Studies on Pd(II)-catalyzed Directing-Group aided Regioselective C-H Functionalization of Carboxamides

A thesis submitted for the partial fulfilment

of the degree of Doctor of Philosophy

By

RAYAVARAPU PADMAVATHI

Department of Chemical Sciences,

Indian Institute of Science Education and Research (IISER) Mohali,

Sector 81, Knowledge City, S. A. S. Nagar, Manauli PO, Mohali, 140306.

Punjab, India.

December, 2020

DEDICATED to

Amma, Nanna, Annaya

Bindu & Aishu

Family & Friends

Declaration

I hereby declare that the matter embodied in this thesis entitled "Studies on Pd(II)-catalyzed Directing-Group aided Regioselective C-H Functionalization of Carboxamides" is the result of investigations carried out by me under the supervision of Dr. S. Arulananda Babu at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, SAS Nagar Mohali, India. This work has not been submitted in part or full for the award of any degree, a diploma or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgements. In keeping with the general practice in reporting scientific observations, acknowledgements has been made whenever the work was described based on the findings of other investigators. Any omission that might have occurred due to oversight or error in judgment is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.

Rayavarapu Padmavathi

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. S. Arulananda Babu

Associate Professor

Department of Chemical Sciences

Indian Institute of Science Education and Research, Mohali

Date:

Place:

Acknowledgement

It's my immense pleasure to express my sincere gratitude to my supervisor Dr. S. Arulananda Babu. His constant guidance during my PhD helped me in my professional growth and the life lessons he taught made me think and take correct decisions during difficult times to continue my work with peace of mind. I could still remember the first day when I met him as a summer intern to work under his supervision, as a part of my graduate study in the year 2011. The ease with which he taught me how to understand synthesis and handle an organic lab has driven and motivated me to choose research as my career. The support which he provided me during one of my toughest phase of my life is incredible, because of which I could stand with the same courage & strength and move forward in the right direction. My deep respect and heartful thanks sir!

Dr. Suman Barman, the first person to introduce me to the fundamentals of research under the guidance of Prof. R. N. Mukherjee, during my graduate study (2010) and taught me all the basics of chemistry and have been a support till date. Thank you suman bhaiya.

I am thankful to all my teachers who not only taught but nurtured and helped me in moving towards the right direction. Among the list, first comes my mother, who has been my guru from the day I was born and has been beside me in every walk of my life. I am thankful to school teachers and professors during my integrated master's study at UOH, who were instrumental in shaping my career throughout the time. During my master's project, I was introduced to the wonders of organic chemistry by the teachings of Prof. Ramachary which led to my passion to choose this field.

I am also extremely thankful to my lab members who played a major role in accomplishing what I started, firstly my seniors: Nayyar bhaiya (has been a pillar of support for me both professionally and personally), Reddy anna & Rajkumar anna (both for timely suggestions during my work), Ramarao (for enormous help in establishing projects of my work), Naveen, Gopalakrishnan (for guiding and teaching the lab techniques during my initial days in the lab), and my colleagues Narendra, Sankar (for helping me in completing my 1st project). It's time that I thank my juniors Arup, Radha, Prabhakar and Debu (four of them partners in crime, naughtiest but the one who made me feel coolest during my rough times). Raman (for support), Shefali & Sonam (both for timely help when needed), Pooja and Yashika. I am

thankful to the post doctoral fellows: Gowri Ma'am, Dipti Ma'am, Vinod sir, Pandu sir who guided me in lab whenever needed.

I am thankful to all the intern students: Nirdosh, Arya, Sruthi, Akshay, Amit, Sonia, Keerat, Debapriya, Deepak, Kavin, Nilamoni, Bubul, Rupal, Pallavi, Nitya, Rajib & Urja.

I am thankful to Ma'am, haruniga and bunny for making me feel this place a home away from home and I always cherish the memories which I spent at their home during festive occasions.

I am thankful to Surbhi, Anjali, Debapriya for their help, while doing azo based project.

I am thankful to Dr. R. Vijaya Anand & Dr. Sugumar Venkataramani (DC members) and Dr. Sripada Ramashastry and Dr. Sanjay Singh for their valuable guidance.

I am thankful to the director of IISER, Mohali for providing the infrastructure and facilities to pursue my research work. NMR, X-ray, HRMS, Library and Computing facilities of IISER Mohali are highly acknowledged. I also thank the Head of the Department of Chemical Sciences for providing access to the single crystal X-ray facility and various departmental facilities. I am thankful to all the technicians of IISER Mohali including Mr. Balbir (NMR) and Mr. Triveni (HRMS) for recording the samples on time.

I am highly indebted to my friends Siri (pillar of strength), Niharika, Sheeba, Apurva, Gayatri, Kuldeep, who didn't leave my side in all my ups and downs. I am thankful to all my friends from school (Pravallika), HCU (Sravani, Sidhu, Ravi) and summer internships.

I am grateful to my family especially my brother, who is a lantern in my dark times and for his immense encouragement in every move of my life. I am thankful to my parents, who believed in me and sister Sruthi who stood by me in all highs and lows. I am deeply grateful to Shabbir sir, who helped our family in crossing each barrier we encountered in our lives. Finally, I am thankful to each and every person who made me achieve what I dreamt for.

List of publications from thesis work:

1) **Padmavathi**, **R**.; Sankar, R.; Gopalakrishnan, B.; Parella, R.; Babu, S. A.* *Eur. J. Org. Chem.* **2015**, 3727.

Title: *$Pd(OAc)_2$/AgOAc Catalytic System Based Bidentate Ligand Directed Regiocontrolled C–H Arylation and Alkylation of the C-3 Position of Thiophene- and Furan-2-carboxamides.*

2) **Padmavathi**, **R**.; Babu, S. A.* *Asian J. Org. Chem.* **2019**, 8, 899.

Title: *Palladium Catalyzed 8-Aminoquinoline-Aided sp^2 δ-C-H Intramolecular Amidation/ Annulation: A Route to Tricyclic Quinolones.*

3) **Padmavathi**, **R**.; Babu, S. A.* *Manuscript to be submitted.*

Title: *Palladium Catalyzed 8-Aminoquinoline C-4 functionalization of Azobenzene Carboxamides.*

List of publications as a co-author:

4) Gopalakrishnan, B.; Babu, S. A.;* **Padmavathi, R**. Tetrahedron 2015, 71, 8333.

Title: *Bidentate ligand 8-aminoquinoline-aided Pd-catalyzed diastereoselective β-arylation of the prochiral secondary sp^3 C-H bonds of 2-phenylbutanamides and related aliphatic carboxamides.*

5) Babu, S. A.*; **Padmavathi, R.**; Aslam, N. A.; Rajkumar, V. *Stud. Nat. Prod. Chem.* **2015**, *46*, 227. (Book chapter)

Title: *Recent Developments on the Synthesis and Applications of Natural Products-Inspired Spirooxindole Frameworks.*

6) Reddy, C.; Babu, S. A.*; **Padmavathi, R.** *ChemistrySelect* **2016**, *1*, 2952.

Title: *The Barbier-Type Allylation/Lactamization Cascade Route to Isoindolinones and the Heck-Type Annulation Route to Isoindolo[2,1- a]quinolines.*

7) Rajkumar, V.; Babu, S.A.*; **Padmavathi, R.** *Tetrahedron* **2016**, *72*, 5578.

Title*: Regio- and diastereoselective construction of a new set of functionalized pyrrolidine, spiropyrrolidine and spiropyrrolizidine scaffolds appended with aryl- and heteroaryl moieties via the azomethine ylide cycloadditions.*

8) Babu, S. A.*; **Padmavathi, R.**; Sonam, S.; Arup, D.; Debabrata, B.; Prabhakar, S.; Radha, T. *Stud. Nat. Prod. Chem.* **2020**, submitted. (Book chapter)

Title: *Recent Developments on the Synthesis of Functionalized Carbohydrate/Sugar Derivatives Involving the Transition Metal-Catalyzed C-H Activation / C-H Functionalization.*

Conferences/Symposia*:*

1) Poster Presentation entitled *"Construction of Phenanthridinone Motifs via Auxiliary Enabled C-H Functionalization of Remote δ-C(sp^2)-H Bond* ", **Padmavathi**, **R.**; Babu, S. A. is presented at the XIII – Junior National Organic Symposium Trust Conference for Research Scholars, Banaras Hindu University, Varanasi, UP, India. (November 9-12, 2017)

2) Participated in RAOBC, 2019 held at IISER Mohali Punjab, India. (February 2019)

3) Participated in 1st CRIKC Symposium (CCS 2019) held at IISER Mohali, Punjab, India. (2nd & 3rd November, 2019)

Preamble

Owing to the great importance of organic molecules in almost all disciplines starting from food, dye, textile, drug industry and innumerable fields, synthesis and modification of organic compounds is a never ending task.Due to their potential importance in severalfields, an organic chemist always quests for their synthesis *via* simple, highly efficient and cost-effective strategies. Dating back to the 1st synthesis of Fredrick Wohler till date, numerous molecules were synthesised in different ways leading to a library of new reactions and large number of new reagents were discovered and till date, there is an endless search for more new efficient protocols. In this context, one such remarkable discovery was made by Suzuki, Negishi and Heck, for which they were awarded noble prize in 2010. Cross-coupling reactions revolutionised the field of organic chemistry. Despite their remarkable advances, these reactions do suffer with some limitations such as prefunctionalised starting materials, thereby leading to the more no.of steps, which affects the cost and also these reactions generate stoichiometric amounts of waste. Instead, functionlization of the most prevalent C-H bond is a valuable alternate than chosing the prefunctionalized starting materials for the synthesis of complex target molecules. This thought laid a stepping stone for C-H activation/Functionalization. This strategy is considered as the most challenging task, as even a simple organic molecule possess more than one single C-H bond, which can lead tovarious regioselective issues. This problem has been resolved to some extent with the help of directing groups (externally installed), functional groups (present within the molecule) and ligands.Inspired by its efficiency and advantages, this thesis work aims to functionalize the molecules *via* directing group aided transition metal catalyzed C-H activation thereby addressing regioselective issues and also construction of important functionalized organic molecules.

Chapter 1 provides an insight into C-H activation, its importance, strategies to perform C-H activation along with mechanistic aspects. In particular, this chapter briefs out the importance of directing group assisted C-H functionalisation followed by some literature reports highlighting the role of a novel bidentate auxiliary i.e, 8-aminoquinoline, most employed auxiliary of this thesis.

Chapter 2 deals with the development of a $Pd(OAc)_2$/ AgOAc catalyst system for the C-3 arylation and alkylation of thiophene and furan-2-carboxamides, thereby addressing the issue of regioselectivity with the aid of a bidentate auxiliary.

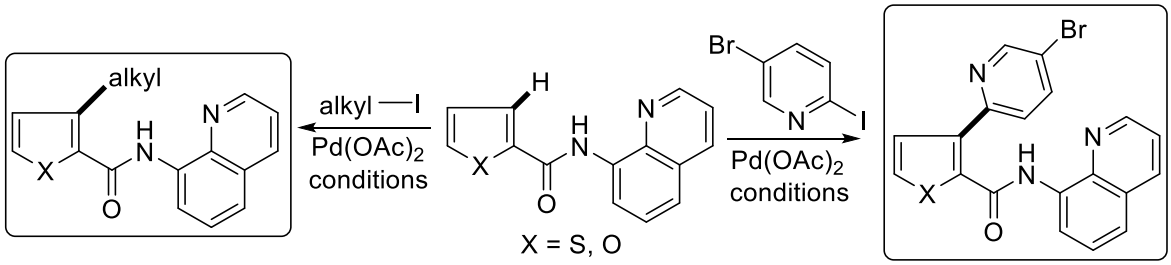
Chapter 3outlines the exploration of the synthesis of phenanthridinones and tricylic quinolones *via*the bidentate auxiliary 8-aminoquinoline aided Pd (II) catalyzed intramolecular $\delta C(sp^2)$-H amidation along withinvestigation of the developed protocol in one pot manner (successive arylation followed by intramolecular amidation).

Chapter 4 focusses mainly towards the Pd (II) catalyzedβ-C-H functionalization (arylation & alkylation, acetoxylation) of azobenzene carboxamides followed by their synthetic transformations into useful products.

Objectives

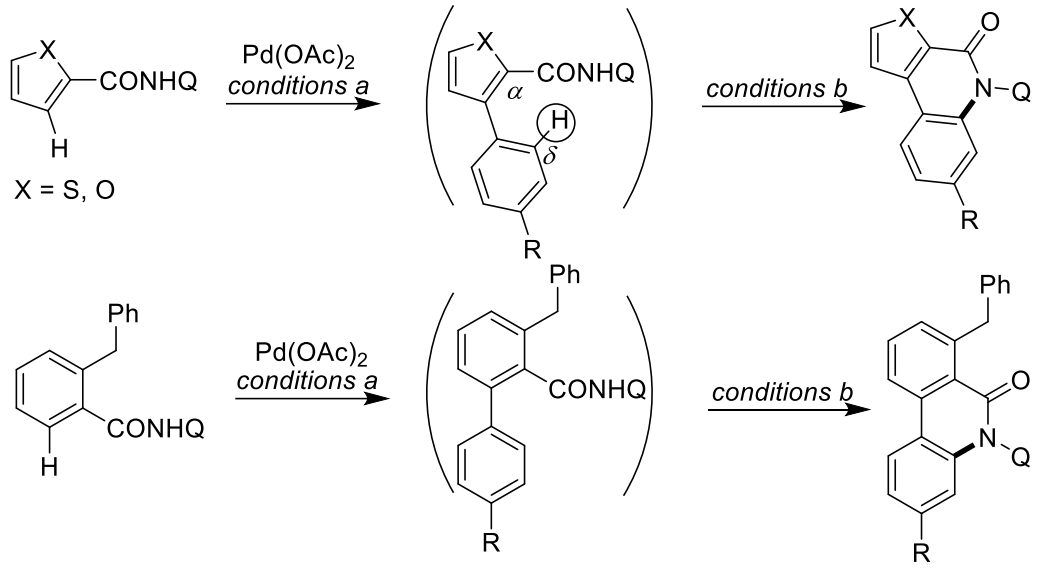
1)Heterobiaryls represent one of the widely distributed skeletons of the pharmaceutical compounds. Especially, heteroaromatic compounds such as thiophene represents the core structure of not only medicinal compounds but also organic materials. Functionalization of C2/C4 sites of heteroarenes is well documented in the literature, as they represent the highly reactive sites. Though, functionalization at other positions such as C3/C4 are explored to some extent using different approaches, still regioselective issues remain persistent. Therefore, we decided to solve this regioselective issue by using directing group aided C-H activation strategy and a part of this thesis work is mainly focussed on the Pd catalyzed C3 functionalization of heteroaromatic compounds involving arylation and alkylation. Several substrates such as thiophene, furan and fused systems such as benzothiophene-2-carboxamides are well explored for arylation, alkylation and benzylation. And also, this chapter reveals the investigation of role of auxiliary in the functionalization of heterocarboxamides.(**Chapter 2**)

Bidentate ligand-directed regioselective C(3)-H activation/alkylation



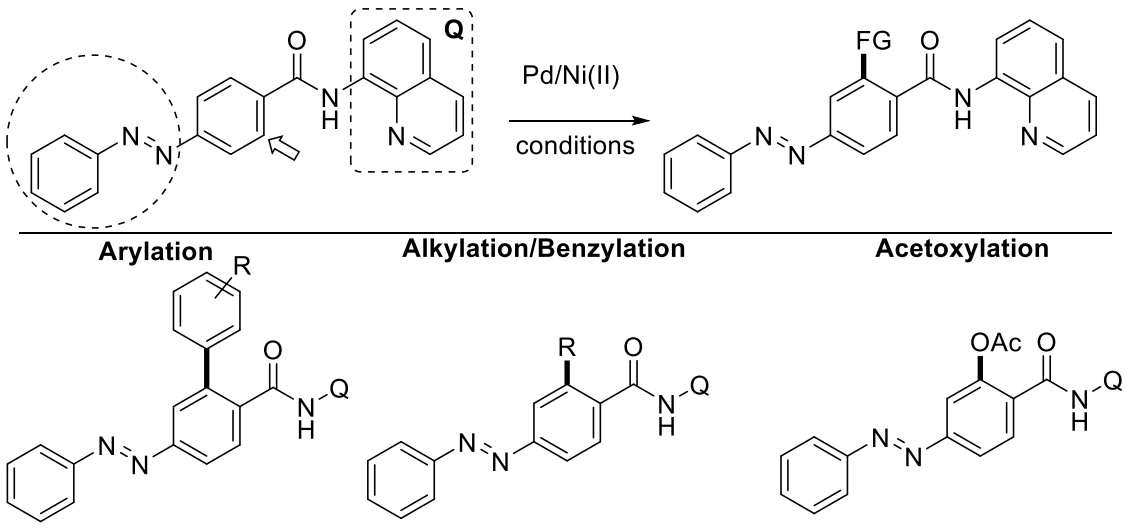
2) Construction of C-N bonds has gained significant attention as they are prevalent bonds found in many natural products such as phenanthridinones, quinolinones etc along with many other biologically important frameworks. Encouraged by its prevalence and importance, a part of thesis work is emphasized on the construction of C-N bonds *via* step economical alternate route *i.e* transition metal catalyzed C-H activation, thereby leading to the synthesis of phenanthridinones and quinolinones (**Chapter3**). Wereported the synthesis of tricylic quinolones *via* the Pd(II) catalyzed bidentate auxiliary 8-aminoquinoline aided intramolecular δ-C(sp^2)-H amidation route. Alongside, this chapter also represents some of the reactions comprising one pot reactions involving arylation followed by intramolecular amidation for the synthesis of tricyclic quinolones.

successive β-C-H arylation and δ-C-H intramolecular amidation reaction in one-pot



3) Azobenzenes are the precious skeletons available due to their unique property of photoisomerization, which have widespread application in material science and photopharmacology. Functionalization of C2 position of azoarenes is well explored, whereas other sites (C3/C4) of azoarenes are not yet explored. A part of thesis is dedicated to functionalize the other sites (C3/C4) of azorenes*via* Pd(II)/Ni(II)catalyzed bidentate directing group aided C-H functionalization route, followed bysynthentic transformation of the functionalized products into useful functionalized azo based compounds. Functionalizations include C-C bond (both arylation and alkylation) as well as C-O bond formation (acetoxylation).Importantly, studies revealing the competition between 8-aminoquinoline (bidentate directing group) and azo directing group are explored.(**Chapter 4)**

Bidentate ligand aided Pd/Ni(II) catalyzed C3-functionalization of azoarene carboxamides



CHAPTER 1

Introduction

(C-H Activation/Functionalization)

Construction of C-C and C-heteroatom bond is the primaryinterest of organic chemists and this is the fundamental step to reachtowards more complex molecules including natural products, bioactive targets. Developing efficient, step economical, environmental friendly and cost-effective strategies for the construction of organic molecules are always desirable. In this context, though the cross-coupling reactions are found to be highly proficient, they still suffer from a few limitations such as, the requirement of pre-functionalized starting materials like organic halides and organometallic reagents. In recent years, chemists started taking advantage of the most prevalent C-H bond present in a molecule, as it cuts down the need for pre-functionalized starting materials. Towards this direction, transition metal catalyzed C-H activation protocol has drawn a great attention of the scientific community, as it directly activates the C-H bond without any need of precursors. Replacement of both pre-functionalized partners (C-X and C-M) with C-H bond would be an ideal strategy, which led to the discovery of cross-dehydrogenative coupling method as depicted in Figure 1.Since cross dehydrogenative coupling suffers from some of the limitations such as homocoupling and regioselective issues, C-H activation protocol is found to be highly attractive. Though some issues related to C-H activation are yet to be addressed, towards which continuous efforts are in progress.

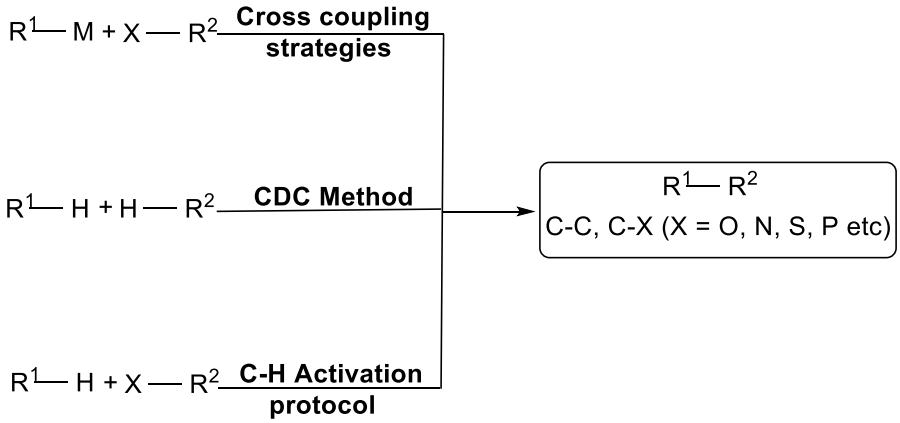
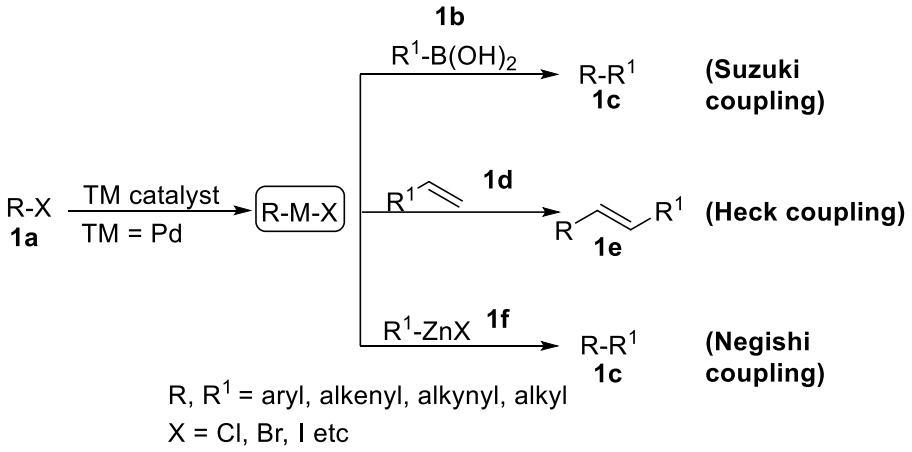


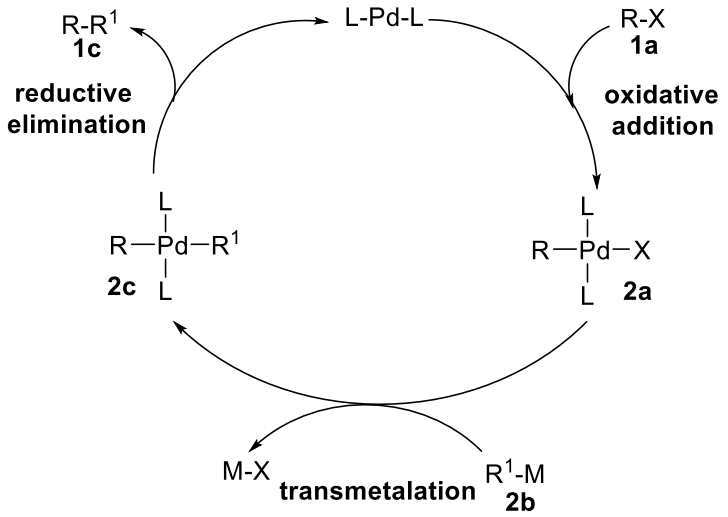
Figure1. Schematic representation of the available methods for the construction of C-C and C-heteroatom bond formations.

Cross Coupling strategies.

Traditional cross coupling strategies[1-3]are considered as one of the valuable tools, synthetic chemists posses for the construction of various C-C and C-heteroatom bonds. Particularly, the Pd-catalyzed Suzuki, Heck and Negishi coupling methods have emerged as one of the benchmark strategies in the past few decades, and the Nobel Prize (2010) was awarded for their practical implications in various disciplines of Chemical Sciences (Scheme 1). These reactions involve the usage of two different pre-activated coupling partners, which undergo coupling with the help of a metal catalyst to generate a new carbon-carbon or carbon-heteroatom bond.



Scheme1. Representative examples of cross coupling reactions.

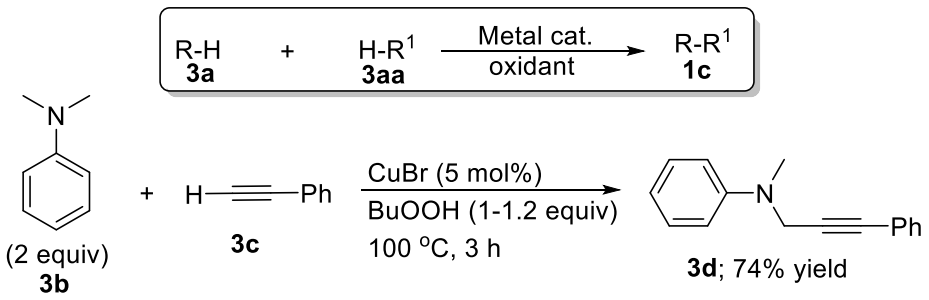


Scheme 2. General mechanism of the Pd-catalyzed cross coupling reactions.

The general mechanism involved in the Pd-catalyzed cross coupling reaction is described in Scheme 2. It is initiated by an oxidative addition of an electrophilic partner **1a** with the Pd catalyst followed by the transmetalation of an organometallic reagent **2b**, resulting in the formation of an intermediate **2c**. Finally, reductive elimination takes places affording the desired target **1c**, thereby regenerating the catalyst as outlined in the Scheme 2. Though, they are proven to be the most promising reactions, they also suffer with a few limitations such as, production of stoichiometric amounts of metal wastes as by-products and require the pre-functionalized starting materials.In order to overcome the problem of the preparation of starting materials, synthetic community started the functionalization of the C-H bond of organic molecules. Towards this path, in recent years various C-H activation and cross-dehydrogenative coupling methods are developed.

Cross Dehydrogenative Coupling (CDC) method.

For the first time, Li's group[4] coined the term cross dehydrogenative coupling (oxidative coupling), stating that C-C bond formation takes place at the cost of two C-H bonds in the presence of an oxidant, with or without metal catalyst along with the release of H_2 as shown inScheme 3. In the year 2004, they reported the synthesis of pharmaceutically important compounds such as propargyl amines **3d***via* the oxidative coupling of *N*,*N*-dimethylaniline**3b** and phenylacetylene**3c** in the presence of $CuBr_2$ (catalyst) and ^{t}BuOOH(oxidant). Functionalization by using the CDC method can be considered as an ideal strategy, as it needs no pre-functionalised starting materials and directly takes advantage of the C-H bonds present in organic molecules. This reaction works well in the case of C-H bonds which are adjacent to a heteroatom *i.e.* activated C-H bonds. It is to be noted that the reaction also suffers from potential limitations such as homocoupling and a lot of regioselective issues (because a given molecule can have more than one C-H bond).



Scheme 3. Synthesis of propargyl amines. (First report of CDC method).

C-H activation protocol.

Transition metal-catalyzed C-H activation methodology involving the formation of C-C or C-heteroatom bond has witnessed a great deal of attention in the past few decades.[5]This is due to the most prevalent C-H bonds present in a molecule are functionalized, making the protocol both step economical and cost effective. As delineated in Figure 2, the C-H activation is a process in which the unreactive C-H bond is converted into a reactive intermediate *i.e.* C-M bond in the presence of a transition metal catalyst, which further undergoes functionalization step with a desired coupling partner. This protocol works in two ways, such as (a) non-directed C-H bond activation and 2) directed C-H bond activation.

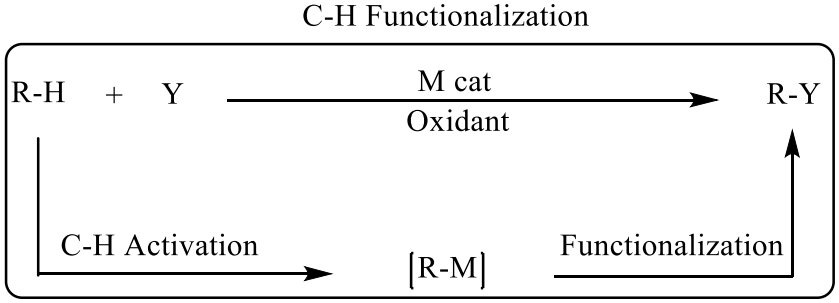


Figure 2. General representation of C-H functionalization/C-H activation route.

Non-directed C-H bond activation.

This strategy can also be referred as the direct C-H bond activation. This is due to the fact that the activation of C-H bond by a transition metal is not mediated by any heteroatom or functional group or directing group. Since more than one C-H bond is present in a given molecule, regioselectivity problem is likely to arise, when this method is employed for the functionalization of a given molecule. Therefore, this method works efficiently in case of heterocyclic substrates containing relatively activated C-H bonds due to their innate reactivity. This clearly hampers its general applicability to other substrates. To overcome the issue of regioselectivity, directed C-H bond activation strategy has been developed.

Directed C-H bond activation.

Transition metal-catalyzed directed C-H bond activation is considered as one of the highly attractive strategies, as it has resolved one of the potential issues of C-H activation *i.e.*regioselectivity. As a given molecule contains many C-H bonds, transition metal initially

coordinates to the heteroatom of the functional group or directing group, resulting in activation of the most proximal bond and this methodology works in three different ways.

a) **Functional group-assisted strategy**: Various functional groups like aldehydes, ketones, amines, carboxylic acids, esters present in a given molecule enable the activation of unreactive C-H bond, as they contain a heteroatom.[6]

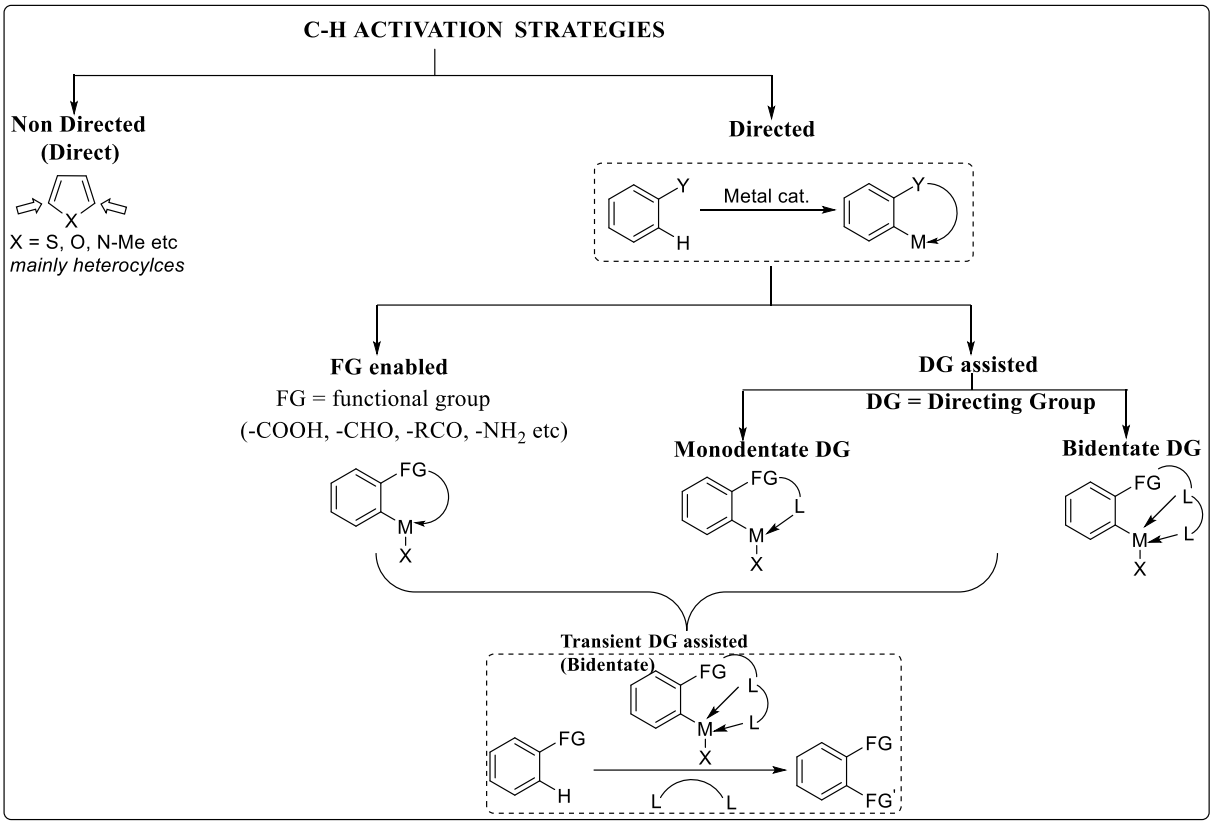
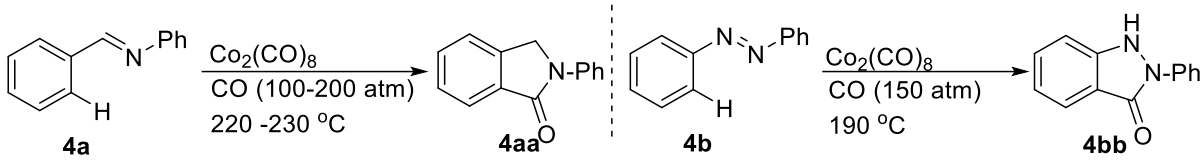


Figure 3. Schematic representation of available methods for C-H functionalization.

b) **Directing group-assisted strategy**: As the name suggests, this strategy works with the aid of a directing group. Basically, functional group present in a molecule is slightly modified by using an extra auxiliary or directing group. For example, acids and amines present in a given molecule are converted into amides by the addition of directing groups. Monodentate and the bidentate directing group[11] are the two existing classes of directing groups. As a given molecule contains many C-H bonds, transition metal initially coordinates to the heteroatom of the directing group, resulting in activation of the most proximal bond *via* a bicyclic metallacycle intermediate. Though the directing group-enabled method is proven to be an efficient strategy in terms of regioselectivity, it still suffers from a limitation of adding two more steps to the synthetic procedure including installation and cleavage of the auxiliary.

Recently, new strategy namely transient directing group-enabled strategy has come into picture. This can be considered as a combined version of the functional group and directing group assisted strategy. This method is still at its nascent stage but considered as one of the effective strategies. This is due to the fact thatthe installation and cleavage of externally added auxiliary occurs *in situ*, without increasing the number of synthetic steps (Figure 3).[11c]

Murahashi[7a, b] was the pioneer to introduce C-H activation to synthetic community in the year 1955 with his breakthrough reaction of carbon monoxide insertion into *ortho* C(sp^2)-H bond of the aldimine **4a**and azobenzene **4b**mediated by $Co_2(CO)_8$ (Scheme 4). Murahashi's, outstanding discovery laid a pathway for a new branch of organic chemistry *i.e.*, transition metal-catalyzed C-H activation.



Scheme4. C-H activation under Co catalysis.

After this remarkable discovery, many research groups reported the stoichiometric metal promoted C-H bond activations (Ni, Fe, Mn, Pd, Ru, Rh).[8a-h] Some of the palladacycle intermediates described by various groups like Shaw,[8d,e]Balavoine and Clinet[8f]are shown in Figure 4.

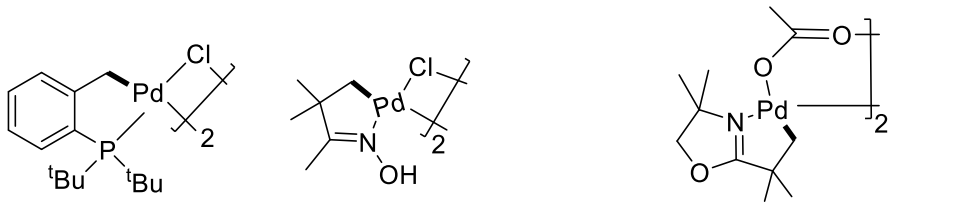
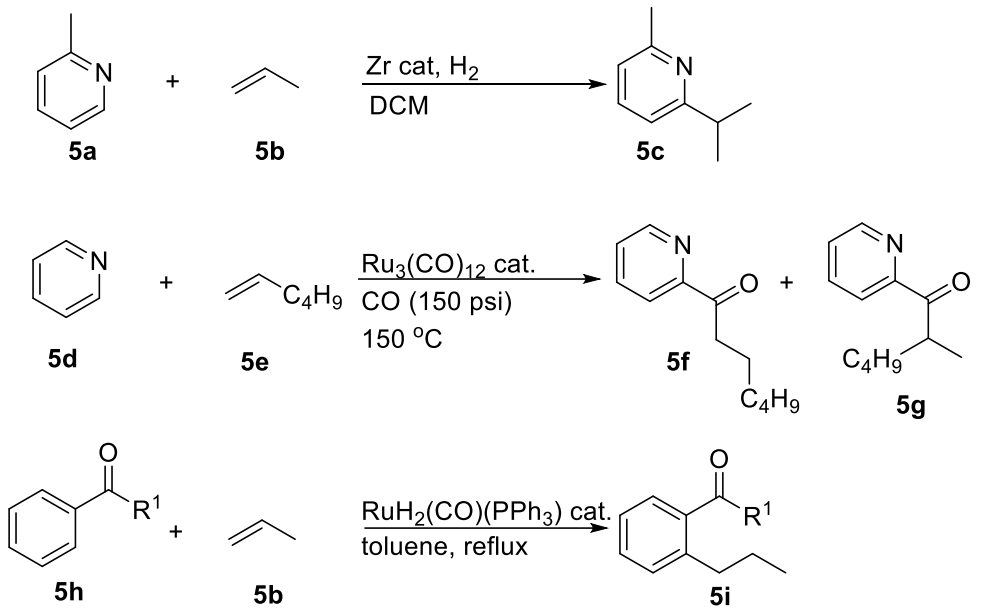


Figure 4. Cyclopalladated species reported in the context of stoichiometric C-H bond activation.

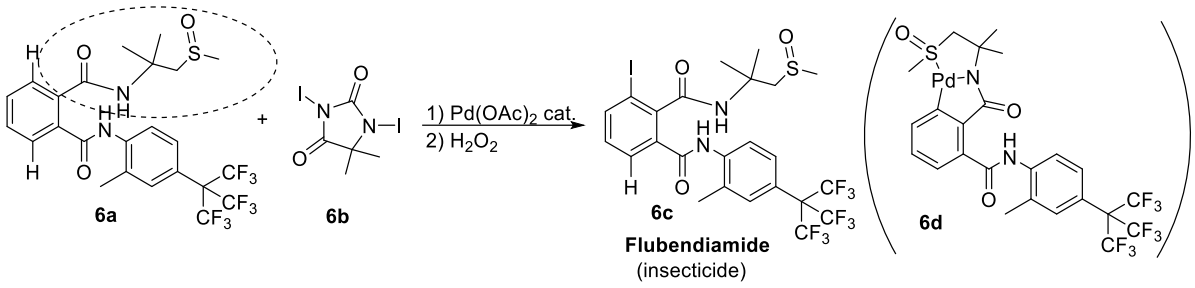


Scheme 5. Outstanding examples of catalytic C-H bond activation.

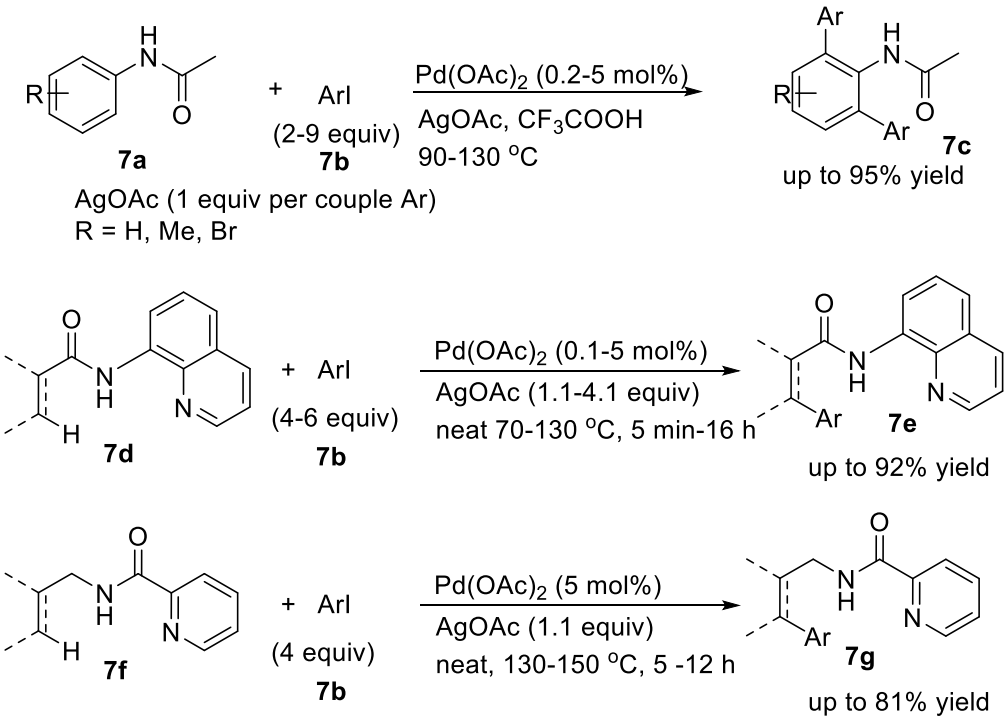
Almost after three decades of Murahashi's report, Jordan's group[9a] reported the catalytic C-H bond activation. This report is focused on the zirconium-catalyzed reaction of *α*–picoline **5a** with propene **5b** for the synthesis of alkylated pyridines (Scheme **5**). Following this report, Moore and co-workers[9b] explored the C-H acylation of pyridine **5d** using CO and olefin **5e** under Ru catalysis (Scheme **5**). Further, Murai's group revealed an interesting reaction of ketone directed C-H alkylation of arenes **5h** by using Ru catalyst (Scheme **5**). Murai's[9c] reaction can be considered as an outstanding example for directed C-H activation of unactivated C-H bonds of arenes, wherein the other two reports emphasizes on considerably activated C-H bonds of heterocycles. This led the synthetic community to screen various other functional groups like carboxylic acids, amines, aldehydes, esters etc, and a gradual progress occurred towards the development of functional group assisted C-H bond activation. In many cases, side reactions are observed, which hampered the developed protocol to a large extent.

On the other hand, in the year 2001, a report revealed by a scientific group at Nihon Nohyaku Co., Ltd.[10] provided an initial route towards the development of directing group enabled C-H activation. This report disclosed the regioselective *ortho* C-H iodination of phthalimide equipped with two different amides in the presence of $Pd(OAc)_2$ catalyst for the synthesis of an insecticide namely Flubendiamide**6c**. Surprisingly, only the *N,S*-bidentate directing group of 2-(methylthio)ethanamine activated the C-H bond proximal to it *via* the bicyclic palladacycle (Scheme 6).Consequently, in the year 2005, Daugulis& co-workers[11b] laid

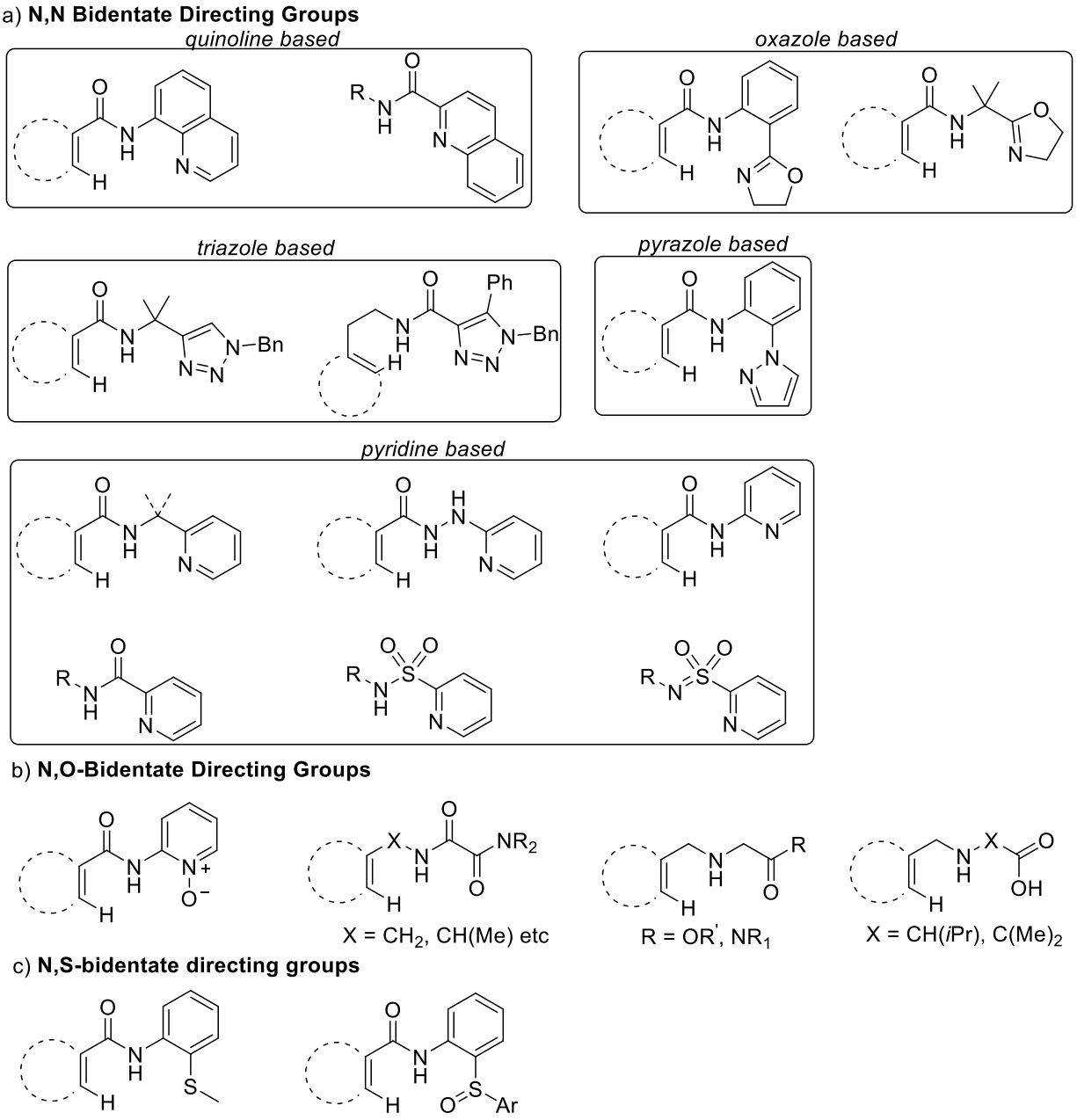
foundation for the directing group assisted Pd(II)-catalyzed C(sp^2)-H and C(sp^3)-H functionalization/arylation of amides **7d**, **7f**. They introduced the bidentate auxiliaries namely 8-aminoquinoline and picolinic acid for carboxylic acids and amines, respectively. Prior to this discovery, the same group[11a] reported the Pd-catalyzed*ortho* arylation of anilides**7a** using aryl iodides **7b**. After the discovery of 8-aminoquinoline, many research groups introduced different heteroatom (O, S) based monodentate as well as bidentate directing groups. Strikingly, bidentate directing groups are proven to be more promising than monodentate auxiliaries, as they strongly coordinate involving a bicyclic metallacyclic intermediate. List of bidentate directing groups is given in Scheme 8.[12]



Scheme6. Synthesis of Flubendiamide*via* Pd-catalyzed directing group-assisted C-H activation.



Scheme 7. Pioneering contributions by Daugulis's group towards the Directing Group assisted C-H activation.

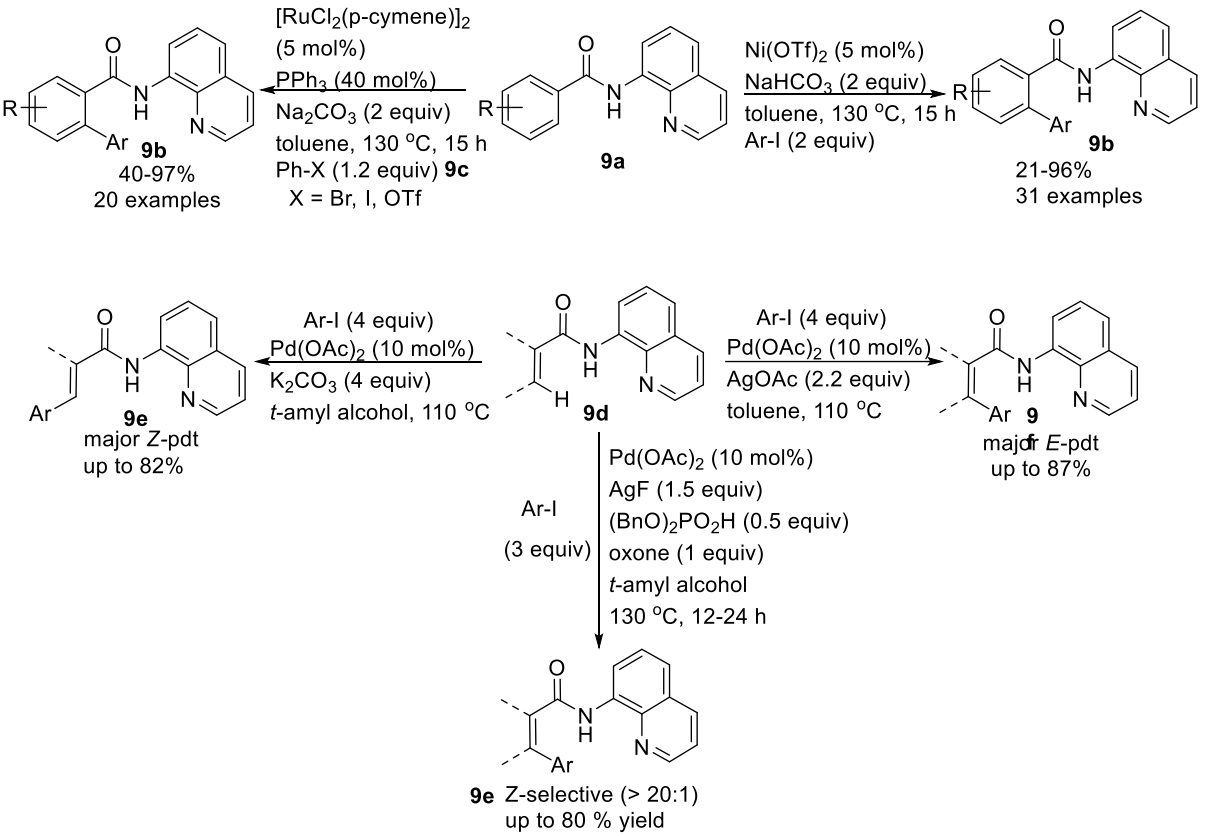


Scheme 8. List of Bidentate directing groups for C-H functionalization.

Given the brief background and history of C-H activation, methodologies available and list of existing directing groups (particularly bidentate), some of the literature reports available on the directing group assisted C-H functionalization of carboxamides are presented below. As major part of this thesis is emphasized on the carboxamides equipped with the auxiliary *i.e.*8-aminoquinoline, literature related to this auxiliary is described in the section below.

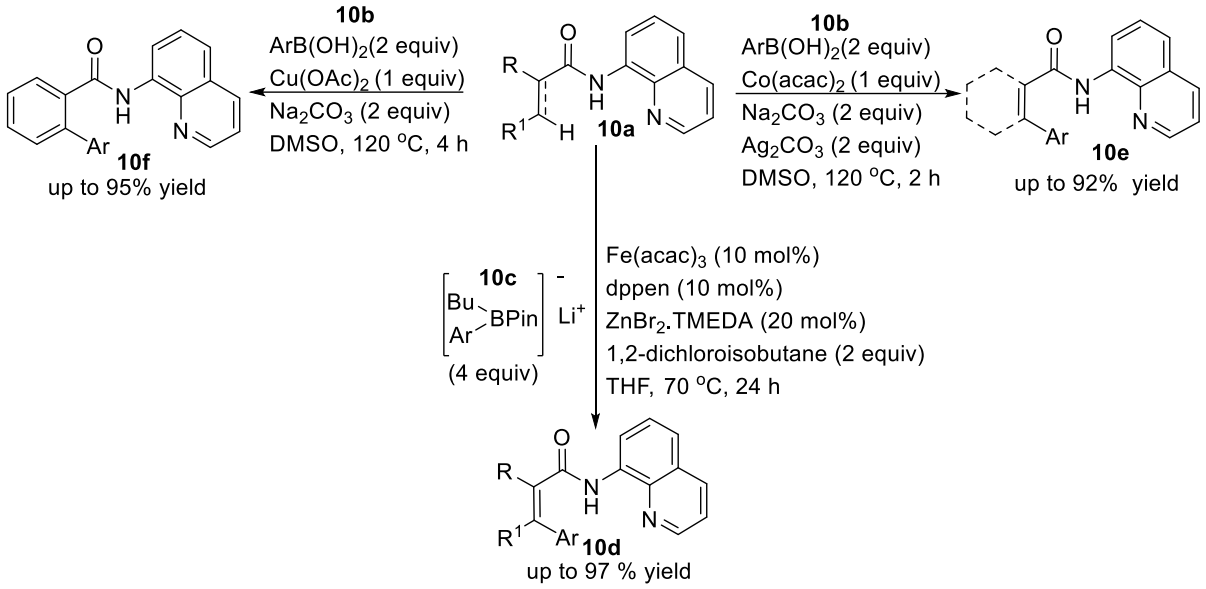
Bidentate auxiliary aided C(sp^2)-H arylation of carboxamides reports:

After the pioneering report published by Daugulis and co-workers, many research groups worked towards the C-H functionalization of carboxamides with the aid of 8-aminoquinoline. These works include arylation, alkylation, allylation, alkenylation, alkynylation, carbonylation, annulation and cyclization, trifluoromethylation, alkoxycarbonylation, cyanation etc by using different transition metals such as Pd, Ni, Rh, Ru, Co, Cu etc. In this chapter, mainly the arylation and alkylation reports are presented, as major part of the thesis is focussed on the construction of biaryls and alkylated carboxamides equipped with 8-aminoquinoline at *β*-position of carboxamides. Following Daugulis's work, Chatani's group reported the synthesis of arylated aromatic amides **9b** under Ru[13a] and Ni[13b]catalysis (Scheme 9). The former report reaction conditions comprised of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, PPh_3 as the ligand and Na_2CO_3in toluene at 130 ^oC. Though they screened aryl bromides as the coupling partners, aryl triflates and aryl iodides also worked well in the *ortho* C-H arylation of benzamides. In the 2nd report published by the authors, benzamides **9a**are coupled with aryl iodides **7b** in the presence of $Ni(OTf)_2$, $NaHCO_3$ as base in toluene at 130^oC (Scheme 9). In this case, other partners like aryl triflates, aryl bromides are not effective.



Scheme 9. C(sp^2)-H arylation of carboxamides using aryl halides as the coupling partners.

In the context of Pd-catalyzed*ortho* C-H arylation, our group[13c] reported the synthesis of arylated acrylamides**9e,f**. In this report, selective synthesis of cinnamamide compounds **9e,f** was shown by tuning the reaction conditions (Scheme 9). The plausible mechanism for the formation of *Z*-selective products **9e** is explained by chelation assisted C-H activation route, wherein *E*-selective product **9f** formation is explained on the basis of ligand free Mizoroki-Heck reaction mechanism (Yao's report[13d]). Jiang's group[13e] reported the Pd-catalyzed vinylic C-H arylation of unsubstituted acrylamides. The optimal conditions involved 10 mol% of $Pd(OAc)_2$, 1.5 equiv of AgF, 0.5 equiv of $(BnO)_2PO_2H$ and 1.0 equiv of oxone at 130 °C for 12 h, which afforded the product **9e** in 80% yield with *Z/E*= >20 : 1 (Scheme 9). Along this line, Kumar's group in the year 2016, disclosed the Pd-catalyzed*ortho* C(sp^2)-H arylation of ferrocene carboxamides.[13f]



Scheme 10. Reports based on the C(sp^2)-H arylation using organoboron compounds as the coupling partners.

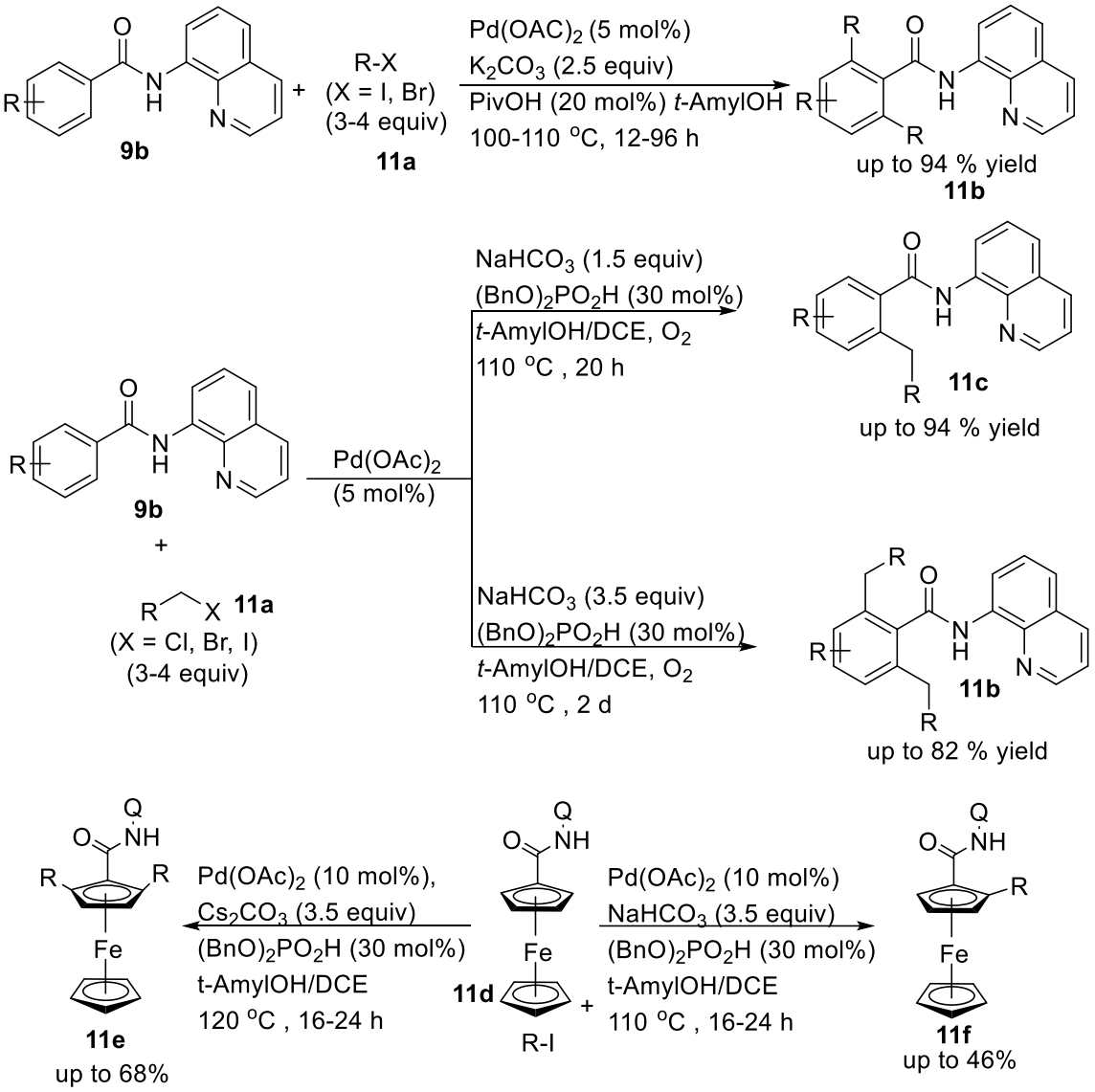
In addition to aryl halides, other coupling partners like organoboron compounds are also screened for the C(sp^2)-H arylation. In this context, Iliesgroup[13g] focussed on the development of Fe-catalyzed C-H arylation of different aromatic, olefinic and heteroaromatic substrates with aryl boronic compounds **10b**(Scheme 10).They disclosed that zinc salt employed in the reaction conditions is helpful for the transfer of organic group from the boron atom to the catalyst, resulting in the formation of an organoiron (III) intermediate, which is believed to play a crucial role in the C-H activation step. In the year 2016, Tan's group[13h] demonstrated the Cu-catalyzed coupling of benzamides with $ArB(OH)_2$ **10b**(Scheme 10).Using the same coupling partner **10b**,they published another paper under Co catalysis.[13i] They observed either decomposition or almost no reaction in case of heteroaromatic compounds under the Cu catalysis.

Reports related to C(sp^2)-H alkylation of carboxamides equipped with 8-aminoquinoline:

In the year 2010, Daugulis's group[14a]is the first one to set a pathway for the alkylation of C(sp^2)-H as well as C(sp^3)-H bonds. In this report, they developed silver free conditions unlike their 1st report on the arylation of 8-aminoquinoline equipped with carboxamides **9b**and presented a glimpse of alkylation reactions (Scheme 11). Further, they extended this methodology for aromatic and aliphatic amines linked with picolinic acid auxiliary along

with carboxamides installed with bidentate ligand 8-aminoquinoline under the Pd catalysis.[14b]This method utilises $Pd(OAc)_2$ catalyst, K_2CO_3 as base, pivalic acid (catalytic amount) as an additive and *t*-amyl alcohol or water as the solvent at 100-110 ^oC. Different electrophilic partners such as primary alkyl iodides, benzyl and allyl bromides seemed to work well for alkylation. Following this report, Chen's group[14c] reported the selective mono and di-alkylation of quinolyl benzamides **9b** using both primary and secondary alkyl halides as the coupling partners (Scheme 11). Kumar and co-workers[14d] revealed the synthesis of mono and dialkylated ferrocene carboxamides using $Pd(OAc)_2$ as the catalyst (Scheme 11). The optimal conditions shown in Scheme 11 suggested that switching bases could selectively result in the formation of mono as well as dialkylated ferrocene carboxamides (**11f**&**11e**) in good yields.

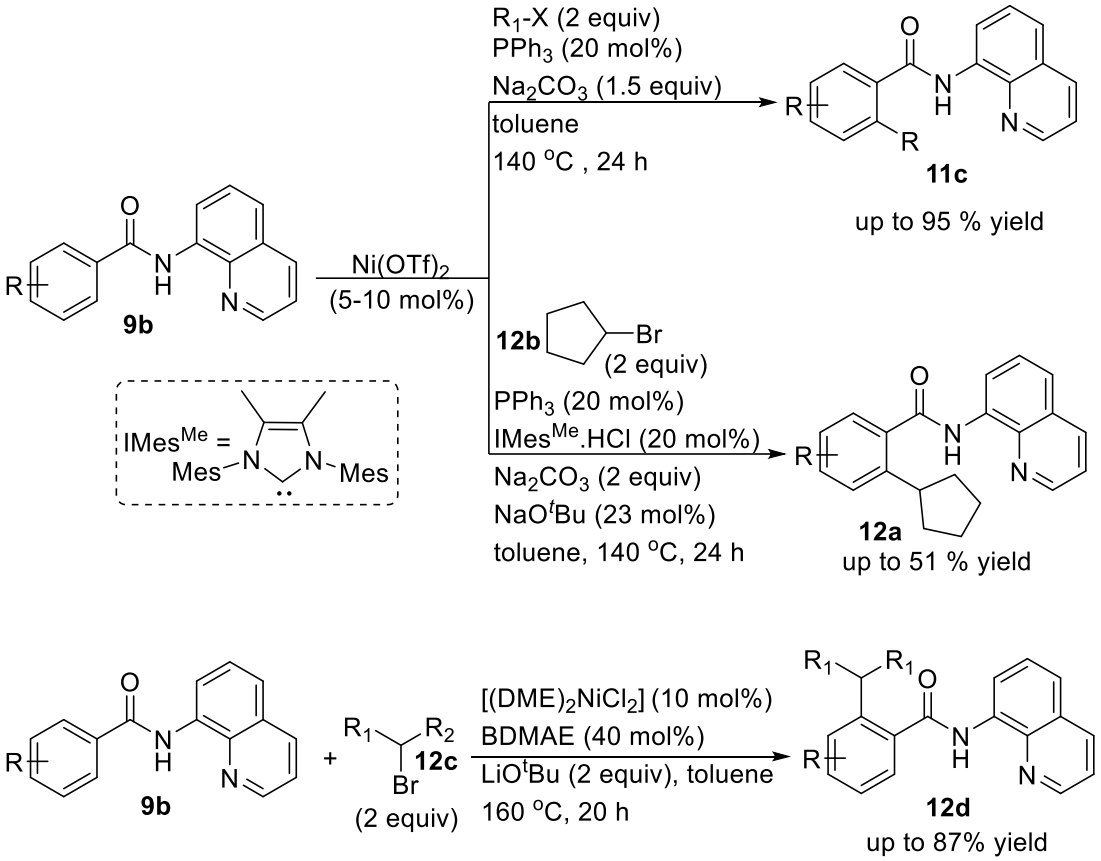
In the year 2013, Chatani and co-workers[14e] disclosed first report on the *ortho* $C(sp^2)$-H alkylation of carboxamides **9b** with primary alkyl halides under the Ni-catalysis. The optimal conditions involve 10 mol% of $Ni(OTf)_2$, 20 mol% of PPh_3 as the ligand and Na_2CO_3 as base in toluene at 140 ^oC (Scheme 12). Later in the year 2015, they extended this Ni-catalyzed protocol for the alkylation of carboxamides using various coupling partners such as secondary alkyl halides, benzyl and allyl halides.[14g] They revealed that when same conditions were applied for secondary alkyl halides **12b**, reaction did not proceed until one more ligand $IMes^{Me}$.HCl was used along with PPh_3. Though alkylation with primary alkyl halides is explored well, secondary alkylation is a challenging task as the secondary alkyl partners are not inclined towards oxidative addition unlike their counter parts and also the formed alkyl metal intermediates has a strong tendency to undergo *β*-hydride elimination. In this regard, Ackermann's group[14f] developed a new nickel-based catalytic system for the alkylation of arene carboxamides with the tricky secondary alkyl halides (Scheme 12). Under the newly developed catalytic conditions, they explored the trifluoroethylations of aromatic carboxamides.



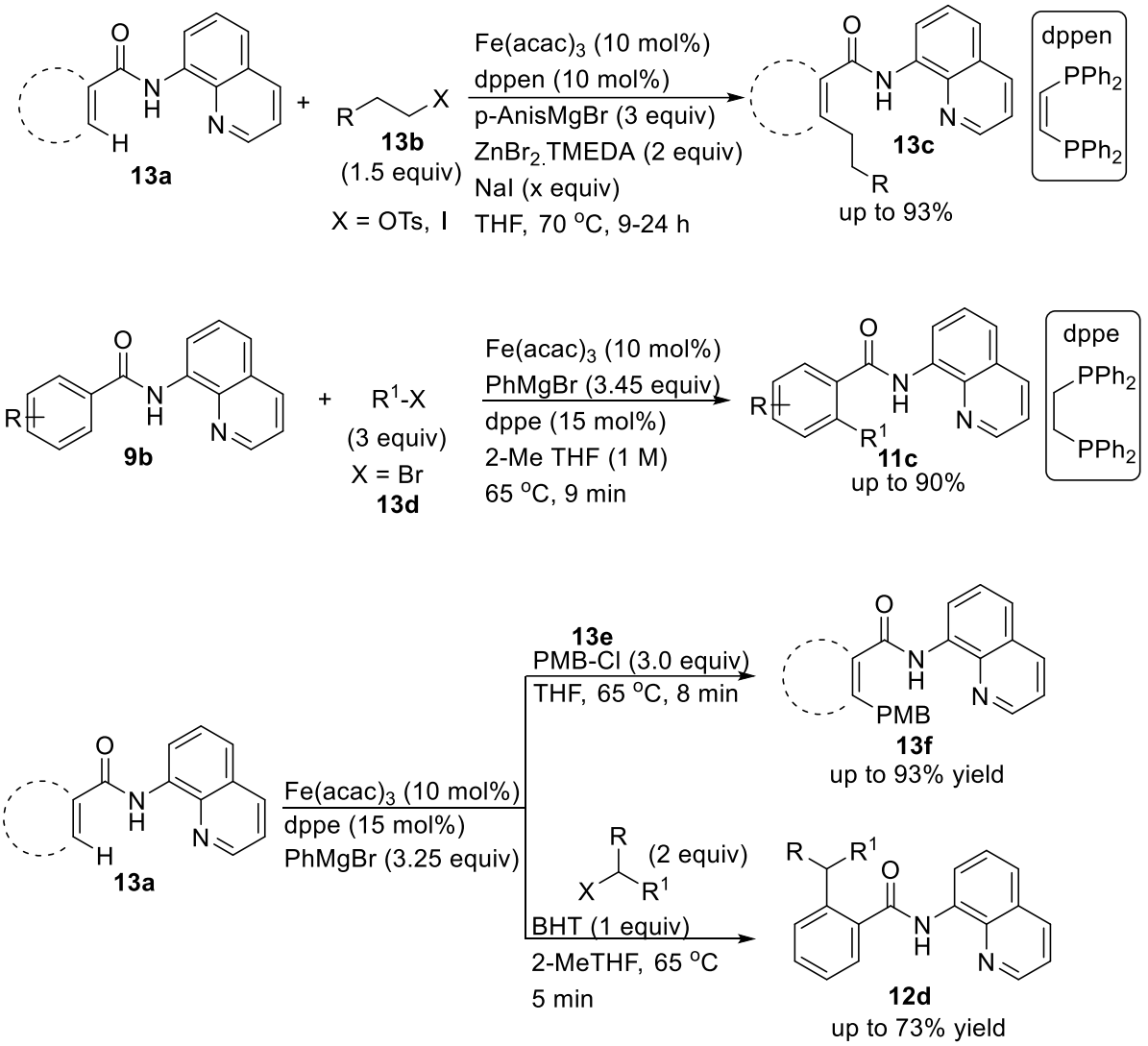
Scheme 11. Pd(II) catalyzed mono and di alkylation of aromatic amides.

Ilies et al,[14h]reported the synthesis of *ortho* C(sp^2)-H alkylation of the arene, heteroarene and alkene carboxamides **13a** using different coupling partners like primary and secondary alkyl tosylates, mesylates and halides**13b**(Scheme 13). They also reported the use of an alcohol as the electrophilic partner in one of the reactions. $Fe(acac)_3$/ diphosphine as a catalyst and ArZnBr (*in situ* formed from the *p*-anisMgBr and $ZnBr_2$) as a base, NaI in THF at 70 °C are the optimal conditions used for the alkylation of carboxamides. Cook's group[14i] published a report disclosing the synthesis of alkylated benzamides using primary electrophiles such as alkyl bromides **13d** under the optimal conditions combining $Fe(acac)_3$ as catalyst to dppe as ligand and PhMgBr as the base in THF (Scheme 13). The generality of the developed reaction conditions is extended to other coupling partners like alkyl iodides and alkyl chlorides along with secondary electrophiles.[14j] In case of secondary alkylation, the radical

inhibitor butylated hydroxytoluene (BHT) addition is found to be of prime importance, as it inhibits the generation of secondary transient radicals, thereby avoiding the formation of over-alkylated products (Scheme 13). Apart from the above described transition metals, Cu and Cr catalyzed ortho C(sp^2)-H alkylation of carboxamides are also reported.[14klm]



Scheme 12. Nickel catalyzed alkylation of carboxamides.



Scheme 13. Alkylation of carboxamides under the Fe catalysis.

Since C-H activation is a broad area dealing with different kinds of directing groups, substrates (both sp^2 and sp^3 C-H bonds along with different kinds of coupling partners) and various metals (Pd, Fe, Ru, Rh,), it is a difficult task to discuss mechanistic manifolds of all these aspects. So, this section is restricted to the most evolved Pd-catalyzed C-H arylation reaction mechanisms. Pd(0) and Pd(II) catalyzed reactions are the existing categories of Pd based reactions. To begin with, Pd(0) undergoes oxidative addition with aryl halide followed by C-H bond activation step and the intermediate formed undergoes reductive elimination, facilitating the formation of arylated product and release of catalyst.

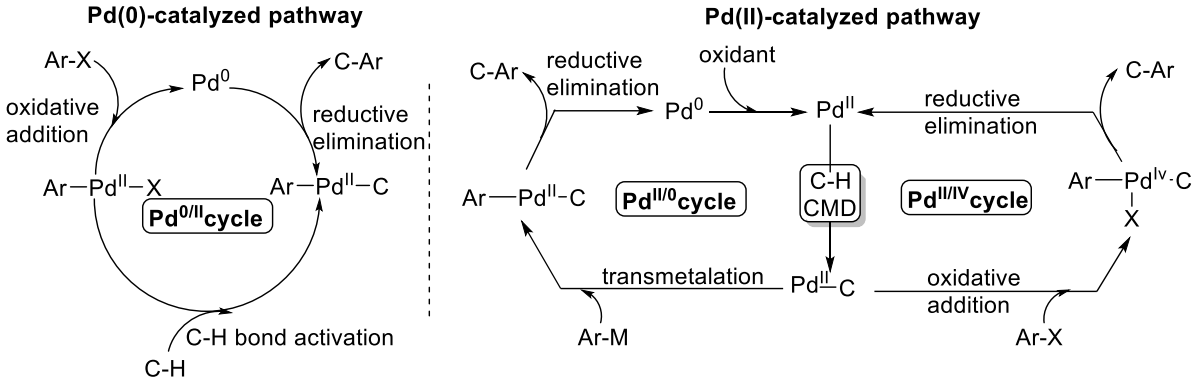
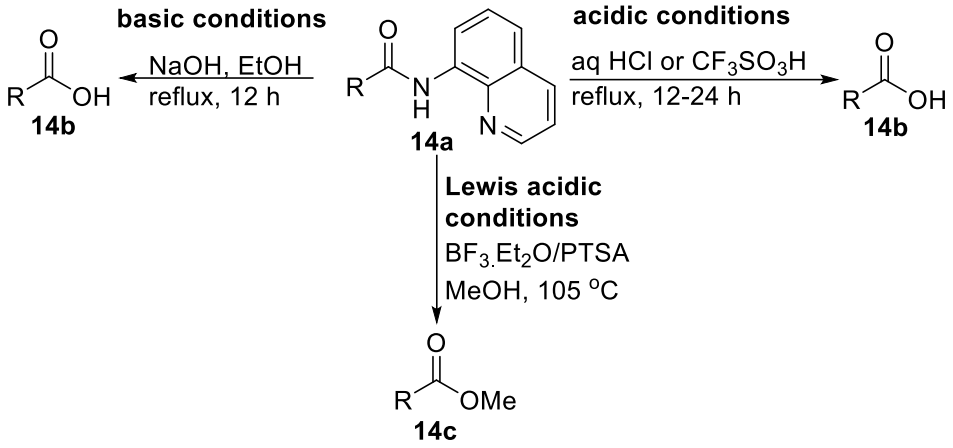


Figure 5. Mechanistic pathway for Pd(0) and Pd(II)-catalyzed C-H arylation reactions.

Next, the Pd(II) catalyzed reactions proceeds via two pathways, Pd(II/0) and Pd(II/IV) cycles. Pd(II/0) cycle starts with C-H activation step, which then undergoes transmetalation, followed by the reductive elimination affording the arylated product and Pd(0). The formed Pd(0)species converts into the Pd(II) in the presence of an oxidant. On the other hand, Pd(II/IV) cycle is initiated by the insertion of Pd(II) into C-H bond, followed by an oxidative addition in the presence of aryl halide to afford Pd(IV) intermediate. Finally, this intermediate undergoes reductive elimination resulting in the formation of desired product along with the regeneration of catalyst (Figure 5).

Methods for the cleavage of the bidentate auxiliary 8-Aminoquinoline.

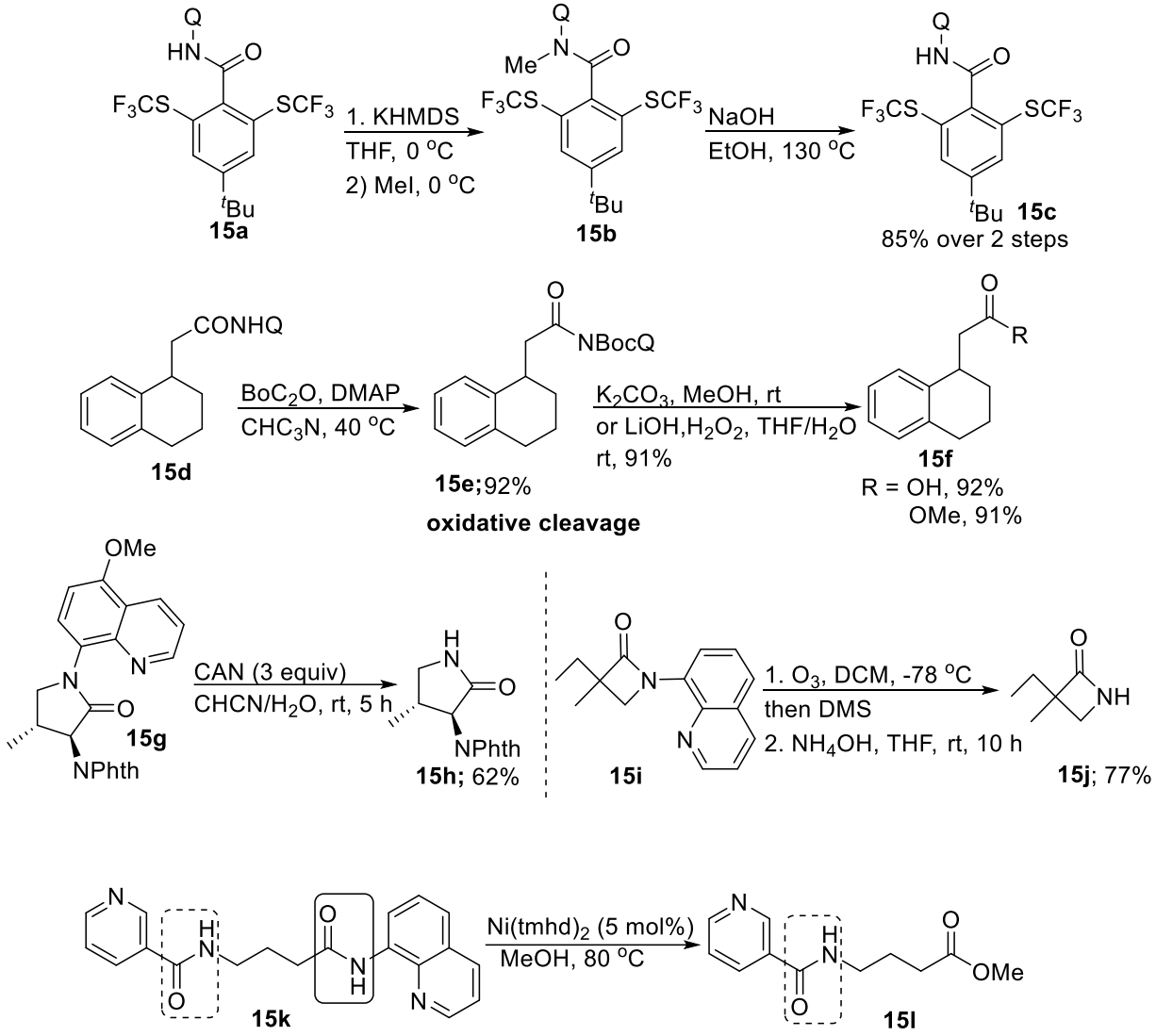
Most of the reactions presented in this thesis are mainly carried out with the aid of bidentate auxiliary 8-aminoquinoline. The practical utility of the reactions can be realised only when the auxiliary or directing group is cleaved. In this regard, some of the available methods for cleavage of the most employed auxiliary 8-aminoquinoline are presented here. Classical conditions were employed for the removal of 8-aminoquinoline includes acidic[15a, b]/ Lewis acidic[15c] and basic conditions[15d, e] at high temperature to give the corresponding carboxylic acids **14b** or esters **14c** (Scheme 14).



Scheme 14. Acid & base-mediated hydrolysis, alcoholysis promoted by Lewis acid.

When the above-mentioned fundamental conditions failed to remove the auxiliary/directing group, especially in case of hindered amides, several modified methods are reported in recent times. In this context, Chen's group[15f, g]disclosed a two-step protocol, *i.e.* Boc protection of amide **15d**followed by hydrolysis(K_2CO_3, MeOH) and alcoholysis ($LiOH,H_2O_2$),which afforded the corresponding desired target **15f** (Scheme 15). Daugulis's group[15h] reported the auxiliary removal of highly substituted benzene carboxamides**15a** by simple protection of amidewith MeI, followed by hydrolysis under basic conditions. In the year 2013, a modified version of the former ones namely 5-methoxy 8-aminoquinoline was introduced by Chen's group[15i], for the cleavage of Ar-N bond of synthesised pyrrolidones**15g***via* Pd catalyzed intramolecular amination, which is otherwise difficult under the classical conditions (Scheme 15).

In 2016, Maulide and co-workers[15j] revealed an interesting strategy for oxidative cleavage of 8-aminoquinoline *via*ozonolysis (Scheme 15). Their results were appealing, as it needs no further modification of 8-aminoquinoline, *i.e.*installation of OMegroup at its 5th position as described by Chen's group. Instead the developed protocol worked well in case of hindered amides as well as in the cleavage of C-N bond of lactams**15i**, equipped with the bidentate auxiliary 8-aminoquinoline (Scheme 15).Oshima's group[15k]accomplished the chemoselectivealcoholysis under Ni catalysis. The authors demonstrated few examples wherein selectively 8-aminoquinoline was cleaved, leaving other directing groups/ functional groups intact (Scheme 15).



Scheme 15. Methods representing the cleavage of amides installed with 8-aminoquinoline.

References:

1) Metal-Catalyzed Cross-Coupling Reactions, 2nd ed. (Eds.: Meijere, A. de; Diederich,F.), Wiley-VCH, Weinheim, **2004**.

2) For reviews, see: (a) Heck, R. F. In *Comprehensive Organic Synthesis*, Vol. 4 (Eds.:Trost, B. M.; Fleming, I.), Pergamon, Oxford, **1991**, 833. (b) Stille, J. K. *Angew. Chem. Int.Ed.* **1986**, *25*, 508. (c) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (e) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian,M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. (f) Surry, D. S.; Buchwald, S. L. *Angew.Chem.Int. Ed.* **2008**, *47*, 6338. (g) Hartwig, J. F. *Nature* **2008**, *455*, 314. (h)Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (i)

Wolfe, J. P.;Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.*, **1998**, *31*, 805. (j) Hartwig,J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

3) For cross-coupling reactions and applications, see: (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*, VCH: Weinheim, **2003**. (b) Torborg, C.; Beller, M. *Adv. Synth.Catal.* **2009**, *351*, 3027. (d) Naso, F.; Babudri, F.; Farinola, G. M. *Pure Appl. Chem.* **1999**, *71*, 1485. (c) Magano, J.; Dunetz, J. R. *Chem.Rev.* **2011**, *111*, 2177.
4) Li, Z.; Li, C. –J. *J. Am. Chem. Soc.***2004**, *126*, 11810.
5) For reviews on C-H activation chemistry, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem.Rev.* **1997**, *97*, 2879. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180. (d) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698. (e) Bergman, R. G. *Nature* **2007**, *446*, 391. (f) Lewis, J. R.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (g) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (h) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (i) Kuhl, N.; Hopkinson, M. N.; Delord, J. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (j) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (k) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (m) Boorman, T.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (n) Delord, J. W.; DrÖge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (o) Baudoin, O. *Chem.Soc. Rev.* **2011**, *40*, 4902. (p) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (q) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. (r) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (s) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (t) Castro, L. C. M.; Chatani, N. *Chem. Lett.***2015**, *44*, 410. (u) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (v) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421. (w) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (x) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.*, **2002**, *35*, 826.
6) For functional group-enabled C-H functionalization, see: a) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.***2015**, *44*, 7764. b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. c) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.***2007**, *349*, 1185. d) Tsuchikama, K.; Kuwata, Y.; Tahara, Y.-K.; Yoshinami, Y.; Shibata, T. *Org. Lett.***2007**, *9*, 3097. e) Lu, Y.; Wang, D.-H.; Engle, K.

M.; Yu, J.-Q. *J. Am. Chem. Soc.***2010**, *132*, 5916. f) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.***2011**, *76*, 3024. g) Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.***2012**, *51*, 8092. h) Iitsuka, T.; Schaal, P.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *J. Org. Chem.* **2013**, *78*, 7216. i) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem. Eur. J.***2013**, *19*, 10511. j) Mamone, P.; Danoun, G.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6704. k) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419. l) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature***2014**, *510*, 129. m) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.***2014**, *356*, 1521. n) Ng, F.-N.; Zhou, Z.; Yu, W.-Y. *Chem. Eur. J.* **2014**, *20*, 4474. o) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. *Nat. Chem.***2015**, *7*, 1009. p) He, C.; Gaunt, M. J. *Angew. Chem., Int. Ed.***2015**, *54*, 15840. q) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. *Org. Chem. Front.***2017**, *4*, 2097.

7) a) Murahashi, S. *J. Am. Chem. Soc.***1955**, *77*, 6403. b) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816.

8) Stoichiometric metal directed C-H activations: a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.***1963**,*85*, 1544. b) Bagga, M. M.; Flannigan, W. T.; Knox, G. R.; Pauson, P. L.;Preston, F. J.; Reed, R. I. *J. Chem. Soc.***1968,**36. c) Knobler, C. B.; Crawford, S. S.; Kaesz, H. D. *Inorg. Chem.***1975**, *14*, 2062. d) Cheney, A. J.; Shaw, B. L. *J. Chem. Soc.,Dalton Trans.***1972**, 860. e) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.***1978**, 1061. f) Balavoine, G.; Clinet, J. C. *J. Organomet. Chem.* **1990**, *390*, 84-88 g) Komiya, S.; Yamamoto, A. *Chem.Lett.***1975**, *4*, 475.h) Foot, R. J.; Heaton, B. T. *J. Chem. Soc., Dalton Trans.***1979**, 295.

9) a) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. b) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S.*J. Am. Chem. Soc.* **1992**, *114*, 5888. c) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature***1993**, *366*, 529.

10) Kodama, H.; Katsuhira, T.; Nishida, T.; Hino, T.; Tsubata, K. Worldwide Patent WO 2001083421 A1, **2001**.

11) a) Daugulis, O.; Zaitsev V. G. *Angew. Chem. Int. Ed.***2005**, *44*, 4046. b)Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. c) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788.

12) a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.***2013**, *52*, 11726. b) Huang, Z.; Dong, G. *Tetrahedron Lett.***2014**, *55*, 5869. c) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. *Asian J. Org. Chem.***2015**, *4*, 846.d) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.***2015**, *48*, 1053. e) Castro, L. C. M.; Chatani, N. *Chem. Lett.***2015**, *44*, 410. f) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron***2015**, *71*, 4450. g) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.***2016**, *358*, 1174. h) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635. i) Wan, J.-P.; Li, Y.; Liu, Y. *Org. Chem. Front.* **2016**, *3*, 768. j) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.***2016**, *57*, 819. k) Kommagalla, Y.; Chatani, N. *Coord. Chem. Rev.* **2017**, *350*, 117. l) Sauermann, N.; Meyer, T. H.; Ackermann, L. *Chem. Eur. J.***2018**, *24*, 16209. m) Chatani, N. Bull. *Chem. Soc. Jpn.***2018**, *91*, 211.

13) For 8-aminoquinoline aided arylation, see a) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664.b) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.***2014**, *79*, 11922. c)Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 12379.d) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.***2003**, *68*, 7528. e)Cheng, X.; Chen, Z.; Gao, Y.; Xue, F.; Jiang, C. *Org. Biomol. Chem.* **2016**, *14*, 3298.f)Sattar, M.; Praveen; Prasad, C. D.; Verma, A.; Kumar, S.; Kumar, S. *Adv. Synth. Catal.* **2016**, *358*, 240.g) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349.h) Gui, Q.; Chen, X.; Hu, L.; Wang, D.; Liu, J.; Tan, Z. *Adv. Synth. Catal.***2016**, *358*, 509.i) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *Org. Biomol. Chem.***2016**, 14, 11070.

14) For 8-aminoquinoline enabled alkylation reactions, see: a)Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.b) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.***2013**, *78*, 9689.c)Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.***2015**, *137*, 531.d)Sattar, M.; Praveen; Prasad, C.D.; Verma, A.; Kumar, S.; Kumar, S. *Adv. Synth. Catal.***2016**, *358*, 240.Ni catalyzed: e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. f) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.***2014**, *53*, 2477. g) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.***2015**, *88*, 438.Fe catalyzed: h) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.***2014**, *136*, 13126.i) Monks, B. M.; Fruchey, E. R.; Cook, S. P. *Angew. Chem., Int. Ed.***2014**, *53*, 11065. j) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130.**Cu/Cr catalyzed** k) Chen, X.; Tan, Z.; Gui, Q.; Hu, L.; Liu, J.; Wu, J.; Wang, G. *Chem. Eur. J.***2016**, *22*, 6218. l) Tang, C.; Zhang, R.; Zhu, B.; Fu, J.; Deng, Y.;

Tian, L.; Guan, W.; Bi, X. *J. Am. Chem. Soc.* **2018**, *140*, 16929. m) Tang, J.; Liu, P.; Zeng, X. Chem. Commun. **2018**, *54*, 9325.

15) Cleavage of 8-aminoquinoline reactions, see: a) Aihara, Y.; Chatani, N. *Chem. Sci.***2013**, *4*, 664. b) Parella, R.; Babu, S. A. *J. Org. Chem.***2015**, *80*, 2339. c) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.***2012**, *51*, 5188. d) Huang, L.; Li, Q.; Wang, C.; Qi, C. *J. Org. Chem.* **2013**, *78*, 3030.e) Wang, X.; Zhu, L.; Chen, S.; Xu, X.; Au, C.-T.; Qiu, R. *Org. Lett.***2015**, *17*, 5228. f) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* 2010, *12*, 3414-3417. g) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.***2010**, 49, 958. h) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.***2012**, *134*, 18237. i) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.***2013**, 52, 11124. j) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N. *Chem. Eur. J.* **2016**, *22*, 16805. k) Deguchi, T.; Xin, H.-L.; Morimoto, H.; Ohshima, T. *ACS Catal.***2017**, *7*, 3157.

CHAPTER 2

Palladium-catalyzed regioselective synthesis of C-3 functionalized thiophene/furan carboxamides *via* directing group assisted C-H activation.

For the purpose of this Thesis work, the work of Chapter 2 is re-used (adapted) with permission from (Padmavathi, R., Sankar, R., Gopalakrishnan, B., Parella, R., Babu, S.A.*Eur. J. Org. Chem.***2015**, (17), pp 3727-3742. Title; $Pd(OAc)_2$/AgOAc catalytic system based bidentate ligand directed regiocontrolled C-H arylation and alkylation of the C-3 position of thiophene- and furan-2-carboxamides).

Introduction

Heterocyclic compounds are considered as the most privileged frameworks of organic molecules, as they constitute 70% of the natural and synthetic drugs. Particularly, heterobiarylsrepresent one of the important skeletal structuresand have their widespread applications in diverse fields such as pharmaceutical, industrial, agricultural sciences,material sciences,polymer science and, various other disciplines.[1-3]As depicted in Figure 1, arylated heteroarenes/ carboxamidesencompassing thiophene and furan motif are found to be prevalent in bioactive compounds including some of the approved drug molecules such as raloxifen (cancer), HCV-086 (hepatitis) etc.[4]Apart from their importance in medicinal chemistry, heterobiaryls (especiallyin case of thiophene) are considered as one of the essential cores in material sciences as they exhibit interesting properties such as, intrinsic electronic nature, thermal stability, special optical and electrical properties.

Given the importance of heterobiaryls both in material science and medicinal chemistry, construction of these molecules in a simple and efficient ways is always desirable. In this regard, synthesis of heterobiaryls is well explored through the transition metal-catalyzed cross coupling strategies,[5]which includes Suzuki, Stille, Negishi, Kumada, Hiyama–Denmark coupling reactions. All these methods need the pre-functionalized starting materials and also produce stoichiometric amounts of metal by-products.

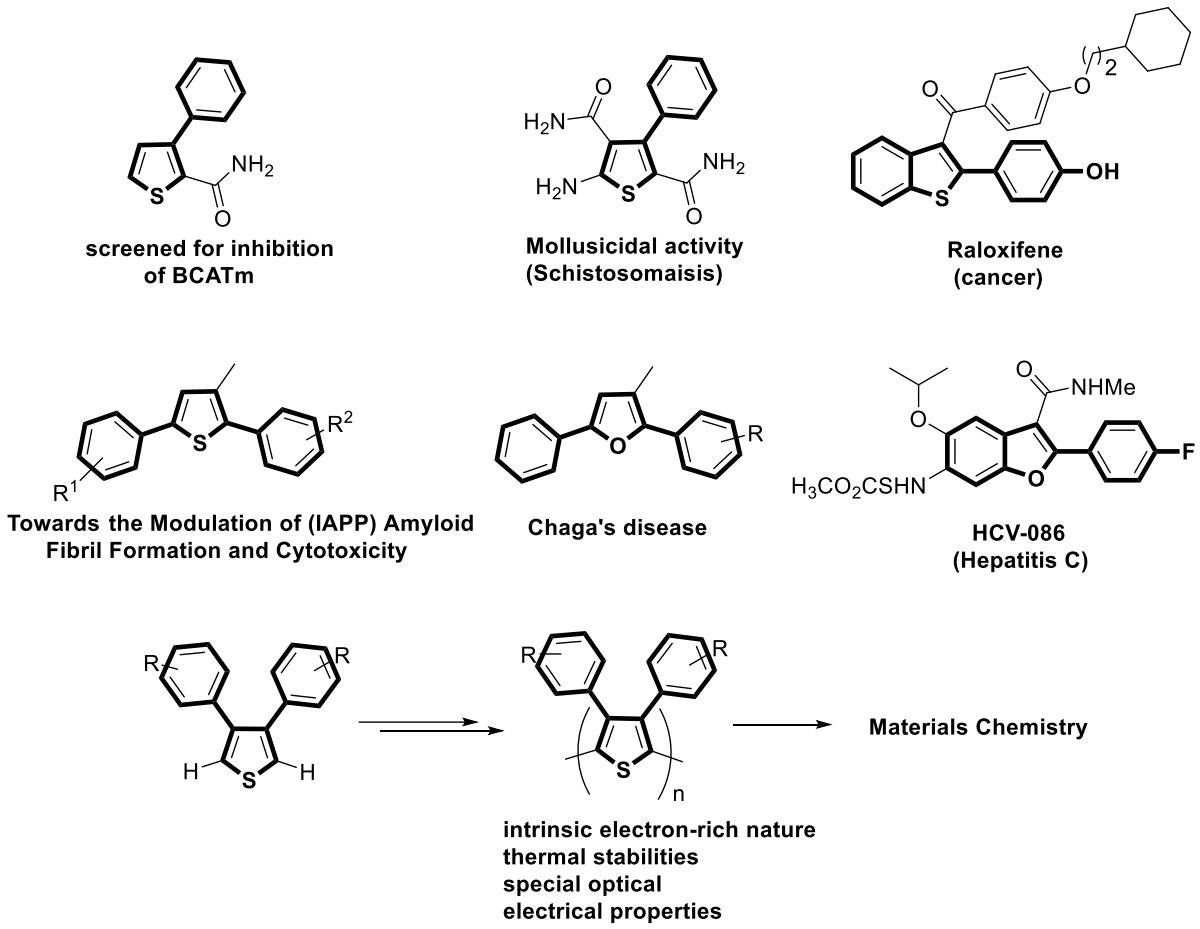


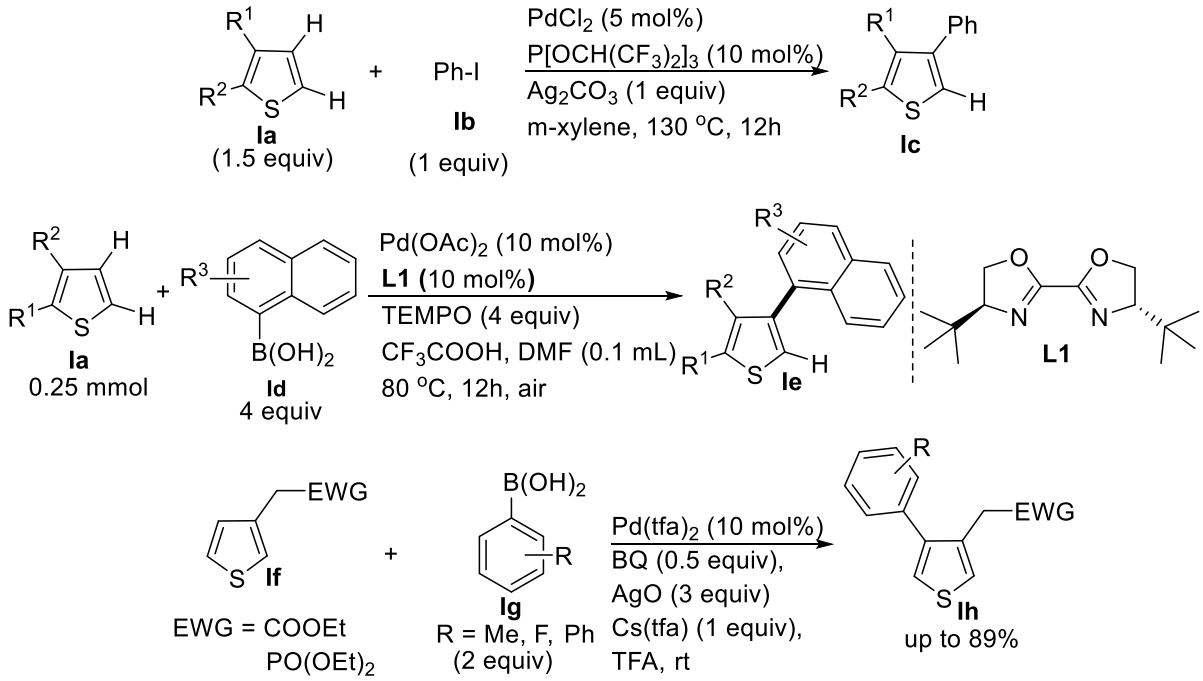
Figure 1. Importance of heterobiaryls consisting of thiophene and furan as their cores.

Recent years witnessed a remarkable development in the transition metal-catalyzed C-H activation-based method. Realizing the importance of heterobiaryls and the efficiency of C-H activation strategy, we decided to synthesise heterobiaryls*via* an efficient and step economical C-H functionalization strategy. In this context, we present some of the literature reports available for heterobiaryl synthesis *via* C-H functionalization route in the next section.

Selected literature reports dealing with the direct C-H arylation of thiophenes and furans (C-3/C-4 positions).

Numerous reports are published in the context of direct arylation of the highly reactive sites such as C-2 and C-5 positions of thiophene and furan using aryl halides and triflates as the coupling partners.[6]Only few reports exist which deal with the C-3 and C-4 functionalization of thiophene and furan, as specific tuning of the compound or the reaction conditions are needed in this case. This section reveals the reports dealing with the construction of C-3/4

arylated heterocycles. In the year 2010, Itami and co-workers[7a] described the selective C-4 arylation (*β*-arylation) of mono and di-substituted thiophenes**Ia** in the presence of$PdCl_2/P[OCH(CF_3)_2]_3/Ag_2CO_3$ catalytic system as shown in the Scheme 1. The authors demonstrated that the arylation of unsubstitued thiophenes yielded a mixture of C-3 and C-2 arylated thiophenes under the optimal conditions in 86% yield with a ratio of 88:12. The same group reported the synthesis of sterically hindered heterobiaryls**Ie**acquiring chirality with their different ortho substituents remarking their importance in asymmetric synthesis, alongside they act as the promising candidates in drug discovery unlike their counter parts *i.e.* flat biaryls.[7b]In the year 2011, Bach's group published an article on the regioselective oxidative coupling of 3-substituted thiophenes**If** with boronic acids**Ig**to afford C-4 arylated targets**Ih**in good yields.[7c] (Scheme 1)

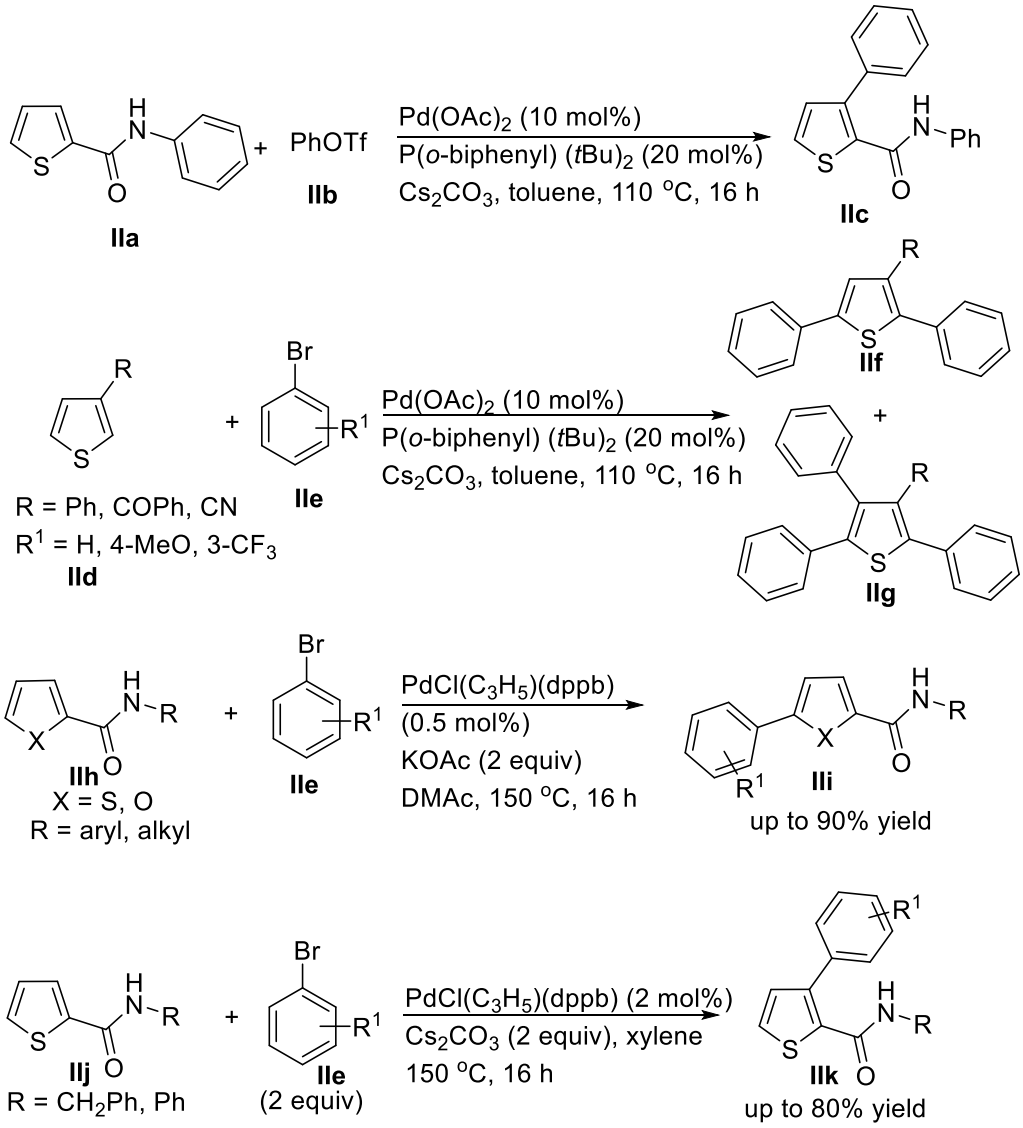


Scheme 1. Pd catalyzed Direct C-3/C-4 arylation of thiophenes.

Selected literature reports dealing with the directed C-H activation strategy for the arylation of thiophenes and furan based compounds (C-3/C-4 positions).

In the year 2002, Okazawa*et al.*[8a]reported the synthesis of mono, di and triarylated thiophenes (**IIc**, **IIf, IIg**) under the palladium catalysis using aryl triflates**IIb**and bromobenzenes**IIe**as the electrophilic partners. Doucet's group[8b] described the synthesis of C-5 arylated carboxamides**IIi***via* Pd-catalyzed direct arylation using aryl bromides**IIe**as the coupling partners. Along with thiophene and furan, pyrazole and pyrrole-based compounds

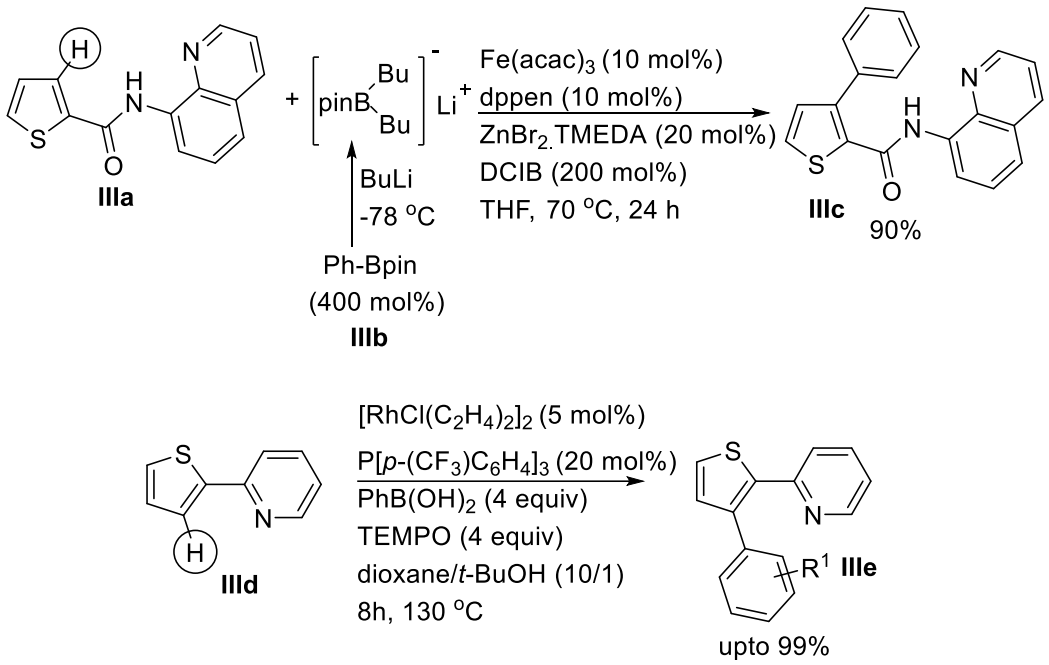
were extensively studied for the selective arylation at C-5 position. It is expected to form C-3 arylated products exclusively, as these compounds are appended with an amide at C-2 position. But authors reported the formation of C-5 arylated targets **IIi**exclusively indicating that under the given conditions, amide doesn't act as a directing group. The same group[8c] reported the synthesis of C-3 arylated thiophene-2-carboxamides **IIk**under palladium catalysis (Scheme 2). The authors achieved the synthesis of C-5 and C-3 arylation selectively by switching base from KOAc to Cs_2CO_3.



Scheme 2. Directed C-3 arylation of heterocyclic-2-carboxamides.

Nakamura's group[9a] demonstrated the Fe catalyzed C-H functionalization of various aromatic and olefinic carboxamides appended with the auxiliary 8-aminoquinoline. When thiophene-2-carboxamide is subjected to the optimal conditions described in Scheme 3 with organoboron

compounds**IIIb**as the coupling partners, it resulted in the formation of C-3 arylated thiophene carboxamide**IIIc** in 90% yield. This reaction can be considered as potential example of directing group assisted C-H functionalization for heteroaromatics, in which reactive sites such as C-2 and C-5 positionsare intact. Studer's group[9b] reported the direct C-H arylation of heteroarenes**IIId**with arylboronic acids *via* an oxidative Rh-catalyzed coupling method. This method described the synthesis of C-3 arylated thiophenes**IIIe**bearing the ortho directing 2-pyridyl group (Scheme 3).

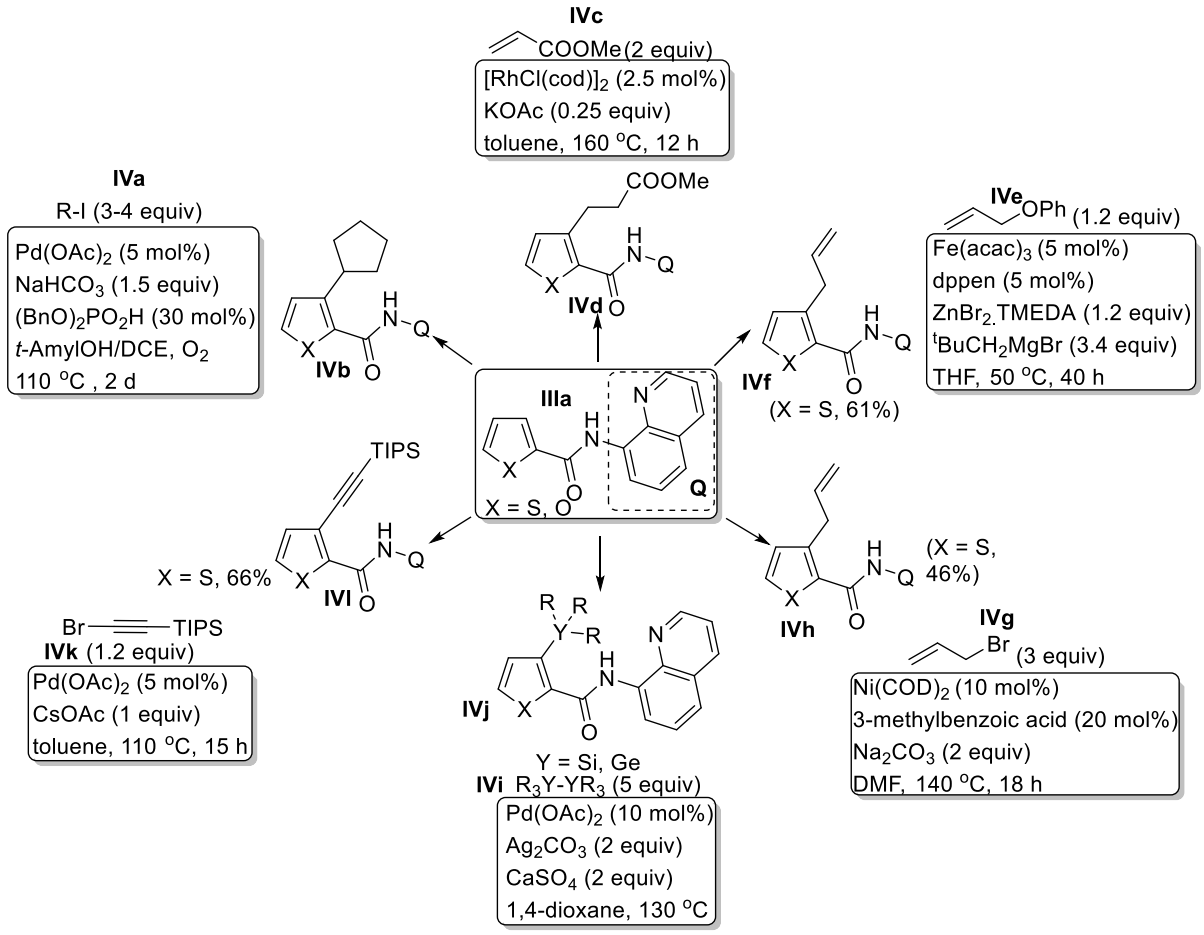


Scheme 3.Directed C-3 arylation of heterocycles.

Selected literature reports dealing with the directed C-H activation strategy for other functionalization (alkylation, allylation etc) of thiophenes and furan based compounds (C-3/C-4 positions).

Apart from arylation, other C-H functionalization of thiophenes and furans are well explored. In this section, some of the reports dealing with the C-H functionalization of thiophene/furan carboxamides appended with the auxiliary 8-aminoquinoline are discussed. In this context, Chen's group[10] reported the *ortho* C-H alkylation to synthesisemonoalkylated benzamides under palladium catalysis. Thiophene-2-carboxamide **IIIa**in the presence of $Pd(OAc)_2$, $NaHCO_3$ as base and $(BnO)_2POOH$ as an additive in *t*-Amyl alcohol/DCE as the solvent at 110 ^oC under oxygen atmosphere yielded the C-3alkylated product**IVb** in 63% yield. Chatani and co-workers[11] reported the alkylation of aromatic and heteroaromatic compounds using *α,*

β-unsaturated esters**IVc**with the help of a rhodium catalyst. Heteroaromatic compounds like thiophene, furan and *N*-methyl pyrrole carboxamides survived well under the reported conditions.Nakamura[12] reported the *ortho* C-H allylation of aromatic amides under Fe catalysis using allyl ethers**IVe**as the coupling partners. Following this report, Sundararaju[13] and co-workers disclosed Ni-catalyzed allylation of aromatic carboxamides equipped with 8-aminoquinoline including heteroaromatic compounds such as thiophene-2-carboxamide**IIIa**. Along with alkylation and allylation, Chatani's group[14] explored the palladium-catalyzed alkynylation of carboxamides using a TIPS-substituted bromoalkyne**IVk**. Apart from the above mentioned reports on C-C bond formation of various aromatic and heteroaromatic compounds, other groups reported the C-heteroatom bond formations such as C-Si, C-Ge in the presence of$Pd(OAc)_2$, Ag_2CO_3 and $CaSO_4$ in dioxane.[15] (Scheme 4)



Scheme 4.Reports on the C-3 functionalization of hetero aromatic carboxamides.

As outlined in the scheme 5, heterocycles possess their own reactive sites for example, in case of thiophenes, furan or pyrrole, C-2 and C-5 are the most reactive positions as compared

to C-3 and C-4 position. Due to this fact, numerous examples of C-H functionalizationof C-2 and C-5 positions are well-known in the literature. But in most of the cases, regioselective issue remains unsolved yielding mixture of products. In order to activate the other sites such as C-3 or C-4 exclusively, there exists a few approaches, one way to achieve this is to block the highly reactive sites such as C-2 and C-5, which might hamper the reaction process. Therefore, from the perspective of regioselective issues, we decided to selectively construct the C-3 heteroarenes by using transition metal-catalyzed directing group-assisted C-H functionalizationapproach. In this regard, a survey of above presented literature enlightened us that though amides (mainly anilides) are employed to solve this issue, still a mixture of C-3 and C-5 products were synthesised and also involve special reaction conditions such as, the *in situ* preparation of catalyst etc. In order to overcome these limitations, we planned to use the highly employed auxiliary 8-aminoquinoline[16] for selective construction of C-3 functionalised heteroaromatic carboxamides, keeping the other positions C-4, C-5(highly reactive) intact.

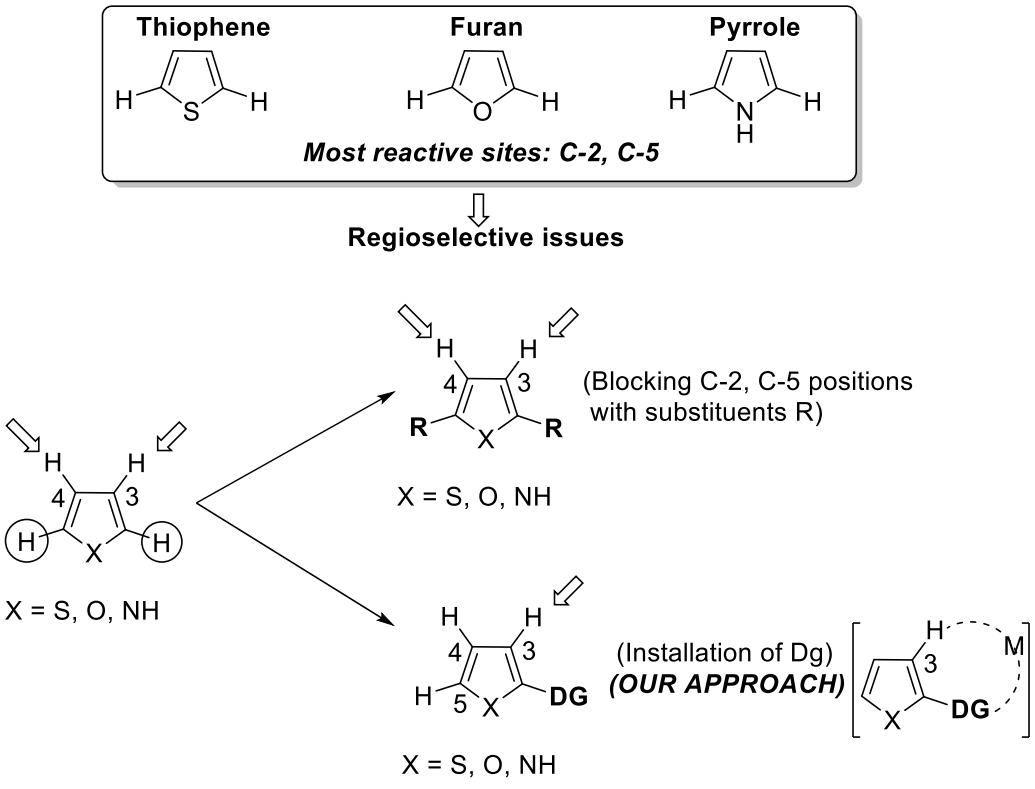
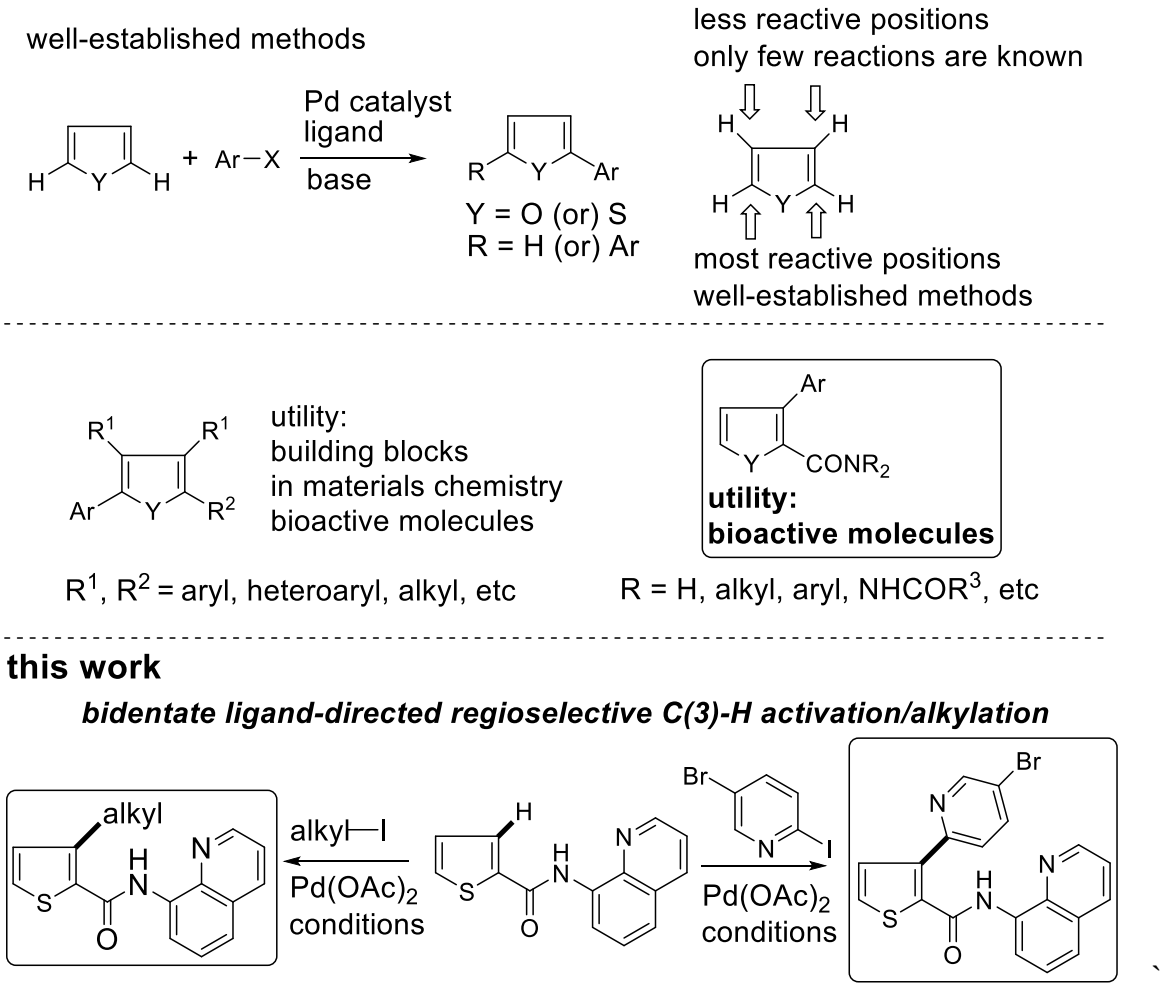


Figure 2. Plan of work for the selective construction of C-3 functionalized heterocycles.

Theme of this work.

Considering the importance of arylated heterocyclic carboxamidesand the challenges associated with the regioselective functionalization of heterocycles, alongside maintaining other reactive positions intact, herein we report the Pd catalyzed bidentate directing group-aided directed C3-H arylation and alkylation of thiophene, furan-2-carboxamides (Scheme 5).[17]



Scheme 5. Generalised scheme for the C-3 arylation and alkylation via ligand assisted C-H activation strategy.

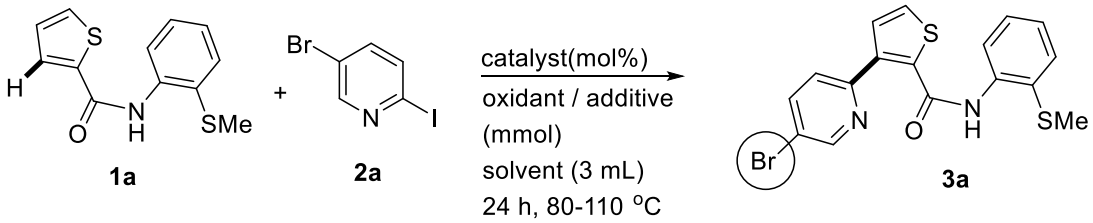
Results and Discussion

To commence our investigation on the $Pd(OAc)_2$/AgOAc catalytic system-based bidentate directing group-aided, C-H arylation of the C3-position of thiophene- and furan-2-carboxamides,we first prepared the compound**1a** (*N*-(2-(methylthio)phenyl)thiophene-2-

carboxamide)by linking thiophene-2-carbonyl chloride with the bidentate ligand 2-(methylthio)aniline (Daugulis's auxiliary).[16]In order to find out the suitablereaction conditions and solvent, we performed various optimization reactions (Table 1).Table 1 is comprised of the Pd-catalyzed direct C-H arylation of the C3 position of the compound**1a** (*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide)with an aryl iodide **2a** (5-bromo-2-iodopyridine). The reaction of a mixture of *N*-(2-(methylthio)phenyl)thiophene-2-carboxamide(**1a**), 5-bromo-2-iodopyridine (**2a**) and AgOAc in the absence of any Pd catalyst in toluene at 110 ^{o}C for 24 h did not yield any C-H arylated products (entry 1, Table 1). On the other hand, the C-H arylation of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in the presence of 5 mol% of $Pd(OAc)_2$ catalyst without any additive in toluene at 110 ^{o}C for 24 h yielded the C3-arylated product **3a** {3-(5-bromopyridin-2-yl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide} in 15% yield (entry 2, Table 1). Next, we performed the C-H arylation of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and an additive AgOAc in toluene at 110 ^{o}C for 24 h, which yielded the C3-arylated product **3a** in 81% yield with very high regioselectivity (entry 3, Table 1).

Then, we performed the Pd-catalyzed *ortho* C-H arylation reaction of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in the presence of Ag_2CO_3 instead of AgOAc. This reaction yielded the C3-arylated thiophene carboxamide **3a** in low yield 29% (entry 4, Table 1). This reaction indicated that AgOAc is acting as an additive, which helps to regenerate the catalyst $Pd(OAc)_2$ in the catalytic cycle. Further, the Pd-catalyzed *ortho* C-H arylation reactions of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in the presence of other additives/bases such as K_2CO_3, Na_2CO_3, potassium acetate and potassium *tert*-butoxide instead of AgOAcafforded the C3-arylated thiophene carboxamide **3a** in low yields (entries 5-8, Table 1). The *ortho* C-H arylation reactions of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in the presence of other Pd catalysts such as $Pd(TFA)_2$, $PdCl_2$, $Pd(PPh_3)_4$ and $Pd(dba)_2$ instead of $Pd(OAc)_2$did not show any significant improvement in the yield (27-66%) of the C3-arylated thiophene carboxamide **3a** (entries 9-12, Table 1). We also performed the Pd-catalyzed *ortho* C-H arylation reactions of the compound**1a** with 5-bromo-2-iodopyridine (**2a**) in other solvents, such as, *tert*-amyl alcohol, *tert*-butanol, 1,2-DCE and MeCN, there was no significant improvement in the yield (12-54%) of the C3-arylated thiophene carboxamide **3a** (entries 13-16, Table 1).

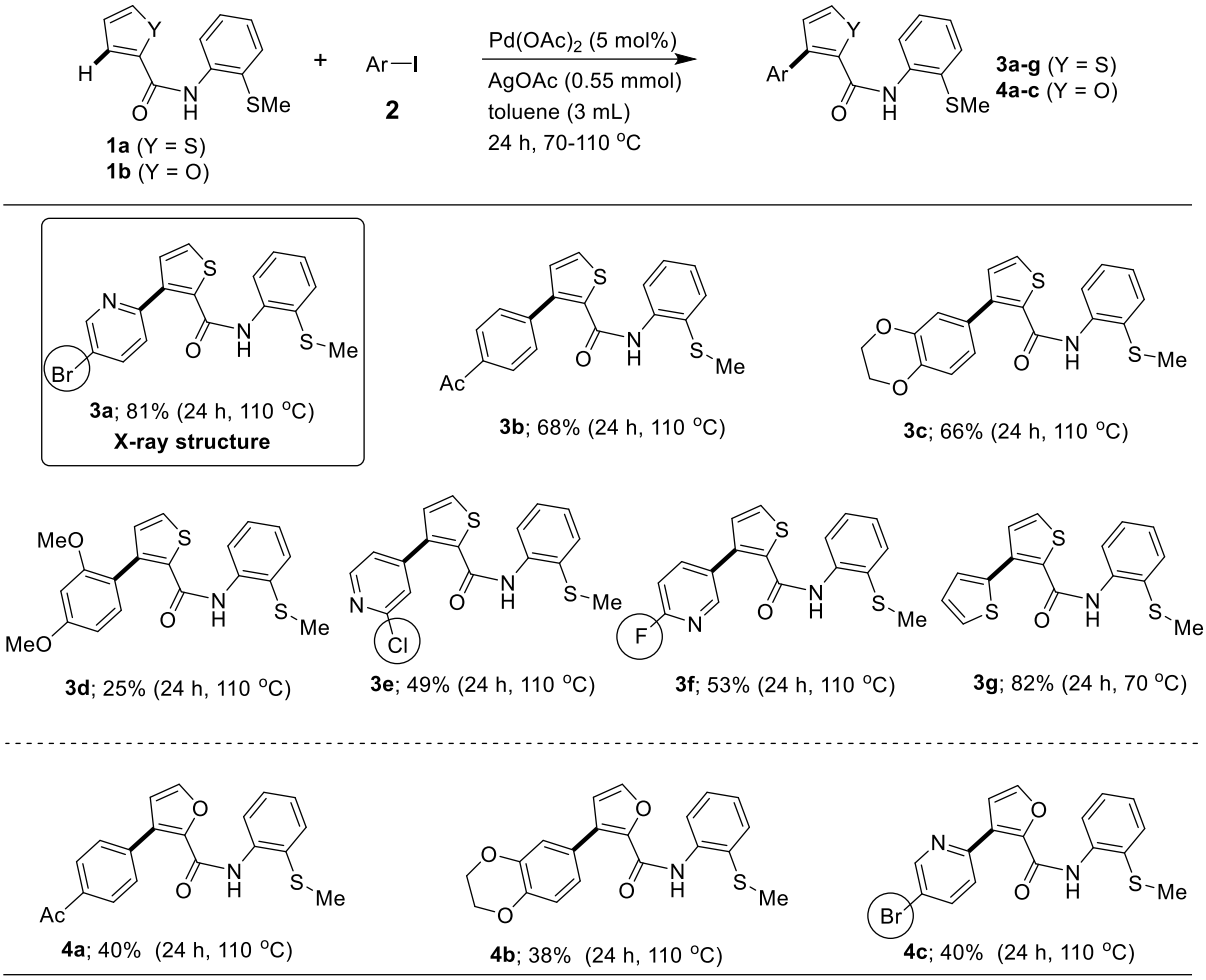
Table 1. Bidentate directing group2-(methylthio)aniline-directed C-H arylation of C3-position of thiophene-2-carboxamide **1a**.[(a)]



entry	PdL_2 (mol%)	oxidant / additive (mmol)	solvent (3 mL)	T (°C)	**3a**; yield (%)
1	nil	AgOAc (0.55)	toluene	110	0
2	$Pd(OAc)_2$ (5)	nil	toluene	110	15
3	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	81
4	$Pd(OAc)_2$ (5)	Ag_2CO_3 (0.55)	toluene	110	29
5	$Pd(OAc)_2$ (5)	K_2CO_3 (0.55)	toluene	110	25
6	$Pd(OAc)_2$ (5)	Na_2CO_3 (0.55)	toluene	110	17
7	$Pd(OAc)_2$ (5)	KOAc (0.55)	toluene	110	14
8	$Pd(OAc)_2$ (5)	KO^{t}Bu (0.55)	toluene	110	0
9	$Pd(TFA)_2$ (5)	AgOAc (0.55)	toluene	110	54
10	$PdCl_2$ (5)	AgOAc (0.55)	toluene	110	66
11	$Pd(PPh_3)_4$ (5)	AgOAc (0.55)	toluene	110	27
12	$Pd(dba)_2$ (5)	AgOAc (0.55)	toluene	110	36
13	$Pd(OAc)_2$ (5)	AgOAc (0.55)	^{t}amylOH	100	53
14	$Pd(OAc)_2$ (5)	AgOAc (0.55)	^{t}BuOH	84	12
15	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,2-DCE	100	54
16	$Pd(OAc)_2$ (5)	AgOAc (0.55)	CH_3CN	80	26

(a) All the reactions were performed using the compound **1a** (0.25 mmol) and iodo compound **2a** (1 mmol).

Table 2. Direct C-H arylation of C3-position of thiophene- and furan 2-carboxamides **1a** and **1b** directed by the bidentate directing group2-(methylthio)aniline.[(a)]



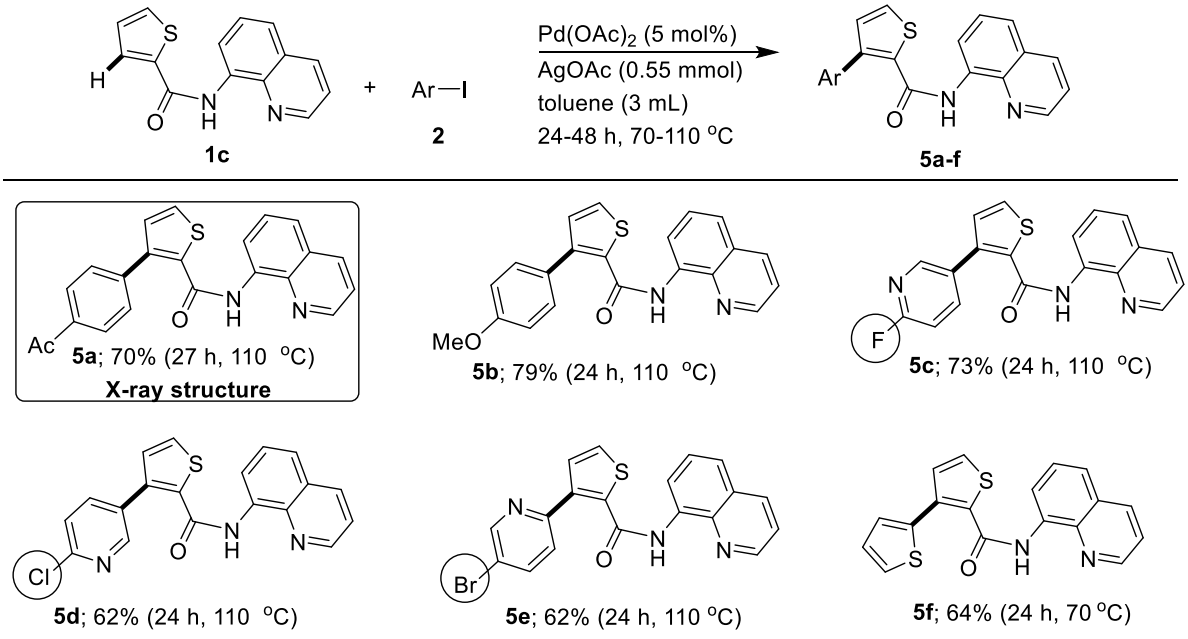
(a) All the reactions were performed using the compounds **1a** or **1b** (0.25 mmol) and an aryl iodide (1 mmol).

Next, we focused our attention to explore the generality and scope of this bidentate ligand (Daugulis's auxiliary,[16]2-(methylthio)aniline-directed Pd-catalyzed regioselective direct arylation of C(3)-H of the compound**1a**(*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide). In this regard, we performed the C-H arylation of the compound**1a** with different aryl iodides such as, 1-(4-iodophenyl)ethanone, 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine and 1-iodo-2,4-dimethoxybenzene in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc, which yielded the corresponding C3-arylated thiophene carboxamides **3b-d** in 25-68% yields (Table 2). The product **3d** was obtained in only 25% yield and in this case, perhaps the presence of the OMe group at the *ortho* position of 1-iodo-2,4-dimethoxybenzene

could have provided a hindrance in the C-H arylation process as a result the product was obtained in low yield.

Consequently, we performed the Pd(II)-catalyzed C(3)-H arylation reactions of compound**1a** with various heteroaryl iodides, which also furnished the corresponding C3-arylated thiophene carboxamides **3e-g** in 49-82% yields with high regioselectivities (Table 2). Accordingly, we also prepared the compound**1b** (*N*-(2-(methylthio)phenyl)furan-2-carboxamide)by linking furan-2-carbonyl chloride with the bidentate ligand, 2-(methylthio)aniline. Then, we performed the C3-H arylation of the compound**1b** with different aryl iodides, such as, 1-(4-iodophenyl)ethanone, 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine and 5-bromo-2-iodopyridine in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc, which yielded the corresponding C3-arylated furan carboxamides **4a-c** in 38-40% yields with very high regioselectivities (Table 2). When compared to the yields obtained in the direct C(3)-H arylation reactions of the compound**1a**(*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide), the direct C(3)-H arylation reactions of the compound**1b**(*N*-(2-(methylthio)phenyl)furan-2-carboxamide) yielded the corresponding C3-arylated products **4a-c** in relatively less yields.

Table 3. Direct C-H arylation of the C3-position of thiophene-2-carboxamide **1c**-directed by the bidentate directing group 8-aminoquinoline.[a]



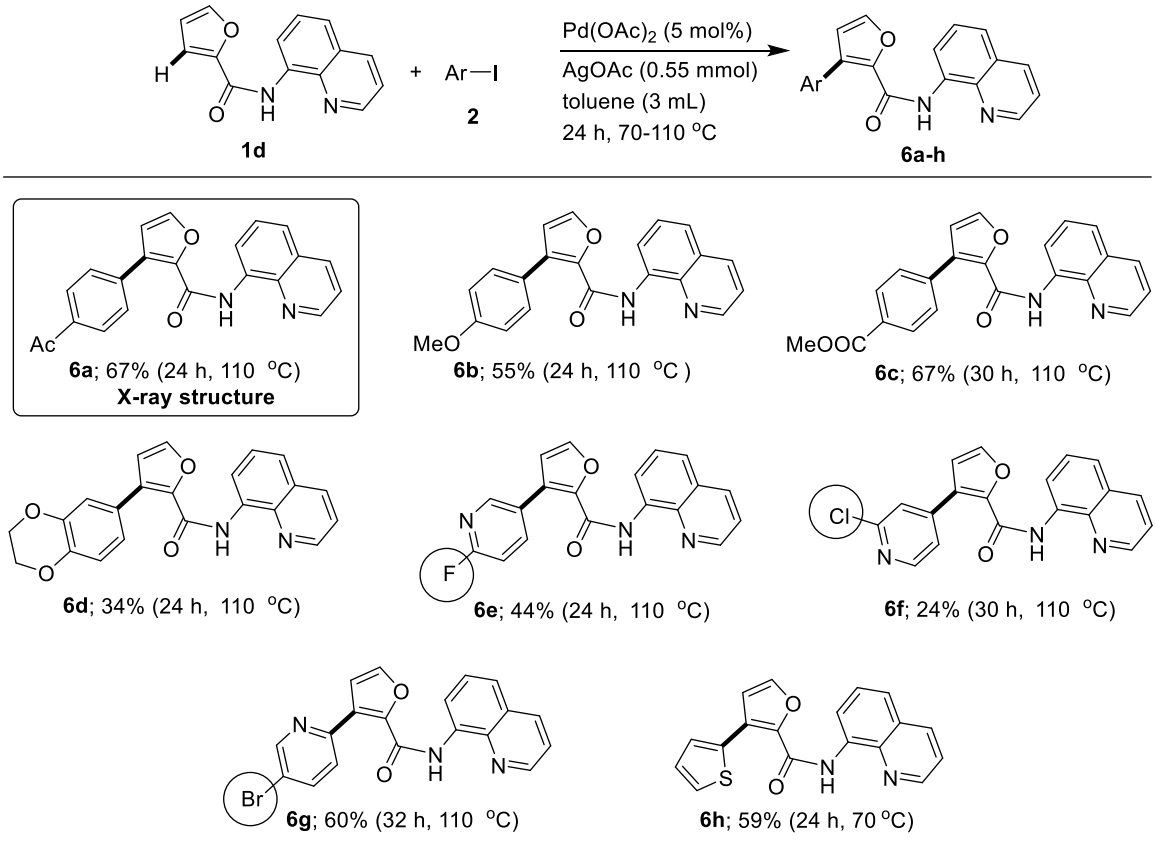
(a) All the reactions were performed using the compound **1c** (0.25 mmol) and an iodo compound (1 mmol).

Next, to examine the capability of a different bidentate ligand and to improve the yield of the Pd(II)-catalyzed direct C-H arylation of the C3-position of thiophene-2-carboxamides, we prepared the compound**1c** [*N*-(quinolin-8-yl)thiophene-2-carboxamide] by linking thiophene-2-carbonyl chloride with the widely used bidentate directing group, 8-aminoquinoline (Daugulis's auxiliary).[16] Then, we performed the C-H arylation of the compound**1c** with different aryl iodides, such as, 1-(4-iodophenyl)ethanone and 1-iodo-4-methoxybenzene in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc, which yielded the corresponding C3-arylated thiophene carboxamides **5a** and **5b** in 70 and 79% yields with very high regioselectivities (Table 3). Further, we performed the Pd(II)-catalyzed bidentate ligand directed direct C-H arylation reactions using the compound**1c** with various heteroaryl iodides, which also yielded the corresponding C3-arylated thiophene carboxamides **5c-f** in 62-73% yields with very high regioselectivities (Table 3). The reactivity of the thiophene-2-carboxamide compound**1a** (which was assembled using the bidentate directing group, 2-(methylthio)aniline, was comparable to the compound**1c** (which was assembled from the bidentate directing group, 8-aminoquinoline) and the yields of the C3-arylated products **5a-f** were also comparable to the products **3a-h**.

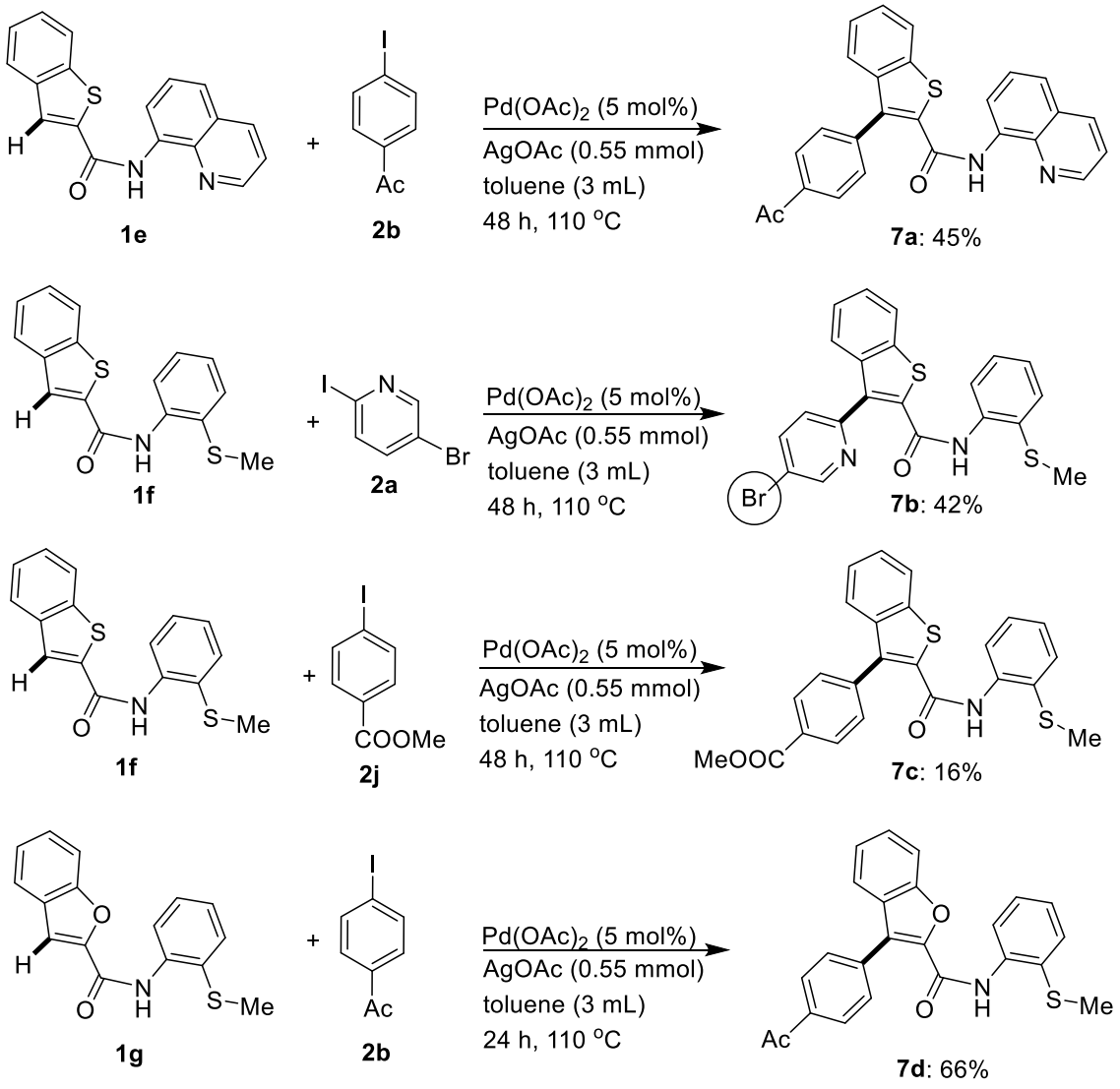
Then, we focused our attention to improve the yield in the Pd(II)-catalyzed direct C-H arylation of the C3-position of furan-2-carboxamides since in the case of the compound**1b** (which was assembled using the bidentate directing group, 2-(methylthio)aniline) the C3-arylataed products **4a-c** were obtained in poor yields. Accordingly, we prepared the compound**1d** (*N*-(quinolin-8-yl)furan-2-carboxamide)by linking furan-2-carbonyl chloride with the bidentate directing group, 8-aminoquinoline. Then, we examined the Pd(II)-catalyzed C-H arylation of the compound**1d** with different aryl iodides, such as, 1-(4-iodophenyl)ethanone, 1-iodo-4-methoxybenzene, methyl 4-iodobenzoate and 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc, which yielded the corresponding C3-arylated furan carboxamides **6a-d** in 34-67% yields with very high regioselectivities (Table 4). Along this line, we performed the Pd(II)-catalyzed bidentate directing group-directed C-H arylation reactions using the compound**1d** with various heteroaryl iodides, which also yielded the corresponding C3-arylated furan carboxamides **6e-h** in 24-60% yields with very high regioselectivities (Table 4). The reactivity of the furan-2-carboxamide compound**1b** (which was assembled using the bidentate directing group, 2-(methylthio)aniline) was almost comparable to the compound**1d** (which was assembled from the bidentate directing group, 8-aminoquinoline) and however,

the yields of the C3-arylated products **6a-h** were slightly higher when compared to the products **4a-c**. Furthermore, we prepared the benzothiophene-2-carboxamides **1e,f** and benzofuran-2-carboxamide **1g** using the corresponding bidentate ligands, 8-aminoquinoline and 2-(methylthio)aniline. Then, we performed the C3-H arylation of compounds **1e-g** with different aryl iodides, such as, 1-(4-iodophenyl)ethanone, 5-bromo-2-iodopyridine and methyl 4-iodobenzoate in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc, which yielded the corresponding C3-arylated benzothiophene-2-carboxamides **7a-d** in 16-66% yields (Scheme 2).

Table 4. Direct C-H arylation of C3-position of furan-2-carboxamide **1d** directed by the bidentate directing group 8-aminoquinoline.[(a)]



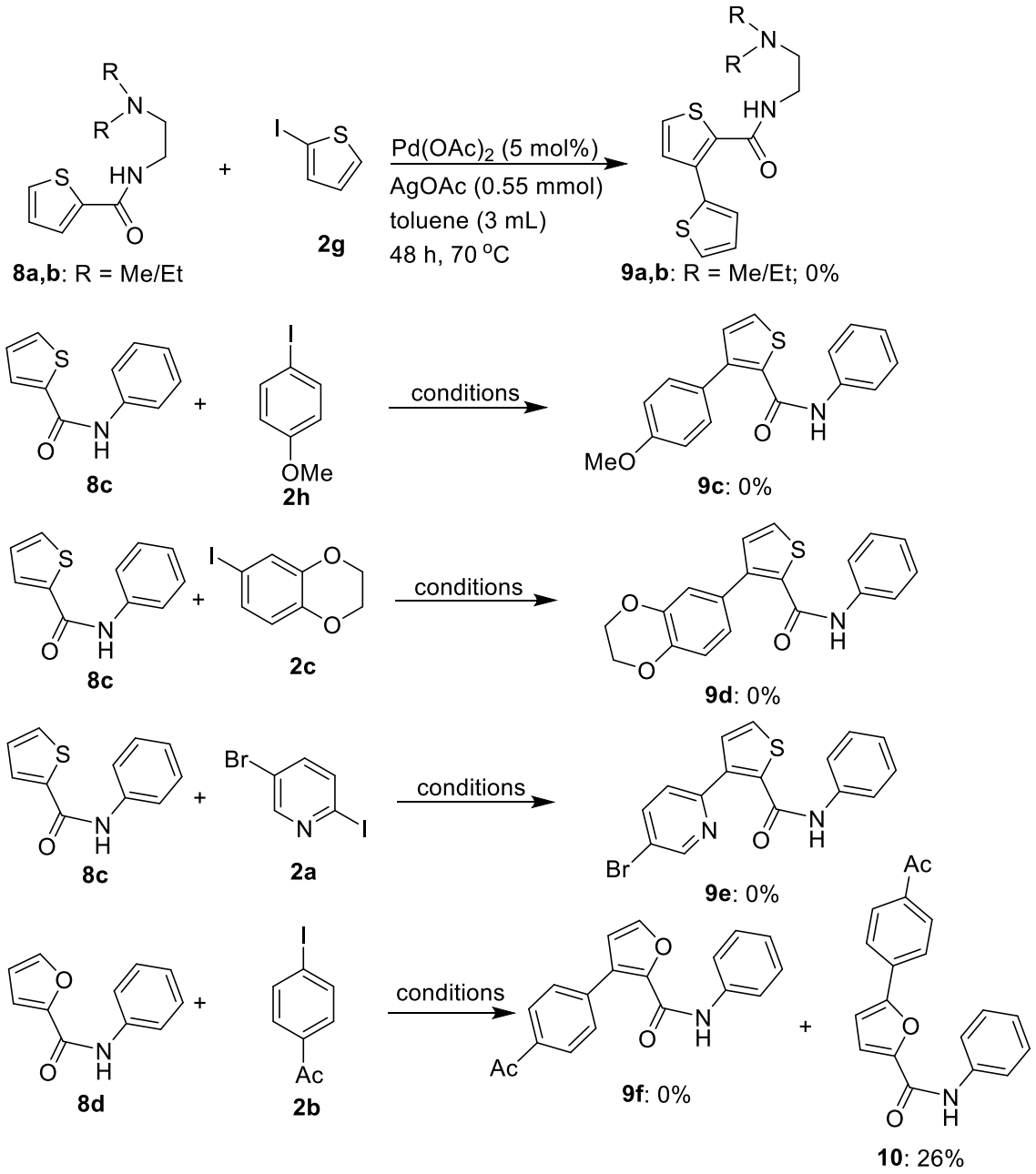
(a) All the reactions were performed using the compound1d (0.25 mmol) and an iodo compound (1 mmol).



Scheme 2. Regiocontrolled direct C-H arylation of C3-position of carboxamides **1e,f** and **1g** (All the reactions were performed using the compounds **1e-g** (0.25 mmol) and an iodo compound (1 mmol).

To extend the scope of this method with regard to the directing groups and to examine the reactivity pattern of thiophene-2-carboxamide and furan-2-carboxamide prepared using some other bidentate auxiliaries, we assembled the compounds **8a,b** by linking thiophene-2-carbonyl chloride with the bidentate ligands such as, *N*,*N*-dimethylethane-1,2-diamine and *N*,*N*-diethylethane-1,2-diamine. Then, we performed the direct C-H arylation of the compounds **8a** and **8b** with **2g**in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and an additive AgOAc, which did not yield the corresponding C3-arylated thiophene carboxamides **9a,b** (Scheme 3). These reactions suggested that the corresponding bidentate ligands, *N*,*N*-dimethylethane-1,2-diamine and *N*,*N*-diethylethane-1,2-diamine were not effective.

Furthermore, by using the optimized reaction conditions (Table 1) we deemed to examine the C3-arylation of thiophene- and furan-2-carboxamides **8c** and **8d**, which were prepared from aniline instead of the bidentate directing groups such as, 2-(methylthio)aniline and 8-aminoquinoline.



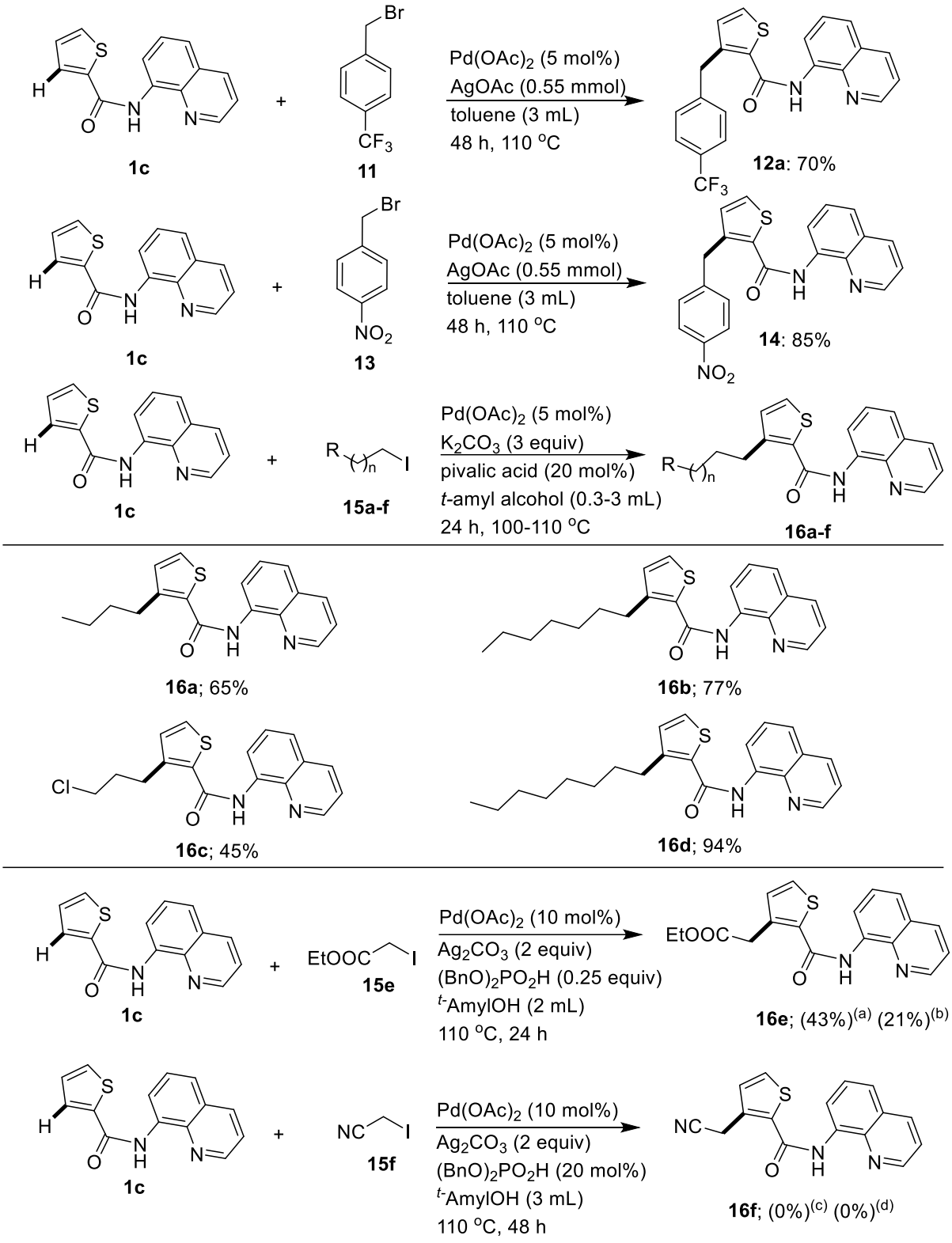
Scheme 3. Pd-Catalyzed C-H Arylation of thiophene- and furan 2-carboxamides **8a-d**.[(a)]

[a] All the reactions were performed using the compounds **8a-d** (0.25 mmol) and an iodo compound (1 mmol). Reaction conditions: $Pd(OAc)_2$ (5 mol %), AgOAc (0.55 mmol), toluene (3 mL), 24 h, 110 °C.

Accordingly, the direct C-H arylation of the compounds **8c** and **8d** with different aryl iodides in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and AgOAc did not yield the

corresponding C3-arylated thiophene carboxamides **9c-f** (Scheme 3). In one of the C3-H arylation reactions involving the compound**8d**, we obtained the product **10.** In this reaction, the arylation occurred at the C5 position of the furan ring of **8d**. These observations suggested that the reaction condition (comprising $Pd(OAc)_2$/AgOAc catalytic system) employed in this investigation works very well only with the thiophene- and furan-2-carboxamides **1a-g** which were prepared using the bidentate ligands, such as, 2-(methylthio)aniline) and 8-aminoquinoline. Further, it is worth to mention that the above investigation is in concurrence with the literature reports as the role of the bidentate auxiliaries (Daugulis's auxiliaries) along with the mechanism of the C-H activation process involving $Pd(OAc)_2$/AgOAc catalytic system has been well documented.[16]

Finally, we wished to expand the usefulness of this C-H functionalization, direct C-C bond forming method and to prepare the C3-alkylated thiophene-2-carboxamides using the bidentate directing group-directed *ortho* C-H functionalization reaction. Along this line, at first, we attempted the benzylation of the compound**1c**. The direct C-H benzylation of the compound**1c** with 1-(bromomethyl)-4-(trifluoromethyl)benzene (**11**) in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and an additive AgOAc in toluene at 110 ^oC for 48 h yielded the C3-benzylated product **12** (*N*-(quinolin-8-yl)-3-(4-(trifluoromethyl)benzyl)thiophene-2-carboxamide) in 70% yield with very high regioselectivity (Scheme 4). Similarly, the Pd-catalyzed benzylation of the compound**1c** with 1-(bromomethyl)-4-nitrobenzene (**13**) yielded the C3-benzylated product **14** in 85% yield (Scheme 4). Furthermore, we wished to perform the alkylation of the C3-position of thiophene-2-carboxamide **1c** using different alkyl iodides (Scheme 4). Accordingly, we performed the direct C-H alkylation of the compound**1c** with various alkyl iodides in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and an additive AgOAc in toluene at 110 ^oC for 48 h, which yielded the corresponding C3-alkylated products **16a-d** in 45-94% yields with very high regioselectivities (Scheme 4). The reaction of compound**1c** with ethyl iodoacetate in the presence of 10 mol% of $Pd(OAc)_2$ and additives Ag_2CO_3 and $(BnO)_2PO_2H$ yielded the C3-alkylated product **16e** in 43% yield (Scheme 4). However, the reaction of compound**1c** with 2-iodoacetonitrile in the presence of 10 mol% of $Pd(OAc)_2$ and additives Ag_2CO_3 and $(BnO)_2PO_2H$ failed to provide the C3-alkylated product **16f** (Scheme 4).



Scheme 4. Pd-Catalyzed C3-H benzylation and alkylation of thiophene-2-carboxamide **1c**. All the reactions were performed using **1c** (0.25 mmol) and benzyl bromide or alkyl iodide (1 mmol). (a) The reaction was performed using **1c** (0.25 mmol) and **15e** (0.5 mmol). (b) **1c** (0.25 mmol), **15e** (1 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (0.75 mmol), PivOH (20 mol%),

^{t}AmylOH (0.3 mL), 100 ^{o}C, 30 h. (c) The reaction was performed using **1c** (0.25 mmol) and **15f** (1 mmol). (d)**1c** (0.25 mmol), **15f** (1 mmol), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (0.75 mmol), PivOH (40 mol%), $^{t-}$AmylOH (3 mL), 100 ^{o}C, 24 h.

The observed regioselectivity in the directing group-enabled Pd-catalyzed direct *ortho* arylation of thiophene-2-carboxamides and structure of the regioisomers**3**, **5**, **12**, **14** and **16**

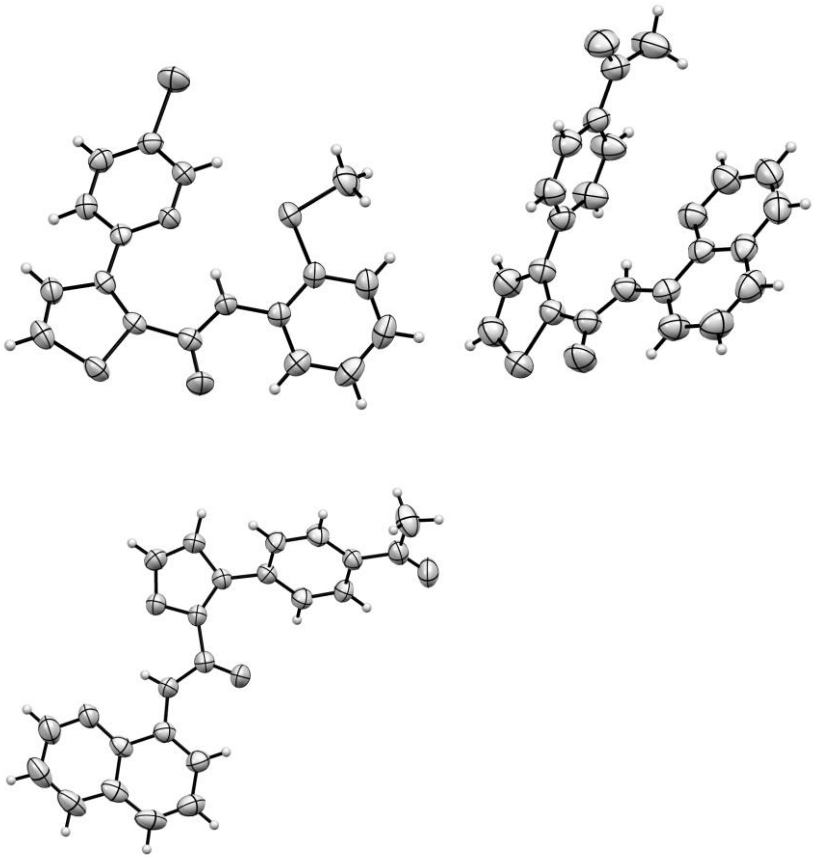


Figure 1. X-ray (ORTEP diagrams) structures of compounds **3e**, **5a** and **6a**.

were ascertained based on the coupling constants (*J*) of the doublet peaks of the C4 and C5 protons which were found to be around 5 Hz (standard value as reported in the literature). Similarly, structure of the regioisomers**4** and **6** were ascertained based on the coupling constants (*J*) of the doublet peaks of the C4 and C5 protons which were found to be around 1.8 Hz (standard value as reported in the literature). The structure of the regioisomer**10** was ascertained based on the coupling constant (*J*) of the doublet peak of the C3 and C4 protons which was found to be 3.6 Hz (standard value as reported in the literature). Furthermore, the observed regioselectivity in the auxiliary enabled Pd-catalyzed direct *ortho* arylation of thiophene-2-carboxamide and furan-2-carboxamide and structures of the representative

regioisomers**3e**, **5a** and **6a** were evidentlyestablished from the X-ray structure analysis (Figure 1).

Conclusions

In summary, in this chapter we have shown a convenient method comprising of the $Pd(OAc)_2$/AgOAc catalytic system-based bidentate directing group-directed, regioselective C-H activation/functionalization and C-C bond formation at the C3-position of thiophene- and furan-2-carboxamides, derived from the bidentate ligands, 8-aminoquinoline or 2-(methylthio)aniline. The importance of the C3 arylated thiophene-2-carboxamides and furan-2-carboxamides as biologically active compounds is well documented in the literature. Accordingly,this method involving $Pd(OAc)_2$-catalyzed C(3)-H arylation of thiophene- and furan-2-carboxamides with aryl iodides or heteroaryl iodides has yielded an access to various C3-arylated thiophene-2-carboxamides and furan-2-carboxamides. We have also shown assembling of various C3-benzylated- and C3-alkylated thiophene-2-carboxamides and furan-2-carboxamides.

All the compounds included in this chapter are characterized by different techniques including ^1H and ^{13}C NMR, IR and HRMS. The observed regioselectivity (exclusively at C-3 position) of the compounds is confirmed bycoupling constant values from the 1H NMR and further strongly supported by single crystal X-ray structure analyses. The relevant characterization data and experimental details of all the compounds are given in the experimental section.

Experimental Section[17,18]

General. Melting points are uncorrected. IR spectra of compounds were recorded as thin films or KBr pellets. ^1H and ^{13}C NMR spectra of compounds were recorded on 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Column chromatography was performed using silica gel 100-200 mesh. Reactions were performed in anhydrous solvent under a nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized. In all the reactions, the column chromatographic purification of the crude reaction mixture yielded only the major regioisomer in pure form. In general, all the reactions were monitored by TLC and the

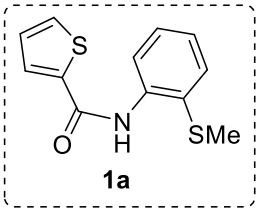
reactions were quenched after the disappearance of the starting materials **1a-g** and in exceptional cases, the reactions were quenched at the reaction time mentioned in the corresponding Table/Schemeas the starting material was not consumed even after prolonged reaction period.In the Pd-catalyzedC(3)-H arylation reactions of substrate **1a** with the corresponding hetero aryl halides having more than one halogen substituent gave the products **3e** (49% yield) and **3f** (53% yield) in moderate yields. Though, we are unable to predict a clear reason for this, however, a plausible reason for the moderate yields in these case may be attributed to the reactivity pattern or extent of the assistance provided by the bidentate ligand (2-(methylthio)aniline) attached with the substrate **1a**. Because, similar type of products **5c** (73% yield) and **5d** (62%) were obtained in relatively good yields from the substrate **1c** prepared using the bidentate ligand 8-aminoquinoline. Further, a similar type reason may also be attributed for the low yields of the products **4a-c** (yield up to 40%) from substrate **1b**, which was prepared using the bidentate ligand (2-(methylthio)aniline) as the substrate **1d**, which was prepared using the bidentate ligand 8-aminoquinoline gave the products **6a-h** in relatively good yields (yield up to 67%). These deliberations possibly indicate that, when compared to the bidentate ligand (2-(methylthio)aniline), the bidentate ligand 8-aminoquinoline provided relatively an effective assistance for the C(3)-H arylation of the furan/thiophene. Apart from this discussion, we cannot ignore that the low yields of the products **3d-f**, **4a-c** and **6d-f** also may be due to the reactivity of the correspondingaryl halides or hetero aryl halides having more than one substituent (e.g., Cl and F (or) O-CH_2-CH_2-O unit).

Procedure for the synthesis of heterocyclic carboxamides 1a-1g/8a-8d. The corresponding carboxylic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h under a nitrogen atmosphere at room temperature. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous dichloromethane (3 mL) under nitrogen atmosphere to afford the corresponding acid chloride as a crude material in DCM. Then, acid chloride in DCM was added to a separate flask containing the corresponding amine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred for 12 h at oom temperature. After this period, the reaction mixture was diluted with dichloromethane (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography furnished the carboxamides **1a-1g/8a-8d**.

General procedure for the direct arylation and benzylation of heterocyclic carboxamides and the preparation of 3a-3g, 4a-4c, 5a-5f, 6a-6h, 7a-7d, 9a-9f, 12 and 14. The correspondinghetero cyclic carboxamide (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol = 5 mol%), iodo compound (1.0 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24-48 h under a nitrogen atmosphere. After the reaction period (see the respective Tables/Schemes), the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel furnished the corresponding arylated and benzylated heterocyclic carboxamides **3a-3g, 4a-4c, 5a-5f, 6a-6h, 7a-7d, 9a-9f, 12 and 14** (see the corresponding Tables/Schemes for specific examples).

General procedure for the alkylation of heterocyclic carboxamides and the preparation of 16a-16d. Heterocyclic carboxamide (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol = 5 mol %), alkyl iodide (1.0 mmol), K_2CO_3 (0.75 mmol = 3 equiv), pivalic acid (20 mol%) in anhydrous *t*-amyl alcohol (0.3 mL) was heated at 100 ^oC for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel furnished the corresponding alkylated heterocyclic carboxamides **16a-16d** (See the corresponding Scheme/Table for specific examples).

***N*-(2-(Methylthio)phenyl)thiophene-2-carboxamide (1a):** Following the general procedure,

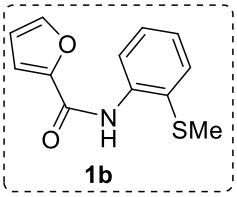


1a

1a was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 05:95) as colorlesssolid; Yield: 90% (224 mg); mp 106-108 ^oC; IR (KBr): 3368, 1654, 1526, 1306, 752 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 9.12 (br s, 1H), 8.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.68 (dd, 1H, J_1 = 3.8 Hz, J_2 = 1.0 Hz), 7.55 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.1 Hz), 7.52 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.33 (td, 1H, J_1 = 8.5 Hz, J_2 = 1.4 Hz), 7.14 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.8 Hz), 7.09 (td, 1H, J= 7.6 Hz, J_2 = 1.3 Hz), 2.39 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 139.6, 138.3, 131.1, 133.3, 129.2, 128.4, 128.0, 125.4, 124.5, 120.4, 19.2; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{12}H_{12}NOS_2$: 250.0360; found 250.0362.

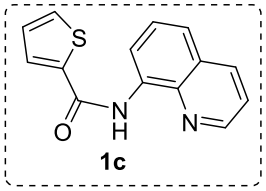
***N*-(2-(Methylthio)phenyl)furan-2-carboxamide (1b):** Following the general procedure, **1b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 30:70) as colorless solid; Yield: 40% (93 mg); mp 76-78 ^oC; IR (KBr): 3326, 1672, 1595, 1530, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 1H), 8.50 (d, 1H, J= 8.2 Hz), 7.57

(s, 1H), 7.54 (d, 1H, *J* = 7.8 Hz), 7.34 (t, 1H, *J*= 8.0 Hz), 7.26 (d, 1H, *J*= 3.4 Hz), 7.10 (t, 1H, *J*= 7.6 Hz), 6.58- 6.56 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 148.0, 144.6, 138.1, 133.3, 129.1, 125.5, 124.5, 120.4, 115.4, 112.6, 19.1; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{12}H_{12}NO_2S$: 234.0589; found 234.0589.



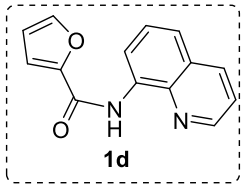
1b

***N*-(Quinolin-8-yl) thiophene-2-carboxamide (1c)**: Following the general procedure, **1c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colorless solid; Yield: 74% (188 mg); mp 85-87 ^{o}C; IR (KBr): 3340, 1658, 1530, 1267, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (br s, 1H), 8.71 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 8.62 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.1 Hz), 7.90 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.66 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.0 Hz), 7.45 (dd, 1H, J_1 = 4.9 Hz, J_2 = 1.0 Hz), 7.36 (t, 1H, *J* = 8.1 Hz), 7.29 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.3 Hz), 7.21 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.02 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.1, 139.0, 138.1, 136.3, 134.0, 131.0, 128.3, 128.0, 127.8, 127.2, 121.7, 121.6, 116.3; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{14}H_{11}N_2OS$: 255.0592; found 255.0589.



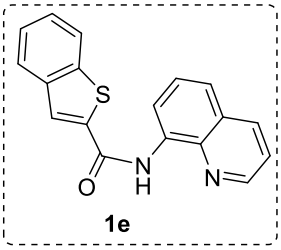
1c

***N*-(Quinolin-8-yl)furan-2-carboxamide (1d):** Following the general procedure, **1d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale brown color solid; Yield: 76% (181 mg); mp 136-140 ^{o}C; IR (KBr): 3331, 1673, 1533, 1274, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.73 (br s,1H), 8.86 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 1.7 Hz, J_2 = 0.8 Hz), 7.55-7.47 (m, 2H), 7.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30 (dd, 1H, J_1 = 3.5 Hz, J_2 = 0.8 Hz), 6.57 (dd, 1H, J_1 = 3.4 Hz, J_2 = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 148.4, 148.3, 144.6, 138.6, 136.3, 134.1, 128.0, 127.3, 121.8, 121.7, 116.6, 115.1, 112.4; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{14}H_{11}N_2O_2$: 239.0821; found 239.0813.



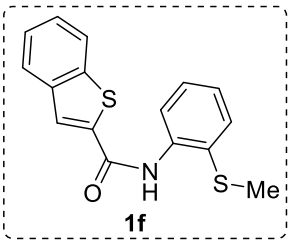
1d

***N*-(Quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (1e):** Following the general procedure, **1e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80)) as colorless solid; Yield: 51% (155 mg); mp 138-140 ^{o}C; IR (KBr): 3340, 1659, 1529, 1484, 1425 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.77 (br s, 1H), 8.92-8.90 (m, 2H), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.09 (s, 1H), 7.97-7.93 (m, 2H),

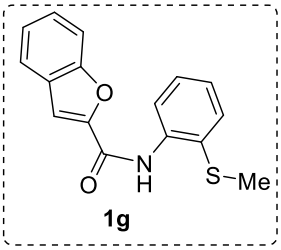


7.64-7.60 (m, 2H), 7.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.49-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 148.4, 141.4, 139.7, 139.3, 138.5, 136.5, 134.2, 128.0, 127.5, 126.5, 125.4, 125.3, 125.0, 122.8, 122.0, 121.8, 116.7; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{18}H_{13}N_2OS$: 305.0749; found 305.0750.

***N*-(2-(Methylthio)phenyl)benzo[*b*]thiophene-2-carboxamide (1f):** Following the general procedure, **1f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale orange color solid; Yield: 70% (209 mg); mp 110-112 ^{o}C; IR (KBr): 3437, 1663, 1573, 1524, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (br s, 1H), 8.52 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.94 (s, 1H), 7.92-7.89 (m, 2H), 7.58 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.49-7.42 (m, 2H), 7.38 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.14 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 141.2, 139.1, 139.1, 138.3, 133.5, 129.4, 126.7, 125.6, 125.4, 125.3, 125.1, 124.7, 122.8, 120.4, 19.4; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{16}H_{14}NOS_2$ 300.0517; found 300.0515.

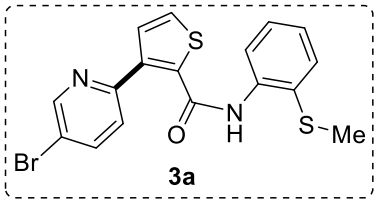


***N*-(2-(Methylthio)phenyl)benzofuran-2-carboxamide (1g):** Following the general procedure, **1g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 30% (85 mg); mp 76-78 ^{o}C; IR (KBr): 3440, 1669, 1581, 1275, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (br s, 1H), 8.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.75-7.72 (m, 1H), 7.65-7.63 (m, 2H), 7.59 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.51-7.47 (m, 1H), 7.41-7.33 (m, 2H), 7.16 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 155.0, 148.8, 137.9, 133.3, 129.1, 127.7, 127.3, 125.8, 124.8, 123.9, 122.8, 120.7, 112.1, 111.5, 19.1; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{16}H_{14}NO_2S$ 284.0745; found 284.0751.



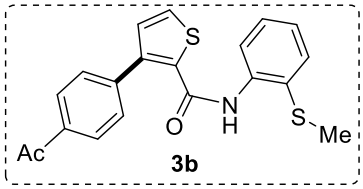
3-(5-Bromopyridin-2-yl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (3a): Following the general procedure, **3a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow solid; Yield: 81% (82 mg); mp 162-164 ^{o}C; IR (KBr): 3440, 1642, 1471, 1260, 753 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 12.52 (br s,1H), 8.87 (dd, 1H, J_1 = 2.4 Hz, J_2 = 0.6 Hz), 8.04 (dd, 1H, J_1 = 8.1 Hz,

J_2 = 1.4 Hz), 7.99 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 7.62 (dd, 1H, J_1 = 8.5 Hz, J_2 = 0.6 Hz), 7.59 (d, 1H, J = 5.3 Hz), 7.41 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.39 (d, 1H, J_1 = 5.3 Hz), 7.26 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.16 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 152.0, 149.8, 140.9, 140.5, 137.2, 137.0, 130.3, 129.9, 129.5, 129.2, 126.9, 125.3, 125.2, 124.1, 119.8, 17.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{17}H_{14}BrN_2OS_2$: 404.9731; found 404.9712.



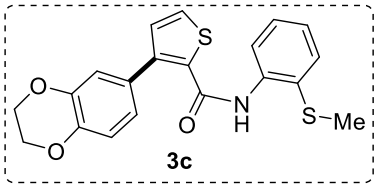
3a

3-(4-Acetylphenyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (3b): Following the general procedure, **3b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 68% (62 mg); mp 121-123 ^{o}C; IR (KBr): 3314, 1680, 1511, 1265, 761 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (br s,1H), 8.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 8.04 (d, 2H, J= 8.5 Hz), 7.64 (d, 2H, J= 8.5 Hz), 7.57 (d, 1H, J= 5.0 Hz), 7.37 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.28 (td, 1H, J_1 = 8.8 Hz, J_2 = 1.4 Hz), 7.12 (d, 1H, J= 5.0 Hz), 7.04 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.63 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 160.2, 141.7, 139.9, 138.2, 137.0, 135.5, 133.2, 131.0, 129.8, 129.5,129.0, 128.9, 125.3, 124.6, 120.4, 26.8, 19.3; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{18}NO_2S_2$: 368.0779; found 368.0770.



3b

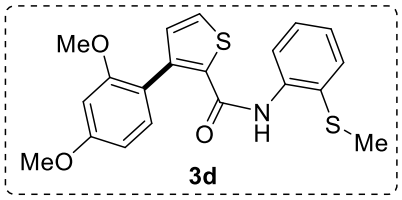
3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (3c): Following the general procedure, **3c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow solid; Yield: 66% (63 mg); mp 113-115 ^{o}C; IR (KBr): 3437, 1651, 1579, 1511, 1260, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (br s,1H), 8.47 (d, 1H, J= 8.2 Hz), 7.52 (d, 1H, J= 5.0 Hz), 7.41 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.32-7.28 (m, 1H), 7.05-7.02 (m, 5H), 4.32-4.28 (m, 4H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 144.4, 144.1, 142.2, 138.7, 135.0, 133.4, 131.6, 129.4, 128.9, 128.2, 125.3, 124.3, 122.7, 120.7, 118.4, 118.1, 64.5, 64.4, 19.4; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{18}NO_3S_2$: 384.0728; found 384.0745.



3c

3-(2,4-Dimethoxyphenyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (3d): Following the general procedure, **3d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow colored thick liquid; Yield:

25% (24 mg); IR (KBr): 3305, 1653, 1512, 1208, 763 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ

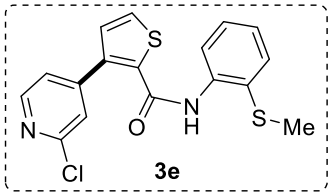


3d

8.77 (br s,1H), 8.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.53 (d, 1H, J= 5.1 Hz), 7.39 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.32-7.26 (m, 2H), 7.04 (d, 1H, J= 5.0 Hz), 7.01 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 6.60 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.55 (d, 1H, J= 2.4 Hz), 3.86 (s, 3H), 3.73 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 161.1, 158.2, 138.8, 138.2, 136.0, 133.2, 132.1, 131.9, 128.8, 128.7, 125.2, 124.0, 120.5, 116.2, 105.2, 99.5, 55.7, 55.5, 19.3; HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{20}H_{19}NNaO_3S_2$: 408.0704; found 408.0683.

3-(2-Chloropyridin-4-yl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide(3e):

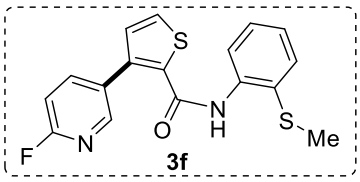
Following the general procedure, **3e** was obtained after purification by column



3e

chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 49% (44 mg); mp 102-104 ^{o}C; IR (KBr): 3318, 1655, 1511, 1304, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s,1H), 8.46 (dd, 1H, J_1 = 5.2 Hz, J_2 = 0.6 Hz), 8.42 (d, 1H, J= 8.2 Hz), 7.61 (d, 1H, J= 5.1 Hz), 7.53 (t, 1H, J= 0.8 Hz), 7.44 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.40 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.5 Hz), 7.33-7.29 (m, 1H), 7.12 (d, 1H, J= 5.1 Hz), 7.09 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 152.2, 150.1, 146.2, 138.7, 137.9, 136.3, 133.0, 130.3, 129.7, 128.9, 125.5, 124.9, 124.5, 123.0, 120.3, 19.3; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{17}H_{14}ClN_2OS_2$: 361.0236; found 361.0217.

3-(6-Fluoropyridin-3-yl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (3f):

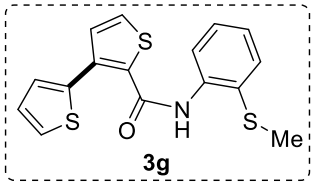


3f

Following the general procedure, **3f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colorless solid; Yield: 53% (45 mg); mp 114-116 ^{o}C; IR (KBr): 3317, 1655, 1578, 1511, 762 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (br s,1H), 8.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 8.41 (d, 1H, J= 2.5 Hz), 8.00-7.96 (m,1H), 7.61 (d, 1H, J= 5.1 Hz), 7.44 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.33-7.29 (m, 1H), 7.12 (d, 1H, J= 5.1 Hz), 7.09 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.06-7.04 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (d, J_{C-F} = 239.9 Hz), 159.9, 147.8, 147.7, 142.4 (d, J_{C-F} = 8.0 Hz), 138.2 (d, J_{C-F} = 10.5 Hz), 135.5, 133.2,

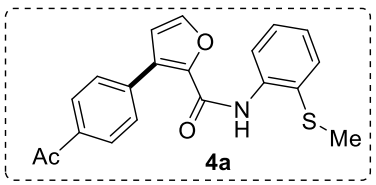
131.0, 129.5, 129.2 (d, J_{C-F} = 4.8 Hz), 129.0, 125.1, 124.7, 120.2, 109.9 (d, J_{C-F}= 37.3 Hz), 19.4; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{17}H_{14}FN_2OS_2$: 345.0532; found 345.0540.

***N*-(2-(Methylthio)phenyl)-[2,3'-bithiophene]-2'-carboxamide (3g):** Following the general procedure, **3g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as green colored thick liquid; Yield: 82% (68 mg); IR (DCM): 3300, 1653, 1578, 1517, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.02 (br s,1H), 8.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.53 (d, 1H, J= 5.1 Hz), 7.46-7.42 (m, 2H), 7.34-7.30 (m, 2H), 7.15 (d, 1H, J= 5.1 Hz), 7.12 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.5 Hz), 7.07 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 2.17 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 138.4, 135.7, 135.5, 134.5, 133.3, 131.9, 129.1, 128.9, 128.8, 128.1, 127.6, 125.6, 124.5, 120.8, 19.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{16}H_{14}NOS_3$: 332.0238; found 332.0225.



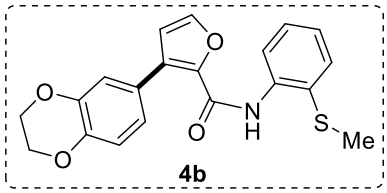
3g

3-(4-Acetylphenyl)-*N*-(2-(methylthio)phenyl)furan-2-carboxamide (4a): Following the general procedure, **4a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale brown color solid; Yield: 40% (35 mg); mp 110-112 ^oC; IR (KBr): 3332, 1679, 1580, 1518, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 8.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 8.05 (d, 2H, J= 8.5 Hz), 7.87 (d, 2H, J= 8.5 Hz), 7.65 (d, 1H, J = 1.8 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.34-7.30 (m, 1H), 7.11 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 6.75 (d, 1H, J= 1.8 Hz), 2.66 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 156.4, 143.6, 142.0, 138.1, 136.6, 136.6, 133.2, 131.5, 129.7, 129.0, 128.2, 125.6, 124.5, 120.6, 114.8, 26.7, 19.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{18}NO_3S$: 352.1007; found 352.1019.



4a

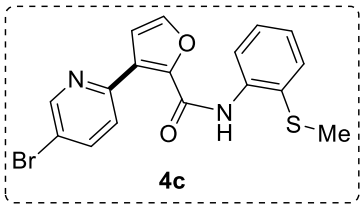
3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(2-(methylthio)phenyl)furan-2-carboxamide (4b): Following the general procedure, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colorless solid; Yield: 38% (35 mg); mp 157-159 ^oC; IR (KBr): 3334, 2923, 1674, 1579, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (br s, 1H), 8.50 (d, 1H, J= 8.2 Hz), 7.57 (d, 1H, J = 1.2 Hz), 7.53 (d, 1H, J=7.6 Hz), 7.34-7.26 (m, 3H), 7.09 (t, 1H, J= 7.5 Hz), 6.95 (d, 1H, J = 8.3 Hz), 6.66 (d, 1H, J = 1.2 Hz), 4.31 (s, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 143.9, 143.3, 143.2, 141.2, 138.5, 133.3, 132.0, 129.0, 125.4, 124.8, 124.2,



4b

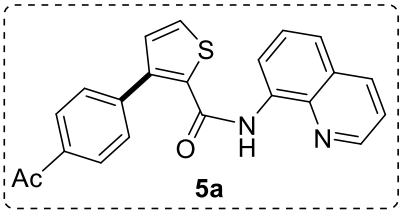
122.9, 120.6, 118.4, 117.1, 114.9, 64.5, 64.3, 19.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{20}H_{18}NO_4S$: 368.0957; found 368.0950.

3-(5-Bromopyridin-2-yl)-*N*-(2-(methylthio)phenyl)furan-2-carboxamide (4c): Following the general procedure, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale brown color solid; Yield: 40% (39 mg); mp 154-156 ^oC; IR (KBr): 3346, 1670, 1580, 1521, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.76 (br s, 1H), 8.82 (t, 1H, *J*= 1.5 Hz), 8.18 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.2 Hz), 7.96 (d, 2H, *J*= 1.6 Hz), 7.68 (d, 1H, *J*= 1.8 Hz), 7.46 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.33-7.29 (m, 1H), 7.16 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.00 (d, 1H, *J*= 1.8 Hz), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 149.9, 148.9, 144.4, 144.2, 139.9, 137.1, 130.5, 128.4, 127.6, 125.2, 125.2, 123.2, 119.8, 113.0, 17.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{17}H_{14}BrN_2O_2S$: 388.9959; found 388.9973.



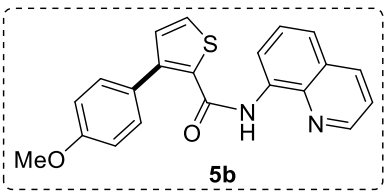
4c

3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5a): Following the general procedure, **5a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow color solid; Yield: 70% (65 mg); mp 159-161 ^oC; IR (KBr): 3305, 1681, 1647, 1527, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br s, 1H), 8.81 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 8.19 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.06 (d, 1H, *J* = 1.6 Hz), 8.03 (d, 2H, *J* = 8.5 Hz), 7.66 (d, 2H, *J* = 8.5 Hz), 7.60 (d, 1H, *J* = 5.1 Hz), 7.51 (t, 1H, *J* = 8.2 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.29 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.14 (d, 1H, *J* = 5.0 Hz), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 160.3, 147.5, 141.9, 140.1, 138.3, 136.8, 136.2, 136.0, 134.2, 130.9, 129.9, 129.6, 129.0, 127.8, 127.3, 121.8, 121.5, 116.5, 26.8; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{17}N_2O_2S$: 373.1011; found 373.1009.



5a

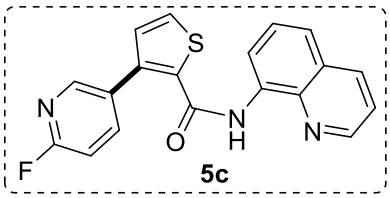
3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5b): Following the general procedure, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colorlesssolid; Yield: 79% (71 mg); mp 188-190 ^oC; IR (KBr): 3344, 2949, 1687, 1579, 1431, 754cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.17 (br s, 1H), 8.86 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 8.32 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56 (d, 1H, *J*= 5.0 Hz),



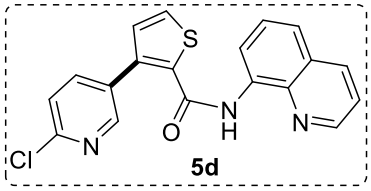
5b

7.53-7.45 (m, 2H), 7.52 (d, 2H, *J*= 8.8 Hz), 7.32 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.10 (d, 1H, *J*= 5.0 Hz), 7.01 (d, 2H, *J*= 8.8 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 160.1, 147.4, 142.9, 138.4, 135.9, 135.4, 134.6, 131.6, 130.8, 129.3, 127.7, 127.4, 127.4, 121.4, 121.4, 116.4, 114.6, 55.4; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{21}H_{17}N_2O_2S$: 361.1011; found 361.1021.

3-(6-Fluoropyridin-3-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5c): Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow solid; Yield: 73% (64 mg); mp 189-191 ^{o}C; IR (KBr): 3440, 1649, 1526, 1250, 763; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 8.79 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.49-8.47 (m, 2H), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00-7.96 (m, 1H), 7.64 (d, 1H, *J* = 5.0 Hz), 7.56-7.48 (m, 2H), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.15 (d, 1H, *J* = 5.0 Hz), 7.04-7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (d, J_{C-F} = 239.0 Hz), 159.9, 147.9, 147.8, 142.5 (d, J_{C-F} = 8.3 Hz), 138.1 (d, J_{C-F} = 31.0 Hz), 137.9, 136.8, 136.2, 134.0, 130.9, 129.9, 129.3 (d, J_{C-F} = 4.6 Hz), 127.8, 127.3, 121.9, 121.7, 116.4, 109.9 (d, J_{C-F} = 37.7 Hz); HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{19}H_{13}FN_3OS$: 350.0763; found 350.0763.

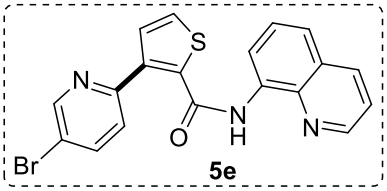


3-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5d): Following the general procedure, **5d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow solid ; Yield: 62% (56 mg); mp 186-188 ^{o}C; IR (KBr): 3385, 1651, 1527, 1454, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (br s, 1H), 8.78 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 8.63 (d, 1H, *J* = 2.4 Hz), 8.52 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.12 (d, 1H, *J* = 8.2 Hz), 7.85 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.4 Hz), 7.64 (d, 1H, *J* = 5.0 Hz), 7.56-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.14 (d, 1H, *J* = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 151.4, 149.7, 148.0, 139.9, 138.2, 137.8, 136.9, 136.2, 134.0, 130.8, 130.3, 129.9, 127.8, 127.3, 124.6, 122.0, 121.7, 116.4; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{19}H_{13}ClN_3OS$: 366.0468; found 366.0478.



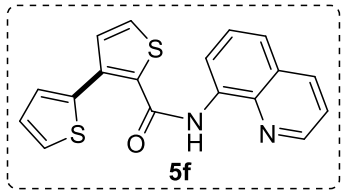
3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5e): Following the general procedure, **5e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow solid; Yield: 62% (63 mg); mp 157-159 ^{o}C; IR (KBr): 3399, 1623, 1546, 1276, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.14 (br s, 1H),

9.01 (dd, 1H, J_1 = 2.4 Hz, J_2 = 0.6 Hz), 8.97 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.4 Hz), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.96 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.62-7.55 (m, 4H), 7.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (d, 1H, J = 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.3, 150.5, 148.3, 140.9, 140.1, 139.7, 137.9, 136.4, 135.6, 130.2, 129.8, 128.3, 127.4, 125.0, 122.3, 121.5, 119.6, 118.7; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{13}BrN_3OS$: 409.9963; found 409.9975.



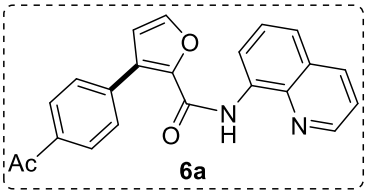
5e

***N*-(Quinolin-8-yl)-[2,3'-bithiophene]-2'-carboxamide (5f)**: Following the general procedure, **5f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow solid; Yield: 64% (54 mg); mp 107-109 ^oC; IR (KBr): 3285, 1647, 1526, 1268, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (br s, 1H), 8.87 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.50 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57-7.53 (m, 2H), 7.51-7.48 (m, 2H), 7.38-7.35 (m, 2H), 7.19 (d, 1H, J = 5.0 Hz), 7.15 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 147.8, 138.6, 136.4, 136.0, 135.3, 134.7, 134.4, 132.0, 129.1, 129.0, 127.9, 127.8, 127.4, 127.2, 121.7, 121.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{18}H_{13}N_2OS_2$: 337.0469; found 337.0461.



5f

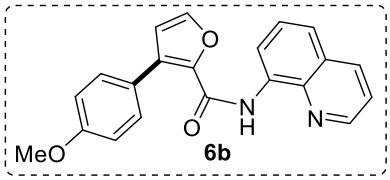
3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6a): Following the general procedure, **6a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow color solid; Yield: 67% (60 mg); mp 192-194 ^oC; IR (KBr): 3358, 1668, 1592, 1525, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.90 (br s,1H), 8.89-8.85 (m, 2H), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.07 (d, 2H, J= 8.6 Hz), 7.90 (d, 2H, J= 8.6 Hz), 7.71 (d, 1H, J = 1.8 Hz), 7.56 (d, 2H, J = 4.4 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.76 (d, 1H, J = 1.8 Hz), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 156.6, 148.4, 143.6, 142.3, 138.7, 136.8, 136.5, 136.4, 134.2, 131.2, 129.8, 128.2, 128.0, 127.4, 121.9, 121.7, 116.8, 114.7, 26.8; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{17}N_2O_3$: 357.1239; found 357.1242.



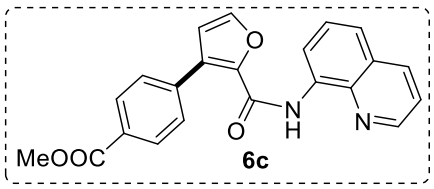
6a

3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6b): Following the general procedure, **6b** was obtained after purification by column chromatography on silica gel

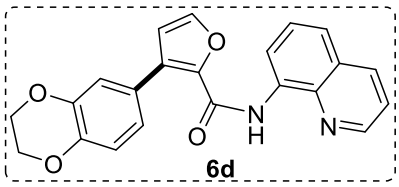
(EtOAc:Hexane = 20:80) as dark brown color solid; Yield: 55% (47 mg); mp 170-172 ^{o}C; IR (KBr): 3390, 1676, 1516, 1252, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.81 (br s, 1H), 8.90 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.9 Hz), 8.85 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.76 (d, 2H, J= 8.7 Hz), 7.65 (d, 1H, J = 1.6 Hz), 7.58-7.52 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.02 (d, 2H, J= 8.8 Hz), 6.70 (d, 1H, J = 1.6 Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 157.1, 148.3, 143.3, 141.5, 138.7, 136.3, 134.5, 132.1, 130.8, 128.0, 127.4, 124.1, 121.6, 121.6, 116.7, 114.8, 113.7, 55.4; HRMS (ESI): *m/z* [M + H]$^{+}$calcd for $C_{21}H_{17}N_2O_3$: 345.1239; found 345.1252.



Methyl 4-(2-(quinolin-8-ylcarbamoyl)furan-3-yl)benzoate (6c): Following the general procedure, **6c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 67% (62 mg); mp 169-171 ^{o}C; IR (KBr): 3335, 1723, 1669, 1533, 1278 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.86 (br s, 1H), 8.87-8.85 (m, 2H), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 8.14 (d, 2H, J= 8.6 Hz), 7.87 (d, 2H, J= 8.6 Hz), 7.69 (d, 1H, J= 1.8 Hz), 7.57-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.74 (d, 1H, J= 1.8 Hz), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 156.6, 148.4, 143.6, 142.3, 138.7, 136.6, 136.4, 134.2, 131.2, 129.7, 129.6, 129.5, 128.0, 127.4, 121.9, 121.7, 116.8, 114.7, 52.2; HRMS (ESI): *m/z* [M + Na]$^{+}$calcd for: $C_{22}H_{16}NaN_2O_4$: 395.1008; found 395.1028.

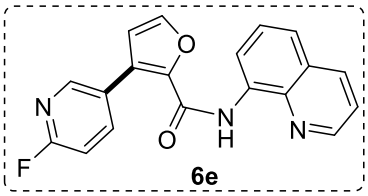


3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6d): Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as black color solid; Yield: 34% (32 mg); mp 146-149 ^{o}C; IR (KBr): 3401, 1671, 1528, 1248, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.79 (br, s,1H), 8.91 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.63 (d, 1H, J = 1.8 Hz), 7.58-7.51 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.35 (d, 1H, J = 2.1 Hz), 7.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 6.98 (d, 1H, J = 8.3 Hz), 6.68 (d, 1H, J = 1.8 Hz), 4.34-4.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 148.2, 143.8, 143.3, 143.2, 141.6, 138.8, 136.3, 134.5, 131.8, 128.0, 127.4, 125.1, 123.0, 121.6, 121.5, 118.5,



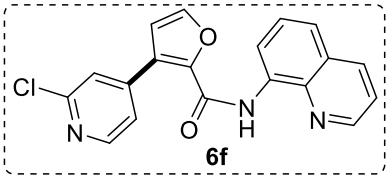
117.1, 116.7, 114.8, 64.5, 64.4; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{17}N_2O_4$: 373.1188; found 373.1174.

3-(5-Fluoropyridin-2-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6e): Following the general procedure, **6e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 44% (37 mg); mp 197-199 ^oC; IR (KBr): 3342, 1673, 1539, 1242, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.91 (br s,1H), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.83 (t, 1H, J = 4.5 Hz), 8.52 (dd, 1H, J_1 = 1.8 Hz, J_2 = 0.8 Hz), 8.43-8.39 (m, 1H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.72 (d, 1H, J = 1.8 Hz), 7.57 (d, 2H, J = 4.4 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.07-7.04 (m, 1H), 6.75 (d, 1H, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3 (d, J_{C-F} = 239.0 Hz), 156.6, 148.5, 147.7 (d, J_{C-F} = 14.9 Hz), 143.8, 142.7 (d, J_{C-F} = 8.0 Hz), 142.4, 138.7, 136.4, 134.1, 128.1, 127.7, 127.3, 126.0 (d, J_{C-F} = 4.8 Hz), 122.0, 121.8, 116.8, 114.3, 108.9 (d, J_{C-F} = 37.2 Hz); HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{13}FN_3O_2$: 334.0992; found 334.0976.



6e

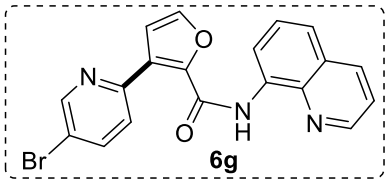
3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6f): Following the general procedure, **6f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow color solid; Yield: 24% (21 mg); mp 217-219 ^oC; IR (KBr): 3401, 1663, 1531, 1260, 778 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 10.91 (br s,1H), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.85-8.81 (m, 1H), 8.68 (d, 1H, J = 2.2 Hz), 8.28 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.5 Hz), 8.21 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.72 (d, 1H, J = 1.8 Hz), 7.57 (d, 2H, J= 4.3 Hz), 7.52 (dd, 1H, J_1= 8.2 Hz, J_2 = 4.2 Hz), 7.44 (d, 1H, J = 8.3 Hz), 6.75 (d, 1H, J= 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 151.0, 149.5, 148.5, 143.9, 142.7, 140.1, 138.7, 136.4, 134.1, 128.1, 127.6, 127.4, 127.0, 123.7, 122.1, 121.8, 116.8, 114.2; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{13}ClN_3O_2$: 350.0696; found 350.0686.



6f

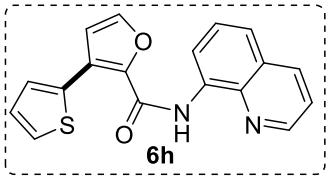
3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (6g): Following the general procedure, **6g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale brown color solid; Yield: 60% (59 mg); mp 172-174 ^oC; IR (KBr): 3434, 1652, 1544, 1046, 784 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 12.59 (br s,1H), 8.96 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.9 Hz), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.88 (dd, 1H,

J_1 = 2.4 Hz, J_2 = 0.6 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.02 (dd, 1H, J_1 = 8.5 Hz, J_2 = 0.6 Hz), 7.90 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 7.67 (d, 1H, J = 1.8 Hz), 7.59-7.52 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.00 (d, 1H, J = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 150.2, 149.1, 148.4, 144.4, 144.0, 139.5, 139.3, 136.4, 135.1, 128.4, 128.2, 127.4, 125.3, 122.2, 121.6, 119.7, 118.1, 113.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{19}H_{13}BrN_3O_2$: 394.0191; found 394.0202.



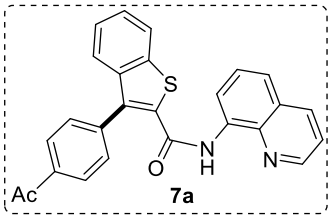
6g

***N*-(Quinolin-8-yl)-3-(thiophen-2-yl)furan-2-carboxamide (6h):** Following the general procedure, **6h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow color solid; Yield: 59% (47 mg); mp 154-156 ^{o}C; IR (KBr): 3331, 1673, 1533, 1274, 755 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (br s,1H), 8.96 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.93 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.2 Hz), 7.62 (d, 1H, J= 1.8 Hz), 7.62-7.54 (m, 2H), 7.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.44 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz), 7.16 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.7 Hz), 6.87 (d, 1H, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 148.4, 143.3,140.8, 138.8, 136.4, 134.4, 133.1, 129.1, 128.1, 127.4, 127.2, 125.7, 121.7, 121.7, 116.7, 113.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{18}H_{13}N_2O_2S$: 321.0698; found 321.0705.



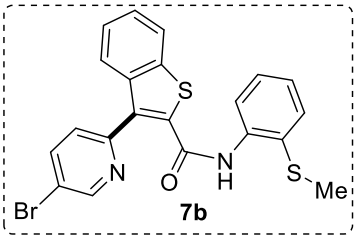
6h

3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (7a): Following the general procedure, **7a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield:45% (47 mg); mp 188-190 ^{o}C; IR (KBr): 3300, 2922, 1680, 1648, 1527, 1425, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ10.06 (br s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 8.24 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.19 (d, 2H, J = 8.4 Hz), 8.08 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.7 Hz), 7.99-7.97 (m, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.56-7.47 (m, 4H), 7.43-7.39 (m, 1H), 7.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 160.6, 147.5, 140.3, 140.1, 138.8, 138.4, 137.4, 137.0, 136.7, 136.1, 134.2, 130.8, 129.4, 127.8, 127.3, 126.8, 125.1, 124.5, 122.7, 121.9, 121.5, 116.7, 26.8; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{26}H_{19}N_2O_2S$: 423.1167; found 423.1181.

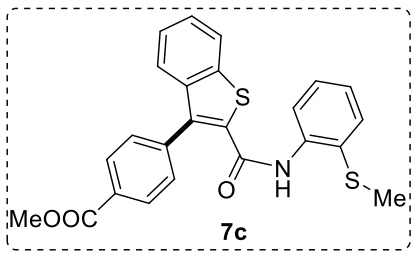


7a

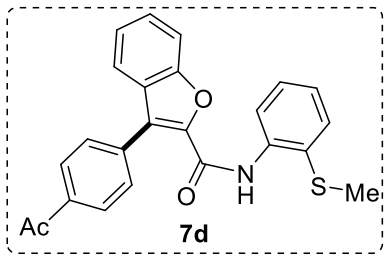
3-(5-Bromopyridin-2-yl)-*N*-(2-(methylthio)phenyl)benzo[*b*]thiophene-2-carboxamide (7b): Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 42% (48 mg); mp 164-166 ^{o}C; IR (KBr): 3400, 1684, 1441, 1265, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (br s, 1H), 8.95 (d, 1H, *J*= 2.2 Hz), 8.24 (d, 1H, *J*= 8.2 Hz), 8.04 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 7.95 (d, 1H, *J*= 8.1 Hz), 7.69 (d, 1H, *J*= 8.2 Hz), 7.59 (d, 1H, *J*= 8.3 Hz), 7.51 (t, 1H, *J*= 7.6 Hz), 7.45-7.41 (m, 2H), 7.31-7.27 (m, 1H), 7.13 (t, 1H, *J*= 7.5 Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 151.4, 151.2, 139.8, 139.8, 139.3, 138.8, 137.5, 134.3, 131.6, 128.0, 127.3, 127.2, 126.7, 125.3, 125.2, 124.2, 122.6, 122.2, 120.7, 18.4; HRMS (ESI): *m/z* [M + H]$^{+}$calcd for: $C_{21}H_{16}BrN_2OS_2$ 454.9887; found 454.9895.



Methyl 4-(2-((2-(methylthio)phenyl)carbamoyl)benzo[*b*]thiophen-3-yl)benzoate (7c): Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale yellow color solid; Yield: 16% (17 mg); mp 184-186 ^{o}C; IR (KBr): 3400, 1579, 1271, 1361, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (br s, 1H), 8.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.9 Hz), 8.26 (d, 2H, *J*= 8.4 Hz), 7.96 (d, 1H, *J*= 8.1 Hz), 7.68 (d, 2H, *J*= 8.4 Hz), 7.53-7.49 (m, 1H), 7.46 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.6 Hz), 7.42-7.40 (m, 1H), 7.39-7.37 (m, 1H), 7.32-7.28 (m, 1H), 7.06 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 4.00 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 160.5, 140.2, 139.9, 138.4, 138.1, 136.5, 136.4, 133.1, 130.8, 130.7, 130.6, 128.8, 126.9, 125.4, 125.1, 124.7, 124.5, 122.6, 120.7, 52.4, 19.4; HRMS (ESI): *m/z* [M + Na]$^{+}$calcd for: $C_{24}H_{19}NNaO_3S_2$ 456.0704; found 456.0703.

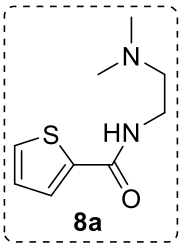


3-(4-Acetylphenyl)-*N*-(2-(methylthio)phenyl)benzofuran-2-carboxamide (7d): Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow color solid; Yield: 66% (66 mg); mp 127-129 ^{o}C; IR (KBr): 3434, 1676, 1510, 1266, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.60 (d, 1H, *J*= 8.1 Hz), 8.14 (d, 2H, *J* = 8.6 Hz), 8.07 (d, 2H, *J* = 8.7 Hz), 8.02 (d, 1H, *J* = 7.3 Hz), 7.62 (dd,



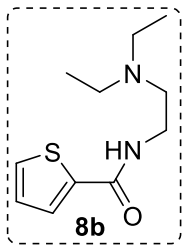
1H, J_1 = 7.2 Hz, J_2 = 0.8 Hz), 7.51 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.46 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 7.44-7.38 (m, 2H), 7.15 (td, 1H, J_1 = 1.4 Hz, J_2 = 7.6 Hz), 2.65 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 161.8, 154.5, 154.1, 138.2, 137.6, 133.5, 133.2, 130.5, 129.0, 128.7, 128.6, 127.0, 126.1, 125.6, 124.9, 124.3, 121.1, 120.6, 114.8, 111.7, 26.8, 19.2; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{24}H_{20}NO_3S$ 402.1164; found 402.1164.

***N*-(2-(Dimethylamino)ethyl)thiophene-2-carboxamide (8a):** Following the general procedure, **8a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as yellow colored thick liquid; Yield: 22% (44 mg); IR (KBr): 3308, 2947, 1630, 1551, 718 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, 1H, J_1 = 3.8 Hz, J_2 = 1.2 Hz), 7.46 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.1 Hz), 7.06 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.7 Hz), 6.86 (br s, 1H), 3.50 (dd, 2H, J_1 = 11.7 Hz, J_2 = 5.6 Hz), 2.50 (t, 2H, J = 6.0 Hz), 2.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 139.3, 129.8, 127.9, 127.5, 57.8, 45.2, 37.1; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_9H_{15}N_2OS$: 199.0905; found 199.0908.



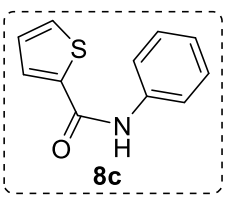
8a

***N*-(2-(Diethylamino)ethyl)thiophene-2-carboxamide (8b):** Following the general procedure, **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as brown colored thick liquid; Yield: 33% (75 mg); IR (KBr): 3313, 2970, 1629, 1550, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.1 Hz), 7.38 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.0 Hz), 7.18 (br s, 1H), 7.00 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.7 Hz), 3.40 (dd, 2H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 2.57 (t, 2H, J = 12.4 Hz), 2.50 (q, 4H, J= 7.2 Hz, J_2 = 7.2 Hz), 0.98 (t, 6H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 139.4, 129.6, 127.8, 127.6, 51.4, 46.8, 37.3, 11.9; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{11}H_{19}N_2OS$: 227.1218; found 227.1213.



8b

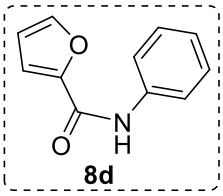
***N*-Phenylthiophene-2-carboxamide (8c):** Following the general procedure, **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as white color solid; Yield: 44% (88 mg); mp 133-136 ^{o}C; IR (KBr): 3421, 1631, 1596, 1534, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (br s, 1H), 7.67 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.1 Hz), 7.65-7.63 (m, 2H), 7.55 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.1 Hz), 7.39-7.34 (m, 2H), 7.18-7.14 (m, 1H), 7.12 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 139.3,



8c

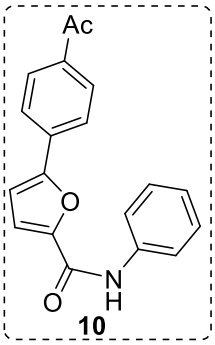
137.6, 130.8, 129.1, 128.6, 127.9, 124.7, 120.4; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{11}H_{10}NOS$ 204.0483; found 204.0487.

***N*-Phenylfuran-2-carboxamide (8d):** Following the general procedure, **8d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as pale orange color solid; Yield: 46% (86 mg); mp 113-115 ^{o}C; IR (KBr): 3410, 1655, 1535, 1165, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.68 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.1 Hz), 7.54 (dd, 1H, J_1 = 1.7 Hz, J_2 = 0.7 Hz), 7.41-7.37 (m, 2H), 7.27 (dd, 1H, J_1 = 3.5 Hz, J_2 = 0.8 Hz), 7.19-7.15 (m, 1H), 6.59 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 147.8, 144.2, 137.4, 129.1, 124.6, 119.9, 115.3, 112.7; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{11}H_{10}NO_2$ 188.0712; found 188.0704.



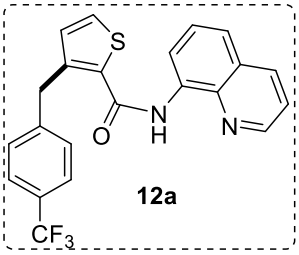
8d

5-(4-Acetylphenyl)-*N*-phenylfuran-2-carboxamide(10): Following the general procedure, **10** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colorless solid; Yield: 26% (20 mg); mp 35-37 ^{o}C; IR (KBr): 3309, 2927, 1624, 1551, 1246, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 8.04 (d, 2H, *J*= 8.6 Hz), 7.85 (d, 2H, *J*= 8.6 Hz), 7.72 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.1 Hz), 7.41 (t, 2H, *J*= 8.4 Hz), 7.36 (d, 1H, *J*= 3.6 Hz), 7.20 (t, 1H, *J*= 7.4 Hz), 6.94 (d, 1H, *J*= 3.6 Hz), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 155.9, 154.5, 154.4, 147.7, 137.2, 136.7, 133.4, 129.2, 129.1, 124.8, 124.5, 120.2, 117.6, 109.9, 26.7; HRMS (ESI): *m/z* [M + H]$^+$calcd for: $C_{19}H_{16}NO_3$ 306.1130; found 306.1139. This compound contains traces of some other isomer.



10

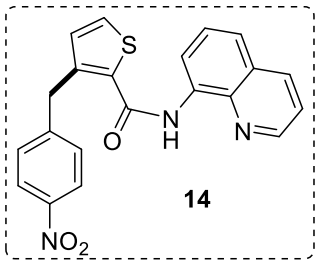
***N*-(Quinolin-8-yl)-3-(4-(trifluoromethyl)benzyl)thiophene-2-carboxamide (12)**: Following the general procedure, **12** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 15:85) as colorless solid; Yield: 70% (72 mg); mp 107-109 ^{o}C; IR (KBr): 3647, 1525, 1227, 754, 593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (br s, 1H), 8.87 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.61-7.53 (m, 4H), 7.46 (dd, 2H, J_1 = 8.2 Hz, J_2 = 3.9 Hz), 7.41 (d, 1H, *J* = 5.1 Hz), 6.92 (d, 1H, *J* = 5.1 Hz), 4.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 148.3, 144.4, 138.5, 136.4, 134.5, 132.2, 131.4, 129.2, 128.6 (q, J_{C-F} = 32 Hz), 128.0, 127.6, 127.4, 125.5



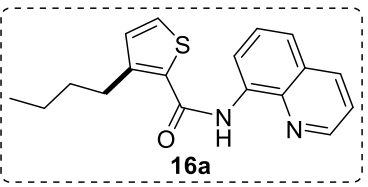
12a

(q, J_{C-F} = 3.8 Hz), 124.4 (q, J_{C-F} = 270.2 Hz), 121.9, 121.8, 120.3, 116.6, 30.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{16}F_3N_2OS$: 413.0935; found 413.0919.

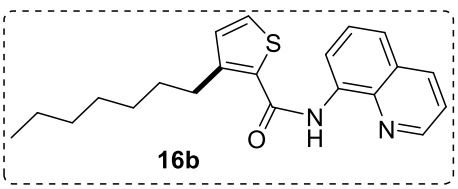
3-(4-Nitrobenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (14): Following the general procedure, **14** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as black color solid; Yield: 85% (82 mg); mp 150-152 ^oC; IR (KBr): 3434, 1654, 1519, 1344, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.48 (br s,1H), 8.84-8.82 (m, 2H), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.16 (d, 2H, *J*= 8.8 Hz), 7.62-7.56 (m, 2H), 7.52-7.48 (m, 3H), 7.46 (d, 1H, *J*= 5.1 Hz), 6.95 (d, 1H, *J*= 5.1 Hz), 4.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 148.4, 148.1, 146.5, 143.8, 138.5, 136.4, 134.4, 132.2, 131.3, 129.6, 128.0, 127.7, 127.4, 123.8, 122.0, 121.8, 116.6, 35.0; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{21}H_{16}N_3O_3S$: 390.0912; found 390.0926.



3-Butyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (16a): Following the general procedure, **16a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 10:90) as colorless solid; Yield: 65% (50 mg); mp 57-59 ^oC; IR (KBr): 3356, 2927, 1679, 1525, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br s, 1H), 8.89 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.82 (d, 1H, *J*= 4.2 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.0 Hz), 7.57 (t, 1H, *J*= 8.0 Hz), 7.52 (d, 1H, *J*= 8.2 Hz), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.41 (d, 1H, *J*= 5.0 Hz), 7.03 (d, 1H, *J*= 5.0 Hz), 3.15 (t, 2H, *J*= 8.0 Hz), 1.83-1.75 (m, 2H), 1.54-1.46 (m, 2H), 1.00 (t, 3H, *J*= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 148.2, 146.4, 138.6, 136.4, 134.7, 132.5, 131.2, 128.0, 127.8, 127.4, 121.7, 121.6, 116.6, 33.1, 29.8, 22.8, 14.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{18}H_{19}N_2OS$ 311.1218; found 311.1202.

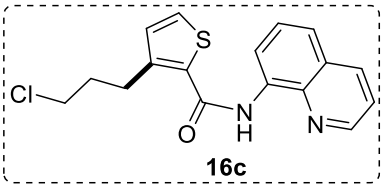


3-Heptyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (16b): Following the general procedure, **16b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 10:90) as brown color solid; Yield: 77% (68 mg); mp 68-69 ^oC; IR (KBr): 3440, 2923, 1650, 1525, 1217cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br s, 1H), 8.89 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.81 (d, 1H, *J*= 4.2 Hz), 8.16 (d, 1H, *J*= 8.2 Hz), 7.59-7.50 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 =

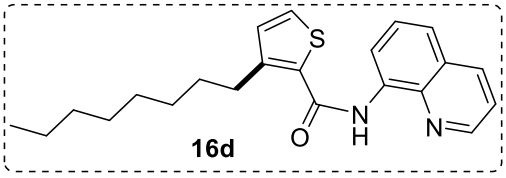


4.2 Hz), 7.41 (d, 1H, *J*= 5.0 Hz), 7.03 (d, 1H, *J*= 5.0 Hz), 3.14 (t, 2H, *J*= 7.9 Hz), 1.83-1.76 (m, 2H), 1.51-1.44 (m, 2H), 1.40-1.25 (m, 6H), 0.88 (t, 3H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 148.2, 146.4, 138.6, 136.3, 134.7, 132.5, 131.2, 128.0, 127.8, 127.4, 121.7, 121.6, 116.6, 31.9, 30.9, 30.0, 29.7, 29.2, 22.7, 14.2; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{21}H_{25}N_2OS$ 353.1688; found 353.1688.

3-(3-Chloropropyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (16c): Following the general procedure, **16c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 10:90) as colorless solid; Yield: 45% (37 mg); mp 102-104 ^oC; IR (KBr): 3357, 2922, 1656, 1526, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 8.86-8.83 (m, 2H), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.44 (d, 1H, *J*= 5.0 Hz), 7.07 (d, 1H, *J*= 5.0 Hz), 3.66 (t, 2H, *J*= 6.6 Hz), 3.30 (t, 2H, *J*= 7.5 Hz), 2.32-2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 148.4, 145.3, 138.6, 136.4, 134.6, 132.3, 131.3, 128.0, 127.7, 127.4, 121.8, 116.5, 44.5, 33.4, 27.0; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{17}H_{16}ClN_2OS$ 331.0672; found 331.0674.

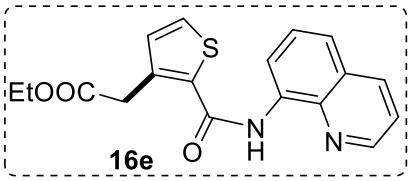


3-Octyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (16d): Following the general procedure, **16d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 10:90) as a pale brown color solid; Yield: 94% (86 mg); mp 68-70 ^oC; IR (KBr): 3359, 2924, 1658, 1525, 789 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (br s, 1H), 8.89 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.58 (t, 1H, *J*= 8.1 Hz), 7.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.42 (d, 1H, *J*= 5.0 Hz), 7.03 (d, 1H, *J*= 5.0 Hz), 3.14 (t, 2H, *J*= 7.9 Hz), 1.83-1.76 (m, 2H), 1.49-1.44 (m, 2H), 1.38-1.23 (m, 8H), 0.88 (t, 3H, *J*= 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 148.2, 146.4, 138.6, 136.3, 134.8, 132.5, 131.2, 128.0, 127.8, 127.4, 121.7, 121.6, 116.6, 31.9, 30.9, 30.0, 29.7, 29.5, 29.3, 22.7, 14.2; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{22}H_{27}N_2OS$ 367.1844; found 367.1851.



Ethyl 2-(2-(quinolin-8-ylcarbamoyl)thiophen-3-yl)acetate (16e): Following the general procedure, **16e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexane = 20:80) as a colourless solid; Yield: 43% (37 mg); mp 143-145 ^oC; IR

(KBr): 3331, 1659, 1525, 1421, 1327, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.48 (br s, 1H), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.83 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.1 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.61-7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.46 (d, 1H, J= 5.0 Hz), 7.13 (d, 1H, J= 5.0 Hz), 4.25-4.19 (m, 4H), 1.27 (t, 3H, J= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 160.8, 148.4, 138.7, 138.6, 136.4, 134.5, 133.0, 131.6, 128.0, 127.4, 127.1, 121.8, 121.7, 116.7, 61.0, 35.0, 14.2; HRMS (ESI): *m/z* $[M + H]^+$calcd for: $C_{18}H_{17}N_2O_3S$ 341.0960; found 341.0966.



16e

References

1) For selected reviews/articles revealing on the bioactivity and other applications of thiophenes/furans, see: a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. b) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011. c) Kobayashi, K.; Ahmed, M. S. M.; Mori, A. *Tetrahedron* **2006**, *62*, 9548. d) Potavathri, S.; Kantak, P.; DeBoef, B. *Chem. Commun.* **2011**, *47*, 4679. e) Hassanpour, A.; De Carufel, C. A.; Bourgault, S.; Forgione, P. *Chem. Eur. J.* **2014**, *20*, 2522; f) Lai, S.; Shizuri, Y.; Yamamura, S.; Kawai, K.; Niwa, M.; Furukawa, H. *Heterocycles* **1991**, *32*, 307. g) Nakatsuka, S.; Feng, B.; Goto, T.; Kihara, K. *Tetrahedron Lett.* **1986**, *27*, 3399. h) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. i) Dang, Y.; Chen, Y. *J. Org. Chem.***2007**, *72*, 6901. j) Lauth, M.; Bergström, Å.; Shimokawa, T.; Toftgård, R. *Proc. Natl. Acad. Sci. U.S.A.***2007**, *104*, 8455. k) Bey, E.; Marchais-Oberwinkler, S.; Werth, R.; Negri, M.; Al-Soud, Y. A.; Kruchten, P.; Oster, A.; Frotscher, M.; Birk, B.; Hartmann, R. W. *J. Med. Chem.* **2008,** *51*, 6725. l) dit Chabert, J. F.; Marquez, B.; Neville, L.; Joucla, L.; Broussous, S.; Bouhours, P.; David, E.; Pellet-Rostaing, S.; Marquet, B.; Moreau, N.; Lemaire, M. *Bioorg. Med. Chem.***2007,** *15*, 4482. m) Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269. n) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.***2011,***7*, 442. o) McCulloch, I.; Heeney, M.; Chabinyc, M. L.; DeLongchamp, D.; Kline, R. J.; Cölle, M.; Duffy, W.; Fischer, D.; Gundlach, D.; Hamadani, B.; Hamilton, R.; Richter, L.; Salleo, A.; Shkunov, M.; Sparrowe, D.; Tierney, S.; Zhang, W. *Adv. Mater.***2009**, *21*, 1091. p) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102*, 1359. q) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. r) Nicolaou, K. C.; Baulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.***2005**, *44*, 4442. s) Malytskyi, V.; Simon, J.-J.; Patrone, L.; Raimundo, J.-

M. *RSC Adv.* **2015**, *5*, 354. t) Zhang, F.; Wu, D.; Xu, Y.; Feng, X. *J. Mater. Chem.***2011**, *21*, 17590.

2) For examples of biologically active candidates of C3-arylated thiophene-2-carboxylic acid derivatives, see: a) Cui, Z.; Zhou, J.; Liu, S.; Cheng, Y.; Chen, S. (South China Agricultural University), CN 103570672 A (**2014**). b) Branch, C. L.; Marshall, H.; Mccritchie, J.; Porter, R. A.; Spada, S. WO 2007080159 A2 (**2007**). c) Nagashima, S.; Kontani, T.; Nagata, H.; Matsushima, Y.; Hamaguchi, H.; Koshika, T. WO 2008096870 A1 (**2008**). d) Aissaoui, H.; Boss, C.; Gude, M.; Koberstein, R.; Lehmann, D.; Sifferlen, T.; Trachsel, D. WO 2009016560 A2 (**2009**).

3) For examples of biologically active candidates of C3-arylated furan-2-carboxylic acid derivatives, see: a) Fujii, A.; Negoro, T.; Migihashi, C.; Murata, M.; Nakamura, K.; Nukuta, T.; Matsumoto, T.; Konno, K. JP 2005060385 A (**2005**). b) Mailliet, P.; Le Brun, A.; Thompson, F.; Tiraboschi, G. WO 2004108685 A1 (**2004**).

4) J. A. Borthwick, N. Ancellin, S. M. Bertrand, R. P. Bingham, P. S. Carter, C. -wa Chung, I. Churcher, N. Dodic, C. Fournier, P. L. Francis, A. Hobbs, C. Jamieson, Stephen D. Pickett, S.E. Smith, D. O. N. Somers, C.Spitzfaden, C. J. Suckling, R. J. Y.J. Med. Chem. **2016**, *59*, 2452-2467, EJMC 46 (2011) 4682-4686, Chem. Eur. J. **2014**, 20, 2522-2528.

5) For selected reviews on classical palladium-catalyzed cross-coupling reactions, see: a) Handbook of organopalladium chemistry for organic synthesis, Part III (Ed.: Negishi, E.), Wiley, New York, 2002, p. 213. b) JGribble, J. Li, G. W. palladium in heterocyclic chemistry, Pergamon, Amsterdam, 2000. c) Metal-catalyzed cross-coupling reactions, 2nd Ed. (Eds. A. de Meijere, F. Diederich), Wiley-VCH, New York, NY, 2004. d) Cross-coupling reactions: A practical guide (Ed. N. Miyaura), Springer, Berlin, 2002.

6) For selected papers dealing on the regioselective arylation of the C2 or C5 positions of furan using aryl halide or triflate, see: a) See refb) Fu, H. Y.; Doucet, H. *Eur. J. Org. Chem.* **2011**, 7163 c) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.***2001**, *3*, 1677.d) Juwaini, N. A. B.; Ng, J. K. P.; Seayad, J. *ACS Catal.***2012**, *2*, 1787.e) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Organometallics***2007**, *26*, 472. f) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.***2005**, *70*, 7578. g) Dong, J. J.; Roger, J.; Pozgan, F.; Doucet, H. *Green Chem.***2009**, *11*, 1832.h) Roger, J.; Pozgan, F.; Doucet, H. *Adv. Synth. Catal.* **2010**, *352*, 696.

7) a) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.***2010**, *49*, 8946.b)Yamaguchi K.; Yamguchi J.; Studer A.; Itami K. *Chem. Sci.***2012**,*3*, 2165.c) Schnapperelle, I.; Breitenlechner, S.; Bach, T. *Org. Lett.* **2011,** 13, 3640-3643.

8) a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura M. *J. Am. Chem. Soc.***2002**, *124*, 5286-5287. b) Laidaoui, N.; Roger, J.; Miloudi, A.; Abed, D. E.; Doucet, H. *Eur. J. Org. Chem.***2011**, 4373–4385. c) Larbi, K. S.; Fu, H. Y.; Laidaoui, N.; Beydoun, K.; Miloudi, A.; Abed, D. E.; Djabbar, S.; Doucet, H. *Chem. Cat. Chem.* **2012**, *4*, 815-823.

9) a) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E.; *J. Am. Chem. Soc.***2014**, *136*, 14349−14352. Volger, T.; Studer, A. *Org. Lett.* **2008**, *10***,** 129-131.

10) Zhang, S. -Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.***2015**, *137*, 531−539.

11) Shibata K.; Chatani, N. *Org. Lett.***2014**, *16*, 5148-5151.

12) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.***2013**, *135*, 17755-17757.

13) Barsu, N.; Kalsi, D.; Sundararaju, B. *Chem. Eur. J.***2015**, *21*, 9364-9368.

14) Kanyiva, K. S.;Kuninobu, Y.; Kanai, M. Org. Lett. 2014, 16, 1968−1971.

15) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.***2012**, 14, 354-357.

16) a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2005**, *127*, 13154. b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2010**, *132*, 3965.

17) Padmavathi, R., Sankar, R., Gopalakrishnan, B., Parella, R., Babu, S.A.*Eur. J. Org. Chem.* **2015**, 3727-3742 and references cited therein.

18) CCDC 1048619 (for **3e**), CCDC 1048620 (for **5a**), CCDC 1048621 (for **6a**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

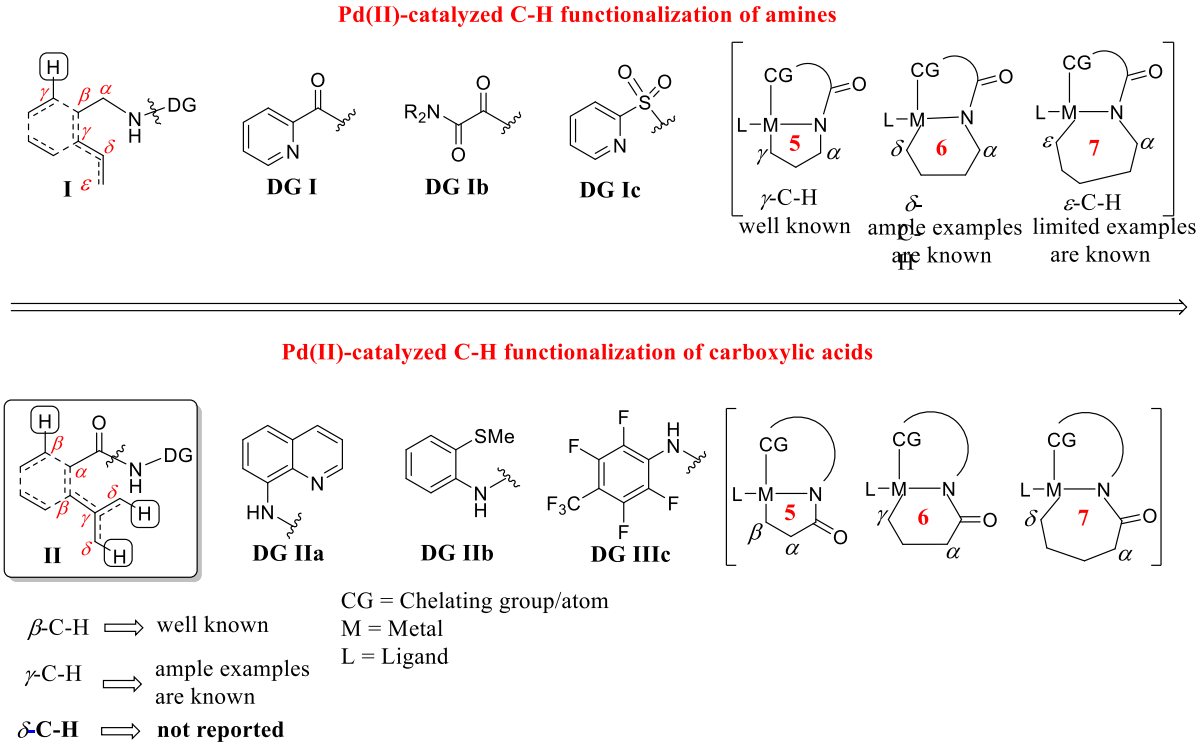
CHAPTER 3

Bidentate directing group-enabled Pd-catalyzed intramolecular amidation of δ-C(sp^2)-H bonds of carboxamides: Synthesis of Phenanthridinone and Quinolinone derivatives.

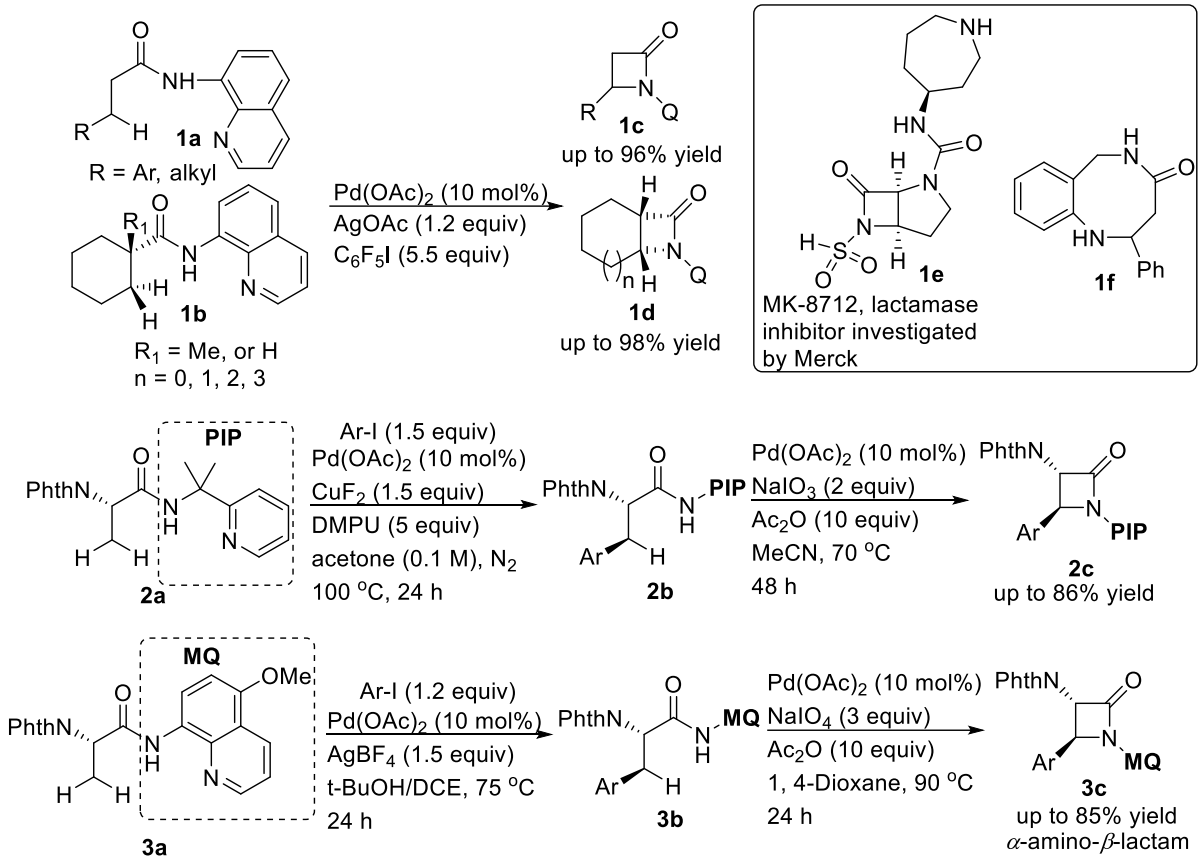
Introduction:

Chapter 1 revealed the recent developments on the directing group-enabled transition metal catalyzed C-H functionalization of amine as well as carboxylic acid based substrates.[1-5]With regard to amine based substrate, this strategy has been well explored for the β-, γ-C-H bonds along with the remote δ-, ε-C-H bonds present in various organic compounds using different directing groups as depicted in the Scheme 1a.[6-8] However, in case of carboxylic acid based substrates, numerous reports are available which reveal the C-H functionalization of the β-position. And limited reports are available which disclose the functionalization of γ-C-H bonds.[9]To the best of our knowledge, there are no reports pertaining to the δ- or ε-C-H functionalization of carboxylic acid substrates. This limitation can be explained on the basis of plausible metallacycle intermediates formed *via* the directing group-aided activation of the desired C-H bonds of amine as well as carboxylic acid-based substrates. As outlined in the Scheme 1a, in case of β-and γ-C-H functionalization of carboxylic acids,[9]there occurs the corresponding formation of a five- and six-membered metallacycle intermediate, whereas in order to activate the δ-C-H bonds, the reaction is expected to proceed *via* a seven-membered metallacycle intermediate.[10] In case of amines, ε-C-H bond activation also requires the generation of a seven-membered metallacycle intermediate. In case of carboxylic acids, the β-, γ-C-H functionalization including intermolecular arylation, alkylation, acetoxylation, amination/amidation, halogenations[1-3,11]intramolecular arylation and amidation are well explored.[9g,12,13]Weenvisioned to examine the bidentate directing group-enabled Pd-catalyzed intramolecular amidation of δ-C(sp^2)-H bonds of carboxylic acids and the synthesis of phenanthridinone skeletons using suitable carboxamide substrates. Representative literature

reports dealing with the directing group-enabled Pd-catalyzed intramolecular amidation of sp^2/sp^3 C-H bonds of carboxylic acids are given below.



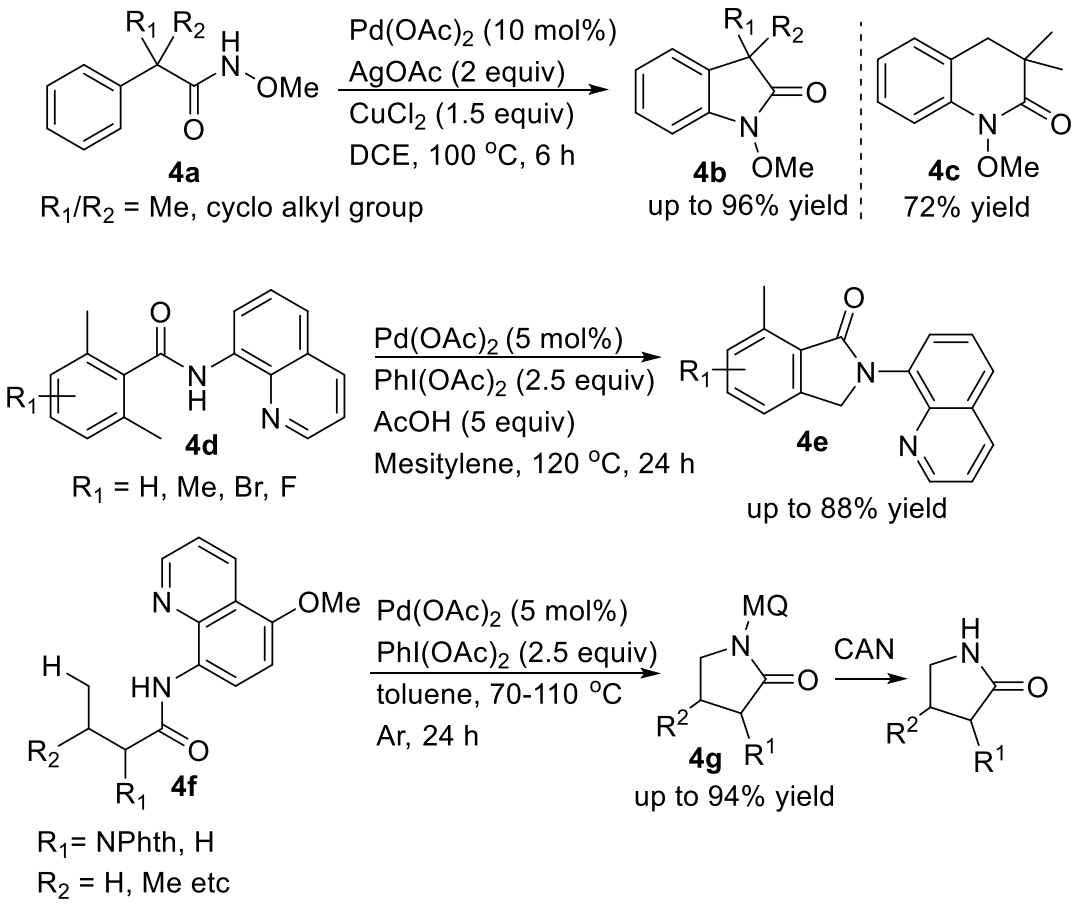
Scheme 1a. Directing group (DG)-aided site-selective C-H functionalization of amines and carboxylic acids.



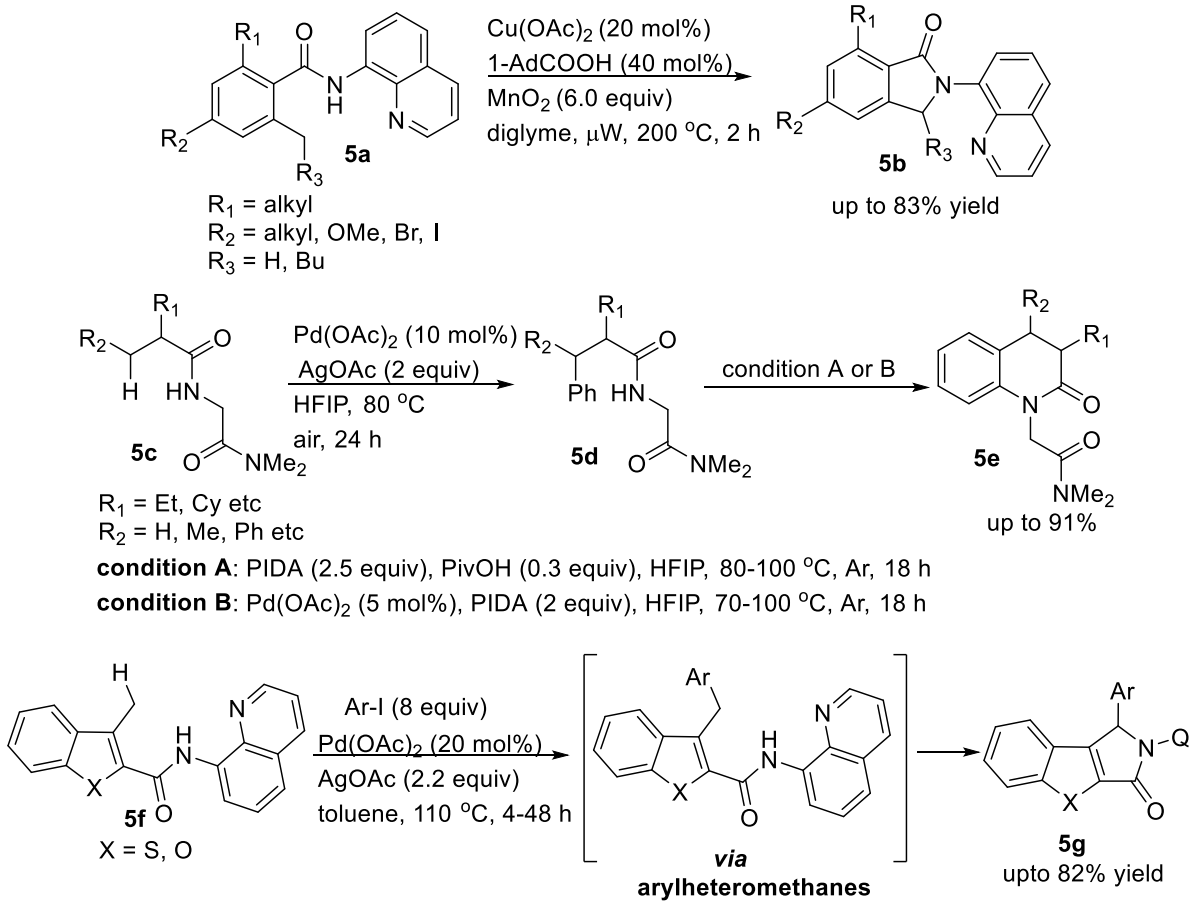
Scheme 1b. Pd-catalyzed intramolecular amination of *β*-C(sp^3)-H bonds of carboxamides.

Wu and co-workers[12a] described the Pd catalyzed sp^3 C-H activation followed by intramolecular amination of carboxamides (**1a**, **1b)** for the synthesis of *β*-lactams (**1c**, **1d**) and the methodology is successfully applied for the construction of *β*-lactamase inhibitor MK-8712**1e** and other medium sized ring nitrogen heterocycles**1f**. The optimal reaction conditions involve 10 mol% of $Pd(OAc)_2$, 1.2 equiv of AgOAc and 5.5 equiv of C_6F_5I. They screened several substituted aryl iodides for the promotion of C-N bond formation and found pentafluoro-iodobenzene is suitable for achieving high regioselectivity along with the improvement of yield of the desired product. This iodo compound is found to play a key role in tuning the electronic and steric properties of the formed intermediates during C-N bond formation process (Scheme 1b).[12a] In the year 2013, Shi's team revealed the $Pd(OAc)_2$catalyzed sequential arylation/intramolecular amination of the *β*-C(sp^3)-H bonds of *N*-protected amino acids**2a** containing PIP as the directing group for the construction of *β*-lactams**2c** (Scheme 1b).[12c]Following this report, in the year 2017, the same group disclosed the synthesis of *β*-lactams**3c***via* Pd-catalyzed monoarylation followed by intramolecular amination of *β*-C(sp^3)-H bonds of *N*-protected amino acids**3a** equipped with the easily removable 5-methoxy-8-aminoquinoline directing group (Scheme 1b).[12b]

In the year 2008, Yu's group disclosed the intramolecular C-N bond formation of *γ*-, *δ*-C(sp^2)-H bonds of benzamides **4a** to synthesise lactams **4b**, **4c** (Scheme 1c).[12d] The optimal reaction conditions involve 10 mol% of $Pd(OAc)_2$, 2 equiv of AgOAc, 1.5 equiv of $CuCl_2$ in DCE at 100 °C for 6 h. The activation of *γ*-C(sp^3)-H bonds of tri-substituted benzamides**4d** was performed to obtain valuable isoindolinone skeletons (Scheme 1c).[13b] The optimal reaction conditions involve 5 mol% of $Pd(OAc)_2$, 2.5 equiv of PIDA and an additive AcOH (5 equiv) in mesitylene at 120 °C for 24 h. Chen and co-workers disclosed the synthesis of pyrrolidones**4g** via palladium-catalyzed intramolecular amination of unactivated*γ*-C(sp^3)-H and C(sp^2)-H bonds (Scheme 1c).[13d]



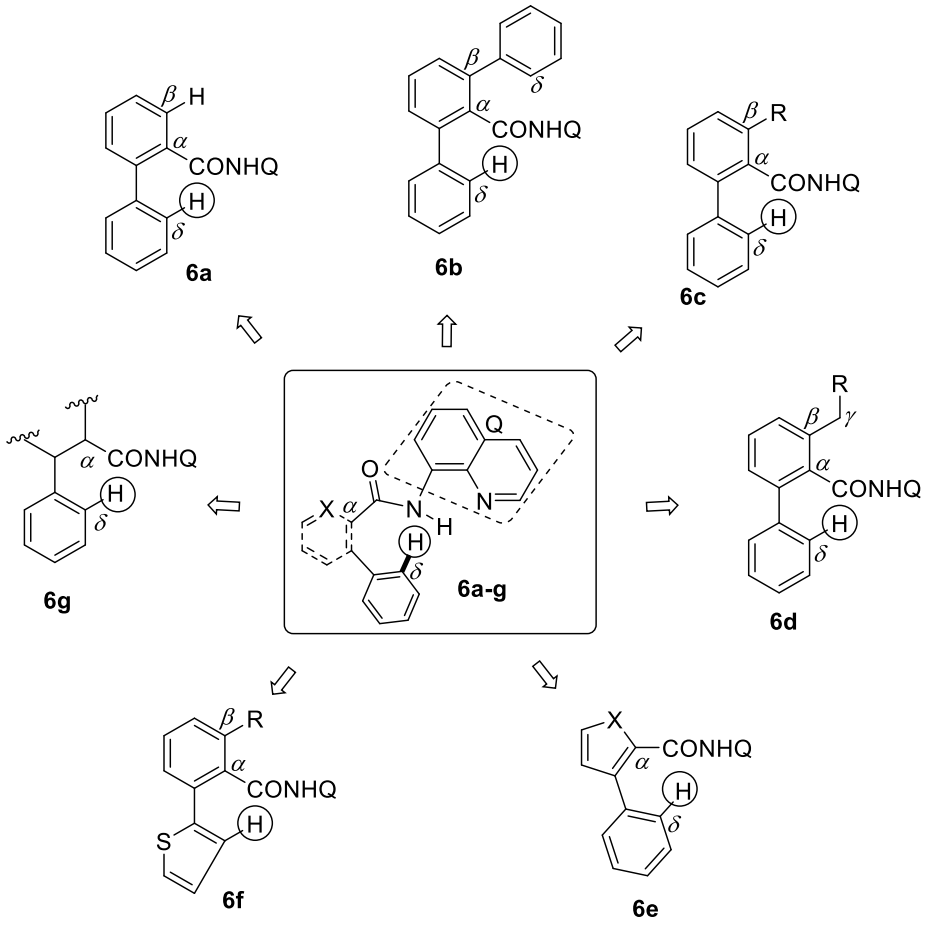
Scheme 1c. Pd-catalyzed*γ*-C-H activation of carboxamides and C-N bond formation.



Scheme 2. Pd-catalyzed*γ*-C-H activation of carboxamides and C-N bond formation

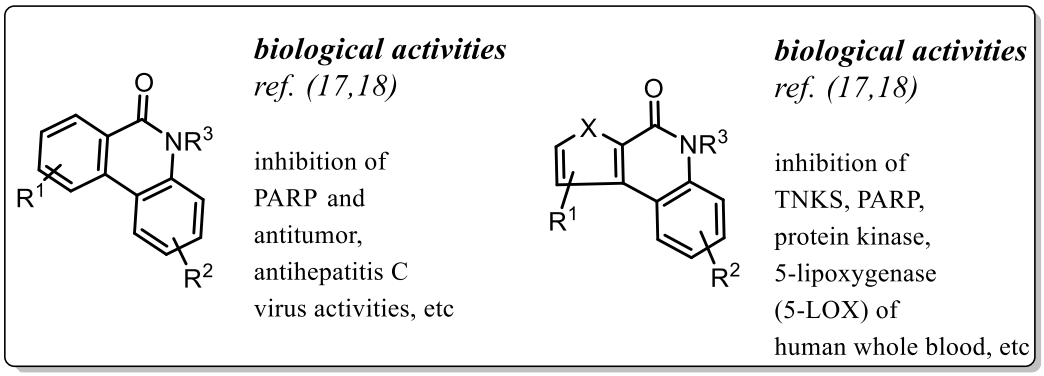
In the year 2016, Miura'sgroup reported the copper-catalyzed intramolecular C-H amination of 2-methyl benzamides **5a**to afford the medicinally valuable skeletons such as isoindolinones**5b**using MnO_2 as the terminal oxidant (Scheme 2). They described interesting mechanistic aspects based on the directing group employed in the reaction system. When 8-aminoquinoline serves as the directing group, Cu-mediated organometallic pathway is followed, whereas in case of naphthyl based carboxamides, aminyl radical promoted Hoffmann-Loffler-Freytag (HLF) type mechanism is observed.[13c]Zhao and co-workers revealed a versatile method for the synthesis of quinolinones **5e***via* sequential arylation of *β*-C(sp^3)-H and intramolecular amination of *δ*-C(sp^2)-H bonds under palladium catalysis. In order to activate the *δ*-C-H bond, the reaction is expected to proceed *via*a seven-membered palladacycle intermediate, for which the authors successfully found glycine dimethylamide (GDMA) as the suitable directing group (Scheme 2).[10]In the year 2017, our group reported the 8-aminoquinoline aided *γ*-C(sp^3)-H bond arylation followed by intramolecular amidation of 3-methylthiophene and furan 2-carboxamides**5f** in one pot manner leading to the construction of pyrrolidone ring annulated thiophene and furan scaffolds **5g**(Scheme 2).[13a]This work comprising the Pd(II)-catalyzed, 8-aminoquinoline-aided successive arylation

and intramolecular amidation of the remote γ-C-H bond of carboxylic acid substrates **5f** (Scheme 2) involvesthe generation of a plausible 6-membered palladacycle intermediate. Along with the other research groups,[14-16b] who contributed towards the C-H functionalization of amines,our group also reported the ε C-H functionalization.



Scheme 3. Substrates with suitably positioned sp^2δ-C-H bond.

Inspired from our previous work towards remote functionalizations,[13a,16c] we envisaged to investigate the BDG-aided δ-C-H functionalization of carboxylic acid substrates. Accordingly, herein we report the assembling of biaryl carboxamides (**6a-g**) with suitably positioned sp^2δ-C-H bond and investigations on the Pd(II)-catalyzedintramolecular amidation/annulations of the remote sp^2δ-C-H bond of biaryl carboxamides(**6a-g**, Schemes3). Notably, these reactions have led to the construction of various tricyclic quinolone (alkaloid)motifs such as, phenanthridin-6(5*H*)-one and thieno-/furo-/pyrrolo-[2,3-*c*]quinolin-4(5*H*)-one motifs.[17,18]



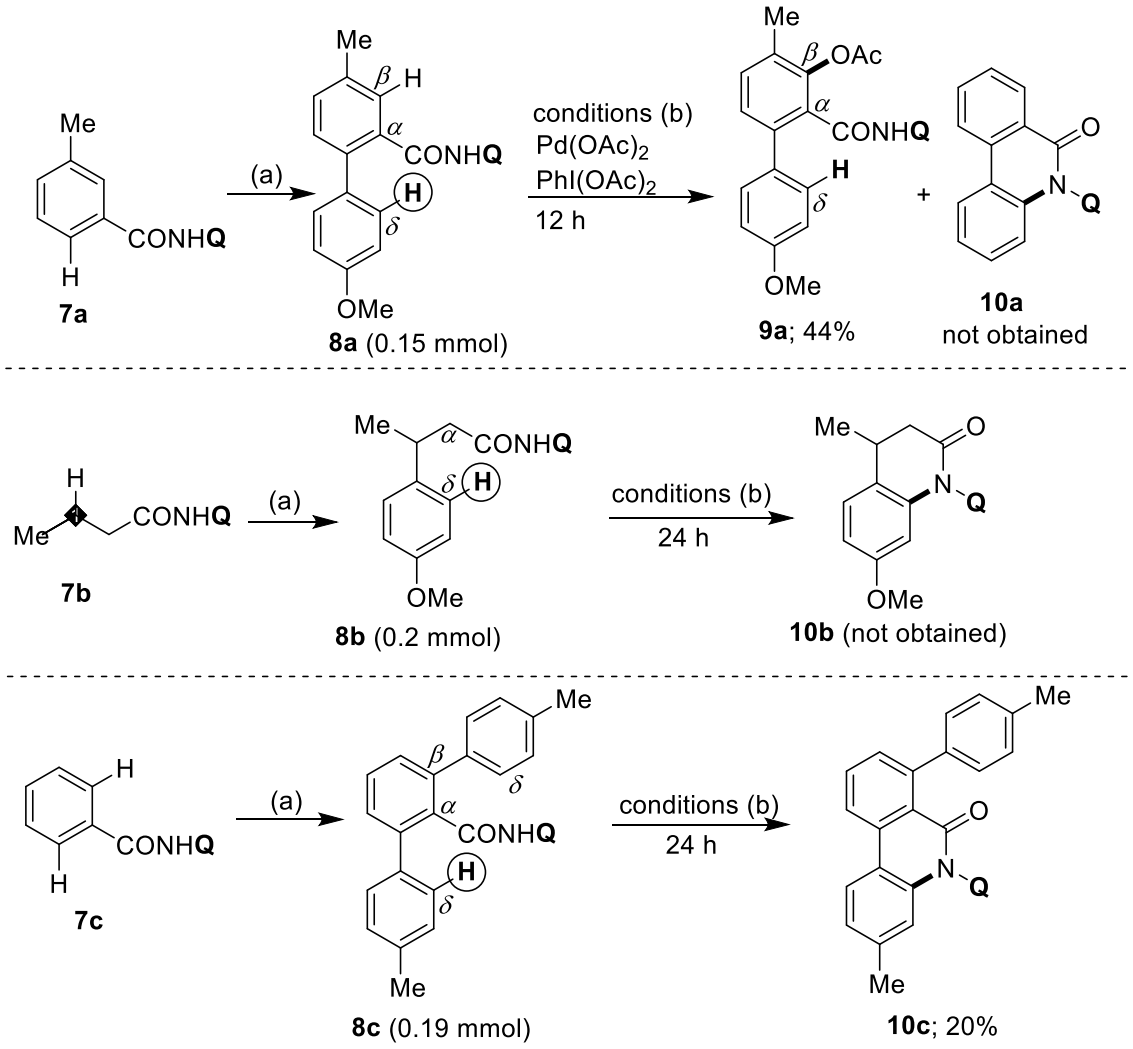
Scheme 4. Bio-active tricyclic quinolones and theme of this work.

Markedly, phenanthridin-6(5*H*)-one and thieno-/furo-/pyrrolo-[2,3-*c*]quinolin-4(5*H*)-one motifs are found in many natural alkaloids and pharmaceutically active molecules and many of them exhibited a wide range of biological activities (Scheme 4).[(17,18)]While diverse synthetic methods have been reported for their synthesis,nevertheless, the emphasis of this work is to demonstrate the BDG-aided functionalization/annulation of the sp^2*δ*-C-H bond of carboxylic acid substrates, especially, intramolecularamidationof carboxylic acid substrates using the carboxamides **6a-g** suitably positioned with the sp^2*δ*-C-H bond(Schemes2 and 3).

Results and Discussion

To begin with our investigations on the Pd(II)-catalyzed,BDG-aided intramolecular amidation/annulation of the sp^2*δ*-C-H bond ofcarboxamides, initially we assembled the carboxamides **8a-c** from **7a-c***via* the BDG 8-aminoquinoline (AQ)-aided *β*-C-H arylation reactions(Scheme 5).[(3a,6a)] Then, we attempted the Pd(II)-catalyzed, AQ-aided intramolecular amidation/annulation of the sp^2*δ*-C-H bond ofbiarylcarboxamide**8a** with PhI(OAc)$_2$(PIDA) as an oxidant.[(15,16)] This reaction gave the sp^2*β*-C-H acetoxylated product[(19)] **9a** in 44% yield instead of the sp^2*δ*-C-H amidation/annulation product **10a**. This reaction indicated that the substitution/acetoxylation of the *β*-C-H bond is a facile process than the intramolecular amidation of the sp^2*δ*-C-H bond.[(2,19)] Next, we attempted the intramolecular amidation of the sp^2*δ*-C-H bond of the carboxamide **8b,** which do not have the sp^2*β*-C-H bond but contains the sp^3*β*-C-H bond. However, this reaction failed to afford the expected product **10b** under the present experimental condition.[(10)] Then, we performed the intramolecular amidation of the sp^2*δ*-C-H bond of the biarylcarboxamide **8c**, which do not have the sp^2*β*-C-H bond. While the *δ*-C-H amidation/annulation was successful, but this reaction afforded the product **10c** in only 20% yield (Scheme 5). Notably, the sp^2*δ*-C-H amidation/annulations process which involves

a plausible 7-membered palladacycle intermediate might have been hampered by the structural complexity present in the bis *β*-C-H arylated carboxamide **8c**.

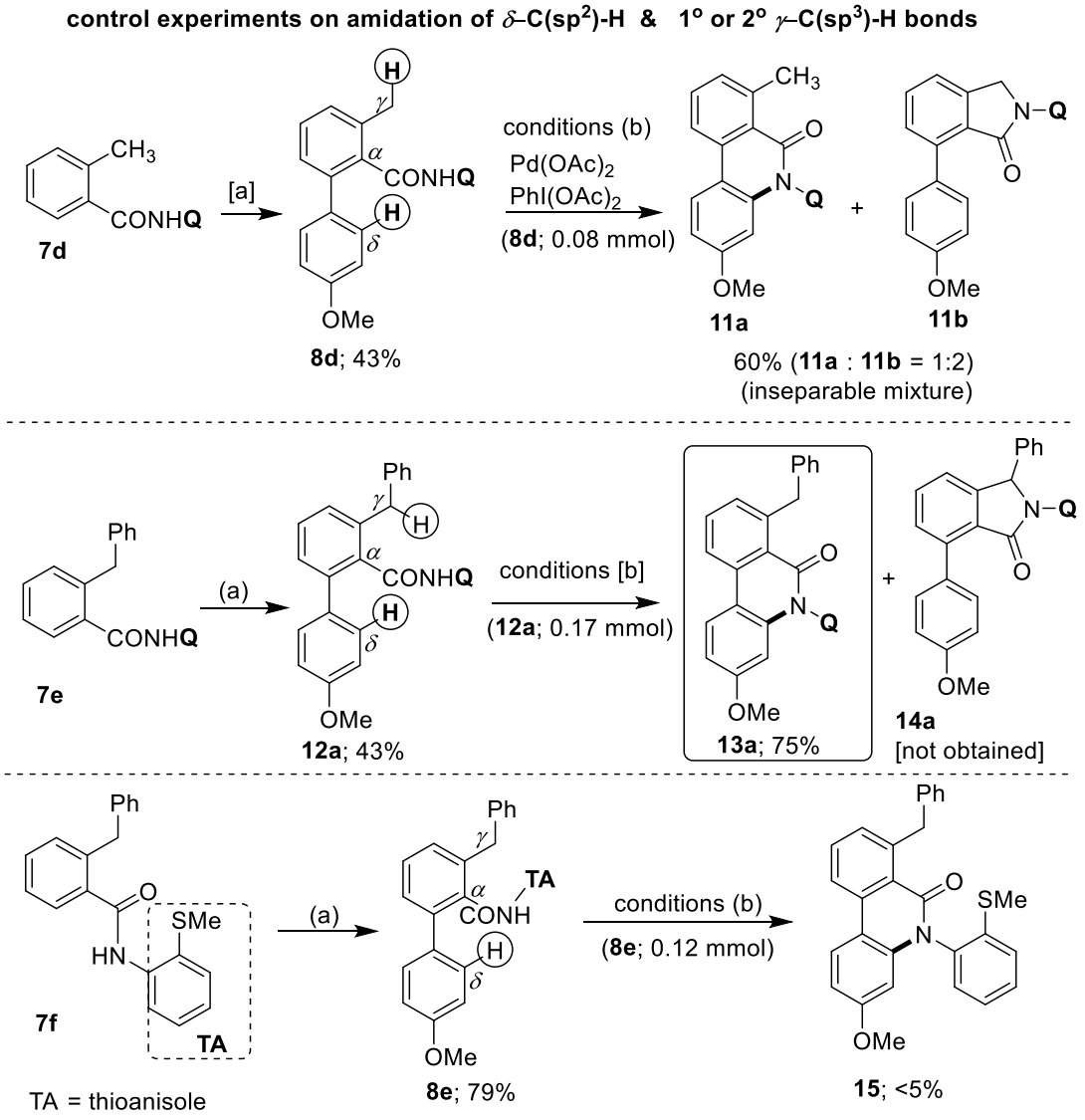


Reagents and conditions:(a) **7** (0.25 mmol),ArI (4 equiv), $Pd(OAc)_2$(10-20 mol%), AgOAc (2.2 equiv), toluene (2-3 mL), 110 °C,15-24 h.[2,21] (b) $Pd(OAc)_2$ (10 mol%, $PhI(OAc)_2$ (2.5 equiv), toluene (1.0 mL), 110 °C.

Scheme 5. Intramolecular amidationof **8a-c**.

We then intended to try the $sp^2\delta$-C-H amidation/annulations reaction using the mono *β*-C-H arylated carboxamides**8d** and **12a** and unlike the substrate **8c**, the substrates **8d** and **12a** haveanalkyl group (e.g., Me and Bn) at the *β*-position (Scheme 6). Accordingly, the biaryl carboxamides **8d** and **12a** were assembled from their corresponding starting materials **7d** and **7e***via* the *β*-C-H arylation reactions.[2] It is to be noted that the biaryl carboxamides **8d** and **12a** possess suitably positioned $sp^2\delta$- as well as $sp^3\gamma$-C-H bonds. At first, we attempted the intramolecular amidation/annulation of the $sp^2\delta$-C-H bond of **8d**, which afforded an inseparable mixture of the $sp^2\delta$-C-H amidation product **11a** and sp^3 *γ*-C-H amidation[13b-d,20] product **11b** (Scheme 6). Then, we attempted the intramolecular amidation/annulations of the

sp^2δ-C-H bond of **12a**. Fortunately, our endeavour for accomplishing the selective δ-C-H functionalization/amidation went right with the biaryl carboxamide **12a**, whichafforded the phenanthridin-6(5*H*)-one derivative**13a** in 75% yield (Scheme 6).



Reagents and conditions: (a)**7** (0.3 mmol), 4-iodoanisole (4 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.2 equiv), toluene (3 mL), 110 °C, 15 h.[2,5] (b) $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (1 mL), 110 °C, 24 h.

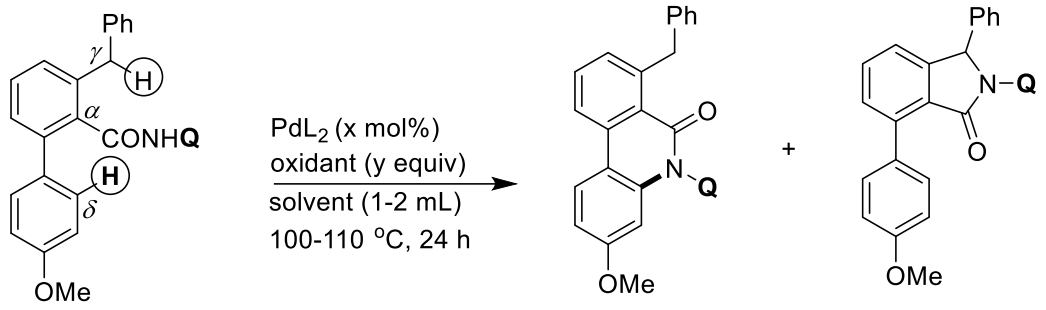
Scheme 6. Intramolecular amidation of **8d,e**/**12a**.

A literature survey revealed that the 1° C(sp^3)-H bond readily undergo the C-H functionalization than the 2° C(sp^3)-H bond.[2,4] Accordingly, the substrate **8d** afforded the corresponding amidation product **11b** *via* the C-H functionalization ofthesp^3γ-C-H bond[13b-d]and the product **11a** *via* the C-H functionalization/annulation ofthesp^2δ-C-H bond. Notably, unlike the substrate **8d**, the substrate **12a** did not afford the amidation product **14a** through the C-H functionalization ofthe(2°benzylic) sp^3γ-C-H bond.[5] This aspect has been addressed

with the relevant control experiments and have been shown in Table 1 and Scheme 7. Next, we also intended to test the intramolecular amidation of biaryl carboxamides with suitably positioned sp^2*δ*-C-H bondusing the 2-(methylthio)aniline[(2)] DG instead of the 8-aminoquinoline DG. Accordingly, we assembled the substrate **8e** (similar to **12a**) from **7f** and it is to be noted that the intramolecular amidation of the sp^2*δ*-C-H bond of**8e** possessing the 2-(methylthio)aniline DG was not fruitful (Scheme 6).

Motivated by the successful attempt on the Pd(II)-catalyzed*δ*-C-H functionalization/amidation reaction of the biaryl carboxamide substrate **12a**, next we performed the optimization of reaction conditions. Accordingly, the Table 1 shows the results of the intramolecular amidation/annulations of the *δ*-C-H bondinvolving the substrate **12a** in the presence of various oxidants and palladium catalysts. The reaction of **12a** with PIDA (2 equiv) and $Pd(OAc)_2$(5 mol%) in toluene at 110 ^oC for 24 h afforded the product **13a** in 20% yield (entry 1, Table 1). The same reaction at rt or without $Pd(OAc)_2$ failed to afford the product **13a** (entries 2 and 3, Table 1). The substrate **12a**was treated withdifferent equiv of PIDA(entries 4-7, Table 1). The reaction of **12a** with 2.5 equiv of PIDA and $Pd(OAc)_2$(10 mol%) found to afford the product **13a** in a maximum of 75% yield (entry 6, Table 1). Notably, the excess use of PIDA gave the product **13a** in low yield and this may be due to some over-reaction. The reaction of **12a** in the presence of the $Pd(TFA)_2$catalyst was not fruitful and the $PdCl_2$-catalyzedreactionof **12a**afforded the product**13a** in 47% yield (entries 8 and 9, Table 1). The reaction of**12a** in 1,4-dioxane solvent afforded the product **13a** in 60% yield and the reactions in other solvents were not fruitful (entries 10-13, Table 1). The usage of other oxidants did not afford the product **13a** (entries 14-17, Table 1).

Table 1. Optimization reactions. Pd(II)-catalyzed*δ*-C-H amidation/annulation of **12a**.



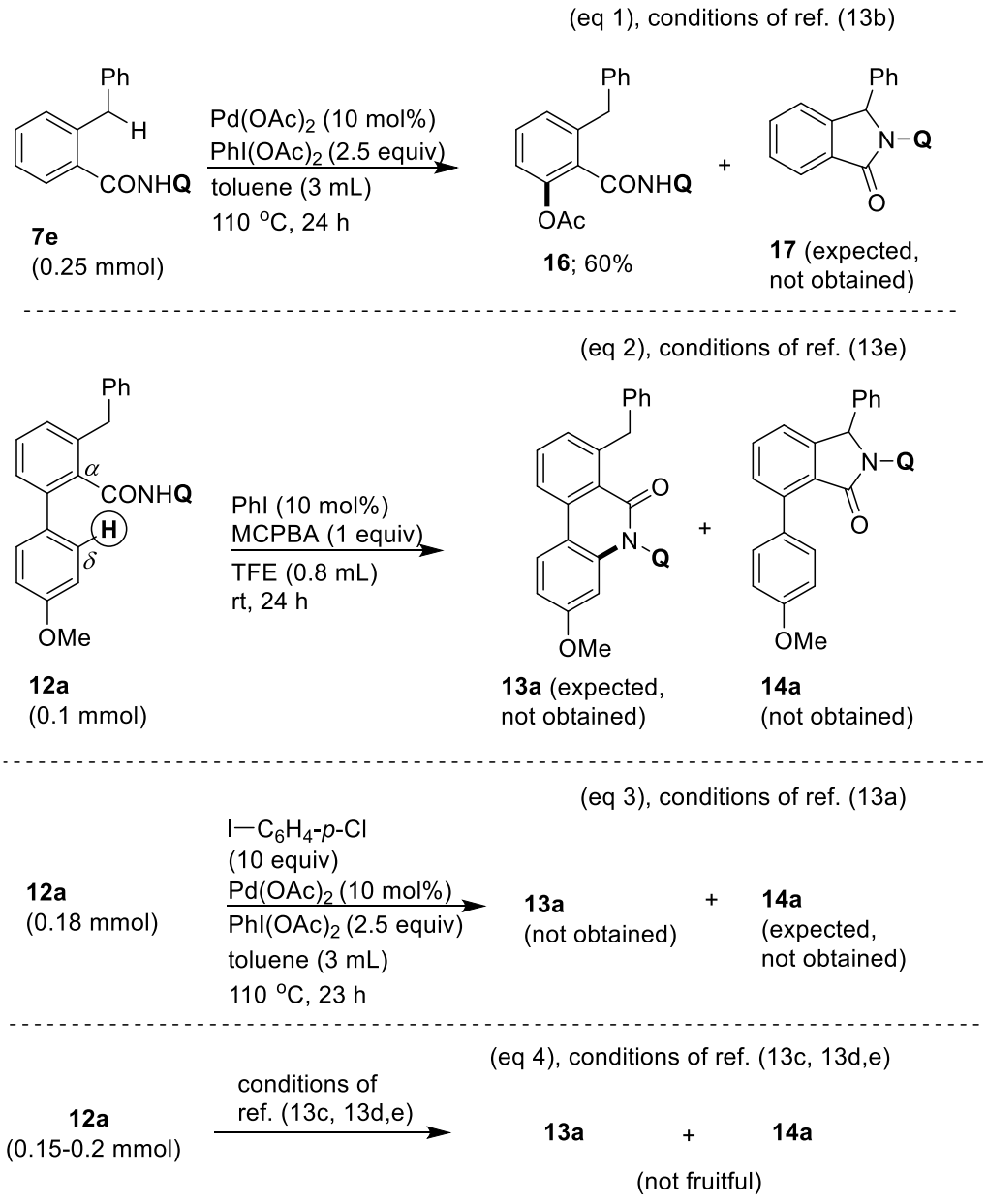
12a [0.15 mmol] **13a** **14a** [not obtained]

entry	PdX_2 (x mol%)	oxidant (y equiv)	solvent (mL)	**13a**: yield (%)
1	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2)	toluene (2)	20
2	nil	$PhI(OAc)_2$ (2)	toluene (2)	-
3[(a)]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	toluene (2)	-
4	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1)	toluene (2)	24
5[(b)]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	toluene (2)	67
6	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.5)	toluene (1)	75
7	$Pd(OAc)_2$ (10)	$PhI[OAc]_2$ (3)	toluene (2)	38
8	$Pd(TFA)_2$ (10)	$PhI(OAc)_2$ (2)	toluene (2)	traces
9	$PdCl_2$ (10)	$PhI(OAc)_2$ (2)	toluene (2)	47
10	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	AcOH (2)	-
11	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	^{t}amylOH (2)	traces
12	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	1,4-dioxane (2)	75
13	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	$AcOH/Ac_2O$ (1:1)	-
14	$Pd(OAc)_2$ (10)	AgOAc (2)	toluene (2)	-
15	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2)	toluene (2)	-
16	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2)	toluene (2)	traces
17	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2)	DMF (2)	-

(a) The reaction was performed at rt. (b) The reaction was done using 0.1 mmol of **12a.** No other side products were isolated in all the above reactions. $PhI(OAc)_2$ = PIDA (phenyliodine(III) diacetate).

Though the biaryl carboxamide **12a** contains both the $sp^2\delta$- and sp^3 γ-C-H bonds, the results of the Table 1 indicated that the Pd(II)-catalyzed intramolecular amidation of **12a** selectively afforded the $sp^2\delta$-C-H amidation/annulation product **13a**. The corresponding sp^3 γ-C-H amidation product **14a** (indolinone derivative) was not obtained from none of the reaction conditions shown in the Table 1. While the sp^3 γ-C-H amidation reactions affording indolinone derivatives have been reported in the literature,[(13)] we intended to check whether the indolinone derivative **14a** can be obtained under the present and some of the reaction

conditions reported in the literature.[13,18k] In this regard, at first, we treated the substrate **7e** with the present reaction conditions (similar to the entry 6, Table 1) including PIDA and $Pd(OAc)_2$ catalyst. This reaction afforded the $sp^2\beta$-C-H acetoxylated product **16** in 60% yield. Though **7e** contains the sp^3 γ-C-H bond, the reaction of **7e** selectively afforded the $sp^2\beta$-C-H acetoxylated product **16** than the sp^3 γ-C-H intramolecular amidation product **17** (Scheme 7). This reaction indicated that the formation of indolinone derivative is not a facile reaction *via* the sp^3 γ-C-H intramolecular amidationof**7e,** this aspect is similar with what we observed with **12a**(Table 1).



Scheme 7. Pd(II)-catalyzed C-H amidation of **7e** and **12a**.

Next, additional control reactions were also performed to check whether sp^3 γ-C-H intramolecular amidation product **14a** can be obtained using some other conditions reported in the literature, however, the trials were not fruitful (Scheme 7). Accordingly, the optimization and control reactions involving substrates **8a** and **7e** have indicated thatthe functionalization of the β-C-H bond is a favored process than the corresponding remote $sp^2\delta$- and sp^3 γ-C-H bonds. From the reactions involving the substrates **7e** and **12a**, it was also observed that the functionalization of the sp^2 C-H bond is a favored process than the functionalization of the sp^3 γ-C-H bond. Along this line, we noted that theremote$sp^2\delta$-C-H amidation was found to be a favored reaction than the sp^3 γ-C-H amidation.

Having the optimized reaction condition in handfor the intramolecular amidation/annulations of the $sp^2\delta$-C-H bond of **12a**, next we wished to explore the substrate scope of this protocol. In this regard, we assembled various biaryl carboxamides **12a-j** from the substrate **7e***via* the AQ-aided β-C-H arylation reaction (Scheme 8).[(2)] We thenperformed the Pd(II)-catalyzed, AQ-aided intramolecular amidation of the $sp^2\delta$-C-H bond of the biarylcarboxamides **12a-j**withPIDA and these reactionsgavethe corresponding phenanthridin-6(5*H*)-one derivatives **13a-h,j** in 21-84% yields (Scheme 9). The product **13j** was obtained in only 21% yield and the product **13i** was not obtained from their corresponding carboxamides **12j** and **12i**, and an exact reason for these poor results is not known at this stage. The structure of the compounds **13a-h,j** obtained from the Pd(II)-catalyzedintramolecular amidation/annulations of **12a-h,j**were unequivocally confirmed by the X-ray structure of the representative phenanthridin-6(5*H*)-one derivative**13a** (Figure 1).

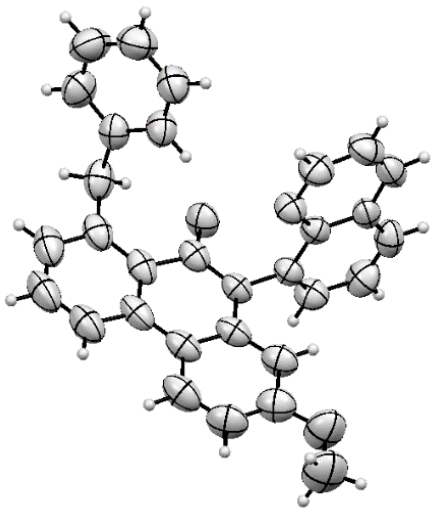
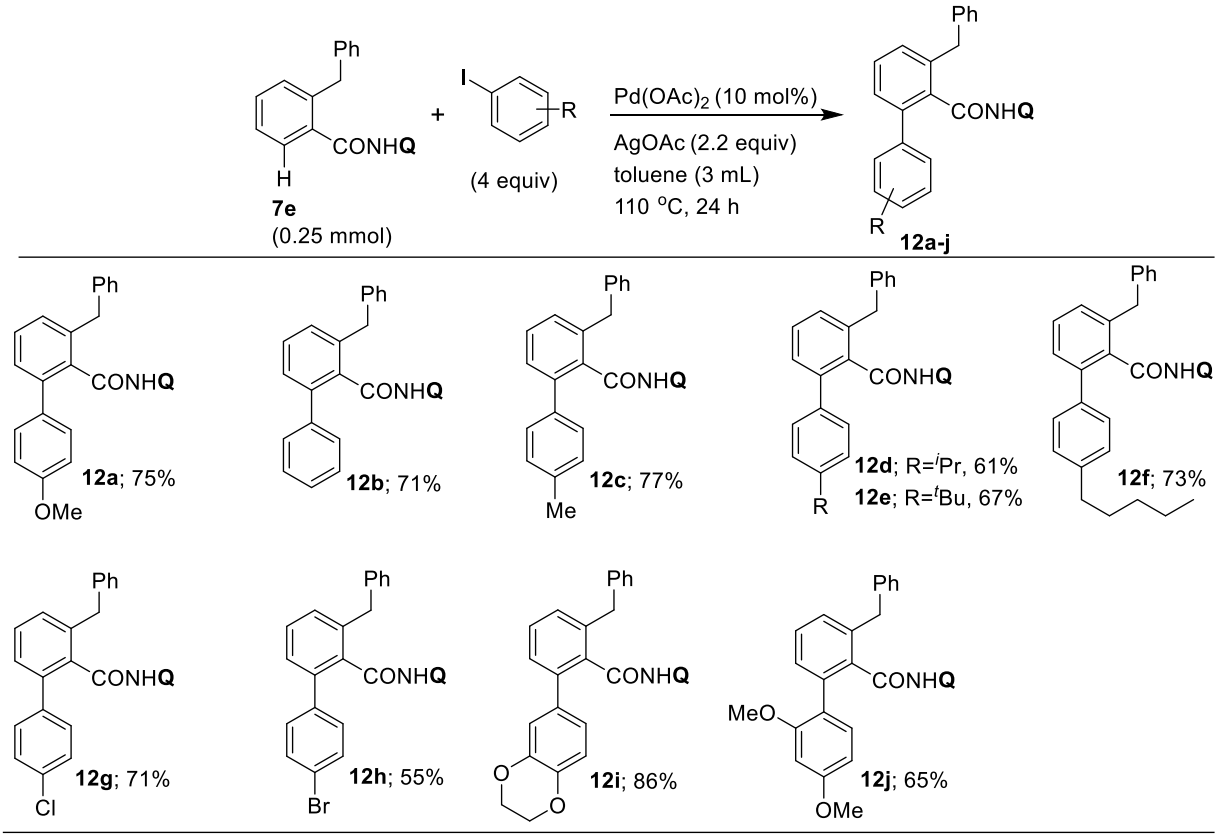
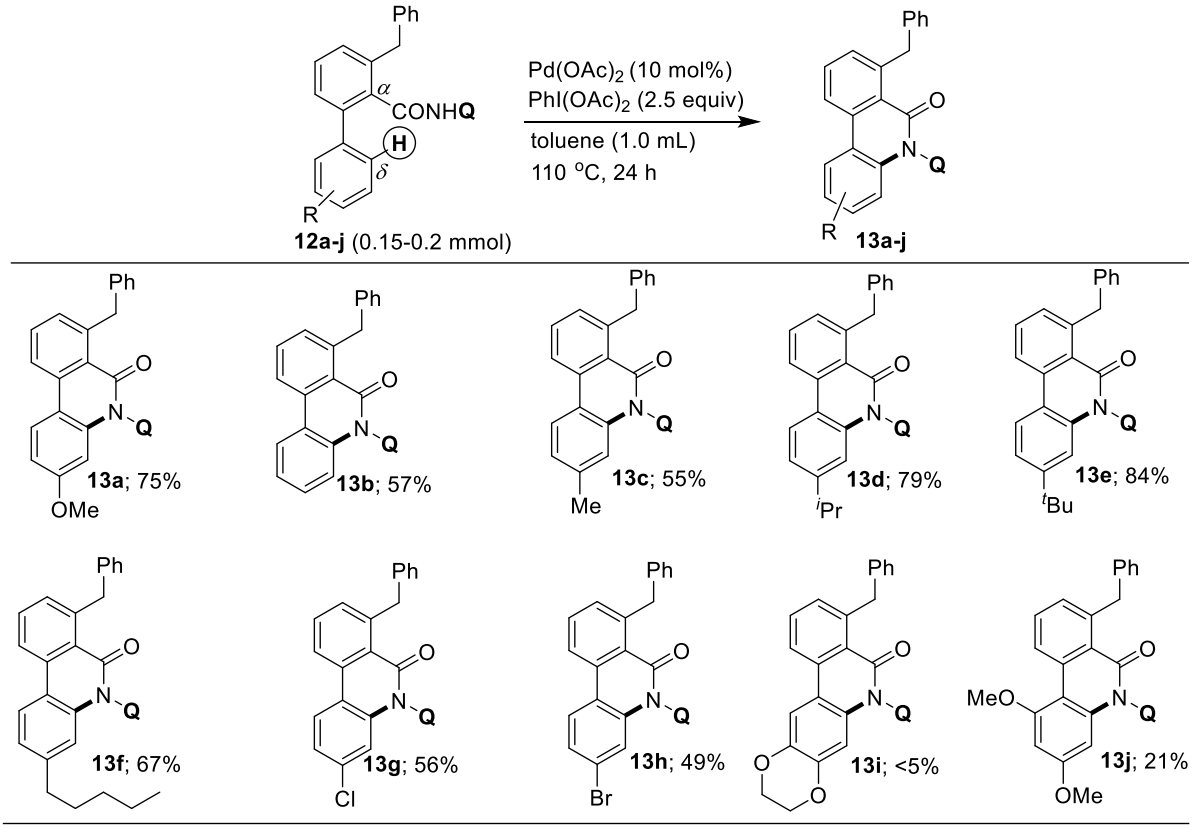


Fig 1. X-ray [ORTEP] structure of the compound **13a**.



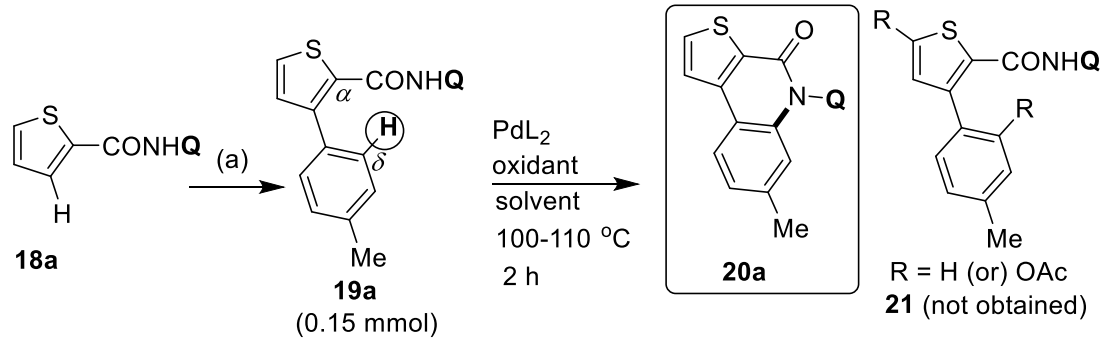
Scheme 8. Assembling of **12a-j** suitably positioned with the sp^2 δ-C-H bond *via* the AQ-aided β-C-H arylation.



Scheme 9. The Pd(II)-catalyzed, AQ-aided intramolecular amidationof **12a-j**.

Next, we intended to elaborate the scope of this method and assemble various thieno[2,3-*c*]quinolin-4(5*H*)-one motifs *via* the Pd(II)-catalyzed, AQ-aided intramolecular amidation/annulation. At first, we assembled the biaryl carboxamide **19a** from **18a***via* the Pd(II)-catalyzed, AQ-aided *β*-C-H arylation of **18a**(Table2). Then, we attempted the Pd(II)-catalyzed, AQ-aided intramolecular amidation/annulation of**19a** with PIDA (Table 2). The Table 2 shows the results of the optimization reactions involving**19a** in the presence of various oxidants, palladium catalysts and solvents. Amongst the optimization reactions performed, the reaction of **19a** with 2.5 equiv of PIDA and $Pd(OAc)_2$(5 mol%) found to afford the thieno[2,3-*c*]quinolin-4(5*H*)-onederivative**20a** in a maximum of 94% yield (entry 2, Table 2). It is to be noted that the C(2)/C(5)-H bond of thiophene/furan systems is known to undergo the direct C-H functionalization (e.g., arylation and acetoxylation).[1h,16c,21f] However, the other possible by-product e.g., the C-H acetoxylatedproduct **21** was not obtained from **19a** under the present experimental conditions.

Table 2. Optimization reactions. The Pd(II)-catalyzed intramolecular amidation of **19a**



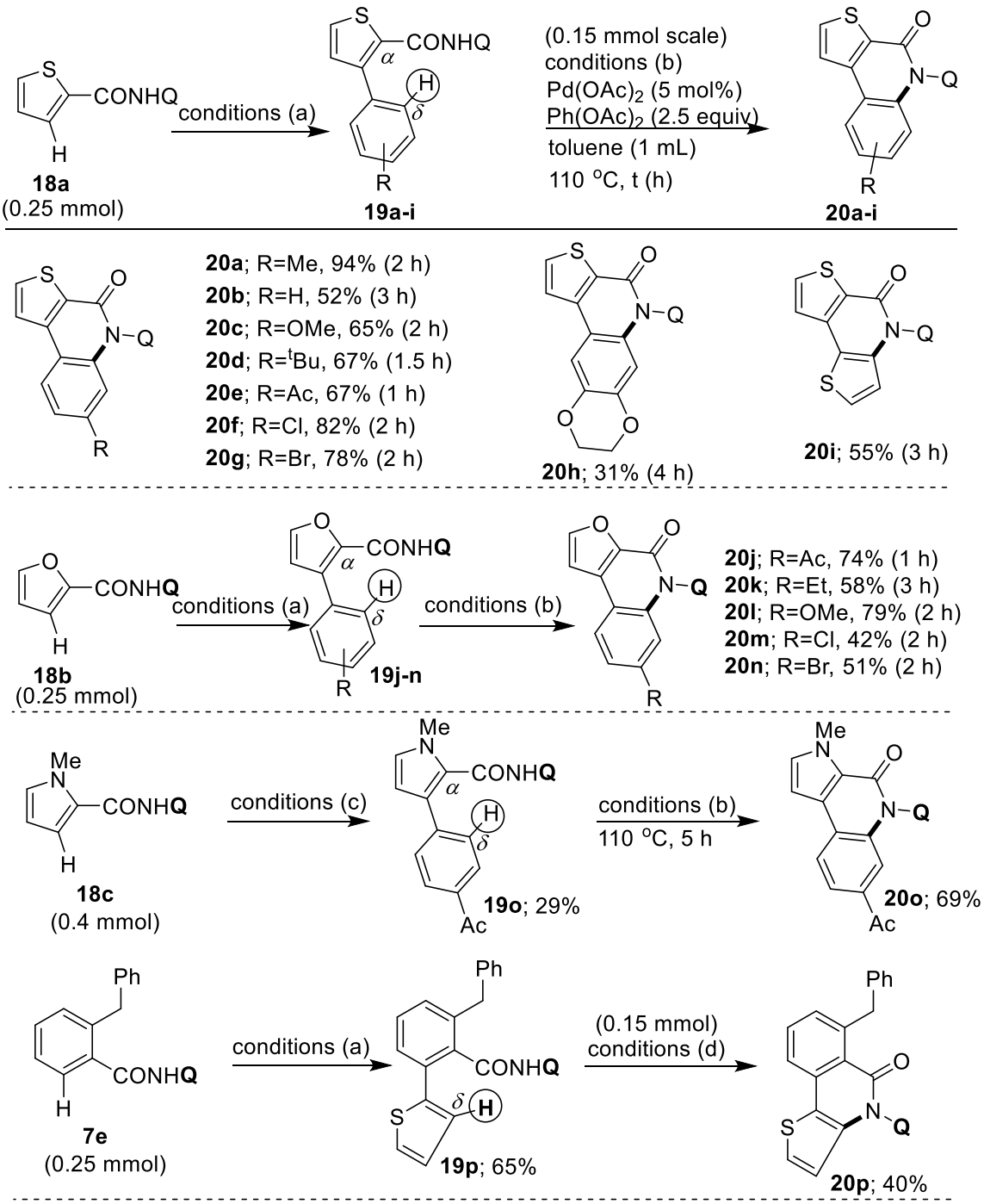
entry	PdL_2 (x mol%)	oxidant (y equiv)	solvent (mL)	**20a**: yield (%)
1	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.5)	toluene (1)	69
2	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	toluene (1)	94
3	$Pd(OAc)_2$ (3)	$PhI(OAc)_2$ (2.5)	toluene (1)	66
4	nil	$PhI(OAc)_2$ (2.5)	toluene (1)	-
5	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2)	toluene (1)	62
6	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (3)	toluene (1)	70
7	$Pd(OAc)_2$ (5)	AgOAc (2.5)	toluene (1)	traces
8	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (2.5)	toluene (1)	-
9	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2.5)	toluene (1)	traces
10	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	AcOH / Ac_2O (1:1)	-
11	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	1,4-dioxane (1)	64
12	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	^{t}amylOH (1)	traces
13	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	AcOH (1)	-
14	$PdCl_2$ (5)	$PhI(OAc)_2$ (2.5)	toluene (1)	-
15	$Pd(TFA)_2$ (5)	$PhI(OAc)_2$ (2.5)	toluene (1)	-

Reagents and conditions: (a) ArI (4 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.2 equiv), toluene (3 mL), 110 °C, 20 h.[21f] $PhI(OAc)_2$ = PIDA (phenyliodine(III) diacetate).

Next, to extend the substrate scope, we assembled various thiophene-based biaryl carboxamides **19a-i** from **18a***via* the AQ-aided *β*-C-H arylation of **18a**(Scheme 10). Then, the Pd(II)-catalyzed, intramolecular amidation/annulation of various biarylcarboxamides **19a-i** with PIDA successfully afforded various thieno[2,3-*c*]quinolin-4(5*H*)-onemotifs**20a-I** in 31-94% yields (Scheme 10).We also assembled various furan and pyrrole-based biaryl carboxamides **19j-n** and **19o***via* the AQ-aided *β*-C-H arylation of **18b**and **18c**, respectively(Scheme 10). Then, the Pd(II)-catalyzed, intramolecular amidation/annulation ofthe biaryl carboxamides **19j-n**and **19o** with PIDA afforded the correspondingfuro- and

pyrrolo[2,3-*c*]quinolin-4(5*H*)-onemotifs **20j-n**and **20o**in 42-79% yields. Additionally, we attempted the Pd(II)-catalyzed, intramolecular amidation/annulations of the thiophene ring ofthe carboxamide **19p** with PIDA, which afforded the thieno[3,2-*c*]isoquinolin-5(4*H*)-one motif**20p** in 40% yield (Scheme 10).

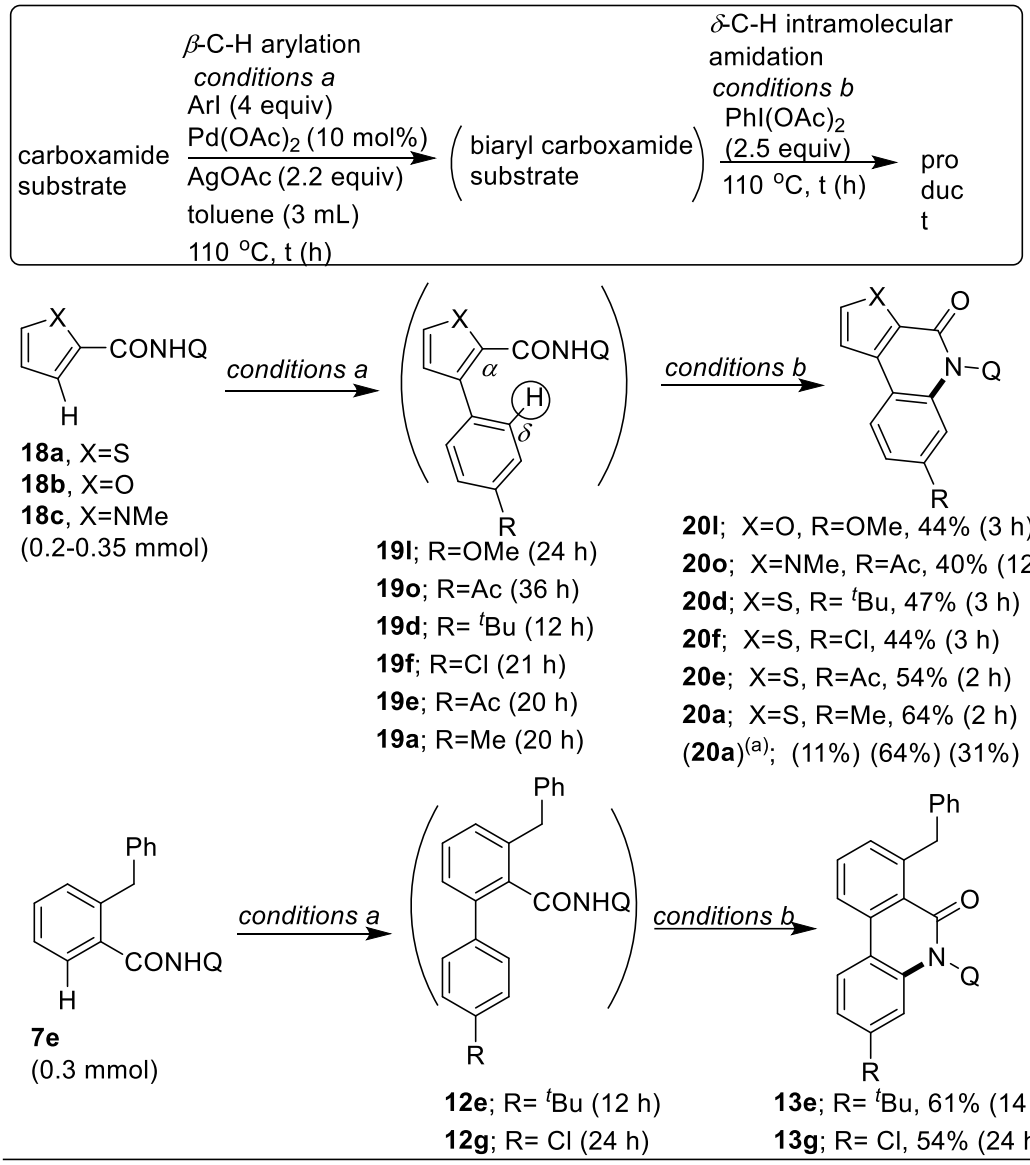
Having done the assembling of biaryl carboxamides **12** and **19***via* the AQ-aided *β*-C-H arylation and intramolecular amidation of the carboxamides **12** and **19**as separate reactions in different flasks, later we also envisioned to attempt theassembling of the required biaryl carboxamides**12**/**19***via* the *β*-C-H arylation and the successive intramolecular amidation/annulation of **12**/**19**in one-pot reaction conditions (Scheme 11).In this regard, the carboxamides**18a-c**and **7e** wereindependently subjected to the *β*-C-H arylation with different aryl iodides in the presence of the $Pd(OAc)_2$ catalyst in toluene for 12-36 h (an appropriate reaction period based on the optimization reactions reported earlier by us).[21f] After the initial arylation reaction period, the PIDAreagent was added to the crude reaction mixture containing the corresponding carboxamides **19a,d-f,l,o** and **12e,g**suitably positioned with the sp^2*δ*-C-H bond, and the reactions were continued in the same flasks with no additional $Pd(OAc)_2$ catalyst. Theseone-pot reaction processeshave afforded the corresponding products **20a,d-f,l,o** and **13e,g** in 40-64% yields (Scheme 11). While the corresponding products **20a,d-f,l,o** and **13e,g** were obtained in moderate yields, notably, the same DG is successively assisting the *β*-C-H arylation and the intramolecular amidation/annulation reactions and the one-pot process also has the following advantages that addition of additional amounts of the $Pd(OAc)_2$ catalyst and purification of the corresponding biaryl carboxamides**12**/**19**have been avoided.



Reagents and conditions: (a) ArI (4 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.2 equiv), toluene (2-3 mL), 110 °C, 12-30 h.[21f](c) 1-(4-bromophenyl)ethanone (1.2 equiv), $(RuCl_2$ (*p*-cymene)$)_2$ (10 mol%), Na_2CO_3 (2 equiv), PPh_3 (0.5 equiv), toluene (2 mL), 140 °C, 36 h.[21g](d) $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (1 mL), 110 °C, 24 h.

Scheme 10. Pd(II)-catalyzed, AQ-aided intramolecular amidation of **19a-i, 19j-n, 19o** and **19p**.

successive β-C-H arylation and δ-C-H intramolecular amidation reaction in one-pot



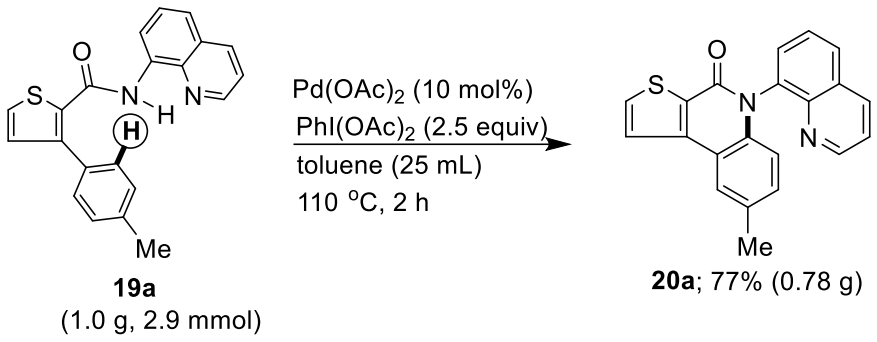
(a) The yields correspond to the usage of 1.5 equiv, 2 equiv and 3 equiv of $PhI(OAc)_2$, respectively.

Scheme 11. Successive β-C-H arylation and $sp^2\delta$-C-H intramolecular amidation/annulations reactions in one-pot.

A gram-scale reaction comprising the Pd(II)-catalyzed, AQ-aided intramolecular amidation/annulations of biaryl carboxamide **19a** with PIDA was performed, which afforded the product**20a** in 77% yield (Scheme 12). Later, we performed some control experiments to explicate the reaction mechanism and the role of 8-aminoquinoline DG in the intramolecular amidation/annulations of the $sp^2\delta$-C-H bond of the carboxamides **8c**, **12** and **19**. In this regard, initially, we performed the Pd(II)-catalyzed, intramolecular amidation/annulation of**19a** with the PIDAreagent in the presence of oneequiv of TEMPO, which gave the product**20a** in 67% yield (Scheme 13). In concurrence with the literature reports, this reaction

indicated that perhaps the sp^2δ-C-H intramolecular amidation/annulations of the substrates **12** and **19**did not proceed *via* the single electron transfer (SET) or free radical pathway.[21,16c]

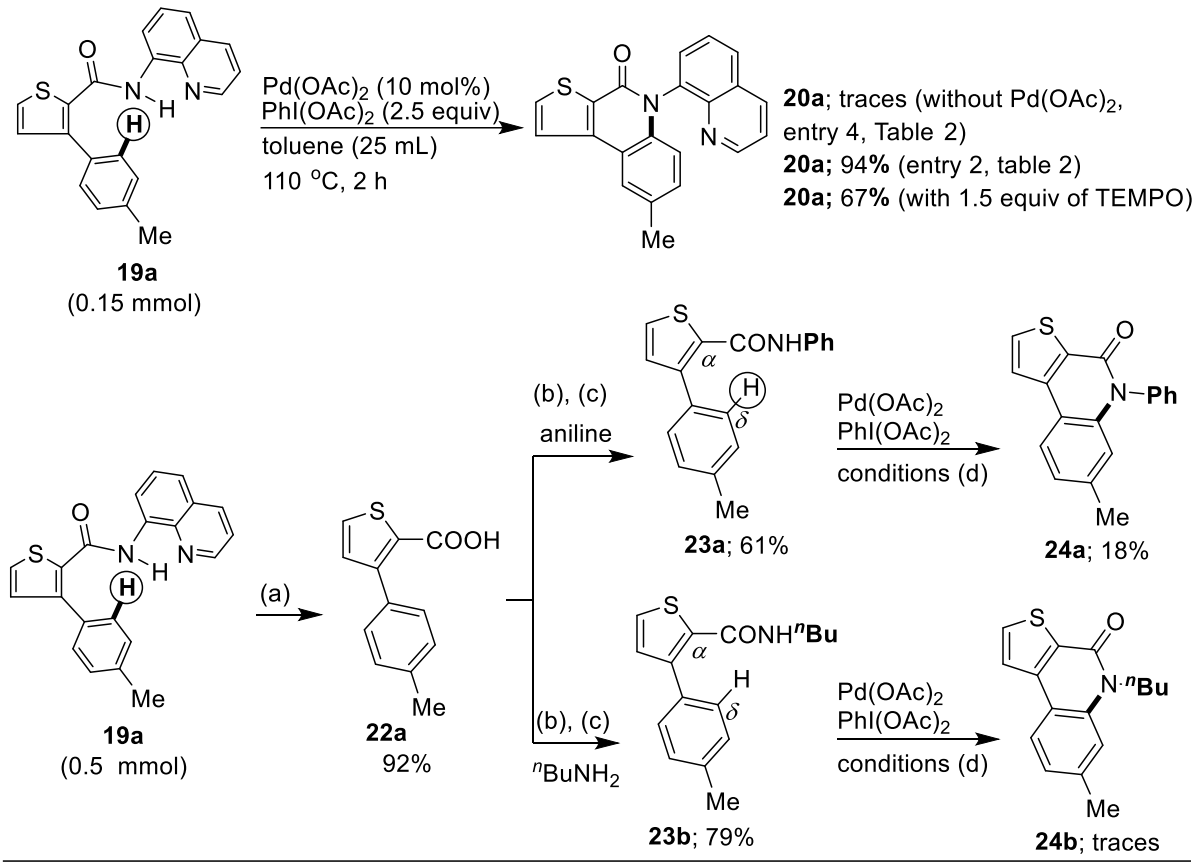
Next,we assembled the biaryl carboxamides **23a** and **23b** from the carboxylic acid **22a**, aniline or *n*-butylamine, respectively. The carboxamides **23a** and **23b** were subjected to the Pd(II)-catalyzed sp^2δ-C-H intramolecular amidation/annulation reaction conditions (Scheme 13). While the substrate**23a** afforded the product **24a** in only 18% yield and however, the substrate **23b** failed to afford the product **24b** (Scheme 13). Unlike the results obtained from the substrates **12** and **19**, the discouraging results noted from the carboxamides **23a** and **23b**might be due to the absence of the 8-aminoquinoline DG in **23a** and **23b**. Accordingly, the simple amide group present in the carboxamides **23a** and **23b** did not effectively assist the sp^2δ-C-H intramolecualramidation/annulation process (Scheme 13). It is to be noted that the phenanthridin-6(5*H*)-one and thieno-/furo-/pyrrolo-[2,3-*c*]quinolin-4(5*H*)-one motifs**13**/**20**are tertiary amides and the 8-aminoquinoline's amino group *N* atom has become a part of the motifs **13**/**20**, our several attempts to remove the quinoline part from motifs**13**/**20**under various reportedconditions[2,3] were not fruitful at this stage. While we understand that the removal of the quinoline part will extend the practical applicability of the method, we have tried various possibilities, which were ineffective and will continue with our efforts to remove the quinoline part from the motifs**13**/**20**and assure to report once we succeed with our trials.



19a
(1.0 g, 2.9 mmol)

20a; 77% (0.78 g)

Scheme 12.Gram scale reaction.



Reagents and conditions: (a) NaOH (24 equiv), EtOH (6 mL), 80 °C, 12h (b) For a scale of **22a** (0.5 mmol); $SOCl_2$ (9 equiv), rt, 12h. (c) amine (0.9 equiv), Et_3N (1.1 equiv), DCM (3 mL), rt, 12 h. (d) **23a, b** (0.45 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (2 mL), 110 °C, 3 h.

Scheme 13. Control experiments.

Conclusions

In conclusion, we have demonstratedtheinvestigationsof the Pd(II)-catalyzed 8-aminoquinolineDG-aidedsp$^2\delta$-C-H functionalization/annulation of different carboxamides. We assembledsome possible carboxamide substrates **8a-e**, **12a-j** and **19a-p** with suitably positioned sp$^2\delta$-C-H bond and these carboxamides werethensubjected to thePd(II)-catalyzedsp$^2\delta$-C-H intramolecularamidation/annulation in the presence of the PIDA reagent. While the carboxamides **8a,b,d,e**did not undergo thesp$^2\delta$-C-H intramolecular amidation/annulation, the biaryl carboxamides **8c**, **12a-j** and **19a-p**underwent the sp$^2\delta$-C-H intramolecular amidation/annulation. These reactions have led to the construction of various tricyclic quinolone(alkaloid)motifs such as,phenanthridin-6(5*H*)-one and thieno-/furo-/pyrrolo-[2,3-*c*]quinolin-4(5*H*)-ones. The structure of a representative phenanthridin-6(5*H*)-one derivative **13a**was unequivocally confirmed by the X-ray structure analysis.[23] Unlike the DG-aided *β*- or*γ*-C-H functionalization,the DG-aided sp$^2\delta$-C-H functionalization of

carboxylic acid substrates are less explored in the literature. Accordingly, the present work comprising the $sp^2\delta$-C-H functionalization/annulations biaryl carboxamides will be a contribution towards the development of functionalization of the remote C-H bond. Further, given the importance of phenanthridin-6(5*H*)-one and thieno-/furo-/pyrrolo-[2,3-*c*]quinolin-4(5*H*)-one motifs in medicinal chemistry research,[17] in addition to the pioneering reports available, the present work will be an additional approach towards diverse tricyclic quinolone (alkaloid)motifs.

All the compounds included in this chapter are characterized by different techniques including ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data and experimental details of all the compounds are given in the experimental section.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra of compounds were recorded (using TMS as an internal standard) in 400 and ~101 MHz spectrometers, respectively. The HRMS analysis data of samples reported here were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. IR spectra of samples reported here were recorded as neat or thin films. Column chromatography purification was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atm wherever required. Organic layers obtained after workup were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel or alumina plates and components were visualized by observation under iodine vapor. Isolated yields of all the products are reported and yields were not optimized. In all of the cases, after the Pd(II)-catalyzed reactions, the respective crude reaction mixtures were subjected to the column chromatographic purification. Then,the fractions were collected according to the TLC; in all of the cases, we focused to isolate the corresponding $sp^2\delta$-C-H intramolecular amidation products reported here to the best of our effort. We did not isolate any of the corresponding acetoxylated products in characterizable amounts during the column chromatographic purification. The corresponding carbonyl chlorides (which were required to assemble the carboxamides **7a-d,7f** and **18a-c**) were assembled using the standard literature procedures[2,13a,21f,h]involving the reaction of the corresponding carboxylic acids with thionyl chloride or oxalyl chloride.

The compounds **11a** and **11b** were obtained as an inseparable mixture and their full characterization data could not be presented and their structures were entrusted based on the

NMR and mass data of the corresponding mixture. For the compounds **13a-c,f-j**, ABq type signals were observed for the benzylicmethylene group, which indicated that the benzylicmethylene group protons are diastereotopic. On the other hand, for the compounds **13d,e** singlet signals were observed for the benzylicmethylene group. These observations indicated that presumably some of these compounds/species may exist as atropisomers.

The compounds **7a**,[21a,22a] **7b**,[6a,24b] **7c**,[21d,22c] **7d**,[21a,22c] **7e**,[21e] **8a**,[21g] **8b**,[3j] **8c**,[21d] **8d**,[21d] **18a**,[21f] **18b**,[21f] and **18c**[21b,21g]are reported in the literature. The compound **12b**[21e] is reported in the literature and we preparedfrom **7e** in 71% (69 mg) yield. Similarly, the compounds **19b**,[21c] **19c**,[21f] **19e**,[21f] **19i**,[21f] **19j**,[21f] and **19l**[21f] are reported in the literature. The compounds **19b** (54% yield, 53 mg), **19c** (78% yield, 70 mg), **19e** (70% yield, 65 mg), **19i** (54% yield, 64 mg), **19j** (67% yield, 60 mg) and **19l** (59% yield, 61 mg) were obtained from**18a,b**.The compound **7e**[21e] was reported in the literature and it was prepared from 2-benzylbenzoic acid and 8-aminoquinoline.

Typical procedure for the synthesis of the carboxamide 7e:

To a solution of 2-benzylbenzoic acid (1 mmol, 212 mg) in dry dichloromethane (4-5 mL), 1-hydroxy benzotriazole hydrate (1.1 mmol, 168 mg) and 1,3-dicyclohexylcarbodiimide (1.1 mmol, 226 mg) were added at 0 ^{o}C under a nitrogen atm. The suspension was warmed to rt and stirred for 1 h. Then, 8-aminoquinoline (0.9 mmol, 130 mg) was added and the mixture was stirred for 24 h at rt. After this period, the resulting suspension was filtered through a celitepad and then, the water (2-3 mL) was added to the filtrate, extracted with chloroform or DCM (3x3 mL), and washed with brine solution. Then, the combined organic layers were evaporated. The resulting crude reaction mixture was purified by silica gel column (100-200 mesh, eluent = EtOAc:hexanes) to afford **7e** in 50% (169 mg) yield.

General procedure for the synthesis of the carboxamides 7a-d,7fand18a-c:[2,13a,21f,h]

A dry RB flask containing amine (1 mmol), Et_3N (1.1 mmol, 112 mg) was stirred for 5−10 min under a nitrogen atm. Then, to the reaction flask was added anhydrous DCM (4 mL) followed by dropwise addition of the corresponding acid chloride, which was prepared from the corresponding carboxylic acid (1 mmol). Then, the reaction mixture was stirred overnight. After this period, the reaction mixture was diluted with dichloromethane (3-5 mL) and washed with water (5-7 mL) and twice with saturated aqueous $NaHCO_3$ solution (3-5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in

vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, eluent = EtOAc/hexanes) furnished the corresponding carboxamides **7a-d,7f** and **18a-c**.

General procedure for the Pd(II)-catalyzed arylation of the carboxamides 7/18 and preparation of the compounds 8/12/19:[2,3,21]

An appropriate carboxamide (0. 25 mmol, 1 equiv), an appropriate aryl iodide (1.0 mmol, 4 equiv), $Pd(OAc)_2$ (2.8-5.6 mg, 5-10 mol%) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (2-3 mL) was heated at 110 ^oC for 10-24 h under a nitrogen atm. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on neutral alumina or silica gel (eluent = EtOAc:hexanes) furnished the corresponding bis arylated carboxamides **8/12/19** (see the corresponding Tables/Schemes for specific examples).

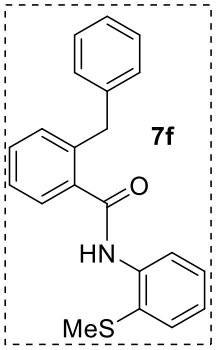
General procedure for the Pd(II)-catalyzed 8-aminoquinoline-aided intramolecular amidation of the remote sp^2 δ-C−H bond of the carboxamides 8/12/19:

A dry RB flask (10 mL capacity) containing a mixture of an appropriate carboxamide **8/12/19** (0.15 mmol), $Pd(OAc)_2$ (1.7-3.4 mg, 5-10 mol%), and $PhI(OAc)_2$ (PIDA, 121 mg, 2.5 equiv) in anhydrous toluene (1-2 mL) was heated at 110 °C for 1-24 h (see the corresponding Tables/Schemes for specific examples). After this period, the reaction mixture was cooled to rt and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (eluent =EtOAc:hexanes) to give the corresponding products (see the corresponding Tables/Schemes for specific examples).

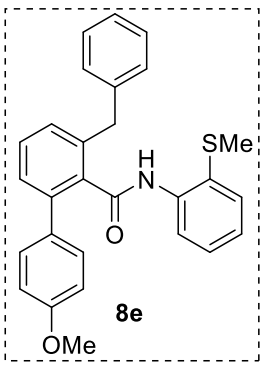
Gram scale reaction comprising the Pd(II)-catalyzed 8-aminoquinoline-aided remote sp^2 δ-C−H intramolecular amidation of the carboxamide 19a:

A dry RB flask (50 mL capacity) containing a mixture of carboxamide **19a** (1 g, 2.9 mmol), $Pd(OAc)_2$ (33 mg, 5 mol%), and $PhI(OAc)_2$ (2.32 g, 2.5 equiv) in anhydrous toluene (25 mL) was heated at 110 °C for 24 h. After this period, the reaction mixture was cooled to rt and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (eluent = EtOAc:hexanes) to give the product **20a** in 77% (0.78 g)yield.

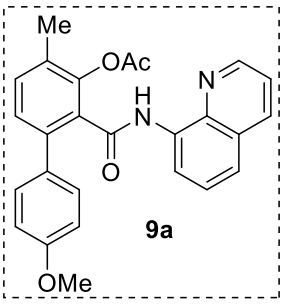
2-Benzyl-*N*-(2-(methylthio)phenyl)benzamide (7f): The compound **7f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a colorless solid; Yield: 73% (490 mg); mp 92-94 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 5:95); IR (DCM): 1681, 1579, 1430, 1304 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (br s, 1H), 8.45 (d, 1H, *J* = 7.9 Hz), 7.60 (d, 1H, *J* = 7.4 Hz), 7.52 (d, 1H, *J* = 7.6 Hz), 7.44 (t, 1H, *J* = 7.5 Hz), 7.39-7.34 (m, 2H), 7.31 (d, 1H, *J* = 7.6 Hz), 7.28-7.22 (m, 4H), 7.19-7.12 (m, 2H), 4.34 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.0, 140.7, 139.9, 138.3, 136.5, 132.8, 131.3, 130.6, 129.1, 128.8, 128.4, 126.9, 126.6, 126.1, 126.0, 124.8, 120.9, 38.8, 18.9; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{21}H_{19}NNaOS$: 356.1085; found 356.1101.



3-Benzyl-4'-methoxy-*N*-(2-(methylthio)phenyl)-[1,1'-biphenyl]-2-carboxamide (8e): The compound **8e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 79% (87 mg); mp 118-120 ^{o}C; R_f = 0.45 (EtOAc:Hexanes = 10:90); IR (DCM): 1677, 1579, 1429, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, *J* = 8.2 Hz), 8.06 (br s, 1H), 7.49 (d, 2H, *J* = 8.5 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 7.7 Hz), 7.33-7.19 (m, 7H), 7.11 (t, 1H, *J* = 7.0 Hz), 7.03 (t, 1H, *J* = 7.6 Hz), 6.89 (d, 2H, *J* = 8.5 Hz), 4.23 (s, 2H), 3.77 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.2, 159.2, 140.4, 139.2, 138.8, 138.3, 136.3, 133.2, 132.5, 129.8, 129.4, 129.2, 129.0, 128.9, 128.4, 128.1, 126.1, 125.4, 124.4, 120.3, 114.0, 55.3, 39.1, 19.0; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{28}H_{25}NNaO_2S$: 462.1504; found 462.1496.

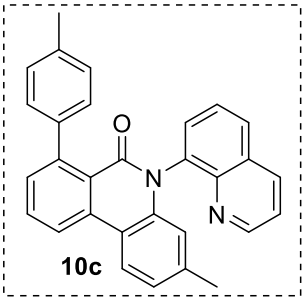


4'-Methoxy-4-methyl-2-(quinolin-8-ylcarbamoyl)-[1,1'-biphenyl]-3-yl acetate (9a): The compound **9a** column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a brown color liquid; Yield: 44% (28 mg); R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 1767, 1677, 1521, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.77 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.55-7.44 (m, 4H), 7.41-7.37 (m, 2H), 7.30 (d, 1H, *J* = 8.0 Hz), 6.78 (dt, 1H, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 3.66 (s, 3H), 2.29 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 169.3, 165.1, 159.1, 148.1, 146.8, 138.7,



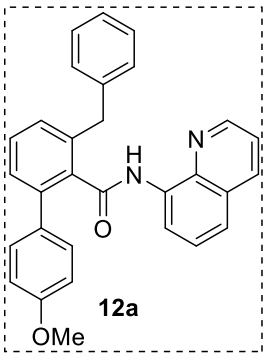
138.4, 136.0, 134.4, 132.0, 131.7, 130.1, 130.0, 129.8, 127.8, 127.8, 127.2, 121.8, 121.5, 116.5, 113.8, 55.1, 20.6, 16.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_4$: 427.1658; found 427.1674.

3-Methyl-5-(quinolin-8-yl)-7-(*p*-tolyl)phenanthridin-6(5*H*)-one (10c): The compound **10c**

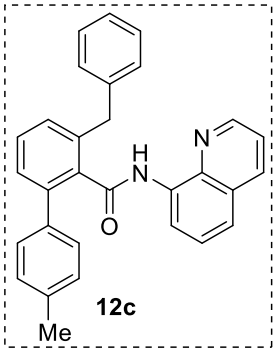


was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow color solid; Yield: 20% (16 mg); mp 235-237 ºC; R_f = 0.30 (EtOAc:Hexanes = 30:70); IR (DCM): 2922, 1665, 1612, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.9 Hz), 8.27 (d, 1H, J = 8.3 Hz), 8.24 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.95 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.7 Hz), 7.77 (d, 1H, J = 7.5 Hz), 7.71-7.66 (m, 2H), 7.42 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.1 Hz), 7.27 (d, 2H, J = 8.9 Hz), 7.11-7.06 (m, 3H), 6.20 (s, 1H), 2.31 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 161.3, 151.1, 145.5, 144.7, 140.9, 139.9, 139.4, 136.6, 136.2, 136.0, 135.7, 131.7, 131.3, 130.9, 129.9, 129.0, 128.2, 126.8, 123.4, 123.4, 123.1, 121.8, 121.2, 116.7, 116.6, 21.7, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}N_2O$: 427.1810; found 427.1825.

3-Benzyl-4'-methoxy-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12a): Thecompound **12a** was obtained after purification by column chromatography on silica gel

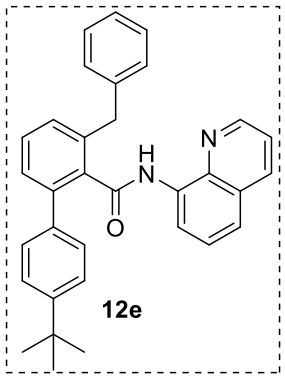


(EtOAc:Hexanes = 20:80) as a colorless solid; Yield: 75% (55 mg); mp 138-140 ºC; R_f = 0.35 (EtOAc:Hexanes = 20:80); IR (DCM): 3343, 1672, 1519, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.80 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55-7.50 (m, 3H), 7.48 (dd 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.43 (t, 1H, J = 7.7 Hz), 7.38-7.33 (m, 2H), 7.28-7.23 (m, 3H), 7.14 (t, 2H, J = 7.7 Hz), 7.04 (t, 1H, J = 7.4 Hz), 6.81 (dd, 2H, J_1 = 8.8 Hz, J_2 = 2.9 Hz), 4.26 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.3, 158.9, 147.9, 140.4, 139.4, 139.1, 138.4, 136.7, 136.0, 134.4, 132.8, 129.9, 129.3, 129.2, 128.9, 128.3, 128.2, 127.7, 127.2, 126.0, 121.7, 121.4, 116.5, 113.7, 55.1, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O_2$: 445.1916; found 445.1899.



3-Benzyl-4'-methyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12c): The compound **12c** was obtained after purification by column chromatography on (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 77% (82 mg); mp 137-139 ^{o}C; R_f = 0.65 (EtOAc:Hexanes = 20:80); IR (DCM): 3343, 1672, 1520, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.80 (d, 1H, *J* = 7.4 Hz), 8.58 (d, 1H, *J* = 3.2 Hz), 8.08 (d, 1H, *J* = 8.2 Hz), 7.56-7.43 (m, 5H), 7.36 (d, 2H, *J* = 7.8 Hz), 7.28-7.25 (m, 3H), 7.15 (t, 2H, *J* = 7.3 Hz), 7.07-7.03 (m, 3H), 4.26 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.3, 147.9, 140.4, 139.8, 139.1, 138.4, 137.4, 137.0, 136.7, 136.0, 134.4, 129.3, 129.2, 129.0, 129.0, 128.6, 128.3, 128.2, 127.7, 127.2, 126.0, 121.6, 121.4, 116.6, 39.2, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O$: 429.1967; found 429.1946.

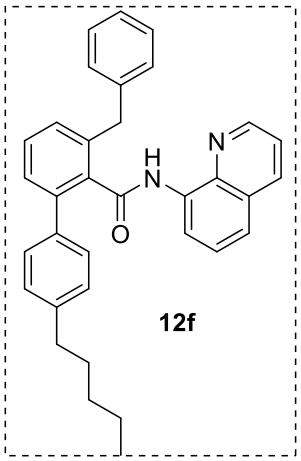
3-Benzyl-4'-isopropyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12d): The compound **12d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes =10:80) as a colorless solid; Yield: 61% (70 mg); mp 118-120 ^{o}C; R_f = 0.76 (EtOAc:Hexanes = 20:80); IR (DCM): 1672, 1520, 1483, 1326 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 8.79 (d, 1H, *J* = 7.5 Hz), 8.55 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.06 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.55-7.43 (m, 5H), 7.38 (d, 1H, *J* = 7.2 Hz), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.31-7.25 (m, 3H), 7.18 (t, 2H, *J* = 7.6 Hz), 7.10-7.06 (m, 3H), 4.30 (s, 2H), 2.72-2.65 (m, 1H), 0.99 (d, 6H, *J* = 6.9 Hz); ^{13}C NMR (~101 MHz,$CDCl_3$): δ 168.3, 147.8, 147.7, 140.5, 139.9, 139.4, 138.3, 137.7, 136.7, 135.9, 134.4, 129.4, 129.3, 129.1, 128.7, 128.4, 128.1, 127.6, 127.2, 126.2, 126.0, 121.5, 121.3, 116.4, 39.1, 33.6, 23.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O$: 457.2280; found 457.2296.



3-Benzyl-4'-(*tert*-butyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12e): The compound **12e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 67% (63 mg); mp 162-164 ^{o}C; R_f = 0.76 (EtOAc:Hexanes = 20:80); IR (DCM): 3339, 1672, 1520, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.76 (d, 1H, *J* = 7.5 Hz), 8.54 (d, 1H, *J* = 4.0 Hz), 8.06 (d, 1H, *J* = 8.2 Hz), 7.52 (t, 1H, *J*

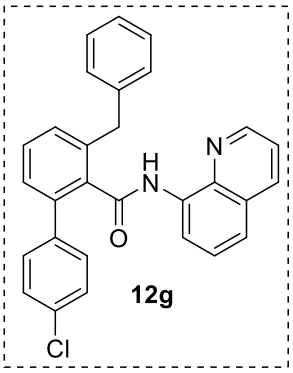
= 7.7 Hz), 7.48-7.42 (m, 4H), 7.39-7.33 (m, 2H), 7.30-7.24 (m, 3H), 7.20-7.16 (m, 4H), 7.08 (t, 1H, *J* = 7.3 Hz), 4.29 (s, 2H), 1.04 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.3, 150.0, 147.7, 140.5, 139.9, 139.4, 138.3, 137.3, 136.7, 135.9, 134.4, 129.4, 129.3, 129.1, 128.4, 128.3, 128.0, 127.6, 127.2, 126.0, 125.0, 121.5, 121.3, 116.4, 39.1, 34.2, 31.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{31}N_2O$: 471.2436; found 471.2451.

3-Benzyl-4'-pentyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12f): The compound



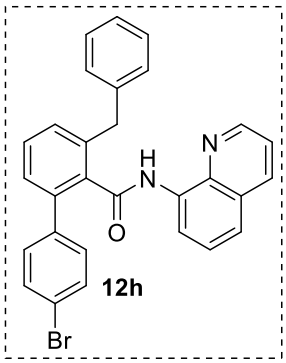
12f was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 73% (88 mg); mp 134-136 °C; R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 2928, 1672, 1521, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 8.78 (d, 1H, *J* = 7.5 Hz), 8.56 (d, 1H, *J* = 3.8 Hz), 8.07 (d, 1H, *J* = 8.2 Hz), 7.55-7.42 (m, 5H), 7.38-7.34 (m, 2H), 7.28-7.24 (m, 3H), 7.16 (t, 2H, *J* = 7.4 Hz), 7.08-7.02 (m, 3H), 4.27 (s, 2H), 2.40 (t, 2H, *J* = 7.3 Hz), 1.35-1.28 (m, 2H), 1.22-1.15 (m, 2H), 1.11-1.03 (m, 2H), 0.79 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.2, 147.8, 142.0, 140.5, 139.9, 139.3, 138.3, 137.6, 136.7, 135.9, 134.4, 129.3, 129.3, 129.0, 128.6, 128.3, 128.2, 128.1, 127.6, 127.2, 126.0, 121.6, 121.3, 116.4, 39.1, 35.4, 31.2, 30.9, 22.4, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{33}N_2O$: 485.2593; found 485.2601.

3-Benzyl-4'-chloro-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12g): The



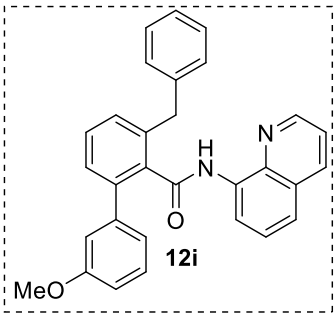
compound **12g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as a colorless solid; Yield: 71% (80 mg); mp 129-131 °C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 1670, 1522, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.81 (d, 1H, *J* = 7.4 Hz), 8.58 (d, 1H, *J* = 4.0 Hz), 8.09 (d, 1H, *J* = 8.2 Hz), 7.57-7.45 (m, 5H), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.4 Hz), 7.35-7.24 (m, 6H), 7.17 (t, 2H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.4 Hz), 4.28 (s, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 167.9, 148.0, 140.2, 139.4, 138.8, 138.5, 138.3, 136.7, 136.1, 134.1, 133.5, 130.1, 129.7, 129.5, 129.2, 128.5, 128.4, 128.1, 127.8, 127.2, 126.1, 122.0, 121.5, 116.6, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}ClN_2O$: 449.1421; found 449.1438.

3-Benzyl-4'-bromo-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12h): The

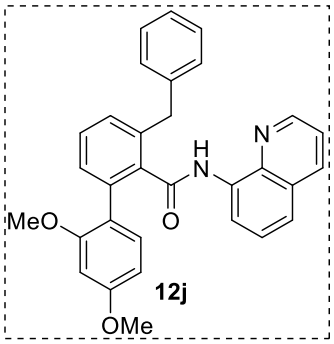


compound **12h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as a colorless solid; Yield: 55% (68 mg); mp 119-121 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 1672, 1520, 1483, 1264 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.77 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.58 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54 (t, 1H, J= 8.2 Hz), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.47-7.44 (m, 3H), 7.40-7.37 (m, 3H), 7.33-7.25 (m, 4H), 7.15 (t, 2H, J= 7.3 Hz), 7.05 (t, 1H, J= 7.3 Hz), 4.26 (s, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 167.8, 148.0, 140.2, 139.4, 139.2, 138.5, 138.3, 136.6, 136.1, 134.1, 131.4, 130.4, 129.7, 129.5, 129.2, 128.4, 128.0, 127.8, 127.2, 126.1, 122.0, 121.8, 121.5, 116.7, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}BrN_2O$: 493.0916; found 493.0901.

3-Benzyl-3'-methoxy-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12i): The

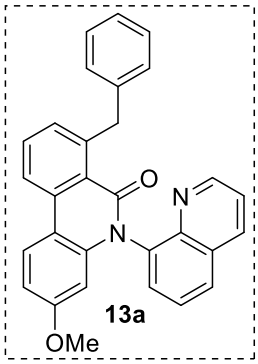


compound **12i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colorless solid; Yield: 77% (55 mg); mp 160-162 ^{o}C; R_f = 0.55 (EtOAc:Hexanes = 20:80); IR (DCM): 3341, 1671, 1520, 1483, 1326 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.78 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52 (t, 1H, J = 8.2 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.44 (d, 1H, J = 7.7 Hz), 7.38-7.35 (m, 2H), 7.27-7.25 (m, 3H), 7.16-7.13 (m, 5H), 7.04 (t, 1H, J = 7.3 Hz), 6.67-6.62 (m, 1H), 4.25 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.1, 159.3, 147.8, 141.6, 140.3, 139.7, 139.2, 138.3, 136.7, 136.0, 134.3, 129.3, 129.2, 129.2, 128.3, 128.0, 127.7, 127.2, 126.0, 121.7, 121.4, 121.2, 116.4, 113.8, 113.6, 55.2, 39.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O_2$: 445.1916; found 445.1902.

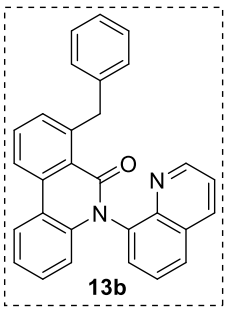


3-Benzyl-2',4'-dimethoxy-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (12j): The compound **12j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colorless solid; Yield: 65% (77 mg); mp 154-156 ^{o}C; R_f = 0.3 (EtOAc:Hexanes = 2:3); IR (DCM): 3336, 1673, 1521, 1484, 1208 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.78 (d, 1H, *J* = 7.0 Hz), 8.63 (d, 1H, *J* = 4.0 Hz), 8.12 (d, 1H, *J* = 8.2 Hz), 7.52-7.46 (m, 2H), 7.41-7.38 (m, 2H), 7.29-7.24 (m, 4H), 7.21 (d, 1H, *J* = 7.7 Hz), 7.16 (t, 2H, *J* = 7.5 Hz), 7.06 (t, 1H, *J* = 7.3 Hz), 6.45 (d, 1H, *J* = 8.3 Hz), 6.26 (s, 1H), 4.24 (s, 2H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.0, 160.4, 157.4, 147.7, 140.5, 138.7, 138.4, 137.8, 136.3, 136.0, 134.6, 131.6, 129.4, 129.1, 129.0, 128.9, 128.3, 127.8, 127.3, 125.9, 121.9, 121.4, 121.4, 116.3, 103.9, 98.3, 55.4, 55.2, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_3$: 475.2022; found 475.2039.

7-Benzyl-3-methoxy-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13a): The compound **13a**



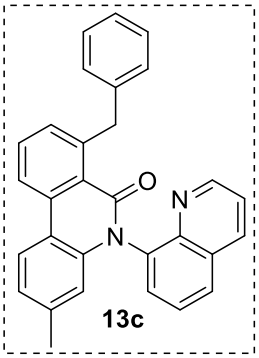
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a brown color solid; Yield: 75% (50 mg); mp 169-171 ^{o}C; R_f = 0.35 (EtOAc:Hexanes = 40:60); IR (DCM): 1657, 1463, 1310, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, 1H, *J* = 4.0 Hz), 8.26 (t, 2H, *J* = 8.3 Hz), 8.21 (d, 1H, *J* = 8.2 Hz), 8.03 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.5 Hz), 7.79-7.74 (m, 2H), 7.63 (t, 1H, *J* = 7.9 Hz), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.31-7.16 (m, 7H), 6.83 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.4 Hz), 5.93 (d, 1H, *J* = 1.0 Hz), 4.93, 4.86 (ABq, 2H, J_{AB}= 16.1 Hz), 3.60 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.9, 160.2, 151.4, 145.6, 144.5, 141.6, 141.0, 136.6, 136.4, 136.4, 132.0, 130.7, 130.1, 129.9, 129.6, 129.3, 128.3, 126.9, 125.7, 125.0, 122.9, 122.0, 120.0, 113.1, 108.5, 101.7, 55.2, 41.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}N_2O_2$: 443.1760; found 443.1742.



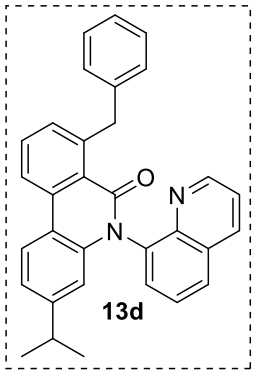
7-Benzyl-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13b): The compound **13b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a pale brown color solid; Yield: 57% (31 mg); mp 155-157 ^{o}C; R_f = 0.35 (EtOAc:Hexanes = 40:60); IR (DCM): 1657, 1600, 1497, 1318 cm^{-1}; ^{1}H

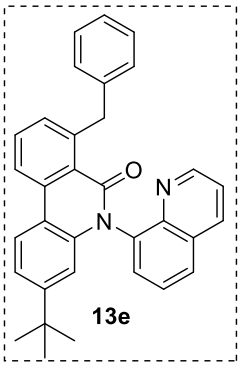
NMR (400 MHz, $CDCl_3$): δ 8.83 (d, 1H, *J* = 3.6 Hz), 8.35 (t, 2H, *J* = 7.8 Hz), 8.30 (d, 1H, *J* = 8.2 Hz), 8.04 (t, 1H, *J* = 4.9 Hz), 7.79-7.78 (m, 2H), 7.68 (t, 1H, *J* = 7.9 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.1 Hz), 7.31-7.19 (m, 8H), 6.42 (d, 1H, *J* = 8.2 Hz), 4.95, 4.88 (ABq, 2H, J_{AB}= 16.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.6, 151.4, 145.7, 144.6, 141.5, 139.6, 136.6, 136.4, 136.2, 132.0, 131.1, 130.7, 129.9, 129.6, 129.3, 129.0, 128.3, 126.9, 125.7, 124.0, 123.5, 122.2, 122.0, 120.5, 119.2, 116.5, 41.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{21}N_2O$: 413.1654; found 413.1637.

7-Benzyl-3-methyl-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13c): The compound **13c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale brown color solid; Yield: 55% (40 mg); mp 172-174 ºC; R_f = 0.35 (EtOAc:Hexanes = 30:70); IR (DCM): 2923, 1657, 1599, 1464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85-8.84 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.31-8.28 (m, 2H), 8.23 (d, 1H, *J* = 8.3 Hz), 8.05 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.8 Hz), 7.81-7.76 (m, 2H), 7.65 (t, 1H, *J* = 7.9 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.19 (m, 6H), 7.07 (d, 1H, *J* = 8.4 Hz), 6.22 (s, 1H), 4.93, 4.87 (ABq, 2H, J_{AB} = 16.1 Hz), 2.19 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.7, 151.4, 145.6, 144.7, 141.5, 139.6, 139.4, 136.8, 136.4, 136.3, 131.9, 130.7, 130.6, 129.9, 129.6, 129.2, 128.2, 126.9, 125.7, 123.6, 123.4, 122.0, 120.3, 116.9, 116.5, 41.1, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{24}N_2O$: 427.1810; found 427.1828.



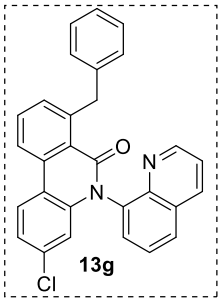
7-Benzyl-3-isopropyl-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13d): The compound **13d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a yellow color solid; Yield: 79% (41 mg); mp 128-130 ºC; R_f = 0.50 (EtOAc:Hexanes = 30:70); IR (DCM): 2961, 1658, 1599, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.31-8.27 (m, 3H), 8.07-8.03 (m, 1H), 7.79 (d, 2H, *J* = 5.1 Hz), 7.65 (t, 1H, *J* = 7.9 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.17 (m, 6H), 7.15 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 6.24 (d, 2H, *J* = 1.4 Hz), 4.91 (s, 2H), 2.71-2.65 (m, 1H), 1.06 (d, 3H, *J* = 6.9 Hz), 1.05 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.8, 151.3, 150.2, 145.5, 144.7, 141.6, 139.5, 136.7, 136.4, 136.3, 131.9, 130.7, 130.6, 129.8, 129.6, 129.2, 128.3, 126.9, 125.6, 123.6, 123.6, 121.9, 120.5, 120.4, 117.2, 114.4, 41.1, 34.0, 23.7, 23.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{27}N_2O$: 455.2123; found 455.2143.





7-Benzyl-3-(*tert*-butyl)-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13e): The compound **13e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow color solid; Yield: 84% (31 mg); mp 125-127 ^{o}C; R_f = 0.65 (EtOAc:Hexanes = 30:70); IR (DCM): 2964, 1658, 1497, 1398 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.31-8.26 (m, 3H), 8.05 (dd, 1H, J_1 = 5.4 Hz, J_2 = 4.3 Hz), 7.80-7.78 (m, 2H), 7.65 (t, 1H, J = 8.0 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29-7.18 (m, 7H), 6.38 (s, 1H), 4.91 (s, 2H), 1.05 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.8, 152.4, 151.2, 145.5, 144.6, 141.6, 139.3, 136.7, 136.4, 136.2, 131.9, 130.7, 130.7, 129.7, 129.5, 129.2, 128.2, 126.8, 125.6, 123.7, 123.2, 121.8, 120.4, 119.8, 116.8, 113.2, 41.1, 34.6, 30.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{29}N_2O$: 469.2280; found 469.2265.

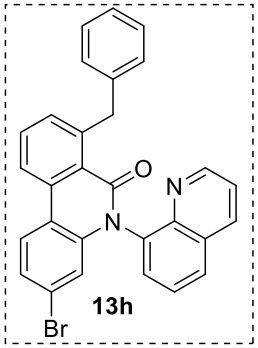
7-Benzyl-3-pentyl-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13f): The compound **13f** was obtained after purification by column chromatography on silica column (EtOAc:Hexanes = 10:90) as a yellow color solid; Yield: 58% (28 mg); mp 155-157 ^{o}C; R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 2927, 1658, 1612, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, 1H, J = 2.0 Hz), 8.31 -8.24 (m, 3H), 8.05 (t, 1H, J = 4.3 Hz), 7.79 (d, 2H, J = 4.3 Hz), 7.65 (t, 1H, J = 7.7 Hz), 7.45 (dd, 1H, J_1 = 7.6 Hz, J_2 = 3.8 Hz), 7.26-7.20 (m, 6H), 7.08 (d, 1H, J = 8.2 Hz), 6.20 (s, 1H), 4.94, 4.88 (ABq, 2H, J_{AB} = 16.1 Hz), 2.42 (t, 2H, J = 7.5 Hz), 1.47-1.38 (m, 2H), 1.22-1.12 (m, 4H), 0.80 (t, 3H, J = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.7, 151.3, 145.6, 144.7, 144.3, 141.6, 139.5, 136.8, 136.4, 131.9, 130.7, 130.6, 129.9, 129.6, 129.2, 128.2, 126.9, 125.6, 123.6, 123.4, 122.8, 121.9, 120.3, 117.0, 116.1, 41.1, 35.7, 31.1, 30.6, 22.4, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}N_2O$: 483.2436; found 483.2450.



7-Benzyl-3-chloro-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13g): The compound **13g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colorless solid; Yield: 56% (35 mg); mp 224-226 ^{o}C; R_f = 0.35 (EtOAc:Hexanes = 40:60); IR (DCM): 1660, 1599, 1497, 1395 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.31 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 8.25 (d, 2H, J = 8.7 Hz), 8.06 (dd, 1H, J_1 = 7.3 Hz, J_2 = 2.4 Hz), 7.81-7.75

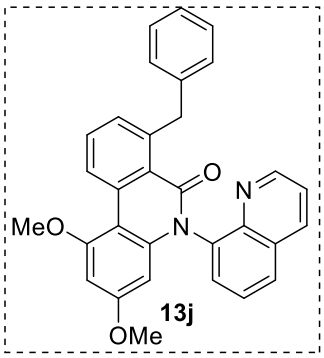
(m, 2H), 7.67 (t, 1H, J = 7.9 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.18 (m, 7H), 6.42 (d, 1H, J = 2.0 Hz), 4.91, 4.84 (ABq, 2H, J_{AB} = 16.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.4, 151.4, 145.8, 144.4, 141.3, 140.5, 136.5, 136.0, 135.5, 134.8, 132.2, 131.4, 130.6, 130.0, 129.6, 129.5, 128.3, 126.9, 125.8, 124.8, 123.8, 122.5, 122.1, 120.5, 117.9, 116.1, 41.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{20}N_2ClO$: 447.1264; found 447.1250.

7-Benzyl-3-bromo-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13h): The compound **13h**



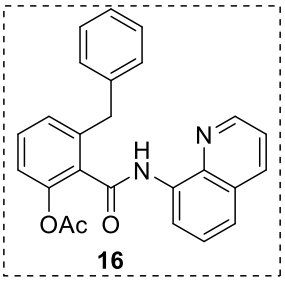
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a black color solid; Yield: 49% (34 mg); mp 80-82 ^oC; R_f = 0.35 (EtOAc:Hexanes = 40:60); IR (DCM): 1661, 1595, 1495, 1393 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.31 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.26 (d, 1H, J = 8.1 Hz), 8.18 (d, 1H, J = 8.8 Hz), 8.06 (dd, 1H, J_1 = 7.6 Hz, J_2 = 2.0 Hz), 7.81-7.74 (m, 2H), 7.67 (t, 1H, J = 8.0 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.34 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.9 Hz), 7.29-7.17 (m, 6H), 6.57 (d, 1H, J = 1.9 Hz), 4.90, 4.84 (ABq, 2H, J_{AB} = 16.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.3, 151.5, 145.9, 144.4, 141.2, 140.6, 136.5, 136.0, 135.5, 132.2, 131.5, 130.6, 130.0, 129.6, 129.5, 128.3, 126.9, 125.8, 125.3, 125.0, 123.8, 123.0, 122.1, 120.5, 119.0, 118.2, 41.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{20}BrN_2O$: 491.0759; found 491.0741.

7-Benzyl-1,3-dimethoxy-5-(quinolin-8-yl)phenanthridin-6(5*H*)-one (13j): The compound



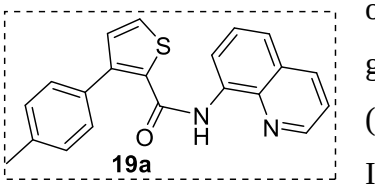
13j was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale brown color solid; Yield: 21% (11 mg); mp 183-185 ^oC; R_f = 0.35 (EtOAc:Hexanes = 30:70); IR (DCM): 1658, 1607, 1495, 1460, 1310 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (d, 1H, J = 8.5 Hz), 8.87 (d, 1H, J = 4.1 Hz), 8.28 (d, 1H, J = 8.3 Hz), 8.02-8.00 (m, 1H), 7.77-7.72 (m, 2H), 7.60 (t, 1H, J = 8.0 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26-7.13 (m, 6H), 6.39 (s, 1H), 5.57 (s, 1H), 4.88, 4.83 (ABq, 2H, J_{AB} = 16.1 Hz), 4.05 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.9, 160.0, 159.6, 151.3, 144.6, 144.5, 142.4, 141.9, 137.3, 136.5, 136.4, 131.5, 130.7, 130.0, 129.8, 129.5, 129.2, 128.1, 126.9, 125.5, 125.3, 123.0, 121.9, 104.0, 94.2, 93.4, 56.0, 55.0, 41.5; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{31}H_{25}N_2O_3$: 473.1865; found 473.1882.

3-Benzyl-2-(quinolin-8-ylcarbamoyl)phenyl acetate (16): The compound **16** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a brown color liquid; Yield: 60% (52 mg); R_f = 0.35 (EtOAc:Hexanes = 20:80); IR (DCM): 3282, 2962, 1510, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.93 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.4 Hz), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.64-7.57 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.22 (d, 2H, J = 7.2 Hz), 7.17-7.12 (m, 4H), 7.06 (t, 1H, J = 7.2 Hz), 4.21 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 169.6, 164.7, 148.4, 147.4, 140.8, 139.8, 138.4, 136.2, 134.2, 130.7, 130.2, 129.2, 128.4, 127.9, 127.9, 127.3, 126.2, 122.2, 121.7, 120.8, 116.9, 38.9, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1552; found 397.1571.



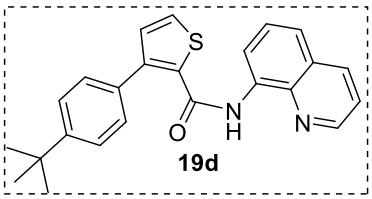
16

***N*-(quinolin-8-yl)-3-(*p*-tolyl)thiophene-2-carboxamide (19a):** The compound **19a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colorless solid; Yield: 61% (210 mg); mp 170-172 °C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 1649, 1525, 1485, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.85 (d, 1H, J = 7.0 Hz), 8.29 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.4 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.56 (d, 1H, J = 5.1 Hz), 7.52 (d, 1H, J = 7.8 Hz), 7.47-7.46 (m, 3H), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, J = 6.4 Hz), 7.11 (d, 1H, J = 5.0 Hz), 2.46 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.8, 147.3, 143.3, 138.5, 138.2, 135.9, 135.4, 134.6, 132.2, 131.6, 129.8, 129.5, 129.3, 127.7, 127.3, 121.5, 121.3, 116.4, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_2OS$: 345.1062; found 345.1075.



19a

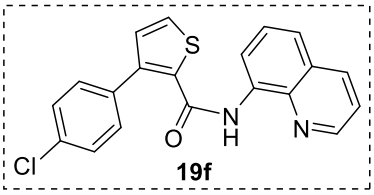
3-(4-(*Tert*-butyl)phenyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (19d): The compound **19d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 5:95) as a colorless solid; Yield: 72% (69 mg); mp 145-147 °C; R_f = 0.80 (EtOAc:Hexanes = 10:90); IR (DCM): 3291, 2964, 1645, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.85 (d, 1H, J = 7.6 Hz), 8.31 (d, 1H, J = 3.3 Hz), 8.06 (d, 1H, J = 8.2 Hz), 7.56-7.51 (m, 4H), 7.47-7.44 (m, 3H), 7.30 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.4 Hz), 7.13 (d, 1H, J = 5.0 Hz), 1.32 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.9, 151.4, 147.6, 143.2, 138.4, 135.9, 135.1, 134.5, 132.2, 131.5, 129.3, 129.1,



19d

127.7, 127.3, 125.8, 121.4, 121.2, 116.4, 34.7, 31.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2OS$: 387.1531; found 387.1549.

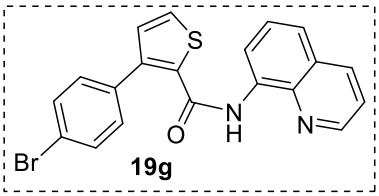
3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (19f): The compound **19f**



19f

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 59% (86 mg); mp 156-158 ^oC; R_f = 0.60 (EtOAc:Hexanes= 20:80); IR (DCM): 3304, 1650, 1531, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.84 (d, 1H, *J* = 7.4 Hz), 8.43 (d, 1H, *J* = 4.1 Hz), 8.10 (d, 1H, *J* = 8.2 Hz), 7.59 (d, 1H, *J* = 5.0 Hz), 7.55-7.45 (m, 6H), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.11 (d, 1H, *J* = 5.0 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.3, 147.7, 141.6, 138.3, 136.1, 136.0, 134.6, 134.4, 133.7, 131.1, 131.0, 129.7, 129.4, 127.8, 127.3, 121.7, 121.5, 116.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2OS$: 365.0515; found 365.0506.

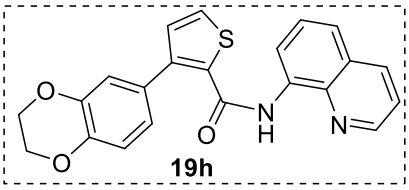
3-(4-Bromophenyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (19g): The compound **19g**



19g

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 32% (52 mg); mp 157-159 ^oC; R_f = 0.60 (EtOAc:Hexanes = 20:80); IR (DCM): 3304, 1650, 1529, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.84 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.45 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.63-7.60 (m, 2H), 7.58 (d, 1H, *J* = 5.0 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.46-7.43 (m, 2H), 7.38 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.10 (d, 1H, *J* = 5.0 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.3, 147.8, 141.6, 138.3, 136.1, 136.0, 134.4, 134.2, 132.3, 131.3, 131.1, 129.7, 127.8, 127.3, 122.8, 121.7, 121.5, 116.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{14}BrN_2OS$: 409.0010; found 409.0026.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide

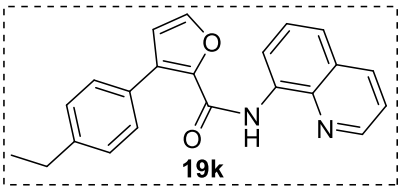


19h

(19h): The compound **19h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a pale yellow color solid; Yield: 92% (89 mg); mp 206-208 ^oC; R_f = 0.50 (EtOAc:Hexanes = 30:70); IR (DCM): 3300, 1645, 1529, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.86 (d, 1H, *J* = 7.6 Hz), 8.47 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3

Hz), 7.55-7.51 (m, 2H), 7.47 (d, 1H, J = 8.1 Hz), 7.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.09 (d, 1H, J = 5.0 Hz), 7.06-7.05 (m, 2H), 7.01 (d, 1H, J = 8.8 Hz), 4.30-4.28 (m, 2H), 4.21-4.19 (m, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.7, 147.4, 144.2, 144.0, 142.5, 138.6, 136.0, 135.5, 134.6, 131.5, 129.3, 128.3, 127.8, 127.4, 122.8, 121.4, 121.3, 118.5, 118.0, 116.5, 64.5, 64.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}N_2O_3S$: 389.0960; found 389.0941.

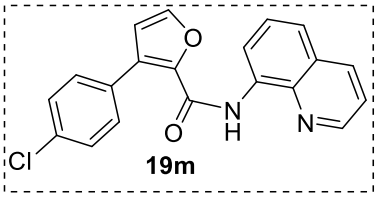
3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (19k): The compound **19k** was



19k

obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a brown color liquid; Yield: 78% (80 mg); R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 1673, 1531, 1483, 1327 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (s, 1H), 8.92 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.74 (d, 2H, J = 8.2 Hz), 7.64 (d, 1H, J = 1.8 Hz), 7.55 (d, 1H, J = 7.3 Hz), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33 (d, 2H, J = 8.2 Hz), 6.72 (d, 1H, J = 1.8 Hz), 2.75 (q, 2H, J = 7.6 Hz), 1.33 (t, 3H, J = 7.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 157.0, 148.2, 144.4, 143.3, 141.7, 138.7, 136.3, 134.5, 132.4, 129.5, 129.1, 128.0, 127.8, 127.4, 121.6, 121.6, 116.7, 115.0, 28.8, 15.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2$: 343.1447; found 343.1454.

3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (19m): The compound **19m**

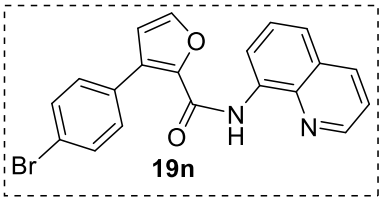


19m

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colorless solid; Yield: 67% (70 mg); mp 173-175 ^{o}C; R_f = 0.60 (EtOAc:Hexanes = 20:80); IR (DCM): 3340, 1671, 1537, 1488 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (s, 1H), 8.88-8.86 (m, 2H), 8.19 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.74 (dt, 2H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.67 (d, 1H, J = 1.7 Hz), 7.58-7.53 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.45 (dt, 2H, J_1 = 8.4 Hz, J_2 = 2.3 Hz), 6.70 (d, 1H, J = 1.7 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 156.7, 148.3, 143.5, 142.0, 138.7, 136.3, 134.3, 134.2, 131.1, 130.9, 130.3, 128.4, 128.0, 127.4, 121.8, 121.7, 116.7, 114.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{14}ClN_2O_2$: 349.0744; found 349.0759.

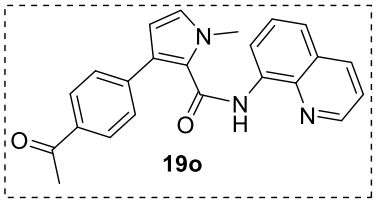
X3-(4-Bromophenyl)-N-(quinolin-8-yl)furan-2-carboxamide (19n): The compound **19n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as an orange color solid; Yield: 59% (69 mg); mp 178-180 ^{o}C; R_f = 0.60

(EtOAc:Hexanes = 20:80); IR (DCM): 3340, 1672, 1526, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.83 (s, 1H), 8.87-8.85 (m, 2H), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.68-7.66 (m, 3H), 7.62-7.58 (m, 2H), 7.56-7.53 (m, 2H), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.70 (d, 1H, J = 1.8 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 156.7, 148.4, 143.6, 141.9, 138.7, 136.4, 134.3, 131.4, 131.2, 130.8, 128.0, 127.4, 122.5, 121.8, 121.7, 116.7, 114.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{14}BrN_2O_2$: 393.0239; found 393.0224.



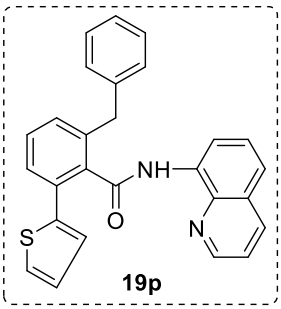
19n

3-(4-Acetylphenyl)-1-methyl-*N*-(quinolin-8-yl)-1*H*-pyrrole-2-carboxamide (19o): The compound **19o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a pale grey color solid; Yield: 29% (43 mg); mp 171-172 °C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3320, 1680, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.84 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.14 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.04 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.85 (d, 2H, J = 8.3 Hz), 7.58 (d, 2H, J = 8.3 Hz), 7.56-7.52 (m, 1H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.25 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.85 (d, 1H, J = 2.6 Hz), 6.29 (d, 1H, J = 2.6 Hz), 4.06 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 198.0, 160.2, 147.3, 140.8, 138.3, 135.9, 135.6, 134.7, 129.8, 128.6, 128.1, 127.8, 127.3, 127.2, 124.0, 121.3, 121.3, 115.7, 109.2, 37.1, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}N_3O_2$: 370.1556; found 370.1549.



19o

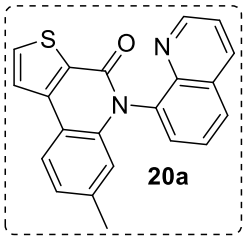
2-Benzyl-*N*-(quinolin-8-yl)-6-(thiophen-2-yl)benzamide (19p): The compound **19p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as a pale yellow color solid; Yield: 69% (73 mg); mp 127-129 °C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3340, 1672, 1519, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.89 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.61 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.57 (t, 1H, J= 7.6 Hz), 7.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.49 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.43-7.38 (m, 2H), 7.31 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.1 Hz), 7.25-7.23 (m, 3H), 7.18 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 7.16-7.12 (m, 2H), 7.04 (t, 1H, J= 7.4 Hz), 6.89 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 4.21 (s, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 168.0, 148.0, 141.4, 140.1, 139.2, 138.4, 136.6, 136.1, 134.3, 132.1, 129.7, 129.4, 129.2, 128.4, 128.3, 127.8,



19p

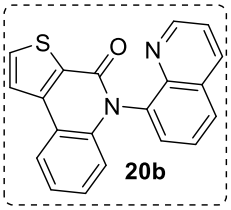
127.6, 127.3, 126.7, 126.1, 126.0, 121.9, 121.5, 116.7, 39.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2OS$: 421.1375; found 421.1393.

7-Methyl-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20a): The compound **20a** was



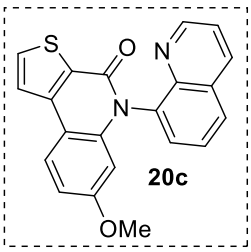
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:100) as a grey color solid; Yield: 92% (47 mg); mp 224-226 ^oC; R_f = 0.30 (EtOAc:Hexanes = 50:100); IR (DCM): 1651, 1615, 1498, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, 1H, *J* = 3.2 Hz), 8.31 (d, 1H, *J* = 8.2 Hz), 8.08-8.06 (m, 1H), 7.96 (d, 1H, *J* = 8.0 Hz), 7.85-7.78 (m, 4H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.10 (d, 1H, *J* = 8.0 Hz), 6.36 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.6, 151.5, 144.7, 143.2, 140.3, 139.0, 136.4, 135.7, 133.6, 130.8, 130.0, 129.8, 129.6, 126.8, 124.1, 123.8, 122.4, 122.0, 117.0, 116.1, 21.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2OS$: 343.0905; found 343.0917.

5-(Quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20b): The compound **20b** was obtained



after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:100) as a brown color liquid; Yield: 52% (23 mg); R_f = 0.30 (EtOAc:Hexanes = 50:100); IR (DCM): 1651, 1581, 1455, 1315 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84-8.83 (m, 1H), 8.31 (d, 1H, *J*= 8.3 Hz), 8.09-8.06 (m, 2H), 7.88-7.84 (m, 2H), 7.82-7.76 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.26 (m, 1H), 7.22 (t, 1H, *J*= 7.2 Hz), 6.57 (d, 1H, *J*= 8.3 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.5, 151.5, 144.6, 143.1, 140.3, 136.5, 135.5, 133.7, 130.9, 130.8, 129.8, 129.8, 128.6, 126.8, 124.2, 122.5, 122.5, 122.0, 118.3, 117.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{13}N_2OS$: 329.0749; found 329.0734.

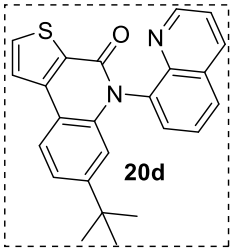
7-Methoxy-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20c): The compound **20c**



was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:100) as a brown color solid; Yield: 65% (42 mg); mp 202-204 ^oC; R_f = 0.25 (EtOAc:Hexanes = 50:100); IR (DCM): 1651, 1614, 1571, 1451, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.29 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.05 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 7.98 (d, 1H, *J* = 8.7 Hz), 7.83 (d, 1H, *J* = 5.2 Hz), 7.81-7.74 (m, 3H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.87 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 6.05 (d, 1H, *J* = 2.4 Hz), 3.60 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ

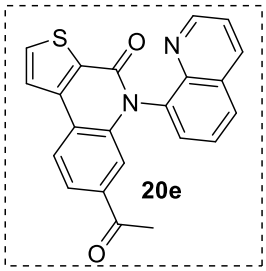
159.9, 158.8, 151.5, 144.6, 143.2, 141.8, 136.4, 135.6, 133.7, 130.8, 129.8, 129.7, 128.6, 126.8, 125.5, 122.1, 122.0, 112.7, 109.0, 102.2, 55.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2O_2S$: 359.0854; found 359.0862.

7-(*Tert*-butyl)-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20d): The compound **20d**



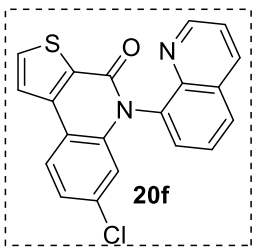
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a brown color solid; Yield: 67% (32 mg); mp 109-111 ^oC; R_f = 0.30 (EtOAc:Hexanes = 40:60); IR (DCM): 2963, 1651, 1614, 1422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.08 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.9 Hz), 8.0 (d, 1H, J = 8.4 Hz), 7.86-7.77 (m, 4H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 6.53 (d, 1H, J = 1.7 Hz), 1.06 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.7, 152.0, 151.4, 144.6, 143.1, 140.0, 136.4, 135.6, 133.6, 130.9, 130.2, 129.6, 129.6, 126.7, 123.8, 122.3, 121.9, 120.2, 116.0, 113.7, 34.8, 30.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2OS$: 385.1375; found 385.1387.

7-Acetyl-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20e): The compound **20e** was



obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a pale yellow color solid; Yield: 67% (31 mg); mp 255-257 ^oC; R_f = 0.20 (EtOAc:Hexanes = 50:50); IR (DCM): 1651, 1533, 1499, 1240, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 8.13 (d, 1H, J = 8.2 Hz), 8.09 (dd, 1H, J_1 = 7.4 Hz, J_2 = 2.2 Hz), 7.89 (d, 1H, J= 5.2 Hz), 7.86 (d, 1H, J= 5.2 Hz), 7.83-7.77 (m, 3H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.18 (d, 1H, J = 1.3 Hz), 2.39 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 197.2, 158.4, 151.5, 144.5, 142.0, 140.2, 136.6, 134.8, 134.1, 132.8, 130.9, 130.1, 129.9, 126.8, 124.5, 122.9, 122.3, 122.1, 121.7, 116.9, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{15}N_2O_2S$: 371.0854; found 371.0840.

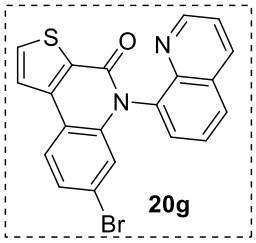
7-Chloro-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20f): The compound **20f** was



obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a pale brown color solid; Yield: 82% (41 mg); mp 170-172 ^oC; R_f = 0.25 (EtOAc:Hexanes = 40:60); IR (DCM): 1657, 1604, 1498, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.3 Hz), 8.32 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz),

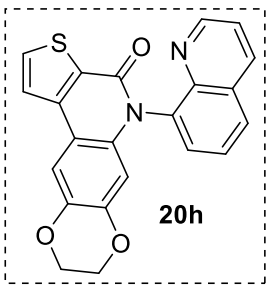
8.09 (t, 1H, J = 4.8 Hz), 7.99 (d, 1H, J = 8.5 Hz), 7.88 (d, 1H, J = 5.2 Hz), 7.80-7.79 (m, 3H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.24 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 6.56 (d, 1H, J = 1.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.3, 151.6, 144.4, 142.4, 141.1, 136.5, 134.9, 134.4, 134.1, 130.8, 130.0, 129.9, 126.8, 125.4, 122.8, 122.4, 122.2, 116.9, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{12}ClN_2OS$: 363.0359; found 363.0369.

7-Bromo-5-(quinolin-8-yl)thieno[2,3-*c*]quinolin-4(5*H*)-one (20g): The compound **20g** was

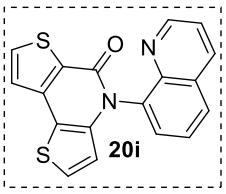


obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale brown solid; Yield: 78% (37 mg); mp 198-200 ^{o}C; R_f = 0.25 (EtOAc:Hexanes = 40:60); IR (DCM): 1651, 1599, 1441, 1390 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.11-8.07 (m, 1H), 7.92 (d, 1H, J = 8.4 Hz), 7.87 (d, 1H, J = 5.2 Hz), 7.79-7.78 (m, 3H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.37 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 6.72 (d, 1H, J = 1.7 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.2, 151.6, 144.4, 142.4, 141.2, 136.5, 134.8, 134.1, 130.9, 130.8, 130.0, 129.9, 126.8, 125.6, 125.5, 122.5, 122.4, 122.2, 119.6, 117.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{12}BrN_2OS$: 406.9854; found 406.9864.

5-(Quinolin-8-yl)-8,9-dihydro-[1,4]dioxino[2,3-*g*]thieno[2,3-*c*]quinolin-4(5*H*)-one (20h):



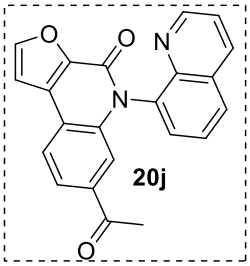
The compound **20h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a brown color solid; Yield: 31% (15 mg); mp 225-227 ^{o}C; R_f = 0.20 (EtOAc:Hexanes = 50:50); IR (DCM): 1649, 1512, 1423, 1316 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.29 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 8.04 (dd, 1H, J_1 = 7.1 Hz, J_2 = 2.6 Hz), 7.82 (d, 1H, J = 5.2 Hz), 7.77-7.73 (m, 2H), 7.69 (d, 1H, J = 5.2 Hz), 7.53 (s, 1H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.06 (s, 1H), 4.27-4.20 (m, 4H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.4, 151.5, 144.6, 144.5, 142.6, 139.7, 136.4, 135.7, 133.5, 130.8, 129.8, 129.6, 129.4, 126.8, 122.3, 122.0, 112.9, 111.4, 105.2, 64.6, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{15}N_2O_3S$: 387.0803; found 387.0815.



4-(Quinolin-8-yl)dithieno[3,2-b:3',2'-*d*]pyridin-5(4*H*)-one (20i): The compound **20i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a brown color solid; Yield: 55% (23 mg); mp 232-234 ^{o}C; R_f = 0.85

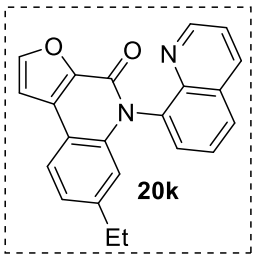
(EtOAc:Hexanes = 50:50); IR (DCM): 1639, 1533, 1497, 1394 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.29 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.04 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.86-7.84 (m, 2H), 7.77-7.73 (m, 1H), 7.48-7.45 (m, 2H), 7.23 (d, 1H, J = 5.4 Hz), 6.24 (d, 1H, J = 5.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.4, 151.5, 144.2, 142.6, 140.1, 136.4, 136.3, 134.7, 130.1, 129.7, 129.7, 128.2, 126.6, 125.1, 122.1, 122.0, 118.7, 114.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{11}N_2OS_2$: 335.0313; found 335.0305.

7-Acetyl-5-(quinolin-8-yl)furo[2,3-*c*]quinolin-4(5*H*)-one (20j): The compound **20j** was



obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a yellow color solid; Yield: 74% (34 mg); mp 195-197 ºC; R_f = 0.20 (EtOAc:Hexanes = 50:50); IR (DCM): 1681, 1492, 1406, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.5 Hz), 8.33 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 8.12-8.10 (m, 1H), 8.01 (d, 1H, J = 8.1 Hz), 7.95 (d, 1H, J = 1.8 Hz), 7.85-7.81 (m, 3H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.23 (d, 1H, J = 1.8 Hz), 7.16 (d, 1H, J = 1.1 Hz), 2.39 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 197.2, 154.0, 151.5, 148.7, 144.4, 143.5, 139.6, 136.6, 136.4, 134.5, 131.0, 130.2, 129.9, 129.8, 126.8, 124.5, 122.3, 122.2, 120.1, 116.9, 106.4, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{15}N_2O_3$: 355.1083; found 355.1098.

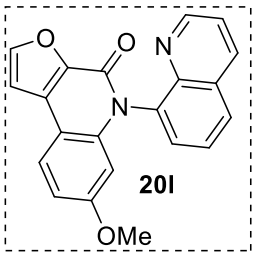
7-Ethyl-5-(quinolin-8-yl)furo[2,3-*c*]quinolin-4(5*H*)-one (20k): The compound **20k** was



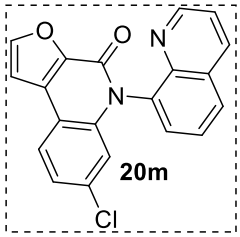
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as a brown color solid; Yield: 58% (45 mg); mp 264-266ºC; R_f = 0.30 (EtOAc:Hexanes = 60:40); IR (DCM): 1674, 1594, 1492, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.30 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.07 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.9 Hz), 7.89 (d, 1H, J = 1.9 Hz), 7.84 (d, 1H, J = 8.0 Hz), 7.81-7.76 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.15-7.13 (m, 2H), 6.34 (s, 1H), 2.47 (q, 2H, J = 7.6 Hz), 1.03 (t, 3H, J = 7.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 154.1, 151.4, 148.3, 145.0, 144.7, 142.1, 139.8, 136.4, 135.4, 131.0, 130.7, 129.8, 129.7, 126.7, 124.2, 122.6, 122.0, 116.1, 114.3, 106.1, 29.1, 15.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1290; found 341.1281.

7-Methoxy-5-(quinolin-8-yl)furo[2,3-*c*]quinolin-4(5*H*)-one (20l): The compound **20l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40)

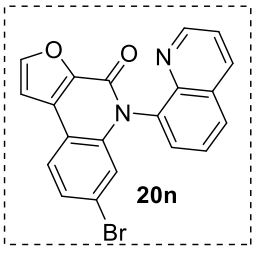
as a pale brown color solid; Yield: 79% (45 mg); mp 206-208 ^{o}C; R_f = 0.30 (EtOAc:Hexanes= 60:40); IR (DCM): 1673, 1493, 1212, 892 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, 1H, *J* = 2.8 Hz), 8.29 (d, 1H, *J* = 7.4 Hz), 8.06 (dd, 1H, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 7.88-7.75 (m, 4H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.11 (d, 1H, *J* = 1.3 Hz), 6.88 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.2 Hz), 6.03 (d, 1H, *J* = 2.2 Hz), 3.59 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 159.8, 154.2, 151.5, 148.3, 144.6, 141.3, 141.2, 136.4, 135.3, 130.9, 130.8, 129.8, 129.8, 126.8, 125.4, 122.0, 110.4, 109.3, 105.9, 102.3, 55.3; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{15}N_2O_3$: 343.1083; found 343.1070.



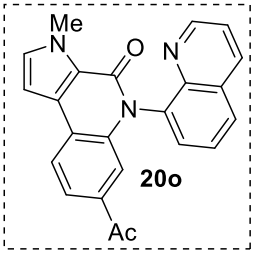
7-Chloro-5-(quinolin-8-yl)furo[2,3-*c*]quinolin-4(5*H*)-one (20m): The compound **20m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a colorless solid; Yield: 42 % (25 mg); mp 228-230 ^{o}C; R_f = 0.25 (EtOAc:Hexanes = 50:50); IR (DCM): 1680, 1583, 1491, 1308 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.33 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 7.1 Hz, J_2 = 2.6 Hz), 7.93 (d, 1H, *J* = 1.9 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 7.83-7.78 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.9 Hz), 7.16 (d, 1H, *J* = 1.9 Hz), 6.54 (d, 1H, *J* = 1.8 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 153.8, 151.6, 148.6, 144.4, 142.3, 140.5, 136.5, 134.6, 134.2, 130.9, 130.2, 130.1, 129.9, 126.8, 125.4, 123.0, 122.2, 116.8, 115.0, 106.1; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{20}H_{12}ClN_2O_2$: 347.0587; found 347.0603.



7-Bromo-5-(quinolin-8-yl)furo[2,3-*c*]quinolin-4(5*H*)-one (20n): The compound **20n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a pale yellow color solid; Yield: 51% (29 mg); mp above 302-304 ^{o}C; R_f = 0.25 (EtOAc:Hexanes = 50:50); IR (DCM): 1673, 1579, 1400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.32 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.9 Hz), 7.91 (d, 1H, *J* = 2.0 Hz), 7.82-7.77 (m, 3H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.39 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.15 (d, 1H, *J* = 2.0 Hz), 6.69 (d, 1H, *J* = 1.7 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 153.7, 151.6, 148.7, 144.4, 142.4, 140.6, 136.6, 134.5, 130.9, 130.2, 130.2, 129.9, 126.8, 125.8, 125.5, 122.3, 122.2, 119.7, 115.3, 106.1; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{20}H_{12}BrN_2O_2$: 391.0082; found 391.0099.

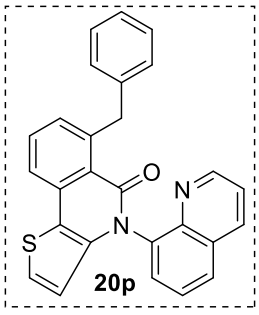


7-Acetyl-3-methyl-5-(quinolin-8-yl)-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one (20o):

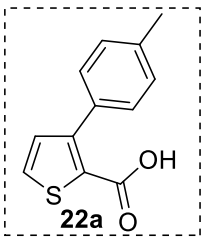


The compound **20o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as a black color solid; Yield: 65% (19 mg); mp 242-244 ^{o}C; R_f = 0.20 (EtOAc:Hexanes = 60:40); IR (DCM): 1655, 1492, 1402, 1319 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, 1H, *J* = 3.8 Hz), 8.32 (d, 1H, *J* = 8.2 Hz), 8.10-8.07 (m, 1H), 8.02 (d, 1H, *J* = 8.2 Hz), 7.82-7.77 (m, 3H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.1 Hz), 7.17 (d, 1H, *J* = 2.4 Hz), 7.08 (s, 1H), 6.87 (d, 1H, *J* = 2.5 Hz), 4.20 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 197.4, 156.6, 151.5, 144.9, 138.3, 136.6, 135.5, 134.7, 131.7, 131.1, 129.8, 129.7, 127.8, 126.8, 123.2, 122.6, 122.5, 122.1, 122.0, 116.6, 101.8, 36.3, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_2$: 368.1399; found 368.1414.

6-Benzyl-4-(quinolin-8-yl)thieno[3,2-*c*]isoquinolin-5(4*H*)-one (20p): The compound **20p**

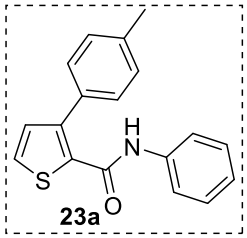


was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown color solid; Yield: 40% (25 mg); mp 98-100 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 30:70); IR (DCM): 1650, 1599, 1491, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.28 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.02 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.83 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 7.72-7.70 (m, 1H), 7.58 (t, 1H, *J* = 7.8 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.23 (m, 4H), 7.21-7.17 (m, 2H), 7.14 (d, 1H, *J* = 7.5 Hz), 6.14 (d, 1H, *J* = 5.4 Hz), 4.93 (d, 1H, *J* = 16.0 Hz), 4.87 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.9, 151.4, 146.1, 144.2, 141.4, 141.0, 137.2, 136.3, 135.1, 132.3, 130.0, 129.8, 129.5, 129.4, 128.3, 126.7, 125.7, 125.2, 125.2, 122.0, 121.9, 121.2, 118.7, 117.4, 40.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{19}N_2OS$: 419.1218; found 419.1234.

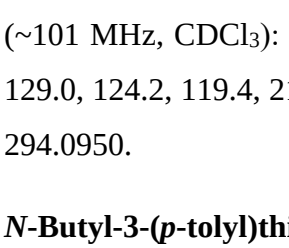


3-(*p*-Tolyl)thiophene-2-carboxylic acid (22a): The compound **22a** was obtained as an orange color solid; Yield: 93% (101 mg); mp 159-161 ^{o}C; IR (DCM): 2552, 1655, 1426, 1290 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H, *J* = 5.0 Hz), 7.39 (d, 2H, *J* = 8.1 Hz), 7.24 (d, 2H, *J* = 7.9 Hz), 7.11 (d, 1H, *J* = 5.0 Hz), 2.43 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 167.7, 150.0, 138.0, 132.4, 132.1, 131.7, 129.2, 128.7, 126.2, 21.4; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{12}H_9O_2S$: 217.0323; found 217.0313.

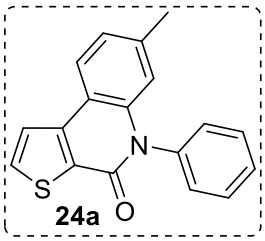
***N*-Phenyl-3-(*p*-tolyl)thiophene-2-carboxamide (23a):** The compound **23a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 10:90) as a pale yellow color solid; Yield: 61% (86 mg); mp 99-101 ^{o}C; R_f = 0.70 (EtOAc:Hexanes = 80:20); IR (DCM): 1658, 1536, 1442, 1317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, *J* = 5.0 Hz), 7.49 (br s, 1H), 7.43 (d, 2H, *J* = 8.1 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.29-7.25 (m, 2H), 7.22-7.19 (m, 2H),7.10-7.05 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 160.1, 142.3, 139.1, 137.6, 135.2, 132.2, 131.1, 130.0, 129.6, 129.3, 129.0, 124.2, 119.4, 21.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{16}NOS$: 294.0953; found 294.0950.



***N*-Butyl-3-(*p*-tolyl)thiophene-2-carboxamide (23b):** The compound **23b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colorless solid; Yield: 79% (96 mg); mp 80-82 ^{o}C; R_f = 0.70 (EtOAc:Hexanes = 20:80); IR (DCM): 3420, 2957, 1643, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J* = 5.0 Hz), 7.34-7.28 (m, 4H), 6.99 (d, 1H, *J* = 5.0 Hz), 3.25-3.21 (m, 2H), 2.44 (s, 3H), 1.33-1.25 (m, 2H), 1.13-1.06 (m, 2H), 0.83 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 162.2, 141.6, 138.5, 135.0, 132.6, 130.8, 129.7, 129.0, 128.4, 39.3, 31.1, 21.3, 19.9, 13.7; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{16}H_{20}NOS$: 274.1266; found 274.1260.



7-Methyl-5-phenylthieno[2,3-*c*]quinolin-4(5*H*)-one (24a): The compound **24a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 40:60) as a pale yellow color solid; Yield: 18% (10 mg); mp 182-184 ^{o}C; R_f = 0.45 (EtOAc:Hexanes = 40:60); IR (DCM): 1651, 1532, 1444, 1317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 5.2 Hz), 7.78 (d, 1H, *J* = 5.2 Hz), 7.67-7.63 (m, 2H), 7.59-7.56 (m, 1H), 7.37-7.35 (m, 2H), 7.14 (d, 1H, *J* = 8.0 Hz), 6.55 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ 158.4, 142.7, 140.0, 139.1, 137.8, 133.7, 130.1, 129.3, 128.9, 124.0, 123.9, 122.2, 117.2, 116.0, 21.9; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{14}NOS$: 292.0796; found 292.0786.



References:

1) For selected reviews, see: a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.***2002**, *35*, 826; b) Kommagalla, Y.; Chatani, N. *Coord. Chem. Rev.* **2017**,*350*, 117. c) Hirano, K.; Miura, M.*Chem. Lett.***2015**, *44*, 868. d) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.***2017**,*117*, 8622. e) Castro, L. C. M.; Chatani, N. *Chem. Lett.***2015**, *44*, 410.f)Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.***2012**, *112*, 5879. g) Banerjee, A.; Sarkar, S.; Patel, B.*Org. Biomol. Chem.***2017**, *15*, 505. h)Bheeter, C. B.; Chen, L.; Soulé, J.-F.; Doucet, H. *Catal. Sci. Technol.* **2016**,*6*, 2005.i) Choy, P. Y.; Wong, S. M.; Kapadi, A.; Kwong, F. Y. *Org. Chem. Front. Chem.* **2018**, *5*, 288. j) Ackermann, L. *Acc. Chem. Res.***2014**, *47*, 281. k) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787. l) L. Ping, D. S. Chung, J. Bouffard, S.-g. Lee, *Chem. Soc. Rev.* **2017**,*46*, 4299. m) Dey, A.; Sinha,S. K.; Achar, T. K.; Maiti, D. *Angew. Chem. Int. Ed.*https://doi.org/10.1002/anie.201812116.

2) For selected reviews of the BDG-aided C-H functionalization, see: a) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.***2013**, *52*, 11726. b) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.***2018**, *47*, 6603. c) Yang, X. ;Shan, G. ; Wang, L.; Rao, Y. *TetrahedronLett.***2016**, *57*, 819. d) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron***2015**, *71*, 4450. e) Hui, C.;Xu, J. *Tetrahedron Lett.***2016**, *57*, 2692. f) Zhang, B.; Guan, H.; Shi, B.-F. *Chin. J. Org. Chem.***2014**, *34*, 1487.

3) For selected articles of the BDG-aided C-H functionalization, see: a) Shabashov, D.; Daugulis,O. *J. Am. Chem. Soc.***2010**, *132*, 3965. b) Castro, L. C. M.; Chatani,N. *Chem. Eur. J.***2014**, *20*, 4548. c) Ling, P.-X.; S.-L. Fang, X.-S. Yin, K. Chen, Z.-B. Sun, B. -F. Shi, *Chem. Eur. J.***2015**, *21*, 17503. d) Thrimurtulu, N.; Dey, A.; Pal, K.; Nair, A.; Kumar, S.; Volla, C. M. R. *ChemistrySelect***2017**, *2*, 7251. e) Reddy, M. D.; Blanton, A. N.; Watkins, E. B. *J. Org. Chem.* **2017**, *82*, 5080. f) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N.*Eur. J. Org. Chem.* **2017**, *22*, 16805.

4) Selected articles of the BDG-aided functionalization of the 1º C(sp^3)-H bond over 2º C(sp^3)-H bond, see: a) Ye, X.; Petersen, J. L.; Shi, X. *Chem. Commun.***2015**, *51*, 7863. b) Wu, X.; Zhao, Y.; Ge, H. *Chem. Eur. J.***2014**, *9*, 2736. c) Liu, Y.-J.; Zhang, Z.-Z.; Yan, S.-Y.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.***2015**, *51*, 7899.

5) BDG-aided functionalization of the sp^2/sp^3 C-H bonds over the benzylic C(sp^3)-H bond, see: Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.***2014**, *50*, 3944.

6) Picolinamide (PA)-type DG-aided*β*-, *γ*-C-H functionalization of amines, see: a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2005**, *127*, 13154. b) Song, H.; Liu, X.; Wang, C.; Qiao, J.; Chu, W.; Sun, Z. *AsianJ. Org. Chem.***2005**, *127*, 13154. c) Pasunooti, K. K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett.***2015**, *17*, 6094. d) Martínez, Á. M.; Echavarren, J.; Alonso, I.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C.*Chem. Sci*. **2015**, *6*, 5802. e) Xu, J.; Qiao, L.; Shen, J.; Chai, K.; Shen, C.; Zhang,P. *Org. Lett.***2017**, *19*, 5661.

7) PA type DG-aided*δ*-C-H functionalization of amines, see: a) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M.*Org. Lett.***2014**, *16*, 2892. b) Zhao, F.; Jia, X.; Zhao, J.; Fei, C.; Liu, L.; Liu, G.; Wang, D.; Chen,F. *RSC Adv*.**2017**, *7*, 25031. c) Han, J.; Liu, P.; Wang, C.; Wang, Q.; Zhang, J.; Zhao, Y.; Shi, D.; Huang, Z.; Zhao, Y. *Org. Lett.***2014**, *16*, 5682. d) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc*. **2016**, *138*, 10750. e) Zhan, B.-B.; Li, Y.; Xu, J.-W.; Nie, X.-L.; Fan, J.; Jin, L.; Shi, B.-F. *Angew. Chem. Int. Ed.***2018**, *57*, 5858.

8) PA type DG-aided*ε*-C-H functionalization of amines, see: a) Wang, Q.; Han, J.; Wang, C.; Zhang, J.; Huang, Z.; Shi, D.; Zhao, Y. *Chem. Sci.***2014**, *5*, 4962. b) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.***2010**, *12*, 2511.

9) 8-Aminoquinoline (AQ) type DG-aided *β*-, *γ*-C-H functionalization of carboxylic acids, see: a) Wang, Z.; Kuninobu, Y.; Kanai, M.*Org. Lett.***2014**, *16*, 4790. b) Hoshiya, N.; Kondo, M.; Fukuda, H.; Arisawa, M.;Uenishi, J.; Shuto, S. *J. Org. Chem.***2017**, *82*, 2535. c) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.***2014**, *16*, 4956. d)Gou, Q. Zhang, Z.-F.; Liu, Z.-C.; Qin, J. *J. Org. Chem.***2015**, *80*, 3176. e) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe,N. *Org. Biomol. Chem.***2015**, *13*, 6803. f) Guin, S.; Deb, A.; Dolui, P.; Chakraborty, S.; Singh,V. K.;Maiti, D. *ACS Catal*.**2018**, *8*, 2664. g) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.***2010**, *12*, 3414. h) Allu, S.; Swamy, K. C. K. *J. Org. Chem.***2014**, *79*, 3963.i) Thrimurtulu, N.; Dey, A.; Maiti, D.; Volla, C. M. R. *Angew. Chem. Int. Ed.***2016**, *55*, 12361. j) Deb, A.; Hazra, A.; Peng, Q.; Paton, R. S.; Maiti, D. *J. Am. Chem. Soc.***2017**, *139*, 763.

10) AQ DG-aided *δ*-C-H functionalization of carboxylic acids, see: Guan, M.; Pang, Y.; Zhang, J.; Zhao, Y. *Chem. Commun.* **2016**, *52*, 7043.

11) Selected reviews of the intramolecular C-H amination/amidation, see: a) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247. c) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. d) J.-P. Wan, Y. Jing, *Beilstein J. Org. Chem.* **2015**, *11*, 2209. e) J. L.

Jeffrey, R. Sarpong, *Chem. Sci.* **2013**, *4*, 4092. f) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901.

12) AQ type DG-aided *β*-C-H amidation of carboxylic acids, see: a) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.***2014**, *16*, 480. b) Ling, P.-X.; Fang, S.-L.; Yin, X.-S.; Zhang, Q.; Chen, K.; Shi, B.-F. *Chem. Commun.* **2017**, *53*, 6351. c) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem. Int. Ed.***2013**, *52*, 13588.

13) AQ type DG-aided *γ*-C-H amidation of carboxylic acids, see: a) Parella, R.; Babu, S. A. *J. Org. Chem.***2017**, *82*, 7123. b) Zhang, M.*J. Chem. Res.***2013**, *37*, 606. c) Yamamoto, C.; Takamatsu, K.; Hirano, K.; Miura, M.*J. Org. Chem.***2016**, *81*, 7675. d) He, G.; Zhang, S.-Y.;Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed.***2013**, *52*, 11124. e) Zhu, C.; Liang, Y.; Hong, X.; Sun, H.; Sun, W.-Y.; Houk, K. N.; Shi, Z. *J. Am. Chem. Soc.***2015**, *137*, 7564.

14) PA-aided *γ*-C-H amidation of amines, see: Zhao, J.; Zhao, X.-J.; Cao, P.; Liu, J.-K.; Wu, B. *Org. Lett.***2017**, *19*, 4880.

15) Selective PA type DG-aided *δ*-C-H amidation of amines, see: a) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. b) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. c) Zhao, J.; Zhao, X.-J.; Cao, P.; Liu, J.-K.; Wu,B. *Org. Lett.* **2017**, *19*, 4880.

16) PA type DG-aided *ε*-C-H amidation of amines, see:a) Pearson, R.; Zhang, S.; He, G.; Edwards, N.; Chen, G. *Beilstein J. Org. Chem.***2013**, *9*, 891. b) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guao, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. *Angew. Chem. Int. Ed.***2014**, *53*, 9884. c) Naveen; Rajkumar, V.; Babu, S. A.; Gopalakrishnan, B. *J. Org. Chem.***2016**, *81*, 12197.

17) For selected reviews/papers dealing with the phenanthridin-6(5*H*)-one motifs, see: a) Keller, P. A. *Science of Synthesis***2005**, *15*, 1089. b) Rafiee, F. *Appl. Organomet. Chem.***2017**, *31*, e3820. c) Nair, J. J.; Staden, J.V.; Bastida, J. *Curr. Med. Chem.* **2016**, *23*, 161. d) Chapleur, Y.; Chretien, F.; Ahmed, S. I.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 341.

18) Selected articles dealing with the synthesis of phenanthridin-6(5*H*)-one motifs, see: a) Ishida, N.; Nakanishi, Y.; Moriya, T.; Murakami, M. *Chem. Lett.* **2011**, *40*, 1047. b) Chen, Z.; Wang, X. *Org. Biomol. Chem.* **2017**, *15*, 5790. c) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1380. d) Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 12116. e) Karthikeyan, J.; Cheng, C.-H. *Angew. Chem. Int.*

Ed. **2011**, *50*, 9880. f) Wang, S.; Shao, P.; Du, G.; Xi, C. *J. Org. Chem.* **2016**, *81*, 6672. g) Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 5353.

19) a) Krylov, I. B.; Vil', V. A.; Terent'ev, A. O. *Beilstein J. Org. Chem.***2015**, *11*, 92. b) Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *Eur. J. Org. Chem.***2016**, 3282.

20) BDG-aided functionalization of the sp^2 C-H bond over sp^3 C-H bond, see: a) Aihara, Y.;Chatani, N. *J. Am. Chem. Soc.***2013**, *135*, 5308. b) Li, C.; Zhang, D.; Zhu, W.; Wan, P.; Liu, H. *Org. Chem. Front.***2016**, *3*, 1080. c) Gui, Q.; Chen, X.; Hu, L.; Wang, D.; Liu, J.; Tan, Z. *Adv. Synth. Catal.***2016**, *358*, 509.

21) a) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *Org. Biomol. Chem.***2016**, *14*, 11070. b) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.***2014**, *136*, 13130. c) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.***2014**, *136*, 14349. d) Liu, Y.; Zhang, Y.; Huang, M.; Wan, J.-P. *RSC Adv.***2015**, *5*, 46192. e) Li, J.; Zheng,Z.; Xiao, T.; Xu, P. -F.; Wei, H. *Asian J. Org. Chem.* **2018**, *7*, 133. f) Padmavathi, R.; Sankar, R.; Gopalakrishnan, B.; Parella, R.; Babu, S. A. *Eur. J. Org. Chem.***2015**, 3727. g) Aihara, Y.; Chatani, N.; *Chem. Sci.***2013**, *4*, 664. h) Reddy, C.; Bisht, N.;Parella, R.; Babu, S. A. *J. Org. Chem.***2016**, *81*, 12143.

22) a) Shibata, K.; Chatani, N. *Org. Lett.***2014**, *16*, 5148. b) Kubo, T.; Aihara, Y.; Chatani, N. *Chem. Lett.***2015**, *44*, 1365. c) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M.*Org. Lett.***2009**, *11*, 5726.

23) **13a:**CCDC 1850442 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Chapter 4

Pd(II)-catalyzed directing-group aided regioselective C-H functionalization of azobenzene carboxamides.

Introduction

Azobenzenes were first described in the year 1834 and gradually evolved as the most promising candidates of chemical industry. For example, till date, they serve as potential candidates in food and dye industry.[1a-c] After a century, G. Hartley's remarkable finding of azobenzenes ability to switch from cis to trans conformation and *vice-versa* on irradiation of light made them as one of the most unique scaffolds in modern chemistry (shown in figure 1). This finding has driven synthetic community to target azobenzenesfor more potential applications such as liquid crystals,[1d] photochemical molecular switches,[1e] molecular shuttles,[1f] nanotubes[1g] and in the manufacture of protective eye glasses and filters.[1h] More recently, azobenzenes also opened door for a new discipline such as photopharmacology. The main objective of this field is the ability to change drug's activity with the help of light. This can be done by the incorporation of photo switchable units into the drug. On irradiation of light, photo switchable moieties change their conformation, thereby altering the drug's pharmacodynamic and pharmacokinetic properties. Though photopharmacology is still at its nascent stage in the field of medicine, it is strongly believed that it can provide an alternate pathway to resolve some of the highly addressed issues in near future. Due to their importance in various disciplines, synthesis and modification of azobenzenes is always

desirable. Some of the important examples of azobenzenes such as prontosil **I** (an antibacterial approved drug), sunset yellow SCF **II** (a food colorant) along with photoswitchable targets like azopropofol**III** and azoquinolone**IV** are listed in figure 1.[1i]Azobenzenes can be synthesised from some of the traditional methods such as azo-coupling reactions (coupling of diazonium salts with activated aromatic compounds), Mills reaction (anilines react with aromatic nitroso compounds), Gill's synthesis (acid mediated conversion of azoxybenzenes into 4-hydroxysubstituted azoderivatives) and many other strategies were well documented in the literature. As numerous reports were cited for their synthesis, chemists are now more inclined towards the functionalization of azobenzenes, thereby its structural and photophysical properties can be altered, which can have a potential impact in new disciplines such as photopharmacology and as molecular switches. On the other hand, transition metal catalyzed C-H activation protocol[(2-5)] has drawn attention of synthetic chemists from the past few decades due to its step economical and cost effective strategy. Motivated by the importance of photo switchable units in the area of photopharmacology, we planned to synthesize the azobenzene attached bioactive compounds such as phenanthridinones and lactones *via* directed C-H activation strategy. It is worth to mention that in the field of C-H activation, azo benzenes serve as the directing groups. In this regard, some of the representative examples related to functionalization of azobenzenes are presented in the section below.

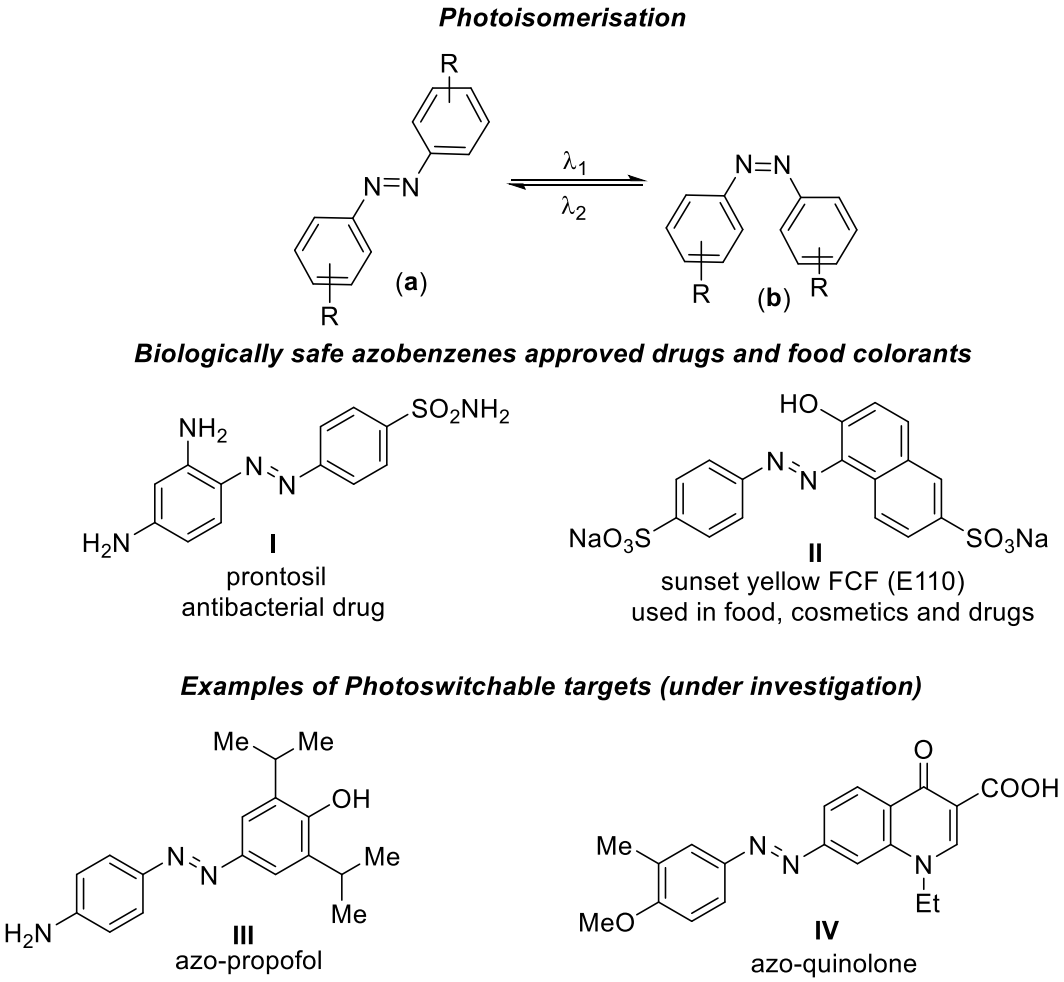


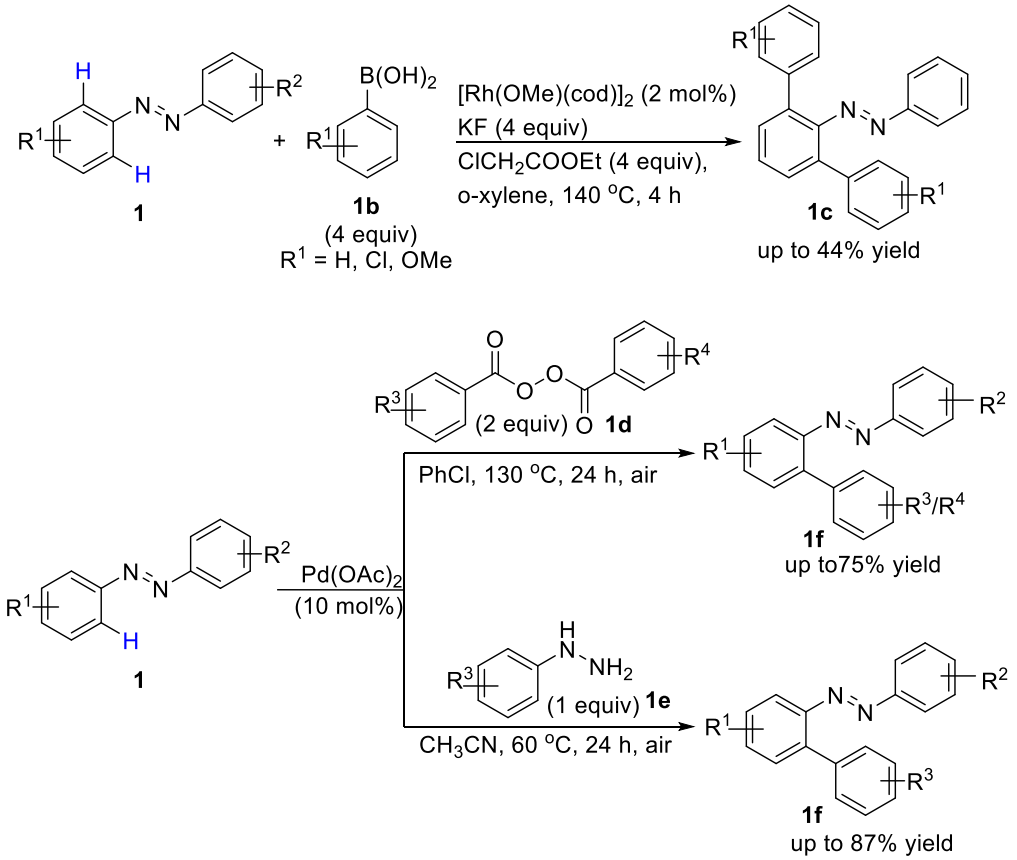
Figure 1. Examples of biologically active azo based compounds.

Literature reports dealing with the representative examples of arylation and alkylation of azobenzenes:

Arylation of Azobenzenes:

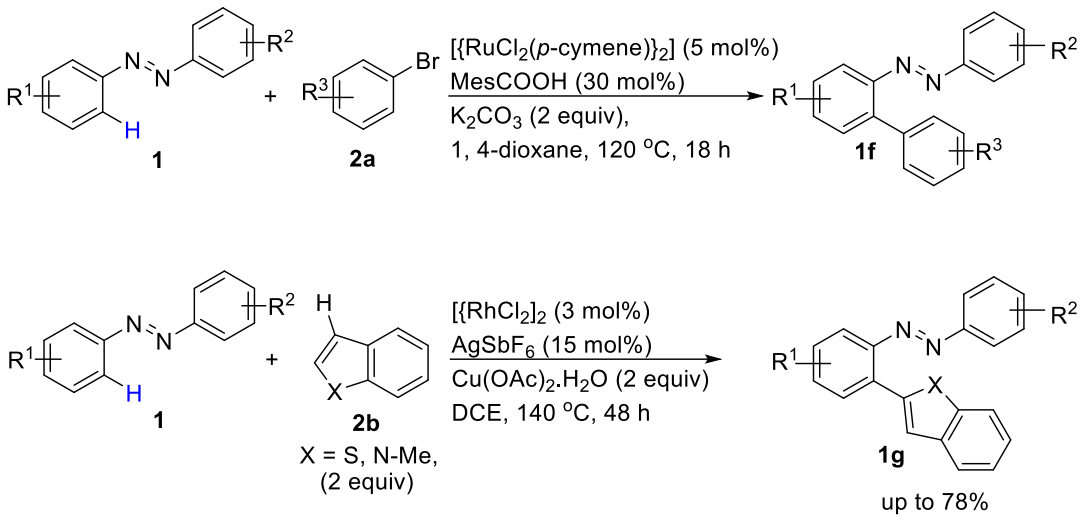
In 2008, Miura and co-workers[6a] demonstrated the first example of polyfunctionalization under rhodium catalysis (Scheme 1a). Motivated by the fact that no example related to phenylation of azobenzene reported so far, they subjected azobenzene substrate **1**to phenylboronic acids **1b** in thepresence of a catalytic amount of $[Rh(OMe)(cod)]_2$ and ethylα-chloroacetate (serves as hydrogen acceptor) and double orthophenylatedproducts **1c** were obtained. In 2014, for the first time, Zeng's group[6b] disclosed the Pd catalyzed C-H arylation of azoarenes using aryl acyl peroxides **1d** as the coupling partner (Scheme 1a). After a year, Ye and co-workers[6c] described the synthesis of ortho-arylated azoarenes **1f** under palladium catalysis, wherein aryl hydrazines**1e** serve as the coupling partners (scheme **1a**). Both groups

disclosed a radical pathway with optimal reaction conditions such as $Pd(OAc)_2$ as the catalyst and atmospheric oxygen as the oxidant.



Scheme **1a**. Rh and Pd calayzed*ortho* C-H arylation of azoarenes.

In the year 2015, Ackermann's group[6d] demonstrated the C-H arylation of azoarenes **1** enabled by ruthenium(II) carboxylate complex (formed from Ru catalyst and MesCOOH) using aryl halides **2a** as the coupling partners (scheme 1b). In addition, they were also successful in synthesising ortho arylated anilines in one pot manner using the developed protocol. Wang and co-workers[6e] successfully developed a cross-dehydrogenative coupling route for the ortho C-H functionalization of azobenzenes with heteroarenes **2b** such as indole, benzothiophene and benzothiazole under rhodium catalysis (scheme 1b).

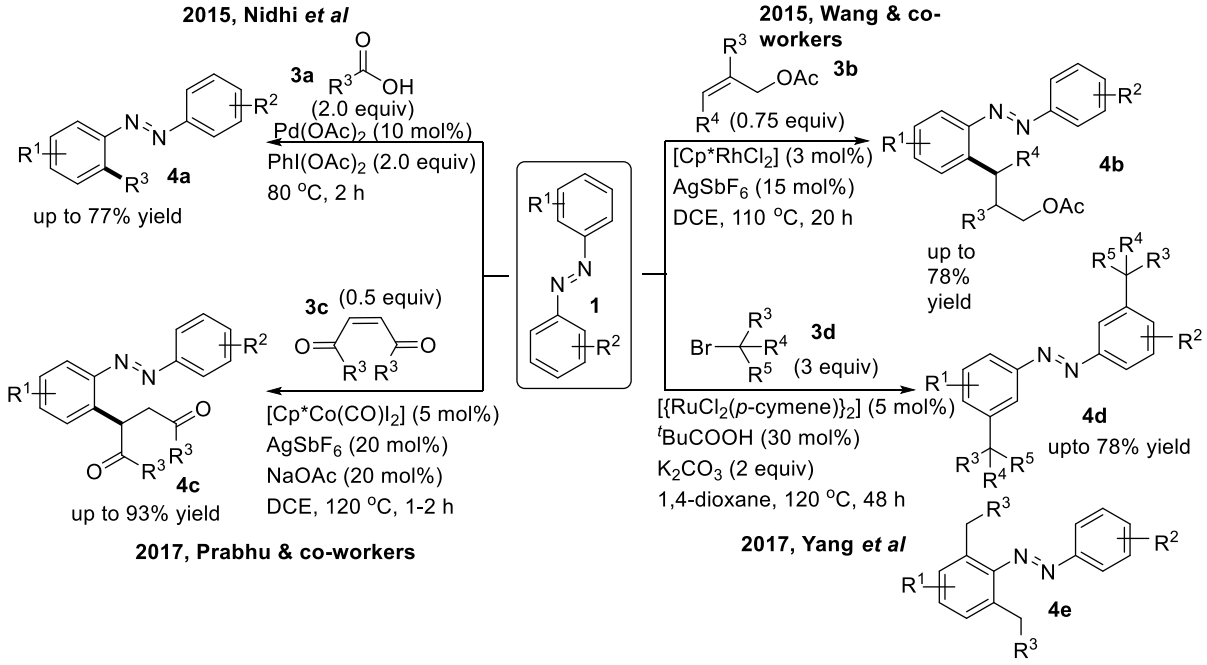


Scheme **1b**. *ortho* C-H arylation of azobenzenes.

Alkylation of azoarenes:

Though numerous reports have appeared in the context of C-H alkylation,[5]it is still of synthetic community's interest due to its limitations such as oxidative addition of alkyl halides is not favourable and also the resulting alkyl metal intermediates likely to undergo β-hydride elimination. In the year 2015, Wang and co-workers[7a] demonstrated the direct C-H alkylation of azobenzenes**1**with allyl acetates **3b** as the source of alkyl electrophiles under $[Cp^*RhCl_2]_2$/ $AgSbF_6$ catalyst system. Under this catalyst system, no olefinated products were observed. In the same year, Nidhi's group[7b] were the 1st ones to explorethe Pd catalyzed decarboxylative cross coupling strategy for the direct alkylation of azobenzenes**1** (Scheme 1c). The reaction proceeds *via* a solvent free pathway in combination with 10 mol% of $Pd(OAc)_2$ and 2.0 equiv of PIDA. A wide variety of secondary or tertiary α- substituted cyclic and acyclic aliphatic carboxylic acids **3a** were employed as alkyl source to afford monoalkylated products **4a** in good yields along with trace amounts of dialkylated products (Scheme 1c). In the year 2017, the first synthesis of *meta* alkylated azoarenes was revealed by Yang & co-workers[7c] under ruthenium catalysis (scheme **3**). The optimal reaction conditions involve $\{RuCl_2(p\text{-cymene})\}_2$ (5 mol%), *t*-BuCOOH (30 mol%) as an additive and K_2CO_3as a base. They demonstrated an interesting phenomenon: switch in site selectivity is based on the alkyl bromide **3d** chosen. They noticed the formation of *meta* alkylated products, when tertiary alkyl bromides were employed, wherein ortho alkylation happens with primary and secondary alkyl bromides. Apart from this, theyalso observed the formation of *ortho*-dialkylated products by doubling the stoichiometric amount of alkyl halides **3d**.

Following this report, Prabhu's group[7d] accomplished the highly regioselective alkylation of azoarenes with maleimides and maleate esters **3c** with the aid of Co catalyst (Scheme 1c). The reaction conditions involve [Cp*Co(CO)I_2] catalyst, $AgSbF_6$ and NaOAcadditives in DCE at 120 °C (Scheme 1c). Addition of acetate additive was found to play a key role in the improvement of yield and also to reduce the difunctionalized product formation.



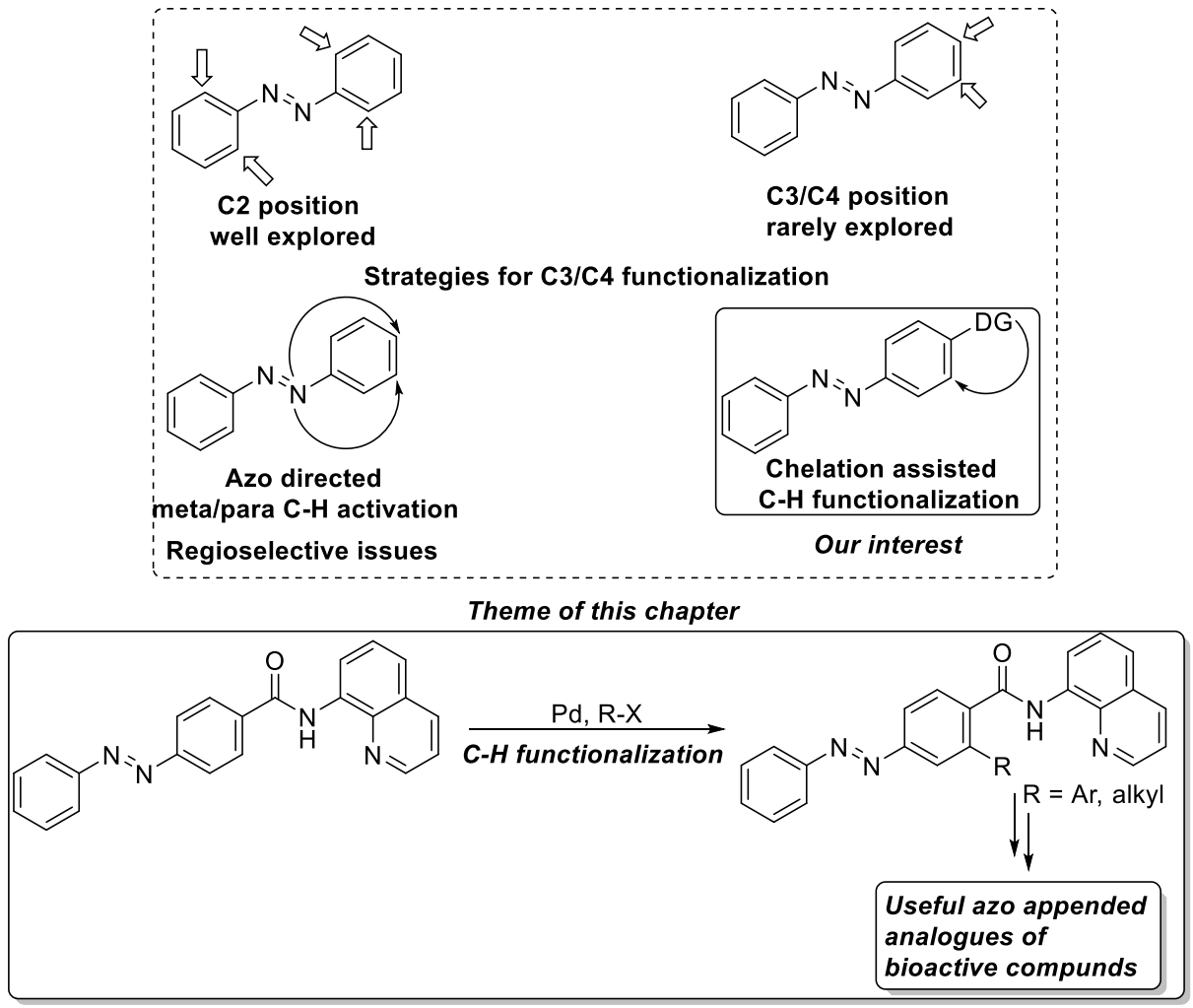
Scheme **1c**. Direct *ortho*/*meta* C-H alkylation of azoarenes by different transition metals (Pd, Rh, Co, Ru)

Apart from the above mentioned C-H functionalization of azoarenes (arylation as well as alkylation) catalyzed by various transition metals, Pd catalyzed C-C bond formations such as acylation,[8a] carbonylation,[8b] and other C-heteroatom bond constructions like acyloxylation,[8c,d] halogenation,[8e] alkoxylation,[8f] hydroxylation,[8g] nitration,[8h] phosphonylation[8i] and sulfonylation[8j] were well explored at the *ortho* C-H position of azoarenes in the past few years.

Background & Design:

Literature reports mentioned above enlightened us that numerous reports were documented on the C-H functionalization of azoarenes at *ortho* position (C2 position).[(6-8)] Wherein, to the best of our knowledge, only a single report is published on the *meta* C-H activation of azoarenes.[7c]This motivated us to work towards the meta C-H functionalization of azoarenes i.e C-3/4 position. Though, azo directed *meta* C-H activation is exceptionally a remarkable

finding, since we work on the directing group based strategy for the C-H functionalization, we decided to slightly tune the azoarene substrates. In this context, we planned to have another functional group/ directing group such as carboxylic acids, carboxamides at the para position of azoarenes, which thereby can coordinate to a transition metal, followed by the activation of proximal *ortho* C-H bond *i.e*, a meta C-H bond of azoarenes as depicted in Scheme 1d. Additionally, this might open a new door to have biologically more important azo based scaffolds, as the importance of carboxamides, carboxylic acids etc is well reported in the literature.

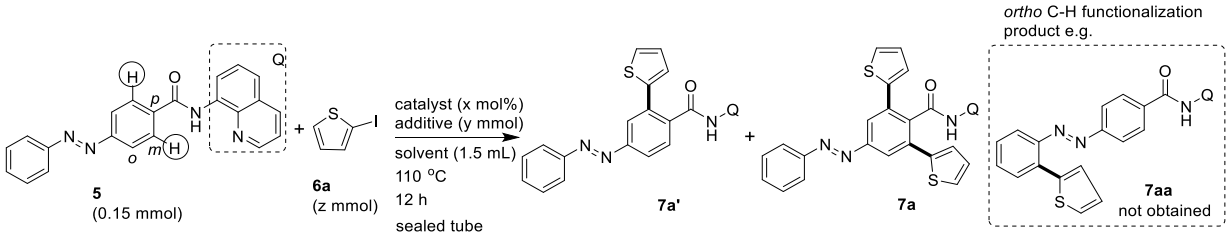


Scheme **1c.**Design Strategy.

Results and discussion

To begin with our investigations towards chemoselective functionalization of azobenzene carboxamides at C3 (*meta*)/C4 (*para*)*via*Pd(II) catalyzed 8-aminoquinoline enabled C-H activation, we have chosen azobenzene carboxamide **5** as the model substrate. We synthesized the model substrate **5**from its corresponding carboxylic acid and 8-aminoquinoline. As shown in Table 1, we then performed *β*-C-H arylation of the azobenzene carboxamide **5** with 2-iodothiophene**6a** under the standard reaction conditions involving a Pd catalyst and an iodide ion scavenger (e.g., AgOAc, Ag_2CO_3, K_2CO_3, etc).Heating a mixture of the azobenzene carboxamide **5**, 2-iodothiophene**6a** (2 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc in toluene at 110 ^oC for a period of 12 h afforded the bis *β*-C-H (*meta*) arylated azobenzene carboxamide **7a** in 32% yield (entry 1, Table 1). When the reaction was performed with the increased concentration of aryl iodide (4 equiv), the yield of bis *β*-C-H (*meta*) arylated azobenzene carboxamide **7a**was increased to 50% (entry 2, Table 1). Under the same reaction conditions, *β*-C-H arylation of the azobenzene carboxamide **5**was performed without palladium catalyst, it did not afford the product **7a**(Entry 3, Table 1). Further, we decreased the catalyst loading to 5% and performed the reaction, the yield of **7a** is dropped to 40% (entry 4, Table 1). We screened different salts such as Ag_2CO_3, K_2CO_3 and $NaHCO_3$ for the *β*-C-H arylation of the azobenzene carboxamide **5** with 2-iodothiophene**6a**(4equiv) (entries 6-8, Table 1). We observed the formation of product **7a**in 35% and 43%, when Ag_2CO_3 and K_2CO_3 were employed as iodide ion scavenger (entries 6, 7, Table 1). However, the reaction involving $NaHCO_3$ did not facilitate the product **7a** formation. We decreased the aryl iodide concentration from 4 equiv to 3 equiv and performed the reaction, surpsrisngly we noticed the formation of bis *β*-C-H (*meta*) arylated azobenzene carboxamide **7a**in an increased yield of 67%. (entry 9, Table 1). In all the attempts, the column chromatography purification of the crude reaction mixture gave the bis *β*-C-H (*meta*) arylated product **7a** and we did not obtain the mono *β*-C-H (*meta*) arylated azobenzene carboxamide **7a′** or any other byproductsuch as,N=N (azo) functionality-assisted *ortho* C-H activation product **7aa**. However, we attempted a reaction by replacing $Pd(OAc)_2$with $Ni(OTf)_2$ and Ag salt with Na_2CO_3 and successfully noticed the formation of mono *β*-C-H (*meta*) arylated azobenzene carboxamide**7a'** in 47% yield**.**

Table 1. Pd(II)-catalyzed*β*-C-H arylation of **5** with **6a**.



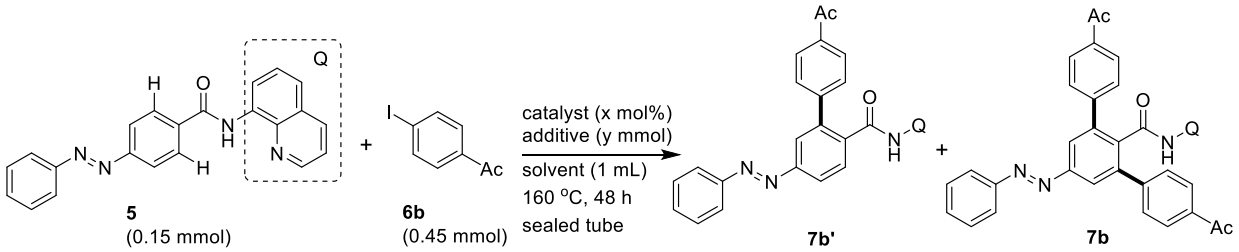
entry	**6a** (z mmol)	catalyst (x mol%)	additive (y mmol)	solvent (1.5 mL)	**7a':** yield (%)	**7a:** yield (%)
1	0.3	$Pd(OAc)_2$ (10)	AgOAc(0.30)	toluene	-	35
2	0.6	$Pd(OAc)_2$(10)	AgOAc (0.38)	toluene	-	50
3	0.6	nil	AgOAc (0.38)	toluene	-	-
4	0.6	$Pd(OAc)_2$ (5)	AgOAc (0.38)	toluene	-	40
5	0.6	$Pd(OAc)_2$ (10)	AgOAc (0.30)	toluene	-	38
6	0.6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.30)	toluene	-	35
7	0.6	$Pd(OAc)_2$ (10)	$NaHCO_3$ (0.30)	toluene	-	-
8	0.6	$Pd(OAc)_2$ (10)	K_2CO_3 (0.30)	toluene	-	43
9	**0.45**	**$Pd(OAc)_2$ (10)**	**AgOAc(0.30)**	**toluene**	**-**	**67**
10[(a)]	0.8	$Ni(OTf)_2$ (10)	Na_2CO_3 (0.4)	toluene	47	-

[a] 0.2 mmol scale of **5** and the reaction time was 36 h.

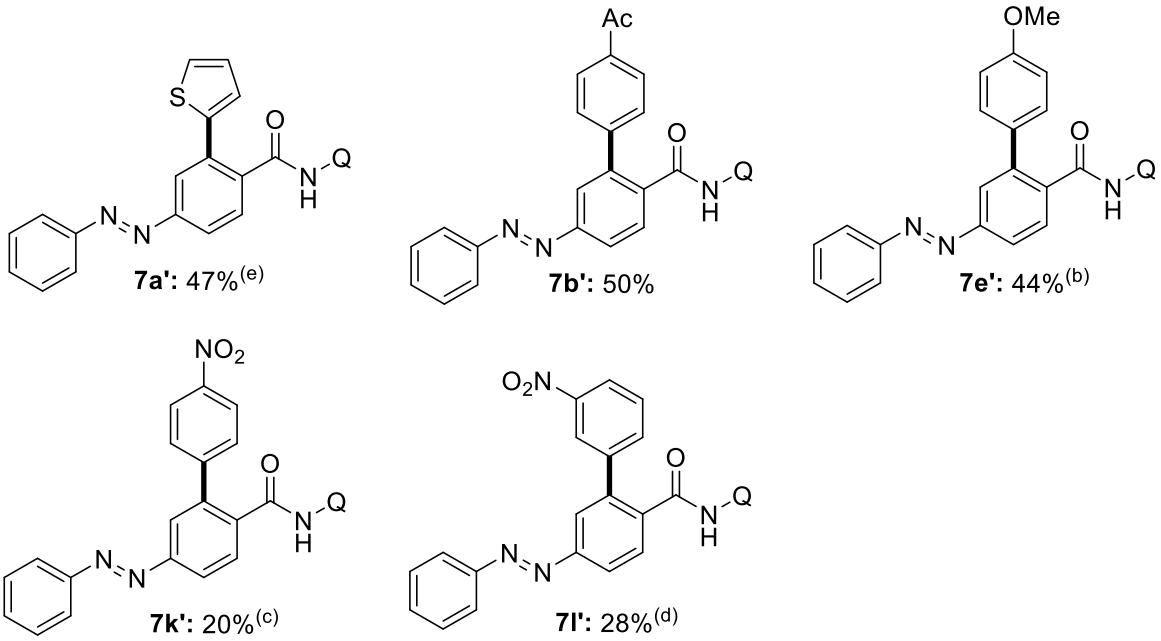
Since we observed the formation of mono *β*-C-H (*meta*) arylated product formation with a different metal catalyst such as $Ni(OTf)_2$ and a salt (Na_2CO_3), we started the optimization studies to achieve the mono *β*-C-H (*meta*) arylation using another aryl iodide 1-acetyl-4-iodobenzene,**6b**as the coupling partner (Table 2). Therefore, we heated a mixture of the azobenzene carboxamide **5**, aryl iodide **6b**(3 equiv), $Ni(OTf)_2$ (10 mol%) and an iodide ion scavenger (e.g., $KHCO_3$ or $NaHCO_3$ or K_2CO_3 or Cs_2CO_3 or KOAc or Na_2CO_3) in toluene at 160 °C. These reactions gave the mono*β*-C-H (*meta*) arylated azobenzene carboxamide **7b′** in 11-50% yields (entries 1-6, Table 2). Further, heating a mixture of **5**, aryl iodide **6b** (3 equiv), $Ni(OTf)_2$ (10 mol%) and Na_2CO_3 in *p*-xylene instead of toluene solvent generateda mixture of the bis *β*-C-H (*meta*) arylated product **7b** (17%) and the mono *β*-C-H (*meta*) arylated product **7b′** (40%) (entry 7, Table 2). The mono *β*-C-H (*meta*) arylation of **5**was also performed in the presence of different Ni catalysts such as, $Ni(acac)_2$ or $NiCl_2$ or $Ni(OAc)_2.4H_2O$ instead of $Ni(OTf)_2$. Employment of these catalysts did not improvise the yield of the product **7b′** (entries 8-10, Table 2).The reaction involving**5**, **6b** (3 equiv), $Ni(OTf)_2$ (10 mol%) and Na_2CO_3 in toluene yielded the mono arylated product **7b′** in a maximum of 50% yield and this condition is found to be the best possible reaction condition

for obtaining the mono *β*-C-H (*meta*) arylated azobenzene carboxamide **7b′** (entry 6, Table 2). We also carried out the C-H arylation of **5** with aryl iodides containing electron withdrawing or donating substitutes at the *para/meta* positions (e.g., OMe, NO_2). Hence, additional examples of mono *β*-C-H (*meta*) arylated azobenzene carboxamides **7e′** (44%), **7k′** (20%) and**7l′** (28%) were obtained in low to satisfactory yields (Table 2)

Table 2. Pd(II)-catalyzedmono*β*-C-H arylation. (Optimization studies and synthesis of mono *β*-C-H(*meta*) arylated azobenzene carboxamides**7a'**, **7b'**, **7e'**, **7k'**, **7l'**)



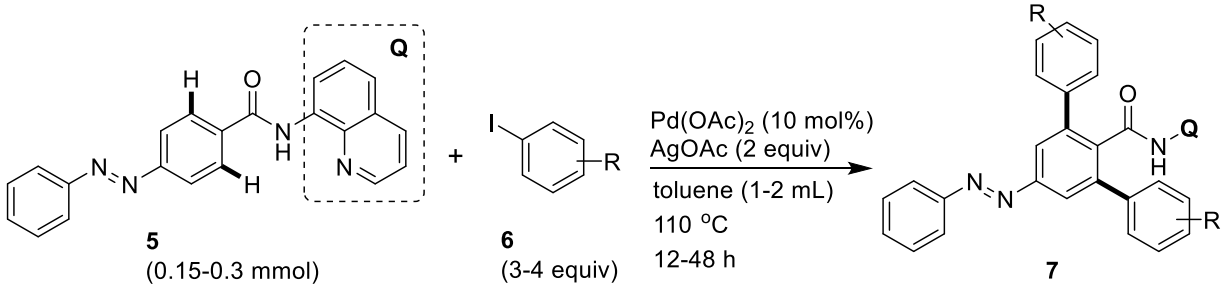
entry	**5** (mmol)	**6b** (mmol)	catalyst (x mol%)	additive (y mmol)	solvent	**7b':** yield (%)	**7b:** yield (%)
1	0.15	0.45	$Ni(OTf)_2$ (10)	$KHCO_3$ (0.45)	toluene	30	traces
2	0.15	0.45	$Ni(OTf)_2$ (10)	$NaHCO_3$ (0.45)	toluene	26	traces
3	0.15	0.45	$Ni(OTf)_2$ (10)	K_2CO_3 (0.45)	toluene	39	traces
4	0.15	0.45	$Ni(OTf)_2$ (10)	Cs_2CO_3 (0.45)	toluene	traces	traces
5	0.15	0.45	$Ni(OTf)_2$ (10)	KOAc (0.45)	toluene	11	traces
6	**0.15**	**0.45**	**$Ni(OTf)_2$ (10)**	**Na_2CO_3 (0.9)**	**toluene**	**50**	traces
7	**0.15**	**0.45**	**$Ni(OTf)_2$ (10)**	**Na_2CO_3 (0.45)**	***p*-xylene**	**40**	**17**
8	0.15	0.45	$Ni(acac)_2$ (10)	Na_2CO_3 (0.6)	toluene	7	traces
9	0.15	0.45	$NiCl_2$ (10)	Na_2CO_3 (0.6)	toluene	traces	traces
10	0.15	0.45	$Ni(OAc)_2.4H_2O$ (10)	Na_2CO_3 (0.6)	toluene	18	traces
11[(a)]	0.125	0.5	$Pd(OAc)_2$ (10)	AgOAc (0.28)	toluene	traces	40
12	0.15	0.45	$Ni(OTf)_2$ (10)	AgOAc (0.3)	toluene	-	-

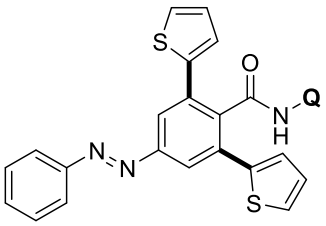


Reaction conditions: (a)The reaction time was 36 h. (b)**5** (0.2 mmol), ArI (0.8 mmol), Na_2CO_3(0.8 mmol). (c) **5** (0.2 mmol) ArI (0.6 mmol), Na_2CO_3(0.6 mmol), 36 h. (d)**5** (0.15 mmol), ArI (0.45 mmol), Na_2CO_3(0.45 mmol), 36 h. (e) **5** (0.2 mmol), ArI (0.8 mmol), Na_2CO_3(0.4 mmol), 36 h.

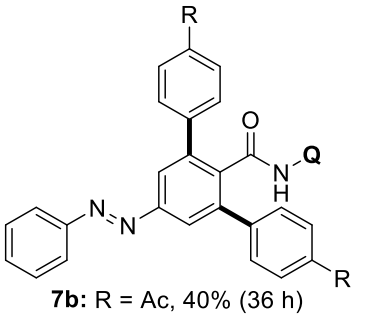
Having done the optimization reactions for both mono and bis arylated *β*-C-H arylation of azobenzene carboxamide, next we planned to explore the generality of this protocol. Therefore, we treated the azobenzene carboxamide **5** with phenyl iodide and aryl iodides containing electron withdrawing or donating substitutes at the *para* position (e.g., Ac, NO_2, COOMe, OMe, OEt, Et) in the presence of $Pd(OAc)_2$catalyst and AgOAc in toluene at 110 ^oC.These reactions afforded the corresponding bis *β*-C-H arylated azobenzene carboxamides**7b-7g,j** in 27-67% yields (Table 3).Similarly, the 8-aminoquinoline aided Pd(II)-catalyzed C-H arylation of azobenzene carboxamide **5** with *p*-hexyl-1-iodobenzene and a heteroaryl iodide compound gave the corresponding bis *β*-C-H arylated azobenzene carboxamides **7h,i** in 57-62% yields (Table 3).

Table 3. Pd(II)-catalyzed bis *β*-C-H arylation of **5**withvarious ArI.

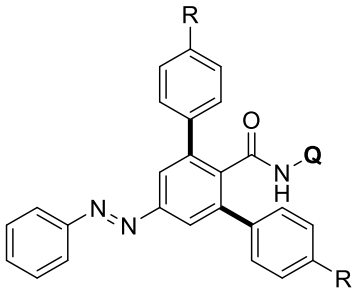




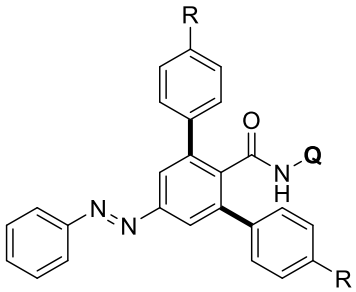
7a: 67% (12 h)



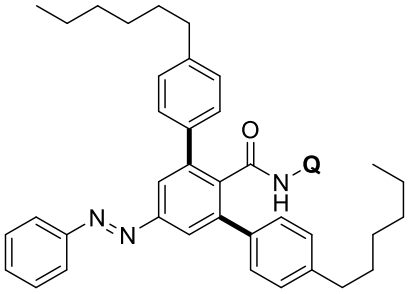
7b: R = Ac, 40% (36 h)
7c: R = NO_2, 67% (40 h)
7d: R = COOMe, 27% (56 h)



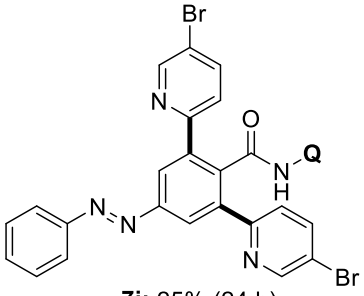
7e: R = OMe, 63% (36 h)
7f: R = OEt, 44% (48 h)



7g: R = H, 42% (48 h)
7j: R = Et, 62% (24 h)



7h: 57% (23 h)

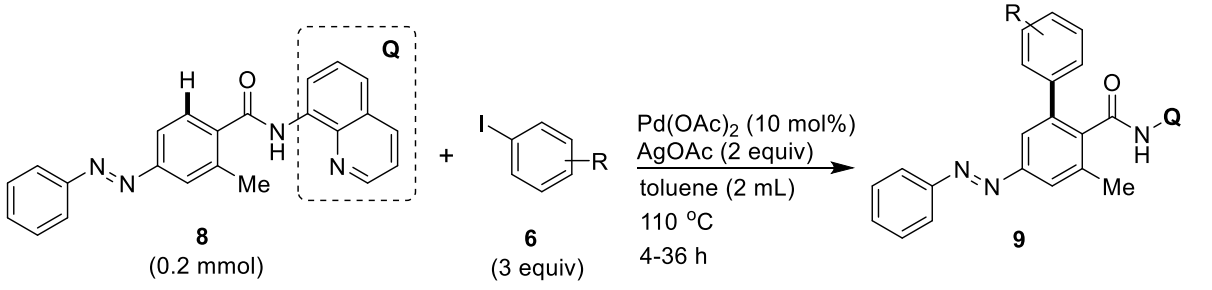


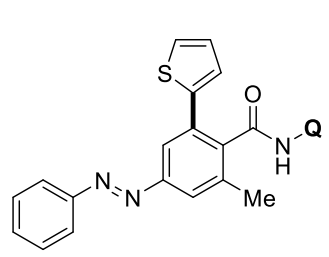
7i: 25% (24 h)

Next, to elaborate the substrate scope of the Pd(II)-catalyzed 8-aminoquinoline-assisted exclusivemono *β*-C-H arylation of azobenzene carboxamide, we prepared the substrate **8**bearing a methyl substituent at the *β*-position from its carboxylic acid and 8-aminoquinoline. Then, we performed the arylation of azobenzene carboxamide **8** with various heteroaryl iodides (e.g., 2-iodothiophene, 5-bromo-2-iodopyridine and 5-iodoindole) in the presence of $Pd(OAc)_2$ catalyst and AgOAc in toluene at 110 ^oC. These reactions generated the corresponding mono*β*-C-H arylated azobenzene carboxamides **9a-c** in moderate to good yields (50-78%, Table 4). Consequently, the azobenzene carboxamide**8** was treated with phenyl iodide and different aryl iodides containing electron withdrawing or donating substitutes at the *para / meta* positions (e.g., Et, OMe, ^{n}Bu, Me, CN, Cl, Ac, NO_2, etc) under the same reaction conditions. These reactions afforded the corresponding mono*β*-C-H arylated azobenzene carboxamides **9d-l**in moderate to good yields (51-78%, Table 4). The

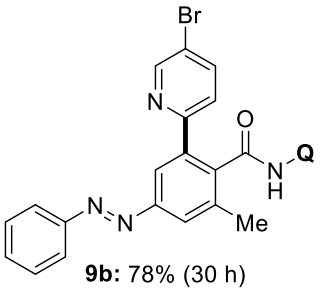
Pd(II)-catalyzed, 8-aminoquinoline-assisted arylation of carboxamide **8** with a disubstituted aryl iodide such as, 6-iodo-1,4-benzodioxane yielded the mono *β*-C-H arylated azobenzene carboxamides **9m** in 69% yield (Table 4). Prior to the preparation of library of mono arylated compounds, we anticipated that 3 equiv of aryl iodides may not be necessary as it is mono arylation process and performed a reaction with 2 equiv of 1-iodo-4-nitrobenzene. The decrease in the yield from 69% to 51% clearly suggested that 3 equiv of aryl iodide is needed for the reaction in order to have good yields (scheme 7).

Table 4. Pd(II)-catalyzed mono *β*-C-H arylation of **8**withvarious ArI.

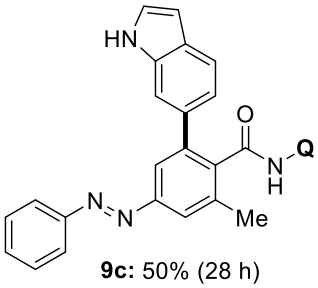




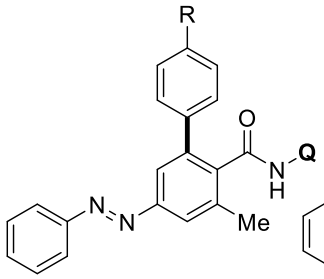
9a: 66% (4 h)



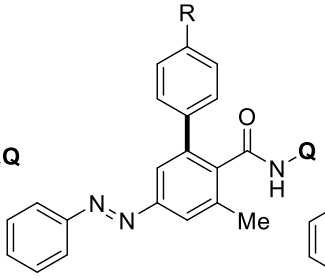
9b: 78% (30 h)



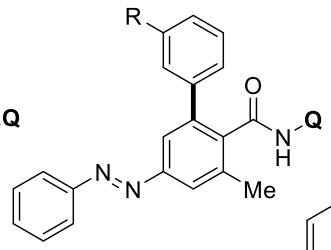
9c: 50% (28 h)



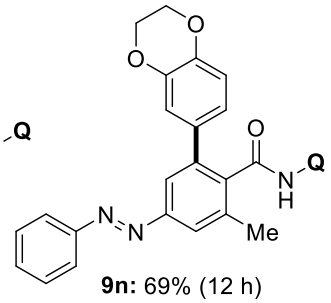
9d: R = H, 70% (36 h)
9e: R = Et, 70% (30 h)
9f: R = OMe, 78% (18 h)
9g: R = ^{n}Bu, 77% (15 h)



9h: R = CN, 59% (30 h)
9i: R = Cl, 65% (28 h)
9j: R = Ac, 56% (24 h)
9k: R = NO_2, 69% (24 h)
9k': R = NO_2, 51% (24 h)[(a)]



9l: R = Me, 77% (28 h)
9m: R = NO_2, 51% (36 h)



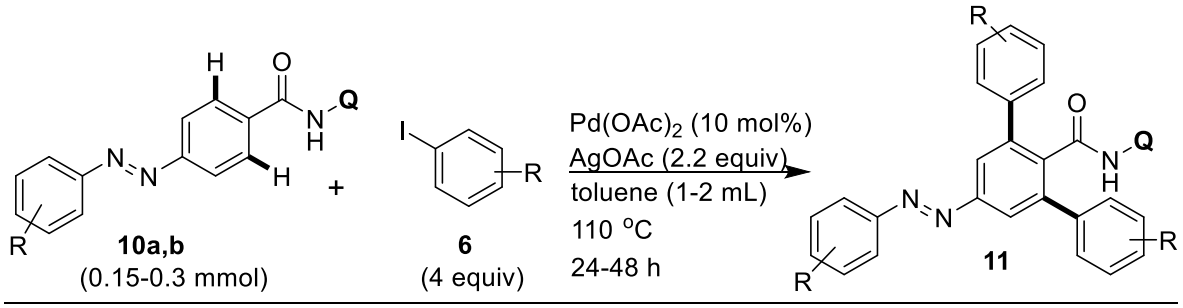
9n: 69% (12 h)

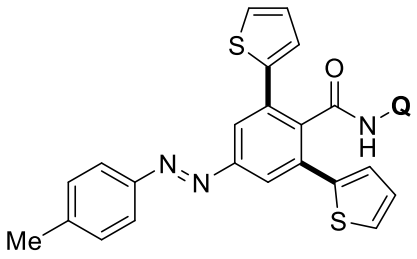
(a) 2 equiv of ArI is used.

Next, to further expand the substrate scope of this method, we prepared the **10 a**,**b** substrates positioned with a methyl substituent at *para* and *ortho* position of azoarene are prepared as shown in Table **5**. Initially, we performed the Pd(II)-catalyzed, 8-aminoquinoline-assisted

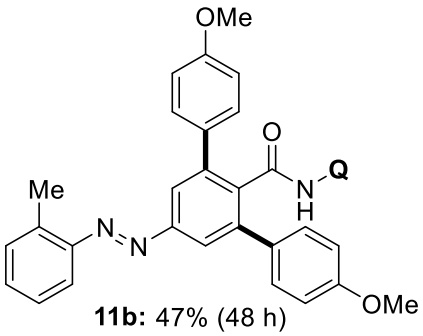
arylation of azobenzene carboxamides**10a,b** with 2-iodothiophene in refluxing toluene, which yielded the corresponding bis *β*-C-H arylated azobenzene carboxamides **11a** and **11c** in 50&61 % yields (Table 5). And, we also treated the azobenzene carboxamides**11a** and **11c***p*-anisyl iodide and 1-acetyl-4-iodobenzene in the presence of $Pd(OAc)_2$ catalyst and AgOAc in refluxing toluene, which gave the corresponding bis *β*-C-H arylated azobenzene carboxamides **11b** and **11d** in satisfactory yields (47% & 42% Table 5).

Table 5. Pd(II)-catalyzed bis *β*-C-H arylation of **10a,b**withvarious ArI.

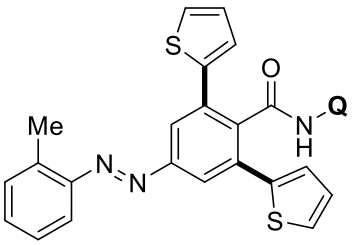




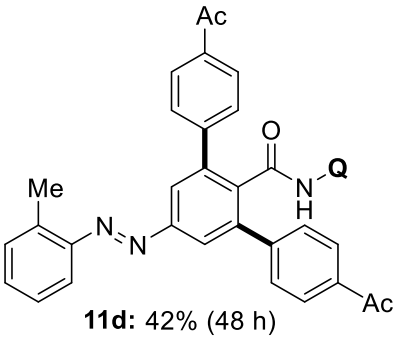
11a: 50% (24 h)



11b: 47% (48 h)



11c: 61% (24 h)

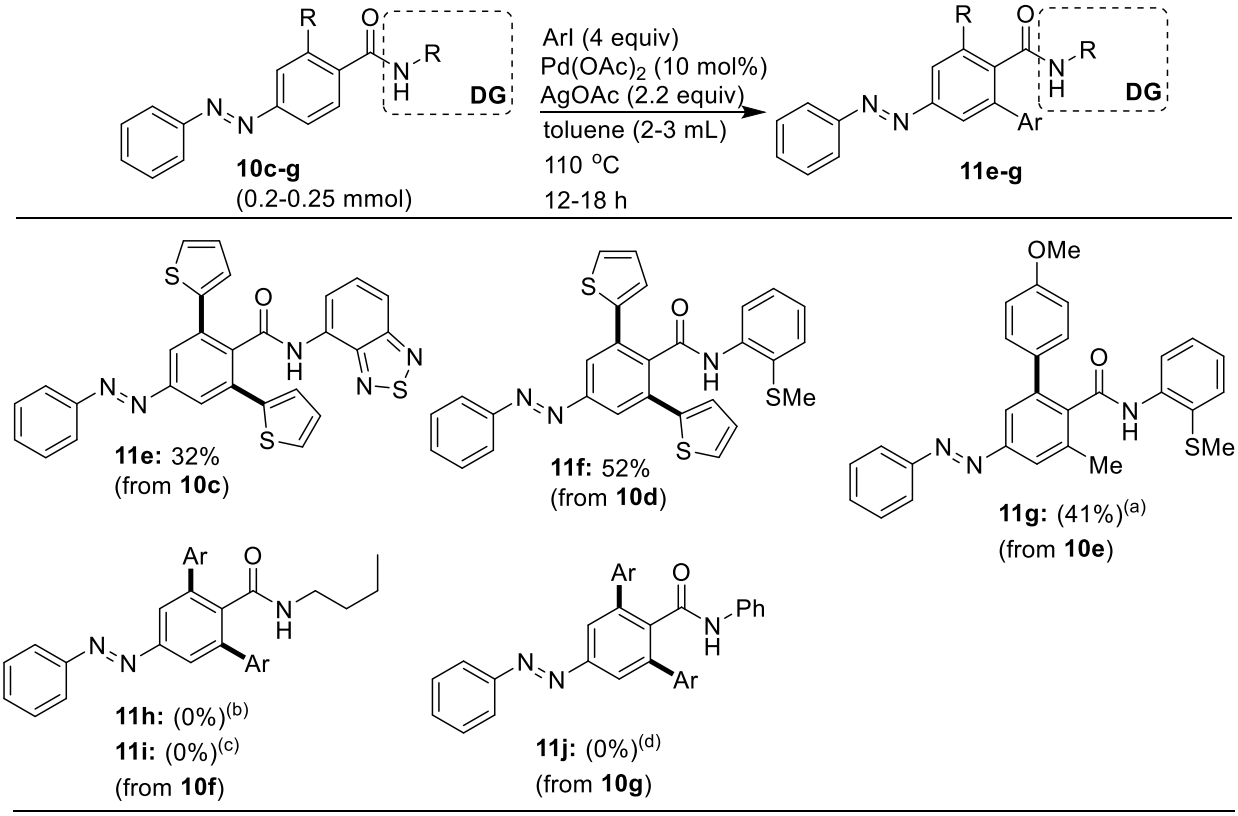


11d: 42% (48 h)

Having done the Pd(II)-catalyzed, *β*-C-H arylation of azobenzene carboxamides**5/8/10a,b**(prepared form their corresponding carboxylic acids) assisted by the bidentate directing group 8-aminoquinoline, we planned to examine the Pd(II)-catalyzed, *β*-C-H arylation of azobenzene carboxamides by using different directing groups. In this regard, we prepared various azobenzene carboxamides **10c-d**from their corresponding carboxylic acids and directing groups (amines). At first, the Pd(II)-catalyzed, bis *β*-C-H arylation of

azobenzene carboxamide **10c** possessingthe 4-amino-2,1,3-benzothiadiazole directing group with2-iodothiophene afforded the product **11e** in only 32% yield (Table 6). Next, the same reaction was performed on azobenzene carboxamide**10d**possessingthe 2-(methylthio)aniline directing group with2-iodothiophene and the product **11f**generated in satisfactory yield (52%,Table 6). We also performed the Pd(II)-catalyzed, mono *β*-C-H arylation of azobenzene carboxamide **10e** possessingthe 2-(methylthio)aniline directing group with*p*-anisyl iodide, which generated the product **11g** in only 41% (41%, Table 6). However, the Pd(II)-catalyzed*β*-C-H arylation of azobenzene carboxamides **10f** and **10g** containing the corresponding simple amide moieties did not yield the anyof the C-H arylation products**11h-j** (Table 6). These results indicated that the bidentate directing group 8-aminoquinoline found to be reasonably effective for the Pd(II)-catalyzed, *β*-C-H arylation of azobenzene carboxamides.

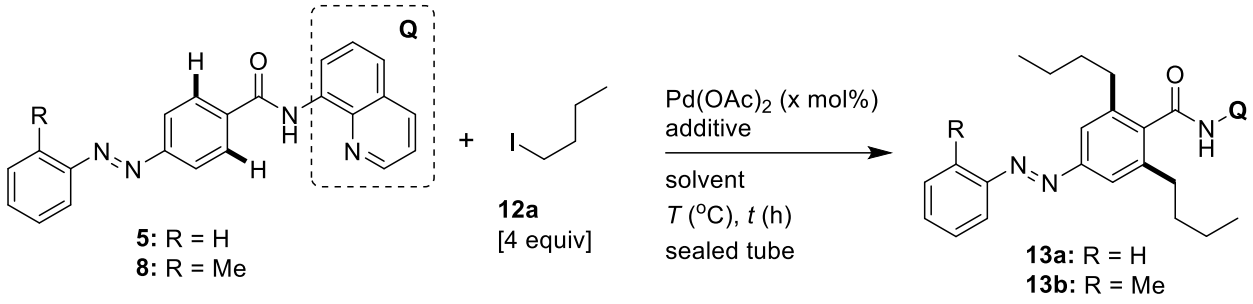
Table 6. C-H arylation of **10c-d**using different directing groups.



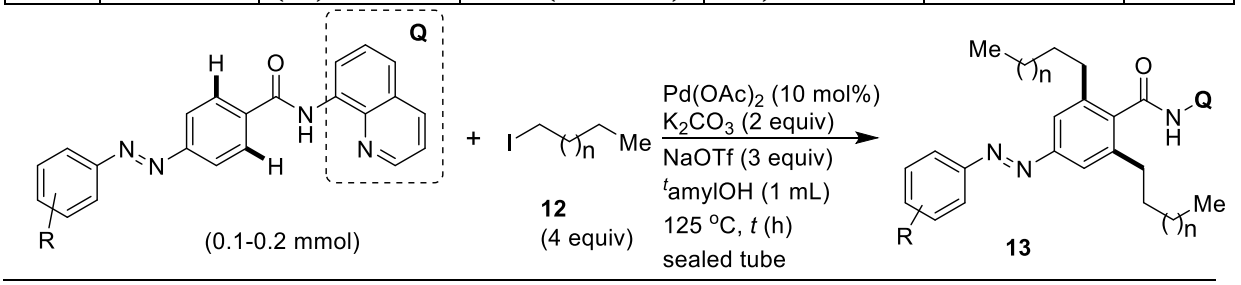
Reaction conditions: (a) Carboxamide (0.2 mmol), ArI (3 equiv), AgOAc (2 equiv), toluene (2 mL), 18 h. (b) Carboxamide (0.15 mmol), 4-iodoanisole (4equiv), AgOAc (2.2equiv), toluene (2 mL), 36 h. (c) Carboxamide (0.15 mmol), 4-iodoacetophenone (3 equiv), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (3equiv), toluene (1 mL), 160 ^oC, 40 h, sealed tube. (d) Carboxamide (0.15 mmol), 4-iodoanisole (4 equiv), AgOAc(2.2 equiv), toluene (2 mL), 36 h.

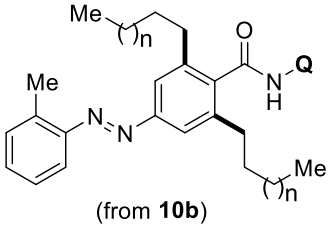
After examining the Pd(II)-catalyzed, *β*-C-H arylation of azobenzene carboxamides enabled by the bidentate directing group 8-aminoquinoline, we intended to expand the scope of this protocol by attempting the Pd(II)-catalyzed, *β*-C-H alkylation of azobenzene carboxamides using simple /long chain alkyl iodides. In this regard, initially, we subjected the azobenzene carboxamide **5** to the Pd(II)-catalyzed, 8-aminoquinoline-assisted bis *β*-C-H alkylation with 1-iodobutane under the standard *β*-C-H alkylation conditions comprising of Ag_2CO_3 and $(BnO)_2PO_2H$ (20 mol%) as an additive in *t*-AmylOH at 110 ^oC for 40 h. However, this reaction did not yield the expected *β*-C-H alkylated product **13a** (entry 1, Table 7). Treatment of carboxamide **5** with 1-iodobutane under the conditions comprising of $KHCO_3$ as an iodide ion scavenger and toluic acid as an additive in 1,2-DCEat 110 ^oC for 40 h did not afford the expected *β*-C-H alkylated product **13a** (entry 2, Table 7). Furthermore, the reaction of carboxamide **5** with 1-iodobutane under the conditions comprising of Ag_2CO_3 as an iodide ion scavenger and $CuBr_2$ as an additive in H_2Oat 120 ^oC for 48 h also did not yield the expected product **13a** (entry 3, Table 7). Notably, the reaction of carboxamide **5** with 1-iodobutane under the reported conditions has failed to afford the product**13a**.In a new attemptcomprising of the Pd(II)-catalyzed, 8-aminoquinoline-assisted bis *β*-C-H alkylation of **5** with 1-iodobutane in the presence of K_2CO_3 as an iodide ion scavenger and NaOTf as an additive in *t*-AmylOH at 125 ^oC for 22 h successfully yielded the **13a** in 88% yield (entry 4, Table 7). Under the same reaction conditions, the substrate with a methyl substituent, also generated the bis alkylated azobenzene carboxamide **13b** in 64% yield (entry 5, Table 7). In order to obtain monoalkylated product, another reactioninvolving the Ni-catalyzed bis *β*-C-H alkylation of **8** with 1-iodobutane was attempted. But we did not observe the formation of the alkylated product (entry 5, Table 7).

Table 7. Synthesis of *β*-C-H alkylated product **13a,b**.



entry	Substrate (mmol)	Catalyst (x mol%)	additive (y mmol)	solvent (mL)	**conditions**	**13:** yield (%)
1	**5** (0.10)	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.20), $(BnO)_2POOH$ (0.2)	^{t}amylOH (1 mL)	110 ^{o}C, 40 h	**13a**: 0
2	**5** (0.10)	$Pd(OAc)_2$ (10)	$KHCO_3$ (0.20), *o*-toluic acid (0.2)	1,2-DCE (1 mL)	110 ^{o}C, 40 h	**13a**: 0
3	**5** (0.10)	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.40), $CuBr_2$ (0.04)	H_2O (1 mL)	120 ^{o}C, 48 h	**13a**: 0
4	**5** (0.10)	$Pd(OAc)_2$ (10)	K_2CO_3 (0.20), NaOTf (0.3)	^{t}amylOH (1 mL)	125 ^{o}C, 42 h	**13a**: 88
4	**8** (0.15)	$Pd(OAc)_2$ (10)	K_2CO_3 (0.30), NaOTf(0.45)	^{t}amylOH (1 mL)	125 ^{o}C, 22 h	**13b**: 64
5	**8** (0.15)	$Ni(OTf)_2$ (10)	Na_2CO_3 (0.30), PPh_3 (20 mol%)	Toluene (1 mL)	150 ^{o}C, 50 h	**13b**: 0



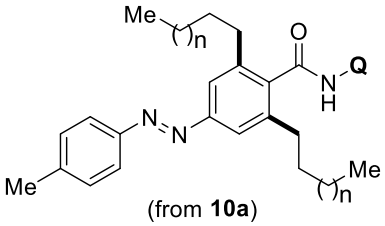


13b: n = 1, 64%
(0.15 mmol scale, 22 h)

13c: n = 2, 83%
(0.15 mmol scale, 48 h)

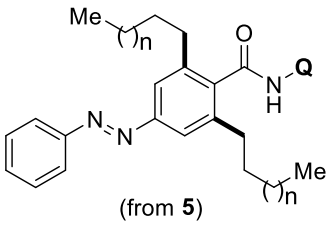
13d: n = 4, 51%
(0.15 mmol scale, 48 h)

13e: n = 5, 76%
(0.15 mmol scale, 22 h)



13f: n = 1, 35%
(0.125 mmol scale, 36 h)

13g: n = 5, 64%
(0.15 mmol scale, 48 h)



13a: n = 1, 88%
(0.1 mmol scale, 42 h)

13h: n = 2, 64%
(0.15 mmol scale, 48 h)

13i: n = 4, 68%
(0.15 mmol scale, 26 h)

13j: n = 5, 79%
[0.15 mmol scale, 24 h]

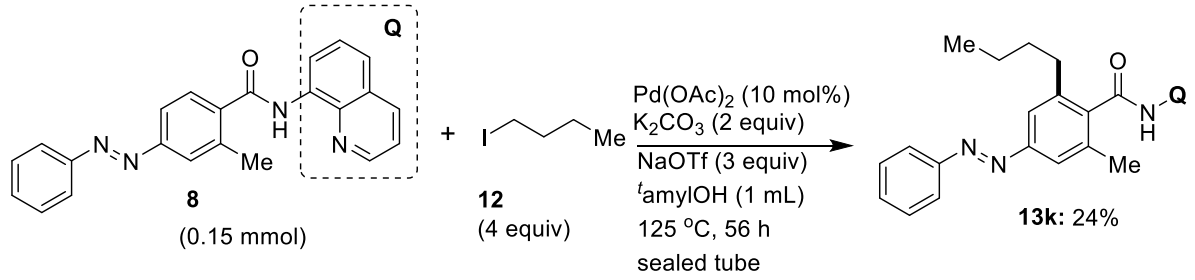
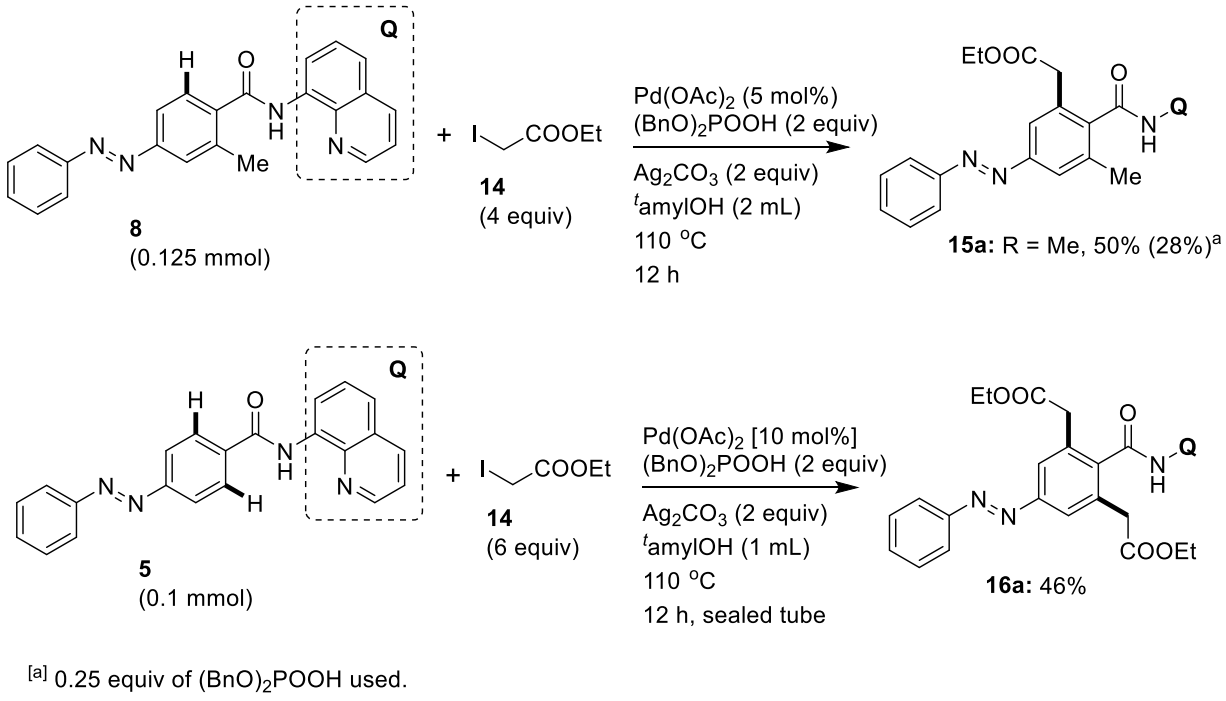


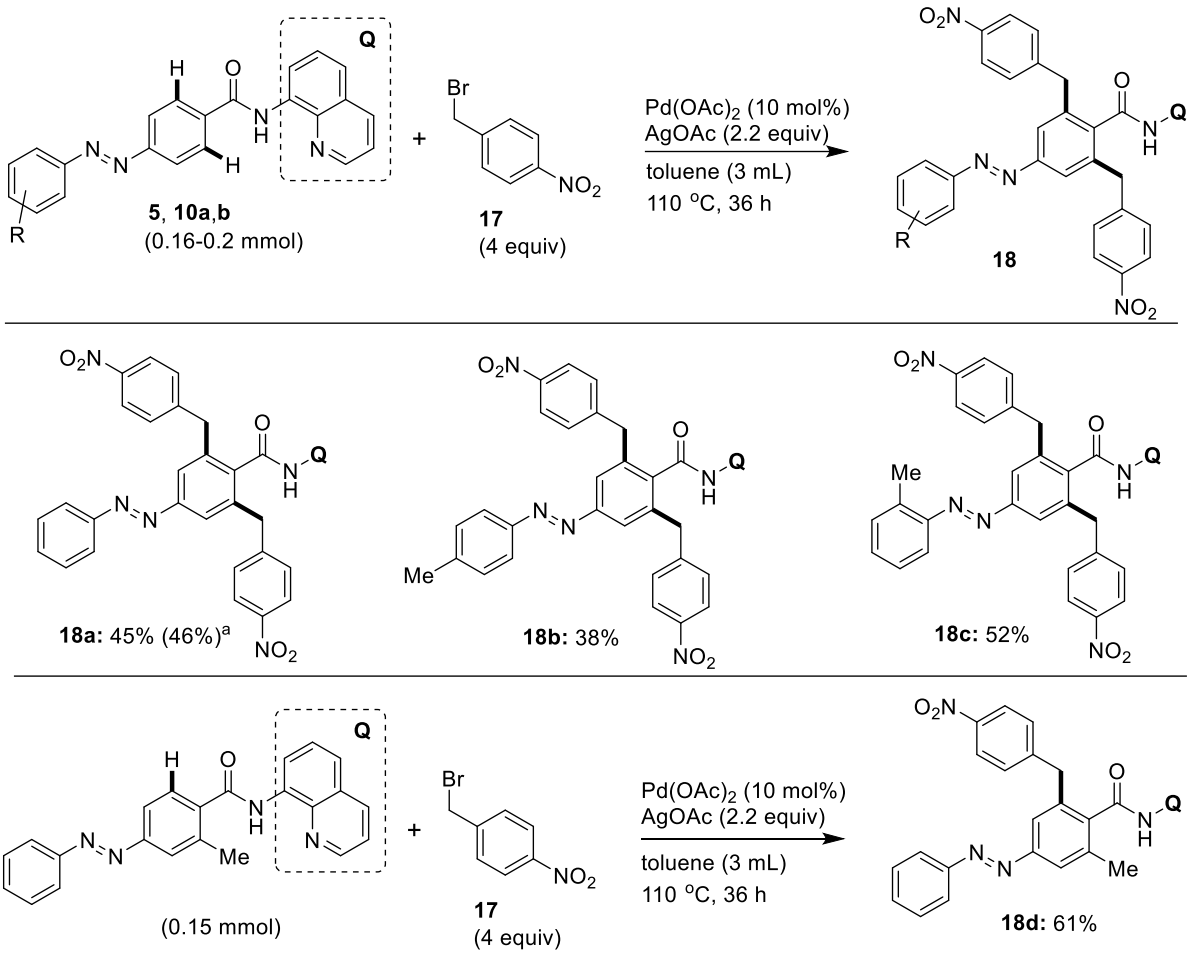
Table 8. Synthesis of *β*-C-H alkylated product **13b-k**.

Having found a suitable reaction conditions for the Pd(II)-catalyzed aminoquinoline-assisted *β*-C-H alkylation of azobenzene carboxamide **5**, next we planned to explore the generality of the *β*-C-H alkylation protocol. In this regard, initially, we performed the Pd(II)-catalyzed, 8-aminoquinoline-assisted bis *β*-C-H alkylation of carboxamide **10b** with various long chain alkyl iodides in the presence of K_2CO_3 as an iodide ion scavenger and NaOTf as an additive in *t*-AmylOH at 125 ^oC for 22-48 h (Table 3). These reactions yielded the corresponding bis *β*-C-H alkylated azobenzene carboxamides **13b-d** in 64-83% yields (Table 8). Similarly, the Pd(II)-catalyzed bis *β*-C-H alkylation of carboxamides **5** and **10a** with various long chain alkyl iodides successfully yielded the corresponding bis *β*-C-H alkylated azobenzene carboxamides **13e-k** in 35-88% yields (Table 8). On the other hand, we performed the Pd(II)-catlyzed 8-aminoquinoline-aided*β*-C-H alkylation on the azobenzene carboxamide **8**with 1-iodobutaneand this reaction successfully facilitated the formation of asymmetrical alkylated product**13k** in 24% yield (Table 8).



[a] 0.25 equiv of $(BnO)_2POOH$ used.

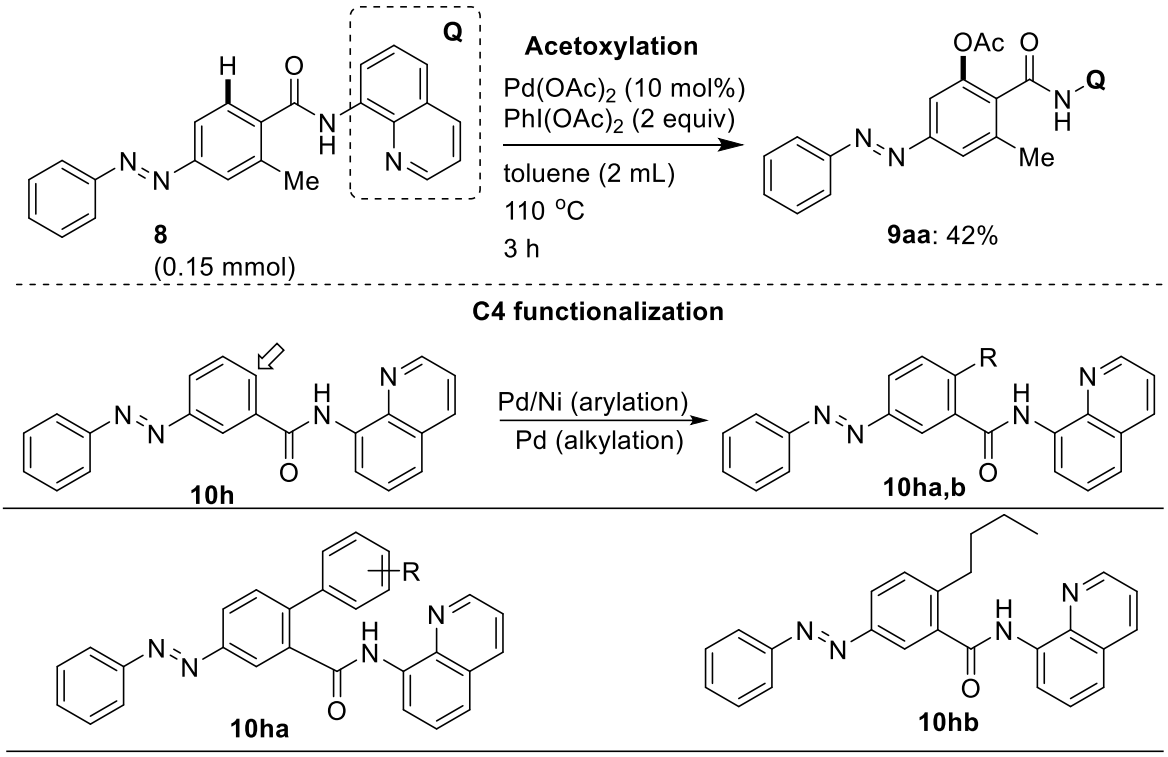
Scheme 2. Synthesis of *β*-C-H alkylated products **15a/16a**.



Scheme 3. Synthesis of *β*-C-H benzylated products **18**.[(a)]1.5 equiv of AgOAc

After investigating the *β*-C-H alkylation of azobenzene carboxamides withsimple /long chain alkyl iodides, we planned to perform the *β*-C-H alkylation of azobenzene carboxamides with activated alkyl halides. In this regard, we initially performed the Pd(II)-catalyzed, 8-aminoquinoline-assisted mono *β*-C-H alkylation of azobenzene carboxamide **8** with ethyl iodoacetate, Ag_2CO_3 as an iodide ion scavenger and $(BnO)_2PO_2H$ (0.2 equiv) as an additive in *t*-AmylOH at 110 ^oC for 12 h. This reaction yielded the mono *β*-C-H alkylated azobenzene carboxamide **15a** in 28% yield (Scheme2). Encouraged by this result, the reaction is repeated with the same conditions for substrate **8** by increasing the equivalents of the additive $(BnO)_2POOH$ to 2 equiv and the yield is improved to 50% yield. Similarly, the Pd(II)-catalyzed, 8-aminoquinoline-assisted bis *β*-C-H alkylation of azobenzene carboxamide **5** with ethyl iodoacetate generated the bis *β*-C-H alkylated azobenzene carboxamide **16a** in 46% yield. Encouraged by the success obtained in the *β*-C-H alkylation of azobenzene carboxamides **5/8**, we attempted the *β*-C-H benzylation of azobenzene carboxamides **5, 8, 10a,b**. Accordingly, we treated the azobenzene carboxamides**5, 8, 10a,b**with *p*-

nitrobenzylbromide in the presence of the $Pd(OAc)_2$ catalyst and AgOAc in refluxing toluene. These reactions generated the bis *β*-C-H benzylated azobenzene carboxamides **18a-d** in satisfactory to moderate yields (38-61%, Scheme 3).



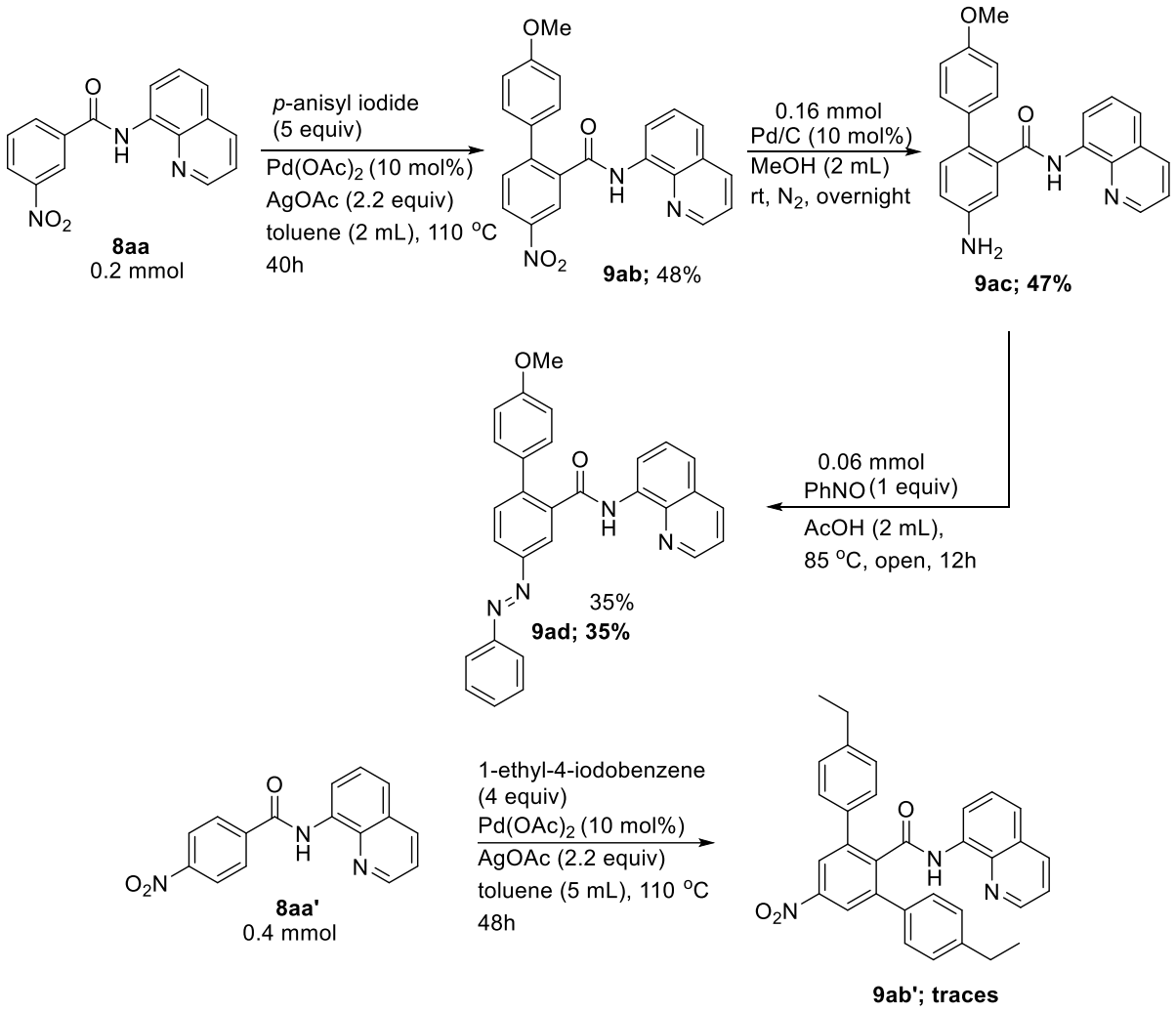
Scheme 4. Pd catalyzed*β*-C-H acetoxylation of azobenzene carboxamides

We also planned to explore the usefulness of the Pd(II)-catalyzed, bidentate directing group 8-aminoquinoline assisted C-Hfunctionalization for obtaining functionalized azobenzene derivatives. In this line, we performed the Pd(II)-catalyzed, bidentate directing group 8-aminoquinoline assisted *β*-C-H acetoxylation of azobenzene carboxamide **8** with $PhI(OAc)_2$ in toluene at 110 ^oC for 3 h. This reaction yielded the *β*-C-H acetoxylated azobenzene carboxamide **9aa** in good yield 42% (Scheme 4). Having explored the C3 functionalization of azobenzene carboxamides, we are also interested in the synthesis of C4 functionalized azobenzene carboxamides. In this regard, we prepared a precursor meta positioned azobenzene carboxamide **10h** and exposed to the above established reaction conditions Pd/Ni catalyzed arylation reactions (Scheme 4)and also to the Pd catalyzed*β*-C-H alkylation reaction conditions. Unfortunately, we could not obtain product (**10ha,b**) in any of the reaction conditions (Scheme 4). We assembled the 3-nitrobenzamide **8aa** from 3-nitrobenzoic acid and 8-aminoquinoline. Then, we carried out the Pd(II)-catalyzed, 8-aminoquinoline-assisted *β*-C-H arylation of carboxamide**8aa** with *p*-anisyl iodide, which afforded the *β*-C-H

arylated 3-nitro benzamide **9ab**. The 3-nitro benzamide **9ab** was subjected to the Pd-catalyzed reduction of nitro moiety to afford the 3-aminobenzamide **9ac**, which was then treated with nitrosobenzene to afford the azobenzene derivative **9ad** (Scheme 4).

Alternate route for the synthesis of azo attached compounds *via* conventional/ Azologisation approach:

We are interested to explore the same *via* the traditional approach i.eazologisation route, through which usually azo based compounds are prepared. Azologisation can be initiated with a nitro compound or an aniline compound. Since our approach is based on C-H activation methodology, it is not appropriate to start the reaction using aniline compound, as the number of steps might increase in protecting and deprotecting the $-NH_2$ group. Keeping this in mind, we have prepared the precursors 3-nitro benzamide **8aa** and 4- nitro benzamide **8aa'** and exposed to the Pd catalyzed*β*-C-H arylation as shown in scheme **5**. To our surprise, we could only observe arylated product **9ab** in case of 3-nitro benzamide **8aa**in considerable yield (48%) and a trace amount of product **9ab**' in case of 4-nitro benzamide **8aa'.** The obtained mono arylated product **9ab** is subjected to reduction with the help of Pd/C (10 mol%) in MeOH at room temperature for a period of 12 h under hydrogen atmosphere. As a result, reduced product **9ac** is obtained in 47% yield, which is further treated with the nitrosobenzene**21e**to afford the azobenzene derivative **9ad** in 35% yield (scheme 14). In order to prepare bis arylated azobenzene carboxamides, we couldn't find this as the suitable approach as the first step i.e arylation failed to give the desired targets in considerable yields. In case of **21a**, we tried screening other aryl iodides, none of them are found to be fruitful to afford the arylated targets. This clearly suggested us thatthe developed Pd catalyzed*β*-C-H arylation is relatively a better methodin order to obtain functionalized products of azobenzene carboxamides, as compared to the conventional azologisation approach.

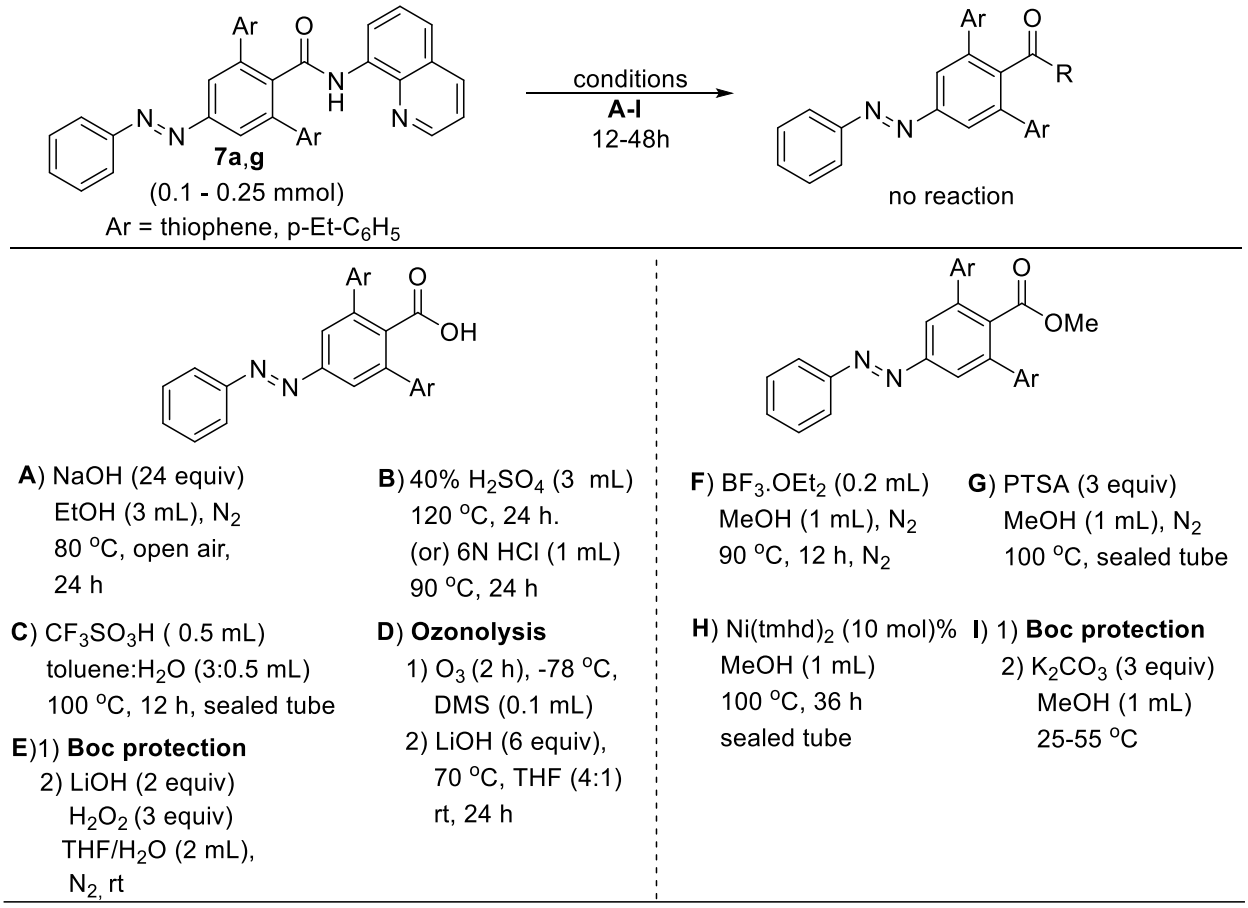


Scheme 5. Alternate approach for the synthesis of functionalized azo benzene carboxamides.

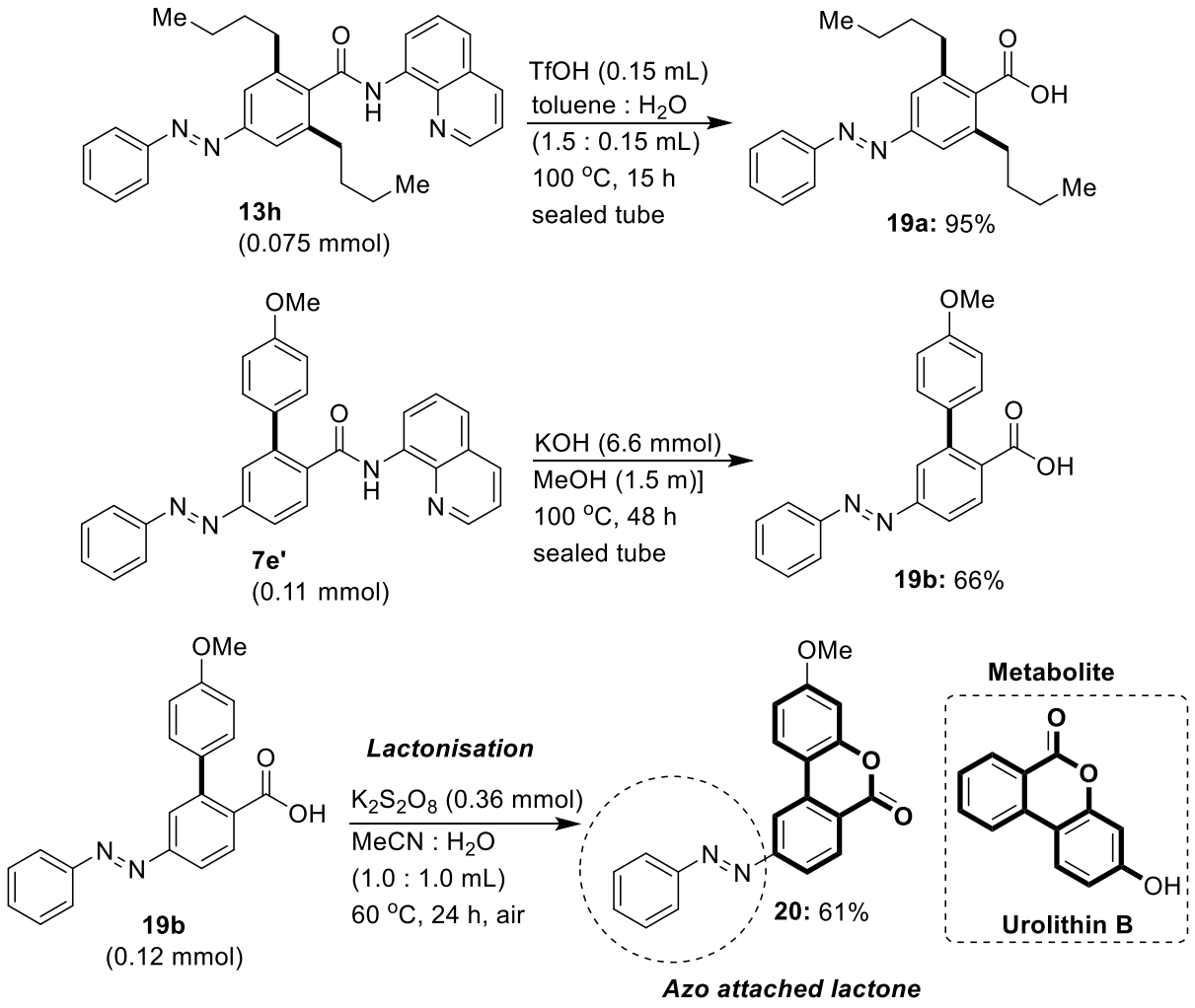
To disclose the synthetic utility of this method, we wished to carry out the removal of the 8-aminoquinoline bidentate directing group after performing the Pd(II)-catalyzed*β*-C-H alkylation and arylation of azobenzene carboxamides. In this regard, both arylated and alkylated azobenzene carboxamides are subjected to basic, acidic and several other conditions as per literature precedents.[9] None of the reactions yielded any positive result (scheme 6). Out of various attempts, we succeeded in removing the 8-aminoquinoline bidentate directing group from the bis *β*-C-H alkylated azobenzene carboxamides **13h** by treating itwith TfOH in toluene/H_2O at 100^{o}C and this reaction yield the azobenzene carboxylic acid **19a** in 95% yield (Scheme 7). Similarly, we also succeeded in removing the 8-aminoquinoline bidentate directing group from the mono *β*-C-H arylated azobenzene carboxamides **7e′** by treating itwith KOH in MeOH at 110 ^{o}C and this reaction afforded the azobenzene carboxylic acid **19b** in 66% yield (Scheme 7). Subsequently, we also attempted the conversion of the

carboxylic acid **19b** into the azobenzene lactone derivative **20** via the δ-C-H lactonization of the azobenzene carboxylic acid **19b**. Treatment of **19b** with $K_2S_2O_8$ in MeCN/ H_2O at 60 ^oC for 24 h generated the azobenzene lactone derivative **20** in 61% yield, which is in close resemblance with a metabolite named Urolithin **B** (Scheme 4).

The structure of the azobenzene lactone derivative **20** unequivocally assigned based on the X-ray structure analysis. Further, it may be noted that the X-ray structure of **20** also validates the following that (a) the Pd(II)-catalyzed C-H alkylation and arylation of azobenzene carboxamides chemoselectively occurredat the β-C-H bonds next to the carboxamide moiety, (b) the N=N functionality is intact under the experimental conditions (including $Pd(OAc)_2$/ AgOAc catalytic system as well as $Ni(OTf)_2/Na_2CO_3$) and (c) the azo group-assisted *ortho* C-H functionalization and other expected byproducts can be eliminated.



Scheme6. Trials for the cleavage of auxilliary (8-aminoquinoline).



Scheme 7. Synthetic transformations of *β*-C-H functionalized products **13h, 7e′**and **19b**.

Conclusions:

In summary, we have shown our investigations on the Pd(II)-catalyzed bidentate directing group aminoquinoline-assisted, *β*-C-H activation/functionalization (arylation, alkylation, acetoxylation etc) of azobenzene carboxamides. Azobenzene derivatives are valuable substrates in chemical sciences, especially, in the history of C-H functionalization. This is because the N=N (azo) group served as an inherent directing in the transition metal-catalyzed*ortho* C-H functionalization of azobenzenes. On the contrary, in this work, we have exemplified the usefulness of the Pd(II)-catalyzed aminoquinoline-assisted C-H functionalization for the synthesis of various *β*-C-H functionalized azobenzene carboxamides by negating the N=N (azo) group assistance. We did not isolate any *ortho* C-H functionalized azobenzenes in characterizable amounts under the present experimental conditions. Considering the importance and applications of azobenzenes in chemical sciences, this

method comprising of the Pd(II)-catalyzed aminoquinoline-assisted, *β*-C-H functionalization should serve as a useful method for enriching the libraries azobenzene derivatives. Our laboratory is currently working to further elaborate the bidentate directing group assisted functionalization of azobenzenes and to reveal the applications of the synthesized compounds.

All the compounds included in this chapter are characterized by different techniques including ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data and experimental details of all the compounds are given in the experimental section.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra of compounds were recorded (using TMS as an internal standard) in 400 and ~101 MHz spectrometers, respectively. The HRMS analysis data of samples reported here were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. IR spectra of samples reported here were recorded as neat or thin films. Column chromatography purification was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atm wherever required. Organic layers obtained after workup were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel or alumina plates and components were visualized by observation under iodine vapor. Isolated yields of all the products are reported and yields were not optimized. In all of the cases, after the Pd(II)-catalyzed reactions, the respective crude reaction mixtures were subjected to the column chromatographic purification and we were focused to isolate the corresponding products shown in the respective Schemes/Tables and we did not obtain any other by products in characterizable amounts. While in most of the cases the azobenzenes with *trans* geometry were isolated in pure form, in some cases, the NMR spectra revealed the presence of partial amounts azobenzenes with *cis* geometry. In some cases, to obtain pure NMR spectra we gently heated the isolated azobenzenes to convert the azobenzenes with *cis* geometry into azobenzenes with *trans* geometry. The corresponding azobenzene carboxylic acids (required to assemble the carboxamides **10a,b**) were assembled using the standard literature procedures (H. Nishioka, X. Liang, H. Kashidaa, H. Asanuma, *Chem. Commun.***2007**, 4354-4356) and the carboxamide **5/8** were assembled from the commercially available azobenzene carboxylic acids. Starting material **10g** is a known compound in the literature (E. O. Woolfolk, E. H. Roberts, *J. Org. Chem.***1956**, *21,* 436-438). Starting material **8aa** is a known compound in the literature (L. Grigorjeva, O. Daugulis,*Org. Lett.* **2014**, *16*, 4688-4690).

General procedure for the synthesis of the azobenzene carboxylic acid (10a,b): To a solution of *p*-aminobenzoic acid (1.2 equiv, 2.4 mmol) suspended in glacial acetic acid (1.5 mL) was added a solution of nitrosobenzene (1 equiv, 2 mmol) in glacial acetic acid (2 mL) and the mixture was stirred at rt for 24 h. After the reaction period, an orange colored precipitate is observed, which is then filtered using a suction apparatus, washed with ice cold water and finally dried to obtain the desired azobenzene carboxylic acid as anorangecolored solid.

General procedure for the synthesis of the carboxamides 5/8/10a/10b-f: A dry RB flask containing amine (0.9 mmol, 0.9 equiv), Et_3N (1.1 mmol,1.1 equiv) was stirred for 5-10 min under a nitrogen atm. Then, tothe reaction flask was added anhydrous DCM (4 mL) followed bydropwise addition of the corresponding acid chloride, which wasprepared from the corresponding carboxylic acid (1 mmol) and $SOCl_2$ (6 equiv) after refluxing for 12 h. Then, the reaction mixture was stirred overnight. After this period, the reaction mixture was diluted with dichloromethane (3-5 mL) and washed with water (5-7 mL) and twice with saturated aqueous $NaHCO_3$ solution (3-5 mL). The combined organic layers were washed with minimum quantity of dilute HBr for 2 times to remove excess amine and then dried over anhydrous Na_2SO_4, concentrated in vacuum furnished the corresponding carboxamides.

General procedure for the Pd(II)-catalyzed arylation/benzylation of the carboxamides 5/8/10 and preparation of the compounds 7a-7j/9/11/18/19: An appropriate carboxamide (0.2-0.25 mmol, 1 equiv), anappropriate aryl/benzyl iodide (0.6-1.0 mmol, 3-4 equiv), $Pd(OAc)_2$ (4.5-5.6 mg, 10 mol%) and AgOAc (0.4-0.55 mmol, 2.0-2.2 equiv) inanhydrous toluene (2-3 mL) was heated at 110 ^oC for 4-48 hunder a nitrogen atm. After the reaction period, the reactionmixture was concentrated in vacuum and purification of theresulting reaction mixture by column chromatography on neutralalumina or silica gel (eluent = EtOAc:hexanes) furnished thecorresponding arylated carboxamides **7a-7j/9a-9n/11a-11g** and benzylated carboxamides **18a-c** (see thecorresponding Tables/Schemes for specific examples).

General procedure for the Ni(II)-catalyzed mono arylation of the carboxamides 5 and preparation of the compounds 7b'-7i': An appropriate carboxamide (0.15 mmol, 1 equiv), anappropriate aryl iodide (0.6 mmol, 3 equiv), $Ni(OTf)_2$ (mg, 10 mol%) and Na_2CO_3 (0.6 -0.9 mmol, 4-6 equiv) was suspended anhydrous toluene (1 mL) in a 10 mL pressure tube. was The pressure tube was flushed with N_2 for 2 minutes and sealed with a PTFE-lined cap, and then heated at 150 C ^oC for 22-48 h. After the reaction period, the reactionmixture was concentrated in vacuum and purification of theresulting reaction mixture by column

chromatography on neutralalumina or silica gel (eluent = EtOAc:hexanes) furnished thecorresponding mono arylated carboxamides **7b'-7i'** (see thecorresponding Tables/Schemes for specific examples).

General procedure for the Pd(II)-catalyzed alkylation of the carboxamides 5/10a/10b and preparation of the compounds 13: A mixture of carboxamide 1 (0.15 mmol, 1 equiv), alkyl iodide (0.6 mmol, 3 equiv), anhydrous K_2CO_3 (0.3 mmol, 2 equiv), NaOTf (0.45 mmol, 3 equiv), $Pd(OAc)_2$ (10 mol%, 3.4 mg), was suspended *t*-AmylOH(1.0 mL) in a 10 mL pressure tube. The pressure tube was flushed with N_2 for 2 min and sealed with a PTFE-lined cap, and then heated at 125 ^oC for 22-48 h. After the reaction period, the reactionmixture was concentrated in vacuum and purification of theresulting reaction mixture by column chromatography on neutralalumina or silica gel (eluent = EtOAc:hexanes) furnished thecorresponding alkylated carboxamides **13** (see thecorresponding Tables/Schemes for specific examples). This reaction conditionswas adapted from Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850-4853.

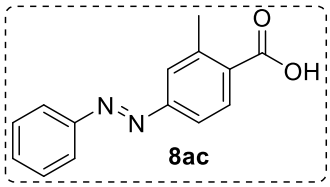
General procedure for the Pd(II)-catalyzed alkylation of the carboxamides 5/8/ preparation of the compounds 15a/16a: A mixture of carboxamide 1 (0.1-0.125 mmol, 1 equiv), alkyl iodide (0.4 mmol, 4 equiv), $(BnO)_2POOH$ (0.3 mmol, 0.25 equiv), Ag_2CO_3 (0.45 mmol, 2 equiv), $Pd(OAc)_2$ (5-10 mol%), was suspended *t*-AmylOH(1.0-2.0 mL) in a 10 mL pressure tube. The pressure tube was flushed with N_2 for 2 minutes and sealed with a PTFE-lined cap and then heated at 125 ^oC for 12-36 h. After the reaction period, the reactionmixture was concentrated in vacuum and purification of theresulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) furnished thecorresponding alkylated carboxamides **15a** and **16a** (see thecorresponding Tables/Schemes for specific examples).

Procedure for the Hydrolysis of the alkylated azobenzenecarboxamides13h. An appropriate amount of bis alkylated azobenzene carboxamides (0.075 mmol) was taken in a sealed tube, to which trifluoromethanesulfonic acid (0.15 mL), and toluene:H_2O (1.5 mL: 0.15 mL) were added under air. The reaction mixture was stirred at 110^oC for 24 h and the reaction mixture was cooled down to room temperature and excess TfOH was quenched by slow addition of saturated solution of Na_2CO_3 (5 mL) followed by the extraction using ethyl acetate (3 times). The collected organic layers are combined and washed with dilute HBr for 2 times in order to remove amine. Purification of the resulting reaction mixture by column chromatography on silica gel eluent=EtOAc:Hexanes) gave the corresponding alkylated azobenzene carboxylic acid in 95% yield.

Procedure for the Hydrolysis of the arylated azobenzenecarboxamides19b. The corresponding arylated azobenzenecarboxamide 7e' (0.11 mmol) and KOH (6.6 mmol) in methanol (1.5 mL) were heated at 110 °C for 36 h in a pressure tube. After this period, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL), and then acidified with 1 N HCl to get a pH ≈ 2. Extraction with ether (2 × 10 mL) and drying of the combined organic layers over Na_2SO_4 followed by evaporation of the solvent in vacuum afforded the corresponding carboxylic acid **19b** in 66% yield.

Procedure for the lactonisation of the arylated azobenzenecarboxamides19b. To a 10 mL RB flask were added mono-arylated azobenzene carboxamide **19b** (0.12 mmol), $K_2S_2O_8$ (0.36 mmol, 3 equiv) in MeCN:H_2O (1:1) (2 mL) and heated at 60 °C for 24 h under air. After this period, the reaction mixture was washed with saturated solution of $NaHCO_3$ (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, followed by evaporation of the solvent in vacuum afforded the corresponding cyclised product **20**.

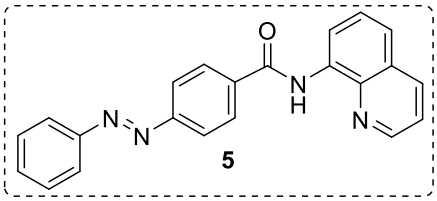
(*E*)-2-Methyl-4-(phenyldiazenyl)benzoic acid (8aC): The compound **8aC**was obtained



8ac

after workup as an orange coloured solid; Yield: 83% (400 mg, 2 mmol scale); mp 198-200 ^oC; IR (DCM): 1691, 1571, 1413, 1269 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, 1H, *J*= 8.2 Hz), 7.91-7.89 (m, 2H), 7.77 (s, 1H), 7.73 (d, 1H, *J*= 8.4 Hz), 7.62-7.59 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.6, 153.6, 152.3, 141.1, 133.2, 132.5, 130.0, 126.1, 123.2, 119.8, 21.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_2$: 241.0977; found 241.0965 (in the proton NMR the OH peak could not be identified).

(*E*)-4-(Phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (5): The compound **5** was obtained after workup as an orange coloured solid; Yield: 89% (940 mg, 3 mmol scale); mp 150-152

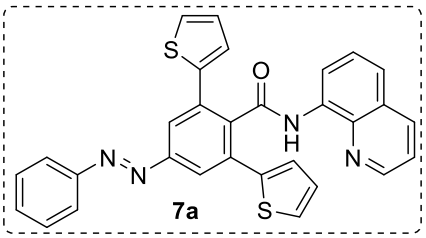


5

^oC; IR (DCM): 3350, 1672, 1530, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.85 (s, 1H), 8.98 (d, 1H, *J*= 7.4 Hz), 8.90 (d, 1H, *J*= 7.4 Hz), 8.27-8.20 (m, 3H), 8.09 (d, 1H, *J*= 8.1 Hz), 8.00 (d, 1H, *J*= 7.8 Hz), 7.65-7.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.5, 152.6, 148.4, 138.8, 136.8, 136.5, 134.4, 131.7, 129.2, 128.3, 128.0, 127.5, 123.2, 122.0, 121.8, 116.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_4O$: 353.1402; found 353.1395.

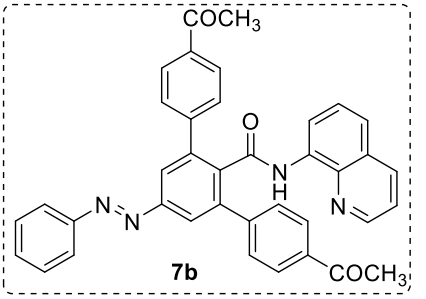
(*E*)-4-(Phenyldiazenyl)-*N*-(quinolin-8-yl)-2,6-di(thiophen-2-yl)benzamide (7a): The compound **7a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as an orange coloured solid; Yield: 67% (52 mg, 0.15 mmol

scale); mp 153-155 °C; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3334, 1676, 1522, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.81 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 8.67-8.66 (m, 1H), 8.15 (s, 2H), 8.11-8.08 (m, 1H), 8.03-8.01 (m, 2H), 7.61-7.50 (m, 5H), 7.45-7.44 (m, 2H), 7.39-7.36 (m, 1H), 7.27-7.26 (m, 2H), 6.96 (d, 1H, J= 5.1 Hz), 6.95 (d, 1H, J= 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 152.5, 152.3, 148.2, 140.3, 138.4, 137.1, 136.1, 134.3, 134.2, 131.7, 129.2, 127.8, 127.7, 127.5, 127.3, 126.6, 124.0, 123.2, 122.2, 122.1, 121.6, 116.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{21}N_4OS_2$: 517.1157; found 517.1133.



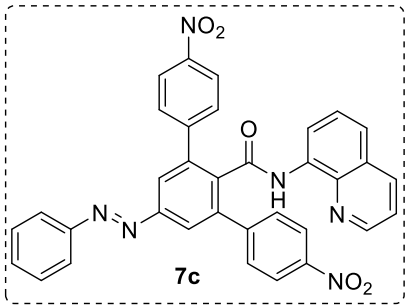
7a

(*E*)-4,4''-Diacetyl-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (7b): The compound **7b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 50:50) as an orange coloured solid; Yield: 40% (29 mg, 0.125 mmol scale); mp 200-202 °C; R_f = 0.37 (EtOAc:Hexanes = 40:60); IR (DCM): 3333, 1681, 1522, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.59 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.52 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.6 Hz), 8.09 (s, 2H), 8.01-8.06 (m, 1H), 8.01-7.99 (m, 2H), 7.91 (d, 4H, J= 8.3 Hz), 7.75 (d, 4H, J= 8.3 Hz), 7.59-7.54 (m, 3H), 7.47-7.45 (m, 2H), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.50 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 166.3, 152.5, 152.5, 148.1, 144.4, 140.9, 138.2, 137.5, 136.3, 136.2, 133.7, 131.9, 129.3, 129.0, 128.5, 127.7, 127.2, 124.0, 123.2, 122.2, 121.6, 116.7, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{29}N_4O_3$: 589.2240; found 589.2219.



7b

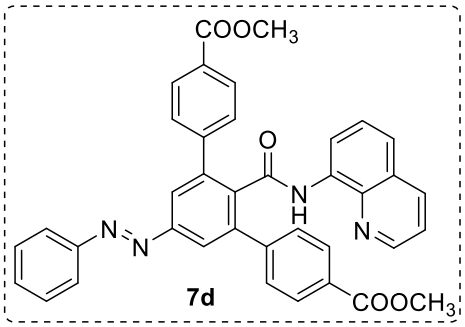
(*E*)-4,4''-Dinitro-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (7c): The compound **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 45% (80 mg, 0.3 mmol scale); mp 249-251 °C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3328, 1674, 1521, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.59 (d, 1H, J= 3.1 Hz), 8.48 (d, 1H, J= 7.2 Hz), 8.20 (d, 4H, J= 8.6 Hz), 8.12 (s, 2H), 8.13-8.11 (m, 1H), 8.02-8.00 (m, 2H), 7.82 (d, 4H, J= 8.6 Hz), 7.60-7.46 (m, 5H), 7.41-7.38



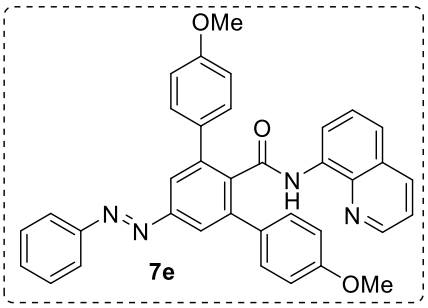
7c

(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 152.6, 152.4, 148.2, 147.5, 146.0, 139.9, 138.1, 137.4, 136.4, 133.3, 132.2, 129.7, 129.4, 128.6, 127.8, 127.2, 127.0, 124.4, 123.4, 123.3, 122.7, 121.8, 116.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{23}N_6O_5$: 595.1730; found 595.1708.

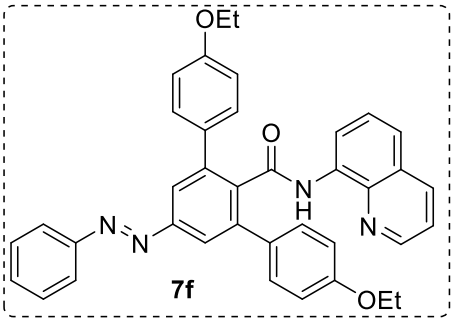
Dimethyl (*E*)-5'-(phenyldiazenyl)-2'-(quinolin-8-ylcarbamoyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7d): The compound **7d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:80) as an orange coloured solid; Yield: 27% (34 mg, 0.2 mmol scale); mp 191-193 ^oC; R_f = 0.30 (EtOAc:Hexanes = 40:80); IR (DCM): 3333, 1723, 1523, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.60 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.51 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.4 Hz), 8.09-8.07 (m, 1H), 8.08 (s, 2H), 8.01-7.99 (m, 6H), 7.73 (d, 4H, J= 8.3 Hz), 7.60-7.55 (m, 3H), 7.48-7.43 (m, 3H), 7.37 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 3.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 166.2, 152.5, 152.4, 148.1, 144.3, 140.9, 138.2, 137.6, 136.2, 133.7, 131.8, 129.7, 129.5, 129.3, 128.8, 127.7, 127.2, 124.0, 123.2, 122.1, 121.6, 116.7, 52.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{29}N_4O_5$: 621.2138; found 621.2126.



(*E*)-4,4''-Dimethoxy-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (7e): The compound **7e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 63% (44 mg, 0.125 mmol scale); mp 181-183 ^oC; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3337, 1675, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.63-8.59 (m, 2H), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 8.00-7.99 (m, 3H), 7.96-7.92 (m, 1H), 7.59-7.52 (m, 7H), 7.48-7.46 (m, 2H), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.86-6.82 (m, 4H), 3.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 159.2, 152.6, 152.4, 148.0, 141.4, 138.3, 138.2, 137.7, 136.1, 134.2, 132.2, 131.5, 129.9, 129.2, 127.7, 127.2, 123.3, 123.1, 121.7, 121.5, 116.5, 113.8, 55.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{29}N_4O_3$: 565.2240; found 565.2216.

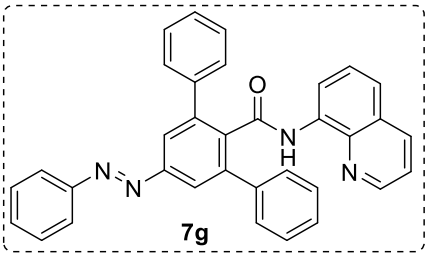


(*E*)-4,4''-Diethoxy-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-



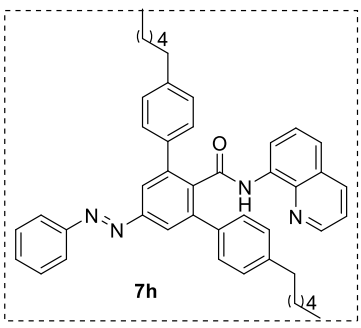
carboxamide (7f): The compound **7f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80)as an orange coloured solid;Yield: 44% (52 mg, 0.2 mmol scale); mp 152-154 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3341, 1678, 1518, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.63-8.60 (m, 2H), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 8.00 (s, 2H), 8.00-7.98 (m, 2H), 7.58-7.53 (m, 7H), 7.49-7.44 (m, 2H), 7.37 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.85-6.81 (m, 4H), 3.92 (q, 4H, J= 7.0 Hz), 1.33 (t, 6H, J= 7.0 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 158.6, 152.6, 152.4, 148.0, 141.4, 138.4, 137.8, 136.0, 134.3, 132.2, 131.5, 129.9, 129.2, 127.7, 127.2, 123.3, 123.1, 121.6, 121.4, 116.5, 114.4, 63.3, 14.8;HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{38}H_{33}N_4O_3$: 593.2553; found593.2529.

(*E*)-5'-(Phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide(7g):The



compound **7g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 42% (42 mg, 0.2 mmol scale); mp 151-153 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3337, 1677, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.62-8.56 (m, 2H), 8.07 (s, 2H), 8.08-8.06 (m, 1H), 8.01 (d, 2H, J_1 = 7.4 Hz), 7.67 (d, 4H, J= 7.5 Hz), 7.60-7.54 (m, 3H), 7.45-7.44 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.6, 152.4, 147.9, 141.8, 139.9, 138.3, 137.9, 136.0, 134.2, 131.6, 129.2, 128.7, 128.4, 127.7, 127.6, 127.2, 123.7, 123.1, 121.6, 121.4, 116.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{34}H_{25}N_4O$: 505.2028; found 505.2042.

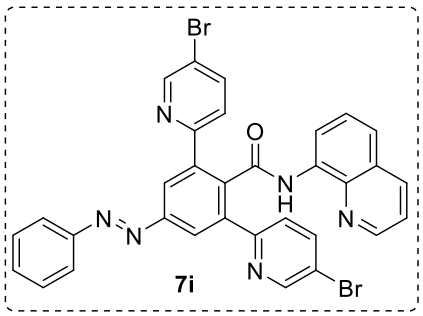
(*E*)-4,4''-Dihexyl-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-



carboxamide (7h): The compound **7h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 5:95) as an orange coloured solid; Yield: 57% (120 mg, 0.3 mmol scale); mp 73-75 ^{o}C; R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3339, 2927, 1680 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.61 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.58 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.07 (dd, 1H, J_1 = 6.8 Hz, J_2

= 2.2 Hz), 8.04 (s, 2H), 8.00-7.98 (m, 2H), 7.59-7.53 (m, 7H), 7.48-7.43 (m, 2H), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.10 (d, 4H, J= 8.1 Hz), 2.49 (t, 4H, J= 7.9 Hz), 1.44-1.37 (m, 4H), 1.25-1.19 (m, 12H), 0.87 (t, 6H, J= 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.7, 152.4, 147.8, 142.4, 141.9, 138.3, 137.9, 137.2, 135.9, 134.4, 131.5, 129.2, 128.6, 128.4, 128.4, 127.6, 127.2, 123.5, 123.1, 121.5, 121.4, 116.4, 35.6, 31.7, 31.2, 28.9, 22.6, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{46}H_{49}N_4O$: 673.3906; found 673.3929.

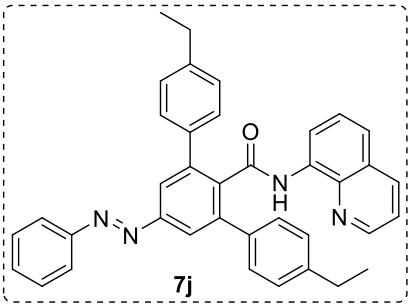
(*E*)-2,6-Bis(5-bromopyridin-2-yl)-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (7i):



7i

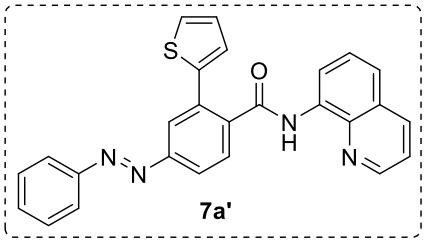
The compound **7i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 25% (49 mg, 0.3 mmol scale); mp 181-183 ºC; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3337, 1675, 1524, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.63-8.58 (m, 4H), 8.33 (s, 2H), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.02-7.99 (m, 2H), 7.76 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.66 (dd, 2H, J_1 = 8.4 Hz, J_2 = 0.6 Hz), 7.59-7.51 (m, 5H), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 155.6, 152.6, 152.5, 150.5, 148.2, 139.8, 139.0, 138.4, 137.4, 136.0, 134.3, 131.8, 129.2, 127.8, 127.2, 124.6, 123.2, 122.0, 121.6, 120.1, 116.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{20}Br_2N_6NaO$: 684.9963; found 684.9987.

(*E*)-4,4''-Diethyl-5'-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (7j): The compound **7j**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as an orangecolored liquid;Yield: 62% (69 mg, 0.2 mmol scale);R_f = 0.60 (EtOAc:Hexanes = 10:90); IR (DCM): 3337, 1677, 1522, 1481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.63-8.61 (m, 2H), 8.11-8.00 (m, 4H), 7.96-7.93 (m, 1H), 7.62-7.52 (m, 7H), 7.47-7.42 (m, 2H), 7.35 (dd, 1H, J_1= 8.3 Hz, J_2= 4.3 Hz), 7.15 (d, 4H, J = 8.2 Hz), 2.55 (q, 4H, J = 7.6 Hz), 1.09 (t, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 152.2, 151.0, 147.8, 143.7, 142.0, 138.3, 137.4, 137.2, 135.9, 134.3, 129.5, 129.2, 128.7, 128.7, 128.0, 127.6, 127.2, 124.4, 123.6, 123.1, 121.6, 121.4, 116.5, 28.5, 15.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{33}N_4O$: 561.2654; found 561.2632.



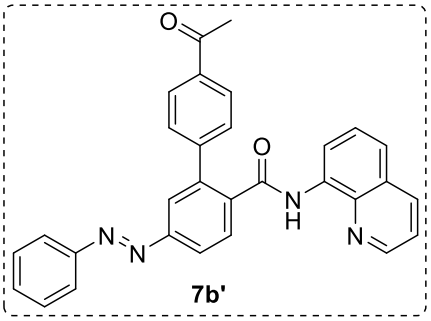
7j

(*E*)-4-(Phenyldiazenyl)-*N*-(quinolin-8-yl)-2-(thiophen-2-yl)benzamide (7a′): The

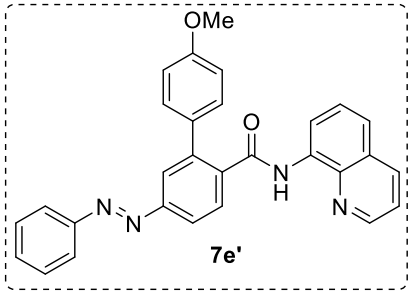


compound **7a′**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange colored solid; Yield: 47% (41 mg, 0.2 mmol scale); mp 191-193 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 1673, 1523, 1482, 1326 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.79 (dd, 1H, J_1= 7.5 Hz, J_2= 1.2 Hz), 8.53 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.04-8.00 (m, 2H), 7.91-7.86 (m, 4H), 7.49-7.40 (m, 5H),7.29 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.23 (dd, 1H, J_1= 3.6 Hz, J_2= 1.1 Hz), 7.17 (dd, 1H, J_1= 5.1 Hz, J_2= 1.1 Hz), 6.85-6.83 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 167.1, 153.2, 152.6, 148.0, 140.4, 138.5, 138.0, 136.1, 134.5, 133.6, 131.6, 130.0, 129.2, 127.9, 127.7, 127.6, 127.3, 126.8, 125.5, 123.2, 121.9, 121.9, 121.6, 116.5; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{26}H_{19}N_4OS$: 435.1280; found 435.1266.

(*E*)-4'-Acetyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (7b′):



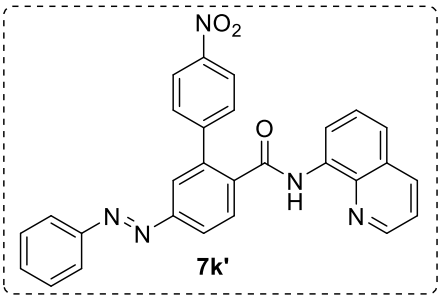
The compound **7b′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as an orange coloured solid; Yield: 50% (35 mg, 0.15 mmol scale); mp 189-191 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 40:60); IR (DCM): 3332, 1679, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.82 (d, 1H, J= 7.2 Hz), 8.56 (br s, 1H), 8.13-8.07 (m, 4H), 8.01 (s, 1H), 8.00 (s, 1H), 7.94 (d, 2H, J= 7.7 Hz), 7.72 (d, 2H, J= 7.6 Hz), 7.58-7.51 (m, 5H), 7.40-7.38 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 166.7, 153.5, 152.5, 147.9, 144.4, 140.4, 138.4, 137.8, 136.4, 136.2, 134.2, 131.8, 130.3, 129.3, 129.2, 128.6, 127.8, 127.3, 124.8, 123.2, 122.5, 122.0, 121.6, 116.5; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{30}H_{23}N_4O_2$: 471.1821; found 471.1841.



(*E*)-4'-Methoxy-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (7e′): The compound **7e′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as an orange coloured solid; Yield: 44% (40 mg, 0.2 mmol scale); mp 181-183 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3328, 1670, 1523, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.88 (d,

1H, *J*= 7.5 Hz), 8.57 (d, 1H, *J*= 4.0 Hz), 8.12-7.99 (m, 6H), 7.57-7.7.50 (m, 7H), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.89 (d, 2H, *J*= 8.2 Hz), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 159.6, 153.4, 152.6, 147.8, 141.1, 138.5, 137.6, 136.1, 134.5, 131.8, 131.6, 130.5, 130.3, 129.2, 127.8, 127.3, 125.2, 123.1, 121.7, 121.5, 121.3, 116.4, 114.1, 55.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_4O_2$: 459.1821; found 459.1833.

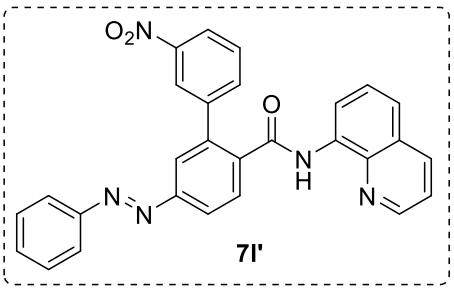
(*E*)-4'-Nitro-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (7k′):



7k'

The compound **7k′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:95) as an orange coloured solid; Yield: 19% (18 mg, 0.2 mmol scale); mp 142-144 ^oC; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3332, 1673, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.81 (d, 1H, *J*= 6.5 Hz), 8.60 (d, 1H, *J*= 3.8 Hz), 8.22 (d, 2H, *J*= 7.8 Hz), 8.16-8.09 (m, 1H), 8.14 (s, 2H), 8.05-8.00 (m, 3H), 7.78 (d, 2H, *J*= 7.8 Hz), 7.59-7.54 (m, 6H), 7.44-7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 153.5, 152.5, 148.0, 147.5, 146.4, 137.7, 136.4, 134.0, 132.0, 130.4, 129.9, 129.3, 127.9, 127.3, 124.6, 123.8, 123.3, 123.2, 122.3, 121.8, 116.6, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{20}N_5O_3$: 474.1566; found 474.1553.

(*E*)-3'-Nitro-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (7l′):

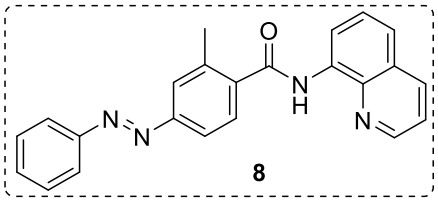


7l'

The compound **7l′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as an orange coloured solid; Yield: 28% (20 mg, 0.15 mmol scale); mp 169-171 ^oC; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3333, 1673, 1527, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 8.78 (d, 1H, *J*= 6.6 Hz), 8.58-8.55 (m, 2H), 8.14-8.01 (m, 7H), 7.87 (d, 1H, *J*= 7.6 Hz), 7.59-7.52 (m, 5H), 7.47-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 153.5, 152.5, 148.4, 148.1, 141.4, 139.1, 138.3, 137.8, 136.3, 135.2, 134.0, 131.9, 130.4, 129.4, 129.3, 127.8, 127.3, 124.6, 123.9, 123.2, 122.8, 122.2, 121.8, 116.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{20}N_5O_3$: 474.1566; found 474.1551.

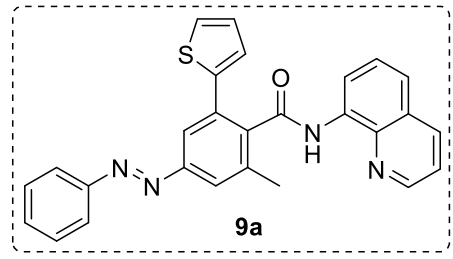
(*E*)-2-Methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (8): The compound **8** was obtained (from **8aC**) as an orange coloured solid; Yield: 87% (320 mg, 1 mmol scale);

mp163-165 ^{o}C; IR (DCM): 3357, 1678, 1524, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.31 (s, 1H), 8.99 (d, 1H, J = 7.1 Hz), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.23 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 8.00-7.98 (m, 2H), 7.90-7.85 (m, 3H), 7.66-7.53 (m, 5H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 153.4, 152.6, 148.4, 138.6, 138.5, 138.1, 136.4, 134.6, 131.4, 129.2, 128.3, 128.0, 127.4, 125.6, 123.1, 122.0, 121.8, 120.5, 116.7, 20.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{23}H_{19}N_4O$: 367.1559; found 367.1547.



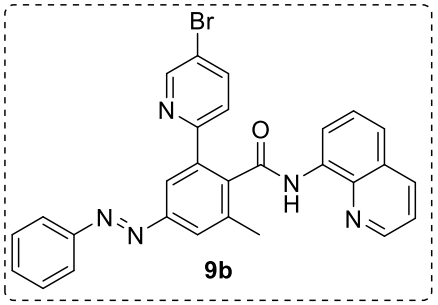
8

(*E*)-2-Methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)-6-(thiophen-2-yl)benzamide (9a): The compound **9a** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 66% (59 mg, 0.2 mmol scale); mp 125-127 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3337, 1674, 1521, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.94 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 8.70 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 8.03-8.00 (m, 3H), 7.84 (s, 1H), 7.63-7.54 (m, 5H), 7.42-7.39 (m, 2H), 7.22 (dd, 1H, J_1 = 5.1 Hz, J_2 = 0.4 Hz), 6.94-6.91 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 152.6, 152.5, 148.3, 140.8, 138.4, 138.3, 137.3, 136.2, 134.3, 133.2, 131.5, 129.2, 127.9, 127.7, 127.3, 127.0, 126.3, 123.4, 123.1, 122.6, 122.1, 121.7, 116.8, 19.9; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{27}H_{21}N_4OS$: 449.1436; found 449.1451.



9a

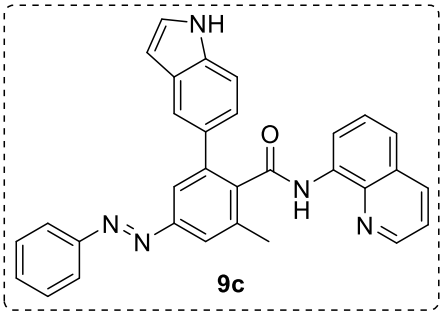
(*E*)-2-(5-Bromopyridin-2-yl)-6-methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (9b): The compound **9b** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 78% (81 mg, 0.2 mmol scale); mp 121-123 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3341, 1675, 1521, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.85 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.58 (d, 1H, J= 1.9 Hz), 8.17-8.15 (m, 2H), 8.00-7.95 (m, 3H), 7.74 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.3 Hz), 7.67 (d, 1H, J= 8.4 Hz), 7.60-7.53 (m, 5H), 7.43 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 155.6, 152.6, 150.4, 148.3, 139.0, 138.5, 138.4, 138.3, 137.8, 136.2, 134.4, 131.5, 129.2, 127.9, 127.3, 125.2, 124.3, 123.1, 122.0, 121.7, 121.6,



9b

119.9, 116.8, 19.9; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{21}BrN_5O$: 522.0929; found 522.0945.

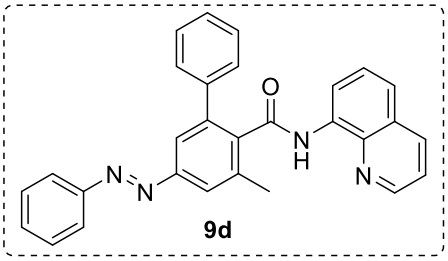
(*E*)-2-(1*H*-Indol-5-yl)-6-methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (9c): The compound **9c** was obtained after purification by column chromatography on silica



9c

(EtOAc:Hexanes = 50:60) as an orange coloured solid; Yield: 50% (48 mg, 0.2 mmol scale); mp 176-178 ^oC; R_f = 0.20 (EtOAc:Hexanes = 50:60); IR (DCM): 3320, 1650, 1520, 1484, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.79 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.54 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (brs, 1H), 8.01-7.97 (m, 4H), 7.93 (d, 1H, *J*= 0.8 Hz), 7.85 (d, 1H, *J*= 1.1 Hz), 7.59-7.52 (m, 3H), 7.50-7.46 (m, 1H), 7.44-7.40 (m, 2H), 7.30-7.27 (m, 1H), 7.16 (d, 1H, *J*= 8.4 Hz), 7.06 (t, 1H, *J*= 2.8 Hz), 6.48 (t, 1H, *J*= 2.2 Hz), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.7, 152.5, 148.0, 142.1, 138.9, 138.4, 137.1, 136.0, 135.3, 134.3, 131.6, 131.3, 129.2, 128.0, 127.7, 127.2, 124.6, 123.0, 123.0, 122.7, 121.7, 121.4, 121.1, 116.6, 110.9, 102.9, 20.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{31}H_{24}N_5O$: 482.1981; found 482.1964.

(*E*)-3-Methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9d):

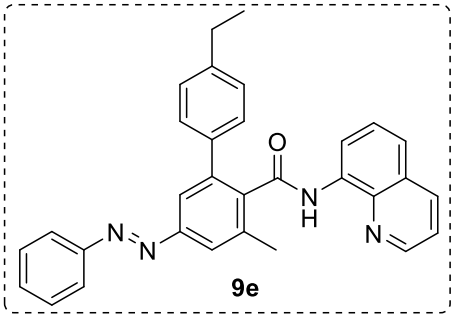


9d

The compound **9d**was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 70% (62 mg, 0.2 mmol scale);mp 120-122 ^oC; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3342, 1673, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.82 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 8.01-7.99 (m, 2H), 7.92-7.89 (m, 2H), 7.66-7.64 (m, 2H), 7.60-7.53 (m, 4H), 7.50 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.28 (t, 2H, *J*= 7.5 Hz), 7.16 (t, 1H, *J*= 7.4 Hz), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 152.6, 152.5, 148.1, 140.8, 139.8, 138.7, 138.4, 137.3, 136.1, 134.3, 131.4, 129.2, 128.7, 128.3, 127.8, 127.6, 127.3, 123.5, 123.0, 122.2, 121.9, 121.5, 116.5, 20.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{23}N_4O$: 443.1872; found 443.1859.

(*E*)-4'-Ethyl-3-methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9e): The compound **9e** was obtained after purification by column

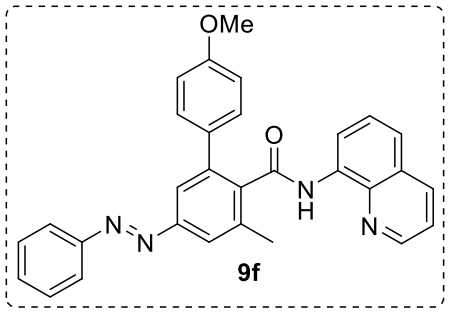
chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 70%



9e

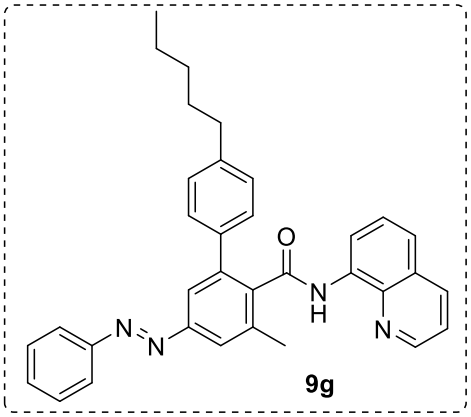
(66 mg, 0.2 mmol scale); mp 73-75 ^{o}C; R_f = 0.60 (EtOAc:Hexanes = 20:80); IR (DCM): 3339, 1674, 1522, 1483 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.82 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00-7.97 (m, 2H), 7.91-7.86 (m, 2H), 7.59-7.49 (m, 7H), 7.39 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.09 (d, 2H, J = 8.1 Hz), 2.67 (s, 3H), 2.48 (q, 2H, J = 7.6 Hz), 1.01 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 152.6, 152.5, 148.0, 143.0, 140.9, 138.7, 138.4, 137.3, 137.1, 136.1, 134.3, 131.4, 129.2, 128.6, 127.8, 127.8, 127.3, 123.3, 123.0, 122.3, 121.8, 121.5, 116.6, 28.4, 20.0, 15.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_4O$: 471.2185; found 471.2198.

(*E*)-4'-Methoxy-3-methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9f): The compound **9f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 78% (73 mg, 0.2 mmol scale); mp 87-89 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3342, 1674, 1521, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.83 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 8.66 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.90-7.97 (m, 2H), 7.88-7.84 (m, 2H), 7.59-7.51 (m, 7H), 7.41 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.83-6.80 (m, 2H), 3.68 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 159.2, 152.6, 152.5, 148.1, 140.1, 138.7, 138.4, 137.2, 136.2, 134.3, 132.2, 131.4, 129.9, 129.2, 127.8, 127.3, 123.0, 122.3, 121.9, 121.6, 116.6, 113.8, 55.1, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_4O_2$: 473.1978; found 473.1997.



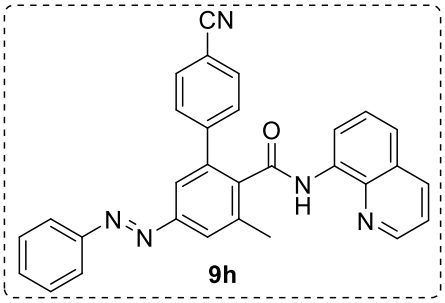
9f

(*E*)-3-Methyl-4'-pentyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9g): The compound **9g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as an orange coloured solid; Yield: 77% (79 mg, 0.2 mmol scale); mp 61-63 ^{o}C; R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3340, 2930, 1676, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.83 (d, 1H, J= 7.5 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.09 (d, 1H, J= 8.2 Hz), 7.99 (d, 1H, J= 7.1 Hz), 7.92 (s, 1H), 7.87 (s, 1H), 7.59-7.48 (m, 7H), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.1



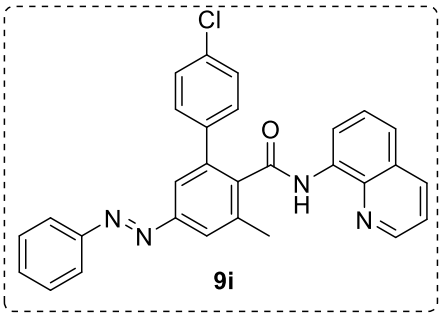
Hz), 7.08 (d, 2H, *J*= 7.9 Hz), 2.68 (s, 3H), 2.43 (t, 2H, *J*= 7.7 Hz), 1.36-1.30 (m, 2H), 1.24-1.18 (m, 2H), 1.12-1.06 (m, 2H), 0.80 (t, 3H, *J*= 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 152.7, 152.5, 148.0, 142.4, 141.0, 138.7, 138.4, 137.3, 137.1, 136.1, 134.4, 131.3, 129.2, 128.5, 128.4, 127.8, 127.2, 123.3, 123.0, 122.2, 121.8, 121.5, 116.5, 35.4, 31.2, 30.8, 22.4, 20.0, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{33}N_4O$: 513.2654; found 513.2672.

(*E*)-4'-Cyano-3-methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9h): The compound **9h** wasobtained after purification by column chromatography on silica (EtOAc:Hexanes = 20:80) as an orange coloured solid;Yield: 59% (55 mg, 0.2 mmol scale);mp 91-93 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM):



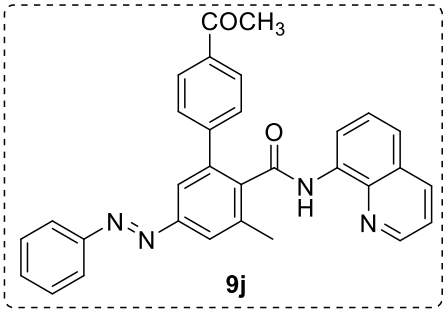
3337, 1674, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.77 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00-7.98 (m, 2H), 7.94 (d, 1H, *J*= 1.0 Hz), 7.86 (d, 1H, *J*= 1.0 Hz), 7.76-7.73 (m, 2H), 7.61-7.55 (m, 7H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 152.6, 152.5, 148.2, 144.6, 138.8, 138.4, 138.3, 137.8, 136.4, 133.8, 132.1, 131.7, 129.4, 129.2, 127.9, 127.3, 124.9, 123.1, 122.4, 121.8, 121.6, 118.6, 116.7, 111.5, 20.0;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{22}N_5O$: 468.1824; found 468.1808.

(*E*)-4'-Chloro-3-methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9i): The compound **9i** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 65% (62 mg, 0.2 mmol scale); mp 82-84 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3338, 1674, 1522, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.81 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.66 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 8.00-7.98 (m, 2H), 7.89 (s, 1H), 7.86 (s, 1H), 7.60-7.53 (m, 7H), 7.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.26 (d, 2H, *J*= 8.5 Hz), 2.66 (s, 3H); ^{13}C NMR



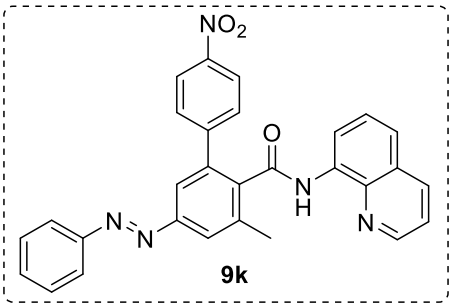
(100 MHz, $CDCl_3$): δ 167.5, 152.6, 152.5, 148.2, 139.5, 138.6, 138.4, 138.3, 137.4, 136.2, 134.1, 133.9, 131.5, 130.0, 129.2, 128.6, 127.9, 127.3, 123.9, 123.1, 122.2, 122.0, 121.7, 116.7, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}ClN_4O$: 477.1482; found 477.1469.

(*E*)-4'-Acetyl-3-methyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9j): The compound **9j** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 30:70) as an orange coloured solid; Yield: 56% (54 mg, 0.2 mmol scale); mp 92-94 ^oC; R_f = 0.20 (EtOAc:Hexanes = 30:70); IR (DCM): 3342, 1676, 1521, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.79 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00-7.98 (m, 2H), 7.92-7.89 (m, 4H), 7.74-7.72 (m, 2H), 7.60-7.51 (m, 5H), 7.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.68 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 167.3, 152.6, 152.5, 148.2, 144.6, 139.6, 138.5, 138.3, 137.6, 136.2, 136.1, 134.0, 131.6, 129.2, 129.0, 128.4, 127.9, 127.3, 124.3, 123.1, 122.1, 121.9, 121.6, 116.7, 26.6, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}N_4O_2$: 485.1978; found 485.1958.



9j

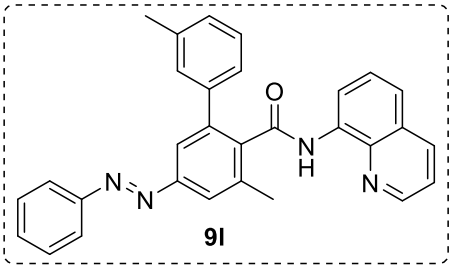
(*E*)-3-Methyl-4'-nitro-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9k): The compound **9k** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 15:95) as an orange coloured solid; Yield: 69% (67 mg, 0.2 mmol scale); mp 93-95 ^oC; R_f = 0.50 (EtOAc:Hexanes = 30:70); IR (DCM): 3335, 1674, 1519, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.78 (dd, 1H, J_1 = 6.2 Hz, J_2 = 1.8 Hz), 8.65 (d, 1H, J= 2.6 Hz), 8.15-8.13 (m, 3H), 7.99 (d, 2H, J= 6.7 Hz), 7.96 (s, 1H), 7.88 (s, 1H), 7.80 (d, 2H, J= 8.6 Hz), 7.60-7.53 (m, 5H), 7.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.6, 152.5, 148.3, 147.3, 146.5, 138.5, 138.4, 138.3, 137.8, 136.4, 133.8, 131.7, 129.7, 129.3, 127.9, 127.3, 125.1, 123.6, 123.1, 122.4, 121.8, 121.6, 116.8, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}N_5O_3$: 488.1723; found 488.1711.



9k

(*E*)-3,3'-Dimethyl-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9l): The compound **9l** was obtained after purification by column chromatography on silica

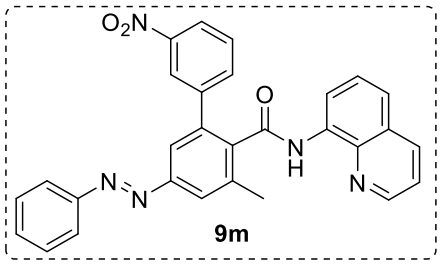
(EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 77% (70 mg, 0.2 mmol scale);



9l

mp 98-100 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 3053, 1674, 1522, 1263 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.80 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 8.66 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 8.00-7.98 (m, 2H), 7.90 (s, 1H), 7.87 (s,1 H), 7.60-7.49 (m, 5H), 7.45 (s, 1H), 7.42-7.39 (m, 2H), 7.14 (t, 1H, J= 7.6 Hz), 6.95 (d, 1H, J= 7.6 Hz), 2.67 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 152.7, 152.5, 148.0, 141.0, 139.7, 138.7, 138.4, 137.9, 137.3, 136.1, 134.3, 131.4, 129.5, 129.2, 128.4, 128.2, 127.8, 127.3, 125.7, 123.4, 123.0, 122.2, 121.8, 121.5, 116.5, 21.3, 20.0; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{30}H_{25}N_4O$: 457.2028; found 457.2043.

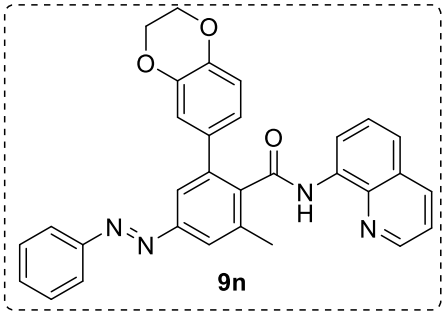
(*E*)-3-Methyl-3'-nitro-5-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-



9m

carboxamide (9m): The compound **9m**was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 51% (50 mg, 0.2 mmol scale);mp 196-198 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 30:70); IR (DCM): 3335, 1674, 1526, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.76 (d, 1H, J= 6.6 Hz), 8.63 (d, 1H, J= 3.8 Hz), 8.55 (s, 1H), 8.12 (d, 1H, J= 8.2 Hz), 8.01-7.90 (m, 6H), 7.59-7.52 (m, 5H), 7.41-7.37 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.6, 152.5, 148.3, 148.2, 141.5, 138.6, 138.3, 138.3, 137.8, 136.3, 134.7, 133.8, 131.7, 129.2, 127.8, 127.2, 125.0, 123.8, 123.1, 122.5, 122.3, 121.8, 121.6, 116.7, 20.0; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{22}N_5O_3$: 488.1723; found 488.1703.

(*E*)-2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-

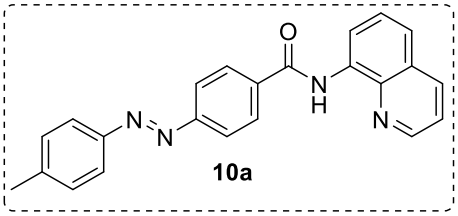


9n

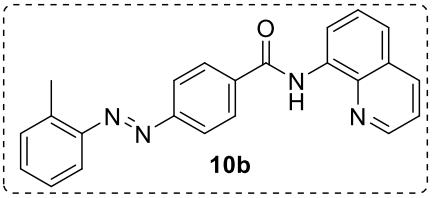
yl)benzamide (9n): The compound **9n** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 69% (69 mg, 0.2 mmol scale);mp 91-93 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3338, 1674, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.83 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.69 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.14 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 7.99-7.97 (m, 2H), 7.87-7.84 (m, 2H), 7.59-7.51 (m, 5H),

7.42 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.3 Hz), 7.17 (d, 1H, J= 2.1 Hz), 7.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.2 Hz), 6.73 (d, 1H, J= 8.4 Hz), 4.14-4.09 (m, 4H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 152.6, 152.5, 148.1, 143.4, 143.3, 140.3, 138.6, 138.4, 137.3, 136.1, 134.4, 133.2, 131.4, 129.2, 127.8, 127.3, 123.3, 123.0, 122.1, 121.9, 121.8, 121.5, 117.8, 117.1, 116.6, 64.2, 64.2, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}N_4O_3$: 501.1927; found 501.1903.

(*E*)-*N*-(Quinolin-8-yl)-4-(*p*-tolyldiazenyl)benzamide (10a): The compound **10a** after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 38% (280 mg, 2 mmol scale); mp 97-99 ^{o}C; IR (DCM): 3354, 1673, 1530, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 8.98 (d, 1H, J= 7.5 Hz), 8.89 (d, 1H, J= 3.8 Hz), 8.25-8.19 (m, 3H), 8.06 (d, 2H, J_1 = 7.8 Hz), 7.90 (d, 2H, J = 7.6 Hz), 7.65-7.56 (m, 2H), 7.50 (dd, 1H, J_1 = 4.1 Hz, J_2 = 8.0 Hz), 7.36 (d, 2H, J_1 = 7.8 Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.6, 150.7, 148.4, 142.4, 138.8, 136.5, 136.4, 134.4, 129.9, 128.3, 128.0, 127.5, 123.2, 123.0, 121.9, 121.8, 116.6, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O$: 367.1559; found 367.1543.

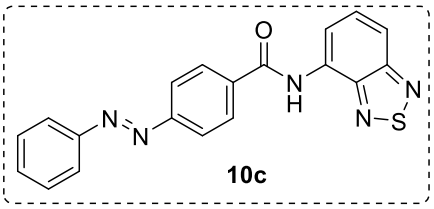


(*E*)-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (10b): The compound **10b** was obtained after workup as an orange coloured solid; Yield: 74% (543 mg, 2 mmol scale); mp 175-177 ^{o}C; IR (DCM): 3350, 1672, 1530, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 8.98 (d, 1H, J= 7.4 Hz), 8.88 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.26-8.19 (m, 3H), 8.08 (d, 2H, J= 8.4 Hz), 7.71 (d, 1H, J_1 = 7.9 Hz), 7.64-7.56 (m, 2H), 7.50 (dd, 1H, J_1 = 4.2 Hz, J_2 = 8.2 Hz), 7.44-7.38 (m, 2H), 7.33-7.28 (m, 1H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.8, 150.6, 148.4, 138.9, 138.7, 136.5, 136.4, 134.4, 131.7, 131.4, 128.3, 128.0, 127.5, 126.5, 123.2, 121.9, 121.8, 116.6, 115.4, 17.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_4O$: 367.1559; found 367.1551.



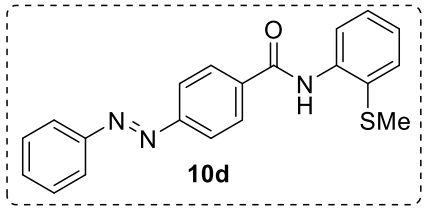
(*E*)-*N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-(phenyldiazenyl)benzamide (10c): The compound **10c** was obtained after workup as an orange coloured solid; Yield: 70% (250 mg, 1 mmol scale); mp 189-191 ^{o}C; IR (DCM): 3316, 1648, 1548, 1410 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ9.33 (s, 1H), 8.69 (d, 1H, J= 7.3 Hz), 8.20 (d, 1H, J = 8.3 Hz), 8.10 (d, 1H, J

= 8.2 Hz), 8.00 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.71-7.67 (m, 1H) 7.59-7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 154.8, 154.7, 152.5, 148.0, 135.7, 131.8, 131.2, 129.9, 129.2, 128.3, 123.3, 123.2, 116.2, 115.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{14}N_5OS$: 360.0919; found 360.0902.



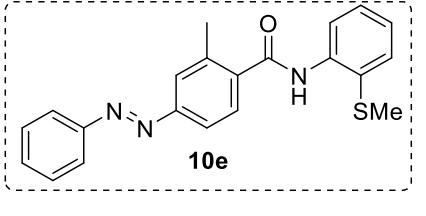
10c

(*E*)-*N*-(2-(Methylthio)phenyl)-4-(phenyldiazenyl)benzamide (10d): The compound **10d** was obtained after workup as an orange coloured solid; Yield: 69% (238 mg, 1 mmol scale); mp 120-122 ^{o}C;IR (DCM): 3339, 1677, 1518, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.58 (d, 1H, *J*= 8.3 Hz), 8.14 (d, 1H, *J*= 8.3 Hz), 8.07 (d, 1H, *J*= 8.3 Hz), 8.01-7.93 (m, 2H), 7.60-7.53 (m, 4H), 7.41 (t, 1H, *J*= 7.8 Hz), 7.16 (d, 1H, *J*= 7.6 Hz), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 154.5, 152.5, 138.4, 136.4, 133.1, 131.8, 129.2, 129.1, 128.2, 125.9, 124.8, 123.2, 123.2, 120.7, 19.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3OS$: 348.1171; found 348.1186.



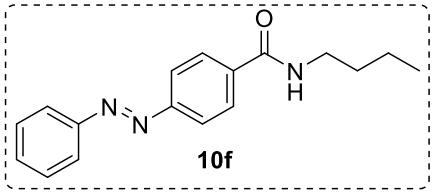
10d

(*E*)-2-Methyl-*N*-(2-(methylthio)phenyl)-4-(phenyldiazenyl)benzamide (10e): The compound **10e** was obtained after workup as an orange coloured solid; Yield: 96% (448 mg, 1.3 mmol scale); mp 92-94 ^{o}C; IR (DCM): 3333, 1678, 1510, 1432 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.54 (d, 1H, *J*= 7.6 Hz), 7.99-7.97 (m, 2H), 7.87-7.85 (m, 2H), 7.75 (d, 1H, *J*= 8.4 Hz), 7.59-7.53 (m, 4H), 7.42-7.7.38 (m, 1H), 7.17 (td, 1H, J_1 = 7.6 Hz, J_1 = 1.7 Hz), 2.70 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.2, 152.3, 151.5, 137.2, 137.1, 137.0, 131.9, 130.5, 128.1, 127.9, 126.8, 124.6, 123.8, 122.0, 119.7, 119.4, 28.7, 19.2, 18.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3OS$: 362.1327; found 362.1316.



10e

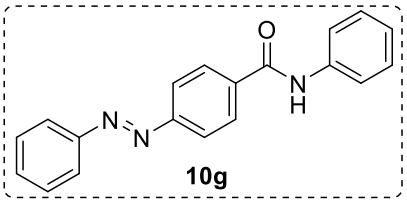
(*E*)-*N*-Butyl-4-(phenyldiazenyl)benzamide (10f): The compound **10f** was obtained after workup as an orange coloured solid; Yield: 92% (258 mg, 1 mmol scale); mp 92-94 ^{o}C; IR (DCM): 3317, 2659, 1633, 1542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.91 (m, 6H), 7.56-7.52 (m, 3H), 6.55 (br s, 1H), 3.51-3.46 (m, 2H), 1.67-1.60 (m, 2H), 1.40-1.41 (m, 2H), 0.98 (t, 3H, *J* = 7.3 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.1, 152.5, 136.6, 131.6, 129.2, 127.9, 123.1, 122.9, 40.0,



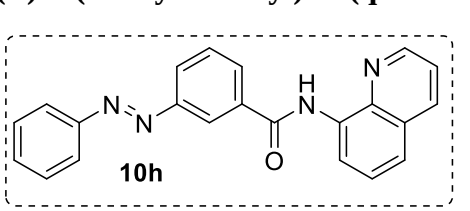
10f

31.7, 20.2, 13.8; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O$: 282.1606; found 282.1595.

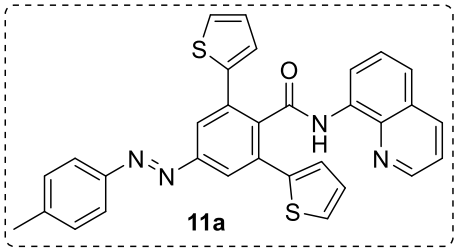
(*E*)-*N*-Phenyl-4-(phenyldiazenyl)benzamide (10g): The compound **10g** was obtained after purification by column chromatography on silica gel(EtOAc:Hexanes = 20:80) as an pale orange colored solid; Yield: 33% (150 mg, 1.5 mmol scale); mp 205-207 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3351, 1649, 1527, 1438 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.18 (d, 2H, *J* = 8.5 Hz), 8.02 (d, 2H, *J* = 8.5 Hz), 7.97-7.95 (m, 2H), 7.81 (d, 2H, *J* = 7.6 Hz), 7.66-7.61 (m, 3H), 7.40-7.37 (m, 2H), 7.14 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.2, 153.9, 152.4, 139.5, 137.5, 132.6, 130.0, 129.5, 129.1, 124.4, 123.3, 122.9, 120.9;HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{16}N_3O$: 302.1293; found302.1280.



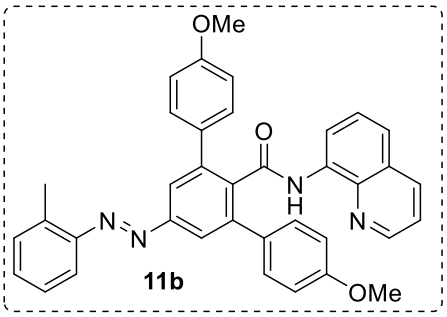
(*E*)-3-(Phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (10h): The compound **10h**was obtainedafter workup procedure as an orange colored solid; Yield: 72% (27 mg, 0.6 mmol scale);mp 143-145 ^{o}C; IR (DCM): 3349, 1674, 1482, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 8.99 (d, 1H, *J* = 7.5 Hz), 8.86 (d, 1H, *J* = 4.0 Hz), 8.64 (s, 1H), 8.20 (d, 1H, *J* = 7.6 Hz), 8.14 (t, 2H, *J* = 9.3 Hz), 8.00 (d, 2H, *J* = 7.6 Hz), 7.69 (t, 2H, *J* = 7.8 Hz), 7.62-7.50 (m, 5H), 7.45 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 152.7, 152.4, 148.4, 138.7, 136.4, 136.2, 134.4, 131.5, 129.6, 129.5, 129.2, 128.0, 127.4, 125.4, 123.1, 122.3, 122.0, 121.8, 116.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_4O$: 353.1402; found 353.1392.



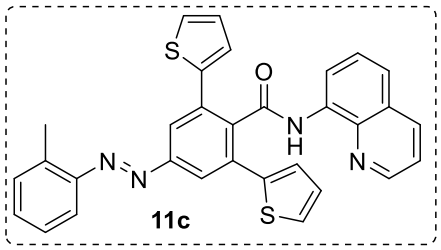
(*E*)-*N*-(Quinolin-8-yl)-2,6-di(thiophen-2-yl)-4-(*p*-tolyldiazenyl)benzamide (11a): The compound **11a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 50% (40 mg, 0.15 mmol scale); mp 178-180 ^{o}C; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3335, 1675, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.80 (d, 1H, *J* = 7.2 Hz), 8.67 (d, 1H, *J* = 4.1 Hz), 8.13-8.10 (m, 3H), 7.92 (d, 2H, *J* = 7.8 Hz), 7.57-7.50 (m, 2H), 7.43 (d, 2H, *J* = 3.4 Hz), 7.40-7.36 (m, 3H), 7.26 (d, 2H, *J* = 5.0 Hz), 6.96-6.94 (m, 2H), 2.49 (s, 3H);



^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.4, 150.7, 148.2, 142.5, 140.4, 138.4, 136.8, 136.1, 134.2, 134.2, 129.9, 127.8, 127.7, 127.5, 127.3, 126.6, 123.9, 123.2, 122.0, 121.6, 116.8, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{23}N_4OS_2$: 531.1313; found 531.1307.

(*E*)-4,4''-Dimethoxy-*N*-(quinolin-8-yl)-5'-(*o*-tolyldiazenyl)-[1,1':3',1''-terphenyl]-2'-carboxamide (11b): 

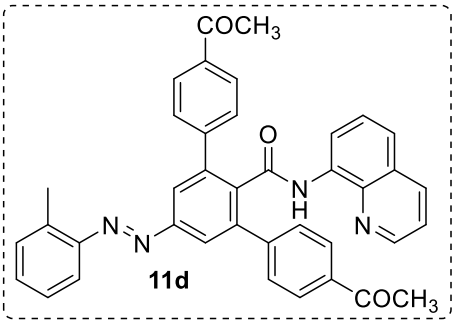
The compound **11b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 47% (54 mg, 0.2 mmol scale); mp 191-193 ^oC; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3340, 1677, 1518, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.64-8.62 (m, 2H), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00 (s, 2H), 7.73 (d, 1H, J_1 = 7.6 Hz), 7.66 (dt, 2H, J_1 = 8.7 Hz, J_2 = 0.6 Hz), 7.48-7.31 (m, 6H), 7.40 (dt, 1H, J_1 = 8.8 Hz, J_2 = 2.9 Hz), 3.71 (s, 6H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 159.2, 152.8, 150.8, 148.0, 141.4, 138.7, 138.3, 137.6, 136.1, 134.3, 132.4, 131.5, 131.4, 129.9, 127.7, 127.2, 126.5, 123.3, 121.7, 121.5, 116.5, 115.5, 113.9, 55.1, 17.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{31}N_4O_3$: 579.2396; found 579.2419.

(*E*)-*N*-(Quinolin-8-yl)-2,6-di(thiophen-2-yl)-4-(*o*-tolyldiazenyl)benzamide (11c): 

The compound **11c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 61% (65 mg, 0.2 mmol scale); mp 146-148 ^oC; R_f = 0.40 (EtOAc:Hexanes = 20:80); IR (DCM): 3335, 1676, 1522, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.81 (d, 1H, J = 7.2 Hz), 8.67 (d, 1H, J = 4.0 Hz), 8.13-8.10 (m, 3H), 7.73 (d, 1H, J = 8.0 Hz), 7.58-7.51 (m, 2H), 7.45-7.37 (m, 5H), 7.33 (t, 1H, J = 8.0 Hz), 7.27 (d, 2H, J = 5.3 Hz), 6.96 (t, 1H, J = 4.0 Hz), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.7, 150.6, 148.2, 140.4, 138.9, 138.4, 136.9, 136.1, 134.2, 134.2, 131.7, 131.5, 127.8, 127.7, 127.5, 127.3, 126.6, 126.5, 124.1, 122.1, 121.6, 116.8, 115.5, 17.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{23}N_4OS_2$: 531.1313; found 531.1338.

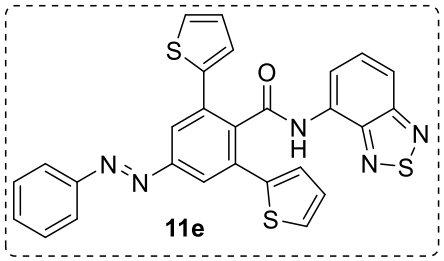
(*E*)-4,4''-Diacetyl-*N*-(quinolin-8-yl)-5'-(*o*-tolyldiazenyl)-[1,1':3',1''-terphenyl]-2'-carboxamide (11d): The compound **11d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as an orange coloured solid; Yield:

42% (50 mg, 0.2 mmol scale); mp 238-240 °C; R_f = 0.30 (EtOAc:Hexanes = 40:65); IR



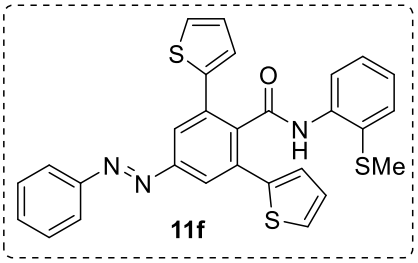
(DCM): 3331, 1681, 1522, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.59 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.51 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.4 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.06 (s, 2H), 7.92 (d, 4H, J= 8.4 Hz), 7.76-7.71 (m, 5H), 7.49-7.43 (m, 3H), 7.41-7.37 (m, 2H), 7.34-7.30 (m, 1H), 2.77 (s, 3H), 2.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 166.3, 152.8, 150.6, 148.1, 144.5, 140.9, 140.0, 138.2, 137.4, 136.2, 136.2, 133.7, 131.9, 131.5, 129.0, 128.5, 127.7, 127.2, 126.6, 124.0, 121.2, 121.6, 116.8, 115.5, 26.6, 17.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{31}N_4O_3$: 603.2396; found 603.2383.

(*E*)-*N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-(phenyldiazenyl)-2,6-di(thiophen-2-



yl)benzamide (11e): The compound **11e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 32% (42 mg, 0.25 mmol scale); mp172-173 °C;R_f = 0.50 (EtOAc:Hexanes = 20:85); IR (DCM): 1680, 1546, 1521, 1409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.67 (d, 1H, J= 7.3 Hz), 8.16 (d, 2H, J= 8.2 Hz), 8.11 (s, 1 H), 8.06 (d, 2H, J= 8.4 Hz), 8.00-7.97 (m, 3H), 7.75-7.64 (m, 3H), 7.61-7.53 (m, 5H), 7.40 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.1 Hz), 7.30 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.98 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 154.7, 154.7, 152.5, 148.0, 140.0, 135.7, 134.3, 131.8, 131.1, 130.0, 129.2, 128.3, 127.8, 127.6, 126.9, 124.0, 123.3, 123.2, 116.2, 115.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{18}N_5OS_3$: 524.0673; found 524.0656.

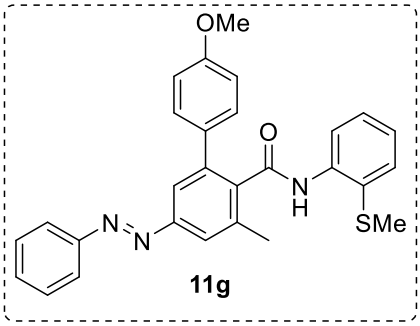
(*E*)-*N*-(2-(Methylthio)phenyl)-4-(phenyldiazenyl)-2,6-di(thiophen-2-yl)benzamide (979,



11f): The compound **11f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as an orange coloured solid; Yield: 51% (66 mg, 0.25 mmol scale); mp 112-114 °C; R_f = 0.50 (EtOAc:Hexanes = 10:90); IR (DCM): 3322, 1679, 1507, 1433 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.30 (dd, 1H, J_1 = 8.2, J_2 = 1.2 Hz), 8.09 (s, 2H), 7.98-7.96 (m, 2H), 7.57-7.52 (m, 3H), 7.42-7.40 (m, 3H), 7.35-7.33 (m, 2H), 7.32-7.28 (m, 1H), 7.07-7.02 (m, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7,

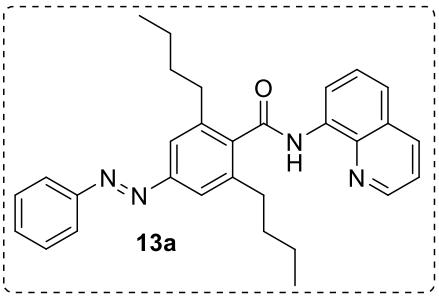
152.5, 152.4, 140.2, 138.1, 136.7, 134.0, 133.5, 131.8, 129.2, 129.1, 127.9, 126.8, 125.8, 124.8, 124.0, 123.2, 123.2, 120.9, 18.8; HRMS (ESI):*m/z* [M - H]$^+$ calcd for $C_{28}H_{22}N_3OS_3$:510.0769; found 510.0749.

(*E*)-4'-Methoxy-3-methyl-*N*-(2-(methylthio)phenyl)-5-(phenyldiazenyl)-[1,1'-biphenyl]-2-carboxamide (11g): The compound **11g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 41% (38 mg, 0.2 mmol scale); mp 99-101 ^oC; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3327, 1673, 1506, 1431 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 1H, *J*= 8.2 Hz), 8.19 (s, 1H), 7.98 (d, 2H, *J*= 7.7 Hz), 7.87 (s, 1H), 7.82 (s, 1H), 7.60-7.52 (m, 5H), 7.41 (d, 1H, *J*= 7.8 Hz), 7.32 (t, 1H, *J*= 8.2 Hz), 7.08 (t, 1H, *J*= 7.2 Hz), 6.94 (d, 2H, *J*= 8.4 Hz), 3.80 (s, 3H), 2.64 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 159.4, 152.6, 152.6, 139.8, 138.2, 137.9, 137.3, 132.8, 132.0, 131.4, 129.9, 129.2, 128.7, 126.1, 124.8, 123.0, 122.9, 122.3, 120.8, 114.1, 55.3, 19.9, 18.8; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{26}N_3O_2S$: 468.1746; found 468.1738.



11g

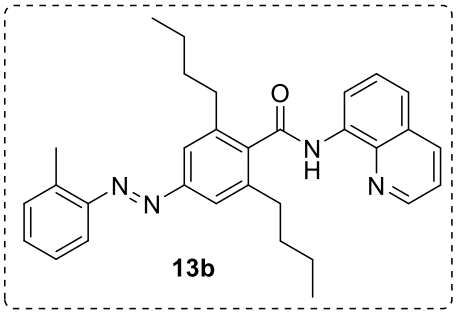
(*E*)-2,6-Dibutyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (13a): The compound **13a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 5:95) as an orange coloured solid;Yield: 88% (41 mg, 0.1 mmol scale);R_f = 0.70 (EtOAc:Hexanes = 10:90); IR (DCM): 3334, 2956, 1678, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 9.03 (d, 1H, *J* = 7.3 Hz), 8.77 (d, 1H, *J* = 1.7 Hz), 8.22 (d, 1H, *J* = 8.2 Hz), 7.99-7.98 (m, 2H), 7.75 (s, 2H), 7.69-7.52 (m, 5H), 7.49-7.47 (m, 1H), 2.84 (t, 4H, *J* = 7.8 Hz), 1.84-1.74 (m, 4H), 1.40-1.32 (m, 4H), 0.86 (t, 6H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.7, 148.3, 140.9, 139.6, 138.5, 136.4, 134.3, 131.1, 129.1, 128.0, 127.5, 122.9, 122.1, 121.8, 121.2, 116.8, 33.7, 33.3, 22.7, 13.9;HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{33}N_4O$: 465.2654; found 465.2633.



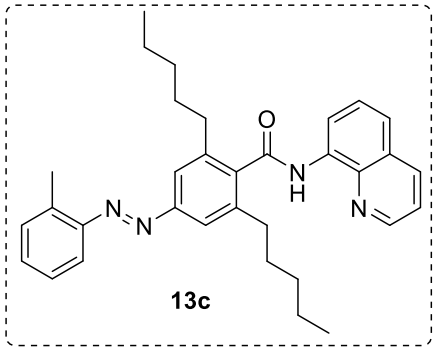
13a

(*E*)-2,6-Dibutyl-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (13b): The compound **13b** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 64% (46 mg, 0.15 mmol scale); R_f = 0.70 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 2956, 1678, 1521 cm^{-1}; ^{1}H NMR (400 MHz,

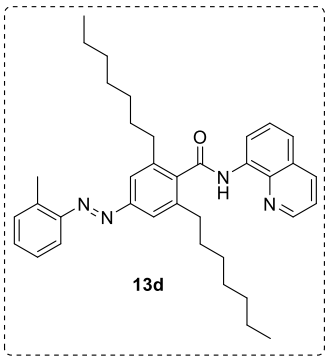
$CDCl_3$): δ 10.00 (s, 1H), 9.02 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.72 (s, 2H), 7.68-7.64 (m, 2H), 7.61 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.43-7.38 (m, 2H), 7.34-7.29 (m, 1H), 2.83 (t, 4H, J= 8.0 Hz), 2.78 (s, 3H), 1.80-1.72 (m, 4H), 1.39-1.32 (m, 4H), 0.84 (t, 6H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 153.1, 150.9, 148.3, 140.8, 139.4, 138.5, 138.2, 136.4, 134.3, 131.3, 131.1, 128.0, 127.5, 126.5, 122.1, 121.8, 121.3, 116.8, 115.5, 33.6, 33.3, 22.6, 17.6, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{35}N_4O$: 479.2811; found 479.2792.



(*E*)-2,6-Dipentyl-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (13c): The compound **13c** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 83% (63 mg, 0.15 mmol scale); R_f = 0.70 (EtOAc:Hexanes = 20:80); IR (DCM): 3344, 2928, 1678, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 9.03 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (s, 2H), 7.68-7.65 (m, 2H), 7.62 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.44-7.38 (m, 2H), 7.34-7.30 (m, 1H), 2.83 (t, 4H, J= 8.0 Hz), 2.79 (s, 3H), 1.82-1.75 (m, 4H), 1.36-1.24 (m, 8H), 0.80 (t, 6H, J= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 153.1, 150.9, 148.3, 140.8, 139.5, 138.5, 136.4, 134.3, 131.3, 131.1, 128.0, 127.5, 126.5, 122.1, 121.7, 121.3, 116.8, 115.5, 33.5, 31.7, 31.1, 22.5, 17.6, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{39}N_4O$: 507.3124; found 507.3145.

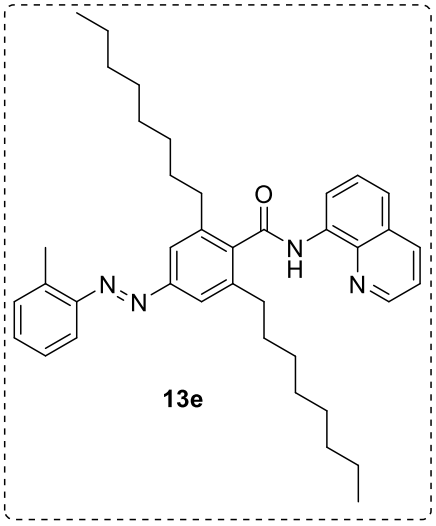


(*E*)-2,6-Diheptyl-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (13d): The compound **13d** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 51% (44 mg, 0.15 mmol scale); R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 2926, 1678, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 9.03 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6



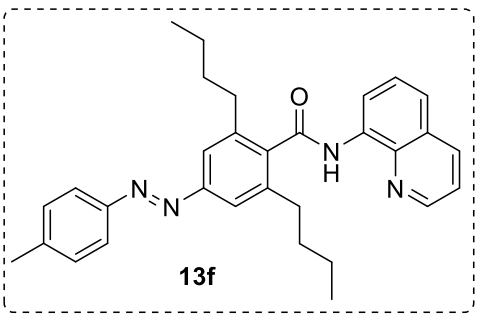
Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (s, 2H), 7.68-7.64 (m, 2H), 7.61 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.44-7.38 (m, 2H), 7.34-7.30 (m, 1H), 2.83 (t, 4H, J= 8.0 Hz), 2.79 (s, 3H), 1.82-1.74 (m, 4H), 1.37-1.29 (m, 4H), 1.24-1.14 (m, 12H), 0.78 (t, 6H, J= 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 153.1, 150.9, 148.3, 140.8, 139.4, 138.5, 138.2, 136.3, 134.3, 131.3, 131.1, 128.0, 127.5, 126.5, 122.0, 121.7, 121.3, 116.8, 115.5, 33.5, 31.6, 31.5, 29.5, 29.0, 22.6 17.6, 14.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{37}H_{47}N_4O$: 563.3750; found 563.3733.

(*E*)-2,6-Dioctyl-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (13e): The compound **13e** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 76% (67 mg, 0.15 mmol scale); R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 2926, 1679, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 9.03 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.72 (s, 2H), 7.68-7.64 (m, 2H), 7.61 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.43-7.38 (m, 2H), 7.34-7.30 (m, 1H), 2.83 (t, 4H, J= 8.1 Hz), 2.78 (s, 3H), 1.82-1.74 (m, 4H), 1.37-1.29 (m, 6H), 1.25-1.10 (m, 14H), 0.81 (t, 6H, J= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 153.1, 150.9, 148.3, 140.8, 139.4, 138.5, 138.2, 136.5, 134.3, 131.3, 131.1, 128.0, 127.5, 126.5, 120.1, 121.7, 121.3, 116.8, 115.5, 33.5, 31.8, 31.5, 29.6, 29.3, 29.1, 22.6 17.6, 14.1; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{39}H_{51}N_4O$: 591.4063; found 591.4038.



13e

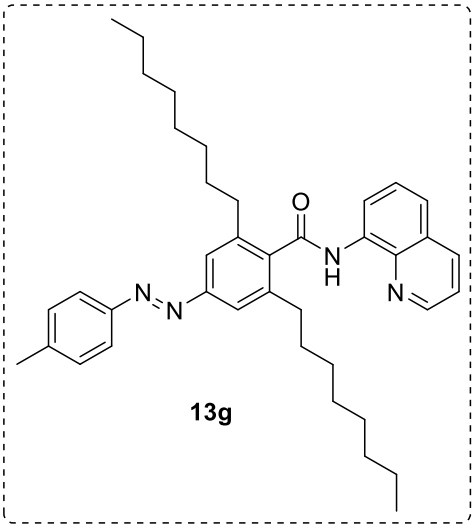
(*E*)-2,6-Dibutyl-*N*-(quinolin-8-yl)-4-(*p*-tolyldiazenyl)benzamide (13f): The compound **13f** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 35% (21 mg, 0.125 mmol scale); R_f = 0.70 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 2956, 1678, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 9.01 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.89 (d, 2H, J = 8.2 Hz), 7.72 (s, 2H), 7.68-7.64 (m, 1H), 7.61 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.36 (d, 2H, J = 8.2 Hz), 2.82 (t,



13f

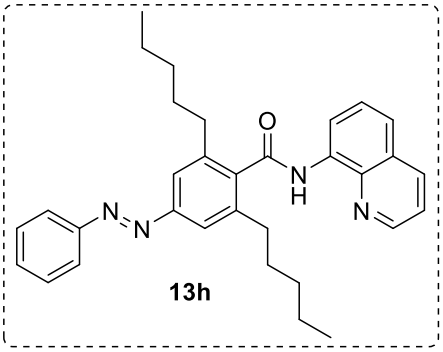
4H, *J* = 8.0 Hz), 2.48 (s, 3H), 1.81-1.73 (m, 4H), 1.40-1.31 (m, 4H), 0.84 (t, 6H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.8, 150.8, 148.3, 141.7, 140.8, 139.3, 138.5, 136.3, 134.3, 129.8, 128.0, 127.5, 122.9, 122.0, 121.7, 121.1, 116.8, 33.7, 33.3, 22.7 21.6, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{35}N_4O$: 479.2811; found 479.2826.

(*E*)-2,6-Dioctyl-*N*-(quinolin-8-yl)-4-(*p*-tolyldiazenyl)benzamide (13g): The compound **13g**



was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 64% (57 mg, 0.15 mmol scale); R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3345, 2926, 1678, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 9.02 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.89 (d, 2H, *J* = 8.2 Hz), 7.71 (s, 2H), 7.68-7.64 (m, 1H), 7.61 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.36 (d, 2H, *J* = 8.1 Hz), 2.82 (t, 4H, *J* = 8.1 Hz), 2.48 (s, 3H), 1.84-1.73 (m, 4H), 1.34-1.28 (m, 4H), 1.22-1.10 (m, 16H), 0.81 (t, 6H, *J*= 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 152.9, 150.9, 148.3, 141.7, 140.9, 139.3, 138.5, 136.3, 134.3, 129.8, 128.0, 127.5, 123.0, 122.0, 121.7, 121.1, 116.8, 33.6, 31.8, 31.5, 29.6, 29.3, 29.1, 22.6 21.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{51}N_4O$: 591.4063; found 591.4045.

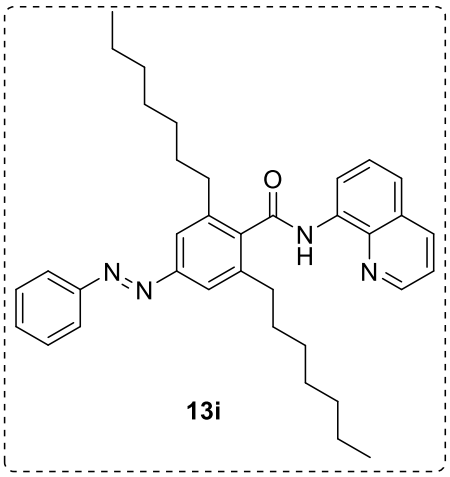
(*E*)-2,6-Dipentyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (13h): The compound



13h was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 5:95) as an orange coloured liquid; Yield: 64% (47 mg, 0.15 mmol scale); R_f = 0.70 (EtOAc:Hexanes = 10:90); IR (DCM): 3344, 2955, 1678, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 9.04 (d, 1H, *J* = 7.3 Hz), 8.78 (d, 1H, *J* = 3.8 Hz), 8.21 (d, 1H, *J* = 8.2 Hz), 8.00-7.93 (m, 2H), 7.79-7..74 (m, 2H), 7.69-7.52 (m, 5H), 7.48 (dd, 1H, = 8.2 Hz, J_2 = 4.1 Hz), 2.84 (t, 4H, *J* = 7.8 Hz), 1.81-1.76 (m, 4H), 1.32-1.24 (m, 8H), 0.80 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ168.3, 152.8, 152.8, 148.3, 140.9, 139.6, 138.5, 136.3, 134.3,

131.1, 129.1, 128.0, 127.5, 122.9, 122.0, 121.7, 121.2, 116.8, 33.5, 31.8, 31.1, 22.4, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{37}N_4O$: 493.2967; found 493.2964.

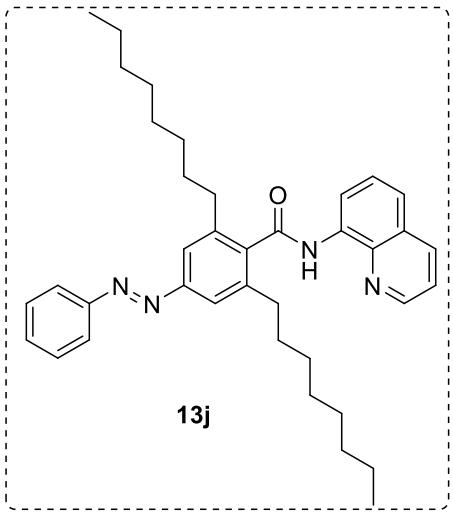
(*E*)-2,6-Diheptyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (13i): The compound



13i

13i was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 68% (56 mg, 0.15 mmol scale); R_f = 0.70 (EtOAc:Hexanes = 20:80); IR (DCM): 3343, 2926, 1678, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 9.05 (d, 1H, *J*= 7.3 Hz), 8.76 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.22 (d, 1H, *J*= 8.2 Hz), 7.99-7.92 (m, 2H), 7.77-7.52 (m, 7H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 2.82 (t, 4H, *J*= 7.9 Hz), 1.81-1.84 (m, 4H), 1.36-1.13 (m, 16H), 0.77 (t, 6H, *J*= 6.8 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.2, 152.8, 152.8, 148.3, 140.9, 139.6, 138.5, 136.3, 134.3, 131.1, 129.1, 128.0, 127.5, 122.9, 122.0, 121.7, 121.2, 116.8, 33.5, 31.6, 31.5, 29.5, 29.0, 22.0, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{45}N_4O$: 549.3593; found 549.3572.

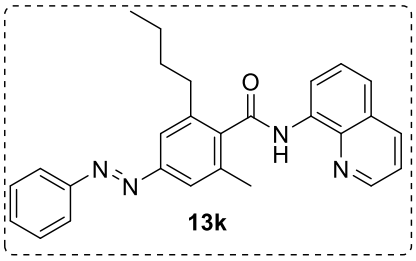
(*E*)-2,6-Dioctyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (13j): The compound **13j**



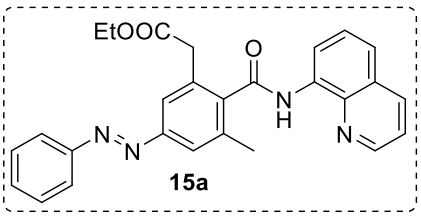
13j

was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 79% (68 mg, 0.15 mmol scale); R_f = 0.80 (EtOAc:Hexanes = 20:80); IR (DCM): 3344, 2923, 1678, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 9.04 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00-7.98 (m, 2H), 7.75 (s, 2H), 7.68-7.65 (m, 1H), 7.63-7.60 (m, 1H), 7.59-7.55 (m, 2H), 7.54-7.51 (m, 1H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 2.84 (t, 4H, *J*= 8.2 Hz), 1.83-1.75 (m, 4H), 1.35-1.28 (m, 6H), 1.24-1.13 (m, 14H), 0.82 (t, 6H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.8, 152.7, 148.3, 140.9, 139.6, 138.5, 136.3, 134.3, 131.1, 129.1, 128.1, 127.5, 122.9, 122.1, 121.7, 121.2, 116.8, 35.6, 31.8, 31.5, 29.6, 29.3, 29.1, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{49}N_4O$: 577.3906; found 577.3928.

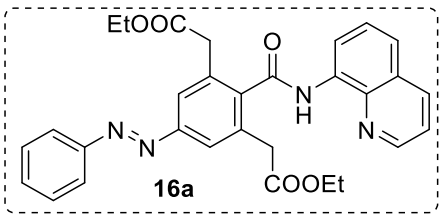
(*E*)-2-Butyl-6-methyl-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (13k): The compound **13k**, was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as an orange coloured liquid; Yield: 24% (15 mg, 0.15 mmol scale); R_f = 0.40 (EtOAc:Hexanes = 15:85); IR (DCM): 3338, 1674, 1521, 1482 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.99 (dd, 1H, J_1= 7.4, J_2= 1.5 Hz), 8.75 (dd, 1H, J_1= 4.2, J_2= 1.6 Hz), 8.20 (dd, 1H, J_1= 8.2, J_2= 1.6 Hz), 7.96-7.94 (m, 2H), 7.72 (d, 1H, J= 1.3 Hz), 7.67-7.66 (m, 1H), 7.59 (dd, 1H, J_1= 8.3, J_2= 1.4 Hz), 7.56-7.49 (m, 3H),7.46 (dd, 1H, J_1= 8.3, J_2= 4.2 Hz), 2.82 (t, 2H, J= 8.0 Hz), 2.53 (s, 3H), 1.78-1.72 (m, 2H), 1.38-1.32 (m, 2H), 0.83 (t, 3H, J= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.7, 152.7, 148.4, 140.9, 139.8, 138.5, 136.4, 135.9, 134.3, 131.2, 129.2, 128.0, 127.4, 122.9, 122.1, 121.8, 121.8, 121.6, 116.9, 33.7, 33.2, 22.7, 19.7, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_4O_3$: 423.2185; found 423.2168.



Ethyl (*E*)-2-(3-methyl-5-(phenyldiazenyl)-2-(quinolin-8-ylcarbamoyl)phenyl)acetate (15a): The compound **15a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 61% (34 mg, 0.125 mmol scale); mp 95-97 ^oC; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3337, 1734, 1674, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 9.03 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.99-7.96 (m, 2H), 7.82 (s, 1H), 7.81 (s, 1H), 7.67-7.62 (m, 2H), 7.60-7.52 (m, 3H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.03 (q, 2H, J = 7.1 Hz), 3.93 (s, 2H), 2.60 (s, 3H), 1.04 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 167.5, 152.6, 152.6, 148.4, 140.1, 138.6, 136.4, 136.3, 134.2, 132.5, 131.3, 129.2, 128.0, 127.4, 123.6, 123.0, 122.7, 122.3, 121.8, 117.0, 61.1, 39.1, 18.8, 19.8, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_4O_3$: 453.1927; found 453.1944.

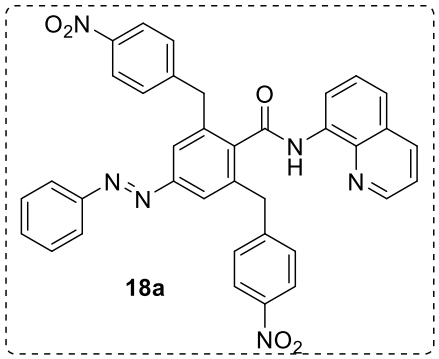


Diethyl 2,2'-(5-(phenyldiazenyl)-2-(quinolin-8-ylcarbamoyl)-1,3-phenylene)(*E*)-diacetate (16a): The compound **16a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured semisolid; Yield: 46% (24 mg, 0.1 mmol scale); R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM):



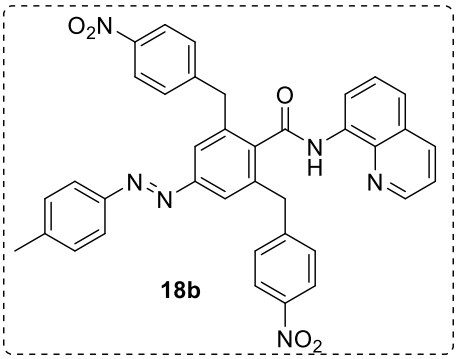
3330, 1734, 1672, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 9.00 (d, 1H, *J*= 6.6 Hz), 8.79 (br s, 1H), 8.21 (d, 1H, *J*= 8.2 Hz), 7.97 (d, 2H, *J*= 7.2 Hz), 7.92 (s, 2H), 7.67-7.61 (m, 2H), 7.58-7.52 (m, 3H), 7.48-7.46 (m, 1H), 7.36-7.35 (m, 1H), 4.03 (q, 4H, *J*= 7.1 Hz), 3.92 (s, 4H), 1.04 (t, 6H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 166.9, 152.6, 152.5, 148.4, 140.1, 138.6, 136.3, 134.1, 132.9, 131.5, 129.2, 128.0, 127.3, 124.1, 123.1, 122.5, 121.8, 117.2, 61.2, 39.2, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_4O_5$: 525.2138; found 525.2114.

(*E*)-2,6-Bis(4-nitrobenzyl)-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (18a): The



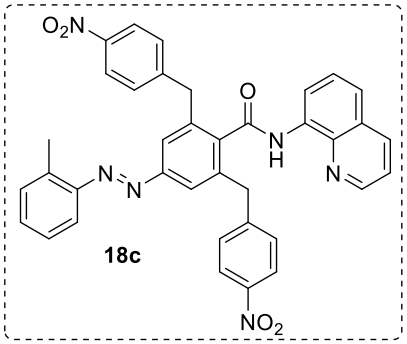
compound **18a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as an orange coloured solid; Yield: 45% (45 mg, 0.16 mmol); mp 168-170 ^oC; R_f = 0.30 (EtOAc:Hexanes = 30:70); IR (DCM): 1672, 1519, 1484, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 8.81 (dd, 1H, J_1 = 6.1 Hz, J_2 = 2.6 Hz), 8.47 (d, 1H, *J*= 8.2 Hz), 8.16 (d, 1H, *J*= 8.2 Hz) 7.96-7.95 (m, 2H), 7.88 (d, 4H, *J*= 8.3 Hz), 7.81 (s, 2H), 7.63-7.51 (m, 5H), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.34 (d, 4H, *J*= 8.4 Hz), 4.31 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 152.9, 152.4, 148.2, 147.2, 146.3, 139.9, 138.1, 137.8, 136.4, 133.3, 131.8, 129.7, 129.3, 127.7, 127.2, 123.7, 123.5, 123.1, 122.7, 121.9, 116.6, 39.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{27}N_6O_5$: 623.2043; found 623.2062.

(*E*)-2,6-Bis(4-nitrobenzyl)-*N*-(quinolin-8-yl)-4-(*p*-tolyldiazenyl)benzamide (18b): The



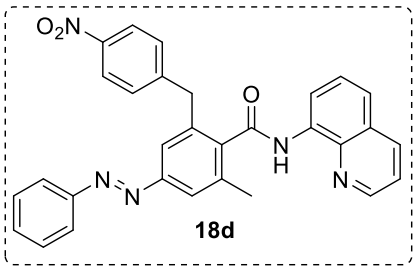
compound **18b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as an orange coloured solid; Yield: 30% (38 mg, 0.2 mmol scale); mp 92-94 ^oC; R_f = 0.30 (EtOAc:Hexanes = 30:70); IR (DCM): 3326, 1672, 1519, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.80 (dd, 1H, J_1 = 6.1 Hz, J_2 = 2.0 Hz), 8.46 (d, 1H, *J*= 4.0 Hz), 8.15 (d, 1H, *J*= 8.2 Hz), 7.88-7.85 (m, 6H), 7.79 (s, 2H), 7.62-7.58 (m, 2H), 7.41-7.33 (m, 7H), 4.30 (s, 4H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 153.0, 150.6, 148.1, 147.3, 146.3, 142.6, 140.0, 138.0, 137.8, 136.4, 133.4, 129.9, 129.7, 127.7, 127.2, 123.7, 123.4, 123.1, 122.7, 121.9, 116.5, 39.4, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{29}N_6O_5$: 637.2199; found 637.2231.

(*E*)-2,6-Bis(4-nitrobenzyl)-*N*-(quinolin-8-yl)-4-(*o*-tolyldiazenyl)benzamide (18c): The



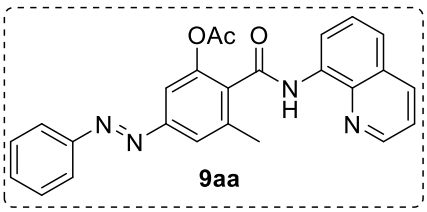
compound **18c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as an orange coloured solid; Yield: 52% (66 mg, 0.2 mmol scale); mp 187-189 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 40:60); IR (DCM): 1672, 1519, 1483, 1344 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H), 8.82 (d, 1H, J= 6.4 Hz), 8.48 (d, 1H, J= 4.1 Hz), 8.16 (d, 1H, J= 8.3 Hz), 7.88 (d, 4H, J= 8.1 Hz), 7.78 (s, 2H), 7.66-7.60 (m, 3H), 7.44-7.27 (m, 8H), 4.32 (s, 4H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 153.3, 150.5, 148.2, 147.3, 146.3, 139.7, 138.8, 138.1, 137.8, 136.4, 133.4, 131.8, 131.5, 129.8, 127.7, 127.2, 126.6, 123.7, 123.5, 122.7, 121.9, 116.6, 115.4, 39.4, 17.6; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{37}H_{29}N_6O_5$: 637.2199; found 637.2226.

(*E*)-2-Methyl-6-(4-nitrobenzyl)-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)benzamide (18d):



The compound **18d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 61% (46 mg, 0.15 mmol scale); mp 174-176 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3335, 1673, 1521, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.91 (d, 1H, J = 7.0 Hz), 8.60 (d, 1H, J = 4.1 Hz), 8.18 (d, 1H, J = 4.1 Hz), 7.97 (d, 2H, J = 7.2 Hz), 7.83-7.79 (m, 3H), 7.74 (s, 1H), 7.65-7.52 (m, 5H), 7.43 (dd, 1H, J_1= 8.2, J_2= 4.2 Hz), 7.33 (d, 2H, J = 8.5 Hz), 4.30 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 152.7, 152.5, 148.3, 147.7, 146.2, 140.0, 138.1, 137.5, 136.6, 136.4, 133.8, 131.5, 129.7, 129.2, 127.8, 127.3, 123.6, 123.1, 123.0, 122.7, 122.5, 121.8, 116.7, 39.5, 19.7; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{30}H_{24}N_5O_3$: 502.1879; found 502.1860.

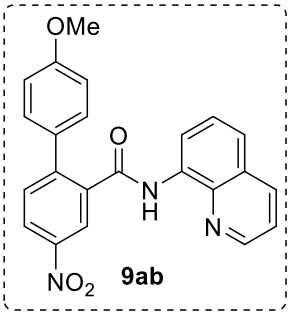
(*E*)-3-Methyl-5-(phenyldiazenyl)-2-(quinolin-8-ylcarbamoyl)phenyl acetate (9aa): The



compound **9aa**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 42% (27 mg, 0.15 mmol scale); mp 149-151 ^{o}C; R_f = 0.30 (EtOAc:Hexanes = 20:80); IR (DCM): 3338, 1772, 1676, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.99-8.97 (m, 1H), 8.82 (dd, 1H, J_1= 4.2, J_2= 1.4 Hz), 8.21 (d, 1H, J = 8.2 Hz), 7.98-

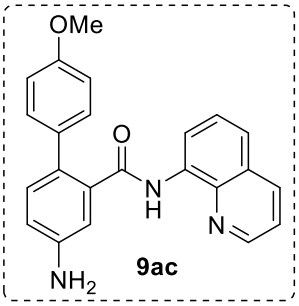
7.96 (m, 2H), 7.82 (br s, 1H), 7.66-7.53 (m, 6H), 7.45 (dd, 1H, J_1= 4.2, J_2= 1.4 Hz), 2.63 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4,164.3, 153.2, 152.4, 148.5, 148.2, 138.5, 136.3, 134.2, 132.3, 131.6, 129.2, 128.0, 127.4, 123.8, 123.1, 122.3, 121.8, 116.9, 113.9, 20.8, 19.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_4O_3$: 425.1614; found 425.1631.

4'-Methoxy-4-nitro-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9ab): The



compound **9ab** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as an pale green coloured solid; Yield: 48% (42 mg, 0.2 mmol scale); mp 183-185 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 20:80); IR (DCM): 2922, 1670, 1604, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.81 (d, 1H, J = 7.0 Hz), 8.77 (s, 1H), 8.55-8.54 (m, 1H), 8.37 (d, 1H, J = 8.5 Hz), 8.12 (d, 1H, J = 8.2 Hz), 7.65 (d, 1H, J = 8.5 Hz), 7.56-7.48 (m, 4H), 7.40 (dd, 1H, J_1= 8.0, J_2= 4.2 Hz), 6.88 (d, 1H, J = 7.9 Hz), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 160.4, 147.9, 146.7, 146.1, 138.3, 136.2, 134.0, 131.6, 130.2, 130.1, 127.8, 127.2, 125.0, 124.8, 122.2, 121.6, 116.7, 114.4, 55.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_4$: 400.1297; found 400.1278.

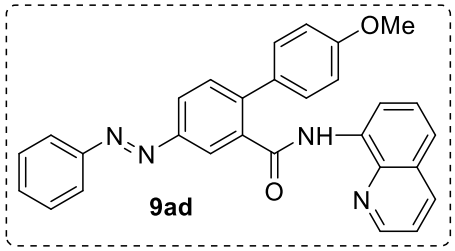
4-Amino-4'-methoxy-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9ac): The



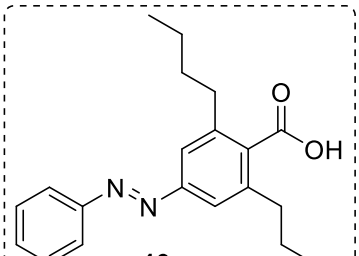
compound**9ac** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as an pale green coloured solid; Yield: 47% (28 mg, 0.16 mmol scale); mp 149-151 ^{o}C; R_f= 0.30 (EtOAc:Hexanes = 40:60); IR (DCM): 3344, 2927, 1608, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.84 (d, 1H, J = 7.6 Hz), 8.54-8.53 (m, 1H), 8.08 (d, 1H, J = 8.2 Hz), 7.56-7.52 (m, 1H), 7.48-7.46 (m, 1H), 7.40 (d, 2H, J = 7.8 Hz), 7.36 (dd, 1H, J_1= 8.2, J_2= 4.2 Hz), 7.28-7.26 (m, 1H), 7.22 (s, 1H), 6.87 (d, 1H, J = 8.2 Hz), 6.80 (d, 2H, J = 7.9 Hz), 3.90 (br s, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.8, 147.7, 145.7, 138.5, 136.6, 136.0, 134.6, 132.6, 131.8, 130.1, 127.7, 127.3, 121.4, 121.4, 117.2, 116.3, 115.4, 113.8, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}N_3O_2$: 370.1556; found 370.1543.

(*E*)-4'-Methoxy-4-(phenyldiazenyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (9ad): The compound **9ad** was obtained after purification by column chromatography on

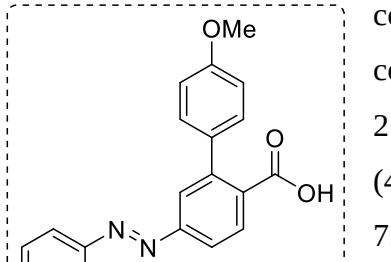
silica gel (EtOAc:Hexanes = 20:80) as an orange coloured solid; Yield: 35% (9 mg, 0.06 mmol scale); mp 182-184 ^{o}C; R_f = 0.50 (EtOAc:Hexanes = 30:70); IR (DCM): 3321, 1597, 1524, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.88 (d, 1H, J = 7.4 Hz), 8.59-8.58 (m, 1H), 8.50 (s, 1H), 8.13 (d, 2H, J = 8.1 Hz), 7.99 (d, 2H, J = 7.6 Hz), 7.65 (d, 1H, J = 8.2 Hz), 7.57-7.53 (m, 7H), 7.40 (dd, 1H, J_1= 8.2, J_2= 4.2 Hz), 6.88 (d, 2H, J = 8.4 Hz), 3.70 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.3, 158.7, 151.6, 150.3, 146.8, 141.2, 137.4, 135.7, 135.0, 133.5, 130.6, 130.5, 130.2, 129.1, 128.1, 126.7, 126.3, 123.4, 123.0, 122.0, 120.7, 120.4, 115.5, 113.1, 54.2; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{23}N_4O_2$: 459.1821; found 459.1841.



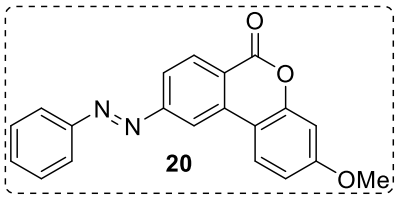
(*E*)-2,6-Dibutyl-4-(phenyldiazenyl)benzoic acid(19a): The compound (**19a)** was obtained after workup as an orange coloured solid; Yield: 95% (24 mg, 0.075 mmol scale); mp 101-103 ^{o}C; IR (DCM): 2928, 2958, 1695, 1462 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94-7.92 (m 2 H), 7.65 (s, 2H), 7.55-7.49 (m, 3H), 2.80 (t, 4H, J = 8.0 Hz), 1.74-1.68 (m, 4H), 1.46-1.39 (m, 4H), 0.96 (t, 6H, J= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 152.9, 152.6, 141.2, 134.4, 131.3, 129.2, 123.0, 121.2, 33.7, 33.5, 22.7, 13.9; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{27}N_2O_2$:339.2073; found 339.2059.



(*E*)-4'-Methoxy-5-(phenyldiazenyl)-[1,1'-biphenyl]-2-carboxylic acid (19b): The compound **19b** was obtained after workup as an orange coloured solid; Yield: 66% (21 mg, 0.098 mmol scale); mp 210-212 ^{o}C; IR (DCM): 2924, 2357, 1695, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 4H), 7.83 (s, 1H), 7.63-7.62 (m, 3H), 7.38 (d, 2H, J = 7.8 Hz), 7.02 (d, 2H, J = 7.9 Hz), 3.82 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 159.4, 153.0, 152.3, 142.1, 132.7, 132.7, 132.6, 131.1, 130.8, 130.1, 130.0, 130.0, 124.7, 123.3, 123.0, 121.0, 114.2;HRMS (ESI): *m/z* [M - H]$^{+}$ calcd for $C_{20}H_{15}N_2O_3$: 333.1083; found 331.1070.



(*E*)-3-Methoxy-9-(phenyldiazenyl)-6*H*-benzo[*c*]chromen-6-one (20): The compound **20** was obtained after workup as a an orange coloured solid;



Yield: 61% (24 mg, 0.12 mmol scale); mp 215-217 ^{o}C; IR (DCM): 1735, 1611, 1430, 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 2H), 8.11 (d, 1H, J = 8.9 Hz), 8.05-7.99 (m, 3H), 7.63-7.58 (m, 3H), 6.99 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 6.92 (d, 1H, J = 2.5 Hz), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 161.0, 156.1, 152.8, 152.4, 136.4, 132.2, 131.9, 129.3, 124.2, 123.4, 121.0, 120.8, 116.5, 112.2, 111.1, 101.6, 55.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}N_2O_3$: 331.1083; found 331.1068.

References:

1) Hunger K. *Industrial Dyes: Chemistry, Properties, Applications* ed. Wiley-VCH, Weinheim, Germany, **2003** (b) Zollinger, H. *Color Chemistry: Syntheses, Properties and Applications of Organic Dyes and Pigments*, VCH, NY, **1987**, p. 85 (c) Gordon P. F.; Gregory, P.; *Organic Chemistry in Colour*, Springer, NY, **1983**, p. 95. d) Ikeda T.; Tsutsumi, O. *Science*, **1995**, *268*, 1873. e) Feringa, B. L.; VanDelden, R. A.; Koumura, N.; Geertsema, E. M. *Chem. Rev.***2000**, *100*, 1789. f) Murakami, H.; Kawabuchi, A.; Kotoo, K.; Kutinake, M.; Nakashima, N. *J. Am. Chem. Soc.***1997**, *119*, 7605. g) Banerjee, I. A.; Yu L.; Matsui, H. *J. Am. Chem. Soc.***2003**, *125*, 6542. h) Crano, J. C.; Guglielmetti, R. *Organic Photochromic and Thermochromic Compounds*, Plenum Press, New York, **1999**. i) Brown, M. A.; de Vito, S. C.; *Crit. Rev. Environ. Sci. Technol.***1993**, *23*, 249.
2) For reviews on C-H activation chemistry, see: (a) Shilov, A. E.; Shuľpin, G. B. *Chem.Rev.* **1997**, *97*, 2879. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180. (d) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698. (e) Bergman, R. G. *Nature* **2007**, *446*, 391. (f) Lewis, J. R.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (g) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (h) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (i) Kuhl, N.; Hopkinson, M. N.; Delord, J. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (j) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (k) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (m) Boorman, T.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (n) Delord, J. W.; DrÖge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (o) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (p) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (q) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. (r) Lyons, T. W.;

Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (s) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (t) Castro, L. C. M.; Chatani, N. *Chem. Lett.***2015**, *44*, 410. (u) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (v) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421. (w) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (x) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.*, **2002**, *35*, 826.

3) For functional group enabled C-H functionalization, see: a) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.***2015**, *44*, 7764. b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. c) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.***2007**, *349*, 1185. d) Tsuchikama, K.; Kuwata, Y.; Tahara, Y.-K.; Yoshinami, Y.; Shibata, T. *Org. Lett.***2007**, *9*, 3097. e) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.***2010**, *132*, 5916. f) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.***2011**, *76*, 3024. g) Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.***2012**, *51*, 8092. h) Iitsuka, T.; Schaal, P.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *J. Org. Chem.***2013**, *78*, 7216. i) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem. Eur. J.***2013**, *19*, 10511. j) Mamone, P.; Danoun, G.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6704. k) Shi, G.; Zhang, Y. *Adv. Synth. Catal.***2014**, *356*, 1419. l) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature***2014**, *510*, 129. m) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.***2014**, *356*, 1521. n) Ng, F.-N.; Zhou, Z.; Yu, W.-Y. *Chem. Eur. J.* **2014**, *20*, 4474. o) Calleja, J.; Pla, D.; Gorman, T. W.; Domingo, V.; Haffemayer, B.; Gaunt, M. J. *Nat. Chem.***2015**, *7*, 1009. p) He, C.; Gaunt, M. J. *Angew. Chem., Int. Ed.***2015**, *54*, 15840. q) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. *Org. Chem. Front.***2017**, *4*, 2097.

4) For 8-aminoquinoline aided arylation, see a) Aihara, Y.; Chatani, N. *Chem. Sci.***2013**, *4*, 664. b) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.***2014**, *79*, 11922. c) Parella, R.; Babu, S. A. *J. Org. Chem.***2015**, *80*, 12379. d) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.***2003**, *68*, 7528. e) Cheng, X.; Chen, Z.; Gao, Y.; Xue, F.; Jiang, C. *Org. Biomol. Chem.***2016**, *14*, 3298. f) Sattar, M.; Praveen; Durga Prasad, C.; Verma, A.; Kumar, S.; Kumar, S. *Adv. Synth. Catal.* **2016**, *358*, 240. g) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.***2014**, *136*, 14349. h) Gui, Q.; Chen, X.; Hu, L.; Wang, D.; Liu, J.; Tan, Z. *Adv. Synth. Catal.***2016**, *358*, 509. i) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *Org. Biomol. Chem.***2016**, 14, 11070.

5) For transition metal catalyzed alkylation reactions, see: a)Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2010**, *132*, 3965.b) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.***2013**, *78*, 9689.c)Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.***2015**, *137*, 531.d)Sattar, M.; Praveen; Durga Prasad, C.; Verma, A.; Kumar, S.; Kumar, S. *Adv. Synth. Catal.***2016**, *358*, 240.Ni catalyzed: e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.***2013**, *135*, 5308. f) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.***2014**, *53*, 2477. g) Aihara, Y.; Wuelbern, J.; Chatani, N. *Bull. Chem. Soc. Jpn.***2015**, *88*, 438. Fe catalyzed: h) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.***2014**, *136*, 13126. i) Monks, B. M.; Fruchey, E. R.; Cook, S. P. *Angew. Chem., Int. Ed.***2014**, *53*, 11065. j) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.***2014**, *136*, 13130. **Cu/Cr catalyzed** k) Chen, X.; Tan, Z.; Gui, Q.; Hu, L.; Liu, J.; Wu, J.; Wang, G. *Chem. Eur. J.***2016**, *22*, 6218. l) Tang, C.; Zhang, R.; Zhu, B.; Fu, J.; Deng, Y.; Tian, L.; Guan, W.; Bi, X. *J. Am. Chem. Soc.***2018**, *140*, 16929. m) Tang, J.; Liu, P.; Zeng, X. Chem. Commun. **2018**, *54*, 9325. n) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen G. *J. Am. Chem. Soc.* **2013**, *135*, 2124-2127. o) Zhao Y.; Chen, G. Org. Lett. 2011, *13*, 4850. p) Nadres,E. T.; Santos,G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 19, 9689.

6) For examples of Arylation of azoarenes: a) Miyamura, S.; Tsurugi, H.; Satoh, T.; Miura, M. J. *Organomet.Chem.* **2008**, 693, 2438. b) Qian, C.; Lin, D.; Deng, Y.; Zhang, X.-Q.; Jiang, H.; Miao, G.; Tang, X.; Zeng, W. *Org. Biomol. Chem.***2014**, 12, 5866. c) Li, M.; Ye, Y. *ChemCatChem***2015**, 7, 4137. d) Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. *ACS Catal*. **2015**, 5, 4089. e) Deng, H.; Li, H.; Wang, L. *Org. Lett*. **2016**, *18*, 3110.

7) For examples of alkylation of azoarenes: a) Premi, C.; Dixit, A.; Jain, N. *Org. Lett*. **2015**, *17*, 2598. b) Deng, H.; Li, H.; Wang, L. *Org. Lett.***2015**, *17*, 2450. c) Li, G.; Ma, X.; Jia, C.; Han, Q.; Wang, Y.; Wang, J.; Yu, L.; Yang, S. *Chem. Commun*. **2017**, *53*, 1261. d) Muniraj, N.; Prabhu, K. R. *J. Org. Chem*. **2017**, *82*, 6913.

8) Pd catalyzed C-H functionalization of azoarenes: a) Xiong, F.; Qian, C.; Lin, D.; Zeng, W.; Lu, X. *Org. Lett.***2013**, *15*, 5444. b) Xu, N.; Li, D.; Zhang, Y.; Wang, L. *Org. Biomol. Chem.***2015**, *13*, 9083. c) Qian, C.; Lin, D.; Deng, Y.; Zhang, X. Q.; Jiang, H.; Miao, G.; Tang, X.; Zeng, W. *Org. Biomol. Chem.***2014**, *12*, 5866. d) Fu, X.; Wei, Z.; Xia, C.; Shen, C.; Xu, J.; Yang, Y.; Wang, K.; Zhang, P. *Catal. Lett.***2017**, *147*, 400. e) Ma, X.-T.; Tian, S.-K. *Adv. Synth. Catal.***2013**, *355*, 337. f)

Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.***2013**, *78*, 10002. g) Nguyen, T. H. L.; Gigant, N.; Delarue-Cochin, S.; Joseph, D. *J. Org. Chem.***2016**, *81*, 1850. h) Majhi, B.; Kundu, D.; Ahammed, S.; Ranu, B. C. *Chem. Eur. J.***2014**, *20*, 9862. i) Hong, G.; Mao, D.; Wu, S.; Wang, L. *J. Org. Chem.***2014**, *79*, 10629. j) Zhang, D.; Cui, X.; Zhang, Q.; Wu, Y. *J. Org. Chem.***2015**, *80*, 1517.

9) Cleavage of 8-aminoquinoline reactions, see: a) Aihara, Y.; Chatani, N. *Chem. Sci.***2013**, *4*, 664. b) Parella, R.; Babu, S. A. *J. Org. Chem.***2015**, *80*, 2339. c) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.***2012**, *51*, 5188. d) Huang, L.; Li, Q.; Wang, C.; Qi, C. *J. Org. Chem.* **2013**, *78*, 3030.e) Wang, X.; Zhu, L.; Chen, S.; Xu, X.; Au, C.-T.; Qiu, R. *Org. Lett.***2015**, *17*, 5228. f) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* 2010, *12*, 3414-3417. g) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.***2010**, 49, 958. h) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.***2012**, *134*, 18237. i) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.***2013**, 52, 11124. j) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N. *Chem. Eur. J.* **2016**, *22*, 16805. k) Deguchi, T.; Xin, H.-L.; Morimoto, H.; Ohshima, T. *ACS Catal.***2017**, *7*, 3157.