Transition Metal Catalyzed Formation of C–C and C–O Bonds: A Substrate Based C–H Functionalization Approach

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
Parents and Brother**

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. This thesis has been submitted by me to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy.

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. I further declare that this work has not been submitted anywhere else for any degree, diploma, associateship or membership etc. of any Institute or University to the best of my knowledge.

October, 2015
IIT Guwahati.

Arghya Banerjee

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Arghya Banerjee has been working under my supervision since July, 2010 as a regular registered Ph. D. student. His thesis entitled "**Transition Metal Catalyzed Formation of C–C and C–O Bonds: A Substrate Based C–H Functionalization Approach**" is an authentic reord 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
IIT Guwahati

Acknowledgement

It is my great pleasure to take this opportunity to express my gratitude and thanks to all the people who have helped and encouraged me during my Ph.D. studies. Nothing in this thesis would have been possible without each and every one of you. Thank you!

First and foremost, I want to express my deepest respect and most sincere gratitude to my supervisor, Prof. Bhisma K. Patel, for offering me the great opportunity to be his Ph.D. student. His guidance, scientific ideas, enthusiasm and inspiration helped me a lot to explore the domain of work assembled in this thesis. His believing in me as a chemist gives me the confidence to go forward to further pursue my research career.

I would also like to express my heartiest thanks to the doctoral committee members, Prof. Biplab Mondal, Dr. Chandan Kumar Jana and Dr. Vikash Kumar Dubey for their timely evaluation of my work and valuable suggestions. I would like to thank all the staff members of Chemistry department especially Nilyotpal da, Diganta da, Santanu da, Aniruddha da for their friendly and coperative nature. My sincere thanks to the Central Instrument Facilty staffs for their guidance about various analytical instruments during this period. I also wish to thank Dr. Babulal das for his enormous help through these years.

I would obviously like to thank department of Chemistry, IIT Guwhati for providing such excellent instrument facilities and Council of Scientific and Industrial Research (CSIR), India for the financial support.

Next, I wish to express my warm and sincere thanks to my lab seniors, Hari da, Ramesh da, Santosh da, Ali di, Srimanta da and Saroj da for their enormous help and advice. I am also very lucky to have labmates like Nilufa, Anupal, Ganesh, Sourav, Wajid, Ahalya, Anju, Prakash, Suresh, Bilal, Prasenjit, Dipti, Joy da and Sutapa di. You all have been very friendly and cooperative under all circumstances. A special thanks to sourav as junior cum friend whose effective collaboration, helpful discussion and friendship have greatly helped me during my five years. I also had the opportunity to work with some enthusiastic M.Sc. students Sourav, Anupam, Aniket, Punarbasu and B.tech student like Deep.

I would also like to express my sincere thanks to my batchmates here in IIT Guwhati like Subrata, Pankaj, Palash, Sukhomoy. All my M.Sc. batchmates here in IIT Guwahati like Satyapriya, Tuhin, Pokhraj, Abhishek, Subrata, Manash, Shyamsundar, Koushik, Somdev, Pritam, Subhajit and many others. I will definitely miss and treasure their friend-ships. I also like to thank all my fantastic M.Sc. juniors here like Prasenjit, Julfikar, Sougata, Shilaj, Subhankar, Nilotpal, Manas, Rana, Ganesh, Utsav and many others. Thanks to Samir for giving his precious time to solve most of the crystals. I am greatly indebted to Satavisha for her endless support, fobearance and believing my ideas throughout these years. Her deep concern for my career is a precious gift to me.

I wish to thanks some of my extraordinary B.Sc. freinds in RKMV Belur like Suman, Mainak, Biplab, Amitabh, Debojyoti, Sourav, Soumya and many others. I can not forget those precious monents of three years in Belur. You all were really fabulous. I also like to thank some of my school friends like Sumanta, Koushik, Subhajit, Anirban and many more. I cannot remember all of those names but I can really miss those school days of my life a lot.

No words to express my feelings for my teachers like Debabrata sir, Jayanta sir, ABH sir, KR sir, AB sir, Subhas sir, Kakali di, Atanu sir, Rejabul sir and all other school and college teachers whose insightful ideas, extraordinary teaching really boost my interst in this field.

Finally, my deepest gratitude goes to my parents and brother for their unflagging love, support and blessings throughout my life. My deepest gratitude to my parents whose enormous sacrifices in evary stages of my life catalyses me to overcome all the hurdles to come upto this stage. I am also greatful to my relatives and neighbours for their love and affection. Many names are still missing whose contribution is worthy to mention.

Arghya Banerjee

Abstract

The contents of this thesis have been divided into six chapters based on the results of experimental works performed during the complete course of the research period. The first chapter of the thesis presents an outline on different aspects of C–H functionalization processes, its challenges and solutions to address these problems. All the other chapters mainly emphasize on the C–C and C–O bond formations *via* various transition metal catalyzed C–H functionalizations by means of strategies like directing group assisted C–H bond functionalization and cross dehydrogenative coupling (CDC).

Chapter II illustrates Pd-catalyzed regioselective *o*-hydroxylation and *o*-acetoxylation of 2-arylbenzothizole and 3,5-diarylisoxazole.

Chapter III describes *o*-aroylation strategies of various directing arenes such as 2-arylbenzothiazole, 2-arylbenzoxazole and 3,5-diarylisoxazole using aldehyde as the aroylating source in presence of Pd-catalyst.

Chapter IV demonstrates the use of ceric ammonium nitrate (CAN) as an efficient and mild oxidant for Pd(II)-catalyzed substrate directed decarboxylative *o*-aroylation of directing arenes.

Chapter V illustrates ruthenium catalyzed regiospecific C–H / O–H annulations of directing arenes *via* weak coordination.

Chapter VI discusses protocols for the regioselective cycloalkylation-peroxidation and cycloalkylation across C3-C4 conjugated double bond of 3-substituted coumarins. The use of Cu(I) / TBHP catalytic system provides C4 cycloalkylation-C3 peroxidation whereas the use of Fe(III) / DTBP system affords C3-cycloalkylation product exclusively.

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

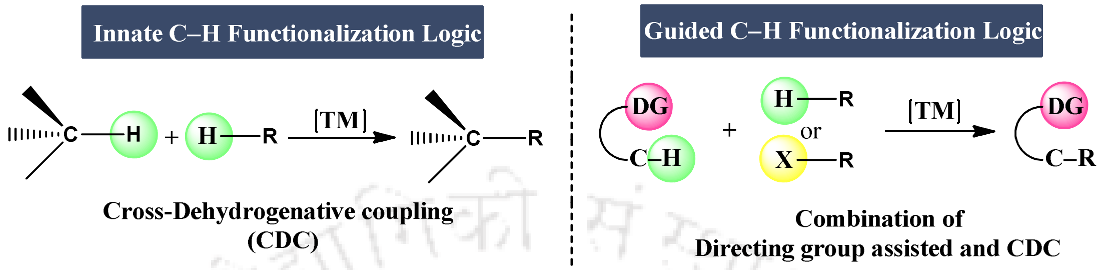
CHAPTER I. An Outline of Transition Metal Catalyzed C–H Functionalizations

This chapter gives an outline on the history of C–H activation, challenges, various strategies adopted in modern days to address these challenges, advantages over traditional cross-coupling reactions and their applications in organic synthesis.

The traditional coupling reactions, which is widely used in both industry and academia for the formation of carbon-carbon (C–C) and carbon-heteroatom (C–X) bonds, involve either the use of stiochiometric organometallic reagents such as Grignard reagent or organolithium reagents or halogenated starting materials as coupling partners. Due to substantial progress in these methods in the last few decades, these processes have been successfully applied for the synthesis of various commercially important products. However all these methods are now-a-days a major concerns to the synthetic chemists due to the use of prefunctionalized starting materials which is undesirable in terms of atom and step economic as well as environmental point of view. The best way to address this issue is to utilize unfunctionalized starting materials by the direct activation of C–H bonds.

The carbon-hydrogen bond is considered as the un-functional group. Its unique position in organic chemistry is well demonstrated 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 functionalize C–H bonds could be developed, it could potentially constitute the most broadly applicable and powerful class of transformations in organic synthesis. It would have the potential to revolutionize the conventional ideas of disconnections and can give access to the unknown territory of complex molecules which were earlier impossible *via* classical approaches.

In this perspective to broadening this radical aspect of organic synthesis, consistent and systematic strides have been made to develop C–H functionalization methods. Among various approaches developed, one such powerful strategy is the use of transition metal catalysts to functionalize the C–H bonds into C–C or C–X bonds. Two elegant approaches are employed in this context *viz.* transition metal catalyzed directed and non-directed process to achieve site selectivite C–H functionalization. (Scheme I.1). In this context our group has been involved in the development of new disconnection approach and generation of various functionalities by cleaving the inert C–H bonds.



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

CHAPTER II.

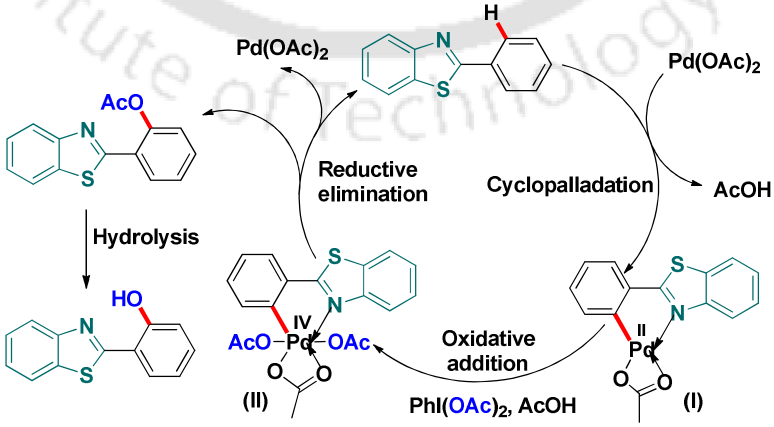
This chapter has been divided into two sections. Section A highlights Pd-catalyzed *o*-hydroxylation protocol of 2-arylbenzothiazole, whereas Section B describes the *o*-acetoxylation of 3,5-diarylisoxazole using Pd-catalyst.

SECTION IIA: Regioselective *ortho*-Hydroxylation of 2-Arylbenzothiazole *via* Substrate Directed C–H Activation

This section focuses on the Pd-catalyzed direct *ortho*-hydroxylation of 2-arylbenzothiazole using either DIB/AcOH or Oxone®/TFA combinations under air atmosphere. Direct and selective functionalization of inert carbon-hydrogen (C–H) bonds is one of the most versatile approaches for the construction of diverse complex molecules. In this context, particularly the Pd catalyzed C–H functionalizations have attracted much attention to construct diverse array of C–C or C–X (X = hetero atoms) bonds in the plethora of synthetic transformations. Such functionalization reactions are favored by the chelation of Pd catalyst to various *N* or *O* donor atoms containing substrates, which assist the cyclometallation step and thus the regioselective functionalizations.

Various directing group containing substrates have been well explored toward palladium catalyzed substrate-directed C–O bond formation in particular *o*-hydroxylation or *o*-acetoxylation. 2-Arylbenzoxazole or benzothiazole possessing *o*-chelating moiety could provide a similar ligand-directed cyclo-metallated intermediate whereby the metal can be selectively delivered to a proximal C–H bond. However, they have rarely being explored toward C–H functionalizations. There are only two instances where the 2-arylbenzoxazole moiety been used, one towards *o*-arylation and the other *o*-acetoxylation. Very recently benzothiazoles have been *o*-arylated *via* proximal C–H functionalization. Benzothiazoles are important heterocycle prevalent in number of pharmacophores which are reported to exhibit diverse biological activities. Hence, further derivatizing this important moiety would pave the path to the useful intermediates. With this objective we envisioned that the 2-arylbenzothiazoles in the presence of transition metal such as Pd would undergo C–H functionalizations at the proximal site to provide the desired functionality. Herein, we report our results on the Pd(II) catalyzed *o*-hydroxylation of various 2-arylbenzothiazoles.

To attain a suitable reaction condition for the synthesis of *o*-hydroxy benzothiazoles, various reaction parameters such as catalysts, oxidants and solvents were screened to achieve the maximum possible yield. After a series of experimentation the optimized reaction condition arrived was $Pd(OAc)_2$ (5 mol %), DIB (1 equiv) in AcOH solvent at 110 ^{o}C. This methodology was equally successful for substrates possessing electron-withdrawing as well as electron donating substituents present in the benzothiazole moiety as well as in the 2-aryl ring. However, electron donating substituents present in the 2-aryl ring give better yields in shorter reaction times compared to substrates bearing electron withdrawing groups. 2-Heteroarylbenzothiazoles having heterocycles such as pyridine, thiophene or furan were completely inert under the present reaction condition providing no hydroxylated product. Based on the observations, mechanistic investigations and literature reports a plausible mechanism was proposed for this transformation (Scheme IIA.1).



Scheme IIA.1. *Pd (II) Catalyzed o-hydroxylation of 2-phenylbenzothiazole*

In conclusion we have developed an efficient protocol to access the *o*-hydroxylated benzothiazoles *via* a Pd catalyzed C–H functionalization/C–O bond formation. Besides, the performance under ambient air and moisture, a broad substrate scope and wide array of functional group tolerance and exhibition of high levels of regioselectivity pertaining to the *meta*-substituted substrates are the remarkable features of this methodology.

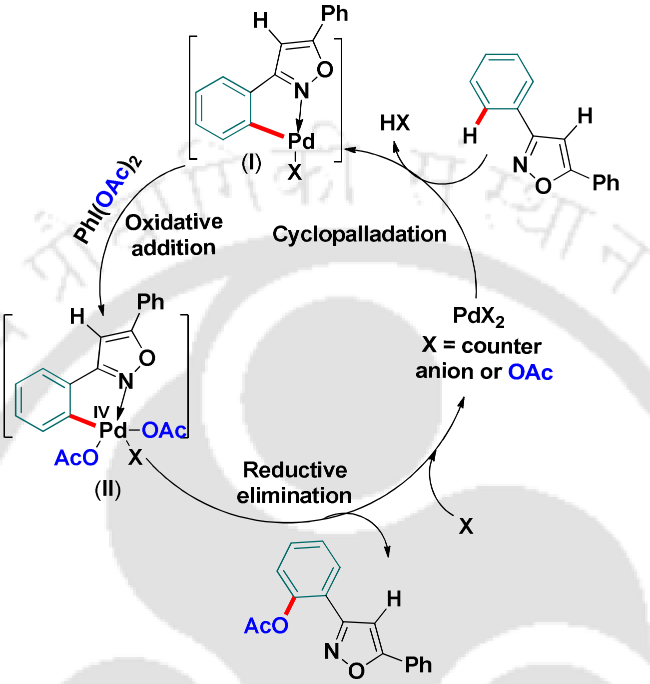
SECTION IIB: Palladium Catalyzed Regioselective Acetoxylation of 3,5-Diarylisoxazole *via ortho* C–H Functionalizations

This section demonstrates regioselective *o*-acetoxylation of another directing group 3,5-diarylisoxazole in presence of $Pd(OAc)_2/PhI(OAc)_2$.After successful *o*-hydroxylation of 2-arylbenzothiazole the search for suitable directing group continued for similar *ortho* C–O bond formation. We envisaged that 3,5-diarylisoxazole possessing both *N* and *O*-chelating atoms in a rigid framework may provide competitive cyclometallated intermediate either through *N* or *O* atoms by anchoring the metal selectively to one of the proximal *ortho* C–H bonds.

There is only one instance where 3,5-diarylisoxazole is *ortho*-arylated using phenylboronic acid as the arylating partner in the presence of stoichiometric Pd salt. Apart from this there is not a single report on catalytic *ortho* C–H functionalisation using this moiety. 3,5-Diarylisoxazole scaffold is an important pharmacophore having diverse array of biological activities. Thus, any further functionalization of this important moiety is likely to generate further interest. There are two *o*-hydrogens each proximal to *N* and *O* atom in 3,5-diarylisoxazole that can be activated (*o*-palladated). Further, functionalization of the isoxazolyl internal sp^2 C_4–H by a non-directing metallation path cannot be ruled out. Thus, it would be interesting to see whether the palladation would occur through –*N* donor *ortho*-site or –*O* donor *ortho*-site or at the C-4 position in 3,5-diarylisoxazoles. Herein we report a Pd-catalyzed *o*-acetoxylation of 3,5-diarylisoxazole using $Pd(OAc)_2$/DIB combination *via* its *N*-directed *ortho* C–H bond.

After rigorous screening of catalysts/oxidants/solvents, the best reaction condition was found to be 10 mol % of $Pd(OAc)_2$, 1.2 equiv of DIB in toluene : AcOH (1: 3) at 110 °C. This methodology was equally successful for substrates possessing electron-withdrawing as well as electron donating substituents in the 3-aryl ring of isoxazole moiety. However electron withdrawing group present in the 3-aryl ring of 3,5-

diarylisoxazole afforded lower yields of desired *o*-acetyoxylated product compared to its electron donating derivatives may be due to oxidative palladacycle. The *o*-acetoxylation (C–O bond formation) is expected to occur *via* a Pd(II)/ Pd(IV) catalytic cycle which is similar to that of 2-arylbenzothiazole (Scheme IIB.1).



***Scheme IIB.1**. Plausible mechanism for Pd (II) catalyzed o-acetoxylation*

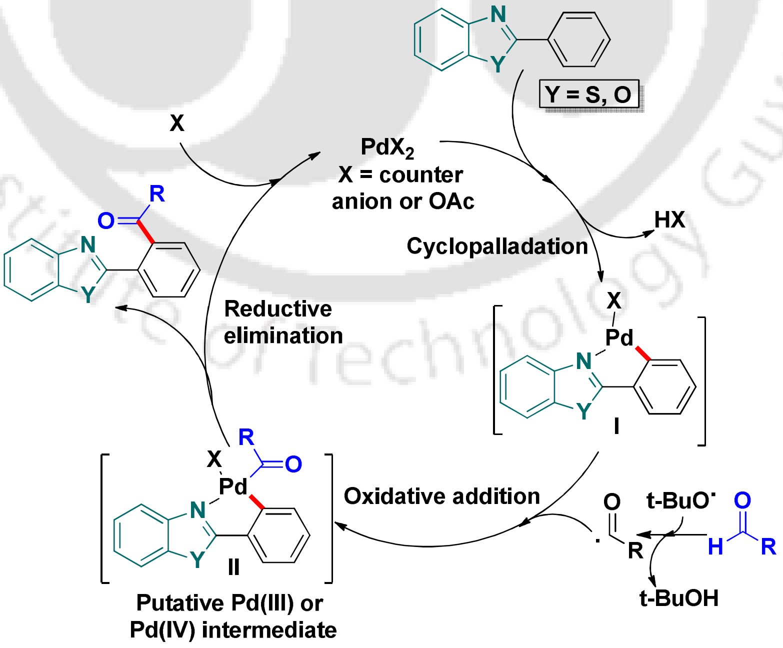
We have demonstrated here the first report of catalytic *o*-acetoxylation of 3,5-diarylisoxazole using Pd(II)/DIB combination. This protocol demonstrates the higher power of directed *o*-metallation over the non-directed metallation pathway *via* the higher acidic isoxazolyl sp^2 C$_4$-H.

CHAPTER III.

This chapter has been divided into two sections. Section A demonstrates Pd-catalyzed *o*-aroylation of 2-arylbenzothiazole and 2-arylbenzoxazole using aldehydes whereas section B describes similar *o*-aroylation of 3,5-diarylisoxazole using similar Pd(II)/TBHP combination.

SECTION IIIA: Palladium Catalyzed *ortho* Aroylation of 2-Arylbenzothiazoles and 2-Arylbenzoxazoles with Aldehydes

This section describes an efficient Pd-catalyzed protocol for the *ortho*-aroylation of 2-arylbenzothiazoles and 2-arylbenzoxazoles using aldehydes as the aroyl source and TBHP as the oxidant. A plethora of methods for *ortho*-acylation / aroylation have been recently reported using transition-metal-catalyzed oxidative C_{sp2}–H bond activation on substrates possessing *N*-donor or *O*-donor atoms. By using an aldehyde or benzyl alcohol (as a latent aldehyde) as an acylating equivalent, various directing groups such as 2-phenylpyridine, *O*-methyl oxime, acetanilide, anilide, and benzamide have been employed in this context. Besides the above strategies, acylation has also been achieved through a substrate-directed decarboxylation of α-keto carboxylic acids. More recently our group has developed a directing group assisted *ortho*-acylation through Pd(II)-catalyzed cross dehydrogenative coupling strategy with alkylbenzene as the synthetic equivalent of the aroyl moiety. The *ortho*-selective functionalization of 2-arylbenzoxazole or benzothiazole containing an *N*-donor atom as the directing group has been less explored. Neither of these substrates has been *ortho*-aroylated by any method. Thus, it would be interesting to develop a protocol for the *ortho*-aroylation of these two important scaffolds.



Scheme IIIA.1. *Proposed mechanism for o-aroylation*

Various reaction parameters such as catalysts, oxidants, solvents and temperature were screened to obtain the optimal conditions for this reaction and it was found that the use of 5 mol % of $Pd(OAc)_2$ and 1.5 equiv of TBHP in toluene solvent at 110 °C was the optimum conditions for our subsequent exploration to extend the scope of this transformation. The optimized conditions were then executed for *o*-aroylation of 2-arylbenzothiazole and 2-arylbenzoxazoles using various substituted aldehydes. 2-Arylbenzothiazole or benoxazoles bearing electron withdrawing groups in the 2-aryl ring provided comparably lower yields than its electron donating derivatives. On the basis of the results obtained from these control experiments as well as the literature reports, a plausible mechanism has been proposed that comprises of two paths (Scheme IIIA.1).

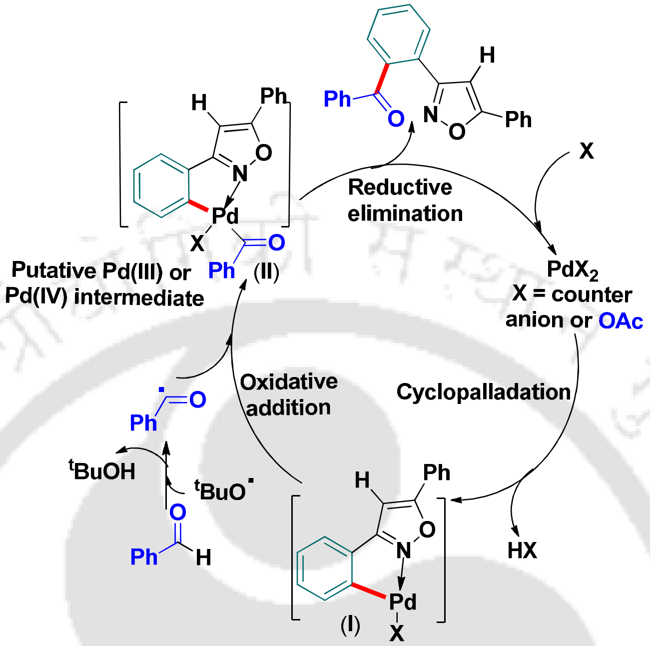
In summary, a simple and efficient protocol has been developed for the *ortho*-aroylation of 2-arylbenzoxazoles and 2-arylbenzothiazoles with aldehyde as the aroylating partner. The high regioselectivity and a wide range of functional group tolerance makes this protocol attractive for the synthesis of functionalized 2-arylbenzoxazoles and 2-arylbenzothiazoles.

SECTION IIIB: Palladium Catalyzed Regioselective Aroylation of 3,5-Diarylisoxazole *via ortho* C–H Functionalizations

This section demonstrates regioselective *o*-aroylation of 3,5-diarylisoxazole in presence of catalytic condition [$Pd(OAc)_2$/TBHP] similar to that of 2-arylbenzazoles. After successful *o*-aroylation of 2-arylbenzothiazole the analogous strategy was applied on 3,5-diarylisoxazole to see whether it can provide similar *o*-aroylation or not?. We envisaged that 3,5-diarylisoxazole possessing both *N* and *O*-chelating atoms in a rigid framework may provide competitive cyclometallated intermediate either through *N* or *O* atoms by anchoring the metal selectively to one of the proximal *ortho* C–H bonds.

Various reaction parameters such as catalysts, oxidants, solvents and temperature were screened to obtain the optimal conditions for this reaction and it was found that the use of 1.2 equiv of aldehydes, 10 mol % of $Pd(OAc)_2$, 1.2 equiv of TBHP in DCE solvent at 110 °C was the optimum reaction conditions. This optimized condition was then successful for substrates possessing electron-withdrawing as well as electron donating substituents in the aldehyde moeity and electron-donating substituents in the 3-aryl ring of 3,5-diarylisoxazole. However, 3,5-diarylisoxazole bearing electron withdrawing groups in the 3-aryl ring did not provided any desired *o*-aroylated product.

Mechanism is similar to that of *o*-aroylation of 2-arylbenzothiazoles and 2-arylbenzoxazoles (Scheme IIIB.1.).



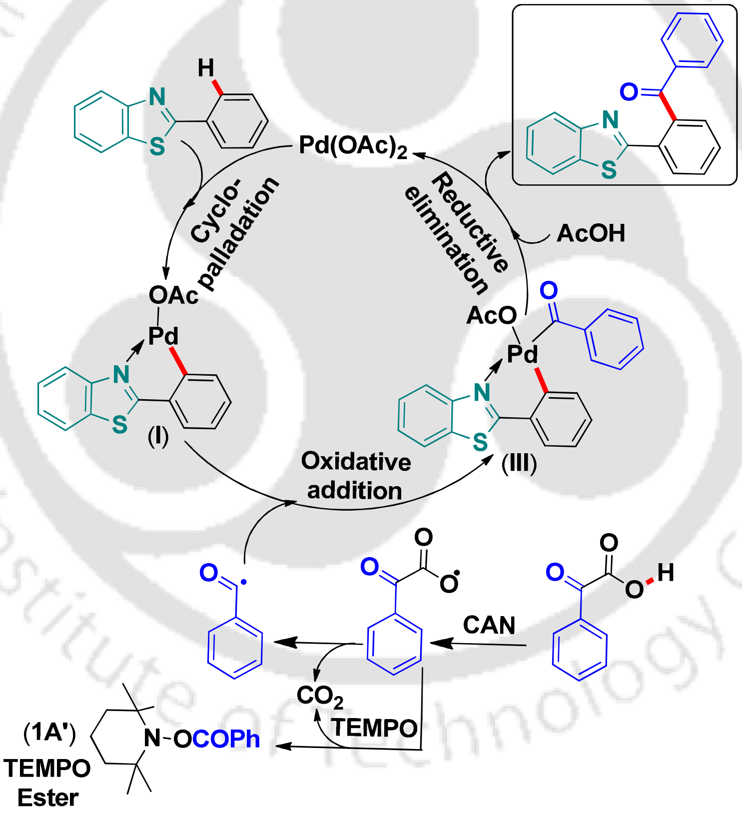
Scheme IIIB.1. *Proposed mechanism for o-aroylation*

CHAPTER IV.

Ceric Ammonium Nitrate (CAN): An Efficient Oxidant for Pd(II)-Catalyzed Substrate Directed Decarboxylative *o*-Aroylation

This chapter demonstrates the use of inexpensive ceric ammonium nitrate (CAN) as an efficient oxidant for the Pd-catalyzed substrate-directed decarboxylative *o*-aroylation of various directing arenes using α-keto acid *viz* aryl glyoxalic acid as the aroylating surrogate. Among the various *o*-aroylating surrogates *viz.* benzaldehyde, benzyl alcohol, alkylbenzene, benzyl amine, terminal alkene, diketone, benzoyl chloride for substrate-directed *o*-aroylation, the most striking *o*-aroylation strategy is through the decarboxylation of α-keto carboxylic acids. A number of substrate-directed *o*-aroylation protocols are reported using α-keto carboxylic acids where the oxidants used are either silver or persulfate ($S_2O_8^{2-}$) source or their combinations. Use of silver salt along with persulphate oxidant makes all these pathways expensive enough. Thus, it would be advantageous and appreciable if the same decarboxylation can be achieved via silver and persulphate free less expensive pathway.

Ceric ammonium nitrate (CAN) is an oxidizing agent used mainly in functional group oxidation *via* one-electron pathway. In spite of its immense applications as an oxidizing agent, its use as a terminal oxidant in transition metal catalyzed processes is completely unexplored. As the reduction potential of Ce(IV)/Ce(III) is + 1.61 V, which is in between Ag(I)/Ag(0) and $S_2O_8^{2-}$/ SO_4^{2-}, thus Ce(IV)/Ce(III) may be capable of forming an aroyl radical through decarboxylation of an α-keto acid. As 2-arylbenzothiazole has never been employed earlier for decarboxylative *o*-aroylation, this substrate was chosen as the model for decarboxylative *o*-aroylation using Pd(II)/CAN combination.



Scheme IV.1. *Proposed mechanism for decarboxylative o-aroylation*

Reaction parameters such as catalysts, oxidants and temperature were varied to obtain the optimal conditions for this reaction and it was found that the use of Pd(OAc)$_2$ (10 mol %), CAN (1.5 equiv) in DMF at 110 °C afforded the maximum yield of the desired ketone. The optimized conditions were then implemented in the coupling reactions between substituted 2-arylbenzothiazole and a set of phenylglyoxalic acids. All these coupling reactions proceeded smoothly providing their respective *o*-aroylated products in good to excellent yields. Furthermore, the same optimized reaction conditions were equally applicable to other directing groups such as 2-arylbenoxazole, 3,5-diarylisoxazole and 2,3-diarylquinoxaline. Taking cues from the above experimental observations a radical mechanism has been proposed for this Pd-catalyzed CAN mediated *o*-aroylation (Scheme IV.1).

In conclusion we have demonstrated the use of a cheap terminal oxidant CAN for Pd-catalyzed substrate directed decarboxylative *o*-aroylation of various directing arenes. A broad substrate scope and exhibition of high levels of regioselectivity pertaining to the *meta*-substituted substrates are the remarkable features of this methodology.

CHAPTER V.

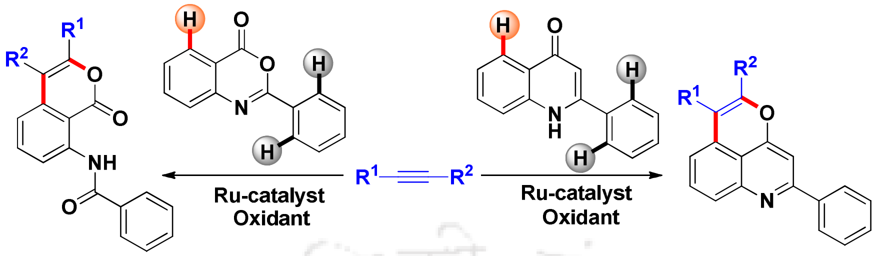
Ruthenium Catalyzed Regiospecific C–H / O–H Annulations of Directing Arene *via* Weak Coordination

This chapter deals with ruthenium(II) catalyzed oxidative C–H / O–H annulation strategies of two different directing arenes 2-arylquinolinone and 2-arylbenzoxazinone. A subtle change in directing substrate from 2-arylquinolinone to 2-arylbenoxazinone provided annulated products *via* the cleavage of oxygen-directed similar C–H bond unaffecting other directed C–H's.

Oxidative annulation reaction of arene / heteroarene C–H's with alkyne has proven to be a powerful method for the concise and step-economical synthesis of bioactive complex polycyclic molecules. In this context the lower cost of ruthenium catalysts as compared to palladium or rhodium catalyst makes these ruthenium-catalyzed annulations as an attractive choice.

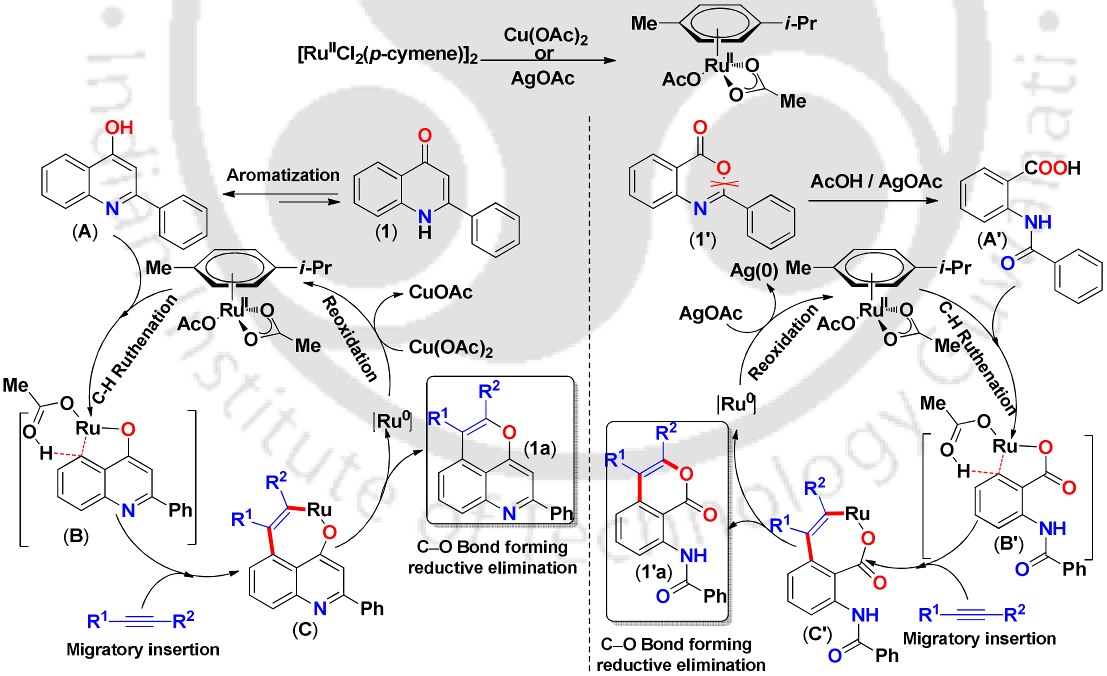
Achieving the preferential selectivity in the C–H functionalization reactions where substrate contains several different types of reactive C–H's is a challenging task. With the explosive growth of this catalytic C–H functionalization in the last decade, catalyst-controlled divergent C–H functionalizations of distinct C–H bonds are reported whereas the substrate-controlled selective C–H functioanlization *via* similar C–H cleavage of different directing arenes is unfamiliar. Herein we report a directing group dependent *o*-selective C–H / O–H annulations where the use of either 2-arylquinolinone or 2-

arylbenoxazinone with internal alkynes provided the anuulated polycycles *via* similar C–H / O–H bond cleavages (Scheme V.1).



Scheme V.1. *Analogous regioselectivity for C–H / O–H annulations*

Rigorous optimizations were carried out to establish suitable reaction conditions for both these transformations. The reaction between 2-arylquinolinone (1 equiv) with diphenyl acetylene (1 equiv) provided optimum yield of desired annulated product when 2.0 mol % of [Ru(*p*-cymene)Cl_2]$_2$, 1.2 equiv of oxidant $Cu(OAc)_2$ was used in DCE solvent at 110 °C. Annulation of 2-arylbenzoxazinone (1 equiv) with diphenyl acetylene (1 equiv) was found to optimum using 2.0 mol % of [Ru(*p*-cymene)Cl_2]$_2$, 1.2 equiv of AgOAc in AcOH at 110 °C.



Scheme V.2. *Proposed mechanisms for oxidative C–H/O–H annulations*

Having established optimal reaction conditions, these oxidative annulations of internal alkynes were then implemented for the reaction between various alkynes with a series of substituted arylquinolinone as well as arylbenzoxazinone derivatives. Both these methodology were applicable to a diverse range of substituted arylquinolinone as well as arylbenzoxazinone and alkynes irrespective of the nature of their substituents present in any ring; providing good to excellent yields of corresponding annulated products. Based on the extensive cross-over experiments performed, plausible mechanisms have been proposed for both these strategies (Scheme V.2).

In conclusion, we have developed strategies for ruthenium-catalyzed regioselective annulations of 2-arylquinolinone / 2-arylbenzoxazinone with internal alkynes *via* the C–H/O–H bond cleavage with a diverse substrates scope.

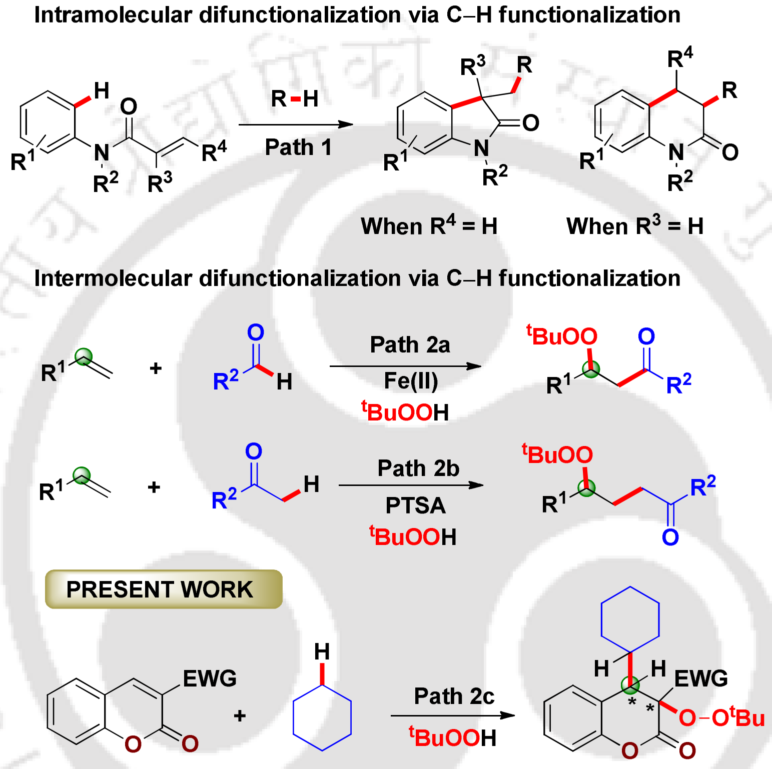
CHAPTER VI.

This chapter has been divided into two sections. Section A describes a copper (I) promoted C-4 cycloalkylation-C-3 peroxidation strategy across the conjugated double bond of 3-substituted coumarin using cycloalkanes and oxidant *tert*-butyl hydroperoxide (TBHP) whereas Section B describes iron (III) catalyzed C-3 cycloalkylation / benzylation of 3-substituted coumarin using cycloalkanes or alkylbenzenes and oxidant di-*tert*-butylperoxide (DTBP).

SECTION VIA: Copper(I) Promoted Cycloalkylation-Peroxidation of Unactivated Alkenes *via* sp^3 C–H Functionalization

This section focuses on a copper (I) promoted cycloalkylation-peroxidation strategy *via* a three-component reaction involving cycloalkanes, *tert*-butyl hydroperoxide (TBHP) and 3-substituted coumarin. Difunctionalization of alkene is an attractive approach to build molecular complexity in a single operation. Of late a number of intramolecular hetero difunctionalization of alkenes have been reported, where the direct CDC of sp^3 and sp^2 C–H bonds has been employed for the construction of various heterocycles *via* tandem processes (path 1, VIA.1). Previous examples of intermolecular classical difunctionalization include palladium, nickel or ruthenium catalyzed carbohalogenation, dihydroxylation, oxyarylation, oxyamination, aminofluorination, aminocyanation and hydroalkylation reactions.

However, intermolecular difunctionalization of olefins has rarely been explored following C–H functionalization strategy *viz.* Fe(II)-catalyzed carbonylation-peroxidation of olefins was was reported *via* a sp^2 C–H functionalisation using aldehydes and *tert*-butyl hydroperoxide (TBHP) (path 2a, VIA.1), acid catalyzed oxidative keto-peroxidation of olefins using ketones and TBHP (path 2b, VIA.1). In this context an obvious query arises as to whether unreactive cycloalkane can similarly be used as an alkyl source towards alkene difunctionalizations. To execute the envisaged strategy, 3-acetylcoumarin an important pharmacophoric unit was chosen as the test substrate as it contains internally conjugated C3-C4 double bond (Scheme VIA.1).

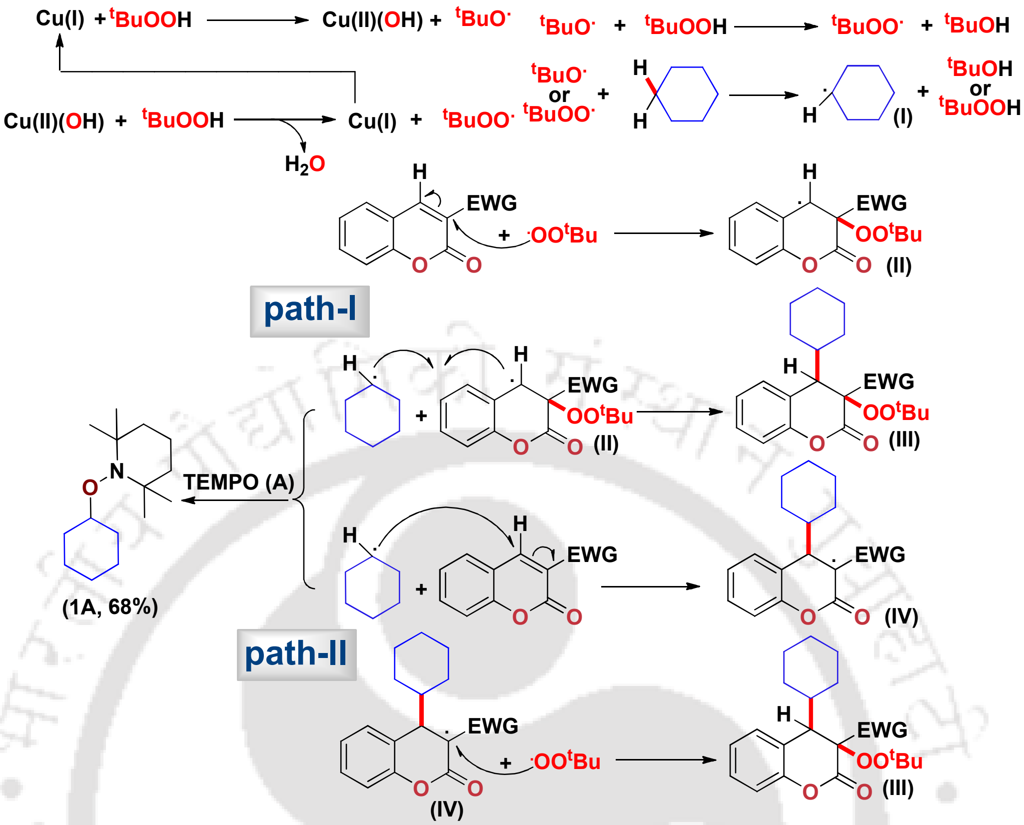

Intramolecular difunctionalization via C–H functionalization

Intermolecular difunctionalization via C–H functionalization

PRESENT WORK

Scheme VIA.1. Strategies for difunctionalization via C–H functionalization

Reaction parameters such as catalysts, oxidants and temperature were varied to obtain the optimal conditions for this reaction. It was found that the use of 40 mol % of Cu_2O, ^{t}BuOOH (4.0 equiv) as oxidant in cyclohexane solvent-cum-reagent at 110 °C was the best conditions affording desired C4 cycloalkylation-C3 peroxy product in optimum yield. The optimized conditions were then implemented for the difunctionalization of various 3-substituted coumarins using cycloalkanes and oxidant TBHP. All these reactions proceeded smoothly providing their respective cycloalkyl α-peroxy products in good to excellent yields. Based on the extensive cross-over experiments performed, a plausible mechanism has been proposed for this process (Scheme VIA.2).

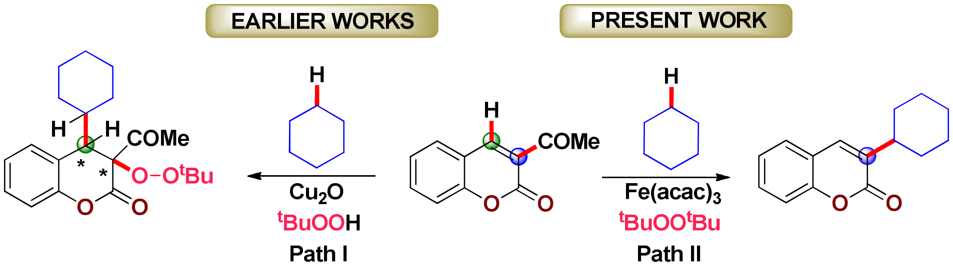


Scheme VIA.2. Proposed mechanism for cycloalkylation-peroxidation

In conclusion, the present protocol demonstrates three component Cu(I) promoted reaction where the components are coumarin, TBHP and cycloalkane as reactant-cum-solvent. C–O and C–C Bonds are installed in this process *via* sp^3 C–H fucntionalization with concurrent generation of two stereocentres. These tertiary α-peroxy esters so generated have several structural analogies to well-known antimalarial drugs artemisinin and cardamom peroxide.

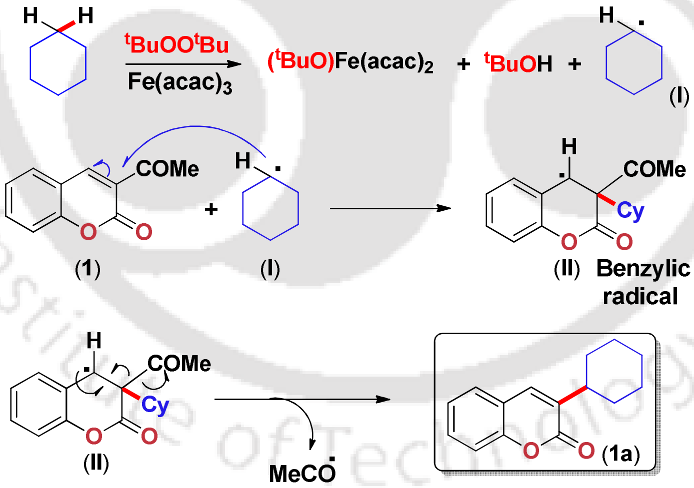
SECTION VIB: Iron(III) Catalyzed C-3 Alkylation of Coumarins *via* sp^3 C–H Bond

This section deals with an exclusive C-3 benzylation / cycloalkylation of 3-substituted coumrins using cycloalkanes or alkylbenzenes in the presence of di-*tert*-butylperoxide (DTBP) and Fe^{III} catalyst. A differential selectivity is observed when Fe^{III} / DTBP combination was used in lieu of Cu^{I} / TBHP. Under this Fe^{III} / DTBP combination, an exclusive C-3 cycloalkylation was observed at the C-3 site of 3-acetyl coumarin with the expulsion of acetyl group (–COMe) (Scheme VIB.1).



Scheme VIB.1. *C-3 vs C-4 cycloalkylation of 3-acetyl coumarin*

Rigorous optimizations were carried out to establish the suitable conditions for this C-3 cycloalkylation (opposite selectivity). It was found that the optimum yield was obtained between the reaction of 3-acetylcoumarin and cyclohexane by using 5 mol% of $Fe(acac)_3$, 4.0 equiv of DTBP and chlorobenzene as solvent at 110 °C. The optimized conditions were then implemented for the C-3 cycloalkylation of various 3-substituted coumarins using cycloalkanes in presence of Fe(III)/DTBP combination. The use of alkylbenzene in lieu of cycloalkane provided the C-3 benzylated coumarin as exclusive product when reacted under optimized reaction conditions. Based on the extensive cross-over experiments performed, a plausible mechanism has been proposed for this process (Scheme VIB.2).



Scheme VIB.2. *Plausible mechanism for C-3 cycloalkylation*

In conclusion, we have developed the first site selective C-3 cycloalkylation / benzylation of 3-substitued coumarins under cat. Fe(III) / DTBP condition. This mono-functionalization is taking place at the expense of an existing C–C bond along with the generation of new C–C bond at C3.

Contents

Chapter IIA. Regioselective *ortho*-Hydroxylation of 2-Arylbenzothiazole *via* Substrate Directed C–H Activation

Chapter IIB. Palladium Catalyzed Regioselective Acetoxylation of 3,5-Diarylisoxazole *via* *o*-C–H Functionalization

Chapter VIA. Copper(I) Promoted Cycloalkylation-Peroxidation of Unactivated Alkenes *via* sp^3 C–H Functionalization

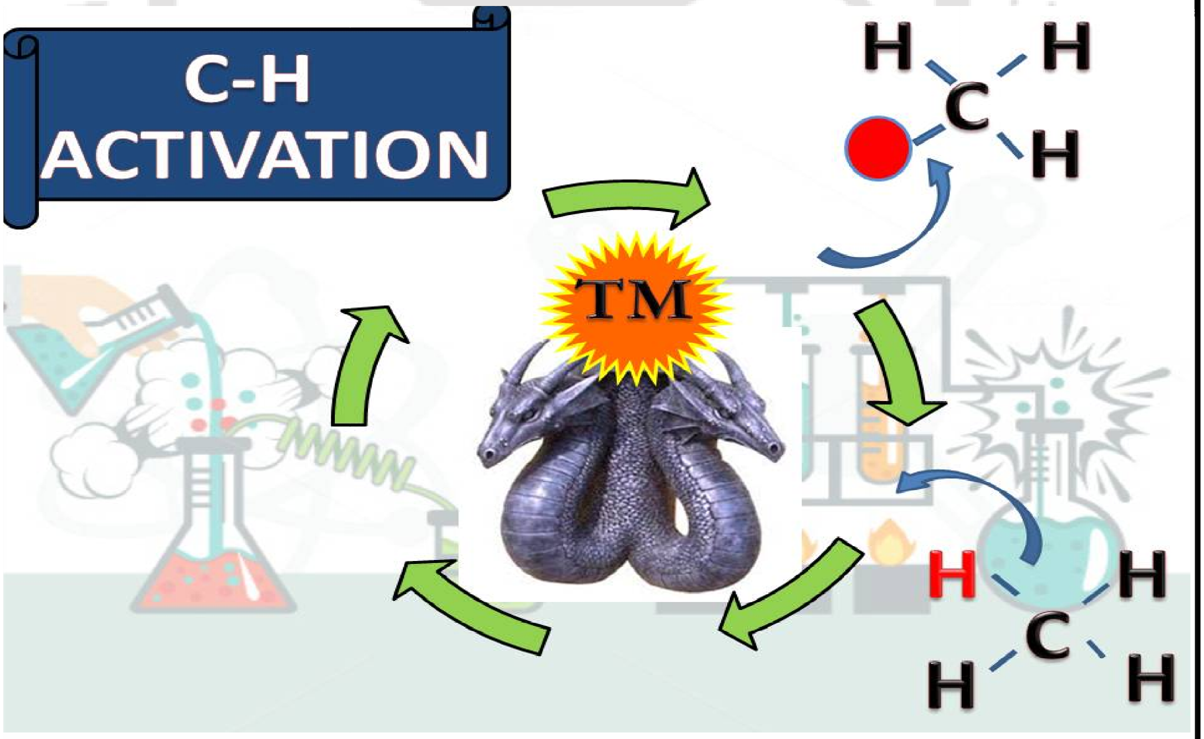
Chapter VIB. Iron(III) Catalyzed C-3 Alkylation of Coumarins *via* sp^3 C–H Functionalization

ABBREVIATIONS

AcOH	acetic acid
AIBN	azobisisobutylnitrile
$AgSbF_6$	silver hexafluoroantimonate (V)
CCDC	cambridge crystallographic data centre
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIB	diacetoxy iodobenzene
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DTBP	di-*tert*-butyl peroxide
ESI-MS	electrospray ionisation mass spectrometry
EWG	electron withdrawing group
HRMS	high resolution mass spectrometry
IR	infrared
K_2HPO_4	dipotassium phosphate
$K_2S_2O_8$	potasium persulphate
LED	light emitting diode
mp	melting point
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMS	trimethylsilyl
TLC	thin layer chromatography
XRD	x-ray diffraction

Chapter I

An Outline of Transition Metal Catalyzed C–H Functionalizations



CHAPTER I

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

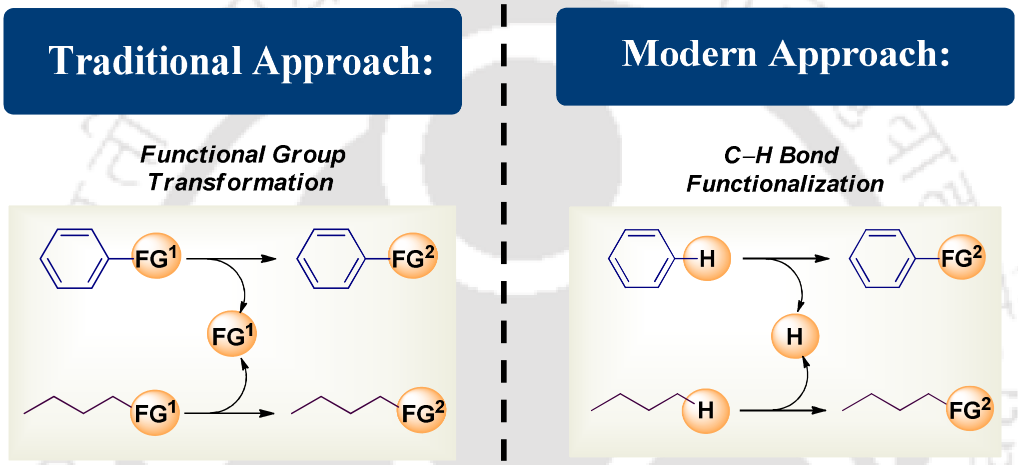
I.1. Introduction

Over the past two decades the extensive use of cross-coupling strategy in both industry and academia has greatly improved the carbon-carbon and carbon-heteroatom bond forming processes.[1] Traditional coupling reactions involve either the use of stoichiometric organometallic reagents, or the transition metal catalyzed coupling of both prefunctionalized components. Recent progress in cross-coupling strategies has been enormous, allowing them to be applied in the synthesis of commercially important products.[2] Despite of tremendous advances, these efficient and selective methodologies suffer from significant drawbacks. The two coupling components introduced in this process must be independently preactivated through halogenation or metallation, thus lengthening the synthetic route and invariably resulting stoichiometric chemical waste in the overall process. The best way to address this issue is to utilize un-functionalized coupling components by the direct activation of carbon-hydrogen bonds[3] which would increase the efficiency of chemical process by reducing the number of synthetic steps and also the chemical wastes.

The carbon-hydrogen (C–H) bond is regarded simply as the absence of any functional group. C–H Bonds are one of nature's most ubiquitous chemical bonds and there is tremendous synthetic potential hidden within them. If their dormant reactivity can be exploited i.e. if this C–H bonds could be selectively functionalized, it will constitute the most broadly applicable and powerful class of transformations in organic synthesis. In accordance of the basic principles of retrosynthetic analysis, C–H functionalization can drastically shorten possible routes to a given synthetic target by providing unprecedented disconnections in both early and late stages.

I.2. Comparison Between Traditional and Modern Approach

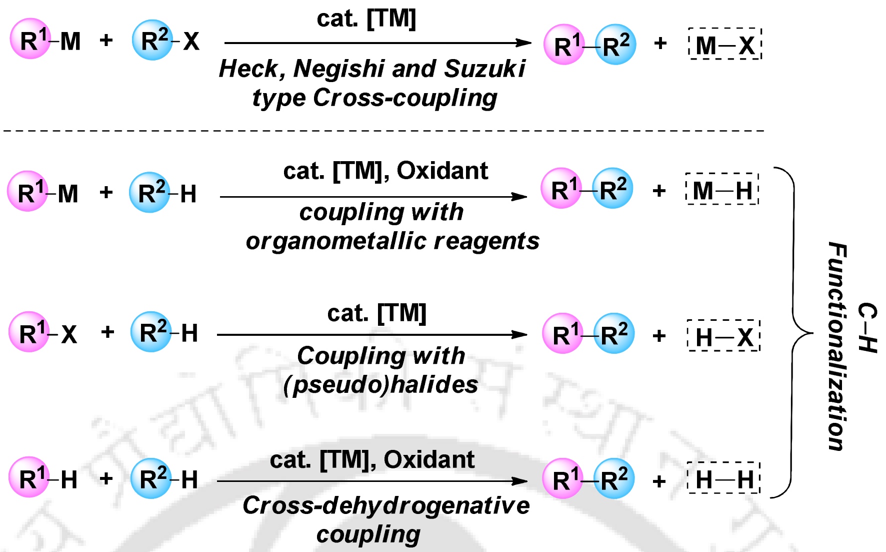
Traditional organic synthesis relies on functional-group-based manipulation (Scheme I.2.1) that is exchanging one functional group (FG) for another. Thus, installment of a new bond requires pre-functionalized starting materials, which decreases both efficiency and atom economy. It also adds extra step and cost to the transformation, because FG^1 must be first installed and then lost as a byproduct in the installation of FG^2 (Scheme I.2.1). On the other hand C–H functionalization does not need any prefunctionalized starting materials (Scheme I.2.1).



Scheme I.2.1. *Traditional functional-group transformation vs. C–H bond functionalization*

The advent of modern approach started with the discovery of transition metal catalyzed cross-coupling raction. In this context it is important to mention that in 2010 the Nobel prize in chemistry was awarded to *R. F. Heck*, *E. Negishi* and *A. Suzuki* for their significant contributions to the development of palladium-catalyzed cross-coupling reactions.[4] Other transition metals are also known to catalyze these reactions.[5a-b]

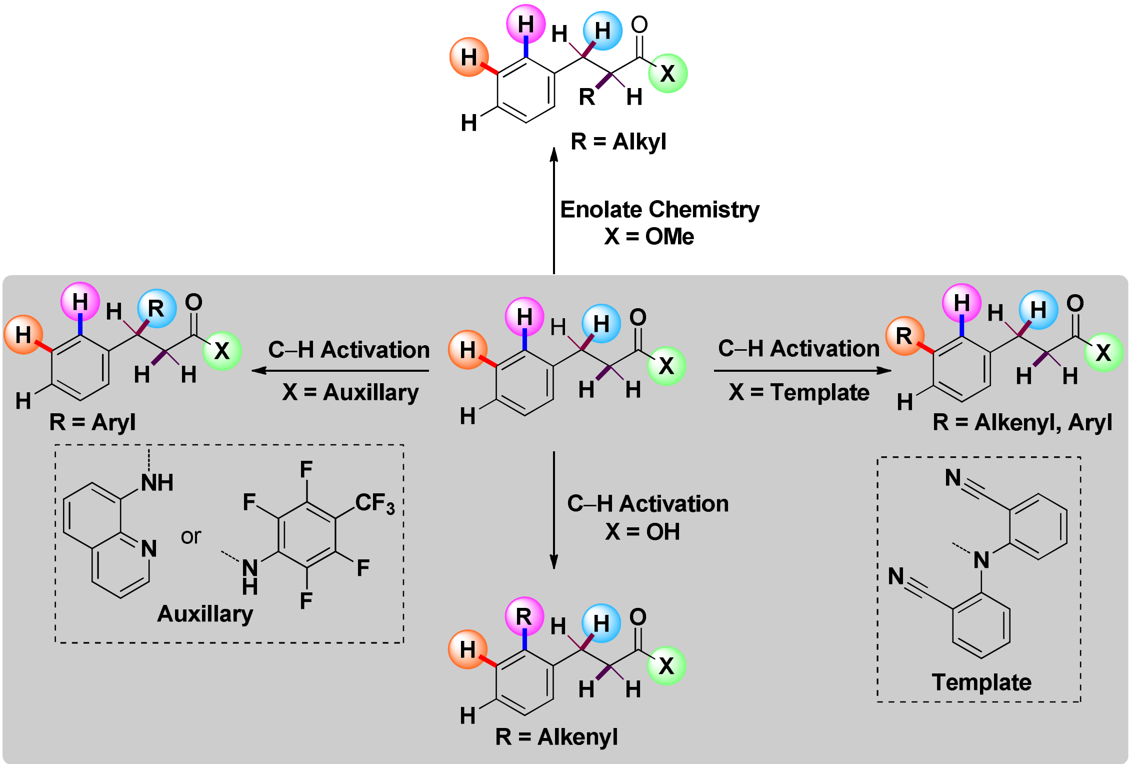
With respect to ecological and economical aspects of organic synthesis new concept for more sustainable transition metal-catalyzed direct C–H bond functionalization has been envisaged.[6,7] Direct C–H bond functionalizations have the advantage, as the prefunctionalization of the starting materials is redundant and it is accompanied with a reduction of waste material. Scheme I.2.2 displays evolving algorithms of different strategies in recent organic synthesis starting from transition metal-catalyzed cross-coupling to C–H bond functionalization.



Scheme 1.2.2. *Evolving algorithms of strategies in organic synthesis*

In an idealistic setting, it can be imagined that if every C–H bond of an organic molecule could be selectively functionalized, the fields of chemical synthesis and drug discovery would be forever revolutionized. While nature evolves specific enzymes to achieve site-selective C–H oxidation of specific structures, a practical and broadly useful approach for organic chemists would be to target representative classes of substrates and develop selective catalysts for each type to achieve predictable site-selectivity. Perhaps the most readily available and renewable source of simple organic building blocks are those isolated from nature. Thus the ability to diversify these molecules represents progress towards sustainable drug discovery and fine chemical production.

The given example is hydrocinnamic acid where depending on electrophilicity, nucleophilicity of specific position in the structure and acidity of various C–H bonds targeted, different catalytic routes are designed precisely (Scheme I.2.3).[8] Target oriented selective functionalizaiton of various C–H bonds from a common precursor gives access to multiple targets from a single starting material which are earlier not accessible *via* classical strategy. This sharply distinguishes with traditional approaches, wherein multistep, and often distinct, de novo sequences are required for each derivative.



Scheme I.2.3 *Diversification of hydrocinnamic acids by unconventional routs*

Compare to traditional couplings, C–H functionalization processes are thus advantageous because of the following reasons:

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

I.3. Challenges to C–H Functionalizations

While these C–H functionalization processes represent a chemical ideal from the standpoint of step and atom economy, the ubiquitous nature of C–H bonds and their relative strength pose a significant challenge for selectivity and reactivity, which has been the focus of research efforts over the past decade.

- **Inherent low reactivity:**

Most of the C–H bonds are either sp^2 or sp^3 hybridized; whose pK_a values are greater than 30–35. These bonds are also associated with high bond dissociation energy i.e. large kinetic barrier needed to cleave these C–H bonds. Hence it is difficult to cleave these extremely inert bonds *via* both homolytic and heterolytic paths.

- **Regioselctivity:**

C–H Bonds are ubiquitous in organic molecules; therefore tuning of a process to selectively target a desired C–H bond leaving all other C–H's intact is difficult. For example, the pharmaceutical and biological probe quinine shown in Figure I.3.1, possesses multiple, unique C–H bonds, including differently substituted aromatic and heteroaromatic sp^2 C–H bonds as well as allylic, secondary, and tertiary sp^3 C–H bonds. Selective functionalization of any C–H bond among all these C–H's would give access to multiple biologically important target molecules from a single starting material.

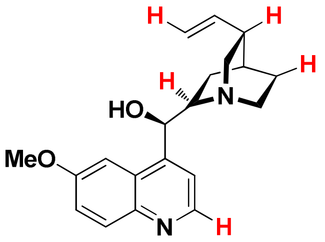
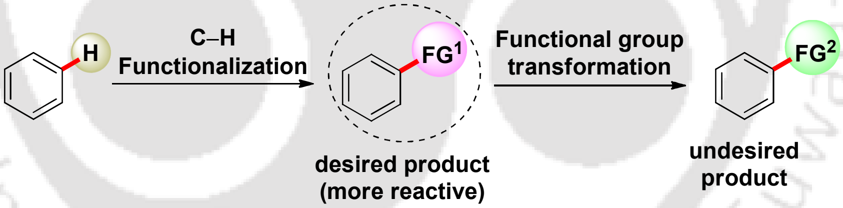


Figure I.3.1. *Pharmaceutical and biological probe Quinine contains multiple, unique C–H bonds*

- **Chemoselectivity:**

If the product is more reactive than the starting material in a C–H functionalization process, then the product is susceptible to undergo further functional group transformation or may be functionalized under the same reaction conditions. It would lead to undesirable products i.e. deviating from the actual target molecule (Scheme I.3.1).



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

- **Stereoselectivity:**

Due to the inertness of the C–H bonds, harsh reaction conditions and elevated temperatures are generally required to ensure a fruitful C–H activation which might have a detrimental impact on the stability of the chiral complex and the efficiency of asymmetric induction. Therefore construction of new stereogenic centre during C–H activation process in a highly diastereoselective and/or enantioselective way is the most formidable challenge in recent times.

Apart from these three vital challenges, a C–H functionalization process is also associated with many other issues such as preserving the existing functional group(s) in the starting precursor under the reaction conditions and controlling competing side reactions such as homo- and hetero-couplings.

I.4. Classification of Reactions

As proposed by Sanford two fundamentally different mechanistic manifolds have emerged for transition metal catalyzed C–H functionalizations *viz.* ‘inner-sphere’ and ‘outer-sphere’.[9] The inner-sphere mechanism proceeds through the insertion of a transition metal into a C–H bond to form a defined C–M bond, this *in situ* generated organometallic species can be converted to a new functional groups by reaction with either an external reagent or an organyl ligand attached to the metal center.[10] The key distinguishing feature of ‘outer-sphere’ mechanism is that a C–H bond within the substrate is not converted to an M–C bond during the process, but instead reacts with an actively coordinated ligand of the transition metal ([M]=X, M is transition metal, X is ligand).[10] Shul’pin divided all the C–H bond splitting reactions into three groups based on their mechanisms.[11] Crabtree labeled the mechanisms as ‘organometallic’ and ‘co-ordination’, which was similar to Sanford’s ‘inner-sphere’ and ‘outer-sphere’ classification method mentioned above.[12] As these ‘inner-sphere’ and ‘outer-sphere’ classification of C–H activation mechanisms was later found not to be general i.e. limited to saturated alkane C–H bonds, a broader view was necessary. Bercaw gave a more detailed classification: ‘oxidative addition’, ‘σ-bond metathesis’, ‘electrophilic activation’, ‘metalloradical activation’, and ‘1,2-addition’.[13] Among these five distinct mechanisms by which stable organometallic species are formed; three of these are quite common, while the other two are rare.[13]

(a) Oxidative addition

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

A qualitative molecular orbital diagram showing only the C–H–M π interaction is shown in Figure I.4.1. The resulting organometallic intermediate can then be further manipulated to release different carbon–X bonds, where X is halogen, oxygen, nitrogen, carbon etc. Oxidative addition reactions are typical for electron-rich, low-valent complexes of the 'late' transition metals found towards the right side of the periodic table such as Re, Fe, Ru, Os, Rh, Ir, Pt.

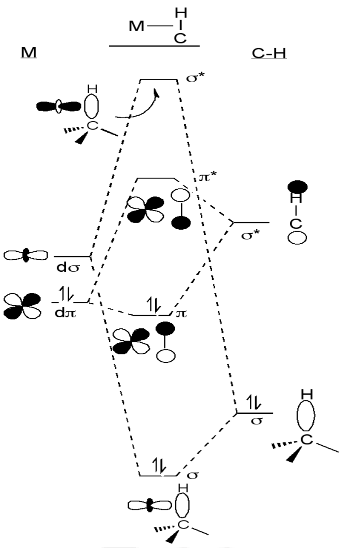
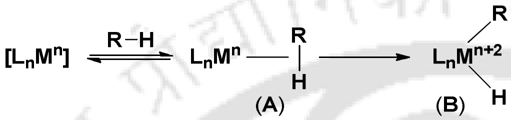
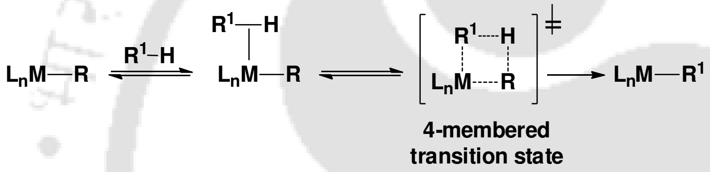


Fig. I.4.1. *A qualitative MO diagram for oxidative addition*



Scheme I.4.1. *An oxidative addition mechanism*

(b) Sigma-bond metathesis



Scheme I.4.2. *A σ-bond metathesis mechanism*

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

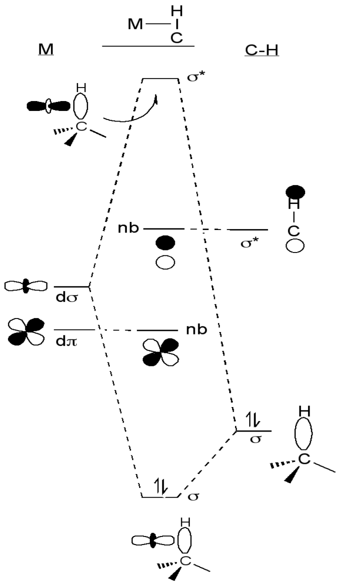
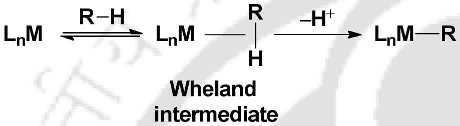


Fig. I.4.2. *A qualitative MO diagram for σ-bond metathesis*

(c) Electrophilic activation

Late transition metals in a higher oxidation state take part in electrophilic substitutions. Electrophilic metalation of an aromatic nucleus proceeds in two stages; the electrophilic species first adds to the arene with the formation of a Wheland intermediate, while in the second step there is a loss of proton to give a distinct σ-organyl complex (Scheme I.4.3).

An analogous intermediate might be formed during the interaction of a saturated hydrocarbon with an electrophilic metal-containing species, but should be much less stable.



$$L_nM \underset{}{\overset{R-H}{\rightleftharpoons}} L_nM - \overset{R}{\underset{H}{|}} \xrightarrow{-H^+} L_nM{-}R$$

Scheme I.4.3. *An electrophilic activation mechanism*

A qualitative MO diagram in Figure I.4.3 shows that it usually involves later transition metals where the d orbitals have dropped in energy.

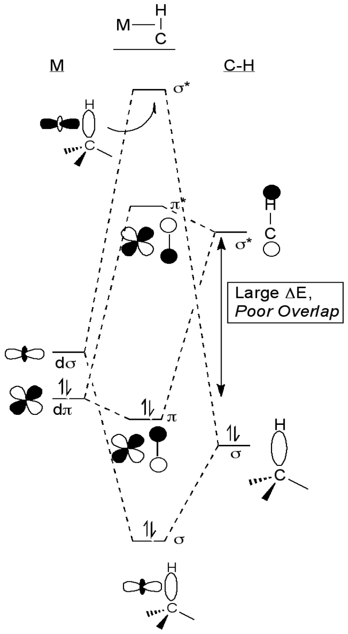


Fig. I.4.3. *A qualitative MO diagram for electrophilic activation*

(d) Metalloradical activation

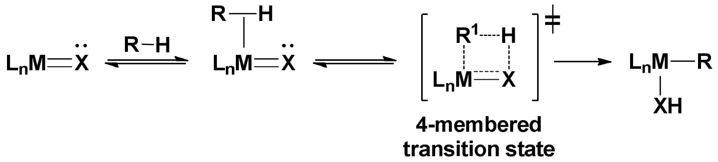
This type of mechanism is known for alkane C–H activation only. A transition metal complex existing in monomer–dimer equilibrium can reversibly break alkane C–H bonds, with the attachment of two fragments to two separate halves of the metal complex (Scheme I.4.4). Methane is the most reactive hydrocarbon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

$$L_nM{-}ML_n \xrightarrow{R-H} L_nM{-}R + L_nM{-}H$$

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

(e) 1,2-Addition

1,2-Addition reactions involve the addition of an C–H bond to a metal-nonmetal double bond (Scheme I.4.5). Although alkane additions across M=N and M=C double bonds of early and middle transition-metal centres are known, the scope of this type of reaction and its potential for alkane functionalization remain unclear.

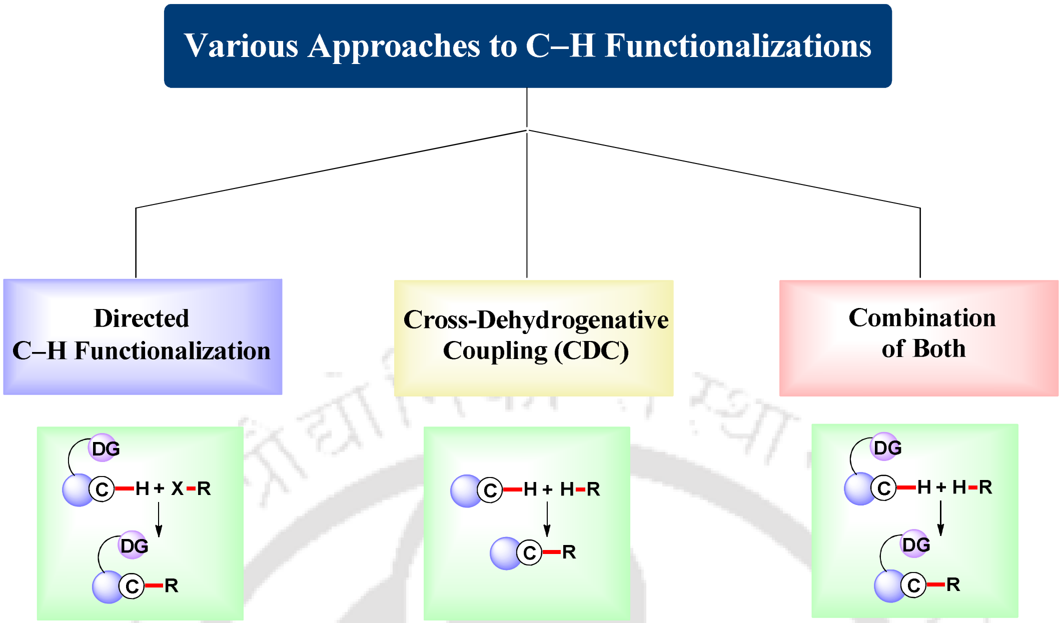


Scheme I.4.5. *A 1,2-addition mechanism*

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

I.5. Modern Era of C–H Functionalization

The historical survey tells that the beginning of C–H bond activation started long time ago. For the several billion years bacteria have been practicing it in nature at ambient conditions. While Mother Nature evolves specific enzymes such as cytochrome P450 enzymes, methane monooxygenase for metal based C–H functionalization for the several billion years, a practical and broadly useful C–H functionalization approach for organic chemists started just few decades early. Early 1990's can be assigned as the 'golden era' of C–H functionalization because from that time onwards there was a remarkable increase in the number of metal salts and complexes that were employed to catalyze C–H activation process. Since then there has been a tremendous growth in this area of synthetic organic chemistry. The strategies generally adopted in these reactions can be classified into two major heads namely (i) directing group assisted C–H functionalizations and (ii) cross-dehydrogenative coupling (CDC). Also there are methodologies which are based on the combination of two aforementioned approaches (Scheme I.5.1).



Scheme I.5.1. *Various approaches to C–H functionalizations*

I.5.1 Directed C–H functionalizations

Due to the ubiquitous nature and low reactivity of C–H bonds, selective functionalization of the desired C–H bond is a formidable challenge for the transition metal catalysts. One of most common solutions is using organic substrates that contain one or more preexisting directing group(s) which can chelate the metal catalyst and position it adjacent to a proximal C–H bond (positional selectivity). This precoordination can overcome the paraffin nature of C–H bonds by increasing the effective concentration of the substrate. The resulting metallacycle, usually a five- or six-membered ring, serves as a versatile intermediate to products containing new C–C or C–X bonds. Directed metallation is a powerful approach for selective functionalization of C–H bonds in substrates possessing a variety of C–H bonds.[14] This strategy is known to function well with a variety of transition metals in combination with oxidants. However, among the many the most widely used transition metals are Ru, Rh, Pd and Cu. Besides these other transiton metals *viz.* Mn, Fe, Co, Ni, Re, Ir, Pt, Ag, Au are also put to use.

Advantages:

- Direct the transition metal to activate the adjacent proximal C–H bond.
- Higher effective concentration of the catalyst at the site of interest.
- High levels of regioselectivity and increased reactivity.

Limitations:

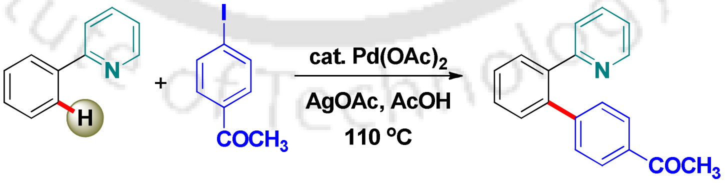
- Additional synthetic steps involving installation and removal of directing groups. (In many cases the directing group is an integral part of the substrate).
- In most cases, directed functionalizations are limited to proximity controlled *ortho* C–H bond.

I.5.1.1. Representative examples of directed C–C bond formation

Carbon-carbon bond formation is a fundamental transformation in synthetic organic chemistry. Recently, the most widely studied area in this field is transition metal catalyzed ligand-directed C–H activation followed by C–C coupling to afford *ortho*-aryl, alkyl, alkenyl, alkynyl, carbonyl, trifluoromethyl and cyano products. Reactions pertinent to each of these categories are exemplified below.

- ***Ortho* arylation *via* C_{sp2}–H / C_{sp2}–X**

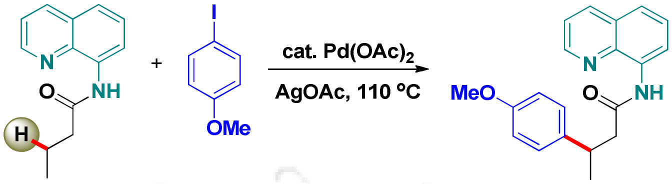
Daugulis and co-workers developed a Pd(II) catalyzed *ortho* sp^2 C–H arylation protocol using 2-arylpyridines as the directing arene, AgOAc as the oxidant and AcOH as additive (Scheme I.5.1.1.1).[15a-b] Aryl iodides were used as the aryl surrogate. A related *ortho*-arylation has also been applied to other directing arenes such as substituted anilides,[15c] benzoxazoles,[15d] and benzoic acid derivatives.[15e] Amide[15f] and oxime ether[15g] directed reactions have also been used as the first step in tandem sequences to generate fluorenones. All of these transformations show broad scope and functional group tolerance. Apart from aryl iodides, a variety of other arylating agents such as diphenyliodonium salts,[16a-c] aryl chlorides,[16d] arylboronic acids,[16d-e] arylsilyl ethers[16f-g] and even aryl acyl peroxides[16h] have also been used for this purpose very effectively.



Scheme I.5.1.1.1. *Pd-catalyzed ortho-arylation of 2-phenylpyridine with aryl iodides*

- **Arylation *via* C_{sp3}–H / C_{sp2}–X**

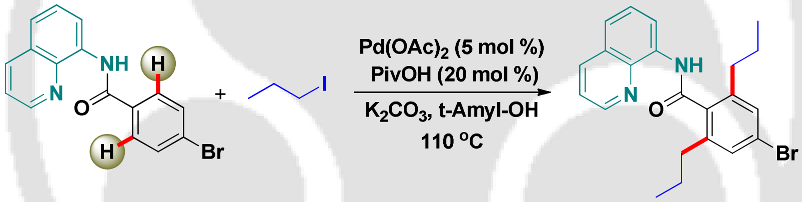
Pd-Catalyzed arylation of unactivated 1° and 2° sp^3 C–H bonds has been achieved using the combination of Ag(I) and Ar-I (Scheme I.5.1.1.2)[17a] using the assistance of bidentate directing groups *viz.* aminoquinolines and picolinamides.[17a] The coupling of aryl iodides with sp^3 C–H bonds in carboxylic acid derivatives has also been achieved using a slight modification of the above conditions i.e. using cat. Pd(II) in combination with oxidant Ag_2CO_3, 2 equiv of NaOAc and 1 equiv of K_2HPO_4.[17b]



Scheme I.5.1.1.2. *Pd-catalyzed* sp^3 *C–H arylation with aryl iodides*

➢ *Ortho* alkylation *via* C_{sp2}–H / C_{sp3}–X

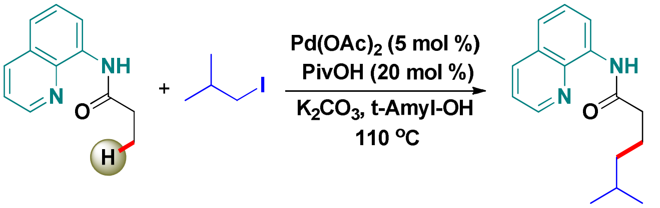
Similar to the arylation, Daugulis group has also demonstrated Pd(II) catalyzed *ortho* alkylation of arenes bearing 8-aminoquinolines as auxillary directing group (Scheme I.5.1.1.3).[18a] The alkyl sources used in this transformation are alkyl iodides or bromides. Similar directing group assisted alkylation has also been achieved using other alkyl sources that include tetra-alkyl tin reagents,[18b] methylboroxines,[18c] and dicumylperoxide.[18d]



Scheme I.5.1.1.3. *Pd-catalyzed* sp^2 *C–H alkylation with alkyl iodides*

➢ Alkylation *via* C_{sp3}–H / C_{sp3}–X

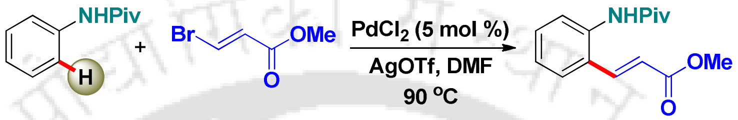
Using 8-aminoquinoline as auxillary ligand, Pd(II) catalyzed alkylation at sp^3 C–H bonds has been achieved in the presence of alkyl iodides or bromides as alkyl sources (Scheme I.5.1.1.4).[18a] Yu group also developed a similar alkylation protocol cleaving sp^3 C–H of *N*-methoxy amides using Pd(II) catalyst and alkylboronic acids as alkyl sources.[19]



Scheme I.5.1.1.4. *Pd-catalyzed* sp^3 *C–H alkylation with alkyl iodides*

➢ ***Ortho* alkenylation *via* C_{sp2}–H / C_{sp2}–X**

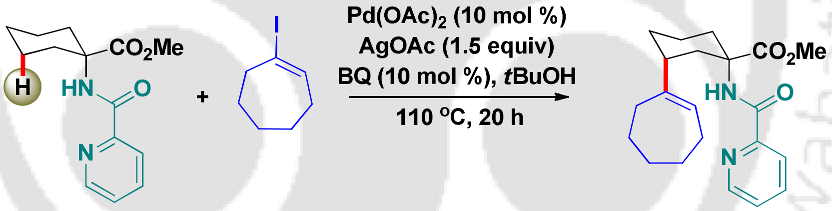
Daugulis group demonstrated an interesting methodology for *ortho*-alkenylation using 3-halo acrylates as alkene substrates, $PdCl_2$ as catalyst and Ag(I) as oxidant (Scheme I.5.1.1.5).[20a] In one of their independent works, they have also employed 2-bromovinyl benzene as the styrene source for *ortho*-alkenylation of amides.[18a] Recently, Kakiuchi group has shown that alkenyl ethers and esters can be employed for Ru-catalyzed *ortho*-selective alkenylation of aromatic compounds.[20b]



Scheme I.5.1.1.5. *Pd-catalyzed coupling of haloolefins with anilides*

➢ **Alkenylation *via* C_{sp3}–H / C_{sp2}–X**

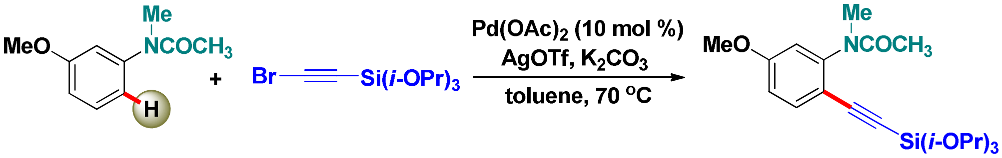
Chen group developed a highly effective protocol for Pd(II) catalyzed picolinamide-directed γ-alkenylation of unactivated C_{sp3}–H bonds using cyclic vinyl iodide coupling partners with high levels of regioselectivity under mild reaction conditions (Scheme I.5.1.1.6).[20c]



Scheme I.5.1.1.6. *Picolinamide-directed Pd-catalyzed sp^3 C–H alkenylation*

➢ ***Ortho* alkynylation *via* C_{sp2}–H / C_{sp}–X**

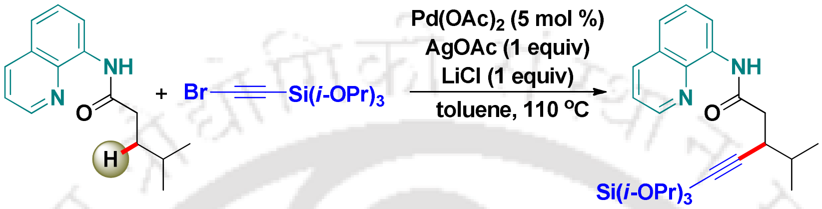
Chatani group reported a Pd(II) catalyzed *ortho*-alkynylation protocol of anilides with a silyl-protected bromoalkyne in the presence of AgOTf, and K_2CO_3 (Scheme I.5.1.1.7).[21] Other Ru and Rh catalyzed protocols were also reported using pre-activated alkynylating reagents such as alkynyl halides[22] and benziodoxolone-based hypervalent iodine reagents[23] as coupling partners.



Scheme I.5.1.1.7. *Pd-catalyzed ortho-alkynylation of anilides with haloalkynes*

➢ Alkynylation *via* C_{sp3}–H / C_{sp}–X

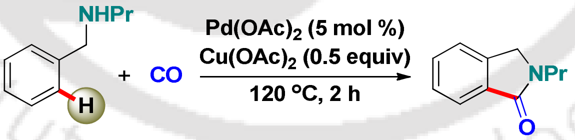
Using 8-aminoquinoline as auxillary ligand, Chatani group for the first time developed a Pd(II)-catalyzed coupling of C(sp^3)–H bonds with alkynyl halides *via* Pd(II)/Pd(IV) catalytic system (Scheme I.5.1.1.8).[24a] Using an *N*-arylamide auxiliary similar β-C(sp^3)–H alkynylation was also reported by Yu group using Pd(0)/NHC and Pd(0)/PR$_3$-catalytic combinaions.[24b]



Scheme I.5.1.1.8. *Pd-catalyzed sp^3 C–H alkynylation with haloalkynes*

➢ *Ortho* sp^2 C–H carbonylation

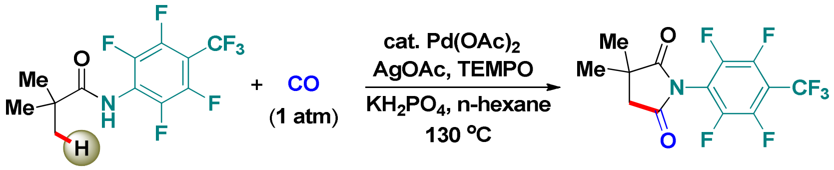
An early example of Pd-catalyzed directed sp^2 C–H carbonylation was achieved using mono-protected benzylamines as the directing sustrate generating benzolactam derivatives using Cu(OAc)$_2$ as co-oxidants under an atmosphere of CO (Scheme I.5.1.1.9).[25a]. *Ortho*-carbonylation of other directing groups is reported using CO as the carbonyl source for the synthesis of *ortho*-esters.[25b-c] Diethyl azodicarboxylate (DEAD) has also been used as a substitute of toxic CO for ethoxycarbonylation of direcing substrates such as pyridine-, amide-, and oxime ether in the presence of Pd(OAc)$_2$ as the catalyst and oxone as the terminal oxidant.[25d]



Scheme I.5.1.1.9. *o-Carbonylation of benzylamines for the synthesis of benzolactams*

➢ sp^3 C–H Carbonylation

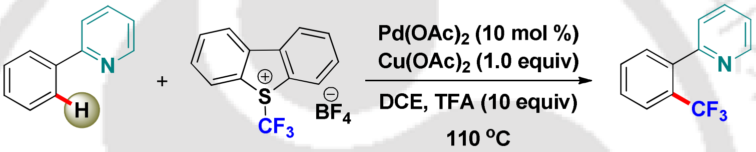
Yu group achieved a Pd(II)-catalyzed primary β-C(sp^3)–H carbonylation of *N*-arylamides under CO (1 atm) for the synthesis of their corresponding succinimides (Scheme I.5.1.1.10).[26] This method was equally effective towards methylene C(sp^3) –H carbonylation of cyclopropanes. Yu group recently demonstrated monoselective γ-C–H carbonylation of aliphatic acids using a weakly coordinating amide directing group in combination with a quinoline-based ligand.[27]



Scheme I.5.1.1.10. *Pd-catalyzed β-C(sp^3)–H carbonylation of amides*

➢ *Ortho* sp^2 C–H trifluoromethylation

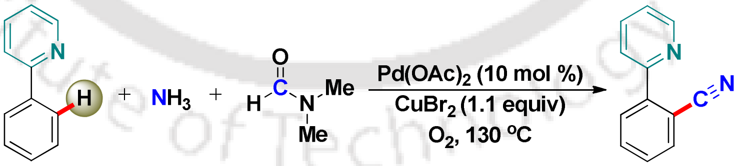
The first example of *ortho*-trifluoromethylation of 2-arylpyridines or analogous substrates reported by Yu group using Pd(II) catalyst in combination with trifluoroacetic acid (TFA) and $Cu(OAc)_2$ as crucial promoters (Scheme I.5.1.1.11).[28a] There has been an evolution of several methods on *ortho*-trifluoromethylation of several other directing group possessing substrates.[28b-d]



Scheme I.5.1.1.11. *Pd-catalyzed ortho-trifluoromethylation of 2-phenylpyridine*

➢ *Ortho* sp^2 C–H cyanation

Chang group developed an fascinating protocol for *ortho* sp^2 C–H cyanation of 2-arylpyridines or analogous substrates employing *N*,*N*-dimethylformamide and ammonia as a combined source for the cyano "CN" unit (Scheme I.5.1.1.12).[29a] Other cyano surrogates such as copper(I) cyanide,[29b] potassium ferricyanide,[29c] benzyl nitrile,[29d] acetonitrile,[29e] AIBN,[29f] *tert*-butyl isonitrile[29g] etc. have also been used for similar *o*-cyanation.



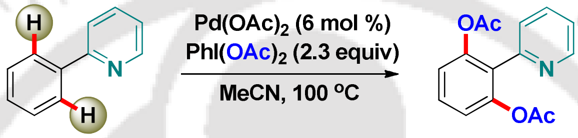
Scheme I.5.1.1.12. *Pd-catalyzed ortho-cyanation of 2-phenylpyridine*

I.5.1.2. Representative examples of C–O bond formation

The C–O bond installations *via* C(sp^2)–H or C(sp^3)–H cleavage occur in several ways; the common forms being acetoxylation, benzoxylation, hydroxylation and alkoxylation. Representative examples pertaining to various forms of C–O bond formations are shown below. A detailed discussion of various *ortho* C–O bond formation reacions will be discussed in chapter-II.

- ***Ortho* acetoxylation *via* sp^2 C–H**

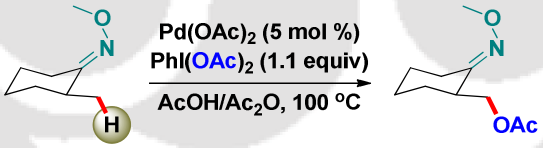
The first example of sp^2 C–H bond acetoxylation of 2-arylpyridines or analogous substrates was demonstrated by Sanford group using PhI(OAc)$_2$ as a stoichiometric oxidant in conbination with catalytic Pd(OAc)$_2$ (Scheme I.5.1.2.1).[30a] Other nitrogen-based stronger directing groups, including imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles (e.g., pyrazoles and isoxazolines) were also effective. Other iodine oxidants or peroxides have been utilized towards acetoxylation reactions.[30b-c]



Scheme I.5.1.2.1. *Pd-catalyzed sp^2 C–H acetoxylation*

- **sp^3 C–H Acetoxylation**

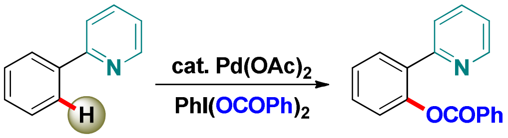
In addition to the sp^2 C–H acetoxylation, the same group also reported a Pd-catalyzed ligand-directed sp^3 C–H bond oxygenation using PhI(OAc)$_2$ as the terminal oxidant. Both benzylic and unactivated sp^3 C–H bonds were readily functionalized by the assistance of oxime ether and pyridine directing groups (Scheme I.5.1.2.2).[30a,d]



Scheme I.5.1.2.2. *Pd-catalyzed sp^3 C–H acetoxylation*

- ***Ortho* benzoxylation *via* sp^2 C–H**

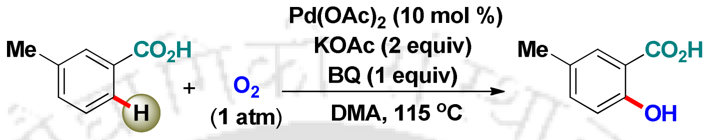
A Pd(II) catalyzed *o*-benzoxylation of 2-phenylpyridines was developed by Sanford *et al.* using benzoate iodonium salts as the ArCOO–surrogates for the first time (Scheme I.5.1.2.3).[31a] Later, Shi group achieved a similar Pd(II) catalyzed *o*-benzoxylation of ketoxime ether *via in situ* generation of benzoate iodonium salts.[31b]



Scheme I.5.1.2.3. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

➢ ***Ortho* hydroxylation *via* sp^2 C–H**

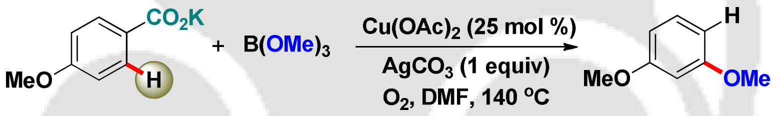
Yu group demonstrated a highly selective Pd-catalyzed *ortho*-hydroxylation of potassium benzoates *via* activation of dioxygen using weak oxygen co-ordination (Scheme I.5.1.2.4).[32a] The same group has also described a Cu-catalyzed *ortho*-hydroxylation of 2-arylpyridines which goes *via* acetoxylation/hydrolysis sequence.[32b] Many Ru-catalyzed hydroxylation of arenes bearing various directing groups are also reported in literature.[32c]



Scheme I.5.1.2.4. *Pd-catalyzed ortho-hydroxylation of arylcarboxylic acids*

➢ ***Ortho* alkoxylation *via* sp^2 C–H**

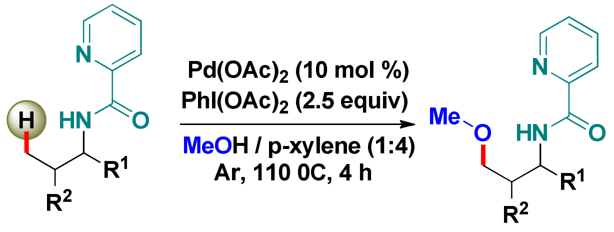
Gooβen group demostrated a regiospecific Cu(II) catalyzed *ortho*-alkoxylation of aromatic carboxylates with concomitant decarboxylation (Scheme I.5.1.2.5).[33] This protocol gives access to the important substrate class of aromatic ethers from widely available carboxylic acids.



Scheme I.5.1.2.5. *Cu-catalyzed ortho-alkoxylation of arylcarboxylates*

➢ **sp^3 C–H Alkoxylaion**

Chen and co-workers reported a picolinamide directed Pd(OAc)$_2$-catalyzed, efficient synthesis of alkyl ethers by the functionalization of unactivated sp^3 hybridized C–H bonds with a range of alcohols, including ^{t}BuOH, to give alkoxylated products. (Scheme I.5.1.2.6).[34] Similar Pd(II) catalyzed sp^3 C–H alkoxylation protocols also developed by Rao group using 8-aminoquinoline as the directing auxillary.[35]



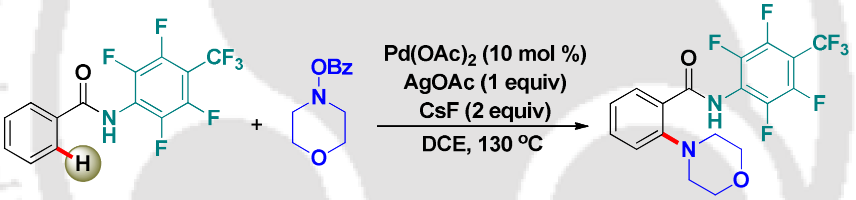
Scheme I.5.1.2.6. *Pd-catalyzed auxillary assisted sp^3 C–H* alkoxylation

I.5.1.3. Representative examples of C–N bond formation

Transition metal catalyzed ligand-directed C–H activation has also been utilized for the construction of C–N bonds, which are important features of many biologically active molecules. Representative examples pertaining to various forms of C–N bond formations are shown below.

- ***Ortho* amination *via* sp^2 C–H**

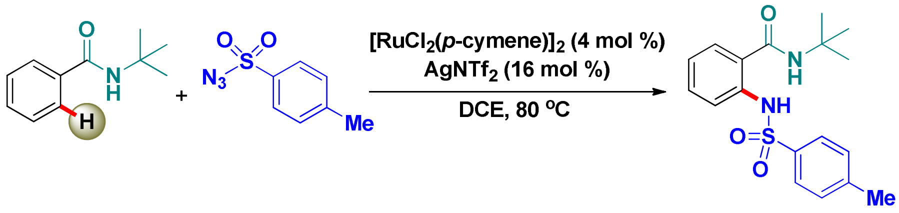
By using a broad range of weakly coordinating amide directing group Yu and co-workers developed a novel protocol to achieve C–H amination with electrophilic *O*-benzoyl hydroxylamines using either Pd(II) or Pd(0) catalysts (Scheme I.5.1.3.1).[36a] The compatibility of this amination reaction with several different *O*-benzoyl hydroxylamine reagents derived from simple dialkylamines allows for the convergent synthesis of an important class of tertiary and secondary aryl-alkyl amines starting from benzoic acids. Similar sp^2 C–H amination strategies are also reported using Rh catalyst and *N*-halo amines as electrophilic aminating partners.[36b-d]



Scheme I.5.1.3.1. *Pd-catalyzed intermolecular amination with alkylamines*

- ***Ortho* amidation *via* sp^2 C–H**

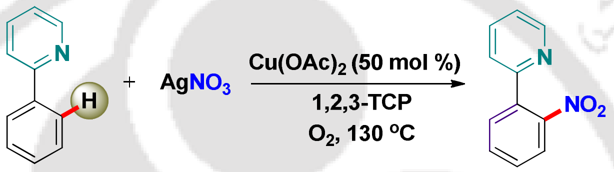
Glorius and others demonstrated sp^2 C–H bond amidations of various directing arenes using *N*-carboxylates, *N*-tosylates and *N*-mesitylsulfonates as electrophilic amidating partners.[37] Recently, organic azides were introduced as pre-activated aminating reagents in C–H activation protocols. Chang and co-workers demonstrated a ruthenium-catalyzed C–H bond amidations on arenes bearing synthetically useful directing groups, such as amides or ketones using sulfonyl azides (Scheme I.5.1.3.2).[38] The practical importance of the products was showcased by the preparation of a wide range of heterocycles with potential biological activities. Analogous amidation reactions using sulfonyl azides as precursors are illustrated using Ru catalytic systems, notably by Ackermann,[32c,39a] Sahoo[39b-c] and Jiao[39d].



Scheme I.5.1.3.2. *Ru-catalyzed ortho-amidation of benzamides with sulfonyl azides*

- ***Ortho* nitration of sp^2 C–H bond**

Liu and Bi group demonstrated a novel Cu(II) mediated protocol for the *ortho* nitration of 2-arylpyridines using $AgNO_3$ as the source of 'NO_2' group. In this reaction, O_2 is used as the terminal oxidant (Scheme I.5.1.3.3).[40]



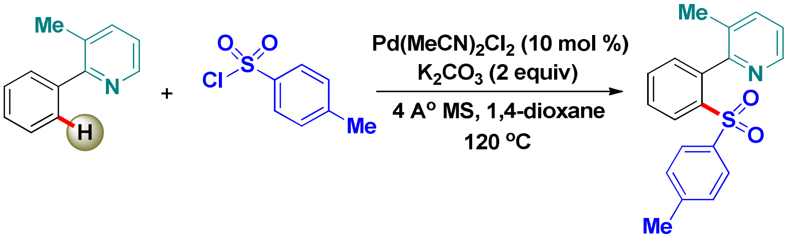
Scheme I.5.1.3.3. *Cu-catalyzed sp^2 C–H nitration of 2-phenylpyridine*

I.5.1.4. Representative examples of C–S bond formation

Despite the potential importance of sulfur-containing compounds in the pharmaceutical and agrochemical industries, the latest developments on transition metal catalyzed formation of carbon-sulfur (C–S) bonds remains relatively rare due to competing oxidation of sulfur compounds which diminishes the reactivity to give the desired products. Most examples involve intramolecular cyclization reactions to generate the C–S linkage.[41]

- ***Ortho* sp^2 C–H sulfonylation**

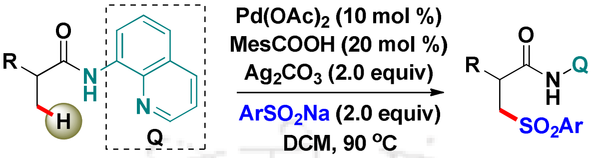
Dong group demonstrated an interesting example of intermolecular $Pd(MeCN)_2Cl_2$ catalyzed *ortho*-sulfonylation of direcing arenes *viz.* arylpyridines, arylpyrazoles, and aryloxime ethers employing $ArSO_2Cl$ as the sulfonating reagent *via* the cleavage of sp^2 C–H bond (Scheme I.5.1.4.1).[42]



Scheme I.5.1.4.1. *Pd-catalyzed ortho-sulfonylation of 2-phenylpyridine*

- **Sulfonylation *via* sp^3 C–H**

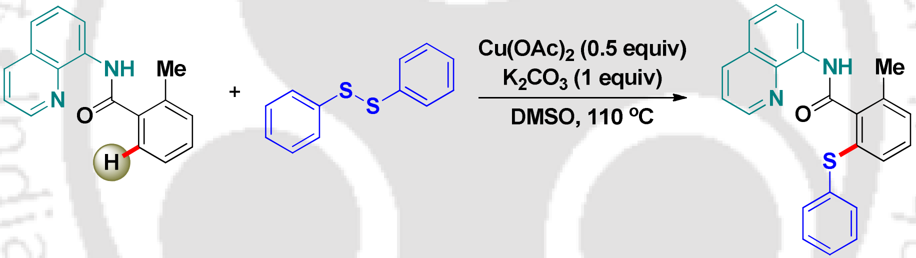
Shi group recently developed a Pd(II)-catalyzed 8-aminoquinoline directed sulfonylation protocol of unactivated C(sp^3)–H bonds with sodium arylsulfinates affording a broad range of aryl alkyl sulfones (Scheme I.5.1.4.2).[43]



Scheme I.5.1.4.2. *Pd-catalyzed direct sp^3 C–H sulfonylation*

- ***Ortho* sp^2 C–H sulfenylation**

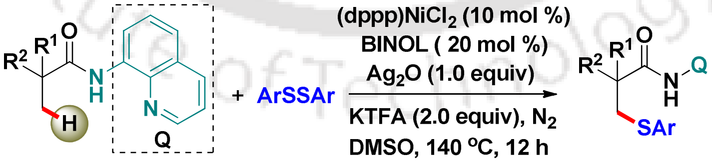
Daugulis group has developed an auxiliary-assisted, copper catalyzed or promoted practical sulfenylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of benzylamine derivatives using disulfide reagents as sulfenylating source (Scheme I.5.1.4.3).[44]



Scheme I.5.1.4.3. *Pd-catalyzed sp^2 C–H sulfenylation of benzoic acid derivatives*

- **Sulfenylation *via* sp^3 C–H**

Recently, Shi group has demonstrated a nickel-catalyzed auxillary directed thiolation /sulfenylation of C(sp^3)–H bonds to form thioethers (Scheme I.5.1.4.4).[45]



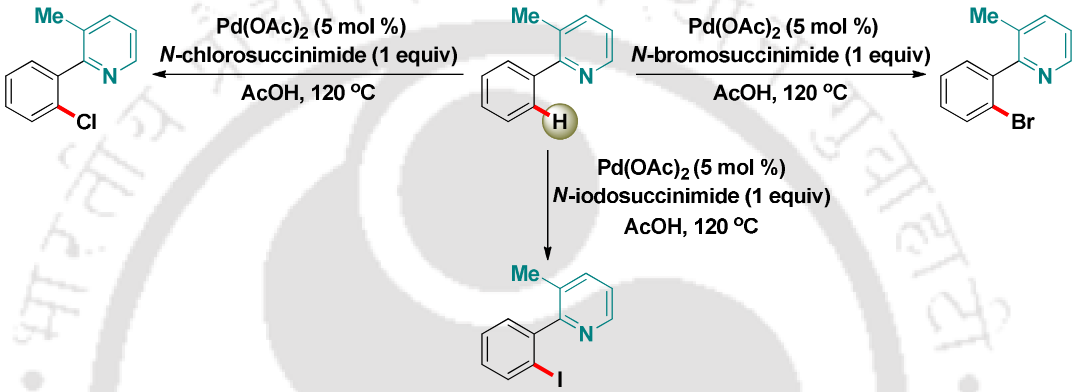
Scheme I.5.1.4.4. *Ni-catalyzed sp^3 C–H sulfenylation*

I.5.1.5. Representative examples of carbon-halogen bond formation

The installation of a C–X (X = Cl, Br, I) bond *via* C–H activation has got special synthetic importance from the perspective of their use in coupling chemistry for further functionalizations.

➢ *Ortho* sp^2 C–H chlorination, bromination and iodination

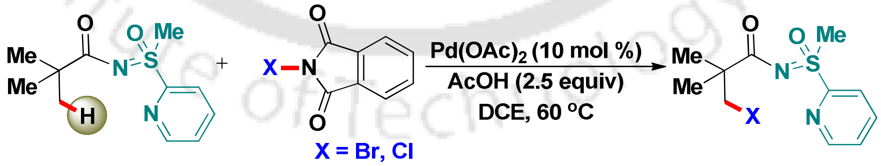
A patent by Kodama and co-workers demonstrated that the combination of Pd(OAc)$_2$ and *N*-iodosuccinimide promotes the *ortho*-iodination of benzoic acids.[46a] Sanford group applied similar conditions to the directed chlorination, bromination and iodination of arenes with a variety of directing arenes including pyridines, oxime ethers, isoquinolines, amides, and isoxazolines (Scheme I.5.1.5.1).[46b-c] Apart from the *N*-halo succinimides, other halogenating agents were also used such as CuX$_2$ (X = Cl, Br)[46c-d] and Suárez reagents (XOAc, X = Br, I).[46e-f]



Scheme I.5.1.5.1. *Pd-catalyzed ortho sp^2 C–H halogenation of 2-phenylpyridine*

➢ Bromination and chlorination at sp^3 C–H bond of directing substrates

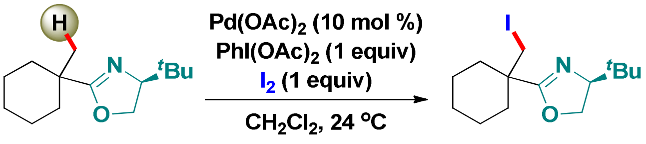
A Pd(II) catalyzed protocol for bromination and chlorination at β-sp^3 C–H bonds of directing arene was first developed by Sahoo group. Using removable directing auxillary *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) and *N*-halophthalimides as the coupling partners this method gave an easy access for halogenations (Br/Cl) at β-sp^3 C–H bonds of acid derivatives (Scheme I.5.1.5.2).[47]



Scheme I.5.1.5.2. *Pd-catalyzed sp^3 C–H halogenations (Br/Cl) of sulfoximine*

➢ Iodination *via* sp^3 C–H

Pd(II) catalyzed sp^3 C–H iodination was reported by Yu group using a combination of PhI(OAc)$_2$ and I$_2$, that generates *in situ* IOAc (Scheme I.5.1.5.3).[46e-f]

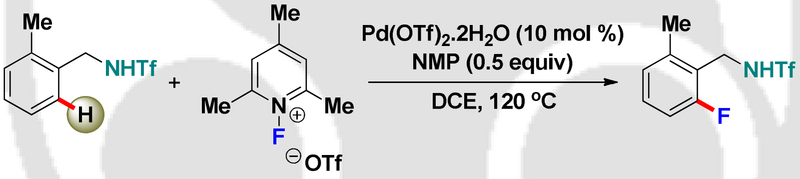


Scheme I.5.1.5.3. *Pd-catalyzed sp^3 C–H iodination*

Recently Yu group developed a Pd(II) catalyzed cheap and practical *ortho* iodination protocol of various directing substates by switching the costly electrophilic iodinating reagents to cheap iodine as the only oxidant.[48]

➢ *Ortho* sp^2 C–H fluorination

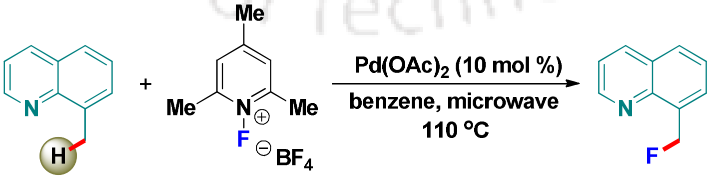
Yu group achieved a Pd(OTf)$_2$-catalyzed C–H fluorination of triflamide-protected benzylamines-based substrates using *N*-fluoro-2,4,6-trimethylpyridinium triflate as the "F$^+$" source along with *N*-methylpyrrolidinone (NMP) as a key promoter (Scheme I.5.1.5.4).[49a] This triflamide-based subsrates could be converted to a broad range of useful functional groups including benzaldehydes, benzylamines, nitriles, and benzylmalonates, thereby providing access to a variety of functionalized aryl fluoride containing products.



Scheme I.5.1.5.4. *Pd-catalyzed ortho fluorination of benzylamine derivatives*

➢ Fluorination *via* sp^3 C–H

Sanford group first demonstrated a Pd-catalyzed fluorination of benzylic sp^3 C–H using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the electrophilic fluorinating reagent for this transformation under microwave heating conditions (Scheme I.5.1.5.5).[49b]



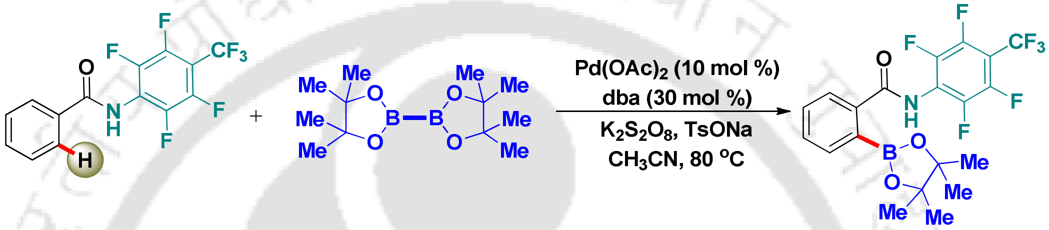
Scheme I.5.1.5.5. *Pd-catalyzed benzylic sp^3 C–H fluorination*

I.5.1.6. Representative example of C–B, C–Si, and C–Se bond formations

Reactions pertinent to each of these categories *viz.* ligand directed *ortho* C–B, C–Si, and C–Se bond formation reactions are exemplified below.

➢ ***Ortho* sp^2 C–H borylation**

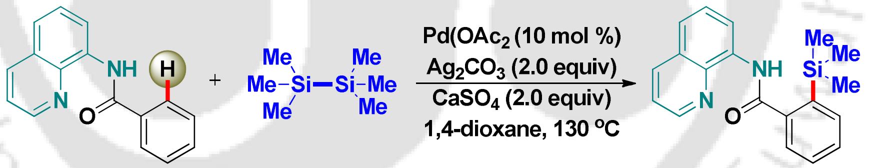
Pd-catalyzed *ortho* C–H borylation of amide derivatives was reported by Yu group employing diboron reagents (B$_2$Pin$_2$) as coupling partners in the presence of electron deficient dibenzylideneacetone (dba) ligand, weak base TsONa and a oxidant K$_2$S$_2$O$_8$ (Scheme I.5.1.6.1).[50]



Scheme I.5.1.6.1. *Pd-catalyzed sp^2 C–H borylation of benzamide*

➢ ***Ortho* sp^2 C–H silylation**

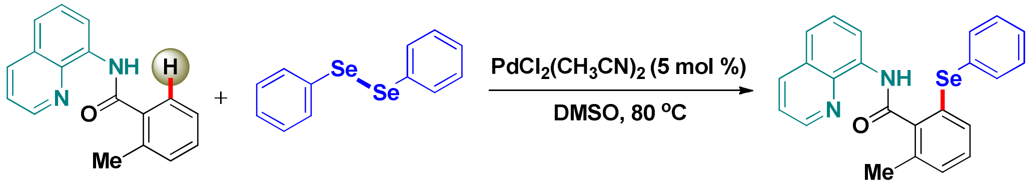
A Pd-catalyzed *o*-silylation protocol was developed by Kanai and co-workers using 8-aminoquinoline as the auxiliary ligands with hexamethyldisilane as the silicon source in presence of Ag(I) oxidant and additive calcium sulphate (Scheme I.5.1.6.2).[51]



Scheme I.5.1.6.2. *Pd-catalyzed sp^2 C–H silylation of benzamide*

➢ ***Ortho* sp^2 C–H selenation**

Nishihara group demonstrated a Pd(II) catalyzed direct *o*-sp^2 C–H selenation of directed substrates *viz.* benzamides, benzylamines, 2-arylpyridines and benzo[*h*]quinolines by utilizing diselenides as the coupling partners (Scheme I.5.1.6.3).[52]



Scheme I.5.1.6.3. *Pd-catalyzed sp^2 C–H selenation of benzamide*

I.5.2. Cross-dehydrogenative coupling (CDC): The cross-dehydrogenative coupling (CDC) reaction generally refers to a cross-coupling reaction between two C–H bonds or C–H and X–H (X = heteroatoms) bonds.[53] This strategy represents one of the most ideal synthetic procedures for selective C–C and C–X bond forming reactions in terms of atom economy. These reactions require a hydrogen acceptor which can take the form of oxygen, hydrogen peroxide, organic peroxides, for example, *tert*-butyl hydrogen peroxide (TBHP) or *tert*-butyl peroxide (TBP), and *N*-halosuccinimides, for example, *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS). A variety of metal catalysts such as Cu, Fe, and Pd are generally employed for these CDC reactions. There are also examples which function without metal catalysts. Interestingly, there are some examples of CDC's that have been successfully applied in water, consequently, further enhancing their environmental compatability.

Advantages:

- No need of any directing groups or pre-functionalization of starting materials.
- Ambient reaction conditions and simple starting materials
- High degree of C–H bond activation.

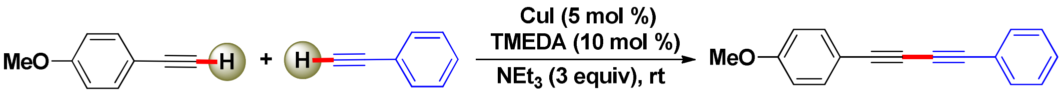
Limitations:

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

I.5.2.1. Representative examples of C–C bond formation

- **C_{sp}–H and C_{sp}–H Coupling**

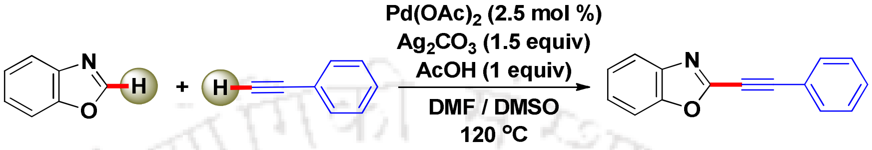
A facile and efficient pathway for the homo-coupling reaction of terminal alkynes was reported by Zhang group employing CuI as catalyst and ligand *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) under ambient temperature and air as the oxidant (Scheme I.5.2.1.1).[54] This process provides symmetrical as well as unsymmetrical 1,4-disubstituted 1,3-diynes in good to excellent yields.



Scheme I.5.2.1.1 *Copper (I)-catalyzed homo-coupling of two terminal alkynes*

➢ C_{sp}–H and C_{sp2}–H Coupling

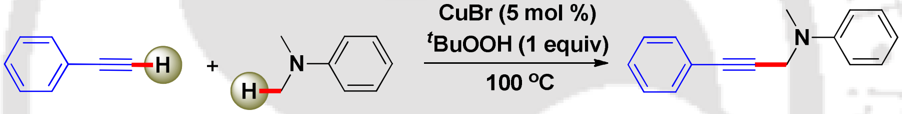
A Pd(II) catalyzed oxidative C_{sp}–C_{sp2} coupling reaction was developed by Murai group using a variety of widely applicable five-membered heteroarenes such as imidazole, oxazole, thiazole etc. and terminal alkynes in the presence of Ag(I) as oxidant and AcOH as additive (Scheme I.5.2.1.2).[55]



Scheme I.5.2.1.2. *Palladium(II)-catalyzed direct alkynylation of heteroarenes*

➢ C_{sp}–H and C_{sp3}–H Coupling

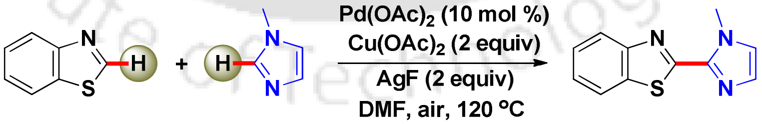
Li group developed a simple and efficient catalytic method to synthesize propargylamine by using CuBr and ^{t}BuOOH *via* a combination of sp^3 C–H bond and sp C–H bond followed by C–C bond formation (Scheme I.5.2.1.3).[56]



Scheme I.5.2.1.3. *Copper(I)-catalyzed direct alkynylation at sp^3 C–H*

➢ C_{sp2}–H and C_{sp2}–H Coupling

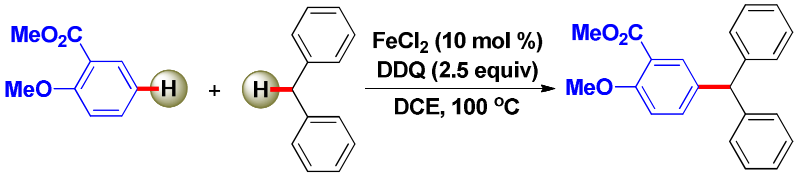
Ofial and co-workers reported an efficient Pd(II)-catalyzed protocol for the direct C2 heteroarylation of benzazoles with N–, O–, and S–containing azoles in presence of co-oxidants $Cu(OAc)_2$ and AgF by strategically supressing usual homocoupling process (Scheme I.5.2.1.4).[57]



Scheme I.5.2.1.4. *Pd(II)-catalyzed oxidative C_{sp2}–H/ C_{sp2}–H coupling*

➢ C_{sp2}–H and C_{sp3}–H Coupling

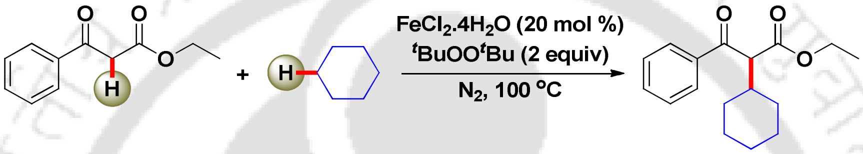
Shi *et al.* introduced a $FeCl_2$-catalyzed oxidative cross-coupling between compounds containing benzylic sp^3 C–H and arene sp^2 C–H in the presence of DDQ as oxidant (Scheme I.5.2.1.5) for the synthesis of di- or tri- phenylmethane derivatives.[58]



Scheme I.5.2.1.5. *Fe(II)-catalyzed direct arylation at benzylic sp^3 C–H*

➢ C_{sp3}–H and C_{sp3}–H Coupling

Li group developed a simple Fe(II)-catalyzed C–C bond formation by direct alkylation of activated methylene compounds such as phenyl β-ketone ester and diketone etc. by using inert cycloalkanes (Scheme I.5.2.1.6).[59]

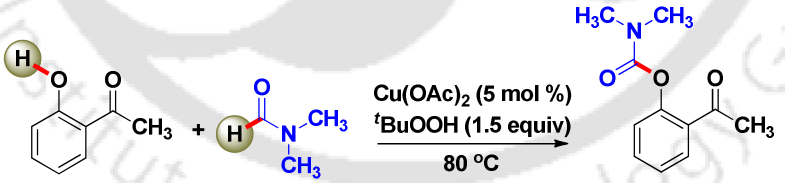


Scheme I.5.2.1.6. *Iron(II)-catalyzed direct cycloalkylation of β-dicarbonyl compounds*

I.5.2.2. Representative examples of C–O bond formation

➢ C_{sp2}–H and O_{sp3}–H Coupling

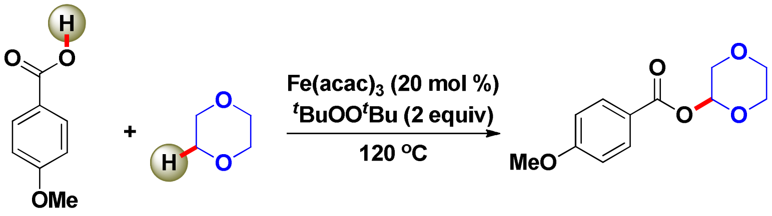
Reddy group developed a novel route for the synthesis of carbamates *via* Cu(II)-catalyzed oxidative C–O bond formation of sp^2 C–H bond of formamides with phenol and enols (Scheme I.5.2.2.1).[60] This strategy was also extended to oxidative esterification of *o*-carbonyl-substituted phenols.



Scheme I.5.2.2.1. *Synthesis of carbamates via C_{sp2}–H and O_{sp3}–H coupling*

➢ C_{sp3}–H and O_{sp3}–H Coupling

Synthesis of α-acyloxy ethers was developed by Pan group *via* an Fe-catalyzed oxidative esterification of unactivated C(sp^3)–H bonds from symmetric and asymmetric ethers using carboxylic acids as the carboxy source and di-*tert*-butyl peroxide (DTBP) as the oxidant *via* a cross dehydrogenative coupling (CDC) reaction (Scheme I.5.2.2.2).[61]

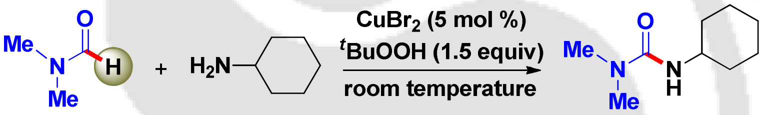


Scheme I.5.2.2.2. *Iron(III)-catalyzed C_{sp3}–H esterification*

I.5.2.3. Representative examples of C–N bond formation

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

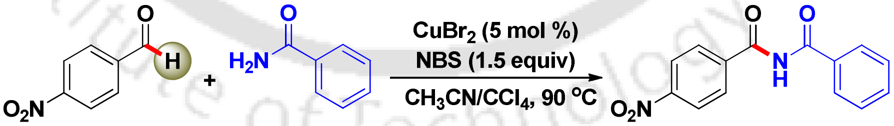
A highly efficient Cu catalyzed protocol for the synthesis of unsymmetrical ureas through CDC reaction of sp^2 C–H bonds of formamides and sp^3 N–H bonds of primary amines was developed by Reddy *et al.* (Scheme I.5.2.3.1).[62] Noteworthy features of the present work are utilization of *N*-methylformamide as a formamide source and also application towards the synthesis of chiral urea derivatives.



Scheme I.5.2.3.1. *Copper(II)-catalyzed sp^2 C–H amination of N-substituted formamides*

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

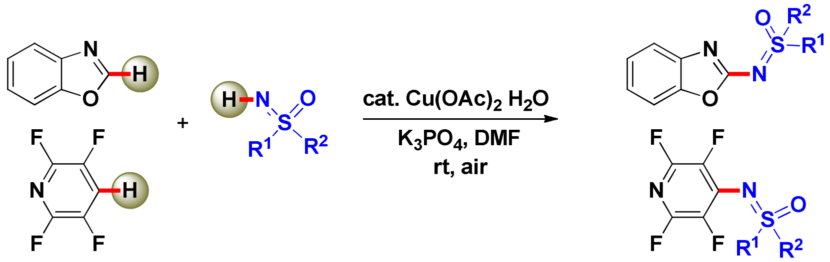
Fu group demonstrated a hetero-CDC protocol for the synthesis of imides using simple aldehydes and either secondary or tertiary amides as the coupling partners in the presence of CuBr$_2$ as the catalyst and *N*-bromosuccinamide (NBS) as the oxidant with excellent functional group tolerance and good to excellent product yields (Scheme I.5.2.3.2).[63]



Scheme I.5.2.3.2. *Copper(II)-catalyzed sp^2 C–H amidation*

➢ C_{sp2}–H and N_{sp2}–H (imine) Coupling

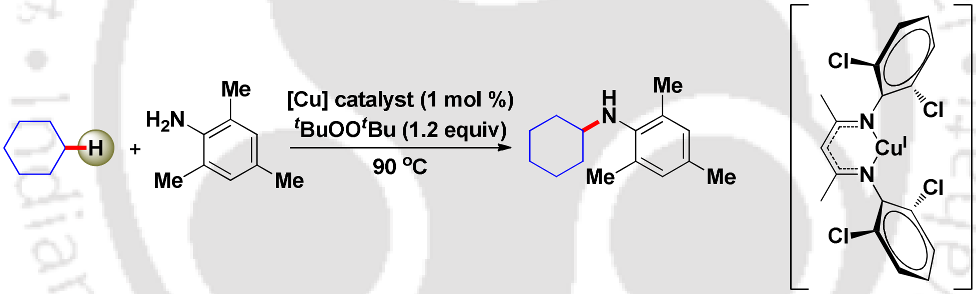
The direct dehydrogenative C–N coupling of azoles or polyfluoroarene sp^2 C–H's with N–H sulfoximines proceeds effectively in the presence of a Cu(II) catalyst at room temperature under air to afford the corresponding *N*-arylsulfoximines in good yields (Scheme I.5.2.3.3).[64]



Scheme I.5.2.3.3. *Cu(II)-catalyzed coupling of* C_{sp2}*–H and imine* N_{sp2}*–H*

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

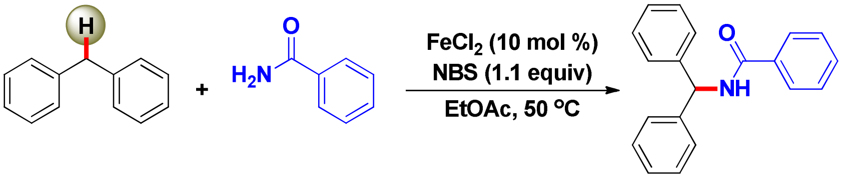
The first general use of commercially available anilines in C–H aminations demonstrated by Warren group with a range of C_{sp3}–H bond containing substrates in the presence of copper(I) catalyst [{(Cl$_2$NN)Cu}$_2$(benzene)] in conjunction with the mild oxidant ^{t}BuOO^{t}Bu (Scheme I.5.2.3.4).[65] Even strong, unactivated C(sp^3)–H bonds could be efficiently functionalized by using low catalyst loadings and electron-poor anilines which suppress the formation of diazene.



Scheme I.5.2.3.4. *Copper(I)-catalyzed direct sp*^{3} *C–H amination of alkanes*

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

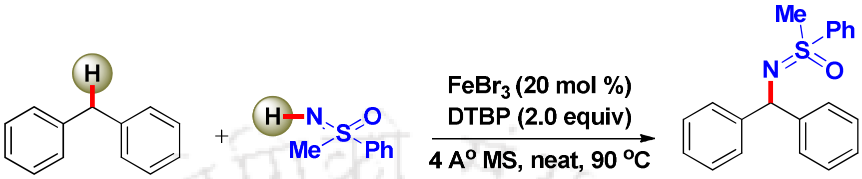
An interesting protocol demonstrated by Fu *et al.* for the amidation of benzylic sp^3 C–H bonds of diarylmethanes utilizing benzamide as the coupling counterpart. This method provided reasonable yields of corresponding *N*-alkylated products under mild conditions using FeCl$_2$ as the catalyst, NBS as the oxidant and ethyl acetate as the solvent (Scheme I.5.2.3.5).[66]



Scheme I.5.2.3.5. *Iron(II)-catalyzed benzylic sp*^{3} *C–H amidation*

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

Bolm group reported a Fe-catalyzed interesting protocol for the synthesis of *N*-alkylated sulfoximines *via* the direct coupling of N_{sp2}–H bond of sulfoximines and C_{sp3}–H bond of diarylmethanes through hetero-CDC reaction (Scheme I.5.2.3.6).[67]

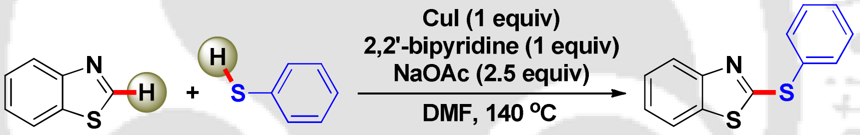


Scheme I.5.2.3.6. *Fe-catalyzed coupling of C_{sp3}–H and imine N_{sp2}–H*

I.5.2.4. Representative examples of C–S bond formation

➢ C_{sp2}–H / S_{sp3}–H Coupling

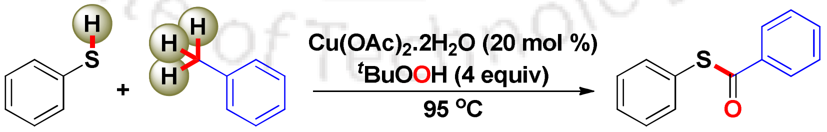
Liu and co-workers reported the synthesis of a variety of aryl or alkylsubstituted 2-mercaptobenzothiazoles by the direct thiolation of benzothiazoles with aryl or alkyl thiols in the presence of stoichiometric CuI, 2,2′-bipyridine and NaOAc (Scheme I.5.2.4.1).[68]



Scheme I.5.2.4.1. *Copper(I)-catalyzed direct thiolation of benzothiazole*

➢ C_{sp3}–H / S_{sp3}–H Coupling

Our group has developed a Cu(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes for the synthesis of thioesters in presence of *tert*-butyl hydroperoxide as oxidant as well oxygen source *via* three sp^3 C–H bonds and one sp^3 S–H bond activation (Scheme I.5.2.4.2).[69]

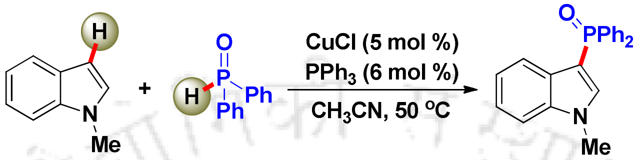


Scheme I.5.2.4.2. *Copper(II)-catalyzed synthesis of thioesters*

I.5.2.5. Representative examples of C–P bond formation

- **C_{sp2}–P Bond formation *via* CDC**

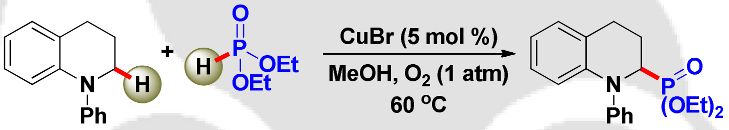
A highly efficient oxidative C_{sp2}–P bond formation protocol developed by Yang group for the preparation of various 3-phosphoindoles *via* a Cu(I)-catalyzed CDC between substituted indoles and disubstituted phosphine oxide (Scheme I.5.2.5.1).[70]



Scheme I.5.2.5.1. *Copper(I)-catalyzed direct phosphorylation of indoles*

- **C_{sp3}–P Bond formation *via* CDC**

Li group has developed an efficient CDC reaction between sp^3 C–H and H–P bonds using catalytic Cu(I) and oxygen (O_2) as the terminal oxidant. This methodology provides an easy access to biologically important α-aminophosphonates (Scheme I.5.2.5.2).[71]



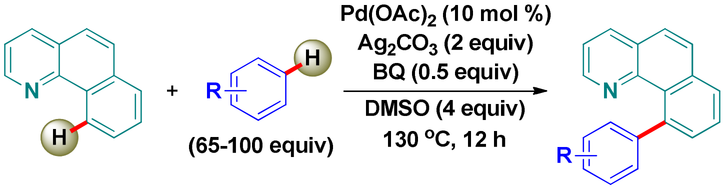
Scheme I.5.2.5.2. *Cu(I)-catalyzed C $_{sp3}$–H bond formation via CDC*

I.5.3. Directing group assisted cross-dehydrogenative coupling: The most powerful approach to selectively functionalize *ortho* C–H bonds to form C–C or C–X (X = hetero atom) bonds is *via* the combination of directing group assisted and cross-dehydrogenative coupling (CDC) strategies.

I.5.3.1. Representative examples of directed CDC reactions

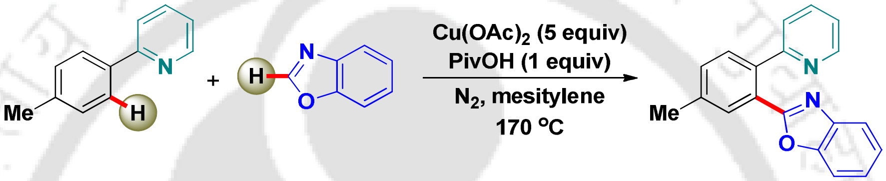
- ***Ortho*-arylation *via* C_{sp2}–H / C_{sp2}–H**

Sanford *et al.* reported a Pd(II) catalyzed highly chemo and regioselective sp^2 C–H arylation of directing arene benzo[*h*]quinoline using Ag_2CO_3 and *p*-benzoquinone as terminal oxidants. This transformation is proposed to proceed *via* two discrete C–H activation steps following the idea of directed CDC reactions (Scheme I.5.3.1.1).[72] A variety of directing arene such as 2-arylpyridine, 1-arylpyrazole, 2-arylpyrimidine and 8-methylquinoline derivatives were all effective under this reaction condition providing similar cross-coupled products. Directed C_{sp2}–H / C_{sp2}–H coupling was also applied to directing arenes such as indolines, arylguanidines for similar *ortho* arylations.[73]



Scheme I.5.3.1.1. *Pd(II)-mediated direct biaryl coupling of benzo[h]quinoline*

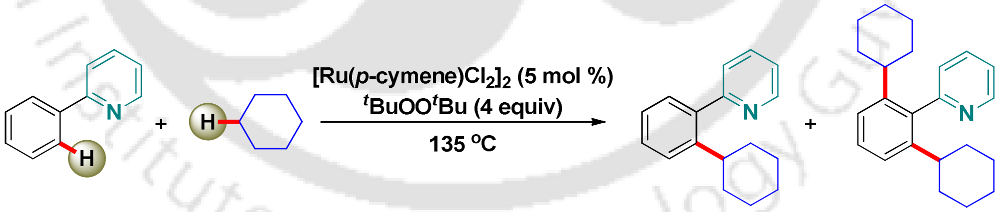
Later on Miura group achieved a Pd-free, Cu-mediated intermolecular direct C_{sp2}–H / C_{sp2}–H coupling of arylazines and azoles (Scheme I.5.3.1.2).[74]



Scheme I.5.3.1.2. *Copper(II)-mediated biaryl coupling of 2-arylpyridines and azoles*

- ***Ortho* alkylation *via* C_{sp2}–H / C_{sp3}–H**

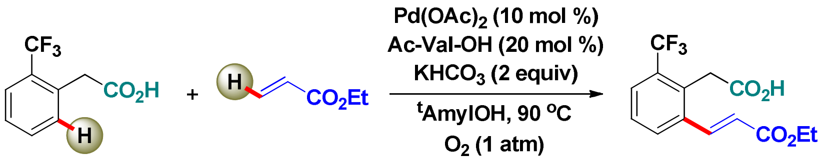
Li group have demonstrated a lone strategy for the substrate directed arene–alkane coupling of 2-arylpyridine or analogous substrates with inert cycloalkanes as the coupling partner in presence of Ru(II) catalyst in combination of di-*tert*-butylperoxide (DTBP) as oxidant (Scheme I.5.3.1.3).[75]



Scheme I.5.3.1.3. *Ruthenium(II)-catalyzed ortho cycloalkylation of 2-phenylpyridine*

- ***Ortho* alkenylation *via* C_{sp2}–H / C_{sp2}–H**

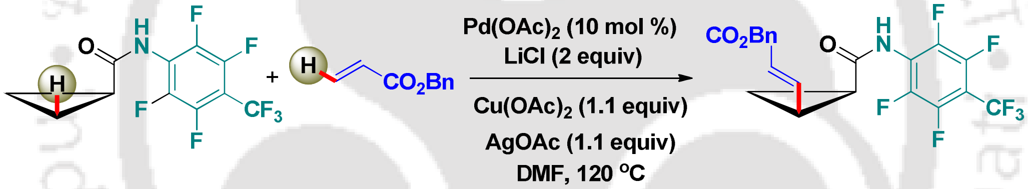
Yu group developed a protocol for aerobic Pd(II)-catalyzed C–H olefination of phenylacetic acid using a amino acid ligand, Ac-Val-OH. This interesting protocol demonstrates the use of suitable amino acid ligand to achieve *o*-alkenylaion involving double C–H's (Scheme I.5.3.1.4).[76]



Scheme I.5.3.1.4. *Palladium(II)-catalyzed C–H olefination of phenylacetic acid*

➢ Alkenylation *via* C_{sp3}–H / C_{sp2}–H

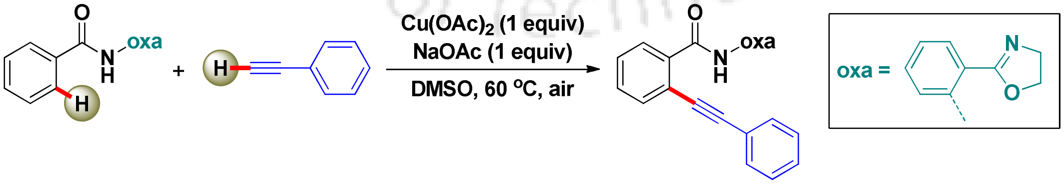
In addition to the sp^{2} C–H olefination, Yu group also developed an amide group assisted Pd(II)-catalyzed reaction for the direct olefination of sp^{3} C–H bonds (Scheme I.5.3.1.5).[77a] The reaction conditions could also be applied to promote olefination of cyclopropyl methylene C–H bonds and substrates containing α-hydrogens. Later, the same group applied this method for the generation of β-quaternary carbon centers.[27] Recently they have also demonstrated monoselective γ-C–H olefination of aliphatic acids using a combination of a quinoline-based ligand and a weakly coordinating amide directing group.[77b]



Scheme I.5.3.1.5. *Pd-catalyzed amide directed sp^{3} C–H alkenylation*

➢ *Ortho* alkynylation *via* C_{sp2}–H / C_{sp}–H

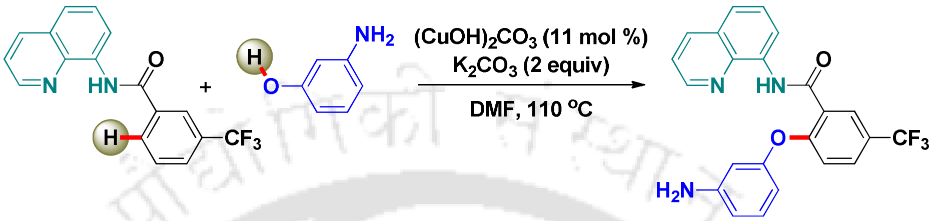
Yu group recently reported a Cu(II)-promoted *ortho*-alkynylation of arenes and heteroarenes with terminal alkynes to prepare aryl alkynes (Scheme I.5.3.1.6).[78] A variety of arenes and terminal alkynes bearing different substituents are compatible with this reaction, thus providing an alternative disconnection to Sonogashira coupling.



Scheme I.5.3.1.6. *Copper(II)-catalyzed auxillary assisted alkynylation of arenes*

➢ ***Ortho*** **alkoxylation** ***via*** **C_{sp2}–H / O_{sp3}–H**

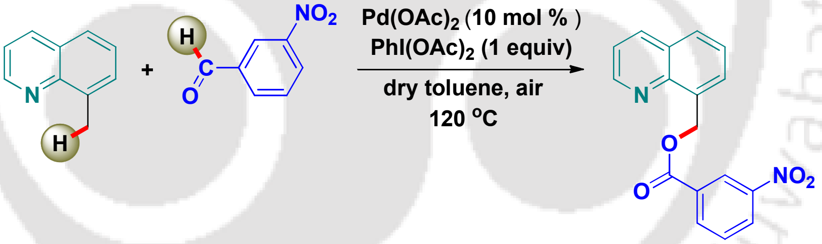
Daugulis group developed a method for auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of amine derivatives using aromatic or aliphatic alcohol as coupling partners and $(CuOH)_2CO_3$ as the catalyst (Scheme I.5.3.1.7).[79]



Scheme I.5.3.1.7. *Copper(II)-catalyzed auxillary assisted sp^2 C–H phenoxylation*

➢ ***Ortho*** **benzoxylation** ***via*** **C_{sp3}–H / O_{sp3}–H**

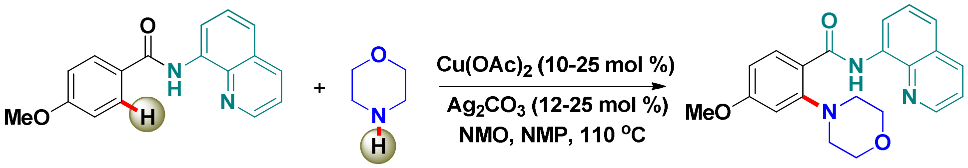
Cheng group described a chelation-assisted Pd(II)-catalyzed acyloxylation of the benzyl sp^3 C–H bond with carboxylic acid employing $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme I.5.3.1.8).[80] This procedure tolerates a series of functional groups, providing the acyloxylated products in moderate to good yields.



Scheme I.5.3.1.8. *Palladium(II)-catalyzed benzoxylation of benzylic sp^3 C–H bond*

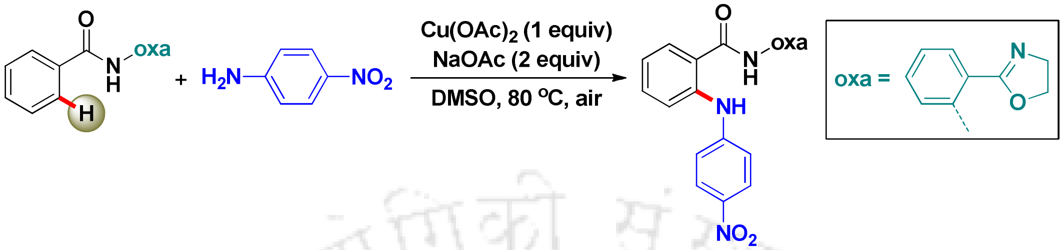
➢ ***Ortho*** **amination** ***via*** **C_{sp2}–H / N_{sp3}–H**

Using aminoquinoline as directing axillary Daugulis and co-workers reported the C–H / N–H coupling between morpholines and carboxylic acid derivatives (Scheme I.5.3.1.9).[81] The reaction is catalyzed by a dual Cu^{II}–Ag^{I} catalytic system using *N*-methylmorpholine oxide (NMO) as the terminal oxidant.



Scheme I.5.3.1.9. *CDC amination of benzamides with aliphatic amines*

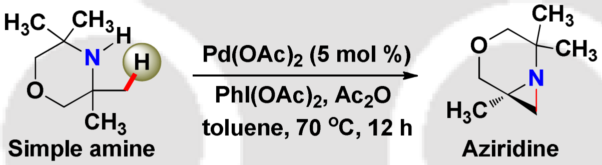
Recently Yu group demonstrated a Cu(II)-mediated C−H amination of arenes with a variety of anilines (Scheme I.5.3.1.10).[82a] The exceptional compatibility of this amination with multiple heteroatoms present in both reactants renders this reaction highly valuable.



Scheme I.5.3.1.10. *Copper(II)-catalyzed amide directed amination of arenes*

➢ Amination *via* C_{sp3}–H / N_{sp3}–H

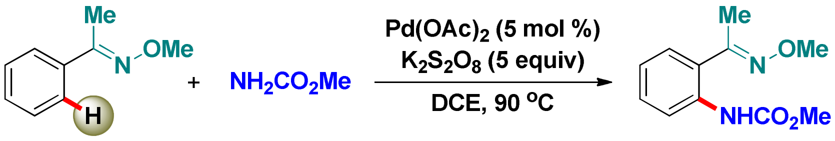
Gaunt and his coworkers developed a Pd-catalyzed C_{sp3}–H activation of aliphatic amines that proceeds through an unusual four-membered ring cyclopalladation pathway. This intramolecular sp^3 C–H chemistry described here leads to the selective transformation of a methyl group that is adjacent to an unprotected secondary amine into a synthetically versatile nitrogen heterocycle (Scheme I.5.3.1.11).[82b]



Scheme I.5.3.1.11. *Amine directed Pd(II)-catalyzed intramolecular sp³ C–H amination*

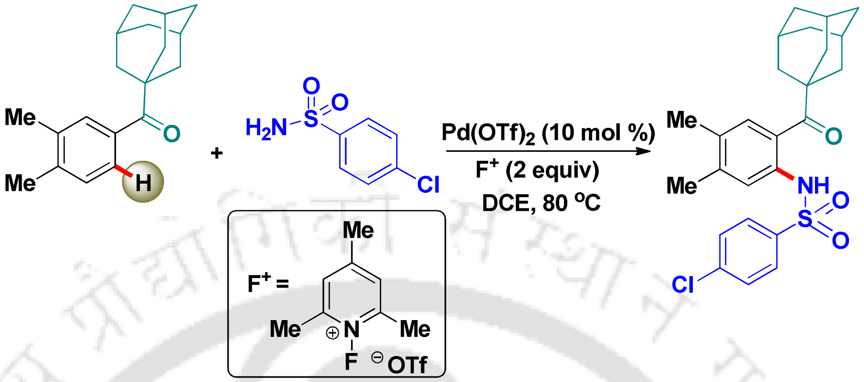
➢ *Ortho* amidation *via* C_{sp2}–H / N_{sp3}–H

CDC protocol on intermolecular C–N bond formation demonstrated by Che group *via* a Pd-catalyzed pyridine and oxime ether directed C–H amidation (Scheme I.5.3.1.12).[83] In this system, $Pd(OAc)_2$ served as the catalyst and a combination of $K_2S_2O_8$ and NH_2R was used to introduce the nitrogen functionality.



Scheme I.5.3.1.12. *Ketoxime ether directed palladium(II)-catalyzed amidation of arenes*

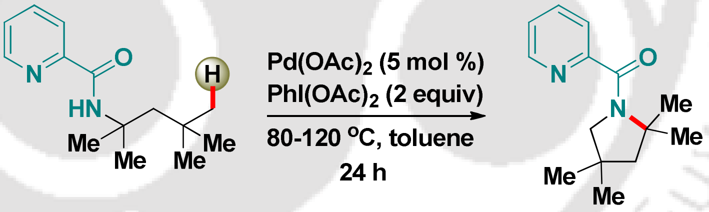
In 2010 Li and co-workers published *o*-amidaion of arylpyridines using acetanilides as amidaing surrogate in presence of CuBr / di-*tert*-butyl peroxide (DTBP) catalytic combination.[84] Thereafter in 2011, Liu and his team published the condensation of phenone derivatives with sulfonamides using Pd(II) catalyst. This process requires two equivalents of non atom economical electrophilic fluoro-oxidant (Scheme I.5.3.1.13).[85a]



Scheme I.5.3.1.13. *Keone direced amidation of phenones with sulfonamides*

➢ Amidation *via* C_{sp3}–H / N_{sp3}–H

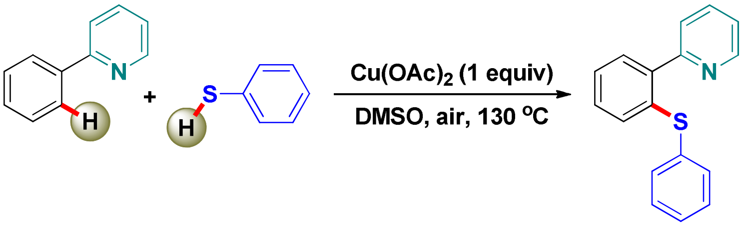
Using picolinamide as directing auxillary, Daugulis group developed first Pd(II) catalyzed intramolecular amidation of unactivated sp^3 carbons. (Scheme I.5.3.1.14).[85b] Later on similar auxillary directed intramolecular sp^3 C–H amidation methods demonstrated by Chen, Ge and Kanai.[85c-g]



Scheme I.5.3.1.14. *Pd(II) catalyzed intramolecular sp^3 C–H amidation*

➢ *Ortho* sp^2 C–H sulfenylation *via* C_{sp2}–H / S_{sp3}–H

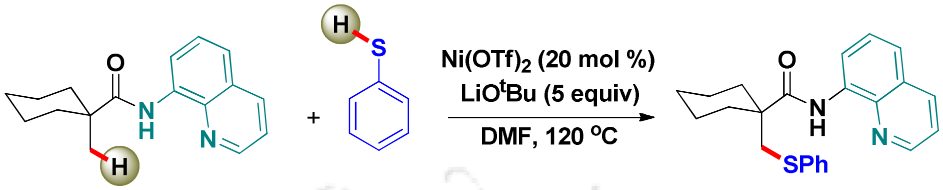
In 2006 Yu group has accomplished a Cu(II)-catalyzed direct sulfenylation at sp^2 C–H of 2-arylpyridine using benzene thiol as the coupling partner (Scheme I.5.3.1.15).[32b]



Scheme I.5.3.1.15. *Copper(II)-catalyzed ortho-thiolation of arenes*

➢ Sulfenylation *via* C_{sp3}–H / S_{sp3}–H

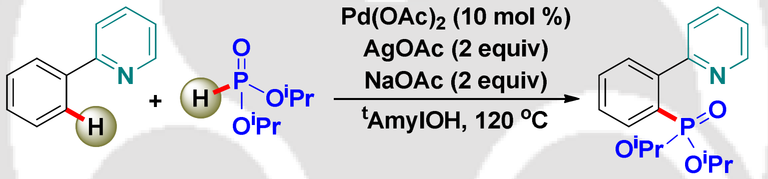
Recently, Shi group demonstrated the nickel-catalyzed 8-aminoquinoline directed thiolation /sulfenylation of C(sp^3)–H bonds to form thioethers (Scheme I.5.1.3.16).[45d]



Scheme I.5.3.1.16. *Ni(II)-catalyzed sp^3 C–H sulfenylation*

➢ *Ortho* sp^2 C–H phosphorylation *via* CDC

Yu group has reported the first Pd(II)-catalyzed C–H phosphorylation of 2-arylpyridines using both *H*-phosphonates and diaryl phosphine oxides as suitable coupling partners for this reaction (Scheme I.5.3.1.17).[86a] Later on Murakami group reported a similar *o*-phosphorylation using *N*-directed substrates such as 2-phenylpyridines, quinolines, isoquinolines, benzo[*h*]quinolines and pyrimidines.[86b]

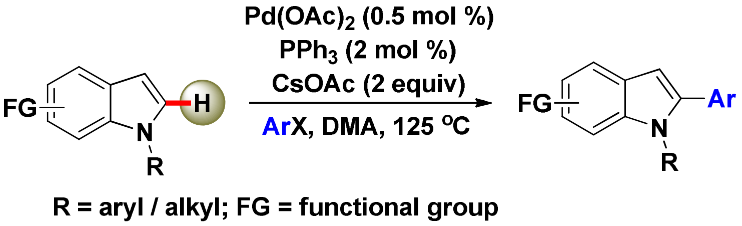


Scheme I.5.3.1.17. *Palladium(II)-catalyzed C–H phosphorylation of 2-phenylpyridine*

I.5.4. An array of exceptions: Reactions which are not included in the above three classes are exemplified below.

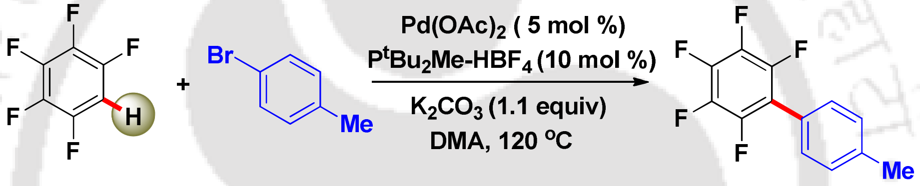
I.5.4.1. Non-directed C–H functionalization *via* C_{sp2}–H and C_{sp2}–X coupling

The Heck reaction (also called the Mizoroki-Heck reaction) is the early example of C–H functionalizaion / C–C bond-forming reaction of an unsaturated halide (or triflate) with an olefin in the presence of a base and a Pd(0)-catalyst to form a substituted alkene.[87a-b] Lately in 2004 Sames group developed a Pd(II) catalyzed C-2 selective C–H arylation of electron rich *N*-substituted indoles using aryl halides as coupling partner with good yields, and a high degree of functional group tolerance (Scheme I.5.4.1.1).[87c]



Scheme I.5.4.1.1. *Pd(II)-catalyzed C-2 arylation of electron rich arenes*

Intermolecular direct arylation of electron-withdrawing perfluorobenzenes was introduced by Fagnou group using a wide variety of arylhalides. The reactions require only a slight excess of the perfluoroarene reagent, and utilize commercially available, air-stable catalyst precursors. Inverse reactivity is observed compared to the common electrophilic aromatic substitution pathway since electron-deficient C–H acidic arenes react preferentially (Scheme I.5.4.1.2).[88]



Scheme I.5.4.1.2. *Pd(II)-catalyzed direct arylation of electron deficient arenes*

I.5.4.2. Directed C–H bond functionalization using oxidizing groups

Compared with the well-established directed C–H bond functionalization using external stoitiometric oxidants, mainly silver or copper salts, oxidizing group directed redox-neutral C–H bond functionalization presents unparalleled advantages:

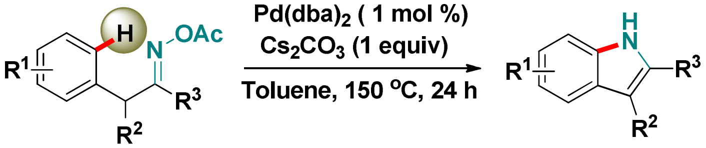
(1) No external oxidants required for the catalytic cycle.

(2) Simple and mild reaction conditions.

(3) Very good functional group tolerance.

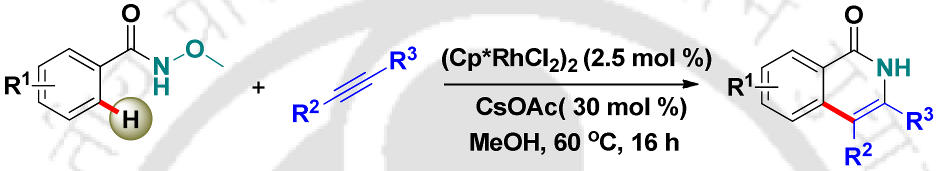
(4) High regioselectivity.

The oxidizing group directed redox-neutral C–H bond functionalization was pioneered in 2009 by Wu, Cui and co-workers.[89] They ingeniously employed pyridine *N*-oxides as substrates cum oxidants in the oxidative Heck reaction. Further progress was made by Hartwig during the synthesis of indole using oxime ester as oxidising directing group (Scheme I.5.4.2.1).[90]



Scheme I.5.4.2.1. *Pd-catalyzed redox-neutral intramolecular ortho sp^2 C–H amination*

Inspired by previous work in palladium chemistry, the Fagnou group developed first example of Rh(III)-catalyzed redox-neutral C–H bond functionalization of *N*-methoxybenzamides and C–N bond formation sequence to afford isoquinolone derivatives.(Scheme I.5.4.2.2).[91]



Scheme I.5.4.2.2. *Rh(III)-catalyzed redox neutral intermolecular ortho sp^2 C–H annulaion*

Similar directing group assisted redox-neutral annulation strategies were further extended by Glorius,[92a-b] Rovis,[92c-e] Cramer[92f-g] and others.[92h-o] In a conceptual way structures of various oxidizing directing groups are depicted below which are shown in Figure I.5.4.2.1

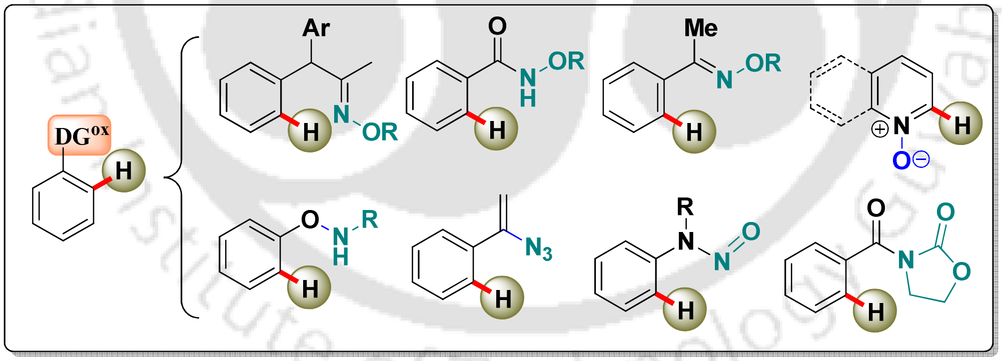


Fig. I.5.4.2.1. *Oxidizing directing groups with internal oxidants*

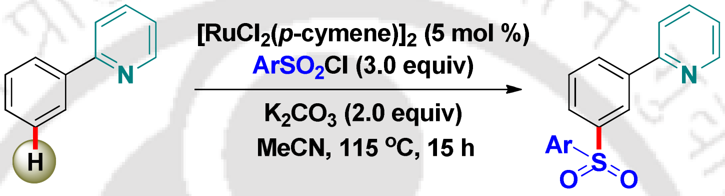
I.5.4.3. Directing group assisted site selectivity beyond *ortho* site

Comapred to proximity controlled well-established *ortho* directing groups *via* five- or six-membered metallacycles, the elusive *meta*- and *para* selective C–H transformations may require larger metallacycles, which are often very difficult to generate. Traditionally, *meta*-selective C–H transformations have been realized initially by steric control[93] or ligand promotion.[94] During that time Gaunt and co-workers disclosed a few *meta* and *para*-

selective C–H functionalizations in the presence or absence of copper catalyst.[95] Stimulated by these studies, several new *meta* or *para*-selective transformations and new strategies appeared very recently.

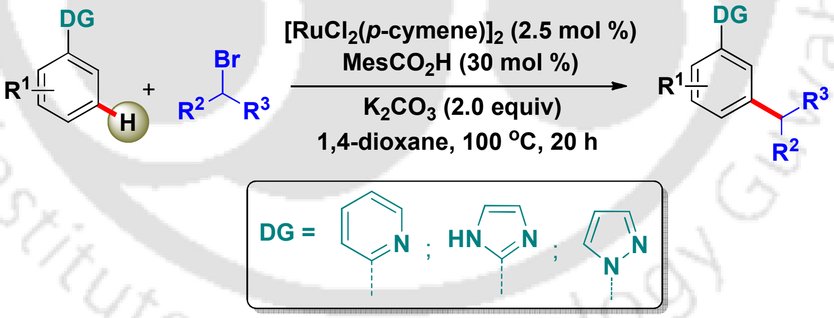
➢ *Meta*-C–H bond functionalization controlled by electronic effects

Recently, Frost and co-workers reported a strategy for a *meta* selective C–H functionalization, namely the sulfonation of 2-phenylpyridines, with the assistance of a ruthenium catalyst (Scheme I.5.4.3.1).[96] This protocol represents the first example of a catalytic σ-activation process.



Scheme I.5.4.3.1. *Ru(II)-catalyzed meta-selective sp*^{2} *C–H sulfonation*

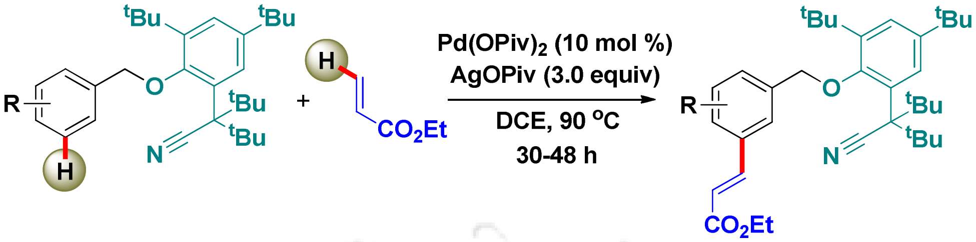
Similarly Ackermann group developed a *meta*-selective C–H alkylation strategy of *N*-heterocycle-containing arenes with secondary alkyl bromides where an initial reversible cycloruthenation increased the reactivity of arenes to undergo electrophilic-type substitutions *para* to carbon-ruthenum (C-Ru) bond (Scheme I.5.4.3.2).[97]



Scheme I.5.4.3.2. *Ru(II)-catalyzed meta-selective alkylation*

➢ Template assisted *meta*-selective C–H functionalization

In contrast to achieving *meta*-selectivity by controlling the electronic bias, Yu group chose to take advantage of spatial proximity for obtaining challenging *meta* selectivity by employing an elaborately designed template. In 2012, Yu and co-workers successfully demonstrated a Pd(II)-catalyzed *meta*-C–H olefination of toluene derivatives using nitrile based removable directing template (Scheme I.5.4.3.3).[98] In this seminal work, the long-range directing group was thought to coordinate the palladium catalyst *via* a cyclophanetype transition state, which could facilitate the approach of the catalyst to induce the *meta*-C–H functionalization.



Scheme I.5.4.3.3. *Pd(II) catalyzed meta-selective olefination of toluene derriavtives*

This template-based idea of *meta* sp^2 C–H functionalization was further exemplified by Yu and others for *meta*-selective arylation, acetoxylation and olefination using a range of modified nitrile based removable directing templates.[99] In a simplified way structures of various *meta* selective directing templates are depicted below in Figure I.5.4.3.1.

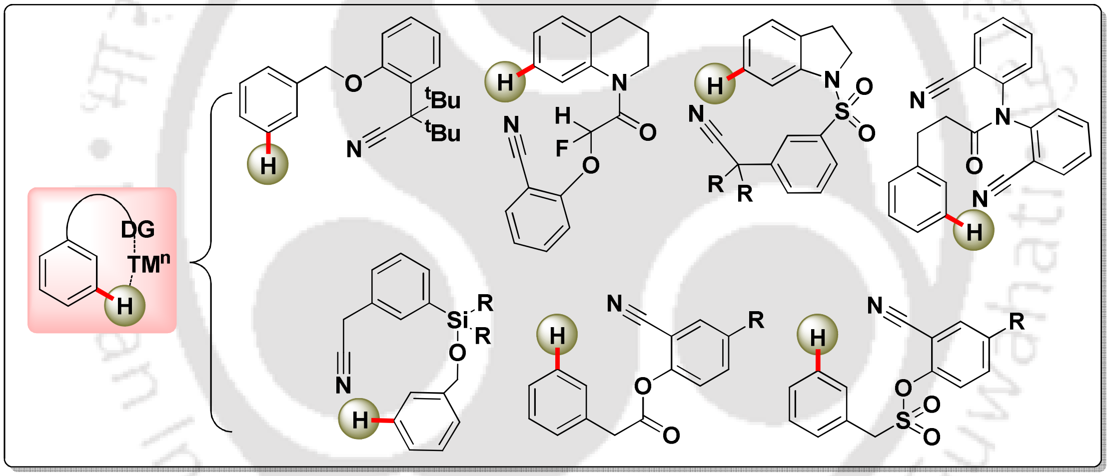
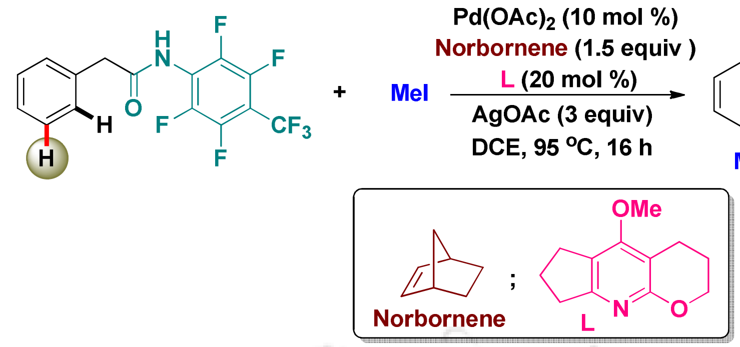


Fig. I.5.4.3.1. *Overview of nitrile based removable meta-directing templates*

➢ ***Meta*-C–H bond functionalization using norbornene as a transient mediator**

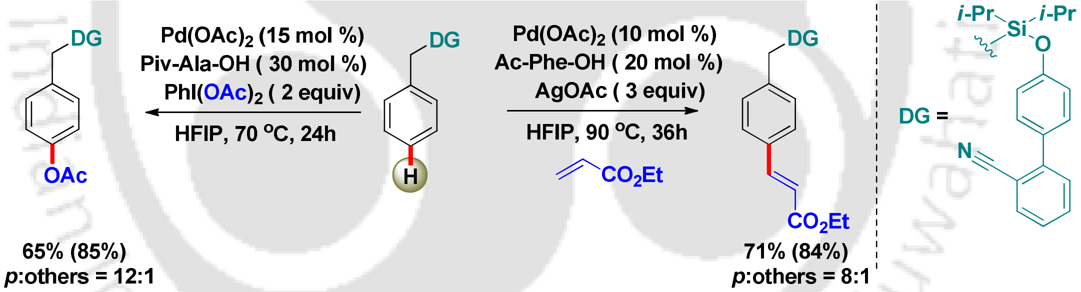
Yu and co-workers reported an alternative ligand enabled Pd(II) catalyzed *meta*-selective C–H activation with a simple and common *ortho* directing group employing norbornene as a transient mediator.[100] The use of a newly developed pyridine-based ligand is crucial for relaying the palladium catalyst to the *meta* position by norbornene after initial *ortho*-C–H activation (Scheme I.5.4.3.4).



Scheme I.5.4.3.4. *meta-C–H alkylation of phenylacetic amides using norbornene*

- ***Para*-C–H bond functionalization controlled by directing template**

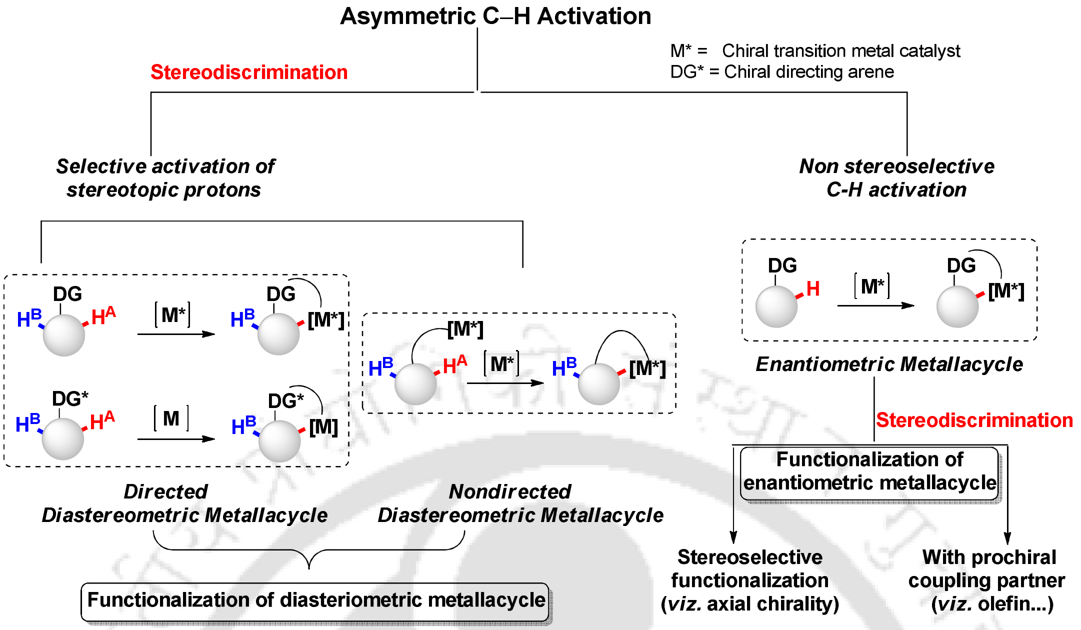
Very recently Maity and coworkers reported a Pd(II) catalyzed novel Si-containing biphenyl-based D-shaped template that directs efficient functionalization of the distal *p*-C–H bond of toluene derivatives (Scheme I.5.4.3.5).[101] This DG allows the required flexibility to support the formation of an oversized pre-transition state. By overcoming electronic and steric bias, *para*-olefination and acetoxylation were successfully performed while undermining *o*- and *m*-C–H activation.



Scheme I.5.4.3.5. *Pd(II) catalyzed para-selective functionalization of toluene derrivatives*

I.6. Asymmetric C–H Activation

With regard to rapid expansion of the C–H bond activation field, the asymmetric version of the C–H-activation-based transformation has attracted a growing interest.[102] However, an efficient induction of stereochemical information during the C–H functionalization is a challenging task as harsh reaction conditions and elevated temperatures are generally required to ensure a fruitful C–H activation and such drastic conditions might have a detrimental impact on the stability of the chiral complex and the efficiency of asymmetric induction.



Scheme I.6.1. *Simplified classification of asymmetric C–H activation*

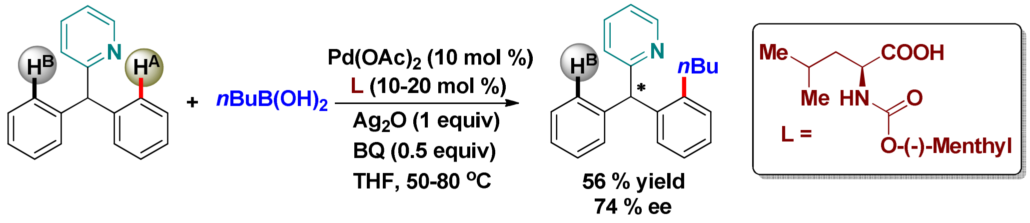
From a conceptual point of view, two distinct strategies can be envisioned to achieve stereoselective C–H activation-based transformations (Scheme I.6.1.):

(1) The chiral discrimination occurs during the C–H activation event.

(2) The chirality is induced subsequent to the C–H activation step and results from a stereocontrolled functionalization of the metallacycle.

I.6.1. Intermolecular stereoselective C–H activation *via* diasteriometric metallation

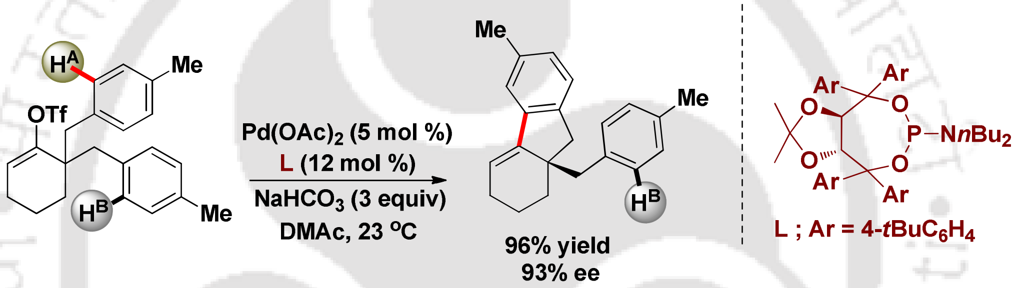
The seminal contribution came in 2008 by Yu group where they developed direct desymmetrization reaction of prochiral 2-[di(phenyl)methyl]pyridine using monoprotected amino acids [*N*-protected leucine (L)] for the first time as a source of chirality in the Pd-catalyzed alkylation reactions (Scheme I.6.1.1).[103] The potential of this class of ligand is probably due to the bidentate coordination of the Pd catalyst and the efficient control of the chiral environment by minimising steric repulsion in the key transition states.[104]



Scheme I.6.1.1. *Asymmetric desymmetrization via sp^2 C–H alkylation*

I.6.2. Intramolecular Stereoselective C–H activation *via* diasteriometric metallation

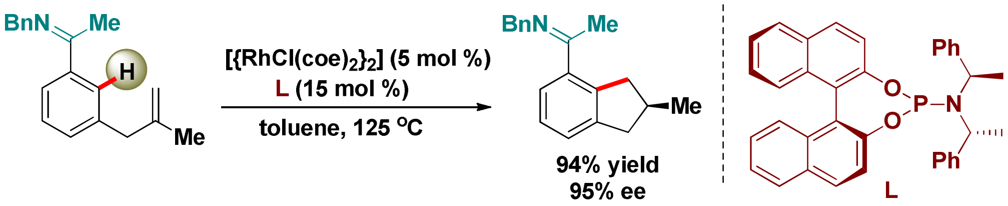
A complementary method to ensure a stereoselective outcome of a C–H activation consists of initial coordination of a low oxidative state catalyst to the substrate by means of oxidative addition followed by "intramolecular" C–H metalation. A pioneering contribution in this field was made by Cramer in 2009 (Scheme I.6.2.1).[105] The Pd(0)/Pd(II) catalytic cycle was envisioned to enable firstly the oxidative addition of the catalyst to a vinyl triflate moiety of the substrate followed by the C–H activation of one of the enantiotopic C_{sp2}–H bonds of two aryl substituents. Moreover, the mechanistic consideration suggested that a monodentate taddol-based phosphoramidite (L; see Scheme I.6.2.1. for the structure) ligand is crucial to ensure a free coordination site for the C–H activation step.



Scheme I.6.2.1. *Indanes syntsheis via intramolecular asymmetric C–H activation*

I.6.3. C–H Activation followed by stereoselective functionalization *via* enantiometric metallation

In this context Bergman and Ellman reported enantioselective cyclization of aromatic imines by means of an *ortho*-directed C_{sp2}–H activation followed by the migratory insertion of the *meta*-tethered alkene moiety has been developed (Scheme I.6.3.1.).[106] An axially chiral phosphoramidite ligand (L) was identified as the best chiral inductor. The stereocontrol of such transformations, which is probably due to diastereoselective migratory insertion of the olefin into the Rh–H bond, is determined predominantly by binol backbone.



Scheme I.6.3.1. *Intramolecular asymmetric alkylation of aromatic imines*

Hence, such transformations became a key step of the efficient synthesis of (+)-lithospermic acid which will be discussed in the next section.[107]

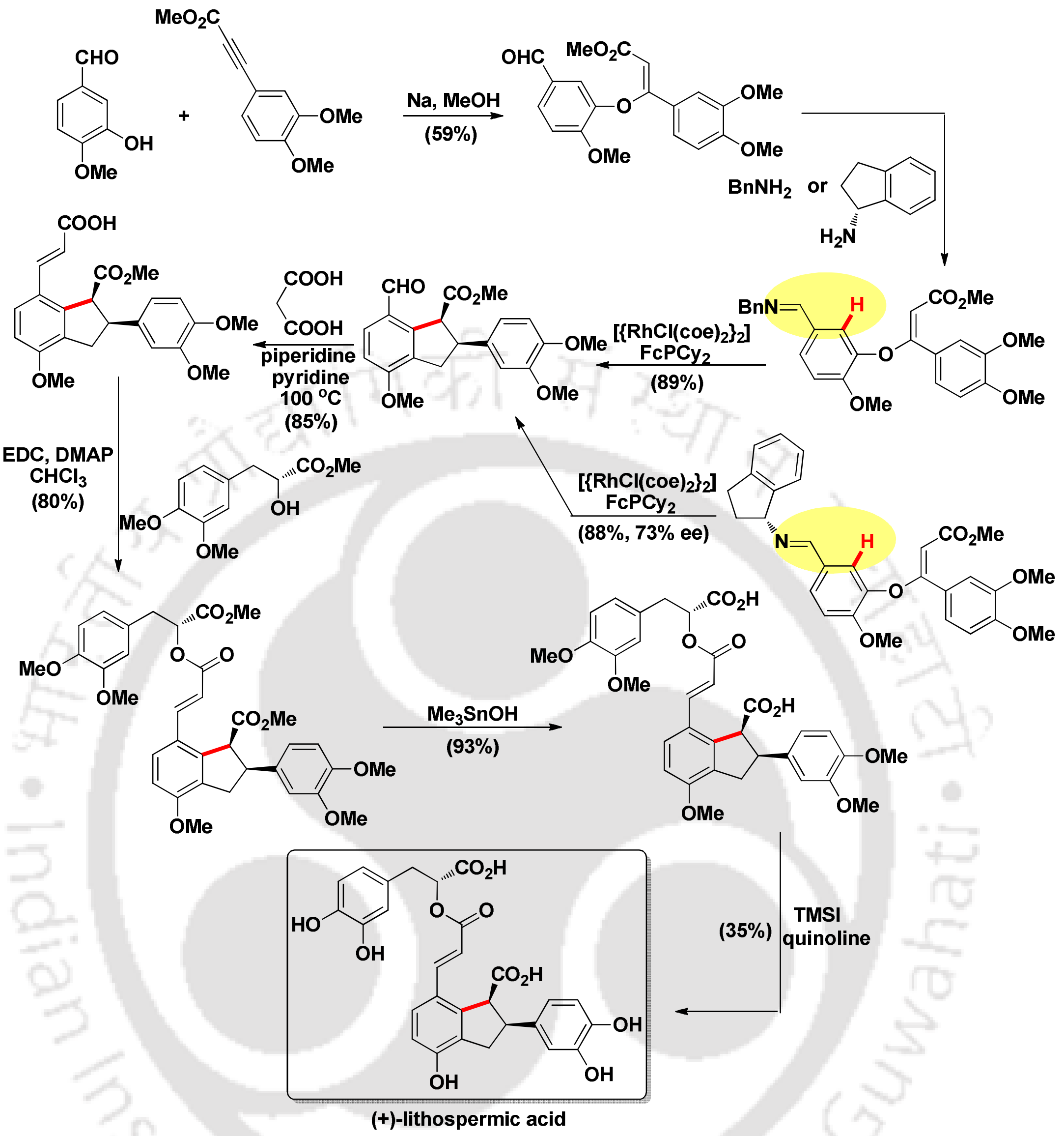
I.7. C–H Activation: A Complementary Tool in Total Synthesis

The current knowledge in the field has enabled the use of C–H functionalization as a reliable tool for natural product synthesis, even as a late-stage manipulation in complex targets. However C–H activation in the context of total synthesis of complex natural products are beginning to blossom.[108] Herein mentioned below is one example of total synthesis showcasing creative and ingenious incorporation of C–H activation as a strategic plan compared to the traditional methods, enlightening a new paradigm in strategic synthetic design.

I.7.1. Total synthesis of (+)-Lithospermic Acid

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

Bergman and Ellman reported first total synthesis of this important natural product (+)-lithospermic acid (Scheme I.7.1.1).[107] The efficient synthesis features an asymmetric alkylation via C–H bond activation to assemble the dihydrobenzofuran core of the natural product. This was accomplished via a chiral imine-directed C–H bond functionalization and represents the first application of this C–H activation method to natural product synthesis. Furthermore, a challenging deprotection of a late-stage permethylated lithospermic acid was achieved.



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

I.8. References

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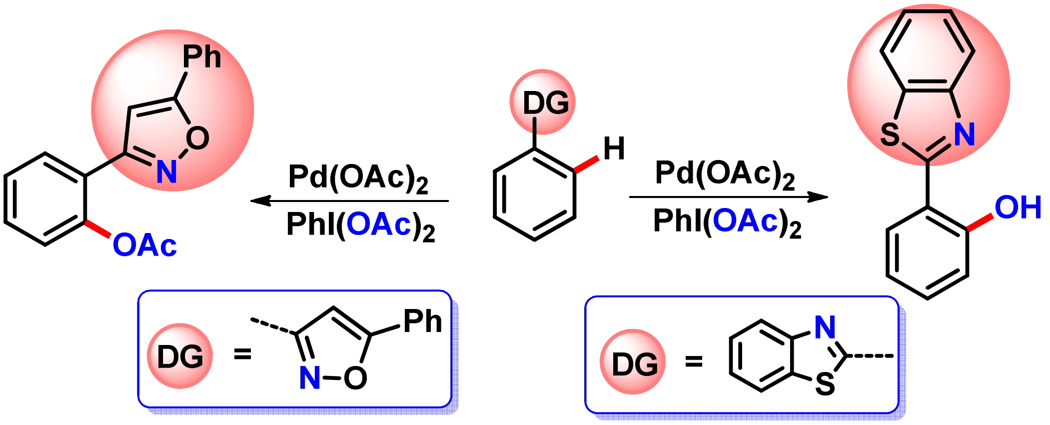
Chapter II

Palladium(II) Catalyzed Regioselective o-Hydroxylation and o-Acetoxylation of 2-Arylbenzothizole and 3,5-Diarylisoxazole



Abstract: *Efficient protocols have been developed for the ortho C_{sp2}–H hydroxylation and o-acetoxylation of 2-arylbenzothiazole and 3,5-diarylisoxazole using $Pd(OAc)_2$ as the catalyst and DIB as the oxidant under air atmosphere. Both these strategies tolerate a diverse array of substituents giving good to excellent yields of corresponding ortho-hydroxylated / acetoxylated products.*

CHAPTER II

This chapter is divided into two sections. Section-A describes regioselective *o*-hydroxylation of 2-arylbenzothiazole whereas Section-B demonstrates *o*-acetoxylation of an another directing arene, 3,5-diarylisoxazole.

IIA. Regioselective *ortho*-Hydroxylation of 2-Arylbenzothiazole *via* Substrate Directed C–H Activation

IIA.1. Introduction

Direct and selective functionalization of inert carbon-hydrogen (C–H) bonds is one of the most powerful approach for the construction of complex organic molecules.[1,2] This approach, facilitated by various transition metals, has led to organic C–H bonds viewed as dormant synthetic equivalents of many reactive functional groups. The installation of new functionality otherwise none existed previously, has led to the construction of complex molecular architecture. While various transition metal catalysts have been employed for this purpose, palladium-catalyzed reactions are especially effective and thus have attracted much attention to construct diverse array of C–C or C–X (X = hetero atoms) bonds in the plethora of synthetic transformations.[3] In this context Pd-catalyzed substrate-directed C–H functionalizations are privileged due to its preferential *ortho* directed chelation of Pd catalyst *via* the assiatance of various *N* or *O* donor atoms containing substrates,[4] which assist the cyclometallation step and thus the regioselective functionalizations.

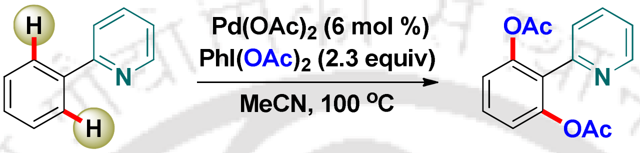
Various directing group containing substrates have been well explored toward palladium catalyzed oxidative C–O bond formation, in particular *o*-acetoxylation, *o*-benzoxylation, *o*-alkoxylation and *o*-hydroxylation.[5]

IIA.2. Strategies for *ortho* C–O Bond Formation

Representative examples pertaining to various forms of C–O bond formations are discussed below.

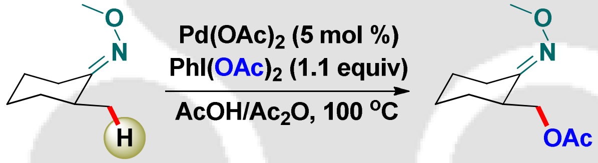
➢ C–H Acetoxylation

Sanford group reported the first example of ligand-directed sp^2 C–H bond oxygenation using PhI(OAc)$_2$ as a stoichiometric oxidant in combination with catalytic Pd(OAc)$_2$ (Scheme IIA.2.1).[6a] Other nitrogen-based directing groups, including imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles (e.g., pyrazoles and isoxazolines) and even amides were also effective. Other hypervalent iodine oxidants or peroxide oxidants have also been utilized towards acetoxylation reactions.[6b-c]



Scheme IIA.2.1. *Pd-catalyzed sp^2 C–H acetoxylation of 2-phenylpyridines*

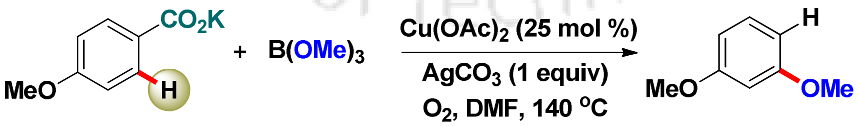
The same group also reported a Pd-catalyzed ligand-directed sp^3 C–H bond oxygenation using PhI(OAc)$_2$ as the terminal oxidant (Scheme IIA.2.2).[6a,d] Oxime ether and pyridine directing groups could be utilized for these transformations.[6a,d]



Scheme IIA.2.2. *Pd-catalyzed sp^3 C–H acetoxylation of ketoxime ethers*

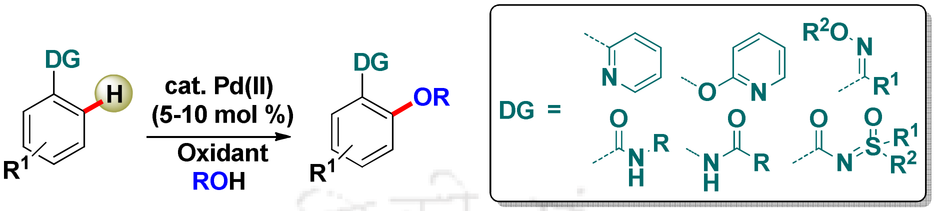
➢ C–H Alkoxylation

Gooβen group demostrated a regiospecific Cu(II) catalyzed *ortho*-alkoxylation of aromatic carboxylates with concomitant decarboxylation (Scheme IIA.2.3).[7] This protocol gives access to the important substrate class of aromatic ethers from widely available carboxylic acids.



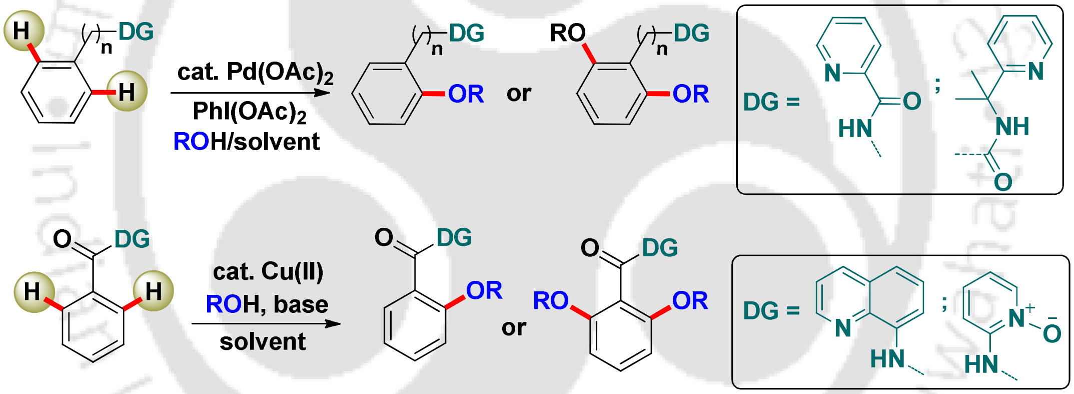
Scheme IIA.2.3. *Cu-catalyzed ortho-alkoxylation of arylcarboxylates*

A number of Pd-catalyzed *ortho* sp^2 C–H alkoxylation protocols are reported for various directing arenes *viz.* 2-arylpyridines, 2-aryloxypyridines, arylnitriles, arylamides, azoles, sulfoximines, *O*-methyl aryl oximes etc. (Scheme IIA.2.4).[8] The use of suitable oxidants (such as oxone, persulfate ($S_2O_8^{2-}$) or hypervalent iodine species) in combination with palladium catalyst and alcholoic solvent (ROH) are the crucial factors for the *ortho* selective C–H alkoxylation of various directing arenes.



Scheme IIA.2.4. *Pd-catalyzed o-alkoxylation of directing arenes*

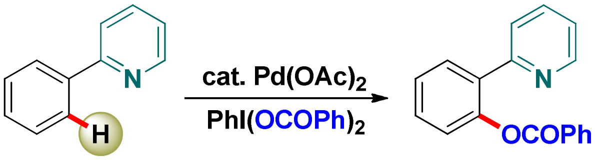
Recently a number of Pd and Cu-catalyzed *ortho* sp^2 and sp^3 C–H alkoxylations by the assistance of bidentate chelating systems such as picolinamide[9a], *N*-(1-methyl-1-(pyridin-2-yl)ethyl)amides[9b], 8-aminoquinoline,[9c] pyridine-N-oxide[9d] and *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS)[9e] (Scheme IIA.2.5) appeared in literature.



Scheme IIA.2.5. *Ortho C–H alkoxylation using bidentate chelation*

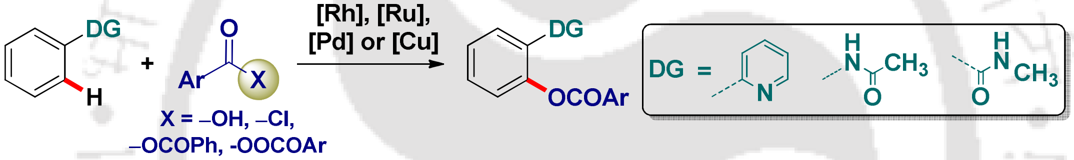
➢ C–H Benzoxylation

Sanford *et al.* reported a palladium catalyzed *o*-benzoxylation of 2-phenylpyridines using benzoate iodonium salts as the ArCOO– surrogates. (Scheme IIA.2.6).[10a] Later, Shi group developed a similar palladium catalyzed *o*-benzoxylation of ketoxime ether *via* the *in situ* generation of benzoate iodonium salts.[10b]



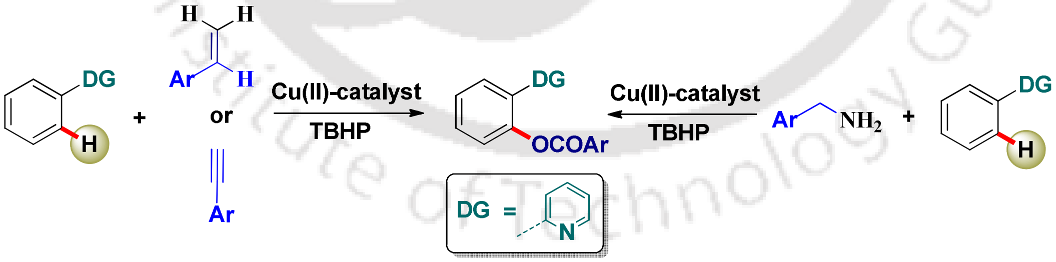
Scheme IIA.2.6. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

Cheng group has demonstrated the use of aromatic carboxylic acids as the ArCOO– source for *o*-benzoxylation of 2-arylpyridines using rhodium catalyst.[11a] The same group has shown that acid derivatives in the form of carboxylic acid salt,[11b] anhydride[11c] and acid chloride[11d] could be used for the similar purpose (Scheme IIA.2.7). Zhong group has also achieved an oxidative *o*-benzoxylation of 2-phenylpyridines with aromatic carboxylic acids under ligand-free conditions using palladium catalyst along with copper and silver salts as additives.[11e] Aryl acylperoxides has also been found to be an effective benzoxy surrogate as illustrated by Yu group in a palladium catalyzed *o*-benzoxylation of 2-phenylpyridines.[11f] Pertinent to the *o*-benzoxylation in substrates possessing other directing groups, very recently Jeganmohan *et. al.* have reported a ruthenium catalyzed *o*-benzoxylation of acetanildes[12a] and benzamides[12b] using aryl carboxylic acids as coupling partners (Scheme IIA.2.7).



Scheme IIA.2.7. *o-Benzoxylation of directing arenes using carboxylic acid derivatives*

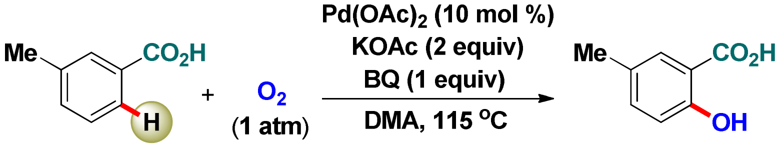
Very recently our group[13] has developed Cu(II)-catalyzed protocols for the *o*-benzoxylation of 2-phenylpyridine using terminal alkenes / alkynes and benzylamines as the benzoxy surrogates (Scheme IIA.2.8).



Scheme IIA.2.8. *o-Benzoxylation of 2-phenylpyridines via sp^2 C–H bond cleavage*

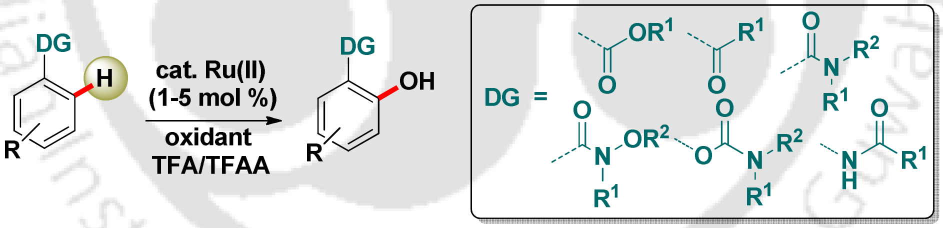
➢ C–H Hydroxylation

Yu group achieved a highly selective Pd-catalyzed *ortho*-hydroxylation of potassium benzoates *via* activation of dioxygen giving synthetically useful salicyclic acid derivatives (Scheme IIA.2.9).[14a] Apart from this; the same group has also described a Cu-catalyzed *ortho*-hydroxylation of 2-arylpyridines which goes *via* acetoxylation/hydrolysis sequence.[14b]



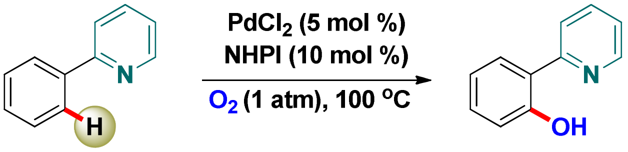
Scheme IIA.2.9. *Pd-catalyzed ortho-hydroxylation of arylcarboxylic acids*

In recent times tremendous progress has taken place in the substrate-directed hydroxylation of sp^2 C–H bonds in arenes and heteroarenes using readily accessible ruthenium catalysts.[15] Rao group has developed an ester directed *o*-hydroxylation using $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst and $K_2S_2O_8$ or selectflour as the oxidant.[15a] Ackermann *et al.* have employed $[RuCl_2(p\text{-cymene})]_2$, as well as other ruthenium complexes such as ruthenium(II)biscarboxylate complex $[Ru(O_2CMes)_2(p\text{-cymene})]$,[15b-c] or inexpensive $[RuCl_3, nH_2O]$ as the catalyst in combination with (diacetoxyiodo)benzene $[PhI(OAc)_2]$ as the oxidant (Scheme IIA.2.10) for *o*-hydroxylation. For this chelation-assisted *o*-hydroxylation process the solvent mixture comprising of TFA and TFAA was found to be critical for the successful hydroxylation of various substrates.[15]



Scheme IIA.2.10. *Ru(II)-catalyzed o-hydroxylation of weak directing arenes*

Jiao *et al.* recently developed a $PdCl_2$ and *N*-hydroxyphthalimide co-catalyzed protocol for the sp^2 C–H hydroxylation of 2-phenylpyridine using molecular oxygen (O_2) as the sole oxidant source (Scheme IIA.2.11).[16]



Scheme IIA.2.11. *o-Hydroxylation of 2-phenylpyridine using molecular oxygen*

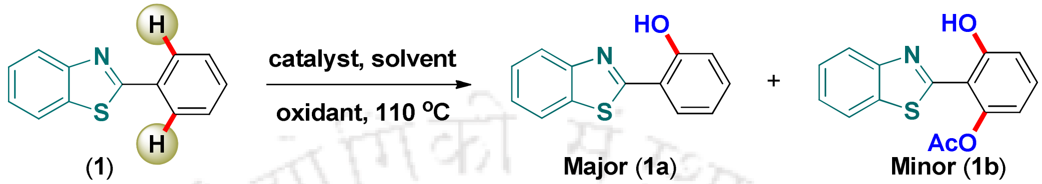
IIA.3. Present Work

Inspired by these developments on directing group assisted C–O bond formations particularly using Pd catalyst, we anticipated that a Pd based strategy could similarly be applied to construct *ortho* C–O bond of a new directing arene *viz.* 2-arylbenzothiazole. We envisioned that 2-arylbenzothiazole possessing *o*-chelating moiety could provide a similar ligand-directed cyclo-metallated intermediate whereby the metal can be selectively delivered to a proximal C–H bond.[17] However, they have rarely being explored toward C–H functionalizations. There are only two instances where the 2-arylbenzoxazole moiety has been used, one towards *o*-arylation[18] and the other for *o*-acetoxylation.[19] Very recently benzothiazoles have been *o*-arylated *via* proximal C–H functionalization.[20] Benzothiazoles are important heterocycle prevalent in number of pharmacophores which are reported to exhibit a diverse array of biological activities.[21] Hence, further derivatizing this important moiety would pave the path to the useful intermediates that may find applications in medicinal chemistry[22] and material science,[23] particularly as sensors.[24] Herein, we report our results on the Pd(II) catalyzed *o*-hydroxylation of various benzothiazoles.

Optimization of reaction conditions. To execute the above envisaged strategy, the initial experimentation was performed with 2-phenylbenzothiazole (**1**) as the model substrate. Treatment of substrate (**1**) with $Pd(OAc)_2$ (2 mole %), Oxone® (1 equiv) in AcOH at 110 ^{o}C provided the *o*-hydroxylated product (**1a**) rather than the expected *o*-acetoxylated product but in a mere yield of 20% (Table IIA.3.1, entry 1). A survey of the literature on such directing group assisted hydroxylation/acetoxylation entail that $Pd(OAc)_2$/DIB in acetic acid is one of the efficient combination in producing either the *o*-acetoxylated or *o*-hydroxylated product depending upon the reaction conditions.[5] Thus, in order to further improve the yield, the substrate (**1**) was subjected to treatment under a similar reaction condition *i.e* $Pd(OAc)_2$ (2 mol %), DIB (1 equiv) in acetic acid (Table IIA.3.1, entry 2). Encouragingly, an improvement in yield (58%) was observed under this condition. Upon further increase in the catalytic quantity (3 mole %) the yield improved up to 73% (Table IIA.3.1, entry 3). It was gratifying to observe that under the aforesaid reaction condition with a catalyst load of 5 mole %, a high yield (90%) was obtained (Table IIA.3.1, entry 4). There was no further substantial improvement in the yield even when a 10 mole % of the catalyst was used (Table

IIA.3.1, entry 5). With this initial condition in hand other reaction parameters such as catalysts, oxidants, solvents and temperature were varied to check if there was any further improvement in the yield. The results are summarized in Table IIA.3.1.

Table IIA.3.1. *Screening of reaction conditions*^{a,b}



Entry	Catalyst (mol %)	Solvent	Oxidant	Time (h)	Yield (%)^{a,b} (**1a**:**1b**)
1	$Pd(OAc)_2$ (2.0)	AcOH	oxone®	5.5	20 (95:5)
2	$Pd(OAc)_2$ (2.0)	AcOH	DIB	5.0	58 (85:15)
3	$Pd(OAc)_2$ (3.0)	AcOH	DIB	5.0	73 (88:12)
4	**$Pd(OAc)_2$ (5.0)**	**AcOH**	**DIB**	**5.0**	**90** (90:10)
5	$Pd(OAc)_2$ (10.0)	AcOH	DIB	6.0	91 (90:10)
6	$Pd(OAc)_2$ (5.0)	AcOH	PhIO	5.0	65 (100:0)
7	$Pd(OAc)_2$ (5.0)	AcOH	BTI	6.0	70 (100:0)
8	$Pd(OAc)_2$ (5.0)	AcOH	HTIB	6.0	80 (98:2)
9	$PdCl_2$ (5.0)	AcOH	DIB	6.0	70 (95:5)
10	$PdBr_2$ (5.0)	AcOH	DIB	6.0	85 (93:7)
11	$Cu(OTf)_2$ (10.0)	AcOH	DIB	6.5	45 (100:0)
12	$Cu(OAc)_2$ (10.0)	AcOH	DIB	6.5	50 (100:0)
13	$Pd(OAc)_2$ (10.0)	TFA	DIB	6.0	92 (97:3)
14	$Pd(OAc)_2$ (5.0)	TFA	Oxone®	5.0	85 (100:0)
15	$Pd(OAc)_2$ (5.0)	Toluene	DIB	6.0	10 (100:0)
16	$Pd(OAc)_2$ (5.0)	1,4-dioxane	DIB	5.0	00
17	$Pd(OAc)_2$ (5.0)	DMF	DIB	5.0	00
18	$Pd(OAc)_2$ (5.0)	DMSO	DIB	5.0	00

[a] Combined isolated yield of major hydroxyolated (**1a**) and minor bifunctionalized product (**1b**).
[b] All reactions were performed under air atmosphere.

As can be seen from Table IIA.3.1 among the various oxidants tested such as iodoxybenzene (PhIO), *bis*-trifluoroacetoxyiodobenzene (BTI), and hydroxytosyloxyiodobenzene (HTIB) (Table IIA.3.1, entry 6–8), all gave inferior results as compared to DIB (diacetoxyiodobenzene) (Table IIA.3.1, entry 4). The other palladium salts such as $PdCl_2$ and $PdBr_2$ were found to be less effective than $Pd(OAc)_2$ (Table IIA.3.1, entry 9–10). The use of Cu salts such as $Cu(OTf)_2$ and $Cu(OAc)_2$ in lieu of $Pd(OAc)_2$ provided poorer yields even though used in higher catalytic quantity (Table IIA.3.1, entry 11–12). Notably, the replacement of AcOH with trifluoroacetic acid (TFA) provided a marginal improvement in the yield (92%) (Table IIA.3.1, entry

13) but the former was preferred due to cost consideration. Interestingly, cheap oxidant Oxone® in combination with TFA (Table IIA.3.1, entry 14) gave a comparable yield (85%) as that of DIB/AcOH combination. Other solvents such as toluene, 1,4-dioxane, DMSO or DMF examined did not give satisfactory results (Table IIA.3.1, entry 15–18) under similar catalyst-oxidant combination. The reaction either did not proceed or gave a poor yield of the desired product. The use of *tert*-butanol as solvent gave only traces of product under the identical reaction condition, although it was found to be an efficient solvent during *o*-hydroxylation of 2-arylpyridine.[5d] Thus the combination of $Pd(OAc)_2$ as the catalyst, DIB as co-oxidant in acetic acid at 110 °C (Table IIA.3.1, entry 4) gave most satisfactory yield which was used for subsequent reactions.

Substrate scope for *o*-hydroxylation. Having arrived at the optimized condition, we proceeded to investigate the scope and generality of this methodology. The results illustrated in Scheme IIA.3.1 attest that the methodology is compatible to a wide array of functionalities. Substrates possessing electron-donating groups such as *p*–Me (**2**), *p*–OMe (**3**), *p*–CMe_3 (**4**), *p*–OBu (**5**), 2,5–diOMe (**6**), 2,4–diOMe (**7**) and 3,4–diOMe (**8**) (Scheme IIA.3.1) in the 2-aryl ring underwent smooth reaction to afford the corresponding hydroxylated products. The structure of the product (**2a**) has been further confirmed by X–ray crystallography as shown in Figure IIA.3.1.

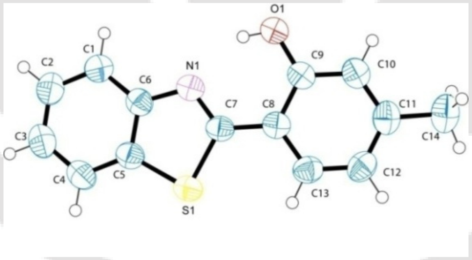
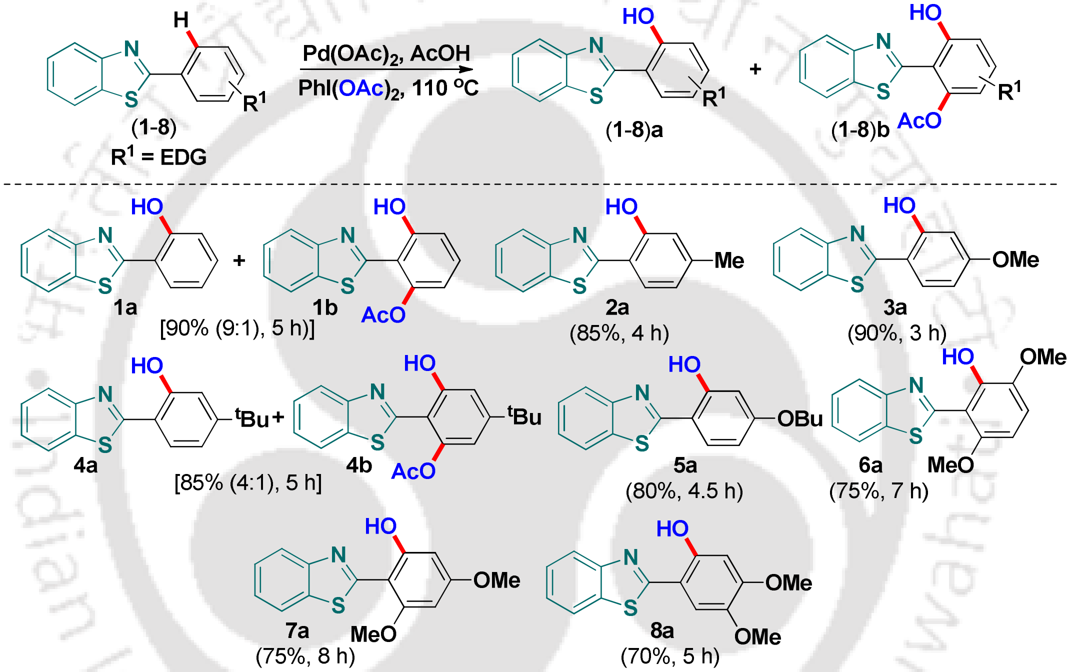


***Fig. IIA.3.1.** ORTEP view of compound (**2a**)*

Similar results were obtained with substrates bearing electron-withdrawing groups such as *p*–Cl (**9**), *o*–Cl (**10**), 2,4–diF (**11**), *m*–Br (**12**), *m*–NO_2 (**13**) and *m*–F (**14**) (Scheme IIA.3.2). Notably, the electron-donating groups on the 2-arylbenzothiazoles exhibited an accelerating effect on the reaction rate except on steric ground as in substrates (**6**) and (**7**), while those with electron-withdrawing substituents exerted a deactivating effect on the reaction rates. However, irrespective of the nature of the substituents no major differences in the yields of the corresponding products were observed. Probably due to the chelation of Pd catalyst to the hydroxyl group and the nitrogen, mostly monoselective *o*-hydroxylated product was observed which is consistent with the literature report.[14b] However, an exception to this observation was the formation of products bearing both *o*-hydroxyl and *o*-acetoxy groups probably obtained through simultaneous C–O bond formation for certain substrates (**1**, **4**). Noteworthy to mention that for substrates (**1**) and (**4**), the mono hydroxylated product (**1a** and **4a**) was obtained in major amount while the hydroxyl-acetoxy product (**1b** and **4b**) was obtained in minor quantity.

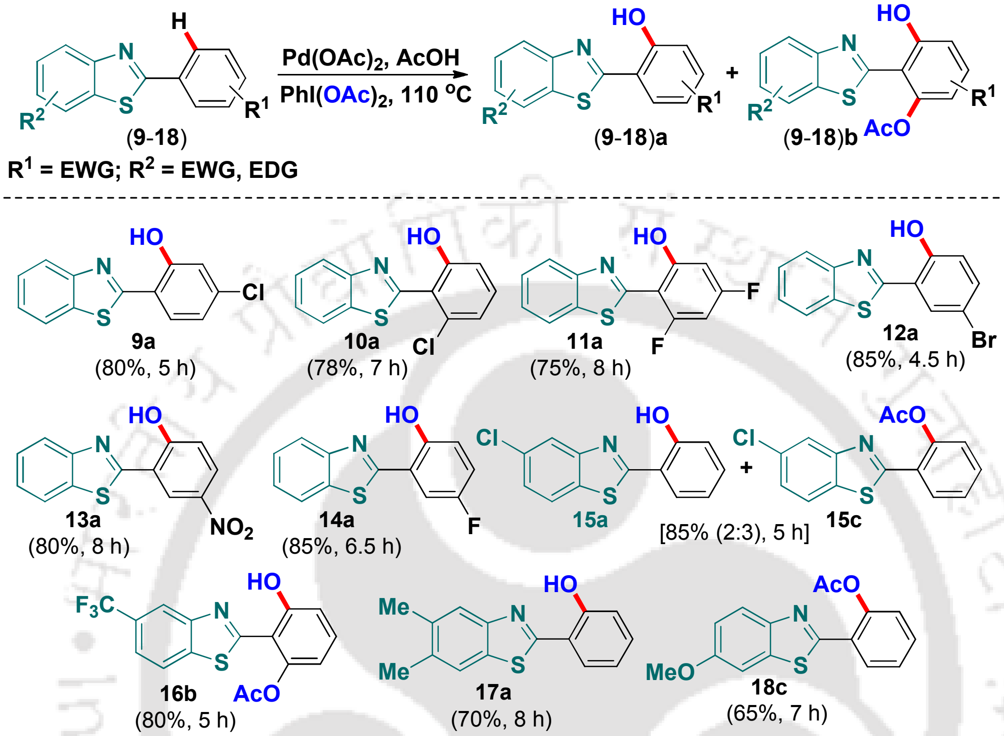
Scheme IIA.3.1. *Substrate scope for o-hydroxylation of 2-arylbenzothiazole*[a,b]



[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Yields after silica gel column chromatography.

Similar *o*-diacetoxy products have been reported in the presence of acetic acid using analogous substrate directing moiety 2-phenyl pyridine.[14b] The formation of the partial hydroxyl-acetoxy products (**1b** and **4b**) suggest that the mono-hydroxylated products (**1a–14a**) are obtained probably *via* hydrolysis of their corresponding mono acetoxylated products. For substrates possessing substituent at their *meta* position (**8**, **12–14**), exclusively a single regioisomer was obtained with the hydroxylation occurring at the sterically less hindered *ortho* site. The exclusive formation of single regioisomer is governed by the steric effect of the substituent due to the preferential palladation at the sterically less hindered position as has been demonstrated by Sanford group.[5g]

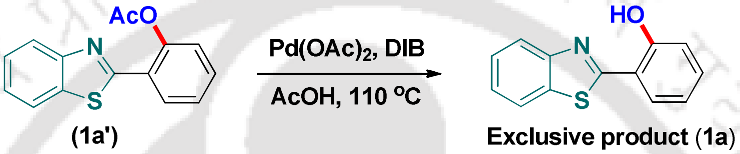
Scheme IIA.3.2. *Substrate scope for o-hydroxylation of 2-arylbenzothiazole*[a,b]



[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b]Yields after silica gel column chromatography.

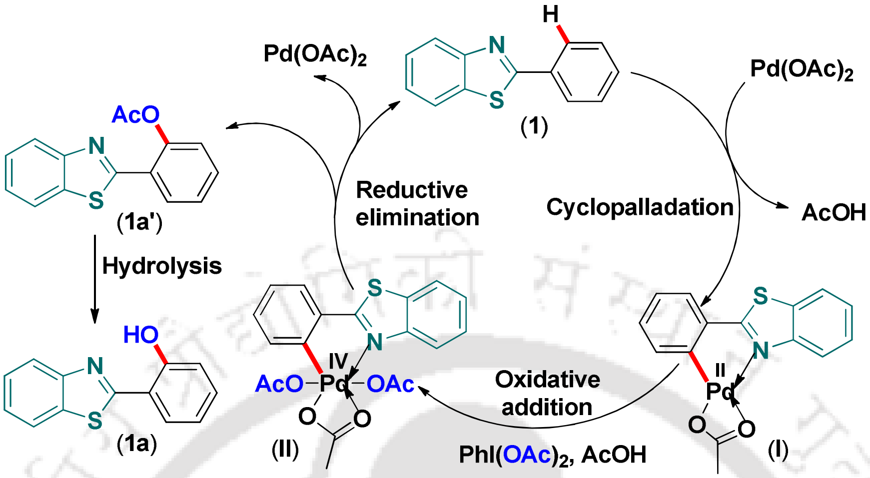
This methodology was equally successful for substrates possessing electron-withdrawing as well as electron donating substituents (**15**-**18**) in the benzothiazole moiety. Substrate (**15**) having a –Cl group in the benzothiazole moiety gave the expected *o*-hydroxylated (**15a**) along with o-acetoxylated (**15c**) product in the ratio of 2:3 after 5 h (Scheme IIA.3.2). This ratio remained unchanged even after prolonged reaction time (12 h). An exception to the earlier trend, substrate (**16**) having a –CF_3 group in the benzothiazole moiety also provided the hydroxy-acetoxy product (**16b**) exclusively rather than the usual mono *o*-hydroxylated product. While substrate (**17**) possessing two –Me groups in the benzothiazole ring gave hydroxylated product (**17a**) exclusively, the other substrate (**18**) possessing a –OMe group in the benzothiazole moiety gave o-acetoxylated as the major product (**18c**) (Scheme IIA.3.2). The reason behind the resistant to hydrolysis to yield corresponding hydroxylated product in the later case is not clear at this moment. Surprisingly no general trend in their reactivity could be observed for substitutents present on the benzothiazole rings (**15**-**18**). However, 2-heteroarylbenzothiazoles having heterocycles such as pyridine, thiophene or furan were completely inert under the present reaction condition providing no hydroxylated product. This is probably due to the chelation of suitably placed hetero atoms N, O, and S of pyridine, thiophene and furan respectively to Pd which renders the catalyst inactive.

Mechanistic Studies. Treatment of separately synthesized acetoxylated product (**1a'**) under the reaction condition gave hydroxylated product (**1a**) supporting the hydrolytic path for hydroxylated product (Scheme IIA.3.3).



Scheme IIA.3.3. *Control experiment*

An insight into the mechanism could be had from some of the basic observations of this methodology. This methodology worked better for substrates containing electron-donating substituents in the aryl ring compared to the substrates having electron-withdrawing ones, suggesting the possible occurrence of an oxidative addition of Pd to the aryl ring. The fact that the reaction worked well with other non acetate bearing terminal oxidants such as PhIO, BTI, HTIB and Oxone® in acetic acid there by suggesting that DIB does not suffice as the major source of acetate (hydroxyl functionality) and acetic acid is probably the source of hydroxy functionality. The use of toluene as the solvent in lieu of acetic acid with DIB as the terminal oxidant did not give satisfactory result which further supports our assumption. These observations imply that acetic acid is possibly the major source of the hydroxyl functionality and DIB acts merely as an oxidant. Keeping in view the above observations and earlier literature reports[5d-g] a plausible mechanism has been proposed (Scheme IIA.3.4). This reaction is expected to occur *via* a Pd(II)/Pd(IV) catalytic cycle involving the following steps: (i) the Pd(II) precursor coordinates to the substrate followed by a cyclopalladation step to afford the intermediate (**I**); (ii) two electron oxidation employing DIB to generate the Pd(IV) species (**II**); (iii) reductive elimination of the metal resulting the C–O bond formation and concomitant release of the *o*-acetoxy product; (iv) a ligand exchange step releases the catalyst for next catalytic cycle. The acetoxylated product thus produced undergoes an *in situ* hydrolysis to give the hydroxyl functionality (Scheme IIA.3.4).



Scheme IIA.3.4. *Pd (II) Catalyzed formation 2-(benzothiazol-2-yl)-phenol (**1a**) from 2-phenylbenzothiazole (**1**)*

These hydroxylated derivatives are sufficiently fluorescent active. Photoluminicent and UV data of some representative compounds have also been recorded. Substrates possessing electron-donating groups such as p–OMe (**3**), p–^{t}Bu (**4**) and electron-withdrawing group m–F (**14**) in the 2-aryl ring show their absorption bands at around 289 nm and 336 nm in ethanol solvent (Fig. IIA.3.2). Upon excitation at 336 nm all three compounds show their excitation band at around 378 nm (Figure IIA.3.3). These bidentate fluorescent compounds may find potential application as various sensors and in material science as LED.[23,24]

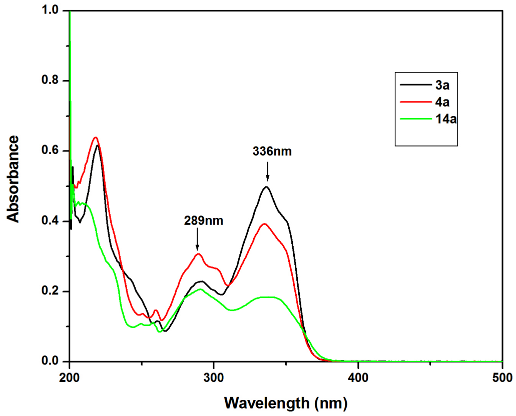


Fig. IIA.3.2. *UV-vis spectra of **3a, 4a, 14a***

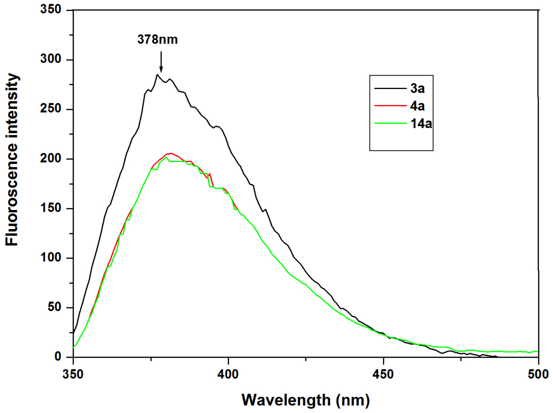


Fig. IIA.3.3. *Photoluminescence spectra of compounds (**3a, 4a, 14a**)*

In conclusion we have developed an efficient protocol to access the hydroxylated benzothiazoles *via* a palladium catalyzed C–H functionalization/C–O bond formation. The functionalized benzothiazoles form the basis of many pharmacophores and there have not been many reports on the exploitation of this moiety. Besides, the performance under ambient air and moisture, a broad scope and wide array of functional group tolerance and exhibition of high levels of regioselectivity pertaining to the *meta*-substituted substrates are the remarkable features of this methodology. Further applications of this synthetic methodology are currently underway.

IIB. Palladium Catalyzed Regioselective Acetoxylation of 3,5-Diarylisoxazole *via o*-C–H Functionalizations

IIB.1. Introduction

After the successful *ortho* hydroxylation / acetoxylation of 2-arylbenzothiazole using cat. Pd(II) / DIB combinations, we searched for analogous direcing systems for similar *ortho* C–O bond formation. 3,5-Diarylisoxazole was choosen as the model unit as it possess both *N* and *O*-chelating atoms in a rigid framework which may provide competitive cyclometallated intermediate either through *N* or *O* atoms by anchoring the metal selectively to one of the proximal *ortho* C–H bonds. There is only one instance where 3,5-diarylisoxazole is *ortho*-arylated using phenylboronic acid as the arylating partner in the presence of stoichiometric Pd salt.[25] Apart from this there is not a single report on catalytic *ortho* C–H functionalization using this moiety. 3,5-Diarylisoxazole scaffold is an important pharmacophore having a diverse array of biological activities.[26] The reductive *N–O* bond cleavage of 3,5-disubstituted isoxazoles lead to various bi-functional molecules[27] that can be utilized for the synthesis of other important heterocycles.[28] Thus, any further functionalization of this important moiety is likely to generate further interest. There are two *o*-hydrogens each proximal to *N* and *O* atom in 3,5-diarylisoxazole that can be activated (*o*-palladated). Further, functionalization of the isoxazolyl internal sp^2 C$_4$–H by a non-directing metallation path cannot be ruled out. *o*-C–H functionalization in isoxazoles having dual-directing atoms such as *N* and *O* has not been investigated so far. Thus, it would be interesting to see whether the palladation would occur through –*N* donor *ortho*-site or –*O* donor *ortho*-site or at the C-4 position in 3,5-diarylisoxazoles.

IIB.2. Strategies for *ortho* C–O Bond Formation

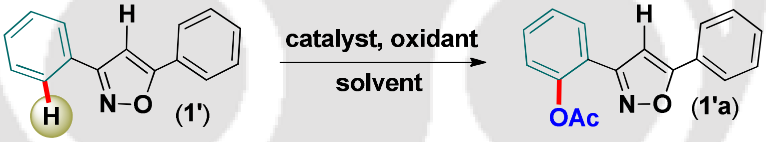
Various forms of *ortho* C–O bond formations *via* C–H functionalization are already discussed in Section-A (page no 60-63).[6-16]

IIB.3. Present Work

From the literature reports discussed in Section-A, it is well established that directing group promoted hydroxylation/acetoxylation goes better with a combination of diacetoxyiodobenzene (DIB), AcOH and Pd(OAc)$_2$. Herein, we report our results on the Pd(II) catalyzed *o*-acetoxylation of various 3,5-diarylisoxazoles.

Optimization of reaction conditions. To assess this, 3,5-diarylisoxazoles (1 equiv) (**1′**) was treated with Pd(OAc)$_2$ (5.0 mol %), DIB (1.2 equiv) in AcOH (2 mL) at 110 °C which provided *o*-acetoxylated product (**1′a**) in 44% isolated yield. With this initial result in hand further optimizations in terms of solvent, catalyst and their quantities were examined. Details of optimization reactions that were performed are summarized in Table IIB.3.1. The most surprising aspect of the optimization reaction is the use of combination of solvents AcOH : toluene (3 : 1) which gave the best possible yield (Table IIB.3.1). The other ratios of AcOH : toluene [(1 : 1), (2 : 1) and (1 : 2)] tried were found to be less effective. Thus all further reactions were performed taking substrate (1 equiv), DIB (1.2 equiv), Pd(OAc)$_2$ (0.1 equiv) in a mixture of AcOH : toluene (3 : 1) at a temperature of 110 °C.

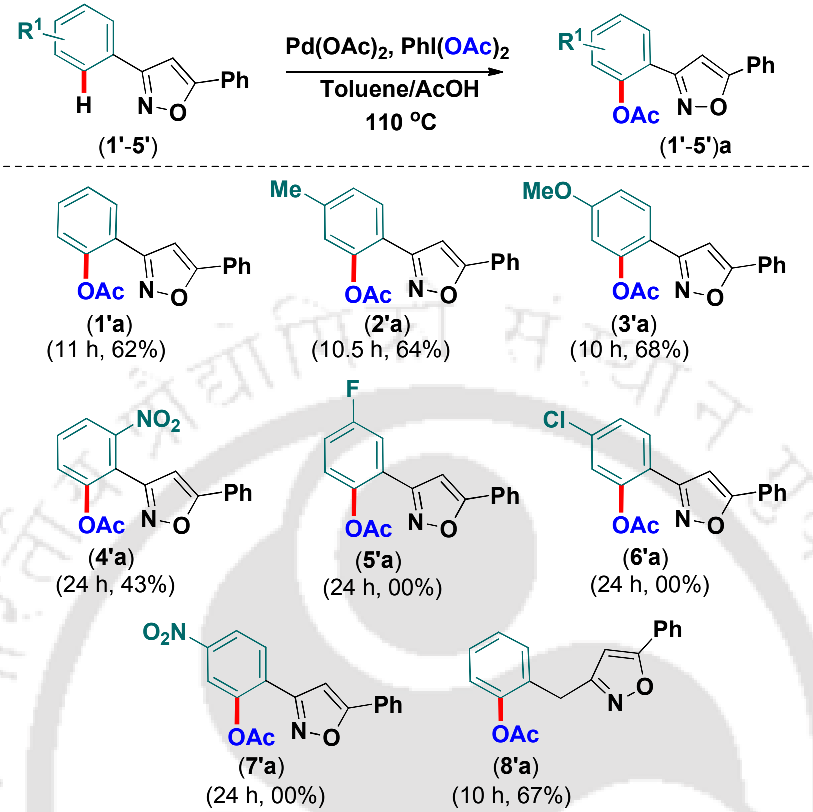
Table IIB.3.1. *Screening of reaction conditions*



Entry	Catalyst (mol %)	Solvent	Oxidant (equiv)	Yield (%)^{a,b}
1	Pd(OAc)$_2$ (5.0)	AcOH	DIB (1.2)	40
2	Pd(OAc)$_2$ (5.0)	1,4-dioxane	DIB (1.2)	00
3	Pd(OAc)$_2$ (5.0)	Toluene	DIB (1.2)	00
4	Pd(OAc)$_2$ (5.0)	DMSO	DIB (1.2)	00
5	Pd(OAc)$_2$ (5.0)	DMF	DIB (1.2)	00
6	Pd(OAc)$_2$ (5.0)	DCE	DIB (1.2)	00
7	Pd(OAc)$_2$ (10.0)	AcOH	DIB (1.2)	45
8	Pd(OAc)$_2$ (10.0)	AcOH	DIB (1.5)	50
9	**Pd(OAc)$_2$ (10.0)**	**AcOH:toluene**	**DIB (1.2)**	**65**^{c}
10	Pd(OAc)$_2$ (15.0)	AcOH:toluene	DIB (1.2)	66^{c}
11	PdBr$_2$ (10.0)	AcOH	DIB (1.2)	25
12	Pd(TFA)$_2$ (10.0)	AcOH	DIB (1.2)	30
13	PdCl$_2$ (10.0)	AcOH	DIB (1.2)	20

^{a}Isolated yield of *o*-acetoxyted product (**1'a**) after 12 h. ^{b}All reactions were performed under air atmosphere at 110 °C. ^{c}AcOH:toluene used in (3:1) ratio.

Scheme IIB.3.1. *Substrates scopes in Pd-catalyzed o-acetoxylation of diarylisoxazole*[a]

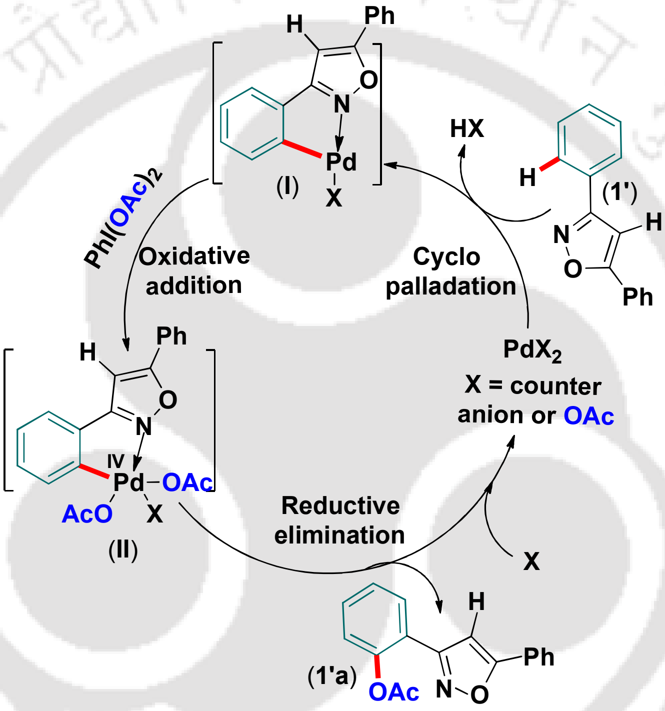


[a]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.[b]Yields of pure isolated products after silica gel column chromatography.

The above optimized conditions were then applied toward the *o*-acetoxylation of various 3,5-diphenylisoxazoles. It was observed that electron-donating substituents such as *p*–Me (**2′**) and *p*–OMe (**3′**) present in the 3-aryl ring of 3,5-diarylisoxazole afforded their corresponding *o*-acetoxylated products (**2'a**) and (**3'a**) in good yields (Scheme IIB.3.1). Electron-withdrawing substituent such as *o*–NO_2 (**4′**) present in the 3-aryl ring of 3,5-diarylisoxazole underwent slow reaction giving a poor yield (43%) of the product (**4'a**). Other substrates possessing electron-withdrawing substituents such as *m*–F (**5′**), *p*–Cl (**6′**) were completely unproductive under this optimized reaction conditions. Substrate having *p*–NO_2 (**7′**) did not yield any product supporting our argument for the unreactive nature of substrate having deactivating groups for *o*-acetoxylation reaction. The unusual reactivity of (**4′**) in spite of possessing deactivating *o*–NO_2 group giving *o*-acetoxylated product (**4'a**) could not be ascertained at this moment. Interestingly 3-benzyl-5-phenylisoxazole afforded the desired *ortho*-

acetoxylated product (**8′a**) in a modest yield (Scheme IIB.3.1). The reaction in the later case is expected to proceed *via* a 6-membered palladacycle intermediate.

The mechanism is expected to be similar to our Pd (II) catalyzed *o*-hydroxylation of 2-arylbenzothiazole discussed in section A (page no 69-70). The C–O bond forming path (*o*-acetoxylation) is illustrated in (Scheme IIB.3.2). Mechanism is initiated by initial *N*-directed cyclopalladation of 3,5-diphenylisoxazole (**1'**) generating intermediate **I**. This upon oxidative addition in presence of oxidant DIB generates intermediate **II**. Finally reductive elimination afforded *o*-acetoxylated product (**1'a**).



Scheme IIB.3.2. *Plausible mechanism for C–O bond formation*

In conclusion we have demonstrated the higher directing ability of *N* over *O* in 3,5-diarylisoxazole *via* a chelation assisted approach in accomplishing the site selective *ortho*-functionalizations. In spite of the higher acidic character of the isoxazolyl sp^2 C_4–H directed *o*-metallation is preferred over the non-directed metallation pathway. This is the first report of catalytic *o*-functionalization of this scaffold for the construction of C–O bond.

II.4. Experimental Section

II.4.1. General information. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using silica gel 60 F_{254} (0.25mm) with detection by UV or iodine. Chromatography was performed using silica gel (60-120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on FT-400 MHz instrument using TMS as an internal standard. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. Melting points were recorded and are uncorrected. IR spectra were recorded in KBr or neat. UV-visible spectra were recorded by dissolving calculated amount of the sample in an appropriate solvent on a Perkin-Elmer Lambda UV-visible spectrophotometer. Photoluminescence measurements were done using a Varian Cary Eclipse fluorescence spectrophotometer. For both UV visible and florescence studies, solutions of hydroxylated derivatives (**3a**, **4a** and **14a**) were made in 1:1 ethanol and water mixed solvent. Concentration of monomer was maintained at 20 x 10^{-6} M for UV visible studies, and it was maintained at around 20 x 10^{-6} M for photoluminescence studies. The 2-arylbenzothiazoles were prepared from corresponding *N*-phenylbenzothioamides using hypervalent iodine mediated oxidative cyclization following the reported procedure.[29] 3,5-Diarylisoxazoles were prepared by the method of click chemistry using phenyl acetylene derivatives with substituted aldoximes.[30]

II.4.2. Crystallographic description

- **IIA.4.2.**

CCDC number for compound 2a: CCDC 846544. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif.

Crystallographic description of 2a: Crystal dimension (mm): 0.42 x 0.34 x 0.28. $C_{14}H_{11}NOS$, Mr = 241.31. Monoclinic, space group P 21/c; a = 10.4932(9) Å, b = 7.6375(6) Å, c = 14.7440(13) Å; α = 90.00°, β = 100.306(4) °, γ = 90.00°, V = 1162.55(17) Å^3; Z = 4; ρ_{cal} = 1.379 mg/m^3; μ (mm^{-1}) = 0.259; *F (000)* = 504.0; Reflection collected / unique = 2888 / 1920; Refinement method = Full-matrix least-squares on F^2; Final R indices [$I>2\sigma_I$] R1 = 0.0641, wR2 = 0.2228, R indices (all data) R1 = 0.0857, wR2 = 0.2318; goodness of fit = 1.088.

II.4.3. General procedures for *o*-hydroxylation and *o*-acetoxylation

➢ **IIA.4.3. General procedure for the synthesis of substituted 2-(benzo[*d*]thiazole-2-yl) phenol from substituted 2-phenylbenzo[*d*]thiazole (1-18).** An oven-dried flask was charged with $Pd(OAc)_2$ (0.011 g, 0.05 mmol), diacetoxyiodobenzene (DIB) (0.321 g, 1.0 mmol), substituted 2-phenylbenzo[*d*]thiazole (**1-18**) (0.211 g, 1.0 mmol), and acetic acid (2 mL). Then the reaction vessel was kept in an oil bath preheated to 110 °C and allowed to stir for the stipulated period of time. The progress of the reaction was monitored by TLC. During this period complete disappearance of substituted 2-phenylbenzo[*d*]thiazole was observed with the appearance of one major product having higher R_f [in some cases (**1b**, **4b**, **16b**, **15c**, **18c**)] another product was also observed having lower R_f with respect to the substrate). The reaction mixture was then cooled and admixed with water (5 mL). The product was extracted with ethyl acetate (2 x 10 mL) and the combined organic layer was washed with saturated sodium bicarbonate ($NaHCO_3$) solution. Organic layer was dried over anhydrous sodium sulphate (Na_2SO_4) and evaporated under reduced pressure. The crude product so obtained was further purified through silica gel column chromatography (EtOAc/hexane) to yield the pure product. The identity and purity of the products were confirmed by spectroscopic analysis.

➢ **IIB.4.3. General experimental procedure for preparation of 2-(5-phenylisoxazol-3-yl)phenyl acetate (1'a) from 3,5-diphenylisoxazole (1').** An oven-dried flask was charged with 3,5-diphenylisoxazole (**1'**) (0.221 g, 1.0 mmol), diacetoxy iodobenzene (DIB) (0.386 g, 1.2 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol), and acetic acid :toluene (2 mL in 3 : 1 ratio). After that the reaction mixture was subjected to reflux in a preheated oil bath at 110 °C and allowed to stir for the stipulated period of time. The progress of the reaction was monitored by TLC. After the completion of the reaction as judged from TLC the reaction mixture was cooled and admixed with water (5 mL). The product was extracted with ethyl acetate (2 x 10 mL) and the combined organic layer was washed with saturated sodium bicarbonate ($NaHCO_3$) solution. Organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), and evaporated under reduced pressure. The crude product obtained here was further purified through silica gel column chromatography (10% EtOAc/hexane) to yield the pure 2-(5-phenylisoxazol-3-yl)phenyl acetate (**1'a**) (0.172 g, yield 62%). The identity and purity of the product was confirmed by spectroscopic analysis. The same procedure was also followed for *o*-acetoxylation of other substituted isoxazoles (**2'**-**8'**).

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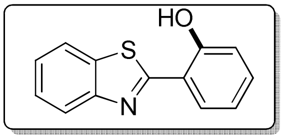
II.6. Spectral Data

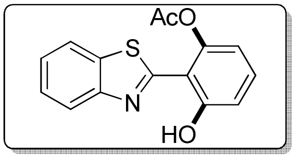
➢ IIA.6.

2-(Benzo[*d*]thiazole-2-yl)-phenol (1a):



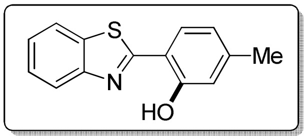
M.p. 120–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.51 (1H, s), 7.98 (d, 1H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.70–7.67 (1H, m), 7.51–7.47 (1H, m), 7.41–7.37 (2H, m), 7.10 (d, 1H, *J* = 8.0 Hz), 6.95 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 158.2, 152.1, 137.7, 132.9, 130.4, 128.6, 126.9, 125.7, 122.4, 121.7, 119.7, 118.1; IR (KBr, cm^{-1}): 3781, 3433, 3053, 2952, 2923, 2852, 1893, 1781, 1616, 1589, 1479, 1434, 1401, 1314, 1257, 1219, 1095, 1032, 972, 817, 742; HRMS (ESI) calcd for $C_{13}H_9NOS$ (M + H$^+$) 228.0478, found 228.0475; Elemental Analysis: found C, 68.76; H, 4.04; N, 6.11. $C_{13}H_9NOS$ requires C, 68.70; H, 3.99; N, 6.16%.

2-(Benzo[*d*]thiazol-2-yl)-3-hydroxyphenyl acetate (1b):



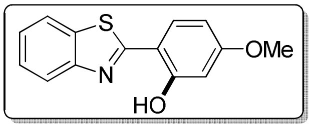
M.p. 132–133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.82 (s, 1H), 8.04 (d, 1H, *J* = 8.8 Hz,), 7.95 (d, 1H, *J* = 8.4 Hz,), 7.55 (t, 1H, *J* = 8.4 Hz,), 7.46 (t, 1H, *J* = 8.0 Hz,), 7.37 (t, 1H, *J* = 7.2 Hz,), 7.03 (d, 1H, *J* = 8.0 Hz,), 6.76 (d, 1H, *J* = 8.4 Hz), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 166.0, 160.3, 149.5, 148.9, 135.5, 130.5, 125.6, 123.9, 122.2, 121.5, 116.0, 115.7, 113.5, 21.9; IR (KBr, cm^{-1}): 3384, 3054, 2921, 2846, 1773, 1635, 1577, 1473, 1434, 1369, 1314, 1278, 1248, 1186, 1102, 1056, 1031, 1012, 968, 907, 886, 853, 816, 796, 757, 728; Elemental Analysis: found C, 63.20; H, 3.95; N, 4.86. $C_{15}H_{11}NO_3S$ requires C, 63.14; H, 3.89; N, 4.91%.

2-(Benzo[*d*]thiazole-2-yl)-5-methyl-phenol (2a):



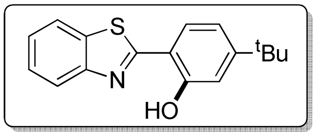
M.p. 140–141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.45 (s, 1H), 7.95 (d, 1H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.49 (t, 1H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 6.92 (s, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 158.1, 152.1, 144.0, 132.7, 128.5, 126.8, 125.5, 122.2, 121.7, 120.9, 118.3, 114.6, 21.9; IR (KBr, cm^{-1}): 3435, 2919, 1628, 1577, 1479, 1434, 1377, 1313, 1256, 1221, 1108, 960, 935, 878, 781, 758, 728; HRMS (ESI) calcd for $C_{14}H_{11}NOS$ (M + H$^+$) 242.0634, found 242.0630; Elemental Analysis: found C, 69.74; H, 4.65; N, 5.75. $C_{14}H_{11}NOS$ requires C, 69.68; H, 4.59; N, 5.80%.

2-(Benzo[*d*]thiazole-2-yl)-5-methoxy-phenol (3a):



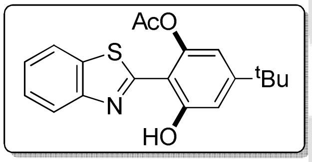
M.p. 130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.72 (s, 1H), 7.89 (d, 1H, *J* = 8.4 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.8 Hz), 7.44 (t, 1H, *J* = 7.4 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 6.56 (s, 1H), 6.49 (d, 1H, *J* = 8.8 Hz), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 163.6, 160.1, 152.0, 132.3, 129.8, 126.7, 125.2, 121.8, 121.5, 110.6, 107.8, 101.5, 55.6; IR (KBr, cm^{-1}): 3775, 3435, 3058, 2957, 2929, 2842, 1632, 1585, 1530, 1480, 1439, 1393, 1338, 1315, 1282, 1222, 1186, 1164, 1146, 1125, 1029, 976, 951, 852, 755, 727; Elemental Analysis: found C, 65.42; H, 4.38; N, 5.39. $C_{14}H_{11}NO_2S$ requires C, 65.35; H, 4.31; N, 5.44%.

2-(Benzo[*d*]thiazole-2-yl)-5-*tert*-butyl-phenol (4a):



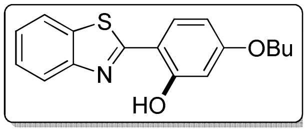
M.p. 126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.32 (s, 1H,), 7.85 (d, 1H, *J* = 8.0 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.49 (d, 1H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 7.05 (s, 1H), 6.89 (d, 1H, *J* = 8.4 Hz), 1.26 (s, 9H,); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 157.9, 157.1, 152.1, 132.6, 128.2, 126.7, 125.4, 122.1, 121.6, 117.3, 114.8, 114.4, 35.2, 31.2; IR (KBr, cm^{-1}): 3439, 3049, 2958, 2862, 2697, 1629, 1568, 1437, 1367, 1314, 1281, 1219, 1199, 1098, 1012, 976, 925, 872, 856, 810, 774, 728; HRMS (ESI) calcd for $C_{17}H_{17}NOS$ (M + H$^+$) 284.1104, found 284.1103; Elemental Analysis: found C, 72.08; H, 6.11; N, 4.90. $C_{17}H_{17}NOS$ requires C, 72.05; H, 6.05; N, 4.94%.

5-*tert*-Butyl-2-(benzo[*d*]thiazol-2-yl)-3-hydroxyphenyl acetate (4b):



M.p. 94–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.63 (s, 1H), 8.02 (d, 1H, *J* = 8.4 Hz), 7.92 (d, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.43 (t, 1H, *J* = 7.6 Hz), 7.05 (s, 1H), 6.76 (s, 1H,), 2.56 (s, 3H,), 1.33 (s, 9H,); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 163.9, 159.8, 156.7, 149.7, 148.7, 132.9, 126.9, 125.7, 122.1, 121.3, 112.7, 111.3, 108.2, 35.4, 31.0, 22.4; IR (KBr, cm^{-1}): 3434, 3060, 2954, 2923, 2857, 1776, 1635, 1571, 1454, 1434, 1384, 1316, 1286, 1234, 1223, 1183, 1111, 1075, 1057, 1020, 974, 921, 891, 876, 847, 822, 752, 725; HRMS (ESI) calcd for $C_{19}H_{19}NO_3S$ (M + H$^+$) 342.1158, found 342.1156; Elemental Analysis: found: C, 66.92; H, 5.65; N, 4.04. $C_{19}H_{19}NO_3S$ requires C, 66.84; H, 5.61; N, 4.10%.

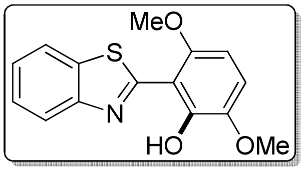
2-(Benzo[*d*]thiazole-2-yl)-5-butoxy-phenol (5a):



M.p. 107–108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.67 (s, 1H), 7.90 (d, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.8 Hz), 7.45 (t, 1H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.6 Hz,), 6.57 (s, 1H,), 6.50 (d, 1H, *J* = 8.8 Hz), 3.99 (t, 2H, *J* = 6.4

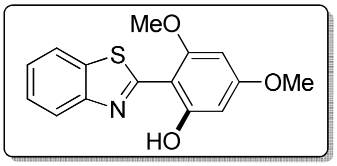
Hz), 1.79–1.74 (m, 2H), 1.52–1.47 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 163.2, 160.1, 152.0, 132.3, 129.7, 126.7, 125.1, 121.8, 121.5, 110.4, 108.2, 101.9, 68.1, 31.3, 19.4, 14.0; IR (KBr, cm^{-1}): 3434, 3054, 2954, 2938, 2869, 1633, 1583, 1483, 1472, 1439, 1388, 1334, 1317, 1282, 1257, 1241, 1218, 1197, 1188, 1120, 1072, 1038, 1011, 980, 961, 933, 902, 837, 807, 755, 726, 700, 648; HRMS (ESI) calcd for $C_{17}H_{17}NO_2S$ (M + H$^+$) 300.1053, found 300.1051; Elemental Analysis: found: C, 68.25; H, 5.76; N, 4.63. $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.72; N, 4.68%.

2-(Benzo[*d*]thiazole-2-yl)-3,6-dimethoxy-phenol (6a):



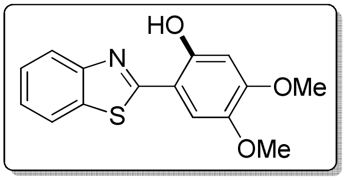
M.p. 157–159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.38 (t, 1H, *J* = 7.2 Hz), 6.92 (d, 1H, *J* = 8.8 Hz), 6.39 (d, 1H, *J* = 9.2 Hz), 3.98 (s, 3H,), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 152.1, 150.7, 149.1, 143.3, 133.6, 126.5, 125.1, 121.6, 121.1, 115.1, 107.9, 99.6, 57.1, 56.0; IR (KBr, cm^{-1}): 3432, 3081, 3047, 2997, 2924, 2845, 2672, 2571, 2044, 1904, 1787, 1756, 1605, 1591, 1502, 1471, 1438, 1418, 1337, 1314, 1247, 1237, 1163, 1118, 1093, 1009, 853, 757;Elemental Analysis: found: C, 62.74; H, 4.61; N, 4.86. $C_{15}H_{13}NO_3S$ requires C, 62.70; H, 4.56; N, 4.87%.

2-(Benzo[*d*]thiazole-2-yl)-3,5-dimethoxy-phenol (7a):



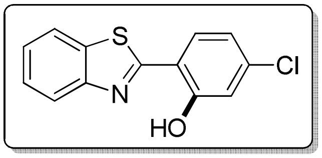
M.p. 119–120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 7.6 Hz), 7.35 (t, 1H, *J* = 7.2 Hz), 6.30 (s, 1H), 6.11 (s, 1H), 4.02 (s, 3H,), 3.86 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 163.6, 162.2, 159.4, 149.4, 133.2, 126.3, 124.5, 122.5, 121.1, 101.7, 94.2, 90.7, 55.7; IR (KBr): 3433, 2961, 2924, 2851, 2472, 1610, 1594, 1466, 1437, 1389, 1345, 1316, 1286, 1262, 1231, 1216, 1198, 1151, 1121, 1048, 964, 932, 825, 800, 752, 724; Elemental Analysis: found: C, 62.72; H, 4.59; N, 4.84. $C_{15}H_{13}NO_3S$ requires C, 62.70; H, 4.56; N, 4.87%.

2-(Benzo[*d*]thiazole-2-yl)-4,5-dimethoxy-phenol (8a):



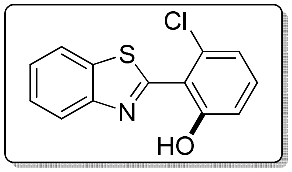
M.p. 148–149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 7.2 Hz,), 7.37 (t, 1H, *J* = 8.4 Hz), 7.04 (s, 1H), 6.63 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 154.4, 153.7, 152.2, 142.8, 132.3, 126.8, 125.1, 121.8, 121.6, 110.4, 108.3, 101.2, 56.9, 56.2; IR (KBr, cm^{-1}): 3431, 2919, 2849, 2649, 1709, 1633, 1601, 1528, 1505, 1468, 1434, 1358, 1351, 1314, 1272, 1245, 1203, 1185, 1154, 1130, 1037, 1012, 956, 882, 827, 807, 752, 721; HRMS (ESI) calcd for $C_{15}H_{13}NO_3S$ (M + H$^+$) 288.0689, found 288.0687; Elemental Analysis: found: C, 62.74; H, 4.62; N, 4.84. $C_{15}H_{13}NO_3S$ requires C, 62.70; H, 4.56; N, 4.87%.

2-(Benzo[*d*]thiazol-2-yl)-5-chlorophenol (9a):



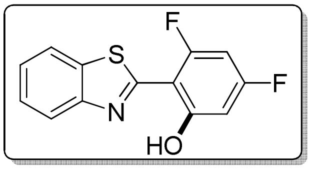
M.p. 107–108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.68 (s, 1H), 8.04 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.8 Hz), 7.84 (t, 1H, *J* = 8.8 Hz), 7.51–7.43 (m, 1H), 7.42 (d, 1H, *J* = 8.8 Hz), 7.38–7.34 (m, 1H,), 7.07 (s, 1H,); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 158.8, 154.2, 137.2, 135.2, 132.2, 128.8, 126.6, 125.5, 123.4, 121.6, 120.1, 118.1; IR (KBr, cm^{-1}): 3775, 3435, 3047, 2922, 2851, 1907, 1616, 1573, 1504, 1474, 1454, 1434, 1399, 1370, 1315, 1249, 1204, 1088, 1012, 973, 903, 829, 800, 756, 730; Elemental Analysis: found: C, 59.70; H, 3.12; N, 5.30. $C_{13}H_8ClNOS$ requires C, 59.66; H, 3.08; N, 5.35%.

2-(Benzo[*d*]thiazole-2-yl)-3-chloro-phenol (10a):



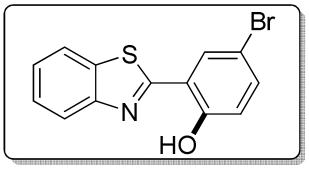
M.p. 141–142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, 1H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 8.0 Hz), 7.45 (t, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 8.8 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 7.02 (d, 1H, *J* = 8.4 Hz,), 6.97 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.1, 160.9, 148.6, 133.4, 132.9, 131.7, 126.8, 125.9, 121.8, 121.5, 121.40, 121.1, 117.3; IR (KBr, cm^{-1}): 3439, 3053, 2923, 2851, 2666, 1910, 1832, 1567, 1465, 1432, 1370, 1311, 1269, 1244, 1215, 1180, 1155, 1060, 966, 900, 827, 783, 757, 725; Elemental Analysis: found: C, 59.72; H, 3.13; N, 5.31. $C_{13}H_8ClNSO$ requires C, 59.66; H, 3.08; N, 5.35%.

2-(Benzo[*d*]thiazol-2-yl)-3,5-difluorophenol (11a):



M.p. 100–101 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.97 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 7.53–7.48 (m, 1H), 7.43–7.39 (m, 1H), 6.64–6.60 (m, 1H), 6.50–6.44 (m, 1H,); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.9, 163.5, 163.3, 163.2, 163.0, 162.9, 162.2, 161.6, 161.5, 161.4, 160.6, 160.5, 160.3, 160.2, 152.6, 149.3, 135.6, 135.5, 133.0, 132.9, 131.3, 131.2, 126.9, 126.5, 125.8, 125.5, 123.4, 121.9, 121.6, 121.4, 112.6, 112.4, 105.0, 104.7, 104.5, 101.3, 101.0, 95.7, 95.4, 95.1; IR (KBr, cm^{-1}): 3417, 3054, 2917, 2846, 2521, 1901, 1777, 1648, 1598, 1593, 1508, 1472, 1435, 1392, 1315, 1263, 1225, 1175, 1125, 1103, 1053, 1001, 979, 815, 754, 724, 701, 628; HRMS (ESI) calcd for $C_{13}H_7F_2NOS$ (M + H$^+$) 264.0289, found 264.0285; Elemental Analysis: found: C, 59.36; H, 2.75; N, 5.27. $C_{13}H_7 F_2NOS$ requires C, 59.31; H, 2.68; N, 5.32%.

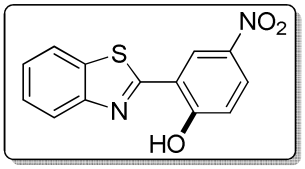
2-(Benzo[*d*]thiazole-2-yl)-4-bromo-phenol (12a):



M.p. 153–155 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.55 (s, 1H), 7.99 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.78 (s, 1H,), 7.52 (t, 1H, *J* = 7.2 Hz), 7.45–7.41 (m, 2H,), 6.99 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 168.0, 157.2, 151.8, 135.5, 132.8, 130.7, 127.1, 126.2, 122.6, 121.8, 120.0, 118.5, 111.2; IR (KBr, cm^{-1}): 3848, 3445, 2913, 1618, 1572, 1477, 1434, 1370, 1297, 1267, 1239, 1207, 1082, 979, 756, 721; Elemental Analysis: found: C, 51.08; H, 2.69; N, 4.50. $C_{13}H_8BrNOS$

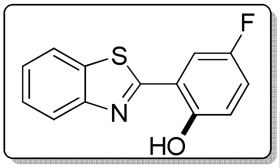
requires C, 51.00; H, 2.63; N, 4.57%.

2-(Benzo[*d*]thiazole-2-yl)-4-nitro-phenol (13a):



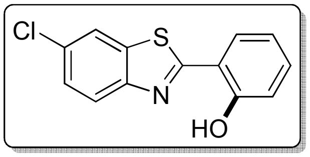
M.p. 197−199 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 13.52 (s, 1H), 8.64 (s, 1H), 8.28−8.25 (m, 1H,), 8.04 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 7.60−7.56 (m, 1H,), 7.52−7.48 (m, 1H,), 7.19 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.5, 163.4, 151.4, 140.5, 132.8, 127.9, 127.5, 126.7, 124.7, 122.7, 122.0, 188.9, 116.7; IR (KBr, cm^{-1}): 3434, 3065, 2924, 2853, 2428, 1736, 1626, 1578, 1525, 1485, 1382, 1331, 1278, 1237, 1215, 1104, 984, 902, 886, 808, 747; Elemental Analysis: found: C, 57.41; H, 2.99; N, 10.23. $C_{13}H_8N_2O_3S$ requires C, 57.35; H, 2.96; N, 10.29%.

2-(Benzo[*d*]thiazole-2-yl)-4-fluoro-phenol (14a):



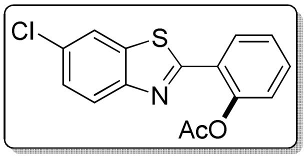
M.p. 118−119 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.23 (s, 1H), 8.02 (d, 1H, *J* = 8.0 Hz), 7.79−7.76 (m, 1H), 7.74−7.71 (m, 1H,), 7.44−7.38 (m, 1H), 7.36−7.28 (m, 2H,), 7.12−7.07 (m, 1H,); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.4, 164.3, 161.8, 154.0, 135.7, 135.6, 135.1, 130.7, 130.6, 126.5, 125.6, 123.5, 122.3, 121.7, 117.9, 117.7, 114.4, 114.2; IR (KBr, cm^{-1}): 3423, 2923, 1610, 1587, 1555, 1488, 1456, 1436, 1385, 1314, 1267, 1242, 1214, 1172, 1124, 1012, 998, 877, 858, 815, 785, 759, 728; Elemental Analysis: found: C, 63.71; H, 3.34; N, 5.66. $C_{13}H_8FNOS$ requires C, 63.66; H, 3.29; N, 5.71%.

2-(6-Chlorobenzo[*d*]thiazol-2-yl)phenol (15a):



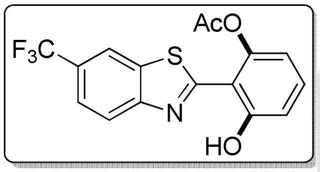
M.p. 133−134 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.21 (s, 1H,), 8.04−8.02 (m, 2H), 7.74 (d, 1H, *J* = 8.4 Hz), 7.48−7.46 (m, 3H), 7.33−7.30 (m, 1H,); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 170.0, 158.1, 155.1, 133.4, 133.3, 132.4, 131.5, 129.2, 127.7, 125.8, 123.1, 122.4, 118.1; IR (KBr, cm^{-1}): 3439, 2924, 2855, 1624, 1581, 1471, 1433, 1384, 1256, 1210, 1062, 963, 884, 807, 756; Elemental Analysis: found: C, 59.69; H, 3.13; N, 5.30. $C_{13}H_8ClNSO$ requires C, 59.66; H, 3.08; N, 5.35%.

2-(6-Chlorobenzo[*d*]thiazol-2-yl)phenyl acetate (15c):



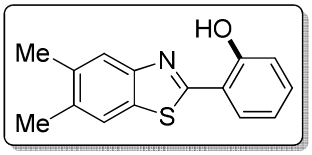
M.p. 181–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H,), 7.85 (d, 1H, *J* = 8.4 Hz), 7.43–7.37 (m, 3H,), 7.03 (d, 1H, *J* =8.4 Hz), 6.77 (d, 1H, *J* =8.0 Hz), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 165.7, 160.3, 150.4, 148.9, 133.2, 132.6, 131.3, 126.5, 122.1, 121.9, 115.8, 113.6, 110.4, 22.4; IR (KBr, cm^{-1}): 3425, 3079, 2923, 2857, 1888, 1757, 1624, 1578, 1461, 1434, 1371, 1313, 1066, 1026, 963, 879, 804, 727; HRMS (ESI) calcd for $C_{15}H_{10}ClNO_2S$ (M + H$^+$) 304.0194, found 304.0198; Elemental Analysis: found: C, 59.36; H, 3.37; N, 4.55. $C_{15}H_{10}ClNO_2S$ requires C, 59.31; H, 3.32; N, 4.61%.

2-(6-(Trifluoromethyl)benzo[*d*]thiazol-2-yl)-3-hydroxyphenyl acetate (16b):



M.p. 121–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.41 (s, 1H,), 8.29 (s, 1H,), 8.04 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 8.8 Hz), 7.39 (t, 1H, *J* = 8.2 Hz), 7.02 (d, 1H, *J* = 8.4 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 2.56 (s, 3H,); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 166.0, 160.3, 149.3, 149.1, 136.4, 132.8, 130.5, 122.2, 122.0, 119.4, 115.8, 113.6, 110.2, 22.3; IR (KBr, cm^{-1}): 3423, 3345, 3224, 2925, 2851, 2402, 1761, 1686, 1630, 1589, 1466, 1371, 1322, 1277, 1179, 1022, 965, 887, 789, 721, 701; HRMS (ESI) calcd for $C_{16}H_{10}F_3NO_3S$ (M + H$^+$) 354.0406, found 354.0405; Elemental Analysis: found: C, 54.45; H, 2.92; N, 3.90. $C_{16}H_{10}F_3NO_3S$ requires C, 54.39; H, 2.85; N, 3.96%.

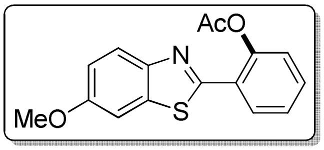
2-(5,6-dimethylbenzo[*d*]thiazol-2-yl)phenol (17a):



M.p. 135–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.60 (s, 1H), 7.75 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.62 (s, 1H,), 7.34 (t, 1H, *J* = 7.8 Hz), 7.07 (d, 1H, *J* = 8.2 Hz), 6.92 (t, 1H, *J* =

7.5 Hz), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 157.8, 150.5, 136.0, 135.2, 132.3, 129.9, 129.2, 122.4, 121.5, 119.4, 117.7, 117.0, 20.3; IR (KBr, cm^{-1}): 3436, 2924, 2846, 1742, 1621, 1585, 1484, 1454, 1404, 1311, 1270, 1251, 1222, 1196, 1155, 1138, 1034, 960, 858, 806, 753; Elemental Analysis: found: C, 70.58; H, 5.16; N, 5.47. $C_{15}H_{13}NSO$ requires C, 70.56; H, 5.13; N, 5.49%.

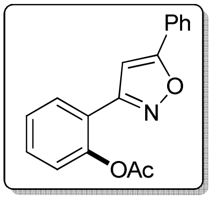
2-(6-methoxybenzo[*d*]thiazol-2-yl)phenyl acetate (18c):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, 1H, *J* = 8.8 Hz), 7.35 (d, 1H, *J* = 2.4 Hz), 7.32 (t, 2H, *J* = 8.4 Hz), 7.11 (dd, 1H, *J* = 9.0 Hz), 6.99 (dd, 1H, *J* = 8.8 Hz), 6.73 (dd, 1H, *J* = 8.8 Hz), 3.89 (s, 3H,), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 161.1, 159.7, 158.1, 148.4, 143.8, 134.4, 131.0, 122.7, 116.5, 115.5, 113.2, 110.6, 103.4, 55.7, 22.5; IR (KBr, cm^{-1}): 3435, 2926, 2846, 1769, 1744, 1626, 1604, 1476, 1371, 1234, 1185, 1025, 968, 817; Elemental Analysis: found: C, 64.24; H, 4.40; N, 4.65. $C_{16}H_{13}NSO_3$ requires C, 64.20; H, 4.38; N, 4.68%.

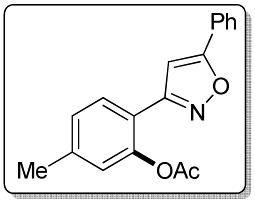
➢ IIB.6.

2-(5-Phenylisoxazol-3-yl)phenyl acetate (1'a):



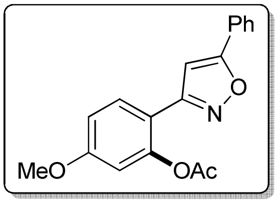
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, 1H, *J* = 7.2 Hz), 7.84–7.79 (m, 2H), 7.51–7.46 (m, 4H), 7.37 (t, 1H, *J* = 7.0 Hz), 7.22 (d, 1H, *J* = 8.0 Hz), 6.79 (s, 1H), 2.35 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.7, 160.3, 148.5, 133.9, 131.1, 130.4, 130.0, 129.2, 128.7, 126.7, 126.0, 123.8, 99.3, 21.4; IR (KBr, cm^{-1}): 3065, 2928, 2846, 1766, 1621, 1593, 1572, 1495, 1464, 1445, 1400, 1369, 1207, 1192, 1088, 948, 913, 820, 803, 762, 689; HRMS (ESI) calcd for $C_{17}H_{13}NO_3$ (M + H$^+$) 280.0968, found 280.0977.

5-Methyl-2-(5-phenylisoxazol-3-yl)phenyl acetate (2'a):



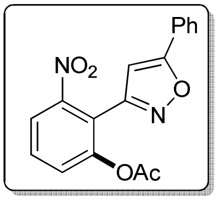
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.48–7.43 (m, 3H), 7.16 (d, 1H, *J* = 8.0 Hz), 7.01 (s, 1H), 6.74 (s, 1H), 2.40 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.2, 169.7, 162.2, 150.0, 133.9, 131.1, 130.4, 130.0, 129.2, 128.7, 126.7, 126.0, 122.8, 99.3, 21.8, 21.1; IR (KBr, cm^{-1}): 2928, 2846, 1768, 1618, 1569, 1522, 1495, 1450, 1368, 1204, 1086, 969, 949, 807, 766, 690; HRMS (ESI) calcd for $C_{18}H_{15}NO_3$ (M + H$^+$) 294.1125, found 294.1127.

5-Methoxy-2-(5-phenylisoxazol-3-yl)phenyl acetate (3'a):



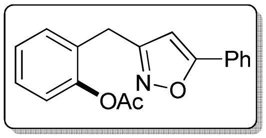
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.83–7.80 (m, 2H), 7.72 (d, 1H, *J* =8.4 Hz), 7.48–7.45 (m, 3H), 6.90 (d, 1H, *J* = 8.8 Hz), 6.79–6.75 (m, 1H), 6.74 (s, 1H), 3.86 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 164.9, 161.7, 149.6, 130.4, 129.2, 127.6, 125.9, 123.7, 121.7, 115.1, 112.6, 109.4, 99.0, 55.8, 21.4; IR (KBr, cm^{-1}): 2937, 2843, 1767, 1690, 1617, 1572, 1525, 1494, 1450, 1390, 1369, 1251, 1203, 1157, 1080, 948, 811, 765, 690, 630, 608; HRMS (ESI) calcd for $C_{18}H_{15}NO_4$ (M + H$^+$) 310.1074, found 310.1078.

3-Nitro-2-(5-phenylisoxazol-3-yl)phenyl acetate (4'a):



Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.97 (d, 1H, *J* = 8.0 Hz), 7.93 (d, 1H, *J* = 7.6 Hz), 7.80–7.77 (m, 1H), 7.75–7.69 (m, 1H), 7.65–7.61 (m, 1H), 7.48 (d, 2H, J = 9.6 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 6.64 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.4, 163.2, 160.2, 149.4, 133.2, 131.8, 129.3, 128.2, 126.2, 124.1, 120.5, 119.5, 113.4, 100.4, 22.0; IR (KBr, cm^{-1}): 2922, 2851, 1766, 1736, 1615, 1572, 1531, 1450, 1401, 1349, 1186, 1094, 949, 789, 765; HRMS (ESI) calcd for $C_{17}H_{12}N_2O_5$ (M + H$^+$) 325.0819, found 325.0817.

2-((5-Phenylisoxazol-3-yl)methyl)phenyl acetate (8'a):

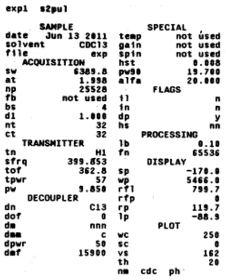


Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70–7.68 (m, 2H), 7.43–7.37 (m, 3H), 7.30 (t, 2H, *J* = 7.8 Hz), 7.23–7.19 (m, 1H), 7.08 (d, 1H, *J* = 8.0 Hz), 6.23 (s, 1H), 3.96 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.1, 169.5, 162.8, 149.2, 130.9, 130.2, 129.5, 129.0, 128.5, 127.5, 126.6, 125.9, 122.9, 99.5, 27.5, 20.9; IR (KBr, cm^{-1}): 2922, 2840, 1760, 1647, 1486, 1448, 1419, 1378, 1218, 1171, 1094, 816, 766, 743, 699, 690; HRMS (ESI) calcd for $C_{18}H_{15}NO_3$ (M + H$^+$) 294.1125, found 294.1121.

II.7. Spectra

➢ IIA.7.

2-(Benzo[*d*]thiazole-2-yl)-phenol (1a): ^{1}H NMR (400 MHz, CDCl$_3$):



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np           25528         FLAGS
fb        not used   il                  n
bs               4   in                  n
d1           1.000   dp                  y
nt              32   hs                 nn
ct              32        PROCESSING
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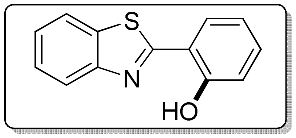
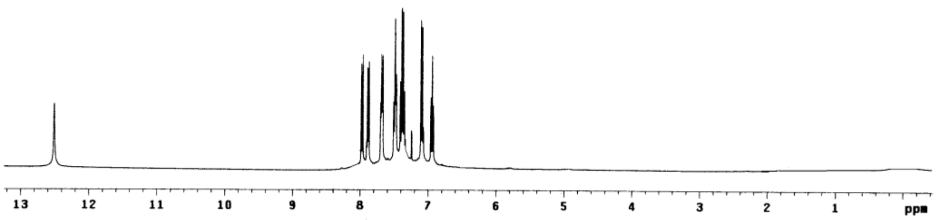
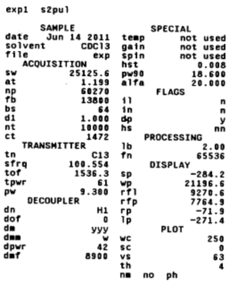
                     nm  cdc  ph
```





2-(Benzo[*d*]thiazole-2-yl)-phenol (1a): ^{13}C NMR (100 MHz, CDCl$_3$):



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np           60270         FLAGS
fb           13800   il                  n
bs              64   in                  n
d1           1.000   dp                  y
nt           10000   hs                 nn
ct            1472        PROCESSING
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sfrq       100.554         DISPLAY
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tpwr            61   wp            21196.6
pw           9.300   rfl            9270.6
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dn              H1   rp              -71.9
dof              0   lp             -271.4
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dmm              w   wc                250
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dmf           8900   vs                 63
                     th                  4
                     nm  no  ph
```
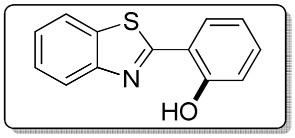
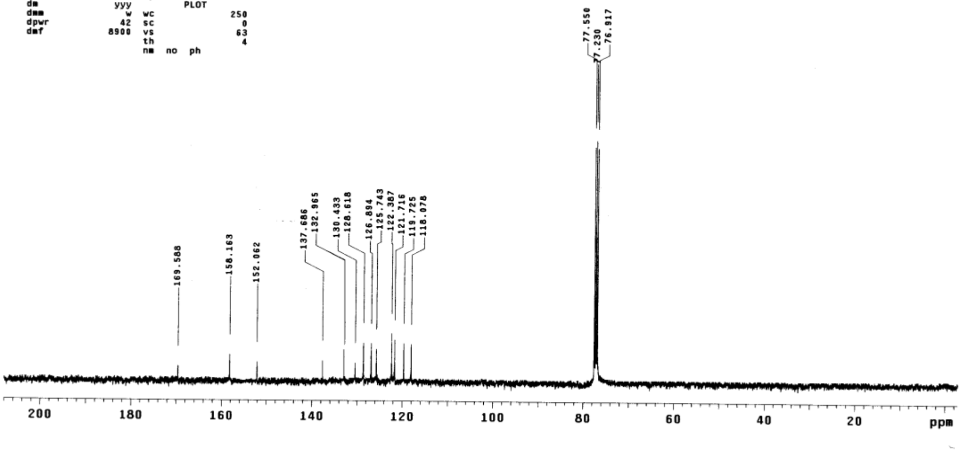
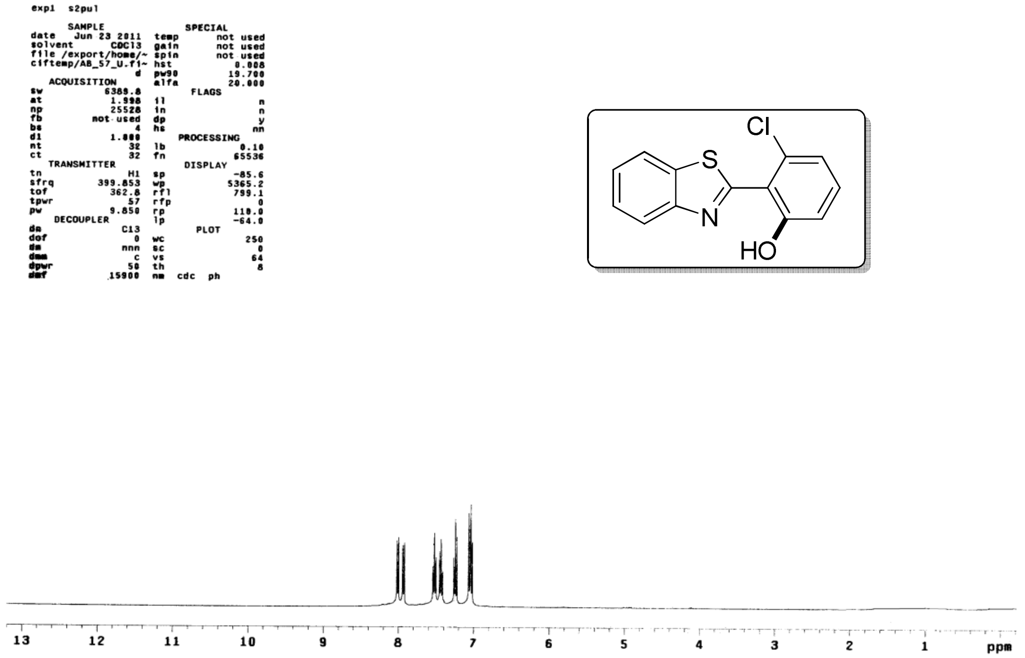





2-(Benzo[*d*]thiazole-2-yl)-3-chloro-phenol (10a): ^{1}H NMR (400 MHz, $CDCl_3$):



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                  d     pw90           19.700
   ACQUISITION          alfa           20.000
sw           6388.8             FLAGS
at            1.998     il                  n
np            25528     in                  n
fb         not used     dp                  y
bs                4     hs                 nn
d1            1.000            PROCESSING
nt               32     lb               0.10
ct               32     fn              65536
   TRANSMITTER                  DISPLAY
tn               H1     sp              -85.6
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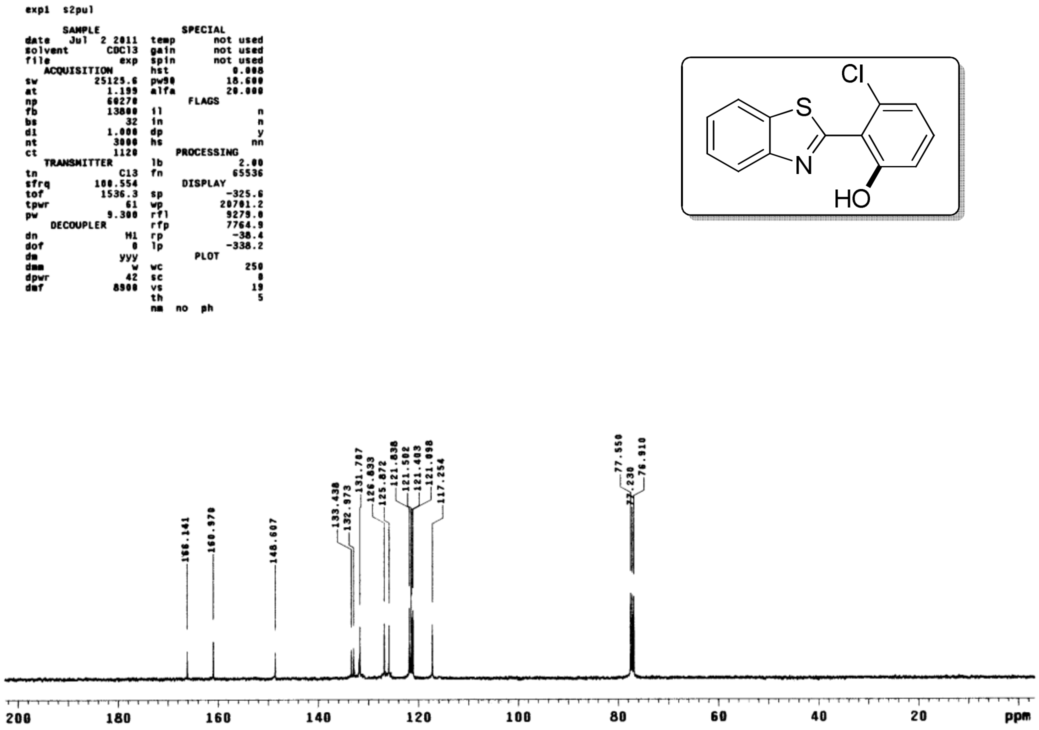
tof           362.8     rfl             799.1
tpwr             57     rfp                 0
pw            9.850     rp              110.0
    DECOUPLER           lp              -64.0
dn              C13              PLOT
dof               0     wc                250
dm              nnn     sc                  0
dmm               c     vs                 64
dpwr             50     th                  8
dmf           15900     nm  cdc  ph
```

2-(Benzo[*d*]thiazole-2-yl)-3-chloro-phenol (10a): ^{13}C NMR (100 MHz, $CDCl_3$):



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np            60270             FLAGS
fb            13800     il                  n
bs               32     in                  n
d1            1.000     dp                  y
nt             3000     hs                 nn
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pw            9.300     rfl            9279.0
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dm              yyy              PLOT
dmm               w     wc                250
dpwr             42     sc                  0
dmf            8900     vs                 19
                        th                  5
                        nm  no  ph
```
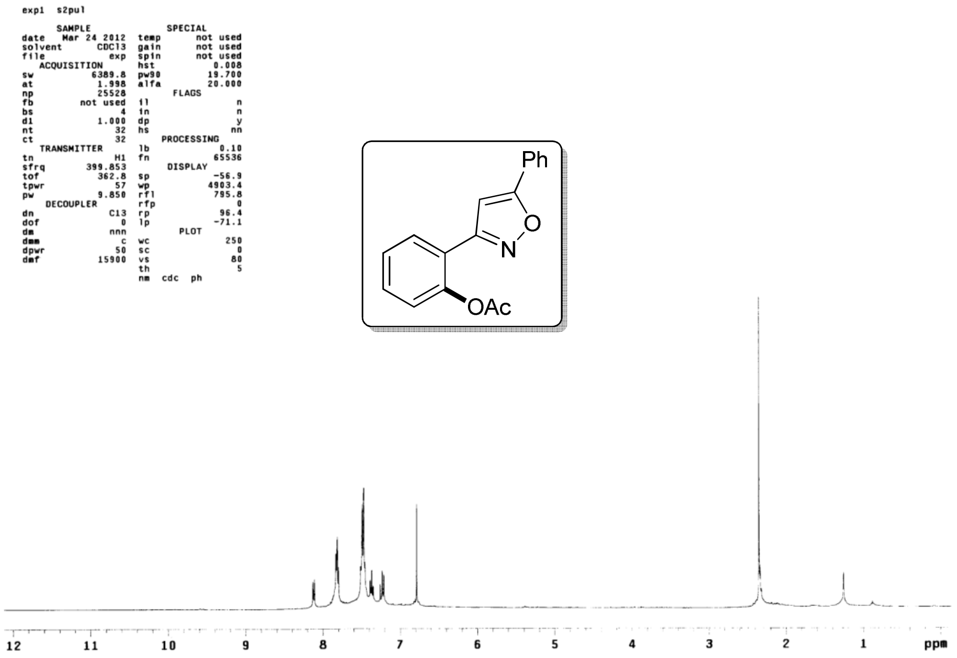

➢ IIB.7.

2-(5-Phenylisoxazol-3-yl)phenyl acetate (1'a): ^{1}H NMR (400 MHz, CDCl$_3$):



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solvent      CDC13  gain        not used
file           exp  spin        not used
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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             -56.9
tpwr            57  wp            4903.4
pw           9.850  rfl            795.8
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dn             C13  rp              96.4
dof              0  lp             -71.1
dm             nnn          PLOT
dmm              c  wc               250
dpwr            50  sc                 0
dmf          15900  vs                80
                    th                 5
                    nm  cdc  ph
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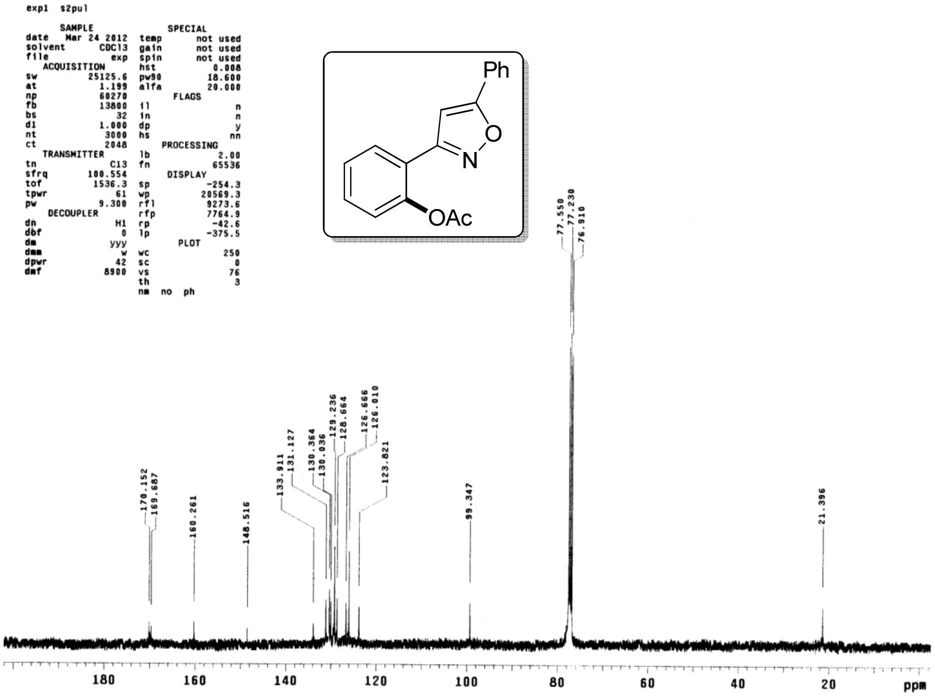
2-(5-Phenylisoxazol-3-yl)phenyl acetate (1'a): ^{13}C NMR (100 MHz, CDCl$_3$):



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expl  s2pul

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solvent      CDC13  gain        not used
file           exp  spin        not used
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at           1.199  alfa          20.000
np           60270         FLAGS
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bs              32  in                 n
d1           1.000  dp                 y
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ct            2048       PROCESSING
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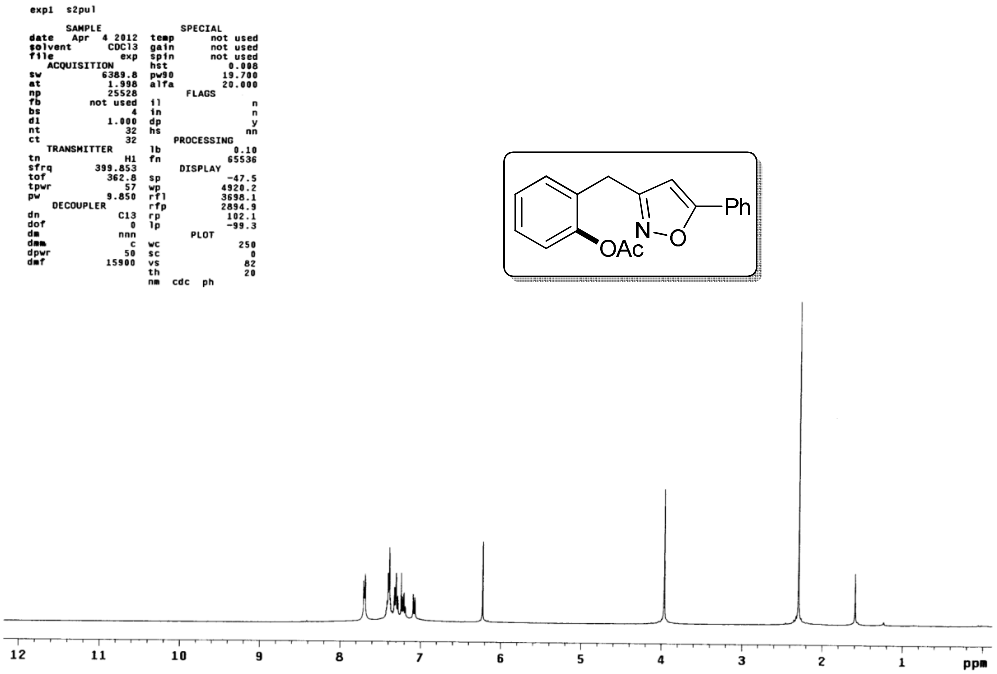
dpwr            42  sc                 0
dmf           8900  vs                76
                    th                 3
                    nm  no  ph
```

2-((5-Phenylisoxazol-3-yl)methyl)phenyl acetate (8'a): **^{1}H NMR (400 MHz, $CDCl_3$):**



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file            exp  spin        not used
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np            25528           FLAGS
fb         not used  il                 n
bs                4  in                 n
d1            1.000  dp                 y
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ct               32         PROCESSING
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dof               0  lp             -99.3
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dpwr             50  sc                 0
dmf           15900  vs                82
                     th                20
                     nm   cdc   ph
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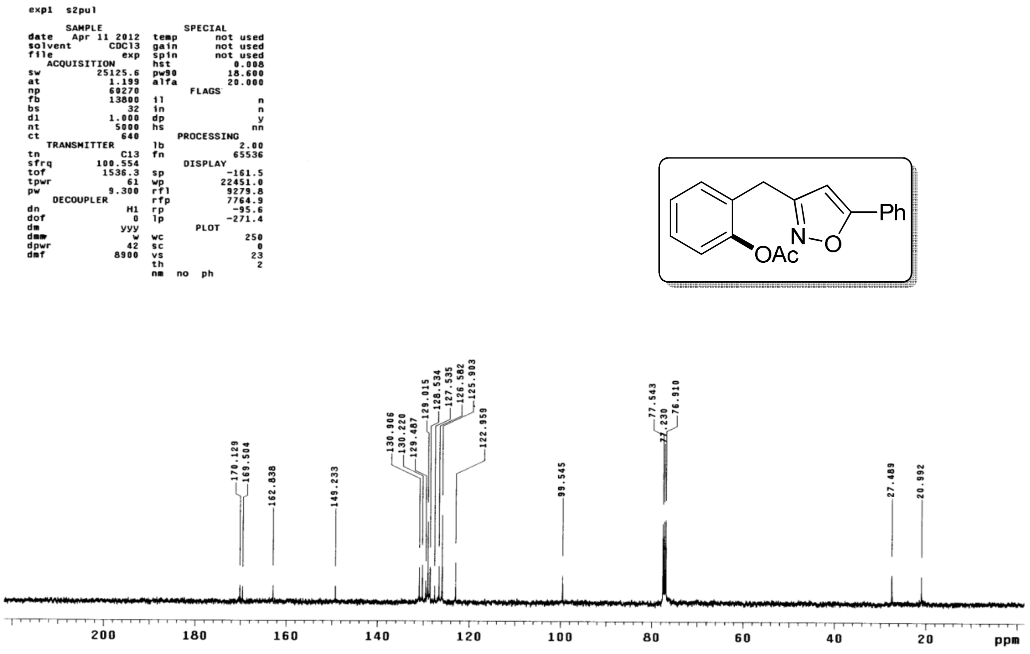
2-((5-Phenylisoxazol-3-yl)methyl)phenyl acetate (8'a): ^{13}C NMR (100 MHz, $CDCl_3$):



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file            exp  spin        not used
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np            60270           FLAGS
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bs               32  in                 n
d1            1.000  dp                 y
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pw            9.300  rfl           9279.8
    DECOUPLER        rfp           7764.9
dn               H1  rp             -95.6
dof               0  lp            -271.4
dm              yyy            PLOT
dmm               w  wc               250
dpwr             42  sc                 0
dmf            8900  vs                23
                     th                 2
                     nm   no   ph
```
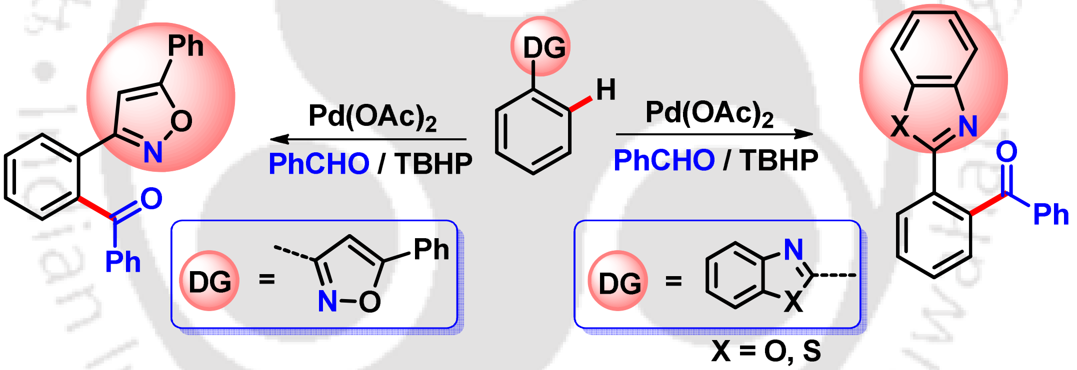

Chapter III

Palladium(II) Catalyzed o-Aroylation of 2-Arylbenzothizole, 2-Arylbenzoxazole and 3,5-Diarylisoxazole with Aldehyde



Abstract: ***Efficient protocols for the ortho-aroylation of 2-arylbenzothiazole, 2-arylbenzoxazole and 3,5-diarylisoxazole have been developed using aldehyde as the aroyl surrogate. This Pd(II)-catalyzed directed C_{sp2}–H bond functionalization occurs in the presence of the oxidant tert-butyl hydroperoxide (TBHP). Tolerance of a variety of functional groups on the directing arenes as well as aldehydes, excellent regioselectivity and performance of these reactions under air atmosphere makes it exceptionally practical.***

CHAPTER III

This chapter is divided into two Sections. Section-A demonstrates Pd(II) catalyzed *o*-aroylation of 2-arylbenzothiazole and 2-arylbenzoxazole whereas Section-B describes *o*-aroylation of another directing substrate 3,5-diarylisoxazole.

IIIA. Pd(II)-Catalyzed *o*-Aroylation of 2-Arylbenzothiazoles and 2-Arylbenzoxazoles with Aldehydes

IIIA.1. Introduction

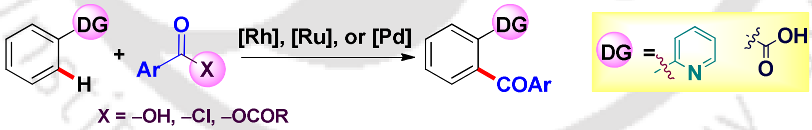
The selective functionalization of C–H bonds using palladium catalyst is one of the most powerful approaches to construct diverse arrays of complex organic molecules.[1] With the assistance of various directing groups and a cross-dehydrogenative coupling (CDC) technique *ortho* C–H bonds can be selectively functionalized to form C–C or C–X (X = hetero atom) bonds.[2] In this approach the combination of cross-dehydrogenative coupling (CDC) and directing group assisted protocols have been successfully employed for the formation of aryl ketones through selective C–H functionalization / C–C bond formation.[3] A survey of the literature entails that pertaining to the formation of aryl ketones, a plethora of methods have been recently reported using transition-metal-catalyzed oxidative sp^2 C–H bond activation on substrates possessing *N*-donor or *O*-donor atoms.

IIIA.2. Strategies for *ortho*-Aroylation

Diaryl and aryl alkyl ketones which are the fundamental intermediates in the synthesis of pharmaceutical, natural products, functional materials and agrochemicals[4] are typically synthesized by Friedel–Crafts acylation reaction. This classical Friedel-Crafts acylation reactions, involving the use of stoichiometric Lewis acid, has poor functional group compatibility and are non regioselective.[5] The oxidation of secondary alcohols is an alternative pathway to access ketones, but stoichiometric amounts of the oxidant are generally required which generates stoichiometric waste too.[6] The reactions of carboxylic acid derivatives, such as nitriles, Weinreb amides, anhydrides, or acid chlorides with lithium, magnesium, or aluminum reagents are alternative methods for the synthesis of the corresponding ketones.[7] However, these transformations require harsh reaction conditions such as highly basic and nucleophilic or acidic conditions, which results in low compatibility with various sensitive functional groups. To outwit these drawbacks, in recent years transition metal catalyzed aroylation of arenes *via* C–H bond cleavage has emerged as a direct and promising approach to access ketones.[8] The various methods that have been employed can be classified into four types as follows, (i) *ortho*-selective Friedel-Crafts acylation using carboxylic acids or its derivatives; (ii) the carbonylative processes; (iii) the cross dehydrogenative coupling with various aroyl surrogates and (iv) decarboxylative couplings of α-oxoacids. Some of the recent advances on each of these categories are summarized below.

(i) *o*-Selective Friedel-Crafts acylation using carboxylic acids or its derivatives

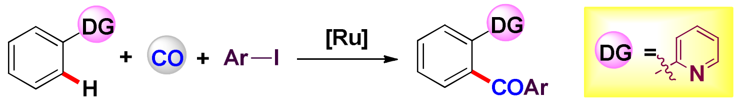
The direct use of carboxylic acids or its derivatives for *ortho*-acylation of arenes are scarce in literature. Kakiuchi and co-workers achieved a Ru catalyzed *ortho*-selective acylation of arylpyridines with acyl chlorides *via* C–H bond cleavage under oxidant-free conditions.[9a] In an analogous Pd-catalyzed reaction, selective aromatic C–H bond acylation with readily available carboxylic acids has also been reported by Fu *et al.*[9b] Recently, Gooβen group has demonstrated a Rh catalyzed method for the *ortho*-acylation of benzoic acid with carboxylic anhydrides (Scheme IIIA.2.1).[9c]



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

(ii) The carbonylative processes

Beller group has reported the synthesis of ketones *via* the *ortho*-directed carbonylative coupling reactions of 2-phenylpyridine with aryl halides using Ru catalyzed C–H bond activation (Scheme IIIA.2.2).[10a] Apart from this directed *ortho*-acylation, similar non-directed carbonylative coupling reaction between aryl iodide and heterocycle has also been achieved by the same group in the presence of Pd and Cu.[10b] Lei *et al.* developed an elegant Pd catalyzed process for the double C–H oxidative carbonylation of diphenyl ether derivatives to obtain xanthones.[10c]



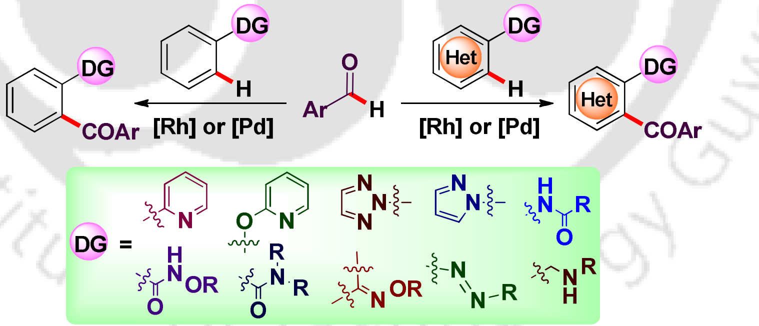
Scheme IIIA.2.2. *Directed o-aroylation via carbonyl insertion*

(iii) Cross dehydrogenative coupling approach with various aroyl surrogates

There are numbers of CDC based protocols appeared for the directing group assisted *ortho*-selective aroylation of various directing substrates possessing hetero-donar atoms. Some of the recent protocols on *ortho*-aroylation using various ArCO– sources are enlisted below.

(a) Aldehyde as ArCO– source

By using aldehyde as the aroyl source, various directing substrates possessing *N* and *O* donor atoms have been employed for the *o*-aroylation (Scheme IIIA.2.3). In a pioneering study Cheng *et al.* have developed a Pd catalyzed *ortho*-aroylaion strategy of 2-arylpyridines with benzaldehydes to give aromatic ketones using dioxygen as oxidant.[11a] Using Pd/TBHP combination Li group has demonstrated a similar CDC coupling of 2-arylpyridines with aliphatic aldehydes.[11b] A number of other *ortho*-chelating groups such as ketoxime ether,[11c-d] anilide,[11e-i] benzamide,[11j] triazole[11k] and even azobenzene[11l] have been studied toward similar *ortho*-acylation using aldehydes as the ArCO– source (Scheme IIIA.2.3).

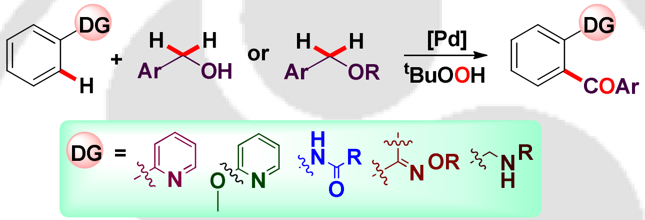


Scheme IIIA.2.3. *o-Aroylation using aldehydes as ArCO− source*

Although a fewer number of *ortho*-aroylation of heteroarenes have been reported using aldehydes as the aroylating agents. The two precendence that exist are a Rh-catalyzed oxidative C-2 acylation of indoles with aryl and alkyl aldehydes developed by Li group[11m] and a Pd catalyzed C-3 acylation of benzofurans and bezothiophenes as reported by Pan group.[11n]

(b) Benzyl alcohol or ethers as ArCO– source

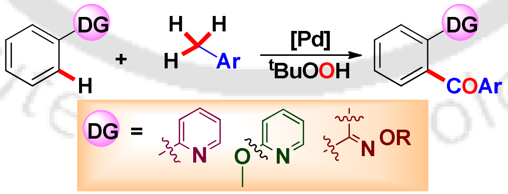
Primary alcohols have the ability to generate aldehydes *via in situ* oxidation, thus they have been used in various *ortho*-aroylation protocols as aroyl equivalents. Using alcohols as the latent aldehyde functionality a Pd-catalyzed regioselective *o*-aroylation of aromatic C–H bonds afforded ketones in good yields in the presence of peroxide (Scheme IIIA.2.4).[12a] Later various primary alcohols have been used as the aroyl equivalents for various *ortho* directing substrates.[12b-e] The use of ethers as the aroyl surrogate has also been reported by Kim and co-workers during directing group assisted *ortho* C–H functionalization. They have shown that not just alcohols but ethers can also act as the acyl surrogate to afford ketones *via* C–O bond cleavage of ethers eventually leading to the formation of C–C bond (Scheme IIIA.2.4).[12f]



Scheme IIIA.2.4. o-Aroylation using benzyl alcohols or ethers as ArCO– source

(c) Alkylbenzenes as ArCO– source

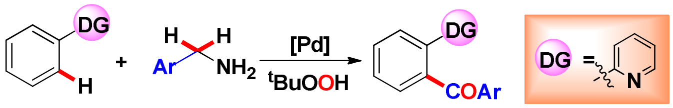
For the first time using inert alkylbenzene as the synthetic equivalent of the aroyl moiety our group has developed a directing group assisted *ortho*-aroylation through Pd(II)-catalyzed cross dehydrogenative coupling in the presence of TBHP (Scheme IIIA.2.5).[13]



Scheme IIIA.2.5. o-Aroylation using alkylbenzenes as ArCO– source

(d) Benzylamine as ArCO– source

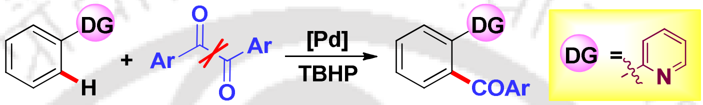
Wu group has recently developed an efficient protocol for Pd-catalyzed *ortho*-aroylation of 2-aryl pyridines using arylmethyl amines as an aroyl source in presence of TBHP (Scheme IIIA.2.6).[14]



Scheme IIIA.2.6. *o-Aroylation using benzylamine as ArCO− source*

(e) Benzil as ArCO– source

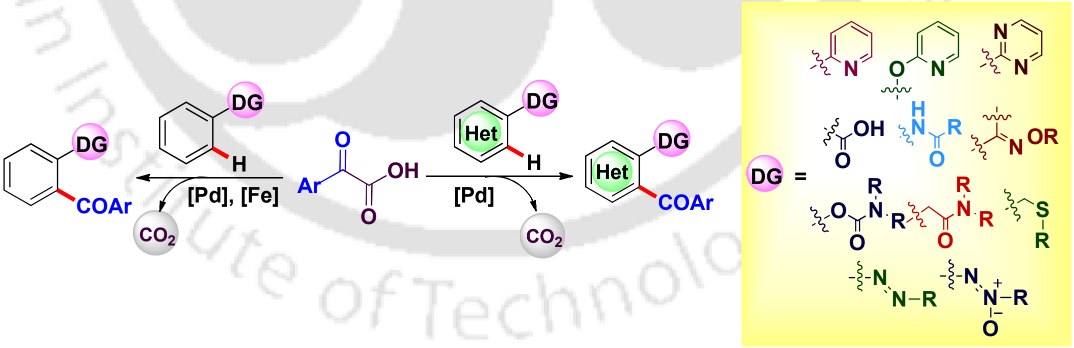
Wang group has achieved an efficient carbo-acylation reaction of 2-arylpyridines with α-diketones *via* a Pd-catalyzed C–H bond activation and C–C bond cleavage in the presence of TBHP as the radical initiator (Scheme IIIA.2.7).[15]



Scheme IIIA.2.7. *o-Aroylation using benzil as ArCO− source*

(f) Decarboxylative couplings of α-oxoacids

Besides the above strategies, *o*-aroylation has also been achieved through a substrate-directed decarboxylation of α-keto carboxylic acids. Pertaining to directed *ortho*-aroylation, Ge and co-workers has demonstrated a novel Pd catalyzed protocol to access *o*-aroyl acetanilides *via* decarboxylative coupling of α-oxoacids with acetanilides.[16a] Later the same group has achieved a similar *ortho*-acylation of 2-arylpyridines[16b] as well as carboxylic acids (Scheme IIIA.2.8).[16c]



Scheme IIIA.2.8. *o-Aroylation via decarboxylative coupling*

The decarboxylative coupling of α-oxoacids for ketone synthesis has also been implemented on other directing arenes such as 2-aryloxypyridines,[16d] ketoxime ether,[16e-f] cyclic enamides,[16g] carbamates,[16h] acetamide,[16i] azobenzene,[16j-k] azoxybenzene[16l] and even thioether.[16m] Pertinent to such strategy in heteroarenes, C-2 acylation in indoles has been reported using α-oxoacids as the aroyl source.[16n]

IIIA.3. Present Work

In light of the above-mentioned protocols, the present protocol on *o*-aroylation of directing arene *viz.* 2-arylbenzothiazole with aldehydes is unfamiliar in literature. The *ortho*-selective functionalization of 2-arylbenzoxazole or benzothiazole containing an *N*-donor atom as the directing group has been less explored. Thus far, neither of these substrates has been *ortho*-aroylated by any methods. There are instances in which only 2-arylbenzoxazole has been utilized for *ortho*-functionalization, once towards *o*-arylation[17] and the other *o*-acetoxylation.[18] Recently, benzothiazoles have been *o*-arylated through a proximal C–H functionalization.[19] Thus, it would be interesting to develop a protocol for the *ortho*-aroylation of these two important scaffolds. As privileged heterocycles benzoxazoles and benzothiazoles are recognized as significant pharmacophores which exhibit diverse biological activities.[20] Thus, further functionalizations of these two important molecules would lead to useful derivatives that might have potential applications in other areas.

Optimization of reaction conditions. Taking a cues from the earlier results,[17-19] we wanted to invoke the advantages of chelation assisted and CDC approach for the *ortho*-aroylation (C–C bond formation) of these important scaffolds by using aldehyde as the aroyl equivalent in the presence of Pd. Our initial experiments focused on the *ortho*-aroylation of 2-arylbenzothiazoles with aromatic aldehydes by using a combination of oxidants and a Pd catalyst. The optimization studies were initiated by using 2-phenylbenzothiazole (**1**) (1 equiv) and benzaldehyde (**a**) (1.2 equiv), $Pd(OAc)_2$ (2 mol %) and *tert*-butyl hydroperoxide (TBHP) (1 equiv) in dioxane solvent at 110 °C. The reaction provided *ortho*-aroylated product (**1a**) in an isolated yield of 25% (Table IIIA.3.1, entry 1).The structure of (**1a**) was further confirmed by X-ray crystal structure analysis. (Fig. IIIA.3.1).

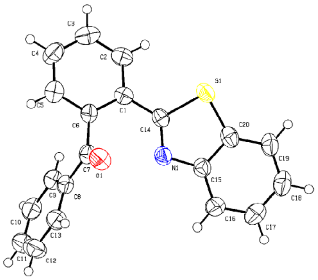
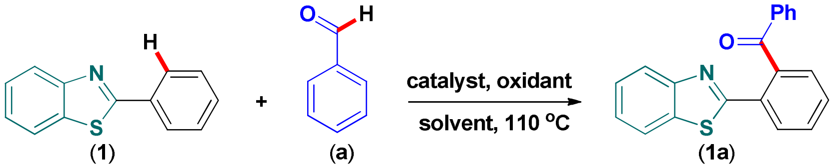


Fig. IIIA.3.1. *ORTEP molecular diagram of (**1a**)*

Table IIIA.3.1. *Screening of reaction conditions*



Entry	Catalyst (mol %)	Solvent	Oxidant	Yield (%)^a
1	Pd(OAc)$_2$ (2.0)	Dioxane	TBHP	25
2	Pd(OAc)$_2$ (2.0)	Cyclohexane	TBHP	30
3	Pd(OAc)$_2$ (2.0)	*O*-xylene	TBHP	28
4	Pd(OAc)$_2$ (2.0)	DCE	TBHP	35
5	Pd(OAc)$_2$ (2.0)	DMF	TBHP	N. R.
6	Pd(OAc)$_2$ (2.0)	DMSO	TBHP	N. R.
7	Pd(OAc)$_2$ (2.0)	Toluene	TBHP	50
8	Pd(OAc)$_2$ (5.0)	Toluene	TBHP	70
9	Pd(OAc)$_2$ (10.0)	Toluene	TBHP	72
10	PdCl$_2$ (5.0)	Toluene	TBHP	30
11	PdBr$_2$ (5.0)	Toluene	TBHP	40
12	Pd(TFA)$_2$ (5.0)	Toluene	TBHP	50
13	Pd(OAc)$_2$ (5.0)	Toluene	TBHP	73^b
14	**Pd(OAc)$_2$ (5.0)**	**Toluene**	**TBHP**	**75**^{c}
15	Pd(OAc)$_2$ (5.0)	Toluene	(PhCOO)$_2$	10
16	Pd(OAc)$_2$ (5.0)	Toluene	DIB	00
17	Pd(OAc)$_2$ (5.0)	Toluene	Ag$_2$O	00
18	Pd(OAc)$_2$ (5.0)	Toluene	K$_2$S$_2$O$_8$	00
19	Cu(OTf)$_2$ (5.0)	Toluene	TBHP	00
20	Cu(OAc)$_2$ (5.0)	Toluene	TBHP	00

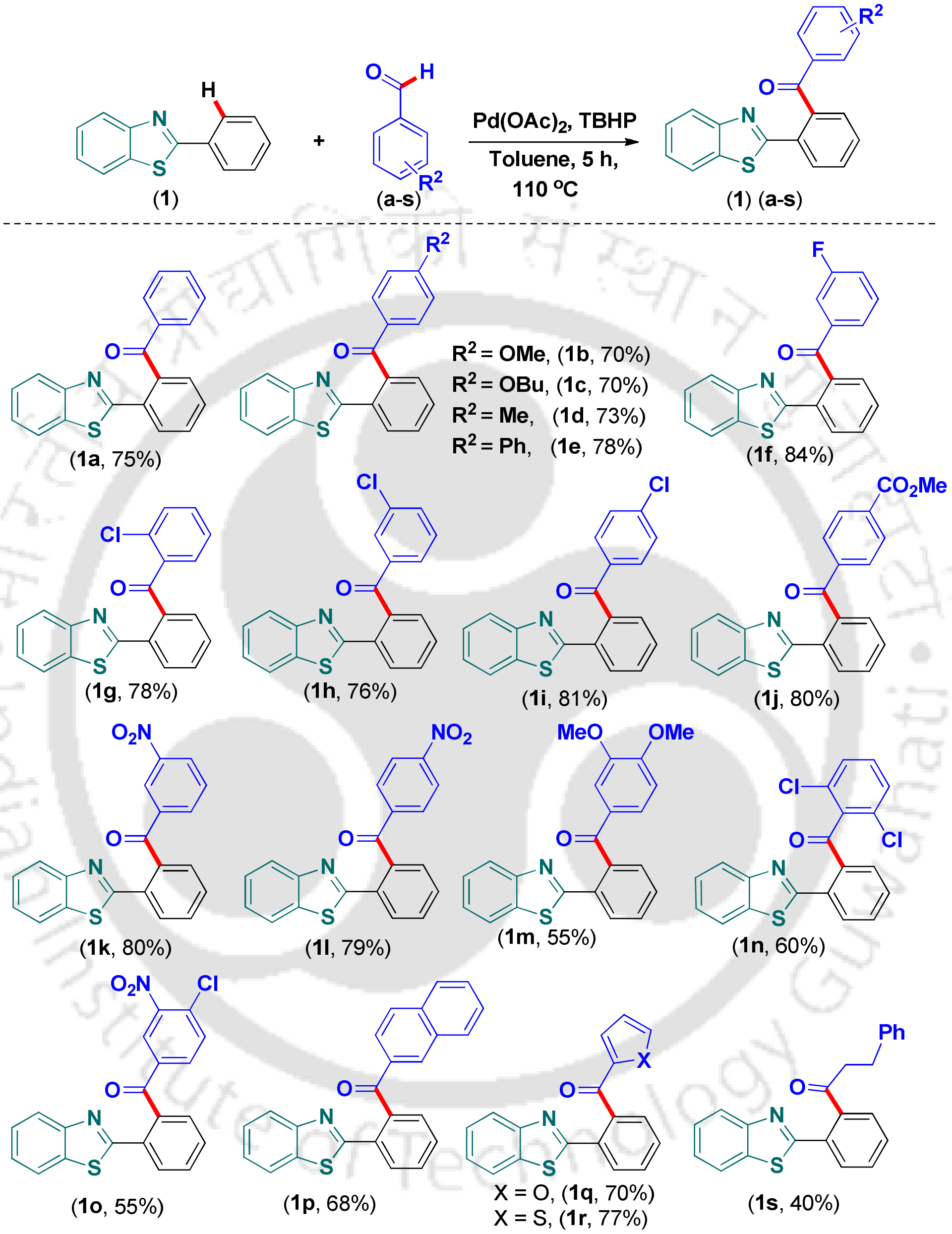
[a] Isolated yield *o*-aroylated product (**1a**) after 5 h. TBHP (1 equiv) was added in 5 lots after every1 h. [b] 1.2 equiv of TBHP. [c] Using 1.5 equiv of TBHP.

In a quest to improve the product yield, the reaction was performed with other solvents. Toluene gave a modest yield of 50% compared to the yields of the other solvents, such as cyclohexane (30%), *o*-xylene (28%), 1,2-dichloroethane(DCE) (35%), *N*,*N*’-dimethyl (DMF), (0%), and dimethylsulfoxide DMSO (0%); (Table IIIA.3.1, entries 2-7). A further improvement in the yield to 70% was observed by increasing the catalyst loading to 5 mol %. No substantial effect on the product yield (i.e, 72%) was observed by using 10 mol % of the catalyst. Using other palladium salts such as PdCl$_2$, PdBr$_2$, Pd(TFA)$_2$ gave inferior results compared to using Pd(OAc)$_2$ under identical reaction conditions (Table IIIA.3.1, entries 8, 10-12). By keeping the catalyst loading to 5 mol % and increasing the TBHP quantity to 1.2 and

1.5 equiv, a marginal improvement in the yields (73% and 75% respectively) were obtained (Table IIIA.3.1, entries 13-14). The oxidant TBHP was superior over the other oxidants screened, such as benzoyl peroxide [$(PhCOO)_2$], diacatoxy iodobenzene (DIB), Ag_2O and $K_2S_2O_8$ (Table IIIA.3.1, entries 15-18). The use of copper salts such as $Cu(OTf)_2$, $Cu(OAc)_2$ in lieu of the palladium catalyst was completely unsatisfactory (Table IIIA.3.1, entries 19-20). Thus, for all subsequent reactions, we used optimized reaction conditions, which were determined to be the combination of $Pd(OAc)_2$ (5 mol %), TBHP (1.5 equiv) and aldehyde (1.2 equiv) in toluene at 110 ^{o}C.

Substrate scope for *o*-aroylation. Using these optimized conditions, the scope and generality of this methodology was further investigated with 2-phenylbenzothiazole (**1**) and a variety of aldehydes. Aromatic aldehydes containing electron withdrawing and electron donating groups on the aromatic ring coupled efficiently with 2-phenylbenzothiazole (**1**) to give the desired aroylated products in moderate to good yields. Aldehydes that were *para*-substitured with the strong electron donating groups such as –OMe (**b**), –OBu (**c**) and the moderately electron donating groups such as –Me (**d**), –Ph (**e**) gave moderate yields of the desired products (**1b**), (**1c**), (**1d**) and (**1e**) respectively (Scheme IIIA.3.1). Aldehydes that contain either the weakly electron withdrawing groups such as –F (**f**), –Cl (**g**-**i**) or the strongly electron withdrawing groups such as $-CO_2Me$ (**j**), $-NO_2$ (**k**-**l**) afforded the corresponding *o*-aroylated products (**1f**-**1l**) in better yields irrespective of the position of the electron withdrawing group on the phenyl ring. Aldehydes that were di-substituted with the 3,4 di–OMe (**m**), 2,6 di–Cl (**n**) and 4–Cl, $3-NO_2$ (**o**) groups respectively gave poor yields of the corresponding coupled products (**1m**), (**1n**) and (**1o**). The poor yield obtained in the case of the di-substituted substrates could be, in part, because of the instability of intermediate aroyl radical, a steric factor, or a combination of both. In these cases, a substantial amount of carboxylic acid by-products, which resulted from the corresponding aldehydes, were obtained along with the formation of the desired products. Furthermore, the reactions of 2-phenylbenzothiazole (**1**) with fused aromatic aldehyde (**p**) and hetero-aromatic aldehydes (**q** and **r**) gave decent yields of the coupled products (**1p**), (**1q**) and (**1r**) respectively (Scheme IIIA.3.1). However, in the case of aliphatic aldehyde (**s**), product (**1s**) was obtained in a poor yield of 40% which could be a result of the instability of the intermediate aliphatic acyl radical.

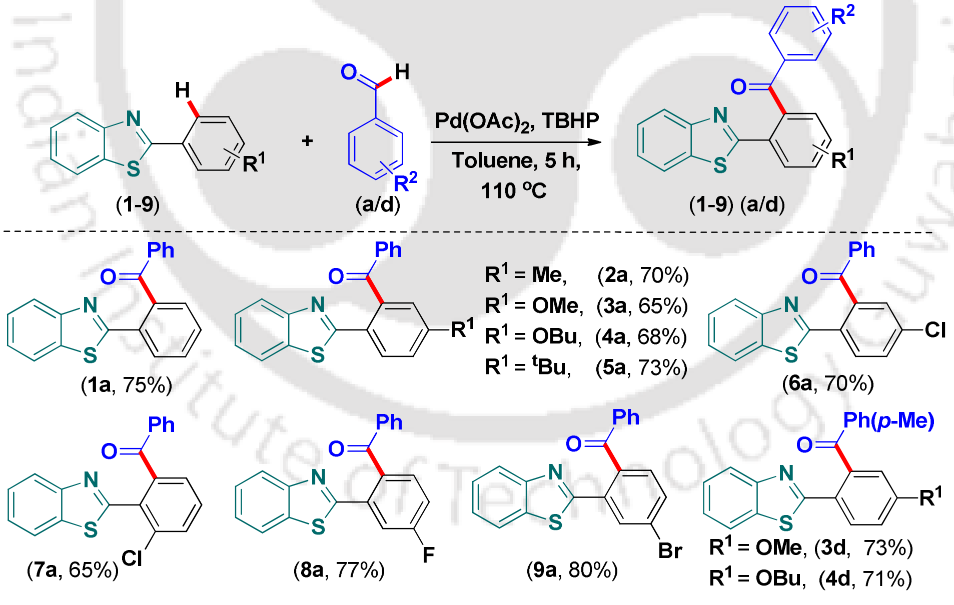
Scheme IIIA.3.1. *Scope of aldehydes in o-aroylation of 2-phenylbenzothiazole*[a,b]



[a]Reaction conditions: 2-phenylbenzothiazole (1 mmol), aldehyde (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP (1.5 mmol), toluene (2 mL), 110 °C, time 5 h. [b]Reactions were monitored by TLC, confirmed by spectroscopic analysis, yield of isolated pure product reported.

Next, the protocol was extended to various 2-aryl substituted benzothiazoles to examine the substituent effects on the product yields. Unlike the marginal substituent effects observed with the aryl substituted aldehydes, there were no such substitution effects observed for the various 2-aryl substituted benzothiazoles as evident from Scheme IIIA.3.2. Irrespective of their positions on the 2-phenyl ring, the 2-arylsubstituted benzothiazoles with the electron donating groups such as –Me (**2**), –OMe (**3**), –OBu (**4**), –*t*Bu (**5**), or the moderately electron withdrawing groups –Cl (**6**–**7**), –F (**8**), –Br (**9**) respectively underwent coupling with benzaldehyde to give a similar range of yields. The 2-arylbenzothiazoles that were substituted at its *meta*-position provided *ortho*-aroylated products (**8a**, **9a**) at the less sterically hindered *ortho*-position (Scheme IIIA.3.2). This is a result of the palladation preferentially occurring at the less sterically hindered *ortho*-site. The structure of the regioselective product (**8a**) has been further confirmed by X-ray crystallographic analysis as shown in Figure IIIA.3.2. In addition, 2-arylbenzothiazoles (**3** and **4**), which contain the electron donating substituents such as –OMe and –OBu on the 2-aryl ring, coupled with *p*-tolualdehyde to give the corresponding aroylated products (**3d**) and (**4d**) respectively in good yields.

Scheme IIIA.3.2. *Scope of 2-arylbenzothiazoles in Pd-catalyzed o-aroylation*[a,b]



[a]Reaction conditions: 2-arylbenzothiazole (1 mmol), aldehyde (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP (1.5 mmol), toluene (2 mL), 110 °C, time 5 h. [b]Reactions were monitored by TLC, confirmed by spectroscopic analysis, yield of isolated pure product reported.

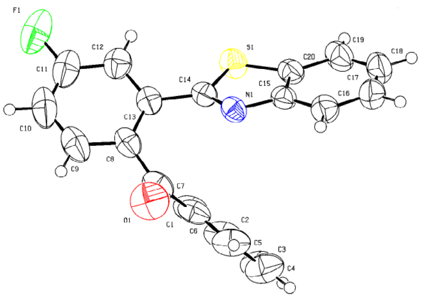
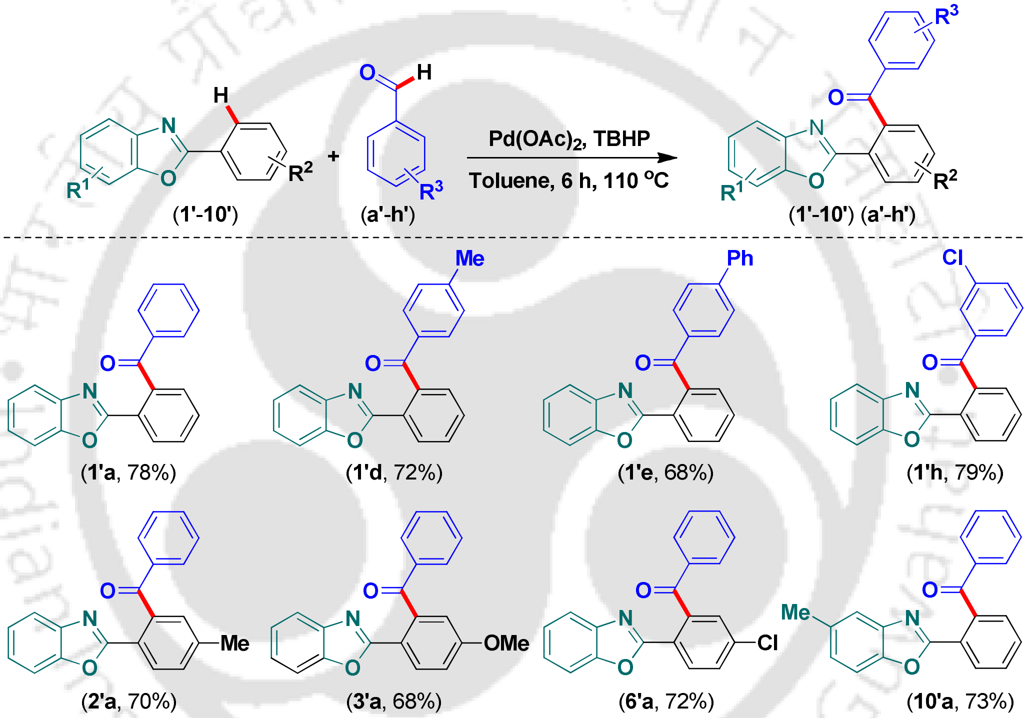


Fig. IIIA.3.2. *ORTEP molecular diagram of (**8a**)*

Scheme IIIA.3.3. *Scope of 2-arylbenzoxazoles and aldehydes in o-aroylation*[a,b]

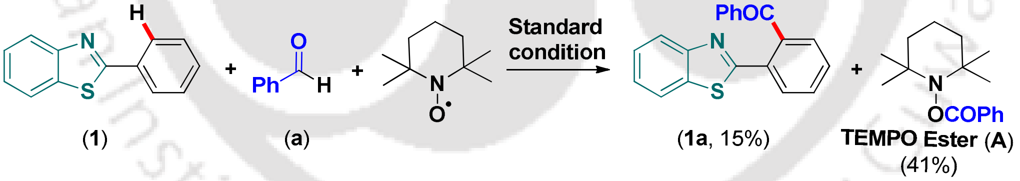


[a] Reaction conditions: 2-arylbenzoxazole (1 mmol), aldehyde (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP (1.5 mmol), toluene (2 mL), 110 °C, time 6 h. [b] Reactions were monitored by TLC, confirmed by spectroscopic analysis, yield of isolated pure product reported.

Nitrogen has better chelating ability particularly towards Pd compared to oxygen and sulfur and is expected to control the *ortho*-functionalization if suitably positioned on a substrate. Taking cues from the above work, to ascertain the predominating directing ability of nitrogen over oxygen and sulfur, the analogous compound 2-arylbenoxazole was chosen for *o*-aroylation. Interestingly the same optimized conditions were applicable for the *o*-aroylation of 2-arylbenzoxazoles as well. Under the above optimized conditions 2-phenylbenzoxazole (**1'**) underwent reaction with benzaldehyde (**a**) to give *o*-aroylated product (**1'a**) in good yield.

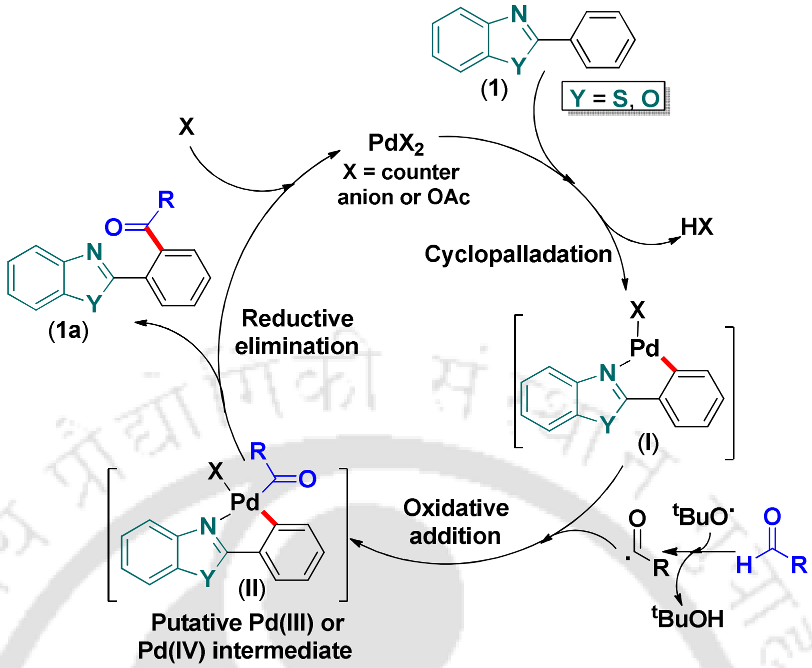
Aldehydes containing the moderately activating groups such as –Me, –Ph as well as the moderately deactivating group such as –Cl coupled efficiently with 2-phenylbenzoxazole to give the desired aroylated products (**1'd**), (**1'e**) and (**1'h**) respectively as shown in Scheme IIIA.3.3. As was the case with 2-aryl benzothiazole, the presence of either electron-donating (–Me and –OMe) or electron withdrawing (–Cl) substituents on the phenyl ring of 2-arylbenzoxazole had no effect on the coupling reaction giving almost identical yields of corresponding aroylated products (**2'a**), (**3a'**) and (**6'a**) (Scheme IIIA.3.3). Even methyl substituted benzoxazole coupled with benzaldehyde to give product (**10'a**) in good yield.

Mechanistic studies. A plausible mechanism for this transformation can be speculated from some of the basic observations of these experiments. Arylaldehydes with electron withdrawing substituents gave better yields than arylaldehydes with electron donating substituents. The use of an aliphatic aldehyde in lieu of an aromatic aldehyde as the acylating partner afforded a lower yield. A substantial rate retardation in the presence of a radical scavenger, such as 2,2,6,6-tetramethyl piperidin-1-oxyl (TEMPO) and considerable decrease in the yield (15%) along with the formation of benzoyl-TEMPO adduct (**A**) in 41% isolated yield (Scheme IIIA.3.4) indicates a radical pathway of the reaction. This observation is consistent with similar aroylation reactions with other directing groups.[11,12]



Scheme IIIA.3.4. *Reaction in the presence of radical scavanger TEMPO*

Thus a plausible mechanism can be envisaged for this aroylation reaction (Scheme IIIA.3.5). The initial step involves cyclopalladation of the directing scaffold 2-aryl benzoxazole or 2-aryl benzothiazole to generate intermediate (**I**). In the next step, the *in situ* generated aroyl radical, which is obtained by the hydrogen-atom abstraction of the aldehyde and is initiated by TBHP, forms either reactive Pd(IV)[21] or dimeric Pd(III)[22] intermediate (**II**). In the final stage a reductive elimination leads to C–C bond formation to afford the *ortho*-aroylated product along with the regeneration of the Pd(II) species which maintains the catalytic cycle (Scheme IIIA.3.5).



Scheme IIIA.3.5. *Plausible mechanistic cycle*

In summary, a simple and efficient protocol, which occurs through a Pd(II) catalyzed C–H activation / C–C bond formation, has been developed for the *ortho*-aroylation of 2-arylbenzoxazoles and 2-arylbenzothiazoles with an aldehyde as the aroylating partner. This reaction is carried out without an inert atmosphere and is compatibility with a wide range of functional groups. The high regioselectivity makes this protocol attractive for the synthesis of functionalized 2-arylbenzoxazoles and 2-arylbenzothiazoles.

IIIB. Palladium Catalyzed Regioselective Aroylation of 3,5-Diarylisoxazole *via o*-C–H Functionalizations

IIIB.1. Introduction

After successful *ortho* aroylation of 2-arylbenzothiazole and 2-arylbenzoxazole using cat. Pd(II) / TBHP combination, we searched for analogous direcing systems for similar *ortho* aroylation. 3,5-Diarylisoxazole was chosen as the model unit as it possess both *N* and *O*-chelating atoms in a rigid framework which may provide competitive cyclometallated intermediate either through *N* or *O* atoms by anchoring the metal selectively to one of the proximal *ortho* C–H bonds. *o*-C–H functionalization in isoxazoles having dual-directing atoms such as *N* and *O* has not been investigated so far. Thus, it would be interesting to see whether the palladation would occur through –*N* donor *ortho*-site or –*O* donor *ortho*-site or at the C-4 position in 3,5-diarylisoxazoles.

IIIB.2. Strategies for *ortho*-Aroylation

Pertaining to the formation of aryl ketones, a plethora of transition-metal-catalyzed directing group assisted *o*-aroylation strategies have been already discussed in Section-A of this chapter (page no 101-105).[9-16]

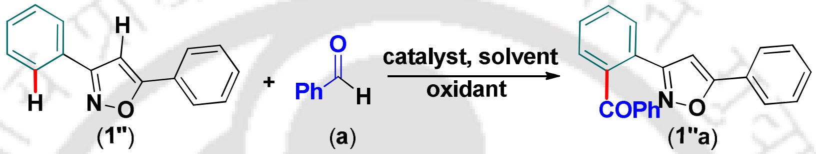
IIIB.3. Present Work

The present protocol on *o*-aroylation of directing arene, 3,5-diarylisoxazole with aldehydes is unfamiliar in literature. Similar to 2-arylbenzazoles, aldehyde was chosen as the aroylating surrogate among various aroylating partners for the *o*-aroylation of 3,5-diarylisoxazole. Apart from this, 3,5-diarylisoxazole scaffold is an important pharmacophore having diverse array of biological activities.[23] The reductive *N–O* bond cleavage of 3,5-disubstituted isoxazoles lead to various bi-functional molecules[24] that can be utilized for the synthesis of other important heterocycles.[25] Thus, any further functionalization of this important moiety is likely to generate further interest.

Optimization of reaction conditions. An initial experiment for the aroylation of 3,5-diphenylisoxazole was performed using aromatic aldehyde as the aroyl source.

Thus 3,5-diphenylisoxazole (**1''**) (1 equiv) was reacted with an equivalent of benzaldehyde (**a**) in the presence of $Pd(OAc)_2$ (5 mol %) and oxidant *tert*-butylhydroperoxide (TBHP, 1 equiv) in toluene solvent. A product having lower R_f was isolated with a mere yield of 18% (Table IIIB.3.1, entry 1). Spectroscopic (^1H and ^{13}C NMR) analysis of the product (**1''a**) showed the presence of an aroyl group and retention of the internal C-4 hydrogen in its ^1H NMR at 6.54 ppm. Thus, the aroylation is taking place most probably at one of the *ortho* positions proximal to either *N* or *O* donor site of the isoxazole moiety.

Table IIIB.3.1. *Screening of reaction conditions*



Entry	Catalyst (mol %)	Solvent	Oxidant	Yield (%)[a,b]
1	$Pd(OAc)_2$ (5.0)	Toluene	TBHP (1.0)	18
2	$Pd(OAc)_2$ (5.0)	1,4-dioxane	TBHP (1.0)	00
3	$Pd(OAc)_2$ (5.0)	AcOH	TBHP (1.0)	27
4	$Pd(OAc)_2$ (5.0)	DMSO	TBHP (1.0)	00
5	$Pd(OAc)_2$ (5.0)	DMF	TBHP (1.0)	00
6	$Pd(OAc)_2$ (5.0)	DCE	TBHP (1.0)	41
7	$Pd(OAc)_2$ (10.0)	DCE	TBHP (1.0)	53
8	**$Pd(OAc)_2$ (10.0)**	**DCE**	**TBHP (1.2)**	**64**
9	$Pd(OAc)_2$ (15.0)	DCE	TBHP (1.2)	65
10	$PdCl_2$ (10.0)	DCE	TBHP (1.2)	8
11	$PdBr_2$ (10.0)	DCE	TBHP (1.2)	16
12	$Pd(TFA)_2$ (10.0)	DCE	TBHP (1.2)	22

[a]Isolated yield of *o*-aroylated product (**1''a**) after 12 h, TBHP (1.2 equiv) was added in 4 portions at 3 h intervals. [b]All reactions were performed under air atmosphere using 1.2 equiv of benzaldehyde at 110 °C.

In a pursuit to improve the yield of the product (**1''a**) reaction was again performed under identical conditions using 1,4-dioxane as the solvent. No product formation (Table IIIB.3.1, entry 2) was observed and the starting material was recovered completely. Switching the solvent to acetic acid provided an improved yield of 27% (Table IIIB.3.1, entry 3). Further screening of solvents such as DMSO, DMF, and dichloroethane (DCE) (Table IIIB.3.1, entries 4-6) revealed DCE to be the better solvent giving moderate yield (41%) of the product. The use of 10 mol % of the catalyst improved the yield up to 53% (Table IIIB.3.1, entry 7). Improvement in the yield up to 64% (Table IIIB.3.1, entry 8) was observed when the oxidant quantity was increased to 1.2 equivalents. No further enhancement in the yield was observed even when the catalyst loading was increased to 15 mol % (Table IIIB.3.1, entry 9). Other palladium (II) catalysts such as $PdCl_2$, $PdBr_2$ and $Pd(TFA)_2$ were found to be not so effective as compared to $Pd(OAc)_2$ (Table IIIB.3.1, entries 10-12). The use of hydrogen peroxide (H_2O_2) and benzoyl peroxide $(PhCOO)_2$ as oxidants were unsuccessful in giving the anticipated product.

The scope and generality of this aroylation reaction was further explored using various aromatic aldehydes and 3,5-diarylisoxazoles. The 3-aryl ring of 3,5-diarylisoxazoles possessing electron-donating substituents such as *p*–Me (**2''**), *p*–OMe (**3''**) coupled efficiently with benzaldehyde (**a**) giving corresponding *o*-aroylated products (**2''a**) and (**3''a**) respectively in moderate yields. However the presence of electron-withdrawing substituents such as *o*–NO_2, *m*–F, *p*–Cl in the 3-aryl ring of 3,5-diarylisoxazole were completely unproductive under this present reaction conditions. Due to the deactivating nature of 3-phenyl rings, they are reluctant to form palladacycle intermediate thereby preventing the aroylation process. Aromatic aldehydes possessing electron-donating substituents such as *p*–Me (**d**), *p*–^{t}Bu (**t**), *p*–OMe (**b**) served as excellent aroyl precursors toward the aroylation of 3,5-diphenylisoxazole (**1''**) giving products (**1''d**), (**1''t**) and (**1''b**) respectively in moderate yields (Scheme IIIB.3.1). The structure of the product (**1''b**) has been confirmed by X-ray crystallographic analysis (Fig. IIIB.3.1). As can be clearly seen from the crystal structure of (**1''b**) an aroyl moiety has been incorporated into the 3-aryl ring of 3,5-diarylisoxazole (**1''**) proximal to the *N* atom.

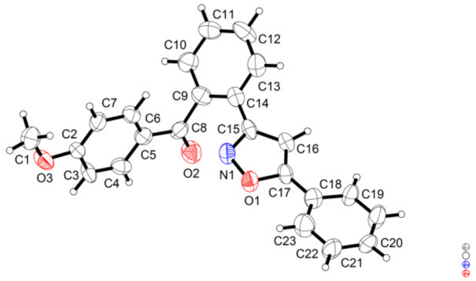
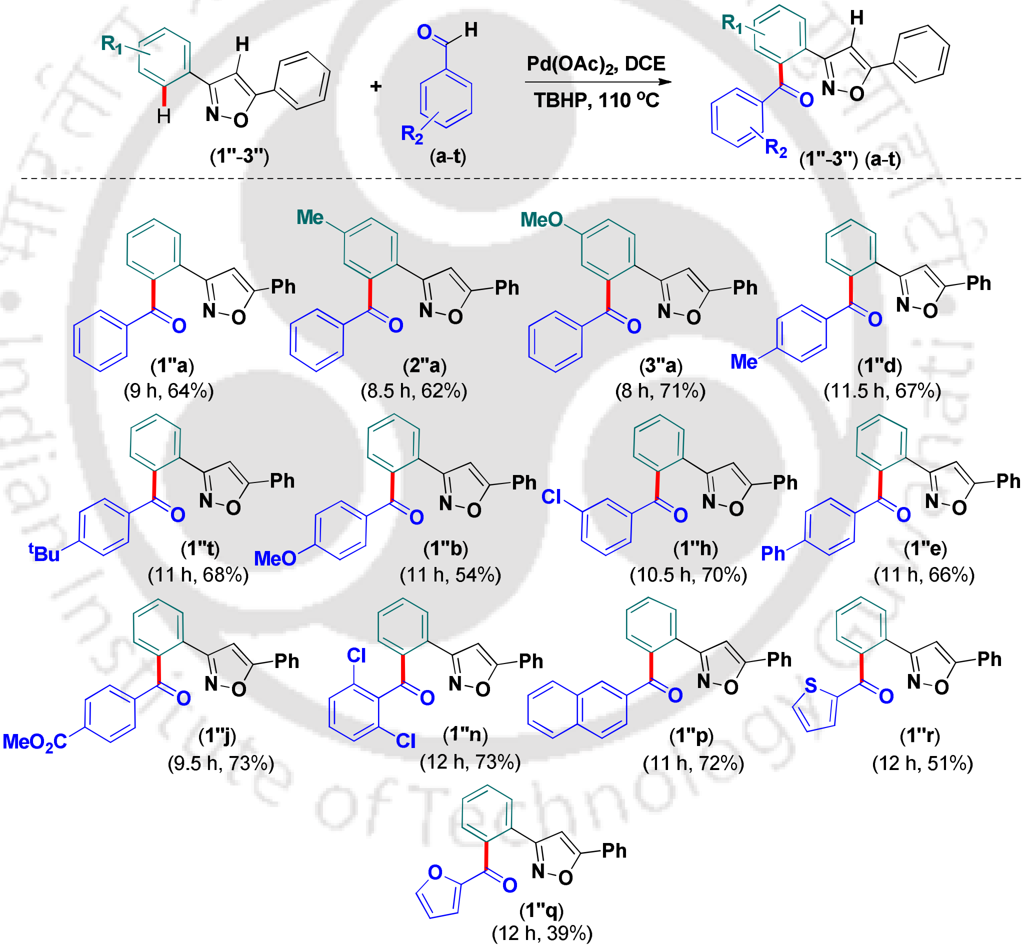


Fig. IIIB.3.1. *ORTEP molecular diagram of (**1''b**)*

Aromatic aldehydes possessing electron-withdrawing substituents such as *m*–Cl (**h**), *p*–Ph (**e**), *p*–CO_2Me (**j**), 2,6 di–Cl (**n**), underwent reactions giving better yields of their *o*-aroylated products (**1''h**), (**1''e**), (**1''j**) and (**1''n**) as compared to the aldehydic substrates possessing electron-donating substituents as shown in Scheme IIIB.3.1. The structure of the product (**1''j**) has been reconfirmed by X-ray crystallography (Fig. IIIB.3.2). Here again, the aroylation is directed by the *N* atom in the 3,5-diarylisoxazole. The fused aromatic aldehyde (**p**) provided better yield of *o*-aroylated product (**1''p**) compared to heteroaromatic aldehydes (**q**) and (**r**) in giving their corresponding products (**1''q**) and (**1''r**). The reductive *N–O* bond cleavage of 3,5-disubstituted isoxazoles provide *β*-aminoenones or 1,3-diketones,[24d] thus these *ortho*-aroylated products may be useful precursors to triketones.

Scheme IIIB.3.1. *Scope of substrates for ortho-aroylation of 3,5-diarylisoxazole*[a,b]



[a]Reaction conditions: 3,5-diphenylisoxazole (1 mmol), aldehyde (1.2 mmol), $Pd(OAc)_2$ (0.10 mmol), TBHP (1.2 mmol), toluene (2 mL), 110 °C, time 12 h.[b]Yields of pure isolated products after silica gel column chromatography.

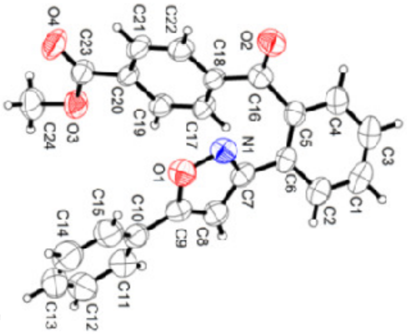


***Fig. IIIB.3.2.** ORTEP molecular diagram of* (**1''j**)

Recently alkylbenzenes have been demonstrated to be synthetic equivalent of aroyl moiety during substrate directed *o*-aroylation.[13] In this case even though alkylbenzene (toluene) is used as the solvent no aroylation was observed. This is because of the inability of toluene getting converted into alcohol and aldehyde under the reaction conditions. It is clear from Scheme IIIB.3.1 that the presence of electron-withdrawing substituents the reactions are completely unproductive while the presence of electron-donating substituents facilitates the reactions. Thus, if an electron-withdrawing substituent is placed in the 3-aryl ring (towards *N* side) and an electron-donating group in the 5-aryl ring (towards *O* side) can oxygen in 3,5-diarylisoxazole direct the *o*-aroylation? With this objective the designed substrate (**4''**) (Fig. IIIB.3.3) was subjected to the present *o*-aroylation conditions but no *o*-aroylation whatsoever was observed suggesting the inability of *O* as directing group in this case.

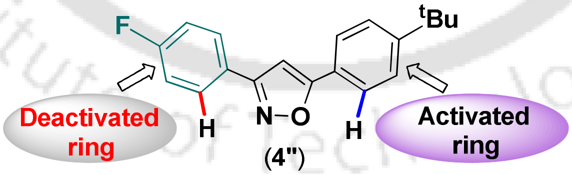
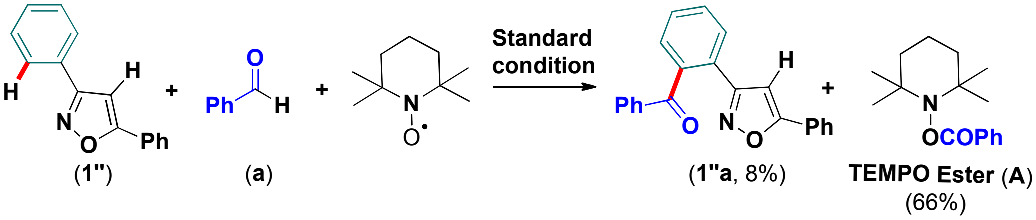


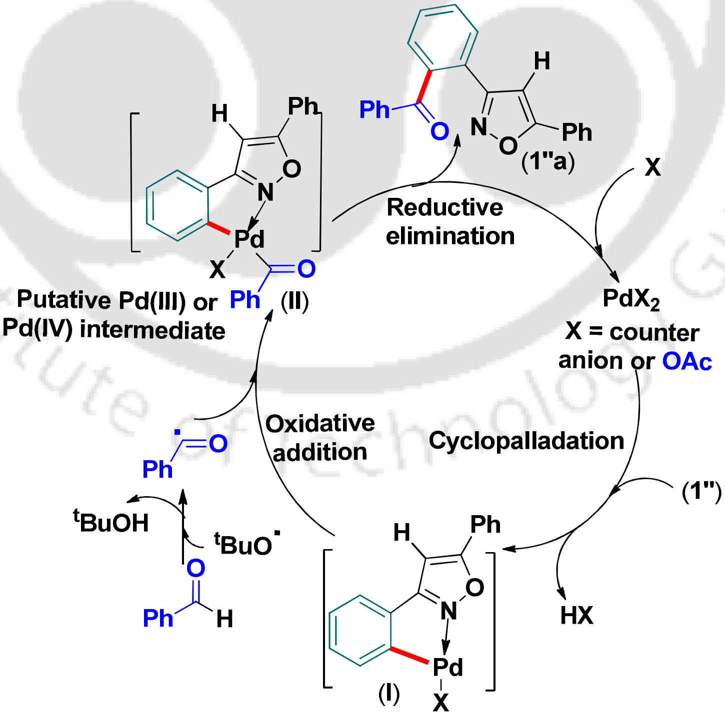
***Fig. IIIB.3.3.** Competitive metallation paths*

Presence of radical scavenger, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) greatly suppressed the rate of this *o*-aroylation reaction and only a trace amount (8%) of *ortho*-aroylated product was formed along with the formation of benzoyl-TEMPO adduct (**A**) in 66% isolated yield (Scheme IIIB.3.2).



Scheme IIIB.3.2. *Reaction in the presence of radical scavanger TEMPO*

Although we have not thoroughly probed the mechanism of this *o*-aroylation reaction but mechanism is expected to be similar to those recently proposed by us for *o*-aroylation of 2-arylbenzazoles in section IIIA (Scheme IIIB.3.3). Thus, a plausible mechanism can be depicted for this *o*-aroylation reaction. The first step of the *o*-aroylation reaction involves the cyclopalladation to form intermediate (**I**) towards the *N* side *i.e.* 3-aryl ring in 3,5-diarylisooxazole (**1''**). The aroyl radical generated *in situ* by the reaction of aldehyde and TBHP undergoes oxidative addition with intermediate (**I**) to form either reactive Pd(IV)[21] or a dimeric Pd(III)[22] intermediate (**II**) (Scheme IIIB.3.3). In the final stage reductive elimination afford C–C bond formation leading to *ortho*-aroylated product (**1''a**) and regenerating Pd(II) catalyst which maintains the subsequent catalytic cycle (Scheme IIIB.3.3).



Scheme IIIB.3.3. *Plausible mechanism for o-aroylation*

In conclusion we have demonstrated the higher directing ability of *N* over *O* in 3,5-diarylisoxazole *via* a chelation assisted approach in accomplishing the site selective *ortho*-aroylation. In spite of the higher acidic character of the isoxazolyl sp^2 C_4-H directed *o*-metallation is preferred over the non-directed metallation pathway. This is the first report of catalytic *o*-functionalization of this scaffold for the construction of C–C bond.

III.4. Experimental Section

III.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. The 2-arylbenzothiazoles were prepared from corresponding *N*-phenylbenzothioamides using hypervalent iodine mediated oxidative cyclization following the reported procedure.[26a] The 2-arylbenoxazoles were prepared from corresponding ortho-halobenzanilides *via* ligand-accelerated copper-catalyzed cyclizations.[26b] 3,5-Diarylisoxazoles were prepared by the method of click chemistry using phenyl acetylene derivatives with substituted aldoximes.[26c]

III.4.2. Crystallographic description

- **IIIA.4.2:**

CCDC number for compounds 1a and 8a: CCDC 889591 and 889592. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif.

Crystallographic description of 1a: Crystal dimension (mm): 0.32 x 0.28 x 0.26. $C_{20}H_{13}NOS$, Mr = 315.38. Triclinic, space group P-1; a = 7.300(2) Å, b = 10.932(3) Å, c = 11.142(2) Å; α = 118.643(14)°, β = 96.025(17) °, γ = 94.158(18)°, V = 768.3(3)Å^3; Z = 2; ρ_{cal} = 1.363 g/cm^3; μ (mm^{-1}) = 0.212; *F (000)* = 328.0; Reflection collected / unique = 3894 / 2438; Refinement method = Full-matrix least-squares on F^2; Final R indices $[I>2\sigma_I]$ R1 = 0.1103, wR2 = 0.2606, R indices (all data) R1 = 0.1315, wR2 = 0.2739; goodness of fit = 1.477.

Crystallographic description of 8a: Crystal dimension (mm): 0.30 x 0.26 x 0.24. $C_{20}H_{12}FNOS$, Mr = 333.38. Triclinic, space group P-1; a = 7.5170(7) Å, b = 8.8619(8) Å, c = 12.8151(11) Å; α = 86.442(7)°, β = 74.225(7)°, γ = 81.160(7)°, V = 811.58(13) Å^3; Z = 2; ρ_{cal} = 1.364 g/cm^3; μ (mm^{-1}) = 0.215; *F (000)* = 344.0; Reflection collected / unique = 3952 / 2849; Refinement method = Full-matrix least-squares on F^2; Final R indices $[I>2\sigma_I]$ R1 = 0.0441, wR2 = 0.1070, R indices (all data) R1 = 0.0609, wR2 = 0.1181; goodness of fit = 1.024.

➢ IIIB.4.2

CCDC number for compounds 1''b and 1''j: CCDC 945395 and 945394. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif.

Crystallographic description of 1''b: Crystal dimension (mm): 0.38 x 0.28 x 0.24. $C_{23}H_{17}NO_3$, Mr = 355.38 Triclinic, space group P -1; a = 8.8993 (11) Å, b = 10.4759 (13) Å, c = 11.0032 (14) Å; α = 70.634 (7)°, β = 72.001 (5) °, γ = 73.148 (7)°, V = 900.14 (19) Å^3; Z = 2; ρ_{cal} = 1.311 mg/m^3; μ (mm^{-1}) = 0.087; *F (000)* = 372.0; Reflection collected / unique = 2964 / 2188; Refinement method = Full-matrix least-squares on F^2; Final R indices $[I>2\sigma_I]$ R1 = 0.1770, wR2 = 0.4251, R indices (all data) R1 = 0.1980, wR2 = 0.4315; goodness of fit = 1.131.

Crystallographic description of 1''j: Crystal dimension (mm): 0.54 x 0.42 x 0.30. $C_{24}H_{17}NO_4$, Mr = 241.31. triclinic, space group P -1; a = 6.2208 (3) Å, b = 12.7931 (5) Å, c = 13.3551 (5) Å; α = 113.491 (2)°, β = 91.551 (2) °, γ = 97.433 (2)°, V = 962.95 (7) Å^3; Z = 2; ρ_{cal} = 1.322 mg/m^3; μ (mm^{-1}) = 0.091; *F (000)* = 400.0; Reflection collected / unique = 1645 / 1333; Refinement method = Full-matrix least-squares on F^2; Final R indices $[I>2\sigma_I]$ R1 = 0.0338, wR2 = 0.0825, R indices (all data) R1 = 0.0441, wR2 = 0.0893; goodness of fit = 1.070.

III.4.3. Synthesis of *o*-aroylated 2-arylbenzothiazole and 3,5-diarylisoxazole

➢ **IIIA.4.3. General procedure for the synthesis of (2-(benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a) from 2-phenylbenzothiazole (1):** An oven-dried flask was charged with Pd(OAc)$_2$ (0.011 g, 0.05 mmol), benzaldehyde (0.127 g, 1.2 mmol), 2-phenylbenzo[*d*]thiazole (**1**) (0.211 g, 1.0 mmol), and toluene (2 mL). TBHP (1.5 mmol) was added in 5 lots over a period of 5 hrs. Then the reaction vessel was kept in an oil bath preheated to 110 ^{o}C and allowed to stir for the stipulated period of time. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled and admixed with water (5 mL). The product was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was washed with saturated sodium bicarbonate (NaHCO$_3$) solution. Organic layer was dried over anhydrous sodium sulphate (Na$_2$SO$_4$), and evaporated under reduced pressure. The crude product so obtained was further purified through silica gel column chromatography (hexane / ethyl acetate, 10:0.7) to yield the pure (2-(benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (**1a**) (0.236 g, yield 75%). The identity and purity of the product was confirmed by spectroscopic analysis. The same procedure was also followed for *o*-aroylation of other substituted benzothiazole (**2**-**9**) benzoxazole (**1'**-**10'**) derrivatives with various aldehydes (**a**-**s**).

➢ **IIIB.4.3. General procedure for the synthesis of phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''a) from 3,5-diphenylisoxazole (1''):** An oven-dried flask was charged with Pd(OAc)$_2$ (0.022 g, 0.10 mmol), benzaldehyde (0.127 g, 1.2 mmol), 3,5-diphenylisoxazole (**1''**) (0.221 g, 1.0 mmol) and 1,2-dichloroethane DCE (2 mL). The reaction vessel was then subjected to reflux in an oil bath preheated to 110 ^{o}C and stirring was maintained for the stipulated period of time. TBHP (1.2 mmol) was then added in 4 equal portions over a period of 12 h. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled and admixed with water (5 mL). The product was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was washed with saturated sodium bicarbonate (NaHCO$_3$) solution. Organic layer was dried over anhydrous sodium sulphate (Na$_2$SO$_4$), and evaporated under reduced pressure. Further purification of crude product was done through silica gel column chromatography (8% EtOAc/hexane) to yield the pure phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (**1''a**) (0.208 g, yield 64%). The identity and purity of the product was confirmed by spectroscopic analysis. The same procedure was also followed for *o*-aroylation of other isoxazole (**2''-3''**) derrivatives with various aldehydes (**a**-**t**).

III.4.4. Mechanistic investigations

- **IIIA.4.4. *o*-Aroylation of 2-arylbenzothiazole in the presence of radical scavenger TEMPO:** An oven-dried reaction vessel was charged with 2-phenylbenzo[*d*]thiazole (**1**) (0.211 g, 1.0 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), benzaldehyde (0.127 g, 1.2 mmol), TBHP in decane (5-6 M) (300 μL, 1.5 mmol) and TEMPO (0.187 g, 1.2 mmol) in toluene (2 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^{o}C for 5 h. The reaction after 5 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**A**) in 41% yield along with paltry yield (15%) of the desired product (**1a**). This experiment supports the formation of benzoyl radical in the medium from benzaldehyde (**1**) induced radically by $Pd(OAc)_2$/TBHP and also the radical nature of the mechanism.

- **IIIB.4.4. *o*-Aroylation of 3,5-diarylisoxazole in the presence of radical scavenger TEMPO:** An oven-dried reaction vessel was charged with 3,5-diphenylisoxazole (**1''**) (0.221 g, 1.0 mmol), benzaldehyde (0.127 g, 1.2 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol), TBHP in decane (5-6 M) (240 μL, 1.2 mmol) and TEMPO (0.187 g, 1.2 mmol) in DCE (2 mL). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 120 ^{o}C for 12 h. The reaction after 12 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**A**) in 66% yield along with traces (<8%) of the desired product (**1''a**). This experiment supports the formation of benzoyl radical in the medium from benzaldehyde (**a**) induced radically by Pd/TBHP and also the radical nature of the mechanism.

III.5. References

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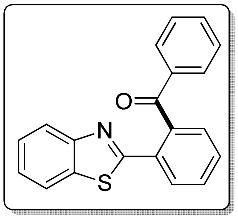
III.6. Spectral Data

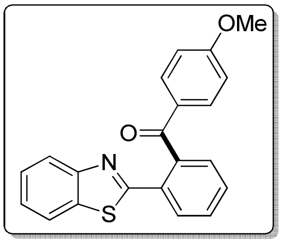
➢ IIIA.6.

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



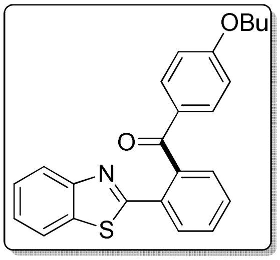
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.12 (d, 1H, *J* = 7.6 Hz), 7.92 (d, 1H, *J* = 7.2 Hz), 7.79 (d, 1H, *J* = 8.4 Hz), 7.76 (d, 1H, 7.6 Hz), 7.64–7.57 (m, 2H), 7.54 (d, 1H, *J* = 6.8 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.39–7.32 (m, 2H), 7.31–7.25 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.7, 165.6, 153.4, 139.7, 137.8, 135.3, 133.8, 132.8, 132.1, 130.4, 130.3, 129.4, 128.5, 128.3, 126.3, 125.4, 123.4, 121.5; IR (KBr, cm^{-1}): 3060, 2923, 2849, 2725, 2553, 1686, 1667, 1596, 1580, 1450, 1427, 1316, 1283, 1255, 1179, 1154, 1126, 1026, 968, 923, 759; HRMS (ESI) calcd for $C_{20}H_{13}NOS$ (M + H$^+$) 316.0791, found 316.0790.

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



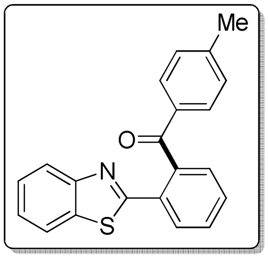
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.05 (d, 1H, *J* = 9.2 Hz), 7.94 (d, 1H, *J* = 7.2 Hz), 7.82 (d, 1H, *J* = 7.8 Hz), 7.78–7.72 (m, 2H), 7.61–7.54 (m, 2H), 7.47 (d, 1H, *J* = 6.8 Hz), 7.37–7.33 (m, 1H), 7.30–7.26 (m, 1H), 6.93 (d, 1H, *J* = 8.4 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 3.85 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.5, 164.2, 163.5, 153.7, 140.2, 135.6, 132.5, 132.0, 130.9, 130.3, 130.1, 129.9, 128.6, 126.3, 125.4, 123.6, 121.6, 113.8, 55.5; IR (KBr, cm^{-1}): 2934, 2840, 2541, 1662, 1601, 1577, 1510, 1427, 1303, 1259, 1167, 1149, 1026, 965, 928, 844, 761; Anal. calcd for $C_{21}H_{15}NO_2S$: C 73.02, H 4.38, N 4.06; found: C 73.07, H 4.44, N 4.03.

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



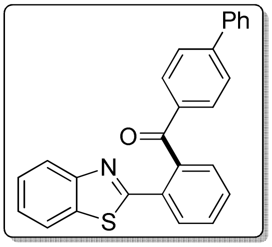
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.96 (d, 1H, *J* = 7.4 Hz), 7.84 (d, 1H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 7.6 Hz), 7.74 (d, 2H, *J* = 8.8 Hz), 7.62–7.56 (m, 2H), 7.49 (d, 1H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 7.6 Hz), 6.72 (d, 2H, *J* = 10.0 Hz), 3.93 (t, 2H, *J* = 6.4 Hz), 1.75–1.70 (m, 2H), 1.53–1.48 (m, 2H), 0.90–0.85 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.3, 165.7, 163.2, 153.6, 140.2, 135.6, 132.4, 131.9, 130.5, 130.2, 130.0, 129.9, 128.5, 126.2, 125.4, 123.6, 121.6, 114.3, 68.1, 31.2, 19.2, 13.9; IR (KBr, cm^{-1}): 3060, 2958, 2929, 2871, 1655, 1599, 1561, 1509, 1465, 1434, 1381, 1311, 1255, 1176, 1150, 1068, 1026, 966, 928, 844, 762; Anal. calcd for $C_{24}H_{21}NO_2S$: C 74.39, H 5.46, N 3.61; found: C 74.45, H 5.52, N 3.55.

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



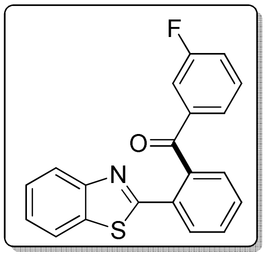
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.94 (d, 1H, *J* = 7.4 Hz), 7.81 (d, 1H, *J* = 8.2 Hz), 7.78 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.63–7.56 (m, 2H), 7.49 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 2.29 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.5, 165.6, 153.7, 143.8, 140.2, 135.6, 135.4, 132.2, 130.4, 130.2, 129.9, 129.7, 129.2, 128.9, 126.3, 125.4, 123.7, 121.6, 21.8; IR (KBr, cm^{-1}): 2967, 2850, 2772, 1638, 1510, 1479, 1458, 1432, 1313, 1224, 1071, 964, 766; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ (M + H$^+$) 330.0947, found 330.0943.

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



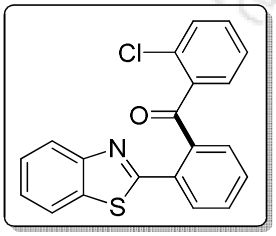
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.96 (d, 1H, *J* = 7.2 Hz), 7.85–7.82 (m, 2H), 7.80–7.77 (m, 2H), 7.66–7.59 (m, 2H), 7.56–7.50 (m, 4H), 7.42–7.38 (m, 2H), 7.37–7.32 (m, 2H), 7.30–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 165.5, 153.7, 145.5, 140.1, 139.9, 136.7, 135.5, 132.2, 130.5, 130.3, 130.1, 129.9, 129.0, 128.9, 128.3, 127.4, 127.1, 126.3, 125.5, 123.6, 121.6; IR (KBr, cm^{-1}): 3057, 3027, 2961, 2923, 2846, 1666, 1601, 1483, 1432, 1403, 1312, 1262, 1152, 1060, 966, 929, 855, 759; HRMS (ESI) calcd for $C_{26}H_{17}NOS$ (M + H$^+$) 392.1104, found 392.1104.

(2-Benzo[*d*]thiazol-2-yl-phenyl)-(3-fluoro-phenyl)-methanone (1f):



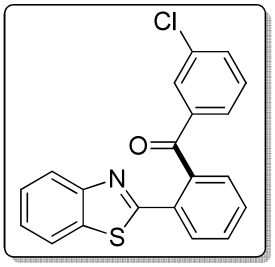
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, 1H, *J* = 8.4 Hz), 7.79 (d, 1H, *J* = 7.2 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 7.67–7.59 (m, 2H), 7.54 (d, 1H, *J* = 7.6 Hz), 7.50–7.48 (m, 2H), 7.36 (t, 1H, *J* = 7.1 Hz), 7.31 (t, 1H, *J* = 7.4 Hz), 7.26–7.22 (m, 1H), 7.08–7.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 164.2, 163.9, 153.5, 140.3, 139.2, 135.2, 132.1, 130.6, 130.0, 129.9, 129.7, 129.0, 126.4, 125.6, 125.0, 123.5, 121.6, 119.8, 119.6, 115.8, 115.5; IR (KBr, cm^{-1}): 3068, 2919, 2844, 2360, 2341, 1668, 1607, 1586, 1505, 1479, 1446, 1434, 1286, 1258, 1123, 1069, 970, 888, 836, 801, 772, 760; Anal. calcd for $C_{20}H_{12}FNOS$: C 72.05, H 3.63, N 4.20; found: C 72.10, H 3.67, N 4.15.

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



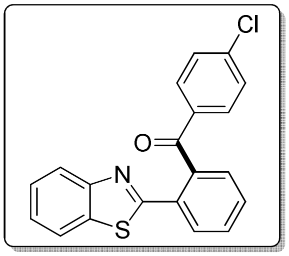
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, 1H, *J* = 8.0 Hz), 7.81–7.75 (m, 2H), 7.71 (d, 1H, *J* = 5.8 Hz), 7.66–7.59 (m, 2H), 7.40 (t, 1H, *J* = 7.6 Hz), 7.35–7.29 (m, 2H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.7 Hz), 6.99 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.8, 165.6, 153.6, 139.9, 137.5, 135.6, 133.2, 133.0, 131.9, 131.3, 131.1, 130.9, 130.6, 130.4, 130.1, 126.3, 126.1, 125.5, 123.9, 121.5; IR (KBr, cm^{-1}): 3060, 2923, 1672, 1585, 1502, 1468, 1453, 1430, 1312, 1296, 1253, 1170, 1061, 1036, 1012, 968, 930, 856, 767, 758; Anal. calcd for $C_{20}H_{12}ClNOS$: C 68.67, H 3.46, N 4.00; found: C 68.72, H 3.50, N 3.95.

(2- Benzo[*d*]thiazol-2-yl-phenyl)-(3-chloro-phenyl)-methanone (1h):



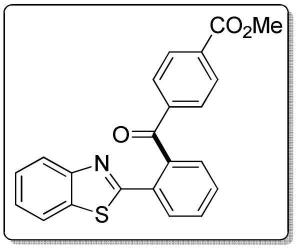
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.91 (d, 1H, *J* = 7.2 Hz), 7.79 (d, 2H, *J* = 8.6 Hz), 7.75 (d, 1H, *J* = 5.2 Hz), 7.66–7.57 (m, 3H), 7.53 (d, 1H, *J* = 8.0 Hz), 7.37 (t, 1H, *J* = 7.4 Hz), 7.32–7.28 (m, 2H), 7.19 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.3, 165.2, 153.4, 139.7, 139.0, 135.2, 134.5, 132.5, 132.1, 130.7, 130.6, 129.7, 129.6, 128.9, 128.3, 127.3, 126.4, 125.6, 123.4, 121.6; IR (KBr, cm^{-1}): 3059, 2928, 2854, 1669, 1590, 1570, 1507, 1482, 1431, 1281, 1255, 1242, 1156, 1073, 967, 897, 850, 807, 753; Anal. calcd for $C_{20}H_{12}ClNOS$: C 68.67, H 3.46, N 4.00; found: C 68.73, H 3.53, N 3.97.

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



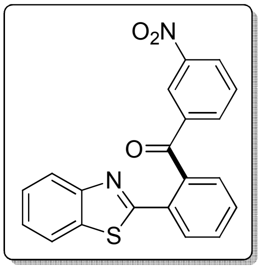
White solid; M.p. 135.5 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 6.8 Hz), 7.82–7.79 (m, 1H), 7.77–7.75 (m, 1H), 7.70–7.66 (m, 2H), 7.64–7.59 (m, 2H), 7.51 (d, 1H, *J* = 6.8 Hz), 7.39–7.35 (m, 1H), 7.34–7.29 (m, 1H), 7.27–7.24 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.5, 165.2, 153.6, 139.4, 139.1, 136.5, 135.4, 132.1, 130.7, 130.5, 129.8, 128.9, 128.8, 126.5, 125.7, 123.6, 121.6; IR (KBr, cm^{-1}): 3088, 3055, 2956, 2923, 2845, 1670, 1584, 1571, 1483, 1428, 1401, 1304, 1288, 1263, 1240, 1181, 1151, 1090, 1013, 968, 936, 923, 844, 753; Anal. calcd for $C_{20}H_{12}ClNOS$: C 68.67, H 3.46, N 4.00; found: C 68.74, H 3.51, N 3.96.

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



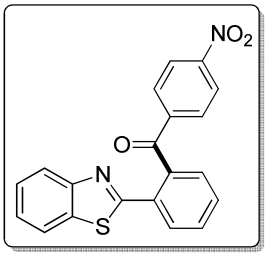
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 2H, *J* = 8.6 Hz), 7.79–7.77 (m, 3H), 7.73–7.71 (m, 1H), 7.68–7.61 (m, 3H), 7.58–7.56 (m, 1H), 7.45 (t, 1H, *J* = 7.4 Hz), 7.29 (t, 1H, *J* = 7.3 Hz), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.1, 166.5, 165.1, 153.5, 141.6, 139.3, 135.2, 133.3, 130.8, 129.7, 129.6, 129.2, 128.9, 126.5, 125.7, 123.5, 121.7, 52.5; IR (KBr, cm^{-1}): 2955, 2920, 2847, 1717, 1674, 1500, 1434, 1406, 1279, 1104, 1015, 970, 928, 865, 757; Anal. calcd for $C_{22}H_{15}NO_3S$: C 70.76, H 4.05, N 3.75; found: C 70.80, H 4.08, N 3.70.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(3-nitrophenyl)methanone (1k):



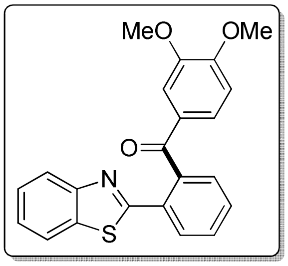
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 8.17 (d, 1H, *J* = 8.2 Hz), 8.06 (d, 1H, *J* = 7.6 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 7.78 (d, 1H, *J* = 7.6 Hz), 7.73–7.66 (m, 3H), 7.60 (d, 1H, *J* = 7.2 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.37–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 164.9, 153.4, 148.2, 139.9, 138.3, 135.1, 134.3, 132.1, 131.3, 131.0, 129.8, 129.5, 129.3, 126.7, 126.6, 125.9, 123.6, 123.4, 121.7; IR (KBr, cm^{-1}): 3077, 3056, 2919, 2858, 1679, 1610, 1524, 1433, 1346, 1315, 1294, 1276, 1258, 1160, 1070, 970, 934, 855, 810, 755; Anal. calcd for $C_{20}H_{12}N_2O_3S$: C 66.65, H 3.36, N 7.77; found: C 66.68, H 3.40, N 7.70.

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



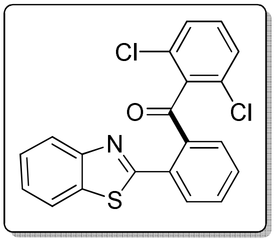
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, 2H, *J* = 8.8 Hz), 7.94 (d, 1H, *J* = 6.6 Hz), 7.87 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 1H, *J* = 7.4 Hz), 7.72–7.65 (m, 3H), 7.59 (d, 1H, *J* = 6.6 Hz), 7.37 (d, 1H, *J* = 7.2 Hz), 7.34–7.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.0, 164.9, 153.3, 149.8, 143.2, 138.6, 135.1, 132.2, 131.2, 131.0, 129.7, 129.3, 126.7, 126.0, 123.6, 123.4, 121.8; IR (KBr, cm^{-1}): 3099, 3067, 2847, 1703, 1673, 1602, 1519, 1454, 1428, 1382, 1342, 1318, 1283, 1196, 1103, 1007, 974, 930, 849, 816, 761; Anal. calcd for $C_{20}H_{12}N_2O_3S$: C 66.65, H 3.36, N 7.77; found: C 66.70, H 3.42, N 7.72.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(3,4-dimethoxyphenyl)methanone (1m):



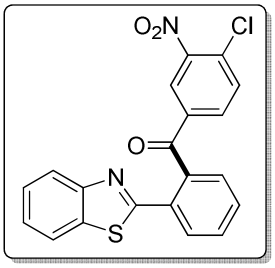
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.10–8.08 (m, 3H), 7.93 (d, 1H, *J* = 8.0 Hz), 7.52–7.47 (m, 3H), 7.41–7.38 (m, 3H), 7.03 (s, 1H), 4.02 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.2, 164.2, 153.7, 150.7, 144.7, 135.6, 131.4, 130.4, 129.9, 129.6, 129.4, 129.2, 126.9, 126.7, 125.1, 124.1, 123.4, 122.7, 116.1, 112.1; IR (KBr, cm^{-1}): 3060, 2961, 2900, 2867, 1668, 1603, 1510, 1459, 1432, 1407, 1314, 1266, 1192, 1106, 1015, 966, 930, 850, 760; Anal. calcd for $C_{22}H_{17}NO_3S$: C 70.38, H 4.56, N 3.73; found: C 70.40, H 4.61, N 3.70.

(2-Benzo[*d*]thiazol-2-yl-phenyl)-(2,6-dichloro-phenyl)-methanone (1n):



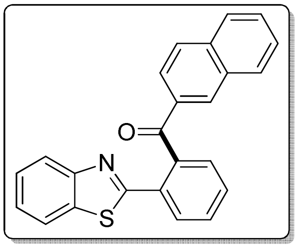
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.08 (d, 1H, *J* = 7.6 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 1H, *J* = 8.0 Hz), 7.72–7.66 (m, 2H), 7.62–7.58 (m, 1H), 7.50–7.45 (m, 1H), 7.40–7.33 (m, 2H), 7.14 (d, 1H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 8.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 191.9, 166.7, 153.3, 137.5, 136.8, 136.5, 135.1, 133.0, 132.8, 131.9, 131.7, 130.6, 130.5, 128.6, 128.4, 126.2, 125.4, 123.8, 121.5; IR (KBr, cm^{-1}): 3064, 2953, 2923, 2852, 1735, 1680, 1647, 1580, 1516, 1430, 1368, 1258, 1194, 1090, 966, 926, 806, 761; MS (ESI) calcd for $C_{20}H_{11}Cl_2NOS$ (M + H$^+$) 384.0011, found 384.0019.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(4-chloro-3-nitrophenyl)methanone (1o):



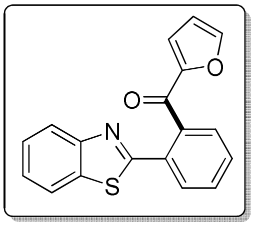
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.36 (s, 1H), 8.03 (d, 1H, *J* = 8.4 Hz), 7.94 (d, 1H, *J* = 7.0 Hz), 7.85–7.81 (m, 1H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.71–7.64 (m, 2H), 7.56–7.54 (m, 1H), 7.45 (d, 1H, *J* = 8.4 Hz), 7.40–7.33 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 194.3, 164.8, 153.2, 147.8, 138.1, 137.7, 135.5, 134.9, 132.9, 132.5, 132.0, 131.0, 129.7, 129.0, 126.7, 126.4, 125.9, 125.5, 123.3, 121.8; IR (KBr, cm^{-1}): 3097, 3067, 3031, 2856, 2731, 2360, 2341, 1703, 1676, 1599, 1567, 1536, 1431, 1356, 1295, 1238, 1201, 1049, 968, 918, 830, 817, 762; HRMS (ESI) calcd for $C_{20}H_{11}ClN_2O_3S$ (M + H$^+$) 395.0252, found 395.0257.

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



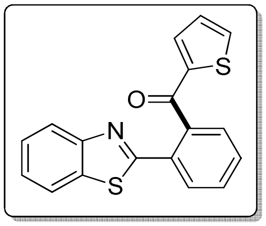
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.08 (s, 1H), 8.05 (d, 1H, *J* = 7.8 Hz), 7.99 (d, 1H, *J* = 6.6 Hz), 7.82–7.71 (m, 5H), 7.69–7.61 (m, 2H), 7.59–7.57 (m, 1H), 7.50 (t, 1H, *J* = 7.6 Hz), 7.43 (t, 1H, *J* = 7.1 Hz), 7.30 (t, 1H, *J* = 7.6 Hz), 7.25–7.22 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.8, 165.5, 153.6, 140.0, 135.6, 132.5, 132.3, 131.5, 130.5, 130.4, 129.9, 129.7, 129.0, 128.5, 127.9, 126.7, 126.3, 125.5, 124.9, 123.6, 121.5; IR (KBr, cm^{-1}): 3056, 3022, 2921, 2849, 1664, 1625, 1508, 1463, 1430, 1351, 1299, 1284, 1231, 1200, 1149, 1120, 968, 918, 869, 847, 827, 755; HRMS (ESI) calcd for $C_{24}H_{15}NOS$ (M + H$^+$) 366.0947, found 366.0941.

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



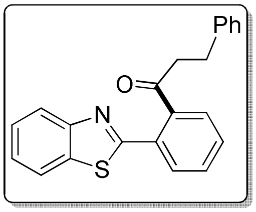
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.2 Hz), 7.83 (d, 1H, *J* = 7.8 Hz), 7.66–7.59 (m, 3H), 7.46–7.45 (m, 1H), 7.41 (t, 1H, *J* = 7.6 Hz), 7.34 (t, 1H, *J* = 7.4 Hz), 6.91 (d, 1H, *J* = 3.4 Hz), 6.36–6.34 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 184.7, 165.8, 153.8, 153.2, 147.1, 138.7, 135.6, 132.6, 130.9, 130.4, 130.1, 129.2, 126.4, 125.6, 123.8, 121.6, 119.4, 112.4; IR (KBr, cm^{-1}): 3060, 2950, 2922, 2851, 1657, 1566, 1512, 1462, 1432, 1390, 1308, 1226, 1186, 1151, 1079, 1019, 967, 889, 761; HRMS (ESI) calcd for $C_{18}H_{11}NO_2S$ (M + H$^+$) 306.0583, found 306.0588.

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



Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.96 (d, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.66–7.57 (m, 4H), 7.40 (t, 1H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.6 Hz), 7.27–7.26 (m, 1H), 6.92 (t, 1H, *J* = 4.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 189.8, 165.5, 153.8, 145.3, 139.6, 135.7, 134.5, 132.1, 130.6, 130.4, 130.1, 128.8, 128.0, 126.4, 125.5, 123.8, 121.6; IR (KBr, cm^{-1}): 2964, 2921, 2850, 1642, 1512, 1432, 1411, 1354, 1298, 1262, 1100, 1042, 967, 841, 807, 761; HRMS (ESI) calcd for $C_{18}H_{11}NOS_2$ (M + H$^+$) 322.0355, found 322.0354.

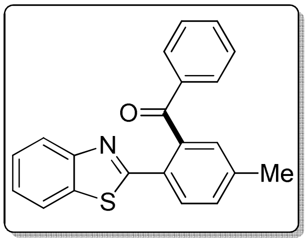
1-(2-Benzo[*d*]thiazol-2-yl-phenyl)-3-phenyl-propan-1-one (1s):



Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.02 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.82–7.79 (m, 1H), 7.53–7.47 (m, 2H), 7.43–7.39 (m, 1H), 7.38–7.35 (m, 1H), 7.19–7.15 (m, 2H), 7.12–7.03 (m, 2H), 7.02 (d, 2H, *J* = 7.2 Hz), 3.09 (t, 2H, *J* = 7.6 Hz), 2.97–2.93 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 206.1, 166.1, 153.0, 141.9, 141.3, 135.5, 130.8, 130.3, 129.9, 128.7, 128.6, 128.5, 127.4, 126.8, 126.1, 125.9, 123.8, 121.9, 45.5, 30.9; IR (KBr, cm^{-1}): 3081, 3060, 3026, 3023, 2852, 1735, 1700, 1636, 1602, 1495, 1480, 1453, 1433, 1404, 1312, 1291, 1228, 1203, 1160, 1075, 1029, 968, 760;

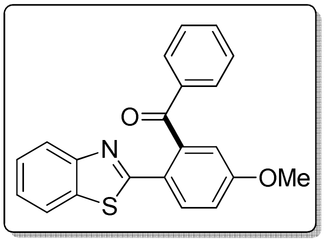
HRMS (ESI) calcd for $C_{22}H_{17}NOS$ (M + H^+) 344.1104, found 344.1101.

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



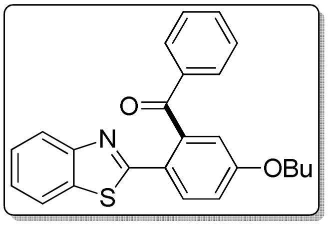
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, 1H, *J* = 8.0 Hz), 7.76–7.71 (m, 4H), 7.41 (d, 1H, *J* = 8.0 Hz), 7.38–7.33 (m, 3H), 7.30–7.24 (m, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 165.6, 153.5, 141.0, 139.7, 137.9, 135.2, 133.7, 132.7, 130.9, 129.7, 129.4, 129.3, 128.3, 126.2, 125.2, 123.3, 121.4, 21.5; IR (KBr, cm^{-1}): 3053, 3024, 2920, 2855, 1669, 1597, 1561, 1511, 1476, 1449, 1432, 1400, 1315, 1287, 1256, 1208, 1177, 1116, 1073, 975, 957, 854, 826, 789, 757; Anal. calcd for $C_{21}H_{15}NOS$: C 76.57, H 4.59, N 4.25; found: C 76.62, H 4.63, N 4.22.

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



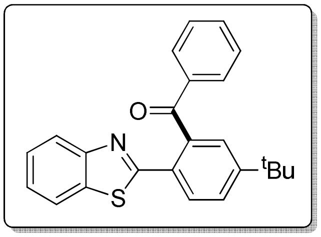
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 1H, *J* = 8.8 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 1H, *J* = 7.4 Hz), 7.37 (t, 2H, *J* = 7.4 Hz), 7.29–7.24 (m, 1H), 7.22–7.16 (m, 1H), 7.02 (d, 1H, *J* = 8.4 Hz), 6.94 (s, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.5, 165.3, 161.3, 153.5, 141.4, 137.7, 135.2, 133.9, 131.3, 130.3, 129.4, 128.6, 126.2, 125.1, 123.2, 121.4, 116.0, 114.1, 55.8; IR (KBr, cm^{-1}): 3071, 2963, 2916, 2834, 2676, 2558, 1687, 1602, 1583, 1453, 1424, 1326, 1292, 1179, 1099, 1072, 1026, 934, 807, 762; Anal. calcd for $C_{21}H_{15}NO_2S$: C 73.02, H 4.38, N 4.06; found: C 73.05, H 4.40, N 4.01.

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



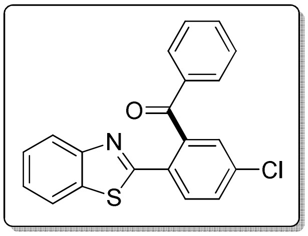
White solid; M.p. 133 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.85 (d, 1H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.73 (t, 2H, *J* = 7.2 Hz), 7.38 (t, 1H, *J* = 7.2 Hz), 7.34–7.23 (m, 4H), 7.11 (d, 1H, *J* = 8.6 Hz), 7.01 (s, 1H), 4.05 (t, 2H, *J* = 6.4 Hz), 1.82–1.77 (m, 2H), 1.53–1.48 (m, 2H), 0.98 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.5, 165.3, 160.9, 153.7, 141.4, 137.8, 135.2, 132.8, 131.3, 129.4, 128.4, 126.1, 125.0, 124.4, 123.2, 121.4, 116.4, 114.6, 68.4, 31.3, 19.3, 13.9; IR (KBr, cm^{-1}): 3056, 2961, 2934, 2870, 1672, 1605, 1566, 1511, 1482, 1437, 1414, 1294, 1224, 1111, 1074, 1043, 972, 953, 856, 841, 823, 810, 762; Anal. calcd for $C_{24}H_{21}NO_2S$: C 74.39, H 5.46, N 3.61; found: C 74.43, H 5.50, N 3.57.

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



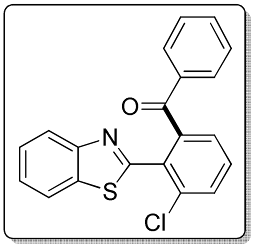
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.86 (d, 1H, *J* = 12.0 Hz), 7.78–7.74 (m, 3H), 7.63 (d, 1H, *J* = 8.4 Hz), 7.53 (s, 1H), 7.38–7.33 (m, 2H), 7.31–7.24 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 198.3, 165.5, 154.2, 153.7, 139.5, 138.1, 135.3, 132.7, 129.6, 129.4, 128.3, 127.4, 126.2, 125.9, 125.3, 123.4, 121.5, 35.3, 31.3; IR (KBr, cm^{-1}): 3069, 3028, 2967, 2930, 2867, 1671, 1596, 1558, 1515, 1481, 1449, 1431, 1395, 1362, 1314, 1253, 1162, 1103, 1023, 972, 902, 857, 840, 800, 757; Anal. calcd for $C_{24}H_{21}NOS$: C 77.59, H 5.70, N 3.77; found: C 77.64, H 5.75, N 3.73

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



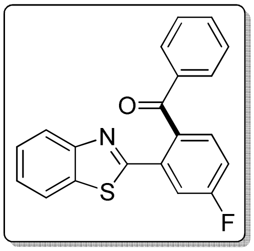
White solid; M.p. 132 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.87 (d, 1H, *J* = 8.4 Hz), 7.78–7.75 (m, 3H), 7.60 (d, 1H, *J* = 8.4 Hz), 7.51 (s, 1H), 7.43–7.38 (m, 2H), 7.36–7.26 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.1, 164.1, 153.5, 141.3, 137.4, 136.9, 135.4, 133.2, 130.9, 130.7, 130.4, 129.4, 129.0, 128.5, 126.5, 125.7, 123.6, 121.6; IR (KBr, cm^{-1}): 3063, 3022, 2923, 2848, 1670, 1593, 1581, 1560, 1508, 1474, 1452, 1432, 1378, 1313, 1291, 1263, 1181, 1156, 1128, 1100, 1021, 1001, 968, 947, 876, 817, 782, 755; Anal. calcd for $C_{20}H_{12}ClNOS$: C 68.67, H 3.46, N 4.00; found: C 68.71, H 3.52, N 3.93.

(2-(Benzo[*d*]thiazol-2-yl)-3-chlorophenyl)(phenyl)methanone (7a):



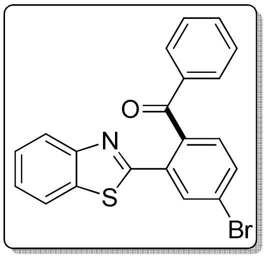
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.80–7.75 (m, 1H), 7.70–7.58 (m, 3H), 7.54 (t, 1H, *J* = 7.6 Hz), 7.50–7.46 (m, 1H), 7.41–7.33 (m, 2H), 7.31–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 168.4, 152.3, 143.1, 137.1, 133.9, 133.0, 131.9, 130.4, 129.8, 129.4, 129.1, 128.3, 127.6, 126.2, 125.8, 123.7, 121.4; IR (KBr, cm^{-1}): 3058, 3022, 2920, 2839, 2360, 2340, 1669, 1595, 1579, 1556, 1506, 1482, 1447, 1429, 1415, 1315, 1282, 1255, 1177, 1155, 1141, 1127, 1072, 1012, 968, 952, 924, 853, 798, 759; Anal. calcd for $C_{20}H_{12}ClNOS$: C 68.67, H 3.46, N 4.00; found: C 68.69, H 3.49, N 3.94.

(2-Benzo[*d*]thiazol-2-yl-4-fluoro-phenyl)-phenyl-methanone (8a):



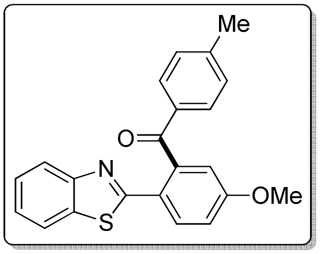
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (t, 2H, *J* = 7.8 Hz), 7.74 (d, 2H, *J* = 7.2 Hz), 7.64 (d, 1H, *J* = 9.2 Hz), 7.57–7.54 (m, 1H), 7.40–7.34 (m, 2H), 7.33–7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 164.6, 164.1, 153.5, 137.8, 135.9, 135.6, 133.0, 131.4, 131.3, 129.4, 128.5, 126.5, 125.8, 123.8, 121.6, 117.5, 117.2, 116.9, 116.7; IR (KBr, cm^{-1}): 3079, 3059, 3024, 1666, 1602, 1577, 1507, 1485, 1459, 1446, 1430, 1315, 1279, 1261, 1238, 1173, 1146, 1126, 1113, 1072, 998, 955, 927, 897, 873, 832, 821, 795, 761; Anal. calcd for $C_{20}H_{12}FNOS$: C 72.05, H 3.63, N 4.20; found: C 72.10, H 3.68, N 4.15.

(2-Benzo[*d*]thiazol-2-yl-4-bromo-phenyl)-phenyl-methanone (9a):



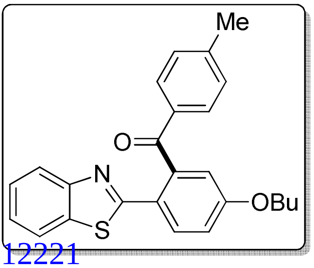
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 1H), 7.79 (d, 1H, *J* = 8.0 Hz), 7.75 (t, 2H, *J* = 9.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.39–7.33 (m, 3H), 7.31–7.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 163.8, 153.4, 138.1, 137.6, 136.3, 135.5, 134.0, 133.1, 130.5, 130.4, 129.6, 129.4, 128.4, 126.5, 125.8, 123.7, 121.6; IR (KBr, cm^{-1}): 3070, 3053, 3022, 2925, 2841, 1665, 1596, 1681, 1551, 1500, 1473, 1445, 1434, 1381, 1316, 1276, 1251, 1239, 1151, 1096, 1012, 984, 934, 871, 827, 793, 763; HRMS (ESI) calcd for $C_{20}H_{12}BrNOS$ (M + H$^+$) 393.9896, found 393.9894.

(2-(Benzo[*d*]thiazol-2-yl)-5-methoxyphenyl)(p-tolyl)methanone (3d):



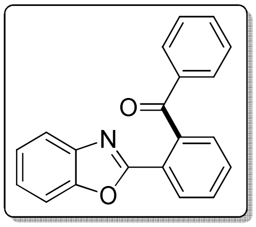
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, 2H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 7.74 (t, 1H, *J* = 6.8 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.32 (t, 1H, *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 8.4 Hz), 7.11–7.07 (m, 2H), 6.97 (s, 1H), 3.87 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.2, 161.3, 153.7, 144.7, 143.9, 141.7, 135.2, 131.4, 130.5, 129.7, 129.4, 129.2, 126.2, 125.1, 123.3, 121.5, 115.9, 113.9, 55.9, 21.8; IR (KBr, cm^{-1}): 3055, 2960, 2917, 2832, 2538, 1670, 1604, 1569, 1482, 1409, 1317, 1293, 1267, 1227, 1179, 1112, 1040, 971, 884, 858, 842, 811, 756; HRMS (ESI) calcd for $C_{22}H_{17}NO_2S$ (M + H$^+$) 360.1053, found 360.1052.

(2-(Benzo[*d*]thiazol-2-yl)-5-butoxyphenyl)(*p*-tolyl)methanone (4d):



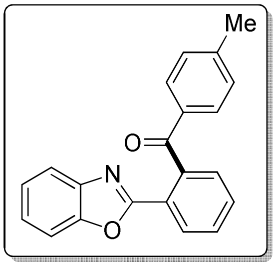
White solid; M.p. 145–146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, 1H, *J* = 8.8 Hz), 7.75 (t, 2H, *J* = 7.0 Hz), 7.69 (d, 2H, *J* = 8.4 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 7.27–7.23 (m, 2H), 7.09 (d, 2H, *J* = 7.6 Hz), 6.97 (d, 1H, *J* = 2.4 Hz), 4.04 (t, 2H, *J* = 6.6 Hz), 2.29 (s, 3H), 1.81–1.77 (m, 2H), 1.55–1.47 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.2, 165.4, 160.9, 153.7, 143.8, 141.6, 135.3, 135.2, 131.4, 130.4, 129.7, 129.2, 126.1, 125.0, 123.3, 121.4, 116.3, 114.4, 68.4, 31.3, 21.8, 19.3, 13.9; IR (KBr, cm^{-1}): 2963, 2939, 2919, 2869, 1672, 1603, 1567, 1482, 1438, 1412, 1313, 1292, 1264, 1223, 1184, 1110, 1044, 971, 909, 877, 858, 810, 762; Anal. calcd for $C_{25}H_{23}NO_2S$: C 74.78, H 5.77, N 3.49; found: C 74.80, H 5.82, N 3.45.

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



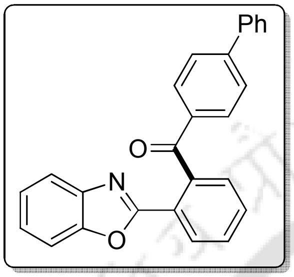
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.13 (d, 2H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.68–7.59 (m, 4H), 7.50–7.44 (m, 4H), 7.36–7.32 (m, 1H), 7.25–7.23 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.3, 161.0, 150.7, 141.5, 140.1, 137.4, 133.9, 133.2, 131.3, 130.3, 129.6, 129.5, 128.8, 128.6, 125.5, 124.8, 120.4, 110.6; IR (KBr, cm^{-1}): 3071, 3025, 2880, 2836, 2672, 2602, 2557, 2084, 1989, 1788, 1687, 1601, 1582, 1495, 1453, 1424, 1326, 1291, 1180, 1127, 1070, 1026, 999, 933, 809, 746; Anal. calcd for $C_{20}H_{13}NO_2$: C 80.25, H 4.38, N 4.68; found: C 80.30, H 4.40, N 4.62.

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



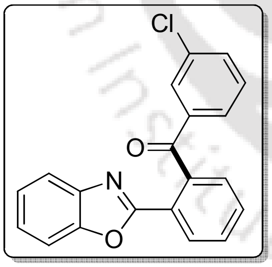
White solid; M.p. 126–127 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.24–8.21 (m, 1H), 7.63 (d, 1H, *J* = 8.0 Hz), 7.58–7.53 (m, 4H), 7.43–7.41 (m, 1H), 7.29–7.26 (m, 1H), 7.19–7.14 (m, 2H), 7.07 (d, 2H, *J* = 8.4 Hz), 2.25 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.9, 161.6, 150.8, 144.1, 141.8, 140.5, 134.9, 131.2, 130.1, 129.8, 129.4, 129.3, 128.6, 125.4, 124.6, 120.5, 110.7, 21.8; IR (KBr, cm^{-1}): 3065, 3037, 2919, 2851, 1734, 1660, 1603, 1557, 1451, 1434, 1298, 1280, 1236, 1180, 1150, 1112, 1064, 1029, 930, 835, 810, 795, 770, 759, 741;HRMS (ESI) calcd for $C_{21}H_{15}NO_2$ (M + H$^+$) 314.1176, found 314.1177.

(2-(Benzo[*d*]oxazol-2-yl)phenyl)(4-biphenyl)methanone (1'e):



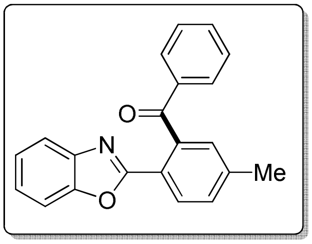
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.34–8.32 (m, 1H), 8.13 (d, 2H, *J* = 7.6 Hz), 7.89–7.87 (m, 1H), 7.71–7.62 (m, 4H), 7.59–7.53 (m, 4H), 7.48 (t, 2H, *J* = 7.6 Hz), 7.44–7.40 (m, 1H), 7.38–7.34 (m, 1H), 7.26–7.23 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 190.9, 166.1, 150.8, 145.9, 141.7, 137.5, 133.9, 131.3, 130.4, 129.5, 129.1, 128.7, 128.4, 127.4, 127.3, 125.5, 124.8, 120.5, 110.7, 109.9; IR (KBr, cm^{-1}): 3069, 3030, 2953, 2924, 2849, 2670, 2555, 1688, 1601, 1582, 1559, 1452, 1423, 1325, 1291, 1179, 1126, 1071, 1026, 933, 854, 810, 760, 744; Anal. calcd for $C_{26}H_{17}NO_2$: C 83.18, H 4.56, N 3.73; found: C 83.23, H 4.60, N 3.71.

(2-(Benzo[*d*]oxazol-2-yl)phenyl)(3-chlorophenyl)methanone (1'h):



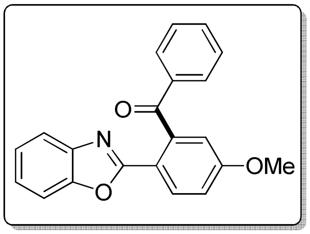
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.31 (d, 1H, *J* = 6.8 Hz), 7.82 (s, 1H), 7.70–7.64 (m, 3H), 7.63–7.60 (m, 1H), 7.52 (d, 1H, *J* = 6.8 Hz), 7.43–7.38 (m, 2H), 7.30–7.24 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.0, 161.2, 150.7, 141.7, 139.5, 139.2, 134.9, 133.9, 133.2, 131.4, 130.7, 130.4, 130.0, 129.9, 129.4, 128.7, 127.8, 125.5, 124.9, 120.5, 110.7; IR (KBr, cm^{-1}): 3064, 2950, 2924, 2853, 1678, 1614, 1572, 1467, 1452, 1424, 1343, 1287, 1243, 1195, 1154, 1074, 1034, 1001, 943, 927, 892, 814, 761; Anal. calcd for $C_{20}H_{12}ClNO_2$: C 71.97, H 3.62, N 4.20; found: C 72.01, H 3.66, N 4.16.

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



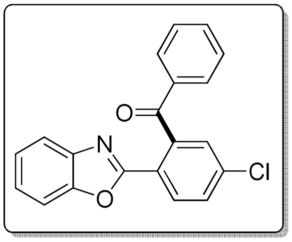
White solid; M.p. 120–121 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz), 7.58–7.56 (m, 1H), 7.46–7.43 (m, 1H), 7.40 (d, 1H, *J* = 7.2 Hz), 7.33–7.28 (m, 4H), 7.21–7.19 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.6, 161.7, 150.7, 142.1, 141.9, 140.2, 137.6, 133.2, 131.1, 129.6, 129.4, 129.3, 128.5, 125.2, 124.6, 122.8, 120.3, 110.6, 21.7; IR (KBr, cm^{-1}): 3067, 3034, 2921, 2852, 1773, 1672, 1613, 1593, 1555, 1494, 1451, 1396, 1343, 1314, 1291, 1264, 1241, 1213, 1178, 1127, 1047, 1002, 964, 926, 890, 843, 824, 812, 762; Anal. calcd for $C_{21}H_{15}NO_2$: C 80.49, H 4.82, N 4.47; found: C 80.54, H 4.86, N 4.45.

(2-(Benzo[*d*]oxazol-2-yl)-5-methoxyphenyl)(phenyl)methanone (3'a):



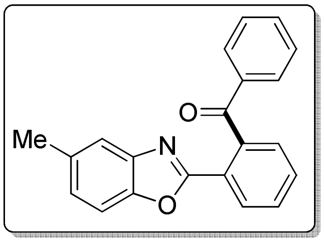
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.25 (d, 1H, *J* = 8.8 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.58–7.56 (m, 1H), 7.49–7.43 (m, 2H), 7.36–7.29 (m, 3H), 7.22–7.15 (m, 3H), 7.01 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.6, 162.3, 161.9, 150.7, 142.0, 137.4, 133.3, 131.2, 130.4, 129.6, 128.7, 128.6, 124.9, 124.5, 120.1, 116.1, 113.8, 110.5, 55.9; IR (KBr, cm^{-1}): 3061, 3003, 2964, 2931, 2837, 1737, 1672, 1617, 1598, 1577, 1557, 1493, 1452, 1414, 1315, 1296, 1270, 1243, 1230, 1177, 1123, 1103, 1061, 1028, 1001, 963, 925, 893, 843, 815, 790, 762; Anal. calcd for $C_{21}H_{15}NO_3$: C 76.58, H 4.59, N 4.25; found: C 76.65, H 4.64, N 4.20.

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



Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.68 (s, 1H), 8.25 (d, 1H, *J* = 8.8 Hz), 8.12 (d, 1H, *J* = 7.6 Hz), 7.86–7.83 (m, 1H), 7.80 (d, 1H, *J* = 7.8 Hz), 7.65–7.59 (m, 2H), 7.50–7.45 (m, 2H), 7.39–7.33 (m, 2H), 7.27–7.23 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 195.7, 162.4, 150.7, 141.6, 137.8, 136.9, 133.9, 133.6, 131.4, 130.7, 130.5, 130.4, 129.7, 128.9, 128.7, 128.6, 125.7, 124.9, 120.5, 110.7; IR (KBr, cm^{-1}): 3072, 2925, 2842, 2442, 1735, 1675, 1612, 1593, 1557, 1477, 1450, 1384, 1343, 1313, 1280, 1240, 1183, 1154, 1096, 1046, 951, 929, 881, 828, 807, 778, 761; Anal. calcd for $C_{20}H_{12}ClNO_2$: C 71.97, H 3.62, N 4.20; found: C 71.98, H 3.69, N 4.18.

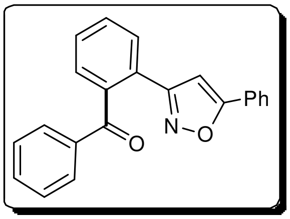
(2-(5-Methylbenzo[*d*]oxazol-2-yl)phenyl)(phenyl)methanone (10'a):



White solid; M.p. 108.5 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.13 (d, 2H, *J* = 7.8 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.67–7.60 (m, 3H), 7.54–7.43 (m, 4H), 7.34 (t, 1H, *J* = 7.6 Hz), 7.21 (d, 1H, *J* = 8.4 Hz), 2.39 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.4, 161.6, 148.9, 141.8, 140.1, 137.5, 133.9, 133.2, 131.2, 130.4, 129.6, 129.4, 128.8, 128.7, 128.5, 126.6, 120.3, 110.0, 21.6; IR (KBr, cm^{-1}): 3071, 3011, 2961, 2889, 2850, 2677, 2559, 1787, 1687, 1601, 1582, 1453, 1424, 1326, 1291, 1180, 1127, 1072, 1026, 933, 802, 707; HRMS (ESI) calcd for $C_{21}H_{15}NO_2$ (M + H$^+$) 314.1176, found 314.1176.

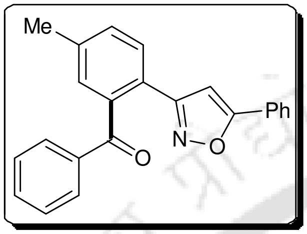
➢ IIIB.6.

Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''a):



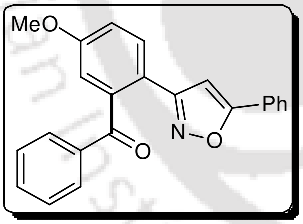
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (d, 1H, *J* = 7.2 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 7.73 (d, 1H, *J* = 7.2 Hz), 7.67-7.63 (m, 2H), 7.60 (d, 1H, *J* = 7.2 Hz), 7.57-7.53 (m, 1H), 7.50-7.46 (m, 2H), 7.43 (d, 2H, *J* = 7.6 Hz), 7.41-7.34 (m, 3H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.7, 170.2, 162.2, 139.5, 137.2, 133.9, 133.5, 130.5, 130.2, 129.6, 129.5, 129.1, 128.7, 128.6, 128.0, 127.4, 125.9, 100.0; IR (KBr, cm^{-1}): 3120, 3063, 2918, 2846, 1789, 1736, 1667, 1596, 1573, 1486, 1449, 1400, 1315, 1287, 1264, 1229, 1177, 1149, 1089, 1069, 1025, 1000, 946, 929, 803, 763, 731, 709, 690, 636; HRMS (ESI) calcd for $C_{22}H_{15}NO_2$ $(M + H^+)$ 326.1176, found 326.1175.

(5-Methyl-2-(5-phenylisoxazol-3-yl)phenyl)(phenyl) methanone (2''a):



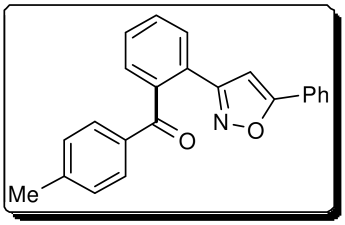
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 1H, *J* = 6.8 Hz), 7.69 (d, 1H, *J* = 8.0 Hz), 7.66-7.63 (m, 2H), 7.47 (t, 2H, *J* = 7.4 Hz), 7.42-7.33 (m, 6H), 7.29 (s, 1H), 6.50 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 170.1, 162.1, 140.0, 139.4, 137.3, 133.5, 131.2, 130.3, 130.2, 129.4, 129.2, 129.1, 128.6, 127.4, 125.9, 125.1, 99.9, 21.5; IR (KBr, cm^{-1}): 3060, 2922, 2846, 1672, 1611, 1593, 1568, 1491, 1447, 1403, 1317, 1292, 1260, 1209, 1179, 1155, 1069, 1023, 961, 946, 919, 846, 833, 791, 752, 766, 752, 711, 689, 648; HRMS (ESI) calcd for $C_{23}H_{17}NO_2$ $(M + H^+)$ 340.1332, found 340.1331.

(5-Methoxy-2-(5-phenylisoxazol-3-yl)phenyl)(phenyl) methanone (3''a):



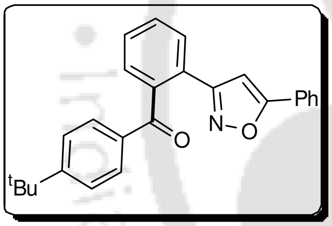
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 8.4 Hz), 7.65-7.63 (m, 2H), 7.49-7.45 (m, 2H), 7.39-7.33 (m, 5H), 7.11 (d, 1H, *J* = 8.8 Hz), 6.98 (s, 1H), 6.47 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 170.0, 161.8, 160.6, 140.8, 137.0, 133.6, 130.9, 130.3, 130.2, 129.1, 128.6, 127.4, 125.9, 120.1, 116.2, 113.9, 99.8, 55.8; IR (KBr, cm^{-1}): 2921, 2840, 1786, 1733, 1666, 1604, 1566, 1492, 1449, 1402, 1316, 1286, 1257, 1231, 1168, 1086, 1064, 1026, 965, 946, 839, 801, 764, 688; HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ $(M + H^+)$ 356.1281, found 356.1273.

(2-(5-Phenylisoxazol-3-yl)phenyl)(*p*-tolyl)methanone (1''d):



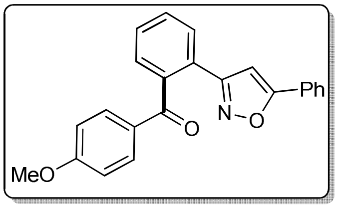
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.93 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 7.6 Hz), 7.63-7.60 (m, 2H), 7.55 (t, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 7.4 Hz), 7.41 (d, 1H, *J* = 7.6 Hz), 7.36-7.33 (m, 2H), 7.21-7.19 (m, 2H), 7.06 (d, 1H, *J* = 8.0 Hz), 6.48 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.5, 172.4, 162.2, 144.8, 139.7, 134.7, 130.4, 130.3, 129.6, 129.5, 129.4, 129.0, 128.6, 127.8, 127.4, 126.8, 125.9, 100.0, 21.9; IR (KBr, cm^{-1}): 2972, 2857, 2652, 1786, 1663, 1610, 1572, 1447, 1418, 1402, 1286, 1182, 1152, 1116, 1020, 949, 927, 833, 757, 714, 688, 606, 541; HRMS (ESI) calcd for $C_{23}H_{17}NO_2$ (M + H$^+$) 340.1332, found 340.1321.

(4-*tert*-Butylphenyl)(2-(5-phenylisoxazol-3-yl)phenyl) methanone (1''t):



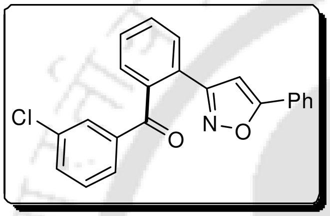
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, 1H, *J* = 7.6 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 7.68-7.65 (m, 2H), 7.59 (t, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 7.4 Hz), 7.47 (d, 1H, *J* = 7.6 Hz), 7.43-7.38 (m, 5H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.4, 170.1, 161.9, 157.4, 141.5, 139.8, 134.6, 130.3, 129.6, 129.1, 128.7, 128.0, 126.0, 125.7, 124.7, 122.9, 122.2, 100.3, 35.3, 31.2; IR (KBr, cm^{-1}): 2962, 2923, 2862, 1785, 1733, 1667, 1607, 1603, 1573, 1459, 1450, 1363, 1314, 1286, 1266, 1185, 1155, 1106, 1017, 949, 931, 851, 803, 763, 690; HRMS (ESI) calcd for $C_{26}H_{23}NO_2$ (M + H$^+$) 382.1802, found 382.1805.

(4-Methoxyphenyl)(2-(5-phenylisoxazol-3-yl)phenyl) methanone (1''b):



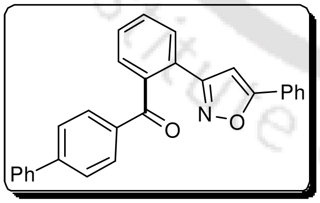
White solid; M.p. 132 °C ,^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08 (d, 1H, *J* = 8.8 Hz), 7.81 (d, 1H, *J* = 7.2 Hz), 7.75 (d, 2H, *J* = 8.8 Hz), 7.68-7.65 (m, 2H), 7.58 (t, 1H, *J* = 7.6 Hz), 7.54 (t, 1H, *J* = 7.4 Hz), 7.45 (d, 1H, *J* = 7.6 Hz), 7.42-7.37 (m, 2H), 6.98 (d, 2H, *J* = 9.2 Hz), 6.54 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 170.0, 163.9, 162.2, 139.8, 132.9, 132.5, 130.3, 130.1, 129.5, 129.4, 128.9, 128.3, 127.6, 127.3, 125.9, 113.9, 99.9, 55.5; IR (KBr, cm^{-1}): 2925, 2842, 2570, 1655, 1596, 1573, 1504, 1464, 1448, 1419, 1398, 1301, 1288, 1257, 1149, 1070, 1046, 1016, 951, 929, 843, 806, 771, 757, 713, 691, 610; HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ (M + H$^+$) 356.1281, found 356.1287.

(3-Chlorophenyl)(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''h):



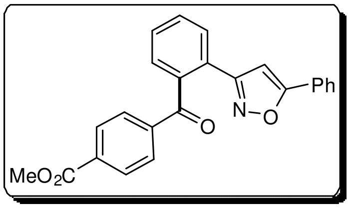
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.71 (m, 2H), 7.65-7.62 (m, 2H), 7.61-7.55 (m, 2H), 7.52 (t, 1H, *J* = 7.4 Hz), 7.45-7.35 (m, 5H), 7.24 (t, 1H, *J* = 8.0 Hz), 6.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 170.5, 162.0, 138.9, 138.8, 134.9, 133.3, 130.9, 130.5, 129.9, 129.8, 129.6, 129.1, 128.8, 128.3, 127.9, 127.3, 126.0, 99.6; IR (KBr, cm^{-1}): 3127, 3069, 2917, 1667, 1614, 1589, 1569, 1492, 1463, 1448, 1426, 1403, 1286, 1254, 1154, 1068, 1050, 1026, 948, 920, 895, 840, 824, 802, 780, 734, 687, 635; HRMS (ESI) calcd for $C_{22}H_{14}ClNO_2$ (M + H$^+$) 360.0786, found 360.0783.

[1,1'-Biphenyl]-4-yl(2-(5-phenylisoxazol-3-yl)phenyl) methanone (1''e):



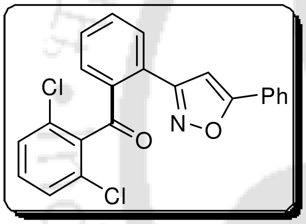
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (t, 2H, *J* = 9.4 Hz), 7.69-7.66 (m, 2H), 7.63 (t, 2H, *J* = 8.0 Hz), 7.59-7.50 (m, 6H), 7.46-7.35 (m, 6H), 6.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 170.3, 162.2, 156.2, 146.2, 139.9, 139.7, 135.9, 130.8, 130.5 130.4, 129.7, 129.6, 129.1, 128.7, 128.4, 127.9, 127.5, 127.3, 126.0, 100.0; IR (KBr, cm^{-1}): 3049, 3027, 2923, 2846, 1786, 1728, 1663, 1600, 1566, 1484, 1448, 1399, 1314, 1283, 1261, 1185, 1149, 1070, 949, 930, 761, 743, 691; HRMS (ESI) calcd for $C_{28}H_{19}NO_2$ (M + H$^+$) 402.1489, found 402.1481.

Methyl 4-(2-(5-phenylisoxazol-3-yl)benzoyl)benzoate (1''j):



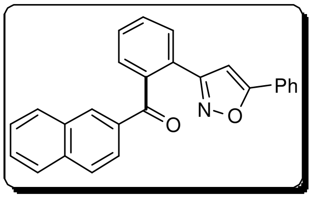
White solid; M.p. 156-157 °C ,^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 2H, *J* = 8.4 Hz),7.80 (d, 2H, *J* = 8.8 Hz), 6.39 (s, 1H), 7.67-7.62 (m, 3H), 7.58 (t, 1H, *J* = 7.4 Hz), 7.51 (d, 1H, *J* = 7.6 Hz), 7.40-7.39 (m, 3H), 6.56 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 170.4, 166.2, 161.9, 140.6, 138.9, 133.9, 130.8, 130.4, 129.8, 129.7, 129.4, 129.0, 128.8, 127.9, 127.1, 125.9, 99.5, 52.5; IR (KBr, cm^{-1}): 2951, 2923, 2851, 1717, 1664, 1574, 1445, 1438, 1403, 1280, 1195, 1106, 1015, 952, 932, 864, 821, 795, 764, 723, 689; HRMS (ESI) calcd for $C_{24}H_{17}NO_4$ (M + H$^+$) 384.1230, found 384.1237.

(2,6-Dichlorophenyl)(2-(5-phenylisoxazol-3-yl)phenyl) methanone (1''n):



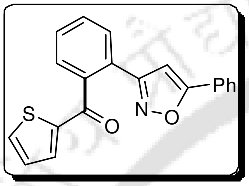
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.71 (t, 2H, *J* = 5.8 Hz), 7.68-7.65 (m, 2H), 7.57-7.53 (m, 2H), 7.49-7.43 (m, 2H), 7.33-7.31 (m, 2H), 6.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 169.3, 163.4, 137.9, 135.7, 133.5, 132.5, 132.1, 131.6, 131.2, 130.7, 130.2, 130.1, 129.1, 128.4, 128.3, 127.6, 126.9, 126.0, 101.1; IR (KBr, cm^{-1}): 3065, 2925, 2852, 1818, 1750, 1684, 1613, 1588, 1574, 1489, 1429, 1400, 1259, 1211, 1195, 1163, 1115, 1091, 1070, 1026, 988, 948, 926, 805, 781, 761, 736, 689, 662; HRMS (ESI) calcd for $C_{22}H_{13}Cl_2NO_2$ (M + H$^+$) 394.0396, found 394.0393.

(Naphthalen-2-yl)(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''p):



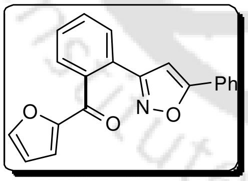
Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.99 (d, 1H, *J* = 8.8 Hz), 7.85 (t, 2H, *J* = 7.6 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 7.67-7.59 (m, 4H), 7.55 (t, 3H, *J* = 7.9 Hz), 7.47 (t, 1H, *J* = 7.9 Hz), 7.36-7.35 (m, 2H), 6.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 170.2, 162.2, 139.7, 136.1, 135.9, 134.7, 132.9, 132.5, 130.5, 130.3, 129.9, 129.6, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 127.9, 126.8, 125.9, 125.6, 124.9, 99.9; IR (KBr, cm^{-1}): 3053, 2924, 2852, 1662, 1626, 1593, 1572, 1463, 1445, 1399, 1353, 1293, 1233, 1198, 1150, 1114, 1020, 949, 920, 866, 850, 823, 760, 710, 688; HRMS (ESI) calcd for $C_{26}H_{17}NO_2$ (M + H$^+$) 376.1332, found 376.1326.

(2-(5-Phenylisoxazol-3-yl)phenyl)(thiophen-2-yl)methanone (1''r):



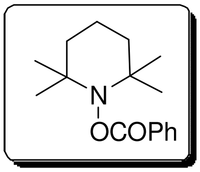
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.83 (d, 1H, *J* = 7.6 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 1H, *J* = 5.2 Hz), 7.60 (d, 1H, *J* = 9.2 Hz), 7.57-7.55 (m, 2H), 7.43-7.39 (m, 3H), 7.34 (d, 1H, *J* = 3.6 Hz), 7.01 (t, 1H, *J* = 4.4 Hz), 6.58 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 189.7, 171.1, 163.9, 144.6, 139.3, 135.9, 135.5, 130.7, 130.4, 129.7, 129.6, 129.1, 128.5, 128.4, 127.8, 127.5, 126.0, 100.2; IR (KBr, cm^{-1}): 3085, 2925, 2852, 1722, 1641, 1571, 1513, 1489, 1448, 1410, 1353, 1293, 1260, 1226, 1149, 1070, 1049, 948, 913, 888, 843, 803, 761, 725, 687, 640; HRMS (ESI) calcd for $C_{20}H_{13}NO_2S$ (M + H$^+$) 332.0740, found 332.0740.

(Furan-2-yl)(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''q):



Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 (t, 1H, *J* = 6.8 Hz), 7.72-7.70 (m, 1H), 7.64-7.53 (m, 5H), 7.45-7.36 (m, 3H), 6.95 (d, 1H, J = 4.0 Hz), 6.59 (s, 1H), 6.43 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 162.9, 162.8, 159.1, 155.9, 147.8, 140.4, 135.4, 131.1, 129.8, 129.2, 126.1, 121.5, 120.1, 112.7, 110.0, 100.1; IR (KBr, cm^{-1}): 3125, 3062, 2923, 2851, 1793, 1727, 1655, 1613, 1569, 1463, 1400, 1306, 1261, 1227, 1186, 1152, 1081, 1020, 950, 889, 762, 689, 650; HRMS (ESI) calcd for $C_{20}H_{13}NO_3$ (M + H$^+$) 316.0968, found 316.0970.

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

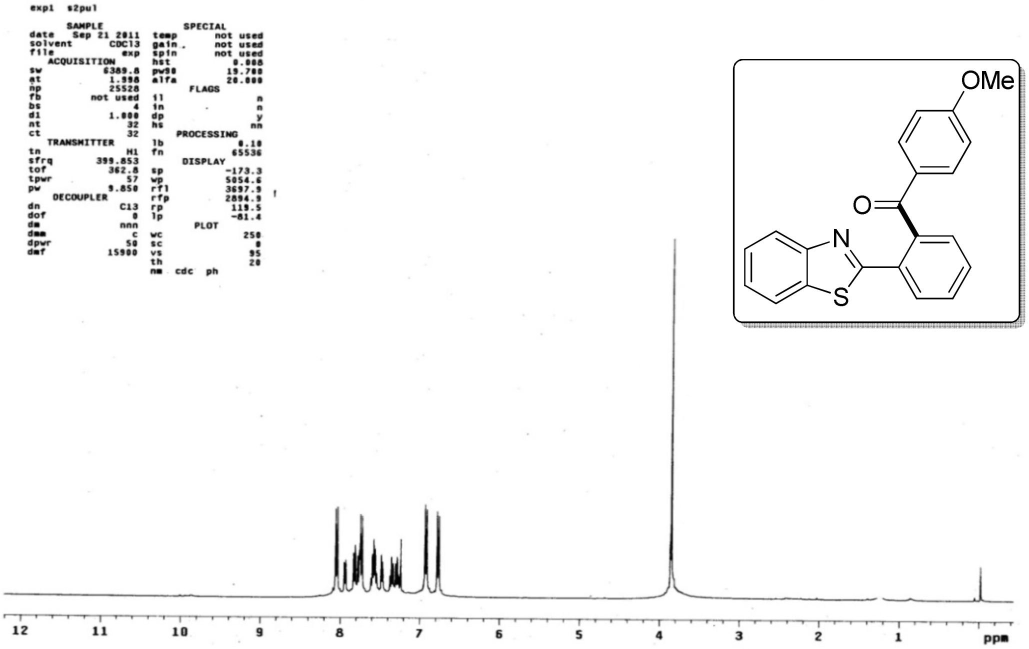


White solid; ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.12 (s, 6H), 1.26 (s, 6H), 1.42-1.45 (m, 1H), 1.55-1.58 (m, 2H), 1.66-1.78 (m, 3H), 7.43 (t, 2H, *J* = 7.8 Hz), 7.54 (t, 1H, *J* = 7.8 Hz), 8.03-8.06 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 17.2, 21.0, 32.1, 39.2, 60.6, 128.6, 129.7, 129.9, 133.0, 166.6; IR (KBr, cm^{-1}): 3007, 2973, 2940, 1741, 1641, 1452, 1365, 1253, 1238, 1083, 1062, 1026, 913, 718; HRMS (ESI) calcd. for $C_{16}H_{23}NO_2$ (M + H$^+$) 262.1802; found 262.1801.

III.7. Spectra

➢ IIIA.7.

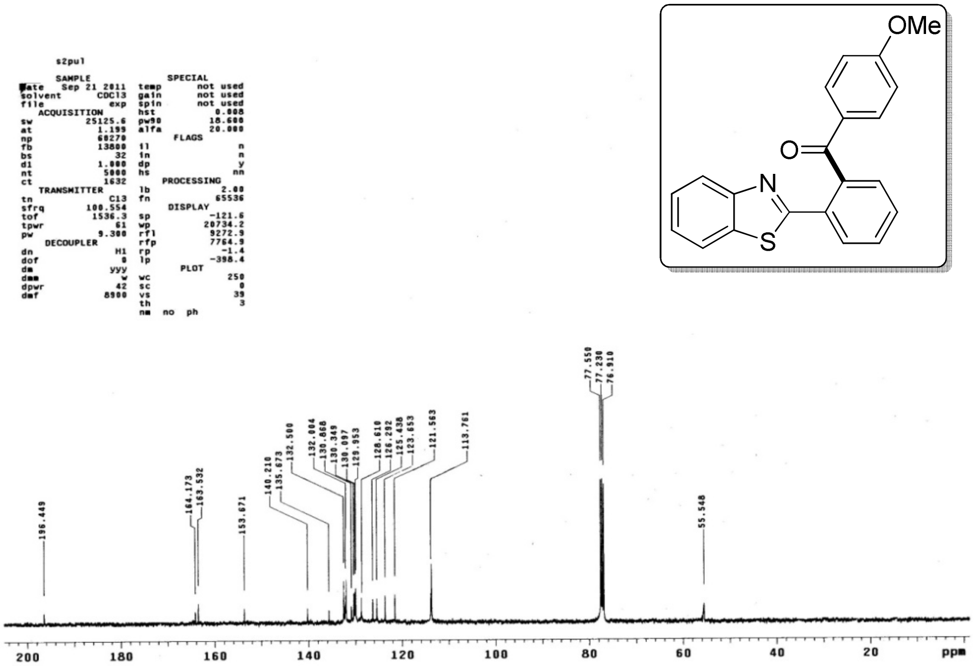
(2-Benzo[*d*]thiazol-2-yl-phenyl)-(4-methoxy-phenyl)-methanone (1b): ^{1}H NMR (400 MHz, $CDCl_3$):



```
exp1  s2pul

      SAMPLE                 SPECIAL
date   Sep 21 2011    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            -173.3
tpwr             57   wp            5054.6
pw            9.850   rfl           3697.9
   DECOUPLER          rfp           2894.9
dn              C13   rp             119.5
dof               0   lp             -81.4
dm              nnn          PLOT
dmm               c   wc               250
dpwr             50   sc                 0
dmf           15900   vs                95
                      th                20
                      nm   cdc   ph
```

(2-Benzo[*d*]thiazol-2-yl-phenyl)-(4-methoxy-phenyl)-methanone (1b): ^{13}C NMR (100 MHz, $CDCl_3$):



```
         s2pul

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date   Sep 21 2011    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             5000   hs                nn
ct             1632        PROCESSING
   TRANSMITTER        lb              2.00
tn              C13   fn             65536
sfrq        100.554         DISPLAY
tof          1536.3   sp            -121.6
tpwr             61   wp           20734.2
pw            9.300   rfl           9272.9
   DECOUPLER          rfp           7764.9
dn               H1   rp              -1.4
dof               0   lp            -398.4
dm              yyy          PLOT
dmm               w   wc               250
dpwr             42   sc                 0
dmf            8900   vs                39
                      th                 3
                      nm   no   ph
```
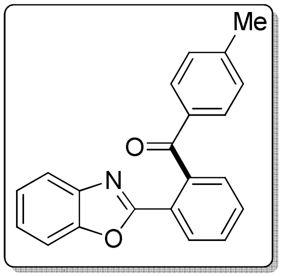
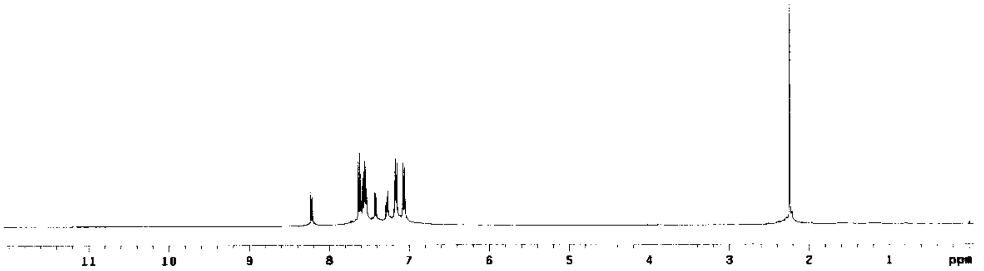

(2-(Benzo[*d*]oxazol-2-yl)phenyl)(*p*-tolyl)methanone (1'd): ^{1}H NMR (400 MHz, CDCl$_3$):

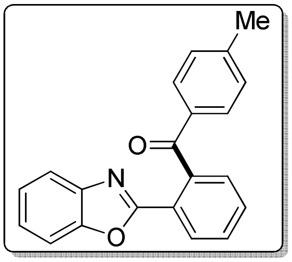
```
exp1  s2pul

      SAMPLE               SPECIAL
date   Mar 28 2012   temp        not used
solvent      CDC13   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             -36.5
tpwr            57   wp            4861.5
pw           9.850   rfl            826.0
    DECOUPLER        rfp                0
dn             C13   rp             100.7
dof              0   lp             -89.0
dm             nnn            PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                55
                     th                 7
                     nm  cdc  ph
```

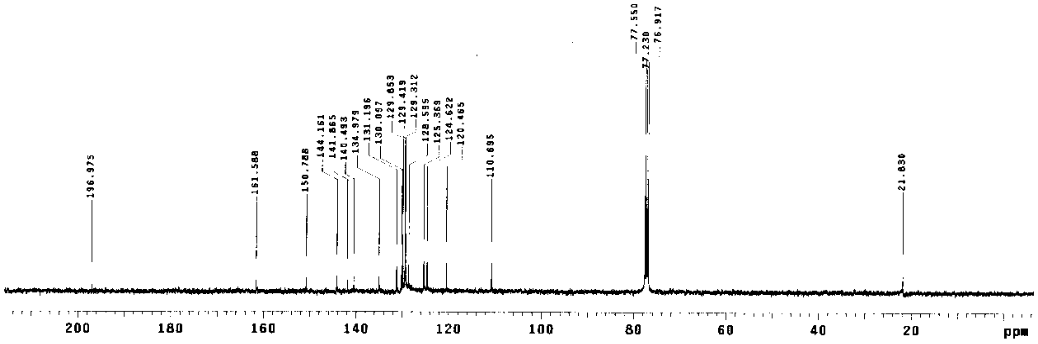




(2-(Benzo[*d*]oxazol-2-yl)phenyl)(*p*-tolyl)methanone (1'd): ^{13}C NMR (100 MHz, CDCl$_3$):

```
exp1  s2pul

      SAMPLE               SPECIAL
date   Feb 15 2012   temp        not used
solvent      CDC13   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            5000   hs                nn
ct            2048          PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554           DISPLAY
tof         1536.3   sp            -650.7
tpwr            61   wp           22352.1
pw           9.300   rfl           9273.6
    DECOUPLER        rfp           7764.9
dn              H1   rp             -13.5
dof              0   lp            -461.5
dm             yyy            PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                33
                     th                 2
                     nm  no  ph
```

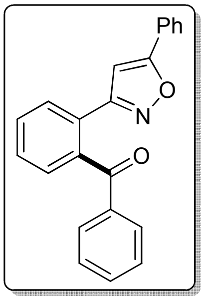


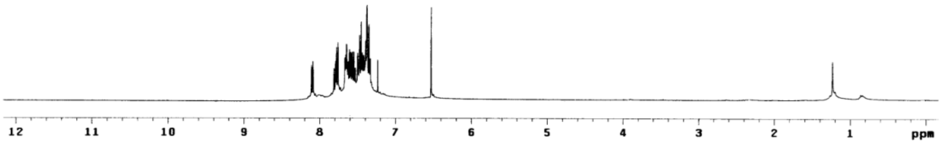


➢ IIIB.7.

Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''a): ^{1}H NMR (400 MHz, CDCl$_3$):

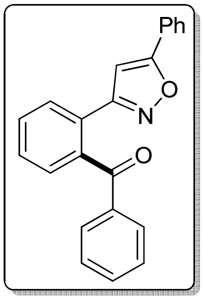
```
exp1  stdlh

      SAMPLE                SPECIAL
date   Mar 28 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             -66.8
tof              0  wp            4932.6
tpwr            57  rfl           3869.1
pw           7.000  rfp           2894.9
    DECOUPLER       rp              72.5
dn             C13  lp             -45.8
dof              0            PLOT
dm             nnn  wc               250
dmm              c  sc                 0
dpwr            50  vs                28
dmf          15900  th                20
                    nm   cdc   ph
```

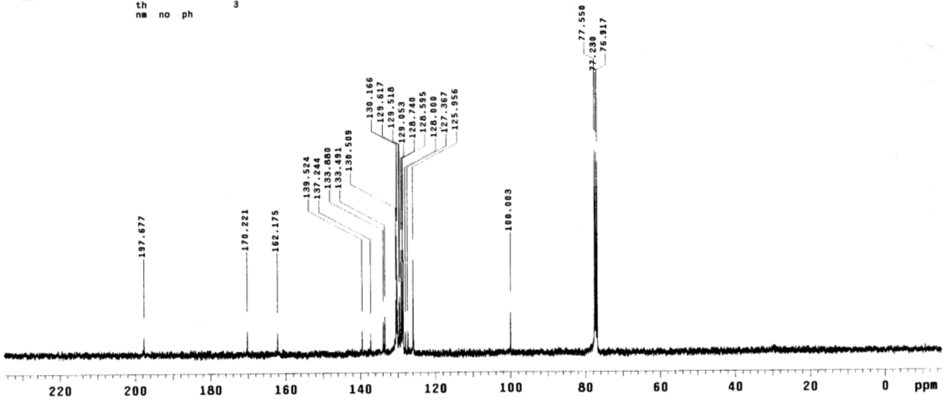




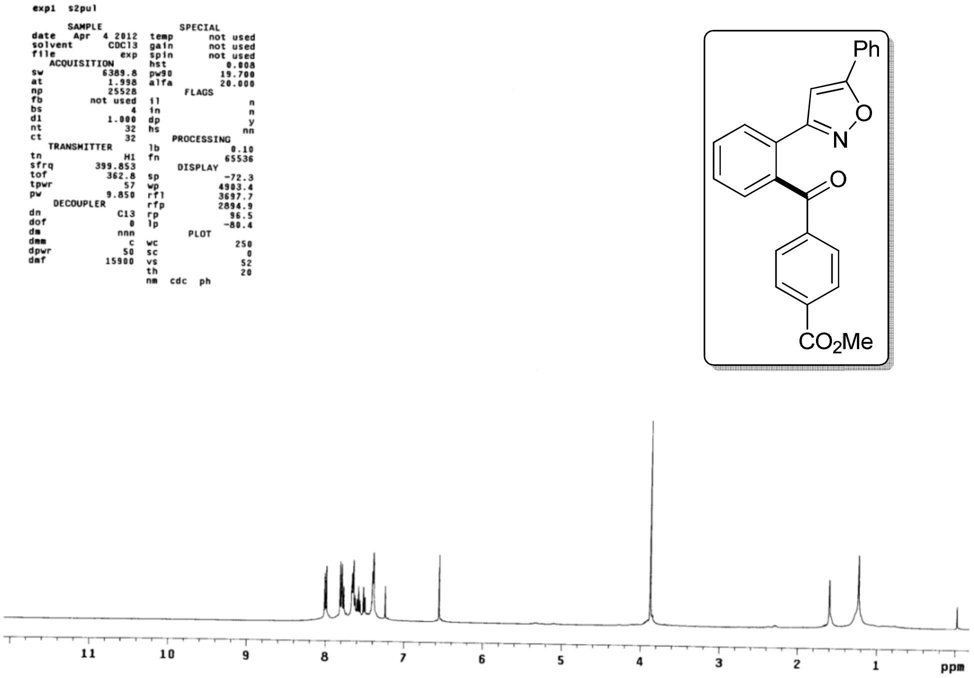
Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (1''a): ^{13}C NMR (100 MHz, CDCl$_3$):

```
exp1  s2pul

      SAMPLE                SPECIAL
date   Mar 28 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           10000  hs                nn
ct            2848        PROCESSING
   TRANSMITTER      lb              2.00
tn             C13  fn             65536
sfrq       100.554          DISPLAY
tof         1536.3  sp           -1511.0
tpwr            61  wp           25125.6
pw           9.300  rfl           9275.9
    DECOUPLER       rfp           7764.9
dn              H1  rp             -44.4
dof              0  lp            -356.8
dm             yyy            PLOT
dmm              w  wc               250
dpwr            42  sc                 0
dmf           8900  vs                50
                    th                 3
                    nm   no   ph
```



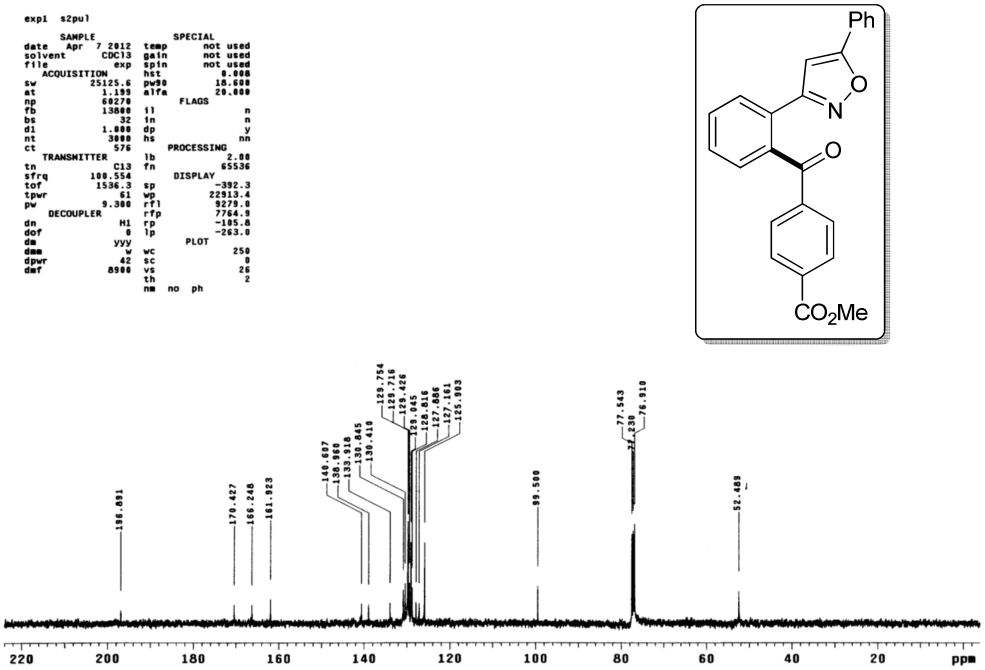


Methyl 4-(2-(5-phenylisoxazol-3-yl)benzoyl)benzoate (1''j): **^{1}H NMR (400 MHz, CDCl$_3$):**



```
exp1  s2pul

      SAMPLE              SPECIAL
date   Apr  4 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            -72.3
tpwr             57  wp           4903.4
pw            9.850  rfl          3697.7
    DECOUPLER        rfp          2894.9
dn              C13  rp             96.5
dof               0  lp            -80.4
dm              nnn          PLOT
dmm               c  wc              250
dpwr             50  sc                0
dmf           15900  vs               52
                     th               20
                     nm  cdc  ph
```

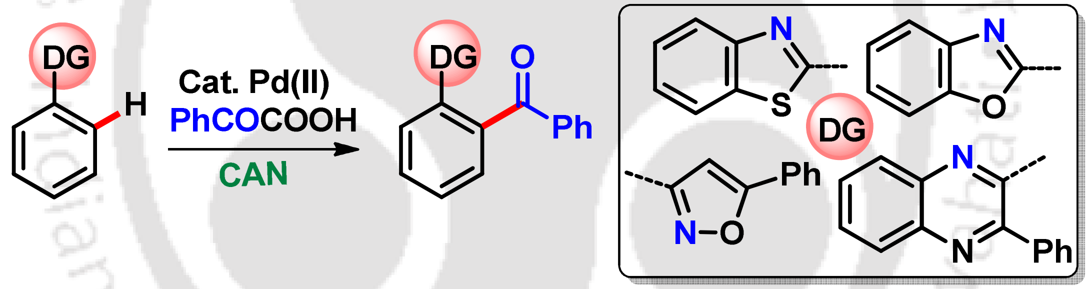
Methyl 4-(2-(5-phenylisoxazol-3-yl)benzoyl)benzoate (1''j): ^{13}C NMR (100 MHz, CDCl$_3$):



```
exp1  s2pul

      SAMPLE              SPECIAL
date   Apr  7 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             3000  hs               nn
ct              576       PROCESSING
   TRANSMITTER       lb             2.00
tn              C13  fn            65536
sfrq        100.554         DISPLAY
tof          1536.3  sp           -392.3
tpwr             61  wp          22913.4
pw            9.300  rfl          9279.0
    DECOUPLER        rfp          7764.9
dn               H1  rp           -105.8
dof               0  lp           -263.0
dm              yyy          PLOT
dmm               w  wc              250
dpwr             42  sc                0
dmf            8900  vs               26
                     th                2
                     nm  no  ph
```

Chapter IV

Ceric Ammonium Nitrate (CAN) Promoted Pd^{II}-Catalyzed Substrate-Directed Decarboxylative o-Aroylation



Abstract: *Inexpensive ceric ammonium nitrate (CAN) is an efficient oxidant for the Pd-catalyzed substrate-directed decarboxylative o-aroylation process. In presence of CAN, the reaction of various directing arenes with α-keto acids resulted in o-aroylated products via decarboxylation. Mechanistic investigations reveal a radical pathway for this process.*

CHAPTER IV

IV. Ceric Ammonium Nitrate (CAN) Promoted Pd^{II}-Catalyzed Substrate-Directed Decarboxylative *o*-Aroylation

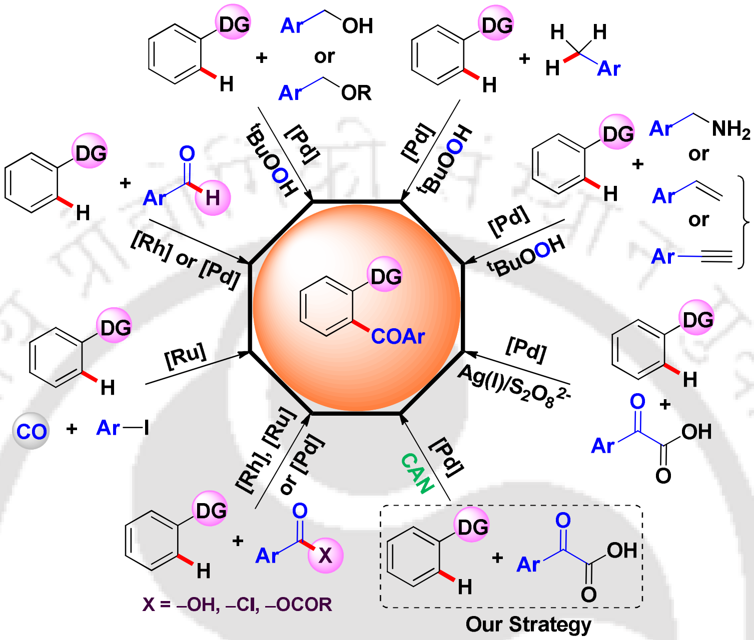
IV.1. Introduction

Carboxylic acids are the cheap but versatile and useful source of carbon-centered radicals which can be successfully implemented for the selective alkylation and aroylation of protonated aromatics and heteroaromatics. The use of aryl carboxylic acids in transition metal catalyzed decarboxylative cross-coupling has thus emerged as one of the most promising strategy for the construction of C–C and C–heteroatom bonds.[1] In this conext the use of α-keto acids for transition metal catalyzed decarboxylative cross-coupling reacions is in the vanguard as these α-ketoacids are highly susceptible to undergo decarboxyation under mild oxidative conditions. This capability has led them to be used as the aroyl source in various transition metal catalyzed ketone synthesis.

A survey of literature indicates that pertaining to the formation of aryl ketones, a plethora of methods have been recently reported using transition-metal-catalyzed substrate-directed sp^2 C–H bond activation.

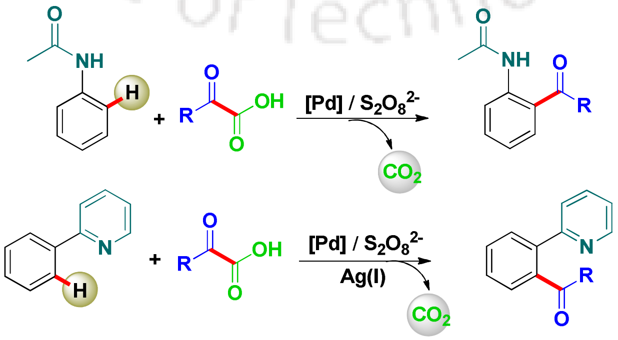
IV.2. Strategies for *ortho*-Aroylation

Diaryl and aryl alkyl ketones, important intermediates in the synthesis of pharmaceuticals, natural products, functional materials and agrochemicals,[2] are typically synthesized by Friedel–Crafts acylation. The classical synthetic recipes for the synthesis of diaryl or alkylaryl ketones however suffers from various drawbacks such as poor regioselectivity or harsh acidic / basic conditions.[3] The advent of modern techniques like cross-dehydrogenative coupling (CDC) in combination with directing group assisted techniques has come out as potential methods for the synthesis of diaryl or arylalkyl ketones.[4] The various methods that have been employed for the synthesis of diaryl or arylalkyl ketones can be classified into many types as follows; (i) *ortho*-selective Friedel-Crafts acylation using carboxylic acids or its derivatives[5] (ii) the carbonylative processes[6] (iii) the cross dehydrogenative coupling with various aroyl surrogates such as aldehydes,[7] alcohols,[8] ethers,[9] alkylbenzenes,[10] benzylamines,[11] terminal alkenes/alkynes[12] and diketones[13] (iv) decarboxylative couplings of α-oxoacids.[14] All these *o*-aroylation protocols are already demonstrated in Chapter IIIA (page no 101-105) in an elaborate manner. A schematic diagram for these *o*-aroylations is depicted below in Scheme IV.2.1.



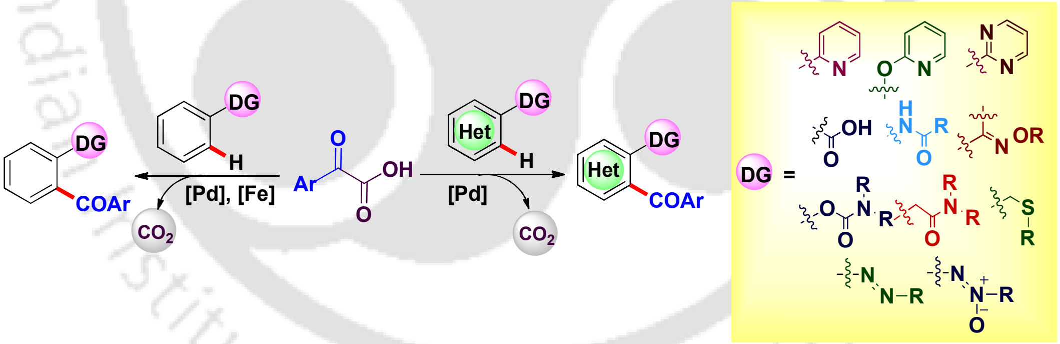
Scheme IV.2.1. *Various recent methods for the synthesis of ketones*

In the context of decarboxylative aroylation reactions the use of α-keto acid as the aroyl surrogate was firstly developed by Gooβen *et al.* They developed a Pd-catalyzed decarboxylative non-directed aroylation of aryl bromide using α-keto carboxylate salts as aroyl surrogates.[15] However the use of α-keto acid in directing group assisted decarboxylative *o*-aroylation reactions was first demonstrated by Ge *et al.* They reported *ortho*-aroylation strategy of various directing arenes such as 2-arylpyridines, acetanilides and even carboxylic acids[14a-c] *via* decarboxylation of α-keto acids (Scheme IV.2.2).



Scheme IV.2.2. *Pd(II) catalyzed decarboxylative o-aroylation using α-ketoacids*

This procedure was further improved by Saxena and co-workers.[14d] By using the purple-colored iron peroxo complex [$Fe^{III}(edta)(\eta^2\text{-}O^2)]^{3-}$ (edta=ethylenediaminetetraacetic acid) as the oxidant, which could be generated *in situ* by treating [Fe^{III}(edta)] with H_2O_2 at pH 7.2–7.8, the transformation was realized at room temperature in water with $Pd(OAc)_2$ (1–2 mol %) as the only catalyst (Scheme IV.2.3). Using Pd(II) as the catalyst and $Ag^I/S_2O_8^{2-}$ as the oxidant this decarboxylative coupling of α-oxoacids for ketone synthesis was further extended by Kim, Wang and other groups on various directing arenes such as 2-aryloxypyridines,[14e] ketoxime ethers,[14f-g] cyclic enamides,[14h] carbamates,[14i] acetamides,[14j] azobenzenes,[14k-l] azoxybenzenes,[14m] benzoic acids[14n] and even thioethers[14o] (Scheme IV.2.3). Pertinent to such strategy in heteroarenes, C-2 acylation in indoles[14p] and C-3 acylation of benzothiophenes or benzofurans[14q] have been reported using α-oxoacids as aroyl source. All these above mentioned directed[14]or non-directed[15] decarboxylative aroylations using α-ketoacids are effective in the presence of either silver, a persulfate ($S_2O_8^{2-}$) source, or combination thereof, which makes the processes economically unviable for large scale synthesis. Thus, it would be advantageous and appreciable if the same decarboxylative *o*-aroylation can be achieved *via* silver and persulphate free path.



Scheme IV.2.3. *o-Aroylation via decarboxylative coupling*

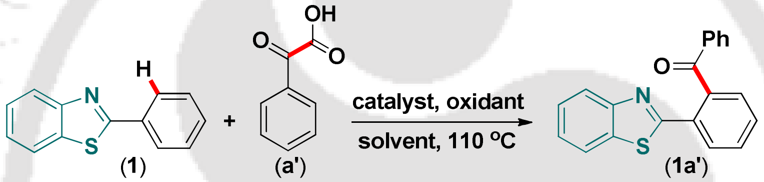
Ce(IV) in ceric ammonium nitrate (CAN) is an powerful oxidizing agent used mainly in functional group oxidation *via* one-electron pathway.[16a-g] as well as for the synthesis of various heterocycles.[16h-i] The reduction potential of well-known oxidants that are used for decarboxylative *o*-aroylation reactions are + 0.80 V for Ag(I)/Ag(0) and + 2.01 V for $S_2O_8^{2-}/SO_4^{2-}$. In comparision, the reduction potential of Ce(IV)/Ce(III) is + 1.61 V, which is in between Ag(I)/Ag(0) and $S_2O_8^{2-}/SO_4^{2-}$. Thus, Ce(IV)/Ce(III) is moderately oxidizing in nature and as a single electron oxidant, it may be capable of forming an aroyl radical through decarboxylation of α-keto acid and thus can be used as an suitable alternative to silver/persulphate combination during decarboxylative *o*-aroylation process.

IV.3. Present Work

In light of the above-mentioned protocols, the present protocol on decarboxylative *o*-aroylation of directing arene 2-arylbenzothiazole with phenylglyoxalic acid is unreported so far using $Pd(OAc)_2$ / CAN combinations.

Optimization of reaction conditions. To check the efficacy of CAN as a terminal oxidant, a CDC reaction between 2-phenylbenzothiazole (**1,** 1 equiv) and phenylglyoxylic acid (**a′**) (1.2 equiv) was carried out in the presence of $Pd(OAc)_2$ (5 mol %) and CAN (1.5 equiv) in 1,2-dichloroethane. The desired *o*-aroylated product **1a′** was obtained in a paltry yield of 26%.

Table IV.3.1. *Screening of reaction conditions for o-aroylation*



Entry	Catalyst (mol %)	Solvent	Oxidant	Yield (%)[a,b]
1	$Pd(OAc)_2$ (5.0)	DCE	CAN	26
2	$Pd(OAc)_2$ (5.0)	Cyclohexane	CAN	08
3	$Pd(OAc)_2$ (5.0)	Dioxane	CAN	34
4	$Pd(OAc)_2$ (5.0)	Toluene	CAN	39
5	$Pd(OAc)_2$ (5.0)	DMF	CAN	47
6	$Pd(OAc)_2$ (5.0)	DMSO	CAN	00[c]
7	**$Pd(OAc)_2$ (10.0)**	**DMF**	**CAN**	**68**
8	$Pd(OAc)_2$ (2.0)	DMF	CAN	32
9	$Pd(TFA)_2$ (10.0)	DMF	CAN	44
10	$PdCl_2$ (10.0)	DMF	CAN	53
11	$PdBr_2$ (10.0)	DMF	CAN	35
12	$Pd(OAc)_2$ (10.0)	DMF	Ag_2CO_3	00[c]
13	$Pd(OAc)_2$ (10.0)	DMF	$K_2S_2O_8$	60
14	$Pd(OAc)_2$ (10.0)	DMF	$(NH_4)_4Ce(SO_4)_4$ $.2H_2O$	41

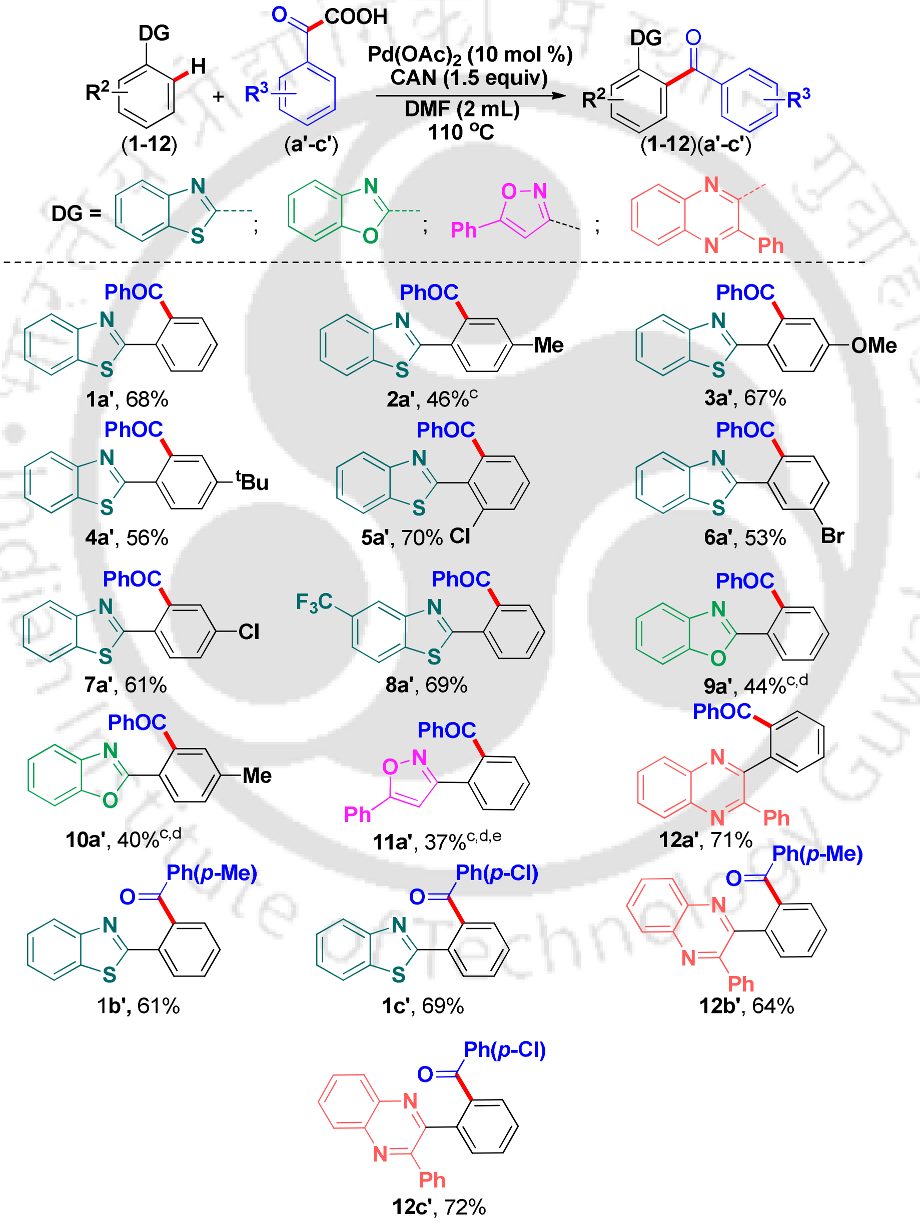
[a]Reaction conditions: 2-arylbenzothiazole (0.25 mmol), phenylglyoxalic acid (0.30 mmol) and oxidant (0.38 mmol) at 110 °C for 8 h. [b]Isolated yield. [c]Complete recovery of starting materials.

With this preliminary success, to achieve the best possible conversion, other reaction parameters such as solvent, catalyst, oxidant, and their quantities were varied (see Table IV.3.1). Other oxidants were also examined for comparison. The results for various trial reactions are summarized in Table IV.3.1. The optimization results indicate that the decarboxylative coupling between 2-phenylbenzothiazole (**1**, 1 equiv) and phenylglyoxylic acid (**a′**, 1.2 equiv) was best achieved by using $Pd(OAc)_2$ (10 mol %) and CAN (1.5 equiv) in DMF at 110 °C (see Table IV.3.1). These standardized conditions were used to examine the decarboxylative *o*-aroylation reactions of a range of directing arenes.

Substrate scope for *o*-aroylation. Using above standardized conditions, we scrutinized the scope and generality of a decarboxylative coupling reaction with various 2-arylsubstituted benzothiazoles and phenylglyoxylic acid (**a′**). 2-Phenylbenzothiazole that contained electro-neutral –H (**1**), electron-donating *p*-Me (**2**), *p*-OMe (**3**), and *p*-^{t}Bu (**4**), and electron-withdrawing *o*-Cl , *m*-Br, and *p*-Cl (i.e. **5**, **6**, and **7**) substituents on the 2-phenyl ring coupled efficiently with **a'** to provide the desired *o*-aroylated products in moderate to good yields (Scheme IV.3.1). However, no correlation could be ascertained between the effect of substituents on the 2-phenyl ring of the 2-arylbenzothiazole and the yield of the product. *m*-Br Substituted 2-arylbenzothiazole **6** provided the *o*-aroylated product **6a′** with the reaction occurring at the less sterically hindered *o*-site as a result of a favorable cyclopalladation step. The presence of the strongly electron-withdrawing $–CF_3$ substitient on the benzothiazole ring of **8** provided a comparable yield of **8a′** to that of electro-neutral substrate **1** (Scheme IV.3.1). 2-Phenylbenzoxazole (**9**), a structural analogue of 2-phenylbenzothiazole (**1**) provided *o*-aroylated product **9a′** in low yield (44%), even by using an excess amount of $Pd(OAc)_2$ (15 mol %) and after a prolong reaction time (48 h). Similarly, *p*-Me substituted 2-phenylbenzoxazole (**10**) gave a meager yield of 40% under the identical conditions (Scheme IV.3.1). However, for substrate (**9**) well established oxidants[14] such as Ag^I failed to give the desired product, whereas the use of persulfate ($S_2O_8^{2-}$) gave comparable yield to that by using CAN. The usefulness of CAN as an oxidizing agent was then successfully applied to directing arene 3,5-diphenylisoxazole (**11**). 3,5-Diphenylisoxazole (**11**) with *N* or *O*-chelating atoms provided expected *o*-aroylated product (**11a′**) but in lower yield (37%). The product yields for these oxygen containing *N*-directed substrates **9**, **10** and **11** are less than those of the sulfur containing *N*-directed substrates (Scheme IV.3.1). Because of its oxophilic nature, the cerium atom possibly remains bound to oxygen atom of oxygen containing directing arenes, thereby making it unavailable for the oxidative addition and giving lower yields. However, directing arene that contains two nitrogen atoms, as in the case of 2,3-diphenylquinoxaline (**12**), provided the *o*-aroylated product (**12a′**) in good yield (71%) under the optimized reaction conditions. It is worth noting that none of the above-mentioned directing groups have been previously employed in a decarboxylative *o*-aroylation reaction with phenylglyoxylic acid.

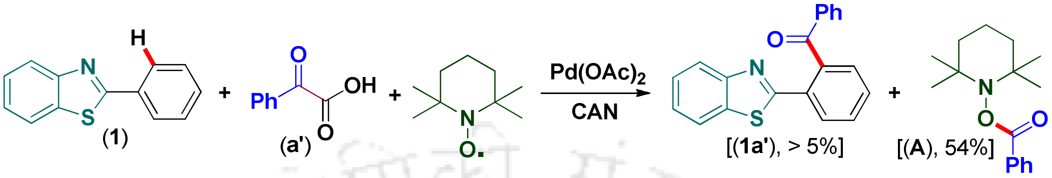
Further *o*-aroylations of directing arenes **1** and **12** were carried out with substituted phenylglyoxylic acids. *p*-Me Substituted phenylglyoxylic acid **b'** coupled efficiently with both the directing arenes **1** and **12** to provide their desired products **1b′** and **12b′** in almost identical yields (Scheme IV.3.1). The coupling reaction of *p*-Cl substituted phenylglyoxylic acid **c'** with **1** and **12** proceeded better than those of *p*-Me substituted phenylglyoxylic acid **b'** and provided *o*-aroylated products **1c′** and **12c′**.

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



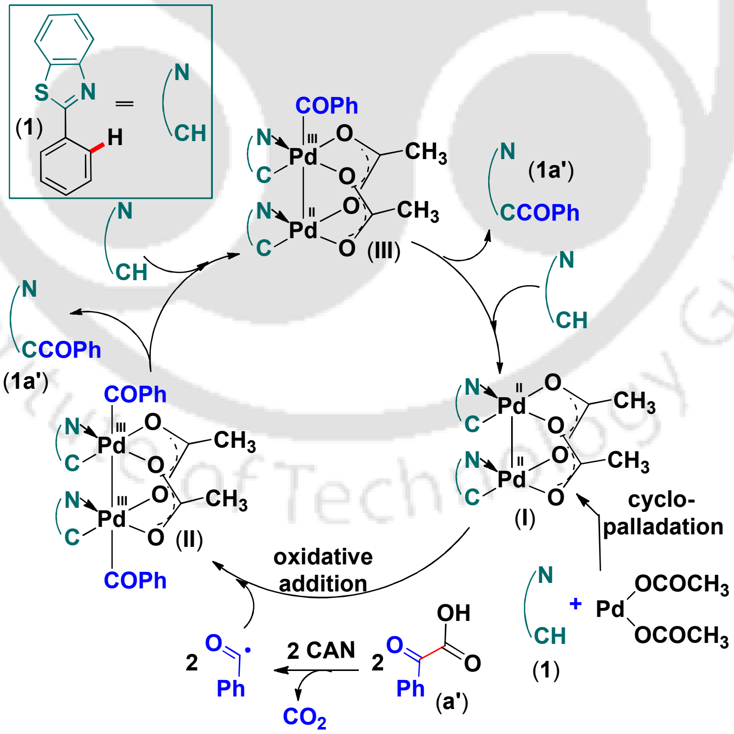
[a]Reaction conditions: directing arenes (0.25 mmol), α-keto acids (0.30 mmol), CAN (0.38 mmol) at 110 °C for 8 h. [b]Isolated yield. [c]The rest is recovered starting materials. [d]Reactions were performed for 48 h using 15 mol % $Pd(OAc)_2$. [e]DCE used in lieu of DMF.

Mechanistic studies. When a typical *o*-aroylation of **1** was carried out in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv), significant reduction in the product yields (>5 %) were observed along with the detection of TEMPO-ester (**A**) supports the formation of an aroyl radical (Scheme IV.3.2).



Scheme IV.3.2. *Reaction in presence of radical scavenger TEMPO*

When the *o*-aroylation of **1** was carried out in the presence of 1, 1.5, and 2 equiv of oxidant (CAN) under otherwise identical conditions the isolated yields of the product after 12 h were 56%, 68% and 69% respectively. These experiments suggest a minimum requirement of one equiv of oxidant for this transformation, thereby indicating a Pd^{II}/Pd^{III} catalytic cycle.[17] Taking cues from the above experimental observations, plausible mechanisms can be speculated for this decarboxylative *o*-aroylation reaction (Scheme IV.3.3).



Scheme IV.3.3. *Proposed mechanism for o-aroylation*

For *o*-aroylation process, the initial cyclopalladation of 2-phenylbenzothiazole (**1**) leads to the formation of acetate bridged binuclear Pd^{II} intermediate **I** (Scheme IV.3.3). This dimeric Pd^{II} complex further undergoes a bimetallic oxidative addition with the *in situ* generated aroyl radical that is obtained by the action of CAN with phenylglyoxalic acid (**a'**) with concurrent decarboxylation. The proximity of the two Pd-centers might facilitate cooperative redox chemistry; in which both metals participate synergistically to lower the barrier of the redox transformation. The oxidative addition product is a dimeric Pd(III)[17] intermediate **II**. Although the formation of a monomeric Pd(IV)[18] species in the reaction medium *via* the Pd–Pd cleavage in dimeric Pd(III) intermediate **II** can not be overruled. A reductive elimination leads to the *o*-aroylated product and forms the active dimeric species **III**. Intermediate **III** further releases another *o*-aroylated product by C–C bond formation and regenerates dinuclear Pd^{II} active species **II** for the next catalytic cycle.

In summary, we have demonstrated the use of the inexpensive terminal oxidant CAN as an efficient substitute for a set of expensive oxidants/additives in the Pd-catalyzed substrate-directed decarboxylative *o*-aroylation processes. Mechanistic investigations reveal a radical pathway for this process.

IV.4. Experimental Section

IV.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. FT-IR spectra were recorded in KBr or neat. HRMS spectra were recorded using ESI mode. Elemental analyses were recorded on CHNS analyzer.

IV.4.2. General procedure for the synthesis of (2-benzo[*d*]thiazol-2-yl-phenyl)-phenyl-methanone (1a') from 2-phenylbenzo[*d*]thiazole and phenylglyoxylic acid (a'). An oven-dried flask was charged with 2-phenylbenzo[*d*]thiazole (**1**) (0.053 g, 0.25 mmol), phenylglyoxylic acid (**a'**) (0.045 g, 0.30 mmol), ceric ammonium nitrate (0.206 g, 0.38

mmol), and $Pd(OAc)_2$ (0.006 g, 0.025 mmol) in DMF (2 mL). The reaction mixture was then stirred in a preheated oil bath at 110 ^{o}C for 8 h. After the stipulated time, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was subsequently washed with a saturated solution of sodium bicarbonate solution (2 x 5 mL). The ethyl acetate layer was then dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product so obtained was further purified through silica gel column chromatography(hexane / ethyl acetate, 10:0.5) to yield the pure (2-benzo[*d*]thiazol-2-yl-phenyl)-phenyl-methanone **1a'** (0.054g, yield 68%). The same procedure was also followed for decarboxylaive *o*-aroylation of other directing arenes (**1**-**12**) derrivatives with various α-keto acids (**a'**-**c'**).

IV.4.3. Mechanistic investigation in the presence of radical scavenger TEMPO: An oven-dried reaction vessel was charged with 2-phenylbenzo[*d*]thiazole (**1**) (0.053 g, 0.25 mmol), phenylglyoxylic acid (**a'**) (0.045 g, 0.30 mmol), CAN (0.206 g, 0.38 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) and TEMPO (0.187 g, 1.2 mmol) in 2 mL DMF. The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath at 110 ^{o}C for 8 h. The reaction after 8 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**A**) in 54% yield along with traces (<5%) of the desired product (**1a'**). This experiment supports the formation of benzoyl radical in the medium from phenylglyoxylic acid (**a'**) *via* decarboxylation and also the radical nature of the mechanism.

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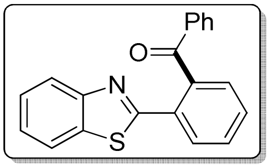
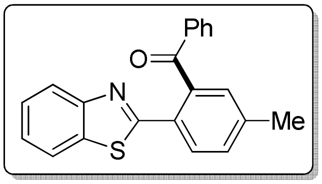
IV.6. Spectral Data

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



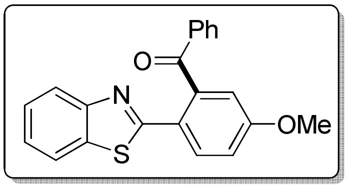
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.12 (d, 1H, *J* = 7.6 Hz), 7.92 (d, 1H, *J* = 7.2 Hz), 7.80–7.75 (m, 2H), 7.64–7.57 (m, 2H), 7.54 (d, 1H, *J* = 6.8 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.39–7.31 (m, 2H), 7.30–7.24 (m, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.7, 165.5, 153.4, 139.7, 137.8, 135.3, 133.8, 132.8, 132.1, 130.4, 130.3, 129.4, 128.5, 128.3, 126.2, 125.4, 123.4, 121.4; IR (KBr, cm^{-1}): 3060, 2923, 2849, 2725, 2553, 1686, 1667, 1596, 1580, 1450, 1427, 1316, 1283, 1255, 1179, 1154, 1126, 1026, 968, 923, 759; HRMS (ESI) calcd for $C_{20}H_{13}NOS$ [M+H]$^+$ 316.0796, found 316.0790.

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



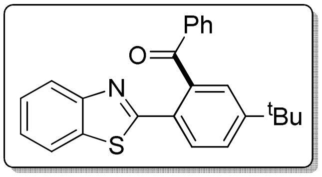
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.82 (d, 1H, *J* = 8.0 Hz), 7.77–7.71 (m, 4H), 7.41 (d, 1H, *J* = 8.0 Hz), 7.38–7.32 (m, 3H), 7.30–7.23 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.6, 165.6, 153.5, 141.0, 139.7, 137.9, 135.2, 133.7, 132.7, 130.9, 129.6, 129.4, 129.3, 128.3, 126.2, 125.2, 123.3, 121.4, 21.4; IR (KBr, cm^{-1}): 3053, 3024, 2920, 2855, 1669, 1597, 1561, 1511, 1476, 1449, 1432, 1400, 1315, 1287, 1256, 1208, 1177, 1116, 1073, 975, 957, 854, 826, 789, 757; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ $[M+H]^+$ 330.0952, found 330.0960.

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



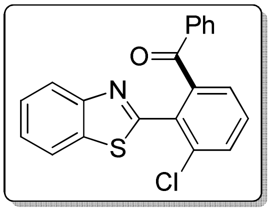
Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 1H, *J* = 8.8 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 1H, *J* = 7.4 Hz), 7.37 (t, 2H, *J* = 7.4 Hz), 7.29–7.25 (m, 1H), 7.22–7.17 (m, 1H), 7.02 (d, 1H, *J* = 8.4 Hz), 6.95 (s, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 165.3, 161.3, 153.5, 141.4, 137.7, 135.2, 133.9, 131.4, 130.3, 129.4, 128.6, 126.2, 125.1, 123.2, 121.4, 116.0, 114.1, 55.8; IR (KBr, cm^{-1}): 3071, 2963, 2916, 2834, 2676, 2558, 1687, 1602, 1583, 1453, 1424, 1326, 1292, 1179, 1099, 1072, 1026, 934, 807, 762; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ $[M+H]^+$ 346.0902, found 346.0911.

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



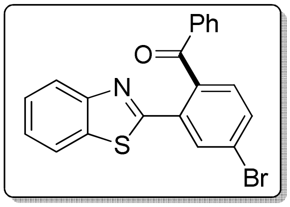
Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, 1H, *J* = 12.0 Hz), 7.78–7.73 (m, 3H), 7.63 (d, 1H, *J* = 8.4 Hz), 7.53 (s, 1H), 7.37–7.34 (m, 2H), 7.31–7.25 (m, 4H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 165.5, 154.2, 153.7, 139.6, 138.0, 135.3, 132.7, 129.6, 129.4, 128.3, 127.4, 126.2, 125.9, 125.3, 123.4, 121.5, 35.3, 31.3; IR (KBr, cm^{-1}): 3069, 3028, 2967, 2930, 2867, 1671, 1596, 1558, 1515, 1481, 1449, 1431, 1395, 1362, 1314, 1253, 1162, 1103, 1023, 972, 902, 857, 840, 800, 757; HRMS (ESI) calcd for $C_{24}H_{21}NOS$ $[M+H]^+$ 372.1422, found 372.1428.

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



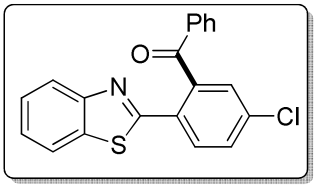
Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.80–7.76 (m, 1H), 7.70–7.57 (m, 3H), 7.54 (t, 1H, *J* = 7.6 Hz), 7.50–7.46 (m, 1H), 7.40–7.34 (m, 2H), 7.31–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 168.4, 152.3, 143.1, 137.1, 133.9, 133.0, 131.9, 130.4, 129.8, 129.4, 129.0, 128.3, 127.6, 126.2, 125.8, 123.7, 121.4; IR (KBr, cm^{-1}): 3058, 3022, 2920, 2839, 2360, 2340, 1669, 1595, 1579, 1556, 1506, 1482, 1447, 1429, 1415, 1315, 1282, 1255, 1177, 1155, 1141, 1127, 1072, 1012, 968, 952, 924, 853, 798, 759; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ $[M+H]^+$ 350.0406, found 350.0412.

(2-Benzo[*d*]thiazol-2-yl-4-bromo-phenyl)-phenyl-methanone (6a'):



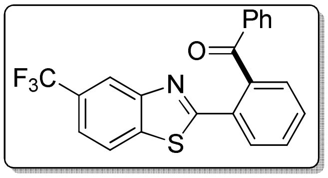
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.91 (s, 1H), 7.79 (d, 1H, *J* = 8.0 Hz), 7.75 (t, 2H, *J* = 9.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.39–7.32 (m, 3H), 7.31–7.24 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.7, 163.8, 153.4, 138.1, 137.6, 136.4, 135.5, 134.0, 133.1, 130.5, 130.4, 129.6, 129.4, 128.5, 126.5, 125.8, 123.7, 121.6; IR (KBr, cm^{-1}): 3070, 3053, 3022, 2925, 2841, 1665, 1596, 1681, 1551, 1500, 1473, 1445, 1434, 1381, 1316, 1276, 1251, 1239, 1151, 1096, 1012, 984, 934, 871, 827, 793, 763; HRMS (ESI) calcd for $C_{20}H_{12}BrNOS$ $[M+H]^+$ 393.9901, found 393.9894.

(2-(Benzo[*d*]thiazol-2-yl)-5-chlorophenyl)(phenyl)methanone (7a'):



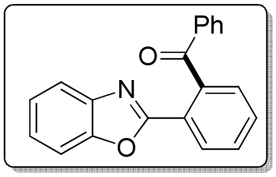
White solid; M.p. 130–132 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.87 (d, 1H, *J* = 8.4 Hz), 7.78–7.74 (m, 3H), 7.60 (d, 1H, *J* = 8.4 Hz), 7.51 (s, 1H), 7.43–7.38 (m, 2H), 7.36–7.25 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.1, 164.1, 153.6, 141.3, 137.4, 136.9, 135.4, 133.2, 130.9, 130.6, 130.4, 129.4, 129.0, 128.5, 126.5, 125.7, 123.7, 121.6; IR (KBr, cm^{-1}): 3063, 3022, 2923, 2848, 1670, 1593, 1581, 1560, 1508, 1474, 1452, 1432, 1378, 1313, 1291, 1263, 1181, 1156, 1128, 1100, 1021, 1001, 968, 947, 876, 817, 782, 755; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ $[M+H]^+$ 350.0406, found 350.0411.

Phenyl(2-(5-(trifluoromethyl)benzo[*d*]thiazol-2-yl)phenyl)methanone (8a'):



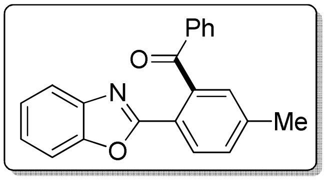
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.0 (s, 1H), 7.92 (d, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.0 Hz), 7.65–7.60 (m, 2H), 7.54–7.50 (m, 2H), 7.42 (t, 1H, *J* = 6.8 Hz), 7.32 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 197.4, 167.8, 153.2, 140.1, 138.8, 137.7, 133.1, 131.7, 130.9, 130.5, 130.0, 129.5, 129.1, 128.5, 125.2, 123.3, 122.3, 121.8, 120.7; ^{19}F NMR (CDCl$_3$ + Trifluoroacetic acid); *δ* -62.4 (s); IR (KBr, cm^{-1}): 3080, 3061, 3022, 1673, 1596, 1580, 1511, 1483, 1463, 1452, 1437, 1423, 1328, 1288, 1269, 1247, 1218, 1180, 1166, 1149, 1123, 1076, 1056, 1043, 964, 931, 920, 911, 810, 799; HRMS (ESI) calcd for $C_{21}H_{12}F_3NOS$ [M+H]$^+$ 384.0669, found 384.0678.

(2-(Benzo[*d*]oxazol-2-yl)phenyl)(phenyl)methanone (9a'):



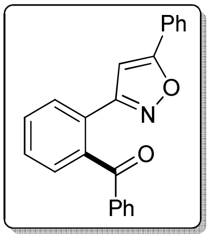
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.13 (d, 2H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.68–7.58 (m, 4H), 7.50–7.44 (m, 4H), 7.36–7.33 (m, 1H), 7.25–7.24 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.3, 161.0, 150.7, 141.5, 140.1, 137.4, 133.9, 133.3, 131.3, 130.3, 129.6, 129.5, 128.8, 128.6, 125.5, 124.8, 120.4, 110.6; IR (KBr, cm^{-1}): 3071, 3025, 2880, 2836, 2672, 2602, 2557, 2084, 1989, 1788, 1687, 1601, 1582, 1495, 1453, 1424, 1326, 1291, 1180, 1127, 1070, 1026, 999, 933, 809, 746; HRMS (ESI) calcd for $C_{20}H_{13}NO_2$ [M+H]$^+$ 300.1024, found 300.1031.

(2-(Benzo[*d*]oxazol-2-yl)-5-methylphenyl)(phenyl)methanone (10a'):



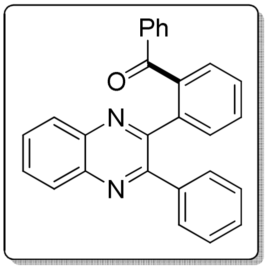
White solid; M.p. 120–121 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz), 7.58–7.56 (m, 1H), 7.46–7.42 (m, 1H), 7.40 (d, 1H, *J* = 7.2 Hz), 7.33–7.27 (m, 4H), 7.21–7.18 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 197.6, 161.7, 150.7, 142.1, 141.9, 140.3, 137.6, 133.2, 131.1, 129.6, 129.4, 129.3, 128.5, 125.2, 124.6, 122.8, 120.3, 110.6, 21.7; IR (KBr, cm^{-1}): 3067, 3034, 2921, 2852, 1773, 1672, 1613, 1593, 1555, 1494, 1451, 1396, 1343, 1314, 1291, 1264, 1241, 1213, 1178, 1127, 1047, 1002, 964, 926, 890, 843, 824, 812, 762; HRMS (ESI) calcd for $C_{21}H_{15}NO_2$ [M+H]$^+$ 314.1181, found 314.1188.

Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (11a'):



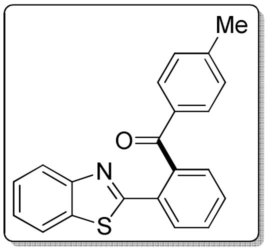
Gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (d, 1H, *J* = 7.2 Hz), 7.80 (d, 1H, *J* = 7.6 Hz), 7.73 (d, 1H, *J* = 7.2 Hz), 7.67−7.64 (m, 2H), 7.60 (d, 1H, *J* = 7.2 Hz), 7.57−7.54 (m, 1H), 7.51−7.45 (m, 2H), 7.43 (d, 2H, *J* = 7.6 Hz), 7.41−7.34 (m, 3H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.7, 170.2, 162.2, 139.5, 137.2, 133.9, 133.5, 130.5, 130.2, 129.6, 129.5, 129.0, 128.7, 128.6, 128.0, 127.4, 125.9, 100.0; IR (KBr, cm^{-1}): 3120, 3063, 2918, 2846, 1789, 1736, 1667, 1596, 1573, 1486, 1449, 1400, 1315, 1287, 1264, 1229, 1177, 1149, 1089, 1069, 1025, 1000, 946, 929, 803, 763, 731, 709, 690, 636; HRMS (ESI) calcd for $C_{22}H_{15}NO_2$ [M+H]$^+$ 326.1176, found 326.1175.

Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (12a'):



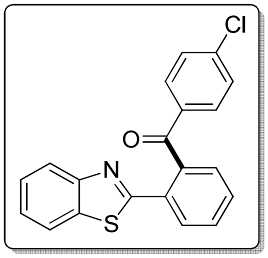
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.13 (d, 1H, *J* = 9.2 Hz), 8.01 (d, 1H, *J* = 8.0 Hz), 7.75−7.69 (m, 2H), 7.66 (d, 1H, *J* = 7.6 Hz), 7.61−7.58 (m, 1H), 7.45−7.38 (m, 7H), 7.28 (t, 2H, *J* = 9.0 Hz), 7.23 (d, 1H, *J* = 7.2 Hz), 7.16 (t, 2H, *J* = 7.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 196.5, 153.8, 153.4, 141.3, 141.0, 140.9, 138.8, 138.5, 137.1, 132.6, 131.6, 131.3, 130.3, 130.2, 130.1, 129.9, 129.8, 129.3, 129.1, 128.8, 128.3, 127.9; IR (KBr, cm^{-1}): 3052, 2922, 2851, 1789, 1736, 1658, 1597, 1572, 1475, 1446, 1393, 1342, 1315, 1291, 1269, 1218, 1059, 1025, 977, 937, 919, 761; HRMS (ESI) calcd for $C_{27}H_{18}N_2O$ [M+H]$^+$ 387.1497, found 387.1485.

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



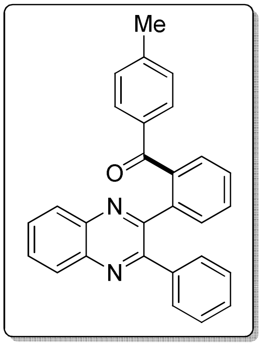
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, 1H, *J* = 7.4 Hz), 7.82–7.77 (m, 2H), 7.67 (d, 2H, *J* = 8.0 Hz), 7.63–7.56 (m, 2H), 7.49 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 7.30 (t, 1H, *J* = 7.5 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.5, 165.6, 153.7, 143.8, 140.2, 135.6, 135.4, 132.2, 130.4, 130.2, 129.9, 129.7, 129.2, 128.9, 126.3, 125.4, 123.7, 121.5, 21.8; IR (KBr, cm^{-1}): 2967, 2850, 2772, 1638, 1510, 1479, 1458, 1432, 1313, 1224, 1071, 964, 766; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ $[M+H]^+$ 330.0952, found 330.0943.

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



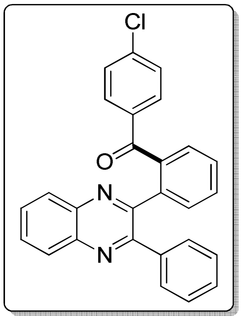
White solid; M.p. 135–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 6.8 Hz), 7.81–7.74 (m, 2H), 7.70–7.65 (m, 2H), 7.64–7.60 (m, 2H), 7.51 (d, 1H, *J* = 6.8 Hz), 7.39–7.36 (m, 1H), 7.34–7.30 (m, 1H), 7.27–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 165.2, 153.6, 139.4, 139.1, 136.5, 135.4, 132.1, 130.7, 130.6, 129.8, 128.9, 128.8, 126.5, 125.7, 123.6, 121.6; IR (KBr, cm^{-1}): 3088, 3055, 2956, 2923, 2845, 1670, 1584, 1571, 1483, 1428, 1401, 1304, 1288, 1263, 1240, 1181, 1151, 1090, 1013, 968, 936, 923, 844, 753; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ $[M+H]^+$ 350.0406, found 350.0414.

(2-(3-Phenylquinoxalin-2-yl)phenyl)(p-tolyl)methanone (12b'):



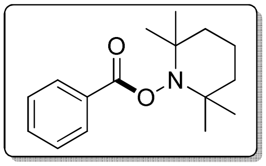
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, 1H, *J* = 7.2 Hz), 7.98 (d, 1H, *J* = 7.2 Hz), 7.72–7.66 (m, 2H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.56–7.52 (m, 1H), 7.43–7.40 (m, 4H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 1H, *J* = 5.6 Hz), 7.17–7.10 (m, 2H), 7.07 (d, 2H, *J* = 8.0 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 153.9, 153.5, 143.4, 141.4, 141.1, 140.9, 139.3, 138.6, 134.7, 131.6, 131.1, 130.4, 130.3, 130.0, 129.8, 129.4, 129.2, 128.9, 128.8, 128.3, 127.9, 21.8; IR (KBr, cm^{-1}): 3054, 2912, 2846, 1659, 1602, 1443, 1399, 1338, 1262, 1050, 1024, 927, 801, 771; HRMS (ESI) calcd for $C_{28}H_{20}N_2O$ $[M+H]^+$ 401.1654, found 401.1656.

(4-Chlorophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (12c'):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, *J* = 8.6 Hz), 8.01 (d, 1H, *J* = 8.6 Hz), 7.77–7.70 (m, 2H), 7.67 (d, 1H, *J* = 6.8 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.47–7.39 (m, 4H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 3H, *J* = 7.2 Hz), 7.17 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 153.6, 153.4, 141.5, 141.1, 140.9, 139.1, 138.5, 135.5, 131.8, 131.6, 131.5, 130.4, 130.2, 130.0, 129.9, 129.4, 129.2, 128.9, 128.6, 128.4, 128.1; IR (KBr, cm^{-1}): 3058, 2918, 2845, 1661, 1585, 1479, 1443, 1398, 1343, 1270, 1218, 1174, 1090, 1054, 977, 929, 849, 771; HRMS (ESI) calcd for $C_{27}H_{17}ClN_2O$ $[M+H]^+$ 421.1107, found 421.1112.

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



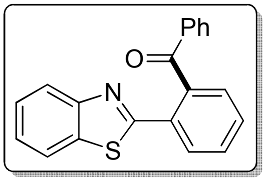
White solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03–8.06 (m, 2H), 7.54 (t, 1H, *J* = 7.8 Hz), 7.43 (t, 2H, *J* = 7.8 Hz), 1.66–1.78 (m, 3H), 1.55–1.58 (m, 2H), 1.42–1.45 (m, 1H), 1.26 (s, 6H), 1.12 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ166.6, 133.0, 129.9, 129.7, 128.6, 60.6, 39.2, 32.1, 21.0, 17.2; IR (KBr, cm^{-1}): 3007, 2973, 2940, 1741, 1641, 1452, 1365, 1253, 1238, 1083, 1062, 1026, 913, 718; HRMS (ESI) calcd for $C_{16}H_{23}NO_2$ $[M+H]^+$ 262.1807, found 262.1801.

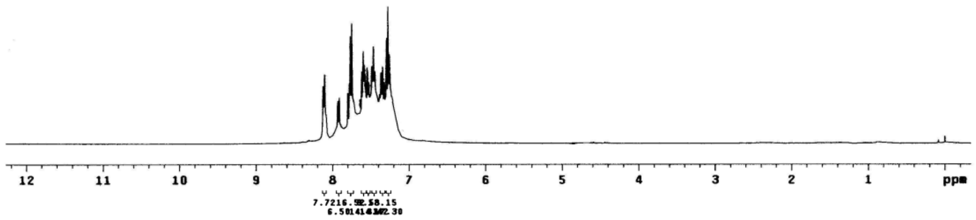
IV.7. Spectra

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a'): ^{1}H NMR (400 MHz, CDCl$_3$):

```
expl  s2pul

      SAMPLE                 SPECIAL
date   Sep 20 2013   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            -136.7
tpwr              57  wp            5046.2
pw             9.850  rfl            799.9
     DECOUPLER        rfp                0
dn               C13  rp             134.0
dof                0  lp             -95.5
dm               nnn             PLOT
dmm                c  wc               250
dpwr              50  sc                 0
dmf            15900  vs                36
                      th                20
                      nm   cdc   ph
```

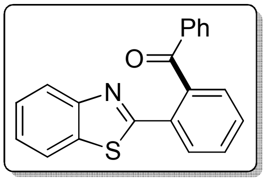


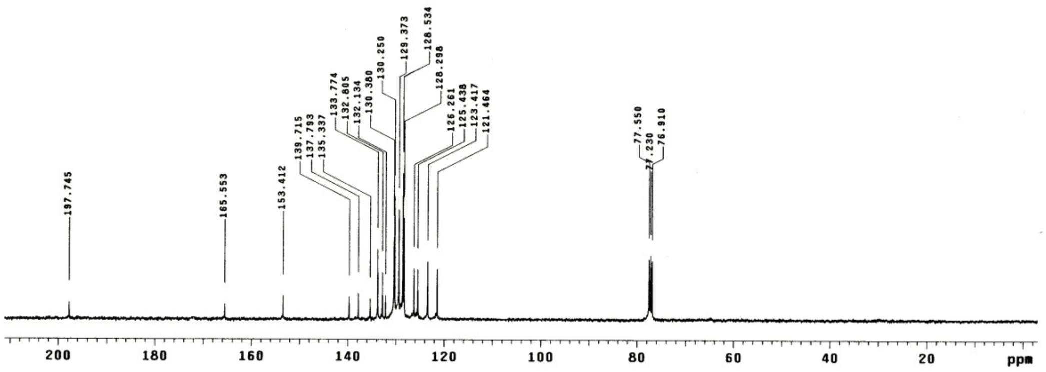


(2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1a'): ^{13}C NMR (100 MHz, CDCl$_3$):

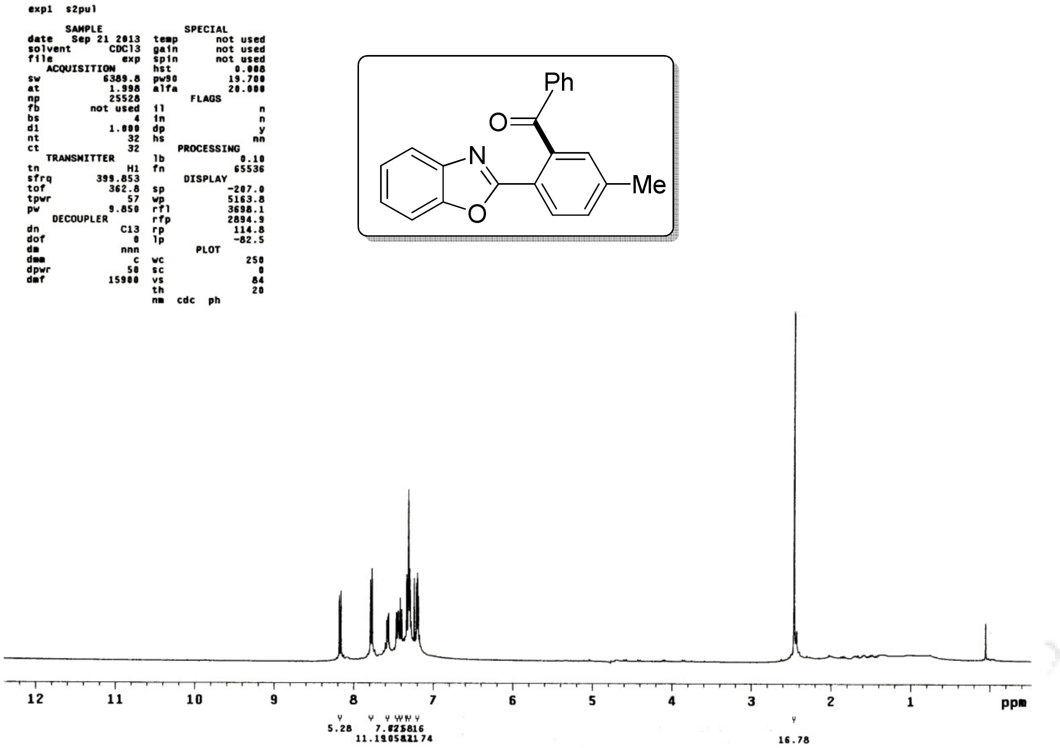
```
expl  s2pul

      SAMPLE                 SPECIAL
date   Sep 21 2013   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              3000  hs                nn
ct              1248          PROCESSING
    TRANSMITTER       lb              2.00
tn               C13  fn             65536
sfrq         100.554           DISPLAY
tof           1536.3  sp            -301.0
tpwr              61  wp           21526,3
pw             9.300  rfl           9287.4
     DECOUPLER        rfp           7764.9
dn                H1  rp             -36.0
dof                0  lp            -356.1
dm               yyy             PLOT
dmm                w  wc               250
dpwr              42  sc                 0
dmf             8900  vs                35
                      th                 2
                      nm   no   ph
```

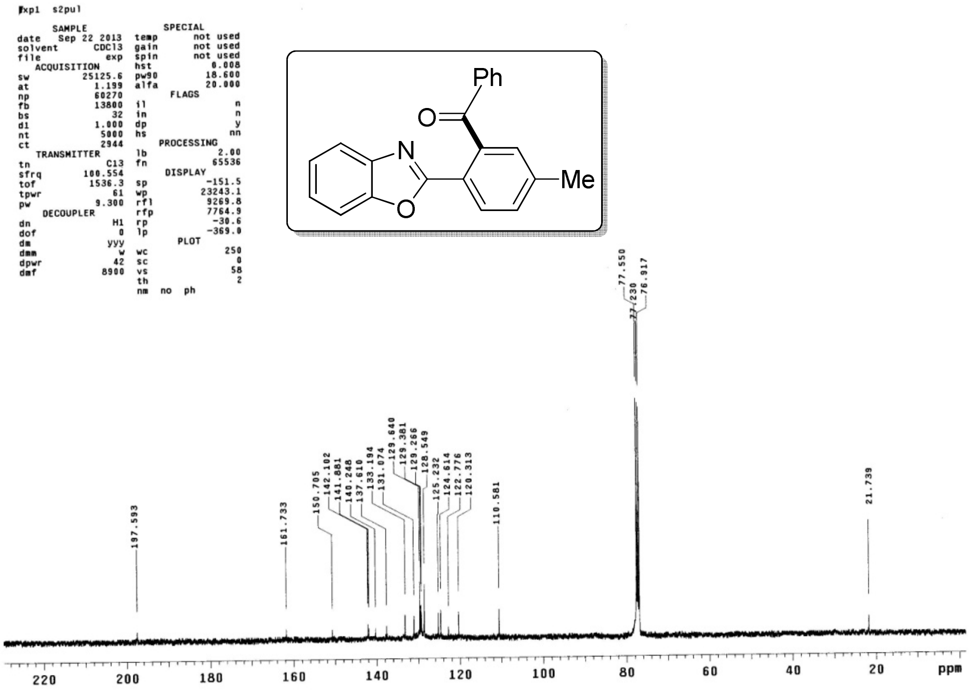




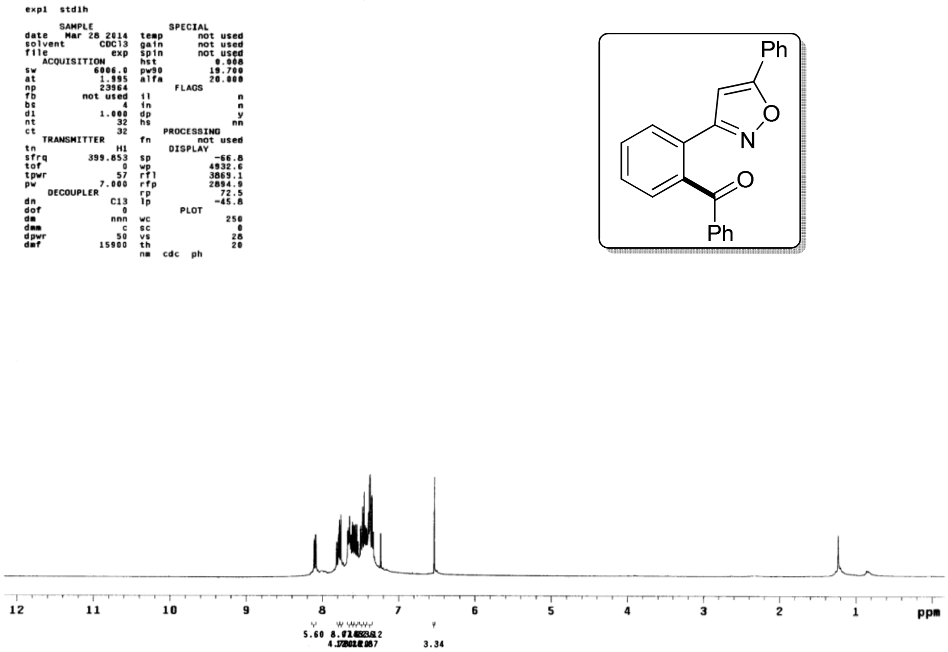
(2-(Benzo[*d*]oxazol-2-yl)-5-methylphenyl)(phenyl)methanone (10a'): ^{1}H NMR (400 MHz, CDCl$_3$):



(2-(Benzo[*d*]oxazol-2-yl)-5-methylphenyl)(phenyl)methanone (10a'): ^{13}C NMR (100 MHz, CDCl$_3$):



Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (11a'): ^{1}H NMR (400 MHz, $CDCl_3$):



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exp1  stdlh

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file           exp   spin       not used
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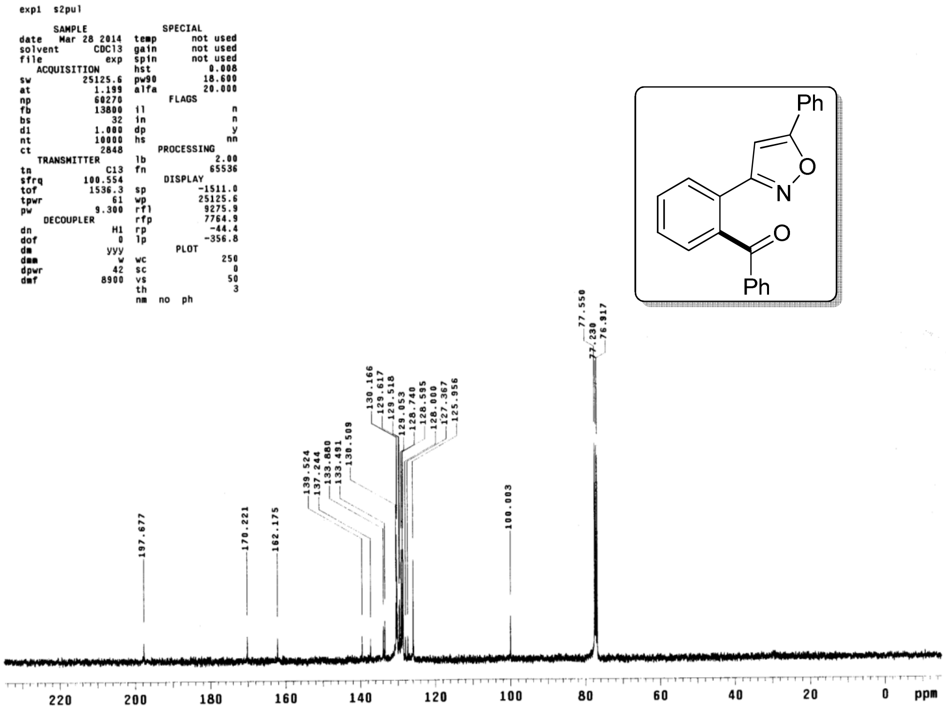
sw          6006.0   pw90         19.700
at           1.995   alfa         20.000
np           23964         FLAGS
fb        not used   il                n
bs               4   in                n
d1           1.000   dp                y
nt              32   hs               nn
ct              32       PROCESSING
   TRANSMITTER       fn         not used
tn              H1         DISPLAY
sfrq       399.853   sp            -66.8
tof              0   wp           4932.6
tpwr            57   rfl          3869.1
pw           7.000   rfp          2894.9
    DECOUPLER        rp             72.5
dn             C13   lp            -45.8
dof              0           PLOT
dm             nnn   wc              250
dmm              c   sc                0
dpwr            50   vs               28
dmf          15900   th               20
                     nm   cdc   ph
```

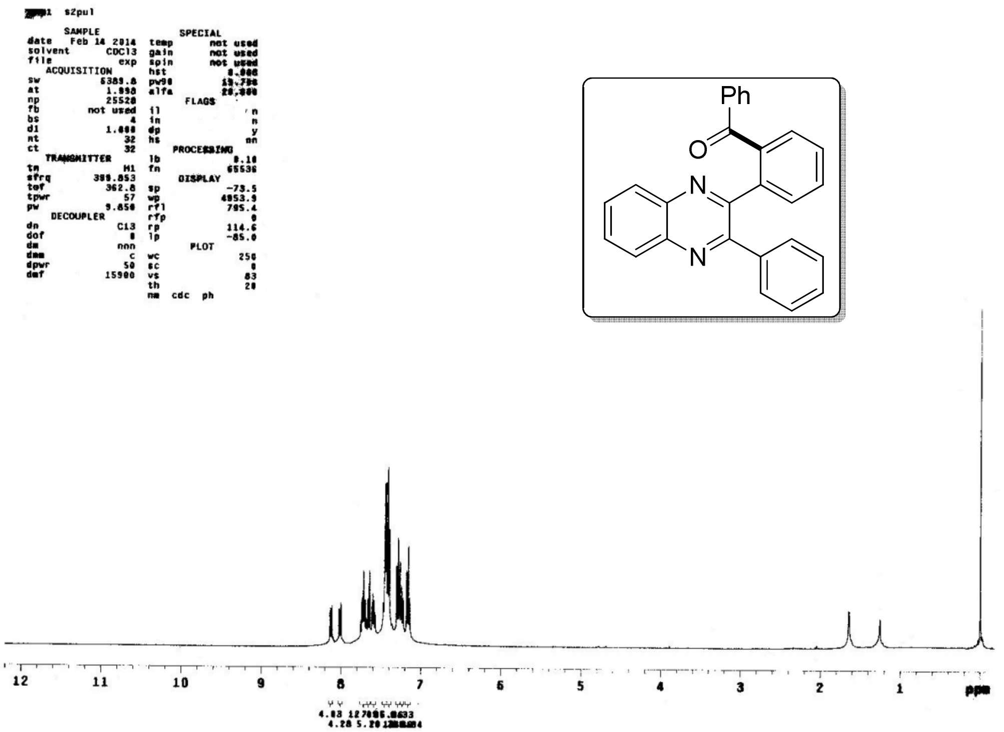
Phenyl(2-(5-phenylisoxazol-3-yl)phenyl)methanone (11a'): ^{13}C NMR (100 MHz, $CDCl_3$):



```
exp1  s2pul

      SAMPLE                 SPECIAL
date   Mar 28 2014   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           10000   hs               nn
ct            2848       PROCESSING
   TRANSMITTER       lb             2.00
tn             C13   fn            65536
sfrq       100.554         DISPLAY
tof         1536.3   sp          -1511.0
tpwr            61   wp          25125.6
pw           9.300   rfl          9275.9
    DECOUPLER        rfp          7764.9
dn              H1   rp            -44.4
dof              0   lp           -356.8
dm             yyy           PLOT
dmm              w   wc              250
dpwr            42   sc                0
dmf           8900   vs               50
                     th                3
                     nm   no   ph
```

Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (12a'): ^{1}H NMR (CDCl$_3$, 400 MHz)



```
[illegible]1  s2pul

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file            exp    spin        not used
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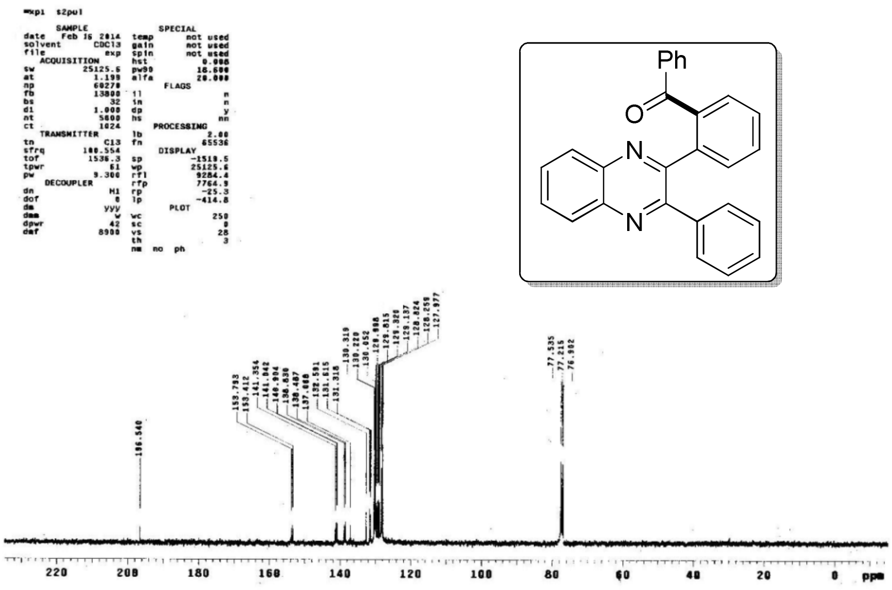
sw           5389.8    pw90          15.700
at            1.998    alfa          20.000
np            25528          FLAGS
fb         not used    il                 n
bs                4    in                 n
d1            1.000    dp                 y
nt               32    hs                nn
ct               32        PROCESSING
    TRANSMITTER        lb              0.10
tn               H1    fn             65536
sfrq        399.853          DISPLAY
tof           362.8    sp             -73.5
tpwr             57    wp            4953.9
pw            9.850    rfl            795.4
     DECOUPLER         rfp                0
dn              C13    rp             114.6
dof               0    lp             -85.0
dm              nnn             PLOT
dmm               c    wc               250
dpwr             50    sc                 0
dmf           15900    vs                83
                       th                20
                       nm   cdc   ph
```

Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (12a'): ^{13}C NMR (CDCl$_3$, 100 MHz)



```
[illegible]xp1  s2pul

       SAMPLE                  SPECIAL
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solvent       CDCl3    gain        not used
file            exp    spin        not used
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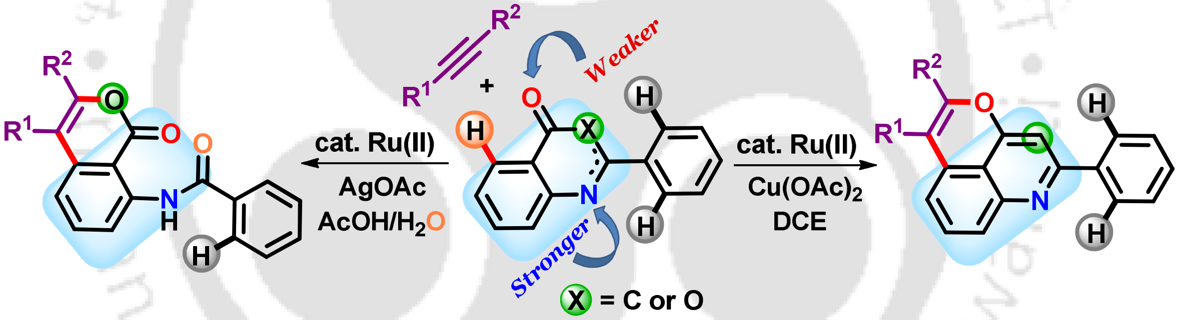
sw          25125.6    pw90          16.600
at            1.199    alfa          20.000
np            60270          FLAGS
fb            13800    il                 n
bs               32    in                 n
d1            1.000    dp                 y
nt             5600    hs                nn
ct             1024        PROCESSING
    TRANSMITTER        lb              2.00
tn              C13    fn             65536
sfrq        100.554          DISPLAY
tof          1536.3    sp           -1519.5
tpwr             61    wp           25125.6
pw            9.300    rfl           9284.4
     DECOUPLER         rfp           7764.9
dn               H1    rp             -25.3
dof               0    lp            -414.8
dm              yyy             PLOT
dmm               w    wc               250
dpwr             42    sc                 0
dmf            8900    vs                28
                       th                 3
                       nm   no   ph
```

Chapter V

Ruthenium(II) Catalyzed Regiospecific C–H / O–H Annulations of Directing Arenes via Weak Coordination



Abstract: *Ruthenium(II) catalyzed oxidative C–H / O–H annulations have been demonstrated using two different directing arenes viz. 2-arylquinolinone and 2-arylbenzoxazinone with internal alkynes. Regiospecific annulations are observed for both directing arenes via the assistance of weaker carbonyl oxygen in the presence of a stronger nitrogen-directing site. This is first such substrate-controlled convergent protocol, where the weaker directing group dictates the annulation path.*

CHAPTER V

V. Ruthenium(II) Catalyzed Regiospecific C–H / O–H Annulations of Directing Arenes *via* Weak Coordination

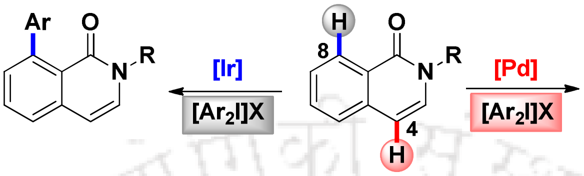
V.1. Introduction

Controlling site selective C–H activation in substrates possessing more than one types of C–H bond is an inherent and long-standing challenge in organic chemistry. One possible solution to this problem is either *via* catalyst or substrate control. Despite of having the fast-paced progress in catalytic C–H functionalizations, strategies for preferential site selectivity is limited.[1] The ability to induce site-selectivity in substrates having multiple C–H's has tremendous importance in the field of diversity oriented synthesis of complex molecules.[2] Oxidative C–H annulation is one such powerful atom and step economical strategy, applied for the synthesis of bioactive complex polycyclic molecules.[3] Site selective annulation of substrates add extra values as it enables the construction of diverse molecular scaffolds from single starting material. A vast majority of oxidative annulations have been achieved using Rh or Pd catalysts, whereas the relatively inexpensive Ru-catalysts have recently came into play as a suitable alternative.[4] Synthesis of polycyclic π-conjugated aromatics and hetero-aromatics have received considerable attention in recent times due to their potential utility as organic electronic materials.[5] Their synthesis using C–H annulations is obvious and attractive alternatives to multi-step routs. Inspired by nature approach in site selective C–H functionalizations, efforts are on designing catalysts, substrates or manipulation of ligands to provide switchable site-selective C–H functionalizations.[2f,6]

- **Catalyst controlled C–H functionalization**

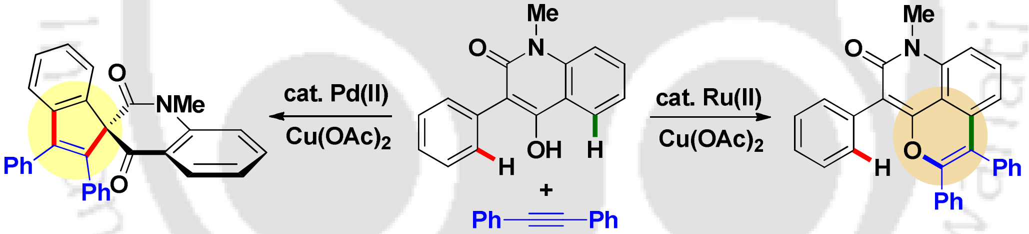
The development of catalyst control strategies capable of divergent functionalizations at distinct C–H sites is limited.[7] Gaunt group developed a first site-selective Cu(II)-catalyzed C–H bond functionalization process that selectively arylated indoles at either the C3 or C2 position.[7a,7b] Hong and co-workers recently developed a catalyst-controlled

C4/C8 site-selective C–H arylation of isoquinolones using aryliodonium salts as the coupling partners. The C4-selective arylation was successfully achieved *via* an electrophilic palladation pathway whereas C–H arylaion exclusively observed at the C8 position using Ir(III) catalyst (Scheme V.1.1).[7c]



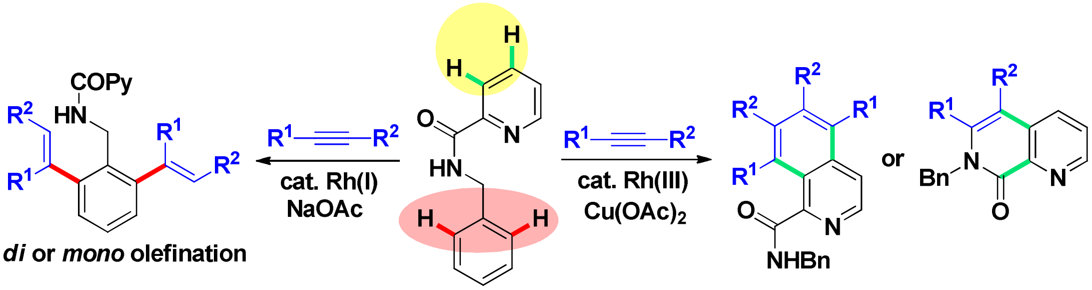
Scheme V.1.1. *Catalyst controlled C4/C8 arylation of isoquinoline*

Lam *et al.* demonstrate the divergent C–H functionalization of unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds that contain two distinct, nonadjacent sites for initial C–H functionalization, where product selectivity is achieved through a catalyst control.[7d] Using Pd–*N*-heterocyclic carbene complex as the catalyst, these substrates afforded spiroindenes exclusively through the oxidative annulation with alkynes whereas a ruthenium-based catalyst provided benzopyrans as the major products (Scheme V.1.2).



Scheme V.1.2. *Catalyst controlled divergent C–H annulations*

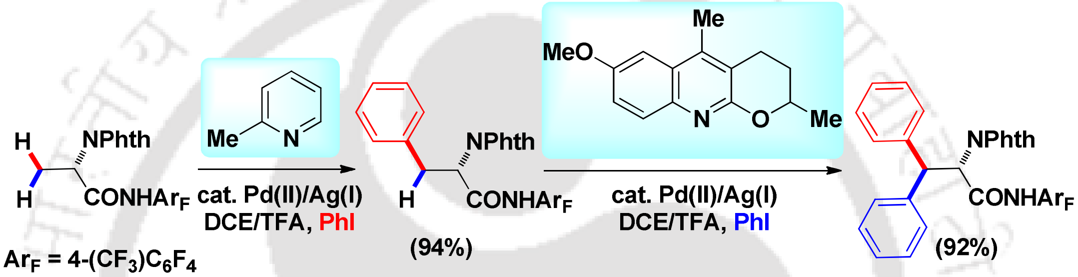
Another catalyst controlled divergent aryl/heteroaryl C–H functionalization appeared recently using aromatic picolinamide derivatives and alkynes. The use of Rh(III) catalyst provided isoquinoline unit *via* heteroaryl C–H functionalization however a Rh(I)-catalyst afforded *o*-olefinated benzylamine derivatives *via* aryl C–H cleavage (Scheme V.1.3).[7e]



Scheme V.1.3. *Catalyst controlled divergent C–H annulations of picolinamides*

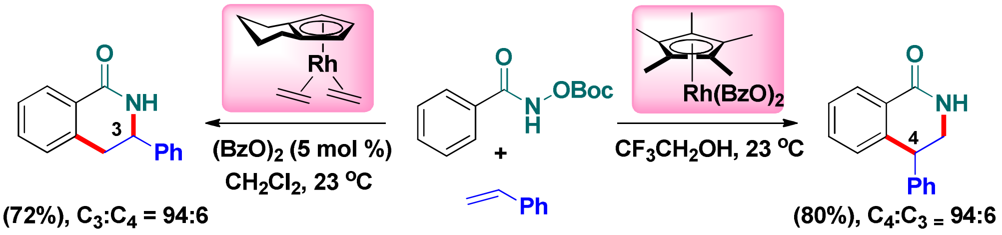
➢ Ligand controlled C–H functionalization

Manipulation of ligands is another way to tune the reactivity and selectivity of transition metal catalyzed C–H bond functionalization reactions.[6a-b] Yu group reported a unique example of ligand-controlled sp^3 C–H arylation using pyridine and quinoline derivatives as ligands. The use of pyridine ligand promotes exclusive mono arylation, whereas the latter activates the catalyst further to achieve diarylation (Scheme V.1.4).[6a] Successive application of these ligands enable the sequential diarylation of a methyl group in an alanine derivative with two different aryl iodides, affording a wide range of β-Ar-β-Ar′-α–amino acids with excellent levels of diastereoselectivity.



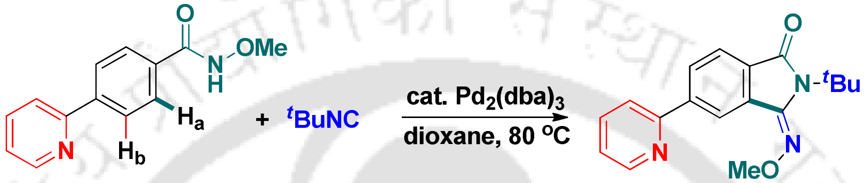
Scheme V.1.4. *Ligand controlled sequential sp^3 C–H arylation*

The power of ligand controlled C–H functionalizaion strategy was demonstrated by Cramer and co-workers for the synthesis of dihydroisoquinolone using Rh(III) catalyzed regiodivergent annulaion. Rh(III) catalysts equipped with tailored cyclopentadienyl ligands allow high catalyst control for regiodivergent pathways for C–H functionalizations of aryl hydroxamates with styrenes. While a 1,2-disubstituted cyclopentadienyl ligand–Cp^{Cy}–selectively gives 3-aryl dihydroisoquinolones, the Cp*-bearing complex selectively provides synthetically valuable 4-aryl dihydroisoquinolones. Both the steric bulk of the cyclopentadienyl group of the ligand and the Boc substituent of the built-in hydroxamate oxidant play critical and synergistic roles in the regioselectivity determining alignment of the styrene acceptor (Scheme V.1.5).[7f]



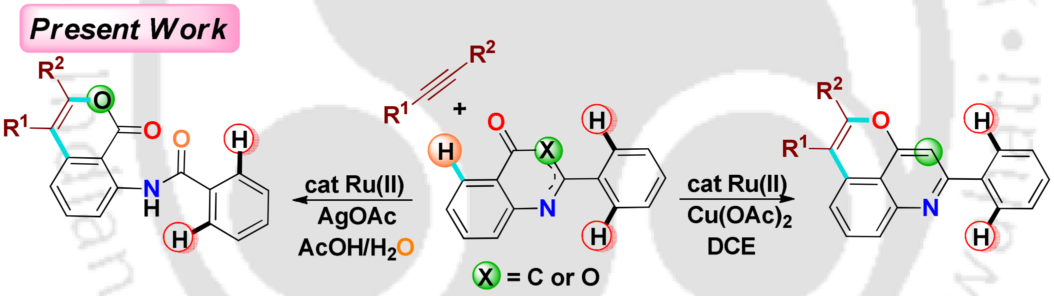
Scheme V.1.5. *Ligand controlled regiodivergent synthesis of dihydroisoquinolones*

Controlling site selective C–H activation in multi-directing systems is more complicated issue. In case of multidirecting systems the stronger directing group generally controls the C–H functionalization in presence of weak directing group. However in contrary to this, Yu *et al.* have designed a directing system where a weak directing group overrides the stronger one and controls the C–H activation (Scheme V.1.6).[8a] Similar weak directing group assisted C–H annulation reactions are also reported by Ackermann and Jeganmohan groups.[8b-e]



Scheme V.1.6. *Substrate control C–H functionalization via weak co-ordination*

Herein, we report a first oxygen-directed C–H annulation in the presence of a strong nitrogen-directing group in two directing substrates (Scheme V.1.7).



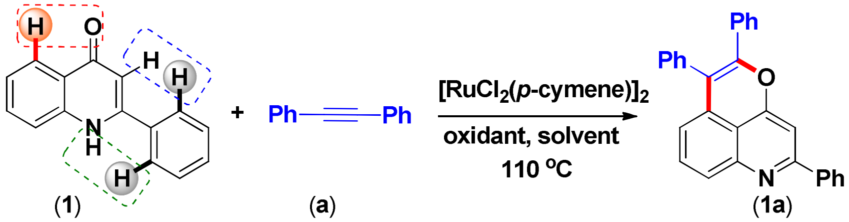
Scheme V.1.7. *Substrate control C–H annulations via weak co-ordination*

V.2. Present Work

Although a few catalyst and ligand-controlled divergent C–H functionalizations at distinct C–H sites are reported in recent times, substrate-controlled selectivity in C–H functionalizations through the cleavage of similar C–H bonds in analogous directing arenes is unfamiliar so far. There is only single precedence by Yu *et al.* where the weaker directing group dictates the C–H activation in presence of a stronger directing group[8a], there is no other report of this kind. Herein, we report a first weaker oxygen-directed C–H annulation in presence of a stronger nitrogen-directing group in 2-arylquinolinones and 2-arylbenoxazinones *via* substrate-control C–H functionalization.

Optimization of reaction conditions. Our initial investigation started with the evaluation of reaction conditions for oxidative annulation of 2-phenylquinolinone (**1**) with diphenyl acetylene (**a**). 2-Arylquinolinone was chosen as the model substrate as this core represents a highly privileged, biologically important molecular scaffold[9] which has several possible C–H's (*via* C–H / N–H, C–H / C–H and C–H / O–H bonds) for oxidative annulations with an alkyne. In an initial reaction 2-phenylquinolinone (**1**) was treated with diphenylacetylene (**a**) in the presence of a well explored $[RuCl_2(p\text{-cymene})]_2$ (2 mol %) catalyst,[4] $Cu(OAc)_2$ (1.0 equiv) as the terminal oxidant and Cs_2CO_3 (1 equiv) as the base in toluene (2 mL). A new product was isolated by column chromatography, spectroscopic (^1H and ^{13}C NMR) analysis of the product (**1a**) revealed the presence of two extra phenyl moieties and the absence of singlets for –NH and C-3 protons. This confirms the aromatization of 2-arylquinolinone to 2-aryl-4-hydroxyquinoline along with the addition of a diphenyl acetylene moiety *via* C–H / O–H annulation. However, this unprecedented annulated product was obtained in a low yield of 37% (Table V.2.1, entry 1). Since the tautomerization of quinone to its corresponding phenol is favourable, 2-arylquinolinone acts as a "masked" phenolic substrate to trigger the C–H / O–H annulation over other possible (*via* C–H / N–H and C–H / C–H) annulation paths (Scheme in Table V.2.1). Switching the solvent from toluene to chlorobenzene (PhCl) under identical reaction conditions provided the annulated product (**1a**) in an improved yield of 60% (Table V.2.1, entry 2). Among other solvents such as DMF, NMP, DMSO and DCE tested (Table V.2.1, entries 3-6), later provided the best yield (70%) (Table V.2.1, entry 6). Further, by varying the oxidant from $Cu(OAc)_2$ to $Cu(OAc)_2 \cdot H_2O$, AgOAc, $AgCO_3$ and $AgSbF_6$ under identical conditions to that of entry 6, did not improve the yield of product (**1a**) (Table V.2.1, entries 7-10). Later, it was found that the use of Cs_2CO_3 was redundant as the yield remained unaltered (68%) (Table V.2.1, entry 11) even when the reaction was performed in its absence. Reaction when carried out without co-oxidant $[Cu(OAc)_2]$ under otherwise identical conditions (to that of entry 11) provided the annulated product (**1a**) in low yield (25%) (Table V.2.1, entry 12). No annulated product was formed in the absence of Ru(II) catalyst (Table V.2.1, entry 13).

Table V.2.1. *Optimization of reaction conditions*

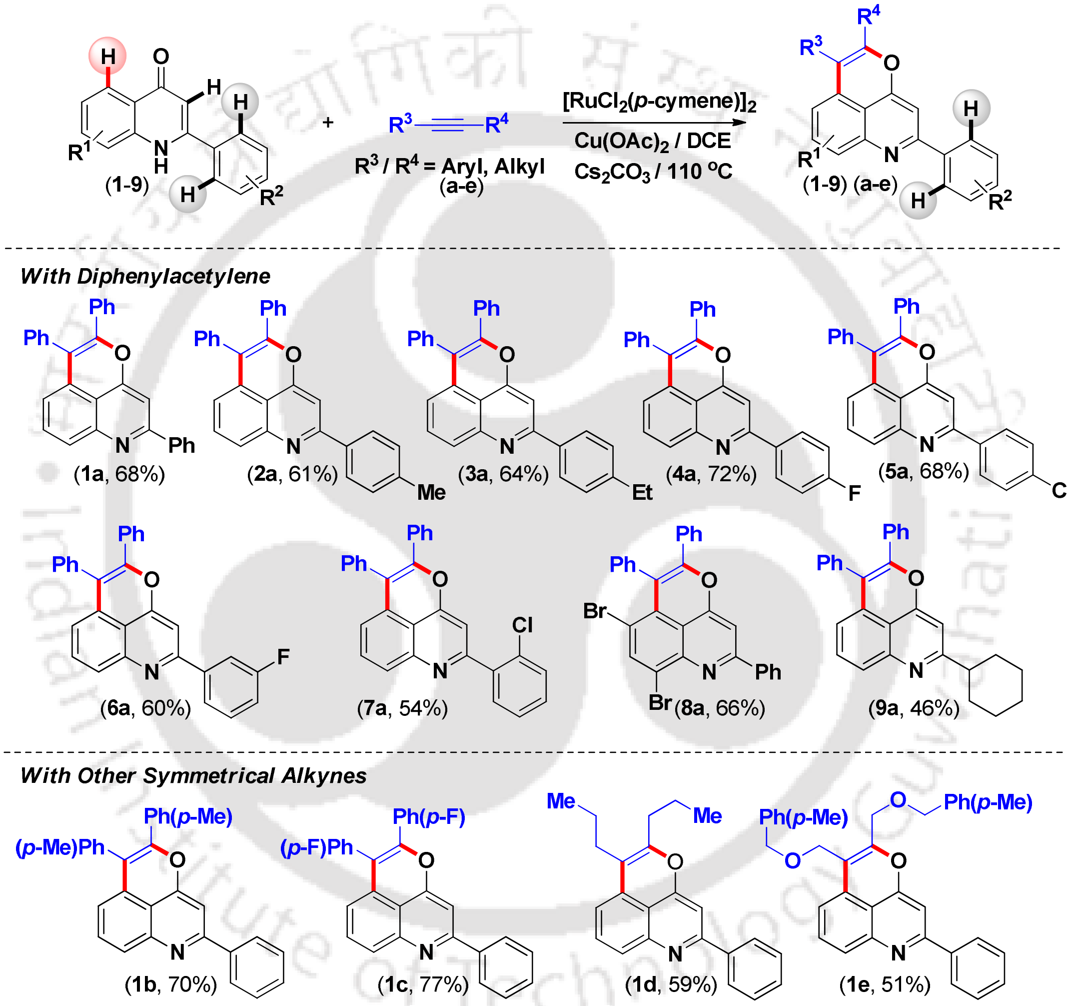


Entry	Oxidant (equiv)	Base	Solvent	Yield (%)^{a,}
1	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	PhMe	37
2	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	PhCl	60
3	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	DMF	52
4	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	NMP	40
5	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	DMSO	21
6	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	DCE	70
7	Cu(OAc)$_2$·H$_2$O (1)	Cs$_2$CO$_3$ (1)	DCE	55
8	AgOAc (1)	Cs$_2$CO$_3$ (1)	DCE	62
9	AgCO$_3$ (1)	Cs$_2$CO$_3$ (1)	DCE	21
10	AgSbF$_6$ (1)	Cs$_2$CO$_3$ (1)	DCE	64
11	**Cu(OAc)$_2$ (1)**	-	**DCE**	**68**
12	-	Cs$_2$CO$_3$ (1)	DCE	25
13	Cu(OAc)$_2$ (1)	Cs$_2$CO$_3$ (1)	DCE	00

^{a}Reaction conditions: (**1**) (0.50 mmol), diphenylacetylene (**a**) (0.60 mmol), [RuCl$_2$ (*p*-cymene)]$_2$ (2 mol %), in DCE (2.0 mL) at 110 °C for 12 h. ^{b}Isolated yield.

After establishing the optimized reaction condition for annulation (Table V.2.1, entry 11), we started to explore the coupling between various 2-arylquinolinone (**1**-**9**) with symmetrical internal alkynes (**a**-**e**). 2-Aryl ring of quinolinone bearing electron-donating as well as electron-withdrawing substituents were all compatible providing their desired annulated products in moderate yields (Scheme V.2.1). 2-Arylquinolinone containing electron-donating substituents such as *p*-Me (**2**), *p*-Et (**3**) in the 2-aryl ring provided their expected annulated products (**2a**) and (**3a**) in moderate yields (Scheme V.2.1). Electron-withdrawing substituents such as *p*-F (**4**), *p*-Cl (**5**), *m*-F (**6**) and *o*-Cl (**7**) present in the 2-aryl ring of 2-arylquinolinone also underwent annulations giving their corresponding products (**4a**), (**5a**), (**6a**) and (**7a**) respectively in decent yields (Scheme V.2.1). The structure of the annulated product (**5a**) has been further confirmed by X-ray crystallographic analysis as shown in Figure V.2.1. For directed C–H functionalization, C–H metallation generally occurs at the less sterically hindered C–H site of phenyl rings having the *meta*-substituent. However, in 6,8 di-bromo substituted quinolinone (**8**) the annulation took place smoothly even at the sterically hindered site of quinolinone ring, giving 66% yield of (**8a**) along with retaintion of both the bromo functionality. This observation suggests the preferential C–H / O–H annulation over other C–H / N–H and C–H / C–H annulation paths. This protocol is equally compatible with 2-cyclohexyl substituted quinolinone (**9**) providing (**9a**) in a relatively low yield (46%).

Scheme V.2.1. *Annulation of 2-arylquinolinones with internal alkynes*[a,b]



[a]Reaction conditions: (**1-9**) (0.50 mmol), (**a-e**) (0.60 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (2 mol %), Cu(OAc)$_2$ (0.50 mmol), in DCE (2.0 mL) at 110 °C for 12 h. [b]Isolated yield.

To evaluate the scope and generality of this annulation strategy, other symmetrical alkynes (**b-e**) were investigated using 2-phenylquinoloinone (**1**) as the coupling partner (Scheme V.2.1). Symmetrical 1,2-diarylacetylene possessing electron-donating *p*-Me substituent (**b**) when coupled with (**1**) provided the product (**1b**) in good yield (70%) (Scheme V.2.1). Symmetrical 1,2-diarylacetylene having electron-withdrawing *p*-F substituents (**c**) when reacted with (**1**) provided an improved yield (77%) of the annulated product (**1c**). Aliphatic internal alkynes *viz.* 4-octyne (**d**) and 1,4-*bis*((4-methylbenzyl)oxy)but-2-yne (**e**) when treated with (**1**) afforded their annulated products (**1d**) and (**1e**) in 59% and 51% yields respectively

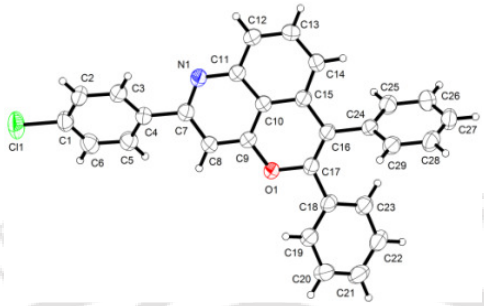
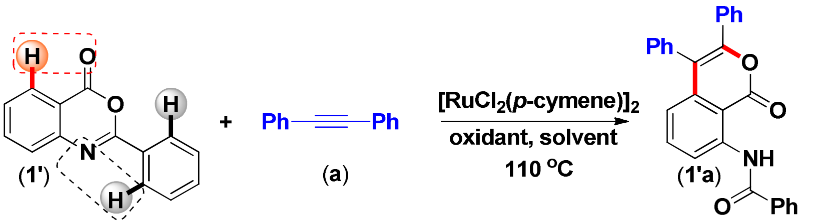


Fig. V.2.1. *Ortep view of compound* (***5a***)

After the successful C–H/O–H annulation of 2-arylquinolinone (**1**) directed *via* its weaker carbonyl oxygen in the presence of stronger nitrogen (*N*) directing group, we looked for analogous systems. With this in mind, 2-phenylbenzoxazinone (**1'**) was selected as it is structurally analogous to 2-phenylquinolinone (**1**) except its C3 carbon is replaced with an oxygen atom. 2-Phenylbenzoxazinone (**1'**) having two different directing sites *viz.* nitrogen (*N*1) and carbonyl oxygen atoms both of which can potentially direct the oxidative annulations. The objective was to see whether the stronger nitrogen directs the anuulation or here as well, the weaker oxygen dictates the annulation as was observed in 2-phenylquinolinone (**1**). To verify this, coupling of 2-phenylbenzoxazinone (**1'**) and diphenylacetylene (**a**) was carried out under identical conditions to that of coupling between (**1**) and (**a**) (Table V.2.2, enrty 1). A product was isolated by column chromatography, spectroscopic (^{1}H and ^{13}C NMR) analysis revealed its structure to be *N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (**1'a**). The amidic group in (**1'a**) might have originated by the hydrolytic cleavage of one of the C–O bonds in 2-phenylbenzoxazinone (**1'**). Therefore, hydrated $Cu(OAc)_2 \cdot H_2O$ was used in lieu of anhydrous $Cu(OAc)_2$ which gave a slight improvement in the yield (17%) (Table V.2.2, entry 2). Among various other solvents such as PhCl (38%), DMSO (00%), DMF (00%), NMP (00%), ^{t}BuOH (14%) and AcOH (50%) tested (Table V.2.2, entries 3-8), the later was found to be superior (Table V.2.2, entry 8). Co-oxidant AgOAc was found to be ideal giving 78% yield compared to other co-oxidants such as $Cu(OAc)_2$ (44%), $AgSbF_6$ (62%), $AgCO_3$ (56%) and Ag_2O (41%) screened (Table V.2.2, entries 9-13).

Table V.2.2. *Optimization of reaction conditions*

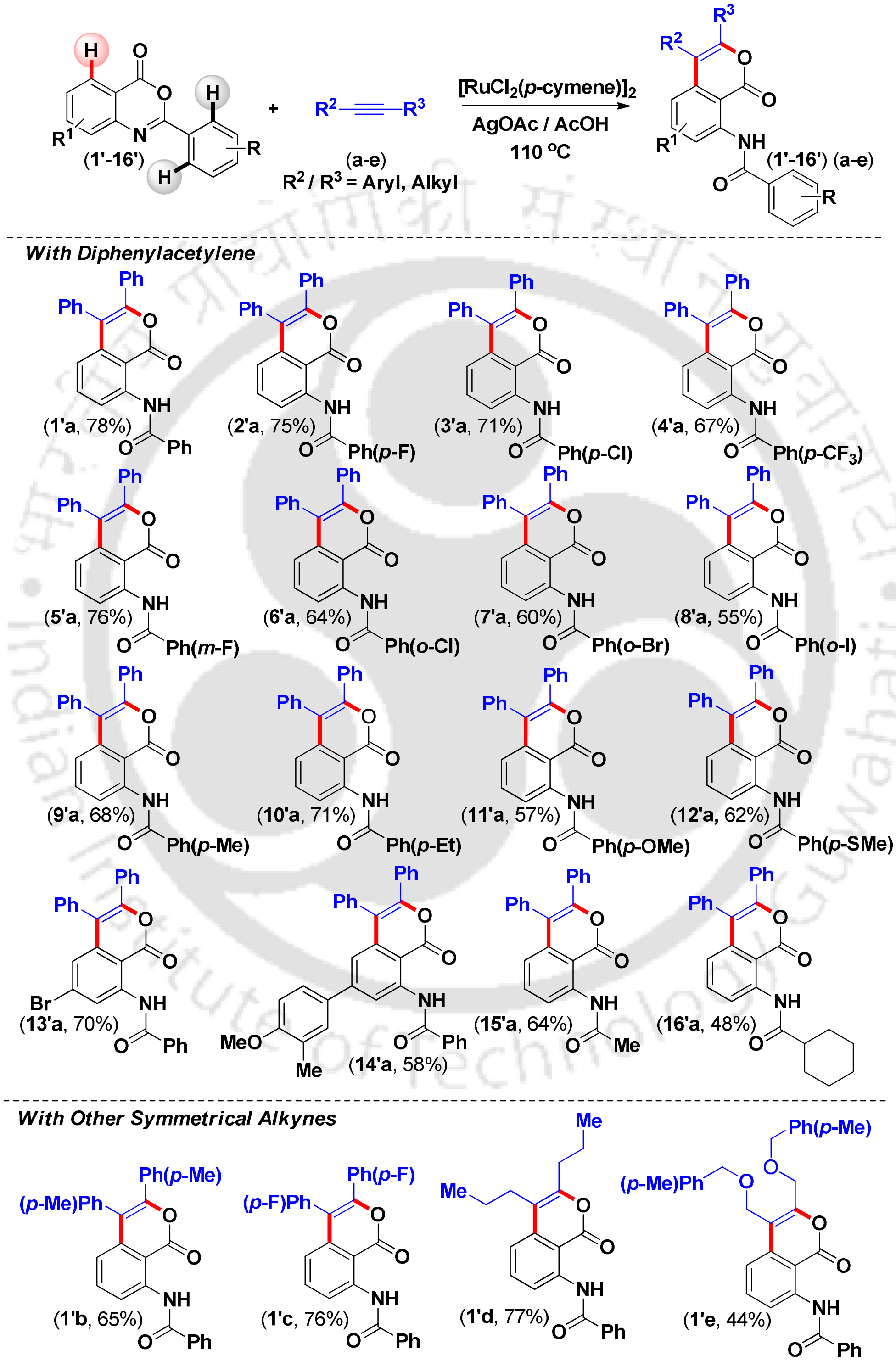


Entry	Oxidant (equiv)	Solvent	Yield (%)^{a,b}
1	$Cu(OAc)_2$ (1)	DCE	11
2	$Cu(OAc)_2 \cdot H_2O$(1)	DCE	17
3	$Cu(OAc)_2 \cdot H_2O$(1)	PhCl	38
4	$Cu(OAc)_2 \cdot H_2O$(1)	DMSO	00
5	$Cu(OAc)_2 \cdot H_2O$(1)	DMF	00
6	$Cu(OAc)_2 \cdot H_2O$(1)	NMP	00
7	$Cu(OAc)_2 \cdot H_2O$(1)	^{t}BuOH	14
8	$Cu(OAc)_2 \cdot H_2O$(1)	AcOH	50
9	$Cu(OAc)_2$ (1)	AcOH	44
10	**AgOAc (1)**	**AcOH**	**78**
11	$AgSbF_6$ (1)	AcOH	62
12	$AgCO_3$ (1)	AcOH	56
13	Ag_2O (1)	AcOH	41

^{a}Reaction conditions: (**1'**) (0.50 mmol), diphenylacetylene (**a**) (0.60 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mol %), in AcOH (2.0 mL) at 110 °C for 12 h. ^{b}Isolated yield.

After establishing the optimized condition for yet another C–H / O–H annulation directed by weaker carbonyl oxygen, we then implemented this strategy for various 2-arylbenzoxazinones (**1'-16'**) and symmetrical internal alkynes (**a-e**). 2-Arylbenzoxazinone containing electron-withdrawing as well as electron-donating substituents present in the 2-aryl ring all coupled efficiently with diphenylacetylene (**a**) providing their respective annulated products in moderate yields (Scheme V.2.2). Irrespective of their positions, the presence of electron-withdrawing substituents in the 2-aryl ring of 2-arylbenzoxazinones such as *p*-F (**2'**), *p*-Cl (**3'**), *p*-CF_3 (**4'**), *m*-F (**5'**), *o*-Cl (**6'**), *o*-Br (**7'**) and *o*-I (**8'**) all provided their annulated products (**2'a**), (**3'a**), (**4'a**), (**5'a**), (**6'a**), (**7'a**) and (**8'a**) respectively in decent yields (Scheme V.2.2). The presence of moderately electron-donating *p*-Me (**9'**), *p*-Et (**10'**) and strongly electron-donating *p*-OMe (**11'**), *p*-SMe (**12'**) substituents in the 2-aryl ring of benzoxazinone all afforded moderate yields of their annulated products (**9'a**), (**10'a**), (**11'a**) and (**12'a**) respectively (Scheme V.2.2). Electron-withdrawing Br substituent presents at the C7 position of benzoxazinone provided the annulated product (**13'a**) in a good yield (70%).

Scheme V.2.2. *Annulation of 2-arylbenoxazinones with alkynes*[a,b]



[a]Reaction conditions: (**1'-16′**) (0.50 mmol), (**a-e**) (0.60 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (2 mol %), AgOAc (1 equiv), in AcOH (2.0 mL) at 110 °C for 12 h. [b]Isolated yield.

Further, the presence of an extra aryl ring at C7 of benzoxazinone afforded the annulated product (**14'a**) in moderate yield (58%). The presence of methyl and cyclohexyl substituents at the C2 position of benzoxazinone yielded annulated products (**15'a**) and (**16'a**) in 64% and 48% yields respectively. The scope of other symmetrical alkynes was then tested using 2-phenylbenzoxazinone (**1'**) as the coupling partner (Scheme V.2.2). Symmetrical 1,2-diarylalkynes having electron-donating–Me (**b**) and electron-withdrawing–F (**c**) substituents present at their 4 position when reacted with (**1'**) provided their annulated products (**1′b**) and (**1′c**) in good yields (Scheme V.2.2). Aliphatic internal alkynes such as 4-octyne (**d**) and 1,4-*bis*((4-methylbenzyl)oxy)but-2-yne (**e**) when treated with (**1'**) afforded their annulated products (**1'd**) and (**1'e**) respectively in 77% and 44% yields.

Mechanistic Studies. To check the regioselectivity in both these annulations, an unsymmetrical alkyne 1-phenyl-1-propyne (**f**) was reacted separately with 2-phenylquinolinone (**1**) and 2-phenylbenzoxazinone (**1'**) under their respective optimized reaction conditions [(Table V.2.1, entry 11) and (Table V.2.2, entry 10)]. Both these directing substrates (**1**) and (**1'**) provided single regioisomer (**1f**) and (**1'f**) (Scheme V.2.3). The structure of compound (**1'f**) was further confirmed by X-ray crystallographic analysis as shown in Figure V.2.2.

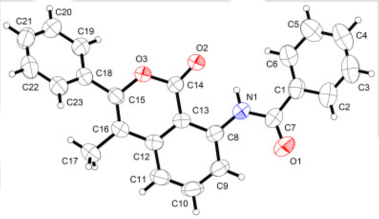
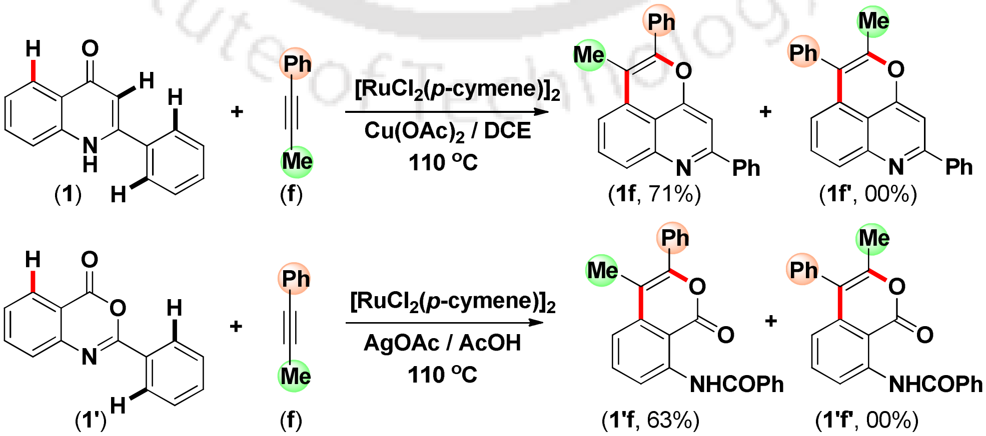
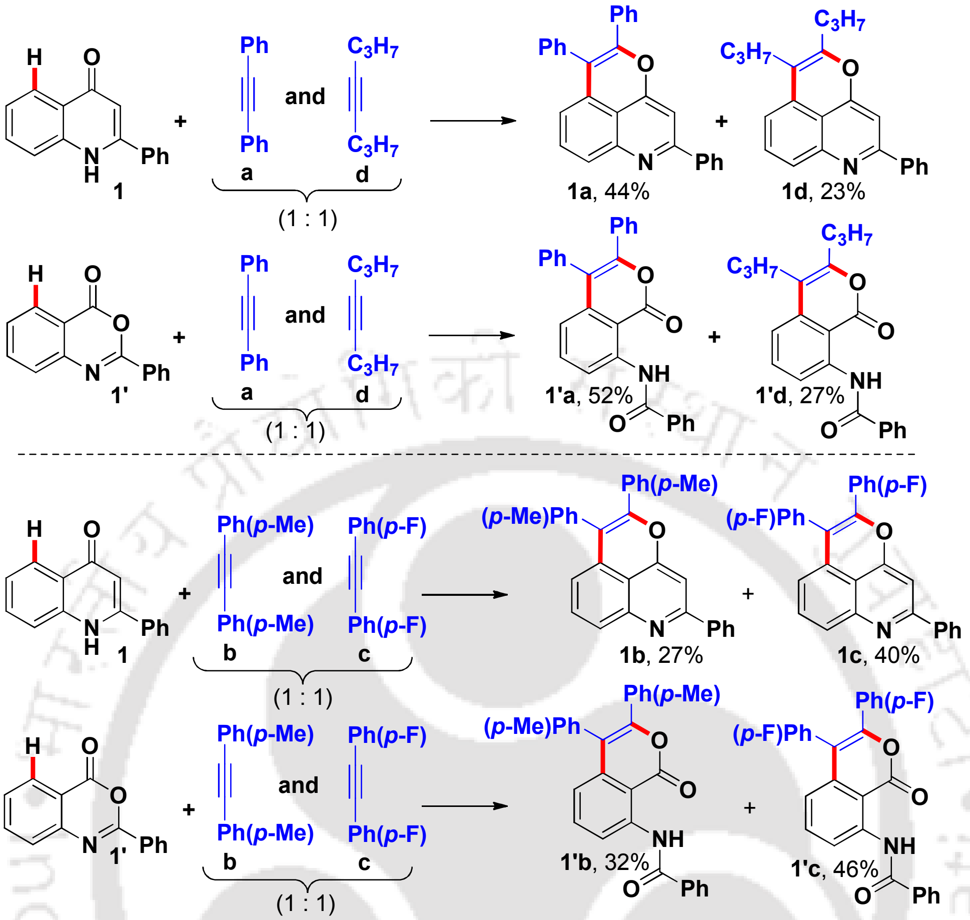


Fig. V.2.2. *Ortep view of compound (1'f)*

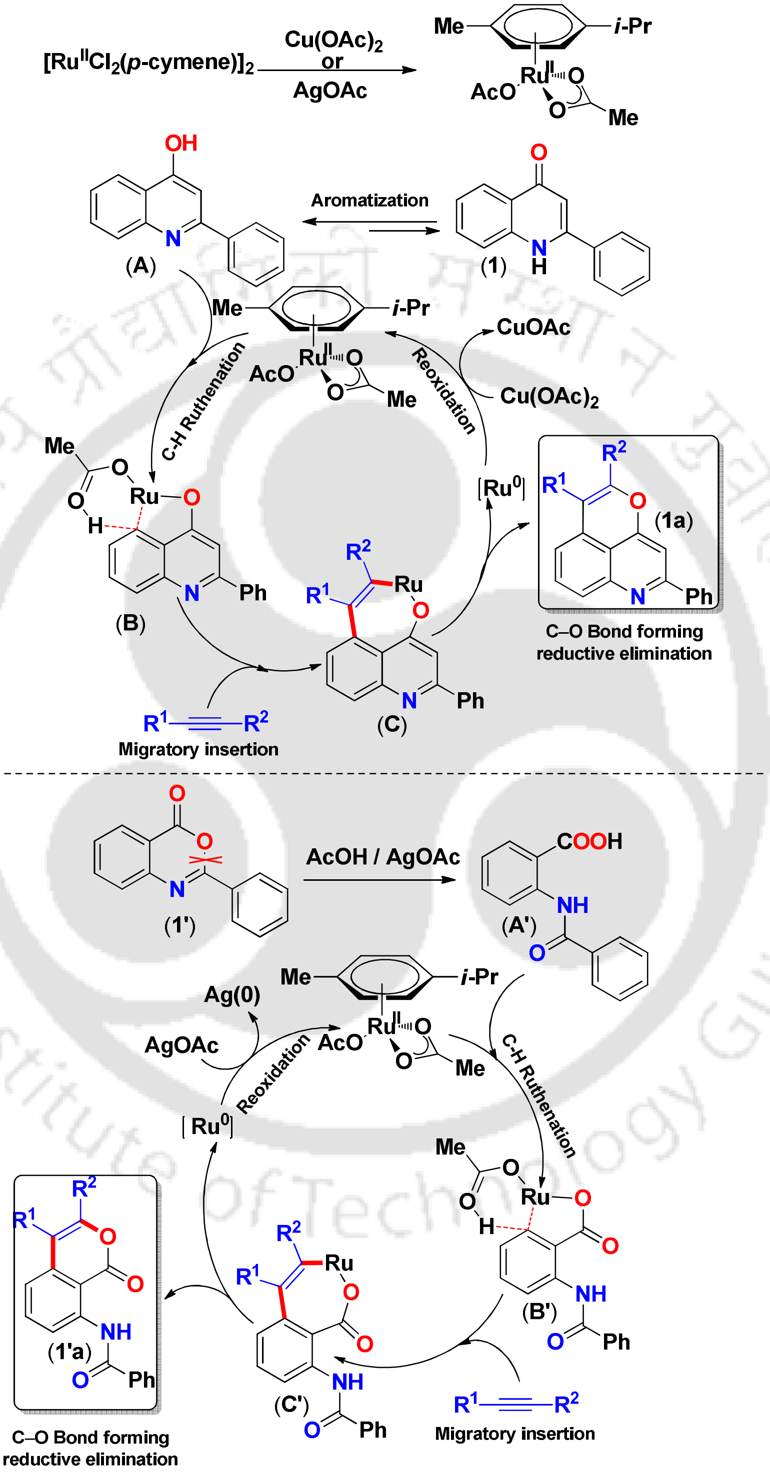


Scheme V.2.3. *Regioselectivity evaluation*



Scheme V.2.4. *Competitive experiments*

To check whether the electron-deficient diphenylacetylene (**a**) or the electron-rich 4-octyne (**d**) undergoes preferential annulation, intermolecular competitive reactions were performed. Directing substrates 2-phenylquinolinone (**1**) and 2-phenylbenzoxazinone (**1'**) were reacted separately in the presence of an equimolar mixture (1:1) of (**a**) and (**d**) under their respective optimized conditions. In both these cases annulated products originating from the electron-deficient alkyne (**a**) were obtained in higher proportions [(**1a**, 44%), (**1'a**, 52%)] than products [(**1d**, 23%), (**1'd**, 27%)] derived from electron-rich (**d**) counterpart (Scheme V.2.4). Thus, in both these annulations electron defficient alkynes are better annulating partners. This has been reconfirmed in yet another set of competitive experiments where an equimolar mixture of electron-deficient 1,2-di(*p*-fluorophenyl)ethyne (**c**) and electron-rich 1,2-di-*p*-tolylethyne (**b**) were reacted separately with (**1**) and (**1'**). Here again, electron-deficient alkyne (**c**) annulated preferentially giving higher yields of products [(**1c**, 40%), (**1'c**, 46%)] than annulated products derived from electron-rich alkyne (**b**) [(**1b**, 27%). (**1'b**, 32%)] (Scheme V.2.4).



Scheme V.2.5. *Plausible mechanisms for annulations*

Based on experiments performed (Scheme V.2.3 and V.2.4) and earlier reports, plausible mechanisms are depicted for these annulations (Scheme V.2.5). In both these cases the reactions are initiated *via* the displacement of chloride ligand of [RuCl$_2$(*p*-cymene)]$_2$ with acetate anion either from AgOAc or Cu(OAc)$_2$. Under the reaction conditions 2-phenylquinolinone (**1**) aromatizes to 4-hydroxy-2-phenylquinoline (**A**). In the next step, a five-membered ruthenacycle intermediate (**B**) is generated from (**A**) (Scheme V.2.5). Migratory insertion of alkyne into the Ru-carbon bond of intermediate (**B**) afforded the intermediate (**C**). For unsymmetrical alkynes the Ru-carbon bond will be favourable at the alkyne carbon having higher electron density thus accounting for the regioselectivity in Scheme V.2.3. Finally, reductive elimination provided expected annulated product (**1a**) along with the generation of catalyst Ru(0) (Scheme V.2.5). This Ru(0) is oxidized to active Ru(II) catalyst in the presence of oxidant Cu(OAc)$_2$ or by areal oxidation.[4j] Directing substrate 2-phenylbenzoxazinone (**1′**) undergoes initial hydrolytic cleavage under the reaction conditions to give *N*-benzoylanthranilic acid (**A′**). To confirm this when substrate (**1'**) was subjected to the reaction conditions but in the absence of diphenylaetylene (**a**), gave *N*-benzoylanthranilic acid (**A′**) as the exclusive product. Further, *N*-benzoylanthranilic acid (**A′**) when treated with diphenylaetylene (**a**) under the exact reaction condition (Table V.2.2, entry 10) provided product (**1′a**) but in a lower yield (28%). Lower yield of product (**1′a**) obtained using (**A′**) may be due to the chelation of cat. Ru(II) with large excess of (**A′**).[10] In the next step, the *in-situ* generated (**A′**) forms a five-membered ruthenacycle intermediates (**B′**) *via* weak oxygen directed selective metallation (Scheme V.2.5). Migratory insertion of alkyne into the Ru-carbon bond of intermediate (**B′**) generates the intermediate (**C′**). Reductive elimination in the next step provided annulated product (**1'a**) along with the generation of Ru(0) (Scheme V.2.5) which is oxidized further to Ru(II).

In conclusion weaker oxygen directed regiospecific annulations have been developed for directing arenes *viz.* 2-arylquinolinone and 2-arylbenzoxazinone in the presence of stronger nitrogen-directing group. This is a unique demonstration of directing group controlled annulation in multi-directing systems.

V.3. Experimental Section

V.3.1. General Information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 and 600 MHz), $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. 2-arylquinolinones (**1**-**9**) are prepared from corresponding *N*-(2-acetylphenyl)benzamides in presence of KO^tBu using the following the procedure.[11] 2-Arylbenzoxazinones (**1'**-**16'**) are prepared from the oxidative cyclization of *N*-aroylanthranilic acid using acetic anhydride under reflux condition.[12]

V.3.2. (A) General procedure for the synthesis of 2,5,6 triphenylpyrano[2,3,4-*de*]quinoline (1a) from 2-phenylquinolin-4(1*H*)-one (1) and diphenylacetylene (a): To an oven-dried 10 mL round bottom flask fitted with a reflux condenser were added 2-phenylquinolin-4(1*H*)-one (**1**) (0.110 g, 0.50 mmol), diphenylacetylene (**a**) (0.107 g, 0.60 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.006 g, 2 mol %), $Cu(OAc)_2$ (0.090 g, 0.50 mmol), and DCE (2.0 mL). The reaction mixture was refluxed in an oil bath preheated to 110 °C. After completion of the reaction (12 h), solvent was evaporated under reduced pressure. Reaction mixture was then cooled and admixed with water (2 mL). The product was extracted with ethyl acetate (2 x 10 mL), organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), and evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 10:0.5) to give pure 2,5,6 triphenylpyrano[2,3,4-*de*]quinoline (**1a**) (0.135 g, yield 68%). The identity and purity of the product was further confirmed by spectroscopic analysis. The same procedure was also followed for *o*-annulation of other substituted quinolinones (**2**-**9**) with (**a**-**f**).

(B) General procedure for the synthesis of *N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (1'a) from 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (1') and diphenylacetylene (a): To an oven-dried 10 mL round bottom flask fitted with a reflux condenser were added 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1'**) (0.111 g, 0.50 mmol), diphenylacetylene (**a**) (0.107 g, 0.60 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.006 g, 2 mol %), AgOAc (0.083 g, 0.50 mmol), and AcOH (2.0 mL). The reaction mixture was refluxed in an oil bath preheated at 110 °C. After completion of the reaction (12 h) solvent was evaporated under a reduced pressure. Reaction mixture was then cooled and admixed with water (2 mL). The product was extracted with ethyl acetate (2 x 10 mL) and the resultant organic layer was washed with saturated $NaHCO_3$ solution (1 x 2 mL). Ethyl acetate layer was dried over anhydrous sodium sulphate (Na_2SO_4), and evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 10:0.5) to give pure *N*-(1-oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (**1'a**) (0.162 g, yield 78%). The identity and purity of the product was further confirmed by spectroscopic analysis. The same procedure was also followed for *o*-annulation of other substituted benzoxazinones (**2'**-**16'**) with (**a**-**f**).

V.4. References

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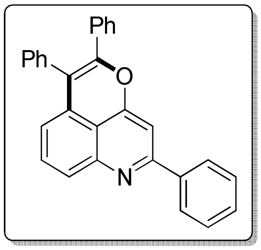
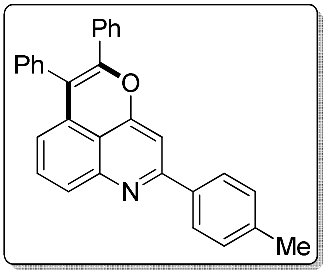
V.5. Spectral Data

2,5,6-Triphenylpyrano[2,3,4-*de*]quinoline (1a):



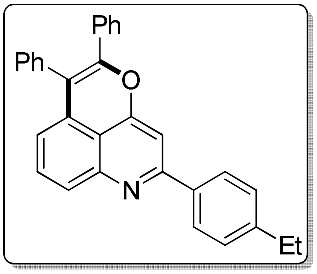
Solid; M.p. 170–174 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 8.10 (d, 2H, *J* = 7.2 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 7.54–7.49 (m, 3H), 7.47–7.44 (m, 2H), 7.40 (t, 2H, *J* = 7.2 Hz), 7.37–7.35 (m, 1H), 7.32 (d, 2H, *J* = 7.2 Hz), 7.29–7.20 (m, 5H), 6.64 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 160.3, 159.9, 150.1, 149.4, 140.0, 134.9, 133.7, 131.7, 131.3, 130.9, 129.6, 129.4, 129.2, 129.0, 128.9, 128.1, 128.0, 127.6, 125.6, 119.5, 117.4, 116.2, 100.8; IR (KBr, cm^{-1}): 3050, 2929, 2854, 1632, 1602, 1590, 1559, 1490 1444, 1370, 1218, 1005, 830, 767, 745; HRMS (ESI) calcd for $C_{29}H_{19}NO$ (M + H$^+$) 398.1546, found 398.1558.

5,6-Diphenyl-2-(*p*-tolyl)pyrano[2,3,4-*de*]quinoline (2a):



Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 8.00 (d, 2H, *J* = 7.8 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 7.60 (d, 1H, *J* = 8.4 Hz), 7.54–7.52 (m, 1H), 7.50-7.46 (m, 2H), 7.40 (t, 2H, *J* = 7.2 Hz), 7.37–7.32 (m, 6H), 7.28–7.26 (m, 1H), 7.23–7.20 (m, 1H), 6.62 (d, 1H, *J* = 7.2 Hz), 2.43 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 160.2, 159.9, 150.1, 149.4, 139.7, 137.1, 134.9, 133.7, 133.6, 131.6, 130.9, 129.7, 129.3, 129.2, 128.9, 128.1, 128.0, 127.5, 125.5, 119.5, 117.3, 116.0, 100.5, 21.6; IR (KBr, cm^{-1}): 3022, 2923, 2848, 1634, 1591, 1558, 1492, 1463, 1442, 1367, 1260, 1219, 1207, 1174, 114, 1038, 1004, 996, 932, 821, 813, 783, 773, 701; HRMS (ESI) calcd for $C_{30}H_{21}NO$ (M + H$^+$) 412.1702, found 412.1715.

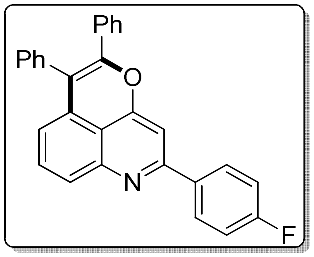
2-(4-Ethylphenyl)-5,6-diphenylpyrano[2,3,4-*de*]quinoline (3a):



Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 8.03 (d, 2H, *J* = 7.8 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 7.48 (d, 1H, *J* = 9.0 Hz), 7.40 (t, 2H, *J* = 7.2 Hz), 7.37–7.32 (m, 5H), 7.27–7.25 (m, 3H), 7.24–7.20 (m, 3H), 6.62 (d, 1H, *J* = 7.2 Hz), 2.72 (q, 2H, *J* =

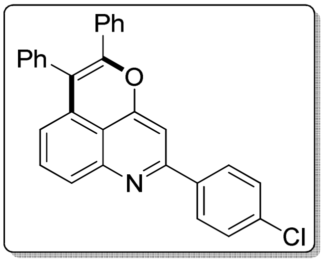
7.2 Hz), 1.29 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.3, 160.0, 150.1, 149.4, 146.0, 137.4, 134.9, 133.7, 131.6, 131.3, 130.9, 129.3, 129.2, 128.9, 128.5, 128.1, 128.0, 127.6, 125.5, 119.5, 117.4, 116.0, 100.5, 28.9, 15.8; IR (KBr, cm^{-1}): 3027, 2961, 2924, 2853, 1639, 1592, 1559, 1492, 1445, 1405, 1371, 1264, 1219, 1126, 1114, 1035, 1006, 932, 824, 759; HRMS (ESI) calcd for $C_{31}H_{23}NO$ (M + H$^+$) 426.1859, found 426.1866.

2-(4-Fluorophenyl)-5,6-diphenylpyrano[2,3,4-*de*]quinoline (4a):



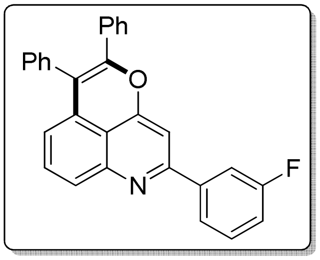
Solid; M.p. 172–174 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.11–8.09 (m, 2H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 7.8 Hz), 7.42–7.40 (m, 2H), 7.37 (d, 1H, *J* = 7.2 Hz), 7.32 (d, 2H, *J* = 7.2 Hz), 7.28–7.25 (m, 5H), 7.22 (t, 2H, *J* = 7.2 Hz), 7.19–7.18 (m, 1H), 6.64 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.9, 163.2, 160.4, 158.8, 150.1, 149.4, 134.9, 133.6, 131.8, 131.3, 130.9, 129.5, 129.4, 129.38, 129.2, 129.0, 128.2, 128.1, 125.5, 119.6, 117.3, 116.2, 115.9, 115.8, 100.4; IR (KBr, cm^{-1}): 3050, 2905, 2850, 1631, 1597, 1564, 1495, 1442, 1361, 1254, 1230, 1116, 1077, 1006, 830, 764, 747, 712; HRMS (ESI) calcd for $C_{29}H_{18}FNO$ (M + H$^+$) 416.1452, found 416.1441.

2-(4-Chlorophenyl)-5,6-diphenylpyrano[2,3,4-*de*]quinoline (5a):



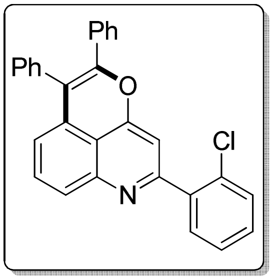
Solid; M.p. 200–202 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.06 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 7.8 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.41 (t, 2H, *J* = 7.2 Hz), 7.37 (d, 1H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 7.8 Hz), 7.28–7.26 (m, 4H), 7.25–7.21 (m, 2H), 6.66 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.4, 158.6, 150.1, 149.4, 138.4, 135.7, 134.8, 133.6, 131.9, 131.3, 130.9, 129.4, 129.2, 129.1, 129.0, 128.9, 128.2, 128.1, 125.5, 119.6, 117.5, 116.3, 100.4; IR (KBr, cm^{-1}): 3053, 3014, 2922, 2851, 1633, 1590, 1575, 1559, 1491, 1484, 1461, 1450, 1445, 1369, 1262, 1214, 1127, 1116, 1088, 1013, 1004, 996, 932, 825, 819, 775, 766, 753, 728, 701; HRMS (ESI) calcd for $C_{29}H_{18}ClNO$ (M + H^+) 432.1156, found 432.1147.

2-(3-Fluorophenyl)-5,6-diphenylpyrano[2,3,4-*de*]quinoline (6a):



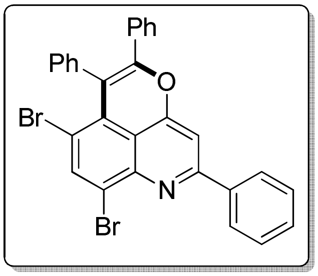
Solid; M.p. 161−162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.86 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 7.53–7.50 (m, 1H), 7.47–7.46 (m, 1H), 7.41 (t, 2H, *J* = 7.2 Hz), 7.38–7.36 (m, 1H), 7.32 (d, 2H, *J* = 7.2 Hz), 7.28–7.26 (m, 4H), 7.25–7.21 (m, 2H), 7.16 (t, 1H, *J* = 8.1 Hz), 6.66 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.3, 162.7, 160.5, 158.5, 150.1, 149.5, 142.3, 134.9, 133.6, 131.9, 131.3, 130.9, 130.4, 130.3, 129.4, 129.2, 129.1, 128.2, 128.1, 125.6, 123.1, 119.6, 116.5, 116.4, 116.3, 114.7, 114.5, 100.6; ^{19}F NMR ($CDCl_3$ + Trifluoroacetic acid): δ -110.5 (s); IR (KBr, cm^{-1}): 3056, 2919, 2851, 1645, 1594, 1559, 1489, 1444, 1363, 1261, 1237, 1117, 1068, 1010, 830, 772, 764, 755, 747, 739; HRMS (ESI) calcd for $C_{29}H_{18}FNO$ (M + H^+) 416.1452, found 416.1438.

2-(2-Chlorophenyl)-5,6-diphenylpyrano[2,3,4-*de*]quinoline (7a):



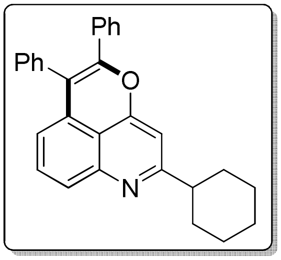
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, 2H, *J* = 7.8 Hz), 7.78 (d, 1H, *J* = 8.4 Hz), 7.53–7.50 (m, 3H), 7.48–7.46 (m, 1H), 7.41 (t, 2H, *J* = 7.8 Hz), 7.37 (d, 1H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 7.8 Hz), 7.30 (s, 1H), 7.28–7.26 (m, 2H), 7.24-7.21 (m, 2H), 6.64 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.3, 160.0, 150.1, 149.4, 140.0, 134.9, 133.7, 131.7, 131.4, 131.3, 130.9, 129.6, 129.4, 129.2, 128.99, 128.95, 128.1, 128.0, 127.6, 125.6, 117.4, 116.2, 100.8; IR (KBr, cm^{-1}): 3053, 2924, 2853, 1632, 1602, 1590, 1551, 1488, 1444, 1370, 1219, 1111, 1003, 930, 822, 775, 758, 702; HRMS (ESI) calcd for $C_{29}H_{18}ClNO$ (M + H^+) 432.1156, found 432.1142.

7,9-Dibromo-2,5,6-triphenylpyrano[2,3,4-*de*]quinoline (8a):



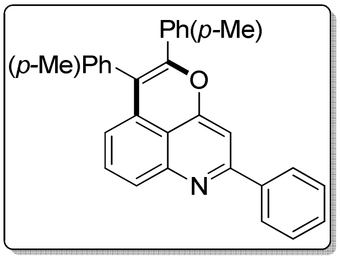
Solid; M.p. 190–192 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (d, 2H, *J* = 7.2 Hz), 7.80 (d, 1H, *J* = 7.8 Hz), 7.53–7.50 (m, 2H), 7.49–7.46 (m, 1H), 7.42–7.38 (m, 3H), 7.31 (d, 2H, *J* = 7.8 Hz), 7.26–7.25 (m, 3H), 7.23–7.20 (m, 2H), 6.49 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.3, 159.8, 149.6, 146.6, 141.6, 139.2, 135.0, 134.5, 133.3, 131.1, 130.8, 130.0, 129.5, 129.2, 128.9, 128.3, 128.1, 127.7, 120.1, 119.2, 118.1, 116.5, 100.9; IR (KBr, cm^{-1}): 3035, 2925, 2849, 1631, 1590, 1582, 1548, 1490, 1444, 1363, 1214, 1179, 1113, 1069, 1008, 927, 893, 830, 772, 763, 758, 703; HRMS (ESI) calcd for $C_{29}H_{17}Br_2NO$ (M + H$^+$) 555.9731, found 555.9742.

2-Cyclohexyl-5,6-diphenylpyrano[2,3,4-*de*]quinoline (9a):



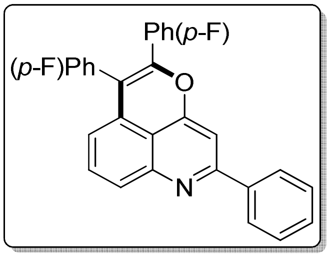
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.17 (d, 1H, *J* = 7.8 Hz), 7.98 (d, 1H, *J* = 8.4 Hz), 7.70–7.64 (m, 2H), 7.46–7.42 (m, 2H), 7.39–7.37 (m, 1H), 7.30 (d, 2H, *J* = 7.2 Hz), 7.24–7.22 (m, 1H), 7.21–7.18 (m, 2H), 6.81–6,79 (m, 1H), 6.62 (s, 1H), 2.86–2.81 (m, 1H), 2.02-2.01(m, 2H), 1.89-1.88 (m, 2H), 1.79–1.77 (m, 1H), 1.60-1.54 (m, 2H), 1.50–1.42 (m, 2H), 1.36–1.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.2, 159.9, 149.7, 149.0, 144.9, 133.7, 131.3, 130.9, 130.0, 129.3, 129.2, 128.0, 128.0, 125.2, 123.8, 121.8, 117.4, 115.7, 100.8, 41.7, 33.1, 26.7, 26.3; IR (KBr, cm^{-1}): 3012, 2960, 2943, 2912, 2884, 2859, 1646, 1583, 1533, 1479, 1452, 1400, 1367, 1256, 1212, 1146, 1112, 1040, 1002, 948, 834, 752; HRMS (ESI) calcd for $C_{29}H_{25}NO$ (M + H$^+$) 404.2015, found 404.2026.

2-Phenyl-5,6-di-*p*-tolylpyrano[2,3,4-*de*]quinoline (1b):



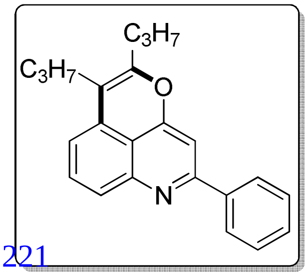
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, 2H, J = 7.2 Hz), 7.75 (d, 1H, J = 8.4 Hz), 7.51 (t, 2H, J = 7.8 Hz), 7.46 (t, 2H, J = 7.2 Hz), 7.27 (s, 1H), 7.22 (t, 4H, J = 8.4 Hz), 7.16–7.14 (m, 2H), 7.03 (d, 2H, J = 7.8 Hz), 6.63 (d, 1H, J = 7.8 Hz), 2.40 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.3, 159.9, 150.1, 149.4, 140.1, 138.9, 137.7, 132.0, 131.7, 130.9, 130.7, 130.1, 129.5, 129.0, 128.9, 128.8, 127.6, 125.3, 118.9, 117.4, 116.0, 100.7, 21.6, 21.5; IR (KBr, cm^{-1}): 3022, 2917, 2846, 1642, 1595, 1583, 1557, 1510, 1488, 1464, 1405, 1368, 1262, 1220, 1210, 1183, 1125, 1112, 1025, 1003, 934, 836, 808, 777, 769; HRMS (ESI) calcd for $C_{31}H_{23}NO$ (M + H$^+$) 426.1859, found 426.1848.

5,6-Bis(4-fluorophenyl)-2-phenylpyrano[2,3,4-*de*]quinoline (1c):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, 2H, J = 7.2 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.53–7.50 (m, 3H), 7.48–7.45 (m, 1H), 7.30–7.28 (m, 3H), 7.24–7.22 (m, 2H), 7.12 (t, 2H, J = 9.0 Hz), 6.93 (t, 2H, J = 9.0 Hz), 6.59 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.7, 163.4, 162.0, 161.7, 160.03, 160.00, 150.1, 148.7, 139.8, 132.6, 132.5, 131.7, 131.2, 131.1, 130.9, 130.7, 130.6, 129.6, 128.9, 127.6, 125.8, 118.5, 117.2, 116.7, 116.5, 115.9, 115.4, 115.2, 100.8; ^{19}F NMR ($CDCl_3$ + Trifluoroacetic acid): δ -111.2 (s), -113.5 (s); IR (KBr, cm^{-1}): 3040, 2959, 2922, 2846, 1639, 1604, 1591, 1504, 1489, 1408, 1374, 1266, 1234, 1222, 1154, 1124, 1115, 1090, 1028, 1006, 932, 894, 855, 774, 762; HRMS (ESI) calcd for $C_{29}H_{17}F_2NO$ (M + H$^+$) 434.1357, found 434.1365.

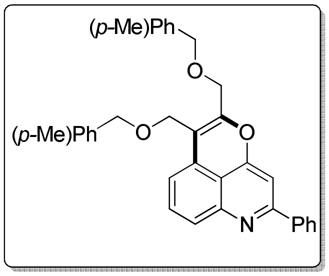
2-Phenyl-5,6-dipropylpyrano[2,3,4-*de*]quinoline (1d):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.06 (d, 2H, J = 7.2 Hz), 7.71 (d, 1H, J = 9.0 Hz), 7.59 (t, 1H, J = 7.8 Hz), 7.49 (t, 2H, J = 7.8 Hz), 7.44 (d, 1H, J = 7.2 Hz), 7.14 (s, 1H), 6.92

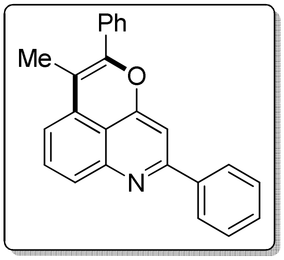
(d, 1H, J = 7.2 Hz), 2.52–2.46 (m, 4H), 1.76–1.72 (m, 2H), 1.62–1.60 (m, 2H), 1.05 (q, 6H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 159.5, 152.3, 150.4, 140.2, 131.7, 130.3, 129.3, 128.9, 127.6, 124.5, 117.6, 114.4, 112.9, 100.4, 32.7, 28.8, 21.6, 21.3, 14.5, 14.1; IR (KBr, cm^{-1}): 2960, 2927, 2864, 1652, 1635, 1599, 1491, 1464, 1456, 1405, 1370, 1261, 1212, 1168, 1137, 1050, 1019, 837, 773; HRMS (ESI) calcd for $C_{23}H_{23}NO$ (M + H$^+$) 330.1859, found 330.1867.

5,6-Bis(((4-methylbenzyl)oxy)methyl)-2-phenylpyrano[2,3,4-*de*]quinoline (1e):



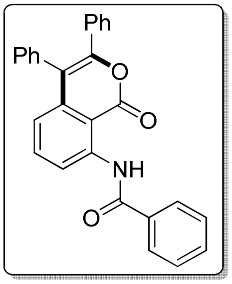
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.09–8.04 (m, 3H), 7.88 (d, 1H, J = 7.8 Hz), 7.79–7.76 (m, 2H), 7.62–7.58 (m, 2H), 7.52–7.48 (m, 3H), 7.25–7.20 (m, 3H), 7.17–7.14 (m, 3H), 4.56 (s, 2H), 4.51 (s, 2H), 4.44 (s, 2H), 4.31 (s, 2H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.8, 158.3, 151.2, 149.9, 146.4, 137.9, 134.9, 131.7, 130.7, 130.2, 129.4, 129.0, 128.9, 128.8, 128.3, 127.8, 127.6, 126.9, 126.0, 124.1, 123.7, 122.0, 121.8, 117.8, 115.5, 115.2, 100.9, 72.8, 72.3, 66.2, 64.1, 22.9, 21.4; IR (KBr, cm^{-1}): 2950, 2924, 2885, 2831, 1645, 1590, 1484, 1462, 1451, 1416, 1378, 1212, 1159, 1116, 1008, 944, 824, 770, 763, 758, 706; HRMS (ESI) calcd for $C_{35}H_{31}NO_3$ (M + H$^+$) 514.2383, found 514.2370.

6-Methyl-2,5-diphenylpyrano[2,3,4-*de*]quinoline (1f):



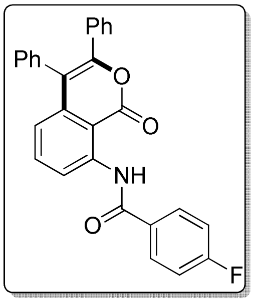
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, 2H, J = 7.8 Hz), 7.82 (d, 1H, J = 8.4 Hz), 7.67 (t, 1H, J = 8.4 Hz), 7.61 (d, 2H, J = 7.2 Hz), 7.51–7.47 (m, 4H), 7.46–7.43 (m, 2H), 7.23 (s, 1H), 7.03 (d, 1H, J = 7.2 Hz), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 159.7, 150.2, 149.6, 140.1, 134.1, 131.8, 131.0, 129.5, 129.4, 128.9, 128.6, 127.6, 125.5, 117.2, 113.9, 111.9, 100.7, 14.0; IR (KBr, cm^{-1}): 2959, 2919, 2849, 1640, 1592, 1493, 1407, 1370, 1217, 1150, 1108, 1019, 930, 824, 772, 761, 756, 700; HRMS (ESI) calcd for $C_{24}H_{17}NO$ (M + H$^+$) 336.1389, found 336.1380.

N-(1-Oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (1'a):



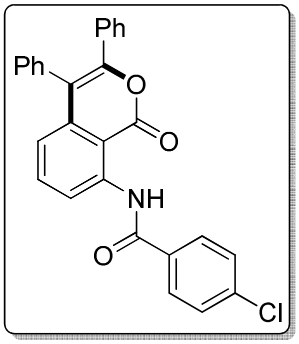
Solid; M.p. 170–172 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.81 (s, 1H), 9.04 (d, 1H, *J* = 7.8 Hz), 8.15 (d, 2H, *J* = 7.8 Hz), 7.65 (t, 1H, *J* = 8.4 Hz), 7.58 (t, 1H, *J* = 6.0 Hz), 7.54 (t, 2H, *J* = 7.2 Hz), 7.44–7.40 (m, 3H), 7.32 (d, 2H, *J* = 7.8 Hz), 7.27–7.24 (m, 3H), 7.20 (t, 2H, *J* = 6.0 Hz), 6.86 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.2, 164.7, 150.6, 142.7, 140.4, 136.5, 134.8, 134.3, 132.5, 132.4, 131.4, 129.4, 129.2, 129.1, 128.5, 128.2, 127.8, 120.1, 118.8, 118.0, 107.4; IR (KBr, cm^{-1}): 3111, 3053, 2922, 2854, 1695, 1678, 1600, 1566, 1492, 1470, 1445, 1406, 1306, 1288, 1253, 1242, 1209, 1180, 1134, 1095, 1075, 1061, 1029, 1007, 816, 763, 709; HRMS (ESI) calcd for $C_{28}H_{19}NO_3$ (M + H$^+$) 418.1444, found 418.1436.

4-Fluoro-N-(1-oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (2'a):



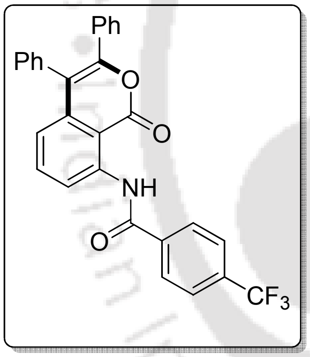
Solid; M.p. 164–166 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.79 (s, 1H), 9.00 (d, 1H, *J* = 8.4 Hz), 8.17–8.15 (m, 2H), 7.65 (t, 1H, *J* = 8.4 Hz), 7.44–7.40 (m, 3H), 7.33–7.31 (m, 2H), 7.27–7.23 (m, 3H), 7.22–7.18 (m, 4H), 6.87 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.3, 166.2, 165.1, 164.8, 150.7, 142.6, 140.4, 136.6, 134.3, 132.4, 131.5, 131.4, 130.9, 130.3, 130.2, 129.5, 129.4, 129.2, 128.6, 128.2, 128.1, 120.2, 118.8, 118.1, 116.2, 116.1, 107.4; IR (KBr, cm^{-1}): 3053, 3016, 2919, 2846, 1734, 1718, 1678, 1602, 1569, 1538, 1504, 1487, 1469, 1442, 1312, 1277, 1252, 1239, 1205, 1167, 1090, 1072, 1051, 1029, 1006, 979, 850, 813, 770, 760; HRMS (ESI) calcd for $C_{28}H_{18}FNO_3$ (M + H$^+$) 436.1350, found 436.1362.

4-Chloro-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (3'a):



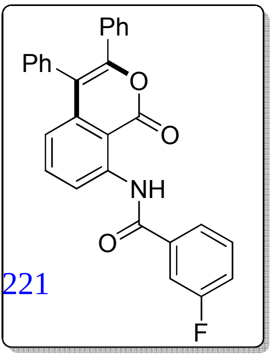
Solid; M.p. 186–188 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.83 (s, 1H), 9.01 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 2H, *J* = 7.6 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.43 (bs, 3H), 7.33 (d, 2H, *J* = 7.2 Hz), 7.26 (bs, 3H), 7.20 (d, 2H, *J* = 7.2 Hz), 6.89 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 165.2, 164.8, 150.7, 142.5, 140.5, 138.8, 136.6, 134.3, 133.2, 132.5, 131.4, 129.5, 129.4, 129.3, 129.2, 128.6, 128.2, 120.3, 118.8, 118.1, 107.4; IR (KBr, cm^{-1}): 3056, 2922, 2846, 1711, 1678, 1600, 1568, 1537, 1488, 1469, 1441, 1312, 1279, 1239, 1207, 1191, 1112, 1090, 1030, 1005, 848, 812, 770, 761, 745; HRMS (ESI) calcd for $C_{28}H_{18}ClNO_3$ (M + H$^+$) 452.1054, found 452.1049.

***N*-(1-Oxo-3,4-diphenyl-1*H*-isochromen-8-yl)-4-(trifluoromethyl)benzamide (4'a):**



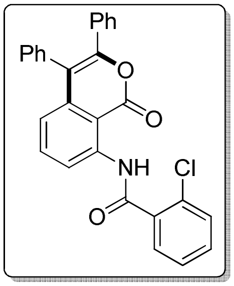
Solid; M.p. 185–186 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.93 (s, 1H), 9.01 (d, 1H, *J* = 8.8 Hz), 8.25 (d, 2H, *J* = 8.0 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.45–7.43 (m, 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.28–7.26 (m, 3H), 7.24–7.19 (m, 2H), 6.91 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 164.8, 150.8, 142.2, 140.5, 137.9, 136.8, 134.2, 132.4, 131.4, 130.8, 129.5, 129.4, 129.3, 128.9, 128.8, 128.6, 128.2, 126.1, 120.6, 118.9, 118.0, 107.5; ^{19}F NMR (CDCl$_3$ + Trifluoroacetic acid): δ -63.7 (s); IR (KBr, cm^{-1}): 2961, 2922, 2851, 1700, 1674, 1644, 1606, 1569, 1549, 1506, 1471, 1444, 1410, 1329, 1307, 1292, 1207, 1172, 1128, 1110, 065, 1016, 856, 817, 764; HRMS (ESI) calcd for $C_{29}H_{18}F_3NO_3$ (M + H$^+$) 486.1318, found 486.1309.

3-Fluoro-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (5'a):



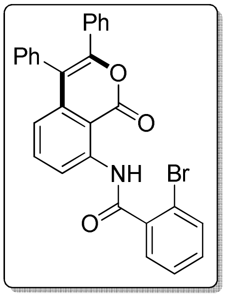
Solid; M.p. 175–176 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.77 (s, 1H), 8.94 (d, 1H, *J* = 8.4 Hz), 7.86 (d, 1H, *J* = 7.8 Hz), 7.78 (d, 1H, *J* = 9.6 Hz), 7.60 (t, 1H, *J* = 8.4 Hz), 7.47–7.44 (m, 1H), 7.37–7.36 (m, 3H), 7.26 (d, 2H, *J* = 7.8 Hz), 7.23–7.18 (m, 4H), 7.15–7.13 (m, 2H), 6.83 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.9, 164.8, 164.1, 162.4, 150.7, 142.4, 140.5, 136.6, 134.3, 132.4, 131.4, 130.8, 130.7, 129.5, 129.4, 129.3, 128.6, 128.2, 123.1, 120.4, 119.5, 119.4, 118.9, 118.0, 115.4, 115.2, 107.5; ^{19}F NMR ($CDCl_3$ + Trifluoroacetic acid): δ -111.8 (s); IR (KBr, cm^{-1}): 3266, 3224, 3061, 2917, 2846, 1699, 1671, 1596, 1586, 1576, 1563, 1539, 1485, 1469, 1443, 1310, 1286, 1270, 1240, 1204, 1170, 1025, 870, 815, 773, 762, 742; HRMS (ESI) calcd for $C_{28}H_{18}FNO_3$ (M + H$^+$) 436.1350, found 436.1344.

2-Chloro-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (6'a):



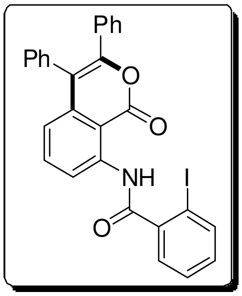
Solid; M.p. 134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.31 (s, 1H), 9.01 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 2H, *J* = 8.0 Hz), 7.68 (t, 1H, *J* = 8.0 Hz), 7.54–7.48 (m, 3H), 7.46–7.40 (m, 3H), 7.38–7.34 (m, 2H), 7.30 (d, 2H, *J* = 8.4 Hz), 7.24–7.18 (m, 2H), 6.91 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.2, 164.2, 150.7, 142.0, 140.4, 136.5, 134.9, 133.7, 132.6, 131.8, 131.7, 131.4, 130.9, 129.4, 129.39, 129.3, 128.6, 128.4, 128.2, 127.4, 126.9, 120.6, 119.1, 107.6; IR (KBr, cm^{-1}): 2927, 2846, 1701, 1683, 1591, 1568, 1527, 1489, 1470, 1445, 1407, 1312, 1292, 1266, 1240, 1209, 1095, 1050, 914, 812, 763, 756, 734, 700; HRMS (ESI) calcd for $C_{28}H_{18}ClNO_3$ (M + H$^+$) 452.1054, found 452.1040.

2-Bromo-*N*-(1-oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (7'a):



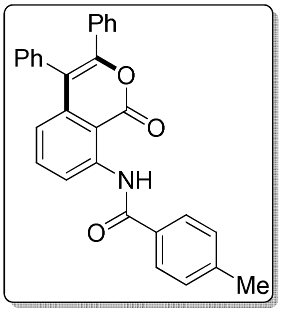
Solid; m.p. 176–178 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): *δ* 12.22 (s, 1H), 8.99 (d, 1H, *J* = 8.4 Hz), 7.70–7.67 (m, 3H), 7.45–7.42 (m, 4H), 7.36–7.35 (m, 1H), 7.33–7.30 (m, 2H), 7.29–7.26 (m, 3H), 7.24–7.19 (m, 2H), 6.90 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 166.9, 164.1, 150.7, 141.9, 140.3, 138.3, 136.4, 134.3, 134.1, 131.9, 131.4, 129.4, 129.3, 129.2, 129.0, 128.6, 128.1, 127.9, 127.8, 120.6, 120.1, 119.0, 117.9, 107.5; IR (KBr, cm^{-1}): 3258, 3053, 2917, 2841, 1701, 1680, 1599, 1568, 1534, 1488, 1469, 1444, 1428, 1405, 1307, 1290, 1241, 1208, 1158, 1122, 1095, 1076, 1030, 817, 780, 763, 733, 702; HRMS (ESI) calcd for $C_{28}H_{18}BrNO_3$ (M + H^+) 498.0527, found 498.0516.

2-Iodo-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (8'a):



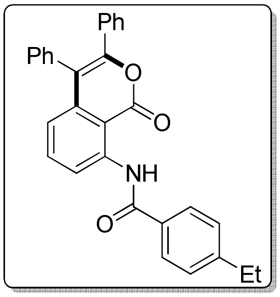
Solid; M.p. 144–145 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 12.20 (s, 1H), 8.98 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 7.69–7.64 (m, 2H), 7.49–7.42 (m, 4H), 7.30 (d, 2H, *J* = 7.6 Hz), 7.26–7.23 (m, 3H), 7.21–7.18 (m, 3H), 6.91 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.2, 164.2, 150.7, 142.0, 140.8, 140.4, 136.5, 134.3, 133.5, 132.4, 131.9, 131.4, 129.4, 129.37, 129.2, 128.7, 128.6, 128.5, 128.2, 120.6, 119.1, 117.9, 107.6, 93.0; IR (KBr, cm^{-1}): 3051, 2925, 2849, 1698, 1679, 1598, 1568, 1535, 1483, 1469, 1440, 1406, 1291, 1241, 1209, 1100, 1014, 814, 763, 761, 732, 702; HRMS (ESI) calcd for $C_{28}H_{18}INO_3$ (M + H^+) 544.0410, found 544.0419.

4-Methyl-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (9'a):



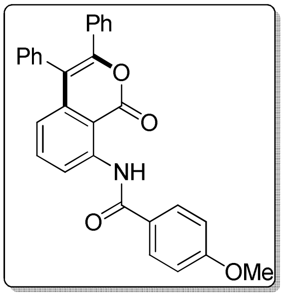
Solid; M.p. 192–194 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 12.80 (s, 1H), 9.02 (d, 1H, *J* = 8.0 Hz), 8.05 (d, 2H, *J* = 8.0 Hz), 7.65 (t, 1H, *J* = 8.0 Hz), 7.44–7.42 (m, 3H), 7.35–7.32 (m, 4H), 7.28–7.25 (m, 4H), 7.24–7.20 (m, 1H), 6.86 (d, 1H, *J* = 8.0 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.3, 164.7, 150.6, 144.7, 143.0, 140.3, 136.5, 134.4, 132.5, 131.9, 131.4, 130.4, 129.8, 129.4, 129.2, 128.5, 128.2, 127.8, 119.9, 118.8, 118.0, 107.3, 21.9; IR (KBr, cm^{-1}): 3066, 2919, 2841, 1690, 1674, 1606, 1566, 1535, 1507, 1469, 1446, 1412, 1306, 1276, 1209, 1182, 1113, 815, 766, 745, 703; HRMS (ESI) calcd for $C_{29}H_{21}NO_3$ (M + H^+) 432.1600, found 432.1608.

4-Ethyl-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (10'a):



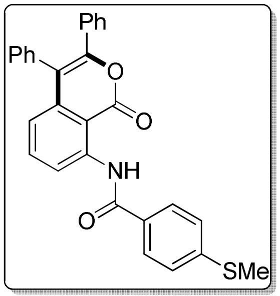
Solid; M.p. 96–101°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.80 (s, 1H), 9.04 (d, 1H, J = 8.0 Hz), 8.07 (d, 2H, J = 8.0 Hz), 7.64 (t, 1H, J = 8.0 Hz), 7.43 (bs, 3H), 7.41–7.35 (m, 2H), 7.33–7.31 (m, 2H), 7.27–7.25 (m, 3H), 7.22–7.20 (m, 2H), 6.84 (d, 1H, J = 8.0 Hz), 2.73 (q, 2H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.6 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 166.3, 164.6, 150.5, 149.2, 142.8, 140.3, 136.5, 134.4, 132.5, 132.2, 131.4, 129.4, 129.2, 128.6, 128.5, 128.1, 127.9, 119.9, 118.8, 118.0, 107.3, 29.0, 15.5; IR (KBr, cm^{-1}): 3061, 2964, 2843, 1760, 1729, 1691, 1675, 1606, 1566, 1536, 1507, 1490, 1470, 1444, 1278, 1209, 1179, 1119, 1029, 814, 761, 700; HRMS (ESI) calcd for $C_{30}H_{23}NO_3$ (M + H$^+$) 446.1757, found 446.1770.

4-Methoxy-*N*-(1-oxo-3,4-diphenyl-1*H*-isochromen-8-yl)benzamide (11'a):



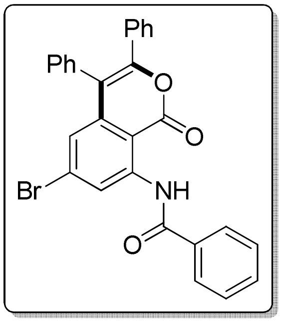
Solid; M.p. 148–150 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.72 (s, 1H), 9.02 (d, 1H, J = 8.0 Hz), 8.10 (d, 2H, J = 8.4 Hz), 7.63 (t, 1H, J = 8.0 Hz), 7.42–7.38 (m, 4H), 7.30 (d, 2H, J = 7.6 Hz), 7.26–7.16 (m, 4H), 7.01 (d, 2H, J = 8.4 Hz), 6.83 (d, 1H, J = 8.4 Hz), 3.88 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.1, 163.0, 161.0, 150.7, 143.0, 136.6, 134.4, 131.4, 129.8, 129.5, 129.3, 129.1, 129.0, 128.5, 128.4, 128.3, 128.2, 128.0, 119.8, 118.7, 114.3, 108.7, 55.7; IR (KBr, cm^{-1}): 2956, 2924, 2853, 1723, 1688, 1670, 1645, 1603, 1565, 1558, 1507, 1467, 1444, 1403, 1307, 1265, 1249, 1207, 1172, 1102, 1058, 1024, 813, 762; HRMS (ESI) calcd for $C_{29}H_{21}NO_4$ (M + H$^+$) 448.1550, found 448.1560.

4-(Methylthio)-*N*-(1-oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (12'a):



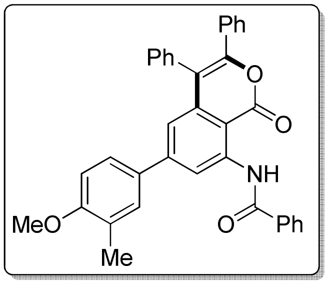
Solid; M.p. 142–144 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.78 (s, 1H), 9.03 (d, 1H, J = 8.0 Hz), 8.06 (d, 2H, J = 8.8 Hz), 7.66 (t, 1H, J = 8.0 Hz), 7.44–7.43 (m, 3H), 7.37–7.32 (m, 4H), 7.27–7.19 (m, 5H), 6.86 (d, 1H, J = 7.6 Hz), 2.55 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.6, 164.6, 150.5, 144.7, 142.7, 140.3, 136.5, 134.3, 132.4, 131.3, 130.7, 129.3, 129.2, 129.1, 128.5, 128.1, 128.0, 125.6, 119.9, 118.7, 117.9, 107.2, 15.1; IR (KBr, cm^{-1}): 3053, 2959, 2922, 2854, 1704, 1674, 1606, 1594, 1565, 1538, 1491, 1470, 1442, 1278, 1240, 1207, 1198, 1189, 1124, 1087, 1058, 1031, 1011, 814, 773, 763, 700; HRMS (ESI) calcd for $C_{29}H_{21}NO_3S$ (M + H$^+$) 464.1321, found 464.1316.

_N_-(6-Bromo-1-oxo-3,4-diphenyl-1_H_-isochromen-8-yl)benzamide (13'a):



Solid; M.p. 214–215 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.78 (s, 1H), 9.28 (s, 1H), 8.12 (d, 2H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.8 Hz), 7.54 (t, 2H, J = 7.2 Hz), 7.45–7.44 (m, 3H), 7.29 (d, 2H, J = 7.2 Hz), 7.28–7.24 (m, 3H), 7.20 (t, 2H, J = 7.8 Hz), 6.99 (d, 1H, J = 1.2 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.2, 164.2, 151.6, 143.3, 141.4, 134.3, 133.6, 132.7, 132.5, 132.1, 131.3, 129.7, 129.6, 129.3, 129.1, 128.9, 128.2, 127.8, 122.7, 121.7, 117.1, 105.9; IR (KBr, cm^{-1}): 3260, 3224, 3111, 3064, 1708, 1680, 1600, 1585, 1551, 1529, 1493, 1444, 1428, 1303, 1288, 1259, 1244, 1205, 1192, 1063, 1030, 1008, 866, 799, 776, 700; HRMS (ESI) calcd for $C_{28}H_{18}BrNO_3$ (M + H$^+$) 498.0527, found 498.0539.

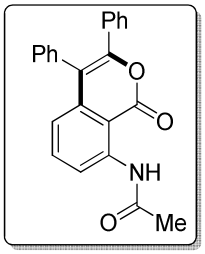
_N_-(6-(4-Methoxy-3-methylphenyl)-1-oxo-3,4-diphenyl-1_H_-isochromen-8-yl)benzamide (14'a):



Solid; M.p. 182-184 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.86 (s, 1H), 9.35 (s, 1H), 8.18 (d, 2H, J = 7.2 Hz), 7.60–7.54 (m, 3H), 7.45–7.42 (m, 2H), 7.38–7.35 (m, 4H), 7.34–7.31 (m, 3H), 7.31–7.28 (m, 1H), 7.24–7.20 (m, 2H), 7.05 (s, 1H), 6.86–6.84 (m, 1H), 3.85 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 168.9, 166.4, 164.7, 158.9, 149.0, 142.9, 140.7, 139.9, 134.8, 133.7, 132.4, 131.5, 129.9, 129.4, 129.3, 129.1, 129.07, 129.01, 128.6, 128.4, 128.2, 127.8, 127.6, 126.4, 118.2, 117.8, 117.0, 110.4, 55.6, 21.1; IR (KBr, cm^{-1}):

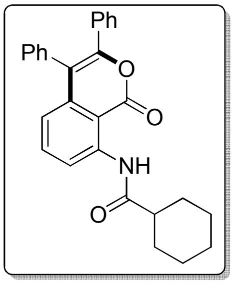
3053, 2951, 2922, 2854, 1753, 1691, 1677, 1606, 1564, 1559, 1556, 1507, 1492, 1442, 1391, 1375, 1303, 1258, 1202, 1143, 1093, 1064, 1028, 814, 699; HRMS (ESI) calcd for $C_{36}H_{27}NO_4$ (M + H^+) 538.2019, found 538.2024.

N-(1-Oxo-3,4-diphenyl-1*H*-isochromen-8-yl)acetamide (15'a):



Solid; M.p. 190–194 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.80 (s, 1H), 8.81 (d, 1H, *J* = 7.8 Hz), 7.60 (t, 1H, *J* = 8.4 Hz), 7.42–7.41 (m, 3H), 7.31 (d, 2H, *J* = 7.8 Hz), 7.25–7.23 (m, 3H), 7.20 (t, 2H, *J* = 7.8 Hz), 6.82 (d, 1H, *J* = 8.4 Hz), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.8, 164.3, 150.6, 142.5, 140.2, 136.4, 134.4, 132.5, 131.4, 129.4, 129.3, 129.28, 128.5, 128.2, 119.9, 118.7, 117.9, 107.0, 25.9; IR (KBr, cm^{-1}): 3056, 3024, 2951, 2919, 2849, 1697, 1684, 1607, 1600, 1570, 1542, 1489, 1474, 1443, 1408, 1366, 1315, 1292, 1244, 1211, 1096, 1067, 1031, 814, 768, 760, 722, 702; HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ (M + H^+) 356.1287, found 356.1298.

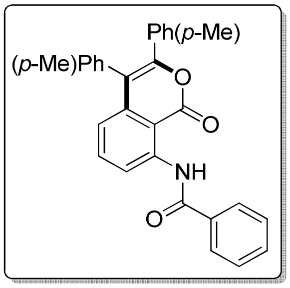
N-(1-Oxo-3,4-diphenyl-1*H*-isochromen-8-yl)cyclohexanecarboxamide (16'a):



Solid; M.p. 144-147 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.86 (s, 1H), 8.85 (d, 1H, *J* = 8.4 Hz), 7.58 (t, 1H, *J* = 8.4 Hz), 7.42–7.41 (m, 3H), 7.30 (d, 2H, *J* = 7.8 Hz), 7.25–7.23 (m, 3H), 7.20 (t, 2H, *J* = 7.8 Hz), 6.80 (d, 1H, *J* = 7.8 Hz), 2.45–2.41 (m, 1H), 2.09 (d, 2H, *J* = 9.6 Hz), 1.88–1.86 (m, 2H), 1.74–1.72 (m, 1H), 1.64–1.57 (m, 3H), 1.43–1.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 176.2, 164.4, 150.5, 142.8, 140.2, 136.4, 134.4, 132.6, 131.4, 129.4, 129.2, 128.7, 128.5, 128.2, 119.7, 118.9, 117.9, 107.1, 47.6, 29.8, 25.98, 25.96; IR (KBr, cm^{-1}): 3053, 2927, 2853, 1707, 1683, 1605, 1570, 1536, 1490, 1476, 1446, 1409, 1315, 1285, 1268, 1242, 1204, 1169, 1097, 1066, 1031, 1006, 820, 763, 701; HRMS

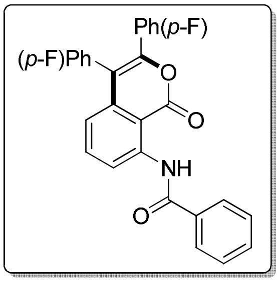
(ESI) calcd for $C_{28}H_{25}NO_3$ (M + H$^+$) 424.1913, found 424.1917.

N-(1-Oxo-3,4-di-*p*-tolyl-1*H*-isochromen-8-yl)benzamide (1'b):



Solid; M.p. 168–170 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.84 (s, 1H), 9.02 (d, 1H, J = 8.4 Hz), 8.15 (d, 2H, J = 7.2 Hz), 7.63 (t, 1H, J = 8.4 Hz), 7.59–7.57 (m, 1H), 7.54 (t, 2H, J = 7.2 Hz), 7.25–7.23 (m, 4H), 7.14 (d, 2H, J = 7.8 Hz), 7.02 (d, 2H, J = 8.4 Hz), 6.86 (d, 1H, J = 8.4 Hz), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.2, 164.8, 150.6, 142.6, 140.8, 139.5, 138.2, 136.4, 134.8, 132.3, 131.4, 131.2, 130.1, 129.3, 129.1, 128.9, 127.8, 127.4, 120.1, 118.5, 117.4, 107.3, 21.6, 21.5; IR (KBr, cm^{-1}): 2951, 2917, 2843, 1694, 1678, 1603, 1559, 1556, 1537, 1468, 1407, 1284, 1203, 1187, 1181, 1124, 1090, 1059, 1024, 815, 763, 731; HRMS (ESI) calcd for $C_{30}H_{23}NO_3$ (M + H$^+$) 446.1757, found 446.1765.

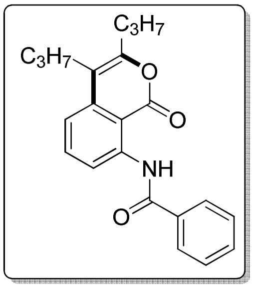
N-(3,4-Bis(4-fluorophenyl)-1-oxo-1*H*-isochromen-8-yl)benzamide (1'c):



Solid; M.p. 178–180 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.74 (s, 1H), 9.05 (d, 1H, J = 8.4 Hz), 8.14 (d, 2H, J = 7.8 Hz), 7.67 (t, 1H, J = 8.4 Hz), 7.60–7.58 (m, 1H), 7.55–7.52 (m, 2H), 7.31–7.28 (m, 2H), 7.26–7.22 (m, 2H), 7.15 (t, 2H, J = 8.4 Hz), 6.93 (t, 2H, J = 9.0 Hz), 6.83 (d, 1H, J = 7.8 Hz); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.2, 164.4, 163.9, 163.7, 162.3, 162.0, 149.9, 142.8, 140.1, 136.7, 134.7, 133.1, 133.09, 132.5, 131.3, 131.2, 129.7, 129.69, 129.1, 128.5, 127.7, 119.7, 119.0, 116.8, 116.6, 115.6, 115.4, 107.2; ^{19}F NMR (CDCl$_3$ + Trifluoroacetic acid): δ -110.9 (s), -113.1 (s); IR (KBr, cm^{-1}): 3108, 3051, 2914, 2849, 1696, 1679, 1603, 1567, 1531, 1507, 1472, 1446, 1406, 1312, 1288, 1241, 1222, 1209, 1161, 1133, 1094, 1059, 1026, 1019, 857, 842, 833, 816, 708; HRMS

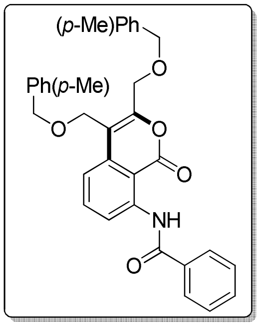
(ESI) calcd for $C_{28}H_{17}F_2NO_3$ (M + H$^+$) 454.1255, found 454.1267.

N-(1-Oxo-3,4-dipropyl-1H-isochromen-8-yl)benzamide (1'd):



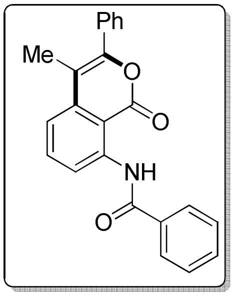
Solid; M.p. 90–92 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.85 (s, 1H), 8.98 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 2H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.56 (t, 1H, *J* = 7.2 Hz), 7.51 (t, 2H, *J* = 7.2 Hz), 7.22 (d, 1H, *J* = 7.8 Hz), 2.61–2.57 (q, 4H, *J* = 7.8 Hz), 1.78–1.74 (m, 2H), 1.61–1.57 (m, 2H), 1.05–1.00 (m, 6H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.1, 165.2, 154.0, 142.9, 139.4, 136.4, 134.8, 132.3, 128.9, 127.7, 117.9, 117.1, 113.5, 107.8, 32.7, 28.6, 22.9, 21.2, 14.4, 13.9; IR (KBr, cm^{-1}): 2960, 2926, 2863, 1692, 1676, 1609, 1570, 1547, 1476, 1464, 1407, 1309, 1288, 1261, 1180, 1130, 1088, 1044, 1028, 894, 814, 755, 721; HRMS (ESI) calcd for $C_{22}H_{23}NO_3$ (M + H$^+$) 350.1757, found 350.1769.

N-(3,4-Bis(((4-methylbenzyl)oxy)methyl)-1-oxo-1H-isochromen-8-yl)benzamide (1'e):



Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.63 (s, 1H), 9.07 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 2H, *J* = 7.8 Hz), 7.78 (t, 1H, *J* = 7.8 Hz), 7.58–7.56 (m, 1H), 7.54–7.52 (m, 2H), 7.43 (d, 1H, *J* = 7.8 Hz), 7.22–7.19 (m, 4H), 7.17–7.14 (m, 4H), 4.57 (s, 2H), 4.54 (s, 2H), 4.51 (s, 2H), 4.37 (s, 2H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.2, 164.3, 152.4, 142.8, 138.2, 138.0, 136.8, 134.7, 134.6, 132.4, 129.4, 129.3, 129.0, 128.3, 128.0, 127.7, 126.4, 119.3, 118.5, 114.2, 108.1, 73.2, 72.6, 66.2, 63.5, 21.4; IR (KBr, cm^{-1}): 3050, 2941, 2928, 2850, 1758, 1684, 1627, 1600, 1563, 1560, 1557, 1508, 1442, 1391, 1367, 1302, 1265, 1093, 1061, 1033, 811, 702; HRMS (ESI) calcd for $C_{34}H_{31}NO_5$ (M + H$^+$) 534.2281, found 534.2272.

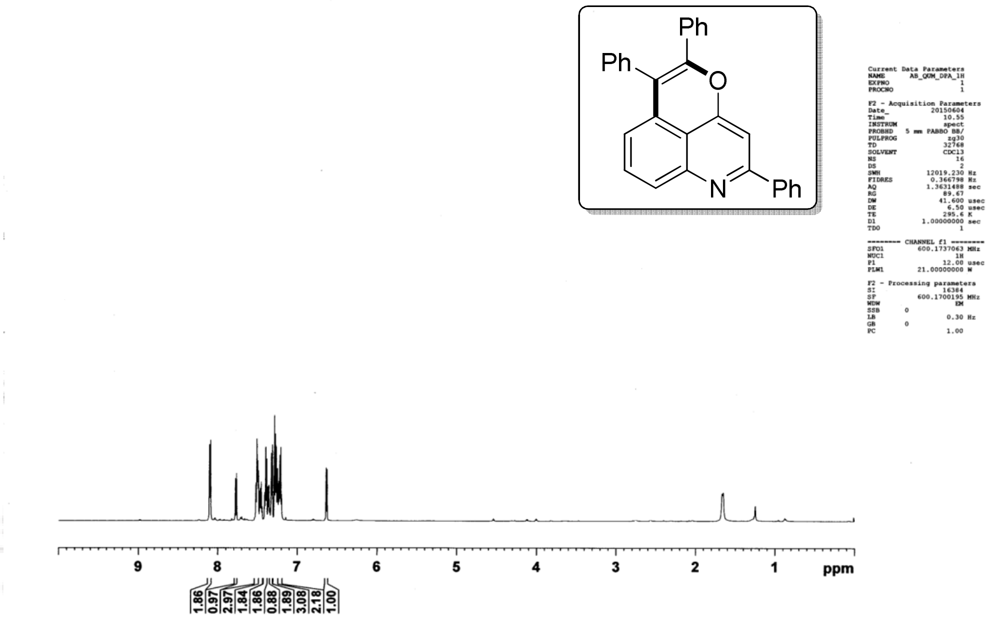
N-(4-Methyl-1-oxo-3-phenyl-1H-isochromen-8-yl)benzamide (1'f):



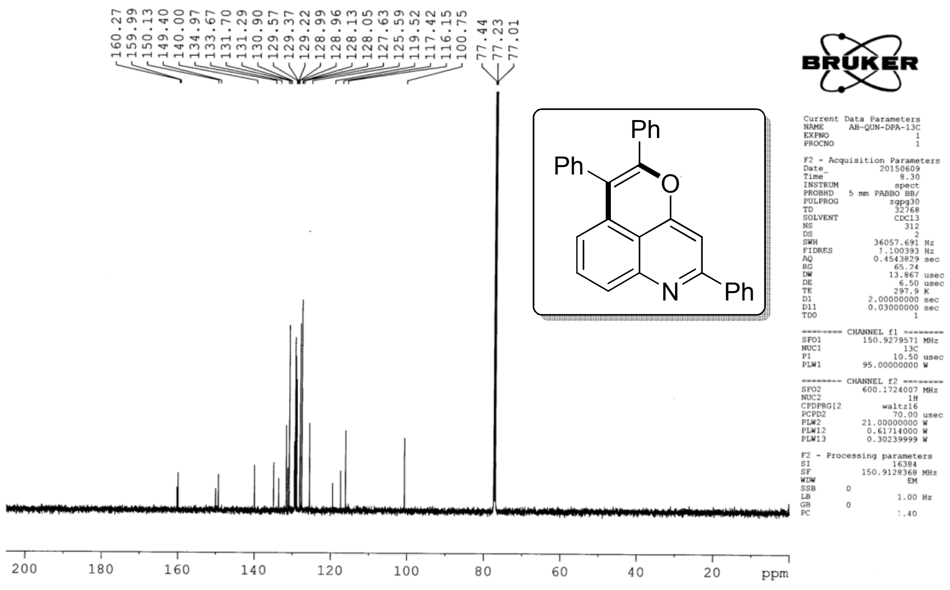
Solid; M.p. 196–197 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 12.83 (s, 1H), 9.08 (d, 1H, J = 8.4 Hz), 8.14–8.10 (m, 2H), 7.83 (t, 1H, J = 8.4 Hz), 7.60 (d, 2H, J = 7.2 Hz), 7.53 (d, 2H, J = 7.2 Hz), 7.50–7.46 (m, 3H), 7.36–7.33 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.3, 164.9, 151.0, 142.9, 140.2, 136.7, 134.8, 132.4, 129.8, 129.1, 128.8, 128.6, 128.5, 127.8, 118.7, 117.8, 110.4, 107.6, 14.2; IR (KBr, cm^{-1}): 3058, 2993, 2930, 2851, 1736, 1676, 1622, 1597, 1539, 1480, 1446, 1373, 1283, 1260, 1241, 1177, 1114, 1047, 1028, 978, 846, 702; HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ (M + H$^+$) 356.1287, found 356.1296.

V.5. Spectra

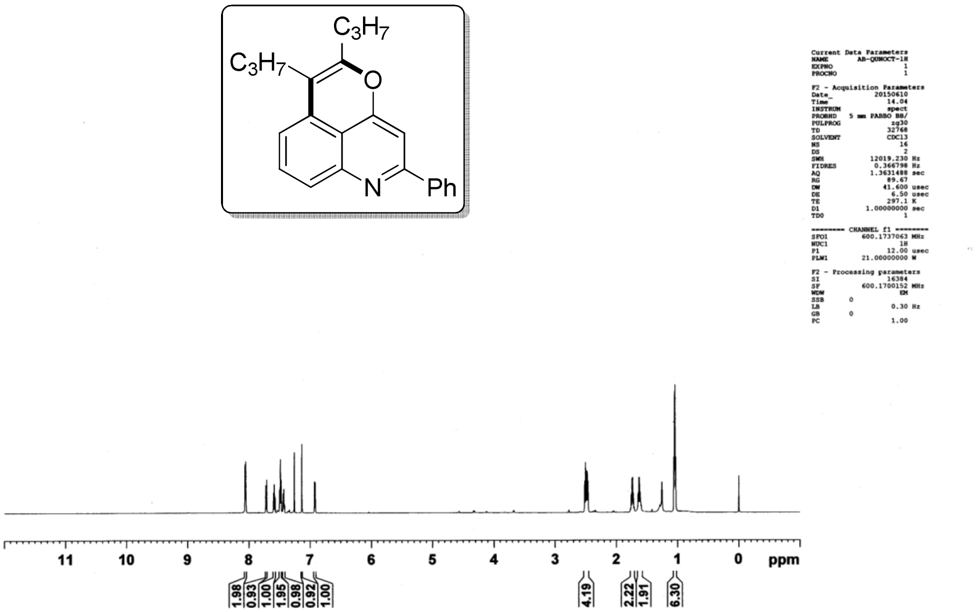
2,5,6-Triphenylpyrano[2,3,4-*de*]quinoline (1a): ^{1}H NMR (CDCl$_3$, 600 MHz)



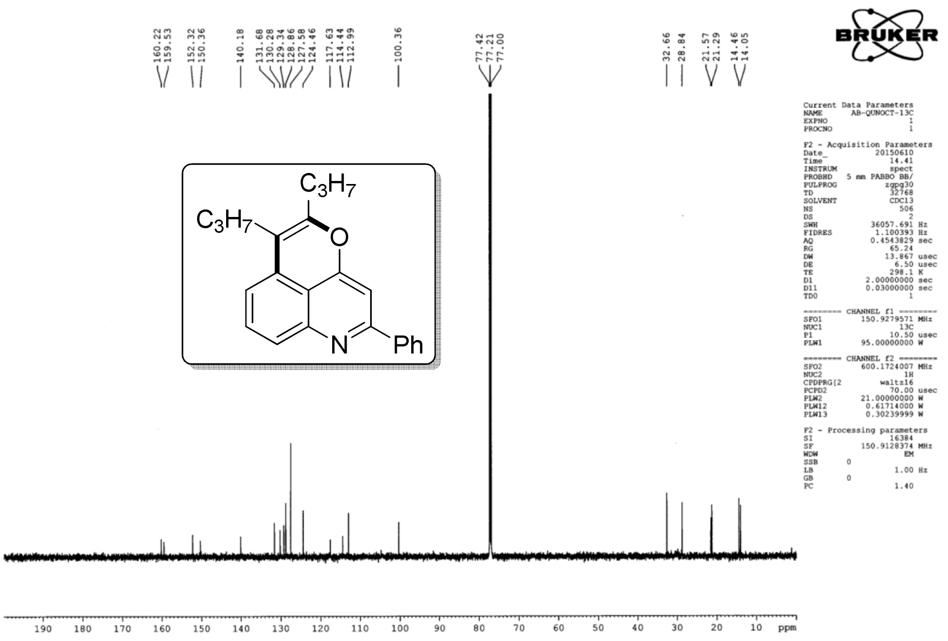
2,5,6-Triphenylpyrano[2,3,4-*de*]quinoline (1a): ^{13}C NMR (CDCl$_3$, 150 MHz)



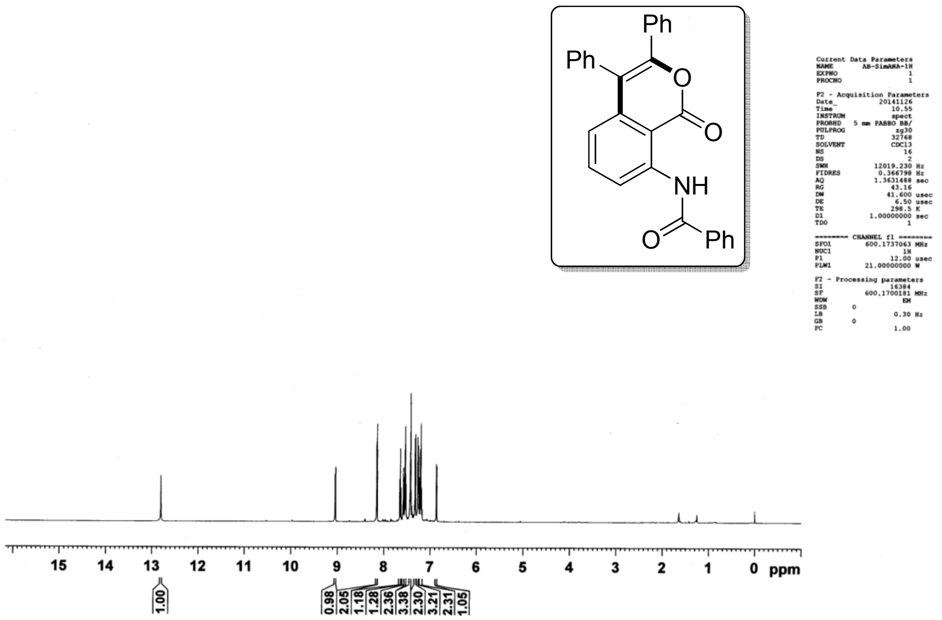
2-Phenyl-5,6-dipropylpyrano[2,3,4-*de*]quinoline (1d): ^{1}H NMR (CDCl$_3$, 600 MHz)



2-Phenyl-5,6-dipropylpyrano[2,3,4-*de*]quinoline (1d): ^{13}C NMR (CDCl$_3$, 150 MHz)



N-(1-Oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (1'a): ^{1}H NMR (CDCl$_3$, 600 MHz)



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PROCNO                  1

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D1             1.00000000 sec
TD0                     1

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

F2 - Processing parameters
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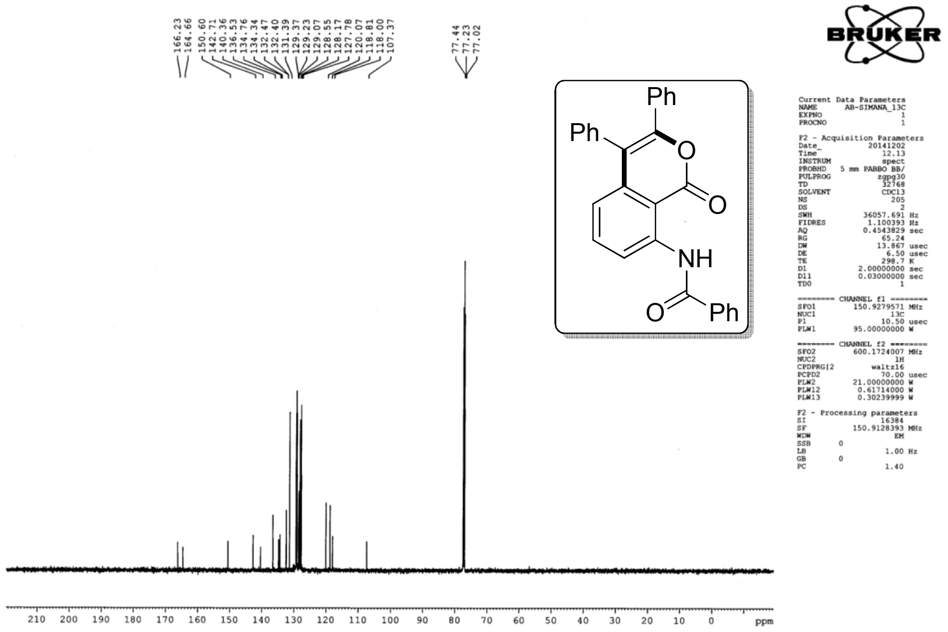
N-(1-Oxo-3,4-diphenyl-1H-isochromen-8-yl)benzamide (1'a): ^{13}C NMR (CDCl$_3$, 150 MHz)



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NS                    205
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SWH             36057.691 Hz
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AQ              0.4543829 sec
RG                  65.24
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DE                   6.50 usec
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D11            0.03000000 sec
TD0                     1

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NUC1                  13C
P1                  10.50 usec
PLW1          95.00000000 W

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

F2 - Processing parameters
SI                  16384
SF            150.9128393 MHz
WDW                    EM
SSB      0
LB                   1.00 Hz
GB       0
PC                   1.40
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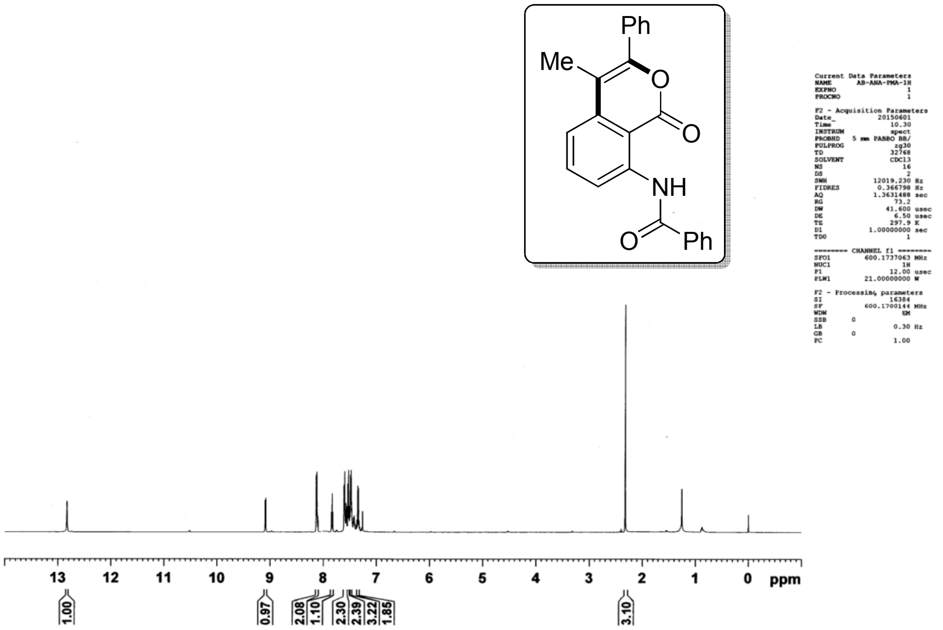
N-(4-Methyl-1-oxo-3-phenyl-1*H*-isochromen-8-yl)benzamide (1'f): ^{1}H NMR (CDCl$_3$, 600 MHz)



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Current Data Parameters
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PROCNO                 1

F2 - Acquisition Parameters
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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                  73.2
DW                41.600 usec
DE                  6.50 usec
TE                 297.9 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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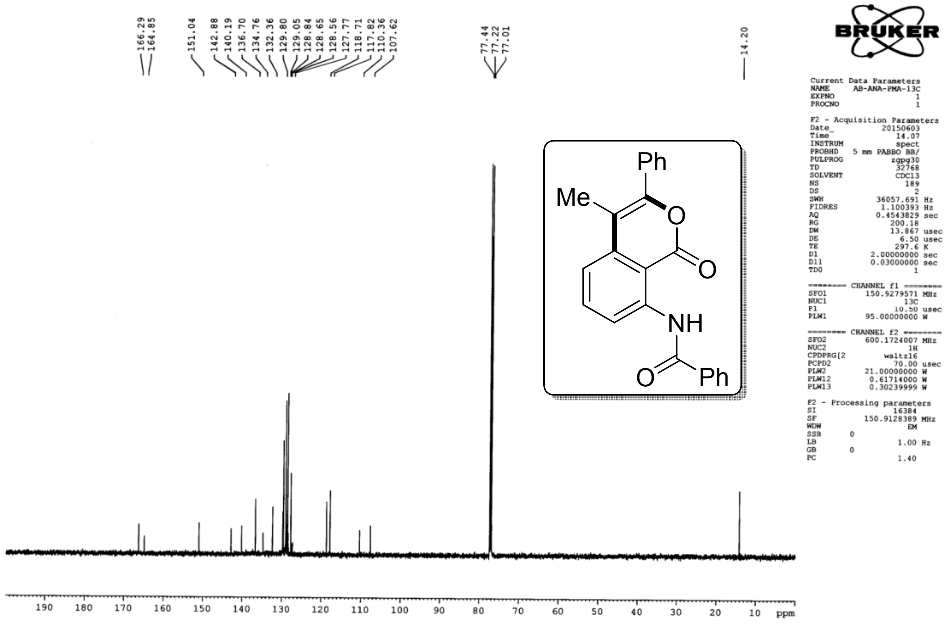

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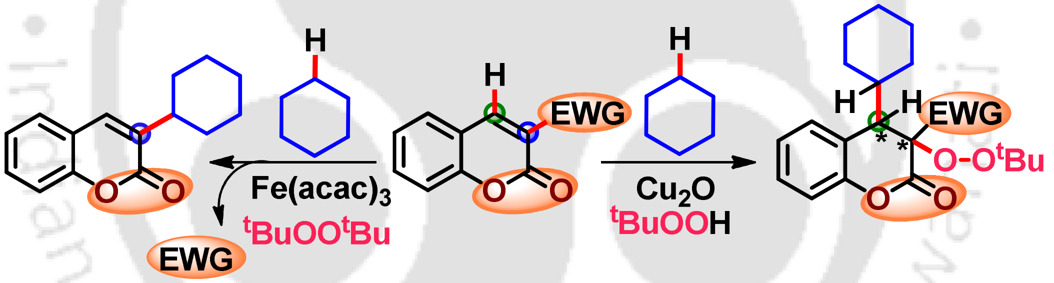
Chapter VI

Oxidant Controlled Regioselective Mono- and Difunctionalizations of Coumarins



Abstract*: C-3 Alkylation of coumrins has been accomplished using cycloalkanes or alkylbenzenes in the presence of di-tert-butylperoxide (DTBP) and Fe(III) catalyst. Using a Cu(I) catalyst and just by switching the oxidant from DTBP to TBHP, an exclusive C-4 cycloalkylation-C-3 peroxidation reaction takes place. During C-3 alkylation, the C–C bond formation is at the expense of an existing C–C bond, while the C-4 alkylation is associated with the formation of new C–C and C–O bonds*.

CHAPTER VI

This chapter is divided into two sections. Section A deals with the Cu(I) catalyzed 1,2-difunctionalization (C4 cycloalkylation-C3 peroxidation) of 3-substituted coumarins using cycloalkane and TBHP. Section B demonstrates a Fe(III) catalyzed C3 cycloalkylation of 3-substituted coumarins using cycloalkane and DTBP *via* the cleavage of an existing C–C bond.

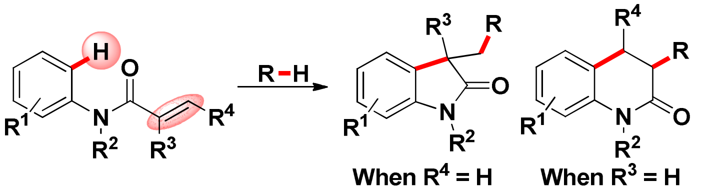
VIA. Copper(I) Promoted Cycloalkylation-Peroxidation of Unactivated Alkenes *via* sp^3 C–H Functionalization

VIA.1. Introduction

Construction of C–C or C–X bonds *via* C–H bond functionalizations in targeted synthesis has undergone a renaissance in modern organic synthesis.[1] In this perspective a number of cross dehydrogenative coupling (CDC) protocols have been developed towards the formation of C_{sp}–C_{sp}, C_{sp}–C_{sp2} and C_{sp2}–C_{sp2} bonds.[1j,2] In addition notable progresses have been made recently for the formation of C_{sp3}–C bonds following CDC process. Various C_{sp3}–H bonds such as benzylic, allylic,[3] C–H adjacent to heteroatoms[4] and even C–H bonds of alkanes[5] can now be cross coupled with numerous other C–H bonds. Selective functionalization of multiple C–H bonds in one-pot sequence is still in its infancy. Difunctionalization of alkene is one such approach to build molecular complexity in a single operation.

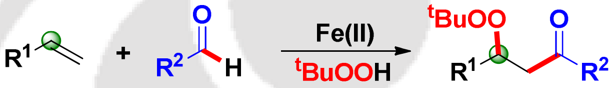
VIA.2. Strategies for 1,2-Difunctionalization

Of late intramolecular hetero difunctionalization of alkenes has been attractive, where the direct CDC of sp^3 and sp^2 C–H bonds has been employed for the construction of various heterocycles *via* tandem processes (Scheme VIA.2.1).[6] Intramolecular alkene difunctionalizations are more selective and thermodynamically favorable compared to intermolecular processes. Previous examples of intermolecular difunctionalization include palladium, nickel or ruthenium catalyzed carbohalogenation,[7(a-b)] dihydroxylation,[7c] oxyarylation,[7d] oxyamination,[7e] aminofluorination,[7f] aminocyanation[7g] and hydroalkylation.[7h]



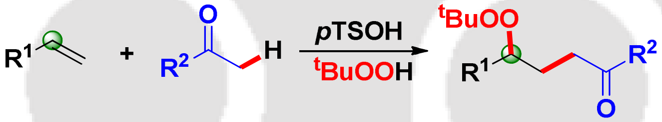
Scheme VIA.2.1. *Intramolecular difunctionalization involving sp^3 C–H bond*

In this context intermolecular difunctionalization of olefins has rarely been explored following C–H functionalization strategy. Recently a Fe(II)-catalyzed carbonylation-peroxidation of olefins was reported *via* a sp^2 C–H functionalization using aldehydes and *tert*-butyl hydroperoxide (TBHP) (Scheme VIA.2.2).[8] Complimentary asymmetric carbofunctionalization of olefins using aldehydes has been demonstrated by MacMillan *et al.* following the concept of singly occupied molecular orbital (SOMO).[9]



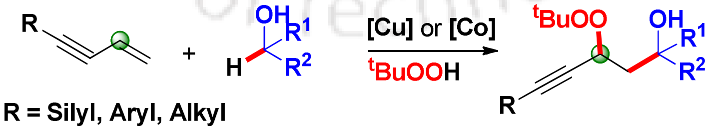
Scheme VIA.2.2. *Strategies for carbonylation-peroxidation involving sp^3 C–H bond*

Klussmann *et al.* have reported *p*-toluenesulfonic acid (*p*TsOH) catalyzed oxidative keto-peroxidation of olefins using ketones and TBHP (Scheme VIA.2.3).[10]



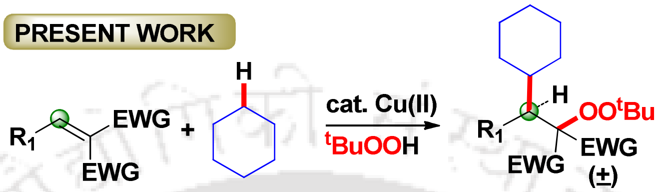
Scheme VIA.2.3. *Strategies for keto-peroxidation involving sp^3 C–H bond*

Very recently Loh group reported copper- and cobalt-catalyzed three component coupling between the sp^3 α-carbon of alcohols and hydroperoxides with alkenes *viz.* 1,3-enynes where the hydroperoxides acted as a radical initiator as well as a coupling partner (Scheme VIA.2.4).[11]



Scheme VIA.2.4. *Strategies for alkylation-peroxidation involving sp^3 C–H bond*

In this context an obvious query arises as to whether unreactive cycloalkane can similarly be used as an alkyl source towards alkene difunctionalizations. Compared to other C–H bonds (sp and sp^2), selective functionalization of sp^3 C–H bonds during targeted synthesis is always challenging. Few examples of C–H functionalizations using unactivated sp^3-carbon of cycloalkanes are reported in the literature with[5b,12] or without [6c, 5a,5(c-i),13] chelation control. Taking cues from the literature and from our recent success on sp^3 C–H functionalizations[14] we contemplated using cycloalkanes as alkyl equivalents for the intermolecular difunctionalization of alkenes (Scheme VIA.2.5).

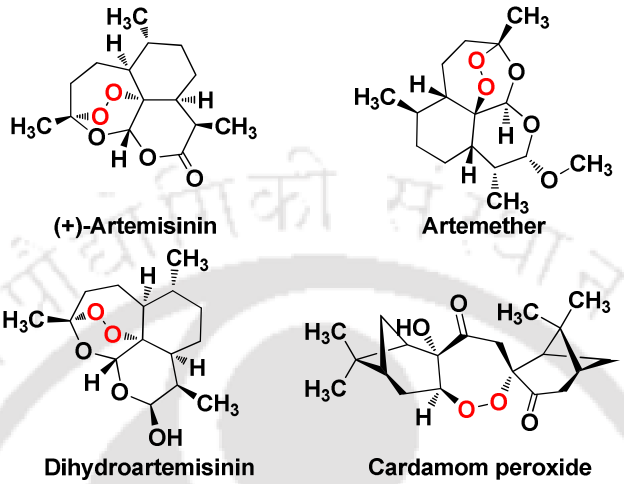


Scheme VIA.2.5. *Strategies for cycloalkylation-peroxidation*

VIA.3. Present Work

Although carbonylation-peroxidation, keto-peroxidation and alkylation-peroxidation strategies are reported using C–H functionalization, combination of both cycloalkylation and peroxidation has never been investigated on an unactivated olefin so far.

Optimization of reaction conditions. As mentioned above our envisioned route aimed towards the synthesis of cycloalkyl α-peroxy compounds by three component coupling involving sp^3 C–H fnctionalization. To give a practical shape to the above mentioned concept, 3-acetylcoumarin (**1**) (1 equiv) was treated with TBHP (**a**) (4.0 equiv), CuBr (20 mol %) in cyclohexane (2.5 mL) at 110 °C. Spectroscopic (^{1}H and ^{13}C NMR) analysis of the isolated product (**1a**) showed the presence of *tert*-butyl and cyclohexyl moiety. Presence of a doublet at 2.97 ppm (J = 3.2 Hz) and absence of C-4 olefinic proton confirm the addition of cyclohexyl and *tert*-butyl groups across the internal olefinic double bond of (**1**). This unprecedented cycloalkylation-peroxidation product (**1a**) was however obtained in a yield of only 21% (Table VIA.3.1, entry 1). 3-Acetylcoumarin (**1**), an important pharmacophoric unit was chosen as the test substrate as it represents a major class of naturally occurring compounds and privileged medicinal scaffolds that exhibit a broad range of biological and pharmaceutical properties, including anti-HIV, anti-tumor, anti-hypertension, anti-arrhythmia, antiinflammatory, anti-osteoporosis, antiseptic, analgesic and anticoagulant activities.[15] Thus, any further functionalizations of this important moiety would pave the path for useful intermediates which may find potential applications. Interestingly, this tertiary α-peroxy ester (**1a**) has structural analogy with some of the most potent anti-malarial drugs such as artemisinin, artemether, dihydroartemisinin and cardamom peroxide (Fig. VIA.3.1).[16]


(+)-Artemisinin

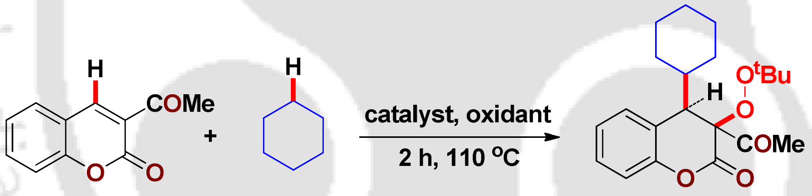
Artemether

Dihydroartemisinin

Cardamom peroxide

Fig. VIA.3.1. *Some potent anti-malarial drugs containing peroxy linkage*

Table VIA.3.1. *Screening of reaction conditions for cycloalkylation-peroxidation*[a,b]



(1) **(a)** **(1a)(±)**

Entry	Cu cat. (mol %)	Solvent	Oxidant (equiv)	Yield (%)[a,b]
1	CuBr (20.0)	C_6H_{12}	TBHP (4.0)	21
2	Cu_2O (20.0)	C_6H_{12}	TBHP (4.0)	47
3	CuCl (20.0)	C_6H_{12}	TBHP (4.0)	23
4	CuI (20.0)	C_6H_{12}	TBHP (4.0)	20
5	$CuBr_2$ (20.0)	C_6H_{12}	TBHP (4.0)	18
6	$CuCl_2$ (20.0)	C_6H_{12}	TBHP (4.0)	02
7	$Cu(OAc)_2$ (20.0)	C_6H_{12}	TBHP (4.0)	15
8	Cu_2O (30.0)	C_6H_{12}	TBHP (4.0)	54
9	**Cu_2O (40.0)**	**C_6H_{12}**	**TBHP (4.0)**	**60**
10	Cu_2O (40.0)	C_6H_{12}	DTBP (4.0)	07
11[c]	Cu_2O (40.0)	C_6H_{12}	TBHP (4.0)	45
12	——	C_6H_{12}	TBHP (4.0)	00

[a]Reaction conditions: **1** (0.5 mmol), cyclohexane (C_6H_{12}) (**a**) (2.5 mL) at 110 °C for 2 h. [b]Isolated yield. [c]TBHP in 70% water was used in lieu of TBHP in decane.

Encouraged by this preliminary success, to arrive at the best possible yield, other reaction parameters such as solvents, oxidants and catalysts were screened. Keeping all other parameters constant the use of an equivalent load of Cu_2O gave the best yield of 47% (**1a**) compared to other catalysts such as CuCl (23%), CuI (20%), $CuBr_2$ (18%), $CuCl_2$ (2%), $Cu(OAc)_2$ (15%) tested (Table VIA.3.1, entries 2-7). The yield marginally improved (54%) when the catalyst loading was increased to 30 mol % under otherwise identical conditions (Table VIA.3.1, entry 8). The yield improved by another 6% (total of 60%) (Table VIA.3.1, entry 9) when the catalyst Cu_2O quantity was increased from 30 to 40 mol %. Beyond a catalyst loading of 40 mol % no further improvement in the product yield was observed. Other peroxides such as di-*tert*-butyl peroxide (DTBP) and 70% aqueous TBHP as oxidant were found to be inferior to TBHP in decane (Table VIA.3.1, entries 10-11). It is pertinent to mention here that no product (**1a**) was formed in the absence of any catalyst (Table VIA.3.1, entry 12). Thus, after rigorous optimization it was found that the use of 3-acetylcoumarin (**1**) (0.5 mmol), cyclohexane (2.5 mL), Cu_2O (40 mol %) and TBHP in decane (4 equiv) at 110 ^{o}C gave the best yield (60%) of (**1a**) (Table VIA.3.1, entry 9).

Substrate scope for cycloalkyl α-peroxy coumarins. Encouraged by this success the reaction between various 3-acetylcoumarins and different cycloalkanes were evaluated under the optimized condition. This methodology is compatible for a variety of 3-acetylcoumarins possessing electron-donating and electron-withdrawing substituents. Coumarins possessing moderately and strongly electron-withdrawing substituents such as 6–Cl (**2**), 6–Br (**3**) and 6–NO_2 (**4**) provided corresponding di-functionalized products (**2a**), (**3a**) and (**4a**) in 63%, 59% and 67% yields respectively (Scheme VIA.3.1). The structure of product (**2a**) has been confirmed by X-ray crystallographic analysis as shown in Figure VIA.3.2. From the X-ray crystal structural analysis of (**2a**) it was found that the protons at C-4 of coumarin and cyclohexyl *tert*-proton are *cis* to each other (Fig. VIA.3.2).

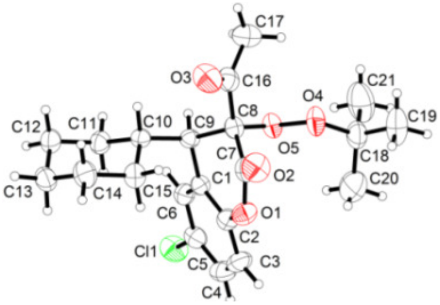
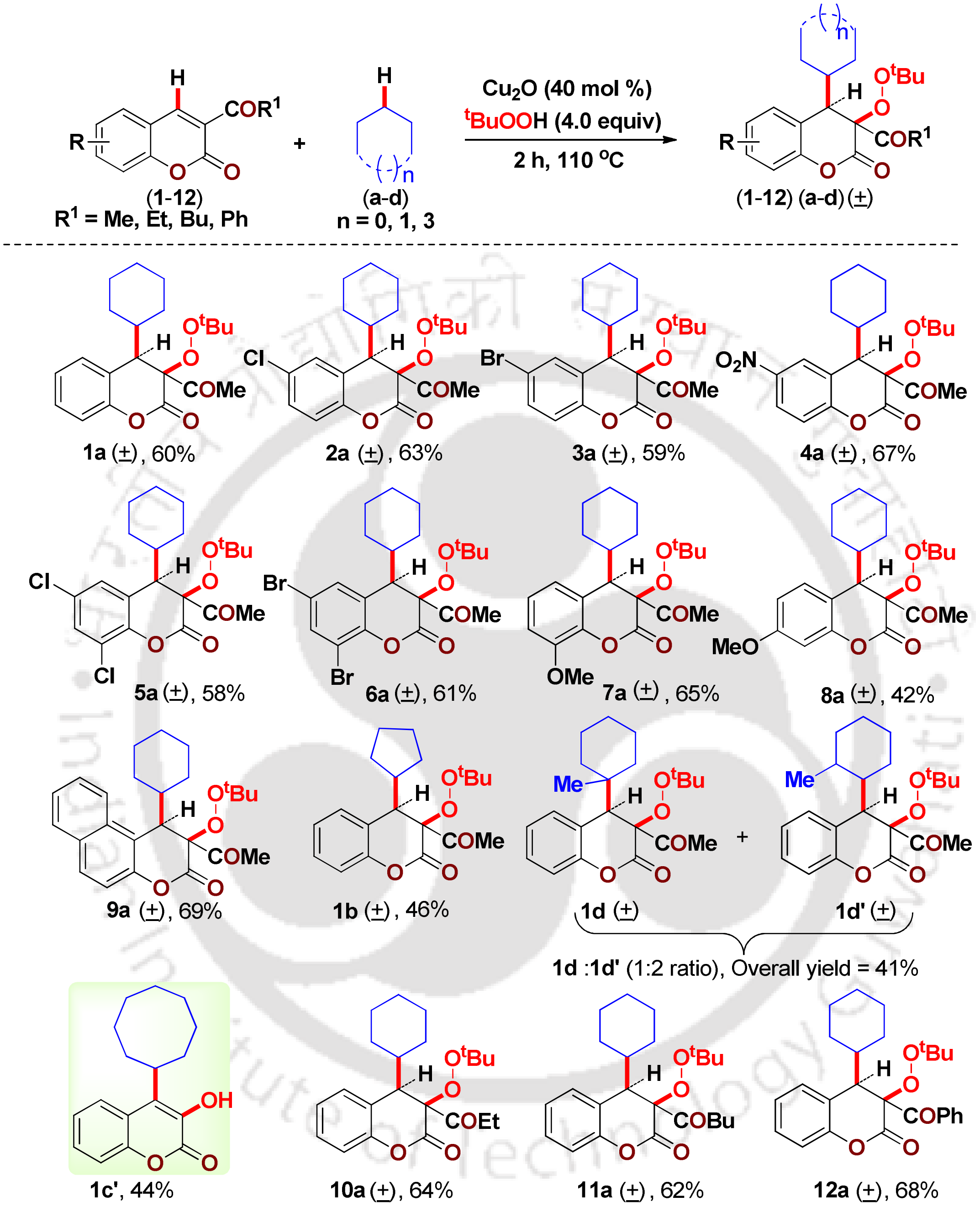


***Fig. VIA.3.2.** ORTEP molecular diagram of (**2a**)*

Scheme VIA.3.1. *Scope of 3-acyl/aroyl coumarins and cycloalkanes*[a,b]

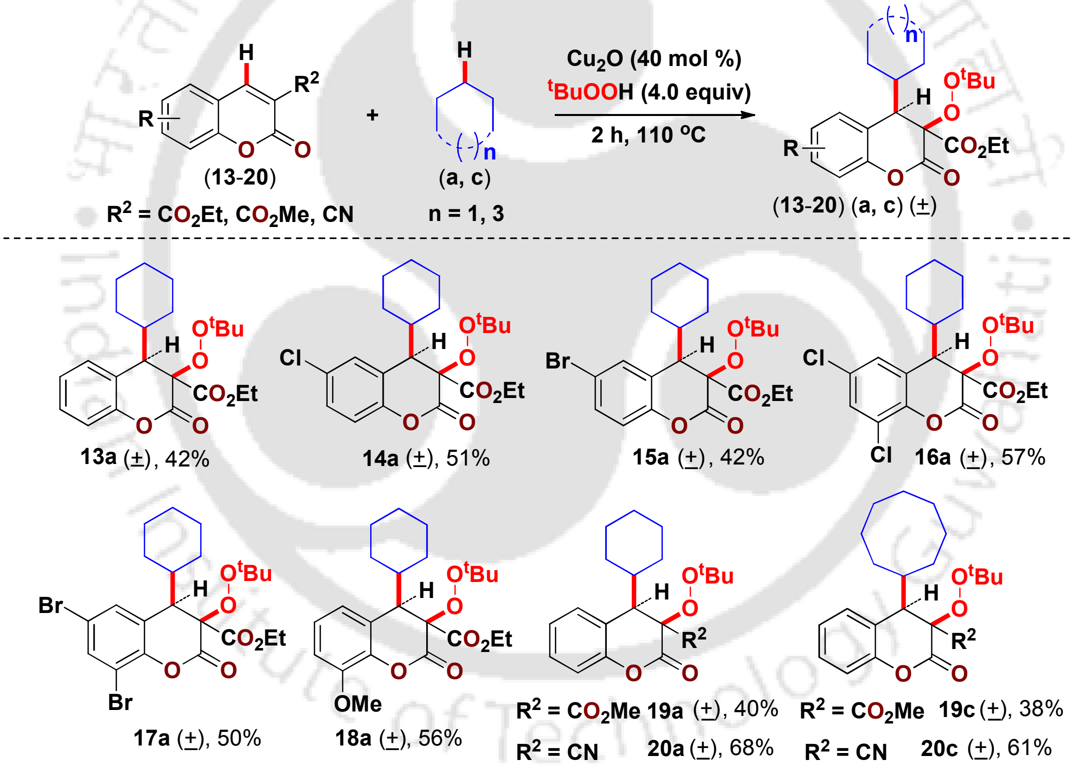


[a] Reaction conditions: coumarins (**1**–**12**) (0.5 mmol), cycloalkane (**a**–**d**) (2.5 mL) at 110 °C for 2 h.
[b] Isolated yield.

Disubstituted 3-acetylcoumarins possessing electron-withdrawing substituents in their 6 and 8-positions such as 6,8-dichloro (**5**) and 6,8-dibromo (**6**) underwent cycloalkylation-peroxidation giving products (**5a**) and (**6a**) in decent yields (Scheme VIA.3.1). 3-Acetylcoumarin bearing electron donating group 8–OMe (**7**) provided corresponding cycloalkylation-peroxidation product (**7a**) in good yield (65%), whereas when the methoxy group is at the C-7 position, the desired bi-functionalized product (**8a**) was formed in a meager yield of 42%. These observations suggest the significance of electronic effects of substituents and their positions of attachments in the phenyl ring of 3-acetylcoumarin. 3-Acetylcoumarin possessing an additional phenyl ring fused at C5–C6 afforded good yield of the corresponding addition product (**9a**). This method is also amenable to five member cyclic alkane such as cyclopentane (**b**), providing moderate yield (46%) of bi-functionalized product (**1b**). Higher member cycloalkane such as cyclooctane yielded cycloalkyl α-hydroxy product (**1c′**) in 44% yield instead of the expected cycloalkyl α-peroxy product but with the loss of an acetyl (–COMe) group. From subsequent experimentation it was found that the product (**1c′**) is obtained *via* the decomposition of cycloalkyl α-peroxy intermediate, which is discussed later. To see, whether methylcyclohexane (**d**) can selectively give one regioisomer or not, 3-acetylcoumarin (**1**) was reacted with (**d**) under the optimized reaction condition. The ^{1}H and ^{13}C NMR analysis of the product revealed the formation of two distinct regioisomers (**1d**:**1d′**) in the ratio of 1:2 giving a combined yield of 41%. The major regioisomer (**1d'**) was obtained *via* the coupling of secondary cyclohexylmethyl radical rather than with the stable tertiary cyclohexylmethyl radical which is possibly to avoid steric crowding with the adjacent peroxy *tert*-butyl group in the later case (Scheme VIA.3.1). This methodology is equally amenable to the use of other 3-acyl/aroyl substituted coumarins such as –COEt (**10**), –COBu (**11**) and –COPh (**12**) providing cyclohexyl α-peroxy products (**10a**), (**11a**) and (**12a**) respectively in decent yields (Scheme VIA.3.1).

Besides 3-acyl/aroyl (–COR/Ar) groups bearing coumarins other similar electron-withdrawing groups such as –CO_2Et, –CO_2Me and –CN were tested and all provided their expected addition products with equal ease as shown in Scheme VIA.3.2. A weakly electron withdrawing group such as (–CO_2Et) when present in the double bond of coumarin as in ethyl coumarin-3-carboxylate (**13**) provided the desired product (**13a**) when reacted with (**a**) but in lower yield (42%) compared to coumarin possessing –COMe group (**1a**, 60%). Keeping (–CO_2Et) group fixed at the C-3 position of coumarin, the presence of electron withdrawing groups 6–Cl (**14**), 6–Br (**15**), 6,8-diCl (**16**), 6,8-diBr (**17**) and electron donating group 8–OMe (**18**) all provided their respective cycloalkyl α-peroxy products (**14a**), (**15a**), (**16a**), (**17a**) and (**18a**) respectively (Scheme VIA.3.2). The yields obtained for coumarins possessing –CO_2Et were lower compared to (–COR/Ar)-bearing coumarins having the same substituents at identical positions in their phenyl rings (Scheme VIA.3.1 and VIA.3.2). Coumarin bearing weakly electron withdrawing group –CO_2Me (**19**) also reacted similarly to that of –CO_2Et substituted coumarin (**13**) with cyclohexane (**a**) and cyclooctane (**c**) providing their addition products (**19a**) and (**19c**) in 40% and 38% isolated yields respectively. This cycloalkylation-peroxidation strategy was also found equally compatible with coumarin bearing strongly electron-withdrawing group such as –CN at its 3 position (**20**). 3-Cyanocoumarin (**20**) reacted with cyclohexane (**a**) and cyclooctane (**c**) providing their corresponding difunctionalized products (**20a**) and (**20c**) in 68% and 61% yields respectively.

Scheme VIA.3.2. *Scope of 3-substituted coumarins and cycloalkanes*[a,b]



[a]Reaction conditions: coumarins (**13-20**) (0.5 mmol), cycloalkane (**a**,**c**) (2.5 mL) at 110 °C for 2 h. [b]Isolated yield.

The yields obtained for –CN bearing coumarins (**20**) were superior compared to –CO_2Et (**13-18**) and –CO_2Me (**19**) bearing coumarins. The presence of strongly electron withdrawing –CN group probably facilitates the radical addition across the coumarin double bond. The structure of (**20a**) has been unambiguously confirmed by X-ray crystallographic analysis (Fig. VIA.3.3). The *cis* orientation of C-4 proton in coumarin and cyclohexyl *tert*-proton is again confirmed from the X-ray crystal structure of **20a**. The trend in yields of various C3-substituted coumarins follow the order –CN ≈ –COPh > –COEt ~ –COBu ~ –COMe > $-CO_2Et$ ~ $-CO_2Me$, which is closely in accordance with their electron-withdrawing tendency.

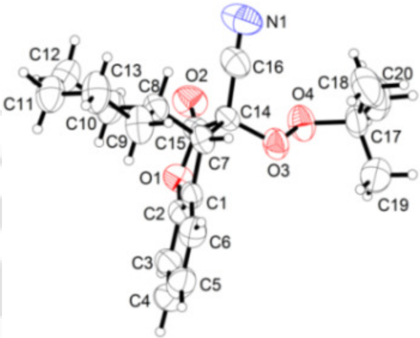
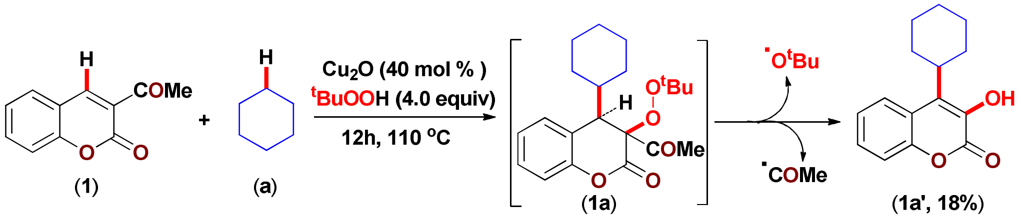


Fig. VIA.3.3. *ORTEP molecular diagram of (**20a**)*

These synthesized tertiary organic peroxides are stable for several days at room temperature and no decomposition was observed even after three months. However, on leaving the reaction to precede for a longer time (12 h) these *in situ* generated peroxides decomposed completely giving multitudes of unidentified products. The reaction between 3-acetylcoumarin (**1**) and cyclohexane (**a**) was heated for 12 h at 110 °C from which one of the decomposed products (**1a′**) could be isolated. The structure of the isolated product was found to be that of cyclohexyl α-hydroxy coumarin (**1a′**) as confirmed by X-RD (Fig. VIA.3.4). The product (**1a′**) is obtained with concurrent loss of –COMe and *tert*-butyl groups possibly from the intermediate (**1a**) (Scheme VIA.3.3). This explains the formation of cyclooctylated-hydroxylated product (**1c′**) by the reaction of 3-acetylcoumarin (**1**) and cyclooctane (**c**) in Scheme VIA.3.1. The formation of (**1c′**) from its corresponding peroxide intermediate could be due to the unfavorable steric strain imparted by adjacent cyclooctyl ring and the peroxy *tert*-butyl group.



Scheme VIA.3.3. *Cleavage of in situ generated difunctionalized product*

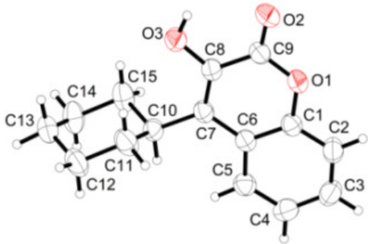
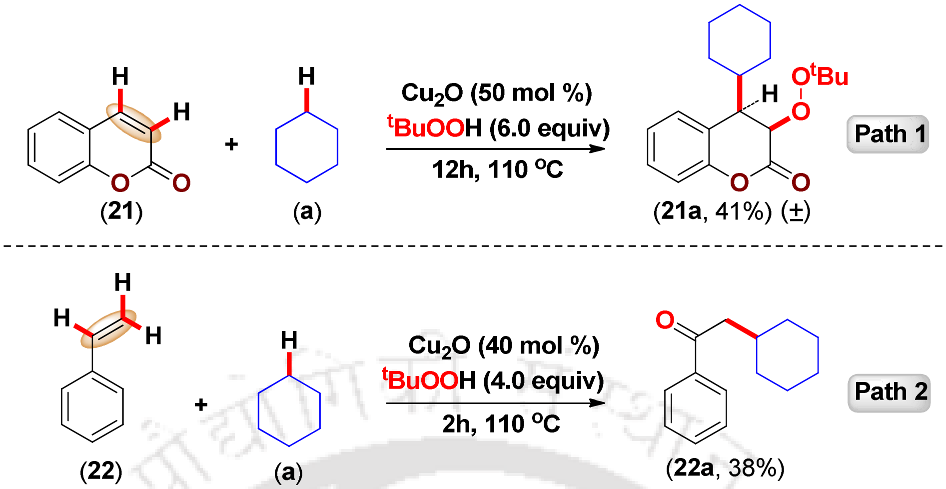


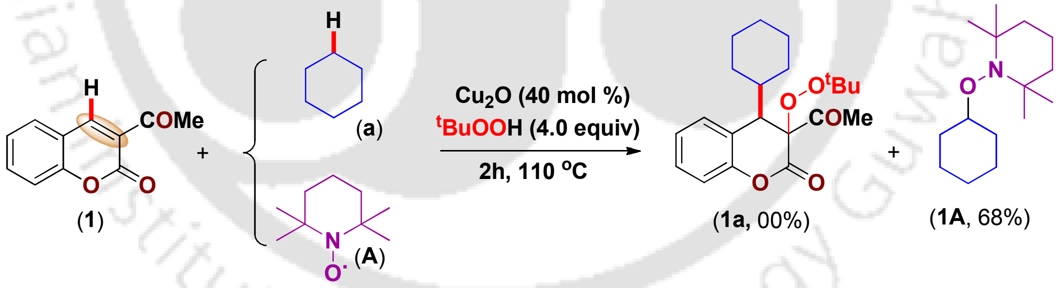
Figure V.3.4. *ORTEP molecular diagram of (**1a'**)*

Styrenes are reported to undergo carbonylation-peroxidation[8] or keto-peroxidation[10] regioselectively in the presence of *tert*-butyl hydroperoxide (TBHP) where the peroxide is attached to the benzylic carbon. Although 3-acetylcoumarin has similar olefinic system to that of styrene, in the present case the peroxidation occurs exclusively at the carbon (C-3) adjacent to the benzylic position. So the query arises as to whether the differential selectivity in the present system is due to the coumarin skeleton alone or whether the EWG present at C-3 position has some influence? To ascertain the role of EWG, unsubstituted coumarin (**21**) and cyclohexane (**a**) were reacted under otherwise identical condition which gave < 10% yield of the cycloalkyl α-peroxy product (**21a**) (path 1, Scheme VIA.3.4). However, when the quantity of Cu_2O was increased to 50 mol % and the oxidant (TBHP) to 6 equiv after 12h, the product (**21a**) was isolated in 41% yield. Spectral analysis of (**21a**) revealed identical regioselectivity to that of EWG substituted coumarins (Scheme VIA.3.1 and Scheme VIA.3.2). Thus EWGs have no effect on the regioselectivity rather it is the intrinsic reactivity of coumarin system itself. To re-ascertain the influence of coumarin system on regioselectivity, styrene (**22**) was treated with cyclohexane (**a**) and TBHP under otherwise identical reaction condition. Surprisingly the product was found to be 2-cyclohexyl-1-phenylethanone (**22a**), obtained in 38% isolated yield (path 2, Scheme VIA.3.4). The product (**22a**) might have originated *via* cycloalkylation-peroxidation path similar to keto-peroxidation[10] and carbonylation-peroxidation.[8] Irrespective of its origin the regioselectivity in syrene system is exactly opposite to that in the coumarin system.



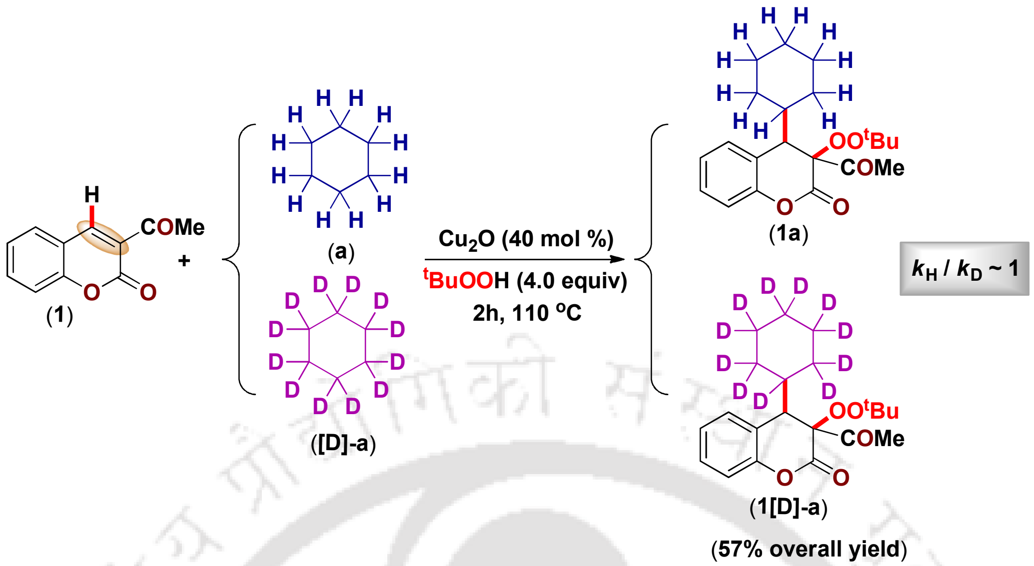
Scheme VIA.3.4. *Reactions with unsubstituted coumarin and styrene*

Mechanistic studies. When a typical reaction between (**1**) and cyclohexane (**a**) was carried out under otherwise identical condition but in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv), no functionalization of coumarin was detected. Formation of TEMPO-cyclohexane adduct (**1A**) confirms the radical nature of the reaction (Scheme VIA.3.5). This experiment supports the formation of cyclohexyl radical in the medium from cyclohexane (**a**) induced radically by Cu_2O/TBHP and also the radical nature of the mechanism.



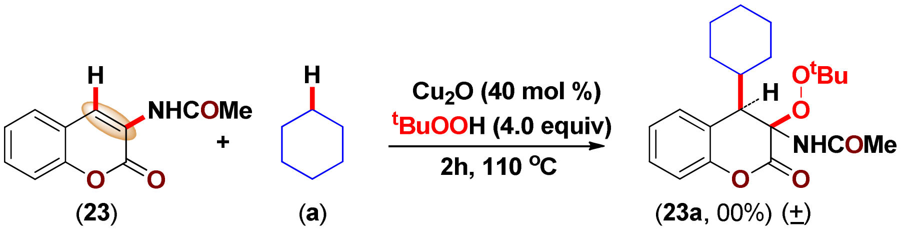
Scheme VIA.3.5. *Reaction in the presence of radical scavanger TEMPO*

No kinetic isotope effect (KIE) ($K_H/K_D \sim 1$) was observed (Scheme VIA.3.6) when 3-acetylcoumarin (**1**) was treated with deuterated cyclohexane (C_6D_{12}) there by ruling out the cleavage of cyclohexyl C–H in the rate determining step.



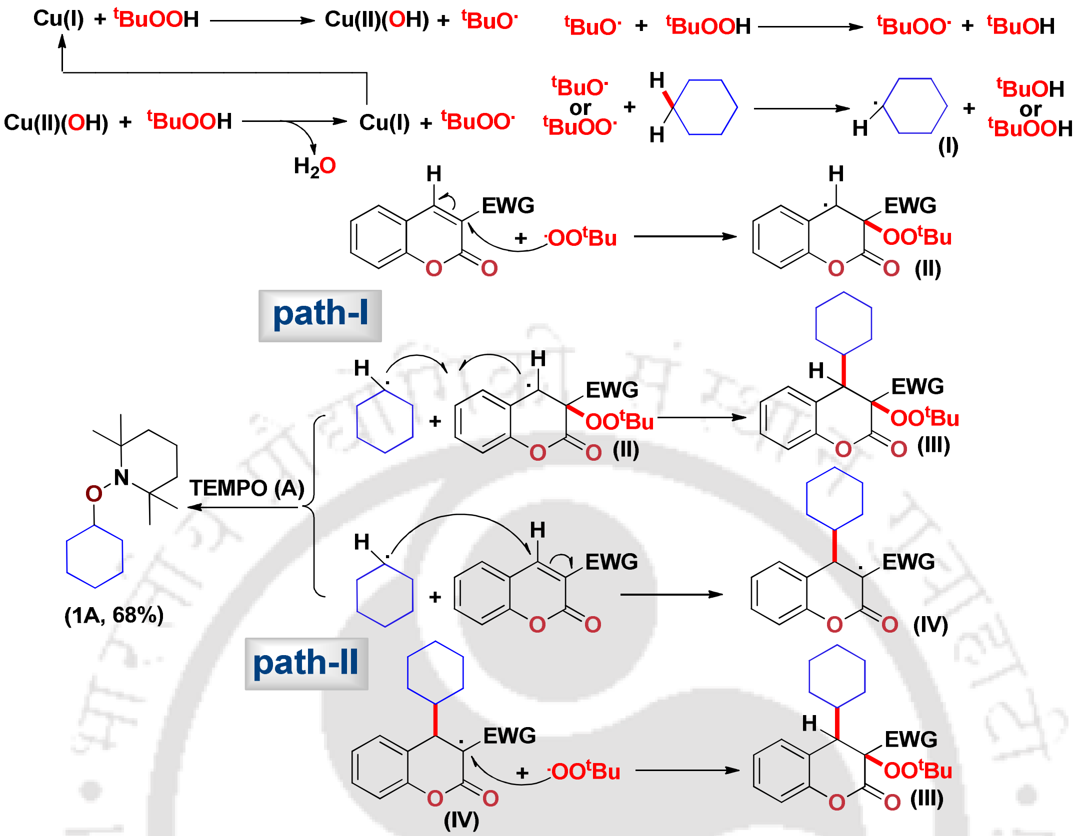
***Scheme VIA.3.6.** KIE experiment with deuterated cyclohexane*

The presence of electron withdrawing groups at C-3 position facilitates attack of ^{t}BuOO radical at the position of the coumarin double bond. An electron-donating group such as –OMe when present *para* to the benzylic position (C-7 of 3-substituted coumarin) as in (**8**) it gives the addition product (**8a**) in lower yield (42%). However when the same substitutent is *meta* to benzylic position (C-8 of 3-substituted coumarin) as in (**7**) the yield obtained was far superior (65%) (Scheme VIA.3.1). Compared to (**8a**), when using 3-acetylcoumarins bearing moderately electron-withdrawing groups such as −Cl, −Br, and strongly electron-withdrawing group $-NO_2$, *meta* to benzylic (C-6 position) as in (**2**), (**3**) and (**4**) products were obtained in good yields (**2a**, 63%), (**3a**, 59%) and (**4a**, 67%) (Scheme VIA.3.1). It was therefore observed that factors stabilizing benzylic radical enhances yields and any destabilizing factors reduces, supporting the generation of benzyl radical at C4 position *via* the attack of *tert*-butylperoxy (^{t}BuOO) radical at C3 of 3-substituted coumarins. To confirm whether the alternate mechanism can be possible or not, weakly electron-donating substituent at C-3 position *viz.* 3-acetamidocoumarin (**23**) was reacted under the optimized reactions. Substrate (**23**) failed to provide any trace of cycloalkylation-peroxidation product (Scheme VIA.3.7) in this case. This confirms that the attack of cyclohexyl radical can also be possible at C4 generating radical at C3 position of 3-substituted coumarins.



Scheme VIA.3.7. *Control experiment*

Based on the above observations and results of the control experiments, alternate mechanisms have been proposed for this Cu(I)-promoted cycloalkylation-peroxidation process (Scheme VIA.3.8). The Cu(I)-assisted cleavage of *tert*-butylhydroperoxide (TBHP) generates *tert*-butoxy radical and Cu(II) species in the medium. The Cu(II) species with another equivalent of TBHP produce ^{t}BuOO radical and Cu(I) for further reaction.[13b] This *tert*-butylperoxy (^{t}BuOO) radical can also be generated by the action of TBHP and *tert*-butoxy (^{t}BuO) radical. The *in situ* generated radical species ^{t}BuO or ^{t}BuOO abstract a proton from cycloalkane to generate a cycloalkyl radical species (**I**). Thus, the attack of ^{t}BuOO radical at the C-3 carbon of coumarin generating a benzylic radical (**II**) could be the rate determining step. Finally the radical cross-coupling between cycloalkyl (**I**) and benzylic (**II**) furnish the cycloalkyl α–peroxy product (**III**) (Scheme VIA.3.8, path I). In an alternate path, initial attack of cycloalkyl radical at the C-4 position of coumarin can generate the radical (**IV**) at the C-3 position which can be stabilized due to the presence of two electron withdrawing groups. The radical cross-coupling between intermediate (**IV**) and ^{t}BuOO radical yields the desired product (Scheme V.3.8, path II).



Scheme VIA.3.8. Proposed mechanism for cycloalkylation-peroxidation

In conclusion, the present protocol demonstrates regioslective cycloalkylation-peroxidation of 3-substituted coumarins. In this three component Cu(I) promoted process the components are coumarin, TBHP and cycloalkane as reactant-cum-solvent where C–O and C–C bonds are installed *via* sp^3 C–H fucntionalization with concurrent generation of two stereocentres. Significant electronic effect was observed in this addition reaction. Interestingly this regioselective difunctionalization in coumarin system is opposite to that of styrene. These tertiary α-peroxy esters so generated have several structural analogy *viz* tertiary peroxy linkage, ester or keto carbonyl and hydrophobic cycloalkyl moiety to well-known antimalarial drugs artemisinin and cardamom peroxide, and thus they may find potential applications in anti-malarial research.

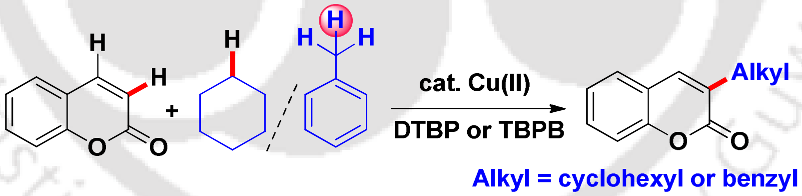
VIB. Iron(III) Catalyzed C-3 Alkylation of Coumarins *via* sp^3 C–H Functionalization

VIB.1. Introduction

Coumarins, a major class of naturally occurring compounds, display a wide range of biological and pharmaceutical activities such as *anti*-breast cancer,[17] *anti*-HIV,[18] *anti*-Alzheimer,[19] vasorelaxant and platelet *anti*-aggregatory.[20] They are also used in organic materials for their competent optical properties.[21] Due to their versatile utility in various fields, any further functionalizations of coumarin moiety may enhance their properties for further applications.

VIB.2. Strategies for Mono Functionalization of Coumarin

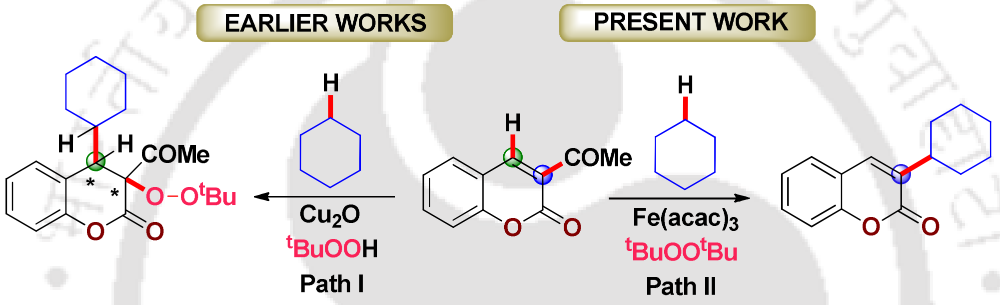
Few direct C–H mono-functionalizations are reported at C-3 and C-4 positions in coumarin using Pd catalysts *viz.* C-4 and C-3 arylation,[22] C-3 olefination[23] and C-3 phosphorylation.[24] Because of their inherent inertness and non availability of coordinating sites for metal binding, direct functionalization of C_{sp3}–H bonds of alkanes is challenging. Recently, C_{sp3}–C_{sp2} type coupling has been established using alkylbenzenes[25] / cycloalkanes[5i] and coumarins (C-3 position) using Cu(II) catalyst (Scheme VIB.2.1).



Scheme VIB.2.1. *Cu(II) catalyzed mono-functionalization involving sp^3 C–H*

In this perspective, ours and other groups[1k,5e-h,6c,13a-b,14a,c-d,26] have made pioneering contribution on sp^3 C–H bond functionalization of alkylbenzenes and cycloalkanes with various coupling partners *via* cross dehyogenative couplings (CDC). Achieving site selectivity in C–H functionalization is one of the major challenges in synthetic organic chemistry. There are only few instances where oxidant dependent regioselective mono and di-functionalizations are reported on internal and terminal alkenes.[7h,8,10,27] Recently Li *et al.* reported selective mono and di-functionalizations of terminal alkenes. The use of DTBP in combination with Fe(III) provided α,β-unsaturated amides whereas oxidant

TBHP under a metal free condition afforded di-functionalized product, α-amino ketones.[28] However, strategy for oxidant dependent regioselective installation of cycloalkanes either at the C-3 or C-4 positions of internal conjugated double bonds is unfamiliar. In section A, we have demonstrated C4 cycloalkylation-C3 peroxidation of 3-subsituted coumarins using cat. Cu(I) / TBHP (Scheme VIB.2.2, path I)[29], a query arrises whether the opposite selectivity is possible or not?. In a quest to achieve the reverse selectivity, we switched the catalyst from Cu(I) to Fe(III) and oxidant TBHP to DTBP which provied the opposite selectivity (C3 cycloalkylation). Herein, we report selective C-3 benzylation / cycloalkylation of 3-substituted coumarins using cat. Fe(III) / DTBP combination (Scheme VIB.2.2, path II).

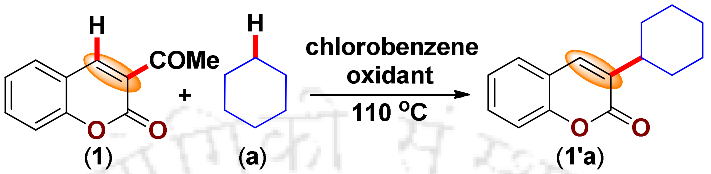


Scheme VIB.2.2. C-3 vs C-4 cycloalkylation of 3-substituted coumarin

VIB.3. Present Work

Initially we investigated the reaction between 3-acetylcoumarin (**1**) and cyclohexane (**a**) using different oxidants/catalysts combinations. At first 3-acetylcoumarin (**1**) was reacted with cyclohexane (**a**) and DTBP (3 equiv) in chlorobenzene at 110 °C. A new product was isolated by column chromatography, spectroscopic (^{1}H and ^{13}C NMR) analysis of the product (**1'a**) showed the presence of a cyclohexyl moiety and the absence of the acetyl (–COMe) group. This confirms the addition of a cyclohexyl moiety and elimination of an acetyl group during the process. Further, comparison of spectral data of (**1'a**) with the literature reported compound[51.25] confirms the cycloalkylation at C-3 position. This unprecedented C-3 cycloalkylation product (**1'a**) was however obtained in a low yield of 20% (Table VIB.3.1, entry 1). Increasing the oxidant (DTBP) quantity from 3.0 to 4.0 equiv the mono-functionalized product was obtained in an improved yield of 40% (Table VIB.3.1, entry 2). A variety of metal catalysts were then screened to get the optimum yield of (**1'a**). The use of 10 mol % of Cu(II) catalysts such as $Cu(OAc)_2$ and $CuCl_2$ provided comparable yields (34% and 38%) (Table VIB.3.1, entries 3-4) to that of metal free reaction. Among the iron catalysts such as $FeCl_2$, Fe_3O_4 and $Fe(acac)_3$ screened, the later provided best yield of 53% (Table VIB.3.1, entries 5-7). Further, the yield remain unaltered (52%) even when the catalyst $Fe(acac)_3$ loading was reduced to 5 mol % under otherwise identical conditions (Table VIB.3.1, entry 8).

Table VIB.3.1. *Optimization of reaction parameters*



Entry	Catalyst (mol %)	Oxidant (equiv)[c]	Yield (%)[a,b] **1'a**
1	——	DTBP (3.0)	20
2	——	DTBP (4.0)	40
3	$Cu(OAc)_2$(10.0)	DTBP (4.0)	34
4	$CuCl_2$(10.0)	DTBP (4.0)	38
5	$FeCl_2$(10.0)	DTBP (4.0)	26
6	Fe_3O_4(10.0)	DTBP (4.0)	Trace
7	$Fe(acac)_3$ (10.0)	DTBP (4.0)	53
8	**$Fe(acac)_3$ (5.0)**	**DTBP (4.0)**	**52**

[a]Reaction conditions: **1** (0.25 mmol), cyclohexane (**a**) (0.5 mL) in chlorobenzene (1.0 mL) at 110 °C for 12 h. [b]Isolated yield. [c]Oxidant DTBP was used portion wise (four times).

After establishing the optimized C-3 alkylation process (Table VIB.3.1, entry 8), we first started the coupling of 3-acetyl coumarin (**1**) with cyclohexane (**a**) in the presence of $Fe(acac)_3$/DTBP. 3-Acetylcoumarins containing electron-donating and withdrawing substituents are compatible for this methodology providing the desired C-3 alkylation products. Coumarins containing electron-donating substituents such as 7-OMe (**7**), 8-OEt (**24**) and 6,8-di-^{t}Bu (**25**) all provided their desired C-3 cycloalkylated products (**7'a**), (**24'a**) and (**25'a**) in moderate to good yields (Scheme VIB.3.1). Mono and disubstituted 3-acetylcoumarins having electron-withdrawing groups in their 6 and 8 positions such as 6-NO_2 (**4**), 6,8-diCl (**5**) and 6,8-diBr (**6**) all underwent C-3 cycloalkylation providing their desired products (**4'a**), (**5'a**) and (**6'a**), however in relatively lower yields (Scheme VIB.3.1). 3-Acetylcoumarin containing an extra phenyl ring fused to C5-C6 position also coupled with cyclohexane to provide the desired product (**9'a**) in fair yield. This methodology is compatible to five member cyclic alkane cyclopentane (**b**) giving moderate yield of 3-cyclopentylcoumarin as the product (**1'b**). Cyclooctane (**c**), a higher membered cycloalkane, when reacted with 3-acetylcoumarin (**1**) under the optimized reaction conditions provided the desired product (**1'c**) in good yield (Scheme VIB.3.1). The structure of product (**1'c**) has been further confirmed by X-ray crystallographic analysis as shown in Fig. VIB.3.1.

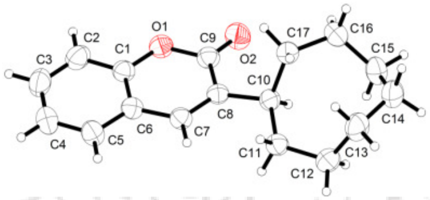
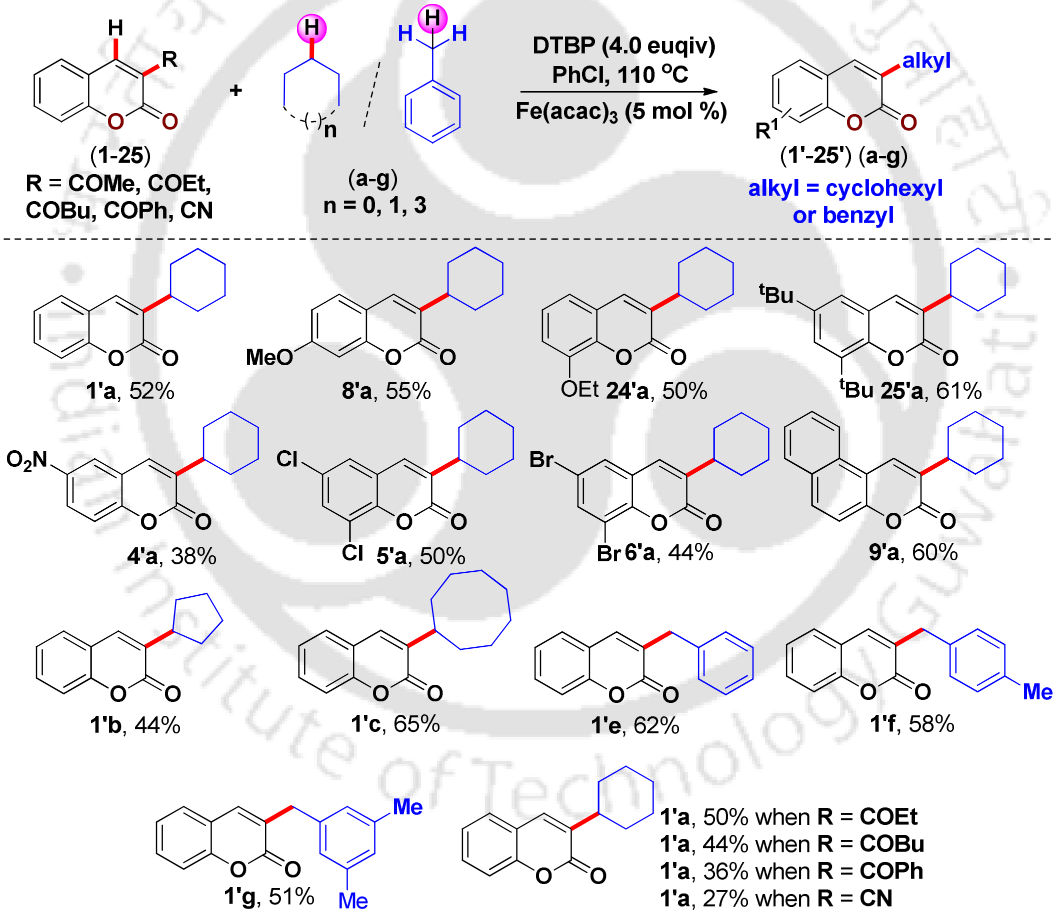


Fig. VIB.3.1. *Ortep view of compound (**1'c**)*

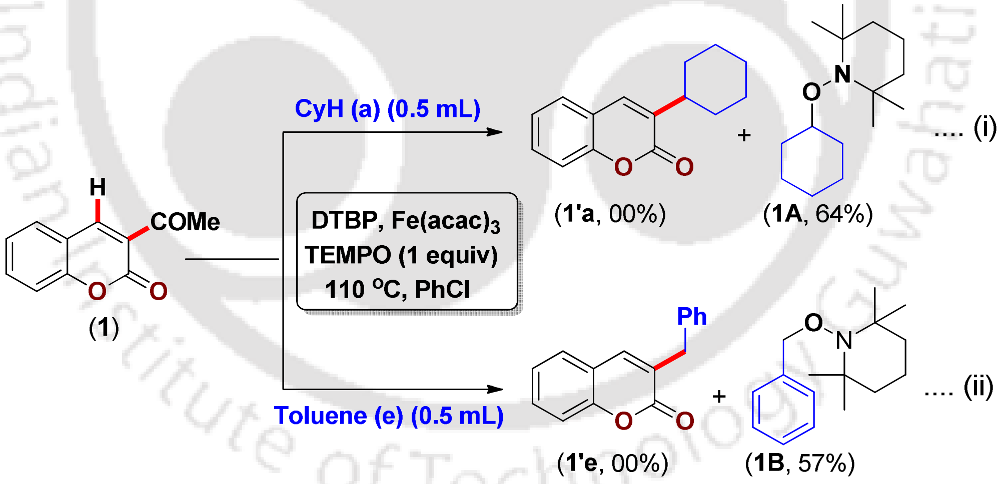
Scheme VIB.3.1. *Substrate scope for C-3 alkylation of coumarins*[a,b]



[a]Reaction conditions: **1** (0.25 mmol), DTBP (4 equiv), Fe(acac)$_3$ (5 mol %), cyclohexane (**a**) (0.5 mL) in chlorobenzene (1.0 mL) at 110 °C for 12 h. [b]Isolated yield.

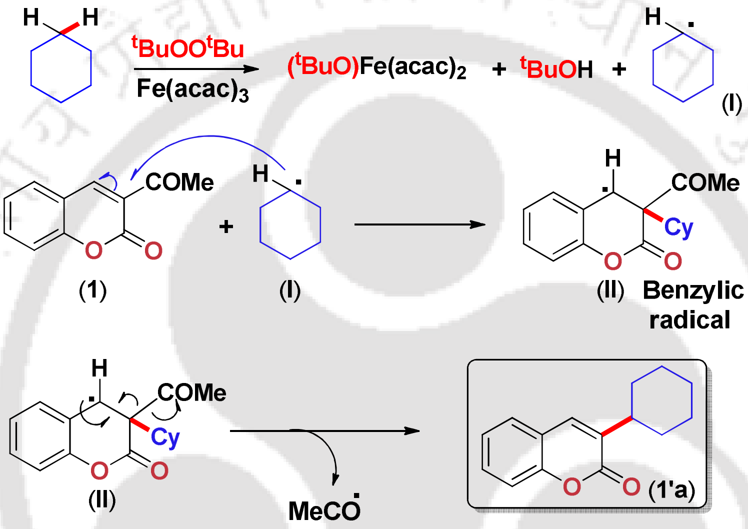
To explore the scope and generality of this methodology, other solvents containing C_{sp3}–H bonds like alkylbenzene, 1,4-dioxane were tested with substrate (**1**) for this C-3 functionalization. Toluene (**e**), *p*-xylene (**f**) and mesitylene (**g**) all underwent smooth reaction when treated with (**1**) under otherwise identical conditions to provide their desired products (**1e**), (**1f**) and (**1g**) in 62%, 58% and 51% yields (Scheme VIB.3.1). However, surprisingly no targeted product was observed when 1,4-dioxane was used as the coupling counterpart. Other C-3 substituted coumarins such as 3-propionyl (-COEt) (**10**), 3-pentanoyl (-COBu) (**11**), 3-benzoyl (-COPh) (**12**) and 3-CN (**13**) under otherwise identical conditions all provided their expected C-3 cycloalkylated product (**1'a**) in moderate to low yields using cyclohexane as the coupling partner (Scheme VIB.3.1).

Several controlled experiments were conducted to elucidate the possible mechanism of this C3 alkylation process. To ascertain whether this reaction is going *via* radical pathways or not, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (**A**) was used as the radical scavenger for this reaction. During C-3 alkylation process when a typical reaction was carried out between 3-acetylcoumarin (**1**) and cyclohexane (**a**) or toluene (**e**) in the presence of TEMPO under otherwise identical conditions, no C-3 alkylated products (**1'a**) or (**1'e**) were obtained (Scheme VIB.3.2, path i and ii). However, TEMPO-cyclohexyl (**1A**) and TEMPO-benzylic (**1B**) adducts were isolated in good yields (Scheme VIB.3.2, path i and ii).



Scheme VIB.3.2. *Control experiments*

No kinetic isotope effects (K_H/K_D~1) were observed when 3-acetylcoumarin (**1**) was treated with an equal mixture (1:1) of cyclohexane (C_6H_{12}):deuterated cyclohexane (C_6D_{12}) during mono functionalization process under identical conditions. Thus, the sp^3 C–H cleavage of cyclohexane is not the rate determining step for this process. Based on the results of control experiments and previous reports, plausible mechanism has been proposed for this selective *mono* functionalization process. For C-3 alkylation the cleavage of DTBP is facilitated by Fe(III)(acac)$_3$ generating *tert*-butoxy (^{t}BuO$^\cdot$) radical which abstract a proton from cycloalkane giving cycloalkyl radical (**I**) and ^{t}BuOH (Scheme VIB.3.3). The attack of cycloalkyl radical at C-3 carbon generates a coumarin benzylic radical (**II**) (Scheme VIB.3.3, path I). The cleavage of acetyl group from (**II**) regenerates C3-C4 double bond leading to product (**1'a**) (Scheme VIB.3.3). Similar addition reaction with simple coumarin (without C-3 substitution) is completely inefficient suggesting the involvement of C-3 substituents during addition as well as elimination processes.



Scheme VIB.3.3. *Proposed mechanism for mono functionalization*

In conclusion, we have developed the first site selective C-3 cycloalkylation / benzylation of 3-substitued coumarins under Fe(III) / DTBP condition. This mono-functionalization is taking place at the expense of an existing C–C bond along with the generation of new C–C bond at C3. The use of cheap iron(III) catalyst for C-3 alkylation process makes this protocol more practical.

VI.4. Experimental Section

VI.4.1. General Information: All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F$_{254}$ (0.25 mm). NMR spectra were recorded in CDCl$_3$

with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz), $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. Starting materials (3-substituted coumarins) are prepared by reacting salicylaldehydes with active methylene compounds (diethyl malonate / ethylcyanoacetate / ethyl acetoacetate etc.) in presence of catalytic amount of piperidine using Knoevenagel condensation.[30]

VI.4.2. Crystallographic description

- **VIA.4.2:**

CCDC number for compounds 2a, 20a and 1a': CCDC 1011616, 1011614 and 1011615. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif.

Crystallographic description of 2a: Crystal dimension (mm): 0.34 x 0.22 x 0.20. $C_{21}H_{27}ClO_5$, Mr = 394.88. monoclinic, space group p 21/n; a = 17.6306(4)Å, b = 6.5284(2)Å, c = 18.1875(4) Å; $\alpha = 90^o$, $\beta = 96.701(1)^o$, $\gamma = 90^o$, V = 2079.07(9) $Å^3$; Z = 4; ρ_{cal}= 1.262g/cm^3; μ (mm^{-1}) = 0.211; *F (000)* = 840.0; Reflection collected / unique = 3665 / 3560; Refinement method = Full-matrix least-squares on F^2; Final R indices [$I>2\sigma_I$] R1 = 0.0395, wR2 = 0.0988, R indices (all data) R1 = 0.0484, wR2 = 0.1038; goodness of fit = 1.078.

Crystallographic description of 20a: Crystal dimension (mm): 0.34 x 0.22 x 0.20. $C_{20}H_{25}NO_4$, Mr = 343.41. monoclinic, space group p 21/n; a = 9.6382(7) Å, b = 12.5190(9) Å, c = 16.1542(12) Å; $\alpha = 90^o$, $\beta = 101.439(2)^o$, $\gamma = 90^o$, V = 1910.5(2) $Å^3$; Z = 4; ρ_{cal}= 1.194g/cm^3; μ (mm^{-1}) = 0.083; *F (000)* = 736.0; Reflection collected / unique = 1879 / 1469; Refinement method = Full-matrix least-squares on F^2; Final R indices [$I>2\sigma_I$] R1 = 0.0374, wR2 = 0.0980, R indices (all data) R1 = 0.0483, wR2 = 0.1100; goodness of fit = 1.150.

Crystallographic description of 1a': Crystal dimension (mm): 0.32 x 0.20 x 0.18. $C_{15}H_{16}O_3$, Mr = 244.28. monoclinic, space group p 21/n; a = 5.518(2)) Å, b = 26.082(10) Å, c = 8.581(5) Å; $\alpha = 90^o$, $\beta = 94.23(4)^o$, $\gamma = 90^o$, V = 1231.6(10) $Å^3$; Z = 4; ρ_{cal}= 1.379 g/cm^3; μ (mm^{-1}) = 0.091; *F (000)* = 520.0; Reflection collected / unique = 2175 / 2174; Refinement method = Full-matrix least-squares on F^2; Final R indices [$I>2\sigma_I$] R1 = 0.0522, wR2 = 0.1400, R indices (all data) R1 = 0.0677, wR2 = 0.1497; goodness of fit = 1.144.

➢ **VIB.4.2:**

CCDC number for compound 1'c: CCDC 1412809. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif.

Crystallographic description of 1'c: Crystal dimension (mm): 0.38 x 0.20 x 0.16. $C_{17}H_{20}O_2$, Mr = 256.33. triclinic, space group p -1; a = 6.7321 (3) Å, b = 9.3720 (4) Å, c = 11.4758 (5) Å; α = 95.498 (3)°, β = 99.490 (3)°, γ = 104.725 (3)°, V = 683.45 (5) $Å^3$; Z = 2; ρ_{cal}= 1.246g/cm^3; μ (mm^{-1}) = 0.080; *F (000)* = 276.0; Reflection collected / unique = 2348 / 1909; Refinement method = Full-matrix least-squares on F^2; Final R indices [$I>2\sigma_I$] R1 = 0.0389, wR2 = 0.0985, R indices (all data) R1 = 0.0480, wR2 = 0.1132; goodness of fit = 1.079.

VI.4.3. General procedure for di and monofunctionalizations:

➢ **VIA.4.3. General procedure for the synthesis of 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (1a) from 3-acetyl-2H-chromen-2-one (1), cyclohexane (a) and *tert*-butyl hydroperoxide:** To an oven-dried 25 mL round bottom flask fitted with a reflux condenser was added 3-acetylcoumarin (**1**) (0.094 g, 0.5 mmol), decane solution of TBHP (5–6 M) (400 μL, 2.0 mmol), Cu_2O (0.030 g, 0.2 mmol), and cyclohexane (**a**) (2.5 mL). The reaction mixture was refluxed in an oil bath preheated to 110 °C. After completion of the reaction (2 h) solvent was evaporated under reduced pressure. The reaction mixture was cooled to room temperature, admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x10 mL). The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 10:0.1) to give pure 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (**1a**) (0.108 g, yield 60%). The identity and purity of the product was confirmed by spectroscopic analysis. The same procedure was also followed for cycloalkylaion-peroxidaion of other 3-substituted coumarins (**2**-**23**) with cycloalkanes (**a**-**d**).

➢ **VIB.4.3. General procedure for the synthesis of 3-cyclohexyl-2H-chromen-2-one (1'a) from 3-acetyl-2H-chromen-2-one (1) and cyclohexane (a):** To an oven dried 25 mL round bottom flask fitted with reflux condenser, 3-acetylcoumarin (**1**) (0.047 g, 0.25

mmol), di-*tert*-butylperoxide DTBP (0.146 g, 1.0 mmol), Fe(acac)$_3$ (0.004 g, 0.013 mmol) and cyclohexane (**a**) (0.5 mL, 4.6 mmol) were added together in chlorobenzene (1.0 mL) solvent. The reaction mixture was then heated in an oil bath at 110 ^{o}C. The progress of the reaction was monitored by TLC and after completion of reaction (12 h) solvents were evaporated under reduced pressure. The reaction mixture was then cooled to room temperature, admixed with water (2 mL). It was then extracted with ethyl acetate (3 x 10 mL), dried over anhydrous sodium sulphate Na_2SO_4, and evaporated under reduced pressure. The crude product obtained here was further purified over a short column of silica gel (hexane / ethyl acetate, 10:0.1) to give pure 3-cyclohexyl-2*H*-chromen-2-one (**1'a**) (0.030 g, yield 52%). The identity and purity of the product was confirmed by spectroscopic analysis. The same procedure was also followed for C-3 cycloalkylaion of other 3-substituted coumarins (**4**-**25**) with alkanes (**a**-**g**).

VI.4.4. Mechanistic investigations

- **VIA.4.4. Trapping of radical intermediate with radical scavenger TEMPO during difunctionalization:** An oven-dried 25 mL round bottom flask was charged with 3-acetylcoumarin (**1**) (0.094 g, 0.5 mmol), Cu_2O (0.030 g, 40 mol %), decane solution of TBHP (5–6 M) (400 µL, 4 mmol), TEMPO (**A**) (0.078 g, 0.5 mmol) in cyclohexane (**a**) (2.5 mL). The flask was fitted to a reflux condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^{o}C for 2 h. After completion of the reaction the cyclohexyl-TEMPO adduct 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (**1A**) was isolated in 68% yield but no traces of the desired product (**1a**) was obtained. This experiment supports the formation of cyclohexyl radical in the medium from cyclohexane (**a**) induced radically by Cu_2O/TBHP and also the radical nature of the mechanism.

- **VIB.4.4. Trapping of radical intermediates (cyclohexyl and benzyl) with TEMPO during mono-functionalization:** An oven-dried 25 mL round bottom flask was charged with 3-acetylcoumarin (**1**) (0.047 g, 0.25 mmol), di-*tert*-butylperoxide DTBP (0.146 g, 1.0 mmol), Fe(acac)$_3$ (0.004 g, 0.013 mmol), TEMPO (**A**) (0.039 g, 0.25 mmol) and cyclohexane (**a**) (0.5 mL, 4.6 mmol) in chlorobenzene (1.0 mL). The flask was fitted with a reflux condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^{o}C for 12 h. After 12 h of the reaction and usual work up the cyclohexyl-TEMPO adduct 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (**1A**) was obtained in 64% isolated yield with no traces of the desired product (**1'a**). Similar reaction between 3-acetylcoumarin (**1**)

(0.047 g, 0.25 mmol) and toluene (**e**) (0.5 mL, 4.7 mmol) in the presence of radical scavenger TEMPO (**A**) (0.039 g, 0.25 mmol) under otherwise identical reaction conditions to that of above provided benzyl-TEMPO adduct 1-(benzyloxy)-2,2,6,6-tetramethylpiperidine (**1B**) in 57% isolated yield with no trace of desired product (**1'e**).

VI.4.5. Kinetic isotope effect studies

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

- **VIA.4.5. (a) Kinetic isotope effect studies with deuterated cyclohexane during difunctionalization:** To an oven-dried 25 mL round bottom flask fitted with a reflux condenser was added 3-acetylcoumarin (**1**) (0.047 g, 0.25 mmol), decane solution of TBHP (5–6 M) (200 µL, 1.0 mmol), Cu_2O (0.015 g, 0.1 mmol) in cyclohexane (**a**) (1.2 mL) and d_{12}-cyclohexane (**[D]-a**) (1.2 mL). The reaction mixture was refluxed in an oil bath preheated to 110 °C. After completion of the reaction (2 h) solvent was evaporated under reduced pressure. The reaction mixture was then worked up in usual procedure and the crude product was purified over a column of silica gel eluted with 1% ethyl acetate in hexane to give cyclohexyl α-peroxy coumarins (**1a** and **1[D]-a**) in 57% overall yield. The k_H / k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed no significant KIE (k_H / k_D = 1.00). This result indicated that the cyclohexane's sp^3 C–H bond cleavage is not involved in the rate-determining step during this cycloalkylation-peroxidation process.

- **VIB.4.5. (a) Kinetic isotope effect studies with deuterated cyclohexane duing mono functionalization:** An oven-dried 25 mL round bottom flask was charged with 3-acetylcoumarin (**1**) (0.094 g, 0.50 mmol), di-*tert*-butylperoxide DTBP (0.292 g, 2.0 mmol), $Fe(acac)_3$ (0.008 g, 0.026 mmol) in cyclohexane (**a**) (0.5 mL, 4.6 mmol) and d_{12}-cyclohexane (**[D]-a**) (0.5 mL) in presence of chlorobenzene (1.0 mL) solvent. The flask was fitted with a reflux condenser and the reaction mixture was stirred in a preheated oil bath at 110 °C for 12 h. The reaction mixture was then worked up in usual procedure and the crude product was purified over a column of silica gel eluted with 1% ethyl acetate in hexane to give cyclohexyl coumarins (**1'a** and **1'[D]-a**) in 17% overall yield. The k_H / k_D calculated on the basis of ^{1}H NMR analysis of the pure product showed no significant KIE

(k_H / k_D ≈ 1.00). This result indicated that the cyclohexane's sp^3 C–H bond cleavage is not involved in the rate-determining step of this process.

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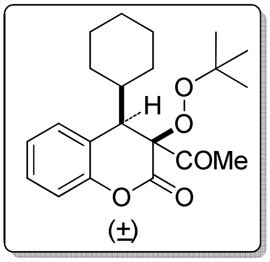
VI.6. Spectral Data

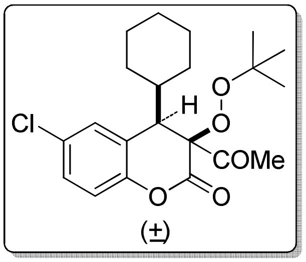
➢ VIA.6.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (1a):



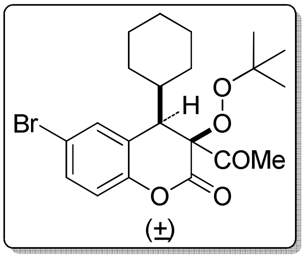
Solid; M.p. 179–181 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31–7.27 (m, 1H), 7.14–7.07 (m, 2H), 7.03 (d, 1H, J = 8.0 Hz), 2.97 (d, 1H, J = 3.2 Hz), 2.47 (s, 3H), 1.76–1.51 (m, 6H), 1.30–1.12 (m, 3H), 1.01 (s, 9H), 0.91–0.81 (m, 1H), 0.64–0.53 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 203.5, 161.2, 151.2, 130.2, 128.6, 123.9, 121.1, 116.3, 86.1, 82.3, 48.9, 38.4, 32.4, 27.1, 26.9, 26.7, 26.2, 25.9, 25.8; IR (KBr, cm^{-1}): 2985, 2976, 2935, 2956, 1779, 1717, 1615, 1587, 1491, 1462, 1451, 1422, 1389, 1380, 1365, 1355, 1303, 1261, 1241, 1197, 1179, 1118, 1068, 1015, 918, 876, 779, 774; HRMS (ESI) calcd for $C_{21}H_{28}O_5$ (M + Na$^+$) 383.1829, found 383.1830.

3-Acetyl-3-(*tert*-butylperoxy)-6-chloro-4-cyclohexylchroman-2-one (2a):



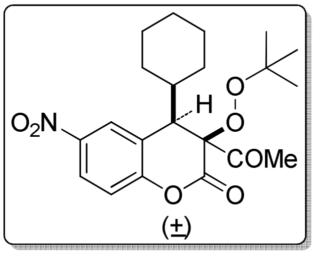
Solid; M.p. 167–170 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28–7.25 (m, 1H), 7.08 (d, 1H, J = 2.4 Hz), 6.98 (d, 1H, J = 9.2 Hz), 2.95 (d, 1H, J = 2.4 Hz), 2.47 (s, 3H), 1.74–1.71 (m, 2H), 1.61–1.54 (m, 4H), 1.29–1.12 (m, 3H), 1.03 (s, 9H), 0.94–0.84 (m, 1H), 0.62–0.52 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 203.0, 160.6, 149.7, 129.8, 128.9, 128.7, 122.8, 117.5, 85.5, 82.5, 48.7, 38.2, 32.2, 27.0, 26.9, 26.5, 26.2, 25.8, 25.7; IR (KBr, cm^{-1}): 2983, 2945, 2924, 2857, 1794, 1723, 1482, 1452, 1415, 1364, 1357, 1273, 1258, 1227, 1215, 1196, 1179, 1147, 1118, 1094, 1083, 1066, 1042, 1029, 930, 911, 898, 891, 882, 873, 848, 835, 812, 790, 759, 745, 745, 713; HRMS (ESI) calcd for $C_{21}H_{27}ClO_5$ (M + Na$^+$) 417.1439, found 417.1438.

3-Acetyl-6-bromo-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (3a):



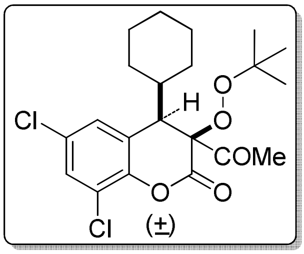
Solid; M.p. 152–154 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.38 (d, 1H, J = 8.4 Hz), 7.19 (d, 1H, J = 2.4 Hz), 6.89 (d, 1H, J = 9.2 Hz), 2.91 (d, 1H, J = 2.8 Hz), 2.44 (s, 3H), 1.71–1.68 (m, 2H), 1.59–1.51 (m, 4H), 1.23–1.09 (m, 3H), 1.00 (s, 9H), 0.92–0.86 (m, 1H), 0.56–0.52 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 202.9, 160.6, 150.4, 132.7, 131.7, 131.2, 118.9, 118.0, 85.6, 82.6, 48.8, 38.4, 32.3, 27.1, 26.9, 26.6, 26.3, 25.9, 25.8; IR (KBr, cm^{-1}): 2940, 2926, 2852, 1791, 1702, 1697, 1684, 1653, 1633, 1559, 1478, 1450, 1412, 1389, 1364, 1260, 1245, 1225, 1175, 1153, 1093, 1022, 912, 891, 873, 858, 812, 773; HRMS (ESI) calcd for $C_{21}H_{27}BrO_5$ (M + Na$^+$) 461.0934, found 461.0928.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexyl-6-nitrochroman-2-one (4a):



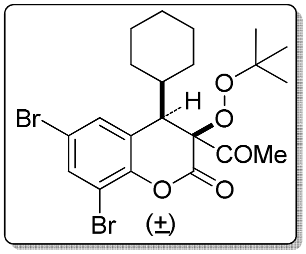
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.21 (d, 1H, J = 9.0 Hz), 8.02 (d, 1H, J = 2.8 Hz), 7.17 (d, 1H, J = 8.8 Hz), 3.09 (d, 1H, J = 2.8 Hz), 2.49 (s, 3H), 1.74–1.53 (m, 6H), 1.29–1.08 (m, 3H), 1.01 (s, 9H), 0.90–0.79 (m, 1H), 0.56–0.47 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 202.4, 159.6, 155.6, 143.8, 125.7, 124.7, 122.6, 117.2, 85.2, 82.8, 48.8, 38.2, 32.1, 27.1, 26.9, 26.4, 26.2, 25.8, 25.6; IR (KBr, cm^{-1}): 3090, 2984, 2925, 2853, 1792, 1726, 1627, 1589, 1559, 1527, 1483, 1450, 1433, 1392, 1367, 1341, 1322, 1308, 1260, 1232, 1219, 1184, 1154, 1119, 1087, 1066, 1043, 1029, 1010, 967, 932, 915, 902, 868, 841, 812, 777, 757, 752, 742; HRMS (ESI) calcd for $C_{21}H_{27}NO_7$ (M + Na$^+$) 428.1680, found 428.1678.

3-Acetyl-3-(*tert*-butylperoxy)-6,8-dichloro-4-cyclohexylchroman-2-one (5a):



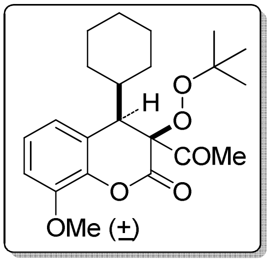
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J = 2.0 Hz), 2.92 (d, 1H, J = 3.2 Hz), 2.41 (s, 3H), 1.67–1.64 (m, 2H), 1.55–1.48 (m, 4H), 1.22−1.04 (m, 3H), 0.98 (s, 9H), 0.88−0.78 (m, 1H), 0.56−0.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.6, 159.4, 145.8, 129.1, 128.8, 128.2, 124.3, 122.1, 85.2, 82.6, 49.0, 38.0, 32.2, 27.0, 26.9, 26.4, 26.0, 25.8, 25.6; IR (KBr, cm^{-1}): 3084, 2979, 2928, 2853, 1795, 1721, 1458, 1420, 1363, 1262, 1249, 1212, 1182, 1154, 1123, 1100, 1070, 1044, 1014, 973, 937, 917, 900, 881, 869, 855, 825, 786, 754, 747; HRMS (ESI) calcd for $C_{21}H_{26}Cl_2O_5$ (M + Na$^+$) 451.1049, found 451.1054.

3-Acetyl-6,8-dibromo-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (6a):



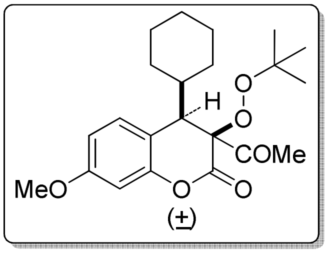
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 1H, *J* = 2.4 Hz), 7.13 (d, 1H, *J* = 2.0 Hz), 2.91 (d, 1H, *J* = 3.2 Hz), 2.44 (s, 3H), 1.70−1.49 (m, 6H), 1.23−1.09 (m, 3H), 1.01 (s, 9H), 0.92−0.85 (m, 1H), 0.56−0.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.6, 159.5, 147.4, 134.8, 131.8, 124.8, 116.4, 111.1, 85.3, 82.8, 49.2, 38.2, 32.3, 27.1, 27.0, 26.9, 26.5, 26.2, 25.8, 25.7; IR (KBr, cm^{-1}): 2959, 2928, 2854, 1801, 1723, 1683, 1646, 1566, 1558, 1449, 1413, 1365, 1261, 1244, 1189, 1148, 1095, 1023, 931, 865, 802; HRMS (ESI) calcd for $C_{21}H_{26}Br_2O_5$ (M + Na$^+$) 539.0039, found 539.0038.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexyl-8-methoxychroman-2-one (7a):



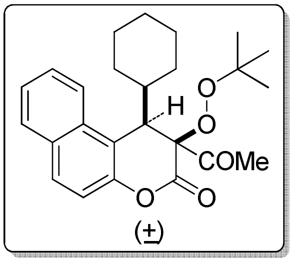
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.02 (d, 1H, *J* = 7.8 Hz), 6.87 (d, 1H, *J* = 7.8 Hz), 6.64 (d, 1H, *J* = 7.2 Hz), 3.86 (s, 3H), 2.94 (d, 1H, *J* = 3.0 Hz), 2.46 (s, 3H), 1.73−1.48 (m, 6H), 1.26−1.10 (m, 3H), 0.99 (s, 9H), 0.87−0.83 (m, 1H), 0.64−0.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 203.5, 160.6, 147.1, 140.4, 123.7, 122.2, 121.8, 111.4, 85.8, 82.2, 56.2, 48.9, 38.2, 32.5, 27.2, 27.0, 26.7, 26.1, 25.9, 25.8; IR (KBr, cm^{-1}): 2980, 2931, 2855, 1781, 1721, 1618, 1588, 1558, 1506, 1485, 1458, 1366, 1322, 1305, 1276, 1248, 1185, 1161, 1108, 1062, 1016, 971, 913, 869, 800, 785, 761, 734; HRMS (ESI) calcd for $C_{22}H_{30}O_6$ (M + Na$^+$) 413.1934, found 413.1940.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexyl-7-methoxychroman-2-one (8a):



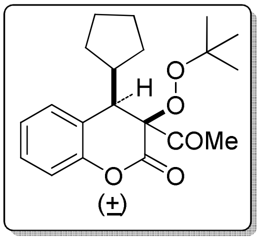
Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 6.96 (d, 1H, J = 8.4 Hz), 6.66 (dd, 1H, J_1 = 9.0 Hz, J_2 = 3.0 Hz), 6.58 (d, 1H, J = 2.4 Hz), 3.80 (s, 3H), 2.91 (d, 1H, J = 3.0 Hz), 2.45 (s, 3H), 1.73–1.66 (m, 2H), 1.58–1.49 (m, 4H), 1.27–1.12 (m, 3H), 1.03 (s, 9H), 0.88–0.85 (m, 1H), 0.59–0.57 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 203.5, 161.2, 159.9, 151.9, 130.7, 112.9, 109.9, 101.9, 86.2, 82.3, 55.7, 48.3, 38.6, 32.3, 27.0, 26.8, 26.7, 26.3, 25.9, 25.8; IR (KBr, cm^{-1}): 2990, 2969, 2927, 2850, 1775, 1722, 1624, 1585, 1559, 1507, 1453, 1432, 1364, 1321, 1285, 1277, 1238, 1210, 1189, 1156, 1124, 1090, 1045, 1030, 922, 902, 886, 870, 859, 838, 806, 792, 763, 747, 712; HRMS (ESI) calcd for $C_{22}H_{30}O_6$ (M + Na$^+$) 413.1934, found 413.1944.

2-Acetyl-2-(*ter*t-butylperoxy)-1-cyclohexyl-1H-benzo[*f*]chromen-3(2H)-one (9a):



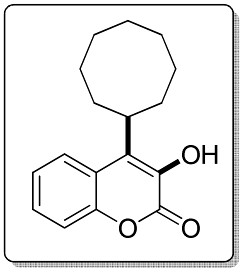
Solid; M.p. 153–155 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.88 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.55 (d, 1H, J = 7.2 Hz), 7.45 (t, 1H, J = 7.0 Hz), 7.20 (t, 1H, J = 9.2 Hz), 3.75 (d, 1H, J = 3.6 Hz), 2.54 (s, 3H), 1.84–1.42 (m, 6H), 1.18–1.05 (m, 3H), 0.88 (s, 9H), 0.85–0.79 (m, 1H), 0.75–0.66 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 203.7, 161.3, 148.8, 132.3, 131.2, 129.4, 129.1, 127.1, 125.1, 123.9, 116.7, 116.2, 85.5, 82.3, 44.3, 39.1, 33.3, 28.6, 27.5, 26.8, 26.4, 26.2, 25.6; IR (KBr, cm^{-1}): 2942, 2927, 2851, 1786, 1747, 1721, 1628, 1603, 1559, 1516, 1507, 1463, 1438, 1395, 1367, 1264, 1220, 1186, 1161, 1117, 1080, 1063, 1045, 1028, 975, 91, 864, 817, 789, 752; HRMS (ESI) calcd for $C_{25}H_{30}O_5$ (M + Na$^+$) 433.1985, found 433.1990.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclopentylchroman-2-one (1b):



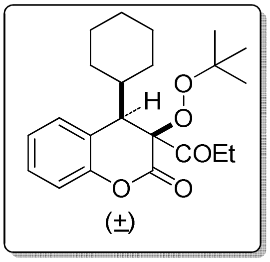
Solid; M.p. 160–162 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.29–7.25 (m, 1H), 7.12–7.06 (m, 2H), 7.01 (d, 1H, *J* = 8.0 Hz), 3.25 (d, 1H, *J* = 4.0 Hz), 2.46 (s, 3H), 1.93–1.84 (m, 1H), 1.69–1.65 (m, 2H), 1.43–1.35 (m, 4H), 1.29–1.21 (m, 1H), 0.99 (s, 9H), 0.79–0.68 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 203.3, 161.2, 151.3, 130.4, 128.7, 123.9, 121.7, 116.3, 86.5, 82.3, 45.6, 39.7, 31.1, 27.2, 26.5, 26.2, 24.4, 23.5; IR (KBr, cm^{-1}): 2987, 2957, 2872, 1781, 1717, 1615, 1588, 1489, 1460, 1423, 1377, 1366, 1356, 1226, 1197, 1169, 1132, 1117, 1093, 1056, 1017, 988, 918, 904, 774, 754, 720; HRMS (ESI) calcd for $C_{20}H_{26}O_5$ (M + Na$^+$) 369.1672, found 369.1674.

4-Cyclooctyl-3-hydroxy-2H-chromen-2-one (1c'):



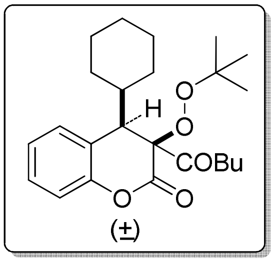
Solid; M.p. 149–152 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.69 (d, 1H, *J* = 8.4 Hz), 7.46–7.43 (m, 1H), 7.41–7.23 (m, 2H), 6.42 (s, 1H), 2.22–2.14 (m, 1H), 1.88–1.54 (m, 14H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.7, 152.9, 149.4, 136.5, 130.5, 128.3, 127.4, 124.3, 117.4, 38.2, 31.9, 27.1, 26.9, 26.6; IR (KBr, cm^{-1}): 3427, 3353, 3282, 2921, 2850, 1705, 1630, 1600, 1558, 1489, 1455, 1372, 1339, 1299, 1275, 1250, 1176, 1156, 1120, 1002, 943, 775, 753, 740; HRMS (ESI) calcd for $C_{17}H_{20}O_3$ (M - H$^+$) 271.1332, found 271.1323.

3-(*tert*-Butylperoxy)-4-cyclohexyl-3-propionylchroman-2-one (10a):



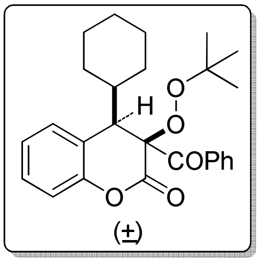
Solid; M.p. 159–161 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28 (t, 1H, *J* = 8.0 Hz), 7.13–7.07 (m, 2H), 7.03 (d, 1H, *J* = 8.4 Hz), 3.05–2.97 (m, 1H), 2.95 (d, 1H, *J* = 2.4 Hz), 2.84–2.74 (m, 1H), 1.79–1.67 (m, 2H), 1.59–1.48 (m, 4H), 1.34–1.21 (m, 2H), 1.17 (t, 3H, *J* = 7.0 Hz), 1.00 (s, 9H), 0.96–0.81 (m, 2H), 0.63–0.53 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 205.9, 161.3, 151.2, 130.1, 128.5, 123.9, 121.2, 116.2, 86.2, 82.2, 49.2, 38.4, 32.3, 31.9, 26.9, 26.6, 26.2, 25.9, 25.8, 7.6; IR (KBr, cm^{-1}): 2973, 2931, 2857, 1784, 1718, 1615, 1588, 1490, 1458, 1401, 1389, 1376, 1368, 1363, 1351, 1323, 1260, 1225, 1179, 1155, 1119, 1082, 1066, 1020, 965, 940, 907, 898, 875, 842, 788, 757, 749, 703; HRMS (ESI) calcd for $C_{22}H_{30}O_5$ (M + Na$^+$) 397.1985, found 397.1981.

3-(*tert*-Butylperoxy)-4-cyclohexyl-3-pentanoylchroman-2-one (11a):



Solid; M.p. 130–134 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28 (t, 1H, *J* = 7.4 Hz), 7.13–7.06 (m, 2H), 7.02 (d, 1H, *J* = 8.4 Hz), 2.96 (s, 1H), 2.92–2.88 (m, 1H), 2.78–2.70 (m, 1H), 1.78–1.67 (m, 4H), 1.58–1.53 (m, 4H), 1.24–1.12 (m, 4H), 1.00 (s, 9H), 0.99–0.93 (m, 3H), 0.89–0.80 (m, 2H), 0.62–0.56 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 205.3, 161.3, 151.2, 130.1, 128.5, 123.8, 121.2, 116.2, 86.0, 82.2, 49.1, 40.4, 38.3, 32.3, 26.8, 26.7, 26.2, 25.9, 25.8, 16.7, 13.9; IR (KBr, cm^{-1}): 2976, 2926, 2854, 1783, 1723, 1614, 1585, 1488, 1457, 1365, 1259, 1222, 1185, 1157, 1147, 1114, 1084, 1021, 966, 948, 911, 898, 877, 791, 764, 705; HRMS (ESI) calcd for $C_{24}H_{34}O_5$ (M + Na$^+$) 425.2298, found 425.2302.

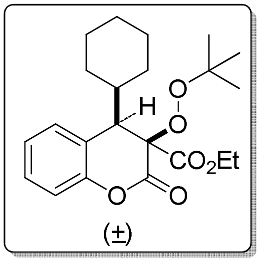
3-Benzoyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (12a):



Solid; M.p. 158–160 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.21 (d, 2H, *J* = 7.2 Hz), 7.57 (t, 1H, *J* = 7.0 Hz), 7.45 (t, 2H, *J* = 7.4 Hz), 7.31–7.28 (m, 1H), 7.14–7.13 (m, 2H), 7.06 (d, 1H, *J* = 8.4 Hz), 3.35 (s, 1H), 1.90–1.87 (m, 1H), 1.71–1.58 (m, 4H), 1.53–1.49 (m, 2H), 1.32–1.18 (m, 3H), 0.89 (s, 9H), 0.73–0.58 (m, 1H); ^{13}C NMR (CDCl$_3$, 100

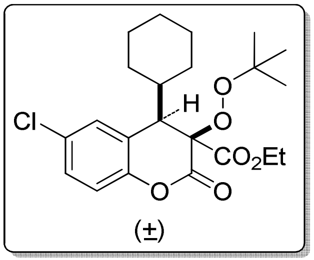
MHz): δ 194.3, 160.5, 151.2, 136.4, 132.9, 130.2, 129.6, 128.7, 128.3, 123.9, 120.9, 116.2, 87.8, 82.3, 50.6, 38.6, 32.4, 26.7, 26.6, 26.2, 25.9, 25.8; IR (KBr, cm^{-1}): 2977, 2927, 2853, 1778, 1737, 1689, 1615, 1600, 1489, 1457, 1446, 1365, 1276, 1247, 1223, 1198, 1171, 1131, 1116, 1066, 1019, 952, 924, 880, 812, 770, 754; HRMS (ESI) calcd for $C_{26}H_{30}O_5$ (M + Na$^+$) 445.1985, found 445.1992.

Ethyl 3-(*tert*-butylperoxy)-4-cyclohexyl-2-oxochroman-3-carboxylate (13a):



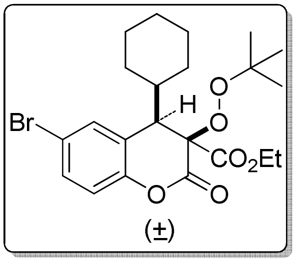
Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.29–7.28 (m, 1H), 7.09 (t, 1H, *J* = 7.2 Hz), 7.06–7.02 (m, 2H), 4.49–4.46 (m, 1H), 4.37–4.34 (m, 1H), 3.08 (d, 1H, *J* = 3.0 Hz), 1.79–1.69 (m, 1H), 1.68–1.63 (m, 2H), 1.62–1.58 (m, 2H), 1.55–1.53 (m, 1H), 1.39 (t, 3H, *J* = 7.2 Hz), 1.25–1.21 (m, 2H), 1.20–1.14 (m, 1H), 1.01 (s, 9H), 0.89–0.87 (m, 1H), 0.65–0.62 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.7, 160.7, 151.1, 130.1, 128.6, 123.9, 120.9, 116.2, 83.4, 81.9, 62.1, 50.0, 39.3, 32.1, 27.0, 26.8, 26.3, 26.1, 25.8, 14.4; IR (KBr, cm^{-1}): 2982, 2932, 2857, 1797, 1743, 1587, 1490, 1457, 1389, 1365, 1346, 1319, 1305, 1280, 1248, 1224, 1194, 1178, 1161, 1115, 1066, 1046, 1038, 991, 878, 863, 840, 808, 768, 758, 742, 706; HRMS (ESI) calcd for $C_{22}H_{30}O_6$ (M + Na$^+$) 413.1934, found 413.1936.

Ethyl 3-(*tert*-butylperoxy)-6-chloro-4-cyclohexyl-2-oxochroman-3-carboxylate (14a):



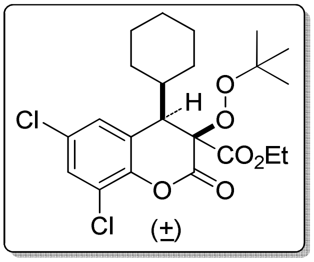
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.25 (d, 1H, *J* = 8.8 Hz), 7.05 (d, 1H, *J* = 2.4 Hz), 6.99 (d, 1H, *J* = 8.8 Hz), 4.52–4.44 (m, 1H), 4.40–4.32 (m, 1H), 3.06 (d, 1H, *J* = 3.2 Hz), 1.77–1.55 (m, 6H), 1.39 (t, 3H, *J* = 7.0 Hz), 1.32–1.27 (m, 1H), 1.24–1.11 (m, 2H), 1.03 (m, 9H), 0.97–0.87 (m, 1H), 0.68–0.58 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 166.3, 160.1, 149.7, 129.7, 128.9, 128.6, 122.8, 117.5, 82.9, 82.0, 62.2, 49.9, 39.1, 31.9, 27.0, 26.7, 26.2, 25.9, 25.7, 14.4; IR (KBr, cm^{-1}): 2983, 2928, 2855, 1795, 1741, 1653, 1628, 1559, 1539, 1507, 1483, 1451, 1416, 1366, 1339, 1281, 1250, 1228, 1195, 1160, 1126, 1092, 1032, 975, 923, 861, 812, 754, 733; HRMS (ESI) calcd for $C_{22}H_{29}ClO_6$ (M + Na$^+$) 447.1545, found 447.1558.

Ethyl 6-bromo-3-(*tert*-butylperoxy)-4-cyclohexyl-2-oxochroman-3-carboxylate (15a):



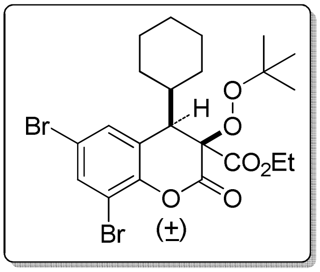
Gummy; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.40 (d, 1H, *J* = 8.4 Hz), 7.19 (d, 1H, *J* = 1.8 Hz), 6.93 (d, 1H, *J* = 8.4 Hz), 4.48–4.45 (m, 1H), 4.38–4.35 (m, 1H), 3.05 (d, 1H, *J* = 3.0 Hz), 1.76–1.55 (m, 6H), 1.39 (t, 3H, *J* = 7.5 Hz), 1.30–1.13 (m, 3H), 1.02 (s, 9H), 0.94–0.91 (m, 1H), 0.64–0.62 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 166.3, 159.9, 150.2, 132.6, 131.6, 123.2, 117.9, 116.4, 82.9, 82.0, 62.2, 49.8, 39.2, 31.9, 27.1, 26.6, 26.2, 25.9, 25.7, 14.3; IR (KBr, cm^{-1}): 2981, 2930, 2855, 1796, 1747, 1479, 1451, 1414, 1388, 1365, 1336, 1274, 1248, 1193, 1176, 1158, 1126, 1093, 1067, 1044, 1032, 876, 848, 818, 757; HRMS (ESI) calcd for $C_{22}H_{29}BrO_6$ (M + Na$^+$) 491.1040, found 491.1039.

Ethyl 3-(*tert*-butylperoxy)-6,8-dichloro-4-cyclohexyl-2-oxochroman-3-carboxylate (16a):



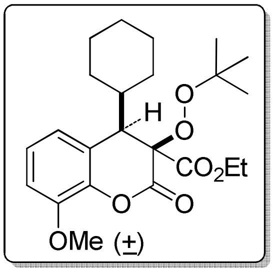
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.34 (d, 1H, *J* = 2.4 Hz), 6.93 (d, 1H, *J* = 2.4 Hz), 4.49–4.41 (m, 1H), 4.38–4.29 (m, 1H), 3.04 (d, 1H, *J* = 3.2 Hz), 1.73–1.53 (m, 6H), 1.36 (t, 3H, *J* = 7.2 Hz), 1.26–1.09 (m, 3H), 0.99 (s, 9H), 0.95–0.83 (m, 1H), 0.65–0.55 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 165.9, 158.9, 145.8, 129.2, 128.8, 128.2, 124.3, 122.2, 82.6, 82.3, 62.4, 50.3, 38.9, 32.1, 27.2, 26.6, 26.1, 25.9, 25.7, 14.3; IR (KBr, cm^{-1}): 2982, 2931, 2855, 1805, 1748, 1578, 1457, 1366, 1260, 1245, 1245, 1214, 1192, 1181, 1154, 1127, 1099, 1069, 1045, 1031, 996, 901, 860, 828, 755; HRMS (ESI) calcd for $C_{22}H_{28}Cl_2O_6$ (M + Na^+) 481.1155, found 481.1160.

Ethyl 6,8-dibromo-3-(*tert*-butylperoxy)-4-cyclohexyl-2-oxochroman-3-carboxylate (17a):



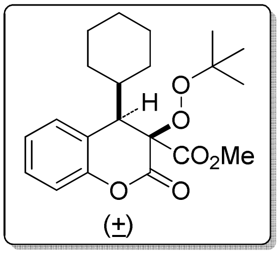
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, 1H, *J* = 2.4 Hz), 7.11 (d, 1H, *J* = 2.4 Hz), 4.49–4.41 (m, 1H), 4.36–4.28 (m, 1H), 3.03 (d, 1H, *J* = 3.2 Hz), 1.73–1.53 (m, 6H), 1.36 (t, 3H, *J* = 7.0 Hz), 1.26–1.10 (m, 3H), 0.99 (s, 9H), 0.95–0.80 (m, 1H), 0.64–0.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.9, 158.9, 147.4, 134.7, 131.7, 124.7, 116.4, 110.9, 82.7, 82.3, 62.4, 50.3, 39.1, 32.1, 27.2, 26.7, 26.2, 25.9, 25.7, 14.3; IR (KBr, cm^{-1}): 2981, 2929, 2854, 1803, 1747, 1606, 1568, 1559, 1506, 1448, 1388, 1365, 1337, 1283, 1259, 1241, 1189, 1174, 1151, 1127, 1095, 1068, 1044, 1031, 995, 930, 900, 860, 798, 770, 752; HRMS (ESI) calcd for $C_{22}H_{28}Br_2O_6$ (M + Na^+) 569.0145, found 569.0146.

Ethyl 3-(*tert*-butylperoxy)-4-cyclohexyl-8-methoxy-2-oxochroman-3-carboxylate (18a):



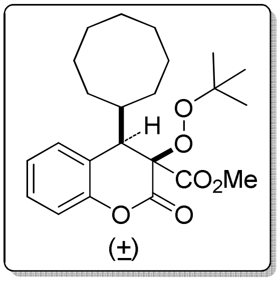
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (t, 1H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 8.0 Hz), 6.64 (d, 1H, *J* = 7.2 Hz), 4.52–4.44 (m, 1H), 4.39–4.31 (m, 1H), 3.89 (s, 3H), 3.08 (d, 1H, *J* = 2.8 Hz), 1.81–1.53 (m, 6H), 1.39 (t, 3H, *J* = 7.2 Hz), 1.27–1.15 (m, 3H), 1.01 (s, 9H), 0.94–0.86 (m, 1H), 0.74–0.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8, 160.1, 147.1, 140.4, 123.7, 122.0, 121.8, 111.4, 83.2, 81.8, 62.1, 56.3, 50.1, 39.1, 32.2, 27.1, 26.8, 26.1, 26.0, 25.8, 14.4; IR (KBr, cm^{-1}): 2981, 2928, 2856, 1789, 1733, 1589, 1485, 1462, 1445, 1379, 1367, 1347, 1322, 1304, 1272, 1235, 1210, 1185, 1163, 1129, 1107, 1042, 1028, 985, 943, 900, 878, 856, 824, 805, 784, 753, 738, 713; HRMS (ESI) calcd for $C_{23}H_{32}O_7$ (M + Na^+) 443.2040, found 443.2050.

Methyl 3-(*tert*-butylperoxy)-4-cyclohexyl-2-oxochroman-3-carboxylate (19a):



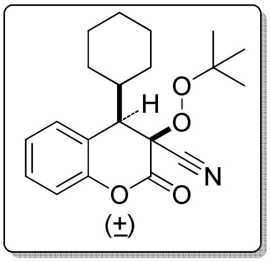
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28 (t, 1H, *J* = 7.2 Hz), 7.12–7.03 (m, 3H), 3.94 (s, 3H), 3.09 (s, 1H), 1.84–1.53 (m, 6H), 1.32–1.13 (m, 3H), 1.01 (s, 9H), 0.94–0.85 (m, 1H), 0.68–0.59 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 167.4, 160.7, 151.1, 130.1, 128.6, 123.9, 120.9, 116.2, 83.6, 82.0, 52.9, 50.1, 39.5, 32.1, 27.1, 26.7, 26.3, 26.2, 25.8; IR (KBr, cm^{-1}): 2986, 2933, 2857, 1784, 1730, 1587, 1490, 1459, 1434, 1389, 1365, 1350, 1304, 1292, 1256, 1222, 1198, 1179, 1169, 1127, 1118, 1068, 1044, 1032, 1022, 924, 876, 834, 805, 777, 760, 742; HRMS (ESI)) calcd for $C_{21}H_{28}O_6$ (M + Na$^+$) 399.1778, found 399.1783.

Methyl 3-(*tert*-butylperoxy)-4-cyclooctyl-2-oxochroman-3-carboxylate (19c):



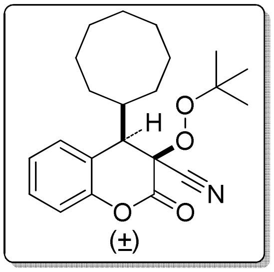
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.36–7.30 (m, 2H), 7.10 (t, 1H, *J* = 7.4 Hz), 7.04 (d, 1H, *J* = 8.0 Hz), 3.49 (s, 3H), 2.65 (m, 1H), 2.02–1.92 (m, 2H), 1.76–1.59 (m, 13H), 0.96 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 168.1, 166.4, 151.9, 130.9, 130.5, 124.0, 121.3, 116.4, 80.9, 79.3, 61.9, 52.7, 38.8, 30.2, 29.1, 27.8, 27.3, 26.8, 26.2, 25.8, 24.4; IR (KBr, cm^{-1}): 2987, 2923, 2855, 1781, 1736, 1558, 1539, 1506, 1489, 1458, 1434, 1363, 1339, 1260, 1228, 1193, 1151, 1126, 1005, 879, 759; HRMS (ESI) calcd for $C_{23}H_{32}O_6$ (M + Na$^+$) 427.2091, found 427.2090.

3-(*tert*-Butylperoxy)-4-cyclohexyl-2-oxochroman-3-carbonitrile (20a):



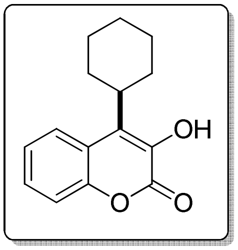
Solid; M.p. 152–154 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.34 (t, 1H, *J* = 8.0 Hz), 7.18 (t, 1H, *J* = 7.4 Hz), 7.13–7.07 (m, 2H), 3.24 (d, 1H, *J* = 3.2 Hz), 2.17–2.11 (m, 1H), 1.83–1.75 (m, 2H), 1.68–1.55 (m, 3H), 1.40–1.19 (m, 3H), 1.09 (s, 9H), 0.96–0.86 (m, 1H), 0.73–0.62 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 159.5, 150.5, 130.2, 129.3, 124.8, 119.1, 116.6, 114.5, 83.3, 80.8, 50.1, 39.6, 32.1, 27.2, 26.4, 26.1, 25.8, 25.6; IR (KBr, cm^{-1}): 2982, 2928, 2858, 2210, 1765, 1619, 1558, 1489, 1457, 1367, 1364, 1260, 1239, 1223, 1148, 1136, 1064, 1048, 1030, 1008, 910, 899, 856, 796, 767, 751, 705; HRMS (ESI) calcd for $C_{20}H_{25}NO_4$ (M + Na$^+$) 366.1676, found 366.1677.

3-(*tert*-Butylperoxy)-4-cyclooctyl-2-oxochroman-3-carbonitrile (20c):



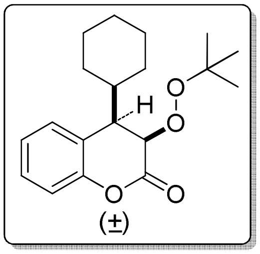
Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.35–7.31 (m, 1H), 7.19–7.14 (m, 2H), 7.07 (d, 1H, *J* = 8.0 Hz), 3.30 (d, 1H, *J* = 2.8 Hz), 2.44–2.39 (m, 1H), 1.84–1.71 (m, 2H), 1.65–1.60 (m, 2H), 1.57–1.36 (m, 10H), 1.09 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 159.4, 150.5, 129.9, 129.3, 124.9, 119.7, 116.7, 114.6, 83.3, 81.1, 51.4, 39.2, 33.3, 28.2, 26.7, 26.3, 26.2, 26.1, 25.2; IR (KBr, cm^{-1}): 2981, 2927, 2854, 2215, 1776, 1586, 1558, 1506, 1488, 1458, 1390, 1221, 1180, 1149, 1117, 1055, 1034, 1016, 903, 867, 764, 752; HRMS (ESI) calcd for $C_{22}H_{29}NO_4$ (M + Na$^+$) 394.1989, found 394.1998.

4-Cyclohexyl-3-hydroxy-2H-chromen-2-one (1a'):



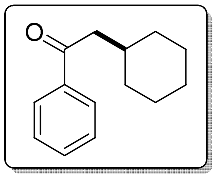
Solid; M.p. 196–200 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.76 (t, 1H, *J* = 8.0 Hz), 7.42–7.30 (m, 3H), 6.40 (s, 1H), 3.03 (bs, 1H), 2.20–2.05 (m, 2H), 1.91–1.72 (m, 4H), 1.46–1.34 (m, 3H), 0.87–0.84 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.0, 149.1, 139.8, 137.3, 130.7, 128.4, 125.0, 121.1, 117.4, 37.8, 29.1, 27.1, 26.2; IR (KBr, cm^{-1}): 3424, 3349, 3274, 2916, 2852, 1707, 1631, 1602, 1558, 1489, 1455, 1400, 1364, 1305, 1282, 1253, 1233, 1185, 1159, 1123, 754; HRMS (ESI) calcd for $C_{15}H_{16}O_3$ (M - H$^+$) 243.1019, found 243.1014.

3-(*tert*-Butylperoxy)-4-cyclohexylchroman-2-one (21a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.34 (m, 2H), 7.14 (t, 1H, J = 7.6 Hz), 7.03 (d, 1H, J = 8.0 Hz), 4.95 (d, 1H, J = 1.2 Hz), 3.07 (d, 1H, J = 8.8 Hz), 1.84–1.54 (m, 7H), 1.37–1.26 (m, 1H), 1.19–1.09 (m, 2H), 1.06 (s, 9H), 0.89–0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 152.3, 131.0, 130.9, 124.3, 119.2, 116.7, 80.8, 78.8, 50.3, 36.8, 31.3, 31.1, 26.3, 26.0, 25.9, 25.8; IR (KBr, cm^{-1}): 2977, 2990, 2854, 1771, 1717, 1613, 1590, 1486, 1459, 1386, 1363, 1352, 1291, 1243, 1221, 1186, 1155, 1127, 1109, 1085, 1052, 1025, 983, 966, 951, 903, 890, 877, 782, 760; HRMS (ESI) calcd for $C_{19}H_{26}O_4$ (M + Na$^+$) 341.1723, found 341.1730.

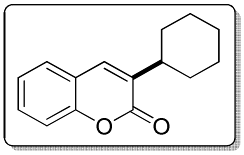
2-Cyclohexyl-1-phenylethanone (22a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 2H, J = 8.0 Hz), 7.55 (t, 1H, J = 7.8 Hz), 7.45 (t, 2H, J = 8.0 Hz), 2.82 (d, 2H, J = 6.4 Hz), 2.0–1.95 (m, 1H), 1.77–1.71 (m, 3H), 1.67–1.59 (m, 2H), 1.33–1.24 (m, 2H), 1.20–1.14 (m, 1H), 1.05–0.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.5, 137.7, 133.0, 128.7, 128.3, 46.4, 34.8, 33.6, 26.5, 26.4; IR (KBr, cm^{-1}): 2922, 2851, 1716, 1684, 1597, 1581, 1493, 1448, 1355, 1314, 1270, 1222, 1193, 1177, 1111, 1070, 1026, 1001, 956, 750, 712; HRMS (ESI) calcd for $C_{14}H_{18}O$ (M + H$^+$) 203.1438, found 203.1440.

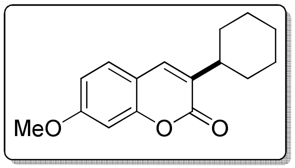
- **VIB.6.**

3-Cyclohexyl-2*H*-chromen-2-one (1'a):



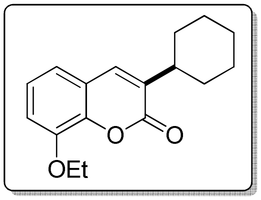
Semi-solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47–7.44 (m, 3H), 7.31 (d, 1H, J = 8.4 Hz), 7.24 (t, 1H, J = 7.2 Hz), 2.81–2.76 (m, 1H), 1.98 (dd, 2H, J = 15.6, 4.2 Hz), 1.87–1.84 (m, 2H), 1.80–1.77 (m, 1H), 1.49–1.41 (m, 2H), 1.34–1.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.8, 152.9, 136.5, 135.2, 130.2, 127.5, 124.4, 119.9, 116.5, 38.4, 32.3, 26.7, 26.4; IR (KBr, cm^{-1}): 3058, 2928, 2850, 1710, 1652, 1632, 1609, 1488, 1455, 1387, 1277, 1255, 1234, 1184, 1173, 1136, 1064, 1042, 986, 956, 924, 890, 781, 754; HRMS (ESI) calcd for $C_{15}H_{16}O_2$ (M + H$^+$) 229.1229, found 229.1224.

3-Cyclohexyl-7-methoxy-2*H*-chromen-2-one (8'a):



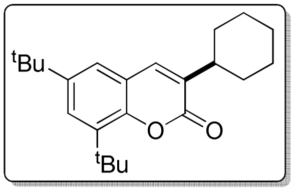
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.38 (s, 1H), 7.33 (d, 1H, *J* = 8.4 Hz), 6.83–6.79 (m, 2H), 3.85 (s, 3H), 2.75–2.71 (m, 1H), 1.96 (d, 2H, *J* = 12.0 Hz), 1.86–1.82 (m, 2H), 1.78–1.75 (m, 1H), 1.45–1.40 (m, 2H), 1.30–1.26 (m, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 162.1, 161.9, 154.6, 136.6, 131.2, 128.4, 113.5, 112.5, 100.6, 55.9, 38.2, 32.4, 26.8, 26.4; IR (KBr, cm^{-1}): 2959, 2924, 2850, 1701, 1652, 1628, 1593, 1572, 1464, 1433, 1403, 1297, 1265, 1158, 1138, 1034, 964, 937, 774; HRMS (ESI) calcd for $C_{16}H_{18}O_3$ (M + H$^+$) 259.1335, found 259.1327.

3-Cyclohexyl-8-ethoxy-2*H*-chromen-2-one (24'a):



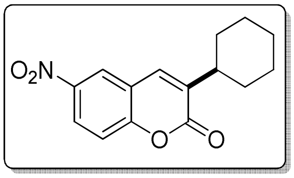
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.41 (s, 1H), 7.14 (t, 1H, *J* = 8.4 Hz), 6.99 (d, 2H, *J* = 7.2 Hz), 4.19–4.16 (q, 2H, *J* = 7.2 Hz), 2.81–2.76 (m, 1H), 1.97 (d, 2H, *J* = 12.6 Hz), 1.86–1.82 (m, 2H), 1.78–1.76 (m, 1H), 1.48 (t, 3H, *J* = 10.0 Hz), 1.46–1.41 (m, 2H), 1.32–1.23 (m, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.3, 146.5, 142.8, 136.6, 135.3, 124.2, 120.7, 118.9, 113.9, 65.1, 38.3, 32.3, 26.7, 26.4, 14.9; IR (KBr, cm^{-1}): 2977, 2926, 2852, 1719, 1608, 1579, 1471, 1449, 1392, 1355, 1276, 1181, 1114, 1098, 1064, 1044, 982, 770, 731; HRMS (ESI) calcd for $C_{17}H_{20}O_3$ (M + H$^+$) 273.1492, found 273.1485.

6,8-Di-*tert*-butyl-3-cyclohexyl-2*H*-chromen-2-one (25'a):



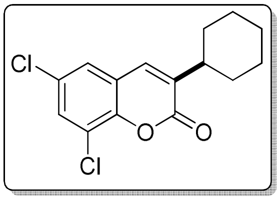
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.49 (d, 1H, *J* = 2.4 Hz), 7.43 (s, 1H), 7.26 (s, 1H), 2.79–2.76 (m, 1H), 1.97 (d, 2H, *J* = 12.0 Hz), 1.86–1.83 (m, 2H), 1.78–1.76 (m, 1H), 1.51 (s, 9H), 1.46–1.42 (m, 3H), 1.35 (s, 9H), 1.33–1.29 (m, 2H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.6, 149.6, 146.5, 137.8, 137.0, 133.8, 125.8, 122,2, 119.7, 38.1, 35.2, 34.8, 32.4, 31.6, 30.1, 26.7, 26.4; IR (KBr, cm^{-1}): 2961, 2929, 2853, 1711, 1586, 1477, 1445, 1393, 1363, 1243, 1217, 1170, 1135, 1068, 1032, 1004, 983, 939, 888, 783; HRMS (ESI) calcd for $C_{23}H_{32}O_2$ (M + H$^+$) 341.2482, found 341.2470.

3-Cyclohexyl-6-nitro-2*H*-chromen-2-one (4'a):



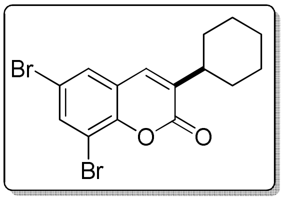
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 8.39 (d, 1H, *J* = 2.4 Hz), 8.33 (d, 1H, *J* = 9.6 Hz), 7.51 (s, 1H), 7.42 (d, 1H, *J* = 9.0 Hz), 2.82–2.77 (m, 1H), 1.99 (d, 2H, *J* = 12.0, 4.2 Hz), 1.88 (dt, 2H, *J* = 13.2, 3.0 Hz), 1.80 (d, 1H, *J* = 13.2 Hz), 1.49–1.42 (m, 2H), 1.35–1.27 (m, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 160.1, 156.5, 144.2, 137.7, 135.2, 125.5, 123.4, 119.9, 117.6, 38.8, 32.2, 26.6, 26.2; IR (KBr, cm^{-1}): 2927, 2855, 1728, 1652, 1632, 1617, 1529, 1486, 1342, 1270, 1169, 1090, 1060, 1041, 983, 935, 844, 836, 749, 668; HRMS (ESI) calcd for $C_{15}H_{15}NO_4$ (M + H$^+$) 274.1081, found 274.1074.

6,8-Dichloro-3-cyclohexyl-2*H*-chromen-2-one (5'a):



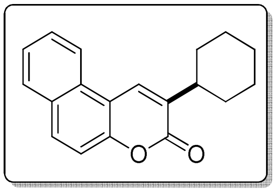
Semi-solid; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50 (d, 1H, *J* = 2.4 Hz), 7.35–7.34 (m, 2H), 2.81–2.75 (m, 1H), 1.98–1.95 (m, 2H), 1.88–1.77 (m, 3H), 1.50–1.39 (m, 2H), 1.33–1.19 (m, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 159.9, 147.3, 137.4, 134.9, 130.6, 129.4, 125.4. 122.3, 121.7, 38.6, 32.2, 26.6, 26.3; IR (KBr, cm^{-1}): 2927, 2853, 1733, 1660, 1635, 1564, 1452, 1352, 1252, 1172, 1135, 1063, 992, 888, 859, 830, 778, 736; HRMS (ESI) calcd for $C_{15}H_{14}Cl_2O_2$ (M + H^+) 297.0450, found 297.0442.

3-Cyclohexyl-6-nitro-2*H*-chromen-2-one (6'a):



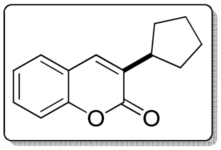
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.79 (s, 1H), 7.53 (s, 1H), 7.31 (s, 1H), 2.80–2.76 (m, 1H), 1.96 (d, 2H, *J* = 12.0 Hz), 1.86–1.84 (m, 2H), 1.79–1.76 (m, 1H), 1.45–1.41 (m, 2H), 1.35–1.27 (m, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 160.0, 148.9, 137.3, 136.1, 134.8, 129.1, 122.2, 116.8, 111.0, 38.6, 32.2, 26.6, 26.3; IR (KBr, cm^{-1}): 2964, 2922, 2846, 1735, 1658, 1641, 1635, 1448, 1260, 1020, 796; HRMS (ESI) calcd for $C_{15}H_{14}Br_2O_2$ (M + H^+) 384.9433, found 384.9424.

2-Cyclohexyl-3*H*-benzo[*f*]chromen-3-one (9'a):



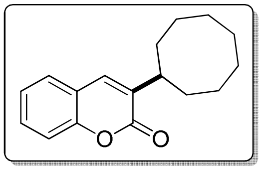
Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 8.28 (d, 1H, *J* = 8.4 Hz), 8.24 (s, 1H), 7.91 (t, 2H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 7.8 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.45 (d, 1H, *J* = 9.0 Hz), 2.88–2.86 (m, 1H), 2.06 (d, 2H, *J* = 12.0 Hz), 1.91–1.89 (m, 2H), 1.81 (d, 1H, *J* = 13.2 Hz), 1.51–1.42 (m, 4H), 1.34–1.27 (m, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.8, 152.2, 134.3, 132.2, 131.8, 130.5, 129.2, 128.0, 125.9, 121.7, 116.9, 113.8, 38.8, 32.5, 26.8, 26.4; IR (KBr, cm^{-1}): 3066, 2921, 2849, 1705, 1635, 1591, 1517, 1448, 1438, 1236, 1213, 1171, 1135, 1088, 1075, 1044, 986, 882, 813, 782, 738; HRMS (ESI) calcd for $C_{19}H_{18}O_2$ (M + H^+) 279.1386, found 279.1389.

3-Cyclopentyl-2*H*-chromen-2-one (1'b):



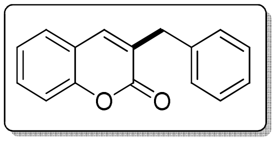
Semi-solid; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50 (s, 1H), 7.45 (m, 2H), 7.31 (m, 1H), 7.26–7.23 (m, 1H), 3.20–3.11 (m, 1H), 2.14–2.06 (m, 2H), 1.85–1.76 (m, 4H), 1.73–1.53 (m, 2H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.9, 153.1, 136.2, 133.7, 130.6, 127.4, 124.4, 119.8, 116.5, 40.9, 31.9, 25.3; IR (KBr, cm^{-1}): 2955, 2872, 1722, 1630, 1609, 1454, 1276, 1224, 1173, 1121, 1057, 1022, 948, 922, 755; HRMS (ESI) calcd for $C_{14}H_{14}O_2$ (M + H$^+$) 215.1073, found 215.1064.

3-Cyclooctyl-2*H*-chromen-2-one (1'c):



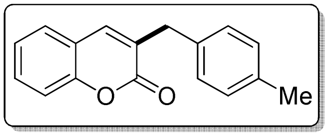
Crystalline niddles; M.p. 85–86 °C; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.46 (s, 1H), 7.44 (d, 2H, *J* = 6.0 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 3.10–3.03 (m, 1H), 1.84–1.82 (m, 2H), 1.80–1.73 (m, 4H), 1.72–1.64 (m, 8H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.7, 152.9, 139.8, 136.5, 130.5, 127.4, 124.3, 119.8, 116.4, 38.2, 31.8, 26.9, 26.4, 25.8; IR (KBr, cm^{-1}): 3057, 2963, 2922, 2856, 1717, 1627, 1608, 1489, 1473, 1462, 1454, 1388, 1360, 1281, 1274, 1258, 1230, 1182, 1274, 1258, 1230, 1181, 1174, 1146, 1124, 1058, 1011, 1027, 1000, 971, 956, 932, 923, 872, 853, 830, 777, 754, 733; HRMS (ESI) calcd for $C_{17}H_{20}O_2$ (M + H$^+$) 257.1543, found 257.1539.

3-Benzyl-2*H*-chromen-2-one (1'e):



Semi-solid; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.44 (t, 1H, *J* = 7.2 Hz), 7.34–7.31 (m, 2H), 7.29–7.24 (m, 5H), 7.19 (t, 2H, *J* = 7.2 Hz), 3.86 (s, 2H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 161.9, 153.3, 139.5, 137.8, 130.9, 130.0, 129.6, 128.9, 127.6, 127.0, 124.5, 119.6, 116.6, 36.8; IR (KBr, cm^{-1}): 3022, 2988, 2917, 2841, 1712, 1631, 1608, 1489, 1455, 1434, 1387, 1224, 147, 1123, 1075, 1051, 1028, 956, 930, 825, 753, 731, 726, 700; HRMS (ESI) calcd for $C_{16}H_{12}O_2$ (M + H$^+$) 237.0917, found 237.0920.

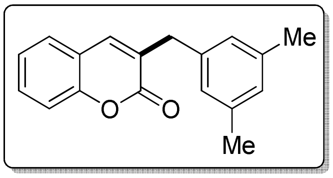
3-(4-Methylbenzyl)-2*H*-chromen-2-one (1'f):



Semi-solid; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.44 (t, 1H, *J* = 7.4 Hz), 7.35–7.29 (m, 2H), 7.25–7.23 (m, 1H), 7.21–7.14

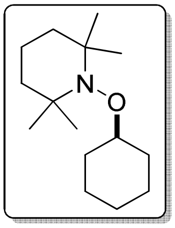
(m, 5H), 3.82 (s, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.2, 153.2, 139.3, 136.6, 134.7, 130.9, 129.9, 129.7, 129.5, 127.6, 124.4, 119.7, 116.6, 36.3, 21.3; IR (KBr, cm^{-1}): 2956, 2923, 2846, 1709, 1631, 1608, 1533, 1513, 1487, 1455, 1388, 1287, 1230, 1125, 1050, 956, 786, 752, 722; HRMS (ESI) calcd for $C_{17}H_{14}O_2$ (M + H$^+$) 251.1073, found 251.1086.

3-(3,5-Dimethylbenzyl)-2*H*-chromen-2-one (1'g):



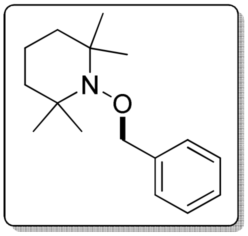
Semi-solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (t, 1H, *J* = 7.4 Hz), 7.30 (d, 1H, *J* = 7.6 Hz), 7.25–7.19 (m, 2H), 7.15 (t, 1H, *J* = 7.2 Hz), 6.83 (s, 3H), 3.75 (s, 2H), 2.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.9, 153.3, 139.4, 138.5, 137.7, 130.9, 129.8, 128.7, 127.6, 127.4, 124.4, 119.7, 116.6, 36.5, 21.5; IR (KBr, cm^{-1}): 3043, 3014, 2995, 2919, 2849, 1714, 1632, 1606, 487, 1456, 1429, 1386, 1257, 1232, 1196, 1163, 1124, 1055, 958, 923, 854, 837, 753, 704; HRMS (ESI) calcd for $C_{18}H_{16}O_2$ (M + H$^+$) 265.1229, found 265.1220.

1-(Cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (1A):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.58 (bs, 1H), 2.04 (bs, 2H), 1.74 (bs, 2H), 1.54–1.45 (m, 7H), 1.31–1.19 (m, 5H), 1.14 (s, 6H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 81.9, 59.8, 40.5, 34.7, 33.1, 26.2, 25.3, 17.6; IR (KBr, cm^{-1}): 2972, 2931, 2855, 1467, 1452, 1374, 1359, 1257, 1242, 1208, 1132, 1058, 1044, 1021, 966, 913, 785, 710; HRMS (ESI) calcd for $C_{15}H_{29}NO$ (M + H$^+$) 240.2329, found 240.2335.

1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (1B):

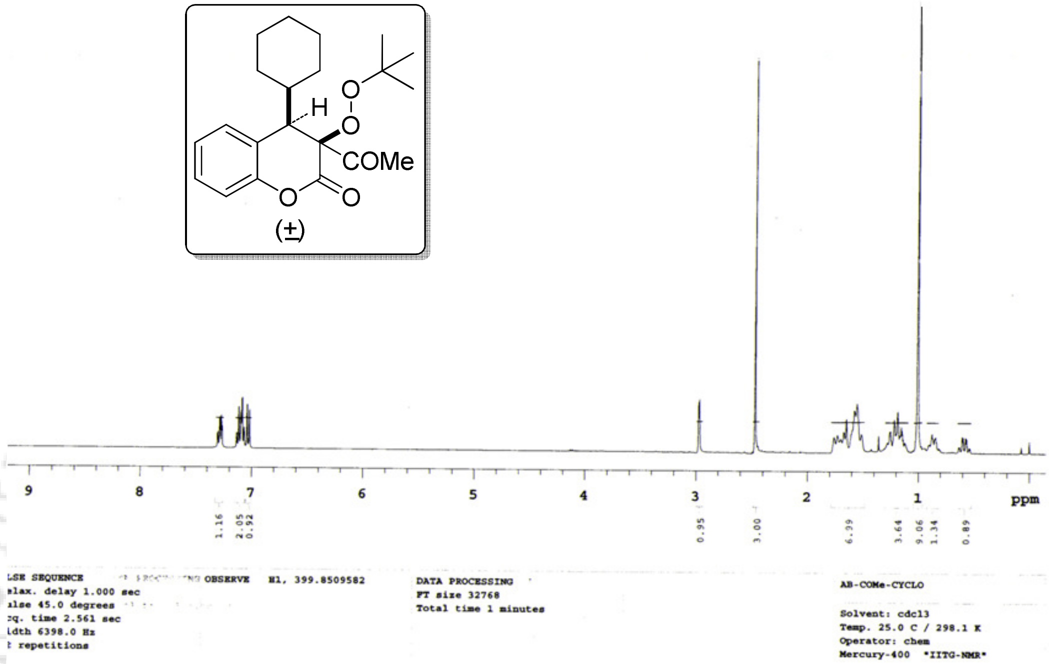


Gummy; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.38-7.25 (m, 5H), 4.82 (s, 2H), 1.58–1.48 (m, 5H), 1.37–1.33 (m, 1H), 1.26 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 138.5, 128.4, 127.7, 127.5, 78.9, 60.2, 39.9, 33.3, 20.5, 17.3; IR (KBr, cm^{-1}): 2973, 2929, 2871, 1496, 1469, 1452, 1373, 1359, 1262, 1243, 1207, 1183, 1133, 1081, 1045, 1028, 992, 955, 926, 732; HRMS (ESI) calcd for $C_{16}H_{25}NO$ (M + H$^+$) 248.2016, found 248.2011.

VI.7. Spectra

➢ VIA.7.

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (1a): ^{1}H NMR (CDCl$_3$, 400 MHz)



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LSE SEQUENCE                    OBSERVE   H1, 399.8509582     DATA PROCESSING              AB-COMe-CYCLO
elax. delay 1.000 sec                                         FT size 32768
alse 45.0 degrees                                             Total time 1 minutes         Solvent: cdcl3
cq. time 2.561 sec                                                                         Temp. 25.0 C / 298.1 K
ldth 6398.0 Hz                                                                             Operator: chem
: repetitions                                                                              Mercury-400  *IITG-NMR*
```
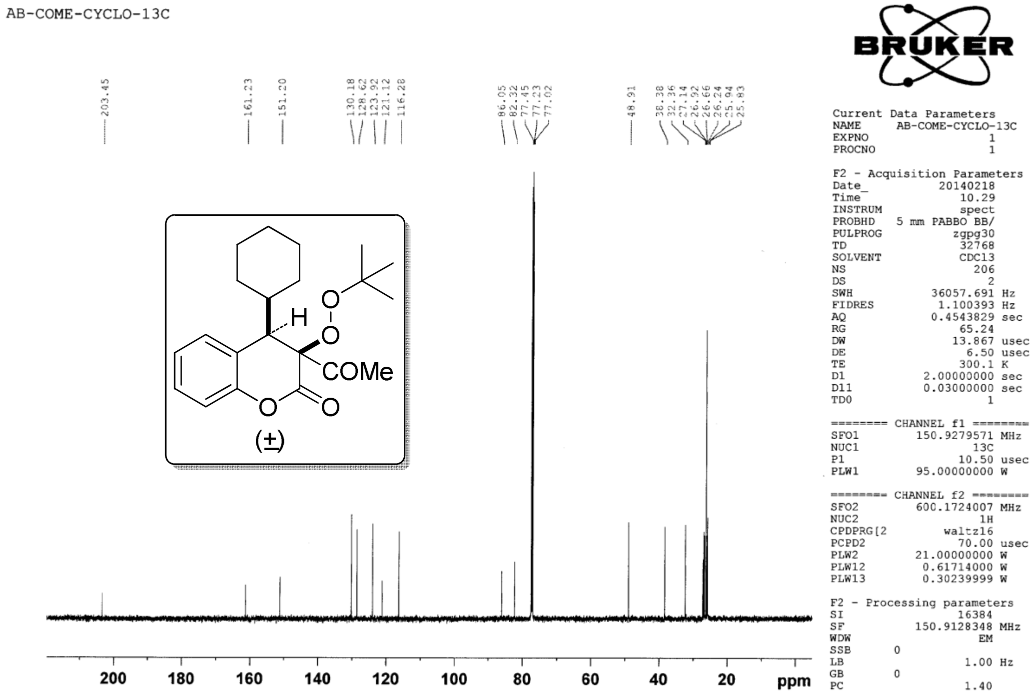
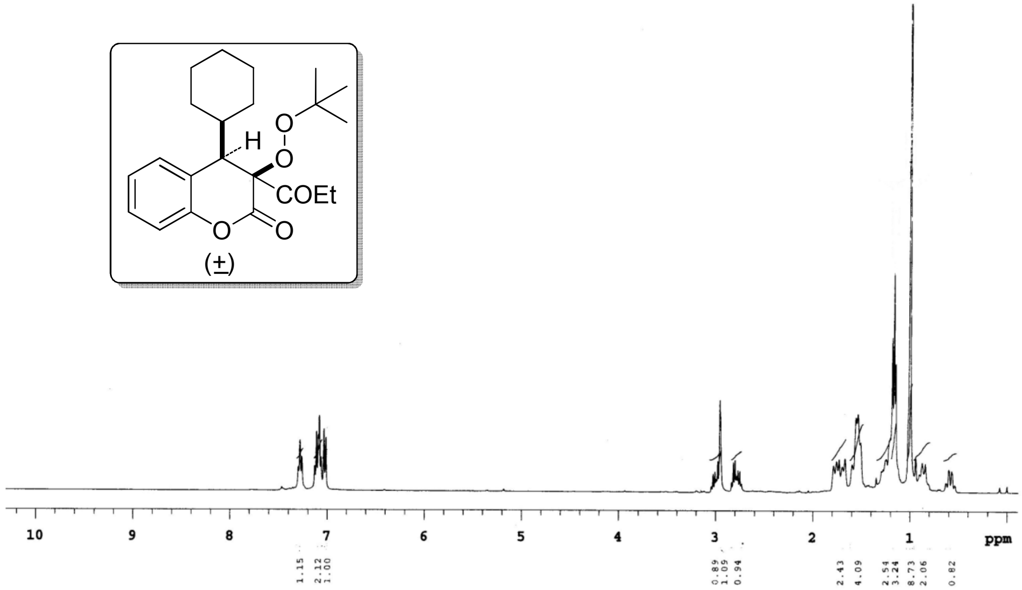

3-Acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (1a): ^{13}C NMR (CDCl$_3$, 150 MHz)



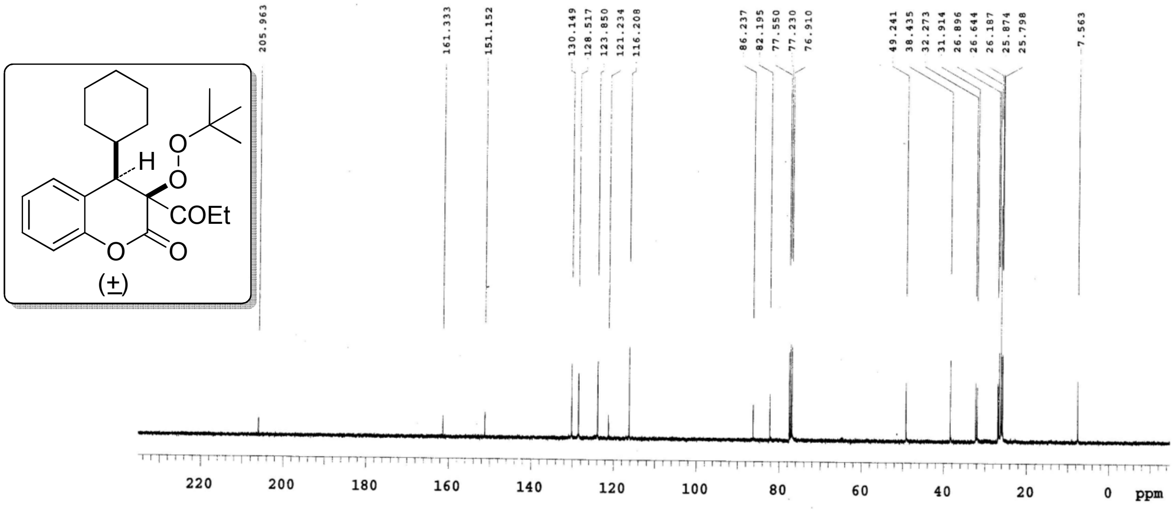
```
Current Data Parameters
NAME     AB-COME-CYCLO-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140218
Time                 10.29
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     206
DS                       2
SWH             36057.691 Hz
FIDRES           1.100393 Hz
AQ              0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   300.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                  10.50 usec
PLW1          95.00000000 W

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

F2 - Processing parameters
SI                  16384
SF           150.9128348 MHz
WDW                    EM
SSB      0
LB                   1.00 Hz
GB       0
PC                   1.40
```

3-(*tert*-Butylperoxy)-4-cyclohexyl-3-propionylchroman-2-one (10a): ^{1}H NMR (CDCl$_3$, 400 MHz)



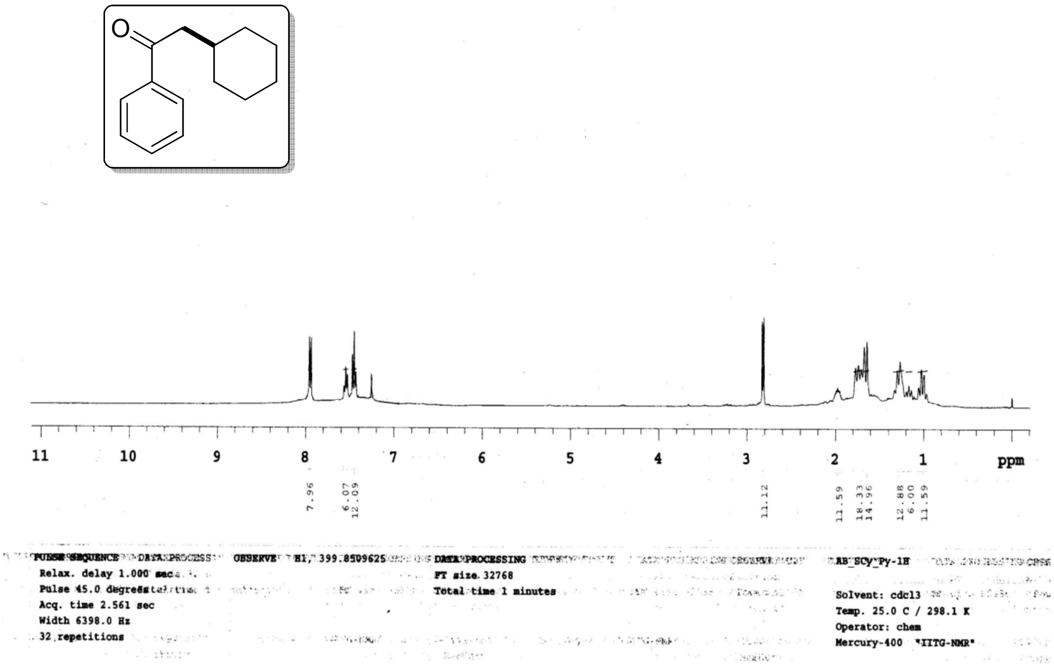
```
PULSE SEQUENCE                OBSERVE   H1, 399.8509531     DATA PROCESSING              AB-COEt-Cy-1H
 Relax. delay 1.000 sec                                     FT size 32768
 Pulse 45.0 degrees                                         Total time 1 minutes         Solvent: cdcl3
 Acq. time 2.561 sec                                                                     Temp. 25.0 C / 298.1 K
 Width 6398.0 Hz                                                                         Operator: chem
 32 repetitions                                                                          Mercury-400  "IITG-NMR"
```

3-(*tert*-Butylperoxy)-4-cyclohexyl-3-propionylchroman-2-one (10a): ^{13}C NMR (CDCl$_3$, 100 MHz)

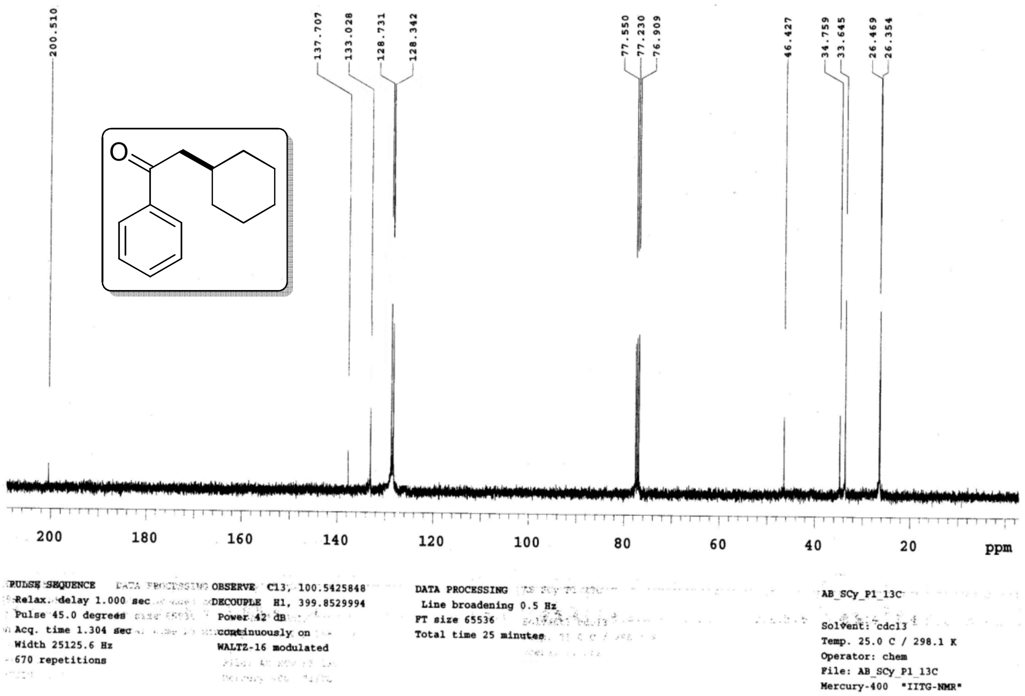


```
PULSE SEQUENCE            OBSERVE  C13, 100.5425855    DATA PROCESSING                AB-COEt-Cy-13C
 Relax. delay 1.000 sec   DECOUPLE  H1, 399.8529994     Line broadening 0.5 Hz
 Pulse 45.0 degrees        Power 42 dB                 FT size 65536                  Solvent: cdcl3
 Acq. time 1.304 sec       continuously on             Total time 19 minutes          Temp. 25.0 C / 298.1 K
 Width 25125.6 Hz          WALTZ-16 modulated                                         Operator: chem
 500 repetitions                                                                      Mercury-400  "IITG-NMR"
```

2-Cyclohexyl-1-phenylethanone (22a): ^{1}H NMR (CDCl$_3$, 400 MHz)

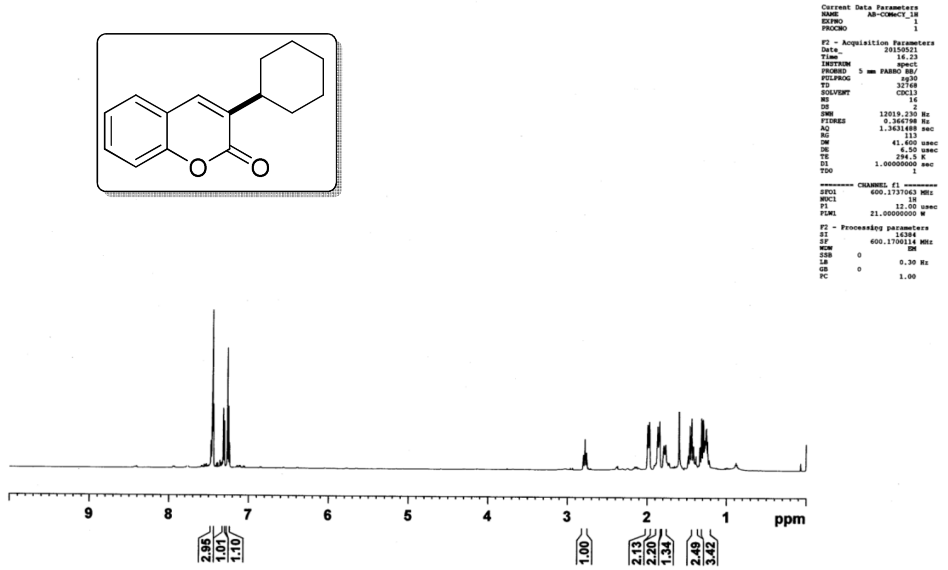


2-Cyclohexyl-1-phenylethanone (22a): ^{13}C NMR (CDCl$_3$, 100 MHz)



➢ VIB.7.

3-Cyclohexyl-2*H*-chromen-2-one (1'a): ^{1}H NMR ($CDCl_3$, 600 MHz)



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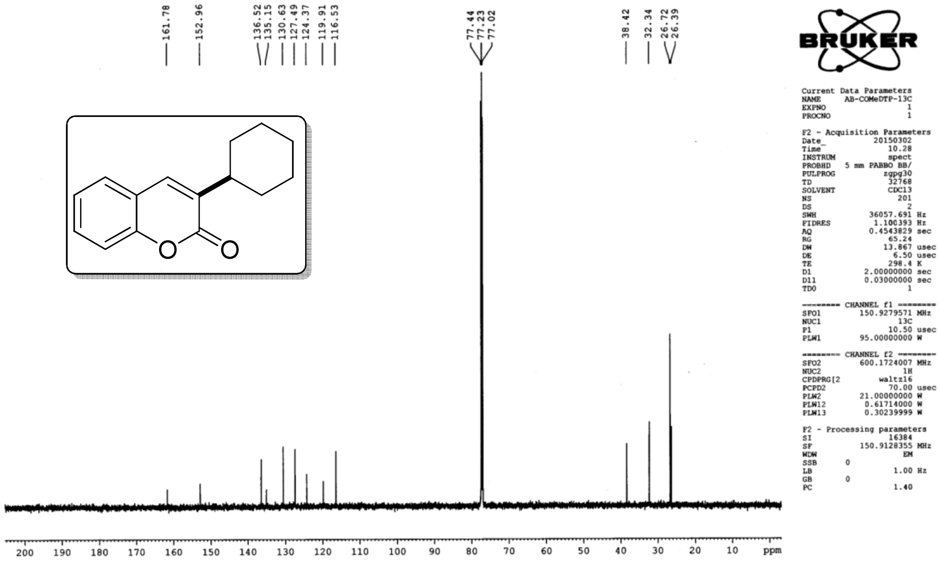
Current Data Parameters
NAME        AB-COMeCY_1H
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150521
Time               16.23
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                   113
DW                41.600 usec
DE                  6.50 usec
TE                 294.5 K
D1            1.00000000 sec
TD0                    1

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

F2 - Processing parameters
SI                 16384
SF           600.1700114 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

3-Cyclohexyl-2*H*-chromen-2-one (1'a): ^{13}C NMR ($CDCl_3$, 150 MHz)



```
Current Data Parameters
NAME       AB-COMeDTP-13C
EXPNO                  1
PROCNO                 1

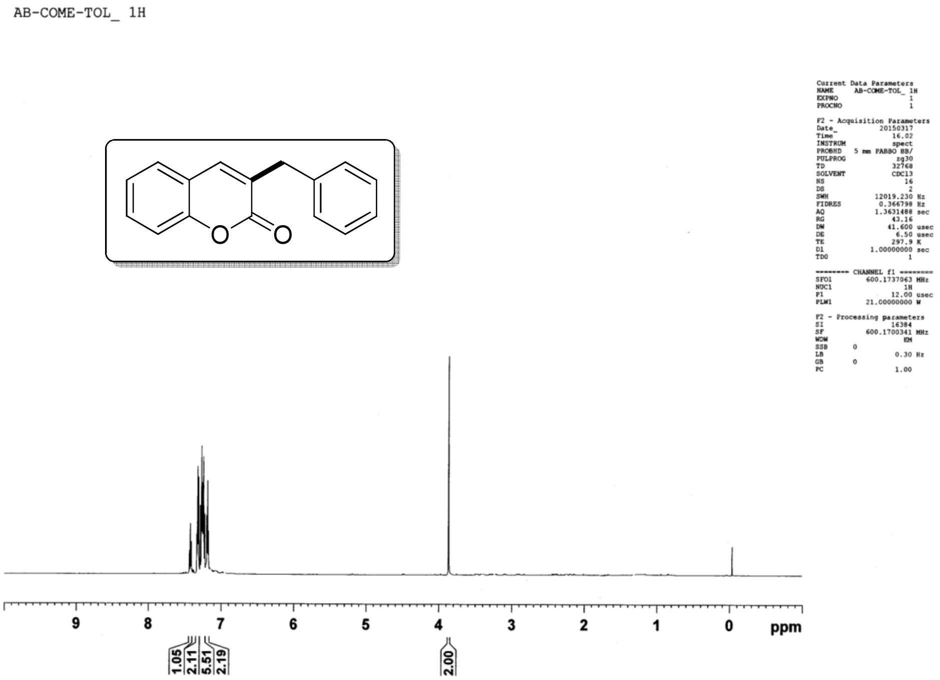
F2 - Acquisition Parameters
Date_           20150302
Time               10.28
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   201
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 298.4 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

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

F2 - Processing parameters
SI                 16384
SF           150.9128355 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

3-Benzyl-2*H*-chromen-2-one (1'e): ^{1}H NMR ($CDCl_3$, 600 MHz)



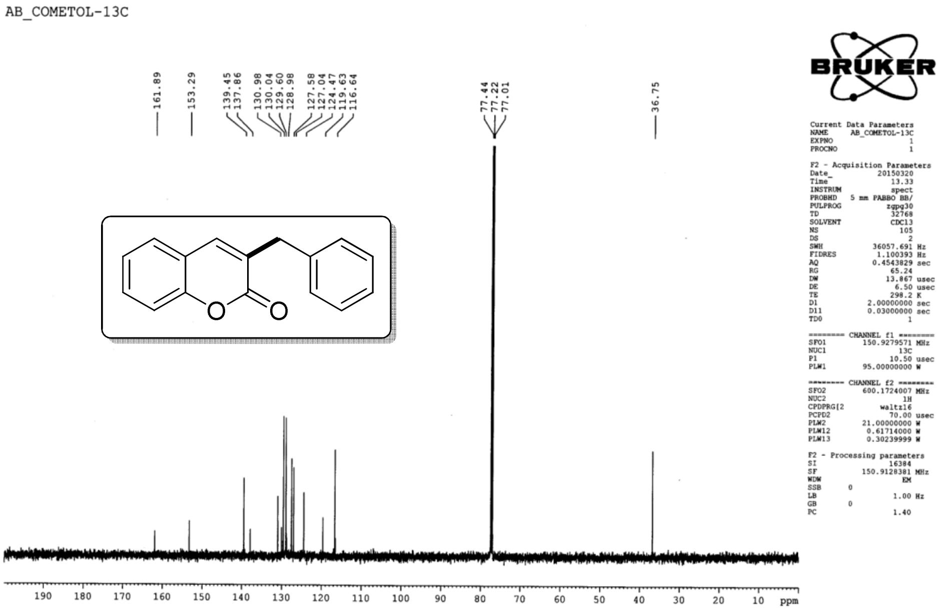
```
Current Data Parameters
NAME      AB-COME-TOL_ 1H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150317
Time                16.02
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             12019.230 Hz
FIDRES           0.366798 Hz
AQ              1.3631488 sec
RG                  43.16
DW                 41.600 usec
DE                   6.50 usec
TE                  297.9 K
D1             1.00000000 sec
TD0                     1

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

F2 - Processing parameters
SI                  16384
SF            600.1700341 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```

3-Benzyl-2*H*-chromen-2-one (1'e): ^{13}C NMR ($CDCl_3$, 150 MHz)



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Current Data Parameters
NAME      AB_COMETOL-13C
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150320
Time               13.33
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   105
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 298.2 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

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

F2 - Processing parameters
SI                 16384
SF           150.9128381 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```
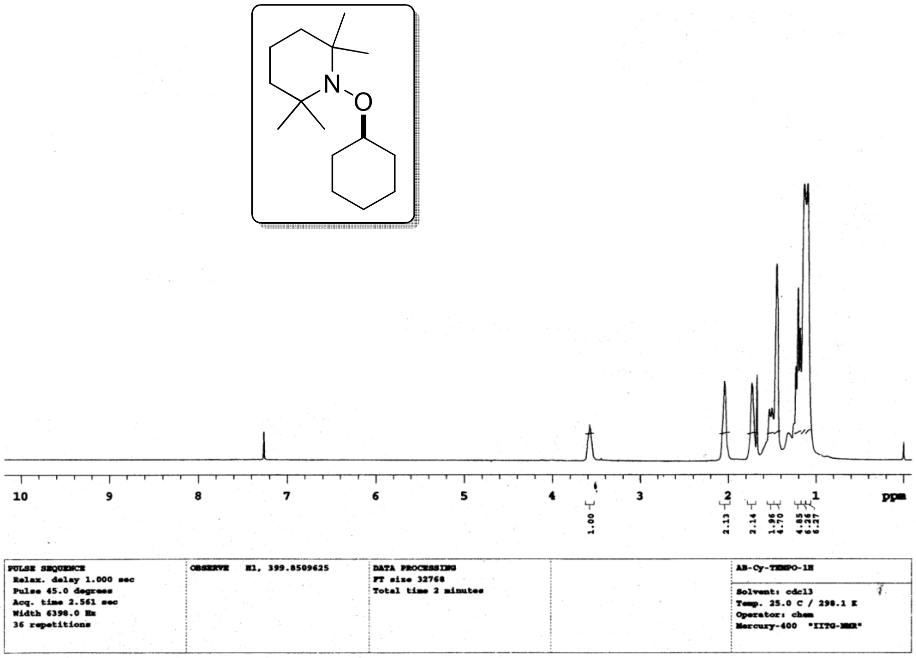
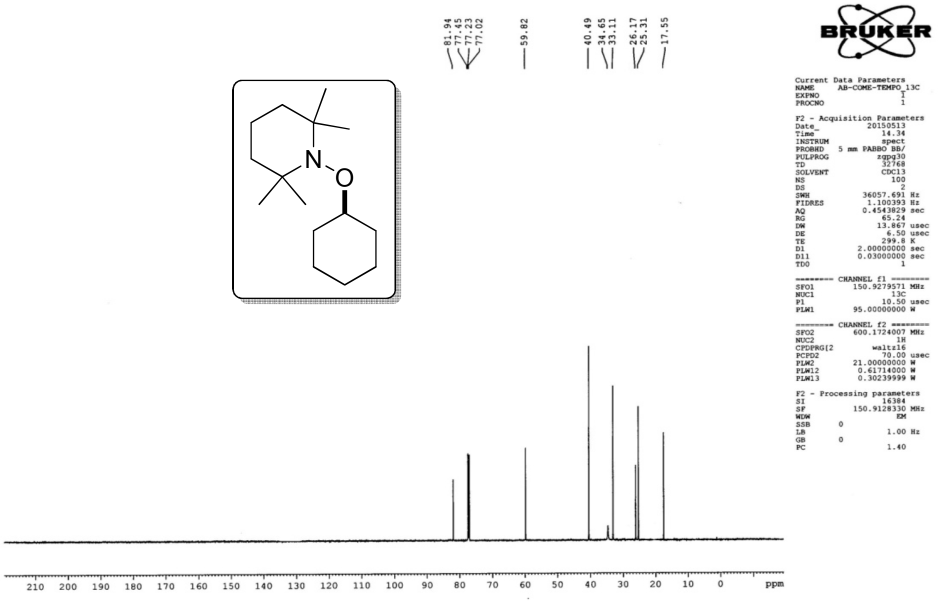

1-(Cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (1A): ^{1}H NMR (CDCl$_3$, 400 MHz)



```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 36 repetitions
OBSERVE   H1, 399.8509625
DATA PROCESSING
FT size 32768
Total time 2 minutes
AB-Cy-TEMPO-1H
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

1-(Cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (1A): ^{13}C NMR (CDCl$_3$, 150 MHz)



```
Current Data Parameters
NAME      AB-COME-TEMPO_13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150513
Time                14.34
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   100
DS                     2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                 65.24
DW                13.867 usec
DE                  6.50 usec
TE                 299.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

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

F2 - Processing parameters
SI                 16384
SF           150.9128330 MHz
WDW                   EM
SSB        0
LB                  1.00 Hz
GB         0
PC                  1.40
```

List of Publications:

1. Ruthenium catalyzed regiospecific C–H/O–H annulations of directing arenes *via* weak coordination. **A. Banerjee,** S. K. Santra, P. Mohanta and B. K. Patel, *Org. Lett.,* 2015, **17**, 5678.
2. Oxidant controlled regioselective mono- and *bis*-functionalisation of coumarins *via* sp^3 C–H bond. **A. Banerjee,** S. K. Santra, N. Khatun, W. Ali and B. K. Patel, *Chem. Commun.*, 2015, **51**, 15422.
3. Copper(I) promoted cycloalkylation-peroxidation of unactivated alkenes *via* sp^3 C–H functionalization. **A. Banerjee,** S. K. Santra, A. Mishra, N. Khatun and B. K. Patel, *Org. Biomol. Chem.*, 2015, **13**, 1307.
4. Ceric ammonium nitrate (CAN) promoted Pd^{II}-catalyzed substrate-directed *o* benzoxylation and decarboxylative *o*-aroylation. S. K. Santra,[‡] **A. Banerjee,**[‡] N. Khatun and B. K. Patel, *Eur. J. Org. Chem.*, 2015, 350.
   ([‡] Both authors contributed equally)
5. Palladium-catalyzed regioselective aroylation and acetoxylation of 3,5-diarylisoxazole *via ortho* C–H functionalizations. **A. Banerjee,** A. Bera, S. K. Santra, S. Guin and B. K. Patel, *RSC Adv.*, 2014, **4**, 8558.
6. A ligand free copper(II) catalyst is as effective as a ligand assisted Pd(II) catalyst towards intramolecular C–S bond formation *via* C–H functionalization. **A. Banerjee,** S. K. Santra, S. K. Rout and B. K. Patel, *Tetrahedron*, 2013, **69**, 9096.
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