Construction of C–C & C–Heteroatom Bonds via C–H Functionalization and Cascade Strategies

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DEDICATED TO

MY PARENTS

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FAMILY

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Indian Institute of Technology Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

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

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CERTIFICATE

This is to certify that Wajid Ali has been working under my supervision since July, 2012 as a regular registered Ph. D. student. His thesis entitled **"Construction of C–C & C–Heteroatom Bonds via C–H Functionalization and Cascade Strategies"** is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis to submit for the Ph. D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

September, 2017.

Prof. Bhisma K. Patel
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SYNOPSIS

The contents of this thesis have been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview on different aspects of C–H functionalization and cascade reactions: advantages, challenges and solutions of them. All the other chapters emphasize on C–C, C–O, C–S and C–N bond forming reactions via metal-catalyzed/mediated C–H functionalization using strategies like cross-dehydrogenative coupling, functional group directed C–H bond functionalization and cascade reactions involving isocyanides, 2-alkynylanilines and aryl isothiocyanates.

Chapter II illustrates a protocol for copper-catalyzed synthesis of phenol carbamates from dialkylformamides and phenols possessing benzothiazole, quinoline and formyl as directing groups at their *ortho*-position.

Chapter III describes the use of methylarenes as aroyl surrogates toward *S*-aroylation of thiols and regiospecific acylation of *N*-heterocycles catalyzed by copper and aluminum salts respectively.

Chapter IV demonstrates a cascade synthesis of dihydrobenzofurans and Aurones via palladium-catalyzed insertion of isocyanides into 2-halophenoxy acrylates.

Chapter V describes about the cascade reactions involving internal alkynes for the synthesis of benzofuran [3,2-*c*] quinolin-6[5-*H*]ones using Cs_2CO_3 as carbonyl as well as oxygen source and indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates in the presence of copper and silver salts respectively.

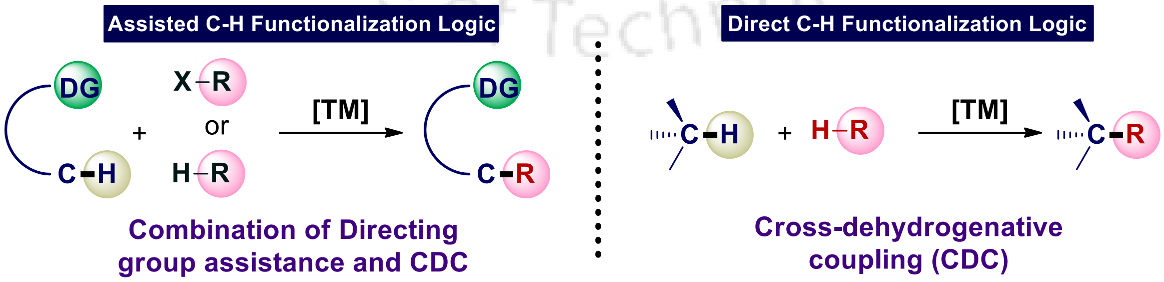
Each of these chapters comprises of introduction, previous work, present work, experimental section, references, spectral data and few representative spectra.

CHAPTER I: An Overview of Metal-Catalyzed C–H Functionalization and Cascade Reactions

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

Coupling chemistry is an important synthetic strategy, widely used in both industry and academia for the formation of carbon–carbon and carbon–heteroatom bonds. The traditional coupling procedures involve either the use of stoichiometric organometallic reagents or the transition metal-catalyzed coupling of functionalized hydrocarbons. There has been substantial progress in these methods over the last few decades and they are successfully applied in the synthesis of commercially important products. However, the use of pre-functionalized starting materials in these methods adds extra step towards the formation of desired chemical bond, is a major concern for the modern day synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize un-functionalized starting materials by the direct functionalization of C–H bonds.

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



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

With the motive of broadening this revolutionary aspect of organic synthesis, in modern times more systematic and concerted efforts have been made in C–H bond activation and its application in coupling chemistry. As a result exceptionally useful methods for organic synthesis have been developed and one such way is the transition metal catalyzed C–H bond functionalization to achieve C–C and C–X bonds. Most of these methodologies stand on the two pillars of the C–H bond activation: (a) cross-dehydrogenative coupling and (b) substrate directed C–H bond functionalization (Scheme I.1). In this context our group has been involved in the development of new disconnection approach and generation of various functionalities by cleaving the inert C–H bonds.

The second part of this chapter provides an overview about the cascade reactions especially transition metal-catalyzed/mediated reactions of isocyanide insertion, 2-alkynylaniline, and aryl isothiocyanates towards heterocycles synthesis.

Increasing a molecular complexity has long been a dream of chemists as it resembles the nature, where very complicated molecules could be synthesized, in terms of creating many bonds, rings, and stereocenters in a single transformation. Most of the complex compound found in the nature can be synthesized by a linear total synthesis applying advance version of chemical synthetic process. Therefore the main challenge in future is to produce these molecules in a more efficient and economical way which will enable the use of more sophisticated structures in industry and academia. Since accessibility highly depends upon the number of steps required to achieve the desired compound, step economy is an important factor to be addressed. In this regards sequential reaction involving several distinct transformations into a single step are one of the most powerful synthetic tools in modern organic chemistry. Compared to traditional stepwise reaction, sequential transformation (e.g. cascade, domino and tandem reaction) possess unique atom economy feature and significant advantages. Cascade reactions are sequence of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process repeats until a stable product formed under the reaction conditions. L. F. Tietze, defines domino/cascade reactions as;

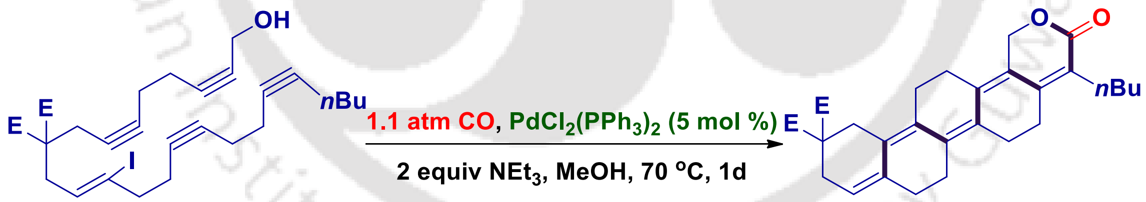
"*A process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*"

Cascade reactions are also considered to contribute to green chemistry because of the reduced waste production and increased atom efficiency. Cascade reactions require a combination of highly selective transformations compatible with different functional groups, which can be challenging to engineer. Consequently, a good understanding of the combined processes is required in order to develop such combinations.

Domino reactions can be classified based on the nature of transformations involves during the cascade mechanisms.

1. Cationic 2. Anionic 3. Radical 4. Pericyclic 5. Photochemical 6. Transition metal-catalyzed 7. Oxidation or Reduction initiated 8. Enzyme assisted.

During cascade reactions preserving the functional group in a molecule is one of the challenging tasks for synthetic organic chemists. As a result, to address such issue a good synthetic combination is required. In last few decades use of transition metals in organic transformation has increased tremendously. Transition metals have been found as of immense importance in cascade reactions. Various transition metals such as Cu, Pd, Ru, Rh, Ir, Mn, Fe, Ag, Co, and Au have been utilized in the cascade reactions. However, the chemistry of palladium, silver and copper are versatile and quite well understood. Therefore, there are numerous reports on palladium, silver and copper-catalyzed cascade reactions in recent time. In 1994 Negishi developed a Pd(II)-catalyzed enetetraynes cyclization that display a good example of metal-catalyzed cascade reaction (Scheme I.2).



Scheme I.2. *Pd-catalyzed cascade annulation of enetetraynes*

CHAPTER II: Copper(II)-Catalyzed Cross-Dehydrogenative Coupling of *N,N*-Disubstituted Formamides and Phenols: A Direct Access to Carbamates

This chapter focuses on the copper(II)-catalyzed synthesis of phenol carbamates from cross-dehydrogenative coupling of *N,N*-Disubstituted Formamides and Phenols having moiety like benzothiazole, quinoline and formyl group as directing groups at their *ortho* position.

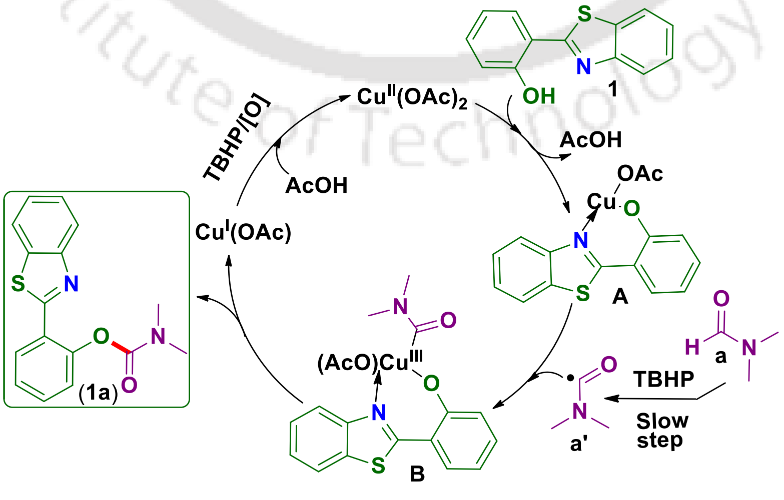
Organic carbamates are useful agrochemicals, pharmaceuticals and are also present in a wide range of biologically active natural products. In addition, carbamates play an important role as intermediates in organic synthesis and serve as a protecting group during peptide synthesis. The general methods for the carbamates synthesis require intermediates such as chloroformates or isocyanates which, in turn are prepared from phosgene or its derivatives. Thus, a phosgene-free synthesis of carbamates is most appreciable from the environmental point of view. This motive has led to the synthesis of carbamates by other methods such as (i) oxidative and reductive carbonylation of amines and nitro aromatics, (ii) reaction of amines with CO_2, (iii) metal-catalyzed cross coupling of isocyanate with alcohols and (iv) via C–H functionalizations.

The drawbacks of traditional cross coupling reactions have been very much sought out with the emergence of the direct C–H bond activation as an alternative route in organic synthesis. First method for the synthesis of carbamates via sp^2 C–H bond activation of dialkylformamides was reported by the Reddy and co-workers in 2011. They achieved this novel strategy by using *ortho* acetyl as directing group with the help of Cu(II) salt as the catalyst and *tert*-butylhydroperoxide (TBHP) as terminal oxidant. Since this early work, a number of other protocols were already developed by the different other groups using directing group assistance as well as without directing group.

N,*N*–Dialkylformamides have attracted much attention because of their polygonal utility in C–H functionalizations. They have been reported as surrogates of various functional groups depending upon the reaction conditions. For example *N*,*N*-dimethylformamide (DMF) is known to act as the source of –Me, –CO, $-NMe_2$, $-CONMe_2$, –CHO and –CN groups in various synthetic protocols. Among these groups, the synthetic utility of dialkylformamides as an aminocarbonyl ($-CONR_2$) group is well documented in the literature. All of the aforementioned reactions proceed via oxidative C–C or C–N bond formations. In the C–O bond forming segment, the use of dialkylformamides as an aminocarbonyl surrogate has been utilized for the synthesis of carbamates by reacting them with phenols and enols possessing *ortho* carbonyl directing groups.

Our motive to choose benzothiazole as directing group present *ortho* to the –OH group because of the biological and pharmaceutical importance of it, as well as the co-ordination ability of *N*-atom to the transition metal. The functionalizations of benzothiazole would provide pathways for the synthesis of intermediates that may find potential applications in various other fields. This has been realized through some of our recent achievements on transition metal-catalyzed directing group-assisted (*N*-atom) functionalizations of *ortho* C–H bond of 2-aryl moiety in benzothiazole. Where *N*-atom of benzothiazole co-ordinate with transition metal and direct it for functionalization of *ortho* C–H bond of 2-aryl moiety. Thus, we envisaged that the directing *N*-atom of benzothiazole could facilitate a metal-catalyzed aminocarbonylation of the hydroxyl group present at the proximal carbon atom. Such aminocarbonylation would lead to the formation of a hybrid benzothiazole–carbamate moiety.

To reach the suitable reaction condition for the synthesis of phenol carbamates various reaction parameters such as catalyst, oxidant, solvent and temperature were scrutinized. After a series of optimization experiments it was found that the use of 5 mol % of $Cu(OAc)_2$ in the presence of aqueous TBHP (3 equiv) at 80 ^{o}C were the best condition. With this optimized conditions in hand, we investigated the scope of this transformation with different formamides and phenols possessing *N*-directing groups. It was found that various formamide including cyclic as well as acyclic were reacted with 2-(benzo[*d*]thiazol-2-yl)phenol and its derivatives to give good to excellent yield. However, acyclic formamides gives slightly better yield as compare to cyclic one. Apart from the benzothiazole, the *N*-atom in 8-hydroxyquinoline provided a similar chelation assistance towards *O*-formamidation. As we previously explore that the formyl group of salicylaldehyde acts as a direction group toward *O*-aroylation. In a similar way different salicylaldehyde reacts with formamides to afford the corresponding carbamates in good yields.



Scheme II.1. *Plausible mechanism for Cu(II)-catalyzed C–O bond formation*

Based on our results, experimental observations and literature precedents a radical mechanism for this transformation was predicted that involves formation of aminoacyl radical as the crucial step (Scheme II.1).

In conclusion, we have developed an efficient protocol for the synthesis of phenol carbamates from dialkylformamides and phenols possessing benzothiazole, quinoline and formyl as directing groups at their *ortho*-position. This directing group-assisted cross-dehydrogenative coupling (CDC) occurs between the formyl C–H of dialkylformamides and the phenolic O–H bond in the presence of the Cu(II) catalyst and oxidant aqueous TBHP. A plausible radical mechanism has been proposed for the reaction.

CHAPTER III.

This chapter has been divided in to two sections. Section A describes the copper(II)-catalyzed *S*-aroylation of thiols with alkylbenzenes under oxidative condition, whereas Section B highlights $AlCl_3$-catalyzed regiospecific acylation of electron deficient *N*-heterocycles with methylarenes under oxidative condition.

SECTION IIIA: Thioesterification of Alkylbenzenes with Thiols via Copper-Catalyzed Cross Dehydrogenative Coupling without a Directing Group

This chapter deals with the thioesterification of alkylbenzene with the thiols catalyzed by copper(II) under oxidative condition through cross-dehydrogenative coupling.

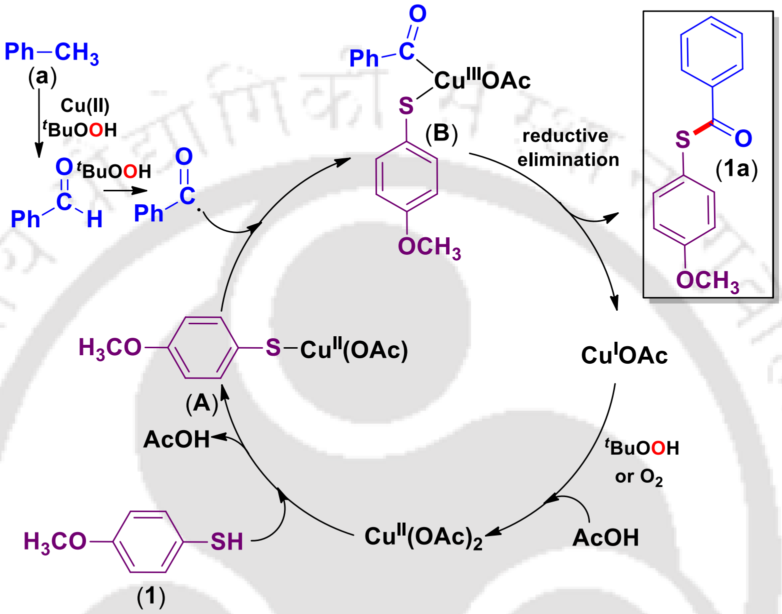
In spite of reaching great advances, the vast majority of functionalization processes at sp^3 C–H bonds via CDC have been achieved by the sp^3 C–C bond forming reactions. The sp^3 C–heteroatom bond formation by CDC strategy is mostly confined to the construction of C–N and C–O bonds with only few examples of C–S bond formations. Thus, it is imperative to develop protocols for the later bonds since sulfur-containing compounds find potential uses in the pharmaceutical and agrochemical industries. One of the problems associated with the use of thiols as coupling partner during C–S bond formation is its propensity to undergo oxidative self-dimerization which inhibits the desired C–S bond formation. To combat this disadvantage of thiols, they are mostly employed in the form of their disulfides, sulfonylhydrazides or sulfonylchlorides that generate *in situ* reactive free radical or cationic intermediates essential for CDC reactions. Few direct thiolations using thiols or their derivatives have been demonstrated at sp^3 C–H bonds α to a heteroatom or a carbonyl group under metal free conditions, but no such relevant examples at the relatively un-activated benzylic sp^3 C–H have been reported in the literature.

Thioesters have been synthesized previously by applying various strategies. These include (i) thioesterfication or trans-thioesterification of carboxylic acids or its derivatives, (ii) thiocarbonylation of iodoarenes with thiols and carbon monoxide using Pd catalyst, (iii) recently developed oxidative coupling of aldehydes or benzyl alcohols with thiols in the presence of *N*-heterocyclic carbene (NHC) or (iv) via a radical path. In this context, the present CDC approach using simple alkylbenzene and thiol to afford thioester is distinctive.

Our recent success on substrate directed *O*-aroylation of phenol using alkylbenzene as the aroyl source prompted us to investigate how alkylbenzene would react with thiol under similar conditions. Ideally, a radical CDC between thiol and alkylbenzene should result in the formation of an *S*-benzyl thioether via C–S bond formation. A benzylic oxidation of *S*-benzyl ether at the expense of two benzylic C–H bonds would give the thioester as was observed in our earlier report with phenol. To initiate the envisaged strategy *p*-methoxybenzenethiol and toluene were reacted in the presence of catalyst $Cu(OAc)_2$ (20 mol %) and oxidant TBHP (4 equiv) at 95 ^{o}C. To our delight the reaction afforded the corresponding thioester in 67% yield after 6 h. It may be noted here that a similar *O*-aroylation required the assistance of *o*-carbonyl as the directing group. The non-requirement of directing group in this case is possibly because of the efficient binding of soft Cu with soft thiol nucleophile.

Various reaction parameters such as catalysts, oxidants and temperature were screened to obtain the optimal conditions for this reaction and it was found that the use of $Cu(OAc)_2.2H_2O$ (20 mol %), oxidant TBHP 5–6 M in decane (4 equiv) at a reaction temperature of 95 ^{o}C under air atmosphere is the most suitable conditions for our further exploration to extend the scope of this transformation. The optimized condition then implemented for the *S*-aroylation of thiols with different alkylbenzens. Irrespective to their electronic environments both on thiols and alkylbenzenes coupled efficiently to give the desired thioesters in moderate to good yield. Aliphatic thiols such as propane, butane and dodecane thiols also underwent *S*-aroylation when coupled with *p*-xylene under the present reaction conditions affording their corresponding thioester in moderate yield. One of the interesting features of this protocol is that in case of polyalkylated benzene only one of them reacts while other remains as such.

Several experimental studies were performed to clarify the mechanism of this transformation. Based on the observations of these experiments and previous related literature reports, a plausible mechanism has been proposed. In this thioesterification the reagent TBHP serves the twin role of an oxidant and a radical initiator (Scheme IIIA.1).



Scheme IIIA.1. *Proposed mechanism for thioesterification*

In conclusion a CDC protocol has been developed for the *S*-aroylation of thiols using alkylbenzenes as aroyl surrogates in the presence of Cu/TBHP. In this reaction, simultaneously C–S and C–O bonds are installed at the expense of three sp^3 C–H bonds of alkylbenzene and an sp^3 S–H bond of thiol.

SECTION IIIB: Regiospecific Benzoylation of Electron-Deficient *N*-Heterocycles with Methylbenzenes via a Minisci-Type Reaction

This chapter demonstrates the regiospecific acylation of electron deficient *N*-heterocycles catalyzed by AlCl$_3$ through CDC reaction using alkylbenzene as synthetic equivalent of aroyl moiety under oxidative condition.

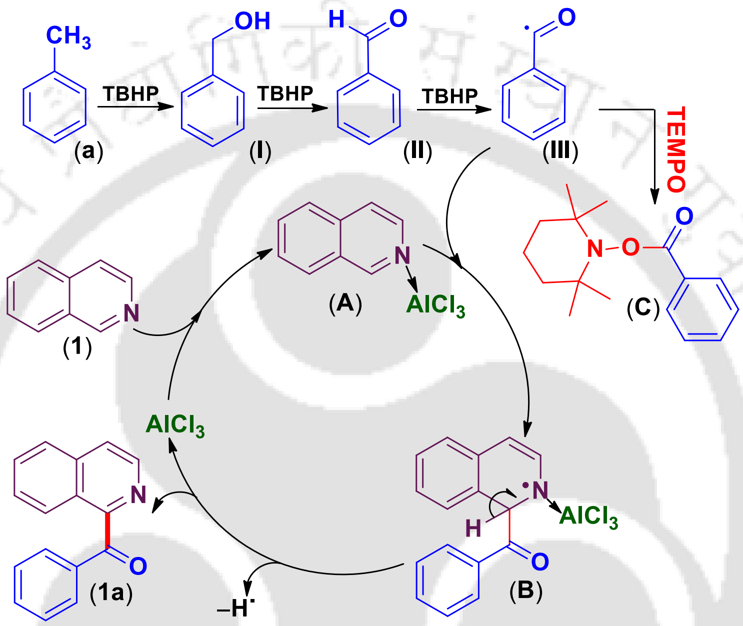
Of significant interest are methods that provide access to molecules in step- and atom-economic fashion from readily available precursors. In the past few decades, the construction of C–C bonds through C–H bond activation is a rapidly expanding field of research as it provides an atom-economical and shorter route for the synthesis of organic compounds and offers substantial benefits.

Nitrogenous heterocycles are widely distributed in nature and present in large proportion in commercial drugs. These heterocycles also have enormous applications in both chemistry and biology. Heterocyclic moieties bearing an acyl group have been found in drugs which are important in pharmacological studies. Until now, a number of methods have been developed for the synthesis of electron-deficient heterocycles, but their functionalization using cross-dehydrogenative coupling is far less visited.

In contrast to electron-rich heterocycles, acylation of electron-deficient heterocycles is much more challenging and only a few reports are available. Among these, the Minisci reaction is the most commonly used approach, which involves the addition of an *in situ* generated nucleophilic acyl radical from aldehyde to an electron-deficient heterocycles. Although it represents a straightforward strategy but suffers from certain drawbacks such as harsh reaction conditions, poor site selectivity, limited substrate scope and the use of transition-metal salts up to stoichiometric amounts. To overcome these aspects, the Antonchick and Prabhu groups independently reported metal-free analogues of the Minisci reaction under ambient conditions.

In continuation to our efforts in utilizing alkylbenzenes as different surrogates via metal and metal-free C–H functionalization strategies, we envisaged that an acyl radical (generated *in situ* from methylarenes under oxidative conditions) could be utilized for the direct acylation of *N*-heterocycles. Intrigued by the key mechanistic feature of Antonchick report; we anticipated that the direct use of CF_3COOH could generate a similar protonated intermediate. On the other hand, employing TBHP as the oxidant is expected to afford the other coupling counterpart to the acyl radical from methylarenes.

A number of screening experiments were carried out to reach the optimum reaction condition. It was found that the use of $AlCl_3$ (25 mol %) and TBHP (5–6 M in decane) (3 equiv) at 95 ^{o}C under N_2 atmosphere is the best optimized condition to explore the substrate scope of present protocol. With this optimized conditions in hand, we examined the scope of this cross-dehydrogenative couplings by reacting isoquinoline with a set of alkylbenzenes possessing both electron-donating as well as electron-withdrawing substituents. Under the present conditions, isoquinolines were smoothly acylated with various alkylbenzenes to afford the corresponding coupled products in moderate to good yields. In case of isoquinoline we got exclusively C1-acylated product. Similarly quinoline also underwent cross-dehydrogenative coupling with different alkylbenzenes to give exclusive C2-monoacylated products. It is to be noted that in case of quinolines the acylation took place regioselectively at its C2 position only with no traces of other regioisomers. No C4-aroylation product was observed even when the C2 position was blocked with a methyl or a *tert*-butyl group, suggesting the strong regioselective nature of the present transformation.



Scheme IIIB.1. *Plausible mechanism for C1 acylation*

On the basis of the experimental observations and literature precedence, a plausible mechanism is proposed (Scheme IIIB.1). Generation of acyl radical is the key step in the present transformation.

In conclusion, we have developed an efficient, mild and cost-effective method for the regiospecific acylation of electron-deficient *N*-heterocycles using methylbenzenes. In this transformation, Lewis acid $AlCl_3$ is used as catalyst and TBHP as oxidant. The reaction serves as complement to classical Minisci reaction.

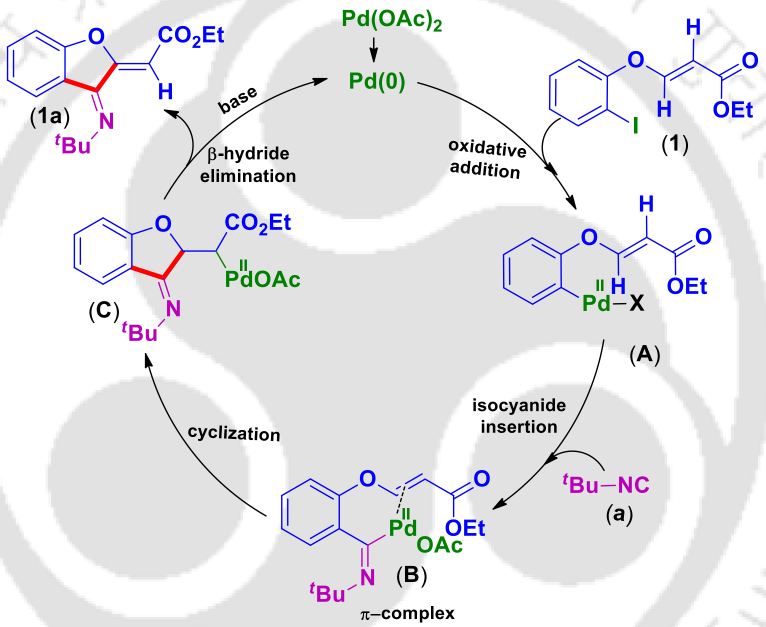
CHAPTER IV: Cascade Synthesis of Dihydrobenzofurans and Aurones via Palladium-Catalyzed Isocyanides Insertion into 2-Halophenoxy Acrylates

This chapter describes about palladium(II)-catalyzed synthesis of 2,3-disubstituted benzofurans and aurones using isocyanides as C1 building block.

Dihydrobenzofurans are important building blocks in organic synthesis and also key structural motif of numerous natural products with biological activities. Aurones have been described as antifungal agents, as inhibitors of tyrosinase and as antioxidants. Similarly, dihydrobenzofuran moiety have been reported to present in a vast array of natural products and numerous synthetic compounds with useful biological activities. Numerous efforts have been reported for the synthesis of dihydrobenzofuran skeleton including intramolecular Friedel-Craft reaction and Wittig reaction. With advancement of transition metal-catalyzed C–C and C–O bond formation reactions, 2,3-disubstituted benzofurans can be synthesized from *o*-functionalized phenols and their derivatives through palladium-, copper-, platinum- and silver-catalyzed reactions. Dihydrobenzofurans and aurones can also be synthesized by the Rh-catalyzed intramolecular carbene insertion and Heck reaction of salicylaldehydes with acrylates respectively. In the past few years palladium-catalyzed cascade reactions have emerged as an attractive strategy to avoid the requirement of decorated precursors and therefore enhance the efficiency to achieve the target molecules.

Migratory insertions of isocyanides during palladium-catalyzed reactions have appeared as powerful methods for the preparation of carbo and heterocyclic products. Both the electro- and nucleophilic nature of isocyanides have established them as powerful and versatile C1 building blocks in organic synthesis. Apart from participating in multicomponent reaction palladium-catalyzed isocyanide insertion offer great potential for the synthesis of oxygen containing heterocycles. In light of these aspects herein we wish to report the synthesis of 2,3-disubstituted benzofurans and aurones via palladium-catalyzed isocyanides insertion reaction with 2-iodophenoxy acrylate.

To attain the suitable reaction condition for the synthesis of 2,3-disubstituted benzofurans various reaction parameters such as catalyst, base, solvent and reaction temperature were screened to achieve the maximum product yield. After a series of screening experiments, the optimized reaction condition was found as $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (3 equiv) at 90 ^{o}C in toluene. Once optimized condition was achieved, we examined the scope of this palladium-catalyzed cascade process. It was found that both electron-donating and electron-withdrawing substituents are well tolerated under the present reaction conditions. The compound formed bearing two interesting exocyclic double bonds that can be utilized for rapid construction of molecuclar complexity. Approaches to synthesize such a skeleton were quite limited so far. The compound formed contains exocyclic imine functionality that can be hydrolyzed by refluxing it with 5N HCl in THF to give the various substituted aurones. Interestingly when iodo was replaced with bromo the product formed with reduced exocyclic imine. Based on our observation and literature precedence plausible mechanism has been proposed (Scheme IV.1).



Scheme IV.1. *Plausible mechanism for the synthesis of 2,3-dihydrobenzofurans*

In summary, we have developed a palladium-catalyzed cascade process involving isocyanide insertion and $C_{sp}{}^2$–H cross coupling for the synthesis of 2,3-disubstitued benzofurans. The advantage of this work includes the synthesis of oxygen heterocycle from simple and commercially available starting material, phosphine-ligand free condition, and formation of two new C–C bond.

CHAPTER V.

This chapter has been divided in to two sections. Section A illustrates the use of Cs_2CO_3 as carbonyl and oxygen in copper(II)-catalyzed cascade synthesis of benzofuran[3,2-*c*] quinolin-6[5-*H*]ones, whereas Section B highlights Ag_2CO_3-mediated cascade synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocynates.

SECTION VA: Cs_2CO_3 as a Source of Carbonyl and Ethereal Oxygen in a Cu-Catalyzed Cascade Synthesis of Benzofuran[3,2-*c*] quinolin-6[5-*H*]ones

This chapter highlights about copper(II)-catalyzed synthesis of benzofuran[3,2-*c*] quinolin-6[5-*H*]ones using Cs_2CO_3 as the source of carbonyl and ethereal oxygen.

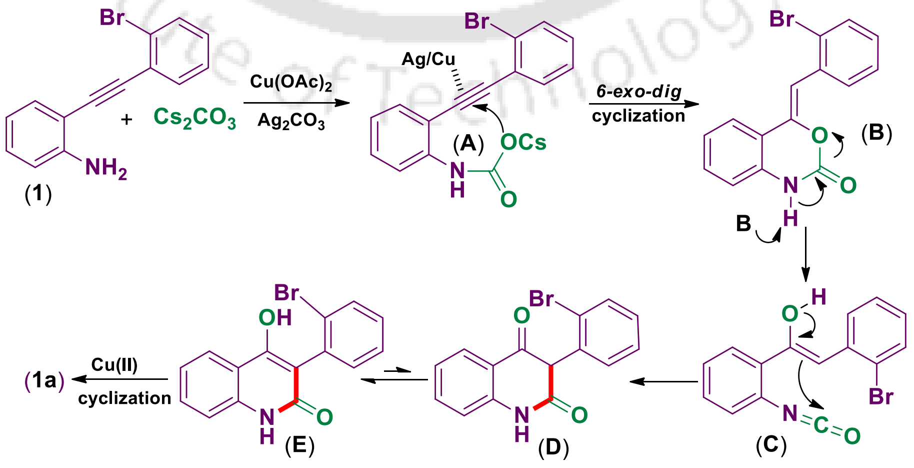
In the modern era of organic chemistry, the synthesis of highly functionalized and structurally diverse heterocycles is a challenging task. In this regard, domino reactions are a most promising approach for the synthesis of complex organic molecules. Formation of multiple C–C and C–heteroatom bonds for rapid access to fused and complex polycyclic skeletons is an attractive feature of any domino reaction. Recently, the strategy has emerged as a powerful “Synthetic Avenue” for the conversion of internal alkynes into biologically interesting polycycles or spiro heterocycles.

Benzofuro[3,2-*c*]quinolin-6(*5H*)-one derivatives are reported to show activity against osteoporosis and malaria. Surprisingly, the literature contains only a few reports describing the synthesis of benzofuro[3,2-*c*]quinolin-6(*5H*)-ones.

In continuation of our effort towards copper-catalyzed synthesis of heterocycles, when 2-((2-bromophenyl)ethynyl)aniline was treated with L-alanine in the presence of $Cu(OAc)_2$ and Cs_2CO_3 in DMSO at 130 ^oC a product was isolated in 57% yield. Spectroscopic analysis (NMR, IR and HRMS) and subsequent crystal structure determination of one of its derivative confirms its structure to be benzofuro[3,2-*c*]quinolin-6(*5H*)-one. The product structure demonstrates a few interesting facets of this transformation *viz.* the incorporation of carbonyl as well as an ethereal oxygen functionality in the resultant heterocycle and their origin. The unique feature of this heterocycle is the simultaneous formation of three types of bonds *viz.* two C–O and both one C–C and one C–N bond.

It is well established that metal carbonates and bicarbonates act as CO_2 source. It has been reported that Cs_2CO_3 serves as a CO_2 source for the synthesis of cyclic or acyclic carbonates. Recently, Cs_2CO_3 as an oxygen source for the synthesis of ester by the coupling of acid chloride and alkyl halide has been reported. So far, the synthesis of biologically active heterocycles using CO_2 generated from metal carbonates is unfamiliar. On the other hand, gaseous CO_2 has been extensively utilized for the synthesis of carbonates, acid, ester and lactone. Silver-catalyzed incorporation of gaseous CO_2 in a variety of internal and terminal alkynes, allenes, *o*-alkynylacetophenone, and allylsilane as well as carboxylation of terminal alkynes are summarized by Yamada *et al*. The inserted CO_2 undergo various kinds of rearrangements to afford various heterocycles. Similarily, Cu(II)-catalyzed incorporation of CO_2 into alkene, alkyne, allene and other systems has been reported by other groups. To the best of our knowledge the cascade synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones is being reported for the first time utilizing CO_2 from Cs_2CO_3.

To find out the appropriate optimized condition a series of experiment have been carried out and it was found that the use of $Cu(OAc)_2$ (5 mol %), Cs_2CO_3 (4 equiv), Ag_2CO_3 (1 equiv) in DMSO (3 mL) at 130 ^oC is best condition for the present transformation. With the this optimized conditions in hand, we explore the generality and scope of this protocol and the experimental results suggest that irrespective of the substituent on the either ring, underwent efficient cascade cyclization to afford their corresponding cyclized product in moderate to good yield. When the bromo substituent was replaced with an iodo group the yields of products were marginally better than their bromo analogues.



Scheme VA.1. *Plausible mechanism for the synthesis of benzofuro[3,2-c]quinolinones*

To understand the nature of this unprecedented carbonylation-etherification process and to gain insight into the reaction mechanism, a number of experiments have been carried out. On the basis of the results obtained from control experiment and literature precedence a plausible mechanism has been proposed that proceeds through the isocyanate type of intermediate (Scheme VA.1).

In conclusion, we have developed a novel protocol for the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives catalyzed by Cu(II). Concomitant installation of three types of bonds *viz.* two C–O and both one C–C and one C–N achieved in a tandem process. In this carbonylation-etherification cascade process both carbonyl and ethereal oxygen originates from Cs_2CO_3.

SECTION VB: Microwave-Assisted Cascade Strategy for the Synthesis of Indolo[2,3-*b*]quinolines from 2-(Phenylethynyl)anilines and Aryl Isothiocyanates

This chapter describes Ag_2CO_3-mediated synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates.

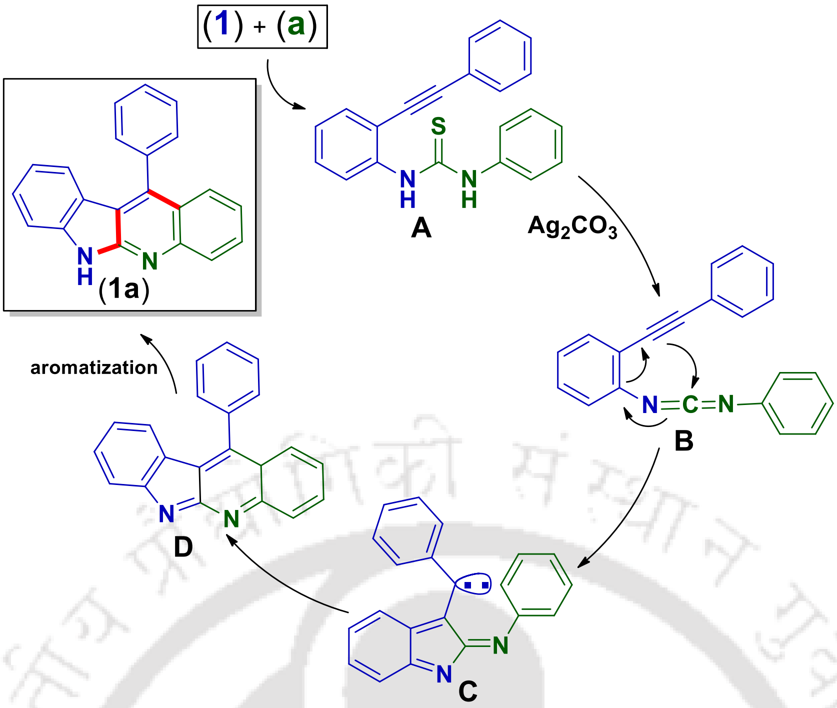
There has been continuous interest in the synthesis of natural product like compounds with privileged scaffolds that are likely to have potential biological activities. Among these privilege scaffolds, indoloquinoline alkaloids represent one of the important classess of heterocycles due to their immense biological activity including the ability to interact with DNA as an intercalator to inhibit topoisomerase II activity. Recent results reveals that some new indolo[2,3-*b*]quinoline (norcryptotackieine) types of natural products isolated from the leaves of *Justicia betonica* exhibit exceptional pharmacological properties such as potent antiplasmodial, antiproliferative, and antitumor activity. Therefore, developing strategies for the synthesis of indolo-fused quinolines that are more efficient, cost-effective, atom-economical and practical are sought-after.

Currently, cascade reactions are one of the most promising approaches in organic synthesis due to their high atom economy, better efficiency and easy handling during the assembly of complex molecular structures. Furthermore, microwave assisted organic synthesis have the advantage of greater reactivity, mild reaction conditions, high selectivity and shorter reaction times. Therefore, cascade reaction carried out under a microwave conditions are further advantageous to conventional heating.

Most of the available synthetic strategies for the synthesis of indolo[2,3-*b*]quinolines rely on the use of indole and its derivative as one of the coupling partners. The indoloquinoline system has also been assembled through a thermal cyclization of an enyne-carbodiimide. In 2003 Curran *et al.* reported the synthesis of indolo[2,3-*b*]quinoline via a cascade radical annulation of *o*-alkynyl thiourea that involves irradiation of UV light (with medium pressure Hg lamp) in a pyrex glass tube requiring a large excess of *tris*(trimethylsilyl) silane (TTMSH) (4 equiv), AIBN (1 equiv) in anhydrous benzene. Although this method provides fruitful access to indoloquinolines, the use of certain carcinogens (benzene) and expensive and excess amounts of reagents and the requirements of a specialized setup to give moderate yields and lower substrate scope limit their applications. Thus in an attempt to obliterate the limitations of the earlier methods, we developed a straightforward and versatile protocol for the synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates.

Various reaction parameters were scrutinized to reach the optimum reaction condition and it was use of 1 equiv of Ag_2CO_3 in DMSO at 130 ^{o}C under microwave heating (MW 150W) for 30 minutes. Under the optimized conditions various 2-(phenylethynyl)anilines and aryl isothiocyanates were subjected to the reaction conditions to explore the scope of this cascade protocol. Phenyl isothiocyanates possessing electron-donating (EDG) substituents at their *para* position afforded the corresponding products in better yields compared to un-substituted and electron-withdrawing (EWG) substituents. Effect of substituent present on the other phenyl ring found similar to the substituent on phenyl isothiocyanates.

To understand the mechanism of this process, control experiments were conducted. The formation of Ag_2S in the reaction medium has been confirmed by powder XRD and EDX analysis. On the basis of our experimental findings and previous literature, a plausible reaction mechanism has been proposed (Scheme VB.1).



Scheme VB.1. *Proposed mechanistic pathway*

In conclusion, we have developed an elegant cascade approach for the synthesis of indoloquinolines. This protocol allows the practical synthesis of many valuable indolquinoline alkaloids through Ag_2CO_3-mediated cascade annulation of internal alkynes under microwave heating.

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ABBREVIATIONS

AcOH	acetic acid
AIBN	azobisisobutylnitrile
$AgSbF_6$	silver hexafluoroantimonate
CCDC	Cambridge crystallographic data center
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
ESI-MS	electrospray ionization mass spectrometry
HRMS	high resolution mass spectrometry
IR	infrared
LED	light emitting diode
M.p.	melting point
MO	molecular orbital
NHC	*N*-heterocyclic carbene xxiv
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NBS	*N*-bromosuccinamide
NCS	*N*-chlorosuccinamide
NIS	*N*-iodosuccinamide
ORTEP	oak ridge thermal ellipsoid program
PivOH	pivalic acid
rt	room temperature
TM	transition metal
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TLC	thin layer chromatography
XRD	x-ray diffraction

Chapter I

An Overview of Metal-Catalyzed C–H Functionalization and Cascade Reactions

CHAPTER IA

IA. A Sketch of Metal-Catalyzed C–H Functionalizations

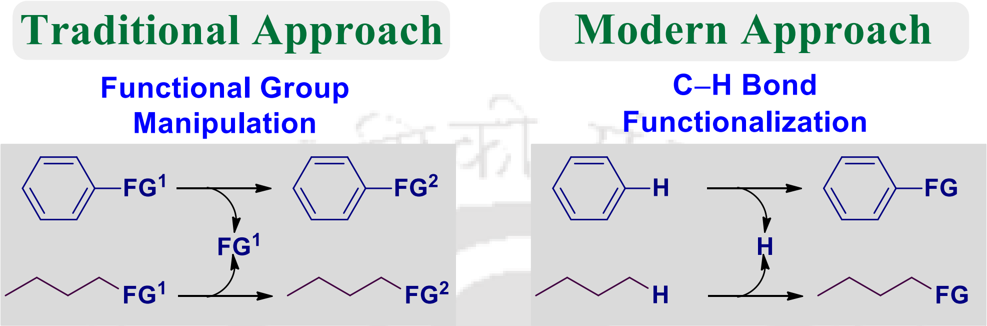
IA.1. Introduction

Of late strategies for the formation of carbon–carbon and carbon–heteroatom bonds in both industry and academia has improved significantly with the use of coupling chemistry.[1] The traditional coupling reactions either involves transition metal-catalyzed coupling of functionalized substrates or the use of stoichiometric organometallic reagents. The advance version of cross coupling chemistry has been successfully applied to the synthesis of commercially useful products.[2] Although, there is significant advancement in these selective and efficient methodologies but they suffer from certain drawbacks. The two components undergoing coupling must be pre-activated through halogenation, metallation or other measures, thereby increasing the number of synthetic steps and invariably resulting in chemical waste in the overall process. One of the best ways to address this issue is the direct utilization of un-activated carbon–hydrogen (C–H's) bonds.[3]

In every organic compound C–H bonds are ubiquitous and regarded as un-functionalized group (i.e. absence of any other bond) containing tremendous synthetic potential hidden within them. If their hidden reactivity can be exploited, it could potentially establish the most broadly applicable and powerful class of transformations in organic synthesis. An extensive investigation into transition metal-catalyzed C–H activation processes has greatly improved our understanding of how to selectively functionalize the inert C–H bonds. The formations of carbon–carbon and carbon–heteroatom bonds directly from un-activated C–H bonds show enormous potential for advancing the field of chemical synthesis. The C–H bond functionalization provides the shortest possible route to give the targeted natural and un-natural products.

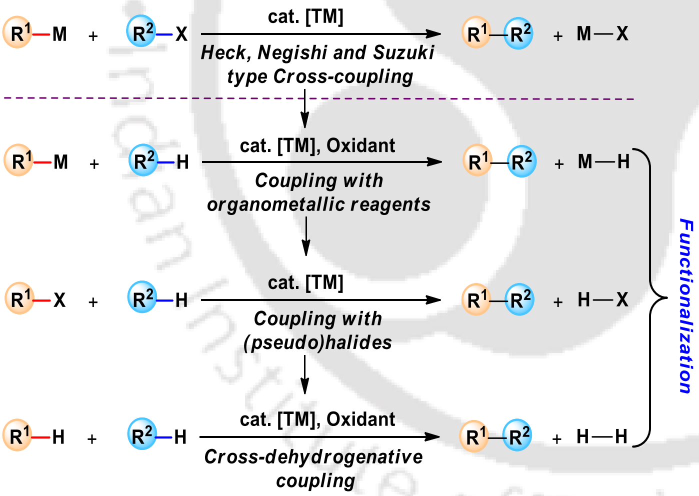
IA.2. Traditional Vs Modern Approach

Traditional organic reactions depend on functional-group-based transformation that is putting a new functional group (FG) in place of the existing one. So, in order to install a new functional group requires a pre-functionalized starting material, which means a functional group (FG^1) is first installed and then removed as the byproduct during the second installation. This process decreases both the efficiency and atom economy and also adds extra step and cost to the overall transformation. On the other hand C–H functionalization strategy does not require any prefunctionalized starting materials.



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

A new era in the synthetic organic chemistry started with the development of transition metal-catalyzed cross-coupling reaction by R. F. Heck, E. Negishi and A. Suzuki. In 2010, they were awarded with Noble Prize in chemistry for their significant contribution to the development of palladium-catalyzed cross-coupling reactions.[4] Later, other transition metals were also applied for the same purpose.

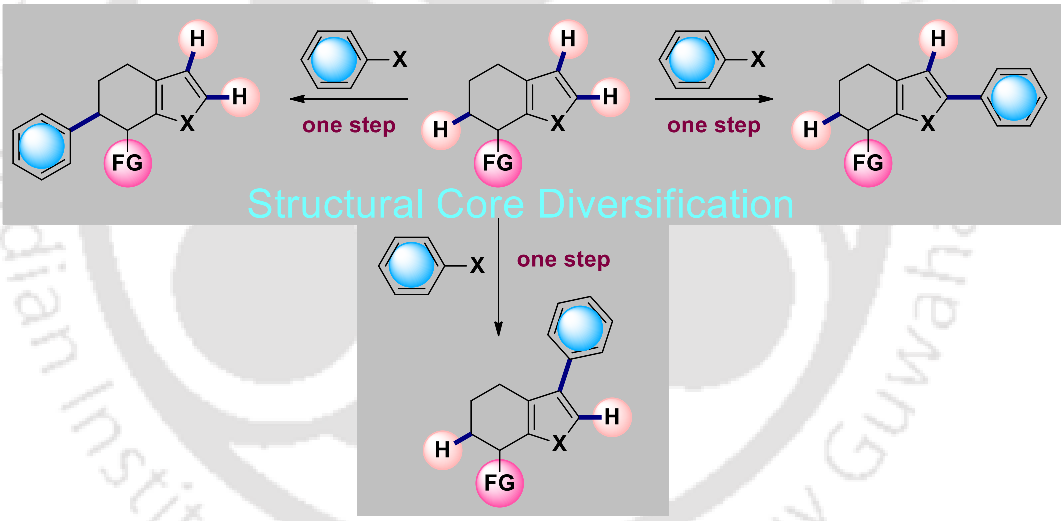


Scheme IA.2.2. *Evolving algorithms of strategies in organic chemistry*

To avoid the use of pre-functionalized starting materials chemists developed a new approach i.e. transition metal-catalyzed functionalization of C–H bonds. In recent time, a variety of C–H functionalization processes were applied in organic synthesis as shown in Scheme IA.2.2. The above Scheme shows the evolving algorithms of different strategies used in synthetic organic chemistry starting from transition metal-catalyzed cross-coupling reactions to C–H bond functionalization approach.

Because of the ubiquitous nature of C–H bonds in organic molecule, selective functionalization of every C–H bond is quite challenging. If C–H bonds of an organic molecule could be selectively functionalized, the area of chemical synthesis and drug discovery would be revolutionized forever. Nature have specific enzyme to achieve site selective C–H oxidation because of the specific structure of that particular enzyme. However, to achieve these target organic chemists need to develop selective catalyst or substrates to reach any predictable site selectivity. Molecules isolated from nature are the only readily available and renewable source of simple organic molecule. Thus, the selective diversification of these molecules represents progress towards sustainable drug discovery and useful chemical production.

Furthermore, C–H bond functionalization also provides an alternative synthetic route for the preparation of a series of compounds in order to assemble the specific target molecule [“structural core diversification” (Scheme IA.2.3)].



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

The differential reactivity of each type of C–H bond in a complex molecule permits direct access to multiple analogues of a common structural ancestor which were earlier not accessible via traditional coupling strategy. Thus, by viewing C–H bonds as “ubiquitous functionality”, a new chapter is being opened in organic synthesis with many exciting opportunities.

IA.3. Challenges to C–H Functionalizations

Although C–H bond functionalization are advantageous over traditional coupling reactions and provides chemical ideals from step and atom economic point of view, the ubiquitous nature and inherent low reactivity due to relative bond strength pose significant challenge for selectivity and reactivity, which is the main issue over the past decades for the researchers.

- **Inherent Low Reactivity:**

Most of the naturally occurring organic compounds, the C–H bonds are either sp^2 or sp^3 hybridized; whose pK_a values are ranging between 30–35. These kinds of bond are usually associated with very high bond dissociation energy i.e. large amount of kinetic energy required to break these C–H bonds. So it is very difficult to cleave these bonds both via homolytic and heterolytic pathways.

- **Regioselectivity:**

Selective functionalization of a particular C–H bond in a complex organic molecule leaving others intact is a difficult task due to its ubiquitous nature. For example, the pharmaceutical Fluoxetine, sold as "Prozac" shown in Figure IA.3.1, possesses multiple, unique C–H bonds. Site-selective functionalization of any one of these various sites could be desirable for structure-activity relationship studies in the pursuit of new drug derivatives or to study the pharmacokinetics.

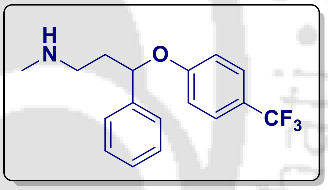
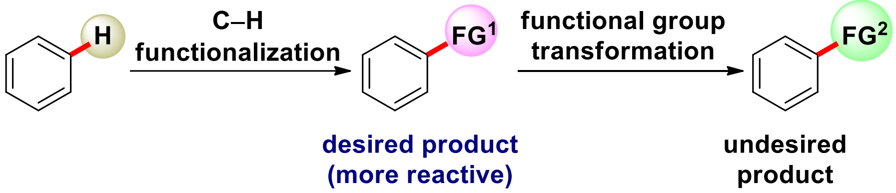


***Figure IA.3.1.** The pharmaceutical Prozac contains multiple, unique C–H bonds*

- **Chemoselectivity:**

Chemoselectivity issue arises when a molecule contain more than one reactive functional group, therefore selective transformation of one of the functional group in the presence of others is difficult. In the process of C–H functionalization, if the desired product formed is more reactive than the starting material it may undergo further functional group transformation under the same reaction condition leading to undesirable products (Scheme IA.3.1)



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

- **Stereoselectivity:**

Most of the C–H functionalization reactions take place under harsh reaction condition and at higher temperature due to its inertness. So it might have detrimental effect on the stability of chiral complex and efficiency of asymmetric induction. As a result, during C–H bond activation process generation of new stereogenic centers with high diastereo or enantioselective isomer is the most challenging task in recent times.

Apart from the above issues, C–H functionalization process is also associated with some minor issues such as preserving the existing functionality in the precursor molecules during transformation as well as controlling the competing side reactions such as homo- and hetero-coupling. Hence, the two major issues that minimize the effect of these points and that need to be resolved are *reactivity* and *selectivity*.

IA.4. Mechanism of C–H Functionalizations

Most of the challenges mentioned above can be overcome by the use of transition metal catalyst. A catalyst is defined as “reagents or substrate which lowers the activation barrier of a particular reaction without being consumed or changed in nature during that transformation”. Transition metal possesses the unique character to “activate” the C–H bond by lowering the activation energy for bond breaking without being consumed or transformed. According to Bercaw there are five different mechanisms possible for these reactions by which stable organometallic species are formed *viz.* oxidative addition, σ-bond metathesis, electrophilic activation, metalloradical activation and 1,2-addition; out of these initial three are quite common, while the other two are rare.[5]

(a) Oxidative Addition

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

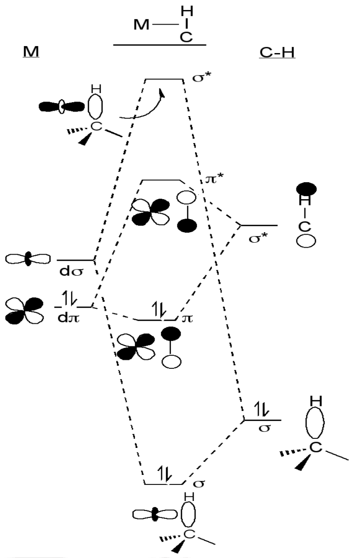
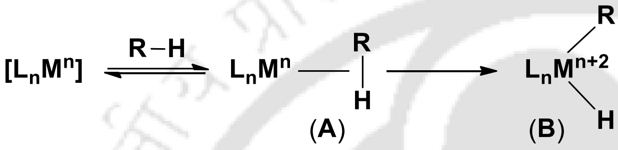


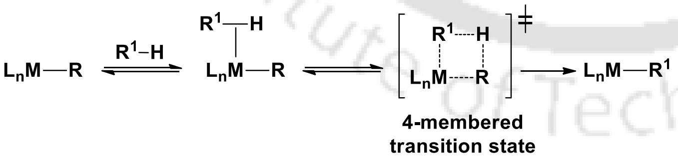
Figure. IA.4.1. *A qualitative MO diagram for oxidative addition*



Scheme IA.4.1. *An oxidative addition mechanism*

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

(b) Sigma-Bond Metathesis



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

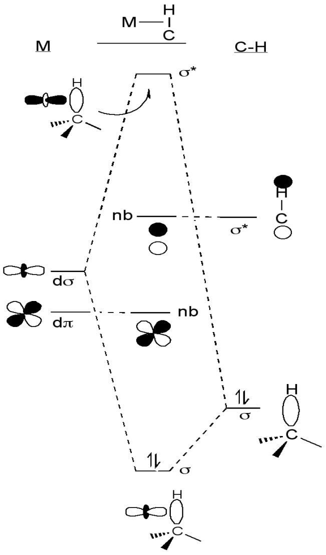


Figure IA.4.2. *A qualitative MO diagram for σ-bond metathesis*

This activation mechanism consists of cleavage and formation of σ-bond 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 IA.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 (Figure IA.4.2).

(c) Electrophilic Activation

Late transition metals in their higher oxidation state are involved 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 IA.4.3). For saturated hydrocarbons, an analogous intermediate might be formed with an electrophilic metal containing species.

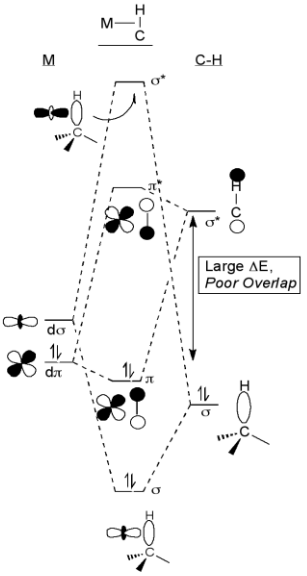
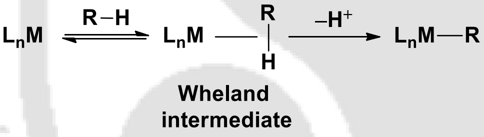


Figure IA.4.3. *A qualitative MO diagram for electrophilic activation*



Scheme IA.4.3. *An electrophilic activation mechanism*

A qualitative molecular orbital diagram (Figure IA.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.

(d) Metalloradical Activation

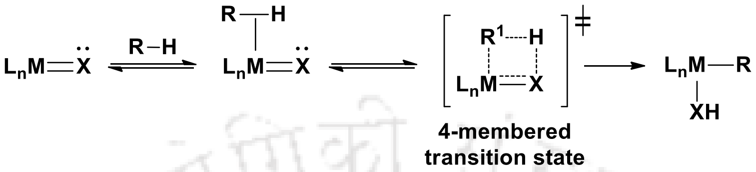
Alkene C–H activation proceeds via this type of mechanism. The transition metal complex existing in monomer-dimer equilibrium can reversibly break alkane C–H bonds and two fragments of C–H bonds are attached to two separate halves of the metal complex (Scheme IA.4.4). Complexes of rhodium and ruthenium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

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

Scheme IA.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 a 4-membered transition state (Scheme IA.4.5). C–H bond addition across metal-nitrogen and metal-carbon double bonds of early and middle transition metal are known, but the scope and its potentiality remain unclear.

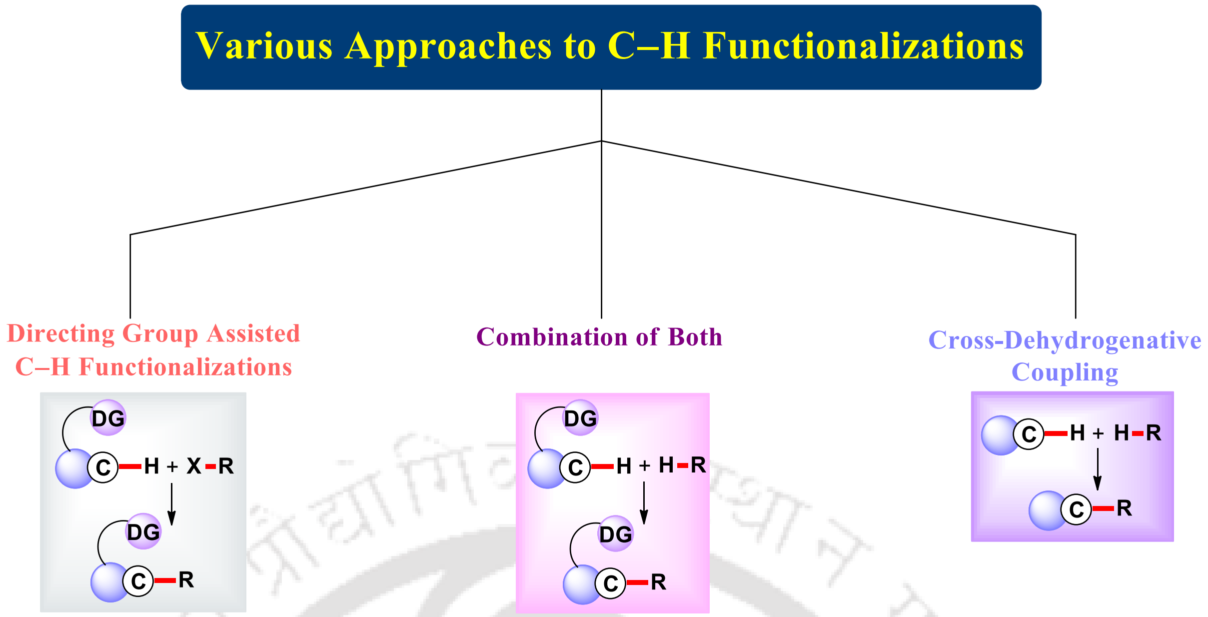


Scheme IA.4.5. *A 1,2-addition mechanism*

For the entire classified mechanistic path for the C–H bond activation a transition metal complex is required. C–H activation that involves the insertion of metal in to C–H bonds 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).

IA.5. Various Strategies for C–H Functionalizations

The transition metal-catalyzed C–H functionalization processes took off in early 1990's, which is considered as the "golden age" of C–H functionalization. Since then increase in the number of metal salts and complexes that can initiate C–H activation process has increased dramatically. The strategies generally adopted in these reactions can be classified into two major heads namely (i) directing group assisted C–H functionalizations and (ii) cross-dehydrogenative coupling (CDC) (Scheme IA.5.1). Also there are methodologies which are based on the combination of two aforementioned approaches (Scheme IA.5.1).



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

IA.5.1. Directing Group Assisted C–H Functionalizations: Inert nature and low reactivity of the C–H bond makes selective C–H functionalization process more challenging. One way by which this problem can be resolved is the use of substrate containing electronegative atom such as nitrogen (N), oxygen (O) or sulfur (S) at the proximal site to the C–H bond going to be functionalized (proximal selectivity). These substrate containing heteroatom directs the metal ions to the proximal C–H bond and increase the effective concentration of transition metal ions at that particular site, thereby overcoming the 'paraffin' (not enough affinity) nature of C–H bonds. The direct metallation of metal in to C–H bonds is so powerful that a variety of C–H bonds; including those of isolated alkyls can be selectively functionalized.[6] The transition metal usually forms 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 C–H functionalization. For this purpose, the transition metals which are used includes Ru, Rh, Pd and Cu. Apart from this, other transition metal *viz.* Mn, Fe, Co, Ni, Re, Ir, Pt, Ag, Au are also employed.

Advantages:

- Direct the transition metal into close proximity to the C–H bond to be activated.
- Higher effective concentration of the catalyst at the site of interest.
- Regioselectivity and reactivity is enhanced.

Limitations:

- In most cases, only C–H bond *ortho* to the directing groups are functionalized.

- Additional synthetic steps are required for the installation and removal of directing groups while in many cases the directing group is an integral part of the substrate.

Despite above mentioned limitations, directing group assisted C–H functionalization provides many fascinating results for the construction of C–C and C–X bond. Since the work reported in the present thesis does not belongs to directing group assisted C–H functionalization, therefore detail discussion about directing group assisted various kind of bond formation are not discussed here.

IA.5.2. Cross-Dehydrogenative Coupling (CDC): Cross-dehydrogenative coupling represents advance state of the C–H functionalization process. The term CDC generally refers as the cross-coupling reaction between two C–H bonds or C–H and X–H (X = heteroatoms) bonds.[7] CDC strategy is one of the most idealistic synthetic route for the construction of C–C and C–X bonds so far, as atom economy is concerned. CDC reactions take place in the presence a hydrogen acceptor i.e. oxidant that may be in the form of oxygen, such as hydrogen peroxide, organic peroxides, for example, *tert*-butyl hydrogen peroxide (TBHP) or *tert*-butyl peroxide (TBP) and *N*-halosuccinimides, for example, *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS). Transition metals having capability to activate the electrophilic coupling partner such as Cu, Fe, and Pd have been employed in the CDC reactions. As the process advanced, these reactions can be performed without the use of any metal salts; even they are successfully applied in the aqueous medium, consequently, further enhancing their environmental compatibility. Only limited examples of enantioselective CDC reaction have been reported.

Advantages:

- Non-requirement of any directing groups or installation of functional groups in starting materials.
- Ambient reaction conditions and simple starting materials.
- More advance version of C–H bond activation.

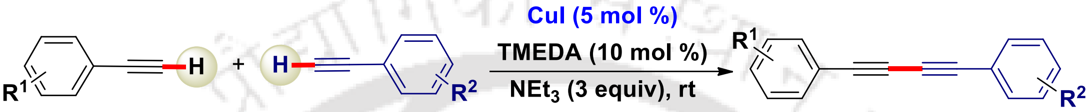
Limitations:

- Regioselectivity issues: functionalization can occur at any of the C–H bonds.
- Lack of chemoselectivity due to over-functionalization.

IA.5.2.1. Representative Examples of CDC Reactions

- **$C_{(sp)}$–$C_{(sp)}$ Bond Formation**

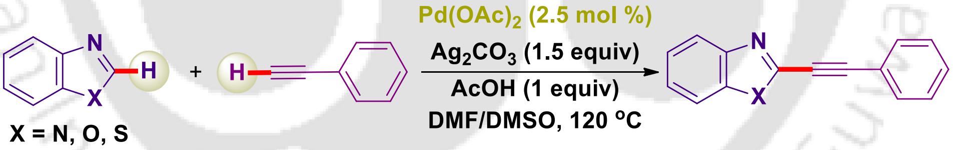
A copper(I)-catalyzed homocoupling reaction of terminal alkynes at room temperature using air as the sole oxidant was reported by Zhang *et al.* (Scheme IA.5.2.1.1)[8] in the presence of ligand *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA). All type of alkyne underwent homocoupling to afford symmetrical as well as unsymmetrical 1,4-disubstituted 1,3-diynes in good to excellent yields.



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

- **$C_{(sp)}$–$C_{(sp2)}$ Bond Formation**

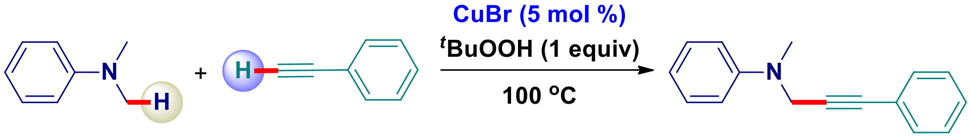
An oxidative coupling of heteroarenes such as imidazole, benzimidazole, imidazo[1,5-*a*]pyridines, oxazole, benzoxazole, thiazole, and benzothiazole with terminal alkynes was developed by Murai and co-worker (Scheme IA.5.2.1.2).[9] They used a combination of palladium and silver salts in polar solvent like DMF or DMSO at 120 °C.



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

- **$C_{(sp)}$–$C_{(sp3)}$ Bond Formation**

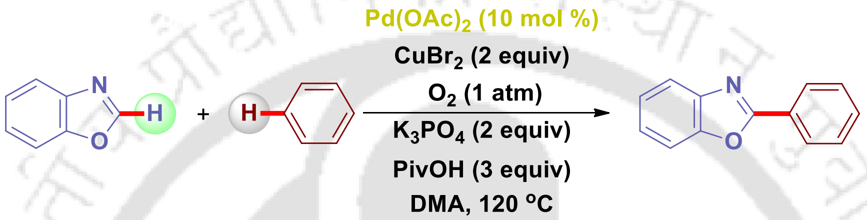
Li group achieved a simple and effective catalytic method to construct propargylamine using copper(I) bromide and *tert*-BuOOH via a combination of sp^3 C−H bond and sp C−H bond activations followed by a C−C bond formation (Scheme IA.5.2.1.3).[10]



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

➢ $C_{(sp2)}$–$C_{(sp2)}$ Bond Formation

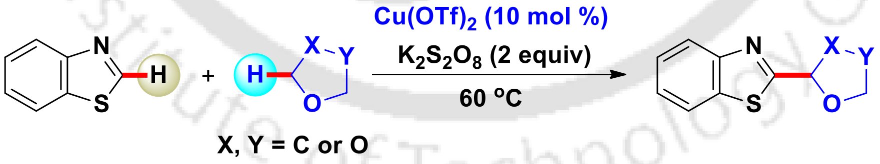
A palladium-catalyzed intermolecular sp^2 C–H–C–H cross-coupling between benzoxazoles and unactivated simple arenes has been developed by Su *et al.* (Scheme IA.5.2.1.4).[11] In this process, $CuBr_2$ was used as additive and K_3PO_4 as base in the presence of O_2 atmosphere. Homocoupling was successfully suppressed such that no traces of bisheteroaryls were obtained through the selective cleavage of C–H bonds in both substrates without the requirement of prefunctionalized substrate and designed ligands.



Scheme IA.5.2.1.4. *Palladium(II)-catalyzed oxidative sp^2 C–H/sp^2 C–H coupling*

➢ $C_{(sp2)}$–$C_{(sp3)}$ Bond Formation

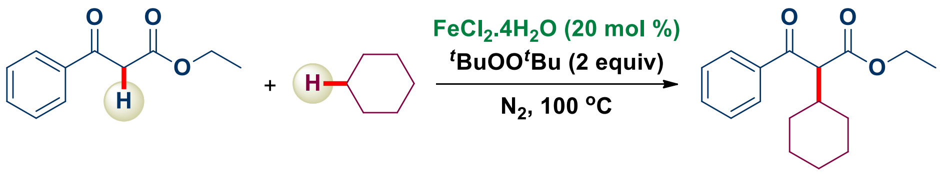
The group of Pan developed a Cu(II)-catalyzed oxidative cross-coupling between benzothiazoles and cyclic ethers in the presence of $K_2S_2O_8$ as oxidant (Scheme IA.5.2.1.5).[12] This protocol provides a new avenue to form new C–C bonds between azoles, especially non-benzo-fused azoles and inactive ethers and also an aldehyde-free synthesis for the acetals.



Scheme IA.5.2.1.5. *Copper(II)-catalyzed CDC reaction of benzothiazole and cyclic ethers*

➢ $C_{(sp3)}$–$C_{(sp3)}$ Bond Formation

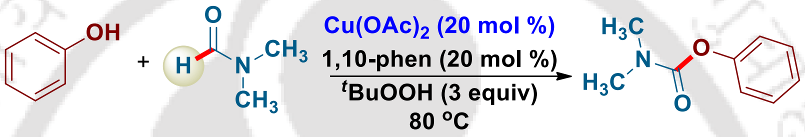
A simple $FeCl_2$-catalyzed C–C bond formation by direct alkylation of activated methylene using simple cycloalkanes was developed by Li group (Scheme IA.5.2.1.6).[13] Several kinds of alkanes were found to react with phenyl β-ketoester and diketone compounds to afford alkylated 1,3-dicarbonyl compounds.



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

➢ $C_{(sp2)}$–O Bond Formation

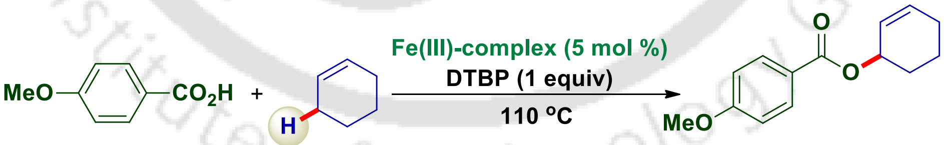
Reddy and co-worker developed a novel phosgene-free route to carbamates via copper-catalyzed oxidative C–O bond formation of formamides with phenols (Scheme IA.5.2.1.7).[14] A ligand 1,10-phenanthroline was used along with external oxidant TBHP for this transformation.



Scheme IA.5.2.1.7. *Copper(II)-catalyzed synthesis of carbamates via C–O bond formation*

➢ $C_{(sp3)}$–O Bond Formation

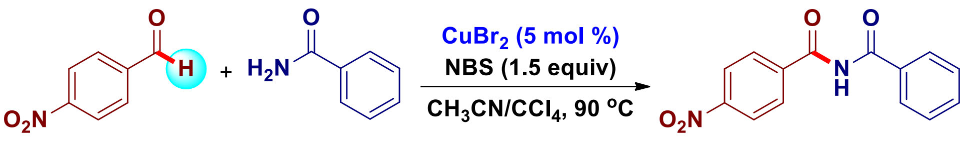
An efficient iron-catalyzed esterification of allylic sp^3 C–H bonds with carboxylic acids using ionic iron(III) complexes as a catalyst and DTBP as an oxidant has been developed by Sun *et al.* (Scheme IA.5.2.1.8).[15] A variety of allylic esters were synthesized in good to excellent yields.



Scheme IA.5.2.1.8. *Iron(III)-catalyzed synthesis of α-acyloxy ethers*

➢ $C_{(sp2)}$–N Bond formation

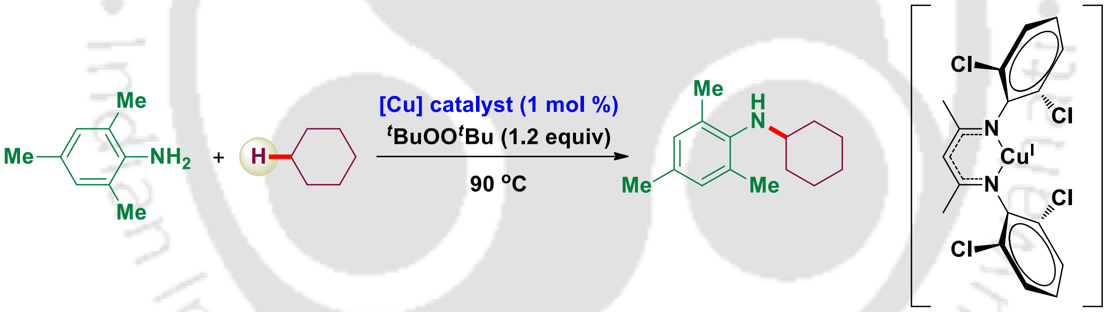
A CDC reaction with heteroatom–H bond for the synthesis of imides has been developed by Fu group (Scheme IA.5.2.1.9).[16] In this process aldehydes coupled with either a secondary or tertiary amides in the presence of copper(II) bromide as the catalyst and NBS as oxidant. The corresponding target products were obtained in good to excellent yields and an array of functional groups are tolerated under the mild conditions with respect to both amides and aldehydes.



Scheme IA.5.2.1.9. *Copper(II)-catalyzed synthesis of imides via sp^2 C–H amidation*

➢ **$C_{(sp3)}$–N Bond Formation**

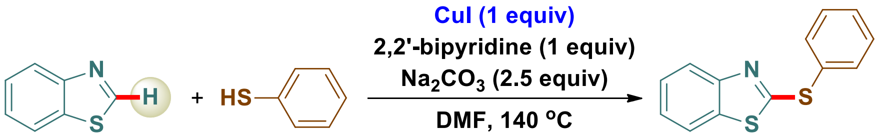
Warren *et al.* demonstrated the first general use of anilines in the C–H amination of a range of substrates with C_{sp3}–H bonds (Scheme IA.5.2.1.10).[17] They used copper(I) catalyst [{(Cl_2NN)Cu}$_2$(benzene)] in conjunction with a mild oxidant ^{t}BuOO^{t}Bu for the coupling of a variety of commercially available anilines for C–H amination. Even strong, unactivated C(sp^3)–H bonds could be efficiently functionalized using low catalyst loadings.



Scheme IA.5.2.1.10. *Copper(I)-catalyzed direct amination at inert sp^3 C–H of alkanes*

➢ **$C_{(sp2)}$–S Bond Formation**

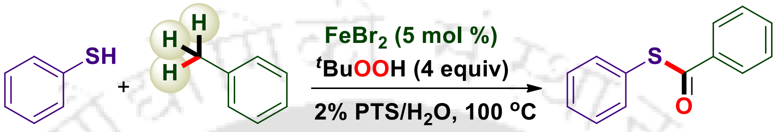
Liu *et al.* reported the synthesis of a series of aryl- or alkylsubstituted 2-mercaptobenzothiazoles by the direct thiolation of benzothiazoles with aryl or alkyl thiols in the presence of stoichiometric amount of CuI, 2,2′-bipyridine and Na_2CO_3 (Scheme IA.5.2.1.11).[18]



Scheme IA.5.2.1.11. *Copper(I)-catalyzed direct thiolation of benzothiazole*

➢ $C_{(sp3)}$–S Bond Formation

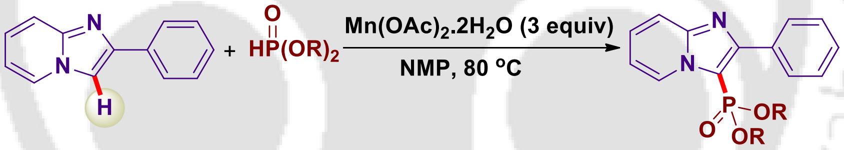
A unique Fe(II)-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes has been recently developed by He and co-worker for the synthesis of thioesters in the presence of *tert*-butyl hydroperoxide as oxidant as well as oxygen source (Scheme IA.5.2.1.12).[19] A thioester moiety is created via successive C–S and C–O bond formation at the expense of three sp^3 C–H bonds of the alkylbenzene and one sp^3 S–H bond of the thiol in water.



Scheme IA.5.2.1.12. *Iron(II)-catalyzed synthesis of thioesters*

➢ $C_{(sp2)}$–P Bond Formation

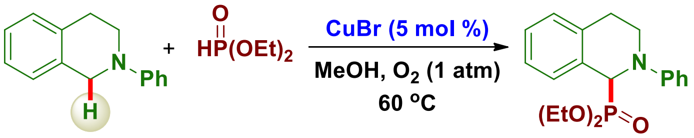
Singh group developed a highly efficient protocol for the preparation of various 3-phosphoimidazolepyridines via a $Mn(OAc)_2$-promoted cross-dehydrogenative coupling of substituted imidazopyridine and disubstituted phosphite (Scheme IA.5.2.1.13).[20]



Scheme IA.5.2.1.13. *Mn(II)-promoted phosphorylation of 2-phenyl imidazopyridine*

➢ $C_{(sp3)}$–P Bond Formation

Li group reported an efficient cross-dehydrogenative coupling (CDC) between sp^3 C–H and H–P bonds using copper salt as catalyst and molecular oxygen as the terminal oxidant. This methodology provides an easy access to biologically important α-aminophosphonates (Scheme IA.5.2.1.14).[21]



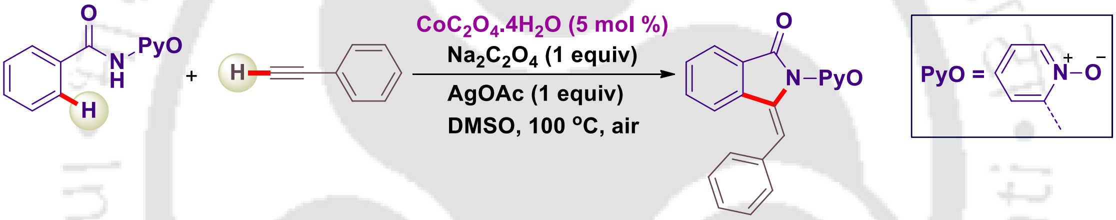
Scheme IA.5.2.1.14. *Copper(I)-catalyzed synthesis of α-aminophosphonates via CDC between sp^3 C–H and P–H bonds*

IA.5.3. Directing Group Assisted Cross-Dehydrogenative Coupling: The most powerful and appealing results are obtained when both directing group and cross-dehydrogenative coupling strategy works in tandem. This approach provides selective functionalization of *ortho* C–H bonds to form C–C or C–X (X = hetero atom) bonds. This methodology has advantage in term of both regioselectivity and chemoselectivity and offers a higher degree of C–H bond cleavages.

IA.5.3.1. Representative Examples of Directed CDC Reactions

- ***Ortho*-Alkynylation**

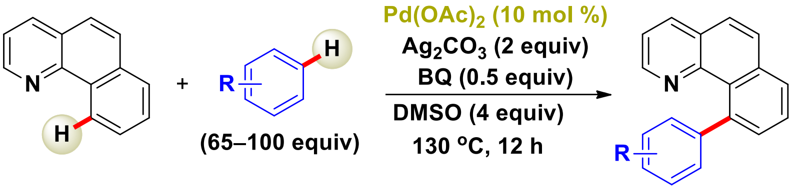
The group of Song reported a Co(II)-catalyzed *ortho*-alkynylation/annulation of arenes with terminal alkynes (Scheme IA.5.3.1.1).[22] This protocol is characterized by wide substrate scope utilizing cheap cobalt catalysts, and offers a new approach to 3-methyleneisoindolin-1-one, which can be converted into an oxadiazine salt in one step.



Scheme IA.5.3.1.1. *Cobalt(II)-catalyzed auxillary assisted alkynylation of arenes*

- ***Ortho*-Arylation**

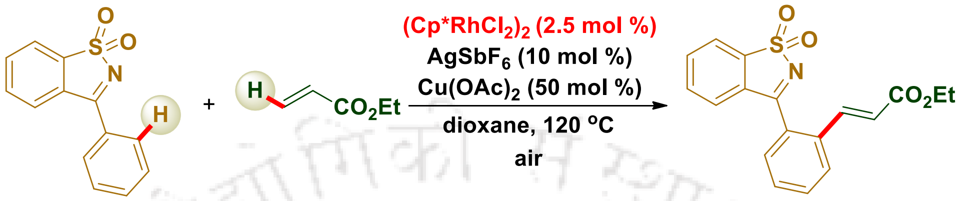
Sanford *et al.* reported a Pd-catalyzed reaction with a highly chemo- and regioselectivity by the oxidative cross-coupling of aromatic C−H bonds. A variety of directing arenes such as benzo[*h*]quinoline, 2-arylpyridine, 1-arylpyrazole, 2-arylpyrimidine and 8-methylquinoline derivatives were effectively employed under this reaction condition providing similar cross-coupled products using Ag_2CO_3 and *p*-benzoquinone as terminal oxidants (Scheme IA.5.3.1.2).[23]



Scheme IA.5.3.1.2. *Pd(II)-catalyzed direct biaryl coupling of benzo[h]quinoline*

➢ $C_{(sp2)}$–$C_{(sp2)}$-(Alkenyl) Bond Formation

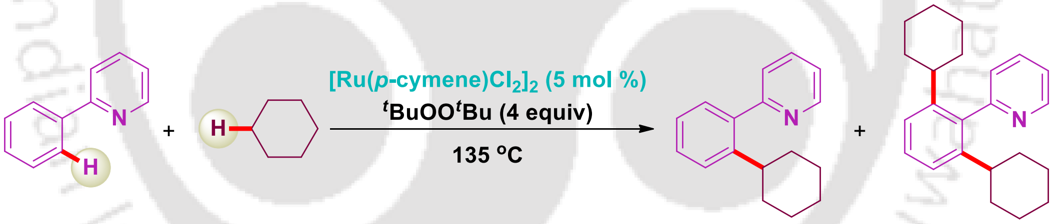
A useful method for the synthesis of *ortho* olefinated ketimines from readily accessible cyclic *N*-sulfonyl ketimines and various olefins has been developed by Wei *et al.* (Scheme IA.5.3.1.3) using Rh(III)/Ag(I) combination.[24] $Cu(OAc)_2$ in combination with air serves as the oxidant to regenerate the catalyst.



Scheme IA.5.3.1.3. *Rhodium(III)-catalyzed C–H olefination of Cyclic N-Sulfonyl Ketimines*

➢ $C_{(sp2)}$–$C_{(sp3)}$ Bond Formation

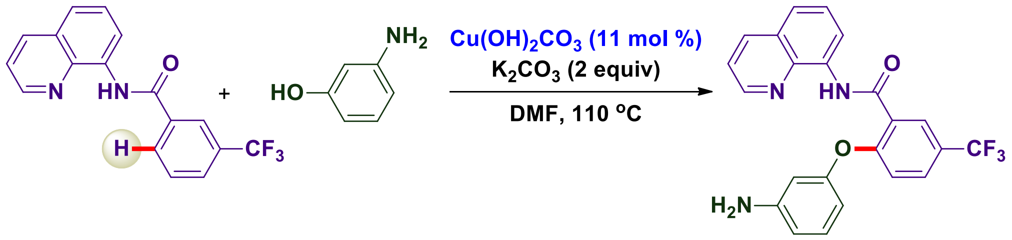
A novel C–C bond formation based on the direct oxidative C_{sp2}–H/C_{sp3}–H coupling of directing arenes and cycloalkanes has been developed by Li group in the presence of Ru(II)-catalyst and di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme IA.5.3.1.4).[25]



Scheme I.5.3.1.4. *Ru(II)-catalyzed C–H cycloalkylation of 2-phenylpyridine*

➢ $C_{(sp2)}$–O Bond Formation

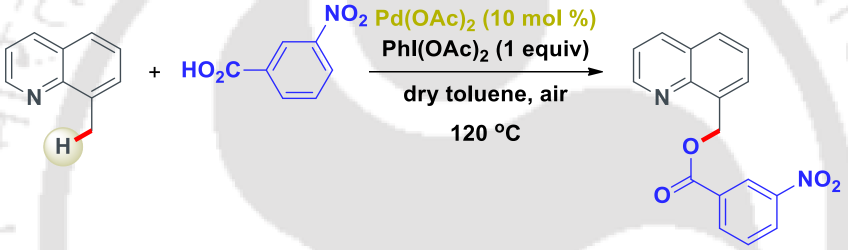
Daugulis group developed a method for direct alkoxylation and phenoxylation of β-sp^2 C–H bonds of benzoic acid derivatives and γ-sp^2 C–H bonds of amine derivatives using auxiliary-assisted C–H functionalization approach (Scheme IA.5.3.1.5).[26] The reaction was performed using $CuCO_3.Cu(OH)_2$ as catalyst, air as the oxidant, phenol or alcohol as coupling partners in DMF, pyridine, or DMPU solvent, and K_2CO_3, tetramethylguanidine, or K_3PO_4 as base at 70–130 °C.



Scheme IA.5.3.1.5. *Copper(II)-catalyzed auxillary assisted C–H alkoxylation*

➢ $C_{(sp3)}$–O Bond Formation

Cheng group reported a chelation-assisted palladium-catalyzed acyloxylation of the sp^3 C–H bond of benzyl group with carboxylic acid employing $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme IA.5.3.1.6).[27a] The procedure tolerates a series of functional groups, providing the acyloxylated products in good to moderate yields.

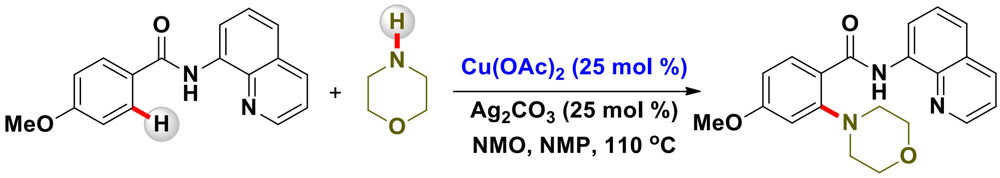


Scheme IA.5.3.1.6. *Palladium(II)-catalyzed acyloxylation of the benzylic sp^3 C–H bond*

Later, Sahoo group reported a novel *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) directed highly selective acetoxylation of the unactivated C(sp^3)–H bond.[27b] This method provides convenient access to α,α′-disubstituted-β-hydroxycarboxylic acids.

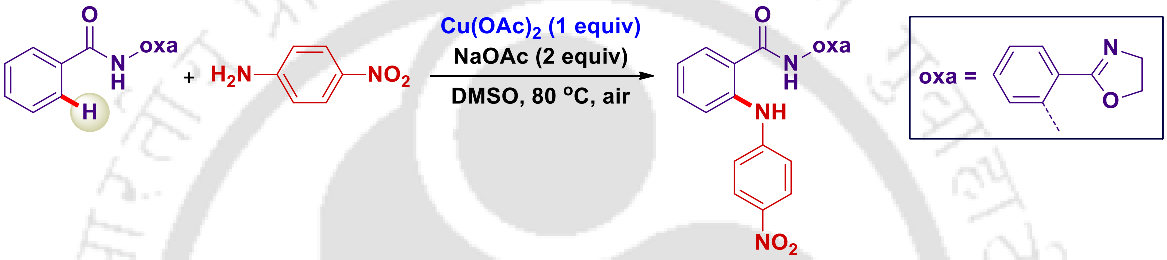
➢ ***Ortho*-Amination via C_{sp2}-H / N_{sp3}–H**

A 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 auxiliary (Scheme IA.5.3.1.7).[28a] 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 IA.5.3.1.7. *Aminoquinoline directed copper(II)-catalyzed amination of arenes*

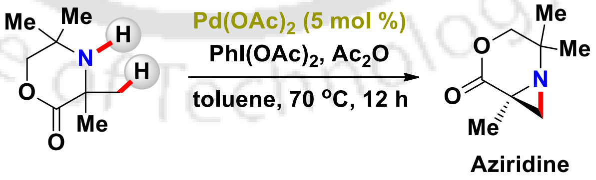
In a recent report, Yu group describes a Cu(II)-mediated C−H amination of arenes with a variety of anilines (Scheme IA.5.3.1.8).[28b] The exceptional compatibility of this amination with multiple heteroatoms present in both reactants renders this reaction highly valuable.



Scheme IA.5.3.1.8. *Copper(II)-catalyzed amide directed amination of arenes*

➢ Amination via C_{sp2}-H / N_{sp3}–H

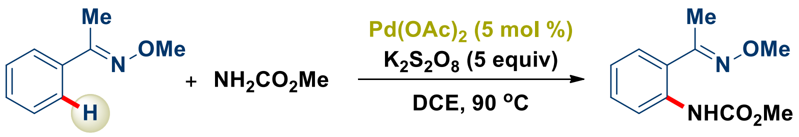
Gaunt group developed a novel Pd-catalyzed intramolecular C_{sp3}–H amination that proceeds through an unusual four-membered-ring cyclopalladation pathway (Scheme IA.5.3.1.9).[29] Methyl group present adjacent to an unprotected secondary amine underwent intramolecular cyclization and transform into synthetically versatile nitrogen heterocycle such as aziridines and β-lactams *via* carbonylation processes.



Scheme IA.5.3.1.9. *Amine directed Pd(II)-catalyzed intramolecular sp^3 C–H amination*

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

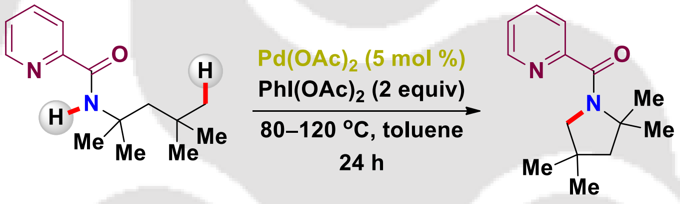
An intermolecular directed CDC reaction for the C–N bond formation was developed by Che group using Pd(II) as the catalyst and pyridine and oxime ethers as directing groups (Scheme IA.5.3.1.10).[30] In this Pd(OAc)$_2$-catalyzed protocol, a combination of $K_2S_2O_8$ and NH_2R was used to introduce the nitrogen functionality.



Scheme IA.5.3.1.10. *Ketoxime ether directed palladium(II)-catalyzed amidation of arenes*

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

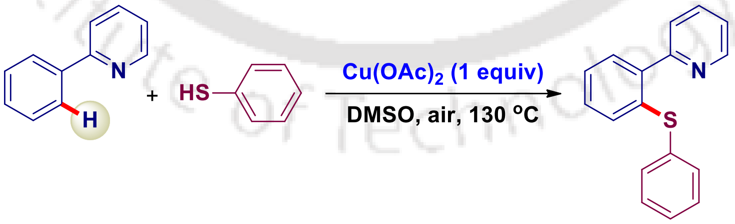
Daugulis group developed Pd(II)-catalyzed intramolecular amidation of unactivated sp^3 carbon using picolinamides as directing auxiliary (Scheme IA.5.3.1.11).[31a] Later on a similar type of auxiliary directed intramolecular sp^3 C–H amidation methods were reported by Chen, Ge and Kanai groups.[31b-f]



Scheme IA.5.3.1.11. *Pd(II)-catalyzed intramolecular sp^3 C–H amidation*

- **$C_{(sp2)}$–S Bond Formation**

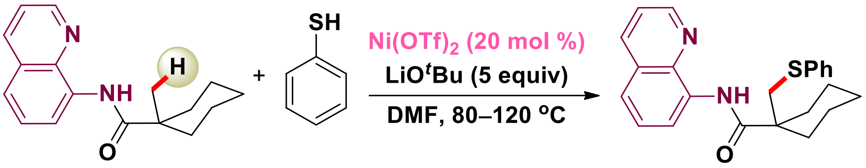
Yu group has accomplished a Cu(II)-promoted direct sulfenylation at sp^2 C–H of 2-arylpyridine using benzene thiol as the coupling partner (Scheme IA.5.3.1.12).[32]



Scheme IA.5.3.1.12. *Copper(II)-catalyzed ortho-thiolation of arenes*

- **Sulfenylation via C_{sp3} / S_{sp3}-H**

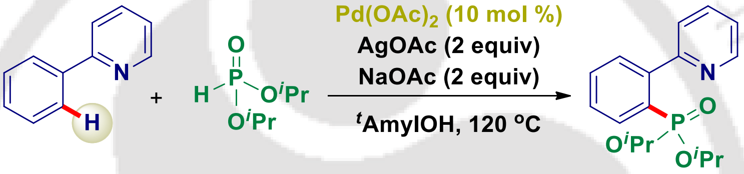
Group of Shi demonstrated the 8-aminoquinoline directed nickel-catalyzed thiolation of sp^3 C–H bond to form thioethers (Scheme IA.5.3.1.13).[33]



Scheme IA.5.3.1.13. *Ni(II)-catalyzed sp^3 C–H sulfenylation*

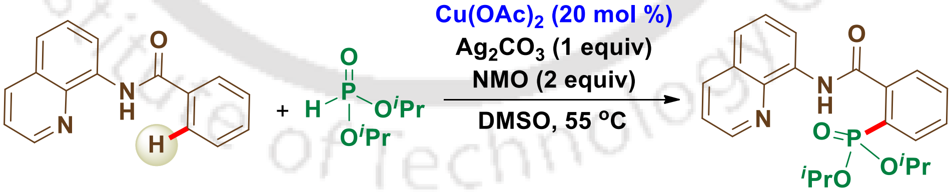
- **C$_{(sp2)}$–P Bond Formation**

Yu group has developed a Pd(II)-catalyzed protocol for the C−H phosphorylation of 2-arylpyridines with both H-phosphonates and diaryl phosphine oxides as suitable coupling partners for this reaction (Scheme IA.5.3.1.14).[34a] A variety of heterocyclic substrates were phosphorylated to give N−P bidentate compounds that are potentially useful in medicinal chemistry and catalysis.



Scheme IA.5.3.1.14. *Palladium(II)-catalyzed C−H phosphorylation of 2-phenylpyridine*

A Cu(II)-catalyzed phosphorylation of the *ortho* C–H bonds of benzamides using 8-aminoquinoline as a bidented directing group with H-phosphonate has been developed by Yu group (Scheme IA.5.3.1.15).[34b] This procedure shows high functional group compatibility and selectively giving mono-substituted products.



Scheme IA.5.3.1.15. *Copper(II)-catalyzed C−H phosphorylation of benzamides*

IA.5.4. An Array of Exceptions: Reactions which are not included in the above three classes of C–H functionalization are discussed below.

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

Introduction of an internal oxidative functional group to enable the site 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[35] whereas benzophenone and hydroperoxide derivatives have been employed as internal oxidant for the C–H activation through a single-electron-transfer.[36]

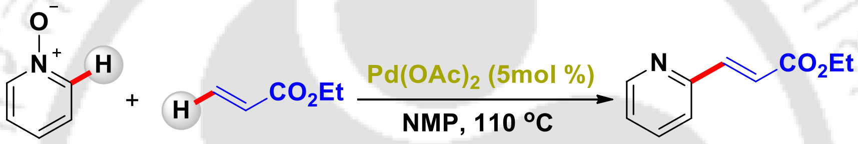
Advantages of Redox Neutral Process:

(i) No external oxidants needed for the catalytic cycle.

(ii) Simple and mild reaction condition with good functional group tolerance.

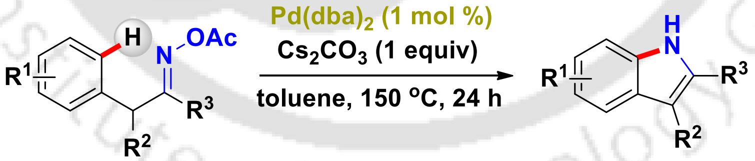
(iii) High regioselectivity.

Oxidizing group directed redox-neutral cross-coupling reaction was introduced by Cui and co-worker in 2009. They employed pyridine-*N*-oxide as substrate cum oxidant in a palladium-catalyzed Heck reaction with an olefin (Scheme IA.5.4.1.1).[37]



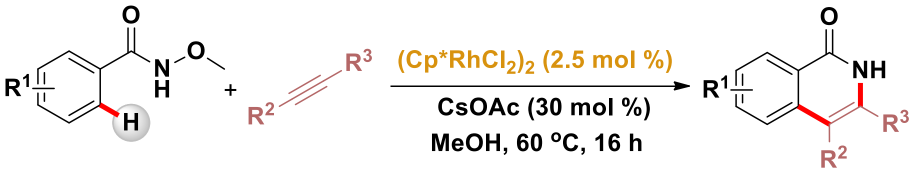
Scheme IA.5.4.1.1. *Pd(II)-catalyzed redox-neutral alkenylation*

Further advancement in this redox-neutral process was made by Hartwig for the indole synthesis using oxime ester as the oxidizing directing group. This palladium-catalyzed aromatic C−H bond amination process requires relatively low catalyst loading of 1 mol % under redox-neutral conditions (Scheme IA.5.4.1.2).[38]



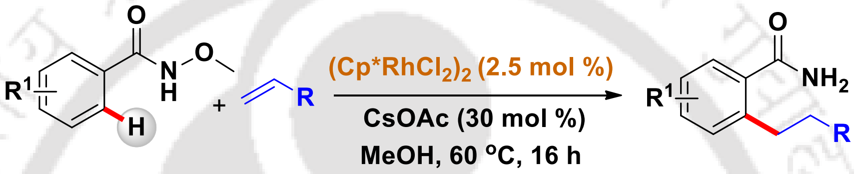
Scheme IA.5.4.1.2. *Pd-catalyzed redox-neutral intramolecular ortho sp^2 C–H amination*

Fagnou group describes a Rh(III)-catalyzed external oxidant-free process to access the isoquinolone motif via cross-coupling/cyclization of benzhydroxamic acid with alkynes (Scheme IA.5.4.1.3).[39a-b]



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

Glörious group introduced a Rh(III)-catalyzed external-oxidant-free process for the oxidative olefination of *N*-methoxybenzamides by directed C–H bond activation. The reaction features a regioselective cleavage of a C–H bond on the benzhydroxamic acid coupling partner and N–O bond act as an internal oxidant (Scheme IA.5.4.1.4).[39c]

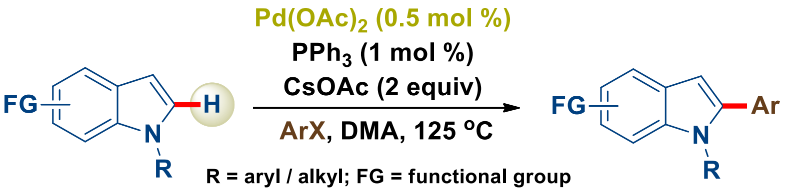


Scheme IA.5.4.1.4. *Rh(III)-catalyzed redox neutral intermolecular ortho sp^2 C–H alkenylation*

Similar directing group assisted redox-neutral annulation strategies were further extended by Glörius,[39c,40a] Rovis,[40b-e] Cramer[40f-g] and others.[40h-n]

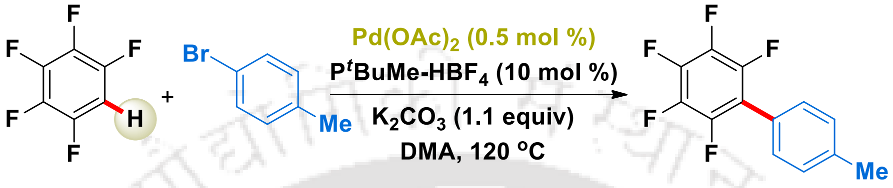
IA.5.4.2. Non Directed C-H Functionalization via C_{sp2}-H and C_{sp2}-X Coupling

Heck reaction (also called Mizoroki-Heck reaction) represents the earliest example of C–C bond formation via C–H functionalization of olefin through coupling with unsaturated halides in presence of base and Pd(0) catalyst.[41a-b] Later on Sames group reported a Pd(II)-catalyzed C2-selective C–H arylation of activated *N*-substituted indoles by coupling with aryl halides in a good yields, and excellent functional group tolerance (Scheme IA.5.4.2.1).[41c]



Scheme IA.5.4.2.1. *Pd(II)-catalyzed C2 arylation of electron rich indoles*

Fagnou *et al.* introduced a Pd(II)-catalyzed direct coupling of electron-withdrawing perfluorobenzene with a variety of aryl halides. Inverse reactivity is observed compared to the common electrophilic aromatic substitution pathway since electron-deficient and acidic C−H arene reacts preferentially. Computational studies indicates that C−H bond cleavage occurs via a concerted carbon−palladium and carbon−hydrogen bond cleaving event involving a carbonate or a bromide ligand (Scheme IA.5.4.2.2).[42]



Scheme IA.5.4.2.2. *Pd(II)-catalyzed direct arylation of electron deficient arenes*

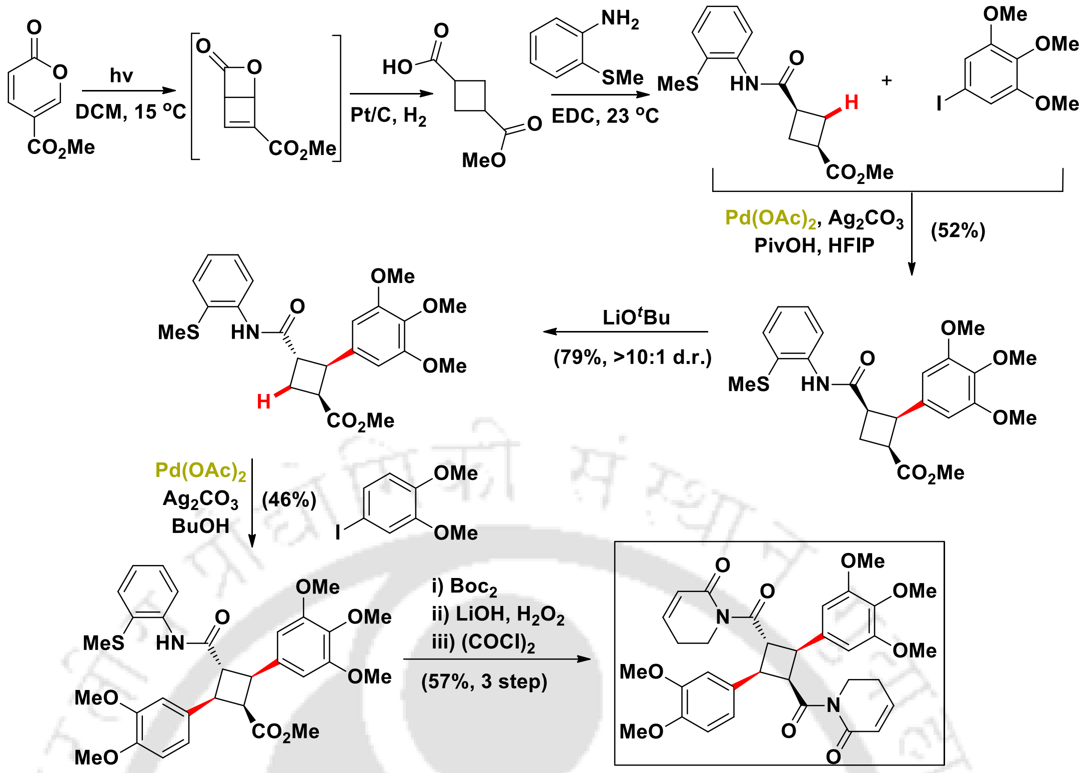
IA.6. C–H Activation: A New Archetype for Total Synthesis

As C–H functionalization process has become more and more popular among the synthetic organic chemists, people have started its application in total synthesis of complex natural products even, as late stage manipulation in complex targets.[43] Herein mentioned below is one examples of total synthesis showcasing creative and ingenious incorporation of C–H activation as a strategic maneuver compared to the traditional methods, illuminating a new paradigm in strategic synthetic design.

IA.6.1. Total Synthesis of Piperaborenine B

The piperarborenines were isolated from the stems of the creeping shrub *Piper arborescens* and exhibit in vitro cytotoxicity against P-388, HT-29, and A549 cancer cell lines ($IC_{50} < 4$ μg/mL). This family of natural products can be classified into two distinct stereochemical classes and both are arising from the head-to-tail dimerization of piplartine-type monomers with varying degrees of oxidation on the aryl rings.

Baran group demonstrated the total synthesis of this important natural product which exploits two successive C–H activation reactions as key steps (Scheme IA.6.1.1).[44] This short route for the synthesis of piperaborenine B demonstrate a power of guided C–H functionalization logic to enable a fundamentally new approach to cyclobutane natural products. The notable step of this synthesis is the Pd(II)-catalyzed C–H activation on a cyclobutane ring. This is the first example of sequential sp^3 C–H arylation reaction performed in any natural product synthesis.



(piperaborenine B)

Scheme IA.6.1.1. *Total synthesis of piperaborenine B*

IA.7. References

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CHAPTER IB

IB. An Outline of Metal-Catalyzed Cascade Reactions

IB.1. Introduction

Synthetic organic chemistry have achieved tremendous transformations in past six-seven decades. Earlier, chemists used to synthesized only simple molecules, however today's organic chemists can synthesized highly complex molecule such as palytoxin, maitotoxin and other complex molecule in terms of creating many bonds, rings and stereocenters in a single transformation.[1] Especially, the last few decades has countersigned a revolution in chemical synthesis. Despites this achievements and importance of chemistry in our daily life its public image has been far from acceptable. This might be due to increasing importance of environmental issues to our society and the public perception that chemistry has been negatively influencing the ecological balance. So, today's challenge is not only what we can synthesize, but also how we achieve it in a sustainable manner.

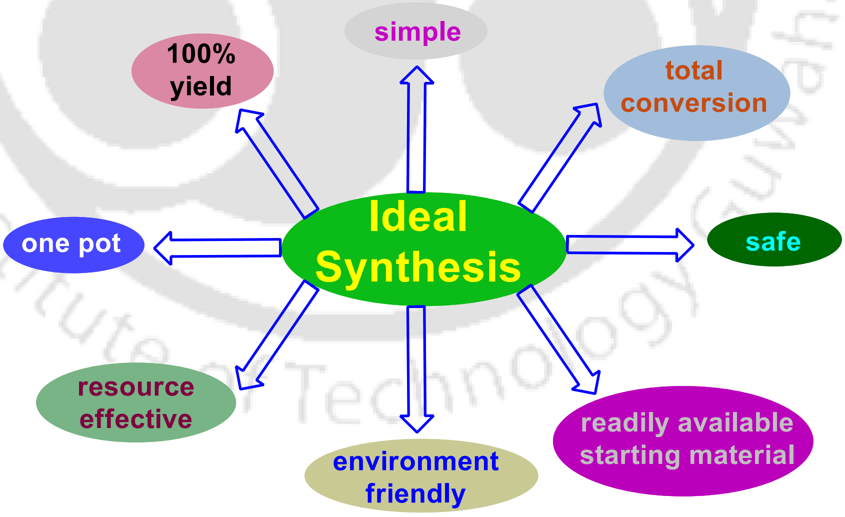


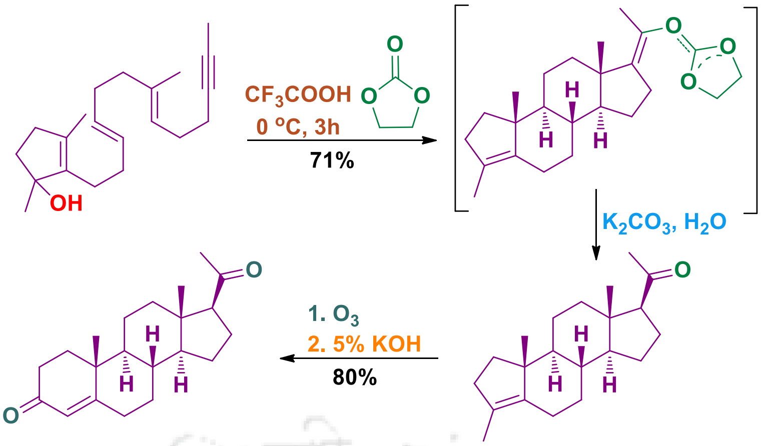
Figure IB.1.1. *The ideal synthesis as proposed by Wender*

Major challenges during chemical production are the handling of the waste product, eco-friendly procedures, preservation of resources and enhancement in the efficiency of the production. If these challenges resolved, it is not only better for the environment but also reduction in the production cost. In this respect step economy is an important factor, since accessibility highly depends on the number of steps required to reach the desired compound.[2] The other important issues currently challenging organic chemists are nicely summarized in the ideal synthesis proposed by Wender *et al.* (Figure IB.1.1).[3]

Usually the synthesis of target organic compound involves a stepwise formation of individual bonds. This procedure requires each step workup followed by the isolation of intermediate. Therefore, considering the issues related to chemical transformation one must seek procedures that enables the construction of several bonds in a cascade fashion, *i.e.* several C–C, C–O, C–S or C–N bond can be constructed without the isolation of intermediates.[4] Thus, it is apparent that this kind of transformation would allow to minimize waste and hence making the waste management redundant. Hence, the reaction would allow the synthesis of organic compounds in an ecologically and economically favorable fashion. Such kind of transformation has been named as “domino reaction or domino process”. It is also termed as cascade reaction or cascade transformation with few exceptions. These types of reaction involves two or more bond formation under an identical reaction condition, where the later transformation takes place at the functionalities generated in the previous bond forming step. This strategy is advantageous in terms of number of bonds formed in one sequence, increasing in molecular complexity and suitability for a general application.

IB.2. Historical Background

Nature synthesized a variety of compounds such as fatty acids from acetate,[5] steroid,[6] progesterone,[7] daphnilactone A[8] and (+)-codaphniphylline[9] via cascade reactions. In nature cascade process are more common, but cannot be compared directly with reaction performed in laboratory as the former involve multi-enzymes which allows the catalysis of different steps. A beautiful example of cascade reaction taking place in nature is the biosynthesis of steroid from squaline epoxide which is transformed selectively into lanosterol with the formation of four C–C bonds and generation of six stereogenic centers. This strategy has been utilized by Johnson for the synthesis of progesterone by an acid catalyzed domino cyclization of the monocyclic trieneyne (Scheme IB.2.1).[7]



Scheme IB.2.1. *Biomimetic domino synthesis of progesterone*

Schöpf and Robinson[10] performed first cascade reaction for the synthesis of natural product tropinone and cocaine alkaloid structural component by putting together of a mixture of succinaldehyde, methylamine and acetonedicarboxylic acid. The key step in this synthesis is a double Mannich reaction. Mannich reaction[11] is presumably the first domino reaction described in the literature.

IB.3. Classification of Cascade Reactions

To differentiate between any two reactions and development of new cascade reactions, these transformations have been classified in to different categories. All the reactions do not meet the criteria as set by its definition. Tietze defined domino reactions as, *reactions involves two or more bond forming process under the same reaction conditions without adding additional reagents and catalysts and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*. Also if a substrate bears several functionalities and all of them underwent transformation individually in the same pot is not considered as a cascade reaction. The preliminary step of any reaction involving formation of reactive intermediate such as carbocation or carbanion is not included as the step of the reaction. However, formation of diene by retro-Diels-Alder reaction with a subsequent cycloaddition would be considered as a domino reaction. Based on the nature of the first step in the mechanism a cascade reaction can be classified into following categories.

1. Cationic Domino Reaction
2. Anionic Domino Reaction
3. Radical Domino Reaction
4. Pericyclic Domino Reaction
5. Photochemically-Induced Domino Reaction
6. Transition Metal-Induced Domino Reaction
7. Domino Reaction Initiate by Oxidation or Reduction
8. Enzyme-Induced Domino Reaction

Combination of the reactions with the same mechanism in every step is termed as homo-domino reactions such as cationic-cationic, anionic-anionic, radical-radical, pericyclic-pericyclic and transition metal-catalyzed reactions and are found frequently in the literature, while sequences of reaction with different mechanisms in every step are called as hetero-domino reaction. Some very powerful hetero-domino reactions such as the anionic-pericyclic or even anionic-pericyclic-pericyclic sequence with different kind of mechanism are also reported.

Since the work reported in this thesis solely belongs to transition-metal assisted cascade transformations, description pertaining to this is only discussed here.

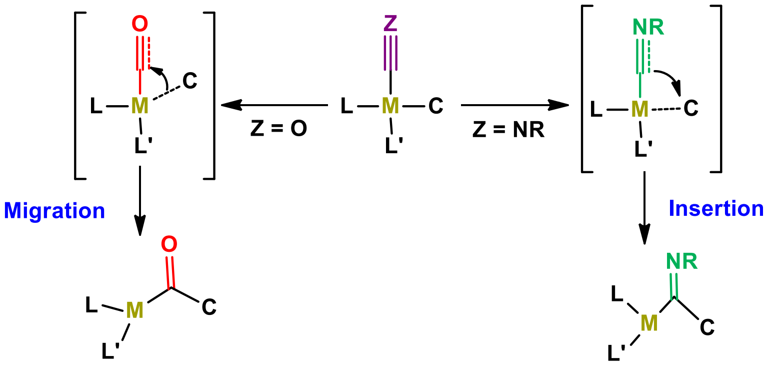
IB.4. Transition Metal-Induced Cascade Reactions

Preserving the functional group in a molecule during the synthetic transformation is one of the challenging tasks for the synthetic chemists during cascade reactions. Therefore, developing a good combination is required to address such issues. In last few decades use of transition metals in organic transformation has increased tremendously. Therefore, the use of transition metals in cascade reactions will be of immense importance. Poli and co-worker in 2002 classified transition metal-catalyzed cascade reaction as pure cascade processes that utilizes single metal catalyst during the formation of multiple bonds in a single catalytic cycle and the pseudo cascade processes that utilizes one or more metals in the formation of multiple bonds in a distinctly multiple catalytic cycle.[12] According to MacMillan and co-workers[13] pseudo cascade reaction involving only one metal also included as cascade catalysis. Various transition metals such as Cu, Pd, Ru, Rh, Ir, Mn, Fe, Ag, Co, and Au have been utilized in the cascade reactions.

However, the chemistry of palladium, silver and copper are versatile and quite well understood. Therefore, there are numerous reports on palladium, silver and copper-catalyzed cascade reactions. Recent examples of the palladium-catalyzed oxidative migratory insertion of isocyanides for heterocycles synthesis and reactions involving *o*-alkynylanilines and phenyl isothiocyanates catalyzed by different transition metal are discussed below.

IB.4.1. Representative Examples of Pd-Catalyzed Migratory Insertion of Isocyanides Leading to Heterocycles

Isocyanides are highly versatile reagents having widespread applications in organic, medicinal and combinatorial chemistry.[14] Because of the isoelectronic nature of isocyanides with CO, they shows similar kind of reactivity towards palladium and undergoes analogous transformation. Isocyanides have the advantage over CO as isocyanides are usually liquids or solids as a result easy to handle and maintain desired stoichiometry, whereas CO is a toxic gas and used in excess quantity under a high pressure. Moreover, isocyanides can bear diverse substituents on nitrogen atom which make them more flexible. Therefore, palladium-catalyzed isocyanides insertion reactions offer a great opportunity for the synthesis of fine chemicals bearing nitrogen functionality. As a result this kind of chemistry has seen a surge in recent years. Insertion of isocyanides into M–C bonds start with the initial coordination with metal center by the lone pair electron present onto the carbon atom followed by a rapid migratory insertion into the adjacent M–C bond. In contrast to CO insertion, whose mechanism involves an anionic ligand migration to the carbon atom of CO ligand, the isocyanides insertion usually occurs as the true insertion of carbon atom into M–C bond. Detailed study about isocyanides insertion into palladium-aryl, palladium-alkyl and palladium-allyl bond has been reported by various researchers.[15] In recent time it is observed that isocyanides differs in electronic and steric factor have the same coordinating ability with Pd(II) species but different rate of migratory insertion.[16] Many excellent reviews are available that describe the reactivity of isocyanides and their use in organic synthesis.[17]



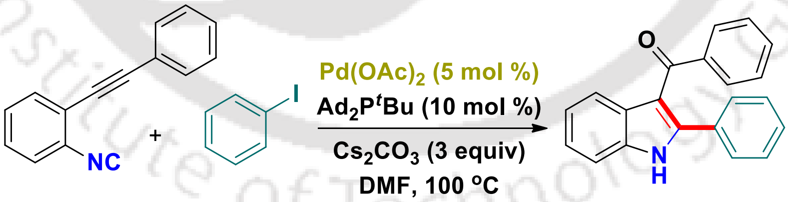
Scheme IB.4.1.1. *Mechanism of CO and isocyanide insertion*

Few examples of palladium-catalyzed heterocycles synthesis involving migratory insertion of isocyanides are given below.

IB.4.1.1. Heterocycles Synthesis via C–C Bond Formation

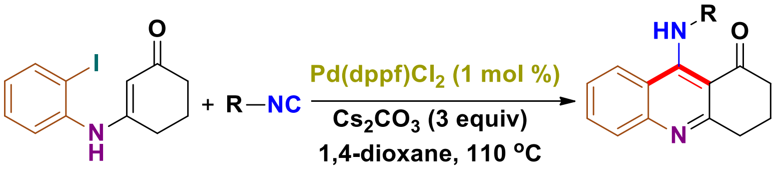
In the past few years palladium-catalyzed C–C bond formations for the construction of heterocycles have been extensively investigated by various groups. Few representative examples are given below.

Takemoto and co-worker developed a cascade protocol for the synthesis of 3-acyl-2-arylindole via palladium-catalyzed isocyanide insertion and oxypalladation of alkyne (Scheme IB.4.1.1.1).[18] In this process construction of two new C–C bond takes place via isocyanide insertion. This strategy was extended for the synthesis of tetracyclic indole skeleton by introducing an internal nucleophile.



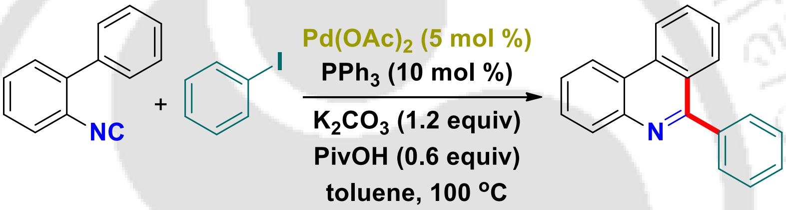
Scheme IB.4.1.1.1. *Palladium-catalyzed synthesis of 3-acyl-2-arylindole*

Ji *et al.* achieved a Pd(dppf)$_2$Cl$_2$-catalyzed synthesis of 4-aminoquinoline derivatives through a cascade reaction of isocyanides and enaminones (Scheme IB.4.1.1.2).[19] This protocol opens a new strategy for the synthesis of drugs based on 4-aminoquinoline derivatives in almost quantitative yield using very low catalyst loading (1 mol %).



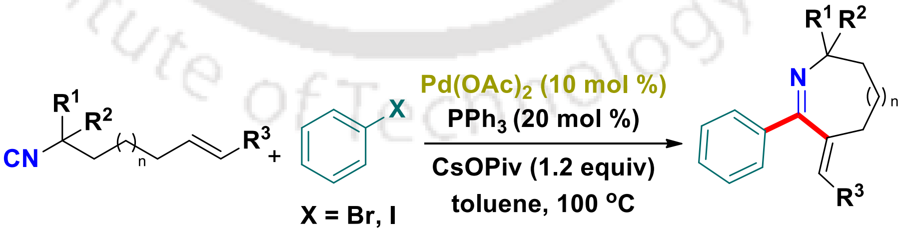
Scheme IB.4.1.1.2. *Pd-catalyzed synthesis of 4-aminoquinolines from enaminones*

A Pd-catalyzed intramolecular C(sp^2)–H imidoylation for the synthesis of *N*-heterocycles was developed by Zhu and co-worker (Scheme IB.4.1.1.3).[20] The process involves sequential intermolecular insertion of isocyanide to an aryl-Pd(II) intermediate and intramolecular aromatic C–H activation. Furthermore, this strategy was extended for the alkyl-Pd(II) intermediate lacking β-hydrogen for the synthesis of bis-heterocyclic scaffold where three sequential C–C bond formation takes place.



Scheme IB.4.1.1.3. *Intramolecular imidoylation for the N-heterocycle synthesis*

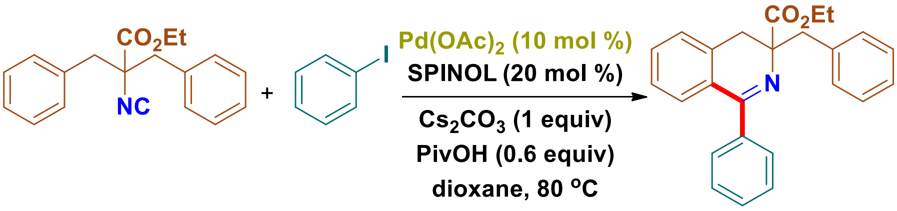
Zhu *et al.* demonstrated a Pd-catalyzed intramolecualr imidoylative Heck reaction for the synthesis of cyclic ketoimines from functionalized isocyanides (Scheme IB.4.1.1.4).[21] Consecutive isocyanide and alkene insertion into aryl or alkyl-Pd(II) intermediate results in the formation of five to seven member ketoimines in the presence of base CsOPiv.



Scheme IB.4.1.1.4. *Five-seven member ketoimines synthesis via imidoylative Heck reaction*

Recently, a facile and efficient pathway for the synthesis of 3,4-dihydroisoquinolines containing C3 quaternary stereogenic centers has been developed by You and co-worker (Scheme IB.4.1.1.5) via enantioselective C$_{sp2}$–H imidoylation using a Pd-catalyst.[22]

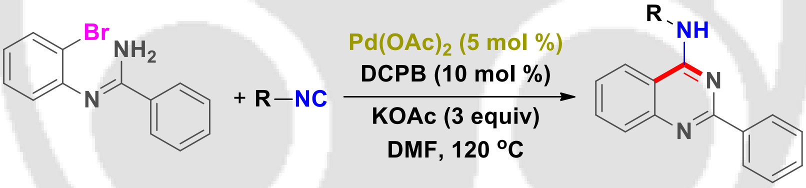
Tetrahydroisoquinolines containing two chiral centers were easily obtained by selective reduction which may serve as important building blocks in organic synthesis for biological evaluation or ligand design.



Scheme IB.4.1.1.5. *Pd-catalyzed enantioselective* $C_{(sp2)}$*–H imidoylation*

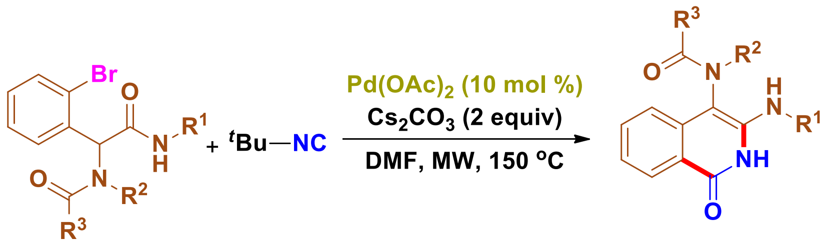
IB.4.1.2. Heterocycles Synthesis via C–C and C–N Bonds Formation

Orru *et al.* developed an efficient palladium-catalyzed intramolecular imidoylation of *N*-(2-bromoaryl)amidines for the construction of 4-aminoquinazoline derivatives (Scheme IB.4.1.2.1).[23] The use of biphenyl phosphine ligand DCPB along with the base KOAc is effective for this transformation. The products formed in this approach are interesting from medicinal chemistry prospective.



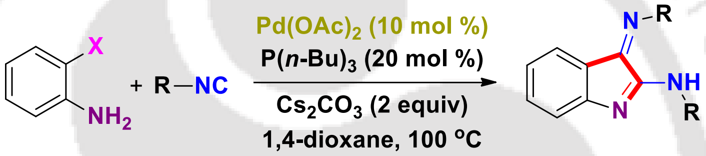
Scheme IB.4.1.2.1. *Pd-catalyzed construction of 4-aminoquinazoline derivatives*

A microwave assisted Pd-catalyzed cascade reaction for the synthesis of a highly diverse isoquinolin-1(2*H*)-one derivative from isocyanide and amide precursors has been reported by the Chauhan and co-workers (Scheme IB.4.1.2.2).[24] This protocol provides a ligand free pathway for the synthesis of biologically important molecules in a straightforward and atom-economical fashion. The transformation takes place through tandem isocyanide insertion, intramolecular cyclization followed by Mazurciewitcz-Ganesan type sequence to afford the product in good yields. Non requirement of phosphine ligands, use of microwave heating instead of conventional heating and shorter reaction times makes this process greener.



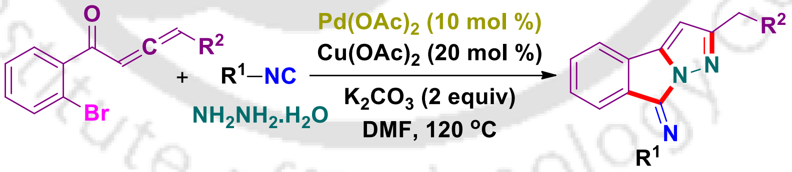
Scheme IB.4.1.2.2. *Ligand free Pd-catalyzed cascade synthesis of isoquinolin-1(2H)-one*

Jiang *et al.* introduced a palladium-catalyzed synthesis of 3-iminoindol-2-amines through cascade reaction involving isocyanides insertion followed by cyclization (Scheme IB.4.1.2.3).[25] In this transformation simultaneous insertion of two isocyanides takes place. Along with the $Pd(OAc)_2$ as catalyst, a ligand $P(n\text{-}Bu)_3$ and a base Cs_2CO_3 is required for the synthesis of 3-iminoindol-2-amines.



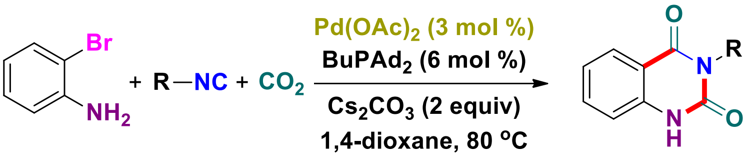
Scheme IB.4.1.2.3. *Synthesis of 3-iminoindol-2-amines via double isocyanides insertion*

Zhang and co-worker reported an efficient palladium-catalyzed synthesis of pyrazolo[5,1-*a*]isoindoles through a one-pot three component cascade reactions of 1-(2-bromophenyl)buta-2,3-dien-1-ones with isocyanide and hydrazine (Scheme IB.4.1.2.4).[26]



Scheme IB.4.1.2.4. *Pd-catalyzed one pot synthesis of pyrazolo[5,1-a]isoindoles*

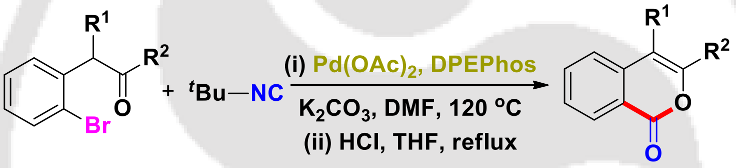
Very recently Beller group developed a Pd-catalyzed three-component reaction of 2-bromoanilines, carbon dioxide and isocyanides for the synthesis of N_3-substituted quinazoline-2,4(1*H*,3*H*)-diones (Scheme IB.4.1.2.5).[27] The present synthetic strategy is the first example in which a kinetically and thermodynamically unreactive carbon dioxide (CO_2) and reactive isocyanides (RNC) serves as C1-source in a transition metal-catalyzed three-component reaction. The protocol is completely regio- and chemoselective even at 1 atm CO_2.



Scheme IB.4.1.2.5. *Pd-catalyzed synthesis of quinazoline-2,4(1H,3H)-diones*

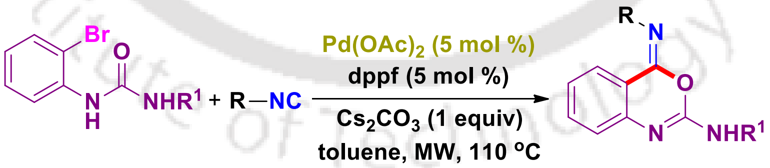
IB.4.1.3. Heterocycles Synthesis via C–C and C–O Bonds Formation

A novel and efficient strategy for the synthesis of isocoumarines and phthalides has been developed by Ji *et al*. For this purpose $Pd(OAc)_2$ was used as catalyst along with the DPEPhos ligand and K_2CO_3 as the base in DMF. Hydrolysis of intermediate is achieved by refluxing it in the presence of HCl in THF (Scheme IB.4.1.3.1).[28]



Scheme IB.4.1.3.1. *Pd-catalyzed synthesis of isocoumarines via isocyanide insertion*

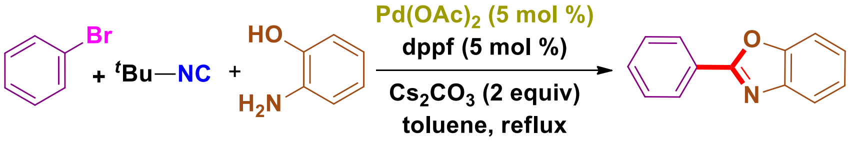
A microwave-assisted palladium-catalyzed isocyanide insertion into 2-bromophenylureas for the efficient synthesis of 4-substituted imino 4*H*-benzo[*d*][1,3]-oxazin-2-amines has been developed by Batra group (Scheme IB.4.1.3.2).[29]



Scheme IB.4.1.3.2. *MW-assisted synthesis of imino 4H-benzo[d][1,3]-oxazin-2-amines*

IB.4.1.3. Heterocycles Synthesis via C–C, C–N and C–O Bonds Formation

Lang and co-worker introduced a $PdCl_2$-catalyzed synthesis of benzoxazoles and oxazolines via three-component couplings of an aryl halide, isocyanide, and an amino alcohol (Scheme IB.4.1.4.1).[30] In this methodology isocyanides serve as the C1 synthon.

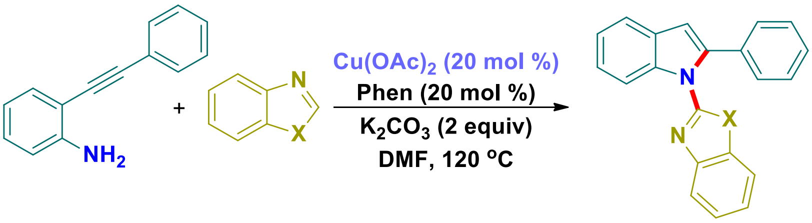


Scheme IB.4.1.4.1. *Pd-catalyzed three-component couplings for the synthesis of benzoxazoles*

IB.4.2. Representative Examples of Transition Metal-Assisted Heterocycles Synthesis from *o*-Alkynylaniline and Phenyl Isothiocyanate

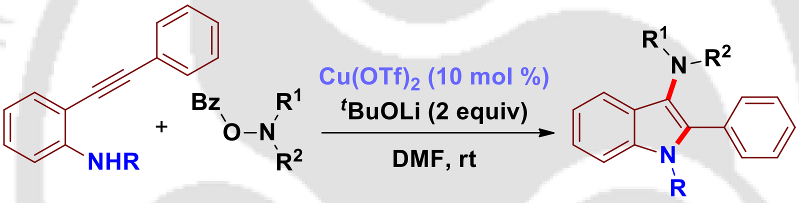
The development of new reactions derived from the readily available starting material with high product selectivity is most promising challenge in current organic synthesis. As a result organic chemists started heterocycles synthesis from the same set of substrate for the synthesis of different heterocyclic skeleton.[31] Alkyne and its derivative are most valuable chemical entities because of its easy availability and versatile reactivity. They can be utilized as molecular building blocks for the designing novel organic reactions and assembling functional materials.[32] With the recent advancement in transition metal-catalyzed transformations, they have been employed for the rapid access to complex molecular scaffold.[33] Among alkyne derivatives, 2-alkynylaniline and its derivatives are useful synthetic intermediates to assemble different indoles and *N*-heterocycles scaffolds. 2-Alkynylaniline derivatives can be easily prepared via classical Sonogashira reaction between 2-iodo/bromoaniline and terminal alkyne which are employed for the synthesis of various heterocycles having privileged molecular scaffold.[34] Various transition metals such as Pd, Rh, Cu, Ag, and Au are known to activate the internal alkyne for the development of a variety of methods for heterocycles synthesis. Transition metal-catalyzed cascade reactions involving 2-alkynylaniline have been proven to be powerful synthetic means for the construction of polycyclic heterocycles.[35] In a similar way, isothiocyanates are also useful synthons in organic chemistry especially for the synthesis of simple and spiro-fused heterocycles.[36] In recent years, heterocycles synthesis from 2-alkynylanilines and isothiocyanates have been extensively investigated. Few representative examples are discussed below.

Miura and co-worker developed a copper-catalyzed direct C–H/N–H coupling between amines and azoles which is followed by the benzannulation to form the corresponding *N*-azolylindole (Scheme IB.4.2.1).[37] In this domino process formation of two C–N bonds takes place in the presence of molecular oxygen as the sole oxidant. This protocol can be applied for the synthesis of the π-extended *N*-azolylbenzodipyrrole structure.



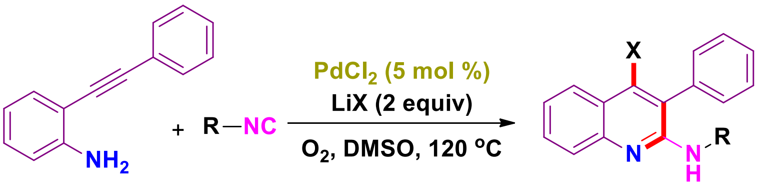
Scheme IB.4.2.1. *Copper-catalyzed synthesis of N-azolylindole*

Later, the same group developed a Cu-catalyzed annulative amination for the synthesis of 3-aminoindoles from *o*-alkynylanilines (Scheme IB.4.2.2).[38] In this transformation *O*-acylated hydroxylamine is used as the amine source in presence of base ^{t}BuOLi at room temperature.



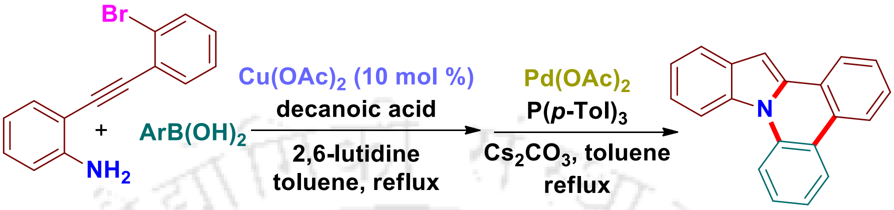
Scheme IB.4.2.2. *Copper-catalyzed synthesis of 3-aminoindoles*

Jiang *et al.* achieved a palladium-catalyzed intermolecular oxidative cascade cyclization of 2-alkynylanilines with isocyanides for the synthesis of 4-halo-2-aminoquinolines (Scheme IB.4.2.3).[39] In this transformation lithium halides (LiCl or LiBr) are utilized as halogen source and atmospheric oxygen as terminal oxidant. Furthermore, this strategy was extended for the synthesis of 6*H*-indolo[2,3-*b*]quinoline derivatives via an intramolecular Buchwald-Hartwig cross-coupling reaction.



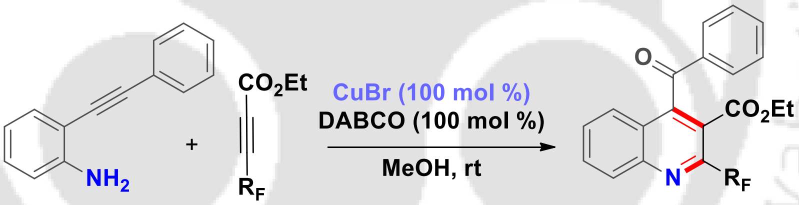
Scheme IB.4.2.3. *Pd-catalyzed synthesis of 4-halo-2-aminoquinolines*

Wang *et al.* developed a one pot bimetallic (Cu/Pd)-catalyzed tandem reaction for the synthesis of polycyclic indole derivatives (Scheme IB.4.2.4).[40] Initially, the 1,2-disubstituted indoles is formed via a Cu-catalyzed domino coupling cyclization process under an aerobic condition followed by a Pd-catalyzed intramolecular direct $C_{(sp2)}$–H arylation in the same pot.



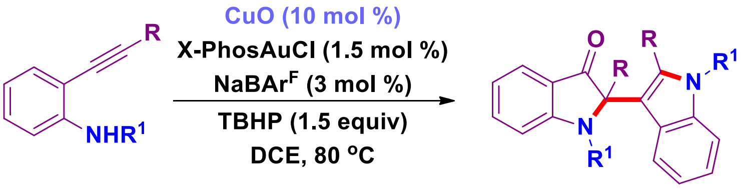
Scheme IB.4.2.4. *Cu/Pd-catalyzed synthesis of polycyclic indoles*

A Cu(II)-promoted aerobic cascade cyclization of 2-alkynylanilines and methyl perfluoroalk-2-ynoates for the synthesis of 4-carbonyl-2-perfluoroalkylquinolines was developed by Cao *et al.* (Scheme IB.4.2.5).[41] The reaction affords quinoline derivatives in good to excellent yields with the tolerance of a wide range of functional groups.



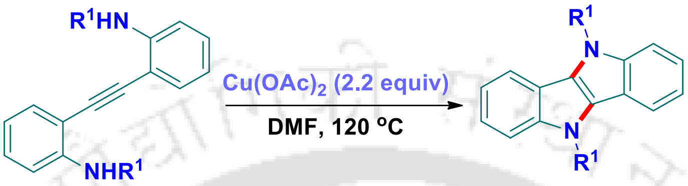
Scheme IB.4.2.5. *Cu(II)-promoted synthesis of substituted quinolines*

Zhao group demonstrated a new route for the synthesis of 2,3′-bisindolin-3-one derivatives via Au/Cu-co-catalyzed cascade reaction of 2-alkynylanilines in the presence of TBHP as the terminal oxidant as well as oxygen-atom source (Scheme IB.4.2.6).[42] The process involves cascade intermolecular nucleophilic addition, intramolecular cyclization followed by oxidative cross-dehydrogenative coupling leading to the formation of four new bonds and two indole rings.



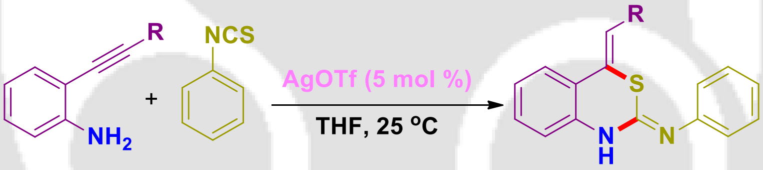
Scheme IB.4.2.6. *Au/Cu-co-catalyzed synthesis of 2,3′-bisindolin-3-ones*

Du and co-worker recently introduced an unusual Cu(II)-promoted cascade cyclization for the synthesis of 5,10-dihydroindolo[3,2-*b*]indoles (Scheme IB.4.2.7).[43] This unprecedented process involves two sequential C−N bond formation, allowing an efficient synthesis of biologically important indoloindole derivatives. The $Cu(OAc)_2$ used in the present transformation serves as the catalyst during the first step and as an oxidant in the second step of the reaction.



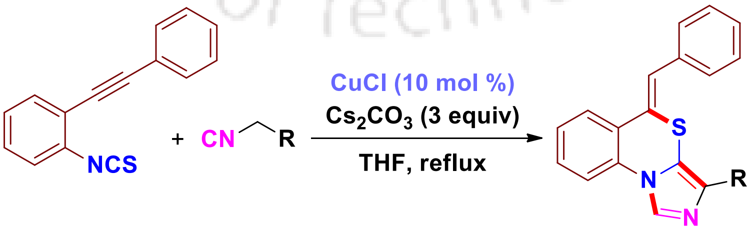
Scheme IB.4.2.7. *Cu-promoted synthesis of 5,10-dihydroindolo[3,2-b]indole derivatives*

Wu group developed a novel and efficient method for the synthesis of 2,4-dihydro-1*H*-benzo[*d*]-[1,3]thiazine derivatives via cascade addition-cyclization reaction of 2-alkynylanilines with isothiocyanates catalyzed by AgOTf (Scheme IB.4.2.8).[44]



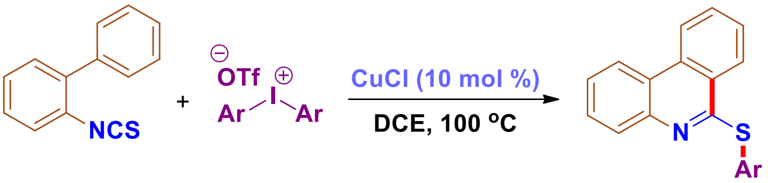
Scheme IB.4.2.8. *Ag-catalyzed synthesis of 2,4-dihydro-1H-benzo[d]-[1,3]thiazines*

A copper(I)-catalyzed cascade reaction of 2-alkynylphenyl isothiocyanates and isocyanides has been employed for the synthesis of 5*H*-benzo[*d*]imidazo-[5,1-*b*][1,3]thiazines by Cai and co-worker (Scheme IB.4.2.9).[45]



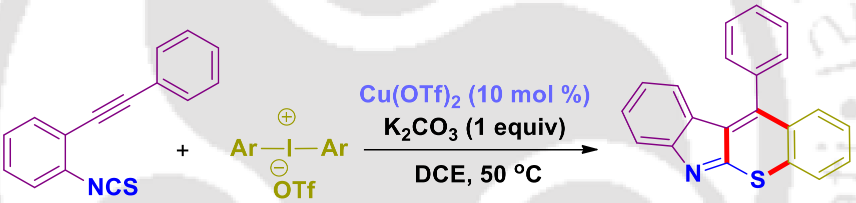
Scheme IB.4.2.9. *Cu-catalyzed synthesis of 5H-benzo[d]imidazo-[5,1-b][1,3]thiazines*

Chen and co-worker introduced a copper-catalyzed tandem C–S and C–C bond forming reaction for the synthesis of substituted phenanthridines by reacting 2-biaryl isothiocyanates and diaryliodinium salts (Scheme IB.4.2.10).[46] This approach has been extended for the synthesis of alkaloid trisphaeridine.



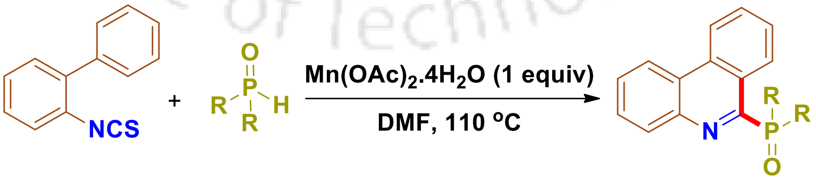
Scheme IB.4.2.10. *Cu-catalyzed synthesis of substituted phenanthridines*

A domino arylation-cyclization approach for the synthesis of thiochromeno[2,3-*b*]indoles via a copper-catalyzed coupling reaction between 2-alkynylphenyl isothiocyanates with diaryliodonium salts has been developed by Li *et al.* (Scheme IB.4.2.11).[47] The reaction operates sequentially through chemoselective *S*-arylation, regioselective 5-*endo*-*trig* cyclization and Friedel-Crafts-type cyclization process.



Scheme IB.4.2.11. *Cu-catalyzed synthesis of thiochromeno[2,3-b]indoles*

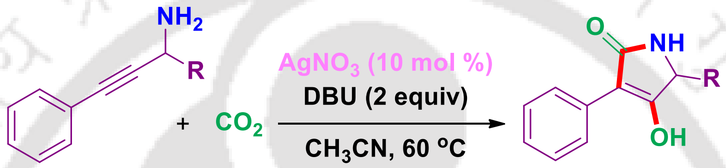
Recently, a Mn(II)-promoted desulfurative tandem phosphorylation/cyclization reaction between 2-biaryl isothiocyanates with phosphine oxides for the synthesis of 6-phosporylated phenanthridines has been developed by Li and co-worker (Scheme IB.4.2.12).[48]



Scheme IB.4.2.12. *Mn(II)-promoted synthesis of 6-phosporylated phenanthridines*

Among transition metal-catalyst used for cascade reactions, sliver-catalyzed reactions are widely utilized in organic synthesis. Silver-catalyzed cyclization of alkyne and allenes are the most promising synthetic strategy for the heterocycles synthesis. Different silver-catalyzed/mediated reactions have been summarized in the form of reviews[49] and books.[50] It has been revealed that silver have the additional potential to activate the internal alkyne during sequential cyclization reaction for heterocycles synthesis. Due to the superior alkynophilicity of silver, it is established as an ideal catalyst for alkyne based organic reactions. A representative example of silver-catalyzed reaction involving internal alkyne is given below.

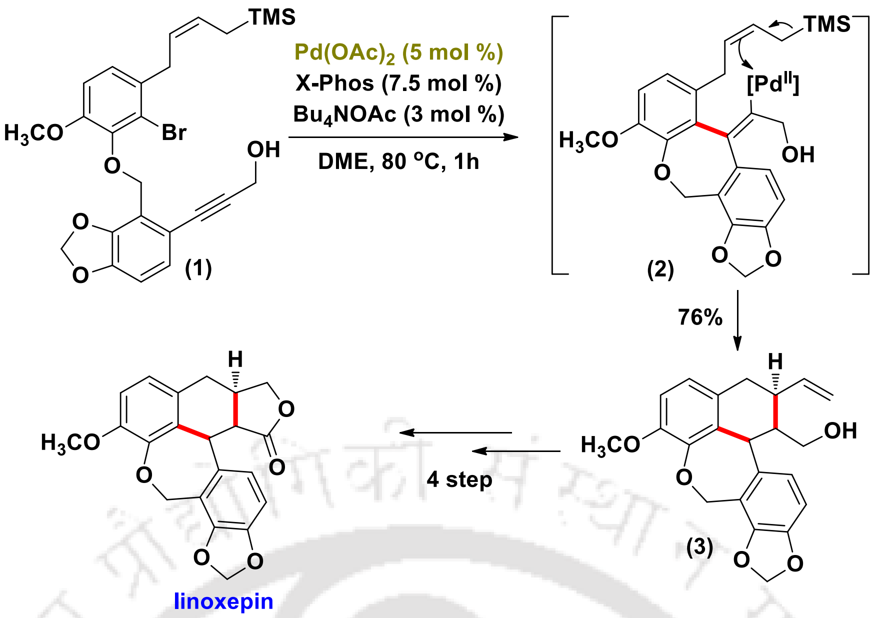
A novel strategy for the tetramic acid synthesis has been developed by Yamada *et al.* via silver-catalyzed carbon dioxide incorporation into propargylic amine followed by intramolecular rearrangement (Scheme IB.4.2.13).[51]



Scheme IB.4.2.13. *Ag-catalyzed synthesis tetramic acids*

IB.5. Cascade Reactions in Natural Product Synthesis

In organic chemistry total synthesis of natural products is the utmost achievement and is also essential for the successful industrial level synthesis of natural products or their derivatives having biological importance. With their classic creativity, synthetic organic chemist can design and achieve synthesis of complex bioactive natural products despite the discovery of new catalytic processes (such as C–H activation, organocatalysis and photoredox chemistry). The most important synthetic approach for the modern synthetic chemists is the cascade or domino transformation and by implementing this strategy, one can not only achieve significant molecular complexity and reduction in overall steps but also demonstrate synthetic class and creativity.[52] An example of a first metal-catalyzed cascade synthesis of natural product linoexpin by Tietze group is given below.[53] This process involves domino cyclization of an aryl bromide onto an alkyne (**1**), with capture of intermediate alkenylpalladium species by an appended allylsilane (**2**) which gives a high yield of the pentacyclic product (**3**) (Scheme IB.5.1).



Scheme IB.5.1. *Carbopalladation cascades in the synthesis of linoxepin*

IB.6. References

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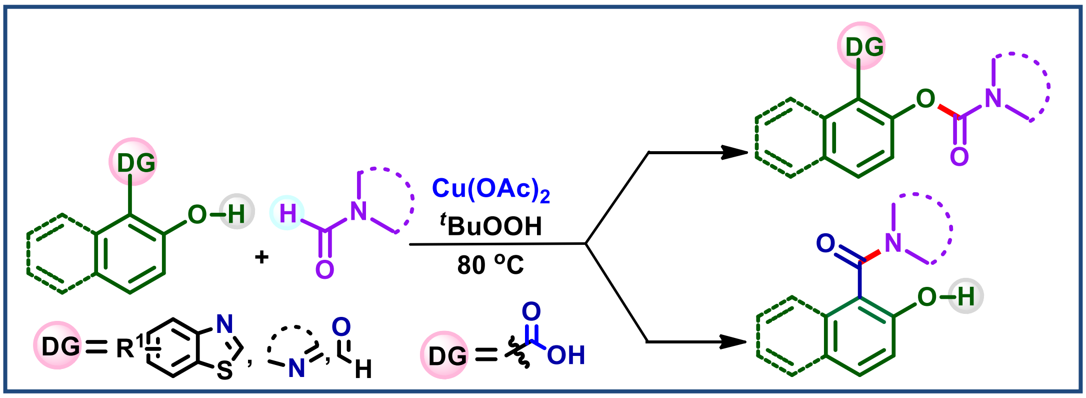
Chapter II

Copper(II)-Catalyzed Cross-Dehydrogenative Coupling of N,N-Disubstituted Formamides and Phenols: A Direct Access to Carbamates



Abstract: *An efficient copper–catalyzed protocol has been developed for the synthesis of carbamates from dialkylformamides and phenols possessing directing groups such as benzothiazole, quinoline and formyl at their ortho-position. In this chelation assisted approach, C–O bond formation takes place via a cross-dehydrogenative coupling (CDC) between formyl C–H of dialkylformamides and phenolic O–H in the presence of copper(II)acetate/aqueous tert-butyl hydroperoxide. Under identical conditions salicylic acid derivatives underwent amidation rather than the formation of expected phenol carbamates. The use of cheap and environmentally benign catalyst along with the tolerance of a wide range of functional groups makes this an easy phosgene free route to carbamates.*

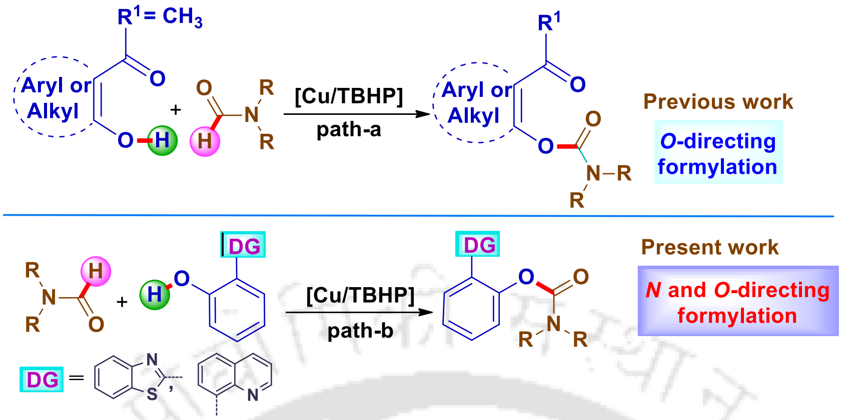
CHAPTER II

II. Copper(II)-Catalyzed Cross-Dehydrogenative Coupling of *N*,*N*-Disubstituted Formamides and Phenols: A Direct Access to Carbamates

II.1. Introduction

The transition metal-catalyzed cross-coupling reactions are useful for the construction of C–C and C–heteroatom bonds.[1] However, these traditional couplings suffer from some serious drawbacks in term of the use of stoichiometric organometallic reagents as well as requirements of pre-functionalized starting materials. To address some of these problems, the direct C–H bond functionalization processes have emerged as viable alternatives in modern organic synthesis.[2] Two pillars on which the activation of inert C–H bonds stand are: (a) chelation assisted C–H bond functionalization[3] and (b) the cross-dehydrogenative coupling (CDC).[4] In particular, the CDC is an important tool employed mainly for the construction of C–C[4a,d,5] and C–N bonds.[6] However, of late the number of C–O bond forming processes through this strategy is also increasing. In this respect our group and others have developed several CDC protocols for C–O bond formation that leads to the synthesis of various esters.[7]

N,*N*–Dialkylformamides have attracted much attention because of their polygonal utility in C–H functionalizations. They have served as surrogates of various functional groups depending upon the reaction conditions.[8] For example *N*,*N*-dimethylformamide (DMF) is known to act as the source of –Me, –CO, –NMe_2, –$CONMe_2$, –CHO and –CN groups in various synthetic protocols.[9] Among these groups, the synthetic utility of dialkylformamides as an aminocarbonyl (–$CONR_2$) group is well documented in the literature. Some recent achievements include aminocarbonyl (from DMF) insertion into alkenes and alkynes,[10] synthesis of α-ketoamides[7a] and direct aminocarbonylation of azoles.[11] All of the aforementioned reactions proceed via oxidative C–C or C–N bond formations. In the C–O bond forming segment, the use of dialkylformamide as an aminocarbonyl surrogate has been utilized for the synthesis of carbamates by reacting them with phenols and enols possessing *ortho* carbonyl directing group (path-a, Scheme II.1.1).[12]



Scheme II.1.1. *Methods of carbamates synthesis from phenols and formamides*

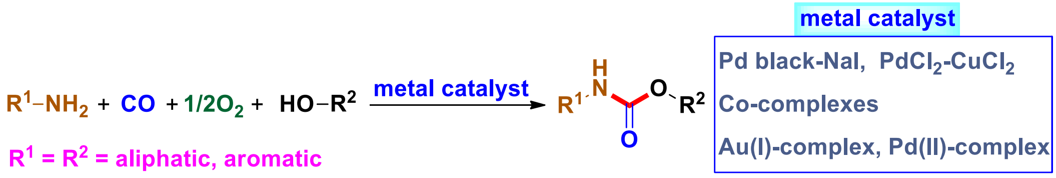
II.2. Strategies for the Synthesis of Carbamates

Organic carbamates are useful agrochemicals, pharmaceuticals and are also present in a range of biologically active natural products.[13] In addition, carbamates plays an important role as intermediates in organic synthesis and serves as a protecting group during peptide synthesis.[14] However, the general methods for their synthesis require intermediates such as chloroformates or isocyanates which, in turn are prepared from phosgene or its derivatives.[15] Thus, a phosgene-free synthesis of carbamates is most appreciable from the environmental point of view.[16] This motive has led to the synthesis of carbamates by other methods such as (i) oxidative and reductive carbonylation of amines and nitro aromatics;[16a-e,17] (ii) reaction of amines with CO_2;[16f-n] (iii) metal catalyzed cross coupling of isocyanate with alcohols;[18] and (iv) C–H functionalization.[12]

(i) Oxidative and Reductive Carbonylation of Amines and Nitro Aromatics

- **Oxidative Carbonylation of Amines**

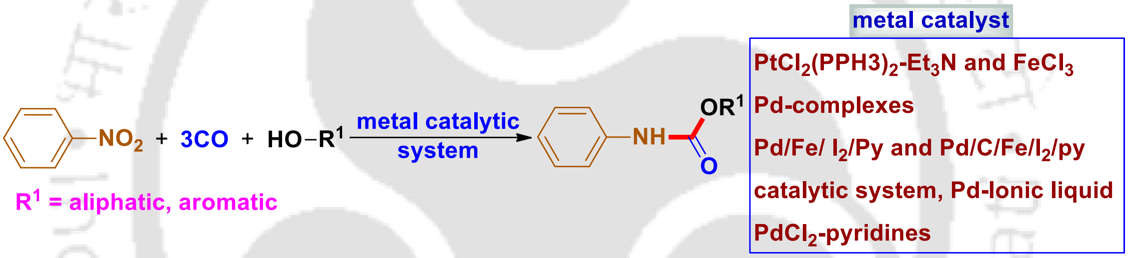
Oxidative carbonylation of aliphatic as well as aromatic amines to carbamates are carried out with various metal catalytic system such as Au(I) complex,[16a] Co-complex,[16b] $PdCl_2$-$CuCl_2$,[16c] Pd black-NaI[16d] and Pd(II) complex[16e] (Scheme II.2.1.1). However all of them suffer from certain drawbacks such as requirements of expensive metal catalyst, harsh reaction conditions as well as requirement of poisonous CO gas. Furthermore, the use of CO as carbonylating source requires special equipment to carry out the reaction.



Scheme II.2.1.1. *Synthesis of carbamates by oxidative carbonylation of amines*

- **Reductive Carbonylation of Nitro Aromatics**

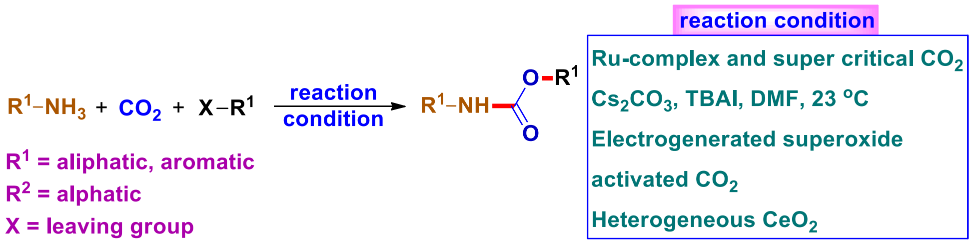
Aromatic nitro compound can be carbonylated to carbamate in the presence of various metal catalyst. These metal catalytic system includes $PtCl_2(PPh_3)_2$-Et_3N along with $FeCl_3$,[17a] Pd-complex,[17b] Pd/Fe/Py and Pd/C/Fe/I_2/Py,[17c] Pd-ionic liquid[17d] and $PdCl_2$-pyridines systems[17e] (Scheme II.2.1.2). These reactions also suffer with certain drawbacks similar to previous one such as expensive catalytic system, harsh reaction condition as well as requirement of poisonous CO gas.



Scheme II.2.1.2. *Synthesis of carbamates by reductive carbonylation of nitro aromatics*

(ii) Reaction of Amines with CO_2

Aliphatic and aromatic amine can be transformed into carbamates by reacting them with carbon dioxide and alkyl halide in the presence of metal and metal free conditions (like in the presence of base as well as electrochemical) to produce the corresponding carbamates (Scheme II.2.2).[16f-n] The metal involves in the reaction are either transition metals such as Ru and Ni or lanthanides like Ce.

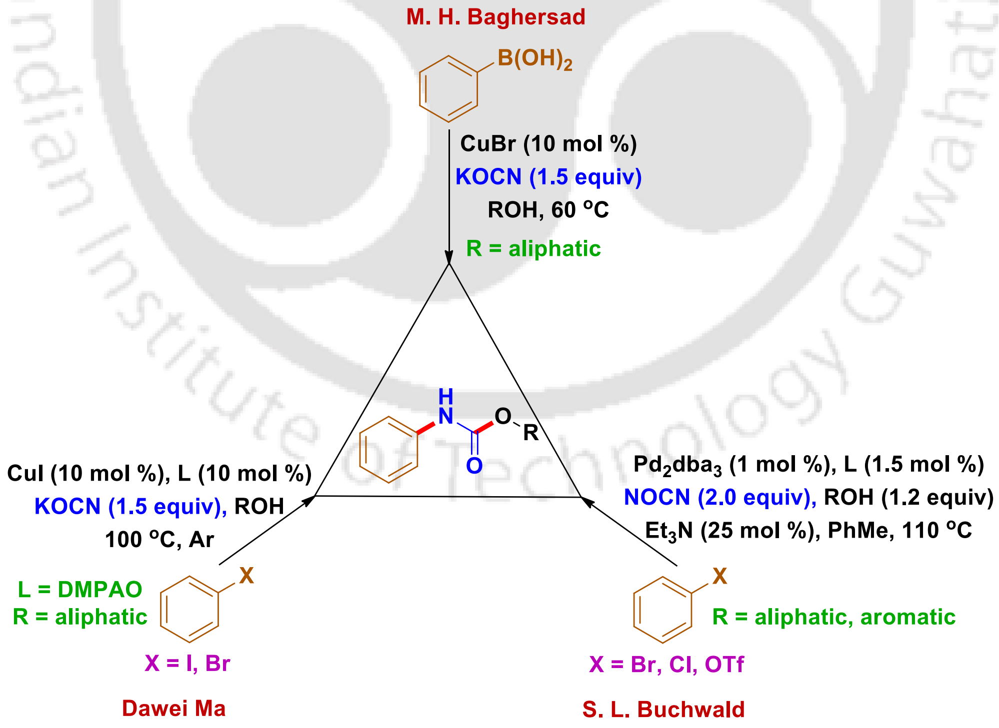


Scheme II.2.2. *Synthesis of carbamates by reaction of amine with CO_2 and alkyl halide*

(iii) Metal-Catalyzed Cross Coupling of Isocyanates with Alcohols

With the advancement of cross coupling reactions for the construction of C–C and C–heteroatom bonds, these strategies have been applied for the synthesis of carbamates via transition metals catalyzed cross coupling of isocyanates with alcohols (Scheme II.2.3).

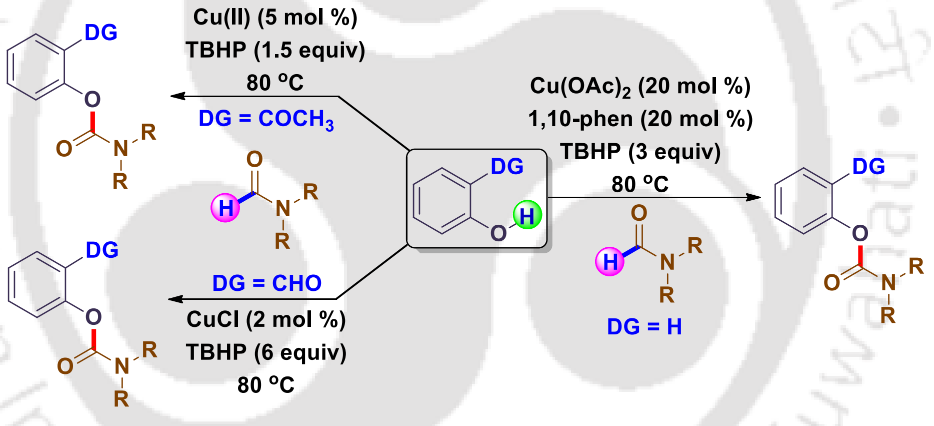
Baghersad and co-worker first reported Cu(I) catalyzed cross coupling of aryl boronic acid with potassium cyanate and alcohol.[18a] An analogous CuI-catalyzed synthesis of carbamates was reported by the Ma's group using aryl iodide and bromide as coupling partner in place of aryl boronic acid using 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO) as ligand.[18b] Similarly Buchwald group demonstrated a Pd(II)-catalyzed protocol for the synthesis of carbamates. They utilized aryl chloride, bromide and triflate as coupling partner along with sodium cyanate.[18c] The advantages of this strategy over previous one is that both aliphatic as well as aromatic alcohols can be used as coupling partner. These methods provide straightforward protocol for the synthesis of Carbamates, but suffer certain drawback such as requirement of pre-synthesized metal cyanates as well as pre-functionalized coupling precursor.



Scheme II.2.3. *Synthesis of carbamates by metal-catalyzed cross coupling reaction*

(iv) C–H Functionalizations

The direct C–H bond activation has emerged as an alternative route in organic synthesis to overcome the drawbacks of traditional cross coupling reactions. First method for the synthesis of carbamates via sp^2 C–H bond activation of dialkylformamides was reported by the Reddy and co-workers in 2011 (Scheme II.2.4).[12a] They achieved this using *ortho* acetyl as the directing group with the help of Cu(II) salt as the catalyst and *tert*-butylhydroperoxide (TBHP) as terminal oxidant. A similar protocol have been reported by Chang and co-worker via oxidative coupling of formamides with phenol having *ortho* formyl as the directing group using Cu/TBHP combination (Scheme II.2.4).[12b,c] Later on Reddy *et al.* reported a ligand assisted copper-catalyzed oxidative coupling of phenol with dialkylformamides without the assistance of any directing group (Scheme II.2.4). Since these early works, a number of other protocols were developed by the other groups.[12d-g]



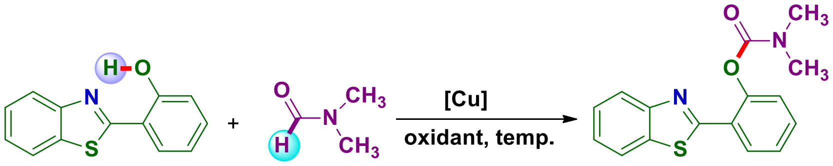
Scheme II.2.4. *Synthesis of carbamates by C–H functionalization strategy*

II.3. Present Work

Benzothiazole derivatives have found immense importance due to their biological and pharmaceutical activities.[19] Therefore, functionalizations of benzothiazole would provide pathways for the synthesis of intermediates that may find potential applications in various other fields.[20] This has been realized through some of our recent achievements on transition metal-catalyzed directing group-assisted (*N*-atom) functionalizations of *ortho*-C–H bond of 2-aryl moiety in benzothiazole.[21] Where *N*-atom of benzothiazole co-ordinate with transition metal and direct it towards functionalization of *ortho*-C–H bond of 2-aryl moiety. Thus, we envisaged that the directing *N*-atom of benzothiazole could facilitate a metal-catalyzed aminocarbonylation of the hydroxyl group present at the proximal carbon atom. Such an aminocarbonylation would lead to the formation of a hybrid benzothiazole–carbamate moiety.

Optimization of Reaction Conditions: To verify our above envisaged hypothesis, 2-(benzo[*d*]thiazol-2-yl)phenol (**1**) and DMF (**a**) were reacted in the presence of CuBr (5 mol %) and TBHP in decane (2 equiv) at 80 ^{o}C. As anticipated phenol carbamate (**1a**) was formed but in a low yield of 34% (Table II.3.1, entry 1). To arrive at the optimized reaction condition different salts of copper such as $CuBr_2$, CuCl, $CuCl_2$, $Cu(OAc)_2$ and $Cu(OTf)_2$ were tested among which $Cu(OAc)_2$ provided the best yield of 57% (Table II.3.1, entries 2–6). When the catalyst loading was increased from 5 mol % to 10 mol % the yield did not improve significantly (Table II.3.1, entry 7). The use of aqueous TBHP (70%) provided an improved yield (63%) compared to the 5–6 M decane solution of TBHP (Table II.3.1, entry 8). The yield was enhanced up to 74% (Table II.3.1, entry 9) when 3 equiv of oxidant were used. No further improvement in the yield was observed even when the oxidant quantity was increased beyond 3 equiv (Table II.3.1, entry 10). The oxidant, 70% aqueous TBHP, turned out to be the best (Table II.3.1, entry 9) compared to other peroxides such as aqueous H_2O_2, DTBP, BPO and $(NH_4)_2S_2O_8$ (Table II.3.1, entries 11–14) screened. An increase (100 ^{o}C) or decrease (70 ^{o}C) in the reaction temperature led to a slight reduction in the yield (Table II.3.1, entry 15 and 16). Absence of either copper catalyst or oxidant failed to produce any cross coupled product revealing the requirement of both Cu(II) and TBHP in bringing about this transformation (Table II.3.1, entry 17 and 18). When the reaction was carried out under a metal-free conditions using tetrabutylammonium iodide (TBAI) as the catalyst and TBHP as the oxidant the desired carbamate did not form at all (Table II.3.1, entry 19). No further improvement in the product yield was observed even when a standard reaction was performed under N_2 atmosphere. Hence, it was found that the use of 5 mol % of $Cu(OAc)_2$ in the presence of aqueous TBHP (3 equiv) at 80 ^{o}C was the best condition for the conversion of (**1**) to (**1a**).

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



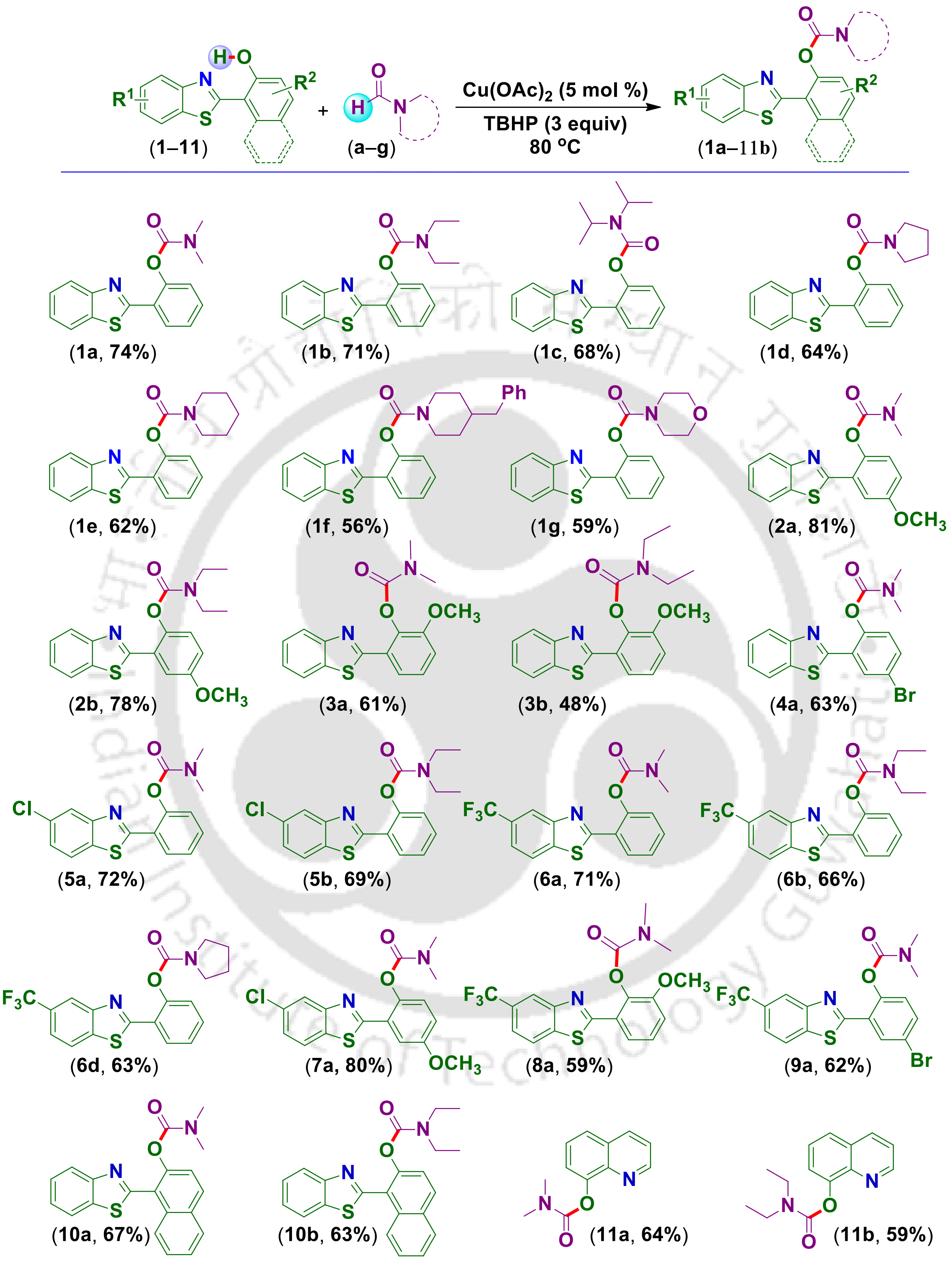
(**1**) (**a**) (**1a**)

Entry	Catalyst (mol %)	Oxidant (equiv)	Temp. (^{o}C)	Yield %[b]
1	CuBr (5)	TBHP[c] (2)	80	34
2	$CuBr_2$ (5)	TBHP[c] (2)	80	41
3	CuCl (5)	TBHP[c] (2)	80	30
4	$CuCl_2$ (5)	TBHP[c] (2)	80	39
5	$Cu(OTf)_2$ (5)	TBHP[c] (2)	80	32
6	$Cu(OAc)_2$ (5)	TBHP[c] (2)	80	57
7	$Cu(OAc)_2$ (10)	TBHP[c] (2)	80	59
8	$Cu(OAc)_2$ (5)	TBHP[d] (2)	80	63
9	**$Cu(OAc)_2$ (5)**	**TBHP[d] (3)**	**80**	**74**
10	$Cu(OAc)_2$ (5)	TBHP[d] (4)	80	74
11	$Cu(OAc)_2$ (5)	Aq. H_2O_2[e] (3)	80	< 10
12	$Cu(OAc)_2$ (5)	DTBP[f] (3)	80	< 8
13	$Cu(OAc)_2$ (5)	BPO[g] (3)	80	< 6
14	$Cu(OAc)_2$ (5)	$(NH_4)_2S_2O_8$ (3)	80	< 3
15	$Cu(OAc)_2$ (5)	TBHP[d] (3)	100	73
16	$Cu(OAc)_2$ (5)	TBHP[d] (3)	70	70
17	Nil	TBHP[d] (3)	80	00
18	$Cu(OAc)_2$ (5)	Nil	80	00
19	TBAI (20)	TBHP[d] (3)	80	00

[a] Reaction condition: 2-(Benzo[*d*]thiazol-2-yl)phenol (**1**) (0.5 mmol), formamide (**a**) (1 mL), at 80 °C for 10 h. [b] Isolated yield. [c] 5–6 M Decane solution. [d] 70% aqueous solution. [e] 50% aqueous solution. [f] Di-*tert*-butyl peroxide. [g] Benzoyl peroxide.

Substrate Scopes for *O*-Formylation of *N*-directing Phenols: With this optimized condition in hand, we further investigated the scope of this transformation with different formamides and phenols possessing *N*-directing groups (Scheme II.3.1). Initially various formamides (**a–g**) were reacted with 2-(benzo[*d*]thiazol-2-yl)phenol (**1**) and it was found that both acyclic (**a–c**) and cyclic (**d–g**) formamides coupled well with (**1**) giving corresponding carbamates in moderate to good yields (Scheme II.3.1, **1a–c** and **1d–g**). However, cyclic formamides (**d–g**) gave marginally lower yields compared to acyclic ones (**a–c**). Further, the effect of substituents on phenol moiety was investigated by reacting them with various formamides and the results are summarized in Scheme II.3.1. Phenol ring bearing electron-donating group such as *p*-OCH_3 (**2**) underwent efficient coupling with *N*,*N*-dimethylformamide (**a**) and *N*,*N*-diethylformamide (**b**) affording carbamates (**2a**) and (**2b**) in 81% and 78% yields, respectively. However, yields of the

Scheme II.3.1. *Substrate scope for the oxidative coupling of phenols with formamides*[a,b]



[a]Reaction conditions: phenols (**1–11**) (0.5 mmol), formamides (**a–g**) (1 mL), Cu(OAc)$_2$ (0.05 mmol), TBHP (3 equiv), 80 °C, for 8–12 h. [b]Yield of isolated pure product given.

product (**3a**) and (**3b**) dropped to 61% and 48% when the –OCH_3 group is present *ortho* to –OH (**3**), which could be due to the *ortho* steric hindrance. Phenol ring bearing a moderately electron-withdrawing group such as *p*-Br (**4**) when reacted with *N*,*N*-dimethylformamide provided its carbamate (**4a**) in slightly lower yield (63%) compared to the electron-donating counterpart (**2a**). Relative to electron-neutral (–H) analogue (**1**) the presence of the moderately electron-withdrawing group –Cl (**5**) and strongly electron-withdrawing group –CF_3 (**6**) on the aryl ring of benzothiazole moiety had negligible influence on the product yields (Scheme II.3.1, **5a, 5b**, **6a, 6b** and **6d**). The structure of the product (**6a**) was further confirmed by single X-ray crystallography (Figure II.3.1). Synthesis of different carbamates (**7a**), (**8a**) and (**9a**) from their respective coupling partners reveal the versatility of this protocol. This methodology is also equally applicable for the synthesis of β-naphthyl carbamates (**10a**) and (**10b**) by reacting 1-(benzo[*d*]thiazol-2-yl) naphthalen-2-ol (**10**) with formamides (**a**) and (**b**).

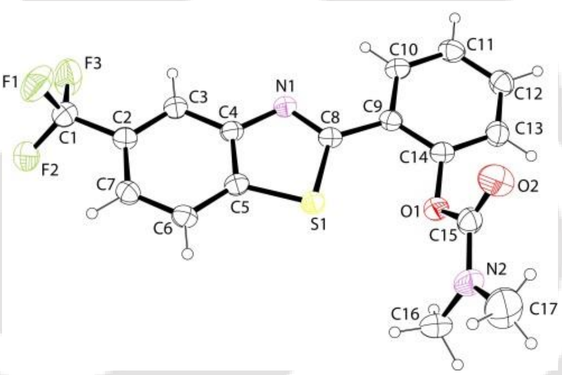


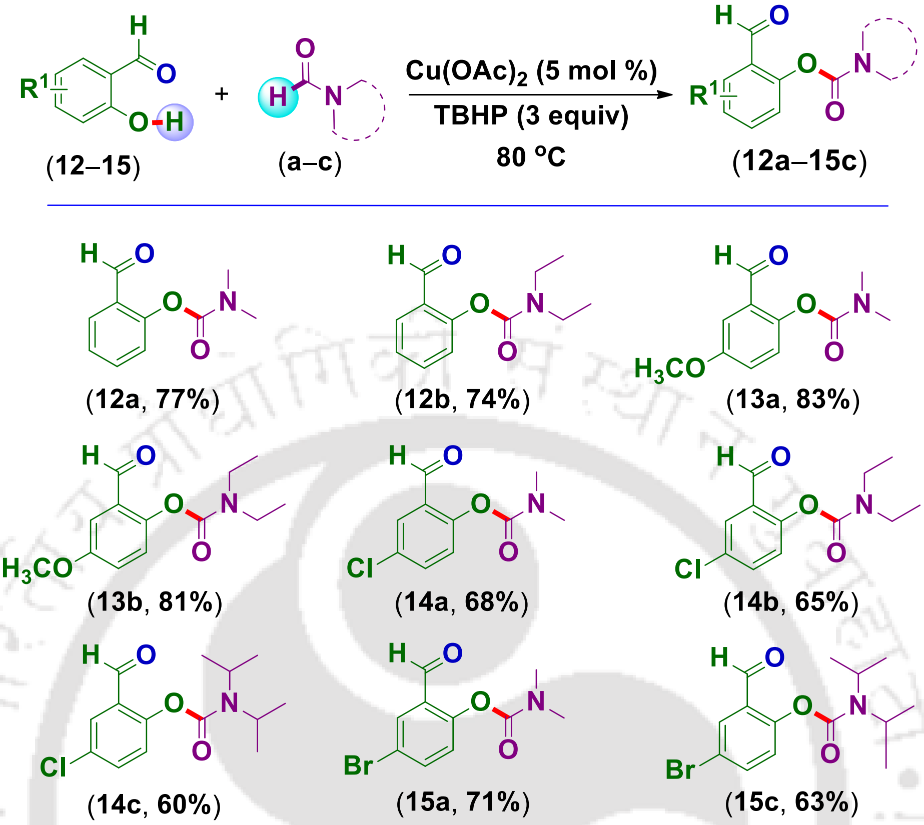
Figure II.3.1. *ORTEP view of compound (**6a**)*

Besides benzothiazoles, the *N*-atom in 8-hydroxyquinoline (**11**) provided similar chelation assistance towards *O*-formamidation giving products (**11a**) and (**11b**) when treated with their respective formamides (**a**) and (**b**) under otherwise identical reaction conditions. When 2-(benzo[*d*]thiazol-2-yl)phenol (**1**) and 8-hydroxyquinoline (**11**) were reacted with *N*-methylformamide or an arylformamide such as the monoaryl (*N*-methyl-*N*-phenyl formamide) and diaryl (*N*,*N*-diphenylformamide) species in all cases the reaction failed to provide any carbamates. It may be mentioned here that traditionally the phenolic –OH group is protected as its ether, ester, silyl ether, acetate etc. which require harsh reaction conditions as well as expensive and toxic chemicals.[14a] Compared to these, the present phenolic –OH protection via carbamate formation using simple formamides may find useful applications in organic synthesis.

For past few years our group has developed various CDC reactions using metals as well as metal-free conditions.[7f-k,21] During one of the investigations, we have demonstrated the oxidative coupling of alkylbenzenes with salicylaldehydes which formed phenol esters without affecting the formyl group.[7i] Inspired by this result, we envisaged a similar cross dehydrogenative coupling of formamide and salicylaldehyde. Thus, when salicylaldehyde (**12**) and DMF (**a**) were reacted under the above optimized conditions 2-formyl phenyl carbamate was obtained in 77% isolated yield. Gratifyingly, similar to our previous report on esterfication,[7i] herein as well the oxidation sensitive formyl group remained unaffected under the reaction conditions which can be transformed into other useful functionality if desired. Coincidentally, while the work was under progress the group of Wang and Chang[12c] independently reported a similar *O*-formamidation of salicylaldehyde; the only difference being the use of copper(I) chloride instead of Cu(II) acetate and a different stoichiometry of TBHP. The same group has also demonstrated an Fe-catalyzed selective C–O bond formation via α C–H bond functionalization of cyclic ethers in the presence of a labile formyl group.[22] Thus, the present methodology using Cu(II) was demonstrated only with a limited number of substrates.

Salicylaldehyde (**12**) when treated with formamides (**a**) and (**b**) resulted in the formation of carbamates (**12a**) and (**12b**) in good yields (Scheme II.3.2). The reaction of salicylaldehyde bearing strong electron donating group like –OCH_3 (**13**) led to the formation of expected carbamates (**13a**) and (**13b**) in higher yields compared to un-substituted salicylaldehyde (**12**) when coupled with formamides (**a**) and (**b**) respectively (Scheme II.3.2). Salicylaldehyde bearing halogen substituents such as –Cl (**14**) and –Br (**15**) afforded slightly lower yields compared to the un-substituted salicylaldehyde (**12**) when treated with various dialkylformamides (**a**), (**b**) and (**c**) as shown in Scheme II.3.2.

Scheme II.3.2. *Synthesis of carbamates from salicylaldehydes*[a,b]



[a]Reaction conditions: salicylaldehydes (**12–15**) (1.0 mmol), formamides (**a**–**c**) (1 mL), $Cu(OAc)_2$ (0.05 mmol), TBHP (3 equiv), 80 °C for 3 h. [b]Yields of isolated pure products given.

During our earlier substrate directed *O*-aroylation, both formyl (CHO) and acetyl ($COCH_3$) served as excellent directing groups while the carboxy (COOH) group was completely ineffective.[7i] So curiosity arose whether *O*-formamidation can be achieved with carboxy (COOH) as the directing group in salicylic acid? Salicylic acid (**16**) bearing COOH directing group at the *ortho* position when treated with DMF (**a**) gave an amide (**16a**) rather than the expected phenol carbamate (Scheme II.3.3). The structure of the product (**16a**) has been confirmed by single X-ray crystallography (Figure II.3.2). This is not a singular exception; salicylic acid (**16**) with other formamide (**b**) and methyl substituted salicylic acid (**17**) with formamides (**a**) and (**b**) also yielded amides (**16b**), (**17a**) and (**17b**) as the major products. A similar amidation of benzoic acid with formamide has been reported under identical conditions.[23] Thus this reaction might be proceeding via a radical path as has been proposed in the literature.[23]

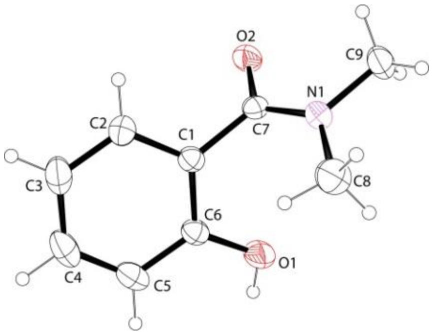
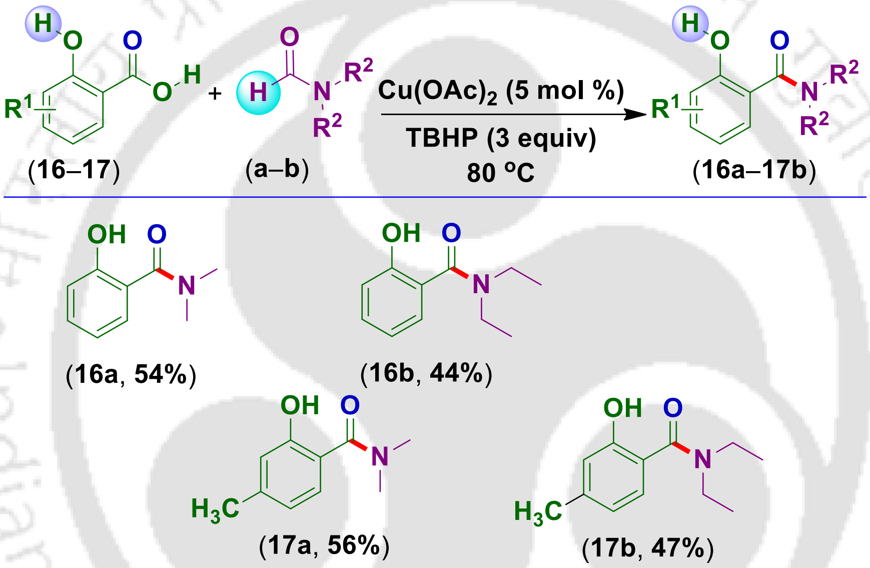


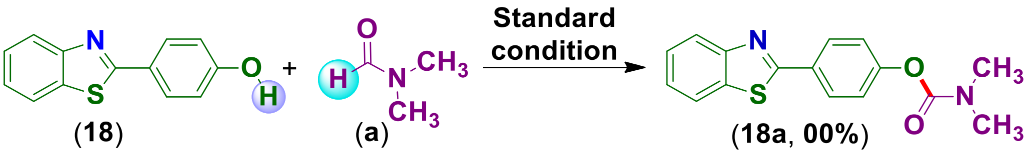
Figure II.3.2. *ORTEP view of product (**16a**)*

Scheme II.3.3. *Oxidative coupling of salicylic acids with formamides*[a,b]



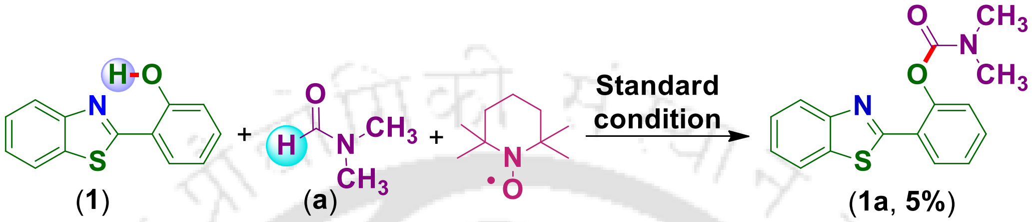
[a] Reaction conditions: salicylic acids (**16** or **17**) (1.0 mmol), formamide (**a** or **b**) (1 mL), $Cu(OAc)_2$ (0.05 mmol), TBHP (3 equiv), 80 °C for 6 h. [b] Yields of isolated pure products given.

Mechanistic Studies: So far as the mechanism of *O*-formamidation with different directing groups is concerned, the complex forming ability of 2-(benzo[*d*]thiazol-2-yl)phenol and salicylaldehyde through co-ordination with Cu salts could be one of the crucial factors. Furthermore, reaction of 4-(benzo[d]thiazol-2-yl)phenol (**18**) with formamide (**a**) failed to produce the target phenol carbamates; thus suggesting the involvement of an adjacent directing group (Scheme II.3.4).



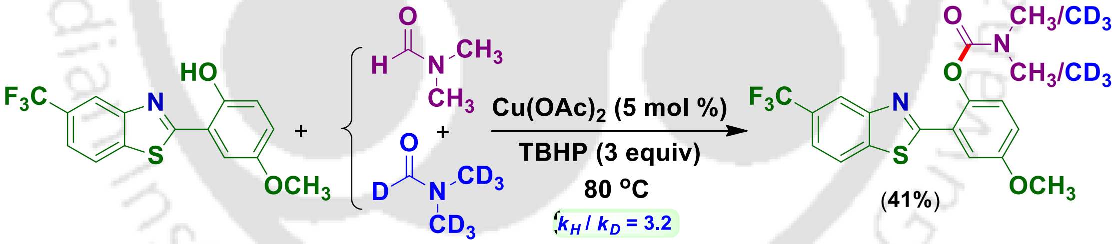
Scheme II.3.4. *Reaction of non-directing phenol with formamide*

The reaction between 2-(benzo[*d*]thiazol-2-yl)phenol (**1**) and DMF (**a**) in the presence of a radical scavenger such as TEMPO [2,2,6,6-tetramethylpipridine-1-oxyl] resulted in the formation of carbamate (**1a**) in < 5% yield indicating a radical path for the reaction (Scheme II.3.5).[22a] Surprisingly, when the reaction was performed in the presence of another radical scavenger such as 1,4-cyclohexadine there was no retardation of the reaction rate and the yield remained unaltered.



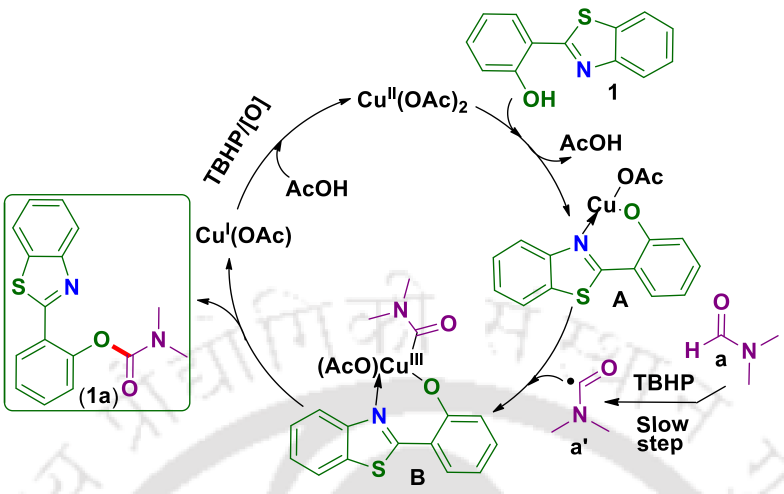
Scheme II.3.5. *Reaction in the presence of radical scavenger TEMPO*

A significant kinetic isotope effect (K_H/K_D ~3.2) was observed in the reaction between 4-methoxy-2-(5-(trifluoromethyl)benzo[*d*]thiazol-2-yl)phenol with DMF-d_7 demonstrating that sp^2 C–H bond cleavage of formamide is possibly the slow step in the reaction (Scheme II.3.6).



Scheme II.3.6. *KIE experiment with deuterated formamide*

Based on literature precedents and our experimental observations, a radical mechanism for this transformation is predicted that involves formation of an aminoacyl radical (**a′**) as the crucial step.[7a,11,24] A six membered copper complex (**A**) is formed via the chelation of Cu(II) with (**1**) through *N*-binding of benzothiazole and *O*-binding of phenolic group. Simultaneously, a butoxy radical generated by the dissociation of TBHP abstracts a hydrogen atom from the DMF to produce an aminoacyl radical (**a′**). This aminoacyl radical (**a′**) reacts with complex (**A**) to form a Cu(III) intermediate (**B**). Reductive elimination of intermediate (**B**) results in the formation of the desired carbamate (**1a**) and releasing a Cu(I) species, which is re-oxidized to Cu(II) in the medium for a further catalytic cycle (Scheme II.3.7). A similar mechanism is likely to operate for the other directing groups as well.



Scheme II.3.7. *Plausible mechanism for Cu(II)-catalyzed C–O bond formation*

In conclusion, we have developed an efficient synthesis of phenol carbamates from dialkylformamides and phenols possessing benzothiazole, quinoline and formyl as directing groups at their *ortho*-positions. This directing group-assisted cross-dehydrogenative coupling (CDC) occurs between the formyl C–H of dialkylformamides and the phenolic O–H bond in the presence of the Cu(II) catalyst and oxidant aqueous TBHP. However, an exception was observed for salicylic acid derivatives which gave *o*-hydroxyamides. A plausible radical mechanism has been proposed for the reaction. The use of a cheap and environmentally benign catalyst and tolerance of a range of functional groups makes this an alternative phosgene free route to phenol carbamates.

II.4. Experimental Section

II.4.1. General Information: All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium 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) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

II.4.2. Crystallographic Description

CCDC Number for Compounds 6a and 16a: CCDC 997031 and 997032. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 6a: $C_{17}H_{13}F_3N_2O_2S$, crystal dimensions 0.40 x 0.34 x 0.26 mm, M_r = 366.36, Orthorhombic, space group P 21 21 21, a = 6.3877(5), b = 13.530(1), c = 19.4862(14) Å, $\alpha = 90^o$, $\beta = 90^o$, $\gamma = 90^o$, V = 1684.1(2) Å^3, Z = 4, ρ_{calcd} = 1.445 g/cm^3, μ = 0.236 mm^{-1}, F(000)= 752.0, reflection collected / unique = 3585 / 3174, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0382, wR_2 = 0.1195, R indices (all data): R_1 = 0.0444, wR_2 = 0.1251, goodness of fit = 0.967.

Crystallographic Description of 16a: $C_9H_{11}NO_2$, crystal dimensions 0.40 x 0.34 x 0.26 mm, M_r = 165.19, Orthorhombic, space group P b c a, a = 9.0824(4), b = 11.7546(4), c = 16.6734(6) Å, $\alpha = 90^o$, $\beta = 90^o$, $\gamma = 90^o$, V = 1780.05(12) Å^3, Z = 8, ρ_{calcd} = 1.233 g/cm^3, μ = 0.088 mm^{-1}, F(000)= 704.0, reflection collected / unique = 1454 / 1249, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0391, wR_2 = 0.1490, R indices (all data): R_1 = 0.0457, wR_2 = 0.1582, goodness of fit = 0.939.

II.4.3. General Procedure for the Synthesis of 2-(Benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate (1a): An oven-dried round-bottom flask was charged with 2-(benzo[*d*]thiazol-2-yl)phenol (0.5 mmol, 114 mg), $Cu(OAc)_2$ (0.025 mmol, 4.5 mg), 70% aqueous TBHP (1.5 mmol, 215 µL), and DMF as formamide source (1 mL), and the mixture was stirred in a preheated oil bath at 80 ^oC for 10 h. After cooling to room temperature, the reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under vacuum. The crude product so obtained was purified over a short column of silica gel (ethyl acetate / hexane, 1:9) to afford 2-(benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate **1a**; yield: 110 mg, 74%.

II.4.4. General Procedure for the Synthesis of 2-Formylphenyl dimethylcarbamate (12a): An oven-dried round-bottom flask was charged with salicylaldehyde (122 mg, 1 mmol), $Cu(OAc)_2$ (0.050 mmol, 9.0 mg), 70% aqueous TBHP (3 mmol, 430 µL), and

DMF as formamide source (1 mL) and the mixture was stirred in a preheated oil bath at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under vacuum. The crude product so obtained was purified over a short column of silica gel (ethyl acetate / hexane, 2:8) to afford corresponding 2-formylphenyl dimethylcarbamate **12a**; yield: 149 mg, 77%.

II.4.5. Genaral Procedure for the Synthesis of 2-Hydroxy-*N,N*-dimethylbenzamide (16a): An oven-dried round-bottom flask was charged with salicylic acid (138 mg, 1 mmol), $Cu(OAc)_2$ (0.05 mmol, 9.0 mg), 70% aqueous TBHP (3 mmol, 430 μL), and DMF as formamide source (1 mL), and the mixture was stirred in a preheated oil bath at 80 °C for 6 h. After cooling to room temperature, the reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The ethyl acetate layer was washed with 5% sodium bicarbonate solution (2 x 2 mL). Organic layer was dried over anhydrous Na_2SO_4 and solvent removed under vacuum. The crude product so obtained was purified over a short column of silica gel (ethyl acetate / hexane, 3:7) to afford 2-hydroxy-*N*,*N*-dimethylbenzamide **16a**; yield: 89 mg, 54%.

II.4.6. Reaction of 2-(Benzo[*d*]thiazol-2-yl)phenol (1) with DMF (a) in the Presence of Radical Scavenger TEMPO: An oven-dried round-bottom flask was charged with 2-(benzo[*d*]thiazol-2-yl)phenol (0.5 mmol, 114 mg), $Cu(OAc)_2$ (0.025 mmol, 4.5 mg), 70% aqueous TBHP (1.5 mmol, 215 μL), TEMPO (234 mg, 1.5 mmol) and DMF as formamide source (1 mL), and the mixture was stirred in a preheated oil bath at 80 °C for 10 h. The reaction after 10 h shows the formation of desired product (**1a**) only in < 5% yield.

II.4.7. Intermolecular Competing Kinetic Isotope Effect (KIE) Experiment with Deuterated Formamide: To a solution of 4-methoxy-2(5-(trifluoromethyl)benzo[*d*]thiazol-2-yl)phenol (81 mg, 0.25 mmol) in DMF and d_7-DMF (1:1, 0.5 mL) was added $Cu(OAc)_2$ (5 mol %) followed by aqueous TBHP (3 equiv) and the resultant reaction mixture was put into a pre heated oil bath at 80 °C for 12 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuum. The crude product was purified over a column of silica gel. The product obtained was subjected to ^{1}H NMR analysis. The ratio of the deuterated and non-deuterated product was calculated on the basis of the integration ratio of the –CH_3 proton at δ 3.30 ppm and –OCH_3 proton at δ 3.92. The k_H/k_D calculated on the basis of ^{1}HNMR analysis of the pure product showed a significant KIE (k_H/k_D = 3.2). This result suggests that the formamide sp^2 C−H bond cleavage is involved in the rate-determining step of this transformation.

Calculation:

For three methoxy protons at δ 3.92, the integration value is 3.00.

Thus for a single proton the integration corresponds to 3.00 / 3 = 1.00.

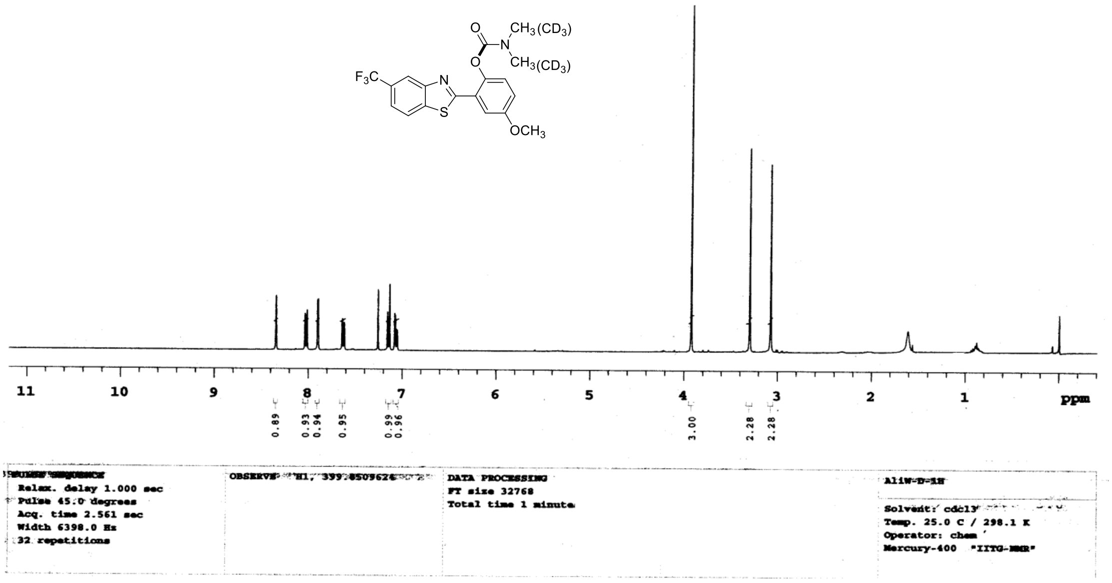
Now for the integration value of the protons originating from formamide at δ 3.30 is 2.28.

Thus the number of protons corresponding to this integration value is 2.28 / 1.00 = 2.28.

Upon correlation with the –OCH_3 proton the number of proton at δ 3.30 should be 3.

Hence the proton difference in this region is 3.00 – 2.28 = 0.720

Thus the K_H / K_D = 2.28 / 0.720~3.2.



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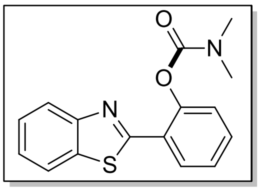
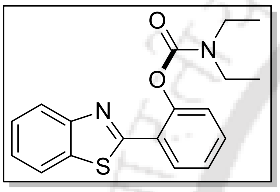
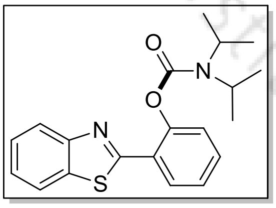
II.6. Spectral Data



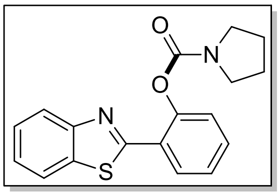
2-(Benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate (1a): Light yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06 (s, 3H), 3.28 (s, 3H), 7.25 (d, 1H, *J* = 8.0 Hz), 7.34–7.41 (m, 2H), 7.47–7.52 (m, 2H), 7.92 (d, 1H, *J* = 8.0Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 36.7, 36.8, 121.3, 123.1, 123.9, 125.1, 125.7, 126.1, 126.3, 129.8, 131.2, 135.4, 149.1, 152.7, 154.0, 162.5; IR (KBr): 2924, 1723, 1434, 1383, 1148, 1104, 967, 800, 756 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_2S$ (MH$^+$) 299.0882; found 299.0876.



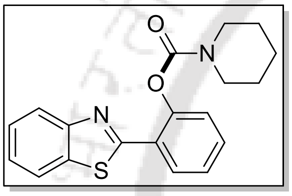
2-(Benzo[*d*]thiazol-2-yl)phenyl diethylcarbamate (1b): Light yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 3.41 (q, 2H, *J* = 8.2.0 Hz), 3.63 (q, 2H, *J* = 8.0 Hz), 7.24 (d, 1H, *J* = 8.2 Hz), 7.33–7.41 (m, 2H), 7.47–7.51 (m, 2H), 7.91 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 8.28 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.4, 14.4, 42.1, 42.4, 121.4, 123.3, 123.9, 125.2, 125.8, 126.2, 126.8, 130.1, 131.4, 135.6, 149.4, 153.0, 153.6, 163.0; IR (KBr): 3062, 2975, 2933, 1723, 1454, 1417, 1314, 1270, 1149, 970, 757 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{18}N_2O_2S$ (MH$^+$) 327.1162; found 327.1170.



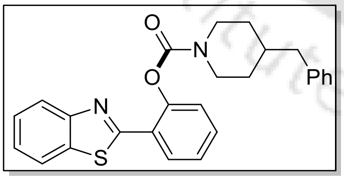
2-(Benzo[*d*]thiazol-2-yl)phenyl diisopropylcarbamate (1c): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31–1.37 (m, 12H), 3.82–3.86 (m, 1H), 4.39–4.42 (m, 1H), 7.21 (d, 1H, *J* = 8.2 Hz), 7.33–7.41 (m, 2H), 7.49 (t, 2H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.08 (d, 1H, *J* = 8.0 Hz), 8.27 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.7, 21.6, 46.6, 47.5, 121.4, 123.4, 124.0, 125.2, 125.8, 126.3, 127.1, 130.3, 131.5, 135.8. 149.4, 152.6, 153.1, 163.2; IR (KBr): 3061, 2971, 2932, 1715, 1455, 1433, 1315, 1280, 1155, 981, 732 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{22}N_2O_2S$ (MH$^+$) 355.1475; found 355.1479.



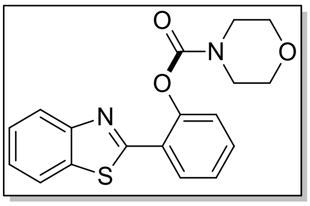
2-(Benzo[*d*]thiazol-2-yl)phenyl pyrrolidine-1-carboxylate (1d): White solid; M.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95–2.08 (m, 4H), 3.52 (t, 2H, *J* = 6.6 Hz), 3.79 (t, 2H, *J* = 6.6 Hz), 7.28 (d, 1H, *J* = 8.2 Hz), 7.34–7.41 (m, 2H), 7.47–7.52 (m, 2H), 7.92 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.33 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.2, 26.1, 46.9, 121.5, 123.3, 124.1, 125.3, 125.9, 126.3, 126.6, 130.1, 131.5, 135.7, 149.3, 152.5, 152.9, 162.9; IR (KBr): 3017, 2950, 2884, 1739, 1696, 1503, 1456, 1394, 1337, 1282, 1249, 1169, 1124, 1102, 1079, 1055, 986, 917, 850, 751 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}N_2O_2S$ (MH^+) 325.1005; found 325.1001.



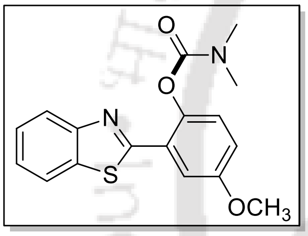
2-(Benzo[*d*]thiazol-2-yl)phenyl piperidine-1-carboxylate (1e): Yellow solid; M.p. 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.65–1.74 (m, 6H), 3.54–3.56, (m, 2H), 3.79–3.80 (m, 2H), 7.25 (d, 1H, *J* = 7.4 Hz), 7.33–7.41 (m, 2H), 7.46–7.52 (m, 2H), 7.91 (d, 1H, *J* = 8.2 Hz), 8.09 (d, 1H, *J* = 8.8 Hz), 8.34 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.4, 25.7, 26.2, 45.5, 46.0, 121.4, 123.3, 124.0, 125.2, 125.8, 126.3, 126.6, 130.0, 131.4, 135.7, 149.4, 152.9, 162.8; IR (KBr):3060, 2937, 2856, 1723, 1422, 1222, 1196, 1138, 1019, 966, 758 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{18}N_2O_2S$ (MH^+) 339.1162; found 339.1168.



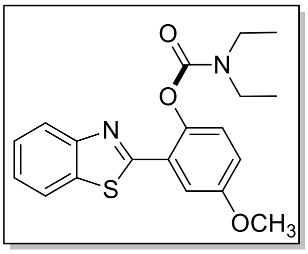
2-(Benzo[*d*]thiazol-2-yl)phenyl 4-benzylpiperidine-1-carboxylate (1f): Light yellow solid; M.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25–1.44 (m, 2H), 1.72–1.84 (m, 3H), 2.57–2.65 (m, 2H), 2.84 (t, 1H, *J* = 7.8 Hz), 3.07 (t, 1H, *J* = 7.0 Hz), 4.23 (d, 1H, *J* = 8.2 Hz), 4.50 (d, 1H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 6.8 Hz), 7.20–7.25 (m, 2H), 7.29–7.43 (m, 4H), 7.46–7.53 (m, 2H), 7.91 (d, 1H, *J* = 7.8 Hz), 8.09 (d, 1H, *J* = 7.6 Hz), 8.31 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.7, 32.2, 37.8, 42.9, 44.6, 45.1, 121.3, 123.2, 123.9, 125.2, 125.7, 126.0, 126.2, 126.5, 128.3, 129.1, 129.9, 131.3, 135.5, 139.9, 149.2, 152.7, 152.8, 162.7; IR (KBr):3061, 2920, 2853, 1723, 1423, 1266, 1190, 1107, 1057, 757, 732 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{24}N_2O_2S$ (MH$^+$) 429.1631; found 429.1637.



2-(Benzo[*d*]thiazol-2-yl)phenyl morpholine-4-carboxylate (1g): Yellow solid; M.p. 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.59–3.85 (m, 8H), 7.25–7.27 (m, 1H), 7.36–7.43 (m, 2H), 7.48–7.53 (m, 2H), 7.92 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.0 Hz), 8.27 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 44.5, 45.3, 66.8, 121.5, 123.4, 124.0, 125.4, 126.2, 126.4, 126.6, 130.4, 131.5,135.5, 148.9, 153.08,153.09, 162.8; IR (KBr): 3015, 2944, 1733, 1642, 1394, 1237, 1182, 1076, 958, 840, 770 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}N_2O_3S$ (MH$^+$) 341.0954; found 341.0957.

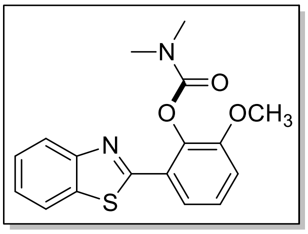


2-(Benzo[*d*]thiazol-2-yl)-4-methoxyphenyl dimethylcarbamate (2a): Yellow solid; M.p. 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06 (s, 3H), 3.28 (s, 3H), 3.91 (s, 3H), 7.04 (q, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.50 (t, 1H, J = 7.8 Hz), 7.88 (d, 1H, J = 7.2 Hz), 7.92 (d, 1H, J = 7.6 Hz), 8.08 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.0, 37.1, 56.0, 113.2, 118.3, 121.5, 123.4, 125.1, 125.3, 126.3, 127.1, 135.7, 143.1, 152.8, 154.6, 157.2,162.6; IR (KBr): 3025, 2923, 2838, 1740, 1682, 1507, 1387, 1290, 1164, 1123, 994, 883, 774 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3S$ (MH$^+$) 329.0954; found 329.0951.

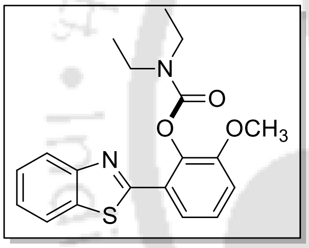


2-(Benzo[*d*]thiazol-2-yl)-4-methoxyphenyl diethylcarbamate (2b): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (t, 3H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.0 Hz), 3.41 (q, 2H, J = 7.2 Hz), 3.63 (q, 2H, J = 7.2 Hz), 3.91 (s, 3H), 7.03 (d, 1H, J = 6.0 Hz), 7.13, (d, 1H, J = 9.2 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.50 (t, 1H, J = 7.2 Hz), 7.83 (s, 1H,), 7.91 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 14.4, 42.4, 42.5, 56.0, 113.4, 118.2, 121.4, 123.4, 124.9, 125.3, 126.3, 127.3, 135.8, 143.2, 150.8, 152.9, 154.0, 157.1, 162.8; IR

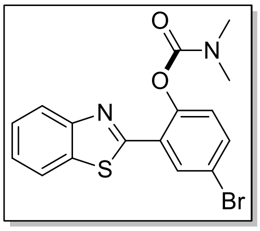
(KBr): 2977, 2937, 1752, 1643, 1463, 1249, 1124, 1098, 915, 768 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_3S$ (MH$^+$) 357.1267; found 357.1265.



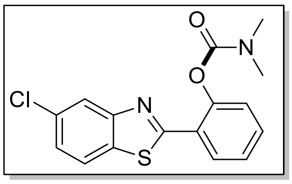
2-(Benzo[*d*]thiazol-2-yl)-6-methoxyphenyl dimethylcarbamate (3a): Red solid; M.p. 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.09 (s, 3H), 3.30 (s, 3H), 3.90 (s, 3H), 7.07 (d, 1H, *J* = 8.2 Hz), 7.31 (t, 1H, *J* = 8.2 Hz), 7.39 (t, 1H, *J* = 8.2 Hz), 7.49 (t, 1H, *J* = 7.8 Hz), 7.91 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 8.0 Hz), 8.08 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.0, 37.1, 56.4, 114.0, 121.0, 121.4, 123.3, 125.2, 126.2, 127.8, 135.7, 139.1, 152.5, 152.6, 153.6, 162.5; IR (KBr): 2924, 2851, 1722, 1577, 1476, 1432, 1391, 1273, 1160, 1096, 991 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3S$ (MH$^+$) 329.0954; found 329.0960.



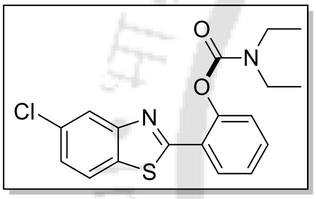
2-(Benzo[*d*]thiazol-2-yl)-6-methoxyphenyl diethylcarbamate (3b): Red solid; M.p. 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz), 3.40–3.52 (m, 4H), 3.89 (s, 3H), 7.06 (d, 1H, *J* = 8.2 Hz), 7.30 (t, 1H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.90 (d, 1H, *J* = 7.4 Hz) 7.98 (d, 1H, *J* = 8.0 Hz), 8.08 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.5, 14.3, 42.4, 42.6, 56.4, 114.1, 121.2, 121.4, 123.4, 125.2, 126.1, 126.2, 128.0, 135.9, 139.5, 152.6, 152.8, 153.2, 162.7; IR (KBr): 3061, 2974, 2935, 1723, 1583, 1454, 1417, 1316, 1272, 1149, 1098, 995, 761 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_3S$ (MH$^+$) 357.1267; found 357.1275.



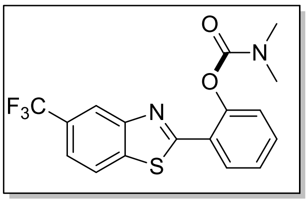
2-(Benzo[*d*]thiazol-2-yl)-4-bromophenyl dimethylcarbamate (4a): White solid; M.p. 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.04 (s, 3H), 3.26 (s, 3H), 7.10 (d, 1H, *J* = 8.4 Hz), 7.40 (t, 1H, *J* = 8.0 Hz), 7.50 (t, 1H, *J* = 7.6 Hz), 7.55 (d, 1H, *J* = 8.8 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 8.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.1, 37.3, 119.2, 121.5, 123.6, 125.7, 125.8, 126.6, 128.3, 132.5, 134.2, 135.8, 148.4, 152.7, 153.8, 161.0; IR (KBr): 2924, 2854, 1741, 1493, 1384, 1158, 1118, 875, 759 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}BrN_2O_2S$ (MH$^+$) 376.9953; found 376.9955.



2-(5-Chlorobenzo[*d*]thiazol-2-yl) phenyl dimethylcarbamate (5a): Light yellow solid; M.p. 118–119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.07 (s, 3H), 3.29 (s, 3H), 7.25 (d, 1H, *J* = 8.0 Hz), 7.35–7.39 (m, 2H), 7.51 (t, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 8.05 (s, 1H), 8.33 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.0, 37.2, 122.2, 123.0, 124.1, 125.8, 126.0, 126.2, 130.0, 131.8, 132.3, 133.9, 149.4, 153.7, 154.1, 164.6; IR (KBr): 3062, 2924, 2846, 1721, 1494, 1428, 1384, 1202, 1155, 1107, 1004, 908, 760, 748 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2S$ (MH$^+$) 333.0459; found 333.0463.

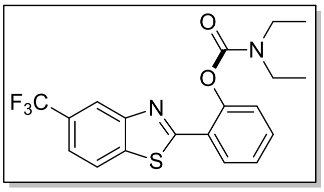


2-(5-Chlorobenzo[*d*]thiazol-2-yl)phenyl diethylcarbamate (5b): Light yellow solid; M.p. 76–77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (t, 3H, *J* = 7.0 Hz)), 1.32 (t, 3H, *J* = 7.0 Hz), 3.41 (q, 2H, *J* = 6.8 Hz), 3.63 (q, 2H, *J* = 6.8 Hz), 7.24 (t, 1H, *J* = 7.8Hz), 7.34–7.37 (m, 2H), 7.50 (t, 1H, *J* = 7.6 Hz), 7.81 (d, 1H, *J* = 8.8 Hz,), 8.04 (s, 1H), 8.27 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.4, 14.5, 42.2, 42.5, 122.2, 123.1, 124.0, 125.7, 125.9, 126.4, 130.2, 131.8, 132.2, 134.0, 149.6, 153.5, 153.9, 164.9; IR (KBr): 2971, 2928, 2855, 1720, 1411, 1382, 1270, 1195, 1149, 1090, 1034, 952, 903, 868, 758, 579 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}ClN_2O_2S$. (MH$^+$) 361.0772; found 361.0779.

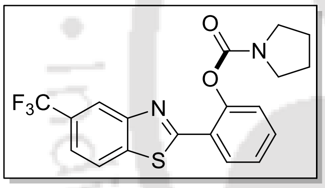


2-(5-(Trifluoromethyl)benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate (6a): Light yellow solid; M.p. 97–99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.07 (s, 3H), 3.29 (s, 3H), 7.25 (d, 1H, *J* = 8.0 Hz), 7.36 (t, 1H, *J* = 8.0 Hz), 7.51 (t, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 7.2 Hz), 8.00 (d, 1H, *J* = 8.0 Hz), 8.32 (s, 1H), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.0, 37.2, 120.5, 121.6, 122.2, 124.1, 126.0, 126.1, 128.8, 129.1, 130.1, 132.1, 139.0, 149.5, 152.5,154.5, 164.9; IR (KBr):

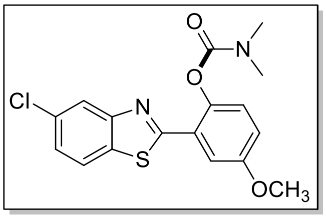
2924, 2853, 1715, 1607, 1445, 1388, 1334, 1203, 1145, 971, 817, 757 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2O_2S$ (MH$^+$) 367.0723; found 367.0716.



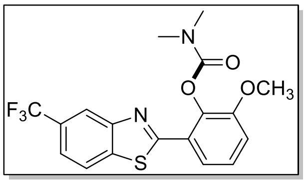
2-(5-(Trifluoromethyl)benzo[*d*]thiazol-2-yl) phenyl diethylcarbamate (6b): Light Yellow solid; M.p. 133–134 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.20 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.2 Hz), 3.42 (q, 2H, *J* = 6.8 Hz), 3.64 (q, 2H, *J* = 6.8 Hz), 7.24 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.6Hz), 7.52 (t, 1H, *J* = 8.2 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 8.00 (d, 1H, *J* = 8.4 Hz), 8.29–8.32 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 13.4, 14.5, 42.2, 42.5, 120.5, 120.5, 121.6, 122.2, 124.1, 126.1, 126.3, 130.3, 132.1, 139.1, 149.7, 152.7, 153.5, 165.2; IR (KBr): 3079, 2979, 2937, 1726, 1611, 1422, 1333, 1270, 1197, 1149, 1121, 971, 755 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}F_3N_2O_2S$ (MH$^+$) 395.1036; found 395.1037.



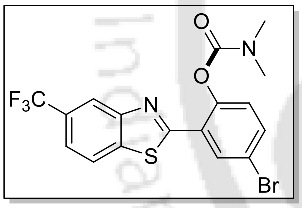
2-(5-(Trifluoromethyl)benzo[*d*]thiazol-2-yl) phenyl pyrrolidine-1-carboxylate (6d): Yellow solid; M.p. 109–111 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.98–2.08 (m, 4H), 3.53 (t, 2H, *J* = 6.8 Hz), 3.80 (t, 2H, *J* = 6.4 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 8.33 (s, 1H), 8.37 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 25.2, 26.1, 47.0, 120.5, 121.6, 122.2, 123.1, 124.2, 125.8, 126.0, 128.9, 129.2, 130.2, 132.1, 139.1, 149.5, 152.4, 152.5, 165.0; IR (KBr): 2981, 2880, 1727, 1608, 1466, 1395, 1332, 1249, 1172, 1114, 1050, 913, 882, 817, 748, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}F_3N_2O_2S$ (MH$^+$) 393.0879; found 393.0869.



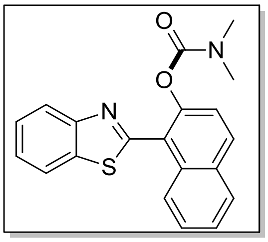
2-(5-Chlorobenzo[*d*]thiazol-2-yl)-4-methoxyphenyl dimethylcarbamate (7a): Brown solid; M.p. 137–138 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.07 (s, 3H), 3.29 (s, 3H), 3.92 (s, 3H), 7.05 (d, 1H, *J* = 9.0 Hz), 7.14 (d, 1H, *J* = 9.2 Hz), 7.37 (d, 1H, *J* = 10.4 Hz), 7.51 (d, 1H, *J* = 8.4 Hz), 7.86 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 37.1, 37.3, 56.1, 113.2, 118.8, 122.3, 123.2, 125.1, 125.9, 126.8, 132.4, 134.1, 143.2, 153.7, 154.6, 157.3, 164.5; IR (KBr): 3008, 2960, 2911, 1747, 1505, 1464, 1387, 1305, 1260, 1166, 1093, 1033, 918, 747 cm$^{-1;}$ HRMS (ESI): calcd. for $C_{17}H_{15}ClN_2O_3S$ (MH$^+$) 363.0565; found 363.0570.



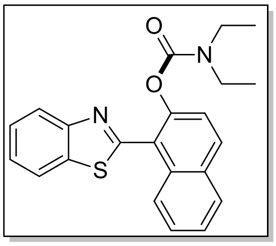
2-Methoxy-6-(5-(trifluoromethyl)benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate (8a): Yellow solid; M.p. 97–98 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.10 (s, 3H), 3.31 (s, 3H), 3.91 (s, 3H), 7.11 (d, 1H, *J* = 8.2 Hz), 7.34 (t, 1H, *J* = 8.0 Hz), 7.62 (d, 1H, *J* = 9.0 Hz), 8.01 (t, 2H, *J* = 8.9 Hz), 8.35 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 37.2, 37.3, 56.6, 114.7, 120.6, 121.1, 121.6, 122.2, 126.5, 127.4, 128.8, 129.1, 139.2, 139.4, 152.3, 152.6, 153.6, 164.7; IR (KBr): 2927, 2854, 1728, 1498, 1477, 1389, 1335, 1323, 1150, 1123, 1053, 996, 783 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}F_3N_2O_3S$ (MH$^+$) 397.0828; found 397.0830.



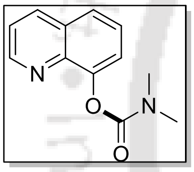
4-Bromo-2-(5-(trifluoromethyl)benzo[*d*]thiazol-2-yl)phenyl dimethylcarbamate (9a): White solid; M.p. 151–152 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.05 (s, 3H), 3.28 (s, 3H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.43 (d, 1H, *J* = 9.0 Hz), 7.62 (d, 1H, *J* = 7.8 Hz), 8.00 (d, 1H, *J* = 8.4 Hz), 8.31 (s, 1H), 8.36 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 37.1, 37.3, 120.8, 120.8, 122.0, 122.3, 123.5, 125.3, 125.6, 127.4, 129.2, 129.4, 129.6, 131.7, 131.8, 139.1, 148.1, 152.3, 153.8 163.3; IR (KBr): 3082, 2925, 2850, 1725, 1495, 1333, 1202, 1118, 922, 731 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}BrF_3N_2O_2S$ (MH$^+$) 444.9827; found 444.9830.



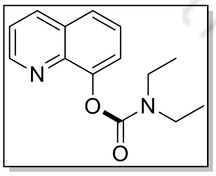
1-(Benzo[*d*]thiazol-2-yl) naphthalen-2-yl dimethylcarbamate (10a): Red gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.82 (s, 3H), 2.93 (s, 3H), 7.44–7.50 (m, 4H), 7.56 (t, 1H, *J* = 7.7 Hz), 7.88–8.00 (m, 4H), 8.20 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 36.6, 36.9, 121.7, 122.3, 122.5, 123.8, 125.5, 125.6, 126.0 126.3, 127.7, 128.3, 131.5, 131.7, 132.8, 136.6, 148.0, 153.5, 154.5, 162.6; IR (KBr): 3054, 2928, 1728, 1435, 1386, 1334, 1224, 1160, 1012, 760 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{16}N_2O_2S$ (MH^+) 349.1005; found 349.0999.



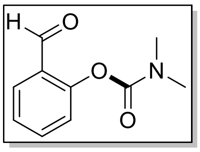
1-(Benzo[*d*]thiazol-2-yl) naphthalen-2-yl diethylcarbamate (10b): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.80 (t, 3H, *J* = 7.0 Hz), 1.06 (t, 3H, *J* = 7.0 Hz), 3.15 (q, 2H, *J* = 7.6 Hz), 3.27 (q, 2H, *J* = 7.6 Hz), 7.43–7.56 (m, 5H), 7.84–7.90 (m, 2H), 7.97 (t, 2H, *J* = 8.8 Hz), 8.17 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.3, 13.8, 41.9, 42.4, 121.6, 122.3, 122.6, 123.8, 125.6, 125.6, 125.9, 126.3, 127.6, 128.3, 131.4, 131.6, 132.9, 136.6, 148.1, 153.5, 153.9, 162.8; IR (KBr): 3062, 2973, 2933, 1715, 1422, 1380, 1263, 1215, 1153, 1101, 984, 761 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{20}N_2O_2S$ (MH^+) 377.1318; found 377.1320.



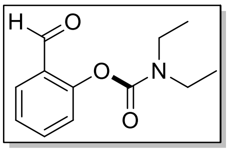
Quinolin-8-yl dimethylcarbamate (11a): Brow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.07 (s, 3H), 3.29 (s, 3H), 7.40–7.43 (m, 1H), 7.46–7.54 (m, 2H), 7.67 (d, 1H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 8.4 Hz), 8.95 (d, 1H, *J* = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 36.9, 121.6, 121.8, 125.4, 126.3, 129.6, 136.1, 141.9, 148.0, 150.4, 155.3; IR (KBr): 3043, 2929, 1723, 1470, 1384, 1242, 1169, 1089, 787, 735 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{12}N_2O_2$ (MH^+) 217.0972; found 217.0967.



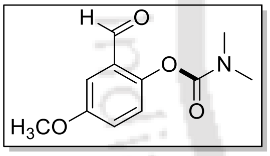
Quinolin-8-yl diethylcarbamate (11b): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (t, 3H, *J* = 6.8 Hz), 1.40 (t, 3H, *J* = 8.8 Hz), 3.45 (q, 2H, *J* = 7.2 Hz), 3.64 (q, 2H, *J* = 7.2 Hz), 7.36–7.39 (m, 1H), 7.46–7.52 (m, 2H), 7.66 (d, 1H, *J* = 7.0 Hz), 8.12 (d, 1H, *J* = 8.4 Hz), 8.90 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.5, 14.3, 42.4, 121.6, 121.8, 125.2, 126.3, 129.6, 136.0, 142.1, 148.2, 150.3, 154.8; IR (KBr): 2972, 1717, 1665, 1467, 1273, 1155, 1092, 956, 779, 752 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}N_2O_2$ (MH^+) 245.1285; found 245.1290.



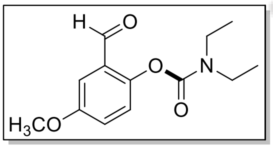
2-Formylphenyl dimethylcarbamate (12a): Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.04 (s, 3H), 3.16 (s, 3H), 7.23 (d, 1H, *J* = 8.0 Hz), 7.34 (t, 1H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 7.6 Hz), 10.19 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 36.9, 37.2, 123.9, 126.0, 128.7, 130.1, 135.4, 153.2, 154.5, 189.1; IR (KBr): 3077, 2932, 2858, 1732, 1701, 1477, 1386, 1158, 812, 759 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{11}NO_3$ (MH^+) 194.0811; found 194.0815.



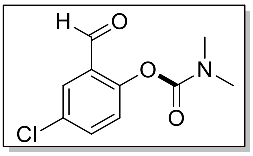
2-Formylphenyl diethylcarbamate (12b): Light yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.21 (t, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 3.39 (q, 2H, *J* = 6.6 Hz), 3.49 (q, 2H, *J* = 7.2 Hz), 7.25 (d, 1H, *J* = 8.4 Hz), 7.32 (t, 1H, *J* = 7.2 Hz), 7.59 (t, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 7.8 Hz), 10.12 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.4, 14.4, 42.3, 42.4, 123.7, 125.8, 128.7, 129.8, 135.3, 153.3, 153.8, 188.9; IR (KBr): 3079, 2977, 2935, 1725, 1604, 1582, 1422, 1210, 1153, 809, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{15}NO_3$ (MH^+) 222.1124; found 222.1120.



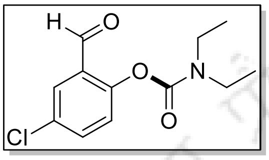
2-Formyl-4-methoxyphenyl dimethylcarbamate (13a): Brown gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.01 (s, 3H), 3.04 (s, 3H), 3.85 (s, 3H), 7.15 (d, 1H, *J* = 2.4 Hz), 7.27 (s, 1H), 7.34 (d, 1H, *J* = 2.4 Hz), 10.16 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 36.8, 37.1, 56.0, 111.6, 122.6, 125.0, 129.0, 147.4, 154.8, 157.4, 188.7; IR (KBr): 2929, 2858, 1729, 1693, 1491, 1385, 1274, 1153, 735 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{13}NO_4$ (MH^+) 224.0917; found 224.0920.



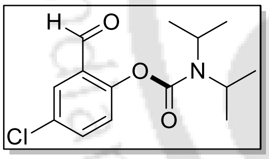
2-Formyl-4-methoxyphenyl diethylcarbamate (13b): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19 (t, 3H, *J* = 6.8 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 3.37 (q, 2H, *J* = 7.2 Hz), 3.47 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 3H), 7.12 (s, 2H), 7.32 (s, 1H), 10.13 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.5, 14.5, 42.2, 42.7, 56.0, 111.3, 122.6, 124.9, 129.1, 147.6, 154.2, 157.3, 188.6; IR (KBr): 2974, 2931, 2855, 1724, 1695, 1585, 1422, 1272, 1150, 1037 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{17}NO_4$ (MH^+) 252.1230; found 252.1237.



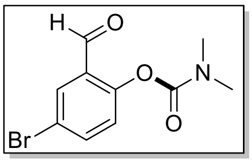
4-Chloro-2-formylphenyl dimethylcarbamate (14a): Brown semi solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.03 (s, 3H), 3.15 (s, 3H), 7.20 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 8.4 Hz), 7.82 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 36.8, 37.2, 125.4, 129.3, 129.6, 131.8, 135.0, 151.7, 154.0, 187.6; IR (KBr): 2930, 2858, 1735, 1692, 1474, 1384, 1278, 1215, 1159, 1004, 862, 749 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}ClNO_3$ (MH$^+$) 228.0421; found 228.0425.



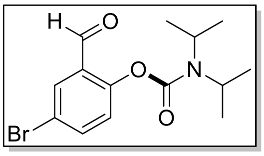
4-Chloro-2-formylphenyl diethylcarbamate (14b): Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (t, 3H, J = 6.8 Hz), 1.25 (t, 3H, J = 7.6 Hz), 3.36 (q, 2H, J = 6.8 Hz), 3.46 (q, 2H, J = 6.8 Hz), 7.17 (d, 1H, J = 8.4 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.79 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.4, 14.4, 42.3, 42.7, 125.3, 129.0, 129.1, 131.6, 135.0, 151.8, 153.3, 187.4; IR (KBr): 2977, 2934, 2880, 1726, 1693, 1422, 1275, 1208, 1181, 1151, 896, 705 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}ClNO_3$ (MH$^+$) 256.0730; found 256.0725.



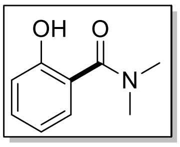
4-Chloro-2-formylphenyl diisopropylcarbamate (14c): Light yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27–1.33 (m, 12H), 3.95–3.98 (m, 1H), 4.07–4.10 (m, 1H), 7.14 (d, 1H, J = 8.8 Hz), 7.51 (d, 1H, J = 8.8 Hz), 7.81 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.6, 21.6, 47.1, 47.3, 125.4, 128.9, 129.9, 131.6, 135.0, 151.8, 152.8, 187.5; IR (KBr): 2979, 2930, 2874, 2850, 1719, 1688, 1432, 1316, 1205, 1041, 891, 748 cm^{-1} HRMS (ESI): calcd. for $C_{14}H_{18}ClNO_3$ (MH$^+$) 284.1047; found 284.1050.



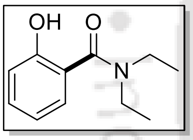
4-Bromo-2-formylphenyl dimethylcarbamate (15a): White semi solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.00 (s, 3H), 3.12 (s, 3H), 7.12 (d, 1H, J = 8.8 Hz), 7.64 (d, 1H, J = 6.8 Hz), 7.94 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 36.8, 37.2, 119.2, 125.7, 129.9, 132.3, 138.0, 152.2, 153.9, 187.4; IR (KBr): 2923, 2848, 1736, 1685, 1592, 1470, 1386, 1254, 1162, 861, 808 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}BrNO_3$ (MH$^+$) 271.9916; found 271.9920.



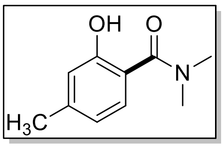
4-Bromo-2-formylphenyl diisopropylcarbamate (15c): Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20–1.32 (m, 12H), 3.94–3.97 (m, 1H), 4.06–4.10 (m, 1H), 7.07 (d, 1H, *J* = 8.4 Hz), 7.65 (d, 1H, *J* = 8.4 Hz), 7.96 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.5, 21.6, 47.1, 47.3, 119.1, 125.7, 130.2, 132.0, 137.9, 152.3, 152.7, 187.4; IR (KBr): 2971, 2932, 2872, 1720, 1592, 1431, 1315, 1203, 1040, 888 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{18}BrNO_3$ (MH^+) 328.0542; found 328.0545.



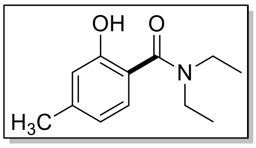
2-Hydroxy-*N*,*N*-dimethylbenzamide (16a): White solid; M.p. 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.13 (s, 6H), 6.82 (t, 1H, *J* = 8.0 Hz), 6.96 (d, 1H, *J* = 8.8 Hz), 7.26–7.31 (m, 2H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.0, 118.0, 118.5, 128.7, 132.6, 159.0, 171.9; IR (KBr): 3396, 3076, 2932, 1622, 1599, 1453, 1293, 1117, 918, 761 cm^{-1}; HRMS (ESI): calcd. for $C_9H_{11}NO_2$ (MH^+) 166.0862; found 166.0870.



***N*,*N*-Diethyl-2-hydroxybenzamide (16b):** Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (t, 6H, *J* = 7.6 Hz), 3.49 (q, 4H, *J* = 7.2 Hz), 6.82 (t, 1H, *J* = 8.0 Hz), 6.97 (d, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.29 (t, 1H, *J* = 8.4 Hz), 9.78 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.6, 42.3, 118.1, 118.5, 118.7, 127.5, 132.4, 158.8, 171.6; IR (KBr): 3417, 2975, 2872, 1725, 1594, 1448, 1294, 1216, 1086, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{15}NO_2$ (MH^+) 194.1175; found 194.1180.



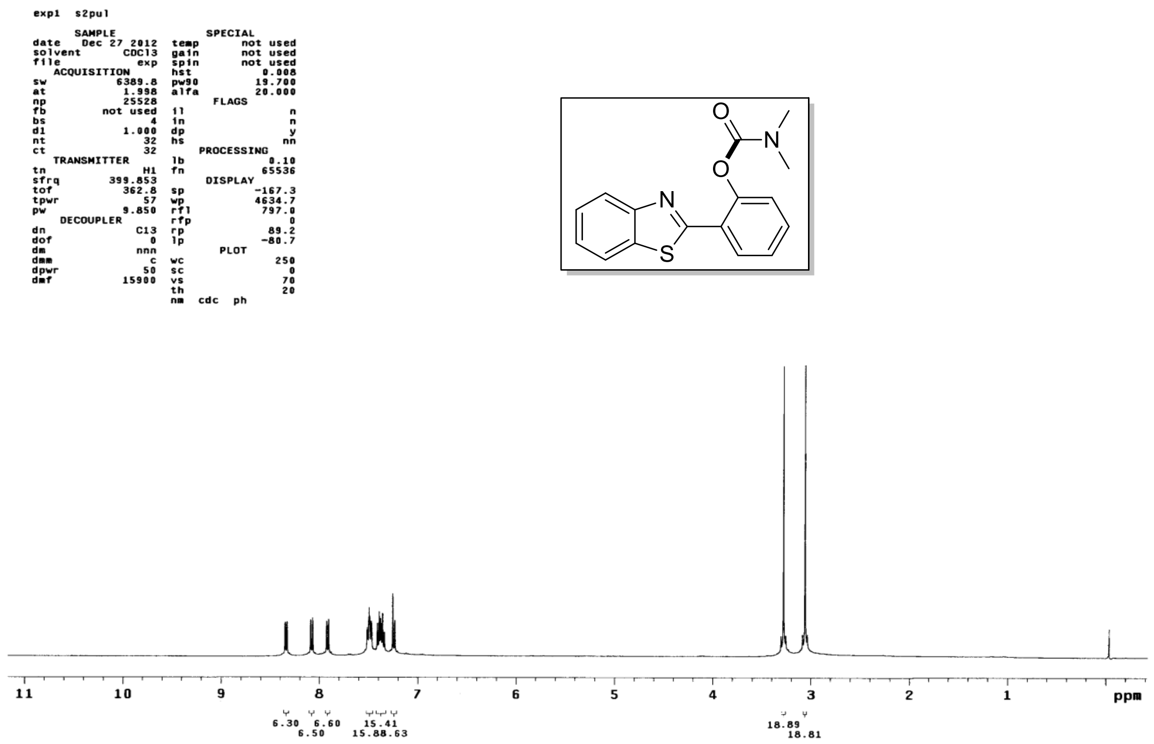
2-Hydroxy-*N*,*N*,5-trimethylbenzamide (17a): Light yellow gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.15 (s, 6H), 6.65 (d, 1H, *J* = 8.4 Hz), 6.81 (s, 1H), 7.20 (d, 1H, *J* = 7.8 Hz), 10.12 (s,1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 38.6, 114.3, 118.5, 119.4, 128.7, 143.7, 159.8, 172.4; IR (KBr): 3173, 2925, 2851, 1727, 1618, 1401, 1264, 1128, 813, 737 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{13}NO_2$ (MH^+) 180.1018; found 180.1025.



***N,N*-Diethyl-2-hydroxy-5-methylbenzamide (17b):** Light yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (t, 6H, *J* = 6.8 Hz), 2.32 (s, 3H), 3.51 (q, 4H, *J* = 6.8 Hz), 6.64 (d, 1H, *J* = 7.2 Hz), 6.81 (s, 1H), 7.16 (d, 1H, *J* = 7.6 Hz), 9.98 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.6, 21.7, 42.4, 115.3, 118.5, 119.5, 127.4, 143.4, 159.3, 171.9; IR (KBr): 3412, 3073, 2972, 2929, 1728, cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{17}NO_2$ (MH^+) 208.1331; found 208.1331.

II.7. Spectra

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



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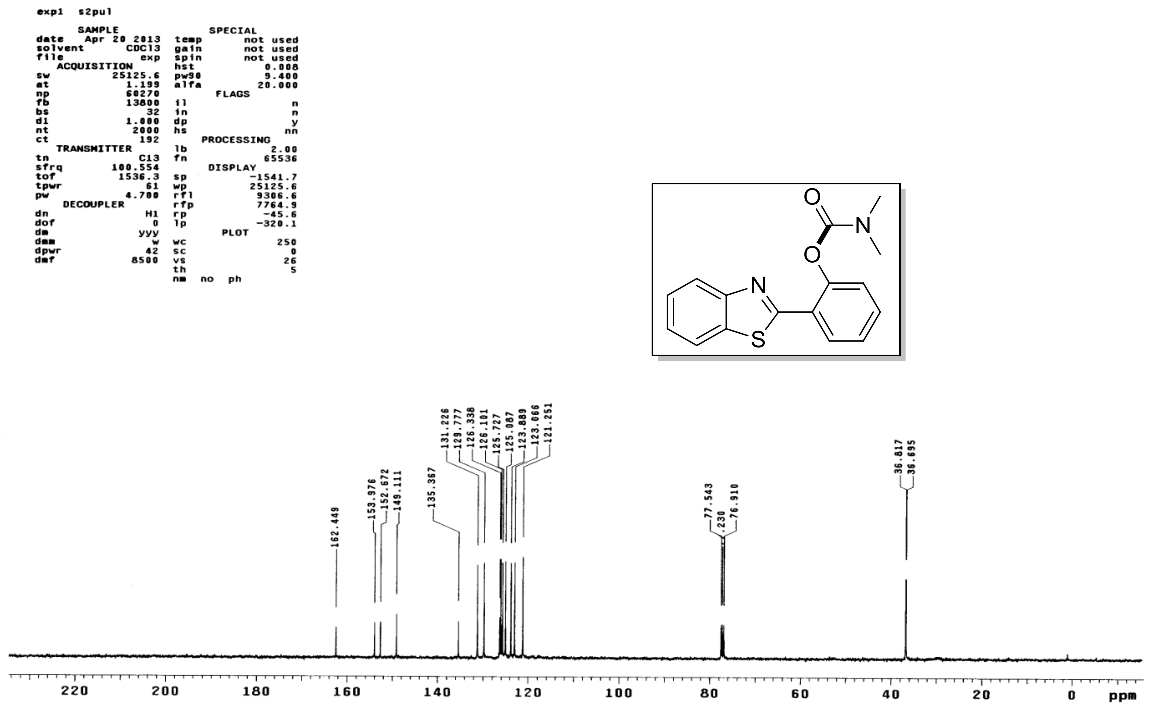
solvent       CDCl3   gain         not used
file            exp   spin         not used
   ACQUISITION        hst             0.008
sw           6389.8   pw90           19.700
at            1.998   alfa           20.000
np            25528            FLAGS
fb         not used   il                  n
bs                4   in                  n
d1            1.000   dp                  y
nt               32   hs                 nn
ct               32          PROCESSING
   TRANSMITTER        lb               0.10
tn               H1   fn              65536
sfrq        399.853           DISPLAY
tof           362.8   sp             -167.3
tpwr             57   wp             4634.7
pw            9.850   rfl             797.0
    DECOUPLER         rfp                 0
dn              C13   rp               89.2
dof               0   lp              -80.7
dm              nnn             PLOT
dmm               c   wc                250
dpwr             50   sc                  0
dmf           15900   vs                 70
                      th                 20
                      nm   cdc   ph
```

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



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expl   s2pul

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solvent       CDCl3   gain         not used
file            exp   spin         not used
   ACQUISITION        hst             0.008
sw          25125.6   pw90            9.400
at            1.199   alfa           20.000
np            60270            FLAGS
fb            13800   il                  n
bs               32   in                  n
d1            1.000   dp                  y
nt             2000   hs                 nn
ct              192          PROCESSING
   TRANSMITTER        lb               2.00
tn              C13   fn              65536
sfrq        100.554           DISPLAY
tof          1536.3   sp            -1541.7
tpwr             61   wp            25125.6
pw            4.700   rfl            9306.6
    DECOUPLER         rfp            7764.9
dn               H1   rp              -45.6
dof               0   lp             -320.1
dm              yyy             PLOT
dmm               w   wc                250
dpwr             42   sc                  0
dmf            8500   vs                 26
                      th                  5
                      nm   no   ph
```
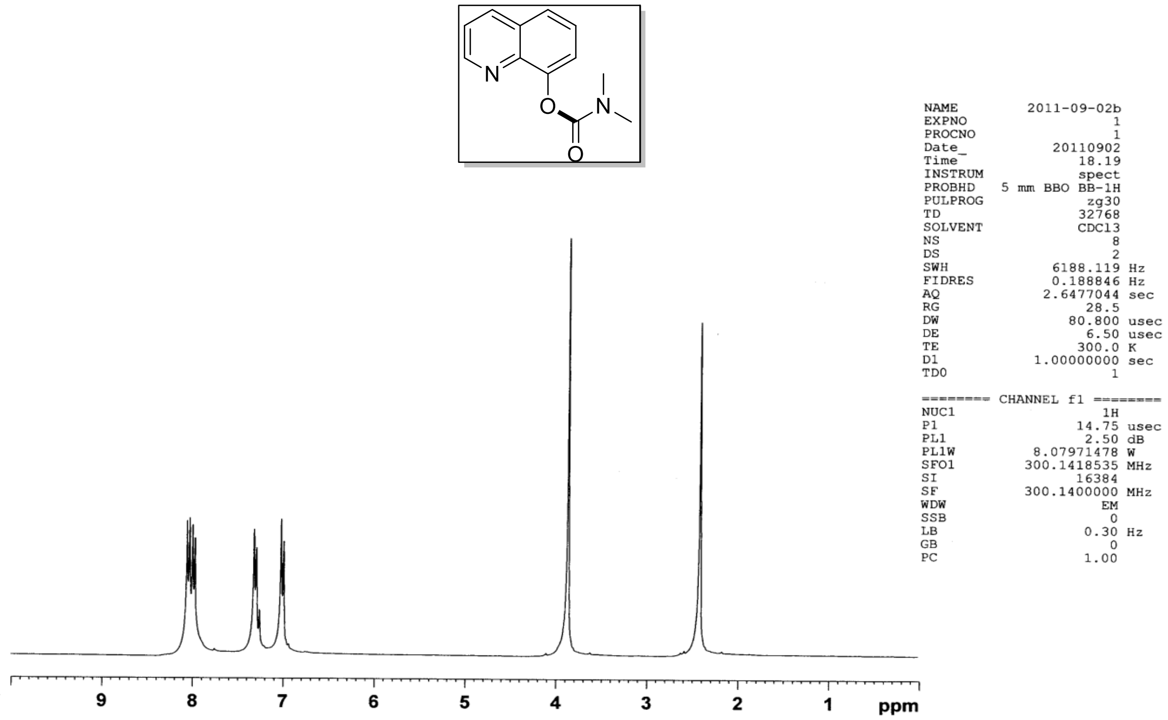

Quinolin-8-yl dimethylcarbamate (11a): ^{1}HNMR (600 MHz, $CDCl_3$)



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PROCNO                  1
Date_            20110902
Time                18.19
INSTRUM             spect
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PULPROG              zg30
TD                  32768
SOLVENT             CDC13
NS                      8
DS                      2
SWH              6188.119 Hz
FIDRES           0.188846 Hz
AQ              2.6477044 sec
RG                   28.5
DW                 80.800 usec
DE                   6.50 usec
TE                  300.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.75 usec
PL1                  2.50 dB
PL1W           8.07971478 W
SFO1          300.1418535 MHz
SI                  16384
SF            300.1400000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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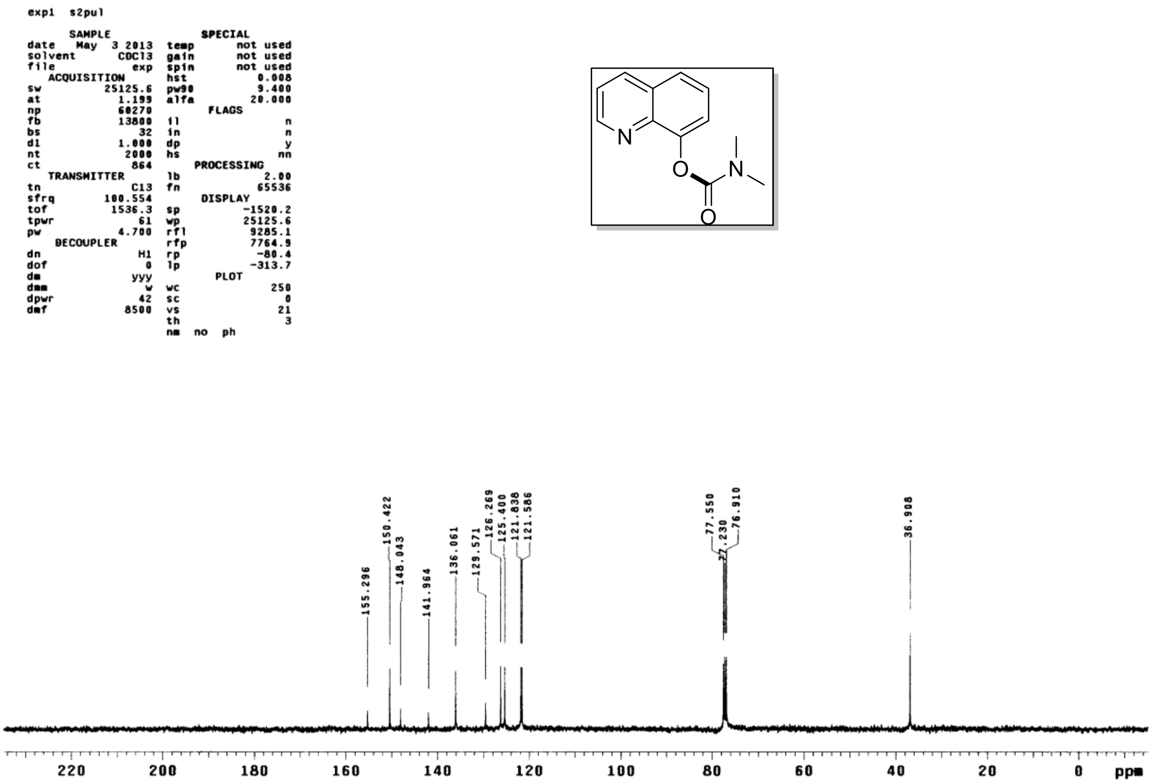
Quinolin-8-yl dimethylcarbamate (11a): ^{13}CNMR (100 MHz, $CDCl_3$)



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exp1  s2pul

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solvent       CDC13   gain       not used
file            exp   spin       not used
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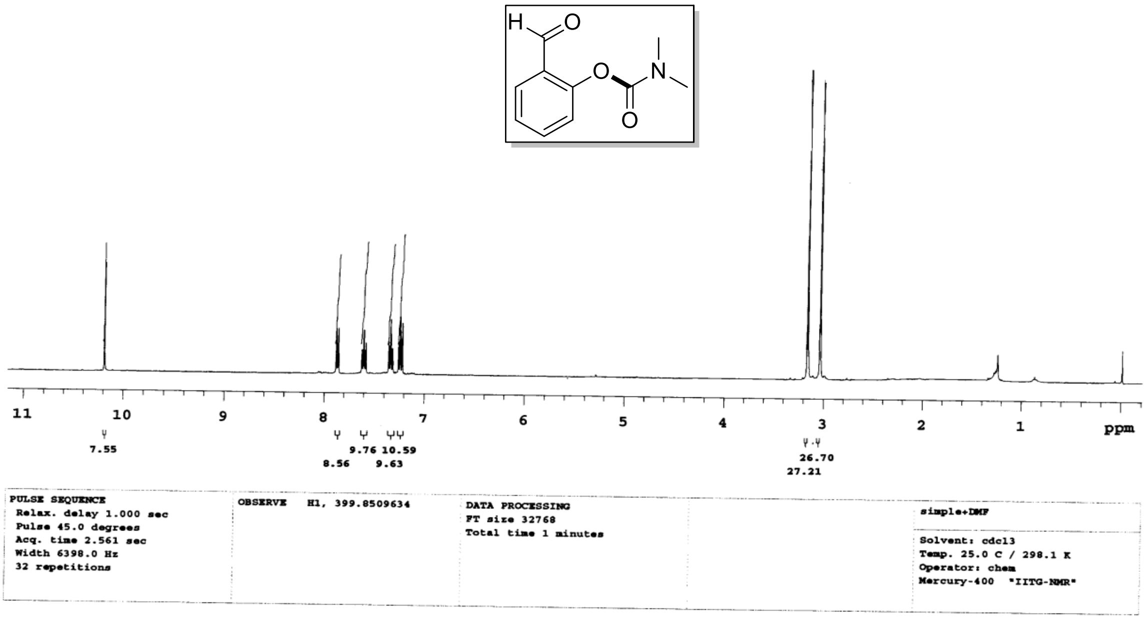
sw          25125.6   pw90          9.400
at            1.199   alfa         20.000
np            60270          FLAGS
fb            13800   il                n
bs               32   in                n
d1            1.000   dp                y
nt             2000   hs               nn
ct              864        PROCESSING
   TRANSMITTER        lb             2.00
tn              C13   fn            65536
sfrq        100.554         DISPLAY
tof          1536.3   sp          -1520.2
tpwr             61   wp          25125.6
pw            4.700   rfl          9285.1
    DECOUPLER         rfp          7764.9
dn               H1   rp            -80.4
dof               0   lp           -313.7
dm              yyy            PLOT
dmm               w   wc              250
dpwr             42   sc                0
dmf            8500   vs               21
                      th                3
                      nm   no   ph
```

2-Formylphenyl dimethylcarbamate (12a): ^{1}HNMR (400 MHz, $CDCl_3$)



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 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions
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DATA PROCESSING
FT size 32768
Total time 1 minutes
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simple+DMF

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```
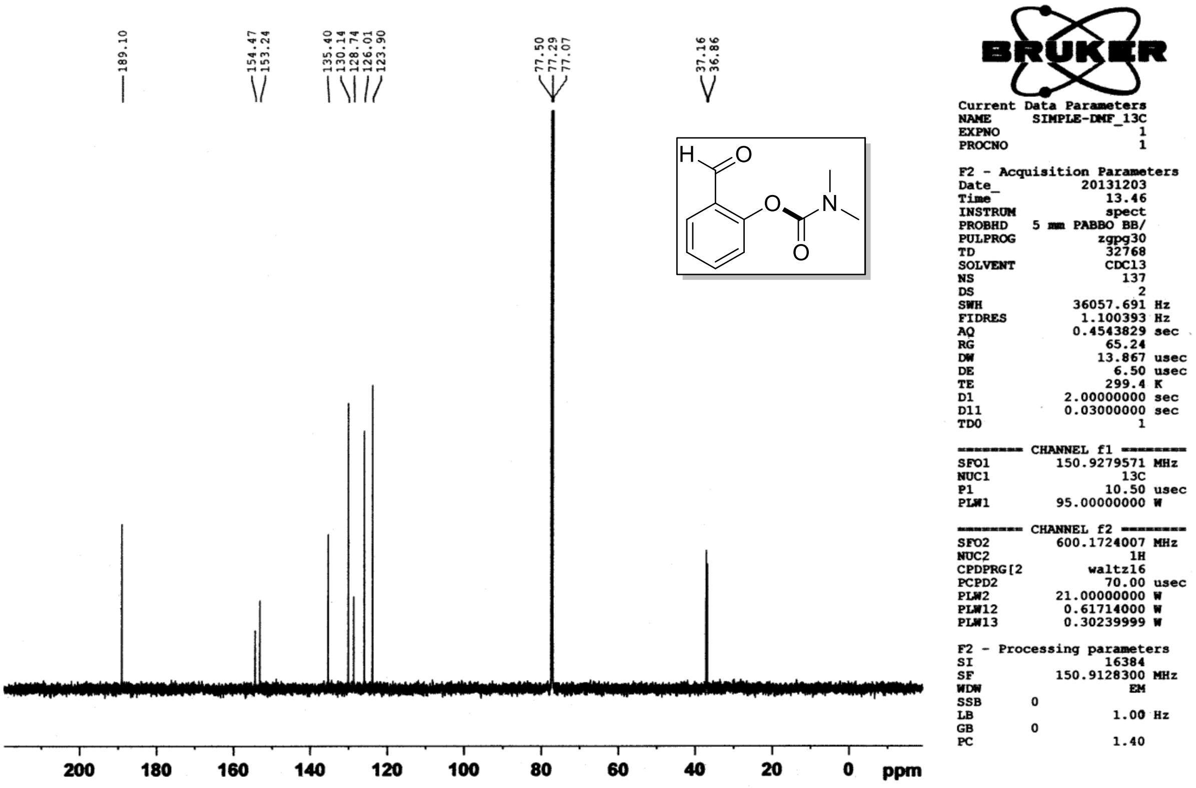

2-Formylphenyl dimethylcarbamate (12a): ^{13}CNMR (150 MHz, $CDCl_3$)



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PROCNO                  1

F2 - Acquisition Parameters
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Time                13.46
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PULPROG            zgpg30
TD                  32768
SOLVENT             CDC13
NS                    137
DS                      2
SWH             36057.691 Hz
FIDRES           1.100393 Hz
AQ              0.4543829 sec
RG                  65.24
DW                 13.867 usec
DE                   6.50 usec
TE                  299.4 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

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

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

F2 - Processing parameters
SI                  16384
SF            150.9128300 MHz
WDW                    EM
SSB        0
LB                   1.00 Hz
GB         0
PC                   1.40
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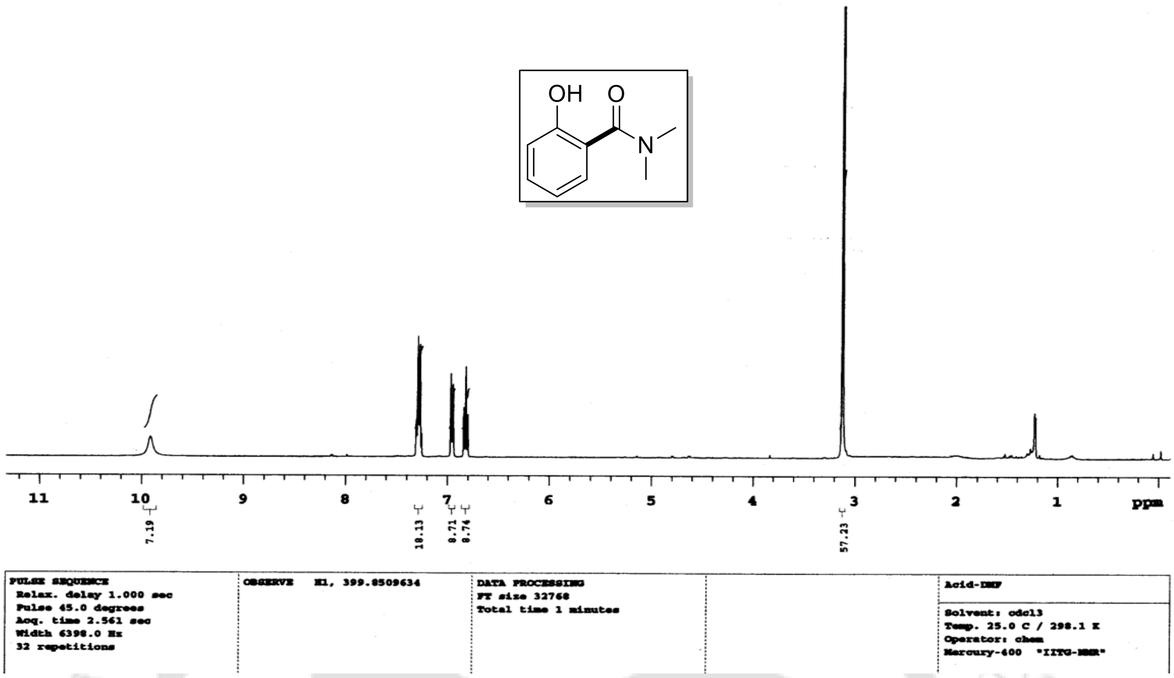
2-Hydroxy-*N*,*N*-dimethylbenzamide (16a): ^{1}HNMR (400 MHz, $CDCl_3$)



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PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions

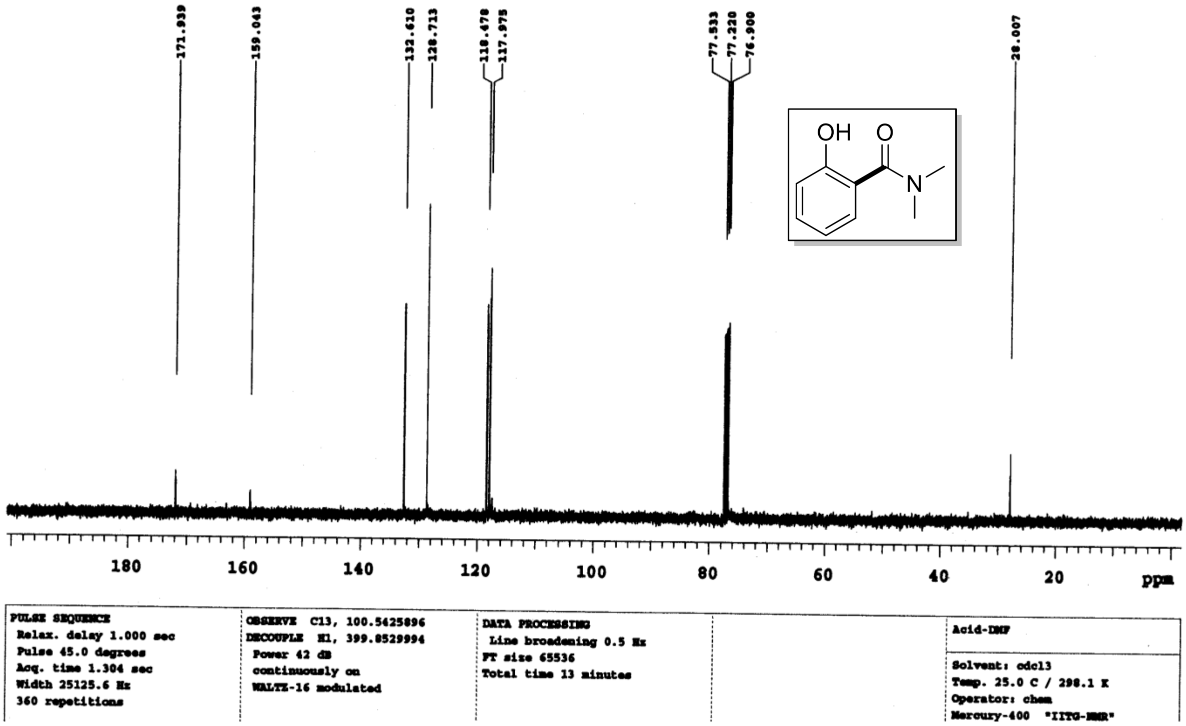
OBSERVE   H1, 399.8509634

DATA PROCESSING
FT size 32768
Total time 1 minutes

Acid-DMF

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```

2-Hydroxy-*N*,*N*-dimethylbenzamide (16a): ^{13}CNMR (100 MHz, $CDCl_3$)



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PULSE SEQUENCE
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 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 360 repetitions

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DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 13 minutes

Acid-DMF

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
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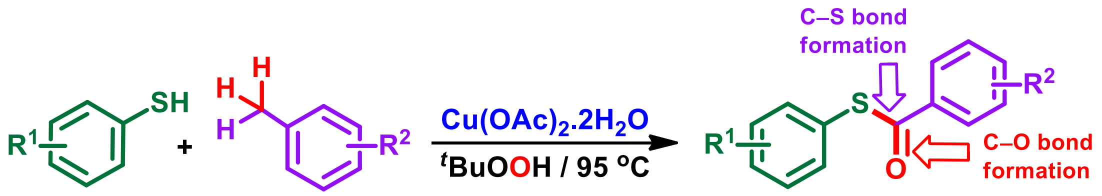
Chapter IIIA

Thioesterification of Alkylbenzenes with Thiols via Copper(II)-Catalyzed Cross-Dehydrogenative Coupling without a Directing Group



- C–S & C–O bond formation
- without directing group
- sp^3 C–H functionalization

Abstract: *A unique copper-catalyzed cross-dehydrogenative coupling (CDC) of thiols and alkylbenzenes has been developed for the synthesis of thioesters without the assistance of any directing group. A thioester moiety is created via successive C–S and C–O bond formations at the expense of three sp^3 C–Hs of alkylbenzene and one sp^3 S–H of thiol. Aromatic as well as aliphatic thiols underwent efficient coupling to give thioesters in moderate to good yields. Selective mono S-aroylation was observed in poly-methylated benzene.*

CHAPTER IIIA

IIIA. Thioesterification of Alkylbenzenes with Thiols via Copper-Catalyzed Cross-Dehydrogenative Coupling without a Directing Group

IIIA.1. Introduction

In the modern era of synthetic organic chemistry, cross-dehydrogenative coupling (CDC) has become an impactful strategy in the field of C–H bond functionalizations.[1] C–H bonds which were previously considered to be dormant can now be functionalized selectively employing the CDC strategy. Thus the avoidance of prefunctionalization of precursors for a CDC based methodology has led to a reduction in the number of steps thereby making the process more atoms economic. Even though the utilization of a CDC strategy has been applied to C–H's bonds of all types (sp, sp^2, sp^3),[2] the most appealing results, however is with the functionalizations of inert sp^3 C–H bonds.[1a,b] Pertinent to the sp^3 C–H bond functionalizations via CDC, alkylbenzenes have recently serves as precursors to several latent motifs such as ArCOO–,[3a,b] ArCO–,[3c-f] $ArCH_2O$–[3g] and $ArCH_2$–,[3a] which are integral parts of organic synthesis.

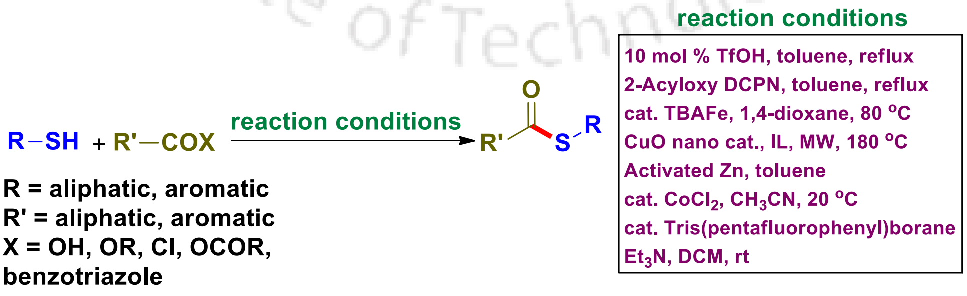
In spite of reaching great advances, the vast majority of functionalization processes at sp^3 C–H bonds via CDC have been achieved by the sp^3 C–C bond forming reactions.[1a,b] The sp^3 C–heteroatom bond formation by CDC strategy is mostly confined to the construction of C–N[4] and C–O bonds[3a-f,4,5] with only few examples of C–S bond formations.[6] Thus, it is imperative to develop protocols for the later bonds since sulfur-containing compounds find potential uses in pharmaceutical and agrochemical industries. One of the problems associated with the use of thiol as coupling partner during C–S bond formation is its propensity to undergo oxidative self-dimerization which inhibits the desired C–S bond formation. To combat this disadvantage of thiols, they are mostly employed in the form of their disulfides,[6,7] sulfonylhydrazides[8] or sulfonylchlorides[9] that generate *in situ* reactive free radical or cationic intermediates essential for CDC reactions. Few direct thiolations process using thiols or their derivatives have been demonstrated at sp^3 C–H bonds α to a heteroatom[7] or a carbonyl group[10] under metal free conditions, but no such relevant examples at the relatively unactivated benzylic sp^3 C–H bonds have been reported in the literature.

IIIA.2. Strategies for the Thioesters Synthesis

Because of high reactivity of thioester with various nucleophiles, they serve as acylating agents in biochemical processes, therefore makes them a striking synthetic intermediate in a variety of chemical transformation. Organic compounds having thioester functionality also have biological relevance, with application in *in vivo* tumor suppression.[11] Due to biological and chemical importance thioesters have been synthesized previously by applying various strategies. These include (i) thioesterfication or trans-thioesterification of carboxylic acids or its derivatives[12] (ii) thiocarbonylation of iodoarenes with thiols and carbon monoxide using metal catalyst[13] (iii) *N*-heterocyclic carbene (NHC)-catalyzed redox coupling of aldehyde with thiols[14] (iv) oxidative radical coupling of disulphides/thiols with aldehyde or alcohol[15] and (v) oxidative decarboxylative thioesterification.[16]

(i) Thioesterfication or Trans-thioesterification of Carboxylic Acids or Its Derivatives

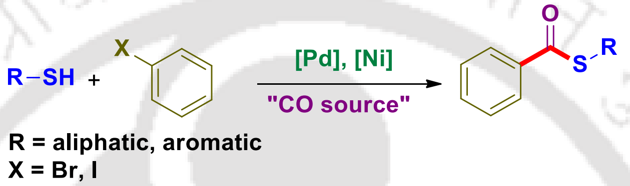
The most popular methods for the preparation of thioesters are the thioestrification or trans-thioestrification of carboxylic acid or its derivatives with thiols in the presence of various activating reagents. Direct thioestrification of carboxylic acid with thiols can be achieved in the presence of bronsted acid and 4,5-dichloropyridazin-3(2*H*)-one (DCPN).[12a-b] Different derivatives of carboxylic acid underwent trans-thioestrification with thiols in the presence of metal and metal-free conditions (Scheme IIIA.2.1).[12c-h]



Scheme IIIA.2.1. *Synthesis of thioesters from acid and its derivatives*

(ii) Thiocarbonylation of Iodoarenes with Thiols and Carbon Monoxide

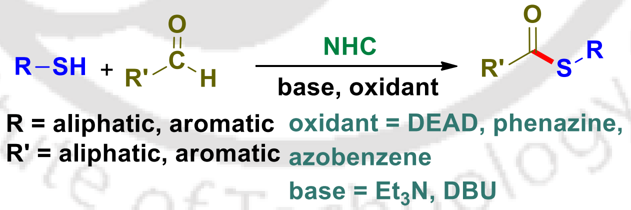
The very first report on Pd-catalyzed thiocarbonylation of iodoarenes was achieved by the Alper and co-worker.[13a] They achieved the task via employing the trihexyl(tetradecyl)phosphonium hexafluorophosphate ionic liquid with the help of Pd(II) catalyst and Et_3N as a base.[13b] Later on Skrydstrup *et al.* reported a Pd(II)-catalyzed thiocarbonylation of aryl/alkyl halide using 9-methylfluorene-9-carbonyl chloride as the *in situ* CO source in a two-chamber system.[13c] Very recently $Cr(CO)_6$ has been utilized as the CO precursor in Ni(II)-catalyzed thiocarbonylation of iodoarenes by Nasser *et al.* (Scheme IIIA.2.2).[13d]



Scheme IIIA.2.2. *Thiocarbonylation of haloarene with thiols and carbon monoxide*

(iii) *N*-Heterocyclic Carbene-Catalyzed Redox Coupling of Aldehydes with Thiols

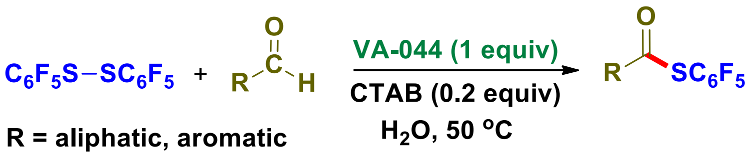
Murata *et al.* have shown for the first time that thioesters can be synthesized by the coupling of thiols and aldehyde catalyzed by the NHC in the presence of oxidant azobenzene.[14a] Later, an analogous NHC-catalyzed protocol have been reported by different other groups using a variety of oxidant and base (Scheme IIIA.2.3).[14b-e]



Scheme IIIA.2.3. *NHC-catalyzed redox coupling of aldehyde and thiols*

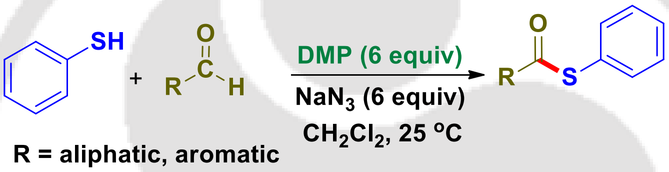
(iv) Oxidative Radical Process for Thioesters Synthesis

First reports for the thioester synthesis via the radical coupling of aldehyde with disulfide in water was reported by Kita *et al.* using radical initiator, 2,2-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA–044), and surfactant, cetyltrimethylammonium bromide (CTAB) (Scheme IIIA.2.4.1).[15a] This process provides the thioester moiety in moderate to good yield, however suffer with certain drawbacks such as requirements of equimolar quantity of water soluble radical initiator, also the scope of the substrate is limited to dipentafluorophenyl disulfide along with the requirements of surfactant cetyltrimethylammonium bromide (CTAB).



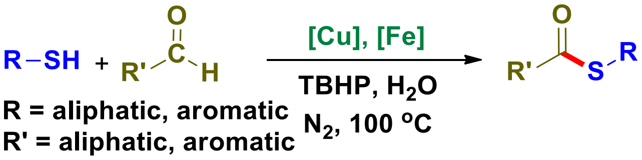
Scheme IIIA.2.4.1. *Radical reaction of aldehydes with dipentafluorophenyl disulfide*

Bandgar group has demonstrated the Dess-Martin periodinane (DMP)-mediated thioester synthesis from aldehyde and thiols. For this purpose they use 6 equiv of Dess–Martin periodinane in combination with 6 equiv of NaN_3 (Scheme IIIA.2.4.2).[15b]



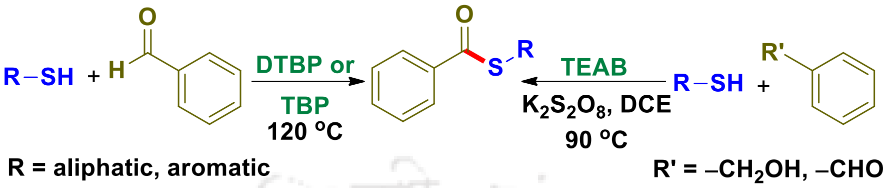
Scheme IIIA.2.4.2. *Dess–Martin periodinane-mediated synthesis of thioesters from aldehydes*

In recent times tremendous progress has taken place for the construction of C–C and C–heteroatom bond via metal and metal-free cross-dehydrogenative coupling under oxidative condition. Chin-Fa Lee *et al.* reported thioester synthesis through copper(I)-catalyzed cross-dehydrogenating coupling of thiols with aldehydes using *tert*-butyl hydroperoxide (TBHP) as external oxidant in water medium.[15c] The same group also shown that the Fe(II) catalyst could be used for the same propose (Scheme IIIA.2.4.3).[15d]



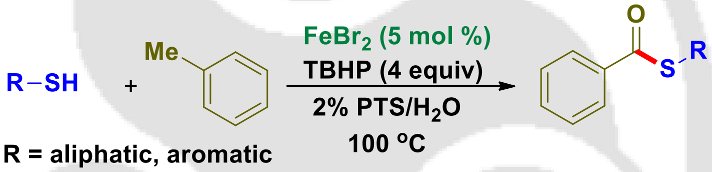
Scheme IIIA.2.4.3. *Metal-catalyzed thioesterification of thiols with aldehydes*

Thioesters can also be synthesized under metal-free conditions using di-*tert*-butyl peroxide (DTBP) and *tert*-butyl peroxide (TBP) as oxidant via the cross coupling of aldehydes with disulfides as demonstrated by the Chin-Fa Lee[15e] and Peipei Sun[15f] groups independently. Zhu *et al.* developed an elegant tetraethylammonoum bromide (TEAB)-catalyzed oxidative coupling of aldehyde and benzyl alcohols with thiols or disulfides using $K_2S_2O_8$ as oxidant (Scheme IIIA.2.4.4).[15g]



Scheme IIIA.2.4.4. *Metal-free thioesterification of thiols with aldehydes and alcohols*

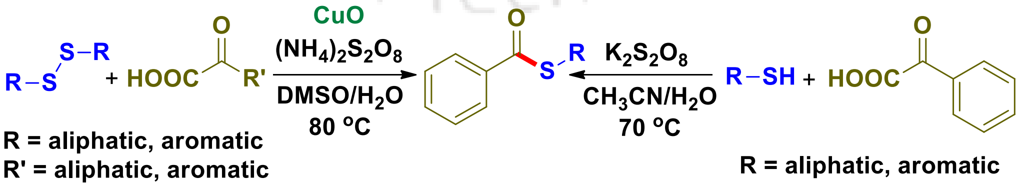
Pushing the thioesters synthesis to extreme limit of C–H functionalization later Wang group developed an efficient Fe(II)-catalyzed CDC using TBHP as the external oxidant in 2% PTS/water solvent (Scheme IIIA.2.4.5).[15h]



Scheme IIIA.2.4.5. *Fe(II)-catalyzed thioesterification of thiols with methylarenes*

(v) Decarboxylative Thioesterification

The decarboxylative coupling of α-oxoacids with thiols or disulfide for the thioester synthesis has also been developed by Mao *et al.* using copper(II) oxide as catalyst and $(NH_4)_2S_2O_8$ as oxidant.[16a] Later catalyst free approach for the same purpose has been developed by Yang and co-worker using $K_2S_2O_8$ as oxidant (Scheme IIIA.2.5).[16b]



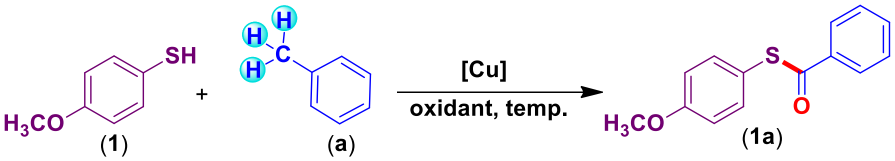
Scheme IIIA.2.5. *Oxidative decarboxylation thioesterification of α-ketoacids*

IIIA.3. Present Work

Our recent success on substrate directed *O*-aroylation of phenol using alkylbenzene as the aroyl source[3f] prompted us to investigate how alkylbenzene would react with thiol under similar conditions. Ideally, a radical CDC between thiol and alkylbenzene should result in the formation of an *S*-benzyl thioether via C–S bond formation. A benzylic oxidation of *S*-benzyl ether at the expense of two benzylic C–H bonds would give the thioester as was observed in our earlier report with phenol.[3f] To initiate the envisaged strategy *p*-methoxybenzenethiol (**1**) and toluene (**a**) were reacted in the presence of catalyst $Cu(OAc)_2$ (20 mol %) and oxidant TBHP (4 equiv) at 95 ^{o}C. To our delight the reaction afforded the corresponding thioester (**1a**) in 67% yield after 6 h (Table IIIA.3.1, entry 1). It may be noted here that a similar *O*-aroylation required the assistance of *o*-carbonyl as the directing group. The non-requirement of directing group in this case is possibly because of the efficient binding of soft Cu with soft thiol nucleophile.

Optimization of Reaction Conditions: Encouraged by this unprecedented thioesterification further optimizations were carried out with various Cu(I) and Cu(II) salts (Table IIIA.3.1, entries 1–9) among which $Cu(OAc)_2.2H_2O$ was found to be superior (Table IIIA.3.1, entry 9). An increase in the catalyst loading from 20 mol % to 30 mol % did not improve the yield significantly (Table IIIA.3.1, entry 10) while a decrease (15 mol %) resulted in the lowering of product yield (Table IIIA.3.1, entry 11). The use of an aqueous solution of TBHP in lieu of a decane solution was found to be relatively less effective (Table IIIA.3.1, entry 12). Other similar oxidants such as aqueous H_2O_2 and di-*tert*-butyl peroxide (DTBP) were almost ineffective giving the desired product in merely trace amount (Table IIIA.3.1, entry 13 and 14). The yield remained unaffected even when the oxidant quantity was increased to 5 equiv, however a substantial drop in the yield occurred when its quantity was decreased to 3 equiv (Table IIIA.3.1, entry 15 and 16). An increase (100 ^{o}C, 105 ^{o}C and 110 ^{o}C) or decrease (90 ^{o}C, 85 ^{o}C, 80 ^{o}C) in reaction temperatures provided inferior yields. This reaction failed to proceed either in the absence of catalyst or oxidant signifying their cooperative role in bringing about the transformation. Thus, the use of *p*-methoxybenzenethiol (**1**) (1 equiv), toluene (5 equiv), catalyst $Cu(OAc)_2.2H_2O$ (20 mol %), oxidant TBHP 5–6 M in decane (4 equiv) at a reaction temperature of 95 ^{o}C under air atmosphere was found to be the most suitable condition.

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

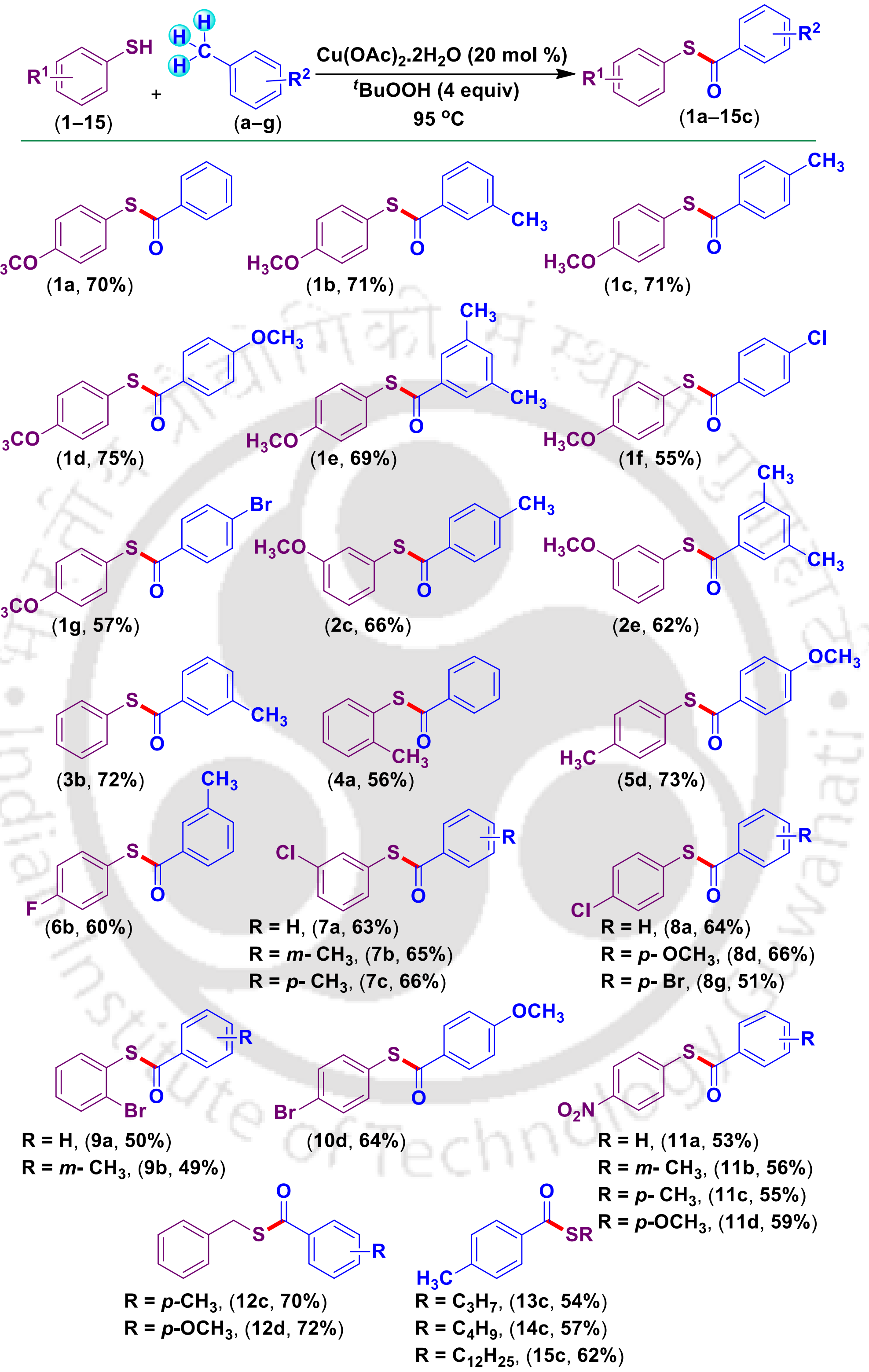


Entry	Catalyst (mol %)	Oxidant (equiv)	Yield (%)[b]
1	$Cu(OAc)_2$ (20)	TBHP (4)	67
2	$CuCl_2.2H_2O$ (20)	TBHP (4)	43
3	$CuBr_2$ (20)	TBHP (4)	19
4	$Cu(OTf)_2$ (20)	TBHP (4)	51
5	CuO (20)	TBHP (4)	59
6	CuCl (20)	TBHP (4)	32
7	CuI (20)	TBHP (4)	26
8	Cu_2O (20)	TBHP (4)	35
9	**$Cu(OAc)_2.2H_2O$ (20)**	**TBHP (4)**	**73**
10	$Cu(OAc)_2.2H_2O$ (30)	TBHP (4)	74
11	$Cu(OAc)_2.2H_2O$ (15)	TBHP (4)	68
12	$Cu(OAc)_2.2H_2O$ (20)	aq. TBHP (4)	65
13	$Cu(OAc)_2.2H_2O$ (20)	aq. H_2O_2 (4)	<5
14	$Cu(OAc)_2.2H_2O$ (20)	DTBP (4)	<2
15	$Cu(OAc)_2.2H_2O$ (20)	TBHP (5)	73
16	$Cu(OAc)_2.2H_2O$ (20)	TBHP (3)	54

[a]Reaction conditions: thiol (**1**) (0.5 mmol), toluene (**a**) (2.5 mmol), at 95 °C for 6 h.
[b]Isolated yield.

Substrates Scope for *S*-Aroylation with Alkylbenzene: Having established the optimized reaction condition for the formation of thioester, the substrates scope of the protocol was then surveyed. The effect of substituents on thiols and alkylbenzenes were investigated under the optimized reaction condition. As illustrated in Scheme IIIA.3.1, regardless of their electronic environments all the substrates examined coupled efficiently giving the desired thioesters in moderate to good yields. Initially *p*-methoxybenzenethiol (**1**) was treated with a set of alkylbenzenes bearing both electron-donating and electron-withdrawing substituents. Alkylbenzenes possessing electron-donating groups such as *m*-CH_3 (**b**), *p*-CH_3 (**c**), *p*-OCH_3 (**d**) served as efficient aroyl surrogates when treated with thiol (**1**) providing moderate yield of *S*-aroylated products (**1b**), (**1c**) and (**1d**) respectively. The structure of the product (**1d**) has been further confirmed by X-ray crystallography (Figure IIIA.3.1). It may be noted that the reaction of di-alkylated benzenes *m*-xylene (**b**) and *p*-xylene (**c**) provided monoaroylated products exclusively. Selective mono *S*-aroylation was observed even using tri-alkyl benzene such as mesitylene (**e**) giving product (**1e**) in a decent yield of 69% (Scheme IIIA.3.1). For

Scheme IIIA.3.1. *Substrate scope for S-aroylation of thiols from alkylbenzenes*[a,b]



[a]Reaction condition: thiols (**1–15**) (1 mmol), alkylbenzenes (**a–g**) (5 mmol), $Cu(OAc)_2.2H_2O$ (0.2 mmol), TBHP (4 mmol), 95 °C, time 6–17 h. [b]Yield of isolated pure product reported.

alkylbenzenes possessing *p*-substituted moderately electron-withdrawing groups such as –Cl (**f**) and –Br (**g**), the reactions were sluggish giving products (**1f**) and (**1g**) in lesser yields (55% and 57% respectively) compared to unsubstituted (**a**) or activated (**b–e**) alkylbenzenes.

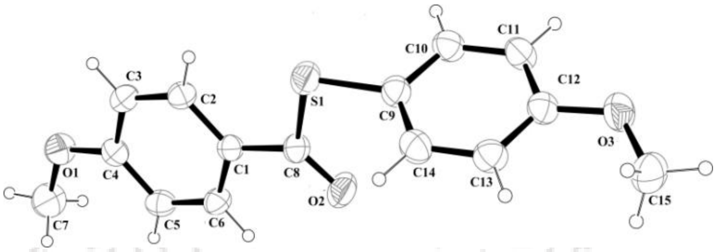
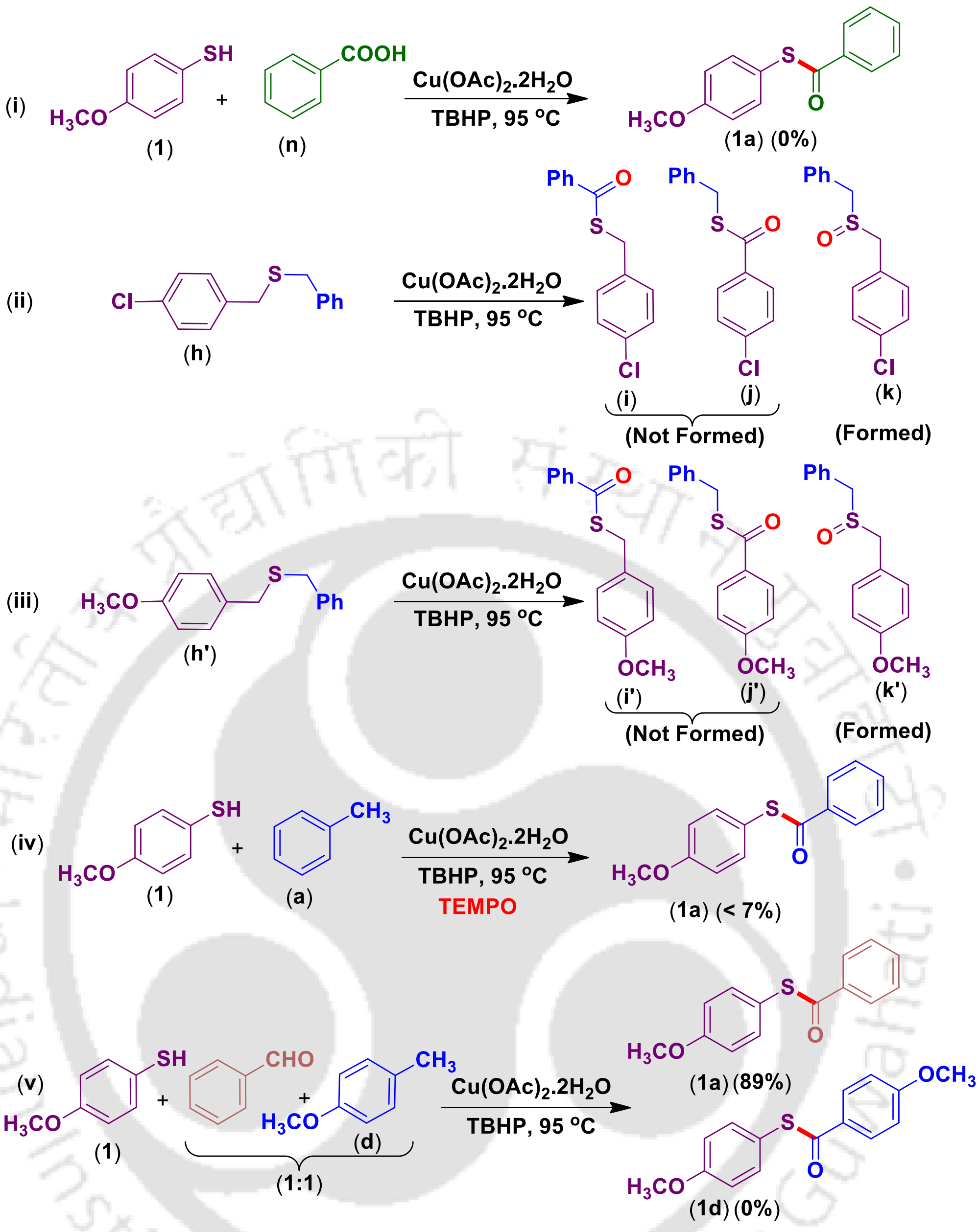


Figure IIIA.3.1*. ORTEP view of (****1d****)*

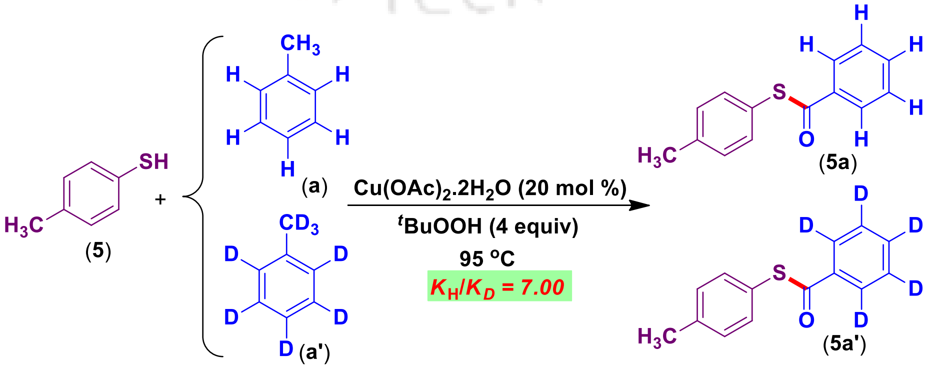
Next, we scrutinized the effect of substituents in the phenyl ring of thiols and observed that a range of substituted thiols underwent *S*-aroylation with various alkylbenzenes efficiently furnishing their respective thioesters (Scheme IIIA.3.1). Electron-donating substituents $-OCH_3$ when present *meta* to –SH as in (**2**) have slightly retarding effect compared to its *para* analogue (**1**) providing lower yields of their coupled products (**2c**) and (**2e**) with alkylbenzenes (**c**) and (**e**) respectively. Synthesis of various thioesters (**3b**), (**4a**) and (**5d**) via oxidative couplings of their respective counterparts demonstrate the versatility of this strategy. The presence of electron-withdrawing groups in the phenyl ring of thiols (**6–11**) has similar impeding effect on the cross-couplings as was observed for deactivating alkylbenzenes (**f**) and (**g**) (Scheme IIIA.3.1). Maximum yields were observed when both the coupling partners possess electron-donating groups (Scheme IIIA.3.1). Replacement of an electron-donating group in any of the partners either with an electron neutral or electron-withdrawing substituent reduced the yields. A further drop in the yields were noticed when both the coupling counterparts bear electron-withdrawing groups. All other factors remaining identical steric factor imparted due to *o*-substituents in thiols as in (**4**) and (**9**) decreased the yields of their thioesters (**4a**), (**9a**) and (**9b**) respectively. This protocol is also amenable to benzylthiol (**12**) affording thioesters (**12c**) and (**12d**) when coupled with alkylbenzenes (**c**) and (**d**) respectively. Other aliphatic thiols such as propane thiol (**13**), butane thiol (**14**) and dodecane thiol (**15**) also underwent *S*-aroylation when coupled with *p*-xylene (**c**) under the present reaction conditions affording their corresponding thioester (**13c**), (**14c**) and (**15c**) respectively in moderate yields (Scheme IIIA.3.1).

Mechanistic Investigation: To ascertain the nature of the reaction mechanism various control experiments were performed. Analysis of the reaction mixture between thiol (**1**) and toluene (**a**) revealed the presence of benzyl alcohol, benzaldehyde and benzoic acid along with other intermediates. The presence of these intermediates gives rise to three possibilities *viz.* (i) coupling of thiol with benzyl radical/cation followed by benzylic oxidation, (ii) oxidative coupling of thiol with aldehyde and (iii) direct thioesterification of benzoic acid with thiol. Treatment of benzoic acid with thiol (**1**) under the experimental conditions failed to yield (**1a**) there by ruling out the later possibility (Scheme IIIA.3.2.i). Furthermore, the formation of thioester via the intermediacy of thioether obtained by coupling of thiol with benzyl radical/cation was ruled out because of the results obtained from control experiments in Scheme IIIA.3.2.ii and iii. A presynthesized benzyl(4-chlorobenzyl) suflane (**h**) having two benzylic carbons failed to undergo benzylic oxidation under the reaction conditions in either of the benzylic positions rather gave the sulfur oxidation product 1-(benzylsulfinyl)methyl)-4-chlorobenzene (**k**) (Scheme IIIA.3.2.ii). Similarly benzyl(4-methoxybenzyl) suflane (**h′**) also failed to undergo benzylic oxidation under the present reaction conditions and gave sulfur oxidation product (**k′**) (Scheme IIIA.3.2.iii). The coupling reaction between thiol (**1**) and toluene (**a**) was considerably hampered in the presence of radical scavenger (TEMPO) giving < 7% yield of product indicating a radical nature of the reaction (Scheme IIIA.3.2.iv). Hence the formation of thioester could possibly via radical coupling of thiol and benzoyl radical generated from benzaldehyde.[17] Furthermore, reaction of *p*-methoxybenzenethiol (**1**) with an equimolar mixture of benzaldehyde and 1-methoxy-4-methylbenzene (**d**) gave the product (**1a**) exclusively, suggesting the coupling of benzoyl radical with thiol (**1**) (Scheme IIIA.3.2.v).

The reaction between toluene and d_8-toluene (1:1) with *p*-methylbenzenethiol (**5**) showed a significant kinetic isotope effect ($K_H/K_D \sim 7.00$) indicating the cleavage of benzylic C–H bond or formation of benzoyl radical from benzaldehyde to be the rate determining step (Scheme IIIA.3.3).

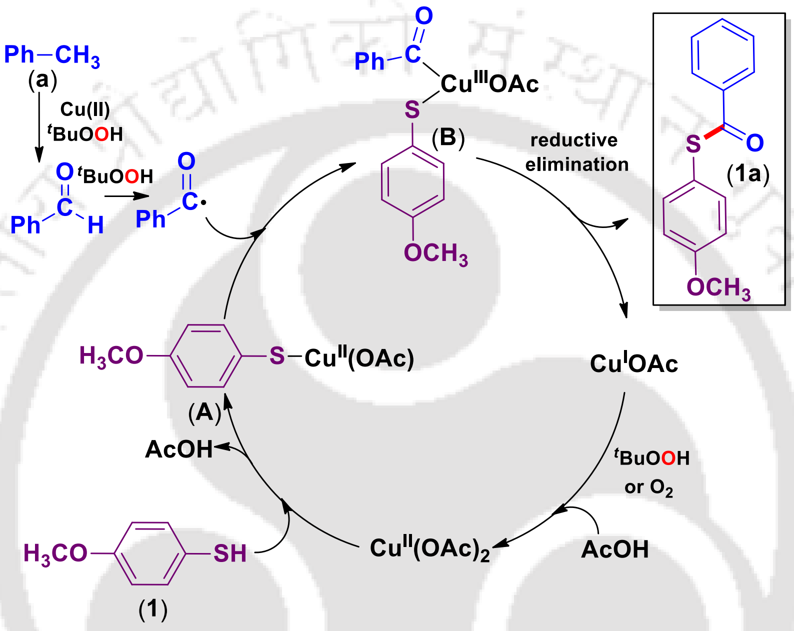


Scheme IIIA.3.2. Control experiments performed



Scheme IIIA.3.3. Kinetic isotope study

In this thioesterification the reagent TBHP serves the twin role of an oxidant and a radical initiator. The intermediate copper thiolate (**A**) generated upon treatment of thiol (**1**) with Cu(II) reacts with the *in situ* generated benzoyl radical obtained from alkylbenzene (**a**) to afford copper (III) intermediate (**B**) (Scheme IIIA.3.4). A reductive elimination of intermediate (**B**) results in the formation of *S*-aroylated product (**1a**) releasing the catalyst. The Cu(I) catalyst is re-oxidized to Cu(II) for the next catalytic cycle.



Scheme IIIA.3.4. *Proposed reaction mechanism for thioesterification*

In conclusion a CDC protocol has been developed for the *S*-aroylation of thiols using alkylbenzenes as aroyl surrogates in the presence of Cu/TBHP. In this reaction, simultaneously C–S and C–O bonds are installed at the expense of three sp^3 C–H bonds of alkylbenzene and a sp^3 S–H bond of thiol. Good functional group tolerance along with the non-requirement of directing group enhances the substrate scope.

IIIA.4. Experimental Section

IIIA.4.1. General Information: All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

IIIA.4.2. Crystallographic Description

CCDC Number for Compounds 1d: CCDC 983611. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 1d: Crystal dimensions 0.40 x 0.34 x 0.26 mm, Mr = 274.33,Orthorhombic, space group P 21 21 21, a = 5.4072(4), b = 7.9548(6), c = 31.445(2) Å, $\alpha = 90^{o}$, $\beta = 90^{o}$, $\gamma = 90^{o}$, V = 1352.56(17) $Å^{3}$, Z = 4, ρcalcd = 1.347 g/cm3, μ = 0.240 mm-1, F(000) = 576.0, reflection collected / unique = 3249 / 2393, refinement method = full-matrix least-squares on F2, final R indices [$I > 2\sigma(I)$]: R1 = 0.0371, wR2 = 0.0871, R indices (all data): R1 = 0.0580, wR2 = 0.0976, goodness of fit = 0.914.

IIIA.4.3. Typical Procedure for Synthesis of *S*-4-Methoxyphenyl benzothioate (1a): An oven dried round bottom flask was charged with 4-methoxy benzenethiol (**1**) (140 mg, 1 mmol), toluene (**a**) (461 mg, 5 mmol), $Cu(OAc)_2.2H_2O$ (43 mg, 20 mol %) and 5–6 M decane TBHP (800 μL, 4 mmol) and the resultant reaction mixture was stirred in a preheated oil bath at 95 ^{o}C for 6 h. After cooling to room temperature the reaction mixture was admixed with ethyl acetate (35 mL) which was washed with 5% solution of sodium bicarbonate (2 x 5 mL). The ethyl acetate was dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude product was purified over a column of silica gel and eluted with 9:1 (hexane / ethyl acetate) to furnish *S*-4-methoxyphenyl benzothioate (**1a**) (170 mg, 70%).

IIIA.4.4. Intermolecular Competing Kinetic Isotope Effect (KIE) Experiment with Deuterated Toluene: To a solution of 4-methyl benzenethiol (**5**) (124 mg, 1 mmol) in toluene (**a**) (230 mg, 2.5 mmol), and d_8-toluene (**a'**) (250 mg, 2.5 mmol) was added $Cu(OAc)_2.2H_2O$ (43 mg, 20 mol %) followed by 5–6 M decane TBHP (800 μL, 4 mmol) and then the reaction mixture was put into a pre heated oil bath for 7 h. The resultant reaction mixture was admixed with water (10 mL) and the product was extracted with ethyl acetate (35 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The crude product was purified over a column of silica gel and eluted with hexane to give the expected product in 38% yield (**5a** and **5a'**). The ratio of the deuterated (**5a'**) and nondeuterated (**5a**) *S*-aroylated product was calculated on the basis of the integration ratio of the aromatic proton peak at δ 8.02 (originating from toluene) and $-CH_3$ proton at δ 2.41 (originating from thiol).

Calculation:

For three methyl protons at 2.41, the integration value is 3.00.

Thus for a single proton the integration corresponds to 3.00 / 3 = 1.00.

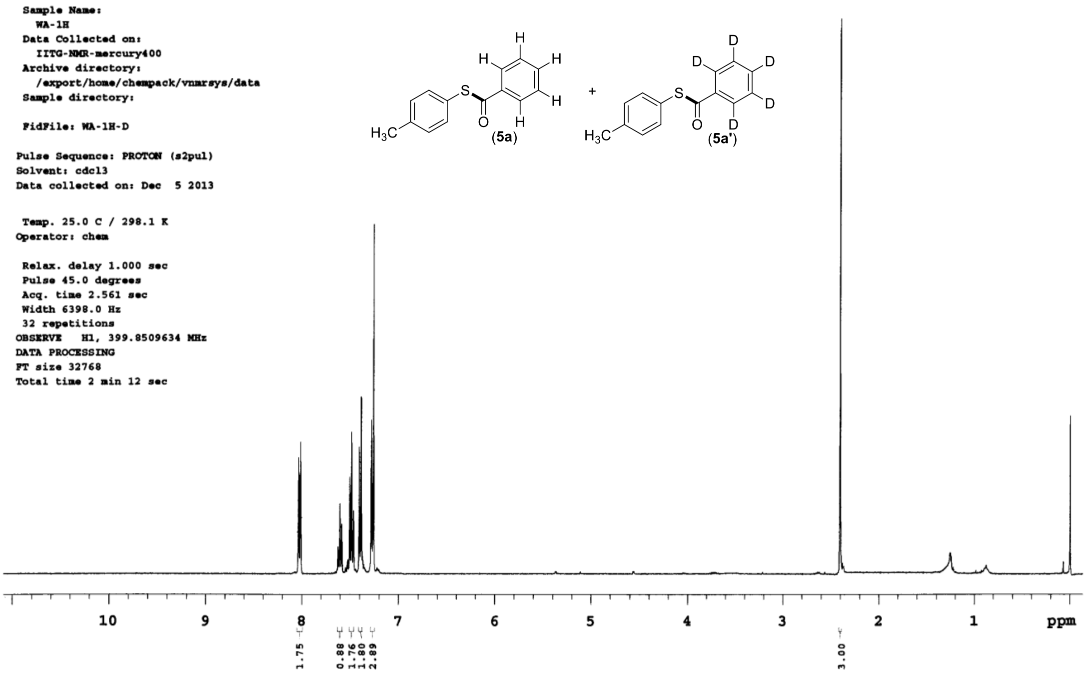
Now for the integration value of the protons originating from toluene at 8.02 is 1.75.

Thus the number of protons corresponding to this integration value is 1.75 / 1.00 = 1.75.

Upon correlation with original spectra of (**5a**) the number of proton at 8.02 should be 2.

Hence the proton difference in this region is 2 – 1.75 = 0.250

Thus the $K_H / K_D = 1.750 / 0.250 = 7.00$.



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Data Collected on:
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Archive directory:
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FidFile: WA-1H-D

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec  5 2013

Temp. 25.0 C / 298.1 K
Operator: chem

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Pulse 45.0 degrees
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IIIA.5. References

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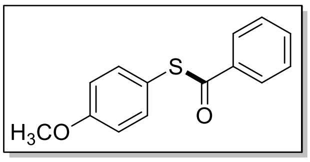
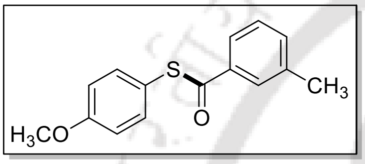
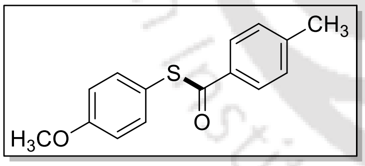
IIIA.6. Spectral Data



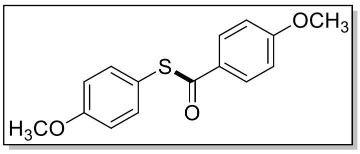
***S*-(4-Methoxyphenyl) benzothioate (1a):** Yellow solid; M.p. 95–96 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.83 (s, 3H), 6.97 (d, 2H, *J* = 4.2 Hz), 7.40 (d, 2H, *J* = 9.0 Hz), 7.47 (t, 2H, *J* = 7.8 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 8.00 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 55.6, 115.2, 118.1, 127.7, 128.9, 132.9, 133.8, 136.8, 161.0, 191.3; IR (KBr): 2960, 2926, 2853, 1666, 1590, 1493, 1446, 1249, 901 cm^{-1}; Anal. calcd. for $C_{14}H_{12}O_2S$: C 68.83, H 4.95; found: C 69.01, H 5.02.



***S*-(4-Methoxyphenyl) 3-methylbenzothioate (1b):** Light yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 3.83 (s, 3H), 6.98 (d, 2H, *J* = 4.8 Hz), 7.35 (t, 1H, *J* = 7.8 Hz), 7.39–7.42 (m, 3H), 7.82 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 55.5, 115.1, 118.2, 124.8, 128.1, 128.8, 134.5, 136.8, 136.9, 138.8, 160.9, 191.3; IR (KBr): 3010, 2970, 2940, 2839, 1670, 1590, 1491, 1288, 1160, 938, 823 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_2S$ (MH^{+}) 259.0789; found 259.0794.

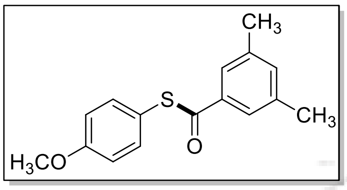


***S*-(4-Methoxyphenyl) 4-methylbenzothioate (1c):** White solid; M.p. 133–135 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 3.84 (s, 3H), 6.98 (d, 2H, *J* = 9.0 Hz), 7.26 (d, 2H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* = 7.8 Hz), 7.92 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.9, 55.5, 115.1, 118.3, 127.7, 129.5, 134.3, 136.8, 144.6, 160.9, 190.7; IR (KBr): 3052, 2964, 1660, 1493, 1288, 1172, 903, 828 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_2S$ (MH^{+}) 259.0789; found 259.0793.

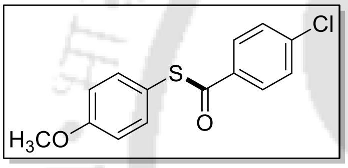


***S*-(4-Methoxyphenyl) 4-methoxybenzothioate (1d):** White solid; M.p. 136–137 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.84 (s, 3H), 3.87 (s, 3H), 6.95 (d, 2H, *J* = 8.4 Hz), 6.98 (d, 2H, *J* = 9.0 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 8.01 (d, 2H, *J* = 9.0

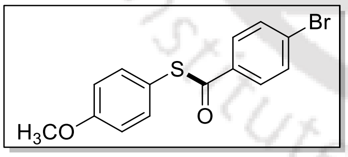
Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.5, 55.7, 114.1, 115.1, 118.4, 129.6, 129.8, 136.9, 160.9, 164.1, 189.7; IR (KBr): 2966, 2936, 2838, 1663, 1596, 1251, 1167, 1022, 906, 791 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_3S$ (MH^+) 275.0735; found 275.0737.



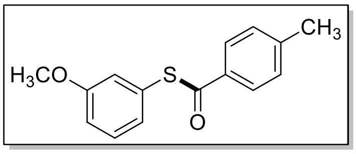
***S*-(4-Methoxyphenyl) 3,5-dimethylbenzothioate (1e):** White solid; M.p. 90–91 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 6H), 3.85 (s, 3H), 6.99 (d, 2H, *J* = 8.4 Hz), 7.23 (s, 1H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.64 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 55.5, 115.1, 118.3, 125.3, 135.4, 136.7, 136.9, 138.6, 160.9, 191.3; IR (KBr): 2954, 1663, 1494, 1290, 1247, 1147, 1030, 778 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_2S$: C 70.56, H 5.92; found: C 70.74, H 5.96.



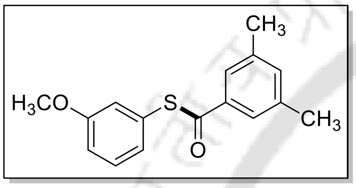
***S*-(4-Methoxyphenyl) 4-chlorobenzothioate (1f):** Yellow solid; M.p. 99–100 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.78 (s, 3H), 6.98 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 9.0 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 8.4 Hz);^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.5, 114.8, 115.2, 128.6, 129.0, 129.2, 132.8, 136.8, 160.1, 190.1; IR (KBr): 3060, 2935, 1667, 1589, 1491, 1247, 1172, 905, 826 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}ClO_2S$ (MH^+) 279.0239; found 279.0243.



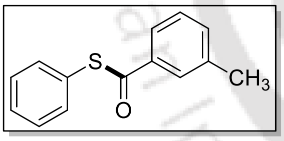
***S*-(4-Methoxyphenyl) 4-bromobenzothioate (1g):** Red solid; M.p. 121–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.83 (s, 3H), 6.97 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.4 Hz), 7.86 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.6, 115.2, 117.5, 128.8, 129.1, 132.2, 135.6, 136.8, 161.1, 190.3; IR (KBr): 2965, 2927, 1666, 1492, 1289, 1250, 1016, 905, 830, 715 cm^{-1}; Anal. calcd. for $C_{14}H_{11}BrO_2S$: C 52.03, H 3.43; found: C 52.20, H 3.38.



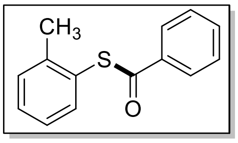
***S*-(3-Methoxyphenyl) 4-methylbenzothioate (2c):** White solid; M.p. 48–50 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 3.81 (s, 3H), 6.98 (d, 1H, *J* = 6.0 Hz), 7.08 (s, 1H), 7.11 (d, 1H, *J* = 7.2 Hz), 7.27 (d, 2H, *J* = 8.4 Hz), 7.35 (t, 1H, *J* = 7.8 Hz), 7.92 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.9, 55.5, 115.8, 120.3, 127.5, 127.7, 128.6, 129.6, 130.1, 134.2, 144.7, 160.1, 189.7; IR (KBr): 3025, 2963, 2923, 1659, 1588, 1423, 1281, 1202, 1042, 868, 803 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_2S$ (MH$^+$) 259.0789; found 259.0791.



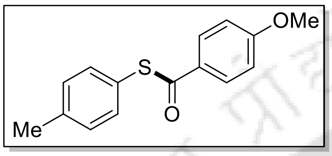
***S*-(3-Methoxyphenyl) 3,5-dimethylbenzothioate (2e):** Yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.32 (s, 6H), 3.74 (s, 3H), 6.74 (d, 1H, *J* = 6.0 Hz), 6.94 (s, 1H), 7.07 (d, 1H, *J* = 8.4 Hz), 7.18–7.24 (m, 2H), 7.47 (s, 2H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.3, 55.3, 112.6, 113.2, 119.6, 127.0, 127.6, 129.9, 136.2, 138.3, 138.8, 160.1, 192.8; IR (KBr): 3062, 2934, 2834, 1698, 1589, 1477, 1311, 1246, 1040, 854 cm^{-1}; Anal. calcd. for $C_{16}H_{16}O_2S$: C 70.56, H 5.92; found: C 70.73, H 5.98.



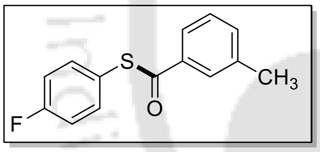
***S*-Phenyl 3-methylbenzothioate (3b):** Light yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.43 (s, 3H), 7.36 (t, 1H, *J* = 8.4 Hz) 7.41 (d, 1H, *J* = 7.8 Hz), 7.45–7.46 (m, 3H), 7.51–7.53 (m, 2H), 7.84 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 124.9, 128.1, 128.8, 129.2, 129.4, 129.6, 134.6, 135.3, 136.9, 138.8, 190.4; IR (KBr): 3059, 2960, 2924, 1680, 1584, 1479, 1245, 1151, 956, 787 cm^{-1}; Anal. calcd. for $C_{14}H_{12}OS$: C 73.65, H 5.30; found: C 73.91, H 5.37.



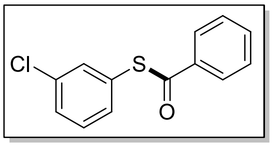
***S-o*-Tolyl benzothioate(4a):** Light yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 7.26 (t, 1H, *J* = 7.8 Hz), 7.36 (d, 2H, *J* = 7.8 Hz), 7.46–7.49 (m, 3H), 7.59 (t, 1H, *J* = 7.2 Hz), 8.05 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.0, 126.8, 127.0, 127.7, 128.9, 130.4, 131.0, 133.8, 136.6, 137.0, 142.9, 189.8; IR (KBr): 3062, 2977, 1677, 1449, 1204, 1176, 899, 771 cm^{-1} Anal. calcd. for $C_{14}H_{12}OS$: C 73.65, H 5.30; found: C 73.58, H 5.35.



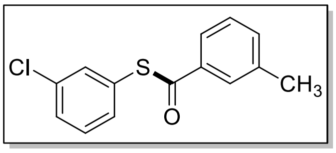
***S-p*-Tolyl 4-methoxybenzothioate (5d):** Light yellow solid; M.p. 63–65 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.90 (s, 3H), 6.97 (d, 2H, *J* = 9.0 Hz), 7.28 (d, 2H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* =8.4 Hz), 8.02 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 55.7, 114.1, 124.3, 129.7, 129.9, 130.2, 135.3, 139.8, 164.1, 189.2; IR (KBr): 3010, 2970, 2924, 1664, 1598, 1263, 1166, 1026, 904, 840, 796 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{14}O_2S$ (MH^+) 259.0789; found 259.0794.



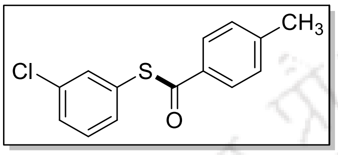
***S*-(4-Fluorophenyl) 3-methylbenzothioate (6b):** Light yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.16 (t, 2H *J* = 8.4 Hz), 7.38 (t, 1H, *J* = 8.4 Hz), 7.43 (d, 1H, *J* = 7.8 Hz), 7.49 (t, 2H, *J* = 9.0 Hz), 7.83 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 116.5, 116.6, 122.8, 124.7, 126.2, 128.0, 128.7, 129.0, 134.6, 136.5, 137.1, 137.2, 138.8, 162.8, 164.5, 190.2; IR (KBr): 3065, 2978, 2923, 1681, 1589, 1489, 1243, 1153, 957, 829 cm^{-1};Anal. calcd. for $C_{14}H_{11}FOS$: C 68.27, H 4.50; found: C 68.45, H 4.56.



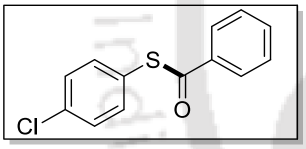
***S*-(3-Chlorophenyl) benzothioate (7a):** White solid; M.p. 71–72 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.37–7.42 (m, 3H), 7.48 (t, 2H, *J* = 7.8 Hz), 7.53 (s, 1H), 7.61 (t, 1H, *J* = 7.8 Hz,), 8.01 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 127.6, 128.9, 129.2, 129.8, 130.3, 133.3, 134.0, 134.78, 134.81, 136.3, 189.3; IR (KBr): 3063, 2977, 2926, 1681, 1574, 1460, 1204, 1077, 896, 778 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_9ClOS$ (MH^+) 249.0136; found 249.0139.



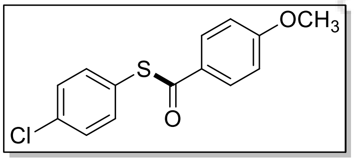
***S*-(3-Chlorophenyl) 3-methylbenzothioate (7b):** Light yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.45 (s, 3H), 7.34–7.44 (m, 5H), 7.54 (s, 1H), 7.83 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 124.9, 128.1, 128.9, 129.5, 129.8, 130.3, 133.4, 134.86, 134.89, 134.94, 136.5, 139.0, 189.5; IR (KBr): 3061, 2977, 2923, 1682, 1603, 1482, 1245, 1152, 956, 781, 739 cm^{-1}; Anal. calcd. for $C_{14}H_{11}ClOS$: C 64.00, H 4.22; found: C 64.16, H 4.28.



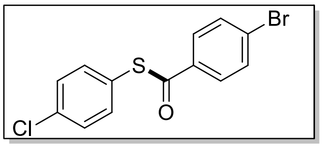
***S*-(3-Chlorophenyl) 4-methylbenzothioate (7c):** White solid; M.p. 96–97 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.35–7.42 (m, 3H), 7.52 (s, 1H), 7.90 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.8, 127.7, 129.4, 129.5, 129.7, 130.2, 133.3, 133.8, 134.7, 134.8, 145.0, 188.8; IR (KBr): 3078, 2922, 2855, 1663, 1568, 1457, 1210, 1172, 903, 822, 786 cm^{-1}; Anal. calcd. for $C_{14}H_{11}ClOS$: C 64.00, H 4.22; found: C 64.12, H 4.25.



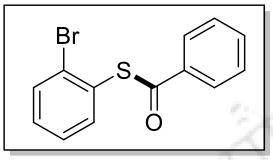
***S*-(4-Chlorophenyl) benzothioate (8a):** Yellow solid; M.p. 73–74 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.41–7.43 (m, 4H), 7.48 (t, 2H, *J* = 7.8 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 8.00 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 126.1, 127.7, 129.0, 129.7, 134.1, 136.2, 136.5, 136.6, 189.8; IR (KBr): 3054, 2922, 2852, 1678, 1473, 1204, 1091, 897, 838 cm^{-1}; Anal. calcd. for $C_{13}H_9ClOS$: C 62.78, H 3.65; found: C 62.89, H 3.70.



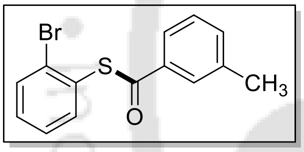
***S*-(4-Chlorophenyl) 4-methoxybenzothioate (8d):** White solid; M.p. 95–97 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.85 (s, 3H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.39–7.42 (m, 4H), 7.97 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 55.7, 114.1, 126.3, 129.2, 129.5, 129.9, 135.9, 136.5, 164.3, 188.1; IR (KBr): 2950, 2923, 2848, 1661, 1602, 1473, 1258, 1169, 911, 831 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}ClO_2S$ (MH$^+$) 279.0241; found 279.0244.



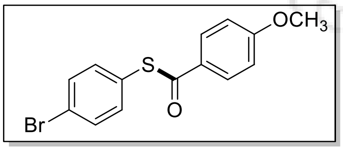
***S*-(4-Chlorophenyl) 4-bromobenzothioate (8g):** White solid; M.p. 127–128 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.12 (s, 4H), 7.62 (d, 2H, *J* = 8.4 Hz), 7.86 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 125.5, 129.1, 129.8, 130.8, 131.6, 132.3, 135.3, 136.3, 188.8; IR (KBr): 3098, 2979, 2927, 1674, 1479, 1387, 1198, 1068, 812 cm$^{-1;}$ Anal. calcd. for $C_{13}H_8ClBrOS$: C 47.66, H 2.46; found: C 47.78, H 2.51.



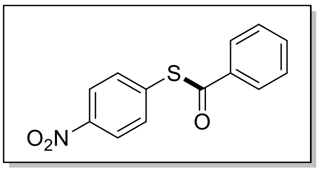
***S*-(2-Bromophenyl) benzothioate (9a):** Colorless liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.31 (t, 1H, *J* = 7.8 Hz), 7.38 (t, 1H, *J* = 7.2 Hz), 7.45 (t, 2H, *J* = 7.8 Hz), 7.60–7.63 (m, 2H), 7.74 (d, 1H, *J* = 7.2 Hz), 8.05 (d, 2H, *J* = 9.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 127.8, 128.2, 129.0, 129.4, 130.2, 131.4, 133.8, 134.0, 136.5, 137.8, 188.5; IR (KBr): 3059, 2923, 2848, 1681, 1448, 1205, 1176, 1021, 896, 770 cm^{-1}; Anal. calcd. for $C_{13}H_9BrOS$: C 53.26, H 3.09; found: C 53.37, H 3.15.



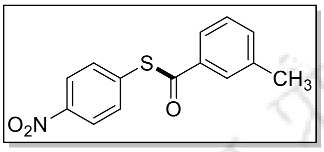
***S*-(2-Bromophenyl) 3-methylbenzothioate (9b):** Light yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 7.30 (t, 1H, *J* = 7.8 Hz), 7.36–7.39 (m, 2H), 7.42 (d, 1H, *J* = 7.8 Hz), 7.61 (d, 1H, *J* = 7.8 Hz), 7.73 (d, 1H, *J* = 7.8 Hz), 7.85 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 125.0, 128.17, 128.22, 128.9, 129.5, 130.2, 131.4, 133.8, 134.8, 136.6, 137.8, 139.0, 188.6; IR (KBr): 3059, 2923, 2855, 1683, 1449, 1246, 1153, 955, 786 cm^{-1}; Anal. calcd. for $C_{14}H_{11}BrOS$: C 54.74, H 3.61; found: C 54.66, H 3.56.



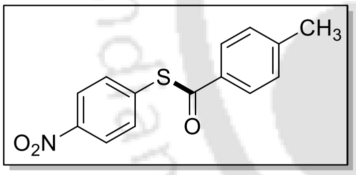
***S*-(4-Bromophenyl) 4-methoxybenzothioate (10d):** White solid; M.p. 104–105 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.89 (s, 3H), 6.97 (d, 2H, *J* = 8.4 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.99 (d, 2H , *J* = 7.2 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 55.8, 114.2, 124.3, 127.0, 129.3, 130.0, 132.6, 136.8, 164.4, 188.1; IR (KBr): 2955, 2923, 2850, 1661, 1601, 1258, 1169, 1018, 909, 830, 813 cm^{-1}; Anal. calcd. for $C_{14}H_{11}BrO_2S$: C 52.03, H 3.43; found: C 52.17, H 3.47.



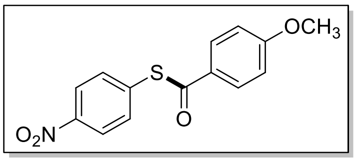
***S*-(4-Nitrophenyl) benzothioate (11a):** Yellow solid; M.p. 121–122 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.50 (t, 2H, *J* = 7.8 Hz), 7.64 (t, 1H, *J* = 7.2 Hz), 7.69 (d, 2H, *J* = 9.0 Hz), 8.00 (d, 2H, *J* = 7.8 Hz), 8.27 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 124.1, 127.8, 129.2, 134.5, 135.6, 136.1, 136.3, 148.5, 188.2; IR (KBr): 3095, 2966, 2923, 1677, 1514, 1340, 1203, 902, 851 cm^{-1}; Anal. calcd. for $C_{13}H_9NO_3S$: C 60.22, H 3.50, N 5.40; found: C 60.41, H 3.53, N 5.35.



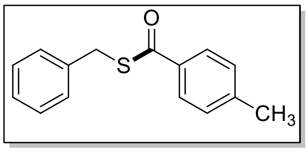
***S*-(4-Nitrophenyl) 3-methylbenzothioate (11b):** Light yellow solid; M.p. 121–123°C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.43 (s, 3H), 7.38 (t, 1H, *J* = 7.2 Hz), 7.44 (d, 1H, *J* = 7.8 Hz), 7.69 (d, 2H, *J* = 9.0 Hz), 7.80 (d, 2H, *J* = 8.4 Hz), 8.27 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 124.1, 125.1, 128.2, 129.1, 135.3, 135.6, 136.2, 136.5, 139.2, 148.4, 188.3; IR (KBr): 3095, 2924, 2851, 1669, 1514, 1343, 1245, 847, 788 cm^{-1}; Anal. calcd. for $C_{14}H_{11}NO_3S$: C 61.52, H 4.06, N 5.12; found: C 61.71, H 4.10, N 5.15.



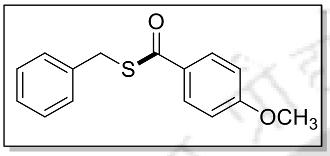
***S*-(4-Nitrophenyl) 4-methylbenzothioate (11c):** White solid; M.p. 115–117 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.45 (s, 3H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.71 (d, 2H, *J* = 9.0 Hz), 7.92 (d, 2H, *J* = 8.4 Hz), 8.29 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.9, 124.0, 127.9, 129.8, 133.6, 135.5, 136.5, 145.6, 148.3, 187.6; IR (KBr): 3066, 2979, 2925, 2853, 1671, 1519, 1366, 1342, 1173, 1037, 848 cm^{-1}; Anal. calcd. for $C_{14}H_{11}NO_3S$: C 61.52, H 4.06, N 5.12; found: C 61.41, H 4.01, N 4.97.



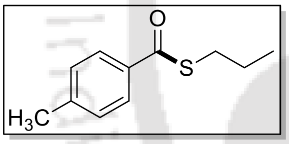
***S*-(4-Nitrophenyl) 4-methoxybenzothioate (11d):** Yellow solid; M.p. 134–136 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 3.88 (s, 3H), 6.97 (d, 2H, *J* = 9.0 Hz), 7.69 (d, 2H, *J* = 8.4 Hz), 7.98 (d, 2H, *J* = 7.2 Hz), 8.26 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 55.8, 113.8, 114.3, 124.0, 130.1, 131.9, 135.6, 148.8, 164.7, 186.5; IR (KBr): 2928, 2841, 1667, 1511, 1347, 1255, 1168, 1099, 902, 848 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}NO_4S$ (MH$^+$) 290.0483; found 290.0486.



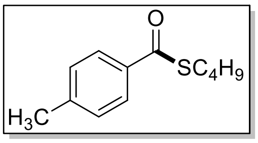
_S_-Benzyl 4-methylbenzothioate (12c): Yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 4.34 (s, 2H) 7.25–7.29 (m, 3H), 7.34 (t, 2H, *J* = 7.2 Hz), 7.40 (d, 2H, *J* = 7.8 Hz), 7.90 (d, 2H, *J* = 7.8); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 33.4, 127.5, 127.6, 128.8, 129.2, 129.5, 134.5, 137.8, 144.5, 191.1; IR (KBr): 3087, 2977, 2928, 1664, 1452, 1386, 1203, 912, 881 cm^{-1}; Anal. calcd. for $C_{15}H_{14}OS$: C 74.34, H 5.82; found: C 74.46, H 5.77.



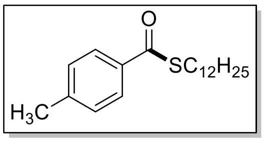
_S_-Benzyl 4-methoxlbenzothioate (12d): Yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.84 (s, 3H), 4.34 (s, 2H) 6.93 (d, 2H, *J* = 9.0 Hz), 7.29 (t, 1H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* = 7.8 Hz), 7.99 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.3, 55.5, 113.9, 127.3, 128.7, 129.0, 129.5, 129.7, 137.9, 163.9, 189.7; IR (KBr): 2968, 2932, 1656, 1601, 1509, 1261, 1167, 913, 836, 702 cm^{-1}; Anal. calcd. for $C_{15}H_{14}O_2S$: C 69.74, H 5.46; found: C 69.85, H 5.51.



_S_-Propyl 4-methylbenzothioate (13c): Colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.03 (t, 3H, *J* = 7.8 Hz), 1.68–1.72 (m, 2H), 2.41 (s, 3H), 3.04 (t, 2H, *J* = 7.2 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.87 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.7, 21.9, 23.3, 31.1, 127.5, 129.4, 135.0, 144.2, 192.0; IR (KBr): 2959, 2923, 2853, 1661, 1607, 1462, 1174, 1018, 913, 817, 794 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{14}OS$ (MH$^+$) 195.0839; found 195.0840.



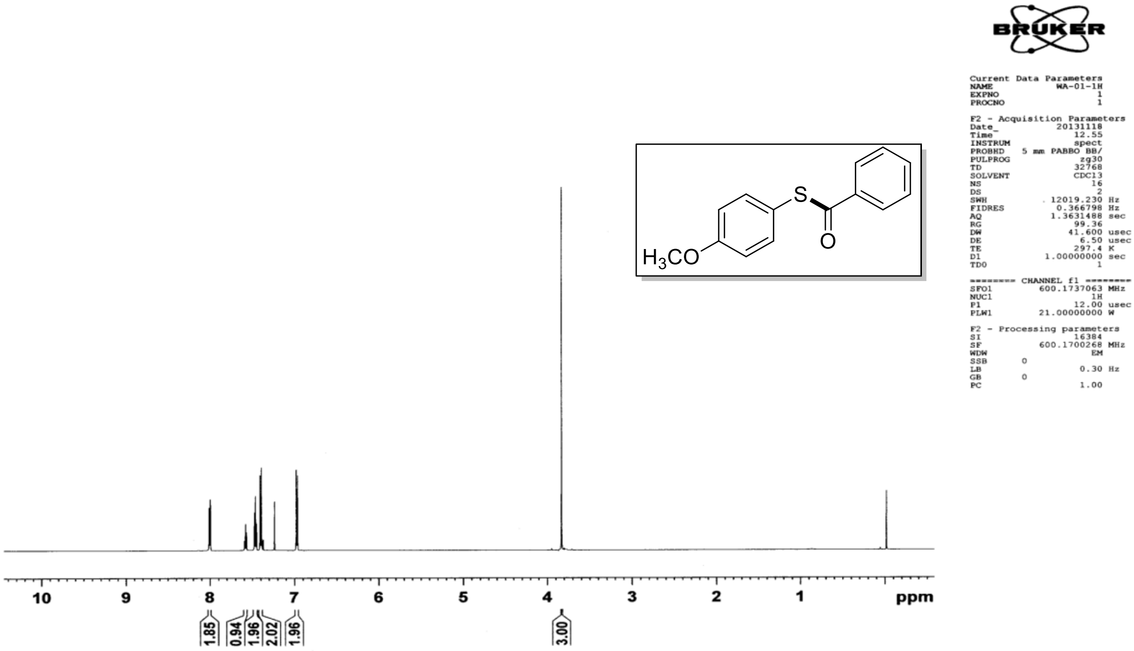
_S_-Butyl 4-methylbenzothioate (14c): Colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.94 (t, 3H, *J* = 7.8 Hz), 1.43–1.46 (m, 2H), 1.62–1.67 (m, 2H), 2.38 (s, 3H), 3.05 (t, 2H, *J* = 7.2 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.86 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.8, 21.8, 22.2, 28.8, 31.9, 127.4, 129.3, 134.9, 144.1, 191.8; IR (KBr): 3032, 2959, 2929, 2869, 1661, 1606, 1460, 1209, 1174, 914, 822, 790 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{16}OS$ (MH$^+$) 209.0996; found 209.0990.



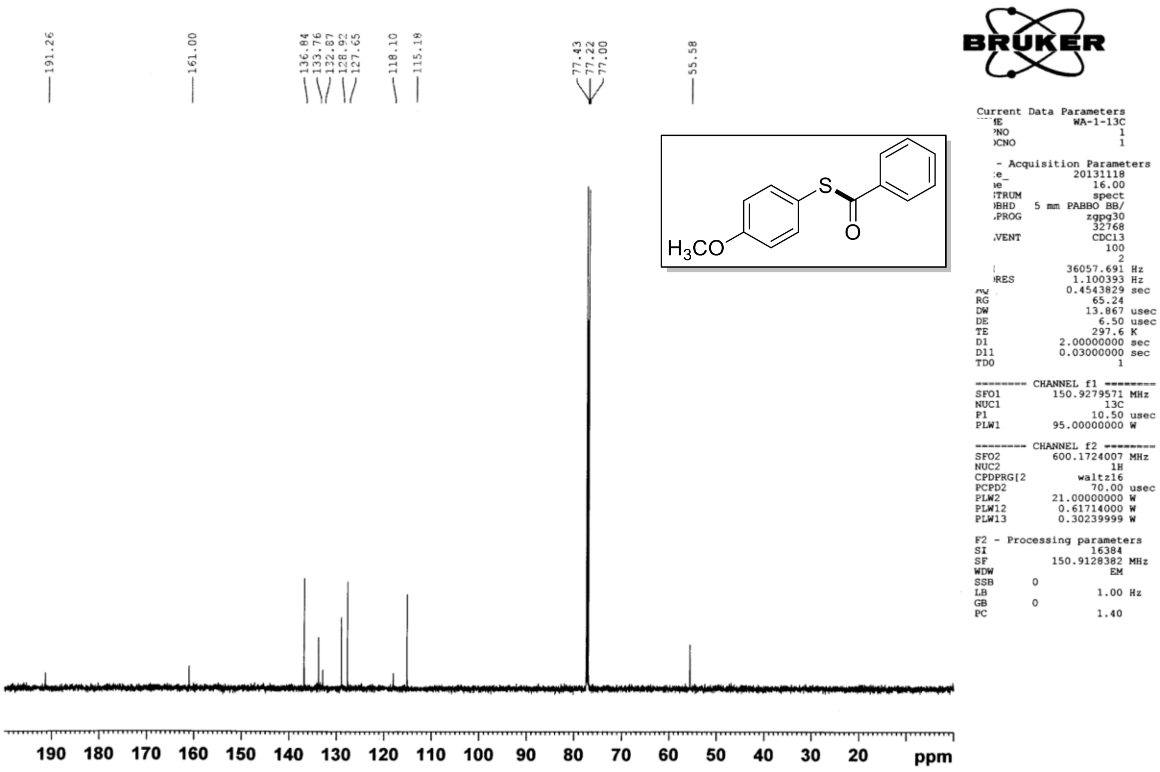
***S*-Dodecyl-4-methylbenzothioate (15c):** Colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, *J* = 6.6 Hz), 1.26–1.43 (m, 18H), 1.65–1.67 (m, 2H), 2.40 (s, 3H), 3.05 (t, 2H, *J* = 7.8 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.87 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.3, 21.8, 22.9, 26.6, 28.1, 29.2, 29.4, 29.6, 29.7, 29.79, 29.84, 32.1, 127.5, 129.4, 135.0, 144.2, 192.0; IR (KBr): 2924, 2853, 1662, 1607, 1462, 1208, 1174, 912, 820, 669 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{32}OS$ (MH^+) 321.2248; found 321.2250.

IIIA.7. Spectra

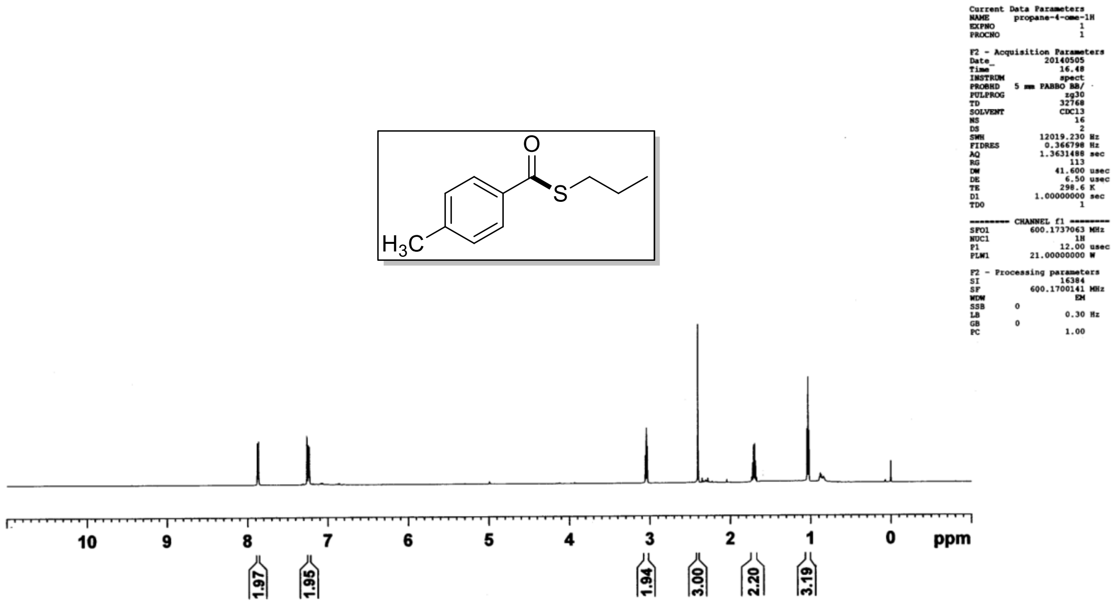
S-(4-Methoxyphenyl) benzothioate (1a): ^{1}H NMR (600 MHz, CDCl$_3$)



S-(4-Methoxyphenyl) benzothioate (1a): ^{13}C NMR (150 MHz, CDCl$_3$)



***S*-Propyl 4-methylbenzothioate (13c): ^{1}H NMR (600 MHz, CDCl$_3$)**



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DS                       2
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FIDRES           0.366798 Hz
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RG                     113
DW                  41.600 usec
DE                    6.50 usec
TE                   298.6 K
D1             1.00000000 sec
TD0                      1

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P1                   12.00 usec
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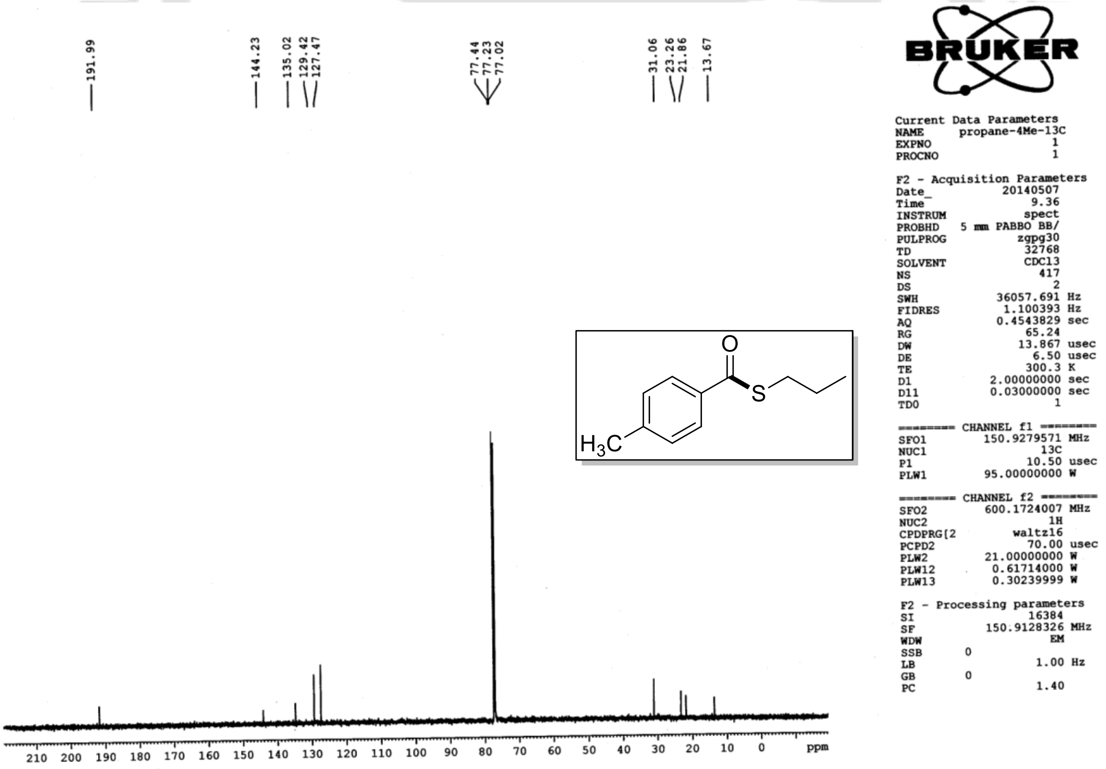
***S*-Propyl 4-methylbenzothioate (13c): ^{13}C NMR (150 MHz, CDCl$_3$)**



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======== CHANNEL f2 ========
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PCPD2                 70.00 usec
PLW2            21.00000000 W
PLW12            0.61714000 W
PLW13            0.30239999 W

F2 - Processing parameters
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WDW                      EM
SSB        0
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GB         0
PC                     1.40
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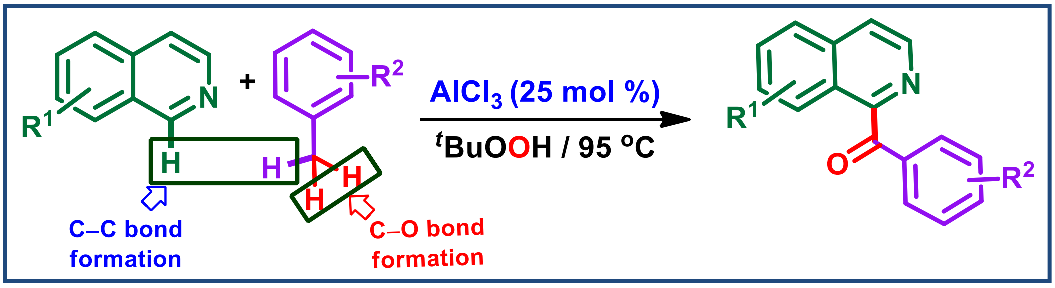
Chapter IIIB

Regiospecific Benzoylation of Electron-Deficient N-Heterocycles with Methylbenzenes via a Minisci-Type Reaction



Abstract: *A regioselective cross-dehydrogenative coupling between electron-deficient N-heterocycles (isoquinoline, quinolines and quinoxalines) and methylbenzenes leading to regiospecific C-aroylation has been accomplished using AlCl$_3$ as the catalyst in the presence of oxidant TBHP. In case of quinolines the acylation took place regioselectively at its C2 position only with no traces of other regioisomers. No C4 aroylation product was observed even when the C2 position was blocked with a substituents, suggesting the strong regioselective nature of the present transformation This protocol is a practical alternative to the classical Minisci reaction.*

CHAPTER IIIB

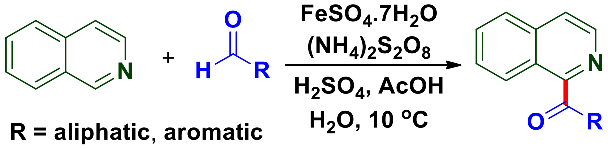
IIIB. Regiospecific Benzoylation of Electron-Deficient *N*-Heterocycles with Methylbenzenes via a Minisci-Type Reaction

IIIB.1. Introduction

In organic chemistry, one of the most important and fundamental challenge is to build C–C bonds in a rapid and efficient manner.[1] Of significant interest are methods that provide access to molecules in step- and atom-economic fashion from readily available precursors. In the past few decades, the construction of C–C bonds through C–H bond activation is a rapidly expanding field of research as it provides an atom-economical and shorter route for the synthesis of organic compounds and offers substantial benefits.[2] In this context, cross-dehydrogenative coupling between two different C–H bonds represent an useful alternative approach toward C–C bond formation between organic components through the functionalization of all types (sp, sp^2, sp^3) of C–H bonds.[1a,d,e,3] Mild reactivity and poor site selectivity are the two important challenges that need to be addressed in CDC protocols. Nitrogenous heterocycles are widely distributed in nature and present in large proportion in commercial drugs.[4] These heterocycles also have enormous applications in both chemistry and biology.[5] Heterocyclic moieties bearing an acyl group have been found in drugs which are important in pharmacological studies.[4] Until now, a number of methods have been developed for the synthesis of electron-deficient heterocycles, but their functionalization using cross-dehydrogenative coupling is far less visited.

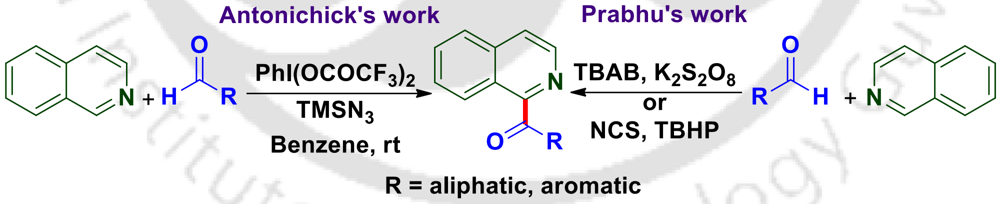
IIIB.2. Strategies for the Acylation of *N*-heterocycles

In contrast to electron-rich heterocycles,[6a-g] acylation of electron-deficient heterocycles is much more challenging and only a few reports are available.[6h-j] Among these, the Minisci reaction is the most commonly used approach,[4a,6i,7-10] which involves the addition of an *in situ* generated nucleophilic acyl radical from aldehyde to an electron-deficient heterocycles (Scheme IIIB.2.1). Although, it represents a straightforward strategy but suffers from certain drawbacks such as harsh reaction conditions, poor site selectivity, limited substrate scope, and the use of transition-metal salts upto stoichiometric amounts.[7a]



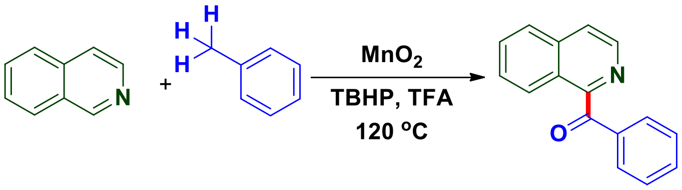
Scheme IIIB.2.1. *Minisci approach for the acylation of N-heterocycles*

To overcome these aspects, first Antonchick[6h] and later on Prabhu[11a] groups independently reported metal-free analogues of the Minisci reaction under ambient conditions (Scheme IIIB.2.1). Antonchick and co-worker used bis(trifluoroacetoxy)iodo benzene [$PhI(OCOCF_3)_2$] (4 equiv) as oxidant along with the $TMSN_3$ (4 equiv) as additive in benzene solvent at room temperature. This protocol is widely applicable for a variety of aldehydes and *N*-heterocycles. This procedure was further improved by Prabhu *et al.* by using *tetra*butylammonium bromide (30 mol %) as the catalyst and $K_2S_2O_8$ (2 equiv) as the oxidant. Later on same group developed a similar *N*-chlorosuccinamide (NCS)-catalyzed aroylation of *N*-heterocycles using TBHP as the oxidant.[11b] The above mentioned procedure provides the acylated *N*-heterocycles in good yields, however suffers from certain drawbacks such as requirements of functionalized starting material as well as poor regioselectivity in other heterocycles like quinoline and pyridine.



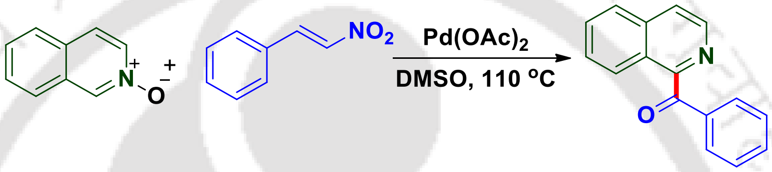
Scheme IIIB.2.2. *Metal-free approach for the acylation of N-heterocycles*

A trifluroacetic acid (TFA) and TBHP mediated cross-dehydrogenative coupling between *N*-heterocycles and aldehydes was developed by Liu *et al.*[11c] Apart from this later the same group has also describes a MnO_2-catalyzed acylation of *N*-heterocycles using methylarenes as aroyl source in the presence of TBHP as oxidant and TFA as additive (Scheme IIIB.2.3).



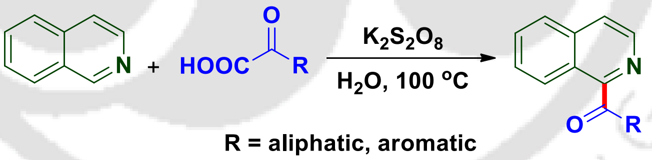
Scheme IIIB.2.3. *Mn(II)-catalyzed aroylation of N-heterocycles with methylarenes*

Wang *et al.* developed a Pd-catalyzed alternative route for the acylation of *N*-heterocycles using β-nitrosyrene as aroyl source.[11e] In this reaction, the N–O bond of isoquinoline *N*-oxide was designed as a directing group in the C–H bond activation as well as the source of an oxygen atom (Scheme IIIB.2.4).



Scheme IIIB.2.4. *Pd(II)-catalyzed aroylation of N-heterocycles with β-nitrosyrene*

Very recently Singh and co-worker developed a facile and efficient decarboxylative protocol for the acylation of isoquinoline in water medium using α-ketoacid as aroyl source and $K_2S_2O_8$ as oxidant without any metal or additives (Scheme IIIB.2.5).[11f]



Scheme IIIB.2.5. *Decarboxylative aroylation of N-heterocycles with α-ketoacids*

Hence, the developments of new and efficient CDC reactions in which such challenges can be overcome are of great significance in synthetic organic chemistry (Scheme IIIB.2.6).

Scheme IIIB.2.6. *Our strategy for acylation of N-heterocycle*

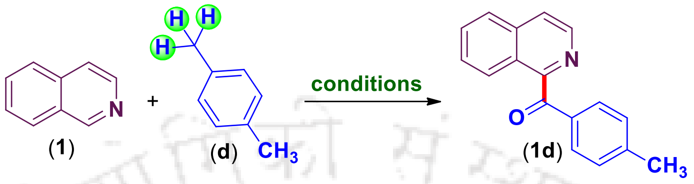
IIIB.3. Present Work

Recently, our group has developed a number of CDC protocols for the construction of C–C and C–O bonds using alkylbenzenes as the surrogates of $ArCH_2O$-,[12a] ArCO-,[12b-d] $ArCH_2$-[12e] and ArCOO-[12e,f] under oxidative conditions. In continuation to our efforts in utilizing alkylbenzenes as different surrogates via metal and metal-free C–H functionalization strategies, we envisaged that an acyl radical (generated *in situ* from methylarenes under oxidative conditions) could be utilized for the direct acylation of *N*-heterocycles. Antonchick *et al.*[6h] in their report demonstrated that the *in situ* generated CF_3COOH from $PhI(OCOCF_3)_2$ protonates the *N*-atom of heterocycle, therefore making α-carbon to nitrogen more electrophilic in nature. This facilitates the attack of the nucleophilic acyl radical on to the α-carbon. Intrigued by the key mechanistic feature; we anticipated that the direct use of CF_3COOH could generate a similar protonated intermediate. On the other hand, employing TBHP as the oxidant is expected to afford the other coupling counterpart to the acyl radical from methylarenes.[12b-d]

Optimization of Reaction Conditions: To give a practical shape to this coupling concept, a reaction between isoquinoline (**1**) and *p*-xylene (**d**) was initiated in the presence of CF_3COOH and TBHP at 110 °C. As hypothesized, the reaction provided C1-aroylated product (**1d**) but in a low yield of 26% (Table IIIB.3.1, entry 1). In a quest to improve the yield, both weak (CH_3COOH) and strong (CF_3SO_3H) organic acids were used in lieu of CF_3COOH; however, poorer yields were obtained in both of these cases (Table IIIB.3.1, entry 2 and 3). Even a 3-fold excess of CF_3COOH had no substantial effect on the product yield (Table IIIB.3.1, entry 4). These observations suggest that neither the strength of acid nor their concentrations are the determining factors for better conversion. Thus, we attempted the reaction in the presence of Lewis acids instead of protic acids. Gratifyingly, the use of Lewis acid $AlCl_3$ afforded the acylated product in an improved yield of 58% (Table IIIB.3.1, entry 5). Encouraged by this result, other Lewis acids such as $FeCl_3$ (42%), $ZnCl_2$ (< 8%), $TiCl_4$ (40%), $SnCl_2$ (48%), and $Cu(OTf)_2$ (38%) were also tested, but all were found to be inferior to $AlCl_3$ (58%) (Table IIIB.3.1, entries 5–10). Interestingly, when the quantity of $AlCl_3$ was reduced to half (50 mol %) and one fourth (25 mol %), the yield virtually remained unaltered (Table IIIB.3.1, entries 11 and 12). However, the yield dropped marginally when $AlCl_3$ loading was decreased to 20 mol % (Table IIIB.3.1, entry 13). A 9% increase in the yield was observed (Table

IIIB.3.1, entry 14) upon performing the reaction at a lower temperature of 95 °C. Better yield (65%) obtained at lower temperature (95 °C) may be related to some of the thermodynamic parameters in the reaction as the acylated product formed is not stable at higher temperature.

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



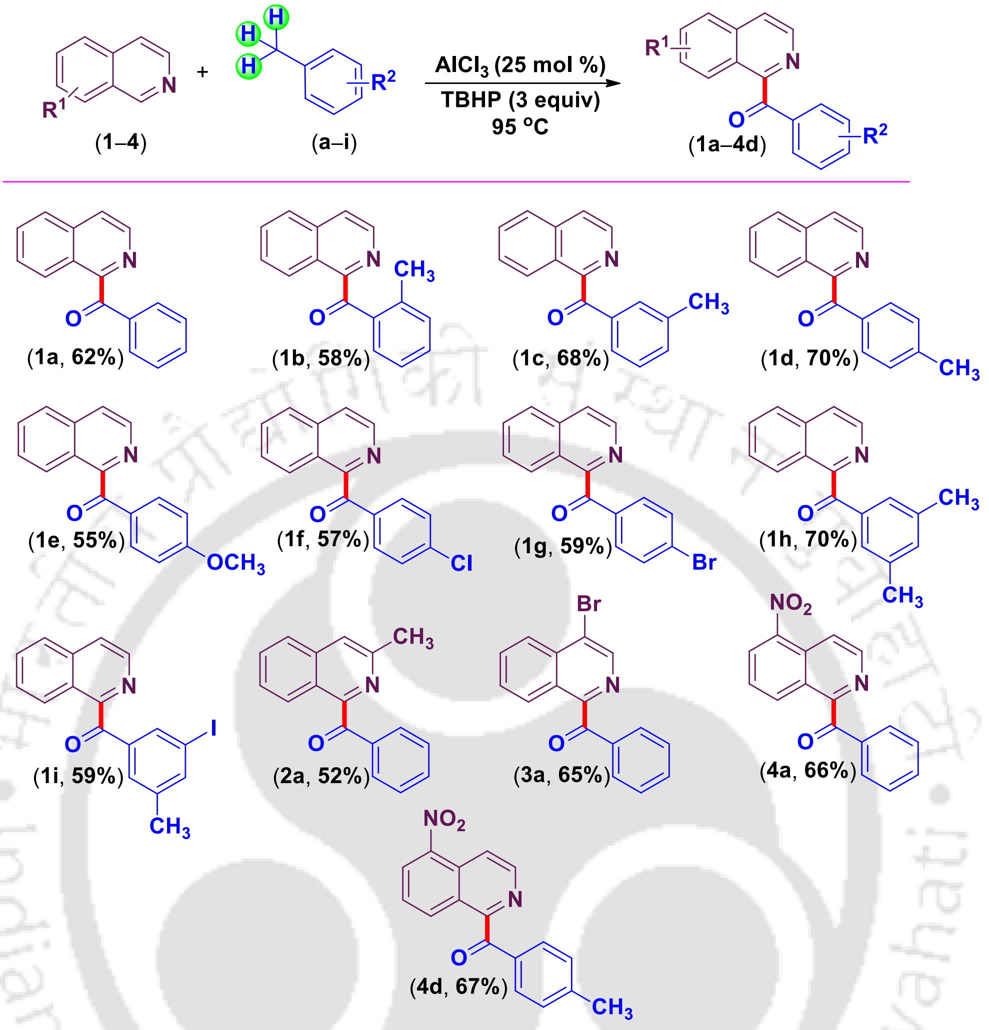
Entry	Catalyst (mol %)	Oxidant (equiv)	Temp (°C)	Yield(%)[b]
1	CF_3COOH (100)	TBHP (3)	110	26
2	CH_3COOH (100)	TBHP (3)	110	09
3	CF_3SO_3H (100)	TBHP (3)	110	13
4	CF_3COOH (300)	TBHP (3)	110	15
5	$AlCl_3$ (100)	TBHP (3)	110	58
6	$FeCl_3$ (100)	TBHP (3)	110	42
7	$ZnCl_2$ (100)	TBHP (3)	110	<8
8	$TiCl_4$ (100)	TBHP (3)	110	40
9	$SnCl_2$ (100)	TBHP (3)	110	48
10	$Cu(OTf)_2$ (100)	TBHP (3)	110	38
11	$AlCl_3$ (50)	TBHP (3)	110	57
12	$AlCl_3$ (25)	TBHP (3)	110	56
13	$AlCl_3$ (20)	TBHP (3)	110	51
14	$AlCl_3$ (25)	TBHP (3)	95	65
15[c]	**$AlCl_3$ (25)**	**TBHP (3)**	**95**	**71**
16[c]	$AlCl_3$ (25)	TBHP (3.5)	95	72
17[c]	$AlCl_3$ (25)	TBHP (2)	95	51
18[c]	$AlCl_3$ (25)	aq. TBHP(3)	95	47
19[c]	-	TBHP (3)	95	<15

[a] Reaction conditions: **1** (0.25 mmol), **d** (1.25 mmol), time 18 h. [b] Isolated pure product. [c] Under N_2 atmoshphere.

Maintaining the temperature at 95 °C and performing the reaction under N_2 atmosphere resulted in 6% further enhancement in the yield (Table IIIB.3.1, entry 15). No major improvements in the product yield was noticed with an increased amount of oxidant (3.5 equiv), while the use of 2 equiv was not sufficient for this transformation (Table IIIB.3.1, entry 16 and 17). Aqueous TBHP was found to be less effective compared to that of a decane solution of TBHP (Table IIIB.3.1, entry 18). Control experiment in the absence of Lewis acid $AlCl_3$ afforded acylated product in < 15% suggesting the essential requirement of $AlCl_3$ to bring about the desired transformation (Table IIIB.3.1, entry 19). To check whether $AlCl_3$ has definite role or the acid (HCl) generated in the reaction medium is activating the *N*-atom a reaction was carried out in the presence of 1 equiv of HCl. The formation of product in a modest yield of 33% ascertains the distinct role of $AlCl_3$ in this transformation. From these screening studies, the optimal condition established was the use of $AlCl_3$ (25 mol %) and TBHP (5–6 M in decane) (3 equiv) at 95 ^{o}C under N_2 atmosphere (Table IIIB.3.1, entry 15).

Substrates Scope for C1-Acylation of Isoquinolines: With this optimized condition in hand, we examined the scope of this cross-dehydrogenative couplings by reacting isoquinoline (**1**) with a set of alkylbenzenes (**a–i**) possessing both electron-donating as well as electron-withdrawing substituents (Scheme IIIB.3.1). Under the present conditions, isoquinoline was smoothly acylated with various alkylbenzenes to afford the corresponding coupled products (**1a–1i**) in moderate to good yields as shown in Scheme IIIB.3.1. Substituents present in the phenyl ring of alkylbenzenes play a role in controlling the product yields as evident from their yields and the reaction times (Scheme IIIB.3.1). Methylbenzenes bearing additional –Me group(s) irrespective of their position like *o*-CH_3 (**b**), *m*-CH_3 (**c**), and *p*-CH_3 (**d**) provided good yields of their corresponding coupled products (**1b–d**) with the retention of other –CH_3 group(s), an observation consistent with our previous reports.[13a-f] However, a slightly lower yield was obtained for *ortho*-substituted alkylbenzene; the difference in *o*-xylene (**b**) compared to *meta* and *para* analogues (**1c** and **1d**) might be due to steric effects imparted by the *ortho*-substituent. A strongly electron-donating –OCH_3 (**e**) group is expected to give better yield of the acylated product (**1e**, Scheme IIIB.3.1), contrary to our prediction it gave less yield of the product. This may be due to the coordination of the methoxy group of alkylbenzene (**e**) with the Lewis acid ($AlCl_3$), thereby making it less available for its catalytic activity. In order to expand the scope of this coupling reaction, isoquinoline substituted with various groups like 3-CH_3 (**2**), 4-Br (**3**), and 5-NO_2 (**4**) were reacted with alkylbenzenes (**a** and **d**) (Scheme IIIB.3.1). As can be seen from Scheme IIIB.3.1, all these isoquinolines underwent efficient coupling with alkylbenzenes (**a** and **d**) under the present reaction conditions to afford products (**2a**), (**3a**), (**4a**), and (**4d**) in good to moderate yields (Scheme IIIB.3.1).

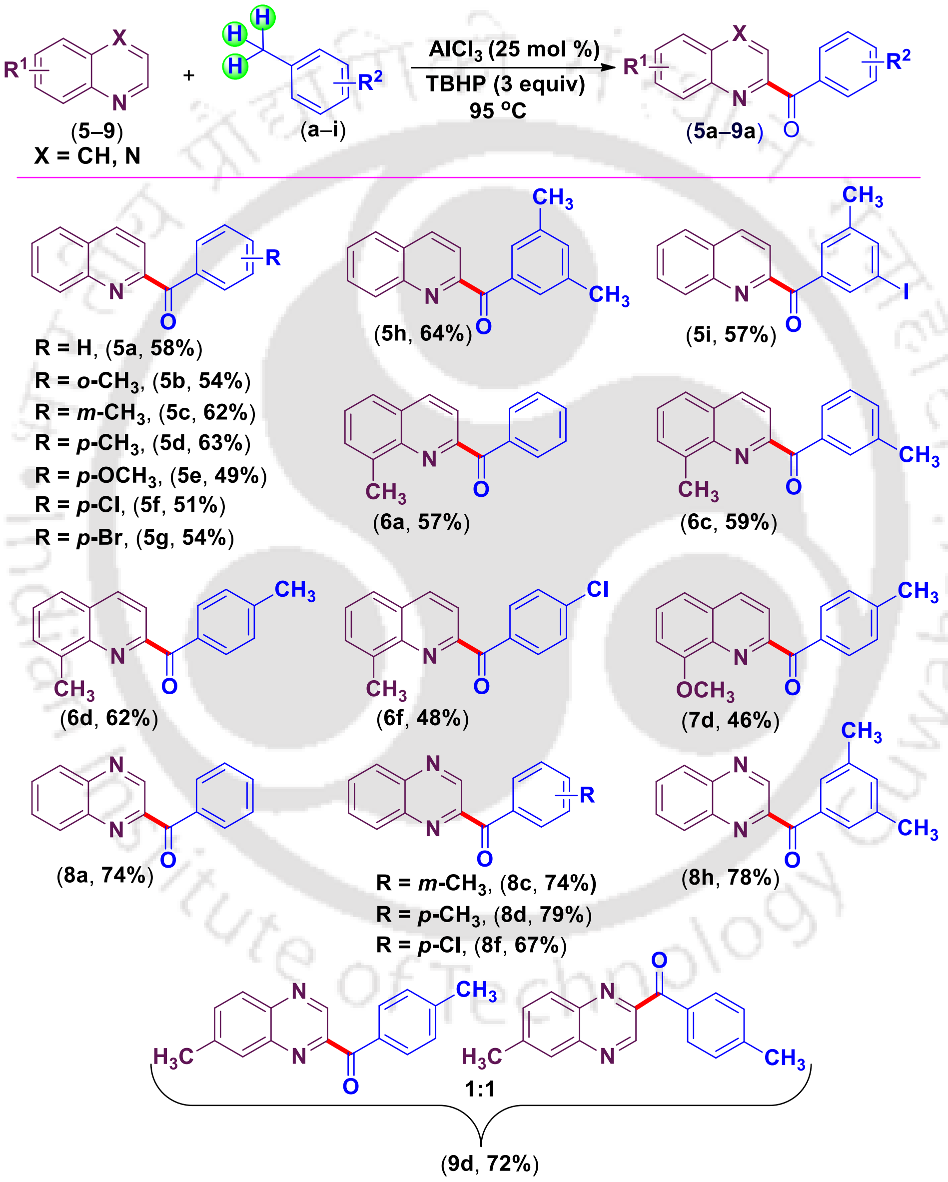
Scheme IIIB.3.1. *Substrate scope for C1-acylation of isoquinolines*[a,b]



[a]Reaction conditions: isoquinoline (0.5 mmol), alkylbenzenes (2.5 mmol), $AlCl_3$ (0.125 mmol), TBHP in decane (5–6 M) (3 equiv), 95 °C, time 18–24 h. [b]Yields of the pure product reported.

Substrates Scope for C2-Acylation of Quinolones and Quinoxalines: The next focus was to acylate other electron-deficient heterocycles such as quinolines and quinoxalines (Scheme IIIB.3.2). Quinoline underwent cross-dehydrogenative coupling with different alkylbenzenes (**a–i**) to give exclusive C2-monoacylated products (**5a–i**, Scheme IIIB.3.2). It is to be noted that in case of quinolines the acylation took place regioselectively at its C2 position only with no traces of other regioisomers. However, in previous reports by Antonchick[6h] and Prabhu[11a] a mixture of both mono- (at the C2 position) and di-acylated (at the C2 and C4 positions) products were formed in various proportions. No C4 aroylation product was observed even when the C2 position was blocked with a methyl or a *tert*-butyl group, suggesting the strong regioselective nature of the present transformation (Scheme IIIB.3.3). It is well known that under an acidic condition (protic acid) both C2 and C4 positions are susceptible towards nucleophilic radical addition because of the *N*-protonation in quinoline. Due to pronounced –I effect of the adjacent protonated *N*-atom there is a higher preference at the C2 position. However, coordination of weak Lewis acid ($AlCl_3$) with nitrogen of quinoline is just sufficient to activate the C2 position and not the C4, therefore giving only one regioisomer. The reactivity of different

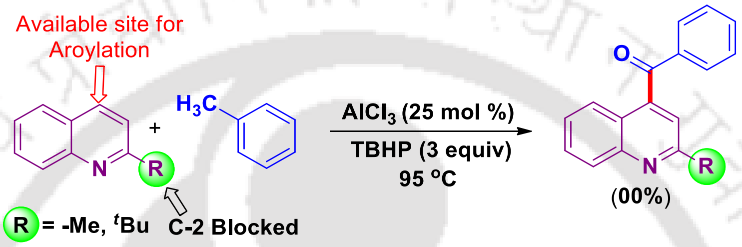
Scheme IIIB.3.2. *Substrate scope for C2-acylation of quinolones and quinoxalines*[a,b]



[a]Reaction conditions: **5–9** (0.5 mmol), alkylbenzenes (2.5 mmol), $AlCl_3$ (0.125 mmol), TBHP in decane (5–6 M) (3 equiv), 95 °C, time 18–24 h. [b]Yields of the pure product reported.

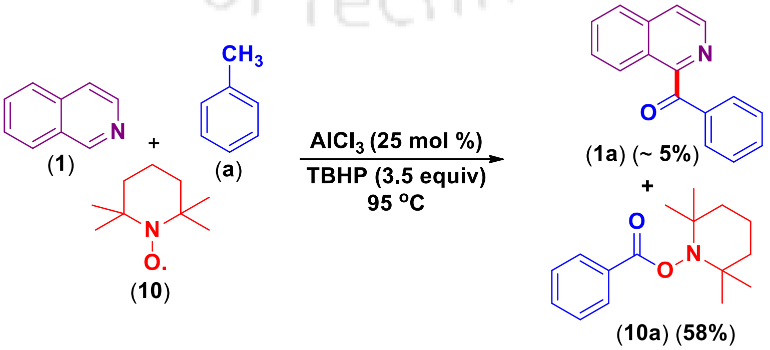
alkylbenzenes with quinoline is similar to that observed for their reaction with isoquinoline, but the overall yields of coupled products were marginally lower (Scheme

IIIB.3.2). Other substituted quinolines like 8–methylquinoline (**6**) and 8-methoxyquinoline (**7**) reacted with alkylbenzenes (**a**, **c**, **d** and **f**) to provide their respective acylated products (**6a**, **6c**, **6d**, **6f** and **7d**) in moderate yields as shown in Scheme IIIB.3.2. Heterocycles bearing two *N*-atoms like quinoxaline (**8**) were also mono functionalized in good yields (**8a–h**, Scheme IIIB.3.3). Similarly, electron-deficient heterocycle, 7–methylquinoxaline (**9**) when coupled with *p*-xylene (**d**) under the optimized reaction conditions resulted in an inseparable mixture of two regioisomeric acylated products (**9d**, Scheme IIIB.3.2).

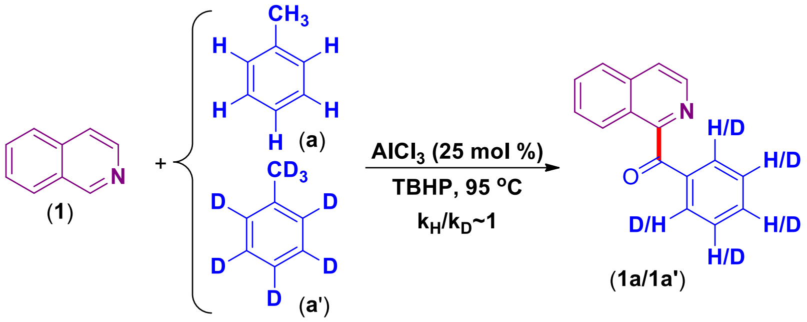


***Scheme IIIB.3.3.** Demonstration of regioselectivity in quinoline*

Mechanistic Studies: Next the mechanism of the direct acylation was investigated. Substantial quenching of product formation in the presence of radical inhibitor (TEMPO) was observed (Scheme IIIB.3.4). Along with the formation of a trace (~ 5%) of coupled product, a TEMPO ester (58%) was also isolated. This provides an evidence for the formation of an acyl radical in the medium, thus supporting a radical pathway. The observed kinetic isotope effect ($k_H/k_D \sim 1$) during an intermolecular competing reaction of toluene and toluene-d_8 with isoquinoline implies sp^3 C–H bond cleavage is not the rate determining step in this process (Scheme IIIB.3.5). On the basis of these observations and literature precedence, a plausible mechanism is proposed in Scheme IIIB.3.6.

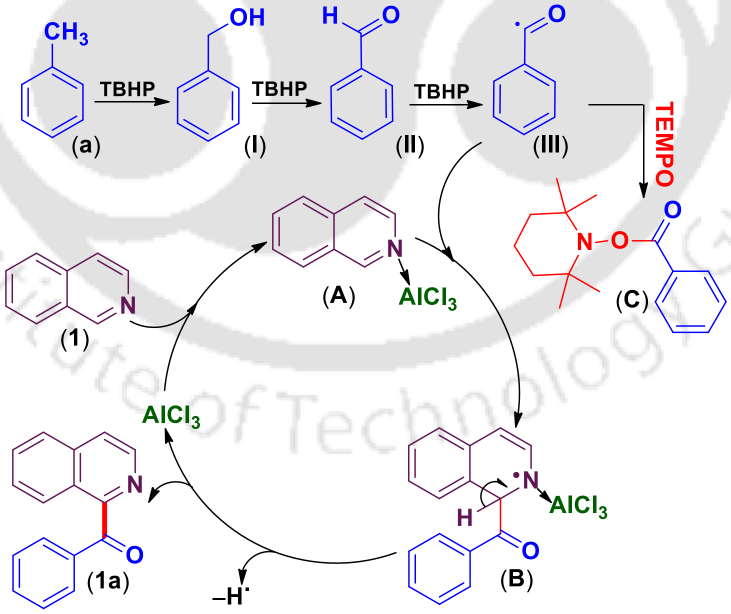


***Scheme IIIB.3.4.** Trapping of acyl intermediate with TEMPO*



***Scheme IIIB.3.5.** Kinetic isotope study*

In the presence of TBHP, alkylbenzene (**a**) is oxidized sequentially to benzyl alcohol (**I**), benzaldehyde (**II**) which subsequently generates acyl radical (**III**) via the cleavage of aldehydic C–H bond. On the other hand, $AlCl_3$ co-ordinates with the *N*-atom of heterocycle (**1**) to form intermediate (**A**), making the heterocyclic ring further electron-deficient. An acyl radical (**III**) formed in the medium is nucleophilic in nature and attacks at the more electrophilic C1 position of the heterocycle to form the corresponding radical intermediate (**B**). Re-aromatization of intermediate (**B**) provides the desired acylated product (**1a**) (Scheme IIIB.3.6).



***Scheme IIIB.3.6.** Plausible mechanism for C1-acylation*

When the reaction was performed either with benzyl alcohol or with benzaldehyde instead of toluene under otherwise identical conditions, the yields of product (**1a**) obtained were 84% and 90%, respectively, therefore supporting the intermediacy of benzylalcohol and aldehyde in this reaction. The selective acylation could be explained in term of nucleophilic character of acyl radical (**III**) generated, which attacks at the more electrophilic position of co-ordinated heterocycle (**A**). A similar mechanism is expected for other *N*-heterocycles.

In conclusion, we have developed an efficient, mild, and cost-effective method for the regiospecific acylation of electron-deficient *N*-heterocycles using methylbenzenes. In this transformation, Lewis acid $AlCl_3$ is used as catalyst and TBHP as oxidant. This reaction tolerates a wide range of functional groups and proceeds efficiently for the acylation of *N*-heterocycles. The reaction serves as complement to classical Minisci reaction.

IIIB.4. Experimental Section

IIIB.4.1. General Information: All the compounds were commercial grade and were used without further purification. Organic extract 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 proton NMR (400 and 600 MHz) $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode (Q-TOF type Mass Analyzer). IR spectra were recorded in KBr or neat.

IIIB.4.2. Typical Procedure for the Synthesis of Isoquinolin-1-yl(*p*-tolyl)methanone (1d): Isoquinoline (0.5 mmol, 64.5 mg), $AlCl_3$ (0.125 mmol, 16.6 mg), *p*-xylene (2.5 mmol, 265 mg) and 5–6 M decane TBHP (1.5 mmol, 300 μL) were added sequentially into an oven-dried 25 mL round-bottom flask. Then the resultant mixture was heated at 95 ^oC for 18 h under an atmosphere of N_2 sealed with a rubber septum. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and admixed with ethyl acetate (30 mL). The organic layer was washed sequentially with a saturated solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under *vacuo*. The crude product so obtained was then purified by column chromatography using EtOAc and hexane (0.4:9.6) to give aroylated product (**1d**, 88 mg, 71%).

IIIB.4.3. Trapping of Radical Intermediates with Radical Scavenger TEMPO: Isoquinoline (0.5 mmol, 64.5 mg), $AlCl_3$ (0.125 mmol, 16.6 mg), toluene (2.5 mmol, 230 mg) and 5–6 M decane TBHP (1.5 mmol, 300 μL) and TEMPO (1.5 mmol, 234 mg) were added sequentially into an oven-dried 25 mL round-bottom flask. Then the resultant mixture was heated at 95 ^{o}C for 18 h. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and admixed with ethyl acetate (30 mL). The organic layer was washed sequentially with a saturated solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in *vacuo*. The crude products so obtained were then purified by column chromatography using EtOAc and hexane as the eluents. TEMPO ester adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**10a**) was isolated in 58% yield along with a trace of (**1a**).

IIIB.4.4. Intermolecular Competing Kinetic Isotope Effect (KIE) Experiment with Deuterated Toluene: To a mixture of isoquinoline (**1**) (0.5 mmol, 64.5 mg) and $AlCl_3$ (0.125 mmol, 16.6 mg) was added an equimolar quantity of toluene (**a**) (1.25 mmol, 115 mg), and toluene-d_8 (**a’**) (1.25 mmol, 125 mg). To this resultant heterogeneous mixture was then added 5–6 M decane TBHP (300 μL, 1.5 mmol) and the resultant mixture was heated in a pre-heated oil bath at 95 ^{o}C for 18 h. The reaction mixture was admixed with water (10 mL) and the product was extracted with ethyl acetate (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The crude product so obtained was purified over a column of silica gel and eluted with hexane/ethyl acetate (9.6:0.4) to give the expected product in 42% yield (**1a** and **1a’**). The ratio of the deuterated (**1a’**) and non deuterated (**1a**) aroylated product was calculated on the basis of the integration ratio of the aromatic proton peak at δ 7.48 (originating from toluene) and aromatic proton at δ 8.60 (originated from *N*-heterocycle).

Calculation:

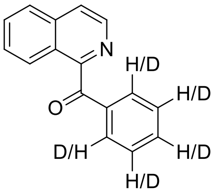
For two protons at δ 7.48, the integration value is 2.00.

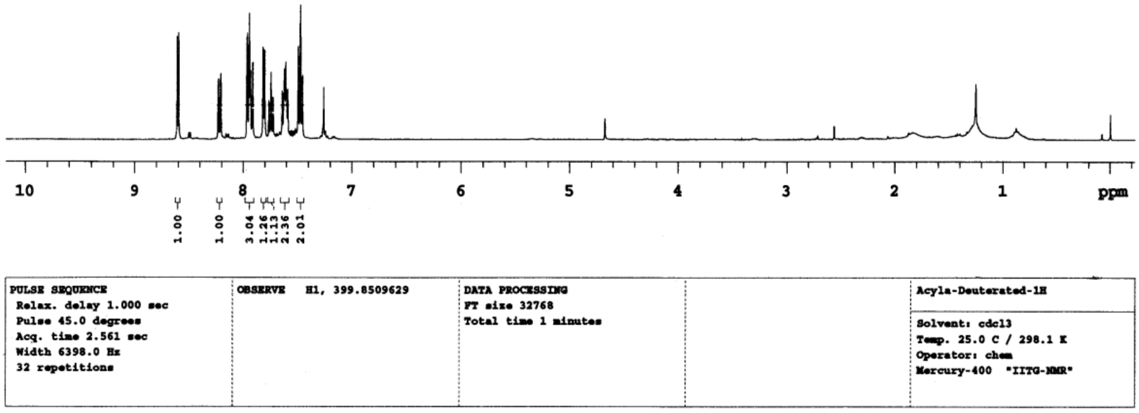
Thus for a single proton the integration corresponds to 2.00 / 2 = 1.00.

Now for the integration value of the protons originating from *N*-heterocycle at δ 8.60 is 1.00.

Thus the number of protons corresponding to this integration value is 1.00 / 1 = 1.00.

Upon correlation with the original spectra of (**1a**) the number of proton at δ 7.48 should be 2 and the found integration for the same is 2.00. Hence the k_H / k_D ~1.





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 Width 6398.0 Hz                                                                                     Operator: chem
 32 repetitions                                                                                      Mercury-400  "IITG-NMR"
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IIIB.5. References

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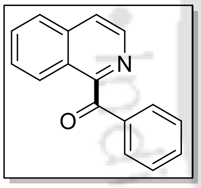
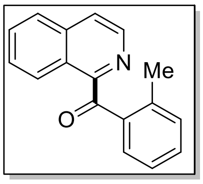
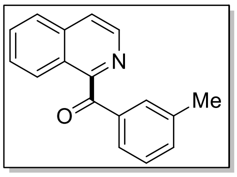
IIIB.6. Spectral Data



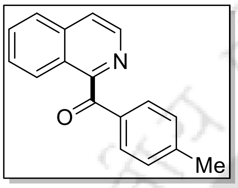
Isoquinoline-1-yl(phenyl)methanone (1a): Orange gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (t, 2H, *J* = 7.6 Hz), 7.59–7.64 (m, 2H), 7.74 (t, 1H, *J* = 7.6 Hz), 7.81 (d, 1H, *J* = 6.0Hz), 7.91–7.96 (m, 3H), 8.22 (d, 1H, *J* = 8.8 Hz), 8.60 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.8, 126.4, 126.6, 127.3, 128.5, 128.7, 130.9, 133.8, 136.8, 136.9, 141.4, 156.6, 194.9; IR (KBr): 3056, 2926, 2851, 1671, 1581, 1248, 1154, 1020 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO$ (MH^+) 234.0913; found 234.0919.



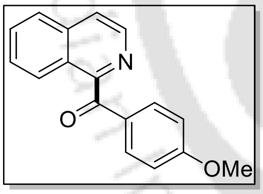
Isoquinolin-1-yl(*o*-tolyl)methanone (1b): Brown gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.53 (s, 3H), 7.21 (t, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.8 Hz), 7.40 (d, 1H, *J* = 7.8 Hz), 7.43 (t, 1H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 6.6 Hz), 7.76 (t, 1H, *J* = 7.8 Hz), 7.79 (d, 1H, *J* = 6.0 Hz), 7.92 (d, 1H, *J* = 7.8 Hz), 8.62 (d, 1H, *J* = 8.4 Hz), 8.86 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 123.1, 125.7, 126.5, 126.6, 127.3, 128.8, 130.9, 131.99, 132.0, 132.3, 137.0, 137.6, 139.9, 141.6, 157.2, 198.0; IR (KBr): 3057, 2926, 2855, 1669, 1576, 1243, 1156, 1041 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1074.



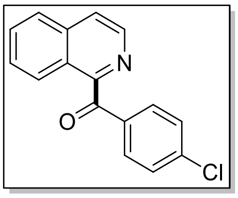
Isoquinolin-1-yl(*m*-tolyl)methanone (1c): Orange gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 7.33 (t, 1H, *J* = 7.6 Hz), 7.40 (d, 1H, *J* = 7.6 Hz), 7.59 (t, 1H, *J* = 6.8 Hz), 7.71 (d, 2H, *J* = 9.6 Hz), 7.74 (d, 1H, *J* = 7.6 Hz), 7.78 (d, 1H, *J* = 5.6 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 8.4 Hz), 8.58 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 122.7, 126.4, 126.5, 127.3, 128.3, 128.4, 128.6, 130.9, 131.2, 134.7, 136.8, 138.5, 141.4, 156.9, 195.2; IR (KBr): 3055, 2924, 2854, 1668, 1584, 1279, 1175, 1049 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1076.



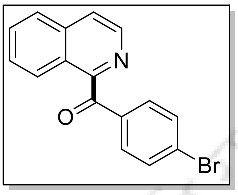
Isoquinolin-1-yl(*p*-tolyl)methanone (1d): Orange gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.79 (d, 1H, *J* = 5.2 Hz), 7.85 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.91 (d, 1H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 122.6, 126.4, 126.6, 127.3, 128.4, 129.4, 130.9, 131.1, 134.3, 136.9, 141.4, 144.9, 157.0, 194.7; IR (KBr): 3054, 2923, 1665, 1604, 1249, 1152, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1073.



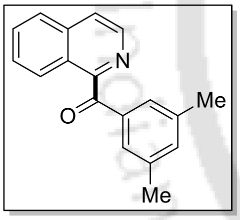
Isoquinolin-1-yl(4-methoxyphenyl)methanone (1e): Brown gummy; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.84 (s, 3H), 6.92 (d, 2H, *J* = 9.0 Hz), 7.57 (t, 1H, *J* = 7.8 Hz), 7.70 (t, 1H, *J* = 7.8 Hz), 7.76 (d, 1H, *J* = 5.4 Hz), 7.88 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 9.0 Hz), 8.56 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.7, 114.0, 122.4, 126.5, 127.2, 128.3, 129.8, 130.0, 130.9, 133.3, 136.9, 141.4, 157.3, 164.3, 193.6; IR (KBr): 3055, 2932, 2840, 1661, 1596, 1422, 1254, 1171, 1074 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2$ (MH^+) 264.1019; found 264.1017.



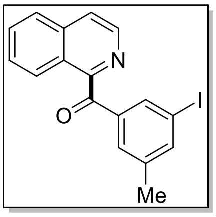
(4-Chlorophenyl)(isoquinolin-1-yl)methanone (1f): Brown solid; M.p. 73–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (d, 2H, *J* = 8.4 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 5.2 Hz), 7.89–7.92 (m, 3H), 8.23 (d, 1H, *J* = 8.4 Hz), 8.58 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 123.2, 126.3, 126.7, 127.4, 128.7, 129.0, 131.0, 132.4, 135.3, 137.0, 140.4, 141.3, 155.9, 193.6; IR (KBr): 3054, 2926, 2854, 1664, 1584, 1249, 1090 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}ClNO$ (MH^+) 268.0524; found 268.0528.



(4-Bromophenyl)(isoquinolin-1-yl)methanone (1g): Brown solid; M.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60–7.66 (m, 3H), 7.75 (t, 1H, *J* = 8.0 Hz), 7.82–7.85 (m, 3H), 7.93 (d, 1H, *J* = 8.4 Hz), 8.26 (d, 1H, *J* = 8.8 Hz), 8.59 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 123.2, 126.3, 126.7, 127.4, 128.7, 129.2, 131.0, 132.0, 132.4, 135.7, 137.0, 141.3, 155.8, 193.8; IR (KBr): 3053, 2925, 2854, 1662, 1580, 1393, 1247, 1070 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH^+) 312.0019; found 312.0024

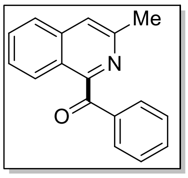


(3,5-Dimethylphenyl)(isoquinolin-1-yl)methanone (1h): Yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 6H), 7.24 (s, 1H), 7.54 (s, 2H), 7.60 (t, 1H, *J* = 8.4 Hz), 7.73 (t, 1H, *J* = 6.8 Hz), 7.79 (d, 1H, *J* = 5.6 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 122.6, 126.4, 126.5, 127.2, 128.4, 128.6, 130.8, 135.7, 136.8, 136.9, 138.3, 141.3, 157.1, 195.5; IR (KBr): 3054, 2919, 2859, 1668, 1601, 1453, 1299, 1144, 1085 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1233.

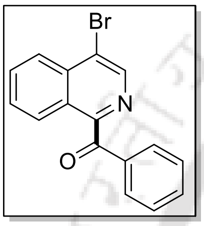


(3-Iodo-5-methylphenyl)(isoquinolin-1-yl)methanone (1i): Brown gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 7.65 (t, 1H, *J* = 8.0 Hz), 7.70 (s, 1H), 7.74–7.78 (m, 2H), 7.84 (d, 1H, *J* = 5.6 Hz), 7.94 (d, 1H, *J* = 8.0 Hz), 8.06 (s, 1H), 8.23 (d, 1H, *J* = 8.4), 8.60 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 94.3, 123.2, 126.3, 126.7, 128.8, 130.8, 131.0, 135.3, 136.8, 138.7, 140.6, 14.6, 141.4, 143.1, 155.8, 193.6; IR (KBr): 2923, 2853, 1667, 1562, 1429, 1277, 1146, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}INO$ (MH^+) 374.0036; found

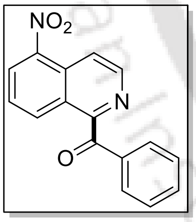
374.0036.



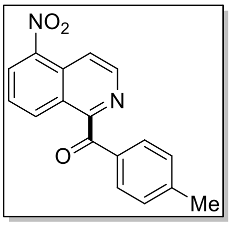
(3-Methylisoquinolin-1-yl)(phenyl)methanone (2a): Brown solid; M.p. 95–97 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.71 (s, 3H), 7.38–7.49 (m, 3H), 7.57–7.60 (m, 2H), 7.65 (t, 1H, *J* = 9.6 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.95 (d, 2H, *J* = 6.6 Hz), 8.05 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.3, 120.6, 124.6, 126.1, 126.4, 126.7, 127.3, 128.6, 130.7, 131.0, 133.9, 136.6, 137.5, 150.4, 195.1; IR (KBr): 3059, 2924, 2855, 1670, 1589, 1447, 1239, 1027 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH^+) 248.1070; found 248.1072.



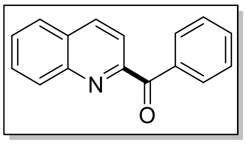
(4-Bromoisoquinolin-1-yl)(phenyl)methanone (3a): Red solid; M.p. 129–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.48 (t, 2H, *J* = 7.8 Hz), 7.62 (t, 1H, *J* = 7.2 Hz), 7.69 (t, 1H, *J* = 7.8 Hz), 7.87 (t, 1H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 7.8 Hz), 8.23 (d, 1H, *J* = 9.0 Hz), 8.29 (d, 1H, *J* = 9.0 Hz), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.0, 126.7, 126.9, 127.8, 128.7, 129.4, 130.9, 132.2, 134.1, 135.7, 136.6, 143.1, 155.9, 194.2; IR (KBr): 3056, 2961, 2855, 1659, 1523, 1268, 1158, 1018 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH^+) 312.0019; found 312.0025.



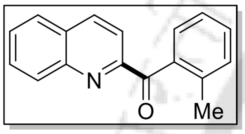
(5-Nitroisoquinolin-1-yl)(phenyl)methanone (4a): White solid; M.p. 106–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.49 (t, 2H, *J* = 7.8 Hz), 7.64 (t, 1H, *J* = 7.2 Hz), 7.72 (t, 1H, *J* = 7.8 Hz), 7.93 (d, 2H, *J* = 7.8 Hz), 8.55 (t, 2H, *J* = 7.2 Hz), 8.62 (d, 1H, *J* = 6.0 Hz), 8.82 (d, 1H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 117.8, 126.89, 126.92, 128.7, 128.8, 129.3, 131.0, 133.4, 134.4, 136.2, 144.6, 145.5, 157.3, 193.9; IR (KBr): 3066, 2922, 2844, 1661, 1526, 1353, 1276, 1161, 1069 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}N_2O_3$ (MH^+) 279.0764; found 279.0770.



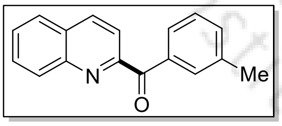
(5-Nitroisoquinolin-1-yl)(*p*-tolyl)methanone (4d): Brown solid; M.p. 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.30 (d, 2H, *J* = 8.4 Hz), 7.72 (t, 1H, *J* = 8.4 Hz), 7.83 (d, 2H, *J* = 8.0 Hz), 7.50–8.57 (m, 2H), 8.62 (d, 1H, *J* = 6.4 Hz), 8.81 (t, 1H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 117.6, 119.5, 126.8, 126.9, 128.7, 129.3, 129.6, 131.1, 133.5, 133.8, 134.0, 144.7, 157.7, 193.6; IR (KBr): 3063, 2924, 2853, 1669, 1448, 1246, 1215, 1180, 1024 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}N_2O_3$ (MH$^+$) 293.0921; found 293.0922.



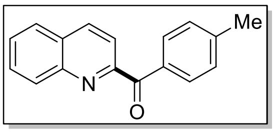
Phenyl(quinolin-2-yl)methanone (5a): Red solid; M.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (t, 2H, *J* = 7.6 Hz), 7.59–7.66 (m, 2H), 7.77 (t, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.17–8.22 (m, 3H), 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 121.0, 127.8, 128.4, 128.6, 129.1, 130.3, 130.8, 131.6, 133.3, 136.4, 137.3, 147.0, 154.9, 194.0; IR (KBr): 3054, 2925, 2853, 1661, 1450, 1317, 1168, 1019 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO$ (MH$^+$) 234.0913; found 234.0915.



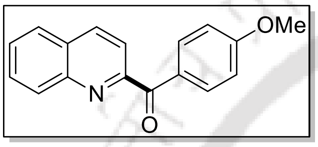
Quinolin-2-yl(*o*-tolyl)methanone (5b): Yellow solid; M.p. 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.28 (t, 1H, *J* = 7.6 Hz), 7.33 (d, 1H, *J* = 7.6 Hz), 7.45 (t, 1H, *J* = 7.2 Hz), 7.60 (d, 1H, *J* = 8.0 Hz,), 7.65 (t, 1H, *J* = 7.2 Hz), 7.75 (t, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 8.14 (t, 2H, *J* = 8.4 Hz), 8.34 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.0, 120.5, 125.2, 127.8, 128.8, 129.2, 130.2, 131.0, 131.3, 131.4, 137.3, 137.4, 138.8, 147.3, 155.0, 197.7; IR (KBr): 3055, 2923, 2853, 1660, 1561, 1454, 1313, 1260, 1092 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH$^+$) 248.1070; found 248.1079.



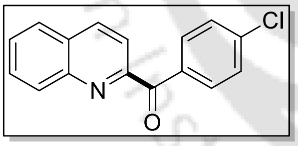
Quinolin-2-yl(*m*-tolyl)methanone (5c): White solid; M.p. 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.38 (d, 1H, *J* = 8.0 Hz), 7.43 (t, 1H, *J* = 7.2 Hz), 7.66 (t, 1H, *J* = 7.2 Hz), 7.79 (t, 1H, *J* = 7.2 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.00 (d, 2H, *J* = 6.8 Hz), 8.08 (d, 1H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 8.4 Hz), 8.34 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 121.0, 127.8, 128.2, 128.5, 129.0, 129.1, 130.3, 130.8, 131.9,134.1, 136.3, 137.2, 138.1, 146.9, 155.1, 194.4; IR (KBr): 3052, 2924, 2856, 1660, 1596, 1458, 1313, 1139, 1013 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH$^+$) 248.1070; found 248.1067.



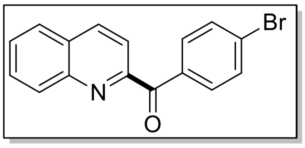
Quinolin-2-yl(*p*-tolyl)methanone (5d): Brown solid; M.p. 62–64 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.44 (s, 3H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.64 (t, 1H, *J* = 6.8Hz), 7.76 (t, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.13 (d, 2H, *J* = 8.0 Hz), 8.18 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 22.0, 121.0, 127.9, 128.5, 129.07, 129.13, 130.3, 130.7, 131.8, 133.8, 137.2, 144.2, 147.0, 155.3, 193.7; IR (KBr): 3066, 2922, 2852, 1659, 1456, 1317, 1161, 1112 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH$^+$) 248.1070; found 248.1077.



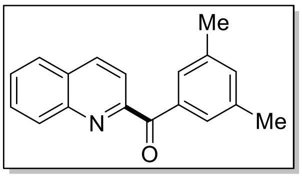
(4-Methoxyphenyl)(quinolin-2-yl)methanone (5e): White solid; M.p. 65–68 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.87 (s, 3H), 6.99 (d, 2H, *J* = 7.2 Hz), 7.65 (t, 1H, *J* = 7.6 Hz), 7.78 (t, 1H, *J* = 7.2 Hz), 7.90 (d, 1H, *J* = 7.6 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.20 (d, 1H, *J* = 8.0 Hz), 8.28 (d, 2H, *J* = 6.8 Hz), 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 55.7, 113.8, 121.1, 127.9, 128.4, 129.0, 129.2, 130.2, 130.7, 134.1, 137.2, 146.9, 155.6, 163.9, 192.4; IR (KBr): 3059, 2927, 2848, 1652, 1507, 1319, 1256, 1157, 1025 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2$ (MH$^+$) 264.1019; found 264.1025.



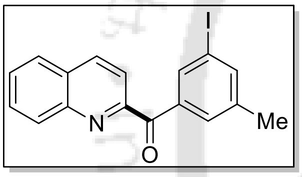
(4-Chlorophenyl)(quinolin-2-yl)methanone (5f): Brown solid; M.p. 105–107 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.47 (d, 2H, *J* = 8.4 Hz), 7.65 (t, 1H, *J* = 8.4 Hz), 7.78 (t, 1H, *J* = 6.8 Hz), 7.89 (d, 1H, *J* = 7.6 Hz), 8.11 (d, 1H, *J* = 8.8 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 8.22 (d, 2H, *J* = 8.8 Hz), 8.34 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 120.9, 127.9, 128.7, 128.8, 129.2, 130.4, 130.7, 133.1, 134.8, 137.5, 139.8, 146.9, 154.5, 192.6; IR (KBr): 2926, 2854, 1663, 1590, 1459, 1316, 1209, 1170, 1089 HRMS (ESI): calcd. for $C_{16}H_{10}ClNO$ (MH$^+$) 268.0524; found 268.0521.



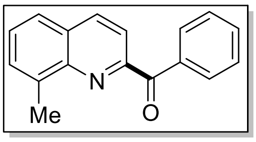
(4-Bromophenyl)(quinolin-2-yl)methanone (5g): Brown solid; M.p. 111–113 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.65 (t, 3H, *J* = 9.6 Hz), 7.78 (t, 1H, *J* = 9.2 Hz), 7.89 (d, 1H, *J* = 7.6 Hz), 8.10–8.17 (m, 4H), 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 120.9, 127.9, 128.5, 128.8, 129.2, 130.4, 130.7, 131.6, 133.2, 135.2, 137.4, 146.9, 154.4, 192.7; IR (KBr): 3048, 2956, 2926, 1664, 1586, 1458, 1316, 1167, 1068 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}BrNO$ (MH$^+$) 312.0019; found 312.0026.



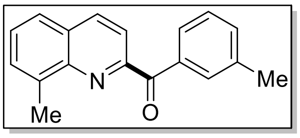
(3,5-Dimethylphenyl)(quinolin-2-yl)methanone (5h): Red solid; M.p. 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 6H), 7.24 (s, 1H), 7.64 (t, 1H, *J* = 8.0 Hz), 7.75–7.79 (m, 3H), 7.89 (d, 1H, *J* = 8.0 Hz), 8.03 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 121.0, 127.8, 128.5, 129.1, 129.3, 130.2, 130.8, 135.1, 136.4, 137.2, 138.0, 147.0, 155.4, 194.7; IR (KBr): 3060, 2923, 2855, 1662, 1598, 1461, 1325, 1143, 1035 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH$^+$) 262.1226; found 262.1229.



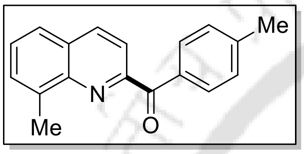
(3-Iodo-5-methylphenyl)(quinolin-2-yl)methanone (5i): Brown solid; M.p. 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 7.66 (t, 1H, *J* = 7.2 Hz), 7.76–7.80 (m, 2H), 7.89 (d, 1H, *J* = 8.0 Hz), 7.95 (s, 1H), 8.08 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 1H, *J* = 8.0 Hz), 8.33 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 93.9, 120.9, 127.9, 128.8, 129.2, 130.4, 130.8, 131.4, 137.4, 137.6, 138.1, 140.2, 142.5, 147.0, 154.3, 192.6; IR (KBr): 2924, 2853, 1664, 1563, 1311, 1143, 1016 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}INO$ (MH$^+$) 374.0036; found 374.0041.



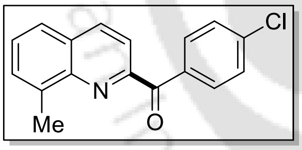
(8-Methylquinolin-2-yl)(phenyl)methanone (6a): White solid; M.p. 63–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.78 (s, 3H), 7.50–7.57 (m, 3H), 7.63 (t, 2H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 8.8 Hz), 8.31 (d, 1H, *J* = 8.4 Hz), 8.36 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.1, 120.6, 125.7, 128.1, 128.6, 129.2, 130.3, 131.9, 132.9, 136.8, 137.4, 139.1, 146.1, 153.3, 193.7; IR (KBr): 3056, 2953, 2922, 1660, 1594, 1445, 1322, 1286, 1159, 1070 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO$ (MH$^+$) 248.1070; found 248.1078.



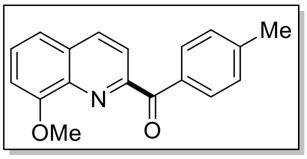
(8-Methylquinolin-2-yl)(*m*-tolyl)methanone (6c): Yellow liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2.44 (s, 3H), 2.77 (s, 3H), 7.38 (t, 1H, *J* = 7.8 Hz), 7.42 (d, 1H, *J* = 7.8 Hz), 7.52 (t, 1H, *J* = 7.8 Hz), 7.62 (d, 1H, *J* = 6.6 Hz), 7.71 (d, 1H, *J* = 8.4 Hz), 8.15 (t, 2H, *J* = 8.4 Hz), 8.20 (s, 1H), 8.28 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 18.1, 21.6, 120.6, 125.7, 127.9, 128.5, 129.15, 129.17, 130.2, 132.4, 133.7, 136.7, 137.3, 137.7, 139.0, 146.0, 153.4, 193.7; IR (KBr): 3043, 2955, 2923, 1659, 1584, 1465, 1374, 1287, 1141, 1079 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH$^+$) 262.1226; found 262.1228.



(8-Methylquinolin-2-yl)(*p*-tolyl)methanone (6d): Yellow liquid; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.47 (s, 3H), 2.80 (s, 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.54 (t, 1H, *J* = 8.0 Hz), 7.63 (d, 1H, *J* = 7.2 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 8.4 Hz), 8.28–8.31 (m, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 18.2, 22.0, 120.7, 125.7, 128.4, 128.9, 129.2, 130.2, 132.1, 134.2, 137.4, 139.0, 143.8, 146.1, 153.7, 193.2; IR (KBr): 3093, 2922, 1653, 1463, 1319, 1250, 1156, 1020 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH$^+$) 262.1226; found 262.1219.

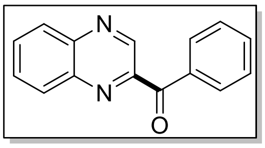


(4-Chlorophenyl)(8-methylquinolin-2-yl)methanone (6f): Yellow solid; M.p. 79–81 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.78 (s, 3H), 7.50 (d, 2H, *J* = 8.8 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.65 (t, 1H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 8.4 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 8.0 Hz), 8.35 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 18.2, 120.6, 125.8, 128.4, 128.8, 129.3, 130.4, 133.4, 135.2, 137.6, 139.0, 139.4, 146.0, 152.9, 192.3; IR (KBr): 2962, 2923, 2855, 1638, 1459, 1311, 1089 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}ClNO$ (MH$^+$) 282.0680; found 282.0685.

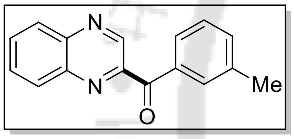


(8-Methoxyquinolin-2-yl)(*p*-tolyl)methanone (7d): Red liquid; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.43 (s, 3H), 4.05 (s, 3H), 7.10 (d, 1H, *J* = 7.2 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 7.2 Hz), 7.56 (t, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.8 Hz), 8.24–8.29

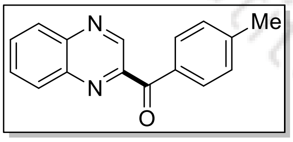
(m, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.9, 56.4, 108.6, 119.5, 121.6, 127.2, 128.9, 130.2, 132.1, 133.8, 137.0, 138.9, 144.0, 153.9, 156.5, 193.0; IR (KBr): 3066, 2928, 2838, 1655, 1606, 1465, 1325, 1260, 1131, 1040 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO_2$ (MH$^+$) 278.1176; found 278.1172.



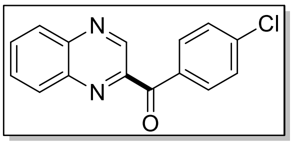
Phenyl(quinoxalin-2-yl)methanone (8a): Black solid; M.p. 100–102 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.52 (t, 2H, *J* = 7.8 Hz), 7.64 (t, 1H, *J* = 7.8 Hz), 7.84 (t, 1H, *J* = 6.6 Hz), 7.88 (t, 1H, *J* = 8.4 Hz), 8.19 (m, 2H), 8.22 (d, 2H, *J* = 7.8 Hz), 9.47 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 128.6, 129.6, 130.6, 130.9, 131.0, 131.5, 132.2, 132.4, 133.8, 143.3, 143.4, 145.5, 192.5; IR (KBr): 3062, 2925, 2853, 1659, 1597, 1322, 1234, 1127, 1014 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{10}N_2O$ (MH$^+$) 235.0866; found 235.0869.



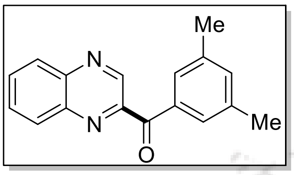
Quinoxalin-2-yl(*m*-tolyl)methanone (8c): Brown gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.44 (s, 3H), 7.43 (t, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 7.2 Hz), 7.85–7.93 (m, 2H), 8.00 (s, 2H), 8.22 (d, 2H, *J* = 8.8 Hz), 9.47 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.6, 128.5, 128.9, 129.6, 130.7, 130.9, 131.7, 132.2, 134.7, 135.8, 138.5, 140.7, 143.3, 145.5, 149.1, 192.9; IR (KBr): 2924, 2854, 1658, 1489, 1317, 1151, 1017 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ (MH$^+$) 249.1022; found 249.1028.



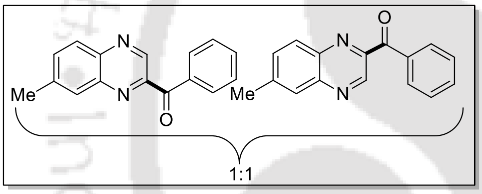
Quinoxalin-2-yl(*p*-tolyl)methanone (8d): Red solid; M.p. 97–99 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.42 (s, 3H), 7.30 (d, 2H, *J* = 7.6 Hz), 7.78–7.87 (m, 2H), 8.11 (d, 2H, *J* = 8.4 Hz), 8.16 (d, 2H, *J* = 8.4 Hz), 9.42 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 22.0, 129.3, 129.5, 130.5, 130.9, 131.5, 132.0, 133.1, 140.6, 143.2, 144.8, 145.5, 149.1, 192.0; IR (KBr): 3053, 2922, 2851, 1657, 1601, 1324, 1229, 1157, 1121 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ (MH$^+$) 249.1022; found 249.1019.



(4-Chlorophenyl)(quinoxalin-2-yl)methanone (8f): Brown solid; M.p. 85–87 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.50 (d, 2H, *J* = 8.4 Hz), 7.83–7.88 (m, 1H), 7.90 (t, 1H, *J* = 8.4 Hz), 8.17–8.23 (m, 4H), 9.49 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 129.0, 129.7, 130.7, 130.9, 131.2, 132.5, 132.9, 134.1, 140.5, 143.3, 145.5, 148.4, 191.2; IR (KBr): 2926, 2855, 1663, 1460, 1313, 1164, 1087 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_9ClN_2O$ (MH$^+$) 269.0476; found 269.0480.



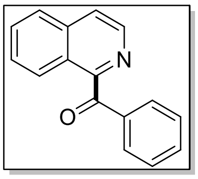
(3,5-Dimethylphenyl)(quinoxalin-2-yl)methanone (8h): Red solid; M.p. 151–152 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 2,40 (s, 6H), 7.30 (s, 1H), 7.78 (s, 2H), 7.86–7.91 (m, 2H), 8.20–8.22 (m, 2H), 9.43 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 21.5, 129.1, 129.6, 130.7, 131.0, 132.1, 135.7, 135.8, 138.3, 140.8, 143.3, 145.4, 149.4, 193.2; IR (KBr): 3063, 2920, 2859, 1659, 1601, 1327, 1214, 1149, 1031 cm^{-1} HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH$^+$) 263.1179; found 263.1184.

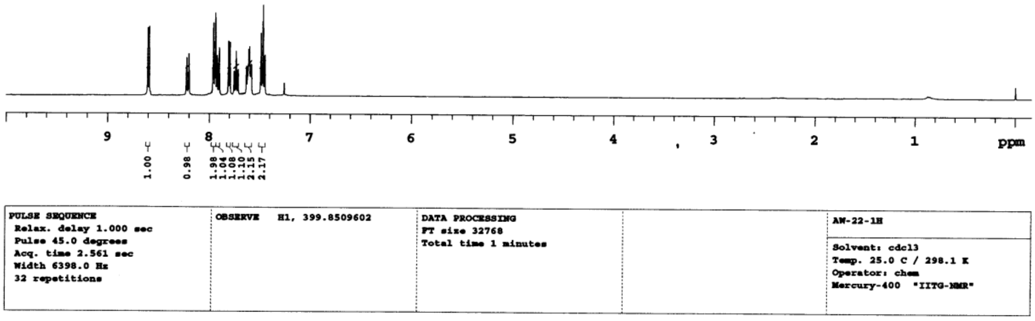


(6-Methylquinoxalin-2-yl)(*p*-tolyl)methanone and (7-Methylquinoxalin-2-yl)(*p*-tolyl)methanone (9d): Red semisolid; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.44 (s, 3H), 2.62 (s, 3H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.65–7.71 (m, 1H), 7.94 (s, 1H), 8.06 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 2H, *J* = 8.0 Hz), 9.39 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm) 22.0, 22.3, 22.9, 128.4, 129.1, 129.3, 129.4, 130.2, 131.6, 133.31, 133.34, 134.5, 139.2, 140.8, 141.7, 141.9, 143.2, 143.4, 144.7, 144.75, 144.8, 145.6, 148.4, 149.2, 192.25, 192.31; IR (KBr): 2953, 2924, 2854, 1656, 1497, 1322, 1276, 1167, 1017 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH$^+$) 263.1179; found 263.1174.

IIIB.7. Spectra

Isoquinoline-1-yl(phenyl)methanone (1a): ^{1}HNMR (400 MHz, $CDCl_3$)





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PULSE SEQUENCE
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 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions

OBSERVE   H1, 399.8509602

DATA PROCESSING
FT size 32768
Total time 1 minutes

AW-22-1H

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
```
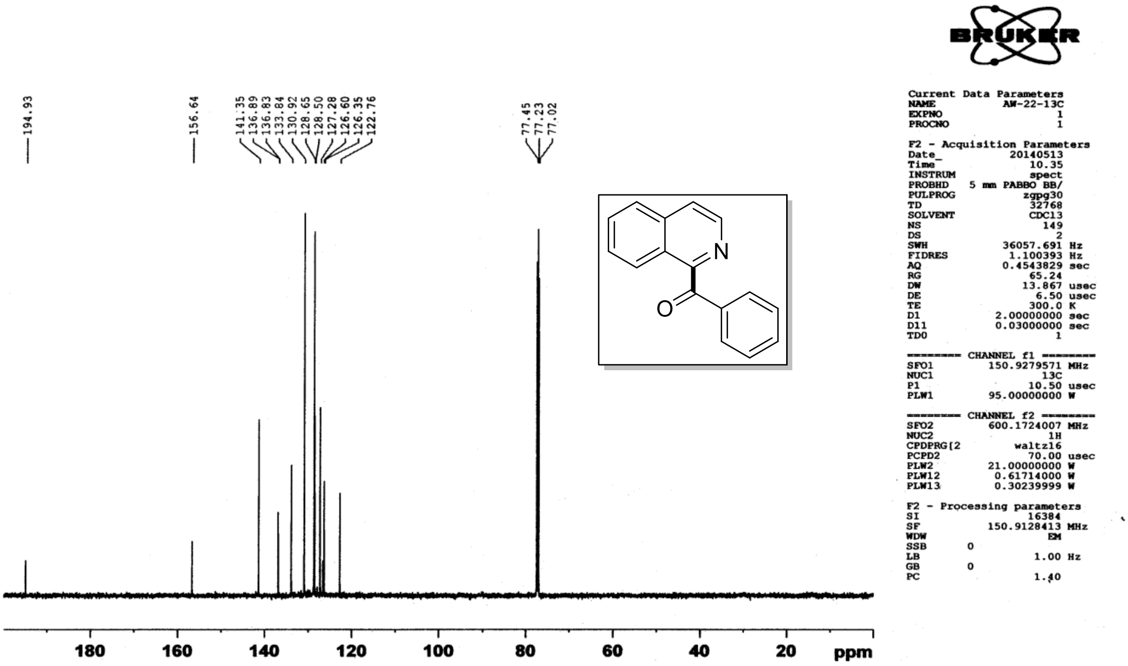

Isoquinoline-1-yl(phenyl)methanone (1a): ^{13}CNMR (150 MHz, $CDCl_3$)



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PROCNO                    1

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INSTRUM               spect
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PULPROG             zgpg30
TD                    32768
SOLVENT               CDC13
NS                      149
DS                        2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                    65.24
DW                   13.867 usec
DE                     6.50 usec
TE                    300.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                    13C
P1                    10.50 usec
PLW1           95.00000000 W

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

F2 - Processing parameters
SI                    16384
SF             150.9128413 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
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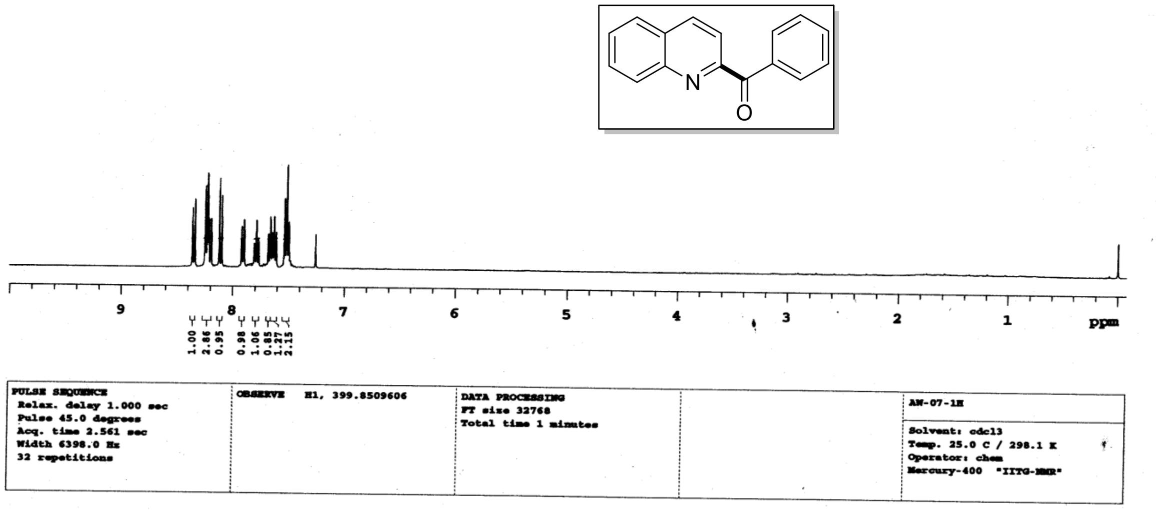
Phenyl(quinolin-2-yl)methanone (5a): ^{1}HNMR (400 MHz, $CDCl_3$)



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PULSE SEQUENCE
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 Pulse 45.0 degrees
 Acq. time 2.561 sec
 Width 6398.0 Hz
 32 repetitions

OBSERVE   H1, 399.8509606

DATA PROCESSING
FT size 32768
Total time 1 minutes

AW-07-1H

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400  "IITG-NMR"
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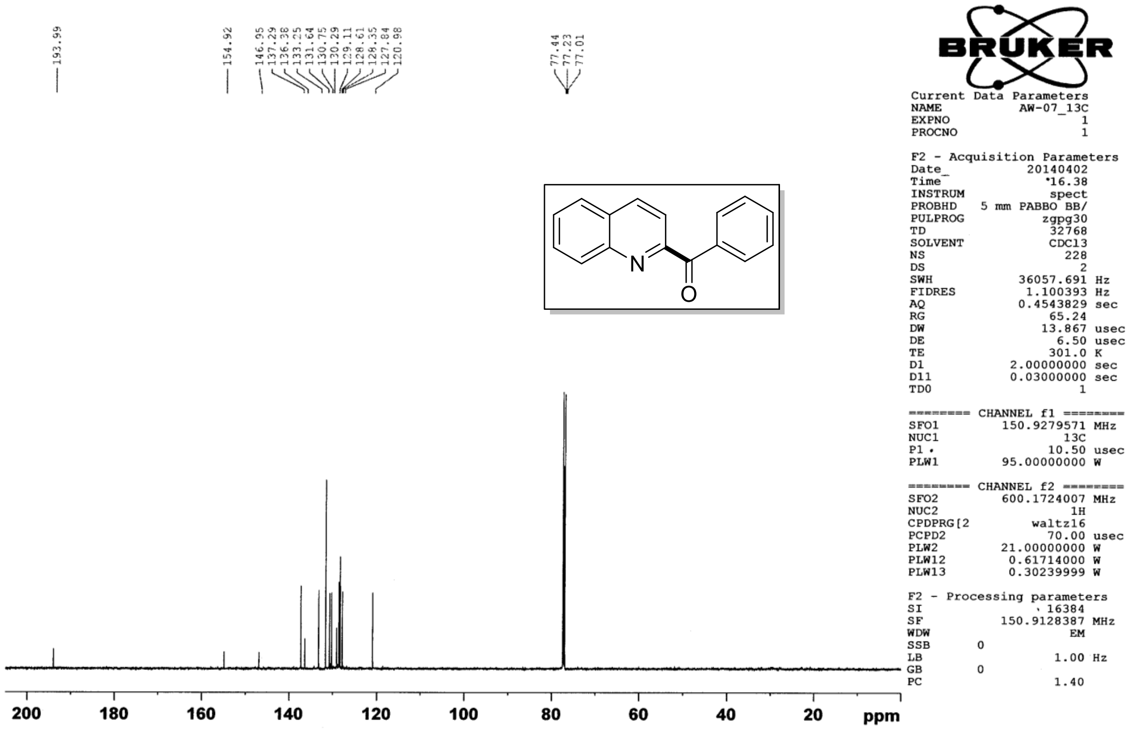
Phenyl(quinolin-2-yl)methanone (5a): ^{13}CNMR (150 MHz, $CDCl_3$)



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EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
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Time                 •16.38
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG            zgpg30
TD                   32768
SOLVENT              CDC13
NS                     228
DS                       2
SWH              36057.691 Hz
FIDRES            1.100393 Hz
AQ               0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   301.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           150.9279571 MHz
NUC1                   13C
P1 •                 10.50 usec
PLW1           95.00000000 W

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

F2 - Processing parameters
SI                   16384
SF             150.9128387 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
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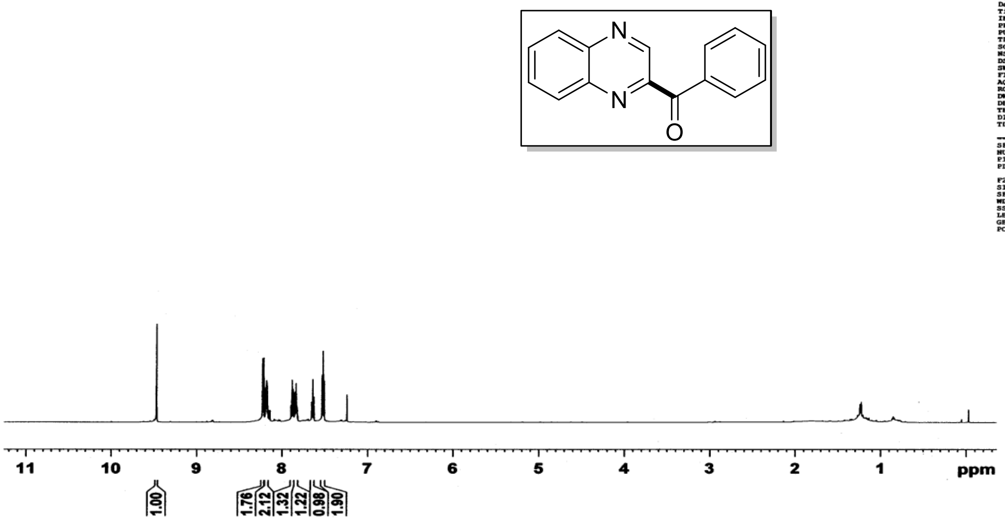
Phenyl(quinoxalin-2-yl)methanone (8a): ^{1}HNMR (600 MHz, $CDCl_3$)



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PROCNO                   1

F2 - Acquisition Parameters
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PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                   65.24
DW                  41.600 usec
DE                    6.50 usec
TE                   301.7 K
D1            1.00000000 sec
TD0                      1

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

F2 - Processing parameters
SI                   16384
SF           600.1700268 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.00
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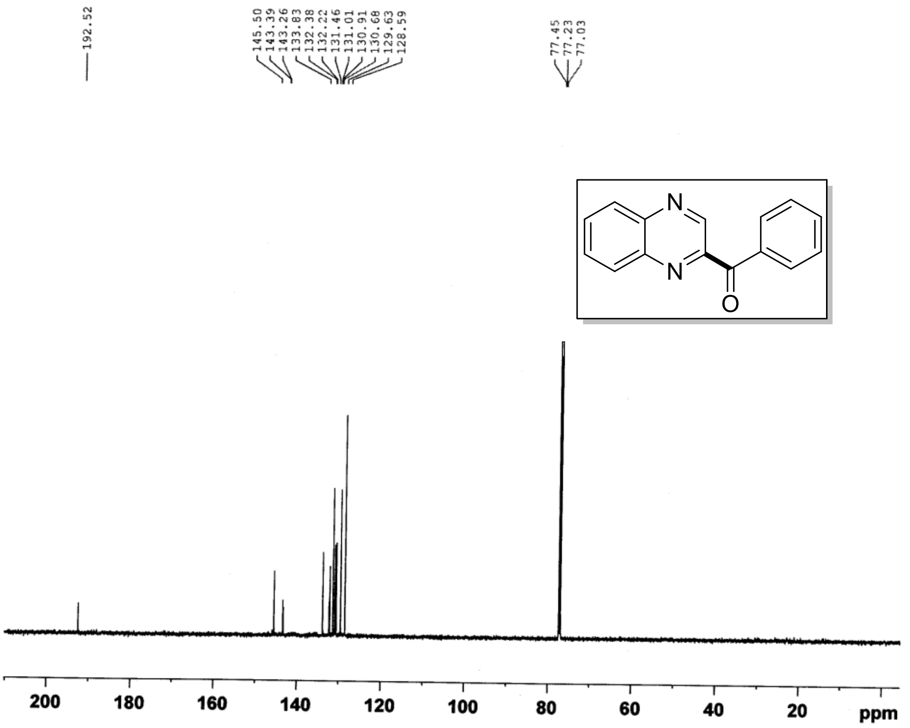
Phenyl(quinoxalin-2-yl)methanone (8a): ^{13}CNMR (150 MHz, $CDCl_3$)



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Current Data Parameters
NAME              AW-17-13C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140425
Time                  9.22
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG             zgpg30
TD                   32768
SOLVENT              CDCl3
NS                     249
DS                       2
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.4543829 sec
RG                   65.24
DW                  13.867 usec
DE                    6.50 usec
TE                   302.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                   13C
P1                   10.50 usec
PLW1         95.00000000 W

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

F2 - Processing parameters
SI                   16384
SF           150.9128349 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
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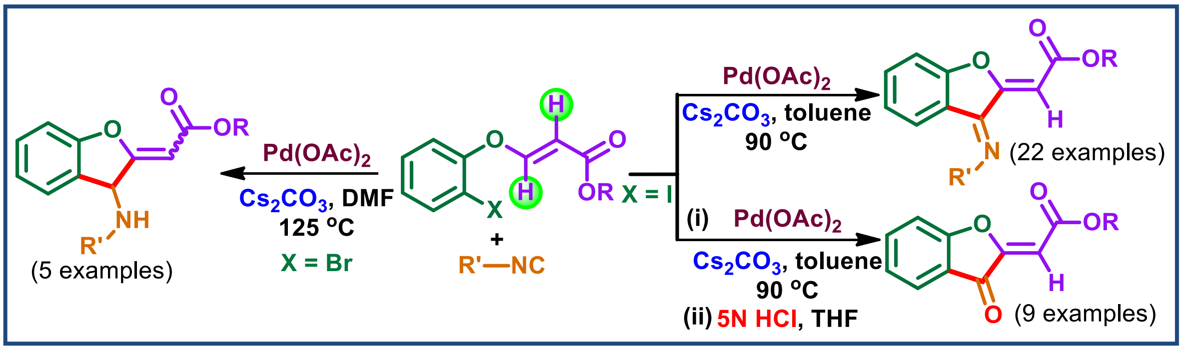
Chapter IV

Cascade Synthesis of Dihydrobenzofurans and Aurones via Palladium-Catalyzed Isocyanides Insertion into 2-Halophenoxy Acrylates



Abstract: *A palladium-catalyzed isocyanides insertion into 2-halophenoxy acrylates leading to an unparalleled synthesis of dihydrobenzofurans (DHBs) having two exocyclic double bonds have been achieved. An acid hydrolysis of the exocyclic imine bond in DHBs produces various aurone esters. The iodo analogue gives dihydrobenzofurans (DHBs) having an exocyclic imine, while the bromo analogue gives product in which the imine bond is in the reduced state. The exact role of water serving as a reducing agent is not clear at this moment.*

CHAPTER IV

IV. Cascade Synthesis of Dihydrobenzofurans and Aurones via Palladium-Catalyzed Isocyanides Insertion into 2-Halophenoxy Acrylates

IV.1. Introduction

Dihydrobenzofurans (DHBs) are important building blocks in organic synthesis and a key structural motif of several natural products possessing various biological activities.[1] Natural products possessing DHB units are reported to show activity against cancer,[1a] tuberculosis,[1b] malaria,[1c] cataracts[1d] as well as selected activity against HIF-1,[1e] glucosidase[1f] and aldose reductase.[1e] Similarly, aurones, which are isomers of flavones, exhibit a range of biological activities[2a] such as antioxidant,[2b] antimicrobial,[2c] insect anti-feedant[2d] and tyrosinase inhibitor.[2d] Few 2,3-disubstituted dihydrobenzofurans and aurones possessing important biological activities are shown in Figure IV.1.1.

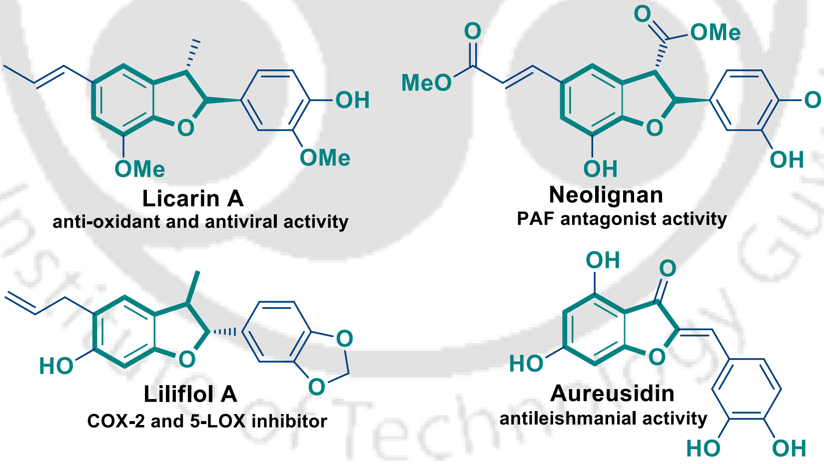


Figure IV.1.1. *Synthetic dihydrobenzofurans and aurones with useful biological activity*

Organic isocyanides have the dual ability to serve both as nucleophile as well as electrophile, which act as powerful and versatile C1 building blocks in many organic reactions.[3] Isocyanides are complementary (isoelectronic) to both carbon monoxide and carbenes, but due the toxic nature of CO and difficulties in the preparation of carbenes, they have been replaced by isocyanides in many organic reactions. Taking advantage of their reactivity they have been applied to a variety of multi-component[4] and transition metal-catalyzed insertion reactions.[5] Recently, Pd-catalyzed cascade reactions have emerged as an attractive tool, as it avoids the requirement of decorated precursors and facilitate a concise synthesis of complex organic frameworks.[6] Further, palladium-catalyzed migratory insertion of isocyanides are advantageous for the preparation of carbo- and heterocyclic products.[7,8]

IV.2. Strategies for the Synthesis of Dihydrobenzofurans and Aurones

As a consequence of the diverse biological activities displayed by these compounds, synthetic chemists have developed many effective methods for accessing the dihydrobenzofurans and aurones skeleton. While numbers of strategies are available for the synthesis of aurones, in contrast synthesis of 2,3-disubstituted dihydrobenzofurans is comparatively fewer in numbers. Nevertheless, few effective strategies are available for the synthesis of DHBs.[2b,9,10,11] The different synthetic approaches leading to DHBs, focusing largely on recent reports are classified according to the method by which the saturated oxygen ring is constructed by Sheppard[10] in his review shown in Figure IV.2.1.

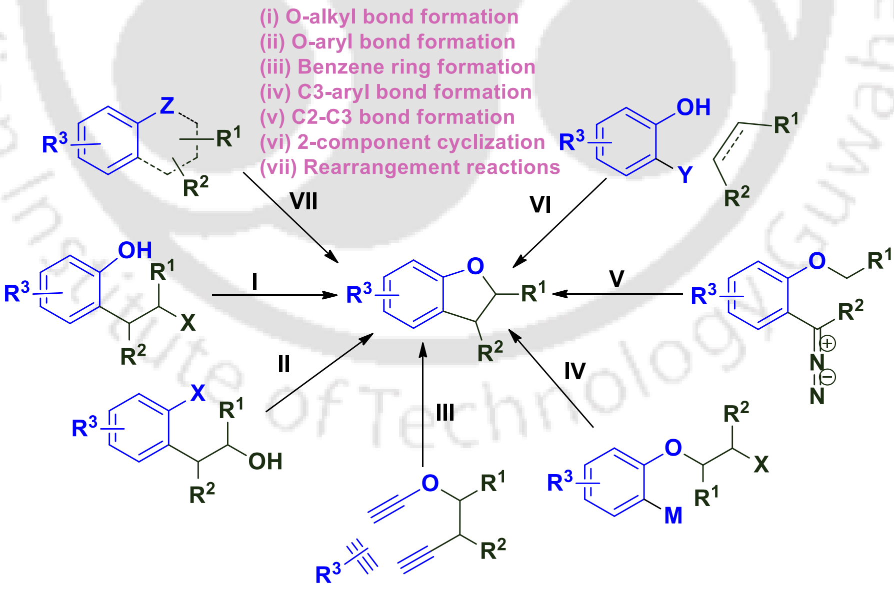
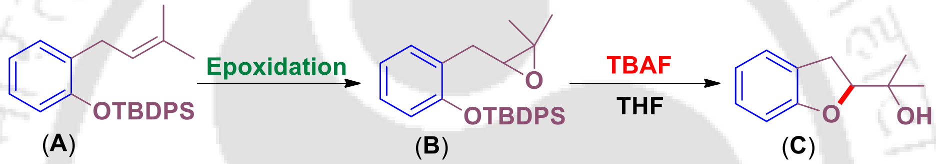


__Figure IV.2.1.__ Various routes to DHB synthesis

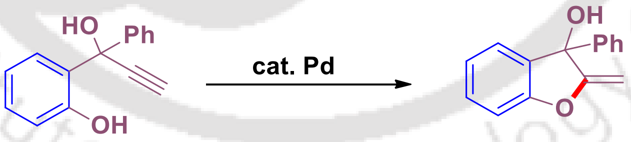
The most obvious strategies involved in DHB synthesis are; classical phenol alkylation approach, *O*-aryl via transition metal-catalyzed cross coupling, construction of C-aryl bond and via transition metal-mediated carbene C–H insertion processes of diazo and triazole compounds. Despite the large number of literature reports for the synthesis of DHB, only the most common approaches that are frequently used are described here.

The intramolecular alkylation of phenol is one of the most frequently used methods for the construction of DHBs, since many natural products bearing hydroxyalkyl group adhered to ring system at C2. Particularly, cyclization through ring opening of an epoxide is an useful approach and has been explored extensively. For example, the epoxidation of compound (**A**) with appropriate reagent give epoxide intermediate (**B**) which provides the corresponding DHB derivatives (**C**) in good yield after deprotection of the phenol with TBAF (Scheme IV.2.1).[12a] Similarly, one of the very common strategy for the construction of DHB ring is the electrophile-mediated cyclization of *o*-allylphenols.[12b-f] Activation of *o*-allylphenols with suitable electrophiles can provide access to DHBs containing halogen, thioether or simple alkyl group.



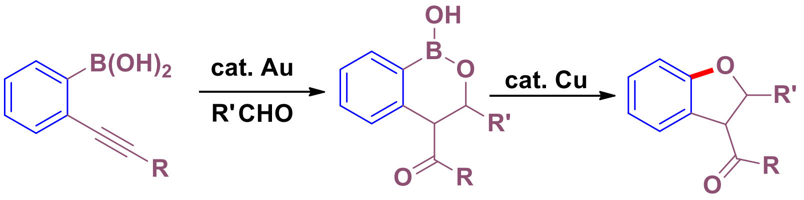
Scheme IV.2.1. *Synthesis of DHB using Shi epoxidation*

In a similar way, Pd-catalyzed cyclization of propargylic phenols give access to DHB containing exocyclic alkene which can be further exploited to introduce different functionality (Scheme IV.2.2).[12g]



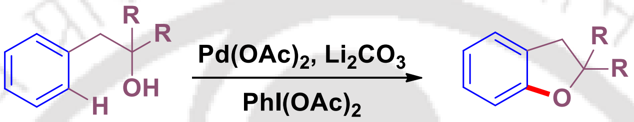
Scheme IV.2.2. *Cyclization of phenol with activated C≡C bond*

Use of transition metal-catalyzed coupling reactions for the synthesis of DHB derivatives were employed several years ago,[12h,i] however only very few recent developments in this area has been take place. An intramolecular Chan-Lam coupling has been reported for the synthesis of 2,3-disubstituted DHBs in two step reaction catalyzed by gold and copper (Scheme IV.2.3).[12j]



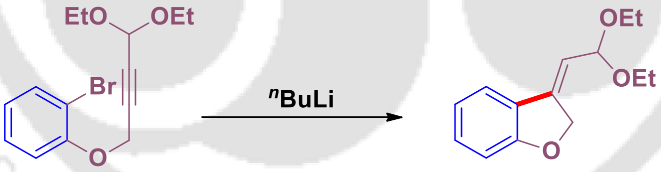
Scheme IV.2.3. *Synthesis of DHBs via an intramolecular Chan-Lam coupling*

Synthesis of DHBs through C–H bond functionalization was first developed by Yu *et al*. through palladium-catalyzed direct cyclization of homo-benzylic alcohols (Scheme IV.2.4).[12k] In this process Li_2CO_3 was used as base and $PhI(OAc)_2$ as an external oxidant.



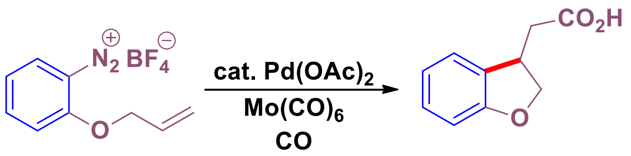
Scheme IV.2.4. *Synthesis of DHBs via C–H activation strategy*

The formation of aryl-carbon bond has been used for the synthesis of a number of DHB systems. For example, bromoarylalkynyls undergo selective carbolithiation to afford DHB skeleton containing an exocyclic double bond upon treatment with *n*-butyl lithium (Scheme IV.2.5).[12l]



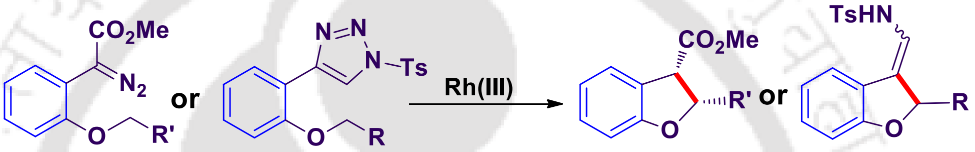
Scheme IV.2.5. *An intramolecular carbolithiation*

One of the straightforward approaches for the construction of the aryl–C3 bond is to use of Heck reaction to cyclize allylic ether. As an example, a palladium-catalyzed carbonylative Heck cyclization of aryldiazonium salts with the pedant alkenes furnishes DHB having a carboxylic acid group at the C3 side chain (Scheme IV.2.6).[12m] Similarly, using aryliodides and arylbromides a series of palladium-catalyzed tandem cyclization/coupling reactions were investigated.[12n]



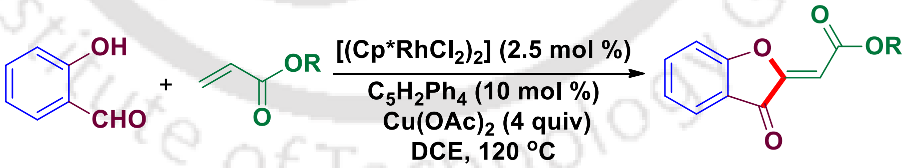
Scheme IV.2.6. *Synthesis of DHB via Heck reaction*

Interestingly, one of the common approaches for the synthesis of DHB involves the formation of alkyl C2–C3 bond. The widely accepted method is the carbene insertion into C–H bond developed by Davies. These reactions are highly stereoselective and provides wide variety of 2,3-disubstitute DHBs. A number of carbene insertions into C–H bond have been developed by various groups using Rh-catalyst (Scheme IV.2.7).[11]



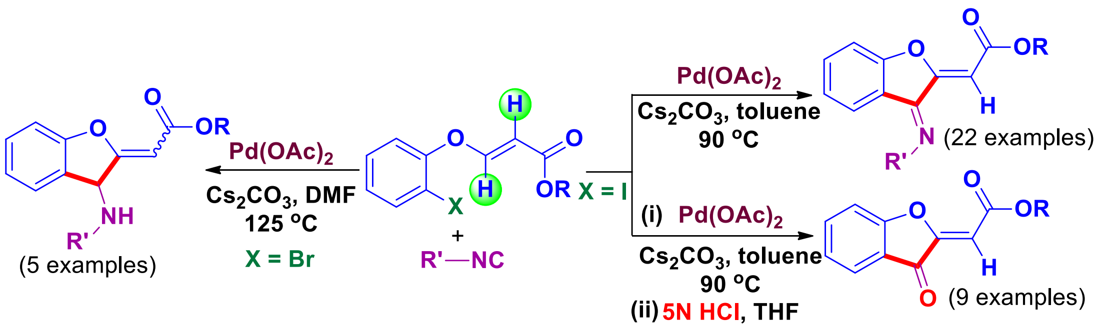
Scheme IV.2.7. *Rh-catalyzed carbene insertion reaction*

Similar to DHBs, aurones also shows immense biological activity and are present in a variety of natural products. There are several reports available for the synthesis of aurones, however aurones having an exocyclic double bond and an ester functionality was reported by Glörius and co-worker via a Rh-catalyzed dehydrogenative Heck reaction with aldehyde and acrylate in the presence of Cu(OAc)$_2$ in DCE (Scheme IV.2.8).[15]



Scheme IV.2.8. *Rh-catalyzed dehydrogenative Heck reaction*

Therefore, exploration of newer, efficient and elegant methods for the DHB synthesis is most desirable. To the best of knowledge a cascade synthesis of ethyl 2-(3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate using isocyanides as C1 source is unprecedented and is described here (Scheme IV.2.9).



Scheme IV.2.9. *Pd-catalyzed synthesis of dihydrobenzofurans and aurones*

IV.3. Present Work

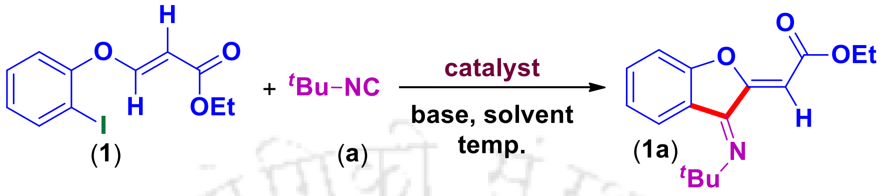
Taking cues from the reactivity of isocyanides and the ability of palladium in triggering cascade and multi-component reactions, we surmise an isocyanide insertion into 2-iodophenoxy acrylate. This may lead to the synthesis of a dihydrobenzofuran (Scheme IV.2.9) via an oxidative addition of Pd across C–I bond, a migratory isocyanide insertion followed by an intra-molecular Heck type coupling with the sp^2 C–H bond adjacent to the oxygen of phenoxy acrylate.

Optimization of Reaction Conditions: To demonstrate our above hypothesis, an initial investigation was carried out by reacting ethyl 2-iodophenoxy acrylate (**1**) and *tert*-butyl isocyanide (**a**) in the presence of $Pd(OAc)_2$ (10 mol %) and K_2CO_3 (2 equiv) in toluene at 80 ^oC under N_2 atmosphere. As anticipated, a dihydrobenzofuran (DHB), ethyl 2-(3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (**1a**) was isolated in 41% yield (Table IV.3.1, entry 1) after 12 h. It was appealing to note that only one isomer of the product (**1a**) was obtained, in which the imine double bond exists in *E*-configuration, while the exocyclic acrylate C=C bond was found to have a *Z*-configuration as confirmed from the NOE experiment (for description see section IV.4.6). Literature delineate few reports for the synthesis of dihydrobenzofuran skeleton containing exocyclic double bonds at the C3 position.[13]

Inspired by the formation of this unusual heterocyclic skeleton we sought to further improve the product yield by varying different reaction parameters. The use of other non-polar solvents such as mesitylene (34%), chlorobenzene (31%), 1,2-dichloroethane (DCE) (37%) (Table IV.3.1, entries 2–4) were slightly less effective compared to that of toluene (41%). Rapid disappearance (within 2 h) of the starting material (**1**) was observed when polar aprotic solvents such as DMF and DMSO (Table IV.3.1, entry 5 and 6) were used.

However the product (**1a**) so formed decomposed to a multitude of other products both during the reaction as well as work up process giving respectively 26% and 19% of isolated yields.

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



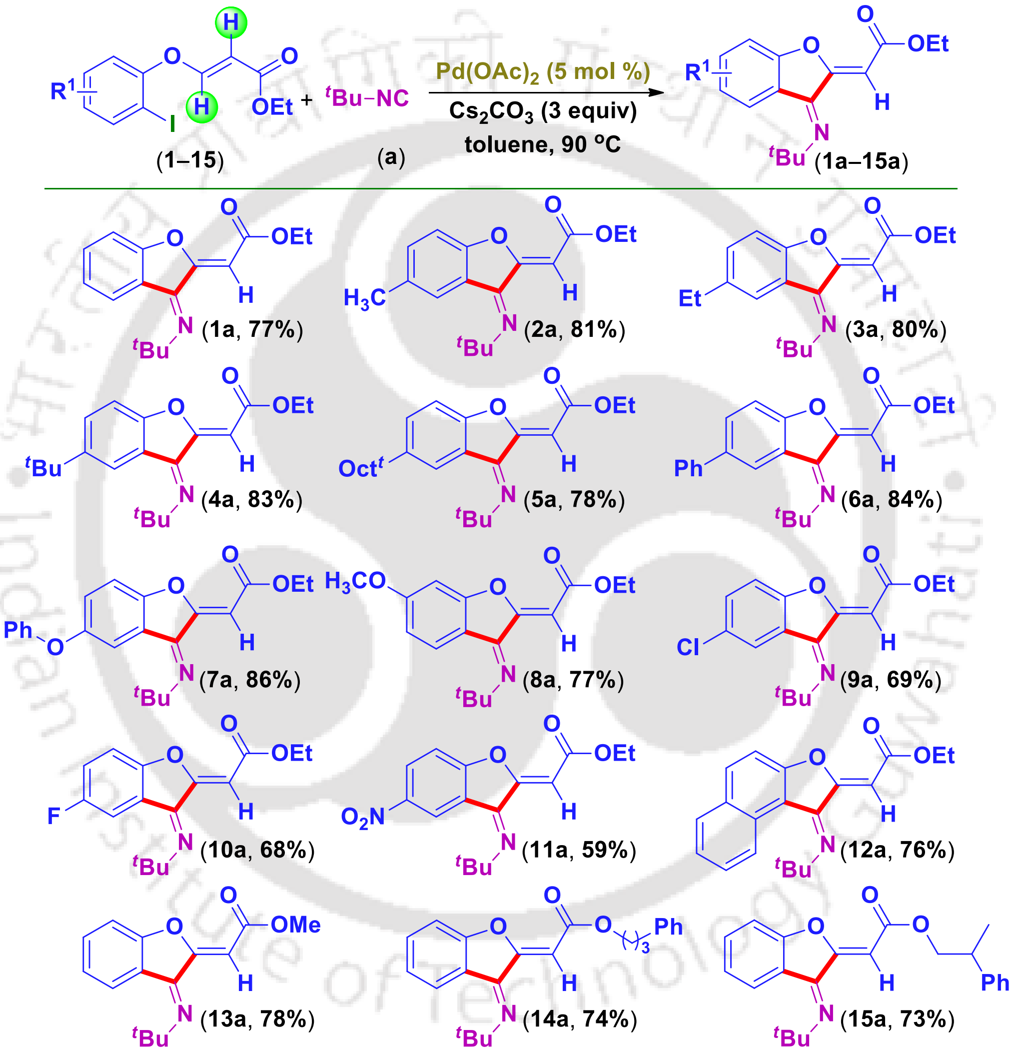
Entry	Catalyst (mol %)	Base (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	Toluene	80	41
2	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	Mesitylene	80	34
3	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	Chlorobenzene	80	31
4	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	DCE	80	37
5[c]	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	DMF	80	26
6[c]	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	DMSO	80	19
7	$PdCl_2$ (10)	K_2CO_3 (2.0)	Toluene	80	36
8	$Pd(PPh_3)_2Cl_2$ (10)	K_2CO_3 (2.0)	Toluene	80	39
9	$PdBr_2$ (10)	K_2CO_3 (2.0)	Toluene	80	25
10	$Pd(TFA)_2$ (10)	K_2CO_3 (2.0)	Toluene	80	19
11	$Pd(CH_3CN)_2Cl_2$ (10)	K_2CO_3 (2.0)	Toluene	80	31
12	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	Toluene	90	52
13	$Pd(OAc)_2$ (10)	K_2CO_3 (2.0)	Toluene	100	43
14	$Pd(OAc)_2$ (10)	Cs_2CO_3 (2.0)	Toluene	90	69
15	$Pd(OAc)_2$ (10)	Na_2CO_3 (2.0)	Toluene	90	47
16	$Pd(OAc)_2$ (10)	KOAc (2.0)	Toluene	90	39
17	$Pd(OAc)_2$ (10)	Et_3N	Toluene	90	trace
18	$Pd(OAc)_2$ (10)	Cs_2CO_3 (3.0)	Toluene	90	78
19	**$Pd(OAc)_2$ (5)**	**Cs_2CO_3 (3.0)**	**Toluene**	**90**	**77**
20	-	Cs_2CO_3 (3.0)	Toluene	90	00
21	$Pd(OAc)_2$ (5)	-	Toluene	90	00
22[d]	$Pd(OAc)_2$ (5)	Cs_2CO_3 (3.0)	Toluene	90	64

[a]Reaction condition: **1** (0.25 mmol), **a** (0.375 mmol), catalyst, solvent (3 mL), 12 h under N_2. [b]Isolated pure product. [c]2 h. [d]**a** (0.25 mmol).

Keeping all other parameters constant and using toluene as the solvent the use of other Pd salts such as $PdCl_2$ (36%) and $Pd(PPh_3)_2Cl_2$ (39%) (Table IV.3.1, entry 7 and 8) gave comparable yields whereas $PdBr_2$ (25%), $Pd(TFA)_2$ (19%) and $Pd(CH_3CN)_2Cl_2$ (31%) (Table IV.3.1, entries 9–11) were found to be less effective. Notably, when the reaction was carried out at 90 °C, the yield of the desired product improved upto 52% (Table IV.3.1, entry 12). A further increase in the reaction temperature (100 °C) was found to be detrimental, giving the desired product in 43% yield (Table IV.3.1, entry 13) along with the formation of benzofuran-3-carboxylate (< 7%) as the side product in which no isocyanide insertion was observed. Replacement of base K_2CO_3 with Cs_2CO_3 improved the product yield upto 69% (Table IV.3.1, entry 14). However, other inorganic bases such as Na_2CO_3 (47%) and KOAc (39%) (Table IV.3.1, entry 15 and 16), gave the expected product in slightly lower yields as compared to K_2CO_3, while the use of organic base Et_3N was completely unproductive (Table IV.3.1, entry 17). Fascinatingly, an increase in the amount of Cs_2CO_3 from 2 to 3 equivalents leads to the formation of (**1a**) in 78% yield (Table IV.3.1, entry 18). Interestingly, a 50% reduction in the catalyst loading *i.e.* (5 mol %) was found to be equally effective affording the anticipated product (**1a**) in 77% yield (Table IV.3.1, entry 19). However, a further lowering (< 5 mol %) of the catalyst loading was found to be less efficient both in terms of yield and reaction time. No reaction was witnessed either in the absence of Pd catalyst (Table IV.3.1, entry 20) or base (Table IV.3.1, entry 21). Unfortunately, a quantitative use of isocyanide diminished the product yield (Table IV.3.1, entry 22). This observation is consistent with the literature report where the presence of an excess isocyanide is reported to deactivate the Pd catalyst due to the formation of Pd-cluster.[14] To maintain the catalytic efficiency and prevent the cluster formation the requisite quantity of isocyanide was added in two equal lots, the first at the beginning and the second after 1 h. Thus, the best condition for the efficient transformation of (**1**) to (**1a**) is the use of $Pd(OAc)_2$ (5 mol %), isocyanide (**a**) (2 x 0.75 equiv), Cs_2CO_3 (3 equiv) in toluene (3 mL) at 90 °C under N_2.

Substrate Scopes for Dihydrobenzofurans: After arriving at the optimized reaction condition (Table IV.3.1, entry 19), we then investigate the scope of this reaction with other substrates (Scheme IV.3.1 and IV.3.2). As reveals from Scheme IV.3.1, reaction of *tert*-butyl isocyanide (**a**) with 2-iodophenoxy acrylates (**1–15**) having various substituents at the phenyl ring reacted smoothly giving their expected dihydrobenzofuran (DHB) derivatives. The reaction proceeded successfully with a series of electron rich substituents such as *p*-CH_3 (**2**), *p*-^{t}Bu (**4**), *p*-^{t}Oct (**5**), *p*-Ph (**6**), *p*-OPh (**7**) and *m*-OCH_3 (**8**) present on the aryl ring of ethyl 2-iodophenoxy acrylate affording their desired products (**2a–8a**) in moderate to good yields (77%–86%). However, presence of electron-withdrawing substituents such as *p*-Cl (**9**), *p*-F (**10**) and *p*-NO_2 (**11**) in the aryl ring of ethyl 2-iodophenoxy acrylate were found to give lower yields (ranging between 59%–69%) of their DHB products (**9a–11a**). The reaction also worked effectively with substrate 1-iodonaphthyl acrylate (**12**) giving its product (**12a**) in 76% yield. Besides ethyl esters, other esters containing substrates such as methyl (**13**), propyl benzene (**14**) and 2-phenylpropyl (**15**) underwent isocyanide insertion giving their corresponding dihydrobenzofuran (DHB) derivatives (**13a**, 82%), (**14a**, 79%) and (**15a**, 78%) respectively.

Scheme IV.3.1. *Synthesis of dihydrobenzofuran derivatives*^{a,b}

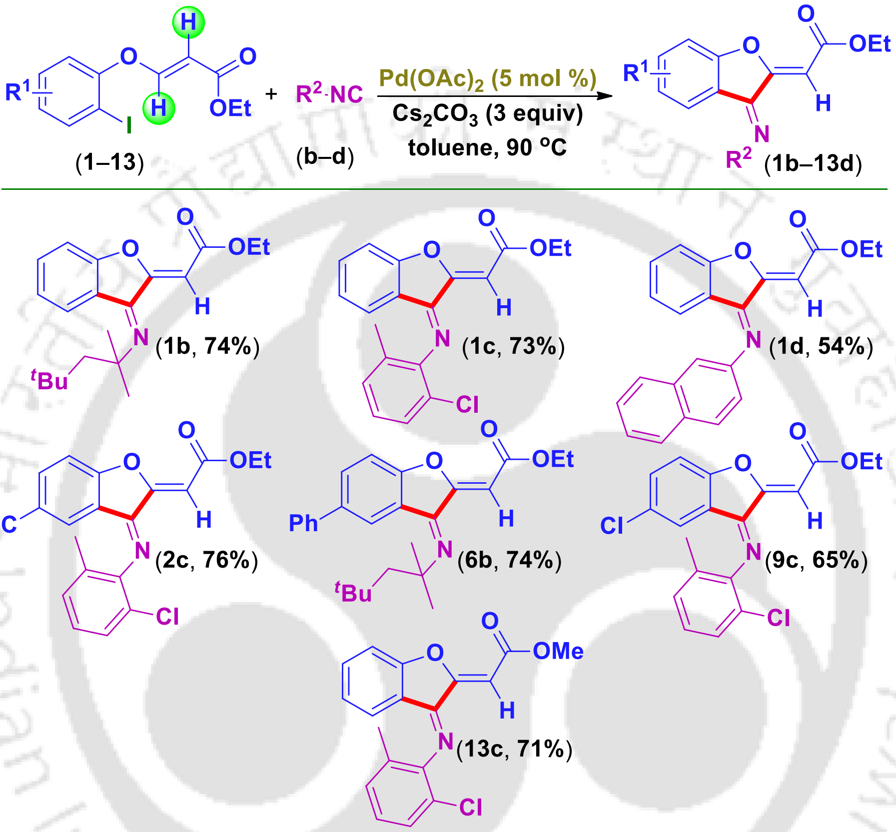


^{a}Reaction condition: (**1–15**) (0.25 mmol), (**a**) (0.375 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (0.75 mmol), toluene (3 mL), at 90 °C for 12 h under N_2. ^{b}Isolated pure products.

Besides *tert*-butyl isocyanide, other isocyanides such as *tert*-octylisocyanide (**b**), 2-chloro-6-methylphenyl isocyanide (**c**) and 2-naphthyl isocyanide (**d**) were all successfully inserted into 2-iodophenoxy acrylates leading to the construction of various dihydrobenzofurans (Scheme IV.3.2). The reactivity of isocyanides (**b**) and (**c**) are similar to that of *tert*-butyl isocyanide (**a**), and both furnished their respective products (**1b**, 74%)

and (**1c**, 73%) in modest yields, while 2-naphthyl isocyanide (**d**) provided lesser yield (54%) of the product (**1d**). Further, the efficient synthesis of products (**2c**, 76%), (**6b**, 74%), (**9c**, 65%) and (**13c**, 71%) demonstrate the versatility of the present protocol (Scheme IV.3.2).

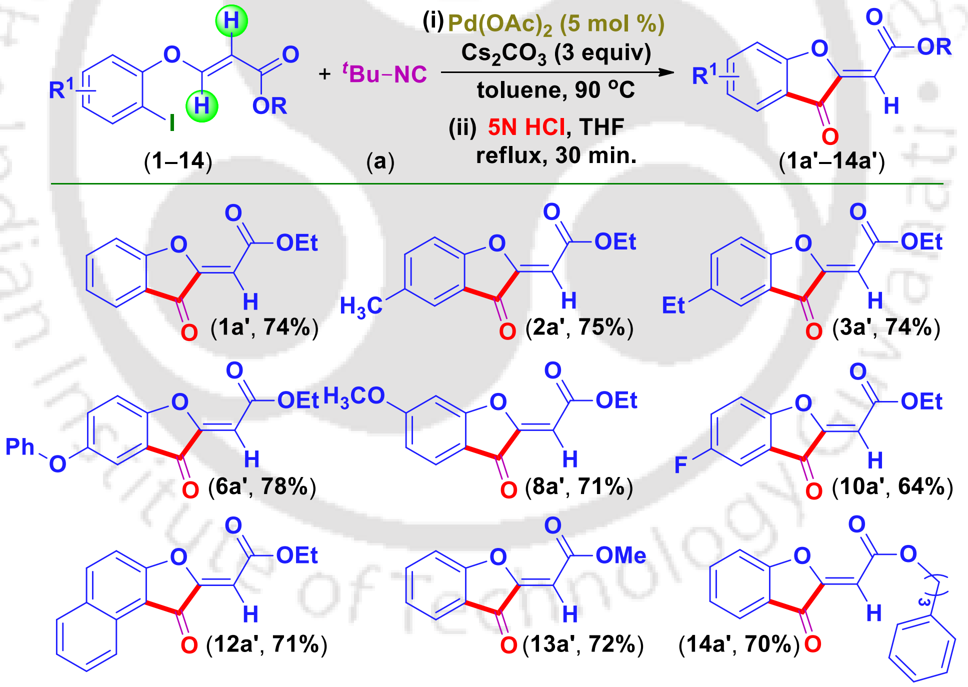
Scheme IV.3.2. *Reaction with other isocyanides*[a,b]



[a]Reaction condition: (**1–13**) (0.25 mmol), (**a**) (0.375 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (0.75 mmol), toluene (3 mL), at 90 °C for 12 h under N_2. [b]Isolated pure products.

Aurones represent another important class of heterocycle having broad biological applications. There is only a single precedence in the literature for the synthesis of aurones having an exocyclic double bond at the C2 position, simultaneously bearing an ester functionality.[15] We assumed that, if the exocyclic imine bond in DHB products as in (Scheme IV.3.1 and IV.3.2) could be selectively hydrolyzed to a keto functionality it would lead to the formation of aurone esters. For this purpose, first a one pot acid hydrolysis was attempted by adding 0.5 mL of 5N HCl to the reaction mixture after the formation of intermediate DHB (**1a**). Formations of a multitude of products along with the hydrolysis of imine leading to a keto group were observed. The formation of side products might be due to the presence of Pd-catalyst and excess of base in the reaction medium. So, it was decided to get rid of the base and catalyst from the reaction mixture. The crude reaction mixture was filtered through a celite pad and solvent was removed under vacuum. To this crude product 0.5 mL of 5N HCl in THF (3 mL) was added and the mixture was heated at 70 °C. After 0.5 h of heating complete hydrolysis of the exocyclic imine bond was observed giving the expected aurone in 74% yield. This method was subsequently applied to other *in situ* generated DHB derivatives leading to the synthesis of various aurones as shown in Scheme IV.3.3. The applicability of the reaction was further tested by synthesizing various aurone esters having substituents such as *p*-CH_3 (**2a′**), *p*-Et (**3a′**), *p*-Ph (**6a′**), *m*-OCH_3 (**8a′**) and *p*-F (**10a′**) giving products in 64%–78% overall yields (Scheme IV.3.3). This methodology was further elaborated by the synthesis of aurones (**12a′**), (**13a′**) and (**14a′**) in 71%, 72% and 70% yields respectively, via the hydrolysis of their *in situ* generated DHB derivatives.

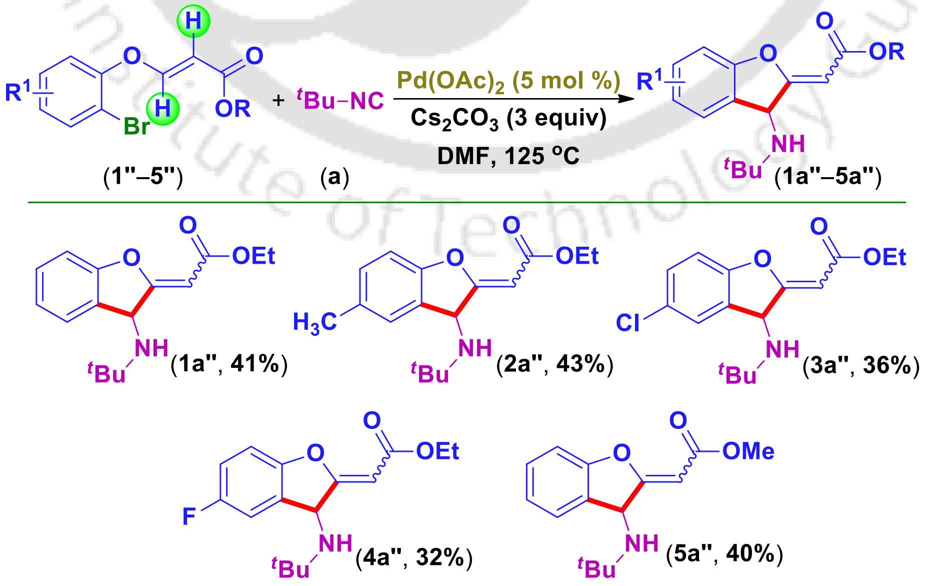
Scheme IV.3.3. *Sequential synthesis of aurone esters*^{a,b}



^{a}Reaction condition: **1–14** (0.25 mmol), **a** (0.375 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (0.75 mmol), toluene (3 mL), at 90 °C for 12 h then filter and solvent evaporated followed by addition of 5N HCl (0.5 mL), THF (3 mL) and reflux for 30 min. ^{b}Isolated pure products.

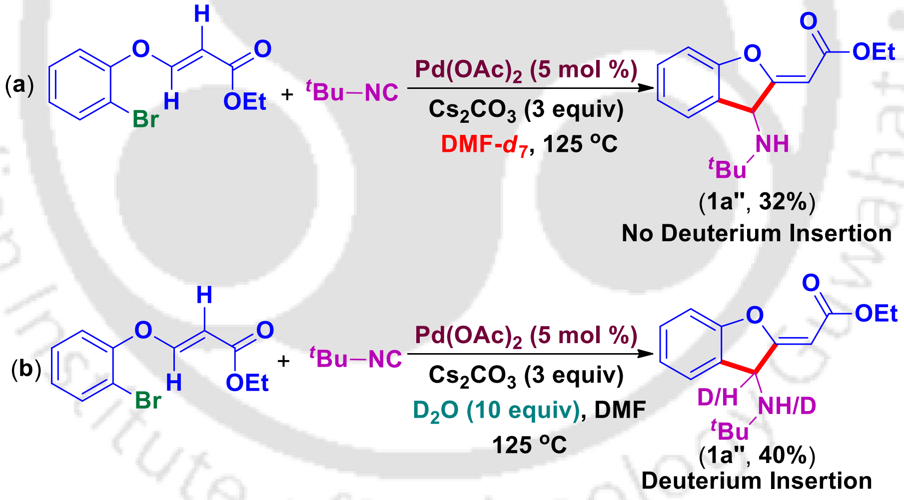
In most of the reported Pd-catalyzed migratory isocyanides insertion both aryl C–I and C–Br bond shows similar reactivity. Therefore, we were curious to see whether C–Br bond in analogous substrate such as ethyl 2-bromophenoxy acrylate (**1″**) would undergo similar isocyanide insertion giving its corresponding DHB derivative? When (**1″**) was subjected to the above optimized reaction condition (Table IV.3.1, entry 19), the starting material remains unchanged. The starting material left unreacted even when the reaction was performed at 110 °C. A brief literature survey reveals that many isocyanides insertion into C–Br bond proceeds well at higher temperature in polar aprotic solvent such as DMF. Therefore, a reaction was performed in DMF at 125 °C under otherwise identical reaction condition (Scheme IV.3.4). Interestingly, in this reaction also an analogous DHB derivative, 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (**1a″**) was obtained. But, surprisingly the exocyclic imine double bond was found to be in its reduced form giving a secondary amine (as confirmed by the appearance of two new peaks at 2.53 and 3.05 ppm in its ^{1}HNMR and a peak at 40.0 ppm in the ^{13}CNMR) as opposed to (**1a**) obtained from (**1**). Now a query arises whether the exocyclic imine bond formed initially, as was the case with (**1**) might *in situ* get reduced to an amine (**1a″**)? If so, what are the reducing agent responsible and the origin of the hydrogen in the medium? This was not the only exception where the reduced amine containing DHB derivative was obtained, other ethyl 2-bromophenoxy acrylates bearing *p*-CH_3 (**2″**), *p*-Cl (**3″**), *p*-F (**4″**) gave their reduced DHB derivatives (**2a″**, 43%), (**3a″**, 36%), (**4a″**, 32%) respectively (Scheme IV.3.4). Similarly, methyl 2-bromophenoxy acrylates (**5″**) also yielded its reduced DHB product (**5a″**) in 40% yield (Scheme IV.3.4).

Scheme IV.3.4. *Reaction with bromo substrates*^{a,b}



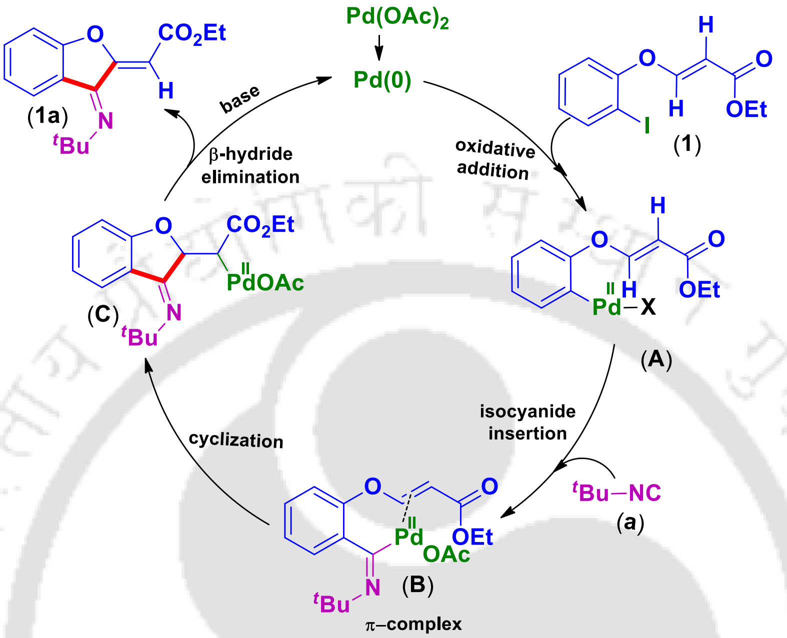
^{a}Reaction condition: **1″–5″** (0.25 mmol), **a** (0.375 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (0.75 mmol), DMF (2 mL), at 125 °C for 10 h. ^{b}Isolated pure products.

Mechanistic Studies: To unearth the origin of hydrogen source responsible for the reduction of exocyclic imine bond some experiments were carried out (Scheme IV.3.5). There are reports of DMF serving as a reducing agent.[16] To ascertain this when a reaction was carried out with DMF-d_7, no deuterium incorporation in the product (**1a″**) was observed (Scheme IV.3.5a) there by confirming DMF not to be the source of hydrogen. Traces of moisture present in the commercial grade DMF seems to be the only other possible source of hydrogen. To ascertain this, a reaction was carried out in the presence of 10 equiv D_2O under otherwise identical condition (Scheme IV.3.5b). Interestingly, the reduced product was obtained bearing two deuterium atom (confirmed from 1HNMR and HRMS analysis) there by confirming water to be the possible source of hydrogen in the reaction. However, when the isolated exocyclic imine (**1a**) was subjected to the identical reaction condition similar to (**1a″**) no reduction of exocyclic imine double bond was observed. Thus, the exact mechanism of water serving as a reducing agent (hydrogen source) and the subsequent *in situ* reduction of the imine double bond is not clear at this moment.



Scheme IV.3.5. *Investigation of H_2 source*

Based on the literature reports a plausible reaction mechanism for this isocyanide insertion leading to DHB derivative is proposed in Scheme IV.3.6.[5a,17] The Pd(II) is reduced to Pd(0) under the basic reaction medium. The catalytic cycle is initiated via the oxidative addition of Pd(0) into C–I bond of ethyl 2-iodophenoxy acrylate (**1**) to form an intermediate (**A**). An imidoylated π-complex (**B**) is obtained via the migratory insertion of isocyanide. This is then followed by the formation of intermediate (**C**) via intramolecular Heck type cyclization with the acrylate double bond and β-hydride elimination of intermediate (**C**) gave the product (**1a**) releasing Pd(II) for the next catalytic cycle (Scheme IV.3.6). The intermediacy of species (**B**) and (**C**) has been confirmed by the HRMS analysis of reaction mixture.



Scheme IV.3.6. *Plausible mechanism for the dihydrobenzofuran synthesis*

In conclusion, we have developed an efficient ligand free Pd-catalyzed isocyanides insertion into 2-halophenoxy acrylates leading to the construction of two new C–C bonds giving 2,3-disubstituted dihydrobenzofurans (DHBs). Various aurone esters can be obtained via the acid hydrolysis of dihydrobenzofurans (DHBs). The iodo analogue gives dihydrobenzofurans (DHBs) having an exocyclic imine, while the bromo analogue gives product in which the imine bond is in the reduced state. The exact role of water serving as a reducing agent is not clear at this moment.

IV.4. Experimental Section

IV.4.1. General Information: All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (300, 400 and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (75, 100 and 150 MHz). HRMS spectra were recorded using ESI mode.

IV.4.2. General Procedure for the Synthesis of (*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (1a): Ethyl 3-(2-iodophenoxy)acrylate (**1**, 0.25 mmol, 79.5 mg), Pd(OAc)$_2$ (5 mol %, 2.8 mg) and Cs_2CO_3 (0.75 mmol, 243.0 mg, 3 equiv), were taken in an oven dried round-bottom flask. The flask was sealed with a septum and backfilled with nitrogen gas. Then dry toluene (3 mL) was added followed by the *tert*-butyl isocyanide (**a**, 0.187 mmol, 16.0 mg, 0.75 equiv) and the resulting mixture was stirred in a preheated oil bath at 90 ^{o}C. After 1 h of heating a further 0.75 equiv (0.187 mmol, 16.0 mg) of *tert*-butyl isocyanide (**a**) was added through a syringe. After completion (12 h), the reaction mixture was admixed with EtOAc (10 mL) and filtered through a short plug of celite. The filtrates were removed under a reduced pressure to provide crude product (**1a**), which was purified on a silica gel column chromatography using hexane / EtOAc (98:2) as the eluent to give pure product (**1a**, 52.0 mg, 77% yield).

IV.4.3. General Procedure for the Synthesis of (*Z*)-Ethyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (1a′): Ethyl 3-(2-iodophenoxy)acrylate (**1**, 0.25 mmol, 79.5 mg), Pd(OAc)$_2$ (5 mol%, 2.8 mg) and Cs_2CO_3 (0.75 mmol, 243.0 mg, 3 equiv), were taken in an oven dried round-bottom flask. The flask was sealed with a septum and backfilled with nitrogen. Then dry toluene (3 mL) was added followed by the *tert*-butyl isocyanide (**a**, 0.187 mmol, 16.0 mg, 0.75 equiv) and the resulting mixture was stirred in a preheated oil bath at 90 ^{o}C. After 1 h of heating a further 0.75 equiv (0.187 mmol, 16.0 mg) of *tert*-butyl isocyanide (**a**) was added through a syringe. After completion (12 h), the reaction mixture was admixed with EtOAc (10 mL) and filtered through a short plug of celite. The crude product obtained after evaporation of the solvent was dissolved in THF (3 mL) followed by the addition of HCl (5N, 500 μL) and the resulting mixture was refluxed for 30 min. During this time complete hydrolysis of the imine double bond was observed. After completion of the hydrolysis solvent was removed under vacuum and the mixture was admixed with EtOAc (20 mL). The EtOAc layer was dried over anhydrous Na_2SO_4 and evaporated under *vacuo*. The crude product was then purified by silica gel column chromatography using EtOAc and hexane (3:97) to give the pure product (**1a′**, 40.5 mg, 74%).

IV.4.4. General Procedure for the Synthesis of Ethyl 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (1a″): A mixture of ethyl 3-(2-bromophenoxy)acrylate (**1″**, 0.25 mmol, 67.5 mg), $Pd(OAc)_2$ (5 mol %, 2.8 mg,) and Cs_2CO_3 (0.75 mmol, 243.0 mg, 3 equiv) in DMF (2 mL) were taken in an oven dried round bottom flask to which *tert*-butyl isocyanide (**a**, 0.375 mmol, 31 mg, 1.5 equiv) was added. Then the resulting mixture was stirred in a preheated oil bath at 125 °C. After completion of the reaction (10 h), the mixture was cooled to room temperature and admixed with EtOAc (20 mL). The organic layer was washed sequentially with water (2 x 5 mL) and saturated solution of NaCl (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under *vacuo*. The crude product so obtained was then purified by silica gel column chromatography using EtOAc and hexane (7:93) to give the pure product (**1a″**, 28.0 mg, 41%).

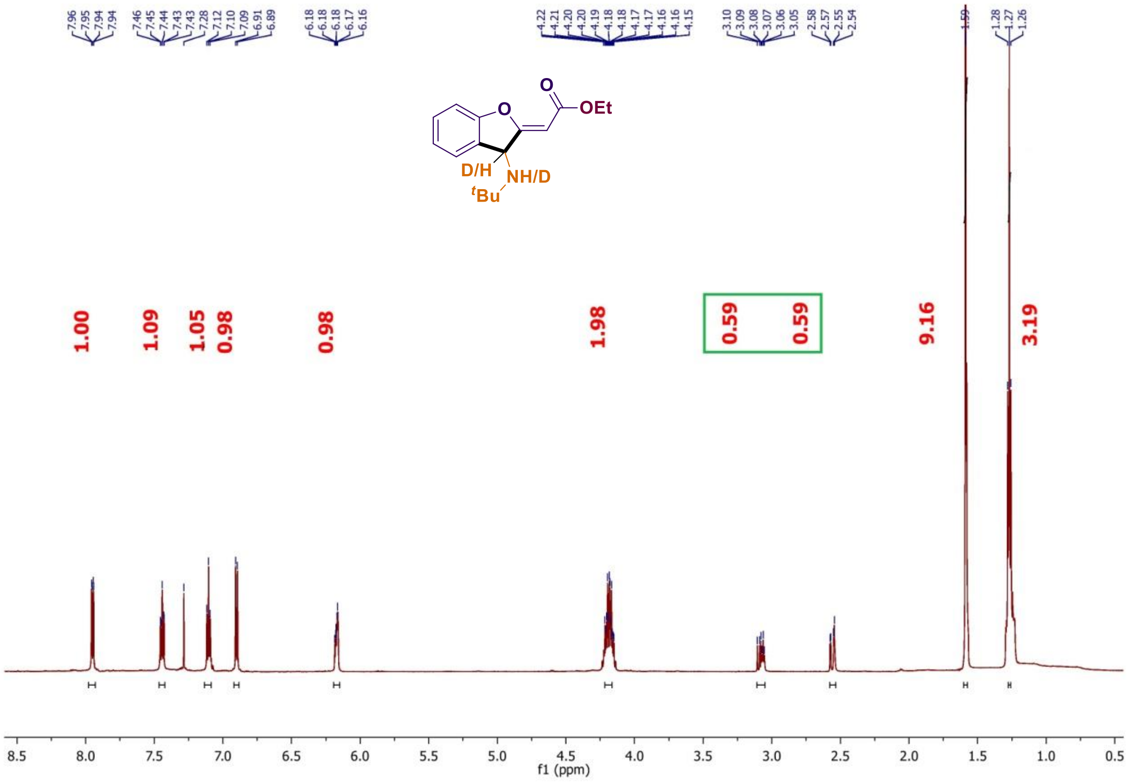
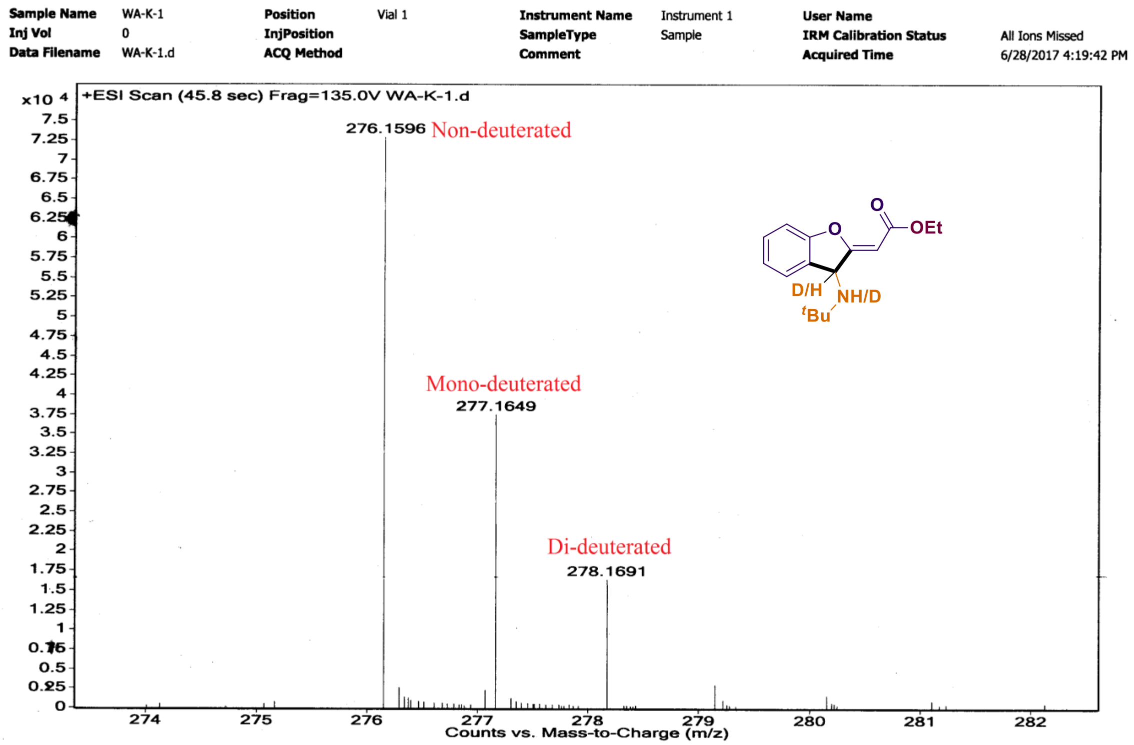


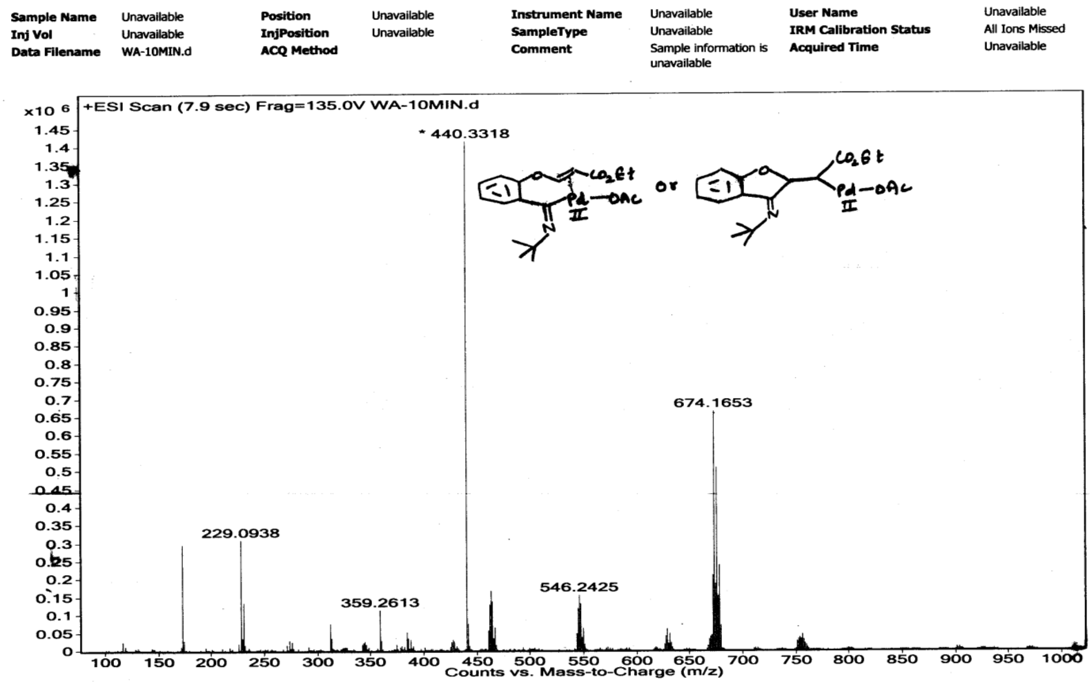
Figure IV.4.1. *^{1}HNMR spectra of the deuterium inserted product*



Sample Name	WA-K-1	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	WA-K-1.d	**ACQ Method**		**Comment**		**Acquired Time**	6/28/2017 4:19:42 PM

Figure IV.4.2. *Mass spectra of the deuterium inserted product*

IV.4.5. Identification of the Reaction Intermediates: In order to detect the intermediate species involved in the reaction mechanism an HRMS analysis of crude reaction mixture was performed. After stirring the reaction for 10 min. 20 µL reaction mixture was taken out and diluted with HPLC grade acetonitrile. The diluted solution was then injected to run ESI-MS analysis. Intermediates (**B**) and (**C**) were detected in the MS analysis as shown below. Based on this reaction mechanism involving Heck type coupling was proposed. Since both the intermediate have same m/z value that may be the reason the peak remains consistent even after in 1 h of reaction mixture.



Sample Name	Unavailable	**Position**	Unavailable	**Instrument Name**	Unavailable	**User Name**	Unavailable
Inj Vol	Unavailable	**InjPosition**	Unavailable	**SampleType**	Unavailable	**IRM Calibration Status**	All Ions Missed
Data Filename	WA-10MIN.d	**ACQ Method**		**Comment**	Sample information is unavailable	**Acquired Time**	Unavailable

Figure IV.4.3. *HRMS spectrum of the reaction mixture after 10 min*

IV.4.6. NOESY Experiment: The relative stereochemistry in the product (**1a–15a**) was determined by the NOESY experiment of (**1a**) as the representative example. When proton H_a was irradiated in the compound (**1a**), peak enhancement of the protons in the *tert*-butyl group H_b was observed. On the other hand, when proton H_b was irradiated, a strong peak enhancement for the proton H_b along with very weak enhancement for proton H_c were observed as expected. Similarly, when proton H_c was irradiated, a very weak peak enhancement for the proton H_b was observed. All these NOE observations ultimately suggests that the relative stereochemistry of the product (**1a**) as **(***Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate. The spatial interactions of the protons are shown in the figures given below.

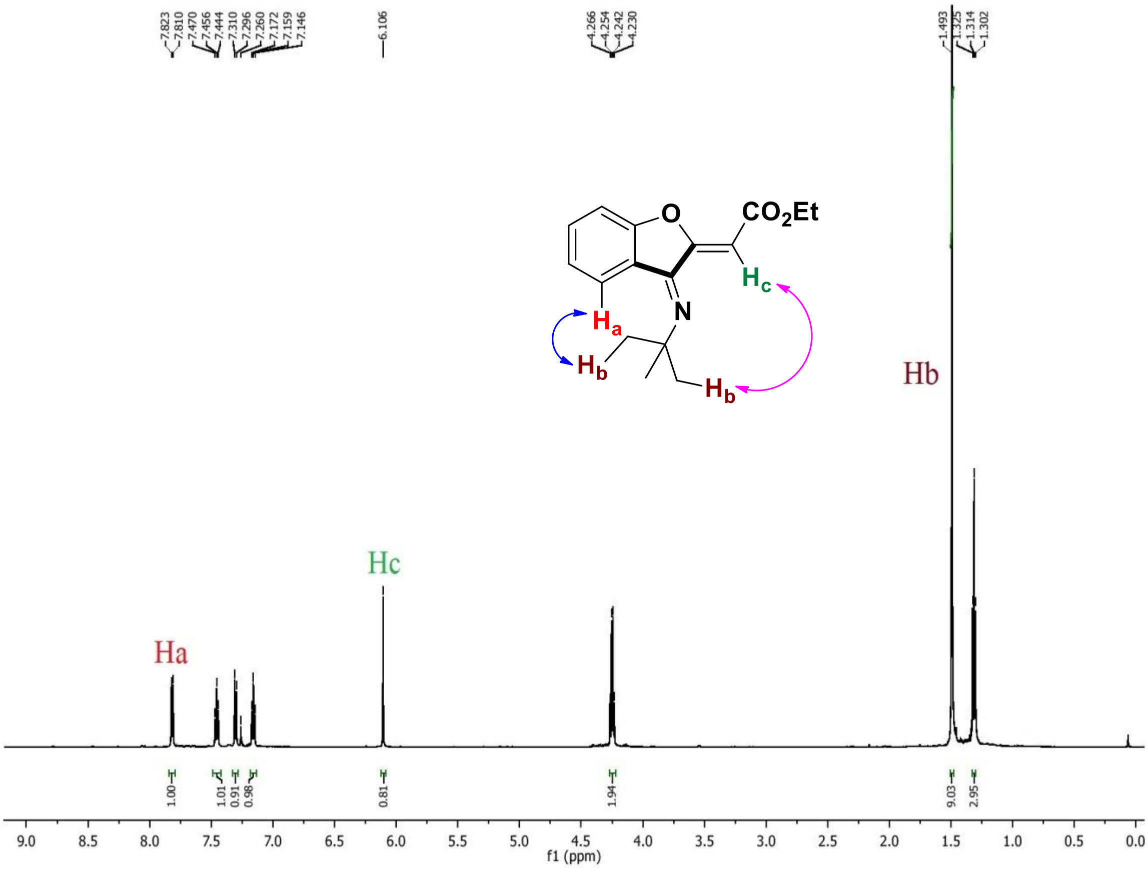


Figure IV.4.4. *^{1}HNMR spectra of compound (**1a**)*

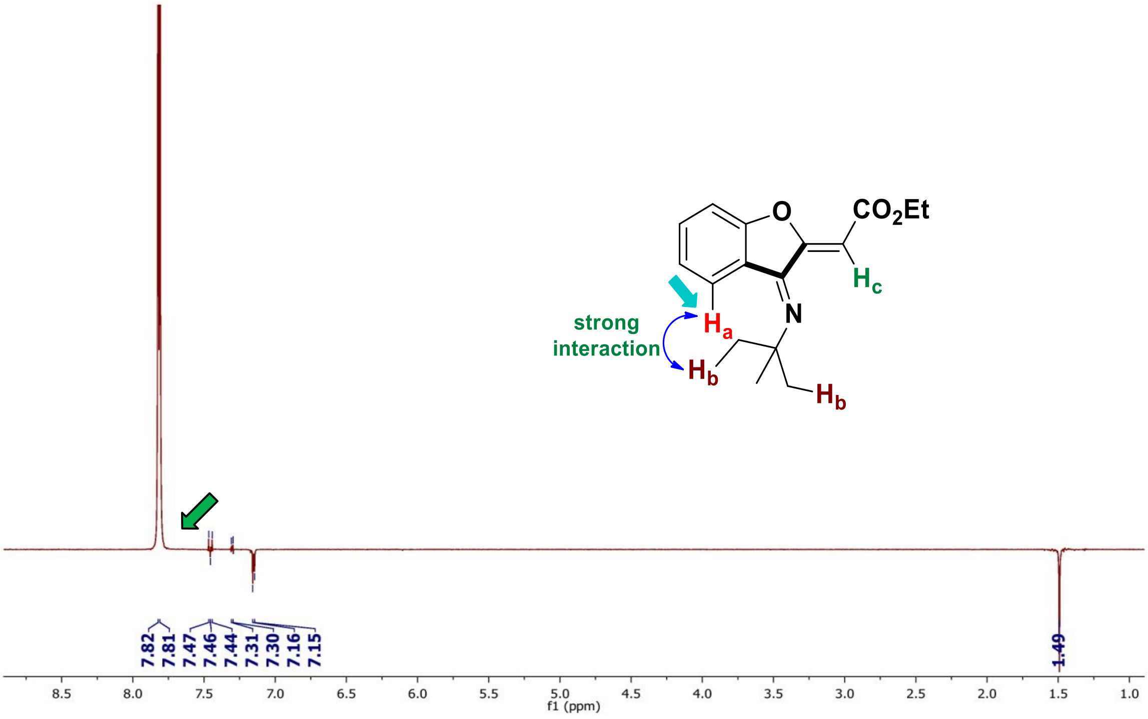


Figure IV.4.5. *NOE spectrum of **1a** with irradiation of H_a at 7.8 ppm (600 MHz, $CDCl_3$)*

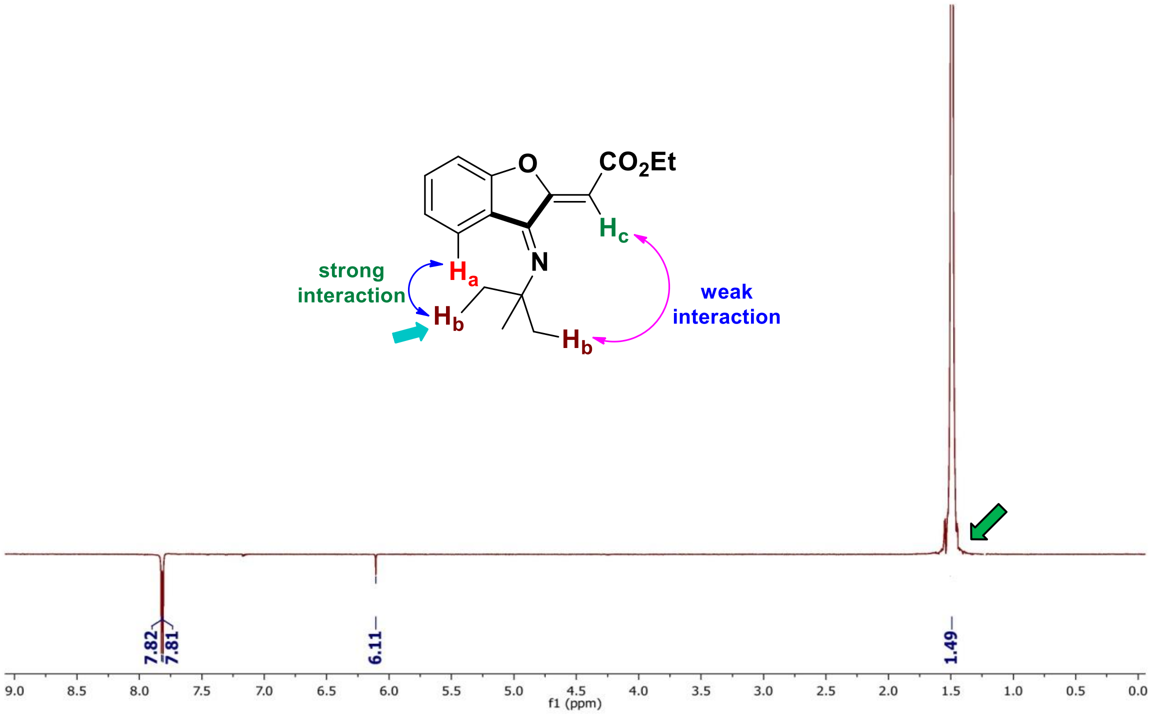


Figure IV.4.6. *NOE spectrum of **1a** with irradiation of H_b at 1.49 ppm (600 MHz, $CDCl_3$)*

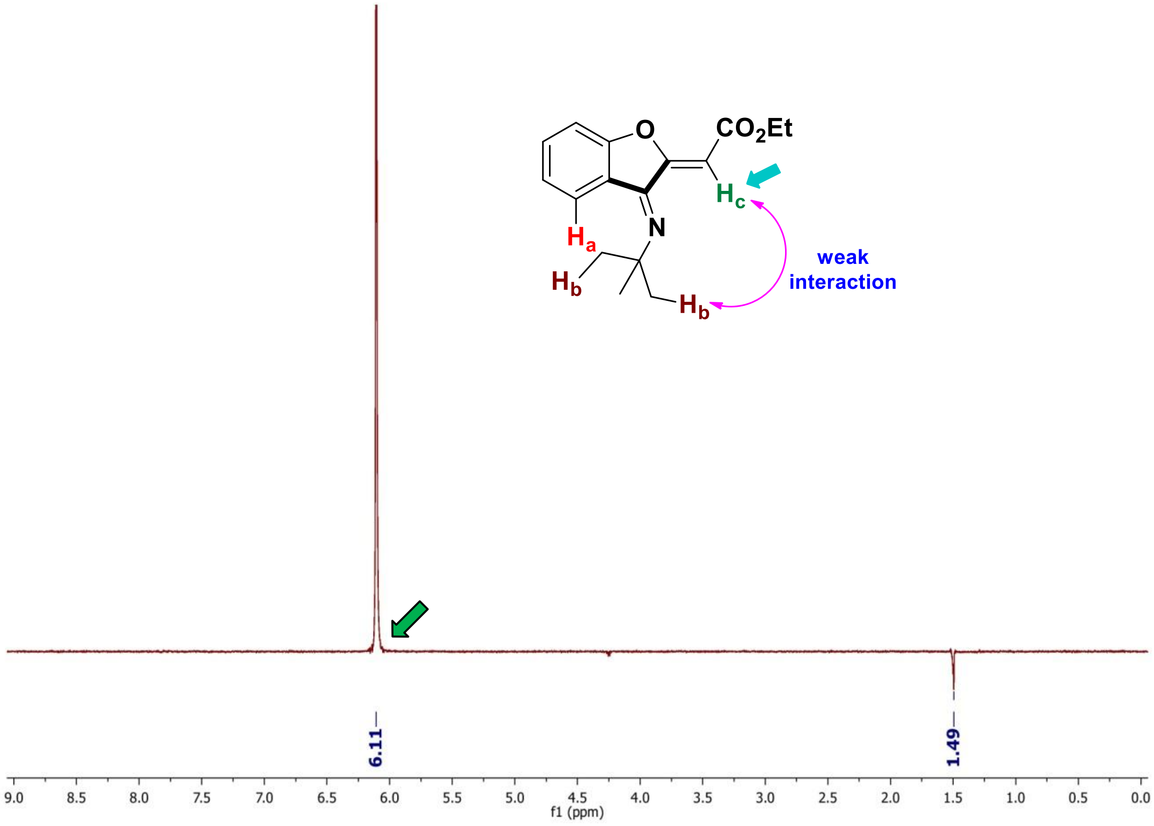


Figure IV.4.7. *NOE spectrum of **1a** with irradiation of H_c at 6.11 ppm (600 MHz, $CDCl_3$)*

IV.5. References

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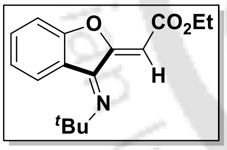
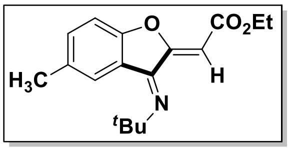
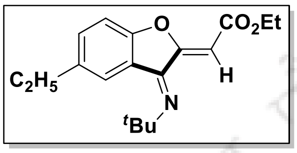
IV.6. Spectral Data



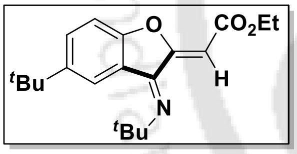
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (1a): Dark red gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 3H, *J* = 7.2 Hz), 1.50 (s, 9H), 4.25 (q, 2H, *J* = 7.2 Hz), 6.11 (s, 1H), 7.16 (t, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.46 (td, 1H, *J* = 7.6 Hz), 7.82 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 29.2, 56.2, 60.4, 93.03, 93.05, 113.3, 117.3, 123.4, 128.8, 133.5, 152.8, 161.0, 164.4, 165.3; HRMS (ESI): calcd. for $C_{16}H_{19}NO_3^+$ (MH$^+$) 274.1438; found 274.1445.



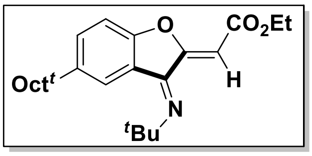
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-methylbenzofuran-2(3*H*)-ylidene)acetate (2a): Dark red gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 3H, *J* = 6.6 Hz), 1.50 (s, 9H), 2.40 (s, 3H), 4.25 (q, 2H, *J* = 7.2 Hz), 6.09 (s, 1H), 7.19 (d, 1H, *J* = 8.4 Hz), 7.27 (d, 1H, *J* = 6.0 Hz), 7.59 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.6, 21.4, 29.3, 56.2, 60.3, 92.8, 112.8, 117.3, 128.9, 132.9, 134.3, 153.0, 161.5, 162.7, 165.4; HRMS (ESI): calcd. for $C_{17}H_{21}NO_3^+$ (MH^+) 288.1594; found 288.1590.



(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-ethylbenzofuran-2(3*H*)-ylidene)acetate (3a): Dark red gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (t, 3H, *J* = 7.6 Hz), 1.23 (t, 3H, *J* = 6.8 Hz), 1.42 (s, 9H), 2.60 (q, 2H, *J* = 7.6 Hz), 4.16 (q, 2H, *J* = 7.2 Hz), 6.01 (s, 1H), 7.12 (d, 1H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 8.4 Hz), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 16.0, 28.7, 29.3, 56.1, 60.2, 92.8, 112.8, 117.2, 127.8, 133.1, 139.3, 153.0, 161.5, 162.8, 165.3; HRMS (ESI): calcd. for $C_{18}H_{23}NO_3^+$ (MH^+) 302.1751; found 302.1750.

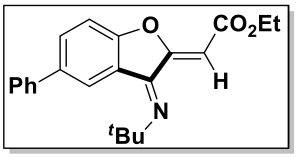


(*Z*)-Ethyl 2-((*E*)-5-(*tert*-butyl)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (4a): Red gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.29 (t, 3H, *J* = 7.2 Hz), 1.33 (s, 9H), 1.50 (s, 9H), 4.24 (q, 2H, *J* = 7.2 Hz), 6.08 (s, 1H), 7.21 (d, 1H, *J* = 8.8 Hz), 7.49 (dd, 1H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 29.3, 31.7, 34.9, 56.0, 60.2, 92.8, 112.4, 116.9, 125.6, 130.8, 146.3, 153.2, 161.6, 162.5, 165.3; HRMS (ESI): calcd. for $C_{20}H_{27}NO_3^+$ (MH^+) 330.2064; found 330.2060.

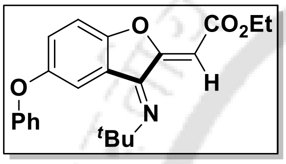


(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-(2,4,4-trimethylpentan-2-yl)benzofuran-2(3*H*)-ylidene)acetate (5a): Red gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.68 (s, 9H), 1.30 (t, 3H, *J* = 7.2 Hz), 1.37 (s, 6H), 1.50 (s, 9H), 1.72 (s, 2H), 4.23 (q, 2H, *J* = 7.2 Hz), 6.08 (s, 1H), 7.20 (d, 1H, *J* = 8.4 Hz), 7.47 (dd, 1H, *J* = 8.8 Hz), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 29.2, 31.9, 32.0, 32.5, 38.7, 56.0, 57.3, 60.2, 92.7, 112.1, 116.5, 126.5, 131.5, 145.1, 153.3, 161.6, 162.3, 165.3; HRMS (ESI):

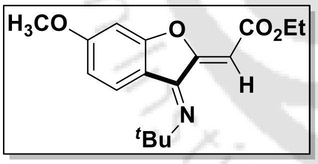
calcd. for $C_{24}H_{35}NO_3^+$ (MH^+) 386.2690; found 386.2695.



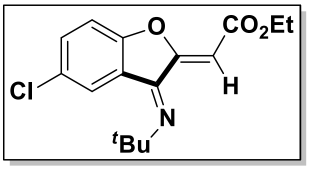
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-phenylbenzofuran-2(3*H*)-ylidene)acetate (6a): Yellow solid; M.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (t, 3H, *J* = 7.2 Hz), 1.54 (s, 9H), 4.27 (q, 2H, *J* = 7.2 Hz), 6.15 (s, 1H), 7.40 (m, 2H), 7.46 (t, 2H, *J* = 7.6 Hz), 7.52 (d, 2H, *J* = 7.2 Hz), 7.67 (dd, 1H, *J* = 8.8 Hz), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 29.3, 56.2, 60.4, 93.2, 113.3, 117.7, 127.2, 127.5, 127.7, 129.2, 132.7, 137.1, 140.4, 152.6, 161.2, 163.8, 165.2; HRMS (ESI): calcd. for $C_{22}H_{23}NO_3^+$ (MH^+) 350.1751; found 350.1751.



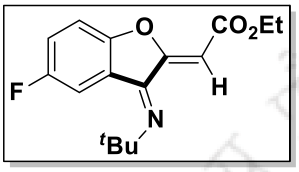
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-phenoxybenzofuran-2(3*H*)-ylidene)acetate (7a): Red solid; M.p. 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31 (t, 3H, *J* = 7.2 Hz), 1.41 (s, 9H), 4.24 (q, 2H, *J* = 7.2 Hz), 6.10 (s, 1H), 6.98 (d, 2H, *J* = 7.6 Hz), 7.08–7.14 (m, 2H), 7.26 (d, 1H, *J* = 8.8 Hz), 7.33 (m, 2H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.5, 29.2, 56.2, 60.3, 93.2, 100.2, 113.8, 117.8, 118.4, 119.2, 123.6, 124.4, 130.1, 152.4, 152.7, 157.4, 160.2, 161.4, 165.1; HRMS (ESI): calcd. for $C_{22}H_{23}NO_4^+$ (MH^+) 366.1700; found 366.1705.



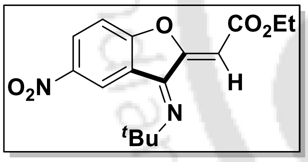
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-6-methoxybenzofuran-2(3*H*)-ylidene)acetate (8a): Black gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.31 (t, 3H, *J* = 7.2 Hz), 1.46 (s, 9H), 3.85 (s, 3H), 4.24 (q, 2H, *J* = 7.2 Hz), 6.09 (s, 1H), 6.69 (dd, 1H, *J* = 8.4 Hz), 6.81 (s, 1H), 7.69 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.5, 29.1, 55.7, 56.0, 60.3, 92.8, 97.6, 110.4, 111.1, 129.7, 152.1, 162.1, 164.1, 165.3, 166.4; HRMS (ESI): calcd. for $C_{17}H_{21}NO_4^+$ (MH^+) 304.1543; found 304.1545.



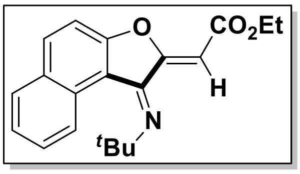
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-chlorobenzofuran-2(3*H*)-ylidene)acetate (9a): White solid; M.p. 139–141 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.29 (t, 3H, *J* = 8.8 Hz), 1.47 (s, 9H), 4.23 (q, 2H, *J* = 7.2 Hz), 6.08 (s, 1H), 7.23 (d, 1H, *J* = 8.8 Hz), 7.41 (dd, 1H, *J* = 8.8 Hz), 7.74 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 14.5, 29.2, 56.5, 60.4, 93.7, 114.3, 118.5, 128.3, 128.7, 133.2, 151.4, 160.7, 162.6, 165.0; HRMS (ESI): calcd. for $C_{16}H_{18}ClNO_3^+$ (MH$^+$) 308.1048; found 308.1050.



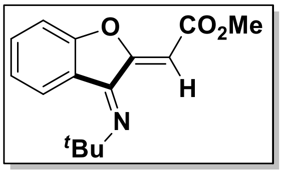
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-fluorobenzofuran-2(3*H*)-ylidene)acetate (10a): Red solid; M.p. 114–116 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.31 (t, 3H, *J* = 7.2 Hz), 1.48 (s, 9H), 4.24 (q, 2H, *J* = 7.2 Hz), 6.10 (s, 1H), 7.18 (d, 1H, *J* = 9.2 Hz), 7.25 (m, 1H), 7.50 (dd, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 14.5, 29.2, 56.4, 60.4, 93.5, 113.9, 114.0, 115.0, 115.2, 117.7, 117.8, 120.2, 120.5, 128.0, 129.0, 152.0, 152.1, 157.3, 159.7, 160.26, 160.28, 161.2, 165.0; HRMS (ESI): calcd. for $C_{16}H_{18}FNO_3^+$ (MH$^+$) 292.1343; found 292.1345.



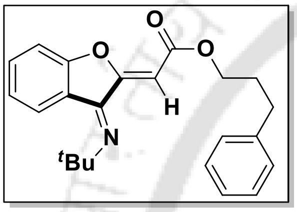
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)-5-nitrobenzofuran-2(3*H*)-ylidene)acetate (11a): Red solid; M.p. 142–144 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.30 (t, 3H, *J* = 7.2 Hz), 1.52 (s, 9H), 4.25 (q, 2H, *J* = 7.2 Hz), 6.17 (s, 1H), 7.42 (d, 1H, *J* = 9.2 Hz), 8.41 (dd, 1H, *J* = 9.2 Hz), 8.71 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 14.4, 29.2, 57.0, 60.7, 95.4, 113.7, 117.8, 124.7, 129.2, 143.8, 150.2, 160.1, 164.5, 167.5; HRMS (ESI): calcd. for $C_{16}H_{18}N_2O_5^+$ (MH$^+$) 319.1288; found 319.1290.



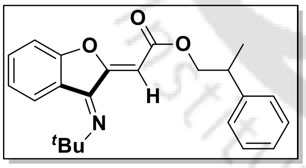
(*Z*)-Ethyl 2-((*E*)-1-(*tert*-butylimino)naphtho[2,1-b]furan-2(1*H*)-ylidene)acetate (12a): Greenish brown solid; M.p. 104–107 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.38 (t, 3H, *J* = 7.2 Hz), 1.63 (s, 9H), 4.32 (q, 2H, *J* = 7.2 Hz), 6.09 (s, 1H), 7.39 (d, 1H, *J* = 9.2 Hz), 7.44 (ddd, 1H, *J* = 6.8 Hz), 7.61 (d, 1H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.8 Hz), 9.27 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 14.5, 29.4, 56.8, 60.9, 103.93, 103.96, 112.2, 123.9, 125.1, 128.9, 129.1, 129.2, 131.1, 134.5, 134.6, 151.6, 153.9, 161.3, 164.7; HRMS (ESI): calcd. for $C_{20}H_{21}NO_3^+$ (MH^+) 324.1594; found 324.1600.



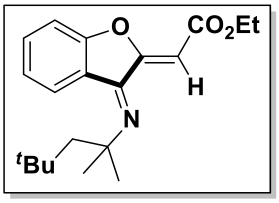
(*Z*)-Methyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (13a): Black gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48 (s, 9H), 3.77 (s, 3H), 6.10 (s, 1H), 7.15 (t, 1H, *J* = 7.2 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.46 (m, 1H), 7.81 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.1, 51.6, 56.2, 92.6, 113.2, 117.2, 123.4, 128.8, 133.5, 152.7, 161.0, 164.2, 165.7; HRMS (ESI): calcd. for $C_{15}H_{17}NO_3^+$ (MH^+) 260.1281; found 260.1285.



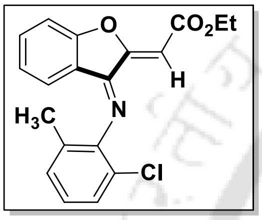
(*Z*)-3-Phenylpropyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (14a): Red gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.53 (s, 9H), 2.00–2.07 (m, 2H), 2.77 (t, 2H, *J* = 8.0 Hz), 4.23 (t, 2H, *J* = 6.4 Hz), 6.14 (s, 1H), 7.15–7.20 (m, 2H), 7.22 (d, 2H, *J* = 7.6 Hz), 7.30 (t, 3H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 29.2, 30.6, 32.4, 56.2, 63.6, 93.0, 113.2, 117.2, 123.4, 126.1, 128.58, 128.64, 128.9, 133.5, 141.5, 152.8, 161.1, 164.3, 165.4; HRMS (ESI): calcd. for $C_{23}H_{25}NO_3^+$ (MH^+) 364.1907; found 364.1910.



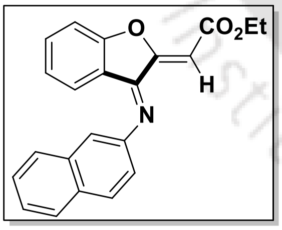
(*Z*)-2-Phenylpropyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (15a): Yellow solid; M.p. 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (d, 3H, *J* = 6.8 Hz), 1.50 (s, 9H), 3.16–3.21 (m, 1H), 4.23–4.27 (m, 1H), 4.36 (m, 1H), 6.09 (s, 1H), 7.15 (t, 1H, *J* = 7.6 Hz), 7.21–7.34 (m, 6H), 7.45 (t, 1H, *J* = 7.6 Hz), 7.81 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.4, 29.1, 39.2, 56.3, 69.4, 92.9, 113.2, 117.2, 123.4, 126.8, 127.6, 128.7, 128.9, 133.5, 143.6, 152.9, 161.1, 164.3, 165.3; HRMS (ESI): calcd. for $C_{23}H_{25}NO_3^+$ (MH^+) 364.1907; found 364.1902.



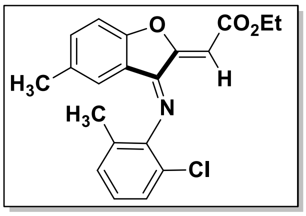
(*Z*)-Ethyl 2-((*E*)-3-((2,4,4-trimethylpentan-2-yl)imino)benzofuran-2(3H)-ylidene)acetate (1b): Black gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 0.98 (s, 9H), 1.32 (t, 3H, *J* = 7.2 Hz), 1.51 (s, 6H), 1.90 (s, 2H), 4.24 (q, 2H, *J* = 7.2 Hz), 6.04 (s, 1H), 7.14 (t, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.5, 30.4, 31.7, 32.1, 52.1, 54.1, 55.1, 60.3, 92.9, 113.3, 117.5, 123.4, 128.5, 133.3, 151.5, 161.2, 164.5, 165.4; HRMS (ESI): calcd. for $C_{20}H_{27}NO_3^+$ (MH$^+$) 330.2064; found 330.2070.



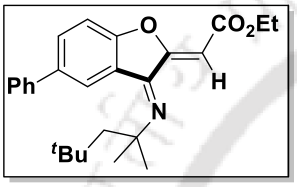
(*Z*)-Ethyl 2-((*E*)-3-((2-chloro-6-methylphenyl)imino)benzofuran-2(3H)-ylidene)acetate (1c): Red solid; M.p. 75–77 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.36 (t, 3H, *J* = 4.8 Hz), 2.07 (s, 3H), 4.32 (q, 2H, *J* = 4.8 Hz), 6.47 (s, 1H), 6.52 (d, 1H, *J* = 5.2 Hz), 6.88 (t, 1H, *J* = 5.2 Hz), 7.06 (t, 1H, *J* = 5.2 Hz), 7.17 (d, 1H, *J* = 5.2 Hz), 7.30 (dd, 2H, *J* = 5.6 Hz), 7.45 (t, 1H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 14.5, 18.3, 60.9, 96.5, 112.8, 118.7, 122.5, 124.2, 125.2, 125.3, 127.7, 128.7, 129.3, 135.3, 146.1, 158.1, 158.7, 163.0, 164.7; HRMS (ESI): calcd. for $C_{19}H_{16}ClNO_3^+$ (MH$^+$) 342.0891; found 342.0895.



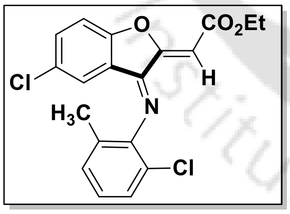
(*Z*)-Ethyl 2-((*E*)-3-(naphthalen-2-ylimino)benzofuran-2(3*H*)-ylidene)acetate (1d): Red solid; M.p. 116–118 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.36 (t, 3H, *J* = 7.2 Hz), 4.32 (q, 2H, *J* = 7.2 Hz), 6.38 (s, 1H), 6.72–6.78 (m, 2H), 7.18 (dd, 1H, *J* = 8.4 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.40 (m, 2H), 7.45–7.52 (m, 2H), 7.79 (d, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.92 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.5, 60.8, 96.1, 112.9, 115.0, 117.9, 119.6, 123.6, 125.5, 126.2, 126.9, 128.0, 128.1, 129.8, 131.4, 134.3, 134.9, 148.0, 157.2, 159.0, 163.6, 164.8; HRMS (ESI): calcd. for $C_{22}H_{17}NO_3^+$ (MH$^+$) 344.1281; found 344.1290.



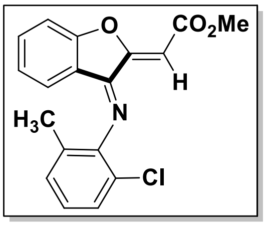
(*Z*)-ethyl 2-((*E*)-3-((2-chloro-6-methylphenyl)imino)-5-methylbenzofuran-2(3H)-ylidene)acetate (2c): Red gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.36 (t, 3H, *J* = 7.2 Hz), 2.07 (s, 3H), 2.11 (s, 3H), 4.31 (q, 2H, *J* = 7.2 Hz), 6.26 (s, 1H), 6.45 (s, 1H), 7.06 (t, 1H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.5, 18.3, 21.1, 60.8, 96.2, 112.4, 118.6, 122.5, 125.07, 125.10, 127.7, 128.6, 129.2, 133.8, 136.2, 146.2, 158.6, 158.9, 161.4, 164.8; HRMS (ESI): calcd. for $C_{20}H_{18}ClNO_3^+$ (MH$^+$) 356.1048; found 356.1040.



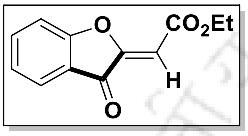
(*Z*)-Ethyl 2-((*E*)-5-phenyl-3-((2,4,4-trimethylpentan-2-yl)imino)benzofuran-2(3*H*)-ylidene)acetate (6b): Red solid; M.p. 106–108 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.00 (s, 9H), 1.33 (t, 3H, *J* = 7.2 Hz), 1.56 (s, 6H), 1.94 (s, 2H), 4.26 (q, 2H, *J* = 7.6 Hz), 6.08 (s, 1H), 7.36 (dd, 2H, *J* = 6.8 Hz), 7.45 (t, 2H, *J* = 8.0 Hz), 7.50 (d, 2H, *J* = 7.2 Hz), 7.65 (dd, 1H, *J* = 8.4 Hz), 8.02 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.5, 30.4, 31.7, 32.1, 52.1, 54.0, 55.3, 60.4, 93.1, 113.3, 117.9, 127.2, 127.9, 129.2, 132.5, 137.1, 140.4, 151.4, 156.7, 161.4, 163.9, 165.4; HRMS (ESI): calcd. for $C_{26}H_{31}NO_3^+$ (MH$^+$) 406.2377; found 406.2380.



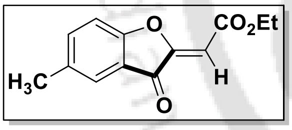
(*Z*)-Ethyl 2-((*E*)-5-chloro-3-((2-chloro-6-methylphenyl)imino)benzofuran-2(3*H*)-ylidene)acetate (9c): Red solid; M.p. 129–131 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 1.36 (t, 3H, *J* = 7.2 Hz), 2.08 (s, 3H), 4.32 (q, 2H, *J* = 7.2 Hz), 6.44 (d, 1H, *J* = 2.0 Hz), 6.48 (s, 1H), 7.09 (t, 1H, *J* = 8.0 Hz), 7.20 (d, 1H, *J* = 8.4 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.33 (d, 1H, *J* = 7.6 Hz), 7.42 (dd, 1H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.4, 18.3, 61.0, 97.3, 114.1, 119.8, 122.2, 124.9, 125.6, 127.9, 128.5, 129.40, 129.45, 135.2, 145.6, 157.7, 157.9, 161.4, 164.4; HRMS (ESI): calcd. for $C_{19}H_{15}Cl_2NO_3^+$ (MH$^+$) 376.0502; found 376.0507.



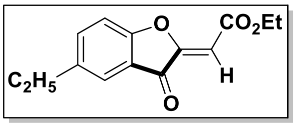
(*Z*)-Methyl 2-((*E*)-3-((2-chloro-6-methylphenyl)imino)benzofuran-2(3*H*)-ylidene)acetate (13c): Orange solid; M.p. 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 3.85 (s, 3H), 6.47 (s, 1H), 6.53 (d, 1H, *J* = 8.0 Hz), 6.88 (t, 1H, *J* = 7.6 Hz), 7.05 (t, 1H, *J* = 7.6 Hz), 7.17 (d, 1H, *J* = 7.6 Hz), 7.29 (t, 2H, *J* = 7.2 Hz), 7.45 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.3, 52.0, 96.1, 112.8, 118.6, 122.5, 124.3, 125.2, 125.3, 127.7, 128.7, 129.3, 135.4, 146.1, 158.2, 158.7, 162.9, 165.1; HRMS (ESI): calcd. for $C_{18}H_{14}ClNO_3^+$ (MH$^+$) 328.0735; found 328.0730.



(*Z*)-Ethyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (1a′): Red solid; M.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 3H, *J* = 7.2 Hz), 4.27 (q, 2H, *J* = 7.2 Hz), 6.09 (s, 1H), 7.21 (t, 1H, *J* = 7.6 Hz), 7.31 (d, 1H, *J* = 8.4 Hz), 7.66 (ddd, 1H, *J* = 7.2 Hz), 7.72 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 61.3, 100.3, 113.6, 120.2, 124.6, 125.2, 138.5, 153.3, 163.9, 167.5, 185.0; HRMS (ESI): calcd. for $C_{12}H_{10}O_4^+$ (MH$^+$) 219.0652; found 219.0650.

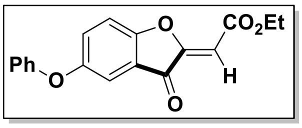


(*Z*)-Ethyl 2-(5-methyl-3-oxobenzofuran-2(3*H*)-ylidene)acetate (2a′): Yellow solid; M.p. 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (t, 3H, *J* = 6.6 Hz), 2.38 (s, 3H), 4.29 (q, 2H, *J* = 7.2 Hz), 6.09 (s, 1H), 7.22 (d, 1H, *J* = 8.4 Hz), 7.47 (d, 1H, *J* = 8.4 Hz), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.4, 20.9, 61.3, 99.82, 99.84, 113.2, 120.4, 124.5, 134.5, 139.5, 153.9, 164.1, 166.1, 185.1; HRMS (ESI): calcd. for $C_{13}H_{12}O_4^+$ (MH$^+$) 233.0808; found 233.0810.

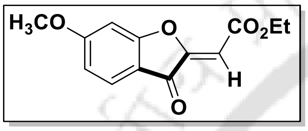


(*Z*)-Ethyl 2-(5-ethyl-3-oxobenzofuran-2(3*H*)-ylidene)acetate (3a′): Yellow solid; M.p. 54–56 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 4.8 Hz), 1.34 (t, 3H, *J* = 4.8 Hz), 2.68 (q, 2H, *J* = 4.8 Hz), 4.29 (q, 2H, *J* = 4.8 Hz), 6.10 (s, 1H), 7.24 (d, 1H, *J* = 5.2 Hz), 7.51 (dd, 1H, *J* = 5.6 Hz), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.4, 15.5, 28.3, 61.3, 99.8, 113.3, 123.6, 127.8, 138.6, 141.0, 153.9, 164.0, 166.2, 185.2; HRMS (ESI):

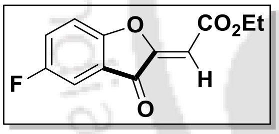
calcd. for $C_{14}H_{14}O_4^+$ (MH^+) 247.0965; found 247.0960.



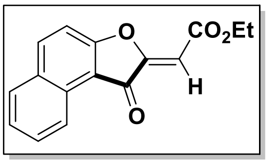
(*Z*)-Ethyl 2-(3-oxo-5-phenoxybenzofuran-2(3*H*)-ylidene)acetate (6a′): Yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.30 (t, 3H, *J* = 7.2 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 6.07 (s, 1H), 6.95 (dd, 2H, *J* = 8.4 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 7.21 (s, 1H), 7.28–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 61.4, 100.4, 113.2, 114.7, 119.3, 120.9, 124.4, 129.8, 130.3, 154.0, 154.6, 156.6, 163.4, 163.9, 184.9; HRMS (ESI): calcd. for $C_{18}H_{14}O_5^+$ (MH^+) 311.0914; found 311.0920.



(*Z*)-Ethyl 2-(6-methoxy-3-oxobenzofuran-2(3*H*)-ylidene)acetate (8a′): Yellow solid; M.p. 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 3H, *J* = 7.2 Hz), 3.89 (s, 3H), 4.28 (q, 2H, *J* = 7.2 Hz), 6.06 (s, 1H), 6.75 (m, 2H), 7.64 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.3, 56.4, 61.3, 97.4, 99.3, 113.2, 113.4, 126.5, 154.7, 164.1, 168.7, 170.1, 182.8; HRMS (ESI): calcd. for $C_{13}H_{12}O_5^+$ (MH^+) 249.0757; found 249.0760.

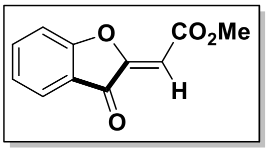


(*Z*)-Ethyl 2-(5-fluoro-3-oxobenzofuran-2(3*H*)-ylidene)acetate (10a′): Yellow solid; M.p. 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (t, 3H, *J* = 7.2 Hz), 4.30 (q, 2H, *J* = 6.8 Hz), 6.14 (s, 1H), 7.32 (dd, 1H, *J* = 10.8 Hz), 7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.3, 61.5, 100.9, 110.7, 111.0, 114.9, 115.0, 121.0, 121.1, 125.7, 126.1, 153.7, 157.7, 161.0, 163.6, 163.8, 184.6; HRMS (ESI): calcd. for $C_{12}H_9FO_4^+$ (MH^+) 237.0558; found 237.0565.

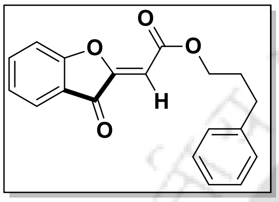


(*Z*)-Ethyl 2-(1-oxonaphtho[2,1-b]furan-2(1*H*)-ylidene)acetate (12a′): Yellow solid; M.p. 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.35 (t, 3H, *J* = 7.2 Hz), 4.31 (q, 2H, *J* = 7.2 Hz), 6.18 (s, 1H), 7.42 (d, 1H, *J* = 8.8 Hz), 7.49 (t, 1H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 9.2 Hz), 8.67 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.4, 61.5, 100.4, 106.4, 113.2, 123.7, 126.5, 128.99, 129.04, 130.5, 140.7, 153.9, 164.1, 170.0, 184.6; HRMS (ESI): calcd. for

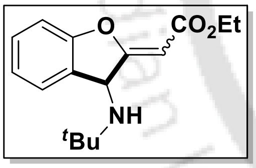
$C_{16}H_{12}O_4^+$ (MH$^+$) 269.0808; found 269.0804.



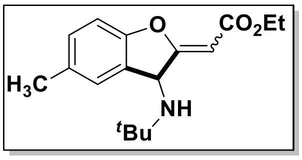
(*Z*)-Methyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (13a′): Yellow solid; M.p. 132–134 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.86 (s, 3H), 6.14 (s, 1H), 7.26 (t, 1H, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 8.4 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.77 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 52.3, 100.0, 113.6, 120.5, 124.7, 125.3, 138.5, 153.4, 164.4, 167.6, 185.0; HRMS (ESI): calcd. for $C_{11}H_8O_4^+$ (MH$^+$) 205.0495; found 205.0490.



(*Z*)-3-Phenylpropyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (14a′): Yellow gummy; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 2.01–2.09 (m, 2H), 2.77 (t, 2H, *J* = 8.0 Hz), 4.27 (t, 2H, *J* = 6.4 Hz), 6.16 (s, 1H), 7.21 (m, 3H), 7.27 (dd, 3H, *J* = 9.2 Hz), 7.34 (d, 1H, *J* = 7.6 Hz), 7.69 (m, 1H), 7.77 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 30.3, 32.2, 64.6, 100.0, 113.6, 120.3, 124.7, 125.3, 126.2, 128.59, 128.63, 138.6, 141.2, 153.4, 164.0, 167.5, 185.1; HRMS (ESI): calcd. for $C_{19}H_{16}O_4^+$ (MH$^+$) 309.1121; found 309.1125.

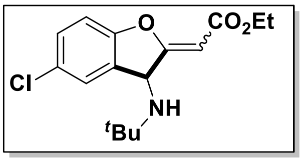


Ethyl 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (1a″): Dark red liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 1.23 (t, 3H, *J* = 7.2 Hz), 1.55 (s, 9H), 2.53 (dd, 1H, *J* = 12.0 Hz), 3.05 (dd, 1H, *J* = 5.4 Hz), 4.10–4.19 (m, 2H), 6.14 (dd, 1H, *J* = 9.6 Hz), 6.87 (d, 1H, *J* = 7.8 Hz), 7.07 (t, 1H, *J* = 7.8 Hz), 7.41 (m, 1H), 7.92 (dd, 1H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 14.3, 28.9, 40.0, 57.6, 61.2, 82.5, 116.9, 119.6, 122.5, 128.1, 134.4, 154.0, 161.5, 168.9; HRMS (ESI): calcd. for $C_{16}H_{21}NO_3^+$ (MH$^+$) 276.1594; found 276.1590.

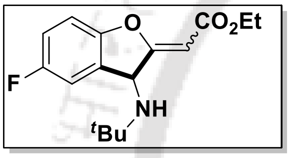


Ethyl 2-(3-(*tert*-butylamino)-5-methylbenzofuran-2(3*H*)-ylidene)acetate (2a″): Dark red liquid; ^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 1.23 (t, 3H, *J* = 7.2 Hz), 1.55 (s, 9H), 2.31 (s, 3H), 2.51 (dd, 1H, *J* = 6.0 Hz), 3.05 (dd, 1H, *J* = 5.4 Hz), 4.15 (m, 2H), 6.11 (dd, 1H, *J* = 6.6 Hz), 6.76 (d, 1H, *J* = 7.8 Hz), 7.21 (dd, 1H, *J* = 8.4 Hz), 7.71 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (ppm)

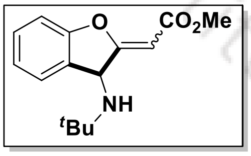
14.3, 20.8, 29.0, 40.1, 57.6, 61.2, 82.5, 116.8, 119.4, 128.1, 132.1, 135.2, 151.9, 161.8, 169.1; HRMS (ESI): calcd. for $C_{17}H_{23}NO_3^+$ (MH^+) 290.1751; found 290.1755.



Ethyl 2-(3-(*tert*-butylamino)-5-chlorobenzofuran-2(3*H*)-ylidene)acetate (3a″): Dark red gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 7.2 Hz), 1.54 (s, 9H), 2.53 (dd, 1H, *J* = 6.0 Hz), 3.01 (m, 1H), 4.10–4.19 (m, 2H), 6.13 (dd, 1H, *J* = 7.2 Hz), 6.83 (d, 1H, *J* = 9.0 Hz), 7.35 (dd, 1H, *J* = 9.0 Hz), 7.88 (d, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 28.9, 40.1, 58.0, 61.3, 82.7, 118.6, 120.8, 127.9, 128.0, 134.3, 152.6, 160.4, 168.7; HRMS (ESI): calcd. for $C_{16}H_{20}ClNO_3^+$ (MH^+) 310.1204; found 310.1210.



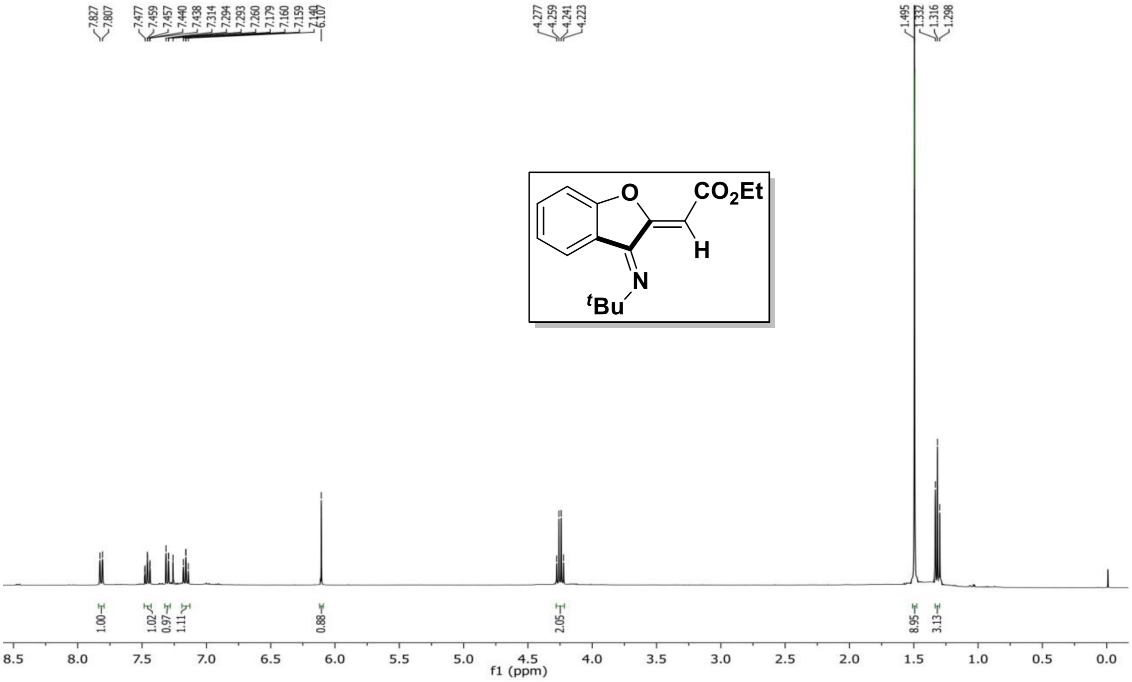
Ethyl 2-(3-(*tert*-butylamino)-5-fluorobenzofuran-2(3*H*)-ylidene)acetate (4a″): Dark red gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.24 (t, 3H, *J* = 7.2 Hz), 1.55 (s, 9H), 2.53 (dd, 1H, *J* = 9.6 Hz), 3.04 (dd, 1H, *J* = 5.4 Hz), 4.13–4.19 (m, 2H), 6.13 (dd, 1H, *J* = 6.6 Hz), 6.85 (dd, 1H, *J* = 9.0 Hz), 7.12 (m, 1H), 7.59 (dd, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.3, 28.9, 40.0, 57.9, 61.3, 82.7, 114.0, 114.2, 116.0, 116.1, 116.4, 118.40. 118.45. 121.5, 121.6, 150.1, 157.4, 159.0, 160.6, 168.8; HRMS (ESI): calcd. for $C_{16}H_{20}FNO_3^+$ (MH^+) 294.1500; found 294.1510.



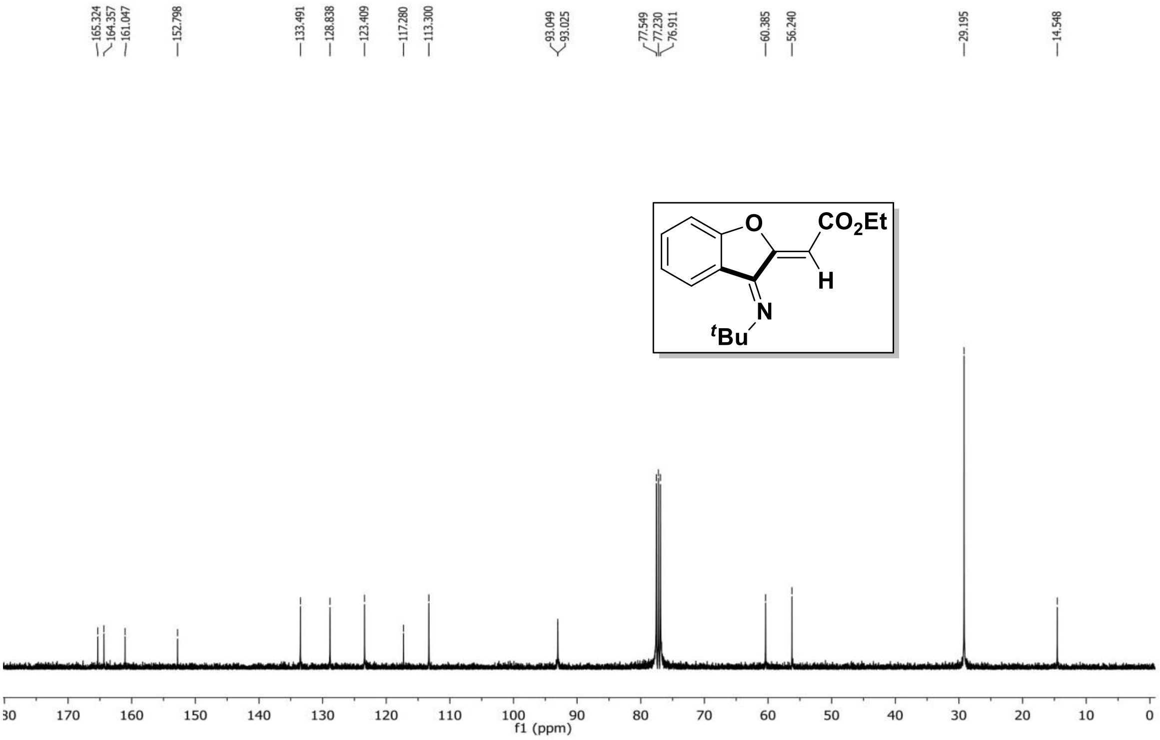
Methyl 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (5a″): Dark red gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.55 (s, 9H), 2.54 (dd, 1H, *J* = 12.0 Hz), 3.07 (dd, 1H, *J* = 5.4 Hz), 3.69 (s, 3H), 6.15(dd, 1H, *J* = 6.6 Hz), 6.87 (d, 1H, *J* = 7.2 Hz), 7.07 (m, 1H), 7.41 (m, 1H), 7.91 (dd, 1H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.0, 39.9, 52.2, 57.7, 82.5, 117.0, 119.7, 122.6, 128.2, 134.4, 154.1, 161.5, 169.5; HRMS (ESI): calcd. for $C_{15}H_{19}NO_3^+$ (MH^+) 262.1438; found 262.1438.

IV.7. Spectra

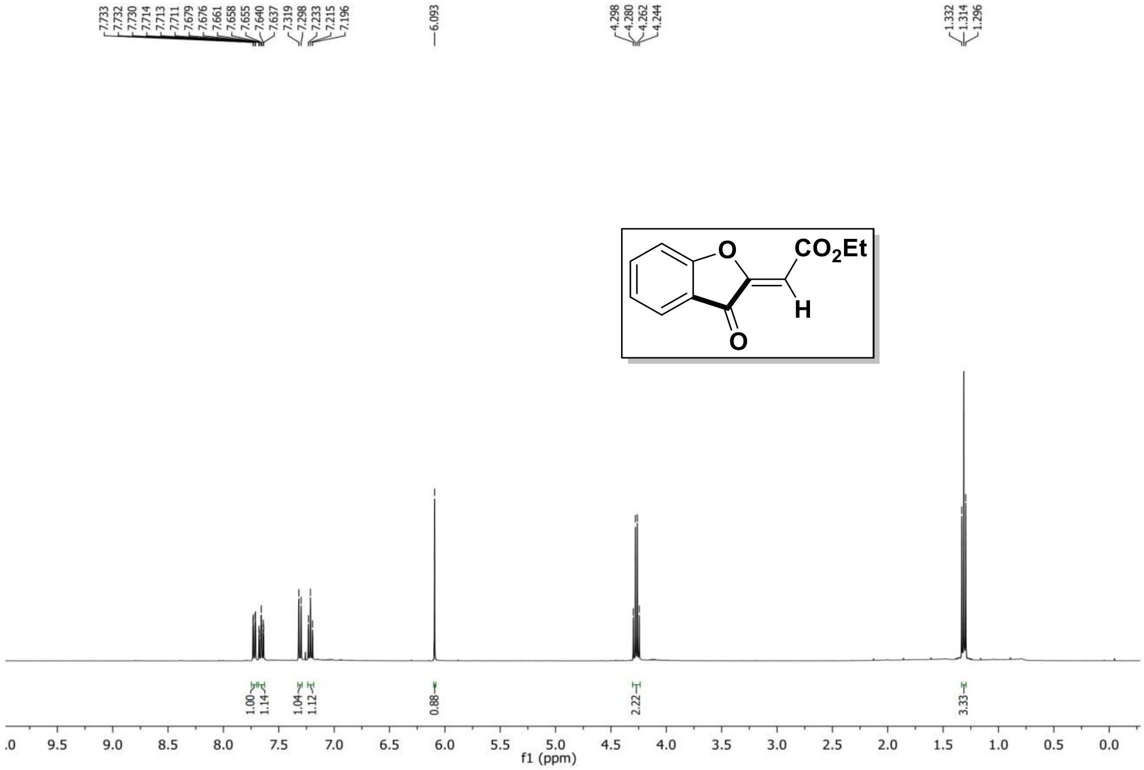
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (1a): ^{1}H NMR (400 MHz, CDCl$_3$):



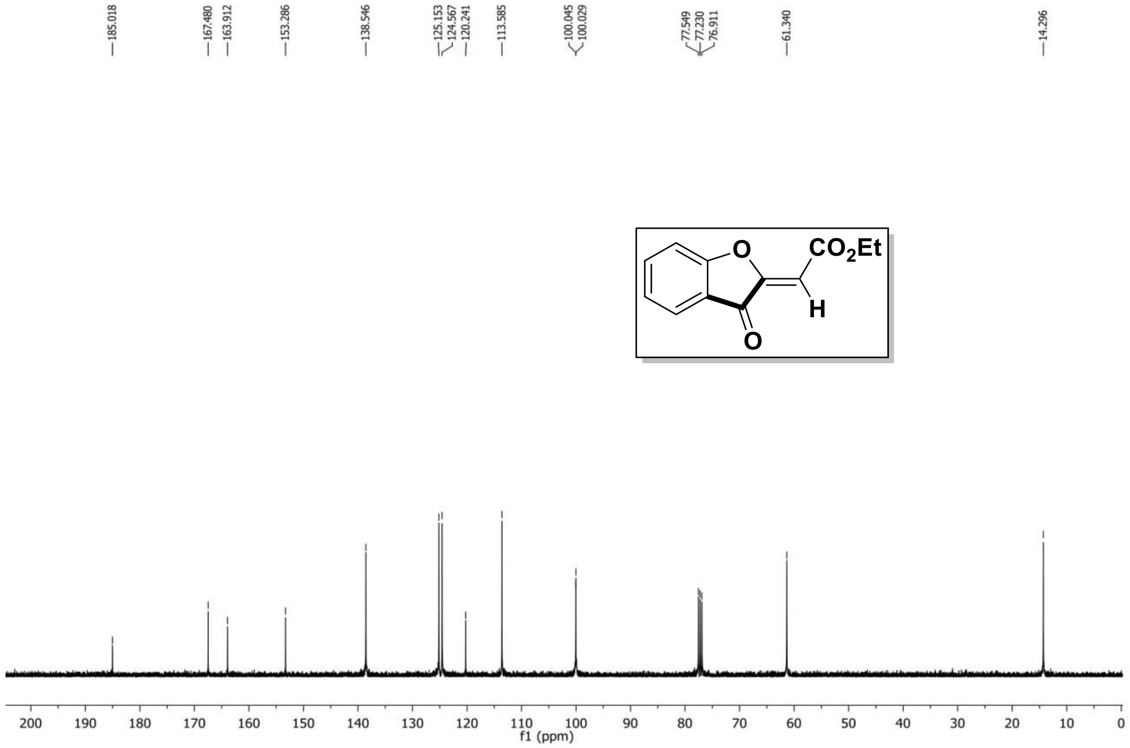
(*Z*)-Ethyl 2-((*E*)-3-(*tert*-butylimino)benzofuran-2(3*H*)-ylidene)acetate (1a): ^{13}C NMR (100 MHz, CDCl$_3$):



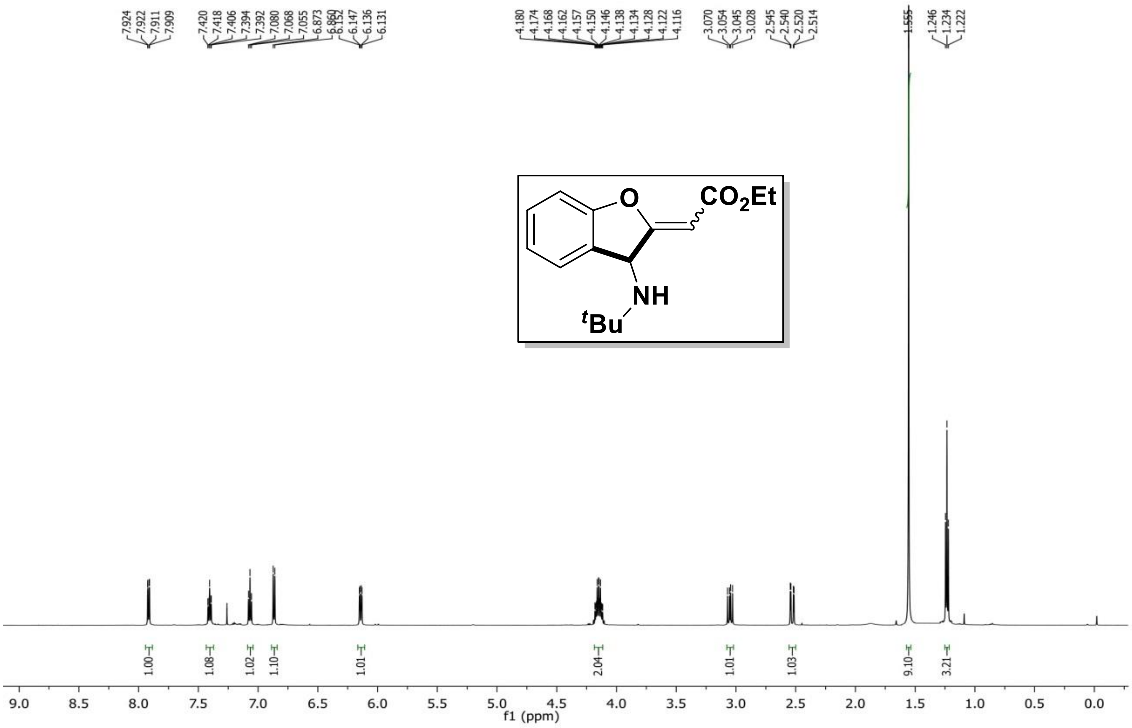
(*Z*)-Ethyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (1a′): ^{1}H NMR (400 MHz, CDCl$_3$):



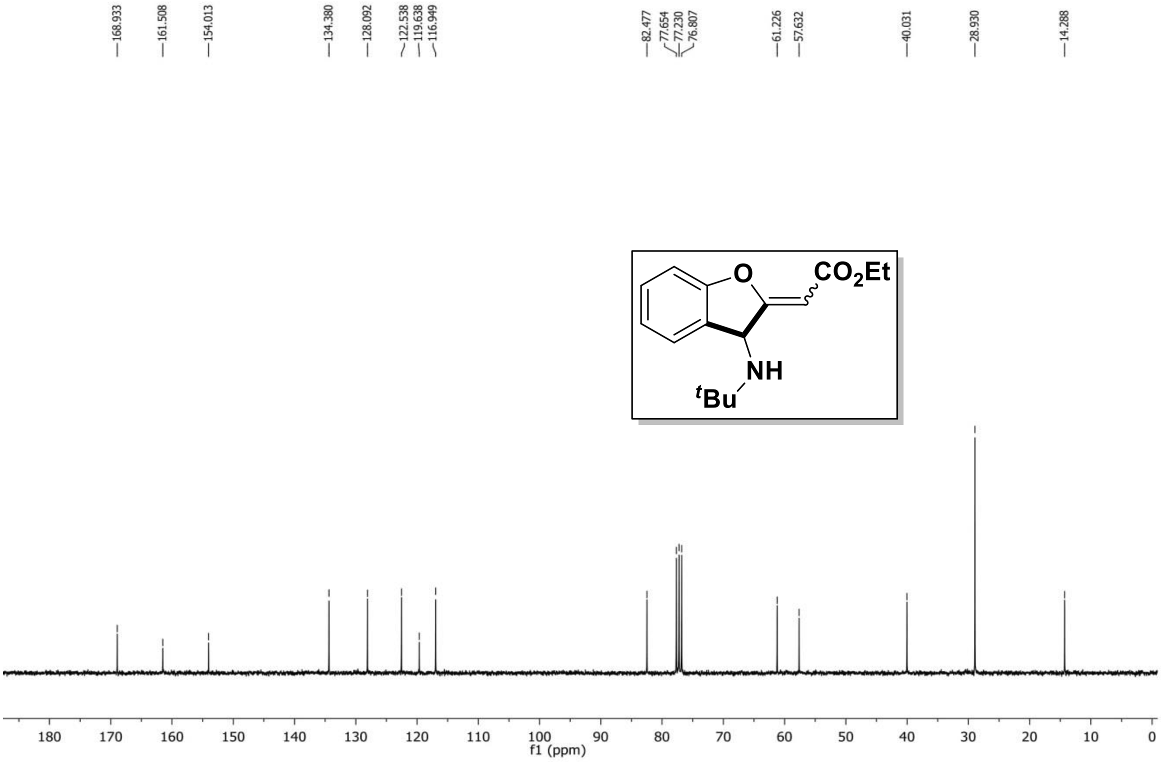
(*Z*)-Ethyl 2-(3-oxobenzofuran-2(3*H*)-ylidene)acetate (1a′): ^{13}C NMR (100 MHz, CDCl$_3$):



Ethyl 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (1a″): ^{1}H NMR (600 MHz, CDCl$_3$):

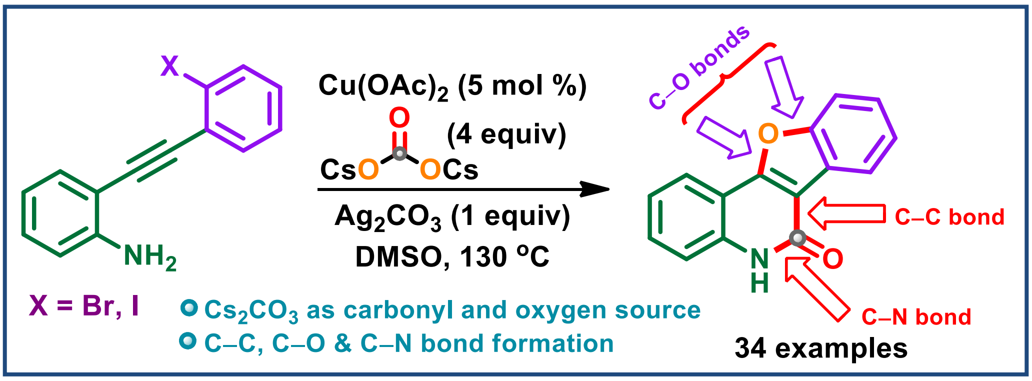


Ethyl 2-(3-(*tert*-butylamino)benzofuran-2(3*H*)-ylidene)acetate (1a″): ^{13}C NMR (75 MHz, CDCl$_3$):



Chapter VA

Cs_2CO_3 as a Source of Carbonyl and Ethereal Oxygen in a Cu-Catalyzed Cascade Synthesis of Benzofuran[3,2-c] quinolin-6[5-H]ones



Abstract: *The simultaneous construction of C–C, C–O, and C–N bonds utilizing Cs_2CO_3 as a source of both carbonyl (CO) and ethereal oxygen for a cascade synthesis of benzofuro[3,2-c]quinolin-6(5H)-one have been achieved using a combination of $Cu(OAc)_2$ and Ag_2CO_3. A plausible mechanism has been proposed for this unprecedented transformation. This reaction tolerates a wide range of functional groups and proceeds efficiently to give the product in moderate to good yields.*

CHAPTER VA

VA. Cs_2CO_3 as a Source of Carbonyl and Ethereal Oxygen in a Cu-Catalyzed Cascade Synthesis of Benzofuran[3,2-*c*] quinolin-6[5-*H*]ones

VA.1. Introduction

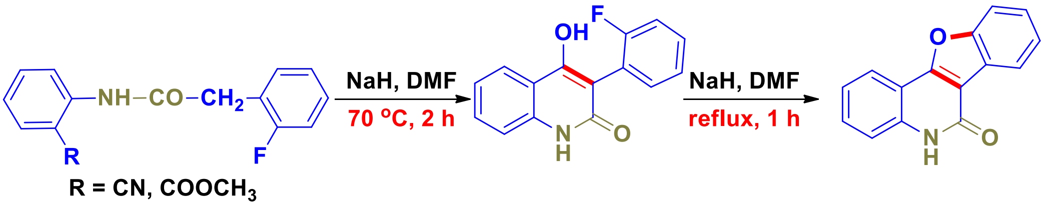
In the modern era of organic chemistry, the synthesis of highly functionalized and structurally diverse heterocycles is a challenging task. In this regard, domino reactions are most promising approach for the synthesis of complex organic molecules.[1] Formation of multiple C–C and C–heteroatom bonds for rapid access to fused and complex polycyclic skeletons is an attractive feature of any domino reaction. Recently, the strategy has emerged as a powerful “Synthetic Avenue” for the conversion of internal alkynes into biologically interesting polycycles[2] or spiro heterocycles.[3] Alkyne tethered substrates possessing nucleophilic groups at appropriate positions are often utilized as substrates for metal-catalyzed cascade transformations.[4] Such substrates may be prefunctionalized with a nucleophile or the desired functionality may be introduced into the substrate via Ullmann type cross-coupling reactions *in situ*. Copper as a catalyst has a great potential in initiating both Ullmann coupling as well as triggering cascade reactions.[5] Hence of late, copper-catalyzed domino synthesis of cyclic compounds in combination with Ullmann coupling has received much attention.[6]

VA.2. Strategies for the Synthesis of Benzofuro[3,2-*c*]quinolin-6(5*H*)-one

Benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives are reported to show activity against osteoporosis and malaria.[7] Despite the biological activity of the molecule surprisingly, literature contains only a few reports describing the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones.[7,8]

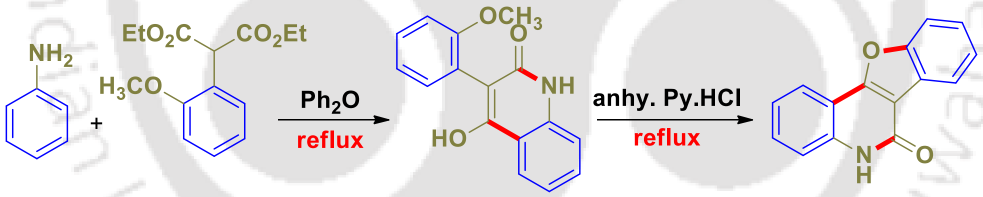
The benzofuro[3,2-*c*]quinolin-6(5*H*)-one molecule synthesized by Walser *et al.* in a two-step process is the only representative example for a long period of time.[7a] This protocol involves heating of *N*-(2-cyanophenyl)-2-(2-fluorophenyl)acetamide or methyl 2-(2-(2-fluorophenyl)acetamido)benzoate in the presence of sodium hydride (NaH) in

DMF at 70 °C followed by the heating of the isolated intermediate 3-(2-fluorophenyl)-4-hydroxyquinolin-2(1*H*)-one at reflux temperature under similar reaction condition (Scheme VA.2.1).



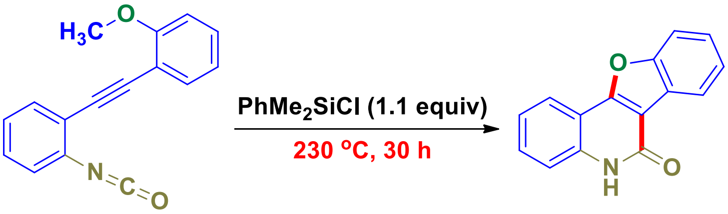
Scheme VA.2.1. *NaH-mediated synthesis of benzofuro[3,2-c]quinolin-6(5H)-one*

Later, Li *et al.* developed a methodology for the synthesis of compound containing lactam moiety acting as potential Pfmrk inhibitors.[7b] They achieved their target molecule in a two-step reaction by reacting aniline with diethyl 2-(2-methoxyphenyl)malonate at reflux temperature in diphenyl ether (Ph_2O) solvent. The intermediate 4-hydroxy-3-(2-methoxyphenyl)quinolin-2(1*H*)-one formed in the previous step is transformed into the desired product benzofuro[3,2-*c*]quinolin-6(5*H*)-one by refluxing it in anhydrous pyridine hydrochloride (Scheme VA.2.2).



Scheme VA.2.2. *By reaction of anilines with diethyl 2-(2-methoxyphenyl)malonates*

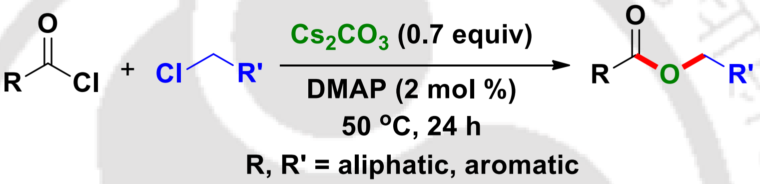
Wang and co-worker developed a one-step protocol for the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-one by the thermolysis of enyne-isocyanates in the presence of dimethylphenylsilylchloride ($PhMe_2SiCl$).[8] A biradical or zwitterion type of mechanism has been proposed for this transformation (Scheme VA.2.3).



Scheme VA.2.3. *Thermolysis of enyne-isocyanates in the presence of $PhMe_2SiCl$*

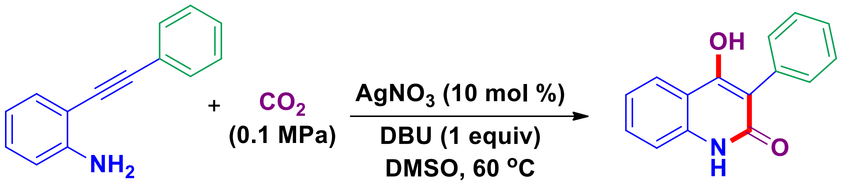
➢ Cs_2CO_3 at a Glance:

Alkali metal carbonates are among the most important and widely used classes of weak base in organic synthesis. In many of the organic reaction Cs_2CO_3 is supposed to be the base of choice if properties related to large cations are required for a reaction to proceed. Cs_2CO_3 is also well known in term of its utility in many of the transition metal catalyzed coupling reactions. Besides this, it is also well established that metal carbonates and bicarbonates acts as CO_2 source in many organic reactions. It has been reported that Cs_2CO_3 serves as a CO_2 source for the synthesis of cyclic or acyclic carbonates.[9] Recently, Cs_2CO_3 as an oxygen source for the synthesis of ester by the coupling of acid chloride and alkyl halide has been reported by Gao *et al.* (Scheme VA.2.4).[10] From the labeling experiment they proved that oxygen in ester moiety originated from Cs_2CO_3.



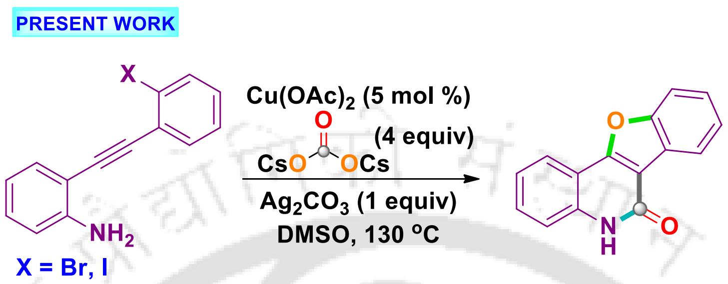
Scheme VA.2.4. *Cs_2CO_3 as oxygen source in ester synthesis*

So far, the synthesis of biologically active heterocycles using CO_2 generated from metal carbonates is unfamiliar. On the other hand, gaseous CO_2 has been extensively utilized for the synthesis of carbonates, acid, ester and lactone, etc.[11] Silver-catalyzed incorporation of gaseous CO_2 in a variety of internal and terminal alkynes, allenes, *o*-alkynylacetophenone, and allylsilane as well as carboxylation of terminal alkynes are summarized by Yamada *et al.*[12a] in his recent review. This inserted CO_2 undergoes various kind of rearrangements to afford various heterocycles.[12] One of the representative example of CO_2 insertion into the internal alkyne for the synthesis of 4-hydroxyquinolin-2(1*H*)-one derivatives through re-arrangement is shown below (Scheme VA.2.5).[12g]



Scheme VA.2.5. *CO_2 insertion into internal alkyne*

Similarly, Cu(II)-catalyzed incorporation of CO_2 into alkene, alkyne, allene and other systems has been reported by various other groups.[13] To the best of knowledge a cascade synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones is being reported for the first time utilizing CO_2 from Cs_2CO_3 as the source of carbonyl and ethereal oxygen (Scheme VA.2.6).



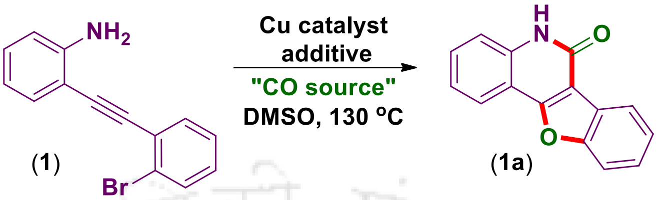
Scheme VA.2.6. *Cs_2CO_3 as carbonyl and oxygen source in heterocycle synthesis*

VA.3. Present Work

In continuation of our effort towards copper-catalyzed synthesis of heterocycles,[14] when 2-((2-bromophenyl)ethynyl)aniline (**1**) was treated with L-alanine in the presence of $Cu(OAc)_2$ and Cs_2CO_3 in dimethyl sulphoxide (DMSO) at 130 ^{o}C a product was isolated in 57% yield (Table VA.3.1, entry 1). Spectroscopic analysis (NMR, IR and HRMS) and subsequent crystal structure determination of one of its derivatives confirm its structure to be benzofuro[3,2-*c*]quinolin-6(5*H*)-one (**1a**) (Scheme VA.2.6). The product structure demonstrates a few interesting facets of this transformation *viz.* the incorporation of carbonyl as well as an ethereal oxygen functionality in the resultant heterocycle and their origin. The unique feature of this heterocycle (**1a**) is the simultaneous formation of three types of bonds *viz.* two C–O, a C–C and a C–N bond.

To determine the origin of the carbonyl group in product (**1a**) some control reactions were carried out. The probable source of carbonyl functionality is either the carboxyl group of L-alanine or Cs_2CO_3. A control reaction was carried out under otherwise identical conditions, but in the absence of L-alanine which gave the same product (**1a**) in similar yield, confirming L-alanine not to be the source of the carbonyl group. This suggests Cs_2CO_3 to be the possible source of the carbonyl group in (**1a**) (Table VA.3.1, entry 2). To check whether other inorganic carbonates or bicarbonates could be possible replacement for Cs_2CO_3; reactions were performed with other inorganic bases (Table VA.3.1, entries 3–6) such as K_2CO_3, Na_2CO_3, $KHCO_3$ and $NaHCO_3$. While K_2CO_3 gave the product in < 8% (Table VA.3.1, entry 3), all other basic salts were completely unproductive suggesting Cs_2CO_3 to be the ideal source of the carbonyl group in (**1a**).

Table VA.3.1. *Optimization of carbonyl source, their quantity and additives*[a]



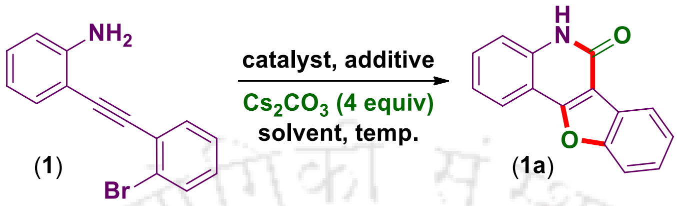
Entry	Catalyst (mol %)	CO Source (equiv)	Additive (equiv)	Yield[b]
1	$Cu(OAc)_2$ (10)	Cs_2CO_3 (3)	L-alanine (2)	57
2	$Cu(OAc)_2$ (10)	Cs_2CO_3 (3)	-	55
3	$Cu(OAc)_2$ (10)	K_2CO_3 (3	-	< 8
4	$Cu(OAc)_2$ (10)	Na_2CO_3(3)	-	00
5	$Cu(OAc)_2$ (10)	$KHCO_3$ (3)	-	00
6	$Cu(OAc)_2$ (10)	$NaHCO_3$ (3)	-	00
7	**$Cu(OAc)_2$ (10)**	**Cs_2CO_3 (4)**	**-**	**62**
8	$Cu(OAc)_2$ (10)	Cs_2CO_3 (6)	-	63

[a] Reaction conditions: 2-((2-bromophenyl)ethynyl)aniline (**1**) (0.2 mmol), $Cu(OAc)_2$ (10 mol %), CO source, additives, DMSO (3 mL), 130 °C, 24 h. [b] Isolated yield.

Optimization of Reaction Conditions: Intrigued by this unprecedented outcome, further screening of the reaction parameters were carried out to enhance the efficacy of this cascade cyclization using 2-((2-bromophenyl)ethynyl)aniline (**1**) as a model substrate. Initially, various copper salts such as $Cu(OAc)_2$ (62%), $Cu(OTf)_2$ (61%), $Cu(C_5HF_6O_2)_2$ (57%), $CuBr_2$ (52%), $CuCl_2$ (58%), CuI (60%), CuBr (56%) and CuCl (51%), were scrutinized (Table VA.3.2, entries 1–9). As can be seen from Table VA.3.2 all the copper salts tested gave the product (**1a**) in comparable yields. However, the reaction was cleaner with few side products using $Cu(OAc)_2$ (Table VA.3.2, entry 1). The use of Ag_2CO_3 as an additive enhanced the yield of the cyclized product by further 6% (Table VA.3.2, entry 10). The incremental improvement in product yield using Ag_2CO_3 leaves the question whether it is also acting as a carbonyl source similar to Cs_2CO_3. To find an answer to this, a reaction was performed under otherwise identical conditions but using Ag_2CO_3 (4 equiv) in lieu of Cs_2CO_3 (Table VA.3.2, entry 11). A complete failure to form product (**1a**) reaffirms that Cs_2CO_3 is the sole source of carbonyl functionality and Ag_2CO_3 might be helping during the cyclization step. Using $Cu(OAc)_2$ as a catalyst and Cs_2CO_3 as the carbonyl source, other silver salts like $Ag(OCOCF_3)$ and $Ag(OSO_2CF_3)$ were examined

(Table VA.3.2, entry 12 and 13); however Ag_2CO_3 turned out to be the most effective (Table VA.3.2, entry 10). Increasing the catalyst loading to 20 mol % was not beneficial in giving better yield (Table VA.3.2, entry 14). A lower catalyst loading (5 mol %) was equally effective to that of higher catalyst loading (10 mol %) (Table VA.3.2, entry 15). An identical reaction carried out in the absence of $Cu(OAc)_2$ gave a lower yield of the product (< 10) suggesting the active role of copper in the overall transformation (Table VA.3.2, entry 16). Besides DMA and DMF which provided the desired product in 10% and 6% (Table VA.3.2, entry 17 and 18) respectively, other solvents such as mesitylene and DCE (Table VA.3.2, entry 19 and 20) were completely ineffective in bringing about this transformation. Any increase (150 °C) or decrease (110 °C) in the reaction

Table VA.3.2. *Screening of reaction conditions*[a]



Entry	Catalyst (mol %)	Additive (equiv)	Solvent	Temp. (°C)	Yield[b]
1	$Cu(OAc)_2$ (10)	-	DMSO	130	62
2	$Cu(OTf)_2$ (10)	-	DMSO	130	59
3	$Cu(C_5HF_6O_2)_2$ (10)	-	DMSO	130	53
4	$CuBr_2$ (10)	-	DMSO	130	52
5	$CuCl_2$ (10)	-	DMSO	130	56
6	CuI (10)	-	DMSO	130	60
8	CuBr (10)	-	DMSO	130	56
9	CuCl (10)	-	DMSO	130	51
10	$Cu(OAc)_2$ (10)	Ag_2CO_3 (1)	DMSO	130	69
11	$Cu(OAc)_2$ (10)	Ag_2CO_3 (4)	DMSO	130	00
12	$Cu(OAc)_2$ (10)	$Ag(OCOCF_3)$ (1)	DMSO	130	61
13	$Cu(OAc)_2$ (10)	$Ag(OSO_2CF_3)$ (1)	DMSO	130	54
14	$Cu(OAc)_2$ (20)	Ag_2CO_3 (1)	DMSO	130	69
15	**$Cu(OAc)_2$ (5)**	**Ag_2CO_3 (1)**	DMSO	130	**67**
16	-	Ag_2CO_3 (1)	DMSO	130	< 10
17	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	DMA	130	< 10
18	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	DMF	130	< 6
19	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	Mesitylene	130	00
20	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	DCE	130	00
21	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	DMSO	150	59
22	$Cu(OAc)_2$ (5)	Ag_2CO_3 (1)	DMSO	110	53

[a] Reaction conditions: 2-((2-bromophenyl)ethynyl)aniline (**1**) (0.2 mmol), copper salts, Cs_2CO_3 (0.8 mmol), additives, solvent (3 mL), temperature, time 24 h. [b] Isolated yield.

temperature does not serve the purpose (Table VA.3.2, entry 21 and 22). Finally, the optimized conditions for this transformation is the use of $Cu(OAc)_2$ (5 mol %), Cs_2CO_3 (4 equiv), Ag_2CO_3 (1 equiv) in DMSO (3 mL) at 130 °C.

Substrate Scope for Benzofuro[3,2-*c*]quinolin-6(5*H*)-ones Synthesis: With the above optimized conditions in hand, we set out to explore the generality and scope of this protocol and the experimental results are summarized in Scheme VA.3.1. Initially, the effect of substituents on the amine bearing ring was explored. The presence of electron-donating groups such as *p*-CH_3 (**2**), *p*-Bu (**3**), *p*-^{i}Pr (**4**), and *p*-^{t}Bu (**5**) on the aromatic ring produced their corresponding products (**2a**–**5a**) in yields ranging between 62–64%. The yields obtained were lower than that of un-substituted analogue (**1a**). The yield plunge further, when the electron-donating –CH_3 group is present at the C3 and C4 position of the amine bearing ring as in (**6a**). The presence of moderately electron-withdrawing groups such as *p*-Cl (**7**), *p*-F (**8**) gave identical yields of their products (**7a**, 70%) and (**8a**, 73%) to that of the un-substituted analogue (**1a**). The structure of the product (**8a**) has been unequivocally established by single crystal X-ray crystallography (Figure VA.3.1). The presence of the strongly electron-withdrawing group *p*-CN (**9**) provided an inferior yield (54%) of the product (**9a**). The position of substitution of moderately electron-withdrawing groups i.e. *m*-Cl (**10**) and *m*-F (**11**), have no significant effect on yields [(**10a**, 68%) and (**11a**, 69%)] compare to the *para* analogues (**7a**) and (**8a**) as is depicted in Scheme VA.3.1. A similar trend in electronic effect was observed for both electron-donating and electron-withdrawing substituents when present in the other ring. The presence of electron-donating groups such as *p*-CH_3 (**12**) and *p*-Bu (**13**) on the halogen bearing aromatic ring gave products (**12a**) and (**13a**) in 60% and 61% yields, respectively. Here again, when electron-donating –CH_3 group is present at the C3 and C4 positions as in (**14**) its product (**14a**) was isolated in 54% yield.

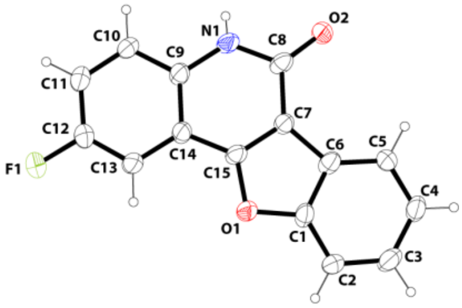
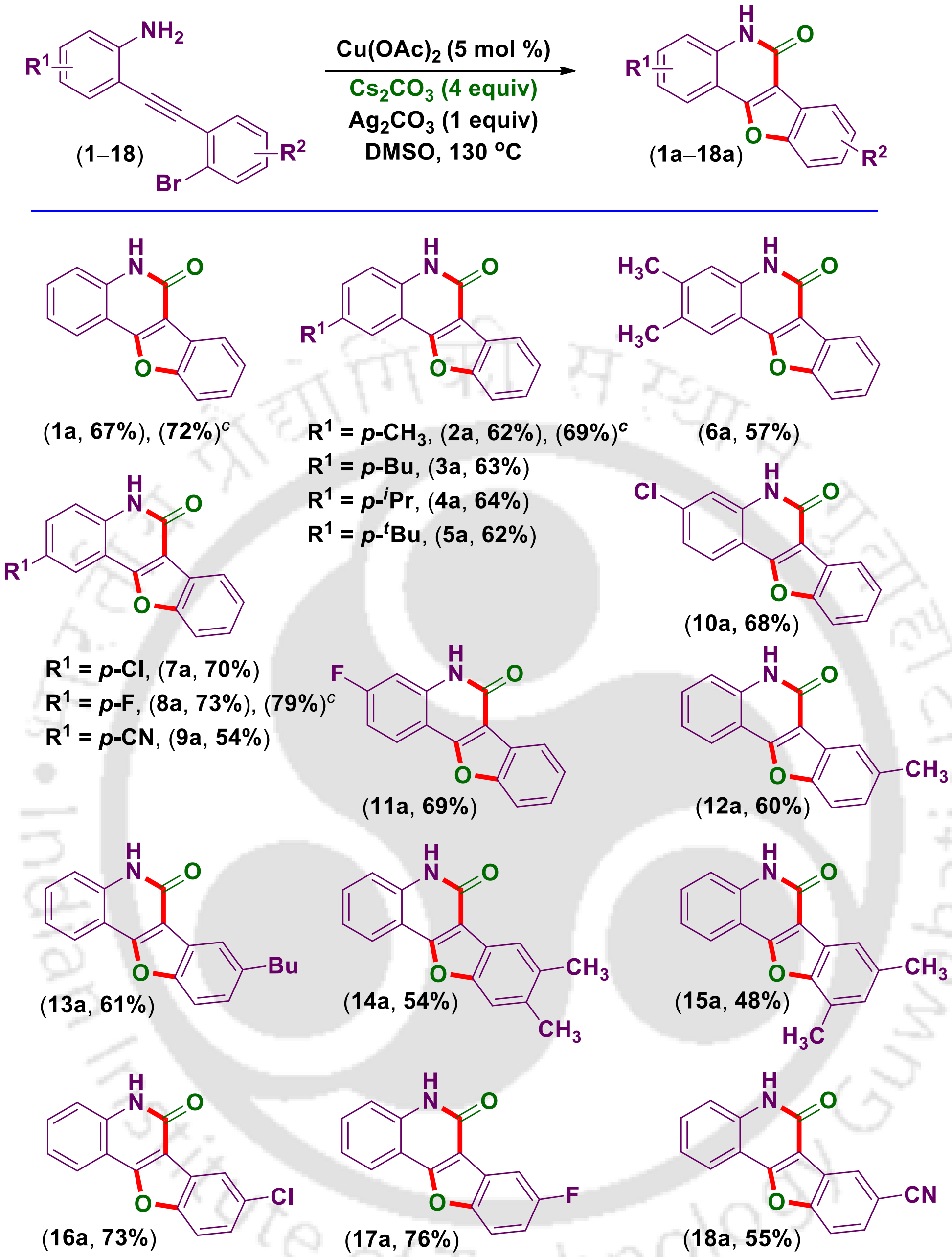


Figure VA.3.1. *ORTEP view of (**8a**)*

Scheme VA.3.1. *Substrate scope of cascade cyclization*[ab]

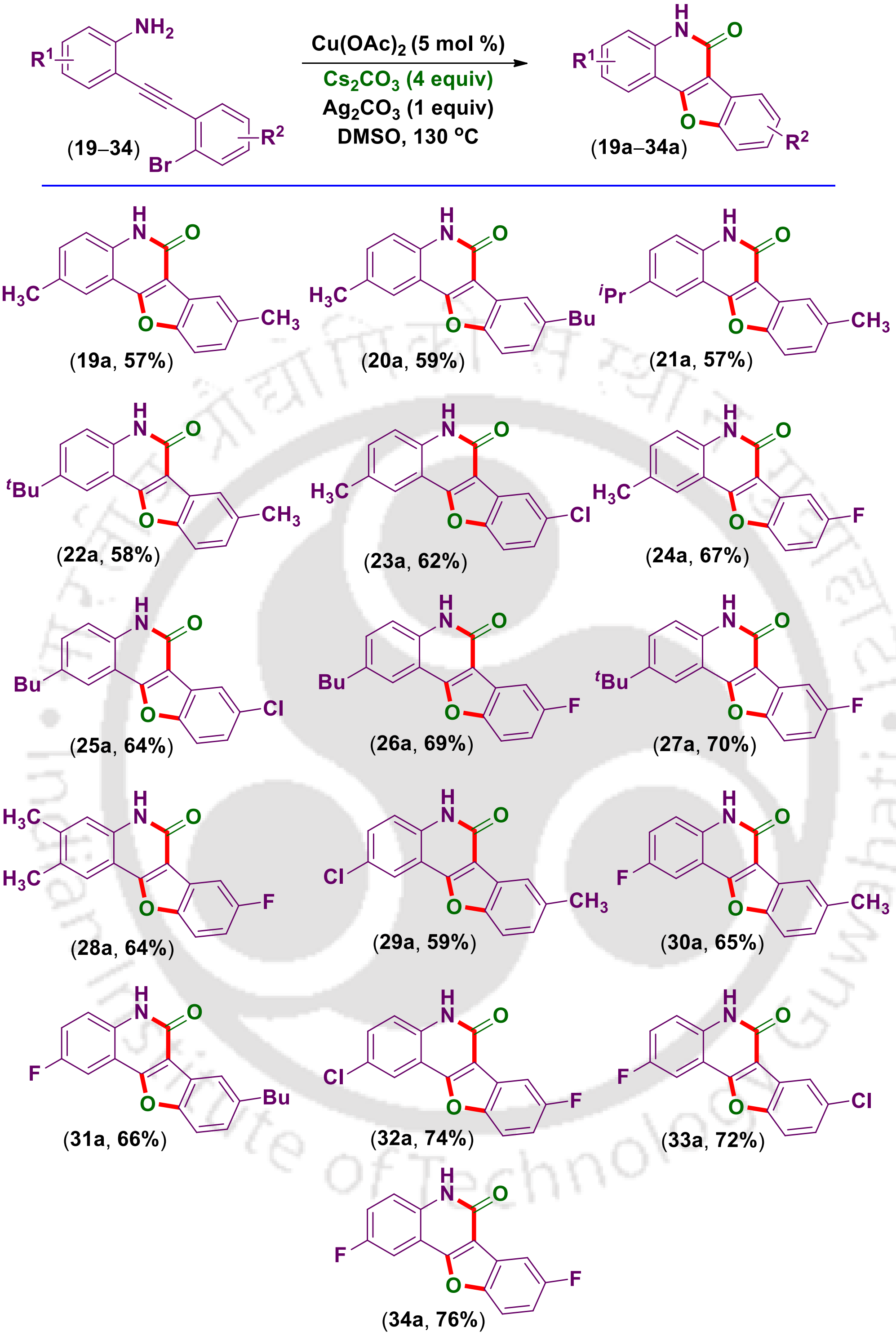


[a]Reaction conditions: **1–18** (0.2 mmol), $Cu(OAc)_2$ (5 mol %), Cs_2CO_3 (0.8 mmol, 4 equiv), Ag_2CO_3 (0.2 mmol, 1 equiv), DMSO (3 mL) at 130 °C for 24 h. [b]Isolated pure product. [c]Raction performed with iodo substrates

However, when the $-CH_3$ group is present at the C2 and C4 positions as in (**15**) the yield of the corresponding product (**15a**) dropped to 48% which is due to both steric and electronic factors. Further, moderately electron-withdrawing groups such as *p*-Cl (**16**) and *p*-F (**17**) in the halogen bearing aromatic ring gave marginally better yields of the product [(**16a**, 73%) and (**17a**, 76%)] than when they were in the amine bearing ring (**7a** and **8a**). Coincidently, a similar yield of the product (**18a**, 55%) was observed even when the electron-withdrawing –CN (**18**) group is present on the other ring. In any cascade reaction several bond making and bond breaking process takes place in multiple directions bearing substituents at various sites. Thus, it is difficult to correlate the true electronic factors and ascertain the exact rate determining step in the reaction on the basis of the final yields. When bromo was replaced with an iodo group, the yields of products were marginally improved than their bromo analogue as demonstrated by the synthesis of (**1a**), (**2a**) and (**8a**) (Scheme VA.3.1).

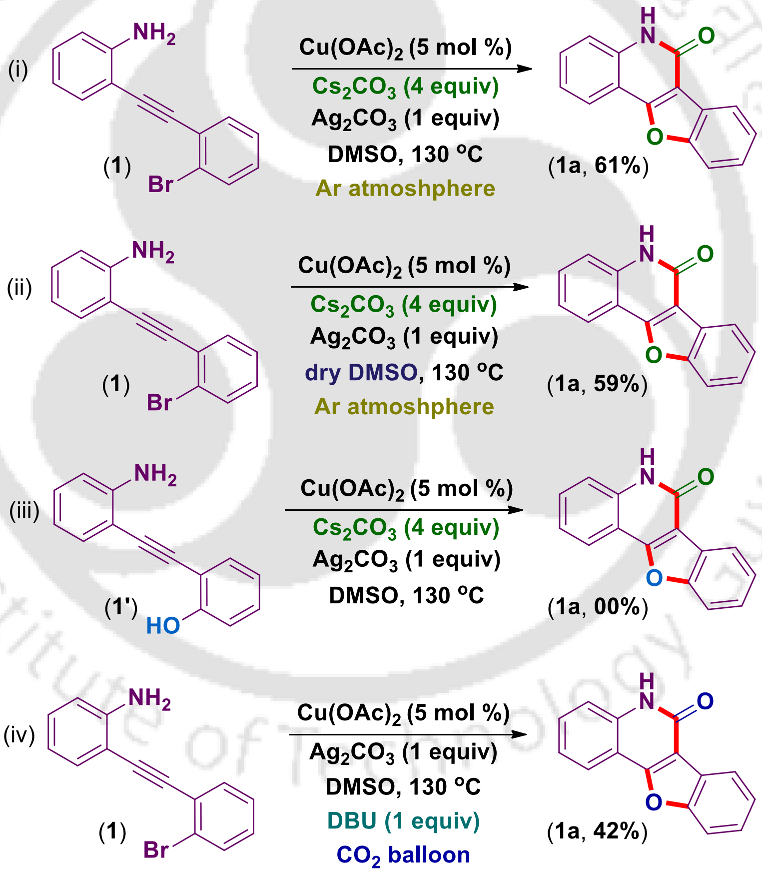
Next, variation in the nature of substituents on both the aryl rings was explored (Scheme VA.3.2). When both the rings possess sets of electron-donating groups such as *p*-CH_3/*p*-CH_3 (**19**), *p*-CH_3/*p*-Bu (**20**), *p*-^{i}Pr/*p*-CH_3 (**21**) and *p*-^{t}Bu/*p*-CH_3 (**22**), lesser yields (57%–59%) of their cyclized products (**19a–22a**) were obtained. On the other hand, when the amine bearing ring is substituted with electron-donating and the other ring with electron-withdrawing groups such as *p*-CH_3/*p*-Cl (**23**), *p*-CH_3/*p*-F (**24**), *p*-Bu/*p*-Cl (**25**), *p*-Bu/*p*-F (**26**), *p*-^{t}Bu/*p*-F (**27**) and 3,4-diCH_3/*p*-F (**28**), the yields of the cascade products (**23a–28a**) isolated were marginally better (in the range of 62–70%). Further, when the amine bearing ring is substituted with electron-withdrawing and the other ring with electron-donating groups *p*-Cl/*p*-CH_3 (**29**), *p*-F/*p*-CH_3 (**30**) and *p*-F/*p*-Bu (**31**) their products (**29a**), (**30a**) and (**31a**) were obtain in 59%, 65% and 66% yield, respectively. Coincidently, the observed trend in yields follows a similar pattern when substituents were swapped across the rings (Scheme VA.3.2). Better yields of the products were obtained when both the rings were substituted with electron-withdrawing groups such as *p*-Cl/*p*-F (**32a**, 74%), *p*-F/*p*-Cl (**33a**, 72%) and *p*-F/*p*-F (**34a**, 76%).

Scheme VA.3.2. *Substrate scope of cascade cyclization*[ab]



[a] Reaction conditions: **19–34** (0.2 mmol), $Cu(OAc)_2$ (5 mol %), Cs_2CO_3 (0.8 mmol, 4 equiv), Ag_2CO_3 (0.2 mmol, 1 equiv), DMSO (3 mL) at 130 °C for 24 h. [b] Isolated pure product.

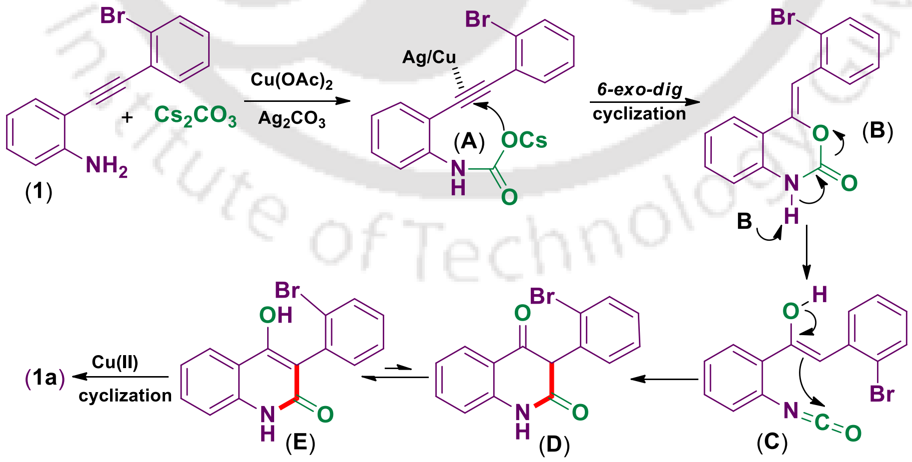
Mechanistic Studies: To understand the nature of this unprecedented carbonylation-etherification process and to gain insight into the reaction mechanism, further investigations were carried out (Scheme VA.3.3). The source of carbonyl in the quinolone part has already been accounted for; however the source of ethereal oxygen in the benzofuran ring is yet to be ascertained. Previously, we envisaged that the possible source of ethereal oxygen could be either the aerial oxygen or the traces of water present in commercial grade DMSO. Comparable yield of (**1a**) was obtained when the reaction was performed under an argon atmosphere, suggesting aerial oxygen not to be the source of benzofuran oxygen (Scheme VA.3.3.i). Another reaction performed using anhydrous DMSO under an inert atmosphere under otherwise identical conditions, gave the desired product (**1a**) in 59% yield (Scheme VA.3.3.ii). This result ruled out moisture/H_2O in commercial grade DMSO being the source of ethereal oxygen in (**1a**). This leaves Cs_2CO_3 as the only possible source of oxygen in benzofuran moiety.[10]



Scheme VA.3.3. *Mechanistic investigations*

There are reports where aryl halides undergoes hydroxylation in the presence of a base and copper catalyst.[15] During this cascade cyclization, the *ortho* bromo group is replaced with an oxygen atom therefore, initial *ortho* hydroxylation via copper catalysis with an appropriate oxygen source (possibly Cs_2CO_3) cannot be completely ruled out. To check the possibility of hydroxylation path, subjecting the presynthesized 2-((2-aminophenyl)ethynyl)phenol (**1′**) to the presented reaction conditions failed to give the expected product (**1a**) even after 36 h (Scheme VA.3.3.iii). This ruled out any possibility of initial hydroxylation via Ullmann coupling path. During the synthesis of 4-hydroxyquinolin-2(1*H*)-ones the carbonyl and oxygen both originate from CO_2 via the intermediacy of isocyanate as demonstrated by Yamada *et al.*[12g] Thus, a reaction was carried out under a CO_2 atmosphere using DBU as the base but in the absence of Cs_2CO_3 under similar reaction conditions (Scheme VA.3.3.iv). The formation of product (**1a**) in 42% yield suggests that both ethereal oxygen and the carbonyl groups originate from CO_2, (i.e. Cs_2CO_3).

Based on the above experimental results, a probable reaction pathway is illustrated in Scheme VA.3.4. The process starts with the an initial *N*-carboxylation with Cs_2CO_3 to give species (**A**), which undergo *6-exo-dig* cyclization assisted by Cu/Ag salts giving a cyclic carbamate intermediate (**B**). A base mediated ring opening of intermediate (**B**) gave intermediate isocyanate (**C**). Intermediate (**C**) undergoes intramolecular cyclization (C–C bond formation) to generate a 1,3-diketone intermediate (**D**). Enolization of (**D**) to (**E**) followed by an intramolecular Ullmann coupling (C–O bond formation) produces benzofuro[3,2-*c*]quinolin-6(5*H*)-one (**1a**) (Scheme VA.3.4). The formations of intermediates (**B**), (**C**), (**D**) and (**E**) in the reaction was detected by HRMS analysis of the reaction mixture at various time intervals.



Scheme VA.3.4. *Plausible mechanism for Cs_2CO_3 acting as both carbonyl and oxygen source*

In conclusion, we have developed a novel protocol for the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives catalyzed by Cu(II). Concomitant installation of three types of bonds *viz.* two C–O and both one C–C and one C–N achieved in a tandem process. In this carbonylation-etherification cascade process both carbonyl and ethereal oxygen originates from Cs_2CO_3.

VA.4. Experimental Section

VA.4.1. General Information: All the compounds were commercial grade and used without further purification. Organic extract were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduce 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 internal standard for proton NMR (400 and 600 MHz) $CDCl_3$ solvent as internal standard for ^{13}C NMR (100 and 150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

VA.4.2. Crystallographic Description

CCDC Number for Compounds 8a: CCDC 1453512. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 2-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (8a): Crystal dimensions 0.35 x 0.25 x 0.21 mm, M_r = 253.22, Triclinic, space group P 21 21 21 ,a = 5.4675(3), b = 9.3791(7), c = 11.1931(9)Å, α = 84.624° (5), β = 79.858° (4), γ = 82.835° (4), V = 559.09 (7)$Å^3$, Z = 2, ρ_{calcd} = 1.504g/cm^3, μ = 0.112mm^{-1}, F(000)= 260.0, reflection collected / unique = 1974 / 1921, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0759, wR_2 = 0.1537, R indices (all data): R_1 = 0.1528, wR_2 = 0.1537, goodness of fit = 0.931.

VA.4.3. Typical Procedure for the Synthesis of Benzofuro[3,2-*c*]quinolin-6(5*H*)-one (1a): A round bottom flask with a magnetic stir bar was charged with 2-((2-bromophenyl)ethynyl)aniline (**1**) (0.2 mmol, 54 mg), $Cu(OAc)_2$ (5 mol %, 0.01 mmol, 1.81 mg), Ag_2CO_3 (1 equiv, 0.2 mmol, 55 mg), Cs_2CO_3 (4 equiv, 0.8 mmol, 260 mg) in 3 mL of DMSO. The reaction mixture was stirred in a preheated oil bath at 130 °C. The reaction was taken out after 24 h and was diluted with EtOAc (15 mL) and filtered through a celite pad. Filtrate was washed with water (2 x 5 mL) and water layer was further extracted with ethyl acetate (2 x 5 mL). After evaporation of the solvent, the crude mixture was purified by silica gel column chromatography using hexane/ethyl acetate (4 : 1) as eluent to give product benzofuro[3,2-*c*]quinolin-6(5*H*)-one (**1a**) in (31.5 mg, 67% yield).

VA.5. References

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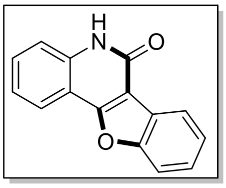
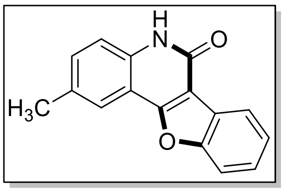
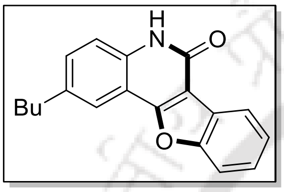
VA.6. Spectral Data



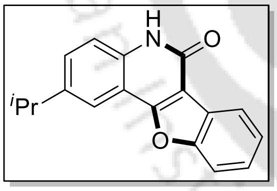
Benzofuro[3,2-*c*]quinolin-6(5*H*)-one (1a): Brown solid; M.p. 307–309 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.33 (t, 1H, *J* = 7.8 Hz), 7.45 (t, 1H, *J* = 7.2 Hz), 7.49–7.52 (m, 2H), 7.59 (t, 1H, *J* = 7.8 Hz), 7.80 (d, 1H, *J* = 6.6 Hz), 8.05 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 7.8 Hz), 12.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 110.0, 110.8, 111.7, 116.2, 121.1, 121.2, 122.3, 123.8, 124.5, 126.2, 130.7, 138.4, 154.8, 157.8, 159.1; IR (KBr): 2923, 2852, 1684, 1449, 1368, 1106, 1018, 734 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_9NO_2^+$ (MH$^+$) 236.0706; found 236.0714.



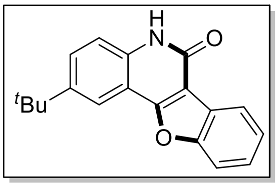
2-Methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (2a): Brown solid; M.p. 317–318 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.42 (s, 3H), 7.40–7.44 (m, 2H), 7.47 (t, 1H, *J* = 7.8 Hz), 7.51 (t, 1H, *J* = 7.8 Hz), 7.83 (t, 2H, *J* = 7.8 Hz), 8.10 (d, 1H, *J* = 7.2 Hz), 11.92 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.5, 110.0, 110.6, 111.8, 116.1, 120.6, 121.2, 123.9, 124.6, 126.3, 131.7, 132.2, 136.5, 154.8, 157.8, 159.0; IR (KBr): 2923, 2853, 1667, 1452, 1338, 1255, 1108, 744 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO_2^+$ (MH$^+$) 250.0863; found 250.0870.



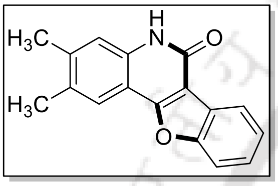
2-Butylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (3a): Brown solid; M.p. 211–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.89 (t, 3H, *J* = 7.6 Hz), 1.28–1.35 (m, 2H), 1.55–1.63 (m, 2H), 2.67 (t, 2H, *J* = 7.6 Hz), 7.43 (s, 2H), 7.46 (d, 1H, *J* = 7.6 Hz), 7.50 (t, 1H, *J* = 6.8 Hz), 7.81 (d, 2H, *J* = 6.4 Hz), 8.10 (d, 1H, *J* = 7.2 Hz), 11.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 21.7, 33.1, 34.2, 109.9, 110.6, 111.8, 116.2, 119.9, 121.2, 123.9, 124.6, 126.2, 131.5, 136.6, 136.7, 154.8, 157.8, 159.0; IR (KBr): 2957, 2924, 2854, 1664, 1450, 1180, 1086, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO_2^+$ (MH$^+$) 292.1332; found 292.1335.



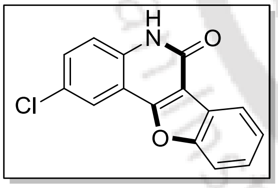
2-Isopropylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (4a): White solid; M.p. 257–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.28 (d, 6H, *J* = 6.8 Hz), 3.01–3.10 (m, 1H), 7.47 (t, 2H, *J* = 8.4 Hz), 7.50–7.56 (m, 2H), 7.85 (d, 1H, *J* = 8.0 Hz), 7.89 (s, 1H), 8.11 (dd, 1H, *J* = 7.6 Hz), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 23.9, 33.0, 109.9, 110.6, 111.8, 116.3, 117.8, 121.2, 123.9, 124.6, 126.3, 129.9, 136.8, 142.7, 154.8, 157.9, 159.0; IR (KBr): 2957, 2923, 2852, 1665, 1453, 1183, 1025, 887 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO_2^+$ (MH$^+$) 278.1176; found 278.1179.



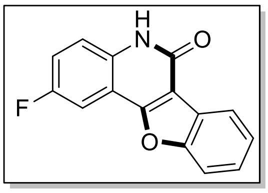
2-(Tert-butyl)benzofuro[3,2-*c*]quinolin-6(5*H*)-one (5a): Brown solid; M.p. 330–333 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.36 (s, 9H), 7.47 (d, 2H, J = 8.8 Hz), 7.52 (td, 1H, J = 7.2 Hz), 7.72 (dd, 1H, J = 8.8 Hz), 7.86 (d, 1H, J = 7.6 Hz), 7.96 (d, 1H, J = 2.0 Hz), 8.10 (dd, 1H, J = 7.6 Hz), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 31.1, 34.4, 109.9, 110.2, 111.9, 116.2, 116.5, 121.2, 123.9, 124.6, 126.2, 129.0, 136.5, 145.0, 154.8, 158.1, 159.1; IR (KBr): 2961, 2901, 2846, 1664, 1450, 1334, 1045, 994 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO_2^+$ (MH$^+$) 292.1332; found 292.1340.



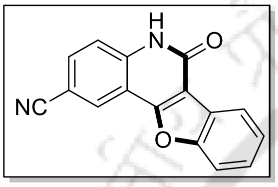
2,3-Dimethylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (6a): Light yellow solid; M.p. 295–298 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.30 (s, 6H), 7.24 (s, 1H), 7.43–7.51 (m, 2H), 7.76 (s, 1H), 7.79 (d, 1H, J = 8.0 Hz), 8.07 (d, 1H, J = 7.2 Hz), 11.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.0, 20.1, 108.7, 109.1, 111.7, 116.4, 120.9, 121.1, 124.0, 124.5, 126.0, 131.2, 136.9, 140.5, 154.6, 157.9, 159.1; IR (KBr): 2959, 2924, 2853, 1658, 1450, 1145, 1000, 864, 743 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2^+$ (MH$^+$) 264.1019; found 264.1025.



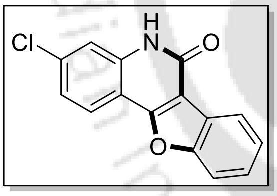
2-Chlorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (7a): Yellowish brown solid; M.p. 310–312 °C ;^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.48–7.57 (m, 3H), 7.66 (d, 1H, J = 8.8 Hz), 7.86 (d, 1H, J = 8.4 Hz), 8.07 (s, 1H), 8.11 (d, 1H J = 7.6 Hz), 12.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 110.9, 111.89, 111.94, 118.2, 120.3, 121.4, 123.5, 124.8, 126.5, 126.8, 130.8, 137.0, 154.9, 156.6, 158.8; IR (KBr): 2958, 2925, 2854, 1658, 1454, 1259, 1104, 1023, 810 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8ClNO_2^+$ (MH$^+$) 270.0316; found 270.0320.



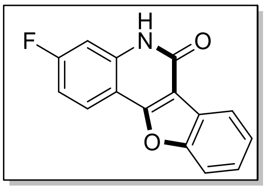
2-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (8a): Light brown solid; M.p. 303–305 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.46–7.56 (m, 4H), 7.83 (t, 2H, *J* = 8.0 Hz), 8.11 (d, 1H, *J* = 7.6 Hz), 12.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 106.3, 106.6, 110.9, 111.2, 111.3, 111.9, 118.3, 118.4, 118.9, 119.1, 121.4, 123.6, 124.8, 126.7, 135.1, 154.9, 156.1, 157.1, 158.5, 158.7; IR (KBr): 2958, 2925, 2854, 1658, 1454, 1259, 1104, 1023, 810 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8FNO_2^+$ (MH$^+$) 254.0612; found 254.0621.



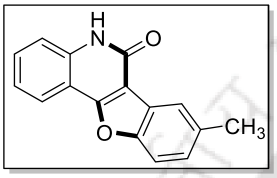
6-Oxo-5,6-dihydrobenzofuro[3,2-*c*]quinoline-2-carbonitrile (9a): Yellowish brown solid; M.p. 327–329 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.49 (t, 1H, *J* = 7.2 Hz), 7.57 (t, 2H, *J* = 8.8 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 7.6 Hz), 8.52 (s, 1H), 12.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 104.6, 111.1, 111.2, 112.0, 117.2, 118.6, 121.5, 123.3, 125.0, 126.5, 127.0, 133.2, 140.8, 154.9, 156.5, 159.0; IR (KBr): 2953, 2924, 2853, 2223, 1643, 1462, 1025, 997, 764 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_8N_2O_2^+$ (MH$^+$) 261.0659; found 261.0665.



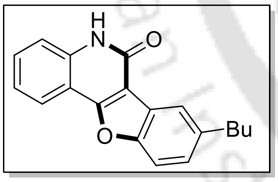
3-Chlorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (10a): Brown solid; M.p. 301–304 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.40 (d, 1H, *J* = 9.0 Hz), 7.49 (t, 1H, *J* = 7.2 Hz), 7.55 (t, 2H, *J* = 7.8 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.10 (t, 2H, *J* = 8.4 Hz), 12.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 109.7, 110.3, 111.9, 115.5, 121.3, 122.7, 123.1, 123.6, 124.8, 126.6, 135.2, 139.2, 154.9, 157.3, 159.0; IR (KBr): 2956, 2923, 2853, 1663, 1442, 1313, 1018, 953 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8ClNO_2^+$ (MH$^+$) 270.0316; found 270.0320.



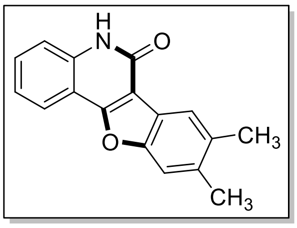
3-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (11a): Light yellow solid; M.p. 270–273 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.20–7.27 (m, 2H), 7.47 (dt, 1H, *J* = 7.6 Hz), 7.52 (dt, 1H, *J* = 7.2 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 8.06–8.13 (m, 2H), 12.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 102.1, 102.4, 107.9, 109.3, 110.7, 111.0, 111.9, 121.2, 123.7, 123.8, 123.9, 124.8, 126.4, 139.9, 140.1, 154.7, 157.5, 159.2, 162.0, 164.5; IR (KBr): 2956, 2922, 2853, 1662, 1462, 1358, 1094, 883 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8FNO_2^+$ (MH$^+$) 254.0612; found 254.0619.



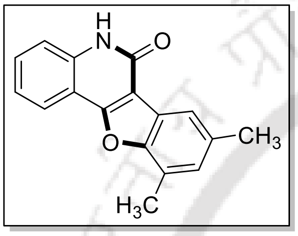
8-Methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (12a): Brown solid; M.p. 321–323 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.17 (s, 3H), 7.02 (d, 1H, *J* = 8.8 Hz), 7.08 (t, 1H, *J* = 7.2 Hz), 7.23 (d, 1H, *J* = 8.4 Hz), 7.34 (t, 1H, *J* = 7.2 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.59 (s, 1H), 7.75 (d, 1H, *J* = 8.0 Hz) 11.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.2, 109.9, 111.0, 111.6, 116.5, 121.2, 123.0, 123.8, 127.7, 131.2, 134.3, 138.2, 147.2, 153.3, 158.3, 159.5; IR (KBr): 3011, 2923, 2852, 1676,1459, 1189, 1136, 1086, 873 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}NO_2^+$ (MH$^+$) 250.0863; found 250.0860.



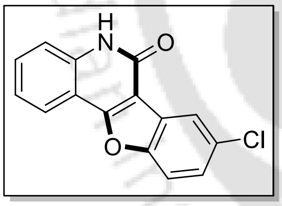
8-Butylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (13a): Brown solid; M.p. 245–247 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.89 (t, 3H, *J* = 7.2 Hz), 1.27–1.35 (m, 2H), 1.54–1.63 (m, 2H), 2.71 (t, 2H, *J* = 7.2 Hz), 7.28–7.33 (m, 2H), 7.49 (d, 1H, *J* = 8.8 Hz), 7.59 (t, 1H, *J* = 7.2 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.88 (s, 1H), 8.01 (d, 1H, *J* = 7.6 Hz) 12.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 21.8, 33.7, 34.7, 109.9, 110.8, 111.4, 116.2, 120.4, 121.1, 122.4, 123.8, 126.8, 130.7, 138.3, 138.9, 153.3, 158.0, 159.2; IR (KBr): 2955, 2924, 2853, 1661, 1458, 1187, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO_2^+$ (MH$^+$) 292.1332; found 292.1338.



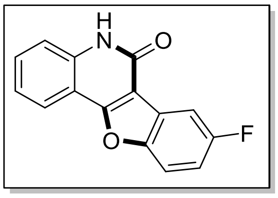
8,9-Dimethylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (14a): Dark yellow solid; M.p. 321–324 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.34 (s, 3H), 2.36 (s, 3H), 7.32 (t, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.57–7.60 (m, 2H), 7.84 (s, 1H), 8.01 (d, 1H, *J* = 8.0 Hz), 11.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.6, 20.2, 110.0, 110.9, 112.0, 116.1, 121.0, 121.2, 121.5, 122.4, 130.5, 133.0, 135.4, 138.1, 153.7, 157.2, 159.1; IR (KBr): 2923, 2852, 1664, 1455, 1400, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2^+$ (MH$^+$) 264.1019; found 264.1019.



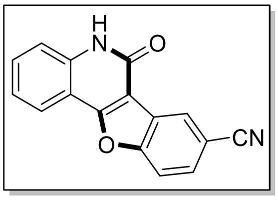
8,10-Dimethylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (15a): Brown solid; M.p. 324–326 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.40 (s, 3H), 2.54 (s, 3H), 7.08 (s, 1H), 7.32 (t, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.68 (s, 1H), 8.01 (d, 1H, *J* = 7.6 Hz), 11.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.7, 20.9, 110.1, 110.9, 116.1, 118.5, 120.8, 121.1, 122.3, 123.4, 128.3, 130.6, 133.8, 138.2, 152.1, 157.6, 159.2; IR (KBr): 2956, 2923, 2853, 1674, 1460, 1166, 1026, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2^+$ (MH$^+$) 264.1019; found 264.1025.



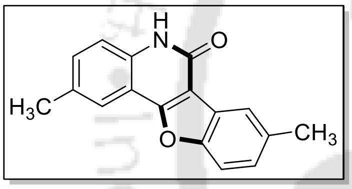
8-Chlorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (16a): Yellow solid; M.p. 334–337 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.36 (t, 1H, *J* = 7.6 Hz), 7.53 (t, 2H, *J* = 8.8 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.8 Hz), 8.01 (s, 1H), 8.04 (d, 1H, *J* = 8.0 Hz), 12.09 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 109.4, 110.5, 113.5, 116.3, 120.3, 121.3, 122.6, 125.5, 126.1, 129.0, 131.4, 138.7, 153.3, 158.7, 159.0; IR (KBr): 2924, 2853, 1670, 1444, 1335, 1140, 906, 819 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8ClNO_2^+$ (MH$^+$) 270.0316; found 270.0320.



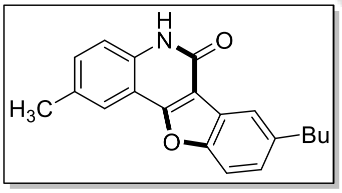
8-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (17a): Yellow solid; M.p. 346–348 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.35–7.40 (m, 2H), 7.52 (d, 1H, *J* = 8.0 Hz), 7.64 (t, 1H, *J* = 8.4 Hz), 7.76 (dd, 1H, *J* = 8.4 Hz), 7.90 (dd, 1H, *J* = 8.8 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 12.07 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 106.7, 106.9, 110.0, 110.6, 113.2, 113.3, 113.6, 113.8, 116.3, 121.3, 122.6, 124.9, 125.0, 131.3, 138.6, 151.1, 158.6, 158.8, 159.4, 160.2; IR (KBr): 2924, 2853, 1645, 1464, 1256, 1026, 995, 828, 767 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_8FNO_2^+$ (MH$^+$) 254.0612; found 254.0609.



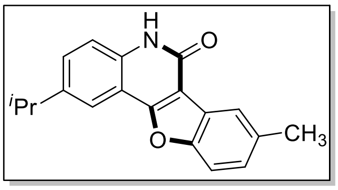
6-Oxo-5,6-dihydrobenzofuro[3,2-*c*]quinoline-8-carbonitrile (18a): White solid; M.p. 369–371 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.39 (t, 1H, *J* = 7.6 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.68 (t, 1H, *J* = 8.4 Hz), 7.99 (dd, 1H, *J* = 8.8 Hz), 8.10 (dd, 2H, *J* = 7.6 Hz), 8.44 (s, 1H), 12.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 107.6, 109.3, 110.2, 113.6, 116.4, 118.8, 121.5, 122.8, 124.8, 125.4, 130.3, 131.8, 138.9, 156.6, 158.6, 159.4; IR (KBr): 2956, 2923, 2853, 1659, 1459, 1157, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_8N_2O_2^+$ (MH$^+$) 261.0659; found 261.0665.



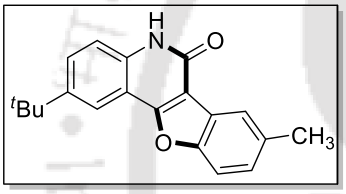
2,8-Dimethylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (19a): Brown solid; M.p. 291–293 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.41 (s, 3H), 2.46 (s, 3H), 7.29 (d, 1H, *J* = 8.4 Hz), 7.40 (d, 2H, *J* = 4.4 Hz), 7.67 (d, 1H, *J* = 8.4 Hz), 7.81 (s, 1H), 7.88 (s, 1H), 11.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.6, 21.1, 109.0, 110.8, 111.4, 116.2, 120.6, 121.2, 124.0, 127.4, 131.9, 132.2, 134.0, 136.4, 153.3, 158.0, 159.1; IR (KBr): 2959, 2923, 2850, 1669, 1460, 1204, 1135, 1046, 997 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}NO_2^+$ (MH$^+$) 264.1019; found 264.1026.



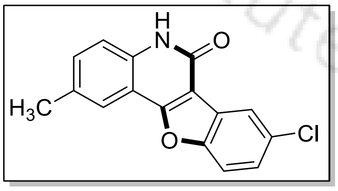
8-Butyl-2-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (20a): Dark white solid; M.p. 257–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.90 (t, 3H, *J* = 7.2 Hz), 1.28–1.37 (m, 2H), 1.55–1.64 (m, 2H), 2.40 (s, 3H), 2.72 (t, 2H, *J* = 7.6 Hz), 7.29 (dd, 1H, *J* = 8.4 Hz), 7.38 (t, 2H, *J* = 6.0 Hz), 7.67 (d, 1H, *J* = 8.8 Hz), 7.79 (s, 1H), 7.87 (s, 1H), 11.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 20.5, 21.8, 33.7, 34.7, 109.9, 110.7, 111.3, 116.1, 120.4, 123.9, 126.7, 131.6, 132.0, 136.4, 138.8, 141.0, 153.3, 157.9, 159.0; IR (KBr): 2955, 2924, 2853, 1663, 1460, 1182, 1025, 996 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{19}NO_2^+$ (MH$^+$) 306.1489; found 306.1495.



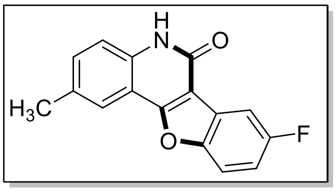
2-Isopropyl-8-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (21a): White solid; M.p. 302–305 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 1.28 (d, 6H, *J* = 6.8 Hz), 2.48 (s, 3H), 3.01–3.08 (m, 1H), 7.32 (d, 1H, *J* = 8.8 Hz), 7.45 (d, 1H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.72 (d, 1H, *J* = 8.8 Hz), 7.87 (s, 1H), 7.91 (s, 1H), 11.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 21.0, 23.9, 33.0, 109.8, 110.7, 111.4, 116.3, 117.8, 121.1, 124.0, 127.3, 129.9, 133.9, 136.7, 142.7, 153.2, 158.1, 159.1; IR (KBr): 2925, 2854, 2814, 1686, 1448, 1256, 1134, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO_2^+$ (MH$^+$) 292.1332; found 292.1329.



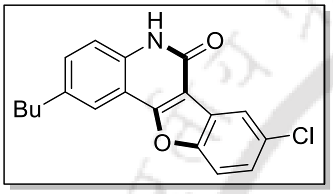
2-(Tert-butyl)-8-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (22a): Brown solid; M.p. 347–349 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 1.37 (s, 9H), 2.47 (s, 3H), 7.31 (dd, 1H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 8.8 Hz), 7.71–7.74 (m, 2H), 7.90 (s, 1H), 7.94 (s, 1H), 11.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 21.0, 31.1, 34.4, 109.8, 110.3, 111.4, 116.2, 116.4, 121.1 124.0, 127.2, 128.9, 133.9, 136.4, 145.0, 153.2, 158.2, 159.1; IR (KBr): 2957, 2923, 2853, 1668, 1457, 1358, 1189, 1079, 877 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{19}NO_2^+$ (MH$^+$) 306.1489; found 306.1494.



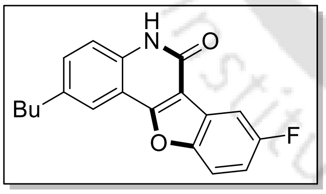
8-Chloro-2-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (23a): Yellow solid; M.p. 332–334 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 2.43 (s, 3H), 7.40 (d, 1H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 7.83 (s, 1H), 7.87 (d, 1H, *J* = 8.8 Hz), 8.00 (s, 1H), 12.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 20.5, 109.3, 110.3, 113.5, 116.3, 120.3, 120.7, 125.5, 126.1, 129.0, 131.9, 132.7, 136.8, 153.3, 158.6, 158.9; IR (KBr): 2923, 2852, 2817, 1657, 1442, 1310, 1090, 1065, 815 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}ClNO_2^+$ (MH$^+$) 284.0473; found 284.0480.



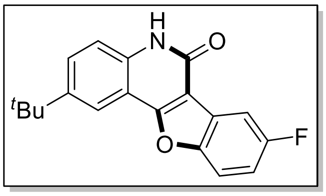
8-Fluoro-2-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (24a): Brown solid; M.p. 328–330 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.41 (s, 3H), 7.35 (t, 1H, *J* = 8.8 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 8.4 Hz), 7.73 (d, 1H, *J* = 8.4 Hz), 7.81 (s, 1H), 7.85 (dd, 1H, *J* = 8.8 Hz), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.5, 106.7, 106.9, 110.0, 110.5, 113.1, 113.2, 113.5, 113.8, 116.3, 120.6, 125.0, 125.1, 131.9, 132.6, 136.7, 151.0, 158.2, 158.7, 159.3, 160.5; IR (KBr): 2923, 2853, 1682, 1462, 1254, 1157, 1025, 996 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}FNO_2^+$ (MH$^+$) 268.0768; found 268.0765.



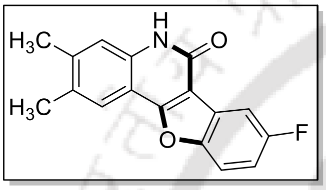
2-Butyl-8-chlorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (25a): Brown solid; M.p. 213–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.91 (t, 3H, *J* = 7.2 Hz), 1.27–1.37 (m, 2H), 1.57–1.64 (m, 2H), 2.69 (t, 2H, *J* = 8.0 Hz), 7.42 (d, 1H, *J* = 8.4 Hz), 7.48 (dd, 1H, *J* = 8.4 Hz), 7.53 (dd, 1H, *J* = 8.4 Hz), 7.81 (s, 1H), 7.87 (d, 1H, *J* = 8.8 Hz), 7.99 (d, 1H, *J* = 4.4 Hz), 12.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 21.7, 33.1, 34.2, 109.3, 110.3, 113.5, 116.3, 120.0, 120.3, 125.6, 126.1, 129.0, 132.1, 136.8, 137.0, 153.3, 158.7, 159.0; IR (KBr): 2924, 2853, 1660, 1442, 1382, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}ClNO_2^+$ (MH$^+$) 326.0942; found 326.0948.



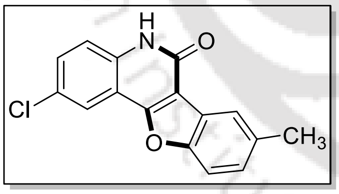
2-Butyl-8-fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (26a): Brown solid; M.p. 262–266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.90 (t, 3H, *J* = 6.4 Hz), 1.29–1.35 (m, 2H), 1.58–1.61 (m, 2H), 2.68 (t, 2H, *J* = 7.6 Hz), 7.34 (t, 1H, *J* = 8.8 Hz), 7.41 (d, 1H, *J* = 8.4 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.72 (d, 1H, *J* = 8.4 Hz), 7.78 (s, 1H), 7.85 (dd, 1H, *J* = 8.8 Hz), 11.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 21.7, 33.1, 34.2, 106.6, 106.9, 109.9, 110.4, 113.1, 113.2, 116.3, 119.9, 125.0, 125.1, 131.9, 136.7, 136.9, 151.0, 158.1, 158.7, 159.2, 160.5; IR (KBr): 2957, 2926, 2856, 1669, 1464, 1339, 1156, 1087, 800 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}FNO_2^+$ (MH$^+$) 310.1238; found 310.1245.



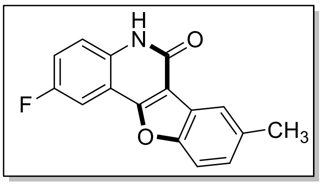
2-(Tert-butyl)-8-fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (27a): Brown solid; M.p. 345–347 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.36 (s, 9H), 7.33 (td, 1H, *J* = 9.2 Hz), 7.45 (d, 1H, *J* = 8.8 Hz), 7.71–7.74 (m, 2H), 7.87 (dd, 1H, *J* = 8.8 Hz), 7.91 (s, 1H), 11.99 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 31.1, 34.4, 106.6, 106.9, 109.9, 110.1, 113.2, 113.3, 113.4, 113.7, 116.3, 116.5, 125.0, 125.1, 129.4, 136.7, 145.1, 151.0, 158.1, 158.8, 159.5, 160.5; IR (KBr): 3011, 2923, 2851, 1676, 1459, 1136, 1086, 873 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}FNO_2^+$ (MH$^+$) 310.1238; found 310.1245.



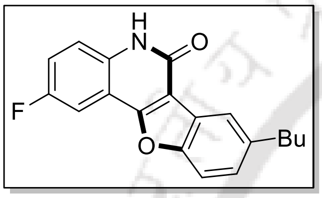
8-Fluoro-2,3-dimethylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (28a): Brown solid; M.p. 332–335 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.28 (s, 6H), 7.20 (s, 1H), 7.31 (td, 1H, *J* = 9.2 Hz), 7.68–7.70 (m, 2H), 7.81 (dd, 1H, *J* = 8.8 Hz), 11.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.0, 20.2, 106.5, 106.7, 108.5, 109.1, 113.0, 113.05, 113.12, 113.4, 116.4, 120.9, 125.1, 125.2, 131.3, 137.1, 141.0, 150.9, 158.1, 158.8, 159.3, 160.5; IR (KBr): 2956, 2854, 1675, 1450, 1280, 1024, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{12}FNO_2^+$ (MH$^+$) 282.0925; found 282.0930.



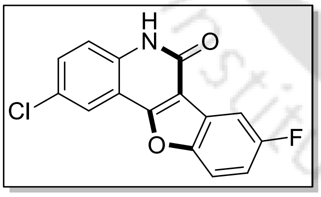
2-Chloro-8-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (29a): Reddish brown solid; M.p. 330–332 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.45 (s, 3H), 7.30 (d, 1H, *J* = 8.4Hz), 7.46 (d, 1H, *J* = 8.8 Hz), 7.60 (dd, 1H, *J* = 8.8 Hz), 7.66 (d, 1H, *J* = 8.4 Hz), 7.85 (s, 1H), 7.95 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.9, 110.7, 111.3, 111.9, 118.0, 120.1, 121.1, 123.5, 126.4, 127.7, 130.5, 134.0, 136.9, 153.3, 156.6, 158.8; IR (KBr): 2959, 2923, 2853, 1648, 1463, 1376, 1025, 995, 827 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}ClNO_2^+$ (MH$^+$) 284.0473; found 284.0470.



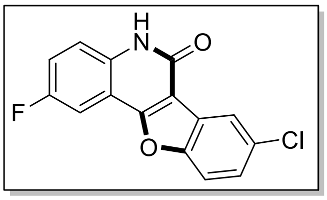
2-Fuoro-8-methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (30a): Yellow solid; M.p. 305–307 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.47 (s, 3H), 7.32 (d, 1H, *J* = 8.8 Hz), 7.51 (d, 2H, *J* = 6.0 Hz), 7.69 (d, 1H, *J* = 8.4 Hz), 7.79 (d, 1H, *J* = 8.8 Hz), 7.89 (s, 1H), 12.05 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.9, 106.2, 106.5, 110.7, 111.28, 111.34, 118.2, 118.3, 118.7, 118.9, 121.2, 123.6, 127.7, 134.0, 135.0, 153.3, 156.1, 157.1, 158.4, 158.8; IR (KBr): 2923, 2853, 1672, 1511, 1462, 1158, 1080, 970 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}FNO_2^+$ (MH$^+$) 268.0768; found 268.0775.



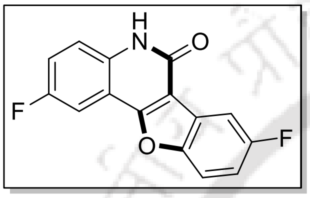
8-Butyl-2-fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (31a): Dark white solid; M.p. 255–257 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.90 (t, 3H, *J* = 7.2 Hz), 1.27–1.35 (m, 2H), 1.55–1.64 (m, 2H), 2.72 (t, 2H, *J* = 7.6 Hz), 7.32 (dd, 1H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 7.2 Hz), 7.68 (d, 1H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 7.87 (s, 1H), 12.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 21.8, 33.7, 34.7, 106.3, 106.5, 110.8, 111.4, 118.2, 118.3, 118.7, 118.9, 119.9, 120.5, 123.6, 127.2, 129.5, 135.0, 139.0, 153.4, 156.1, 157.1, 158.4, 158.8; IR (KBr): 2958, 2924, 2855, 1665, 1511, 1185, 1025, 995 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}FNO_2^+$ (MH$^+$) 310.1238; found 310.1243.



2-Chloro-8-fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (32a): Yellow solid; M.p. 339–341 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.40 (t, 1H, *J* = 9.2 Hz), 7.51 (d, 1H, *J* = 8.8 Hz), 7.67 (dd, 1H, *J* = 8.8 Hz), 7.75 (dd, 1H, *J* = 8.0 Hz), 7.89 (dd, 1H, *J* = 9.2 Hz), 8.04 (s, 1H), 12.19 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 106.8, 107.0, 110.9, 111.7, 11.3, 113.4, 114.1, 114.3, 118.2, 120.4, 124.6, 124.7, 126.6, 131.1, 137.2, 151.2, 158.1, 158.56, 158.58, 160.2; IR (KBr): 2961, 2924, 2854, 1682, 1463, 1157, 1026, 996, 803 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_7ClFNO_2^+$ (MH$^+$) 288.0222; found 288.0230.



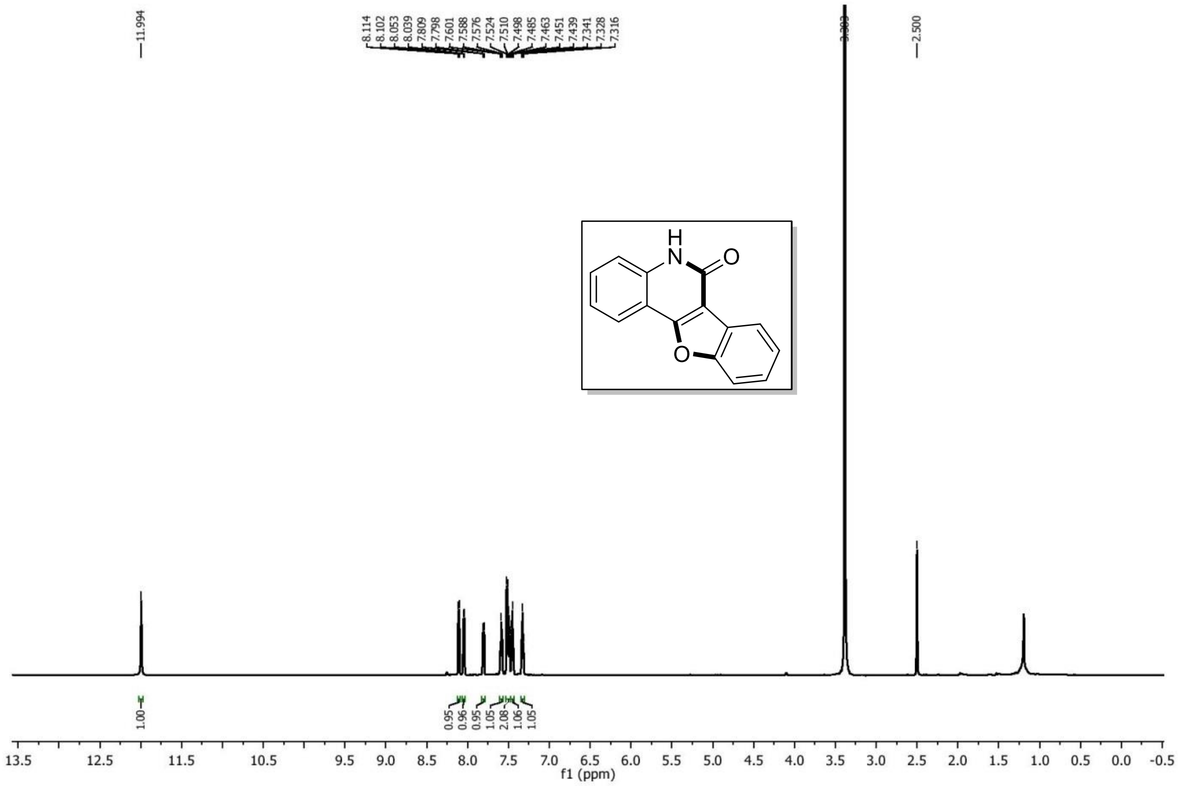
8-Chloro-2-fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (33a): Yellow solid; M.p. 345–348 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.52–7.57 (m, 3H), 7.81 (dd, 1H, *J* = 8.4 Hz), 7.88 (d, 1H, *J* = 8.4 Hz), 8.00 (s, 1H), 12.16 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 106.5, 106.7, 110.3, 110.98, 111.04, 113.6, 118.45, 118.51, 119.5, 119.6, 120.5, 125.2, 126.6, 129.1, 135.4, 153.4, 156.5, 158.1, 158.2, 158.4; IR (KBr): 2923, 2853, 1688, 1445, 1266, 1188, 1063, 970 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_7ClFNO_2^+$ (MH$^+$) 288.0222; found 288.0234.



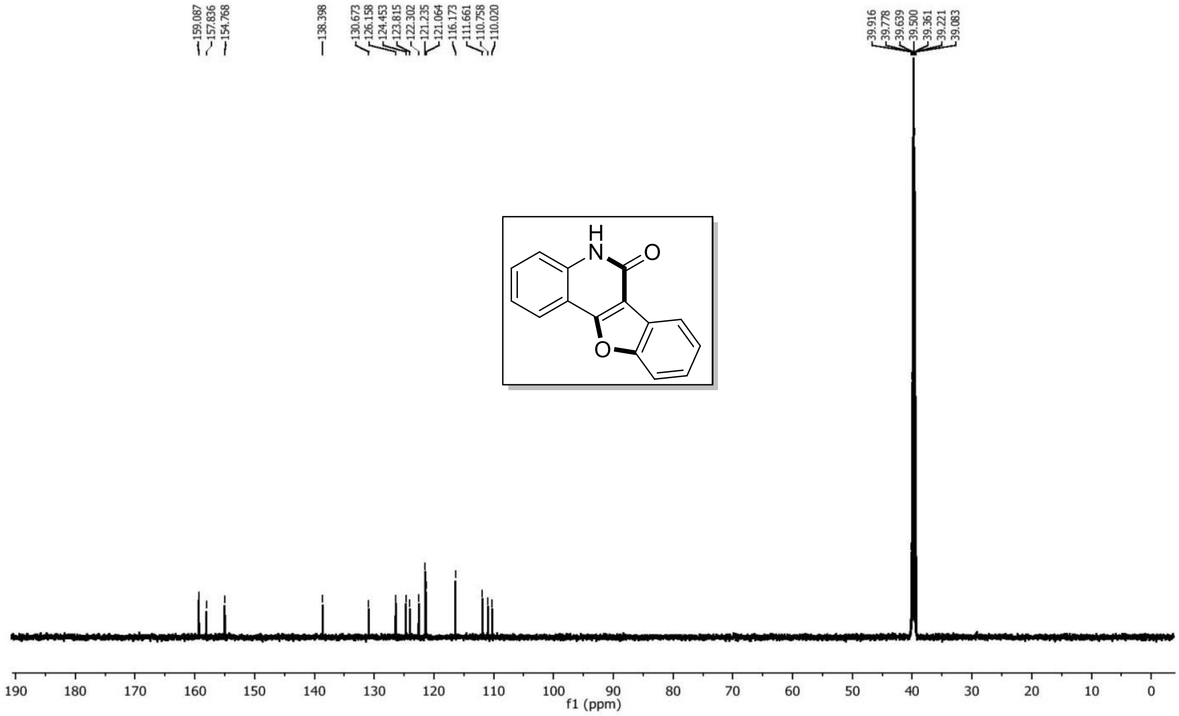
2,8-Difluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (34a): Yellow solid; M.p. 311–313 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.36 (t, 1H, *J* = 9.2 Hz), 7.50 (d, 2H, *J* = 5.6 Hz), 7.70–7.76 (m, 2H), 7.84 (dd, 1H, *J* = 9.2 Hz), 12.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 106.3, 106.6, 106.7, 107.0, 110.78, 110.82, 111.0, 111.1, 113.2, 113.3, 113.9, 114.2, 118.3, 118.4, 119.2, 119.4, 124.6, 124.7, 135.3, 151.1, 156.0, 158.1, 158.38, 158.42, 160.5; IR (KBr): 2960, 2924, 2855, 1685, 1459, 1278, 1178, 1048, 996, 800 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_7F_2NO_2^+$ (MH$^+$) 272.0518; found 272.0525.

VA.7. Spectra

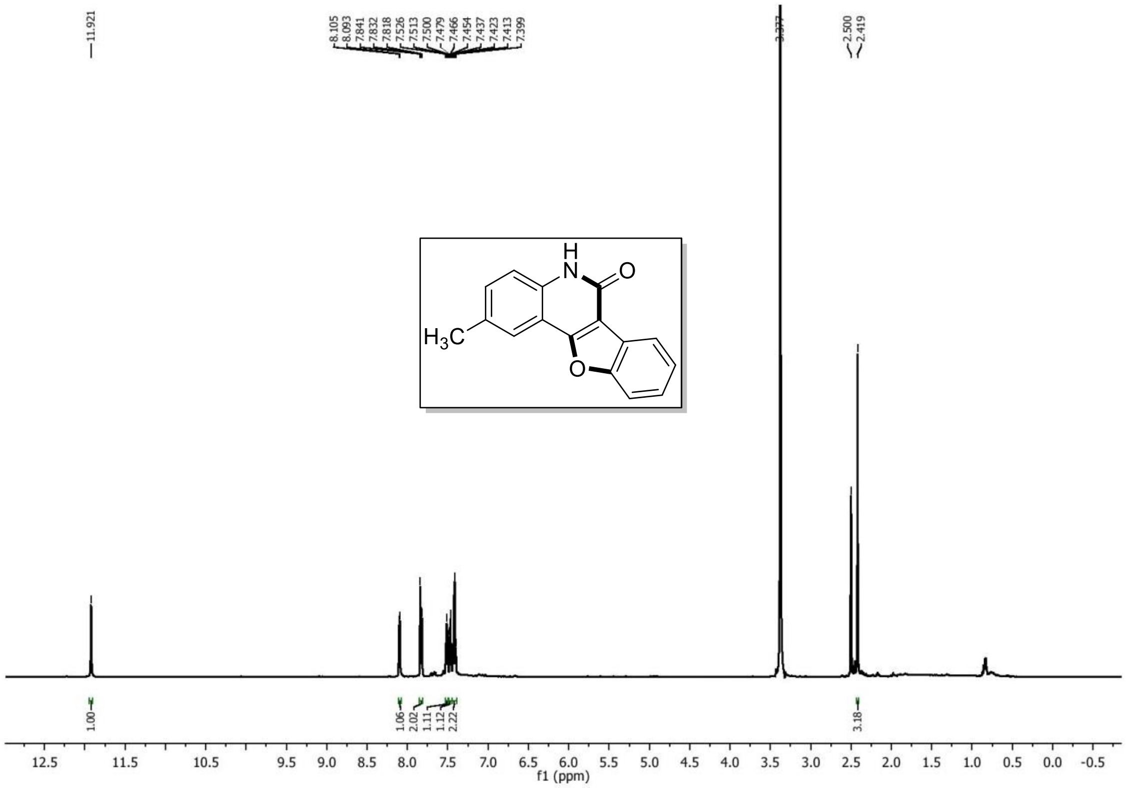
Benzofuro[3,2-*c*]quinolin-6(5*H*)-one (1a): ^{1}HNMR (600 MHz, DMSO-d_6)



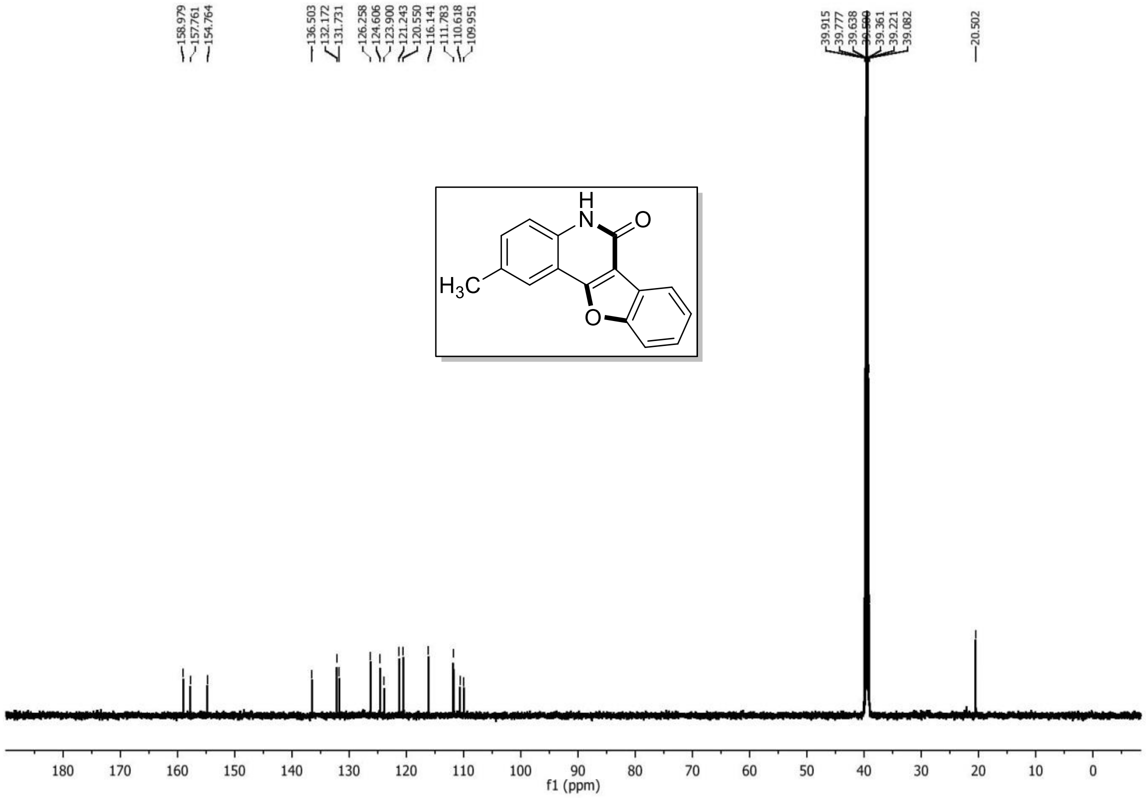
Benzofuro[3,2-*c*]quinolin-6(5*H*)-one (1a): ^{13}CNMR (150 MHz, DMSO-d_6)



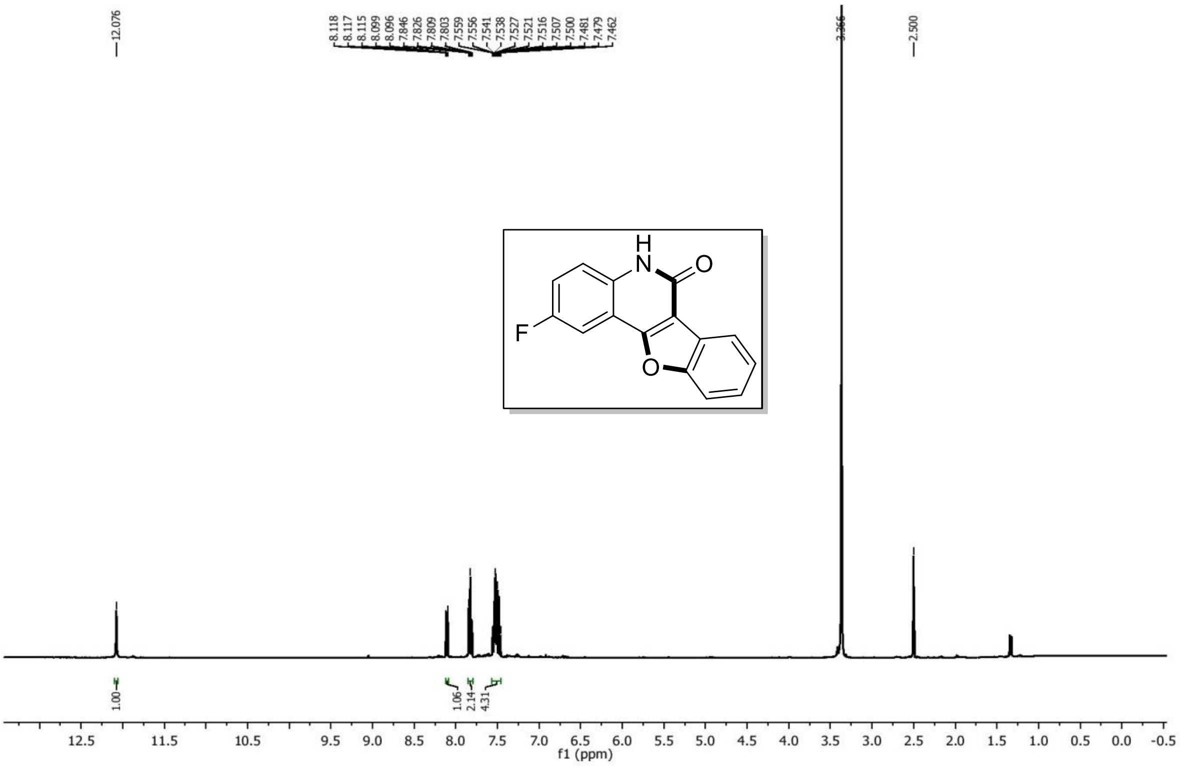
2-Methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (2a): ^{1}HNMR (600 MHz, DMSO-d_6)



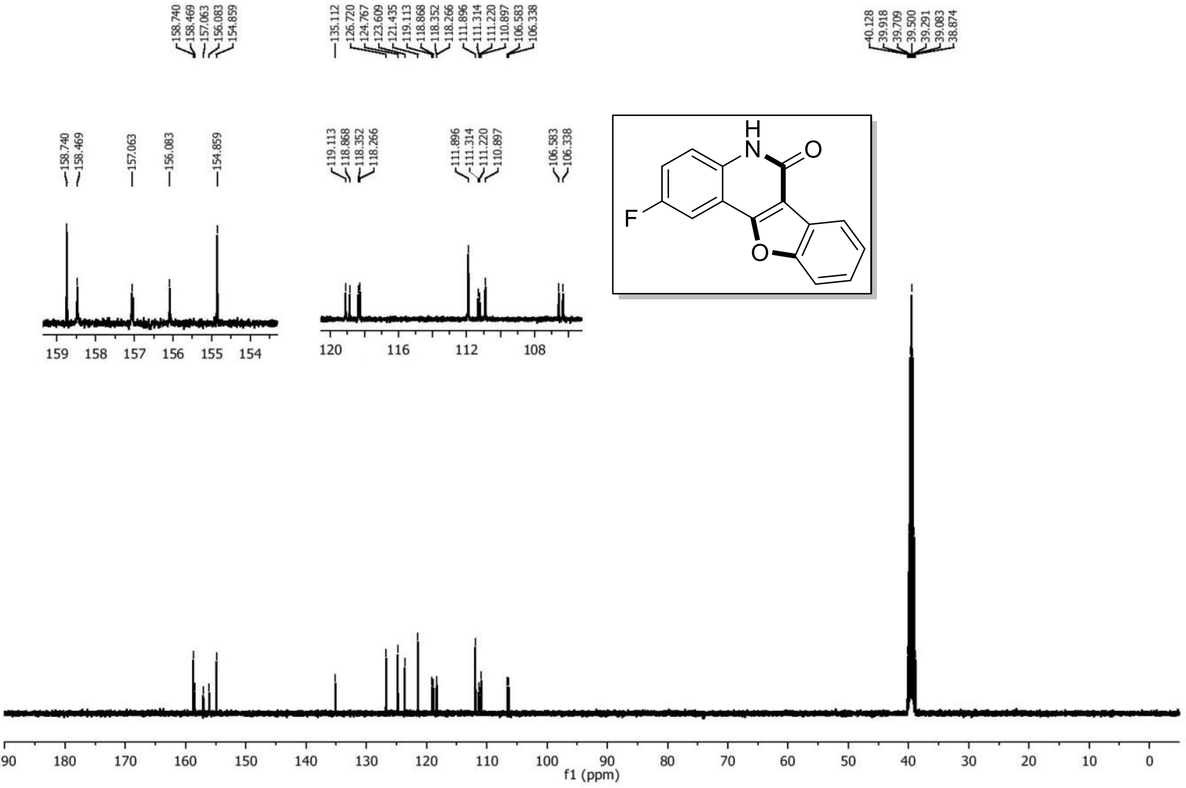
2-Methylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (2a): ^{13}CNMR (150 MHz, DMSO-d_6)



2-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (8a): ^{1}HNMR (400 MHz, DMSO-*d*$_6$)

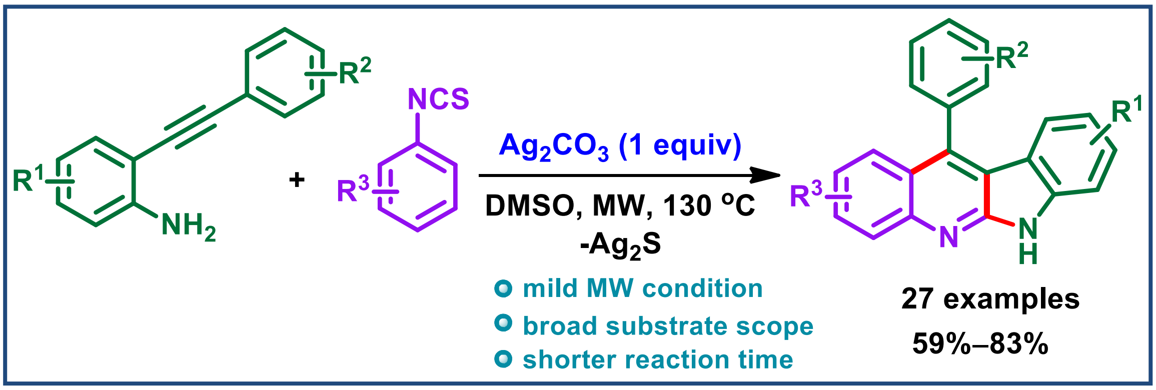


2-Fluorobenzofuro[3,2-*c*]quinolin-6(5*H*)-one (8a): ^{13}CNMR (150 MHz, DMSO-*d*$_6$)



Chapter VB

Microwave-Assisted Cascade Strategy for the Synthesis of Indolo[2,3-b]quinolines from 2-(Phenylethynyl)anilines and Aryl Isothiocyanates



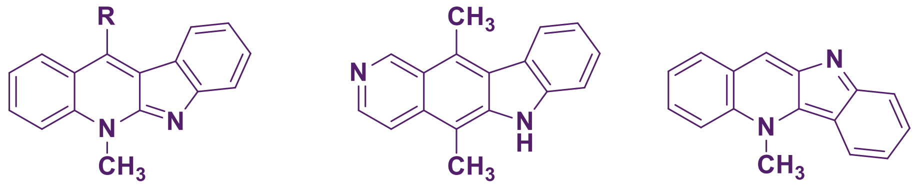
Abstract: *The in situ generated o-alkynyl thioureas obtain by reacting 2-(phenylethynyl)anilines and aryl isothiocyanates undergoes efficient cascade cyclization in the presence of Ag_2CO_3 to form indoloquinolines under microwave heating. The present tandem process allows the generation of a variety of indolo[2,3-b]quinolines derivatives in good to moderate yields with a wide functional group tolerance. Formation of Ag_2S via desulfurization of thiourea has been confirmed by the powder XRD and EDX analysis.*

CHAPTER VB

VB. Microwave-Assisted Cascade Strategy for the Synthesis of Indolo[2,3-*b*]quinolines from 2-(Phenylethynyl)anilines and Aryl Isothiocyanates

VB.1. Introduction

There has been continuous interest in the synthesis of natural product like compounds with privileged scaffolds that are likely to have potential biological activities. Among these privilege scaffolds, indoloquinoline alkaloids represent one of the important classes of heterocycles due to their immense biological activity[1] (Figure VB.1.1) including the ability to interact with DNA as an intercalator to inhibit topoisomerase II activity.[2] Recent results reveal that some new indolo[2,3-*b*]quinoline (norcryptotackieine) types of natural products isolated from the leaves of *Justicia betonica*[3] exhibit exceptional pharmacological properties such as potent antiplasmodial, antiproliferative, and antitumor activity.[4] For example 2-halosubstituted norcryptotackieines are more active against plasmodium falciparum than neocryptolepine and are less cytotoxic. In addition, indoloquinoline alkaloids are an integral part of the design, development, and synthesis of various modern commercial drugs.[5] For these reasons, over the past several years tremendous effort has been devoted for the synthesis of such tetracyclic-fused quinoline alkaloids both by organic and medicinal chemists with an aim to enhance the potency of indolo[2,3-*b*]quinoline, and a variety of approaches have been successfully developed.[6-9] Therefore, developing strategy for the synthesis of indolo-fused quinolines that are more efficient, cost-effective, atom-economical, and practical are most sought-after.



R = H, Neocryptolepine
R = CH_3, 11-Methylneocryptolepine

Ellipticine

Cryptolepine

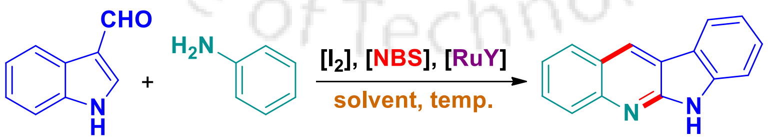
Figure VB.1.1. *Selected indoloquinoline possessing biological activity*

Currently, cascade reactions are one of the most promising approaches in organic synthesis due to their high atom economy, better efficiency and easy handling during the assembly of complex molecular structures.[10] Such reactions have been adopted, and they have emerged as powerful synthetic tools for the conversion of internal alkynes into biologically active polycyclic heterocycles.[11] Furthermore, microwave assisted organic synthesis have the advantage of greater reactivity, mild reaction conditions, high selectivity and shorter reaction times.[12] Therefore, cascade reaction carried out under a microwave conditions are further advantageous over conventional heating.

VB.2. Strategies for the Synthesis of Indoloquinoline

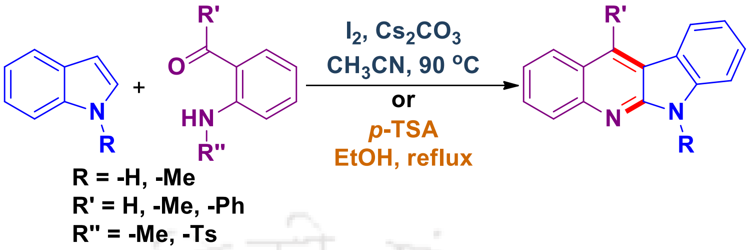
Indolquinolines moiety is found to have activity such as antibacterial, antifungal, antimalarial, anticancer, analgesic and hypertensive agent. Previously these *N*-heterocycles were synthesized by various groups in multistep process.[6] However in a one-step protocol many synthetic routes for the synthesis of indoloquinoline using indole and its derivative as one of the coupling partners have been developed.[7] Some of synthetic strategies are described below.

In 2009 Tilve *et al.* developed molecular iodine (I_2)-catalyzed synthesis of indoloquinoline by refluxing 3-carboxyaldehyde and aryl amines in diphenyl ether.[7a] This process involves sequential imination, nucleophilic addition and annulation catalyzed by I_2. A similar type of reaction has been developed by Khorshidi and co-worker using Ru-exchanged FAU-Y zeolite (RuY) as a recyclable catalyst.[7b] Later on, a similar *N*-bromosuccinimide (NBS)-promoted efficient and solvent free protocol for the synthesis of indoloquinoline at room temperature has been reported by Ghorbani-Vaghei group (Scheme VB.2.1).[7c]



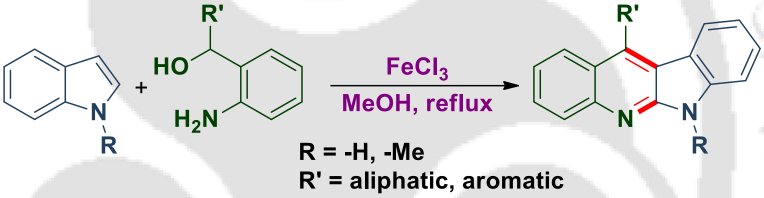
Scheme VB.2.1. *Indoloquinoline synthesis from 3-carboxyaldehyde and aryl amines*

Liang group reported a one pot synthesis of indoloquinoline derivatives by electrophile (I_2) triggered cross amination and Friedel-Crafts alkylation of indoles with aminophenyl ketones in presence of Cs_2CO_3 as base.[7d] The synthetic utility of the protocol has been demonstrated by the synthesis of neocryptolepine and its 11-methyl analogue. Seidel *et al.*[7e] adopted similar strategy for their synthesis using indole and 2-aminobenzaldehyde with help of *p*-toluene sulphonic acid (*p*-TSA) as promoter (Scheme VB.2.2).



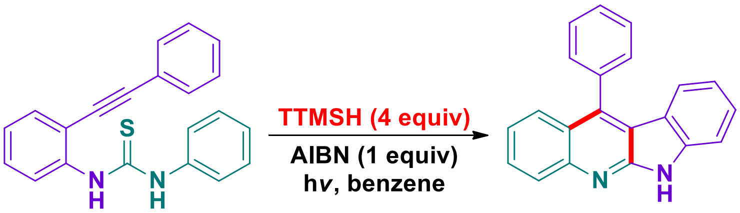
Scheme VB.2.2. *Indoloquinoline synthesis from indoles and aminophenyl ketone*

Wang group recently developed an efficient Fe(III)-promoted synthesis of indoloquinoline by reaction of aminophenyl alcohols and indoles in methanol (Scheme VB.2.3).[7f]



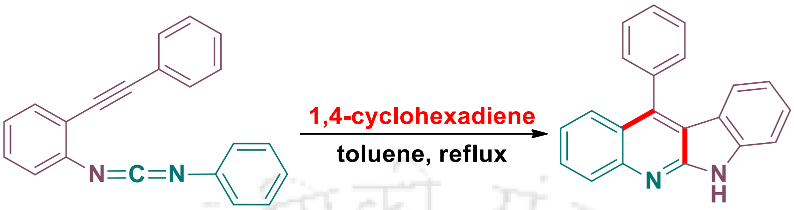
Scheme VB.2.3. *Indoloquinoline synthesis from indoles and aminophenyl alcohols*

In 2003 Curran *et al.* reported the synthesis of indolo[2,3-*b*]quinoline via a cascade radical annulation of *o*-alkynyl thiourea that involves irradiation of UV light (with medium pressure Hg lamp) in a pyrex glass tube requiring excess of tris(trimethylsilyl) silane (TTMSH) (4 equiv), AIBN (1 equiv) in anhydrous benzene (Scheme VB.2.4).[8] Although this method provides fruitful access to indoloquinolines, the use of certain carcinogens and expensive and excess amounts of reagents and requirements of a specialized setup limits their applications.



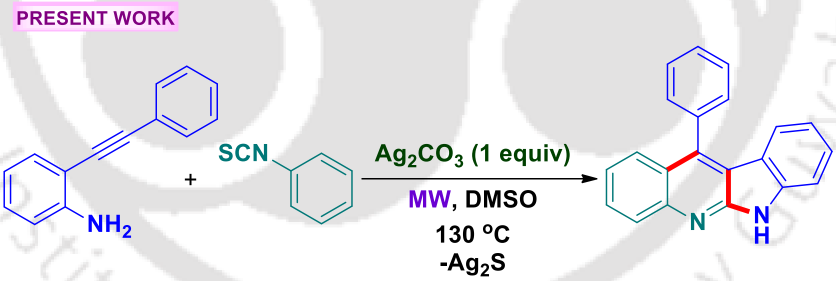
Scheme VB.2.4. *Indoloquinoline synthesis from cascade annulations of o-alkynyl thioureas*

The indoloquinoline system has also been assembled through a thermal cyclization of an enyne-carbodiimide as reported by Schmittel *et al.*[9] By the mechanistic investigation they established the involvement of a carbene type intermediate in this transformation (Scheme VB.2.5).



Scheme VB.2.5. *Indoloquinoline synthesis from thermal cyclization of enyne-carbodiimide*

All the above mentioned protocol provides fruitful access to indoloquinoline derivatives, however suffer with certain drawbacks such as requirements of functionalized indoles, amines precursors which in turn are difficult to prepare as well as need of extra additional step for the synthesis of thioureas and carbodiimides. Thus in an attempt to obliterate the above limitation, methodologies which are more efficient, cost-effective and atom-economical are desirable (Scheme VB.2.6).



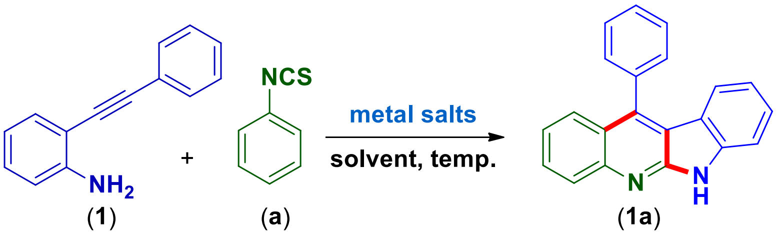
Scheme VB.2.6. *Indoloquinoline synthesis from o-alkynyl aniline and phenyl isothiocyanate*

VB.3. Present Work

Our group has reported the synthesis of various heterocyclic scaffolds through C–H bond functionalization and cascade/tandem reactions.[13] Owing to promising applications of indolo[2,3-*b*]quinolines as biologically active molecules, we plan to develop an alternative and straightforward method for the synthesis of various functionalized indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates. We envisaged that the *o*-alkynyl thiourea formed from 2-(phenylethynyl)aniline (**1**) and phenyl isothiocyanate (**a**) may undergo desulfurization in the presence of thiophilic reagents to produce a carbodiimide intermediate.[14] The enyne-carbodiimide intermediate so generated may undergo a thermal cyclization to produce the expected product indoloquinolines via a subsequent cyclization step.

Optimization of Reaction Conditions: We first treated 2-(phenylethynyl)anilines (**1**) (1 equiv) with phenyl isothiocyanate (**a**) (2 equiv) in the presence of $Cu(OAc)_2$ (0.2 equiv) as the catalyst in DMSO at 110 ^oC for 24 h, but no desired product was observed (Table VB.3.1, entry 1). However, the 2-(phenylethynyl)aniline (**1**) reacted with phenyl isothiocyanate (**a**) to form corresponding thiourea, which did not undergo any further change. This result prompted us to use other thiophilic metal such as silver so as to facilitate simultaneous desulfurization as well as activation of the internal alkyne for effective cyclization. The superior alkynophilicity of silver is due to π-coordination with carbon–carbon multiple bond, making it an ideal catalyst for alkyne-based organic reactions. Based on these facts, we carried out the same reaction under an identical conditions but using Ag_2CO_3 (20 mol %) in lieu of $Cu(OAc)_2$. Gratifyingly, formation of a new product was observed in 21% yield (Table VB.3.1, entry 2). Characterization of the newly formed product through spectroscopic analysis (^{1}HNMR, ^{13}CNMR and HRMS) reveals the formation of our expected product 11-phenyl-*6H*-indolo[2,3-*b*]quinoline (**1a**). Further optimizations were carried out to enhance the product yield using various silver salts [Ag_2SO_4 (12%), AgOAc (09%), $AgNO_3$ (13%), $Ag(SO_3CF_3)$ (10%)] (Table VB.3.1, entries 3–6), but none were found to be superior to Ag_2CO_3. Replacement of silver salt with other metal salt like $Mn(OAc)_2$ (Table VB.3.1, entry 7) did not serve the purpose, and the product was obtained in a mere yield of 08%. The yield of the product was enhanced up to 36% (Table VB.3.1, entry 8), when the loading of Ag_2CO_3 was increased to 1 equivalent. Further increase in the Ag_2CO_3 (1.5 equiv) loading had no substantial improvement in the product yield (38%) (Table VB.3.1, entry 9). Subsequently, we explored the possibility of using nonmetallic thiophilic reagents such as DIB (diacetoxy iodobenzene) (19%) and molecular iodine (21%) (Table VB.3.1, entry 10 and 11) in combination with Ag_2CO_3 (20 mol %). However, the results suggest none of these combinations are suitable for this transformation. To our delight, increasing the reaction temperature to 130 ^oC from 110 ^oC improved the yield up to 47% (Table VB.3.1, entry 12). Further increasing the reaction temperature to 150 ^oC had no substantial effect on the product yield (46%) (Table VB.3.1, entry 13). The reaction in other solvents such as

Table VB.3.1. *Optimization of experimental conditions*[a,b]



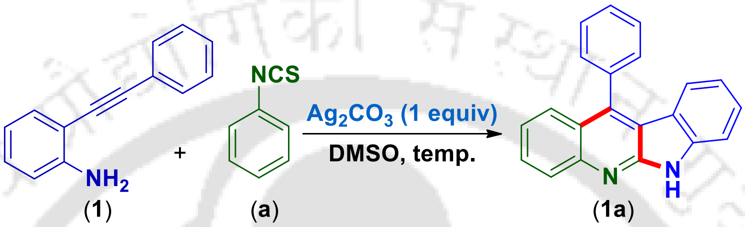
Entry	Metal salt	Solvent	Temp (^{o}C)	Yield (%)[b]
1	$Cu(OAc)_2$ (20%)	DMSO	110	n.d.
2	Ag_2CO_3 (20%)	DMSO	110	21
3	Ag_2SO_4 (20%)	DMSO	110	12
4	AgOAc (20%)	DMSO	110	09
5	$AgNO_3$ (20%)	DMSO	110	13
6	$Ag(SO_3CF_3)$ (20%)	DMSO	110	10
7	$Mn(OAc)_2$ (20%)	DMSO	110	08
8	Ag_2CO_3 (100%)	DMSO	110	36
9	Ag_2CO_3 (150%)	DMSO	110	38
10	Ag_2CO_3 (20%)	DMSO	110	19[c]
11	Ag_2CO_3 (20%)	DMSO	110	21[d]
12	**Ag_2CO_3 (100%)**	**DMSO**	**130**	**47**
13	Ag_2CO_3 (100%)	DMSO	150	46
14	Ag_2CO_3 (100%)	DMF	130	29
15	Ag_2CO_3 (100%)	mesitylene	130	14
16	Ag_2CO_3 (100%)	chlorobenzene	130	22
17	Ag_2CO_3 (100%)	1,4-dioxane	130	15
18	-	DMSO	130	trace

[a]Reaction condition: **1** (0.25 mmol), **a** (0.50 mmol), Ag salts, solvent (3 mL), 24 h. [b]Isolated pure product. [c]1 equivalent DIB. [d]1 equivalent iodine. n. d. = not detected.

DMF, mesitylene, chlorobenzene, and 1,4-dioxane tested did not give satisfactory results compared to that of DMSO (Table VB.3.1, entries 14–17). Formation of a trace of the product in the absence of Ag_2CO_3 (Table VB.3.1, entry 18) suggests its essential role in this overall transformation.

Recently, microwave-assisted organic synthesis has been widely employed, as reaction under microwave conditions improves the product yields and shortens the reaction time. Thus, we thought of performing the above reaction under a microwave conditions. Under microwave condition [(10 min. reaction time at 130 ^{o}C (150 W, closed vial)] the desired product was obtain in an improve yield of 58% (Table VB.3.2, entry 1) under otherwise identical condition. Increasing the reaction time from 10 min. to 30 min. enhance the product yield up to 70%. (Table VB.3.2, entry 2). However, any further increase in the reaction time (60 min.) had a slightly negative effect on the product yield (Table VB.3.2, entry 3). An elevated temperature 150 ^{o}C of the microwave did not lead to any improvement (Table VB.3.2, entry 4). Here again, reaction in the absence of Ag_2CO_3 gave the desired product in trace amounts, suggesting its essential requirement (Table VB.3.2, entry 5). Reduction in the quantity of phenyl isothiocyanate (**a**) from 2 to 1.5 equivalents has no substantial effect on the overall product yield (Table VB.3.2, entry 6) under the present reaction condition. When the molar ratio of **1** and **a** was 1:1 the yield of the product dropped to 62% (Table VB.3.2, entry 7).

Table VB.3.2. *Effect of microwave heating on product yield*[a]



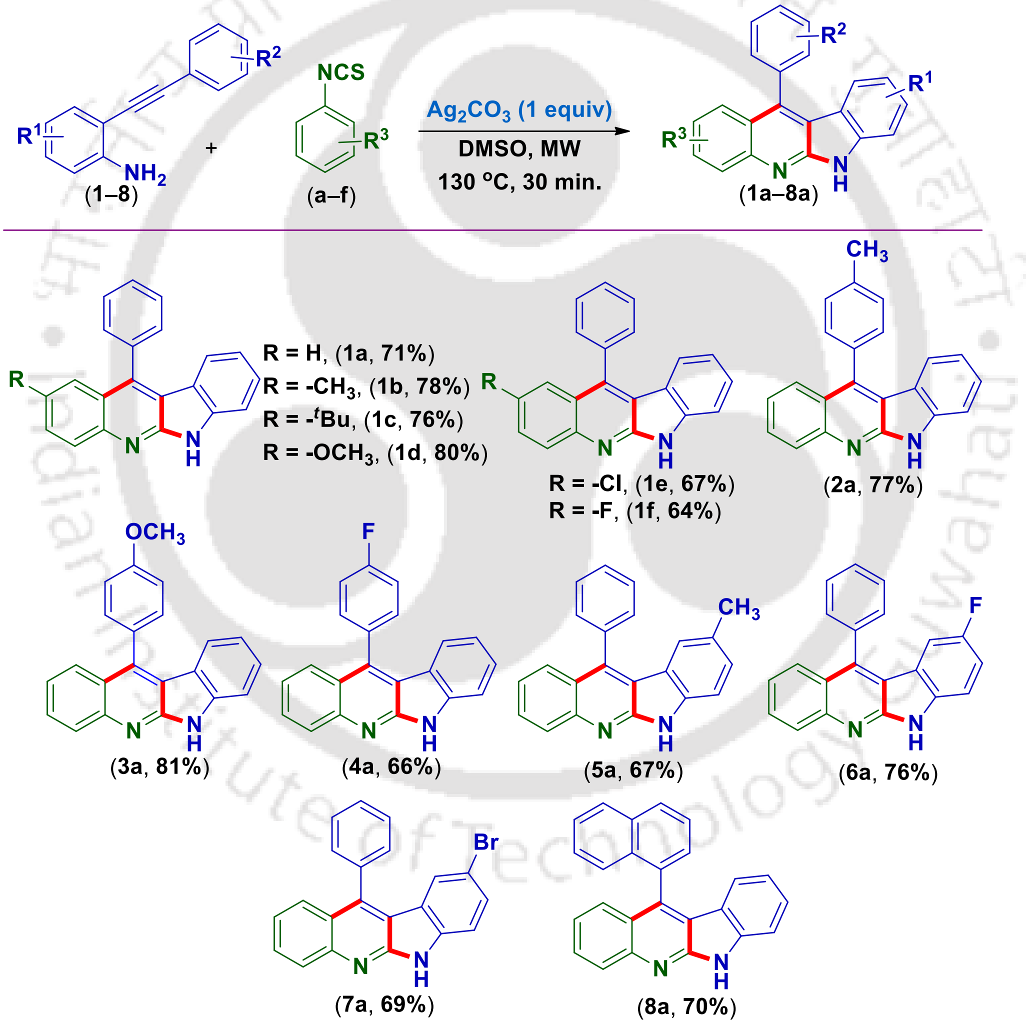
Entry	Metal salt	Temp. (°C)	Yield (%)[b]
1	Ag_2CO_3 (100%)	130	58
2	Ag_2CO_3 (100%)	130	70[c]
3	Ag_2CO_3 (100%)	130	66[d]
4	Ag_2CO_3 (100%)	150	69
5	-	130	trace
6	**Ag_2CO_3 (100%)**	**130**	**71**[e]
7	Ag_2CO_3 (100%)	130	62[f]

[a] Reaction condition: **1** (0.25 mmol), **a** (0.5 mmol), Ag_2CO_3 (0.25 mmol), DMSO (3 mL), MW 10 min. [b] Isolated pure product. [c] 30 min.. [d] 1 h. [e] **a** (0.375 mmol). [f] **a** (0.25 mmol).

Substrate Scope for Indolo[2,3-*b*]quinolines Synthesis: Under the optimized condition (Table VB.3.2, entry 6), various 2-(phenylethynyl)anilines and aryl isothiocyanates were subjected to the reaction condition to explore the scope of this cascade protocol. First, the electronic effect of substituents R^3 on the aryl isothiocyanate was evaluated (Scheme VB.3.1, **1a–f**), and the results are summarized in Scheme VB.3.1. The structure of the product (**1a**) has been unequivocally established by single crystal X-ray crystallography (Figure VB.3.1). Phenyl isothiocyanates possessing electron-donating (EDG) substituents (**b–d**) at their *para* position afforded the corresponding products in better yields compared to un-substituted (**a**) and electron-withdrawing (EWG) substituents (**e, f**). Phenyl isothiocyanates having substituents such as $-CH_3$ (**b**), $-{}^t$Bu (**c**), and $-OCH_3$ (**d**) at their *para* position provided the corresponding products (**1b**, 78%), (**1c**, 76%) and (**1d**, 80%) (Scheme VB.3.1) respectively. Comparatively lower yield of the indolo[2,3-

b]quinolines (**1e** and **1f**, Scheme VB.3.1) were obtained when moderately electron-withdrawing groups [–Cl (**e**, 67%) and –F (**f**, 64%)] were present on the phenyl isothiocyanate. We also examine the effect of substituents R^2 present on the other phenyl ring of 2-(phenylethynyl)aniline on the product yield and found effect similar to that of R^3 substituents present on the phenyl isothiocyanate. Substrates bearing electron releasing groups such as $–CH_3$ (**2**) and $–OCH_3$ (**3**) furnished better yields (**2a**, 77%; **3a**, 81%) of the product. Whereas, electron-withdrawing substituent –F (**4**) gave lesser yields of the product (**4a**, 66%), when reacted with phenyl isothiocyanate (**a**) (Scheme VB.3.1).

Scheme VB.3.1. *Substrate scope for the synthesis of indolo[2,3-b]quinolines*[a,b]



[a]Reaction conditions: **1–8** (0.25 mmol), **a–f** (0.375 mmol), Ag_2CO_3 (0.25 mmol), MW, 130 °C, time 20–30 min. [b]Yields of the pure product reported.

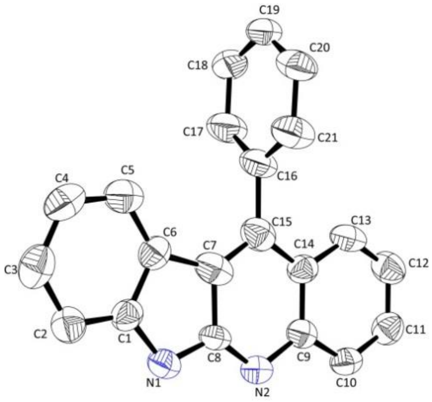
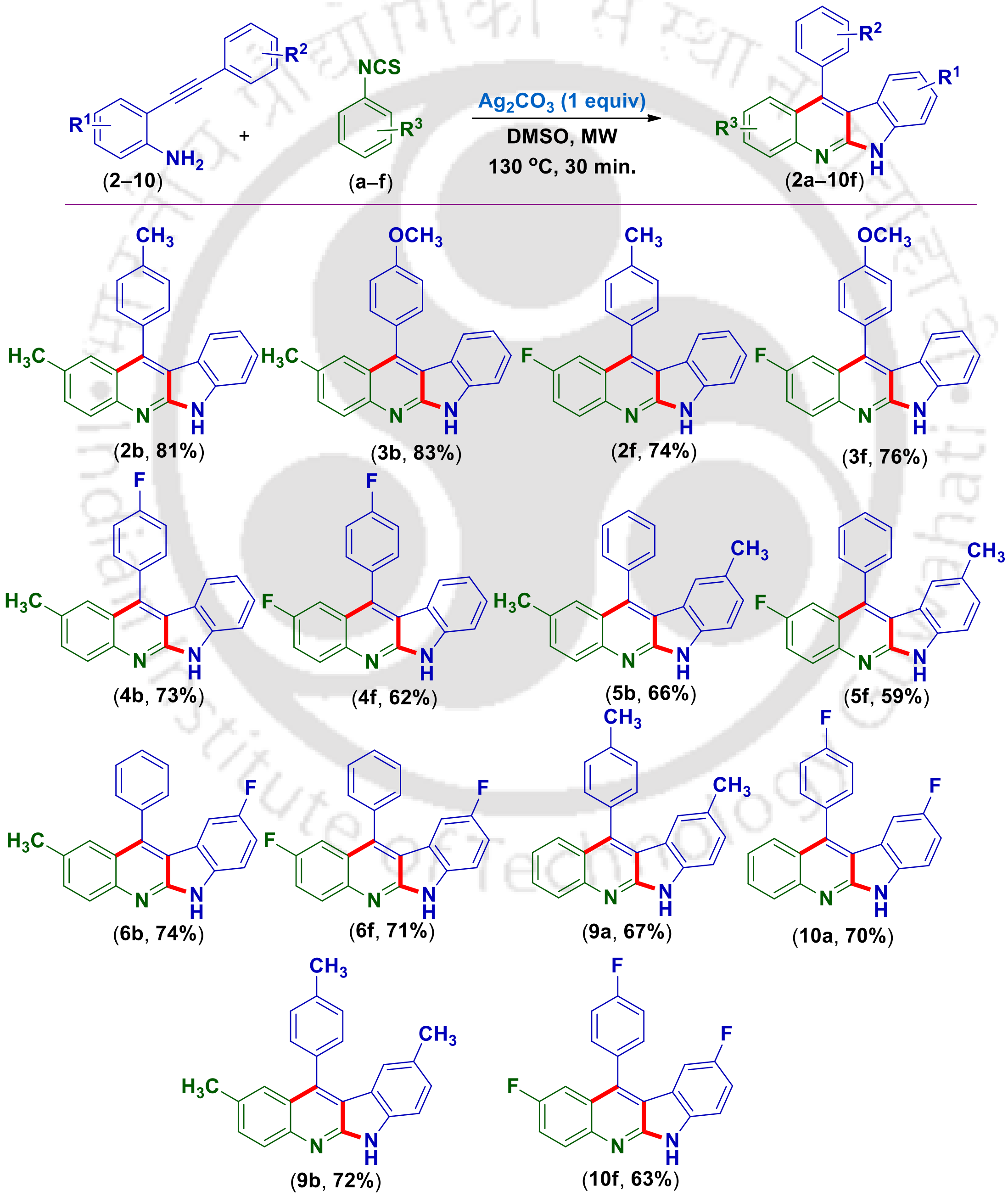


Figure VB.3.1. *ORTEP view of (**1a**)*

Next, the effect of R^1 substituents present on the amine-bearing ring of 2-(phenylethynyl)anilines (**5–7**) on the reaction shows a trend opposite to that of substituents R^2 and R^3 on the product yields. When substituent R^1 is an electron-donating group such as –CH_3 (**5**), the product (**5a**) was obtained in 67% yield, whereas the presence of electron-withdrawing substituents such as –F (**6**) and –Br (**7**) leads to their corresponding products (**6a**) and (**7a**) in 76% and 69% yield, respectively. 2-(Naphthalen-1-ylethynyl)aniline (**8**) also reacted efficiently with phenyl isothiocyanate (**a**) to provide the indoloquinoline (**8a**) in 70% yield (Scheme VB.3.1). To demonstrate the scalability of the present methodology, a reaction was carried out with 2-(phenylethynyl)anilines (**1**) (4.15 mmol, 800 mg) with phenyl isothiocyanate (**a**) (6.23 mmol, 841 mg) under the optimized reaction conditions to give 51% yield of the product. The present strategy was equally successful for any type of substituents (R^1, R^2 and R^3) present anywhere in the aryl ring of the substrates (Scheme VB.3.2). When both the substituents R^2 and R^3 were electron-donating such as *p*-CH_3 (**2**)/*p*-CH_3 (**b**) and *p*-OCH_3 (**3**)/*p*-CH_3 (**b**), good yields (81% and 83%) of their respective products (**2b**) and (**3b**) were obtained. On the other hand, when R^2 is electron-donating and R^3 was electron-withdrawing substituents such as *p*-CH_3 (**2**)/*p*-F (**f**), *p*-OCH_3 (**3**)/*p*-F (**f**), the yields of the isolated products were slightly lower [(**2f**, 74%; **3f**, 76%)]. When the substituent positions are reversed, i.e., R^2 was substituted with an electron-withdrawing group 4-F (**4**) and R^3 with an electron-donating group 4-Me (**b**), the cascade product (**4b**) was obtained in 73% yield. Substitution of R^2 and R^3 with an electron-withdrawing group 4-F (**4**) lead to a further drop in the product yield (**4f**, 62%). Next, when substituents R^1 and R^3 are EDG and EWG or R^1 with an EDG and R^3 with EWG group or vice versa, moderate yields ranges between 59% and 74% of their corresponding products (**5b-6f**) were obtained. Further, when both R^1 and R^2 are either electron-donating 4-CH_3 (**9**) or electron-withdrawing 4-F (**10**) groups, products (**9a**) and (**10a**) were obtained in 67% and 70% yields, respectively. When all of the substituent R^1, R^2, and R^3 were either 4-CH_3 or 4-F, the products (**9b** and **10f**) were isolated in 72% and 63% yields, respectively. In this multistep process it is difficult to determine the exact rate-determining steps; however, from Scheme VB.3.1 and Scheme VB.3.2 it is evident that the electronic effect of substituent R^1 on the product yield is

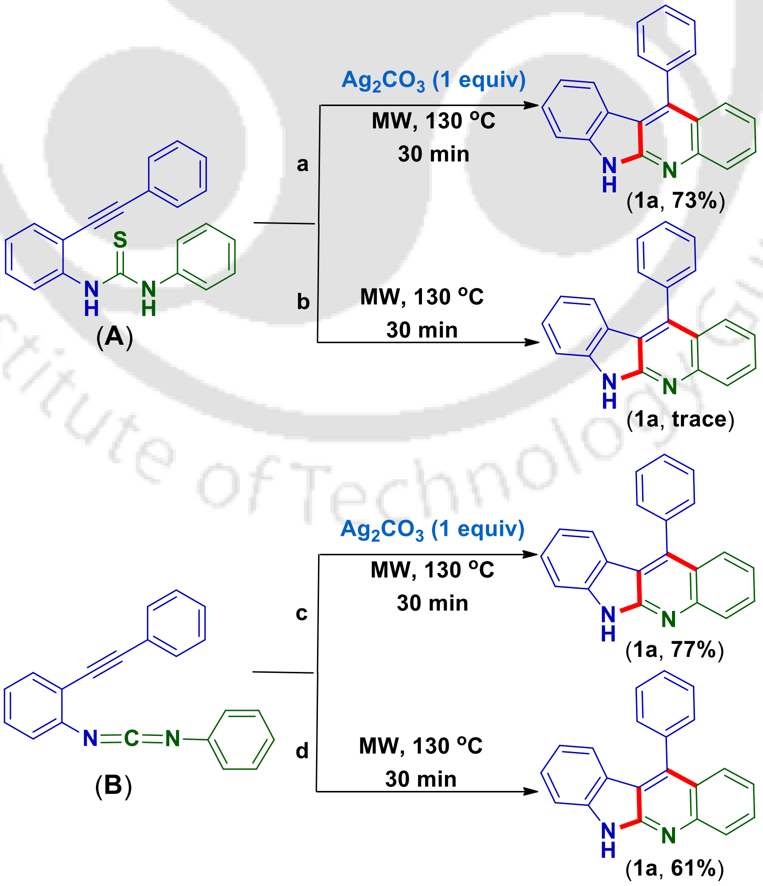
Scheme VB.3.2. *Synthesis of substituted indoloquinoline*[a,b]



[a]Reaction conditions: **2–10** (0.25 mmol), **a–f** (0.0375 mmol), Ag_2CO_3 (0.25 mmol), MW, 130 °C, time 20–30 min. [b]Yields of the pure product reported.

more significant compared to substituents R^2 and R^3. When strongly electron withdrawing substituent such as –NO_2, –CN, and –CF_3 were present on the R^1 ring (amine-bearing ring), the starting materials remained unreacted (even thiourea intermediate was not formed). Nevertheless, when the same electron-withdrawing substituents were present on the R^3 ring (i.e., aryl isothiocyanate), both reacted to form the intermediate thiourea but failed to undergo any further transformation. However, when preformed carbodiimide intermediates were used; similar annulated products were successfully obtained even for substrates bearing strong electron-withdrawing groups as reported.[9b]

Mechanistic Studies: To understand the mechanism of this process, few control experiments were conducted (Scheme VB.3.3). When a presynthesized 1-phenyl-3-(2-(phenylethynyl)phenyl)thiourea (**A**) was subjected to the standard reaction conditions, formation of the expected product (**1a**) in 73% yield suggests the possible formation of a thiourea intermediate (**A**) in the present transformation (Scheme VB.3.3, path-a). However, in the absence of Ag_2CO_3 reaction was completely unproductive, revealing the essential requirements of Ag_2CO_3 in the overall transformation (Scheme VB.3.3, path-b).



Scheme VB.3.3. *Control experiments*

Furthermore, 2-(phenylethynyl)-*N*-((phenylimino)methylene)aniline (**B**) afforded the desired product in the presence of Ag_2CO_3 (77%) (Scheme VB.3.3, path-c) and in its absence (61%) (Scheme VB.3.3, path-d). Thus, the major role of the Ag_2CO_3 is the generation of carbodiimide intermediate (**B**) from thiourea (**A**).

Formation of Ag_2S via desulfurization of thiourea has been confirmed by the powder XRD and EDX analysis as shown in Figure VB.3.2. The powder X-ray diffraction (PXRD) patterns showed the phase purity and crystal structure of the formed Ag_2S, as shown in Figure VB.3.2.i. PXRD pattern of Ag_2S is defined as a monoclinic acanthite phase with (121), (102), (012), (043), (025), (-102), (411), (-103), (-123), (031), (102), (112), (004), (014), (-133), (-215), (041), (-225), (-105), (-116) and (141) crystal planes according to the JCPDS Card No. 24-0715. To further confirm the elemental composition and distribution in Ag_2S, selected area elemental mapping was carried out by energy-dispersive X-ray (EDX) spectroscopic technique which is depicted in the Figure VB.3.2.ii. EDX pattern in Figure VB.3.2.ii shows the elemental compositions (At %) contained in the Ag_2S. It shows that Ag_2S contains a weight ratio of silver to sulfur 2.3:1, which is very close to the expected ratio of Ag_2S (2:1).

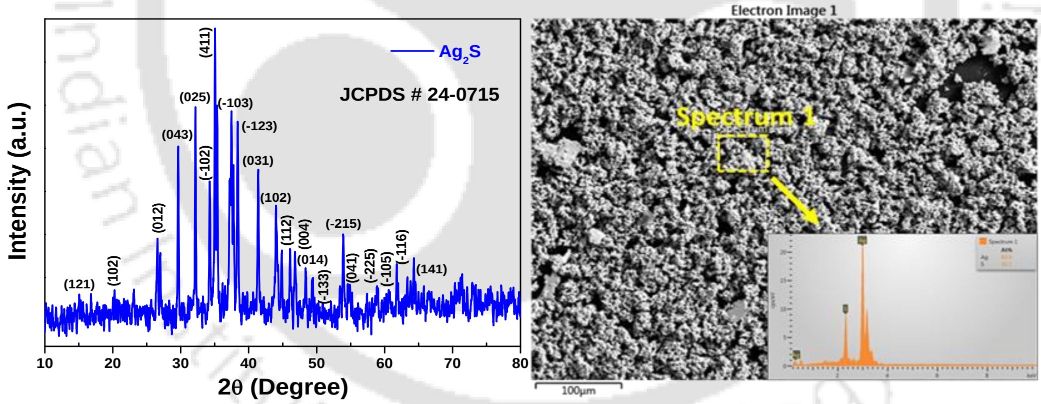
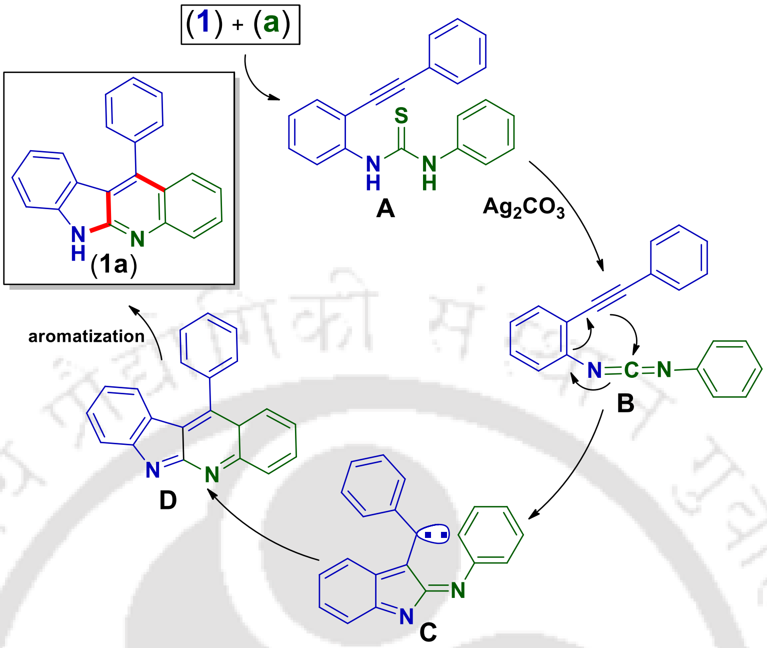


Figure VB.3.2. *(i) Powder X-ray diffraction (PXRD) and (ii) Energy-dispersive X-ray spectroscopy (EDS) pattern of the formed* Ag_2S

On the basis of our experimental findings and previous literature,[9] a plausible reaction mechanism has been proposed as depicted in Scheme VB.3.4. Reaction of 2-(phenylethynyl)anilines (**1**) and phenyl isothiocyanate (**a**) forms intermediate thiourea (**A**), which is desulfurized in the presence of Ag_2CO_3 to a carbodiimide intermediate (**B**).[14] Intramolecular thermal cyclization of (**B**) generated a carbene type intermediate (**C**). The intermediate (**C**) undergo further cyclization via carbene C–H insertion to form a non-aromatic cyclized species (**D**), which is aromatized to give the desired product (**1a**) (Scheme VB.3.4).



Scheme VB.3.4. *Proposed mechanistic pathway*

In conclusion, we have developed an elegant cascade approach for the synthesis of indoloquinolines. This protocol allows the practical synthesis of many valuable indolquinoline alkaloids through Ag$_2$CO$_3$-mediated cascade annulation of internal alkynes under microwave heating. This methodology has the advantage of good functional group tolerance, mild microwave reaction and shorter reaction time.

VB.4. Experimental Section

VB.4.1. General Information: All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Microwave reactions were carried out on the CEM Discover system (Model No. 908010, manufactured by CEM Company, with a vertically focused infrared [IR] temperature control system. Reactions were monitored by TLC on silica gel 60 F$_{254}$ (0.25mm). NMR spectra were recorded in DMSO-d_6, CDCl$_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz and 600 MHz), DMSO-d_6, or CDCl$_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). HRMS spectra were recorded using ESI mode (Q-TOF MS Analyzer).

VB.4.2. Crystallographic Description

CCDC Number for Compounds 1a: CCDC 1519119. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Description of 11-Phenyl-6*H*-indolo[2,3-*b*]quinoline (1a): Crystal dimensions 0.32 x 0.30 x 0.28 mm, M_r = 294.34, Monoclinic, space group P 21/n, a = 13.1263(9), b = 18.8252(13), c = 13.4559(10) Å, $\alpha = 90.0^{\circ}$, $\beta = 112.916^{\circ}$ (9), $\gamma = 90.0^{\circ}$, V = 3060.6 (4)$Å^3$, Z = 8, ρ_{calcd} = 1.277g/cm^3, μ = 0.076mm^{-1}, F(000)= 1232.0, reflection collected / unique = 5401 / 5393, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.1307, wR_2 = 0.1900, R indices (all data): R_1 = 0.0811, wR_2 = 0.1604, goodness of fit = 1.089.

VB.4.3. Typical Procedure for the Synthesis of 11-Phenyl-6*H*-indolo[2,3-*b*]quinolone (1a): 2-(Phenylethynyl)aniline (**1**) (0.25 mmol, 48 mg), phenyl isothiocyanate (**a**) (0.375 mmol, 51 mg), and Ag_2CO_3 (0.25 mmol, 69 mg) in DMSO (1 mL) were taken in an oven-dried microwave reaction tube. The reaction vial was then sealed with a cap and stirred at 130 °C [150 W] under microwave irradiation for 0.5h. The reaction mixture was then cooled to room temperature and admixed with ethyl acetate (25 mL). The organic layer was washed sequentially with a saturated solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product so obtained was then purified by silica gel column chromatography using EtOAc and hexane as eluent to give product (**1a**) (52 mg, 71%).

VB.5. References

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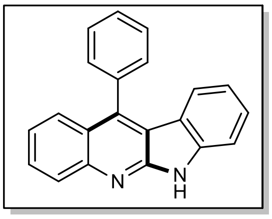
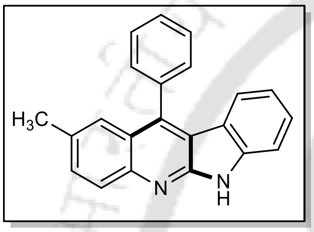
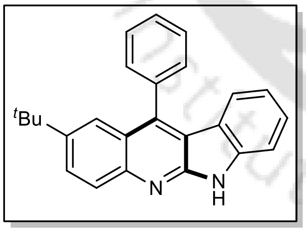
VB.6. Spectral Data



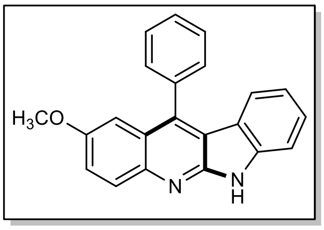
11-Phenyl-6*H*-indolo[2,3-*b*]quinoline (1a). Brown solid; M.p. 251–253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.92–6.93 (m, 2H), 7.34–7.43 (m, 2H), 7.47 (dd, 1H, *J* = 6.8 Hz), 7.53 (dd, 2H, *J* = 8.0 Hz), 7.62–7.71 (m, 5H), 8.04 (d, 1H, *J* = 8.4 Hz), 11.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 110.8, 115.4, 119.2, 120.2, 122.3, 122.7, 122.9, 125.7, 127.2, 127.8, 128.4, 128.6, 128.98, 129.02, 136.0, 141.4, 141.6, 146.3, 152.5; HRMS (ESI): calcd. for $C_{21}H_{15}N_2$ (MH^+) 295.1230, found 295.1224.



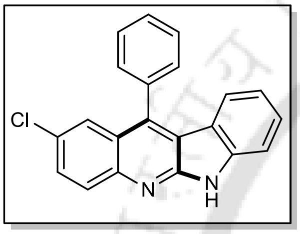
2-Methyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1b). Yellow solid; M.p. 253–255 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.37 (s, 3H), 6.86 (d, 1H, *J* = 7.6 Hz), 6.92 (t, 1H, *J* = 7.6 Hz), 7.38 (s, 1H), 7.41 (t, 1H, *J* = 6.8 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.51–7.55 (m, 3H), 7.64–7.72 (m, 3H), 7.95 (d, 1H, *J* = 8.8 Hz), 11.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.3, 110.9, 115.4, 119.2, 120.3, 122.5, 122.8, 124.3, 127.2, 127.8, 128.7, 129.1, 129.2, 130.8, 131.8, 136.2, 140.8, 141.6, 144.9, 152.1; HRMS (ESI): calcd. for $C_{22}H_{17}N_2$ (MH^+) 309.1386, found 309.1382.



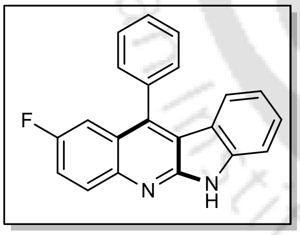
2-(Tert-butyl)-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1c). Yellow solid; M.p. 259–261 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.25 (s, 9H), 6.90–6.96 (m, 2H), 7.40–7.44 (m, 1H), 7.47 (d, 1H, *J* = 8.0 Hz), 7.56 (d, 3H, *J* = 6.8 Hz), 7.66–7.74 (m, 3H), 7.84 (dd, 1H, *J* = 8.8 Hz), 7.99 (d, 1H, *J* = 8.8 Hz) 11.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 30.9, 34.5, 110.9, 115.3, 119.2, 120.2, 120.3, 122.2, 122.3, 127.0, 127.5, 127.8, 128.7, 129.1, 136.1, 141.5, 141.6, 144.8, 144.9, 152.3; HRMS (ESI): calcd. for $C_{25}H_{23}N_2$ (MH^+) 351.1856, found 351.1852.



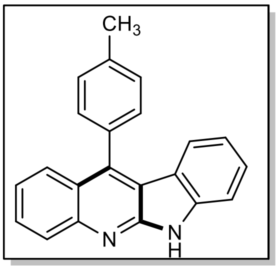
2-Methoxy-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1d). Black solid; M.p. 257–259 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.78 (s, 3H), 6.96 (t, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 7.6 Hz), 7.07 (d, 1H, J = 7.8 Hz), 7.38 (d, 2H, J = 7.6 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.53–7.55 (m, 2H), 7.63–7.70 (m, 3H), 8.11 (d, 1H, J = 9.2 Hz), 12.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 55.7, 105.0, 110.9, 117.0, 119.7, 121.1, 121.2, 123.2, 124.3, 127.9, 128.0, 128.7, 129.3, 129.5, 136.8, 141.6, 141.8, 142.2, 152.3, 155.4; HRMS (ESI): calcd. for $C_{22}H_{17}N_2O$ (MH$^+$) 325.1335, found 325.1337.



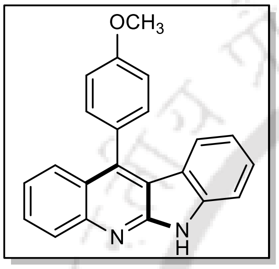
2-Chloro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1e). White solid; M.p. 207–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.90–6.97 (m, 2H), 7.42–7.46 (m, 1H), 7.49 (d, 1H, J = 8.0 Hz), 7.52–7.55 (m, 3H), 7.66–7.73 (m, 4H), 8.04 (d, 1H, J = 8.8 Hz), 11.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 111.0, 116.2, 119.5, 119.9, 122.5, 123.5, 124.0, 127.0, 128.3, 128.8, 128.9, 129.0, 129.2, 129.3, 135.2, 140.5, 141.8, 144.7, 152.6; HRMS (ESI): calcd. for $C_{21}H_{14}ClN_2$ (MH$^+$) 329.0840, found 329.0828.



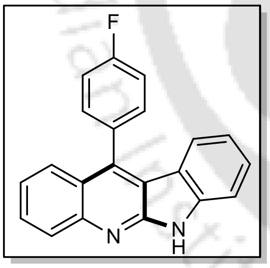
2-Fluoro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1f). Yellow solid; M.p. 266–268 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.91 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 7.23–7.42 (m, 6H), 7.63–7.65 (m, 3H), 8.04 (dd, 1H, J = 8.8 Hz), 12.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 109.6, 109.9, 111.0, 117.3, 118.7, 118.9, 119.9, 120.5, 123.2, 124.0, 124.1, 128.1, 128.2, 128.3, 129.0, 129.3, 129.5, 136.0, 141.9, 142.05, 142.1, 143.0, 152.9, 157.3, 159.7; HRMS (ESI): calcd. for $C_{21}H_{14}FN_2$ (MH$^+$) 313.1136, found 313.1147.



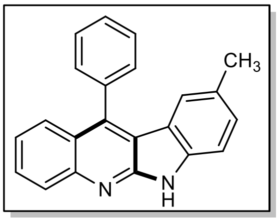
11-(*p*-Tolyl)-6*H*-indolo[2,3-*b*]quinoline (2a). Yellowish solid; M.p. 221–223 °C ;^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.60 (s, 3H), 7.01 (t, 1H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.38–7.45 (m, 4H), 7.46 (d, 2H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.74 (dd, 1H, *J* = 6.8 Hz), 7.83 (dd, 1H, *J* = 8.8 Hz), 8.23 (d, 1H, *J* = 8.0 Hz), 12.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 111.0, 117.1, 119.9, 121.4, 123.0, 123.3, 124.1, 125.6, 126.5, 126.9, 128.0, 129.0, 129.5, 129.8, 133.5, 138.5, 141.8, 143.3, 146.3, 153.6; HRMS (ESI): calcd. for $C_{22}H_{17}N_2$ (MH^+) 309.1386, found 309.1394.



11-(4-Methoxyphenyl)-6*H*-indolo[2,3-*b*]quinoline (3a). Brown solid; M.p. 243–245 °C; ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 3.91 (s, 3H), 6.98 (t, 1H, *J* = 7.8 Hz), 7.06 (d, 1H, *J* = 7.8 Hz), 7.24 (d, 2H, *J* = 9.2 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.43 (dd, 1H, *J* = 7.8 Hz), 7.44–7.49 (m, 3H), 7.67–7.72 (m, 2H), 8.04 (d, 1H, *J* = 8.4 Hz) 11.83 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ (ppm) 55.3, 110.9, 114.5, 115.7, 119.3, 120.4, 122.4, 122.8, 123.3, 125.9, 127.3, 127.8, 127.9, 128.5, 130.5, 141.5, 141.6, 146.4, 152.5, 159.5; HRMS (ESI): calcd. for $C_{22}H_{17}N_2O$ (MH^+) 325.1335, found 325.1334.

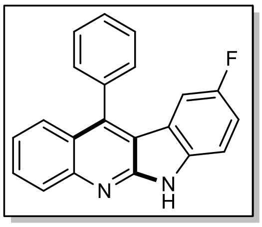


11-(4-Fluorophenyl)-6*H*-indolo[2,3-*b*]quinoline (4a). Brown solid; M.p. 297–299 °C; ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 6.95 (d, 1H, *J* = 7.8 Hz), 7.00 (t, 1H, *J* = 7.2 Hz), 7.40 (t, 1H, *J* = 7.8 Hz), 7.44–7.47 (m, 1H), 7.50 (d, 1H, *J* = 7.8 Hz), 7.54 (t, 2H, *J* = 8.4 Hz), 7.61–7.62 (m, 3H), 7.73 (t, 1H, *J* = 7.8 Hz), 8.05 (d, 1H, *J* = 9.0 Hz), 11.88 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ (ppm) 111.0, 115.7, 116.2, 116.3, 118.2, 119.5, 120.1, 122.3, 123.0, 125.6, 127.3, 128.1, 128.7, 128.8, 131.35, 131.41, 132.2, 140.5, 141.7, 146.3, 152.4, 161.5, 163.2; HRMS (ESI): calcd. for $C_{21}H_{14}FN_2$ (MH^+) 313.1136, found 313.1150.

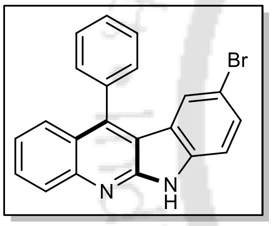


9-Methyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (5a). Pale yellow solid; M.p. 193–195 °C; ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 2.17 (s, 3H), 6.70 (s, 1H), 7.26 (d, 1H, *J* = 7.6 Hz), 7.37 (dd, 2H, *J* = 9.6 Hz), 7.47 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 2H, *J* = 7.8 Hz), 7.61 (d, 1H, *J* = 7.8 Hz), 7.68–7.71 (m, 3H), 8.03 (d, 1H, *J* = 8.4 Hz), 11.73

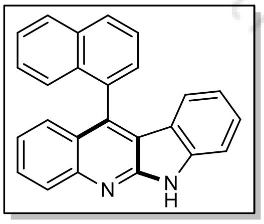
(s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.1, 110.7, 115.4, 118.2, 120.3, 121.8, 122.4, 122.7, 125.7, 127.2, 127.8, 128.5, 128.7, 128.8, 129.1, 136.0, 139.8, 141.4, 146.3, 152.7; HRMS (ESI): calcd. for $C_{22}H_{17}N_2$ (MH^+) 309.1386, found 309.1392.



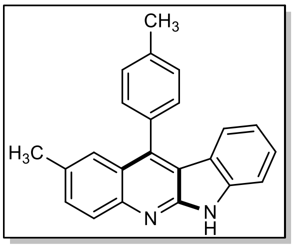
9-Fluoro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (6a). Light yellow solid; M.p. 276–278 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.51 (dd, 1H, J = 9.6 Hz), 7.30 (td, 1H, J = 9.6 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.48 (dd, 1H, J = 8.4 Hz), 7.54 (d, 2H, J = 6.0 Hz), 7.63 (d, 1H, J = 7.8 Hz), 7.68–7.44 (m, 4H), 8.05 (d, 1H, J = 8.4 Hz), 11.89 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 107.8, 108.0, 111.9, 112.0, 115.1, 115.3, 115.4, 120.6, 120.7, 122.6, 123.0, 125.9, 127.4, 128.9, 128.98, 129.03, 129.2, 135.5, 138.1, 142.3, 146.7, 153.0, 155.4, 157.0; HRMS (ESI): calcd. for $C_{21}H_{14}FN_2$ (MH^+) 313.1136, found 313.1150.



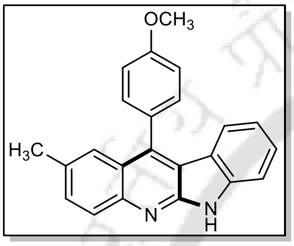
9-Bromo-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (7a). Brown solid; M.p. 229–231 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.93 (s, 1H), 7.27 (t, 2H, J = 7.2 Hz), 7.45 (d, 2H, J = 8.4 Hz), 7.55 (d, 1H, J = 6.0 Hz), 7.63 (d, 1H, J = 8.4 Hz), 7.70–7.76 (m, 4H), 8.06 (d, 1H, J = 8.4 Hz), 12.01 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 111.1, 113.0, 114.5, 118.2, 121.8, 123.3, 124.5, 125.9, 127.4, 128.8, 129.0, 129.3, 130.3, 135.5, 139.7, 140.5, 142.4, 146.8, 152.4; HRMS (ESI): calcd. for $C_{21}H_{14}BrN_2$ (MH^+) 373.0335 found 373.0350.



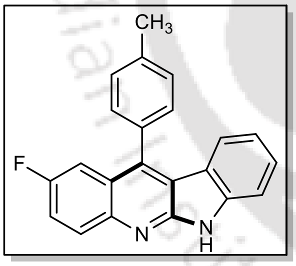
11-(Naphthalen-1-yl)-6*H*-indolo[2,3-*b*]quinoline (8a). Brown solid; M.p. 256–259 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.35 (d, 1H, J = 7.8 Hz), 6.73 (t, 1H, J = 7.8 Hz), 7.09 (d, 1H, J = 8.4 Hz), 7.22 (t, 1H, J = 7.8 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.33–7.38 (m, 2H), 7.48 (d, 1H, J = 8.4 Hz), 7.52 (t, 1H, J = 7.8 Hz), 764 (d, 1H, J = 6.6 Hz), 7.70 (t, 1H, J = 7.8 Hz), 7.79 (t, 1H, J = 7.8 Hz), 8.12 (d, 2H, J = 8.4 Hz), 8.23 (d, 1H, J = 8.4 Hz), 11.93 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 110.9, 116.5, 119.3, 120.0, 122.2, 123.0, 123.5, 124.9, 125.8, 126.0, 126.5, 126.9, 127.1, 127.4, 128.0, 128.6, 128.7, 129.0, 131.0, 133.4, 133.5, 139.5, 141.7, 146.4, 152.6; HRMS (ESI): calcd. for $C_{25}H_{17}N_2$ (MH^+) 345.1386, found 345.1373.



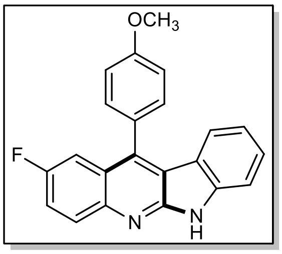
2-Methyl-11-(*p*-tolyl)-6*H*-indolo[2,3-*b*]quinoline (2b). Light Yellow solid; M.p. 303–305 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.16 (s, 3H), 2.29 (s, 3H), 6.69–6.74 (m, 2H), 7.18 (d, 4H, J = 7.6 Hz), 7.26 (t, 3H, J = 7.6 Hz), 7.31 (dd, 1H, J = 8.8 Hz), 7.72 (d, 1H, J = 8.4 Hz) 11.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.1, 21.2, 110.7, 115.5, 118.2, 119.1, 120.3, 122.3, 123.0, 124.4, 127.1, 127.7, 128.9, 129.7, 131.5, 133.1, 137.8, 140.9, 141.6, 144.9, 152.1; HRMS (ESI): calcd. for $C_{23}H_{19}N_2$ (MH$^+$) 323.1543, found 323.1552.



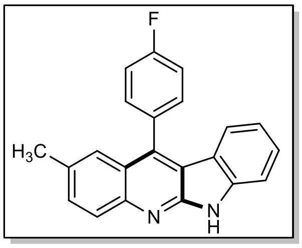
11-(4-Methoxyphenyl)-2-methyl-6*H*-indolo[2,3-*b*]quinoline (3b). Yellow solid; M.p. 275–278 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.38 (s, 3H), 3.91 (s, 3H), 6.96 (t, 1H, J = 7.2 Hz), 7.00 (d, 1H, J = 7.8 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.40–7.45 (m, 5H), 7.53 (d, 1H, J = 9.0 Hz), 7.94 (d, 1H, J = 8.4 Hz), 11.75 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.2, 55.2, 110.8, 114.5, 115.7, 119.2, 120.4, 122.3, 123.2, 124.5, 127.1, 127.8, 128.0, 130.4, 130.7, 131.7, 140.9, 141.6, 145.0, 152.1, 159.4; HRMS (ESI): calcd. for $C_{23}H_{19}N_2O$ (MH$^+$) 339.1492, found 339.1482.



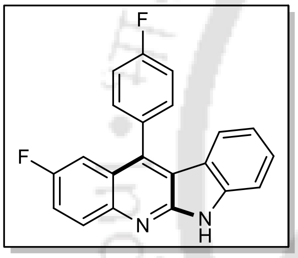
2-Fluoro-11-(*p*-tolyl)-6*H*-indolo[2,3-*b*]quinoline (2f). Pale brown solid; M.p. 280–282 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.49 (s, 3H), 6.94–7.01 (m, 2H), 7.22 (dd, 1H, J = 10.6 Hz), 7.40–7.51 (m, 6H), 7.58–7.65 (m, 1H), 8.08 (dd, 1H, J = 9.2 Hz), 11.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.1, 108.4, 108.7, 111.0, 116.1, 118.2, 118.5, 119.5, 119.8, 122.5, 123.2, 123.3, 128.3, 128.9, 129.7, 129.8, 129.9, 132.4, 138.3, 140.88, 140.93, 141.8, 143.4, 152.3, 156.4, 158.8; HRMS (ESI): calcd. for $C_{22}H_{16}FN_2$ (MH$^+$) 327.1292, found 327.1285.



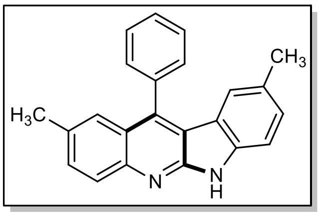
2-Fluoro-11-(4-methoxyphenyl)-6*H*-indolo[2,3-*b*]quinoline (3f). Black solid; M.p. 238–240 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 3.92 (s, 3H), 7.00 (t, 1H, J = 7.2 Hz), 7.07 (t, 2H, J = 7.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.45–7.50 (m, 3H), 7.64 (td, 1H, J = 9.6 Hz), 7.81 (d, 1H, J = 9.0 Hz), 8.09 (dd, 1H, J = 9.6 Hz), 11.85 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 55.3, 108.5, 108.7, 111.0, 112.4, 112.5, 114.5, 114.7, 116.3, 118.3, 118.5, 119.5, 119.9, 122.6, 123.47, 123.52, 127.3, 128.3, 129.5, 130.5, 141.8, 143.8, 143.4, 152.3, 156.8, 159.57, 159.63; HRMS (ESI): calcd. for $C_{22}H_{16}FN_2O$ (MH^+) 343.1241, found 343.1231.



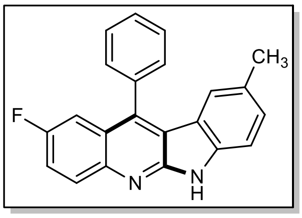
11-(4-Fluorophenyl)-2-methyl-6*H*-indolo[2,3-*b*]quinoline (4b). Pale brown solid; M.p. 288–289 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.39 (s, 3H), 6.89 (d, 1H, $J = 7.6$ Hz), 6.97 (t, 1H, $J = 7.6$ Hz), 7.36 (s, 1H), 7.41–7.48 (m, 2H), 7.52–7.61 (m, 5H), 7.95 (d, 1H, $J = 8.4$ Hz), 11.78 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.4, 111.2, 115.9, 116.4, 116.5, 119.6, 120.3, 122.4, 123.1, 124.4, 127.3, 128.2, 131.2, 131.5, 131.6, 132.3, 132.47, 132.49, 140.1, 141.8, 144.9, 152.1, 161.7, 163.3; HRMS (ESI): calcd. for $C_{22}H_{16}FN_2$ (MH^+) 327.1292, found 327.1274.



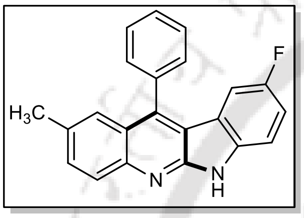
2-Fluoro-11-(4-fluorophenyl)-6*H*-indolo[2,3-*b*]quinoline (4f). Pale brown solid; M.p. 308–310 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.96 (d, 1H, $J = 7.6$ Hz), 7.01 (dd, 1H, $J = 8.0$ Hz), 7.22 (dd, 1H, $J = 7.6$ Hz), 7.43–7.51 (m, 2H), 7.56 (t, 2H, $J = 4.8$ Hz), 7.62–7.69 (m, 3H), 8.11 (dd, 1H, $J = 9.2$ Hz), 11.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 108.7, 108.9, 111.5, 115.5, 115.7, 116.67, 116.72, 116.8, 118.9, 119.1, 119.9, 120.0, 120.5, 120.6, 122.7, 123.4, 123.5, 128.9, 129.86, 129.92, 131.59, 131.64, 140.4, 142.2, 143.3, 152.3, 157.3, 158.9, 161.9, 163.6; HRMS (ESI): calcd. for $C_{21}H_{13}F_2N_2$ (MH^+) 331.1041, found 331.1058.



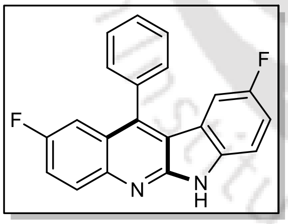
2,9-Dimethyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (5b). Brown solid; M.p. 233–236 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.16 (s, 3H), 2.37 (s, 3H), 6.64 (s, 1H), 7.23 (d, 1H, $J = 7.8$ Hz), 7.36 (d, 2H, $J = 7.8$ Hz), 7.52 (dd, 3H, $J = 9.6$ Hz), 7.66–7.71 (m, 3H), 7.93 (d, 1H, $J = 9.0$ Hz), 11.64 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.1, 21.2, 110.6, 115.4, 120.4, 122.4, 122.7, 124.3, 127.1, 127.7, 128.6, 128.9, 129.08, 129.13, 130.7, 131.7, 136.2, 139.7, 140.7, 144.9, 152.3; HRMS (ESI): calcd. for $C_{23}H_{19}N_2$ (MH^+) 323.1543, found 323.1548.



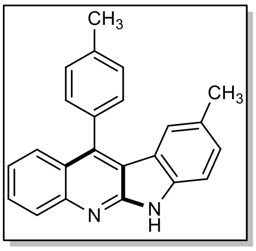
2-Fluoro-9-methyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (5f). Yellow solid; M.p. 211–213 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.17 (s, 3H), 6.70 (s, 1H), 7.19 (dd, 1H, J = 8.4 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.55 (d, 2H, J = 6.6 Hz), 7.63 (td, 1H, J = 9.0 Hz), 7.69–7.74 (m, 3H), 8.08 (dd, 1H, J = 9.6 Hz), 11.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.1, 108.4, 108.6, 110.8, 116.0, 118.3, 118.5, 119.9, 122.6, 122.97, 123.03, 128.0, 128.98, 129.04, 129.3, 129.5, 129.7, 129.8, 135.5, 140.0, 140.7, 143.3, 152.5, 156.8, 158.4; HRMS (ESI): calcd. for $C_{22}H_{16}FN_2$ (MH$^+$) 327.1292, found 327.1278.



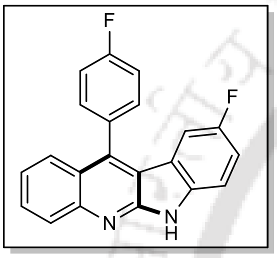
9-Fluoro-2-methyl-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (6b). Yellow solid; M.p. 248–250 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.36 (s, 3H), 6.46 (dd, 1H, J = 9.0 Hz), 7.27 (td, 1H, J = 9.0 Hz), 7.37 (s, 1H), 7.46 (dd, 1H, J = 7.8 Hz), 7.51–7.54 (m, 3H), 7.66–7.71 (m, 3H), 7.93 (d, 1H, J = 8.4 Hz), 11.93 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.2, 107.7, 107.9, 111.8, 111.9, 115.0, 115.07, 115.09, 115.3, 120.68, 120.74, 122.5, 124.4, 127.2, 128.9, 129.0, 129.2, 131.2, 132.0, 135.7, 138.0, 141.6, 145.3, 152.6, 155.3, 156.9; HRMS (ESI): calcd. for $C_{22}H_{16}FN_2$ (MH$^+$) 327.1292, found 327.1303.



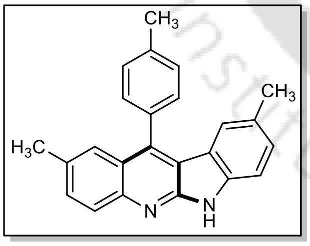
2,9-Difluoro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (6f). Yellow solid; M.p. 296–298 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.52 (dd, 1H, J = 9.0 Hz), 7.20 (dd, 1H, J = 10.2 Hz), 7.31 (td, 1H, J = 9.0 Hz), 7.48 (dd, 1H, J = 9.0 Hz), 7.54 (d, 2H, J = 7.2 Hz), 7.63 (td, 1H, J = 9.6 Hz), 7.00–7.74 (m, 3H), 8.08 (d, 1H, J = 9.0 Hz),11.91 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 107.9, 108.1, 108.5, 108.6, 112.0, 112.1, 115.2, 115.3, 115.7, 115.9, 118.9, 119.0, 120.0, 120.07, 120.13, 120.2, 122.75, 122.81, 128.9, 129.2, 129.4, 129.8, 129.9, 135.0, 138.3, 141.5, 141.6, 143.7, 152.7, 155.4, 156.90, 156.94, 158.5; HRMS (ESI): calcd. for $C_{21}H_{13}F_2N_2$ (MH$^+$) 331.1041, found 331.1058.



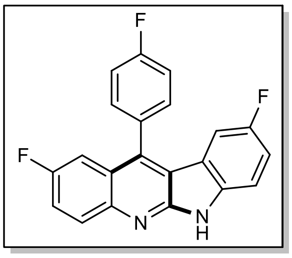
9-Methyl-11-(*p*-tolyl)-6*H*-indolo[2,3-*b*]quinoline (9a). Brown solid; M.p. 258–260 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.18 (s, 3H), 250 (s, 3H), 6.81 (s, 1H), 7.25 (d, 1H, J = 7.8 Hz), 7.34–7.38 (m, 2H), 7.41 (d, 2H, J = 7.8 Hz), 7.49 (d, 2H, J = 7.8 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.69 (t, 1H, J = 7.8 Hz), 8.02 (d, 1H, J = 8.4 Hz), 11.70 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.1, 21.2, 110.6, 115.4, 118.2, 120.4, 122.5, 122.6, 123.0, 125.8, 127.2, 128.5, 128.8, 129.0, 129.6, 133.0, 138.0, 139.7, 141.5, 146.4, 152.7; HRMS (ESI): calcd. for $C_{23}H_{19}N_2$ (MH$^+$) 323.1543, found 323.1541.



9-Fluoro-11-(4-fluorophenyl)-6*H*-indolo[2,3-*b*]quinoline (10a). Yellow solid; M.p. 314–316 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.56 (dd, 1H, J = 9.0 Hz), 7.32 (t, 1H, J = 9.0 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.49 (dd, 1H, J = 9.0 Hz), 7.56 (t, 2H, J = 8.4 Hz), 7.62 (d, 3H, J = 7.8 Hz), 7.74 (t, 1H, J = 7.8 Hz), 8.05 (d, 1H, J = 8.4 Hz), 11.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 107.8, 107.9, 111.97, 112.03, 114.1, 115.3, 115.4, 115.6, 116.2, 116.4, 120.5, 120.6, 122.7, 123.1, 125.7, 127.4, 128.3, 129.1, 131.3, 131.4, 131.7, 138.1, 141.2, 146.7, 152.9, 155.4, 157.0, 161.6, 163.6; HRMS (ESI): calcd. for $C_{21}H_{13}F_2N_2$ (MH$^+$) 331.1041, found 331.1040.



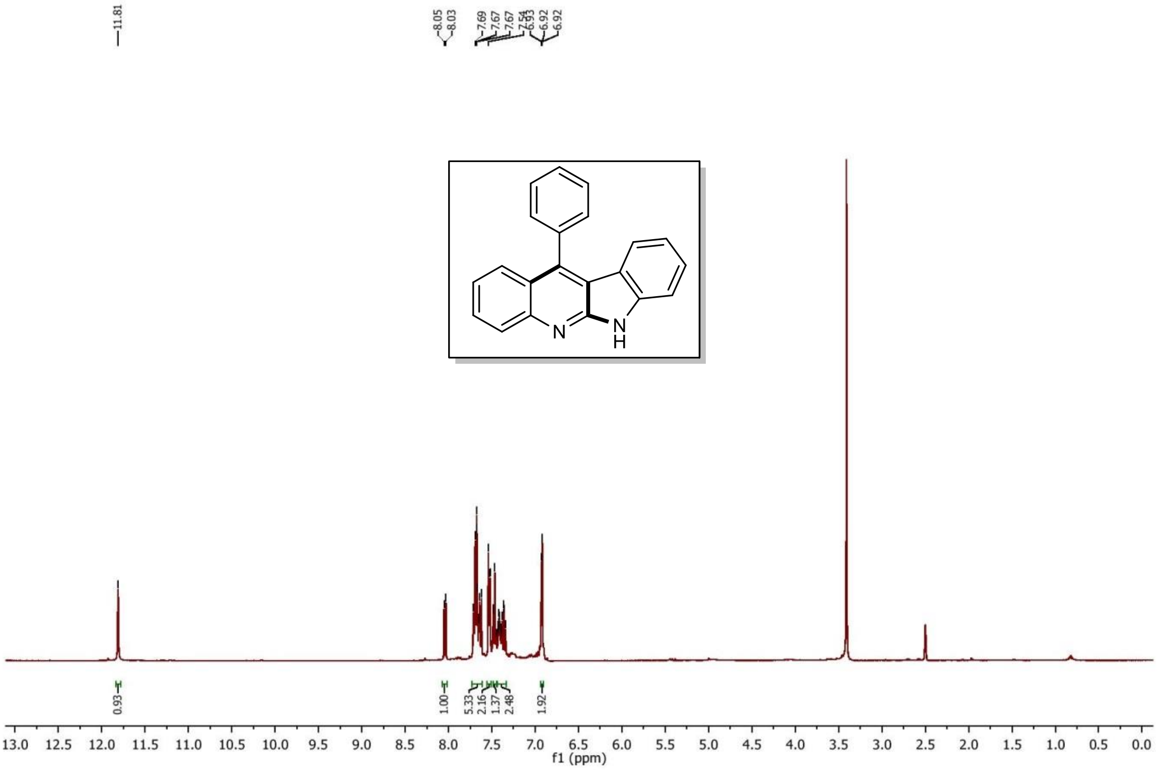
2,9-Dimethyl-11-(*p*-tolyl)-6*H*-indolo[2,3-*b*]quinoline (9b). Pale brown solid; M.p. 308–310 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.18 (s, 3H), 2.38 (s, 3H), 2.52 (s, 3H), 6.74 (s, 1H), 7.24 (d, 1H, J = 7.8 Hz), 7.34–7.40 (m, 4H), 7.51–7.54 (m, 3H), 7.92 (d, 1H, J = 9.0 Hz), 11.58 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.1, 21.18, 21.23, 110.6, 115.4, 120.5, 122.4, 122.9, 124.4, 127.1, 127.6, 128.9, 129.0, 129.7, 130.7, 131.6, 133.1, 137.9, 139.7, 140.9, 144.9, 152.3; HRMS (ESI): calcd. for $C_{24}H_{21}N_2$ (MH$^+$) 337.1699, found 337.1693.



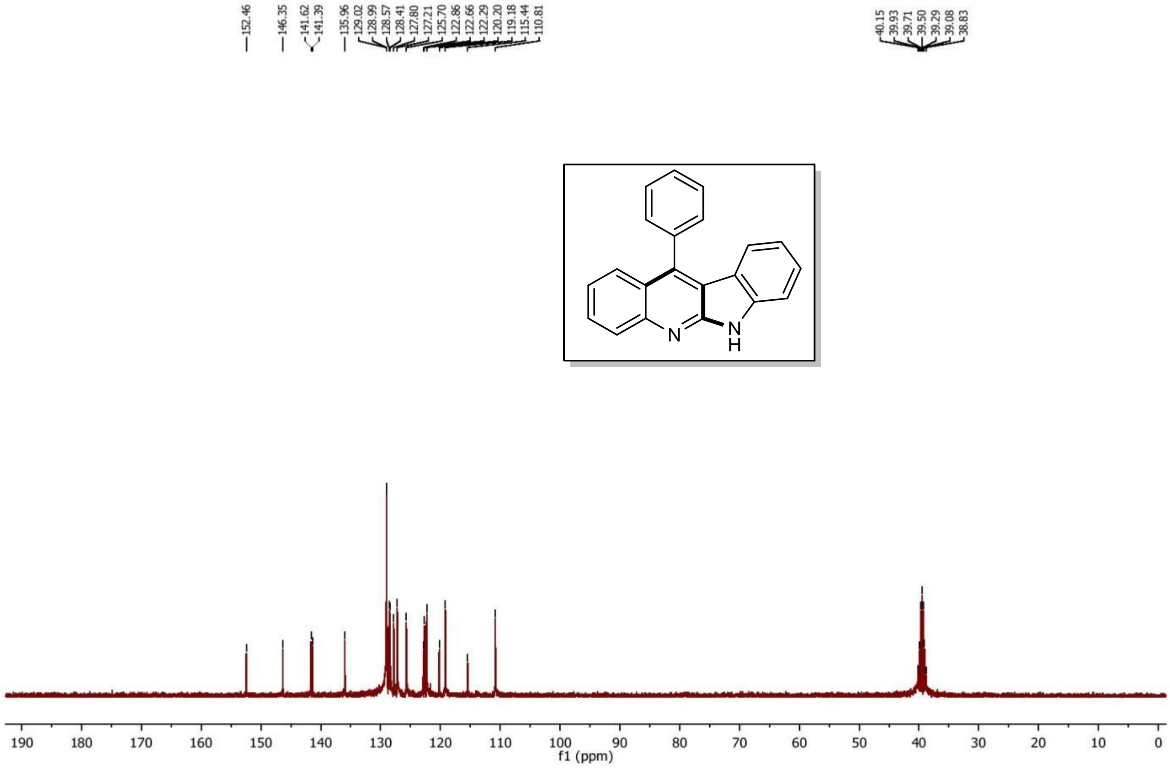
2,9-Difluoro-11-(4-fluorophenyl)-6*H*-indolo[2,3-*b*]quinoline (10f). Greenish brown solid; M.p. 316–318 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.57 (dd, 1H, J = 9.0 Hz), 7.21 (dd, 1H, J = 10.2 Hz), 7.32 (td, 1H, J = 9.0 Hz), 7.46–7.48 (m, 1H), 7.56 (t, 2H, J = 8.4 Hz), 7.63 (dd, 3H, J = 5.4 Hz), 8.07 (dd, 1H, J = 8.4 Hz), 11.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 108.5, 108.7, 109.0, 109.2, 112.68, 112.74, 115.8, 116.0, 116.4, 116.6, 117.0, 117.2, 119.5, 119.6, 120.67, 120.71, 123.48, 123.54, 130.46, 130.52, 131.9, 131.95, 132.01, 138.9, 141.08, 141.12, 144.3, 153.3, 156.0, 157.57, 157.59, 159.2, 162.4, 164.0; HRMS (ESI): calcd. for $C_{21}H_{12}F_3N_2$ (MH^{+}) 349.0947, found 349.0939.

VB.7. Spectra

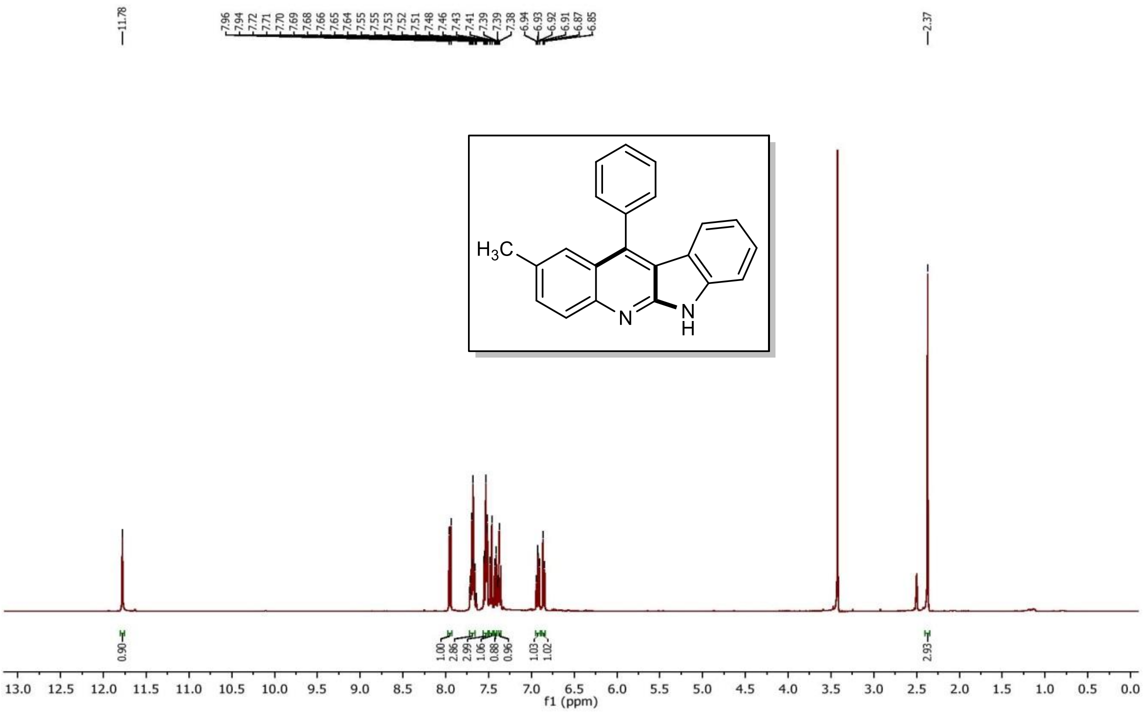
11-Phenyl-6*H*-indolo[2,3-*b*]quinoline (1a): ^{1}HNMR (400 MHz, DMSO-d_6)



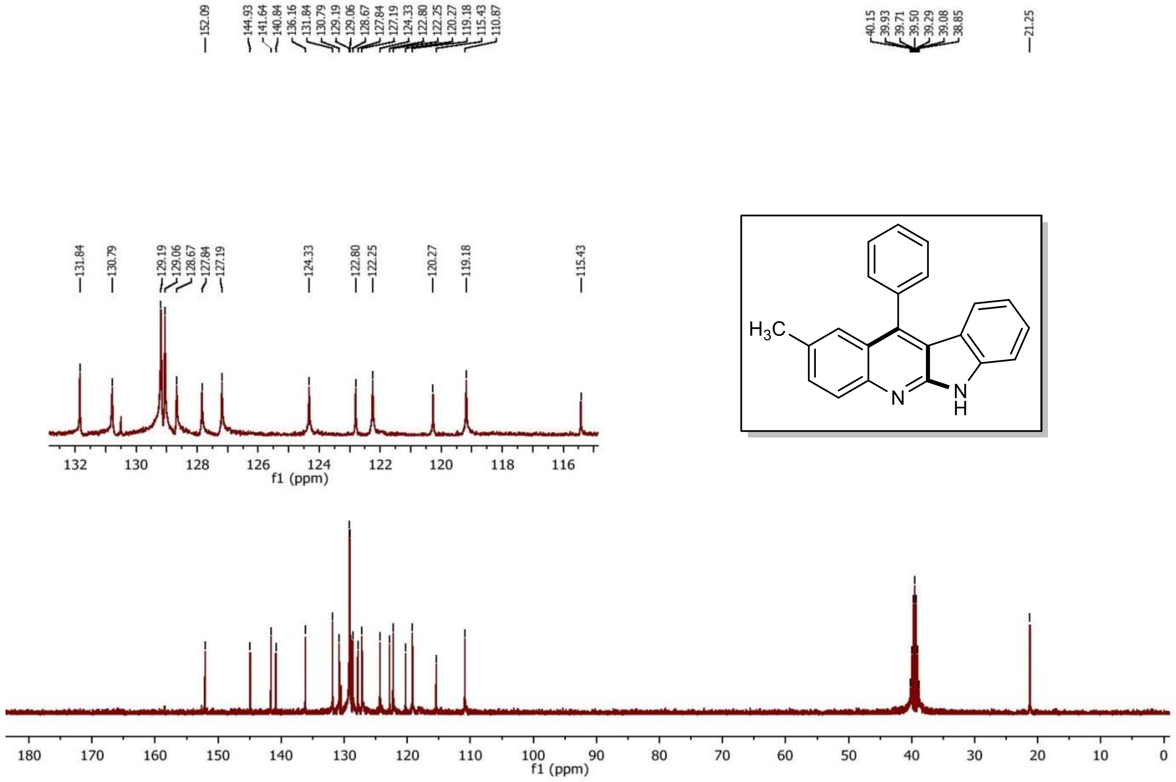
11-Phenyl-6*H*-indolo[2,3-*b*]quinoline (1a): ^{13}CNMR (100 MHz, DMSO-d_6)



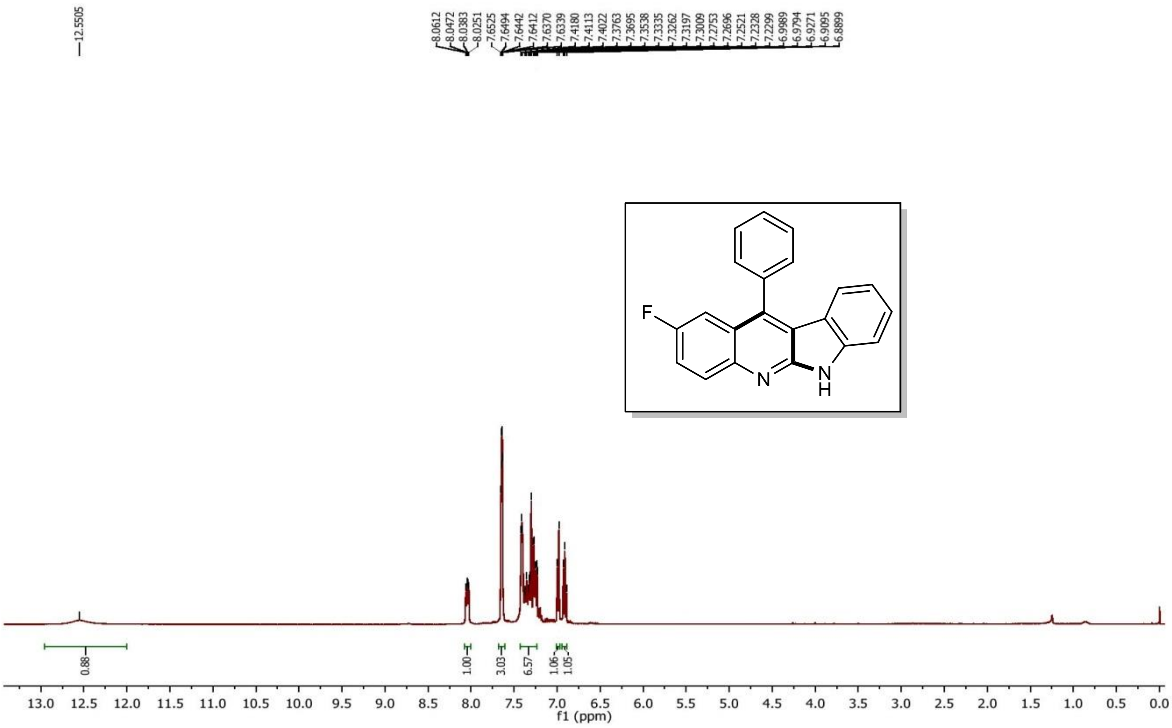
11-(*p*-Tolyl)-6*H*-indolo[2,3-*b*]quinoline (2a): ^{1}HNMR (400 MHz, DMSO-d_6)



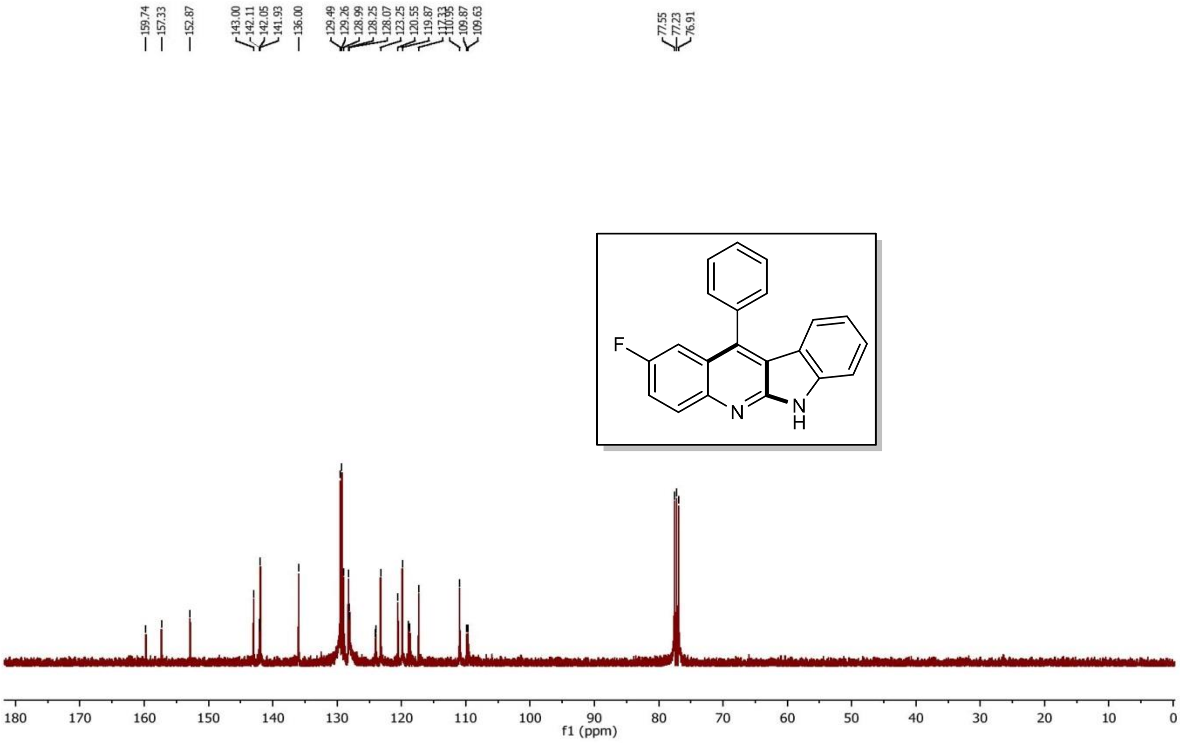
11-(*p*-Tolyl)-6*H*-indolo[2,3-*b*]quinoline (2a): ^{13}CNMR (100 MHz, DMSO-d_6)



2-Fluoro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1f): ^{1}HNMR (400 MHz, CDCl$_3$)



2-Fluoro-11-phenyl-6*H*-indolo[2,3-*b*]quinoline (1f): ^{13}CNMR (100 MHz, CDCl$_3$)



List of Publications:

1. Cascade synthesis of dihydrobenzofurans and aurones via palladium-catalyzed isocyanides insertion into 2-halophenoxy acrylates **Wajid Ali**, Anjali Dahiya, Bhisma K. Patel *Manuscript under communication.*
2. Microwave-assisted cascade strategy for the synthesis of indolo[2,3-*b*]quinolines from 2-(phenylethynyl)anilines and aryl isothiocyanates. **Wajid Ali**, Anjali Dahiya, Ramdhari Pandey, Tipu Alam, Bhisma K. Patel *J. Org. Chem.* **2017**, *82*, 2089.
3. Cs_2CO_3 as a source of carbonyl and ethereal oxygen in a Cu-catalyzed cascade synthesis of benzofuran [3,2-*c*] quinolin-6[5-*H*]ones. **Wajid Ali**, Anju Modi, Ahalya Behera, Prakash Ranjan Mohanta, Bhisma K. Patel *Org. Biomol. Chem.* **2016**, *14*, 5940.
4. Regiospecific benzoylation of electron-deficient *N*-heterocycles with methylbenzenes via a Minisci-type reaction. **Wajid Ali**, Ahalya Behera, Srimanta Guin, Bhisma K. Patel *J. Org. Chem.* **2015**, *80*, 5625.
5. Thioesterification of alkylbenzenes with thiols via copper-catalyzed cross-dehydrogenative coupling without directing group. **Wajid Ali**, Srimanta Guin, Saroj K. Rout, Anupal Gogoi, Bhisma K. Patel *Adv. Synth. Catal.* **2014**, *356*, 3099.
6. Copper-catalyzed cross-dehydrogenative coupling of *N*,*N*-disubstituted formamides and phenols: A direct access to carbamates. **Wajid Ali**, Saroj K. Rout, Srimanta Guin, Anju Modi, Arghya Banerjee, Bhisma K. Patel *Adv. Synth. Catal.* **2015**, *357*, 515.
7. Copper-catalyzed esterification of alkylbenzenes with cyclic ethers and cycloalkanes via $C(sp^3)-H$ activation following cross-dehydrogenative coupling. Saroj Kumar Rout, Srimanta Guin, **Wajid Ali**, Anupal Gogoi, Bhisma K. Patel *Org. Lett.* **2014**, *16*, 3086.]
8. A palladium(II)-catalyzed synthesis of α-ketoamides via chemoselective aroyl addition to cyanamides. Srimanta Guin, Saroj K. Rout, Anupal Gogoi, **Wajid Ali**, Bhisma K. Patel *Adv. Synth. Catal.* **2014**, *356*, 2559.
9. CuO nanoparticle-catalyzed synthesis of 2,3-disubstituted quinazolinones via sequential *N*-arylation and oxidative C−H amidation. Anju Modi, **Wajid Ali**,

Prakash R. Mohanta, Nilufa Khatun, Bhisma K. Patel *ACS Sustainable Chem. Eng.* **2015**, *3*, 2582.

10. Benzyl bromides as aroyl surrogates in substrate directed Pd-catalyzed *o*-aroylation. Ahalya Behera, **Wajid Ali**, Srimanta Guin, Nilufa Khatun, Prakash R. Mohanta, Bhisma K. Patel *RSC Adv.* **2015**, *5*, 3333.
11. Benzylic ethers as arylcarboxy surrogates in substrate directed ortho C–H functionalization catalyzed by copper. Nilufa Khatun, Arghya Banerjee, Sourav Kumar Santra, **Wajid Ali**, Bhisma K. Patel *RSC Adv.* **2015**, *5*, 36461.
12. Oxidant controlled regioselective mono- and difunctionalization reactions of coumarins. Arghya Banerjee, Sourav Kumar Santra, Nilufa Khatun, **Wajid Ali**, Bhisma K. Patel *Chem. Commun.* **2015**, *51*, 15422.
13. Palladium-catalyzed synthesis of 2-aryl-2*H*-benzotriazoles from azoarenes and $TMSN_3$. Nilufa Khatun, Anju Modi, **Wajid Ali**, Bhisma K. Patel *J. Org. Chem.* **2015**, *80*, 9662.
14. *N*,*N*-Dimethylacetamide (DMA) as a methylene synthon for regioselective linkage of imidazo[1,2-*a*]pyridine. Anju Modi, **Wajid Ali**, Bhisma K. Patel *Adv. Synth. Catal.* **2016**, *358*, 2100.
15. Transition metal-free synthesis of α-ketoamides from arylmethyl ketones alkylphosphoramides. Ahalya Behera, **Wajid Ali**, Manisha Tripathy, Diptimayee Sahoo, Bhisma K. Patel *RSC Adv.* **2016**, *6*, 91308.
16. Copper(II)-catalyzed synthesis of indoloquinoxalin-6-ones through oxidative Mannich Reaction. Anupal Gogoi, Prasenjit Sau, **Wajid Ali**, Srimanta Guin, Bhisma K. Patel *Eur. J. Org. Chem.* **2016**, 1449.
17. Organocatalytic regioselective concomitant thiocyanation and acylation of oxiranes using aroyl isothiocyanates. Anju Modi, **Wajid Ali**, Bhisma K. Patel *Org. Lett.* **2017**, *19*, 432.