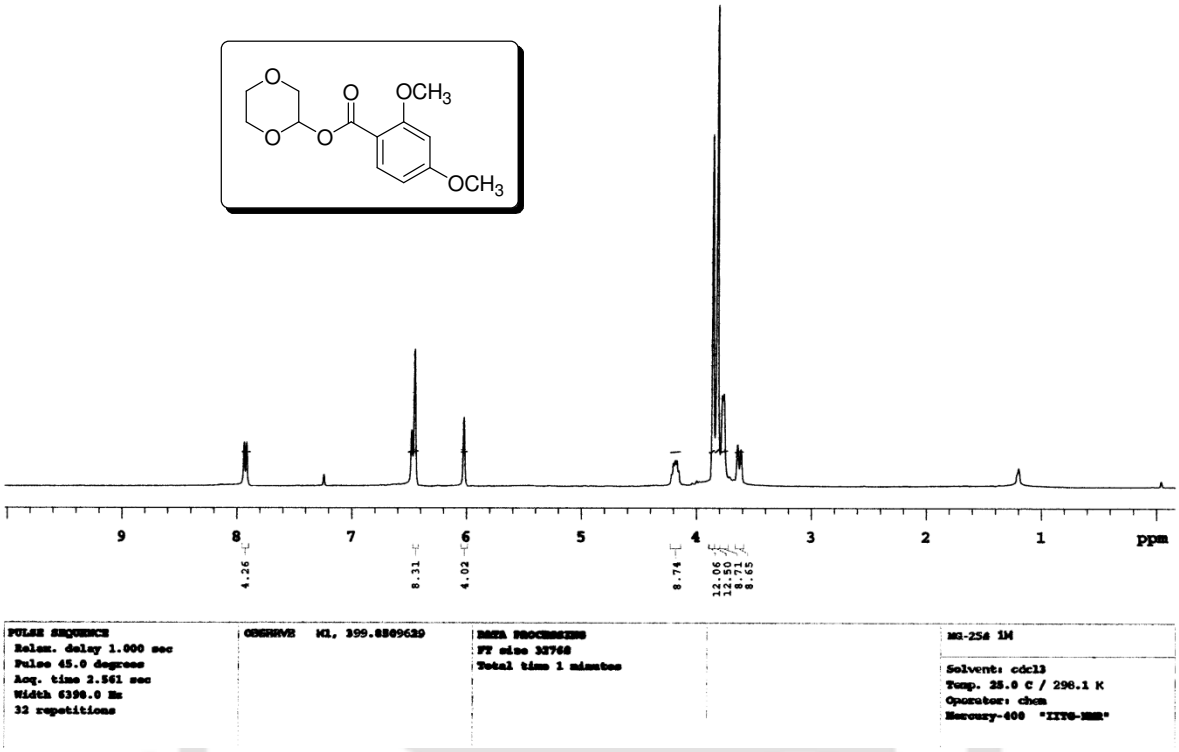
1-Acetoxybutyl benzoate (1c): ^{1}H NMR (600 MHz, $CDCl_3$)



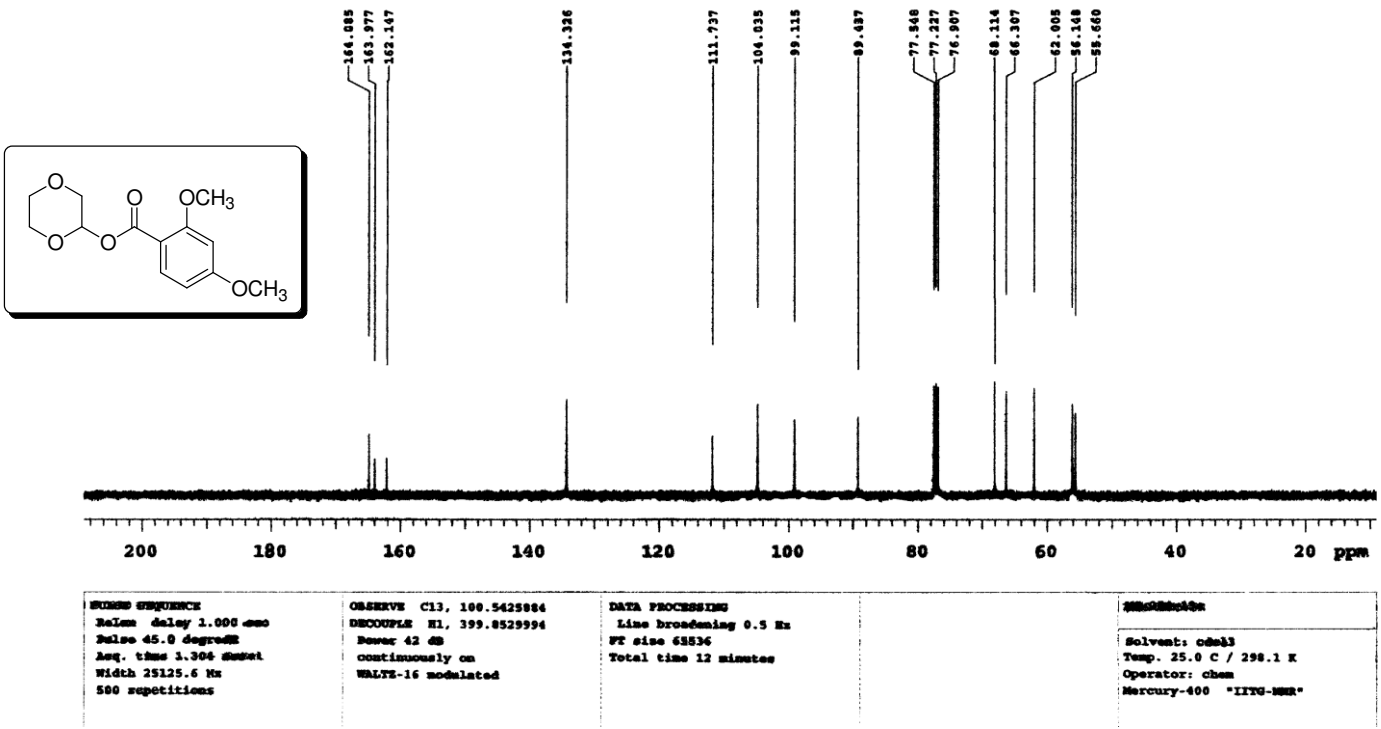
1-Acetoxybutyl benzoate (1c): ^{13}C NMR (150 MHz, $CDCl_3$)



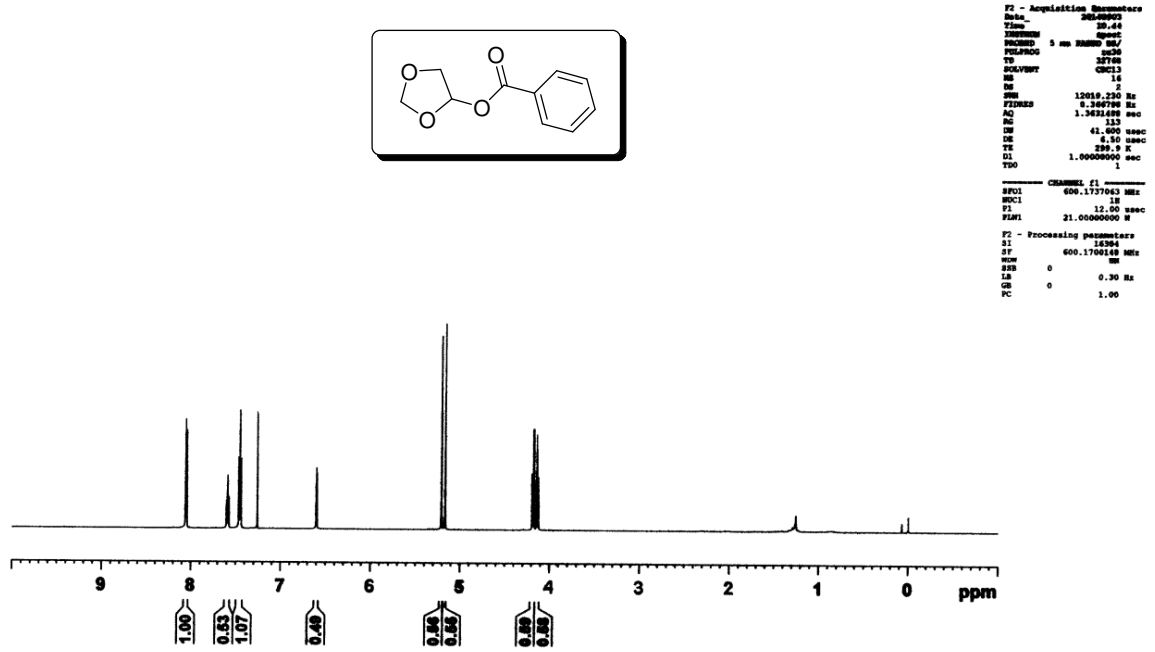
1,4-Dioxan-2-yl 2,4-dimethoxybenzoate (4d): ^{1}H NMR (400 MHz, $CDCl_3$)



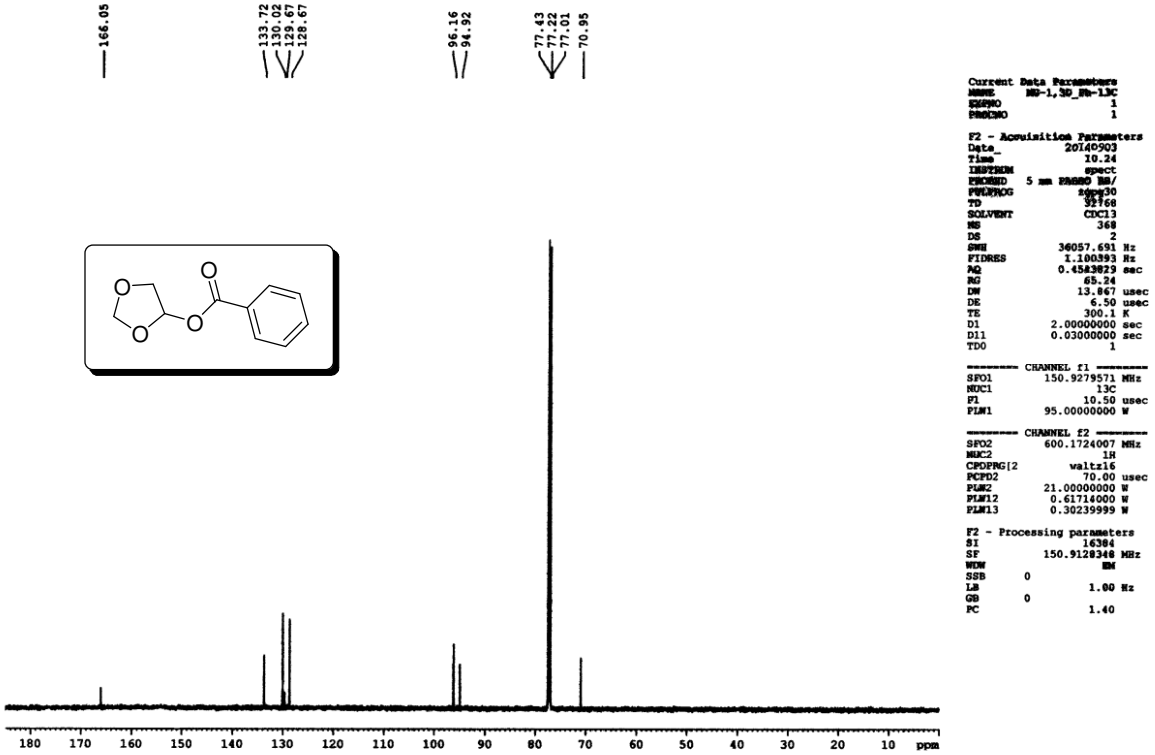
1,4-Dioxan-2-yl 2,4-dimethoxybenzoate (4d): ^{13}C NMR (100 MHz, $CDCl_3$)



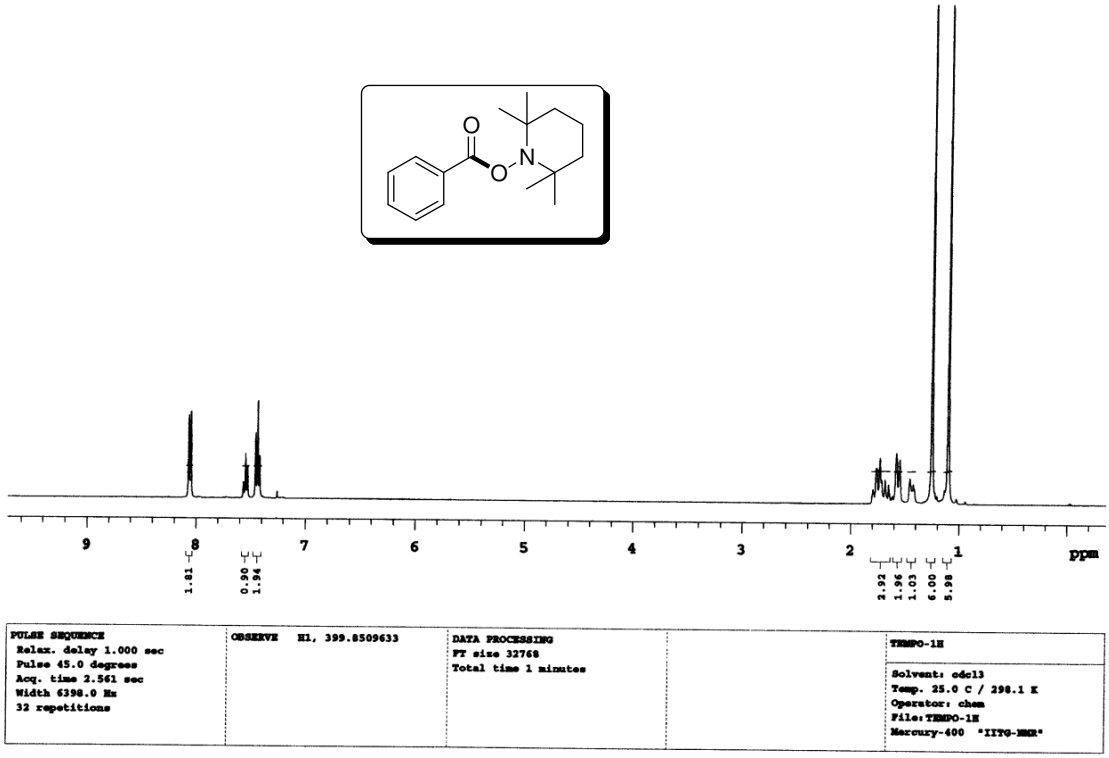
1,3-Dioxolan-4-yl benzoate (1g): ^{1}H NMR (600 MHz, $CDCl_3$)



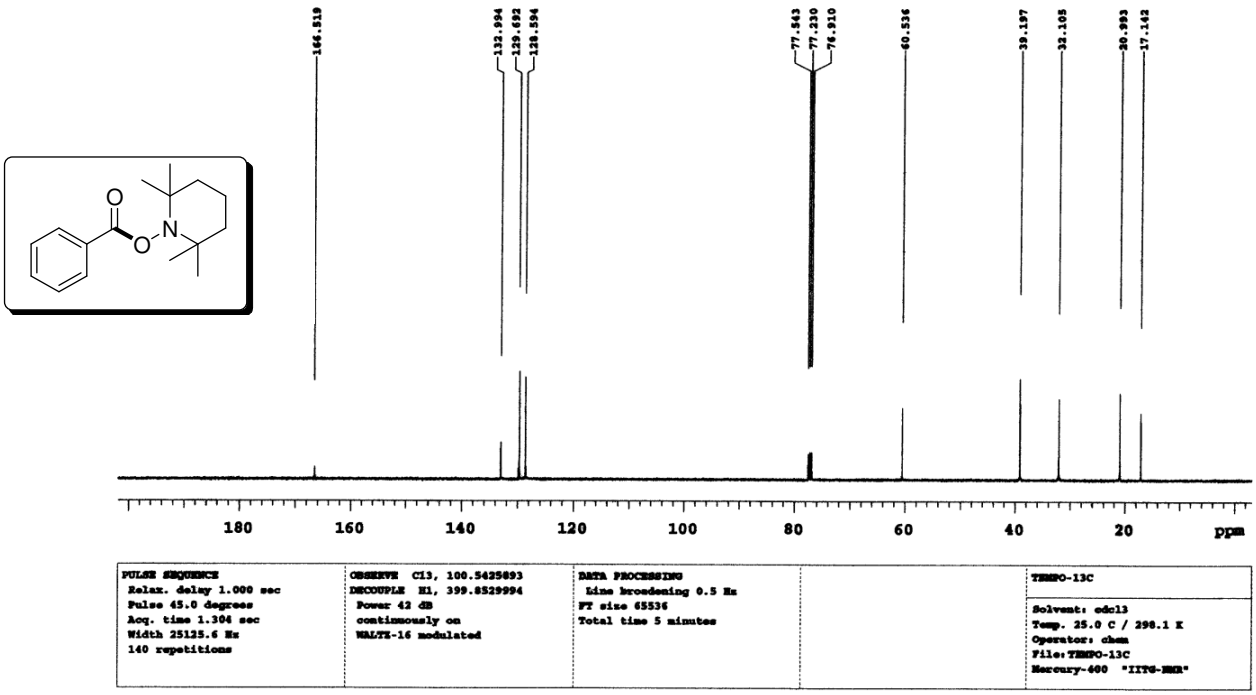
1,3-Dioxolan-4-yl benzoate (1g): ^{13}C NMR (150 MHz, $CDCl_3$)



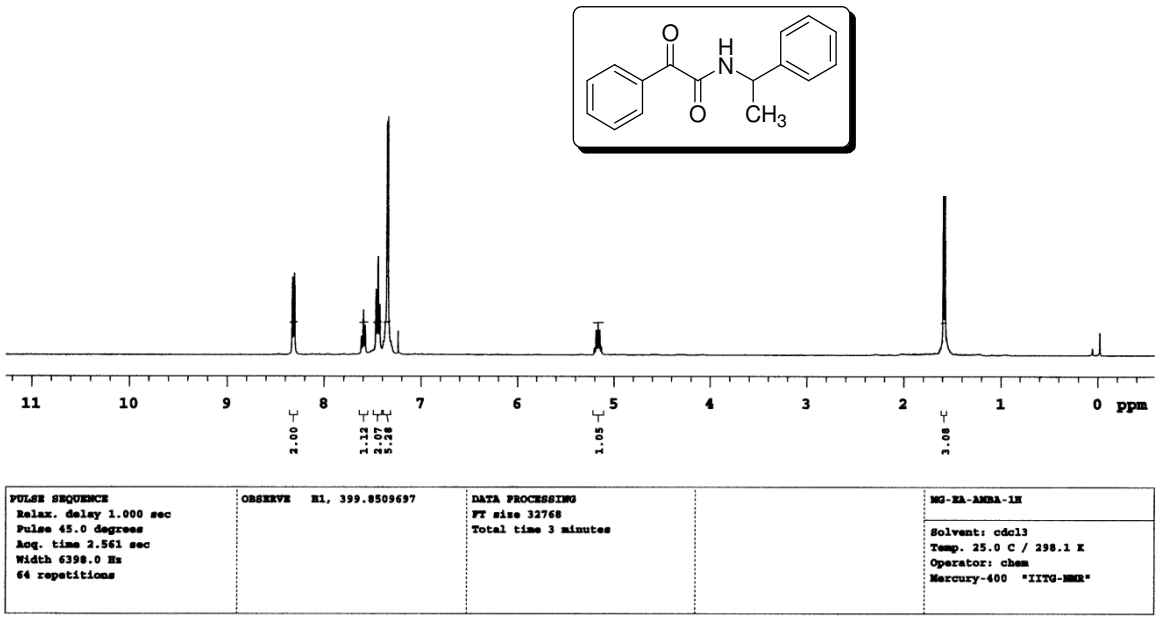
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (G): ^{1}H NMR (400 MHz, $CDCl_3$)



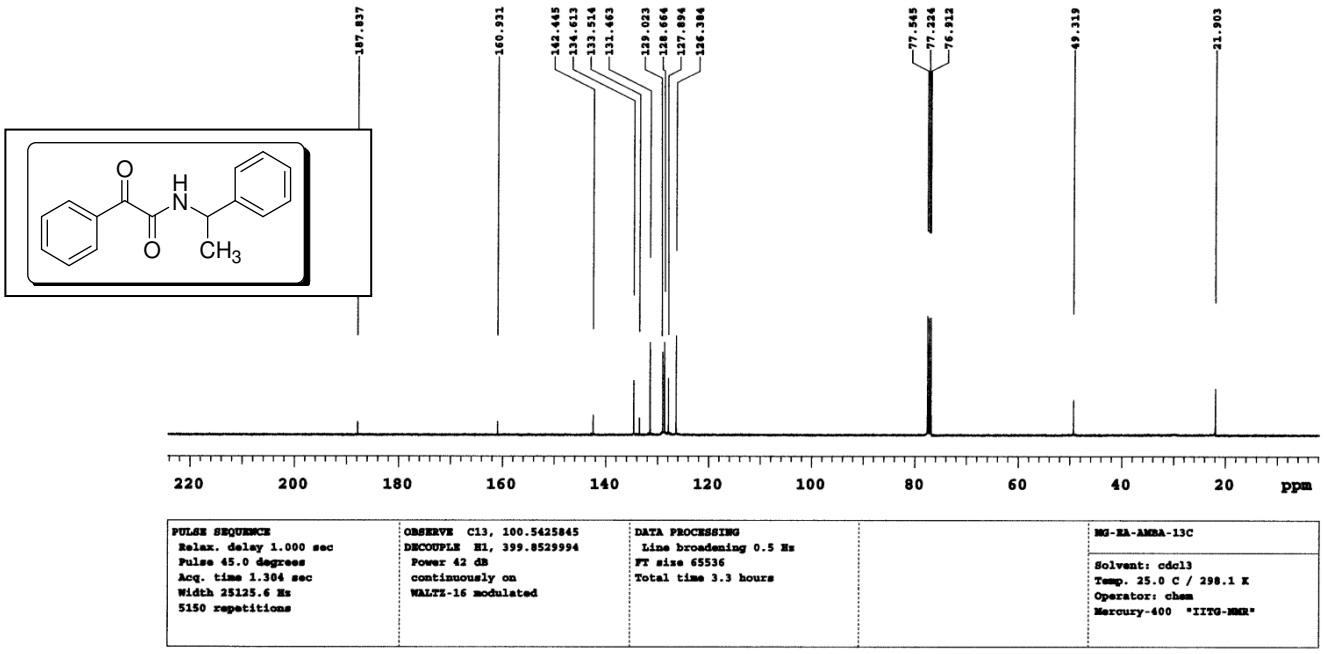
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (G): ^{13}C NMR (100 MHz, $CDCl_3$)



2-Oxo-2-phenyl-*N*-(1-phenylethyl)acetamide (N): ^{1}H NMR (400 MHz, $CDCl_3$)



2-Oxo-2-phenyl-*N*-(1-phenylethyl)acetamide (N): ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER V

RSC Advances

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Iodine-catalysed oxidative cyclisation of acylhydrazones to 2,5-substituted 1,3,4-oxadiazoles†

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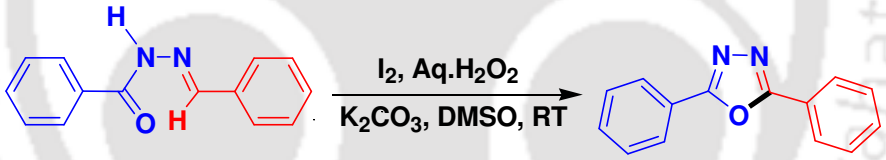


Abstract: **An environmentally benign synthesis of 2,5-disubstituted 1,3,4-oxadiazoles has been developed starting from *N*-aroylhydrazones and *N*-acetylhydrazones at room or ambient temperature using catalytic quantity of iodine in the presence of an aqueous hydrogen peroxide oxidant.**

CHAPTER V

V. Iodine–Catalyzed Oxidative Cyclization of Acylhydrazones to 2,5-Substituted 1,3,4-Oxadiazoles

V.1. Introduction

1,3,4-Oxadiazoles, a π-conjugated heterocycle are an interesting class of compound since molecule possessing this skeleton has been widely used in materials science, particularly in organic light emitting diodes (OLEDs), as electron conducting and hole blocking materials. Due to their electron deficient and electron transporting abilities they are utilised in an energy efficient, full-colour, flat panel display.[1] From the point of view of medicinal chemistry, 1,3,4-oxadiazoles display various biological activities such as anticancer, benzodiazepine receptor agonists, antimicrobial, analgesic, diuretic and tyrosinase inhibitors etc.[2] Besides these, 2,5-disubstituted 1,3,4-oxadiazoles have been used as a bioisosteric replacement of ester, amide and acid functionalities in pharmaceutical chemistry[3a-c] as in Furamizole,[3d] Raltegravir,[3e] Nesapidil[3f] and Zibotentan[3g,h] as shown in Figure. V.1.1. Some other significant molecules possessing 1,3,4-oxadiazole as the core unit include Butyl PBD or b-PBD which is used in the liquid scintillator neutrino detector (LSND) (Figure. V.1.1).[4]

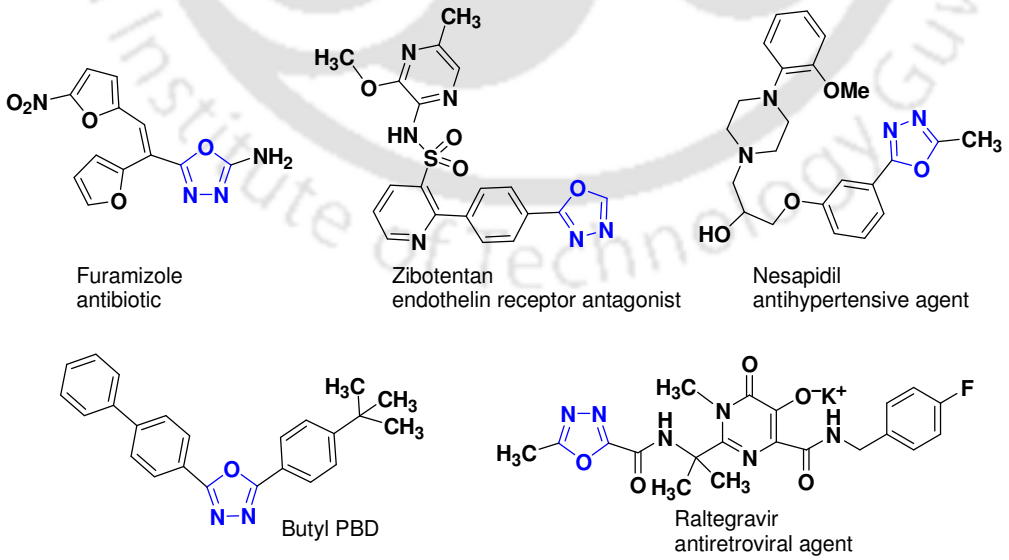


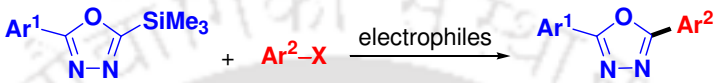
Figure. V.1.1. *Representative examples of bioactive compounds possessing 1,3,4-oxadiazole motif*

V.2. Strategies for the Synthesis of 2,5-Substituted 1,3,4-Oxadiazoles

Due to myriad of applications of 1,3,4-oxadiazole motif several methodologies are described in the literature for their synthesis.

(i) Electrophilic substitution of 2-substituted-5-trimethylsilyl-1,3,4-oxadiazole

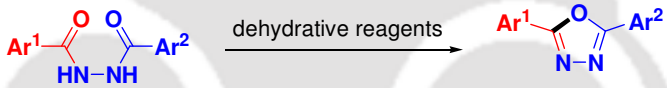
In this method 2,5-disubstituted 1,3,4-oxadiazoles are synthesized by the electrophilic substitution of 2-substituted-5-trimethylsilyl-1,3,4-oxadiazole toward various electrophiles such as Cl_2, Br_2, acyl chlorides or isocyanates (Scheme V.2.1).[5]



Scheme V.2.1. *Synthesis of 1,3,4-oxadiazoles via electrophilic substitution*

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

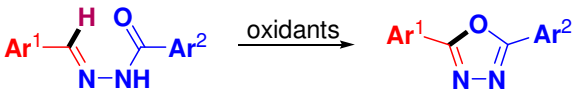
An alternative route to 2,5-disubstituted 1,3,4-oxadiazoles is via the dehydrative cyclization of 1,2-diacylhydrazines. Typically, a dehydrative cyclization is carried out using reagents such as phosphorus oxychloride, sulphuric acid, thionyl chloride, PPA or $[Et_2NSF_2]BF_4$ (Scheme V.2.2).[6]



Scheme V.2.2. *Synthesis of 1,3,4-oxadiazoles via dehydrative cyclization*

(iii) Oxidative cyclization of *N*-acylhydrazones

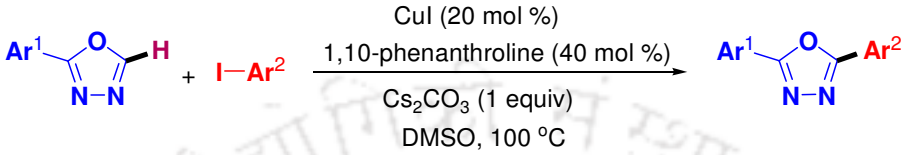
Besides the traditional synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, involving acyl chlorides or carboxylic acids with acid hydrazines or hydrazides,[7] some elegant protocols have also been developed. Oxidative cyclization of *N*-acylhydrazones is another convenient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (Scheme V.2.3). However, the later methods uses stoichiometric amounts of oxidising agents such as $KMnO_4$,[8a] ceric ammonium nitrate,[8b] Br_2,[8c] chloramineT,[8d] $FeCl_3$,[8e] HgO/I_2,[8f] tetravalent lead reagents[8g] or hypervalent iodine reagents.[8h-m] Recently Chang *et al.* reported a similar protocol for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using molecular iodine in stoichiometric quantity.[8n]



Scheme V.2.3. *Synthesis of 1,3,4-oxadiazoles via oxidative cyclization*

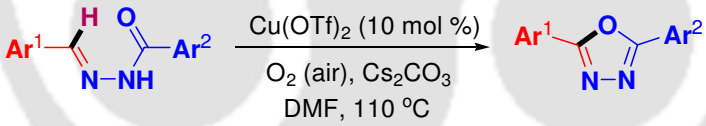
(iv) C–H bond functionalization

Miura's group has developed a copper mediated C–H arylation of a preformed 2-substituted 1,3,4-oxadiazoles with aryl halides for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (Scheme V.2.4.1).[9] Although this method is superior to existing methods, difficulties for the preparation of starting materials make it unattractive.



Scheme V.2.4.1. *Synthesis of 1,3,4-oxadiazoles via C–H activation*

Recently our group achieved direct access to the synthesis of both symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles via the imine C–H bond functionalization of *N*-arylidenearoylhydrazides or aroylhydrazone using catalytic quantity of $Cu(OTf)_2$ (Scheme V.2.4.2).[10] The requirement of an expensive catalyst and need to perform the reaction at a higher temperature in DMF makes it unappealing for a large scale synthesis. Further, the method is not successful with *N*-acetylhydrazone in the preparation of alkyl-substituted 1,3,4-oxadiazoles.[10]

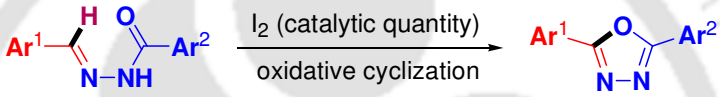


Scheme V.2.4.2. *Synthesis of 1,3,4-oxadiazoles via C–H functionalization*

V.3. Present Work

Usually iodine mediated reactions are preferred over metal catalyzed oxidation in pharmaceutical industries due to avoiding the need for removal of metal impurities, low cost, being environmental benign and operational simplicity. In recent years, several organic transformations have been achieved by our group, and several others, using molecular iodine.[11] The combination of TBHP and I_2 has been widely used in many oxidative transformations to overcome the drawbacks of the metal catalyzed reactions.[11a,11g,12] For any of the iodine catalyzed reactions the reduced iodide species needs to be reoxidized to iodine with an external oxidant to maintain the catalytic cycle. If this process can be achieved at the expense of a cheap and environmentally benign

oxidant such as aqueous hydrogen peroxide the method would be much more attractive. Although the transformation of *N*-acylhydrazones to 2,5-substituted 1,3,4-oxadiazoles has been reported using 20 mol% of iodine in the absence of any base[13] the result could not be reproduced by us. The failure to give any product using 20 mol% of the iodine could possibly be because I_2 gets converted to I^- during the reaction and in the absence of any suitable oxidant the reduced I^- cannot be oxidised back to I_2 to make the reaction catalytic. Further, from our subsequent finding it is clear that a base is a must for deprotonation of the starting material and neutralization of HI generated in the medium. Hence we aspired to report an iodine catalyzed oxidative cyclization of acylhydrazones for the synthesis of densely functionalised 2,5-substituted 1,3,4-oxadiazoles (Scheme V.3.1).

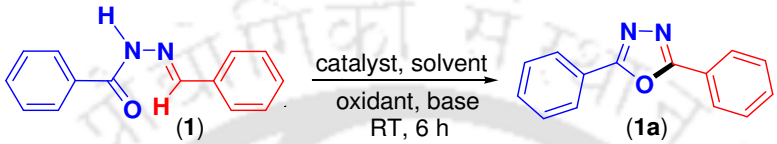


Scheme V.3.1. *Synthesis of 2,5-substituted 1,3,4-oxadiazoles via oxidative cyclization*

Optimization of reaction conditions. Initially *N*-benzylidenebenzohydrazide (1 mmol) was treated with iodine (10 mol %), aq. TBHP (4 equiv) and Cs_2CO_3 (2 equiv) in DMF at room temperature, which afforded the product (**1a**) in 77% isolated yield (Table V.3.1, entry 1). Replacement of DMF with DMSO gave an improved yield of 86% (Table V.3.1, entry 2). Interestingly, when the same reaction was carried out with aq H_2O_2 (4 equiv) and K_2CO_3 (2 equiv) instead of aq. TBHP (4 equiv) and Cs_2CO_3 (2 equiv) in DMSO the yield improved marginally (88%, Table V.3.1, entry 3). Since the latter combination was better both from cost and yield considerations the reaction condition was preset but the pursuit to improve the yield continued. In a quest to improve the yield other solvents such as toluene, THF, CH_3CN and CH_3OH (Table V.3.1, entries 4-7) were screened but all were found to be less effective compared to the use of DMSO. The use of organic bases such as Et_3N, DBU (Table V.3.1, entries 8-9) were found to be inferior to the inorganic carbonate bases. No substantial improvement in the yield (90%) was observed upon increasing the amount of iodine from 10 to 20 mol %. In principle one equivalent of aq H_2O_2 is sufficient to reoxidise I^- to I_2. A decrease in the quantity of H_2O_2 below 4 equiv lowered the yield of the product. This is because iodine is also known to decompose H_2O_2 thereby effectively making it less available for the

reoxidation of I^- to I_2 in the catalytic cycle.[14] In the absence of any external oxidant the desired product was obtained in a mere yield of 9% (Table V.3.1, entry 11), thereby suggesting the requirement of an added oxidant for the reoxidation of I^- to I_2. The transformation was completely unproductive in the absence of either iodine or base; thus suggesting the essential requirement of iodine, oxidant and base for this transformation.

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



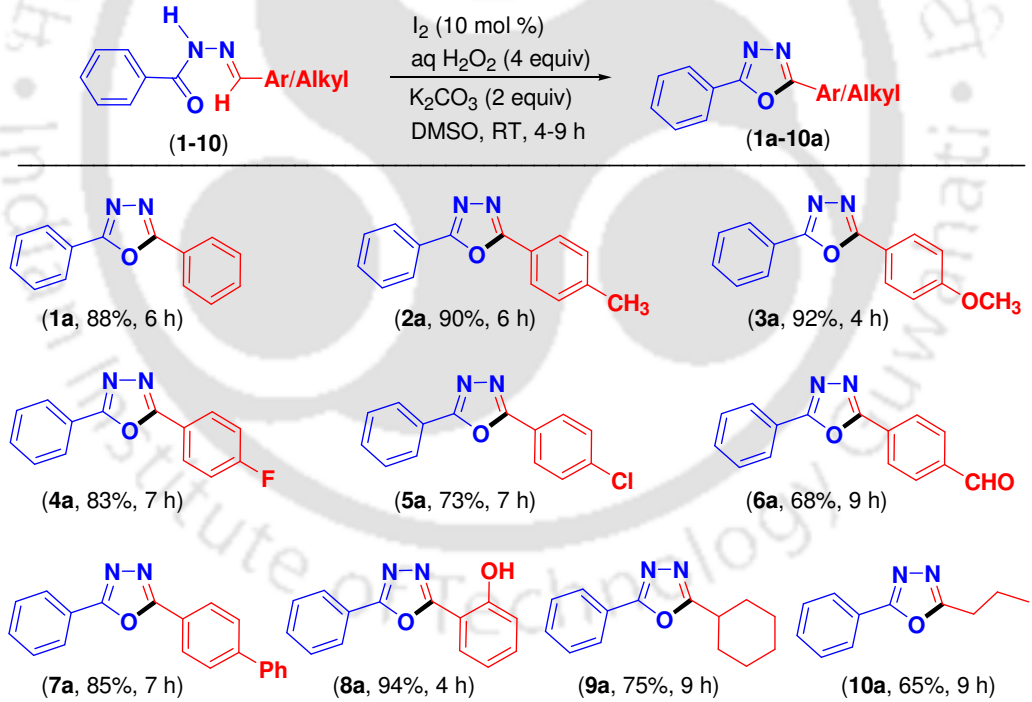
Entry	Catalyst	Oxidant	Solvent	Base	Yield (%)[b]
1	10% I_2	aq TBHP	DMF	Cs_2CO_3	77
2	10% I_2	aq TBHP	DMSO	Cs_2CO_3	86
3	**10% I_2**	**aq H_2O_2**	**DMSO**	**K_2CO_3**	**88**
4	10% I_2	aq H_2O_2	Toluene	K_2CO_3	5
5	10% I_2	aq H_2O_2	THF	K_2CO_3	10
6	10% I_2	aq H_2O_2	CH_3CN	K_2CO_3	10
7	10% I_2	aq H_2O_2	CH_3OH	K_2CO_3	15
8	10% I_2	aq H_2O_2	DMSO	Et_3N	0
9	10% I_2	aq H_2O_2	DMSO	DBU	20
10	20% I_2	aq H_2O_2	DMSO	K_2CO_3	90
11	10% I_2	nil	DMSO	K_2CO_3	09

[a]The reactions were carried out in the same scale under identical reaction conditions.
[b]Isolated yields.

Substrate scope for 2,5-substituted 1,3,4-oxadiazoles. Having the above optimized conditions in hand various *N*-benzoylhydrazones derived from benzoylhydrazide and various aldehydes were subjected to the present reaction conditions and the results are summarized in Scheme V.3.2. This methodology gave better yield of the products for substrates possessing electron donating groups such as *p*–Me (**2a**), *p*–OMe (**3a**) and *o*–OH (**8a**) in the aryl ring of the precursor aldehyde. However, *N*-benzoylhydrazones derived from aldehydic moiety possessing electron-withdrawing groups such as *p*–F (**4a**), *p*–Cl (**5a**), *p*–CHO (**6a**) and *p*–Ph (**7a**) gave lower yields of the products compared to the substrates possessing electron donating groups as shown in Scheme V.3.2. This observation is quite contrary to our recent observation during the Cu(II) catalyzed synthesis of 2,5-disubstituted 1,3,4-oxiadiazoles via an imine C–H functionalization.[10] During the oxadiazole synthesis via the C–H functionalization, substrates possessing

electron withdrawing groups in arylaldehydes gave better yields. This differential observation in the trends of yields is due to the difference in their reaction mechanisms. During the C–H functionalization strategy,[10] the acidity of the imine C–H proton is enhanced when electron withdrawing substituents are present in the aryl ring thereby facilitating the reactions and improving the yields. Mono *N*-benzoylhydrazone derived from phthalaldehyde, gave oxadiazole (**6a**) without affecting the CHO functionality under the reaction conditions. *N*-benzoylhydrazone derived from cyclohexane carboxaldehyde and butyraldehyde gave lower yields of the products (**9a**) and (**10a**) respectively. It may be mentioned here that the benzoylhydrazones obtained from aliphatic aldehydes were found to be inert in the Cu(II) catalyzed synthesis of 2,5-substituted 1,3,4-oxadiazoles[10] suggesting the superiority of this method.

Scheme V.3.2. *Formation of 2,5-substituted 1,3,4-oxadiazoles via oxidative cyclization of N-benzoylhydrazones*[a]

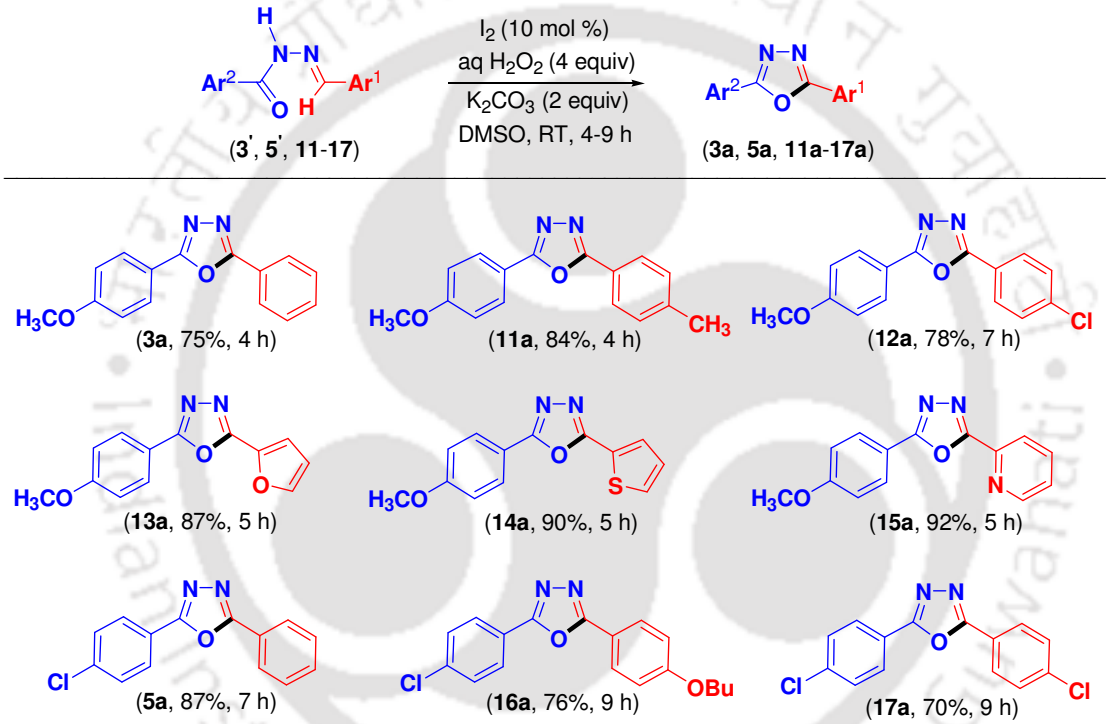


[a]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

This methodology is equally successful with various other *N*-benzoylhydrazones derived from substituted aroylhydrazide possessing electron donating group (*p*-OMe) and an aromatic aldehyde possessing electron neutral –H, electron donating *p*-Me and electron withdrawing *p*-Cl giving corresponding products (**3a**), (**11a**) and (**12a**)

respectively as shown in Scheme V.3.3. The heteroaromatic aldehydes derived *N*-aroylhydrazone underwent smooth transformations giving products (**13a**), (**14a**) and (**15a**) in excellent yields. It may be mentioned here that the synthesis 2,5-substituted 1,3,4-oxadiazoles possessing heterocyclic units required longer reaction time, giving lower yields of products by the C–H functionalization strategy,[10] delineating the superiority of this iodine catalyzed reaction.

Scheme V.3.3. *Formation of 2,5-substituted 1,3,4-oxadiazoles via oxidative cyclization of substituted N-aroylhydrazones*[a]



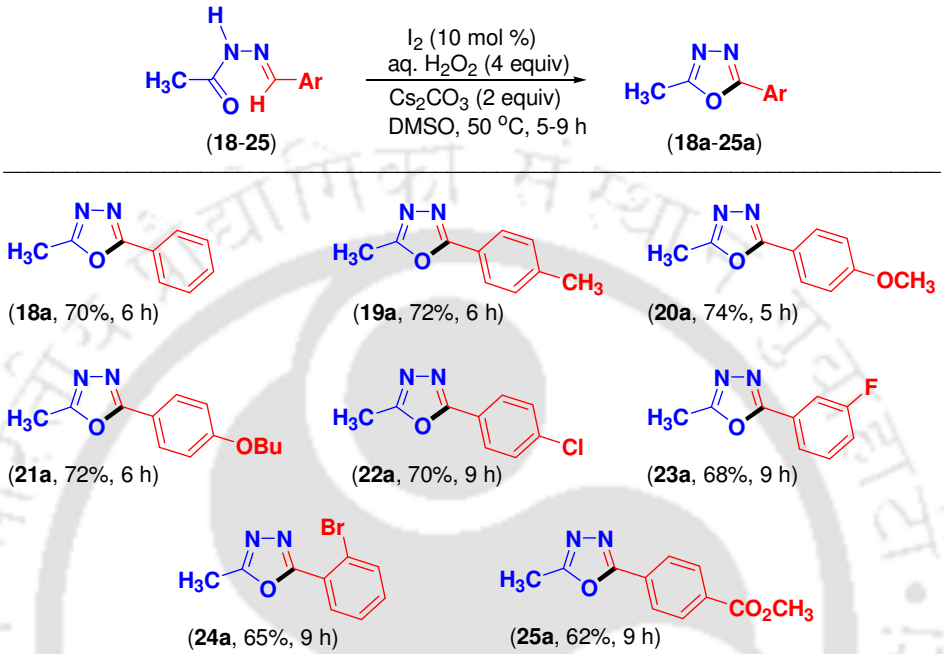
[a]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Further, *N*-aroylhydrazone derived from aroylhydrazide possessing electron withdrawing group (*p*-Cl) and various aromatic aldehydes underwent oxidative cyclization to furnish 2,5-substituted 1,3,4-oxadiazoles (**5a**), (**16a**) and (**17a**) in moderate to good yields. Unlike in Scheme V.3.3, no correlation between the yields of the products obtained and electronic effects of the substituents present in the aryl rings of aldehydes and aroylhydrazides could be derived. The present reaction conditions when applied to various *N*-acetylhydrazone failed to give good yields of the products.

Interestingly upon increasing the reaction temperature to 50 ^{o}C and the use of the stronger base Cs_2CO_3 gave satisfactory yields of various 2,5-substituted 1,3,4-

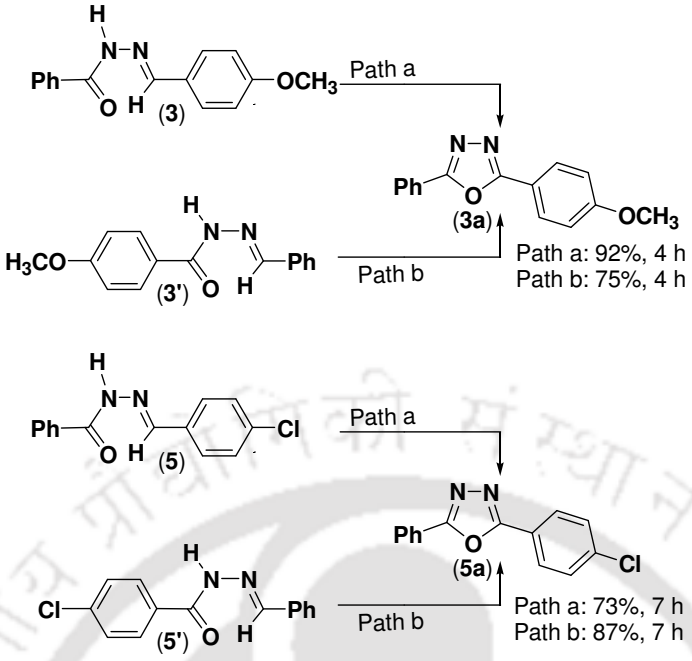
oxadiazoles **18a-25a** as shown in Scheme V.3.4 demonstrating the power of this methodology.

Scheme V.3.4. *Formation of 2,5-substituted 1,3,4-oxadiazoles from oxidative cyclization of N-acetylhydrazones*[a]



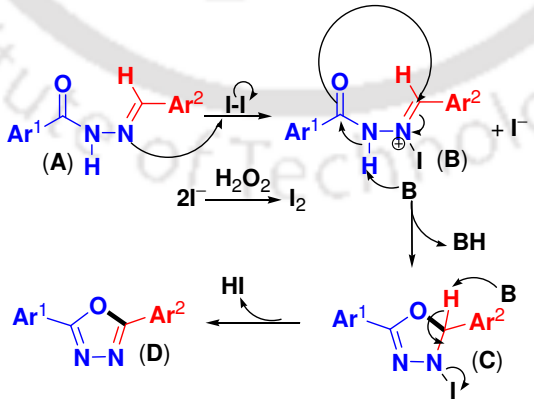
[a]Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported

As the results shown in Scheme V.3.2- V.3.4 demonstrate, this protocol is compatible with a diversity of electron donating and withdrawing groups. This method was however not successful for acylhydrazones derived from aliphatic aldehydes and aliphatic hydrazide as no desired products were observed. These substrates decomposed to an aldehyde along with numerous other inseparable products. If both of the counterparts are aliphatic, for example an aliphatic aldehyde and aliphatic hydrazide, the reaction does not work. If any of the counterparts are aromatic for example an aromatic aldehyde and aliphatic hydrazide, or an aliphatic aldehyde and aromatic hydrazide then the reaction is successful. Products (**9a**) and (**10a**) (Scheme V.3.2) are derived from aliphatic aldehydes and aromatic hydrazide. Some of the heterocyclics (**3a**) and (**5a**) can be prepared by two alternative paths as shown in Scheme V.3.5. For compound (**3a**) path-a gave better yield, while for (**5a**) path-b was superior. No correlation between the substituent present in the aryl ring of the aldehyde or hydrazide could be found.



Scheme V.3.5. *Dual routes to formation of 2,5-substituted 1,3,4-oxadiazoles (**3a**) and (**5a**)*

Mechanistic studies. Based on literature reports[8k,11g] and the control experiments carried out a possible mechanism has been proposed for the formation of 2,5-substituted 1,3,4-oxadiazoles. Initially the imine 'N' of (**A**) attack I_2 to form an iminium iodide (**B**). Subsequently, the iminium carbon in (**B**) is attacked intramolecularly by the amidic oxygen to afford the intermediate (**C**). A base promoted elimination (aromatisation) releases hydroiodicacid (HI) giving the desired product (**D**) (Scheme V.3.6).



Scheme V.3.6*. Proposed mechanism for the formation of 2,5-substituted 1,3,4-oxadiazoles*

Conclusions. In summary, we have developed an oxidative cyclization method using I_2/ H_2O_2 catalytic system for the synthesis of 2,5-substituted 1,3,4-oxadiazoles. An inexpensive, environmental friendly catalyst, mild reaction conditions and compatibility with a wide range of substrates make this method superior to all methods documented in literature.

V.4. Experimental Section

V.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 (400 MHz), $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. The arylidenearoylhydrazides, alkylidenearoylhydrazides were prepared by the condensation of one equivalent of corresponding hydrazides and aldehydes in ethanolic medium under reflux condition for 2-6 h.

V.4.2. Crystallographic description. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART[a] software and refined with SAINT[a] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS[b]. The structure was solved by direct methods implemented in SHELX-97[c] program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. colourless crystals were isolated in rectangular shape from acetonitrile at room temperature.

a. SMART V 4.043 Software for the CCD Detector System; Siemens Analytical Instruments Division: Madison, WI, 1995.

b. SAINT V 4.035 Software for the CCD Detector System; Siemens Analytical Instruments Division: Madison, WI, 1995.

c. Sheldrick, G. M. SHELXL-97, Program for the Refinement of Crystal Structures; University of Göttingen: Göttingen (Germany), 1997.

CCDC number for compound 9a: CCDC 953478. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

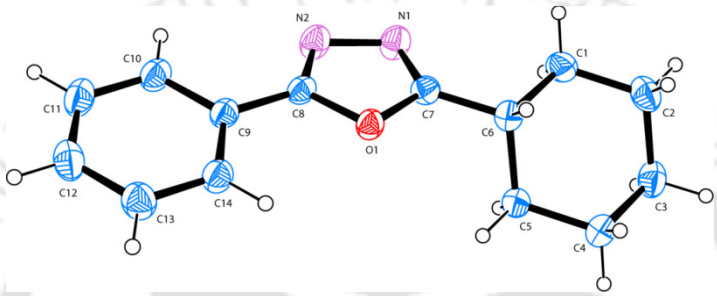


Figure S1: ORTEP view of **9a**

Crystallographic description of 9a: Crystal dimension (mm): 0.42 x 0.35 x 0.26. $C_{14}H_{16}N_2O$, Mr = 228.29 Triclinic, space group P -1; a = 5.7158 (2) Å, b = 9.9633 (4) Å, c = 11.1928 (4) Å; α = 108.896 (2)^o, β = 92.553 (2) ^{o}, γ = 90.149 (2)^o, V = 602.36 (4) Å^3; Z = 2; ρ_{cal} = 1.259 mg/m^3; μ (mm^{-1}) = 0.081; *F (000)* = 244.0; Reflection collected / unique = 3353 / 2055; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0384, wR2 = 0.1139, R indices (all data) R1 = 0.0483, wR2 = 0.1213; goodness of fit = 1.062.

V.4.3. General procedure for the preparation of 2,5-diphenyl-1,3,4-oxadiazole (1a)

A mixture of *N*-benzylidenebenzohydrazide (**1**) (1 mmol, 224 mg), K_2CO_3 (2 mmol, 276 mg) and I_2 (10 mol %, 26 mg) in DMSO (2 mL) was stirred at room temperature. To this reaction mixture H_2O_2 (30% solution in water, 0.45 mL, 4 mmol) was added in nine equal lots over a period of 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was treated with a 5% hypo solution (5 mL). The reaction mixture was then extracted with ethylacetate (2 x 15 mL) and the combined ethylacetate layer was washed with water (1 x 3 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The

product was purified over column of silica gel and eluted with (15% EtOAc / hexane) to give 2,5-diphenyl-1,3,4-oxadiazole (**1a**) (195 mg, 88% yield).

V.5. References

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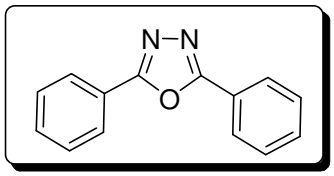
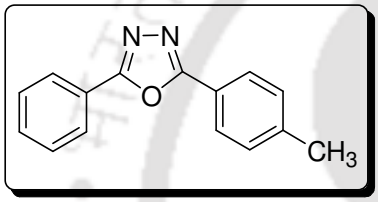
V.6. Spectral Data

2,5-Diphenyl-1,3,4-oxadiazole (1a):



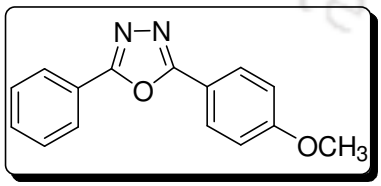
White Solid; M.p. 136-138 ^{o}C (Lit.[1] 138 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.55 (m, 6H), 8.13-8.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.1, 127.1, 129.3, 131.9, 164.8.; IR (KBr): 3058, 2919, 1547, 1484, 1445, 1268, 1155, 1068, 1019, 964, 922, 782, 710, 686 cm^{-1}. HRMS (*m/z*) (M+1) calcd for $C_{14}H_{10}N_2O$: 223.0866, found 223.0863.

2-Phenyl-5-p-tolyl-1,3,4-oxadiazole (2a):



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

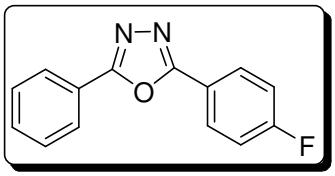
2-(4-Methoxy-phenyl)-5-phenyl-1,3,4-oxadiazole (3a):



White solid; M.p. 149-150 ^{o}C (Lit.[1] 148-150 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 7.02 (d, 2H, *J* = 8.4 Hz), 7.52-7.53 (m, 3H), 8.07 (d, 2H, *J* = 8.4 Hz), 8.11-8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 114.7, 116.6, 124.2, 127.0, 128.9, 129.2, 131.7, 162.5, 164.3, 164.7.; IR (KBr): 2956, 2923, 2848, 1616, 1503, 1262, 1066, 1017,

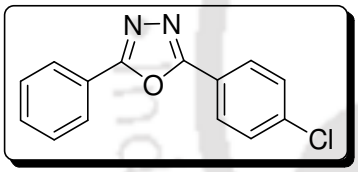
831, 737, 706, 684 cm^{-1}. HRMS (*m/z*) (M+1) calcd for $C_{15}H_{12}N_2O_2$: 253.0972, found 253.0970.

2-(4-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (4a):



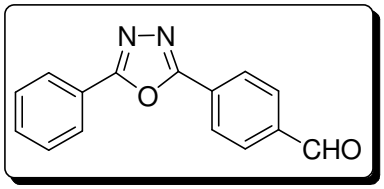
White solid; M.p. 151-152 °C (Lit.[3] 151-152 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.27 (m. 2H), 7.54-7.57 (m, 3H), 8.13-8.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.5, 116.7, 120.5, 124.0, 127.1, 129.28, 129.33, 129.4, 132.0, 163.7, 164.0, 164.8, 166.2.; IR (KBr): 3061, 2921, 1606, 1549, 1496, 1221, 1149, 1069, 841, 733, 703, 687 cm^{-1}. HRMS (*m/z*) (M+1) calcd for $C_{14}H_9N_2OF$: 241.0772, found 241.0770.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (5a):



White solid; M.p. 161-162 °C (Lit.[4] 162-163 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.53 (m, 5H), 8.06 (d, 2H, *J* = 8.0 Hz), 8.11 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.6, 123.9, 127.2, 128.4, 129.3, 129.7, 132.1, 138.2, 164.0, 164.9.; IR (KBr): 3061, 2920, 1605, 1550, 1478, 1406, 1086, 1074, 839, 730, 702, 687 cm^{-1}. HRMS (*m/z*) (M+1) calcd for $C_{14}H_9N_2OCl$: 257.0476, found: 257.0471.

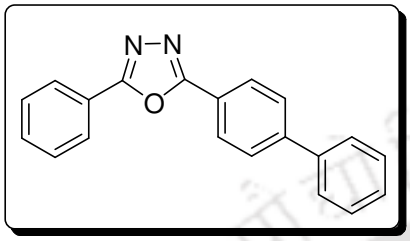
4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-benzaldehyde (6a):



White solid; M.p. 168-169 °C (lit.[5] 162.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.59 (m, 3H), 8.05 (d, 2H, *J* = 8.4 Hz), 8.15 (d, 2H, *J* = 8 Hz), 8.31 (d, 2H, *J* = 8 Hz), 10.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.6, 127.3, 127.6, 129.0, 129.4, 130.4, 132.3,

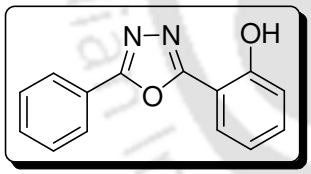
138.3, 163.8, 165.4, 191.5.; IR (KBr): 3060, 2925, 2853, 1703, 1547, 1446, 1271, 1204, 1075, 833, 729, 704, 685 cm^{-1}. HRMS (*m/z*) (M+1) calcd for $C_{15}H_{10}N_2O_2$: 251.0815, found: 251.0815.

2-Biphenyl-4-yl-5-phenyl-1,3,4-oxadiazole (7a):



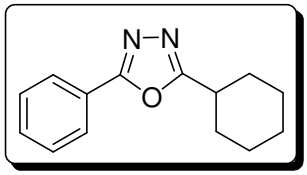
White solid; M.p. 164-166 ^oC (Lit.[6] 166-167 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 2H, *J* = 7.6 Hz), 7.49 (t, 2H, *J* = 16 Hz), 7.55-7.56 (m, 2H), 7.66 (d, 2H, *J* = 7.6 Hz), 7.77 (d, 2H, *J* = 8.4 Hz), 8.16-8.17 (m, 2H) 8.22 (d, 2H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.6, 123.9, 127.1, 127.4, 127.7, 128.2, 129.0, 129.1, 131.8, 139.7, 144.4, 164.5, 164.6.; IR (KBr): 3032, 2917, 1609, 1571, 1546, 1481, 1447, 1409, 1270, 1066, 854, 731, 710, 695cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{20}H_{14}N_2O$: 299.1179, found: 299.1182.

2-(5-Phenyl-1,3,4-oxadiazol-2-yl)-phenol (8a):



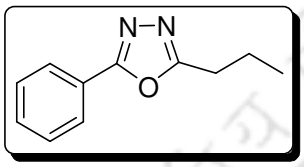
White solid; M.p. 185-187 ^oC (Lit.[7] 183-185 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.69 (m, 4H), 8.10-8.18 (m, 5H), 11.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.1, 123.1, 127.3, 129.4, 132.5, 134.7, 134.8, 142.2, 150.2, 157.5, 163.0, 163.7.; IR (KBr): 3152, 2917, 1535, 1487, 1447, 1377, 1248, 1232, 1066, 823, 749, 707, 683cm^{-1}. Anal calcd for $C_{14}H_{10}N_2O_2$ (238.07): C 70.58, H 4.23, N 11.76.; found C 70.59, H 4.25, N 11.75.

2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole (9a):



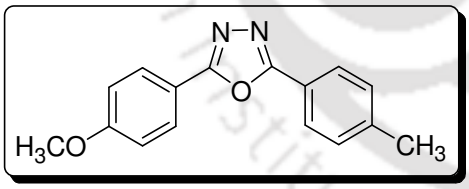
Brown solid; M.p. 107-109 °C (Lit.[8] 104 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.46 (m, 3H), 1.61-1.71 (m, 3H) 1.83-1.87 (m, 2H), 2.11-2.14 (m, 2H), 2.94-2.99 (m, 1H), 7.46-7.48 (m, 3H), 8.00-8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.6, 30.2, 35.2, 124.1, 126.7, 128.9, 131.4, 164.4, 170.0.; IR (KBr): 3058, 2923, 2855, 1565, 1552, 1485, 1448, 1021, 768, 709, 688cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{14}H_{16}N_2O$: 229.1335, found: 229.1340.

2-Phenyl-5-propyl-1,3,4-oxadiazole (10a):



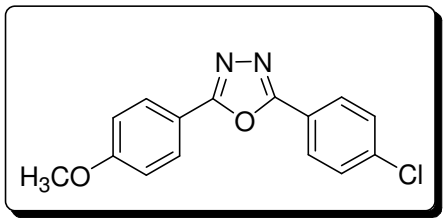
Yellow gummy, M.p. (Lit.[9] 75-76 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, 3H, *J* = 14.8 Hz), 1.83-1.89 (m, 2H), 2.89 (t, 2H, *J* = 15.2 Hz), 7.42-7.52 (m, 3H), 8.00-8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 20.2, 27.4, 126.9, 128.5, 129.1, 133.4, 164.8, 167.0.; IR (KBr): 2964, 2929, 2873, 1717, 1573, 1450, 1253, 1069, 1006, 776, 710, 691cm^{-1}. Anal calcd for $C_{11}H_{12}N_2O$ (188.09): C 70.19, H 6.43, N 14.88.; found C 70.22, H 6.44, N 14.86.

2-(4-Methoxyphenyl)-5-p-tolyl-1,3,4-oxadiazole (11a):



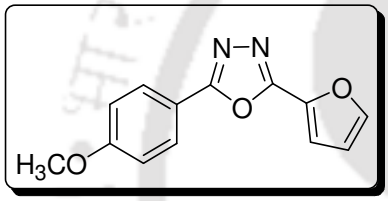
Yellow solid; M.p. 137-139 °C (Lit.[1] 137-138 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.87 (s, 3H), 7.01 (d, 2H, *J* = 11.6 Hz), 7.31 (d, 2H, *J* = 10.4 Hz), 7.98-8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 55.6, 114.7, 116.7, 121.5, 127.0, 128.8, 129.9, 142.2, 162.4, 164.5.; IR (KBr): 2928, 2829, 1612, 1492, 1304, 1254, 1170, 1033, 835, 822, 744 cm^{-1}. Anal calcd for $C_{16}H_{14}N_2O_2$ (266.11): C 72.16, H 5.30, N 10.52.; found C 72.24, H 5.33, N 10.47.

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (12a):



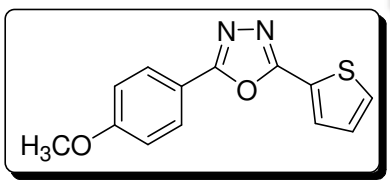
White solid; M.p. 164-165 °C (Lit.[4] 166-167 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.99 (d, 2H, *J* = 11.6 Hz), 7.46 (d, 2H, *J* = 11.2 Hz), 8.01 (d, 4H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 114.7, 116.3, 122.6, 128.2, 128.8, 129.5, 137.9, 162.6, 163.4, 164.8.; IR (KBr): 2929, 2829, 1611, 1495, 1479, 1305, 1252, 1170, 1089, 1028, 834, 743 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{15}H_{11}N_2O_2Cl$: 287.0582, found 287.0582.

2-Furan-2-yl-5-(4-methoxy-phenyl)-1,3,4-oxadiazole (13a):



Brown solid; M.p. 128-130 °C (Lit.[3] 129-130 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.58-6.59 (m, 1H) 6.99 (d, 2H, *J* = 8.8 Hz), 7.18 (d, 1H, *J* = 3.6 Hz), 7.63 (m, 1H), 8.03 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 112.2, 113.8, 114.5, 115.9, 128.7, 139.6, 145.6, 157.0, 162.5, 163.9.; IR (KBr): 3126, 3111, 2924, 1633, 1617, 1504, 1454, 1312, 1265, 1180, 1106, 1083, 1018, 832, 758, 740, 638 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{13}H_{10}N_2O_3$: 243.0764, found: 243.0767.

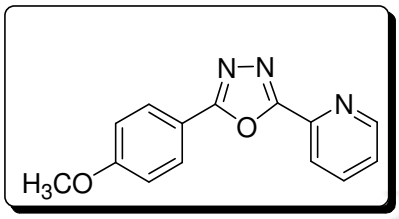
2-(4-Methoxy-phenyl)-5-thiophen-2-yl-1,3,4-oxadiazole (14a):



Brown solid; M.p. 136-137 °C (Lit.[10] 139-141 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.15-7.17 (m, 1H), 7.53 (d, 1H, *J* = 5.2 Hz), 7.78 (d, 1H, *J* = 3.6 Hz), 8.02 (d, 2H, *J* = 8.4 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 114.6, 116.2, 125.5, 128.2, 128.8, 129.6, 130.0, 160.5, 162.5, 164.1.; IR (KBr): 3102, 2939,

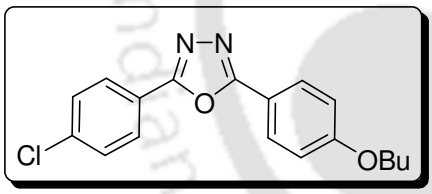
2829, 1611, 1592, 1497, 1421, 1251, 1186, 1026, 836, 739, 720 cm^{-1}. Anal calcd for $C_{13}H_{10}N_2O_2S$ (258.05): C 60.45, H 3.90, N 10.85.; found C 60.49, H 3.95, N 10.83.

2-[5-(4-Methoxy-phenyl)-1,3,4-oxadiazole-2-yl]-pyridine (15a):



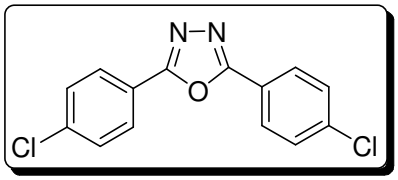
White solid; M.p. 155-156 ^oC (Lit.[11] 154-156 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 7.41-7.45 (m, 1H), 7.86 (t, 1H, *J* = 16 Hz), 8.12 (d, 2H, *J* = 8.8 Hz), 8.26 (d, 1H, *J* = 7.6 Hz), 8.77 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 114.5, 116.1, 123.1, 125.7, 129.1, 137.3, 143.7, 150.3, 162.6, 163.5, 165.6.; IR (KBr): 3053, 2926, 2847, 1614, 1586, 1498, 1458, 1268, 1086, 1020, 832, 741 cm^{-1}. Anal calcd for $C_{14}H_{11}N_3O_2$ (253.09): C 66.40, H 4.38, N 16.59.; found C 66.43, H 4.43, N 16.56.

2-(4-Butoxyphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (16a):



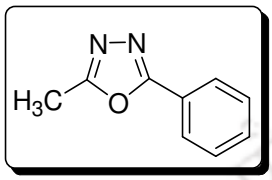
White solid; M.p. 132-133 ^oC (Lit.[2] 132-133 ^oC); ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, 3H, *J* = 9.6 Hz), 1.50-1.56 (m, 2H), 1.78-1.83 (m, 2H), 4.04 (t, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 11.6 Hz), 7.50 (d, 2H, *J* = 11.2 Hz), 8.03-8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.4, 31.3, 68.2, 115.2, 116.1, 122.8, 128.2, 128.9, 129.6, 137.9, 162.3, 163.4, 164.9.; IR (KBr): 3082, 2957, 2872, 1612, 1492, 1483, 1254, 1177, 1088, 1008, 839, 740 cm^{-1}. Anal calcd for $C_{18}H_{17}N_2O_2Cl$ (328.10): C 65.75, H 5.21, N 8.52.; found C 65.79, H 5.23, N 8.48.

2,5-Bis(4-chlorophenyl)-1,3,4-oxadiazole (17a):



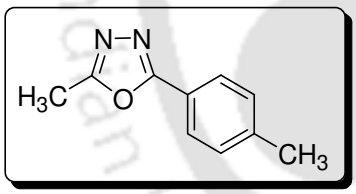
White solid; M.p. 250-251 ^{o}C (Lit.[2] 250-251 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, 4H, *J* = 11.2 Hz), 8.07 (d, 4H, *J* = 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4, 128.4, 129.7, 138.4, 164.2.; IR (KBr): 3084, 2956, .2924, 2853, 1605, 1478, 1461, 1261, 1091, 1073, 1011, 838, 738 cm^{-1}. Anal calcd for $C_{14}H_8N_2OCl_2$ (290.00): C 57.76, H 2.77, N 9.62.; found C 57.79, H 2.80, N 9.57.

2-Methyl-5-phenyl-1,3,4-oxadiazole (18a):



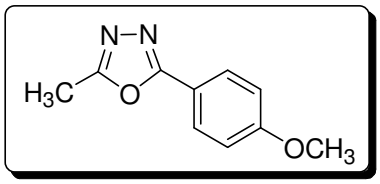
Brown solid; M.p. 60-61 ^{o}C (Lit.[12] 61-64 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.45-7.51 (m, 3H), 8.01 (d, 2H, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 123.9, 126.7, 129.0, 131.5, 163.7, 164.8.; IR (KBr): 2958, 2870, 1679, 1612, 1591, 1500, 1474, 1296, 1249, 1175, 1032, 836, 740, 701, 527 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_9H_8N_2O$: 161.0709, found: 161.0712.

2-Methyl-5-p-tolyl-1,3,4-oxadiazole (19a):



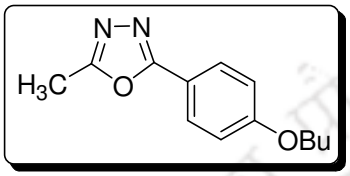
White solid; M.p.107-108 ^{o}C (Lit.[13] 134-135 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.60 (s, 3H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 21.8, 121.3, 126.8, 129.9, 142.2, 163.5, 165.2.; IR (KBr): 3038, 2924, 2851, 2340, 1593, 1577, 1498, 1348, 1247, 1088, 1032, 861, 829, 733, 700, 508 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{10}H_{10}N_2O$: 175.0866, found: 175.0864.

2-(4-Methoxy-phenyl)-5-methyl-1,3,4-oxadiazole (20a):



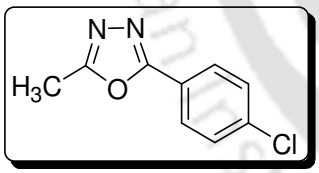
Yellow solid; M.p. 87-88 °C (Lit.[14] 88 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.77 (s, 3H), 6.89 (d, 2H, *J* = 8.8 Hz), 7.85 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 55.5, 114.5, 116.5, 128.5, 162.2, 163.2, 164.8.; IR (KBr): 3079, 2924, 2852, 1615, 1594, 1500, 1425, 1308, 1254, 1177, 1087, 1017, 959, 844, 837, 739, 699, 528 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_{10}H_{10}N_2O_2$: 191.0815, found: 191.0817.

2-(4-Butoxy-phenyl)-5-methyl-1,3,4-oxadiazole (21a):[15]



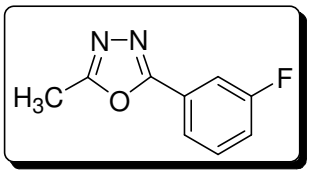
Brown solid; M.p. 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J* = 14.8 Hz), 1.47-1.53 (m, 2H), 1.77-1.80 (m, 2H), 2.58 (s, 3H), 4.00 (t, 2H, *J* = 13.2 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 7.93 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 13.9, 19.3, 31.2, 68.0, 114.9, 116.2, 128.5, 161.8, 163.1, 164.9.; IR (KBr): 3055, 2925, 2853, 1724, 1581, 1556, 1450, 1350, 1248, 1073, 960, 781, 709, 692 cm^{-1}. Anal calcd for $C_{14}H_{19}N_2O_2$ (232.12): C 67.22, H 6.94, N 12.06.; found C 67.28, H 6.96, N 12.01.

2-(4-Chloro-phenyl)-5-methyl-1,3,4-oxadiazole (22a):



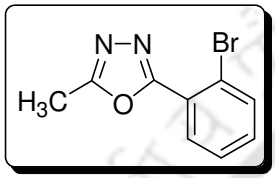
Brown solid; M.p. 96-98 °C (Lit.[16] 106-107 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H), 7.40 (d, 2H, *J* = 8.8 Hz), 7.89 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 122.5, 128.1, 129.5, 137.9, 164.0, 164.2.; IR (KBr): 3071, 2925, 2853, 1607, 1588, 1478, 1408, 1246, 1094, 1009, 848, 819, 730, 687, 507 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_9H_7N_2OCl$: 195.0320, found: 195.0322.

2-(3-Fluoro-phenyl)-5-methyl-1,3,4-oxadiazole (23a):



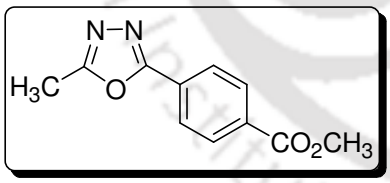
White solid; M.p.81-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.21-7.24 (m, 1H), 7.45-7.50 (m, 1H), 7.68-7.72 (m, 1H), 7.79-7.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 113.6, 113.8, 118.5, 118.7, 122.4, 122.5, 125.7, 125.8, 130.9, 131.0, 161.5, 163.8, 163.9, 164.0, 164.0.; IR (KBr): 2926, 1703, 1578, 1558, 1458, 1436, 1307, 1262, 1197, 1083, 867, 800, 726, 680 cm^{-1}. HRMS (m/z) (M+1) calcd for $C_9H_7N_2OF$: 179.0615, found: 179.0617.

2-(2-Bromo-phenyl)-5-methyl-1,3,4-oxadiazole (24a):[17]



Yellow solid; M.p. 80-81 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H), 7.35 (t, 1H, *J* = 16 Hz), 7.42 (t, 1H, *J* = 12 Hz), 7.71 (d, 1H, *J* = 8 Hz), 7.86 (d, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 121.6, 125.5, 127.7, 131.6, 132.5, 134.6, 163.9, 164.3.; IR (KBr): 3062, 2927, 1577, 1566, 1548, 1471, 1427, 1239, 1022, 773, 730, 697cm^{-1}. Anal calcd for $C_9H_7N_2OBr$ (237.97): C 45.22, H 2.95, N 11.72.; found C 45.25, H 2.99, N 11.67.

4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester (25a):[18]



White solid; M.p.162-163 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.90 (s, 3H), 8.04 (d, 2H, *J* = 8.8 Hz), 8.1 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 52.6, 126.8, 127.8, 130.4, 132.8, 164.3, 164.3, 166.2.; IR (KBr): 3064, 2962, 1717, 1571, 1430, 1413, 1275, 1240, 1106, 1014, 956, 868, 718, 482 cm^{-1}. Anal calcd for $C_{11}H_{10}N_2O_3$ (218.07): C 60.55, H 4.62, N 12.84.; found C 60.57, H 4.66, N 12.81.

References of compound's literature melting point:

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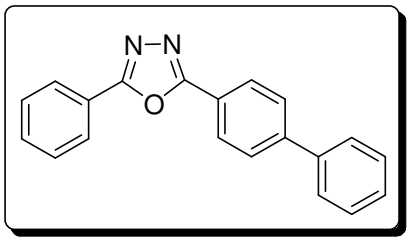
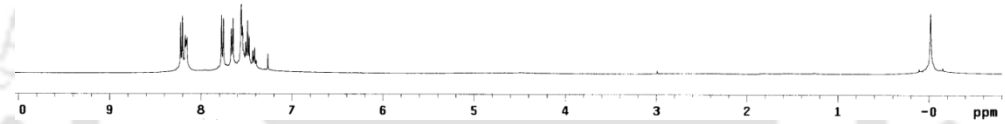
V.7. Selected Spectra

2-Biphenyl-4-yl-5-phenyl-1,3,4-oxadiazole (7a): ^{1}H NMR (400 MHz, $CDCl_3$)

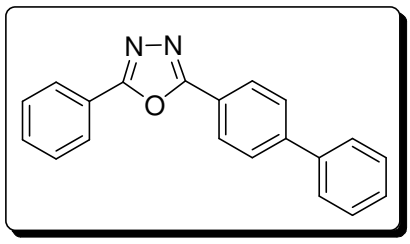
SAMPLE		SPECIAL	
date	Jan 27 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	6389.8	pw90	19.700
at	1.998	alfa	20.000
np	25528	FLAGS	
fb	not used	il	n
bs	4	in	n
d1	1.000	dp	y
nt	32	hs	nn
ct	32	PROCESSING	
TRANSMITTER		lb	0.10
tn	H1	fn	65536
sfrq	399.853	DISPLAY	
tof	362.8	sp	-321.6
tpwr	57	wp	4397.8
pw	9.850	rfl	791.5
DECOUPLER		rfp	0
dn	C13	rp	110.5
dof	0	lp	-89.8
dm	nnn	PLOT	
dmm	c	wc	250
dpwr	50	sc	0
dmf	15900	vs	134
		th	20
		nm	cdc ph

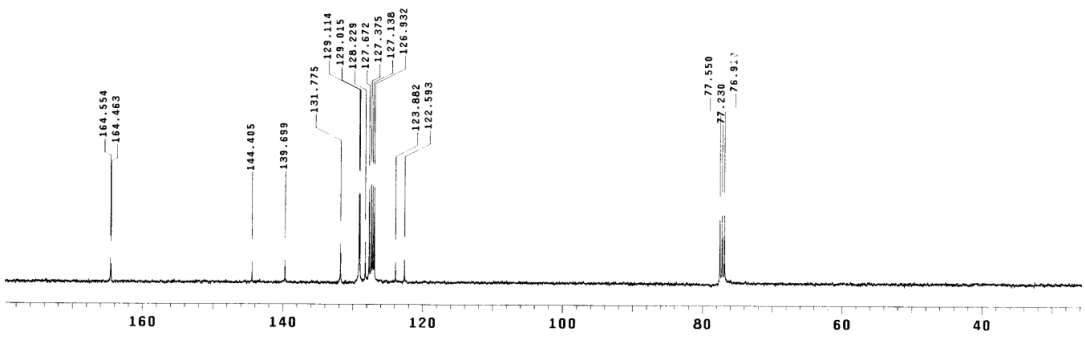




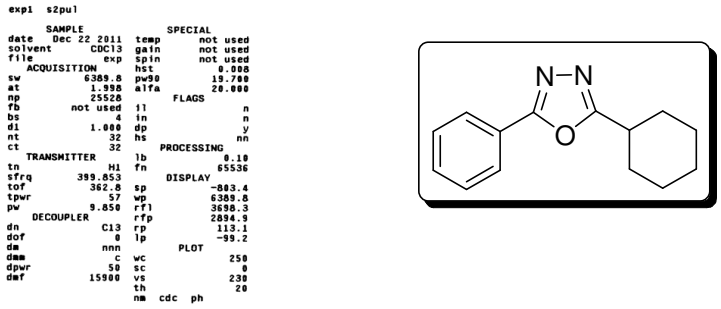
2-Biphenyl-4-yl-5-phenyl-1,3,4-oxadiazole (7a): ^{13}C NMR (100 MHz, $CDCl_3$)

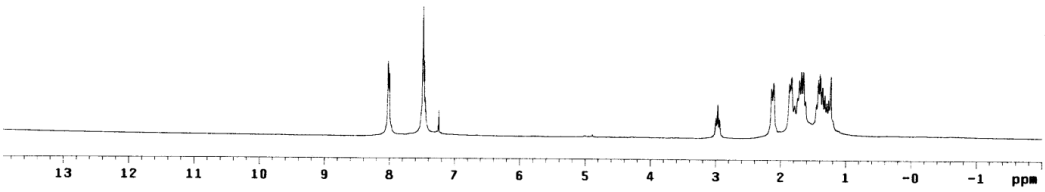
SAMPLE		SPECIAL	
date	Jan 27 2012	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	25125.6	pw90	18.600
at	1.195	alfa	20.000
np	60270	FLAGS	
fb	13800	il	n
bs	10	in	n
d1	1.000	dp	y
nt	10000	hs	nn
ct	940	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	65536
sfrq	100.554	DISPLAY	
tof	1536.3	sp	1944.2
tpwr	61	wp	16111.9
pw	9.300	rfl	9287.4
DECOUPLER		rfp	7764.9
dn	H1	rp	-79.4
dof	0	lp	-304.2
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	42	sc	0
dmf	8900	vs	22
		th	2
		nm	no ph



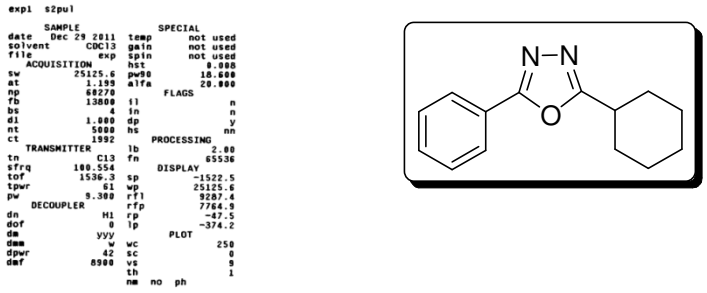


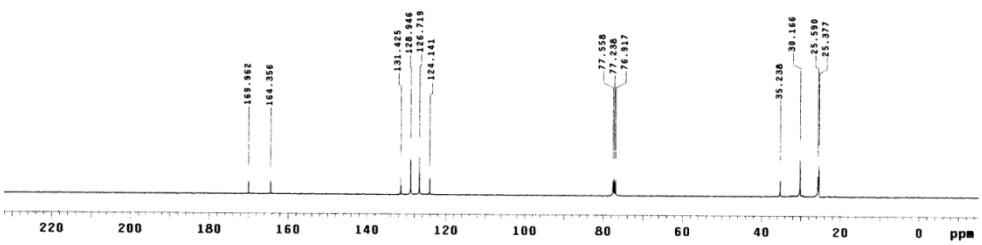
2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole (9a): ^{1}H NMR (400 MHz, $CDCl_3$)



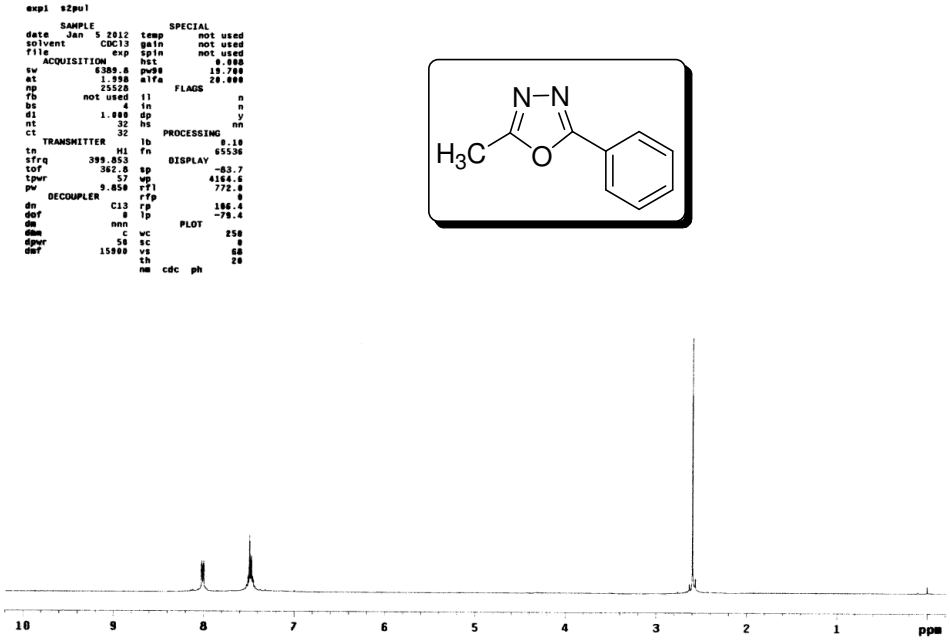


2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole (9a): ^{13}C NMR (100 MHz, $CDCl_3$)

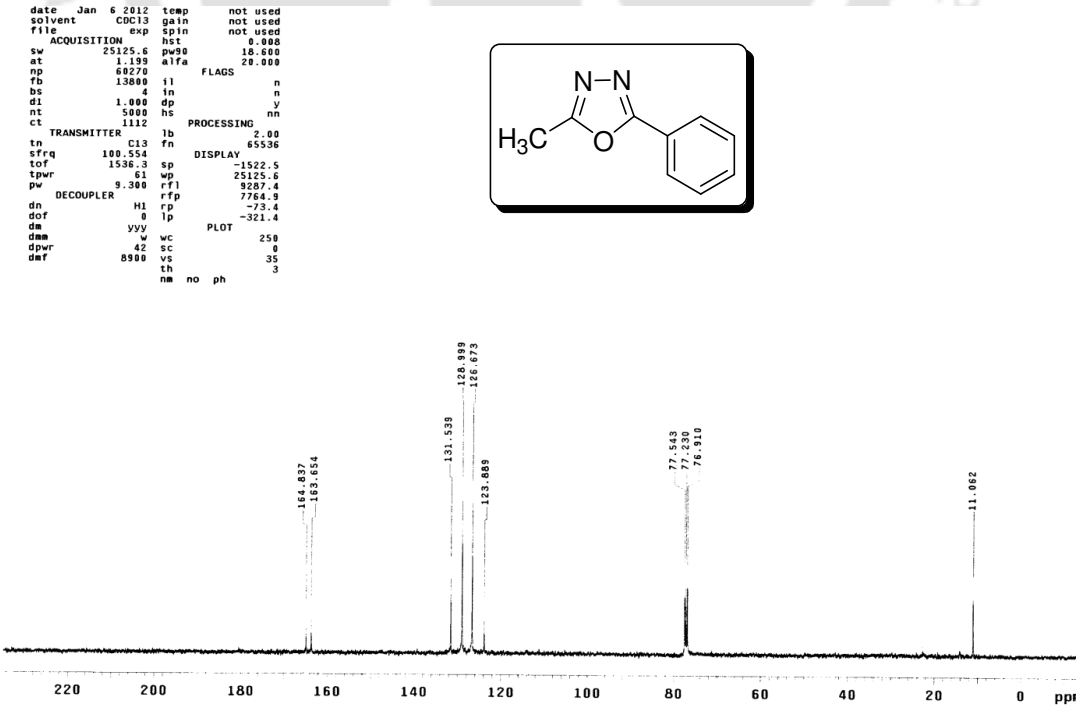




2-Methyl-5-phenyl-1,3,4-oxadiazole (18a): ^{1}H NMR (400 MHz, $CDCl_3$)



2-Methyl-5-phenyl-1,3,4-oxadiazole (18a): ^{13}C NMR (100 MHz, $CDCl_3$)



List of Publications:

(1) "Easy Access to Benzylic Esters Directly From Alkylbenzenes under Metal Free Conditions" **Majji, G.**; Guin, S.; Gogoi, A.; Rout, S. K.; Patel, B. K. *Chem.Commun*. 2013, *49*, 3031.

(2) "Iodine–Catalyzed Oxidative Cyclization of Acylhydrazones to 2,5-Substituted 1,3,4-Oxadiazoles" **Majji, G.**; Rout, S. K.; Guin, S.; Gogoi, A.; Patel, B. K. *RSC Adv.* 2014, *4*, 5357.

(3) "Cyclic Ethers to Esters and Monoesters to *bis*-Esters with Unconventional Coupling Partners under Metal Free Conditions *via* sp^3 C–H Functionalization" **Majji, G.**; Guin, S.; Rout, S. K.; Behera, A.; Patel, B. K. *Chem.Commun*. 2014, *50*, 12193.

(4) "Generation of *bis*-Acyl Ketals from Esters and Benzyl Amines under Oxidative Conditions" **Majji, G.**; Rajamanickam, S.; Khatun, N.; Santra, S. K.; Patel, B. K. *J. Org. Chem.* 2015, *80*, 3440.

(5) "Copper Catalyzed Cascade Synthesis of Imidazolidine-benzothiazole and Imidazolidine-tetrazole Hybrid Heterocycles from *bis*-Thioureas *via* Desulfurization Strategy" **Majji, G.**; Sahoo, S. K.; Khatun, N.; Patel, B. K. (*Manuscript ID: ejoc.201501096, Accepted*).

(6) "A Cu-Catalyzed Synthesis of Substituted 3-Methyleneisoindolin-1-one" Gogoi, A.; Guin, S.; Rout, S. K.; **Majji, G.**; Patel, B. K. *RSC Adv.* 2014, *4*, 59902.

(7) "Formation of Imidazolidinebenzothiazole–Cu(II) Complexes *via* a Copper Mediated Room Temperature C–H Activation of Imidazolidinecarbothiamides" Sahoo, S. K.; Jena, H. S.; **Majji, G.** ; Patel, B. K. *Synthesis* 2014, *46*, 1886.

(8) "Terminal Aryl Alkenes and Alkynes as Arylcarboxy Surrogates Towards *o*-Benzoxylation of 2-Phenylpyridine Catalyzed by Copper" Rout, S. K.; Guin, S.; Gogoi, A.; **Majji, G.**; Patel, B. K. *Org. Lett.* 2014, *16*, 1614.

(9) "A One-Pot Strategy for the Synthesis of 2-Aminobenzothiazole in Water by Copper Catalysis" Khatun, N.; Jamir, L.; **Majji, G.**; Patel, B. K. *RSC Adv.*, 2012, *2*, 11557.

(10) "It is 'Thiazolidine-2,4-dione' and not Thiohydantoins as the Reaction Product of Monosubstituted Thioureas and Chloroacetylchloride" Yella, R.; Singh, R. K.; **Majji, G.**; Patel, B. K. *Journal of Sulfur Chemistry* 2012, *33*, 43.

(11) "Bu_4NI Catalyzed C–N Bond Formation via Cross Dehydrogenative Coupling of Aryl Ethers (Csp^3–H) and Tetrazoles (N–H)" Rajamanickam, S.; **Majji, G.**; Santra, S. K.; Patel, B. K. (*Manuscript under Communication*).

List of Conference:

Oral Presentations:

- 2015: ChemConvene-2015, IIT Guwahati, India. (**Won Best Oral Presentation Award**)
- 2013: IX J-NOST Conference, IISER Bhopal, India.

Poster Presentations:

- 2014: National Symposium on Transcending Frontiers in Organic Chemistry, NIIST, Thiruvananthapuram, India.
- 2014: 8^{th} Mid-Year CRSI National Symposium in Chemistry, NEIST, Jorhat, India.

Online Quiz:

- 2013: Reaxys Green Chemistry Online Quiz 2013 which is being run in all the Asia-Pacific Countries (**Won FIRST PRIZE in Stage 2)**