Transition Metal Catalyzed C–H Functionalization: Construction of C–C, C–O and C–X Bonds

Submitted by

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Dedicated to my

Mother

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STATEMENT

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

August, 2016
IIT Guwahati.

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CERTIFICATE

This is to certify that Sourav Kumar Santra has been working under my supervision since July, 2011 as a regular registered Ph.D. student. His thesis entitled "**Transition Metal Catalyzed C–H Functionalization: Construction of C–C, C–O and C–X Bonds**" is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding his thesis to submit for the Ph.D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

August, 2016.

Prof. Bhisma Kumar Patel
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Sourav Kumar Santra

Abstract

This thesis has been divided into six chapters based on the results of experimental works performed during research period. The first chapter of the thesis describes a sketch out of different features of C–H functionalization strategies. Rest of the five chapters mainly emphasize on the formation of C–C, C–O and C–X (X = halogen) bonds *via* palladium and copper catalyzed ligand directed and non directed C–H bond functionalizations and cross dehydrogenative couplings (CDC).

Chapter II describes Pd-catalyzed mono *ortho* aroylation of 2,3-diarylquinoxaline *via* cross-dehydrogenative coupling using aromatic aldehydes or alkylbenzenes as aroyl surrogate and peroxide free *o*-aroylation of directing arenes using 2-acetoxyacetophenone as the aroyl source.

Chapter III demonstrates the use of ceric ammonium nitrate (CAN) towards Pd(II)-catalyzed substrate-directed *o*-benzoxylation of various directing arenes.

Chapter IV describes Pd(II)-catalyzed *ortho* halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines using *N*-halosuccinamide and copper(II) halide as the halogenating source.

Chapter V illustrates palladium(II) catalyzed keto α-C_{sp3}–H benzoxylation of *N*,*N*-dialkylamides directed by *ortho*-hydroxy group of 2-hydroxybenzaldehyde and 2-hydroxyacetophenone: an oxidative cross coupling approach.

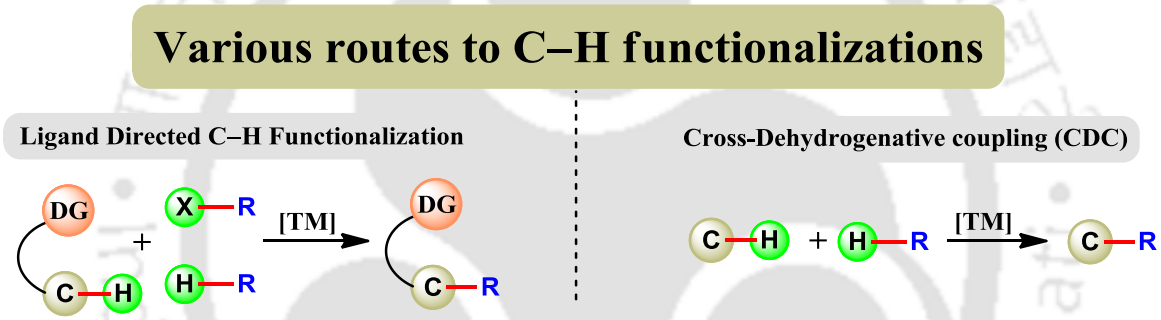
Chapter VI discusses [4+2] cycloaddition of the *in situ* generated diene from trialkylamines and chalcones in the presence of Cu(II)/TBHP combination.

Except chapter I rest of the chapters contain of seven subsections which include introduction, previous works, present work, experimental section, references, spectral data and some selected spectra.

CHAPTER I. Introduction

This chapter gives an outline of the history of C–H activation including advantages over traditional cross-coupling, challenges, classification of C–H activation and their applications in organic synthesis.

C–H Functionalization is one of the common processes in nature. Over several million years specific enzymes such as cytochrome P450 enzymes and methane mono oxygenase that effect metal-based C–H functionalization have evolved. Currently, C–H functionalization protocols have become powerful tools for the construction of organic frameworks. C–H functionalization protocol is divided into two major part (i) directing group assisted C–H functionalizations and (ii) cross-dehydrogenative coupling (CDC). There are also methodologies which are based on the combination of both these strategies. (Scheme I.1).



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

Cross-coupling reactions are widely used in both industry and academia for the installation of functional group and untied a new gate in organic synthesis. However, these processes involve either the use of stoichiometric organometallic reagents such as Grignard reagent or organolithium reagents or halogenated starting materials as the coupling partners. Now-a-days it is desirable to avoid the use of prefunctionalized starting materials as it makes the process atom and step economic. Since carbon-hydrogen (C–H) bond is considered as the un-functional group, the best way to address this issue is to utilize the direct functionalization of C–H bonds. However, the inert nature of C–H bonds and the site selectivities are the two most basic challenges of direct C–H bond functionalizations. The first challenge was addressed using transition metals that can react with C–H bonds to produce more reactive C–M bonds in a process known as "C–H activation". Several transition metals have been employed for this purpose which includes Ru, Rh, Pt, Cu, Ni and Pd. The second major challenge is selective functionalization of a single C–H bond

within a complex molecule. The most common solution of this problem involves the use of substrates possessing directing group. With the help of directing group selectively *ortho*, *meta* and *para* C–H bonds have been functionalized to carbon-oxygen, carbon-halogen, carbon-nitrogen, carbon-sulfur and carbon-carbon bonds. Currently, along with ligand directed C–H functionalization, cross-dehydrogenative coupling (CDC) also participated in various C–C and C–X (X = heteroatoms) bonds formation reaction with the expanse of only two hydrogen atoms. Our group has been involved in the development of new disconnection approach and generation of various functionalities using both ligand directed C–H functionalization and cross-dehydrogenative coupling (CDC).

CHAPTER II.

This chapter has been divided into two sections. Section-A describes mono *o*-aroylation of 2,3-diarylquinoxalines using aldehydes and alkylbenzenes as aroyl surrogate whereas Section-B demonstrates a peroxide free *o*-aroylation of directing arenes using 2-acetoxyacetophenone the as aroyl source.

SECTION A: 2,3-Diarylquinoxaline Directed Mono *ortho* Aroylation *via* Cross Dehydrogenative Coupling Using Aromatic Aldehydes or Alkylbenzenes as Aroyl Surrogate

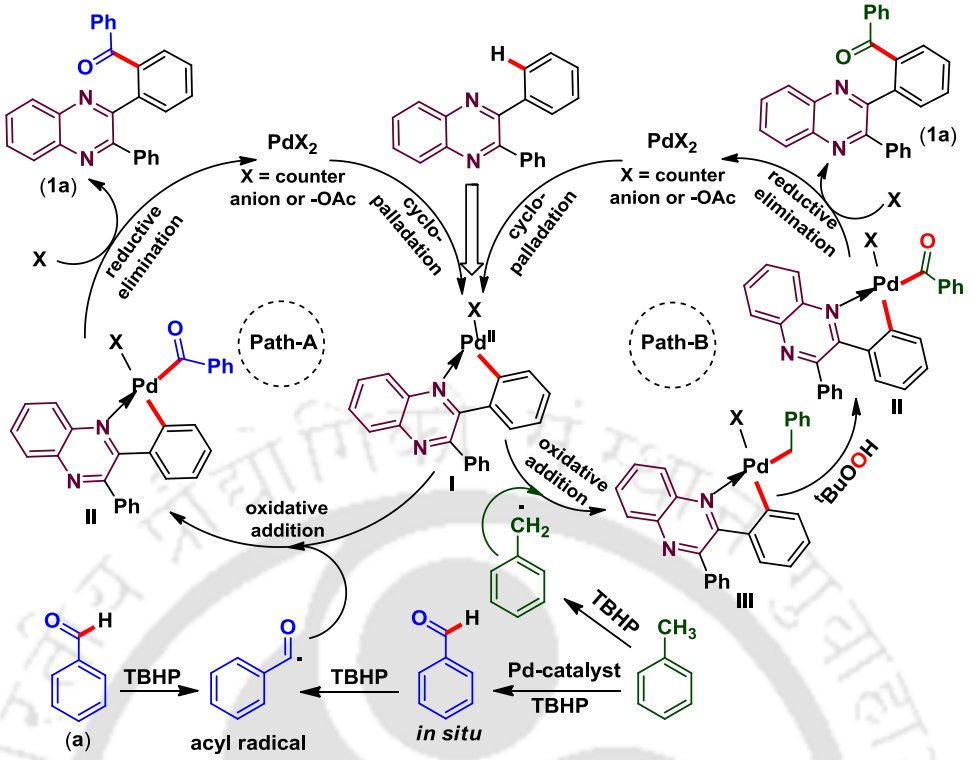
This section focuses on the Pd(II)-catalyzed direct mono *ortho* aroylation of 2,3-diarylquinoxaline using either aromatic aldehydes or alkylbenzenes as the synthetic precursor of aroyl unit in the presence of TBHP oxidant.

Selective functionalization of ubiquitous C–H bonds is one of the most elegant approaches to construct complex organic molecule. Particularly, the Pd-catalyzed chelation assisted regioselective C–H functionalization is of greatest interest from the point of view of high efficacy and valuable products. Combination of directing groups and Pd-catalyst directly installed C–C, C–O, C–N, C–S and C–X (X = halogen) at the *ortho* site of the phenyl ring *via* cleavage of C–H bond(s). However among these transformations, C–C bond formation specially installation of carbonyl functional groups into the phenyl system *via* C–H bond cleavage is attractive in organic chemistry.

Substrates containing different directing groups have been successfully *ortho*-aroylated using diverse aroyl surrogates *viz.* aldehyde, alkene, alkyne, benzil, α-ketoacid, benzyl alcohol, benzylamine and alkylbenzene. 2,3-Diarylquinoxaline possessing *o*-chelating

moiety could provide a similar ligand-directed cyclo-metallated intermediate and hence *ortho*-C–H bond(s) can be functionalized. Quinoxalines are important heterocycle which exhibit diverse biologically activities and are potentially useful in materials science. Thus, further derivatization of this moiety is expected to generate useful intermediates. Till date there is no precedence of *ortho* aroylation of this important scaffold using any of the aroyl surrogates *via* the CDC approach. Herein, a Pd(II)-catalyzed *o*-aroylation of 2,3-diarylquinoxalines has been reported using either aromatic aldehydes or alkylbenzenes in the presence of TBHP oxidant.

To establish a suitable reaction condition various reaction parameters such as solvent, catalyst, oxidants and their quantities were screened. After a series of experiments catalyst $Pd(OAc)_2$ (5 mol %), oxidant TBHP (1.5 equiv) and aroyl source aldehyde (1.2 equiv) in an equivolume mixture of toluene and 1,2-dichloroethane (2 mL) at 110 ^{o}C was found to be the best condition. Both activated and deactivated aromatic aldehydes efficiently coupled with 2,3-diphenylquinoxaline giving mono *o*-aroylated products. This strategy was equally applicable for electron-withdrawing and electron-donating substituted 2,3-diarylquinoxalines. For unsymmetrical 2,3-diarylquinoxalines two regioisomeric mono *ortho* aroylated products were observed. This methodology was also equally successful for alkylbenzenes possessing electron-withdrawing and electron-donating groups. However, the aroylating ability of aromatic aldehydes was better than alkylbenzenes. For both these cases no *ortho* di-aroylation were observed even in the presence of excess aroylating source which may be due to the loss of planarity of the pendant aryl rings with respect to the quinoxaline moiety after mono *o*-arylation. Based on the experimental results, mechanistic investigations and literature reports plausible mechanisms were proposed for both these transformation (Scheme IIA.1).



Scheme IIA.1. *Pd (II)-Catalyzed o-aroylation of 2,3-diphenylquinoxaline*

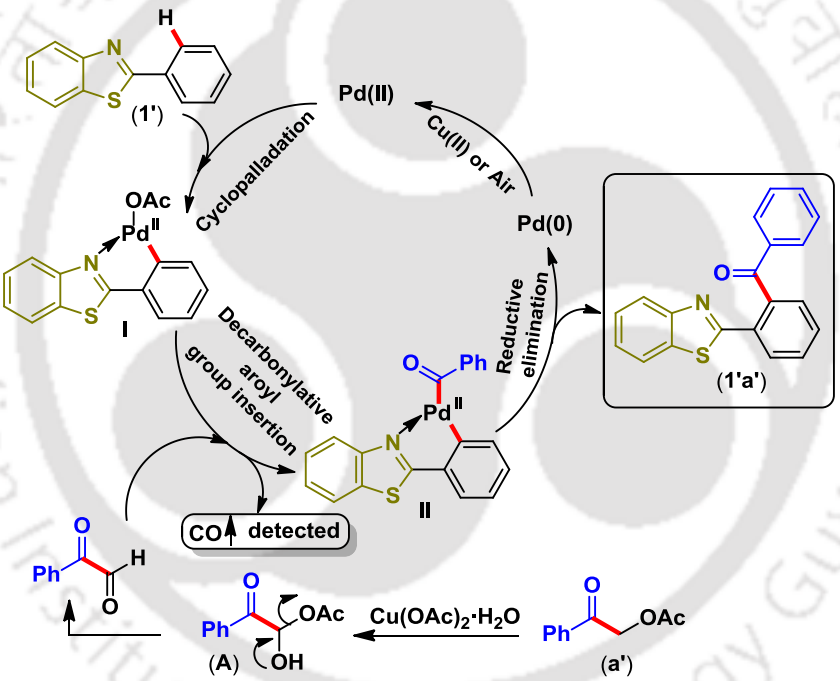
In conclusion, a selective mono *ortho* aroylation protocol for 2,3-diphenylquinoxaline has been developed employing Pd(II)-catalyst in the presence of TBHP oxidant using aryl aldehyde or alkylbenzene as aroyl precursors. This strategy shows a broad substrate scope and wide array of functional group tolerance with high levels of regioselectivity. Using aldehyde as aroyl surrogate the reaction goes *via* aroyl radical path while the use of alkylbenzene as aroyl surrogate it can proceed either *via* an aroyl radical or by a benzyl radical path.

SECTION B: Peroxide Free Pd(II)-Catalyzed *Ortho* Aroylation of Directing Arenes Using 2-Acetoxyacetophenone as the Aroyl Source

This section demonstrates peroxide free *o*-aroylation of directing arenes in the presence of $Pd(OAc)_2/Cu(OAc)_2 \cdot H_2O$ combination using 2-acetoxyacetophenones as aroyl surrogates. To date various aroyl surrogates *viz.* aldehyde, alkene, alkyne, benzil, α-ketoacid, benzyl alcohol, benzylamine and alkylbenzene have been employed for the *ortho* aroylation. However, few of these processes involve the cleavage of inert sp^3 C–H bond and hence require stronger peroxide oxidant for their cleavage. Taking cues from these reports *viz.* peroxide free Pd(II)-catalyzed *ortho*-aroylation of directing arenes and Pd(II)-catalyzed

decarbonylation of phenylglyoxal, a Pd(II)-catalyzed *o*-aroylation of 2-arylbenzothiazoles has been developed using 2-acetoxyacetophenone derivatives under peroxide free condition.

After rigorous screening of reaction parameters (solvent, catalyst and oxidants) the best reaction condition was found to be 10 mol % of $Pd(OAc)_2$, 2.0 equivalents of $Cu(OAc)_2 \cdot H_2O$ and 2.0 equivalents of AcOH in mesitylene (1.5 mL) at 130 ^oC. Both electron-donating and electron-withdrawing group containing 2-acetoxyacetophenone derivatives coupled with 2-arylbenzothiazoles. *Meta* substituted 2-arylbenzothiazole provided regeioselective *o*-aroylated product where aroyl moiety installed at the less sterically hindered site. Based on the control experiments and from the literature report a plausible decarbonylative Pd(II)/Pd(0) catalytic cycle has been proposed for this transformation (Scheme IIB.1).



Scheme IIB.1. *Plausible mechanism for Pd(II)-catalyzed peroxide free o-aroylation*

In summary, a peroxide free catalytic *o*-aroylation of directing arenes has been demonstrated using $Pd(OAc)_2/Cu(OAc)_2 \cdot H_2O$ combination. In this *o*-aroylation process copper(II) salt facilitates the oxidation of 2-acetoxyacetophenone *via* the cleavage of sp^3 C–H bond along with helps to regenerate the Pd(II) catalyst.

CHAPTER III.

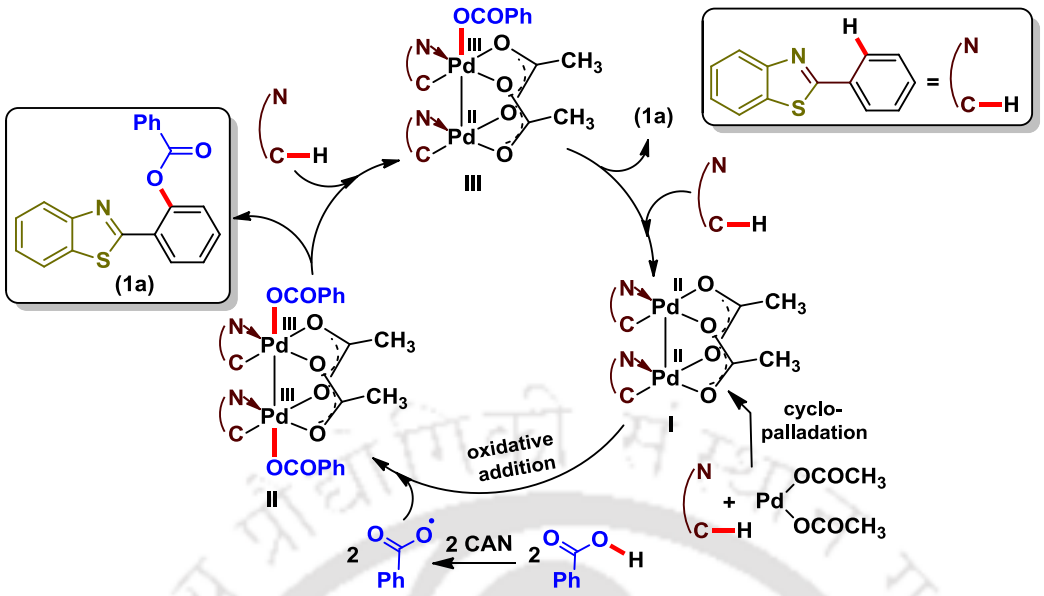
This chapter describes an efficient Pd(II)-catalyzed protocol for the *ortho*-benzoxylation of directing arenes using carboxylic acid and ceric ammonium nitrate (CAN) as the oxidant.

Ceric Ammonium Nitrate (CAN) Promoted Pd(II)-Catalyzed Substrate Directed *o*-Benzoxylation

A plethora of transition metal catalyzed C–O bond formation reactions through C–H bond functionalizations to give an ester have been reported. Carboxylic acids, aroyl peroxides, acid chlorides, acid anhydrides, aldehydes, alkylbenzenes, terminal alkenes and alkynes have been employed as benzoxy surrogates with various directing arenes. Transition metal catalyzed substrate directed *o*-benzoxylation proceeds through a cyclometallation, oxidative addition or ligand exchange, followed by the reductive elimination. The metal is in its reduced state needs to be re-oxidized to maintain the catalytic cycle at the expanse of stoichiometric amount of terminal oxidants such as $AgSbF_6/(NH_4)_2S_2O_8$, CuI/Ag_2CO_3 and $P(Cy)_3{\cdot}HBF_4/CuI$ or other additives. Ceric ammonium nitrate (CAN), a one-electron oxidant, has been well explored for various functional group transformations and in the synthesis of heterocycles. The reduction potential of Ce(IV)/Ce(III) is +1.61 V, thus Ce(IV) is moderately oxidizing in nature and as a single electron oxidant, can be used as the terminal oxidant towards *o*-benzoxylation.

Various reaction parameters such as catalysts, oxidants, solvents were screened to obtain the optimal conditions for this *o*-benzoxylation and it has been found that the use of 5 mol % of $Pd(OAc)_2$ and 1.5 equivalents of CAN in a mixture of 1,2 dichloroethane and acetonitrile (5:1) at 110 ^oC was the best optimum conditions for the coupling of directing arenes and carboxylic acids. This methodology was applicable for the coupling of carboxylic acid with four different types of directing arenes *viz.* 2-arylbenzothiazoles, *O*-methyl oximes, 2-phenylpyridine and 2,3-diphenylquinoxaline. Both aromatic and aliphatic carboxylic acids efficiently coupled with 2-arybezothiazoles in the presence of Pd(II)/CAN. The efficiency of the coupling reaction was poor for aliphatic carboxylic acids compare to aromatic carboxylic acids due to instability of the *in situ* generated aliphatic carboxy radicals.

On the basis of the results obtained from control experiments as well as the literature reports, a plausible mechanism has been proposed for this *o*-benzoxylation as shown in Scheme III.1.



Scheme III.1. *Proposed mechanism for o-benzoxylation*

In conclusion, a simple and efficient protocol has been developed for the *ortho*-benzoxylation of directing arenes using Pd(II)-catalyst and inexpensive terminal oxidant CAN. For the first time CAN have been used in palladium catalyzed C–H activation reaction. The high level of regioselectivity and a wide range of functional group tolerance make this protocol more attractive. Mechanistic investigations reveal the radical pathway for this strategy.

CHAPTER IV.

This chapter has been divided into two sections. Section-A describes Pd(II)-catalyzed *o*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines using *N*-halosuccinamide whereas Section-B demonstrates a copper(II) halide mediated *o*-halogenation of 2-arylbenzothiazoles in the presence of Pd(II)-catalyst.

SECTION A: Palladium Catalyzed *o*-Halogenation of 2-Arylbenzothiazoles and 2,3-Diarylquinoxalines

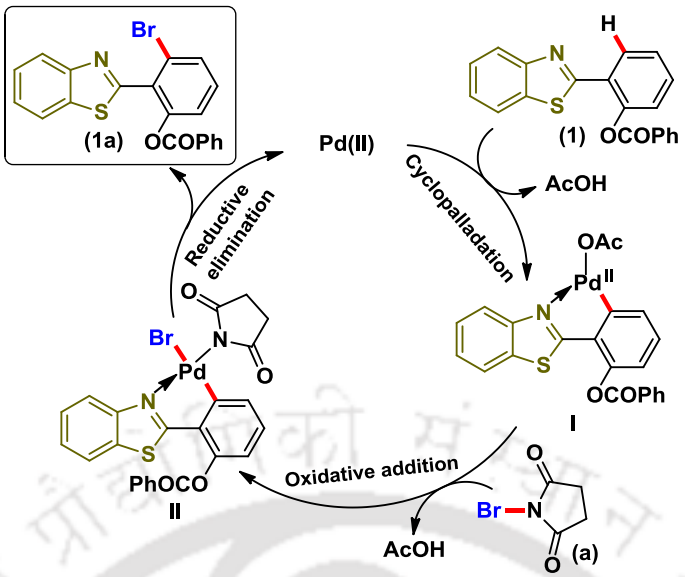
This section illustrates an efficient Pd(II)-catalyzed protocol for the mono and di *ortho* halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines using *N*-halosuccinamide.

Transition metal catalyzed directed and non directed C–H functionalization has emerged as an atom and step economic strategy for the construction of C–C, C–O, C–N, C–S and C–X (X = halogen) at the *ortho* site of the phenyl ring. Specifically, C–X bond formation gives important synthetic intermediates for nucleophilic substitution reactions and

precursors for the synthesis of various organometallic reagents that are used in transition metal catalyzed cross-coupling reactions such as Suzuki, Negishi and Heck type couplings. A few Pd-catalyzed protocols have emerged recently for the selective installation of halo groups at the *ortho* site of various directing groups *via* arene *via* sp^2 C−H activation. 2-Arylbenzothiazoles and 2,3-diarylquinoxalines bearing *o*-chelating moieties may provide cyclometallation at their proximal sites *via* the assistance of their nitrogen donor atom and therefore could be employed for *o*-functionalizations. Herein, a Pd(II)-catalyzed *o*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines has been discussed using *N*-halosuccinamides NXS (X = Cl, Br and I) as halogen sources.

After screening of reaction parameters such as catalysts, solvents and additives 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (1 equiv), catalyst $Pd(OAc)_2$ (5 mol %), additive PTSA (50 mol %) and *N*-bromosuccinimide (**a**) (1.2 equiv) in 1,2 dichloroethane (2 mL) at 90 ^oC was found to be the best conditions for *ortho* bromination. The optimized conditions were then implemented in the coupling reactions between *N*-bromosuccinimide and a set of substituted 2-arylbenzothiazole. Mono *ortho* substituted 2-arylbenzothiazoles provided *o*-brominated products in far better yields compare to *ortho* unsubstituted 2-arylbenzothiazoles. *Ortho* unsubstituted 2-arylbenzothiazoles gave *ortho*-dibromo products rather than the expected mono-*o*-brominated products. Energy calculation of mono *ortho*-halogenated benzothiazole revels that due to sulphur (S)···halo (Cl or Br) interaction benzothiazole and the 2-phenyl ring adopt a periplanar orientation and exposing the other *ortho* site for subsequent palladation for second bromination. In case of 2,3-diarylquinoxalines mono *o*-brominated products were observed under the present optimized condition. However, successfully *ortho* dibrominated product was obtained when the reaction temperature increased to 110 ^oC. Similar tends were observed for chlorination and iodination, but for chlorination reaction was carried out at 110 ^oC and iodination at 60 ^oC temperature.

A possible mechanism has been proposed for this palladium catalyzed *ortho* bromination (Scheme IVA.1). Similar mechanism can be proposed for chlorination and iodination of 2-arylbenzothiazoles and 2,3-diarylquinoalines.



Scheme IVA.1. *Proposed mechanism for o-bromination of 2-arylbenzothiazole*

In summary, an *ortho* halogenation strategy for 2-arylbenzothiazoles and 2,3-diarylquinoxalines has been established using palladium as the catalyst and *N*-halosuccinamide as the halogen source. This method provides mono *o*-halogenated and di-*ortho* halogenated product of 2-arylbenzothiazoles with respect to availability of their *ortho* C–H bond(s) while 2,3-diarylquinoxaline afforded mono *o*-halogenated products under identical reaction conditions.

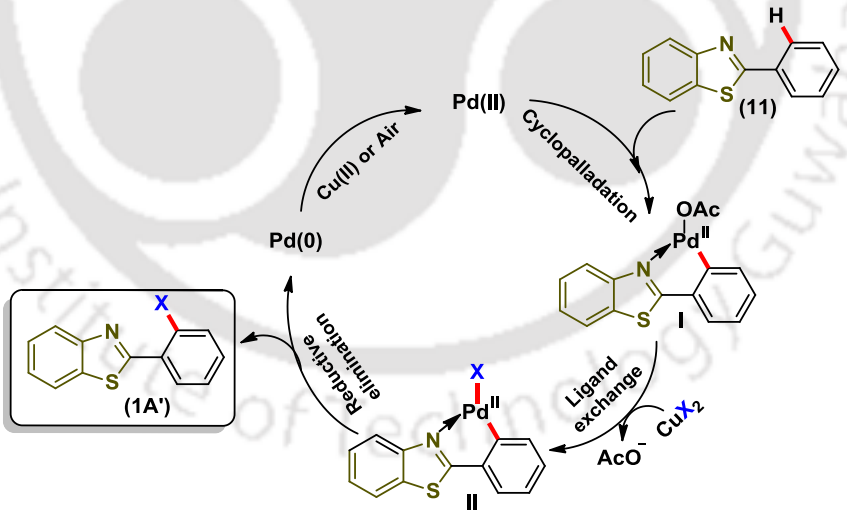
SECTION B: Copper (II) Halide Acts as a Halogenating Agent in Pd-Catalyzed *Ortho* Halogenation of 2-Arylbenzothiazoles

This section demonstrated the utility of copper(II) halide towards Pd(II)-catalyzed *ortho* halogenation of 2-arylbenzothiazoles. Aryl halides are used as synthetic precursors for nucleophilic substitution reactions, synthesis of various organometallic reagents and also used in transition metal catalyzed cross-coupling reactions. Aryl halides can be prepared *via* classical halogenation which suffers from some drawbacks such as poor regioselectivity and polyhalogenations. Recently, as a solution to these problems, transition metal catalyzed directing group assisted regioselective *o*-halogenation protocols have been developed. Diverse halogenating source *viz.* *N*-halosuccinamide, LiX, CuX_2, CaX_2 and DDQ have been employed for *ortho*-halogenation. Recently, our group has reported Pd(II)/$CuBr_2$ catalyzed keto α-C_{sp3}–H benzoxylation of *N*,*N*-dialkylamides where bonus ring bromination took place at the *ortho* or *para* position to –OH group of salicylaldehyde and 2-hydroxyacetophenone derivatives. Thus Pd(II)/$CuBr_2$ combination may be applied for

ligand directed *ortho* bromination *via* C–H activation. 2-Arylbenzothiazoles, a privileged motif present in many naturally occurring molecules and pharmaceuticals having directing ability through nitrogen atoms and therefore could be employed for *o*-functionalizations.

2-Phenylbenzothiazole (1 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) and $CuBr_2$ (2 equiv) in *N*,*N*-dimethylacetamide solvent (1 mL) at 120 ^oC gave the best yield of *ortho* brominated benzothiazole. Like section A, here also *ortho*-dibrominated product was obtained rather than the expected mono *o*-brominated product. 2-Arylbenzothiazole having electron-donating group in its 2-aryl ring gave better yield compared to electron-withdrawing group substituted benzothiazoles. *Meta* substituted benzothiazole provided mono *o*-brominated product where bromination took place at the less sterically hindered site of the 2-aryl ring. However, analogous *o*-chlorination was observed only when the reaction temperature was increased up to 130 ^oC. Then the chlorination strategy was then applied to various substituted 2-arylbenzothiazoles which provided di and mono *o*-chlorinated products as described in section A, but the yield of the products were far better compared to the use of *N*-chlorosuccinamide.

A Pd(II)/Pd(0) catalytic cycle has been proposed for this *o*-halogenation of 2-arylbenzothiazoles (Scheme IVB.1).



Scheme IVB.1. *Proposed mechanisms for o-halogenation of 2-phenylbenzothiazole*

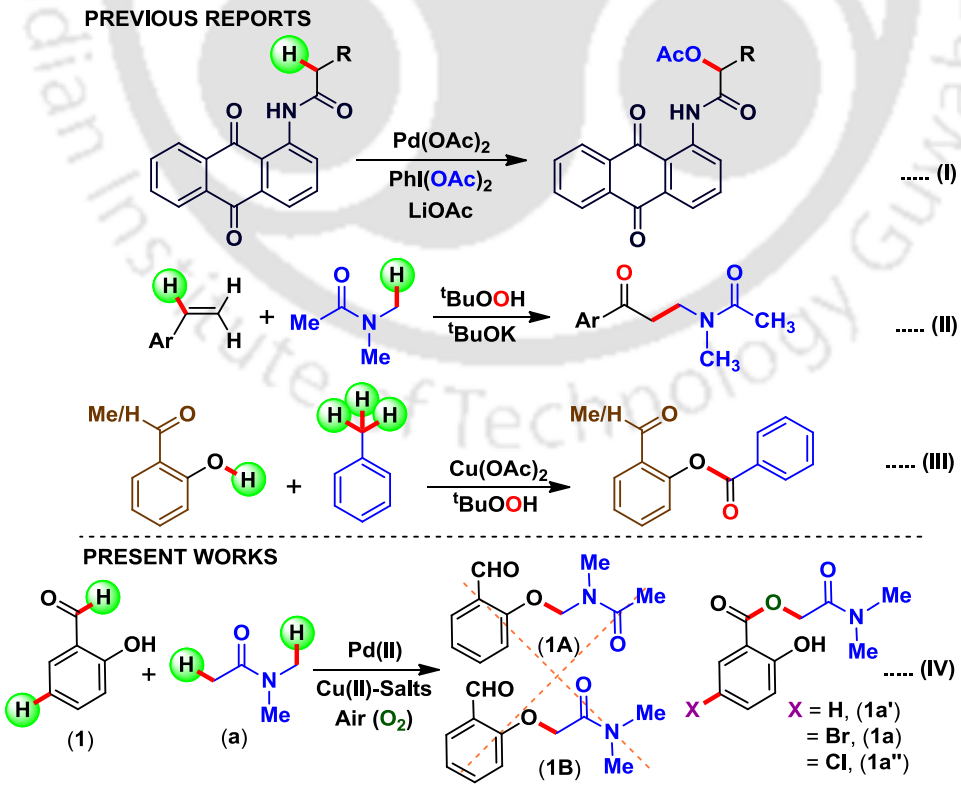
In conclusion, a Pd(II)-catalyzed mild *o*-halogenation of 2-arylbenzothiozoles has been developed using copper(II) halides. Cu(II)-salts play a dual role of halogenating agent as well as co-oxidant. This method provides di and mono *o*-halogenated products in good to excellent yields.

CHAPTER V.

This chapter deals with an efficient Pd-catalyzed oxidative cross-coupling of *N*,*N*-dialkylamides with 2-hydroxybenzaldehyde or 2-hydroxyacetophenone for the synthesis of keto α-C_{sp3}–H benzoxylated products.

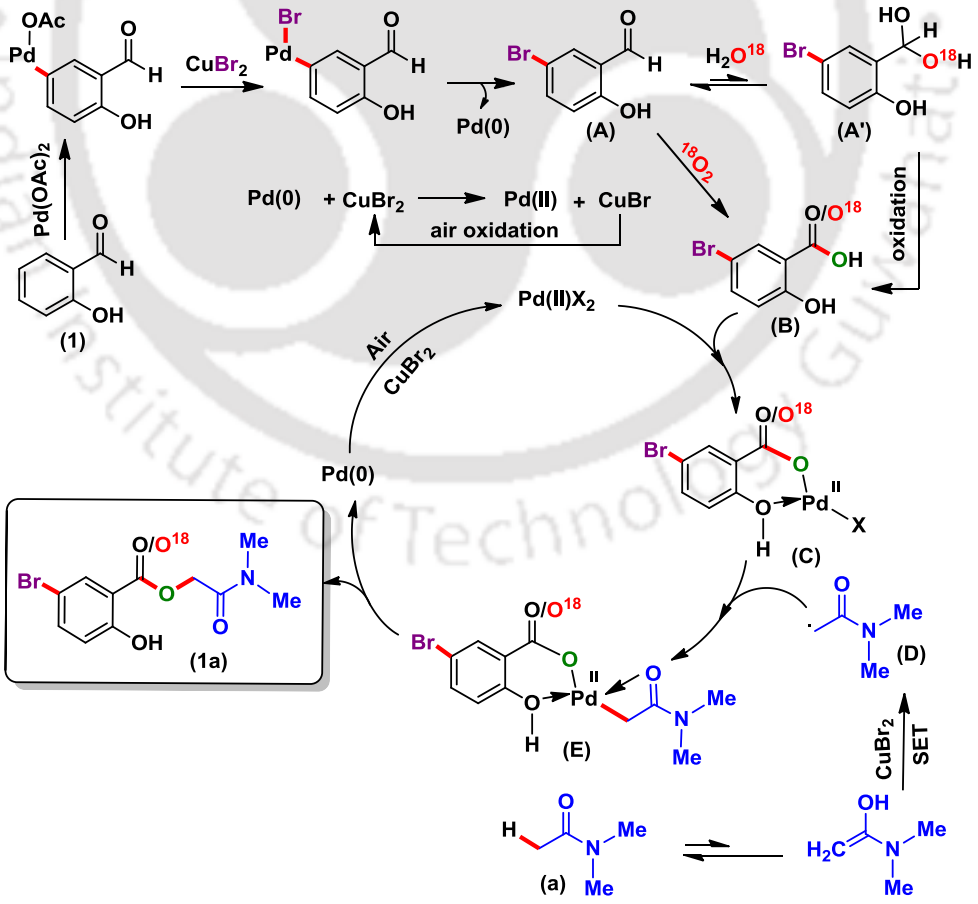
Pd(II)/$CuBr_2$ Catalyzed keto α-C_{sp3}–H Benzoxylation of *N*,*N*-Dialkylamides Directed by *o*-Hydroxy Groups

A plethora of α-Arylation of amides (sp^3 C–H α-to keto) are reported using transition metal catalyzed coupling of aryl halides with alkali metal enolates or their equivalents. To avoid the use of strong bases such as LiHMDS or NaHMDS and anhydrous conditions, recently substrate directed C–H activation strategy has been used to functionalize these α-C_{sp3}–H bonds. Li group has developed an oxidative CDC between *N*,*N*-dialkylamide (*viz.* DMA) and an alkene, where the C–C bond formation is at the α-C_{sp3}–H bond of DMA adjacent to the nitrogen atom (Scheme V.1, path II). Recently, our group has reported an oxidative *O*-aroylation of 2-hydroxybenzaldehydes/2-hydroxyacetophenones with alkylbenzenes, while –CHO or $–COCH_3$ groups acted as the directing moieties and remained intact during the reaction. (Scheme V.1, path III). Taking cues of these reports we wish to developed a cross-coupling between 2-hydroxyacetophenone and DMA.



Scheme V.1. *Some routes to sp^3 C–H functionalization viz. amides*

When a coupling reaction between 2-hydroxyacetophenone (**1**) and DMA (**a**) was carried out using $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (1 equiv) at 120 ^oC gave none of these speculated products (**1A** or **1B**), but an unexpected product (**1a′**) was observed (Scheme V.1, path IV). Interestingly, when the same reaction was carried out in the presence of $CuBr_2$ (1.0 equiv) in lieu of $Cu(OAc)_2$ α-C_{sp3}-esterification of DMA took place along with ring bromination *para* to the –OH group, giving the coupled product (**1a**) (Scheme V.1, path IV). This methodology was then applied to the coupling of DMA and substituted 2-hydroxybenzaldehydes. Both the electron-donating and withdrawing substituted 2-hydroxybenzaldehydes coupled efficiently with DMA. However, for 5-substituted aldehydes bromination occurred exclusively at the *ortho* position with respect to –OH group and for 4-substituted aldehydes bromination took place exclusively at the *para* position. Various *N*,*N*-dialkylacetamides were also used for this α-C_{sp3}-benzoxylation. This strategy was then applied successfully to 2-hydroxyacetophenone derivatives which provided both bromo-esterification and non bromo-esterification products. However, the percentage of the bromo-esterification product was more than non bromo-esterification product.



Scheme V.2. *Proposed mechanism for α-C_{sp3}-benzoxylation of DMA*

From control experiments it has been cleared that both *ortho* hydroxy group and atmospheric oxygen were required for this oxidative cross-coupling. On the basis of control experiments as well as the literature reports a plausible mechanism has been proposed for this α-C_{sp3}-benzoxylation (Scheme V.2).

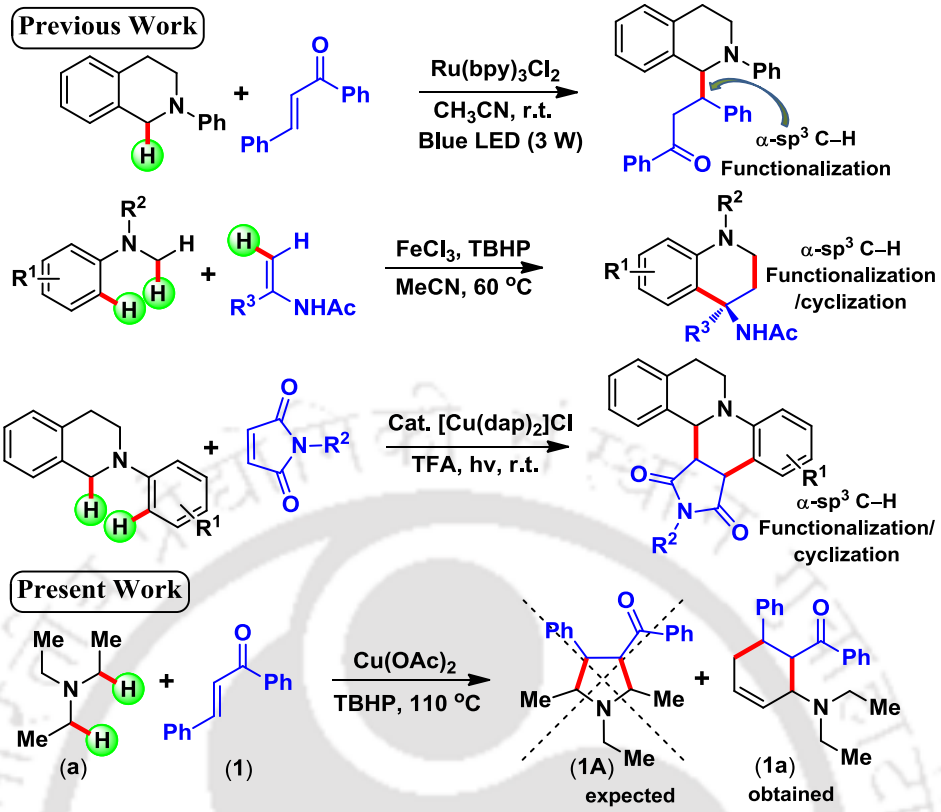
In summary, a keto α-C_{sp3}–H benzoxylation of unactivated *N,N*-dialkylamides/cyclic amides has been achieved *via* an *o*-hydroxy group directed oxidative CDC reaction. In this unique Pd(II)-catalyzed α-C_{sp3}–esterification strategy, $CuBr_2$ not only plays the role of a co-oxidant but also provides an additional ring bromination, thus opening an opportunity for further cross-couplings.

CHAPTER VI.

This chapter describes a copper(II) catalyzed [4+2] cycloaddition of *in situ* generated diene from trialkylamines by the action of *tert*-butyl hydroperoxide (TBHP) oxidant with dienophiles.

Tertiary Alkyl Amine as the Source of Diene for Cycloaddition *via* Copper(II) Catalyzed α,β C_{sp3}–H Functionalization

Selective functionalization of sp^3 C–H bonds of alkane is challenging due to inherent inertness and non-availability of coordinating site for metal binding. In contrast functionalization of alpha sp^3 C–H bonds adjacent to heteroatom is relatively easier due to its lower pKa. Functionalization of sp^3 C–H bonds adjacent to heteroatom is an attractive practical method in organic synthesis for the formation of C–C and C–X bonds. The α sp^3-carbon adjacent to nitrogen atom has the ability to act as an electrophile *via* iminium cation. Further it can serve as a nucleophile *via* classical lithiation chemistry, α-amino radical formation and metal catalyzed C–H activation processes under appropriate reaction conditions. Based on its differential reactivity a variety of methods exist in literature for α C_{sp3}–H functionalization. α C_{sp3}–H functionalization adjacent to heteroatom can be achieved either *via* thermodynamically more favorable intramolecular path or *via* intermolecular path. However, intermolecular α-functionalization and subsequent cyclization processes are rarely reported in literature. A photoredox catalyzed Michael addition of α-amino radicals to the α,β-unsaturated ketone has been developed using $Ru(bpy)_3Cl_2$ or $[Ir(ppy)_2$-(dtb-bpy)$]PF_6$ in the presence of a blue LED (Scheme VI.1).

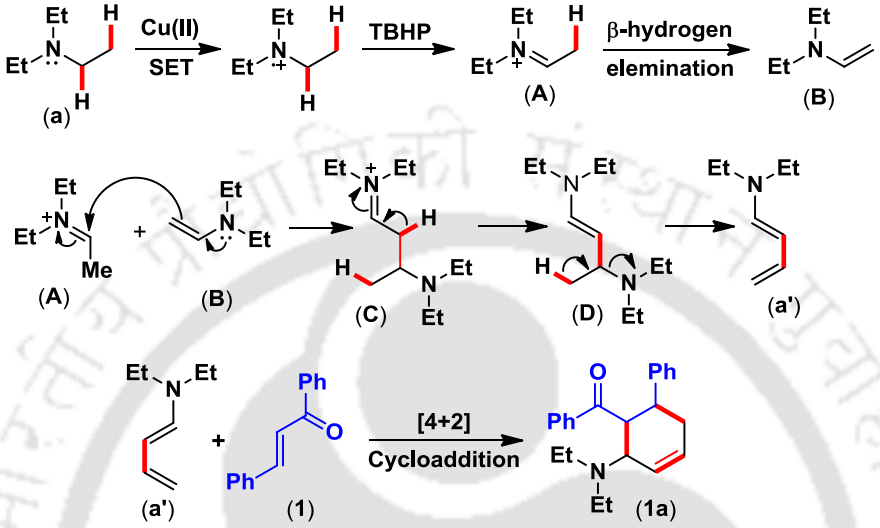


Scheme VI.1. *Strategies for α sp^3 C–H functionalization/cyclization*

Recently, Guan *et al.* reported an iron catalyzed synthesis of tetrahydroquinolines *via* the dehydrogenative [4+2] cycloaddition between tertiary anilines with enamides in the presence of *tert*-butyl hydroperoxide (TBHP). Simultaneously, Bissember *et al.* introduced *bis*(1,10-phenanthroline)-copper(I), a visible light photo-catalyst (VLP) to effect the direct α C−H functionalization and subsequent cyclization of tertiary amines with *N*-phenyl maleimide (Scheme VI.1). In this context the use of tertiary amine like simple triethylamine for such α-C−H functionalization/cyclization processes are unprecedented in literature. Triethylamine, an organic base is used mainly in the synthesis of quaternary ammonium salts for textile auxiliaries, dyes; acid neutralizer and intermediates for the synthesis of pesticides, drugs etc. Tertiary amine contains α-sp^3 C–H bonds which can be similarly functionalized with external electrophiles or nucleophiles.

When (**1**) (1 equiv) was treated with triethylamine in the presence of CuBr catalyst and TBHP oxidant it afforded the Diels-Alder product (**1a**) rather than the expected intermolecular cyclized product (**1A**). After screening of the reaction parameters it was found that the use of 15 mol % of $Cu(OAc)_2$, ^{t}BuOOH (3.5 equiv) as oxidant in triethylamine solvent-cum-reagent at 110–115 ^{o}C provided the best yield of (**1a**). For both

the cases (presence or absence of chalcone) formation of (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine (**a´**) was observed. All these reactions proceeded smoothly providing their respective Diels-Alder products in moderate to good yields. Based on the cross-over experiments performed and literature reports a plausible mechanism has been proposed for this process (Scheme VI.2.).



Scheme VI.2. *Proposed mechanism for Cu(II)-catalyzed Diels-Alder reaction*

In conclusion, triethylamine afforded (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine in the presence of Cu(II)/TBHP combination *via* coupling of the *in situ* generated iminium cation and enamine intermediate. This *in situ* generated diene is trapped with chalcone as the dienophile giving a Diels-Alder product. This is the first example where both α and β C_{sp3}–H bond of trialkylamine are functionalized in the presence of Cu(II)/TBHP combination.

Contents

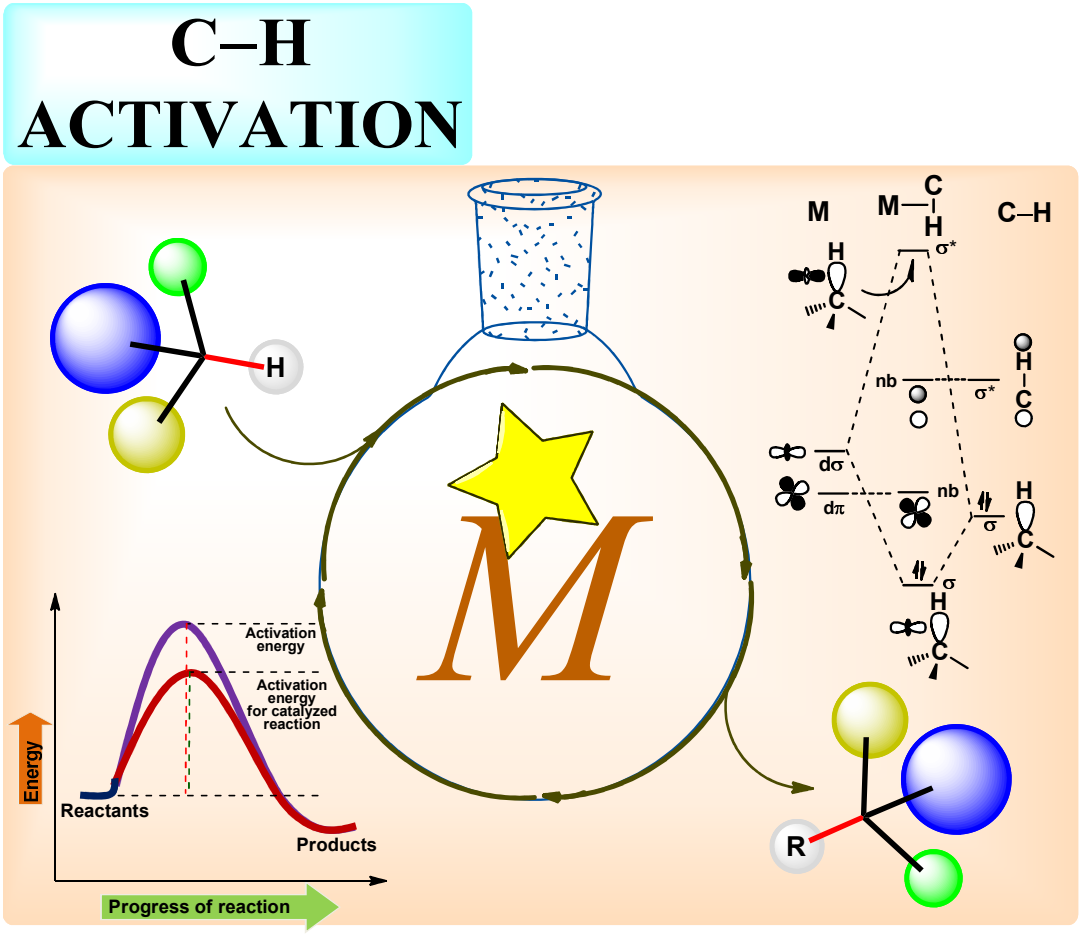
Abbreviation

AcOH	acetic acid
AIBN	azobisisobutylnitrile
Ar	aryl
BQ	benzoquinone
Bu	butyl
OBu	butoxy
Br	bromo
$AgSbF_6$	silver hexafluoroantimonate
CCDC	Cambridge crystallographic data centre
Cl	chloro
CDC	cross-dehydrogenative coupling
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIB	diacetoxy iodobenzene
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DTPB	di-*tert*-butyl peroxide
Et	ethyl
ESI-MS	electrospray ionization mass spectrometry
HRMS	high resolution mass spectrometry
HFIP	hexafluoroisopropanol
I	iodo
IR	infrared
$K_2S_2O_8$	potassium persulfate
LED	light emitting diode
Me	methyl
OMe	methoxy
Mp	melting point
MO	molecular orbital
NHC	*N*-heterocyclic carbene

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NBS	*N*-bromosuccinamide
NCS	*N*-chlorosuccinamide
NIS	*N*-iodosuccinamide
ORTEP	oak ridge thermal ellipsoid program
Ph	phenyl
Pr	propyl
PivOH	pivalic acid
PTSA	*para*-toluenesulfonic acid
rt	room temperature
TM	transition metal
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TLC	thin layer chromatography
^{t}Bu	*tert*-butyl
XRD	x-ray diffraction

Chapter I

A Sketch of Transition Metal Catalyzed C–H Functionalizations



CHAPTER I

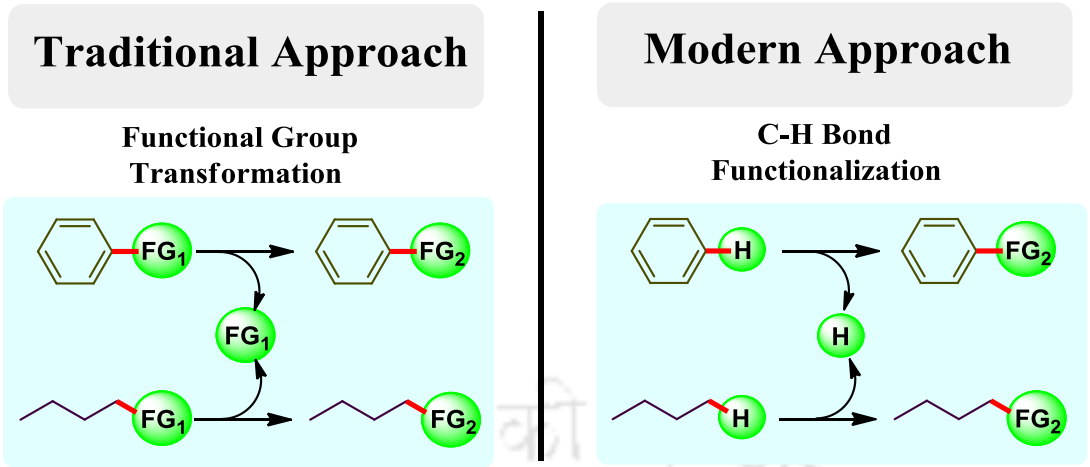
I. A Sketch of Transition Metal Catalyzed C–H Functionalizations

I.1. Introduction

Over the past two decades, various cross-coupling strategies are applied in both industry and academia to construct carbon–carbon and carbon–heteroatom bonds.[1] The advance cross-coupling strategy has been successfully applied to the synthesis of commercially important products.[2] Despite the tremendous advances, it suffer from significant drawbacks such as the use of stoichiometric organometallic reagents or pre-functionalized components for the metal catalyzed cross-coupling which increases the number of synthetic steps. One of the solutions to this problem is to utilize the direct activation of carbon–hydrogen (C–H) bonds.[3] C–H bonds are ubiquitous in nature and are regarded as the un-functionalized group. During the past few decades, extensive investigations into transition metal catalyzed C–H activation process have greatly improved our understanding of how to cleave and functionalize inert C–H bonds effectively. In recent years, it has become evident that the direct formation of carbon–carbon and carbon–heteroatom bonds from unactivated C–H bonds has enormous potential for advancing the field of chemical synthesis. C–H activation is the shortest possible route to give targeted natural product by providing unprecedented disconnections.

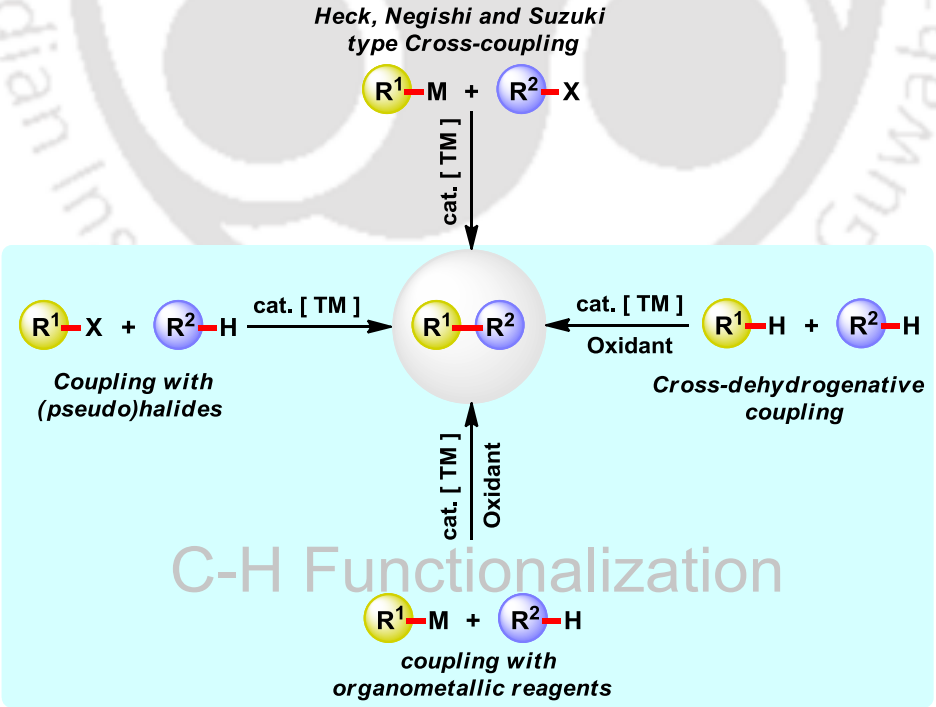
I.2. Traditional Vs Modern Approach

Traditional organic synthesis based on the exchange of one functional group (FG) with another (Scheme I.2.1). In order to install a new functional group needs pre-functionalized starting materials, which means FG_1 must be first installed and then removed as a byproduct in the second installation (Scheme I.2.1). Thus, the process decreases both its efficiency and atom economy and also adds extra step and cost to the overall transformation. The hydrogen (H) atom as an un-functional group, for the C–H functionalization does not need any pre-functionalized starting materials (Scheme I.2.1).



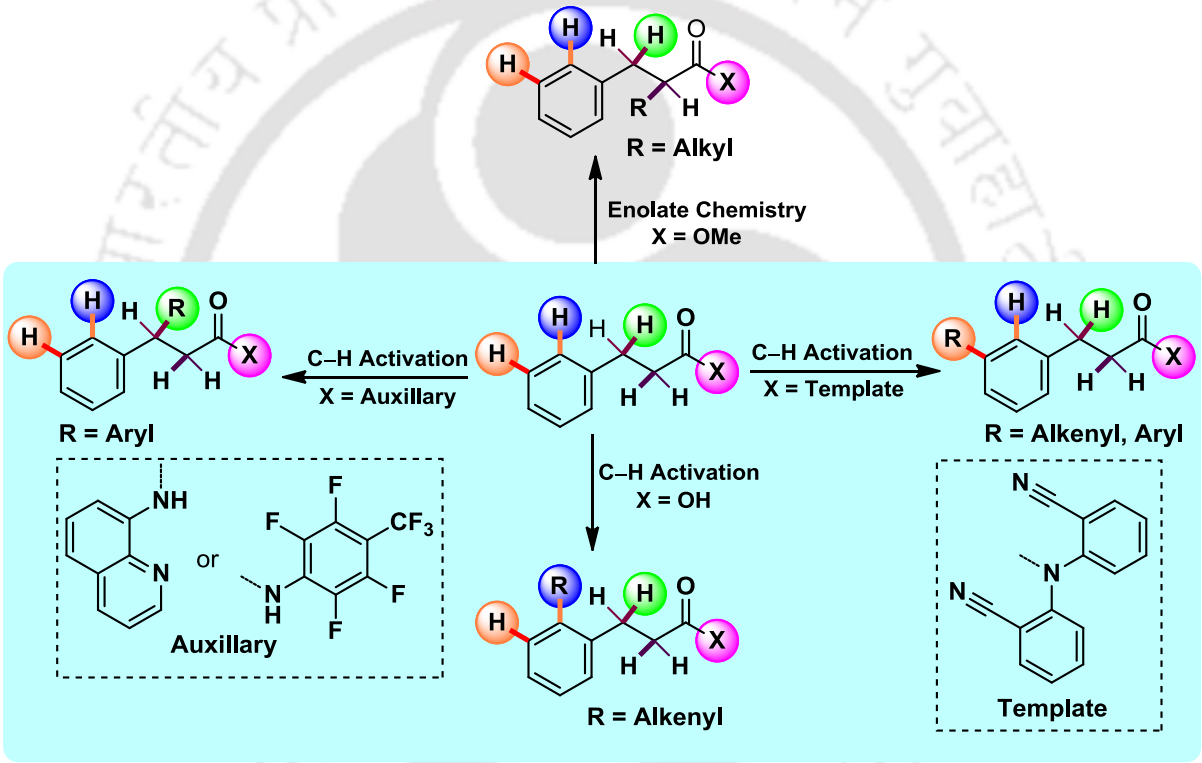
Scheme I.2.1. *Traditional approach vs. C–H bond functionalization*

The discovery of transition metal catalyzed cross-couplings introduced a new era of modern approach. In 2010, R. F. Heck, E. Negishi and A. Suzuki were awarded the Nobel prize in chemistry for their significant contributions to the development of palladium catalyzed cross-coupling reactions.[4] Later, to avoid the use of pre-functionalized starting materials chemist developed a new concept i.e., transition metal catalyzed C–H bond functionalization. Different types of transition metal catalyzed C–H functionalizations applied in recent organic synthesis are shown in Scheme I.2.2.



Scheme I.2.2. *Modern strategies in organic synthesis*

Functionalization of every C–H bond selectively in an organic molecule is quite challenging. Due to specific structure, enzymes easily achieved site-selective C–H oxidation in Nature. Organic chemists developed selective catalysts or designed substrates to achieve predictable site-selectivity. For example hydrocinnamic acid having five different types of C–H bonds, depending on their electrophilicity, nucleophilicity and acidity, each of the C–H bond has been selectively functionalized (Scheme I.2.3).[5] Functionalizaitons of hydrocinnamic acid clearly demonstrate the important of C–H functionalization over classical approach. In classical strategy it is not easy to access multiple targets from a single starting material.



Scheme I.2.3 *C–H Functionalizations of hydrocinnamic acids*

I.3. Challenges to C–H Functionalizations

Though over the past decade C–H functionalizations represent a modern chemical ideal from the step and atom economy point of view, it faced some significant challenges for selectivity and reactivity. Inherent low reactivity, regioselectivity, chemoselectivity and stereoselectivity are the four significant challenges in C–H functionalization.

➢ **Inherent Low Reactivity**

The pK_a values of sp^2 or sp^3 hybridized C–H bonds 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. Thus it is difficult to cleave these bonds *via* both homolytic and heterolytic paths.

➢ **Regioselectivity**

It is difficult to selectively target a desired C–H bond leaving all other C–H bonds intact in a complex molecule. One might expect the reactivity of one of the C−H bond to be similar in reactivity to the others, and most secondary C−H bonds in linear alkanes are expected to react at equal rates (Fig. I.3.1).[6] However, different types of C−H bonds in alkanes are well-known to react with different rates.[7] For example, tertiary C−H bonds are weaker than secondary C−H bonds and are known to be more reactive toward many radicals. Primary C−H bonds are stronger than the secondary C−H bonds and are less reactive toward radicals. So the selective functionalization of any C–H bond among all these C–H's would give access target molecules from a single starting material.

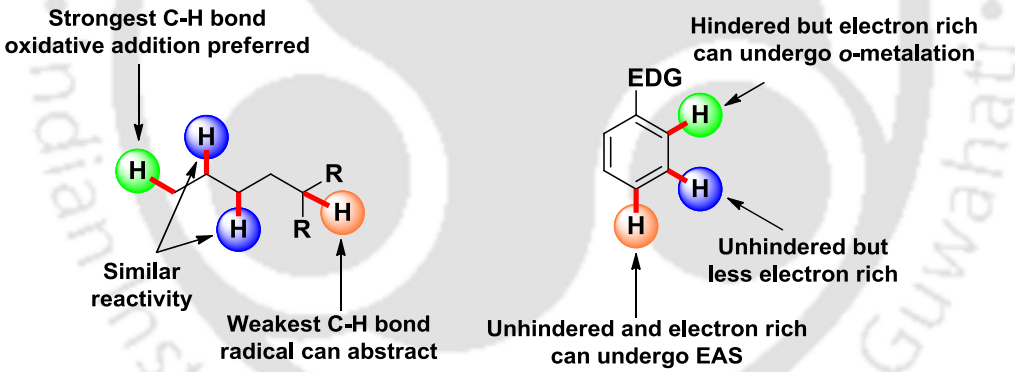
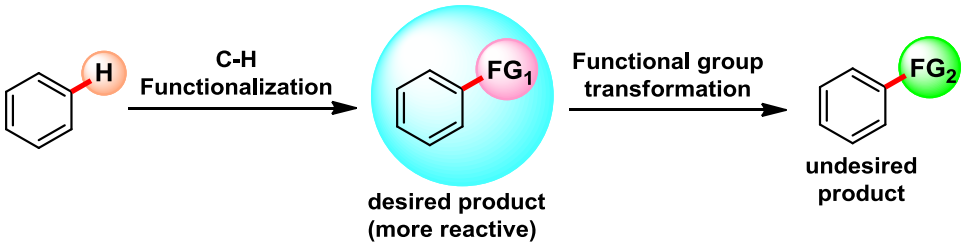


Fig. I.3.1. *Attributes of alkanes and arenes C−H bonds relevant to C−H functionalization*

➢ **Chemoselectivity**

Chemoselectivity refers to the selective reactivity of one of the functional group in the presence of others. In C–H functionalization process if the desired product is more reactive than the starting material it may undergoes further functional group transformation under the same reaction conditions leading to undesirable products (Scheme I.3.1).



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

➢ **Stereoselectivity**

In any C–H activation process harsh reaction conditions and elevated temperatures are generally required to overcome the inertness of the C–H bonds. Therefore it might have an unfavorable impact on the stability of the chiral complex and the efficiency of asymmetric induction. So during C–H activation introducing new stereogenic center with high diastereo or enantioselective isomer is the most challenging task in recent times.

I.4. Mechanisms of C–H Functionalization

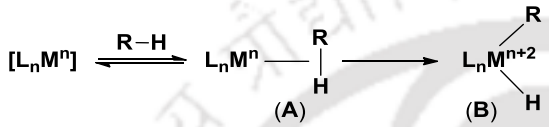
Since C–H bond activation occurred at metal centers, so discussion mainly restricted to the bond formation between a metal and a carbon of C–H bond. Two different mechanistic paths for C–H functionalizations *viz.* 'inner-sphere' and 'outer-sphere have been proposed by Sanford.[8] In the 'inner-sphere' mechanism transition metal insert into a C–H bond and forms a defined C–M bond. Further, the *in situ* generated species can be converted to a new functional group with the reaction of either an external reagent or an organyl ligand attached to the metal center.[9] Whereas, in the 'outer-sphere' mechanism a C–H bond within the substrate reacts with an actively coordinated ligand of the transition metal.[9] However, these 'inner-sphere' and 'outer-sphere' mechanisms were restricted to saturated alkane C–H bonds only. Later the reactions are conveniently classified in a broader view. Bercaw gave a more detailed classification: 'oxidative addition', '*σ*-bond metathesis', 'electrophilic activation', 'metalloradical activation', and '1,2-addition'.[10] Out of these five distinct mechanisms involve in the formation of stable organometallic species, three of these occur quite commonly, while the other two are rare.[10]

(a) Oxidative Addition

In this mechanistic path, transition metal coordinates to a C–H σ-bond and donates the electron density into the σ* orbital of the C–H bond (Scheme I.4.1, complex **A**). This reduces the bond order and weakens the C–H bond; as a result it can lead to the formation

of a new carbon–metal bond (Scheme I.4.1, complex **B**). Thus, the cleavage of the C–H bond proceeds with an increase in the oxidation state of the transition metal.

A qualitative molecular orbital diagram including only the C–H–M π interaction is shown in Figure I.4.1. The typical electron-rich and low-valent complexes of the 'late' transition metals such as Re, Fe, Ru, Os, Rh, Ir, and Pt involved in the oxidative addition reactions. Further, these organometallic intermediate can release different C–X bonds, where X is halogen, oxygen, nitrogen, carbon etc.



Scheme I.4.1. *An oxidative addition mechanism*

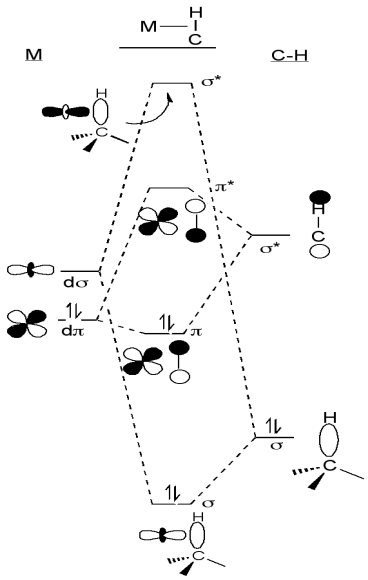
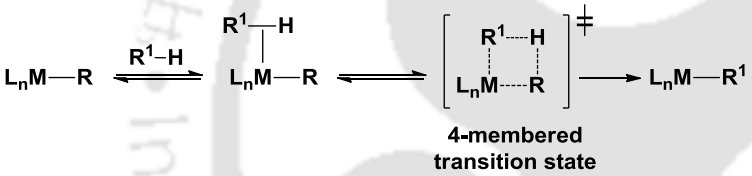


Fig. I.4.1. *A qualitative MO diagram for oxidative addition*

(b) Sigma-Bond Metathesis



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

This activation mechanism consists of σ-bond cleavage and formation catalyzed by alkyl or hydride complexes of 'early' transition metals with d^0 electronic configurations. These transitional metals are most commonly from group III of the periodic table (scandium, lanthanides and actinides), but some examples involving metals of groups IV and V are also known. Extensive experimental and theoretical studies have led to the concept of the general four-center transition state (Scheme I.4.2). A qualitative molecular orbital diagram of this reaction indicates that there is no π interaction because of the absence of any d-electrons (Fig. I.4.2).

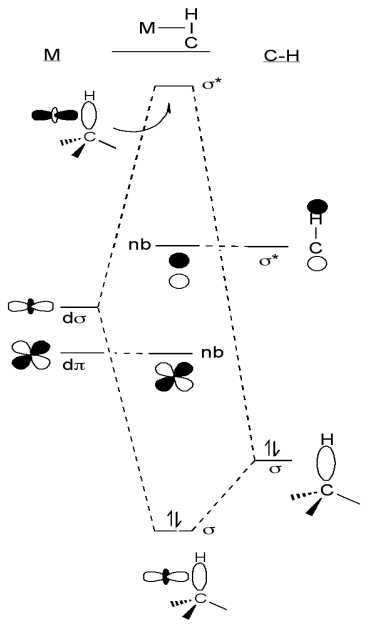
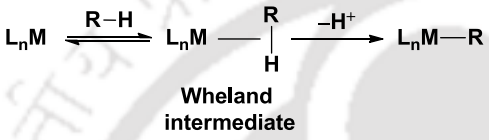


Fig. I.4.2. *A qualitative MO diagram for σ-bond metathesis*

(c) Electrophilic Activation

Late transition metals in their higher oxidation state involve in this type of activation reactions. Electrophilic activation of an aromatic nucleus proceeds in two stages; in the first step electrophilic species adds to the arene and forms a Wheland intermediate followed by a loss of proton giving a distinct σ-organyl complex (Scheme I.4.3). For saturated hydrocarbons an analogous intermediate might be formed with an electrophilic metal containing species.



Scheme I.4.3. *An electrophilic activation mechanism*

A qualitative molecular orbital diagram (Fig. I.4.3) of this reaction shows that it usually involves late or post-transition metals (Pd^{2+}, Pt^{2+}/Pt^{4+}, Hg^{2+} and Tl^{3+}) where d orbital energy is dropped.

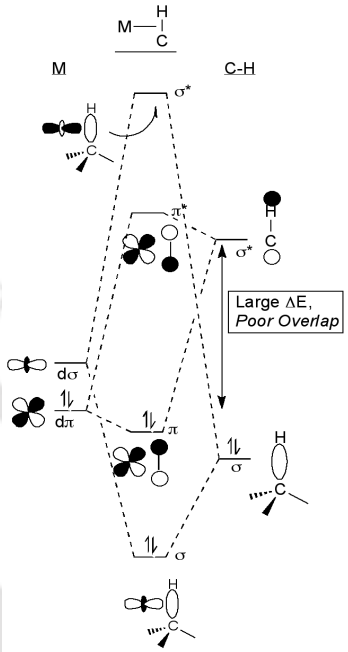
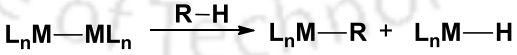


Fig. I.4.3. *A qualitative MO diagram for electrophilic activation*

(d) Metalloradical Activation

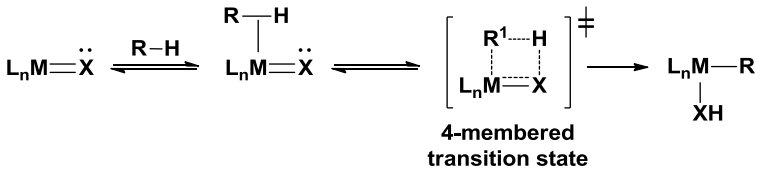
Alkene C–H activation proceeds *via* this type of mechanism. The transition metal complex existing in monomer-dimer equilibrium can reversibly break alkane C–H bonds and two fragments of C–H bonds are attached to two separate halves of the metal complex (Scheme I.4.4). Complexes of rhodium and ruthenium are usually employed for this activation reaction.



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

(e) 1,2-Addition

In this reaction alkane C–H bond adds to a metal-nonmetal double bond and forms 4-membered transition state (Scheme I.4.5). C–H bond additions across metal-nitrogen and metal-carbon double bonds of early and middle transition metal are known, but the scope and its potentiality remain unclear.

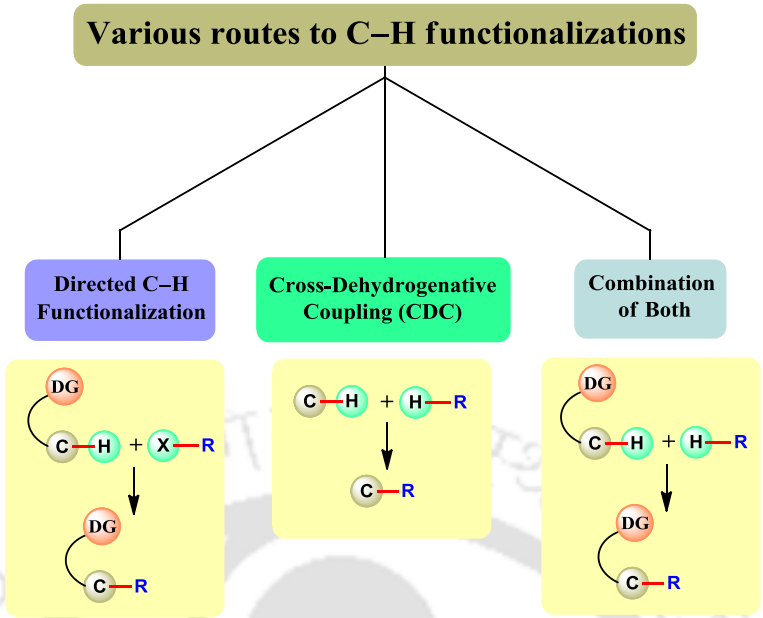


Scheme I.4.5. *A 1,2-addition mechanism*

All the above classified C–H bond activation mechanisms proceed in the presence of a transition metal complex. This type of activation is also called "true" activation as C–H bond containing substrates enter into the coordination sphere of the metal complex in the form of an σ-organyl ligand. Thus, there is a closest contact between the metal ion and the C–H bond (i.e. a normal σ-bond between metal and carbon).

I.5. Modern Era of C–H Functionalization

C–H bond activation is one of the most common processes in Nature. Over several million years, Nature cultivates specific enzymes such as cytochrome P450, methane mono oxygenase for metal based C–H functionalization. However, chemists applied the idea of C–H functionalization in practice during last few decades only. The 'golden era' of C–H functionalizations started during early 1990's, where a number of metal salts and complexes were explored for catalytic C–H activation process. Ongoing progress of research in developing new methodologies for C–H functionalizations can be classified into two major categories *viz.* (i) directing group assisted C–H functionalizations and (ii) cross-dehydrogenative coupling (CDC). Also there are methodologies which are based on the combination of these two (Scheme I.5.1).



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

I.5.1 Directed C–H Functionalizations

Ubiquitous nature and low reactivity of C–H bonds make the selective functionalization of the desired C–H bond more challenging. One solution to these problems is the use of substrates possessing heteroatoms such as nitrogen (N) oxygen (O) and sulfur (S) which can chelate the metal ion and position it adjacent to a proximal C–H bond (positional selectivity). This pre-coordination of transition metal ion increases the effective concentration of the metal and hence overcome the 'paraffin' (not enough affinity) nature of C–H bonds. The transition metal usually formed a five or a six-member metallacycle which is a resourceful intermediate for the construction of new C–C or C–X (X = heteroatoms) bonds *via* functionalization of both sp^2 and sp^3 C–H bonds. The most widely used transition metals for this purpose are Ru, Rh, Pd and Cu. Besides these other transition metals *viz.* Mn, Fe, Co, Ni, Re, Ir, Pt, Ag, Au are also employed. Functionalization of proximal C–H bond (mainly *ortho*), installation and removal of directing groups (in many cases the directing group is also an integral part of the substrate) are the basic limitations of this strategy.

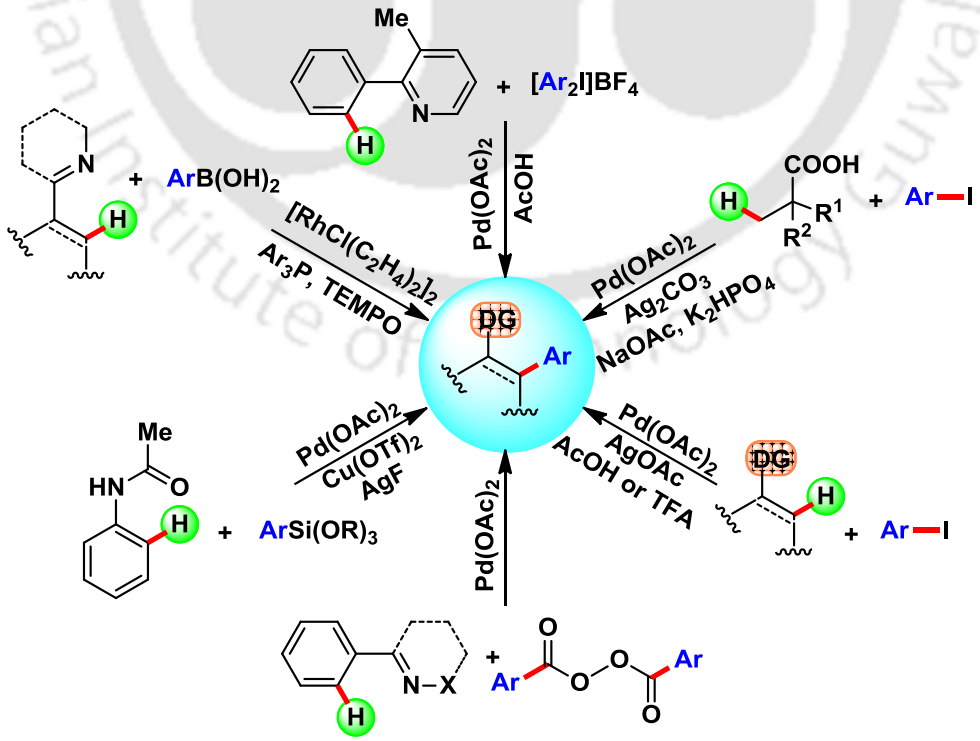
I.5.1.1. Representative Examples of Directed C–C Bond Formation

Carbon–carbon bond formation is the most fundamental transformation in synthetic organic chemistry. Now-a-days transition metal catalyzed ligand directed C–C bond formation *via* C–H activation is the most widely studied which affords *ortho*-aryl, alkyl,

alkenyl, alkynyl, carbonyl, trifluoromethyl and cyano products. Reactions relevant to each of these categories are exemplified below.

➢ **Arylation *via* C_{sp2}–H and C_{sp3}–H Bond Functionalization**

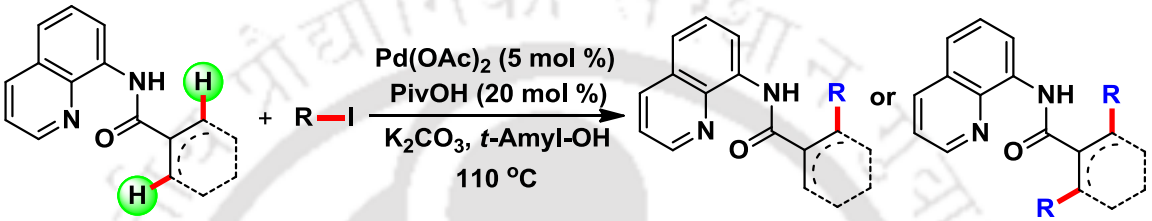
Daugulis and co-workers developed a Pd-catalyzed *o*-arylation protocol of directing arenes (2-arylpyridine, 2-ethylpyridine, 8-methylquinoline and benzo[*h*]quinoline) using aryl iodide as the aryl source and AgOAc as the oxidant.[11a] Later a related *ortho*-arylation strategy has been applied to other directing arenes such as anilides,[11b] benzoic acid derivatives,[11c] 2-arylbenzoxazoles,[11d] oxime ethers[11e] and benzamide[11f] derivatives (Scheme I.5.1.1.1). This Pd-catalyzed arylation strategy is not only limited to sp^2 C–H bond functionalization but also applied to sp^3 C–H bonds.[12] Daugulis and co-workers reported a Pd-catalyzed arylation of unactivated 1° and 2° sp^3 C–H bonds with the assistance of a pre-existing bidentate directing group *viz.* aminoquinolines and picolinamides using a combination of ArI and AgOAc (Scheme I.5.1.1.1).[13a] Arylation of weakly coordinating carboxylic acid derivatives has also been achieved using $Pd(OAc)_2$ in combination with oxidant Ag_2CO_3, NaOAc and K_2HPO_4.[13b] Apart from aryl iodides, a variety of other arylating agents such as diphenyliodonium salts,[12a-c] aryl chlorides,[12d] arylboronic acids,[12d-e] arylsilyl ethers[12f-g] and even aryl acyl peroxides[12h] have also been employed for this purpose.



Scheme I.5.1.1.1. *Pd-catalyzed arylation of directing arenes*

➢ **Alkylation *via* C_{sp2}–H and C_{sp3}–H Bond Functionalization**

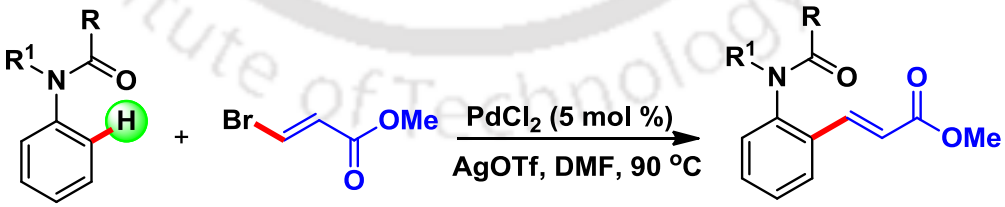
Daugulis group has demonstrated an auxiliary directed Pd(II)-catalyzed β-alkylation of sp^3 and sp^2 C−H bonds in carboxylic acid derivatives (Scheme I.5.1.1.2).[14a] In the presence of Pd-catalyst and inorganic base, 8-aminoquinoline amide substrates provided mono alkylation at the sp^3 C−H sites where as di-alkylation occurs involving sp^2 C−H bonds. Similarly, directing group assisted alkylation has also been achieved using other alkyl sources such as tetra-alkyl tin reagents,[14b] methylboroxines[14c] and dicumylperoxide.[14d]



Scheme I.5.1.1.2. *Pd-catalyzed alkylation with alkyl iodides*

➢ **Alkenylation *via* C_{sp2}–H and C_{sp3}–H Bond Functionalization**

In 2005, Daugulis group reported a $PdCl_2$ catalyzed *ortho*-alkenylation using 3-halo acrylates as alkene substrates in the presence of AgOTf oxidant (Scheme I.5.1.1.3).[15a] Recently, a direct ruthenium catalyzed regioselective alkenylation of aromatic C–H bonds of aryl and heteroarylpyridines or related compounds with alkenyl esters and ethers has been developed by Kakiuchi group. Besides this *ortho* alkenylation of aromatic sp^2 C–H bond a Pd(II)-catalyzed removable picolinamide auxiliary directed remote alkenylation of unactivated sp^3 C−H bonds has also been achieved by Chen group using vinyl iodide as the alkenylating source.[15c]

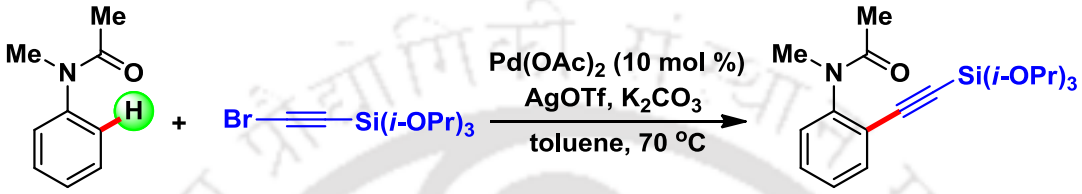


Scheme I.5.1.1.3. *Pd-catalyzed coupling of halo-olefins with anilides*

➢ **Alkynylation *via* C_{sp2}–H and C_{sp3}–H Bond Functionalization**

Chatani group described a Pd(II)-catalyzed *ortho*-alkynylation protocol of anilides with a silyl-protected bromoalkyne in the presence of AgOTf oxidant and K_2CO_3 (Scheme I.5.1.1.4).[16] Besides this Pd-catalyst, Ru, Rh and Ga have also been used for the

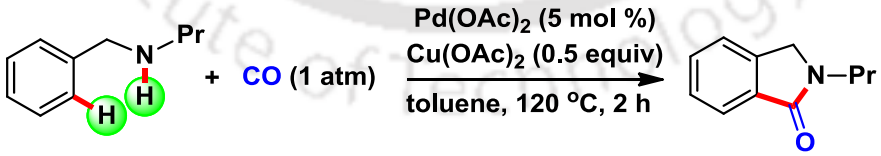
direct alkynylation of arenes and heterocycles with pre-activated alkynylating reagents such as alkynyl halides[17] and benziodoxolone-based hypervalent iodine reagents.[18] Chatani group also developed a Pd(II)-catalyzed direct ethynylation of sp^3 C–H bonds in aliphatic carboxylic acid derivatives using bidentate 8-aminoquinoline auxillary.[19a] Recently, the alkynylation of β-C_{sp3}–H bonds in aliphatic amides with alkynyl halides has been enabled by Yu group using Pd(0)/*N*-heterocyclic carbene (NHC) and Pd(0)/phosphine (PR_3) catalysts.[19b]



Scheme I.5.1.1.4. *Pd-catalyzed ortho-alkynylation of anilides with haloalkynes*

- **Carbonylation *via* C_{sp2}–H and C_{sp3}–H Bond Functionalization**

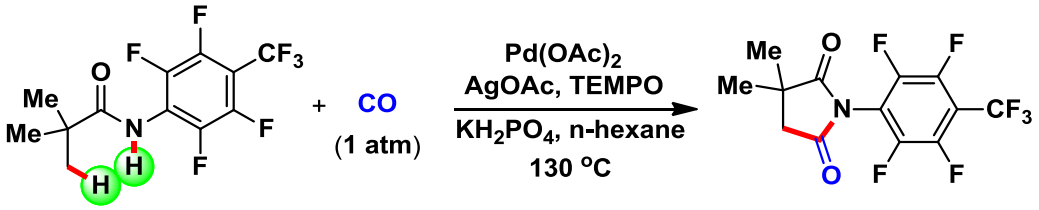
A Pd(II)-catalyzed direct aromatic carbonylation has been achieved in a phosphine free catalytic system using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an atmosphere of CO (Scheme I.5.1.1.5).[20a] The carbonylation of mono-protected benzylamines or *N*-alkylphenethylamines proceeded *via ortho*-palladation, inducing a remarkable site selectivity to afford a variety of five- or six-membered benzolactams. Further, a Pd(II)-catalyzed direct carbonylation has been applied to aniline, benzoic and phenylacetic acid derivatives to form esters[20b] (cyclic or acyclic) and dicarboxylic acids[20c] using CO as the carbonyl source. Diethyl azodicarboxylate (DEAD) has also been used as a substitute of toxic CO for $Pd(OAc)_2$ catalyzed chemo- and regioselective ethoxycarbonylation reactions of 2-arylpyridines, pyrrolidinone, acetylindoline, quinoline and oximes.[20d]



Scheme I.5.1.1.5. *o-Carbonylation of benzylamines for the synthesis of benzolactams*

A Pd(II)-catalyzed β-C_{sp3}–H carbonylation of *N*-arylamides under CO (1 atm) has been achieved by Yu and co-workers (Scheme I.5.1.1.6).[21] This carbonylation protocol proceeds *via* intermolecular CO insertion to amide directed C_{sp3}–H bond followed by intramolecular C–N bond formation giving the corresponding succinimides, which could be readily converted to 1,4-dicarbonyl compounds. Recently, a mono selective γ-C–H

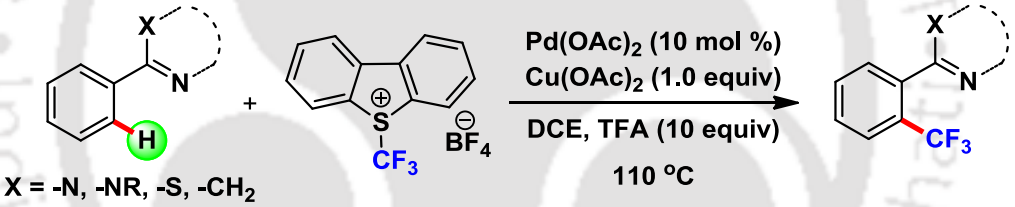
olefination and carbonylation of aliphatic acids has been accomplished by the same group using a combination of quinoline-based ligand and a weakly coordinating amide directing group.[22]



Scheme I.5.1.1.6. *Pd-catalyzed β-C_{sp3}–H carbonylation of amides*

➢ ***Ortho* C–H Trifluoromethylation**

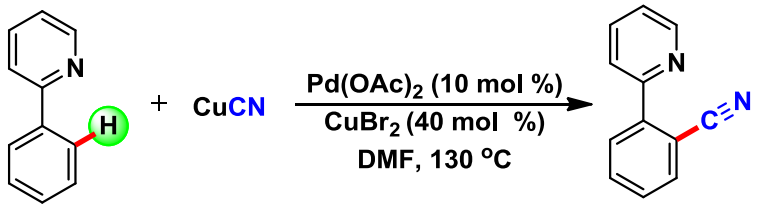
For the first time Yu group developed a Pd(II)-catalyzed *ortho*-trifluoromethylation of diverse heterocycle directing groups using electrophilic CF_3 reagent and trifluoro acetic acid (TFA) as a promoter (Scheme I.5.1.1.7).[23a] Further, this strategy was extended to various directing arenes such as *N*-arylbenzamides,[23b] benzylamines[23c] and acetanilides[23d] using similar type of electrophilic CF_3 reagents.



Scheme I.5.1.1.7. *Pd-catalyzed ortho-trifluoromethylation of directing arenes*

➢ ***Ortho* C–H Cyanation**

Chang group developed an Pd(II)-catalyzed *ortho*-cyanation of 2-arylpyridines using CuCN as the cyanide surrogate (Scheme I.5.1.1.8).[24a] Further, similar *o*-cyanation of different directing groups have been achieved with *N*,*N*-dimethylformamide and ammonia combination,[24b] potassium ferricyanide,[24c] benzyl nitrile,[24d] acetonitrile,[24e] 2,2′-azobisisobutyronitrile (AIBN)[24f] and *tert*-butyl isonitrile[24g] as the cyanide source.



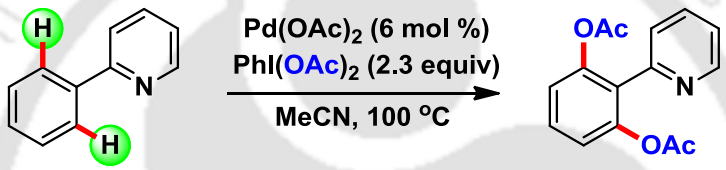
Scheme I.5.1.1.8. *Pd-catalyzed ortho-cyanation of 2-phenylpyridine*

I.5.1.2. Representative Examples of C–O Bond Formation

The C–O bond installations *via* C_{sp2}–H or C_{sp3}–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 discussed below.

- **Acetoxylation *via* sp^2C–H Bond Functionalization**

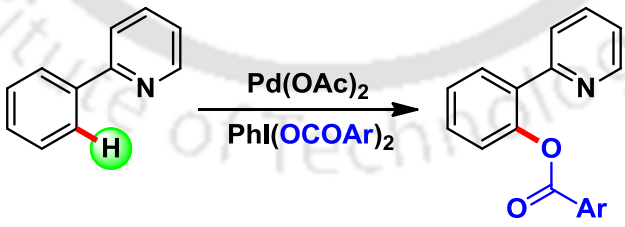
The first example of a Pd-catalyzed *o*-acetoxylation of 2-arylpyridines or analogous substrates was demonstrated by Sanford group using $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme I.5.1.2.1).[25a] The similar strategy was further executed to sp^2/sp^3 C–H acetoxylation of mono and bidentate directing substrates such as pyridine,[25b] oximes,[25c-g] keto amide[25h] and amide pyridines.[25i-j]



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

- **Benzoxylation *via* sp^2 C–H Bond Functionalization**

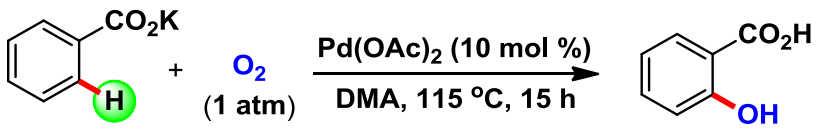
Sanford *et al.* also developed *o*-benzoxylation of 2-phenylpyridines using benzoate hypervalent iodonium salts as the ArCOO–surrogates (Scheme I.5.1.2.2).[26a] Later, a similar Pd(II)-catalyzed *o*-benzoxylation of ketoxime has been described by Shi group *via* the *in situ* generation of benzoate iodonium salts. The resultant intermediate undergo another sp^2 C–H bond activation to construct 6*H*-benzo[*c*]chromen-6-ones.[26b]



Scheme I.5.1.2.2. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

- **Hydroxylation *via* sp^2 C–H Bond Functionalization**

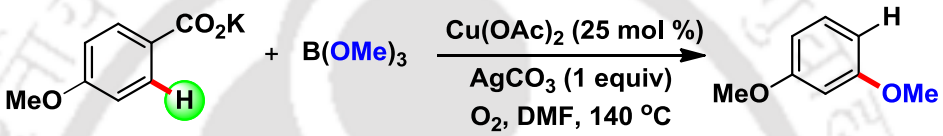
A direct Pd-catalyzed oxygenation (*ortho*-hydroxylation) of aryl C–H bonds of potassium benzoates with molecular oxygen has been demonstrated by Yu group (Scheme I.5.1.2.3).[27a] Ru(II)-catalyst have also been used for hydroxylation of diverse directing arenes.[27b]



Scheme I.5.1.2.3. *Pd-catalyzed ortho-hydroxylation of arylcarboxylic acids*

➢ **Alkoxylation *via* sp^2 C–H Bond Functionalization**

Gooβen group described a regiospecific copper/silver bimetallic catalytic system for the *ortho*-alkoxylation of aromatic carboxylates with concomitant loss of the carboxylate directing group (Scheme I.5.1.2.4).[28a] Several protocols for palladium catalyzed regioselective alkoxylations of arenes were recently reported using of pyridyl,[28b] *N*-methoxyimine,[28c] *N*-methoxybenzamide,[28d] cyano,[28e] and anilide[28f] directing groups.



Scheme I.5.1.2.4. *Cu-catalyzed ortho-alkoxylation of arylcarboxylates*

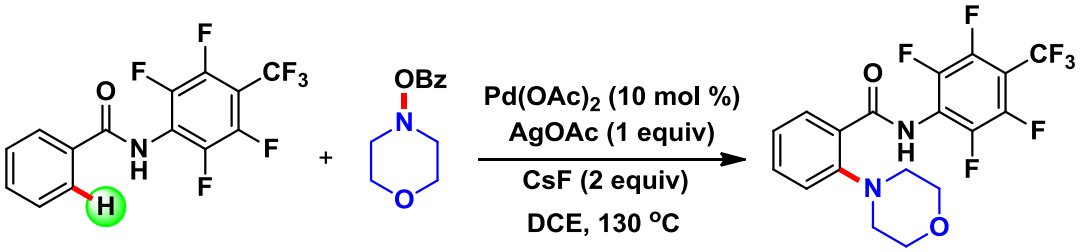
The *ortho*-alkoxylation is not only limited to sp^2 C–H bond, the strategy was also extended to unactivated sp^3 C–H bonds directed by picolinamide[29] and 8-aminoquinoline[30] in the presence of Pd(II)-catalyst.

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. Representative examples pertaining to various forms of C–N bond formations are shown below.

➢ **Amination *via* sp^2 C–H Bond Functionalization**

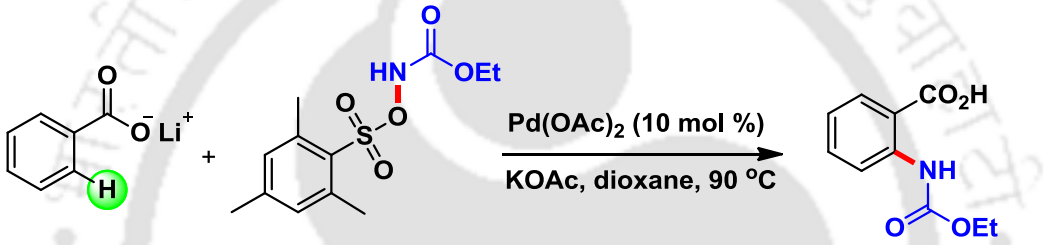
A direct C–H amination of *N*-aryl benzamides has been achieved with *o*-benzoyl hydroxylamines using either Pd(II) or Pd(0) catalysts (Scheme I.5.1.3.1).[31a] Along with Pd-catalyst Rh has also been used for similar amination reaction using *N*-haloamines.[31b-d]



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

➢ **Amidation *via* sp^2 C–H Bond Functionalization**

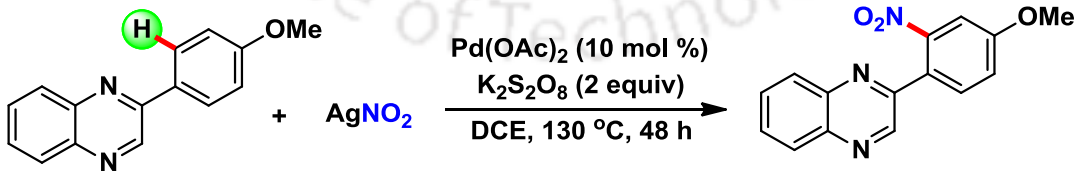
An efficient method for the synthesis of anthranilic acids using Pd-catalyzed *ortho*-C–H amidation of benzoic acids has been disclosed by Yu group (Scheme I.5.1.3.2).[32a] The amidation is proposed to proceed by carboxylate assisted *ortho*-C–H palladation to form an arylpalladium(II) complex, followed by a nitrene insertion into the Pd–C bond. Glorius reported a Rh(III)-catalyzed amidation of C_{sp2}–H bonds using electron-deficient aroyloxycarbamates as the efficient electrophilic amidation partners.[32b] Along with *N*-mesitylsulfonates and *N*-carboxylates recently organic azides have been introduced as pre-activated aminating reagents in C–H activation protocols. Ru(II)-catalyzed amidation reactions using sulfonyl azides as precursors were illustrated notably by Ackermann,[33a] Sahoo[33b-c] and Jiao[33d] groups.



Scheme I.5.1.3.2. *Pd-catalyzed ortho-amidation of benzoates with N-mesitylsulfonates*

➢ ***Ortho* Nitration of sp^2 C–H Bond**

Liu and co-workers described a Pd-catalyzed chelation assisted *ortho* nitration of aromatic C–H bonds in the presence of $K_2S_2O_8$ oxidant (Scheme I.5.1.3.3).[34a] A range of azaarenes, such as 2-arylquinoxalines, pyridines, pyrazoles and *O*-methyl oximes, were nitrated with excellent chemo- and regioselectivity. Later, Liu and Bi group reported a inexpensive Cu(II) mediated protocol for the *ortho* nitration of 2-arylpyridines using $AgNO_3$ as the source of 'NO_2' group.[34b]



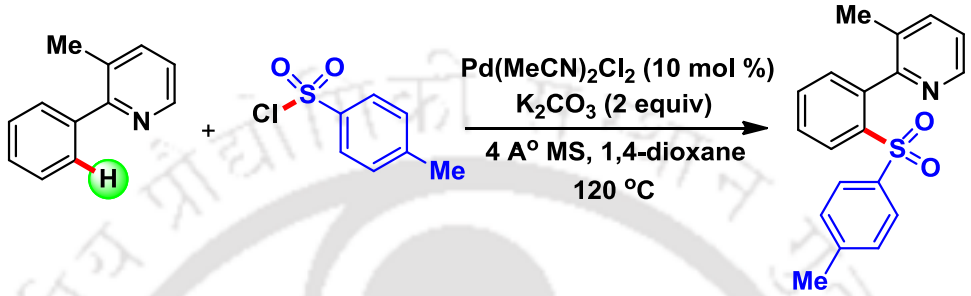
Scheme I.5.1.3.3. *Pd-catalyzed sp^2 C–H nitration of 2-arylquinoxalines*

I.5.1.4. Representative Examples of C–S Bond Formation

Transition metal catalyzed carbon-sulfur (C–S) bond formations are relatively fewer in numbers due to competing oxidation of sulfur compounds. Few examples pertaining to ligand directed C–S bond formations are shown below.

➢ ***Ortho* C–H Sulfonylation**

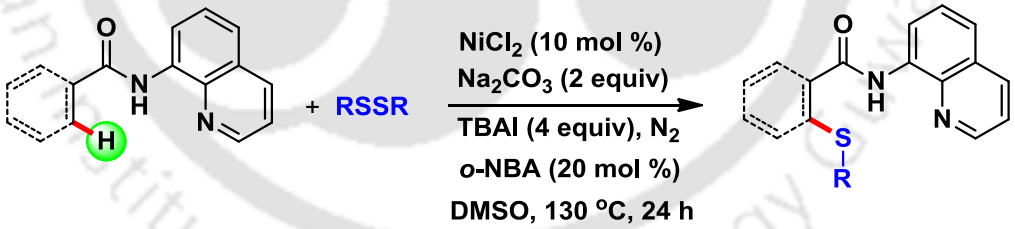
Dong group developed $Pd(MeCN)_2Cl_2$ catalyzed intermolecular *ortho*-arylsulfonylation of direcing arenes *viz.* arylpyridines, arylpyrazoles and aryloxime ethers using arylsulfonyl chlorides ($ArSO_2Cl$) as the sulfonating reagent (Scheme I.5.1.4.1).[35] Recently, Shi group introduced a Pd(II)-catalyzed sulfonylation of unactivated C_{sp3}–H bonds with sodium arylsulfinates using 8-aminoquinoline auxiliary.[36]



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

➢ ***Ortho* C–H Sulfenylation**

In 2012, an auxiliary assisted copper catalyzed or promoted sulfenylation protocol of benzoic acid derivative (β-sp^2 C–H bonds) and benzylamine derivative (γ-sp^2 C–H bonds) has been developed by Daugulis group using disulfide as the thiolating agent.[37] Recently, disulfides[38a-c] and thiols[38d] have been used for nickel catalyzed auxiliary directed thiolation/sulfenylation of sp^2 or sp^3 C–H bonds (Scheme I.5.1.4.2).



Scheme I.5.1.4.2. *Ni-catalyzed sp^2 and sp^3 C–H sulfenylation*

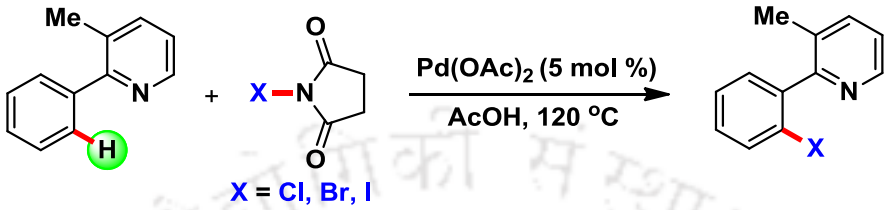
I.5.1.5. Representative Examples of Carbon–Halogen Bond Formation

Aryl halides are synthetic intermediates for organometalic reagent synthesis and cross-coupling reactions. Thus the installation of a C–X (X = Cl, Br, I) bond *via* C–H activation has got special synthetic importance in coupling chemistry for further functionalizations.

➢ ***Ortho* C–H Chlorination, Bromination and Iodination**

Kodama and co-workers developed *ortho*-iodination of benzoic acids in the presence of $Pd(OAc)_2$ and *N*-iodosuccinimide.[39a] Sanford group introduced directed chlorination, bromination and iodination of 2-arylpyridines using *N*-halosuccinimides (Scheme

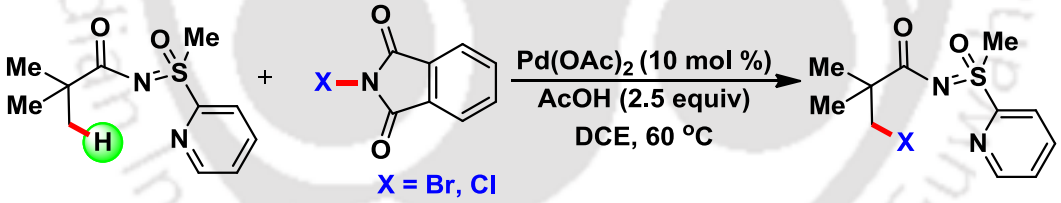
I.5.1.5.1).[39b] Further, various group applied similar strategy for *o*-halogenation with a variety of directing arenes including pyridines, oxime ethers, isoquinolines, anilides, nitriles, *O*-arylcarbamates and isoxazolines.[39c-i] Apart from *N*-halosuccinimides, other halogenating agents such as CuX_2 (X = Cl, Br),[39j] Suárez reagents (XOAc, X = Br, I)[39k-m] and CaX_2[39n] were also used.



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

- **Bromination and Chlorination at sp^3 C–H Bond of Directing Substrates**

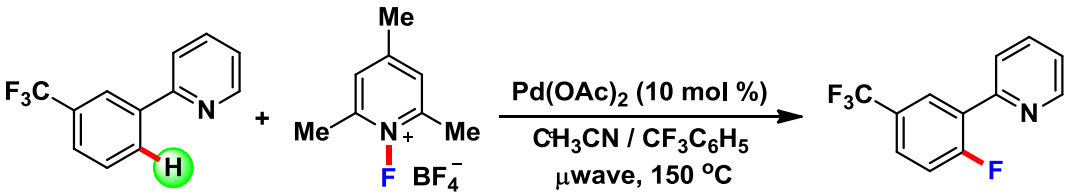
A removable directing auxillary *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) has been used for Pd(II)-catalyzed bromination and chlorination of β-sp^3 C–H bonds by employing *N*-halophthalimides as the halogen source (Scheme I.5.1.5.2).[40] Yu group reported a Pd(II)-catalyzed sp^3 C–H iodination using a combination of $PhI(OAc)_2$ and I_2, that generates IOAc *in situ*.[39e-f] The same group also achieved *ortho* iodination protocol of various directing arenes with cheap molecular I_2 as the sole oxidant.[41]



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

- ***Ortho* C–H Fluorination**

Sanford group described the development of a new Pd(II)-catalyzed method for the fluorination of C–H bond under an oxidative condition using electrophilic *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (Scheme I.5.1.5.3). Microwave irradiation in the presence of catalytic palladium acetate is the optimal condition for the fluorination of both sp^2 and sp^3 C–H bonds in a variety of substituted 2-arylpyridine and 8-methylquinoline derivatives.[42a] Further, a similar Pd(II)-catalyzed C–F bond formation strategy was extended to triflamide-protected benzylamines-based substrates[42b] and benzamides[42c] using *N*-fluoro-2,4,6-trimethylpyridinium triflate as the "F^+" source.



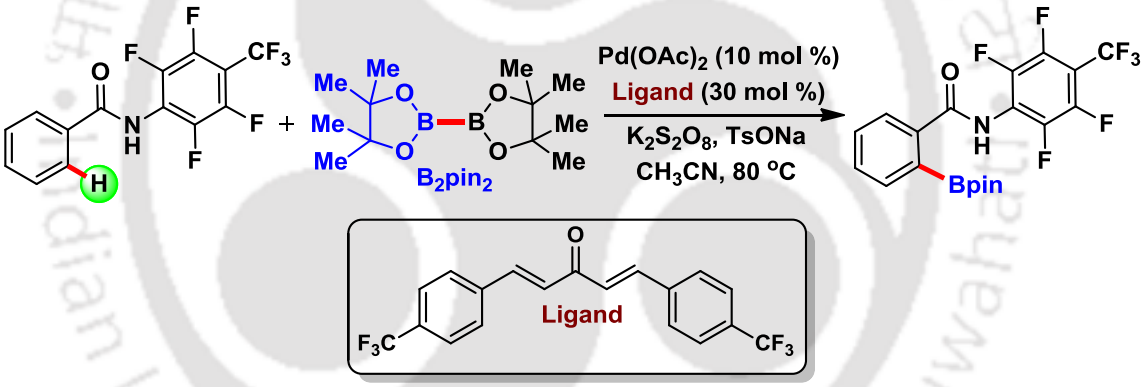
Scheme I.5.1.5.3. *Pd-catalyzed ortho fluorination of 2-arylpyridines*

I.5.1.6. Representative Example of C–B, C–Si and C–Se Bond Formations

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

- ***Ortho* C–H Borylation**

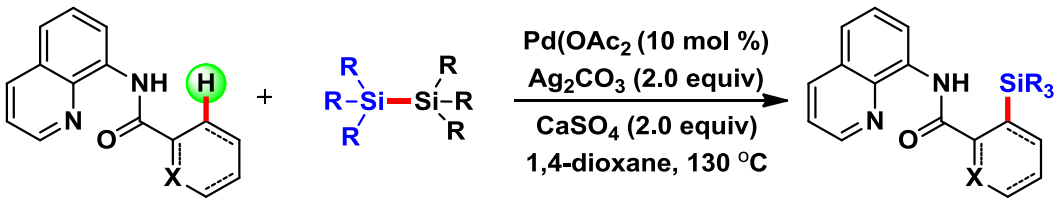
Yu group reported a Pd-catalyzed *ortho* C–H borylation of amides using diboron reagents (B_2Pin_2) as the coupling partner. The reaction proceeds in the presence of dibenzylideneacetone (dba) ligand, a weak base TsONa and an oxidant $K_2S_2O_8$ (Scheme I.5.1.6.1).[43]



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

- ***Ortho* C–H Silylation**

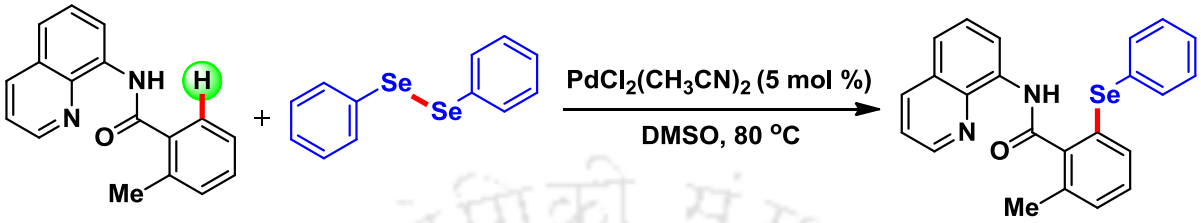
Kanai and co-workers developed a Pd-catalyzed *o*-silylation protocol of bidentate 8-aminoquinoline directing group with hexamethyldisilane as silicon source in the presence of Ag(I) and calcium sulfate (Scheme I.5.1.6.2).[44]



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

➢ ***Ortho* C–H Selenation**

A direct *o*-selenation of directed substrates *viz.* benzamides, benzylamines, 2-arylpyridines and benzo[*h*]quinolines has been reported by Nishihara group in the presence of Pd(II) catalyst and diselenides (Scheme I.5.1.6.3).[45]



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

I.5.2. Cross-dehydrogenative Coupling (CDC)

The formation of C–C bonds directly from two different C–H bonds *via* the formal removal of two hydrogen atoms is called "cross-dehydrogenative coupling" (CDC). Now-a-day, the CDC not only restricted to the coupling of two different C–H bonds but also the coupling of C–H and X–H (X = heteroatoms) bonds.[46] This strategy represents a new conceptual approach in atom economically planning synthesis. Generally a CDC reaction proceeds in the presence of a hydrogen acceptor *viz.* hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP) or di-*tert*-butyl peroxide (DTBP) and *N*-halosuccinimides. A variety of metal catalysts such as Cu, Fe and Pd are employed for CDC reactions. There are also examples of CDC which proceed in the absence of metal catalysts.[47]

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.

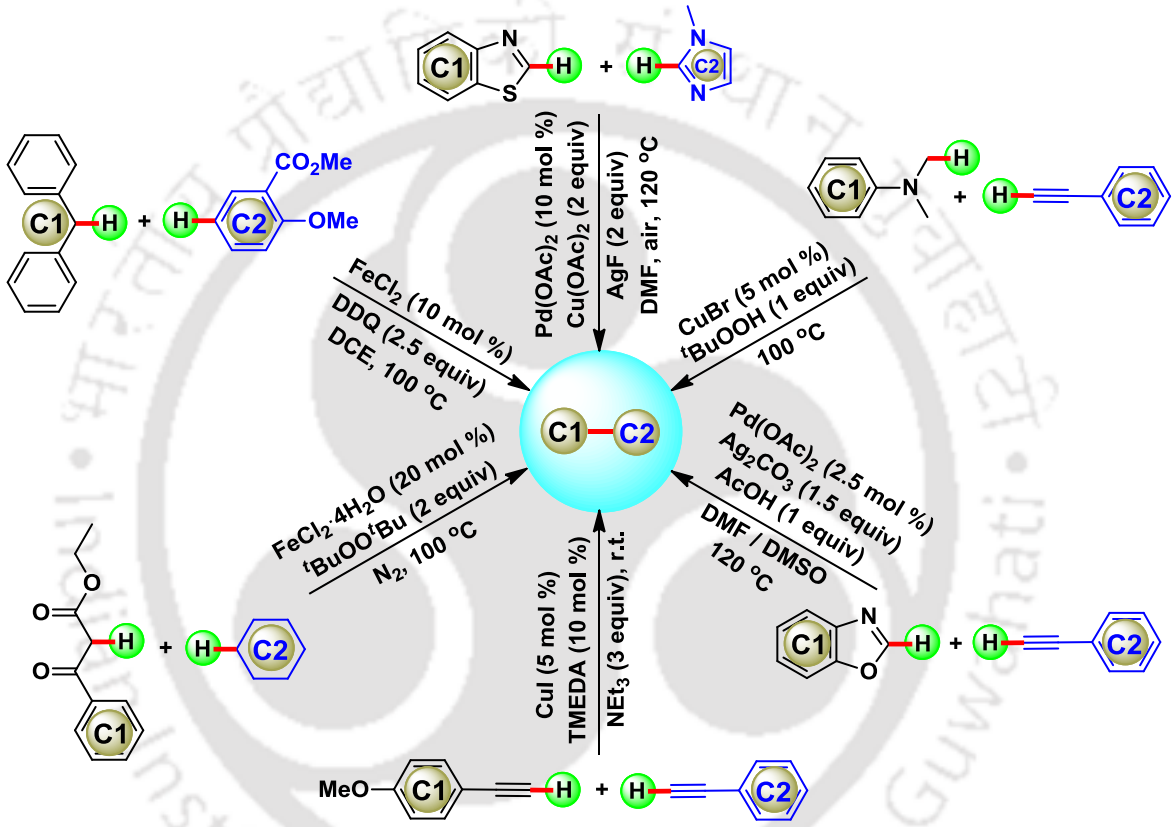
Limitations:

- 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

The first report on CDC reaction (C_{sp}–C_{sp} coupling) was a copper-mediated oxidative homodimerization of alkynes (the Eglinton reaction) over a century ago.[48a] The reaction requires a stoichiometric amount of $Cu(OAc)_2$ as both mediator and oxidant. Later, the Glaser–Hay coupling modified such oxidative homodimerization of alkynes by using a

catalytic Cu(I) catalyst with oxygen as the terminal oxidant.[48b-d] Zhang group has developed a facile and efficient protocol for the homo-coupling of terminal alkynes employing CuI as the catalyst using ligand *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA) under ambient temperature and air as the oxidant (Scheme I.5.2.1.1).[49] This oxidative dimerization provided symmetrical as well as unsymmetrical 1,4-disubstituted 1,3-diynes in good to excellent yields. Other types of cross-dehydrogenative coupling *viz.* C_{sp}–C_{sp2}, C_{sp}–C_{sp3}, C_{sp2}–C_{sp2}, C_{sp2}–C_{sp3} and C_{sp3}–C_{sp3} are discussed below.



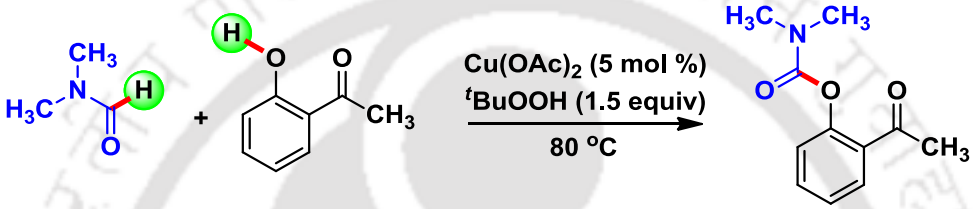
Scheme I.5.2.1.1 *Metal-catalyzed C–C bond formation via CDC*

Murai group introduced a Pd(II) catalyzed oxidative C_{sp}–C_{sp2} coupling between five-membered heteroarenes such as imidazole, oxazole, thiazole etc. and terminal alkynes in the presence of Ag(I) salt as the oxidant and AcOH as additive (Scheme I.5.2.1.1).[50] Li group established a simple and efficient catalytic method to synthesize propargylamine by using CuBr and ^{t}BuOOH *via* coupling of sp C–H and sp^3 C–H bonds (Scheme I.5.2.1.1).[51] An efficient Pd-catalyzed protocol for the direct C-2 heteroarylation of benzazoles (C_{sp2}–C_{sp2} coupling) with N–, O–, and S– containing azoles was developed by Ofial and co-workers in presence of co-oxidants $Cu(OAc)_2$ and AgF (Scheme I.5.2.1.1).[52] Shi *et al.* reported a $FeCl_2$ catalyzed oxidative CDC between arene sp^2 C–H and benzylic sp^3 C–H in

the presence of DDQ as the oxidant for the synthesis of di- or tri-arylmethane derivatives.[53] Li group developed a direct alkylation (C_{sp3}–C_{sp3} coupling) of activated methylene compounds such as β-keto ester and 1,3-diketone in the presence of Fe(II)-catalyst (Scheme I.5.2.1.1).[54]

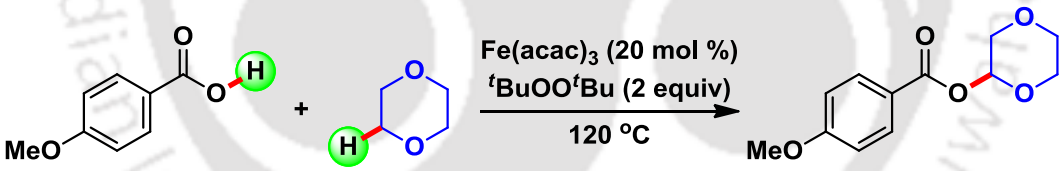
I.5.2.2. Representative Examples of C–O Bond Formation

Reddy group reported a Cu(II)-catalyzed carbamates synthesis *via* oxidative C–O bond formation of sp^2 C–H bond of formamides with phenol and enols (Scheme I.5.2.2.1).[55] Later, this strategy was extended to oxidative esterification of *o*-carbonyl-substituted phenols.



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

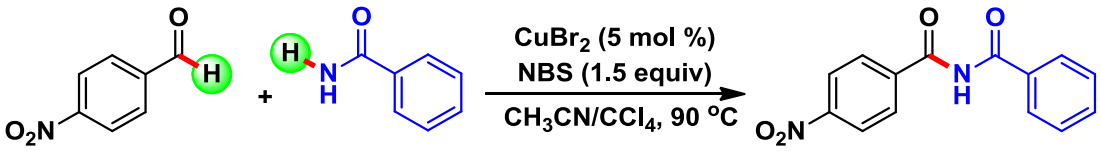
Pan and co-workers developed a Fe-catalyzed oxidative esterification *via* cross-dehydrogenative coupling (CDC) of unactivated C_{sp3}–H bond adjacent to oxygen atom and carboxylic acids using di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme I.5.2.2.2).[56]



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

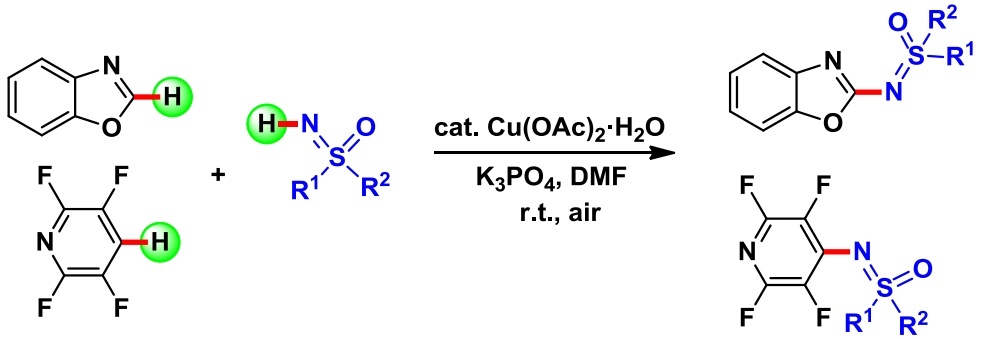
I.5.2.3. Representative Examples of C–N Bond Formation

Fu group introduced a highly efficient protocol for Cu(II)-catalyzed amidation of aldehydes using *N*-bromosuccinamide (NBS) as the oxidant. (Scheme I.5.2.3.1).[57]



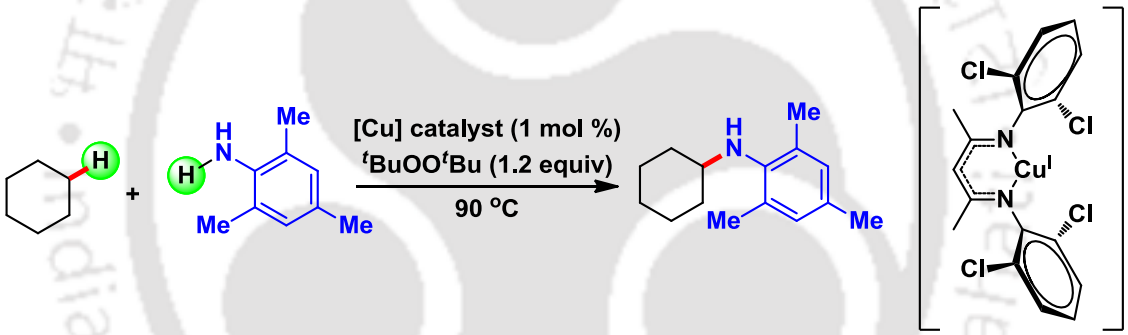
Scheme I.5.2.3.1. *Cu(II)-catalyzed coupling of C_{sp2}–H and amide N_{sp3}–H*

A copper catalyzed sulfoximination of azoles and polyfluoroarenes have been achieved *via* direct dehydrogenative C–N coupling using N–H sulfoximines under ambient conditions (Scheme I.5.2.3.2).[58]



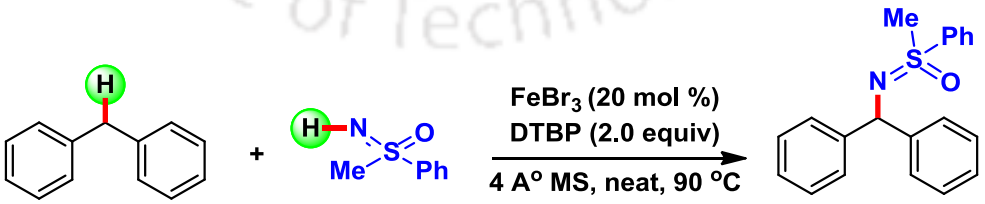
Scheme I.5.2.3.2. *Cu(II)-catalyzed coupling of C_{sp2}–H and imine N_{sp2}–H*

Warren group developed a β-diketiminato copper(I) catalyzed C–H amination of anilines employing low catalyst loadings to prevent oxidation to the diazene ArN=NAr. Electron-poor anilines are particularly resistant towards diazene formation and participate in the amination reaction with strong and unactivated C–H bonds by using low catalyst loadings and mild oxidant ^{t}BuOO^{t}Bu (Scheme I.5.2.3.3).[59]



Scheme I.5.2.3.3. *Copper(I)-catalyzed direct sp^3 C–H amination of alkanes*

A Fe-catalyzed hetero-cross-dehydrogenative coupling reaction of N_{sp2}–H bond of sulfoximines and C_{sp3}–H bond of diarylmethanes has been described by Bolm group. This new route to *N*-alkylated sulfoximines shows good functional group tolerance and provides *N*-alkylated sulfoximines in moderate to good yields (Scheme I.5.2.3.4).[60]

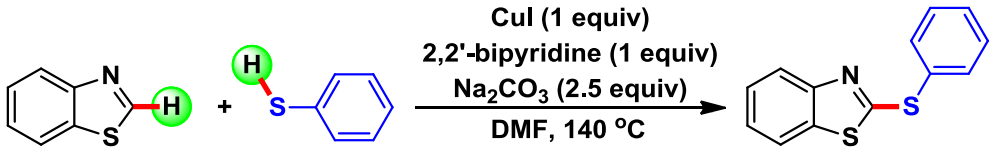


Scheme I.5.2.3.4. *Fe-catalyzed coupling of C_{sp3}–H and imine N_{sp2}–H*

I.5.2.4. Representative Examples of C–S Bond Formation

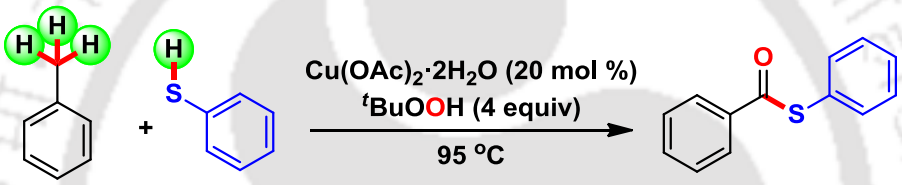
A series of aryl- or alkyl-substituted 2-mercaptobenzothiazoles by direct thiolation of benzothiazoles with aryl or alkyl thiols has been developed by Liu and co-workers *via*

copper-mediated aerobic C_{sp2}–H bond activation in the presence of stoichiometric CuI, 2,2′-bipyridine and Na_2CO_3 (Scheme I.5.2.4.1).[61]



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

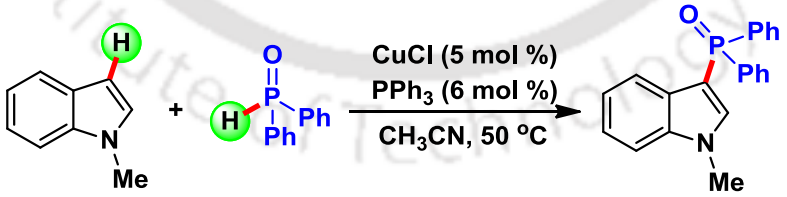
Our group reported a unique copper(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes for the synthesis of thioesters in presence of *tert*-butyl hydroperoxide as the oxidant. A thioester moiety is created *via* successive C–S and C–O bond formation at the expense of three sp^3 C–H bonds of the alkylbenzene and one S–H bond of the thiol (Scheme I.5.2.4.2).[62]



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

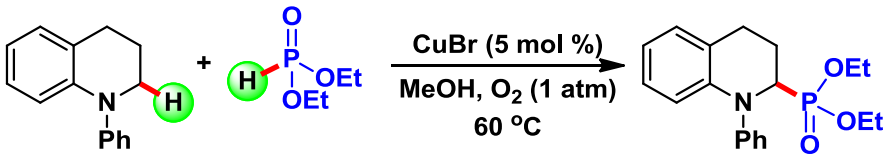
I.5.2.5. Representative Examples of C–P Bond Formation

The first Cu(I)-catalyzed cross-dehydrogenative coupling (CDC) between substituted indoles and disubstituted phosphine oxide has been reported by Yang group. This 3-phosphoindoles synthetic protocol (C_{sp2}–P coupling) completely omits the requirement of oxidant and base, producing hydrogen (H_2) as the only byproduct (Scheme I.5.2.5.1).[63]



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

Li group has demonstrated an efficient cross-dehydrogenative coupling (CDC) between sp^3 C–H adjacent to nitrogen atom and H–P bond of dialkyl phosphonate using copper(I) salt as the catalyst and molecular oxygen as an oxidant. This methodology provides an easy access to biologically important α-aminophosphonates (Scheme I.5.2.5.2).[64]



Scheme I.5.2.5.2. *Cu(I)-catalyzed C_{sp3}–P bond formation via CDC*

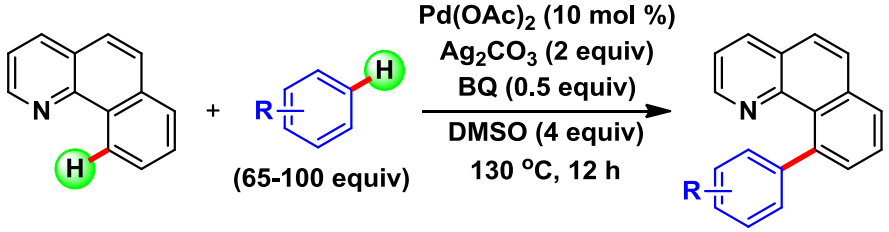
I.5.3. Directing Group Assisted Cross-dehydrogenative Coupling

The directing group assisted and cross-dehydrogenative coupling (CDC) strategies are the two most elegant approach to selectively functionalize *ortho* C–H bonds to form C–C or C–X (X = heteroatom) bonds. The combinations of both installed new functional group(s) at the *o*-site of directing arenes are discussed below.

I.5.3.1. Representative Examples of Directed CDC Reactions

➢ ***Ortho* Arylation**

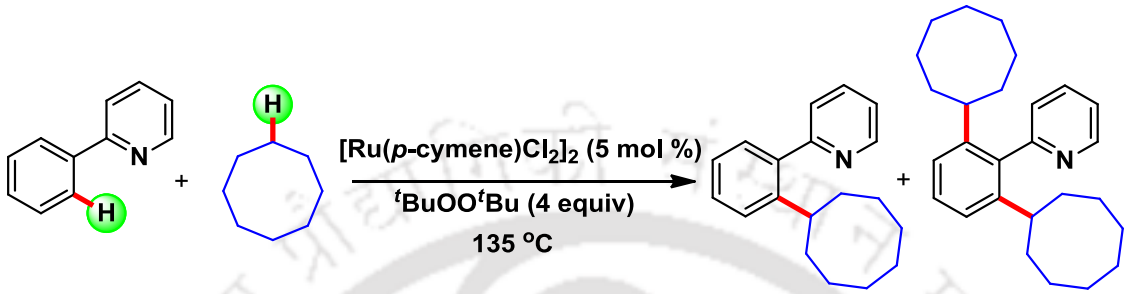
Sanford *et al.* described a Pd-catalyzed reaction for the highly chemo- and regioselective oxidative cross-coupling of aromatic C−H bonds. This transformation is proposed to proceed *via* two discrete C−H activation steps. Selectivities are predominantly controlled by proximity to a ligand (first C−H activation) or by the steric environment around the arene C−H bond (second C−H activation). A variety of directing arenes such as benzo[*h*]quinoline, 2-arylpyridine, 1-arylpyrazole, 2-arylpyrimidine and 8-methylquinoline derivatives were all effective under this reaction condition providing similar cross-coupled products using Ag_2CO_3 and *p*-benzoquinone as terminal oxidants (Scheme I.5.3.1.1).[65] Ligand directed CDC reaction has been applied to directing arenes such as indulines for C-7 arylation and arylguanidines for *o*-arylations.[66]



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

➢ ***Ortho* Alkylation**

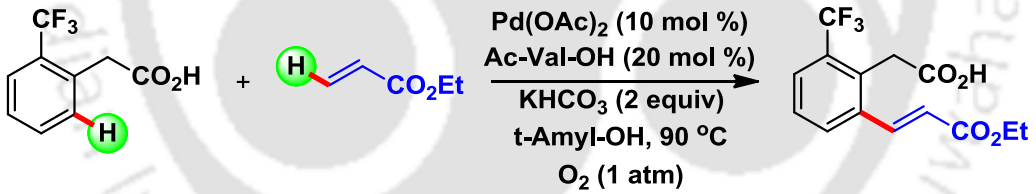
A novel C–C bond formation based on the direct oxidative C_{sp2}–H/C_{sp3}–H coupling involving directing arenes and cycloalkanes has been developed by Li group in the presence of Ru(II)-catalyst and di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme I.5.3.1.2).[67]



Scheme I.5.3.1.2. *Ruthenium(II)-catalyzed ortho cycloalkylation of 2-phenylpyridine*

➢ ***Ortho* Alkenylation *via* C_{sp2}–H/C_{sp2}–H Functionalization**

Yu and co-workers reported a aerobic Pd(II)-catalyzed C–H olefination protocol of phenylacetic acid using an amino acid ligand. In the presence of mono-*N*-protected amino acids ligand the reaction rate is dramatically accelerate, providing *o*-alkenylaion *via* double C–H's activation (Scheme I.5.3.1.3).[68]

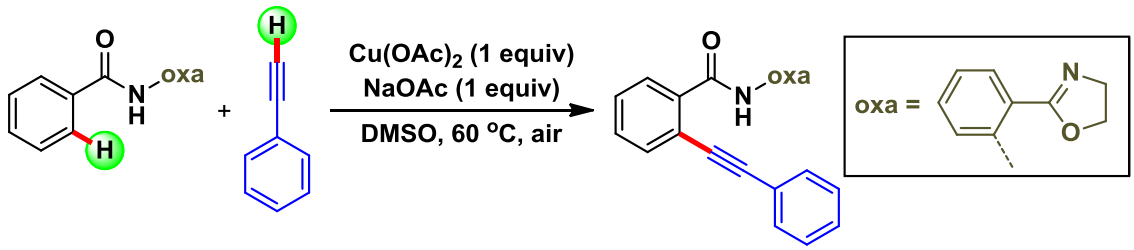


Scheme I.5.3.1.3. *Palladium(II)-catalyzed C–H olefination of phenylacetic acid*

In addition to the sp^2 C–H olefination, Yu group also developed an amide group assisted Pd(II)-catalyzed direct olefination of sp^3 C–H bonds of cyclopropyl methylene.[69a] Recently, they have also demonstrated selective mono γ-C−H olefination for the synthesis of unnatural chiral α-amino acids using a combination of a quinoline-based ligand and a weakly coordinating amide directing group.[69b]

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

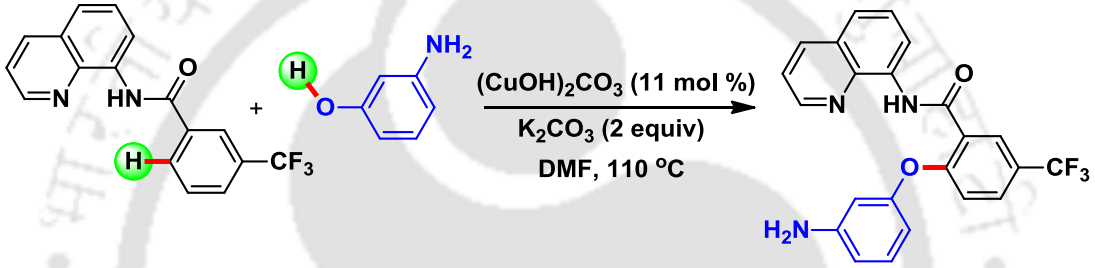
An alternative disconnection to Sonogashira coupling between directing arenes and terminal alkynes has been developed by Yu group to install an alkyne moiety at the *ortho* site of directing arenes using Cu(II) salt (Scheme I.5.3.1.4).[70] A variety of arenes and terminal alkynes bearing different substituents are compatible with this reaction.



Scheme I.5.3.1.4. *Copper(II)-catalyzed auxillary assisted alkynylation of arenes*

➢ ***Ortho* Alkoxylation**

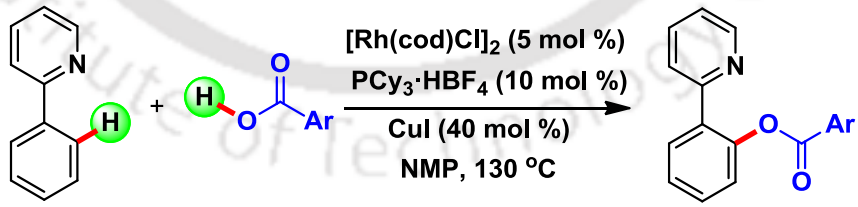
An auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of amine derivatives has been reported by Daugulis *et al*. In the presence of $(CuOH)_2CO_3$ catalyst and air as an oxidant, phenol or alcohol coupled efficiently with directing arenes 8-aminoquinoline (Scheme I.5.3.1.5).[71]



Scheme I.5.3.1.5. *Copper(II)-catalyzed auxillary assisted sp^2 C–H phenoxylation*

➢ ***Ortho* Benzoxylation**

A rhodium-catalyzed *ortho*-benzoxylation of the sp^2 C–H bond by carboxylic acids has been described by Cheng group in the absence of external oxidant. The procedure tolerates carbomethoxy, formyl, bromo, chloro and nitro groups, providing the benzoxylated products in moderate to good yields (Scheme I.5.3.1.6).[72]

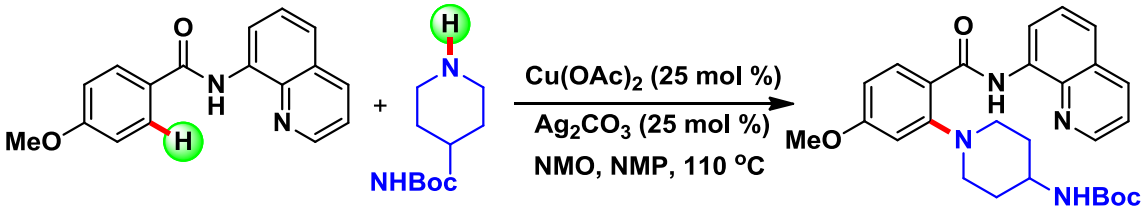


Scheme I.5.3.1.6. *Rhodium-catalyzed benzoxylation of 2-arylpyridines*

➢ ***Ortho* Amination**

A method for direct amination of β-C_{sp2}–H bonds of benzoic acid derivatives and γ-C_{sp2}–H bonds of benzylamine derivatives has been developed by Daugulis and co-workers using aminoquinoline as the directing axillary (Scheme I.5.3.1.7).[73a] In the presence of $Cu(OAc)_2/Ag_2CO_3$ catalytic combinations reaction shows high generality and functional-

group tolerance, as well as providing a straightforward means for the preparation of *ortho*-aminobenzoic acid derivatives.

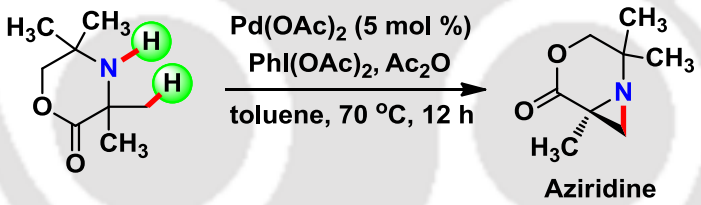


Scheme I.5.3.1.7. *Amination of benzamides with aliphatic amines via CDC*

Recently, Yu group developed a $Cu(OAc)_2$-mediated C–H amidation and amination of arenes and heteroarenes using a readily removable directing group.[73b] A wide range of sulfonamides, amides and anilines function as the amine donors in this reaction.

➢ **Intramolecular Amination**

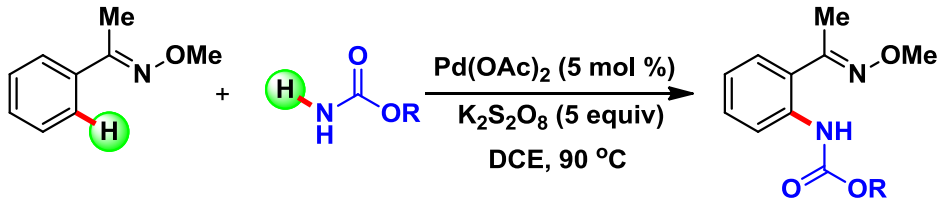
A novel Pd-catalyzed C_{sp3}–H amination that proceeds through an unusual four-membered-ring cyclopalladation pathway has been introduced by Gaunt group (Scheme I.5.3.1.8).[74] This intramolecular cyclization leads to the selective transformation of a methyl group that is adjacent to an unprotected secondary amine into a synthetically versatile nitrogen heterocycle such as aziridines and β-lactams *via* carbonylation processes.



Scheme I.5.3.1.8. *Amine directed Pd(II)-catalyzed intramolecular sp^3 C–H amination*

➢ ***Ortho* Amidation**

An intermolecular amidation of unactivated sp^2 and sp^3 C–H bonds *via* Pd-catalyzed cascade C–H activation protocol has been described by Che group (Scheme I.5.3.1.9).[75] A variety of amides are directly installed at the *ortho* position of oxime ether using $Pd(II)/K_2S_2O_8$ combination.

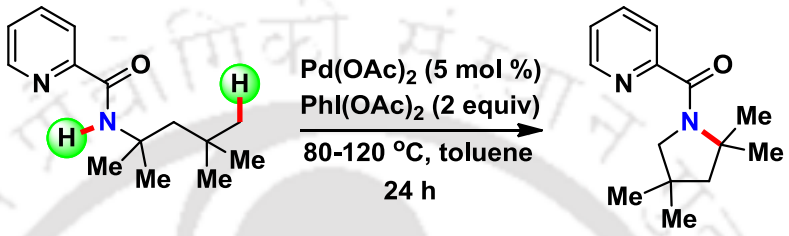


Scheme I.5.3.1.9. *Ketoxime ether directed Pd(II)-catalyzed amidation of arenes*

Later, similar intermolecular amidation strategy was extended to 2-arylpyridines and aromatic ketones using transition metal and suitable oxidant.[76]

➢ **Intramolecular Amidation**

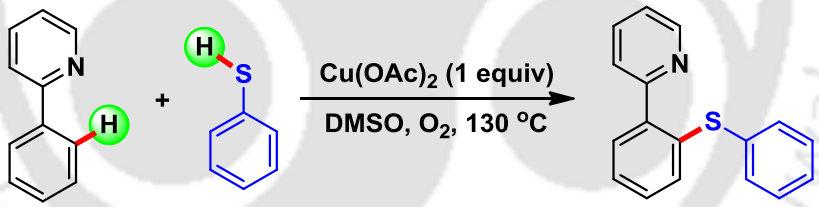
Using picolinamide as directing auxillary, Daugulis group developed a Pd(II)-catalyzed intramolecular amidation at unactivated sp^3 carbons. (Scheme I.5.3.1.10).[77a] Later on a similar auxillary directed intramolecular sp^3 C–H amidation methods has been demonstrated by Chen, Ge and Kanai.[77b-f]



Scheme I.5.3.1.10. *Pd(II)-catalyzed intramolecular sp^3 C–H amidation*

➢ ***Ortho* Sulfenylation**

Yu group has reported a Cu(II)-catalyzed direct thioetherification (sulfenylation) of aryl C_{sp2}–H bonds of 2-arylpyridine using benzene thiol as the coupling partner and O_2 as the stoichiometric oxidant (Scheme I.5.3.1.11).[27b]

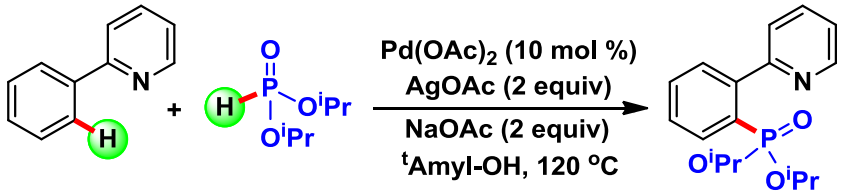


Scheme I.5.3.1.11. *Copper(II)-catalyzed ortho-thiolation of arenes*

Recently, directed sulfenylation of both sp^2 and sp^3 C–H bonds was achieved by Shi group through a nickel catalyzed C–S bond formation.[38d]

➢ ***Ortho* C–H Phosphorylation *via* CDC**

The first Pd(II)-catalyzed *ortho* C–H phosphorylation of 2-arylpyridines has been accomplished by Yu group using both *H*-phosphonates and diaryl phosphine oxides as suitable coupling partners (Scheme I.5.3.1.12).[78a]



Scheme I.5.3.1.12. *Palladium(II)-catalyzed C−H phosphorylation of 2-phenylpyridine*

Later on Murakami group developed a similar *o*-phosphorylation of directing arenes such as 2-phenylpyridines, quinolines, isoquinolines, benzo[*h*]quinolines and pyrimidines using α-Hydroxyalkylphosphonate as the phosphonating reagent.[78b]

I.5.4. An Array of Exceptions: Reactions which are not included in the above three classes are discussed below.

I.5.4.1. Directed C–H Bond Functionalization *via* Redox-Neutral Process

The directing group assisted C–H bond functionalization using external stoichiometric oxidants has been extensively studied. However, the introduction of an internal oxidative functional group to enable the selective activation of C–H bonds has emerged as an alternative to the use of an external oxidant. For example, *N*-haloamine is used in the Hofmann–Löffler–Freytag reaction as an internal oxidant for remote intramolecular free-radical C–H bond activation[79] where as benzophenone and hydroperoxide derivatives have been employed as internal oxidant for the C–H activation through a single-electron-transfer.[80]

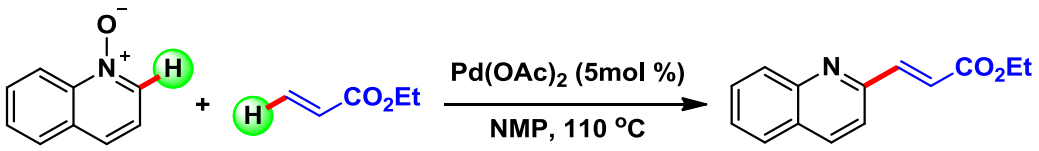
Advantages:

(i) Avoids external oxidants for the catalytic cycle.

(ii) Broad range of functional group tolerance.

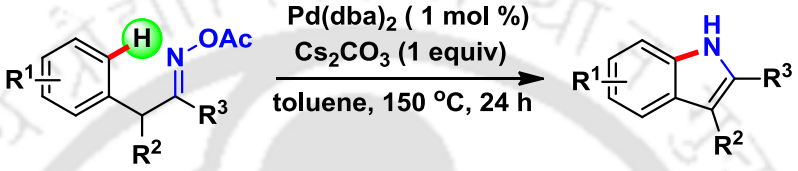
(iii) High regioselectivity.

In 2009, Cui and co-workers introduced oxidizing group directed redox-neutral cross-coupling of quinoline-*N*-oxides with olefin derivatives using palladium acetate as the catalyst (Scheme I.5.4.1.1).[81] The catalytic process proceeds *via* direct C−H bond activation of the quinoline-*N*-oxide and isoquinoline-*N*-oxide with $Pd(OAc)_2$ followed by Heck coupling with an olefin to give 2-alkenylated quinolines and 1-alkenylated isoquinolines in high chemo- and regioselectivity.



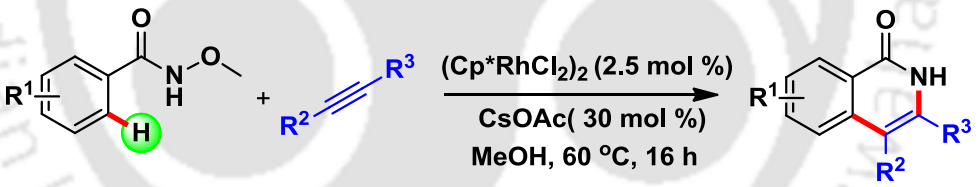
Scheme I.5.4.1.1. *Pd(II)-catalyzed redox-neutral alkenylation*

Further, this redox-neutral strategy was applied to direct amination of aromatic C−H bonds by Hartwig group. In this process, an oxime ester reacts with an aromatic C−H bond under a redox-neutral conditions to give indole derivatives in the presence of relatively low catalyst loading (1 mol %) (Scheme I.5.4.1.2).[82]



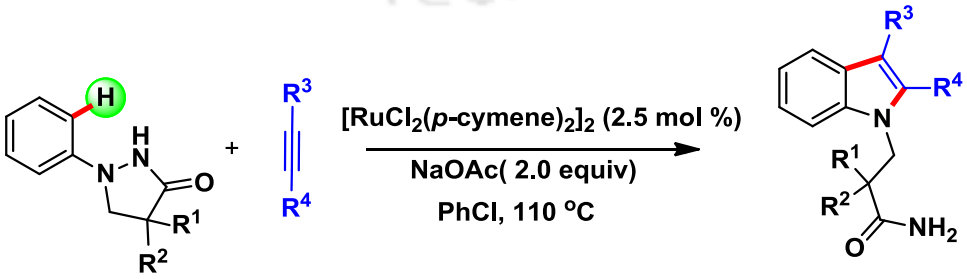
Scheme I.5.4.1.2. *Pd-catalyzed redox-neutral intramolecular ortho sp^2 C–H amination*

Fagnou group introduced a Rh(III)-catalyzed external-oxidant-free process to access the isoquinolone motif *via* cross-coupling/cyclization of benzhydroxamic acid with alkynes. The reaction features a regioselective cleavage of a C−H bond on the benzhydroxamic acid coupling partner as well as a regioselective alkyne insertion (Scheme I.5.4.1.3).[83a-b]



Scheme I.5.4.1.3. *Rh(III)-catalyzed redox neutral intermolecular ortho sp^2 C–H annulaion*

The first Ru-catalyzed redox-neutral C–H activation reaction *via* N–N bond cleavage has been developed by Huang *et al.* In the presence of Ru-catalyst pyrazolidin-3-one triggered the C–H annulation reaction *via* the cleavage of N–N bond. (Scheme I.5.4.1.4).[83c]



Scheme I.5.4.1.4. *Ru(II)-catalyzed redox neutral intermolecular annulaion*

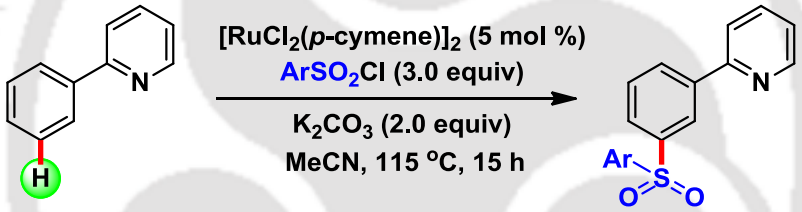
Similar directing group assisted redox-neutral annulation strategies were further extended by Glorius,[84a-b] Rovis,[84c-e] Cramer[84f-g] and others.[84h-o]

I.5.4.2. Directing Group Assisted Site Selectivity Beyond *ortho* Site

Close proximity of metal and C–H bond is a well established protocol for the *ortho*-functionalization. However, for *meta* and *para* functionalization require larger metallacycles, which are quite difficult. Traditionally, *meta*- C–H functionalization can be achieved either *via* steric[85] or ligand[86] control. Gaunt and co-workers have developed few *meta* and *para*-C–H functionalizations in the presence or absence of copper catalyst.[87] Later, following the above strategy several *meta* or *para* functionalizations have been successfully implemented by others as discussed below.

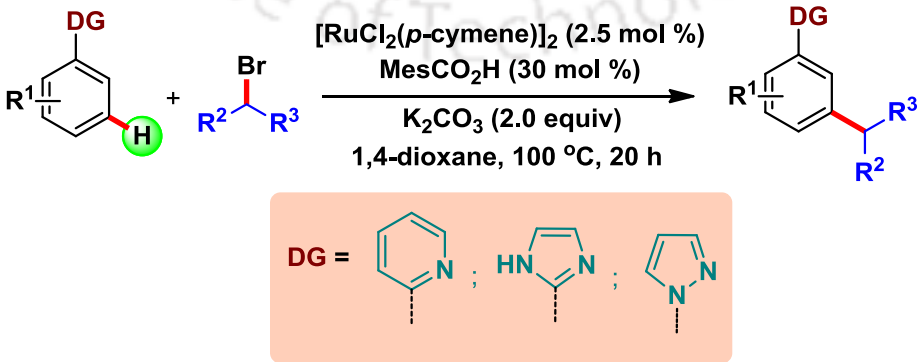
- ***Meta*-C–H Bond Functionalization Controlled by Electronic Effects**

Recently, Frost and co-workers reported a *meta*-sulfonation of 2-phenylpyridines in the presence of a ruthenium catalyst *via* catalytic σ-activation process (Scheme I.5.4.2.1).[88]



Scheme I.5.4.2.1. *Ru(II)-catalyzed meta-selective sp^2 C–H sulfonation*

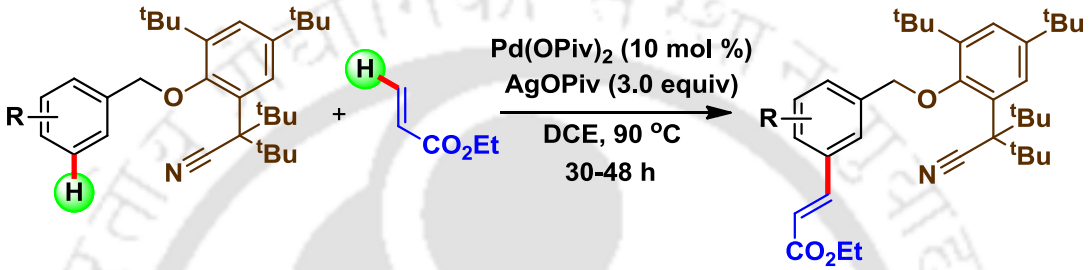
Similarly a Ru-catalyzed *meta*-selective C–H alkylation of *N*-heterocycle-containing arenes with secondary alkyl bromides has been developed by Ackermann group. The reaction proceeds *via* an initial reversible cycloruthenation which increases the reactivity of arenes for electrophilic substitutions *para* to carbon–ruthenum (C–Ru) bond (Scheme I.5.4.2.2).[89]



Scheme I.5.4.2.2. *Ru(II)-catalyzed meta-selective alkylation*

➢ **Template Assisted *meta*-Selective C–H Functionalization**

Functionalizations of a single C–H bond selectively among multiple inequivalent C–H bonds have been carried out successfully. In this unusual approach *σ*-chelating directing groups leads to *ortho*-selectivity through the formation of a five- or a six-membered cyclic pre-transition state. Despite the broad utility of this approach, prevents the activation of remote C–H bonds. Taking advantages of directing group a class of easily removable nitrile-containing templates that direct the activation of distal *meta*-C–H bonds of a tethered arene has been reported by Yu group (Scheme I.5.4.2.3).[90]



Scheme I.5.4.2.3. *Pd(II) catalyzed meta-selective olefination of toluene derivatives*

Remote C–H functionalization strategy based on removable directing template was further applied for *meta*-selective arylation, acetoxylation and olefination.[91] Various *meta* selective directing templates are shown in Figure I.5.4.2.1.

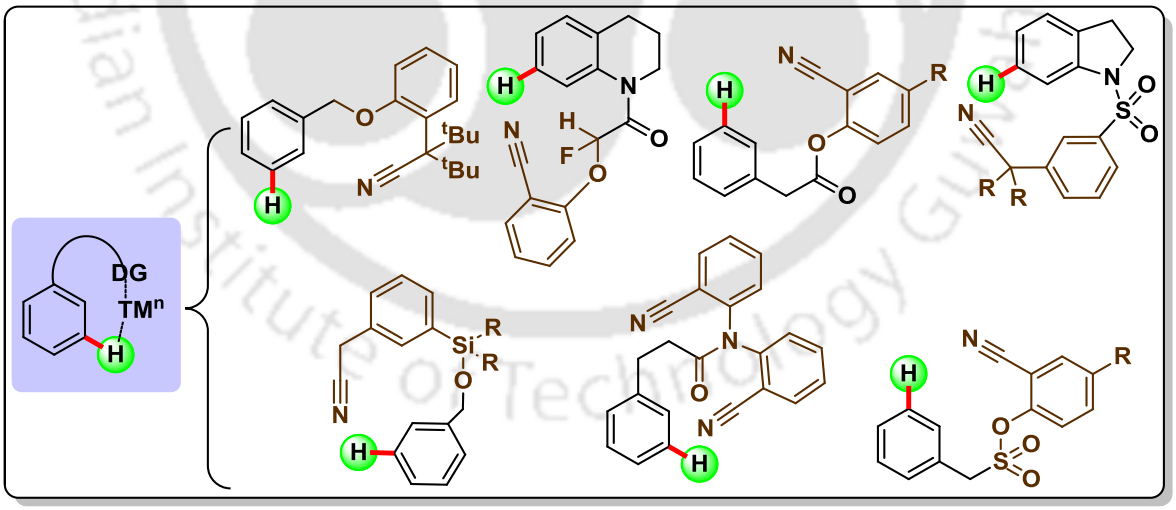
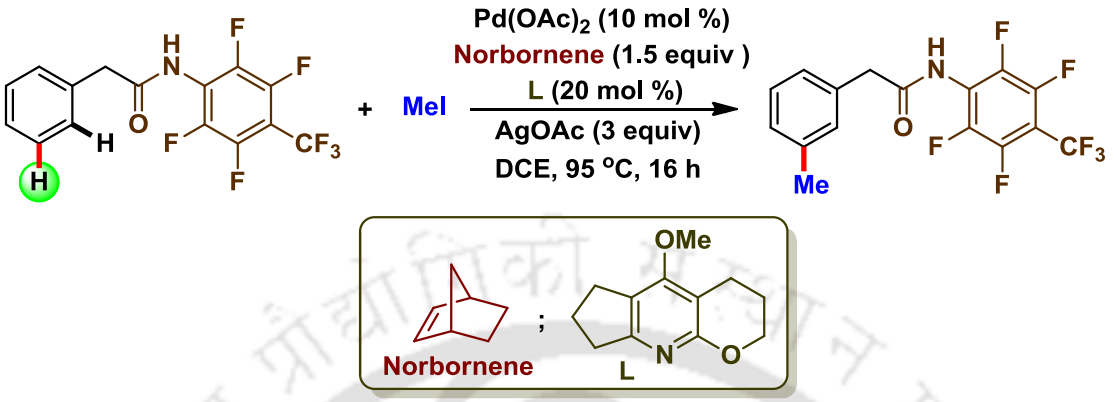


Fig. I.5.4.2.1. *Overview of nitrile based removable meta-directing templates*

➢ ***Meta*-C–H Bond Functionalization Using Norbornene as a Transient Mediator**

Using *ortho* directing moiety an alternative ligand enabled Pd(II)-catalyzed *meta*-selective C–H activation employing norbornene as a transient mediator has been achieved by Yu and co-workers (Scheme I.5.4.2.4).[92a] The reaction occurred *via* a Catellani pathway

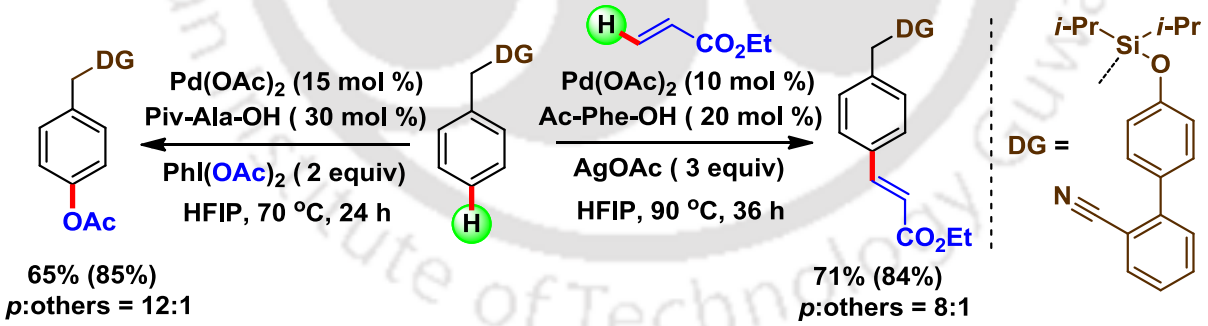
where norbornene delivers the metal to the *meta* position after initial *ortho*-C–H activation. Recently, Dong group introduced a highly meta-selective C–H arylation using simple tertiary amines as the directing group and "acetate cocktail".[92c]



Scheme I.5.4.2.4. *meta-C–H alkylation of phenylacetic amides using norbornene*

➢ ***Para*-C–H Bond Functionalization Controlled by Directing Template**

Very recently Maiti group developed an easily recyclable, novel Si-containing biphenyl-based template for distal *p*-C–H bond functionalization of toluene derivatives (Scheme I.5.4.2.5).[93] This directing group allows the required flexibility to support the formation of an oversized pre-transition state. In the presence of Pd(II)-catalyst and amino acid ligand *para*-olefination and acetoxylation were successfully performed over *ortho* and *meta*.



Scheme I.5.4.2.5. *Pd(II)-catalyzed para-selective functionalization of toluene derrivatives*

I.6. Asymmetric C–H Activation

Asymmetric C–H functionalization reaction is one of the most active and fascinating areas of research in organic chemistry.[94] Introduction of new chiral centre during the C–H functionalization is one of the most challenging issues in organic synthesis and requires precise reaction design. As such, this field is now receiving increasing attention from

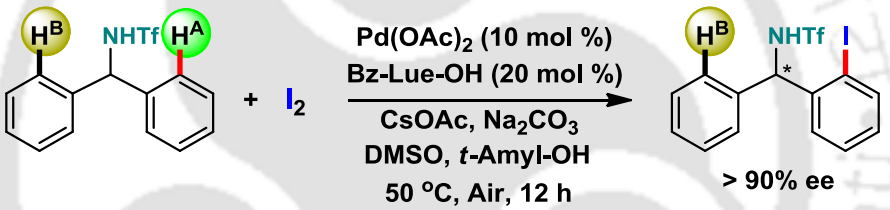
researchers. Two distinct strategies can be visualized to achieve stereoselective C–H activation.

(i) Chiral discrimination during the C–H activation.

(ii) Chirality induction subsequent to the C–H activation and a stereo-controlled functionalization of the metallacycle.

I.6.1. Intermolecular Stereoselective C–H Activation

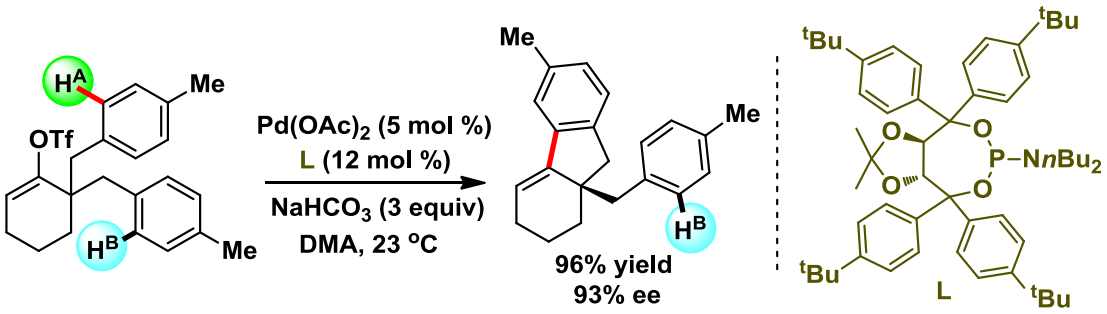
In 2008, Yu group developed substrate directed Pd(II)-catalyzed enantioselective sp^2 C−H alkylation using alkylboronic acid and *N*-protected amino acids ligand.[95] Later, an enantioselective C−H iodination reaction using a mono-*N*-benzoyl-protected amino acid has been achieved for the synthesis of chiral diarylmethylamines by the same group (Scheme I.6.1.1).[96] The reaction proceeds at ambient temperature and under air using iodine as the sole oxidant. The bidentate amino acid ligand coordinates with the Pd-catalyst and efficiently controls the chiral environment.[97]



Scheme I.6.1.1. *Enantioselective substrate directed iodination*

I.6.2. Intramolecular Stereoselective C–H Activation

In 2009, Cramer and co-workers developed a Pd-catalyzed enantiselective intramolecular C–C bond formation. The reaction was carried out in the presence of low valent Pd(0) catalyst ligated by a designed taddol-based phosphoramidite to access indanes with a quaternary stereogenic center in excellent enantioselectivities (Scheme I.6.2.1).[98] The Pd(0) catalyst first undergoes an oxidative addition to a vinyl triflate moiety followed by the C–H activation of one of the enantiotopic C_{sp2}–H bonds of both aryl substituents.



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

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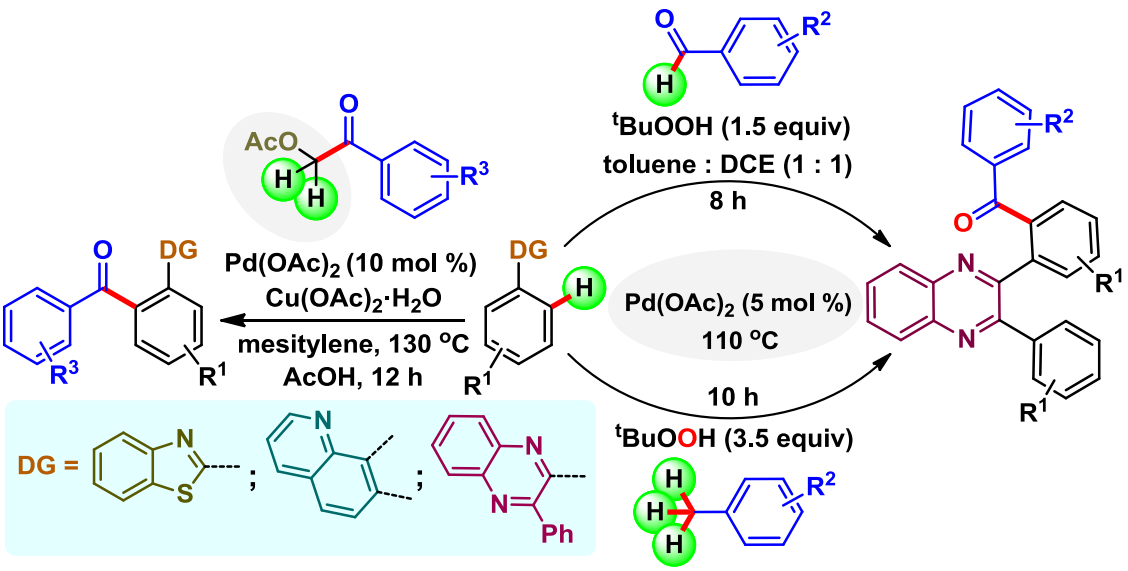
Chapter II

Palladium(II) Catalyzed ortho-Aroylation of Directing Arenes



Abstract: *Palladium(II) catalyzed ortho-aroylation of directing arenes has been developed via cross-dehydrogenative coupling (CDC) in the presence of TBHP or $Cu(OAc)_2{\cdot}H_2O$ oxidant. In case of 2-acetoxyacetophenone o-aroylation proceeds via decarbonylation of the in situ generated phenylglyoxal, while for aromatic aldehydes and alkylbenzenes o-aroylation follows either an aroyl radical or a benzyl radical path.*

CHAPTER II

This chapter is divided into two sections. Section-A describes mono *o*-aroylation of 2,3-diarylquinoxalines using aldehydes and alkylbenzenes as aroyl surrogates whereas section-B demonstrates peroxide free *o*-aroylation of 2-arylbenzothiazoles using 2-acetoxyacetophenone as the aroyl source.

IIA. 2,3-Diarylquinoxaline Directed Mono *ortho*-Aroylation *via* Cross Dehydrogenative Coupling Using Aromatic Aldehydes or Alkylbenzenes as Aroyl Surrogate

IIA.1. Introduction

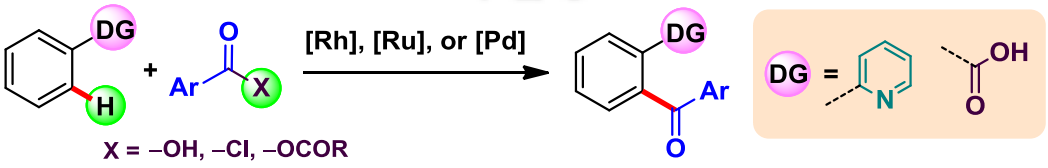
Functionalizations of ubiquitous C–H bonds build complex molecular framework through the construction of C–C and C–X (X = heteroatoms) bonds.[1] The two most elegant approaches applied for this purpose are the directing group assisted C–H functionalization[2] and the cross-dehydrogenative coupling (CDC).[3] In the later approach both the coupling partners are attached through their C–H bonds, whereas in the former only *ortho* C–H bonds are functionalized *via* the chelation of metals through heteroatoms such as nitrogen and oxygen. These two techniques make the protocol highly appreciable due to the requirement of minimal steps and atom economy point of view. However among these transformations, C–C bond formation especially installation of carbonyl functional groups into the phenyl system *via* C–H bond cleavage is attractive in organic chemistry. Combination of directing group assisted C–H functionalization and the cross-dehydrogenative coupling (CDC) directly installs aroyl functionality at the *ortho* site of a directing arenes and hence minimized steps and cost. Substrates having different directing groups have been successfully *ortho*-aroylated using diverse aroyl surrogates *viz.* aldehyde, alkene, alkyne, benzil, α-ketoacid, benzyl alcohol, benzylamine and alkylbenzene.[4]

IIA.2. Strategies for *ortho*-Aroylation

The most classical approach for ketone synthesis is the Friedel-Craft acylation reaction.[5] However, the use of stoichiometric amount of reagents and poor regioselectivity, this classical approach has been lately replaced by transition metal catalyzed cross-couplings.[6] Use of carboxylic acid derivatives, such as nitriles, anhydrides, Weinreb amides or acid chlorides with alkali metals *viz.* lithium, magnesium or aluminum reagents lead to the formation of corresponding ketones.[7] However, these processes involve harsh reaction conditions resulting in low compatibility towards various sensitive functional groups. To avoid the substrate pre-functionalization recently cross-coupling reactions involving C–H bond functionalizations have come into reclaim as a direct and promising approach to access ketones. The modern methods employed for *ortho*-aroylation *via* the cleavage of single or multiple C–H bond(s) can be classified into four types, *viz.* (i) *ortho* 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-keto acids. Some of the recent advances on each of these categories are summarized below.

(i) *o*-Friedel-Crafts Acylation Using Carboxylic Acids or its Derivatives

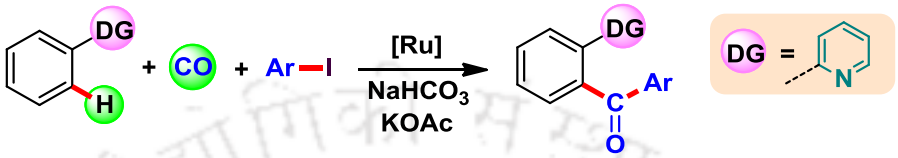
o-Acylations of directing arenes using carboxylic acids or its derivatives are fewer in number. Kakiuchi and co-workers reported a Ru-catalyzed *ortho* selective acylation of arylpyridines using acyl chlorides *via* the C–H bond activation under oxidant free conditions.[8a] Fu *et al.* achieved Pd-catalyzed *ortho*-acylation of same directing arene using readily available carboxylic acids as the aroyl source.[8b] Recently, Gooβen group has demonstrated a Rh-catalyzed method for the *ortho*-acylation of benzoic acid with carboxylic anhydrides (Scheme IIA.2.1).[8c]



Scheme IIA.2.1. *o-Aroylation using carboxylic acids or its derivatives*

(ii) The Carbonylative Processes

Beller group reported a Ru-catalyzed carbonylative *ortho*-acylation of 2-phenylpyridine with aryl halides *via* direct C–H bond activation (Scheme IIA.2.2).[9a] Lei *et al.* developed a Pd-catalyzed double C–H oxidative carbonylation of diphenyl ethers to obtain xanthones.[9b]



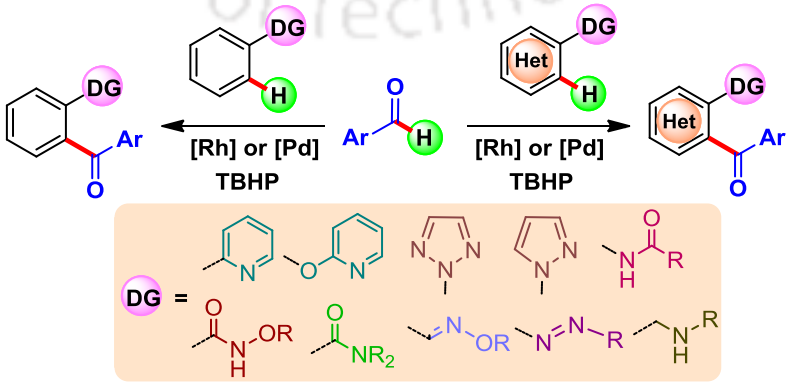
Scheme IIA.2.2. *Directed o-aroylation via carbonyl insertion*

(iii) Cross-dehydrogenative Coupling Approach with Various Aroyl Surrogates

The most elegant approach for *ortho*-aroylation of directing arenes is the CDC reaction. Some of the recent CDC protocols on *ortho*-aroylation of directing substrates possessing hetero-donor atoms along with various ArCO– surrogates are enlisted below.

(a) Aldehyde as the ArCO– Source

Various directing arenes containing *N* and *O* donor atoms have been employed for the *o*-aroylation using aromatic aldehyde as the aroyl surrogate. Cheng *et al.* reported a Pd(II)-catalyzed *ortho*-aroylation of 2-arylpyridines, for the installation of carbonyl functional groups from aromatic aldehydes into the phenyl ring *via* direct sp^2 C–H bond activation.[10a] Later Li group demonstrated a similar CDC coupling of 2-arylpyridines with aldehydes in the presence of Pd-catalyst and TBHP.[10b] Several *ortho*-chelating groups such as ketoxime ether, anilide, benzamide, triazole and even azobenzene have also been applied toward similar *ortho*-aroylation using aldehydes as the ArCO– source (Scheme IIA.2.3).[4]

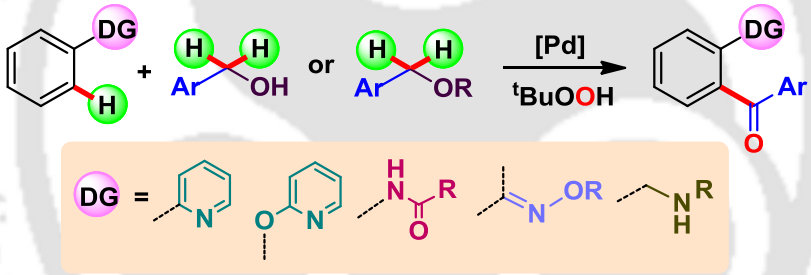


Scheme IIA.2.3. *o-Aroylation using aldehydes as ArCO– source*

Along with aromatic arenes, heretoarenes have also been employed for *ortho*-aroylation using aldehydes as the aroylating source. Li group has developed a Rh-catalyzed oxidative C-2 acylation of indoles with aryl and alkyl aldehydes,[10c] whereas a Pd-catalyzed C-3 acylation of benzofurans and benzothiophenes is reported by Pan group.[10d]

(b) Benzyl Alcohol or Ethers as the ArCO– Source

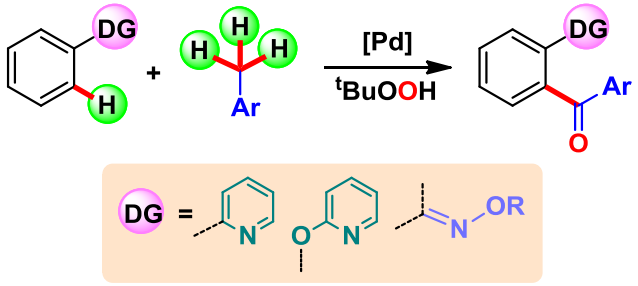
Aldehydes can be generated *in situ via* the oxidation of primary alcohols, thus primary alcohols can be used in various *ortho*-acylation protocols as a synthetic equivalent of aldehydes. Using primary alcohols various group have reported *o*-acylation of directing arenes in the presence of Pd-catalyst and suitable oxidant.[11] Kim and co-workers have developed a *o*-aroylation strategy using benzyl ethers as the aroyl surrogate.[12] They showed that benzyl ethers also served as the aroyl surrogate to afford ketones *via* C–O bond cleavage of ethers eventually leading to the formation of C–C bond (Scheme IIA.2.4).



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

(c) Alkylbenzenes as the ArCO– Source

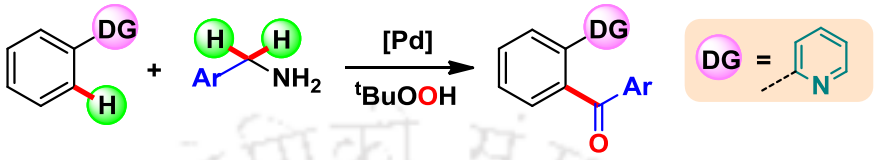
Our group has demonstrated that inert alkylbenzene to be the synthetic equivalent of an aroyl moiety. A Pd(II)-catalyzed *ortho*-aroylation protocol *via* cross-dehydrogenative coupling of directing arenes and alkylbenzenes has been developed in the presence of TBHP (Scheme IIA.2.5).[13]



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

(d) Benzylamine as ArCO– Source

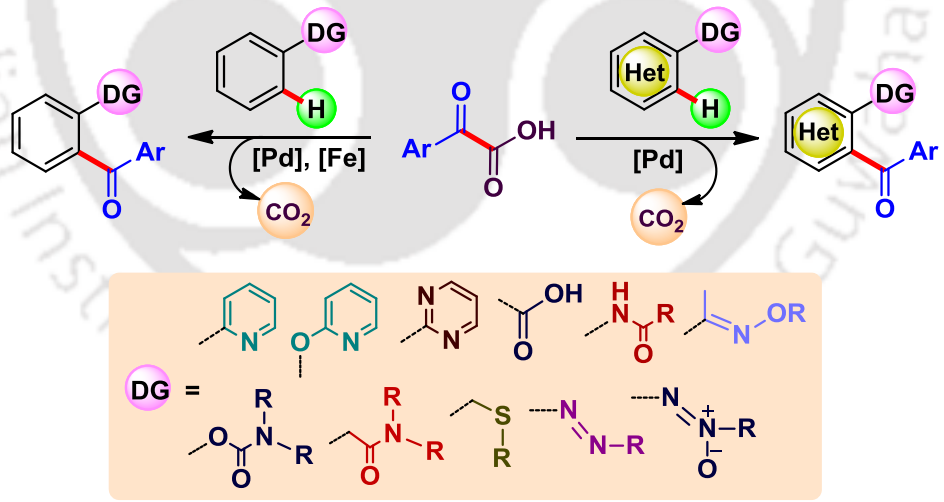
Like primary benzyl alcohol, benzyl amine also served as an aroyl unit in Pd-catalyzed *ortho*-aroylation. Wu group has recently developed an efficient coupling protocol for *ortho*-aroylation of 2-aryl pyridines with benzylamines in the presence of TBHP (Scheme IIA.2.6).[14]



Scheme IIA.2.6. *o-Aroylation using benzylamine as ArCO– source*

(iv) Decarboxylative Couplings of α-Oxoacids

Besides these strategies for *o*-aroylations, a number of substrate directed decarboxylation of α-keto carboxylic acids strategies has also been achieved. Ge and co-workers have developed a Pd-catalyzed protocol to the direct access of *o*-aroyl acetanilides *via* decarboxylative coupling of α-oxoacids with acetanilides.[15a] Later the same group has also achieved a similar *ortho*-acylation of 2-arylpyridines[15b] and carboxylic acids (Scheme IIA.2.7).[15c]



Scheme IIA.2.7. *o-Aroylation via decarboxylative coupling*

Ongoing progress of the decarboxylative coupling of α-ketoacids for *o*-aroylation, α-keto acids have also been implemented on other directing arenes such as 2-aryloxypyridines, ketoxime ether, cyclic enamides, carbamates, acetamide, azobenzene, azoxybenzene and even thioether.[15]

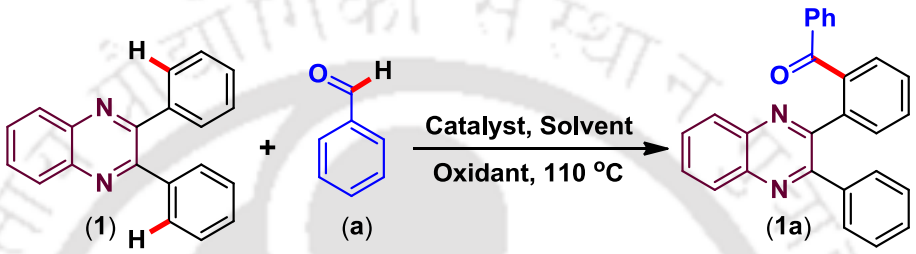
IIA.3. Present Work

Quinoxaline is an important pharmacophoric unit possessing diverse biologically activities and are potentially useful in materials science.[16] Thus, any derivatization of 2,3-diarylquinoxaline is expected to generate further interests. There are three instances of *ortho*-functionalization of 2,3-diarylquinoxaline moiety *viz.* acetoxylation,[17a] fluorination[17b] and nitration.[17c] Till to date there is no precedent for *ortho*-aroylation of this important scaffold using any of the aroyl surrogates *via* the CDC approach.

Optimization of Reaction Conditions. In light of the above mentioned *ortho*-aroylation processes, an initial trial was attempted with the model substrate 2,3-diphenylquinoxaline (**1**) through a chelation assisted CDC approach. 2,3-Diphenylquinoxaline (**1**) (1 equiv) was treated with benzaldehyde (1.2 equiv) in the presence of $Pd(OAc)_2$ (2 mol %) and *tert*-butyl hydroperoxide (TBHP in decane) (1 equiv) in 1,2-dichloroethane (DCE) (2 mL) at 110 ^oC, which yielded the product (**1a**) in an isolated yield of 35% (Table IIA.3.1, entry 1). The formation of mono *ortho*-aroylation of 2,3-diphenylquinoxaline was confirmed by spectroscopic data analysis. To improve the yield of the product, other reaction parameters such as solvent, catalyst, oxidants and their quantities were varied. The use of polar aprotic solvents such as DMF or DMSO failed to give any traces of product (Table IIA.3.1, entries 2 and 3). Solvent toluene was found to be better compared to cyclohexane, *o*-xylene and dioxane tested (Table IIA.3.1, entries 4–7). A careful scrutiny of the literature revealed that toluene to be the most appropriate solvent towards Pd-catalyzed *ortho*-aroylation[4] while for *ortho*-C–H functionalization of 2,3-diphenylquinoxaline DCE to be the most effective solvent.[17] Therefore we contemplate that the use of mixed solvents might improve the product yield. Interestingly, the use of mixture of toluene and DCE (in 1:1 ratio) gave an improved yield of 58% (Table IIA.3.1, entry 8). The yield improved up to 67% when the catalyst loading was increased to 5 mol % (Table IIA.3.1, entry 9). However, no significant improvement in the yield (72%) was observed even when the catalyst loading was increased to 10 mol % (Table IIA.3.1, entry 10). Other palladium catalysts such as $PdCl_2$ and $PdBr_2$ in lieu of $Pd(OAc)_2$ were found to give inferior yields (Table IIA.3.1, entries 11 and 12). The catalyst $Pd(TFA)_2$ was good but slightly less effective compared to $Pd(OAc)_2$ (Table IIA.3.1, entry 13). Changing the oxidant from TBHP to benzoyl peroxide and $K_2S_2O_8$ gave no desired *ortho*-aroylated product (Table

IIA.3.1, entries 14 and 15) suggesting the superiority of TBHP as the oxidant. Interestingly, increasing the oxidant (TBHP) quantity from 1 to 1.2 equivalents and further to 1.5 equivalents improved the yield to 70% and 76% respectively (Table IIA.3.1, entries 16 and 17). Thus, after a series of experimentations catalyst $Pd(OAc)_2$ (5 mol %), oxidant TBHP (1.5 equiv) and aroyl source aldehyde (1.2 equiv) in an equivolume mixture of toluene and 1,2 dichloroethane (2 mL) was found to be the best condition and was subsequently implemented for further reactions.

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



entry	catalyst (mol %)	solvent	oxidant	yield (%)[b]
1	$Pd(OAc)_2$ (2.0)	DCE	TBHP	35
2	$Pd(OAc)_2$ (2.0)	DMF	TBHP	0
3	$Pd(OAc)_2$ (2.0)	DMSO	TBHP	0
4	$Pd(OAc)_2$ (2.0)	cyclohexane	TBHP	32
5	$Pd(OAc)_2$ (2.0)	*o*-xylene	TBHP	41
6	$Pd(OAc)_2$ (2.0)	dioxane	TBHP	42
7	$Pd(OAc)_2$ (2.0)	toluene	TBHP	50
8	$Pd(OAc)_2$ (2.0)	toluene:DCE	TBHP	58[c]
9	$Pd(OAc)_2$ (5.0)	toluene:DCE	TBHP	67[c]
10	$Pd(OAc)_2$ (10.0)	toluene:DCE	TBHP	72[c]
11	$PdBr_2$ (5.0)	toluene:DCE	TBHP	10[c]
12	$PdCl_2$ (5.0)	toluene:DCE	TBHP	7[c]
13	$Pd(TFA)_2$ (5.0)	toluene:DCE	TBHP	46[c]
14	$Pd(OAc)_2$ (5.0)	toluene:DCE	$(PhCO_2)_2$	0[c]
15	$Pd(OAc)_2$ (5.0)	toluene:DCE	$K_2S_2O_8$	0[c]
16	$Pd(OAc)_2$ (5.0)	toluene:DCE	TBHP	70[c,d]
17	**$Pd(OAc)_2$ (5.0)**	**toluene:DCE**	**TBHP**	**76[c,e]**

[a]Reaction conditions: 2,3-Diphenylquinoxaline (**1**) (0.5 mmol), benzaldehyde (**a**) (0.6 mmol), TBHP was added in four equal lots at 1.5 h interval, 110 °C. [b]Isolated yield after 8 h. [c]1:1 ratio of toluene and DCE. [d]1.2 equivalents of TBHP. [e]1.5 equivalents of TBHP.

Substrate Scope for *o*-Aroylation. Using the above optimized condition this methodology was further applied to 2,3-diphenylquinoxaline (**1**) with a variety of aromatic aldehydes. Both activated and deactivated aromatic aldehydes coupled

efficiently with 2,3-diphenylquinoxaline (**1**) giving the desired *ortho*-aroylated products in good to moderate yields. Aldehydes containing moderately electron-donating groups such as *p*–Me (**b**), *p*–^{t}Bu (**c**) and *p*–Ph (**d**) afforded aroylated products (**1b**, 72%), (**1c**, 70%) and (**1d**, 73%), respectively in good yields (Scheme IIA.3.1). The transformation was equally successful for aromatic aldehydes possessing electron-donating substituents such as *p*–OMe (**e**), *p*–OBu (**f**) and 3,4-di–OMe (**g**) giving their products (**1e**, 68%), (**1f**, 66%) and (**1g**, 63%), respectively in moderate yields. The structure of mono-*ortho*-aroylated product (**1e**) was further confirmed by X-ray crystallographic analysis as shown in Fig. IIA.3.1.

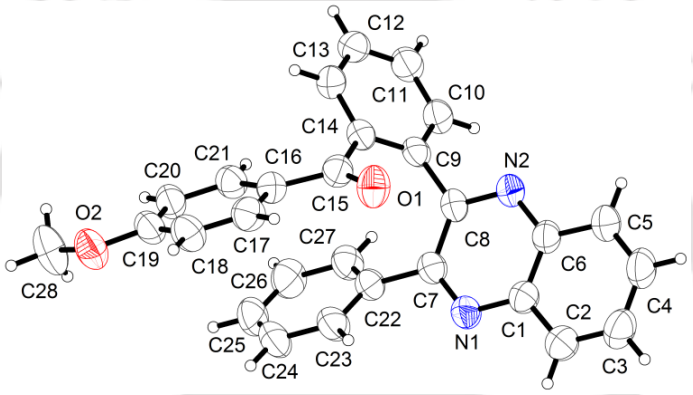
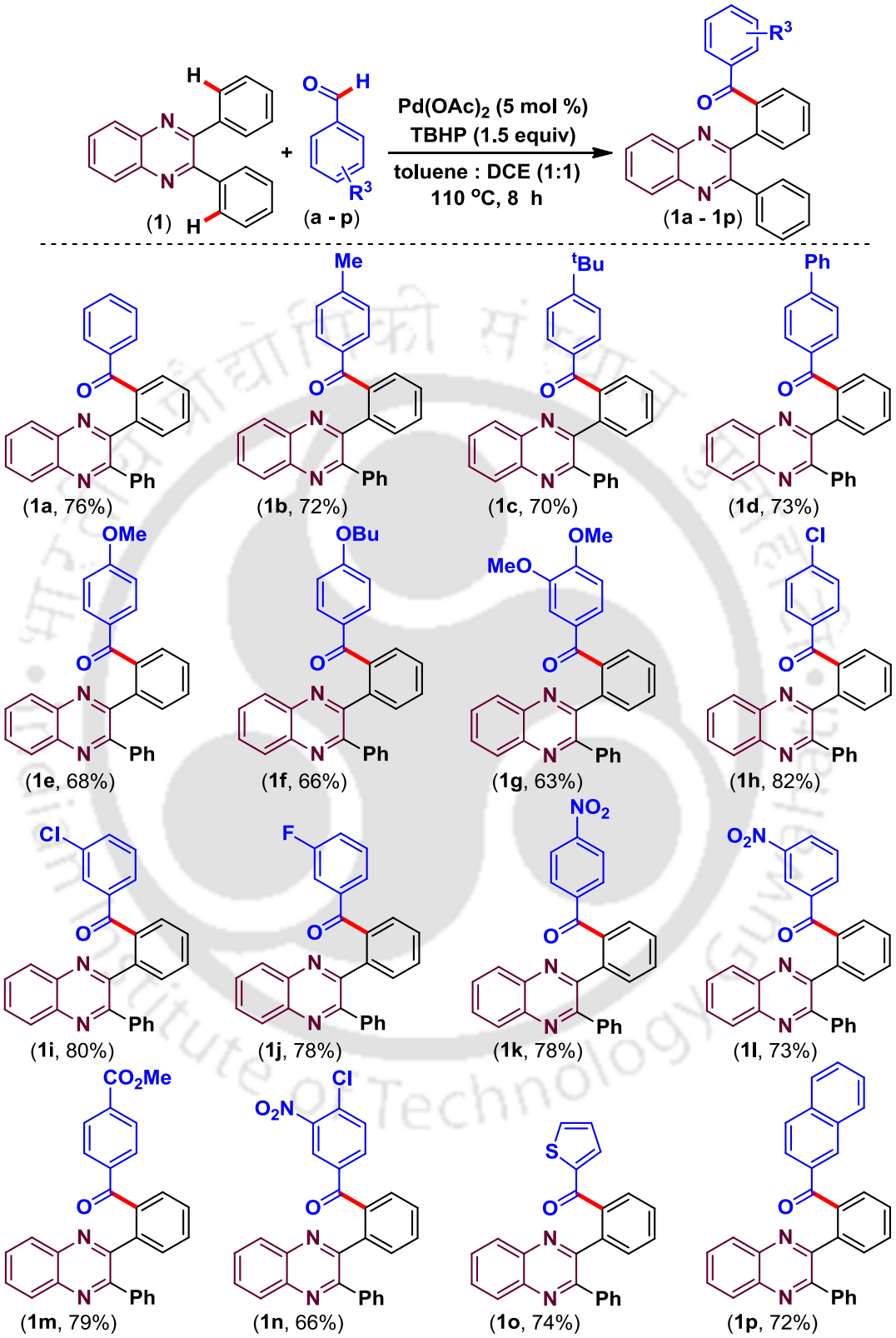


Fig. IIA.3.1. *ORTEP molecular diagram of (**1e**)*

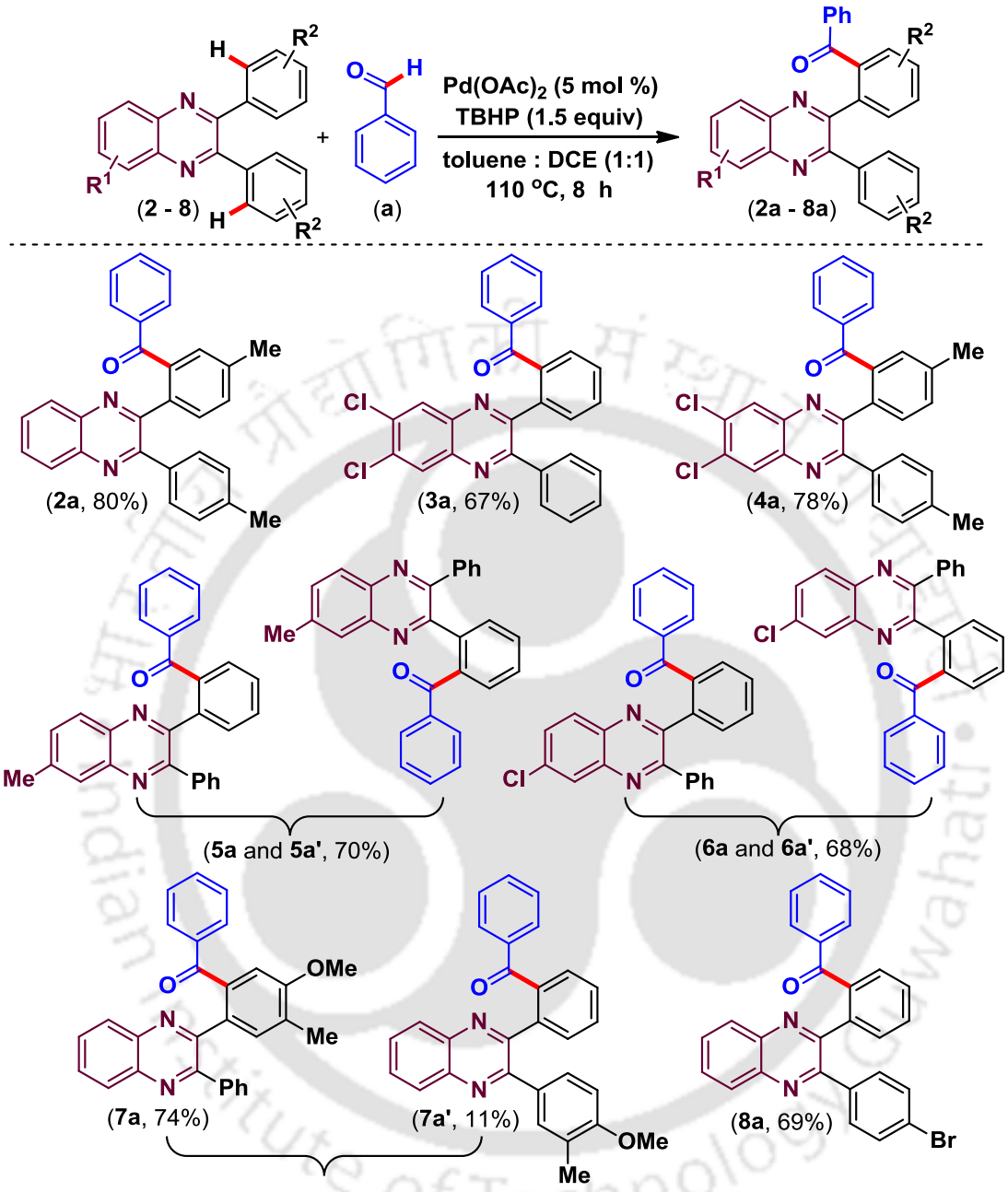
Aromatic aldehydes possessing weekly electron-withdrawing groups, such as *p*–Cl (**h**), *m*–Cl (**i**) and *m*–F (**j**) also underwent efficient conversion giving corresponding *ortho*-aroylated products (**1h**, 82%), (**1i**, 80%) and (**1j**, 78%), respectively in good yields (Scheme IIA.3.1). Aldehydes possessing strongly electron-withdrawing groups such as *p*–NO_2 (**k**), *m*–NO_2 (**l**) and *p*–CO_2Me (**m**) served as good aroyl sources and provided the desired *ortho*-aroylated products (**1k**, 78%), (**1l**, 73%) and (**1m**, 79%), respectively in good yields. Aromatic aldehydes possessing two electron-withdrawing groups as in 4–Cl-3–NO_2 benzaldehyde (**n**) gave slightly lower yield of product (**1n**, 66%) when employed as an aroyl surrogate. Heteroaromatic aldehyde (**o**) and fused aromatic aldehyde (**p**) also afforded good yields of their respective *ortho*-aroylated products (**1o**, 74%) and (**1p**, 72%) when reacted with 2,3-diphenylquinoxaline (**1**) under the optimized condition (Scheme IIA.3.1).

Scheme IIA.3.1. *Scope of aldehydes in o-aroylation of 2,3-diphenylquinoxaline*[a,b]



[a]Reaction conditions: 2,3-Diphenylquinoxaline (**1**) (0.5 mmol), aldehydes (**a**–**p**) (0.6 mmol), $Pd(OAc)_2$ (0.025 mmol), TBHP (0.75 mmol) in toluene and DCE mixture (1:1) (total 2 mL) at 110 °C for 8 h. [b]Isolated yield.

Scheme IIA.3.2. *Scope of 2,3-diarylquinoxalines in Pd-catalyzed o-aroylation*[a,b]



[a]Reaction conditions: 2,3-Diarylquinoxaline (**2**–**8**) (0.5 mmol), benzaldehyde (**a**) (0.6 mmol), $Pd(OAc)_2$ (0.025 mmol), TBHP (0.75 mmol) in toluene and DCE mixture (1:1) (total 2 mL) at 110 °C for 8 h. [b]Isolated yield.

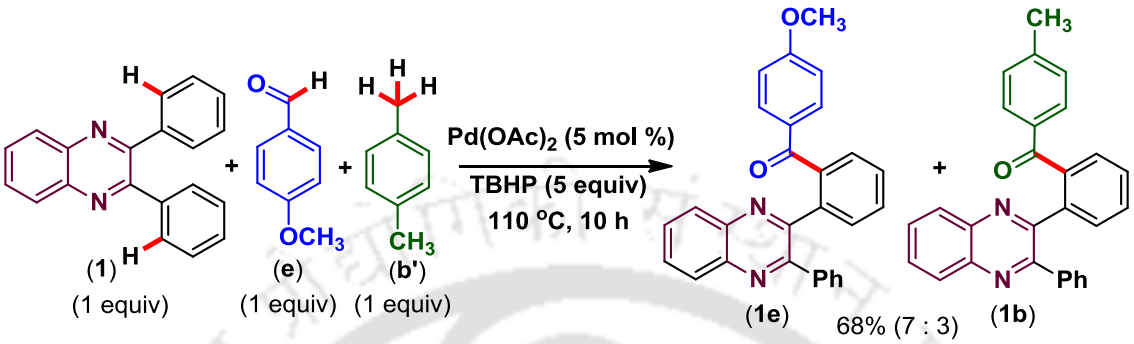
This selective *ortho*-aroylation strategy was further extended to other substituted 2,3-diphenylquinoxalines (**2**–**8**) keeping benzaldehyde (**a**) as fixed aroylating partner (Scheme IIA.3.2). 2,3-Diphenyl substituted-quinoxaline (**2**) containing electron-donating group (–Me) in its aryl rings gave excellent yield of the desire aroylated product (**2a**, 80%) when reacted with benzaldehyde under the reaction conditions.

Chloro substituents present in the quinoxaline ring as in (**3**) on reaction with benzaldehyde (**a**) afforded decent yield (67%) of the mono-*ortho*-aroylated product (**3a**). However, 2,3-aryl ring bearing methyl groups and the quinoxaline possessing chloro groups as in (**4**) afforded better yield of mono-*ortho*-aroylated product (**4a**, 78%). Methyl substituted unsymmetrical 2,3-diphenylquinoxaline (**5**) upon reaction with benzaldehyde gave an inseparable regioisomeric mono *ortho*-aroylated products **5a**/**5a′** in the ratio of 5:4 as can be judged from its ^{1}H and ^{13}C NMR spectra. However, it was not possible to assign the exact regioisomers (**5a** or **5a′**) from its ^{1}H and ^{13}C NMR spectra. The chloro substituted unsymmetrical 2,3-diphenylquinoxaline (**6**) also gave identical results and the two regioisomers **6a**/**6a′** were obtained in the ratio of 5:3 (Scheme IIA.3.2). Further, *ortho*-aroylation reactions were performed using unsymmetrically substituted 2,3-diarylquinoxalines with benzaldehyde as the aroylating source. In case of substrate (**7**) containing two electron-donating substituents (–Me and –OMe) in one of the phenyl ring provided regioisomeric mono *ortho*-aroylated products (**7a** and **7a′**) in the ratio of 6.7:1 suggesting the preferential oxidative palladation at the more electron rich aryl ring. For substrate (**8**) containing weakly electron-withdrawing substituent (–Br) in one of the phenyl ring of 2,3-diarylquinoxaline *o*-aroylation takes place at the other electron neutral phenyl ring giving product (**8a**, 69%) exclusively reconfirming the preferential *ortho*-aroylation at comparatively electron rich phenyl ring (Scheme IIA.3.2).

Recently the inert alkylbenzenes have been exploited as excellent aroyl surrogates by us[13] and several others.[18] Although in present reaction alkylbenzene (toluene) has been used as the solvent in presence of aromatic aldehyde but no *ortho*-aroylated product derived from toluene was observed in any of the reactions. This is possibly due to the presence of slightly excess amount of aromatic aldehydes (1.2 equiv) with respect to the substrate quinoxalines in the reaction. These observations suggest that perhaps the aromatic aldehyde is a facile aroyl source compared to alkylbenzene. To confirm this 2,3-diphenylquinoxaline (**1**) was treated with an equimolar mixture of *p*-methoxy benzaldehyde (1 equiv) and *p*-xylene (1 equiv) under the experimental conditions. The progress of the reaction was monitored by TLC and GC over a period of 10 h. During the first 1 h product derived from *p*-methoxy benzaldehyde (**1e**) was formed with no traces of (**1b**) (Scheme IIA.3.3). After 2 h aroylated products derived

from *p*-xylene (**1b**) was observed in about 10% yield. At the end of the reaction (10 h) products (**1e**) and (**1b**) were isolated in the ratio of 7:3 in overall 68% yield, there by suggesting the higher *ortho*-aroylating ability of aromatic aldehyde over alkylbenzene.

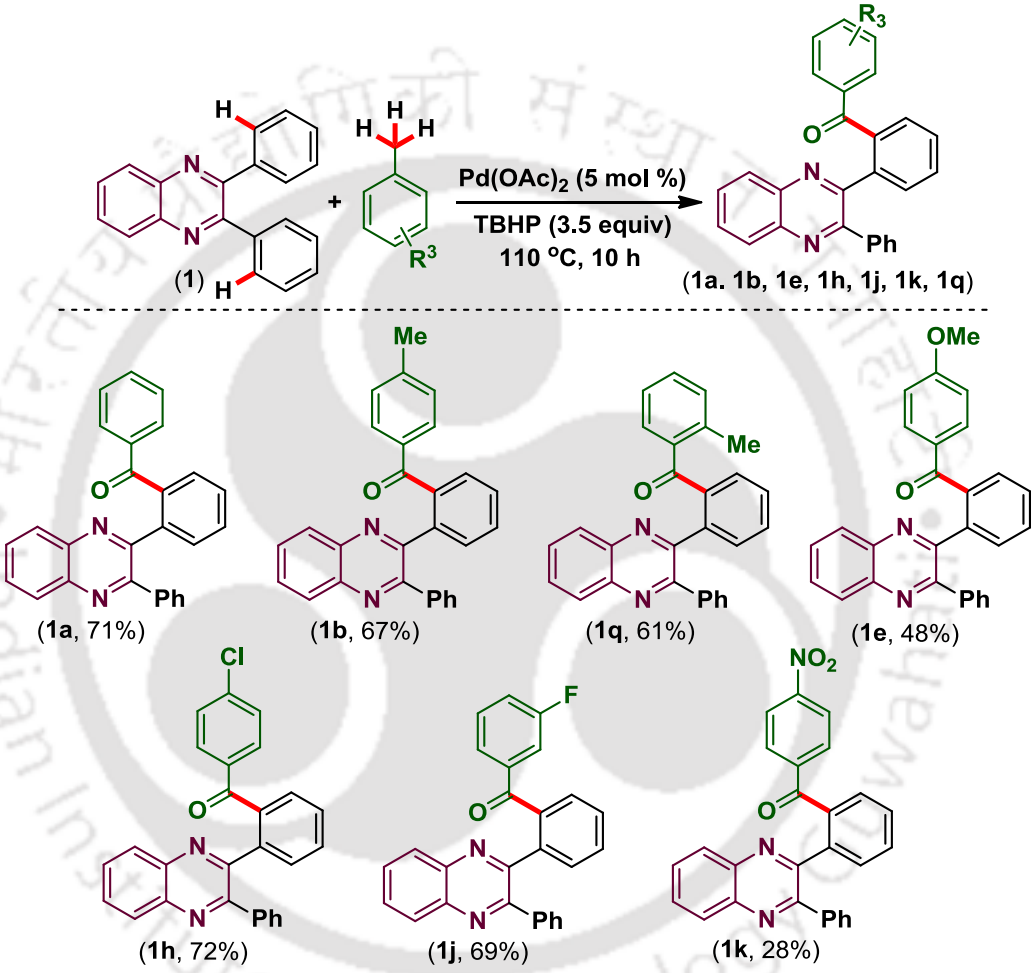
Scheme IIA.3.3.*Competitive reaction of aromatic aldehyde and alkylbenzene*



Taking cues from this and from our previous work[13] under the forcing conditions alkylbenzenes may serve as aroyl surrogate towards *ortho*-aroylation of 2,3-diphenylquinoxalines. Thus, in the absence of aldehyde using toluene as the aroyl source as well as a solvent under the present optimized condition the product (**1a**) was obtained in 22% yield. Interestingly when the oxidant (TBHP) quantity was increased to 3.5 equivalents from 1.5 equivalents and toluene was used as the sole solvent in place of toluene/DCE mixture the yield of the product improved to 71%, whereas using 2 or 3 equivalents of oxidant (TBHP) the yields obtained were 41% and 63%, respectively. However, increasing the oxidant quantity to 4 equivalents and even to 5 equivalents no significant improvement in the yield was observed. Thus in lieu of aromatic aldehydes various alkylbenzenes were reacted with 2,3-diphenylquinoxaline (**1**) and the results are summarized in Scheme IIA.3.4. Alkylbenzenes such as *p*-xylene, *o*-xylene served as good aroyl sources giving *ortho*-aroylated products (**1b**, 67%) and (**1q**, 61%), respectively. Alkylbenzene possessing electron-donating group as in *p*-methoxy toluene gave low yield (48%) of *ortho*-aroylated product (**1e**). This methodology was also equally successful for alkylbenzene possessing weakly electron-withdrawing groups. Thus *p*-chlorotoluene and *m*-fluorotoluene both gave good yields of their *o*-aroylated products (**1h**, 72%) and (**1j**, 69%), respectively (Scheme IIA.3.4). Alkylbenzene possessing strongly electron-withdrawing groups such as *p*-nitrotoluene provided *ortho*-aroylated product (**1k**) in a meager yield of 28%. This is in part due to the inheterogenity of the reaction mixture because of the insolubility of *p*-nitrotoluene

in the reaction medium. When 1,2-dichloroethane was used as the solvent for the above reaction no doubt the reaction mixture was homogeneous but the transformation was not at all effective. It may be mentioned here that the yields obtained using alkylbenzenes were slightly lower as compared to the use of analogous aromatic aldehydes.

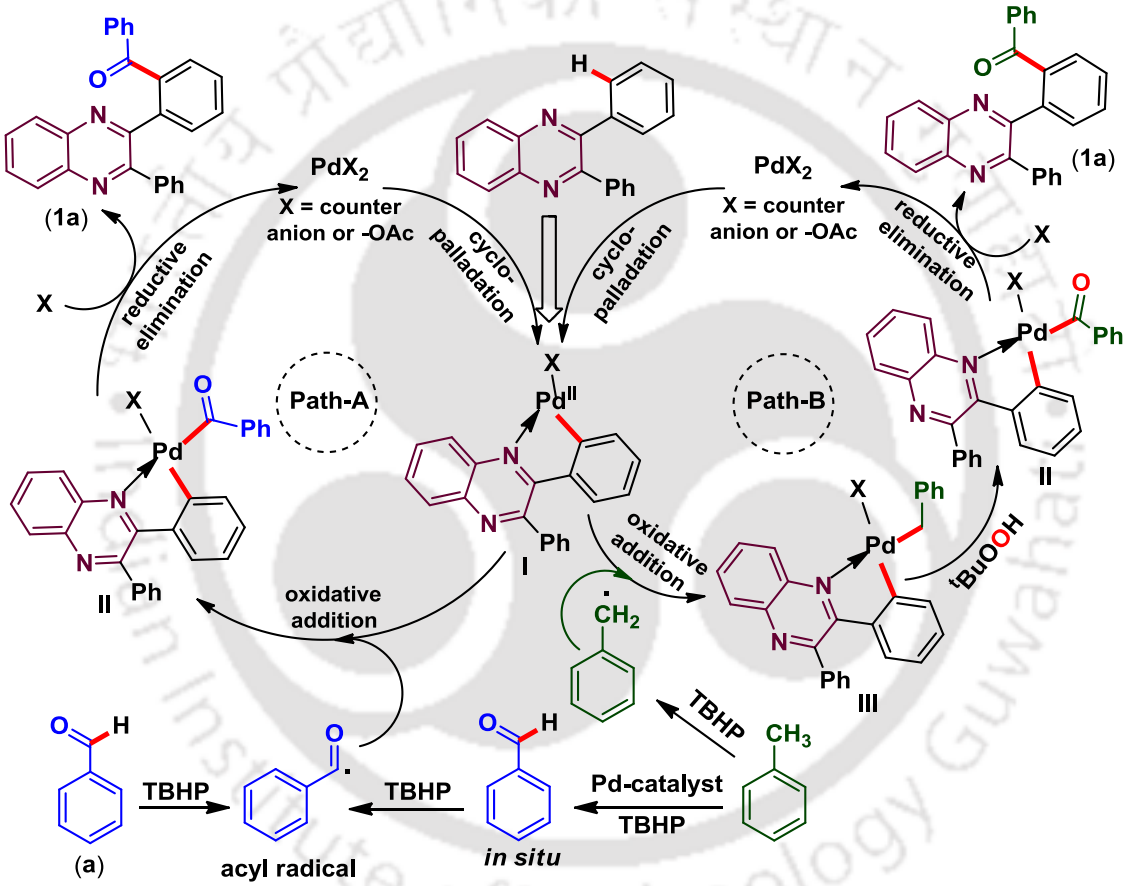
Scheme IIA.3.4. *Scope of alkylbenzenes in o-aroylation of 2,3-diphenylquinoxaline*[a,b]



[a]Reaction conditions: 2,3-Diphenylquinoxaline (**1**) (0.5 mmol), alkylbenzenes (1.5 mL), $Pd(OAc)_2$ (0.025 mmol), TBHP (1.75 mmol) at 110 °C, time 10 h. [b]Isolated yield.

Mechanistic Studies. To ascertain the nature of the mechanism(s) involved in each of these reactions a series of experiments were performed. Rate retardation with <10% conversion along with the formation of TEMPO-ester (**1A**) were observed for both cases when the reaction were performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv). This suggests the radical nature of the reactions for both aroyl surrogates *viz.* aromatic aldehyde and alkylbenzene.

A mechanism similar to *ortho*-aroylation of 2-arylbenzazole (and other directing groups) using aryl aldehyde as aroyl surrogate can be proposed for this reaction as shown in Scheme IIA.3.5, path-A.[19] Cyclopalladation of 2,3-diphenylquinoxaline leads to the formation of intermediate (**I**) followed by the oxidative addition of the *in situ* generated aroyl radical (obtained from aryl aldehyde) to form a dimeric Pd(III) intermediate[20] (**II**). In the final stage reductive elimination gave *ortho*-aroylated product regenerating the active Pd(II) species for further catalytic cycle (Scheme IIA.3.5, path-A).



Scheme IIA.3.5. *Plausible mechanistic cycle for o-aroylation*

Using toluene as the aroyl equivalent it is expected that the reaction may proceed *via* the sequential oxidation of toluene to benzyl alcohol and to aldehyde which then enters in to the catalytic path–A (Scheme IIA.3.5) giving *ortho*-aroylated product. Alternatively, the mechanism is expected to proceed similar to the one recently proposed by us during analogous substrate directed *ortho*-aroylation where a benzyl radical insertion followed by the benzylic oxidation has been proposed.[13] In the later case the *o*-palladated intermediate (**I**) undergoes oxidative addition with the benzylic radical[21] generated *in situ*

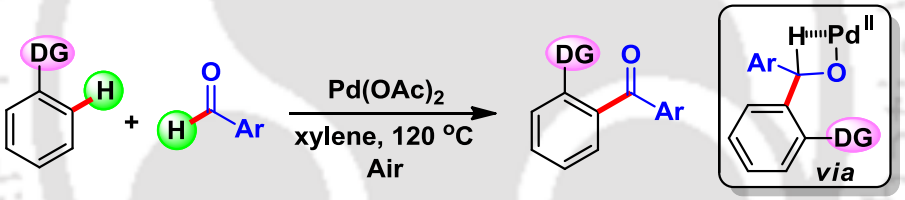
by the action of toluene and TBHP to give intermediate (**III**). Further oxidation at the benzylic carbon of intermediate (**III**) with TBHP provides intermediate (**II**) (path-B, Scheme IIA.3.5). Reductive elimination of the Pd-catalyst from the intermediate (**II**) provides *o*-aroylated product (**1a**). No di-*ortho*-aroylation was observed in the second *ortho* position of the aryl ring or in the two available *ortho* positions of the second aryl ring even with an excess of aroylating source which may be due to the loss of planarity of the pendant aryl rings with respect to the quinoxaline moiety. The out of the plane orientation of the two aryl rings can be clearly seen from one of the mono-*ortho*-aroylated product (**1e**) as shown in Fig. IIA.3.1.

In summary, a selective mono *ortho*-aroylation protocol for 2,3-diphenylquinoxaline has been developed employing Pd-catalyst in the presence of oxidant TBHP in an air atmosphere using aryl aldehyde or alkylbenzene as aroyl precursors. This is the first such aroylation protocol for 2,3-diphenylquinoxaline. Using aldehyde as aroyl surrogate the reaction goes *via* aroyl radical path while the use of alkylbenzene as aroyl surrogate it can proceed either *via* an aroyl radical or by a benzyl radical path.

IIB. Pd(II)-Catalyzed Peroxide Free *ortho*-Aroylation of Directing Arenes

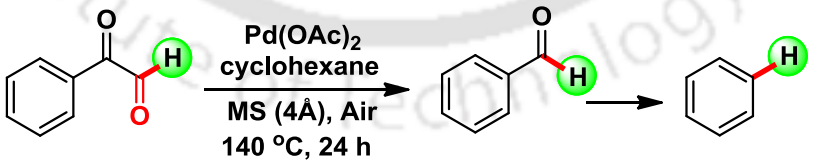
IIB.1. Introduction

After successful *ortho*-aroylation of 2,3-diarylquinoxalines in the presence of Pd-catalyst and TBHP, a mild condition for *ortho*-aroylation has been developed. To date various aroyl surrogates, *viz.* aldehyde, alkene, alkyne, benzil, α-ketoacid, benzyl alcohol, benzylamine and alkylbenzene have been employed for *ortho*-aroylation.[4] However, few of these processes involve the cleavage of inert sp^3 C–H bond(s) and hence requires stronger peroxide oxidant for the cleavage.[11-14] Peroxides are highly reactive, explosive, flammable, and toxic and are also an exceptionally corrosive chemical to skin and mucous membranes and cause respiratory distress. A peroxide free Pd(II)-catalyzed *ortho*-aroylation of directing arenes has been reported only once from aldehydes *via* direct sp^2 C–H bond cleavage using air as the oxidant (Scheme IIB.1.1).[10a]



Scheme IIB.1.1. *Peroxide free o-Aroylation of directing arenes*

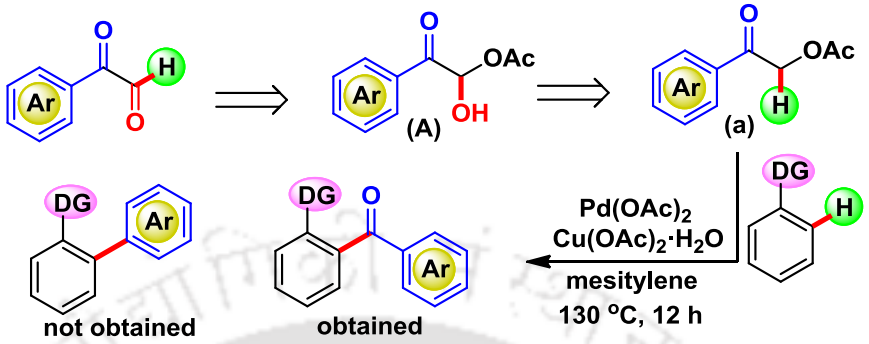
Depending upon the quantity of $Pd(OAc)_2$ used, phenylglyoxal can undergo either mono decarbonylation to benzaldehyde or a double decarbonylation to benzene (Scheme IIB.1.2).[22]



Scheme IIB.1.2. *Pd(II)-Catalyzed decarbonylations of phenylglyoxal*

A careful retrosynthetic analysis of phenylglyoxal shows that it can also be obtained from 1-hydroxy-2-oxo-2-phenylethyl acetate (**A**). Further, (**A**) can be obtained from 2-acetoxyacetophenone (**a**) *via* hydroxylation at the sp^3 C–H bond adjacent to both acetate oxygen atom and the keto group. Now a query arises whether the *in situ* generated phenylglyoxal obtained from 2-acetoxyacetophenone (**a**) would generate an aroyl

(ArCO-) moiety *via* single decarbonylation[22] or to a aryl (Ar-) unit *via* double decarbonylation.[22] Thus, a substrate directed *o*-aroylation[10a] or an *o*-arylation in the presence of Pd(II)/Cu(II) catalytic combination could be achieved (Scheme IIB.1.3).



Scheme IIB.1.3. *Pd(II)-Catalyzed decarbonylative o-aroylation using 2-acetoxyacetophenone*

IIB.2. Strategies for *ortho*-Aroylation

A number of transition metal catalyzed directing group assisted *o*-aroylation strategies have been already discussed in Section-A (page no 52–55).

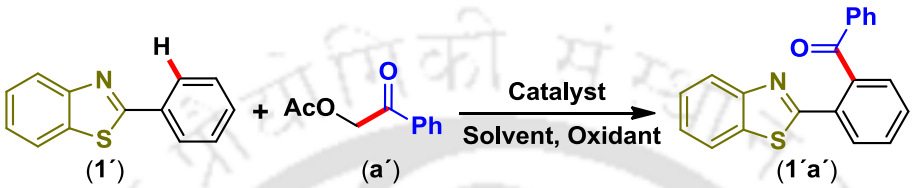
IIB.3. Present Work

2-Arylbenzothiazoles, a privileged motif present in many naturally occurring molecules and pharmaceuticals [23] having directing ability[24] through nitrogen atoms were chosen for decarbonylative *ortho*-aroylation or arylation.

Optimization of Reaction Conditions. To see which of the above possibility (aroylation or arylation) works, initially 2-phenylbenzothiazole (**1´**), was treated with 2-acetoxyacetophenone (**a´**) (1.3 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv) in *p*-xylene at 130 ^oC. From this reaction the *ortho*-aroylated product (**1´a´**) was obtained but only in a minor quantity (21%) without any trace of *ortho*-arylated product (Table IIB.3.1, entry 1). We look forward to improving this *ortho*-aroylation process by changing other reaction parameters such as solvent, catalyst, oxidants and their quantities. Polar aprotic solvents such as DMF and DMSO and non polar solvents like DCE, cyclohexane and toluene all failed to give the desired *ortho*-aroylated product (**1´a´**) (Table IIB.3.1, entries 2–6). However, mesitylene as solvent provided 32% yield of the *o*-aroylated product (**1´a´**) under otherwise identical reaction conditions (Table IIB.3.1, entry 7). Significant improvement in the yield (47%) was

observed when the catalyst loading was increased to 10 mol % (Table IIB.3.1, entry 8). However, a further increase in the catalyst loading to 15 mol % did not affect the product yield (51%) significantly (Table IIB.3.1, entry 9). Changing the oxidant from $Cu(OAc)_2 \cdot H_2O$ to $CuCl_2$, $CuBr_2$ and anhydrous $Cu(OAc)_2$ gave no desired *ortho*-aroylated product (Table IIB.3.1, entries 10–12), whereas $Cu(OAc)_2 \cdot xH_2O$ provided 40% of *o*-aroylated product (**1´a´**) (Table IIB.3.1, entry 13).

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



entry	catalyst (mol %)	solvent	oxidant	additive	yield (%)[b]
1	$Pd(OAc)_2$ (5.0)	*p*-xylene	$Cu(OAc)_2 \cdot H_2O$	-	21
2	$Pd(OAc)_2$ (5.0)	DMF	$Cu(OAc)_2 \cdot H_2O$	-	trace
3	$Pd(OAc)_2$ (5.0)	DMSO	$Cu(OAc)_2 \cdot H_2O$	-	0
4	$Pd(OAc)_2$ (5.0)	DCE	$Cu(OAc)_2 \cdot H_2O$	-	0
5	$Pd(OAc)_2$ (5.0)	cyclohexan	$Cu(OAc)_2 \cdot H_2O$	-	0
6	$Pd(OAc)_2$ (5.0)	toluene	$Cu(OAc)_2 \cdot H_2O$	-	0
7	$Pd(OAc)_2$ (5.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	32
8	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	47
9	$Pd(OAc)_2$ (15.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	51
10	$Pd(OAc)_2$ (10.0)	mesitylene	$CuCl_2$	-	0
11	$Pd(OAc)_2$ (10.0)	mesitylene	$CuBr_2$	-	0
12	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2$	-	0
13	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot xH_2O$	-	40
14	$Pd(TFA)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	42
15	$PdCl_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	34
16	$Pd(PPh_3)_2Cl_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	trace
17	$Pd(MeCN)_2Cl_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	-	trace
18	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	PTSA	49[c]
19	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	AcOH	52[c]
20	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	PivOH	31[c]
21	**$Pd(OAc)_2$ (10.0)**	**mesitylene**	**$Cu(OAc)_2 \cdot H_2O$**	**AcOH**	**58[d]**
22	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	AcOH	31[d,e]
23	$Pd(OAc)_2$ (10.0)	mesitylene	$Cu(OAc)_2 \cdot H_2O$	AcOH	28[d,f]

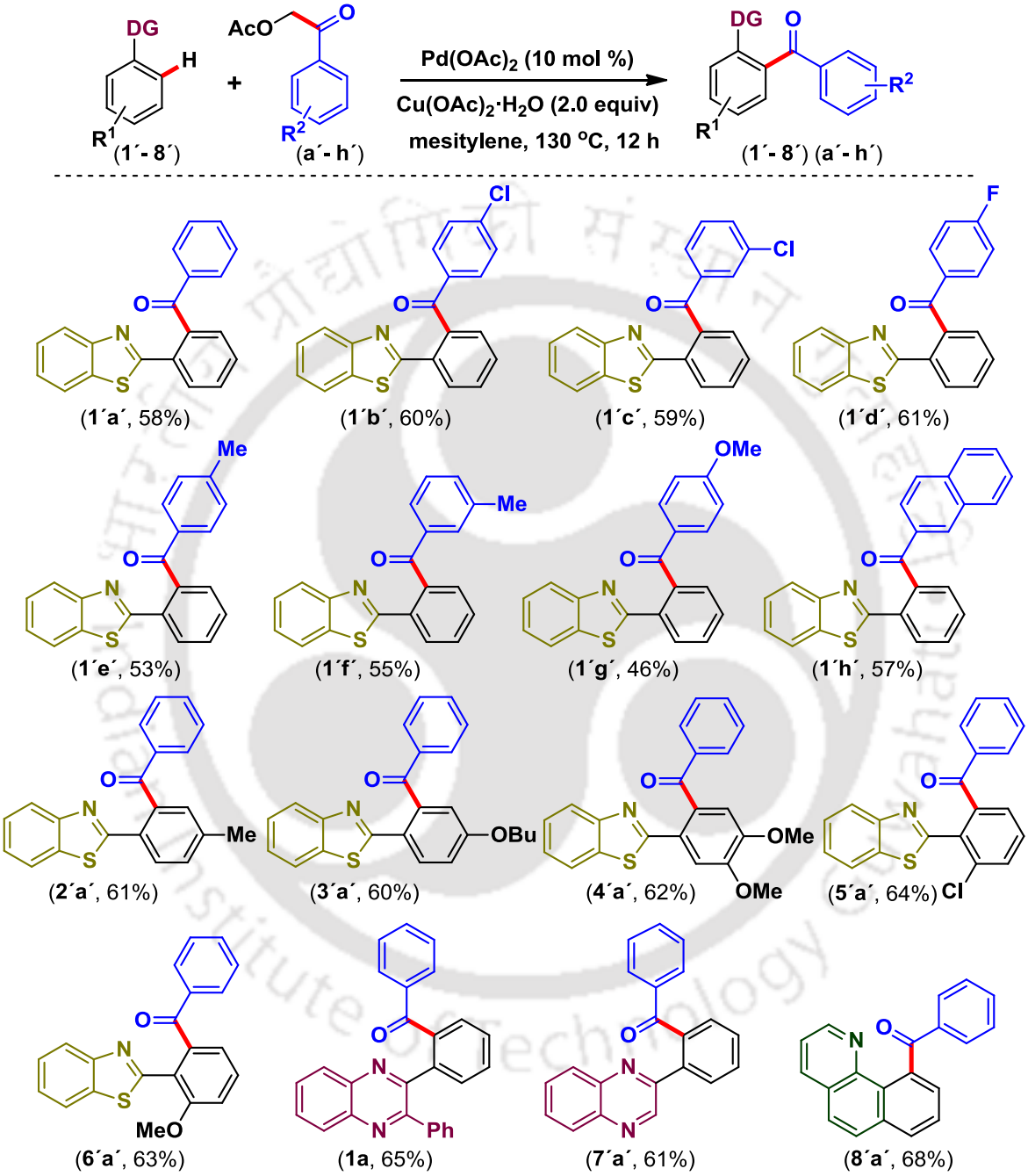
[a]Reaction conditions: 2-Phenylbenzothiazole (**1´**) (0.25 mmol), (**a´**) (0.33 mmol), Cu-salts (1.5 equiv), mesitylene (1 mL) and 130 °C. [b]Isolated yield after 12 h. [c]Acid additives (0.5 mmol). [d]$Cu(OAc)_2 \cdot H_2O$ (2.0 equiv). [e]Oxone (1.0 equiv). [f]$K_2S_2O_8$ (1.0 equiv).

Other Pd-catalysts such as $Pd(TFA)_2$ and $PdCl_2$ gave lower yields, while $Pd(PPh_3)_2Cl_2$ and $Pd(MeCN)_2Cl_2$ afforded only trace amount of the desired *ortho*-aroylated product (**1´a´**) in the presence of $Cu(OAc)_2 \cdot H_2O$ oxidant (Table IIB.3.1, entries 14–17). To check the effect, if any of acid additives in the reaction, acids such as *p*-toluenesulfonic acid (PTSA), acetic acid (AcOH) and pivalic acid (PivOH) were tested during the reaction (Table IIB.3.1, entries 18–20). After the reaction was screened with these additives, it was found that the application of 2.0 equivalents of AcOH under otherwise identical condition enhanced the yield of the desired *ortho*-aroylated product (**1´a´**) up to 52% (Table IIB.3.1, entry 19). Further, increasing the oxidant $Cu(OAc)_2 \cdot H_2O$ quantity from 1.5 to 2.0 equivalents provided the *o*-aroylated product (**1´a´**) in an improved yield of 58% (Table IIB.3.1, entry 21). In order to further increase the yield of the product (**1´a´**), other co-oxidants such as oxone and $K_2S_2O_8$ were tested with $Cu(OAc)_2 \cdot H_2O$, but both were found to be inferior (Table IIB.3.1, entries 22 and 23).

Substrate Scope for Decarbonylative *o*-Aroylation. It may be noted that most of the *o*-aroylation processes proceed in the presence of peroxide oxidants such as TBHP and persulfate.[4,15] Thus, this peroxide-free *o*-aroylation strategy was further pursued using 2-phenylbenzothiazole (**1´**) and a variety of 2-acetoxyacetophenones (**a´-h´**). 2-Acetoxy-acetophenones having activated and deactivated phenyl rings efficiently coupled with 2-phenylbenzothiazole (**1´**) to give the desired *ortho*-aroylated products (**1´a´-1´h´**) in yields ranging from 46 to 66%. 2-Oxo-2-phenylethyl acetate containing moderately electron-withdrawing groups such as *p*–Cl (**b´**), *m*–Cl (**c´**) and *p*–F (**d´**) afforded *o*-aroylated products (**1´b´**, 60%), (**1´c´**, 59%) and (**1´d´**, 61%), respectively, in moderate yields. However, this peroxide free strategy was less effective for electron rich 2-oxo-2-arylethyl acetate possessing *p*–Me (**e´**), *m*–Me (**f´**) and *p*–OMe (**g´**), giving their products (**1´e´**, 53%), (**1´f´**, 55%) and (**1´g´**, 46%), respectively (Scheme IIB.3.1). Then this selective *ortho*-aroylation strategy was further extended to other substituted 2-phenylbenzothiazoles with 2-oxo-2-phenylethyl acetate (**a´**). Substituted 2-phenylbenzothiazoles containing electron-donating groups such as *p*–Me (**2´**), *p*–OBu (**3´**) and 3,4–di-OMe (**4´**) in its aryl rings gave decent yield of their desire aroylated products (**2´a´**, 61%), (**3´a´**, 60%), and (**4´a´**, 62%) when reacted with 2-oxo-2-phenylethyl acetate (**a´**) under the optimized reaction conditions. *Ortho*-substituted 2-phenylbenzothiazoles

such as *o*–Cl (**5´**) and *o*–OMe (**6´**) provided better yields of their desired *o*-aroylated products (**5´a´**, 64%) and (**6´a´**, 63%), respectively (Scheme IIB.3.1).

Scheme IIB.3.1. *Scope of substrates for ortho-aroylation of directing arenes*[a,b]

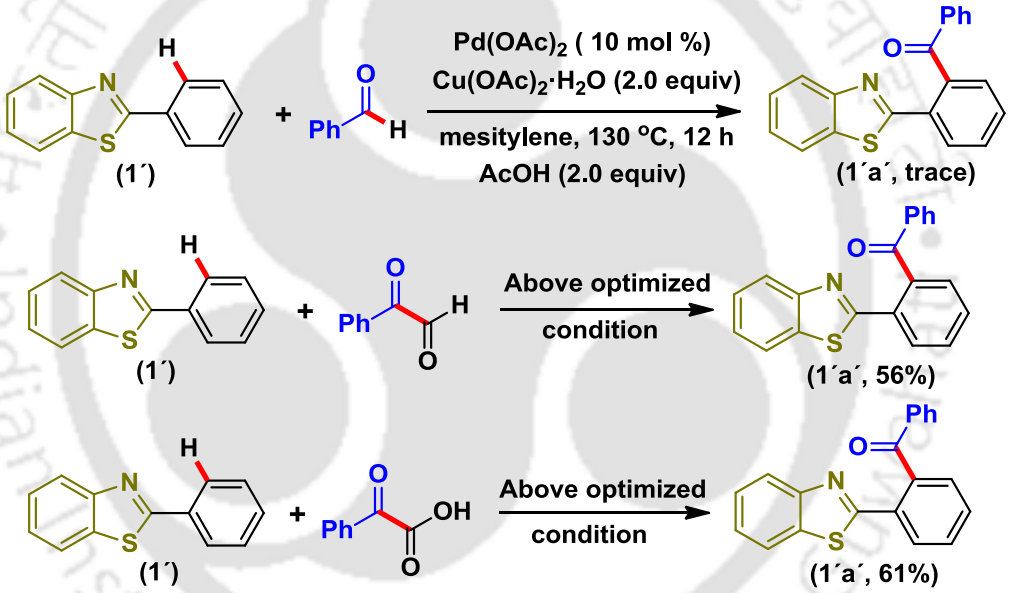


[a]Reaction conditions: Directing arenes (**1´- 8´**) (0.25 mmol), (**a´- h´**) (0.33 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol) and acetic acid (0.5 mmol), in mesitylene (1 mL) at 130 °C, for 12 h.[b]Isolated yield.

To verify whether this sp^3 C–H functionalization strategy for *ortho*-aroylation could be equally applicable to other directing arenes, 2,3-diphenylquinoxaline (**1**), 2-phenylquinoxaline (**7´**), and benzo[*h*]quinoline (**8´**) were treated with 2-oxo-2-

phenylethyl acetate (**a´**) under the above optimized conditions. All the three directing arenes (**1**, **7´** and **8´**) efficiently coupled with (**a´**), affording their *o*-aroylated products (**1a**), (**7´a´**) and (**8´a´**) in 65%, 61% and 68% yields, respectively (Scheme IIB.3.1).

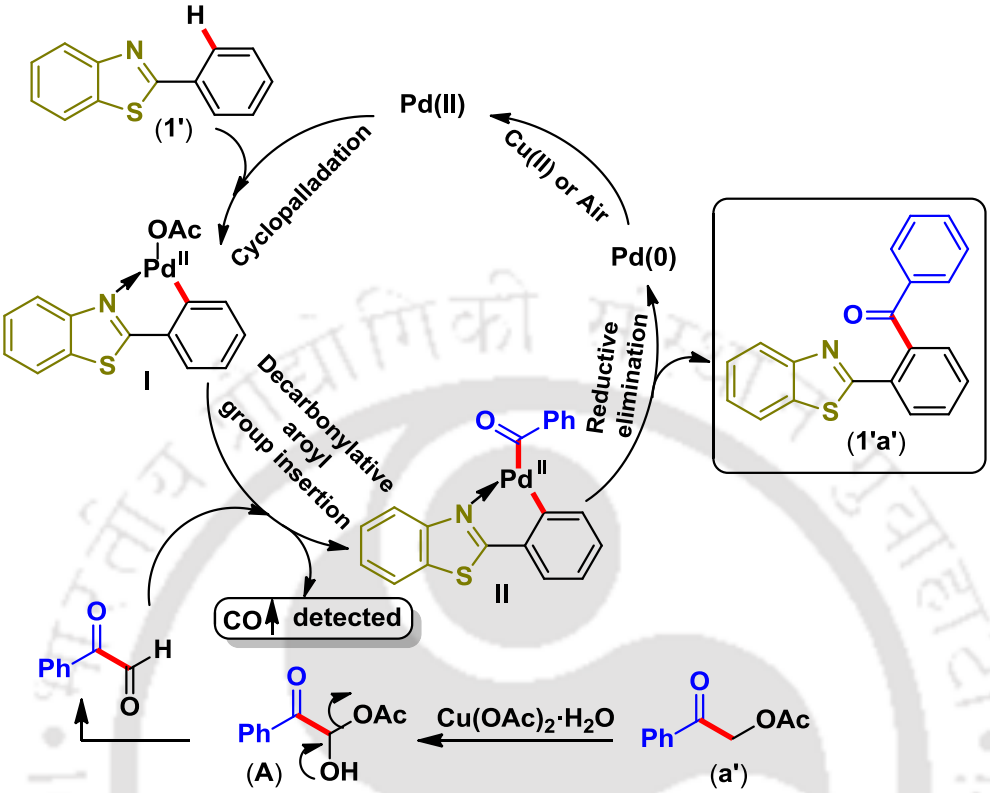
The mechanism is expected to be similar to *ortho*-aroylation of 2-arylpyridine as reported by Cheng *et al. via* direct sp^2 C–H bond cleavage of aromatic aldehydes[10a] or *via* decarboxylation[15] as proposed by various groups. To ascertain the actual intermediate involve in this reaction, three independent experiments were performed using benzaldehyde, phenylglyoxal and phenylglyoxalic acid. Both phenylglyoxal and phenylglyoxalic acid provided desired *o*-aroylated product (**1´a´**) in 56% and 61% yields, respectively, whereas benzaldehyde gave only a trace of the product (**1´a´**) (Scheme IIB.3.2).



Scheme IIB.3.2. *Controlled experiments*

Thus, the reaction may be going *via* either decarbonylation of the *in situ* generated phenylglyoxal or decarboxylation path of phenylglyoxalic acid obtained from the oxidation of 2-acetoxyacetophenone (**a´**). A spot test of the reaction mixture using $PdCl_2$-phousphomolybodicacid (PMA) strip confirmed the evolution of CO, there by supporting the decarbonylation path.[25] Cyclopalladation of 2-phenylbenzothiazole (**1´**) leads to the formation of intermediate (**I**) followed by the insertion of an aroyl moiety obtained *via* decarbonylation of phenylglyoxal to form intermediate (**II**). In the final stage reductive elimination gave *o*-aroylated product releasing Pd(0), which was oxidized to Pd(II) by air/$Cu(OAc)_2$ for the next catalytic cycle. Since phenylglyoxalic

acid also provided the *o*-aroylated product (**1´a´**), a decarboxylation path[15] cannot be completely ruled out.



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

In conclusion, a peroxide free Cu(II)-mediated *ortho*-aroylation for various directing arenes has been developed in the presence of Pd(II)-catalyst. In this process $Cu(OAc)_2 \cdot H_2O$ played the dual role to facilitate the oxidation of 2-acetoxyacetophenone *via* the cleavage of an sp^3 C–H bond along with the regeneration of Pd(II) catalyst. This is the first report on Pd(II)-catalyzed decarbonylative *o*-aroylation using 2-acetoxyacetophenone as the aroyl source in the absence of any peroxide.

II.4. Experimental Section

II.4.1. General Information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). 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. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. IR spectra were recorded in KBr or neat. 2,3-Diarylquinoxalines were prepared from corresponding o-phenylenediamine and benzil derivatives. 2-Arylbenzothiazoles were prepared from corresponding *N*-phenylbenzothioamides using hypervalent iodine mediated oxidative cyclization following the reported procedure.[26]

II.4.2. Crystallographic Description

- **IIA.4.2.**

CCDC number for compounds 1e: CCDC 956425. 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 1e: Crystal dimension (mm): 0.44 x 0.32 x 0.24. $C_{28}H_{20}N_2O_2$, Mr = 416.46. monoclinic, space group C 2/c; a = 28.766 (2) Å, b = 10.9176 (8) Å, c = 14.9704 (18) Å; $\alpha = 90^o$, $\beta = 113.435$ (9) ^{o}, $\gamma = 90^o$, V = 4313.7 (7)Å^3 ; Z = 8; ρ_{cal}= 1.283 g/cm^3; μ (mm^{-1}) = 0.081; *F (000)* = 1744.0; Reflection collected / unique = 3556 / 1957; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0558, wR2 = 0.1134, R indices (all data) R1 = 0.1256, wR2 = 0.1402; goodness of fit = 1.020.

II.4.3. Synthesis of *o*-Aroylated 2,3-Diarylquinoxaline and 2-Arylbenzothiaole

IIA.4.3.1. General Procedure for the Synthesis of Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1a) from 2,3-Diphenylquinoxaline (1) and Benzaldehyde (a): In an oven-dried 25 mL round bottom flask containing 1 mL each of toluene and 1,2-dichloroethane (DCE), 2,3-diphenylquinoxaline (**1**) (0.141g, 0.5 mmol), benzaldehyde (0.064g, 0.6 mmol) and $Pd(OAc)_2$ (0.006g, 0.025 mmol) was added sequentially. Then reaction mixture was kept in an oil bath preheated to 110 ^oC. TBHP (0.75 mmol) was added in four equal lots at an intervals of 1.5 h. The progress of the reaction was monitored by TLC after each addition. After completion of the reaction (8 h) the reaction mixture was cooled to room temperature and was 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 solution (5 mL), dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 9.2/0.8) to give pure phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (**1a**) (0.147g, yield 76%). The identity and purity of the product was confirmed by spectroscopic analysis.

IIA.4.3.2. General Procedure for the Synthesis of Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1a) from 2,3-Diphenylquinoxaline (1) and Toluene: In an oven-dried 25 mL round bottom flask containing 1.5 mL of toluene, 2,3-diphenylquinoxaline (**1**) (0.141g, 0.5 mmol) and $Pd(OAc)_2$ (0.006g, 0.025 mmol) was added in sequence. The reaction mixture was the kept in an oil bath preheated to 110 ^oC. TBHP (1.75 mmol) was added in four equal lots at an intervals of 2 h. The progress of the reaction was monitored by TLC after each addition. After completion of the reaction (10 h) the reaction mixture was cooled to room temperature and was admixed with water (5 mL). The product was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (5 mL), dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 9.2:0.8) to give pure phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (**1a**)

(0.137g, yield 71%). The identity and purity of the product was confirmed by spectroscopic analysis.

IIB.4.3. General Procedure for the Synthesis of (2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1´a´) from 2-Phenylbenzo[*d*]thiazole (1´) and 2-Acetoxyacetophenone (a´): 2-Phenylbenzo[*d*]thiazole (**1´**) (0.053g, 0.25 mmol), 2-oxo-2-phenylethyl acetate (**a´**) (0.059g, 0.33 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol), acetic acid (0.030g, 0.5 mmol) and mesitylene (1.5 mL) were placed in an oven-dried 25 mL round bottom flask. The reaction mixture was then placed in an oil bath preheated at 130 ^oC. After completion of the reaction (12 h) the reaction mixture was cooled to room temperature and the reaction mixture was taken up in with ethyl acetate (30 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 9.4:0.6) to give pure colorless gummy (2-(benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (**1´a´**) (0.046g, yield 58%). The identity and purity of the product were confirmed by spectroscopic analysis.

II.4.4. Mechanistic Investigations

- **IIA.4.4.1. *o*-Aroylation of 2,3-Diarylquinoxaline in the Presence of Radical Scavenger TEMPO:** In an oven-dried 25 mL round bottom flask 2,3-diphenylquinoxaline (**1**) (0.141g, 0.5 mmol), benzaldehyde (0.064g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol) TBHP in decane (5-6 M) (100 µL, 0.5 mmol) TEMPO (0.078g, 0.5 mmol), toluene and dichloroethane (DCE) 1 mL each of were added. The flask was fitted to a condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^oC for 8 h. The reaction after 8 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (1**A**) in 52% yield along with paltry yield (~10%) of the desired product (**1a**). This experiment supports the formation of benzoyl radical in the medium from benzaldehyde (**a**) induced radically by $Pd(OAc)_2$/TBHP and also the radical nature of the mechanism. The same benzoyl-TEMPO adduct (**1A**) was observed when toluene used as an aroyl surrogate in lieu of benzaldehyde.

- **IIB.4.4.1. Determine the Extrusion of CO from the Reaction:** For the detection of evolution of carbon monoxide (CO), a strip containing $PdCl_2$ and PMA (phosphomolybdic acid) was suspended from the neck of the reaction flask as shown in the Fig. IIB.4.4.1. The initial yellow colour of the strip before the reaction (Fig. IIB.4.4.1) turned blue after 3 hrs of the reaction progress (Fig. IIB.4.4.2). This colour change confirms the extrusion of CO from the reaction.

Fig. IIB.4.4.1
$PdCl_2$-PMA test strip before reaction

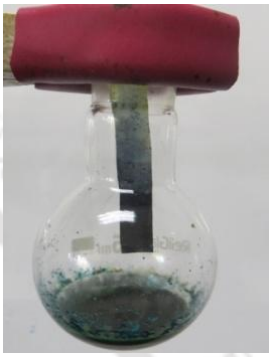


Fig. IIB.4.4.2
$PdCl_2$-PMA test strip after reaction

II.5. References

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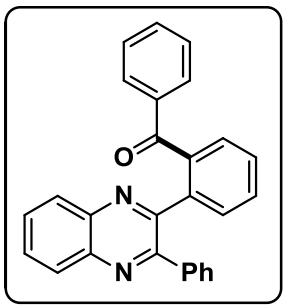
II.6. Spectral Data

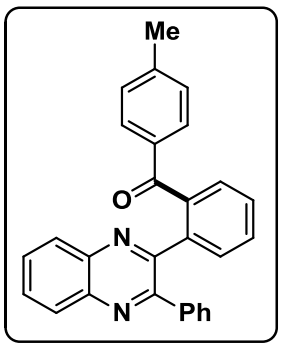
➢ IIA.6.

Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1a):



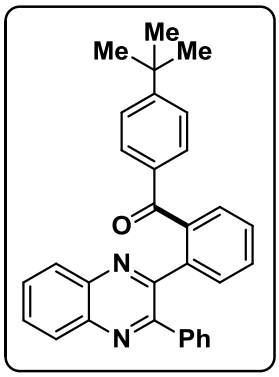
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, J = 9.2 Hz), 8.01 (d, 1H, J = 8.0 Hz), 7.75–7.69 (m, 2H), 7.66 (d, 1H, J = 7.6 Hz), 7.61–7.57 (m, 1H), 7.45–7.39 (m, 7H), 7.28 (t, 2H, J = 9.0 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.16 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 153.8, 153.4, 141.4, 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^+) 387.1492, found 387.1485.

(2-(3-Phenylquinoxalin-2-yl)phenyl)(*p*-tolyl)methanone (1b):



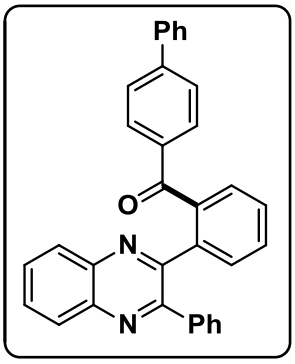
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, 1H, J = 7.2 Hz), 7.98 (d, 1H, J = 7.2 Hz), 7.72–7.66 (m, 2H), 7.59 (d, 1H, J = 7.6 Hz), 7.56–7.52 (m, 1H), 7.43–7.41 (m, 4H), 7.31 (d, 2H, J = 8.4 Hz), 7.22 (d, 1H, J = 5.6 Hz), 7.17–7.11 (m, 2H), 7.07 (d, 2H, J = 8.0 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 153.9, 153.5, 143.4, 141.4, 141.1, 140.9, 139.2, 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; Anal. calcd for $C_{28}H_{20}N_2O$: C 83.98, H 5.03, N 6.99; found: C 84.17, H 5.11, N 7.06.

(4-(Tert-butyl)phenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1c):



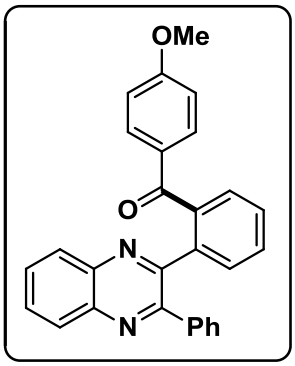
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, 1H, J = 6.8 Hz), 8.02 (d, 1H, J = 6.8 Hz), 7.74–7.68 (m, 2H), 7.66 (d, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.49–7.45 (m, 2H), 7.41 (d, 2H, J = 7.6 Hz), 7.36 (d, 2H, J = 6.4 Hz), 7.27 (d, 2H, J = 7.2 Hz), 7.21 (d, 1H, J = 6.4 Hz), 7.14 (t, 2H, J = 7.2 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 156.3, 154.0, 153.6, 141.5, 141.1, 140.9, 139.2, 138.5, 134.4, 131.6, 131.3, 130.4, 130.2, 130.0, 129.8, 129.4, 129.3, 128.9, 128.3, 128.1, 124.9, 35.2, 31.2; IR (KBr, cm^{-1}): 3057, 2961, 2862, 1728, 1657, 1603, 1476, 1462, 1396, 1343, 1311, 1289, 1268, 1103, 1056, 1025, 977, 931, 845, 789, 763; HRMS (ESI) calcd for $C_{31}H_{26}N_2O$ (M + H^+) 443.2118, found 443.2110.

[1,1'-Biphenyl]-4-yl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1d):



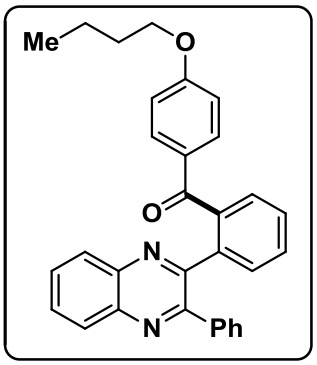
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, J = 6.8 Hz), 8.03 (d, 1H, J = 8.8 Hz), 7.75–7.70 (m, 2H), 7.67 (d, 1H, J = 7.6 Hz), 7.62 (d, 1H, J = 7.2 Hz), 7.58 (d, 3H, J = 7.2 Hz), 7.53–7.45 (m, 10H), 7.39 (t, 1H, J = 7.4 Hz), 7.25 (t, 1H, J = 7.2 Hz), 7.17 (t, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 153.8, 153.5, 145.3, 141.4, 141.1, 140.9, 140.1, 138.9, 138.5, 135.8, 131.7, 131.3, 130.7, 130.4, 130.2, 130.1, 129.9, 129.4, 129.2, 129.1, 128.9, 128.3, 128.1, 127.4, 126.7; IR (KBr, cm^{-1}): 3054, 2956, 2920, 2851, 1651, 1603, 1478, 1397, 1344, 1311, 1275, 1215, 1155, 1056, 1026, 976, 934, 853, 798, 760; Anal. calcd for $C_{33}H_{22}N_2O$: C 85.69, H 4.79, N 6.06; found: C 85.91, H 4.88, N 6.17.

(4-Methoxyphenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1e):



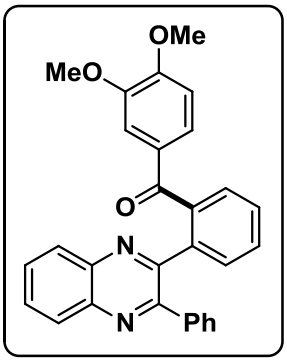
Solid; M.p. 112.8 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, J = 7.6 Hz), 8.06 (d, 1H, J = 8.8 Hz), 8.00 (d, 1H, J = 7.6 Hz), 7.75–7.68 (m, 2H), 7.62 (d, 1H, J = 7.6 Hz), 7.58–7.54 (m, 1H), 7.44 (d, 4H, J = 6.8 Hz), 7.22 (d, 1H, J = 7.6 Hz), 7.16 (t, 2H, J = 7.2 Hz), 6.95 (d, 1H, J = 8.8 Hz), 6.78 (d, 2H, J = 8.8 Hz), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 163.3, 153.9, 153.5, 141.4, 141.1, 140.7, 139.3, 138.5, 132.5, 132.4, 131.6, 130.3, 129.9, 129.8, 129.3, 129.2, 128.8, 128.2, 127.9, 113.8, 113.3, 55.6; IR (KBr, cm^{-1}): 2923, 2835, 2362, 1637, 1595, 1572, 1418, 1341, 1286, 1257, 1176, 1152, 1059, 1026, 924, 845, 775; HRMS (ESI) calcd for $C_{28}H_{20}N_2O_2$ (M + H^+) 417.1598, found 417.1603.

(4-Butoxyphenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1f):



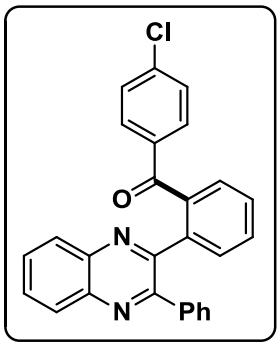
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, 1H, J = 7.6 Hz), 7.98 (d, 1H, J = 7.6 Hz), 7.72–7.65 (m, 2H), 7.59 (d, 1H, J = 7.6 Hz), 7.54–7.51 (m, 1H), 7.43–7.39 (m, 6H), 7.20 (d, 1H, J = 7.2 Hz), 7.14 (t, 2H, J = 7.0 Hz), 6.64 (d, 2H, J = 9.2 Hz), 3.96 (t, 2H, J = 6.4 Hz), 1.79–1.72 (m, 2H), 1.51–1.43 (m, 2H), 0.97 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 162.9, 154.0, 153.5, 141.4, 141.1, 140.8, 139.5, 138.6, 132.6, 131.6, 130.9, 130.4, 130.0, 129.8, 129.4, 129.3, 128.9, 128.3, 127.9, 113.8, 68.1, 31.3, 19.4, 13.9; IR (KBr, cm^{-1}): 3063, 2948, 2867, 1661, 1598, 1573, 1506, 1469, 1418, 1395, 1345, 1280, 1247, 1178, 1151, 1109, 1068, 1025, 977, 929, 841, 766; Anal. calcd for $C_{31}H_{26}N_2O_2$: C 81.20, H 5.72, N 6.11; found: C 81.37, H 5.85, N 6.21.

(3,4-Dimethoxyphenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1g):



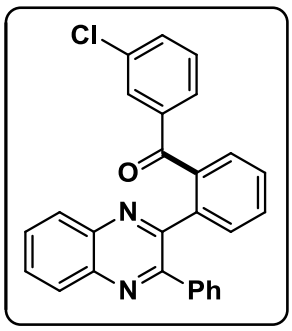
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 1H, J = 8.0 Hz), 7.93 (d, 1H, J = 7.2 Hz), 7.67–7.61 (m, 2H), 7.54–7.46 (m, 2H), 7.42–7.35 (m, 4H), 7.19–7.09 (m, 4H), 6.93 (d, 1H, J = 8.4 Hz), 6.63 (d, 1H, J = 8.4 Hz), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 153.9, 153.5, 153.1, 148.7, 141.4, 141.1, 140.9, 139.3, 138.6, 131.6, 130.9, 130.4, 130.0, 129.9, 129.4, 129.2, 128.9, 128.2, 127.9, 125.8, 111.8, 109.7, 56.2, 56.0; IR (KBr, cm^{-1}): 3054, 2950, 2929, 2829, 1638, 1578, 1511, 1459, 1452, 1417, 1343, 1292, 1267, 1233, 1180, 1134, 1059, 1027, 978, 799, 763; HRMS (ESI) calcd for $C_{29}H_{22}N_2O_3$ ($M + H^+$) 447.1703, found 447.1694.

(4-Chlorophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1h):



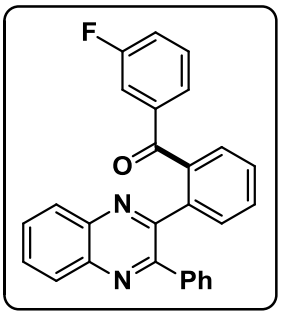
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, J = 8.6 Hz), 8.01 (d, 1H, J = 8.6 Hz), 7.77–7.70 (m, 2H), 7.67 (d, 1H, J = 6.8 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.47–7.39 (m, 4H), 7.34 (d, 2H, J = 8.4 Hz), 7.27 (d, 3H, J = 7.2 Hz), 7.17 (t, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 153.6, 153.4, 141.4, 141.1, 140.9, 139.9, 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 $C_{27}H_{17}ClN_2O$ ($M + H^+$) 421.1102, found 421.1094.

(3-Chlorophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1i):



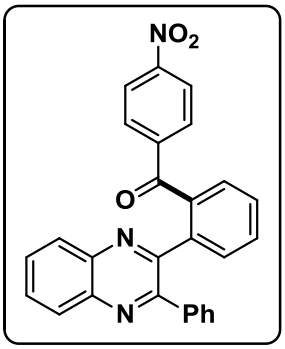
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, J = 6.8 Hz), 8.06 (d, 1H, J = 7.6 Hz), 7.77–7.71 (m, 3H), 7.65 (t, 1H, J = 7.4 Hz), 7.47 (t, 1H, J = 7.6 Hz), 7.43 (s, 1H), 7.41–7.37 (m, 3H), 7.31 (t, 2H, J = 8.4 Hz), 7.26 (t, 2H, J = 2.8 Hz), 7.22–7.16 (m, 2H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 153.5, 153.3, 141.4, 141.1, 141.0, 138.6, 138.4, 138.1, 134.1, 132.6, 131.9, 130.4, 130.2, 129.9, 129.4, 129.2, 129.0, 128.3, 128.2, 127.9; IR (KBr, cm^{-1}): 3053, 2918, 2845, 1660, 1591, 1568, 1477, 1440, 1418, 1390, 1344, 1289, 1257, 1219, 1154, 1071, 1054, 1025, 977, 939, 769; HRMS (ESI) calcd for $C_{27}H_{17}ClN_2O$ ($M + H^+$) 421.1102, found 421.1106.

(3-Fluorophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1j):



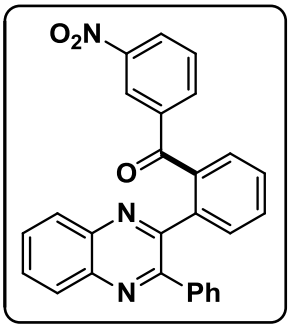
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.76–7.72 (m, 2H), 7.69 (s, 1H), 7.63 (t, 1H, J = 6.7 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.40 (t, 3H, J = 7.6 Hz), 7.26–7.23 (m, 2H), 7.19 (d, 2H, J = 9.2 Hz), 7.15 (d, 2H, J = 7.2 Hz), 7.02 (d, 1H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.2, 163.5, 161.0, 153.6, 153.4, 141.5, 141.1, 141.0, 139.2, 138.5, 138.3, 131.9, 131.7, 130.4, 130.2, 130.0, 129.8, 129.7, 129.4, 129.2, 128.9, 128.4, 128.2, 125.8, 119.8, 119.6, 116.8, 116.6; IR (KBr, cm^{-1}): 3060, 2923, 1840, 1731, 1660, 1585, 1478, 1441, 1394, 1344, 1292, 1270, 1205, 1128, 1056, 1025, 977, 861, 840, 800, 769; HRMS (ESI) calcd for $C_{27}H_{17}FN_2O$ (M + H^+) 405.1402, found 405.1390.

(4-Nitrophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1k):



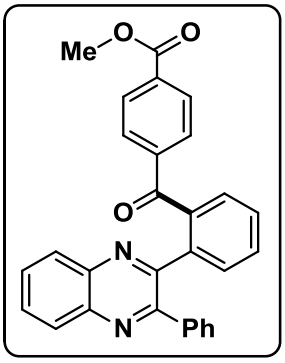
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 2H, J = 8.8 Hz), 8.01 (d, 1H, J = 8.0 Hz), 7.79–7.73 (m, 3H), 7.67 (t, 1H, J = 7.6 Hz), 7.52–7.47 (m, 3H), 7.40 (d, 2H, J = 6.8 Hz), 7.37 (t, 2H, J = 7.0 Hz), 7.29 (d, 1H, J = 6.4 Hz), 7.18 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.8, 153.1, 149.9, 142.1, 141.4, 141.1, 138.5, 137.7, 132.3, 132.1, 130.8, 130.4, 130.3, 130.2, 129.9, 129.4, 129.1, 128.5, 128.4, 123.2; IR (KBr, cm^{-1}): 3060, 2924, 2851, 1731, 1663, 1602, 1523, 1474, 1446, 1393, 1345, 1314, 1265, 1104, 1054, 1025, 977, 932, 864, 851, 771; HRMS (ESI) calcd for $C_{27}H_{17}N_3O_3$ (M + H^+) 432.1343, found 432.1333.

(3-Nitrophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1l):



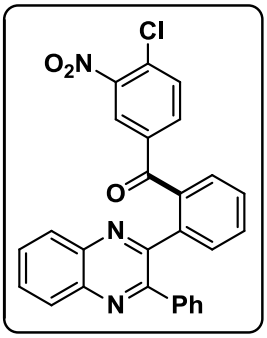
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, 1H, J = 8.4 Hz), 8.11 (d, 1H, J = 6.4 Hz), 8.03 (d, 1H, J = 6.8 Hz), 7.98 (s, 1H), 7.79 (d, 2H, J = 7.2 Hz), 7.75–7.69 (m, 3H), 7.52–7.47 (m, 2H), 7.37–7.33 (m, 3H), 7.15–7.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 153.2, 147.7, 141.5, 141.1, 138.3, 137.4, 135.3, 132.4, 132.2, 130.5, 130.4, 130.2, 129.7, 129.5, 129.2, 129.0, 128.5, 128.4, 127.0, 124.9; IR (KBr, cm^{-1}): 3060, 2956, 2917, 2846, 1665, 1610, 1528, 1476, 1393, 1344, 1297, 1256, 1215, 1080, 1059, 1023, 971, 910, 768; HRMS (ESI) calcd for $C_{27}H_{17}N_3O_3$ (M + H^+) 432.1343, found 432.1336.

Methyl 4-(2-(3-phenylquinoxalin-2-yl)benzoyl)benzoate (1m):



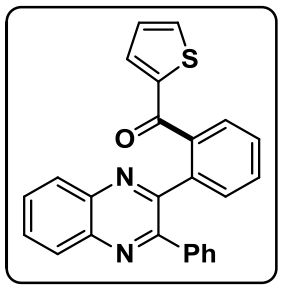
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 1H, J = 7.6 Hz), 7.93 (d, 1H, J = 7.2 Hz), 7.88 (d, 2H, J = 6.8 Hz), 7.69–7.64 (m, 2H), 7.61 (d, 1H, J = 7.6 Hz), 7.55 (t, 1H, J = 7.4 Hz), 7.41–7.31 (m, 6H), 7.19 (t, 1H, J = 7.0 Hz), 7.09 (t, 2H, J = 7.0 Hz), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 166.4, 155.2, 153.5, 153.4, 141.5, 141.1, 141.0, 140.7, 138.6, 133.4, 131.9, 130.4, 130.2, 130.0, 129.9, 129.4, 129.3, 129.2, 128.9, 128.4, 128.2, 52.6; IR (KBr, cm^{-1}): 3058, 2949, 2840, 1723, 1661, 1476, 1435, 1404, 1344, 1274, 1104, 1056, 1018, 977, 931, 868, 798, 768; Anal. calcd for $C_{29}H_{20}N_2O_3$: C 78.36, H 4.54, N 6.30; found: C 78.51, H 4.63, N 6.42.

(4-Chloro-3-nitrophenyl)(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1n):



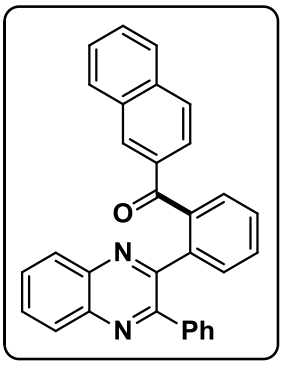
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, J = 6.8 Hz), 8.04 (d, 1H, J = 7.6 Hz), 7.78 (t, 1H, J = 7.0 Hz), 7.76–7.73 (m, 2H), 7.69 (t, 1H, J = 7.6 Hz), 7.61–7.57 (m, 2H), 7.49 (t, 2H, J = 6.8 Hz), 7.34–7.32 (m, 3H), 7.19 (t, 1H, J = 7.2 Hz), 7.12 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.9, 153.1, 147.4, 141.5, 141.1, 138.4, 137.0, 136.4, 133.6, 132.6, 132.3, 131.9, 131.3, 130.6, 130.5, 130.3, 129.5, 129.2, 129.1, 128.6, 128.5, 126.8; IR (KBr, cm^{-1}): 3060, 2926, 2851, 1728, 1664, 1596, 1535, 1390, 1344, 1294, 1273, 1246, 1047, 1023, 977, 949, 908, 770; HRMS (ESI) calcd for $C_{27}H_{16}ClN_3O_3$ (M + H$^+$) 466.0953, found 466.0949.

2-(3-Phenylquinoxalin-2-yl)phenyl)(thiophen-2-yl)methanone (1o):



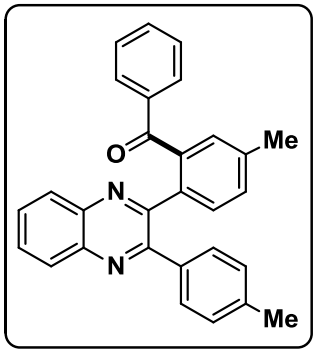
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.75–7.70 (m, 2H), 7.67 (d, 1H, J = 8.0 Hz), 7.62–7.56 (m, 3H), 7.46 (t, 1H, J = 7.4 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.13 (t, 1H, J = 6.6 Hz), 7.07 (d, 2H, J = 7.6 Hz), 7.03 (t, 1H, J = 3.6 Hz), 6.93 (t, 1H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2, 153.7, 153.5, 143.8, 141.5, 141.2, 140.5, 138.7, 138.3, 135.3, 134.4, 131.9, 131.5, 130.4, 130.1, 129.9, 129.5, 129.4, 129.3, 128.8, 128.2, 128.1, 127.8; IR (KBr, cm^{-1}): 3059, 2913, 2851, 1621, 1515, 1474, 1409, 1353, 1342, 1297, 1052, 1023, 976, 845, 760; HRMS (ESI) calcd for $C_{25}H_{16}N_2OS$ (M + H$^+$) 393.1056, found 393.1051.

Naphthalen-2-yl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1p):



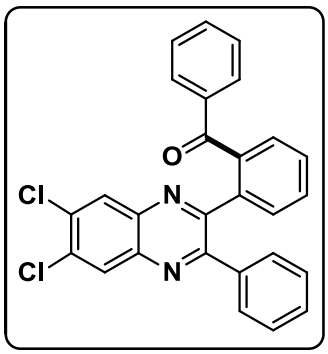
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 1H, J = 6.4 Hz), 7.99 (d, 1H, J = 7.6 Hz), 7.82 (d, 1H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.4 Hz), 7.74 (s, 1H), 7.72–7.66 (m, 3H), 7.65–7.59 (m, 2H), 7.56 (t, 1H, J = 7.4 Hz), 7.52–7.46 (m, 3H), 7.42 (d, 2H, J = 6.8 Hz), 7.13–7.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 153.9, 153.5, 141.4, 141.1, 139.1, 138.6, 135.4, 134.4, 132.3, 132.1, 131.7, 131.4, 130.4, 130.0, 129.8, 129.6, 129.4, 129.2, 128.9, 128.4, 128.2, 128.1, 127.8, 126.7, 125.3; IR (KBr, cm^{-1}): 3056, 2956, 2922, 2846, 1651, 1625, 1594, 1569, 1476, 1462, 1393, 1344, 1292, 1278, 1232, 1149, 1122, 1100, 1055, 1024, 977, 921, 905, 823, 789, 753; HRMS (ESI) calcd for $C_{31}H_{20}N_2O$ (M + H^+) 437.1648, found 437.1639.

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



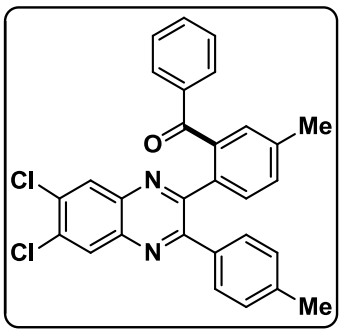
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, 1H, J = 8.4 Hz), 7.98 (d, 1H, J = 7.2 Hz), 7.71–7.64 (m, 2H), 7.55 (d, 1H, J = 7.6 Hz), 7.44–7.38 (m, 4H), 7.29–7.25 (m, 4H), 7.22 (s, 1H), 6.93 (d, 2H, J = 8.0 Hz), 2.39 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 153.7, 153.5, 141.3, 140.9, 138.8, 138.7, 138.2, 137.9, 137.1, 135.7, 132.4, 131.9, 131.5, 130.6, 130.3, 130.0, 129.7, 129.5, 129.2, 129.1, 128.9, 127.8, 21.3; IR (KBr, cm^{-1}): 3038, 2912, 1656, 1593, 1443, 1401, 1341, 1286, 1267, 1179, 1050, 996, 828, 779, 696; Anal. calcd for $C_{29}H_{22}N_2O$: C 84.03, H 5.35, N 6.76; found: C 84.15, H 5.42, N 6.85.

(2-(6,7-Dichloro-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (3a):



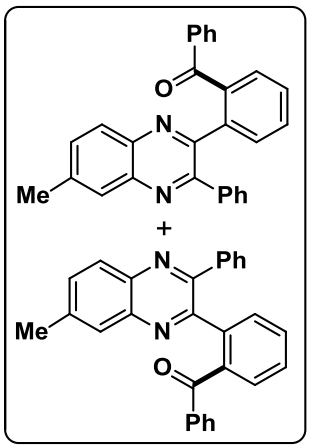
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 8.12 (s, 1H), 7.61–7.59 (m, 2H), 7.49 (d, 1H, J = 7.2 Hz), 7.47–7.45 (m, 2H), 7.41–7.39 (m, 4H), 7.31 (t, 2H, J = 7.6 Hz), 7.25 (t, 1H, J = 7.2 Hz), 7.16 (t, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 155.2, 154.6, 140.4, 140.1, 139.8, 138.7, 137.8, 136.9, 134.4, 134.2, 132.8, 131.5, 130.4, 130.3, 130.1, 129.9, 129.8, 129.3, 128.3, 128.1; IR (KBr, cm^{-1}): 3059, 2956, 2917, 2846, 1655, 1596, 1574, 1441, 1389, 1337, 1315, 1271, 1190, 1152, 1103, 1075, 1056, 1024, 962, 926, 881, 831, 763, 725; HRMS (ESI) calcd for $C_{27}H_{16}Cl_2N_2O$ (M + H^+) 455.0712, found 455.0709.

(2-(6,7-Dichloro-3-(*p*-tolyl)quinoxalin-2-yl)-5-methylphenyl)(phenyl)methanone (4a):



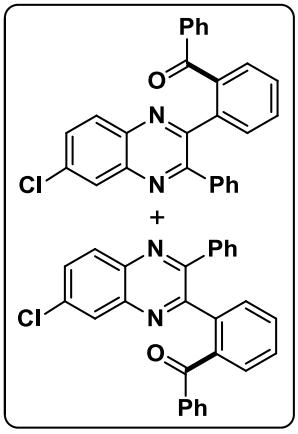
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 8.02 (s, 1H), 7.45 (d, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.34–7.30 (m, 3H), 7.23–7.16 (m, 5H), 6.68 (d, 2H, J = 7.6 Hz), 2.33 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 155.2, 154.7, 140.1, 139.8, 139.4, 138.8, 138.5, 137.7, 136.9, 135.1, 134.2, 133.9, 132.7, 132.2, 131.5, 130.9, 130.3, 130.1, 129.9, 129.8, 129.1, 127.9, 21.4; IR (KBr, cm^{-1}): 3054, 3027, 2920, 2846, 1736, 1655, 1596, 1447, 1386, 1336, 1315, 1293, 1270, 1210, 1182, 1105, 1050, 1020, 963, 880, 824, 800, 759, 715; HRMS (ESI) calcd for $C_{29}H_{20}Cl_2N_2O$ (M + H$^+$) 483.1025, found 483.1017.

(2-(6-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone and (2-(7-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (5a and 5a'):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, 1H, J = 8.8 Hz), 7.88-7.86 (m, 2H), 7.76 (s, 1H), 7.62–7.59 (m, 2H), 7.57–7.50 (m, 5H), 7.45–7.38 (m, 12H), 7.29–7.24 (m, 5H), 7.20 (d, 2H, J = 7.2 Hz), 7.15–7.12 (m, 4H), 2.56 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 153.5, 153.2, 152.7, 152.5, 141.3, 141.0, 140.9, 140.8, 140.4, 140.2, 139.8, 139.5, 138.8, 138.6, 137.1, 132.5, 132.3, 132.1, 131.6, 131.2, 130.2, 130.1, 129.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 21.9; IR (KBr, cm^{-1}): 3056, 3021, 2919, 2857, 1734, 1685, 1619, 1596, 1578, 1486, 1446, 1343, 1314, 1269, 1203, 1178, 1154, 1137, 1074, 1056, 1025, 979, 937, 925, 829, 805, 765, 753, 730; HRMS (ESI) calcd for $C_{28}H_{20}N_2O$ (M + H$^+$) 401.1648, found 401.1653.

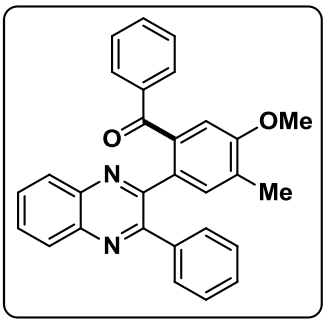
(2-(6-Chloro-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone and (2-(7-Chloro-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (6a and 6a'):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H), 7.99 (d, 1H, J = 9.2 Hz), 7.92 (s, 1H), 7.87 (d, 1H, J = 8.8 Hz), 7.61–7.58 (m, 2H), 7.56–7.49 (m, 4H), 7.42–7.37 (m, 6H), 7.34–7.30 (m, 7H), 7.23 (t, 4H, J = 7.6 Hz), 7.19–7.16 (m, 3H), 7.10–7.07 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 154.9, 154.3, 154.1, 153.6, 141.6, 141.3, 140.6, 139.9, 139.5, 138.7, 138.1, 138.0, 136.9, 135.6, 135.5, 132.7, 131.5, 131.4, 130.9, 130.8, 130.6, 130.3, 130.1, 129.1, 129.0, 128.3, 128.2, 128.0; IR (KBr, cm^{-1}): 3058, 2919, 1850, 1736, 1656, 1596, 1577, 1466, 1446, 1388, 1341, 1314, 1270, 1192, 1174, 1152,

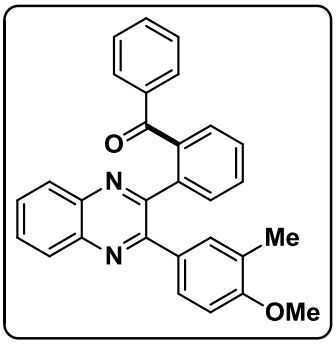
1067, 1025, 978, 926, 876, 833, 804, 763, 727; HRMS (ESI) calcd for $C_{27}H_{17}ClN_2O$ (M + H^+) 421.1102, found 421.1110.

(5-Methoxy-4-methyl-2(3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (7a):



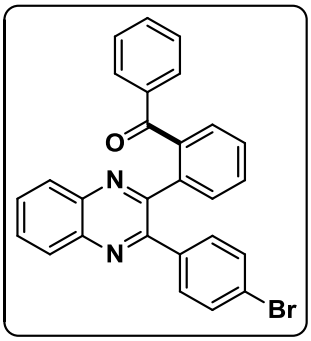
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09-8.05 (m, 2H), 7.72–7.67 (m, 2H), 7.52 (s, 1H), 7.38–7.31 (m, 6H), 7.21 (d, 2H, *J* = 7.6 Hz), 7.18–7.13 (m, 2H), 6.85 (s, 1H), 3.76 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 196.1, 157.3, 153.7, 153.6, 141.1, 141.0, 138.6, 137.4, 137.2, 133.7, 132.8, 132.3, 130.8, 130.3, 129.9, 129.7, 129.2, 128.9, 128.7, 128.2, 127.8, 111.8, 55.7, 16.5; IR (KBr, cm^{-1}): 3442, 3058, 2961, 2924, 2841, 1657, 1598, 1564, 1502, 1478, 1562, 1446, 1339, 1271, 1242, 1220, 1171, 1127, 1110, 1055, 1027, 1013, 968, 907, 872, 813, 766, 732; HRMS (ESI) calcd for $C_{29}H_{22}N_2O_2$ (M + H^+) 431.1759, found 431.1766.

(2-(3-(4-Methoxy-3-methylphenyl)quinoxalin-2-yl)phenyl)(phenyl)methanone (7a'):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 8.4 Hz), 7.78 (d, 1H, *J* = 7.2 Hz), 7.74–7.69 (m, 2H), 7.66 (t, 1H, *J* = 7.2 Hz), 7.47–7.43 (m, 3H), 7.36 (d, 2H, *J* = 7.2 Hz), 7.27 (d, 2H, *J* = 7.6 Hz), 7.16 (s, 1H), 7.07 (d, 1H, *J* = 8.4 Hz), 6.52 (d, 1H, *J* = 8.8 Hz), 3.76 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 195.7, 158.6, 153.9, 153.5, 141.6, 141.4, 141.0, 136.9, 132.9, 132.6, 131.8, 130.4, 130.2, 130.1, 129.9, 129.6, 129.5, 129.3, 129.2, 127.9, 127.8, 126.9, 109.5, 55.5, 16.1; IR (KBr, cm^{-1}): 3442, 3054, 2958, 2923, 2843, 1658, 1609, 1558, 1506, 1447, 1384, 1343, 1268, 1253, 1173, 1134, 1030, 927, 807, 765, 764, 737; HRMS (ESI) calcd for $C_{29}H_{22}N_2O_2$ (M + H^+) 431.1759, found 431.1764.

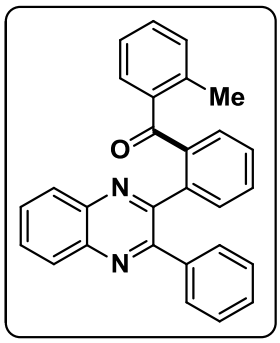
(2-(3-(4-Bromophenyl)quinoxalin-2-yl)phenyl)(phenyl)methanone (8a):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.12 (d, 1H, *J* = 8.4 Hz), 8.04 (d, 1H, *J* = 7.2 Hz), 7.76–7.69 (m, 2H), 7.69 (d, 1H, *J* = 7.8 Hz), 7.65–7.62 (m, 1H), 7.51 (t, 1H, *J* = 7.5 Hz), 7.49–7.43 (m, 3H), 7.41 (d, 2H, *J* = 7.8 Hz), 7.35 (t, 2H, *J* = 7.8 Hz), 7.28–7.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 196.4, 153.7, 152.4, 141.4, 141.3, 140.8, 137.5, 136.8, 132.9, 132.1, 131.8, 131.7, 131.5, 130.4, 130.3, 130.2, 130.1, 129.4, 129.3, 128.4, 128.2, 128.1, 123.8; IR (KBr, cm^{-1}): 3440, 3059, 2961, 2923, 2846, 1657, 1596, 1579, 1489, 1478, 1448, 1343, 1316, 1290, 1270, 1220, 1071, 1056, 1037, 1025, 1011, 977, 937, 927,

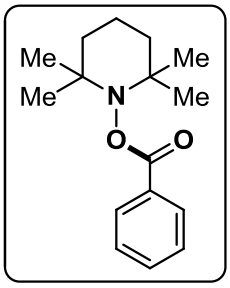
835, 807, 762, 733; HRMS (ESI) calcd for $C_{27}H_{17}BrN_2O$ (M + H^+) 465.0602, found 465.0608.

(2-(3-Phenylquinoxalin-2-yl)phenyl)(*o*-tolyl)methanone (1q):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 6.8 Hz), 8.00 (d, 1H, *J* = 6.4 Hz), 7.76–7.72 (m, 2H), 7.62–7.57 (m, 2H), 7.35–7.29 (m, 3H), 7.26–7.20 (m, 3H), 7.14 (d, 2H, *J* = 6.8 Hz), 7.00 (t, 2H, *J* = 7.2 Hz), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 198.3, 154.4, 153.4, 141.3, 141.0, 140.9, 139.2, 138.8, 138.2, 137.5, 131.8, 131.7, 131.5, 131.0, 130.8, 130.3, 129.9, 129.7, 129.3, 129.1, 128.7, 128.3, 128.2, 124.8, 20.2; IR (KBr, cm^{-1}): 3049, 2961, 2921, 2851, 1742, 1659, 1593, 1563, 1454, 1342, 1297, 1260, 1215, 1098, 1025, 977, 927, 802, 763, 731; HRMS (ESI) calcd for $C_{28}H_{20}N_2O$ (M + H^+) 401.1648, found 401.1642.

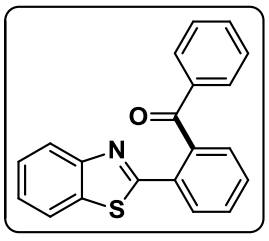
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (1A):



Gummy 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, $CDCl_3$): δ 166.6, 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^+) 262.1802; found 262.1801.

➢ IIB.6.

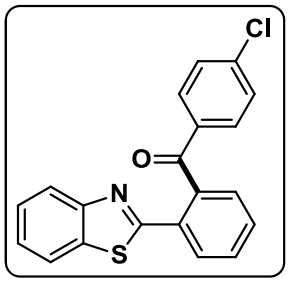
2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1´a´):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.93 (d, 1H, *J* = 7.2 Hz), 7.79–7.75 (m, 4H), 7.65–7.58 (m, 2H), 7.54 (d, 1H, *J* = 6.8 Hz), 7.40–7.33 (m, 2H), 7.31–7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 197.8, 165.4, 153.6, 139.9, 137.9, 135.5, 132.8, 132.3, 130.5, 130.4, 129.8, 129.4, 129.0, 128.4, 126.3, 125.5, 123.6, 121.6; IR (KBr, cm^{-1}): 3055, 3024, 2921, 2853, 1665, 1594, 1579, 1501, 1450, 1426, 1311, 1268, 1243, 1227, 1146, 970, 924, 752, 726; HRMS (ESI) calcd for $C_{20}H_{13}NOS$ (M + H^+) 316.0797, found 316.0806.

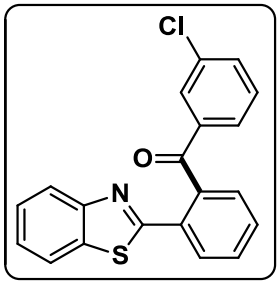
(2-(Benzo[*d*]thiazol-2-yl)phenyl)(4-chlorophenyl)methanone (1´b´):

Solid; M.p. 134.5 ^{o}C–137 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.91 (d, 1H, *J* = 7.6 Hz), 7.78–7.75 (m, 2H), 7.69 (d, 2H, *J* = 8.4 Hz), 7.64–7.57 (m, 2H), 7.50 (d, 1H, *J* = 6.8 Hz), 7.36 (t,



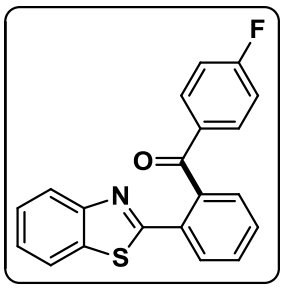
1H, *J* = 7.6 Hz), 7.31 (t, 1H, *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 165.2, 153.5, 139.3, 139.1, 136.4, 135.3, 132.0, 130.6, 130.5, 129.8, 128.9, 128.7, 126.4, 125.6, 123.5, 121.6; IR (KBr, cm^{-1}): 3087, 3051, 2916, 2846, 1670, 1585, 1570, 1489, 1429, 1402, 1315, 1304, 1288, 1264, 1241, 1183, 1152, 1091, 1013, 968, 935, 924, 854, 844, 760, 752, 742, 726; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ ($M + H^+$) 350.0408, found 350.0417.

(2-(Benzo[*d*]thiazol-2-yl)phenyl)(3-chlorophenyl)methanone (1´c´):



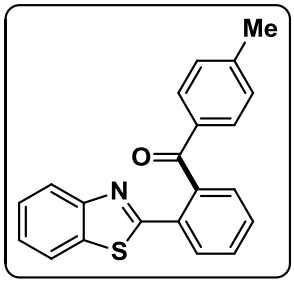
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, 1H, *J* = 6.8 Hz), 7.79–7.74 (m, 3H), 7.64–7.57 (m, 3H), 7.53 (d, 1H, *J* = 6.8 Hz), 7.36 (t, 1H, *J* = 7.6 Hz), 7.32–7.28 (m, 2H), 7.19 (t, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 165.2, 153.5, 139.7, 139.0, 135.3, 134.6, 132.6, 132.1, 130.7, 130.6, 129.8, 129.7, 129.1, 129.0, 127.3, 126.4, 125.7, 123.5, 121.6; IR (KBr, cm^{-1}): 3052, 2921, 2844, 1669, 1569, 1432, 1290, 1281, 1256, 1242, 1158, 1074, 971, 967, 775, 766, 753, 732, 725; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ ($M + H^+$) 350.0408, found 350.0413.

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



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 8.0 Hz), 7.81–7.76 (m, 4H), 7.66–7.59 (m, 2H), 7.53 (d, 1H, *J* = 7.6 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 7.31 (t, 1H, *J* = 7.8 Hz), 6.96 (t, 2H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 196.3, 165.5 (d, $^1J_{C\text{-}F}$ = 253 Hz), 165.3, 153.6, 139.6, 135.4, 134.49, 134.47, 132.2, 131.9 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 130.6, 130.5, 129.9, 128.9, 126.4, 125.6, 123.6, 121.6, 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz); IR (KBr, cm^{-1}): 3058, 2959, 2927, 2850, 1661, 1597, 1502, 1455, 1429, 1411, 1294, 1255, 1239, 1226, 1145, 968, 929, 858, 767, 761, 727; HRMS (ESI) calcd for $C_{20}H_{12}FNOS$ ($M + H^+$) 334.0703, found 334.0709.

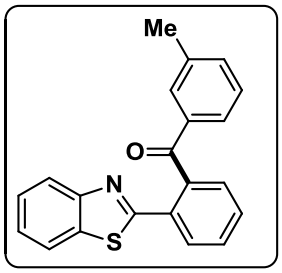
(2-(Benzo[*d*]thiazol-2-yl)phenyl)(p-tolyl)methanone (1´e´):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.63–7.56 (m, 2H), 7.49 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.29 (t, 1H, *J* = 7.6 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, 140.1, 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, 21.9; IR (KBr, cm^{-1}): 3060, 3025, 2921, 2852, 1660, 1603, 1518, 1453,

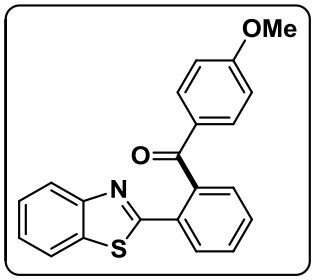
1431, 1308, 1300, 1269, 1227, 1179, 1151, 969, 957, 928, 855, 785, 770, 761, 742, 731; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ (M + H^+) 330.0954, found 330.0961.

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



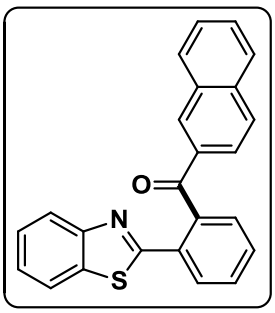
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 8.0 Hz), 7.82–7.77 (m, 2H), 7.65–7.57 (m, 3H), 7.53–7.51 (m, 2H), 7.36 (t, 1H, *J* = 7.2 Hz), 7.29 (t, 1H, *J* = 7.2 Hz), 7.21–7.14 (m, 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 197.9, 165.6, 153.7, 140.1, 138.2, 137.9, 135.6, 133.7, 132.3, 130.4, 130.3, 129.91, 129.87, 129.0, 128.3, 126.9, 126.3, 125.5, 123.6, 121.6, 21.4; IR (KBr, cm^{-1}): 3095, 3059, 2920, 2856, 1668, 1558, 1455, 1432, 1278, 1228, 1207, 1082, 967, 761, 728; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ (M + H^+) 330.0954, found 330.0966.

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



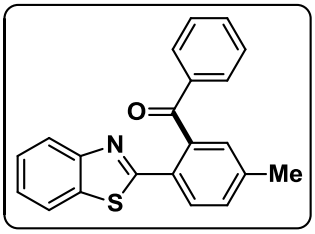
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 1H, *J* = 7.2 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.78–7.74 (m, 3H), 7.62–7.54 (m, 2H), 7.48 (d, 1H, *J* = 7.2 Hz), 7.36 (t, 1H, *J* = 7.8 Hz), 7.29 (d, 1H, *J* = 7.6 Hz), 6.78 (d, 2H, *J* = 8.8 Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 165.6, 163.5, 153.7, 140.2, 135.6, 132.9, 132.1, 131.9, 130.8, 130.3, 129.9, 128.7, 126.3, 125.4, 123.6, 121.5, 113.7, 55.5; IR (KBr, cm^{-1}): 3078, 3057, 2963, 2928, 2831, 1652, 1600, 1575, 1509, 1418, 1302, 1261, 1226, 1175, 1150, 1029, 970, 928, 850, 772, 764, 750; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ (M + H^+) 346.0903, found 346.0910.

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



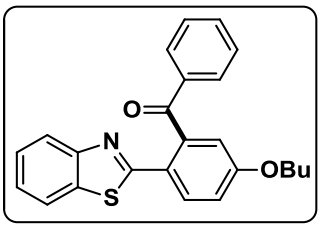
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 8.05 (d, 1H, *J* = 8.8 Hz), 7.97 (d, 1H, *J* = 7.2 Hz), 7.79 (d, 1H, *J* = 8.8 Hz), 7.76–7.74 (m, 3H), 7.69 (d, 1H, *J* = 7.6 Hz), 7.66–7.61 (m, 2H), 7.59–7.56 (m, 1H), 7.48 (t, 1H, *J* = 7.4 Hz), 7.41 (t, 1H, *J* = 7.6 Hz), 7.28 (t, 1H, *J* = 7.6 Hz), 7.21 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.8, 165.4, 153.6, 139.9, 135.54, 135.49, 135.4, 132.4, 132.2, 131.5, 130.5, 130.3, 129.9, 129.7, 128.9, 128.5, 127.9, 126.7, 126.3, 125.4, 124.9, 123.6, 121.5; IR (KBr, cm^{-1}): 3056, 2924, 2852, 1663, 1626, 1593, 1505, 1465, 1431, 1352, 1298, 1285, 1232, 1198, 1149, 1121, 967, 919, 871, 826, 789, 763, 753, 729; HRMS (ESI) calcd for $C_{24}H_{15}NOS$ (M + H^+) 366.0954, found 366.0955.

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



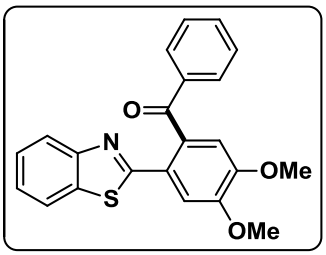
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, 1H, J = 8.0 Hz), 7.69–7.66 (m, 4H), 7.33 (d, 1H, J = 8.0 Hz), 7.29–7.25 (m, 2H), 7.23–7.18 (m, 4H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 165.6, 153.5, 141.1, 139.7, 137.9, 135.3, 132.8, 131.0, 129.7, 129.5, 129.4, 129.3, 128.6, 126.2, 125.3, 123.4, 121.5, 21.6; IR (KBr, cm^{-1}): 3059, 3020, 2916, 2846, 1669, 1597, 1472, 1449, 1431, 1315, 1288, 1256, 1256, 1209, 1075, 975, 957, 826, 757, 730; HRMS (ESI) calcd for $C_{21}H_{15}NOS$ (M + H$^+$) 330.0954, found 330.0963.

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



Solid; M.p. 128.7 ^{o}C–132.3 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, 1H, J = 8.8 Hz), 7.79–7.77 (m, 2H), 7.73 (t, 2H, J = 8.8 Hz), 7.38 (t, 1H, J = 7.4 Hz), 7.34–7.23 (m, 4H), 7.11 (dd, 1H, J_1 = 2.6 Hz, J_2 = 6.0 Hz), 7.01 (d, 1H, J = 2.8 Hz), 4.05 (t, 2H, J = 6.6 Hz), 1.84–1.77 (m, 2H), 1.56–1.46 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 165.3, 160.9, 153.7, 141.4, 137.8, 135.2, 132.9, 131.3, 129.4, 128.4, 126.2, 125.1, 124.4, 123.2, 121.4, 116.5, 114.5, 68.4, 31.3, 19.4, 14.0; IR (KBr, cm^{-1}): 2963, 2944, 2927, 2870, 1672, 1605, 1595, 1567, 1516, 1482, 1472, 1451, 1437, 1414, 1311, 1294, 1224, 1180, 1112, 1074, 1043, 972, 953, 856, 841, 824, 810, 762, 730; HRMS (ESI) calcd for $C_{24}H_{21}NO_2S$ (M + H$^+$) 388.1372, found 388.1379.

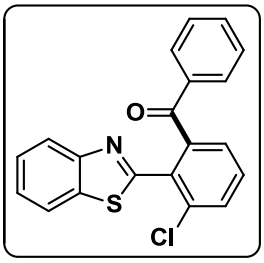
(2-(Benzo[*d*]thiazol-2-yl)-4,5-dimethoxyphenyl)(phenyl)methanone (4´a´):



Solid; M.p. 186 ^{o}C–188.4 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, 1H, J = 8.0 Hz), 7.75–7.71 (m, 3H), 7.39 (s, 1H), 7.36–7.30 (m, 2H), 7.27–7.22 (m, 3H), 7.07 (s, 1H), 4.04 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 165.4, 153.5, 150.6, 150.3, 138.1, 135.5, 132.8, 132.7, 129.3, 128.3, 126.2, 125.7, 125.2, 123.2, 121.4, 111.9, 56.5, 56.4; IR (KBr, cm^{-1}): 3048, 2999, 2955, 2924, 2846, 1653, 1597, 1573, 1521, 1501, 1458, 1430, 1381, 1353, 1290, 1274, 1240, 1174, 1119, 1008, 969, 897, 865, 832, 784, 762, 722; HRMS (ESI) calcd for $C_{22}H_{17}NO_3S$ (M + H$^+$) 376.1009, found 376.1003.

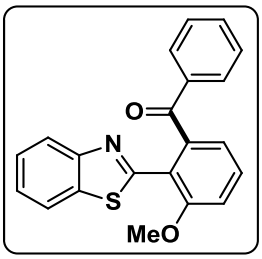
(2-(Benzo[*d*]thiazol-2-yl)-3-chlorophenyl)(phenyl)methanone (5´a´):

Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.69–7.64 (m, 3H), 7.54–7.47 (m, 2H), 7.39–7.29 (m, 3H), 7.24 (t, 2H, J = 7.6 Hz); ^{13}C NMR



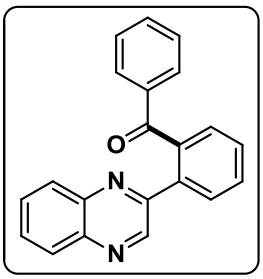
($CDCl_3$, 100 MHz): δ 195.9, 162.2, 152.3, 143.0, 137.1, 136.4, 134.3, 132.9, 132.1, 131.9, 130.7, 129.5, 128.3, 127.6, 126.2, 125.7, 123.7, 121.4; IR (KBr, cm^{-1}): 3057, 2925, 2847, 1670, 1595, 1559, 1416, 1317, 1281, 1236, 1196, 1141, 968, 953, 798, 769, 758, 749, 729; HRMS (ESI) calcd for $C_{20}H_{12}ClNOS$ (M + H^+) 350.0408, found 350.0415.

(2-(Benzo[*d*]thiazol-2-yl)-3-methoxyphenyl)(phenyl)methanone (6´a´):



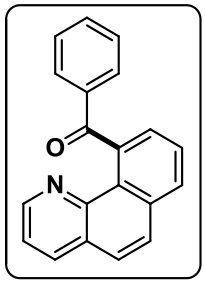
Solid; M.p. 145.4 °C–147.6 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77–7.68 (m, 4H), 7.53 (t, 1H, *J* = 8.0 Hz), 7.32–7.27 (m, 2H), 7.24–7.21 (m, 3H), 7.16 (d, 1H, *J* = 8.4 Hz), 7.12 (d, 1H, *J* = 8.4 Hz), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 160.5, 157.2, 151.5, 142.4, 138.3, 136.0, 132.2, 131.4, 128.8, 128.2, 125.8, 125.0, 123.0, 121.2, 121.1, 120.9, 112.8, 56.2; IR (KBr, cm^{-1}): 3049, 3025, 2984, 2944, 2842, 1669, 1575, 1576, 1449, 1425, 1316, 1303, 1288, 1267, 1161, 974, 956, 834, 782, 760, 744, 734, 724; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ (M + H^+) 346.0903, found 346.0914.

Phenyl(2-(quinoxalin-2-yl)phenyl)methanone (7´a´):



Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 9.11 (s, 1H), 7.99 (d, 1H, *J* = 8.4 Hz), 7.98 (d, 1H, *J* = 7.8 Hz), 7.78–7.75 (m, 3H), 7.71 (t, 1H, *J* = 6.6 Hz), 7.68–7.62 (m, 4H), 7.36 (t, 1H, *J* = 7.6 Hz), 7.26 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 197.9, 151.6, 144.3, 141.6, 141.1, 140.5, 138.0, 136.9, 132.8, 130.7, 130.4, 130.1, 129.8, 129.7, 129.6, 129.4, 129.3, 129.1, 128.4; IR (KBr, cm^{-1}): 3060, 2921, 2849, 1660, 1594, 1579, 1449, 1312, 1286, 1250, 1125, 1037, 957, 937, 923, 769, 753, 706; HRMS (ESI) calcd for $C_{21}H_{14}N_2O$ (M + H^+) 311.1186, found 311.1192.

Benzo[*h*]quinolin-10-yl(phenyl)methanone (8´a´):

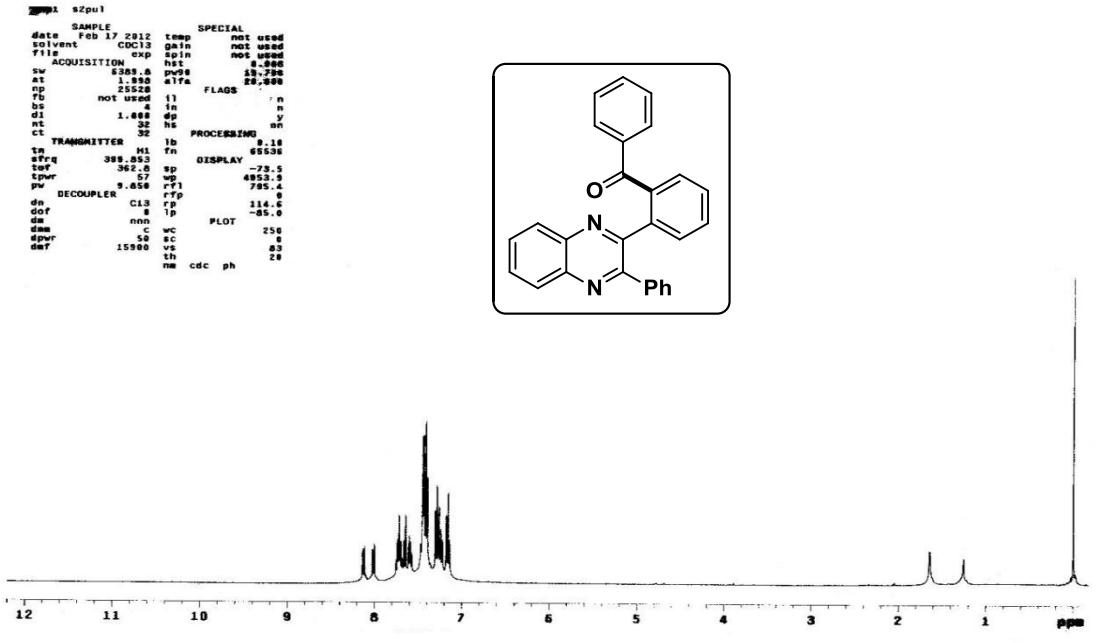


Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.50 (d, 1H, *J* = 3.6 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 7.90 (d, 1H, *J* = 9.0 Hz), 7.79 (t, 1H, *J* = 7.6 Hz), 7.75–7.74 (m, 3H), 7.63 (d, 1H, *J* = 7.2 Hz), 7.41 (t, 1H, *J* = 7.2 Hz), 7.34–7.32 (m, 1H), 7.29 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.9, 147.3, 144.8, 139.4, 139.1, 135.5, 133.9, 131.9, 129.3, 129.2, 128.9, 128.3, 127.98, 127.92, 127.2, 126.6, 126.3, 121.9; IR (KBr, cm^{-1}): 3055, 3028, 2919, 2847, 1673, 1578, 1510, 1450, 1421, 1405, 1315, 1296, 1274, 1212, 1198, 1175, 1138, 1005, 927, 891, 840, 793, 775, 759, 732; HRMS (ESI) calcd for $C_{20}H_{13}NO$ (M + H^+) 284.1077, found 284.1074.

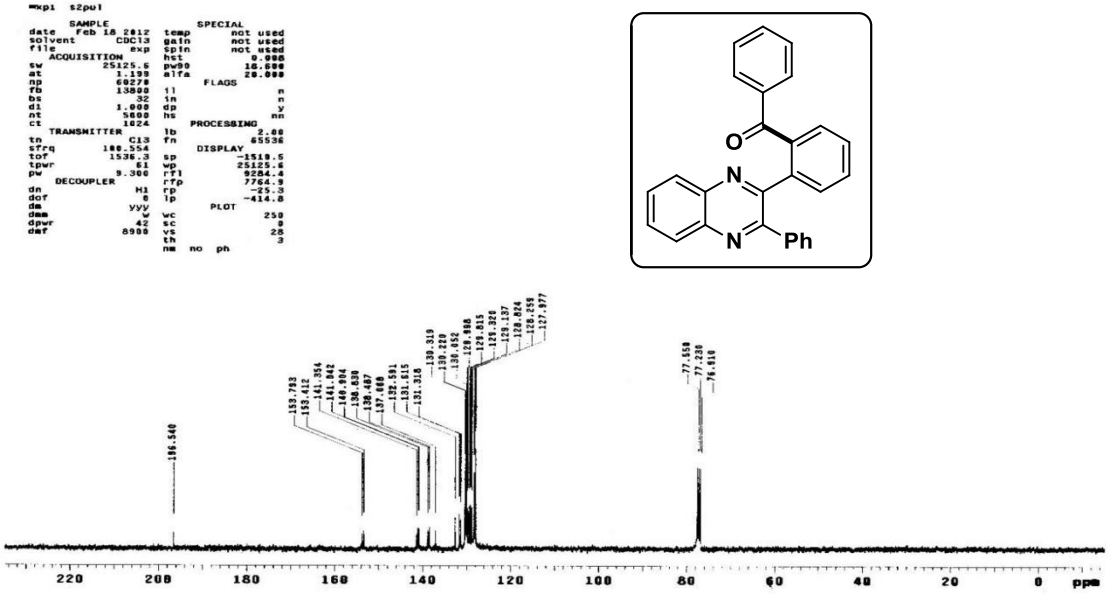
II.7. Spectra

➢ IIA.7.

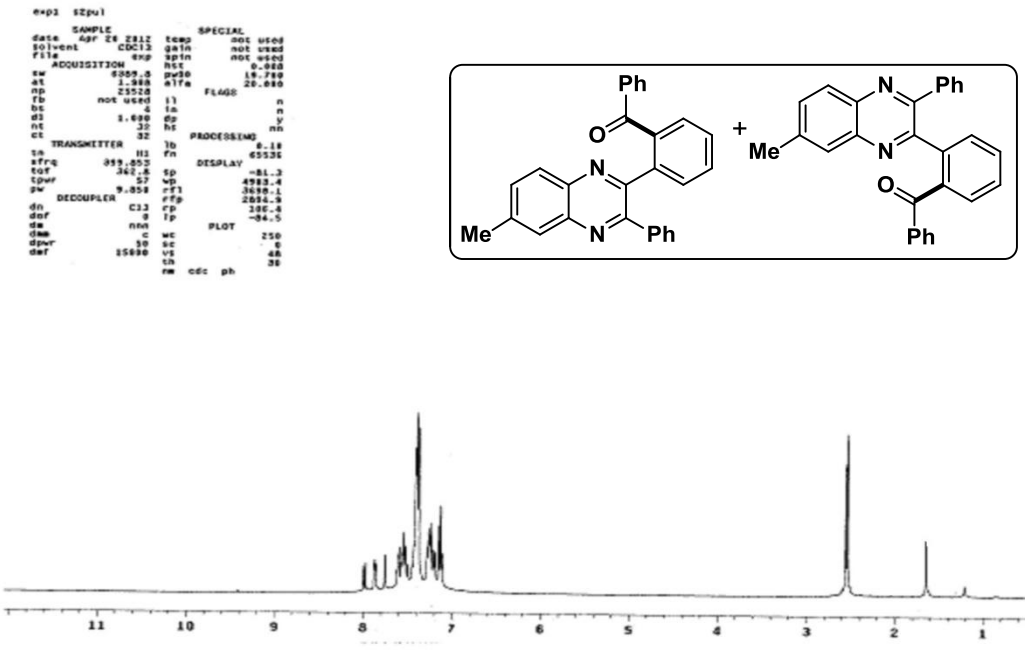
Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



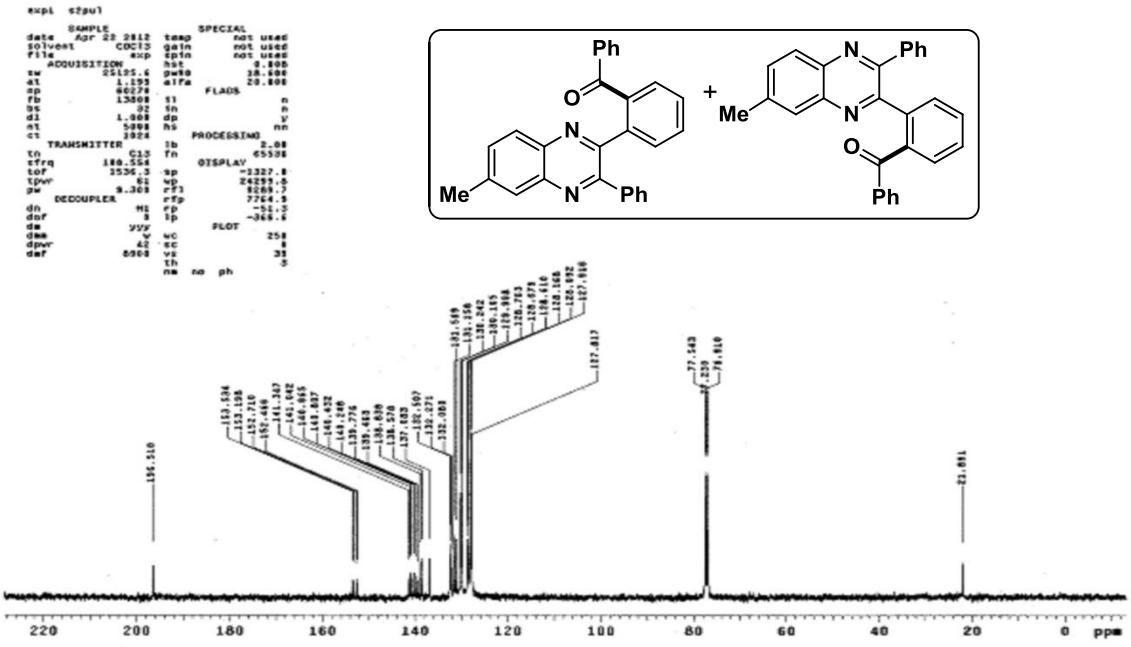
Phenyl(2-(3-phenylquinoxalin-2-yl)phenyl)methanone (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



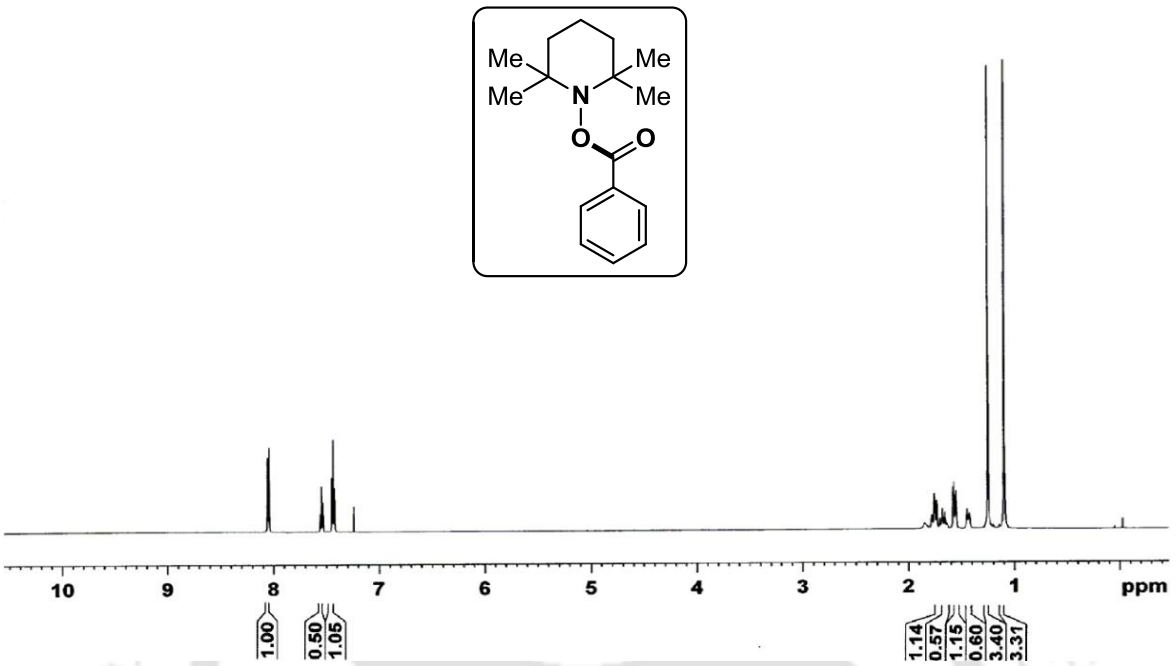
(2-(6-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone and (2-(7-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (5a and 5a'): ^{1}H NMR (400 MHz, $CDCl_3$)



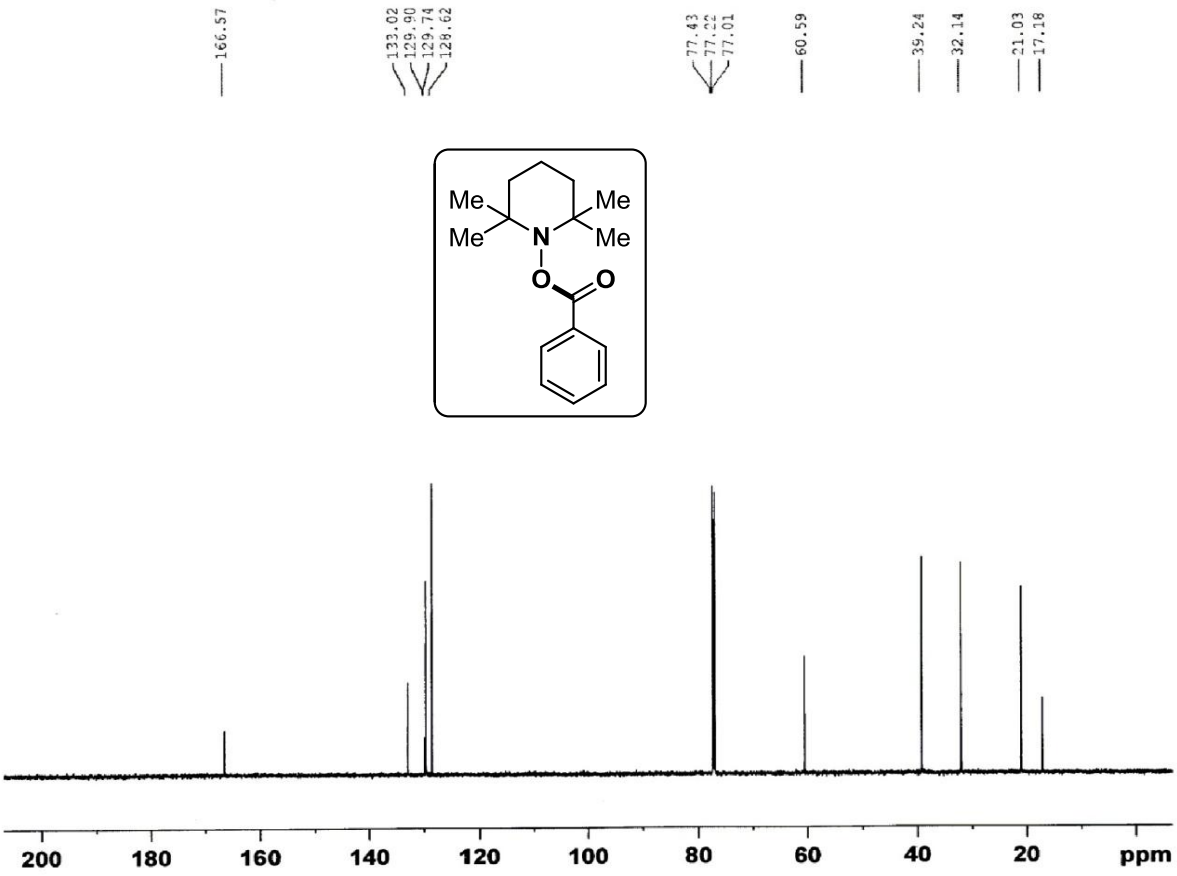
(2-(6-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone and (2-(7-Methyl-3-phenylquinoxalin-2-yl)phenyl)(phenyl)methanone (5a and 5a'): ^{13}C NMR (100 MHz, $CDCl_3$)



2,2,6,6-Tetramethylpiperidin-1-yl benzoate (1A): ^{1}H NMR (600 MHz, $CDCl_3$)

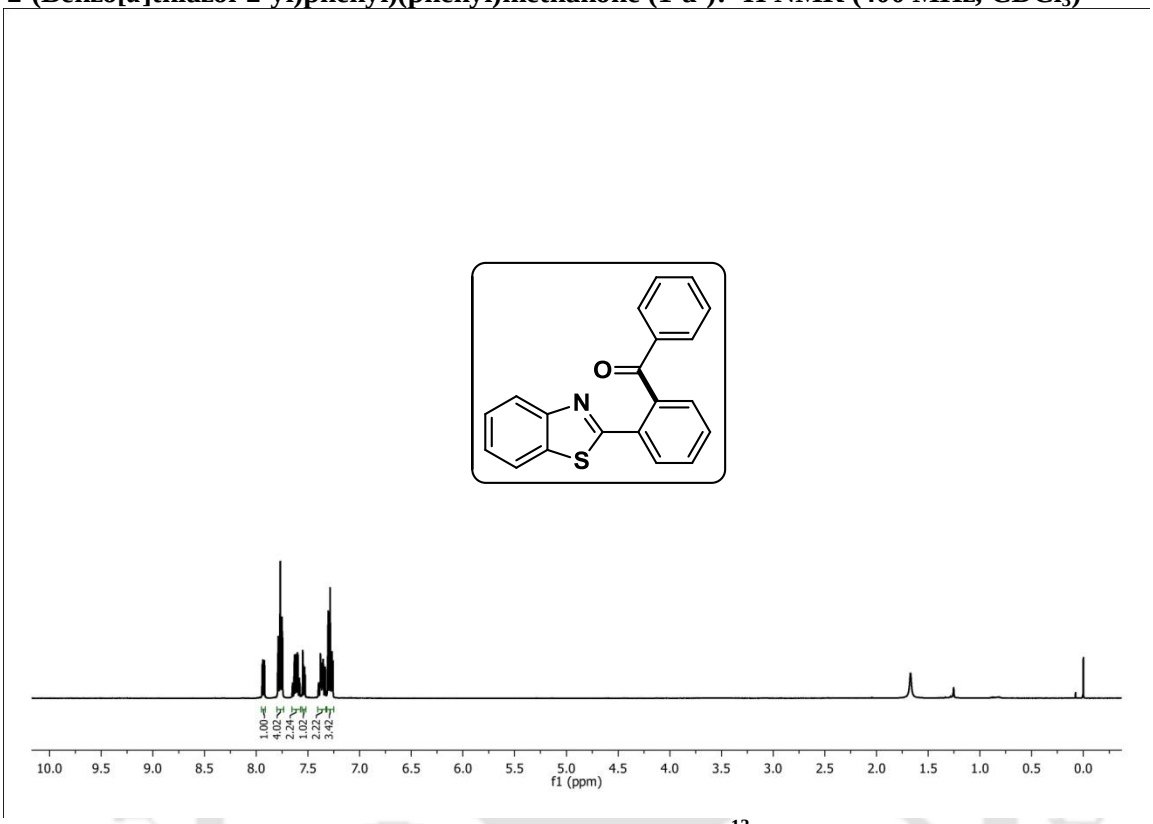


2,2,6,6-Tetramethylpiperidin-1-yl benzoate (1A): ^{13}C NMR (150 MHz, $CDCl_3$)

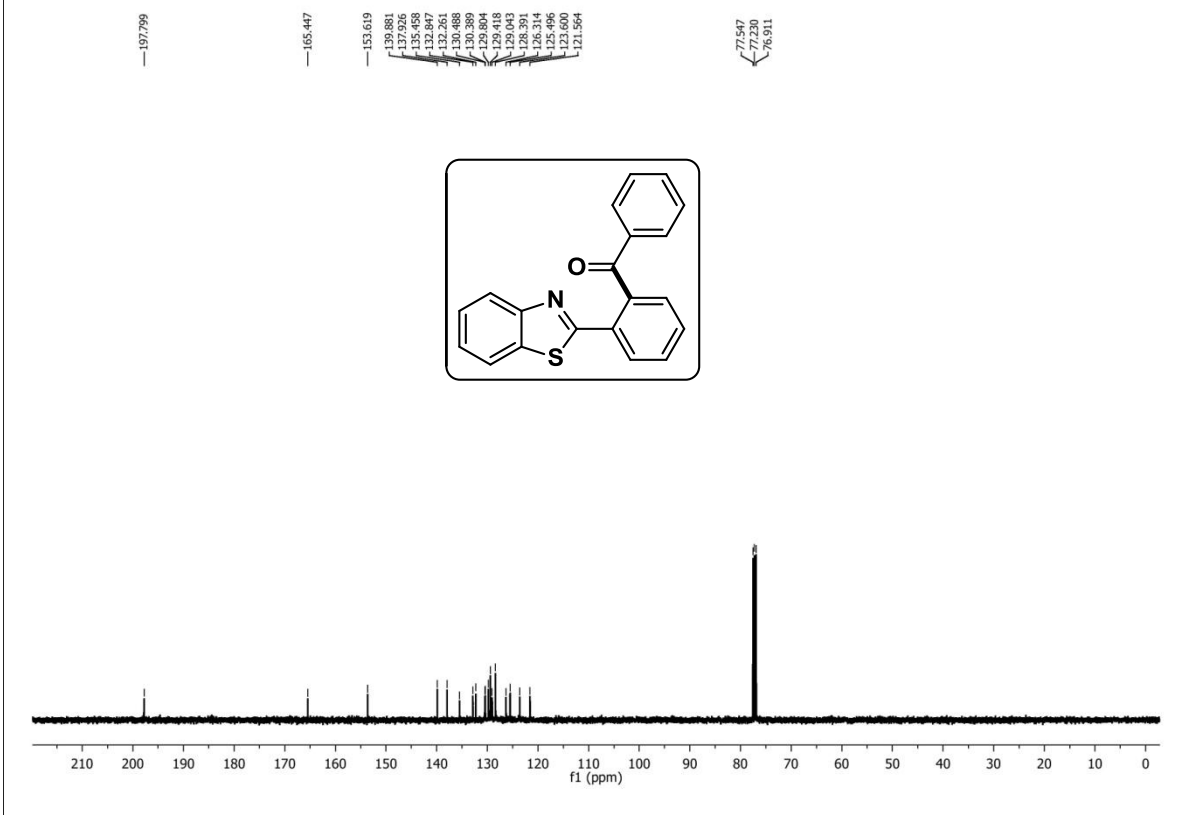


➢ IIB.7.

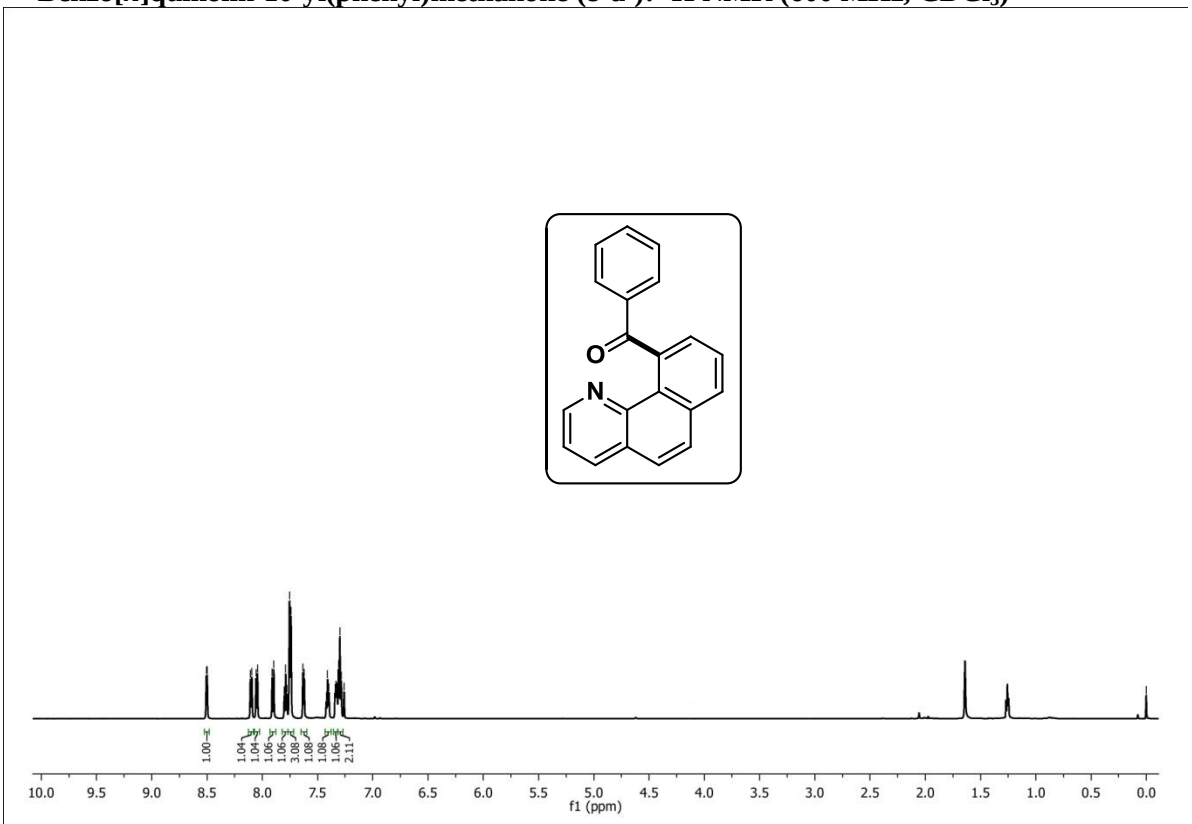
2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1´a´): ^{1}H NMR (400 MHz, $CDCl_3$)



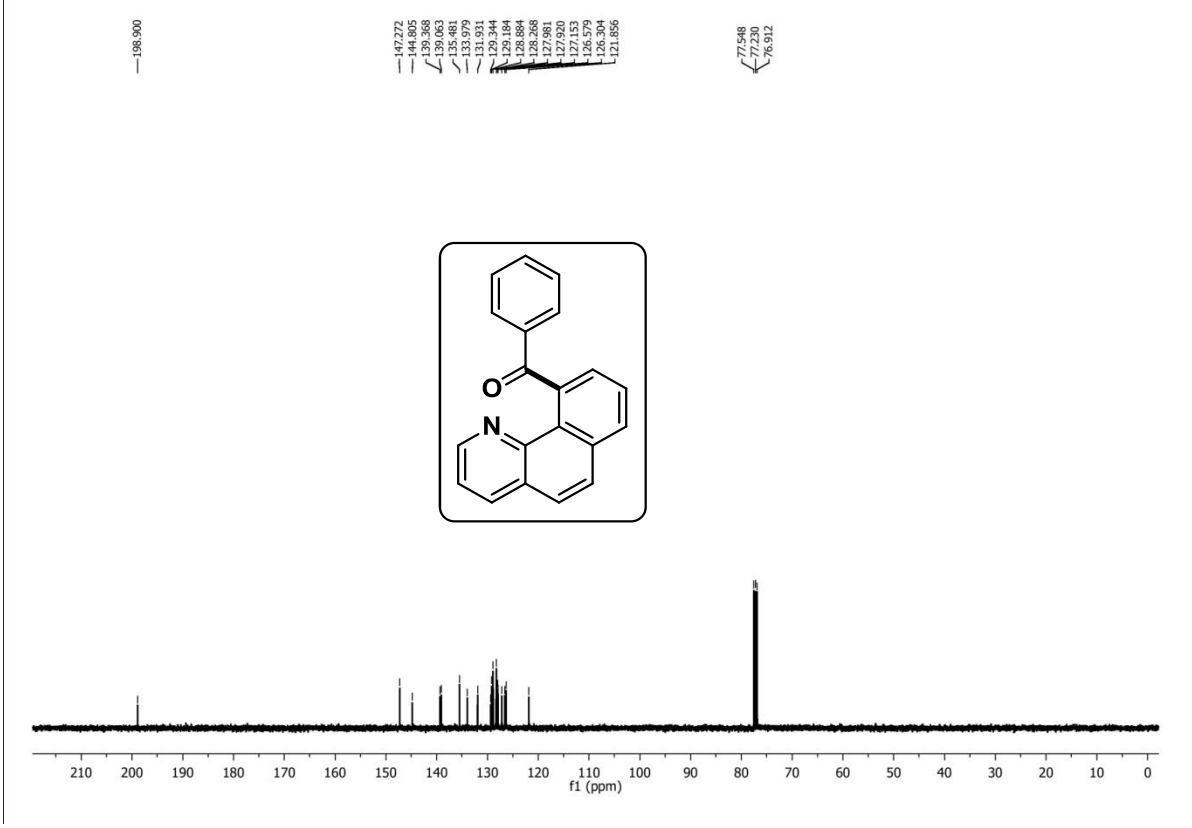
2-(Benzo[*d*]thiazol-2-yl)phenyl)(phenyl)methanone (1´a´): ^{13}C NMR (100 MHz, $CDCl_3$)



Benzo[*h*]quinolin-10-yl(phenyl)methanone (8´a´): ^{1}H NMR (600 MHz, $CDCl_3$)

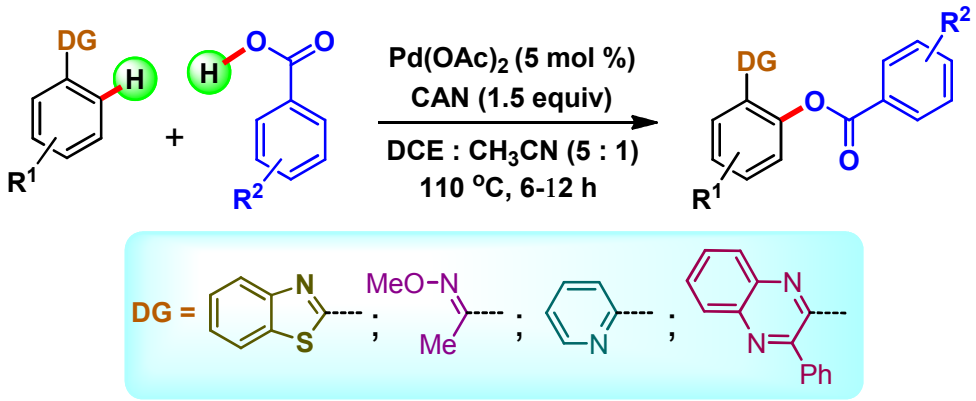


Benzo[*h*]quinolin-10-yl(phenyl)methanone (8´a´): ^{13}C NMR (100 MHz, $CDCl_3$)



Chapter III

Ceric Ammonium Nitrate (CAN) Promoted Palladium(II) Catalyzed Substrate Directed ortho-Benzoxylation



Abstract: *Inexpensive ceric ammonium nitrate (CAN) is an efficient oxidant for the Pd-catalyzed substrate directed o-benzoxylation process. In presence of CAN, the reaction of directing arenes with carboxylic acids resulted in o-benzoxylated products. Mechanistic investigations revels a Pd(II)/Pd(III) catalytic pathway for this process.*

CHAPTER III

III. Ceric Ammonium Nitrate (CAN) Promoted Pd(II)-Catalyzed Substrate Directed *o*-Benzoxylation

III.1. Introduction

The C–O bond formation reaction that proceeds through a C–H bond functionalization to give an ester has led to resurgence in transition metal catalyzed reactions.[1] In this context; directing[2] and nondirecting[3] cross-dehydrogenative coupling (CDC) reactions are the most preferred approaches because of their step and atom economy. In addition to carboxylic acids,[1b,2a-c,e] aroyl peroxides,[1c] acid chlorides,[1g] acid anhydrides,[1k] aldehydes,[2d] alkylbenzenes,[2d] terminal alkenes[1h] and terminal alkynes[1h] have been employed as *o*-benzoxy surrogates. A carboxylic acid has the propensity to form a metal complex, thereby rendering the metal inactive and inhibiting the progress of a reaction. To overcome this problem, a modified carboxylate source such as $PhI(OCOR)_2$ have been employed by Sanford[1a] as well as others.[1b] The combinations of $AgSbF_6/(NH_4)_2S_2O_8$,[2a-b] CuI/Ag_2CO_3,[2c] and $P(Cy)_3{\cdot}HBF_4/CuI$[2e] along with metal catalysts such as Ru, Pd and Rh have, in part, obviated the problem associated with their direct use. No doubt these modifications have improved the yields, but they are economically unviable. Thus, the lack of a cost-effective and generalized strategy for an *o*-benzoxylation that involves a range of directing groups leaves an ample opportunity to devise an alternative approach.

A typical substrate directed transition metal catalyzed *o*-benzoxylation proceeds through a cyclometallation, oxidative addition, or ligand exchange, followed by a reductive elimination. For a ligand exchange path, the metal is in its reduced state and needs to be re-oxidized to maintain the catalytic cycle, which is often done with the aid of stoichiometric amount of sacrificial terminal oxidants or other additives. Ceric ammonium nitrate (CAN), a one-electron oxidant, has been employed for various functional group transformations[4] and in the synthesis of heterocycles.[5] In spite of its immense applications as an oxidizing agent, its use as a terminal oxidant in palladium catalyzed processes is completely unexplored. In continuation to our efforts with regard to transition metal catalyzed substrate directed C–H functionalizations,[1h,6] we have explore the use of CAN as a terminal oxidant. The reduction potential of well-known oxidants that are used for decarboxylative *o*-

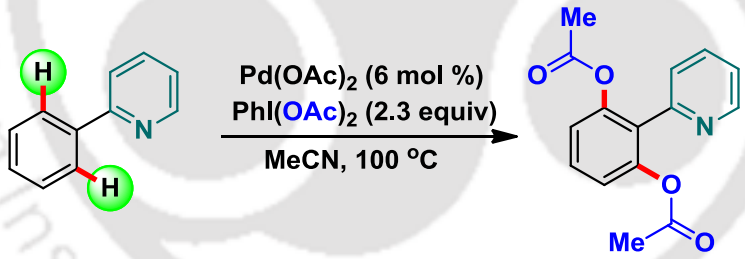
aroylation and *o*-benzoxylation reactions are +0.80 V for Ag(I)/Ag(0) and +2.01 V for $S_2O_8^{2-}/SO_4^{2-}$. In comparison, the reduction potential of Ce(IV)/Ce(III) is +1.61 V, which is in between Ag(I)/Ag(0) and $S_2O_8^{2-}/SO_4^{2-}$. Thus, Ce(IV)/Ce(III) is moderately oxidizing in nature, and as a single electron oxidant, it may be capable of forming a carboxy radical from a carboxylic acid.

III.2. Strategies for *ortho*-Carboxylation

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

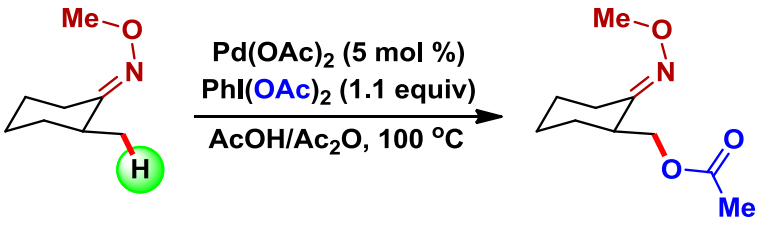
➢ **C–H Acetoxylation**

Sanford group reported the first example of Pd-catalyzed ligand directed sp^2 C–H acetoxylation using $PhI(OAc)_2$ (DIB) as a stoichiometric amount of reagent (Scheme III.2.1).[1s] DIB plays a dual role of oxidant and the source of acetoxy group. Other nitrogen-based directing groups *viz.* oxime ethers, azobenzene derivatives, nitrogen heterocycles (e.g., pyrazoles and isoxazolines) and even amides were also successfully *o*-functionalized. Besides this DIB other hypervalent iodine or peroxide oxidants have also been applied towards acetoxylation reactions.[1q,1v]



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

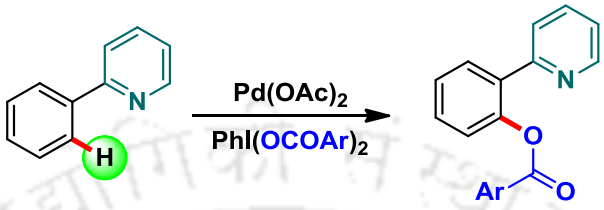
The same group also developed a Pd-catalyzed ligand-directed sp^3 C–H acetoxylation of ketoxime ether using hypervalent iodine oxidant DIB (Scheme III.2.2).[1s,1w]



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

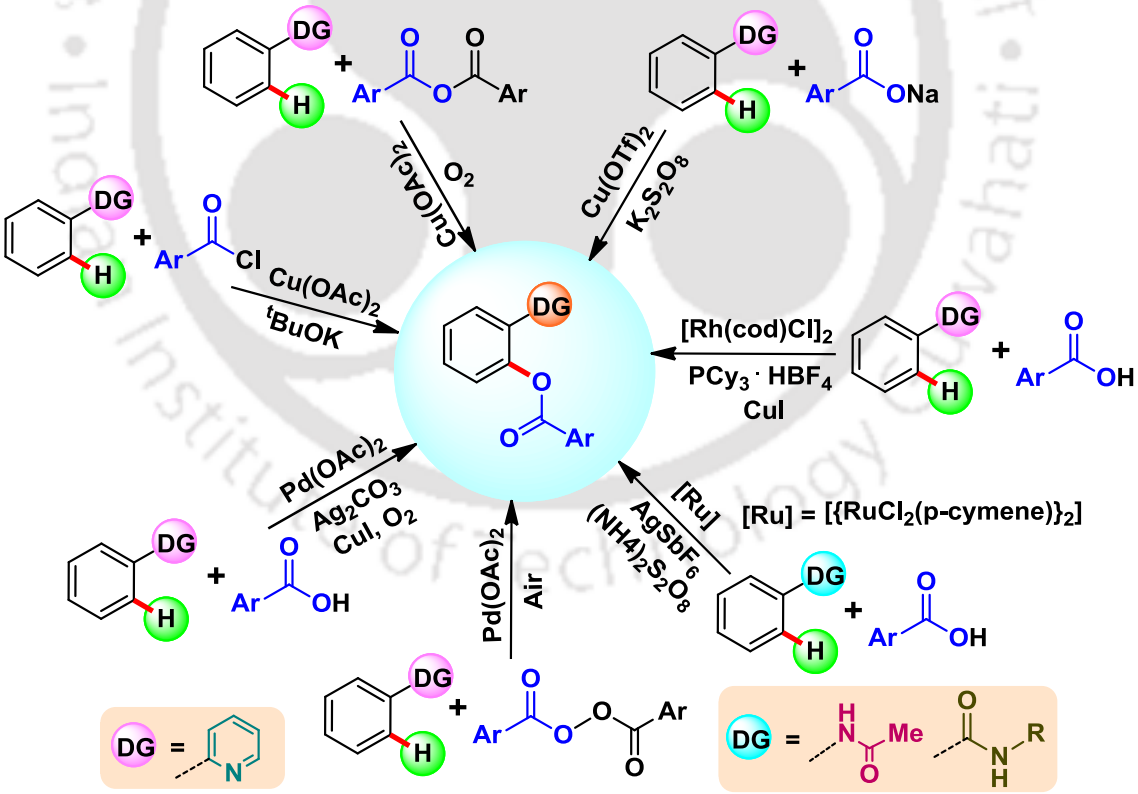
➢ **C–H Benzoxylation**

o-Benzoxylation of 2-phenylpyridines has been achieved by Sanford *et al.* using hypervalent benzoate iodonium salts as the ArCOO– surrogates. (Scheme III.2.3).[1a] Later, Shi group developed a similar Pd-catalyzed *o*-benzoxylation of ketoxime ether *via* the *in situ* generation of benzoate iodonium salts.[1b]



Scheme III.2.3. *Pd-catalyzed ortho-benzoxylation of 2-phenylpyridine*

Cheng group has developed a Rh-catalyzed *o*-benzoxylation of 2-arylpyridines using aromatic carboxylic acids as the ArCOO– source.[2e] Later, the same group has shown that carboxylic acid derivative *viz.* acid salt[1d] anhydride[1k] and acid chloride[1g] could be used for the similar functionalization (Scheme III.2.4).

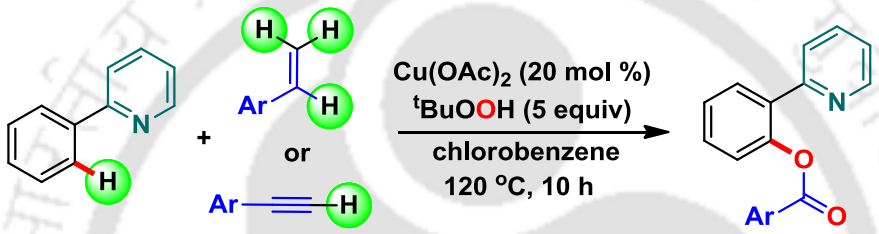


Scheme III.2.4. *o-Benzoxylation of directing arenes using carboxylic acid derivatives*

Zhong group has achieved a Pd-catalyzed *o*-benzoxylation of 2-phenylpyridines with aromatic carboxylic acids in the presence of copper and silver salts as additives (Scheme

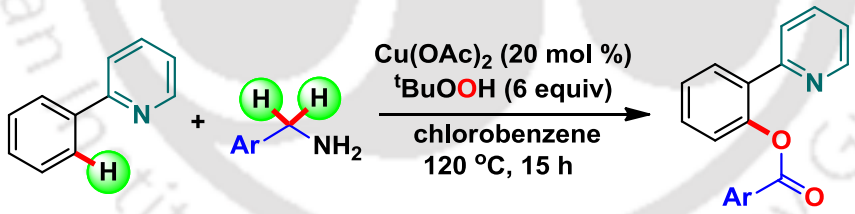
III.2.4).[2c] Aryl acylperoxides has also been found to be an effective benzoxy surrogate in Pd-catalyzed *o*-benzoxylation of 2-phenylpyridines as demonstrated by Yu group (Scheme III.2.4).[1c] Recently, Jeganmohan *et al.* have reported Ru-catalyzed *o*-benzoxylation of acetanildes[2b] and benzamides[2a] using aryl carboxylic acids as coupling partners in the presence of $AgSbF_6/(NH_4)_2S_2O_8$ oxidant combination (Scheme III.2.4).

Very recently, our group[1h] has shown that even terminal alkenes and alkynes could be the source of benzoxy surrogate during Cu(II)-catalyzed *o*-benzoxylation of 2-phenylpyridine in the presence of TBHP oxidant (Scheme III.2.5). The reaction proceeds *via* formation of phenylglyoxal followed by decarbonylation to benzoyl radical/benzaldehyde which acts as the arylcarboxy source.



Scheme III.2.5. *o-Benzoxylation of 2-phenylpyridines via sp^2 C–H bond cleavage*

For the first time our group has demonstrated that benzylamine can be utilized as a synthetic equivalent of an arylcarboxy group. 2-Arylpyridines were successfully *o*-benzoxylated in the presence of $Cu(OAc)_2$/TBHP combination (Scheme III.2.6).[2g]



Scheme III.2.6. *o-Benzoxylation of 2-phenylpyridines using benzylamines*

III.3. Present Work

Inspired by these developments on directing group assisted C–O bond formations leading to ester synthesis particularly using Pd-catalyst, a Pd-catalyzed *ortho*-benzoxylation protocol has been developed. For this *ortho*-benzoxylation strategy 2-arylbenzothiazole was chosen as the model substrate.

Optimization of Reaction Conditions. To test the efficacy of CAN as an oxidant, a CDC reaction between 2-phenylbenzothiazole (**1**) (1 equiv) and benzoic acid (**a**) (1.2 equiv) was carried out by using $Pd(OAc)_2$ (5 mol %) and CAN (1 equiv) in toluene (2.5

mL) at 110 °C. The expected mono-*o*-benzoxylated product (**1a**) was obtained in 38% isolated yield. In addition to spectroscopic analysis for the characterization of the product, the structure of (**1a**) was further confirmed by using XRD analysis (Fig. III.3.1).

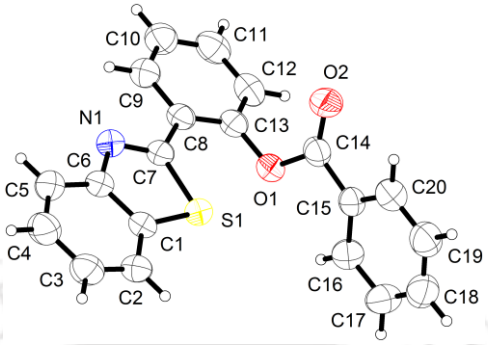
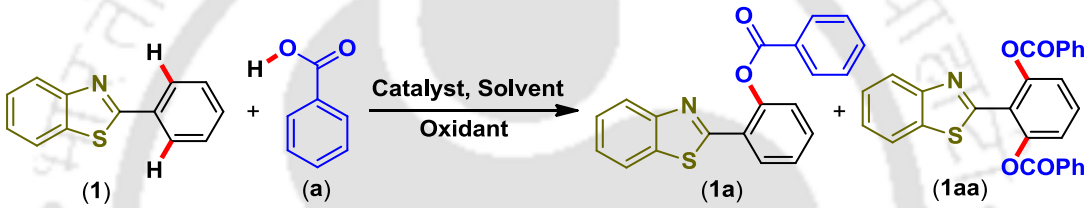


Fig. III.3.1. *ORTEP view of compound (**1a**)*

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



entry	catalyst (mol %)	solvent	oxidant	Yield (%)[b] **1a**/**1aa**
1	$Pd(OAc)_2$ (5.0)	toluene	CAN	38
2	$Pd(OAc)_2$ (5.0)	*o*-xylene	CAN	10
3	$Pd(OAc)_2$ (5.0)	CH_3CN	CAN	0[c]
4	$Pd(OAc)_2$ (5.0)	1,4-dioxane	CAN	0[c]
5	$Pd(OAc)_2$ (5.0)	DMF	CAN	0[c]
6	$Pd(OAc)_2$ (5.0)	DMSO	CAN	0[c]
7	$Pd(OAc)_2$ (5.0)	DCE	CAN	56
8	$Pd(OAc)_2$ (10.0)	DCE	CAN	62
9	$Pd(TFA)_2$ (5.0)	DCE	CAN	41
10	$PdCl_2$ (5.0)	DCE	CAN	43
11	$PdBr_2$ (5.0)	DCE	CAN	48
12	$Pd(OAc)_2$ (5.0)	DCE	CAN	67[d]
13	$Pd(OAc)_2$ (5.0)	DCE	Oxone	0[c]
14	$Pd(OAc)_2$ (5.0)	DCE	Ag_2CO_3/CuI	0[c]
15	$Pd(OAc)_2$ (5.0)	DCE	$K_2S_2O_8$	0[c]
16	**$Pd(OAc)_2$ (5.0)**	**DCE/CH_3CN**	**CAN**	**71[d,e]**
17	$Pd(OAc)_2$ (5.0)	DCE/CH_3CN	CAN	62/11[e,f]

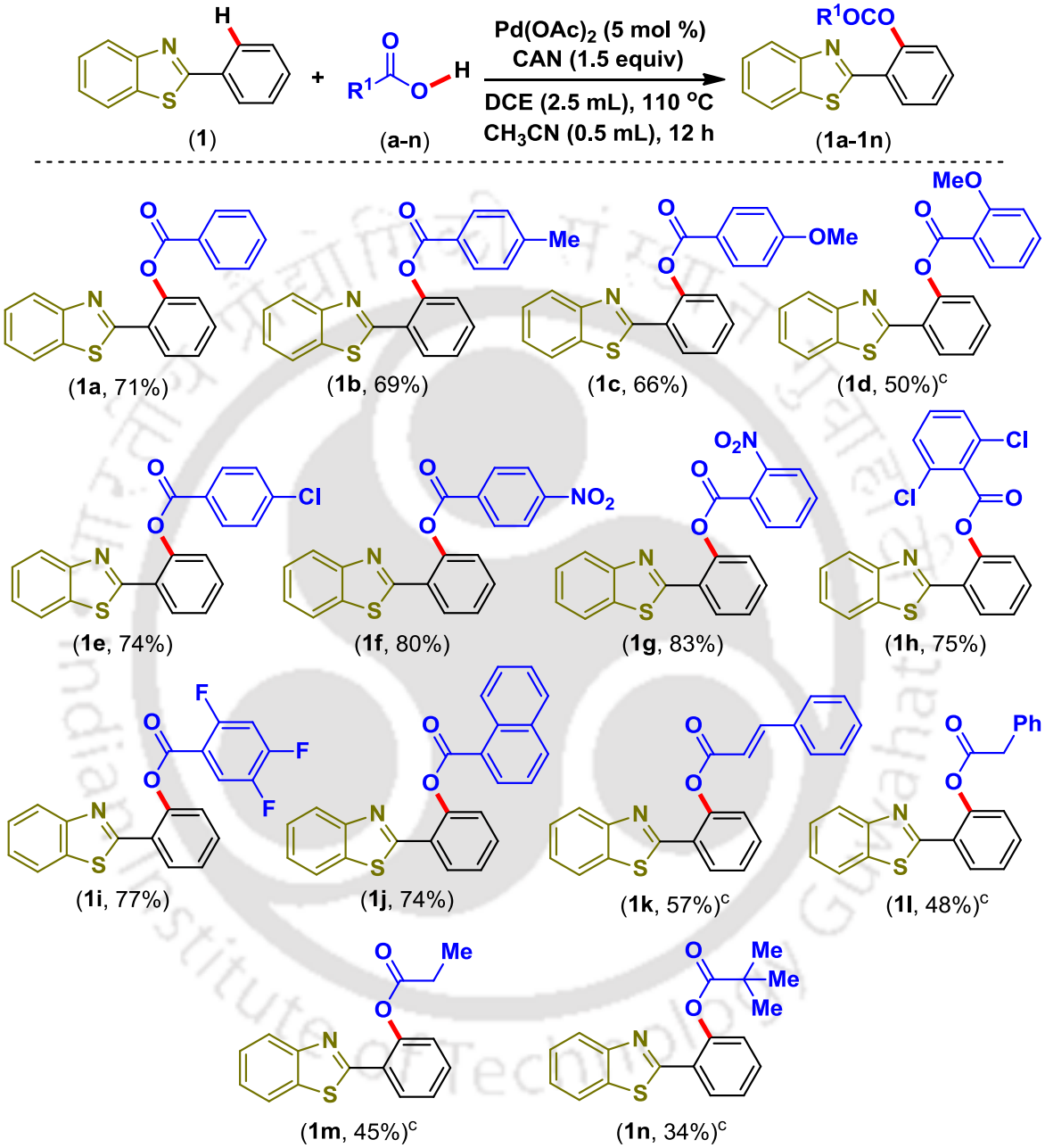
[a]Reaction conditions: 2-Phenylbenzothiazole (**1**) (0.5 mmol), benzoic acid (**a**) (0.60 mmol) and oxidant (0.5 mmol) at 110 °C for 12 h. [b]Isolated yield. [c]Complete recovery of starting materials. [d]0.75 mmol of CAN was used. [e]DCE/CH_3CN used in 5:1 (total 3 mL) ratio. [f]Benzoic acid (1 mmol) and CAN (1 mmol) was used at 110 °C for 17 h.

Fascinated by this preliminary success, we assessed other reaction parameters such as solvent, oxidant, catalyst and their amounts to achieve the best possible yield. *o*-Xylene gave only 10% of the desired product (**1a**) whereas CH_3CN, 1,4-dioxane, DMF and DMSO all failed to provide *o*-benzoxylated product (**1a**) (Table III.3.1, entries 2–6). However changing the solvent to DCE afforded 56% of the desired product (**1a**) (Table III.3.1, entry 7). Further, increasing the catalyst quantity 5 to 10 mol % the yield of the product did not change significantly (Table III.3.1, entry 8). Other potential palladium catalyst *viz.* $Pd(TFA)_2$ $PdCl_2$ and $PdBr_2$ were not so effective compared to $Pd(OAc)_2$ (Table III.3.1, entries 9–11). Increasing the oxidant (CAN) quantity from 1.0 to 1.5 equivalents the yield of the product increased up to 67% (Table III.3.1, entry 12). Other oxidant such as oxone, Ag_2CO_3/CuI and $K_2S_2O_8$ failed to give the desired product (**1a**) (Table III.3.1, entries 13–15). The addition of CH_3CN was necessary to make the medium homogeneous, thereby improving the yield (71%) (Table III.3.1, entry 16). From the optimization table, the conversion of 2-phenylbenzothiazole (**1**, 1 equiv) into *o*-benzoxylated product (**1a**) was best achieved by using benzoic acid (1.2 equiv) and CAN (1.5 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) in a mixture of 1,2-dichloroethane (DCE)/CH_3CN (5:1, 3 mL) at 110 ^oC. When the reaction was carried out with two equivalents of benzoic acid for a longer period of time (17 h), trace amounts (11%) of *o*-dibenzoxylated product (**1aa**) was observed (Table III.3.1, entry 17).

Substrate Scope for *o*-Benzoxylation. Encouraged by the efficacy of CAN as an oxidant, we further implemented the esterification strategy to the coupling between 2-phenylbenzothiazole and a series of carboxylic acids. This strategy was well-suited for a variety of aromatic acids that contained electron-donating and electron-withdrawing substituents. Aromatic acids containing electron-donating groups such as *p*–Me (**b**), *p*–OMe (**c**) and *o*–OMe (**d**) provided the corresponding *o*-benzoxylated products (**1b**, 69%), (**1c**, 66%) and (**1d**, 50%) in good to moderate yields (Scheme III.3.1). Aromatic acids having moderately and strongly electron-withdrawing substituents such as *p*–Cl (**e**), *p*–NO_2 (**f**), and *o*–NO_2 (**g**) afforded their corresponding *o*-benzoxylated products (**1e**), (**1f**) and (**1g**) in 74%, 80% and 83% yields, respectively (Scheme III.3.1). A similar trend in reactivity was observed for di- and trisubstituted aromatic acids that contained electron-withdrawing substituents such as 2,6-dichloro (**h**) and 2,4,5-trifluoro (**i**)

afforded their corresponding *o*-benzoxylated products (**1h**, 75%) and (**1i**, 77%) in decent yields (Scheme III.3.1).

Scheme III.3.1. *Substrate scope for o-esterification of 2-phenylbenzothiazole*[a,b]

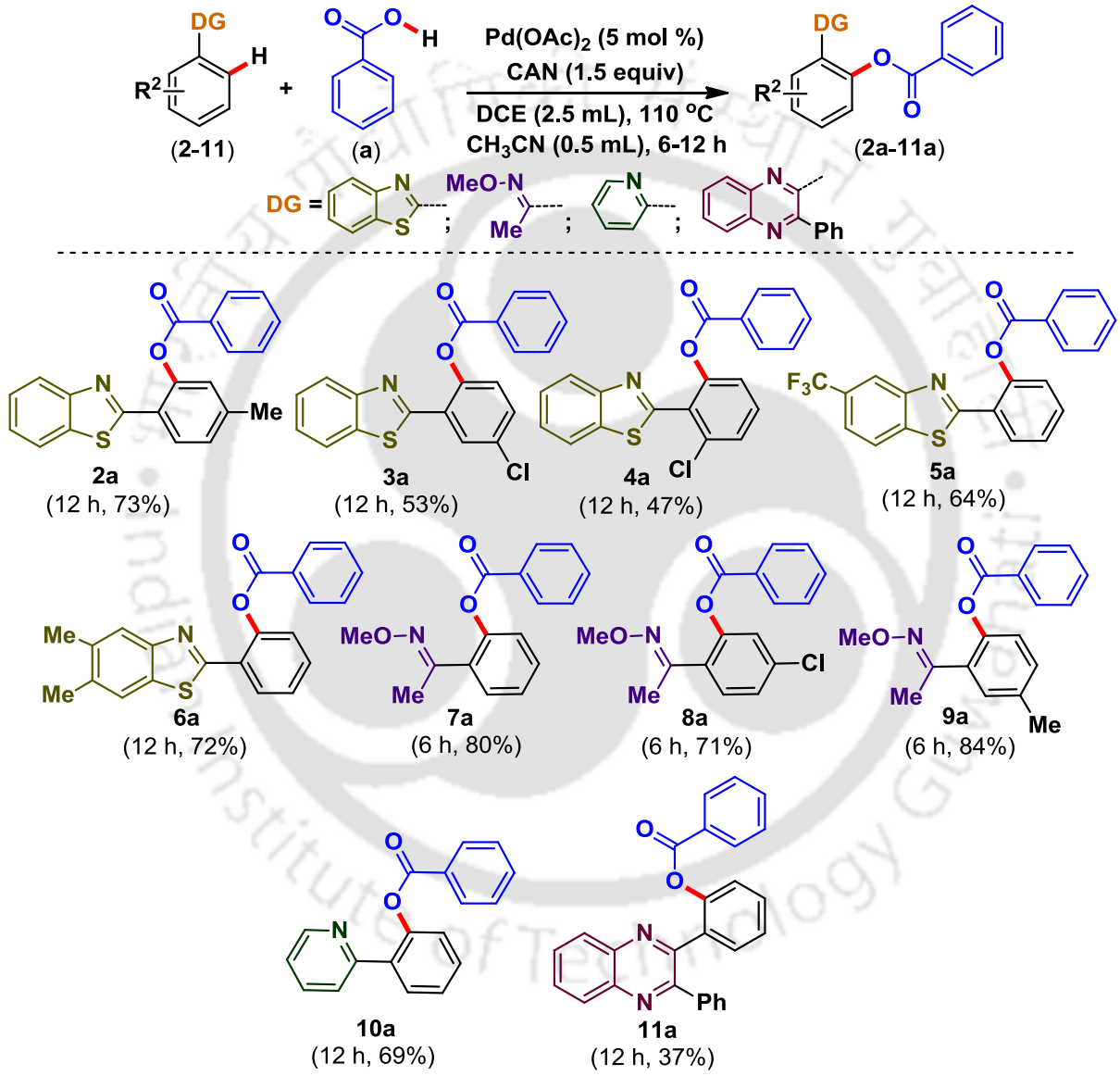


[a]Reaction conditions: 2-Phenylbenzothiazole (**1**) (0.5 mmol), carboxylic acid (**a**–**n**) (0.6 mmol) and CAN (0.75 mmol) at 110 °C for 12 h. [b]Isolated yield. [c]Rest is unreacted starting materials.

Fused aromatic acid (**j**) also afforded a good yield of the *o*-carboxylated product (**1j**, 74%). The oxidant CAN was also amenable to the α,β-unsaturated system *trans*-cinnamic acid (**k**) and, provided a moderate yield (57%) of *o*-functionalized product

(**1k**). The efficiency of the coupling reaction was poor for aliphatic carboxylic acids which may be a result of the instability of the *in situ* generated aliphatic carboxy radicals. Phenylacetic acid (**l**), propanoic acid (**m**) and pivalic acid (**n**) all underwent CDC reaction to afford *o*-carboxylated products (**1l**), (**1m**) and (**1n**) in 48%, 45%, and 34% yield, respectively.

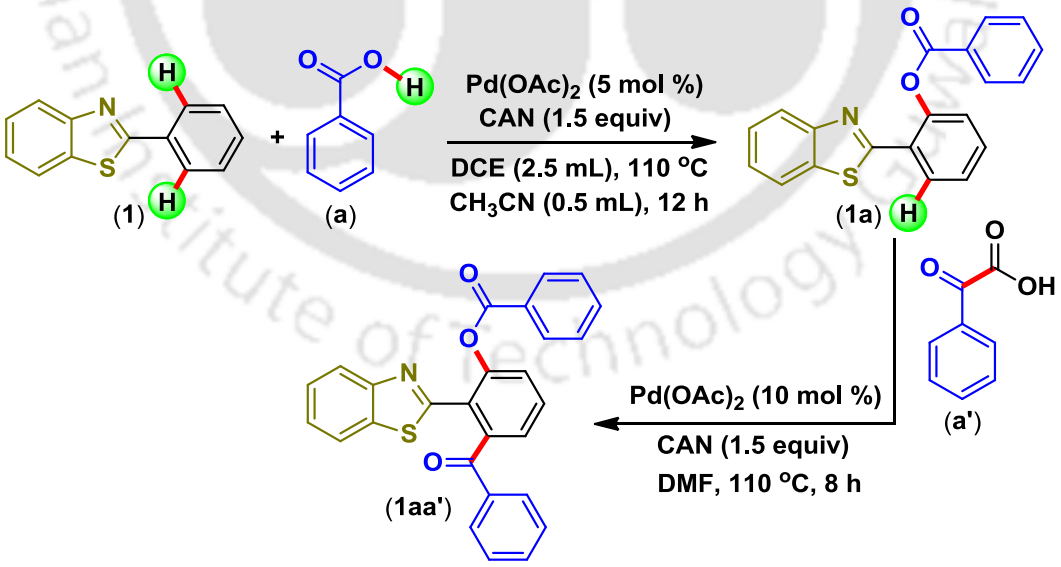
Scheme III.3.2. *Substrate scope for o-benzoxylation of directing arenes*[a,b]



[a]Reaction conditions: directing arenes (**2**–**11**) (0.5 mmol), benzoic acid (**a**) (0.6 mmol) and CAN (0.75 mmol) at 110 °C for 6–12 h. [b]Isolated yield.

This strategy was also successful with 2-aryl-substituted benzothiazoles that contained the electron-donating substituent *p*–Me (**2**) and moderately electron-withdrawing groups *m*–Cl (**3**) and *o*–Cl (**4**). These substituted substrates provided the expected *o*-benzoxylated

products (**2a**, 73%), (**3a**, 53%) and (**4a**, 47%) respectively, as shown in Scheme III.3.2. Substituted benzothiazoles containing electron-withdrawing $-CF_3$ (**5**) group and electron-donating –Me group (**6**) gave *o*-benzoxylated products (**5a**, 64%) and (**6a**, 72%) in good yields (Scheme III.3.2). The versatility of CAN as an oxidizing agent was successfully demonstrated with other well investigated directing arenes such as acetophenone *O*-methyl oxime, 2-phenylpyridine and 2,3-diphenylquinoxaline. Under the present optimized conditions, acetophenone *O*-methyl oxime (**7**) provided the desired *o*-benzoxylated product (**7a**) in good yield (80%) in a shorter reaction time (6 h). Acetophenone *O*-methyl oxime that contained the electron deficient substituent *p*–Cl (**8**) afforded lower yield (71%) of *o*-benzoxylated product (**8a**), whereas electron rich *m*–methylacetophenone *O*-methyl oxime (**9**) gave the regioselective *o*-benzoxylated product (**9a**) in 84% yield (Scheme III.3.2). The most employed directing ligand moiety, 2-phenylpyridine (**10**), provided *o*-benzoxylated product (**10a**) in 69% yield by using CAN. This yield is comparable with those reported by other groups that employed using $Pd^{II}/CuI/Ag_2CO_3$,[2c] and $Rh^{I}/P(Cy)_3{\cdot}HBF_4/CuI$[2e] combinations and is slightly lower than that obtained by using the $Pd^{II}/PhI(OCOR)_2$[1a] catalytic system. However, the 2,3-diphenylquinoxaline (**11**) directed system afforded *o*-benzoxylated product (**11a**) in a mere yield of 37% (Scheme III.3.2).

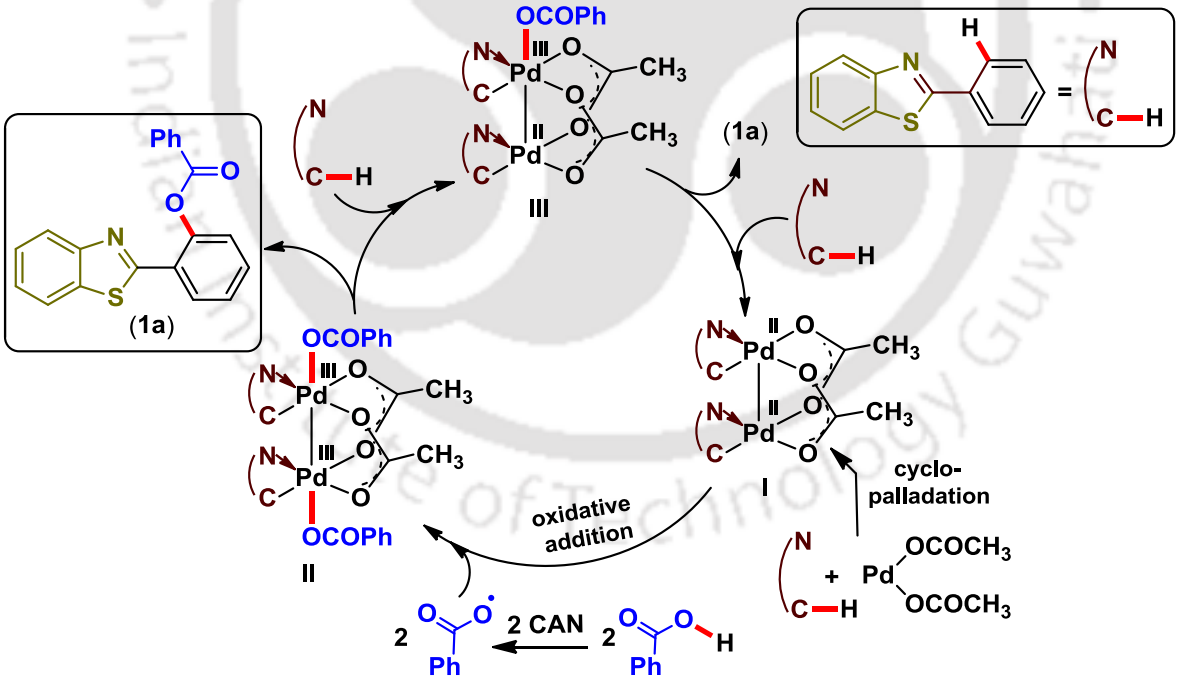


Scheme III.3.3. *One-pot hetero bi-functionalization of 2-phenylbenzothiazole (**1**)*

To demonstrate the synthetic utility of CAN as a terminal oxidant, both *o*-benzoxylation and *o*-aroylation strategies were successfully applied in sequence (as a one-pot reaction) for the construction of the *o*-bifunctionalized compound 2-(benzo[*d*]thiazol-2-yl)-3-

benzoylphenyl benzoate (**1aa′**) (Scheme III.3.3). For this, 2-phenylbenzothiazole (**1**) was chosen as the directing arene, and the product (**1aa′**) was obtained in 30% overall yield.

Mechanistic Studies. Taking cues from the above experimental observations, plausible mechanisms can be speculated for the *o*-benzoxylation (Scheme III.3.4). When a typical *o*-benzoxylation 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 (5–7%) were observed, thereby supporting the radical pathways for these processes. Because of the formation of relatively stable benzoxy radicals in aromatic acids that have electron-withdrawing groups these afforded better yields of products than those obtained by using aromatic acids that have electron-donating groups. When the benzoxylation of (**1**) was carried out in the presence of 1, 1.5 and 2 equivalents of oxidant (CAN) under otherwise identical conditions the isolated yields of the product after 12 h were 66%, 71% and 72% respectively. These experiments suggest a minimum requirement of one equivalent of oxidant for this transformation, thereby indicating a Pd(II)/Pd(III) catalytic cycle.[7]



Scheme III.3.4. *Pd(II)-catalyzed ortho-benzoxylation of 2-phenylbenzothiazole (**1**)*

For *o*-benzoxylation process, the initial cyclopalladation of 2-phenylbenzothiazole (**1**) leads to the formation of acetate bridged binuclear Pd(II) intermediate **I** (Scheme III.3.4). This dimeric Pd(II) complex further undergoes a bimetallic oxidative addition with the *in*

situ generated benzoxy radical that is obtained by the action of CAN with benzoic acid. The proximity of the two Pd-centers might facilitate a 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) intermediate[7] **II** as was detected by mass spectral analysis of the reaction mixture. Furthermore, the detection of a monomeric Pd(IV) species[8] in the reaction aliquot[9] may be the result of a Pd–Pd cleavage in dimeric Pd(III) intermediate **II** to give monomeric Pd(IV) and Pd(II) species.[8d] A reductive elimination leads to the *o*-benzoxylated product and forms the active dimeric species **III**. Intermediate **III** further releases another *o*-benzoxylated product by C–O bond formation and regenerates dinuclear Pd(II) active species **II** for the next catalytic cycle (Scheme III.3.4).

In conclusion, a simple and efficient protocol has been developed for the *ortho*-benzoxylation of directing arenes using Pd(II)-catalyst and inexpensive terminal oxidant CAN. The terminal oxidant CAN as an efficient substitute for a set of expensive oxidants/additives in the Pd-catalyzed substrate directed *o*-benzoxylation that proceeds through a CDC reaction. Mechanistic investigations reveal the radical pathway for this strategy.

III.4. Experimental Section

III.4.1. General Information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). 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.

III.4.2. Crystallographic Description

CCDC number for compounds 1a: CCDC 997276. 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): 0.44 x 0.34 x 0.32. $C_{20}H_{13}NO_2S$, Mr = 331.07. monoclinic, space group p 21/n; a = 8.9143 (3) Å, b = 16.4329 (5) Å, c = 11.7355 (4) Å; $\alpha = 90^o$, $\beta = 111.800$ (2) ^{o}, $\gamma = 90^o$, V = 1596.17 (9)Å^3 ; Z = 4; ρ_{cal}= 1.379 g/cm^3; μ (mm^{-1}) = 0.214; *F (000)* = 688.0; Reflection collected / unique = 2802 / 2164; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0444, wR2 = 0.1173, R indices (all data) R1 = 0.0553, wR2 = 0.1232; goodness of fit = 1.057.

III.4.3. Synthesis of 2-(Benzo[*d*]thiazol-2-yl)phenyl benzoate (1a) and 2-(Benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (1aa′)

III.4.3.1. General Procedure for the Synthesis of 2-(Benzo[*d*]thiazol-2-yl)phenyl benzoate (1a) from 2-Phenylbenzothiazole (1) and Benzoic acid (a): To an oven-dried round bottom flask (25 mL) 2-phenylbenzothiazole (**1**) (0.105g, 0.5 mmol), benzoic acid (0.073g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol), ceric ammonium nitrate (0.411g, 0.75 mmol), 1,2-dichloroethane (2.5 mL) and acetonitrile (0.5 mL) were added. The reaction mixture was heated at reflux in an oil bath that was preheated to 110 ^{o}C. Upon completion of the reaction (12 h), the excess solvent was removed under reduced pressure and the reaction mixture was combined with ethyl acetate (30 mL). The ethyl acetate layer was carefully washed with saturated sodium bicarbonate solution (2 x 5 mL), dried with anhydrous sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over a silica gel column (hexane / ethyl acetate, 9.8:0.2) to give pure 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1a**) (0.117g, yield 71%). The identity and purity of the product was confirmed by spectroscopic analysis.

III.4.3.2. General Procedure for the Synthesis of 2-(Benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (1aa′) from 2-Phenylbenzothiazole (1), Benzoic acid (a) and Phenylglyoxalic acid (a´): To an oven-dried round bottom flask (25 mL) 2-phenylbenzothiazole (**1**) (0.105g, 0.5 mmol), benzoic acid (0.073g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol), ceric ammonium nitrate (0.411g, 0.75 mmol), 1,2-dichloroethane (2.5 mL) and acetonitrile (0.5 mL) were added. The reaction mixture was heated at reflux in an oil bath that was preheated to 110 ^{o}C. Upon completion of the reaction (12 h), phenylglyoxalic acid (**a´**) (0.090g, 0.6 mmol), $Pd(OAc)_2$ (0.011g, 0.05 mmol), ceric ammonium nitrate (0.411g, 0.75 mmol) and DMF (1.5 mL) were added to the same round bottom flask and heated at 110 ^{o}C. After 8 h the reaction mixture was combined with ethyl

acetate (30 mL). The ethyl acetate layer was carefully washed with saturated sodium bicarbonate solution (2 x 5 mL), dried with anhydrous sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over a silica gel column (hexane / ethyl acetate, 9.5:0.5) to give pure 2-(benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (**1aa′**) (0.065g, yield 30%). The identity and purity of the product was confirmed by spectroscopic analysis.

III.4.4. Mechanistic Investigations

- **III.4.4.1. *o*-Benzoxylation of 2-Phenylbenzothiazole (1) in the Presence of Radical Scavenger TEMPO:** In an oven-dried 25 mL round bottom flask 2-phenylbenzothiazole (**1**) (0.105g, 0.5 mmol), benzoic acid (0.073g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol), ceric ammonium nitrate (0.329g, 0.6 mmol), TEMPO (0.078g, 0.5 mmol), 1,2-dichloroethane (2.5 mL) and acetonitrile (0.5 mL) were added. The flask was fitted to a condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^oC for 12 h. After 12 h only trace amount (<10%) of the desired product (**1a**) was observed. This experiment supports the formation of benzoxy radical in the medium from benzoic acid induced by Pd/CAN and also the radical nature of the mechanism.
- **III.4.4.2. ESI-MS Study for the Detection of Reaction Intermediates During *o*-Benzoxylation:** In order to detect the intermediate species in the reaction mixture an electrospray mass spectrometry was performed. In this study, an oven-dried flask was charged with 2-phenylbenzothiazole (**1**) (0.105g, 0.5 mmol), benzoic acid (0.073g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol), ceric ammonium nitrate (0.411g, 0.75 mmol), 1,2-dichloroethane (2.5 mL) and acetonitrile (0.5 mL). Then the reaction mixture was stirred in an oil bath at 110 ^oC. After 1.5 h of reaction, aliquot (100 µL) was withdrawn and diluted with acetonitrile (1 mL). A 20 µL of the diluted solution was injected to run ESI-MS analysis. Various cationic and neutral Pd species were detected in the ESI-MS analysis as shown below in Figure III.4.4.1. The cationic and neutral Pd-species observed in the spectrum are as follows: peaks at m/z 315.9412 corresponding to $[(C_{13}H_8NS)Pd(II)]^+$ (**A**) (Fig. III.4.4.1), at m/z 356.9694 corresponding to $[(C_{13}H_8NS)Pd(II)(NCCH_3)]^+$ (**B**) (Fig. III.4.4.1), at m/z 437.9790 corresponding to $[(C_{13}H_8NS)Pd(II)(OCOPh)]$ (**C**) (Fig. III.4.4.1), at m/z 526.9886 corresponding to $[(C_{13}H_8NS)Pd(II)(C_{13}H_8NS)]$ (**D**) (Fig. III.4.4.1), at m/z 647.0109 corresponding to $[(C_{13}H_8NS)Pd(IV)(C_{13}H_8NS)(OCOPh)]^+$ (**E**) (Fig. III.4.4.1), at

m/z 870.9362 corresponding to $[(C_{13}H_8NS)Pd(III)\ (C_{13}H_8NS)(OAc)_2(OCOPh)]^+$ (**F**) (Fig. III.4.4.1).

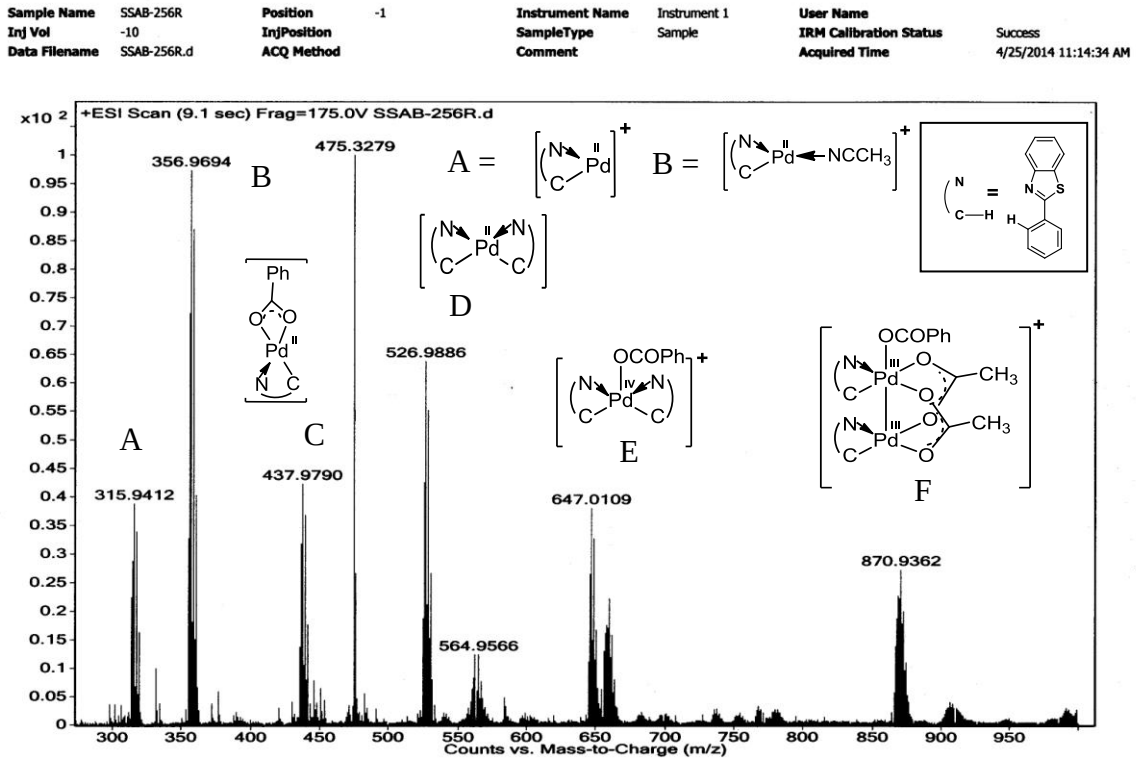


Fig. III.4.4.1. *ESI-MS spectrum of the reaction mixture*

III.5. References

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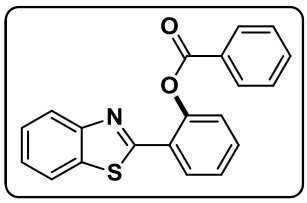
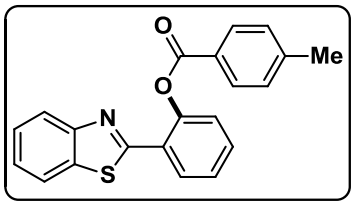
III.6. Spectral Data

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



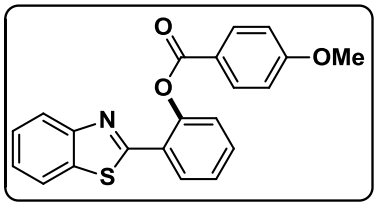
Solid; M.p. 144.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40 (d, 1H, J = 7.6 Hz), 8.32 (d, 2H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.68 (t, 1H, J = 7.2 Hz), 7.57–7.52 (m, 3H), 7.45–7.40 (m, 2H), 7.34–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 162.5, 153.0, 148.8, 135.6, 133.9, 131.6, 130.8, 130.5, 129.6, 128.8, 126.7, 126.6, 126.4, 125.4, 124.1, 123.4, 121.5; IR (KBr, cm^{-1}): 3051, 2923, 2850, 1734, 1600, 1580, 1554, 1503, 1495, 1451, 1430, 1314, 1286, 1262, 1246, 1223, 1196, 1172, 1155, 1105, 1076, 1058, 1044, 1023, 1000, 967, 887, 844, 761, 732; HRMS (ESI) calcd for $C_{20}H_{13}NO_2S$ (M + H$^+$) 332.0745, found 332.0755.

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



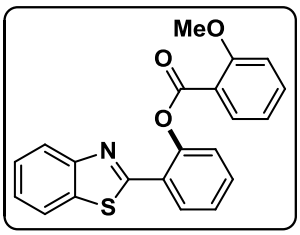
Solid; M.p. 160.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (d, 1H, J = 8.0 Hz), 8.19 (d, 2H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.42 (t, 2H, J = 7.6 Hz), 7.36–7.30 (m, 4H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 162.5, 152.9, 148.9, 144.9, 135.6, 131.6, 130.9, 130.4, 129.6, 126.8, 126.6, 126.4, 125.3, 124.1, 123.4, 121.5, 21.9; IR (KBr, cm^{-1}): 3058, 2910, 2847, 1733, 1609, 1554, 1496, 1443, 1430, 1318, 1262, 1242, 1226, 1193, 1176, 1107, 1063, 1043, 1015, 970, 935, 881, 870, 845, 836, 789, 766, 757, 742, 730; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ (M + H$^+$) 346.0912, found 346.0919.

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



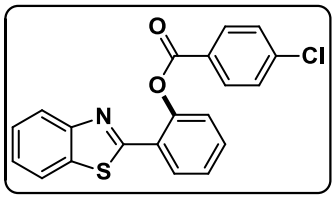
Solid; M.p. 131.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.43 (d, 1H, J = 7.8 Hz), 8.26 (d, 2H, J = 8.4 Hz), 7.96 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 8.4 Hz), 7.53 (t, 1H, J = 7.8 Hz), 7.44–7.40 (m, 2H), 7.32 (t, 2H, J = 7.2 Hz), 7.02 (d, 2H, J = 9.0 Hz), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.8, 164.3, 162.5, 152.9, 148.9, 135.7, 133.1, 131.6, 130.4, 126.7, 126.5, 126.4, 125.4, 124.1, 123.5, 121.9, 121.6, 114.2, 55.7; IR (KBr, cm^{-1}): 3052, 2995, 2962, 2924, 2836, 1727, 1610, 1559, 1514, 1455, 1499, 1446, 1431, 1317, 1266, 1222, 1195, 1183, 1169, 1107, 1070, 1023, 965, 886, 843, 768, 758, 727; HRMS (ESI) calcd for $C_{21}H_{15}NO_3S$ (M + H$^+$) 362.0851, found 362.0862.

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



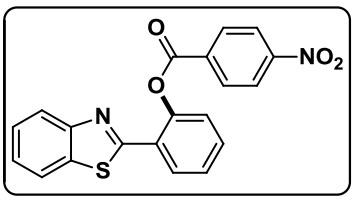
Solid; M.p. 93.3 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (d, 1H, J = 7.8 Hz), 8.25 (d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 7.8 Hz), 7.81 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 9.0 Hz), 7.52 (t, 1H, J = 7.5 Hz), 7.44–7.39 (m, 2H), 7.35–7.31 (m, 2H), 7.09 (t, 1H, J = 7.2 Hz), 7.05 (d, 1H, J = 8.4 Hz), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 162.9, 160.6, 153.2, 148.9, 135.9, 134.9, 133.3, 131.6, 130.5, 126.9, 126.6, 126.4, 125.4, 124.3, 123.5, 121.6, 120.5, 118.9, 112.5, 56.3; IR (KBr, cm^{-1}): 3047, 2965, 2929, 2842, 1752, 1598, 1577, 1490, 1467, 1453, 1434, 1318, 1283, 1258, 1233, 1220, 1189, 1165, 1141, 1106, 1049, 1023, 965, 884, 866, 845, 757, 727, 701; HRMS (ESI) calcd for $C_{21}H_{15}NO_3S$ ($M + H^+$) 362.0851, found 362.0860.

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



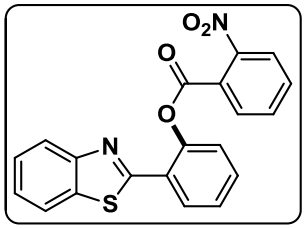
Solid; M.p. 150.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, 1H, J = 8.0 Hz), 8.23 (d, 2H, J = 8.8 Hz), 7.88 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 7.6 Hz), 7.56–7.51 (m, 3H), 7.45–7.40 (m, 2H), 7.33 (t, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 162.4, 153.1, 148.5, 140.5, 135.4, 132.2, 131.7, 130.6, 129.2, 128.2, 126.9, 126.5, 125.5, 124.0, 123.5, 121.5; IR (KBr, cm^{-1}): 3060, 2964, 2932, 2847, 1737, 1591, 1494, 1486, 1445, 1430, 1398, 1316, 1258, 1191, 1171, 1105, 1090, 1065, 1012, 968, 883, 844, 758, 748, 730; HRMS (ESI) calcd for $C_{20}H_{12}ClNO_2S$ ($M + H^+$) 366.0355, found 366.0360.

2-(Benzo[*d*]thiazol-2-yl)phenyl 4-nitrobenzoate (1f):



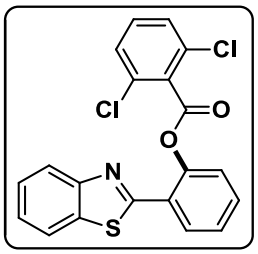
Solid; M.p. 156.4 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.46 (d, 2H, J = 7.8 Hz), 8.39 (d, 2H, J = 7.8 Hz), 8.26 (d, 1H, J = 7.8 Hz), 7.81 (d, 1H, J = 8.4 Hz), 7.70 (d, 1H, J = 7.8 Hz), 7.57 (t, 1H, J = 7.2 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.39 (t, 1H, J = 7.2 Hz), 7.35–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.7, 162.5, 153.4, 151.1, 148.2, 135.3, 135.2, 131.9, 131.8, 130.9, 127.3, 126.6, 126.4, 125.7, 124.0, 123.9, 123.4, 121.6; IR (KBr, cm^{-1}): 3109, 2923, 1741, 1606, 1558, 1523, 1502, 1452, 1432, 1411, 1351, 1320, 1265, 1248, 1187, 1178, 1127, 1108, 1075, 1013, 968, 877, 874, 856, 750, 724; HRMS (ESI) calcd for $C_{20}H_{12}N_2O_4S$ ($M + H^+$) 377.0596, found 377.0602.

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



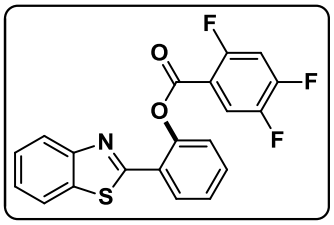
Solid; M.p. 118.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19 (d, 1H, *J* = 7.8 Hz), 8.06 (t, 2H, *J* = 8.1 Hz), 7.96 (d, 1H, *J* = 7.8 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 7.79 (t, 1H, *J* = 7.5 Hz), 7.72 (t, 1H, *J* = 8.1 Hz), 7.58 (t, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 7.8 Hz), 7.48–7.43 (m, 2H), 7.37 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 162.8, 153.4, 147.9, 147.8, 135.2, 133.3, 132.2, 131.9, 130.7, 130.4, 127.6, 127.2, 126.4, 126.3, 125.5, 124.2, 123.5, 123.2, 121.5; IR (KBr, cm^{-1}): 3104, 3052, 2847, 1757, 1617, 1604, 1555, 1527, 1482, 1455, 1443, 1344, 1310, 1281, 1251, 1241, 1216, 1187, 1161, 1097, 1075, 1058, 1034, 962, 887, 880, 840, 859, 814, 762, 754, 738, 730; HRMS (ESI) calcd for $C_{20}H_{12}N_2O_4S$ (M + H^+) 377.0596, found 377.0599.

2-(Benzo[*d*]thiazol-2-yl)phenyl 2,6-dichlorobenzoate (1h):



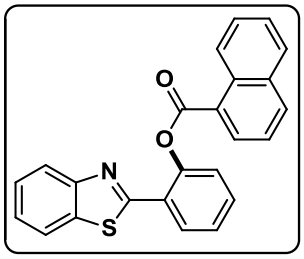
Solid; M.p. 153.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (d, 1H, *J* = 7.8 Hz), 8.10 (d, 1H, *J* = 7.8 Hz), 7.88 (d, 1H, *J* = 7.8 Hz), 7.62–7.58 (m, 2H), 7.49 (t, 1H, *J* = 7.5 Hz), 7.46 (t, 1H, *J* = 7.8 Hz), 7.41–7.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.7, 162.2, 152.9, 148.0, 135.9, 132.7, 132.2, 131.7, 131.4, 130.7, 128.3, 126.9, 126.5, 126.3, 125.3, 123.5, 123.1, 121.4; IR (KBr, cm^{-1}): 3050, 2953, 2914, 2850, 1754, 1577, 1563, 1500, 1463, 1447, 1431, 1318, 1276, 1243, 1181, 1156, 1122, 1103, 1075, 1033, 964, 881, 849, 801, 780, 774, 759, 755, 725, 710; HRMS (ESI) calcd for $C_{20}H_{11}Cl_2NO_2S$ (M + H^+) 399.9966, found 399.9979.

2-(Benzo[*d*]thiazol-2-yl)phenyl 2,4,5-trifluorobenzoate (1i):



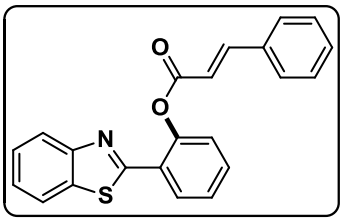
Solid; M.p. 128.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (d, 1H, *J* = 7.8 Hz), 8.17–8.12 (m, 1H), 7.87–7.84 (m, 2H), 7.57 (t, 1H, *J* = 7.2 Hz), 7.48–7.45 (m, 2H), 7.38–7.34 (m, 2H), 7.14–7.10 (m, 1H) ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.7, 160.9, 153.4, 147.9, 135.3, 131.8, 130.9, 127.1, 126.5, 126.4, 125.6, 124.0, 123.4, 121.6, 121.1, 121.0, 107.65, 107.50, 107.46, 107.32; ^{19}F NMR ($CDCl_3$ + Trifluoroacetic acid): δ -109.2 (t), -125.0 (t), -142.2 (m); IR (KBr, cm^{-1}): 3134, 3080, 3068, 1742, 1620, 1612, 1524, 1458, 1434, 1420, 1341, 1318, 1284, 1248, 1224, 1183, 1143, 1106, 1050, 1031, 968, 899, 869, 853, 846, 823, 803, 768, 749, 725; HRMS (ESI) calcd for $C_{20}H_{10}F_3NO_2S$ (M + H^+) 386.0462, found 386.0473.

2-(Benzo[*d*]thiazol-2-yl)phenyl 1-naphthoate (1j):



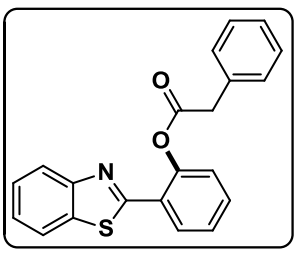
Solid; M.p. 124.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.02 (d, 1H, *J* = 8.4 Hz), 8.68 (d, 1H, *J* = 7.2 Hz), 8.37 (d, 1H, *J* = 7.8 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 7.94 (d, 1H, *J* = 7.8 Hz), 7.84 (d, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 7.8 Hz), 7.64–7.55 (m, 4H), 7.46 (t, 1H, *J* = 7.5 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.6, 162.8, 153.2, 148.8, 135.5, 134.8, 134.1, 132.3, 132.0, 131.7, 130.6, 128.9, 128.5, 126.9, 126.7, 126.6, 126.3, 126.0, 125.8, 125.4, 124.8, 124.3, 123.5, 121.5; IR (KBr, cm^{-1}): 3054, 3022, 2913, 2850, 1738, 1603, 1591, 1575, 1558, 1508, 1501, 1451, 1461, 1431, 1366, 1316, 1273, 1236, 1222, 1186, 1158, 1140, 1108, 977, 962, 883, 853, 835, 782, 775, 756, 720; HRMS (ESI) calcd for $C_{24}H_{15}NO_2S$ (M + H^+) 382.0912, found 382.0916.

2-(Benzo[*d*]thiazol-2-yl)phenyl cinnamate (1k):



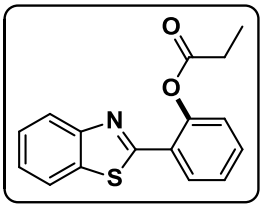
Solid; M.p. 111.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.42 (d, 1H, *J* = 7.8 Hz), 8.06 (d, 1H, *J* = 7.8 Hz), 7.98 (d, 1H, *J* = 16.2 Hz), 7.89 (d, 1H, *J* = 7.8 Hz), 7.67–7.65 (m, 2H), 7.54 (t, 1H, *J* = 7.5 Hz), 7.51–7.40 (m, 5H), 7.37 (t, 1H, *J* = 7.5 Hz), 7.33 (d, 1H, *J* = 7.8 Hz), 6.82 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.1, 162.4, 152.8, 148.4, 147.6, 135.6, 134.1, 131.5, 130.9, 130.2, 129.1, 128.5, 126.4, 126.3, 126.3, 125.3, 123.7, 123.4, 121.4, 117.1; IR (KBr, cm^{-1}): 3055, 3033, 3009, 1726, 1628, 1605, 1594, 1575, 1502, 1449, 1432, 1336, 1317, 1283, 1236, 1223, 1202, 1176, 1158, 1132, 1106, 1000, 992, 981, 968, 951, 928, 859, 843, 820, 762, 748, 721; HRMS (ESI) calcd for $C_{22}H_{15}NO_2S$ (M + H^+) 358.0902, found 358.0911.

2-(Benzo[*d*]thiazol-2-yl)phenyl 2-phenylacetate (1l):



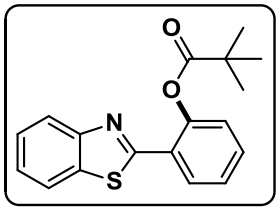
Solid; M.p. 61.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, 1H, *J* = 7.6 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.52–7.44 (m, 3H), 7.42–7.38 (m, 3H), 7.37–7.34 (m, 2H), 7.32–7.29 (m, 1H), 7.18 (d, 1H, *J* = 8.0 Hz), 4.06 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.9, 162.8, 153.2, 148.5, 135.6, 133.2, 131.6, 130.5, 129.9, 128.9, 127.6, 126.7, 126.5, 126.4, 125.5, 123.8, 123.6, 121.6, 41.9; IR (KBr, cm^{-1}): 3055, 3028, 2924, 2844, 1765, 1623, 1605, 1585, 1496, 1482, 1454, 1433, 1316, 1280, 1221, 1189, 1156, 1105, 1031, 1011, 968, 904, 859, 817, 757, 730, 701; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ (M + H^+) 346.0912, found 346.0919.

2-(Benzo[*d*]thiazol-2-yl)phenyl propionate (1m):



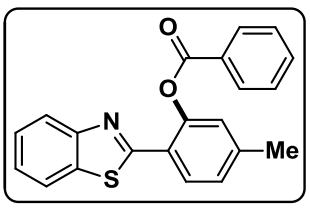
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 7.6 Hz), 7.49 (t, 2H, J = 7.6 Hz), 7.42–7.37 (m, 2H), 7.24 (d, 1H, J = 8.0 Hz), 2.80 (q, 2H, J = 7.4), 1.31 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.8, 162.8, 153.2, 148.6, 135.6, 131.6, 130.5, 126.5, 126.4, 125.5, 123.9, 123.6, 121.6, 28.5, 9.1; IR (KBr, cm^{-1}): 3056, 2978, 2923, 2848, 1768, 1580, 1557, 1501, 1452, 1431, 1414, 1350, 1314, 1280, 1224, 1201, 1107, 1073, 1004, 970, 894, 852, 757; HRMS (ESI) calcd for $C_{16}H_{13}NO_2S$ ($M + H^+$) 284.0745, found 284.0748.

2-(Benzo[*d*]thiazol-2-yl)phenyl pivalate (1n):



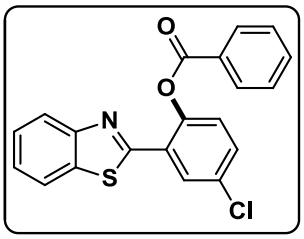
Solid; M.p. 113.9 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.4 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.49 (t, 1H, J = 7.8 Hz), 7.41–7.35 (m, 2H), 7.09 (d, 1H, J = 8.4 Hz), 6.94 (t, 1H, J = 7.6 Hz), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.6, 158.2, 152.1, 132.9, 132.8, 128.6, 126.9, 125.8, 122.4, 121.7, 119.7, 118.1, 117.0, 38.7, 27.2; IR (KBr, cm^{-1}): 3055, 2925, 2853, 1747, 1623, 1589, 1559, 1521, 1487, 1458, 1439, 1405, 1345, 1315, 1272, 1250, 1220, 1165, 1150, 1129, 1033, 973, 933, 896, 860, 817, 756, 741, 734, 727, 701; HRMS (ESI) calcd for $C_{18}H_{17}NO_2S$ ($M + H^+$) 312.1058, found 312.1065.

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



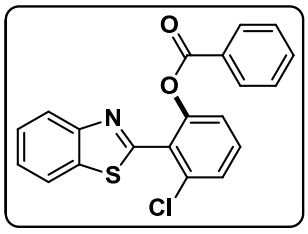
Solid; M.p. 101.8 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (d, 2H, J = 7.2 Hz), 8.28 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.79 (d, 1H, J = 7.8 Hz), 7.69 (t, 1H, J = 7.8 Hz), 7.56 (t, 2H, J = 7.8 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 7.8 Hz), 7.14 (s, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.3, 162.7, 153.1, 148.6, 142.6, 135.4, 133.9, 130.8, 130.2, 129.7, 128.8, 128.1, 127.6, 126.3, 125.2, 124.5, 123.3, 121.5, 21.5; IR (KBr, cm^{-1}): 3055, 3022, 2919, 2839, 1743, 1619, 1599, 1572, 1509, 1472, 1451, 1435, 1409, 1341, 1314, 1261, 1245, 1234, 1217, 1176, 1154, 1118, 1076, 1060, 1023, 963, 936, 894, 877, 848, 837, 753, 722, 704; HRMS (ESI) calcd for $C_{21}H_{15}NO_2S$ ($M + H^+$) 346.0912, found 346.0918.

2-(Benzo[*d*]thiazol-2-yl)-4-chlorophenyl benzoate (3a):



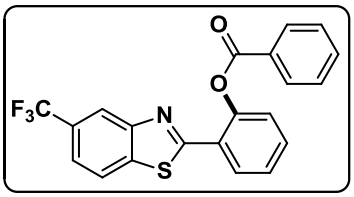
Solid; M.p. 161.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.45 (s, 1H), 8.30 (d, 2H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 8.4 Hz), 7.70 (t, 1H, *J* = 7.5 Hz), 7.57 (t, 2H, *J* = 7.5 Hz), 7.49 (d, 1H, *J* = 8.4 Hz), 7.45 (t, 1H, *J* = 7.8 Hz), 7.35 (t, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.0, 160.9, 152.8, 147.2, 135.7, 134.3, 132.4, 131.4, 130.9, 129.9, 129.3, 128.9, 128.0, 126.7, 125.8, 125.5, 123.7, 121.6; IR (KBr, cm^{-1}): 3058, 3047, 2918, 2847, 1744, 1600, 1557, 1495, 1453, 1430, 1400, 1316, 1255, 1243, 1217, 1198, 1179, 1161, 1123, 1077, 1047, 1022, 997, 891, 880, 866, 811, 798, 756, 729, 708; HRMS (ESI) calcd for $C_{20}H_{12}ClNO_2S$ (M + H$^+$) 366.0355, found 366.0364.

2-(Benzo[*d*]thiazol-2-yl)-3-chlorophenyl benzoate (4a):



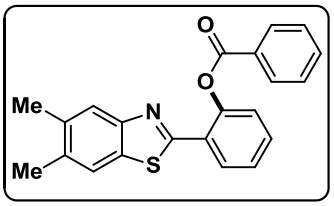
Solid; M.p. 61.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (d, 1H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz), 7.85 (d, 1H, *J* = 7.8 Hz), 7.49–7.46 (m, 3H), 7.44 (t, 1H, *J* = 7.8 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 7.34–7.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8, 160.2, 153.1, 150.5, 136.3, 135.1, 133.9, 131.5, 130.4, 128.8, 128.7, 127.8, 127.1, 126.3, 125.7, 123.9, 122.1, 121.7; IR (KBr, cm^{-1}): 3060, 2922, 2842, 1742, 1600, 1570, 1519, 1492, 1445, 1430, 1344, 1314, 1262, 1228, 1176, 1125, 1078, 1065, 1023, 1002, 964, 892, 855, 760, 745, 729, 705; HRMS (ESI) calcd for $C_{20}H_{12}ClNO_2S$ (M + H$^+$) 366.0355, found 366.0361.

2-(5-(Trifluoromethyl)benzo[*d*]thiazol-2-yl)phenyl benzoate (5a):



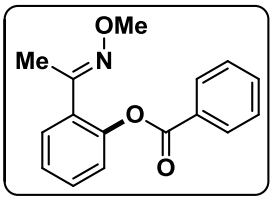
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.43 (d, 1H, *J* = 7.8 Hz), 8.32 (d, 2H, *J* = 7.2 Hz), 8.17 (s, 1H), 7.92 (d, 1H, *J* = 7.8 Hz) 7.72 (t, 1H, *J* = 7.8 Hz) 7.62–7.56 (m, 4H), 7.47 (t, 1H, *J* = 7.2 Hz), 7.36 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 164.6, 152.6, 149.0, 135.7, 138.9, 134.2, 132.3, 130.9, 130.6, 129.5, 128.9, 127.9, 126.9, 126.1, 124.2, 122.3, 121.8, 120.7, 110.2; ^{19}F NMR ($CDCl_3$ + Trifluoroacetic acid): δ -62.6 (s); IR (KBr, cm^{-1}): 3067, 2959, 2925, 2850, 1728, 1602, 1448, 1451, 1421, 1336, 1319, 1270, 1206, 1173, 1145, 1109, 1081, 1053, 1023, 967, 915, 890, 824, 759, 698; HRMS (ESI) calcd for $C_{21}H_{12}F_3NO_2S$ (M + H$^+$) 400.0619, found 400.0626.

2-(5,6-Dimethylbenzo[*d*]thiazol-2-yl)phenyl benzoate (6a):



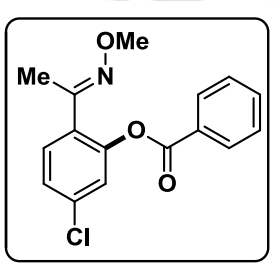
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.38 (d, 1H, *J* = 7.8 Hz), 8.31 (d, 2H, *J* = 7.2 Hz), 8.08 (t, 1H, *J* = 7.2 Hz), 7.69 (s, 1H), 7.68–7.56 (m, 3H), 7.50 (t, 1H, *J* = 6.4 Hz), 7.43 (t, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.8 Hz), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 165.3, 161.3, 151.9, 148.7, 135.7, 135.0, 133.9, 131.3, 130.9, 130.4, 129.9, 129.2, 128.9, 128.7, 127.8, 126.7, 124.0, 123.6, 121.4, 20.4; IR (KBr, cm^{-1}): 3059, 2964, 2920, 2856, 1739, 1630, 1500, 1449, 1302, 1259, 1190, 1176, 1104, 1076, 1057, 1022, 955, 865, 762, 706; HRMS (ESI) calcd for $C_{22}H_{17}NO_2S$ (M + H$^+$) 360.1058, found 360.1064.

(*E*)-2-(1-(Methoxyimino)ethyl)phenyl benzoate (7a):



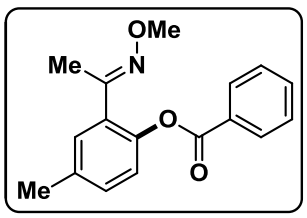
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): *δ* 8.19 (d, 2H, *J* = 7.8 Hz), 7.63 (t, 1H, *J* = 7.2 Hz), 7.52–7.48 (m, 3H), 7.41 (t, 1H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 7.2 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 3.73 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 165.1, 153.2, 148.3, 133.7, 130.5, 130.3, 129.8, 129.5, 128.6, 126.2, 123.5, 61.8, 15.1; IR (KBr, cm^{-1}): 3060, 2962, 2936, 2905, 2811, 1738, 1600, 1530, 1493, 1449, 1366, 1315, 1262, 1201, 1177, 1122, 1080, 1062, 1048, 1024, 892, 845, 755, 736, 707; HRMS (ESI) calcd for $C_{16}H_{15}NO_3$ (M + H$^+$) 270.1129, found 270.1131.

(*E*)-5-Chloro-2-(1-(methoxyimino)ethyl)phenyl benzoate (8a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.17 (d, 2H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.29–7.25 (m, 2H), 3.71 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 164.9, 152.5, 148.8, 135.1, 133.9, 130.5, 130.4, 129.2, 128.8, 126.6, 124.1, 61.9, 15.1; IR (KBr, cm^{-1}): 2959, 2935, 2891, 2811, 1744, 1600, 1488, 1452, 1395, 1367, 1315, 1260, 1204, 1178, 1129, 1097, 1078, 1059, 1024, 902, 819, 706; HRMS (ESI) calcd for $C_{16}H_{14}ClNO_3$ (M + H$^+$) 304.0740, found 304.0731.

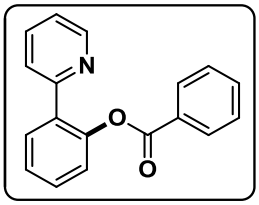
(*E*)-2-(1-(Methoxyimino)ethyl)-4-methylphenyl benzoate (9a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.19 (d, 2H, *J* = 7.6 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.50 (t, 2H, *J* = 7.6 Hz), 7.31 (s, 1H), 7.22 (d, 1H, *J* = 9.2 Hz), 7.11 (d, 1H, *J* = 8.0 Hz), 3.76 (s, 3H), 2.38 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 165.4, 153.6, 146.2, 135.9, 133.7, 131.4, 130.5, 130.4, 130.0, 128.7, 125.0, 123.2, 61.9, 21.0, 15.3; IR (KBr, cm^{-1}): 2935,

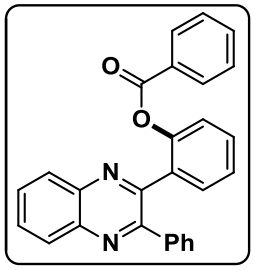
2894, 2820, 1741, 1601, 1585, 1523, 1496, 1451, 1344, 1316, 1264, 1202, 1177, 1134, 1081, 1049, 1024, 918, 870, 832, 804, 707; HRMS (ESI) calcd for $C_{17}H_{17}NO_3$ (M + H^+) 284.1286, found 284.1280.

2-(Pyridin-2-yl)phenyl benzoate (10a):



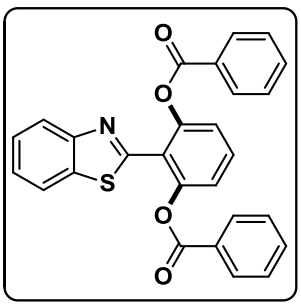
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, 1H, *J* = 4.8 Hz), 8.08 (d, 2H, *J* = 7.6 Hz), 7.78 (d, 1H, *J* = 7.2 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.57 (t, 2H, *J* = 8.0 Hz), 7.51–7.38 (m, 4H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.17 (t, 1H, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.3, 155.6, 149.7, 148.4, 136.5, 133.6, 133.3, 131.1, 130.3, 129.9, 128.7, 128.4, 126.6, 123.9, 123.5, 122.4; IR (KBr, cm^{-1}): 3058, 2992, 2918, 2855, 1734, 1585, 1564, 1494, 1463, 1451, 1425, 1263, 1194, 1177, 1116, 1079, 1062, 1022, 1002, 883, 847, 834, 792, 754, 707; HRMS (ESI) calcd for $C_{18}H_{13}NO_2$ (M + H^+) 276.1024, found 276.1023.

2-(3-Phenylquinoxalin-2-yl)phenyl benzoate (11a):



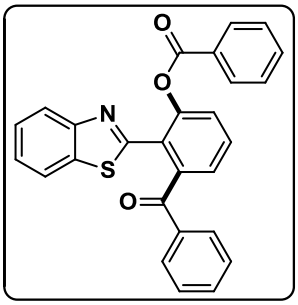
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.13 (d, 1H, *J* = 7.2 Hz), 8.07 (d, 1H, *J* = 7.8 Hz), 7.80 (d, 2H, *J* = 7.8 Hz), 7.75–7.71 (m, 2H), 7.55–7.47 (m, 5H), 7.35–7.31 (m, 5H), 7.28–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.2, 153.9, 150.7, 148.7, 141.6, 141.1, 138.5, 133.6, 132.3, 131.9, 130.4, 130.3, 130.2, 130.1, 129.7, 129.4, 129.3, 129.3, 128.5, 128.4, 126.2, 123.4; IR (KBr, cm^{-1}): 3059, 2923, 2850, 1739, 1601, 1583, 1531, 1493, 1477, 1444, 1395, 1345, 1314, 1261, 1221, 1194, 1176, 1111, 1078, 1060, 1023, 977, 847, 797, 765, 745, 726, 700; HRMS (ESI) calcd for $C_{27}H_{18}N_2O_2$ (M + H^+) 403.1446, found 403.1457.

2-(Benzo[*d*]thiazol-2-yl)-1,3-phenylene dibenzoate (1aa):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 4H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 8.4 Hz), 7.65–7.58 (m, 3H), 7.53 (d, 1H, *J* = 6.4 Hz), 7.45 (t, 4H, *J* = 7.6 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.29–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.1, 158.1, 152.9, 150.1, 135.7, 133.8, 131.2, 130.7, 129.4, 128.7, 126.1, 125.5, 123.6, 121.7, 121.4, 121.2; IR (KBr, cm^{-1}): 3056, 2920, 2853, 1738, 1608, 1598, 1488, 1448, 1428, 1313, 1258, 1239, 1227, 1174, 1164, 1075, 1065, 1057, 1026, 945, 865, 774, 760, 736; HRMS (ESI) calcd for $C_{27}H_{17}NO_4S$ (M + H^+) 452.0956, found 452.0964.

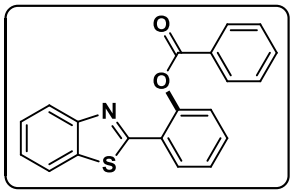
2-(Benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (1aa´):

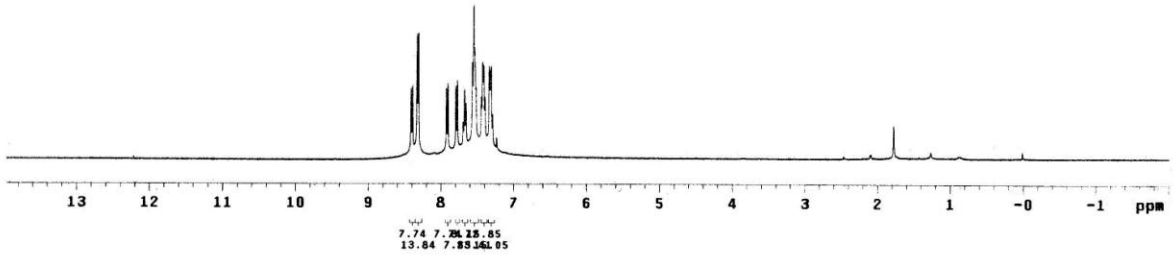


Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.93 (d, 1H, *J* = 7.6 Hz), 7.89 (d, 1H, *J* = 7.2Hz), 7.79–7.75 (m, 3H), 7.66-7.58 (m, 2H), 7.55-7.44 (m, 4H), 7.41–7.33 (m, 3H), 7.31-7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 197.7, 165.5, 160.3, 153.7, 150.6, 138.0, 135.5, 132.8, 130.5, 130.4, 129.8, 129.5, 129.1, 128.7, 128.4, 128.3, 127.8, 126.3, 125.5, 123.6, 122.1, 121.6; IR (KBr, cm^{-1}): 3060, 2922, 2856, 1743, 1669, 1597, 1511, 1448, 1432, 1314, 1262, 1228, 1177, 1076, 1056, 1023, 966, 927, 893, 855, 760, 728; HRMS (ESI) calcd for $C_{27}H_{17}NO_3S$ (M + H^+) 436.1007, found 436.1016.

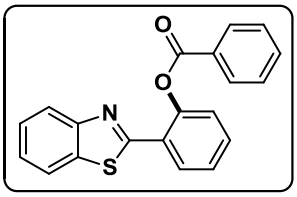
III.7. Spectra

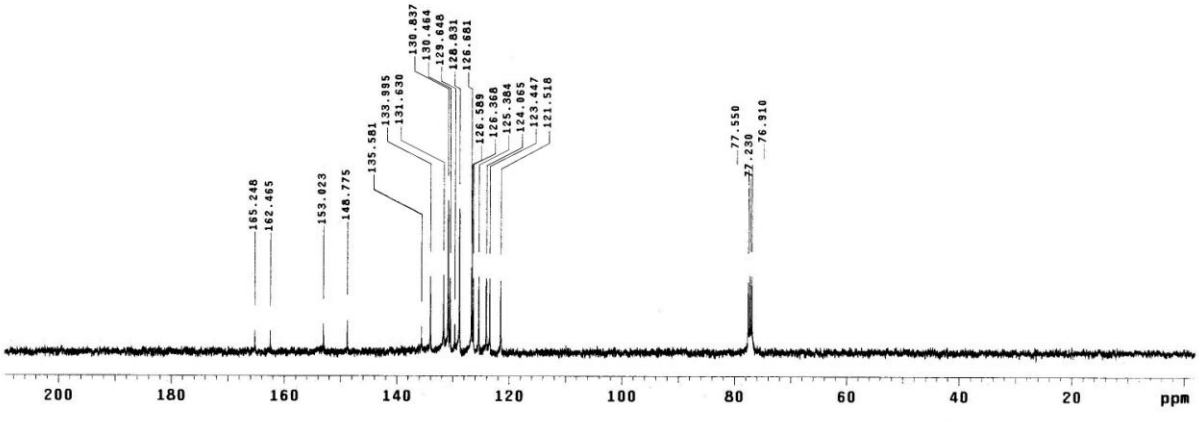
2-(Benzo[*d*]thiazol-2-yl)phenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



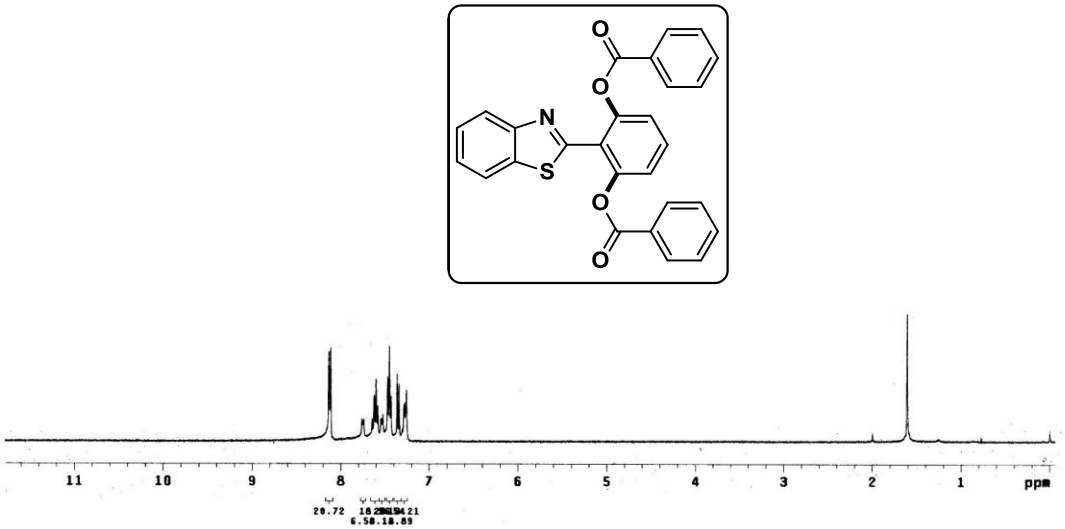


2-(Benzo[*d*]thiazol-2-yl)phenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)

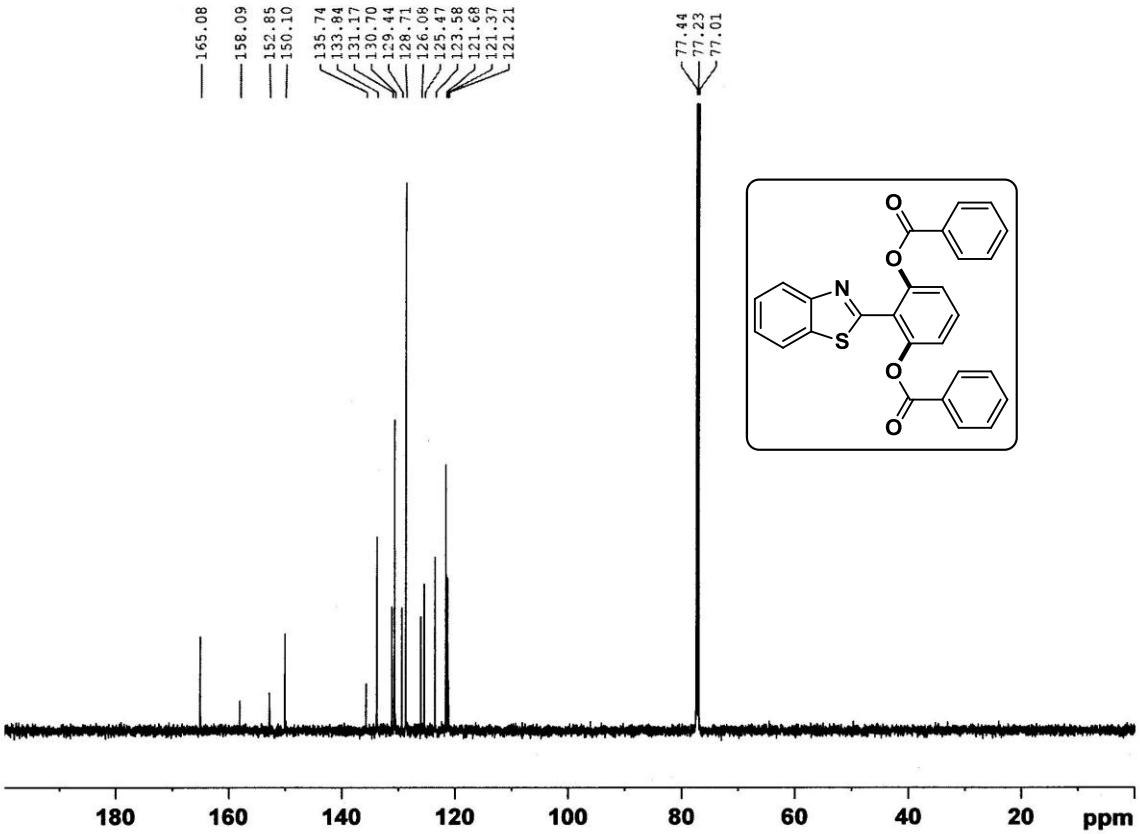




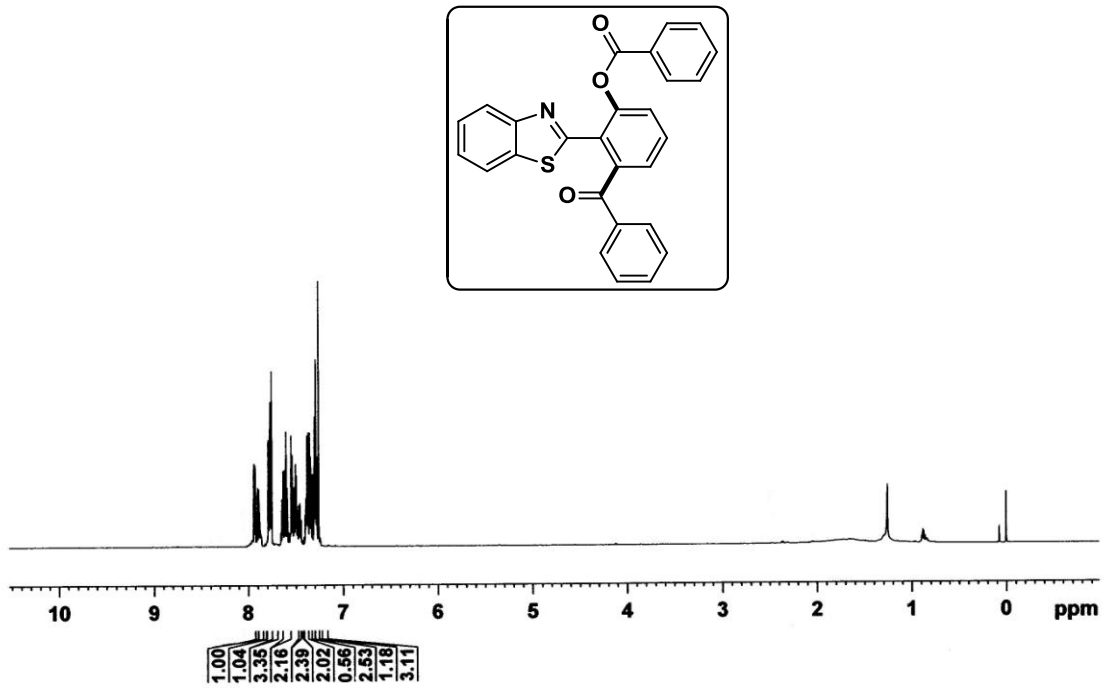
2-(Benzo[*d*]thiazol-2-yl)-1,3-phenylene dibenzoate (1aa): ^{1}H NMR (400 MHz, $CDCl_3$)



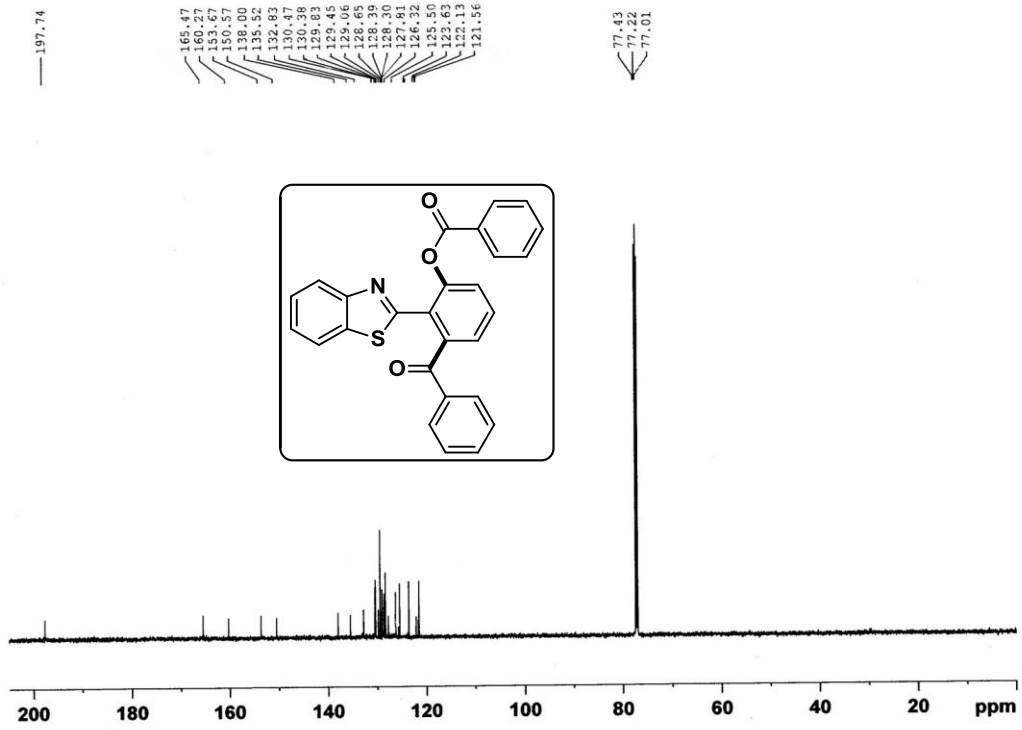
2-(Benzo[*d*]thiazol-2-yl)-1,3-phenylene dibenzoate (1aa): ^{13}C NMR (150 MHz, $CDCl_3$)



2-(Benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (1aa´): ^{1}H NMR (600 MHz, $CDCl_3$)

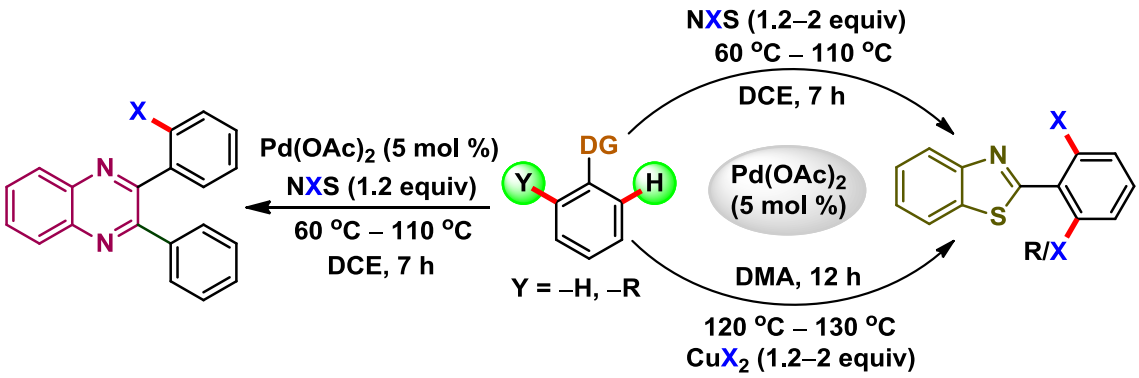


2-(Benzo[*d*]thiazol-2-yl)-3-benzoylphenyl benzoate (1aa´): ^{13}C NMR (150 MHz, $CDCl_3$)



Chapter IV

Palladium(II) Catalyzed o-Halogenation of Direting Arenes Using N-Halosuccinamide and Copper(II) Halide



Abstract: ***Palladium(II) catalyzed ortho-halogenation protocols of directing arenes have been developed using N-halosuccinamide and copper(II) halide. 2-Arylbenzothiazoles provide mono and di-o-halogenated products whereas 2,3-diarylquinoxalines afforded mono-o-halogenated products. The selective formation of di-ortho-halogenated product of ortho-unsubstituted 2-arylbenzothiazole is due to favourable exposure of second ortho site for subsequent halogenations. During the halogenation, CuX_2 (X = Cl, Br) served the dual role of a halogen source as well as a co-oxidant.***

CHAPTER IV

This chapter is divided into two sections. Section-A describes *o*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines using *N*-halosuccinamide whereas Section-B demonstrates *o*-halogenation of 2-arylbenzothiazoles using copper(II) halide as the halogenating source.

IVA. Palladium Catalyzed *ortho*-Halogenation of 2-Arylbenzothiazoles and 2,3-Diarylquinoxalines

IVA.1. Introduction

Transition metal catalyzed directed[1] and non directed[2] C−H functionalization has emerged as an atom and step economic strategy for developing synthetically versatile intermediates *via* unprecedented disconnections. Besides other transition metals, the use of palladium catalyst in chelation directed C−H activation reactions are of interest due to its better efficacy and high turnover numbers.[3] Of late a plethora of Pd-catalyzed *ortho* C–H functionalizations have appeared in the literature using various rigid and flexible directing substrates.[4] Although a number of transition metal catalyzed C−H functionalization strategies are reported for the formation of carbon−carbon (C–C),[5] carbon−heteroatom (C–X) bonds, in particular carbon−halogen bonds, are relatively less explored. Aryl halides (Ar–X) are useful intermediates for synthetic organic chemistry and are valuable precursors for nucleophilic substitution reactions as well as for the synthesis of various organometallic reagents.[6] Aryl halides are also used in transition metal catalyzed cross-coupling reactions such as Suzuki, Negishi and Heck type couplings to construct complex structures.[7] However, preparation of aryl halides *via* classical halogenation suffer from some drawbacks such as poor regioselectivity and polyhalogenations, particularly for activated aromatics.[8] As a solution to these problems, substantial endeavors have been made recently for the regioselective *o*-halogenation of arenes catalyzed by transition metals. A few Pd-catalyzed protocols have emerged recently for the selective installation of halo groups at the *ortho* site of various directing groups *via* arene sp^2 C−H activation.[9] Recently, our group and others have developed strategies for the *ortho* selective C–C and C–X bond formation using benzothiazole and quinoxaline as directing arenes.[10] In continuation to these reports we envisaged that these

two directing arenes *viz.* benzothiazole and quinoxaline could similarly be *ortho* halogenated.

IVA.2. Strategies for *ortho*-Halogenation

Transition metal catalyzed directing group assisted *o*-halogenation strategies have been already discussed in chapter I (page no 19-20).

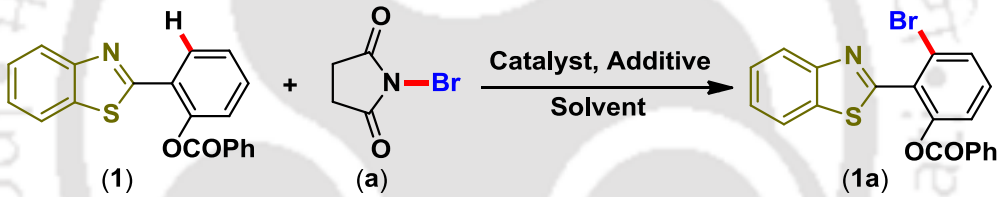
IVA.3. Present Work

2-Arylbenzothiazoles and 2,3-diarylquinoxalines are both privileged motifs present in many naturally occurring molecules and pharmaceuticals[11] bearing *o*-chelating moieties and therefore could be employed for *o*-functionalizations. Thus, further derivatizations of these important scaffolds may provide useful intermediates which may find potential applications. In this section, a Pd-catalyzed *o*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines has been described using *N*-halosuccinamides NXS (X = Cl, Br and I) as halogen sources. From the crystal-structure of 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) it was found that the ester group in 2-aryl ring is towards the sulfur side of benzothiazole and the two aromatic moieties are periplanar.[12] This periplanar orientation with further assistance from *N*-atom of benzothiazole is favorable for cyclopalladation. Thus, 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) was chosen as the model substrate for *ortho*-bromination using *N*-bromosuccinimide as the source of bromine and $Pd(OAc)_2$ as the catalyst.

Optimization of Reaction Conditions. When (**1**) (1 equiv) was reacted with *N*-bromosuccinimide (**a**) (1.2 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) in toluene at 90 ^oC, mono *o*-bromo product (**1a**) was obtained in 39% yield (Table IVA.3.1, entry 1). Absence of any *meta* or *para*-bromo products suggest a substrate directed regioselective *o*-bromination. Encouraged by this success, other reaction parameters such as solvents, catalysts, additives and their quantities were varied to maximize the product yield. Polar aprotic solvents such as DMF or DMSO (Table IVA.3.1, entries 2 and 3) failed to give any trace of product whereas non polar solvents such as cyclohexane, *o*-xylene (Table IVA.3.1, entries 4 and 5) provided very low yield of the product. Interestingly, by switching the solvent from toluene to 1,2-dichloroethane (DCE) (Table IVA.3.1, entry 6) the product yield improved up to 58% under otherwise identical conditions. Other palladium salts such as $Pd(TFA)_2$, $PdCl_2$ and $PdBr_2$ (Table IVA.3.1, entries 7–9), were

relatively less potent compared to $Pd(OAc)_2$. In the absence of catalyst $Pd(OAc)_2$ no *o*-bromination occured (Table IVA.3.1, entry 10). No significant improvement in the product yield was observed even when the catalyst loading was increased from 5 to 10 mol %, (Table IVA.3.1, entry 11). In a pursuit to further improve the yield, acid additives such as pivalic acid (PivOH), *para*-toluenesulfonic acid (PTSA), CF_3COOH (TFA) and CH_3COOH (AcOH) were used during the reaction. After screening the reaction with these acid additives, it was found that the use of 50 mol % PTSA under otherwise identical conditions provided an improved yield (79%) of the desired *o*-brominated product (**1a**) (Table IVA.3.1, entry 12). In the presence of other acid additives such as TFA and AcOH cleavage of ester group in (**1**) was observed along with the formation of *o*-bromo product (**1a**) (Table IVA.3.1, entries 13–14) thereby effectively lowering the product yield. The ester group survived when PivOH was used as the additive but was not so effective toward desired *o*-bromination (Table IVA.3.1, entry 15).

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



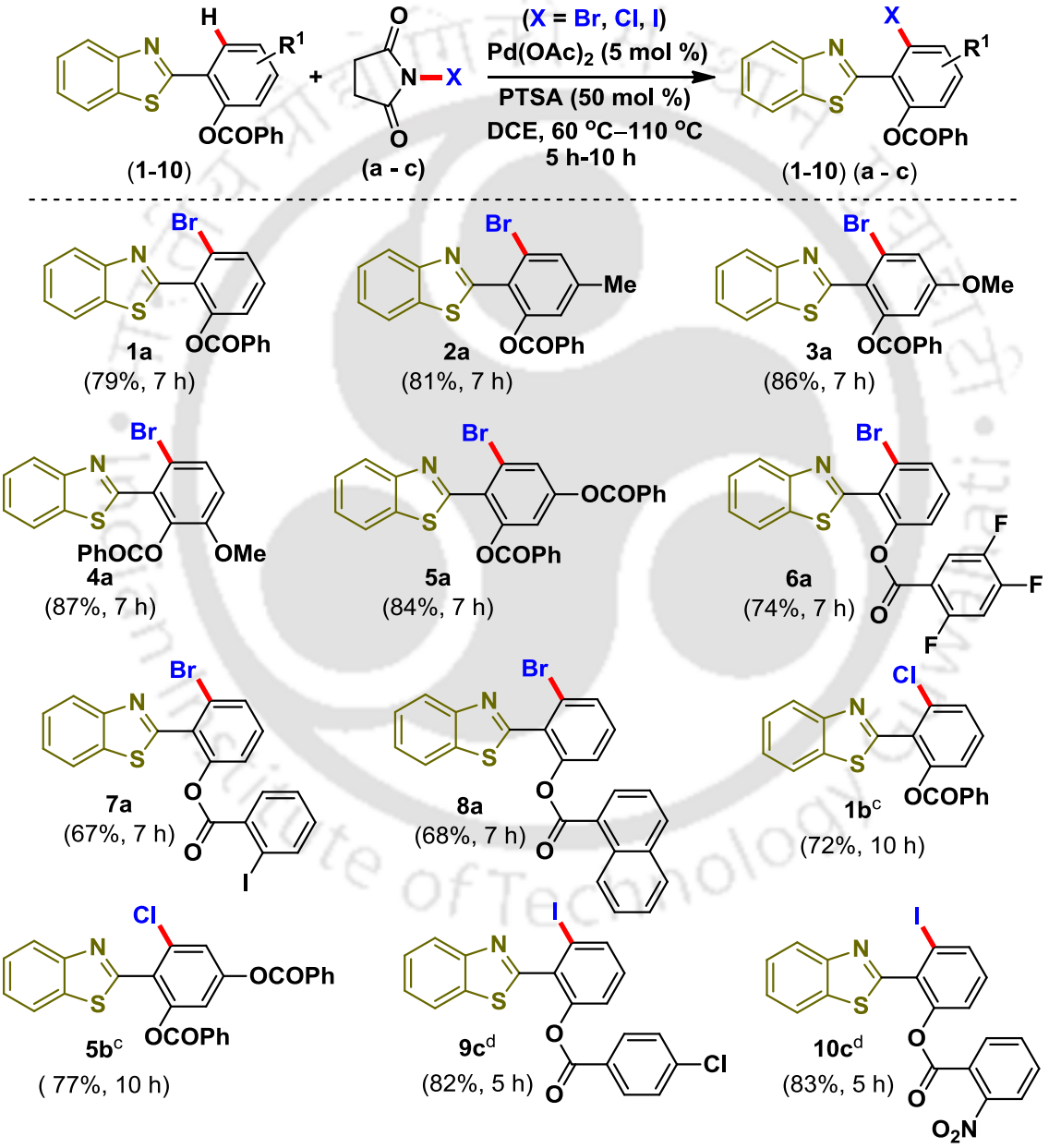
entry	catalyst (mol %)	solvent	oxidant	yield (%)[b]
1	$Pd(OAc)_2$ (5)	toluene	NBS	39
2	$Pd(OAc)_2$ (5)	DMF	NBS	0
3	$Pd(OAc)_2$ (5)	DMSO	NBS	0
4	$Pd(OAc)_2$ (5)	cyclohexane	NBS	trace
5	$Pd(OAc)_2$ (5)	*o*-xylene	NBS	trace
6	$Pd(OAc)_2$ (5)	DCE	NBS	58
7	$Pd(TFA)_2$ (5)	DCE	NBS	46
8	$PdCl_2$ (5)	DCE	NBS	44
9	$PdBr_2$ (5)	DCE	NBS	43
10	-	DCE	NBS	0
11	$Pd(OAc)_2$ (10)	DCE	NBS	62
12	**$Pd(OAc)_2$ (5)**	**DCE**	**NBS/PTSA**	**79[c]**
13	$Pd(OAc)_2$ (5)	DCE	NBS/TFA	68[c]
14	$Pd(OAc)_2$ (5)	DCE	NBS/AcOH	66[c]
15	$Pd(OAc)_2$ (5)	DCE	NBS/PivOH	63[c]

[a]Reaction conditions: 2-Phenylbenzothiazole (**1**) (0.25 mmol), NBS (**a**) (0.3 mmol) at 90 °C for 7 h. [b]Isolated yield. [c]Additive (0.13 mmol).

Thus, after a series of experimentations, 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (1 equiv), catalyst $Pd(OAc)_2$ (5 mol %), additive PTSA (50 mol %) and *N*-bromosuccinimide (**a**) (1.2 equiv) in 1,2 dichloroethane (2 mL) at 90 °C and a reaction time of 7 h was found to be the best conditions for this transformation (Table IVA.3.1, entry 12).

Substrate Scope for *o*-Halogenation. Keeping the above optimized conditions in mind, this methodology was further applied to various substituted 2-(benzo[*d*]thiazol-2-yl)phenyl

Scheme IVA.3.1. *Scope of o-halogenation of 2-arylbenzothiazole*[a,b]



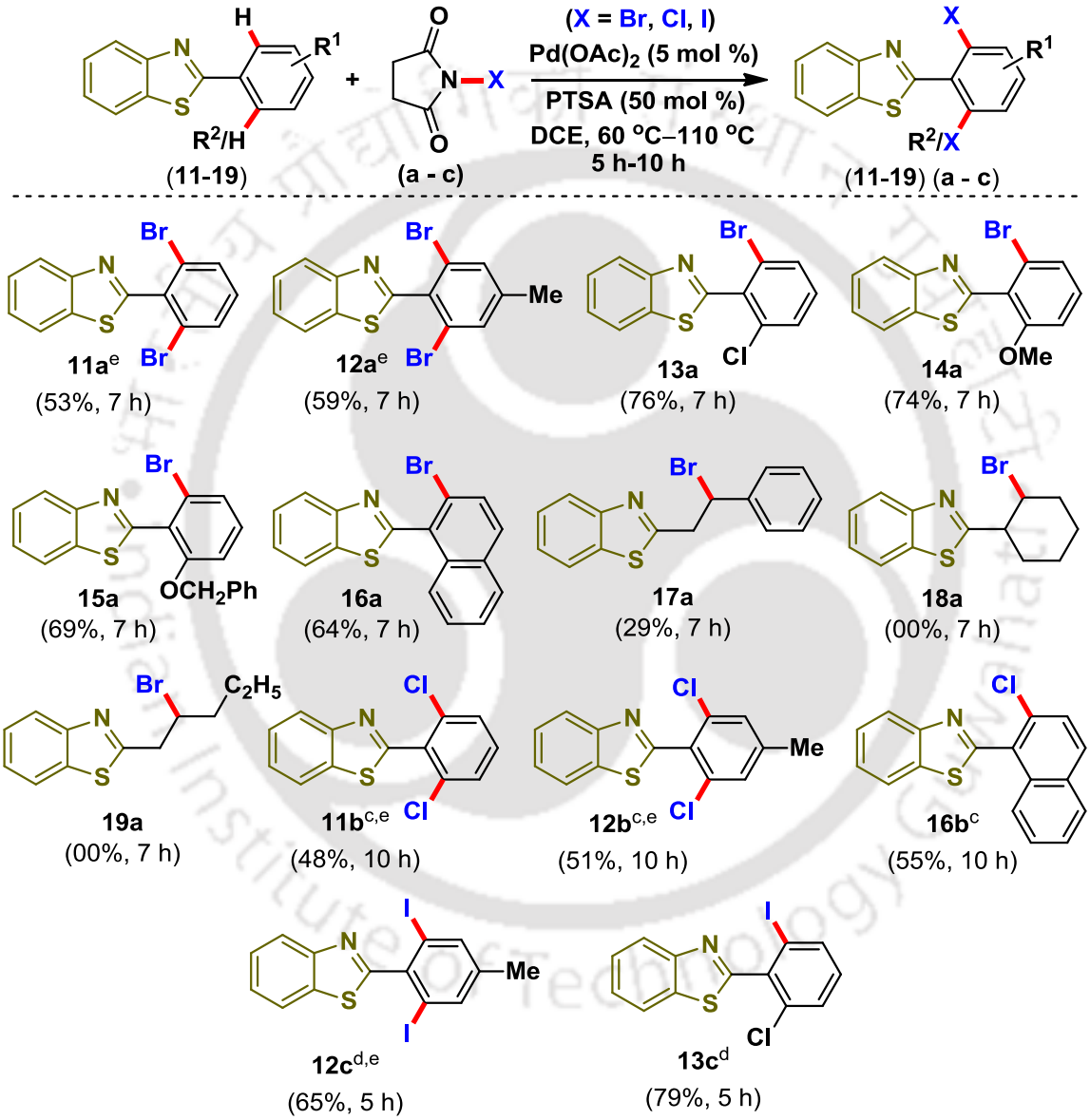
[a]Reaction conditions: 2-Arylbenzothiazoles (**1**–**10**) (0.25 mmol), NBS (**a**) (0.3 mmol) in DCE at 90 °C for 7 h. [b]Isolated yield. [c]NCS (**b**) (0.3 mmol) at 110 °C, [d]NIS (**c**) (0.3 mmol) at 60 °C.

carboxylate with *N*-halosuccinamide (**a**–**c**). 2-(Benzo[*d*]thiazol-2-yl)aryl benzoate containing various substituents at the 2-aryl ring such as *p*–Me (**2**), *p*–OMe (**3**), *m*–OMe (**4**) and *p*–OCOPh (**5**) gave their corresponding *o*-brominated products (**2a**, 81%), (**3a**, 86%), (**4a**, 87%) and (**5a**, 84%) in excellent yields (Scheme IVA.3.1). It is clear from substrates (**1–5**) that no loss of regioselectivity and product yields were observed even with different substitution patterns on the aryl ring. Conversely, for substrates (**6**) and (**7**) the yields of their desired *o*-bromo products (**6a**, 74%) and (**7a**, 67%) were dropped marginally when substituents are present in the phenyl rings possessing the ester group (Scheme IVA.3.1). Naphthyl ester bearing benzothiazole (**8**) also provided moderate yield of its corresponding *o*-bromo product (**8a**, 68%) (Scheme IVA.3.1). When analogous chlorination reaction of (**1**) with *N*-chlorosuccinimide (**b**) was carried out using the above optimized conditions, only 33% yield of *o*-chloro product (**1b**) was obtained. However by increasing the reaction temperature from 90 ^{o}C to 110 ^{o}C and prolonging the reaction time from 7 to 10 h provided the *o*-chlorinated product (**1b**) in an improved yield of 72%. Benzothiazole (**5**) having *ortho* and *para* di-OCOPh group in its 2-aryl ring gave 77% of *o*-chlorinated product (**5b**). Then the strategy was further extended toward *o*-iodination of mono-*o*-protected benzothiazole using *N*-iodosuccinamide. Substrates (**9**) and (**10**) bearing *p*–Cl and *o*–NO_2 groups in their phenyl rings of the ester provided mono-*o*-iodo products (**9c**) and (**10c**) in 82% and 83% yields, respectively (Scheme IVA.3.1). Interestingly, no substantial change in the product yield was observed even when the reaction was performed at lower temperature (60 ^{o}C). However, only trace amount of desired *o*-iodo product was formed when the reaction was carried out at 40 ^{o}C. From these observations it is evident that the rates of halogenation follow the order: iodination > bromination > chlorination.

To verify whether this selective mono-*o*-bromination strategy can be applied to 2-arylbenzothiazole in the absence of *o*-ester functionality, substrate (**11**) with two available *ortho* sites was reacted under the above optimized conditions. When 2-phenylbenzothiazole (**11**) (1 equiv) was treated with NBS (1.2 equiv) under otherwise identical conditions surprisingly rather than the expected mono-*o*-brominated product only *ortho*-di-bromo product (**11a**) was obtained in 41% yield. Typically substrate-directed *o*-halogenation provides mono-halogenated as the major product with trace of di-*ortho*-halogenated product in few cases.[9(a-c),(f-h),13] In the present case exclusive formation

of *ortho*-di-bromo product (**11a**) was rather surprising to us. After the initial *o*-mono bromination the benzothiazole and the 2-phenyl ring possibly adopt a similar periplanar orientation to that of substrate (**1**) exposing the other *ortho* site for subsequent bromination. Even the use of 2 equivalents of (NBS) provided no traces of mono-*o*-bromo product rather the yield of *ortho*-di-bromo product (**11a**) was enhanced to 53%.

Scheme IVA.3.2. *Scope of o-halogenation of 2-arylbenzothiazole*[a,b]



[a]Reaction conditions: 2-Arylbenzothiazoles (**11**–**19**) (0.25 mmol), NBS (**a**) (0.3 mmol) in DCE at 90 °C for 7 h. [b]Isolated yield. [c]NCS (**b**) (0.3 mmol) at 110 °C, [d]NIS (**c**) (0.3 mmol) at 60 °C. [e]2.0 equiv NXS.

2-Arylbenzothiazole having moderately electron-donating group *p*–Me (**12**) in its 2-aryl ring gave 59% yield of di-*o*-brominated product (**12a**) again giving no trace of mono-*o*-bromo product. If our assumption on periplanar orientation of benzothiazole and 2-aryl

ring after first bromination is true then preformed mono *ortho* substituted benzothiazoles should react to provide better yields of *bis-ortho* substituted products. To verify this *o*–Cl (**13**), *o*–OMe (**14**) and *o*–OCH_2Ph (**15**) substituted 2-arylbenzothiazoles were employed for *ortho* bromination. All three substrates provided *o*-brominated products (**13a**, 76%), (**14a**, 74%) and (**15a**, 69%) in far better yields as shown in Scheme IVA.3.2.

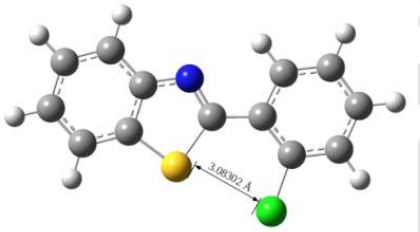


Fig. IVA.3.1 (**a**)

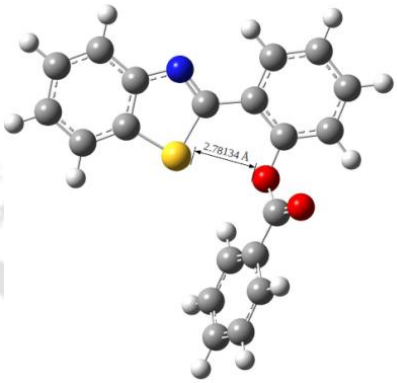


Fig. IVA.3.1 (**b**)

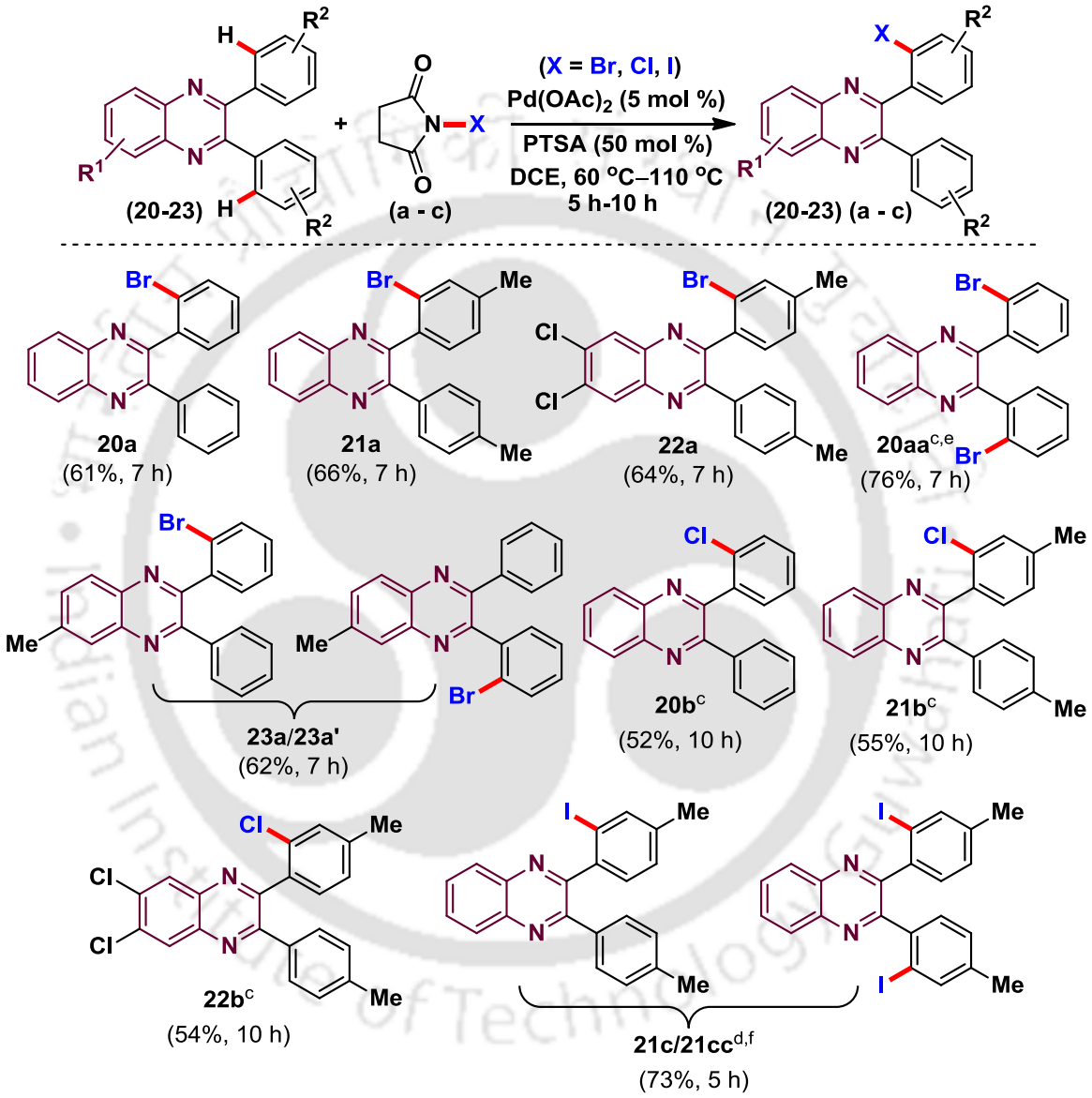
Energy calculation performed using Gaussian 09 package[14] at B3LYP-D3/6-31G (d,p) level of substrate 2-(2-chlorophenyl)benzo[*d*]thiazole (**13**) revealed the periplanar orientation of benzothiazole and 2-chloro phenyl ring to be the most stable conformer with the chloro group orienting toward the sulphur side (*Fig. IVA.3.1* (**a**)). The extra stability of this conformer is due to sulphur (S)···chlorine (Cl) interaction. Similar chloro (halo) and sulphur atom interaction is reported in various organic and inorganic moieties.[15] Such a periplanar arrangement with the oxygen atom of the ester group orienting toward sulphur side is also observed in the energy minimized structure of 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (*Fig. IVA.3.1* (b)). Apparently, the energy minimized structure of (**1**) (*Fig. IVA.3.1* (b)) matches exactly with its X-ray crystal structure.[12] Thus, this type of periplanar orientation is the most favourable for *o*-palladation leading to *o*-halogenation. These results demonstrate the conformational predominance of the substrates over their steric and electronic effects during directed bromination. In case of substrate 2-(naphthalen-1-yl)benzo[*d*]thiazole (**16**) possessing both *ortho* and *peri* C–H bonds, bromination occurred selectively at the *ortho* site giving product (**16a**) in 64% yield. When *o*-bromination strategy was applied to 2-phenethylbenzo[*d*]thiazole (**17**), interestingly bromination occurred at the β C_{sp3}–H bond which happened to be a benzylic carbon as well. Now the query arises whether the bromination is due to classical radical benzylic bromination or a substrate directed metal

catalyzed sp^3 C–H fucntionalization. When the reaction was performed in absence of a Pd-catalyst under otherwise identical conditions, no bromination was observed thereby suggesting the later possibility. The lower yield (29%) obtained for (**17a**) is possibly due to the free rotation of C_{sp3}–C_{sp3} containing benzylic and its adjacent carbon thereby lowering the possibility of cyclopalladation. However other β C_{sp3}–H bearing alkane substrates such as (**18**) and (**19**) failed to provide desired brominated products (Scheme IVA.3.2). Thus, for substrate (**17**) due to the presence of an acidic benzylic β C_{sp3}–H's the bromination was favourable compared to substrates (**18**) and (**19**). The success of this bromination strategy was then extended towards *o*-chlorination of substrates (**11**) and (**12**) using *N*-chlorosuccinimide (**b**) following the previous optimized conditions for chlorination, which provided *o*-di-chloro products (**11b**, 48%) and (**12b**, 51%) respectively in moderate yields (Scheme IVA.3.2). Here again substrate (**16**) possessing both *ortho* and *peri* C–H bonds, the chlorination occurred regioselectively at the *ortho* site giving product (**16b**) in 55% yield. Analogous *o*-iodination of (**12**) and (**13**) using *N*-iodosuccinamide (**c**) gave *o*-iodo products (**12c**) and (**13c**) in 65% and 79% yields, respectively under identical conditions for iodination. Here also the rates of *o*-di-halogenation (Scheme IVA.3.2) follow the same order (iodination > bromination > chlorination) to that of mono-*o*-halogenation (Scheme IVA.3.1).

Unlike in 2-arylbenzothiazoles, 2,3-diarylquinoxaline moiety has four *ortho* sites for possible directed halogenations. Thus, it would be interesting to see during halogenation which one of the products would be formed selectively under a particular condition. A mono-halogenation in one of the phenyl ring, mono-halogenation in each of the phenyl ring; di-halogenation in one of the ring or a di-halogenation in both the rings are some of the possibilities. Thus the above optimized conditions were applied to 2,3-diarylquinoxalines for bromination, chlorination and iodination respectively. 2,3-Diphenyl quinoxaline (**20**), when reacted with NBS (**a**) (1.2 equiv) at 90 ^oC, mono-*o*-bromo product (**20a**) was obtained in 61% yield along with a trace (<5%) of di-bromo (mono-bromination in each of the phenyl ring) product (**20aa**). However, increasing the quantity of (NBS) to 2 equivalents the yield of the di-bromo product (**20aa**) was improved to 12%. Maintaining the (NBS) quantity to 2 equivalents and increasing the reaction temperature to 110 ^oC substantial improvement in the yield (76%) of the di-bromo product (**20aa**) was observed (Scheme IVA.3.3). Presently, however we concentrate on achieving selective

mono-bromination. 2,3-Diphenylquinoxaline (**21**) containing electron-donating group (-Me) in its aryl rings gave 66% of the mono-*o*-bromo product (**21a**). The substrate 6,7-dichloro-2,3-diphenylquinoxaline (**22**) on treatment with NBS (**a**) afforded moderate yield of the mono-*o*-bromo product (**22a**, 64%).

Scheme IVA.3.3. *Scope of o-halogenation of 2,3-diphenylquinoxaline*[a,b]

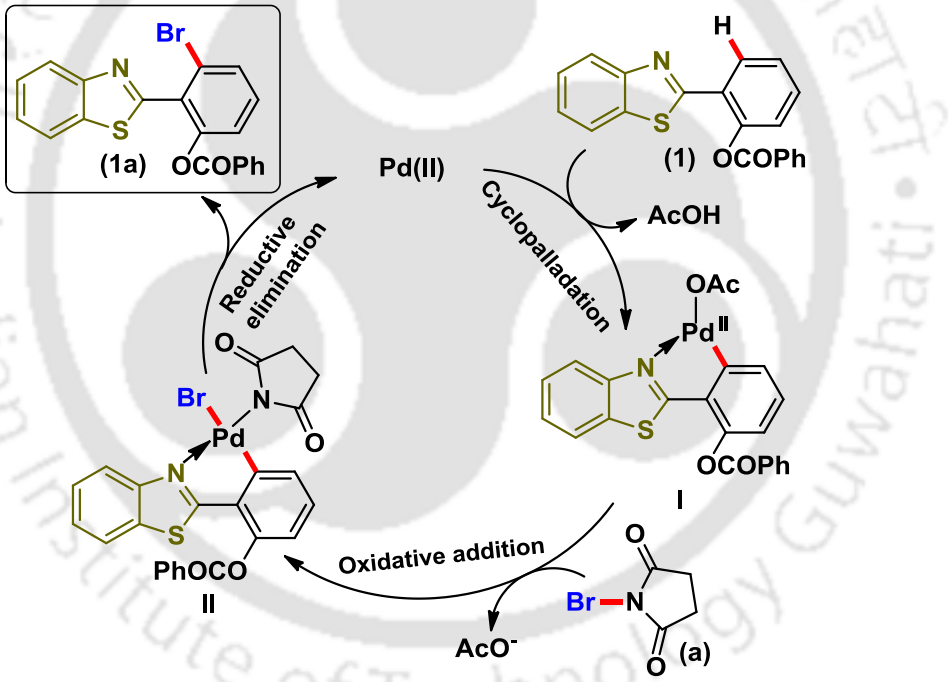


[a]Reaction conditions: 2,3-Diarylquinoxalines (**20**–**23**) (0.25 mmol), NBS (**a**) (0.3 mmol) in DCE at 90 °C for 7 h. [b]Isolated yield. [c]NCS (**b**) (0.3 mmol) at 110 °C, [d]NIS (**c**) (0.3 mmol) at 60 °C. [e]2.0 equiv NXS. [f]Yield calculated from recovery of starting material.

Unsymmetrical 2,3-diphenylquinoxaline (**23**) having a -Me group at its 6th position when reacted with NBS provided an inseparable regioisomeric mono-*o*-bromo products **23a**/**23a′** in the ratio of 55:45 (as judged from its ^{1}H and ^{13}C NMR spectra) in 62% yield.

So far as chlorination is concerned under the optimized conditions various unsubstituted and substituted 2,3-diphenylquinoxaline such as (**20**), (**21**) and (**22**) all provided exclusive mono *ortho*-chlorinated products (**20b**, 52%), (**21b**, 55%) and (**22b**, 54%) respectively in good yields (Scheme IVA.3.3). Like previous cases iodination of substrate (**21**) provided an inseparable mixture of mono (**21c**) and di-iodo (**21cc**) products in a combined yield of 73%. In this system also the same reactivity trend (iodination > bromination > chlorination) to that of mono-*o*-halogenation was observed.

A possible mechanism has been proposed for this palladium catalyzed *ortho*-halogenation reaction as shown in Scheme IVA.3.4. For *o*-bromination process initial cyclopalladation of substrate (**1**) leads to the formation of intermediate (**I**). This intermediate further undergoes oxidative addition with *N*-bromosuccinamide (NBS) forming either a dimeric Pd(III)[16] or a monomeric Pd(IV)[9b,17] intermediate (**II**).



Scheme IVA.3.4. *Plausible mechanism for o-bromination*

Mass spectral analysis of the reaction mixture showed the formation of some of the monomeric Pd(IV) species (see experimental section). However, the formation of a dimeric Pd(III) during the reaction cannot be ruledout.[16] Subsequent reductive elimination of intermediate (**II**) leads to *o*-bromo product (**1a**) *via* C–Br bond formation and regenerating Pd(II) catalyst for the next cycle. The mono-*ortho* bromo product so formed orient favourably for subsequent bromination following similar mechanistic path leading

to the formation of di-bromo product. Similar mechanism can be proposed for chlorination and iodination of 2-aryl benzothiazole and 2,3-diarylquinoaline.

In conclusion, we have developed an *ortho*-halogenation strategy using palladium(II) as the catalyst and *N*-halosuccinamide as the halogen source using benzothiazoles and quinoxalines as the directing substrates. This method provides mono-*o*-halogenated product at the other available *ortho* site of a mono-*ortho* substituted 2-arylbenzothiazole. Although *ortho*-unsubstituted 2-arylbenzothiazole afforded di-*ortho* halogenated product exclusively while *ortho*-unsubstituted 2,3-diarylquinoxaline afforded mono-*o*-halogenated products under identical reaction conditions.

IVB. Copper(II) Halide as a Halogenating Agent in Pd-Catalyzed *ortho*-Halogenation of 2-Arylbenzothiazoles

IVB.1. Introduction

After successful *ortho*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines in the presence of Pd-catalyst and *N*-halosuccinamides, another halogenating source is reported herein. So far various halogenating source such as *N*-halosuccinamide,[9] LiX,[18] CuX_2,[19] CaX_2,[20] DDQ[21] and Suárez reagents (XOAc, X = Br, I)[22] have been employed for *ortho*-halogenation. Recently, we have reported a Pd(II)/$CuBr_2$ catalyzed keto α-C_{sp3}–H benzoxylation of *N*,*N*-dialkylamides where bonus ring bromination took place at the *ortho* or *para* position to –OH group of salicylaldehyde and 2-hydroxyacetophenone derivatives (Chapter V).[23] Since Pd(II)/$CuBr_2$ combination provided ring bromination of activated aromatic ring, this strategy may be applied for ligand directed *ortho*-bromination *via* C–H activation.

IVB.2. Strategies for *ortho*-Halogenation

Transition metal catalyzed directing group assisted *o*-halogenation strategies have been already discussed in chapter I (page no 19-20).

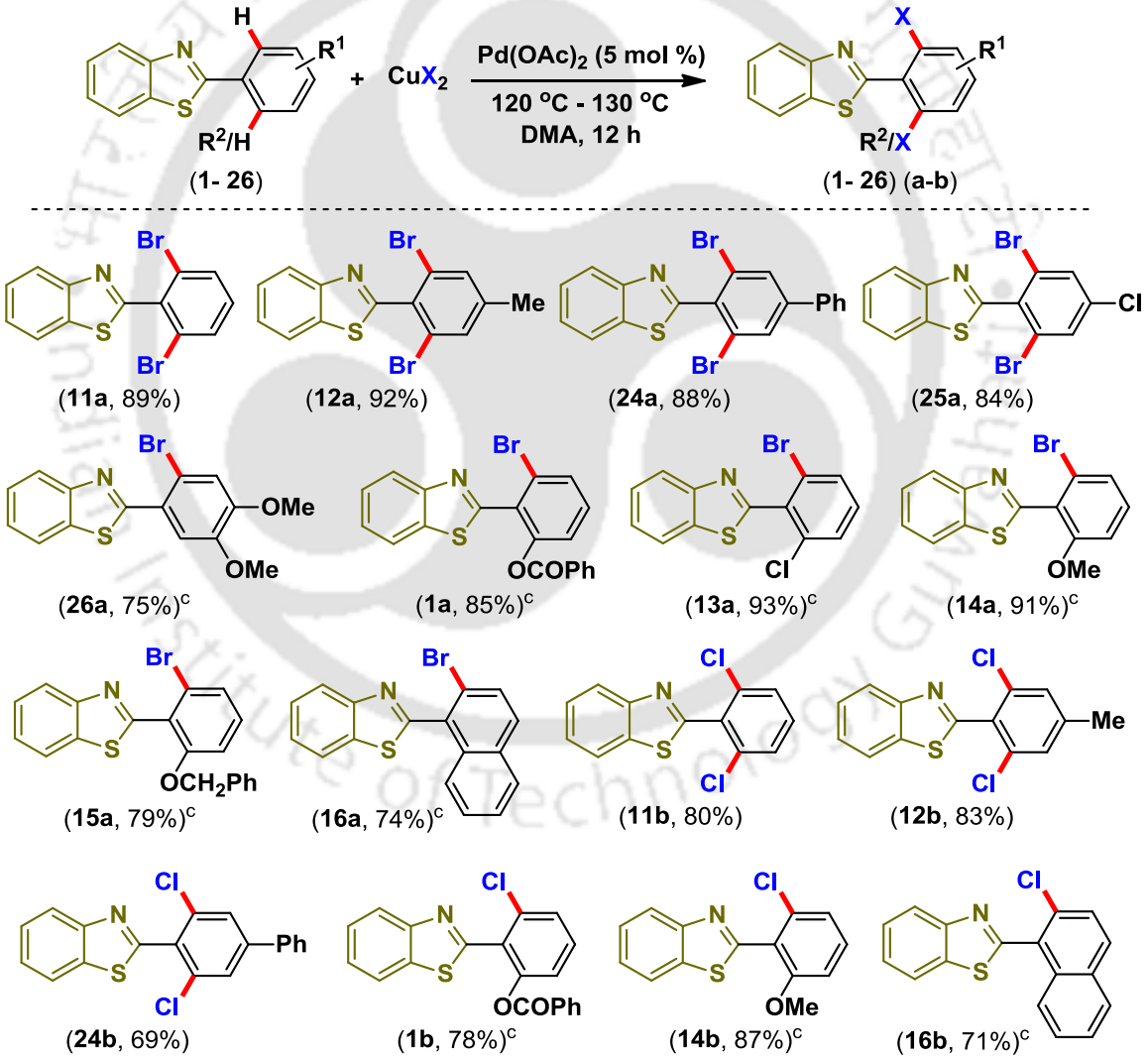
IVB.3. Present Work

2-Arylbenzothiazoles, a privileged motif present in many naturally occurring molecules and pharmaceuticals[11] having directing ability through nitrogen atom could be employed for *o*-functionalizations.

Substrate Scope for *o*-Halogenations. To verify whether Pd(II)/$CuBr_2$ combination can provide *o*-bromination or not, 2-phenylbenzothiazole (**11**) (1 equiv) was treated with $CuBr_2$ (1.2 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) in DMA (1.0 mL). Similar to section A, here also exclusive *o*-di-brominated product (**11a**) was obtained in 57% yield instead of the *ortho*-mono-brominated product along with the unreacted starting material. From the energy calculation[14] and literature reports[15] it is revealed that, due to the sulphur (S)···X (X = –Br, –Cl) interaction, the initially formed mono-*o*-halogenated 2-arylbenzothiazole adopts a periplanar orientation there by facilitating further *o*-palladation for subsequent halogenation. The yield of the *ortho*-dibromo product (**11a**) increased upto

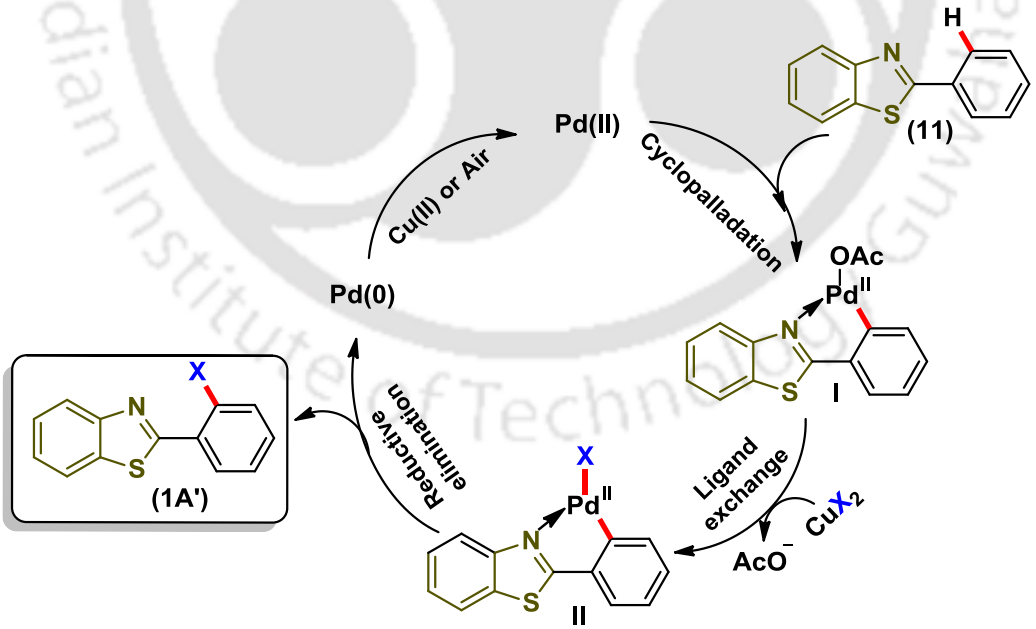
89% by enhancing the quantity of $CuBr_2$ to 2.0 equivalents. 2-Arylbenzothiazoles having moderately electron-donating groups such as *p*–Me (**12**) and *p*–Ph (**24**) in its 2-aryl ring gave 92% and 88% yields of di-*o*-brominated products (**12a**) and (**24a**), respectively (Scheme IVB.3.1). The benzothiazole (**25**), substituted with moderately electron-withdrawing group *p*–Cl, provided 84% yield of the desired *ortho*-dibrominated product (**25a**) under the reaction conditions. An exception to the observation is 3,4-di-OMe substituted benzothiazole (**26**), which gave only the *ortho*-monobrominated product (**26a**) in 75% yield, where bromination took place at the less sterically hindered *o*-site of the 2-aryl ring.

Scheme IVB.3.1. *Pd(II)-Catalyzed ortho-halogenation of 2-arylbenzothiazoles*[a,b]



[a]Reaction conditions: 2-Arylbenzothiazoles (**11**–**26**) (0.25 mmol), CuX_2 (0.5 mmol) in DMA at 120 °C-130 °C for 12 h. [b]Isolated yield. [c]CuX_2 (0.3 mmol).

When the reaction was carried out with *ortho*-monosubstituted benzothiazoles such as *o*–OCOPh (**1**), *o*–Cl (**13**), *o*–OMe (**14**) and *o*–OCH_2Ph (**15**), all substrates provided the *o*-mono brominated products (**1a**, 85%), (**13a**, 93%), (**14a**, 91%) and (**15a**, 79%) in excellent yields as shown in Scheme IVB.3.1. When the *o*-bromination strategy was applied to 2-(naphthalen-1-yl)benzo[*d*]thiazole (**16**), interestingly bromination occurred selectively at the *ortho* site, giving product (**16a**) in 74% yield. To check whether $CuCl_2$ will provide *o*-chlorination similar to *o*-bromination, 2-phenylbenzothiazole (**11**) was treated with $CuCl_2$ in lieu of $CuBr_2$ under otherwise identical conditions, but no trace of *o*-chlorinated product was obtained. However, efficient *o*-chlorination was observed when the reaction temperature was increased from 120 ^oC to 130 ^oC, affording 80% of *o*-dichloro product (**11b**). The success of this chlorination strategy was then applied to other substituted 2-arylbenzothiazoles such as *p*–Me (**12**) and *p*–Ph (**24**), providing *o*-dichloro products (**12b**, 83%) and (**24b**, 69%) in good yields. *Ortho*-mono substituted benzothiazoles such as *o*–OCOPh (**1**) and *o*–OMe (**14**) gave excellent yields of *o*-chlorinated products (**1b**, 78%) and (**14b**, 87%) respectively, at the other available *ortho* site (Scheme IVB.3.1). With substrate (**16**) possessing both *ortho* and *peri* C–H bonds, chlorination occurred regioselectively at the *ortho* site, giving product (**16b**) in 71% yield.



Scheme IVB.3.2. *Plausible mechanistic cycles for o-halogenation*

For *ortho*-halogenation initially cyclopalladation of substrate (**11**) leads to the formation of intermediate (**I**). This intermediate further undergoes ligand exchange with

halide (Br^- or Cl^-) forming a Pd(II) intermediate (**II**). Finally reductive elimination of intermediate (**II**) leads to the formation of mono *o*-halo product (**1A´**) and Pd(0), which is oxidized to Pd(II) by air/$CuBr_2$ for the next catalytic cycle as shown in Scheme IVB.3.2. The mono *ortho*-halo product so formed orient favorably that undergoes for second halogenations *via* similar mechanistic path.

In conclusion, a palladium catalyzed mild *o*-C–H halogenations of 2-arylbenzothiozoles has been developed by using copper(II) halides. Cu(II)-salts plays a dual role of halogenating agent as well as co-oxidant. This method provides di-*o*-halogenated product of mono-*ortho* unsubstituted 2-arylbenzothiazoles in good to excellent yields.

IV.4. Experimental Section

IV.4.1. General Information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). 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). 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.

IV.4.2. Synthesis of *o*-Halogenated 2-Arylbenzothiaoles

IVA.4.2.1 General Procedure for the Synthesis of 2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (1a) from 2-(Benzo[*d*]thiazol-2-yl)phenyl benzoate (1): To an oven-dried 25 mL round bottom flask were added 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (0.083g, 0.25 mmol), *N*-bromosuccinamide (0.053g, 0.3 mmol), $Pd(OAc)_2$ (0.003g, 0.013 mmol), *para*-toluenesulfonic acid (0.024g, 0.13 mmol) and 1,2-dichloroethane (2.0 mL). Then the reaction mixture was refluxed in an oil bath preheated to 90 ^oC. After completion of the reaction (7 h) excess solvent was removed under vacuum (rotary evaporator). The product was extracted with ethyl acetate (3 x 10 mL) and the

combined organic layer was washed carefully with saturated sodium bicarbonate solution (10 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 9.7:0.3) to give pure 2-(benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (**1a**) (0.081g, yield 79%). The identity and purity of the product was confirmed by spectroscopic analysis.

IVB.4.2.1 General Procedure for the Synthesis of 2-(2,6-dibromophenyl)benzo[*d*]thiazole (11a) from 2-Phenylbenzothiazole (11): 2-Phenylbenzothiazole (**11**) (0.053g, 0.25 mmol), $CuBr_2$ (0.112g, 0.5 mmol), $Pd(OAc)_2$ (0.003g, 0.013 mmol) and *N*,*N*-dimethylacetamide (DMA) (1.0 mL) were placed in an oven-dried 25 mL round bottom flask. The reaction mixture was then heated in an oil bath preheated at 120 ^oC. After completion (12 h) the reaction mixture was cooled to room temperature. The product was extracted with ethyl acetate (30 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 9.8:0.2) to give pure yellow gummy 2-(2,6-dibromophenyl)benzo[*d*]thiazole (**11a**) (0.082g, yield 89%). The identity and purity of the product was confirmed by spectroscopic analysis.

IV.4.3. Mechanistic Investigations

IVA.4.3. ESI-MS Study for the Detection of Reaction Intermediates During *o*-Bromination: In order to detect the intermediate species in the reaction mixture an electrospray mass spectrometry was performed. In this study, an oven-dried flask was charged with 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (0.083g, 0.25 mmol), *N*-bromosuccinamide (0.053g, 0.3 mmol), $Pd(OAc)_2$ (0.003g, 0.013 mmol), *para*-toluenesulfonic acid (0.024g, 0.13 mmol) and 1,2-dichloroethane (2.0 mL). Then the reaction mixture was stirred in an oil bath at 90 ^oC. After 0.5 h of reaction, aliquot (100 μL) was withdrawn and diluted with acetonitrile (1 mL). A 20 μL of the diluted solution was injected to run ESI-MS analysis. Various cationic and neutral Pd species were detected in the ESI-MS analysis as shown below in Fig. IVA.4.3.1. The o-brominated product, cationic and neutral Pd-species observed in the spectrum are as follows: peaks at m/z 411.9857 corresponding to 2-(benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (**1a**)

(Fig. IVA.4.3.1), at m/z 614.8975 corresponding to $[C_{24}H_{16}BrN_2O_4Pd(IV)S]^+$ (**A**) (Fig. IVA.4.3.1), at m/z 846.9437 corresponding to $[C_{40}H_{24}BrN_2O_4Pd(IV)S_2]^+$ (**B**) (Fig. IVA.4.3.1), at m/z 962.8334 corresponding to $[C_{48}H_{32}N_4O_8Pd(IV)S_2]$ (**C**) (Fig. IVA.4.3.1).

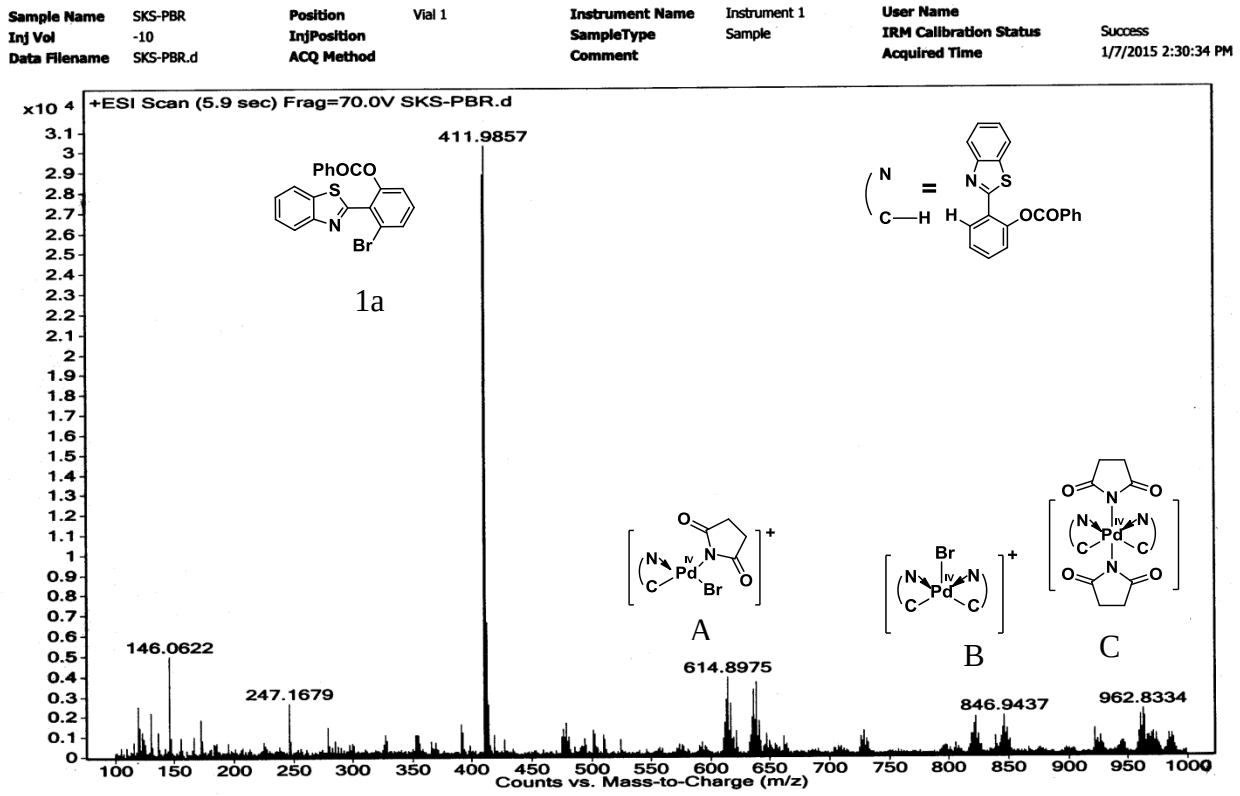


Fig. IVA.4.3.1*. ESI-MS spectrum of the reaction mixture*

IV.5. References

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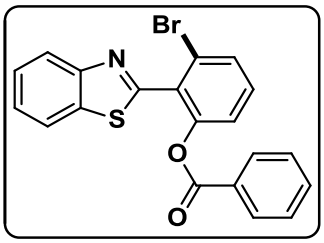
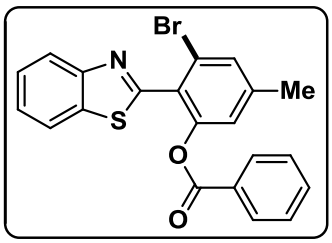
IV.6. Spectral Data

2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (1a):



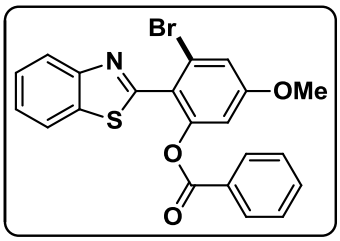
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 1H, *J* = 8.0 Hz), 7.88–7.85 (m, 3H), 7.66 (d, 1H, *J* = 7.6 Hz), 7.50–7.42 (m, 3H), 7.40–7.36 (m, 2H), 7.29 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 161.8, 153.0, 150.4, 136.3, 133.9, 131.8, 130.8, 130.3, 129.0, 128.7, 128.6, 126.3, 125.7, 124.3, 123.9, 122.6, 121.7; IR (KBr, cm^{-1}): 3059, 2914, 2853, 1741, 1598, 1565, 1518, 1441, 1428, 1313, 1261, 1221, 1175, 1137, 1077, 1055, 1023, 962, 873, 855, 760, 729, 707; HRMS (ESI) calcd for $C_{20}H_{12}BrNO_2S$ (M + H^+) 409.9850, found 409.9858.

2-(Benzo[*d*]thiazol-2-yl)-3-bromo-5-methylphenyl benzoate (2a):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, 1H, *J* = 8.4 Hz), 7.87–7.84 (m, 3H), 7.50–7.45 (m, 3H), 7.37 (t, 1H, *J* = 7.6 Hz), 7.30 (t, 2H, *J* = 8.0 Hz), 7.18 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.9, 161.9, 153.1, 150.2, 142.9, 136.5, 133.8, 131.6, 130.3, 128.9, 128.6, 126.2, 126.1, 125.6, 123.9, 123.8, 123.3, 121.7, 21.4; IR (KBr, cm^{-1}): 3061, 2919, 2845, 1741, 1610, 1555, 1451, 1432, 1313, 1237, 1176, 1128, 1077, 1058, 1024, 863, 821, 760, 729, 706; HRMS (ESI) calcd for $C_{21}H_{14}BrNO_2S$ (M + H^+) 424.0007, found 424.0013.

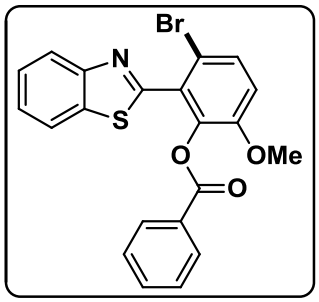
2-(Benzo[*d*]thiazol-2-yl)-3-bromo-5-methoxyphenyl benzoate (3a):



Solid; M.p. 155 ^{o}C–157 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 7.6 Hz), 7.49–7.41 (m, 2H), 7.35 (t, 1H, *J* = 7.6 Hz), 7.29 (t, 2H, *J* = 7.4 Hz), 7.21 (s, 1H), 6.92 (s, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.7, 161.9, 161.7, 152.9, 151.1, 136.5, 133.9, 130.3, 128.8, 128.6, 126.2, 125.6, 124.6, 123.8, 121.6, 121.3, 116.9, 108.8, 56.1; IR (KBr, cm^{-1}): 3075, 2958, 1747, 1609, 1564, 1523, 1461, 1452, 1425, 1316, 1241, 1202, 1176, 1117, 1075, 1054, 1039, 1023, 965, 863, 814, 761, 731; HRMS (ESI) calcd for $C_{21}H_{14}BrNO_3S$ (M + H^+) 439.9956, found 439.9965.

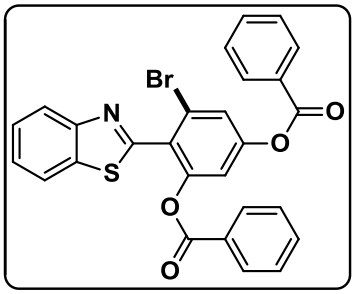
2-(Benzo[*d*]thiazol-2-yl)-3-bromo-6-methoxyphenyl benzoate (4a):

Solid; M.p. 183 ^{o}C–186 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 7.6 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.58 (d, 1H, *J* = 8.8 Hz), 7.50–7.42 (m, 2H),



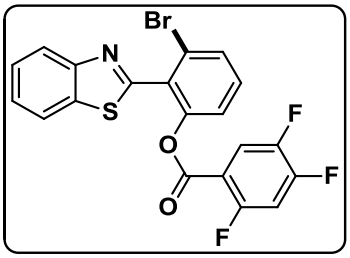
7.37–7.30 (m, 3H), 7.02 (d, 1H, J = 9.2 Hz), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.2, 161.7, 153.1, 151.5, 140.1, 136.4, 133.7, 130.9, 130.4, 130.0, 128.7, 128.6, 126.2, 125.7, 123.9, 121.7, 115.1, 113.8, 56.6; IR (KBr, cm^{-1}): 3058, 2923, 2851, 1742, 1598, 1572, 1558, 1524, 1466, 1451, 1438, 1298, 1258, 1244, 1221, 1196, 1100, 1076, 1055, 1021, 994, 869, 801, 760, 731, 706; HRMS (ESI) calcd for $C_{21}H_{14}BrNO_3S$ (M + H$^+$) 439.9956, found 439.9959.

4-(Benzo[*d*]thiazol-2-yl)-5-bromo-1,3-phenylene dibenzoate (5a):



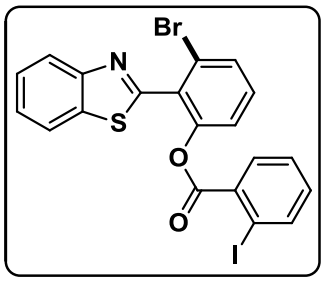
Solid; M.p. 115 ^{o}C–117 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 2H, J = 7.6 Hz), 8.05 (d, 1H, J = 8.4 Hz), 7.89 (d, 1H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.0 Hz), 7.67 (t, 1H, J = 7.4 Hz), 7.64 (s, 1H), 7.54 (t, 2H, J = 7.8 Hz), 7.49–7.46 (m, 2H), 7.43–7.38 (m, 2H), 7.30 (t, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 161.3, 153.1, 152.6, 150.8, 136.5, 134.3, 134.0, 130.6, 130.4, 128.9, 128.8, 128.7, 128.6, 126.6, 126.3, 125.8, 124.4, 124.3, 124.0, 121.7, 116.8; IR (KBr, cm^{-1}): 3055, 2913, 2842, 1742, 1601, 1558, 1507, 1450, 1431, 1409, 1256, 1240, 1132, 1076, 1059, 1024, 951, 886, 754, 695; HRMS (ESI) calcd for $C_{27}H_{16}BrNO_4S$ (M + H$^+$) 530.0061, found 530.0071.

2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl 2,4,5-trifluorobenzoate (6a):



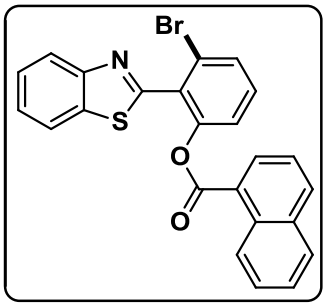
Solid; M.p. 120 ^{o}C–123 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, 1H, J = 8.0 Hz), 7.89 (d, 1H, J = 8.0 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.56–7.49 (m, 1H), 7.47 (d, 1H, J = 8.8 Hz), 7.43–7.41 (m, 2H), 7.37 (t, 1H, J = 7.8 Hz), 6.90–6.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 160.3, 152.9, 149.7, 136.3, 131.9, 131.3, 128.9, 126.5, 125.9, 124.4, 123.9, 122.4, 121.8, 120.5, 120.3, 107.6, 107.4, 107.3, 107.1; IR (KBr, cm^{-1}): 3065, 2923, 2847, 1746, 1623, 1595, 1566, 1522, 1446, 1422, 1341, 1253, 1237, 1191, 1145, 1045, 959, 893, 859, 846, 814, 772, 764, 749, 720, 702; HRMS (ESI) calcd for $C_{20}H_9BrF_3NO_2S$ (M + H$^+$) 463.9567, found 463.9574.

2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl 2-iodobenzoate (7a):



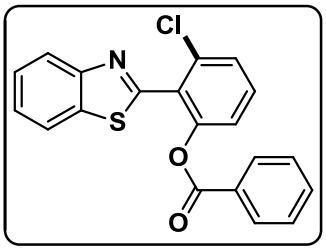
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 1H, *J* = 8.0 Hz), 7.89 (t, 2H, *J* = 7.4 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 7.50–7.38 (m, 5H), 7.12 (t, 1H, *J* = 7.6 Hz), 7.04 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.3, 161.8, 153.1, 150.2, 141.8, 136.5, 133.5, 133.1, 131.9, 131.7, 131.2, 129.2, 128.0, 126.4, 125.9, 124.4, 124.0, 122.7, 121.8, 94.9; IR (KBr, cm^{-1}): 3060, 2922, 2851, 1750, 1581, 1559, 1440, 1428, 1313, 1280, 1216, 1172, 1125, 1071, 1036, 1010, 961, 871, 760, 737; HRMS (ESI) calcd for $C_{20}H_{11}BrINO_2S$ ($M + H^+$) 535.8817, found 535.8828.

2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl 1-naphthoate (8a):



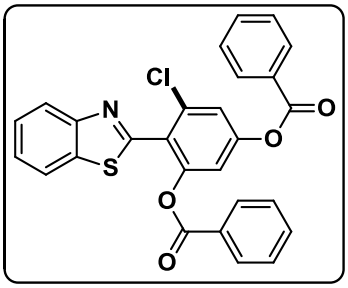
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (d, 1H, *J* = 9.6 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 7.95–7.90 (m, 2H), 7.85–7.79 (m, 2H), 7.69 (d, 1H, *J* = 8.0 Hz), 7.49–7.42 (m, 5H), 7.36 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.3, 162.1, 153.1, 150.6, 136.5, 134.6, 133.9, 131.9, 131.6, 131.5, 130.9, 129.4, 128.7, 128.3, 126.6, 126.3, 125.8, 125.7, 125.1, 124.5, 124.4, 123.9, 122.9, 121.8; IR (KBr, cm^{-1}): 3050, 2959, 2926, 2847, 1736, 1593, 1564, 1507, 1441, 1428, 1277, 1229, 1158, 1109, 1076, 981, 961, 881, 811, 779, 761, 728, 699; HRMS (ESI) calcd for $C_{24}H_{14}BrNO_2S$ ($M + H^+$) 460.0007, found 460.0001.

2-(Benzo[*d*]thiazol-2-yl)-3-chlorophenyl benzoate (1b):



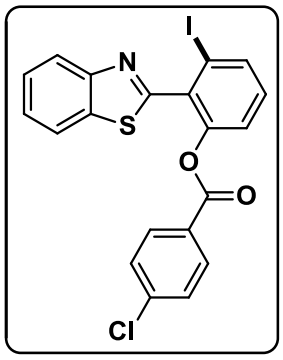
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, 1H, *J* = 8.0 Hz), 7.89 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.0 Hz), 7.51–7.45 (m, 3H), 7.42 (d, 1H, *J* = 7.2 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.34–7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8, 160.2, 152.9, 150.4, 136.2, 135.0, 133.8, 131.5, 130.3, 128.7, 128.6, 127.7, 127.1, 126.2, 125.7, 123.8, 122.1, 121.6; IR (KBr, cm^{-1}): 3061, 2914, 2845, 1741, 1599, 1569, 1518, 1445, 1430, 1313, 1262, 1222, 1176, 1125, 1077, 1056, 1023, 964, 892, 855, 760, 729, 705; HRMS (ESI) calcd for $C_{20}H_{12}ClNO_2S$ ($M + H^+$) 366.0355, found 366.0362.

4-(Benzo[*d*]thiazol-2-yl)-5-chloro-1,3-phenylene dibenzoate (5b):



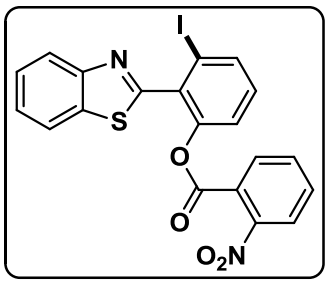
Solid; M.p. 135 °C–138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 2H, J = 8.0 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.89–7.86 (m, 3H), 7.65 (t, 1H, J = 7.4 Hz), 7.54–7.49 (m, 3H), 7.47–7.42 (m, 2H), 7.39–7.36 (m, 2H), 7.30 (t, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 164.3, 159.7, 153.1, 152.4, 150.9, 136.4, 135.5, 134.3, 133.9, 130.5, 130.4, 128.9, 128.8, 128.7, 126.3, 125.8, 124.7, 123.9, 121.7, 121.4, 116.3; IR (KBr, cm^{-1}): 3110, 3061, 2920, 2844, 1743, 1735, 1602, 1572, 1507, 1451, 1431, 1412, 1314, 1260, 1196, 1133, 1078, 1060, 1024, 1001, 984, 953, 880, 840, 795, 754, 721, 711, 695; HRMS (ESI) calcd for $C_{27}H_{16}ClNO_4S$ (M + H$^+$) 486.0567, found 486.0576.

2-(Benzo[*d*]thiazol-2-yl)-3-iodophenyl 4-chlorobenzoate (9c):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, 1H, J = 8.4 Hz), 7.85 (d, 1H, J = 7.6 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.68 (d, 2H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.36–7.32 (m, 2H), 7.23–7.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 163.9, 152.9, 149.4, 140.5, 137.4, 136.3, 132.6, 132.4, 131.6, 129.1, 127.2, 126.5, 125.9, 124.0, 123.2, 121.8, 98.9; IR (KBr, cm^{-1}): 3064, 2923, 2850, 1742, 1592, 1560, 1514, 1487, 1438, 1426, 1401, 1312, 1259, 1220, 1172, 1127, 1090, 1059, 1013, 961, 845, 774, 751, 728; HRMS (ESI) calcd for $C_{20}H_{11}ClINO_2S$ (M + H$^+$) 491.9322, found 491.9332.

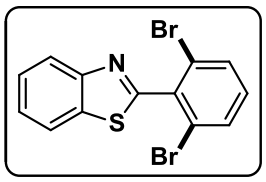
2-(Benzo[*d*]thiazol-2-yl)-3-iodophenyl 2-nitrobenzoate (10c):



Gummy solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.14 (d, 1H, J = 8.4 Hz), 7.96–7.94 (m, 3H), 7.56–7.52 (m, 3H), 7.47 (t, 1H, J = 7.4 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.33 (t, 1H, J = 8.0 Hz), 7.17 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 163.9, 153.0, 148.8, 147.4, 137.9, 136.4, 133.5, 132.7, 132.6, 132.1, 129.5, 127.2, 126.6, 126.0, 124.4, 124.1, 122.9, 121.9, 98.8; IR (KBr, cm^{-1}): 3118, 3054, 1759, 1595, 1558, 1532, 1482, 1438, 1426, 1348, 1312, 1281, 1216, 1174, 1126, 1098, 1052, 1033, 961, 909, 869, 852, 761, 729; HRMS (ESI) calcd for $C_{20}H_{11}IN_2O_4S$ (M + H$^+$) 502.9562, found 502.9565.

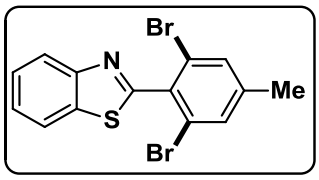
2-(2,6-Dibromophenyl)benzo[*d*]thiazole (11a):

Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 7.6 Hz), 7.67 (d, 2H, J = 8.0 Hz), 7.57 (t, 1H, J = 7.8 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.22 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.5, 152.9,



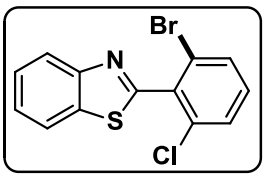
136.4, 135.9, 132.3, 132.1, 126.4, 125.9, 124.7, 124.2, 121.9; IR (KBr, cm^{-1}): 3072, 2959, 2917, 2848, 1575, 1594, 1549, 1514, 1546, 1420, 1316, 1243, 1228, 1195, 1185, 1147, 1123, 1081, 1067, 1015, 962, 941, 900, 852, 776, 765, 741, 730, 724, 707; HRMS (ESI) calcd for $C_{13}H_7Br_2NS$ (M + H^+) 369.8723, found 369.8716.

2-(2,6-Dibromo-4-methylphenyl)benzo[*d*]thiazole (12a):



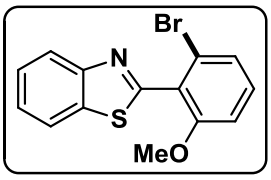
Solid; M.p. 84 °C–86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.8 Hz), 7.48–7.43 (m, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.7, 152.9, 143.3, 136.5, 132.9, 132.7, 130.1, 126.4, 125.9, 124.1, 121.9, 20.9; IR (KBr, cm^{-1}): 3058, 2954, 2921, 2850, 1597, 1526, 1485, 1431, 1379, 1311, 1228, 1195, 1084, 1065, 964, 850, 817, 759, 743, 728, 707; HRMS (ESI) calcd for $C_{14}H_9Br_2NS$ (M + H^+) 383.8880, found 383.8872.

2-(2-Bromo-6-chlorophenyl)benzo[*d*]thiazole (13a):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 8.8 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.47–7.43 (m, 2H), 7.25 (t, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 152.9, 136.4, 135.6, 134.2, 131.9, 131.5, 128.9, 126.4, 125.9, 124.8, 124.1, 121.8; IR (KBr, cm^{-1}): 3055, 2918, 2858, 1579, 1553, 1516, 1456, 1428, 1313, 1240, 1225, 1194, 1091, 1072, 962, 776, 762, 741, 728, 707; HRMS (ESI) calcd for $C_{13}H_7Br_2ClNS$ (M + H^+) 323.9249, found 323.9253.

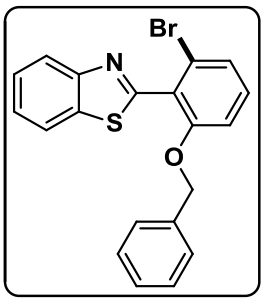
2-(2-Bromo-6-methoxyphenyl)benzo[*d*]thiazole (14a):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, *J* = 7.6 Hz), 7.93 (d, 1H, *J* = 8.0 Hz), 7.51 (t, 1H, *J* = 7.4 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.30–7.28 (m, 2H), 6.94 (t, 1H, *J* = 4.2 Hz), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 159.2, 153.3, 136.7, 132.1, 126.1, 125.5, 125.1, 124.7, 124.5, 123.9, 121.7, 110.3, 56.4; IR (KBr, cm^{-1}): 3061, 2967, 2938, 2835, 1587, 1567, 1518, 1460, 1429, 1312, 1267, 1240, 1221, 1184, 1148, 1125, 1083, 1033, 959, 852, 777, 760, 741, 729; HRMS (ESI) calcd for $C_{14}H_{10}BrNOS$ (M + H^+) 319.9744, found 319.9740.

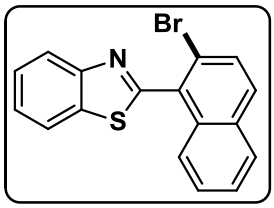
2-(2-(Benzyloxy)-6-bromophenyl)benzo[*d*]thiazole (15a):

Gummy solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.17 (d, 1H, *J* = 8.4 Hz), 7.95 (d, 1H, *J* = 8.4 Hz), 7.52 (t, 1H, *J* = 7.4 Hz),



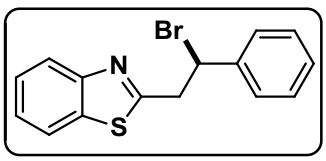
7.44 (t, 1H, *J* = 7.4 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.25–7.21 (m, 6H), 6.95 (d, 1H, *J* = 8.4 Hz), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.7, 158.2, 153.3, 136.7, 136.3. 131.9, 128.8, 128.7, 128.0, 126.9, 126.1, 125.5, 125.2, 124.7, 123.9, 121.8, 112.1, 70.9; IR (KBr, cm^{-1}): 3064, 3031, 2934, 2870, 1587, 1567, 1518, 1496, 1440, 1380, 1311, 1267, 1238, 1222, 1147, 1125, 1080, 1023, 960, 868, 834, 775, 759, 730; HRMS (ESI) calcd for $C_{20}H_{14}BrNOS$ ($M + H^+$) 396.0057, found 396.0063.

2-(2-Bromonaphthalen-1-yl)benzo[*d*]thiazole (16a):



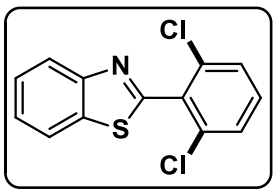
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, *J* = 8.0 Hz), 7.98 (d, 1H, *J* = 8.0 Hz), 7.94 (d, 1H, *J* = 8.4 Hz), 7.88 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 7.8 Hz), 7.72 (d, 1H, *J* = 7.2 Hz), 7.56–7.50 (m, 2H), 7.44 (t, 1H, *J* = 7.6 Hz), 7.32 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 153.2, 136.9, 136.1, 134.4, 131.9, 131.8, 131.6, 130.1, 128.9, 126.9, 126.4, 125.4, 125.1, 123.7, 121.6, 119.7; IR (KBr, cm^{-1}): 3054, 3000, 2970, 2914, 1509, 1493, 1448, 1433, 1357, 1343, 1311, 1278, 1248, 1180, 1106, 1067, 1013, 946, 877, 825, 814, 762, 730, 698; HRMS (ESI) calcd for $C_{17}H_{10}BrNS$ ($M + H^+$) 339.9795, found 339.9801.

2-(2-Bromo-2-phenylethyl)benzo[*d*]thiazole (17a):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 8.0 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.31–7.24 (m, 5H), 5.52 (t, 1H, *J* = 7.6 Hz), 3.87–3.81 (m, 1H), 3.66–3.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 170.7, 152.8, 137.2, 135.8, 129.5, 128.8, 127.5, 126.6, 126.0, 123.8, 122.0, 49.2, 45.2; IR (KBr, cm^{-1}): 3058, 3028, 2926, 2847, 1603, 1558, 1496, 1454, 1434, 1313, 1243, 1178, 1075, 1030, 1013, 930, 758, 729, 699; HRMS (ESI) calcd for $C_{15}H_{12}BrNS$ ($M + H^+$) 317.9952, found 317.9957.

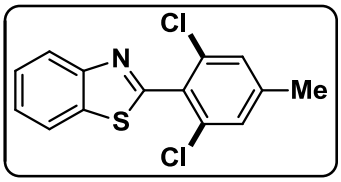
2-(2,6-Dichlorophenyl)benzo[*d*]thiazole (11b):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.48–7.43 (m, 3H), 7.36 (t, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 153.1, 136.5, 135.8, 132.6, 131.7, 128.4, 126.5, 125.9, 124.2, 121.9; IR (KBr, cm^{-1}): 3058, 2924, 2853, 1582, 1558, 1516, 1457, 1431, 1311, 1241, 1224, 1191, 1106, 1076, 1013, 964, 788, 759, 743,

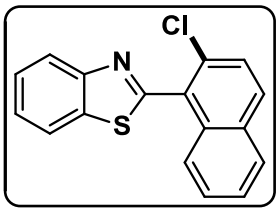
729, 699; HRMS (ESI) calcd for $C_{13}H_7Cl_2NS$ (M + H^+) 279.9754, found 279.9758.

2-(2,6-Dichloro-4-methylphenyl)benzo[*d*]thiazole (12b):



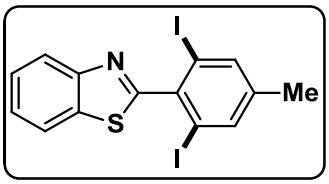
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.47 (t, 1H, *J* = 7.6 Hz), 7.27 (s, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.5, 153.2, 142.6, 136.6, 135.3, 129.5, 129.0, 126.4, 125.9, 124.1, 121.8, 21.2; IR (KBr, cm^{-1}): 3067, 2951, 2918, 1603, 1546, 1524, 1451, 1441, 1430, 1388, 1311, 1279, 1244, 1224, 1201, 1159, 1096, 1070, 1037, 1012, 964, 908, 850, 803, 797, 754, 724, 707; HRMS (ESI) calcd for $C_{14}H_9Cl_2NS$ (M + H^+) 293.9911, found 293.9904.

2-(2-Chloronaphthalen-1-yl)benzo[*d*]thiazole (16b):



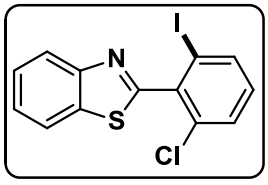
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1H, *J* = 8.4 Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 7.71 (d, 1H, *J* = 7.2 Hz), 7.61–7.53 (m, 3H), 7.48–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 153.2, 136.8, 135.9, 131.8, 131.6, 131.0, 130.8, 130.2, 129.1, 128.3, 126.6, 126.5, 125.4, 125.2, 123.7, 121.6; IR (KBr, cm^{-1}): 3055, 2924, 2844, 1516, 1496, 1451, 1362, 1344, 1327, 1312, 1278, 1199, 1110, 1067, 1013, 959, 884, 820, 758, 728, 705; HRMS (ESI) calcd for $C_{17}H_{10}ClNS$ (M + H^+) 296.0300, found 296.0296.

2-(2,6-Diiodo-4-methylphenyl)benzo[*d*]thiazole (12c):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, *J* = 8.4 Hz), 7.94 (d, 1H, *J* = 8.0 Hz), 7.76 (s, 2H), 7.54 (t, 1H, *J* = 7.8 Hz), 7.46 (t, 1H, *J* = 7.6 Hz), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.1, 152.7, 143.5, 139.9, 139.7, 136.5, 126.5, 126.0, 124.3, 122.0, 97.0, 20.4; IR (KBr, cm^{-1}): 3058, 2919, 2859, 1581, 1518, 1455, 1438, 1426, 1372, 1314, 1242, 1229, 1192, 1159, 1125, 1080, 1056, 1011, 957, 851, 758, 728; HRMS (ESI) calcd for $C_{14}H_9I_2NS$ (M + H^+) 477.8623, found 477.8632.

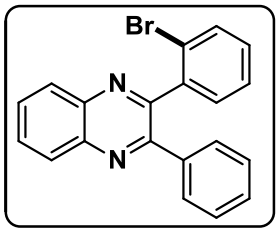
2-(2-Chloro-6-iodophenyl)benzo[*d*]thiazole (13c):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.4 Hz), 7.54 (t, 1H, *J* = 7.6 Hz), 7.49–7.44 (m, 2H), 7.09 (t, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.7, 152.9, 137.9, 137.8, 136.5, 134.5, 131.9, 129.7, 126.5, 126.0, 124.3, 121.9,

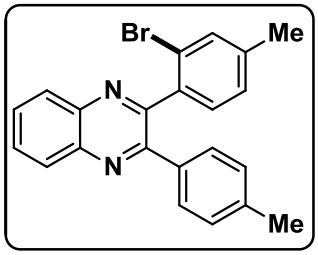
99.3; IR (KBr, cm^{-1}): 3062, 2923, 2845, 1575, 1548, 1514, 1455, 1423, 1314, 1277, 1240, 1224, 1197, 1149, 1124, 1083, 1066, 1016, 959, 853, 775, 759, 738, 728; HRMS (ESI) calcd for $C_{13}H_7ClINS$ ($M + H^+$) 371.9110, found 371.9117.

2-(2-Bromophenyl)-3-phenylquinoxaline (20a):



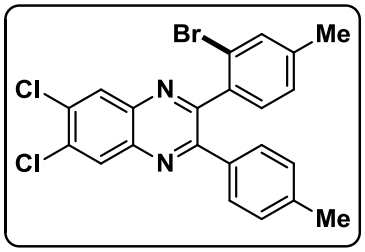
Gummy solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, 1H, *J* = 6.8 Hz), 8.19 (d, 1H, *J* = 7.6 Hz), 7.86–7.79 (m, 2H), 7.56–7.51 (m, 3H), 7.47 (d, 1H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.35–7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 153.7, 153.5, 141.9, 140.5, 138.5, 133.2, 131.6, 130.6, 130.4, 130.3, 129.8, 129.6, 129.5, 129.4, 129.1, 128.2, 127.7, 122.9; IR (KBr, cm^{-1}): 3059, 2928, 2850, 1631, 1563, 1558, 1477, 1431, 1395, 1345, 1261, 1215, 1126, 1077, 1055, 1026, 977, 802, 761, 730; HRMS (ESI) calcd for $C_{20}H_{13}BrN_2$ ($M + H^+$) 361.0340, found 361.0345.

2-(2-Bromo-4-methylphenyl)-3-(*p*-tolyl)quinoxaline (21a):



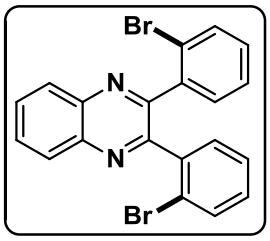
Gummy solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 1H, *J* = 8.4 Hz), 8.15 (d, 1H, *J* = 8.0 Hz), 7.80–7.73 (m, 2H), 7.41 (d, 2H, *J* = 8.0 Hz), 7.36–7.32 (m, 2H), 7.18 (d, 1H, *J* = 7.6 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 153.9, 153.6, 141.9, 140.8, 140.7, 139.0, 137.8, 135.8, 133.6, 131.3, 130.4, 129.9, 129.7, 129.5, 129.4, 128.9, 128.6, 122.5, 21.5, 21.2; IR (KBr, cm^{-1}): 3058, 3022, 2919, 2850, 1606, 1555, 1494, 1475, 1395, 1343, 1264, 1210, 1184, 1126, 1111, 1035, 1019, 977, 847, 821, 805, 762, 727, 709; HRMS (ESI) calcd for $C_{22}H_{17}BrN_2$ ($M + H^+$) 389.0653, found 389.0662.

2-(2-Bromo-4-methylphenyl)-6,7-dichloro-3-(*p*-tolyl)quinoxaline (22a):



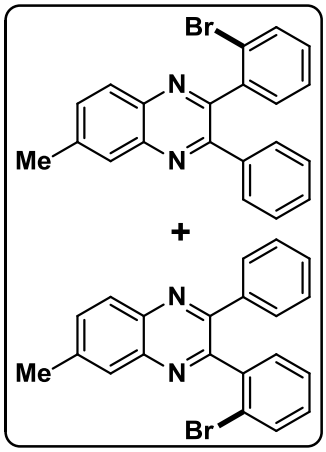
Gummy solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.31 (s, 1H), 8.27 (s, 1H), 7.41–7.37 (m, 3H), 7.32 (d, 1H, *J* = 7.6 Hz), 7.21 (d, 1H, *J* = 7.6 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 2.38 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 154.9, 154.6, 141.1, 140.7, 139.5, 135.1, 134.9, 134.4, 133.7, 131.1, 130.8, 130.1, 129.9, 129.7, 129.1, 128.7, 128.0, 122.3, 21.6, 21.2; IR (KBr, cm^{-1}): 3066, 3030, 2920, 2850, 1604, 1540, 1490, 1445, 1392, 1338, 1269, 1245, 1183, 1107, 1071, 1035, 1019, 964, 881, 855, 821, 800, 731, 705; HRMS (ESI) calcd for $C_{22}H_{15}BrCl_2N_2$ ($M + H^+$) 456.9874, found 456.9886.

2,3-*Bis*(2-bromophenyl)quinoxaline (20aa):



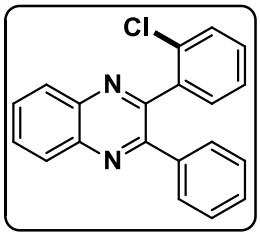
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26–8.23 (m, 2H), 7.88–7.86 (m, 2H), 7.54 (d, 2H, *J* = 7.6 Hz), 7.46 (d, 2H, *J* = 7.2 Hz), 7.26 (t, 2H, *J* = 7.6 Hz), 7.17 (t, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 153.7, 141.3, 139.2, 132.9, 131.2, 130.8, 130.4, 129.6, 127.1, 123.0; IR (KBr, cm^{-1}): 3055, 2919, 1845, 1615, 1596, 1575, 1476, 1436, 1368, 1341, 1314, 1270, 1152, 1134, 1112, 1067, 1005, 979, 936, 879, 833, 814, 762, 726; HRMS (ESI) calcd for $C_{20}H_{12}Br_2N_2$ (M + H^+) 440.9425, found 440.9417.

2-(2-Bromophenyl)-6-methyl-3-phenylquinoxaline compound and 3-(2-Bromo phenyl)-6-methyl-2-phenylquinoxaline (23a and 23a´):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, 1H, *J* = 8.4 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.00 (s, 1H), 7.96 (s, 1H), 7.64 (t, 2H, *J* = 9.2 Hz), 7.54–7.49 (m, 6H), 7.46–7.43 (m, 2H), 7.36 (t, 2H, *J* = 7.8 Hz), 7.31–7.22 (m, 8H), 2.62 (s, 3H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 153.6, 153.3, 152.9, 152.5, 142.0, 141.2, 140.9, 140.8, 140.6, 140.4, 139.3, 138.6, 133.1, 132.9, 132.6, 131.7, 131.6, 130.3, 129.79, 129.77, 129.1, 128.9, 128.89, 128.86, 128.3, 128.2, 128.1, 127.7, 127.1, 122.98, 122.90, 21.1; IR (KBr, cm^{-1}): 3058, 3022, 2921, 2844, 1618, 1595, 1587, 1559, 1488, 1428, 1344, 1263, 1243, 1219, 1199, 1183, 1158, 1137, 1119, 1079, 1070, 1040, 1024, 977, 883, 829, 805, 775, 763, 738, 710; HRMS (ESI) calcd for $C_{21}H_{15}BrN_2$ (M + H^+) 375.0497, found 375.0501.

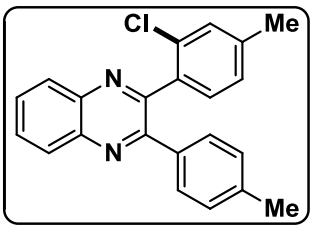
2-(2-Chlorophenyl)-3-phenylquinoxaline (20b):



Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, 1H, *J* = 8.4 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 7.85–7.79 (m, 2H), 7.53–7.50 (m, 3H), 7.37–7.27 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 154.1, 152.3, 141.9, 140.9, 138.7, 138.6, 133.1, 131.6, 130.6, 130.3, 130.2, 129.9, 129.6, 129.5, 129.4, 129.1, 128.3, 127.2; IR (KBr, cm^{-1}): 3056, 3030, 2915, 2853, 1558, 1543, 1478, 1442, 1433, 1395, 1346, 1263, 1219, 1126, 1079, 1045, 1024, 980, 915, 802, 763, 744, 730, 697; HRMS (ESI) calcd for $C_{20}H_{13}ClN_2$ (M + H^+) 317.0845, found 317.0851.

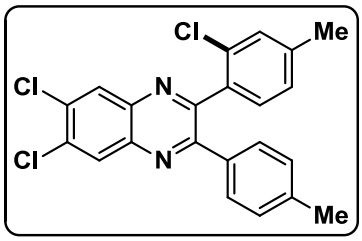
2-(2-Chloro-4-methylphenyl)-3-(*p*-tolyl)quinoxaline (21b):

Solid; M.p. 118 ^{o}C–121 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, 1H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 7.6 Hz), 7.83–7.74 (m, 2H), 7.43–7.38 (m, 3H), 7.17–7.14 (m, 2H), 7.09 (d, 2H,



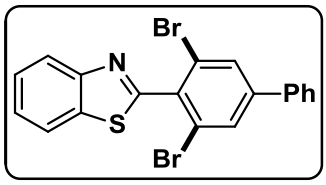
, J = 8.0 Hz), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 152.4, 141.9, 140.9, 140.6, 139.0, 135.9, 132.7, 131.3, 131.2, 130.4, 129.9, 129.5, 129.4, 129.3, 129.0, 128.1, 127.4, 21.5, 21.3; IR (KBr, cm^{-1}): 3060, 3028, 2919, 2855, 1609, 1475, 1392, 1340, 1220, 1210, 1185, 1126, 1075, 1037, 1020, 977, 956, 865, 821, 759, 730, 688; HRMS (ESI) calcd for $C_{22}H_{17}ClN_2$ (M + H^+) 345.1158, found 345.1165.

6,7-Dichloro-2-(2-chloro-4-methylphenyl)-3-(*p*-tolyl)quinoxaline (22b):



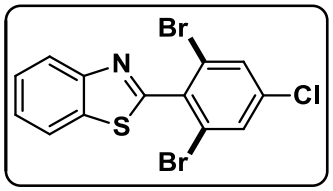
Gummy solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (s, 1H), 8.26 (s, 1H), 7.39–7.36 (m, 3H), 7.18–7.14 (m, 2H), 7.09 (d, 2H, J = 8.4 Hz), 2.38 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.1, 153.5, 141.1, 140.7, 140.1, 139.6, 134.9, 134.4, 131.1, 131.0, 130.5, 130.1, 130.0, 129.9, 129.5, 129.1, 128.2, 127.5, 21.6, 21.3; IR (KBr, cm^{-1}): 3060, 3031, 2920, 2858, 1607, 1544, 1507, 1495, 1446, 1394, 1338, 1271, 1246, 1201, 1183, 1108, 1078, 1040, 1019, 964, 881, 820, 800, 732, 706; HRMS (ESI) calcd for $C_{22}H_{15}Cl_3N_2$ (M + H^+) 413.0379, found 413.0390.

2-(3,5-Dibromo-[1,1'-biphenyl]-4-yl)benzo[*d*]thiazole (24a):



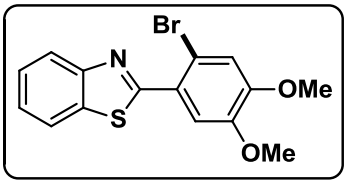
Solid; M.p. 160.2 °C–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 1H, J = 8.0 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.89 (s, 2H), 7.60–7.56 (m, 3H), 7.51–7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.5, 152.9, 145.7, 137.7, 136.5, 134.3, 130.6, 129.3, 129.1, 127.4, 126.5, 126.0, 124.9, 124.3, 121.9; IR (KBr, cm^{-1}): 3054, 3018, 2923, 2845, 1593, 1520, 1428, 1367, 1230, 1204, 1086, 1064, 1013, 961, 876, 762, 742, 731; HRMS (ESI) calcd for $C_{19}H_{11}Br_2NS$ (M + H^+) 445.9038, found 445.9047.

2-(2,6-Dibromo-4-chlorophenyl)benzo[*d*]thiazole (25a):



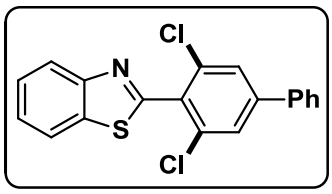
Solid; M.p. 127 °C–129.3 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.18 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 7.8 Hz), 7.69 (s, 2H), 7.57 (t, 1H, J = 7.2 Hz), 7.49 (t, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.6, 152.9, 137.3, 136.5, 134.7, 131.9, 126.6, 126.2, 124.9, 124.3, 121.9; IR (KBr, cm^{-1}): 3071, 2958, 2919, 2855, 1573, 1539, 1527, 1505, 1423, 1406, 1372, 1358, 1233, 1123, 1083, 1064, 965, 860, 789, 758, 742, 736, 729; HRMS (ESI) calcd for C13H6Br_2ClNS (M + H^+) 403.8335, found 403.8341.

2-(2-Bromo-4,5-dimethoxyphenyl)benzo[*d*]thiazole (26a):



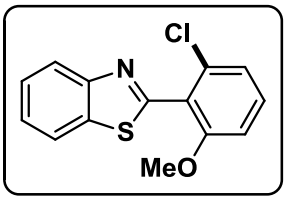
Solid; M.p. 124.1 °C–126.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.11 (d, 1H, J = 7.8 Hz), 7.93 (d, 1H, J = 7.8 Hz), 7.72 (s, 1H), 7.52 (t, 1H, J = 7.2 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.16 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.7, 152.6, 151.1, 148.6, 136.2, 126.8, 126.4, 125.4, 123.4, 121.5, 116.6, 114.3, 113.2, 56.5, 56.4; IR (KBr, cm^{-1}): 2956, 2923, 2838, 1599, 1515, 1458, 1423, 1379, 1338, 1257, 1208, 1159, 1028, 1019, 869, 829, 776, 754, 749, 724; HRMS (ESI) calcd for $C_{15}H_{12}BrNO_2S$ ($M + H^+$) 349.9852, found 349.9844.

2-(3,5-Dichloro-[1,1'-biphenyl]-4-yl)benzo[*d*]thiazole (24b).



Solid; M.p. 142.3 °C–144.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 1H, J = 8.0 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.68 (s, 2H), 7.61–7.55 (m, 3H), 7.51–7.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 153.2, 145.1, 137.9, 136.6, 135.9, 130.9, 129.3, 129.1, 127.3, 126.9, 126.4, 125.9, 124.2, 121.9; IR (KBr, cm^{-1}): 3057, 3028, 2923, 2848, 1597, 1533, 1431, 1375, 1311, 1235, 1206, 1098, 1071, 964, 875, 807, 776, 761, 732; HRMS (ESI) calcd for $C_{19}H_{11}Cl_2NS$ ($M + H^+$) 356.0069, found 356.0058.

2-(2-Chloro-6-methoxyphenyl)benzo[*d*]thiazole (14b):

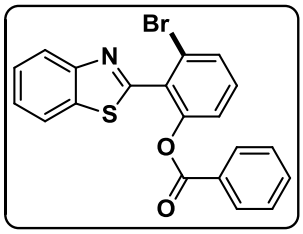


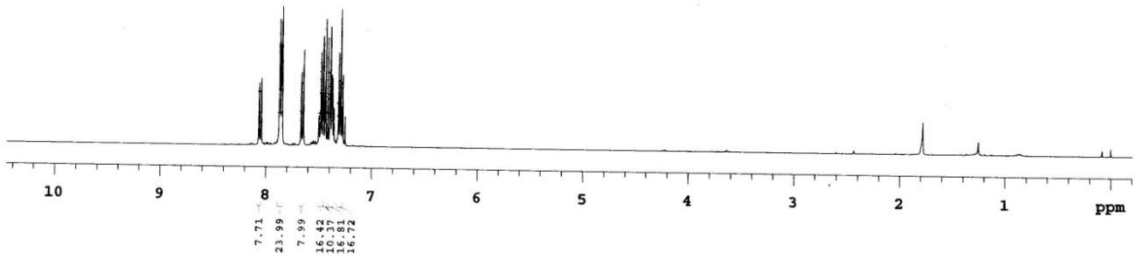
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.52 (t, 1H, J = 7.8 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.37 (t, 1H, J = 8.2 Hz), 7.12 (d, 1H, J = 7.6 Hz), 6.91 (d, 1H, J = 8.4 Hz) 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 159.1, 153.3, 136.7, 135.2, 131.7, 126.1, 125.4, 123.8, 122.6, 122.0, 121.7, 109.7, 56.4; IR (KBr, cm^{-1}): 3058, 2967, 2935, 2838, 1588, 1572, 1462, 1431, 1310, 1269, 1217, 1041, 961, 856, 780, 760, 742, 730; HRMS (ESI) calcd for $C_{14}H_{10}ClNOS$ ($M + H^+$) 276.0251, found 276.0246.

IV.7. Spectra

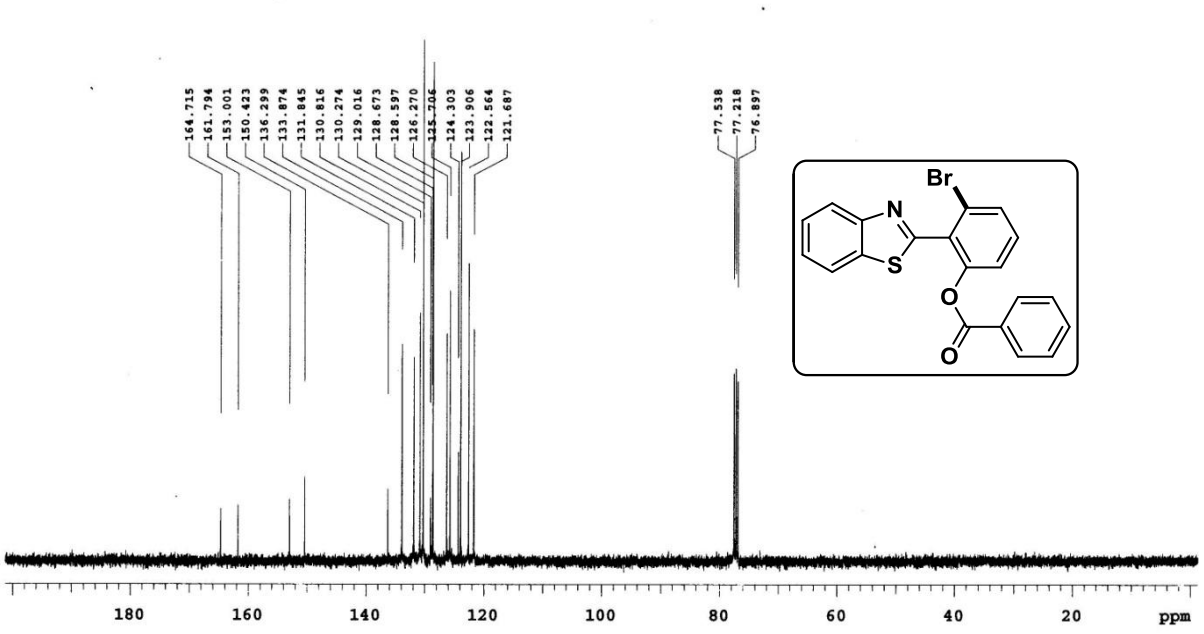
➢ IVA.7.

2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)

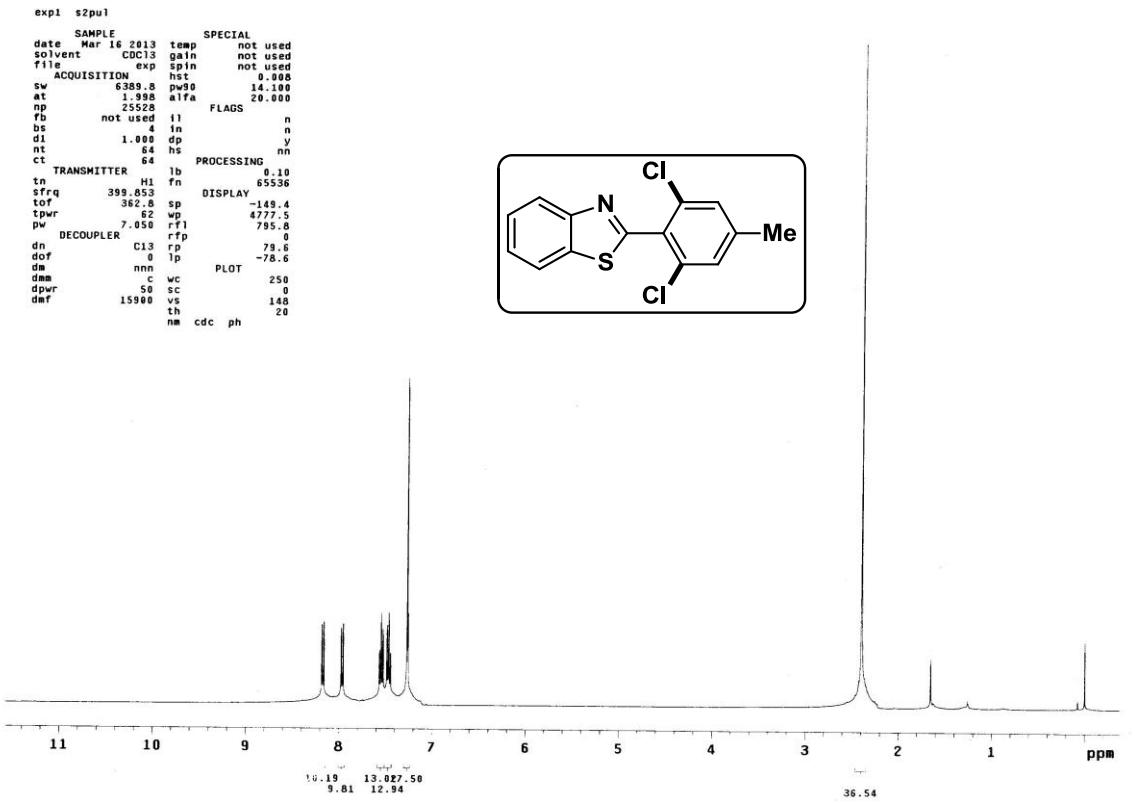




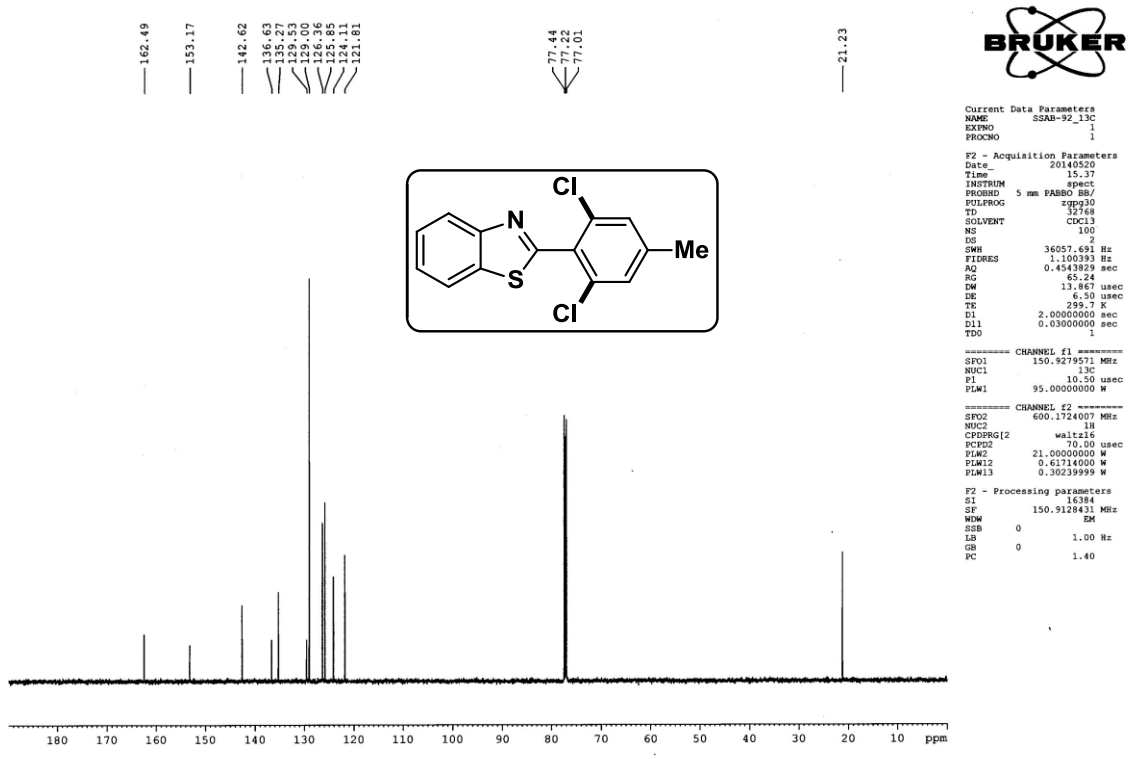
2-(Benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



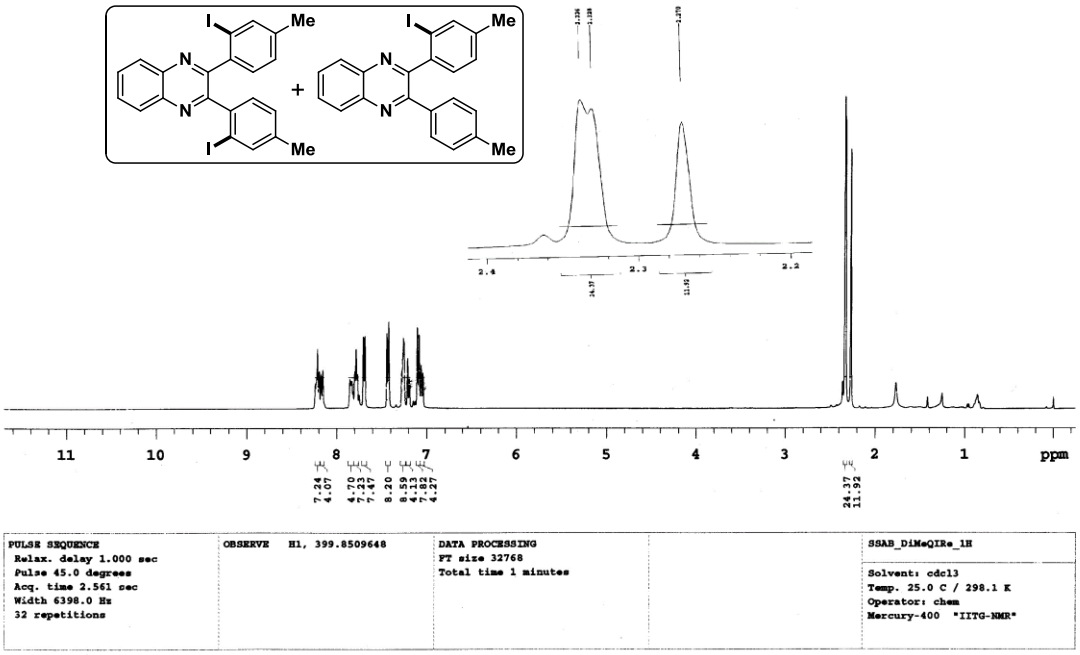
2-(2,6-Dichloro-4-methylphenyl)benzo[*d*]thiazole (12b): ^{1}H NMR ($CDCl_3$, 400 MHz)



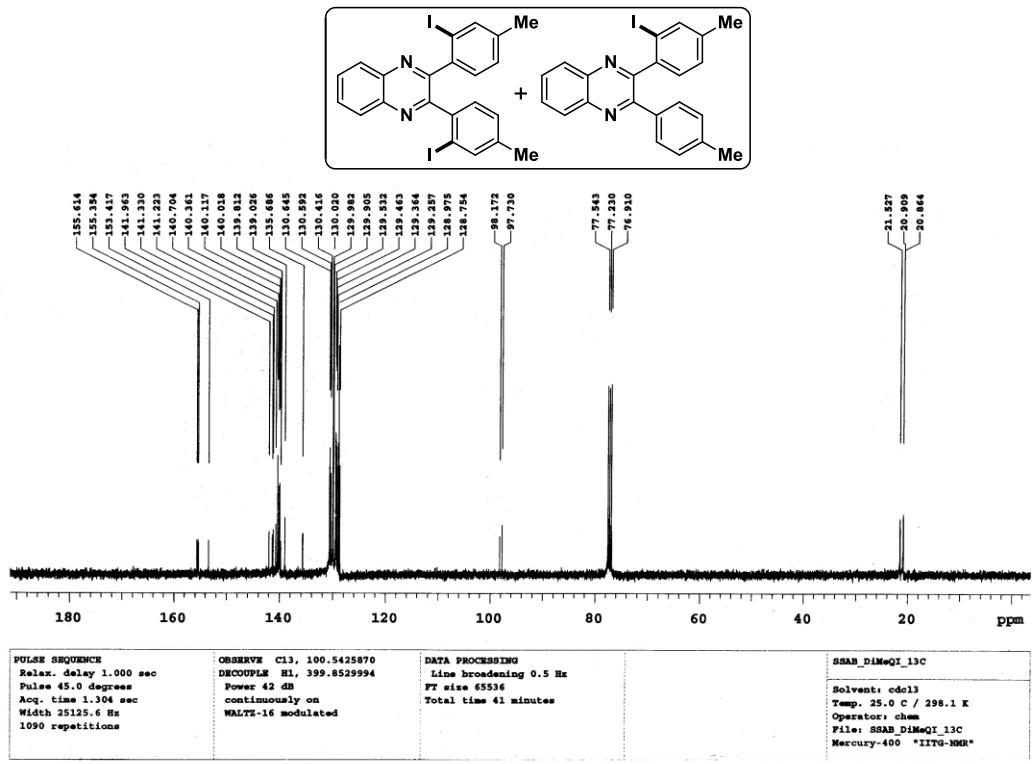
2-(2,6-Dichloro-4-methylphenyl)benzo[*d*]thiazole (12b): ^{13}C NMR (150 MHz, $CDCl_3$)



2,3-*Bis*(2-iodo-4-methylphenyl)quinoxaline compound and 2-(2-Iodo-4-methylphenyl)-3-(*p*-tolyl)quinoxaline (21c and 21cc): ^{1}H NMR (400 MHz, $CDCl_3$)

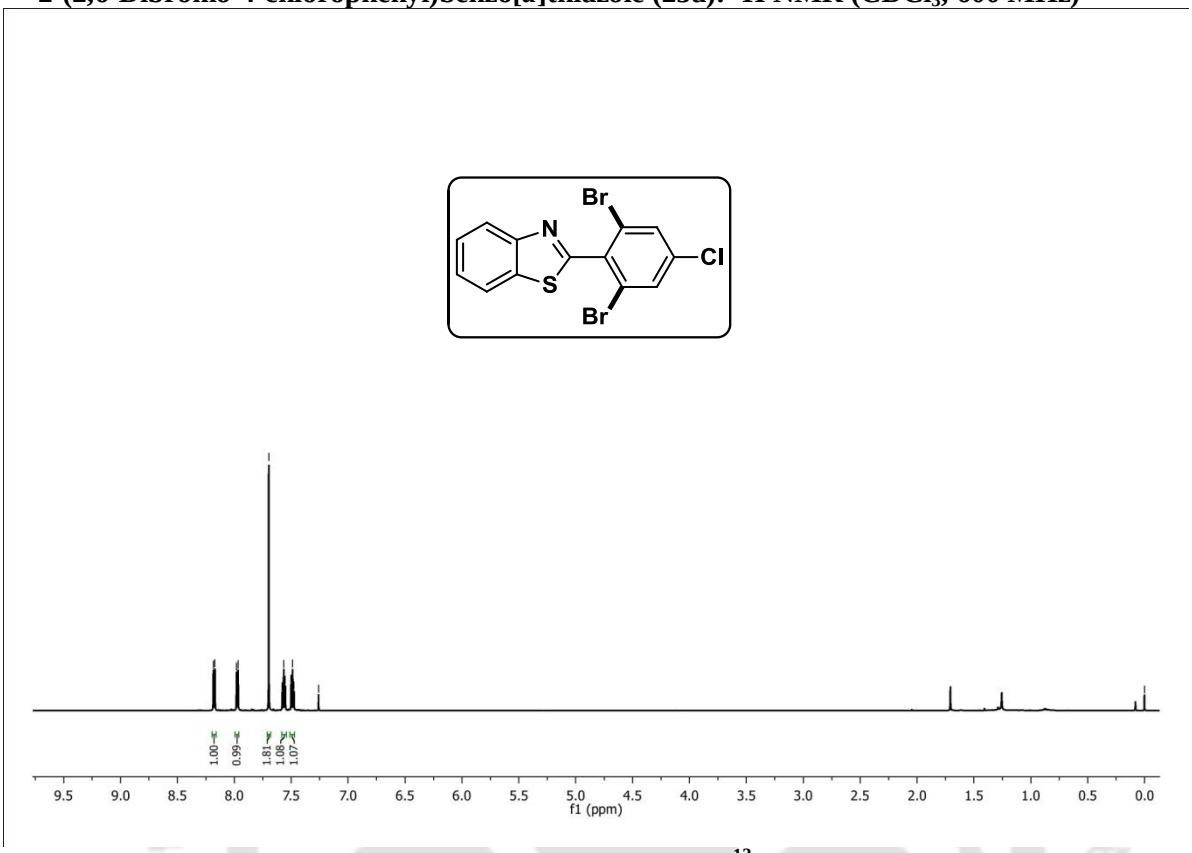


2,3-*Bis*(2-iodo-4-methylphenyl)quinoxaline compound and 2-(2-Iodo-4-methylphenyl)-3-(*p*-tolyl)quinoxaline (21c and 21cc): ^{13}C NMR (100 MHz, $CDCl_3$)

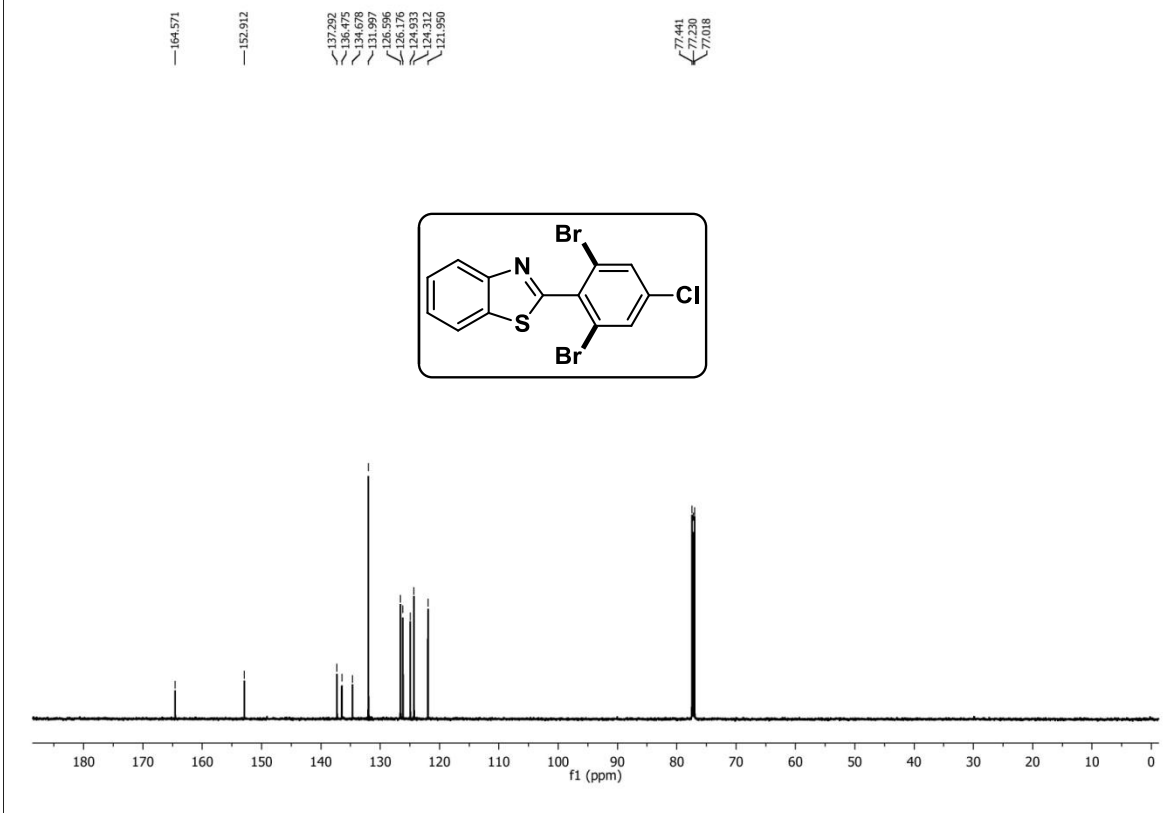


➢ IVB.7.

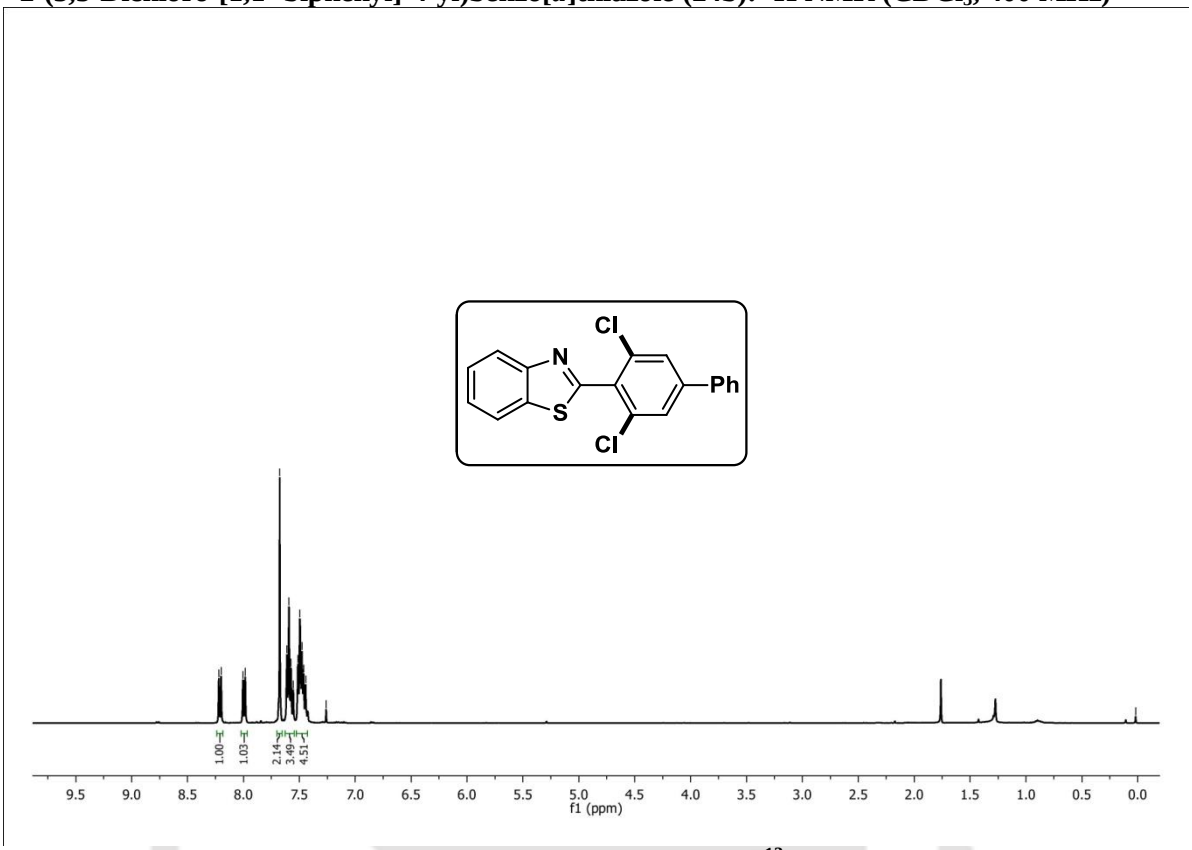
2-(2,6-Dibromo-4-chlorophenyl)benzo[*d*]thiazole (25a): ^{1}H NMR ($CDCl_3$, 600 MHz)



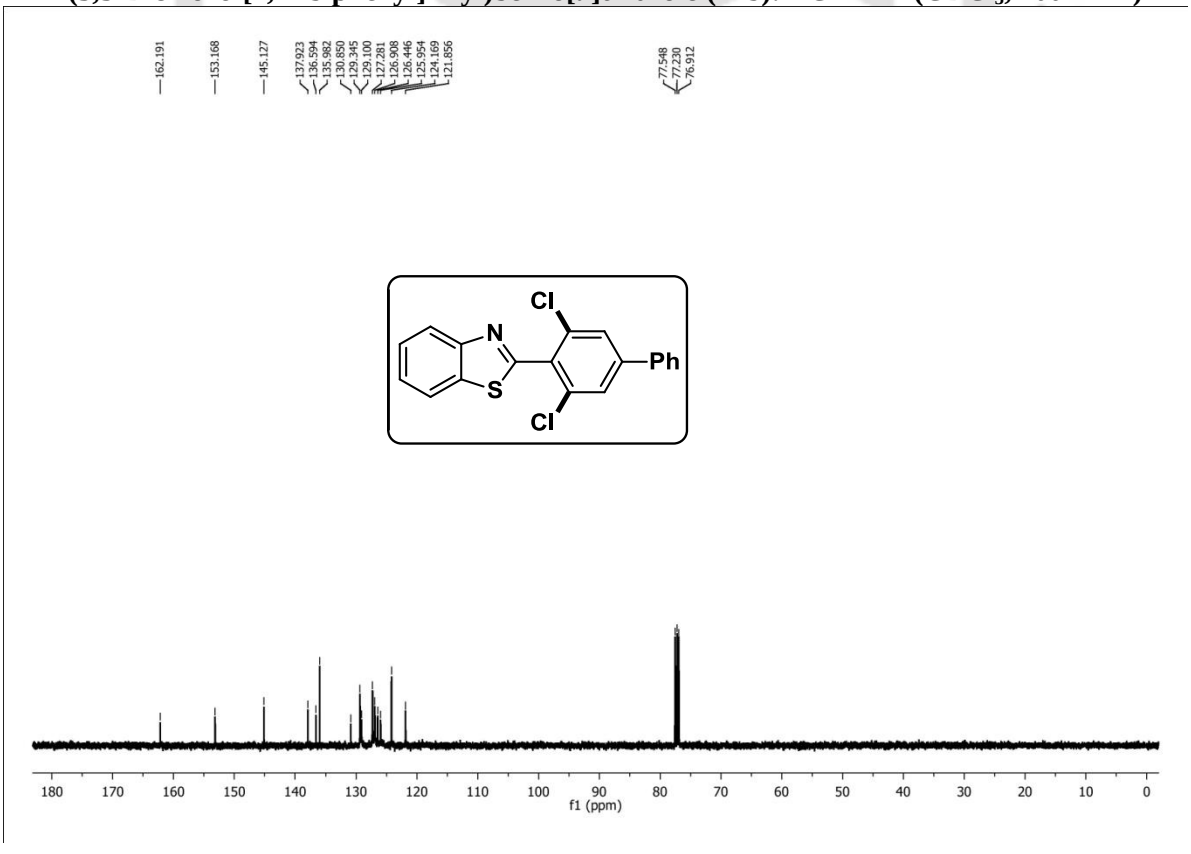
2-(2,6-Dibromo-4-chlorophenyl)benzo[*d*]thiazole (25a): ^{13}C NMR ($CDCl_3$, 150 MHz)



2-(3,5-Dichloro-[1,1'-biphenyl]-4-yl)benzo[*d*]thiazole (24b): ^{1}H NMR ($CDCl_3$, 400 MHz)

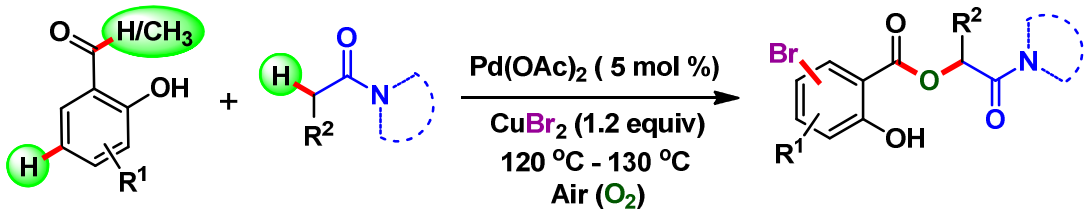


2-(3,5-Dichloro-[1,1'-biphenyl]-4-yl)benzo[*d*]thiazole (24b): ^{13}C NMR ($CDCl_3$, 100 MHz)



Chapter V

Palladium(II)/$CuBr_2$ Catalyzed Keto α-C_{sp3}–H Benzoxylation of N,N-Dialkylamides Directed by o-Hydroxy Groups



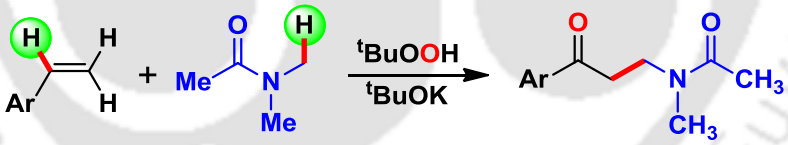
Abstract: *A hydroxy group directed keto α-C_{sp3}–H benzoxylation of amides, including N,N-dialkylamides and cyclic amides, has been accomplished involving ortho-hydroxy substrates possessing either an aldehydic or a keto methyl (–$COCH_3$) group with a Pd(II)/$CuBr_2$ catalytic combination. The carboxy group obtained via the in situ oxidation of –CHO or –$COCH_3$ groups of ortho-hydroxy substrates then undergoes a cross dehydrogenative coupling (CDC) with amides to furnish an α-benzoxylation product with concurrent aromatic ring bromination.*

CHAPTER V

V. Pd(II)/$CuBr_2$ Catalyzed Keto α-C_{sp3}–H Benzoxylation of *N*,*N*-Dialkylamides Directed by *o*-Hydroxy Groups

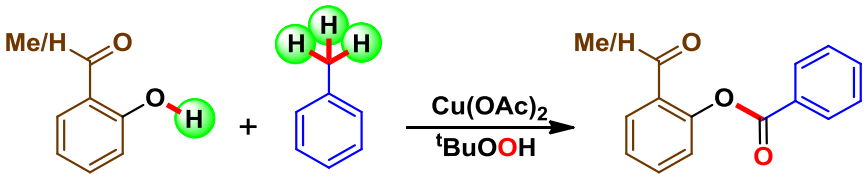
V.1. Introduction

α-Arylation of amides (sp^3 C–H α-to keto) is generally performed *via* the transition metal catalyzed coupling of aryl halides with alkali metal enolates or their equivalents.[1] However, some of these processes require strong bases such as LiHMDS or NaHMDS at low temperature under anhydrous conditions in an inert atmosphere.[2] This problem is overcome *via* the substrate directed C–H activation strategy. Recently, α-C_{sp3}–H acetoxylation of amides using 1-aminoanthraquinone as the bidentate directing group has been reported.[3] Dimethylacetamide (DMA), a polar aprotic solvent possessing two types of inert sp^3 C–H bonds (*viz.* C_{sp3}–H's α to nitrogen and α to keto), selective functionalization of any one of these C_{sp3}–H bonds is a challenging task. Li group has developed an oxidative CDC between *N*,*N*-dialkylamide (*viz.* DMA) and an alkene, where the C–C bond formation is at the α-C_{sp3}–H bond of DMA adjacent to the nitrogen and not at the α-C_{sp3}–H bond adjacent to the keto group (Scheme V.1.1).[4]



Scheme V.1.1. *Oxidative CDC between dimethylacetamide and alkene*

In our previous report during an oxidative *O*-aroylation of 2-hydroxybenzaldehydes/2-hydroxyacetophenones with alkylbenzenes, the latter served as the aroyl surrogates while –CHO or $–COCH_3$ groups acted as the directing moieties and remained intact during the reaction. (Scheme V.1.2).[5]

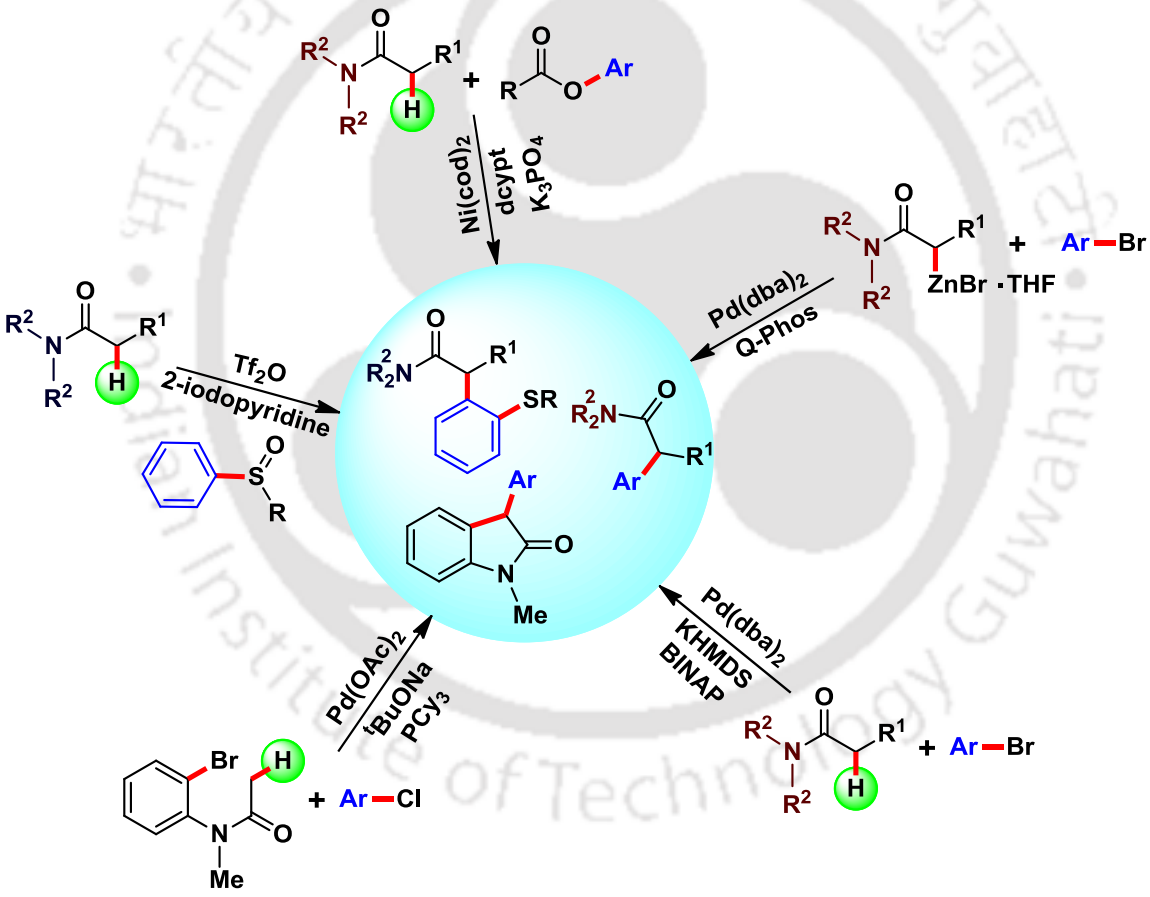


Scheme V.1.2. *Alkylbenzenes served as an aroyl source*

Functionalization of α C_{sp3}–H bonds adjacent to heteroatoms *viz.* nitrogen and oxygen is well-explored towards various CDC reactions.[6] Thus a query arises if DMA is employed as the coupling partner of 2-hydroxybenzaldehyde will it form a C–O bond at the *ortho* –OH group involving its sp^3 C–H α-to nitrogen or α-to keto to give either product (**1A**) or (**1B**) (see Table V.3.1).

V.2. Strategies for *α*-C_{sp3}–H Functionalization of Keto Amides

α-Aryl amides are useful intermediates in organic synthesis and that can be converted into β-arylamines. Hartwig and co-workers reported that a [$Pd(dba)_2$]/BINAP combination can give the α-arylation of amides in the presence of strong base KHMDS.[1h]

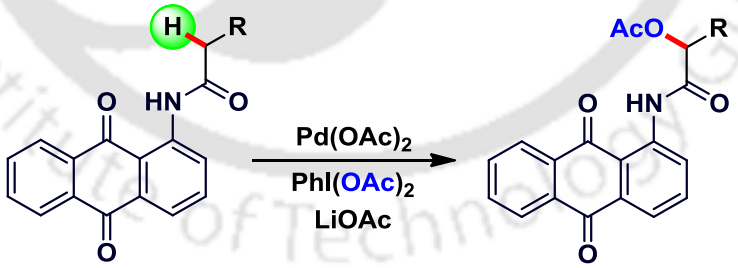


Scheme V.2.1. *Various methods for the α-arylation of keto amides*

α-Arylation of acyclic amides has associated problems, since a stronger base decomposes the catalyst, which resulted in high catalyst loadings along with the quenching of the starting enolate by the α-arylated product. Later, to avoid alkali metal enolates zinc amide enolates have been used as starting materials. In the presence of $Pd(dba)_2$ and Q-Phos Hartwig and co-workers developed an α-arylation method using *in situ* generated zinc

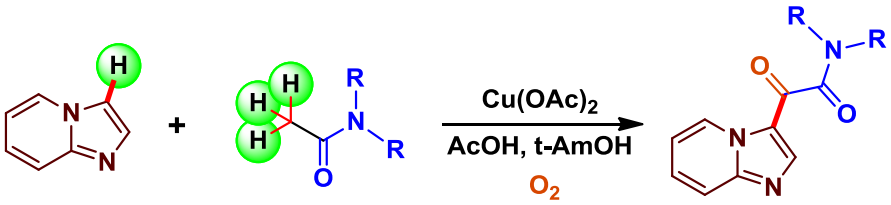
amide enolates (Scheme V.2.1).[1f] A final modification of this α-arylation strategy was completed *via* the use of *in situ* generated Reformatsky reagents (reaction of the amide with *sec*-BuLi generates lithium enolate, which is followed by the reaction with $ZnCl_2$) followed by the use of palladium complex and ligand.[1f] Lee and Hartwig developed another catalytic combination for α-arylation, in which electron-rich monophosphine ligands (PCy_3) has been used with $Pd(OAc)_2$ instead of [$Pd(dba)_2$]/BINAP catalytic system (Scheme V.2.1).[1g] This catalytic combination provided oxindole derivatives *via* intramolecular cyclization. Later, the same catalytic system has been employed for tandem intra- and intermolecular arylation processes, which provided α-arylated oxindoles. A nickel catalyzed α-arylation of amides with phenol derivatives has been developed by Itami group. In the presence of $Ni(cod)_2$ and 3,4-*bis*(dicyclohexylphosphino) thiophene (dcypt) various amides undergo α-arylation with *O*-arylpivalates or *O*-arylcarbamates to afford the corresponding coupling products (Scheme V.2.1).[1d] Maulide and co-workers developed a new approach for the chemoselective α-arylation of amides *via* electrophilic amide activation.[1i] In this process aryl groups from (alkylsulfinyl)benzene can be regioselectively installed at the alpha position of the *in situ* generated activated amide obtained by the reaction of amides and Tf_2O/2-iodopyridine (Scheme V.2.1).

Apart from these C–C bond formation strategies Zhang and co-workers first reported a Pd-catalyzed site selective α-C_{sp3}–H acetoxylation (C–O bond formation) of amides using bidentate directing group 1-aminoanthraquinone (Scheme V.2.2).[3]



Scheme V.2.2. *Pd(II)-Catalyzed α-acetoxylation of keto amides*

Recently, a copper-catalyzed regioselective double carbonylation of imidazo[1,2-*a*]pyridines with *N*,*N*-disubstituted acetamide has been developed using molecular oxygen. This strategy provided a new route to prepare 1,2-dicarbonyl imidazo[1,2-*a*]pyridines derivatives (Scheme V.2.3).[7]



Scheme V.2.3. *Cu(II-catalyzed dicarbonylation of imidazo[1,2-a]pyridines with N,N-disubstituted acetamide*

V.3. Present Work

In light of the above mentioned protocols for α-C_{sp3}–H functionalization of keto amides, we wish to develop a CDC reaction between 2-hydroxybenzaldehyde and dimethylacetamide (DMA).

Optimization of Reaction Conditions. Taking cues from the functionalization of glycine derivatives with active methylene compounds as reported by Li *et al.*[8] a coupling reaction between (**1**) and DMA (**a**) was carried out using $Cu(OAc)_2$ (1 equiv) at 120 ^oC but the reaction was completely unproductive (Table V.3.1, entry 1). The same reaction when carried out in the presence of $Pd(OAc)_2$ (5 mol %) under otherwise identical conditions gave none of these speculated products (**1A** or **1B**), but an unexpected product (**1a′**) was isolated in 12% yield (Table V.3.1, entry 2). A careful scrutiny of product (**1a′**) revealed that it is obtained *via* the coupling of α-keto C_{sp3}–H of DMA and the aldehydic carbonyl group of (**1**). This oxidative esterification of substrate (**1**) with DMA (**a**) is similar to our previous Cu(II) catalyzed oxidative esterification of aldehydes with alkylbenzenes.[9] Interestingly, when the same reaction was carried out in the presence of another copper(II) salt *viz.* $CuBr_2$ (1.0 equiv) in lieu of $Cu(OAc)_2$ α-C_{sp3}-esterification of DMA took place along with the ring bromination *para* to the –OH group, giving the coupled product (**1a**) in 64% yield (Table V.3.1, entry 3).

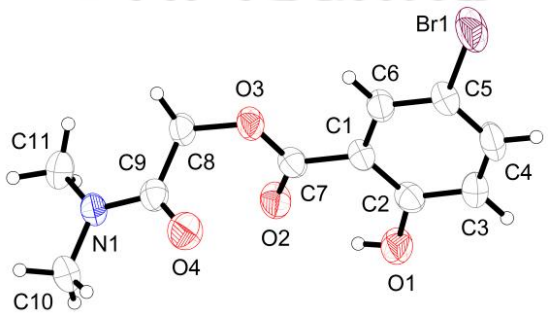
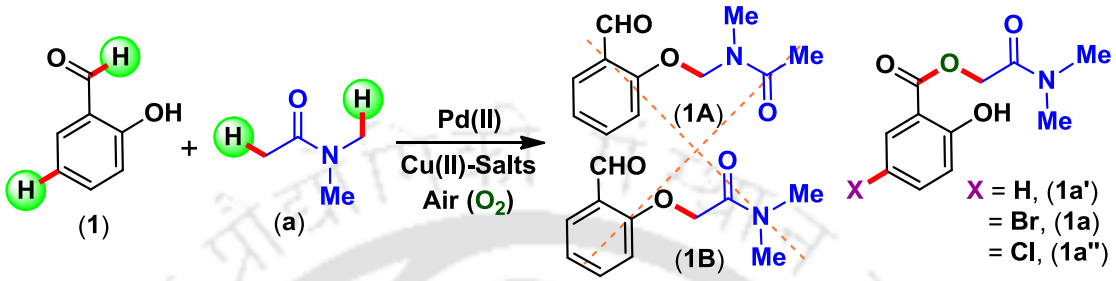


Fig. V.3.1. *ORTEP molecular diagram of (**1a**)*

The structure of product (**1a**) has been further confirmed by X-ray crystallographic analysis as shown in Fig. V.3.1. Thus, the use of $CuBr_2$ as a co-oxidant not only substantially improved the coupling yield but also provided a bonus ring bromination, thereby opening an opportunity for further functionalizations *via* coupling reactions.

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



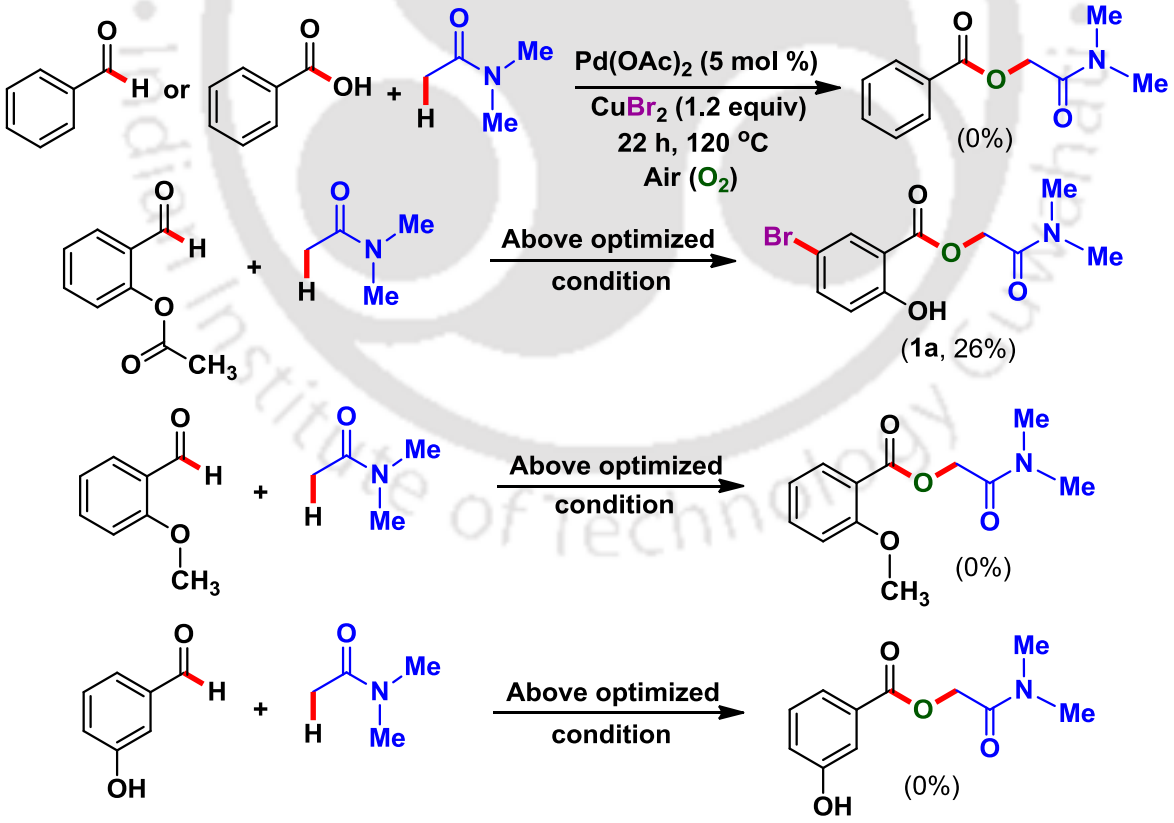
entry	catalyst (mol %)	oxidant (equiv)	yield (%)[b] (**1a**/**1a′**/**1a″**)
1	-	$Cu(OAc)_2$ (1 equiv)	0/0/0
2	$Pd(OAc)_2$ (5.0)	$Cu(OAc)_2$ (1 equiv)	0/12/0
3	$Pd(OAc)_2$ (5.0)	$CuBr_2$ (1 equiv)	64/0/0
4	$Pd(OAc)_2$ (5.0)	$CuCl_2$ (1 equiv)	0/0/40
5	$PdCl_2$ (5.0)	$CuBr_2$ (1 equiv)	54/0/trace
6	$PdBr_2$ (5.0)	$CuBr_2$ (1 equiv)	58/0/0
7	$Pd(TFA)_2$ (5.0)	$CuBr_2$ (1 equiv)	62/0/0
8	**$Pd(OAc)_2$ (5.0)**	**$CuBr_2$ (1.2 equiv)**	**72/0/0**
9	-	$CuBr_2$ (1.2 equiv)	0/0/0
10	$Pd(OAc)_2$ (5.0)	-	0/0/0
11	$Pd(OAc)_2$ (10.0)	$CuBr_2$ (1.2 equiv)	75/0/0

[a]Reaction conditions: salicylaldehyde (**1**) (0.5 mmol), DMA (**a**) (1 mL) and Cu-salts (0.5 mmol and 0.6 mmol) at 120 °C for 20 h. [b]Isolated yield.

Replacement of $CuBr_2$ with $CuCl_2$ provided an analogous chloro product (**1a″**) but in a relatively poor yield (40%) (Table V.3.1, entry 4). Encouraged by this preliminary success other reaction parameters were assessed to arrive at the better possible yield of the coupled product (**1a**). Using $CuBr_2$ (1 equiv) as the oxidant other potential Pd catalysts such as $PdCl_2$ (54%), $PdBr_2$ (58%) and $Pd(TFA)_2$ (62%) were tested to maximize the product yield (Table V.3.1, entries 5–7). All the Pd(II) catalysts tested were found to be good but were slightly less effective compare to $Pd(OAc)_2$ (Table V.3.1, entry 3). Keeping the catalyst $Pd(OAc)_2$ loading the same (5 mol %) but increasing the oxidant ($CuBr_2$) quantity to 1.2 equivalents resulted in an improved yield (72%) of (**1a**) (Table V.3.1, entry 8). No traces of the desired product (**1a**) was observed in the absence of either $Pd(OAc)_2$ or $CuBr_2$ (Table

V.3.1, entries 9 and 10). Increasing the catalyst quantity from 5 to 10 mol % no substantial improvement in the product yield (75%) was observed (Table V.3.1, entry 11). As can be seen from the optimization table the bromo-esterification product (**1a**) obtained *via* the coupling of salicylaldehyde (**1**) (1 equiv) with DMA (**a**) (1 mL) was best achieved using $CuBr_2$ (1.2 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) at 120 ^oC.

To check whether the hydroxy (–OH) group has any role in this benzoxylation process or not, when benzaldehyde (PhCHO) was reacted with DMA under Pd(II)/$CuBr_2$ catalytic conditions, no reaction occurred. This result is in sharp contrast to our previous Cu(II) catalyzed oxidative esterification of aldehydes and alkylbenzenes where there was no involvement of any additional auxiliary or directing groups.[9] This observation suggests the directing role of the *o*-hydroxy group in the process. In this hydroxy directed α-benzoxylation, the –CHO group of *ortho*-hydroxy substrate (**1**) is oxidized *in situ* to a –COOH group. When a reaction was carried out using benzoic acid (PhCOOH) in lieu of benzaldehyde (PhCHO) again no trace of the esterification product was observed (Scheme V.3.1).



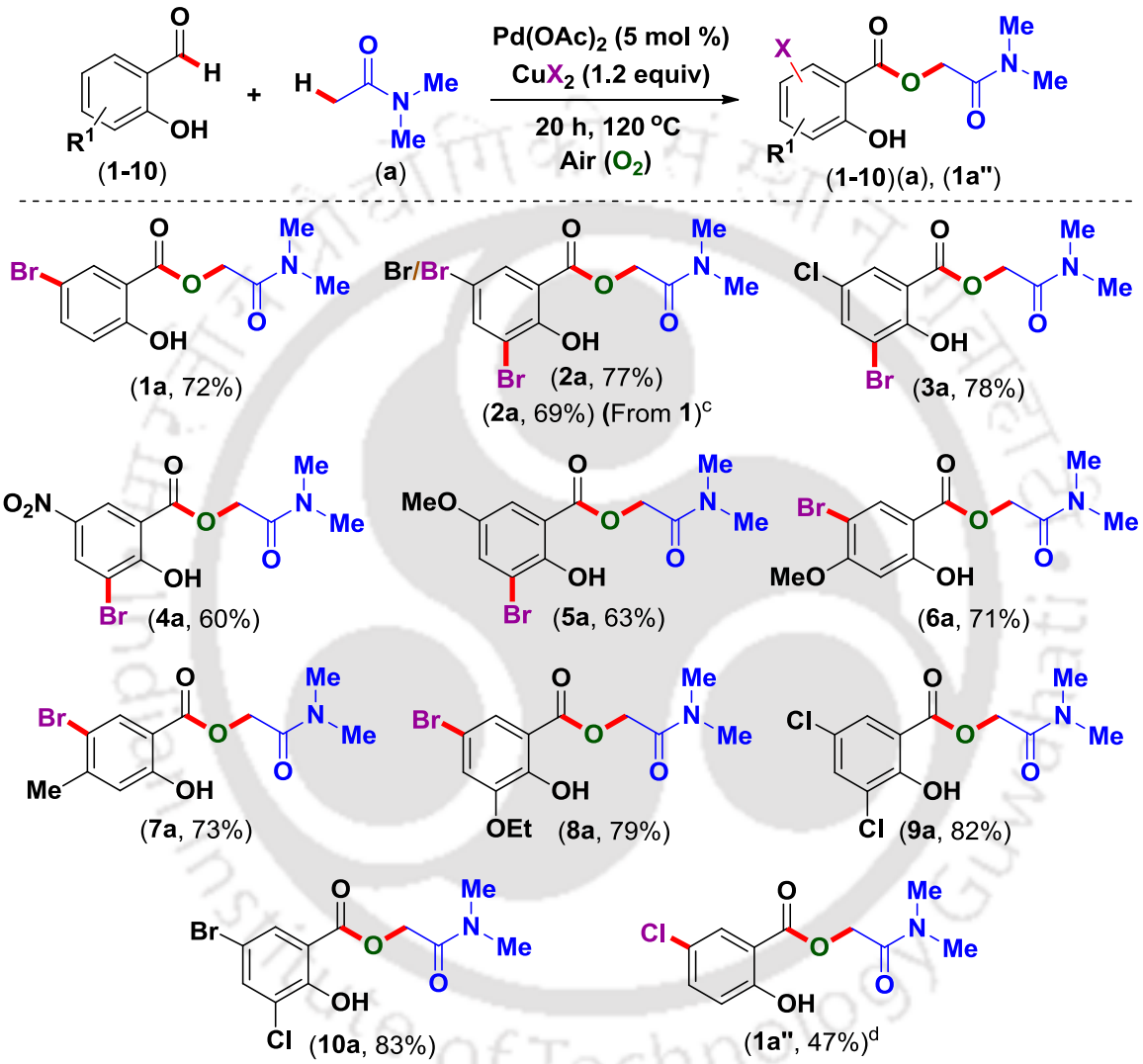
Scheme V.3.1. *Control experiments*

These control experiments reconfirm the definite directing role of hydroxy functionality during the benzoxylation. To further ascertain the involvement of the *ortho* hydroxy group, when *O*-acetyl salicylaldehyde was reacted with DMA under otherwise identical conditions gave the same product (**1a**) as that using salicylaldehyde (**1**), but in a lower yield (26%) (Scheme V.3.1). Inefficient formation of esterification product (**1a**) (26%) from a hydroxy protected salicylaldehyde i.e., *O*-acetyl salicylaldehyde under identical conditions suggests the inability of the *O*-acetyl group in bringing about the coupling. Moreover, the cleavage of the acetyl group in the final product (**1a**) suggests that the 26% product is formed only after the release of the free hydroxy group *via* hydrolysis of the acetyl group under the reaction conditions. However, *o*–OMe benzaldehyde failed to give any trace of the esterification product under the present reaction conditions. Furthermore, when *m*-hydroxy benzaldehyde was reacted with DMA under the present reaction conditions no esterification was observed (Scheme V.3.1). During this process ring bromination (<10%) was observed and the aldehydic group was oxidized to its carboxylic acid. When the reaction was carried out using DMF instead of DMA again no esterification took place and only bromination *para* to the –OH group was observed. Here again, the aldehydic group was oxidized to carboxylic acid. All these experiments suggest the involvement of an *o*-hydroxy group in this process.

Substrate Scope for Halo-Esterification. Inspired by the success of this elegant halo-esterification process, the strategy was further executed for a broad range of substituted 2-hydroxybenzaldehydes and *N*,*N*-dialkylamides as shown in Scheme V.3.2. This methodology is compatible to a range of substituted salicylaldehydes possessing both electron-donating and electron-withdrawing groups. Salicylaldehyde (**1**) when reacted with DMA (**a**) gave 72% yield of the mono bromo-esterification product (**1a**) along with a trace amount (<5%) of the di-bromo product (**2a**). However, when the same reaction was carried out in the presence of 2 equivalents of $CuBr_2$ for 30 h, an exclusive di-bromo-esterification product (**2a**) was isolated in 69% yield. Salicylaldehyde having moderately electron-withdrawing substituents such as 5–Br (**2**), 5–Cl (**3**) and strongly electron-withdrawing groups 5–NO_2 (**4**) provided exclusive *ortho* mono bromo CDC products (**2a**, 77%), (**3a**, 78%) and (**4a**, 60%) in good to moderate yields. Strongly electron-donating 5–OMe (**5**) substituted salicylaldehyde gave 63% yield of the bromo-esterification product (**5a**). For substrates (**2**–**5**) since *para* to the hydroxy group is blocked, the bromination occurred

exclusively at their *ortho* position giving products (**2a**–**5a**). 4-Substituted salicylaldehyde such as 4–OMe (**6**) and 4–Me (**7**) were selected where both *ortho* and *para* positions with respect to the –OH group are available, thus it will be interesting to see which of these positions will undergo preferential bromination.

Scheme V.3.2. *Scope of halo-esterification of salicylaldehydes*[a,b]

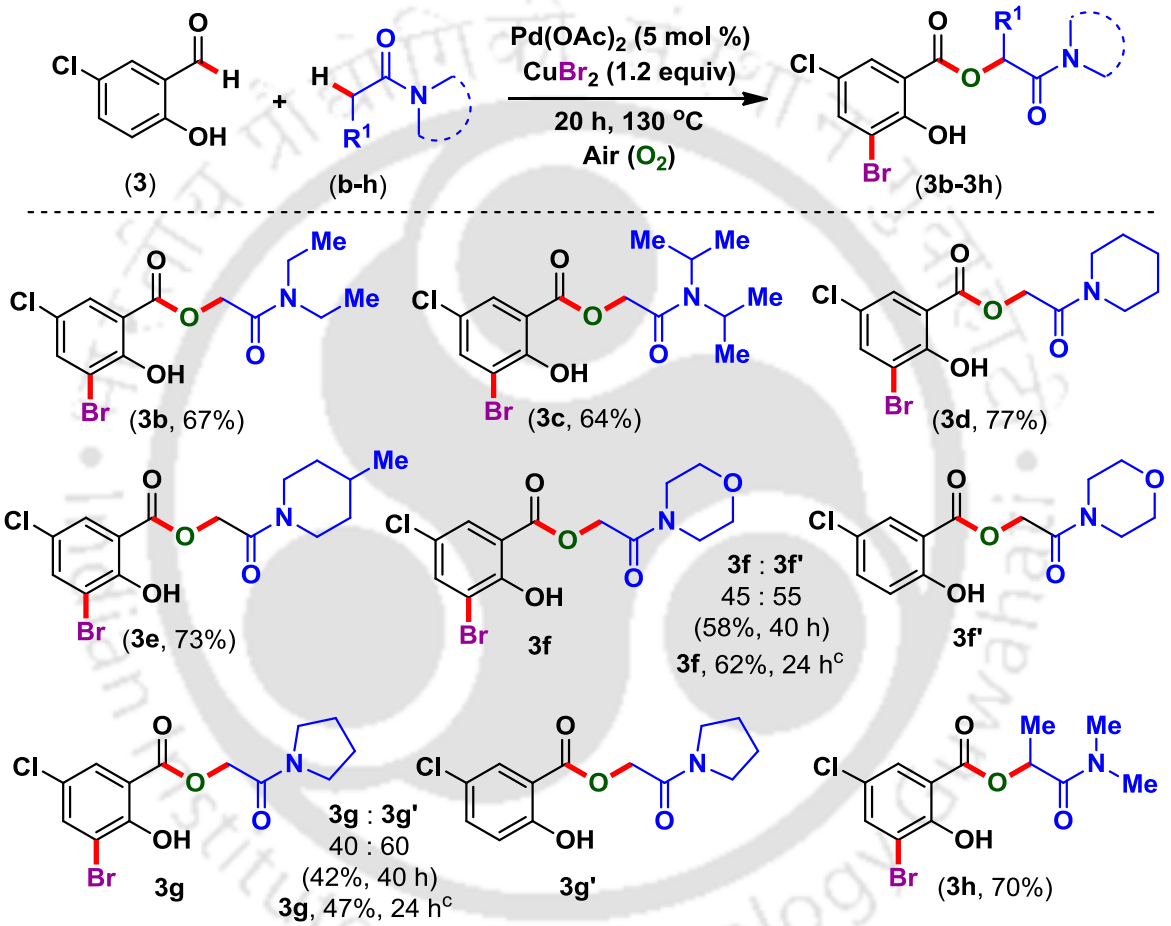


[a]Reaction conditions: salicylaldehydes (**1**–**10**) (0.5 mmol), DMA (**a**) (1 mL) and $CuBr_2$ (0.6 mmol) at 120 °C for 20 h. [b]Isolated yield. [c]Obtained from (**1**) using 1 mmol of $CuBr_2$. [d]$CuCl_2$ (0.6 mmol) was used.

These 4-substituted salicylaldehydes provided coupled products (**6a**) and (**7a**) in 71% and 73% yields, respectively (Scheme V.3.2), where bromination took place exclusively at the *para* position. Similarly, 3-ethoxy salicylaldehyde (**8**) provided good yield of the oxidative bomo-esterification product (**8a**, 79%) under identical reaction conditions. For di-substituted salicylaldehydes possessing moderate electron-withdrawing groups such as 3,5-dichloro-salicylaldehyde (**9**) and 5-bromo-3-chloro-salicylaldehyde (**10**) esterification

products (**9a**, 82%) and (**10a**, 83%) were obtained in excellent yields (Scheme V.3.2), without any ring bromination as both their *ortho* and *para* positions are unavailable. As observed during optimization, the use of $CuCl_2$ in lieu of $CuBr_2$ gave ring chlorination along with esterification. This has been demonstrated using (**1**) which provided low yield (47%) of the chloro-esterification product (**1a′′**) when $CuCl_2$ was used instead of $CuBr_2$ as shown in Scheme V.3.2.

Scheme V.3.3. *Scope of bromo-esterification of 5-Cl salicylaldehyde with amides*[a,b]

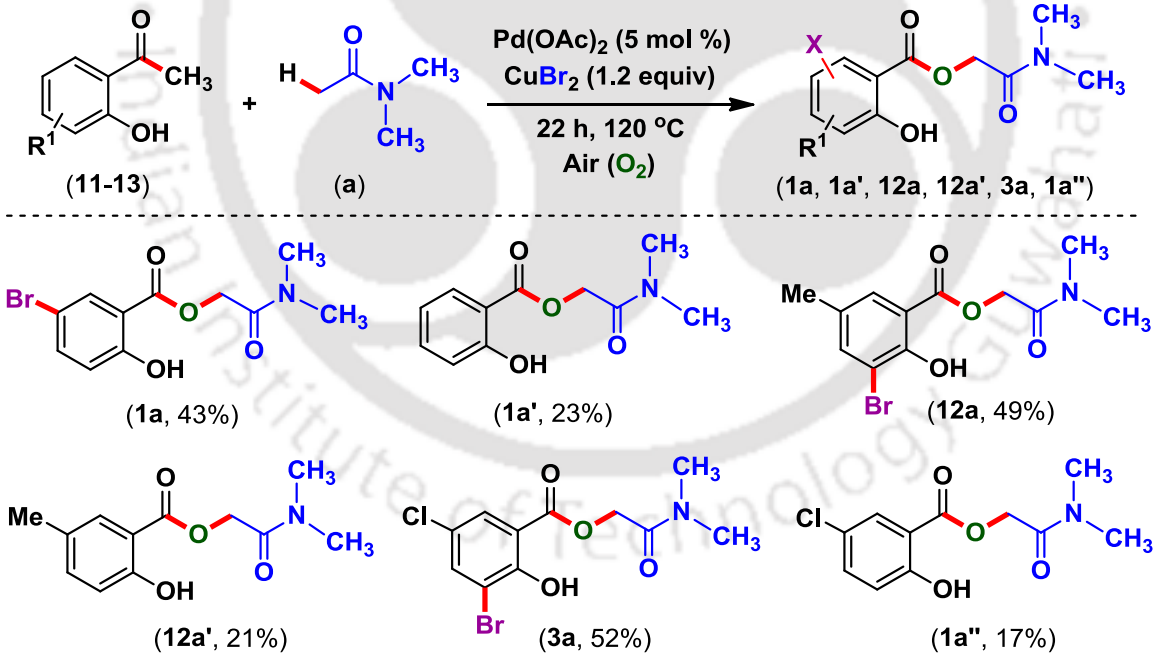


[a]Reaction conditions: 5-Chloro salicylaldehyde (**3**) (0.5 mmol), amides (**b**–**h**) (1 mL) and $CuBr_2$ (0.6 mmol) at 130 °C for 20 h. [b]Isolated yield. [c]1 mmol of $CuBr_2$ was used.

The oxidative halo-esterification strategy was further extended to a variety of *N,N*-dialkylacetamides (Scheme V.3.3). When diethylacetamide (**b**) was treated with 5-chloro salicylaldehyde (**3**) under the optimized reaction conditions it gave 53% yield of the bromo-esterification product (**3b**). The yield of coupled product (**3b**) improved to 67% when the reaction was performed at 130 °C. Diisopropylacetamide (**c**) also provided the corresponding coupled product (**3c**) in moderate yield (64%) (Scheme V.3.3). When the

bromo-esterification of six membered cyclic acetamides such as piperidine (**d**) and 4-methyl piperidine (**e**) was carried out with 5-chloro salicylaldehyde (**3**), all furnished their corresponding bromo-esterification products (**3d**) and (**3e**) in 77% and 73% yields, respectively (Scheme V.3.3). Morpholine acetamide (**f**) provided an inseparable mixture of bromo-esterification product (**3f**) and a non bromo-esterification product (**3f′**) in the ratio of 45:55 in a combined yield of 58% after 40 h. When the same reaction was carried out under identical conditions but using 2 equivalents of $CuBr_2$, product (**3f**) was obtained exclusively in 62% yield. Furthermore, pyrrolidineacetamide (**g**) also yielded an inseparable mixture of bromo-esterification product (**3g**) and a non bromo-esterification product (**3g′**) in the ratio of 40:60 in a combined yield of 42% after 40 h. An exclusive bromo-esterification product (**3g**) was obtained in 47% yield when the reaction was carried out using 2 equivalents of $CuBr_2$ (Scheme V.3.3). *N*,*N*-Dimethylpropionamide (**h**) having a ethyl ($–CH_2CH_3$) group α-to keto amide afforded the bromo-esterification product (**3h**) in 70% yield, where the coupling took place at the methylene site (Scheme V.3.3).

Scheme V.3.4. *Scope of bromo-esterification of 2-hydroxyacetophenones with DMA*[a,b]



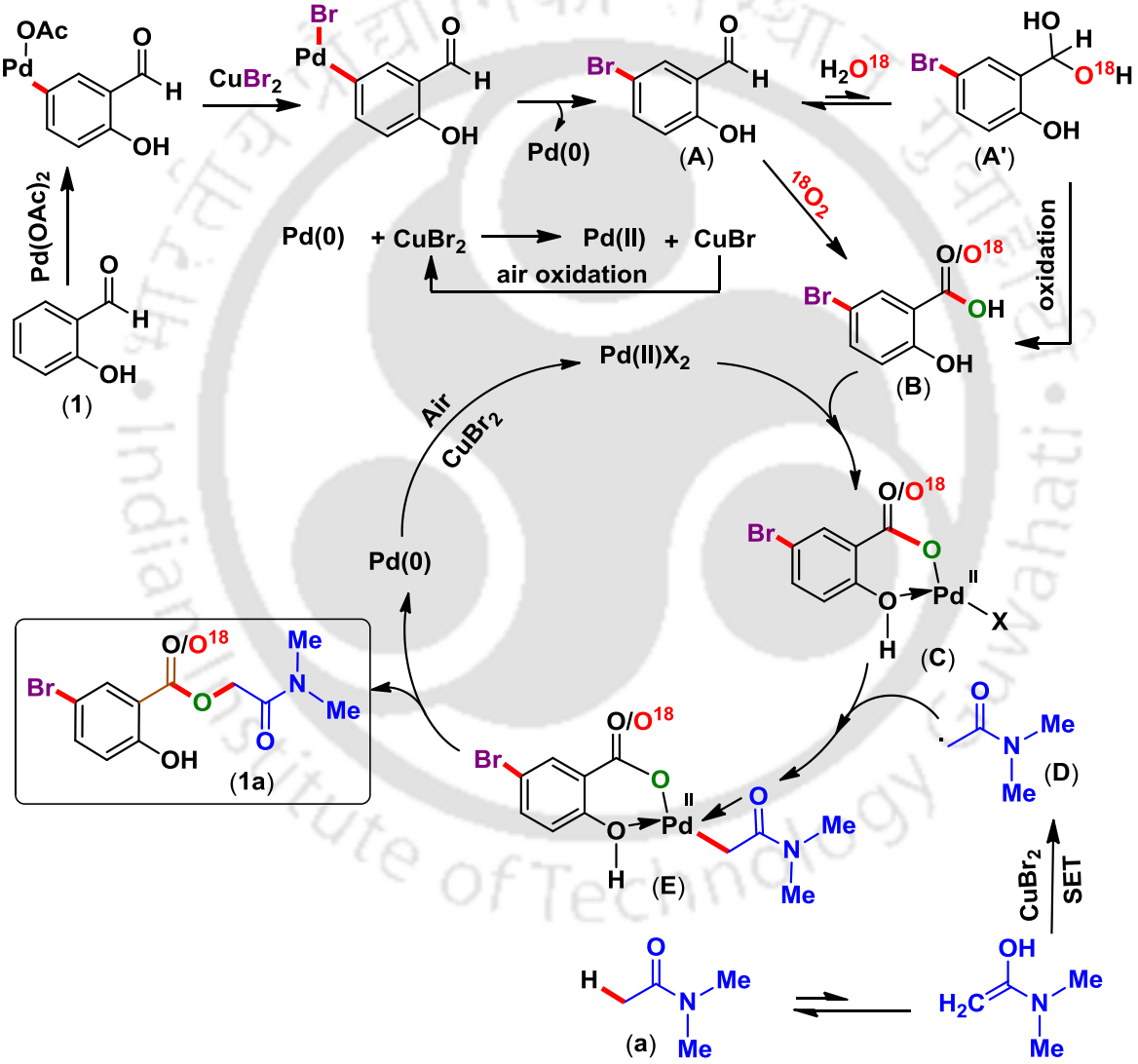
[a]Reaction conditions: 2-hydroxyacetophenone (**11**–**13**) (0.5 mmol), DMA (**a**) (1 mL) and $CuBr_2$ (0.6 mmol) at 120 °C for 22 h. [b]Isolated yield.

Now a curiosity arises if a non-easily oxidizable keto ($–COCH_3$) group is used instead of an aldehyde (–CHO) group, can their role be reversed i.e., C–O bond formation taking place at the –OH site and the keto functionality acting as the directing group as was

observed earlier by us (Scheme V.1.2).[5] With this objective when 2-hydroxyacetophenone (**11**) was treated with DMA (**a**) under identical conditions surprisingly the same bromo-esterification product (**1a**) was obtained in 43% yield along with a non bromo-esterification product (**1a′**) in 23% yield (Scheme V.3.4). The formation of product (**1a**) from (**11**) suggests that the $–COCH_3$ group is oxidized to a –COOH group. Under the reaction conditions the $–COCH_3$ group is first oxidized to a –COCHO, and subsequently to –COCOOH as was observed by Wang *et al*. for a similar system.[10] A decarboxylation of resultant –COCOOH followed by further oxidation generates a –COOH group. This successful strategy was then applied to 5-methyl-2-hydroxyacetophenone (**12**) which provided the bromo-esterification product (**12a**) and a non bromo-esterification product (**12a′**), respectively, in 49% and 21% yields (Scheme V.3.4). Similarly, 5-chloro-2-hydroxyacetophenone (**13**) under identical reaction conditions afforded the bromo-esterification product (**3a**) and a non bromo-esterification product (**1a′′**) in 52% and 17% yields.

Mechanistic Studies. To ascertain the nature of the mechanism involved in this reaction, a set of experiments were performed. Rate retardation giving only 26% yield of product (**1a**) in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv) suggests a possible radical path. Benzaldehyde and benzoic acid failed to give any coupled product with DMA, while both salicylaldehyde (**1**) and salicylic acid gave the bromo-esterification product (**1a**) in 72% and 44% yields, respectively. However, when the reaction was performed using salicylic acid at a slightly higher temperature (130 ^oC) the yield improved up to 62%. This provides the evidence that the presence of excess acid is not detrimental to the reaction. Thus, the success of this reaction is dependent on the presence of an *ortho* hydroxy group with respect to a carbonyl group. The reaction essentially involves three important steps *viz.* ring bromination, oxidation of aldehyde or keto to a carboxylic acid and the hydroxy group directed cross coupling leading to the formation of an ester. Analysis of the reaction mixture between salicylaldehyde (**1**) and DMA (**a**) at various time intervals revealed the initial formation of 5-bromo-salicylaldehyde (**A**) which is oxidized to 5-bromo-salicylic acid (**B**) followed by formation of a CDC coupled product (**1a**). Initial electrophilic palladation of salicylaldehyde (**1**)[11] occurred at the *para* position with respect to the hydroxyl group which is followed by a ligand (Br) exchange. A reductive elimination leads to the formation of 5-bromo-salicylaldehyde (**A**) with the release of Pd(0). Under the oxidative condition 5-bromo-

salicylaldehyde (**A**) is oxidized to 5-bromo-salicylic acid (**B**). When the reaction was carried out in the presence of $H_2{}^{18}O$ (5 equiv) in an air atmosphere labeled ester was formed, suggesting water (moisture) to be one of the oxygen sources. Furthermore, when the reaction was carried out in an argon atmosphere only 5-bromosalicylaldehyde (**A**) was observed with no traces of the bromo-esterification product (**1a**) indicating the essential requirement of atmospheric oxygen. Subsequently, when the reaction was performed in an $^{18}O_2$ atmosphere an ^{18}O labeled ester was formed, suggesting atmospheric oxygen to be the actual source of oxygen in ester (**1a**) (See experimental section).



Scheme V.3.5. *Proposed mechanism for bromo-esterification*

Thus 5-bromosalicylaldehyde (**A**) or its hydrated form (**A′**) both are oxidized in the medium to bromo-salicylic acid (**B**). The *in situ* generated 5-bromo-salicylic acid (**B**) coordinates with Pd(II) salt to give intermediate (**C**). This is then followed by a ligand

exchange with the *in situ* generated radical (**D**) obtained from dimethylacetamide (**a**) *via* a SET mechanism[7] to give intermediate (**E**). Furthermore, HRMS analysis of the reaction mixture suggests the formation of intermediate (**C**) and an equivalent intermediate (**E**) (See experimental section). Finally, a reductive elimination leads to the formation of the bromo-esterification product (**1a**) with the release of Pd(0), which is oxidized to Pd(II) by air/$CuBr_2$ for the next catalytic cycle as shown in Scheme V.3.5.

In conclusion for the first time a keto α-C_{sp3}–H benzoxylation of unactivated *N*,*N*-dialkylamides/cyclic amides has been developed *via* a *o*-hydroxy group directed CDC reaction. In this unique α-C_{sp3}–esterification strategy, $CuBr_2$ not only plays the role of a co-oxidant but also provides an additional ring bromination, thus opening an opportunity for further cross-couplings.

V.4. Experimental Section

V.4.1. General Information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). 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.

V.4.2. Crystallographic Description

CCDC number for compound 1a: CCDC 1429212. 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): 0.38 x 0.24 x 0.22. $C_{11}H_{12}BrNO_4$, Mr = 302.13. monoclinic, space group p 21/n; a = 5.4464 (3) Å, b = 8.7160 (5) Å, c = 25.2572 (4) Å; α = 90°, β = 91.713 (2) °, γ = 90°, V = 1198.44 (12) Å^3; Z = 4; ρ_{cal}= 1.674 g/cm^3; μ (mm^{-1}) = 3.432; *F (000)* = 608.0; Reflection collected / unique = 2071 /

2164; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0402, wR2 = 0.0928, R indices (all data) R1 = 0.0779, wR2 = 0.1047; goodness of fit = 1.039.

V.4.3. Synthesis of α-Benzoxylated Dimethylacetamide

V.4.3. General Procedure for the Synthesis of 2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxybenzoate (1a) from 2-Hydroxybenzaldehyde (1) and DMA (a): To an oven-dried 10 mL round bottom flask were added sequentially 2-hydroxybenzaldehyde (**1**) (0.061g, 0.5 mmol), $CuBr_2$ (0.134g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol) and *N*,*N*-dimethylacetamide (1.0 mL). The reaction mixture was then heated in an oil bath preheated at 120 ^oC. After completion of the reaction (20 h) the crude product was extracted with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 8:2) to give pure 2-(dimethylamino)-2-oxoethyl 5-bromo-2-hydroxybenzoate (**1a**) (0.109g, yield 72%). The identity and purity of the product was confirmed by spectroscopic analysis.

V.4.4. Mechanistic Investigation

V.4.4.1. ^{1}H NMR Study for the Detection of Reaction Intermediates During α-Bromo-esterification of 5-Chlorosalicylaldehyde (3): In order to detect the intermediate species in the reaction mixture for this α-bromo-esterification ^{1}H NMR spectroscopy was performed. In this study, an oven-dried flask was charged with 5-chlorosalicylaldehyde (**3**) (0.078g, 0.5 mmol), $CuBr_2$ (0.134g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol) and *N*,*N*-dimethylacetamide (1.0 mL). Then the reaction mixture was stirred in an oil bath at 120 ^oC. After 1 h of reaction, aliquot (100 μL) was withdrawn and crude product was extracted with ethyl acetate (5 mL) and concentrated under reduced pressure. The crude product so obtained was used for ^{1}H NMR study in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) (Fig. V.4.4.1). In the ^{1}H NMR spectra both brominated (**3A**) and non brominated 5-chlorosalicylaldehyde (**3**) were observed. After 3 h α-bromo-esterification product (**3a**) and α-esterification product (**3a´**) formation were observed. However, during progress of the reaction α-bromo-esterification product (**3a**) formation

was increased faster compare to α-esterification product (**3a´**) formation. This is taken as the representative example.

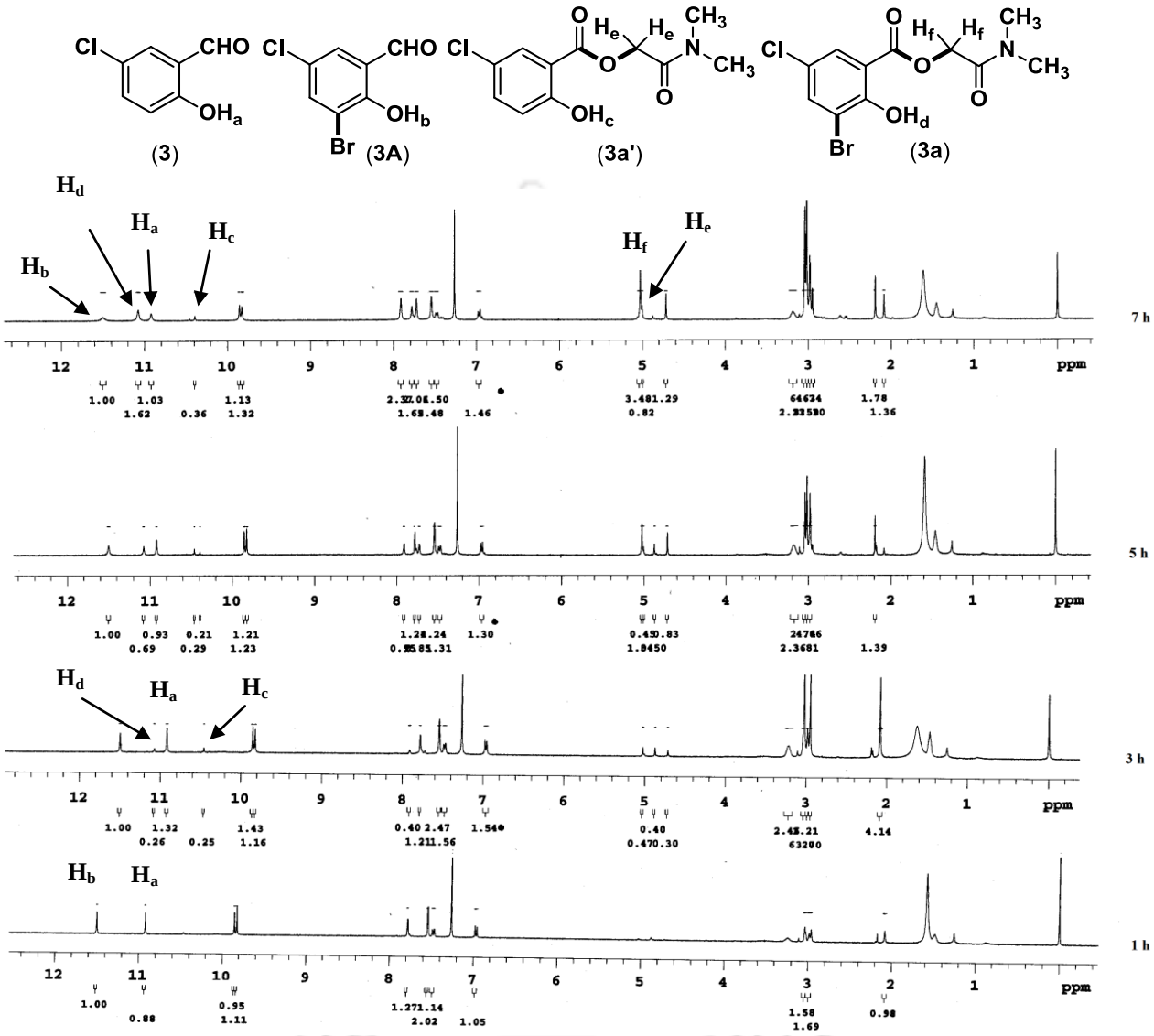


Fig. V.4.4.1. *Progress of the reaction monitored by* ^{1}H *NMR*

V.4.4.2. $^{18}O_2$ Labelling Experiment: To an oven-dried 10 mL round bottom flask were added sequentially 2-hydroxybenzaldehyde (**1**) (0.061g, 0.5 mmol), $CuBr_2$ (0.134g, 0.6 mmol), $Pd(OAc)_2$ (0.006g, 0.025 mmol) and *N*,*N*-dimethylacetamide (1.0 mL). The reaction was carried out in $^{18}O_2$ atmosphere. After completion of the reaction (20 h) the crude product was extracted with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous sodium sulfate

(Na_2SO_4), and concentrated under reduced pressure. The identity of the ^{18}O labeled product was confirmed by HRMS (Fig. V.4.4.2) and ^{13}C-NMR (Fig. V.4.4.3).

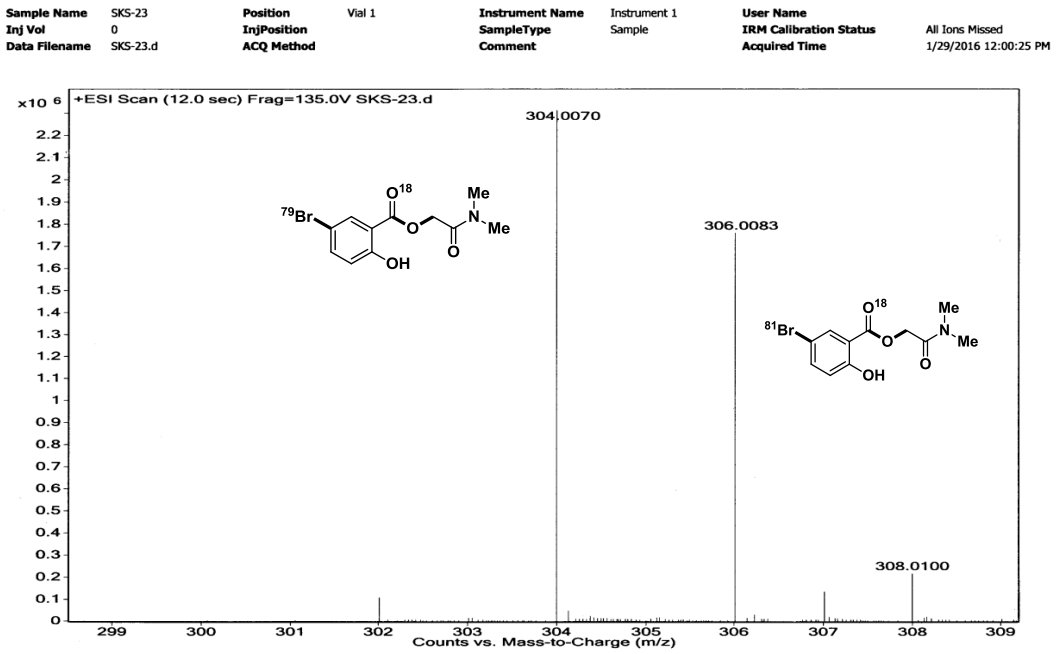


Fig. V.4.4.2. *HRMS spectrum of ^{18}O labeled (**1a**), $^{18}O_2$ as the source of ^{18}O*

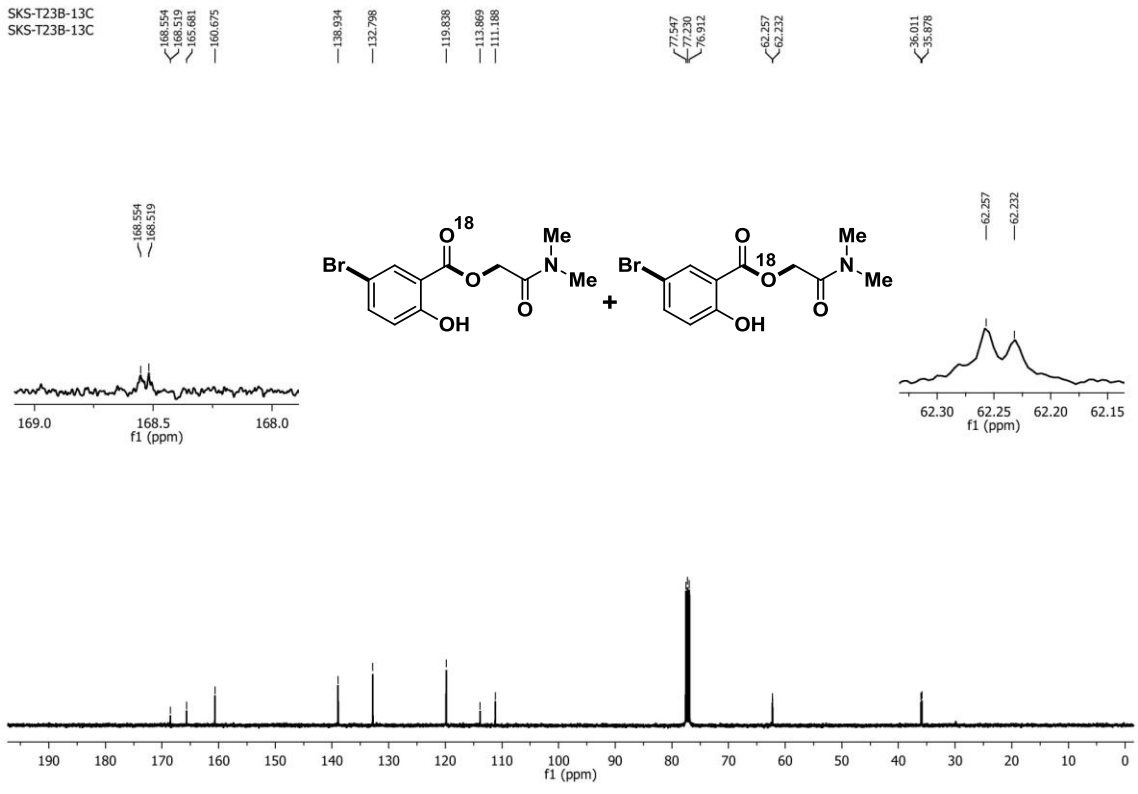


Fig. V.4.4.3. *^{13}C NMR spectrum of ^{18}O labeled (**1a**)*

V.4.4.3. HRMS Study for the Detection of Reaction Intermediates During α-Bromo-esterification of Salicylaldehyde (1): In order to detect the intermediate species in the reaction mixture an electrospray mass spectrometry of crude reaction mixture was performed. In this study, an oven-dried flask was charged with 2-hydroxybenzaldehyde (**1**) (0.061 g, 0.5 mmol), $CuBr_2$ (0.134 g, 0.6 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) and *N*,*N*-dimethylacetamide (1.0 mL). Then the reaction mixture was stirred in an oil bath at 120 ^oC. After 2 h of reaction, aliquot (100 μL) was withdrawn and diluted with acetonitrile (2 mL). A 20 μL of the diluted solution was injected to run APCl and ESI-MS analysis. Various intermediates *viz.* (**C**) and (**E**) were detected in the MS analysis as shown below in Fig. V.4.4.4 and Fig. V.4.4.5. The species observed in the spectrum are as follows: peaks at m/z 380.5093 corresponding to $[C_9H_7BrO_5Pd(II)]$ (**C**) (Fig. V.4.4.4) and at m/z 553.2541 corresponding to $[C_{15}H_{19}NO_8Pd_2(II)]$ (**E**) (Fig. V.4.4.5).

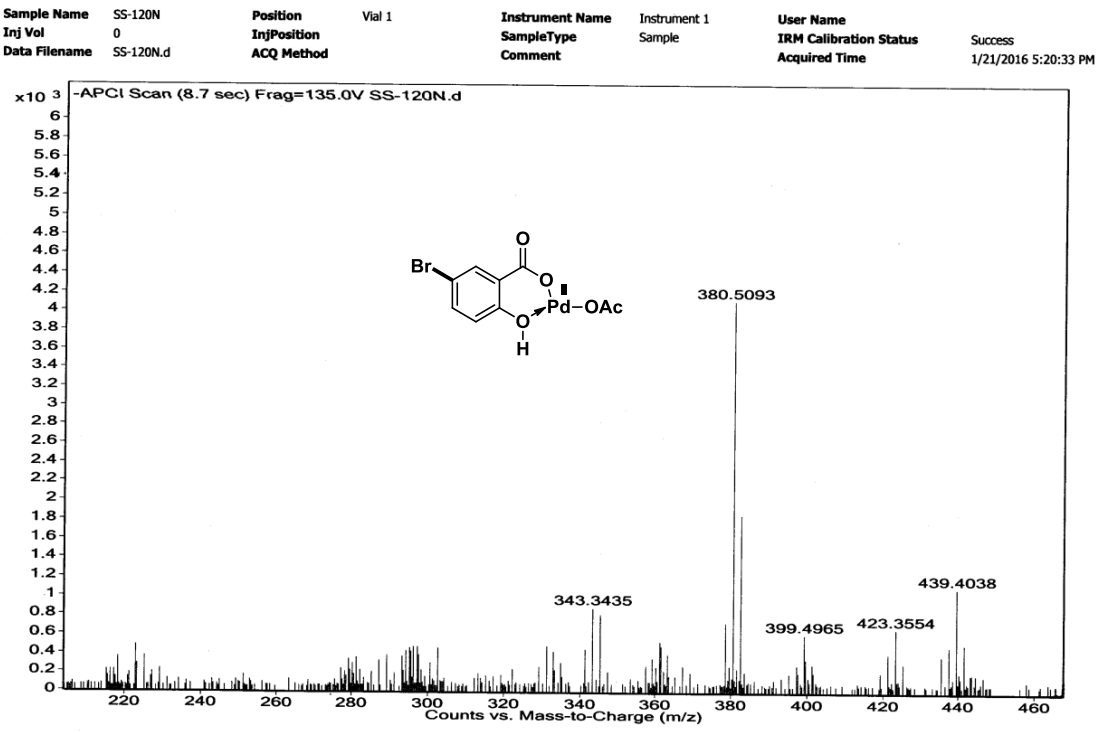


Fig. V.4.4.4. *HRMS spectrum of the reaction mixture after 2 h*

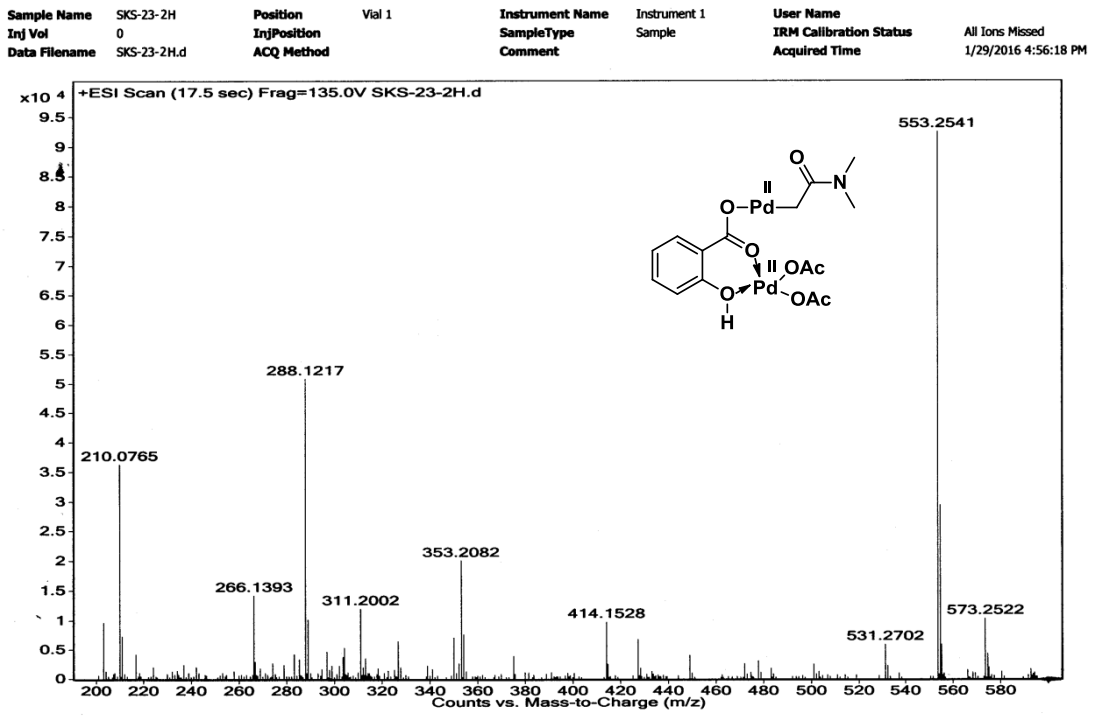


Fig. V.4.4.5. *HRMS spectrum of the reaction mixture after 2 h*

V.5. References

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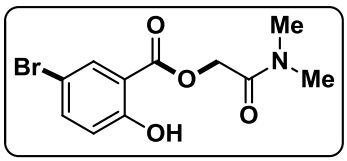
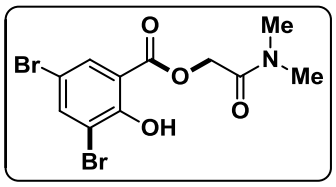
V.6. Spectral Data

2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxybenzoate (1a):



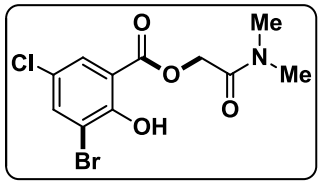
Solid; M.p. 82.6 °C–84.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.39 (s, 1H), 8.01 (s, 1H), 7.27 (d, 1H, J = 9.2 Hz), 6.84 (d, 1H, J = 8.8 Hz), 4.96 (s, 2H), 2.99 (s, 3H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 165.6, 160.6, 138.8, 132.7, 119.8, 113.9, 111.1, 62.2, 35.9, 35.8; IR (KBr, cm^{-1}): 3203, 2998, 2956, 2923, 1689, 1667, 1604, 1573, 1471, 1435, 1399, 1133, 1243, 1177, 1137, 1100, 1023, 1000, 830, 788, 751; HRMS (ESI) calcd for $C_{11}H_{12}BrNO_4$ (M + H^+) 302.0029, found 302.0037.

2-(Dimethylamino)-2-oxoethyl 3,5-dibromo-2-hydroxybenzoate (2a):



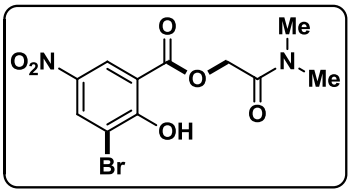
Solid; M.p. 171.3 °C–173.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.09 (s, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 5.02 (s, 2H), 3.03 (s, 3H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.2, 165.4, 157.3, 141.4, 132.2, 114.7, 112.6, 111.1, 62.6, 35.95, 35.87; IR (KBr, cm^{-1}): 3168, 2998, 2961, 2923, 2880, 1664, 1595, 1501, 1438, 1419, 1367, 1334, 1313, 1235, 1177, 1152, 1110, 1025, 872, 812, 787, 757; HRMS (ESI) calcd for $C_{11}H_{11}Br_2NO_4$ (M + H^+) 381.9114, found 381.9119.

2-(Dimethylamino)-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate (3a):



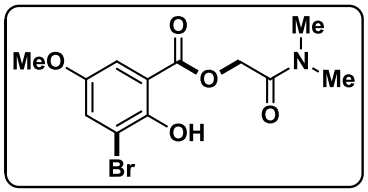
Solid; M.p. 146.9 °C–149.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.07 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 5.00 (s, 2H), 3.01 (s, 3H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.2, 165.4, 156.9, 138.7, 129.2, 124.5, 114.1, 112.2, 62.6, 35.9, 35.8; IR (KBr, cm^{-1}): 3164, 2993, 2952, 2926, 2877, 2850, 1668, 1596, 1501, 1442, 1424, 1395, 1369, 1338, 1314, 1274, 1260, 1234, 1179, 1153, 1143, 1116, 1093, 1061, 1026, 872, 812, 787, 758; HRMS (ESI) calcd for $C_{11}H_{11}BrClNO_4$ (M + H^+) 335.9639, found 335.9636.

2-(Dimethylamino)-2-oxoethyl 3-bromo-2-hydroxy-5-nitrobenzoate (4a):



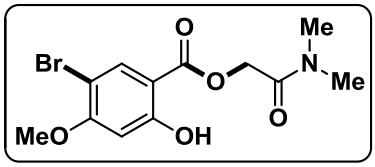
Solid; M.p. 120.0 °C–123.4 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.91 (s, 1H), 8.84 (s, 1H), 8.64 (s, 1H), 5.09 (s, 2H), 3.07 (s, 3H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 167.9, 162.9, 140.2, 133.9, 130.9, 125.9, 113.2, 112.5, 63.1, 35.9; IR (KBr, cm^{-1}): 3255, 3095, 2925, 2853, 1738, 1653, 1612, 1571, 1523, 1477, 1438, 1423, 1348, 1284, 1264, 1240, 1143, 1082, 1025, 917, 800, 782, 744, 728; HRMS (ESI) calcd for $C_{11}H_{11}BrN_2O_6$ (M + H^+) 346.9880, found 346.9891.

2-(Dimethylamino)-2-oxoethyl 3-bromo-2-hydroxy-5-methoxybenzoate (5a):



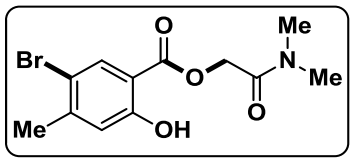
Gummy solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.69 (s, 1H), 7.41 (s, 1H), 7.37 (s, 1H), 5.00 (s, 2H), 3.77 (s, 3H), 3.03 (s, 3H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.0, 165.7, 152.8, 152.2, 127.3, 112.9, 112.8, 111.8, 62.4, 56.3, 35.9, 35.8; IR (KBr, cm^{-1}): 3203, 2952, 2929, 2853, 2834, 1734, 1659, 1608, 1498, 1471, 1431, 1368, 1332, 1298, 1273, 1238, 1226, 1152, 1095, 1067, 1041, 1025, 860, 813, 784, 735; HRMS (ESI) calcd for $C_{12}H_{14}BrNO_5$ (M + H^+) 332.0135, found 332.0144.

2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxy-4-methoxybenzoate (6a):



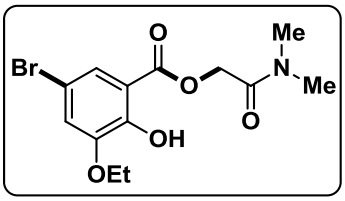
Solid; M.p. 174.2 °C–176.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.63 (s, 1H), 8.07 (s, 1H), 6.64 (s, 1H), 4.94 (s, 2H), 3.89 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.5, 165.9, 163.2, 161.8, 134.3, 106.2, 101.8, 100.5, 61.9, 56.7, 35.9, 35.8; IR (KBr, cm^{-1}): 3333, 3036, 2955, 2942, 1714, 1671, 1608, 1563, 1489, 1443, 1357, 1320, 1271, 1232, 1190, 1170, 1117, 1040, 1021, 974, 893, 865, 778; HRMS (ESI) calcd for for $C_{12}H_{14}BrNO_5$ (M + H^+) 332.0135, found 332.0141.

2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxy-4-methylbenzoate (7a):



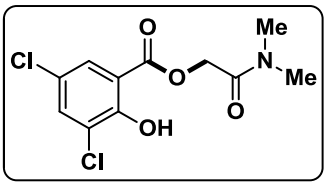
Solid; M.p. 120.7 °C–124.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.29 (s, 1H), 8.07 (s, 1H), 6.88 (s, 1H), 4.97 (s, 2H), 3.03 (s, 3H), 3.00 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.5, 165,8, 160.6, 146.9, 133.4, 119.8, 114.2, 111.7, 62.1, 36.0, 35.9, 23.7; IR (KBr, cm^{-1}): 3212, 2955, 2926, 2874, 2847, 1668, 1614, 1559, 1502, 1477, 1436, 1418, 1398, 1368, 1331, 1252, 1229, 1197, 1167, 1112, 1066, 1022, 947, 903, 857, 807, 787, 749; HRMS (ESI) calcd for $C_{12}H_{14}BrNO_4$ (M + H^+) 316.0186, found 316.0179.

2-(Dimethylamino)-2-oxoethyl 5-bromo-3-ethoxy-2-hydroxybenzoate (8a):



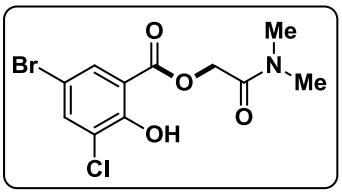
Solid; M.p. 181.4 °C–183.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.65 (s, 1H), 7.65 (s, 1H), 7.11 (s, 1H), 4.98 (s, 2H), 4.08 (q, 2H, J = 6.6 Hz), 3.02 (s, 3H), 2.99 (s, 3H), 1.46 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.9, 165.6, 151.8, 148.9, 123.7, 121.4, 113.5, 110.5, 65.3, 62.3, 35.9, 35.8, 14.8; IR (KBr, cm^{-1}): 3201, 3077, 2978, 2944, 2926, 2850, 1680, 1657, 1575, 1504, 1466, 1438, 1401, 1368, 1336, 1285, 1252, 1226, 1178, 1155, 1108, 1066, 965, 786, 756; HRMS (ESI) calcd for $C_{13}H_{16}BrNO_5$ (M + H^+) 346.0291, found 346.0301.

2-(Dimethylamino)-2-oxoethyl 3,5-dichloro-2-hydroxybenzoate (9a):



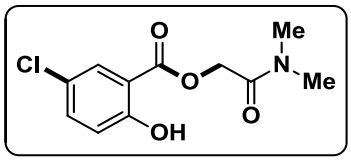
Solid; M.p. 132.2 °C–135.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.96 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 5.00 (s, 2H), 3.01 (s, 3H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.3, 165.4, 155.9, 135.7, 128.4, 124.0, 123.4, 114.3, 62.5, 35.9, 35.8; IR (KBr, cm^{-1}): 3177, 2996, 2961, 2931, 1670, 1601, 1501, 1445, 1429, 1414, 1369, 1339, 1315, 1262, 1235, 1176, 1163, 1147, 1094, 1064, 1028, 951, 872, 850, 817, 788, 757, 728; HRMS (ESI) calcd for $C_{11}H_{11}Cl_2NO_4$ (M + H^+) 292.0145, found 292.0147.

2-(Dimethylamino)-2-oxoethyl 5-bromo-3-chloro-2-hydroxybenzoate (10a):



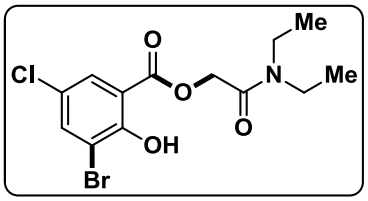
Solid; M.p. 165.8 °C–168.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.08 (s, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 5.00 (s, 2H), 3.01 (s, 3H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.1, 165.4, 157.3, 141.3, 132.1, 131.4, 114.7, 112.5, 62.6, 35.9, 35.8; IR (KBr, cm^{-1}): 3169, 3074, 2996, 2958, 2928, 1665, 1595, 1502, 1438, 1419, 1394, 1368, 1335, 1313, 1285, 1234, 1177, 1152, 1110, 1090, 1061, 1026, 871, 813, 787, 757, 733; HRMS (ESI) calcd for $C_{11}H_{11}BrClNO_4$ (M + H^+) 335.9639, found 335.9630.

2-(Dimethylamino)-2-oxoethyl 5-chloro-2-hydroxybenzoate (1a´´):



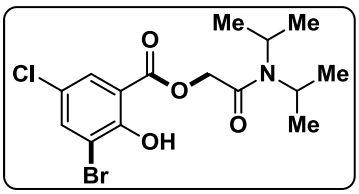
Solid; M.p. 93.6 °C–97.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.41 (s, 1H), 7.92 (s, 1H), 7.42 (d, 1H, J = 9.0 Hz), 6.94 (d, 1H, J = 9.0 Hz), 5.01 (s, 2H), 3.05 (s, 3H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.6, 165.7, 160.2, 136.2, 129.8, 124.3, 119.5, 113.3, 62.3, 36.0, 35.9; IR (KBr, cm^{-1}): 3200, 2950, 2934, 2920, 1750, 1688, 1668, 1609, 1470, 1431, 1378, 1329, 1281, 1241, 1200, 1105, 1082, 1019, 1003, 832, 801, 758, 717; HRMS (ESI) calcd for $C_{11}H_{12}ClNO_4$ (M + H^+) 258.0534, found 258.0538.

2-(Diethylamino)-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate (3b):



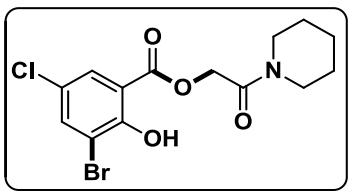
Solid; M.p. 94.1°C–96.2 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.11 (s, 1H), 7.91 (s, 1H), 7.71 (s, 1H), 5.02 (s, 2H), 3.42 (q, 2H, J = 7.2 Hz), 3.29 (q, 2H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.3, 164.6, 156.9, 138.7, 129.3, 124.6, 114.2, 112.3, 62.6, 41.2, 40.9, 14.4, 13.1; IR (KBr, cm^{-1}): 3158, 3071, 2974, 2923, 2872, 1678, 1644, 1496, 1467, 1432, 1381, 1331, 1340, 1269, 1232, 1171, 1117, 1093, 1032, 1015, 946, 904, 887, 813, 790, 725; HRMS (ESI) calcd for $C_{13}H_{15}BrClNO_4$ (M + H^+) 363.9952, found 363.9962.

2-(Diisopropylamino)-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate (3c):



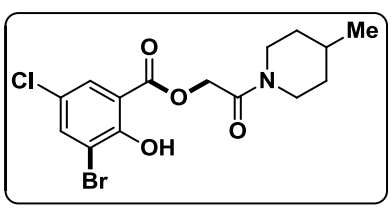
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.17 (s, 1H), 7.90 (s, 1H), 7.70 (s, 1H), 4.97 (s, 2H), 3.77–3.74 (m, 1H), 3.51–3.48 (m, 1H), 1.41 (d, 6H, J = 5.4 Hz), 1.28 (d, 6H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.0, 163.8, 156.7, 138.5, 129.3, 124.5, 114.5, 112.2, 63.3, 47.9, 46.6, 20.9, 20.6; IR (KBr, cm^{-1}): 3222, 2996, 2969, 2935, 1689, 1662, 1598, 1473, 1448, 1369, 1302, 1284, 1235, 1171, 1152, 1135, 1092, 1043, 1019, 884, 826, 788; HRMS (ESI) calcd for $C_{15}H_{19}BrClNO_4$ (M + H^+) 392.0265, found 392.0260.

2-Oxo-2-(piperidin-1-yl)ethyl 3-bromo-5-chloro-2-hydroxybenzoate (3d):



Solid; M.p. 97.5 °C–100.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.09 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 5.01 (s, 2H), 3.55 (t, 2H, J = 4.8 Hz), 3.33 (t, 2H, J = 5.4 Hz), 1.66–1.65 (m, 2H), 1.62–1.61 (m, 2H), 1.57–1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.2, 163.6, 156.8, 138.6, 129.1, 124.4, 114.2, 112.2, 62.7, 45.7, 43.4, 26.3, 25.4, 24.4; IR (KBr, cm^{-1}): 3216, 2998, 2935, 2917, 2856, 1702, 1668, 1473, 1454, 1435, 1368, 1316, 1264, 1254, 1223, 1151, 1136, 1091, 1032, 1004, 951, 875, 849, 837, 826, 778, 759; HRMS (ESI) calcd for $C_{14}H_{15}BrClNO_4$ (M + H^+) 375.9952, found 375.9954.

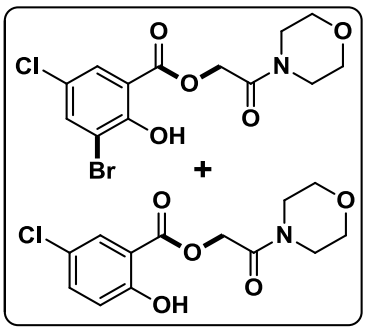
2-(4-Methylpiperidin-1-yl)-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate (3e):



Solid; M.p. 115.0 °C–118.4 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.09 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 5.02 (s, 2H), 4.51 (d, 1H, J = 13.2 Hz), 3.61 (d, 1H, J = 13.2 Hz), 3.08 (t, 1H, J = 12.6 Hz), 2.65 (t, 1H, J = 12.6 Hz), 1.76–1.63 (m, 3H), 1.21–1.14 (m, 2H), 1.13 (d, 3H, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.3, 163.7, 156.9, 138.7, 129.2, 124.5, 114.2, 112.3, 62.7, 45.0, 42.9, 34.5, 33.6, 31.1, 21.8;

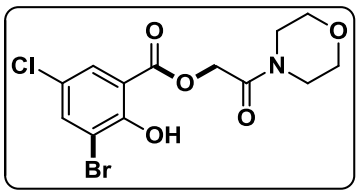
IR (KBr, cm^{-1}): 3234, 3001, 2954, 2907, 2857, 1704, 1671, 1651, 1473, 1451, 1430, 1316, 1270, 1238, 1222, 1149, 1087, 1036, 1013, 971, 876, 802, 786, 732; HRMS (ESI) calcd for $C_{15}H_{17}BrClNO_4$ ($M + H^+$) 390.0109, found 390.0118.

2-Morpholino-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate and 2-Morpholino-2-oxoethyl 5-chloro-2-hydroxybenzoate (3f and 3f´):



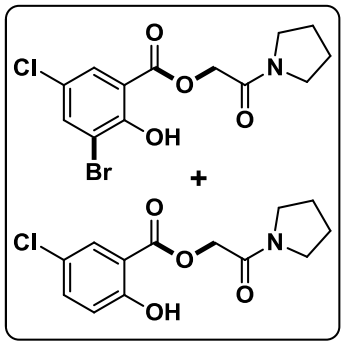
Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 11.01 (s, 1H), 10.33 (s, 1H), 7.88 (s, 2H), 7.72 (s, 1H), 7.41 (d, 1H, J = 9.0 Hz), 6.93 (d, 1H, J = 8.4 Hz), 5.01 (s,2H), 4.99 (s,2H), 3.72 (bs, 8H), 3.64 (bs, 4H); 3.43 (bs, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.6, 168.3, 164.5, 164.2, 160.3, 156.9, 138.9, 136.3, 129.7, 129.1, 124.6, 124.3, 119.5, 113.8, 113.1, 112.3, 66.9, 66.4, 62.4, 62.0, 45.2, 45.1, 42.5; IR (KBr, cm^{-1}): 3220, 3063, 2965, 2923, 2856, 1684, 1673, 1609, 1475, 1450, 1362, 1334, 1274, 1229, 1170, 1114, 1068, 1042, 1003, 854, 829, 791, 783, 718; HRMS (ESI) calcd for $C_{13}H_{13}BrClNO_5$ ($M + H^+$) 377.9745, found 377.9756, and HRMS (ESI) calcd for $C_{13}H_{14}ClNO_5$ ($M + H^+$) 300.0640, found 300.0647.

2-Morpholino-2-oxoethyl 3-bromo-5-chloro-2-hydroxybenzoate (3f):



Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 11.02 (s, 1H), 7.91 (s, 1H), 7.74 (s, 1H), 5.03 (s,2H), 3.75 (bs, 4H), 3.66 (bs, 2H); 3.45 (bs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.4, 164.2, 156.9, 138.9, 129.1, 124.4, 113.9, 112.7, 66.8, 66.5, 62.7, 45.2, 42.5; IR (KBr, cm^{-1}): 3228, 3053, 2961, 2933, 2858, 1663, 1601, 1461, 1448, 1361, 1334, 1274, 1231, 1164, 1062, 1003, 832, 784, 728; HRMS (ESI) calcd for $C_{13}H_{13}BrClNO_5$ ($M + H^+$) 377.9745, found 377.9751.

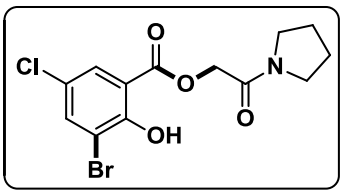
2-Oxo-2-(pyrrolidin-1-yl)ethyl 3-bromo-5-chloro-2-hydroxybenzoate and 2-Oxo-2-(pyrrolidin-1-yl)ethyl 5-chloro-2-hydroxybenzoate (3g and 3g´):



Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 11.08 (s, 1H), 10.39 (s, 1H), 7.91 (s, 2H), 7.71 (s, 1H), 7.40 (d, 1H, J = 8.4 Hz), 6.93 (d, 1H, J = 8.4 Hz), 4.92 (s, 2H), 4.90 (s, 2H), 3.54 (t, 4H, J = 7.2 Hz), 3.44 (t, 4H, J = 6.6 Hz); 2.05–2.02 (m, 4H), 1.91–1.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.7, 168.3, 164.4, 164.0, 160.3, 156.9, 138.8, 136.1, 129.8, 129.2, 124.6, 124.3, 119.5, 114.1, 113.3, 112.2, 63.1, 62.7, 46.41, 46.37, 45.51, 45.46, 26.3, 24.1; IR (KBr, cm^{-1}): 3182, 2965, 2923, 2878, 1672, 1606, 1574, 1468, 1459, 1430, 1361, 1315, 1285, 1233, 1187, 1164, 1107, 1085, 976, 875, 825, 786, 741, 724; HRMS (ESI) calcd for $C_{13}H_{13}BrClNO_4$ ($M + H^+$)

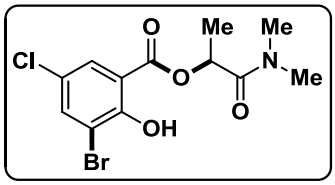
361.9796, found 361.9799 and HRMS (ESI) calcd for $C_{13}H_{14}ClNO_4$ (M + H^+) 284.0691, found 284.0695

2-Oxo-2-(pyrrolidin-1-yl)ethyl 3-bromo-5-chloro-2-hydroxybenzoate (3g):



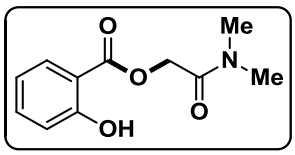
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.06 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 4.92 (s,2H), 3.54 (t, 2H, J = 7.2 Hz), 3.45 (t, 2H, J = 6.8 Hz); 2.06–2.03 (m, 2H), 1.92–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.4, 164.2, 157.0, 138.8, 129.2, 124.6, 114.0, 112.3, 63.1, 46.5, 45.5, 26.2, 24.0; IR (KBr, cm^{-1}): 3211, 2985, 2915, 2858, 1662, 1606, 1574, 1468, 1433, 1351, 1321, 1284, 1189, 1158, 1100, 1075, 875, 828, 748, 718; HRMS (ESI) calcd for $C_{13}H_{13}BrClNO_4$ (M + H^+) 361.9796, found 361.9806.

1-(Dimethylamino)-1-oxopropan-2-yl 3-bromo-5-chloro-2-hydroxybenzoate (3h):



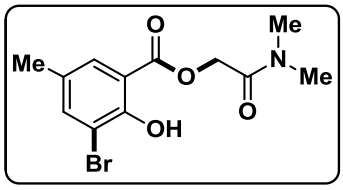
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.10 (s, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 5.63 (q, 1H, J = 6.6 Hz), 3.12 (s, 3H), 3.00 (s, 3H), 1.60 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.4, 168.3, 157.0, 138.8, 129.2, 124.5, 113.9, 112.2, 69.1, 37.0, 36.3, 16.8; IR (KBr, cm^{-1}): 3092, 2992, 2934, 2853, 1746, 1664, 1602, 1506, 1429, 1371, 1317, 1233. 1173, 1115, 1079, 1026, 880, 793, 728; HRMS (ESI) calcd for $C_{12}H_{13}BrClNO_4$ (M + H^+) 349.9796, found 349.9804.

2-(Dimethylamino)-2-oxoethyl 2-hydroxybenzoate (1a´):



Solid; M.p. 56.0 ^{o}C–58.2 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.45 (s, 1H), 7.95 (d, 1H, J = 6.6 Hz), 7.46 (t, 1H, J = 7.5 Hz), 6.97 (d, 1H, J = 8.4 Hz), 6.89 (t, 1H, J = 7.5 Hz), 4.98 (s, 2H), 3.03 (s, 3H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.6, 166.0, 161.7, 136.2, 130.6, 119.5, 117.8, 112.4, 62.1, 36.1, 35.8; IR (KBr, cm^{-1}): 3220, 2957, 2922, 2850, 1685, 1659, 1613, 1584, 1501, 1482, 1435, 1415, 1329, 1303, 1246, 1197, 1180, 1151, 1131, 1096, 850, 793 ,737; HRMS (ESI) calcd for $C_{11}H_{13}NO_4$ (M + H^+) 224.0924, found 224.0927.

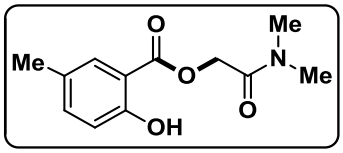
2-(Dimethylamino)-2-oxoethyl 3-bromo-2-hydroxy-5-methylbenzoate (12a):



Solid; M.p. 140.2 ^{o}C–143.6 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.92 (s, 1H), 7.73 (s, 1H), 7.56 (s, 1H), 4.99 (s, 2H), 3.03 (s, 3H), 3.00 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.3, 165.7, 156.0, 140.1, 129.83, 129.80, 113.1, 110.9, 62.3, 35.9, 35.8, 20.3; IR (KBr, cm^{-1}): 3225, 2948,

2927, 2853, 1667, 1613, 1494, 1438, 1397, 1362, 1326, 1214, 1166, 1148, 1101, 1061, 1026, 927, 869, 787, 782, 743; HRMS (ESI) calcd for $C_{12}H_{14}BrNO_4$ (M + H^+) 316.0186, found 316.0180.

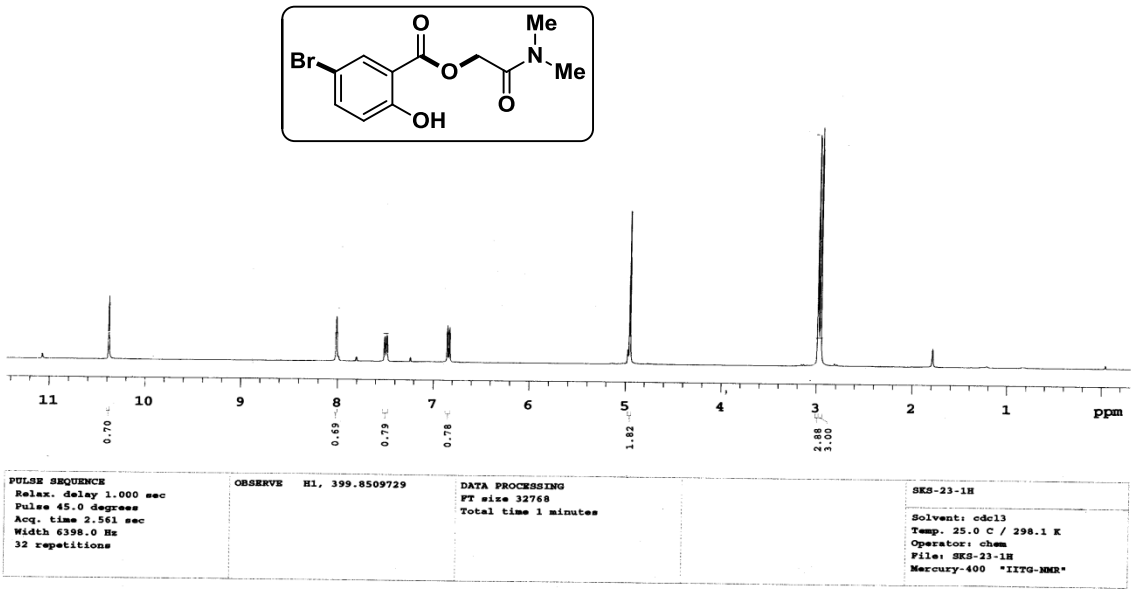
2-(Dimethylamino)-2-oxoethyl 2-hydroxy-5-methylbenzoate (12a´):



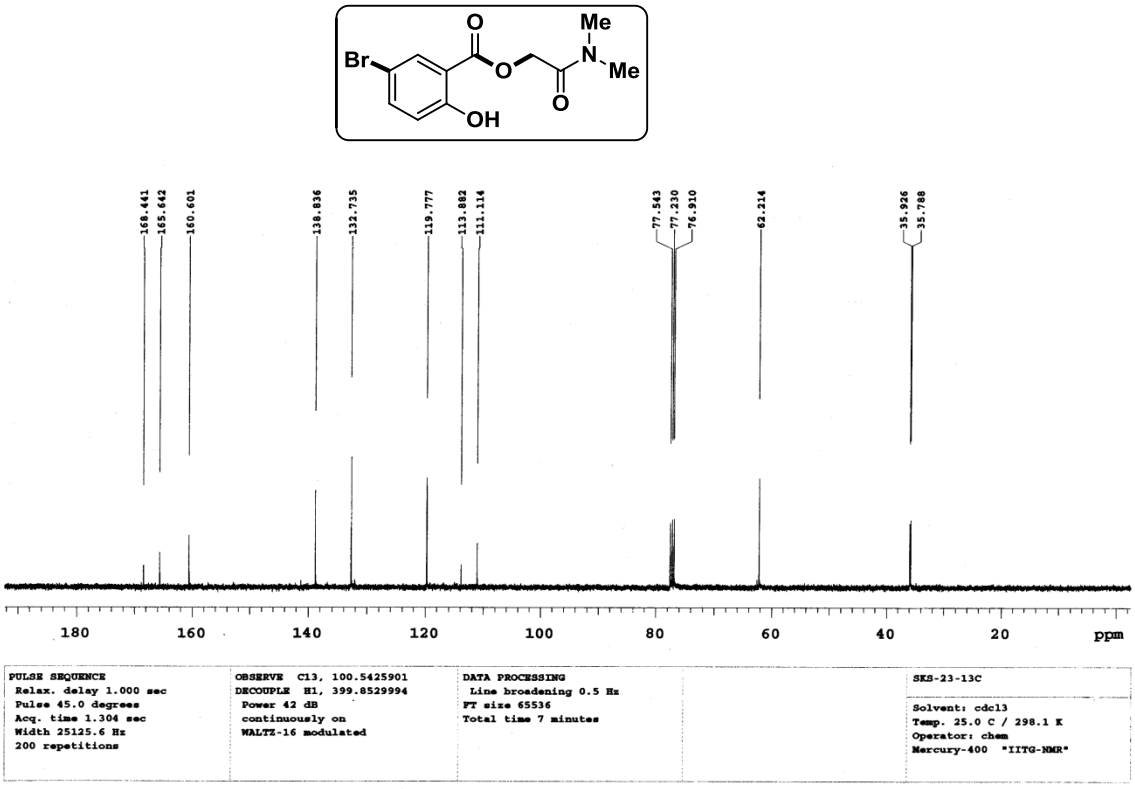
Solid; M.p. 86.4 °C–89.8 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.28 (s, 1H), 7.75 (s, 1H), 7.28 (d, 1H, J = 10.2 Hz), 6.89 (d, 1H, J = 8.4 Hz), 4.99 (s, 2H), 3.05 (s, 3H), 3.02 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.6, 166.2, 159.6, 137.3, 130.2, 128.7, 117.6, 111.8, 61.9, 36.1, 35.9, 20.5; IR (KBr, cm^{-1}): 3236, 2959, 2925, 2856, 1663, 1495, 1435, 1365, 1335, 1290, 1249, 1211, 1187, 1155, 1099, 1022, 825, 789, 740; HRMS (ESI) calcd for $C_{12}H_{15}NO_4$ (M + H^+) 238.1081, found 238.1089.

V.7. Spectra

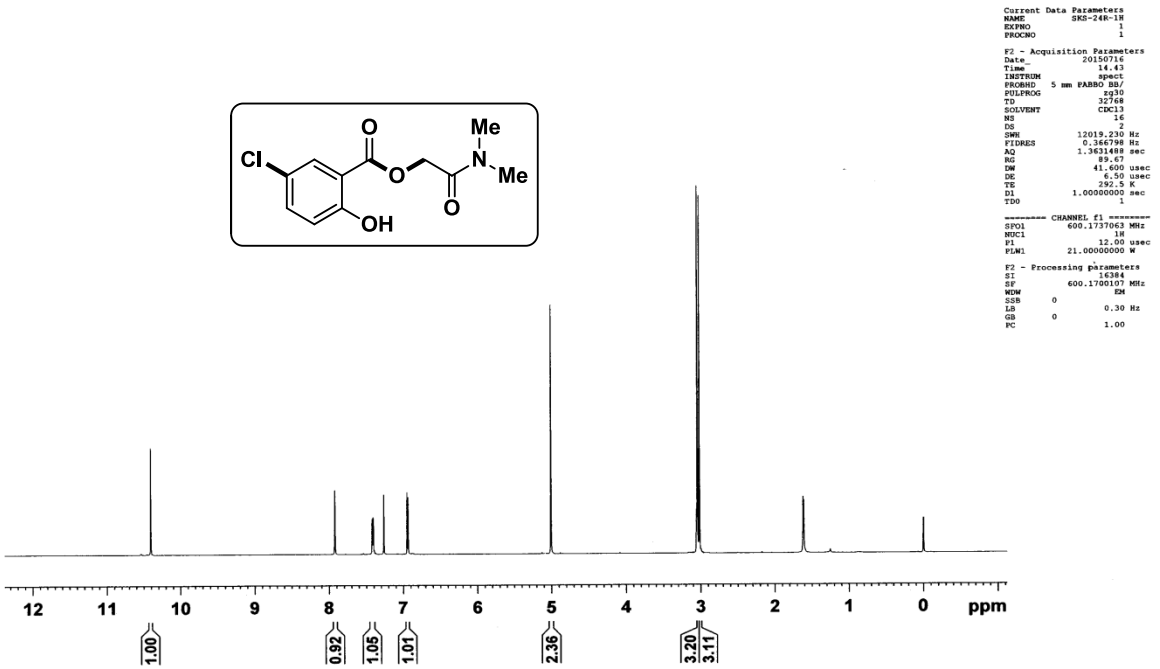
2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxybenzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



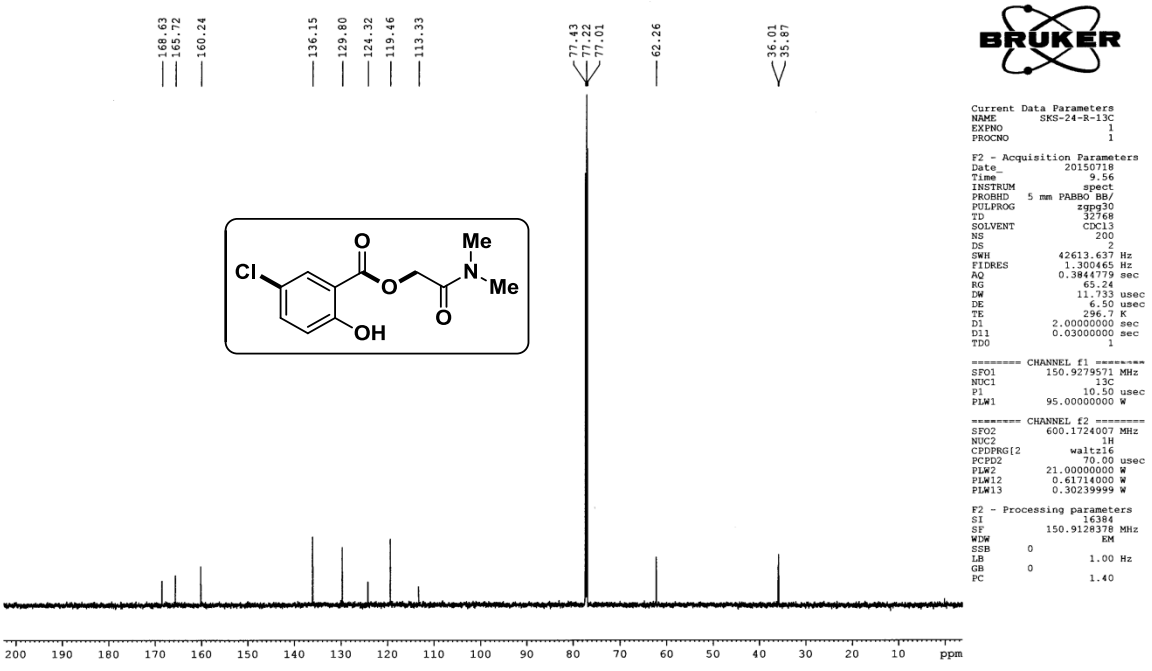
2-(Dimethylamino)-2-oxoethyl 5-bromo-2-hydroxybenzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



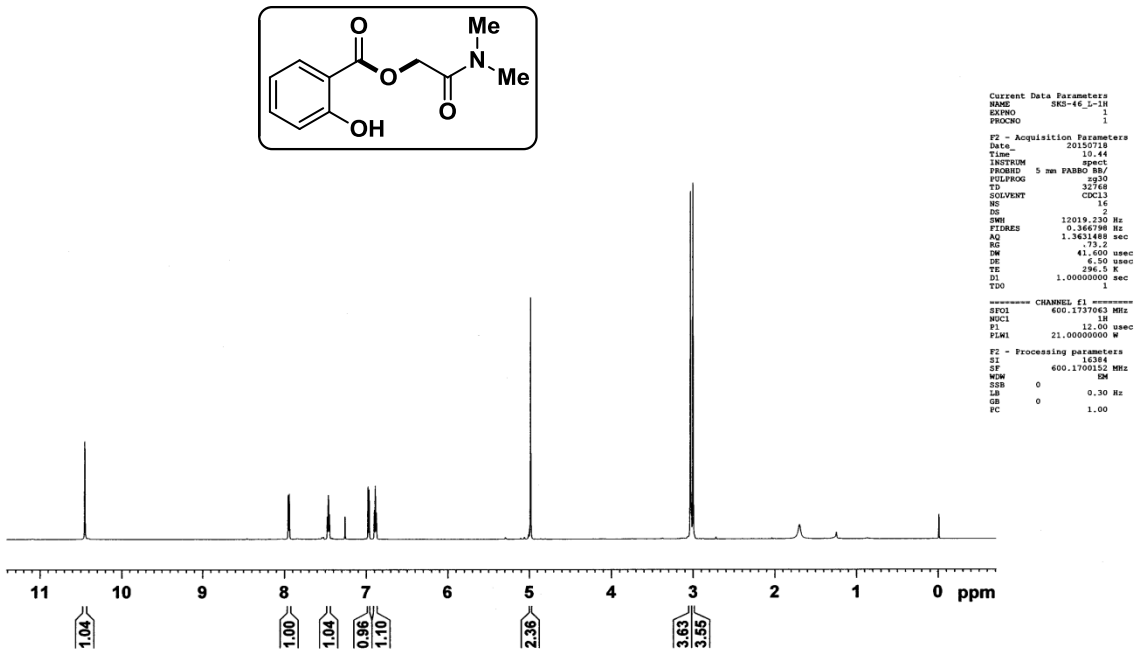
2-(Dimethylamino)-2-oxoethyl 5-chloro-2-hydroxybenzoate (1a´´): ^{1}H NMR (600 MHz, $CDCl_3$)



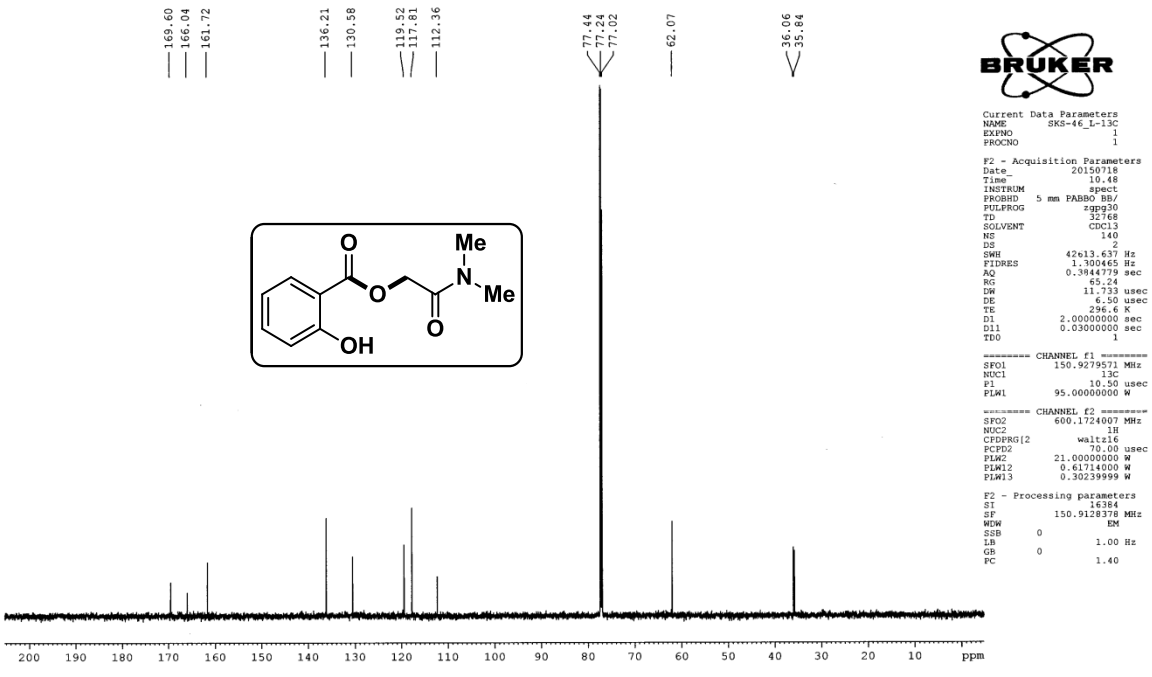
2-(Dimethylamino)-2-oxoethyl 5-chloro-2-hydroxybenzoate (1a´´): ^{13}C NMR (150 MHz, $CDCl_3$)



2-(Dimethylamino)-2-oxoethyl 2-hydroxybenzoate (1a´): ^{1}H NMR (600 MHz, $CDCl_3$)

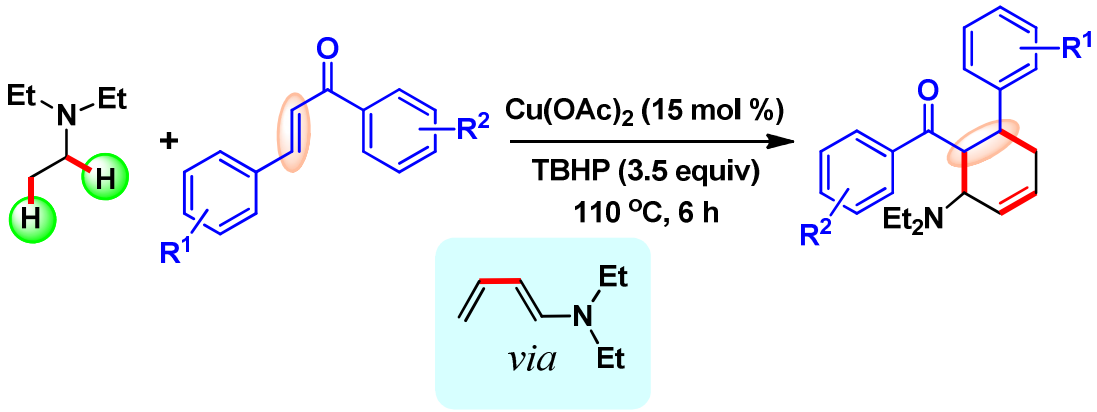


2-(Dimethylamino)-2-oxoethyl 2-hydroxybenzoate (1a´): ^{13}C NMR (150 MHz, $CDCl_3$)



Chapter VI

Tertiary Alkyl Amine as the Source of Diene for Cycloaddition via Copper(II) Catalyzed α,β C_{sp3}–H Functionalization



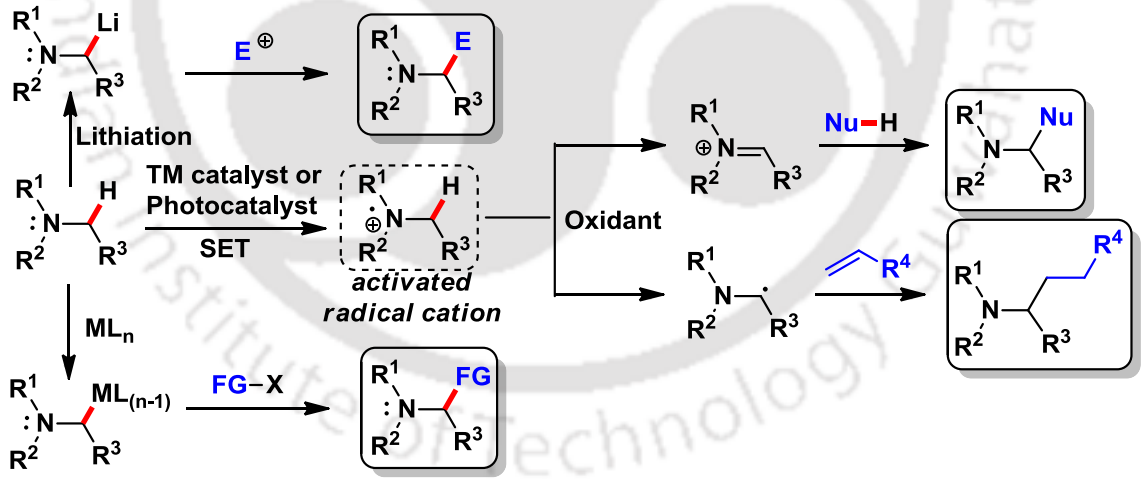
Abstract: *A number of transition metal catalyzed α-C_{sp3}–H Functionalizations of tertiary amine have been reported in literature, herein for the first time both α and β C_{sp3}–H bonds are functionalization using copper(II) catalyst. In the presence of $Cu(OAc)_2$ and TBHP trialkylamine serves as a diene for cycloaddition. The in situ generated diene obtained via the self coupling of trialkylamine was trapped by dienophiles.*

CHAPTER VI

VI. Tertiary Alkyl Amine as the Source of Diene for Cycloaddition *via* Copper(II) Catalyzed α,β C_{sp3}–H Functionalization

VI.1. Introduction

Selective functionalization of sp^3 C–H bonds of alkane is challenging due to inherent inertness and non-availability of coordinating site for metal binding. In contrast functionalization of alpha sp^3 C–H bonds adjacent to heteroatom is relatively easier due to its lower pKa. Functionalization of sp^3 C–H bonds adjacent to heteroatom is an attractive practical method in organic synthesis for the formation of C–C and C–X bonds.[1] The α sp^3-carbon adjacent to nitrogen atom has the ability to act as an electrophile *via* iminium cation. Further it can serve as a nucleophile *via* classical lithiation chemistry, α-amino radical formation and metal catalyzed C–H activation processes under appropriate reaction conditions (Scheme VI.1.1).



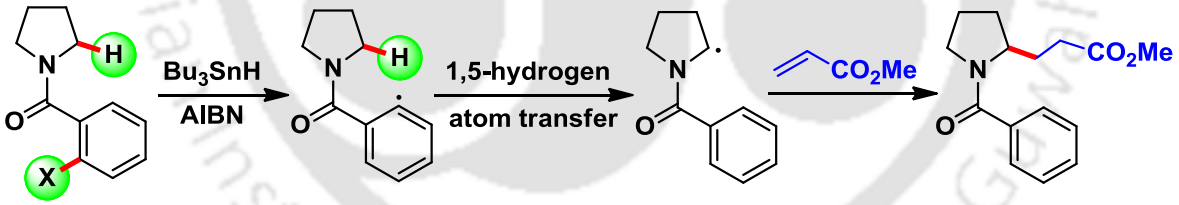
Scheme VI.1.1. *Various routes to α-C_{sp3}–H Functionalization of amines*

Based on its differential reactivity a variety of methods exists in literature for α C_{sp3}–H functionalization. α C_{sp3}–H functionalization adjacent to heteroatom can be achieved either *via* thermodynamically more favourable intramolecular path or *via* intermolecular path. However, intermolecular α-functionalization and subsequent cyclization processes are rarely reported in literature. A photoredox catalyzed Michael addition of α-amino radicals to the α,β-unsaturated ketone has been developed using $Ru(bpy)_3Cl_2$ or $[Ir(ppy)_2$-(dtb-bpy)$]PF_6$ in

the presence of a blue LED.[2] Recently, Guan *et. al.* reported an iron catalyzed synthesis of tetrahydroquinolines *via* the dehydrogenative [4+2] cycloaddition between tertiary anilines with enamides in the presence of *tert*-butyl hydroperoxide (TBHP).[3] Simultaneously, Bissember *et al.* introduced *bis*(1,10-phenanthroline)-copper(I), a visible light photo-catalyst (VLP) to effect the direct α C−H functionalization and subsequent cyclization of tertiary amines with *N*-phenyl maleimide.[4] In this context the use of tertiary amine like simple triethylamine for such α-C−H functionalization/cyclization processes are unprecedented in literature.

VI.2. sp^3 C–H Functionalizations Adjacent to Nitrogen Atom

The oldest reported method for the direct sp^3 C–H functionalization adjacent to nitrogen atom is α-lithiation with alkyllithium/diamine complexes. The strategy produces a dipole-stabilized carbanion which undergoes electrophilic substitution.[5] This type of α-functionalization requires strong base such as BuLi. To avoid such condition Curran and Snieckus reported an α-amino radical coupling of *ortho*-halobenzamides with methyl acrylate in the presence of Bu_3SnH/AIBN combination. Bu_3SnH/AIBN first generates radical from *ortho*-halobenzamides followed by a 1,5-hydrogen atom transfer to give an α-amino radical adjacent to the nitrogen atom (Scheme VI.2.1).[6]

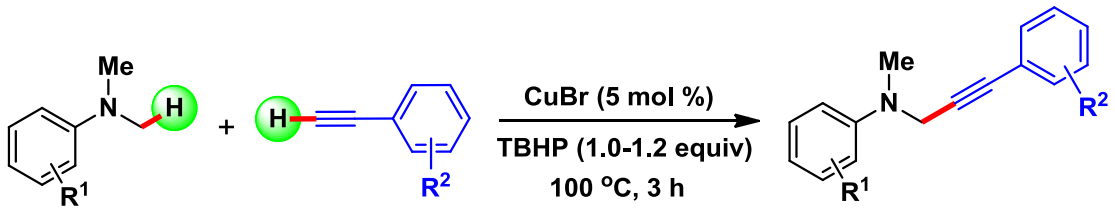


Scheme VI.2.1.*Radical based sp^3 C-H functionaization*

Such type of radical based C–H functionalization are well investigated in the area of sp^3 C–H bond activation, but for all cases stoichiometric amount of reagents or prefunctionalized starting materials have been employed. Despite the inherent difficulty for direct sp^3 C–H bond activation adjacent to nitrogen atom, recently several examples have been reported using a variety of transition metal catalysts and oxidants.

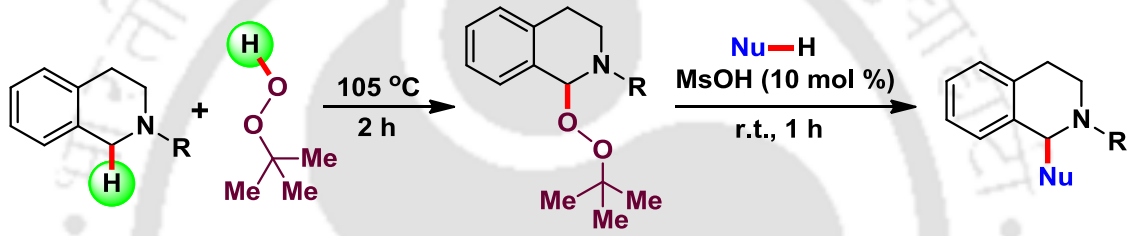
In 2004, Li group reported a Cu(I) catalyzed CDC method to form propargylamine *via* a combination of sp^3 C–H bond and sp C–H bond functionalizations (Scheme VI.2.2).[1a] Later, the same group also developed a highly efficient C–C bond formation *via* CDC reaction

between sp^3 C–H bond of tertiary amine and sp^3 C–H bond of nitroalkane using Cu(I)/TBHP combination.[1c]



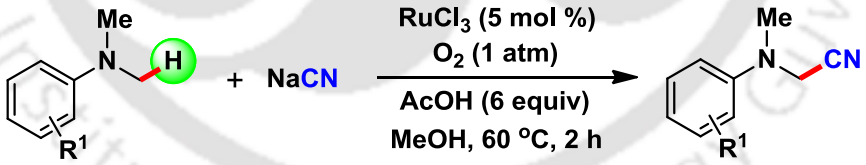
Scheme VI.2.2. *CDC between N,N-dimethylamines and alkynes*

Klussmann group demonstrated an α-sp^3 C–H functionalization of *N*-protected tetrahydroisoquinolines under metal free condition. The reaction proceeds *via* the initial formation of peroxide intermediate which undergoes nucleoplilic substitution reaction catalyzed by methanesulfonic acid (MsOH) (Scheme VI.2.3).[1h]



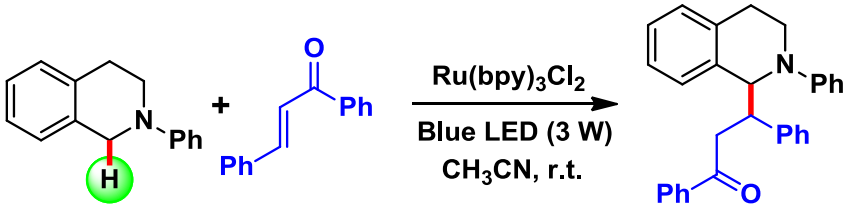
Scheme VI.2.3. *α-C–H Functionalization of N-protected tetrahydroisoquinolines*

Murahashi and co-workers developed a ruthenium catalyzed oxidative α-cyanation of tertiary amines using sodium cyanide and molecular oxygen as the sole oxidant (Scheme VI.2.4).[7]



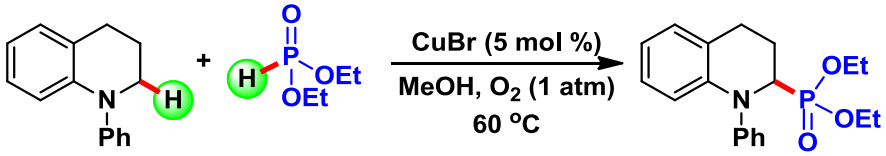
Scheme VI.2.4. *Ru(III)-catalyzed α-cyanation of tertiary amines*

In 2012, Reiser and co-workers reported an efficient intermolecular α-amino radical conjugate addition with chalcones using Ru(bpy)$_3$Cl$_2$ or [Ir(ppy)$_2$-(dtb-bpy)]PF$_6$ photocatalyst (Scheme VI.2.5).[2]



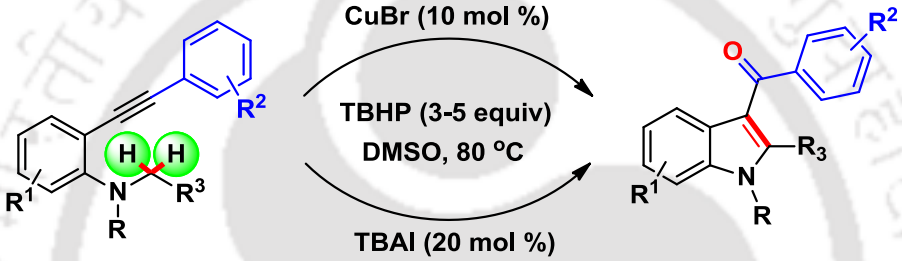
Scheme VI.2.5. *Ru(II)-catalyzed α-amino radical conjugate addition with chalcone*

Li group has demonstrated an efficient protocol for the synthesis of biologically important α-aminophosphonates *via* cross-dehydrogenative coupling (CDC) between sp^3 C–H adjacent to nitrogen atom and H–P bond of dialkyl phosphonate (Scheme VI.2.6.).[1o]



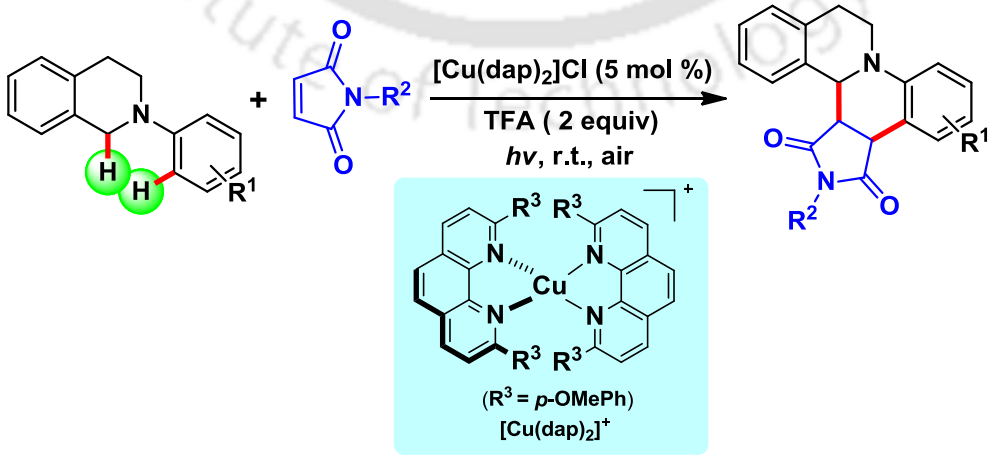
Scheme VI.2.6. *Cu(I)-catalyzed C_{sp3}–P bond formation via CDC*

Our group has reported the synthesis of 3-aroylindoles from *o*-alkynyl-*N*,*N*-dialkylamine *via* intramolecular oxidative coupling involving two α-C_{sp3}–H bonds under metal or metal free condition using TBHP as the oxidant (Scheme VI.2.7).[8]



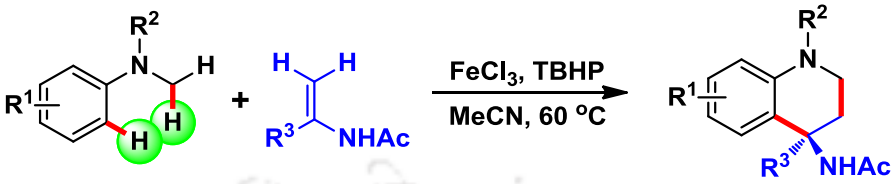
Scheme VI.2.7. *Intramolecular oxidative coupling of o-alkynyl-N,N-dialkylamine*

Recently, the Bissember group demonstrated the first example of the direct functionalization of α-amino C–H bonds promoted by a *bis*(1,10-phenanthroline)-copper(I) visible light photocatalyst (VLP) (Scheme VI.2.8).[4] In the presence of Cu(I)-VLP tertiary amine efficiently coupled with *N*-phenyl maleimide to give important heterocyclic scaffolds such as octahydroisoquinolino[2,1-a]pyrrolo[3,4-c]-quinoline frameworks as a single diastereoisomers.



Scheme VI.2.8. *Copper(I)-VLP catalyzed dehydrogenative [4+2] cycloaddition reaction*

In the same year Guan group developed an iron catalyzed dehydrogenative [4+2] cycloaddition reaction of tertiary anilines and enamides for the synthesis of tetrahydroquinolines with amido-substituted quaternary carbon centers in the presence of TBHP oxidant. (Scheme VI.2.9).[3]



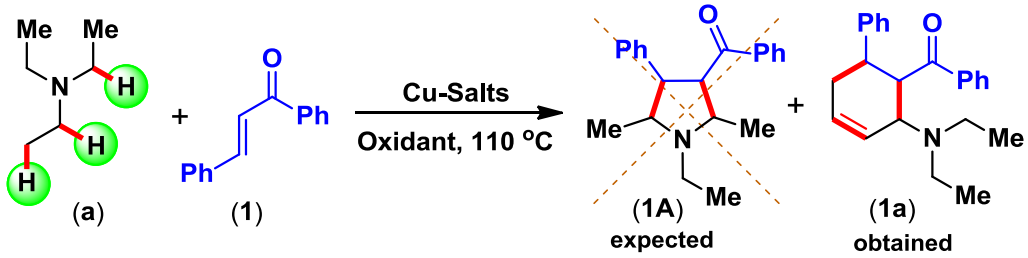
Scheme VI.2.9. *Iron(III)-catalyzed dehydrogenative [4+2] cycloaddition reaction*

VI.3. Present Work

Triethylamine, an organic base is used mainly in the synthesis of quaternary ammonium salts for textile auxiliaries, dyes; acid neutralizer and intermediates for the synthesis of pesticides, drugs etc. Tertiary amine contains α-sp^3 C–H bonds which can be similarly functionalized with external electrophiles or nucleophiles.

Optimization of Reaction Conditions. Taking cues from the *bis*-functionalization of styrene[9] in the presence of Cu(I) catalyst and TBHP oxidant, we wish to developed an α-amino radical cyclization of triethylamine with chalcone. When chalcone (**1**) was treated with triethylamine (**a**; 1.5 mL) in the presence of CuBr (10 mol %) and TBHP (2.0 equiv) at 110 ^{o}C, an unexpected product (**1a**) was isolated in 24% yield rather than the speculated cyclized product (**1A**) (Table VI.3.1, entry 1). Spectroscopic analysis of the newly formed product (**1a**) and comparisons of the literature reported[10] data reveals that it is a Diels-Alder adduct of (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine (**a´**) and chalcone (**1**). Encouraged by this preliminary success, to arrive at the best possible yield of (**1a**), other copper salts were screened under otherwise identical conditions. Copper(II)-salts such as $CuBr_2$, $CuCl_2$ and $Cu(OTf)_2$ provided only minor amount (<20%) of (**1a**), whereas $Cu(OAc)_2$ afforded 40% of the Diels-Alder product (**1a**) (Table VI.3.1, entries 2–5). When $Cu(OAc)_2 \cdot H_2O$ was used in lieu of $Cu(OAc)_2$ it gave 35% of the desired product (**1a**) (Table VI.3.1, entry 6). Significant improvement in the yield (48%) was observed when the catalyst $Cu(OAc)_2$ loading was increased from 10 to 15 mol % (Table VI.3.1, entry 7). However, a further increase in the catalyst loading to 20 mol % did not affect the product yield (51%) significantly (Table VI.3.1, entry 8).

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



entry	catalyst (mol %)	oxidant	yield (%)[b]
1	CuBr (10)	TBHP	24
2	$CuBr_2$ (10)	TBHP	16
3	$CuCl_2$ (10)	TBHP	14
4	$Cu(OAc)_2$ (10)	TBHP	40
5	$Cu(OTf)_2$ (10)	TBHP	19
6	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP	35
7	$Cu(OAc)_2$ (15)	TBHP	48
8	$Cu(OAc)_2$ (20)	TBHP	51
9	$Cu(OAc)_2$ (15)	TBHP	62[c]
10	**$Cu(OAc)_2$ (15)**	**TBHP**	**69[d]**
11	$Cu(OAc)_2$ (15)	TBPB	trace
12	$Cu(OAc)_2$ (15)	BP	trace
13	$Cu(OAc)_2$ (15)	DTBP	31
14	$Cu(OAc)_2$ (15)	$K_2S_2O_8$	0
15	$Cu(OAc)_2$ (15)	TBHP	52[c]

[a]Reaction condition: Chalcone (**1**) (0.3 mmol), Triethylamine (**a**) (1.5 mL), TBHP in decane (2.0 equiv) at 110 °C for 6 h. [b]Isolated yield. [C]TBHP (3.0 equiv). [d]TBHP (3.5 equiv). [e]Triethylamine (5 equiv) in chlorobenzene (1 mL).

Further, to get the optimum yield, TBHP quantity was increased from 2.0 to 3.0 and 3.5 equivalents which provided (**1a**) in an improved yield of 62% and 69% respectively (Table VI.3.1, entries 9 and 10). Other peroxide oxidants such as *tert*-butyl peroxybenzoate (TBPB), benzoyl peroxide (BP), di-*tert*-butyl peroxide (DTBP) and $K_2S_2O_8$ were tested under otherwise identical condition, but all the oxidants were found to be inferior compare to TBHP (Table VI.3.1, entries 11–14). In order to reduce the quantity of triethylamine (**a**) other solvent chlorobenzene (1 mL) and triethylamine (5 equiv) were used for this sp^3 C–H functionalization. However, from this reaction only 52% of the (**1a**) was observed (Table VI.3.1, entry 15). Thus, after screening of reaction parameters it was found that the use of chalcone (**1**) (0.3 mmol), triethylamine (1.5 mL), $Cu(OAc)_2$ (15 mol %) and TBHP in decane (3.5 equiv) at 110 °C gave the best yield (69%) of (**1a**) (Table VI.3.1, entry 10).

Substrate Scope for α,β-sp^3 C-H Functionalization. Encouraged by this success, the reaction between various chalcones and triethylamine were evaluated under the optimized reaction conditions. This methodology is compatible for a variety of chalcones possessing electron-donating and electron-withdrawing substituent present in both the phenyl rings. Chalcones possessing moderately and strongly electron-withdrawing substituents such as *p*–Cl (**2**), *p*–Br (**3**) and *p*–CF_3 (**4**) in the ketone counterpart of enone provided corresponding coupled products (**2a**, 73%), (**3a**, 72%) and (**4a**, 75%) in good yields respectively (Scheme VI.3.1). Moderately electron-donating substituent *m*–Me (**5**) substrate gave decent yield (63%) of the desired coupled product (**5a**). Chalcones derived from fused aromatic and hetero aromatic ketones such as 2-naphthyl (**6**), 2-furyl (**7**) and 2-thiophene (**8**) efficiently coupled with triethylamine and afforded moderate yields of the desired product (**6a**, 61%), (**7a**, 65%) and (**8a**, 66%) respectively (Scheme VI.3.1). Chalcones containing electron-withdrawing group such as *p*–Br (**9**), *m*–Br (**10**), *o*–Cl (**11**) and *o*–F (**12**) in the aldehyde counterpart provided moderate to good yields of the Diels-Alder product (**9a**, 70%), (**10a**, 69%), (**11a**, 56%) and (**12a**, 58%) respectively (Scheme VI.3.1). For substrates (**11**) and (**12**) the lower yield may be due to steric hindrance by the *ortho*-Cl and *ortho*-F group. Moderately electron-donating substituents (*p*–Ph) present in the chalcone (**13**) afforded 66% yield of the corresponding coupled product (**13a**). Further, the structure has been reconfirmed by X-ray crystallographic analysis of (**13a**) as shown in Figure VI.3.1.

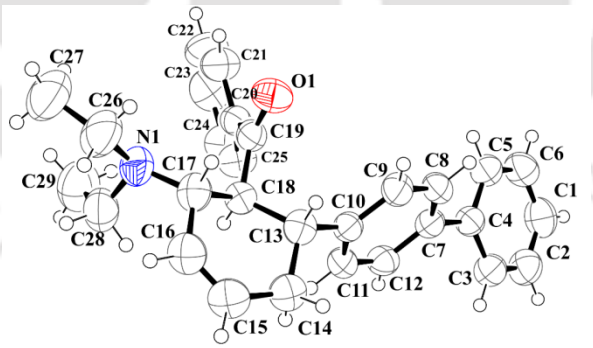
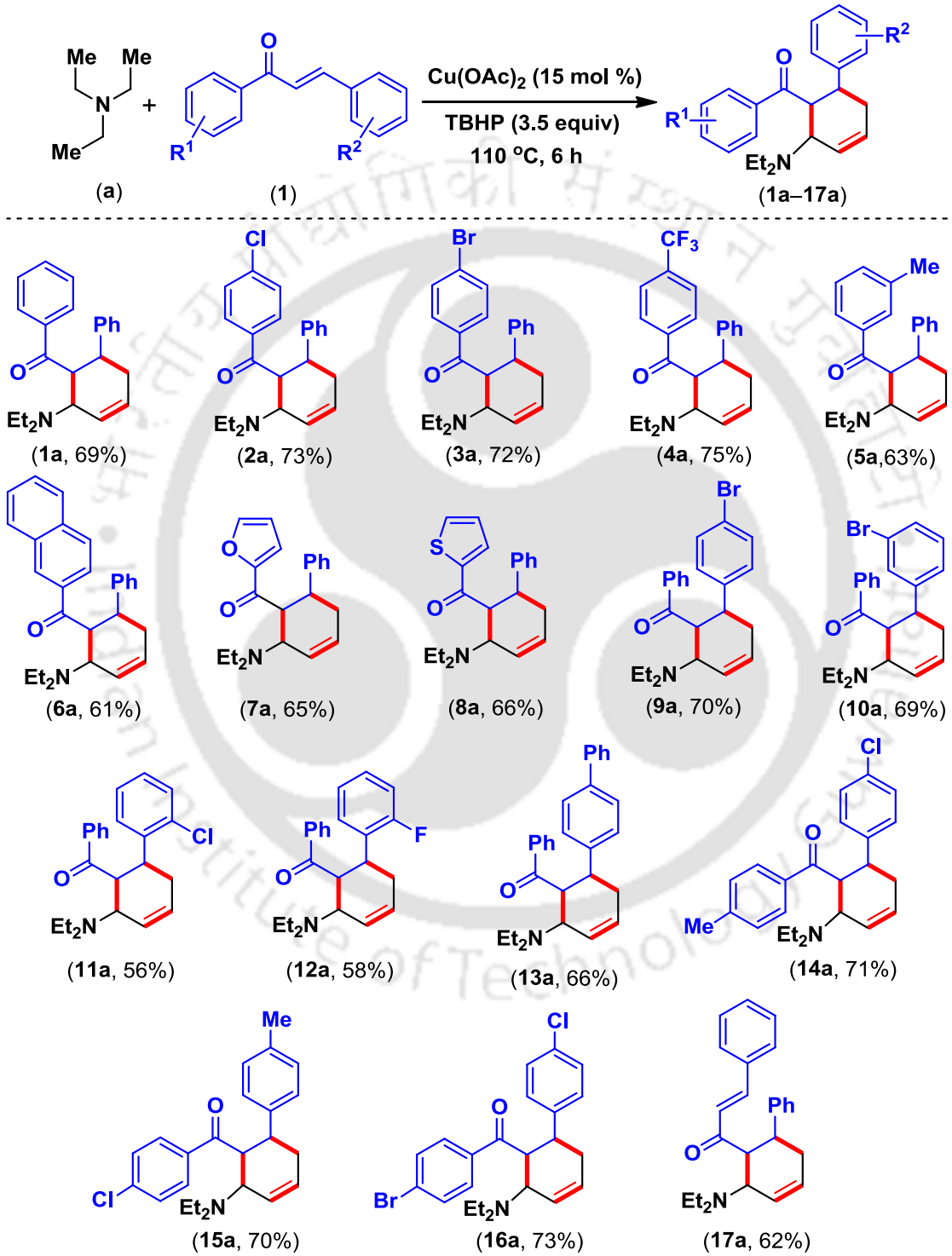


Fig. VI.3.1. *ORTEP molecular diagram of* ***(13a)***

A electron-donating (–Me) / moderately electron-withdrawing (–Cl), moderately electron-withdrawing (–Cl) / electron-donating (–Me) and moderately electron-withdrawing (–Br) / moderately electron-withdrawing (–Cl) groups in the keto and aldehyde counterparts respectively as in substrates (**14**), (**15**) and (**16**) gave their corresponding cycloaddition product (**14a**, 71%), (**15a**, 70%) and (**16a**, 73%) (Scheme VI.3.1). Dibenzylideneacetone

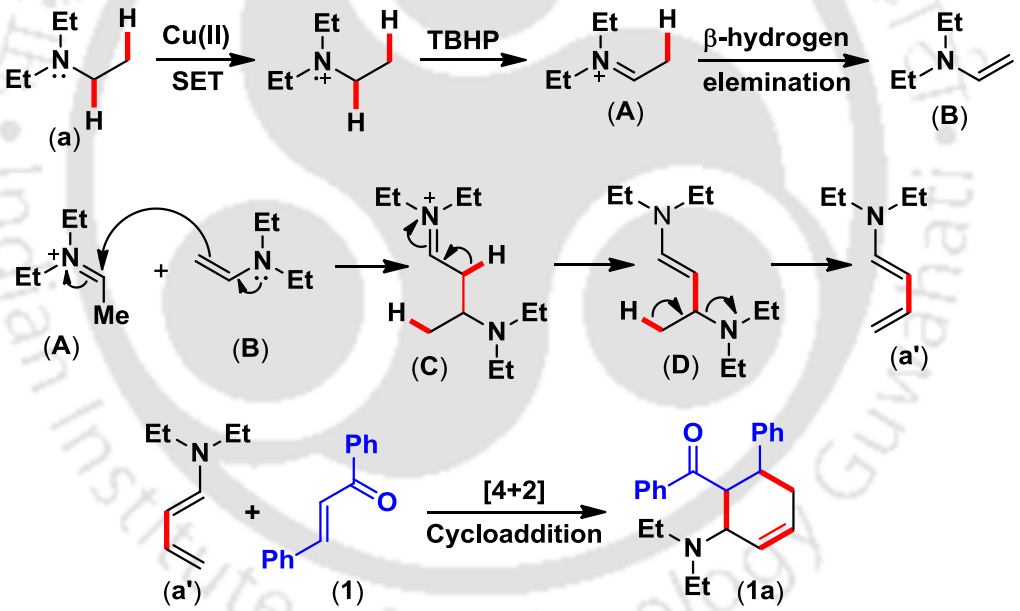
(**17**) having two α,β-unsaturated double bonds when reacted with triethylamine (**a**) under the optimized conditions provided Diels-Alder product (**17a**) in 62% yield, where the reaction took place only at the one unsaturated double bond.

Scheme VI.3.1. *Substrate scope Diels-Alde reaction*[a,b]



[a]Reaction conditions: Chalcones (**1**–**17**) (0.3 mmol), Triethylamine (**a**) (1.5 mL) and TBHP in decane (1.1 mmol) at 110 °C for 6 h. [b]Isolated yield.

Mechanistic Studies. Triethyamine and chalcones provided the cycloaddition product (Diels-Alder) under the optimized reaction conditions, where chalcone served as a dienophile. Retrosynthetic analysis of the product (**1a**) revealed the diene to be (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine (**a´**) which is possibly originating from triethylamine. To confirm the formation of diene, two independent reactions were carried out, one in the presence of chalcone and the other without it. The mass spectral analysis of the reaction aliquot suggest the formation of diene (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine (**a´**) in both the reaction medium (see experimental section). When a typical reaction between chalcone (**1**) and triethylamine (**a**) was carried out under otherwise identical condition but in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), only minor amount of (<15%) cycloaddition product (**1a**) was observed. This experiment suggests the radical nature of the reaction.



Scheme VI.3.2. *Proposed mechanism for α,β C_{sp3}–H functionalization of triethylamine*

Based on the above experimental observations and results from the control experiments, a plausible mechanism has been proposed for this α,β C_{sp3}–H functionalization of trialkylamine. Initially, triethyamine (**a**) forms radical cation intermediate *via* a single electron transfer (SET) mechanism in the presence of $Cu(OAc)_2$, followed by the abstraction of more acidic α-hydrogen by TBHP to give an iminium cation intermediate (**A**). Then β-hydrogen elimination of iminium cation afforded terminal alkene intermediate (**B**). Nucleophilic substitution reaction between (**B**) and (**A**) provides intermediate (**C**) (Scheme

VI.3.2). A β-hydrogen elimination from intermediate (**C**) afforded an enamine intermediate (**D**). A subsequent elimination with the expulsion of diethylamine gave a stable conjugated diene (**a′**). Finally, the *in situ* generated diene (**a´**) from triethylamine undergo [4+2] cycloaddition reaction with chalcone (**1**) to give product (**1a**).

In conclusion, triethylamine afforded (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine in the presence of Cu(II)/TBHP combination *via* coupling of the *in situ* generated iminium cation and enamine intermediate. This *in situ* generated diene is trapped with chalcone as the dienophile giving a Diels-Alder product. This is the first example where both α and β C_{sp3}–H bond of trialkylamine are functionalized in the presence of Cu(II)/TBHP combination.

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 sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{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.

VI.4.2. Crystallographic Description

CCDC number for compounds 13a: CCDC 1499310. 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 13a: Crystal dimension (mm): 0.31 x 0.15 x 0.06. $C_{29}H_{31}NO$, Mr = 409.55. monoclinic, space group p 21/n; a = 10.5345(9) Å, b = 5.8672(5) Å, c = 38.000(3) Å; α = 90°, β = 90.174(5)°, γ = 90°, V = 2348.7(3) Å^3; Z = 4; ρ_{cal} = 1.158 g/cm^3; μ (mm^{-1}) = 0.069; *F (000)* = 880.0; Reflection collected / unique = 3976 / 2026; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0693, wR2 = 0.1698, R indices (all data) R1 = 0.1388, wR2 = 0.2067; goodness of fit = 1.050.

VI.4.3. General Procedure for the Synthesis of Diels-Alder Product (1a):

➢ **VI.4.3.1. General Procedure for the Synthesis of (1a) from Chalcone (1) and Triethylamine (a):** To an oven-dried 25 mL round bottom flask fitted with a reflux condenser was added chalcone (**1**) (0.062g, 0.3 mmol), a decane solution of TBHP (5−6 M) (1.1 mmol), $Cu(OA)_2$ (0.009g, 0.05 mmol), and triethylamine (**a**) (1.5 mL). The reaction mixture was refluxed in an oil bath preheated to 110 ^oC. After completion of the reaction (6 h) excess triethylamine was evaporated under reduced pressure. The reaction mixture was cooled to room temperature, the product was extracted with ethyl acetate (25 mL) and the organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), and solvent was concentrated under reduced pressure. The crude product so obtained was purified over a column of silica gel (hexane / ethyl acetate, 9.7:0.3) to give pure (3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (**1a**) (0.069g, yield 69%). The identity and purity of the product was confirmed by spectroscopic analysis.

VI.4.4. Mechanistic Investigations

➢ **VI.4.4.1. α,β-C_{sp3}–H Functionalization of Triethylamine in the presence of radical scavenger TEMPO:** An oven-dried 25 mL round bottom flask was charged with chalcone (**1**) (0.062g, 0.3 mmol), $Cu(OAc)_2$ (0.009g, 0.05 mmol), TBHP in decane (5−6 M) (1.0 mmol), TEMPO (**A**) (0.156g, 1.0 mmol) and triethylamine (1.5 mL). The flask was fitted to a reflux condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^oC. After 6 h only a trace amount (<15%) of the desired product (**1a**) was observed. This experiment suggests the radical nature of the reaction.

➢ **VI.4.4.2. ESI-MS study for the detection of reaction intermediates during α,β-C_{sp3}–H Functionalization of Triethylamine:** In order to detect the intermediate species in the reaction mixture an electrospray mass spectrometry was performed. In this study, an oven-dried 25 mL round bottom flask was charged with chalcone (**1**) (0.062g, 0.3 mmol), $Cu(OAc)_2$ (0.009g, 0.05 mmol), TBHP in decane (5−6 M) (1.1 mmol), and triethylamine (1.5 mL). The flask was fitted to a reflux condenser and the reaction mixture was stirred in a preheated oil bath at 110 ^oC. After 1 h of reaction, aliquot (50 μL) was withdrawn and diluted with acetonitrile (2 mL). A 20 μL of the diluted solution was injected to run ESI-MS analysis. From the HRMS spectrum the desired product (**1a**) and intermediate (*E*)-*N*,*N*-diethylbuta-1,3-dien-1-amine (**a´**) were observed (Fig. VI.4.4.1).

In the absence of chalcone (**1**) the same diene was also observed, thereby confirming the generation of diene only from triethylamine (Fig. VI.4.4.2).

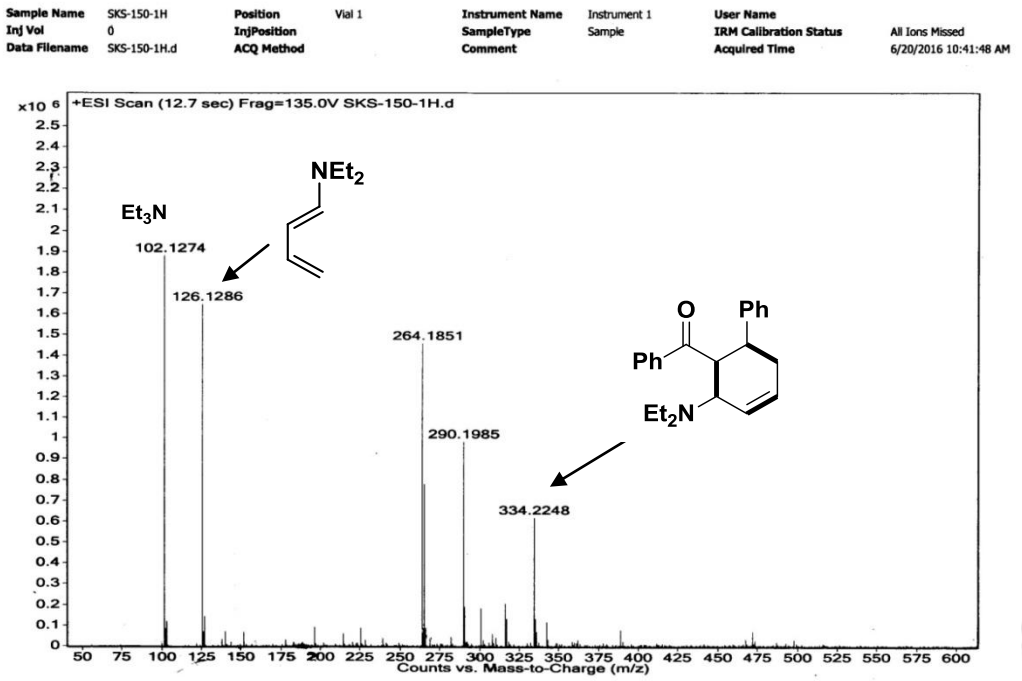


Fig. VI.4.4.1. *ESI-MS spectrum of the reaction mixture in presence of chalcone (**1**)*

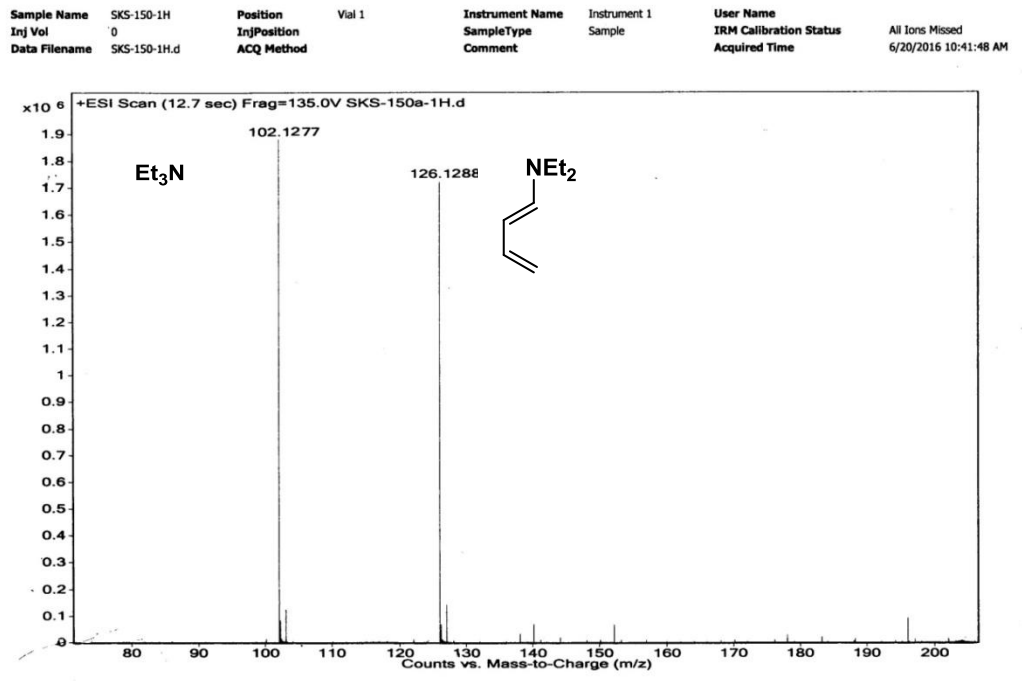


Fig. VI.4.4.2. *ESI-MS spectrum of the reaction mixture in absence of chalcone (**1**)*

VI.5. References

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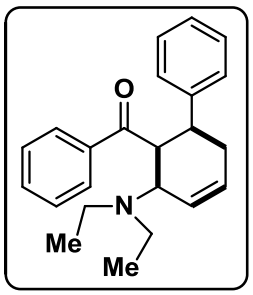
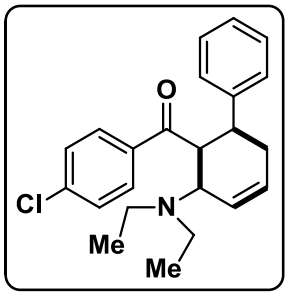
VI.6. Spectral Data

(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (1a):



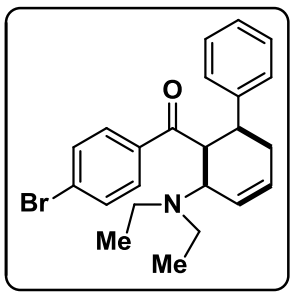
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.58 (d, 2H, J = 7.2 Hz), 7.35 (t, 1H, J = 7.2 Hz), 7.24 (t, 2H, J = 7.2 Hz), 7.15 (d, 2H, J = 7.8 Hz), 7.07 (t, 2H, J = 7.8 Hz), 6.98 (t, 1H, J = 7.2 Hz), 5.92–5.84 (m, 2H), 4.03–3.94 (m, 2H), 3.31–3.26 (m, 1H), 2.54–2.48 (m, 2H), 2.44–2.33 (m, 4H), 0.81 (t, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.0, 142.9, 140.0, 131.9, 128.4, 128.2, 128.1, 128.0, 127.9, 126.6, 62.2, 51.4, 45.1, 44.3, 33.9, 14.1; IR (KBr, cm^{-1}): 3080, 3060, 3025, 2964, 2918, 2819, 1669, 1597, 1494, 1455, 1446, 1387, 1367, 1352, 1328, 1297, 1270, 1217, 1186, 1158, 1108, 1075, 1016, 910, 894, 833, 757, 736; HRMS (ESI) calcd for $C_{23}H_{27}NO$ (M + H^+) 334.2172, found 334.2175.

(4-Chlorophenyl)(3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (2a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, 2H, J = 8.4 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 7.2 Hz), 7.08 (t, 2H, J = 7.4 Hz), 6.99 (t, 1H, J = 7.0 Hz), 5.93–5.83 (m, 2H), 4.01–3.86 (m, 2H), 3.31–3.24 (m, 1H), 2.55–2.46 (m, 2H), 2.44–2.32 (m, 4H), 0.81 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.8, 142.8, 138.33, 138.29, 129.3, 128.5, 128.33, 128.28, 128.0, 127.9, 126.8, 62.2, 51.6, 45.1, 44.3, 33.8, 14.2; IR (KBr, cm^{-1}): 3057, 3020, 2968, 2928, 2888, 2821, 1674, 1586, 1491, 1465, 1453, 1398, 1377, 1342, 1291, 1267, 1214, 1203, 1176, 1108, 1089, 1069, 1013, 900, 843, 830, 759, 759; HRMS (ESI) calcd for $C_{23}H_{26}ClNO$ (M + H^+) 368.1782, found 368.1788.

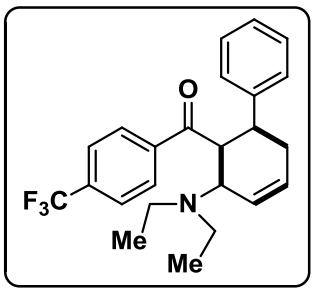
(4-Bromophenyl)(3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (3a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 7.2 Hz), 7.09 (t, 2H, J = 7.4 Hz), 7.00 (t, 1H, J = 7.0 Hz), 5.93–5.83 (m, 2H), 4.01–3.85 (m, 2H), 3.31–3.24 (m, 1H), 2.55–2.46 (m, 2H), 2.44–2.32 (m, 4H), 0.81 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.0, 142.8, 138.7, 131.3, 129.5, 128.5, 128.3, 128.0, 127.9, 127.0, 126.8, 62.3, 51.6, 45.1, 44.3, 33.8, 14.2; IR (KBr, cm^{-1}): 3082, 3059, 3025, 2967, 2923, 2897, 2833, 2806, 1683, 1643, 1627, 1608, 1494, 1449, 1368, 1331, 1303, 1201, 1193, 1183, 1167, 1150, 1076, 1059,

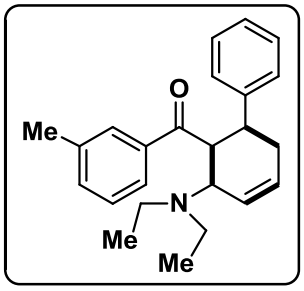
986, 977, 767, 758, 736; HRMS (ESI) calcd for $C_{23}H_{26}BrNO$ ($M + H^+$) 412.1277, found 412.1288.

(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(4-(trifluoromethyl)phenyl) methanone (4a):



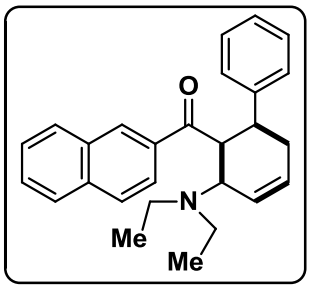
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 7.2 Hz), 7.09 (t, 2H, J = 7.6 Hz), 7.01 (t, 1H, J = 7.4 Hz), 5.94–5.84 (m, 2H), 4.02 (d, 1H, J = 9.6 Hz), 3.92 (t, 1H, J = 10.6 Hz), 3.32–3.25 (m, 1H), 2.56–2.47 (m, 2H), 2.46–2.34 (m, 4H), 0.81 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 205.6, 142.8, 142.6, 133.3, 132.9, 129.3, 128.7, 128.5, 128.4, 128.0, 127.9, 127.6, 126.9, 125.14, 125.10, 125.06, 125.03, 62.2, 52.2, 45.1, 44.2, 33.7, 14.0; IR (KBr, cm^{-1}): 3026, 2965, 2922, 2813, 1684, 1652, 1493, 1455, 1409, 1324, 1168, 1129, 1110, 1066, 1015, 850, 776, 758; HRMS (ESI) calcd for $C_{24}H_{26}F_3NO$ ($M + H^+$) 402.2046, found 402.2056.

(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(m-tolyl)methanone (5a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, 1H, J = 7.6 Hz), 7.36 (s, 1H), 7.17–7.11 (m, 4H), 7.07 (t, 2H, J = 7.6 Hz), 6.98 (t, 1H, J = 7.2 Hz), 5.92–5.83 (m, 2H), 4.03–3.91 (m, 2H), 3.31–3.24 (m, 1H), 2.56–2.49 (m, 2H), 2.46–2.36 (m, 4H), 2.28 (s, 3H), 0.83 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.2, 142.9, 140.0, 137.6, 132.7, 128.4, 128.3, 128.2, 128.1, 127.8, 126.6, 125.2, 62.1, 51.3, 45.1, 44.2, 33.9, 21.5, 14.1; IR (KBr, cm^{-1}): 3060, 3015, 2970, 2922, 2868, 2814, 1677, 1647, 1602, 1577, 1493, 1454, 1425, 1382, 1351, 1296, 1267, 1205, 1183, 1156, 1117, 1069, 1038, 911, 789, 756, 739; HRMS (ESI) calcd for $C_{24}H_{29}NO$ ($M + H^+$) 348.2329, found 348.2325.

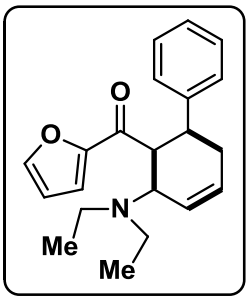
(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(naphthalen-2-yl)methanone (6a):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.13 (s, 1H), 7.86 (d, 1H, J = 7.2 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.68 (bs, 2H), 7.53–7.47 (m, 2H), 7.19 (d, 2H, J = 7.2 Hz), 7.03 (t, 2H, J = 7.8 Hz), 6.91 (t, 1H, J = 7.2 Hz), 5.96–5.87 (m, 2H), 4.14–4.06 (m, 2H), 3.38–3.33 (m, 1H), 2.58–2.52 (m, 2H), 2.48–2.35 (m, 4H), 0.82 (t, 6H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 205.7, 143.0, 137.3, 135.1, 132.5, 129.6, 129.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 126.6, 126.5, 124.2, 62.3, 51.4, 45.2, 44.3, 33.9, 14.2; IR

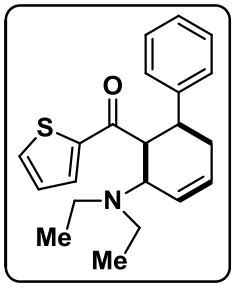
(KBr, cm^{-1}): 3063, 3026, 2961, 2921, 2810, 1677, 1644, 1596, 1575, 1475, 1446, 1382, 1342, 1294, 1259, 1213, 1112, 1055, 1038, 893, 833, 754; HRMS (ESI) calcd for $C_{27}H_{29}NO$ (M + H^+) 384.2329, found 384.2320.

(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(furan-2-yl)methanone (7a):



Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, 1H, *J* = 1.6 Hz), 7.18–7.16 (m, 2H), 7.11 (t, 2H, *J* = 7.4 Hz), 7.02 (t, 1H, *J* = 7.4 Hz), 6.87 (d, 1H, *J* = 3.6 Hz), 6.34 (d, 1H, *J* = 3.6 Hz), 5.91–5.82 (m, 2H), 4.04 (d, 1H, *J* = 9.6 Hz), 3.83 (t, 1H, *J* = 10.4 Hz), 3.31–3.24 (m, 1H), 2.58–2.49 (m, 2H), 2.47–2.39 (m, 2H), 2.36–2.32 (m, 2H), 0.86 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.4, 154.4, 145.6, 142.9, 128.4, 128.3, 128.0, 127.9, 126.6, 116.2, 112.2, 61.4, 51.3, 44.6, 44.3, 34.5, 14.3; IR (KBr, cm^{-1}): 3112, 3095, 3018, 2969, 2928, 2901, 2836, 2813, 1652, 1563, 1493, 1467, 1453, 1395, 1308, 1275, 1238, 1230, 1203, 1181, 1160, 1116, 1087, 1070, 1043, 1026, 1010, 886, 817, 769, 756; HRMS (ESI) calcd for $C_{21}H_{25}NO_2$ (M + H^+) 324.1965, found 324.1969.

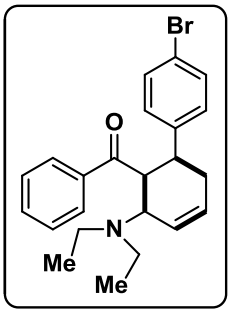
(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(thiophen-2-yl)methanone (8a):



Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.45 (d, 1H, *J* = 3.6 Hz), 7.42 (d, 1H, *J* = 4.8 Hz), 7.18 (d, 2H, *J* = 7.8 Hz), 7.10 (t, 2H, *J* = 7.8 Hz), 7.01 (t, 1H, *J* = 7.2 Hz), 6.93 (t, 1H, *J* = 4.2 Hz), 5.92–5.83 (m, 2H), 4.04 (d, 1H, *J* = 9.6 Hz), 3.72 (t, 1H, *J* = 10.8 Hz), 3.31–3.26 (m, 1H), 2.56–2.49 (m, 2H), 2.45–2.32 (m, 4H), 0.86 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 197.1, 146.8, 142.8, 132.9, 131.4, 128.4, 128.2, 128.1, 127.6, 126.6, 61.6, 53.5, 44.9, 44.3, 33.8, 14.3; IR (KBr, cm^{-1}): 3084, 3018, 2965, 2927, 2866, 2816, 1642, 1518, 1494, 1454, 1415, 1378, 1353, 1300, 1272, 1238, 1214, 1201, 1153, 1114, 1059, 850, 806, 756, 740, 728; HRMS (ESI) calcd for $C_{27}H_{29}NOS$ (M + H^+) 340.1736, found 340.1730.

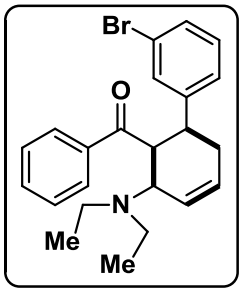
(4'-Bromo-3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (9a):

Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, 2H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.28 (t, 2H, *J* = 7.6 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 5.91–5.83 (m, 2H), 4.00–3.89 (m, 2H), 3.29–3.23 (m, 1H), 2.54–2.46 (m, 2H), 2.45–2.31 (m, 4H), 0.80 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR



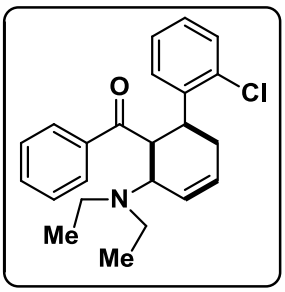
($CDCl_3$, 100 MHz): δ 205.7, 142.1, 139.8, 132.2, 131.5, 129.8, 128.2, 127.96, 127.89, 120.3, 62.2, 51.1, 44.6, 44.2, 33.9, 14.0; IR (KBr, cm^{-1}): 3059, 3016, 2965, 2915, 2836, 2811, 1671, 1597, 1580, 1488, 1445, 1387, 1353, 1299, 1267, 1218, 1204, 1182, 1154, 1100, 1073, 1060, 1037, 1011, 896, 834, 817, 758, 738; HRMS (ESI) calcd for $C_{23}H_{26}BrNO$ (M + H^+) 412.1277, found 412.1290.

(3'-Bromo-3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (10a):



Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, 2H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.2 Hz), 7.31–7.26 (m, 3H), 7.09 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 1H, *J* = 7.6 Hz), 6.92 (t, 1H, *J* = 7.8 Hz), 5.91–5.83 (m, 2H), 4.02–3.89 (m, 2H), 3.27–3.20 (m, 1H), 2.55–2.45 (m, 2H), 2.46–2.33 (m, 4H), 0.82 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.5, 145.3, 139.8, 132.2, 131.1, 129.9, 129.7, 128.3, 128.1, 127.9, 127.8, 126.9, 122.4, 61.9, 51.0, 44.9, 44.3, 33.9, 14.1; IR (KBr, cm^{-1}): 3059, 3021, 2968, 2910, 2826, 1663, 1591, 1582, 1564, 1476, 1447, 1432, 1384, 1342, 1295, 1264, 1212, 1116, 1072, 1060, 1036, 1016, 994, 878, 838, 783, 742; HRMS (ESI) calcd for $C_{23}H_{26}BrNO$ (M + H^+) 412.1277, found 412.1272.

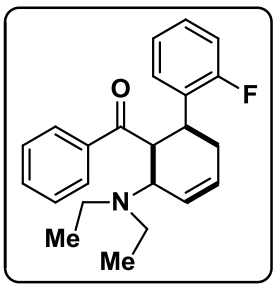
(2'-Chloro-3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (11a):



Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.70 (d, 2H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.2 Hz), 7.29 (t, 2H, *J* = 7.2 Hz), 7.21 (bs, 2H), 6.91 (bs, 2H), 5.91–5.85 (m, 2H), 4.04 (bs, 2H), 2.56–2.51 (m, 2H), 2.46–2.37 (m, 3H), 2.17–2.12 (m, 2H), 0.82 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.9, 140.5, 139.7, 138.8, 132.2, 129.8, 129.2, 128.3, 128.2, 128.1, 127.9, 127.5, 126.7, 62.4, 49.7, 44.1, 39.8, 33.7, 13.9; IR (KBr, cm^{-1}): 3061, 3024, 2972, 2922, 2804, 1677, 1646, 1594, 1476, 1445, 1380, 1343, 1292, 1264, 1211, 1155, 1109, 1054, 1037, 893, 836, 801, 748; HRMS (ESI) calcd for $C_{23}H_{26}ClNO$ (M + H^+) 368.1782, found 368.1790.

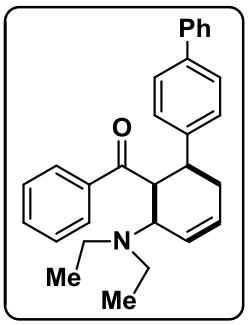
(3-(Diethylamino)-2'-fluoro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (12a):

Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.28 (t, 2H, *J* = 7.2 Hz), 7.12 (t, 1H, *J* = 7.4 Hz), 6.99–6.94 (m, 1H), 6.86 (t, 1H, *J* = 7.4 Hz), 6.78–6.74 (m, 1H), 5.91–5.83 (m, 2H), 4.19 (t, 1H, *J* = 10.6



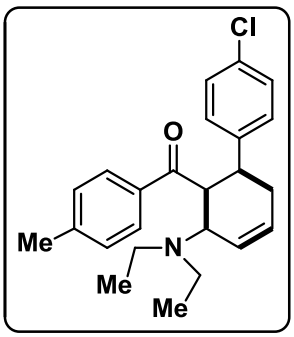
Hz), 3.99 (d, 1H, *J* = 10.0 Hz), 3.48–3.43 (m, 1H), 2.55–2.48 (m, 2H), 2.46–2.23 (m, 4H), 0.81 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 205.7, 162.4, 159.9, 139.6, 132.2, 130.7, 129.6, 129.4, 128.34, 128.26, 128.1, 128.0, 127.9, 124.2, 124.1, 115.9, 115.7, 61.9, 48.9, 44.2, 32.1, 14.1; IR (KBr, cm^{-1}): 3022, 2967, 2926, 2849, 2812, 1677, 1644, 1597, 1580, 1491, 1447, 1380, 1344, 1296, 1272, 1211, 1156, 1103, 1067, 1036, 1017, 933, 902, 883, 840, 812, 788, 757, 737; HRMS (ESI) calcd for $C_{23}H_{26}FNO$ (M + H^+) 352.2078, found 352.2073.

(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1':4',1''-terphenyl]-2-yl)(phenyl)methanone (13a):



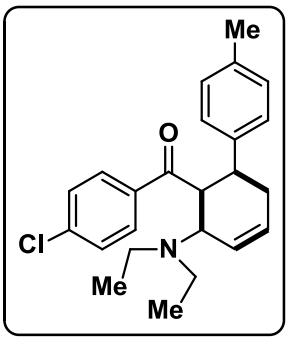
Solid; M.p. 134.0 °C–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.59 (d, 2H, *J* = 7.6 Hz), 7.41 (d, 2H, *J* = 7.6 Hz),7.37–7.32 (m, 3H), 7.30–7.25 (m, 4H), 7.23–7.20 (m, 3H), 5.95–5.85 (m, 2H), 4.06–3.96 (m, 2H), 3.36–3.29 (m, 1H), 2.57–2.48 (m, 2H), 2.47–2.35 (m, 4H), 0.83 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 206.1, 142.1, 141.1, 140.0, 139.5, 131.9, 128.8, 128.5, 128.23, 128.16, 128.0, 127.9, 127.2, 127.1, 62.1, 51.5, 44.9, 44.3, 33.9, 14.1; IR (KBr, cm^{-1}): 3018, 2963, 2927, 2838, 2807, 2767, 1674, 1597, 1579, 1486, 1445, 1386, 1350, 1335, 1300, 1265, 1217, 1204, 1185, 1157, 1108, 1061, 1016, 1008, 912, 896, 837, 763, 736; HRMS (ESI) calcd for $C_{29}H_{31}NO$ (M + H^+) 410.2485, found 410.2474.

(4'-Chloro-3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(p-tolyl)methanone (14a):



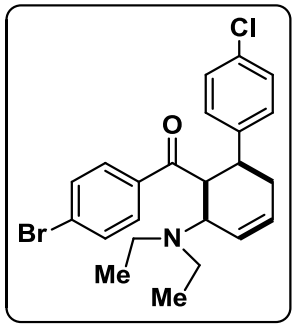
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): *δ* 7.54 (d, 2H, *J* = 8.4 Hz), 7.09–7.07 (m, 4H), 7.04 (d, 2H, *J* = 8.4 Hz), 5.90–5.83 (m, 2H), 3.99–3.59 (m, 2H), 3.29–3.25 (m, 1H), 2.52–2.46 (m, 2H), 2.43–2.37 (m, 2H), 2.33–2.31 (m, 5H), 0.81 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): *δ* 204.9, 142.9, 141.7, 137.2, 132.1, 129.4, 128.9, 128.5, 128.3, 128.1, 127.9, 62.2, 50.7, 44.4, 44.2, 33.9, 21.7, 14.1; IR (KBr, cm^{-1}): 3024, 2970, 2927, 2902, 2871, 2807, 1662, 1607, 1491, 1468, 1411, 1388, 1379, 1349, 1299, 1267, 1224, 1207, 1184, 1153, 1103, 1089, 1066, 1036, 1014, 898, 838, 823, 770, 741; HRMS (ESI) calcd for $C_{24}H_{28}ClNO$ (M + H^+) 382.1939, found 382.1950

(4-Chlorophenyl)(3-(diethylamino)-4'-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl) methanone (15a):



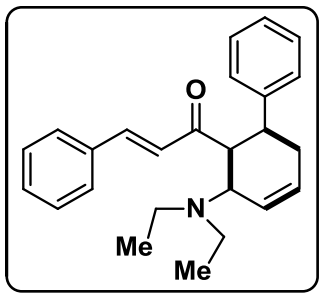
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.54 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 7.03 (d, 2H, J = 7.8 Hz), 6.89 (d, 2H, J = 7.8 Hz), 5.91–5.82 (m, 2H), 3.98–3.85 (m, 2H), 3.27–3.22 (m, 1H), 2.52–2.46 (m, 2H), 2.44–2.32 (m, 4H), 2.16 (s, 3H), 0.79 (t, 6H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 204.9, 139.8, 138.2, 136.2, 129.4, 129.1, 128.4, 128.3, 127.8, 127.7, 62.3, 51.5, 44.5, 44.2, 34.0, 21.1, 14.1; IR (KBr, cm^{-1}): 3016, 2964, 2917, 2813, 1678, 1639, 1589, 1511, 1486, 1449, 1401, 1287, 1273, 1209, 1178, 1116, 1091, 1034, 1012, 895, 832, 812, 758; HRMS (ESI) calcd for $C_{24}H_{28}ClNO$ (M + H$^+$) 382.1939, found 382.1942.

(4-bromophenyl)(4'-chloro-3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl) methanone (16a):



Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.07 (bs, 4H), 5.91–5.82 (m, 2H), 3.97–3.83 (m, 2H), 3.31–3.24 (m, 1H), 2.54–2.45 (m, 2H), 2.44–2.32 (m, 4H), 0.80 (t, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7, 141.4, 138.4, 132.4, 131.5, 129.4, 129.3, 128.6, 128.0, 127.9, 127.4, 62.4, 51.3, 44.3, 44.2, 33.8, 14.1; IR (KBr, cm^{-1}): 3226, 2969, 2927, 2903, 2869, 2814, 1666, 1587, 1568, 1492, 1468, 1397, 1378, 1347, 1298, 1266, 1218, 1205, 1180, 1152, 1088, 1071, 1035, 1010, 896, 826, 771, 736; HRMS (ESI) calcd for $C_{23}H_{25}BrClNO$ (M + H$^+$) 446.0887, found 446.0896.

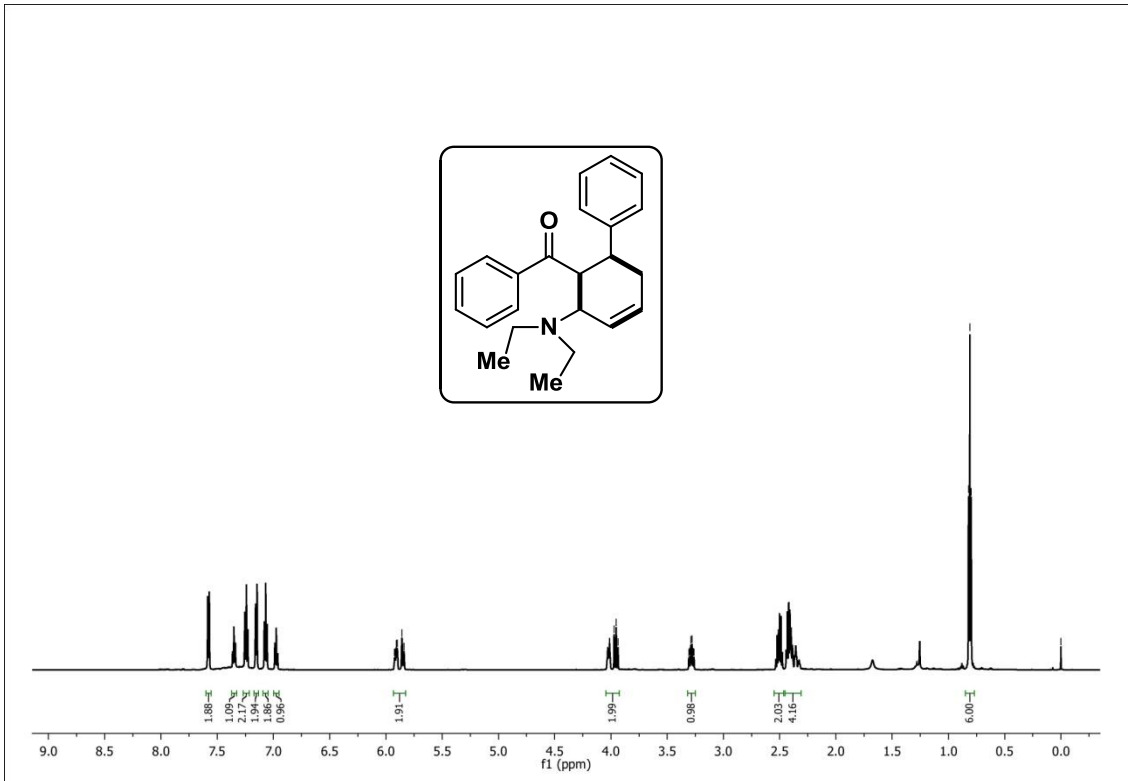
(*E*)-1-(3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)-3-phenylprop-2-en-1-one (17a):



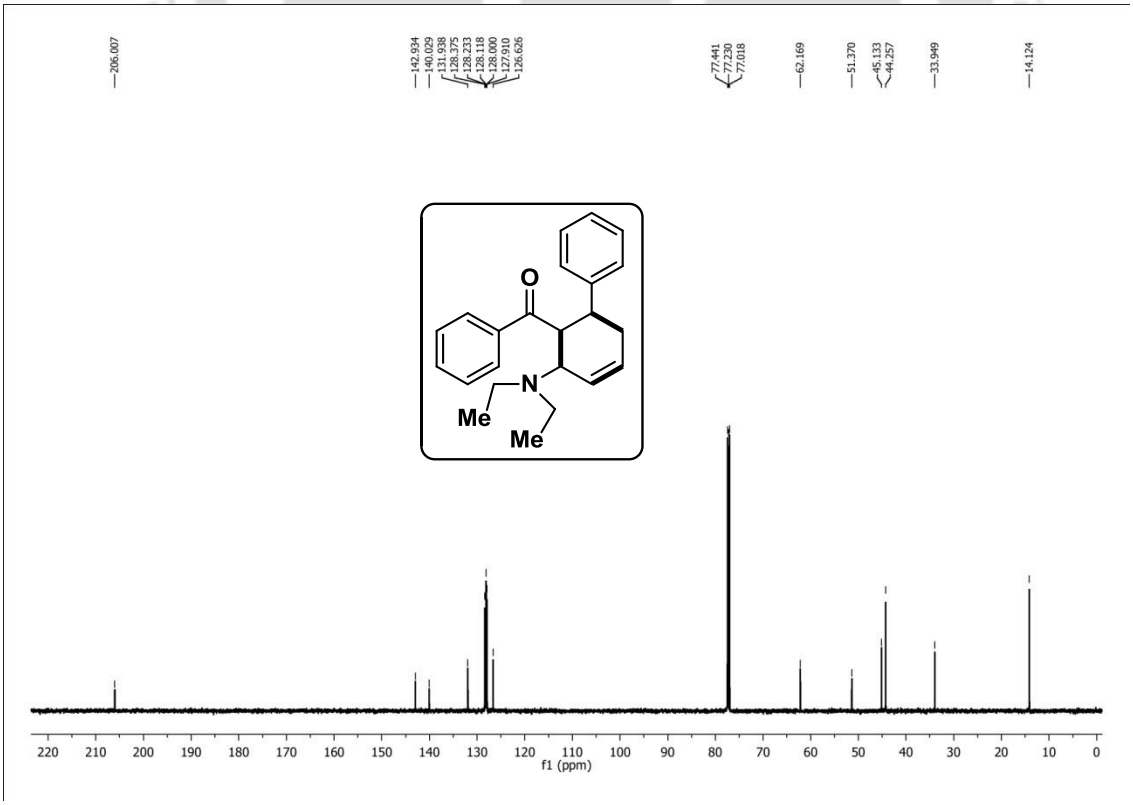
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.36 (m, 2H), 7.34–7.32 (m, 3H), 7.23–7.19 (m, 5H), 7.10–7.06 (m, 1H), 6.51 (d, 1H, J = 16.0 Hz), 5.92–5.80 (m, 2H), 3.97–3.94 (m, 1H), 3.40 (t, 1H, J = 10.8 Hz), 3.24–3.17 (m, 1H), 2.62–2.54 (m, 2H), 2.51–2.43 (m, 2H), 2.34–2.31 (m, 2H), 0.97 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.9, 143.2, 140.9, 135.1, 130.1, 128.9, 128.6, 128.3, 128.2, 127.9, 127.86, 127.81, 126.8, 61.4, 54.6, 44.6, 44.5, 34.3, 14.6; IR (KBr, cm^{-1}): 3082, 3056, 3025, 2967, 2923, 2831, 2808, 1683, 1642, 1608, 1575, 1494, 1448, 1368, 1331, 1303, 1193, 1183, 1167, 1150, 1076, 1060, 986, 767, 758, 736; HRMS (ESI) calcd for $C_{25}H_{29}NO$ (M + H$^+$) 360.2329, found 360.2321.

VI.7. Spectra

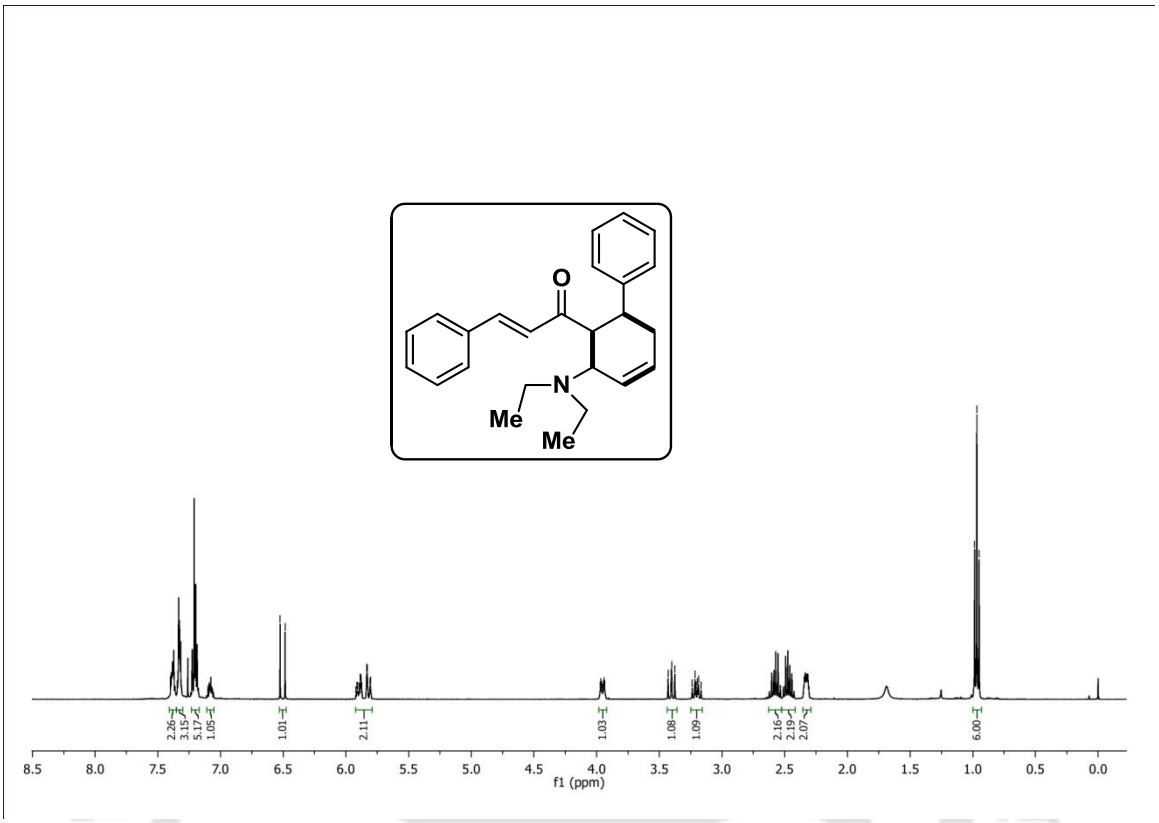
(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (1a): ^{1}H NMR ($CDCl_3$, 600 MHz)



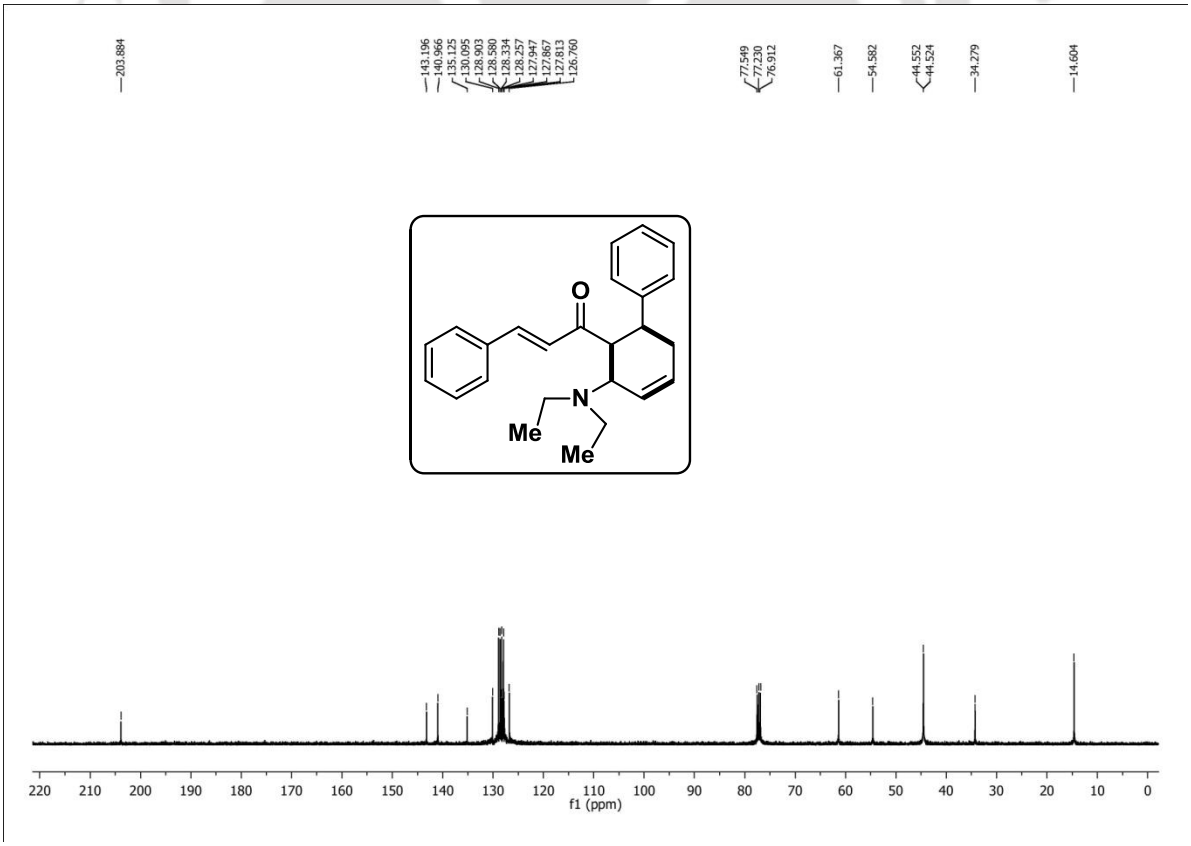
(3-(Diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)(phenyl)methanone (1a): ^{13}C NMR ($CDCl_3$, 150 MHz)



(*E*)-1-(3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)-3-phenylprop-2-en-1-one (17a): ^{1}H NMR ($CDCl_3$, 400 MHz)



(*E*)-1-(3-(diethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-yl)-3-phenylprop-2-en-1-one (17a): ^{13}C NMR ($CDCl_3$, 100 MHz)



List of Publications:

1. Tertiary alkyl amine as the source of diene for cycloaddition *via* copper(II) catalyzed α,β C_{sp3}–H functionalization. **S. K. Santra,** A. Banerjee, S. Rajamanickam, P. R. Mohanta and B. K. Patel, (under preparation).
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