Exploration of Newer Strategies for the Construction of C–C and C–Heteroatom Bonds under Metal and Metal-free Conditions

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted By

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September, 2018

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DEDICATED TO

MY PARENTS AND FAMILY

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 Prof. Bhisma K. Patel.

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

September, 2018
IIT Guwahati

Ahalya Behera

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CERTIFICATE

This is to certify that Ahalya Behera has been working under my supervision since July 2013 as a regular registered Ph. D. student. Her thesis entitled "***Exploration of Newer Strategies for the Construction of C–C and C–Heteroatom Bonds under Metal and Metal-free Conditions***" is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding her thesis to submit for the Ph. D. (Science) degree from this institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

September, 2018

Prof. Bhisma K. Patel
(Thesis Supervisor)
Department of Chemistry
IIT Guwahati

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SYNOPSIS

The contents of this thesis have been divided into six chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview on the newer methodologies such C–H functionalisation, cross dehydrogenative coupling and other newer strategies leading to the formation of C–C and C–heteroatom bonds under metal and metal-free conditions. All the other chapters emphasise on C–C, C–O and C–N bond forming reactions under metal and metal-free conditions using strategies like C–H functionalisations, cross dehydrogenative coupling, one pot sequential and rearrangement reactions.

Chapter II demonstrates a copper catalysed *o*-benzoxylation of 2-phenylpyridines using benzyl amines as the arylcarboxy surrogate.

Chapter III illustrates the use of benzyl bromides as the aroyl source towards substrate directed *o*-aroylation catalysed by palladium salts.

Chapter IV describes the synthesis of α-ketoamides from arylmethyl ketones under a metal free condition using alkylphosphoramides as the aminyl source.

Chapter V demonstrates a one-pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides and *N*-(2-(phenylsulfinyl)phenyl)acetamides from 2-amino benzothiazole, aryl iodide and carboxylic acids *via* ring opening rearrangement functionalisation.

Chapter VI illustrates a cyano sacrificial (arylthio)-arylamination of quinoline and isoquinoline *N*-oxides using *N*-(2-(arylthio)aryl)cyanamides.

CHAPTER I. An Overview of C–H Functionalisation, Cross Dehydrogenative Coupling and Other Newer Aspects of C–C and C–Heteroatom Bond Formations

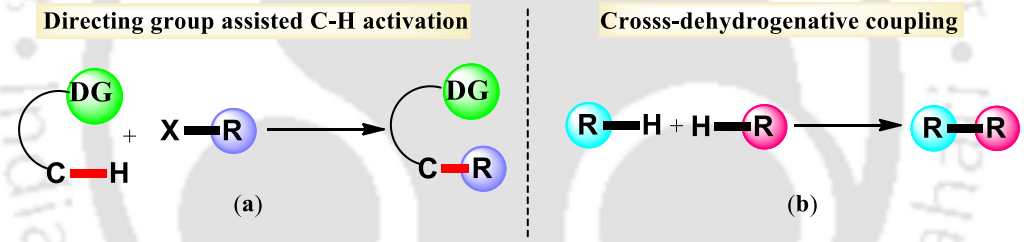
This chapter includes the history of C–H functionalisation, their advantages, challenges and applications in organic synthesis. It also involves other strategies such as cross dehydrogenative coupling, transition metal catalysed one pot sequential and rearrangement reactions for the construction of carbon-carbon and carbon-heteroatom bonds.

Coupling chemistry is an important synthetic strategy, extensively used in both industry and academics for the formation of C–C and C–heteroatom bonds. The traditional coupling procedures involve either the use of stoichiometric organometallic reagents, or the transition metal catalysed coupling of functionalised hydrocarbons. There has been substantial development of these methods over the last few decades, and they are successfully applied in the synthesis of commercially important products. However, the requirement of pre-functionalised starting materials in these methods, adds additional steps towards the formation of desired product, is a major concern along with atom-economic and environmental concerns. The best way to address this issue is to utilise un-functionalised starting materials *via* the direct functionalisation of C–H bonds.

On the other hand, direct C–H bond functionalisation reactions are limited by two fundamental challenges (i) the inert nature of carbon-hydrogen bonds and (ii) the requirement to control site selectivity in molecules that contain diverse C–H groups. However, the first challenge can be overcome by the use of a transition metals which can react with C–H bonds to form reactive C–M bonds. The second major challenge *i.e.* selectivity can be achieved by the use of substrates that contain co-ordinating ligands *viz.* the directing groups. These directing groups have a heteroatom which can co-ordinate with the metal and bring it to the close proximity of the desired C–H bond which is the subject of functionalisation. The process so developed is termed as directing group assisted C–H activation [Scheme I, (a)].

However, one more aspect to construct C–C and C–heteroatom bond is the oxidative coupling in the presence or absence of a metal catalyst is cross-dehydrogenative coupling (CDC) strategy (Scheme I, (b)). It generally refers to a cross-coupling reaction between two C–H bonds. In terms of atom economy, this synthetic method represents one of the most ideal synthetic procedures for selective C–C and C–heteroatom bond forming reactions.

With the motive of broadening the revolutionary aspect of organic synthesis, sometimes chemists use the combination of these two strategies: (a) substrate directed C–H bond functionalisation and (b) cross dehydrogenative coupling for the transformation of C–H bonds to C–C and C–heteroatom bonds. In this context, our group has developed a number of new disconnection approaches and generation of various functionalities *via* cleavage of inert C–H bonds.



Scheme I.1. *(a) Substrate directed C–H bond functionalisation; (b) cross dehydrogenative coupling*

Other than the above two strategies, the reactions like one pot sequential reactions and rearrangement reactions are also utilised tremendously for the construction C–C and C–heteroatom bonds. Among the C–heteroatom bonds, the construction of the C–N bond is of significant importance as it opens avenues for the introduction of nitrogen into organic molecules. Despite significant achievements in this field, the construction of the C–N bond is still a major challenge for organic chemists, due to the involvement of harsh reaction conditions or the use of expensive catalysts in many cases. Thus, it is a challenge to develop alternative, milder and cheaper methodologies for the construction of C–N bonds in one pot. In view of this aspect, the techniques to achieve newer methods for the construction of C–N bonds are the use of transition metals which can

increase the reactivity of the substrate so that it can undergo a rearrangement process. The traditional rearrangement reactions which are mainly based on the electrophillic and nucleophillic nature of the substrates, can be further extended by using transition metal catalysts.

CHAPTER II. Benzylamine as Arylcarboxy Surrogate: A Copper Catalysed *o*-Benzoxylation of 2-Phenylpyridines using Benzyl amines

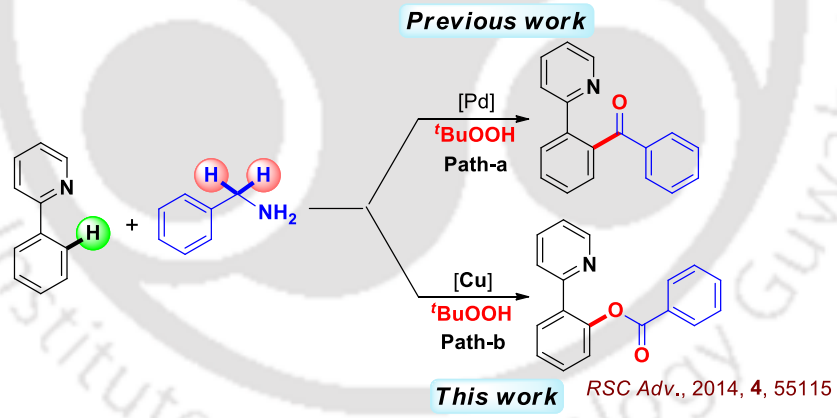
This chapter describes a copper(II) catalysed *o*-benzoxylation of 2-arylpyridines using arylmethylamines as the arylcarboxy- surrogate in the presence of oxidant.

Metal catalysed direct transformation of C–H bonds into C–C or C–heteroatom bonds is one of the reliable and facile tools in current organic chemistry. It renders step and atom economic strategy compared to traditional cross-coupling reactions *via* circuitous use of pre-functionalised starting materials. Even more attractive is the new disconnection approach, which would greatly enhance the number of retrosynthetic steps to build complex molecular scaffolds. Pertinent to this, the directing group assisted C–O bond formation mostly concentrated on acetoxylation and hydroxylation *via* C–H bond activation. However, reports on benzoxylation *via* same strategy are comparatively fewer inspite of their importance in the synthesis of natural products and pharmacological compounds. Previously, the *o*-benzoxylation of 2-phenylpyridine has been achieved using benzoate iodonium salts, carboxylic acids/salts or its derivatives such as acid chlorides, anhydrides or peroxides, aldehydes, alkylbenzenes, terminal alkenes and alkynes as the benzoxy surrogates. Similar *o*-benzoxylation has been achieved with other directing groups such as ketoxime ether, acetanilides and benzamides using carboxylic acids in the presence of Pd and Ru catalysts. In continuation of the search for a suitable precursor that can serve as an unorthodox surrogate of various functionalities, in the present case we took up benzyl amine as the potential candidate. Benzyl amines are highly susceptible to imine formation under an oxidative condition which can be further manipulated in various ways to achieve C–C and C–N bonds.

In 2013, Wu group developed a Pd catalysed protocol for *ortho*-aroylation of 2-phenylpyridine using benzyl amines as ArCO– surrogates (Scheme II.1, path-a). Although Pd and Cu show similar reactivities in coupling reactions, there are instances

where they behave differently for the same reaction. But there are few reports available for the differential reactivity of Pd and Cu catalyst. For example, in the synthesis of 2-aminobenzothiazoles from 2-halothioureas, it was observed that copper prefers dehalogenative path where as palladium favours C–H activation strategy. Moreover, copper and palladium behave differently in the reaction between alkylbenzenes and 2-phenylpyridines giving *o*-benzoxylated (–OCOAr) and *o*-aroylated (–COAr) products respectively. Thus it would be interesting to see how copper catalyst influences the reaction between 2-phenylpyridine and benzyl amine.

For achieving the goal, an initial trial was performed by reacting 2-phenylpyridine (**1**) and *p*-methylbenzyl amine (**c**) in the presence of $Cu(OAc)_2$ (20 mol %) and oxidant TBHP (5–6 M in decane) (5 equiv) in chlorobenzene at 120 ^oC. The reaction led to an exclusive formation of *o*-benzoxylated (–OCOAr) product (**1c**) rather than an *o*-aroylated (–COAr) product (Scheme II.1, path-b) which was observed using Pd catalyst (path-a, Scheme II.1). This observation highlights the divergence in the selectivity achieved with the change of transition metal catalyst.

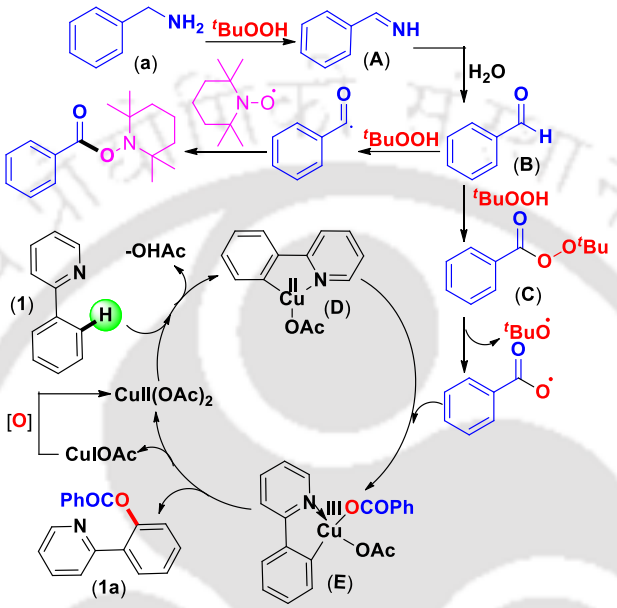


Scheme II.1. *Selectivity achieved in the presence of different transition metal catalysts*

To arrive at the best possible yield of the o-benzoxylation of 2-phenylpyridine, various reaction parameters such as catalyst, oxidant, solvent and temperature were scrutinised. After a series of optimisations, the use of $Cu(OAc)_2$ (20 mol %), TBHP (5-6 M in decane) (6 equiv.) and chlorobenzene (2 mL) at 120 ^oC was found to be the best condition for this transformation. The optimised conditions were then implemented for o-benzoxylation of 2-arylpyridines using various substituted benzylamines. It was found that both the 2-phenylpyridines as well as benzylamines possessing electron-donating

substituents gave the desired products in a better yield as compared to those possessing electron-withdrawing substituents.

From the experimental observations, a tentative mechanism has been proposed for the copper catalysed *o*-benzoxylation of 2-arylpyridines as depicted in Scheme II.2.



Scheme II.2. *Proposed mechanism for ortho-benzoxylation of 2-phenylpyridine*

In conclusion we have developed an *o*-benzoxylation reaction of 2-phenylpyridine using benzyl amines as an unconventional synthetic equivalent of arylcarboxy groups (ArCOO–). A plausible reaction mechanism involving an *in situ* generation of intermediates such as imine and aldehyde from arylmethylamine has been proposed. The radical nature of the reaction has been established by isolation of TEMPO ester. This protocol shows the differential selectivities and reactivities of Cu and Pd catalysts for the same reaction.

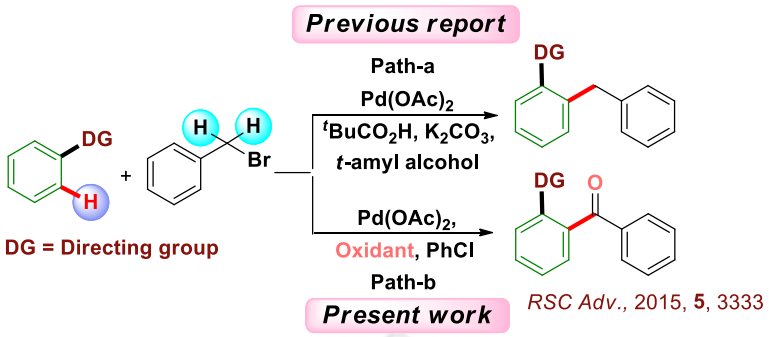
CHAPTER III: Benzyl Bromides as Aroyl Surrogates in Substrate Directed Pd Catalysed *o*-Aroylation

This chapter explains an oxidative cross-coupling between directing substrates and benzyl bromides *via* the directing group assisted C–H functionalisation. The combined

effect of catalyst and oxidants resulted in the *o*-aroylation of directing substrates using benzyl bromides as the efficient aroyl surrogates.

In last two decades, an extensive exploration of Pd-catalysed regioselective C–H functionalisation has been investigated to transform simple precursors into products of significant importance, particularly for the synthesis of complex molecules and natural products. Most of these Pd-catalysed reactions have been intended for the C–C bond forming processes involving sp, sp^2 or sp^3 hybridised C–H's as a mutual or a cross-coupling partners. The classical synthesis of aryl ketones mainly rely on the Friedel-Crafts acylation of aromatics in the presence of corrosive $AlCl_3$ or by the oxidation of corresponding secondary alcohols. Compared to the classical Friedel-Crafts acylation, the direct introduction of carbonyl functionality into aromatic motifs *via* C–H bond cleavage is more eco-friendly alternative. The acylation of 2-phenylpyridines *via ortho*-C–H bond activation has been previously reported by our group and others using aldehydes, α-oxocarboxylic acids, alcohols, α-diketones, toluenes, benzylamines and alkenes / alkynes as aroyl surrogates. The process of aroylation is of significant importance because aryl ketones are useful in pharmaceuticals, fragrance, dye and agrochemical industries. However, the cross-dehydrogenative coupling (CDC) strategy of converting sp^2 C–H bonds of aryl moiety into C–C bonds are challenging. Generally, most of the developed approaches on regioselective C–H activation involve suitable catalysts, functionalised partners and oxidants.

In search of an alternative aroyl source, we envisaged that benzyl bromides which under an oxidative condition can be converted into benzaldehyde may serve as the aroylating source. With this in mind, an initial trial reaction was performed between 2-phenylpyridine (**1**) (0.5 mmol) and benzyl bromide (**a**) (1 mmol) in the presence of $Pd(OAc)_2$ (5 mol%) and oxidant TBHP (5–6 M in decane) (4 equiv.) in chlorobenzene (2 mL) at 120 ^oC and formation of an *o*-aroylated product was observed (Scheme III.1, path-b). It may be mentioned here that in an auxillary assisted Pd catalysed C–C bond forming reaction benzyl bromide served as the benzylating agent for the sp^2 and sp^3 C–H bonds. Herein we disclose the first report on the use of benzyl bromides as aroylating agent in Pd-catalysed substrate directed process (Scheme III.1, path-a).

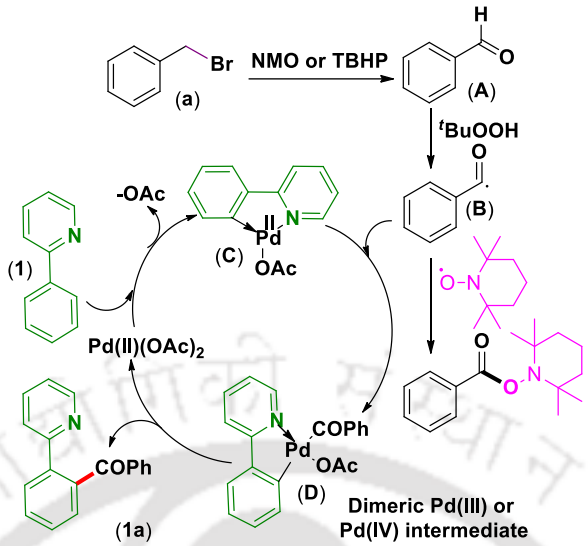


Scheme III.1. *Differential reactivities of benzyl bromides towards directing substrates*

As the initial yield (37%) of the product is very low, we probed the effect of aroylating agent, catalysts, oxidants, additives, and solvents to obtain the best yield of the *o*-aroylated product. The oxidant *N*-methyl morpholine *N*-oxide (NMO) is reported to be quite effective in converting benzyl halides to their corresponding aldehydes, which we presume to be the active aroylating agent. Again it was assumed that the catalytic activity of Pd may be hampered in acidic medium. Since an equivalent amount of HBr is liberated in the medium during the conversion of benzyl bromide to active aroylating species, it was decided to perform the reaction in the presence of a mild base. After screening of all the reagents, catalyst, oxidants and bases, the final optimum condition was found to be the use of 2-phenyl pyridine (**1**) (0.5 mmol), benzyl bromides (**a**) (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (2 equiv.), *N*-methyl morpholine *N*-oxide (2 equiv.), K_2CO_3 (1.5 equiv.) in chlorobenzene (2 mL) at 120 ^oC.

The optimised condition was then implemented for the *o*-aroylation of 2-phenylpyridines using various substituted benzyl bromides. It was observed that both the 2-phenylpyridines as well as benzylamines possessing electron-donating substituents yielded their desired products in a good yield as compared to their electron-withdrawing analogue. Besides the 2-phenylpyridines, benzo[*h*]quinoline, a rigid directing system has similar structural frame to that of 2-phenylpyridine (**1**) was employed to the present *o*-aroylation process. A moderate to good yield of the aroylated product was obtained from the oxidative coupling of benzo[*h*]quinoline and substituted benzyl bromides.

Based on the literature reports and experimental findings, a plausible mechanism for this palladium catalysed carbo-acylation reaction of 2-phenyl pyridine (**1**) with benzyl bromide (**a**) *via* directed C–H bond activation is depicted in Scheme III.2.



Scheme III.2. *Proposed mechanism for o-aroylated product from benzyl bromide and 2-phenylpyridine*

In summary, the present protocol demonstrates a convenient and efficient synthesis of aryl ketones *via* Pd-catalysed *ortho*-C–H activation of 2-phenylpyridines and benzo[*h*]quinoline using commercially available benzyl bromides as unconventional synthetic equivalents of aroyl group (ArCO–). All the benzyl bromides having activating or deactivating groups efficiently gave the desired product with 2-aryl pyridines and benzo[*h*]quinoline.

CHAPTER IV: Transition Metal-free Synthesis of α-Ketoamides from Arylmethyl Ketones and Alkylphosphoramides

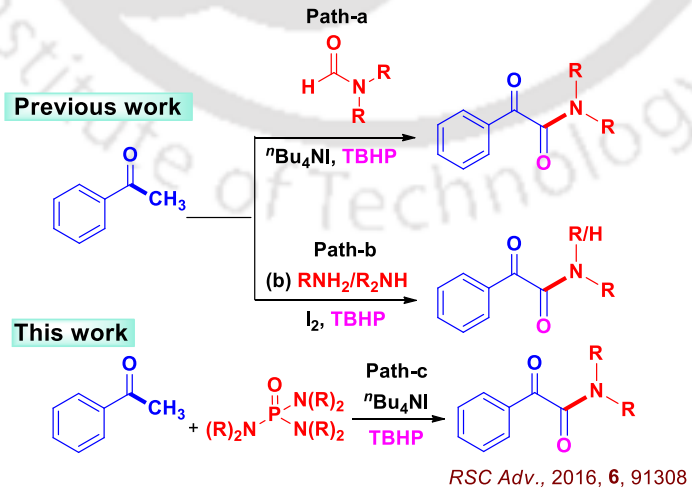
This chapter deals with a cross dehydrogenative coupling reaction (CDC) leading to the synthesis of α-ketoamides from aryl methyl ketones and alkylphosphoramides under a metal–free oxidative condition. Here, alkylphosphoramides has been utilised as the synthetic equivalent of dialkyl amine source (-NR_2).

Cross-dehydrogenative coupling (CDC) has contributed tremendously in the development of atom and step-economic process for the synthesis of complex molecular architectures from simple precursors. The CDC process plays a pivotal role in bringing about the transformation of C–H bonds of all types (sp, sp^2 and sp^3) to C–C and C–heteroatom bonds. Of various C–heteroatom bonds, the construction of C–N bond is one

of the most fundamental challenge in the synthesis of biologically important molecules, natural products, pharmaceuticals and other functional materials.

On the other hand, α-ketoamide constitutes the basic subunits of many synthetically and biologically important molecules. These motifs are used in the designing of peptidase inhibitors, histone deacetylases and human cytosolic phospholipase A_2, which is applicable for inhibiting several classes of proteases such as serine, cysteine and HIV. Because of the wide applicability of α-ketoamides, a number of synthetic routes have been developed for their synthesis.

Previously, arylmethylketones have been employed for the synthesis of α-ketoamide by coupling it with dialkylformamides (Path-a, Scheme IV.1) and primary/secondary amines (Path-b, Scheme IV.1). Arylmethylketone can be converted into phenylglyoxal in the presence of an appropriate oxidant that may serve as a α-ketyl (ArCOCO–) surrogate. This α-ketyl group may couple with the *in situ* generated amines from phosphoramides (which is used as a solvent in organic reactions) under an oxidative condition to afford a α-ketoamide. Keeping this in mind, when acetophenone (**a**) (0.5 mmol) was treated with hexamethylphosphoramide (HMPA) (**1**) (1.5 mmol) in the presence of *tetra*-butylammonium iodide (^{n}Bu$_4$NI) (20 mol%), chlorobenzene (PhCl) (2 mL) and a decane solution of *tert*-butylhydroperoxide (TBHP) (4 equiv.) at 130 ^{o}C, formation of *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (**1a**) was observed in 61% isolated yield.

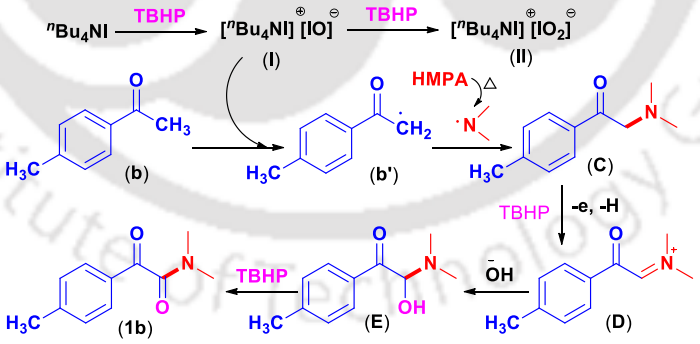


Scheme IV.1. *Synthesis of α-ketoamides from arylmethylketones*

Getting a new route to synthesise α-ketoamides, various reaction parameters such as iodine source, solvent, oxidant, temperature and time were screened for the reaction to further improve the yield. Finally, the optimised condition for this transformation is the use of acetophenone (0.5 mmol), hexamethylphosphoramide (1.5 mmol), $^{n}Bu_4NI$ (20 mol%), chlorobenzene (2 mL) and aq. TBHP (70 wt% in H_2O) (3 mmol) at 130 ^{o}C for 45 minutes.

With this optimised condition in hand, different arylmethylketones bearing both electron-donating and electron-withdrawing groups were subjected to the current reaction condition with hexamethylphosphoramide. It was noticed that arylmethylketones bearing electron-donating groups gave superior yields of the product than their electron-withdrawing partner. Adopting the same optimised condition, a library of α-ketoamides were also synthesised using different arylmethylketones and hexalkylphosphoramides. All the cyclic as well as long chain acyclic alkylphosphoramides are well tolerated the present strategy and furnishing the corresponding α-ketoamides in good yield.

By summing up all the experimental results and from the literature precedences, a plausible mechanism is proposed for the formation α-ketoamide from arylmethylketone and alkylphosphoramide (Scheme IV.2).



Scheme IV.2. *Plausible mechanism for the synthesis of α-ketoamides*

In conclusion, we have developed a novel and efficient metal-free protocol for the synthesis of α-ketoamides from arylmethyl ketones and different alkylphosphoramides in the presence of TBAI as the catalyst and TBHP as the oxidant in a short period of time. A series of alkylphosphoramide having different functional groups have been utilised for the synthesis of corresponding α-ketoamide. This process tolerates a variety of functional

groups and allows the synthesis of α-ketoamide derivatives in moderate to good yields. Based on the experimental findings, a plausible radical mechanism has been proposed for this transformation.

CHAPTER V. One Pot Sequential Synthesis of *N*-(2-(Phenylsulfinyl)phenyl)acetamides: A Ring Opening Rearrangement Functionalisation (RORF)

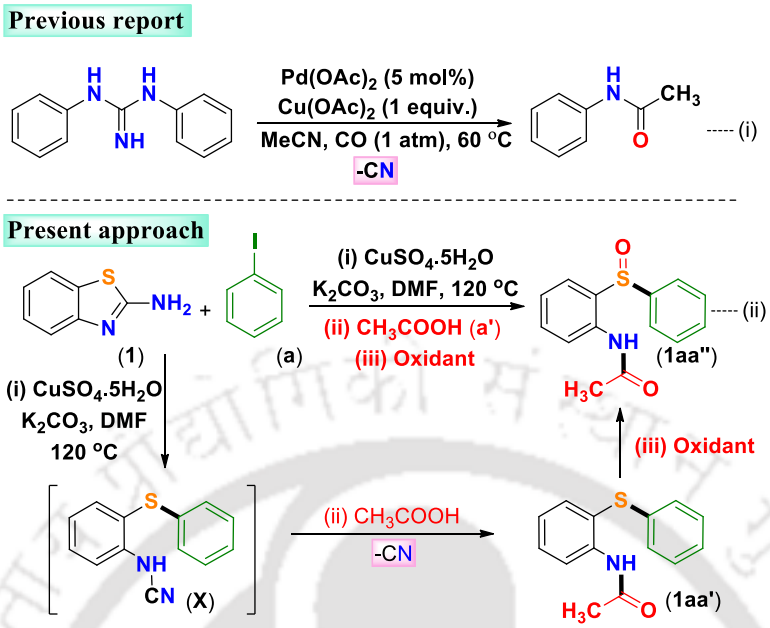
This chapter describes a new one pot synthesis of *N*-(2-(phenylthio)phenyl)acetamides from readily available benzo[*d*]thiazol-2-amine and iodobenzene involving a sequential copper-catalysed intermolecular C−S coupling followed by an intermolecular C–N bond formation with carboxylic acids *via* a rearrangement process. The further sequential addition of an oxidant resulted in the formation of sulfur-oxidised product *N*-(2-(phenylsulfinyl)phenyl)acetamide.

The effectiveness of one pot sequential reactions are important due to several synthetic transformations and bond-forming steps can be carried out in a single pot, while circumventing several purification procedures at the same time. A one pot procedure can thus minimise chemical waste, save time, and simplify practical aspects. In recent years transition metal catalysts are particularly effective reagents in achieving this one pot and multi-step synthesis. This is evidenced by a dramatic increase of impressive syntheses over the past decades. In particular, the copper-mediated C–N bond forming reaction is of high demand due to the use of low cost catalyst.

On the other hand, due to the associated ring strains in three and four membered carbo- and heterocycles, they often undergo ring opening in the presence of appropriate nucleophiles. Although five membered heterocycles such as thiazole, imidazole, oxazole and some of their benzo fused heterocycles *viz.* benzothiazole, benzoimidazole, benzoxazole and benzoisothiazole are more stable in terms of ring strain but are susceptible to ring opening. This type of ring opening is not only restricted to simple benzothiazoles and 1,3-azoles but also observed in 2-aminobenzothiazoles. A coupling reaction between 2-aminobenzothiazole and terminal alkyne resulted in the formation of benzo[*b*][1,4]thiazine-4-carbonitrile. Here, the ring opening is followed by an oxidative coupling with an alkyne and finally the reaction terminates *via* an intermolecular cyclisation process. In yet another method, the synthesis of 2-

(phenylthio)phenylcyanamide from 2-halothiourea and iodobenzene in the presence of $CuSO_4.5H_2O$ or CuI/ligand has been established *via* the intermediacy of 2-aminobenzothiazole. In 2015, a non-enzymatic decomposition of guanidine derivatives into anilides with the loss of a –CN moiety has been developed by Shi group [Scheme V.1, (i)]. Here, a combination of catalyst $Pd(OAc)_2$, an equivalent of $Cu(OAc)_2$ and CO were utilised for the transformation of 1,3-diarylguanidines to acetanilides *via* the cleavage of C–N bond. Taking cues from literature reports, we have designed a telescopic protocol for the synthesis of *N*-(2-(phenylthio)phenyl)acetamides [Scheme V.1, (ii)]. 2-(Phenylthio)phenylcyanamide (**A**) can be obtained from 2-aminobenzothiazole (**1**) and iodobenzene (**a**) in the presence of $CuSO_4.5H_2O$ *via* a ring opening intermolecular C–S cross coupling reaction (Scheme V.1). We anticipated that the *in situ* generated cyanamide (**X**) possesses an electrophilic carbon and a fragile N–CN bond which may undergo a similar cyano sacrificial acetolysis to that of 1,3-diarylguanidine to generate an acetamide (Scheme V.1). The *N*-(2-(phenylthio)phenyl)acetamide (**1aa´**) having a diarylsulfide moiety can be further oxidised to its sulfoxide (**1aa´´**) analogue in the presence of a suitable oxidant [Scheme V.1, (ii)].

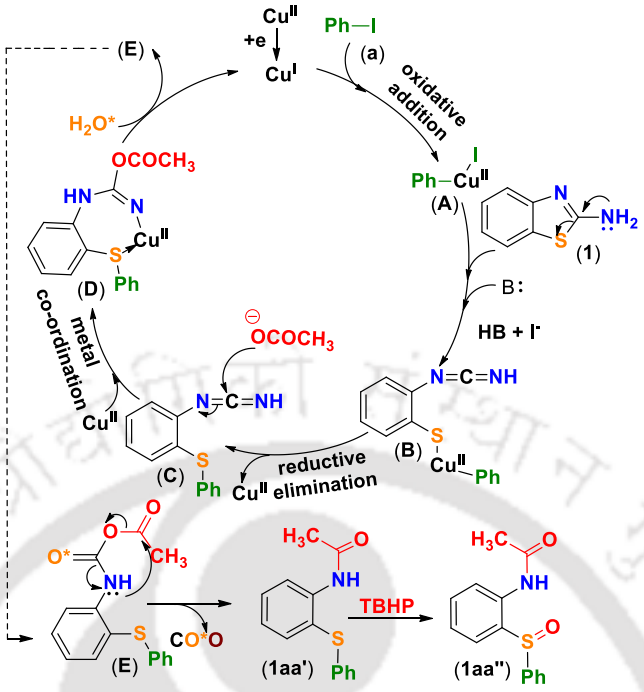
An initial experiment was carried out using 2-aminobenzothiazole (**1**) and iodobenzene (**a**) in the presence of $CuSO_4.5H_2O$ and Cs_2CO_3. The exclusive formation of cyanamide (**X**) was observed after 4 h, which is consistent with the previous literature reports. To check whether the envisioned cyano sacrificial acetolysis could be accomplished in one pot, AcOH (5 equiv.) was added to the same reaction mixture after the initial formation of cyanamide (**X**) and heating was continued further. To our delight, the expected *N*-acetylated product 2-(phenylthio)phenylacetamide (**1aa´**, 29%) was obtained *via* the loss of a cyano (-CN) group. The structure of the product (**1aa´**) was further confirmed by X-ray crystallographic analysis.



Scheme V.1. *Cyano sacrificial functionalisation strategies*

Inspired by the positive outcome, the reaction parameters are again scrutinised to achieve a better yield of the product. The investigation was commenced by using benzo[*d*]thiazol-2-amine (**1**) and 4-methyliodobenzene (**d**) as the reacting partners. Finally, a two-step optimised process was developed for the synthesis of *N*-(2-(*p*-tolylthio)phenyl)acetamide (**1da′**). In the first step the combination of $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.) and DMF (1 mL) at 120 °C for 4 h and in the second step addition of AcOH (20 equiv., 0.6 mL) at 120 °C for 5 h was found to be the best optimal condition for the *N*-acetylation. Further the addition of TBHP (6 equiv.) to the same reaction was found to be the *in situ* oxidation of sulfide (**1da′**) to sulfoxide (**1da″**). Adopting the optimised condition, a series of *N*-(2-(phenylthio)phenyl)acetamides and *N*-(2-(phenylsulfinyl)phenyl)acetamide were synthesised by using several aryliodides, 2-aminobenzothiazoles and both the aliphatic and aromatic carboxylic acids.

Based on the experimental findings and literature reports, a plausible mechanism has been proposed (Scheme V.2).



Scheme V.2. *Proposed mechanism for the one pot synthesis of N-(2-(phenylsulfinyl)phenyl)acetamide*

In conclusion, a one pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides has been accomplished by using benzo[*d*]thiazol-2-amine, aryl iodide and carboxylic acids in presence of Cu catalysts and base. The corresponding oxidised products can be obtained in the presence of TBHP. The process is accompanied with the loss of C and N atoms with concurrent *S*-arylation and *N*-acylation leading to a bi-functionalised amidic product *N*-(2-(phenylsulfinyl)phenyl)acetamide

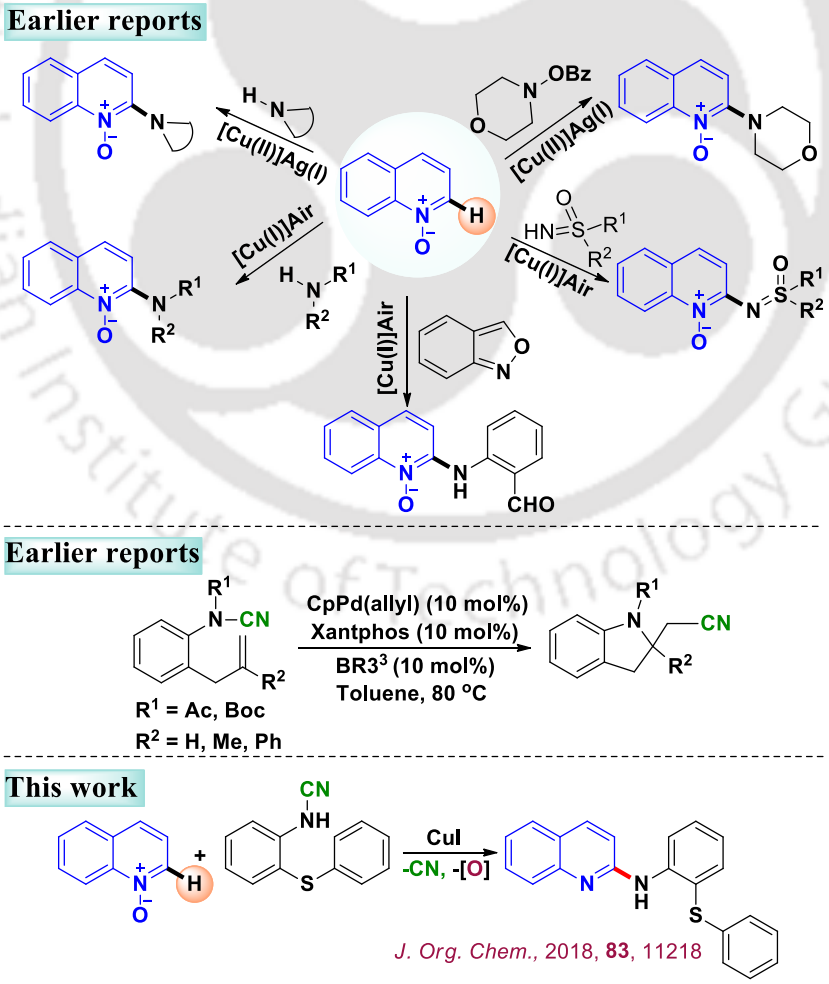
CHAPTER VI. Cyano Sacrificial (Arylthio)-arylamination of Quinoline and Isoquinoline *N*-Oxides using *N*-(2-(Arylthio)aryl)cyanamides

This chapter describes a copper(I) catalysed regioselective arylthio-arylamination of quinoline and isoquinoline *N*-oxides at the expense of a cyano (-CN) group from *N*-(2-(arylthio)aryl)cyanamides. This is a unique illustration of aryl cyanamides serving as arylaminating agents on quinoline/isoquinoline *N*-oxides without any additional *N*-oxide removal step.

Recent advances in transition-metal catalysis have led to the development of effective methods for regioselective C−C and C−heteroatom bond formations. The

construction of C−N bonds has attracted considerable attention since nitrogen containing motifs have found significant applications in biological and medicinal chemistry. Among various nitrogen bearing scaffolds, functionalised quinolines are reported to have antimalarial, antibacterial, antifungal and antimicrobial activities.

Various transition metal catalysed C2 selective functionalisations such as arylation, heteroarylation, alkylation, alkenylation and C−O or C−S bond formations on quinoline *N*-oxide moiety have been successfully accomplished. Undoubtedly, the regioselective C−N bond formation of these heterocyclic *N*-oxides have emerged as powerful tools in organic synthesis. Nevertheless few specialised synthetic methods are available to achieve this in a step-economic way (Scheme VI.1). The C2 selective amination of quinoline *N*-oxides have been achieved by using mostly secondary aliphatic amines in presence of Cu^{I} and Cu^{II} catalysts. However, the use of anthranil is the sole example of an arylamination of quinoline *N*-oxides (Scheme VI.1).



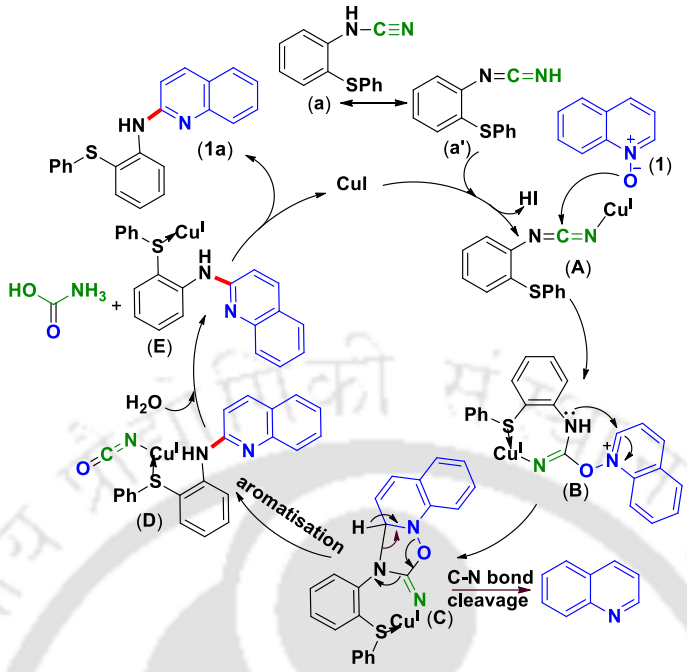
Scheme VI.1. *Differential reactivity of quinoline N-oxides and cyanamides*

Arylcyanamides are previously used for the aminocyanation of alkene. An organic cyanamide possesses a nucleophilic N–H site, an electrophilic cyanamide carbon and a fragile N–CN bond. On the other hand, because of the nucleophilic nature of quinoline *N*-oxide (**1**) and the presence of an electrophilic C2 site, we envisaged that the *N*-(2-(arylthio)aryl)cyanamide (**a**) might serve as an C2-arylthio-arylaminating agent on (**1**). This may be accomplished by the initial nucleophilic attack of the quinoline *N*-oxide (**1**) onto the electrophilic carbon of cyanamide (**a**) followed by an intramolecular nucleophilic attack at the C2 position of (**1**). Here, the sulfur atom of *S*-phenyl ring may further facilitate the reactivity of the cyanamide *via* co-ordination with a Cu-salt. The above anticipated reaction was initially executed using a *N*-(2-(phenylthio)phenyl)cyanamide (**a**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.25 mmol) and CuI (20 mol%) in 1,4-dioxane (2 mL) at 110 ^{o}C. Formation of a new product (**1a**) (43%) was observed along with the isolation of quinoline (23%) and unreacted quinoline *N*-oxide (15%). The spectroscopic analysis of the isolated product revealed its structure to be *N*-(2-(phenylthio)phenyl)quinolin-2-amine (**1a**).

Encouraged by this C2 selective cyano sacrificial arylthio-arylamination, various other reaction parameters were further evaluated to achieve better yield of the product. After a series of experimentation, the ideal optimised condition for this arylamination is the use of *N*-(2-(*p*-tolylthio)phenyl)cyanamide (**b**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.5 mmol) and CuI (15 mol%) in CH_3CN (2 mL) at 80 ^{o}C for 18 h.

The above optimised condition was then implemented to explore the scope and generality of the process. It was found that both the quinoline and isoquinoline *N*-oxide dervatives are successfully coupled with a series arylthio-arylcyanamides and afforded their corresponding products.

Based on the control experiments and the literature reports a possible mechanism for this regioselective arylthio-arylamination is depicted in Scheme VI.2.



Scheme VI.2. *Plausible mechanism for the arylthio-arylamination of quinoline N-oxide by using arylthio-arylcyanamide*

In conclusion, for the first time we have utilised arylcyanamides as an aminating agents towards regioselective C2-arylamination and C1-arylamination of quinoline and isoquinoline respectively. In many aminations of quinoline and isoquinoline *N*-oxides, the *N*-oxide moiety remained intact after the amination thereby requiring additional removal step. Currently the present arylthio-arylamination of quinoline and isoquinoline using *N*-(2-(phenylthio)phenyl)cyanamide as the aminating agent works best.

CONTENTS

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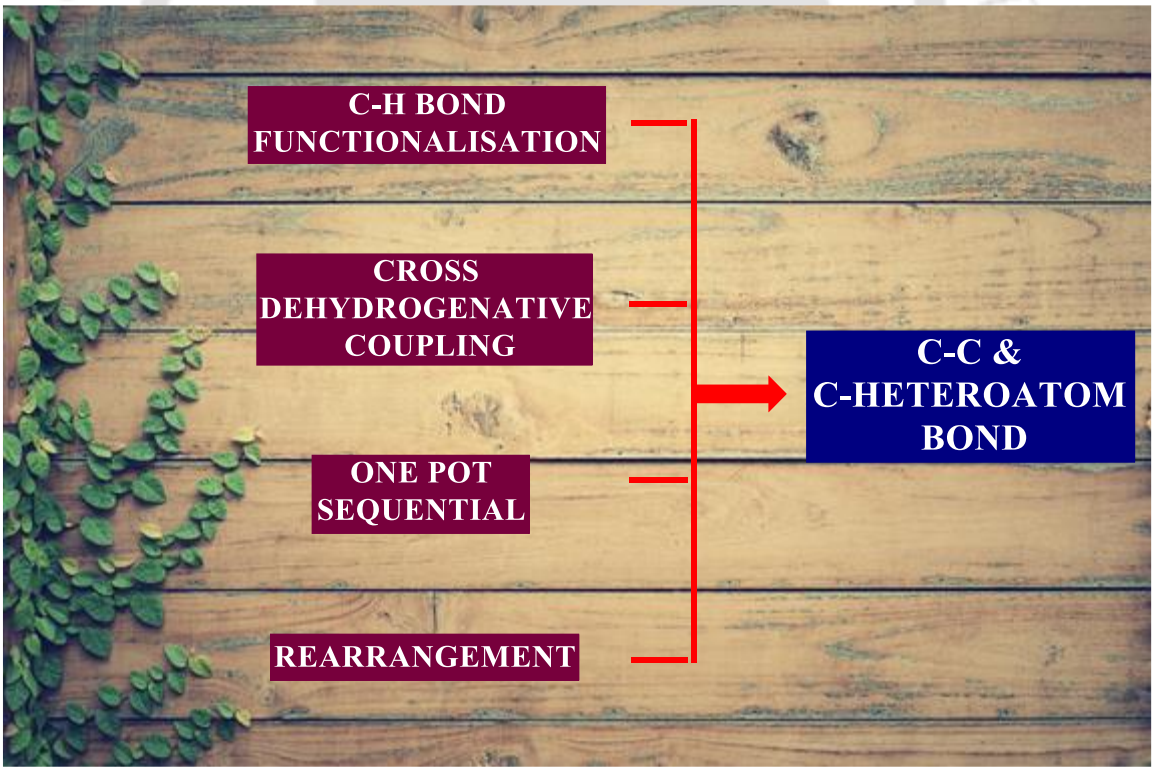
Chapter II- Benzylamine as Arylcarboxy Surrogate: A Copper Catalysed *o*-Benzoxylation of 2-Phenylpyridines Using Benzylamines

CHAPTER I

An Overview of C–H Functionalisation, Cross Dehydrogenative Coupling and Other Newer Aspects of C–C and C–Heteroatom Bond Formations



CHAPTER I

An Overview of C–H Functionalisation, Cross Dehydrogenative Coupling and Other Newer Aspects of C–C and C–Heteroatom Bond Formations

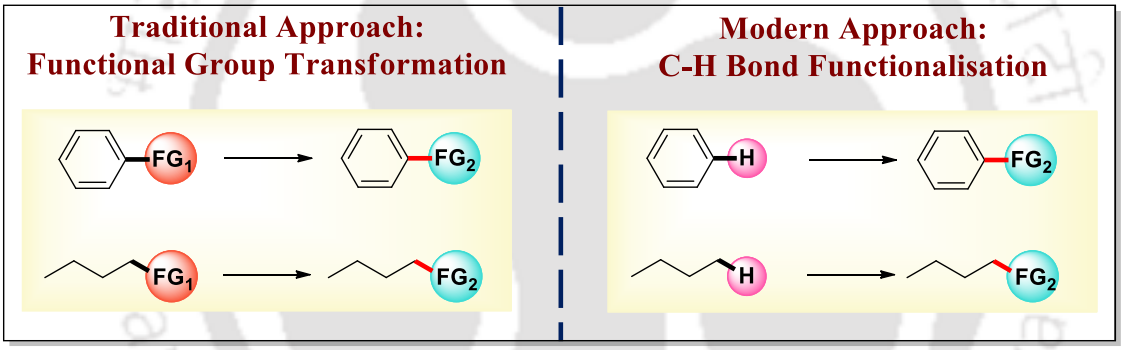
I.1. Introduction

The extensive exploration of cross coupling strategy in both academics and industries has greatly improved the synthetic routes for the construction of carbon-carbon and carbon-heteroatom bonds.[1] Generally, the traditional coupling strategies either require stoichiometric amount of organometallic reagents or the transition metal-catalysed coupling of pre-functionalised hydrocarbons. There was a huge progress in these methods over the decades and the advanced version are fruitfully utilised for the preparation of commercially expedient materials.[2] The requirement of pre-functionalised starting materials is a major drawback of these methods as it is not appreciated in a step-economical point of view. In this aspect, the best way to address the aforementioned issues is the direct use of un-functionalised carbon-hydrogen bonds,[3] so that it can increase the efficacy of the reaction by reducing the number of synthetic steps.

The carbon-hydrogen bonds are ubiquitous in nature as its availability is realised from small molecules to more elaborated natural products. They are also regarded as un-functional groups having tremendous synthetic utility hidden within them. So, if the dormant reactivity of these C–H bonds can be exploited *i.e.* selectively functionalising the C–H bonds would be a most applicable and powerful class of transformation in organic synthesis. Therefore, the direct functionalisation of C–H bonds leading to the formation of new C–C and C–heteroatom bonds has become the most applicable method in recent organic chemistry. According to the principles of retrosynthetic analysis, the C–H activation can drastically shorten the possible synthetic routes to a target molecule by providing unparalleled disconnections in both early and late stages.

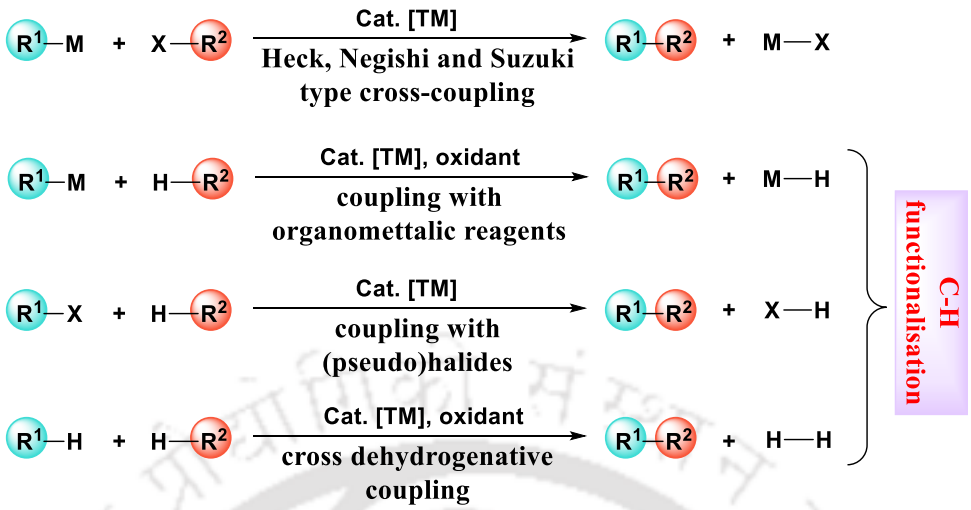
I.2. Traditional vs modern approach

The traditional cross-coupling reactions generally involve the installation of a new functional group in place of a pre-existing functional group which is already present in the starting material. For the installation of a new functional group, it needs a pre-functionalised starting material which often decreases its efficiency and atom economy and also increases step and cost of the overall transformation. Moreover, most of the cross coupling reactions terminated with the generation of stoichiometric amount of waste material. On the other hand, the C–H bond functionalisation does not require a pre-functionalised starting material and emerged as the most powerful and straightforward strategy for the construction of complex organic frameworks from easily available starting materials with reduced chemical waste (Scheme I.2.1).



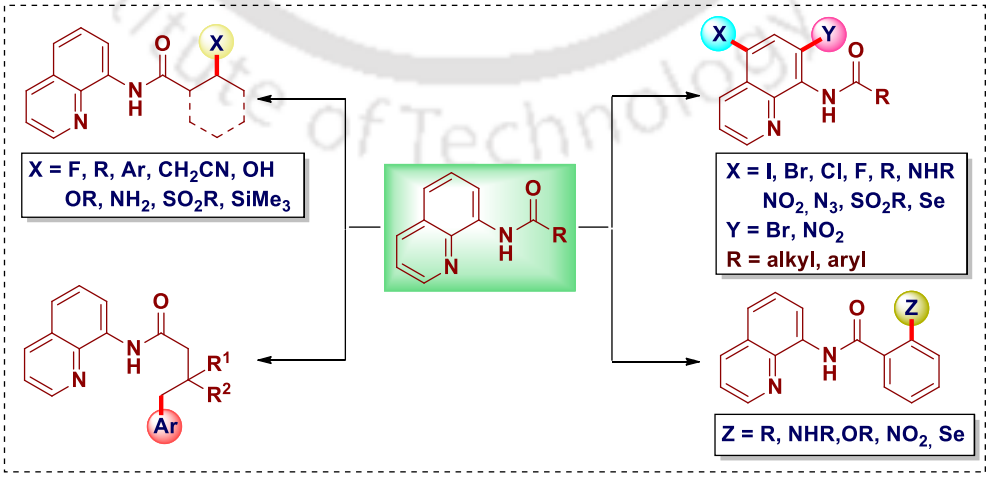
Scheme I.2.1. *Traditional approach vs modern approach*

The development of transition metal-catalysed cross-coupling reaction introduced a new era of modern approach. For the significant contribution in the development of palladium catalysed cross coupling reaction, R. F. Heck, E. Negishi and A. Suzuki were awarded Nobel Prize in 2010.[4] Other transition metals are also known to achieve the same. The use of pre-functionalised starting materials was then avoided by the chemists by developing a new approach *i.e.* transition metal-catalysed C–H bond functionalisation. A sketch of different types of transition metal-catalysed cross coupling and C–H bond functionalisation reactions are enlisted in Scheme I.2.2.



Scheme I.2.2. *Different aspects of cross coupling and C–H bond functionalisation*

It is quite difficult to selectively functionalise a particular C–H bond in an organic molecule. But the ability to selectively target a number of different C–H bonds in a complex organic scaffold permits direct access to multiple analogues from a common structural precursor. To achieve this target, chemists need to develop suitable reaction conditions importantly, selective catalysts or designed substrates to reach any predictable site selectivity. Below in Scheme I.2.3 is an example of *N*-protected (alkyl and aryl) amides of 8-aminoquinoline where depending upon the regioselectivity and acidity of various C–H bonds, different catalytic routes have been achieved for selective functionalisation (Scheme I.2.3).[5,6]



Scheme I.2.3. *Diverse C–H bond functionalisation of amide form of 8-aminoquinoline*

In comparison to traditional cross coupling reactions, C–H bond functionalisation strategies are advantageous due to the following reasons:

- The C–H bonds are ubiquitous in organic molecules and could provide new disconnections
- No need of the presence of a pre-existing functional group in the starting materials
- Step and atom economical
- Cost effective
- Reduction of chemical waste

I.3. Challenges to achieve C–H functionalisation

Although the functionalisation of C–H bonds are advantageous in the viewpoint of their ubiquity, step and atom economic, but to use them as a coupling partner is challenging due to the following reasons:

➢ Intrinsic low reactivity

The C–H bonds involved in C–H bond functionalisation strategies are mostly sp^2 or sp^3 hybridised and have pK_a values more than 30–35. In addition to this, these are also associated with high bond dissociation energies (BDE) which clearly indicates their inert nature. So, it is difficult to cleave them either in a homolytic or in a heterolytic pathway. The bond dissociation energies and pK_a values of various C–H bonds are listed in Table I.3.1.

Bond	BDE (Kcal/mol)	pK_a (water)
H_3C-H	103	48
$CH_2=CH-H$	112	50
$HC\equiv C-H$	133	25
C_6H_5-H	110	43
$CH_2=CHCH_2-H$	88	43
$C_6H_5-CH_2-H$	85	41

Table I.3.1. *Bond dissociation energy and pK_a values of different C–H bonds*

➢ Regioselectivity

Due to the ubiquitous nature of C–H bonds, specifically targeting one C–H bond for functionalisation in a complex organic molecule keeping all other C–H bonds intact, is a very challenging task. For example, *N*-(quinolin-8-yl)cinnamamide and ethyl acrylate which are shown in Figure I.3.1 possess multiple regionally and electronically distinct C–H's. Thus selective functionalisation of any of the C–H bond among all these C–H bonds would result a multiple synthetically or biologically important compound from a single moiety.

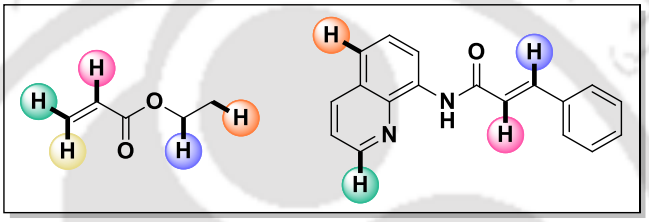
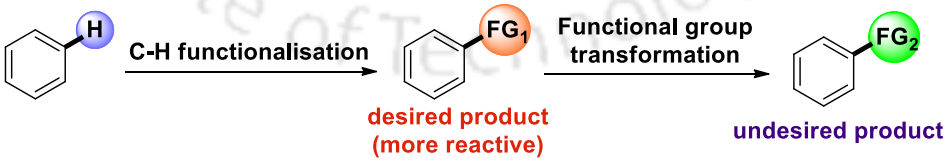


Figure I.3.1. *Ethyl acrylate and N-(quinolin-8-yl)cinnamamide contain multiple unique C–H bonds*

➢ Chemoselectivity

Chemoselectivity is defined as the selective reactivity of one functional group in the presence of other. In a C–H bond functionalisation, if the targeted product is more reactive than the starting material, then there is a possibility to undergo further functional group transformation under the identical reaction condition leading to the undesired product (Scheme I.3.1).



Scheme I.3.1. *Chemoselectivity issue in C–H bond functionalisation*

➢ Stereoselectivity

Many of the C–H functionalisation processes require harsh reaction conditions and elevated temperatures to overcome their inertness. Thus, it might have a negative impact on the stability of the chiral complex and the efficiency of asymmetric induction. So it is

more challenging to install a new stereogenic centre with high diastereo- or enantioselectivity during the C–H bond functionalisation.

In spite of these four major challenges, C–H functionalisation strategy also suffers from certain minor issues such as preservation of the existing functional group that are already present in the starting material and controlling the side reactions such as homo-coupling and hetero-coupling. However, the two major challenges that can minimise these issues and that need to be resolved are reactivity and selectivity.

I.4. Mechanism of C–H functionalisation

In C–H bond activation, the carbon-metal bond formation is the crucial step. Earlier, two distinct mechanistic paths *viz*. "inner sphere" and "outer sphere" have been proposed by Sanford.[7] In an inner sphere mechanism, the transition metal incorporates into the C–H bond and forms a defined C–M bond. Then the *in situ* generated C–M bond bearing species can be converted to a new functional group with the reaction of either an external reagent or an organyl ligand attached to the metal center. On the other hand, in an outer sphere mechanism, the C–H bond within the substrate reacts with an actively chelated ligand of the metal. But these two mechanisms were limited to saturated alkane C–H bonds only. Later, the reactions are classified broadly by Bercaw.[8] The classification includes five different mechanisms such as "oxidative addition", "sigma-bond metathesis", "electrophilic activation", "metalloradical activation" and "1,2-addition". Among these five mechanisms, three are quite common and the other two are rare.

(i) Oxidative addition

Oxidative addition reactions are distinctive for electron-rich, low-valent complexes of the 'late' transition metals such as Re, Fe, Ru, Os, Rh, Ir, Pt generally found towards the right side of the periodic table. In this mechanism, the transition metal co-ordinates to a C–H σ-bond and donates its electron density to the σ^* orbital of the C–H bond. Hence, it reduces the bond order and weakens the C–H bond which can lead to the formation of a new C–M bond (Scheme I.4.1).

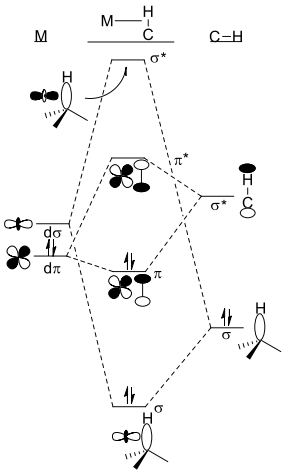
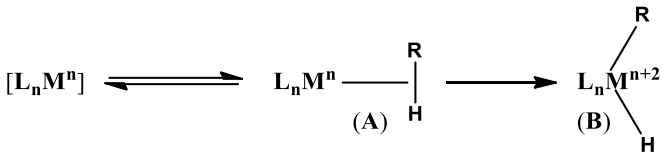


Figure I.4.1. *A qualitative MO diagram for oxidative addition*

Finally the cleavage of the C–H is proceeded with the increase in oxidation state of the metal. Further, these organometallic species releases different C–X bonds where X is halogen, oxygen and carbon etc.



Scheme I.4.1. *Oxidative addition mechanism*

A qualitative molecular orbital diagram showing only the C–H–M π-interaction (M = metal) is displayed in Figure I.4.1.

(ii) Sigma-bond metathesis

This mechanism includes the reversible reaction i.e. σ-bond breaking and forming, catalysed by alkyl or hydride complexes of 'early' transition metals with d^0 electronic configurations. These metals are mostly 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 theoretical and experimental studies have led to the concept of the general four-centered transition state (Scheme I.4.2). A qualitative molecular orbital diagram of this mechanism is shown in Figure I.4.2. The diagram shows that there is no π-interaction because of the absence of any d-electron.

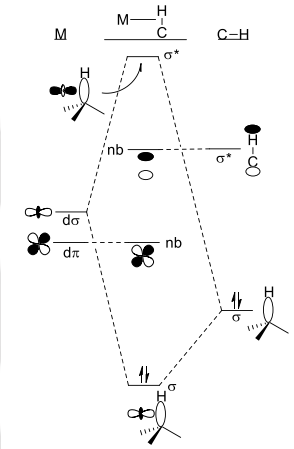
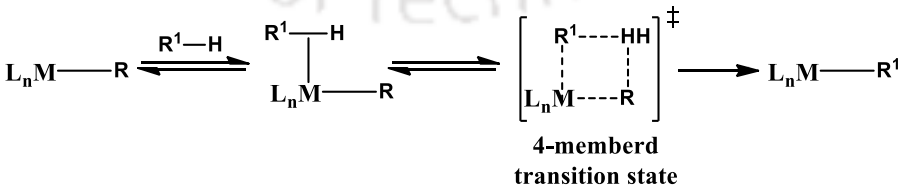


Figure I.4.2. *A qualitative MO diagram for σ-bond metathesis*



Scheme I.4.2. *σ-Bond metathesis mechanism*

(iii) Electrophilic activation

In this activation mechanism, the late transition metals of higher oxidation state are involved. Electrophilic activation of an aromatic nucleus proceeds in two steps: the first step includes the addition of the electrophilic species to the arene and forms a Wheland intermediate followed by a loss of proton giving a distinct σ-organyl complex (Scheme I.4.3). For saturated hydrocarbons, an analogous intermediate might be formed with the electrophilic metal containing species. A qualitative molecular orbital diagram of this reaction shows the involvement of late transition metals such as Pd^{2+}, Pt^{2+}/ Pt^{4+}, Hg^{2+} and Tl^{3+} where d-orbitals have dropped in energy (Figure I.4.3).

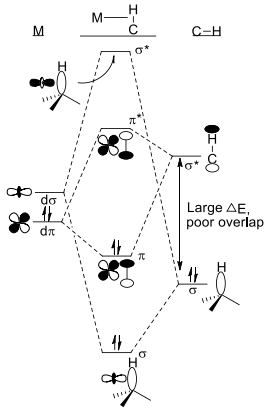
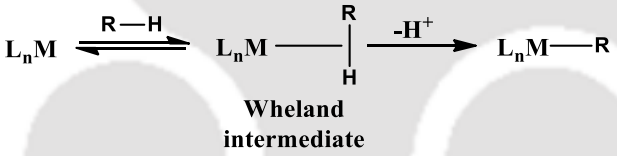


Figure I.4.3. *A qualitative MO diagram for electrophilic activation*



Scheme I.4.3. *Electrophilic activation mechanism*

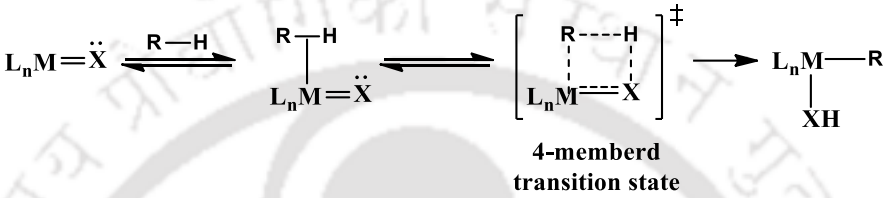
(iv) Metalloradical activation

This type of mechanism generally occurs in alkene C–H activation process. The transition metal complexes exist in a monomer–dimer equilibrium and can reversibly break alkane C–H bonds, with attachment of the two fragments to two separate halves of the metal complex (Scheme I.4.4). Complexes of Rhodium and Ruthenium are usually employed for this activation reaction.

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

(v) 1, 2-Addition

1,2-addition reactions involve the addition of an alkane C–H bond to a metal–nonmetal double bond and formed a four membered transition state (Scheme I.4.5). Alkane C–H bond additions across metal-nitrogen and metal-oxygen double bonds of early and middle transition-metal centres are known, the scope and its potential for alkane functionalisation remains unclear.



Scheme I.4.5. *1, 2-Addition mechanism*

I.5. Modern era of C–H functionalisation

From historical background, it was found that the C–H bond activation has started a long time ago. Although several enzymes such as cytochrome P_{450} and methane mono-oxygenase are catalysing the C–H bond activation since seven billion years, but the practical and applicable C–H functionalisation has initiated from past few decades. Early 1990's, can be assigned as the "golden era" of C–H functionalisation, as an unstoppable research on this strategy has been started from that time onwards. A number of metal salts and complexes have been explored day by day. The most common strategies employed in the C–H functionalisation process can be categorically divided into two segments *viz*. (i) directing group (DG) assisted C–H bond functionalisation and (ii) cross-dehydrogenative coupling (CDC). Also there are methodologies where the combination of these two strategies are realized (Figure I.5.1).

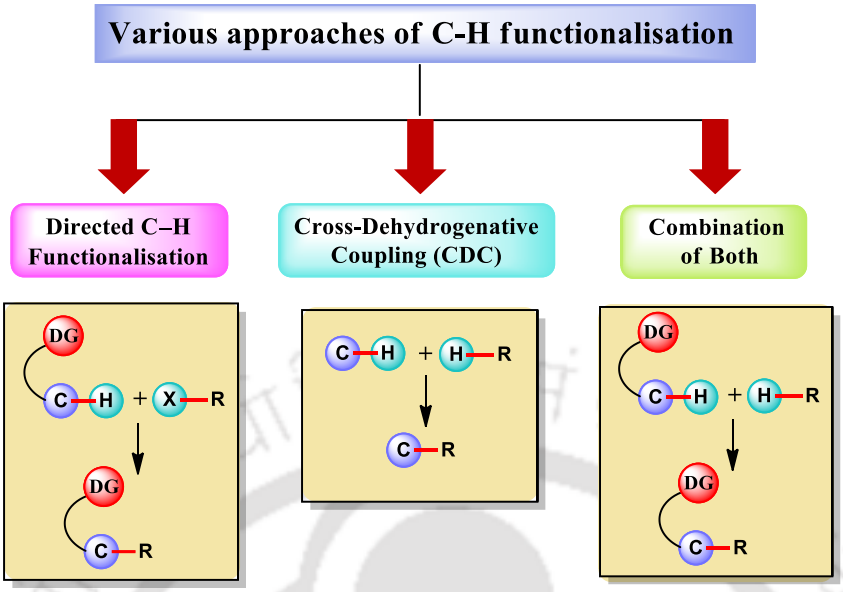


Figure I.5.1. *Various strategies for C–H functionalisation*

I.5.1. Directing group (DG) assisted C–H bond functionalisation

The intrinsic low reactivity i.e. inert nature of the C–H bonds makes the selective C–H bond functionalisation more challenging. The only solution to overcome this issue is the use of the substrates bearing co-ordinating ligands. The co-ordinating ligand generally possesses a heteroatom such as nitrogen (N), oxygen (O) and sulfur (S), so that it can chelate with the metal ion and directs the metal to the close proximity of the C–H bond which is the subject of functionalisation (positional selectivity). Therefore these co-ordinating ligands are termed as "directing groups". In this way, the pre-coordination of the transition metal increases the effective concentration of the metal and thereby overcome the "paraffin" (not enough affinity) nature of the C–H bond. The most favorable five or six membered metallacycle are usually formed by the transition metal ion. The so formed five or six membered metallacycle becomes a resourceful intermediate for the construction of new C–C and C–heteroatom bonds *via* functionalisation of both sp^2 and sp^3 C–H bonds. The transition metals such as Ru, Rh, Pd and Cu are broadly used for this purpose. Inspite of these, other transition metals such as Mn, Fe, Co, Ni, Re, Ir, Pt, Ag and Au are also employed for C–H functionalisation.

Advantages

- Direct the transition metal to activate the close proximity C–H bond.
- Higher effective concentration of the metal catalyst at the site of interest.
- Enhancement of reactivity and regioselectivity.

Limitations

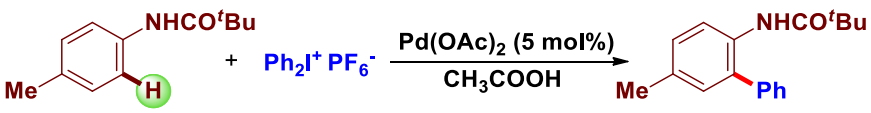
- Involves additional synthetic steps such as installation and removal of directing group (in many cases directing group is also an integral part of the substrate).
- Predominantly, functionalisation of the close proximity C–H bond (mainly *ortho* to the directing group) occurs.

I.5.1.1. Representative examples of directing group assisted C–C bond formation

The construction of carbon-carbon bond is at the forefront of modern organic synthesis. In recent years, the most widely studied area is the transition metal-catalysed directing group assisted C–C bond formation *e.g. ortho*-arylation, alkylation, alkenylation, alkynylation, carbonylation, cyanation and trifluoromethylation *via* Csp^2–H and Csp^3–H bond activation. Representative reactions of each of these category are exemplified below.

- **Csp^2–H Arylation**

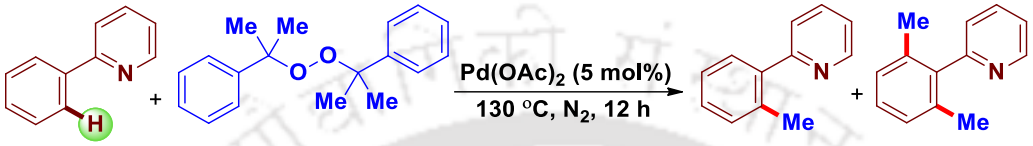
Daugulis group has developed a protocol for the *o*-arylation of anilides with the commercially available $Ph_2I^+PF_6^-$ as the arylating agent in presence of $Pd(OAc)_2$ and acetic acid (Scheme I.5.1.1.1). In the same report, the diarylation of anilides *via* C–H bond activation has been achieved by using aryliodide as the arylating source and $Pd(OAc)_2$/AgOAc as the catalyst in trifluoroacetic acid.[9]



Scheme I.5.1.1.1. *Palladium-catalysed o-arylation of anilides*

➢ **Csp²–H Alkylation**

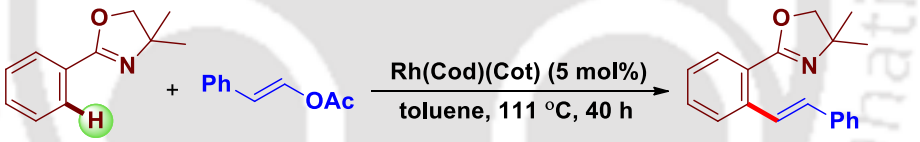
Li *et al*. reported a novel method for the direct methylation of aryl C–H bonds using peroxides as both methylating reagents and hydrogen acceptor (Scheme I.5.1.1.2). This protocol provides a new avenue for the mono- and di-alkylation of the aryl C–H bonds by using alkyl radicals rather than organometallic reagents.[10]



Scheme I.5.1.1.2. *Palladium-catalysed o-alkylation of 2-arylpyridines*

➢ **Csp²–H Alkenylation**

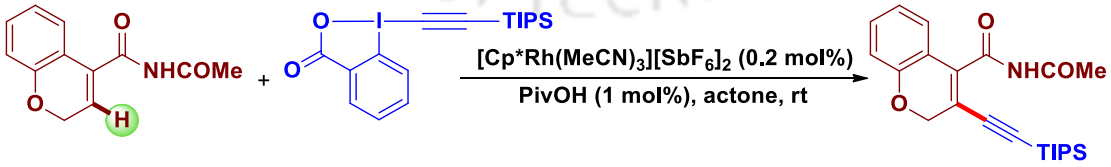
A Rh(cod)(cot)-catalysed alkenylation of aromatic C–H bonds with alkenylacetates has been described by Kakiuchi *et al*. (Scheme I.5.1.1.3). Here, a variety of directing *N*-heterocycles are employed for the alkenylation with different alkenylacetates.[11]



Scheme I.5.1.1.3. *Rhodium-catalysed o-alkenylation*

➢ **Csp²–H Alkynylation**

Loh group has accomplished a Rh(III)-catalysed C–H olefinic alkynylation of enamides by employing the hypervalent alkynyliodonium reagent as the alkynylation source (Scheme I.5.1.1.4).[12]

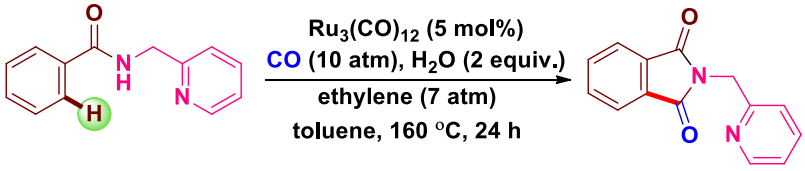


Scheme I.5.1.1.4. *Rhodium(III)-catalysed o-alkynylation of enamides*

➢ **Csp²–H Carbonylation**

Ruthenium-catalysed carbonylation of aromatic amides leading to the formation of phthalimides has been demonstrated by Chatani group (Scheme I.5.1.1.5). Here,

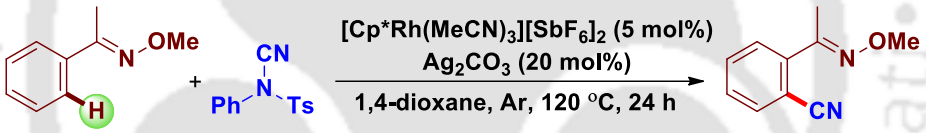
phthalimide was synthesised using a bidentate system *viz*. pyridin-2-ylmethylamine *via* C–H Bond functionalisation.[13]



Scheme I.5.1.1.5. *Ruthenium-catalysed o-carbonylation of pyridin-2-ylmethylamine*

➢ **Csp^2–H Cyanation**

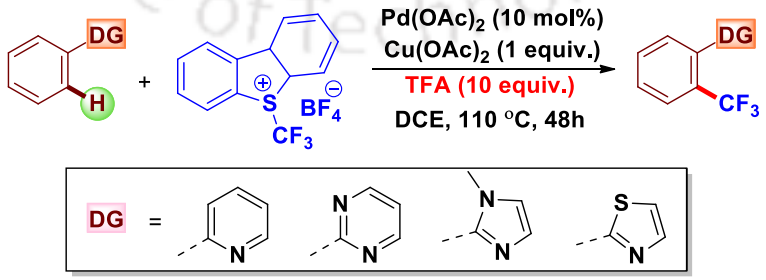
Fu *et al*. reported a Rh-catalysed C−H cyanation of ketoximes with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (Scheme I.5.1.1.6). Instead of ketoximes, they have also used several *N*-atom bearing directing groups such as pyridine, pyrazole, dihydroimidazole, dihydrooxazoles, for the synthesis of a variety of aromatic nitriles *via* Csp^2–H functionalisation.[14]



Scheme I.5.1.1.6. *Rhodium-catalysed o-cyanation of ketoximes*

➢ **Csp^2–H Trifluoromethylation**

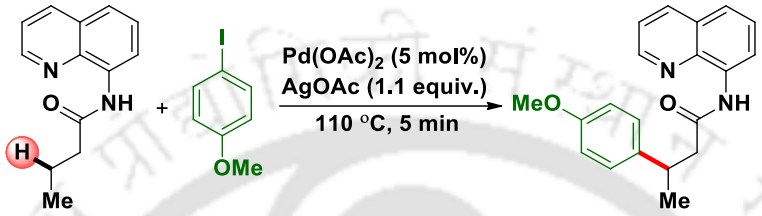
Yu group has illustrated a Pd(II)-catalysed *ortho*-C–H trifluoromethylation reaction of directing arenes using the Umemoto reagent as the CF_3 source through C–H bond functionalisation (Scheme I.5.1.1.7).[15]



Scheme I.5.1.1.7. *Palladium-catalysed o-trifluoromethylation*

➢ **Csp^3–H Arylation**

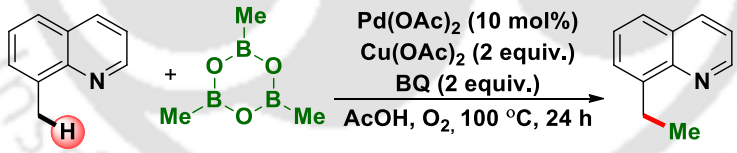
A highly regioselective β-arylation of Csp^3–H bonds in presence of palladium acetate as the catalyst has been achieved by Daugulis group (Scheme I.5.1.1.8). This method is applicable for β-arylation of carboxylic acid derivatives and *γ*-arylation of amine derivatives.[16]



Scheme I.5.1.1.8. *Palladium-catalysed Csp^3–H arylation*

➢ **Csp^3–H Alkylation**

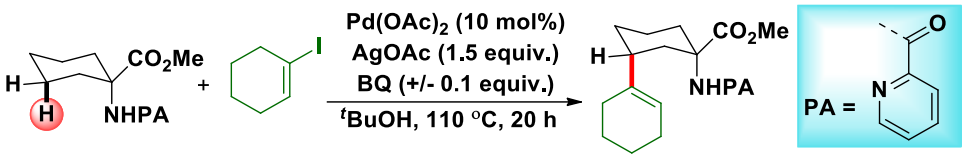
In 2006, Yu and co-workers have developed a palladium-catalysed alkylation of Csp^3–H bonds with methylboroxine *via* an unusual methylboroxine assisted C–H activation (Scheme I.5.1.1.9). In this protocol, a variety of pyridine as well as quinoline based *N*-heterocycles are used as the directing groups. Akyl boronic acids are also treated as the alkylation source for the same purpose.[17]



Scheme I.5.1.1.9. *Palladium-catalysed Csp^3–H alkylation*

➢ **Csp^3–H Alkenylation**

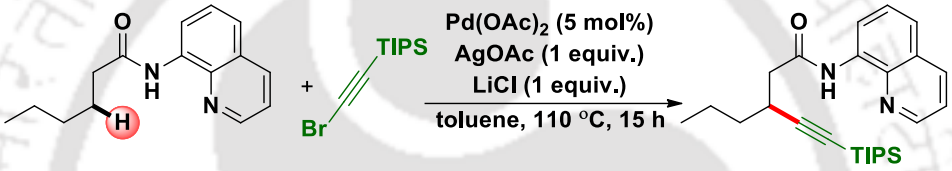
Chen *et al*. have demonstrated a highly effective protocol for the structural diversification of aliphatic scaffolds through a Pd-catalysed picolinamide-directed functionalisation of unactivated Csp^3–H bonds (Scheme I.5.1.1.10). The alkenylation occurred using vinyl iodides as the alkenylating agent under $Pd(OAc)_2$ / AgOAc catalysis.[18]



Scheme I.5.1.1.10. *Palladium-catalysed Csp^3–H alkenylation*

➢ **Csp^3–H Alkynylation**

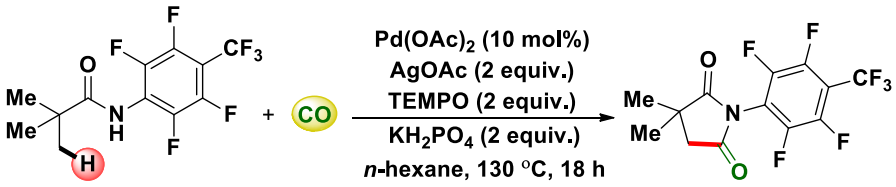
Chatani group reported the catalytic alkynylation of unactivated Csp^3–H bonds of *N*-(quinolin-8-yl)hexanamide.[19] This method allows a straightforward introduction of ethynyl group into aliphatic acid derivatives using $Pd(OAc)_2$ as the catalyst and AgOAc as the oxidant (Scheme I.5.1.1.11).



Scheme I.5.1.1.11. *Palladium-catalysed Csp^3–H alkynylation*

➢ **Csp^3–H Carbonylation**

In 2010, a Pd(II)-catalysed β-Csp^3–H carbonylation of *N*-arylamides using CO (1 atm) as the carbonyl source has been achieved by Yu group (Scheme I.5.1.1.12). Following amide directed Csp^3–H bond cleavage and insertion of CO into the resulting metallated–Csp^3 bond, intramolecular C–N reductive elimination gave the corresponding succinimides, which could be readily converted to 1,4-dicarbonyl compounds. A variety of β-Csp^3–H containing directing substrates are employed in this carbonylation process.[20]



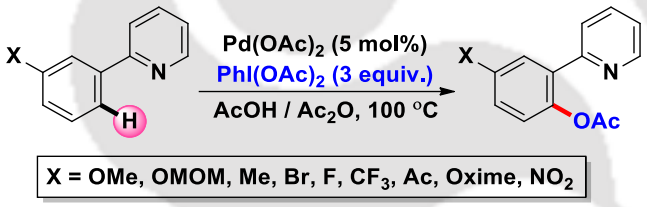
Scheme I.5.1.1.12. *Palladium-catalysed Csp^3–H carbonylation*

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

Acetoxylation, benzoxylation and hydroxylation are the most common forms of C–O bond forming reactions which occurred *via* Csp^2–H and Csp^3–H bond functionalisation. The reactions pertinent to each of these category are discussed below.

- **Csp^2–H Acetoxylation**

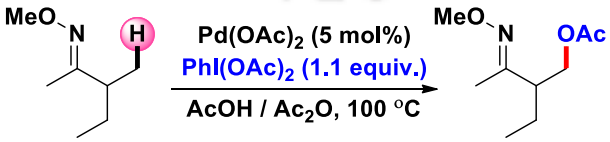
Sanford and co-workers developed a Pd(II)-catalysed acetoxylation of *meta*-substituted arene substrates using $PhI(OAc)_2$ as the acetoxy (AcO–) source (Scheme I.5.1.2.1). This protocol showed a good functional group tolerance with *meta*-substituted arenes.[21a] Later on, a silicon-tethered pyridine was subsequently employed as the directing group for the same Pd-catalysed C–H oxygenation by Gevorgyan group.[21b]



Scheme I.5.1.2.1. *Palladium-catalysed Csp^2–H acetoxylation of 2-arylpyridines*

- **Csp^3–H Acetoxylation**

A pioneer work made by Sanford *et al*. demonstrated that the Pd-catalysed acetoxylation of inactivated Csp^3–H bonds could be achieved by employing oxime as the directing group in the presence of $PhI(OAc)_2$ as the oxidant (Scheme I.5.1.2.2). The high selectivity of the reaction was attributed to the coordination of *O*-methyl oxime with the palladium catalyst. Oxime presented an improved stability than imine as the directing group in this transformation.[22]

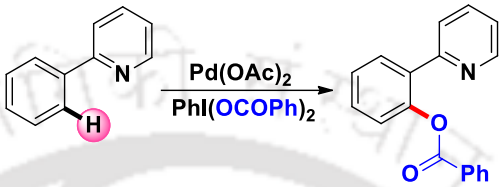


Scheme I.5.1.2.2. *Palladium-catalysed Csp^3–H acetoxylation of oximes*

- **Csp^2–H Benzoxylation**

Sanford and co-workers described a palladium catalysed *o*-benzoxylation of 2-phenyl pyridines using benzoate iodinium salts [$PhI(OCOAr)_2$] as the aryl carboxy (ArCOO–)

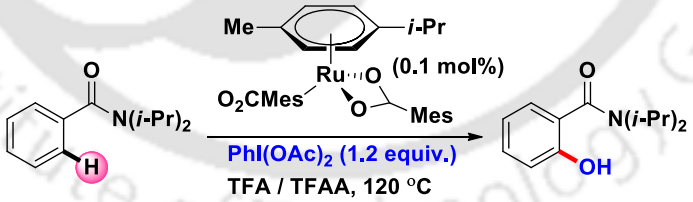
surrogate (Scheme I.5.1.2.3).[23a] In 2011, Shi group reported a similar *o*-benzoxylation reaction of ketoxime ethers with *in situ* generated benzoate iodinium salts.[23b] Later, the *o*-benzoxylation of directing arenes has been disclosed by various research groups using several arylcarboxy (ArCOO–) sources such as benzoic acid and its derivatives,[23c-j] aldehydes and alkylbenzenes,[23k] styrenes and phenylacetylenes[23l] and benzylamines.[23m]



Scheme I.5.1.2.3. *Palladium-catalysed Csp^2–H benzoxylation*

- **Csp^2–H Hydroxylation**

A ruthenium-catalysed *ortho*-selective C–H hydroxylation of weakly coordinating benzamides with $PhI(OAc)_2$ as the terminal oxidant has been accomplished by Ackermann and co-workers (Scheme I.5.1.2.4).[24a] A similar *ortho*-hydroxylation of aryl Weinreb amides was achieved by the same group using commercially available $[RuCl_2(p\text{-cymene})]_2$ as the efficient catalyst.[24b] Rao and co-workers reported a Ru(II)-catalysed mono- and dihydroxylation of anilides for the synthesis of 2-aminophenols.[24c] In addition to this, Jiao group also developed a $PdCl_2$ and *N*-hydroxyphthalimide co-catalysed C–H hydroxylation of 2-arylpyridines.[24d]



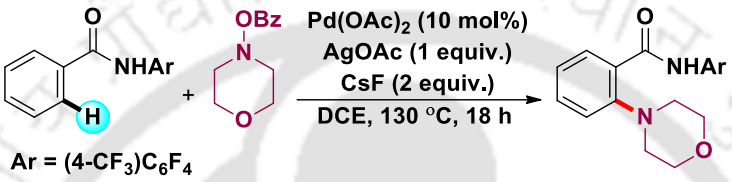
Scheme I.5.1.2.4. *Ruthenium-catalysed Csp^2–H hydroxylation of benzamides*

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

The nitrogen containing compounds are the basic subunits of many biologically active compounds. Hence, the construction of C–N bonds *via* transition metal-catalysed C–H bond activation is also an important strategy in organic synthesis. Some of the representative C–N bond forming reactions such as amination, amidation and nitration which occurred *via* C–H bond activation are discussed below.

➢ **Csp^2–H Amination**

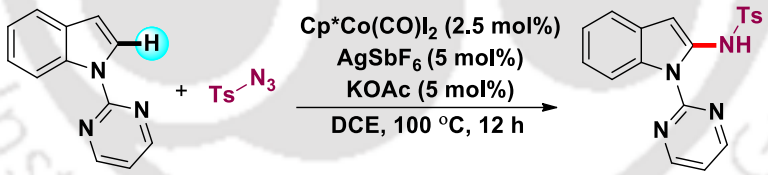
Yu and co-workers have explored the palladium-catalysed intermolecular C–H amination of *N*-aryl benzamides employing electrophilic *O*-benzoyl hydroxylamines as aminating agent in the presence of Pd(II) or Pd(0) catalysts (Scheme I.5.1.3.1). In this work, they showed that secondary amines can be directly used with benzoyl peroxide in a one-pot procedure that proceeds *via* the *in situ* generation of the appropriate *O*-benzoyl hydroxylamines.[25]



Scheme I.5.1.3.1. *Palladium-catalysed Csp^2–H amination of benzamides*

➢ **Csp^2–H Amidation**

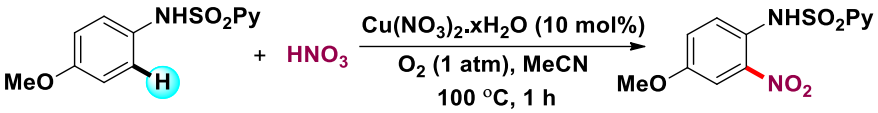
Kanai and co-workers revealed a pioneering example where air stable Cp*Co(CO)I$_2$ complex displayed an excellent reactivity in the amidation of *N*-pyrimidylindole with sulfonyl azides *via* Csp^2–H functionalisation (Scheme I.5.1.3.2).[26]



Scheme I.5.1.3.2. *Cobalt-catalysed Csp^2–H amidation of benzamides*

➢ **Csp^2–H Nitration**

Carretero group described a practical copper-catalysed direct nitration of protected anilines employing nitric acid as the nitrating agent (Scheme I.5.1.3.3). This reaction tolerated a broad substrate scope in terms of *N*-protecting groups such as sulfonamides, carbamates, amides, and ureas. The dinitrated aniline derivatives were also prepared by applying two equivalents of HNO_3 under otherwise identical condition.[27]



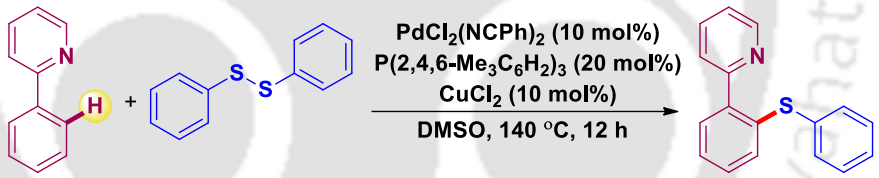
Scheme I.5.1.3.3. *Copper-catalysed Csp^2–H nitration*

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

The presence of organo-sulfur compounds in nature and various biological systems makes a prominent position of the carbon−sulfur (C−S) bond forming reactions in the race for the synthesis of valuable chemical entities. But the highly susceptible oxidative nature of sulfur compounds limit the reaction scope. Some examples of transition metal catalysed C–S bond forming reactions *via* C–H bond functionalisation are shown below.

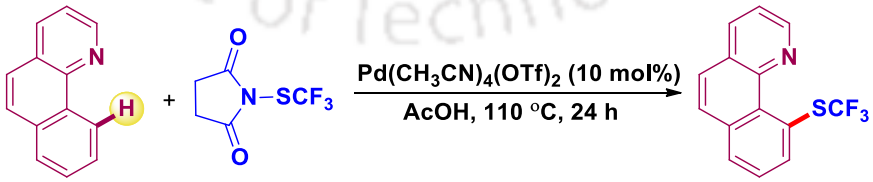
➢ **Csp^2–H Sulfenylation**

A catalytic direct thiolation of 2-arylpyridines with disulfides has been developed under palladium and copper co-catalysis by Nishihara and co-workers (Scheme I.5.1.4.1).[28a]



Scheme I.5.1.4.1. *Palladium-catalysed Csp^2–H sulfenylation*

Xu and Sun has described a highly efficient method for mono-trifluoromethylthiolation of arenes *via* palladium-catalysed directed C−H bond activation (Scheme I.5.1.4.2).[28b]

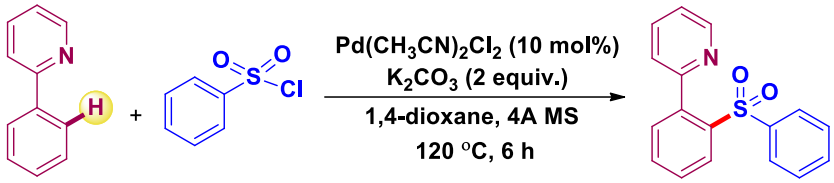


Scheme I.5.1.4.2. *Palladium-catalysed Csp^2–H trifluoromethylthiolation*

➢ **Csp^2–H Sulfonylation**

In 2009, Dong group reported a selective sulfonylation reaction of 2-arylpyridines using arylsulfonyl chlorides *via* Csp^2–H functionalisation (Scheme I.5.1.4.3).[29] Besides

2-arylpyridines, the substrates bearing pyrazole- and oxime as the directing groups were also successfully reacted in this sulfonylation method.



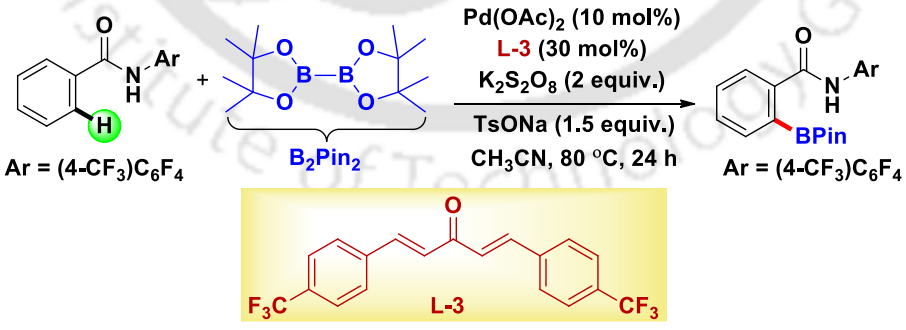
Scheme I.5.1.4.3. *Palladium-catalysed Csp^2–H sulfonyaltion*

I.5.1.5. Representative examples of C–B, C–Si and C–P bond formation

Relevant reactions of directed C–B, C–Si and C–P bond formations *via* transition metal-catalysed C–H activation are exemplified below.

➢ Csp^2–H Borylation

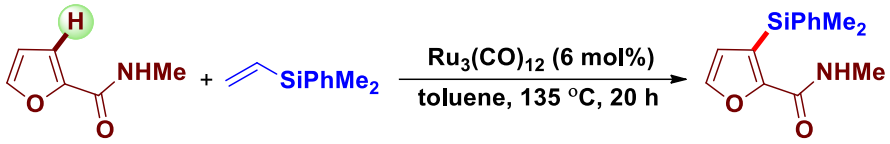
Yu and co-workers developed a Pd-catalysed oxidative *ortho*-C−H borylation of *N*-arylbenzamides with bis(pinacolato)diboron using a modified electron-deficient dibenzylideneacetone (dba) ligand, a weak base TsONa, and a strong oxidant (Scheme I.5.1.5.1).[30a] Later, *ortho*-selective C–H borylation of 2-arylpyridines in presence of palladium catalyst at room temperature has been disclosed by Takai group. The regioselectivity arises from Lewis acid–base interaction between the nitrogen and boron atoms.[30b]



Scheme I.5.1.5.1. *Palladium-catalysed ligand promoted Csp^2–H borylation*

➢ Csp^2–H Silylation

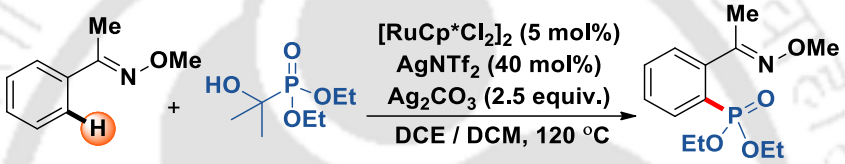
Kakiuchi group has developed a protocol to synthesise heteroarylsilanes by the reaction of heteroaromatic compounds with triorganovinylsilanes with the aid of a $Ru_3(CO)_{12}$ catalyst *via* C–H/SiR_3 coupling (Scheme I.5.1.5.2).[31]



Scheme I.5.1.5.2. *Ruthenium-catalysed Csp^2–H silylation*

➢ **Csp^2–H Phosphorylation**

An efficient rhodium-catalysed direct C–H phosphorylation of (hetero)arenes has been demonstrated by Hong and co-workers (Scheme I.5.1.5.3). The utility of the present method was broadened by the phosphorylation of prominent structural motifs, including indole, isoquinoline, thiophene, and benzofuran.[32]



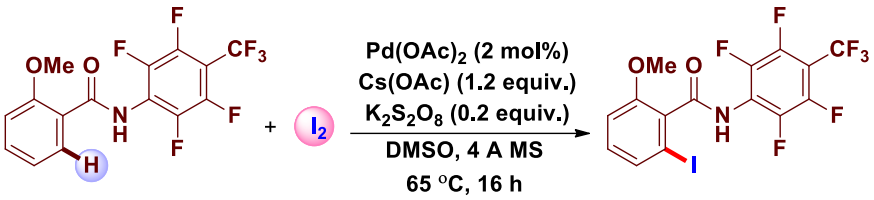
Scheme I.5.1.5.3. *Ruthenium-catalysed Csp^2–H phosphoryaltion*

I.5.1.6. Representative examples of C–X (X = F, Cl, Br, I) bond formation

Aryl halides are important class of compounds as they are widely used in the construction of complex structures in organic syntheses *via* transition metal-catalysed coupling (Suzuki coupling, Negishi coupling and Buchwald/Hartwig amination/amidation) reactions. Also the existence of a halogen atom in any structural motif offers an opportunity for further functionalisation. Reactions pertinent to the formation of C–I, C–Br, C–Cl and C–F bonds are represented below.

➢ **Csp^2–H Iodination**

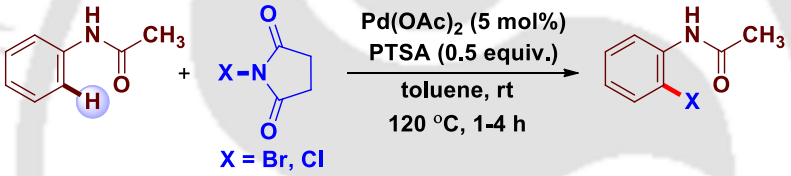
An efficient Pd-catalysed *ortho*-C−H iodination directed by a weakly coordinating amide auxiliary using I_2 as the sole oxidant was developed by Yu group (Scheme I.5.1.6.1). Including benzamides, this protocol is also compatible with a wide range of heterocycles such as pyridines, imidazoles, oxazoles, thiazoles, isoxazoles, and pyrazoles.[33]



Scheme I.5.1.6.1. *Palladium-catalysed Csp^2–H iodination*

➢ **Csp^2–H Bromination and chlorination**

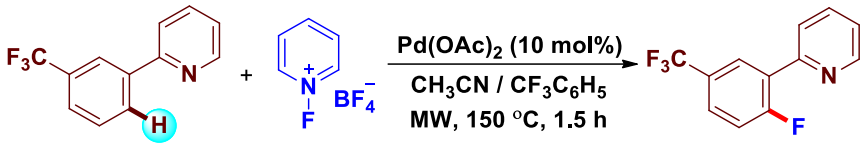
Bedford and co-workers have demonstrated an *ortho*-selective C–H halogenation of anilides using *N*-halosuccinimide (NXS) as the halide source and *p*-toluenesulfonic acid (PTSA) as the crucial additive under aerobic conditions (Scheme I.5.1.6.2).[34a] Earlier, a similar type *ortho*-halogenation of anilides have also been achieved by Shi group using CuX_2 (where X = Br and Cl) as the halogenation source.[34b]



Scheme I.5.1.6.2. *Palladium-catalysed Csp^2–H halogenation*

➢ **Csp^2–H Fluorination**

Sanford *et al.* described a palladium-catalysed fluorination of C–H bonds using electrophilic fluorinating reagents *viz. N*-fluoro-pyridinium tetrafluoroborate under an oxidative condition (Scheme I.5.1.6.3). Microwave irradiation in presence of catalytic amount of $Pd(OAc)_2$ has led to the fluorination of both Csp^2–H and Csp^3–H bonds.[35a] Later a similar C–H fluorination in the presence of a catalytic amount of simple, cheap and nontoxic nitrate as the promoter was developed by Xu and co-workers. They have used *O*-methyl oxime ethers as an efficient directing group. Both aromatic and olefinic Csp^2–H bond could be successfully fluorinated in this transformation using *N*-fluorobenzenesulfonimide as the fluorinating source.[35b]



Scheme I.5.1.6.3. *Palladium-catalysed Csp^2–H fluorination*

I.5.2. Cross-dehydrogenative coupling

The cross-dehydrogenative coupling (CDC) reaction generally refers to a cross-coupling reaction between two C–H bonds. In terms of atom economy,[36] this synthetic method represents one of the most ideal synthetic procedures for selective C–C and C–heteroatom bond forming reactions. Compared to traditional cross-coupling reactions,[37] which usually needs pre-functionalised starting materials (i.e. organohalides and/or organometallic species and thus, lead to stoichiometric amounts of waste), the direct dehydrogenative functionalisation of C–H bonds is a more environmentally friendly process. In general, CDC reactions require hydrogen acceptors which can take the form of oxygen, hydrogen peroxide, organic peroxides, for example, *tert*-butyl hydrogen peroxide (TBHP) or di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxy benzoate (TBPB), benzoyl peroxide (BPO) and *N*-halosuccinimides, for example, *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS).[38,39] The CDC reaction can proceed both with the involvement of a transition metal or without any transition metal.

Advantages

- Non-requirement of any directing groups or installation of functional groups in starting material.
- Ambient reaction conditions and involvement of simple starting materials.
- High degree of C–H bond activation.

Limitations

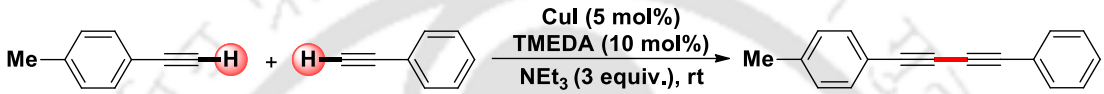
- Regioselectivity issues i.e. functionalisation can occur at any of the C–H bonds.
- Lack of chemoselectivity due to over-functionalisation.

(a) Metal-catalysed cross-dehydrogenative coupling reactions

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

➢ **C–C bond formation *via* Csp–H / Csp–H coupling**

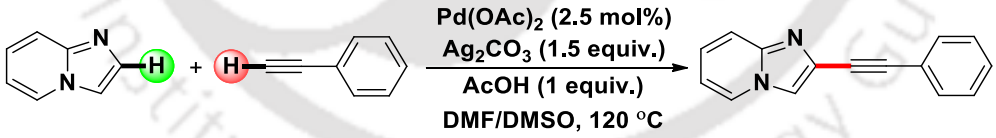
The first report of oxidative Csp–H / Csp–H coupling reaction of terminal alkynes in presence of $Cu(OAc)_2$ is called Eglinton reaction.[40] The second Csp–H / Csp–H coupling is Glaser-Hay coupling where copper(I) catalyst is used instead of Cu(II) (Scheme I.5.2.1.1).[41]



Scheme I.5.2.1.1. *Copper(I)-catalysed C–C bond formation via Csp–H / Csp–H coupling*

➢ **C–C bond formation *via* Csp^2–H / Csp–H coupling**

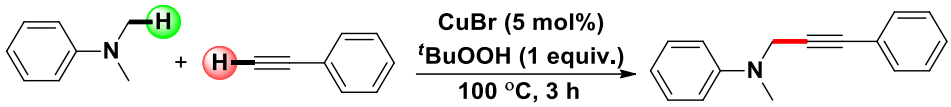
A direct oxidative coupling of azole derivatives and terminal alkynes has been achieved by Murai and co-workers (Scheme I.5.2.1.2). The use of a combination of Pd and Ag salts promotes the coupling of Csp^2–H and Csp–H bonds leading to the formation of C–C bond.[42]



Scheme I.5.2.1.2. *Palladium(I)-catalysed C–C bond formation via Csp^2–H / Csp–H coupling*

➢ **C–C bond formation *via* Csp^3–H / Csp–H coupling**

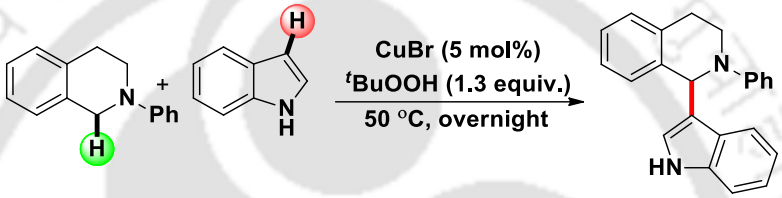
A copper bromide catalysed synthesis of propargylamine has been accompalished by Li *et al*. The cross dehydrogenative coupling of Csp^3–H bond (of *N*,*N*-dimethylaniline) and Csp–H bond (of aryl alkynes) resulted in the formation of new C–C bond. (Scheme I.5.2.1.3).[43]



Scheme I.5.2.1.3. *Copper(I)-catalysed C–C bond formation via Csp^3–H / Csp–H coupling*

➢ **C–C bond formation *via* Csp^3–H / Csp^2–H coupling**

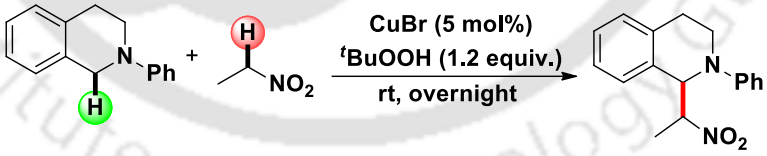
Under the copper bromide catalysis, the indolyl tetrahydroisoquinolines were efficiently synthesised *via* a CDC reaction between Csp^3–H bond and Csp^2–H bond (Scheme I.5.2.1.4).[44]



Scheme I.5.2.1.4. *Copper(I)-catalysed C–C bond formation via Csp^3–H / Csp^2–H coupling*

➢ **C–C bond formation *via* Csp^3–H / Csp^3–H coupling**

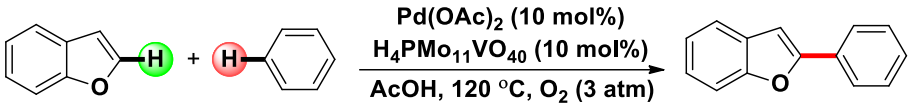
Li *et al.* described a CDC reaction of 2-phenyl-1,2,3,4-tetrahydroisoquinoline with nitroethane in the presence of CuBr / TBHP. This CDC reaction enables the formation of C–C bond *via* Csp^3–H / Csp^3–H coupling. (Scheme I.5.2.1.5).[45]



Scheme I.5.2.1.5. *Copper(I)-catalysed C–C bond formation via Csp^3–H / Csp^3–H coupling*

➢ **C–C bond formation *via* Csp^2–H / Csp^2–H coupling**

DeBoef group developed an oxidative reaction between arenes such as benzofuran and benzene. The cross-dehydrogenative coupling of Csp^2–H / Csp^2–H bond resulted the formation of 2-aryl benzofuran (Scheme I.5.2.1.6).[46]

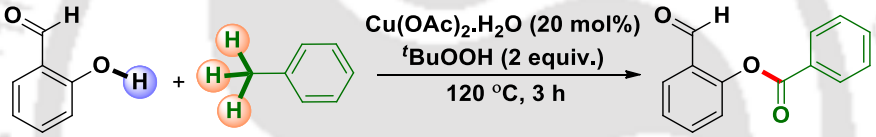


Scheme I.5.2.1.6. *Palladium(II)-catalysed C–C bond formation via Csp^2–H / Csp^2–H coupling*

I.5.2.2. Representative examples of C–O, C–N, C–S and C–P bond formations

➢ **C–O bond formation**

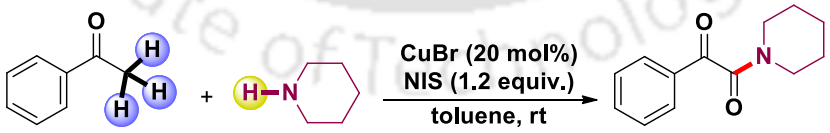
Our group has demonstrated a new and efficient Cu-catalysed esterification between alkylbenzenes and *o*-carbonylphenols using TBHP as the external oxidant (Scheme I.5.2.2.1). This protocol simultaneously installs two C–O bonds at the expense of three benzylic Csp^3–H bonds *via* CDC approach.[47]



Scheme I.5.2.2.1. *Copper-catalysed C–O bond formation via Csp^2–H / Osp^3–H coupling*

➢ **C–N bond formation**

A simple and practical copper-catalysed one-pot oxidative synthesis of α-ketoamides from the coupling of aryl methyl ketones and amines in presence of NIS was developed by Liu and co-workers (Scheme I.5.2.2.2). The new C–N bond formation has been achieved by Csp^2–H / Nsp^3–H coupling.[48]

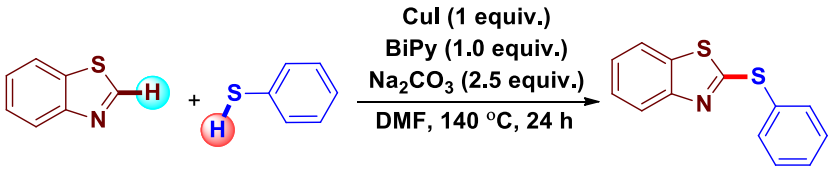


Scheme I.5.2.2.2. *Copper-catalysed C–N bond formation via Csp^2–H / Nsp^3–H coupling*

➢ **C–S bond formation**

Direct thiolation of benzothiazoles with aryl or alkyl thiols in the presence of stoichiometric amount of CuI, 2,2′-bipyridine and Na_2CO_3 has been reported by Liu

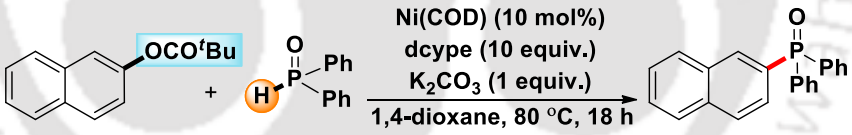
group (Scheme I.5.2.2.3). The construction of C–S bond was achieved *via* cross dehydrogenative coupling of Csp^3–H / Ssp^3–H bond.[49]



Scheme I.5.2.2.3. *Copper-catalysed C–S bond formation via Csp^3–H / Ssp^3–H coupling*

➢ **C–P bond formation**

A very distinguishable Ni-catalysed C−O/P−H cross coupling providing organophosphorus compounds was disclosed by Han and co-workers (Scheme I.5.2.2.4).[50] This strategy features a wide generality in regard to both C−O and P−H compounds. For C−O compounds, the readily available alcohol derivatives of aryl, alkenyl, benzyl, and allyl are applicable, and for P−H compounds, both >P(O)H compounds (secondary phosphine oxide, H-phosphinate, and H-phosphonate) and hydrogen phosphines (>PH) could be utilised for C–P bond formation.



Scheme I.5.2.2.4. *Nickel-catalysed C–P bond formation via C–O / P–H cross coupling*

(b) CDC reactions under metal-free condition

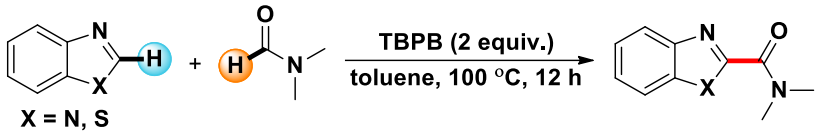
Some selected examples of C–C and C–heteroatom bond forming reactions *via* cross dehydrogenative coupling under metal free condition are enlisted below.

I.5.2.3. Representative examples of C-C, C-O, C-N, C-S, C-Se and C-P bond formation

➢ **C–C bond formation**

A novel and efficient method for the direct amidation of azoles with formamides *via* a dehydrogenative cross-coupling between formamides and azoles has been achieved by

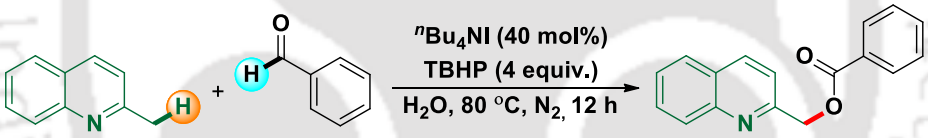
Wang and co-workers (Scheme I.5.2.3.1).[51] The reaction could occur in the presence of *tert*-butyl perbenzoate (TBPB) as an oxidant under a metal-free condition.



Scheme I.5.2.3.1. *C–C bond formation via cross dehydrogenative coupling*

➢ **C–O bond formation**

Wang *et al*. has demonstrated a $^{n}Bu_4NI$-catalysed benzylic C–H acyloxylation of alkylarenes with readily available aromatic aldehydes (Scheme I.5.2.3.2). This reaction proceeds under a mild oxidative condition using *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant and H_2O as the green solvent. Not only the benzylic C–H of 2-methyl quinoline but also the simple arylbenzene could efficiently undergo the C–H acyloxylation in this transformation.[52]



Scheme I.5.2.3.2. *$^{n}Bu_4NI$-catalysed C–O bond formation*

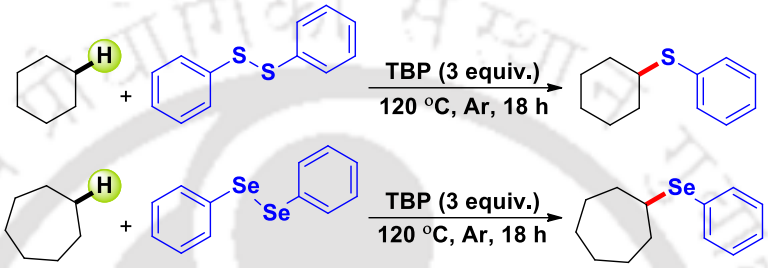
➢ **C–N bond formation**

Direct oxidative coupling of C–H and N–H bonds leading to the formation of acyl azoles has been achieved by Li group (Scheme I.5.2.3.3).[53] The *N*-acylation of azoles from the coupling of azoles and aromatic aldehydes proceeded in the presence of KI and TBHP. They have proposed a radical pathway for this protocol.

Scheme I.5.2.3.3. *KI-catalysed N-acylation of azoles via C–N bond formation*

➢ **C–S and C–Se bond formation**

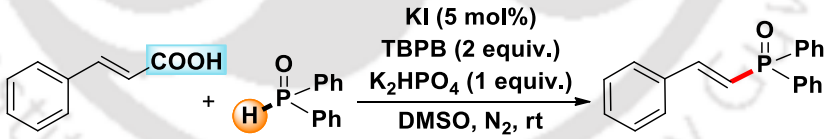
Sun *et al*. reported a highly atom-economic route for the syntheses of sulfides and selenides from the reactions of alkane with disulfides or diselenides in the presence *tert*-butyl peroxide (TBP) (Scheme I.5.2.3.4).[54] The unprecedented C−S and C−Se bond formation based on the direct oxidative cross-couplings of simple alkanes proceed *via* Csp^3–H bond functionalisation of alkanes in the absence of any transition metal catalyst.



Scheme I.5.2.3.4. *Metal free synthesis of sulfides and selenides via C–S and C–Se bond formation*

➢ **C–P bond formation**

Han group has developed a versatile, transition metal-free phosphorylation of cinnamic acids with P(O)H compounds *via* radical promoted decarboxylative coupling (Scheme I.5.2.3.5).[55] This protocol provides direct access to selective (*E*)-alkenylphosphine in the presence of KI and *tert*-butyl peroxybenzoate (TBPB).



Scheme I.5.2.3.5. *KI-catalysed C–P bond formation via decarboxylative coupling*

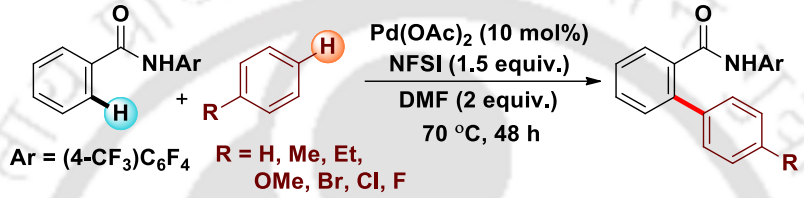
I.5.3. Directing group assisted cross dehydrogenative coupling

Some of the protocols based on the combination of both the strategies *viz*. directing group assisted C–H functionalisation and cross-dehydrogenative coupling are exemplified below.

I.5.3.1. Representative examples of C–C bond formation

➢ **Arylation *via* Csp^2–H / Csp^2–H coupling**

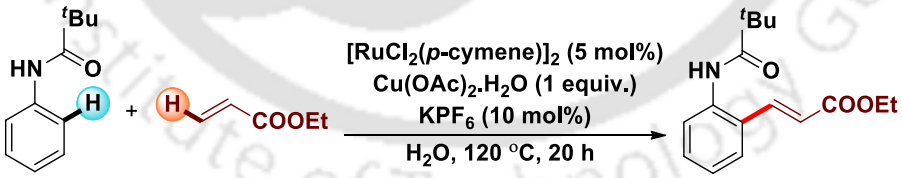
The Pd-catalysed Csp^2–H arylation directed by amides using simple arenes as the arylating agents has been reported by Yu group (Scheme I.5.3.1.1).[56] The reaction featured an exceedingly high para-selectivity for the Csp^2–H / Csp^2–H coupling reactions. The NFSI in the form of F^+ reagents were used as oxidants for the high yields and regioselectivity.



Scheme I.5.3.1.1. *Palladium-catalysed arylation of benzamides via Csp^2–H / Csp^2–H coupling*

➢ **Alkenylation *via* Csp^2–H / Csp^2–H coupling**

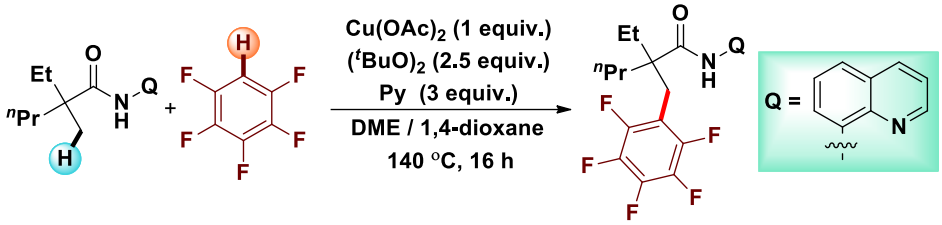
Ackermann group developed a cationic ruthenium(II) complex enabled oxidative alkenylations of anilides *via* the coupling of Csp^2–H / Csp^2–H bond using $Cu(OAc)_2.H_2O$ as an oxidant and KPF_6 as an additive in water (Scheme I.5.3.1.2).[57] This reaction is also efficiently applicable for (hetero)aromatic amides.



Scheme I.5.3.1.2. *Ruthenium-catalysed alkenylation of anilides via Csp^2–H / Csp^2–H coupling*

➢ **Arylation *via* Csp^3–H / Csp^2–H coupling**

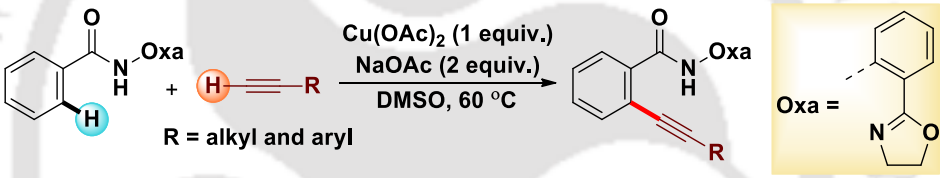
The pyridine-enabled cross dehydrogenative coupling of Csp^2–H bonds of polyfluoroarenes and activation of Csp^3–H bonds of amides was disclosed by Ge *et al.* (Scheme I.5.3.1.3).[58] This protocol displayed great site-selectivity in favoring the Csp^2–H bonds *ortho* to two fluoro atoms of arenes and the Csp^3–H bonds of α-methyl groups over those of the α methylene, β- or γ-methyl groups of the aliphatic amides.



Scheme I.5.3.1.3. *Copper-catalysed arylation of amides via Csp^3–H / Csp^2–H coupling*

➢ **Alkynylation *via* Csp^2–H / Csp–H coupling**

In 2014, Yu and co-workers have developed a Cu(II)-promoted *ortho*-alkynylation of arenes and heteroarenes with terminal alkynes to prepare aryl alkynes *via* Csp^2–H / Csp–H coupling (Scheme I.5.3.1.4). This reaction had a broad substrate scope with a variety of arenes as well as terminal alkynes.[59]

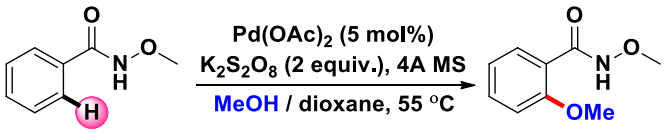


Scheme I.5.3.1.4. *Copper-catalysed alkynylation of amides via Csp^2–H / Csp–H coupling*

I.5.3.2. Represented examples of directed C–O bond formation

➢ **Csp^2–H Alkoxylation**

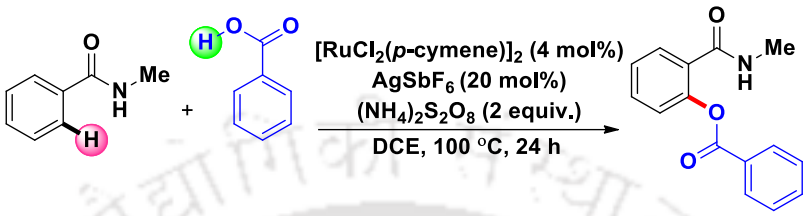
In 2010, Wang *et al.* described a Pd-catalysed *N*-methoxy amide group (–CONHOMe) directed Csp^2–H alkoxylation of *N*-methoxybenzamides using various aliphatic alcohols as the alkoxylation source (Scheme I.5.3.2.1).[60a] Two years later, a similar *o*-alkoxylation of anilides with both primary and secondary alcohols *via* ligand directed C−H activation has been explored by the same group.[60b] Other than amides and anilides, 2-aryl-1,2,3-triazoles[60c] and aromatic azo compounds[60d] were also employed for the *o*-alkoxylation *via* C–H bond functionalisation by various groups.



Scheme I.5.3.2.1. *Palladium-catalysed Csp^2–H alkoxylation of N-methoxy amide*

➢ **Csp^2–H Benzoxylation**

A highly regioselective *o*-benzoxylation of *N*-alkyl benzamide with aromatic acid was developed in the presence of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$ and $(NH_4)_2S_2O_8$ through Csp^2–H activation (Scheme I.5.3.2.2).[61]



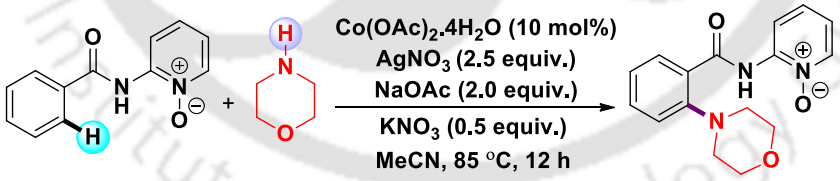
Scheme I.5.3.2.2. *Ruthenium-catalysed benzoxylation of N-methyl benzamides via Csp^2–H / Osp^3–H coupling*

I.5.3.3. Representative examples of directed C–N bond formation

(a) Amination

➢ **Intermolecular Csp^2–H amination**

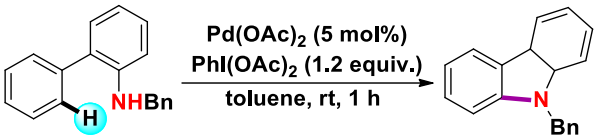
In 2016, Niu and Song, reported an intermolecular arene Csp^2–H amination using 2-benzamidopyridine *N*-oxides as the directing group and alkyl amines as the aminating agent using Co(II) catalyst in the presence of $AgNO_3$ as the oxidant and NaOAc as the base (Scheme I.5.3.3.1).[62]



Scheme I.5.3.3.1. *Cobalt-catalysed intermolecular amination via Csp^2–H / Nsp^3–H coupling*

➢ **Intramolecular Csp^2–H amination**

In 2008, Gaunt *et al*. reported a Pd(II)-catalysed mild synthetic route to prepare carbazoles using $PhI(OAc)_2$ as the oxidant *via* intramolecular Csp^2–H amination (Scheme I.5.3.3.2).[63]

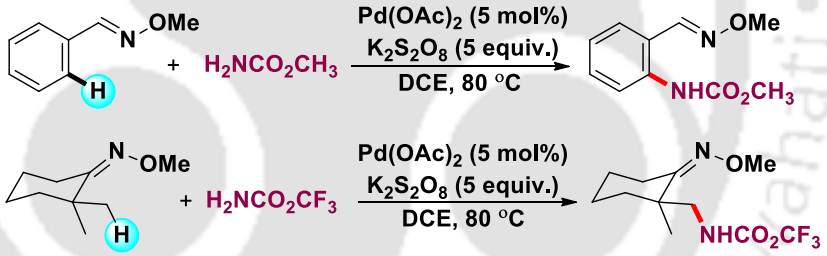


Scheme I.5.3.3.2. *Palladium-catalysed intramolecular amination via Csp^2–H / Nsp^3–H coupling*

(b) Amidation

➢ **Intermolecular amidation**

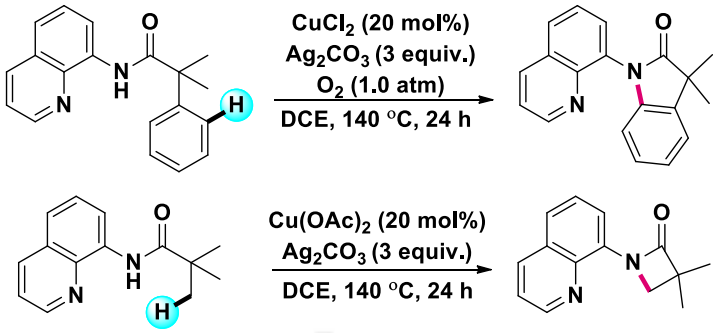
An intermolecular catalytic alkane amidation based on cascade chelation-directed cyclopalladation/amidation reactions of aldoximes and ketoximes using alkyl carbamates as the amidating reagent was developed by Chen group (Scheme I.5.3.3.3).[64] This protocol enables intermolecular amidation of both unactivated sp^2 and sp^3 C–H bonds with remarkable regio- and chemoselectivities *via* Pd-catalysed cascade C–H activation / nitrene insertion.



Scheme I.5.3.3.3. *Palladium-catalysed intermolecular Csp^2–H and Csp^3–H amidation*

➢ **Intramolecular amidation**

Kanai group has described a Cu(II)-catalysed intramolecular Csp^2–H and Csp^3–H oxidative amidation using Ag_2CO_3 as the oxidant (Scheme I.5.3.3.4). They showed that the amidation proceeded at a terminal methyl group as well as at the internal benzylic position of an alkyl chain *via* Csp^3–H functionalisation.[65]

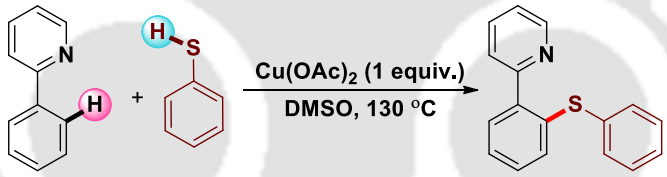


Scheme I.5.3.3.4. *Copper-catalysed intramolecular Csp^2–H and Csp^3–H amidation*

I.5.3.4. Representative examples of directed C–S, C–P, C–Si bond formation

➢ **Csp^2–H Sulfenylation**

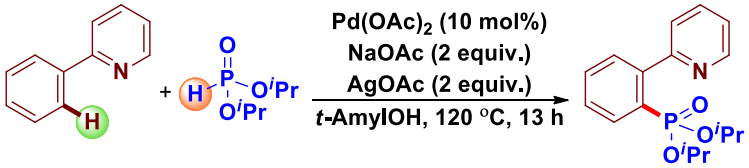
In 2006, Yu and co-workers have demonstrated the cross-coupling reaction 2-phenylpyridine with thiophenol to yield thiolated arenes *via* Cu-catalysed C–H functionalisation (Scheme I.5.3.4.1).[66]



Scheme I.5.3.4.1. *Copper-catalysed thiolation of 2-phenylpyridines via Csp^2–H / Ssp^3–H coupling*

➢ **Csp^2–H Phosphorylation**

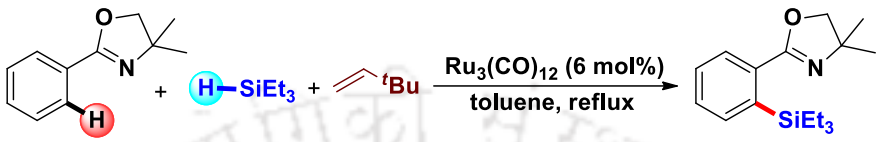
Yu *et al*. described a Pd(II)-catalysed Csp^2–H phosphorylation reaction of directing arenes using diaryl and dialkyl H-phosphonates as the phosphorylating agent. (Scheme I.5.3.4.2).[67]



Scheme I.5.3.4.2. *Palladium-catalysed directing group assisted Csp^2–H phosphorylation*

➢ **C–Si bond formation**

Kakiuchi and co-workers have demonstrated the silylation of aryloxazolines with trialkylhydrosilanes using $Ru_3(CO)_{12}$ complex as a catalyst *via* directed cross dehydrogenative coulpling of Csp^2–H bond and Si–H bond (Scheme I.5.3.4.3).[68]



Scheme I.5.3.4.3. *Ruthenium-catalysed silylation of aryloxazolines*

I.5.4. An array of exceptions

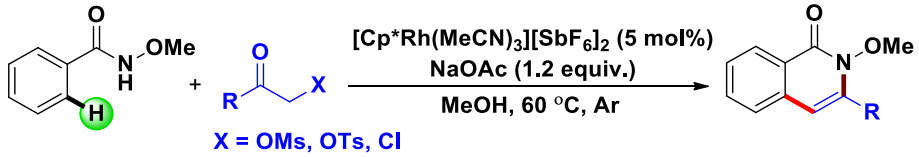
I.5.4.1. Directed C–H bond functionalisation *via* redox neutral process

The well-established C–H functionalisation requires a stoichiometric amount of external oxidant. In addition to this, there are exceptional cases where the internal oxidising group present in the substrate enables the entire C–H functionalisation process. These types of oxidising group directed C–H functionalisation have un-comparable advantages such as:

- Avoids the use of external oxidant for the whole catalytic cycle.
- Tolerates a broad range of functional group.
- Highly regioselective.
- Requires mild reaction condition.

(a) Intermolecular annulation *via* redox–neutral process

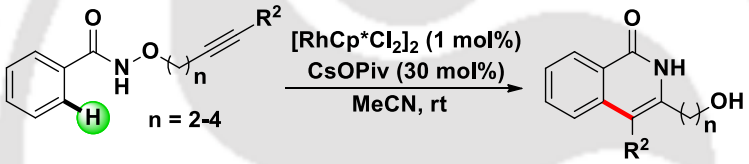
Very recently, Glorius and coworkers have utilised the α-halo and pseudohalo ketones (Csp^3–based electrophiles) for the synthesis of diverse *N*-heterocycles *via* Rh(III)-catalysed C–H activation under mild and redox-neutral reaction conditions (Scheme I.5.4.1.1). The α-(pseudo)halo ketones were recognised as the oxidised alkyne equivalents to undergo intermolecular redox-neutral annulations with *N*-methoxybenzamide. Various important *N*-heterocycles, such as 3-aryl and 3-alkyl-substituted isoquinolones, 2-pyridones, 1,2-benzothiazines, and 2-methylated indole, could be synthesised using this Rh(III) catalysed redox-neutral annulation process.[69]



Scheme I.5.4.1.1. *Rhodium-catalysed redox-neutral intermolecular annulation*

(b) Intramolecular annulation *via* redox–neutral process

Park and co-workers have reported an efficient Rh(III)-catalysed intramolecular annulation of alkyne tethered hydroxamic esters for the facile synthesis of hydroxyalkyl-substituted isoquinolone/2-pyridone derivatives (Scheme I.5.4.1.2).[70] The reaction was performed under mild reaction conditions and obviated the use of external oxidants. Some of the phenanthroindolizidine alkaloids have also been accomplished by using this methodology.



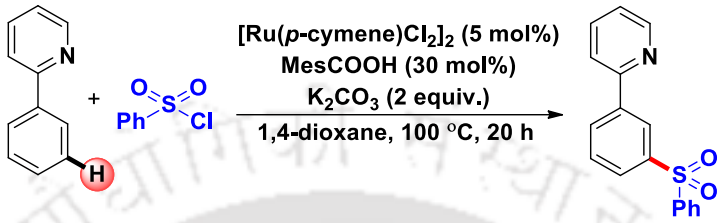
Scheme I.5.4.1.2. *Rhodium-catalysed redox-neutral intramolecular annulation*

I.5.4.2. Directing group assisted site selectivity beyond *ortho* C–H functionalisation

The selective *ortho*-functionalisation of proximal C–H bonds is well-known strategies where a five or six membered metallacycle is usually involved. Compared to *ortho*, it is difficult to achieve a *meta*- or *para*-C–H functionalisation where a large metallacycle is involved. Previously, the *meta*-selectivity was achieved either by steric[71] control or ligand[72] promotion. Few *meta*- and *para*-C–H functionalisation in the presence or absence of copper catalyst has been disclosed by Gaunt *et al*.[73] Inspired by these studies, several new strategies based on *meta* and *para* selective C–H functionalisation have been successfully developed by other groups which are discussed below.

Meta-C-H functionalisation controlled by electronic effects

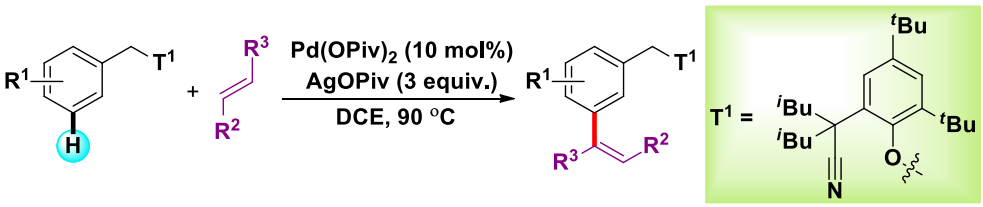
A ruthenium-catalysed direct C–H bond sulfonation of 2-phenylpyridines with unusual *meta*-selectivity was disclosed by Frost and co-workers (Scheme I.5.4.2.1). The mechanistic pathway proposed, involves catalytic chelation assisted cyclometalation.[74]



Scheme I.5.4.2.1. *Rutheium-catalysed meta-selective sulfonation of 2-phenyl pyridine*

Template based *meta*-C–H functionalisation

The remote control of site selectivity, especially *meta*-selective C–H functionalisation of electron-rich arenes is one of the most challenging task in organic synthesis. In 2012, the first report on the template based *meta*-C–H functionalisation was disclosed by Yu and co-workers (Scheme I.5.4.2.2). They have decorated an easily removable nitrile-based template that can direct the activation of distal *meta*-C–H bonds (more than ten bonds away) of a tethered arene through the formation of a macropalladacycle. In this unparalleled report, the olefination of the nitrile-containing templates was carried out *via meta*-selective functionalisation. The nitrile group on the template was weakly chelated to the [Pd(II)–Ar] intermediate and could be successfully displaced by disubstituted olefins, allowing the carbopalladation step. The main advantage is that the template could be easily removed from the *meta*-alkylated products.[75]



Scheme I.5.4.2.2. *Palladium-catalysed template based meta-selective olefination*

Later, a number of nitrile group containing templates based *meta*-selective C–H functionalisation reactions such as *meta*-olefination,[76,77a] acetoxylation,[77a] hydroxylation,[77b] arylation,[78] silylation and germanylation[79] have been explored by various research groups. Some of these templates are shown in Figure I.5.4.2.1.

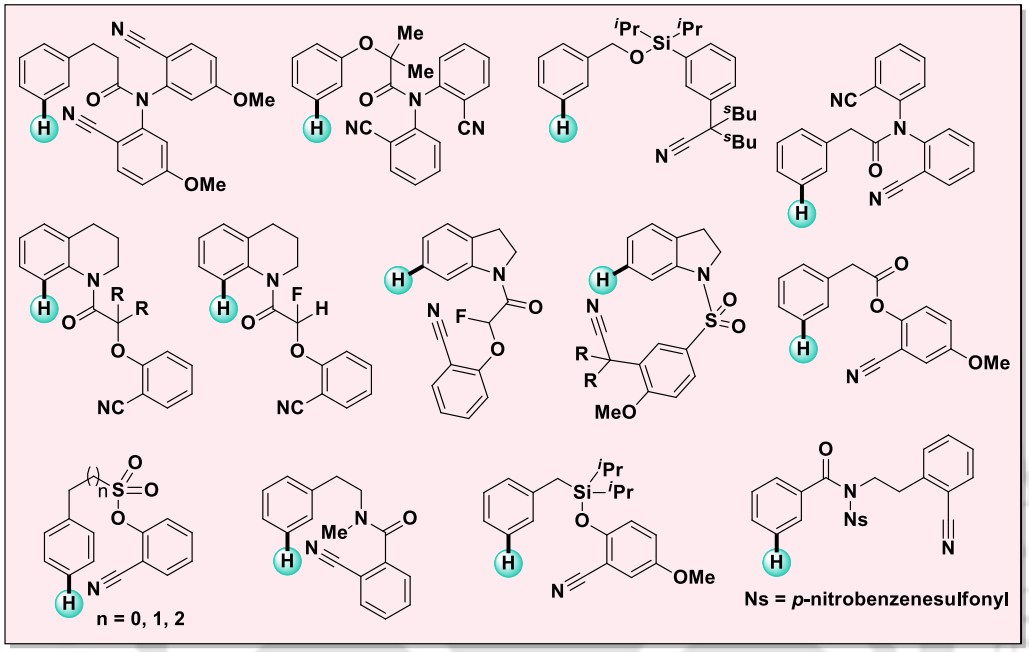
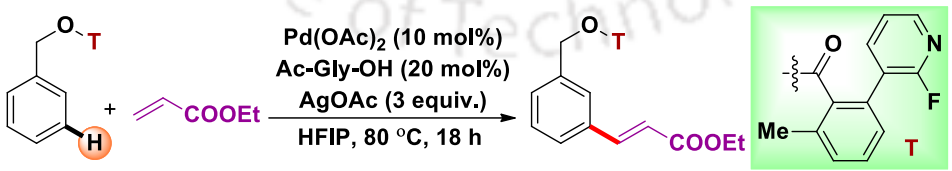


Figure I.5.4.2.1. *Nitrile based templates used for meta-selective C–H functionalisation*

Most of the template based *meta*-selective C–H functionalisations involve a weakly coordinating nitrile group. In 2015, Yu group reported a selective *meta*-C–H functionalisation by replacing the nitrile donor with a 2-fluoropyridine based directing group (Scheme I.5.4.2.3).[80]

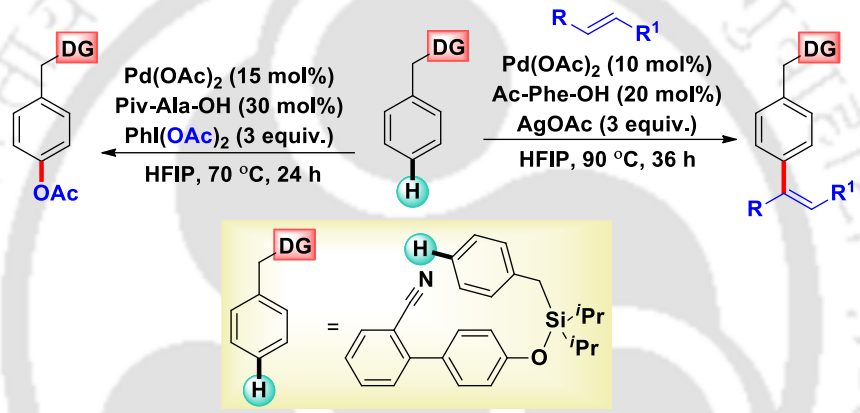


Scheme I.5.4.2.3. *Palladium-catalysed meta-selective C–H olefination*

Template based *para* C–H functionalisation

After establishing, the template based *meta*-C–H functionalisation, it was then extended to the most challenging approach in this domain *i.e.* *para*-C–H functionalisation. An efficient and unprecedented strategy was disclosed by Maiti and

co-workers which includes the use of extended templates to deliver *para*-olefinated and *para*-acetoxylated products *via para* C–H bond activation (Scheme I.5.4.2.4). They have utilised an easily recyclable Si-containing biphenyl-based template that directs the functionalisation of the distal *p*-C−H bond of toluene by forming a D-shaped assembly in the presence of $Pd(OAc)_2$ catalyst.[81a] Very recently, another remote *para* C–H functionalisation of phenol derivatives has been developed by switching the connectivity of carbon to oxygen atoms in the former silicon-containing biphenyl based template by the same group. Various phenol-based natural products have been accomplished by applying this strategy.[81b]



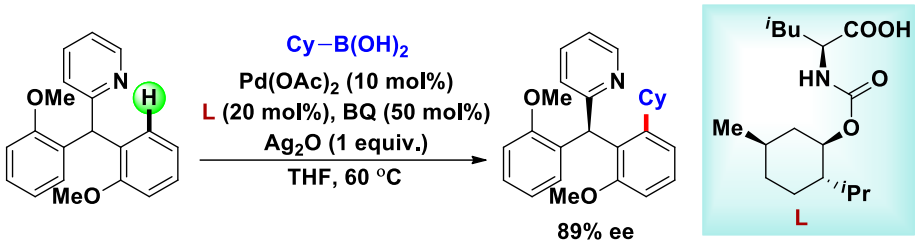
Scheme I.5.4.2.4. *Palladium-catalysed para-selective C–H olefination and acetoxylation*

I.5.4.3. Asymmetric C–H activation

The enantioselective C–H activation leading to the formation of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds is always a long standing challenge in synthetic organic chemistry. Reactions pertinent to this category are shown below.

Intermolecular stereoselective C–H activation

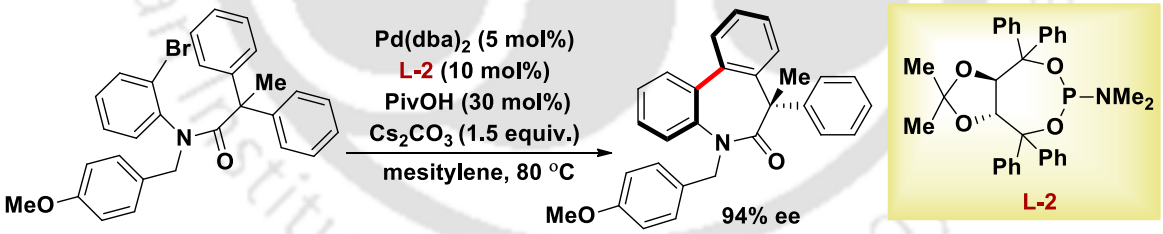
Yu and co-workers disclosed the first report of palladium-catalysed enantioselective C−H activation by incorporating a stereochemistry-generating intermolecular C−H alkylation (Scheme I.5.4.3.1). Here, they have introduced a mono *N*-protected amino acids (MPAA) as viable chiral ligand for this Pd(II)/ Pd(0)-catalysed highly enantioselective alkylation.[82]



Scheme I.5.4.3.1. *Palladium-catalysed intermolecular alkylation via asymmetric C–H activation*

Intramolecular stereoselective C–H activation

An intramolecular direct arylation of vinyl triflates has been reported by Cramer research group. They have designed a taddol based phosphoramidite ligands which is the key factor for the formation of a quaternary stereocenter based indanes with excellent enantioselectivities.[83a] In 2013, Saget and Cramer utilised the same taddol phosphoramidites as chiral ligands for the synthesis of highly functionalised dibenzazepinones possessing a quaternary stereocenter with outstanding enantioselectivities. The reaction proceeds *via* an enantio-discriminating concerted metalation deprotonation (CMD) step which occurs through an unusual eight membered palladacycle formation (Scheme I.5.4.3.2).[83b]



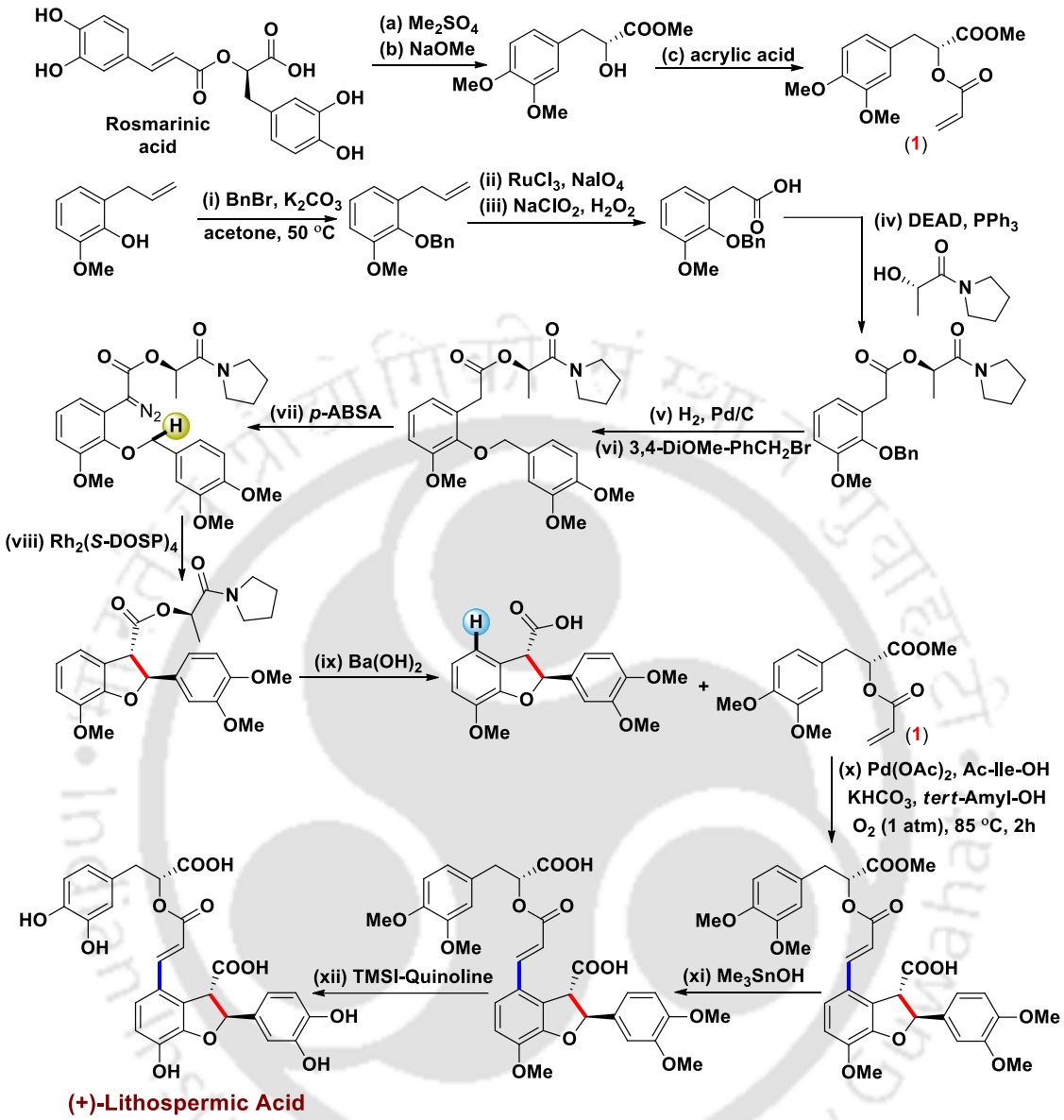
Scheme I.5.4.3.2. *Palladium-catalysed intramolecular alkylation via asymmetric C–H activation*

I.6. C–H activation: A new paradigm for total synthesis

Recently, the C–H functionalisation strategy has been extended to the synthesis of complex natural products. Herein, mentioned below is one example of total synthesis showcasing creative and ingenious incorporation of C–H activation as a strategic maneuver compared to the traditional methods, enlightening a new archetype in strategic synthetic design.

I.6.1. Total synthesis of (+)-Lithospermic Acid

Lithospermic acid is an active component in Danshen which is a popular traditional herb used for the treatment of cardiovascular disorders, cerebrovascular diseases, different types of hepatitis, chronic renal failure, and dysmenorrhea. Recent studies of (+)-lithospermic acid (1) revealed that it has potent and nontoxic anti-HIV activity. However, (+)-lithospermic acid was previously prepared by Jacobson group,[84a] Ellman and Bergman group.[84b,c] But the current method developed by Yu and co-workers, described the synthesis of (+)-lithospermic acid involving two major C–H activation steps (Scheme I.6.1.1). The first C–H activation step involves Rh-catalysed carbene C–H insertion reaction using Davies's catalyst to form dihydrobenzofuran core, and a late-stage intermolecular C–H olefination coupled the olefin unit with the dihydrobenzofuran core to construct the molecule which after deprotection furnish the target molecule.[85]



Scheme I.6.1.1. *Total Synthesis of (+)-Lithospermic Acid*

I.7. Other newer aspects of transition metal catalysed reactions leading to C–C and C–heteroatom bond formations beyond C-H functionalisation

Though C–H functionalisation is an outstanding strategy for the construction of C–C and C–heteroatom bonds, scientists have also concentrated on the development of several newer methodologies for achieving the same beyond C–H bond functionalisation. Some of these newer methodologies are enlisted below.

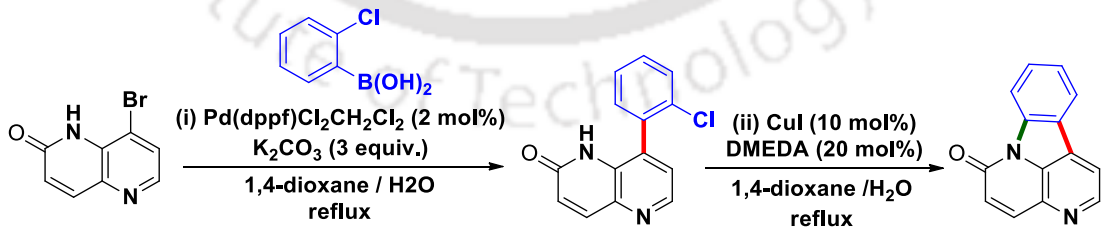
- One pot sequential strategy
- Rearrangement reactions

I.7.1. One pot sequential reaction

In synthetic organic chemistry, a one pot synthesis is a strategy to improve the reaction efficiency thereby a reactant is subjected to successive chemical reactions in just one reaction vessel. This is highly demanding because it avoids a lengthy separation process and purification of the intermediates which could save time and resources while increasing chemical yields. A sequential one pot synthesis with reagents added to a reactor one at a time and without work-up is also termed as telescoping synthesis. Sequential one pot syntheses could be used to generate even complex targets with multiple stereocenters which may significantly shorten the number of steps required and have important commercial implications. The one pot sequential reactions can proceed in the presence or absence of a metal catalyst. In the presence of transition metal catalysts, some relevant reactions to this category are exemplified below.

- **One pot sequential ring-forming reaction**

In 2010, Koutentis developed a two-step total syntheses of Canthin-6-one alkaloids *via* a new one-pot sequential strategy (Scheme I.7.1.1). This protocol relies on the concomitant Pd-catalysed Suzuki-Miyaura C–C coupling followed by a Cu catalysed amidation that can be achieved either stepwise or in a new one-pot protocol starting from the appropriate 8-bromo-1,5-naphthyridine.[86]

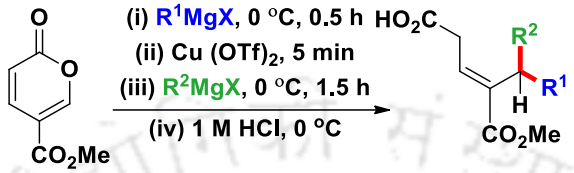


Scheme I.7.1.1. *Synthesis of Canthin-6-one alkaloids*

- **One pot sequential ring-opening reaction**

Thorimbert and co-workers reported a one pot, three step, double alkyl-alkyl or alkyl-hydride 1,6 conjugate addition to methyl coumalate providing a variety of

functionalised β,γ-unsaturated carboxylic acids in a modular way (Scheme I.7.1.2).[87] The metal-catalysed addition of two Grignard reagents (homo-coupling, 2RMgX or hetero-coupling, R^1MgX+R^2MgX) to methyl coumalate was accomplished with high regio-, chemo- and stereoselectivity.



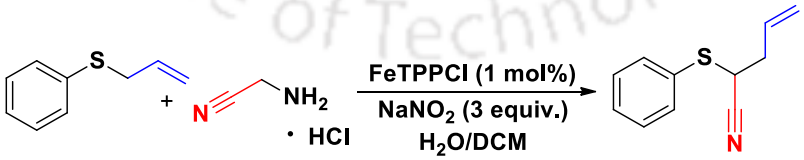
Scheme I.7.1.2. *One pot sequential double 1,6-addition of Grignard reagents*

I.7.2. Rearrangement reaction

From the past few decades, a number of rearrangement reactions leading to the construction of new C–C and C–heteroatom bonds have been well established.[88] However, these reactions involving transition metal-catalysts are fewer in number. The ongoing research on transition metal-catalysed rearrangement reactions proceeds in both intermolecular and intramolecular pathways. Reactions pertinent to this category are exemplified below.

Intermolecular rearrangement

Koenigs and co-workers developed an iron-catalysed synthesis of α-mercapto-nitriles (Scheme I.7.2.1). The reaction is accompanied with the *in situ* generation of diazo compounds. Subsequent carbene formation from the *in situ* generated diazo compound, followed by reaction with allylic and propargylic sulfides, produces an ylide that undergoes a sigmatropic rearrangement to provide α-mercapto-nitriles.[89]

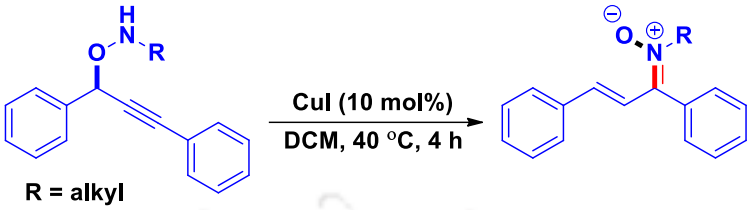


Scheme I.7.2.1. *Iron-catalysed synthesis of α-mercapto-nitriles*

Intramolecular rearrangement

Terada *et al*. have synthesised *N*-Alkylated α,β-unsaturated ketonitrones from propargyloxyamines using Cu catalysts. The rearrangement proceeds *via* Cu-catalysed

intramolecular hydroamination, followed by a thermally induced electrocyclic ring opening (Scheme I.7.2.2).[90]



Scheme I.7.2.2. *Copper-catalysed synthesis N-Alkylated α,β-unsaturated ketonitrones*

I.8. References

(1) (a) J.-P. Corbet and G. Mignani, *Chem. Rev*., 2006, **106**, 2651; (b) S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed*., 2003, **42**, 5400; (c) A. Correa, O. G. Mancheno and C. Bolm, *Chem. Soc. Rev*., 2008, **37**, 1108; (d) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed*., 2009, **48**, 6954.

(2) (a) W. Carruthers and I. Coldham, *Modern Methods of Organic Synthesis*, Cambridge University Press, Cambridge, 2004, 45; (b) D. M. Huryn, *In Comprehensive Organic Synthesis*, Vol 1 (Eds.: B. M. Trost and I. Fleming), Pergamon, Oxford, 1991, 49; (c) T. Banno, Y. Hayakawa and M. Umeno, *J. Organomet. Chem.*, 2002, **653**, 288.

(3) (a) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*; Wiley–VCH: Weinheim, 2005; (b) J.-Q. Yu and Z.-J. Shi, C–H *Activation;* Springer: Berlin, Germany, 2010; (c) *Activation and Functionalisation of C–H Bond*, ed. K. I. Goldberg and A. S. Goldman, ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004; (d) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res*., 2008, **41**, 1013; (e) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun*., 2010, **46**, 677; (f) A. Gunay and K. H. Theopold, *Chem. Rev*., 2010, **110**, 1060; (g) T. W. Lyons and M. S. Sanford, *Chem. Rev*., 2010, **110**, 1147; (h) C.-L. Sun, B.-J. Li and Z.-J Shi, *Chem. Rev*., 2011, **111**, 1293; (i) L. Ackermann, *Chem. Rev*., 2011, **111**, 1315; (j) N. Chatani, *Directed Metallation*, Springer, Berlin, Germany, 2008; (k) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res*., 2009, **42**, 1074; (l) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624.

(4) "The Nobel Prize in Chemistry 2010-Press Release". Nobel prize.org. Nobel Media AB 2013. Web. 25 Feb 2014. http://www.nobelprize.org/nobel_prizes /chemistry/laureates/2010/press.html.

(5) (a) B. K. Singh and R. Jana, *J. Org. Chem*., 2016, **81**, 831; (b) B. K. Singh, A. Polley and R. Jana, *J. Org. Chem*., 2016, **81**, 4295; (c) M. Iwasaki, N. Miki, Y. Tsuchiya, K. Nakajima and Y. Nishihara, *Org. Lett*., 2017, **19**, 1092; (d) C. Du, P.-X. Li, X. Zhu, J.-N. Han, J.-L. Niu, and M.-P. Song, *ACS Catal*., 2017, **7**, 2810; (e) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc*., 2013, **135**, 9797; (f) L. Yu, X. Chen, D. Liu, L. Hu, Y. Yu, H. Huang, Z. Tan and Q. Guib, *Adv. Synth. Catal*., 2018, **360**, 1346; (g) M. D. Reddy, F. R. Fronczek and E. B. Watkins, *Org. Lett*., 2016, **18**, 5620; (h) Y. He, N. Zhao, L. Qiu, X. Zhang and X. Fan, *Org. Lett*., 2016, **18**, 6054; (i) J. Xu, X. Zhu, G. Zhou, B. Ying, P. Ye, L. Su, C. Shen and P. Zhang, *Org. Biomol. Chem*., 2016, **14**, 3016; (j) K. Wang, G. Wang, G. Duan and C. Xia, *RSC Adv*., 2017, **7**, 51313; (k) H. Chen, P. Li, M. Wang and L. Wang, *Eur. J. Org. Chem*., 2018, 2091; (l) Y. Dou, Z. Xie, Z. Sun, H. Fang, C. Shen, P. Zhang and Q. Zhu, *ChemCatChem*, 2016, **8**, 3570; (m) H. Sahoo, A. Mandal, J. Selvakumar and M. Baidya, *Eur. J. Org. Chem*., 2016, 4321.

(6) (a) W.-H. Rao, B.-B. Zhan, K. Chen, P.-X. Ling, Z.-Z. Zhang and B.-F. Shi, *Org. Lett*., 2015, **17**, 3552; (b) Q. Zhu, D. Ji, T. Liang, X. Wang and Y. Xu, *Org. Lett*., 2015, **17**, 3798; (c) J. Hu, T. Lan, Y. Sun, H. Chen, J. Yaob and Y. Rao, *Chem. Commun*., 2015, **51**, 14929; (d) Y. Liu, K. Yang and H. Ge, *Chem. Sci*., 2016, **7**, 2804; (e) J.-L. Pan, Q.-Z. Li, T.-Y. Zhang, S.-H. Hou, J.-C. Kang and S.-Y. Zhang, *Chem. Commun*., 2016, **52**, 13151; (f) T. Kubo, Y. Aihara and N. Chatani, *Chem. Lett*., 2015, **44**, 1365; (g) Y. Zong and Y. Rao, *Org. Lett*., 2014, **16**, 5278; (h) A. Dey, S. Pimparkar, A. Deb, S. Guin and D. Maiti, *Adv. Synth. Catal*., 2017, **359**, 1301.

(7) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439.

(8) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507.

(9) O. Daugulis and V. G. Zaitsev, *Angew. Chem. Int. Ed*., 2005, **44**, 4046.

(10) Y. Zhang, J. Feng and C.-J. Li, *J. Am. Chem. Soc*., 2008, **130**, 2900.

(11) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani and F. Kakiuchi, *J. Am. Chem. Soc*., 2007, **129**, 9858.

(12) C. Feng, D. Feng and T.-P. Loh, *Chem. Commun*., 2014, **50**, 9865.

(13) S. Inoue, H. Shiota, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc*., 2009, **131**, 6898.

(14) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc*., 2013, **135**, 10630.

(15) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc*., 2010, **132**, 3648.

(16) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc*., 2005, **127**, 13154.

(17) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc*., 2006, **128**, 12634.

(18) G. He and G. Chen, *Angew. Chem. Int. Ed*., 2011, **50**, 5192.

(19) Y. Ano, M. Tobisu and N. Chatani, *J. Am. Chem. Soc*., 2011, **133**, 12984.

(20) E. J. Yoo, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc*., 2010, **132**, 17378.

(21) (a) D. Kalyani and M. S. Sanford, *Org. Lett*., 2005, **7**, 4149; (b) A. V. Gulevich, F. S. Melkonyan, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc*., 2012, **134**, 5528.

(22) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc*., 2004, **126**, 9542.

(23) (a) A. R. Dick, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc*., 2005, **127**, 12790; (b) C.-L. Sun, J. Liu, Y. Wang, X. Zhou, B.-J. Li and Z.-J. Shi, *Synlett*, 2011, **7**, 883; (c) Z. Ye, W. Wang, F. Luo, S. Zhang and J. Cheng, *Org. Lett*., 2009, **11**, 3974; (d) W. Wang, F. Luo, S. Zhang and J. Cheng, *J. Org. Chem*., 2010, **75**, 2415; (e) W. Wang, C. Pan, F. Chen and J. Cheng, *Chem. Commun*., 2011, **47**, 3978; (f) L. Li, P. Yu, J. Cheng, F. Chen and C. Pan, *Chem. Lett*., 2012, **41**, 600; (g) C.-J. Hu, X.-H. Zhang, Q.-P. Ding, T. Lv, S.-P. Ge and P. Zhong, *Tetrahedron Lett*., 2012, **53**, 2465; (h) W.-N. Sit, C.-W. Chan and W.-Y. Yu, *Molecules*, 2013, **18**, 4403; (i) K. Padala and M. Jeganmohan, *Chem. Commun*., 2013, **49**, 9651; (j) K. Padala and M. Jeganmohan, *Chem. Eur. J*., 2014, **20**, 4092; (k) Y.-J. Bian, C.-B. Xiang, Z.-M. Chen and Z.-Z. Huang, *Synlett*, 2011, **16**, 2407; (l) S. K. Rout, S. Guin, A. Gogoi, G. Majji

and B. K. Patel, *Org. Lett*., 2014, **16**, 1614; (m) A. Behera, S. K. Rout, S. Guin and B. K. Patel, *RSC Adv.*, 2014, **4**, 55115.

(24) (a) V. S. Thirunavukkarasu, J. Hubrich and L. Ackermann, *Org. Lett*., 2012, **14**, 4210; (b) F. Yang and L. Ackermann, *Org. Lett*., 2013, **15**, 718; (c) X. Yang, G. Shan and Y. Rao, *Org. Lett*., 2013, **15**, 2334; (d) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui and N. Jiao, *Angew. Chem. Int. Ed*., 2013, **52**, 1.

(25) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc*., 2011, **133**, 7652.

(26) B. Sun, T. Yoshino, S. Matsunaga and M. Kanai, *Adv. Synth. Catal*., 2014, **356**, 1491.

(27) E. Hernando, R. R. Castillo, N. Rodrguez, R. G. Arrayas and J. C. Carretero, *Chem. Eur. J*., 2014, **20**, 13854.

(28) (a) M. Iwasaki, M. Iyanaga, Y. Tsuchiya, Y. Nishimura, W. Li, Z. Li and Y. Nishihara, *Chem. Eur. J*., 2014, **20**, 2459; (b) C. Xu and Q. Shen, *Org. Lett*., 2014, **16**, 2046.

(29) X. Zhao, E. Dimitrijevic and V. M. Dong, *J. Am. Chem. Soc*., 2009, **131**, 3466.

(30) (a) H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc*., 2012, **134**, 134; (b) Y. Kuninobu, T. Iwanaga, T. Omura and K. Takai, *Angew. Chem. Int. Ed.*, 2013, **52**, 4431.

(31) F. Kakiuchi, M. Matsumoto, M. Sonoda, T. Fukuyama, N. Chatani, S. Murai, N. Furukawa and Y. Seki, *Chem. Lett.*, 2000, 750.

(32) M. Min, D. Kang, S. Jung and S. Honga, *Adv. Synth. Catal*., 2016, **358**, 1296.

(33) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 10326.

(34) (a) R. B. Bedford, M. F. Haddow, C. J. Mitchell and R. L. Webster, *Angew. Chem. Int. Ed*., 2011, **50**, 5524; (b) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang and Z. Shi, *J. Am. Chem. Soc*., 2006, **128**, 7416.

(35) (a) K. L. Hull, W. Q. Anani and M. S. Sanford, *J. Am. Chem. Soc*., 2006, **128**, 7134; (b) S.-J. Lou, D.-Q. Xu and Z.-Y. Xu, *Angew. Chem., Int. Ed*., 2014, **53**, 10330.

(36) (a) B. M. Trost, *Science*, 1991, **254**, 1471; (b) B. M. Trost, *Acc. Chem. Res*., 2002, **35**, 695; (c) C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci*., USA, 2008, **105**, 13197.

(37) Metal-Catalysed Cross-Coupling Reactions, 2nd ed., Vol. 1–2 (Eds.: A. de Meijere and F. Diederich), Wiley-VCH, Weinheim, 2004.

(38) C. J. Scheuermann, *Chem. Asian J*., 2010, **5**, 436.

(39) Y. Wu, J. Wang, F. Mao and F. Y. Kwong, *Chem. Asian J*., 2014, **9**, 26.

(40) G. Eglinton and A. R. Galbraith, *J. Chem. Soc*., 1959, 889.

(41) (a) C. Glaser, "Untersuchungen über einige Derivate der Zimmtsäure". *Annalen der Chemie und Pharmacie*. 1870, **154**, 137; (b) C. Glaser, "Beiträge zur Kenntniss des Acetenylbenzols". *Berichte der deutschen chemischen Gesellschaft*. 1869, **2**, 422; (c) A. S. Hay, *J. Org. Chem*., 1962, **27**, 3320.

(42) F. Shibahara, Y. Dohke and T. Murai, *J. Org. Chem*., 2012, **77**, 5381.

(43) Z. Li and C.-J. Li, *J. Am. Chem. Soc*., 2004, **126**, 11810.

(44) Z. Li and C.-J. Li, *J. Am. Chem. Soc*., 2005, **127**, 6968.

(45) Z. Li, D. S. Bohle and C.-J. Li, *PNAS*, 2006, **103**, 8928.

(46) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef, *Org. Lett*., 2007, **9**, 3137.

(47) S. K. Rout, S. Guin, A. Banerjee, N. Khatun, A. Gogoi and B. K. Patel, *Org. Lett*., 2013, **15**, 4106.

(48) J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, *Org. Biomol. Chem*., 2012, **10**, 9237.

(49) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J'E. Wu, P. Zhang, K.-W. Huang and X. Liu, *J. Org. Chem*., 2011, **76**, 8999.

(50) J. Yang, T. Chen and L.-B. Han, *J. Am. Chem. Soc*., 2015, **137**, 1782.

(51) T. He, H. Li, P. Lia and L. Wang, *Chem. Commun*., 2011, **47**, 8946.

(52) J. Huang, L.-T. Li, H.-Y. Li, E. Husan, P. Wang and B. Wang, *Chem. Commun*., 2012, **48**, 10204.

(53) J. Zhao, P. Li, C. Xia and F. Li, *Chem. Commun*., 2014, **50**, 4751.

(54) B. Du, B. Jin and P. Sun, *Org. Lett*., 2014, **16**, 3032.

(55) L. Liu, D. Zhou, J. Dong, Y. Zhou, S.-F. Yin and L.-B. Han, *J. Org. Chem*., 2018, **83**, 4190.

(56) X. Wang, D. Leow and J.-Q. Yu, *J. Am. Chem. Soc*., 2011, **133**, 13864.

(57) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, *Org. Lett*., 2012, **14**, 728.

(58) X. Wu, Y. Zhao and H. Ge, *Chem. Sci*., 2015, **6**, 5978.

(59) M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc*., 2014, **136**, 11590.

(60) (a) G.-W. Wang and T.-T. Yuan, *J. Org. Chem*., 2010, **75**, 476; (b) T.-S. Jiang and G.-W. Wang, *J. Org. Chem*., 2012, **77**, 9504; (c) S. Shi and C. Kuang, *J. Org. Chem*., 2014, **79**, 6105; (d) Z. Yin, X. Jiang and P. Sun, *J. Org. Chem*., 2013, **78**, 10002.

(61) K. Padala and M. Jeganmohan, *Chem. Eur. J*., 2014, **20**, 4092.

(62) L.-B. Zhang, S.-K. Zhang, D. Wei, X. Zhu, X.-Q. Hao, J.-H. Su, J.-L. Niu and M.-P. Song, *Org. Lett*., 2016, **18**, 1318.

(63) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck and M. J. Gaunt, *J. Am. Chem. Soc*., 2008, **130**, 16184.

(64) H.-Y. Thu, W.-Y. Yu and C.-M. Che, *J. Am. Chem. Soc*., 2006, **128**, 9048.

(65) Z. Wang, J. Ni, Y. Kuninobu and M. Kanai, *Angew. Chem. Int. Ed*., 2014, **53**, 3496.

(66) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc*., 2006, **128**, 6790.

(67) C.-G. Feng, M. Ye, K.-J. Xiao, S. Li and J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 9322.

(68) F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani and S. Murai, *Chem. Lett*., 2001, 422.

(69) D.-G. Yu, F. de Azambuja and F. Glorius, *Angew. Chem., Int. Ed*., 2014, **53**, 2754.

(70) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed*., 2012, **51**, 9372.

(71) (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi and J. F. Hartwig, *J. Am. Chem. Soc*., 2002, **124**, 390; (b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka Jr., M. R. Smith, *Science*, 2002, **295**, 305.

(72) Y.-H. Zhang, B.-F. Shi and J.-Q. Yu, *J. Am. Chem. Soc*., 2009, **131**, 5072.

(73) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem. Int. Ed*., 2011, **50**, 463; (c) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem*., 2011, **123**, 478.

(74) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc*., 2011, **133**, 19298.

(75) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518.

(76) (a) S. Lee, H. Lee and K. L. Tan, *J. Am. Chem. Soc*., 2013, **135**, 18778; (b) R.-Y. Tang, G. Li and J.-Q. Yu, *Nature*, 2014, **507**, 215; (c) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R. Y. Tang, M. Movassaghi and J. Q. Yu, *J. Am. Chem. Soc*., 2014, **136**, 10807; (d) M. Bera, A. Modak, T. Patra, A. Maji and D. Maiti, *Org. Lett*., 2014, **16**, 5760; (e) Y. Deng and J. Q. Yu, *Angew. Chem*., 2015, **127**, 902; (f) M. Bera, A. Maji, S. K. Sahoo and D. Maiti, *Angew. Chem., Int. Ed*., 2015, **54**, 8515; (g) S. Li, H. Ji, L. Cai and G. Li, *Chem. Sci*., 2015, **6**, 5595.

(77) (a) S. Li, L. Cai, H. Ji, L. Yang and G. Li, *Nat. Commun*., 2016, **7**, 10443; (b) A. Maji, B. Bhaskararao, S. Singha, R. B. Sunoj and D. Maiti, *Chem. Sci*., 2016, **7**, 3147.

(78) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 18056.

(79) A. Modak, T. Patra, R. Chowdhury, S. Raul and D. Maiti, *Organometallics* 2017, **36**, 2418.

(80) L. Chu, M. Shang, K. Tanaka, Q. Chen, N. Pissarnitski, E. Streckfuss and J.-Q. Yu, *ACS Cent. Sci*., 2015, **1**, 394.

(81) (a) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc*., 2015, **137**, 11888; (b) T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak and D. Maiti, *Angew. Chem. Int. Ed*., 2016, **55**, 7751.

(82) B. F. Shi, N. Maugel, Y. H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed*., 2008, **47**, 4882.

(83) (a) M. R. Albicker and N. Cramer, *Angew. Chem*., 2009, **121**, 9303; (b) T. Saget and N. Cramer, *Angew. Chem., Int. Ed*., 2013, **52**, 7865.

(84) (a) R. M. Jacobson and R. A. Raths, *J. Org. Chem*., 1979, **44**, 4013; (b) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc*., 2005, **127**, 13496; (c) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624.

(85) D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc*., 2011, **133**, 5767.

(86) A. Gollner and P. A. Koutentis, *Org. Lett.*, 2010, **12**, 1352.

(87) K. Plevova, L. Chang, E. Martin, Q. Llopis, L. Dechoux and S. Thorimbert, *Adv. Synth. Catal*., 2016, **358**, 3293.

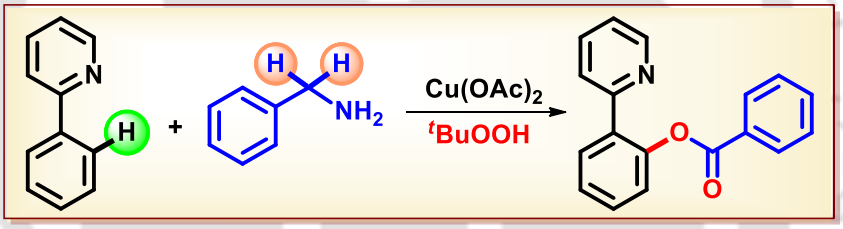
(88) J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed., New York: Wiley, 1985.

(89) K. J. Hock, L. Mertens, R. Hommelsheim, R. Spitzner and R. M. Koenigs, *Chem. Commun*., 2017, **53**, 6577.

(90) I. Nakamura, T. Onuma, R. Kanazawa, Y. Nishigai and M. Terada, *Org. Lett*., 2014, **16**, 4198.

CHAPTER II

Benzylamine as Arylcarboxy Surrogate: A Copper Catalysed *o*-Benzoxylation of 2-Phenylpyridines Using Benzylamines



Abstract: ***Differential reactivities and selectivities of Cu and Pd catalysts have been demonstrated in the reactions of benzylamines with 2-phenylpyridines. Although Pd is reported to give o-aroylation (ArCO–), Cu introduces an arylcarboxy group (ArCOO–) at the proximal site of the directing group. For the first time benzylamine has been utilised as a synthetic equivalent of an arylcarboxy group.***

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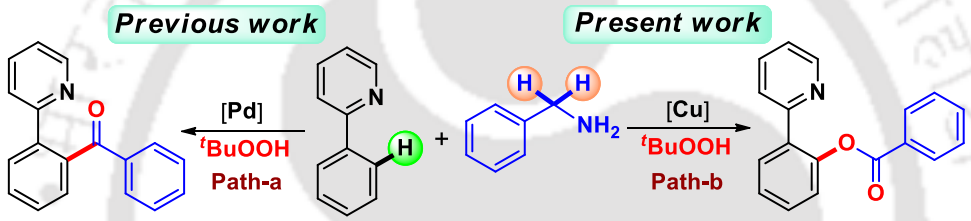
CHAPTER II

Benzylamine as Arylcarboxy Surrogate: A Copper Catalysed *o*-Benzoxylation of 2-Phenylpyridines Using Benzylamines

II.1. Introduction

Metal catalysed direct transformation of C–H bonds into C–C or C–heteroatom bonds is one of the most reliable and facile tools in current organic chemistry.[1] It renders step and atom economic strategy compared to traditional cross-coupling reactions *via* circuitous use of pre-functionalised starting materials. Even more attractive is the new disconnection approach, which would greatly enhance the number of retrosynthetic steps to build complex molecular scaffolds. Pertinent to this, a number of CDC protocols has been developed for the construction of C–C and C–O bond using various precursors such as alkylbenzenes,[2] terminal alkenes and alkynes[3] which act as unconventional synthetic equivalents of $ArCH_2O–$,[2a] ArCO–,[2b,c] ArCOO–.[2d,3] In continuation of the search for a suitable precursor that can serve as an unorthodox surrogate of various functionalities, in the present case benzyl amine was chosen as the potential candidate. Benzyl amines are highly susceptible to imine formation and then hydrolysed to aldehyde, can be further manipulated in various ways to achieve C–C[4a] and C–N[4b] bonds. Recently, Wu group developed a Pd catalysed protocol for the *ortho*-aroylation of 2-phenylpyridine using benzyl amines as ArCO– surrogates (path-a, Scheme II.1.1).[4a] Although Pd and Cu show similar reactivities in coupling reactions there are instances where they behave differently for the same reaction. In one of the recent report on the synthesis of 2-aminobenzothiazoles from 2-halothioureas it was observed that copper prefers dehalogenative path whereas palladium favors C–H activation strategy.[5] Moreover, copper[6] and palladium[2b] behave differently in the reaction between alkylbenzenes and 2-phenylpyridines giving *o*-benzoxylated (–OCOAr) and *o*-aroylated (–COAr) products respectively. Thus it would be interesting to see how copper catalyst influences the reaction between 2-phenylpyridine and benzyl amine. To find an answer to this, an initial trial was performed by reacting 2-

phenylpyridine and benzyl amine in the presence of $Cu(OAc)_2$ and TBHP in chlorobenzene. The reaction led to an exclusive formation of *o*-benzoxylated (–OCOAr) product (path-b, Scheme II.1.1) rather than an *o*-aroylated (–COAr) product which was observed using Pd-catalyst.[5a] This observation highlights the divergence in the selectivity achieved with the change of transition metal catalyst. Moreover, present protocol for the formation of an ester C–O bond using benzyl amine as the new arylcarboxy (ArCOO–) surrogate is unparalleled in the previously literature reports. Moreover, the directing group assisted C–O bond formation generally concentrated on acetoxylation[7] and hydroxylation[7d–f,8] *via* C–H bond activation. However, reports on *o*-benzoxylation by the same strategy are comparatively fewer.



Scheme II.1.1. *Selectivity achieved in the presence of different transition metal catalysts*

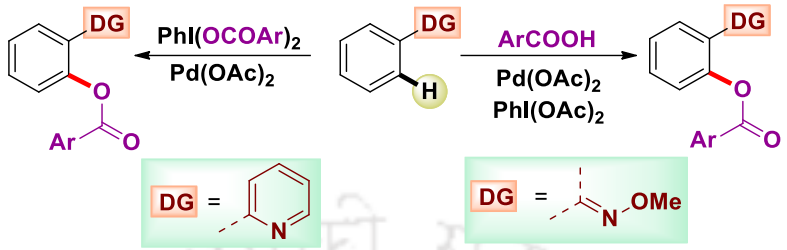
II.2. Strategies for *ortho*-benzoxylation

The importance of esterification reactions are mainly due to the presence of this motifs in many natural and synthetic molecules.[9] Though a number of traditional esterification methods such as Fischer esterification[10] and transesterification[11] are established, but the reaction procedures using harsh conditions such as use of acids and bases are limiting the reaction scope. The oxidative method like Bayer-Villiger oxidation[12] also have a regioselectivity issue. A number of oxidative esterifications are developed from past few decades. Among them, transition metal catalysed C–O bond formations leading to the formation of esters is an important method for ester preparation. Some of the representative examples of esterification reactions specifically *o*-benzoxylation strategies are disclosed below.

(i) *o*-Benzoxylation using benzoate iodinium salts [$PhI(OCOAr)_2$]

A palladium catalysed *o*-benzoxylation of 2-phenyl pyridines using benzoate iodinium salts [$PhI(OCOAr)_2$] as the aryl carboxy (ArCOO–) source has been developed by Sanford

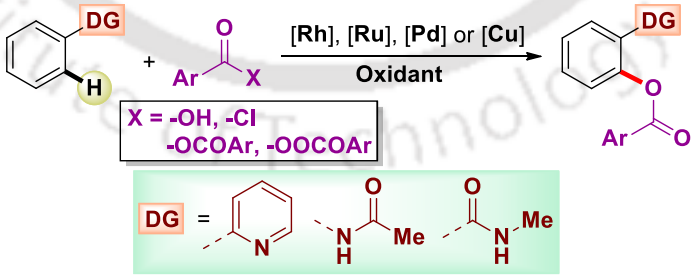
and co-workers.[13a] In 2011, Shi group reported a similar *o*-benzoxylation reaction of ketoxime ethers using *in situ* generated benzoate iodinium salts.[13b] (Scheme II.2.1).



Scheme II.2.1. *o-Benzoxylation using benzoate iodinium salts [PhI(OCOAr)$_2$]*

(ii) *o*-Benzoxylation using benzoic acids and its derivatives

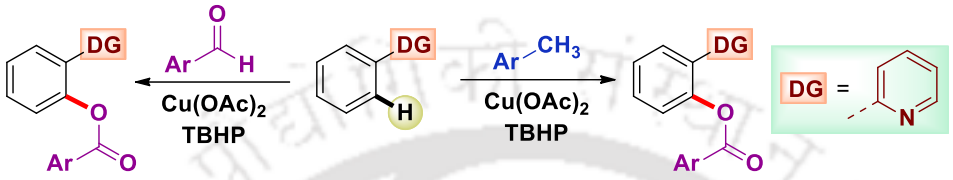
Cheng *et al*. reported a rhodium catalysed *ortho*-benzoxylation of 2-aryl pyridines using benzoic acids as the ArCOO– source.[14a] Later on, anhydrides,[14b] acid chlorides[14c] and aryl carboxylic acid salts[14d] were utilised for the *o*-benzoxylation of 2-aryl pyridines by the same group. Zhong *et al.* has also developed a ligand free protocol for the oxidative acyloxylation of 2-aryl pyridines in presence of palladium catalyst.[14e] Yu group has demonstrated a palladium catalysed *o*-benzoxylation of the same 2-phenyl pyridines using aryl acyl peroxides.[14f] Instead of 2-arylpyridines, acetanilides[14g] and benzamides[14h] were also employed as the directing substrates towards the *o*-benzoxylation using aryl carboxylic acids as the ArCOO– surrogates in the presence of ruthenium catalyst (Scheme II.2.2).



Scheme II.2.2. *o-Benzoxylation using benzoic acids and its derivatives*

(iii) *o*-Benzoxylation using aromatic aldehydes and alkylbenzenes

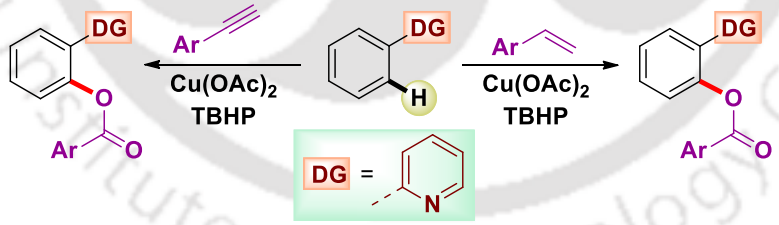
Huang *et al*. reported a copper catalysed *o*-benzoxylation of 2-arylpyridines using aromatic aldehydes and alkyl benzenes as the arylcarboxy (ArCOO–) surrogates. The strategy for the formation of C–O bond *via* C–H bond functionalisation proceeds in the presence of low cost catalyst $Cu(OAc)_2$ and oxidant TBHP (Scheme II.2.3).[15]



Scheme II.2.3. *o-Benzoxylation using aromatic aldehydes and alkylbenzenes*

(iv) *o*-Benzoxylation using styrenes and phenyl acetylenes

Very recently, a new and efficient *o*-benzoxylation protocol has also been developed by our group using styrenes and phenyl acetylenes as the new arylcarboxy (ArCOO–) surrogate in presence of copper acetate and TBHP. This reaction proceeds *via* the formation of phenylglyoxal followed by decarbonylation to benzoyl radical/benzaldehyde which acts as the active arylcarboxy source for the *o*-benzoxylation of 2-arylpyridinrs (Scheme II.2.4).[3]



Scheme II.2.4. *o-Benzoxylation using styrenes and phenyl acetylenes*

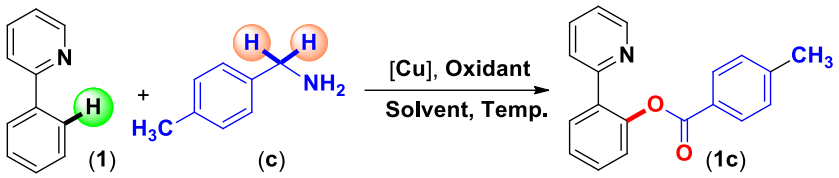
II.3. Present work

In continuation of above *o*-benzoxylation reactions, a new copper mediated *o*-benzoxylation of 2-arlpyridines is reported by using aryl methylamines as the unconventional arylcarboxy (ArCOO–) source.

Optimisation of reaction conditions: An initial trial was performed by reacting 2-phenylpyridine (**1**) and *p*-methylbenzyl amine (**c**) in the presence of $Cu(OAc)_2$ (20 mol%)

and oxidant TBHP (5–6 M in decane) (5 equiv.) in chlorobenzene at 120 °C (Table II.3.1, entry 1). The reaction provided the o-benzoxylated product (**1c**) in 66% yield. To arrive at the best possible yield of the product (**1c**), various counter anions of Cu(I) [CuBr, CuCl and CuI] and Cu(II) [$Cu(OAc)_2$, $CuBr_2$, $CuCl_2$, $Cu(OTf)_2$] salts (Table II.3.1, entries 1–7) were screened. Among all the catalysts screened $Cu(OAc)_2$ (Table II.3.1, entry 1) was found to be the best. Increasing the quantity of TBHP (5–6 M in decane) from 5 to 6 equivalents enhanced the product yield from 66% to 72% (Table II.3.1, entry 8), whereas no significant change in the yield was observed using 7 equivalents of the same (Table II.3.1, entry 9). A decrease in the catalyst loading from 20 mol% to 10 mol% lowered the product yield (Table II.3.1, entry 10) whereas only a marginal improvement in the yield occurred with the use of $Cu(OAc)_2$ (30 mol%) (Table II.3.1, entry 11). The reaction when performed at 140 °C was counterproductive (Table II.3.1, entry 12). Among all the other solvents examined, such as toluene (0%), THF (30%), dioxane (8%), DMSO (17%), DCE (45%) and DMF (12%), chlorobenzene (74%) was found to give superior yield. The use of an aq. TBHP (47%) was less effective compared to that of a decane solution of TBHP (Table II.3.1, entry 13). Control experiments suggest that both catalyst and oxidant combination is indispensable for this transformation (Table II.3.1, entries 14 and 15). Thus, the use of $Cu(OAc)_2$ (20 mol%), TBHP (5–6 M in decane) (6 equiv.) and chlorobenzene (2 mL) at 120 °C was found to be the best optimal condition for this transformation (Table II.3.1, entry 8).

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



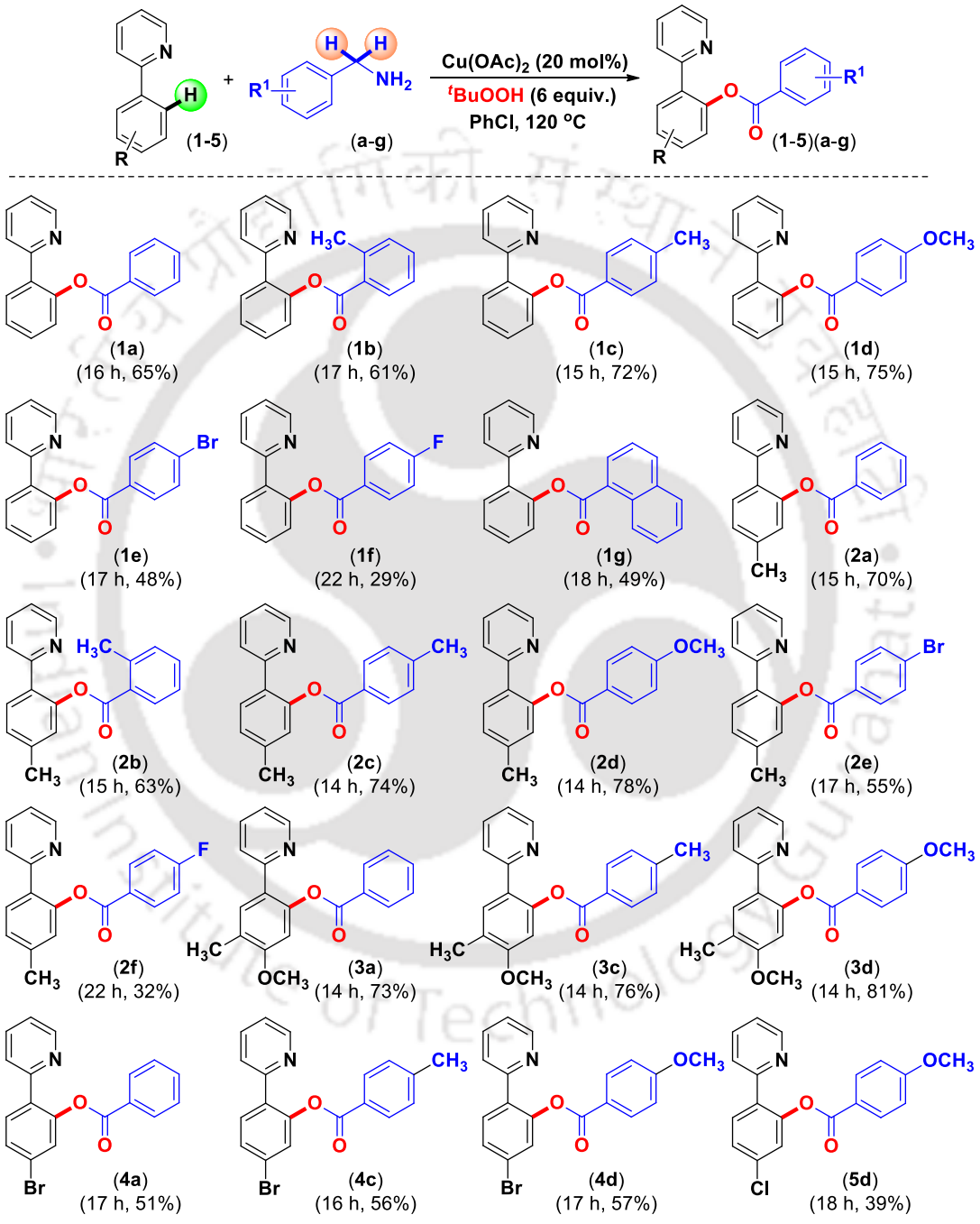
Entry	Catalyst (mol%)	Oxidant (equiv.)[c]	Temp (°C)	Yield[b] (%)
1.	$Cu(OAc)_2$ (20)	TBHP (5)	120	66
2.	CuBr (20)	TBHP (5)	120	37
3.	$CuBr_2$ (20)	TBHP (5)	120	51
4.	CuCl (20)	TBHP (5)	120	28
5.	$CuCl_2$ (20)	TBHP (5)	120	45
6.	$Cu(OTf)_2$ (20)	TBHP (5)	120	25
7.	CuI (20)	TBHP (5)	120	23
8.	**$Cu(OAc)_2$ (20)**	**TBHP (6)**	**120**	**72**
9.	$Cu(OAc)_2$ (20)	TBHP (7)	120	73
10.	$Cu(OAc)_2$ (10)	TBHP (6)	120	58
11.	$Cu(OAc)_2$ (30)	TBHP (6)	120	75
12.	$Cu(OAc)_2$ (20)	TBHP (6)	140	63
13.	$Cu(OAc)_2$ (20)	aq. TBHP (6)	120	47
14.	None	TBHP (6)	120	0
15.	$Cu(OAc)_2$ (20)	None	120	0

[a]Reaction conditions: 2-phenylpyridine (**1**) (0.5 mmol), *p*-methylbenzyl amine (**c**) (1 mmol), chlorobenzene (2 mL), time 15 h. [b]Isolated yield. [c]With respect to benzylamine.

Substrate scopes for *o*-benzoxylation of 2-arylpyridines: The optimised conditions were then implemented for *o*-benzoxylation of 2-arylpyridines (**1**–**5**) using various substituted benzylamines (**a**–**g**) and the results are summarised in Scheme II.3.1. Initially benzyl amine (**a**) and benzyl amines possessing various electron-rich groups *viz*. *o*-Me (**b**), *p*-Me (**c**) and *p*-OMe (**d**) were treated with 2-phenylpyridine (**1**) for *o*-benzoxylation at the proximal site of *N*-atom. All the benzyl amines served as their respective ArCOO– surrogates to provide good to moderate yields of their *o*-benzoxylated products (**1a**–**1d**) as shown in Scheme II.3.1. Moderately electron-deficient groups such as *p*-Br (**e**) and *p*-F (**f**) when present in phenyl ring of the benzyl amine coupled with (**1**) to give *o*-esters (**1e**) and (**1f**) in lower yields of 48% and 29%, respectively (Scheme II.3.1). Arylmethyl amines bearing electron-deficient substituents gave lower yields compared to substrates possessing electron-rich groups suggesting the importance of their electronic effects on

the overall process. Notably, 1-naphthylmethylamine (**g**) having a fused ring reacted smoothly with (**1**) yielding naphthylcarboxylated (**1g**) in 49%.

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

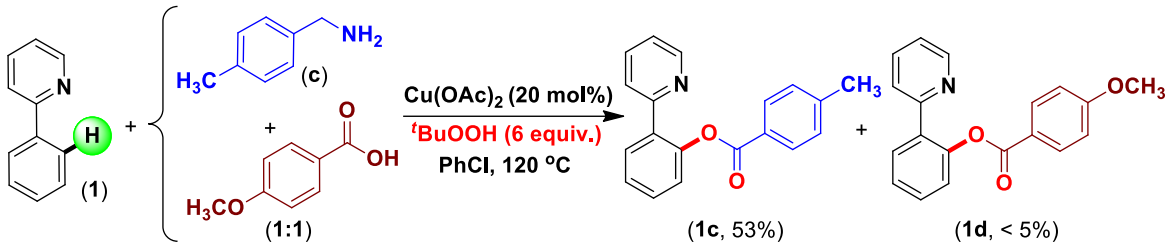


[a]Reaction conditions: 2-phenylpyridine (**1–5**) (0.5 mmol), arylmethylamines (**a–g**) (1 mmol), $Cu(OAc)_2$ (0.1 mmol), TBHP (5–6 M) (6 mmol), temperature 120 °C, in chlorobenzene (2 mL), time 14–22 h. [b]Yield of isolated pure product.

In addition to 2-phenylpyridine (**1**), o-benzoxylation of 2-(p-tolyl)pyridine (**2**) was also investigated with various arylmethyl amines (Scheme II.3.1). The selectivity and reactivity trends of substituted benzyl amines towards o-benzoxylation of (**2**) were found to be identical as was observed for (**1**). Marginally better yields were obtained for o-benzoxylated products (**2a**–**2f**) with (**2**) than (**1**) which could be attributed to its better chelation ability with a metal catalyst due to presence of electron-donating o-tolyl group. Directing arene possessing two electron donating groups (–Me and –OMe) as in 2-(4-methoxy-3-methylphenyl)pyridine (**3**) showed identical reactivity and yield trends as that of (**2**) toward o-benzoxylation when reacted with various benzylamines (**a**), (**c**) and (**d**) as shown in Scheme II.3.1. The scope of o-benzoxylation for 2-(4-bromophenyl)pyridine (**4**) with benzyl amine (**a**) and substituted benzyl amines viz p-Me (**c**), and p-OMe (**d**) were also investigated. All provided o-benzoxylated products (**4a**–**4d**) in moderate yields ranging from 51% to 57% (Scheme II.3.1). Lower yields obtained in 2-(4-bromophenyl)pyridine (**4**) could possibly arise from poor chelating ability of (**4**) as compared to its neutral (**1**) and electron-rich analogues (**2** and **3**). Finally, reaction of 2-(4-chlorophenyl)pyridine (**5**) with p-methoxybenzylamine (**d**) afforded o-benzoxylated products (**5d**) in a modest yield of 39%. Unfortunately, aliphatic amines such as butyl amine and cyclohexylmethylamine failed to undergo any o-acetoxylation with any of the directing arenes under the optimised condition.

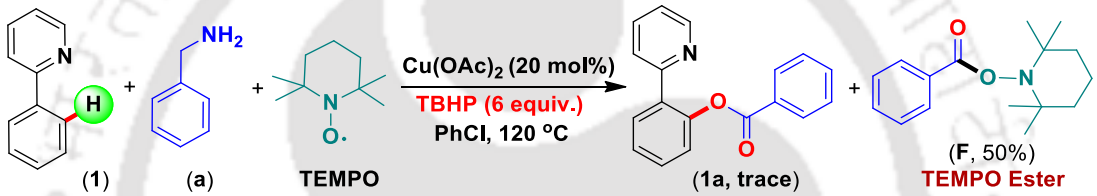
Mechanistic investigation: To find a possible reaction pathway for this protocol systematic investigations were carried out. Analysis of the reaction mixture between (**1**) and (**a**) divulges the presence of benzaldehyde and benzoic acid in the medium suggesting their intermediacy.

Control experiment: A control experiment carried out by reacting (**1**) with an equimolar mixture of p-methylbenzyl amine (**c**) and p-methoxybenzoic acid under the optimized condition gave product (**1c**) predominantly (53%) along with a trace of (**1d**); suggesting arylcarboxylic acid is not the main coupling partner (Scheme II.3.2). The coupling partner is most likely tert-butyl benzoperoxate generated in situ by the reaction of aldehyde and TBHP; similar to the recent o-benzoxylation of (**1**) using terminal alkenes and alkynes.[3] The aldehyde is obtained by the hydrolysis of imine which in turn is formed by the oxidation of benzylamine.[4b]

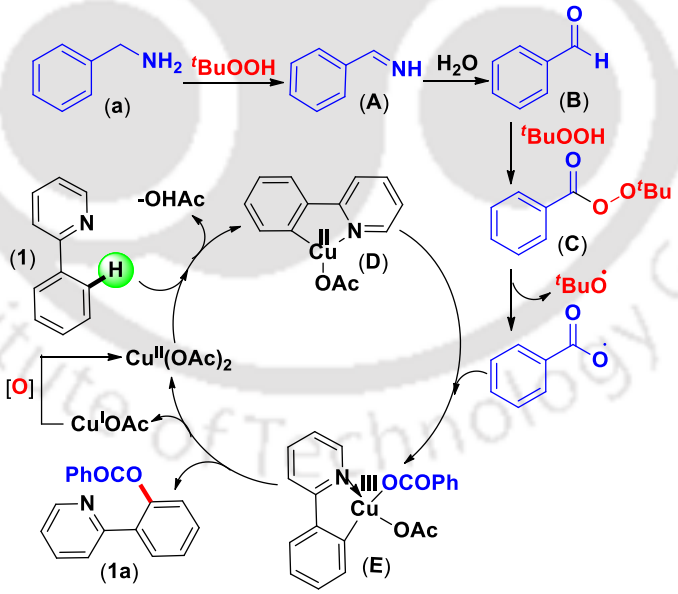


Scheme II.3.2. *Control experiment with benzoic acid*

Reaction with radical scavenger TEMPO: To ascertain the nature of reaction mechanism, a reaction was performed in the presence of radical inhibitor TEMPO (Scheme II.3.3). Substantial quenching of product formation and isolation of TEMPO ester (F) suggest a radical mechanism.



Scheme II.3.3. *Reaction in presence of radical inhibitor TEMPO*



Scheme II.3.4. *Proposed mechanism for the ortho-benzoxylation*

From the above mentioned experimental observations, a tentative mechanism has been proposed for this protocol as depicted in Scheme II.3.4. Benzyl amine oxidises to imine (**A**) which on hydrolysis gives benzaldehyde (**B**). In the presence of excess of TBHP, (**B**) is transformed to *tert*-butyl benzoperoxate (**C**). A loss of ^{t}BuO radical from (**C**) gives

benzoxy radical. The radical species on subsequent ligation with the Cu(II) complex (**D**) gives the Cu(III) intermediate (**E**). The reductive elimination in the final step leads to the *o*-benzoxylated product (**1a**) whereas the Cu(I) generated is re-oxidised to Cu(II) for next catalytic cycle.

In conclusion, this protocol demonstrates the use of benzyl amines as an unconventional synthetic equivalent of arylcarboxy groups (ArCOO–) which has been employed for the *o*-benzoxylation of 2-phenylpyridine derivatives. A plausible reaction mechanism involves the *in situ* generation of intermediates such as imine and aldehyde from arylmethylamine. The radical nature of the reaction has been established by isolation of TEMPO ester. This protocol shows the differential selectivities and reactivities of Cu and Pd catalysts for the same reaction.

II.4. Experimental section

II.4.1. General information: All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 GF_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 and 600 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). Mass spectra were recorded using WATERS MS system, Q-tof premier and data analyzed using Mass Lynx 4.1. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

II.4.2. General procedure for the synthesis of 2-(pyridin-2-yl)phenyl benzoate (1a): A mixture of 2-phenylpyridine (**1**) (77.5 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 20 mol%), benzylamine (**a**) (107 mg, 1 mmol) in chlorobenzene (2 mL) were taken in an oven dried round bottom flask fitted with a reflux condenser. To this mixture a decane solution of TBHP (5−6 M) (1200 µL, 6 equivalent with respect to benzylamine) was added and the reaction mixture was heated in an oil bath at 120 ^oC for 16 h. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (15 mL) and the residual particles were filtered through a filter paper which was washed with ethyl acetate (2 x 2.5 mL). The ethyl acetate layer was washed with a 5% solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL) and the organic layer was dried over anhydrous Na_2SO_4 and the

solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with (92:8, hexane/ethyl acetate) to afford 2-(pyridine-2-yl)phenyl benzoate (**1a**) (89 mg, 65% yield).

II.4.3. Mechanistic investigation in the presence of radical scavenger TEMPO: An oven-dried round bottom flask fitted with a reflux condenser was charged with 2-phenylpyridine (**1**) (77.5 mg, 0.5 mmol), benzylamine (**a**) (54 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 0.1 mmol), TBHP in decane (5–6 M) (600 µL, 6 equivalent with respect to benzylamine), TEMPO (78 mg, 0.5 mmol) in chlorobenzene (1 mL). The resultant reaction mixture was stirred in a preheated oil bath at 120 ºC for 15 h. The reaction mixture was cooled to room temperature and admixed with ethyl acetate (15 mL) and the residual particles were filtered through a filter paper which was washed with ethyl acetate (2 x 2.5 mL). The ethyl acetate layer was washed with a 5% solution of sodium bicarbonate (2 x 5 mL) and water (2 x 5 mL) and the organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel which afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**F**) (65 mg, 50% yield) and traces (<6%) of the desired product (**1a**) was observed.

II.5. References

(1) (a) G Dyker, Handbook of C−H Transformations: Applications in Organic Synthesis; Wiley-VCH: Weinheim, 2005; (b) J.-Q. Yu and Z.-J. Shi, C−H Activation; Springer: Berlin, Germany, 2010; (c) T. Satoh and M. Miura, *Chem. Eur. J*., 2010, **16**, 11212; (d) X Chen, K. M. Engle, D.-H. Wang and J. –Q. Yu, *Angew. Chem., Int. Ed*., 2009, **48**, 5094; (e) T. W. Lyons and M. S. Sanford, *Chem. Rev*., 2010, **110**, 1147; (f) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J Shi, *Chem. Soc. Rev*., 2010, **39**, 712; (g) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624; (h) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev*., 2011, **40**, 4740; (i) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev*., 2011, **40**, 5068; (j) C.-L. Sun, B.-J. Li and Shi, Z.-J, *Chem. Rev*., 2011, **111**, 1293; (k) L. Ackermann, *Chem. Rev*., 2011, **111**, 1315; (l) A. S. Girard, T. Knauber and C.-J. Li, *Angew. Chem. Int. Ed*., 2013, **52**, 2;

(m) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev*., 2013, **113**, 6234.

(2) (a) S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee and B. K. Patel, *Org. Lett*., 2012, **14**, 3982; (b) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett.*, 2012, **14**, 5294; (c) S. K. Rout, S. Guin, A. Banerjee, N. Khatun, A. Gogoi and B. K. Patel, *Org. Lett.*, 2013, **15**, 4106; (d) G. Majji, S. Guin, A. Gogoi, S. K. Rout and B. K. Patel, *Chem. Commun*., 2013, **49**, 3031.

(3) S. K. Rout, S. Guin, A. Gogoi, G. Majji and B. K. Patel, *Org. Lett.*, 2014, **16**, 1614.

(4) (a) Q. Zhang, F. Yang and Y. Wu, *Chem. Commun*., 2013, **49**, 6837; (b) L. Gao, H. Tang and Z. Wang, *Chem. Commun*., 2014, **50**, 4085.

(5) S. K. Sahoo, A. Banerjee, S. Chakraborty and B. K. Patel, *ACS Catal*., 2012, **2**, 544.

(6) Y.-J. Bian, C.-B. Xiang, Z.-M. Chen and Z.-Z. Huang, *Synlett*, 2011, 2407.

(7) (a) D. Kalyani and M. S. Sanford, *Org. Lett*., 2005, **7**, 4149; (b) F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan and Y.-M. Liang, *Org. Lett*., 2009, **11**, 5726; (c) X. Zheng, B. Song and B. Xu, *Eur. J. Org. Chem*., 2010, 4376; (d) L. Wang, X.-D. Xia, W. Guo, J.-R. Chen and W.-J. Xiao, *Org. Biomol. Chem.*, 2011, **9**, 6895; (e) R. K. Rit, R. Yadav and A. K. Sahoo, *Org. Lett*., 2012, **14**, 3724; (f) R. Yadav, R. K. Rit and A. K. Sahoo, *Chem. Eur. J*., 2012, **18**, 5541.

(8) (a) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc*., 2006, **128**, 6790; (b) S. H. Kim, H. S. Lee, S. H. Kim and J. N. Kim, *Tetrahedron Lett*., 2008, **49**, 5863; (c) A. Company and S. Enthaler, *Chem. Soc. Rev*., 2011, **40**, 4912; (d) D. A. Alonso, C. Najera, I. M. Pastor and M. Yus, *Chem. Eur. J*., 2010, **16**, 5274; (e) V. S. Thirunavukkarasu, S. I. Kozhushkov and L. Ackermann, *Chem. Commun*., 2014, **50**, 29.

(9) F. Luo, C. Pan and J. Cheng, *Synlett*, 2012, **23**, 357.

(10) (a) N. Iranpoor, H. Firouzabadi and D. Khalili, *Org. Biomol. Chem*., 2010, **8**, 4436; (b) K. Ishihara, S. Nakagawa and A. Sakakura, *J. Am. Chem. Soc.*, 2005, **127**, 4168; (c) K. Komura, A. Ozaki, N. Ieda and Y. Sugi, *Synthesis*, 2008, 3407; (d) A. K. Chakraborti, B. Singh, S. V. Chankeshwara and A. R. Patel, *J. Org. Chem.*, 2009, **74**, 5967; (e) Z. Chen, Y. Wen, Y. Fu, H. Chen, M. Ye, G. Luo, *Synlett*, 2017, **28**, 981.

(11) (a) J. Otera, *Chem. Rev*. 1993, **93**. 1449; (b) G. A. Grasa, R. Singh and S. P. Nolan, *Synthesis*, 2004, 971; (c) M. Hatano, Y. Furuya, T. Shimmura, K. Moriyama, S.

Kamiya, T. Maki and K. Ishihara, *Org. Lett*., 2011, **13**, 426; (d) J. E. M. Fernando, A. Levens, D. Moock and D. W. Lupton, *Synthesis*, 2017, **49**, 3505; (e) M. Blümel, J.-M. Noy, D. Enders, M. H. Stenzel and T. V. Nguyen, *Org. Lett.*, 2016, **18**, 2208.

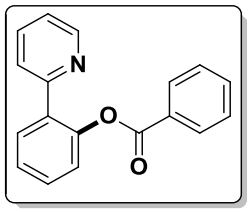
(12) (a) K. Laszlo and C. Barbara, *Strategic Applications of Named Reactions in Organic Synthesis*. Burlington; San Diego; London: Elsevier Academic Press., 2005, 28; (b) M. A. Goodman and M. R. Detty, *Synlett*, 2006, 1100; (c) B. Poladura, A. Martínez-Castañeda, H. Rodríguez-Solla, R. Llavona, C. Concellon and V. del Amo, *Org. Lett*., 2013, **15**, 2810; (d) L. Zhou, X. H. Liu, J. Ji, Y. H. Zhang, X. L. Hu, L. L. Lin and X. M. Feng, *J. Am. Chem. Soc*., 2012, **134**, 17023.

(13) (a) A. R. Dick, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc*., 2005, **127**, 12790; (b) C.-L. Sun, J. Liu, Y. Wang, X. Zhou, B.-J. Li and Z.-J. Shi, *Synlett*, 2011, **7**, 883.

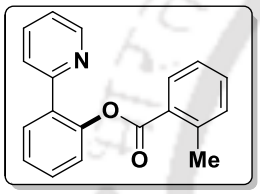
(14) (a) Z. Ye, W. Wang, F. Luo, S. Zhang and J. Cheng, *Org. Lett*., 2009, **11**, 3974; (b) W. Wang, F. Luo, S. Zhang and J. Cheng, *J. Org. Chem*., 2010, **75**, 2415; (c) W. Wang, C. Pan, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 3978; (d) L. Li, P. Yu, J. Cheng, F. Chen and C. Pan, *Chem. Lett*., 2012, **41**, 600; (e) C.-J. Hu, X.-H. Zhang, Q.-P. Ding, T. Lv, S.-P. Ge and P. Zhong, *Tetrahedron Lett*., 2012, **53**, 2465; (f) W.-N. Sit, C.-W. Chan and W.-Y. Yu, *Molecules*, 2013, **18**, 4403; (g) K. Padala and M. Jeganmohan, *Chem. Commun*., 2013, **49**, 9651; (h) K. Padala and M. Jeganmohan, *Chem. Eur. J*., 2014, **20**, 4092.

(15) Y.-J. Bian, C.-B. Xiang, Z.-M. Chen and Z.-Z. Huang, Synlett, 2011, **16**, 2407.

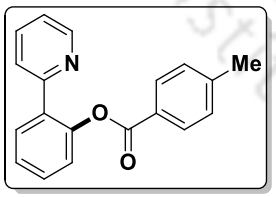
II.6. Spectral data



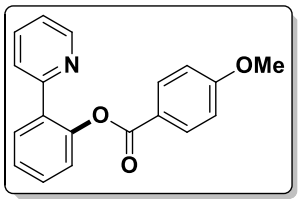
2-(Pyridine-2-yl)phenyl benzoate (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14–7.17 (m, 1H), 7.29–7.32 (m, 1H), 7.38–7.43 (m, 2H), 7.45–7.48 (m, 2H), 7.55–7.64 (m, 3H), 7.77–7.79 (m, 1H), 8.07–8.09 (m, 2H), 8.59–8.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.3, 123.5, 123.9, 126.6, 128.7, 129.7, 129.9, 130.3, 131.1, 133.5, 133.6, 136.3, 148.5, 149.8, 155.8, 165.3; IR (KBr): 3442, 2918, 2853, 1736, 1634, 1585, 1446, 1262, 1194, 1061, 847, 754, 706, 614 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}NO_2$ $[M+H]^+$ 276.1019; found 276.1062.



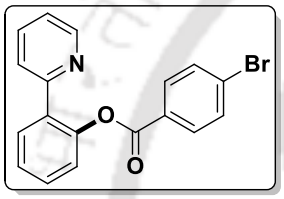
2-(Pyridin-2-yl)phenyl 2-methylbenzoate (1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.53 (s, 3H), 7.17–7.20 (m, 1H), 7.25–7.30 (m, 3H), 7.38–7.51 (m, 3H), 7.54–7.57 (m, 1H), 7.60–7.67 (m, 1H), 7.74–7.77 (m, 1H), 7.98–8.02 (m, 1H), 8.61–8.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 122.3, 123.6, 123.9, 125.9, 126.5, 128.7, 129.9, 131.0, 131.2, 131.9, 132.7, 133.6, 136.4, 141.3, 148.5, 149.6, 155.9, 165.8; IR (KBr): 3062, 2962, 2856, 1743, 1585, 1492, 1467, 1426, 1289, 1250, 1197, 1115, 1040, 1021, 884, 794, 693, 616 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ $[M+H]^+$ 290.1176; found 290.1171.



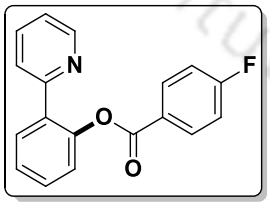
2-(Pyridin-2-yl)phenyl 4-methylbenzoate (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.14–7.18 (m, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.29–7.31 (m, 1H), 7.38–7.42 (m, 1H), 7.46–7.50 (m, 1H), 7.54–7.57 (m, 1H), 7.60–7.64 (m, 1H), 7.77–7.80 (m, 1H), 7.96–7.98 (m, 2H), 8.60–8.62 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.9, 122.3, 123.6, 123.9, 126.5, 127.0 129.4, 129.9, 130.4, 131.1, 133.6, 136.3, 144.5, 148.6, 149.8, 155.8, 165.4; IR (KBr): 3436, 2917, 1733, 1643, 1582, 1454, 1265, 1193, 1066, 985, 894, 748, 677 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ $[M+H]^+$ 290.1176; found 290.1167.



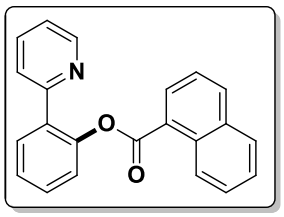
2-(Pyridin-2-yl)phenyl 4-methoxybenzoate (1d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 3H), 6.93 (d, 2H, J = 9.2 Hz), 7.15–7.18 (m, 1H), 7.28–7.31 (m, 1H), 7.37–7.41 (m, 1H), 7.46–7.50 (m, 1H), 7.56 (d, 1H, J = 8.0 Hz), 7.60–7.64 (m, 1H), 7.77–7.79 (m, 1H), 8.04 (d, 2H, J = 8.8 Hz), 8.62 (d, 1H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 113.9, 122.0, 122.3, 123.6, 124.0 126.4, 129.9, 131.1, 132.5, 133.5, 136.3, 148.6, 149.8, 155.8, 164.0, 165.0; IR (KBr): 3413, 2925, 1731, 1605, 1511, 1463, 1254, 1166, 1067, 846, 752, 697, 572 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_3$ $[M+H]^+$ 306.1125; found 306.1133.



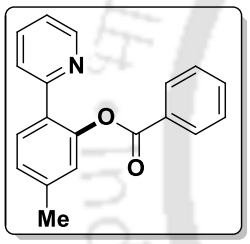
2-(Pyridin-2-yl)phenyl 4-bromobenzoate (1e): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 1H), 7.29 (d, 1H, J = 8.4 Hz), 7.39–7.43 (m, 1H), 7.46–7.53 (m, 2H), 7.58–7.66 (m, 3H), 7.74–7.76 (m, 1H), 7.93 (d, 2H, J = 8.8 Hz), 8.56 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.4, 123.4, 123.8, 126.7, 128.6, 128.7, 128.9, 130.3, 131.1, 131.8, 132.0, 136.4, 148.3, 149.7, 155.7, 164.7; IR (KBr): 3052, 2925, 2850, 1733, 1587, 1492, 1482, 1465, 1450, 1423, 1395, 1261, 1186, 1166, 1068, 1058, 1023, 1008, 849, 795, 761, 749 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}BrNO_2$ $[M+H]^+$ 354.0124; found 354.0117.



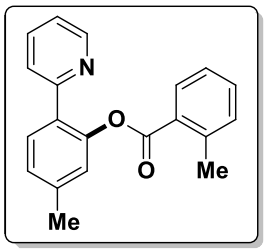
2-(Pyridin-2-yl)phenyl 4-fluorobenzoate (1f): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.08–7.12 (m, 4H), 7.14–7.16 (m, 1H), 7.27–7.40 (m, 1H), 7.45–7.48 (m, 1H), 7.51 (d, 1H, J = 7.8 Hz), 7.60–7.75 (m, 1H), 8.06–8.09 (m, 2H), 8.56 (d, 1H, J = 3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.9 (d, J = 22.5 Hz), 122.4, 123.5, 123.9, 126.0, 126.7, 130.0, 131.1, 132.9, 133.0, 133.5, 136.4, 148.4, 149.7, 155.8, 164.4, 165.4, 167.1; IR (KBr): 3419, 2929, 1739, 1633, 1501, 1462, 1263, 1193, 1068, 860, 753, 682, 573 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}FNO_2$ $[M+H]^+$ 294.0925; found 294.0965.



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

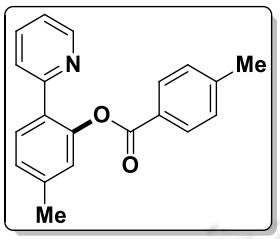


5-Methyl-2-(pyridin-2-yl)phenyl benzoate (2a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.12 (d, 2H, J = 9.6 Hz), 7.20 (d, 1H, J = 7.2 Hz), 7.45 (t, 2H, J = 7.8 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.57–7.60 (m, 2H), 7.68 (d, 1H, J = 7.8 Hz), 8.08–8.10 (m, 2H,), 8.57 (d, 1H, J = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 122.1, 123.7, 124.0, 127.5, 128.7, 129.8, 130.3, 130.6, 130.8, 133.6, 136.3, 140.4, 148.3, 149.7, 155.8, 165.5; IR (KBr): 3505, 2916, 1737, 1622, 1586, 1465, 1256, 1131, 1062, 892, 784, 707, 683, 545 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO_2$ $[M+H]^+$ 290.1176; found 290.1159.

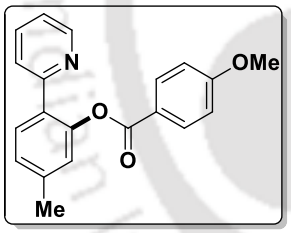


5-Methyl-2-(pyridin-2-yl)phenyl 2-methylbenzoate (2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 2.53 (s, 3H), 7.09 (s, 1H), 7.11–7.15 (m, 1H), 7.18–7.25 (m, 3H), 7.40 (t, 1H, J = 7.6 Hz), 7.51–7.53 (m, 1H), 7.58–7.66 (m, 2H), 8.01 (d, 1H, J = 7.6 Hz), 8.57–8.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 21.8, 122.1, 123.8, 124.0, 125.9, 127.4, 128.9, 130.8, 131.2, 131.9, 132.6, 136.3, 140.4, 141.3, 148.3, 149.7, 156.0, 166.0; IR (KBr) 3062, 2961, 2926, 1737, 1623, 1586, 1573, 1466, 1431,

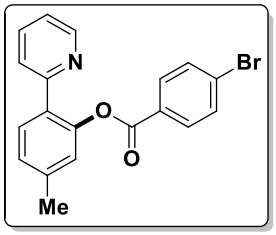
1288, 1245, 1151, 1135, 1045, 893, 782, 736, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_2$ $[M+H]^+$ 304.1332; found 304.1335.



5-Methyl-2-(pyridin-2-yl)phenyl 4-methylbenzoate (2c): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 2.434 (s, 3H), 7.11– 7.15 (m, 1H), 7.20 (d, 1H, *J* = 7.6 Hz), 7.25 (d, 3H, *J* = 6.8 Hz), 7.53 (d, 1H, *J* = 7.6 Hz), 7.57–7.61 (m, 1H), 7.68 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 2H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 21.9, 122.1, 123.8, 124.0, 127.1, 127.4, 129.4, 130.4, 130.7, 130.9, 136.3, 140.4, 144.4, 148.4, 149.8, 155.9, 165.5; IR (KBr): 3442, 2923, 1735, 1612, 1586, 1464, 1257, 1130, 1069, 925, 831, 746, 668, 543 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_2$ $[M+H]^+$ 304.1332; found 304.1348.

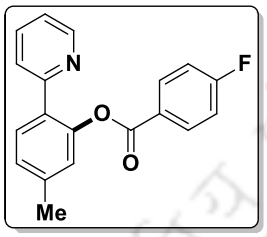


5-Methyl-2-(pyridin-2-yl)phenyl 4-methoxybenzoate (2d): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 3.87 (s, 3H), 6.92–6.94 (m, 2H), 7.10–7.14 (m, 2H), 7.20 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 7.8 Hz), 7.57–7.60 (m, 1H), 7.68 (d, 1H, *J* = 7.8 Hz), 8.03–8.05 (m, 2H), 8.59 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.7, 113.9, 122.0, 122.1, 123.8, 124.0, 127.3, 130.6, 130.8, 132.5, 136.2, 140.3, 148.4, 149.7, 155.9, 164.0, 165.2; IR (KBr): 3464, 2918, 1731, 1606, 1581, 1464, 1254, 1167, 1069, 845, 774, 693, 569 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_3$ $[M+H]^+$ 320.1281; found 320.1276.

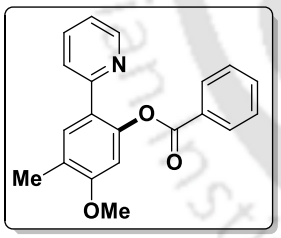


5-Methyl-2-(pyridin-2-yl)phenyl 4-bromobenzoate (2e): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.08–7.13 (m, 2H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 3H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.8 Hz), 8.51–8.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4,

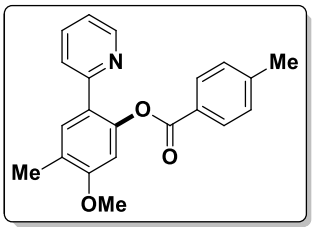
122.2, 123.6, 123.9, 127.6, 128.7, 128.8, 130.4, 130.8, 131.8, 132.0, 136.4, 140.5, 148.1, 149.7, 155.7, 164.8; IR (KBr): 2955, 2922, 2853, 1737, 1621, 1589, 1465, 1431, 1397, 1258, 1173, 1152, 1131, 1071, 1027, 1010, 783, 747, 678 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO_2$ $[M+H]^+$ 368.0281; found 368.0275.



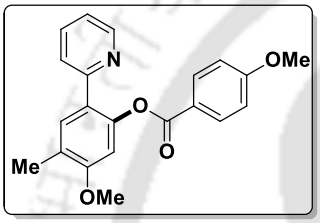
5-Methyl-2-(pyridin-2-yl)phenyl 4-fluorobenzoate (2f): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 7.09–7.12 (m, 4H), 7.19 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.64 (d, 1H, J = 7.8 Hz), 8.07–8.09 (m, 2H), 8.53 (d, 1H, J = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 115.9 (d, J = 22.5 Hz), 122.1, 123.9, 126.1 127.6, 127.7, 130.6, 130.8, 132.9, 133.0, 136.4, 140.5, 148.2, 149.7, 155.9, 164.6, 165.4, 167.1; IR (KBr): 3722, 2920, 1739, 1604, 1507, 1226, 1151, 1071, 782, 684 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}FNO_2$ $[M+H]^+$ 308.1081; found 308.1073.



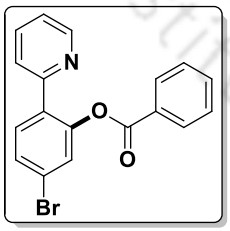
5-Methoxy-4-methyl-2-(pyridin-2-yl)phenyl benzoate (3a): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 3.85 (s, 3H), 6.72 (s, 1H), 7.06–7.10 (m, 1H), 7.45 (t, 2H, J = 7.6 Hz), 7.49–7.53 (m, 1H), 7.55–7.61 (m, 3H), 8.08–8.10 (m, 2H), 8.55–8.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.0, 55.8, 105.4, 121.7, 123.6, 125.0, 125.2 128.7, 129.8, 130.4, 132.3, 133.6, 136.2, 147.3, 149.7, 155.7, 158.8, 165.5; IR (KBr): 3443, 2925, 1736, 1618, 1589, 1464, 1260, 1143, 1060, 968, 890, 747, 612, 574 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_3$ $[M+H]^+$ 320.1281; found 320.1293.



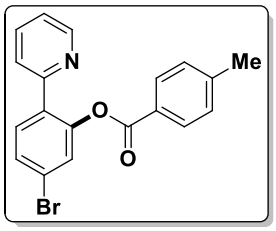
5-Methoxy-4-methyl-2-(pyridin-2-yl)phenyl 4-methylbenzoate (3c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 2.43 (s, 3H), 3.87 (s, 3H), 6.74 (s, 1H), 7.08–7.12 (m, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.51–7.58 (m, 2H), 7.61 (s, 1H), 8.00 (d, 2H, *J* = 8.0 Hz), 8.58 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 16.0, 21.9, 55.8, 105.4, 121.7, 123.7, 125.0, 125.1 127.0, 129.4, 130.5, 132.3, 136.2, 144.5, 147.3, 149.7, 155.7, 158.8, 165.6; IR (KBr): 3442, 2924, 1735, 1614, 1507, 1464, 1263, 1143, 1069, 968, 835, 747, 667, 571 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{19}NO_3$ $[M+H]^+$ 334.1438; found 334.1430.



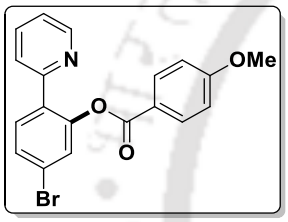
5-Methoxy-4-methyl-2-(pyridin-2-yl)phenyl 4-methoxybenzoate (3d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.73 (s, 1H), 6.94 (d, 2H, *J* = 9.2 Hz), 7.10 (t, 1H, *J* = 5.6 Hz), 7.50–7.60 (m, 3H), 8.06 (d, 2H, *J* = 9.2 Hz), 8.59 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.8, 55.5, 55.6, 105.2, 113.8, 121.5, 121.8, 123.5, 124.7, 124.8, 132.1, 132.3, 136.0, 147.1, 149.5, 155.5, 158.5, 163.8, 165.0; IR (KBr): 3402, 2922, 1730, 1606, 1511, 1464, 1256, 1167, 1069, 965, 895, 781, 610, 574 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{19}NO_4$ $[M+H]^+$ 350.1387; found 350.1356



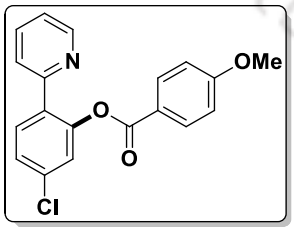
5-Bromo-2-(pyridin-2-yl)phenyl benzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14–7.17 (m, 1H), 7.43–7.48 (m, 3H), 7.51–7.53 (m, 2H), 7.57–7.63 (m, 2H), 7.66 (d, 1H, *J* = 8.8 Hz), 8.03–8.06 (m, 2H), 8.56–8.57 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.6, 122.9, 123.8, 126.9, 128.8, 129.2, 129.8, 130.4, 132.2, 132.6, 133.9, 136.5, 148.9, 149.9, 154.8, 164.9; IR (KBr): 3512, 2918, 1740, 1643, 1595, 1461, 1254, 1195, 1056, 868, 706, 551 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}BrNO_2$ $[M+H]^+$ 354.0124; found 354.0132.



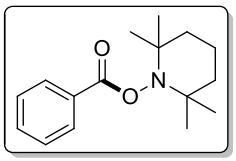
5-Bromo-2-(pyridin-2-yl)phenyl 4-methylbenzoate (4c): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 7.16–7.18 (m, 1H), 7.26 (d, 2H, J = 7.8 Hz), 7.490–7.493 (m, 1H), 7.52–7.54 (m, 2H), 7.59–7.63 (m, 1H), 7.69 (d, 1H, J = 8.4 Hz), 7.95 (d, 2H, J = 7.8 Hz), 8.60 (d, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 122.6, 122.8, 123.8, 126.4, 126.9, 129.5, 129.7, 130.5, 132.2, 132.6, 136.5, 144.8, 148.9, 149.9, 154.8, 165.0; IR (KBr): 3438, 2917, 1738, 1612, 1595, 1462, 1259, 1176, 1061, 987, 830, 744, 668, 545 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO_2$ $[M+H]^+$ 368.0281; found 368.0274.



5-Bromo-2-(pyridin-2-yl)phenyl 4-methoxybenzoate (4d): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.87 (s, 3H), 6.92–6.94 (m, 2H), 7.16–7.18 (m, 1H), 7.486–7.489 (m, 1H), 7.51–7.54 (m, 2H), 7.59–7.63 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz), 8.01–8.03 (m, 2H), 8.60 (d, 1H, J = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 114.1, 121.4, 122.6, 122.8, 123.8, 126.9, 129.7, 132.2, 132.5, 132.6, 136.4, 149.1, 149.9, 154.8, 164.2, 164.6; IR (KBr): 3422, 2926, 1734, 1605, 1511, 1462, 1254, 1166, 1058, 874, 781, 692, 583 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO_3$ $[M+H]^+$ 384.0230; found 384.0259.



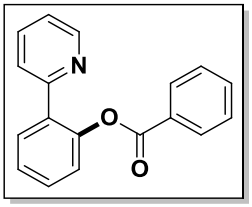
5-Chloro-2-(pyridin-2-yl)phenyl 4-methoxybenzoate (5d): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.87 (s, 3H), 6.94 (d, 2H, J = 8.8 Hz), 7.16–7.19 (m, 1H), 7.34–7.38 (m, 2H), 7.53 (d, 1H, J = 7.6 Hz), 7.62 (t, 1H, J = 7.2 Hz), 7.75 (d, 1H, J = 8.4 Hz), 8.02 (d, 2H, J = 8.8 Hz), 8.61 (d, 1H, J = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.7, 114.1, 121.5, 122.6, 123.9, 124.1, 126.8, 131.9, 132.2, 132.6, 135.1, 136.4, 149.0, 149.9, 154.8, 164.2, 164.6; IR (KBr): 3442, 2924, 1733, 1604, 1461, 1253, 1166, 1059, 844, 762, 646, 587 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}ClNO_3$ $[M+H]^+$ 340.0735; found 340.0748.

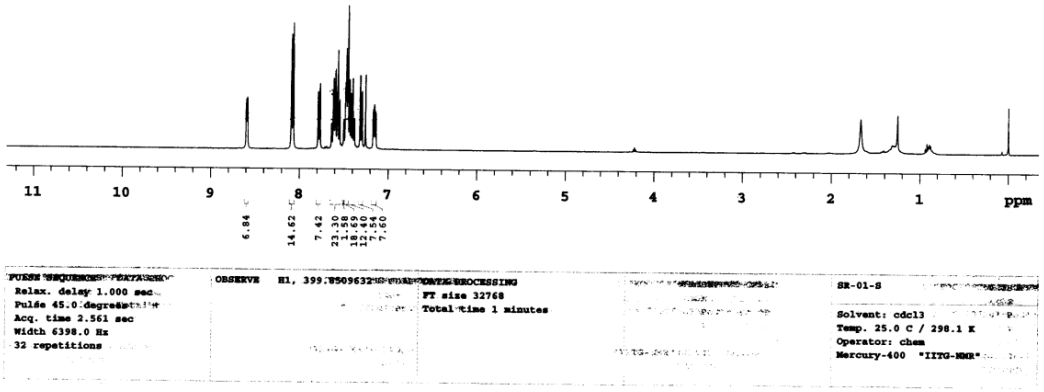


2,2,6,6-Tetramethylpiperidin-1-yl benzoate (F): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.12 (s, 6H), 1.26 (s, 6H), 1.42–1.45 (m, 1H), 1.55–1.58 (m, 2H), 1.66–1.78 (m, 3H), 7.43 (t, 2H, J = 7.8 Hz), 7.54 (t, 1H, J = 7.8 Hz), 8.03–8.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.2, 21.0, 32.1,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

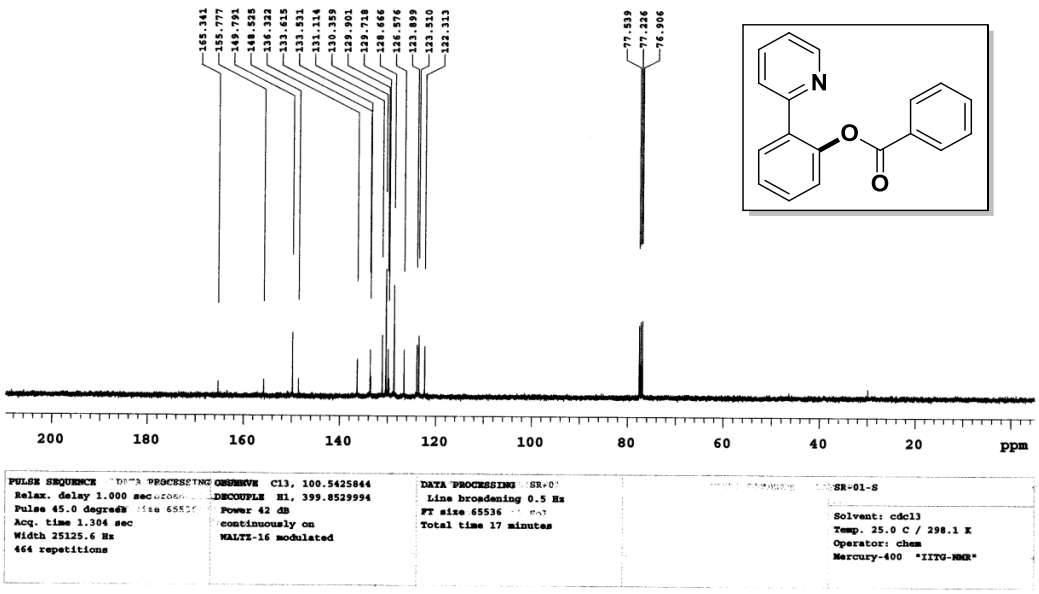
II.7. Spectra

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

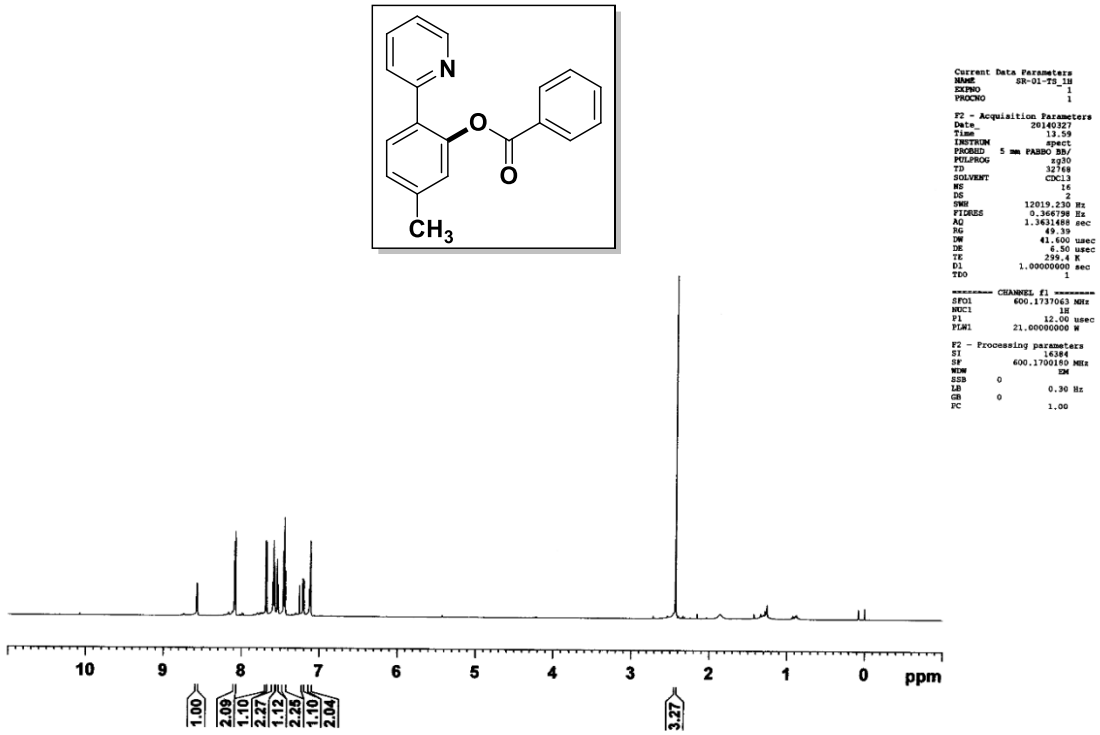




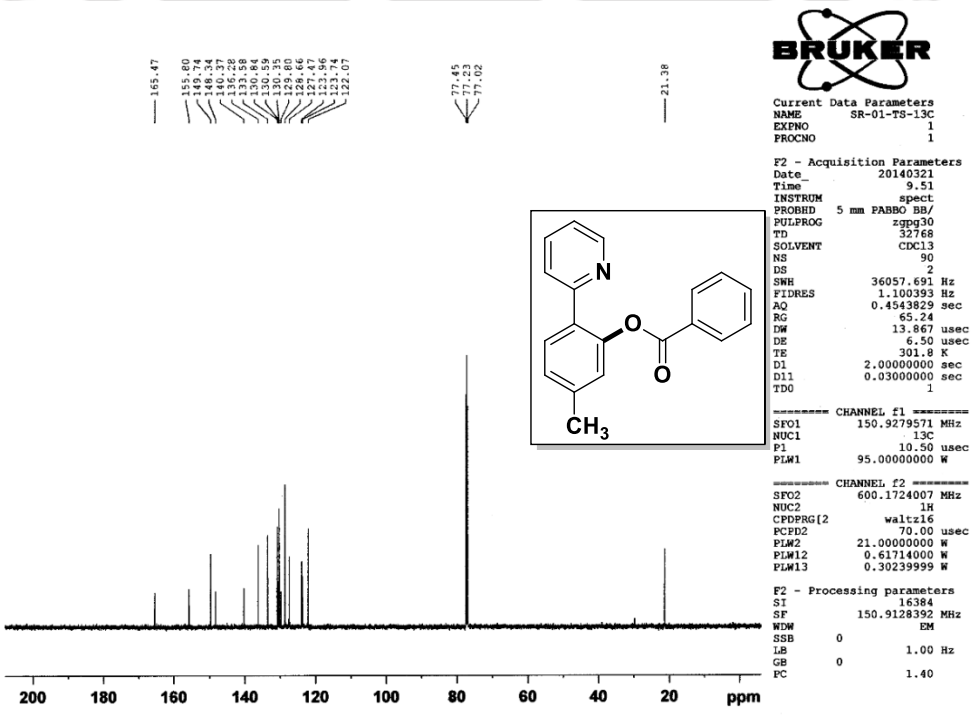
2-(Pyridin-2-yl)phenyl benzoate (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



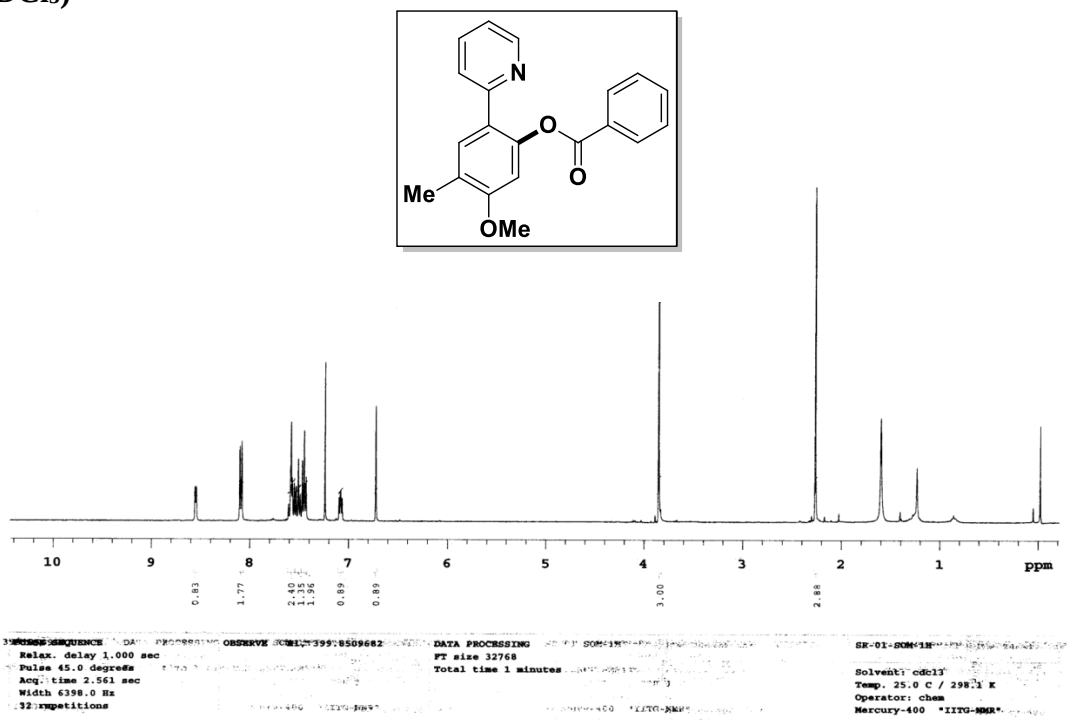
5-Methyl-2-(pyridin-2-yl)phenyl benzoate (2a): ^{1}H NMR (600 MHz, $CDCl_3$)



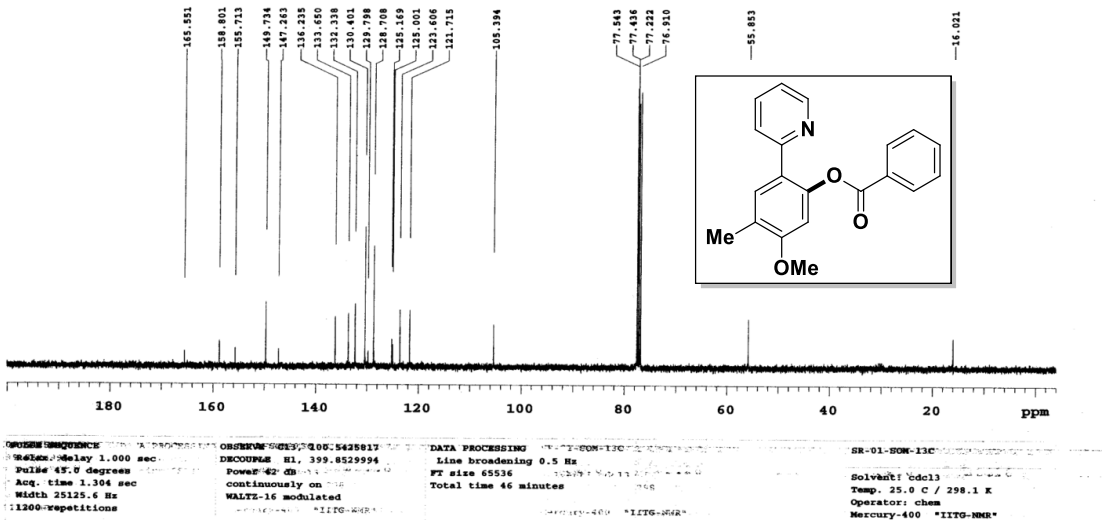
5-Methyl-2-(pyridin-2-yl)phenyl benzoate (2a): ^{13}C NMR (150 MHz, $CDCl_3$)



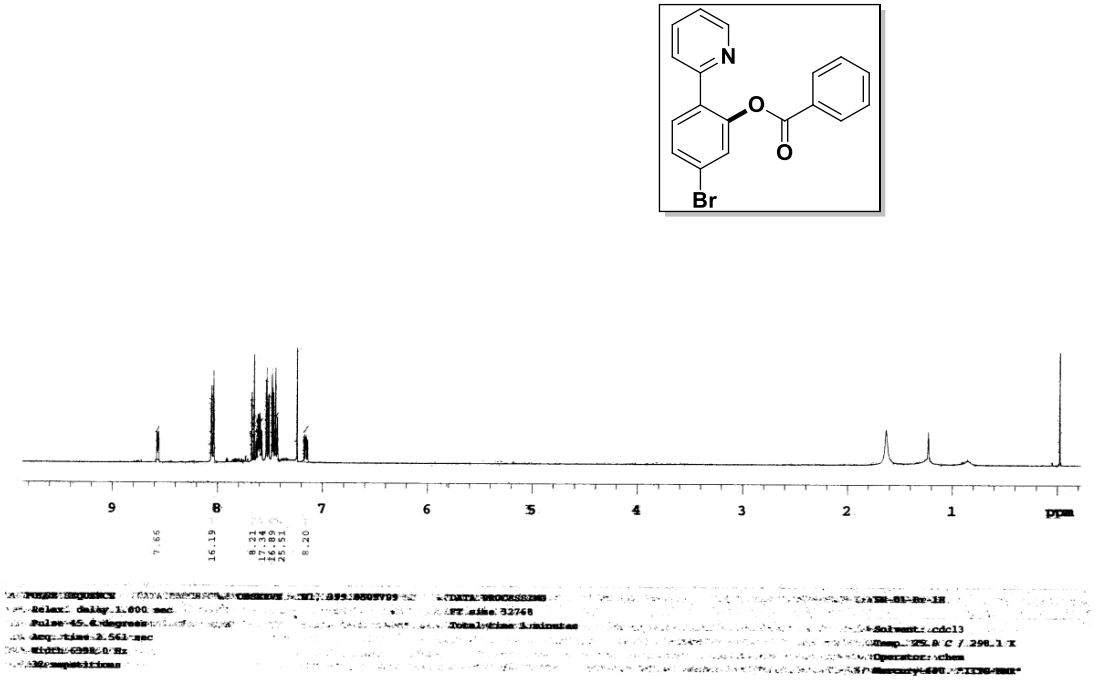
5-Methoxy-4-methyl-2-(pyridin-2-yl)phenyl benzoate (3a): ^{1}HNMR (400 MHz, $CDCl_3$)



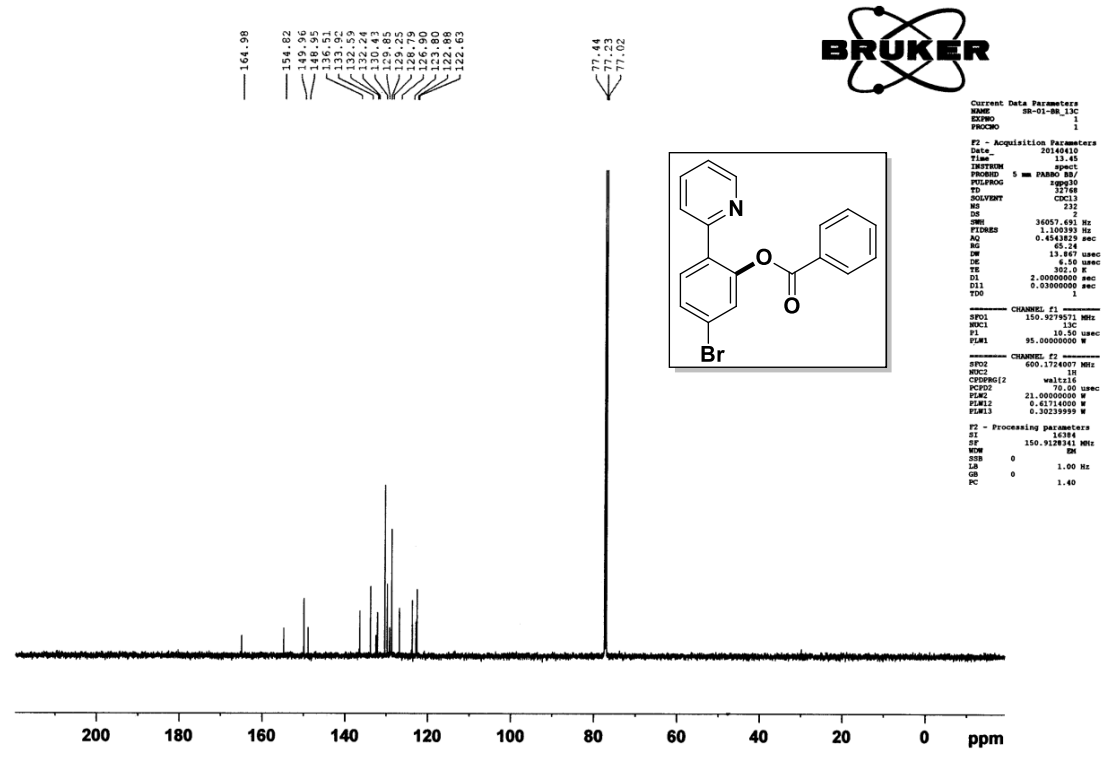
5-Methoxy-4-methyl-2-(pyridin-2-yl)phenyl benzoate (3a): ^{13}C NMR (100 MHz, $CDCl_3$)



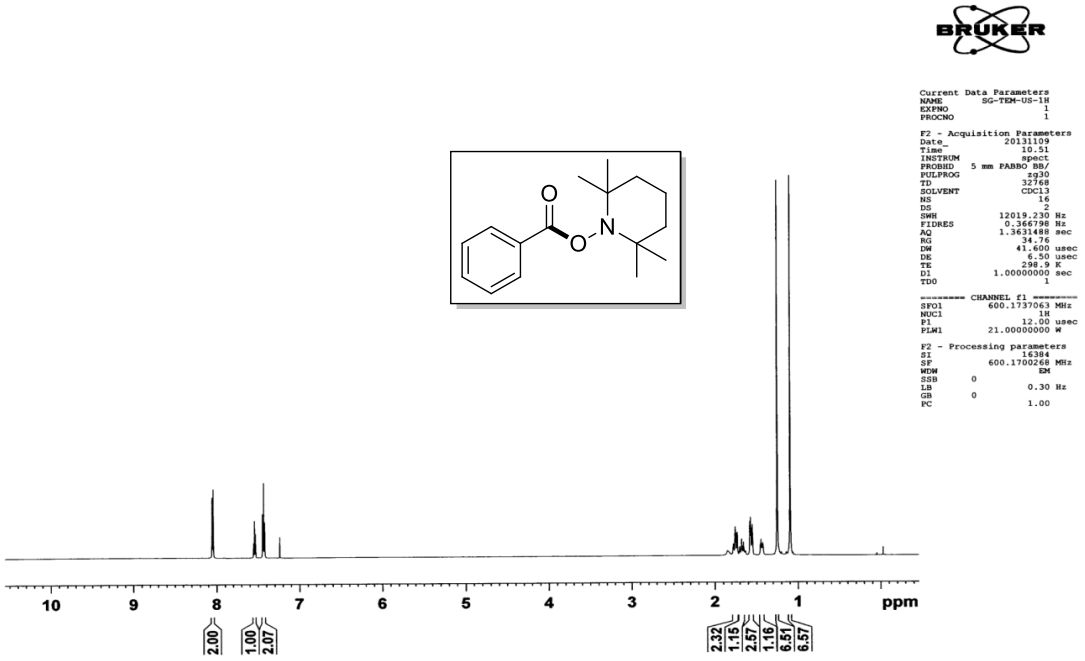
5-Bromo-2-(pyridin-2-yl)phenyl benzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$)



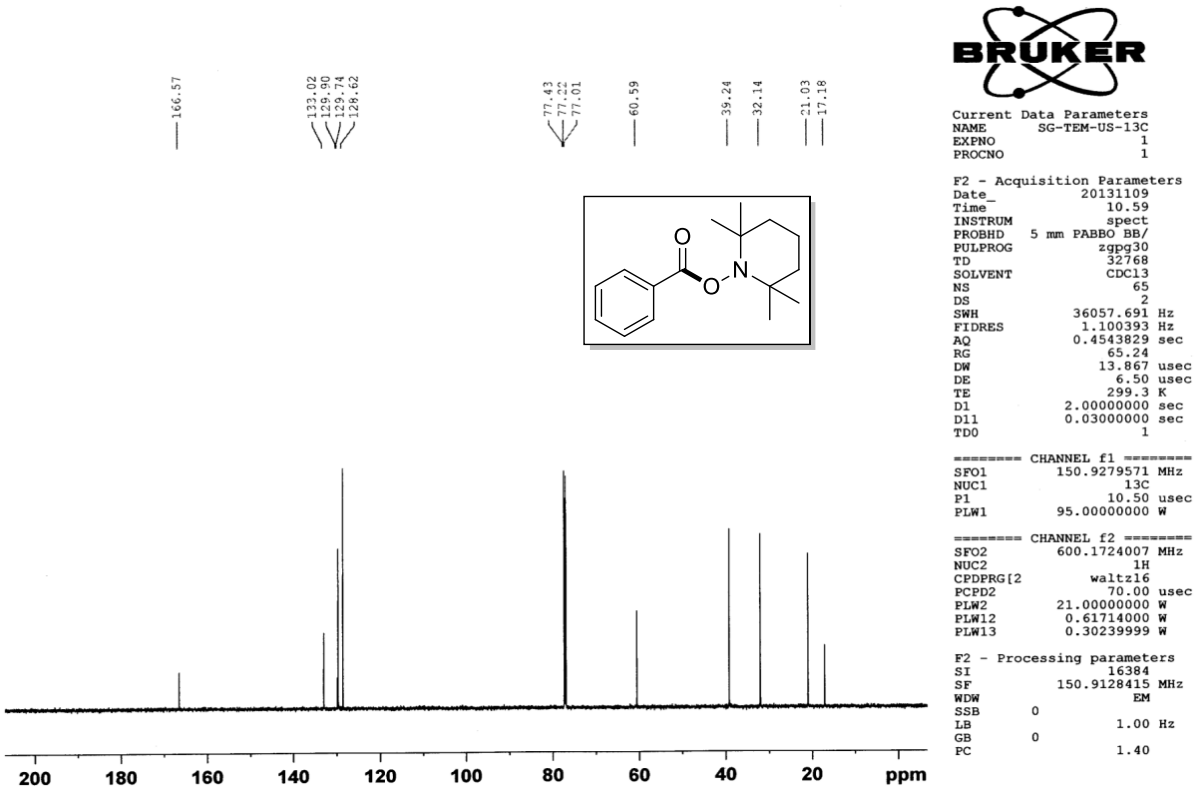
5-Bromo-2-(pyridin-2-yl)phenyl benzoate (4a): ^{13}C NMR (150 MHz, $CDCl_3$)



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

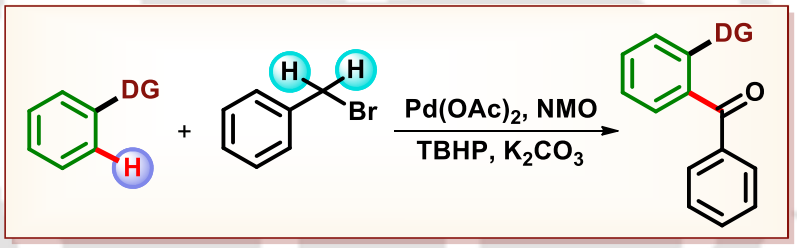


2,2,6,6-Tetramethylpiperidin-1-yl benzoate (F): ^{13}C NMR (150 MHz, $CDCl_3$)



CHAPTER III

Benzyl Bromides as Aroyl Surrogates in Substrate Directed Pd-Catalysed *o*-Aroylation



Abstract: ***An oxidative cross-coupling between directing substrates and benzyl bromides via the combined effect of oxidants TBHP and NMO, catalysed by Pd(II) has been investigated. Benzyl bromides served as efficient aroyl surrogates in this substrate directed C−H functionalisation. The in situ generated benzaldehyde originating from benzyl bromide is the active aroylating source.***

RSC Adv., 2015, 5, 33334

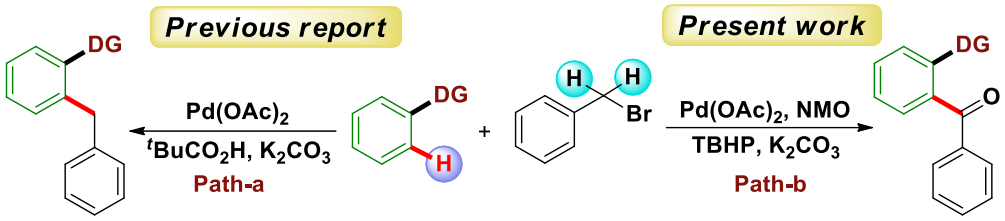
CHAPTER III

Benzyl Bromides as Aroyl Surrogates in Substrate Directed Pd-Catalysed *o*-Aroylation

III.1. Introduction

In past few decades, an extensive exploration of transition metal catalysed regioselective C–H functionalisation has been investigated to transform simple precursors into products of significant importance, particularly for the synthesis of complex molecules and natural products.[1,2] Most of these C–H bond functionalisation reactions rely on the strategies like directing group assisted C–H bond activation and cross dehydrogenative coupling. In particular, the Pd-catalysed reactions have been intended for the C–C bond forming processes involving sp, sp^2 or sp^3 hybridised C–H's as a mutual or a cross-coupling partners.[2d,g,3] Among these C–C bond forming reactions, the process of aroylation *via* directing group assisted cross-dehydrogenative coupling (CDC) strategy of converting sp^2 C–H bonds of aryl moiety into C–C bonds are challenging.[4]

The acylation of 2-phenylpyridines *via* *ortho*-C–H bond activation has been previously reported using aldehydes, α-oxocarboxylic acids, alcohols, α-diketones, toluenes, benzylamines and alkenes / alkynes as the aroyl surrogates. In search of an alternative aroyl source, we envisaged that benzyl bromides which under an oxidative condition can be converted into benzaldehyde may serve as the aroylating source. Keeping this in mind, an initial trial reaction was performed between 2-phenylpyridine and benzyl bromide in the presence of $Pd(OAc)_2$ and oxidant TBHP. The reaction led to the exclusive formation of an *ortho*-aroylated product as expected (path-b, Scheme III.1.1). Previously, in an auxillary assisted Pd catalysed C–C bond forming reaction, benzyl bromide served as the benzylating agent for the sp^2 and sp^3 C–H bonds (path-a, Scheme III.1.1).[5] Herein the first report on the use of benzyl bromides as aroylating agent in Pd-catalysed substrate directed process has been illustrated.



Scheme III.1.1. *Differential reactivities of benzyl bromides towards directing substrates.*

III.2. Strategies for *ortho*-aroylation

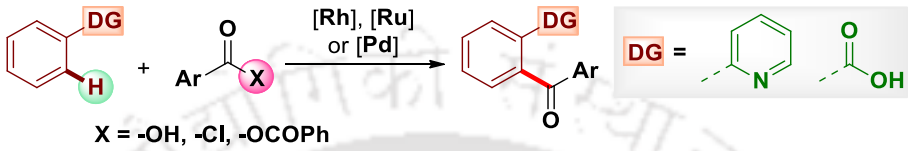
Diaryl ketones are important structural motifs in the pharmaceutical, fragrance, dye, and agrochemical industries.[6] Among numerous methodologies for diaryl ketone synthesis, Friedel-Crafts acylation is the most acceptable classical method for the synthesis of ketones.[7] The use of stoichiometric amount of corrosive Lewis acid, poor functional group compatibility and poor regioselectivity limits the reaction scope. The process involving oxidation of secondary alcohols is also an important method for ketone synthesis.[8] Later, these methods are replaced by transition metal catalysed cross coupling reactions.[9]

Carboxylic acid derivatives such as nitriles, anhydrides, Weinerb amides or acid chlorides are used with alkali metals *viz*. lithium, magnesium and aluminium reagents for the synthesis of ketones.[10] The use of harsh reaction condition e.g. highly basic and nucleophilic or acidic conditions resulted a low compatibility of existing functional groups. To overcome these drawbacks, the cross coupling reactions involving C–H bond functionalisation have emerged as an efficient and powerful tool in the synthesis of diversified ketones. Various methods thus implemented for the synthesis of ketones *via* C–H bond functionalisation can be classified into four categories, *viz*. (i) *o*-selective Friedel-Crafts acylation employing carboxylic acids and its derivatives, (ii) *o*-aroylation *via* carbonylation strategies, (iii) the cross dehydrogenative coupling (CDC) with various aroyl (ArCO–) sources and (iv) decarboxylative coupling of α-oxocarboxylic acids. Some of the recent protocols on these catagories are enlisted below.

(i) *o*-Selective Friedel-Crafts acylation utilising carboxylic acids and its derivatives

Kakiuchi *et al*. reported an *o*-aroylation of 2-arylpyridines using benzoic acid chlorides as the active aroyl (ArCO–) surrogate in the presence of ruthenium as the

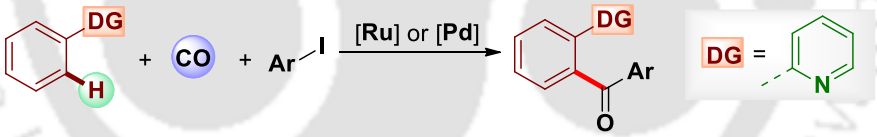
catalyst and air as the oxidant (Scheme III.2.1).[11a] Later, a Pd(II) catalysed *o*-aroylation of the same has been achieved by Fu and co-workers serving aryl carboxylic acids as the ArCO– source.[11b] In addition to this, Gooßen group has also developed a rhodium catalysed protocol for the synthesis of *o*-acylated aryl carboxylic acids utilising anhydrides as the coupling partner (Scheme III.2.1).[11c]



Scheme III.2.1. *o-Aroylation using aryl carboxylic acids and its derivatives as ArCO– source*

(ii) *o*-Aroylation *via* carbonylation strategy

In 2013, Beller *et al*. has developed a ruthenium catalysed carbonylative *o*-aroylation of 2-arylpyridines using aryl halides *via* a directed C–H bond activation (Scheme III.2.2).[12a] Lei and co-workers have also reported the Pd-catalysed double C–H functionalisation/carbonylation of diaryl ethers to form xanthones.[12b]



Scheme III.2.2. *o-Aroylation via carbonyl insertion*

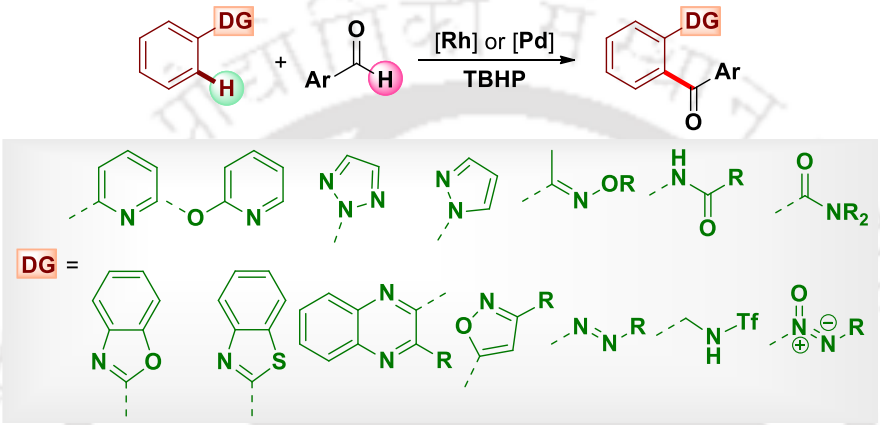
(iii) The cross dehydrogenative coupling (CDC) with various aroyl (ArCO–) sources

Recently, a number of CDC based strategies on *o*-selective acylation of various directing substrates have been achieved by several research groups. Some of these protocols employing various aroyl surrogates (ArCO–) have been described below.

(a) Aldehydes as the ArCO– source

The use of aldehydes as the aroyl group has been extensively studied with various substrates possessing *N* and *O* donor atoms (Scheme III.2.3). Cheng *et al*. reported the palladium catalysed *o*-aroylation of directing substrates such as 2-arylpyridines, 2-aryloxypyridines and *N*-phenyl pyrazoles using aldehydes as the aroyl source and aerial

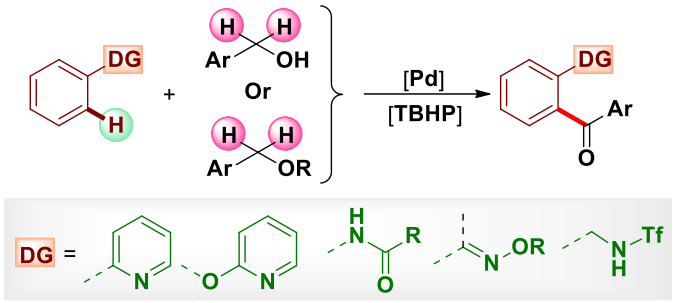
oxygen as the oxidant.[13a] Li and co-workers have documented that both aromatic and aliphatic aldehydes could be successfully applied as the aroyl source under the catalysis of Pd/TBHP in neat conditions.[13b] Aldehydes are also employed for the *o*-aroylation of various directing substrates such as ketoximes,[13c] acetanilides,[13d-g] benzamides [13h], 2-arylbenzothiazole and 2-arylbenzoxazole,[13i,j] 3,5-diarylisoxazole,[13k] azobenzenes,[13l] *N*-benzyltriflamides,[13m] azoxybenzenes [13n] and quinoxalines.[13o]



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

(b) Benzyl alcohols and benzylic ethers as ArCO− source

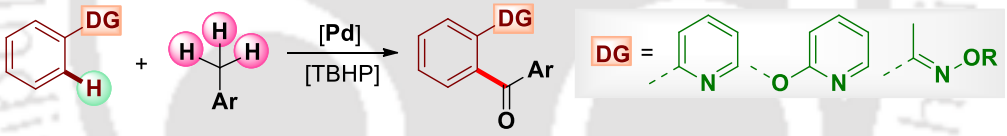
Li et al. has demonstrated an efficient strategy for the direct acylation of arene sp^2 C–H bonds with primary alcohols using Pd-catalyst and TBHP as the oxidant (Scheme III.2.4). In this protocol, the alcohols were oxidised to their corresponding aldehydes *in situ* which then coupled with 2-arylpyridines to give the *o*-aroylated products.[14a] A similar Pd/TBHP catalysed *o*-aroylation process has further developed by various research groups for several directing substrates such as acetanilides,[14b] phenoxy pyridines,[14c] *N*-benzyltriflamides,[14d] ketoximes and aldoximes[14e] using benzyl alcohol as the ArCO− source. Later, a palladium-catalysed oxidative coupling of arene C−H bonds with benzylic ethers has been described by Kim group. Here benzylic ether undergoes an oxidative C–O bond cleavage leading to the formation of new C–C bond with different directing arenes such as ketoximes, 2-arylpyridines and phenoxy pyridines.[14f]



Scheme III.2.4. *o-Aroylation using benzyl alcohol and ethers as the ArCO– source*

(c) Alkylbenzenes as the ArCO– source

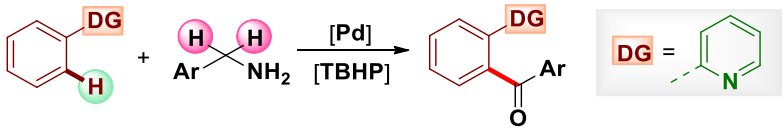
Our group has reported a Pd-catalysed cross dehydrogenative coupling strategy for the *o*-aroylation of directing arenes utilising alkylbenzenes as the synthetic equivalent of an aroyl moiety (Scheme III.2.5). The reaction proceeds *via* sequential C–C and C–O bond formations at the expense of four consecutive C–H bond cleavages to selectively install an aroyl functionality at the proximal site of substrates containing various directing groups.[15]



Scheme III.2.5. *o-Aroylation using alkylbenzenes as the ArCO- source*

(d) Arylmethylamines as the ArCO– source

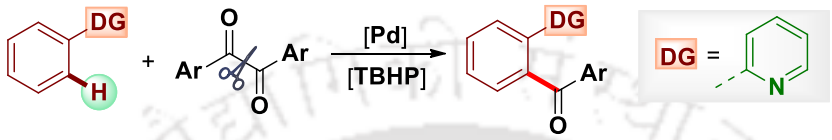
Wu and co-workers has demonstrated a palladium-catalysed *ortho*-acylation of 2-aryl pyridines serving arylmethylamines as the new, cheap and readily available acylation reagents (Scheme III.2.6). In this protocol, benzyl amine is oxidised to the imine which is hydrolysed to form benzaldehyde and finally act as an alternative aroyl source for this *o*-aroylation process.[16]



Scheme III.2.6. *o-Aroylation using arylmethylamines as the ArCO- source*

(e) Benzil as the ArCO– source

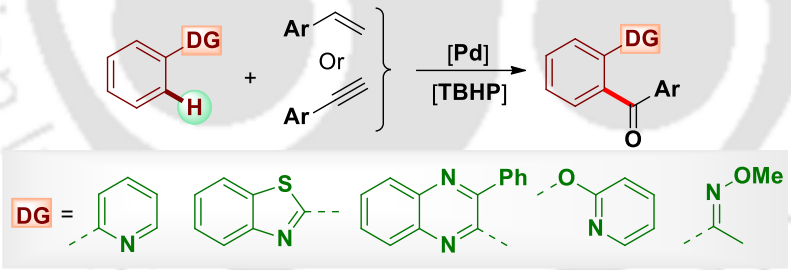
Wang *et. al*. reported a Pd/TBHP catalysed *o*-acylation of 2-arylpyridines with α-diketones *via* C–H bond activation (Scheme III.2.7). Here, α-diketone act as an efficient aroyl (ArCOO–) surrogate by undergoing a C–C bond cleavage in the presence of oxidant TBHP.[17]



Scheme III.2.7. *o-Aroylation using α-diketone as the ArCO– source*

(f) Aryl alkene and alkynes as the ArCO– source

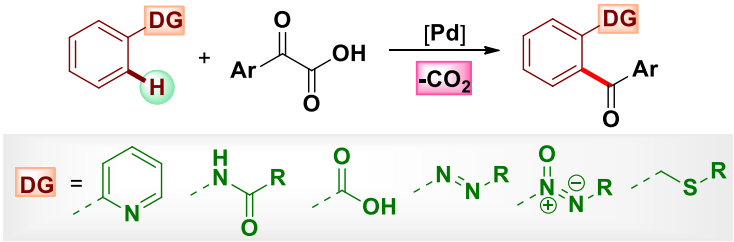
A substrate-directed Pd-catalysed *o*-aroylation strategy has been demonstrated by our group using terminal aryl alkenes and alkynes as new aroyl surrogates in the presence of TBHP (Scheme III.2.8). Here, a variety of directing arenes *viz*. 2-aryl pyridine, 2-arylbenzothiazole, 2,3-arylquinoxaline, aryloxy pyridine and ketoxime successfully underwent the *o*-arolation process with both styrenes and phenylacetylenes.[18]



Scheme III.2.8. *o-Aroylation using aryl alkenes and alkynes as the ArCO– source*

(iv) Decarboxylative coupling of α-oxocarboxylic acids

Ge group reported a Pd-catalysed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids (Scheme III.2.9).[19a] Later, the same group has also achieved a similar *ortho*-acylation from the coupling of different directing substrates such as 2-arylpyridine and aryl carboxylic acids with α-oxocarboxylic acids.[19b,c] Besides this, the decarboxylative *o*-aroylation of α-ketoacids were also employed for other directing groups such as azoxybenzenes,[19d] azobenzenes [19e] and thioethers.[19f]



Scheme III.2.9. *o-Aroylation via decarboxylative couling of α-ketoacids*

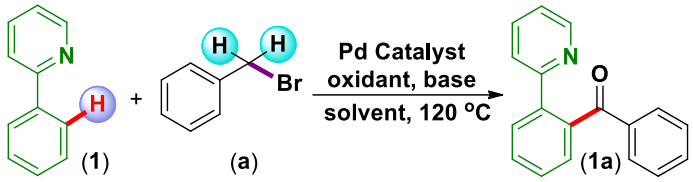
III.3. Present work

In the light of the aforementioned *o*-aroylation protocols, the present method on *o*-aroylation of directing substrates using benzyl bromide as the new aroyl surrogate under oxidative condition is unprecedented in literature.

Optimisation of reaction conditions: As has been mentioned earlier, an initial trial reaction was performed between 2-phenylpyridine (**1**) (0.5 mmol) and benzyl bromide (**a**) (1 mmol) in the presence of $Pd(OAc)_2$ (5 mol%) and oxidant TBHP (5–6 M in decane) (4 equiv.) in chlorobenzene (2 mL) at 120 ^oC. The reaction led to the formation of an *ortho*-aroylated product (**1a**, 37%) (Table III.3.1, entry 1). With the finding of benzyl bromide serving as a new aroyl surrogate, the effect of aroylating agent, catalysts, oxidants, additives and solvents was probed to obtain the best yield of the *o*-aroylated product. Increasing the quantity of benzyl bromide from 2 to 3 equiv., the yield of the product (**1a**) improved up to 48% (Table III.3.1, entry 2). The oxidant *N*-methyl morpholine *N*-oxide (NMO) is reported to be quite effective in converting benzyl halides to their corresponding aldehydes, which is presumed to be the active aroylating agent.[20] Taking cues from this report, when 1 equiv. of NMO was used in the reaction, the yield of the desired product improved to 55% (Table III.3.1, entry 3). A further improvement in the yield (66%) was observed when the quantity of NMO was increased to 2 equiv. (Table III.3.1, entry 4). Since the other oxidant NMO (2 equiv.) is also used along with the primary oxidant TBHP (4 equiv.), thus the reaction is expected to proceed with a lesser quantity of TBHP. With this in mind, keeping all other parameters as such, a reaction was performed with a combination of TBHP (2 equiv.) and NMO (2 equiv.). The reaction furnished a comparable yield of 62% for (**1a**) (Table III.3.1, entry 5). Interestingly, under a TBHP free condition, using NMO as the sole oxidant, formation of the desired product (**1a**) was not observed (Table III.3.1, entry 6) suggesting the essential

requirement of TBHP in bringing about the transformation. Next, various other salts of Pd such as $PdCl_2$ (56%), $PdBr_2$ (53%), $Pd(PPh_3)_2Cl_2$ (39%), $Pd(OCOCF_3)_2$ (43%) (Table III.3.1, entries 7–10), were examined to check their efficacy, from which $Pd(OAc)_2$ was found to be the superior (Table III.3.1, entry 5). A two-fold increase in the catalyst loading had no significant effect on the product yield (Table III.3.1, entry 11). The effects of different oxidants for this transformation were also screened as shown in Table III.3.1. All the primary oxidants such as 70% aq. TBHP (59%), DTBP (45%), $K_2S_2O_8$ (05%) and H_2O_2 (00%) were found to be inferior compared to the use of a decane solution of TBHP (Table III.3.1, entries 12–15). Among various solvents tested such as THF (00%), dioxane (30%), DMSO (27%), DMF (52%), DCE (49%) (Table III.3.1, entries 16–20), chlorobenzene (62%) was found to be the most appropriate (Table III.3.1, entry 5). The catalytic activity of Pd is often hampered in acidic medium. Since an equivalent amount of HBr is liberated in the medium during the conversion of benzyl bromide to active aroylating species, it was decided to perform the reaction in the presence of a mild base. The use of K_2CO_3 (79%) (Table III.3.1, entry 21) was found to be superior compared to other inorganic bases such as Cs_2CO_3 (71%), $NaHCO_3$ (73%) and Na_2CO_3 (56%). Finally, the optimum condition was the use of 2-phenyl pyridine (**1**) (0.5 mmol), benzyl bromides (**a**) (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (2 equiv.), *N*-methyl morpholine *N*-oxide (2 equiv.), K_2CO_3 (1.5 equiv.) in chlorobenzene (2 mL) at 120 ^oC (Table III.3.1, entry 21).

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



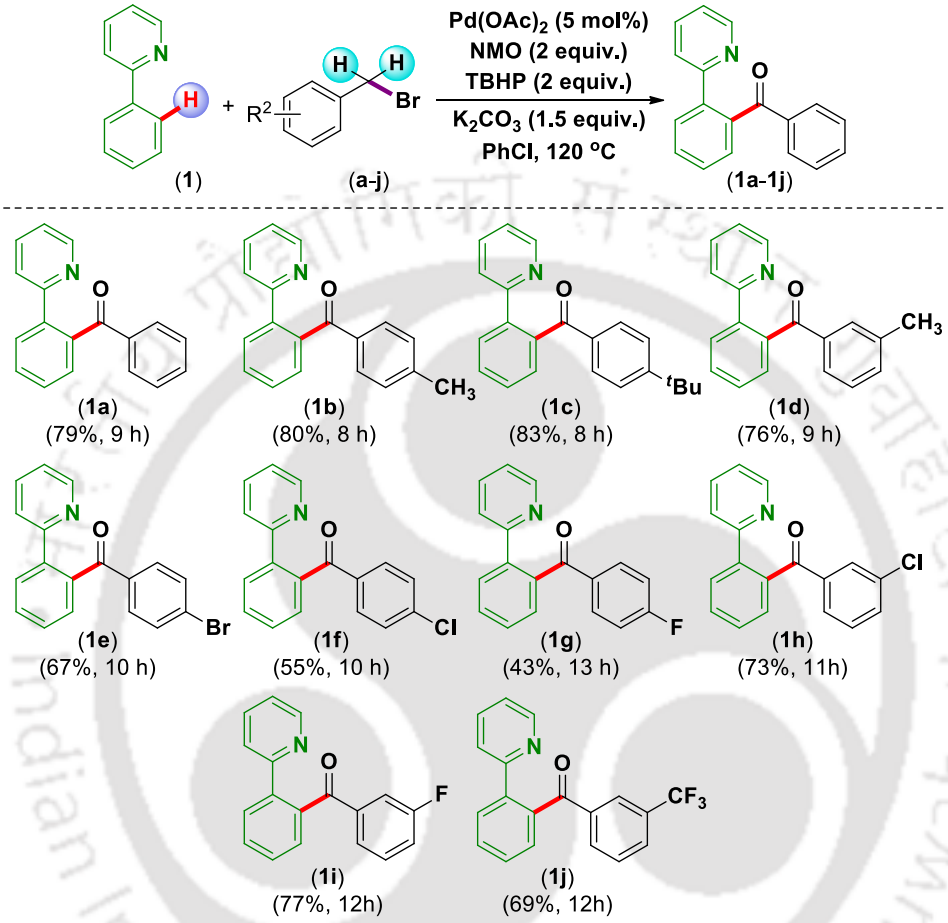
Entry	Catalyst (mol%)	Oxidant (equiv.)	Additive (equiv.)	Solvent	Yield (%)
1	$Pd(OAc)_2$ (5)	TBHP (4)	-	PhCl	37
2	$Pd(OAc)_2$ (5)	TBHP (4)	-	PhCl	48[c]
3	$Pd(OAc)_2$ (5)	TBHP (4)	NMO (1)	PhCl	55[c]
4	$Pd(OAc)_2$ (5)	TBHP (4)	NMO (2)	PhCl	66[c]
5	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	PhCl	62[c]
6	$Pd(OAc)_2$ (5)	-	NMO (2)	PhCl	00[c]
7	$PdCl_2$ (5)	TBHP (2)	NMO (2)	PhCl	56[c]
8	$PdBr_2$ (5)	TBHP (2)	NMO (2)	PhCl	53[c]
9	$Pd(PPh)_3Cl_2$ (5)	TBHP (2)	NMO (2)	PhCl	39[c]
10	$Pd(OCOCF_3)_2$ (5)	TBHP (2)	NMO (2)	PhCl	43[c]
11	$Pd(OAc)_2$ (10)	TBHP (2)	NMO (2)	PhCl	64[c]
12	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	PhCl	59[c,d]
13	$Pd(OAc)_2$ (5)	DTBP (2)	NMO (2)	PhCl	45[c]
14	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2)	NMO (2)	PhCl	05[c]
15	$Pd(OAc)_2$ (5)	H_2O_2 (2)	NMO (2)	PhCl	00[c]
16	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	THF	00[c]
17	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	Dioxane	30[c]
18	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DMSO	27[c]
19	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DMF	52[c]
20	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DCE	49[c]
21	**$Pd(OAc)_2$ (5)**	**TBHP (2)**	**NMO (2)**	**PhCl**	**79**[c,e]

[a]Reaction conditions: arenes (**1**) (0.5 mmol), solvent (2 mL) at 120 °C [b]Yields of isolated pure product. [c]1.5 mmol of benzyl bromide. [d]aq. TBHP. [e]K_2CO_3 (1.5 equiv.).

Substrate scopes for *o*-aroylation of 2-arylpyridines: The optimised conditions were then implemented for the *o*-aroylation of 2-phenyl pyridine (**1**) using various substituted benzyl bromides and the results are summarised in Scheme III.3.1. Benzyl bromides having electron-donating groups such as *p*-Me (**b**), *p*-^{t}Bu (**c**) and *m*-Me (**d**), when treated with 2-phenylpyridine (**1**) afforded corresponding *o*-aroylated products (**1b**–**1d)** in moderate to good yields. Benzyl bromides substituted with moderately electron-withdrawing groups such as *p*-Br (**e**), *p*-Cl (**f**) and *p*-F (**g**) served as less effective acylating agent giving their *o*-aroylated products (**1e**), (**1f**) and (**1g**) in 67%, 55% and 43% yields respectively which are slightly less compared to benzyl bromides possessing electron-donating substituents. However, the influence of electron-withdrawing

substituents such as –Cl (**h**), –F (**i**) and –CF_3 (**j**) when present at the *m*-position had no effect on the products (**1h**–**1j**) yield.

Scheme III.3.1. *Substrate scope for o-aroylation using various benzyl bromides*[a,b].



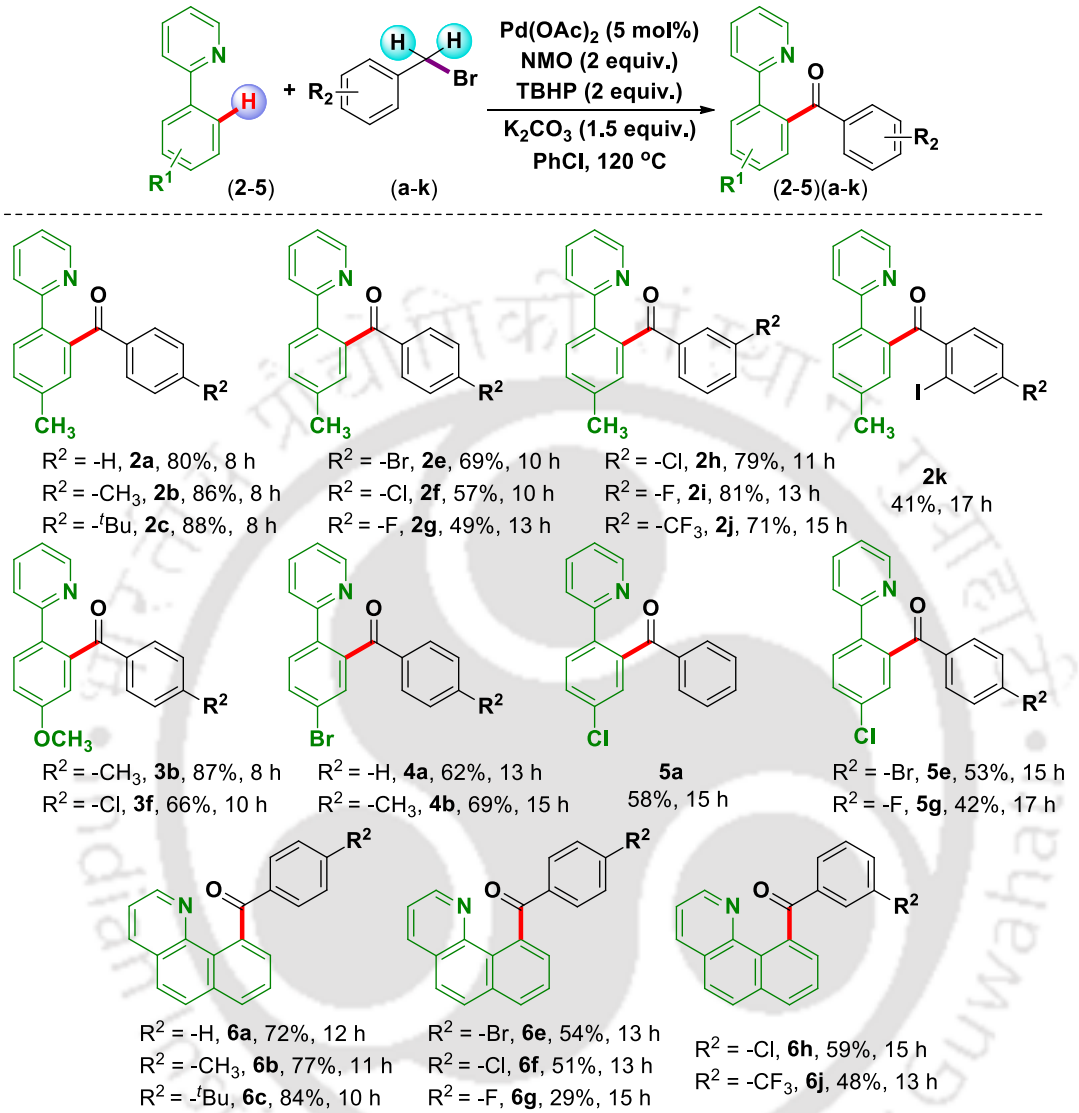
[a]Reaction conditions: **1** (0.5 mmol), **a–j** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (5–6 M in decane) (2 equiv.), NMO (2 equiv.), K_2CO_3 (1.5 equiv.) at 120 °C in chlorobenzene (2 mL), time 8–17 h. [b]Yield of isolated pure product reported

To further explore the scope of this protocol, *o*-aroylation of other 2-aryl pyridines (**2**–**5**) were carried out with a set of substituted benzyl bromides (**a**–**k**) (Scheme III.3.2). The reactivity of substituted benzyl bromides with 2-(*p*-tolyl)pyridine (**2**) were found to be similar to that of (**1**). A slight increase in the product yields (**2a–2c** and **2e**–**2j**) with 2-(*p*-tolyl)pyridine (**2**) could be attributed due to the better chelation of the metal catalyst with the electron rich *p*-tolyl ring in (**2**). 2-Iodo benzyl bromide (**k**) when treated with (**2**), a lower yield of 41% of (**2k**) was observed while its reaction with (**1**) is completely unproductive. The non-reactivity of 2-iodo benzyl bromide (**k**) with (**1**) could be due to the electronic and steric hindrance imparted by the bulky *o*-iodo substituent. However, the better chelation ability of (**2**) leads to the formation of product (**2k**) in 41% yield.

Similarly, 2-(4-methoxyphenyl)pyridine (**3**) when treated with benzyl bromides (**b**) and (**f**), provided the acylated products (**3b** and **3f**) in 87% and 66% yields respectively. 2-(4-Bromophenyl)pyridine (**4**), a moderately deactivated substrate when treated with benzyl bromides (**a** and **b**) provided corresponding *o*-aroylated products (**4a**) and (**4b**) in 62% and 69% yields respectively as shown in Scheme III.3.2. Furthermore, electron neutral (**a**) and electron deficient benzyl bromides (**e** and **g**) provided *o*-aroylated products (**5a**), (**5e**) and (**5g**) in moderate yields when reacted with 2-(4-chlorophenyl)pyridine (**5**). Lesser reactivity of directing arenes possessing electron-withdrawing groups –Br (**4**) and –Cl (**5**) as compared to electron neutral –H (**1**) and electron rich $–CH_3$ (**2**) and $–OCH_3$ (**3**) analogues may be due to their poor chelating ability with the metal catalyst.

Benzo[*h*]quinoline (**6**), a rigid directing system has similar structural frame to that of 2-phenyl pyridine (**1**) where the sp^2 C–H at C10 can be aroylated. When (**6**) was reacted with benzyl bromide (**a**), and those possessing electron-donating groups such as *p*-CH_3 (**b**), *p*-^{t}Bu (**c**) all provided their respective *o*-aroylated products (**6a**), (**6b**) and (**6c**) (Scheme III.3.2). Similarly, benzyl bromides having electron-withdrawing substituents such as –Br (**e**), –Cl (**f**) and –F (**g**) also resulted in their corresponding aroylated products (**6e**), (**6f**) and (**6g**) respectively, but in slightly lesser yields compared to their electron-donating counterparts. When moderately –Cl (**h**) or even strongly $–CF_3$ (**j**) electron-withdrawing substituents are present in the *meta* position of benzyl bromides, corresponding C10 aroylated products (**6h**) and (**6j**) were obtained in 59% and 48% yields respectively.

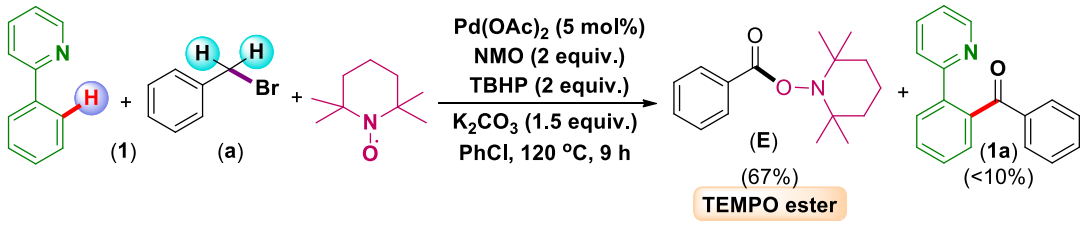
Scheme III.3.2. *Substrate scope for the o-aroylation*[a,b]



[a]Reaction conditions: **2–6** (0.5 mmol), **a–k** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (5–6 M in decane) (2 equiv.), NMO (2 equiv.), K_2CO_3 (1.5 equiv.) at 120 °C in chlorobenzene (2 mL), time 8–17 h. [b]Yield of isolated pure product

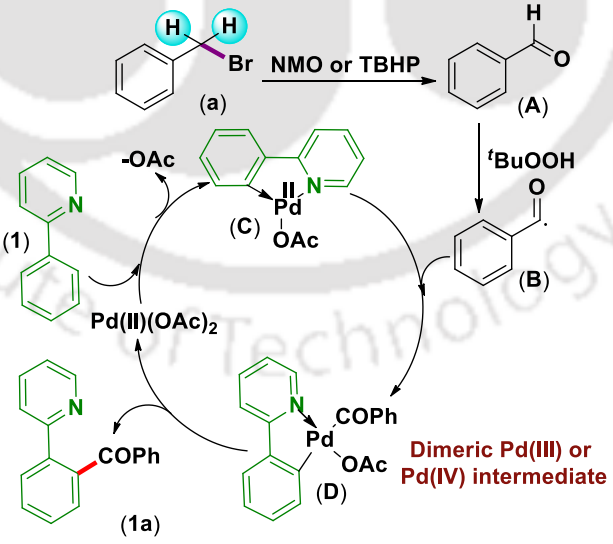
Mechanisic investigation

Reaction with TEMPO: To deduce the nature of this coupling, a reaction between (**1**) and (**a**) was performed in the presence of a radical quencher TEMPO under otherwise identical conditions. The formation of product (**1a**) (< 10%) and isolation of TEMPO ester (**E**) in 67% yield suggests a radical pathway (Scheme III.3.3).



Scheme III.3.3. *Trapping the intermediate with TEMPO*

Taking cues from these experimental results and related literature reports,[17,21] a plausible mechanism for this palladium catalysed carbo-acylation reaction of 2-phenyl pyridine (**1**) with benzyl bromide (**a**) *via* directed C–H bond activation is depicted in Scheme III.3.4. In the presence of oxidants NMO[20] and TBHP, benzyl bromide is first oxidised to benzaldehyde (**A**). The detection of benzaldehyde (**A**) in the crude reaction mixture suggests its intermediacy for this transformation. This *in situ* generated benzaldehyde (**A**) is then converted to benzoyl radical (**B**) with the aid of TBHP. Subsequent ligation of this radical species (**B**) with the chelated complex of Pd(II) (**C**) gives either a dimeric Pd(III) or Pd(IV) intermediate (**D**). Finally, C–C bond formation *via* reductive elimination of Pd formed complex (**D**) afforded the *o*-aroylated product (**1a**) and releasing Pd(II) catalyst in the medium to maintain the catalytic cycle.



Scheme III.3.4. *Proposed mechanism for the o-aroylation of 2-phenyl pyridine.*

In conclusion, this protocol demonstrates a convenient and efficient synthesis of aryl ketones *via* Pd-catalysed *ortho*-C–H activation of 2-phenyl pyridines and benzo[*h*]quinoline using commercially available benzyl bromides as unconventional

synthetic equivalents of aroyl group (ArCO–). All the benzyl bromides having activating or deactivating groups efficiently gave the desired carbo-acylated products with 2-aryl pyridines and benzo[*h*]quinoline.

III.4. Experimental section

III.4.1. General information: All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium 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 GF_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 MHz and 600 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Mass spectra were recorded using MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

III.4.2. General procedure for the synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): A mixture of 2-phenyl pyridine (77.5 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol%), benzyl bromide (256.5 mg, 1.5 mmol), *N*-methyl morpholine *N*-oxide (NMO) (351 mg, 3 mmol, 2 equiv. *w.r.t.* benzyl bromide), chlorobenzene (2 mL) were taken in an oven dried round bottom flask (10 mL). To this mixture, K_2CO_3 (103.5 mg, 0.75 mmol) and decane solution of TBHP (5−6 M) (600 µL, 3 mmol, 2equiv. *w.r.t.* benzyl bromide) were added. Then the flask was fitted with a condenser and heated for 9 h in a pre-heated oil bath maintained at 120 ^oC. During this period, the progress of the reaction was monitored by TLC at regular intervals. After completion of the reaction, it was cooled to room temperature and admixed with ethyl acetate (30 mL) and filtered. The ethyl acetate layer was washed successively with water (3 x 5 mL). The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with a mixture of hexane/ethyl acetate (9.3:0.7) to afford phenyl(2-pyridin-2-yl)phenyl methanone (**1a**) (102 mg, 79% yield).

III.4.3. Mechanistic investigation in the presence of radical scavenger TEMPO: An oven-dried reaction flask was charged with 2-phenylpyridine (**1**) (77.5 mg, 0.5 mmol) $Pd(OAc)_2$ (5.6 mg, 5 mol %), benzyl bromide (256.5 mg, 1.5 mmol), NMO (3 mmol, 351

mg), TEMPO (0.234 g, 1.5 mmol), chlorobenzene (2 mL), K_2CO_3 (0.75 mmol, 103.5 mg) and TBHP in decane (5–6 M) (600 µL, 3 mmol). The flask was fitted to a condenser and the resultant reaction mixture was stirred in a preheated oil bath maintained at 120 ^oC. The reaction after a period of 9 h afforded the benzoyl-TEMPO adduct 2,2,6,6-tetramethylpiperidin-1-yl benzoate (**E**) (67% yield) and the desired product (<10%) was observed.

III.5. References

(1) (a) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*; Wiley–VCH: Weinheim, 2005; (b) J.-Q. Yu, Z.-J. Shi, C–H *Activation;* Springer: Berlin, Germany, 2010; (c) *Activation and Functionalisation of C–H Bond*, ed. K. I. Goldberg and A. S. Goldman, ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004; (d) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res*. 2008, **41**, 1013; (e) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun*., 2010, **46**, 677; (f) A. Gunay and K. H. Theopold, *Chem. Rev*., 2010, **110**, 1060; (g) T. W. Lyons and M. S. Sanford, *Chem. Rev*., 2010, **110**, 1147; (h) C.-L. Sun, B.-J. Li and Z.-J Shi, *Chem. Rev*., 2011, **111**, 1293; (i) L. Ackermann, *Chem. Rev*., 2011, **111**, 1315; (j) N. Chatani, *Directed Metallation*, Springer, Berlin, Germany, 2008; (k) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res*., 2009, **42**, 1074; (l) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624.

(2) (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev*., 2007, **107**, 174; (b) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; (c) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654; (d) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (e) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; (f) W. Shi, C. Liu and A. Lei, *Chem. Soc. Rev.*, 2011, **40**, 2761; (g) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780.

(3) (a) W. J. Yoo and C.-J. Li, *Top. Curr. Chem*., 2010, **292**, 281; (b) B. J. Lie and Z. J. Shi, *Chem. Soc. Rev*., 2012, **41**, 5588.

(4) (a) C.-J. Li, *Acc. Chem. Res*., 2009, **42**, 335; (b) J. A. Ashenhurst, *Chem. Soc. Rev*., 2010, **39**, 540; (c) C. J. Scheuermann, *Chem. Asian J*., 2010, **5**, 436; (d) Y. Wu, J.

Wang, F. Mao and F. Y. Kwong, *Chem. Asian J*., 2014, **9**, 26; (e) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem. Int. Ed*., 2014, **53**, 74.

(5) (a) E. T. Nadres, G. I. F. Santos, D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2013, **78**, 9689.

(6) H. Surburg and J. Panten, *Common Fragrance and Flavor Materials*, 5th ed.; Wiley-VCH, Weinheim, Germany, 2006.

(7) (a) G. A. Olah, *Friedel-crafts Chemistry*, Wiley, New York, 1973; (b) G. Sartori and R. Maggi, *Advances in Friedel–Crafts Acylation Reactions*; CRC Press, Boca Raton, FL, 2010.

(8) (a) M. Hudlicky, *Oxidation in organic Chemistry*; American Chemical Society: Washington Dc, 1990; (b) G. Tojo, M. Fernandez, *in Oxidation of Alcohols to aldehyde and Ketones: A guide to Current Common Practice*; G. Tojo, Ed.; Springer: New York, 2006.

(9) (a) G. W. Kabalka, R. R. Malladi, D. Tejedor and S. Kelley, *Tetrahedron Lett.*, 2000, **41**, 999; (b) J. Lindh, P. J. R. Sjberg and M. Larhed, *Angew. Chem. Int. Ed*., 2010, **49**, 7733; (c) L. J. Gooßen, F. Rudolphi, C. Oppel and N. Rodriguez, *Angew. Chem. Int. Ed*., 2008, **47**, 3043.

(10) (a) R. C. Larock, *Comprehensive Organic Transformations*; VCH: New York, 1989, 685; (b) J. March, *advanced Organic Chemistry*, 3rg ed.; wiley: New York, 1985, 433 and 824.

(11) (a) T. Kochi, A. Tazawa, K. Honda, and F. Kakiuchi, *Chem. Lett.*, 2011, **40**, 1018; (b) J. Lu, H. Zhang, X. Chen, H. Liu, Y. Jiang and H. Fua, *Adv. Synth. Catal*., 2013, **355**, 529; (c) P. Mamone, G. Danoun and L. J. Gooßen, *Angew. Chem*., 2013, **125**, 6836.

(12) (a) A. Tlili, J. Schranck, J. Pospech, H. Neumann and M. Beller, *Angew. Chem. Int. Ed*., 2013, **52**, 1; (b) H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang and A. Lei, *Angew. Chem. Int. Ed*., 2012, **51**, 1.

(13) (a) X. Jia, S. Zhang, W. Wang, F. Luo, and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (b) O. Basle, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal*., 2010, **352**, 1145; (c) C.-W. Chan, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett*., 2010, **12**, 3926; (d) Y. Wu, B. Li, F. Mao, X. Li and F. Y. Kwong, *Org. Lett*., 2011, **13**, 3258; (e) C. Li, L. Wang, P. Li and W. Zhou, *Chem. Eur. J*., 2011, **17**, 10208; (f) F. Szabo, D. Simko

and Z. Novak, *RSC Adv*., 2014, **4**, 3883; (g) F. Szabo, J. Daru, D. Simko, T. Z. Nagy, A. Stirling and Z. Novak, *Adv. Synth. Catal*., 2013, **355**, 685; (h) J. Park, E. Park, A. Kim, Y. Lee, K.-W. Chi, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Lett*., 2011, **13**, 4390; (i) J. Zhao, H. Fang, C. Xie, J. Han, G. Li and Y. Pan, *Asian J. Org. Chem*., 2013, **2**, 1044; (j) A. Banerjee, S. K. Santra, S. Guin, S. K. Rout and B. K. Patel, *Eur. J. Org. Chem.*, 2013, 1367. (k) A. Banerjee, A. Bera, S. K. Santra, S. Guin and B. K. Patel, *RSC Adv*., 2014, **4**, 8558; (l) H. Li, P. Li and L. Wang, *Org. Lett*., 2013, **15**, 620; (m) S. Sharma, J. Park, E. Park, A. Kim, M. Kim, J. H. Kwak, Y. Hoon Jung and I. S. Kim, *Adv. Synth. Catal*., 2013, **355**, 332. (n) M. Sun, L.-K. Hou, X.-X. Chen, X.-J. Yang, W. Sun and Y.-S. Zang, *Adv. Synth. Catal*., 2014, **356**, 3789; (o) S. K. Santra, A. Banerjee and B. K. Patel *Tetrahedron* 2014, **70**, 2422.

(14) (a) F. Xiao, Q. Shuai, F. Zhao, O. Basle, G. Deng and C.-J. Li, *Org. Lett*., 2011, **13**, 1614; (b) Y. Yuan, D. Chen and X. Wang, *Adv. Synth. Catal*., 2011, **353**, 3373; (c) M. Kim, S. Sharma, J. Park, M. Kim, Y. Choi, Y. Jeon, J. H. Kwak and I. S. Kim, *Tetrahedron*, 2013, **69** 6552; (d) J. Park, A. Kim, S. Sharma, M. Kim, E. Park, Y. Jeon, Y. Lee, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Biomol. Chem*., 2013, **11**, 2766; (e) S. Sharma, M. Kim, J. Park, M. Kim, J. H. Kwak, Y. H. Jung, J. S. Oh, Y. Lee and I. S. Kim, *Eur. J. Org. Chem*., 2013, 6656; (f) S. Han, S. Sharma, J. Park, M. Kim, Y. Shin, N. K. Mishra, J. J. Bae, J. H. Kwak, Y. H. Jung and I. S. Kim, *J. Org. Chem*., 2014, **79**, 275.

(15) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett*., 2012, **14**, 5294.

(16) Q. Zhang, F. Yang and Y. Wu, *Chem. Commun*., 2013, **49**, 6837.

(17) W. Zhou, H. Li and L. Wang, Org. Lett., 2012, **14**, 4594.

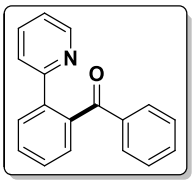
(18) N. Khatun, A. Banerjee, S. K. Santra, A. Behera and B. K. Patel, RSC Adv., 2014, **4**, 54532.

(19) (a) P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc*., 2010, ***132***, 11898; (b) M. Li and H. Ge, *Org. Lett*., 2010, **12**, 3464; (c) J. Miao and H. Ge, *Org. Lett*., 2013, **15**, 2930; (d) H. Li, P. Li, Q. Zhaoa and L. Wang, *Chem. Commun*., 2013, **49**, 9170; (e) H. Li, P. Li, H. Tan and L. Wang, *Chem. Eur. J*., 2013, **19**, 14432; (f) B. Xu, W. Liu and C. Kuang, *Eur. J. Org. Chem*., 2014, 2576.

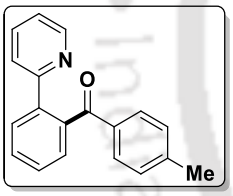
(20) T. Masayuki, K. Moriyama and H. Togo, *Eur. J. Org. Chem.*, 2014, 3402.

(21) S. K. Santra, A. Banerjee, N. Khatun, A. Samanta and B. K. Patel, *RSC Adv.*, 2015, **5**, 11960.

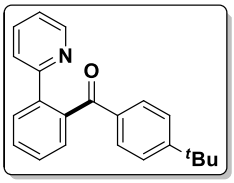
III.6. Spectral Data



Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.99–7.03 (m, 1H), 7.26 (t, 2H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 7.6 Hz), 7.52–7.56 (m, 3H), 7.58–7.63 (m, 1H), 7.68 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 1H, *J* = 7.6 Hz), 8.36 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.1, 122.9, 128.2, 128.7, 128.9, 129.3, 129.7, 130.4, 132.5, 136.5, 138.1, 139.7, 139.9, 149.3, 157.0, 198.5; IR (KBr): 2922, 1665, 1587, 1448, 1313, 1281, 1116, 928, 745, 713, 698, 643 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{13}NO$ $[M+H]^+$ 260.1070; found 260.1079.

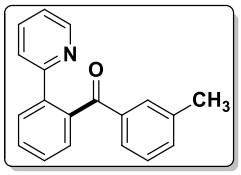


(2-(Pyridin-2-yl)phenyl)(*p*-tolyl)methanone (1b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H), 7.01–7.04 (m, 1H), 7.07 (d, 2H, *J* = 8.4 Hz), 7.47–7.48 (m, 1H), 7.51 (d, 2H, *J* = 7.8 Hz), 7.54–7.58 (m, 1H), 7.58–7.61 (m, 3H), 7.76 (d, 1H, *J* = 7.8 Hz), 8.39 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 122.1, 122.9, 128.5, 128.9, 129.0, 129.1, 129.9, 130.2, 135.4, 136.4, 139.7, 139.9, 143.3, 149.2, 157.1, 198.1; IR (KBr): 2922, 2846, 1663, 1605, 1586, 1469, 1439, 1310, 1281, 1149, 1115, 1021, 921, 751, 687, 602 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO$ $[M+H]^+$ 274.1226; found 274.1231.

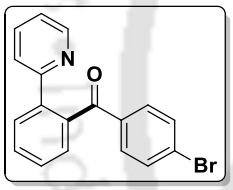


(4-(^{t}Butyl)phenyl)(2-(pyridin-2-yl)phenyl)methanone (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (s, 9H), 7.01–7.04 (m, 1H), 7.32 (d, 2H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 8.4 Hz), 7.50 (d, 2H, *J* = 6.8 Hz), 7.56–7.61 (m, 2H), 7.64 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 8.39–8.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.0, 35.0, 121.8, 122.9, 125.0, 128.3, 128.9, 129.0, 129.6, 130.0, 135.1, 136.2, 139.7, 139.8, 149.1, 156.0, 157.0, 197.9; IR (KBr): 2961, 2866, 1663, 1466, 1433, 1365, 1277, 1194, 1110, 1018, 930, 849, 752, 697, 666

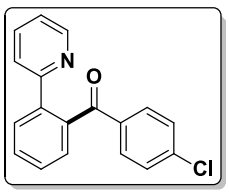
cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{21}NO$ $[M+H]^+$ 316.1696; found 316.1702.



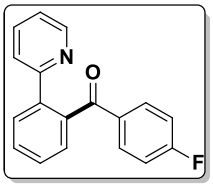
2-(pyridine-2-yl)phenyl(*m*-tolyl)methanone (1d): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 6.99–7.03 (m, 1H), 7.14 (t, 1H, *J* = 7.2 Hz), 7.19–7.24 (m, 1H), 7.45–7.48 (m, 2H), 7.50–7.54 (m, 3H), 7.55–7.58 (m, 1H,), 7.59–7.61 (m, 1H), 7.75 (d, 1H, *J* = 7.6 Hz), 8.36–8.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 122.1, 122.9, 127.1, 128.1, 128.6, 128.7, 129.0, 129.2, 130.1, 130.3, 133.4, 136.4, 137.9, 139.7, 139.9, 149.2, 157.1, 198.5; IR (KBr): 2922, 2859, 1736, 1665, 1587, 1434, 1287, 1206, 1127, 999, 957, 896, 643, 482.cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO$ $[M+H]^+$ 274.1226; found 274.1222.



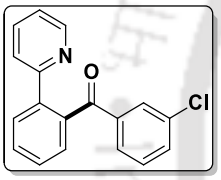
(4-Bromophenyl)(2-(pyridin-2-yl)phenyl)methanone (1e): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.05 (t, 1H, *J* = 6.0 Hz), 7.24 (d, 1H, *J*= 8.0 Hz), 7.40 (d, 2H, *J* = 8.4 Hz), 7.47–7.55 (m, 4H), 7.60 (d, 2H, *J* = 7.6 Hz), 7.77 (d, 1H, *J* = 7.6 Hz), 8.34 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.3, 122.6, 127.5, 128.7, 128.9, 129.2, 130.6, 131.5, 131.8, 136.7, 137.0, 139.2, 139.6, 149.2, 156.6, 197.3; IR (KBr): 2925, 1638, 1590, 1473, 1396, 1281,1068, 927, 748, 649 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}BrNO$ $[M+H]^+$ 338.0175; found 338.0193.



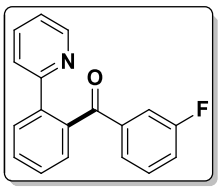
(4-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1f): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.03–7.05 (m, 1H), 7.22–7.24 (m, 2H), 7.51–7.53 (m, 3H), 7.58–7.62 (m, 4H), 7.77 (d, 1H, *J* = 7.8 Hz), 8.34 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.3, 122.6, 128.4, 128.5, 128.7, 128.8, 129.2, 130.5, 130.9, 136.6, 138.7, 139.2, 139.6, 149.1, 156.6, 197.2; IR (KBr): 2928, 2850, 1665, 1640, 1587, 1439, 1308, 1284, 1145, 1089, 929, 838, 793, 667, 528.cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}ClNO$ $[M+H]^+$ 294.0680; found 294.0672.



(4-Fluorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1g): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.91–6.94 (m, 2H), 7.02–7.05 (m, 1H), 7.50 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 2H, *J* = 4.8 Hz), 7.57–7.63 (m, 2H), 7.69–7.71 (m, 2H), 7.77 (d, 1H, *J* = 7.8 Hz), 8.36 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.3 (d, *J* = 22.5 Hz), 122.2, 122.8, 128.8, 128.9, 129.2, 130.5, 132.2 (d, *J* = 9.0 Hz), 134.6, 136.6, 139.4, 139.7, 149.3, 156.9, 166.2, 196.9; IR (KBr): 2928, 2850, 1665, 1640, 1587, 1439, 1308, 1284, 1145, 1089, 929, 838, 793, 667, 528.cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}ClNO$ $[M+H]^+$ 294.0680; found 294.0672.

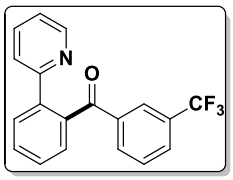


(3-Chlorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1h): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.02–7.04 (m, 1H), 7.19 (t, 1H, *J* = 7.8 Hz), 7.33–7.34 (m, 1H), 7.51–7.55 (m, 4H), 7.59–7.63 (m, 2H), 7.66–7.67 (m, 1H), 7.77 (d, 1H, *J* = 7.8 Hz), 8.33 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.3, 122.5, 127.6, 127.8, 128.8, 128.9, 129.3, 129.5, 130.7, 132.3, 134.4, 136.7, 139.1, 139.7, 139.9, 149.1, 156.5, 196.9; IR (KBr): 3063, 2360, 1669, 1577, 1468, 1289, 1253, 1155, 1082, 992, 894, 749, 634 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}ClNO$ $[M+H]^+$ 294.0680; found 294.0681.

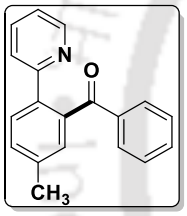


(3-Fluorophenyl)(2-(pyridin-2-yl)phenyl)methanone (1i): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.00–7.05 (m, 1H), 7.06–7.09 (m, 1H), 7.18–7.23 (m, 1H), 7.39–7.42 (m, 2H), 7.53–7.55 (m, 3H), 7.58–7.63 (m, 2H), 7.77 (d, 1H, *J* = 7.2 Hz), 8.32–8.34 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.6 (d, *J* = 22.5 Hz), 119.0 (d, *J* = 21.0 Hz), 125.0, 128.4, 128.6, 129.0, 129.5, 129.54, 130.3, 136.4, 138.9, 139.4, 140.2 (d, *J* = 6.0 Hz), 148.8, 156.3, 161.5, 163.1, 196.7; IR (KBr): 2925, 1955, 1669, 1587, 1477, 1438, 1283, 1207, 1154, 1119, 1017, 962, 869, 793, 685, 642 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}FNO$

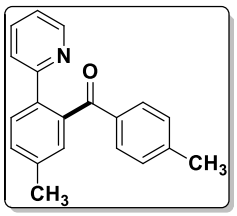
$[M+H]^+$ 278.0976; found 278.0972.



(2-(Pyridin-2-yl)phenyl)(3-(trifluoromethyl)phenyl)methanone (1j): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.98–7.01 (m, 1H), 7.37 (t, 1H, *J* = 7.6 Hz), 7.53–7.66 (m, 6H), 7.78 (d, 1H, *J* = 7.2 Hz), 7.82 (d, 1H, *J* = 7.6 Hz), 7.92 (s, 1H), 8.27–8.28 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.3, 122.5, 122.9, 124.8, 126.0, 128.6, 128.7, 128.8, 129.1, 129.5, 130.8 (q, *J* = 34.5 Hz), 132.5, 136.8, 138.8, 139.0, 139.8, 149.1, 156.5, 196.9; IR (KBr): 3064, 1672.0, 1591.6, 1435.9,1333.5, 1248.2, 1128.2, 1072.1, 993.3, 800.9, 750.7, 659.1, 514.5, cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{12}F_3NO$ $[M+H]^+$ 328.0944; found 328.0949.

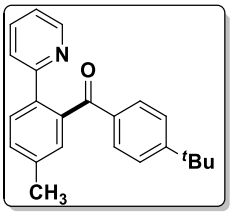


5-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone (2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 6.97 (d, 1H, *J* = 6.0 Hz), 7.24 (d, 2H, *J*= 7.2 Hz), 7.36 (d, 2H, *J*= 9.2 Hz), 7.41 (d, 1H, *J* = 8.0Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 7.2 Hz), 7.67 (d, 3H, *J* = 7.2 Hz), 8.34 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 121.8, 122.6, 128.2, 128.8, 129.6, 129.8, 131.1, 132.4, 136.4, 136.9, 138.2, 138.9, 139.6, 149.1, 156.9, 198.6; IR (KBr): 2921.9, 2853.3, 2059.0, 1662.8, 1461.1, 1285.8, 1210.5, 1172.3, 1027.3, 965.4, 839.3, 787.6, 742.5, 699.6, 650.3, 520.0 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{15}NO$ $[M+H]^+$ 274.1226; found 274.1223.

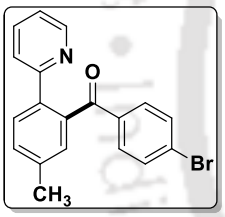


5-Methyl-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone (2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 2.43 (s, 3H), 6.98 (t, 1H, *J* = 5.2 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 7.31 (s, 1H), 7.39 (d, 1H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 7.2 Hz), 7.59 (d, 2H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 8.36 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 21.7, 110.2, 121.8, 122.7, 128.9, 129.6, 129.9, 130.9, 135.5, 136.3, 136.9, 138.7, 139.8, 143.2, 149.1, 157.0, 198.4; IR (KBr) 2922, 2854, 1663, 1606, 1588, 1465, 1398, 1284, 1209, 1116, 1027, 966, 832, 785, 602, 568 cm^{-1}; HRMS (ESI): calcd.

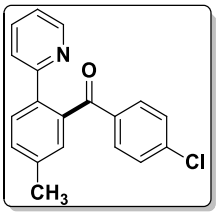
for $C_{20}H_{17}NO$ $[M+H]^+$ 288.1383; found 288.1389.



(4-(^{t}Butyl)phenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (s, 9H), 2.41 (s, 3H), 6.94–6.97 (m, 1H), 7.24–7.29 (m, 3H), 7.36–7.38 (m, 1H), 7.42 (d, 1H, *J*= 8.0 Hz), 7.48–7.53 (m, 1H), 7.60–7.65 (m, 3H), 8.34–8.35 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 31.2, 35.1, 121.7, 122.8, 125.1, 129.0, 129.6, 129.7, 130.9, 135.4, 136.3, 137.1, 138.5, 139.8, 149.2, 156.1, 157.1, 198.3; IR (KBr): 3055, 2961, 2869, 1924, 1665, 1600, 1465, 1388, 1287, 1151, 1106, 1026, 965, 847, 736, 684, 549 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{23}NO$ $[M+H]^+$ 330.1852; found 330.1849.

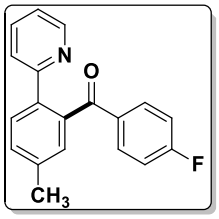


(4-Bromophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2e): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 6.99–7.02 (m, 1H), 7.31 (s, 1H), 7.37–7.42 (m, 3H), 7.45–7.59 (m, 4H), 7.66 (d, 1H, *J* = 8.0 Hz), 8.30 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 122.0, 122.3, 127.4, 128.6, 129.7, 131.0, 131.3, 131.5, 131.8, 136.6, 136.8, 137.2, 139.1, 149.1, 156.5, 197.6; IR (KBr): 2924, 2846, 1665, 1586, 1467, 1428, 1308, 1285, 1122, 1068, 967, 834, 788 676, 526.cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO$ $[M+H]^+$ 352.0332; found 352.0327.

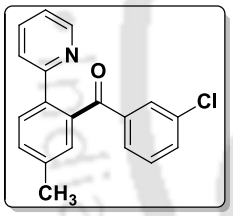


(4-Chlorophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2f): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 7.00 (t, 1H, *J* = 5.6 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.32 (s, 1H), 7.41 (d, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 8.4 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.61 (d, 2H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 7.6 Hz), 8.31 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 122.0, 122.4, 128.5, 128.7, 129.8, 130.9, 131.2, 136.6, 136.7, 136.8, 138.6, 139.1, 139.2, 149.1, 156.6, 197.4; IR (KBr): 2924, 2864, 1668, 1573, 1469, 1427, 1288, 1152, 1073, 987,

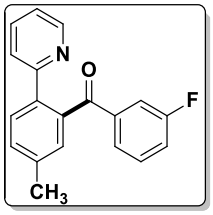
895, 800, 748, 676, 641, 513 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}ClNO$ $[M+H]^+$ 308.0837; found 308.0841.



(4-Fluorophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 6.91 (t, 2H, *J*= 8.4 Hz), 7.00 (t, 1H, *J* = 7.2 Hz), 7.33 (s, 1H), 7.41 (d, 1H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.65–7.70 (m, 3H), 8.33 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 115.3 (d, *J* = 21.0 Hz), 122.0, 122.6, 128.8, 129.7, 131.2, 132.1 (d, *J* = 9.0 Hz), 134.7, 136.5, 136.9, 139.0, 139.3, 149.1, 156.8, 197.2; IR (KBr): 2923, 2854, 1666, 1596, 1503, 1466, 1284, 1153, 1096, 965, 848, 787, 768, 607, 560 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}FNO$ $[M+H]^+$ 292.1132; found 292.1127.

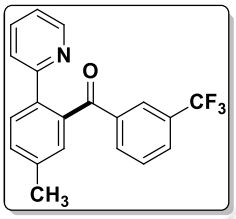


(3-Chlorophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2h): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 6.96–6.99 (m, 1H), 7.14–7.18 (m, 1H), 7.31 (d, 2H, *J* = 7.2 Hz), 7.40 (d, 1H, *J* = 7.6 Hz), 7.49–7.50 (m, 2H), 7.54–7.58 (m, 1H), 7.64 (d, 2H, *J* = 8.0 Hz), 8.27–8.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 122.0, 122.3, 124.9, 127.5, 128.6, 129.1, 129.5, 129.8, 131.4, 132.1, 134.3, 134.4, 136.6, 139.1, 139.9, 148.9, 156.4, 197.2; IR (KBr): 3064, 2924, 2846, 1668, 1573, 1469, 1427, 1288, 1252, 1152, 1073, 1020, 987, 943, 895, 800, 748, 676, 641, 513 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}ClNO$ $[M+H]^+$ 308.0837; found 308.0843.

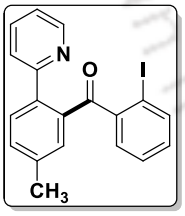


(3-Fluorophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2i): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 6.96–6.99 (m, 1H), 7.02–7.07 (m, 1H), 7.07–7.22 (m, 1H), 7.33 (s, 1H), 7.38–7.41 (m, 3H), 7.51 (d, 1H, *J* = 8.0 Hz), 7.54–7.58 (m, 1H), 7.67 (d, 1H, *J* = 7.6 Hz), 8.29–8.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 115.8 (d, *J* = 22.5 Hz), 119.2 (d, *J* = 21.0Hz), 122.0, 122.2, 125.2, 128.5, 129.8 (t, *J* = 7.5 Hz), 131.3, 136.6, 136.8, 139.1 (d, *J* = 3.0 Hz),

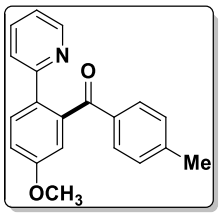
140.6 (d, *J* = 4.5 Hz), 149.0, 156.4, 161.8, 163.4, 197.2; IR (KBr): 3064, 2923, 2860, 2360, 1950, 1718, 1671, 1590, 1438, 1297, 1181, 1149, 1110, 1028, 988, 896, 788, 755, 678, 650, 506, 459 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}FNO$ $[M+H]^+$ 292.1132; found 292.1129.



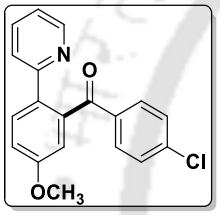
(5-Methyl-2-(pyridin-2-yl)phenyl)(3-(trifluoromethyl)phenyl)methanone (2j): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 6.96 (t, 1H, *J* = 5.6 Hz), 7.36 (t, 2H, *J* = 7.6 Hz), 7.44 (d, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.58 (t, 2H, *J* = 7.6 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 7.6 Hz), 7.91 (s, 1H), 8.24 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 121.2, 122.1 (d, *J* = 25.5), 123.0, 124.8, 125.9 (d, *J* = 4.5 Hz), 128.45 (t, *J* = 4.5 Hz), 128.7, 130.0, 130.6 (q, *J* = 65.2 Hz), 131.5, 132.4, 136.6, 136.9, 138.7, 139.1, 139.3, 148.9, 156.3, 197.0; IR (KBr): 3396, 2924, 1672, 1597, 1465, 1432, 1332, 1284, 1166, 1129, 1073, 982, 915, 828, 772, 702, 661, 521 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{14}F_3NO$ $[M+H]^+$ 342.1100; found 342.1108.



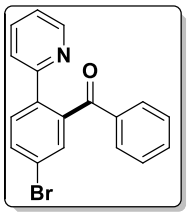
(2-Iodophenyl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone (2k): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.46 (s, 3H), 6.89 (t, 1H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.2 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.17 (d, 1H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 7.6 Hz), 7.49 (s, 1H,), 7.57–7.58 (m, 2H), 7.81 (d, 1H, *J* = 8.0 Hz), 8.55 (d, 1H, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.9, 94.4, 121.3, 122.4, 126.9, 128.9, 130.7, 131.0, 131.4, 131.7, 136.0, 137.8, 138.0, 138.5, 140.9, 141.5, 148.9, 156.8, 197.4; IR (KBr): 3054, 2922, 2856, 1928, 1671, 1586, 1461, 1428, 1293, 1154, 1094, 1018, 964, 897, 839, 786, 745, 657, 527, 481 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}INO$ $[M+H]^+$ 400.0193; found 400.0202.



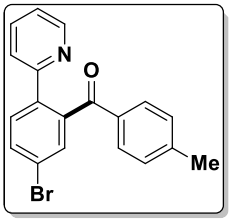
(5-Methoxy-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone (3b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H), 3.85 (s, 3H), 6.94–6.96 (m, 1H), 7.01 (d, 1H, *J* = 2.4 Hz), 7.05 (d, 2H, *J* = 7.8 Hz), 7.09–7.11 (m, 1H), 7.41 (d, 1H, *J* = 7.8 Hz), 7.49–7.52 (m, 1H), 7.60 (d, 2H, *J* = 7.8 Hz), 7.70 (d, 1H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 55.7, 114.0, 116.1, 121.5, 122.4, 128.9, 129.8, 130.2, 132.0, 135.3, 136.3, 141.1, 143.3, 149.0, 156.6, 159.9, 197.8; IR (KBr): 2923, 2850, 1602, 1506, 1461, 1424, 1285, 1231, 1177, 1111, 1045, 962, 841, 753, 578, 526 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}NO_2$ $[M+H]^+$ 304.1332; found 304.1335.



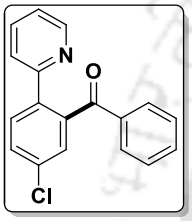
(4-Chlorophenyl)(5-methoxy-2-(pyridin-2-yl)phenyl)methanone (3f): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 3H), 7.02 (d, 1H, *J* = 2.4 Hz), 7.12-7.13 (m, 1H), 7.21–7.23 (m, 2H), 7.25–7.29 (m, 1H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.54–7.56 (m, 2H), 7.61–7.63 (m, 2H), 7.72 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.8, 114.2, 116.4, 121.7, 121.9, 128.5, 130.0, 130.8, 131.9, 136.5, 136.6, 138.7, 140.6, 148.9, 156.2, 160.2, 196.8; IR (KBr): 2923, 2853, 1659, 1591, 1462, 1418, 1285, 1231, 1086, 1015, 965, 838, 761, 679, 580 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}ClNO_2$ $[M+H]^+$ 324.0786; found 324.0793.



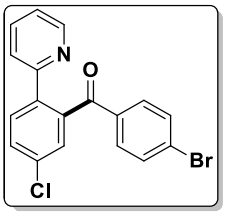
(5-Bromo-2-(pyridin-2-yl)phenyl)(phenyl)methanone (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.01–7.05 (m, 1H), 7.29 (d, 2H, *J* = 7.6 Hz), 7.39–7.43 (m, 1H), 7.48 (d, 1H, *J* = 8.0 Hz), 7.56–7.61 (m, 1H), 7.64–7.68 (m, 4H), 7.72–7.75 (m, 1H), 8.33–8.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.4, 122.6, 123.1, 128.4, 129.6, 130.4, 132.0, 132.9, 133.3, 136.7, 137.5, 138.6, 141.3, 149.3, 155.8, 196.7; IR (KBr): 3059, 2925, 2848, 1666, 1587, 1460, 1385, 1276, 1157, 1092, 1024, 946, 886, 836, 786, 698, 648, 518, 457 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}BrNO$ $[M+H]^+$ 338.0175; found 338.0186.



(5-Bromo-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone (4b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H), 7.03–7.05 (m, 1H), 7.09 (d, 2H, *J* = 7.8 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.55–7.59 (m, 3H), 7.62–7.65 (m, 2H), 7.70–7.72 (m, 1H), 8.37 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 122.4, 122.7, 123.0, 129.1, 129.9, 130.5, 131.9, 133.2, 134.9, 136.6, 138.5, 141.6, 143.8, 149.4, 156.0, 196.4; IR (KBr): 3385, 3055, 2921, 2857, 2360, 1922, 1664, 1599, 1461, 1428, 1385, 1154, 1092, 1024, 887, 758, 683, 606, 521, 479 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{14}BrNO$ $[M+H]^+$ 352.0332; found 352.0323.

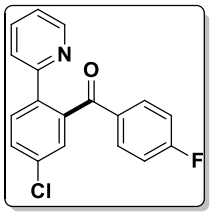


(5-Chloro-2-(pyridin-2-yl)phenyl)(phenyl)methanone (5a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.01–7.03 (m, 1H), 7.28 (t, 2H, *J* = 7.8 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.48 (d, 1H, *J* = 7.8 Hz), 7.51 (s, 1H), 7.57–7.58 (m, 2H), 7.68 (d, 2H, *J* = 7.8 Hz), 7.72 (d, 1H, *J* = 7.8 Hz), 8.34 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 122.4, 122.6, 128.4, 129.2, 129.6, 130.2, 130.4, 132.8, 135.0, 136.7, 137.5, 138.1, 141.2, 149.3, 155.8, 196.8; IR (KBr): 3058, 2920, 2849, 1963, 1667, 1589, 1456, 1428, 1387, 1313, 1277, 1155, 1104, 1066, 1027, 994, 887, 784, 696, 676, 648 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{12}ClNO$ $[M+H]^+$ 294.0680; found 294.0682.

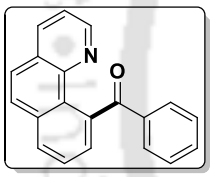


(4-Bromophenyl)(5-chloro-2-(pyridin-2-yl)phenyl)methanone (5e): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.04–7.06 (m, 1H), 7.41 (d, 2H, *J* =8.4 Hz), 7.48 (s, 1H), 7.50–7.54 (m, 3H), 7.57 (d, 1H, *J* = 8.4 Hz), 7.61 (t, 1H, *J* = 7.8 Hz), 7.72 (d, 1H, *J* = 8.4 Hz), 8.31 (d, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.3, 122.6, 127.8, 129.1, 130.0, 130.5, 130.9, 131.7, 135.2, 136.5, 136.9, 137.9, 140.7, 149.2, 155.3, 195.7; IR (KBr): 3059, 2924, 2854, 1916, 1671, 1585, 1465, 1428, 1395, 1274, 1161, 1102, 1067, 1011, 952, 887, 839, 755, 673, 603, 492 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{11}BrClNO$ $[M+H]^+$

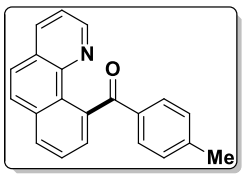
371.9785; found 371.9788.



(4-Fluorophenyl)(5-chloro-2-(pyridin-2-yl)phenyl)methanone (5g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (t, 2H, J = 8.4 Hz), 7.01–7.04 (m, 1H), 7.47 (d, 2H, J = 7.6 Hz), 7.54–7.59 (m, 2H), 7.65–7.71 (m, 3H), 8.31 (d, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 115.5 (d, J = 22.1), 122.6 (d, J = 4.6 Hz), 129.1, 130.2, 130.5, 132.1 (d, J = 9.1 Hz), 135.2, 136.8, 138.0, 140.9, 149.3, 155.6, 166.8, 195.3; IR (KBr): 3063, 2920, 2844, 1668, 1594, 1502, 1463, 1422, 1276, 1237, 1154, 1099, 1019, 953, 888, 846, 773, 676, 604, 513 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{11}ClFNO$ $[M+H]^+$ 312.0586; found 312.0595.

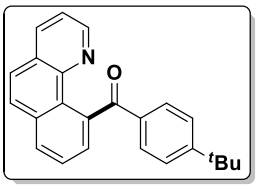


Benzo[*h*]quinolin-10-yl(phenyl)methanone (6a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26–7.32 (m, 3H), 7.39 (t, 1H, J = 7.6 Hz), 7.61 (d, 1H, J = 7.2 Hz), 7.71–7.74 (m, 3H), 7.77 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 8.8 Hz), 8.03 (d, 1H, J = 8.0 Hz), 8.07 (d, 1H, J = 8.0 Hz), 8.48–8.49 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 121.8, 126.3, 126.6, 127.2, 127.9, 128.0, 128.3, 128.9, 129.2, 129.4, 131.9, 134.0, 135.5, 139.1, 139.4, 144.8, 147.3, 198.8; IR (KBr): 3055, 2932, 1668, 1597, 1580, 1511, 1492, 1422, 1313, 1273, 1175, 1120, 1005, 892, 792, 707, 690, 624, 489 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{13}NO$ $[M+H]^+$ 284.1070; found 284.1068.

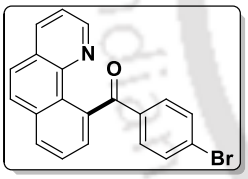


Benzo[*h*]quinolin-10-yl(*p*-tolyl)methanone (6b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H), 7.10 (d, 2H, J = 7.6 Hz), 7.33–7.36 (m, 1H), 7.59–7.61 (m, 1H), 7.65 (d, 2H, J = 8.0 Hz), 7.73–7.80 (m, 2H), 7.90 (d, 1H, J = 8.8 Hz), 8.03–8.05 (m, 1H), 8.09–8.12 (m, 1H), 8.52–8.54 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 121.8, 126.3, 126.6, 127.2, 127.9, 128.0, 129.02, 129.06, 129.1, 129.4, 134.1, 135.5, 136.9, 139.4, 142.5, 145.0, 147.4, 198.7;

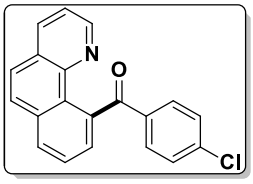
IR (KBr): 3045, 2921, 2595, 1665, 1607, 1510, 1461, 1274, 1209, 1176, 1117, 1007, 893, 837, 742, 688, 605, 545, 488 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}NO$ $[M+H]^+$ 298.1226; found 298.1235.



Benzo[*h*]quinolin-10-yl(4-(*tert*-butyl)phenyl)methanone (6c): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.28 (s, 9H), 7.29–7.34 (m, 2H), 7.39 (d, 1H, *J* = 8.4 Hz), 7.58-7.60 (m, 1H), 7.70 (d, 2H, *J* = 8.4 Hz), 7.74-7.78 (m, 2H), 7.89 (d, 1H, *J* = 8.8 Hz), 8.03 (d, 1H, *J* = 8.0 Hz), 8.07–8.10 (m, 1H), 8.54–8.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.3, 35.1, 121.7, 125.2, 125.6, 126.2, 126.5, 127.0, 127.8, 127.9, 128.9, 129.0, 134.0, 135.4, 136.7, 139.4, 144.9, 147.4, 155.4, 198.7; IR (KBr): 3417, 3050, 2961, 2869, 2245, 1928, 1799, 1668, 1608, 1573, 1512, 1467, 1414, 1365, 1303, 1273, 1213, 1188, 1048, 1009, 897, 764, 696, 629, 582, 485 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{21}NO$ $[M+H]^+$ 340.1696; found 340.1699.

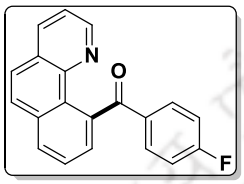


Benzo[*h*]quinolin-10-yl(4-bromophenyl)methanone (6e): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32–7.35 (m, 1H), 7.40 (d, 2H, *J* = 8.8 Hz), 7.56–7.60 (m, 3H), 7.73–7.75 (m, 1H), 7.78 (d, 1H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 8.04 (d, 1H, *J* = 8.4 Hz), 8.09–8.11 (m, 1H), 8.47–8.48 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.0, 126.4, 126.6, 126.8, 127.2, 128.0, 129.3, 129.4, 130.3, 131.6, 134.0, 135.6, 138.4, 138.5, 144.7, 147.3, 197.6; IR (KBr): 3048, 2924, 2853, 1920, 1670, 1583, 1511, 1481, 1396, 1272, 1206, 1169, 1113, 1067, 1004, 891, 836, 739, 677, 624, 546, 485 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{12}BrNO$ $[M+H]^+$ 362.0175; found 362.0177.

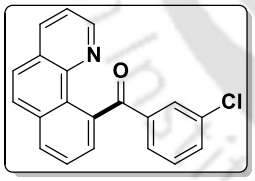


Benzo[*h*]quinolin-10-yl(4-chlorophenyl)methanone (6f): ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26 (d, 2H, *J* = 8.0 Hz), 7.34–7.37 (m, 1H), 7.61 (d, 1H, *J* = 7.2 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.74–7.81 (m, 2H), 7.90 (d, 1H, *J* = 8.4 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 1H, *J*

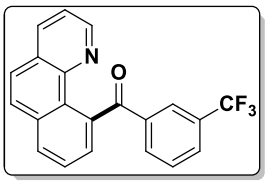
= 7.6 Hz), 8.49 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.0, 126.4, 126.6, 127.2, 128.0, 128.6, 129.3, 129.4, 130.2, 134.0, 135.6, 137.9, 138.1, 138.6, 144.7, 147.3, 197.5; IR (KBr): 2920, 2846, 1667, 1623, 1509, 1488, 1422, 1398, 1135, 1088, 1004, 892, 832, 747, 733, 682, 617, 507 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{12}ClNO$ $[M+H]^+$ 318.0680; found 318.0673.



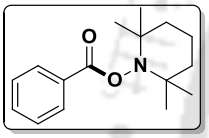
Benzo[*h*]quinolin-10-yl(4-fluorophenyl)methanone (6g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.96 (t, 2H, *J* = 8.8 Hz), 7.34–7.37 (m, 1H), 7.61 (d, 1H, *J* = 7.6 Hz), 7.75 (t, 3H, *J* = 8.8 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 1H, *J* = 8.0 Hz), 8.50 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 115.3 (d, *J* = 21.0 Hz), 121.9, 126.4, 126.5, 127.2, 128.0 (d, *J* = 6.0Hz), 129.3 (d, *J* = 12.0 Hz), 131.3 (d, *J* = 9.0 Hz), 134.0, 135.1, 135.9, 138.8, 144.8, 147.3, 164.2, 166.0, 197.3; IR (KBr): 2920, 2850, 1664, 1633, 1595, 1505, 1427, 1272, 1237, 1150, 1084, 891, 838, 748, 687, 503 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{12}FNO$ $[M+H]^+$ 302.0976; found 302.0999.



Benzo[*h*]quinolin-10-yl(3-chlorophenyl)methanone (6h): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21 (t, 1H, *J* = 8.0 Hz), 7.35–7.39 (m, 2H), 7.56 (d, 1H, *J* = 8.0 Hz), 7.61–7.63 (m, 1H), 7.75–7.82 (m, 3H), 7.92 (d, 1H, *J* = 8.8 Hz), 8.06–8.08 (m, 1H), 8.11–8.14 (m, 1H), 8.50–8.52 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.0, 126.4, 126.6, 126.9, 127.3, 128.0, 128.6, 129.3, 129.5, 129.6, 131.8, 134.1, 134.5, 135.6, 138.3, 141.3, 144.7, 147.2, 197.3; IR (KBr): 3053, 2920, 2837, 1673, 1575, 1508, 1417, 1270, 1156, 1121, 1077, 1012, 899, 838, 793, 737, 674, 625, 544, 465 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{12}ClNO$ $[M+H]^+$ 318.0680; found 318.0683.



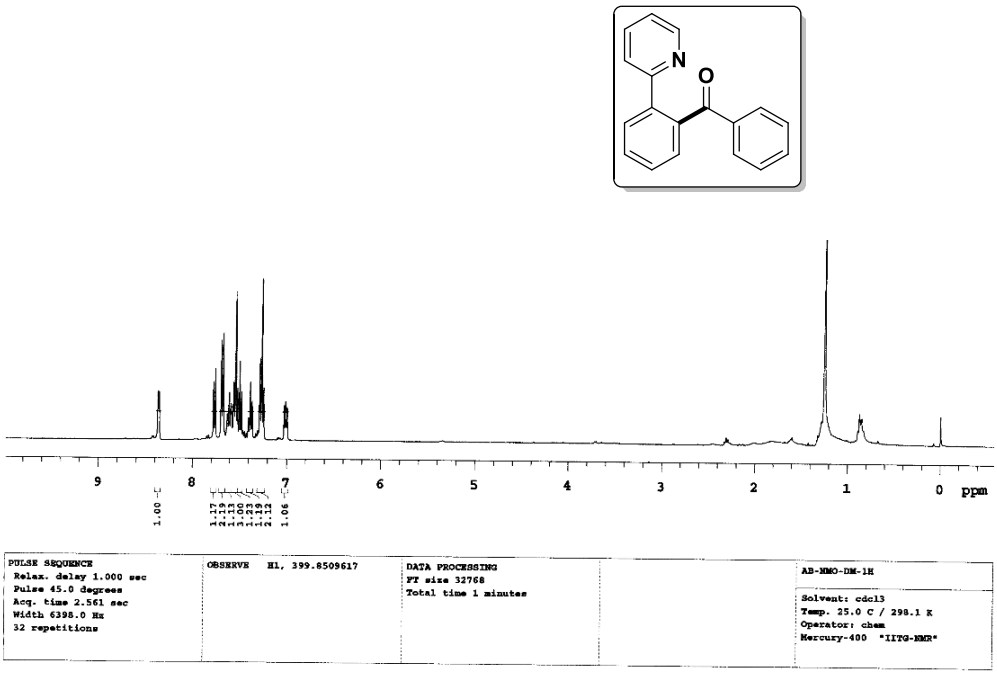
Benzo[*h*]quinolin-10-yl(3-(trifluoromethyl)phenyl)methanone (6j): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34–7.39 (m, 2H), 7.65 (t, 2H, *J* = 7.2 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 6.4 Hz), 7.83 (d, 1H, *J* = 7.6 Hz), 7.93 (d, 1H, *J* = 8.8 Hz), 8.08–8.14 (m, 2H), 8.18 (s, 1H), 8.46–8.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.0, 123.2, 124.9, 125.2 (t, *J* = 4.5 Hz), 126.6 (d, *J* = 24.0Hz), 126.8, 127.3, 128.0 (d, *J* = 4.5 Hz), 128.2, 128.8, 129.3, 129.6, 131.0 (q, *J* = 65.2 Hz), 132.0, 134.1, 135.7, 138.1, 140.3, 144.5, 147.2, 197.2; IR (KBr): 3081, 2936, 1670, 1611, 1512, 1419, 1332, 1269, 1165, 1123, 1066, 917, 839, 743, 689, 627, 541 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{12}F_3NO$ $[M+H]^+$ 352.0944; found 352.0950.



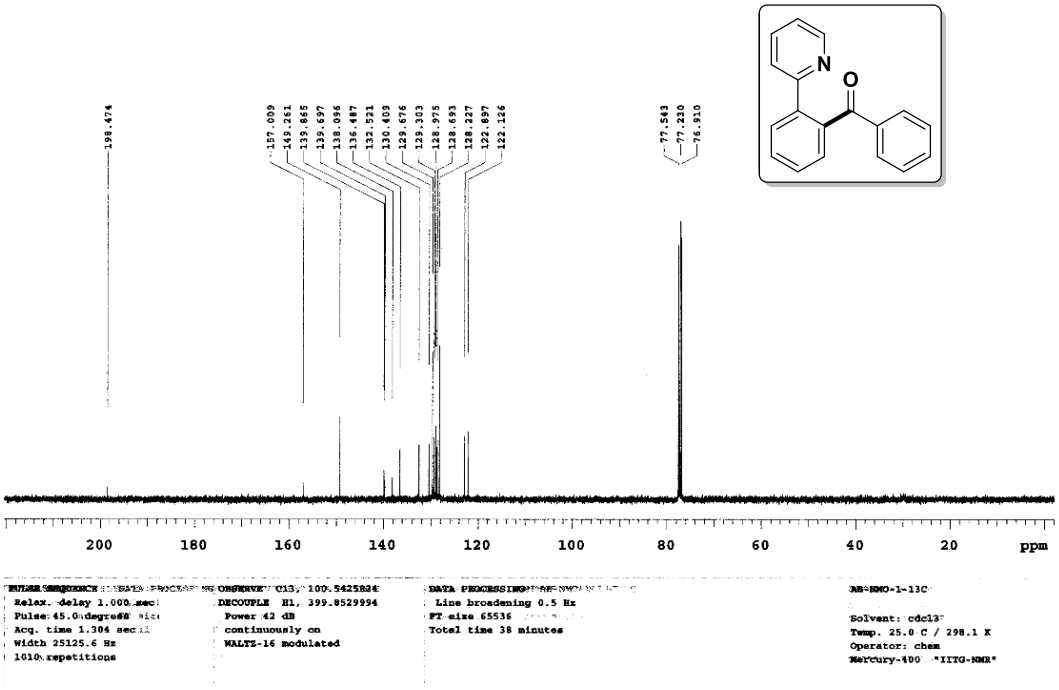
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (E): ^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 1.10 (s, 6H), 1.26 (s, 6H), 1.41–1.45 (m, 1H), 1.55–1.58 (m, 2H), 1.65–1.80 (m, 3H), 7.44 (t, 2H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 7.2 Hz), 8.06 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.1, 21.0, 32.1, 39.2, 60.5, 128.6, 129.7, 129.8, 133.0, 166.5; IR (KBr): 3010, 2980, 2866, 1743, 1601, 1450, 1376, 1256, 1176, 1066, 1023, 993, 909, 871, 801, 712, 581, 506 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{23}NO_2$ $[M+H]^+$ 262.1802; found 262.1796.

III.7. Spectra

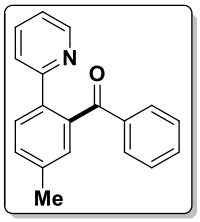
Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{1}H NMR (400 MHz, $CDCl_3$)

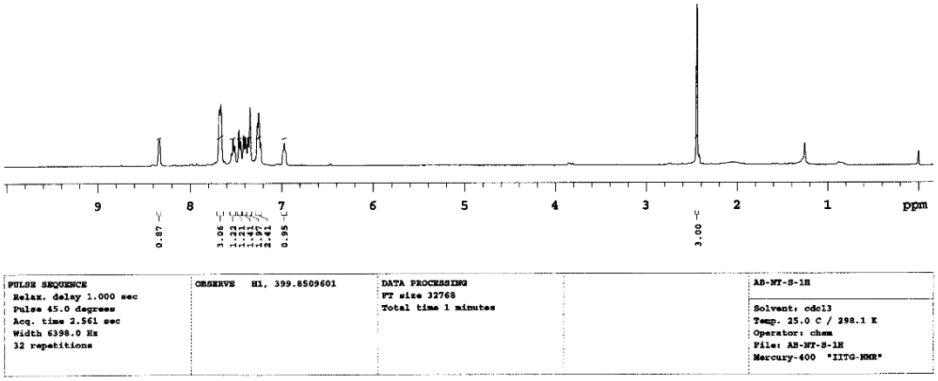


Phenyl(2-(pyridin-2-yl)phenyl)methanone (1a): ^{13}C NMR (100 MHz, $CDCl_3$)

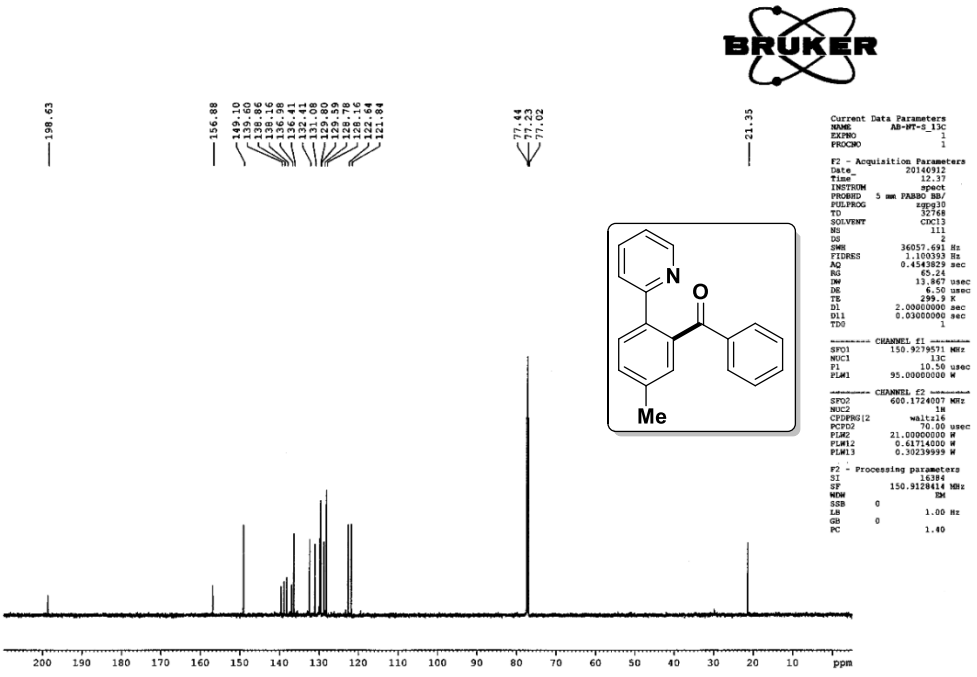


(5-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone (2a): ^{1}H NMR (400 MHz, $CDCl_3$)

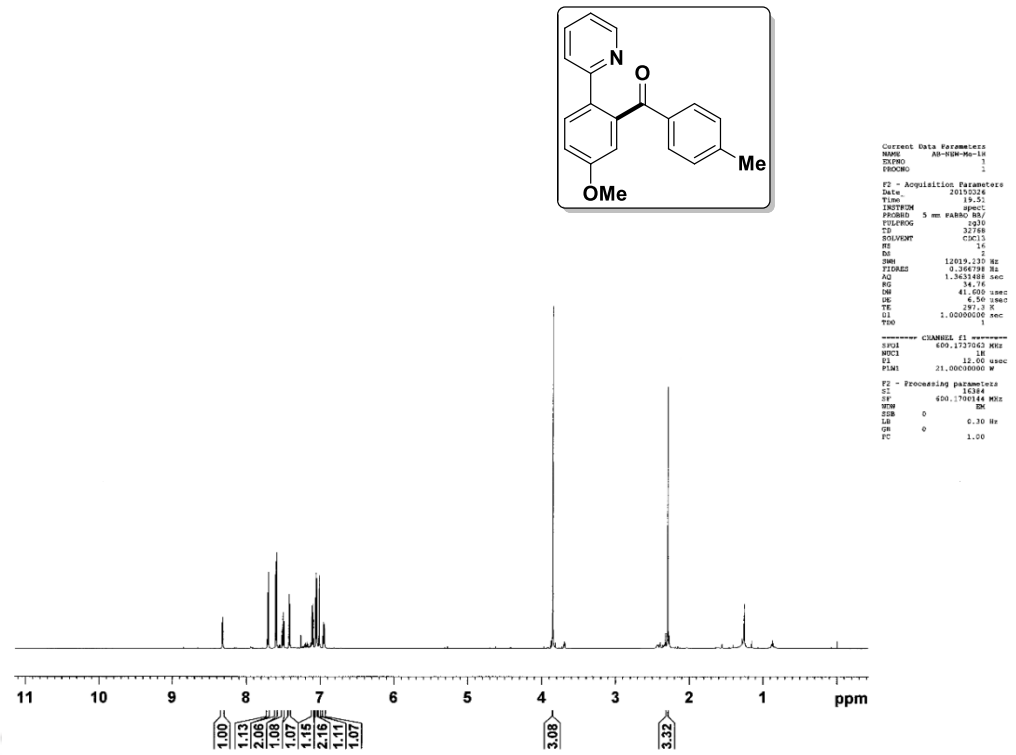




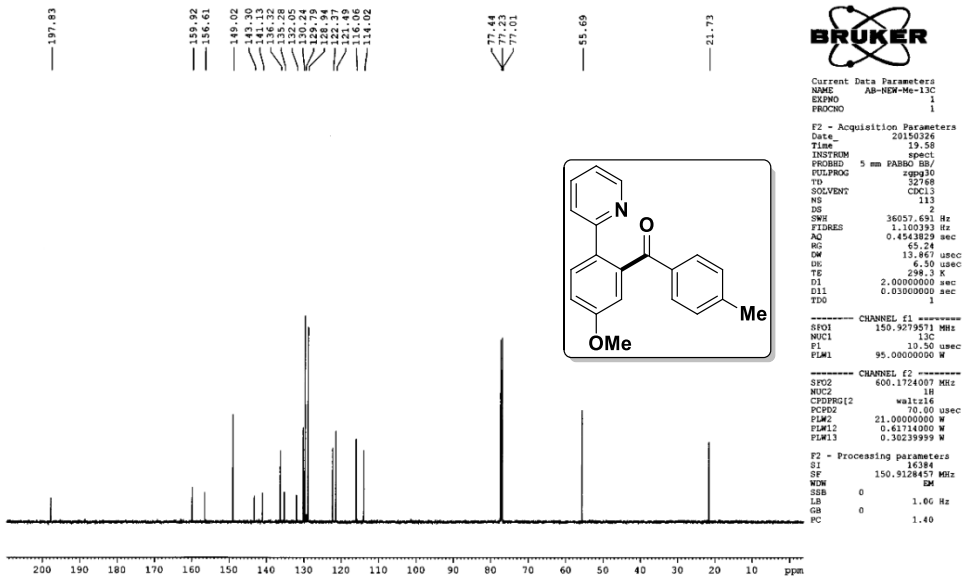
(5-Methyl-2-(pyridin-2-yl)phenyl)(phenyl)methanone (2a): ^{13}C NMR (150 MHz, $CDCl_3$)



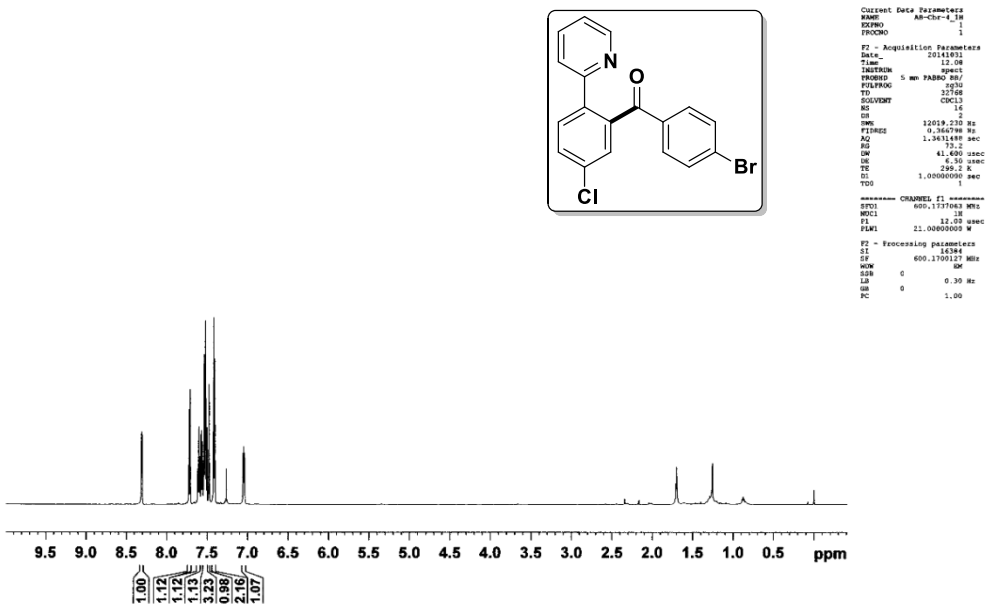
(5-Methoxy-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone (3b): ^{1}H NMR (400 MHz, $CDCl_3$)



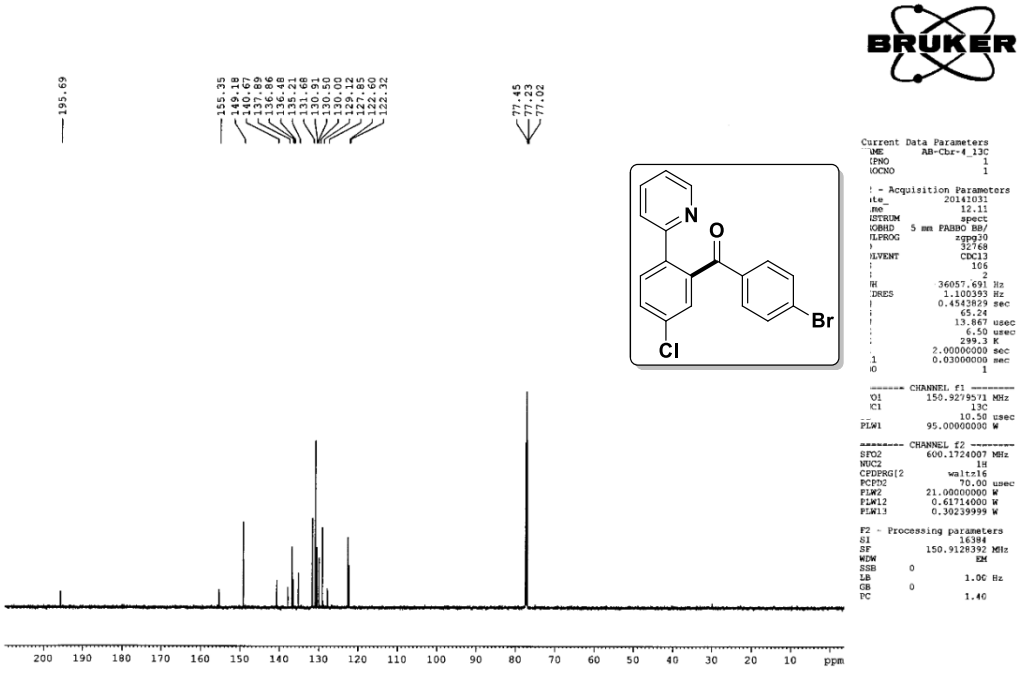
(5-Methoxy-2-(pyridin-2-yl)phenyl)(*p*-tolyl)methanone (3b): ^{13}C NMR (150 MHz, $CDCl_3$)



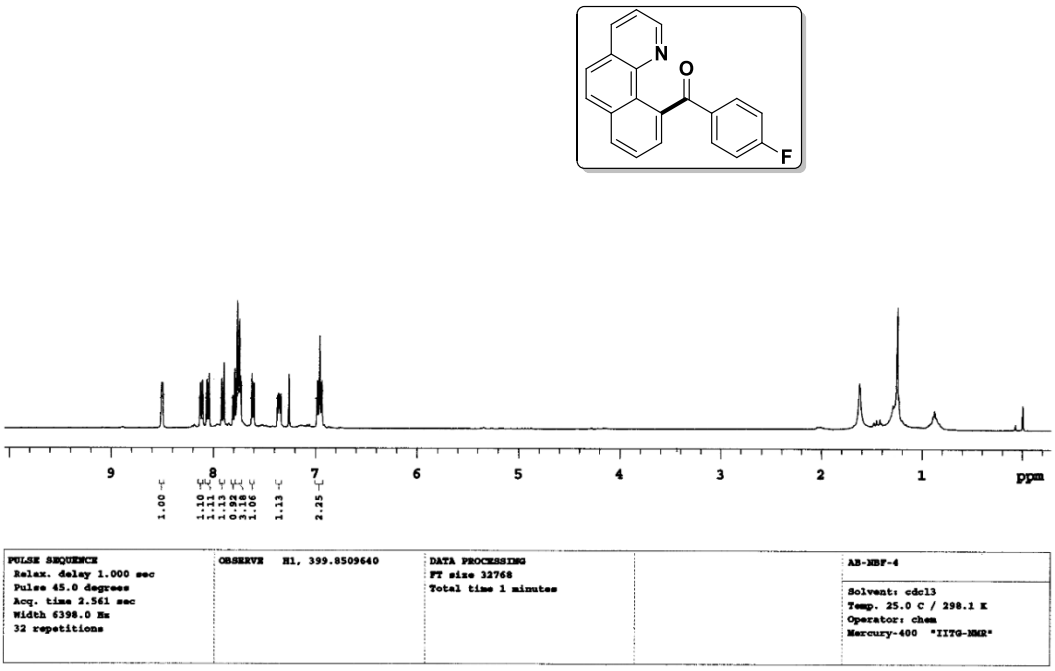
(4-Bromophenyl)(5-chloro-2-(pyridin-2-yl)phenyl)methanone (5e): ^{1}H NMR (600 MHz, $CDCl_3$)



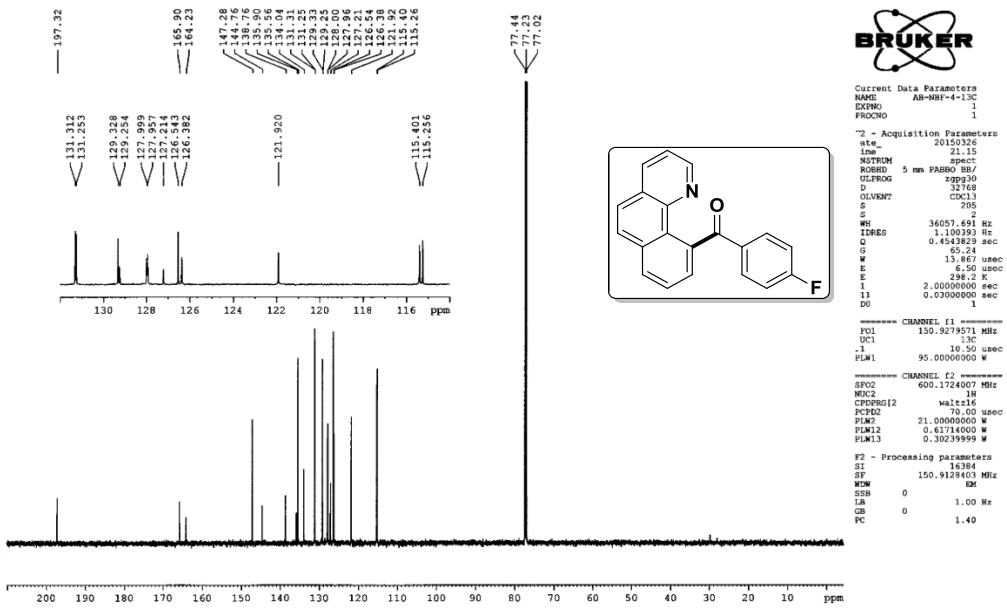
(4-Bromophenyl)(5-chloro-2-(pyridin-2-yl)phenyl)methanone (5e): ^{13}C NMR (150 MHz, $CDCl_3$)



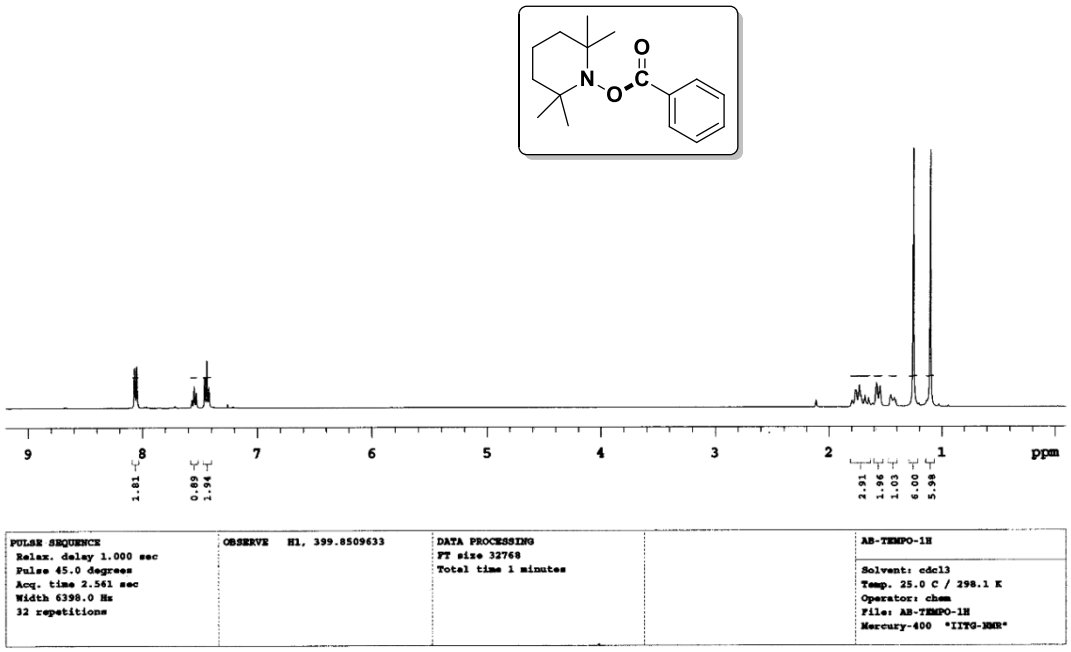
Benzo[*h*]quinolin-10-yl(4-fluorophenyl)methanone (6g): ^{1}H NMR (400 MHz, $CDCl_3$)



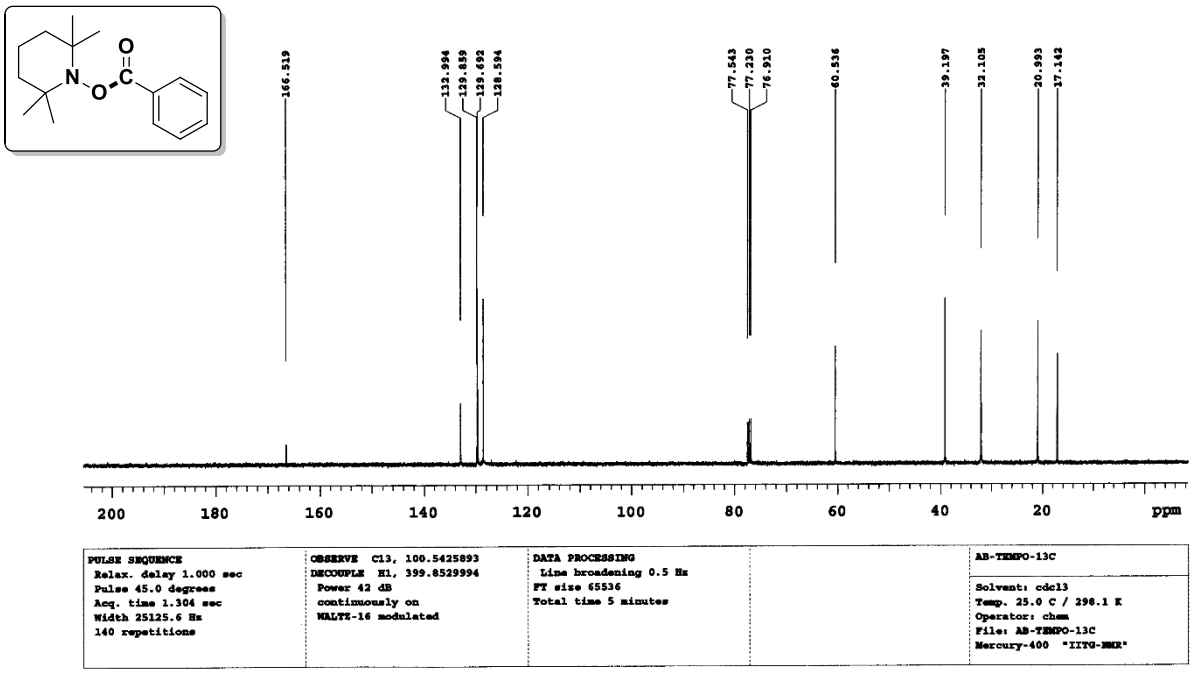
Benzo[*h*]quinolin-10-yl(4-fluorophenyl)methanone (6g): ^{13}C NMR (150 MHz, $CDCl_3$)



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

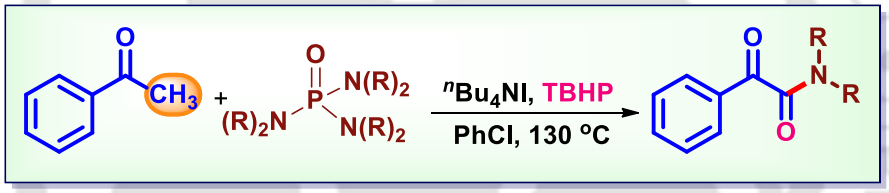


2,2,6,6-Tetramethylpiperidin-1-yl benzoate (E): ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER IV

Transition Metal-free Synthesis of α-Ketoamides from Arylmethyl Ketones and Alkylphosphoramides



Abstract: *A transition metal-free protocol has been developed for the synthesis of α-ketoamides from aryl methyl ketones and alkylphosphoramides in the presence of oxidant, aqueous tert-butyl hydroperoxide (TBHP). A series of aryl methyl ketones having both electron-donating as well as electron-withdrawing groups were successfully employed for the synthesis of their corresponding α-ketoamides using hexamethylphosphoramide and other alkylphosphoramides.*

RSC Adv., 2016, 6, 91308

CHAPTER IV

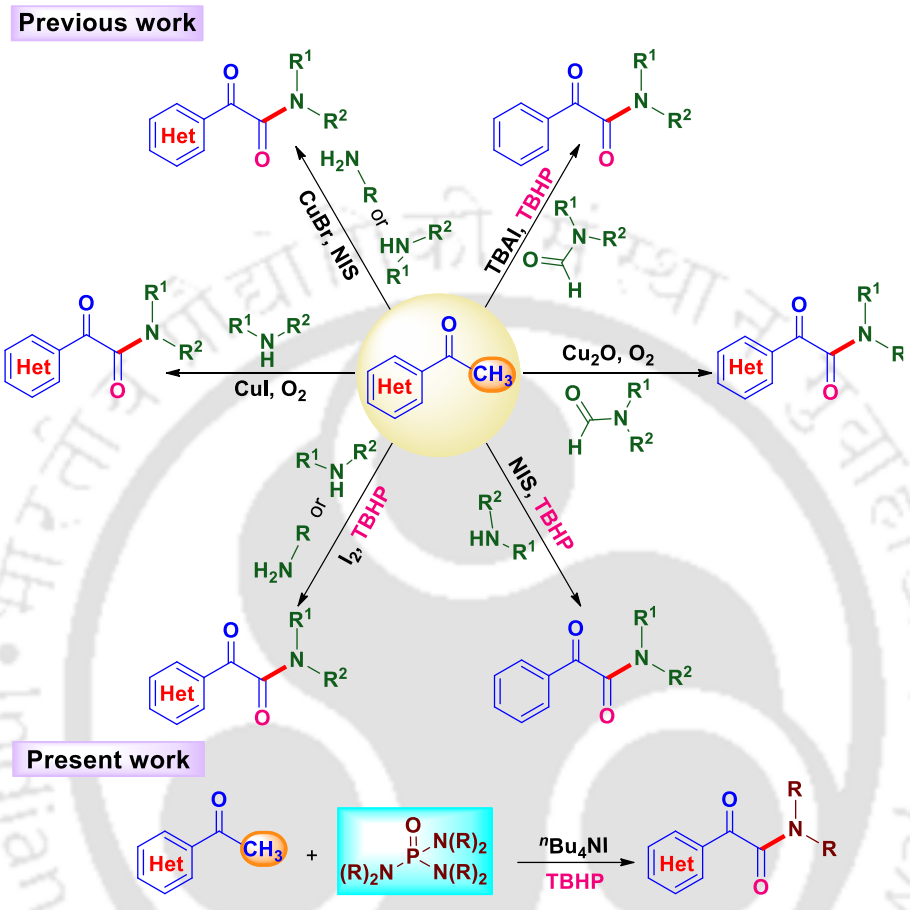
Transition Metal-free Synthesis of α-Ketoamides from Arylmethyl Ketones and Alkylphosphoramides

IV.1. Introduction

Cross-dehydrogenative coupling (CDC) has contributed tremendously in the development of atom and step-economic process for the synthesis of complex molecular architectures from simple precursors. The CDC process plays a pivotal role in bringing about the transformation of C–H bonds of all types (sp, sp^2 and sp^3) to C–C and C–heteroatom bonds.[1] Of various C–heteroatom bonds, the construction of C–N bond is one of the most fundamental challenge in the synthesis of biologically important molecules, natural products, pharmaceuticals and other functional materials.[2] Among diverse C–N bond forming reactions, synthesis of α-ketoamide *via* C–N bond formation is one of the important reaction.

Arylmethylketone can be converted into phenylglyoxal in the presence of an appropriate oxidant that may serve as a α-ketyl (ArCOCO–) surrogate.[3] Based on this idea, there are few literature reports on the synthesis of α-ketoamide from the coupling of arylmethyl ketones and dialkylformamides and primary/secondary amines under metal and metal-free conditions (Scheme IV.1.1).[4a-g] Taking cues from these literature reports, it was envisaged that the α-ketyl group (generated from arylmethyl ketone) may couple with the *in situ* generated amines from phosphoramides under an oxidative condition to afford a α-ketoamide. Keeping this in mind, when acetophenone was treated with hexamethylphosphoramide (HMPA) in the presence of *tetra*-butylammonium iodide (^{n}Bu$_4$NI) and *tert*-butylhydroperoxide (TBHP), the formation of *N*,*N*-dimethyl-2-oxo-2-phenylacetamide was observed (Scheme IV.1.1). The transition metal-free synthesis of α-ketoamides using arylmethylketones as the α-ketoaryl (ArCOCO-) equivalents and alkylphosphoramides as the amine source has not been reported (Scheme IV.1.1). Invariably, hexamethylphosphoramide is used as a solvent in organic reactions, but its

use as the source of amine for the synthesis of α-ketoamide was explored for the first time.



Scheme IV.1.1. Synthesis of α-ketoamides from arylmethyl ketones

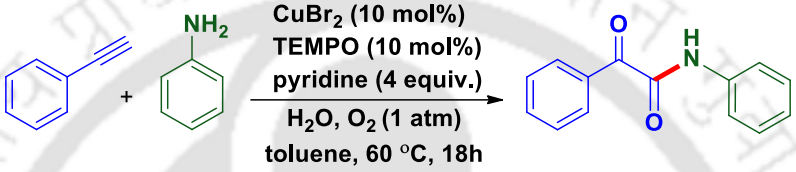
IV.2. Strategies for α-ketoamides synthesis

α-Ketoamide constitutes the basic subunits of many vital molecules. These motifs are used in the designing of peptidase inhibitors,[5a] histone deacetylases[5b] and human cytosolic phospholipase A_2,[5c,d] which is applicable for inhibiting several classes of proteases such as serine, cysteine and HIV.[5e-g] Because of the wide applicability of α-ketoamides, a number of synthetic routes have been developed for their synthesis.[6-10] Some of the representative examples are discussed below.

(i) Synthesis of α-ketoamides using primary/secondary/tertiary amines

(a) Synthesis of α-ketoamides from terminal alkyne

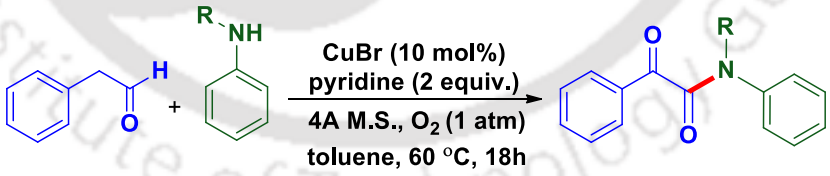
Jiao and co-workers have demonstrated the first Cu-catalysed oxidative amidation-diketonisation reaction of terminal alkynes with aniline leading to α-ketoamides (Scheme IV.2.1). The molecular oxygen (O_2) plays a pivotal role by participating as the ideal oxidant and also undergoes dioxygen activation under ambient conditions *via* a radical process.[11]



Scheme IV.2.1. *Cu-catalysed synthesis of α-ketoamides from terminal alkyne*

(b) Synthesis of α-ketoamides from the coupling of aryl acetaldehyde

In 2011, the synthesis of α-ketoamides *via* Cu-catalysed aerobic oxidative coupling of aryl acetaldehydes with anilines was reported by Jiao group (Scheme IV.2.2). This reaction proceeds through the cleavage of two Csp^3–H, one Csp^2–H, and one N–H bond. Moreover, both *N*-substituted and simple anilines were utilised as the suitable substrates for this transformation.[12]

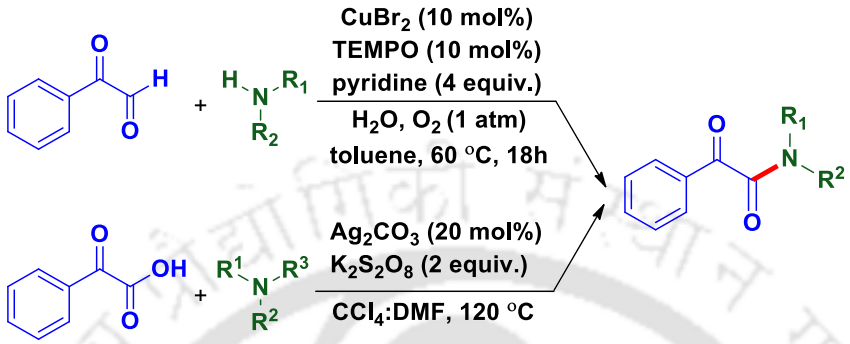


Scheme IV.2.2. *Cu-catalysed synthesis of α-ketoamides from aryl acetaldehyde*

(c) Synthesis of α-ketoamides from the coupling of aryl glyoxaldehyde and aryl glyoxalic acid

Jiao *et al*. developed an efficient synthesis of α-ketoamides from copper catalysed aerobic oxidative cross-dehydrogenative coupling (CDC) of primary and secondary amines with α-carbonyl aldehyde (Scheme IV.2.3).[13a] Later, a similar approach towards the synthesis of α-ketoamides using tertiary amines as aminyl sources *via* C–N bond

cleavage was disclosed by Wang and co-workers (Scheme IV.2.3). In the presence of Ag_2CO_3 and $K_2S_2O_8$, benzoylformic acids undergoes decarboxylative coupling with tertiary amines to afford α-ketoamides.[13b]

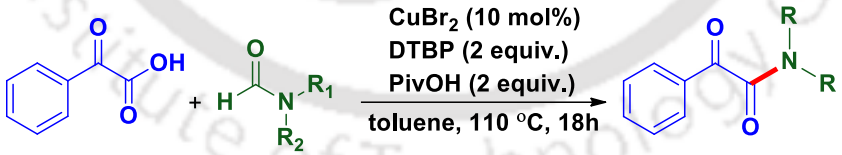


Scheme IV.2.3. *Synthesis of α-ketoamides from phenyl glyoxal and phenyl glyoxalic acid*

(ii) Synthesis of α-ketoamides from alkylformamides

(a) Synthesis of α-ketoamides *via* decarboxylative coupling

In 2013, Wang *et. al*. reported the $CuBr_2$ promoted synthesis of α-ketoamides from α-oxocarboxylic acids and formamides (Scheme IV.2.4). The decarboxylative acylation of the acyl C–H of *N*-monosubstituted and *N*,*N*-disubstituted formamides with α-ketoacids leading to the formation of α-ketoamides.[14a] Duan group has also developed a similar copper catalysed protocol for the synthesis of α-ketoamide from the coupling of α-oxocarboxylic acids and formamides.[14b]

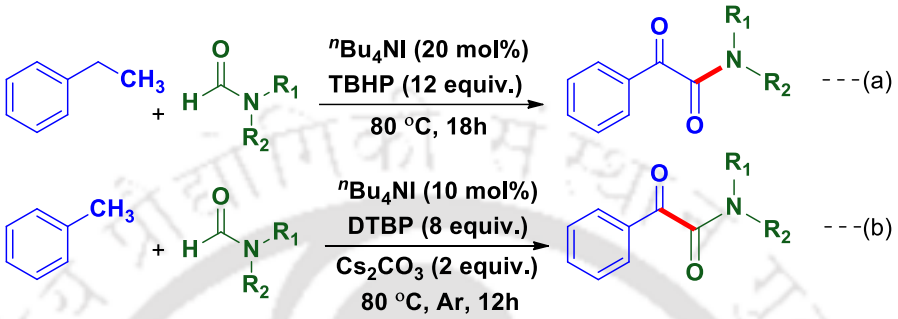


Scheme IV.2.4. *Cu-catalysed synthesis of α-ketoamides from phenyl glyoxalic acid and formamides*

(b) Synthesis of α-ketoamides from ethylbenzenes and formamides

Sun group has demonstrated a $^nBu_4NI$-catalysed synthesis of α-ketoamides using ethylarenes as the aroyl source and *N*,*N*-dialkylformamides as the aminyl source. The sequential formation of C–O and C–N bonds *via* multiple Csp^3–H bond activation of ethylarenes and coupling with the aminyl component of *N*,*N*-dialkylformamide provided

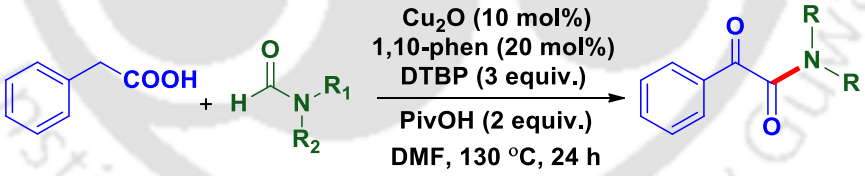
the α-ketoamides [Scheme IV.2.5, (a)].[15a] Later on, a closely related strategy on the one-pot synthesis of α-ketoamides *via* Csp^3–H radical/radical cross-coupling and domino aerobic oxidation was also reported by Feng *et. al*. [Scheme IV.2.5, (b)]. Here, they utilised toluene and dialkylformamides as the coupling partners.[15b]



Scheme IV.2.5. *^{n}Bu$_4$NI-catalysed synthesis of α-ketoamides from alkyl benzenes and formamides*

(c) Synthesis of α-ketoamides from phenyl acetic acid and formamides

A new synthetic approach for the synthesis of α-ketoamides was accomplished from the Cu_2O–catalysed coupling reactions of *N*,*N*-dialkylformamides with phenylacetic acids (Scheme IV.2.6). They have shown that the carbonyl group of α-ketoamide came from the phenyl acetic acid.[16]



Scheme IV.2.6. *Cu-catalysed synthesis of α-ketoamides from phenyl acetic acid and formamides*

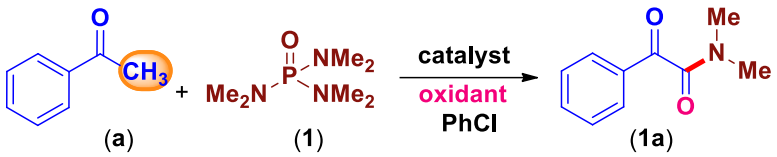
IV.3. Present work

In view of the abovementioned strategies on α-ketoamide synthesis, the present protocol on the synthesis of α-ketoamides using arylmethylketones as the α-ketoaryl (ArCOCO-) source and alkylphosphoramides as the amine source is unparalleled in literature reports.

Optimisation of reaction conditions: As it was mentioned earlier, the initial trial reaction was performed by using arylmethylketone (**a**) (0.5 mmol),

hexamethylphosphoramide (**1**) (1.5 mmol), TBAI (20 mol%) and TBHP (5-6 M in decane) (4 equiv.) in chlorobenzene (2 mL) at 130 ^{o}C. The reaction yielded the desired product (**1a**) in 61 % (Table IV.3.1, entry 1). To further improve the yield of the coupled product (**1a**) obtained from arylmethylketone (**a**) and hexamethylphosphoramide (**1**), various reaction parameters were scrutinised. Initially, a variety of oxidants such as aq. TBHP (66%), DTBP (36%), 30% aq. H_2O_2 (00%), $K_2S_2O_8$ (27%) and $(PhCOO)_2O$ (BPO) (15%), were tested (Table IV.3.1, entries 2–6), from which aq. TBHP was found to be ideal (Table IV.3.1, entry 2). The use of other halogen analogues such as TBAB, I_2 and KI, in lieu of TBAI were found to be far less effective (Table IV.3.1, entries 7–9). An increased amount of catalyst loading (30 mol%) was not so much beneficial (Table IV.3.1, entry 10), nevertheless a higher loading of oxidant (6 equiv.) improved the product yield by another 6% (Table IV.3.1, entry 11). Further, increase in the oxidant loading to 8 equiv., did not show any significant improvement in the product yield (Table IV.3.1, entry 12). To further improve the yield of the product (**1a**), various solvents *viz*. 1,2-dichloroethane (DCE), CH_3CN and EtOAc were screened (Table IV.3.1, entries 13–15) but all were found to be inferior in comparision to PhCl (Table IV.3.1, entry 11). Next, the effect of reaction temperature on the product formation was examined and it was found that the reaction carried out both at higher (145 ^{o}C) and lower (110 ^{o}C) temperature had adversely affected the product (**1a**) yield (Table IV.3.1, entries 16 and 17). Under otherwise identical conditions either in the absence of TBAI or TBHP, failed to give the desired product (Table IV.3.1, entries 18 and 19) suggesting the vital role of both, in achieving the above transformation.

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

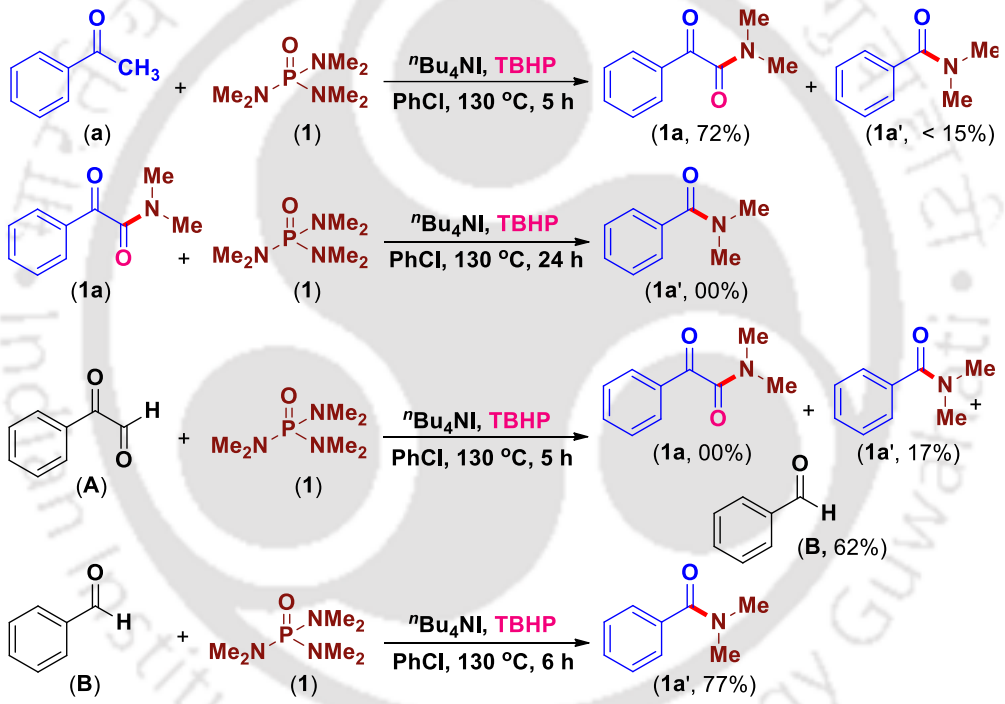


Entry	Catalyst (mol %)	Oxidant (equiv.)	Solvent	Temp (°C)	Yield (%)
1	TBAI (20)	TBHP (4)	PhCl	130	61[c]
2	TBAI (20)	TBHP (4)	PhCl	130	66[d]
3	TBAI (20)	DTBP (4)	PhCl	130	36
4	TBAI (20)	H_2O_2 (4)	PhCl	130	00
5	TBAI (20)	$K_2S_2O_8$ (4)	PhCl	130	27
6	TBAI (20)	BPO (4)	PhCl	130	15
7	TBAB (20)	TBHP (4)	PhCl	130	52
8	I_2 (20)	TBHP (4)	PhCl	130	47[d]
9	KI (20)	TBHP (4)	PhCl	130	12[d]
10	TBAI (30)	TBHP (4)	PhCl	130	67[d]
11	**TBAI (20)**	**TBHP (6)**	**PhCl**	**130**	**72[d]**
12	TBAI (20)	TBHP (8)	PhCl	130	73[d]
13	TBAI (20)	TBHP (6)	DCE	130	54[d]
14	TBAI (20)	TBHP (6)	CH_3CN	130	63[d]
15	TBAI (20)	TBHP (6)	EtOAc	130	65[d]
16	TBAI (20)	TBHP (4)	PhCl	145	62[d]
17	TBAI (20)	TBHP (4)	PhCl	110	50[d]
18	-	TBHP (4)	PhCl	130	00[d]
19	TBAI (20)	-	PhCl	130	00

[a]Reaction conditions: acetophenone (**a**) (0.5 mmol), catalyst, HMPA (1.5 mmol), solvent (2 mL), oxidant. [b]Yields of isolated pure product. [c]decane solution of TBHP, [d]aq. TBHP (70 wt% in water).

During the course of optimisation, it was observed that the duration of reaction plays a significant role on the product yield. When the reaction was heated beyond 45 minutes, in addition to the formation of α-ketoamide (**1a**), appearance of another product in <15% having R_f lower than the α-ketoamide was also noticed. Spectroscopic analysis of the product reveals its structure to be an amide (**1a′**) (Scheme IV.3.1). Now a query arises whether product (**1a′**) is formed *via* the decomposition of α-ketoamide (**1a**) or *via* the coupling of benzaldehyde (obtained from the decomposition of phenylglyoxal) and the dimethylamine (generated by the decomposition of HMPA)? To check this, when a pre-synthesised α-ketoamide (**1a**) was subjected to the present reaction condition, formation of an amide (**1a′**) was not observed even after 24 h (Scheme IV.3.1). Again, when phenylglyoxal (**A**) was taken in lieu of acetophenone (**a**) under otherwise identical

condition, formation of amide (**1a′**) along with the formation of benzaldehyde (**B**) was observed. This observation confirms the formation of phenylglyoxal in small amount from acetophenone, which results in the formation of amide (**1a′**) in the reaction. A similar reaction with benzaldehyde in lieu of phenylglyoxal gave exclusively *N*,*N*-dimethyl benzamide (**1a'**) in 77% yield. This confirms the *in situ* generation of benzaldehyde in the reaction medium. Finally, the optimised condition for this transformation is the use of acetophenone (0.5 mmol), hexamethylphosphoramide (1.5 mmol), $^{n}Bu_4NI$ (20 mol%), chlorobenzene (2 mL) and aq. TBHP (70 wt% in H_2O) (3 mmol) at 130 ^{o}C for 45 minutes (Table IV.3.1, entry 11).

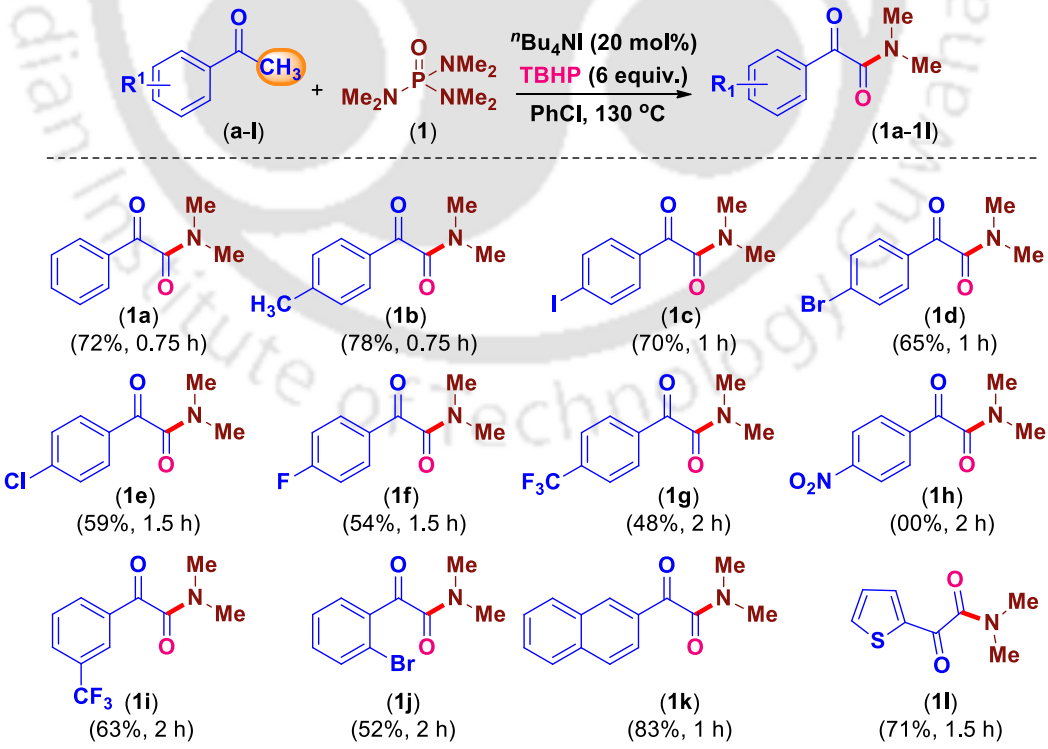


Scheme IV.3.1*. Control experiments for the formation of amide*

Substrate scopes for the synthesis of α-ketoamide using various arylmethylketones: With this optimised condition in hand, different arylmethylketones (**a**–**l**) bearing both electron-donating and electron-withdrawing groups were subjected to the current reaction condition with hexamethylphosphoramide (**1**). As can be seen from Scheme IV.3.2, the presence of substituents on the aryl ring of arylmethylketone play a significant role on the yields of *N*,*N*-dimethyl-2-oxo-2-phenylacetamides. Arylmethylketones substituted with electron-donating group like –Me (**b**) gave its corresponding α-ketoamide (**1b**) in 78% yield. On the other hand, the presence of

moderately electron-withdrawing groups such as –I (**c**), –Br (**d**), –Cl (**e**) and –F (**f**) in the arylmethylketone reduced the product (**1c**–**1f**) yields ranging between 70–54% (Scheme IV.3.2) compared to their electron-neutral analogue. Further reduction in the product (**1g**) yield (48%) was observed when a strongly electron-withdrawing group like $–CF_3$ (**g**) is present at the *para* position of arylmethylketone (**g**). When the electron-withdrawing power of the substituent is increased further, as in *p*-nitroacetopheneone (**h**), a complete failure of the reaction was noticed. However, when the $–CF_3$ group was moved to the *meta* position (**i**), its electronic effect was not such prominent to that when it is present at the *para* position giving product (**1i**) in decent yield (63%). When a moderately electron-withdrawing group such as –Br is present at the *ortho* position of arylmethylketone (**j**) further decrease in the yield was observed which may be due to both electronic as well as steric reasons. Other than these, an excellent yield of *N*,*N*-dimethyl-2-naphthamide (**1k**) was obtained from 2-acetonaphthone (**k**). A good yield of the α-ketoamide (**1l**) formation was also observed when 2-acetylthiophene (**l**) was used in the reaction process.

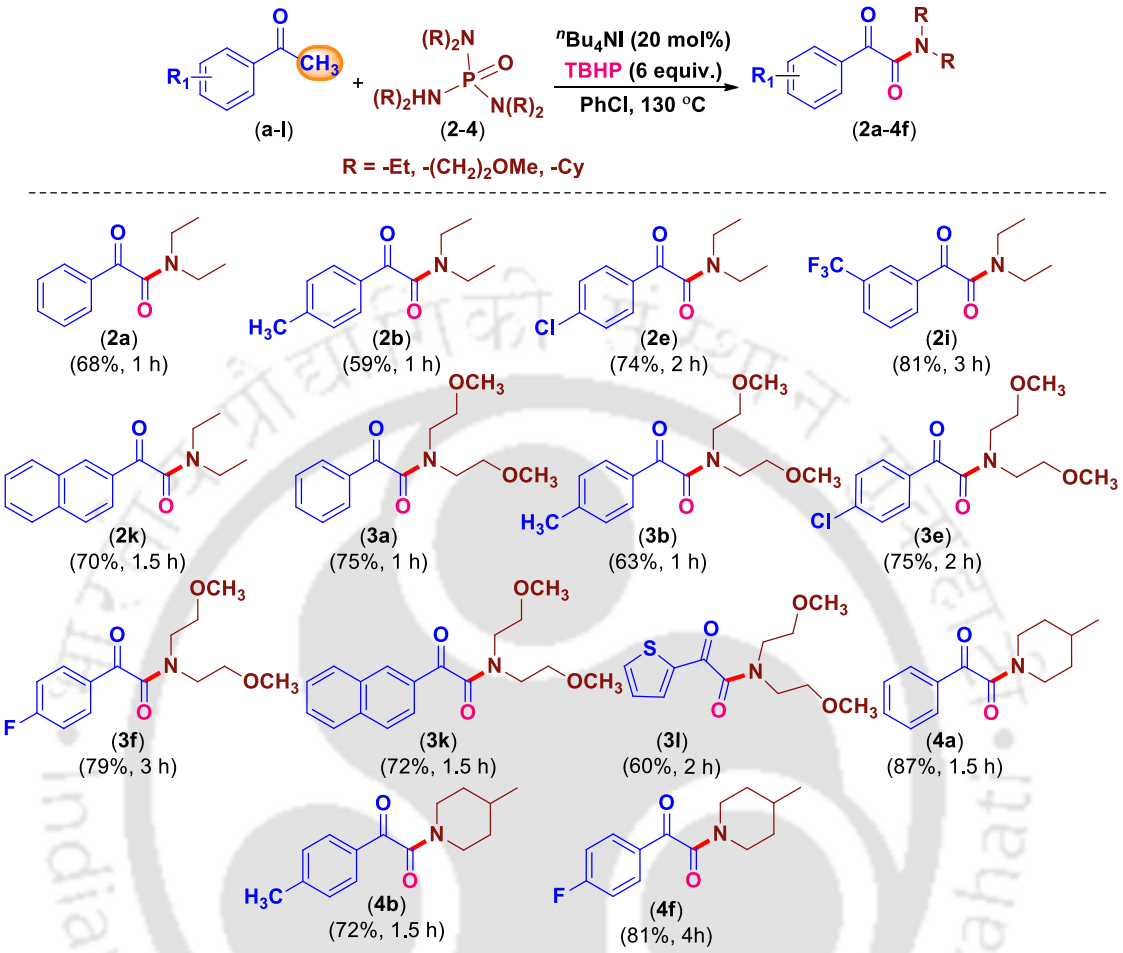
Scheme IV.3.2. *Substrate scope for α-ketoamide using various arylmethylketones* [a,b]



[a]Reaction conditions: arylmethylketones (**a**–**l**) (0.5 mmol), HMPA (**1**) (1.5 mmol), tetrabutylammonium iodide ($^nBu_4NI$) (20 mol%), chlorobenzene (2 mL), TBHP (70 wt% in H_2O) (6 equiv.), time (45 mins–2 h) at 130 °C. [b]Yields of isolated pure product.

Adopting the above optimised condition, a library of α-ketoamides were also synthesised using different arylmethylketones (**a**–**l**) and hexalkylphosphoramides (**2**–**4**) as shown in Scheme IV.3.3. Acetophenone substituted with an electron-donating group like 4′-methylacetophenone (**b**) gave lesser yield of α-ketoamide (**2b**) compared to the un-substituted one (**2a**) when coupled with hexaethylphosphoramide (**2**). On the other hand, presence of electron-withdrawing groups like 4′-Cl (**e**) and 3′-CF_3 (**i**) enhance the reactivity of arylmethylketones, providing their corresponding α-ketoamides (**2e** and **2i**) in 74% and 81% yields respectively. 2′-Acetonaphthone (**k**) was also successfully employed as a good ketoaryl source for the synthesis of α-ketoamide giving product (**2k**) in 70% yield. Hexa(methoxyethyl)phosphoramide (**3**) was successfully used as the amine source for the formation of different *N*,*N*-bis(methoxyethyl) substituted phenylacetamides (**3a**, **3b**, **3e**, **3f**, **3k** and **3l**). Cyclic amine based phosphoramides were also utilised as the amine source similar to acyclic phosphoramides. Tri(4-methylpiperidine)phosphoramide (**4**) reacted with electron-neutral (**a**), electron-donating 4′-Me (**b**) as well as electron-withdrawing 4′-F (**f**) acetophenones gave their respective α-ketoamide (**4a**, 87%), (4b, 72%) and (**4f**, 81%) in good yields (Scheme IV.3.3).

Scheme IV.3.3. *Substrate scope for the formation of N,N-disubstituted α-ketoamides*[a,b]

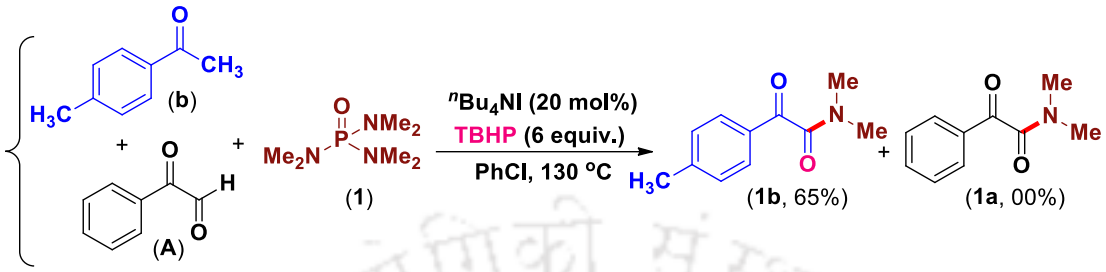


[a]Reaction conditions: acetophenone (**a**) (0.5 mmol), phosphoric acid triamide (**2-4**) (1.5 mmol), tetrabutylammoniun iodide ($^{n}Bu_4NI$) (20 mol%), TBHP (70 wt% in H_2O) (6 equiv.), time (1–4 h) at 130 ^{o}C .[b]Yields of isolated pure product.

Mechanistic investigation

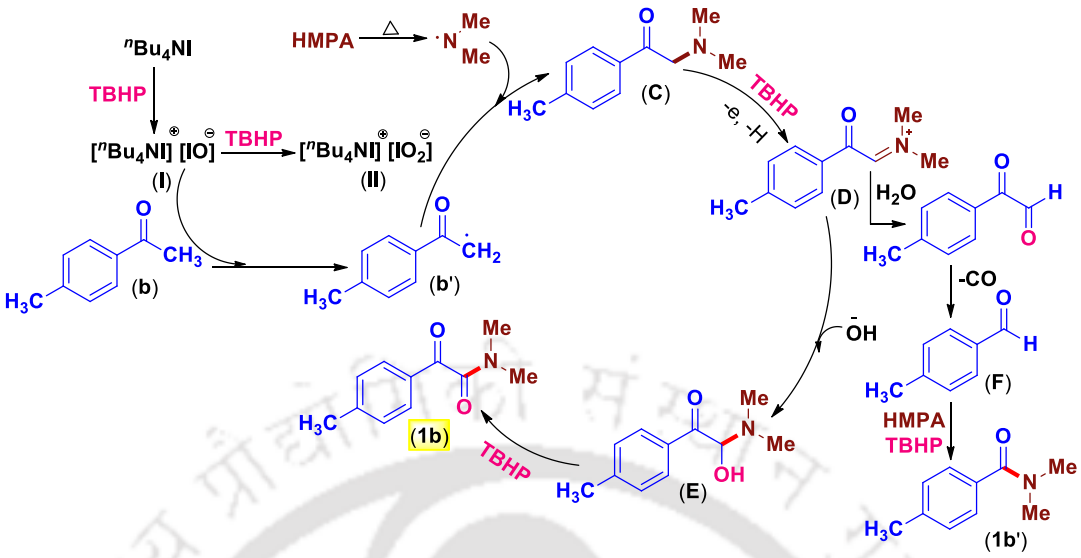
Control experiments: It is known that acetophenone in the presence of a suitable oxidant such as SeO_2 is transformed to a phenylglyoxal.[17] Therefore; it was envisaged that in the presence of an oxidant such as TBHP instead of SeO_2, acetophenone may be converted to phenylglyoxal in the reaction medium. To ascertain the exact reaction intermediate when a reaction was performed with an equimolar mixture of phenylglyoxal (**A**) and 4′-methylacetophenone (**b**) under an otherwise identical condition. Isolation of the only product *N*,*N*-dimethyl-2-oxo-2-(*p*-tolyl)acetamide (**1b**) (derived from the coupling of 4′-methylacetophenone (**b**) and the *in situ* generated dimethylamine from HMPA) in 65% yield suggests that the phenylglyoxal is not the active intermediate in the

reaction (Scheme IV.3.4). This observation is consistent with the observation in Scheme IV.3.1.



Scheme IV.3.4. *Cross-over experiment between 4′-methylacetophenone (**b**) and phenylglyoxal*

By summing up all the above experimental results and from the literature precedence,[1i,4] a plausible mechanism is proposed for the formation α-ketoamide (Scheme IV.3.5). Initially, from "^{n}Bu$_4$NI-TBHP" combination, the active iodine species ammonium hypoiodite ([^{n}Bu$_4$N]$^+$[IO]$^-$) (**I**) or iodite ([^{n}Bu$_4$N]$^+$[IO$_2$]$^-$) (**II**) is generated.[4l,18] The formation of hypervalent iodine species ([^{n}Bu$_4$N]$^+$[IO]$^-$) (**I**) and ([^{n}Bu$_4$N]$^+$[IO$_2$]$^-$) (**II**) have been confirmed by the detection of [IO]$^-$ and [IO$_2$]$^-$ from the ESI mass analysis of the reaction mixture (see experimental section).[1i,4l] The hypervalent iodine species (**I**) or (**II**) then abstracts a hydrogen atom from the aryl methyl ketone to generate a α-keto methyl radical (**b′**). This radical species (**b′**) couples subsequently with the dimethylaminyl radical (generated from the thermal decomposition of HMPA) to give the intermediate (**C**). Another intermediate (**D**) is generated from intermediate (**C**) *via* a one electron oxidation. HRMS analysis of the reaction mixture confirmed the intermediacy of both (**C**) and (**D**) (see experimental section). Then nucleophilic attack of a hydroxide ion to the intermediate (**D**) produce a keto-hydroxy intermediate (**E**), which is finally oxidised to the desired α-ketoamide (**1b)** in the presence of TBHP. This mechanism also accounts for the formation of a small amount of amidic product (**1b′**) (Scheme IV.3.5). A small quantity of phenylglyoxal is formed by the partial hydrolysis of the intermediate (**D**), which on decarbonylation gave benzaldehyde.[1h,19] The *in situ* generated benzoyl radical from benzaldehyde in the presence of TBHP couples with the dimethylaminyl radical generated from HMPA to give *N*,*N*-dimethylbenzamide (**1b′**) as the side product (Scheme IV.3.5).



Scheme IV.3.5. *Plausible mechanism for the synthesis of α-ketoamides*

In conclusion, a novel and efficient metal-free protocol for the synthesis of α-ketoamides from arylmethyl ketones and different alkylphosphoramides has been developed in the presence of TBAI as the catalyst and TBHP as the oxidant in a short period of time. A series of alkylphosphoramide having different functional groups have been utilised for the synthesis of corresponding α-ketoamide. This process tolerates a variety of functional groups and allows the synthesis of α-ketoamide derivatives in moderate to good yields. Based on the experimental findings, a plausible radical mechanism has been proposed for this transformation.

IV.4. Experimental section

IV.4.1. General information: All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 GF_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz and 600 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Mass spectra were recorded using MS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat.

IV.4.2. General procedure for the synthesis of *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (1a): An oven-dried round bottom flask was charged with acetophenone (**a**) (60 mg, 0.5 mmol), $^{n}Bu_4NI$ (20 mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL) and TBHP (70 wt% in H_2O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The reaction progress was monitored by TLC. After 45 minutes, the reaction mixture was cooled to room temperature. Then the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography with an eluent hexane / ethylacetate (80 / 20) to afford the desired product (**1a**) in an isolated yield of 72% (63.7 mg).

IV.4.3. Experiments performed for mechanistic investigation

IV.4.3.1. Control reaction with *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (1a): A pre-synthesised *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (**1a**) (0.25 mmol), $^{n}Bu_4NI$ (20 mol%, 18.5 mg), HMPA (**1**) (134 mg, 0.75 mmol), chlorobenzene (1 mL) and TBHP (70 wt% in H_2O) (6 equiv.) were added to a 10 mL round bottom flask. The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The progress of the reaction was monitored by TLC. Starting material (**1a**) remained unchanged even after 24 h without giving any trace of amide product (**1a′**). Thus, ruling out the formation of amide product (**1a′**) *via* the decomposition of ketoamide (**1a**).

IV.4.3.2. Treatment of phenylglyoxal (A) with hexamethylphosphoramide (1): An oven-dried round bottom flask was charged with phenylglyoxal (**A**) (67 mg, 0.5 mmol), $^{n}Bu_4NI$ (20 mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL) and TBHP (70 wt% in H_2O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The progress of the reaction was monitored by TLC. The reaction after a period of 5 h afforded 62% of benzaldehyde (**B**) and 17% of *N*,*N*-dimethylbenzamide (**1a′**).

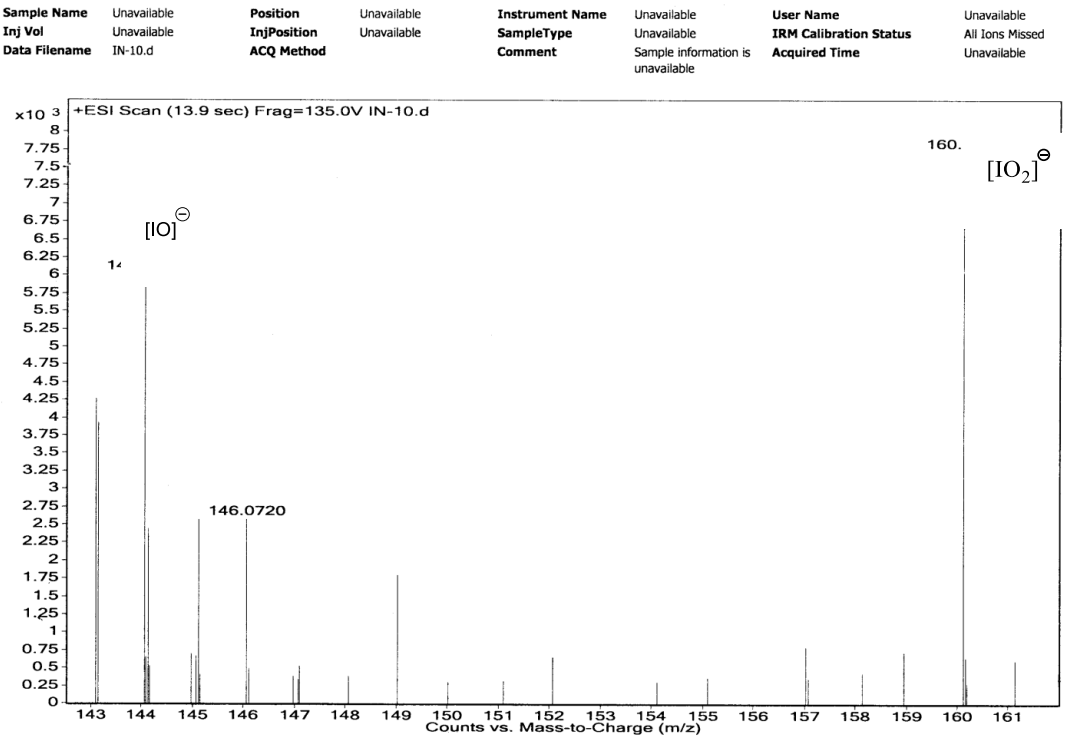
IV.4.3.3. Reaction of benzaldehyde (B) with hexamethylphosphoramide (1): An oven-dried round bottom flask was charged with benzaldehyde (**a**) (53 mg, 0.5 mmol), $^{n}Bu_4NI$ (20 mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL) and TBHP (70 wt% in H_2O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The reaction progress was monitored by TLC. After completion of the reaction, it was cooled to room temperature. Then the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography with an eluent hexane / ethyl acetate (65 / 35) to afford the *N*,*N*-dimethyl benzamide (**1a´**) in an isolated yield of 77%. This confirms the *in situ* generation of benzaldehyde in the reaction medium.

IV.4.3.4. Control experiment with 4′-methyl acetophenone (b) and phenylglyoxal (A): An equimolar mixture of 4′-methyl acetophenone (**b**) (33.5 mg, 0.25 mmol), phenylglyoxal (**A**) (33.5 mg, 0.25 mmol) and $^{n}Bu_4NI$ (20 mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL), TBHP (70 wt% in H_2O) (6 equiv.) were placed in an oven-dried round bottom flask. Then it was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The progress of the reaction was monitored by TLC. The reaction resulted the formation of *N*,*N*-dimethyl-2-oxo-2-(*p*-tolyl)acetamide (**1b**) in 65% yield. Formation of ketoamide from phenylglyoxal was not observed, thereby ruling out the intermediacy of phenylglyoxal (**A**).

IV.4.3.5. Experimental procedure for the detection of hypervalent iodine species: An oven-dried round bottom flask was charged with acetophenone (**a**) (60 mg, 0.5 mmol), $^{n}Bu_4NI$ (20mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL), TBHP (70 wt% in H_2O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. After 10 minutes, a 10 µL of the reaction mixture was collected and diluted with HPLC grade CH_3CN (1 mL). Then this diluted sample was filtered through a syringe filter having pore size 0.2 µm and was subjected to mass spectral analysis under ESI mode. The peak

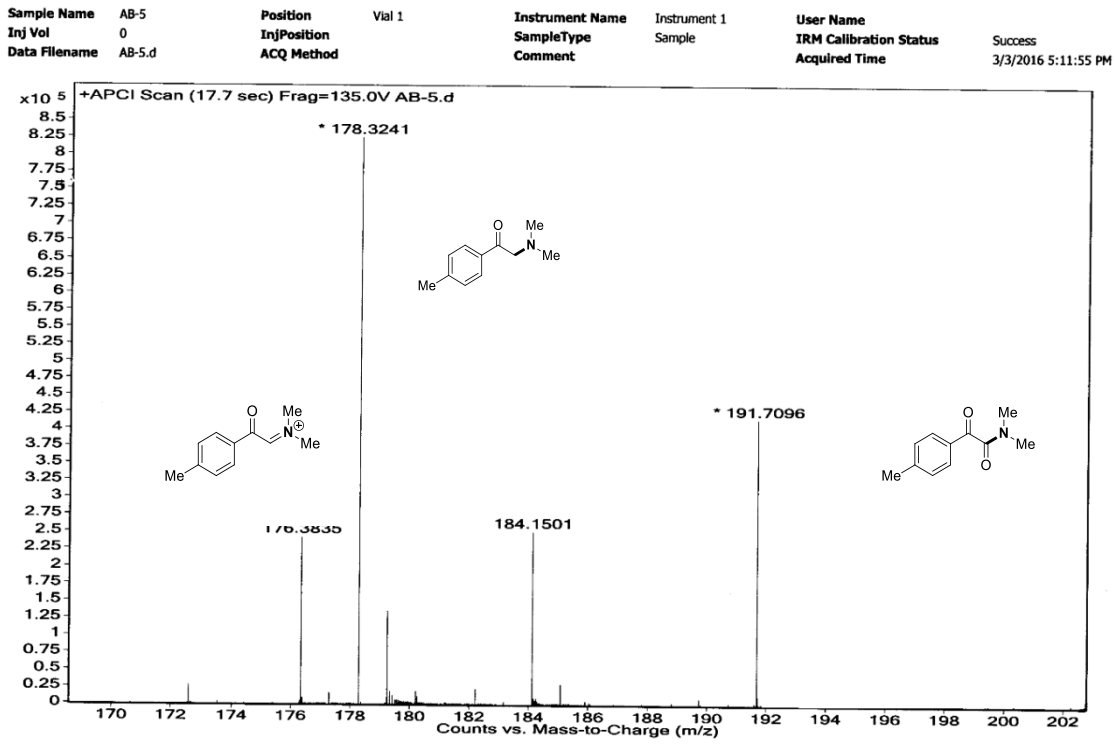
at 144.0683 and 160.1340 correspond to IO^- and IO_2^- species, respectively as shown below.

Mass spectra of quarter-ion of intermediates (I) and (II):



IV.4.3.6. Experimental procedure for the intermediate study: An oven-dried round bottom flask was charged with 4′-methyl acetophenone (**b**) (67 mg, 0.5 mmol), $^nBu_4NI$ (20mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL), TBHP (70 wt% in H_2O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^oC. Then small quantities of reaction mixtures were collected in different time intervals such as 5, 10, 15, 20, 30, 45 minutes. Those collecting reaction mixtures are quenched with saturated $Na_2S_2O_3$ solution and extracted with ethyl acetate. From those organic layers, small amount of the worked up reaction mixtures was taken in different vials and diluted with HPLC grade CH_3CN as appropriate for mass samples. Then those diluted mass samples are filtered through mass filter having pore size 0.2 µm. Then the filtered mass samples are recorded in mass machine.

Mass spectra of intermediates (C) and (D):



IV.5. References

(1) (a) C.-J. Li, *Acc. Chem. Res*., 2009, **42**, 335; (b) S. A. Girard, T. Knauberand and C.-J. Li, *Angew. Chem., Int. Ed*., 2014, **53**, 74; (c) J. A. Ashenhurst, *Chem. Soc. Rev*., 2010, **39**, 540; (d) C. J. Scheuermann, *Chem. Asian J*., 2010, **5**, 436; (e) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem*., 2013, 5769; (f) X.-F. Wu, J.-L. Gong and X. Qi, *Org. Biomol. Chem*., 2014, ***12***, 5807; (g) Y. Wu, J. Wang, F. Mao and F. Y. Kwong, *Chem. Asian J*., 2014, **9**, 26; (h) G. Majji, S. Guin, S. K. Rout, A. Behera and B. K. Patel, *Chem. Commun*., 2014, **50**, 12193; (i) S. Rajamanickam, G. Majji, S. K. Santra and B. K. Patel, *Org. Lett.*, 2015, **17**, 5586; (j) X. Zhu and S. Chiba, *Chem. Soc. Rev*., 2016, **45**, 4504; (k) I. B. Krylov, V. A. Vil and A. O. Trent'ev, *Beilstein J. Org. Chem.*, 2015, **11**, 92; (l) C. Liu, D. Liu and A. Lei, *Acc. Chem. Res*., 2014, **47**, 3459; (m) C. Zhang, C. Tanga and N. Jiao, *Chem. Soc. Rev*., 2012, **41**, 3464; (n) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev*. 2007, **107**, 5318.

(2) (a) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem*., 2006, **4**, 2337; (b) A. Sood and R. Panchagnula, *Chem. Rev*., 2001, **101**, 3275; (c) T. Cupido, J. T. Puche, J. Spengler and F. Albericio, *Curr. Opin. Drug Discovery Dev*., 2007, **10**, 768; (d) M. A. Mintzer and E. E. Simanek, *Chem. Rev*., 2009, **109**, 259; (e) S. Guha, V. Rajeshkumar, S. Kotha Surya and G. Sekar, *Org. Lett*., **2015**, 17, 406.

(3) (a) B. Qin, X. Liu, J. Shi, K. Zheng, H. Zhao and X. Feng, *J. Org. Chem.*, 2007, **72**, 2374; (b) A. K. Padala, N. Mupparapu, D. Singh, R. A. Vishwakarma and Q. N. Ahmed, *Eur. J. Org. Chem.*, 2015, **16**, 3577.

(4) (a) W.-P. Mai, H.-H. Wang, Z.-C. Li, J.-W. Yuan, Y.-M. Xiao, L.-R. Yang, P. Mao and L.-B. Qu, *Chem. Commun*., 2012, **48**, 10117; (b) M. Zhou and Q. Song, *Synthesis*, 2014, **46**, 1853; (c) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, *J. Org. Chem*., 2012, **77**, 7157; (d) M. Lamani and K. R. Prabhu, *Chem. -Eur. J*., 2012, **18**, 14638; (e) X. Zhang and L. Wang, *Green Chem*., 2012, **14**, 2141; (f) J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, *Org. Biomol. Chem*., 2012, **10**, 9237; (g) F. T. Duand, J.-X. Ji, *Chem. Sci*., 2012, **3**, 460; (h) Z. J. Liu, J. Zhang, S. L. Chen, E. Shi, Y. Xu and B. Wan, *Angew. Chem., Int. Ed*., 2012, **51**, 3231; (i) L. Chen, E. Shi, Z. J. Liu, S. L. Chen, W. Wei, H. Li, K. Xu and X. B. Wan, *Chem.-Eur. J*., 2011, **17**, 4085; (j) W. Wei, C. Zhang, Y. Xu and X. B. Wan, *Chem. Commun*., 2011, **47**, 10827; (k) X. Zhang, M. Wang, P. Li and L. Wang, *Chem. Commun.*, 2014, **50**, 8006; (l) G. Majji, S. Guin, A. Gogoi, S. K. Rout and B. K. Patel, *Chem. Commun.*, 2013, **49**, 3031; (m) S. Nekkanti, K. Veeramani, N. P. Kumar and N. Shankaraiah, *Green Chem.*, 2016, **18**, 3439; (n) S. Liu, Q. Gao, X. Wu, J. Zhang, K. Ding and A. Wu, *Org. Biomol. Chem*., 2015, **13**, 2239; (o) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett*., 2014, **16**, 2888; (p) N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmedand and R. A. Vishwakarma, *Org. Lett*., 2014, **16**, 1152.

(5) (a) T. D. Ocain and D. H. Rich, *J. Med. Chem*., 1992, **35**, 451; (b) T. Jenuwein and C. D. Allis, *Science*, 2001, **293**, 1074; (c) D. A. Six, E. Barbayianni, V. Loukas, V. Constantinou-Kototou, D. Hadjipavlou-Litina, D. Stephens, A. C. Wong, V. Magrioti, P. Moutevelis-Minakakis, F. S. Baker, E. A. Dennis and G. Kokotos, *J. Med. Chem*., 2007, **50**, 4222; (d) G. Kokotos, D. A. Six, V. Loukas, M. Smith, V. C. Kokotou, D. Hadjipavlou-Litina, S. Kotsovolou, A. Chiou, C. C. Beltzner and E. A.

Dennis, *J. Med. Chem*., 2004, **47**, 3615; (e) H. H. Wasserman and A. K. Petersen, *J. Org. Chem*., 1997, **62**, 8972; (f) Z. Li, A. C. Ortega-Vilain, G. S. Patil, D. L. Chu, J. E. Foreman, D. D. Eveleth and J. C. Powers, *J. Med. Chem*., 1996, **39**, 4089; (g) Y. Shirasaki, H. Miyashita and M. Yamaguchi, *Bioorgan. Med. Chem*., 2006, **14**, 5691.

(6) (a) R. P. Singh and J. M. Shreeve, *J. Org. Chem*., 2003, **68**, 6063; (b) G. M. Dubowchik, J. L. Ditta, M. V. Vrudhula, B. DasGupta, J. Ditta, T. Chen, S. Sheriff, K. Sipman, M. Witmer, J. Tredup, D. M. Vyas, T. A. Verdoorn, S. Bollini and A. Vinitsky, *Org. Lett*., 2001, **3**, 3987; (c) R. Hua, H. Takeda, Y. Abe and M. Tanaka, *J. Org. Chem*., 2004, **69**, 974; (d) C. Jian-Xin and F. C. Robert, *J. Org. Chem*., 2004, **69**, 5509; (e) A. Chiou, T. Markidis, V. C. Kokotou, R. Verger and G. Kokotos, *Org. Lett*., 2000, **2**, 347.

(7) (a) D. Shanmugapriya, R. Shankar, G. Satyanarayana, V. H. Dahanukar, U. K. Syam Kumar and N. Vembu, *Synlett*, 2008, 2945; (b) S. Dutta, S. S. Kotha and G. Sekar, *RSC Adv*., 2015, **5**, 47265.

(8) (a) J. E. Semple, T. D. Owens, K. Nguyen and O. E. Levy, *Org. Lett*., 2000, **2**, 2769; (b) L. Banfi, G. Guanti and R. Riva, *Chem. Commun*., 2000, 985; (c) L. El. Kaim, R. Gamez-Montano, L. Grimaud and T. Ibarra-Rivera, *Chem. Commun*., 2008, 1350.

(9) (a) T. Zhou and Z. C. Chen, *J. Chem. Res*., 2001, 116; (b) J. Liu, R. Zhang, S. Wang, W. Sun and C. Xia, *Org. Lett.*, 2009, **11**, 1321; (c) M. Iizuka and Y. Kondo, *Chem. Commun*., 2006, 1739; (d) E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald and K. F. Jensen, *Angew. Chem., Int. Ed*., 2007, **46**, 1734; (e) T. Fukuyama, S. Nishitani, T. Inouye, K. Morimoto and I. Ryu, *Org. Lett*., 2006, **8**, 1383.

(10) (a) Z. F. Al-Rashid, L. J. Whitney, P. H. Richard, W. Yonggang, Y. Peiyuan, L. Renhei and Z. Kang, *J. Org. Chem*., 2008, **73**, 8780; (b) D. Kumar, S. R. Vemula and G. R. Cook, *ACS Catal*., 2016, **6**, 4920.

(11) C. Zhang and N. Jiao, *J. Am. Chem. Soc*., 2010, **132**, 28.

(12) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem*., 2011, **123**, 11284.

(13) (a) C. Zhang, X. Zong, L. Zhang, and N. Jiao, *Org. Lett*., 2012, **14**, 3280; (b) X. Zhang, W. Yanga and L. Wang, *Org. Biomol. Chem*., 2013, **11**, 3649.

(14) (a) D. Li, M. Wang, J. Liu, Q. Zhaoa and L. Wang, *Chem. Commun*., 2013, **49**, 3640; (b) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Biomol. Chem*., 2013, **11**, 4573.

(15) (a) B. Du, B. Jin and P. Sun, *Org. Biomol. Chem*., 2014, **12**, 4586; (b) W. Fan, D. Shi and B. Feng, *Tetrahedron Lett*., 2015, **56**, 4638.

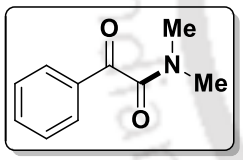
(16) L. Zhang, J. Pu, J. Ren, Z. Li, H. Xiang and X. Zhou, *Synthetic Commun*., 2015, **45**, 1848.

(17) H. Batchu and S. Batra, *Eur. J. Org. Chem.*, 2012, 2935.

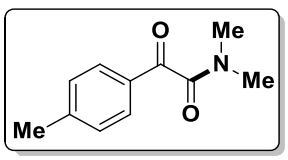
(18) L. Ma, X. Wang, W. Yu and B. Han, *Chem. Commun*., 2011, **47**, 11333; (b) Y. Siddaraju and K. R. Prabhu, *Org. Biomol. Chem*., 2015, **13**, 11651; (c) W. Xu and B. J. Nachtsheim, *Org. Lett*., 2015, **17**, 1585; (d) M. Uyanik, D. Suzuki, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed*., 2011, **50**, 5331; (e) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett*., 2011, **13**, 3754.

(19) S. K. Rout, S. Guin, A. Gogoi, G. Majji and B. K. Patel, *Org. Lett*., 2014, **16**, 1614; (b) N. Khatun, A. Banerjee, S. K. Santra, A. Behera and B. K. Patel, *RSC Adv*., 2014, **4**, 54532.

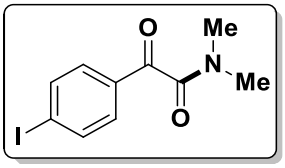
IV.6. Spectral data



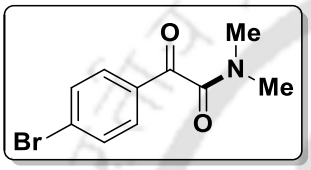
***N,N*-Dimethyl-2-oxo-2-phenylacetamide (1a):** Reddish gummy (63.7 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.95 (s, 3H), 3.11 (s, 3H), 7.48–7.52 (m, 2H), 7.61–7.65 (m, 1H), 7.92–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 34.0, 37.1, 129.1, 129.6, 132.9, 134.8, 167.1, 191.9; IR (KBr): 2937, 2814, 1679, 1647, 1597, 1511, 1408, 1247, 1146, 996, 726, 692, 642, 462 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{11}NO_2$ $[M+H]^+$ 178.0863; found 178.0858.



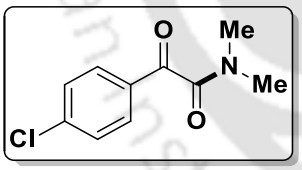
***N,N*-Dimethyl-2-oxo-2-(*p*-tolyl)acetamide (1b):** Brownish gummy (74.5 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 2.95 (s, 3H), 3.11 (s, 3H), 7.31 (d, 2H, J = 8.0 Hz), 7.83 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.1, 34.2, 37.3, 129.9, 130.0, 130.8, 146.2, 167.4, 191.7; IR (KBr): 2924, 2855, 1718, 1645, 1607, 1456, 1406, 1251, 1146, 998, 756, 618, 474 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1019; found 192.1027.



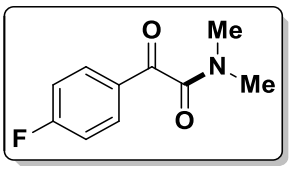
2-(4-Iodophenyl)-*N*,*N*-dimethyl-2-oxoacetamide (1c): Brownish gummy (106 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.95 (s, 3H), 3.11 (s, 3H), 7.65 (dd, 2H, J = 8.4 Hz), 7.88 (dd, 2H, J = 8.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.3, 37.3, 103.5, 131.0, 132.6, 138.6, 166.6, 191.1; IR (KBr): 2927, 2851, 1681, 1646, 1581, 1394, 1248, 1146, 1051, 994, 882, 760, 646, 466 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}INO_2$ $[M+H]^+$ 303.9829; found 303.9831.



2-(4-Bromophenyl)-*N*,*N*-dimethyl-2-oxoacetamide (1d): Brownish gummy (82.9 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.96 (s, 3H), 3.11 (s, 3H), 7.65 (d, 2H, J = 8.8 Hz), 7.81 (d, 2H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.3, 37.3, 130.4, 131.3, 132.1, 132.6, 166.7, 190.7; IR (KBr): 2926, 2851, 1682, 1648, 1585, 1399, 1247, 1146, 1069, 994, 883, 765, 646, 473 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}BrNO_2$ $[M+H]^+$ 255.9968; found 255.9972.

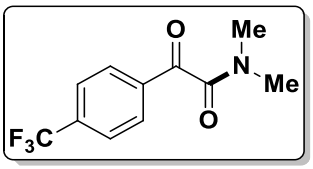


2-(4-Chlorophenyl)-*N*,*N*-dimethyl-2-oxoacetamide (1e): Brownish gummy (62.2 mg, 59% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.96 (s, 3H), 3.12 (s, 3H), 7.49 (d, 2H, J = 7.8 Hz), 7.89 (d, 2H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.3, 37.3, 129.6, 131.3, 131.7, 141.6, 166.7, 190.5; IR (KBr): 2925, 2855, 1682, 1649, 1589, 1401, 1248, 1147, 1089, 995, 846, 768, 691, 472 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}ClNO_2$ $[M+H]^+$ 212.0473; found 212.0469.

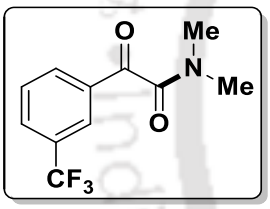


2-(4-Fluorophenyl)-*N*,*N*-dimethyl-2-oxoacetamide (1f): Brownish gummy (52.7 mg, 54% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.97 (s, 3H), 3.11 (s, 3H), 7.16–7.20 (m, 2H), 7.97–8.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.3, 37.3, 116.6 (d, J = 22.2 Hz), 129.8, 132.7 (d, J = 9.6 Hz), 166.0,

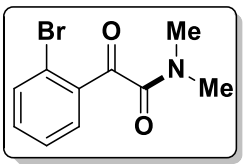
166.9, 167.8, 190.2; IR (KBr): 2926, 2855, 1681, 1645, 1598, 1409, 1239, 1146, 996, 853, 773, 612, 506 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}FNO_2$ $[M+H]^+$ 196.0768; found 196.0764.



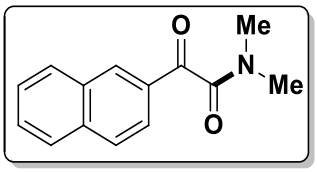
***N,N*-Dimethyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide (1g):** Yellowish gummy (58.8 mg, 48% yield); ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.98 (s, 3H), 3.14 (s, 3H), 7.78 (d, 2H, *J* = 7.2 Hz), 8.08 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.4, 37.3, 124.5, 126.2 (q, *J*= 3.6 Hz), 130.3, 130.6, 135.8, 136.0 (d, *J* = 7.8 Hz), 166.3, 190.4; IR (KBr): 2937, 2867, 1690, 1652, 1409, 1326, 1246, 1131, 1066, 996, 857, 715, 647, 592 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{10}F_3NO_2$ $[M+H]^+$ 246.0736; found 246.0733.



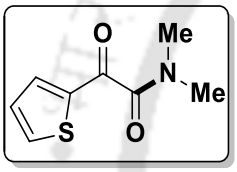
***N,N*-Dimethyl-2-oxo-2-(3-(trifluoromethyl)phenyl)acetamide (1i):** Light yellow liquid (77.2 mg, 63% yield); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.99 (s, 3H), 3.14 (s, 3H), 7.66 (t, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 8.14 (d, 1H, *J* = 7.6 Hz), 8.22 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.4, 37.3, 126.6 (q, *J* = 3.4 Hz), 129.2, 129.9, 130.6, 131.2 (t, *J* = 3.6 Hz), 133.2, 134.0, 166.2, 190.1; IR (KBr): 2932, 2855, 1688, 1650, 1407, 1332, 1238, 1131, 1073, 922, 760, 698, 544 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{10}F_3NO_2$ $[M+H]^+$ 246.0736; found 246.0745.



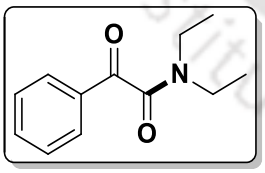
2-(2-Bromophenyl)-*N,N*-dimethyl-2-oxoacetamide (1j): Yellow liquid (66.3 mg, 52% yield); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.08 (s, 3H), 3.09 (s, 3H), 7.42–7.44 (m, 1H), 7.62–7.65 (m, 2H), 7.81–7.83 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.9, 37.5, 121.8, 127.9, 132.9, 134.3, 134.4, 135.6, 166.6, 191.1; IR (KBr): 2931, 2859, 1731, 1681, 2651, 1587, 1434, 1406, 1283, 1154, 1028, 992, 881, 747, 632, 494 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{10}BrNO_2$ $[M+H]^+$ 255.9968; found 255.9972.



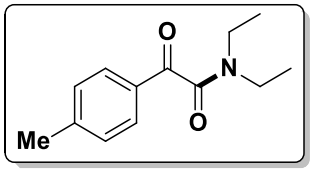
***N,N*-Dimethyl-2-(naphthalen-2-yl)-2-oxoacetamide (1k):** Brownish gummy (94.2 mg, 83% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.00 (s, 3H), 3.18 (s, 3H), 7.58 (t, 1H, *J* = 7.2 Hz), 7.65 (t, 1H, *J* = 6.6 Hz), 7.90 (d, 1H, *J* = 8.4 Hz), 7.94–7.98 (m, 2H), 8.03 (d, 1H, *J* = 8.4 Hz), 8.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.3, 37.4, 123.9, 127.3, 128.2, 129.3, 129.6, 130.1, 130.6, 132.7, 133.2, 136.6, 167.4, 192.1; IR (KBr): 2924, 2855, 1673, 1644, 1464, 1405, 1282, 1116, 997, 824, 781, 475 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}NO_2$ $[M+H]^+$ 228.1019; found 228.1012.



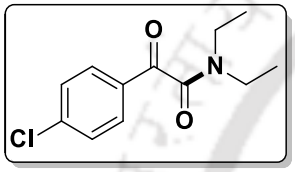
***N,N*-Dimethyl-2-oxo-2-(thiophen-2-yl)acetamide (1l):** Brownish gummy (64.9 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.04 (s, 3H), 3.10 (s, 3H), 7.17–7.19 (m, 1H), 7.78–7.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.7, 37.6, 126.9, 129.0, 136.4, 136.6, 166.1, 183.7; IR (KBr): 2926, 2855, 1673, 1649, 1521, 1408, 1253, 1145, 1055, 844, 736, 642, 560 cm^{-1}; HRMS (ESI): calcd. for $C_8H_9NO_2S$ $[M+H]^+$ 184.0427; found 184.0422.



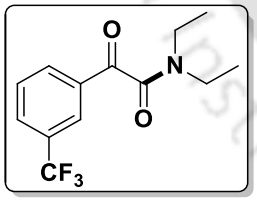
***N,N*-Diethyl-2-oxo-2-phenylacetamide (2a):** Reddish gummy (69.7 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15 (t, 3H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 3.24 (q, 2H, *J* = 7.2 Hz), 3.56 (q, 2H, *J* = 7.2 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.94 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.1, 14.3, 39.0, 42.3, 129.2, 129.8, 133.4, 134.8, 166.9, 191.8; IR (KBr) 2977, 2932, 1679, 1638, 1447, 1231, 1145, 1021, 720, 687, 631 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{15}NO_2$ $[M+H]^+$ 206.1176; found 206.1182.



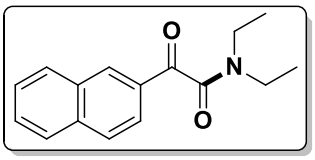
***N,N*-Diethyl-2-oxo-2-(*p*-tolyl)acetamide (2b):** Reddish gummy (64.6 mg, 59% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.13 (t, 3H, *J* = 7.2 Hz), 1.27 (t, 3H, *J* = 7.2 Hz), 2.42 (s, 3H), 3.22 (q, 2H, *J* = 7.2 Hz), 3.54 (q, 2H, *J* = 7.2 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.82 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.0, 14.3, 22.1, 38.9, 42.3, 129.8, 131.0, 146.0, 167.1, 191.5; IR (KBr) 2978, 2937, 1679, 1641, 1448, 1300, 1236, 1145, 1027, 754, 611, 480 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{17}NO_2$ $[M+H]^+$ 220.1332; found 220.1329.



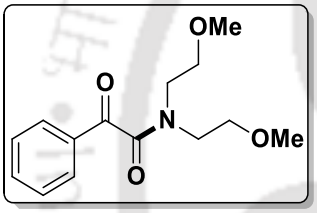
2-(4-Chlorophenyl)-*N,N*-diethyl-2-oxoacetamide (2e): Reddish gummy (88.4 mg, 74% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.16 (t, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 3.24 (q, 2H, *J* = 7.2 Hz), 3.55 (q, 2H, *J* = 7.2 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.0, 14.4, 39.1, 42.3, 129.6, 131.2, 131.9, 141.4, 166.4, 190.4; IR (KBr) 2978, 2934, 1680, 1641, 1447, 1231, 1145, 1089, 1013, 836, 764, 687, 548 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{14}ClNO_2$ $[M+H]^+$ 240.0786; found 240.0788.



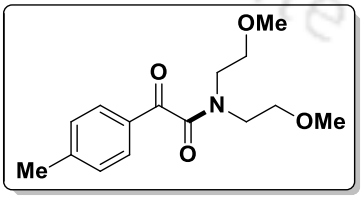
***N,N*-Diethyl-2-oxo-2-(3-(trifluoromethyl)phenyl)acetamide (2i):** Brownish gummy (110.6 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (t, 3H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 3.6 Hz), 3.26 (q, 2H, *J* = 7.2 Hz), 3.58 (q, 2H, *J* = 7.6 Hz), 7.66 (t, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 8.22 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.0, 14.4, 39.3, 42.4, 124.6, 126.5 (q, *J* = 3.6 Hz), 129.9, 131.1 (q, *J* = 2.8 Hz), 131.8, 132.1 (d, *J* = 6.1 Hz), 133.1, 134.1, 166.0, 190.0; IR (KBr) 2927, 2855, 1688, 1642, 1443, 1333, 1216, 1171, 1073, 756, 695, 636 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{14}F_3NO_2$ $[M+H]^+$ 274.1049; found 274.1050.



***N,N*-Diethyl-2-(naphthalen-2-yl)-2-oxoacetamide (2k):** Reddish gummy (89.3 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (t, 3H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz), 3.28 (q, 2H, *J* = 7.2 Hz), 3.62 (q, 2H, *J* = 7.2 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.94 (t, 2H, *J* = 10.8 Hz), 8.02 (d, 1H, *J* = 8.8 Hz), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.1, 14.4, 39.1, 42.4, 124.0, 127.3, 128.2, 129.2, 129.5, 130.1, 130.8, 132.6, 133.0, 136.5, 167.0, 191.9; IR (KBr) 2977, 2934, 1674, 1639, 1460, 1359, 1257, 1218, 1190, 869, 651, 475 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1332; found 256.1333.

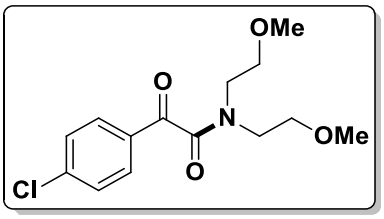


***N,N*-Bis(2-methoxyethyl)-2-oxo-2-phenylacetamide (3a):** Yellowish gummy (99.4 mg, 75% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.11 (s, 3H), 3.38 (s, 3H), 3.43 (t, 2H, *J* = 5.4 Hz), 3.52 (t, 2H, *J* = 5.4 Hz), 3.65 (t, 2H, *J* = 5.4 Hz), 3.77 (t, 2H, *J* = 5.4 Hz), 7.46 (t, 2H, *J* = 7.8 Hz), 7.59 (t, 1H, *J* = 7.8 Hz), 7.94 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 45.4, 48.4, 58.7, 59.0, 70.6, 70.7, 128.8, 130.1, 133.6, 134.5, 167.9, 191.2; IR (KBr) 2927, 2892, 1679, 1640, 1448, 1256, 1190, 1118, 1012, 967, 722 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{19}NO_4$ $[M+H]^+$ 266.1387; found 266.1395.

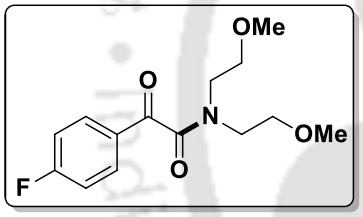


***N,N*-Bis(2-methoxyethyl)-2-oxo-2-(*p*-tolyl)acetamide (3b):** Yellowish gummy (83.9 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H), 3.17 (s, 3H), 3.40 (s, 3H), 3.45 (t, 2H, *J* = 5.2 Hz), 3.52 (t, 2H, *J* = 5.2 Hz), 3.67 (t, 2H, *J* = 5.6 Hz), 3.79 (t, 2H, *J* = 5.2 Hz), 7.29 (d, 2H, *J* = 8.0Hz), 7.85 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 45.4, 48.4, 57.9, 58.8, 70.6, 70.9, 129.7, 130.2, 131.2, 145.8, 168.1, 191.1; IR (KBr) 2926, 2855, 1674, 1642, 1448, 1296, 1179, 1118, 1012, 967, 833, 755, 613, 480 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{21}NO_4$ $[M+H]^+$ 280.1543; found

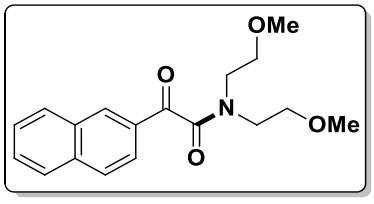
280.1552.



2-(4-Chlorophenyl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (3e): Yellowish gummy (112.2 mg, 75% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.08 (s, 3H), 3.38 (s, 3H), 3.41 (t, 2H, *J* = 5.4 Hz), 3.55 (t, 2H, *J* = 5.4 Hz), 3.64 (t, 2H, *J* = 5.4 Hz), 3.75 (t, 2H, *J* = 5.4 Hz), 7.44 (d, 2H, *J* = 8.4 Hz), 7.89 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 45.5, 48.5, 58.6, 59.1, 70.4, 70.6, 129.1, 131.5, 132.2, 140.9, 167.4, 189.6; IR (KBr) 2931, 2891, 1680, 1641, 1487, 1400, 1255, 1192, 1118, 1012, 968, 769, 690, 544, 483 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{18}ClNO_4$ $[M+H]^+$ 300.0997; found 300.0999.

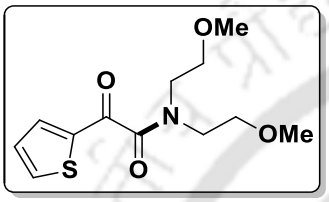


2-(4-Fluorophenyl)-*N*,*N*-bis(2-methoxyethyl)-2-oxoacetamide (3f): Yellowish gummy (111.8 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.11 (s, 3H), 3.39 (s, 3H), 3.43 (t, 2H, *J* = 5.6 Hz), 3.56 (t, 2H, *J* = 5.2 Hz), 3.65 (t, 2H, *J* = 5.2 Hz), 3.77 (t, 2H, *J* = 5.2 Hz), 7.13–7.17 (m, 2H), 7.98–8.01 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 45.5, 48.5, 58.7, 59.1, 70.5, 70.7, 114.3, 116.1 (d, *J* = 21.9 Hz), 130.3, 133.0 (d, *J* = 9.4 Hz), 165.7, 167.5 (d, *J* = 30.3 Hz), 189.5; IR (KBr) 2926, 2856, 1680, 1642, 1460, 1232, 1119, 1011, 968, 852, 744, 611, 569, 506 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{18}FNO_4$ $[M+H]^+$ 284.1293; found 284.1301.

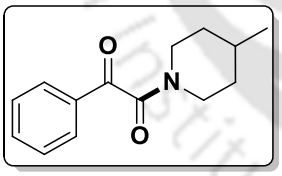


***N*,*N*-Bis(2-methoxyethyl)-2-(naphthalen-2-yl)-2-oxoacetamide (3k):** Reddish gummy (113.4 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.12 (s, 3H), 3.45 (s, 3H), 3.48 (d, 2H, *J* = 5.6 Hz), 3.58 (t, 2H, *J* = 5.2 Hz), 3.72 (t, 2H, *J* = 5.2 Hz), 3.85 (t, 2H, *J* = 5.2 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.90 (t, 1H, *J* =

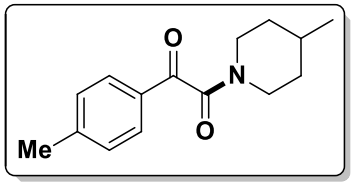
4.8 Hz), 7.95 (t, 2H, *J* = 8.0 Hz), 8.02 (d, 1H, *J* = 8.4 Hz), 8.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 45.4, 48.5, 58.8, 59.2, 70.6, 70.8, 124.3, 127.1, 128.1, 128.8, 129.4, 130.1, 131.0, 132.6, 133.4, 136.4, 168.1, 191.4; IR (KBr) 2924, 2854, 1730, 1637, 1461, 1362, 1263, 1113, 1012, 763, 476 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{21}NO_4$ $[M+H]^+$ 316.1543; found 316.1538.



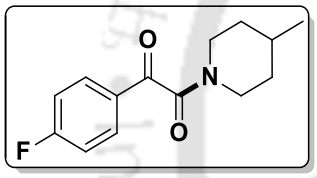
***N,N*-Bis(2-methoxyethyl)-2-oxo-2-(thiophen-2-yl)acetamide (3l):** Yellowish gummy (81.3 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.15 (s, 3H), 3.35 (s, 3H), 3.37 (s, 2H), 3.47 (t, 2H, *J* = 5.2 Hz), 3.60–3.65 (m, 2H), 3.75 (t, 2H, *J* = 5.2 Hz), 7.41–7.46 (m, 1H), 7.74 (d, 1H, *J* = 7.2 Hz), 7.81 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 45.9, 48.6, 58.8, 59.1, 70.6, 70.9, 128.6, 136.1, 136.3, 140.9, 166.8, 183.3; IR (KBr) 3098, 2926, 1739, 1640, 1409, 1255, 1117, 964, 839, 738, 635, 565 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{17}NO_4S$ $[M+H]^+$ 272.0951; found 272.0950.



1-(4-Methylpiperidin-1-yl)-2-phenylethane-1, 2-dione (4a): Yellowish gummy (100.5 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.97 (d, 3H, *J* = 6.4 Hz), 1.09–1.20 (m, 2H), 1.23–1.30 (m, 2H), 1.78–1.81 (m, 1H), 2.76–2.83 (m, 1H), 3.02–3.09 (m, 1H), 3.51–3.54 (m, 1H), 4.61–4.64 (m, 1H), 7.51 (t, 2H, *J* = 8.0 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.94 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 31.4, 33.8, 34.3, 41.7, 46.5, 129.2, 129.7, 133.4, 134.8, 165.6, 192.1; IR (KBr) 2925, 2868, 1679, 1641, 1451, 1372, 1264, 1213, 1142, 1085, 962, 859, 729, 690, 648 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{17}NO_2$ $[M+H]^+$ 232.1332; found 232.1345.



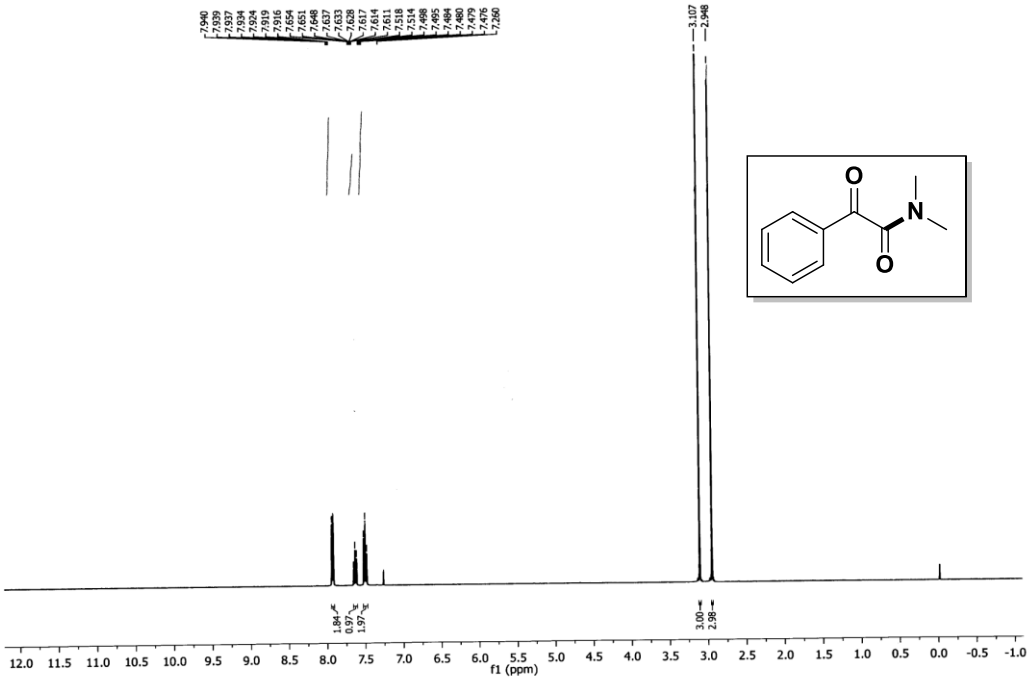
1-(4-Methylpiperidin-1-yl)-2-(*p*-tolyl)ethane-1,2-dione (4b): Yellowish gummy (88.2 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.97 (d, 3H, J = 6.4 Hz), 1.08–1.20 (m, 2H), 1.23–1.29 (m, 2H), 1.79 (d, 1H, J = 13.2 Hz), 2.43 (s, 3H), 2.75–2.79 (m, 1H), 3.04–3.08 (m, 1H), 3.51 (d, 1H, J = 13.6 Hz), 4.62 (d, 1H, J = 13.2 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.83 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.1, 31.3, 33.8, 34.5, 41.7, 46.5, 129.9, 131.1, 146.1, 165.8, 191.9; IR (KBr) 2926, 2869, 1676, 1643, 1453, 1373, 1266, 1216, 1178, 1143, 1086, 962, 865, 755, 693, 614, 480 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{19}NO_2$ $[M+H]^+$ 246.1489; found 246.1488.



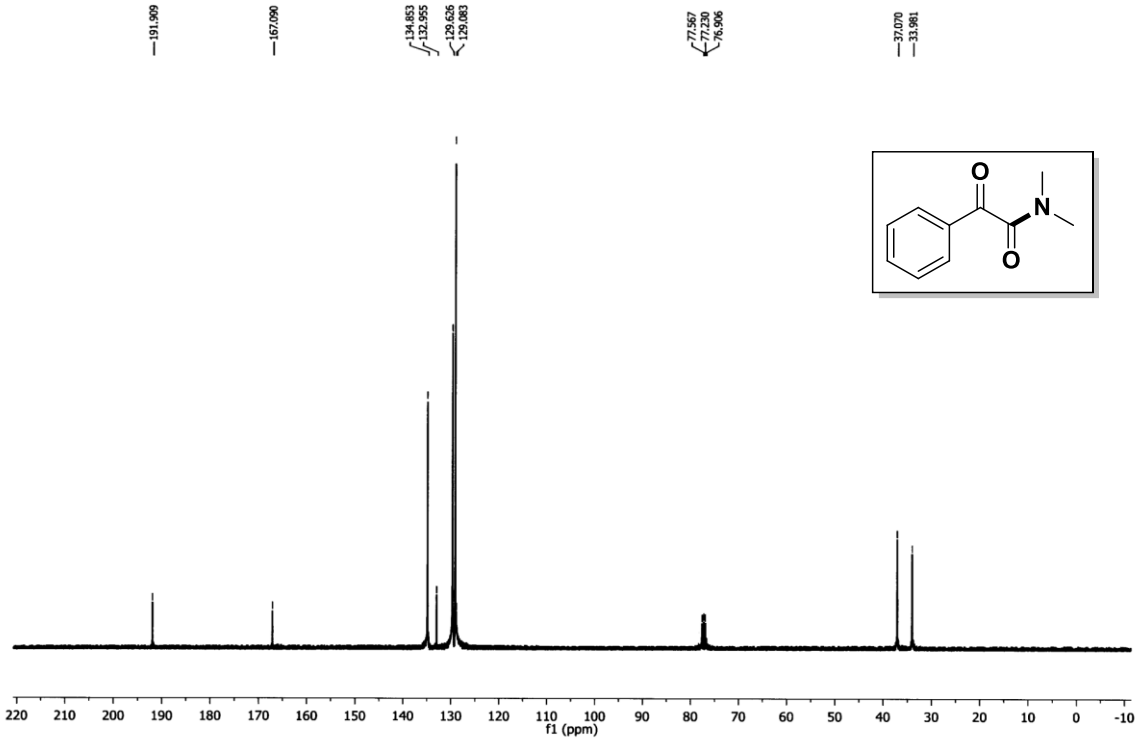
1-(4-Fluorophenyl)-2-(4-methylpiperidin-1-yl)ethane-1,2-dione (4f): Brownish gummy (100.9 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.98 (d, 3H, J = 6.4 Hz), 1.09–1.20 (m, 2H), 1.25 (t, 2H, J = 15.2 Hz), 1.80 (d, 1H, J = 13.2 Hz), 2.76–2.83 (m, 1H), 3.06–3.09 (m, 1H), 3.52 (d, 1H, J = 13.6 Hz), 4.61 (d, 1H, J = 13.2 Hz), 7.18 (t, 2H, J = 8.8 Hz), 7.96–8.0 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 31.3, 33.8, 34.3, 41.8, 46.6, 116.5 (d, J = 22.2 Hz), 130.0, 132.6 (d, J = 9.7 Hz), 165.3, 166.0, 167.7, 190.4; IR (KBr) 2925, 2855, 1634, 1510, 1440, 1373, 1308, 1227, 1115, 1088, 970, 760, 577 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{16}FNO_2$ $[M+H]^+$ 250.1238; found 250.1241.

IV.7. Spectra

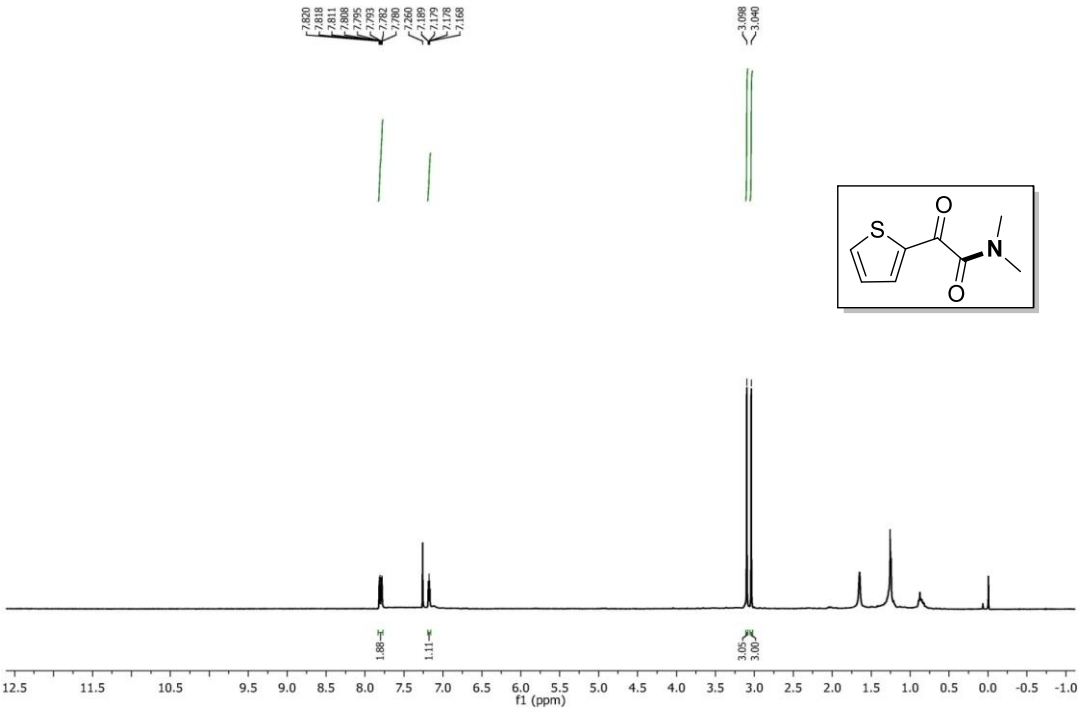
_N,N_-Dimethyl-2-oxo-2-phenylacetamide (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



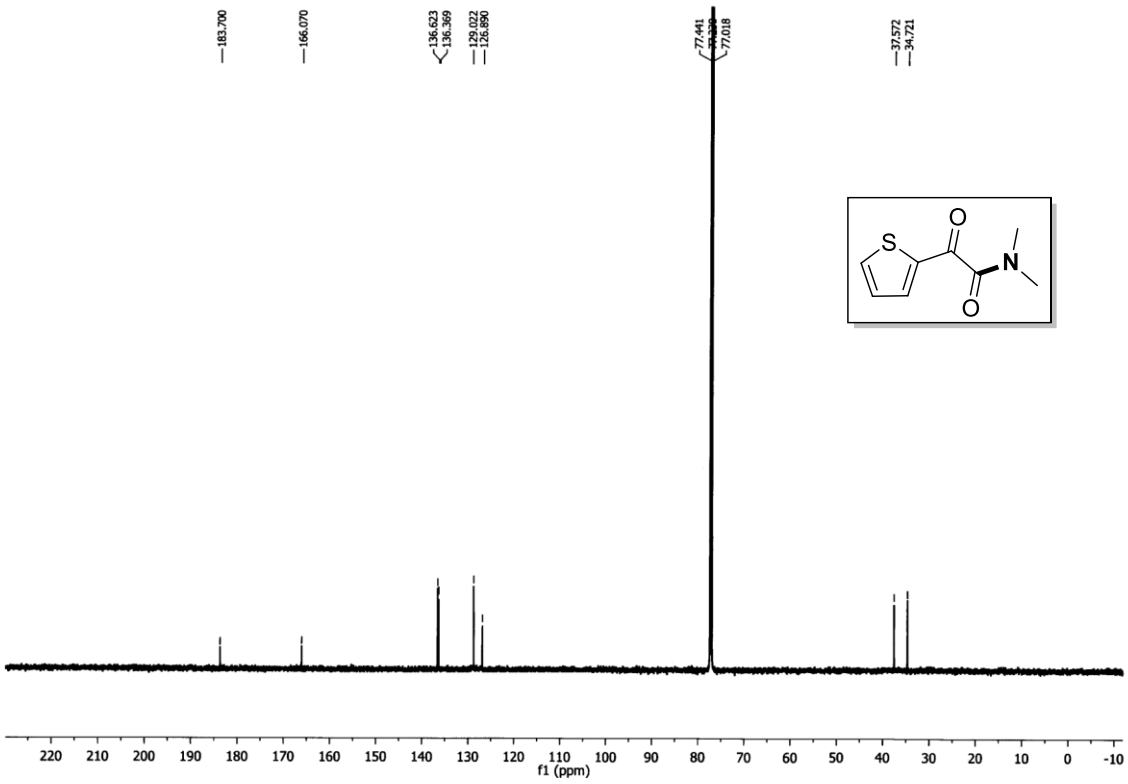
_N,N_-Dimethyl-2-oxo-2-phenylacetamide (1a): ^{13}C NMR (100 MHz, $CDCl_3$)



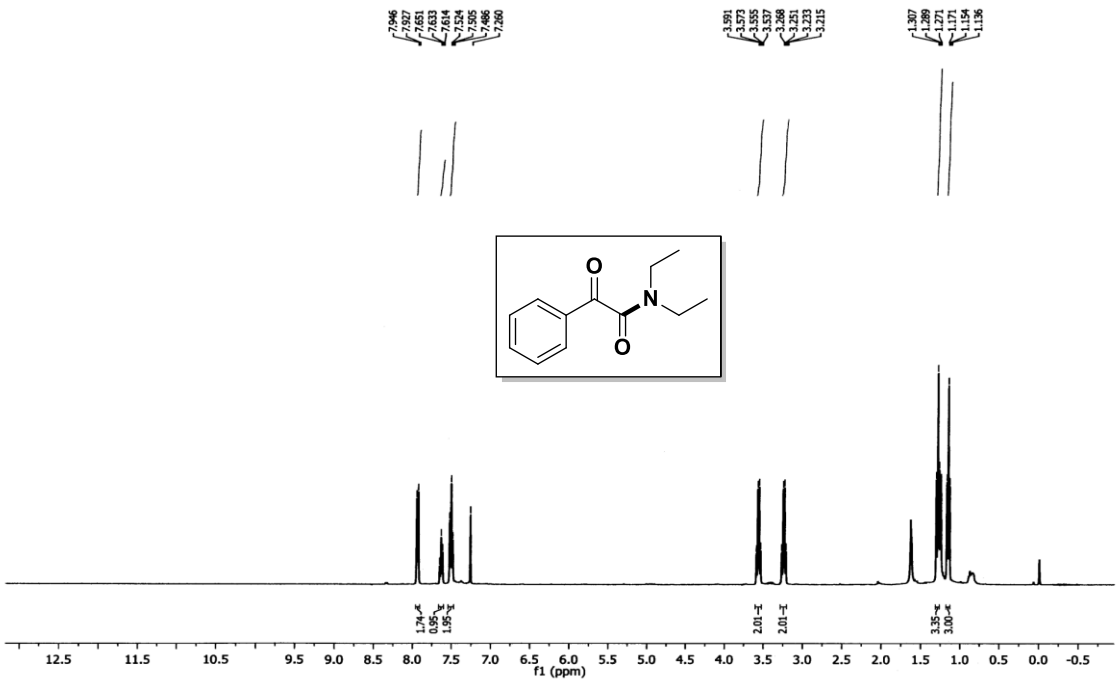
_N,N_-Dimethyl-2-oxo-2-(thiophen-2-yl)acetamide (1l): ^{1}H NMR (400 MHz, $CDCl_3$)



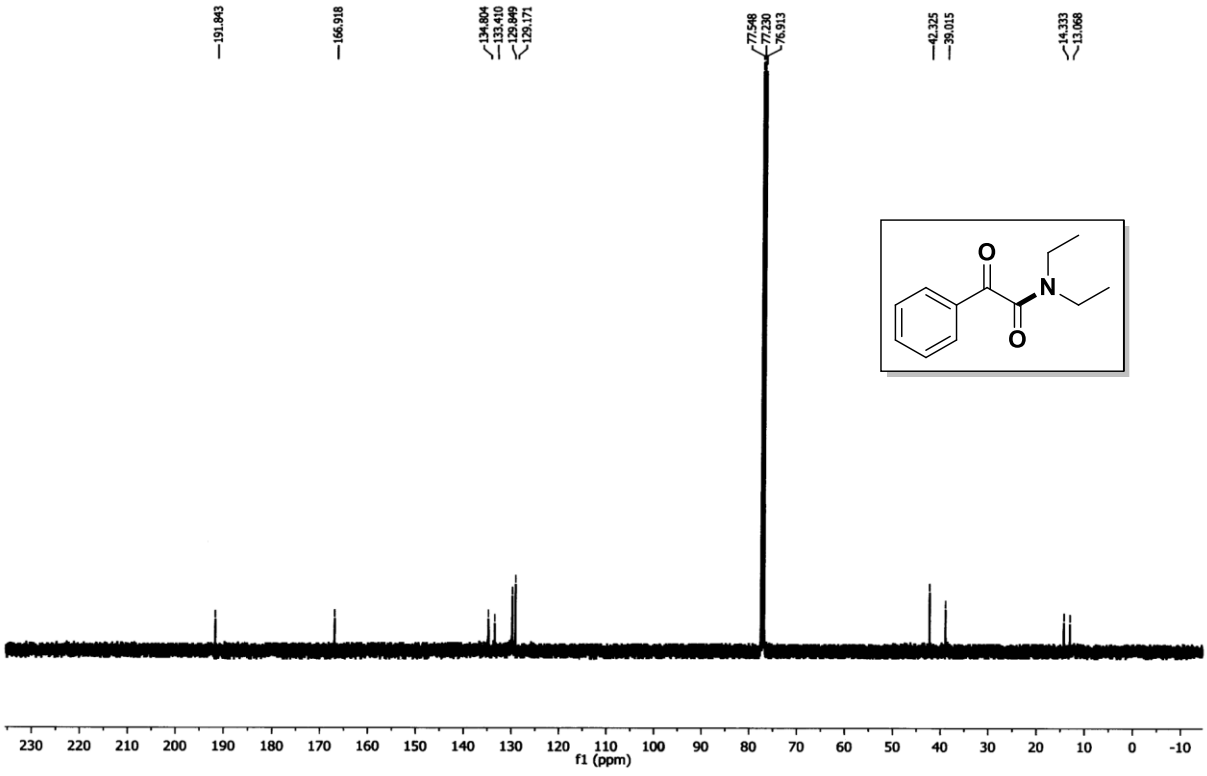
_N,N_-Dimethyl-2-oxo-2-(thiophen-2-yl)acetamide (1l): ^{13}C NMR (150 MHz, $CDCl_3$)



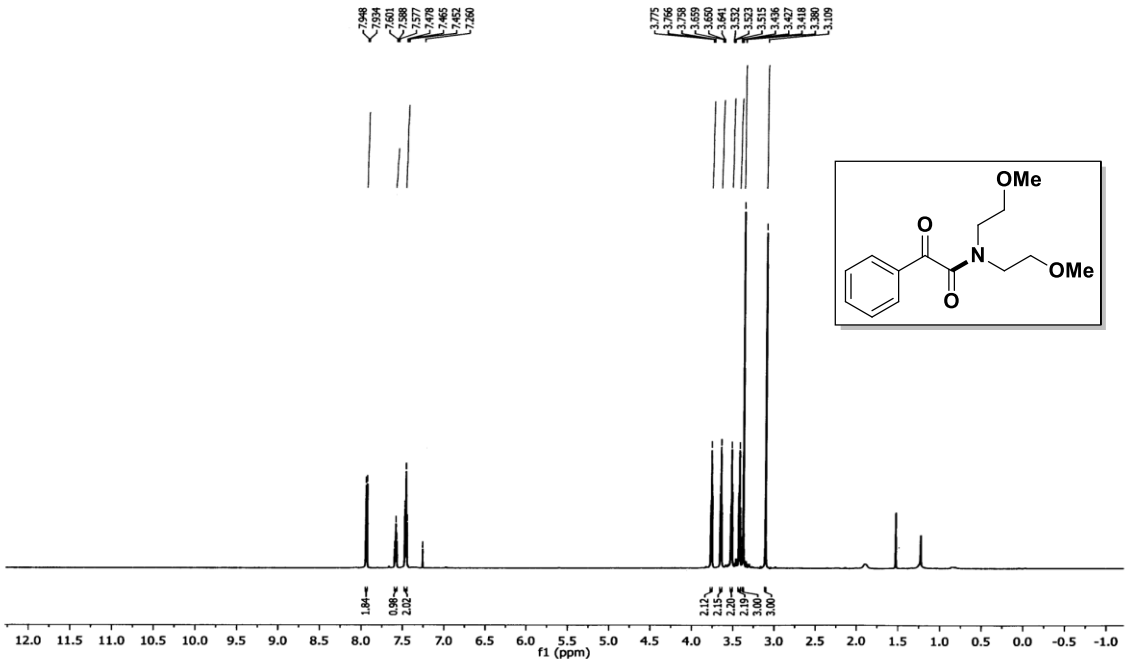
_N,N_-Diethyl-2-oxo-2-phenylacetamide (2a): ^{1}H NMR (400 MHz, $CDCl_3$)



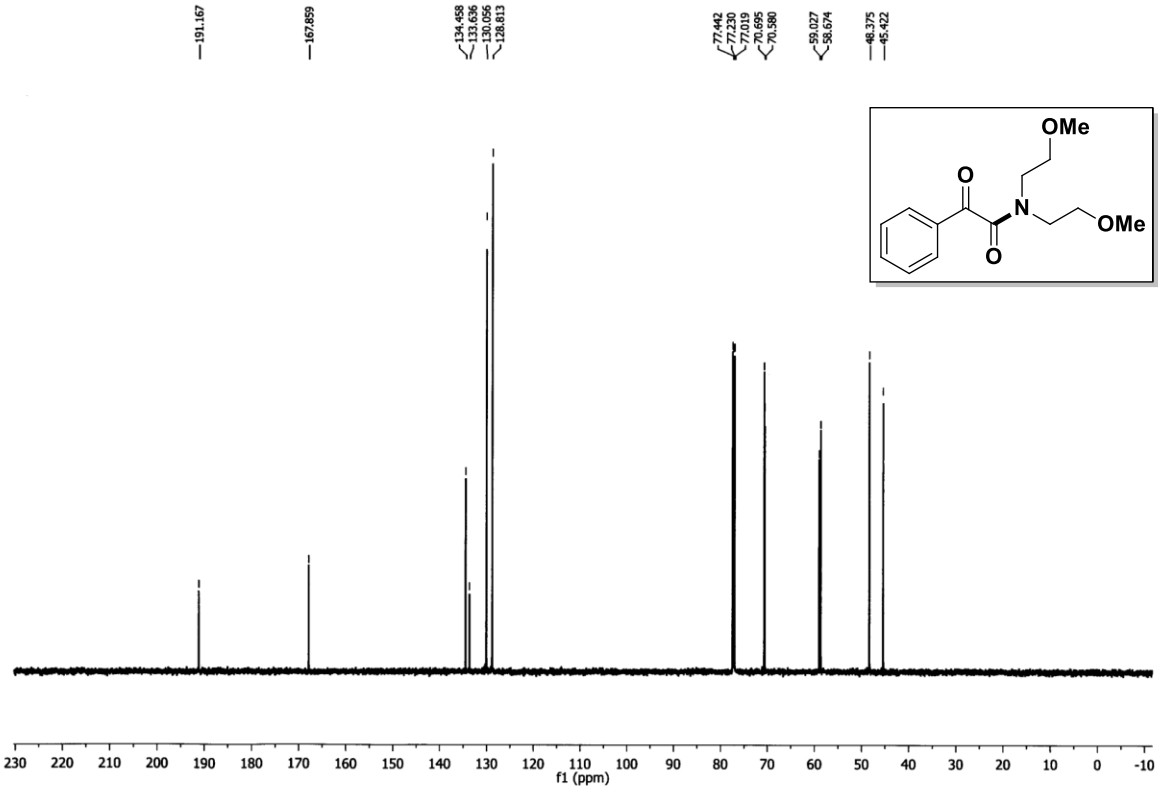
_N,N_-Diethyl-2-oxo-2-phenylacetamide (2a): ^{13}C NMR (100 MHz, $CDCl_3$)



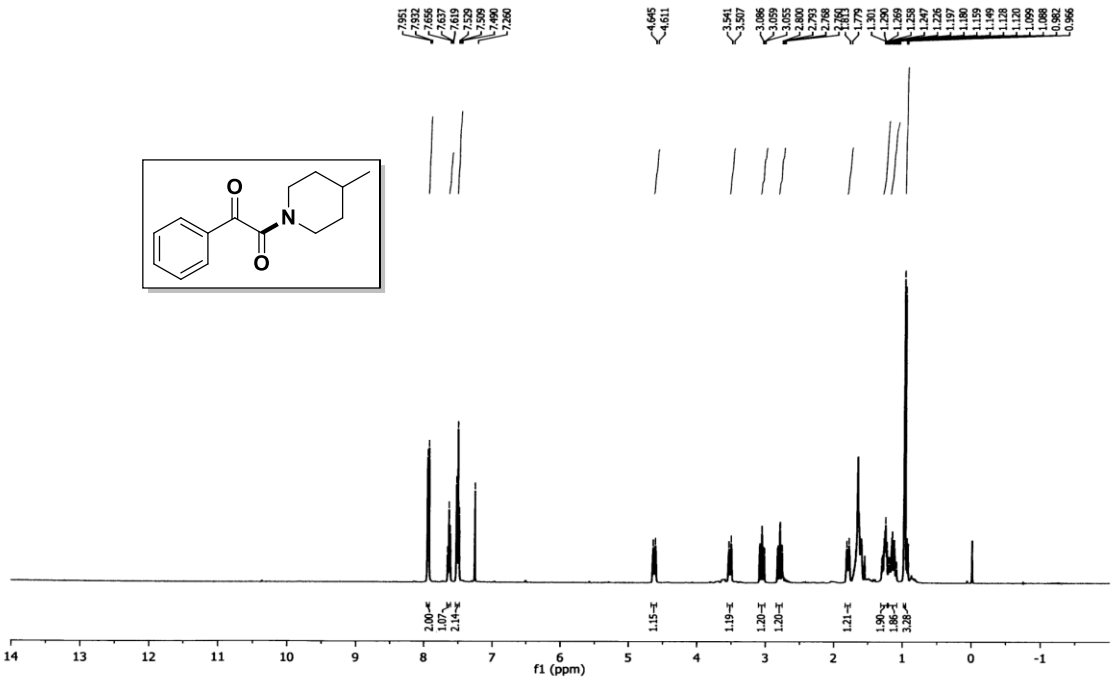
_N,N_-Bis (2-methoxyethyl)-2-oxo-2-phenylacetamide (3a): ^{1}H NMR (600 MHz, $CDCl_3$)



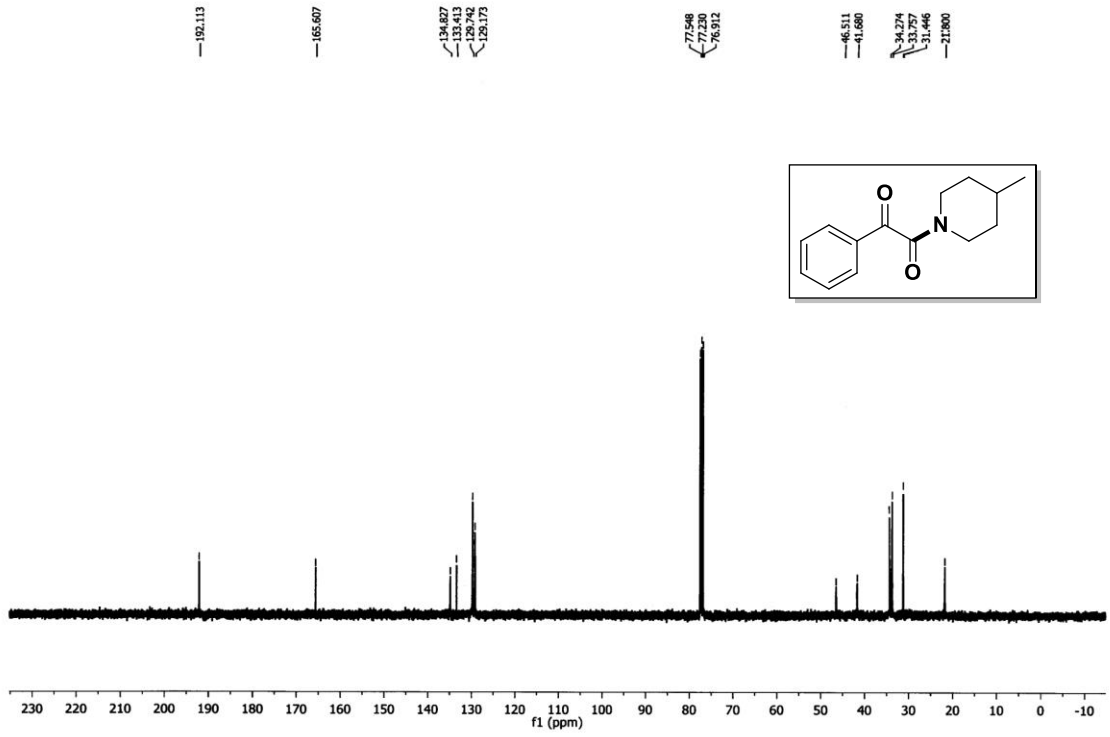
_N,N_-Bis(2-methoxyethyl)-2-oxo-2-phenylacetamide (3a): ^{13}C NMR (150 MHz, $CDCl_3$)



1-(4-Methylpiperidin-1-yl)-2-phenylethane-1, 2-dione (4a): ^{1}H NMR (400 MHz, $CDCl_3$)

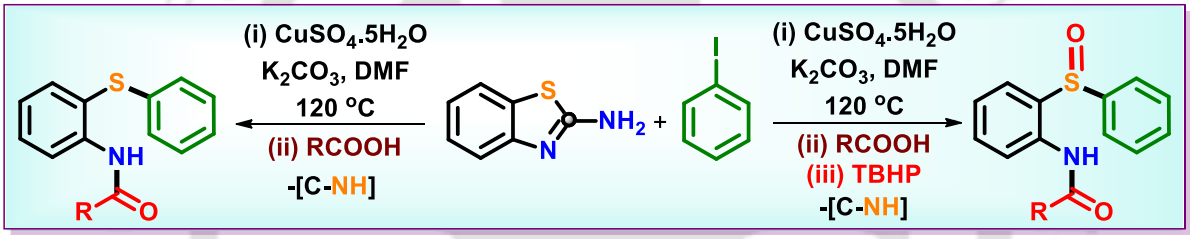


1-(4-Methylpiperidin-1-yl)-2-phenylethane-1,2-dione (4a): ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER V

One Pot Sequential Synthesis of *N*-(2-(Phenylsulfinyl)phenyl)acetamides: A Ring Opening Rearrangement Functionalisation (RORF)



Abstract: *A Cu(II) catalysed one-pot sequential synthesis of N-(2-(phenylthio)phenyl)acetamides from benzo[d]thiazol-2-amines, iodoarenes and carboxylic acids (RCOOH) has been accomplished via ring opening rearrangement functionalisation (RORF). Here, the ring opening is associated with the loss of carbon and nitrogen atoms with concurrent S-arylation and N-acylation leading to ortho-bifunctionalised products. A further sequential addition of tert-butyl hydroperoxide (TBHP) results in the formation of a sulfur oxidised product, N-(2-(phenylsulfinyl)phenyl)acetamide. A plausible mechanism has been proposed for this unprecedented ring opening rearrangement functionalisation (RORF).*

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CHAPTER V

One Pot Sequential Synthesis of *N*-(2-(Phenylsulfinyl)phenyl)acetamides: A Ring Opening Rearrangement Functionalisation (RORF)

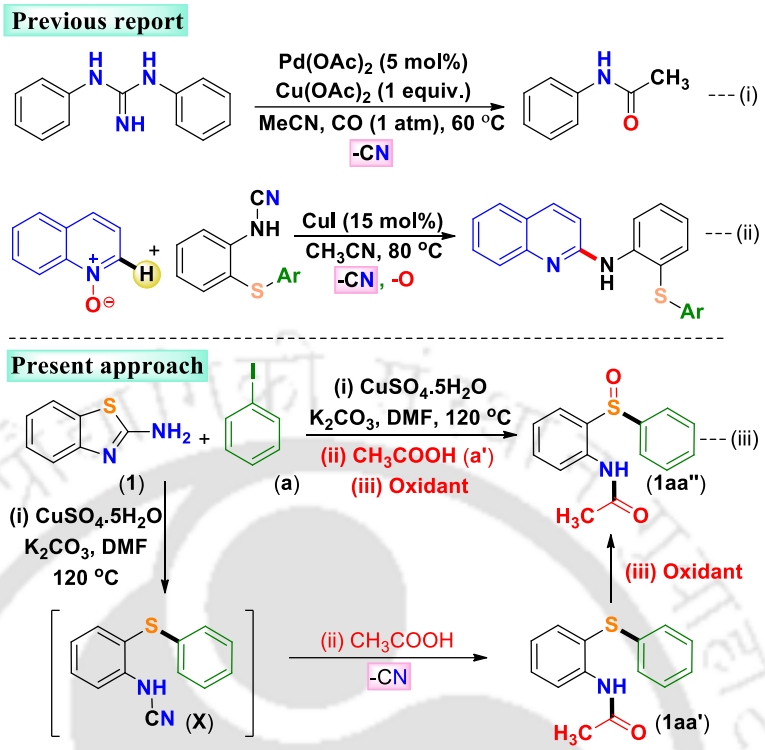
V.1. Introduction

The transition metal-catalysed concurrent construction of C–S and C–N bonds leading to functionally diverse structural motifs are in great demand.[1] Recently the C–N bond formations have attracted much attention and become one of the most promising strategy in organic reactions.[2] Similarly, owing to the importance of organo-sulfur compounds in biological, pharmaceutical and material chemistry, the C–S bond forming process has also gained considerable attention in organic synthesis.[3] On the other hand one pot sequential strategies are effective as several bond-forming process can be carried out in a single-pot, circumventing purification at each step, thereby creating high diversity per step. A further appealing aspects of this strategy is to produce large molecular diversity and complexity in a single transformation.[4]

Due to the associated ring strains in three and four membered carbo- and heterocycles, they often undergo ring opening in the presence of appropriate nucleophiles.[5] Although five membered heterocycles such as thiazole, imidazole, oxazole and some of their benzo-fused heterocycles *viz.* benzothiazole, benzoimidazole, benzoxazole and benzoisothiazole are more stable in terms of ring strain but are susceptible to ring opening.[6-8] The ring opening reactions are not only restricted to simple benzothiazoles and 1,3-azoles but also observed in 2-aminobenzothiazoles. In a coupling reaction between 2-aminobenzothiazole and terminal alkyne resulted in the formation of benzo[*b*][1,4]thiazine-4-carbonitrile.[9a] Here, the ring opening is followed by an oxidative coupling with an alkyne and finally the reaction terminates *via* an intermolecular cyclisation process. In yet another method, the synthesis of 2-(phenylthio)phenylcyanamide from 2-halothiourea and iodobenzene in the presence of $CuSO_4.5H_2O$ or CuI/ligand has been established *via* the intermediacy of 2-aminobenzothiazole.[9b,c] In 2015, a non-enzymatic decomposition of guanidine

derivatives into anilides with the loss of a –CN moiety has been developed by Shi group [Scheme V.1.1, (i)]. Here, a combination of catalyst $Pd(OAc)_2$, an equivalent of $Cu(OAc)_2$ and CO were utilised for the transformation of 1,3-diarylguanidines to acetanilides *via* the cleavage of C–N bond.[10] Very recently, our group has developed another -CN sacrificial arylthio-arylamination of quinoline/isoquinoline *N*-oxides where, 2-(arylthio)arylcyanamides serves as efficient arylaminating agents [Scheme V.1.1, (ii)].[11] The later proceeds *via* the attack of a nucleophilic *N*-oxide onto electrophilic cyano (-CN) group of the 2-(arylthio)arylcyanamide followed by a rearrangement to provide an auto-reduced C2-arylaminated quinoline/isoquinoline. In both these examples the -CN bearing moiety *viz.* 2-(arylthio)arylcyanamides and guanidines, loses their cyano group in the presence of respective nucleophiles *viz.* quinoline *N*-oxides and acetate anions.

Inspired by the recent advances in transition metal-catalysed one pot sequential reactions,[12] ring opening processes[5-8] and N–CN bond activation strategies,[13] we envisaged a telescopic protocol for the synthesis of *N*-(2-(phenylthio)phenyl)acetamides [Scheme V.1.1, (iii)]. 2-(Phenylthio)phenylcyanamide can be obtained from 2-aminobenzothiazole and iodobenzene in the presence of $CuSO_4.5H_2O$ *via* a ring opening intermolecular C–S cross coupling reaction.[9b] We anticipated that the *in situ* generated cyanamide possesses an electrophilic carbon,[14] and a fragile N–CN bond which may undergo a similar cyano sacrificial acetolysis to that of 1,3-diarylguanidine to generate an acetamide [Scheme V.1.1, (iii)]. The *N*-(2-(phenylthio)phenyl)acetamide having a diarylsulfide moiety can be further oxidised to its sulfoxide analogue in the presence of a suitable oxidant [Scheme V.1.1, (iii)].



Scheme V.1.1. *Cyano sacrificial functionalisation strategies*

An initial experiment was carried out using 2-aminobenzothiazole and iodobenzene in the presence of $CuSO_4.5H_2O$ and Cs_2CO_3. The exclusive formation of cyanamide was observed after 4 h, which is consistent with the previous literature reports.[9b,c] To check whether the envisioned cyano sacrificial acetolysis could be accomplished in one pot, AcOH (5 equiv.) was added to the same reaction mixture after the initial formation of cyanamide and heating was continued further. To our delight, the expected *N*-acetylated product 2-(phenylthio)phenylacetamide was obtained via the loss of a cyano (-CN) group. Thus, herein, we report a one pot sequential ring opening rearrangement functionalisation (RORF) using 2-aminobenzothiazole, iodobenzene and acetic acid. The notable features of this transformation is the sequential formation of two new C–heteroatom bonds such as C–S and C–N *ortho* to each other providing a 1,2-bifunctionalised product *N*-(2-(phenylthio)phenyl)acetamide.

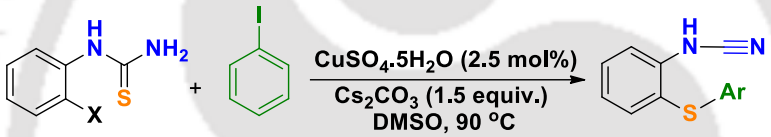
V.2. Strategies for the synthesis of arylthio-arylcyanamide

Cyanamide bearing compounds are important structural motifs in synthetic chemistry due to their unique structure and reactivity.[15,16] They are important reactive intermediates in the synthesis of biologically active compounds such as monoxidil[17] and herbicides.[18]

In addition to this, arylthio-arylcyanamides possessing one more important moiety *viz.* ArS- again enhances its significance in both synthetic and biological field. Due to enormous utility, a number of synthetic routes were developed for the synthesis of arylthio-arylcyanamides.

(i) Synthesis of 2-(arylthio)arylcyanamides from 2-(haloaryl)thioureas

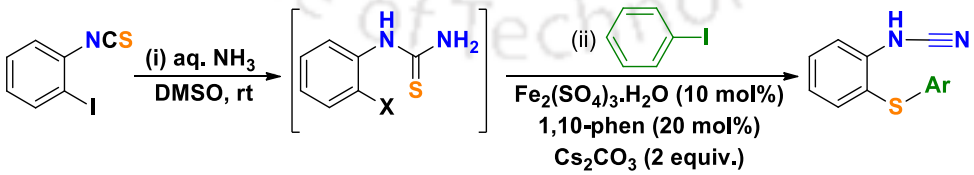
Punniyamurthy *et. al*. reported a one pot synthesis of 2-(arylthio)arylcyanamides from 2-(iodoaryl)thioureas and iodobenzene using $CuSO_4.5H_2O$ as the catalyst and Cs_2CO_3 as the base (Scheme V.2.1).[9b] The reaction proceeds via an intermolecular C–S coupling with iodobenzene. In the same year, our group has also developed a similar protocol for the synthesis 2-(arylthio)arylcyanamides from the coupling of different 2-(haloaryl)thioureas and iodobenzene in presence of CuI, DMEDA and NaOH.[9c]



Scheme V.2.1. *Synthesis of 2-(arylthio)arylcyanamides from 2-(haloaryl)thioureas*

(ii) Syntheis of 2-(arylthio)arylcyanamides from 1-iodo-2-isothiocyanatobenzene

A one pot three component reaction of 1-iodo-2-isothiocyanatobenzene, aq. ammonia and iodobenzene leading to the synthesis of 2-(arylthio)arylcyanamides has been described by Rudraraju and co-workers (Scheme V.2.2). Here, the $Fe_2(SO_4)_3.H_2O$ and 1,10-phenanthroline were utilised for accomplishing the intermolecular C–S coupling reaction of the *in situ* generated 2-(haloaryl)thioureas and iodobenzene.[9d]



Scheme V.2.2. *Synthesis of 2-(arylthio)arylcyanamides from 1-iodo-2-isothiocyanatobenzene*

V.3. Present work

Optimisation of reaction conditions: As mentioned above, an initial experiment was carried out using 2-aminobenzothiazole (**1**) and iodobenzene (**a**) in the presence of $CuSO_4.5H_2O$ and Cs_2CO_3. Then AcOH (**a′**) (5 equiv.) was added to the same reaction mixture after the initial formation of cyanamide (**X**). The expected *N*-acetylated product 2-(phenylthio)phenylacetamide (**1aa′**, 29%) was obtained *via* the loss of a cyano (-CN) group. The structure of the product (**1aa′**) was further confirmed by X-ray crystallographic analysis (Figure V.3.1).

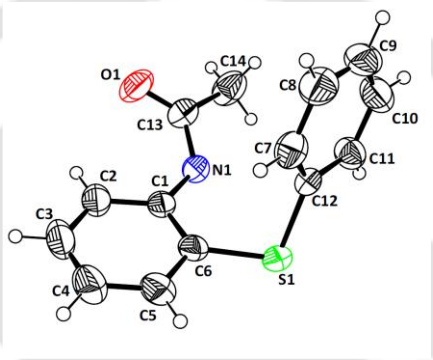
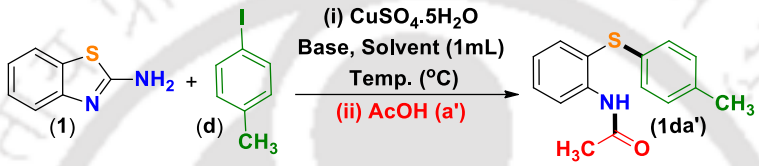


Figure V.3.1. *ORTEP diagram of N-(2-(phenylthio)phenyl)acetamide (**1aa′**) with 40% ellipsoid contour probability*

Inspired by this positive outcome, various reaction parameters were again scrutinised to achieve an improved yield of the 1,2-bifunctionalised product (**1da′**). The investigation was commenced by using benzo[*d*]thiazol-2-amine (**1**) and 4-methyliodobenzene (**d**) as the reacting partners (Table V.3.1, entry 1). As most of the N–CN bond cleaving reactions proceed in the presence of a metal catalyst,[10,13] the quantity of $CuSO_4.5H_2O$ was first optimised. An increase in the catalyst ($CuSO_4.5H_2O$) loading to 10 mol% improve the yield to 47 % (Table V.3.1, entry 3). However, the yield (48%) remained virtually unchanged even using 15 mol% of the catalyst loading (Table V.3.1, entry 4). The use of base K_2CO_3 (2 equiv.) is found to be equally effective to that of Cs_2CO_3 (1.5 equiv.) for the ring opening leading to the formation of intermediate cyanamide (**X**) in DMSO (Table V.3.1, entry 5). Use of solvent DMF (58%) (Table V.3.1, entry 6) was found to be marginally superior to DMSO (53%). Keeping all other parameters constant, the addition of 10 and 20 equivalents of AcOH improved the yield of the final product (**1da′**) to 63% and 69% respectively (Table V.3.1, entry 7 and 8).

The yield of the product improved progressively when the reaction was carried out at 100 °C (76%), 110 °C (79%) and 120 °C (84%) (Table V.3.1, entries 9-11). Finally, a two-step optimised process was developed for the ring opening rearrangement functionalisation (RORF) strategy. In the first step the combination of $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.) and DMF (1 mL) at 120 °C for 4 h and in the second step addition of AcOH (20 equiv., 0.6 mL) at 120 °C for 5 h was found to be the best optimal condition for this telescopic synthesis (Table V.3.1, entry 11).

Table V.3.1. *Optimisation for N-acetylation*[a,b]



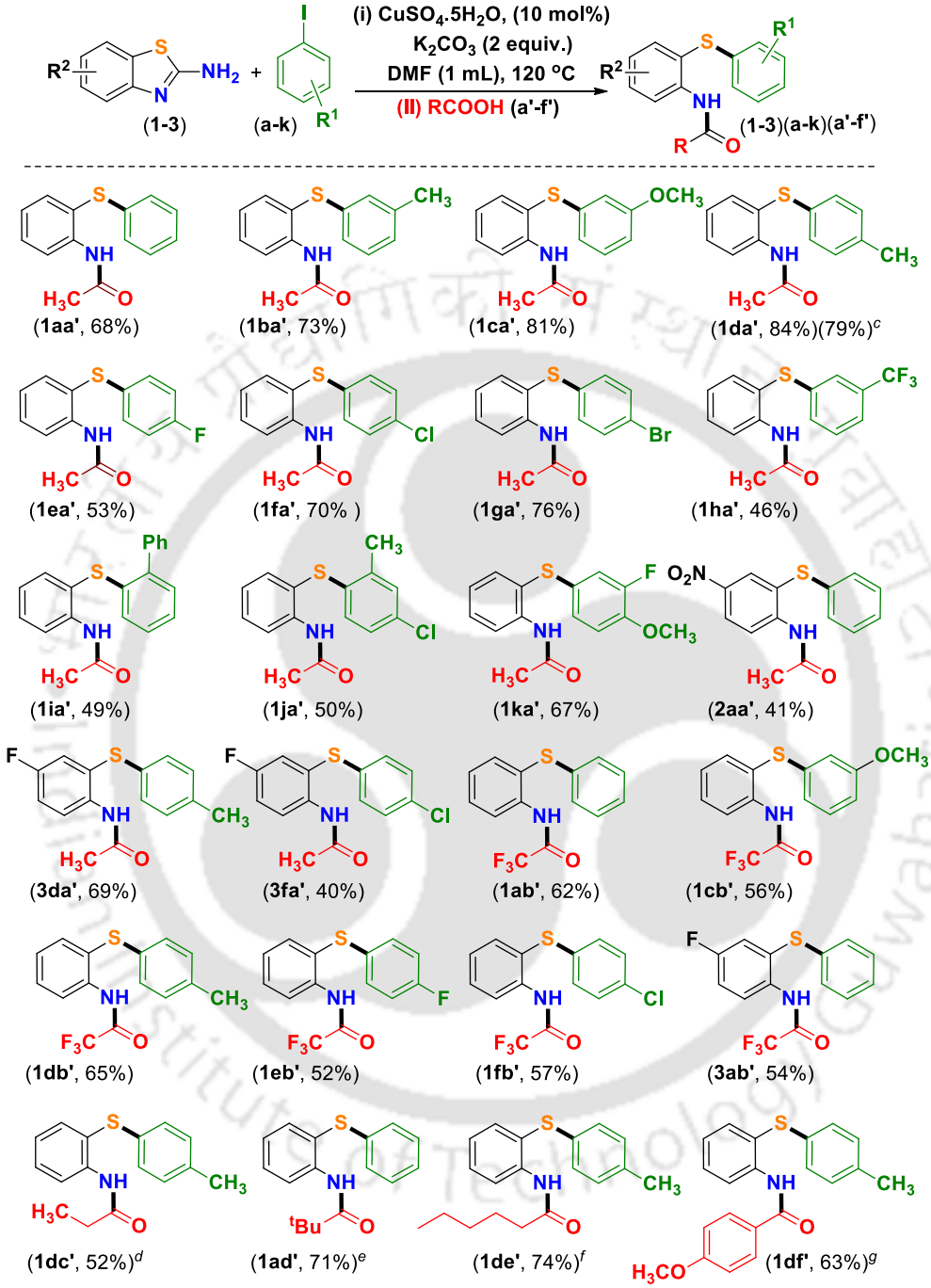
Entry	Catalyst (mol %)	Base (equiv.)	Solvent	AcOH	Temp °C	Yield (%)
1	$CuSO_4.5H_2O$ (2.5)	Cs_2CO_3 (1.5)	DMSO	5 equiv.	90	37
2	$CuSO_4.5H_2O$ (5)	Cs_2CO_3 (1.5)	DMSO	5 equiv.	90	39
3	$CuSO_4.5H_2O$ (10)	Cs_2CO_3 (1.5)	DMSO	5 equiv.	90	47
4	$CuSO_4.5H_2O$ (15)	Cs_2CO_3 (1.5)	DMSO	5 equiv.	90	48
5	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMSO	5 equiv.	90	53
6	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMF	5 equiv.	90	58
7	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMF	10 equiv.	90	63
8	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMF	20 equiv.	90	69
9	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMF	20 equiv.	100	76
10	$CuSO_4.5H_2O$ (10)	K_2CO_3 (2)	DMF	20 equiv.	110	79
11	**$CuSO_4.5H_2O$ (10)**	**K_2CO_3 (2)**	**DMF**	**20 equiv.**	**120**	**84**

[a]Reaction conditions: benzo[*d*]thiazol-2-amine (**1**) (0.5 mmol), 4-iodotoluene (**d**) (0.5 mmol), solvent (1 mL), time (4 h). (ii) acetic acid (a´), time (5 h).[b]Yields of isolated pure product.

With this stepwise optimal reaction conditions in hand, the generality and versatility of this one pot sequential 1,2-difunctionalisation strategy was demonstrated using different benzo[*d*]thiazol-2-amines (**1-3**) with various aryl iodides (**a-k**) bearing electron-donating and electron-withdrawing groups in the presence of acetic acid (**a´**) (Scheme V.3.1). Here, the iodoarenes having electron-neutral –H (**a**) and electron-donating substituents such as *m*-CH_3 (**b**) and *m*-OCH_3 (**c**), all yielded their desired ring opened *N*-acetylated products (**1aa´**, 68%), (**1ba´**, 73%) and (**1ca´**, 81%) in good yields (Scheme V.3.1). Further, aryl iodides possessing moderately electron-withdrawing substituents

such as *p*-F (**e**), *p*-Cl (**f**), *p*-Br (**g**) and strongly-electron-withdrawing substituent *m*-CF_3 (**h**) all furnished their respective 1,2-bifunctionalised *N*-acetylated products (**1ea´**, 53%), (**1fa´**, 70%), (**1ga´**, 76%) and (**1ha´**, 46%) (Scheme V.3.1). A *o*-phenyl substituted iodobenzene (**i**) reacted with benzo[*d*]thiazol-2-amine (**1**) in the presence of acetic acid (**a´**) affording its corresponding bi-functionalised product (**1ia´**, 49%). In addition to these mono-substituted aryl iodides, the di-substituted aryl iodides, such as 2-CH_3-4-Cl (**j**) and 3-F-4-OCH_3 (**k**) all underwent efficient transformations with benzo[*d*]thiazol-2-amine (**1**) and acetic acid (**a´**) giving the desired *N*-acetylated products (**1ja´**, 50%) and (**1ka´**, 67%) respectively. Subsequently, presence of substituents on the 2-aminobenzothiazole was investigated. Benzothiazoles possessing 6-NO_2 (**2**) and 6-F (**3**), all experienced efficient RORF giving their respective 1,2-bifunctionalised products. The 6-nitrobenzo[*d*]thiazol-2-amine (**2**) reacted smoothly with iodobenzene (**a**) in presence of AcOH (**a´**), providing its *N*-acetylated product (**2aa´**) in 41% yield. Further, the presence of a least deactivating substituent 6-F (**3**) in the benzothiazole ring underwent the *N*-acetylation with a variety of substituted iodoarenes and AcOH (**a´**). The electron-donating *p*-CH_3 (**d**) and electron-withdrawing *p*-Cl (**f**) iodoarenes, all endured the present one pot RORF strategy with 6-fluorobenzo[*d*]thiazol-2-amine (**3**) and acetic acid (**a´**) furnishing their bi-functionalised products (**3da´**, 69%) and (**3fa´**, 40%) respectively. From the trend in the yields obtained in Scheme V.3.1, no appropriate correlation between the nature of substituents and their position of attachment with the actual yield obtained could be rationalised. To check the scalability of the present methodology, a reaction of benzo[*d*]thiazol-2-amine (**1**) (1 mmol), 4-methyliodobenzene (**d**) (1 mmol) and acetic acid (**a´**) (20 equiv.), under the standard optimised reaction condition provided a 79% yield of product (**1da´**) (Scheme V.3.1).

Scheme V.3.1. *Demonstration of RORF using AcOH and other carboxylic acids*[a,b]



[a]Reaction conditions: (i) benzo[*d*]thiazol-2-amine (**1**) (0.5 mmol), aryl iodide (**a–k**) (0.5 mmol), $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.) and DMF (1 mL), time (4 h), (ii) AcOH (**a´**) (20 equiv.), (1 mmol scale)[c], TFA (**b´**) (20 equiv.), propanoic acid (**c´**) (10 equiv.)[d], pivalic acid (**d´**) (8 equiv.)[e], hexanoic acid (**e´**) (10 equiv.)[f] and benzoic acids (**f´**) (6 equiv.)[g], time (5 h) at 120 °C. [b]Yields of isolated pure products.

Now a query arises whether the acetic acid could be replaced with its halogen analogue such as trifluoroacetic acid to provide their corresponding *N*-trifluoroacylated

products. With this objective, when acetic acid (**a´**) was substituted with trifluoroacetic acid (**b´**), using benzo[*d*]thiazol-2-amine (**1**) and iodobenzene (**a**) as the reacting partners under otherwise identical condition, the reaction furnished the anticipated *N*-trifluoroacetylated product (**1ab´**) in 62% yield. Inspired by the positive outcome, several other iodoarenes (**c**-**f**) bearing electron-donating and electron-withdrawing groups were examined with benzo[*d*]thiazol-2-amine (**1**) using TFA (**b´**) as the trifluoroacylation partner (Scheme V.3.1). Initially, aryliodides bearing electron-donating substituents such as *m*-OCH_3 (**c**) and *p*-CH_3 (**d**) were employed with benzo[*d*]thiazol-2-amine (**1**) and TFA (**b´**) under the present reaction condition, all provided their corresponding products (**1cb´**, 56%) and (**1db´**, 65%) respectively. Similarly, iodoarenes bearing moderately electron-withdrawing substituents such as *p*-F (**e**) and *p*-Cl (**f**), all yielded their corresponding rearranged diaryl-sulfide products (**1eb´**) and (**1fb´**) in 52% and 57% yields respectively. Besides these substituted iodoarenes, 6-F-2-aminobenzothiazole (**3**) also successfully underwent the present transformation with iodobenzene (**a**) and TFA (**b´**) to result the corresponding trifluoroacetamide (**3ab´**) in 54% yield. Here, similar to acetic acid, no proper correlation between the nature of substituents and their position of attachment with the actual yield obtained could be ascertained. Besides AcOH and TFA, this protocol is also applicable to other aliphatic acids such as propanoic acid (**c´**), pivalic acid (**d´**) and hexanoic acid (**e´**), all afforded their corresponding *ortho*-bifunctionalised products (**1dc´**), (**1ad´**) and (**1de´**) in 52%, 71% and 74% yields respectively (Scheme V.3.1). An aromatic carboxylic acid such as *p*-methoxy benzoic acid (**f´**) also provided a decent yield of the bi-functionalised amidic product (**1df´**, 63%) (Scheme V.3.1).

We believe that the bi-functionalised acetamides obtained after the addition of carboxylic acids, possessing a diarylsulfide moiety, can be further oxidised to their corresponding sulfoxide analogue in the same pot using a suitable oxidant. The *in situ* treatment of $K_2S_2O_8$ (3 equiv.) provided sulfoxide product (**1da´´**) in a modest 21% yield after 17 h at 120 ^oC leaving behind substantial amount of unoxidised product (**1da´**) (Table V.3.2, entry 1). Spectroscopic and HRMS analysis of the product confirmed its structure to be *N*-(2-(*p*-tolylsulfinyl)phenyl)acetamide (**1da´´**). This positive outcome is interesting because, sulfoxides exhibit a broad range of biological properties, including anticancer,[19a-d] anti-viral[19e] and anti-bacterial activities.[19f] They are also important

structural motifs in marketed therapeutic drugs, such as Nexium for heartburn and esophagitis[20a] and Provigil for narcolepsy (Figure V.3.2).[20b]

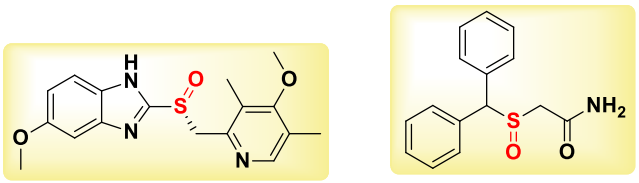
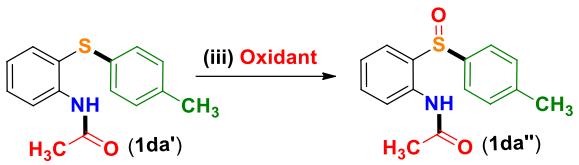


Figure V.3.2. *Representative sulfoxide containing therapeutics*

Since the final yield (21%) of the oxidised product (**1da´´**) obtained was not promising, various other oxidants were then examined to achieve an improve yield of (**1da´´**) (Table V.3.2). Among the oxidants such as $(NH_4)_2S_2O_8$ (08%), TBHP (5–6 M in decane) (59%), aq.TBHP (32%), benzoylperoxide (BPO) (00%), *tert*-butylperoxy benzoate (TBPB) (18%), di-*tert*-butyl peroxide (DTBP) (26%) and H_2O_2 (48%) tested (Table V.3.2, entries 2–8), TBHP (5–6 M in decane) was found to be the most suitable oxidant for the conversion of sulfide (**1da´**) to sulfoxide (**1da´´**) analogue (Table V.3.2, entry 3). Gratifyingly, using 6 equiv. of TBHP, an improved yield (67%) of product (**1da´´**) was observed (Table V.3.2, entry 9). A further increase in the oxidant quantity to 8 equiv., gave no significant enhancement in the product (**1da´´**) yield (Table V.3.2, entry 10). Thus, TBHP (5–6 M in decane) (6 equiv.) was used for the *in situ* oxidation of rest of the diarylsulfides in Scheme V.3.2.

Table V.3.2. *Optimisation for sulfoxide formation*[a,b]



Entry	Oxidant (equiv.)	Temp (^{o}C)	Yield (%)
1	$K_2S_2O_8$ (3)	120	21
2	$(NH_4)_2S_2O_8$ (3)	120	08
3	TBHP (3)	120	59[h]
4	aq. TBHP (3)	120	32
5	BPO (3)	120	00
6	TBPB (3)	120	18
7	DTBP (3)	120	26
8	H_2O_2 (3)	120	48
9	**TBHP (6)**	**120**	**67[h]**
10	TBHP (8)	120	68[g]

[a]Reaction conditions: (i) benzo[*d*]thiazol-2-amine (**1**) (0.5 mmol), 4-iodotoluene (**d**) (0.5 mmol), $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.) and DMF (1 mL) at 120 ^{o}C for 4 h, (ii) AcOH (**a**) (20 equiv.), time (5 h). [h]TBHP (5–6 M in decane). [b]Yields of isolated pure product.

The above optimised oxidative condition was then implemented to explore the scope and generality of the developed RORF strategy via the *in situ* oxidation of sulfide to sulfoxide and the results are summarized in Scheme V.3.2. Initially, the variation of both electron-donating and electron-withdrawing substituents on aryliodides (**a**–**i**) with unsubstituted benzo[*d*]thiazol-2-amine (**1**) using acetic acid (**a´**) was surveyed. Here again, the iodoarenes bearing electron neutral –H (**a**) and electron-donating substituents such as *m*-OCH_3 (**c**) provided their corresponding bifunctionalised sulfoxide products (**1aa´´**, 60%) and (**1ca´´**, 58%) respectively (Scheme V.3.2). Further, the iodoarenes possessing moderately electron-withdrawing substituents such as *p*-F (**e**), *p*-Cl (**f**), *p*-Br (**g**) and strongly electron-withdrawing substituent *m*-CF_3 (**h**) all resulted their corresponding oxidised 1,2-disubstituted products (**1ea´´**, 52%), (**1fa´´**, 63%), (**1ga´´**, 65%) and (**1ha´´**, 27%) respectively (Scheme V.3.2). Besides this, *o*-phenyl substituted iodobenzene (**i**) provided its corresponding sulfoxide product (**1ia´´**) in 36% yield. A fluoro substituted 2-aminobenzothiazole *viz.* 6-fluorobenzo[*d*]thiazol-2-amine (**3**) reacted smoothly with various substituted iodoarenes bearing electron neutral -H (**a**), electron-donating *p*-CH_3 (**d**) and electron-withdrawing *p*-Cl (**f**) groups in the presence of AcOH

(**a**′) and TBHP affording their *N*-acetylated sulfoxides (**3aa**′′), (**3da**′′) and (**3fa**′′) in 50%, 58% and 37% yields respectively.

Analogous to acetic acid, the one pot sequential RORF protocol was also performed in the presence of TFA (**b**′) under an identical reaction condition. Surprisingly, oxidation of the *in situ* generated sulfide (**1ab**′) to sulfoxide (**1ab**″) failed completely. May be under a strongly acidic condition, the oxidant TBHP rapidly decomposes, thereby failed to oxidise the sulfide. However, the sulfoxide products (**1ab**″) could be obtained in a decent yield (58%) by oxidising the isolated sulfide analogue (**1ab**′) using TBHP as the oxidant in CH_3CN at room temperature for 24 h. The same strategy was applied for other diarylsulfides (**1cb**′-**1fb**′ and **3ab**′). The yields of the sulfoxide products (**1cb**′′-**1fb**″ and **3ab**″) reported in Scheme V.3.2 are from the oxidation of their respective diarylsulfides. The structure of the product (**1ab**″) was further reconfirmed by X-ray crystallographic analysis (Figure V.3.3).

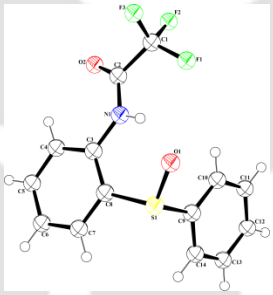
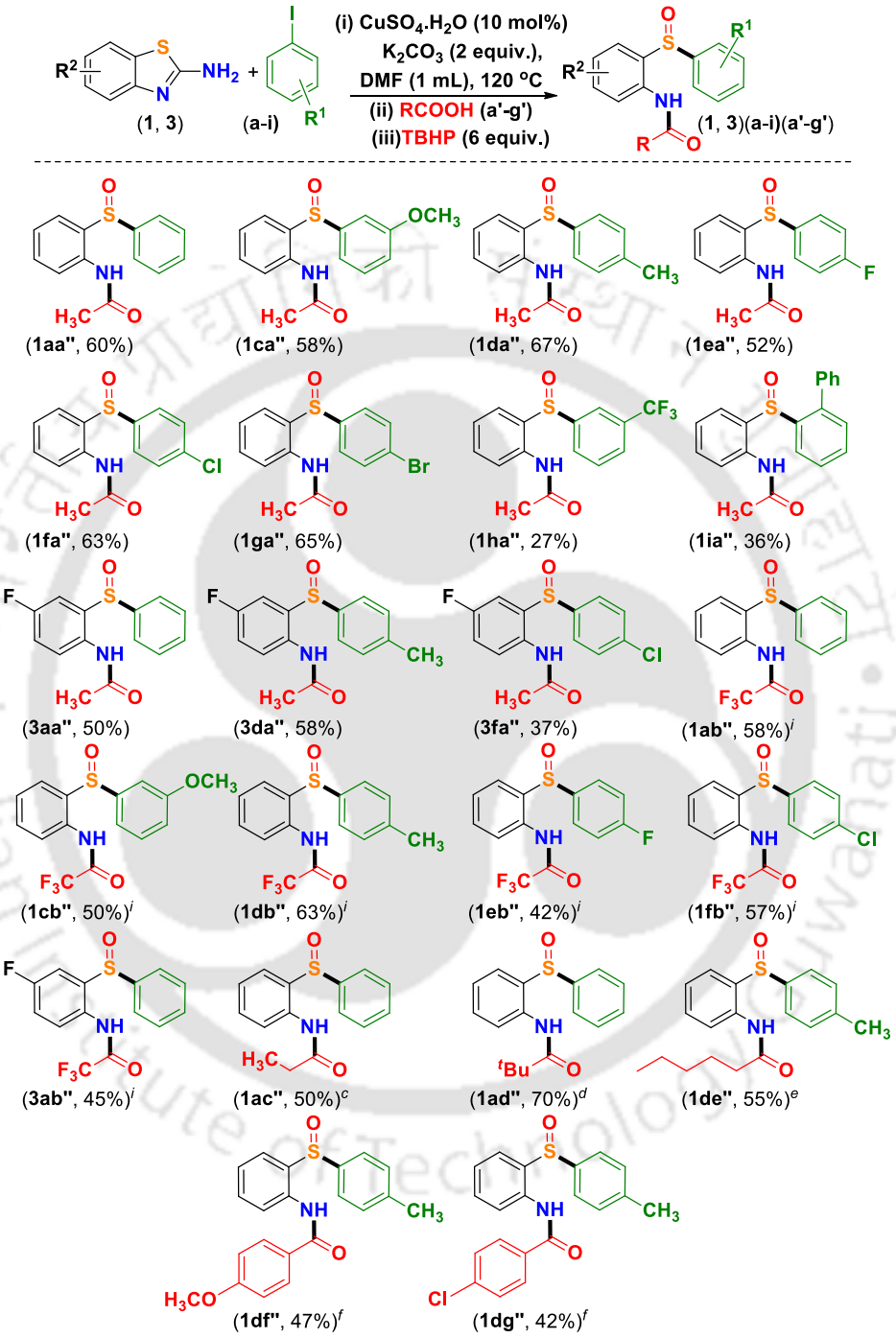


Figure V.3.3. *ORTEP diagram of 2,2,2-trifluoro-N-(2-(phenylsulfinyl)phenyl)acetamide (**1ab**″):with 50% ellipsoid contour probability*

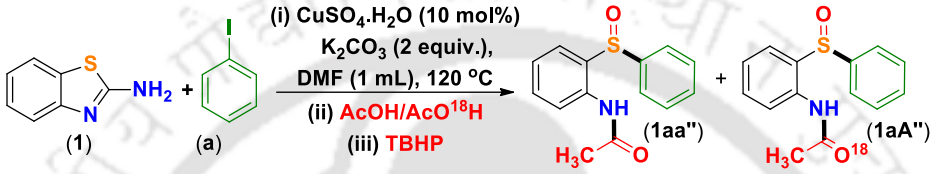
Other biaryl-sulfoxides (**1ac**′′, 50%), (**1ad**′′, 70%), (**1de**′′, 55%), (**1df**′′,47%) and (**1dg**′′, 42%) were also obtained via this one pot sequential RORF strategy using other aliphatic and aromatic acids such as propanoic (**c**′), pivalic (**d**′), hexanoic acid (**e**′), *p*-methoxy benzoic acid (**f**′) and *p*-chloro benzoic acid (**g**′) as shown in Scheme V.3.2. It may be noted here, that the yields of the unoxidised products in Scheme V.3.1 are generally superior to their corresponding oxidised products in Scheme V.3.2.

Scheme V.3.2. *Demonstration of RORF using AcOH and other carboxylic acids under oxidative condition*[a,b]



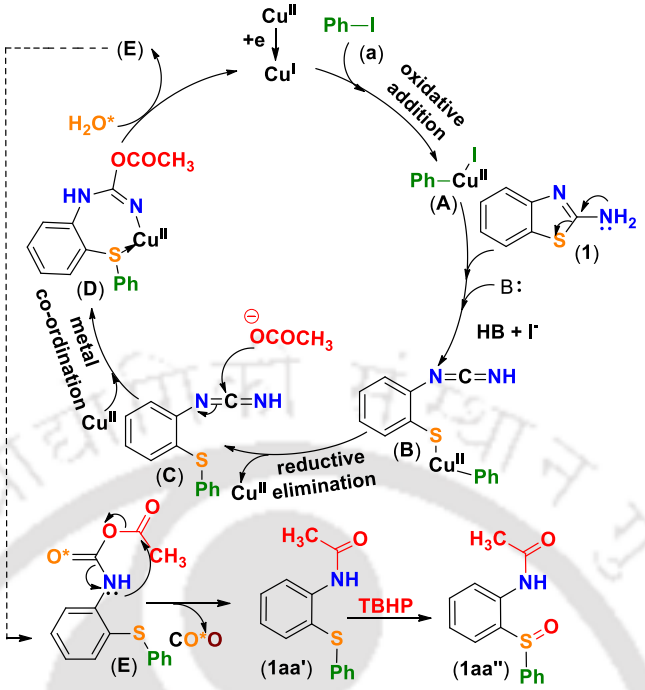
[a]Reaction conditions: (i) benzo[*d*]thiazol-2-amine (**1**) (0.5 mmol), aryl iodide (**a–n**) (0.5 mmol), $CuSO_4.5H_2O$ (10 mol%), K_2CO_3 (2 equiv.), DMF, (1 mL) time (4 h), (ii) AcOH (**a´**) (20 equiv.), propanoic acid (**c´**) (10 equiv.)[d], pivalic acid (**d´**) (8 equiv.)[e] hexanoic acid (**e´**) (10 equiv.)[f] and benzoic acids (**f´** and **g´**) (6 equiv.)[g], time (5 h) (iii) TBHP (5**–**6 M in decane) (6 equiv.) time (17 h) at 120 °C. [i]Reaction conditions: *N*-trifluoroacetylated diarylsulfides (0.25 mmol), TBHP (6 equiv.), CH_3CN (1 mL), time (24 h) at room temp. [b]Yields of isolated pure product.

To illuminate the probable mechanism of this one pot sequential ring opening rearrangement functionalisation (RORF), some control experiments were carried out. When the reaction was performed in the presence of ^{18}O labeled water no ^{18}O incorporated product was observed suggesting none of the oxygen in the product originates from water. However, when a reaction was carried out using ^{18}O labeled acetic acid, the product was found to have an ^{18}O labeled oxygen (Scheme V.3.3). This result confirms carboxylic acids to be the acyl or aryl sources in this transformation.



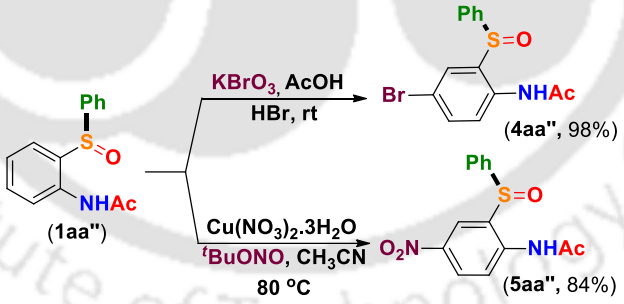
Scheme V.3.3. *Isotopic labelling experiment*

Based on the literature reports[9b,c] and experimental findings, a plausible reaction mechanism is depicted in Scheme V.3.4. In this reaction, aryliodide undergoes an oxidative addition with Cu to form species (**A**). The 2-aminobenzothiazole (**1**) opens up to a carbodiimide in the presence of a base which then reacts with the species (**A**) via the soft sulfur atom to generate intermediate (**B**). The intermediate (**B**) undergoes reductive elimination to form the diarylsulfide cyanamide intermediate (**C**). The resultant cyanamide intermediate (**C**) is attacked by the acetate ion which is assisted *via* the metal co-ordination to form a metal bound carbamimidic anhydride species (**D**). The intermediate (**D**) is hydrolyzed to a carbamic anhydride (**E**). The final acylated product (**1aa´**) is obtained *via* the loss of a CO_2 moiety. The acylated diarylsulfide (**1aa´**) is oxidised to sulfoxide (**1aa˝**) in the presence of an oxidant.



Scheme V.3.4. *Plausible mechanism for one pot sequential RORF*

To further extend the functionalisation, the isolated bifunctionalised product so obtained can be subsequently functionalised *via* aromatic electrophilic substitution reactions *viz.* bromination[21a] and nitration[21b] as demonstrated in Scheme V.3.5.



Scheme V.3.5. *Further functionalisation of the product (**1aa″**)*

In conclusion, a one pot sequential synthesis of *N*-(2-(phenylthio)phenyl)acetamides has been developed using benzo[*d*]thiazol-2-amine, aryliodide and carboxylic acid *via* a copper catalysed ring opening rearrangement functionalisation (RORF). The sequential addition of TBHP leads to the formation of *N*-(2-(phenylsulfinyl)phenyl)acetamide. This RORF process is accompanied with the loss of C and N atoms with *S*-arylation followed by *N*-acylation leading to a bifunctionalised amidic product.

V.4. Experimental section

V.4.1. General information: All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 GF_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ and DMSO with tetramethylsilane as the internal standard for ^1H NMR (400 MHz and 600 MHz), $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz and 150 MHz). Mass spectra were recorded using ESI mode and APCI mode (Q-TOF MS analyzer). IR spectra were recorded in KBr or neat.

V.4.2. Crystallographic Description:

V.4.2.1. CCDC number for compound *N*-(2-(phenylthio)phenyl)acetamide (1aa′): CCDC-1836285. 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 *N*-(2-(phenylthio)phenyl)acetamide (1aa′): $C_{14}H_{12}NOS$, crystal dimensions 0.29 x 0.22 x 0.19 mm, M_r = 242.31, Monoclinic, space group Cc,a =13.537(6), b = 9.725(4), c = 10.028(4)Å, α = 90 °, β = 103.125(5)°, γ = 90°, V = 1285.7(10) $Å^3$, Z = 4, ρ_{calcd} = 1.257mg/m^3, μ = 0.234 mm^{-1}, F(000)= 508.0, refinement method = full-matrix least-squares on F^2, final Rindices:R_1 = 0.0439, wR_2 = 0.0855, R indices (all data): R_1 = 0.0351, wR_2 = 0.0814, goodness of fit = 1.045.

V.4.2.2. CCDC number for compound 2,2,2-trifluoro-*N*-(2-(phenylsulfinyl)phenyl)acetamide (1ab″): CCDC-1834795. 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 2,2,2-trifluoro-*N*-(2-(phenylsulfinyl)phenyl)acetamide (1ab″): $C_{14}H_{10}F_3NO_2S$, crystal dimensions 0.28 x 0.22 x 0.19 mm, M_r = 313.29, Monoclinic, space group P c a 21,a =4.9427(2), b = 10.3535(8), c = 26.5991(13) Å, α = 90 °, β = 92.180(4) °, γ = 90°, V = 1360.22(14)$Å^3$, Z = 4, ρ_{calcd} = 1.530 mg/m^3, μ = 0.276mm^{-1}, F(000)= 640.0, reflection collected / unique = 2401 / 1920, refinement method = full-matrix least-squares on F^2, final Rindices [I> 2\s(I)]:R_1 =

0.0638, wR_2 = 0.1420, *R* indices (all data): R_1 = 0.0508, wR_2 = 0.1321, goodness of fit = 1.018.

V.4.3. General procedure

V.4.3.1 General procedure for the formation of *N*-(2-(phenylthio)phenyl)acetamide (1aa′): An oven-dried round bottom flask was charged with benzo[*d*]thiazol-2-amine (**1**) (75 mg, 0.5 mmol), iodobenzene (**a**) (102 mg, 0.5 mmol), $CuSO_4.5H_2O$ (10 mol%, 12.5 mg), K_2CO_3 (1 mmol, 138 mg) and DMF (1 mL). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 120 ^oC. The reaction progress was monitored by TLC. The formation of *N*-(2-(phenylthio)phenyl)cyanamide (**X**) was observed with the consumption of benzo[*d*]thiazol-2-amine (**1**) and iodobenzene (**a**). After 4 h, AcOH (**a′**) (20 equiv., 0.6 mL) was added to the same reaction mixture. The heating of the reaction mixture was continued at 120 ^oC. The reaction progress was monitored by TLC. After 5 h, the reaction mixture was cooled to room temperature. Then the reaction mixture was admixed with ethyl acetate (35 mL) and then washed successively with ice cold saturated $NaHCO_3$ solution (2 × 20 mL). The ethyl acetate layer was separated and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product so obtained was purified over a column of silica gel using hexane:EtOAc (89:11) as the eluents to afford the desired bi-functionalised product (**1aa′**) in an isolated yield of 68% (83 mg).

V.4.3.2 General procedure for the formation of *N*-(2-(phenylsulfinyl)phenyl)acetamide (1aa″): An oven-dried round bottom flask was charged with benzo[*d*]thiazol-2-amine (**1**) (75 mg, 0.5 mmol), iodobenzene (**a**) (102 mg, 0.5 mmol), $CuSO_4.5H_2O$ (10 mol%, 12.5 mg), K_2CO_3 (1 mmol, 138 mg) and DMF (1 mL). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 120 ^oC. The reaction progress was monitored by TLC. The formation of *N*-(2-(phenylthio)phenyl)cyanamide (**X**) was observed with the consumption of benzo[*d*]thiazol-2-amine (**1**) and iodobenzene (**a**). After 4 h, AcOH (**a′**) (20 equiv., 0.6 mL) was added to the same reaction mixture. The heating of the reaction mixture was continued at 120 ^oC. The reaction progress was monitored by TLC. After 5 h, the consumption of the *in situ* generated cyanamide was observed with the formation

of *N*-(2-(phenylthio)phenyl)acetamide (**1aa″**). To the same reaction, TBHP (5-6 M in decane) (6 equiv.) was added. Again the reaction mixture was heated at 120 °C. The formation of the sulfoxide was observed from the TLC. After 17 h, the reaction mixture was cooled to room temperature. Then the reaction mixture was admixed with ethyl acetate (35 mL) and then was washed successively with ice cold saturated $NaHCO_3$ solution (2 × 20 mL). The ethyl acetate layer was separated and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product so obtained was purified over a column of silica gel using hexane:EtOAc (60:40) as the eluents to afford the desired sulfoxide product (**1aa″**) in an isolated yield of 60% (78 mg).

V.4.4. General procedure for post-functionalisation

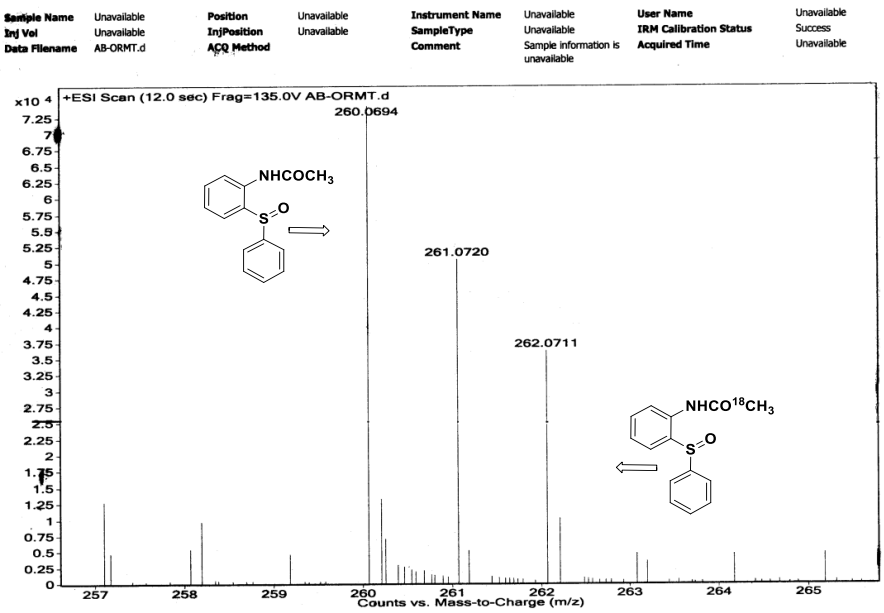
V.4.4.1 General procedure for the bromination of *N*-(2-(phenylsulfinyl)phenyl)acetamide (1aa″): An oven-dried round bottom flask was charged with *N*-(2-(phenylsulfinyl)phenyl)acetamide (**1aa″**) (52 mg, 0.2 mmol), $KBrO_3$ (0.06 mmol, 11 mg), AcOH (0.3 mL) and stirred at room temperature. Then 48% hydrobromic acid (0.04 mL) was added to the stirred reaction mixture. The reaction progress was monitored by TLC. After 30 min, the reaction mixture was admixed with ethyl acetate (25 mL) and the organic layer was washed with saturated $NaHCO_3$ solution. The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography with eluents hexane:EtOAc (60:40) to afford the desired product (**4aa″**) in an isolated yield of 98% (66 mg).

V.4.4.2. General procedure for the nitration of *N*-(2-(phenylsulfinyl)phenyl)acetamide (1aa″): *N*-(2-(Phenylsulfinyl)phenyl)acetamide (**1aa″**) (52 mg, 0.2 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (4.8 mg, 0.02 mmol), TBN (0.029 mL, 0.24 mmol) and CH_3CN (3.0 mL) were taken in an oven-dried round bottom flask. The resulting mixture was heated in an oil bath at 80 °C for 2 h, and the progress of the reaction was monitored by TLC. After cooling the mixture to room temperature, the volatiles were removed in vacuo, and the residue was purified by column chromatography with eluents hexane:EtOAc (53:47) to afford the desired product (**5aa″**) in an isolated yield of 84% (51 mg).

V.4.5. Experiments performed for mechanistic investigation

V.4.5.1. Experimental procedure for the isotopic labelling experiment: An oven-dried round bottom flask was charged with benzo[*d*]thiazol-2-amine (**1**) (37.5 mg, 0.25 mmol), iodobenzene (**a**) (0.25 mmol, 51 mg), $CuSO_4.5H_2O$ (10 mol%, 6.2 mg), K_2CO_3 (0.5 mmol, 69 mg) and DMF (0.5 mL). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 120 ^oC. The reaction progress was monitored by TLC. The formation of *N*-(2-(phenylthio)phenyl)cyanamide (**X**) was observed with the consumption of benzo[*d*]thiazol-2-amine (**1**) and iodobenzene (**a**). After 4 h, the O^{18} labelled AcOH mixture was added to the same reaction. The flask was fitted with a condenser and the resultant reaction mixture was again stirred in a pre-heated oil bath maintained at 120 ^oC. The reaction progress was monitored by TLC. After 5 h, the consumption of *in situ* generated cyanamide was observed with the formation of *N*-(2-(phenylthio)phenyl)acetamide. To the same reaction, TBHP (5-6 M in decane) (6 equiv.) was added. The heating of the reaction mixture was continued at 120 ^oC. Then small quantities of reaction mixtures were collected at different time intervals and subjected to HRMS analysis.

Mass spectra of O^{18} labelled AcOH product:



V.5. References

(1) (a) X. Tang, Z. Zhu, C. Qi, W. Wu and H. Jiang, *Org. Lett*., 2016, **18**, 180; (b) P. Qian, Y. Deng, H. Mei, J. Han, J. Zhou and Y. Pan, *Org. Lett*., 2017, **19**, 4798; (c) M. Li, H. Cao, Y. Wang, X. -L. Lv and L.–R. Wen, *Org. Lett*., 2012, **14**, 3470; (d) H. Cao, X. Liu, L. Zhao, J. Cen, J. Lin, Q. Zhu and M. Fu, *Org. Lett*., 2014, **16**, 146.

(2) (a) A. Gogoi, S. Guin, S. Rajamanickam, S. K. Rout and B. K. Patel, *J. Org. Chem*., 2015, **80**, 9016; (b) S. Tanii, M. Arisawa, T. Tougo and M. Yamaguchi, *Org. Lett*., 2018, **20**, 1756; (c) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res*., 2015, **48**, 1040; (d) Y. Park, Y. Kim and S. Chang, *Chem. Rev*., 2017, **117**, 9247.

(3) (a) S. Sharma, R. S. Pathare, A. K. Maurya, K. Gopal, T. K. Roy, D. M. Sawant and R. T. Pardasani, *Org. Lett*., 2016, **18**, 356; (b) W.–C. Yang, K. Wei, X. Sun, J. Zhu and L. Wu, *Org. Lett*., 2018, **20**, 3144; (c) X. Zhang, W. Zeng, Y. Yang, H. Huang and Y. Liang, *Org. Lett*., 2014, **16**, 876; (d) M. Cong, Y. Fan, J.–M. Raimundo, J. Tang and L. Peng, *Org. Lett*., 2014, **16**, 4074; (e) F.–J. Chen, G. Liao, X. Li, J. Wu and B.–F. Shi, *Org. Lett*., 2014, **16**, 5644.

(4) (a) Y. Hayashi, *Chem. Sci*., 2016, **7**, 866; (b) V. Gembus, J.-F. Bonfanti, O. Querolle, P. Jubault, V. Levacher and C. Hoarau, *Org. Lett*., 2012, **14**, 6012.

(5) (a) H. R. Benjamin, Z. Serge, R. Vishal and K. Y. Andrei, *Chem. Rev*., 2014, **114**, 8323; (b) C.-Y. Huang and A. G. Doyle, *Chem. Rev*., 2014, **114**, 8153.

(6) (a) V. L. Blair, W. Clegg, A. R. Kennedy, Z. Livingstone, L. Russo and E. Hevia, *Angew. Chem., Int. Ed*., 2011, **50**, 9857; (b) R. Chinchilla, C. Najera and M. Yus, *Chem. Rev*., 2004, **104**, 2667; (c) M. Schlosser, *Organometallics in Synthesis*, 2nd ed. (Ed.: M. Schlosser), Wiley, New York, 2002, chap. 1; (d) O. Bayh, H. Awad, F. Mongin, C. Hoarau, L. Bischoff, F. Trcourt, G. Quguiner, F. Marsais, F. Blanco, B. Abarca and R. Ballesteros, *J. Org. Chem*., 2005, **70**, 5190.

(7) (a) E. Crowe, F. Hossner and M. J. Hughes, *Tetrahedron*, 1995, **51**, 8889; (b) C. Hilf, F. Bosold, K. Harms, M. Marsch and G. Boche, *Chem. Ber. Recl.*, 1997, **130**, 1213; (c) G. Boche, F. Bosold, H. Hermann, M. Marsch, K. Harms and J. C. W. Lohrenz, *Chem. -Eur. J*., 1998, **4**, 814; (d) D. J. Pippel, C. M. Mapes and N. S. Mani, *J. Org. Chem*., 2007, **72**, 5828; (e) M. Shilai, Y. Kondo and T. Sakamoto, *J. Chem. Soc*., Perkin Trans. 1, 2001, 442; (f) A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem*., 2006, **118**, 3024; *Angew. Chem., Int. Ed*., 2006, **45**, 2958.

(8) (a) Q. Song, Q. Feng and M. Zhou, *Org. Lett*., 2013, **15**, 5990; (b) L. Racane, V. Tralic-Kulenovic, Z. Mihalic, G. Pavlovic and G. Karminski-Zamola, *Tetrahedron*, 2008, **64**, 11594; (c) J. Metzger, *In Comprehensive Heterocyclic Chemistry*; A. R. Katritzky and C. W. Rees, Eds.; Pergamon: Oxford, 1984, **6**, 235; (d) G. Bartoli, F. Ciminale and P. E. Todesco, *Tetrahedron Lett*., 1975, **16**, 1785; (e) G. Bartoli, M. Lelli, F. Ciminale and O. *J.* Attanasi, *Chem. Soc*., Perkin Trans. 2, 1977, 20; (f) M. R. Chedekel, D. E. Sharp and G. A. Jeffery, *Synth. Commun*., 1980, 167; (g) G. Bartoli, M. Fiorentino, F. Ciminale and P. E. Todesco, *J. Chem. Soc., Chem. Comm.*, 1974, 732; (h) M. Aresta, C. F. Nobile, F. Ciminale and G. Bartoli, *J. C. S. Dalton*, 1976.

(9) (a) S. Mitra, A. Chakraborty, S. Mishra, A. Majee and A. Hajra, *Org. Lett*., 2014, **16**, 5652; (b) T. Ramana, P. Saha, M. Das and T. Punniyamurthy, *Org. Lett*., 2010, **12**, 84; (c) S. K. Sahoo, L. Jamir, S. Guin and B. K. Patel, *Adv. Synth. Catal*., 2010, **352**, 2538; (d) S. Pinapati, U. Mandapati, R. Tamminana and R. Rudraraju, *NewJ.Chem*., 2017, **41**, 8711.

(10) D. Chang, D. Zhu, P. Zou and L. Shi, *Tetrahedron*, 2015, **71**, 1684.

(11) A. Behera, P. Sau, A. K. Sahoo and B. K. Patel, *J. Org. Chem*., 2018, DOI: 10.1021/acs.joc.8b01797.

(12) (a) A. Gollner and P. A. Koutentis, *Org. Lett.*, 2010, **12**, 1352; (b) S. Guo, M. H. Lim and H. V. Huynh, *Organometallics*, 2013, **32**, 7225; (c) J. Chae, J. Yun and S. L. Buchwald, *Org. Lett*., 2004, **6**, 4809; (d) P.-Y. Yao, Y. Zhang, R. P. Hsung and K. Zhao, *Org. Lett*., 2008, **10**, 4275; (e) S. Yugandar, S. Konda and H. Ila, *Org. Lett*., 2017, **19**, 1512; (f) Y. Hayashi, K. Okano and A. Mori, *Org. Lett*., 2018, **20**, 958; (g) N. K. Nandwana, K. Pericherla, P. Kaswan and A. Kumar, *Org. Biomol. Chem*., 2015, **13**, 2947; (h) G. Kleinhans, G. Guisado-Barrios, D. C. Liles, G. Bertrand and D. I. Bezuidenhout, *Chem. Commun*., 2016, **52**, 3504; (i) X. Zhang, A. Liu and W. Chen, *Org. Lett*., 2008, **10**, 3849.

(13) Q. Wang, Y. Su, L. Li and H. Huang, *Chem. Soc. Rev*., 2016, **45**, 1257.

(14) (a) J. Li and L. Neuville, *Org. Lett*., 2013, **15**, 6124; (b) P. Li, G. Cheng, H. Zhang, X. Xu, J. Gao and X. Cui, *J. Org. Chem*., 2014, **79**, 8156; (c) L. Q. Tran, J. Li and L. Neuville, *J. Org. Chem*., 2015, **80**, 6102; (d) S. M. Sajadi and M. Maham, *Lett. Org. Chem*., 2014, **11**, 136.

(15) (a) G. Kaupp, J. Schmeyers and J. Boy, *Chem. -Eur. J*., 1998, **4**, 2467; (b) C.-Y. Chen, F. F. Wong, J. J. Huang, S.-K. Lin and M.-Y. Yeh, *Tetrahedron Lett*., 2008, **49**, 6505; (c) K. H. Chaudhuri, U. S. Mahajan, D. S. Bhalerao and K. G. Akamanchi, *Synlett*, 2007, 2815.

(16) (a) H. Miyasaka, R. Clerac, C. S. Campos-Fernandez and K. R. Dunbar, *Inorg. Chem*., 2001, **40**, 1663; (b) S. Kamijo, T. Jin and Y. Yamamoto, *Angew. Chem., Int. Ed*., 2002, **41**, 1780; (c) H. Brand, P. Mayer, A. Schulz, T. Soller and A. Villinger, *Chem. Asian J*., 2008, **3**, 1050; (d) A. Renodon-Corniere, S. Dijols, C. Perollier, D. Lefevre-Groboillot, J.-L. Boucher, R. Attias, M.-A. Sari, D. Stuehr and D. Mansuy, *J. Med. Chem*., 2002, **45**, 944; (e) T. V. Hughes, S. D. Hammond and M. P. Cava, *J. Org. Chem*., 1998, **63**, 401.

(17) J. M. McCall, R. E. TenBrink and J. J. Ursprung, *J. Org. Chem*., 1975, **40**, 3304.

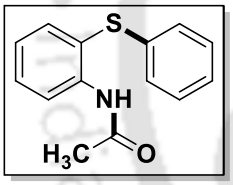
(18) (a) L. Y. Hu, J. Guyo, S. S. Magar, J. B. Fischer, K. J. Burke-Howie and G. J. Durant, *J. Med. Chem*., 1997, **40**, 4281; (b) J. R. Robinson and W. H. Brown, *Can. J. Chem*., 1951, **29**, 1069.

(19) For review, see: (a) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev*., 2007, **107**, 5133 and references cited therein: (b) C. Jiang, D. J. Covell, A. F. Stepan, M. S. Plummer and M. C. White, *Org. Lett*., 2012, **14**, 1386; (c) E. M. Stang and M. C. White, *J. Am. Chem. Soc*., 2011, **133**, 14892; (d) P. K. Dorman, P. L. Leung and V. M. Dong, *Tetrahedron*, 2011, **67**, 4378; (e) J. Chen, J. Chen, F. Lang, X. Zhang, L. Cun, J. Zhu, J. Deng and J. Liao, *J. Am. Chem. Soc*., 2010, **132**, 4552; (f) R. Mariz, X. Luan, M. Gatti, A. Linden and R. Dorta, *J. Am. Chem. Soc*., 2008, **130**, 2172.

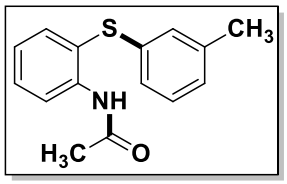
(20) (a) Astra Aktiebolag Patent: US5877192 A, 1998; (b) Laboratoire L. Lafon Patent: US4927855A, 1990.

(21) (a) P. F. Schatz, *J. Chem. Educ*., 1996, **73**, 267; (b) Y.-f. Ji, H. Yan and Q.-b. Jiang, *Eur. J. Org. Chem*., 2015, 2051.

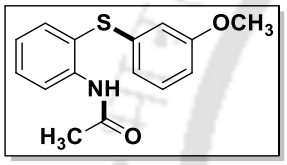
V.6. Spectral data



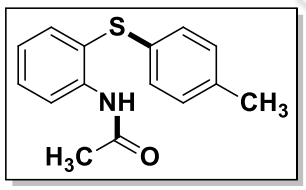
***N*-(2-(Phenylthio)phenyl)acetamide (1aa′):** Brownish solid; mp 75–77 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 7.08–7.13 (m, 3H), 7.17 (t, 1H, J = 7.2 Hz), 7.24 (d, 2H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.57 (d, 1H, J = 7.2 Hz), 8.20 (s, 1H), 8.43 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 120.0, 121.05, 124.6, 126.5, 127.3, 129.5, 131.2, 135.9, 136.6, 140.0, 168.6; IR (KBr): 3319, 2925, 2853, 1675, 1576, 1511, 1476, 1435, 1370, 1295, 1240, 1164, 1068, 1008, 944, 870, 757, 689, 672, 597, 543, 502 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}NOS$ $[M+H]^+$ 244.0791; found 244.0783.



***N*-(2-(*m*-Tolylthio)phenyl)acetamide (1ba′):** Brownish solid; mp 71–73 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 2.27 (s, 3H), 6.87 (d, 1H, *J* = 7.8 Hz), 6.92 (s, 1H), 6.98 (d, 1H, *J* = 7.8 Hz), 7.10–7.14 (m, 2H), 7.43 (t, 1H, *J* = 7.8 Hz), 7.56 (d, 1H, *J* = 7.2 Hz), 8.21 (s, 1H), 8.42 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 25.0, 120.2, 121.0, 124.6, 127.5, 128.0, 129.4, 131.0, 135.5, 136.5, 139.5, 140.0, 168.6; IR (KBr): 3290, 3056, 2923, 1666, 1576, 1517, 1473, 1434, 1362, 1297, 1245, 1163, 1037, 1017, 964, 938, 876, 853, 781, 756, 685, 601, 548, 525, 470 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NOS$ $[M+H]^+$ 258.0947; found 258.0939.

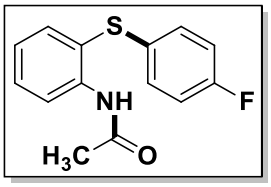


***N*-(2-((3-Methoxyphenyl)thio)phenyl)acetamide (1ca′):** Brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.69 (s, 3H), 6.60 (s, 1H), 6.64 (d, 1H, *J* = 7.8 Hz), 6.69 (d, 1H, *J* = 7.8 Hz), 7.09 (t, 1H, *J* = 7.2 Hz), 7.14 (t, 1H, *J* = 7.8 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 8.20 (s, 1H), 8.41 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 55.4, 112.0, 112.8, 119.4, 119.8, 121.0, 124.6, 130.3, 131.2, 136.7, 137.2, 140.1, 160.3, 168.6; IR (KBr): 3549, 3292, 2934, 2835, 1700, 1588, 1520, 1477, 1426, 1367, 1299, 1230, 1182, 1160, 1096, 1069, 1038, 947, 858, 759, 652, 590, 546, 487 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NO_2S$ $[M+H]^+$ 274.0896; found 274.0903.

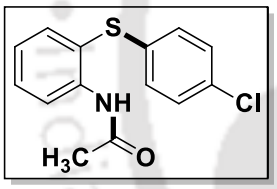


***N*-(2-(*p*-Tolylthio)phenyl)acetamide (1da′):** Brownish solid; mp 74–76 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H), 2.29 (s, 3H), 7.01 (d, 2H, *J* = 8.4 Hz), 7.06–7.10 (m, 3H), 7.41 (t, 1H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 8.20 (s, 1H), 8.40 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 25.0, 121.0, 124.5, 127.7, 128.0, 130.3, 130.8, 132.0, 136.2, 136.7, 139.7, 168.5; IR (KBr): 3306, 2918, 2861, 1670, 1577, 1525, 1460, 1435, 1367, 1301, 1244, 1164, 1103, 1036, 1017, 960, 835, 809, 753, 709, 669, 597, 544, 505, 450 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NOS$ $[M+H]^+$ 258.0947; found

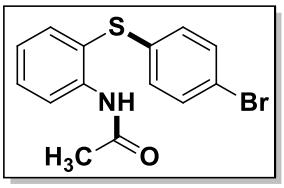
258.0958.



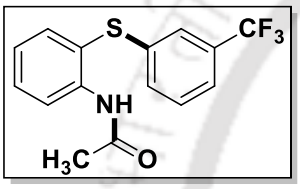
***N*-(2-((4-Fluorophenyl)thio)phenyl)acetamide (1ea′):** White solid; mp 93–95 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.08 (s, 3H), 6.96 (t, 2H, *J* = 8.4 Hz), 7.07–7.11 (m, 3H), 7.41 (t, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 7.2 Hz), 8.16 (s, 1H), 8.39 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 116.7 (d, *J* = 22.1 Hz), 120.8, 121.2, 124.7, 129.7 (d, *J* = 7.7 Hz), 130.7, 131.1, 136.2, 139.7, 160.6, 163.1, 168.5; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -118.4 (s); IR (KBr): 3291, 2924, 2853, 1893, 1662, 1584, 1525, 1487, 1436, 1395, 1370, 1270, 1223, 1156, 1036, 1014, 943, 867, 833, 814, 758, 676, 636, 599, 543, 515, 473 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}FNOS$ $[M+H]^+$ 262.0696; found 262.0722.



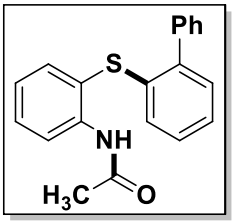
***N*-(2-((4-Chlorophenyl)thio)phenyl)acetamide (1fa′):** Light brownish solid; mp 78–80 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 6.98 (d, 2H, *J* = 8.4 Hz), 7.11 (t, 1H, *J* = 7.8 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.44 (t, 1H, *J* = 7.8 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 8.15 (s, 1H), 8.42 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 119.6, 121.2, 124.8, 128.4, 129.6, 131.4, 132.4, 134.5, 136.6, 140.0, 168.6; IR (KBr): 3447, 3827, 2924, 2853, 1663, 1577, 1520, 1473, 1433, 1369, 1298, 1251, 1092, 1013, 822, 760, 676, 601, 551, 504, 457 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}ClNOS$ $[M+H]^+$ 278.0401; found 278.0408.



***N*-(2-((4-Bromophenyl)thio)phenyl)acetamide (1ga′):** White solid; mp 121–123 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 6.91 (d, 2H, *J* = 8.4 Hz), 7.12 (t, 1H, *J* = 7.8 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.45 (t, 1H, *J* = 7.2 Hz), 7.54 (d, 1H, *J* = 7.8 Hz), 8.14 (s, 1H), 8.43 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 25.0, 119.4, 120.3, 121.3, 124.8, 128.7, 131.5, 132.6, 135.3, 136.7, 140.1, 168.5; IR (KBr): 3284, 2925, 2854, 1661, 1579, 1513, 1464, 1433, 1376, 1297, 1265, 1086, 1008, 815, 741, 589 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}BrNOS$ $[M+H]^+$ 321.9896; found 321.9892.

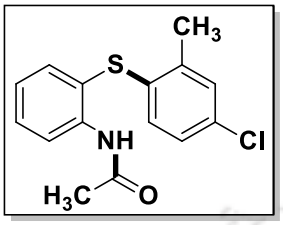


***N*-(2-((3-(Trifluoromethyl)phenyl)thio)phenyl)acetamide (1ha′):** Brownish solid; mp 81–83 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 7.10 (d, 1H, *J* = 7.8 Hz), 7.14 (t, 1H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.8 Hz), 7.41 (d, 2H, *J* = 7.2 Hz), 7.48 (t, 1H, *J* = 7.8 Hz), 7.57 (d, 1H, *J* = 7.2 Hz), 8.16 (s, 1H), 8.46 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 25.0, 118.5, 121.3, 123.1, 123.7, 124.9, 129.9 (d, *J* = 14.1 Hz), 131.9 (t, *J* = 13.3 Hz), 136.9, 137.7, 140.3, 168.5; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.1 (d, *J* = 0.9 Hz); IR (KBr): 3265, 2925, 2853, 1660, 1582, 1524, 1438, 1423, 1365, 1321, 1272, 1188, 1167, 1118, 1069, 1016, 971, 945, 905, 880, 854, 791, 763, 694, 649, 606, 550, 492 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NOS$ $[M+H]^+$ 312.0664; found 312.0649.

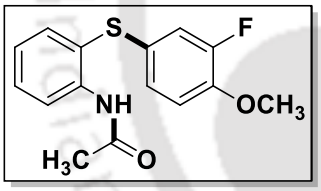


***N*-(2-([1,1'-Biphenyl]-2-ylthio)phenyl)acetamide (1ia′):** Light brownish solid; mp 58–60 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.0 (s, 3H), 6.93 (d, 1H, *J* = 7.8 Hz), 7.10 (t, 1H, *J* = 7.2 Hz), 7.21 (t, 1H, *J* = 7.2 Hz), 7.28 (d, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.8 Hz), 7.42 (t, 1H, *J* = 7.8 Hz), 7.46 (d, 3H, *J* = 6.6 Hz), 7.49–7.53 (m, 3H), 7.95 (s, 1H), 8.39 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 120.9, 124.5, 126.6, 128.1, 128.2, 128.5, 129.5, 130.7, 130.9, 134.4, 136.7, 139.9, 140.3, 141.6, 168.5; IR (KBr): 3363, 2925, 2853, 1700, 1579,

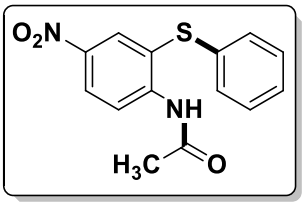
1511, 1460, 1430, 1368, 1298, 1235, 1160, 1073, 1036, 1007, 752, 702, 677, 652, 686, 548, 493, 455 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NOS$ $[M+H]^+$ 320.1104; found 320.1101.



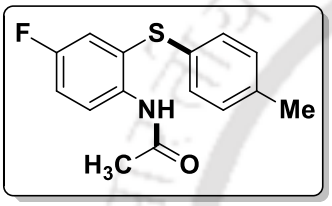
***N*-(2-((4-Chloro-2-methylphenyl)thio)phenyl)acetamide (1ja′):** Brownish solid; mp 97–99 °C; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.08 (s, 3H), 2.40 (s, 3H), 6.61 (d, 1H, J = 8.4 Hz), 7.0 (d, 1H, J = 7.8 Hz), 7.11 (t, 1H, J = 7.2 Hz), 7.19 (s, 1H), 7.42–7.45 (m, 2H), 8.05 (s, 1H), 8.42 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.3, 25.0, 119.6, 121.3, 124.9, 127.2, 128.3, 130.5, 131.1, 132.2, 133.4, 136.1, 137.8, 139.9, 168.5; IR (KBr): 3239, 2924, 2853, 1681, 1654, 1577, 1528, 1466, 1437, 1367, 1297, 1257, 1199, 1158, 1098, 1050, 940, 870, 819, 749, 681, 599, 576, 548, 481, 457 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{15}ClNOS$ $[M+H]^+$ 292.0557; found 292.0551.



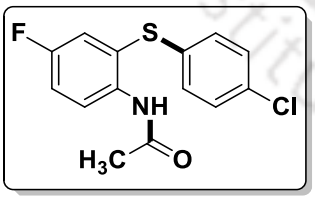
***N*-(2-((3-Fluoro-4-methoxyphenyl)thio)phenyl)acetamide (1ka′):** Dark brownish solid; mp 76–78 °C; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.10 (s, 3H), 3.84 (s, 3H), 6.82–6.91 (m, 3H), 7.09 (t, 1H, J = 7.2 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 7.6 Hz), 8.16 (s, 1H), 8.38 (d, 1H, J = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 25.0, 56.5, 114.4 (d, J = 2.2 Hz), 116.7 (d, J = 20.1 Hz), 121.2 (d, J = 11.1 Hz), 124.7 (d, J = 9.1 Hz), 126.9 (d, J = 6.0 Hz), 130.9, 135.9, 139.5, 147.0 (d, J = 10.5 Hz), 151.9, 153.5, 168.5; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -135.9 (s); IR (KBr): 3360, 2927, 2849, 1696, 1580, 1510, 1432, 1368, 1300, 1269, 1209, 1181, 1133, 1077, 1025, 894, 865, 808, 758, 687, 645, 593, 547, 477 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{15}FNO_2S$ $[M+H]^+$ 292.0802; found 292.0809.



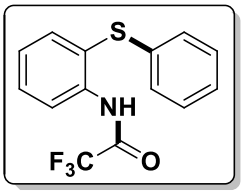
***N*-(4-Nitro-2-(phenylthio)phenyl)acetamide (2aa′):** Brownish solid; mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.13 (s, 3H), 7.16 (d, 2H, *J* = 6.8 Hz), 7.28–7.33 (m, 3H), 8.27 (dd, 1H, *J* = 9.2, 2.8 Hz), 8.46 (d, 2H, *J* = 2.4 Hz), 8.68 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.1, 120.1, 126.4, 127.4, 127.5, 128.6, 129.6, 130.0, 131.4, 133.6, 145.1, 168.8; IR (KBr): 3447, 2924, 2854, 1621, 1577, 1499, 1337, 1262, 1092, 1022, 802, 742, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_3S$ $[M+H]^+$ 289.0641; found 289.0641.



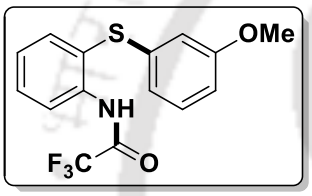
***N*-(4-Fluoro-2-(*p*-tolylthio)phenyl)acetamide (3da′):** Brownish solid; mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 2.31 (s, 3H), 7.02–7.15 (m, 6H), 7.93 (s, 1H), 8.25 (dd, 1H, *J* = 9.2, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 24.6, 116.6 (d, *J* = 21.8 Hz), 120.9 (d, *J* = 23.3 Hz), 123.1 (d, *J* = 7.8 Hz), 125.0 (d, *J* = 7.8 Hz), 130.1 (d, *J* = 95.5 Hz), 135.0, 137.7, 157.6, 160.0, 168.4; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -120.3 (s); IR (KBr): 3232, 2924, 2854, 1647, 1544, 1474, 1392, 1302, 1239, 1190, 1018, 899, 853, 811, 738, 608, 504 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{15}FNOS$ $[M+H]^+$ 276.0856; found 276.0872.



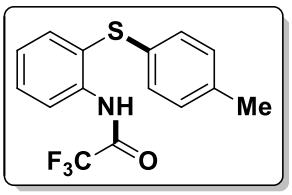
***N*-(2-((4-Chlorophenyl)thio)-4-fluorophenyl)acetamide (3fa′):** Brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 7.06 (d, 2H, *J* = 8.4 Hz), 7.10–7.15 (m, 1H), 7.19–7.21 (m, 1H), 7.25–7.27 (m, 2H), 7.89 (s, 1H), 8.33 (dd, 1H, *J* = 8.8, 5.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 117.7 (d, *J* = 21.7 Hz), 121.8 (d, *J* = 23.3 Hz), 122.9, 123.2 (d, *J* = 8.3 Hz), 129.8 (d, *J* = 25.8 Hz), 133.3 (d, *J* = 18.6 Hz), 135.7, 157.6, 160.0, 168.4; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -119.9 (s); IR (KBr): 3437, 2963, 2856, 1646, 1526, 1475, 1392, 1261, 1094, 1021, 801, 700, 505 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{12}ClFNOS$ $[M+H]^+$ 296.0307; found 296.0337.



2,2,2-Trifluoro-*N*-(2-(phenylthio)phenyl)acetamide (1ab′): Light brownish solid; mp 53–55 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.12 (d, 2H, *J* = 7.2 Hz), 7.21 (t, 1H, *J* = 7.2 Hz), 7.25–7.28 (m, 3H), 7.51 (t, 1H, *J* = 8.4 Hz), 7.68 (d, 1H, *J* = 7.8 Hz), 8.40 (d, 1H, *J* = 7.8 Hz), 9.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.7, 116.7, 121.3, 122.5, 126.6, 127.2, 128.2, 129.7, 131.3, 132.0, 134.6, 136.8, 137.3, 154.8 (q, *J* = 37.3 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.2 (t); IR (KBr): 3451, 2926, 2855, 1637, 1534, 1443, 1154, 1024, 742, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}F_3NOS$ $[M+H]^+$ 298.0508; found 298.0519.

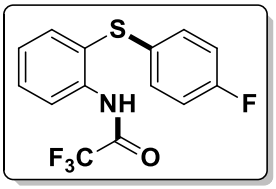


2,2,2-Trifluoro-*N*-(2-((3-methoxyphenyl)thio)phenyl)acetamide (1cb′): Brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.73 (s, 3H), 6.64–6.75 (m, 3H), 7.17 (t, 1H, *J* = 8.0 Hz), 7.24–7.28 (m, 1H), 7.50 (t, 1H, *J* = 8.8 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 8.39 (d, 1H, *J* = 8.4 Hz), 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 112.9, 113.8, 120.4, 121.4, 122.4, 126.6, 130.6, 131.4, 135.9, 136.9, 137.5, 160.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.2 (s); IR (KBr): 3329, 2924, 2854, 1720, 1587, 1540, 1444, 1413, 1148, 1095, 1025, 801, 690, 621 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NO_2S$ $[M+H]^+$ 328.0614; found 328.0632.

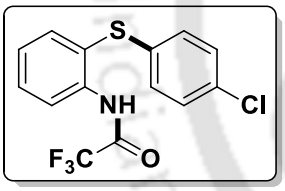


2,2,2-Trifluoro-*N*-(2-(*p*-tolylthio)phenyl)acetamide (1db′): Light brownish solid; mp 100–102 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 7.07 (q, 4H, *J* = 7.6 Hz), 7.23 (t, 1H, *J* = 7.8 Hz), 7.47 (t, 1H, *J* = 6.6 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 8.37 (d, 1H, *J* = 8.4 Hz), 9.13 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 114.8, 116.7, 121.2, 123.5, 126.6, 129.0, 130.5, 130.8, 130.9, 136.4, 137.0, 137.6, 154.8 (q, *J* = 37.3 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.2 (s); IR (KBr): 3254, 2920, 1670, 1581, 1512, 1433, 1400, 1292, 1185, 1018,

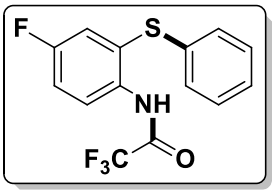
803, 756, 535 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NOS$ $[M+H]^+$ 312.0664; found 314.0461.



2,2,2-Trifluoro-*N*-(2-((4-fluorophenyl)thio)phenyl)acetamide (1eb′): Light brownish solid; mp 73–75 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.98 (t, 2H, J = 8.4 Hz), 7.13–7.16 (m, 2H), 7.23–7.27 (m, 1H), 7.49 (t, 1H, J = 7.2 Hz), 7.63 (d, 1H, J = 7.6 Hz), 8.37 (d, 1H, J = 8.0 Hz), 9.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 114.4, 117.0 (d, J = 22.2 Hz), 117.2, 121.5, 123.3, 126.7, 129.6 (d, J = 3.3 Hz), 130.8 (d, J = 8.2 Hz), 131.3, 136.4, 137.0, 154.6, 155.0, 162.3 (d, J = 246.5 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -117.2 (s), -79.1 (s); IR (KBr): 3318, 2924, 1713, 1588, 1490, 1261, 1154, 1093, 1018, 800, 622, 515 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}F_4NOS$ $[M+H]^+$ 316.0414; found 316.0425.

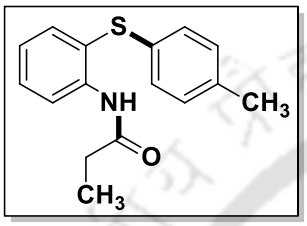


***N*-(2-((4-Chlorophenyl)thio)phenyl)-2,2,2-trifluoroacetamide (1fb′):** Light brownish solid; mp 84–86 °C; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.04 (d, 2H, J = 8.4 Hz), 7.23–7.29 (m, 3H), 7.52 (t, 1H, J = 8.4 Hz), 7.66 (d, 1H, J = 7.8 Hz), 8.40 (d, 1H, J = 8.4 Hz), 9.06 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.7, 116.7, 121.5, 122.1, 126.8, 129.4, 129.9, 131.6, 133.2, 133.3, 136.8, 137.3, 154.8 (q, J = 37.5 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.1 (s); IR (KBr): 3261, 2920, 1695, 1583, 1434, 1294, 1152, 1092, 1036, 815, 757, 535 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}ClF_3NOS$ $[M+H]^+$ 332.0118; found 332.0139.

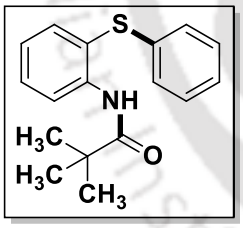


2,2,2-Trifluoro-*N*-(4-fluoro-2-(phenylthio)phenyl)acetamide (3ab′): Brownish gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.21 (m, 3H), 7.28–7.34 (m, 4H), 8.31 (dd, 1H, J = 9.2, 5.2 Hz), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 117.2, 117.6 (d, J = 22.1 Hz), 122.4 (d, J = 23.4 Hz), 123.2 (d, J = 8.1

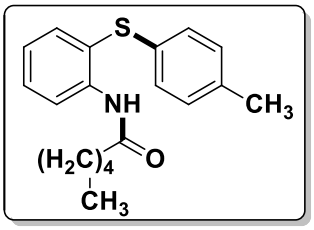
Hz), 125.9 (d, *J* = 8.0 Hz), 128.0, 129.4, 130.0, 132.9 (d, *J* = 3.2 Hz), 133.4, 154.7, 155.0, 159.9 (d, *J* = 248.2 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -117.0 (s), -79.1 (s); IR (KBr): 3314, 2923, 1708, 1584, 1485, 1253, 1150, 1089, 1015, 797, 618, 511 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}F_4NOS$ $[M+H]^+$ 316.0414; found 316.0418.



***N*-(2-(*p*-Tolylthio)phenyl)propionamide (1dc′):** Yellowish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.11 (t, 3H, *J* = 7.8 Hz), 2.27–2.30 (m, 5H), 7.00 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 7.8 Hz), 7.09 (t, 1H, *J* = 7.8 Hz), 7.41 (t, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 8.25 (s, 1H), 8.45 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 9.6, 21.1, 31.2, 120.8, 120.9, 124.4, 127.8, 130.3, 130.9, 132.0, 136.3, 136.6, 139.8, 172.2; IR (KBr): 3367, 2975, 2921, 1695, 1579, 1410, 1433, 1294, 1182, 1083, 1016, 805, 756 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}NOS$ $[M+H]^+$ 272.1104; found 272.1091.

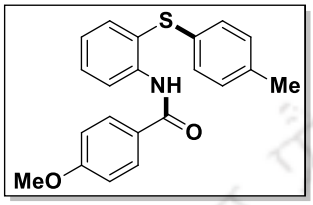


***N*-(2-(Phenylthio)phenyl)pivalamide (1ad′):** Yellowish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.10 (s, 9H), 7.03 (d, 2H, *J* = 7.2 Hz), 7.09–7.15 (m, 2H), 7.22 (t, 2H, *J* = 7.2 Hz), 7.44–7.49 (m, 1H), 7.61 (d, 1H, *J* = 8.0 Hz), 8.52 (d, 1H, *J* = 8.4 Hz), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 27.4, 40.2, 119.6, 120.8, 124.3, 126.3, 126.6, 129.5, 130.3, 131.4, 135.7, 136.1, 136.9, 140.3, 176.9; IR (KBr): 3384, 2926, 1690, 1580, 1511, 1478, 1421, 1301, 1175, 1025, 741, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{20}NOS$ $[M+H]^+$ 286.1260; found 286.1238.

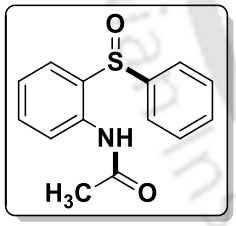


***N*-(2-(*p*-Tolylthio)phenyl)hexanamide (1de′):** Brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.84–0.89 (m, 3H), 1.22–1.26 (m, 4H), 1.51–1.58 (m, 2H), 2.24 (t, 2H, *J* = 7.6 Hz), 2.29 (s, 3H), 6.99–7.11 (m, 5H), 7.42 (t, 1H, *J* = 8.4 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 8.22 (s, 1H), 8.46 (d, 1H, *J* = 8.0 Hz);

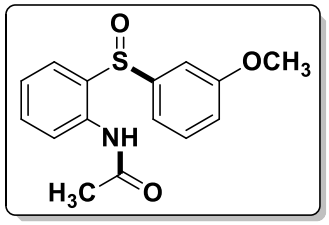
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 19.4, 21.1, 22.5, 25.3, 31.4, 115.5, 118.9, 127.3, 130.0, 130.3, 130.9, 131.0, 133.2, 135.7, 137.7, 148.8; IR (KBr): 3368, 2924, 2855, 1699, 1510, 1459, 1262, 1092, 1021, 803, 702, 501 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{24}NOS$ $[M+H]^+$ 314.1573; found 314.1590.



4-Methoxy-*N*-(2-(*p*-tolylthio)phenyl)benzamide (1df′): Brownish solid; mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 3.85 (s, 3H), 6.90 (d, 2H, J = 8.8 Hz), 7.05 (s, 4H), 7.12 (t, 1H, J = 7.2 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 7.6 Hz), 7.65 (d, 2H, J = 8.8 Hz), 8.66 (d, 1H, J = 8.0 Hz), 9.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 55.6, 114.1, 120.6, 120.9, 124.4, 127.2, 127.8, 129.1, 130.3, 131.1, 132.0, 136.5, 136.7, 140.2, 162.7, 165.0; IR (KBr): 3366, 2927, 2839, 1677, 1606, 1575, 1502, 1432, 1303, 1251, 1177, 1100, 1030, 837, 843, 806, 760, 692, 579, 507 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{20}NO_2S$ $[M+H]^+$ 350.1209; found 350.1202.

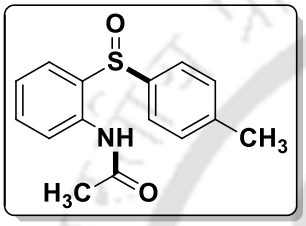


***N*-(2-(Phenylsulfinyl)phenyl)acetamide (1aa″):** Dark brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 7.17 (t, 1H, J = 7.2 Hz), 7.43–7.47 (m, 3H), 7.47–7.50 (m, 3H), 7.57 (d, 1H, J = 7.2 Hz), 8.31 (d, 1H, J = 8.4 Hz), 10.04 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 123.4, 123.5, 124.4, 128.2, 129.4, 131.0, 133.4, 140.2, 142.9, 159.3, 168.7; IR (KBr): 3270, 2925, 2856, 1694, 1586, 1527, 1473, 1439, 1371, 1303, 1252, 1159, 1082, 1019, 925, 754, 692, 599, 553, 490, 486, 457 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{14}NO_2S$ $[M+H]^+$ 260.0740; found 260.0741.

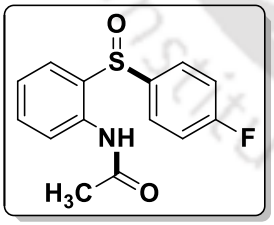


***N*-(2-((3-Methoxyphenyl)sulfinyl)phenyl)acetamide (1ca″):** Dark brownish solid; mp 121–123 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 3.78 (s, 3H), 6.93 (d, 1H, J = 8.4 Hz), 6.98 (d, 1H, J = 7.8 Hz), 7.08 (s, 1H), 7.16 (t, 1H, J = 7.2 Hz), 7.33 (t, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.8 Hz), 7.54 (d,

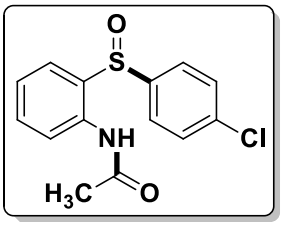
1H, *J* = 7.8 Hz), 8.31 (d, 1H, *J* = 8.4 Hz), 10.04 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm): 24.8, 55.7, 109.8, 116.5, 116.6, 123.3, 123.5, 128.09, 128.1, 130.5, 133.3, 140.2, 144.3, 160.4, 168.6; IR (KBr): 3242, 3050, 2926, 2852, 1693, 1592, 1539, 1471, 1428, 1365, 1307, 1285, 1230, 1184, 1164, 1072, 1040, 1020, 956, 915, 841, 772, 688, 600, 568, 515, 493, 468 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NO_3S$ $[M+H]^+$ 290.0845; found 290.0848.



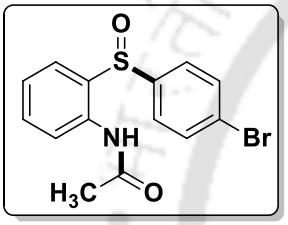
***N*-(2-(*p*-Tolylsulfinyl)phenyl)acetamide (1da″):** Dark brownish solid; mp 85–87 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 2.36 (s, 3H), 7.16 (t, 1H, *J* = 7.2 Hz), 7.25 (d, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.46–7.49 (m, 1H), 7.53 (d, 1H, *J* = 7.2 Hz), 8.32 (d, 1H, *J* = 8.4 Hz), 10.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 24.9, 120.0, 123.2, 123.5, 124.4, 127.9, 128.3, 130.2, 133.2, 139.7, 140.2, 141.6, 168.7; IR (KBr): 3451, 3259, 2925, 2853, 1700, 1589, 1532, 1467, 1435, 1370, 1302, 1249, 1161, 1082, 1021, 894, 811, 760, 705, 619, 597, 549, 533, 494, 468 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NO_2S$ $[M+H]^+$ 274.0896; found 274.0907.



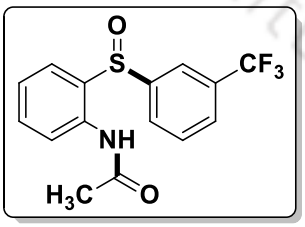
***N*-(2-((4-Fluorophenyl)sulfinyl)phenyl)acetamide (1ea″):** Dark brownish solid; mp 99–101 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 7.14–7.19 (m, 3H), 7.47–7.51 (m, 3H), 7.53 (d, 1H, *J* = 7.8 Hz), 8.31 (d, 1H, *J* = 7.8 Hz), 10.0 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 116.8 (d, *J* = 22.6 Hz), 123.6 (d, *J* = 21.1 Hz), 126.7 (d, *J* = 8.8 Hz), 128.0, 133.5, 138.5 (d, *J* = 3.0 Hz), 140.2, 163.5, 165.1, 168.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -111.9 (s); IR (KBr) 3441, 2925, 2853, 1697, 1589, 1532, 1492, 1466, 1436, 1372, 1032, 1230, 1156, 1082, 1021, 837, 813, 761, 673, 650, 594, 533, 474 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}FNO_2S$ $[M+H]^+$ 278.0646; found 278.0658.



***N*-(2-((4-Chlorophenyl)sulfinyl)phenyl)acetamide (1fa″):** Dark brownish solid; mp 106–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 7.17 (t, 1H, *J* = 7.8 Hz), 7.42 (s, 4H), 7.48–7.51 (m, 1H), 7.54 (d, 1H, *J* = 7.8 Hz), 8.30 (d, 1H, *J* = 5.4 Hz), 9.95 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 119.9, 123.5, 123.7, 125.8, 128.0, 129.7, 133.6, 137.4, 140.2, 141.5, 168.6; IR (KBr): 3443, 2925, 2853, 1661, 1587, 1525, 1473, 1434, 1371, 1302, 1250, 1169, 1090, 1034, 1009, 825, 762, 741, 703, 650, 600, 559, 526, 507, 464 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}ClNO_2S$ $[M+H]^+$ 294.0350; found 294.0363.

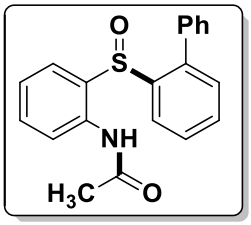


***N*-(2-((4-Bromophenyl)sulfinyl)phenyl)acetamide (1ga″):** Brownish solid; mp 95–97 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 7.18 (t, 1H, *J* = 7.2 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.2 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 8.32 (d, 1H, *J* = 7.8 Hz), 9.95 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 123.5, 123.6, 125.7, 125.9, 127.7, 128.0, 132.6, 133.6, 140.2, 142.1, 168.6; IR (KBr): 3477, 3278, 2924, 2852, 1697, 1659, 1587, 1521, 1470, 1434, 1370, 1301, 1248, 1172, 1127, 1064, 1036, 1005, 820, 762, 723, 650, 598, 555, 502 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}BrNO_2S$ $[M+H]^+$ 337.9845; found 337.9850.

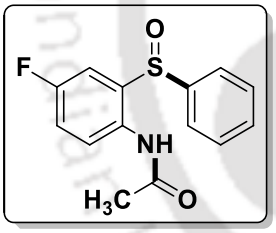


***N*-(2-((3-(Trifluoromethyl)phenyl)sulfinyl)phenyl)acetamide (1ha″):** Dark brownish solid; mp 86–88 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H), 7.20 (t, 1H, *J* = 7.2 Hz), 7.48–7.52 (m, 2H), 7.54 (t, 1H, *J* = 7.8 Hz), 7.61 (dd, 1H, *J* = 7.8, 1.3 Hz), 7.69 (d, 1H, *J* = 7.8 Hz), 7.96 (s, 1H), 8.27 (d, 1H, *J* = 8.4 Hz), 9.86 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.5, 121.2 (q, *J* = 3.7 Hz), 122.6, 123.7 (d, *J* = 29.2 Hz), 124.4, 127.7 (t, *J* = 3.3 Hz), 127.9, 128.1, 131.9 (q, *J* = 33.0 Hz), 133.9, 140.1, 144.5, 168.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr) 3487, 3255, 2924, 2852, 1664, 1585, 1523, 1467, 1433, 1375, 1327, 1304, 1280, 1173, 1129, 1098, 1069, 1035, 913, 806,

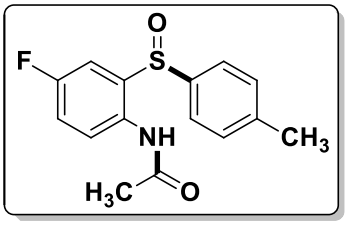
761, 695, 648, 626, 600, 578, 509, 476 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NO_2S$ $[M+H]^+$ 328.0614; found 328.0621.



***N*-(2-([1,1'-Biphenyl]-2-ylsulfinyl)phenyl)acetamide (1ia″):** Dark brownish solid; mp 73–75 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.09 (s, 3H), 6.17 (d, 1H, *J* = 7.6 Hz), 6.59 (t, 1H, *J* = 7.6 Hz), 7.09 (d, 2H, *J* = 7.2 Hz), 7.22 (t, 2H, *J* = 7.6 Hz), 7.32–7.42 (m, 3H), 7.49 (t, 1H, *J* = 7.6 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 8.09 (d, 1H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 7.6 Hz), 9.67 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 122.8, 122.84, 123.9, 126.7, 127.7, 128.4, 128.5, 128.8, 129.5, 131.2, 131.5, 132.3, 138.1, 139.4, 139.9, 140.9, 168.3; IR (KBr) 3261, 2925, 1700, 1587, 1530, 1434, 1368, 1301, 1245, 1159, 1072, 1007, 756, 702, 552, 519, 489 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{18}NO_2S$ $[M+H]^+$ 336.1053; found 336.1068.

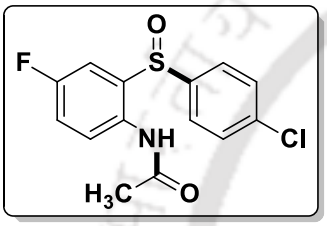


***N*-(4-Fluoro-2-(phenylsulfinyl)phenyl)acetamide (3aa″):** Yellowish gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H), 7.17–7.22 (m, 1H), 7.28–7.30 (m, 1H), 7.47–7.54 (m, 5H), 8.30 (dd, 1H, *J* = 9.2, 4.8 Hz), 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.7, 114.8 (d, *J* = 24.3 Hz), 119.9 (d, *J* = 21.6 Hz), 124.4, 125.0 (d, *J* = 4.4 Hz), 125.4 (d, *J* = 6.9 Hz), 129.3 (d, *J* = 4.4 Hz), 129.7, 129.9 (d, *J* = 5.4 Hz), 131.3 (d, *J* = 5.8 Hz), 131.5, 136.4 (d, *J* = 2.9 Hz), 142.3, 156.8, 159.2, 168.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -119.8 (s); IR (KBr) 3258, 2926, 2856, 1690, 1602, 1485, 1396, 1301, 1244, 1193, 1124, 1080, 1025, 896, 812, 750, 689, 584, 545, 499 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}FNO_2S$ $[M+H]^+$ 278.0646; found 278.0647.

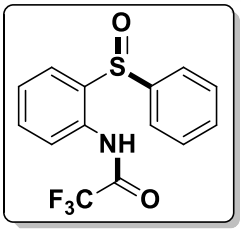


***N*-(4-Fluoro-2-(*p*-tolylsulfinyl)phenyl)acetamide (3da″):** Light brownish solid; mp 153–155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H), 2.35 (s, 3H), 7.12–7.17 (m, 1H), 7.20–7.26 (m, 3H), 7.37 (d, 2H, *J* = 8.0 Hz), 8.27 (dd, 1H, *J* =

8.8, 4.8 Hz), 9.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 24.8, 114.6 (d, J = 24.2 Hz), 119.6 (d, J = 21.6 Hz), 124.5, 125.2 (d, J = 6.9 Hz), 130.1 (d, J = 4.9 Hz), 130.4, 136.3 (d, J = 3.0 Hz), 139.1, 142.1, 156.7, 159.2, 168.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -120.0 (s); IR (KBr) 3434, 3272, 2925, 2856, 1663, 1598, 1517, 1471, 1391, 1265, 1242, 1181, 1117, 1057, 1024, 888, 841, 815, 680, 632, 584, 506, 451 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{15}FNO_2S$ $[M+H]^+$ 292.0802; found 292.0802.

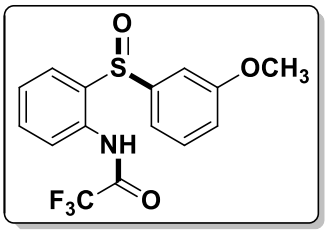


***N*-(2-((4-Chlorophenyl)sulfinyl)-4-fluorophenyl)acetamide (3fa″):** Light brownish solid; mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H), 7.18–7.23 (m, 1H), 7.26–7.29 (m, 1H), 7.46 (s, 4H), 8.29 (dd, 1H, J = 9.2, 4.8 Hz), 9.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.7, 114.7 (d, J = 24.3 Hz), 120.2 (d, J = 21.5 Hz), 125.6 (d, J = 7.0 Hz), 125.8, 129.7 (d, J = 5.0 Hz), 129.9, 136.3, 137.9, 140.8, 156.8, 159.3, 168.5; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -119.4 (s); IR (KBr) 3423, 3273, 2926, 2855, 1661, 1598, 1515, 1476, 1391, 1373, 1245, 1184, 1089, 1058, 1015, 888, 825, 740, 679, 587, 506, 477 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{12}ClFNO_2S$ $[M+H]^+$ 312.0256; found 312.0354.

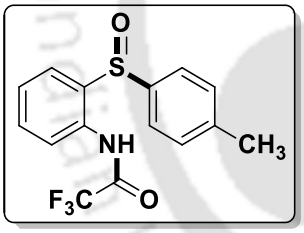


2,2,2-Trifluoro-*N*-(2-(phenylsulfinyl)phenyl)acetamide (1ab″): Brownish solid; mp 92–94 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.25 (t, 1H, J = 7.2 Hz), 7.40 (q, 3H, J = 6.3 Hz), 7.45 (d, 2H, J = 7.2 Hz), 7.48 (t, 1H, J = 7.2 Hz), 7.56 (d, 1H, J = 7.8 Hz), 8.28 (d, 1H, J = 8.4 Hz), 11.51 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.8, 116.7, 123.1, 126.4, 127.3, 129.5, 129.9, 130.2, 134.4, 135.6, 140.5, 155.0 (q, J = 37.8 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.1 (s); IR (KBr): 3441, 2924, 2854, 1728, 1614, 1554, 1462, 1441, 1280, 1186, 1160, 1138, 1018, 897, 800, 758, 738, 682, 549, 530, 494 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}F_3NO_2S$ $[M+H]^+$

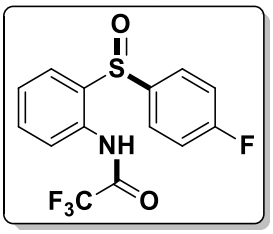
314.0457; found 314.0461.



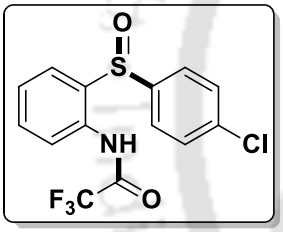
2,2,2-Trifluoro-*N*-(2-((3-methoxyphenyl)sulfinyl)phenyl)acetamide (1cb″): Brownish solid; mp 95–97 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.81 (s, 3H), 6.95–6.99 (m, 2H), 7.14 (s, 1H), 7.30–7.33 (m, 1H), 7.35 (t, 1H, *J* = 7.8 Hz), 7.54–7.57 (m, 1H), 7.62 (dd, 1H, *J* = 7.8, 1.3 Hz), 8.36 (d, 1H, *J* = 8.4 Hz), 11.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 108.9, 116.4, 117.5, 123.4, 125.6, 128.0, 129.3, 130.7, 133.3, 138.1, 143.4, 155.1 (d, *J* = 37.8 Hz), 160.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.1 (s); IR (KBr): 3434, 2923, 2852, 1734, 1595, 1467, 1440, 1282, 1248, 1158, 1037, 896, 762, 683, 613, 593, 513, 464 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NO_3S$ $[M+H]^+$ 344.0563; found 344.0558.



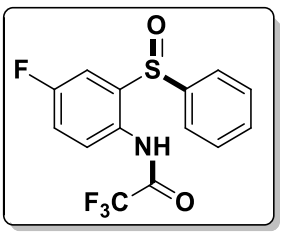
2,2,2-Trifluoro-*N*-(2-(*p*-tolylsulfinyl)phenyl)acetamide (1db″): Brownish solid; mp 80–82 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.30 (t, 1H, *J* = 7.8 Hz), 7.40 (d, 2H, *J* = 7.8 Hz), 7.53–7.55 (m, 1H), 7.58–7.59 (m, 1H), 8.36 (d, 1H, *J* = 8.4 Hz), 11.68 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 114.8, 116.7, 121.4, 123.5, 124.4, 125.6, 127.9, 129.5, 129.6, 132.2, 133.2, 138.0, 140.0, 141.8, 155.1 (q, *J* = 37.7 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.1 (s); IR (KBr): 3441, 2926, 1733, 1604, 1547, 1444, 1281, 1199, 1158, 1080, 1012, 900, 808, 761, 619, 549, 530, 492 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}F_3NO_2S$ $[M+H]^+$ 328.0614; found 328.0617.



2,2,2-Trifluoro-*N*-(2-((4-fluorophenyl)sulfinyl)phenyl)acetamide (1eb″): Dark brownish solid; mp 99–101 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.18 (t, 2H, J = 8.4 Hz), 7.33 (t, 1H, J = 7.2 Hz), 7.50–7.52 (m, 2H), 7.56–7.59 (m, 1H), 7.61–7.62 (m, 1H), 8.37 (d, 1H, J = 8.4 Hz), 11.52 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.8, 116.7, 117.1 (d, J = 22.6 Hz), 123.7, 125.7, 126.6 (d, J = 9.0 Hz), 127.8, 129.2, 133.5, 137.6 (d, J = 3.0 Hz), 138.1, 155.2 (q, J = 37.8 Hz), 163.7, 165.4; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -111.2 (s), -79.1 (s); IR (KBr): 3441, 3061, 2924, 1729, 1613, 1553, 1489, 1438, 1281, 1234, 1192, 1162, 1069, 899, 831, 758, 734, 531, 475 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}F_4NO_2S$ $[M+H]^+$ 332.0363; found 332.0372.

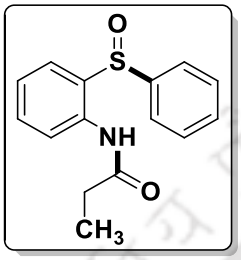


***N*-(2-((4-Chlorophenyl)sulfinyl)phenyl)-2,2,2-trifluoroacetamide (1fb″):** Brownish solid; mp 100–102 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.33 (t, 1H, J = 7.2 Hz), 7.45 (s, 4H), 7.57 (t, 1H, J = 9.0 Hz), 7.61–7.63 (m, 1H), 8.36 (d, 1H, J = 8.4 Hz), 11.48 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 118.0, 118.2, 123.6, 125.6, 125.7, 127.9, 128.5, 129.0, 129.5, 130.0, 133.6, 137.9, 138.1, 140.6, 155.1 (q, J = 37.8 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -79.1 (s); IR (KBr): 3459, 2925, 2855, 1717, 1615, 1551, 1474, 1446, 1391, 1281, 1243, 1200, 1161, 1090, 1024, 1009, 901, 823, 758, 741, 617, 578, 556, 523, 485, 455 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}ClF_3NO_2S$ $[M+H]^+$ 348.0067; found 348.0065.

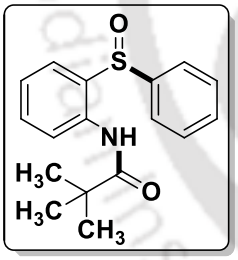


2,2,2-Trifluoro-*N*-(4-fluoro-2-(phenylsulfinyl)phenyl)acetamide (3ab″): Brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.23–7.26 (m, 1H), 7.35 (dd, 1H, J = 6.9, 2.9 Hz), 7.49–7.52 (m, 3H), 7.53–7.55 (m, 2H), 8.35 (dd, 1H, J = 9.1, 4.6 Hz), 11.45 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 112.0 (d, J = 25.3 Hz), 114.8, 116.7, 119.5 (d, J = 22.8 Hz), 121.1, 129.7, 130.3 (d, J = 8.1 Hz),

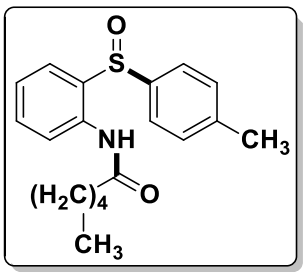
132.0, 143.6, 143.8 (d, *J* = 5.7 Hz), 155.5, 155.7, 160.6, 162.2; ^{19}F NMR (DMSO-d_6 + hexafluorobenzene): δ -112.9 (s), -76.4 (s); IR (KBr): 3429, 1649, 1384, 1047, 1026, 997, 827, 766, 740, 640, 431 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}F_4NO_2S$ $[M+H]^+$ 332.0363; found 332.0566.



***N*-(2-(Phenylsulfinyl)phenyl)propionamide (1ac″):** Dark brownish solid; mp 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (t, 3H, *J* = 7.6 Hz), 2.20–2.35 (m, 2H), 7.17 (t, 1H, *J* = 7.6 Hz), 7.43–7.52 (m, 6H), 7.57 (d, 1H, *J* = 7.6 Hz), 8.38 (d, 1H, *J* = 8.4 Hz), 10.05 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 9.6, 31.2, 123.2, 123.3, 124.5, 124.9, 128.2, 129.4, 131.0, 133.4, 140.5, 143.0, 172.5; IR (KBr): 3403, 2924, 2852, 1695, 1586, 1531, 1466, 1439, 1380, 1297, 1261, 1188, 1155, 1086, 1019, 804, 753, 692, 542, 439 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{16}NO_2S$ $[M+H]^+$ 274.0896; found 274.0897.

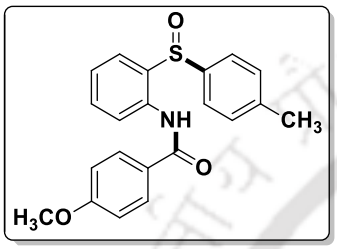


***N*-(2-(Phenylsulfinyl)phenyl)pivalamide (1ad″):** Dark brownish solid; mp 139 –141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (s, 9H), 7.15–7.19 (m, 1H), 7.41–7.48 (m, 5H), 7.49–7.56 (m, 2H), 8.53 (d, 1H, *J* = 8.4 Hz), 10.3 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 27.5, 40.1, 123.07, 123.1, 125.0, 127.3, 128.4, 129.4, 131.0, 133.4, 141.0, 143.3, 177.7; IR (KBr): 3257, 2963, 2856, 1689, 1586, 1534, 1476, 1435, 1398, 1367, 1301, 1228, 1124, 1080, 1019, 919, 808, 754, 690, 592, 569, 532, 497 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{20}NO_2S$ $[M+H]^+$ 302.1209; found 302.1194.

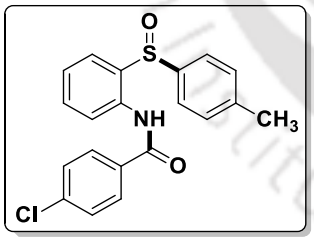


***N*-(2-(Phenylsulfinyl)phenyl)hexanamide (1de″):** Dark brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, *J* = 7.2 Hz), 1.23–1.32 (m, 4H), 1.56–1.61 (m, 2H), 2.17–2.22 (m, 1H), 2.26–2.31 (m, 1H), 2.35 (s, 3H), 7.14 (t, 1H, *J* = 7.8 Hz), 7.23 (d, 2H, *J* = 8.4 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 7.8 Hz), 8.39 (d, 1H, *J* = 8.4 Hz), 10.12 (s,

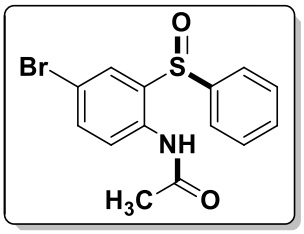
1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.1, 21.4, 22.6, 25.1, 31.5, 38.1, 123.0, 123.2, 124.5, 127.8, 128.0, 130.1, 133.2, 139.7, 140.4, 141.5, 171.9; IR (KBr): 3358, 2927, 2857, 1706, 1588, 1526, 1465, 1440, 1378, 1315, 1225, 1148, 1092, 1041, 1019, 812, 734, 712, 653, 580, 554, 521 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{24}NO_2S$ $[M+H]^+$ 330.1522; found 330.9066.



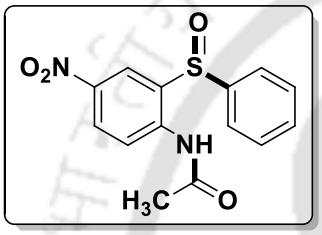
4-Methoxy-*N*-(2-(*p*-tolylsulfinyl)phenyl)benzamide (1df˝): Yellowish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 3.87 (s, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 1H, *J* = 7.4 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.49–7.55 (m, 2H), 7.98 (d, 2H, *J* = 8.8 Hz), 8.60 (d, 1H, *J* = 8.0 Hz), 11.1 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 55.6, 114.1, 123.0, 123.2, 124.5, 126.4, 127.8, 127.9, 129.5, 130.1, 133.1, 139.6, 141.5, 141.6, 162.8, 164.8; IR (KBr): 3244, 2958, 2843, 1676, 1605, 1540, 1509, 1463, 1436, 1255, 1180, 1114, 1080, 1024, 896, 845, 810, 761, 735, 686, 624, 578, 543, 475 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{20}NO_3S$ $[M+H]^+$ 366.1158; found 366.1152.



4-Chloro-*N*-(2-(*p*-tolylsulfinyl)phenyl)benzamide (1dg˝): Yellowish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.20 (t, 1H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.8 Hz), 7.55 (d, 2H, *J* = 7.6 Hz), 7.94 (d, 2H, *J* = 8.4 Hz), 8.59 (d, 1H, *J* = 8.0 Hz), 11.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 123.1, 123.7, 124.5, 127.9, 128.0, 129.0, 129.2, 130.2, 132.5, 133.2, 138.6, 139.6, 140.7, 141.7, 164.1; IR (KBr): 3430, 3243, 2923, 1682, 1598, 1540, 1489, 1436, 1315, 1256, 1103, 1012, 893, 848, 808, 756, 674, 620, 547, 524, 477 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{17}ClNO_2S$ $[M+H]^+$ 370.0663; found 370.0645.



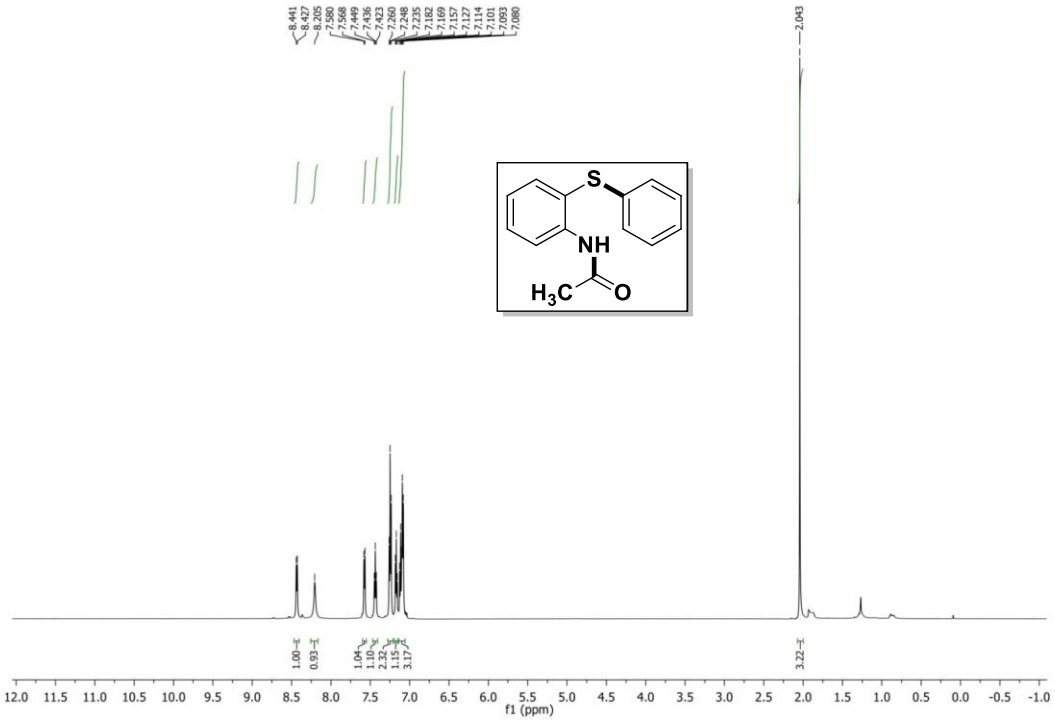
***N*-(4-Bromo-2-(phenylsulfinyl)phenyl)acetamide (4aa″):** White solid; mp 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H), 7.45–7.56 (m, 6H), 7.66 (s, 1H), 8.21 (d, 1H, J = 8.4 Hz), 10.0 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.8, 115.8, 124.4, 124.7, 129.6, 129.9, 130.2, 131.4, 135.9, 139.1, 142.2, 168.5; IR (KBr): 3433, 3253, 2926, 2854, 1664, 1577, 1505, 1468, 1375, 1286, 1244, 1140, 1080, 1036, 929, 828, 751, 694, 662, 592, 559, 498, 484, 427 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}BrNO_2S$ $[M+H]^+$ 337.9845; found 337.9827.



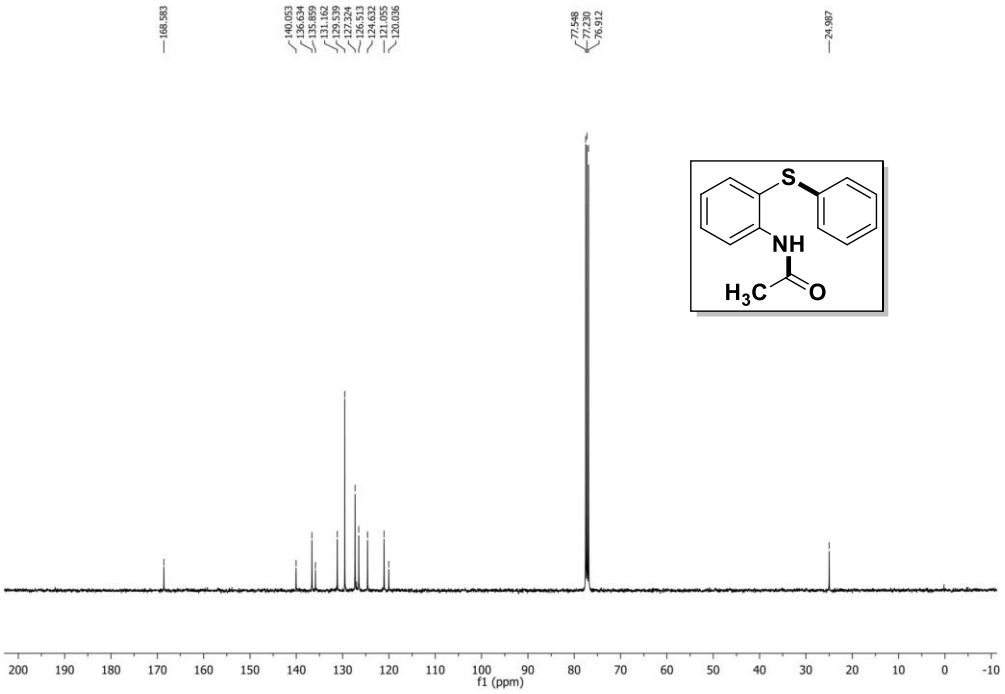
***N*-(4-Nitro-2-(phenylsulfinyl)phenyl)acetamide (5aa″):** Brownish solid; mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.16 (s, 3H), 7.51–7.57 (m, 5H), 8.31 (dd, 1H, J = 9.2, 2.5 Hz), 8.44 (d, 1H, J = 2.8 Hz), 8.65 (d, 1H, J = 9.2 Hz), 10.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.2, 122.4, 123.4, 124.4, 127.8, 128.4, 129.9, 131.9, 141.6, 142.3, 145.9, 169.1; IR (KBr): 3421, 3200, 2924, 2854, 1711, 1611, 1587, 1500, 1400, 1348, 1318, 1284, 1226, 1131, 1076, 1020, 908, 858, 749, 686, 603, 555, 533, 497, 448 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_4S$ $[M+H]^+$ 305.0591; found 305.0577.

V.7. Spectra

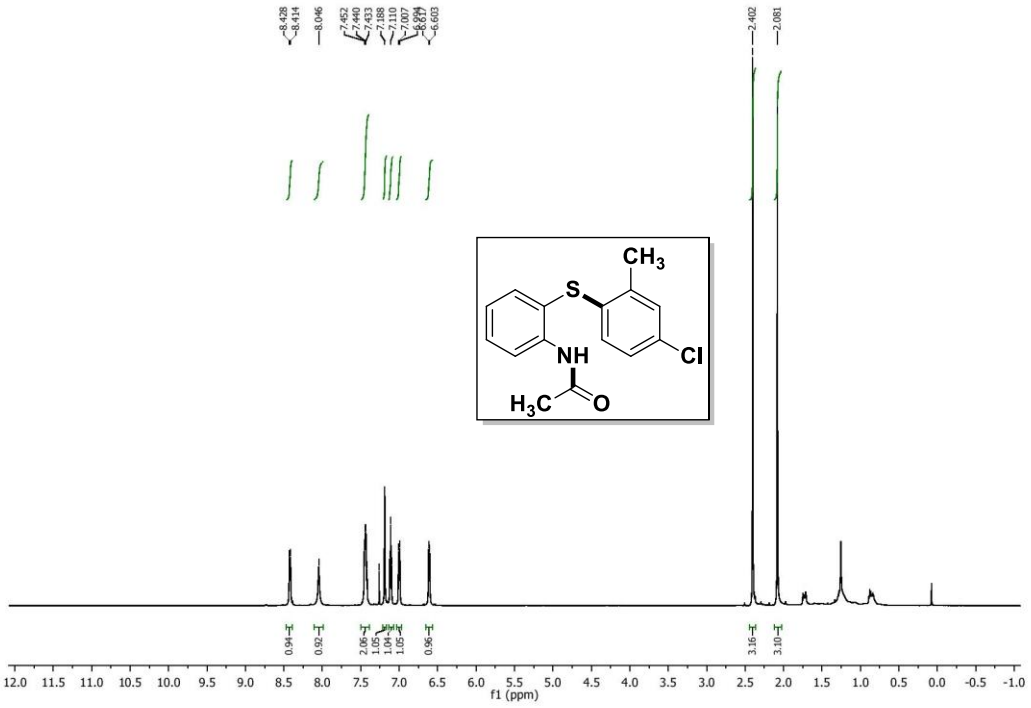
***N*-(2-(Phenylthio)phenyl)acetamide (1aa′): ^{1}H NMR (600 MHz, $CDCl_3$)**



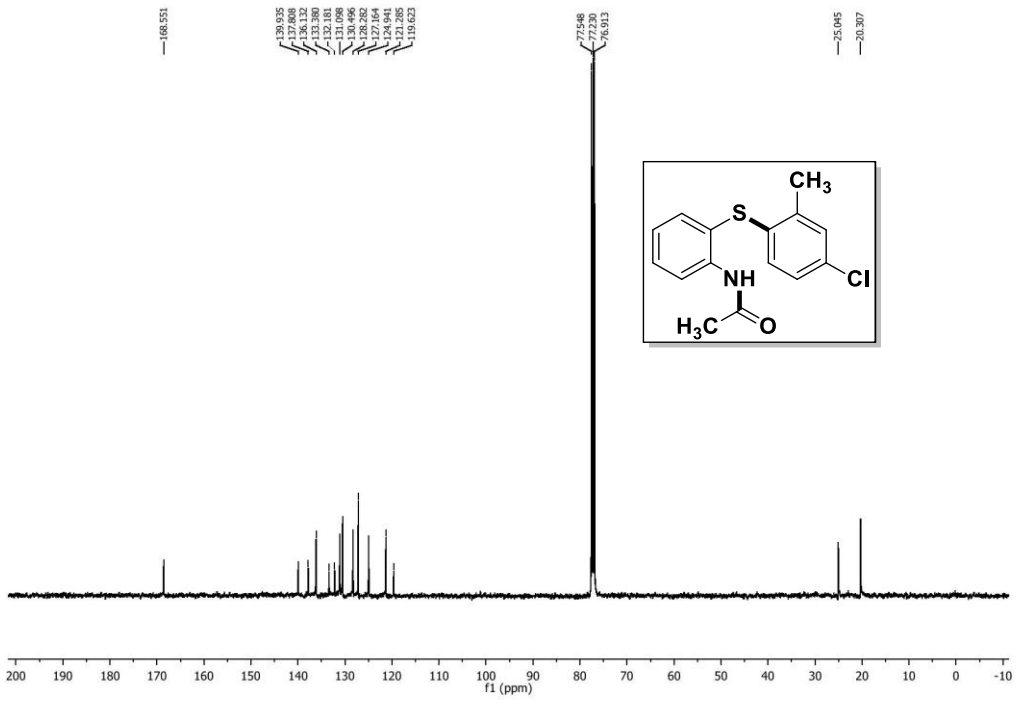
***N*-(2-(Phenylthio)phenyl)acetamide (1aa′): ^{13}C NMR (100 MHz, $CDCl_3$)**



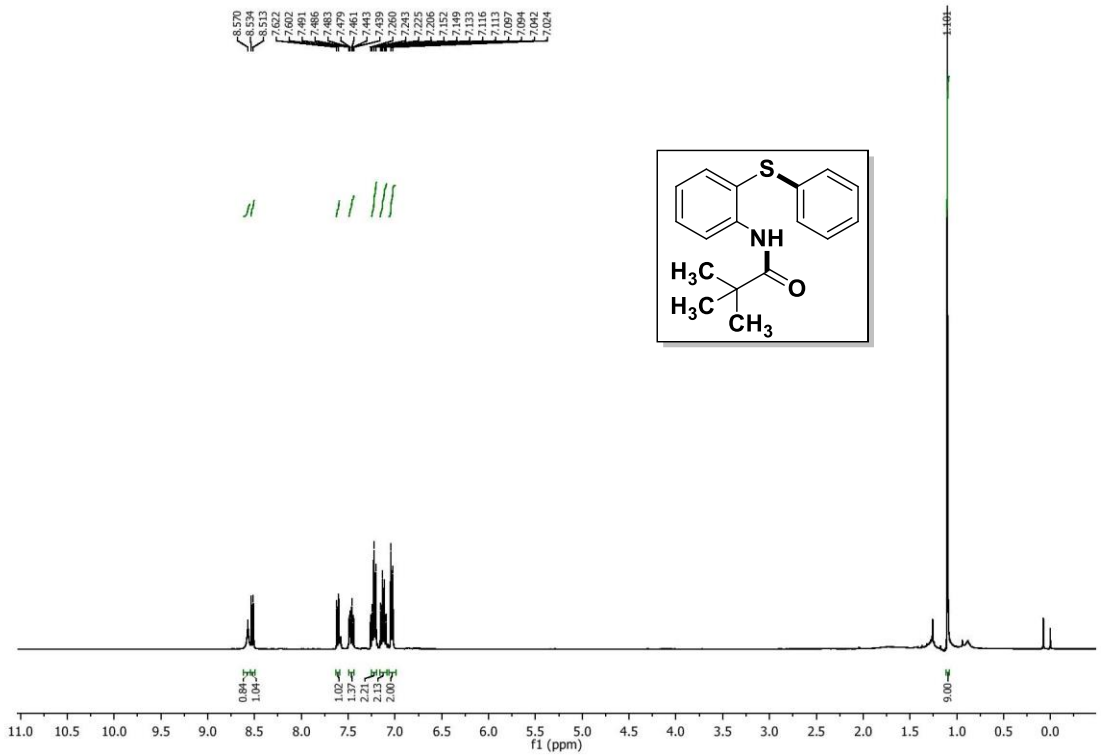
_N_-(2-((4-Chloro-2-methylphenyl)thio)phenyl)acetamide (1ja′): ^{1}H NMR (600 MHz, $CDCl_3$)



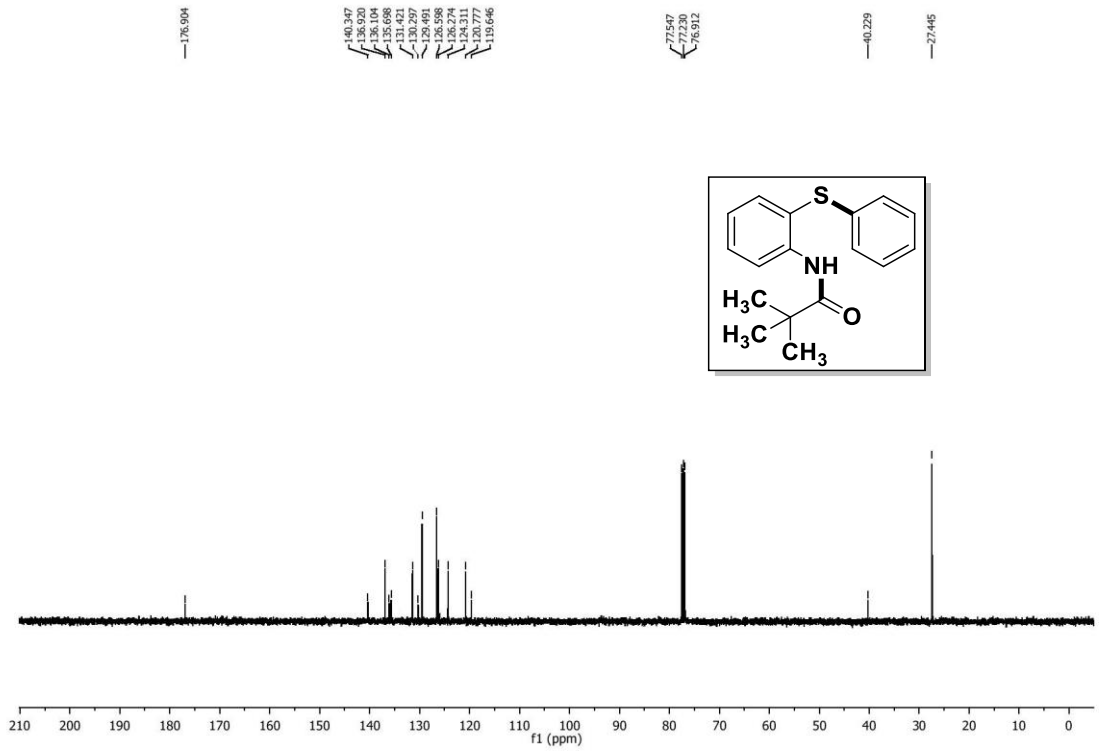
_N_-(2-((4-Chloro-2-methylphenyl)thio)phenyl)acetamide (1ja′):^{13}C NMR (150 MHz, $CDCl_3$)



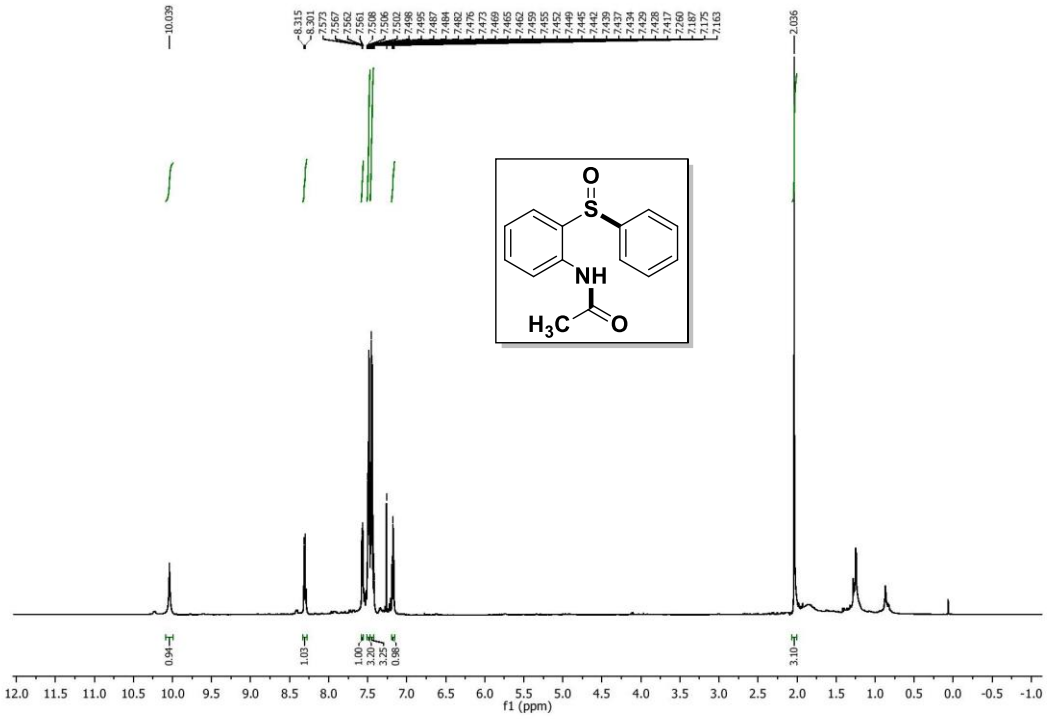
_N_-(2-(Phenylthio)phenyl)pivalamide (1adʹ): ^{1}H NMR (400 MHz, $CDCl_3$)



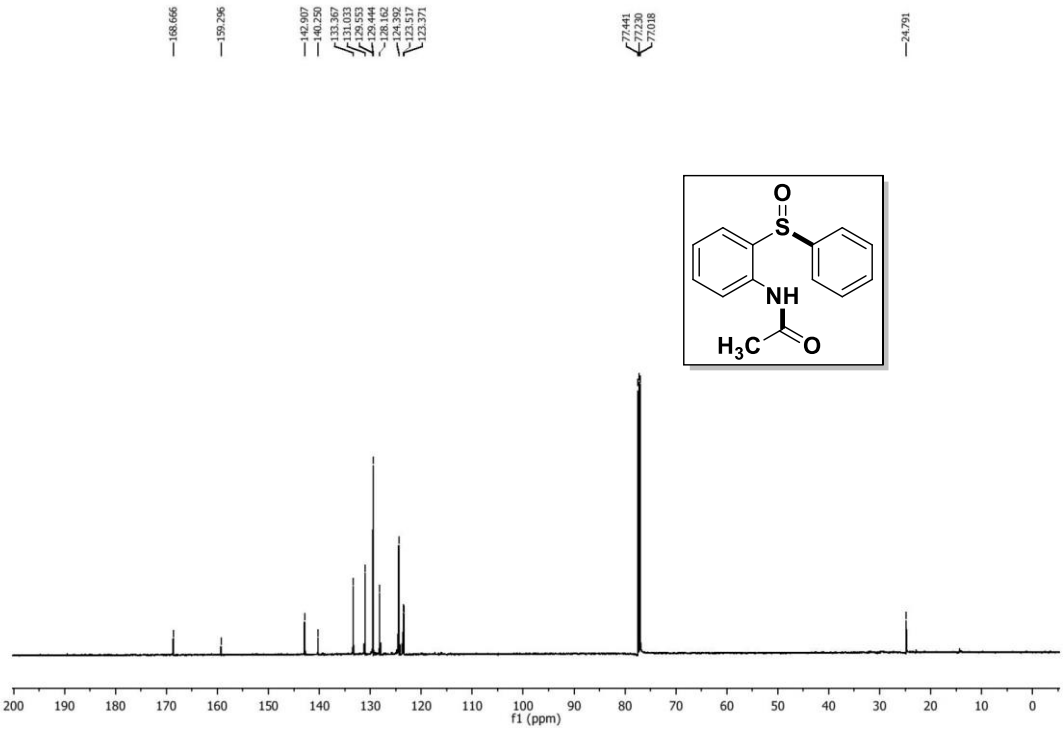
_N_-(2-(Phenylthio)phenyl)pivalamide (1adʹ): ^{13}C NMR (100 MHz, $CDCl_3$)



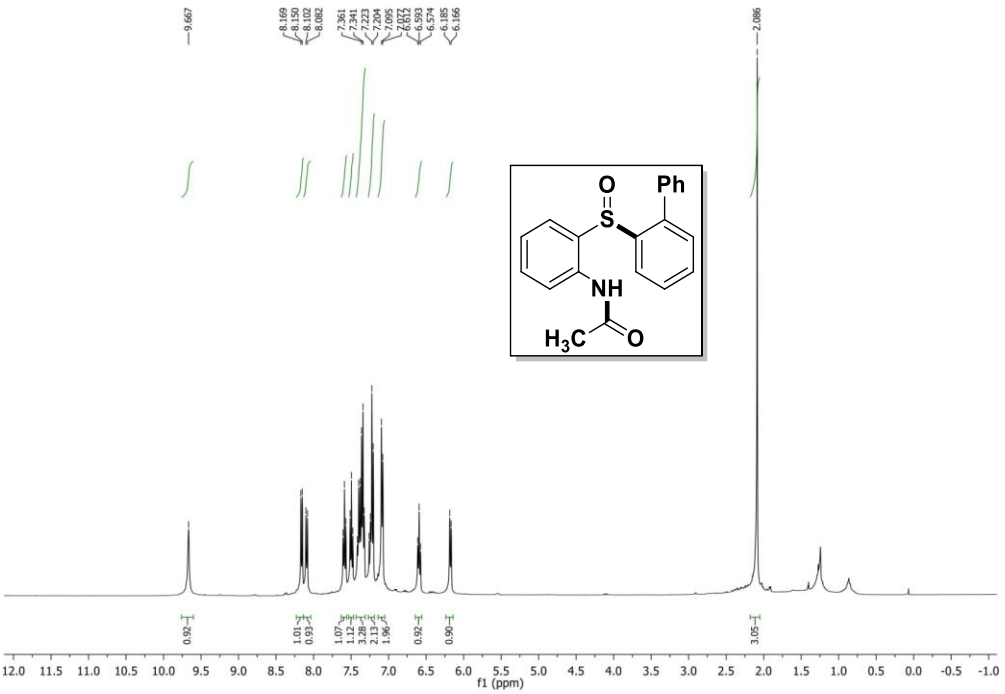
***N*-(2-(phenylsulfinyl)phenyl)acetamide (1aa″): ^{1}H NMR (600 MHz, $CDCl_3$)**



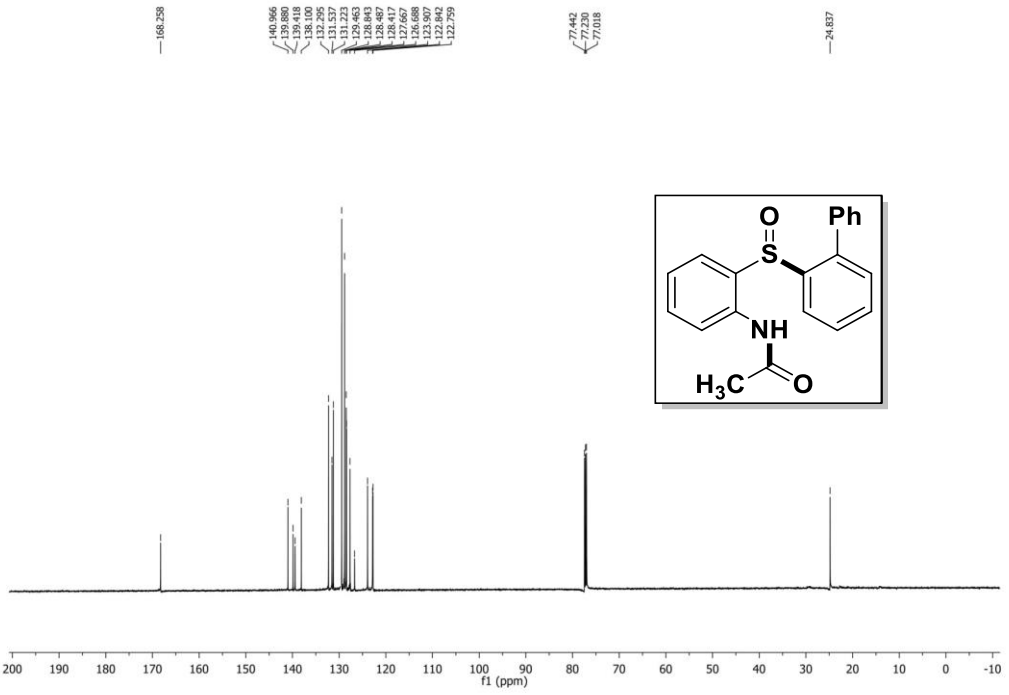
***N*-(2-(Phenylsulfinyl)phenyl)acetamide (1aa″): ^{13}C NMR (150 MHz, $CDCl_3$)**



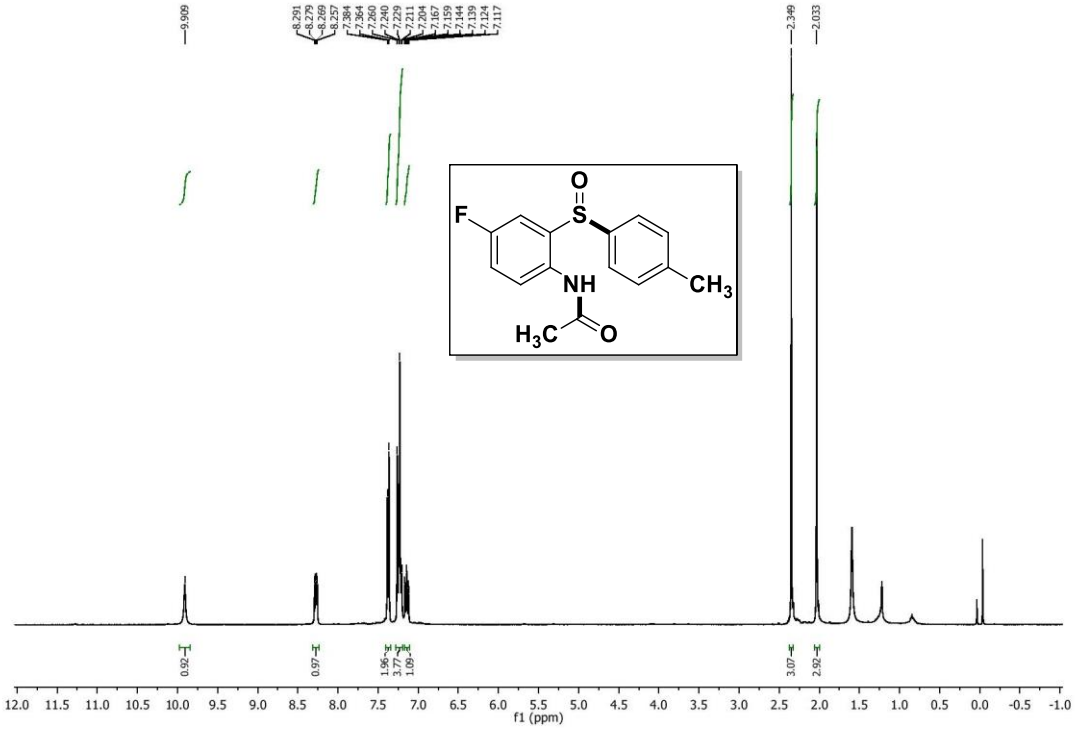
***N*-(2-([1,1'-biphenyl]-2-ylsulfinyl)phenyl)acetamide (1ia″): ^{1}H NMR (400 MHz, $CDCl_3$)**



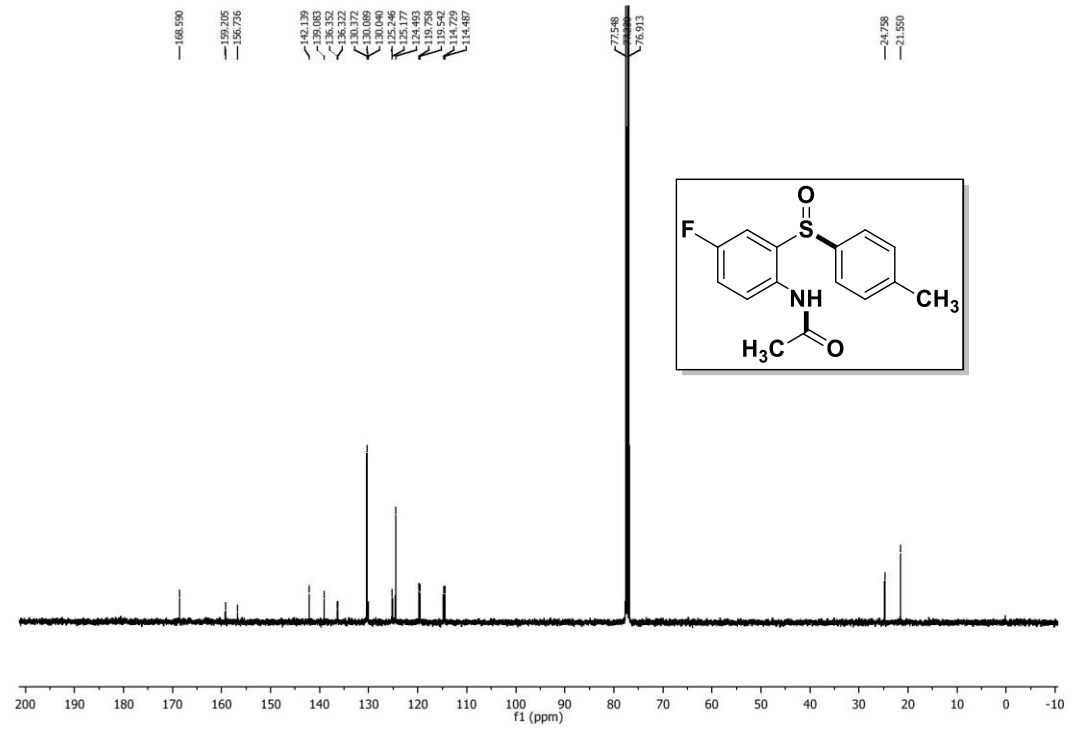
***N*-(2-([1,1'-biphenyl]-2-ylsulfinyl)phenyl)acetamide (1ia″): ^{13}C NMR (150 MHz, $CDCl_3$)**



_N_-(4-Fluoro-2-(_p_-tolylsulfinyl)phenyl)acetamide (3da″): ^{1}H NMR (400 MHz, $CDCl_3$)

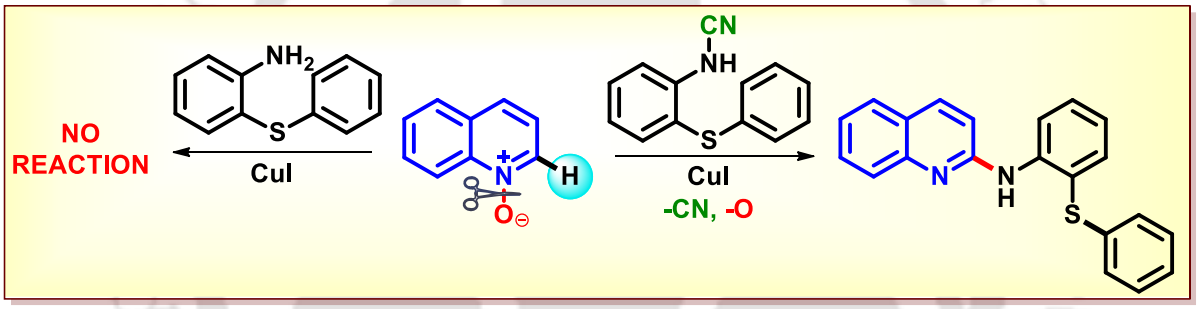


_N_-(4-Fluoro-2-(_p_-tolylsulfinyl)phenyl)acetamide (3da″): ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER VI

Cyano-Sacrificial (Arylthio)arylamination of Quinoline and Isoquinoline *N*-Oxides Using *N*-(2-(Arylthio)aryl)cyanamides



Abstract: *A copper(I)-catalysed regioselective arylthio-arylamination of quinoline and isoquinoline N-oxides has been achieved at the expense of a cyano (CN) group from N-(2-(arylthio)aryl)cyanamides. This reductive amination proceeds in one pot at 80 °C in the absence of any additives. This is a unique demonstration of aryl cyanamides serving as arylaminating agents on quinoline/isoquinoline N-oxides with concurrent autoreduction of N-oxide.*

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CHAPTER VI

Cyano-Sacrificial (Arylthio)arylamination of Quinoline and Isoquinoline *N*-Oxides Using *N*-(2-(Arylthio)aryl)cyanamides

VI.1. Introduction

Recent advances in transition-metal catalysis have led to the development of effective methods for regioselective C−C and C−heteroatom bond formations.[1,2] The construction of C−N bonds has attracted considerable attention since nitrogen containing motifs have found significant applications in biological and medicinal chemistry.[1a,3] Among various nitrogen-bearing scaffolds, functionalised quinolines are reported to have antimalarial, antibacterial, antifungal and antimicrobial activities (Figure VI.1.1).[4] Representative examples of 2-aminoquinoline moieties exhibiting various biologically activities are shown in Figure VI.1.1. Compound (**I**) is a potent antagonist that selectively modulates native TRPC4/C5 ion channels and has been used in physiological and pathophysiological studies.[4c] Quinoline derivative (**II**) is an antagonist of the MCH-1R for the treatment of obesity.[4d] The potential activity of compound (**II**) demonstrated an IC_{50} value of 55 nM in a primary screening and exhibited antagonist properties in a functional cellular assay measuring Ca^{2+} release. Compound (**III**) exhibits antibacterial activity against Gram-positive bacteria.[4e] 2-Aminiquinoline (**IV**) displays an IC_{50} value of 1.2 μM against EZH2, decreased global H3K27me3 level in cells and also good antiviability activities against tumor cell lines.[4f]

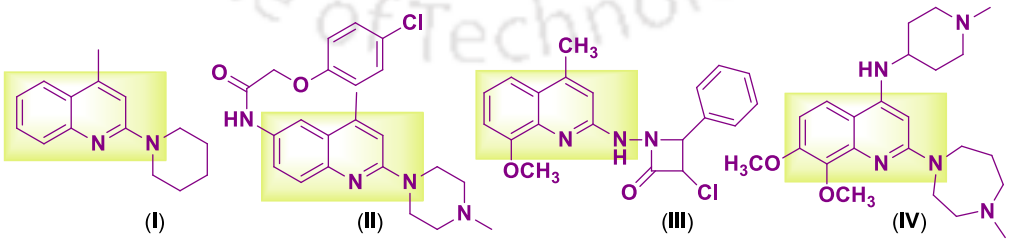
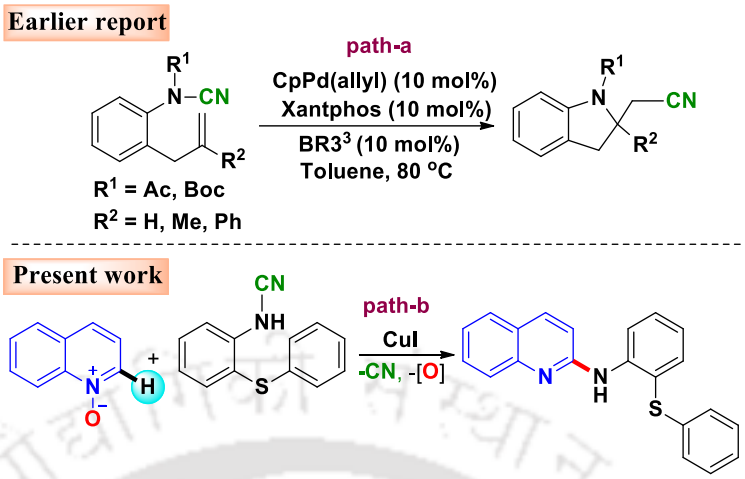


Figure VI.1.1. *Representative biologically active 2-aminoquinolines*

Various transition-metal-catalysed C2-selective functionalisations such as arylation,[5] heteroarylation,[6] alkylation,[7] alkenylation[8] and C−O or C−S bond formations[9,10] on the

quinoline *N*-oxide moiety have been successfully accomplished. Undoubtedly, the regioselective C−N bond formation of these heterocyclic *N*-oxides have emerged as powerful tools in organic synthesis.

A Pd/xantphos-catalysed intramolecular regioselective aminocyanation of alkene has been achieved *via* the cleavage of N–CN bond by the Nakao group (Scheme VI.1.1, path-a).[11a] Here, simultaneous installation of a cyano (-CN) group and tetra or trisubstituted carbon afforded various indolines and pyrrolidines. An organic cyanamide possesses a nucleophilic N–H site, an electrophilic cyanamide carbon,[11b-e] and a fragile N–CN bond. On the other hand, because of the nucleophilic nature of quinoline *N*-oxide and the presence of an electrophilic C2 site, we envisaged that the *N*-(2-(arylthio)aryl)cyanamide might serve as an C2-arylthio-arylaminating agent on quinoline *N*-oxide. This may be accomplished by the initial nucleophilic attack of the quinoline *N*-oxide onto the electrophilic carbon of cyanamide followed by an intramolecular nucleophilic attack at the C2 position of quinoline *N*-oxide. Here the sulfur atom of *S*-phenyl ring may further facilitate the reactivity of the cyanamide *via* coordination with a Cu-salt. The above anticipated reaction was initially executed using a *N*-(2-(phenylthio)phenyl)cyanamide, quinoline *N*-oxide and CuI in 1,4-dioxane. The formation of *N*-(2-(phenylthio)phenyl)quinolin-2-amine is observed (Scheme VI.1.1, path-b). Here formation of a C2-selective product using cyanamide is associated with the concurrent reduction of quinoline *N*-oxide and loss of a cyano (CN) group. However, organic cyanamides are utilised previously as the effective nitrile source in cyanation reactions *via* N–CN bond activation strategy.[12] To the best of our knowledge, such type of arylamination of quinoline *N*-oxide using arylcyanamide as the arylaminating agent is unprecedented in the literature.



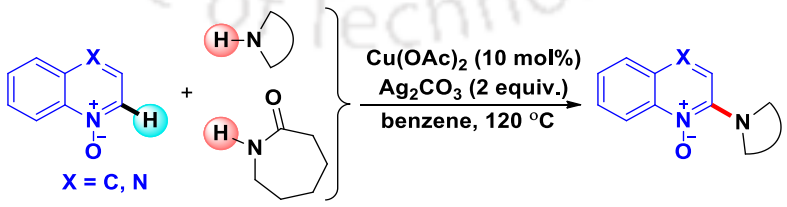
Scheme VI.1.1. *Differential reactivity of aryl cyanamides*

VI.2. Strategies for C2-amination of quinoline *N*-oxides

Due to the enormous utility of 2-aminoquinolines in both biological and synthetic fields, a number of C2-selective amination of quinoline *N*-oxide has been thrived. Several methods thus implemented for the synthesis of 2-aminoquinolines *via* C–H functionalisation are enlisted below.

(i) Amination of quinoline *N*-oxides by lactams and cyclamines

In 2013, Sun *et al*. has demonstrated a C–H/N–H dehydrogenative coupling of quinoline *N*-oxides with lactams/cyclamines in the presence of $Cu(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant (Scheme VI.2.1). They demonstrated a direct functionalisation of aryl C–H bonds leading to the formation of C2-aminated quinoline *N*-oxide.[13]

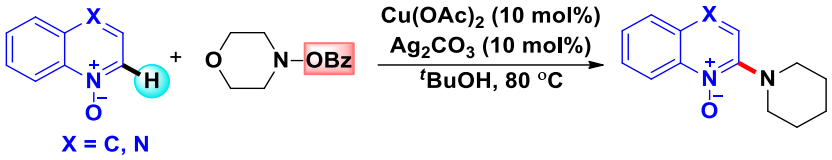


Scheme VI.2.1. *C2-amination of quinoline N-oxides using lactams and cyclamines*

(ii) Amination of quinoline *N*-oxides using *O*-benzoyl hydroxylamines

A copper(II)-catalysed C–H amination of quinoline *N*-oxides has been achieved by Wu group by serving *O*-benzoyl hydroxylamine as an electrophilic aminating reagent

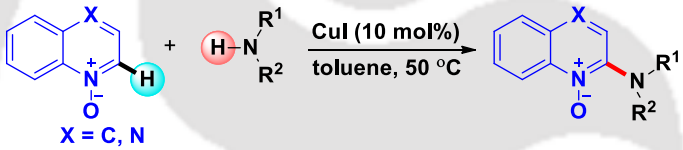
(Scheme VI.2.2). Here, quinoline, isoquinoline as well as quinoxaline *N*-oxides are implemented as the reacting substrates for the C2-selective amination.[14]



Scheme VI.2.2. *C2-amination of quinoline N-oxides using O-benzoyl hydroxylamines*

(iii) Amination of quinoline *N*-oxides using secondary aliphatic amines

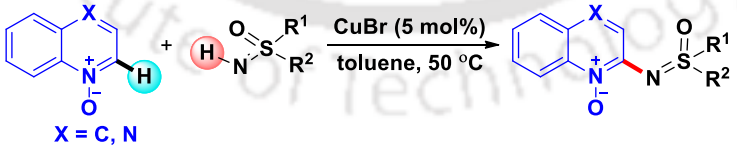
Cui and co-workers reported a direct amination protocol for the synthesis of 2-aminoquinolines from the coupling of quinoline *N*-oxide and secondary aliphatic amines (Scheme VI.2.3). The dehydrogenative C–N coupling proceeds in presence of CuI catalyst and air as the oxidant.[15]



Scheme VI.2.3. *C2-amination of quinoline N-oxides using secondary aliphatic amines*

(iv) C2-Sulfoximination of quinoline *N*-oxides using sulfoximines

An external oxidant free protocol for the synthesis of *N*-(hetero)arylsulfoximines *via* a dual C–H/N–H dehydrogenative coupling of quinoline *N*-oxides with sulfoximines has been disclosed by Bolm group (Scheme VI.2.4).[16]

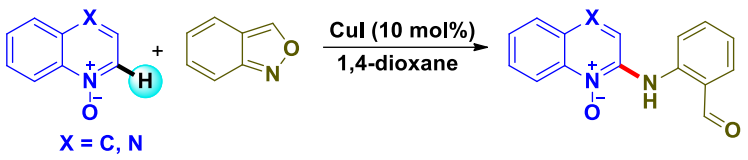


Scheme VI.2.4. *C2-amination of quinoline N-oxides using sulfoximines*

(v) Arylamination of quinoline *N*-oxides using anthranils

Samanta *et al.* has demonstrated an efficient copper(I)-catalysed regioselective arylamination of various heterocyclic *N*-oxides under redox-neutral conditions where anthranils are utilised as the active arylaminating agents (Scheme VI.2.5). Anthranil

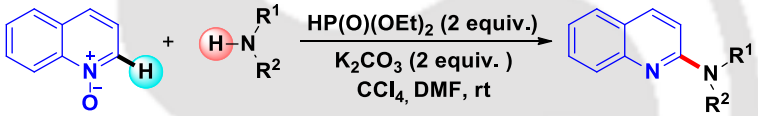
undergoes a ring opening reaction *via* the cleavage of N–O bond and served as an alternative arylaminating source.[17]



Scheme VI.2.5. *C2-amination of quinoline N-oxides using anthranils*

(vi) Metal-free C2-amination of quinoline *N*-oxides

Very recently Zhao group has reported a reductive amination of quinoline *N*-oxides using ammonia, primary and secondary amines (Scheme VI.2.6). However, the method requires a stoichiometric amount of reducing agent such as H-phosphonate in the presence of potassium carbonate.[18]



Scheme VI.2.6. *Metal-free C2-amination of quinoline N-oxides*

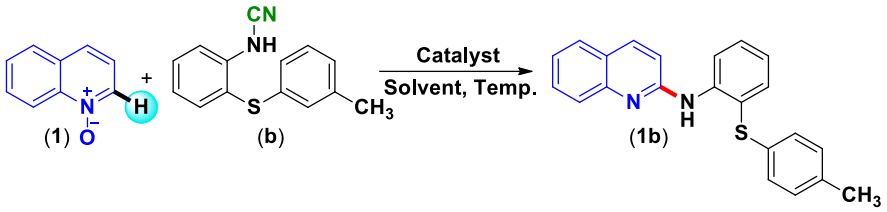
VI.3. Present work

Optimisation of reaction conditions: As mentioned earlier an initial trial was executed using a *N*-(2-(phenylthio)phenyl)cyanamide (**a**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.25 mmol) and CuI (20 mol%) in 1,4-dioxane (2 mL) at 110 °C. Formation of a new product (**1a**) (43%) was observed along with the isolation of quinoline (23%) and unreacted quinoline *N*-oxide (15%).

Encouraged by this C2-selective cyano sacrificial arylthio-arylamination, various other reaction parameters were further evaluated to achieve a better yield of the product. The initial investigation was commenced by taking *N*-(2-(*p*-tolylthio)phenyl)cyanamide (**b**) and quinoline *N*-oxide (**1**) as the reacting partner (Table VI.3.1, entry 1). Because a substantial amount of quinoline by product was observed, this may originate from the *N*-oxide (**1**) *via* a reductive path, thereby decreasing the net yield of (**1a**). Gratifyingly, an improved yield (65%) of the product (**1b**) was found when a reaction was carried out using 2 equiv. of (**1**) (Table VI.3.1, entry 2). As solvent systems play a pivotal role in any organic transformations, a few solvents were screened for the present C2-amination

process. Among various solvents, *viz.* chlorobenzene (39%), *p*-xylene (27%), CH_3CN (79%), DMSO (45%) and methanol (51%), surveyed (Table VI.3.1, entries 3–7), CH_3CN turned out to be the best (Table VI.3.1, entry 5). The yield of the product remained unaltered (78%) even when the reaction was performed at 80 ^oC (Table VI.3.1, entry 8). The reaction took a longer time, giving a lower yield of the product when carried out below 80 ^oC. Using CH_3CN as the solvent at 80 ^oC, the efficacy of other copper I and II salts such as CuCl, CuBr and $Cu(OAc)_2$ were screened (Table VI.3.1, entries 9–11). All turned out to be inferior to initially used CuI (Table VI.3.1, entry 8). Product (**1b**) yield (76%) remained unchanged even by performing the reaction with 15 mol% catalyst loading (Table VI.3.1, entry 12). However, a 12% reduction in the yield (*i.e.*, 68%) was noticed by further lowering the catalyst loading to 10 mol% (Table VI.3.1, entry 14). Interestingly, the same reaction in the absence of any catalyst also gave a decent yield (22%) of the product (**1b**) (Table VI.3.1, entry 14). Nevertheless, CuI is found to be essential for obtaining a better yield, as it enhances the electrophilicity of the cyanamide and brings quinolone *N*-oxide (**1**) and cyanamide (**b**) to its proximity *via* chelation. Thus, the ideal optimised condition for this arylamination is the use of *N*-(2-(*p*-tolylthio)phenyl)cyanamide (**b**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.5 mmol) and CuI (15 mol%) in CH_3CN (2 mL) at 80 ^oC for 18 h (Table VI.3.1, entry 12).

Table VI.3.1. *Optimisation of the arylthio-amination of quinoline N-oxide*[a,b]

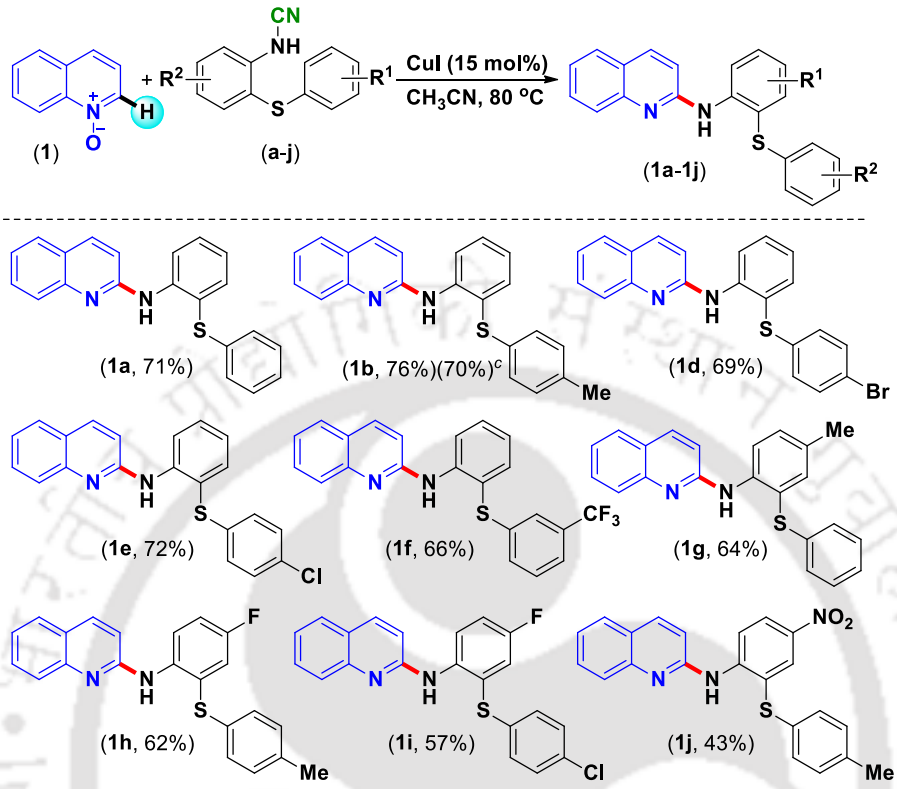


Entry	Catalyst (mol %)	Solvent	Temp °C	Yield (%)
1	CuI (20)	Dioxane	110	49[c]
2	CuI (20)	Dioxane	110	65
3	CuI (20)	PhCl	110	39
4	CuI (20)	*p*-Xylene	110	27
5	CuI (20)	CH_3CN	110	79
6	CuI (20)	DMSO	110	45
7	CuI (20)	MeOH	110	51
8	CuI (20)	CH_3CN	80	78
9	CuCl (20)	CH_3CN	80	72
10	CuBr (20)	CH_3CN	80	53
11	$Cu(OAc)_2$(20)	CH_3CN	80	51
12	**CuI (15)**	**CH_3CN**	**80**	**76**
13	CuI (10)	CH_3CN	80	68
14	-	CH_3CN	80	22

[a]Reaction conditions: *N*-(2-(*p*-tolylthio)phenyl)cyanamide(**b**) (0.25 mmol), quinoline *N*-oxide (**1**) (0.5 mmol), solvent (2 mL). [b]Isolated yield. [c]1 equiv. of quinoline *N*-oxide (**1**).

Substrate scope for Arylthio-amination: After establishing the above unprecedented arylamination, the feasibility of the strategy was surveyed with a variety of substituted *N*-(2-(arylthio)aryl)cyanamides (**a**–**f**) having electron-donating and electron-withdrawing groups (R^1) on the *S*-phenyl ring with quinoline *N*-oxide (**1**) (Scheme VI.3.1). *N*-(2-(Phenylthio)phenyl)cyanamide (**a**) reacted efficiently with (**1**) giving C2-aminated product (**1a**) in 71% yield. Presence of moderately [*p*-Br (**d**), *p*-Cl (**e**)] and strongly [*m*-CF_3 (**f**)] electro-withdrawing groups (R^1) on the *S*-phenyl ring of aryl cyanamides, allowed C2-amination with quinoline *N*-oxide (**1**), affording arylaminated products (**1d**), (**1e**), and (**1f**) in 69%, 72% and 66% yields, respectively (Scheme VI.3.1). The structure of product (**1e**) has been reconfirmed by X-ray crystallographic analysis (Figure VI.3.1).

Scheme VI.3.1. *Demonstration of C2-arylamination using arylthiophenyl cyanamides*[a,b]



[a]Reaction conditions: *N*-(2-(phenylthio)phenyl)cyanamide (**a-j**) (0.25 mmol), quinoline *N*-oxide (0.5 mmol) (**1**), CuI (15 mol%), CH_3CN (2 mL), for 20 h at 80 °C. [b]Yields of isolated pure products. [c]1 mmol scale

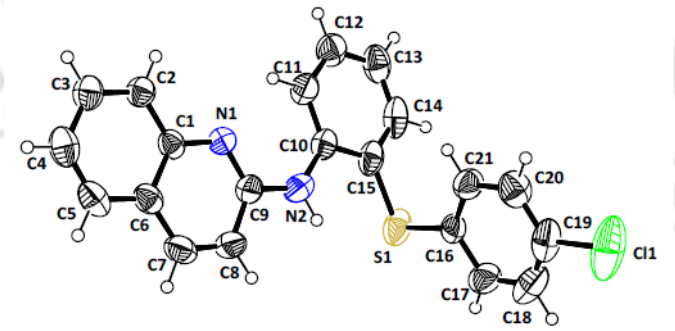


Figure VI.3.1. *ORTEP diagram of N-(2-((4-chlorophenyl)thio)phenyl)quinolin-2-amine* ***(1e)***

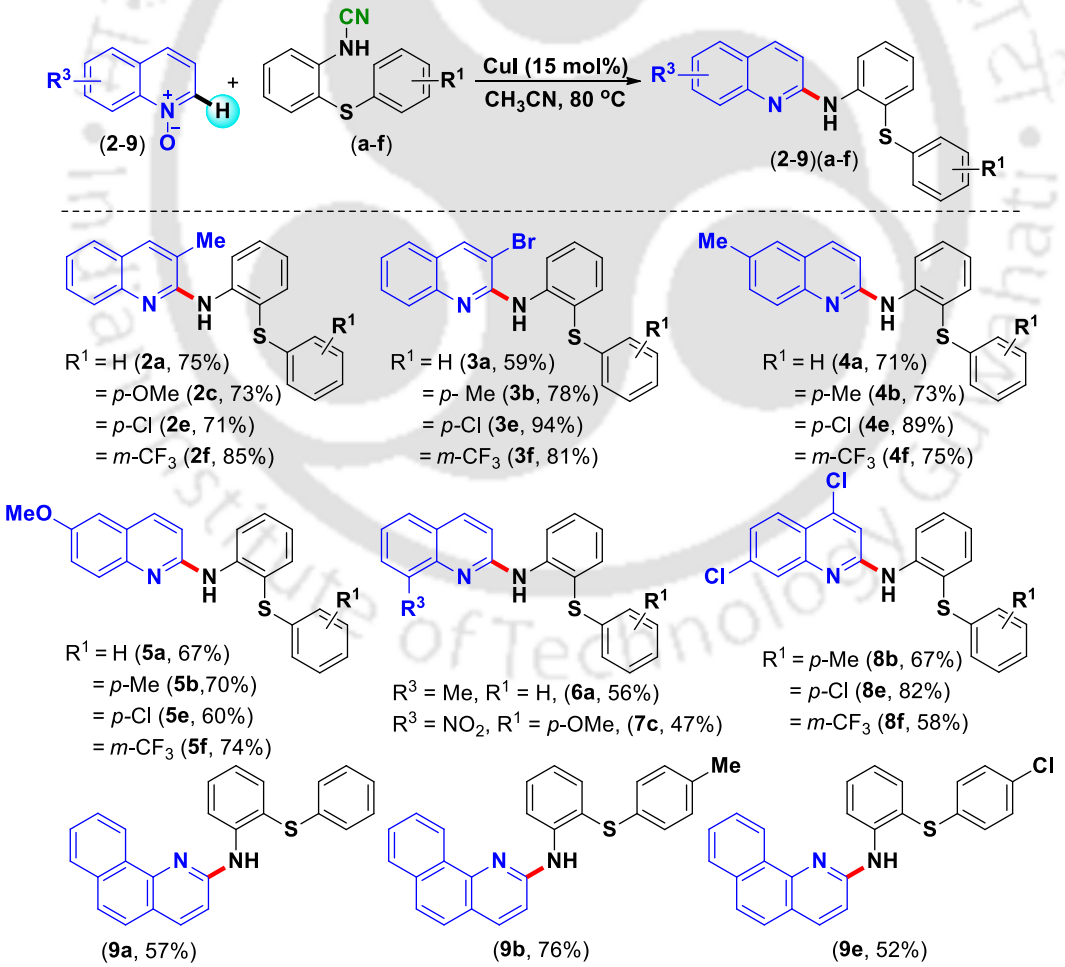
Subsequently, the variation of substituents (R^1 and R^2) on both the aryl rings of arylcyanamides was explored (Scheme VI.3.1). When the substituent cyanamide possessing an electron-donating group such as 4-Me (**g**) was treated with quinoline *N*-oxide (**1**), a moderate yield (64%) of the C2-aminated product (**1g**) was obtained. Further, compounds with the cyanamide-bearing ring substituted with electron-

withdrawing (-F/-NO_2) and the *S*-phenyl ring with either electron-donating (-Me) or electron-withdrawing (-Cl) groups were tested. Various combinations of substituents (R^1 and R^2) such as *p*-Me/4-F (**h**), *p*-Cl/4-F (**i**), and *p*-Me/4-NO_2 (**j**) all provided their respective aryl-aminated products (**1h**, 62%), (**1i**, 57%) and (**1j**, 43%) in modest yields (Scheme VI.3.1). To demonstrate the scalability of the present methodology, a reaction of *N*-(2-(*p*-tolylthio)phenyl)cyanamide (**b**) (1 mmol) and quinoline *N*-oxide (2 mmol), under the standard optimized reaction conditions gave a 70% yield of product (**1b**) [Scheme VI.3.1, (**1b**)^c].

After successful demonstration of the C2-selective arylthio-arylamination of quinoline *N*-oxide (**1**), the scope and versatility of the process was assessed with other substituted quinoline *N*-oxides (Scheme VI.3.2). We were delighted to observe that the developed protocol displayed a broad scope across various sterically and electronically distinct quinoline *N*-oxides (**2**–**9**). Both electron-donating 3-Me (**2**) and electron-withdrawing 3-Br (**3**) groups on quinoline *N*-oxide at the C3-position did not encounter any significant steric effect. 3-Methylquinoline *N*-oxide (**2**) reacted smoothly with cyanamides having a variety of substituents (R^1). The electron-neutral (**a**), electron-donating *p*-OMe (**c**) and electron-withdrawing *p*-Cl (**e**) and *m*-CF_3 (**f**) all afforded the corresponding products (**2a**, 75%), (**2c**, 73%), (**2e**, 71%) and (**2f**, 85%) respectively (Scheme VI.3.2). The presence of a C3-Br group (**3**) in lieu of a C3-Me group (**2**) at the C-3 position of quinoline *N*-oxide was equally successful with a similar set of substituted arylcyanamides (**a**-**f**), providing the arylaminated products (**3a**, 59%), (**3b**, 78%), (**3e**, 94%) and (**3f**, 81%) respectively (Scheme VI.3.2). The cyano-sacrificial C2-amination strategy was equally effective with quinoline *N*-oxides substituted with electron-donating groups such as 6-Me (**4**) and 6-OMe (**5**) when reacted with a set of cyanamides (**a**-**f**) as shown in Scheme VI.3.2. The C2-aminated products (**4a**-**5f**) were isolated in the range of 60-89%, and product yields are summarized in Scheme VI.3.2. It was not possible to correlate the actual yield of product with the electronic and steric effects of the substituents present in quinoline *N*-oxides or cynamides. This strategy was feasible when electron-donating 8-Me (**6**) and electron-withdrawing 8-NO_2 (**7**) substituents (R^3) are present at the C-8 position of quinoline *N*-oxide. Despite the anticipated steric crowding due to (R^3) when *N*-oxide (**6**) was reacted with cyanamide (**a**) and *N*-oxide (**8**) with cyanamide (**c**) decent yields of the C2-aminated products (**6a**, 56%) and (**7c**, 47%) were

obtained. In addition to these monosubstituted quinoline *N*-oxides (**1**–**7**), 4,7-dichloroquinoline *N*-oxide (**8**) underwent C2-amination with *N*-(2-(phenylthio)phenyl)cyanamides bearing *p*-Me (**b**), *p*-Cl (**e**) and *m*-CF_3 (**f**) substituents on the *S*-phenyl ring, providing the corresponding products (**8b**, 67%), (**8e**, 82%) and (**8f**, 58%) respectively. Besides quinoline *N*-oxides (Scheme VI.3.1 and VI.3.2), benzo-fused analogue, benzo[*h*]quinoline *N*-oxide (**9**) underwent effective C2-amination with a variety of cyanamides such as H (**a**), *p*-Me (**b**) and *p*-Cl (**e**), all providing the respective C2-arylaminated products (**9a**), (**9b**) and (**9e**) in 57%, 76% and 52% yields (Scheme VI.3.2). Surprisingly, this arylamination strategy, using pyridine *N*-oxide and quinoxaline *N*-oxides as the C2-aminating sites, failed to react with *N*-(2-(phenylthio)phenyl)cyanamide (**a**).

Scheme VI.3.2. *Demonstration of C2-arylamination using various quinoline N-oxides*[a,b]



[a]Reaction conditions: *N*-(2-(phenylthio)phenyl)cyanamide (**a–f**) (0.25 mmol), quinoline *N*-oxides (**2**–**9**) (0.5 mmol), CuI (15 mol%), CH_3CN (2 mL), time (20 h) at 80 °C. [b]Yields of isolated pure products.

We wondered whether the present C2-arylamination strategy of quinoline *N*-oxide (**1**) would be applicable to isoquinoline *N*-oxide (**10**) as well to provide analogous C1-arylamination. To our delight, the reaction of isoquinoline *N*-oxide (**10**) with *N*-(2-(phenylthio)phenyl)cyanamide (**a**), resulted in the formation of an exclusive C1-arylaminated product (**10a**) in 73% yield (Scheme VI.3.3). This result is significant, because 1-aminoisoquinolines are found to have interesting biological activities (Figure VI.3.2). The amino isoquinoline core in compound (**V**) is reported to have potent antitumor activity in xenograft models.[19a] Compound (**VI**) possesses antimalarial activity and was found to be submicromolar inhibitor *in vitro* toward drug-resistant *Plasmodium falciparum*, possessing the best activity compared to chloroquine.[19b]

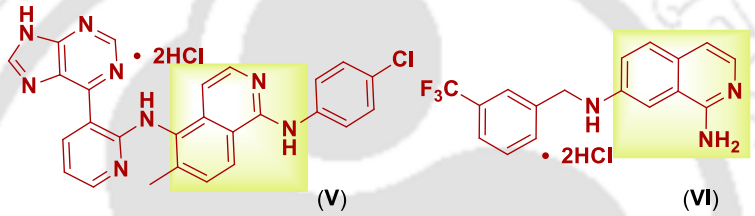
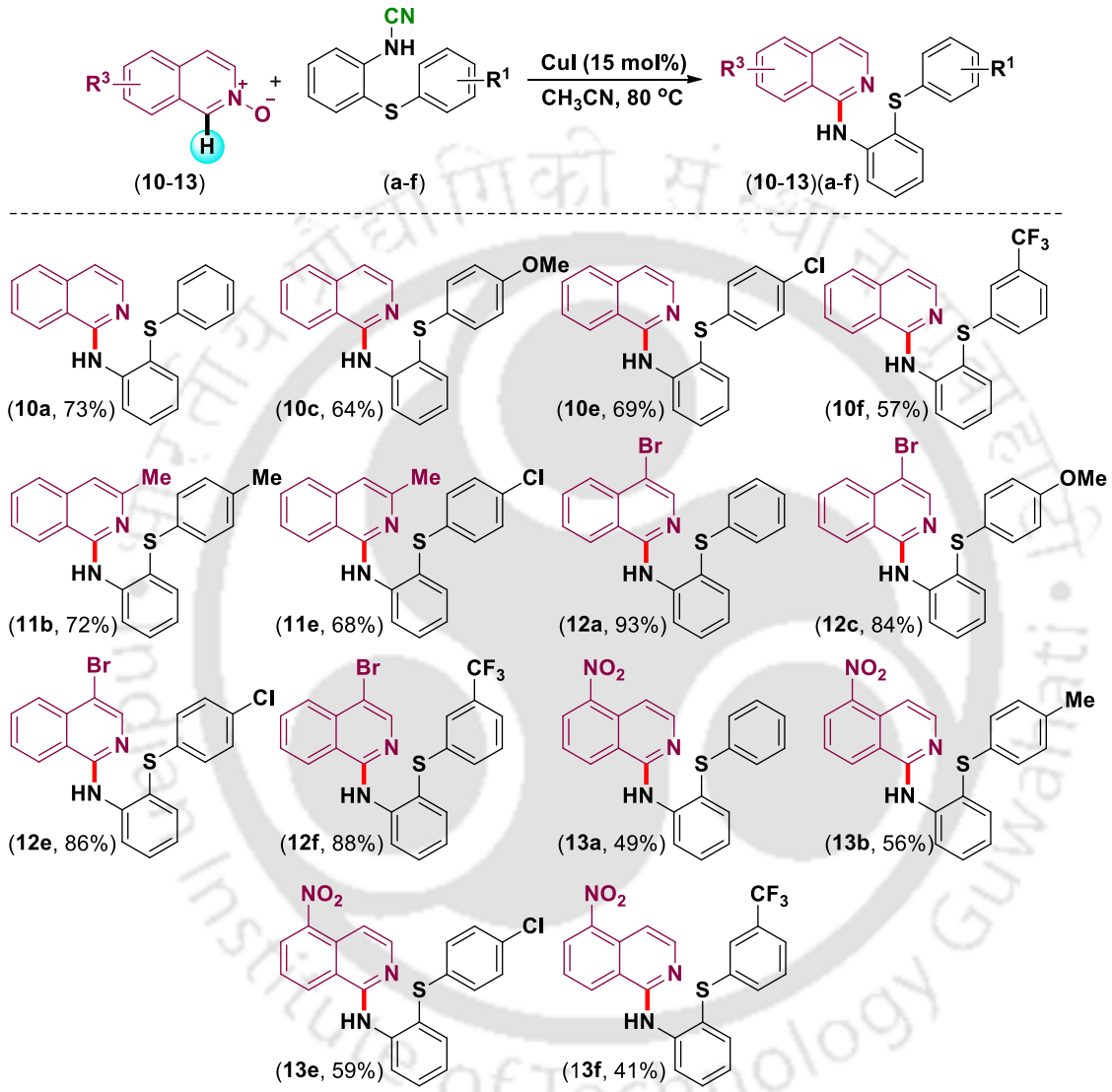


Figure VI.3.2. *Representative examples of biologically active 1-aminoisoquinoline moieties*

Encouraged by this positive outcome, the scope of this protocol was then extended to other substituted cyanamides (**c**–**f**) and isoquinoline *N*-oxides (**10**–**13**). Initially, the electronic effect of the substituents such as *p*-OMe (**c**), *p*-Cl (**e**) and *m*-CF_3 (**f**) present on the S-phenyl ring of *N*-(2-(phenylthio)phenyl)cyanamides (**c**–**f**) was investigated (Scheme VI.3.3). *N*-(2-(Phenylthio)phenyl)cyanamides containing electron-donating [*p*-OMe (**c**)] or electron-withdrawing [*p*-Cl (**e**) and *m*-CF_3 (**f**)] substituents, all underwent effective C1-amination with isoquinoline *N*-oxides (**10**) giving products [(**10c**, 64%), (**10e**, 69%) and (**10f**, 57%)] as shown in Scheme VI.3.3. Next, the effect of the substituents (R^3) present on the isoquinoline *N*-oxides (**11**–**13**) were examined with substituted cyanamides (**b–f**). Isoquinoline *N*-oxides bearing an electron-donating group such as 3-Me (**11**) reacted smoothly with (R^1) substituted cyanamides *p*-Me (**b)** and *p*-Cl (**e**), furnishing the corresponding C1-arylaminated products (**11b**, 72%) and (**11e**, 68%). Similarly, 4-bromo isoquinoline *N*-oxide (**12**) reacted with differentially (R^1) substituted *N*-(2-(arylthio)phenyl)cyanamides (**a**–**f**) and yielded the C1-aminated products (**12a**–**12e**) in a range of 84–93% (Scheme VI.3.3). Moderate to lower yields of C1-

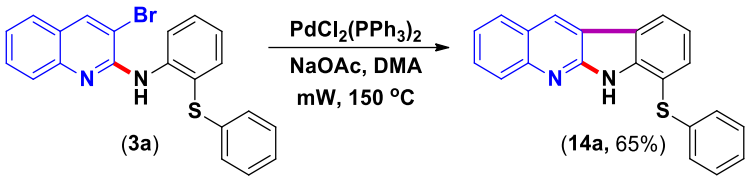
aminated products (**13a**–**13f**) were obtained *via* the coupling of 5–NO_2 isoquinoline *N*-oxide (**13**) with (R^1) substituted cyanamides (**a**–**f**) (Scheme VI.3.3).

Scheme VI.3.3. *Demonstration of C1-arylamination with isoquinoline N-oxide*[a,b]



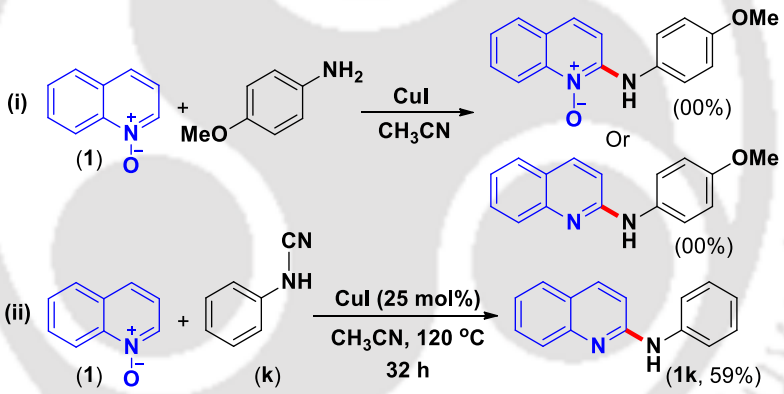
[a]Reaction conditions: *N*-(2-(phenylthio)phenyl)cyanamide (**a-f**) (0.25 mmol), isoquinoline*N*-oxides (**10-13**) (0.5 mmol), CuI (15 mol%), CH_3CN (2 mL), time (20 h) at 80 °C. [b]Yields of isolated pure products.

To demonstrate the applicability of our protocol, biologically active indoloquinoline moiety (**14a**) was synthesised in good yield (65%), utilising product (**3a**) (in Scheme VI.3.2) *via* an intramolecular Heck coupling (Scheme VI.3.4).[20]



Scheme VI.3.4. *Post synthetic modifications*

To understand the mechanistic aspect for this cyano-sacrificial regioselective arylthio-arylamination of quinoline and isoquinoline *N*-oxides, some experiments were carried out (Scheme VI.3.5). Most of the C2-amination protocols of quinoline *N*-oxides use secondary amines directly or indirectly as the aminating source. In this strategy as well, arylamine might be generated from arylcyanamide which could be the actual aminating source. To ascertain this, when a reaction was executed using *p*-anisidine in lieu of (**a**) under otherwise identical conditions, no product was observed which rules out arylamine as the possible aminating source [Scheme VI.3.5, (i)].

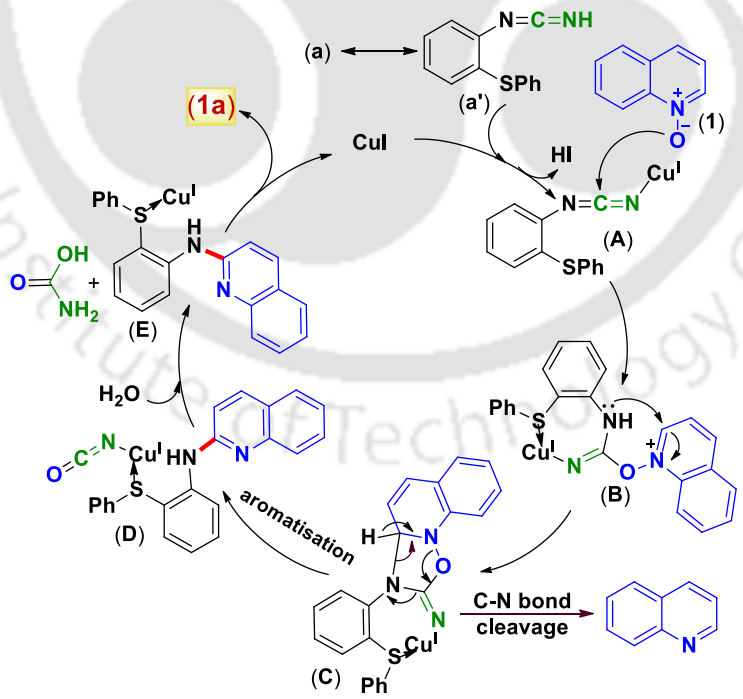


Scheme VI.3.5. *Control experiments*

The question of whether the S atom of the (arylthio)aryl)cyanamides plays any specific role in achieving the C2-amination, or whether other simple arylcyanamides could also serve as possible aminating source toward quinoline/isoquinoline *N*-oxides was addressed. When phenyl cyanamide (**k**) was employed for the C2-amination of quinoline *N*-oxide (**1**) under the present reaction conditions, a trace amount of C2-aminated product (<10%) was observed. However, after further optimisation, an acceptable yield (59%) could be achieved using 25 mol% of catalyst (CuI), at 120 °C for 32 h [Scheme VI.3.5, (ii)]. This observation suggests that the S atom in (arylthio)aryl)cyanamides is playing an active role *via* chelation with the metal. However, other aryl cyanamides can

serve as the alternative amine source only at high temperature and high catalyst loading at longer reaction times.

Based on the control experiments and the literature reports,[11,15] a possible mechanism for regioselective arylthio-arylamination is depicted in Scheme VI.3.6. The imidic form (**a'**) of cyanamide coordinates with Cu(I), forming a reactive intermediate (**A**). Quinoline *N*-oxide (**1**) attacks the electrophilic carbon of (**A**) to form a new Cu intermediate (**B**) by bringing both reacting partners in proximity, which is facilitated by the S atom of cyanamide (**a**). An intramolecular nucleophilic attack of the amine on the metal-bound C2-site of quinoline *N*-oxide generates intermediate (**C**). Rearomatization of the quinoline part of (**C**) with transfer of *N*-oxide oxygen forms species (**D**). The unstable N-C=O-bound Cu moiety is hydrolyzed to amine carbonate (which is decomposed to CO_2 and ammonia), releasing the metalated product (**E**). Finally, the C2-aminated product (**1a**) is released from intermediate (**E**) with regeneration of CuI for the subsequent catalytic cycle. An unfavorable reversible cleavage of N–C bond (C2 carbon of quinoline *N*-oxide) of intermediate (**C**) leads to the formation of byproduct quinoline. A similar mechanism can be proposed for the C1-amination of isoquinoline *N*-oxide.



Scheme VI.3.6. *Plausible mechanism for C2-arylthio-arylamination of quinoline N-oxide*

In conclusion, for the first time arylcyanamides have been utilised as an aminating agent toward regioselective C2-arylamination and C1-arylamination of quinoline and isoquinoline, respectively. In many aminations of quinoline and isoquinoline *N*-oxides, the *N*-oxide moiety remained intact thereby requiring an additional reduction step; however, here it is removed *in situ via* an autoreduction process. The present arylthio-arylamination of quinoline and isoquinoline using *N*-(2-(phenylthio)phenyl)cyanamide as an aminating agent works best. Nevertheless, there are avenues to develop other aryl and alkyl cyanamides as aminating agents for various heterocyclic *N*-oxides.

VI.4. Experimental section

VI.4.1. General information: All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium 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 GF_{254} (0.25 mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (400 and 600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 and 150 MHz). Mass spectra were recorded using ESI mode and APCI mode (Q-TOF MS analyzer). IR spectra were recorded in KBr or neat.

VI.4.2. Crystallographic description:

CCDC number for compound *N*-(2-((4-chlorophenyl)thio)phenyl)quinolin-2-amine (1e): CCDC-1851029. 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 *N*-(2-((4-chlorophenyl)thio)phenyl)quinolin-2-amine (1e): $C_{21}H_{15}ClN_2S$, crystal dimensions 0.27 x 0.21 x 0.17 mm, M_r = 362.86, Monoclinic, space group P2(1)/c,a =20.3423(7), b = 5.7998(2), c = 15.8289(6)Å, α = 90 °, β = 109.501(2)°, γ = 90°, V = 1760.39(11)Å^3, Z = 4, ρ_{calcd} = 1.369mg/m^3, μ = 0.341mm^{-1}, F(000) = 792.0, reflection collected / unique = 3084 / 2208, refinement method = full-matrix least-squares on F^2, final R indices >2sigma(I):R_1 = 0.0657, wR_2 = 0.1635, R indices (all data): R_1 = 0.0437, wR_2 = 0.1406, goodness of fit = 1.087.

VI.4.3. General procedure for the formation of *N*-(2-(phenylthio)phenyl)quinolin-2-amine (1a). An oven-dried round-bottom flask was charged with *N*-(2-(phenylthio)phenyl)cyanamide (**a**) (56.5 mg, 0.25 mmol), quinoline *N*-oxide (**1**) (72.5

mg, 0.5 mmol), CuI (15 mol%, 7 mg), and CH_3CN (2 mL). The flask was fitted with a condenser, and the resultant reaction mixture was stirred in a preheated oil bath maintained at 80 ^oC. The reaction progress was monitored by TLC. After 18 h, the reaction mixture was cooled to room temperature. The reaction mixture was evaporated under reduced pressure to remove CH_3CN. Then it was admixed with ethyl acetate (25 mL) and washed with saturated brine solution (5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography with an eluent hexane / ethylacetate (98 / 02) to afford the desired product (**1a**) in an isolated yield of 71% (58 mg).

VI.4.4. General procedure for the synthesis of 7-(phenylthio)-6*H*-indolo[*2,3-b*]quinoline (14a): A 5 mL microwave vial was charged with bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), 3-bromo-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (**3a**) (0.2 mmol, 81 mg) and sodium acetate (65 mg, 0.8 mmol) followed by *N*,*N*-dimethylacetamide (3 mL) and flushed with argon. The reaction was irradiated at 150 ^oC for 120 min. After completion of the reaction, the reaction mixture was cooled to room temperature. Then it was admixed with ethyl acetate (25 mL) and washed with ice-cooled water (3 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure, and the residue was purified by column chromatography with hexane / ethylacetate (93 / 07) eluent to afford 7-(phenylthio)-6*H*-indolo[2,3-b]quinoline (**14a**) in an isolated yield of 65% (42 mg).

VI.4.5. General procedure for control experiments

General procedure for the synthesis of *N*-phenylquinolin-2-amine (1k): *N*-Phenylcyanamide (**k**) (29 mg, 0.25 mmol), quinoline *N*-oxide (**1**) (72.5 mg, 0.5 mmol), CuI (25 mol%, 11 mg), and CH_3CN (2 mL) were placed in a round bottom flask. Then it was fitted with a condenser, and the resultant reaction mixture was stirred in a preheated oil bath maintained at 120 ^oC. The reaction progress was monitored by TLC. After 32 h, the reaction mixture was cooled to room temperature. The reaction mixture was evaporated under reduced pressure to remove CH_3CN. Then it was admixed with ethyl acetate (25 mL) and washed with brine solution (2 x5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure,

and the residue was purified by column chromatography with hexane / ethylacetate (97 / 03) eluent to afford the desired product (**1k**) in an isolated yield of 59% (32 mg).

VI.5. References

(1) (a) J. A. Halfen, *Curr. Org. Chem*., 2005, **9**, 657; (b) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev*., 2011, **40**, 4740; (c) C.-J. Li, *Acc. Chem. Res*., 2009, **42**, 335; (d) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev*., 2014, **43**, 901; (e) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res*., 2015, **48**, 1053; (f) Y. Qin, L. Zhu and S. Luo, *Chem. Rev*., 2017, **117**, 9433.

(2) (a) W. Han and A. R. Ofial, *Chem. Commun*., 2009, 5024; (b) J. Zhang, B. Tiwari, C. Xing, X. Chen and Y. R. Chi, *Angew. Chem., Int. Ed*., 2012, **51**, 3649; (c) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim and S. Chang, *J. Am. Chem. Soc*., 2012, **134**, 9110; (d) L. Wang, D. L. Priebbenow, W. Dong and C. Bolm, *Org. Lett*., 2014, **16**, 2661.

(3) (a) C. G. Espino and J. Du Bois, *In Modern Rhodium-Catalysed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005, 379; (b) P. Sau, A. Rakshit, A. Modi, A. Behera and B. K. Patel, *J. Org. Chem*., 2018, **83**, 1056.

(4) (a) R. G. Ridley, *Nature*, 2002, **415**, 686; (b) T. J. Egan, D. C. Ross and P. A. Adams, *FEBS Lett*., 1994, **352**, 54; (c) M. Miller, J. Shi, Y. Zhu, M. Kustov, J.-b. Tian, A. Stevens, M. Wu, J. Xu, S. Long, P. Yang, A. V. Zholos, J. M. Salovich, C. D. Weaver, C. R. Hopkins, C. W. Lindsley, O. McManus, M. Li and M. X. Zhu, *J. Biol. Chem*., 2011, **286**, 33436; (d) D. E. Clark, C. Higgs, S. P. Wren, H. J. Dyke, M. Wong, D. Norman, P. M. Lockey and A. G. Roach, *J. Med. Chem*., 2004, **47**, 3962; (e) R. Kharb and H. Kaur, *Int. Res. J. Pharm*., 2013, **4**, 63; (f) P. Xiang, H. Jie, Y. Zhou, B. Yang, H.-J. Wang, J. Hu, J. Hu, S. Y. Yang and Y. L. Zhao, *Molecules*, 2015, **20**, 7620.

(5) (a) L. C. Campeau, D. R. Stuart, J. P. Leclerc, M. Bertrand-Laperle, E. Villemure, H. Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc*., 2009, **131**, 3291; (b) S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc*., 2008, **130**, 9254; (c) L. Ackermann and S. Fenner, *Chem. Commun*., 2011, **47**, 430; (d) B. Liu, Z. Wang, N. Wu, M. Li, J. You and J. Lan, *Chem. -Eur. J*., 2012, **18**, 1599.

(6) (a) R. Odani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem*., 2015, **80**, 2384; (b) F. Gosselin, S. J. Savage, N. Blaquiere and S. T. Staben, *Org. Lett*., 2012, **14**, 862;

(c) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc*., 2010, **132**, 1822; (d) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan and J. You, *Chem. -Eur. J.*, 2012, **18**, 16616; (e) Z. Wang, K. Li, D. Zhao, J. Lan and J. You, *Angew. Chem., Int. Ed*., 2011, **50**, 5365; (f) X. Gong, G. Y. Song, H. Zhang and X. W. Li, *Org. Lett*., 2011, **13**, 1766; (g) W. Liu, X. Yu, Y. Li and C. Kuang, *Chem. Commun*., 2014, **50**, 9291.

(7) (a) O. V. Larionov, D. Stephens, A. Mfuh and G. Chavez, *Org. Lett*., 2014, **16**, 864; (b) B. Xiao, Z. J. Liu, Z. L. Liu and Y. Fu, *J. Am. Chem. Soc*., 2013, **135**, 616; (c) J. Ryu, S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 3677; (d) A. K. Jha and N. Jain, *Chem. Commun*., 2016, **52**, 1831.

(8) J. Wu, X. Cui, L. Chen, G. Jiang and Y. Wu, *J. Am. Chem. Soc*., 2009, **131**, 13888.

(9) X. Chen, C. Zhu, X. Cui and Y. Wu, *Chem. Commun*., 2013, **49**, 6900.

(10) (a) Z. Wu, H. Song, X. Cui, C. Pi, W. Du and Y. Wu, *Org. Lett*., 2013, **15**, 1270; (b) B. Du, P. Qian, Y. Wang, H. Mei, J. Han and Y. Pan, *Org. Lett*., 2016, **18**, 4144.

(11) (a) Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, *J. Am. Chem. Soc*., 2014, **136**, 3732; (b) J. Li and L. Neuville, *Org. Lett*., 2013, **15**, 6124; (c) P. Li, G. Cheng, H. Zhang, X. Xu, J. Gao and X. Cui, *J. Org. Chem*., 2014, **79**, 8156; (d) L. Q. Tran, J. Li and L. Neuville, *J. Org. Chem*., 2015, **80**, 6102; (e) S. M. Sajadi and M. Maham, *Lett. Org. Chem*., 2014, **11**, 136.

(12) (a) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed*., 2011, **50**, 519; (b) J. Li and L. Ackermann, *Angew. Chem*., 2015, **127**, 3706; (c) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vasquez-Cespedes and F. Glorius, *J. Am. Chem. Soc*., 2014, **136**, 17722; (d) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc*., 2013, **135**, 10630.

(13) G. Li, C. Jia and K. Sun, *Org. Lett*., 2013, **15**, 5198.

(14) G. Li, C. Jia, K. Sun, Y. Lv, F. Zhao, K. Zhou and H. Wu, *Org. Biomol. Chem*., 2015, **13**, 3207.

(15) C. Zhu, M. Yi, D. Wei, X. Chen, Y. Wu and X. Cui, *Org. Lett*., 2014, **16**, 1840.

(16) H. Yu, C. A. Dannenberg, Z. Li and C. Bolm, *Chem. -Asian J*., 2016, **11**, 54.

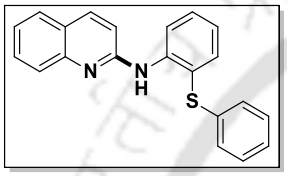
(17) A. Biswas, U. Karmakar, S. Nandi and R. Samanta, *J. Org. Chem*., 2017, **82**, 8933.

(18) W.-Z. Bi, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu, S.-H. Zhu, X. Li, H.-T. Wu, L.-K. Duana and Y.-F. Zhao, *Org. Chem. Front*., 2017, **4**, 1595.

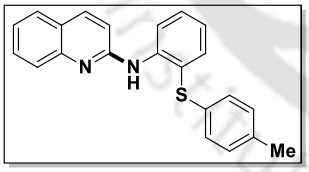
(19) (a) A. L. Smith, F. F. DeMorin, N. A. Paras, Q. Huang, J. K. Petkus, E. M. Doherty, T. Nixey, J. L. Kim, D. A. Whittington, L. F. Epstein, M. R. Lee, M. J. Rose, C. Babij, M. Fernando, K. Hess, Q. Le, P. Beltran and J. Carnahanz, *J. Med. Chem*., 2009, **52**, 6189; (b) C. E. Gutteridge, M. M. Hoffman, A. K. Bhattacharjee, W. K. Milhous and L. Gerena, *Bioorg. Med. Chem. Lett*., 2011, **21**, 786.

(20) B. Boganyi and J. Kaman, *Tetrahedron*, 2013, **69**, 9512.

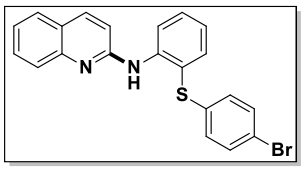
VI.6. Spectral data



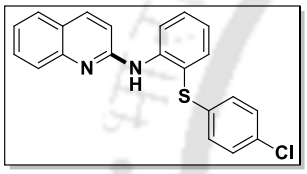
***N*-(2-(Phenylthio)phenyl)quinolin-2-amine (1a):** Yield 71% (58 mg) as a brownish solid; mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.79 (d, 1H, *J* = 8.8 Hz), 7.03–7.17 (m, 4H), 7.17–7.24 (m, 3H), 7.32 (t, 1H, *J* = 7.6 Hz), 7.45–7.53 (m, 1H), 7.59–7.64 (m, 3H), 7.87 (t, 2H, *J* = 8.4 Hz), 8.94 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 113.6, 115.5, 118.9, 119.5, 122.5, 123.7, 124.4, 126.2, 126.6, 127.2, 127.4, 127.5, 129.2, 129.4, 130.0, 131.1, 136.3, 136.9, 137.8, 142.4, 147.3, 153.5; IR (KBr): 3449, 2927, 2856, 1625, 1587, 1523, 1437, 1317, 810, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2S$ $[M+H]^+$ 329.1107; found 329.1117.



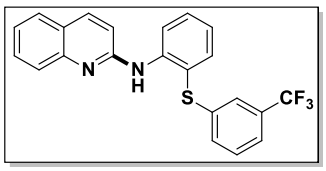
***N*-(2-(*p*-Tolylthio)phenyl)quinolin-2-amine (1b):** Yield 76% (65 mg) as a light yellowish solid; mp 84–86 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm); 2.25 (s, 3H), 6.79 (d, 1H, *J* = 9.0 Hz), 7.03 (d, 3H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* = 7.8 Hz), 7.30–7.33 (m, 1H), 7.45–7.48 (m, 1H), 7.55 (d, 1H, *J* = 7.2 Hz), 7.59–7.61 (m, 1H), 7.63 (d, 1H, *J* = 7.8 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 8.86 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 113.6, 119.7, 122.6, 123.7, 124.4, 127.2, 127.5, 128.3, 129.9, 130.2, 130.6, 132.5, 136.3, 136.5, 137.7, 142.0, 147.4, 153.6; IR (KBr): 3448, 2925, 2855, 1623, 1586, 1524, 1438, 1316, 806, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2S$ $[M+H]^+$ 343.1263; found 343.1269.



***N*-(2-((4-Bromophenyl)thio)phenyl)quinolin-2-amine (1d):** Yield 69% (70 mg) as a brownish solid; mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.80 (d, 1H, *J* = 8.8 Hz), 7.0 (d, 2H, *J* = 8.4 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 7.33 (t, 3H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 8.0 Hz), 7.57–7.66 (m, 3H), 7.76 (s, 1H), 7.88 (dd, 2H, *J* = 17.6, 8.8 Hz), 8.94 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 113.5, 118.8, 119.6, 119.9, 122.6, 123.8, 124.5, 127.3, 127.6, 128.8, 130.0, 131.4, 132.4, 135.8, 136.9, 137.8, 142.6, 147.4, 153.4; IR (KBr): 3367, 2964, 2928, 2854, 1630, 1582, 1524, 1438, 1260, 1091, 1012, 814, 750, 630 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}BrN_2S$ $[M+H]^+$ 407.0212; found 407.0233.

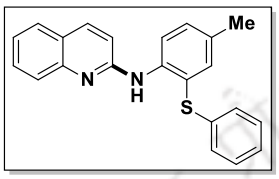


***N*-(2-((4-Chlorophenyl)thio)phenyl)quinolin-2-amine (1e):** Yield 72% (65 mg) as a brownish solid; mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.80 (d, 1H, *J* = 8.8 Hz), 7.03–7.09 (m, 3H), 7.18 (d, 2H, *J* = 7.4 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 7.50–7.54 (m, 1H), 7.57–7.65 (m, 3H), 7.76 (s, 1H), 7.88 (dd, 2H, *J* = 17.2, 8.8 Hz), 8.93 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 113.5, 119.0, 119.6, 122.6, 123.8, 124.5, 127.3, 127.6, 128.6, 129.5, 130.0, 131.4, 132.1, 135.0, 136.9, 137.8, 142.6, 147.4, 153.4; IR (KBr): 3369, 2963, 2929, 2853, 1631, 1585, 1525, 1439, 1262, 1092, 1010, 813, 752, 576 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2S$ $[M+H]^+$ 363.0717; found 363.0718.

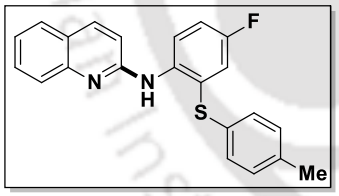


***N*-(2-((3-(Trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (1f):** Yield 66% (65 mg) as a light brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.82 (d, *J* = 8.8 Hz, 1H), 7.08 (t, 1H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 7.28–7.35 (m, 3H), 7.45 (s, 1H), 7.55 (t, 1H, *J* = 7.6 Hz), 7.59–7.65 (m, 3H), 7.73 (s, 1H), 7.85 (d, 1H, *J* = 8.4 Hz), 7.90 (d, 1H, *J* = 8.8 Hz), 8.91 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 113.4, 118.0, 119.8, 122.7, 122.8 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 3.8 Hz), 123.9, 124.5, 127.4, 127.6, 129.8, 129.9, 130.0, 131.8, 137.2,

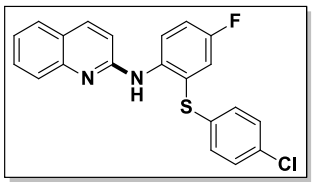
137.9, 138.3, 142.9, 147.5, 153.4; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr): 3448, 2921, 2851, 1626, 1587, 1523, 1321, 1127, 1073, 749, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{16}F_3N_2S$ $[M+H]^+$ 397.0981; found 397.0994.



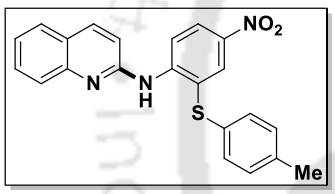
***N*-(4-Methyl-2-(phenylthio)phenyl)quinolin-2-amine (1g):** Yield 64% (55 mg) as a brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 2.34 (s, 3H), 6.76 (d, 1H, *J* = 9.0 Hz), 7.12 (t, 1H, *J* = 7.2 Hz), 7.16 (d, 2H, *J* = 8.4 Hz), 7.21 (t, 2H, *J* = 7.2 Hz), 7.29–7.32 (m, 2H), 7.42 (s, 1H), 7.58–7.63 (m, 2H), 7.69 (s, 1H), 7.85 (t, 2H, *J* = 8.4 Hz), 8.76 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ(ppm) 20.8, 113.4, 119.8, 123.5, 124.3, 126.1, 127.2, 127.4, 127.5, 129.4, 129.8, 131.6, 132.2, 136.5, 137.0, 137.6, 140.0, 147.5, 153.7; IR (KBr): 3435, 2923, 2853, 1620, 1599, 1520, 1395, 1313, 814, 740, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2S$ $[M+H]^+$ 343.1263; found 343.1275.



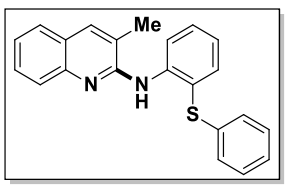
***N*-(4-Fluoro-2-(*p*-tolylthio)phenyl)quinolin-2-amine (1h):** Yield 62% (56 mg) as a brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 2.29 (s, 3H), 6.75 (d, 1H, *J* = 8.4 Hz), 7.07–7.10 (m, 3H), 7.11–7.14 (m, 2H), 7.17 (d, 2H, *J* = 8.4 Hz), 7.31 (t, 1H, *J* = 7.8 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.64 (d, 1H, *J* = 8.4 Hz), 7.81 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 9.0 Hz), 8.67 (dd, 1H, *J* = 9.0, 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ(ppm) 21.2, 113.0, 116.4 (d, *J* = 21.6 Hz), 120.6 (d, *J* = 23.2 Hz), 122.0 (q, *J* = 7.4 Hz), 123.6, 124.4, 125.4 (d, *J* = 7.3 Hz), 127.1, 127.6, 128.2, 129.9, 130.0, 130.2, 130.5, 130.7, 137.1, 137.6, 137.9, 147.4, 153.9, 158.0 (d, *J* = 242.7 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -122.8 (s); IR (KBr): 3361, 2924, 2854, 1619, 1526, 1396, 1314, 1256, 1119, 901, 811, 754 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}FN_2S$ $[M+H]^+$ 361.1169; found 361.1179.



***N*-(2-((4-Chlorophenyl)thio)-4-fluorophenyl)quinolin-2-amine (1i):** Yield 57% (54 mg) as a brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.74 (d, 1H, *J* = 8.8 Hz), 7.13–7.17 (m, 2H), 7.18–7.23 (m, 4H), 7.30–7.34 (m, 1H), 7.58–7.65 (m, 2H), 7.82 (d, 1H, *J* = 8.4 Hz), 7.90 (d, 1H, *J* = 8.8 Hz), 8.78 (dd, 1H, *J* = 8.8, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 113.0, 117.4 (d, *J* = 21.6 Hz), 121.5, 121.7, 122.0 (d, *J* = 7.4 Hz), 123.8, 124.5, 127.2, 127.6, 129.8, 129.9, 130.1, 133.1, 133.5, 138.0, 147.3, 153.6, 157.8 (d, *J* = 243.2 Hz); ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -122.7 (s); IR (KBr): 3445, 2924, 1620, 1525, 1476, 1395, 1188, 1091, 1011, 813, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}ClFN_2S$ $[M+H]^+$ 381.0623; found 381.0632.

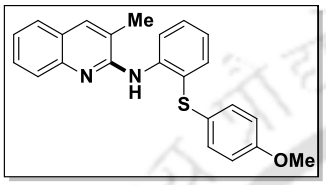


***N*-(4-Nitro-2-(*p*-tolylthio)phenyl)quinolin-2-amine (1j):** Yield 43% (42 mg) as a yellowish solid; mp 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H), 6.84 (d, 1H, *J* = 8.8 Hz), 7.09 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.41 (t, 1H, *J* = 8.0 Hz), 7.65–7.71 (m, 2H), 7.93 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 8.30 (s, 1H), 8.35 (dd, 1H, *J* = 9.6, 2.8 Hz), 8.51 (d, 1H, *J* = 2.8 Hz), 9.36 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 114.1, 117.5, 120.4, 124.9, 125.0, 126.7, 127.7, 127.8, 128.9, 130.4, 130.5, 130.7, 132.0, 137.8, 138.4, 140.9, 147.0, 147.7, 152.1; IR (KBr): 3447, 2921, 2853, 1630, 1584, 1504, 1321, 1266, 1121, 745 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_2S$ $[M+H]^+$ 388.1114; found 388.1139.

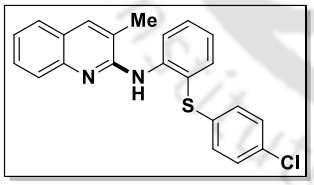


3-Methyl-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (2a): Yield 75% (64 mg) as a brownish solid; mp 97–99 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.17 (s, 3H), 7.06 (t, 1H, *J* = 7.2 Hz), 7.10–7.15 (m, 3H), 7.21 (t, 2H, *J* = 7.8 Hz), 7.30 (t, 1H, *J* = 7.2 Hz), 7.54–7.59 (m, 3H), 7.67–7.68 (m, 2H), 7.89 (d, 1H, *J* = 8.4 Hz), 8.06 (s, 1H), 9.40 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150

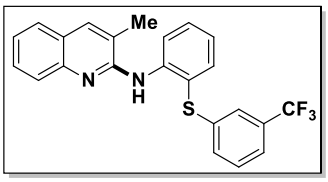
MHz, $CDCl_3$): δ (ppm) 17.4, 118.0, 119.2, 121.3, 121.9, 123.6, 124.7, 126.0, 126.6, 126.7, 127.0, 128.2, 128.8, 129.4, 129.7, 131.6, 136.1, 136.5, 137.3, 142.7, 146.2, 152.5; IR (KBr): 3345, 2940, 2841, 1634, 1586, 1527, 1438, 1416, 1249, 1170, 1012, 830, 754, 708, 619 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2S$ $[M+H]^+$ 343.1263; found 343.1289.



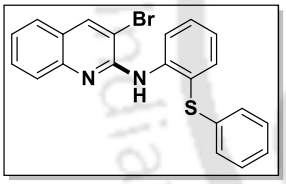
***N*-(2-((4-Methoxyphenyl)thio)phenyl)-3-methylquinolin-2-amine (2c):** Yield 73% (68 mg) as a brownish solid; mp 74–76 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 3.72 (s, 3H), 6.79 (d, 2H, *J* = 8.8 Hz), 7.04 (t, 1H, *J* = 7.6 Hz), 7.15 (d, 2H, *J* = 8.8 Hz), 7.30 (t, 1H, *J* = 6.8 Hz), 7.52–7.59 (m, 3H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.70 (s, 1H), 7.89 (d, 1H, *J* = 8.4 Hz), 8.08 (s, 1H), 9.34 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.6, 55.5, 115.1, 119.3, 120.1, 121.2, 121.9, 123.5, 124.7, 126.4, 126.7, 127.0, 128.8, 129.3, 130.9, 136.4, 136.5, 142.2, 146.3, 152.6, 158.6; IR (KBr): 3344, 2938, 2842, 1632, 1587, 1526, 1436, 1417, 1248, 1172, 1011, 829, 753, 709, 617 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2OS$ $[M+H]^+$ 373.1369; found 373.1379.



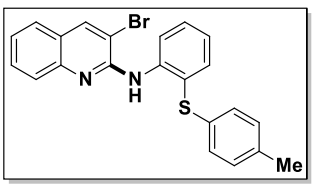
***N*-(2-((4-Chlorophenyl)thio)phenyl)-3-methylquinolin-2-amine (2e):** Yield 71% (67 mg) as a white solid; mp 139–141 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.20 (s, 3H), 7.05–7.09 (m, 3H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.31 (t, 1H, *J* = 6.8 Hz), 7.58 (q, 3H, *J* = 8.4 Hz), 7.65 (d, 1H, *J* = 7.6 Hz), 7.69 (s, 1H), 7.89 (d, 1H, *J* = 8.4 Hz), 8.01 (s, 1H), 9.41 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.4, 117.5, 119.3, 121.1, 122.0, 123.7, 124.7, 126.7, 127.1, 127.8, 128.9, 129.5, 131.8, 131.9, 134.9, 136.6, 137.3, 142.7, 146.2, 152.4; IR (KBr): 3370, 2920, 2859, 1637, 1587, 1522, 1438, 1304, 1152, 1088, 1007, 900, 808, 757, 710 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}ClN_2S$ $[M+H]^+$ 377.0874; found 377.0875.



3-Methyl-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (2f): Yield 85% (87 mg) as a light brownish solid; mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 7.06 (t, 1H, *J* = 7.6 Hz), 7.16 (d, 1H, *J* = 7.6 Hz), 7.27 (dd, 2H, *J* = 17.6, 8.4 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.48 (s, 1H), 7.52–7.61 (m, 3H), 7.65 (d, 2H, *J* = 9.6 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 7.94 (s, 1H), 9.38 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.3, 116.8, 119.5, 121.0, 122.8 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 3.8 Hz), 123.7, 124.8, 126.7, 127.1, 128.9, 129.5, 129.9, 132.1, 136.6, 137.4, 138.1, 142.9, 146.2, 152.4; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr): 3379, 2923, 2856, 1632, 1586, 1526, 1417, 1319, 1166, 1120, 1071, 893, 795, 760, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}F_3N_2S$ $[M+H]^+$ 411.1173; found 411.1178.

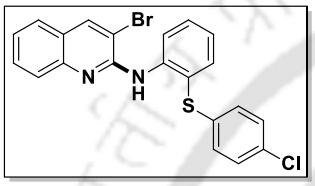


3-Bromo-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (3a): Yield 59% (60 mg) as a light brownish solid; mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.10 (dd, 2H, *J* = 13.6, 8.0 Hz), 7.16–7.22 (m, 4H), 7.32 (t, 1H, *J* = 7.2 Hz), 7.56 (t, 2H, *J* = 8.0 Hz), 7.61 (t, 1H, *J* = 8.4 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.16 (s, 1H), 8.85 (s, 1H), 9.25 (d, 1H, *J*= 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 109.2, 119.2, 119.6, 122.7, 124.2, 125.1, 126.1, 126.6, 127.2, 127.3, 129.3, 130.2, 131.2, 136.2, 137.3, 139.5, 142.3, 146.0, 149.1; IR (KBr): 3432, 2924, 2855, 1602, 1527, 1474, 1401, 1318, 1227, 1089, 1007, 895, 813, 747 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}BrN_2S$ $[M+H]^+$ 407.0212; found 407.0216.

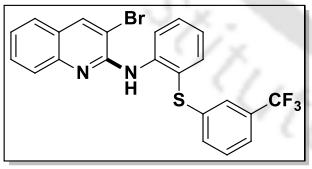


3-Bromo-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (3b): Yield 78% (82 mg) as a light brownish solid; mp 104–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 7.04 (d, 2H, *J* = 7.8 Hz), 7.01 (t, 1H, *J* = 7.2 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.31 (t, 1H, *J* = 7.8 Hz), 7.54 (d, 2H, *J* = 7.2 Hz), 7.60–7.62 (m, 1H),

7.68 (d, 1H, *J* = 7.8 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.14 (s, 1H), 8.91 (s, 1H), 9.25 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 109.2, 119.2, 120.6, 122.6, 124.2, 125.1, 126.6, 127.2, 128.0, 130.0, 130.1, 130.8, 132.5, 136.2, 137.0, 139.5, 142.0, 146.0, 149.0; IR (KBr): 3299, 2922, 2854, 1581, 1528, 1438, 1402, 1301, 1204, 1158, 1004, 907, 800, 755, 612 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}BrN_2S$ $[M+H]^+$ 421.0369; found 421.0343.

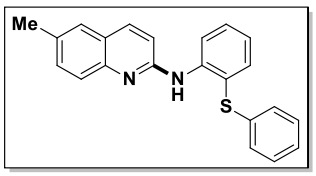


3-Bromo-*N*-(2-((4-chlorophenyl)thio)phenyl)quinolin-2-amine (3e): Yield 94% (103 mg) as a brownish solid; mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.10 (t, 3H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.8 Hz), 7.32 (t, 1H, *J* = 7.6 Hz), 7.56 (d, 2H, *J* = 9.8 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.15 (s, 1H), 8.80 (s, 1H), 9.26 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 109.1, 119.1, 119.3, 122.8, 124.3, 125.2, 126.6, 127.2, 128.5, 129.4, 130.2, 131.5, 132.0, 134.9, 137.3, 139.6, 142.2, 145.9, 148.9; IR (KBr): 3321, 3053, 2922, 1581, 1526, 1441, 1315, 1160, 1117, 1070, 1002, 851, 793, 746, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}BrClN_2S$ $[M+H]^+$ 440.9822; found 440.9831.

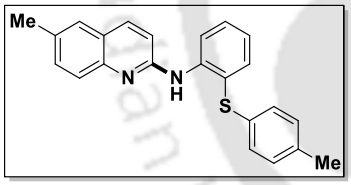


3-Bromo-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (3f): Yield 81% (96 mg) as a light yellowish solid; mp 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11 (t, 1H, *J* = 7.6 Hz), 7.20–7.35 (m, 4H), 7.50–7.62 (m, 4H), 7.68 (d, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 8.0 Hz), 8.14 (s, 1H), 8.73 (s, 1H), 9.26 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 109.0, 118.2, 119.6, 122.9 (t, *J* = 3.2 Hz), 124.0 (q, *J* = 3.8 Hz), 124.4, 125.2, 126.6, 127.3, 129.7, 130.0, 130.2, 131.4, 131.8, 137.5, 138.0, 139.6, 142.3, 145.9, 148.9; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr) 3327, 3059, 2924, 1583, 1528, 1443, 1318, 1165, 1120, 1071, 1003, 854, 794, 750,

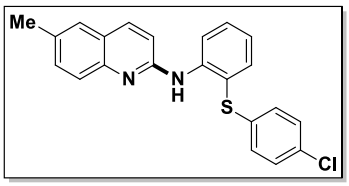
695 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}BrF_3N_2S$ $[M+H]^+$ 475.0086; found 475.0088.



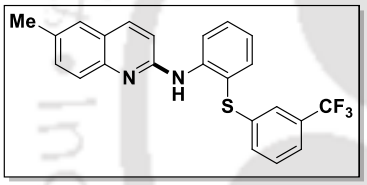
6-Methyl-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (4a): Yield 71% (61 mg) as a light brownish solid; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H), 6.76 (d, 1H, *J* = 8.8 Hz), 7.04 (t, 1H, *J* = 7.6 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 2H, *J* = 7.2 Hz), 7.20–7.25 (m, 2H), 7.41 (s, 1H), 7.45 (d, 1H, *J* = 8.8 Hz), 7.51 (t, 1H, *J* = 8.4 Hz), 7.62 (d, 1H, *J* = 7.6 Hz), 7.79 (t, 3H, *J* = 8.4 Hz), 8.95 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 113.6, 119.16, 119.2, 122.2, 124.4, 126.2, 126.7, 127.1, 127.4, 129.2, 129.4, 131.1, 131.9, 133.3, 136.5, 136.9, 137.1, 142.7, 145.7, 153.0; IR (KBr) 3362, 3054, 2960, 2922, 1611, 1587, 1521, 1435, 1314, 1127, 1023, 808, 755, 738, 688 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2S$ $[M+H]^+$ 343.1263; found 343.1266.



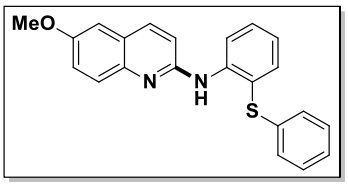
6-Methyl-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (4b): Yield 73% (65 mg) as a brownish solid; mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 2.47 (s, 3H), 6.77 (d, 1H, *J* = 8.8 Hz), 6.99–7.04 (m, 3H), 7.09 (d, 2H, *J* = 8.4 Hz), 7.41–7.48 (m, 3H), 7.55 (d, 1H, *J* = 7.6 Hz), 7.78 (dd, 3H, *J* = 21.6, 8.8 Hz), 8.87 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 21.5, 113.6, 119.3, 120.4, 122.2, 124.4, 126.7, 127.1, 128.1, 130.2, 130.7, 131.9, 132.6, 133.3, 136.4, 137.1, 142.4, 145.8, 153.1; IR (KBr) 3361, 3052, 2958, 2921, 1610, 1585, 1518, 1434, 1315, 1125, 1020, 810, 754, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2S$ $[M+H]^+$ 357.1420; found 357.1428.



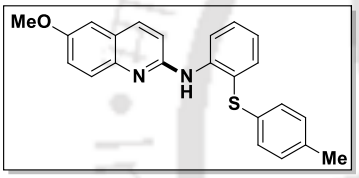
***N*-(2-((4-Chlorophenyl)thio)phenyl)-6-methylquinolin-2-amine (4e):** Yield 89% (84 mg) as a white solid; mp 158–160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H), 6.77 (d, 1H, *J* = 8.8 Hz), 7.01–7.08 (m, 3H), 7.17 (d, 2H, *J* = 8.8 Hz), 7.42–7.46 (m, 2H), 7.51 (t, 1H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 7.6 Hz), 7.71 (s, 1H), 7.76 (d, 1H, *J* = 8.4 Hz), 7.82 (d, 1H, *J* = 8.8 Hz), 8.91 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 113.5. 118.7, 119.3, 122.3, 124.5, 126.7, 127.1, 128.5, 129.5, 131.4, 132.0, 132.1, 133.5, 135.1, 136.9, 137.3, 142.8, 145.7, 152.9; IR (KBr) 3365, 3059, 2961, 2924, 1614, 1590, 1523, 1431, 1315, 1128, 1025, 809, 759, 740, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}ClN_2S$ $[M+H]^+$ 377.0874; found 377.0882.



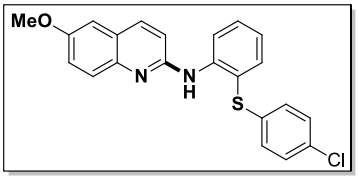
6-Methyl-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (4f): Yield 75% (77 mg) as a brownish solid; mp 89–91 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 6.80 (d, 1H, *J* = 8.8 Hz), 7.06 (t, 1H, *J* = 7.6 Hz), 7.19 (d, 1H, *J* = 7.6 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 7.6 Hz), 7.42 (s, 1H), 7.43 (d, 2H, *J* = 8.8 Hz), 7.53 (t, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.6 Hz), 7.69 (s, 1H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 8.8 Hz), 8.88 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 113.4, 117.4, 119.5, 122.5, 122.8 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 3.7 Hz), 124.5, 125.2, 126.7, 127.1, 129.8, 129.9, 131.5, 131.8, 131.9, 132.1, 133.5, 137.3, 137.4, 138.4, 143.0, 145.7, 152.8; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr) 3386, 2924, 2857, 1635, 1589, 1527, 1419, 1320, 1167, 1124, 1077, 895, 797, 761, 703 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}F_3N_2S$ $[M+H]^+$ 411.1137; found 411.1142.



6-Methoxy-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (5a): Yield 67% (60 mg) as a brownish solid; mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.89 (s, 3H), 6.78 (d, 1H, *J* = 8.8 Hz), 6.98–7.03 (m, 2H), 7.11–7.17 (m, 3H), 7.21 (t, 2H, *J* = 8.0 Hz), 7.26–7.29 (m, 1H), 7.49 (t, 1H, *J* = 8.8 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 7.75 (s, 1H), 7.79 (dd, 2H, *J* = 11.6, 9.2 Hz), 8.88 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 106.4, 113.9, 118.9, 121.5, 122.0, 125.0, 126.2, 127.3, 128.8, 129.4, 131.1, 136.5, 136.7, 137.0, 142.9, 152.1, 156.1; IR (KBr) 3426, 2923, 2855, 1611, 1585, 1520, 1451, 1364, 1229, 1090, 1032, 813, 750 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2OS$ $[M+H]^+$ 359.1213; found 359.1237.

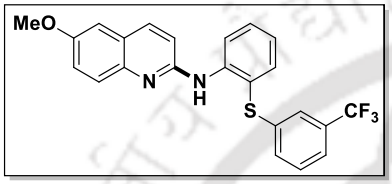


6-Methoxy-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (5b): Yield 70% (65 mg) as a brownish solid; mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.15 (s, 3H), 3.78 (s, 3H), 6.68 (d, 1H, *J* = 8.8 Hz), 6.87–6.94 (m, 4H), 7.00 (d, 2H, *J* = 8.4 Hz), 7.17 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.36 (t, 1H, *J* = 8.8 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.64 (s, 1H), 7.69 (dd, 2H, *J* = 8.8, 5.6 Hz), 8.75 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 55.7, 106.3, 113.9, 118.9, 120.1, 121.4, 122.0, 124.9, 128.0, 128.7, 130.2, 130.7, 132.6, 136.3, 136.4, 136.6, 142.5, 142.9, 152.1, 156.0; IR (KBr) 3420, 2921, 2852, 1610, 1583, 1520, 1449, 1362, 1227, 1085, 1031, 808, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2OS$ $[M+H]^+$ 373.1369; found 373.1375.

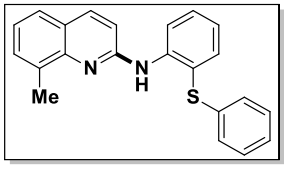


***N*-(2-((4-Chlorophenyl)thio)phenyl)-6-methoxyquinolin-2-amine (5e):** Yield 60% (59 mg) as a brownish solid; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.89 (s, 3H), 6.80 (d, 1H, *J* = 8.8 Hz), 6.98–7.04 (m, 2H), 7.06 (d, 2H, *J* = 8.8 Hz), 7.17 (d, 2H, *J* = 8.8 Hz), 7.27–7.30 (m, 1H), 7.50 (t, 1H, *J* = 7.6 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.68 (s, 1H), 7.80

(dd, 2H, *J* = 18.8, 9.2 Hz), 8.86 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 106.4, 113.8, 118.4, 119.0, 121.6, 122.2, 125.0, 128.5, 128.7, 129.5, 131.4, 132.0, 135.2, 136.8, 137.0, 142.9, 142.94, 152.0, 156.1; IR (KBr) 3438, 2926, 2857, 1613, 1587, 1521, 1452, 1363, 1230, 1091, 1034, 811, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}ClN_2OS$ $[M+H]^+$ 393.0823; found 393.0831.

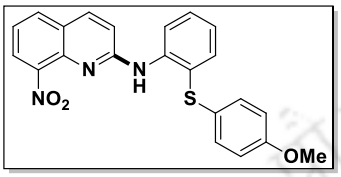


6-Methoxy-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (5f): Yield 74% (79 mg) as a brownish solid; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.88 (s, 3H), 6.81 (d, 1H, *J* = 8.8 Hz), 6.97 (d, 1H, *J* = 2.8 Hz), 7.04 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 7.6 Hz), 7.25–7.29 (m, 2H), 7.33 (d, 1H, *J* = 8.0 Hz), 7.44 (s, 1H), 7.52 (t, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 7.65 (s, 1H), 7.77 (d, 1H, *J* = 9.2 Hz), 7.82 (d, 1H, *J* = 8.8 Hz), 8.84 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.7, 106.3, 113.7, 117.4, 119.2, 121.7, 122.3, 122.5, 122.7 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 3.9 Hz), 125.1, 125.2, 128.8, 129.8, 129.9, 131.5, 131.8, 136.9, 137.3, 138.4, 142.9, 143.2, 151.9, 156.2; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr): 3369, 2945, 2849, 1613, 1589, 1520, 1450, 1365, 1319, 1245, 1162, 1122, 1072, 906, 833, 751, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}F_3N_2OS$ $[M+H]^+$ 427.1036; found 427.1039.

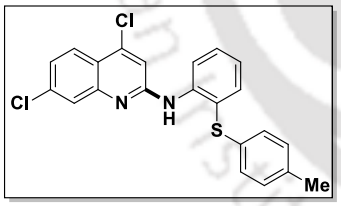


8-Methyl-*N*-(2-(phenylthio)phenyl)quinolin-2-amine (6a): Yield 56% (47 mg) as a yellowish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.75 (s, 3H), 6.68 (d, 1H, *J* = 8.8 Hz), 7.01 (t, 1H, *J* = 7.2 Hz), 7.09 (t, 1H, *J* = 7.2 Hz), 7.13–7.21 (m, 5H), 7.45 (d, 2H, *J* = 8.4 Hz), 7.51 (t, 1H, *J* = 8.8 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.8 Hz), 7.94 (s, 1H), 9.23 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.6, 113.5, 118.4, 119.1, 121.9, 123.4,

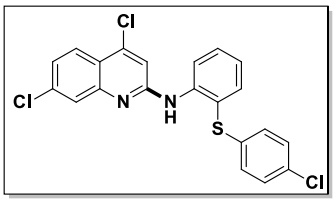
124.1, 125.4, 126.1, 127.2, 129.4, 130.1, 131.2, 135.2, 136.6, 137.1, 137.8, 142.9, 146.3, 152.4; IR (KBr) 3357, 3053, 2919, 1619, 1589, 1524, 1433, 1342, 1312, 1142, 1025, 822, 741, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2S$ $[M+H]^+$ 343.1263; found 343.1290.



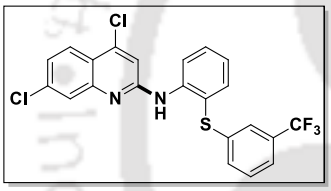
***N*-(2-((4-Methoxyphenyl)thio)phenyl)-8-nitroquinolin-2-amine (7c):** Yield 47% (47 mg) as a yellowish gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 3H), 6.82 (d, 2H, J = 8.8 Hz), 7.12–7.16 (m, 3H), 7.38 (t, 1H, J = 8.0 Hz), 7.43–7.51 (m, 2H), 7.57–7.60 (m, 2H), 7.64 (t, 1H, J = 2.0 Hz), 8.56 (d, 1H, J = 8.4 Hz), 8.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.6, 115.5, 121.0, 122.8, 124.9, 125.3, 125.4, 127.5, 130.3, 130.4, 130.7, 132.1, 135.2, 135.8, 136.8, 139.1, 159.2, 164.1; IR (KBr) 3430, 2923, 2853, 1624, 1592, 1519, 1449, 1313, 1262, 1085, 1017, 756 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_3S$ $[M+H]^+$ 404.1063; found 404.1069.



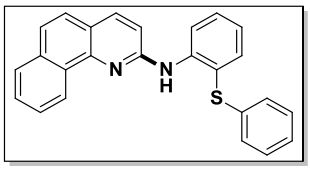
4,7-Dichloro-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (8b): Yield 67% (69 mg) as a brownish solid; mp 80–82 ^oC; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 6.83 (s, 1H), 7.04 (d, 2H, J = 7.8 Hz), 7.07–7.10 (m, 3H), 7.29–7.31 (m, 1H), 7.47 (t, 1H, J = 6.6 Hz), 7.56 (d, 1H, J = 7.8 Hz), 7.78 (s, 1H), 7.82 (d, 1H, J = 1.8 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.72 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 113.0, 120.5, 121.1, 122.0, 123.4, 125.0, 125.4, 126.6, 128.4, 130.3, 130.5, 132.1, 136.1, 136.7, 136.8, 141.1, 142.9, 148.8, 154.0; IR (KBr): 3436, 2924, 2859, 1606, 1564, 1493, 1428, 1353, 1272, 1177, 1078, 959, 810, 749, 659 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{17}Cl_2N_2S$ $[M+H]^+$ 411.0484; found 411.0479.



4,7-Dichloro-*N*-(2-((4-chlorophenyl)thio)phenyl)quinolin-2-amine (8e): Yield 82% (88 mg) as a brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.88 (s, 1H), 7.05 (d, 2H, *J* = 8.4 Hz), 7.10 (t, 1H, *J* = 7.8 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 7.33 (dd, 1H, *J* = 9.0, 2.4 Hz), 7.52 (t, 1H, *J* = 9.0 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.74 (s, 1H), 7.84 (d, 1H, *J* = 2.4 Hz), 7.95 (d, 1H, *J* = 9.0 Hz), 8.78 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 113.0, 120.1, 120.4, 121.2, 123.5, 125.2, 125.5, 126.6, 128.7, 129.6, 131.3, 132.4, 134.6, 136.8, 137.0, 141.6, 143.1, 148.7, 153.8; IR (KBr) 3437, 2927, 2863, 1609, 1561, 1494, 1429, 1352, 1271, 1179, 1079, 961, 812, 748, 667 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}Cl_3N_2S$ $[M+H]^+$ 430.9938; found 430.9941.

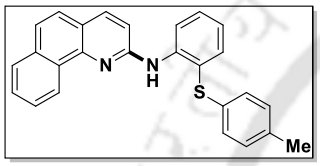


4,7-Dichloro-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (8f): Yield 58% (67 mg) as a white solid; mp 121–123 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.79 (s, 1H), 7.04 (t, 1H, *J* = 7.2 Hz), 7.10 (d, 1H, *J* = 7.6 Hz), 7.17–7.28 (m, 3H), 7.35 (s, 1H), 7.46 (t, 1H, *J* = 8.4 Hz), 7.52 (d, 1H, *J* = 7.6 Hz), 7.63 (s, 1H), 7.74 (d, 1H, *J* = 2.0 Hz), 7.84 (d, 1H, *J* = 8.8 Hz), 8.70 (d, 1H, *J* = 8.4 Hz): ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 112.9, 119.0, 120.6, 121.3, 122.5, 123.0 (q, *J* = 3.7 Hz), 123.7, 123.8 (q, *J* = 3.8 Hz), 125.3, 125.4, 126.7, 129.9, 130.1, 131.7, 132.0, 137.0, 137.1, 138.0, 141.9, 143.2, 148.7, 153.7; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.1 (s); IR (KBr) 3436, 3340, 2923, 2853, 1618, 1579, 1528, 1452, 1321, 1164, 1121, 1073, 963, 791, 758, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{14}Cl_2F_3N_2S$ $[M+H]^+$ 465.0201; found 465.0200.

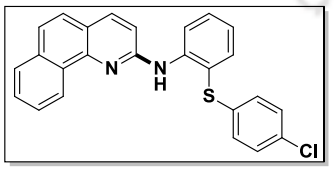


***N*-(2-(Phenylthio)phenyl)benzo[*h*]quinolin-2-amine (9a):** Yield 57% (54 mg) as a brownish solid; mp 122–124 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.88 (d, 1H, *J* = 8.4 Hz), 7.06–7.14 (m, 2H), 7.20 (dd, 4H, *J* = 12.0, 6.8 Hz), 7.57 (d, 1H, *J* = 8.8 Hz),

7.64 (q, 4H, *J* = 7.0 Hz), 7.71 (t, 1H, *J* = 6.8 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 8.4 Hz), 9.11 (d, 1H, *J* = 8.4 Hz), 9.16 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 112.8, 119.0, 119.1, 121.4, 122.2, 124.5, 124.8, 125.3, 126.2, 126.6, 127.3, 127.9, 129.4, 131.0, 131.1, 134.4, 136.5, 137.1, 137.7, 142.8, 145.5, 153.2; IR (KBr) 3357, 2928, 2857, 1624, 1585, 1529, 1455, 1359, 1315, 1243, 1087, 828, 809, 758, 652 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{19}N_2S$ $[M+H]^+$ 379.1263; found 379.1273.

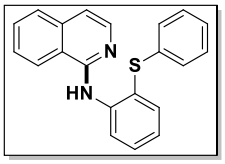


***N*-(2-(*p*-Tolylthio)phenyl)benzo[*h*]quinolin-2-amine (9b):** Yield 76% (74 mg) as a white solid; mp 110–112 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 6.88 (d, 1H, *J* = 8.4 Hz), 7.08 (dd, 3H, *J* = 16.2, 7.8 Hz), 7.16 (d, 2H, *J* = 7.8 Hz), 7.57 (d, 1H, *J* = 9.0 Hz), 7.59–7.69 (m, 4H), 7.73 (t, 1H, *J* = 7.2 Hz), 7.89 (d, 1H, *J* = 7.8 Hz), 7.93 (d, 1H, *J* = 9.0 Hz), 7.95 (s, 1H), 9.09 (d, 1H, *J* = 8.4 Hz), 9.19 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 112.7, 119.2, 120.3, 121.3, 122.1, 124.4, 124.8, 125.3, 126.5, 127.8, 127.9, 128.1, 130.2, 130.7, 131.0, 132.6, 134.4, 136.4, 136.5, 137.6, 142.4, 145.5, 153.2; IR (KBr) 3349, 2921, 2854, 1621, 1584, 1528, 1452, 1357, 1310, 1240, 1081, 826, 800, 746, 649 cm^{-1}; HRMS (ESI): calcd. for $C_{26}H_{21}N_2S$ $[M+H]^+$ 393.1420; found 393.1422.

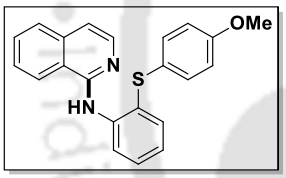


***N*-(2-((4-Chlorophenyl)thio)phenyl)benzo[*h*]quinolin-2-amine (9e):** Yield 52% (53 mg) as a light yellowish solid; mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.89 (d, 1H, *J* = 8.4 Hz), 7.10 (d, 3H, *J* = 8.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.57–7.74 (m, 6H), 7.92 (dd, 3H, *J* = 27.2, 8.4 Hz), 9.14 (dd, 2H, *J* = 19.2, 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 112.7, 118.6, 119.4, 121.5, 122.3, 124.6, 124.7, 125.3, 126.6, 128.0, 128.5, 129.5, 131.0, 131.4, 132.1, 134.4, 135.2, 137.0, 137.8, 142.8, 145.5, 153.1; IR (KBr) 3433, 3349, 2924, 2854, 1584, 1528, 1356, 1136, 1087, 1007, 828, 752, 649 cm^{-1}; HRMS (ESI): calcd.

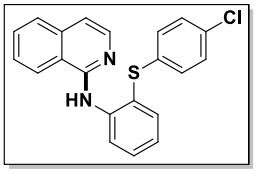
for $C_{25}H_{18}ClN_2S$ $[M+H]^+$ 413.0874; found 413.0883.



***N*-(2-(Phenylthio)phenyl)isoquinolin-1-amine (10a):** Yield 73% (60 mg) as a brownish gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.04 (t, 1H, *J* = 7.2 Hz), 7.10–7.15 (m, 2H), 7.21–7.24 (m, 4H), 7.44 (t, 1H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 7.2 Hz), 7.61 (dd, 2H, *J* = 18.0, 8.4 Hz), 7.69 (dd, 2H, *J* = 16.4, 8.0 Hz), 8.13 (d, 1H, *J* = 6.0 Hz), 8.58 (s, 1H), 8.91 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 114.1, 118.8, 119.3, 119.7, 121.5, 122.1, 126.2, 126.9, 127.1, 127.5, 129.5, 130.1, 131.4, 136.4, 137.2, 137.5, 140.8, 142.7, 151.7; IR (KBr) 3372, 3056, 2924, 2852, 1627, 1589, 1565, 1526, 1438, 1398, 1322, 1024, 806, 740, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{17}N_2S$ $[M+H]^+$ 329.1107; found 329.1095.

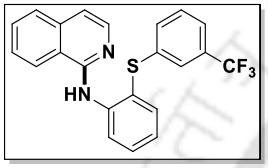


***N*-(2-((4-Methoxyphenyl)thio)phenyl)isoquinolin-1-amine (10c):** Yield 64% (57 mg) as a brownish solid; mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.72 (s, 3H), 6.78 (d, 2H, *J* = 8.8 Hz), 7.02 (t, 1H, *J* = 7.6 Hz), 7.14 (d, 1H, *J* = 6.0 Hz), 7.22 (d, 2H, *J* = 8.8 Hz), 7.44–7.51 (m, 2H), 7.60–7.64 (m, 2H), 7.75 (dd, 2H, *J* = 17.6, 8.4 Hz), 8.13 (d, 1H, *J* = 5.6 Hz), 8.59 (s, 1H), 8.84 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.5, 113.9, 115.0, 115.2, 119.6 (d, *J* = 8.5 Hz), 121.3, 121.6, 122.2, 126.5, 126.9, 127.5, 129.9, 130.1 (d, *J* = 10.0 Hz), 130.6, 136.2, 137.5, 140.8, 142.0, 151.9, 158.9; IR (KBr) 3364, 2925, 2841, 1624, 1590, 1563, 1530, 1493, 1436, 1400, 1323, 1248, 1207, 1027, 827, 800, 753, 581 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{19}N_2OS$ $[M+H]^+$ 359.1213; found 359.1235.

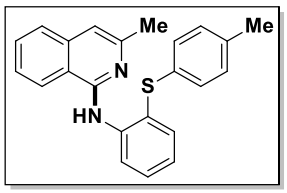


***N*-(2-((4-Chlorophenyl)thio)phenyl)isoquinolin-1-amine (10e):** Yield 69% (62 mg) as a brownish solid; mp 73–75 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.05 (t, 1H, *J* = 7.2 Hz), 7.10 (d, 2H, *J* = 9.0 Hz), 7.16 (d, 3H, *J* = 8.4 Hz), 7.49 (t, 1H, *J* = 7.2 Hz), 7.53

(t, 1H, *J* = 7.2 Hz), 7.61–7.65 (m, 2H), 7.68 (d, 1H, *J* = 8.4 Hz), 7.73 (d, 1H, *J* = 7.8 Hz), 8.13 (d, 1H, *J* = 5.4 Hz), 8.52 (s, 1H), 8.88 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.3, 118.4, 119.6, 119.7, 121.4, 122.3, 127.1, 127.7, 128.3, 129.6, 130.2, 131.7, 132.1, 135.0, 137.2, 137.6, 140.8, 142.7, 151.7; IR (KBr): 3376, 2921, 2850, 1624, 1578, 1563, 1534, 1401, 1115, 1064, 805, 739, 692 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2S$ $[M+H]^+$ 363.0717; found 363.0688.

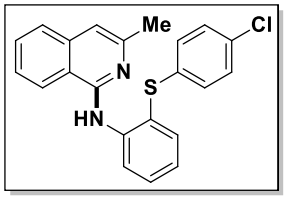


***N*-(2-((3-(Trifluoromethyl)phenyl)thio)phenyl)isoquinolin-1-amine (10f):** Yield 57% (56 mg) as a brownish solid; mp 123–125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.06 (t, 1H, *J* = 7.2 Hz), 7.15 (d, 1H, *J* = 6.0 Hz), 7.21 (d, 1H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 7.6 Hz), 7.33 (d, 1H, *J* = 7.6 Hz), 7.45 (t, 1H, *J* = 7.6 Hz), 7.52–7.56 (m, 2H), 7.58–7.67 (m, 3H), 7.71 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 1H, *J* = 5.6 Hz), 8.46 (s, 1H), 8.89 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 114.4, 117.5, 119.6, 119.8, 121.3, 122.4, 122.9 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 3.8 Hz), 127.1, 127.6, 129.8 (d, *J* = 1.1 Hz), 129.9, 130.2, 132.0, 137.3, 137.5, 138.2, 140.7, 142.8, 151.6; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.0 (s); IR (KBr): 3382, 2923, 2853, 1626, 1582, 1567, 1535, 1402, 1119, 1070, 806, 742, 697, cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{16}F_3N_2S$ $[M+H]^+$ 397.0981; found 397.0989.

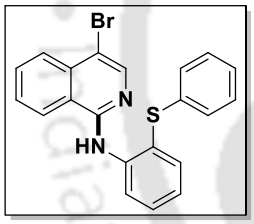


3-Methyl-*N*-(2-(*p*-tolylthio)phenyl)isoquinolin-1-amine (11b): Yield 72% (64 mg) as a red gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H), 2.59 (s, 3H), 6.98 (s, 1H), 7.02 (t, 1H, *J* = 7.2 Hz), 7.04 (d, 2H, *J* = 7.8 Hz), 7.14 (d, 2H, *J*= 7.8 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.50 (t, 1H, *J* = 7.2 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.61 (t, 2H, *J* = 7.2 Hz), 7.65 (d, 1H, *J* = 7.8 Hz), 8.71 (s, 1H), 9.09 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 24.5, 117.7, 117.9, 118.6, 119.1, 121.5, 121.7, 125.8, 126.9, 127.5, 129.9, 130.2, 131.1, 132.7, 136.2, 137.0, 138.3, 142.7, 149.7, 151.1; IR (KBr) 3367, 2926, 2845, 1627, 1591, 1564, 1535, 1492, 1437, 1404, 1322,

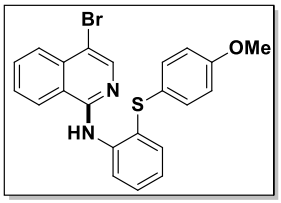
1249, 1208, 1026, 829, 801, 754, 582 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2S$ $[M+H]^+$ 357.1420; found 357.1435.



***N*-(2-((4-Chlorophenyl)thio)phenyl)-3-methylisoquinolin-1-amine (11e):** Yield 68% (64 mg) as a brownish gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.61 (s, 3H), 7.00 (s, 1H), 7.04 (t, 1H, *J* = 7.8 Hz), 7.13 (d, 2H, *J* = 9.0 Hz), 7.19 (d, 2H, *J* = 9.0 Hz), 7.39 (t, 1H, *J* = 7.2 Hz), 7.52–7.57 (m, 2H), 7.61–7.66 (m, 3H), 8.64 (s, 1H), 9.12 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 24.5, 112.0, 117.7, 117.8, 118.8, 121.2, 121.8, 126.0, 127.0, 128.2, 129.5, 130.0, 131.7, 132.0, 135.0, 137.2, 138.3, 142.9, 149.6, 150.9; IR (KBr) 3370, 2928, 2847, 1629, 1592, 1567, 1537, 1493, 1438, 1405, 1321, 1253, 1209, 1027, 830, 802, 755, 583 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}ClN_2S$ $[M+H]^+$ 377.0874; found 377.0897.

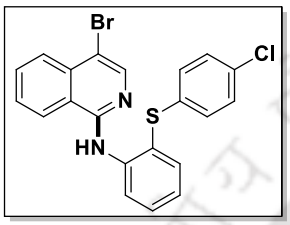


4-Bromo-*N*-(2-(phenylthio)phenyl)isoquinolin-1-amine (12a): Yield 93% (94 mg) as a light brownish solid; mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.92–7.00 (m, 2H), 7.06–7.11 (m, 4H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 7.2 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.54 (t, 2H, *J* = 7.6 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 8.15 (s, 1H), 8.46 (s, 1H), 8.71 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 110.3, 119.2, 119.5, 120.9, 121.7, 122.5, 126.3, 126.9, 127.1, 127.7, 129.5, 131.1, 131.3, 135.6, 136.2, 137.1, 140.1, 142.1, 151.1; IR (KBr): 3447, 3378, 3051, 2924, 1620, 1590, 1527, 1438, 1403, 1312, 1180, 1070, 901, 748, 689 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}BrN_2S$ $[M+H]^+$ 407.0212; found 407.0220.

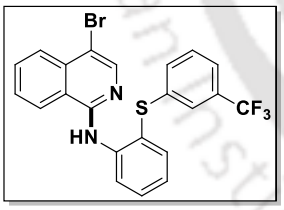


4-Bromo-*N*-(2-((4-methoxyphenyl)thio)phenyl)isoquinolin-1-amine (12c): Yield 84% (92 mg) as a light brownish solid; mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.71 (s, 3H), 6.77 (d, 2H, *J* = 8.8 Hz), 7.04 (t, 1H, *J* = 7.6 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.54 (t, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.69–7.74 (m, 2H), 8.07 (d, 1H, *J* = 8.4 Hz), 8.28 (s, 1H), 8.58 (s, 1H), 8.74 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz,

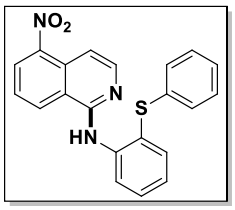
$CDCl_3$): δ (ppm) 55.5, 110.2, 115.2, 119.9, 120.1, 121.7, 121.9, 122.6, 126.2, 127.0, 127.7, 130.2, 130.6, 131.1, 135.7, 136.1, 141.4, 142.2, 151.3, 158.9; IR (KBr): 3357, 2924, 2837, 1618, 1587, 1529, 1493, 1436, 1404, 1313, 1248, 1175, 1028, 944, 827, 754, 664 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}BrN_2SO$ $[M+H]^+$ 437.0318; found 437.0319.



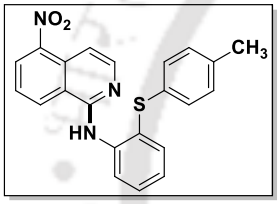
4-Bromo-*N*-(2-((4-chlorophenyl)thio)phenyl)isoquinolin-1-amine (12e): Yield 86% (95 mg) as a brownish solid; mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.05–7.10 (m, 3H), 7.17 (d, 2H, *J* = 8.8 Hz), 7.53 (dd, 2H, *J* = 13.6, 6.8 Hz), 7.65 (t, 2H, *J* = 8.4 Hz), 7.72 (t, 1H, *J* = 8.0 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.29 (s, 1H), 8.52 (s, 1H), 8.80 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 110.6, 118.9, 119.8, 120.9, 121.6, 122.7, 127.1, 127.9, 138.3, 129.6, 131.2, 131.6, 132.3, 134.8, 135.8, 137.1, 142.2, 151.1; IR (KBr): 3367, 3040, 2916, 1614, 1587, 1521, 1435, 1392, 1312, 1158, 1123, 1069, 939, 745, 687 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}BrClN_2S$ $[M+H]^+$ 440.9822; found 440.9823.



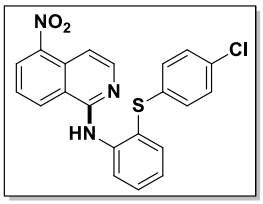
4-Bromo-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)isoquinolin-1-amine (12f): Yield 88% (104 mg) as a light yellowish solid; mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.07 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.32 (d, 1H, *J* = 7.6 Hz), 7.46–7.55 (m, 3H), 7.58 (d, 1H, *J* = 8.4 Hz), 7.66 (dd, 2H, *J* = 14.8, 7.2 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 8.25 (s, 1H), 8.44 (s, 1H), 8.80 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 110.6, 117.9, 120.0, 120.8, 121.5, 122.8, 123.0 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 3.8 Hz), 127.1, 127.9, 129.8, 130.0, 131.2, 131.6, 131.9, 135.7, 137.3, 138.0, 142.1, 142.3, 151.0; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.1 (d, *J* = 7.8 Hz); IR (KBr): 3375, 3044, 2921, 1619, 1588, 1525, 1439, 1399, 1317, 1159, 1124, 1070, 940, 748, 692, 662 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}BrF_3N_2S$ $[M+H]^+$ 475.0086; found 475.0095.



5-Nitro-*N*-(2-(phenylthio)phenyl)isoquinolin-1-amine (13a): Yield 49% (46 mg) as a orange solid; mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11–7.22 (m, 6H), 7.48–7.56 (m, 2H), 7.68 (d, 1H, *J* = 7.6 Hz), 7.81 (d, 1H, *J* = 6.0 Hz), 7.89 (d, 1H, *J* = 8.4 Hz), 8.32 (dd, 2H, *J* = 19.6, 8.0 Hz), 8.59 (s, 1H), 8.81 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 108.3, 119.7, 120.1, 120.6, 123.2, 125.1, 126.5, 127.1, 127.6, 128.0, 129.4, 129.6, 130.4, 131.4, 136.0, 137.1, 141.8, 144.8, 145.9, 152.0; IR (KBr): 3337, 2923, 2851, 1623, 1590, 1516, 1433, 1315, 1089, 1009, 869, 801, 755, 592 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}N_3O_2S$ $[M+H]^+$ 374.0958; found 374.0952.

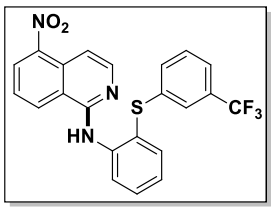


5-Nitro-*N*-(2-(*p*-tolylthio)phenyl)isoquinolin-1-amine (13b): Yield 56% (54 mg) as a reddish solid; mp 93–95 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 3H), 7.03 (d, 2H, *J* = 7.8 Hz), 7.08–7.10 (m, 3H), 7.51 (t, 2H, *J* = 7.8 Hz), 7.66 (d, 1H, *J* = 7.8 Hz), 7.81 (d, 1H, *J* = 6.0 Hz), 7.94 (d, 1H, *J* = 8.4 Hz), 8.30 (d, 1H, *J* = 6.0 Hz), 8.36 (d, 1H, *J* = 7.8 Hz), 8.60 (s, 1H), 8.78 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 108.2, 120.1, 120.6, 123.1, 125.1, 127.6, 127.7, 127.8, 128.1, 130.2, 130.3, 130.4, 130.5, 131.0, 132.2, 136.6, 136.8, 141.5, 144.8, 145.8, 152.1; IR (KBr) 3332, 2921, 2850, 1621, 1585, 1517, 1431, 1313, 1081, 1002, 862, 799, 753, 585 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_2S$ $[M+H]^+$ 388.1114; found 388.1093.

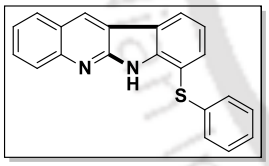


***N*-(2-((4-Chlorophenyl)thio)phenyl)-5-nitroisoquinolin-1-amine (13e):** Yield 59% (60 mg) as a orange solid; mp 113–115 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.07–7.10 (m, 3H), 7.16–7.18 (m, 2H), 7.53–7.57 (m, 2H), 7.66 (d, 1H, *J* = 7.8 Hz), 7.84 (d, 1H, *J* = 6.6 Hz), 7.98 (d, 1H, *J* = 8.4 Hz), 8.31 (d, 1H, *J* = 6.0 Hz), 8.38 (d, 1H, *J* = 7.2 Hz), 8.54 (s, 1H), 8.79 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 108.5, 119.4, 120.3, 120.6, 123.3, 125.2 127.7, 127.8, 128.3, 129.5, 129.7, 130.4, 131.6, 132.4, 134.6, 137.1, 141.8, 144.8, 146.0, 152.0; IR (KBr) 3340, 2924, 2853, 1626, 1591,

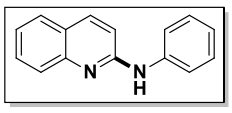
1519, 1434, 1316, 1091, 1010, 871, 802, 758, 597 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}ClN_3O_2S$ $[M+H]^+$ 408.0568; found 408.0575.



5-Nitro-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)isoquinolin-1-amine (13f): Yield 41% (45 mg) as a yellowish gummy; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14 (t, 1H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 8.0 Hz), 7.34 (t, 2H, *J* = 7.6 Hz), 7.52–7.58 (m, 3H), 7.69 (d, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 6.4 Hz), 7.95 (d, 1H, *J* = 8.4 Hz), 8.30 (d, 1H, *J* = 6.4 Hz), 8.37 (d, 1H, *J* = 7.6 Hz), 8.48 (s, 1H), 8.79 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 108.6, 115.7, 118.6, 120.5, 120.7, 123.1 (q, *J* = 3.4 Hz), 123.5, 123.7 (q, *J* = 3.8 Hz), 125.3, 127.7, 127.74, 129.9, 130.1, 130.4, 132.0, 137.3, 137.9, 138.0, 142.0, 144.7, 151.9; ^{19}F NMR ($CDCl_3$ + hexafluorobenzene): δ -66.1 (s); IR (KBr) 3345, 2929, 2854, 1627, 1593, 1522, 1434, 1317, 1094, 1012, 877, 806, 759, 599 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_3O_2S$ $[M+H]^+$ 442.0832; found 442.0835.



7-(Phenylthio)-*6H*-indolo[*2,3-b*]quinoline (14a): Yield 65% (42 mg) as a brownish solid; mp 110–112 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.96 (t, 2H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 8.0 Hz), 7.50 (t, 1H, *J* = 8.0 Hz), 7.70–7.75 (m, 2H), 8.04 (dd, 2H, *J* = 14.0, 8.4 Hz), 8.19 (d, 1H, *J* = 8.0 Hz), 8.76 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 113.4, 118.7, 121.3, 122.1, 123.0, 123.9, 124.7, 127.7, 128.6, 128.7, 128.74, 129.4, 129.6, 132.2, 134.5, 134.9, 143.0, 147.0, 152.5; IR (KBr) 3441, 2918, 2851, 1635, 1603, 1475, 1400, 1224, 1090, 1011, 814, 748, 477 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}N_2S$ $[M+H]^+$ 327.0950; found 327.0964.

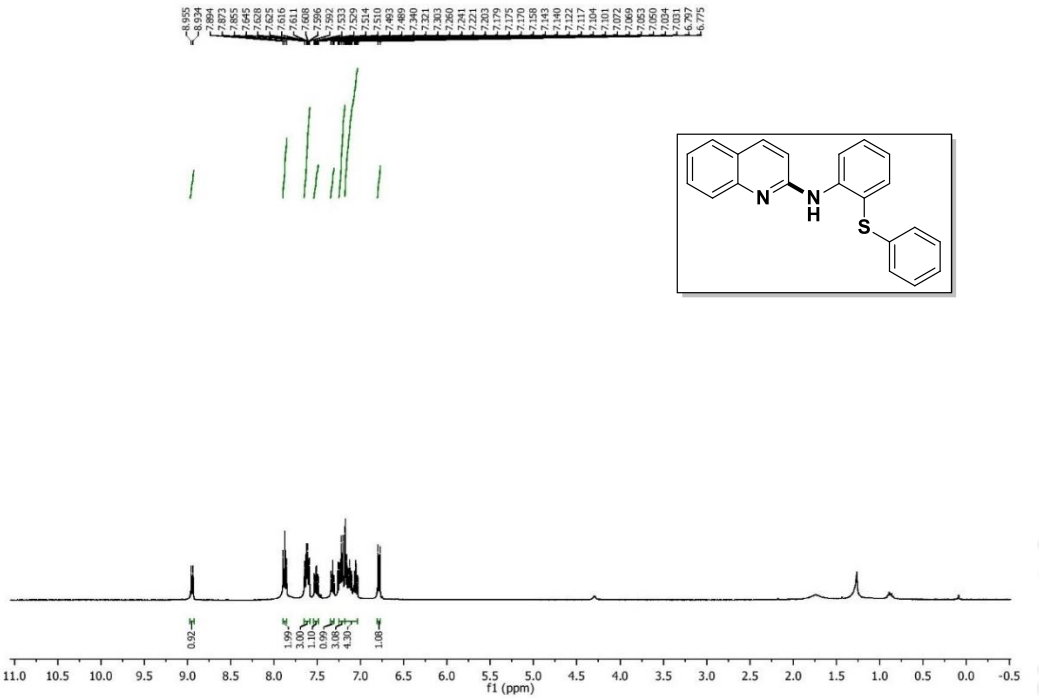


***N*-Phenylquinolin-2-amine (1k):** Yield 59% (32 mg) as a yellowish gummy; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.92 (s, 1H), 7.00 (d, 1H, *J* = 8.4 Hz), 7.10 (t, 1H, *J* = 7.2 Hz), 7.30 (t, 1H, *J* = 8.4 Hz),

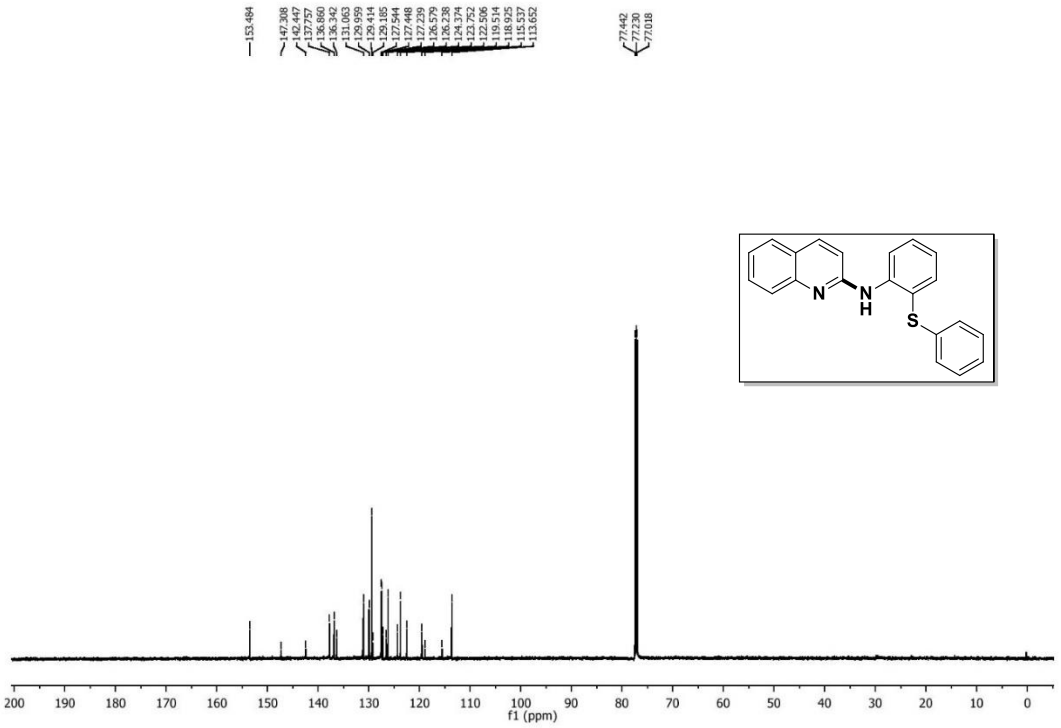
7.37 (t, 2H, J = 7.2 Hz), 7.56–7.60 (m, 3H), 7.65 (d, 1H, J = 8.4 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 111.8, 119.2, 120.7, 123.3, 124.3, 126.8, 127.6, 129.4, 130.0, 138.0, 140.3, 147.8, 154.5; IR (KBr) 3406, 2924, 1618, 1597, 1532, 1500, 1442, 1324, 1248, 1148, 817, 754, 693, 496 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}N_2$ $[M+H]^+$ 221.1073; found 221.1081.

VI.7. Spectra

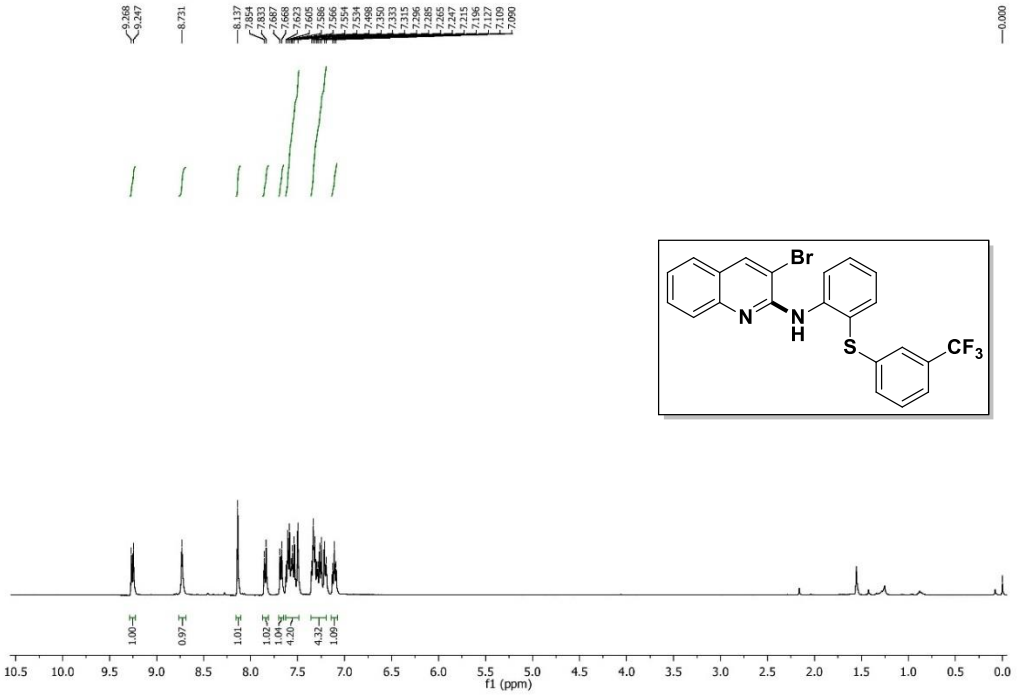
_N_-(2-(Phenylthio)phenyl)quinolin-2-amine (1a): ^{1}H NMR (400 MHz, $CDCl_3$)



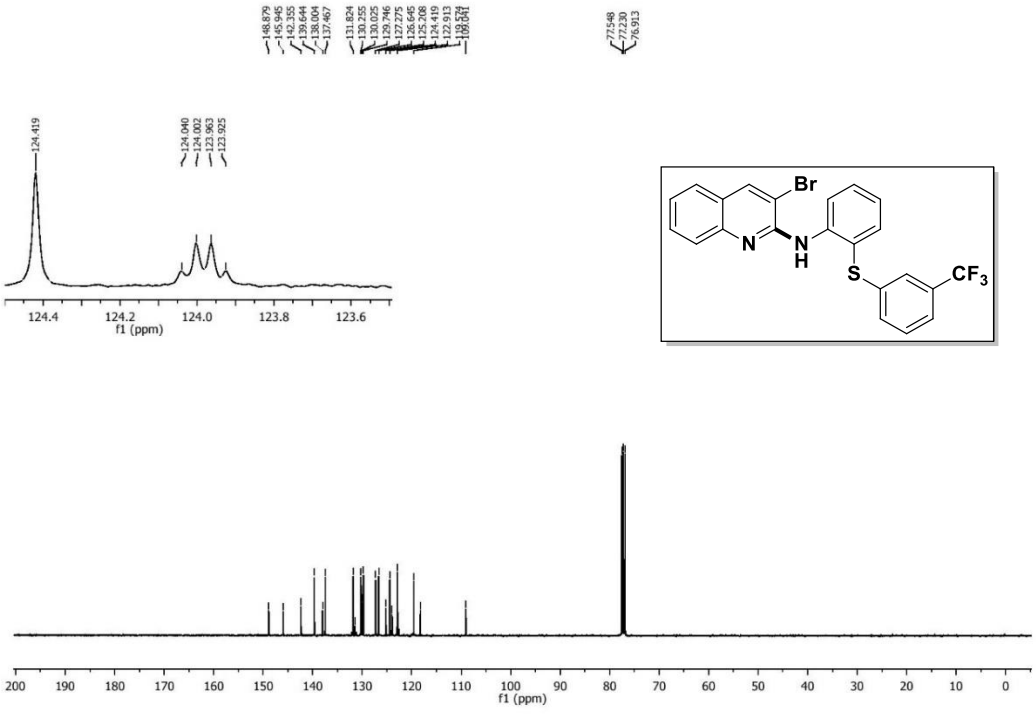
_N_-(2-(Phenylthio)phenyl)quinolin-2-amine (1a): ^{13}C NMR (150 MHz, $CDCl_3$)



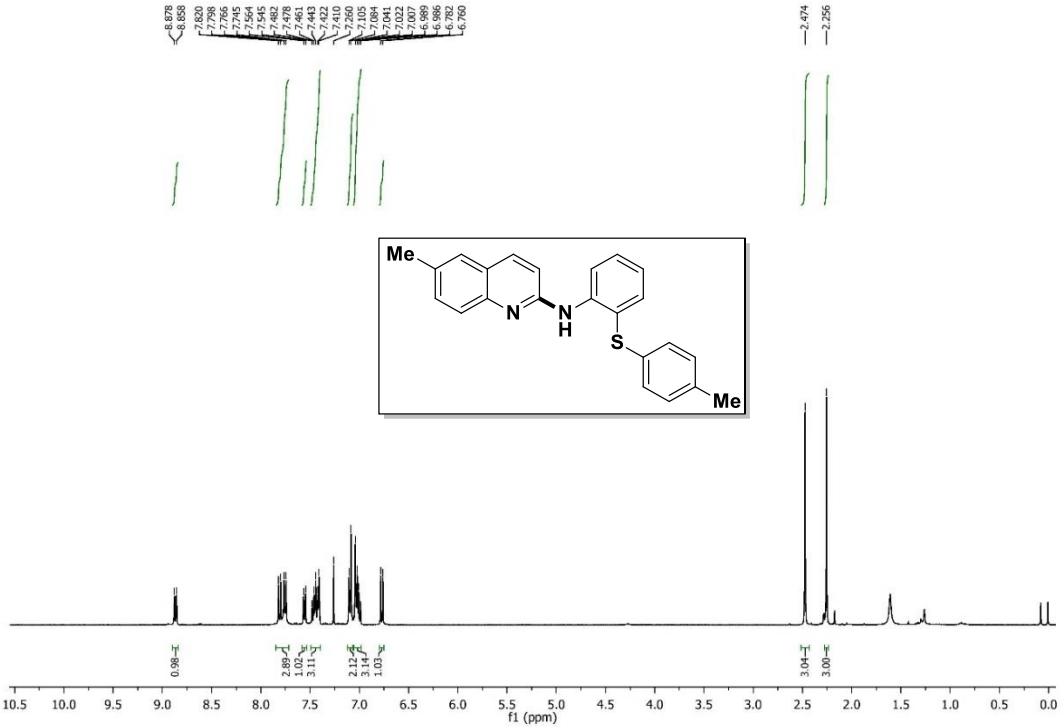
3-Bromo-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (3f): ^{1}H NMR (400 MHz, CDCl3)



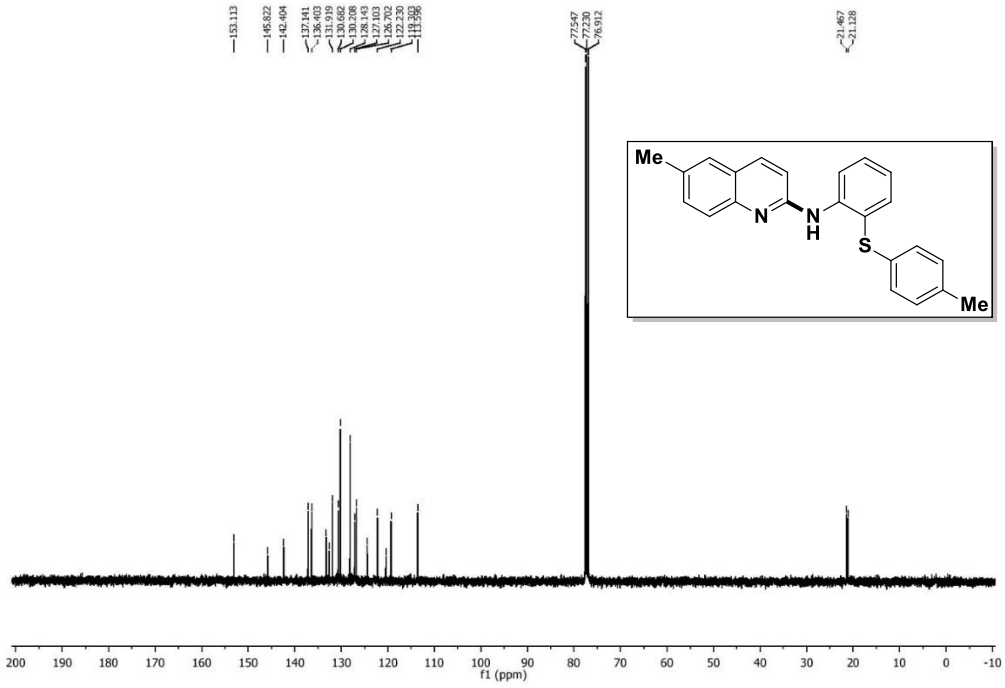
3-Bromo-*N*-(2-((3-(trifluoromethyl)phenyl)thio)phenyl)quinolin-2-amine (3f): ^{13}C NMR (100 MHz, $CDCl_3$)



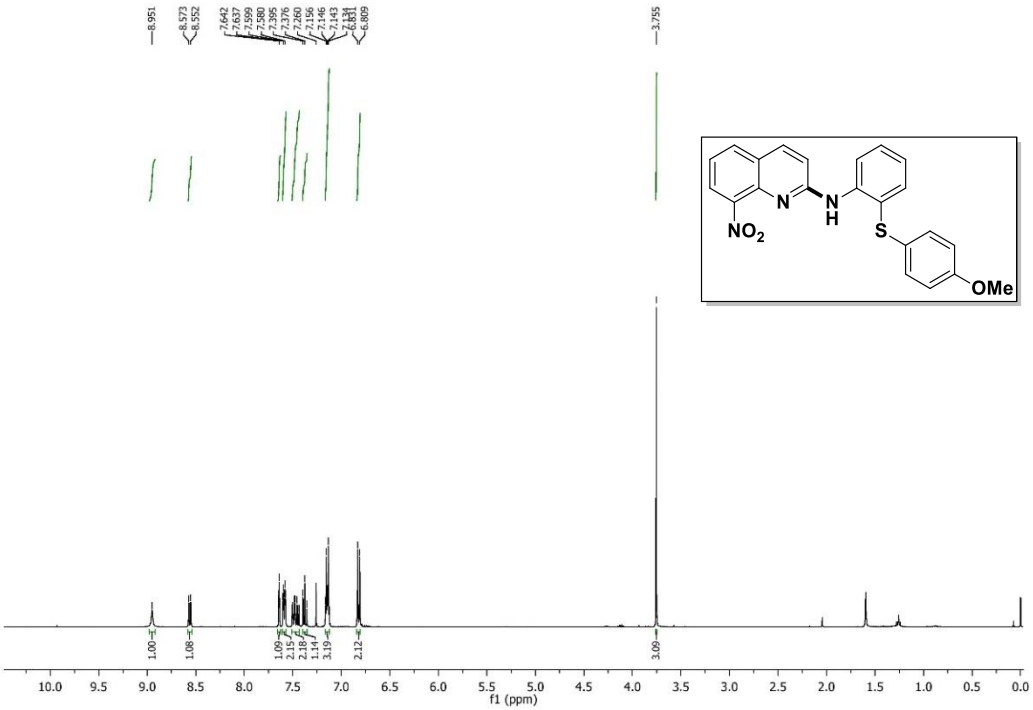
6-Methyl-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (4b): ^{1}H NMR (400 MHz, $CDCl_3$)



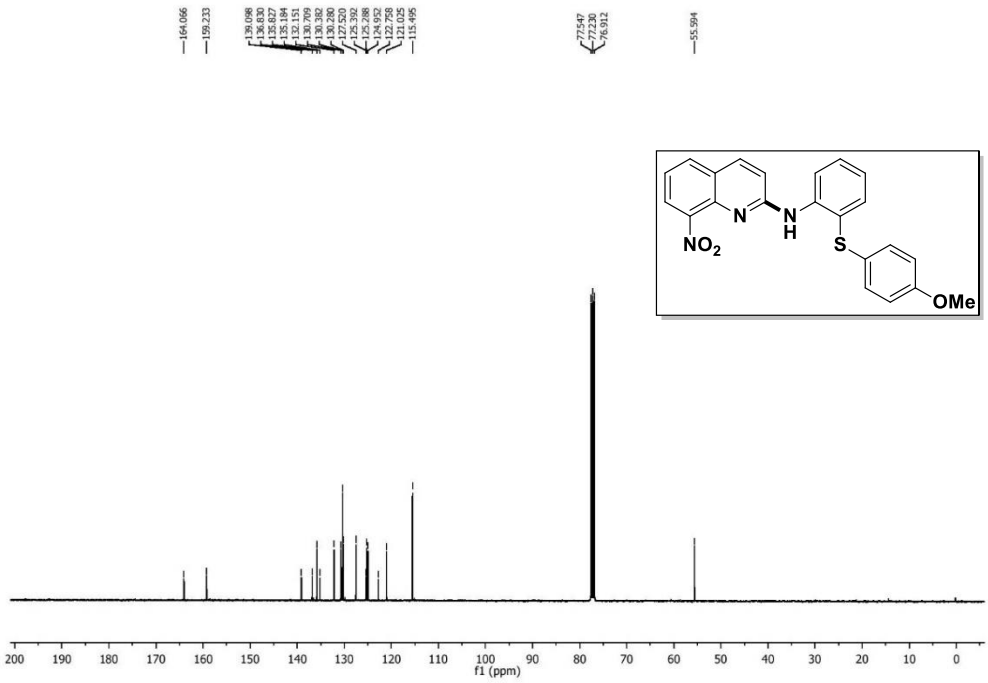
6-Methyl-*N*-(2-(*p*-tolylthio)phenyl)quinolin-2-amine (4b): ^{13}C NMR (100 MHz, $CDCl_3$)



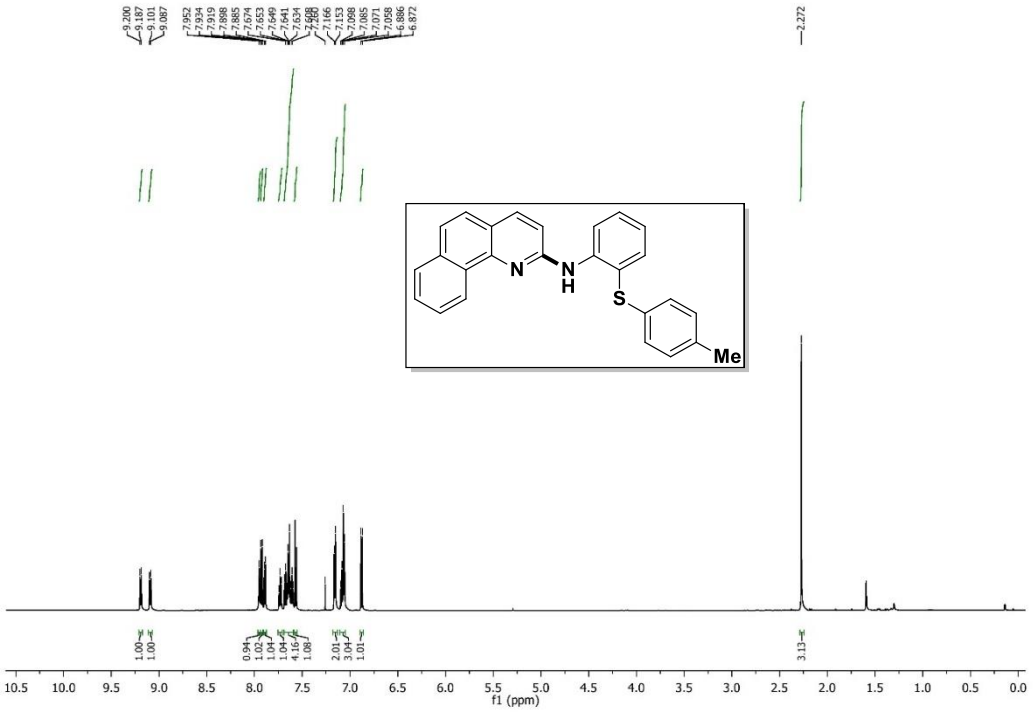
_N_-(2-((4-Methoxyphenyl)thio)phenyl)-8-nitroquinolin-2-amine (7c): ^{1}H NMR (400 MHz, $CDCl_3$)



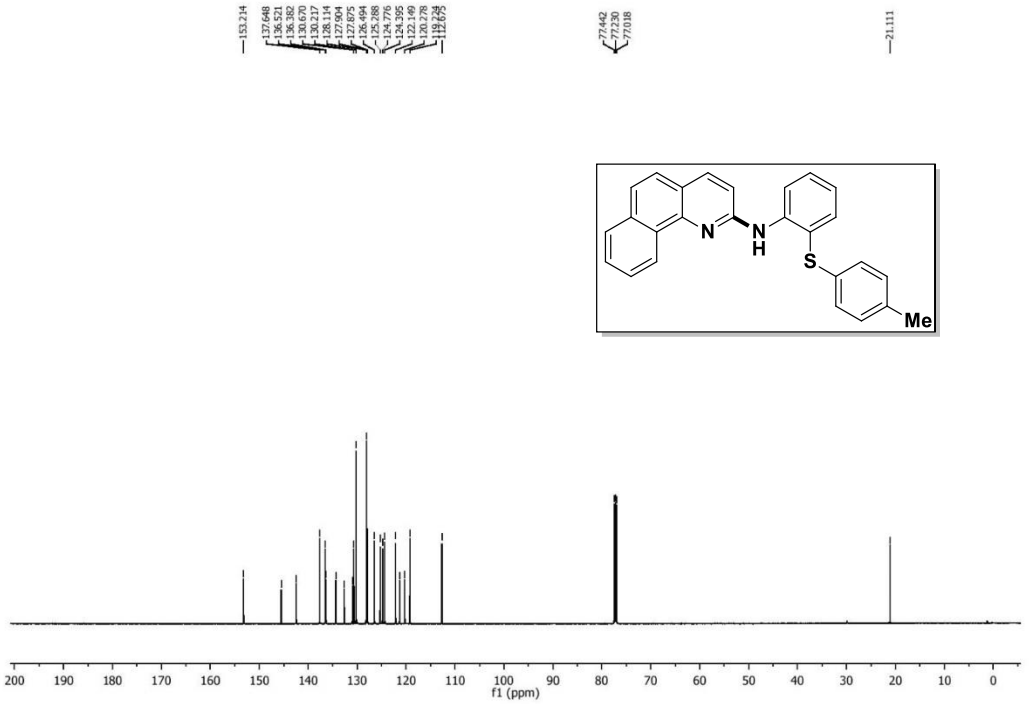
_N_-(2-((4-Methoxyphenyl)thio)phenyl)-8-nitroquinolin-2-amine (7c): ^{13}C NMR (100 MHz, $CDCl_3$)



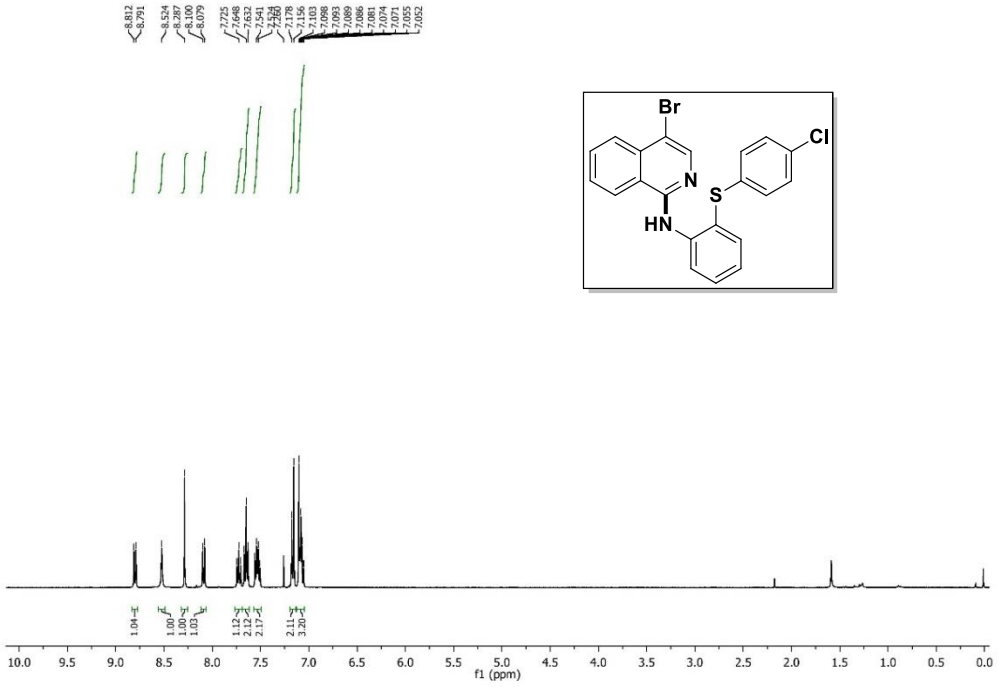
_N_-(2-(_p_-Tolylthio)phenyl)benzo[_h_]quinolin-2-amine (9b): ^{1}H NMR (600 MHz, $CDCl_3$)



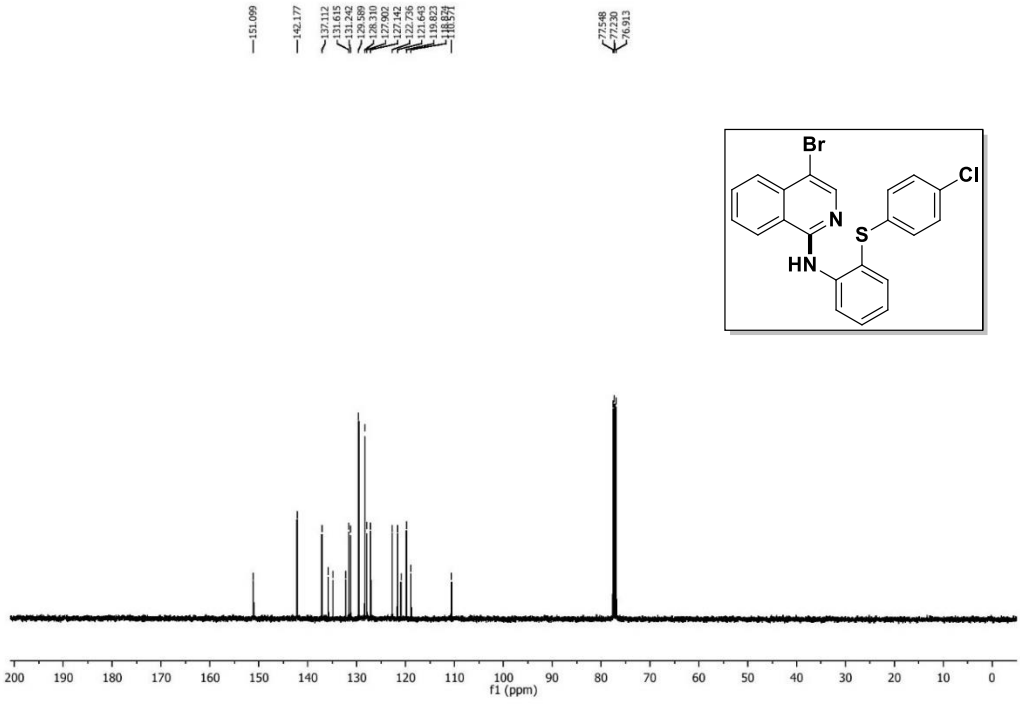
_N_-(2-(_p_-Tolylthio)phenyl)benzo[_h_]quinolin-2-amine (9b): ^{13}C NMR (150 MHz, $CDCl_3$)



4-Bromo-*N*-(2-((4-chlorophenyl)thio)phenyl)isoquinolin-1-amine (12e): ^{1}H NMR (400 MHz, $CDCl_3$)



4-Bromo-*N*-(2-((4-chlorophenyl)thio)phenyl)isoquinolin-1-amine (12e): ^{13}C NMR (100 MHz, $CDCl_3$)



PUBLICATIONS

(1) **"Benzylamine as arylcarboxy surrogate: A copper catalysed *o*-benzoxylation of 2-phenylpyridines using benzyl amines"**

Ahalya. Behera, Saroj K. Rout, Srimanta Guin and Bhisma. K. Patel, *RSC Adv.*, 2014, **4**, 55115.

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

Ganesh Majji, Srimanta Guin, Saroj K. Rout, Ahalya Behera and Bhisma K. Patel, *Chem. Commun.*, 2014, **50**, 12193.

(3) **"Pd(II)-catalysed *o*-aroylation of directing arenes using terminal aryl alkenes and alkynes"**

Nilufa Khatun, Arghya Banerjee, Sourav Kumar Santra, Ahalya Behera and Bhisma K. Patel, *RSC Adv.*, 2014, **4**, 54532.

(4) **"Benzyl bromides as aroyl surrogates in substrate directed Pd-catalysed *o*-aroylation"**

Ahalya Behera, Wajid Ali, Srimanta Guin, Nilufa Khatun, Prakash R. Mohanta and Bhisma K. Patel, *RSC Adv.*, 2015, **5**, 3333.

(5) **"Regiospecific benzoylation of electron-deficient *N*-heterocycles with methylbenzenes *via* a Minisci-type reaction"**

Wajid Ali, Ahalya Behera, Srimanta Guin and Bhisma K. Patel, *J. Org. Chem.*, 2015, **80**, 5625.

(6) **"Transition metal-free synthesis of a-ketoamides from arylmethyl ketones alkylphosphoramides"**

Ahalya Behera, Wajid Ali, Manisha Tripathy, Diptimayee Sahoo and Bhisma K. Patel, *RSC Adv.*, 2016, **6**, 91308.

(7) **"Cs_2CO_3 as a source of carbonyl and ethereal oxygen in a Cu-catalysed cascade synthesis of benzofuran [*3,2-c*] quinolin-6[*5-H*]ones"**

Wajid Ali, Anju Modi, Ahalya Behera, Prakash Ranjan Mohanta and Bhisma K. Patel, *Org. Biomol. Chem.*, 2016, **14**, 5940.

(8) **"Acylperoxycoumarins as *ortho*-C–H acylating agent *via* a palladium(II)-catalysed redox-neutral process"**

Prakash Ranjan Mohanta, Arghya Banerjee, Sourav Kumar Santra, Ahalya Behera, and Bhisma K. Patel, *Adv. Synth. Catal*., 2016, **358**, 2047.

(9) **"Three sequential C−N bond formations: *tert*-butyl nitrite as a N1 synthon in a three component reaction leading to imidazo[*1,2-a*]quinolines and imidazo[*2,1-a*]isoquinolines"**

Prasenjit Sau, Amitava Rakshit, Anju Modi, Ahalya Behera, and Bhisma K. Patel, *J. Org. Chem*., 2018, **83**, 1056.

(10) **"Cyano sacrificial (arylthio)-arylamination of quinoline and isoquinoline *N*-oxides using *N*-(2-(Arylthio)aryl)cyanamides"**

Ahalya Behera, Prasenjit Sau, Ashish Kumar Sahoo and Bhisma K. Patel, *J. Org. Chem.*, 2018, **83**, 11218.

(11) **"One pot sequential synthesis of *N*-(2-(phenylsulfinyl)phenyl)acetamides: A ring opening rearrangement functionalisation (RORF)"**

Ahalya Behera, Amitava Rakshit, Ashish Kumar Sahoo and Bhisma K. Patel, *Eur. J. Org. Chem*. DOI: 10.1002/ejoc.201801597.