Studies on the Synthesis of Functionalized Arenes and Heteroarenes *via* Directing Group-Assisted C-H Functionalization

A thesis submitted for the partial fulfillment of

the degree of Doctor of Philosophy

by

NARENDRA BISHT

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.

July, 2019

Dedicated to

MY BELOVED PARENTS

BHAGWATI AND ANAND

BROTHER

KAMLESH

Declaration

I hereby declare that the matter embodied in this thesis entitled "**Studies on the Synthesis of Functionalized Arenes and Heteroarenes *via* Directing Group-Assisted C-H Functionalizatio**n" 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 acknowledgments. In keeping with the general practice of reporting scientific observations, acknowledgmentshavebeen 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.

Narendra Bisht

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

& Head of Department (HOD)

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

Date:

Place:

Acknowledgments

"Really great people make you feel that you, too, can become great."–Mark Twain

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Sometimes the questions are complicated, and the answers are simple.

Dr. Seuss

List of publications from thesis work

Bisht, N.; Babu, S. A. *Tetrahedron* **2016**, *72*, 5886.

Title: Synthesis of ortho-arylated/benzylated arylacetamide derivatives: Pd-catalyzed bidentate ligand-aided arylation and benzylation of the γ-C-H bond of arylacetamides

Reddy, C. K.; **Bisht, N.;** Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 12143.

Title: 4-Amino-2,1,3-Benzothiadiazole (ABTD) as a Removable Bidentate Directing Group for the Pd(II)-Catalyzed Arylation/ Oxygenation of sp^2/sp^3 β-C–H Bonds of Carboxamides

Conferences/Symposia

1) Poster presentation entitled "4-Amino-2,1,3-Benzothiadiazole (ABTD) as a Removable Bidentate Directing Group for the Pd(II)-Catalyzed Arylation/ Oxygenation of sp^2 β-C–H Bonds of Carboxamides" **Bisht, N.;** S. A. Babu at the *21st CRSI National Symposium (NSC-21)* held at the Indian Institute of Chemical Technology (IICT) Hyderabad, India (13-17 July, 2017).

2) Participated in the *National Seminar on Crystallography 43A* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30 March, 2014).

Preamble

In recent years, transition-metal-catalyzed reactions led to the development of effective methods for the construction of complex organic molecules.In this perspective, C-H functionalization reactions emerged as a powerful synthetic tool for the conversion of ubiquitous C-H bonds into new C-C or C-X (X = heteroatom) bonds. To accomplish a C-H functionalization reaction in a practically useful manner, issues regarding reaction efficiency and site-selectivity need to address.The most effective and well-practiced approaches to attain site-selectivity is the use of a heteroatom directing group. In this regard, over the past few years, diverse directing groups have been designed and employed successfully for the development of versatile C-H functionalization reactions such as arylation, alkylation, alkenylation, halogenation, amination, acetoxylation, olefination etc. Therefore, further development of new and efficient directing groups, functionalization reactions broadens the structural diversity.

This thesis aimstowards the development of a new set of biological active molecules using new bidentate directing groups4-amino-2,1,3-benzothiadiazole (ABTD). Accordingly, several functionalized arenes and heteroarenes systems were used. Next multiple substitutedphenylacetamide was prepared using double C-(sp^2)-H activation.

Accordingly, this thesis entitled *"Studies on the Synthesis of Functionalized Arenes and Heteroarenes via Directing Group-Assisted C-H Functionalization."* consists of the following **Six chapters** along with objectives of the thesis work. Individual chapters contain the sub-sections, such as introduction, results and discussion and conclusions, the experimental section and references.

Chapter 1: Introduction to C-H bond activation/ functionalization,this chapter gave us the historical background of C-H activation/functionalization.

Chapter 2: Functionalization of phenylacetamide and heterocyclic amides via the Pd-(II)-catalyzed bidentate directing group assisted γ-C-(sp^3/sp^2)-H bond arylation/benzylation and acetoxylation.

Chapter 3: 4-amino-2,1,3-benzo thiadiazole (ABTD) assisted Pd(II)-catalyzed: β-γ-C-(sp^2)-H bond arylation/benzylation/Acetoxylation and amination of aryl carboxamides.

Chapter 4: Pd(II)-catalyzed 4-amino-2,1,3-benzothiadiazole (ABTD) assisted β-γ-C-(sp^3)-H functionalization of natural/unnatural amino acid derivatives and heterocarboxamides system.

Chapter 5: Pd-(II)-catalyzed arylation of *ortho*-C-(sp^2)-H bond of chiral and nonchiral methyl/ ethyl benzylamine picolinamides.

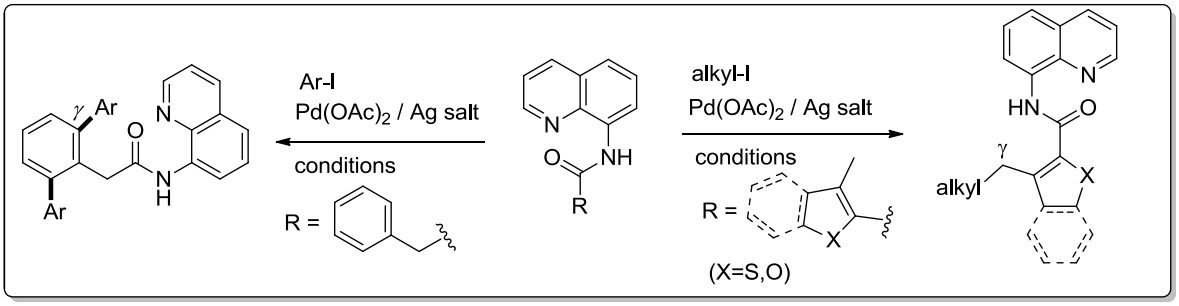
Chapter 6: Thiophene directed Pd-catalyzed regioselective activation / functionalization of the aromatic system: a new approach to synthesize, multiple-substituted phenylacetyl.

Objectives of this thesis work

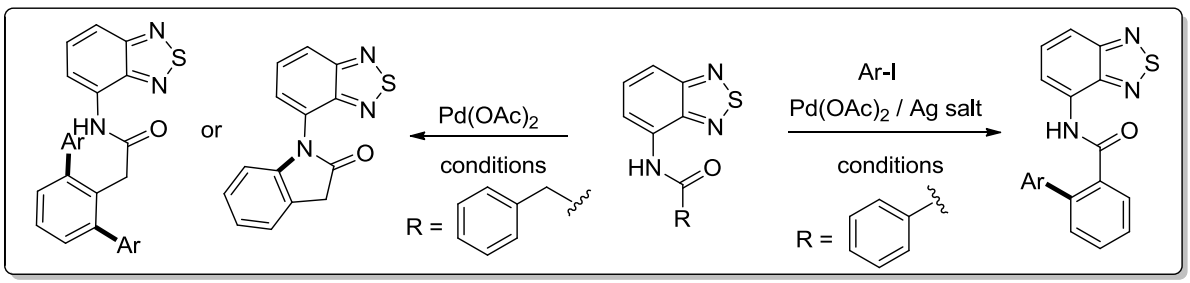
Chapter 1: Chapter 1 provides a brief historical background, and the evolution of the directing group assisted C-H functionalization in last decades with its utility to modern synthetic chemistry.

The research work mainly focused on accomplishing construction of functionalized arenes and heteroarenes by newly developed fluorescent and biological active bidentate directing group 4-amino-2,1,3-benzothiadiazole (ABTD).

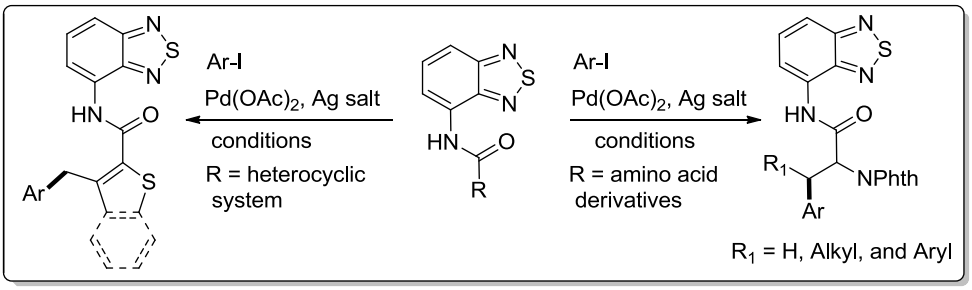
Chapter 2: The significance of functionalized phenylacetamides molecules in the field of medicinal chemistry. Our focus on the development of a variety of substituted phenylacetamide and heteroarenes derivatives by using 8-aminoquinoline as a directing group. In this **chapter 2,** we investigate the Pd(II)-catalyzed C-H functionalization of heteroarenes and phenylacetamides.



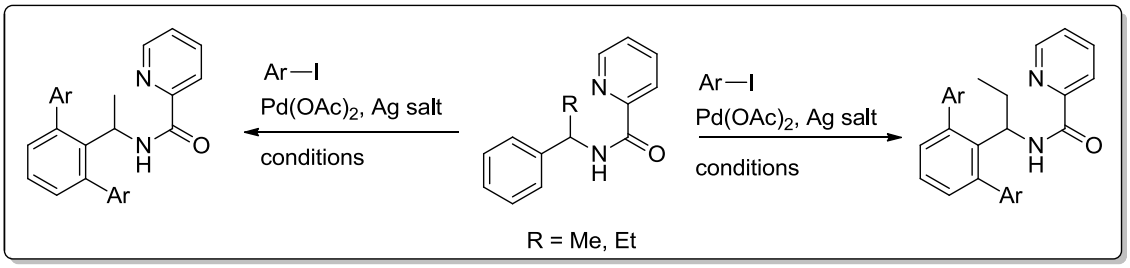
Chapter 3: In this **Chapter 3** we generally focused on the synthesis of natural product core containing molecules such as indolinone and their derivatives along with that the development of functionalized benzamides and the formation of C-O bond directed by 4-amino-2,1,3-benzothiadiazole (ABTD).



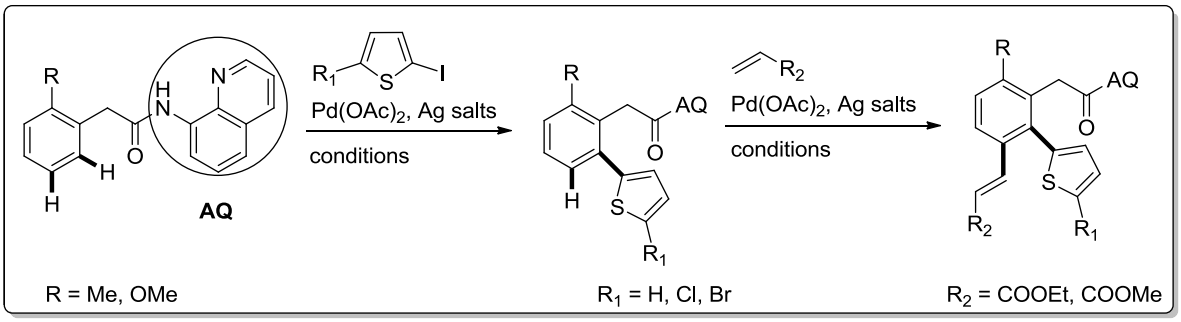
Chapter 4: Development of natural/unnatural amino acid derivatives, and triarylmethane derivatives focusing towards their importance in the medicinal and biological field. A part of this **chapter 4** focused on studies the C-H functionalization of natural/unnatural aminoacid as well as arylation of heteroarenes system.



Chapter 5: Importance of functionalized chiral molecules in the field of medicinal chemistry; a part of this **chapter 5** mainly focusing the development of functionalized chiral methylbenzylamine via C-H activation methodology.



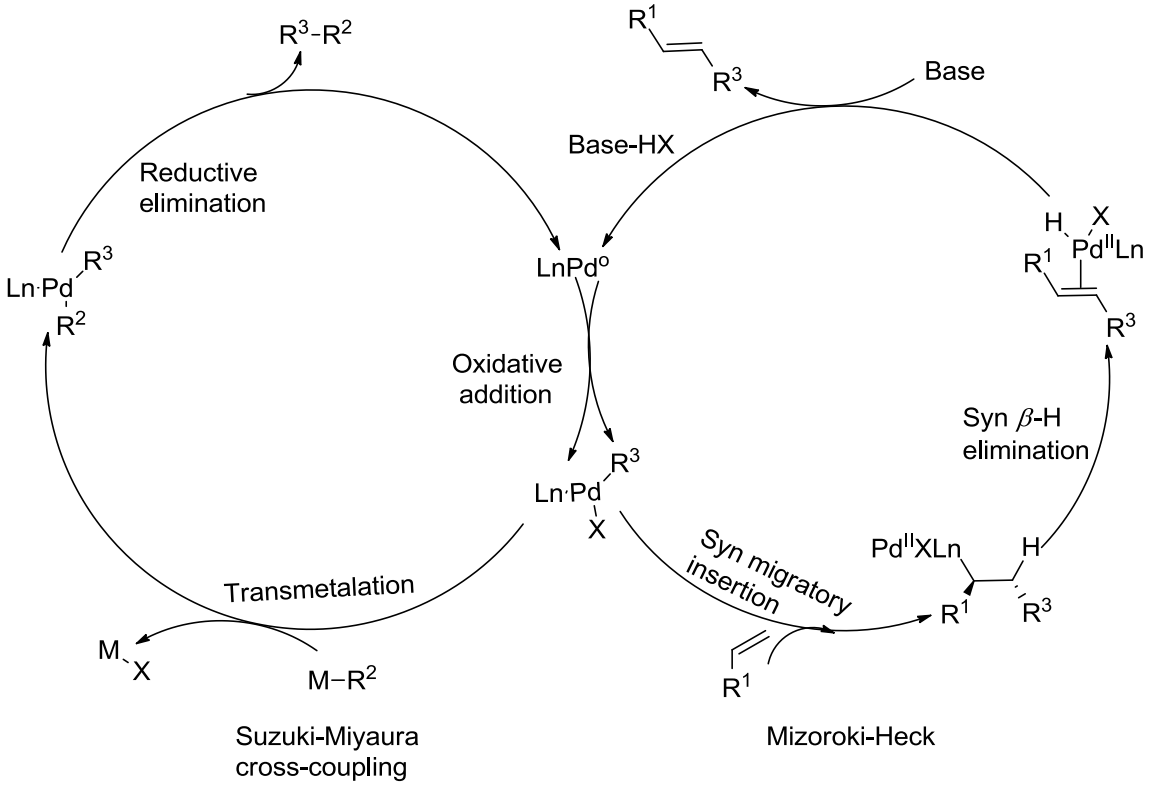
Chapter 6: Given the importance of multiple substituted phenylactamides and thiophene containing core molecules in biological studies. A part of this **chapter 6** envisages the synthesis of multiply substituted phenylacetamides directed by thiophene via double C-H activation/functionalization methodology.



Chapter 1

Introduction on C-H activation

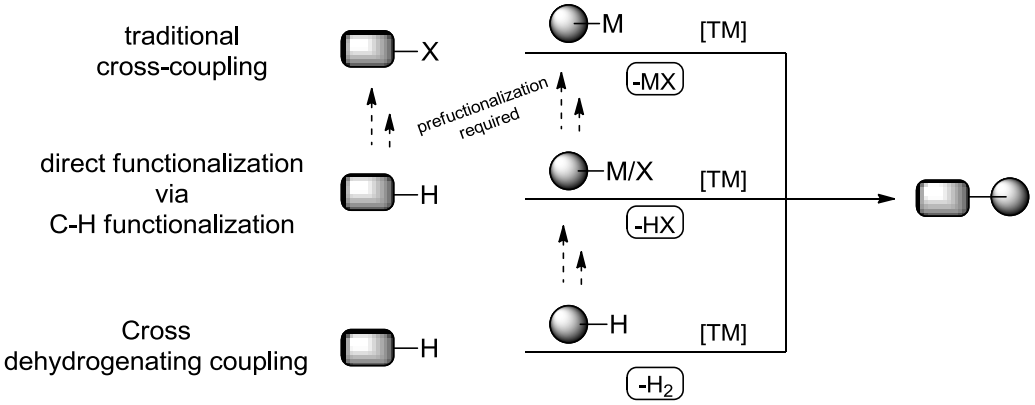
The carbon-carbon bond synthesis is one of the most imperative reactions in organic synthesis. Reactions involving aryl-aryl or aryl-alkene coupling using conventional noncatalytic methods generally involve many steps. To sort out this problem, scientist discovered a new methodology known as palladium-catalyzed cross coupling reactions. Afterthat,the significant discovery in the cross-coupling reactionsis the transition metal-catalyzed C-H functionalization, which has emerged as a principal technique for the chemoselective and regioselective synthesis of C-C and C-X (X = hetero) bonds.[1] Besides the research field, this approach brings the opportunity to widely employed in the chemical, pharmaceutical and agrochemical industries.[2] C-H activation access to a widespread of the substrate for C-H functionalization due to no pre-functionalization of the starting materials is required and explored the synthetic utility of this methodology. In 2010, R. F. Heck, E. Negishi, and A. Suzuki were awarded Nobel prize for theiroutstanding contribution in coupling reaction and C-H activation.The commonly accepted mechanisms for these palladium-catalyzed cross-coupling transformations is depicted in Scheme 1.



Scheme 1 A general mechanism for Mizoroki-Heck, Suzuki, and Negishi reactions.

In thecross-coupling functionalization, the first step is the oxidative addition of the aryl halide or masked halide to the catalytically active palladium species which initiates the catalytic cycle. In the Mizoroki-Heck reaction, the reaction progresses by coordination of an alkene to the palladium species followed by syn-migratory insertion and syn-β-hydride elimination to form the substituted alkene product, and subsequently base-assisted elimination to regenerate the active palladium. In the other cross-coupling reactions such as Suzuki-Miyaura and Negishi cross-coupling reactions,[2, 3] the oxidative addition is followed by transmetalation of an organometallic or main group element species to generate a Palladium intermediate. Following reductive elimination results in C-C bond formation with the regeneration of palladium species to complete the catalytic cycle.

Though these reaction have wide applications, the use of pre-functionalized starting materials and the generation of undesired by-products remain significant disadvantages. As a supplementary step- and atom-economical alternative, direct C-H functionalization has recently come out as a valuable tool allowing the transformation of unreactive C-H bonds (Scheme 2). Furthermore, the direct construction of C-C bonds by functionalizing two C-H bonds including C-(sp^3)-H bonds, which isknown as cross-dehydrogenative coupling (CDC), has been comprehensively studied.

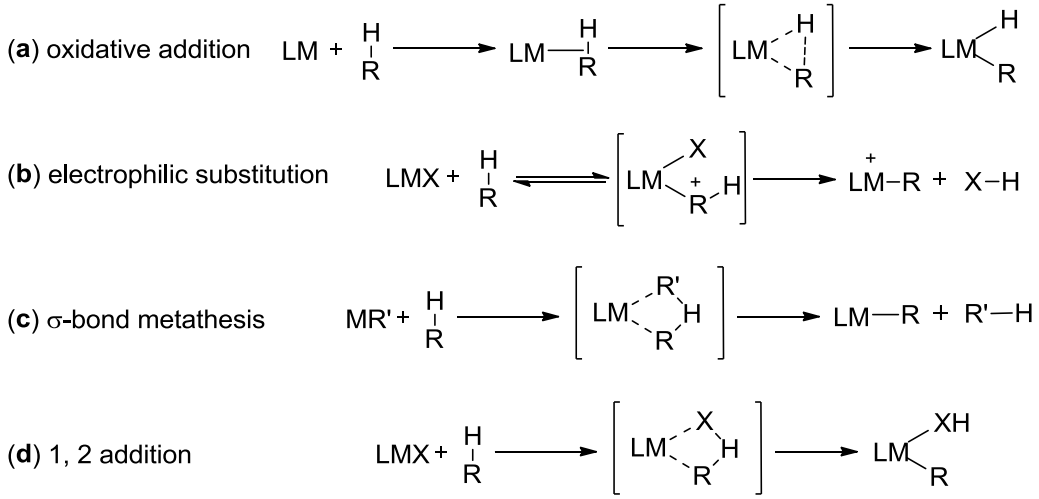


Scheme 2 Approach for the C-C and C-X bond formation.

There are three key challenges in developing a selective C-H bond functionalization methodology. (1) C-H bonds are thermodynamically stableand kinetically inert. (2) C-H bonds are ubiquitous in organic molecules;so required a synthetically useful method to functionalize a single C-H bond in a molecule selectively. (3) The reactions must allow for the incorporation of a various array of functionalities under similar reaction conditions.[4.]Nevertheless, transition metals are known to activate C-H bonds to form C-

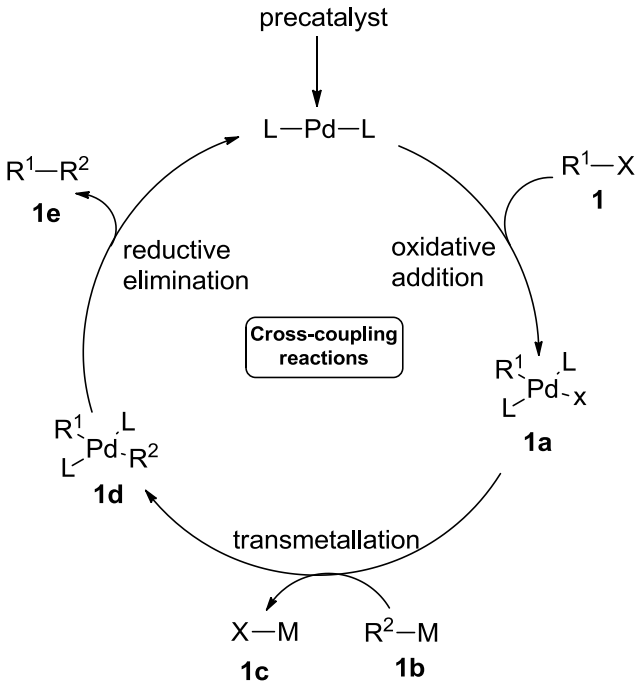
Mbonds. Basedon the nature of the transition metal catalyst (M) and the ligand (L), the primary step of C-H bond metalation was anticipated to proceed via different pathways.

Eisenstein, Ackermann, and co-workers concussed four generally accepted lanes for this process which is shown in Scheme 3.[1, 3]The oxidative addition is a general mechanism in which a C-H bond first coordinates to the empty metal site and then cleaved to form an M-H bond and M-C bond (Scheme 3a). This process often occurs for electron-rich and low-valent transition metals (Pt, Fe, Ru, andIr). Similar reactivity experienced for transition metals (Pd^{2+}, Pt^{2+}, Pt^{4+}) in the strongly polar medium. In this process,metal acts as a Lewis acid and thus classified as electrophilic substitution reactions (Scheme 3b).On the other hand, early transition metal groups 3, 4 and lanthanides (d^0 configuration) usually do not undergo oxidative addition. Therefore, for these metals σ-bond metathesis (SBM) is more common (Scheme 3c). C-H bond activation can also proceed via 1,2-addition to unsaturated M−X bonds (Scheme 3d).



Scheme 3 The different widely accepted mechanism for C-H activation.

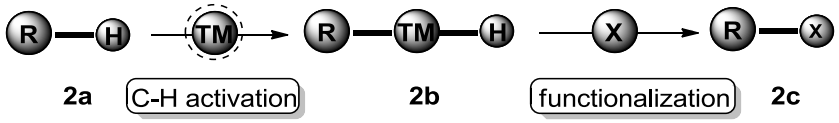
A general mechanism for the Pd(0)-catalyzed cross-coupling reactions is depicted in Scheme 4.[3, 4]The reaction commonly start with oxidative addition (OA) of an electrophile **1** with the transition metal to give an intermediate **1a**. Further, Transmetallation (Tm) of transition metal reagent **1b** with **1a** leads an intermediate **1d**. In the end, Reductive elimination (RE) step involving **1d** affords the desired C-C or C-X (X = O, N, S) coupled product **1e** with the regeneration of the catalyst.



Scheme 4 The general mechanism of transition metal catalyzed cross-coupling reactions.

Although, a number of significant discoveries and developments have been made the traditional coupling reactions undergo various limitations. Therefore, development of an alternate method (atom, step-economical and eco-friendly) for the synthesis of C-C and C-X (X = O, N, S) bond through the C-H activation methodology is always desirable.

In this process, we need the catalytic or stoichiometric amount of transition metal catalyst and unreactive C-H bonds of alkanes, alkenes, arenes, and heteroarenes **2a** to form a new metal-carbon (C-M) bond **2b**(Scheme 5).Then, the newly generated C-M intermediate **2b** readily undergoesreactions with a wide range of aryl or alkyl halides to form miscellaneous C-X(C-C, C-O, and C-N) bond **2c**, the transformation of C-H bond **2a** to C-Xbond **2c** is known as C-H bond functionalization (Scheme 5).[5a, b]

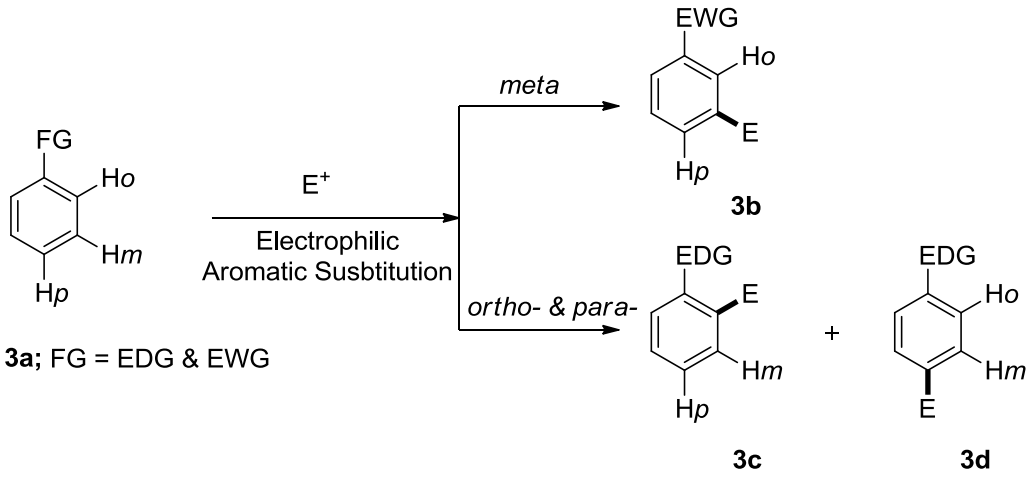


Scheme 5 General representation of C-H activation/functionalization.

Site-Selectivity in C-C Bond Formation

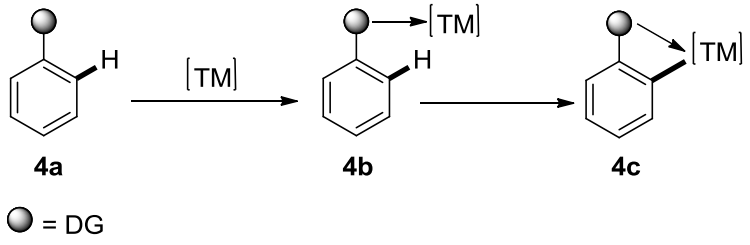
C-H bonds are very common in organic molecules, scientist activated the C-H bond for the elaboration of more complex structures. Nevertheless, on the other hand, this makes a

grandchallenge to control the site-selectivity of C-H functionalization. In electrophilic aromatic substitution, it has been well-known that electron-withdrawing substituentdirects incoming electrophiles to the *meta*- position **3b**, whereas electron-donating substituentleads to the **3c** *ortho*- and **3d** *para*-positions (Scheme 6).



Scheme 6 Site-selectivity in electrophilic aromatic substitution.

However, the synthetic significance of this traditional methodology, it accessing the number of isomers which are not expected product. So to get the desired product by this rules remained a challenge. Over the past few decades, transition metal catalyzed activation reactions of C-H bonds have opened a new aspect in synthetic organic chemistry. The C-H functionalization involving the use of directing groups (DGs) has become the most familiar approach that allows access to *ortho*-functionalized aromatic compounds by the chelation-assisted cyclometalation[5c, d]or weak coordination.[2n]A directing group usually bears a heteroatom, of which the lone pair of electrons can coordinate to the transition metal catalyst (TM) (Scheme 7). There are various directing groups (monodentate and bidentate) known in literature with the help of them we can achieve the desired product.



Scheme 7 Coordination mode of a DG in transition metal-catalyzed C-H functionalization.

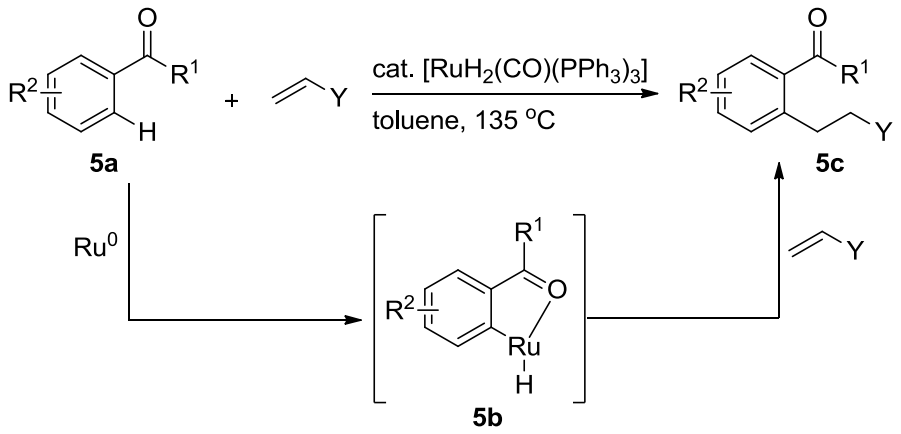
Representative literature dealing with the directing group enabled activation/functionalization.

C-H bonds are the most ubiquitous among chemical bonds in organic molecules. However, the development of methods to regioselective functionalize these abundant bonds have faced remarkable problems. The most common strategies for achieving the regioselective functionalization of single C-H bond involve the use of chelating groups that cancontrol the proximal C-H bond. These chelating group generally consist a heteroatom and co-ordinates to the metal center via the formation of a thermodynamically stable five or six-membered metallacyclic intermediate, resulting in the enhancement of regioselectivity.[5e, 6] For that, variety of directing groups (monodentate and bidentate) is developed for the regioselective synthesis of C-C and C-X (X = O, N, S) bonds. Various functional groups, including carboxylic acid, ester, ketone, amide, anilide, imine, heterocyclic, amine and hydroxyl groups have been employed as directing groups for transition metal catalyzed C-H bond functionalizations.

In general point of view, although the significant development in the field of transition metal catalyst directed C-H bond functionalization/activation have been made.[6, 7]Still, a large number and intrinsic limitations of transformations remain to beexposed to understand and extend the concept of C-H activation/functionalization beyond its limits.[1p] The various groups working for the development of a new type of directing group, which is a promising strategy for achieving the regioselective C-H bond functionalization that cannotbe acheivedwiththe presently availabledirecting group. The newly developed directing group promotes the activation and the regioselectivity of the C-H bond with the catalytic amount of transition metal catalyst via metallacycle intermediate. Accordingly, some related papers dealing with the directing group's based activation/functionalization of C-(sp^2)-H and C-(sp^3)-H bonds that are relevant to this thesis work described as in following sections.

Monodentate directing groups for the C-H functionalization.

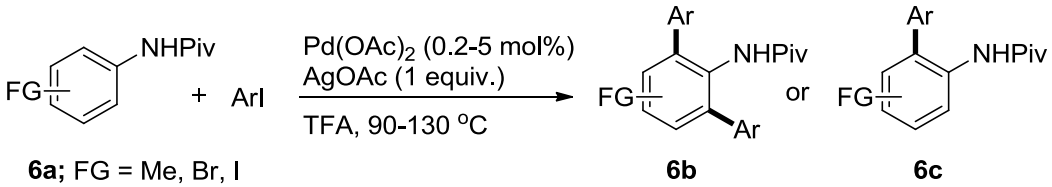
In 1993, Murai and co-workers[8a] reported a highly efficient and selective ruthenium catalyzed *ortho*-alkylation of aromatic ketones with olefins. The reaction of substrate **5a** with 5 equiv. of olefins in the presence of [$RuH_2(CO)(PPh_3)_3$] (20 mol%) catalyst and 3 mL of toluene vigorously refluxed at 135 ^oC for several hours to give the olefin coupled product **5c** via the intermediate **5b** (Scheme 8).



Scheme 8 Ru-catalyzed ortho-alkylation of aromatic ketones with olefins.

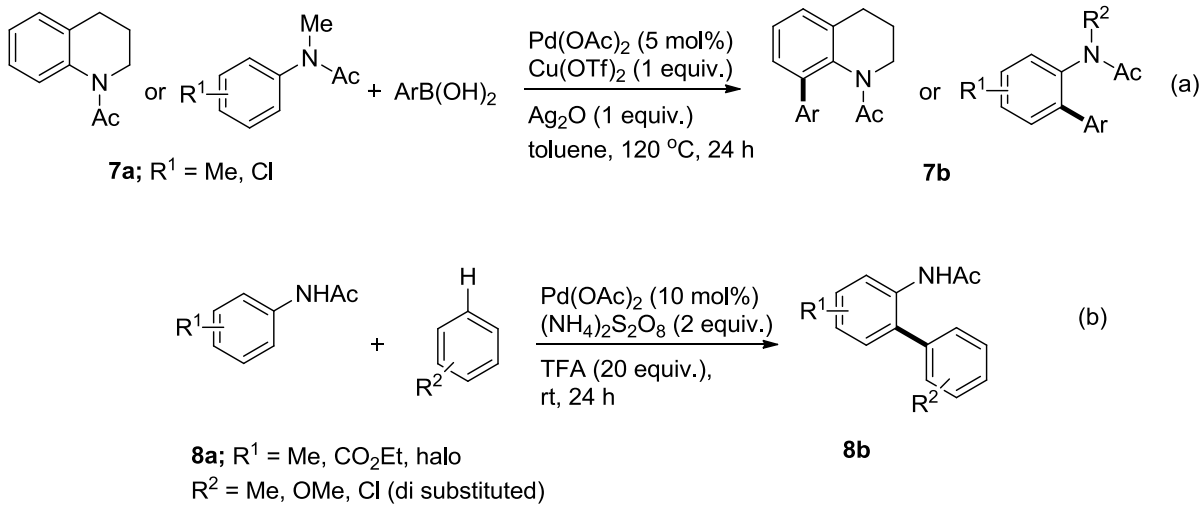
This result represented a real breakthrough in this field. It showed, the first time direct C-H bond functionalization strategy could be used as an efficient and valuable tool in organic synthesis.

In 2005, Daugulis and co-workers[8b] reported anilideto serve as a monodentate directing group. For the ortho arylation of pivaloyl derivatives **6a,** with various aryl iodide source in the presence of $Pd(OAc)_2$ (0.2-5 mol%), AgOAc (1 equiv.) and trifluoroacetic acid (TFA, 2 mL) in screw-capvial heated at 90°C for 3 days gave the bis and monoarylated product **6b** and **6c** in good yield (Scheme 9).



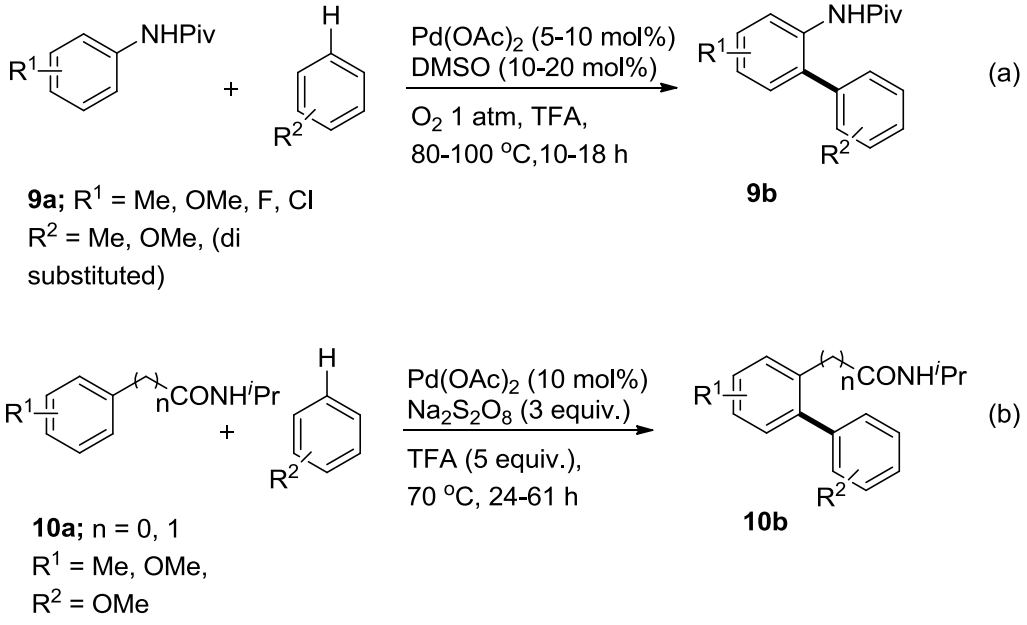
Scheme 9 The Pd-catalyzed anilide directed *ortho*-arylation of system **6a**.

Shi and co-workers[8c,d,e] reported *N*-alkyl acetamino as a directing group for the system **7a**. Arylation of substrate **7a** with the variety of boronic acid in the presence of $Pd(OAc)_2$ (5.0 mol%) as a catalyst, $Cu(OTf)_2$ (1.0 equiv.) as an additives and Ag_2O (1.0 equiv.) as an oxidant in toluene at 120 °C for 24 h leads to the product **7b** in moderate to good yield (Scheme 10a). You and co-workers[8f] reported *ortho*-arylation of anilides with environmentally friendly $(NH_4)_2S_2O_8$ oxidant. The arylation of anilide system **8a** with the variety of arenesin the presence of $Pd(OAc)_2$ (10 mol%), $(NH_4)_2S_2O_8$ (2 equiv.) as an environmentally friendly oxidant in TFA at rt for 24 h afforded to the product **8b** in moderate to good yield (Scheme 10b).



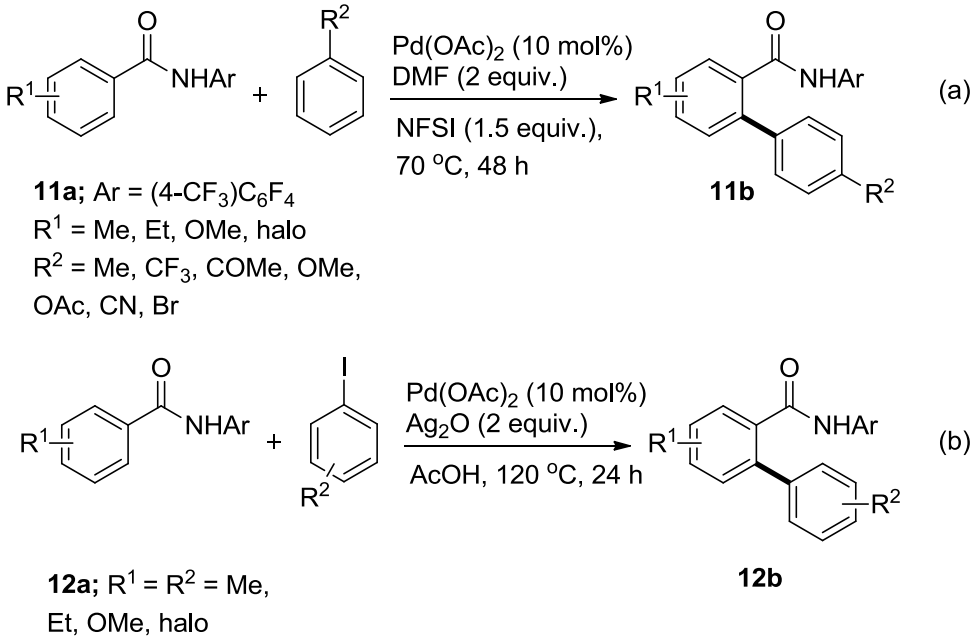
Scheme 10 Pd-catalyzed *ortho*-arylation of acetanilides with different arylating sources.

Buchwald and co-workers[8g] reported ortho arylation of pivalanilide substrate **9a**. The Pd(II)-catalyzed coupling of pivalanilide**9a** with substituted benzene in the presence of $Pd(OAc)_2$ (5-10 mol%), DMSO (10-20 mol%) under 1 atm Oxygen atmosphere in TFA at 80-100 ^oC for 10-18 h to afford **9b** in excellent yield (Scheme 11a). Dong et al.[8h] reported *ortho*-arylation of phenylacetamides, benzamides, and anilides with simple arenes using sodium persulfate as the oxidant. The Pd (II)-catalyzed C-H activation of substrate **10a** with a variety of arenesin the presence of $Pd(OAc)_2$ (10 mol%), $Na_2S_2O_8$ (3 equiv.) as an oxidant in TFA at 70 ^oC for 24-61 h gave the product **10b** in moderate yield (Scheme 11b).



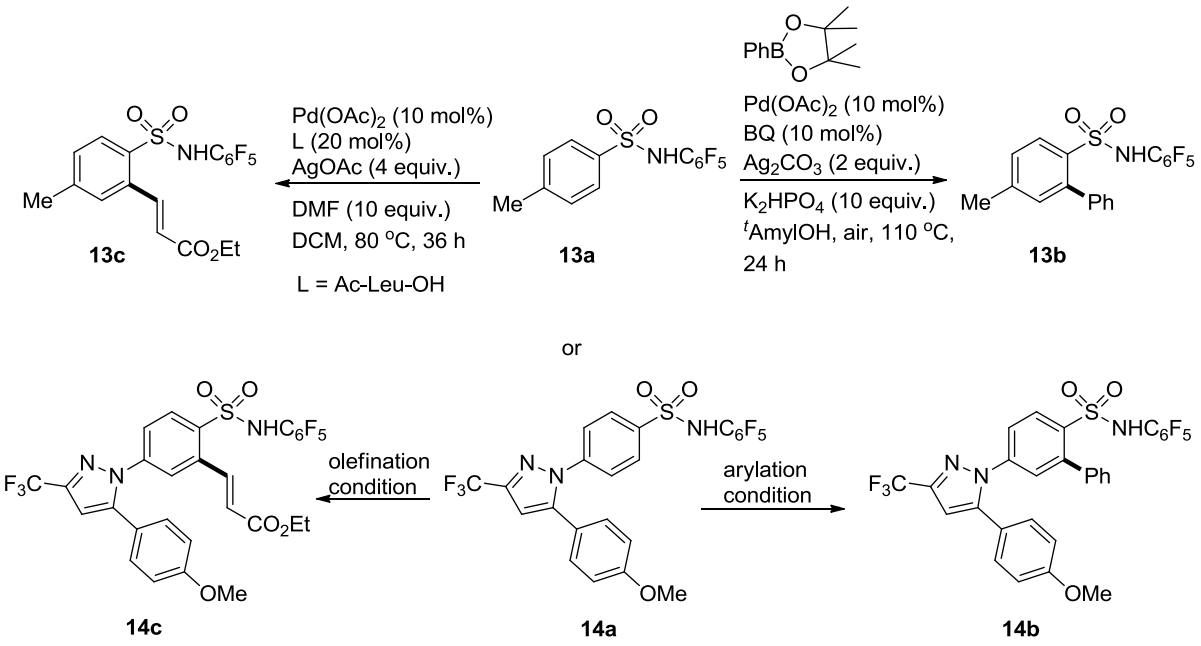
Scheme 11 Pd-catalyzed *ortho*-arylation with simple arene sources.

Yu group's reported[8i] the Pd(II)-catalyzed C-H arylation of carboxamide **11a** directed by amides using simple arenes as the arylating agents. The carboxamide **11a** react with arenes in the presence of $Pd(OAc)_2$ (10 mol%), NFSI (1.5 equiv.) in DMF at 70 ^oC for 48 h to afford the product **11b** in excellent yield (Scheme 12a). In this reaction condition, they used NFSI for bystanding oxidants for the improvement of yield and regioselectivity. Wang and co-workers[10j] developed a Pd(II)-catalyzed *ortho*-arylation of benzamides by aryl iodides with simple amide $CONH_2$ as a directing group. The reaction of substrate **12a** with a variety of aryl iodide in the presence of $Pd(OAc)_2$ (5 mol%), Ag_2O (2 equiv.) in AcOH at120 ^oC for 24 h offered to the product **12b** in excellent yield (Scheme 12b).



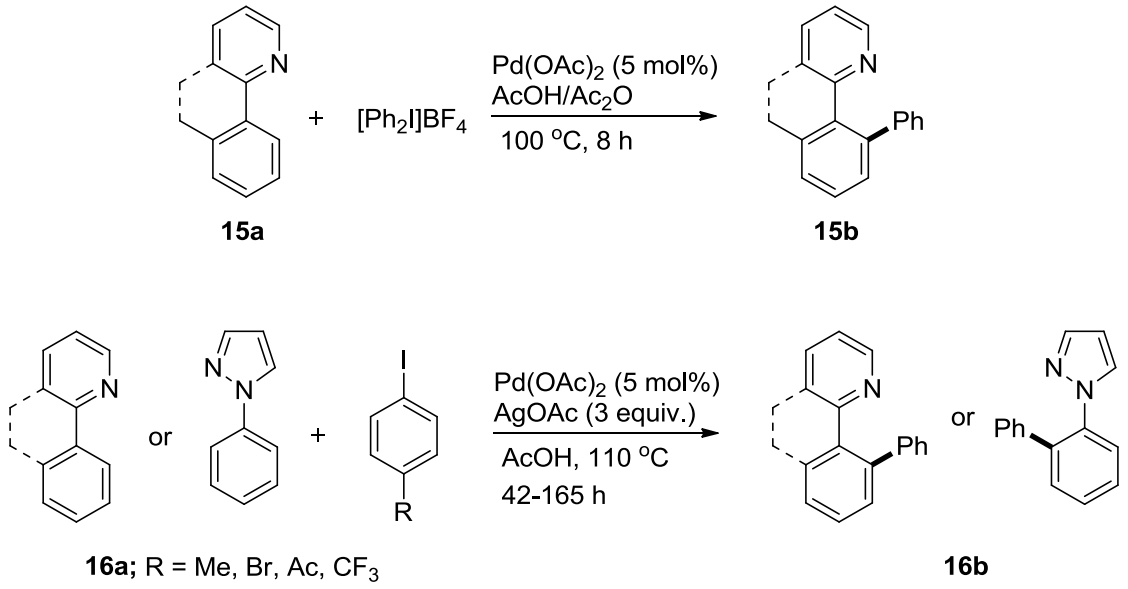
Scheme 12 Pd-catalyzed C(sp^2)-H arylation with simple arenes and amide as a directing group.

Yu and co-workers reported[9a] sulfonamide as a directing group for the arylation and olefination of system **13a/14a**. The Pd(II)-catalyzed monoarylation of the system **13a/14a** with pinacolphenylborate in the presence of $Pd(OAc)_2$ (10 mol%), BQ (10 mol%) and K_2HPO_4 (1 equiv.) in *ter*t-AmylOH under air at 110 ^oC for 24 h offered the product **13b/14b** in moderate yield (Scheme 13). For the mono olefination, the substrate **13a/14a** react with ethyl acrylate in the presence of $Pd(OAc)_2$ (10 mol%), Ligand (Ac-Leu-OH) (20 mol%), AgOAc (4 equiv.)and DMF (10 equiv.) in DCM at 80 ^oC for 36 h offered the product **13c/14c** in good yield (Scheme 13).



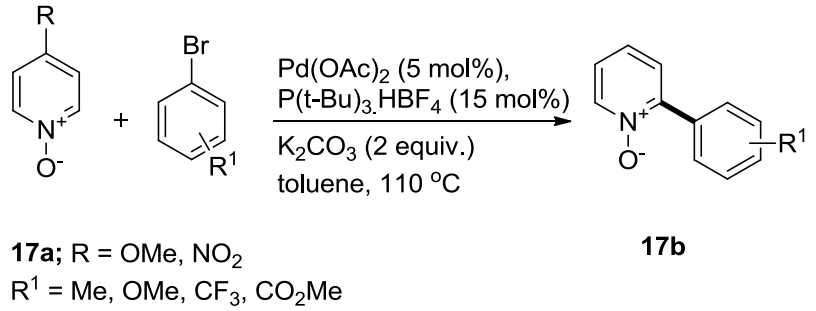
Scheme 13 Sulfonamide directed arylation and olefination of **13a**/**14a**.

Sanford and co-workers[9b,c,d] reported selective *ortho*-arylation of different aryl-pyridines, benzodiazepines, pyrrolidinones, oxazolidinones and quinolines, achieved via Pd(II)-catalytic cycle using diphenyl iodonium salts as arylation source in a mixture of AcOH and Ac_2O at 100 °C for 8 h to give the desired product **15b** (Scheme 14a). Daugulis and co-workers reported[9e] Pd(II)-catalyzed *ortho*-arylation of substituted 2-phenyl pyridine **16a** with wide range of aryl iodide in the presence of $Pd(OAc)_2$ (5 mol%), AgOAc (3 equiv.) in AcOH at 110 °C for 42 h offered the product **16b** in good yield (Scheme 14b).



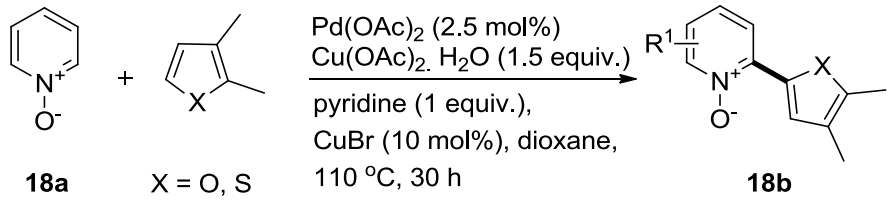
Scheme 14 Pd catalyzed arylation of 2-aryl pyridine system **15a** and **16a**.

In 2005, Fagnou and co-workers[10a-d] reported palladium-catalyzed regioselective arylation of pyridine *N*-oxides and their various derivatives. The *N*-oxide substrate **17a** react with a variety of aryl bromide in the presence of $Pd(OAc)_2$ (5 mol%), $P(t\text{-}Bu)_3.HBF_4$ (15 mol%) and K_2CO_3 (2 equiv.) in toluene at 110 ^oC offered the product **17b** in good yield (Scheme 15).



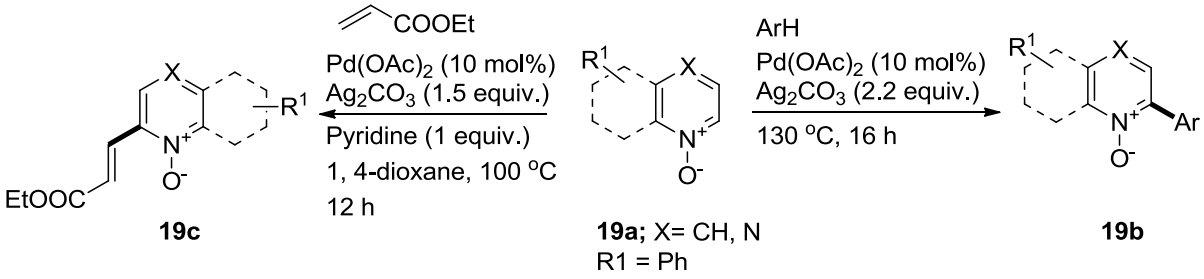
Scheme 15 Pd-catalyzed arylation of pyridine *N*-Oxides system **17a**.

You and co-workers[10e,f] reported cross-coupling of heteroarenes with *N*-oxides in the presence of $Pd(OAc)_2$ (2.5 mol%), $Cu(OAc)_2.H_2O$ (1.5 equiv.), pyridine (1 equiv.) and CuBr (10 mol%) in dioxane at 110 ^oC for 30 h to give the product **18b** in good yield (Scheme 16).



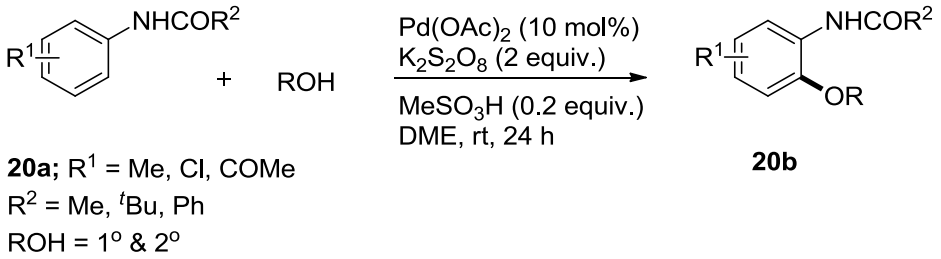
Scheme 16 Pd-catalyzed hetero arylation of pyridine *N*-Oxide systems **18a**.

Chang and co-workers[10g] reported monoarylation of various*N*-oxide derivatives such as pyridine, pyrazine, benzoquinolone, quinoxaline and quinoline with simple arenes as coupling partner. The monoarylation of a variety of *N*-Oxides **19a** with unactivated arenes in the presence of $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2.2 equiv.) at 130 ^oC for 16 h offered product **19b** in good yield (Scheme 17). Simultaneously, they also performed the olefination of *N*-oxide derivatives with ethyl acrylate in the presence of Pd(II)-catalyst, Ag_2CO_3 (1.5 equiv.), pyridine (1 equiv.) as an additive in 1, 4-dioxane solvent at 100 ^oC for 12 h to give the product **19c** in good yield (Scheme 17).



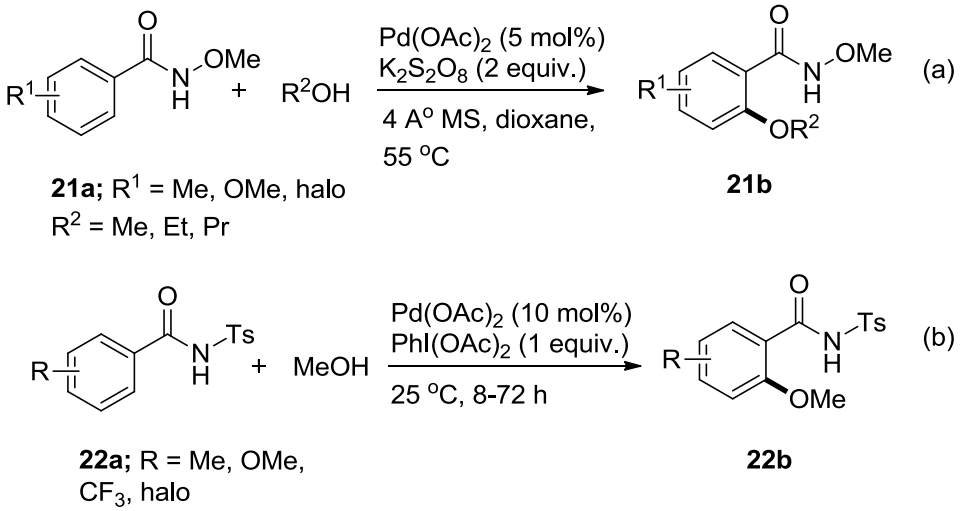
Scheme 17 Pd catalyzed arylation of pyridine *N*-Oxide system **19a.**

Wang and co-workers reported[11a, b] Palladium-catalyzed *ortho*-alkoxylation of anilides via C-H activation. Pd(II)-catalyzed alkoxylation of acetanilides **20a** with both primary and secondary alcohols in the presence of $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2 equiv.) and $MeSO_3H$ (0.2 equiv.) in DME at rt for 24 h offered the product **20b** in good yield (Scheme 18).



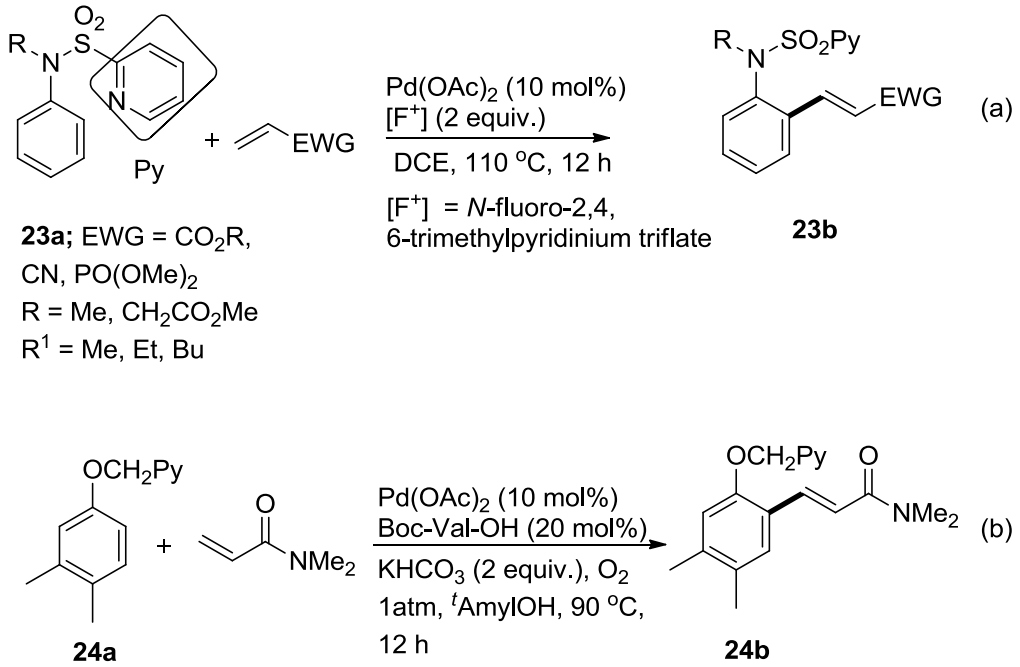
Scheme 18 Pd-catalyzed alkoxylation and alkenylation of **20a**.

Wang and co-workers[11c] reported Pd(II)-catalyzed *ortho*-alkoxylation by using N-Methoxy benzamide group via $C(sp^2)$-H bond activation. The substrate **21a** treated with various alcohols in the presence of $Pd(OAc)_2$ (5 mol%), oxidant $K_2S_2O_8$ (2 equiv.) and 4 A^o molecular sieves in dioxane at 55 $^oC$for 48 h offer to the alkoxylated product **21b** in high yield (Scheme 19a). In this reaction, they disclosed that the $K_2S_2O_8$was a superior oxidant from other oxidant and molecular sieves were necessary for the high yield of the reaction. Fabis and co-workers[11d] reported Pd(II)-catalyzed ortho C-H alkoxylation of substituted arenes directed by the *N*-tosyl carboxamide group. The substrate **22a** was treated with MeOH in the presence of $Pd(OAc)_2$ (10 mol%) and oxidant $PhI(OAc)_2$ (1 equiv.) at 25 $^oC$for 8-72 h to offer the alkoxylatedproduct **22b** in excellent yield (Scheme 19b).



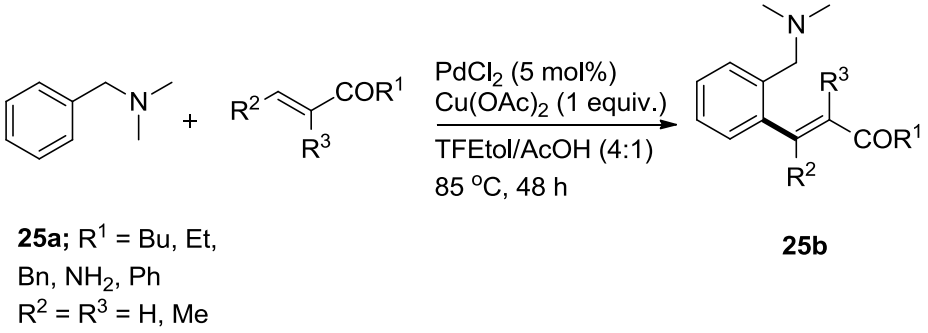
Scheme 19 Pd-catalyzed intermolecular C-O bond formation of system**21a** and **22a**.

Carretero and co-workers[11e] reported Pd(II)-Catalyzed C-H Olefination of *N*-(2-Pyridyl)sulfonyl as a directing group via remote co-ordination of substrate **23a**. The Pd(II)-catalyzed reaction of substrate **23a** with various olefination agent in the presence of $Pd(OAc)_2$ (10 mol%), N-fluoro-2,4,6-trimethyl pyridinium triflate (2 equiv.) in DCE at 110^{o}C for 12 h gave the olefinated product **25b** in good yield (Scheme 20a). You and Lan[11f] reported 2-pyridyl methyl ether as a removable andactive directing group for the protected phenol substrate **24a**. The Pd(II)-catalyzed direct *ortho*-C-H olefination through the formation of a seven-membered cyclo palladated intermediate. The reaction of protected phenol substrate **24a** with *N*,*N*-dimethylacrylamide in the presence of $Pd(OAc)_2$ (10 mol%), ligand Boc-Val-OH (20 mol%) and $KHCO_3$ (2 equiv.), under 1 atm oxygen atmosphere in*tert*-AmylOH at90^{o}C for 12 h gave the olefinated product **24b** in good yield (Scheme 20b).



Scheme 20 Pd-catalyzed C-(sp^2)-H olefination using pyridines as directing groups.

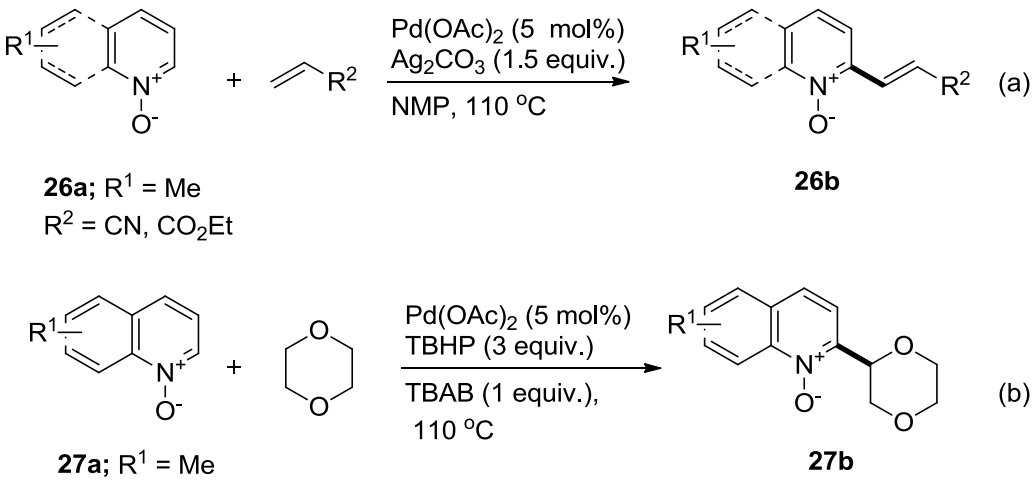
Shi and co-workers[11g] reported *N*,*N*-dimethyl benzylamine directed C-H functionalization of substrate **25a**. The Pd(II)-catalyzed reaction of substrate **25a** with various acrylate sources in the presence of $PdCl_2$ (10 mol %), $Cu(OAc)_2$ (1 equiv.) and AcOH in 2,2,2-trifluoroethanol (TFEol) at 85 ^oC for 48 h offered the olefinated product **25b** in excellent yield (Scheme 21).



Scheme 21 Pd-catalyzed ortho-olefination of *N, N*-dimethylbenzylamine system **25a**.

Wu and co-workers[11h] reported the Pd(II)-catalyzed selective alkenylation of quinoline-*N*-oxides via C-H activation. The substrate **26a** with a various alkenes reagent in the presence of $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1.5 equiv.) in NMP at 110 ^oC for 20 h offered the olefinated product **26b** in good yield (Scheme 22a). The same group[11i] reported palladium-catalyzed dehydrogenative cross-coupling of quinoline *N*-oxides atthe C-2position. The alkylation of quinoline *N*-oxides **27a**with various cyclic ethers in the presence of $Pd(OAc)_2$ (5 mol %),

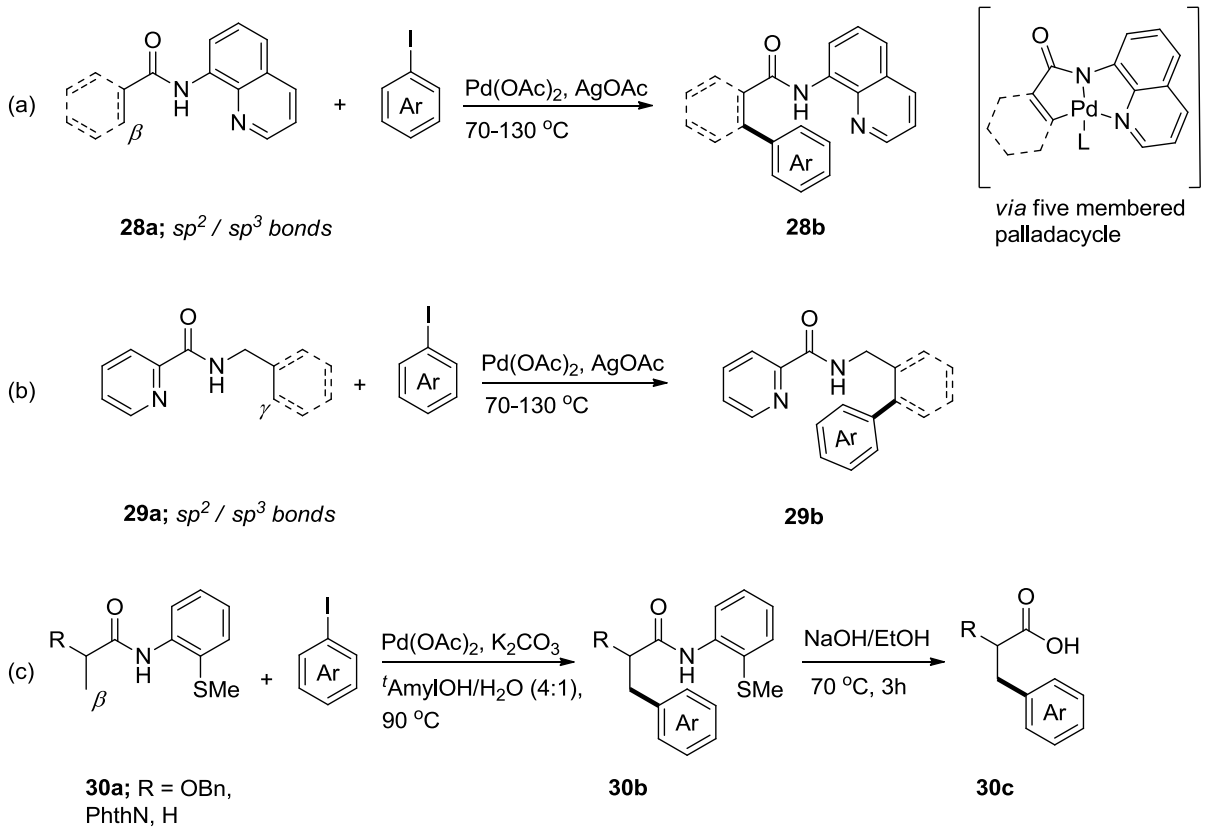
TBHP (3 equiv.) and TBAB (1 equiv.)in the airat 110 ^{o}C for 8 h offered to the C-2 alkylated product **27b** in good yield (Scheme 22b).



Scheme 22 Pd-catalyzed hetero alkenylation and alkylation of pyridine *N*-Oxides system **26a** and **27a.**

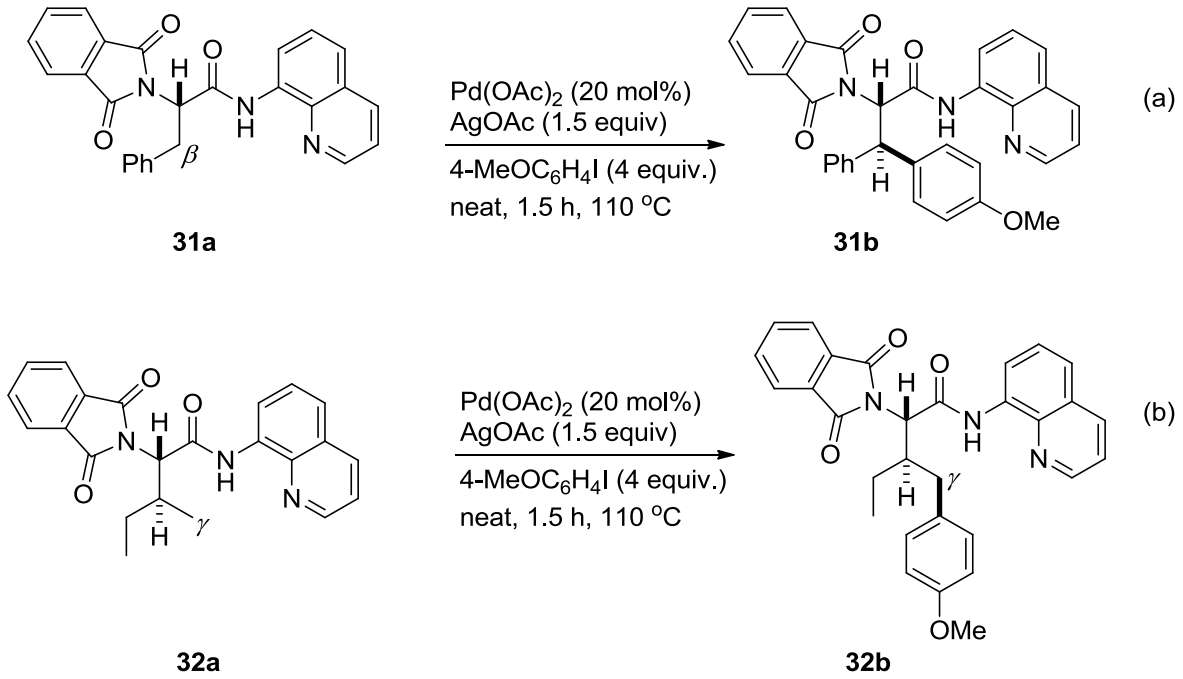
Bidentate directing groups for the C-H functionalization.

In 2005, Daugulis and coworkers[12a] highlighted C-(sp^3)-H bond functionalization, directed by bidentate directing groups (8-Aminoquinoline, Picolinamide). They also showed 8-Aminoquinoline as directing group for the palladium-catalyzed arylation of β-C-(sp^2)-H/ β-C-(sp^3)-H bonds of various aliphatic and arenes system. The Pd(II)-catalyzed 8-Aminoquinoline directed β-C-(sp^2)-H/ β-C-(sp^3)-H arylation of C-Hbond of carboxamides **28a** with aryl iodide sources gave the β-arylated carboxamide **28b** (Scheme 23a). Similarly,Picolinamides directedγ-C-(sp^2)-H arylation of C-H bond of aliphatic and aromatic carboxamides **29a** with arylating agents gave the γ-arylated carboxamide **29b**(Scheme 23b). Same group, Daugulis and co-workers[12b] reported 2-methyl thioaniline directed regioselective monoarylation of primary β-C-(sp^3)-H bond ofaliphatic carboxamide **30a**. The reaction of 2-methyl thioaniline derived carboxamides **30a** with aryl iodidein the presence of $Pd(OAc)_2$,and K_2CO_3in ^{t}AmylOH gave the monoarylated product**30b** (Scheme 23c). Finally, they removed the directing group under NaOH/EtOH reaction condition in 70 ^{o}C tolead the final product **30c** in excellent yield.



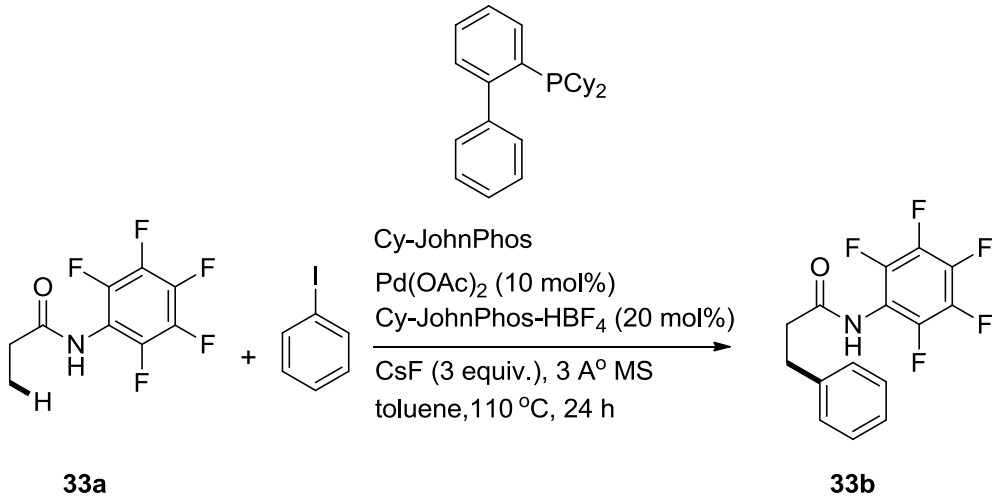
Scheme 23 Daugulis's report on the Pd-catalyzed bidentate directing group.

Corey and co-workers[12c] reported Pd(II)-catalyzed β-γ-C(sp^3)-H arylation of α-amino acid derivatives. The Pd(II)-catalyzed arylation of *N*-phthaloylated phenylanaline amide **31a**with *p*-Iodoanisole in the presence of $Pd(OAc)_2$ (20 mol%) and AgOAc (1.5 equiv.) without any solvent at 110 ^oC for 1.5 hgave the monoarylated product **31b** (Scheme 24a). Same reaction condition applies on the substrate **32a** with iodoanisole to give the γ-monoarylated product **32b** (Scheme 24b).



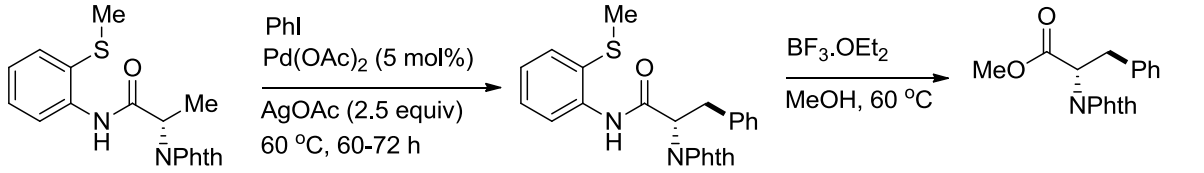
Scheme 24 Pd-catalyzed β and γ-C-(sp^3)-H arylation.

Yu and co-workers[12d] reported the weak co-ordinating directing group (pentafluorocarboxamide) for C-H activation of aliphatic and aromatic carboxamide. Pd(II)-catalyzed arylation of carboxamide **33a** with various aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%), Cy-JohnPhos-HBF_4 (20 mol%) as ligand, CsF (3 equiv.) and 3 A° MS in toluene at 110 °C for 24 h gave the arylated product **33b** (Scheme 25).



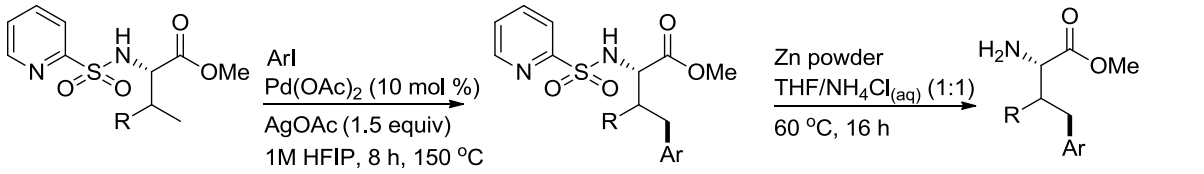
Scheme 25 β-arylation using acidic *N*-arylamide directing group **33a.**

Daugulis and co-workers[12e] reported Pd(II)-catalyzed thiomethylaniline directed selective monoarylationof amino acid derivatives. The arylation ofalanine carboxamides **34a** with a wide range of aryl iodide in the presence of $Pd(OAc)_2$ (5 mol%) and AgOAc (2.5 equiv.) in toluene at 60 $^oC$for 60-72 h offered the arylated phenylalanine derivatives **34b** as enantiopure products in good yields. Further, hydrolysis of phenylalanine derivatives **34b** in the presence of $BF_3{\cdot}Et_2O$ in MeOH at 60^oC gave to the ester of phenylalanine derivativesas product **34c** in excellent yield (Scheme 26).



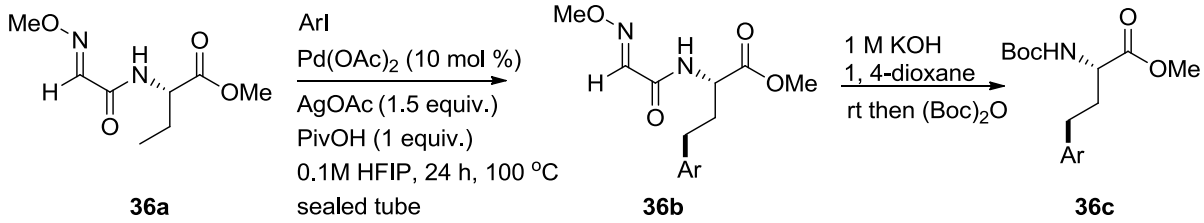
Scheme 26 Pd-catalyzed *β*-C-(sp^3)-H arylation of amino acid derivatives.

Carretero and co-workers[12f] reported 2-pyridylsulfonylas a directing group for Pd-catalyzed bis-arylation of amino acid derivatives. The Pd(II)-catalyzed arylation of the **35a** with a wide range of aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv.) in 1M HFIP at 150 $^oC$for 8 h offered enantiopure arylated product **35b** in good yields(Scheme 27). The cleavage of the sulfonyl moiety,in the presence of Zn powder at 60 ^oC for 16 h gave the enantiopure product **35c** in good yield with excellent enantioselectivity (Scheme 27).



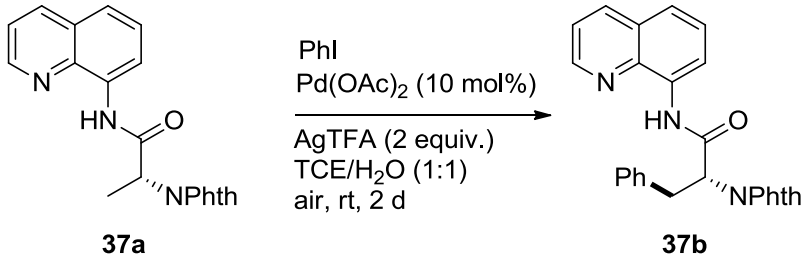
Scheme 27 Pd-catalyzed *γ*-C-(sp^3)-H arylation of *N*-(2-pyridyl) sulfonyl substrate **35a.**

Ma and co-workers[12g]reported 2-methoxyiminoacetyl (MIA) directed Pd-catalyzed arylation of 2-aminobutanoic acid derivatives. The Pd(II)-catalyzed arylation of substrate **36a** with aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv.) and PivOH (1 equiv.) as additive in 0.1M HFIP at 100 $^oC$for 24 h offered arylated product **36b** in good yields(Scheme 28). After completion of arylation simple KOH mediated cleavage of the directing group leads to the formation of amino acids followed by protection with $(Boc)_2O$ to afford **36c**with good yields and excellent enantiopurity.



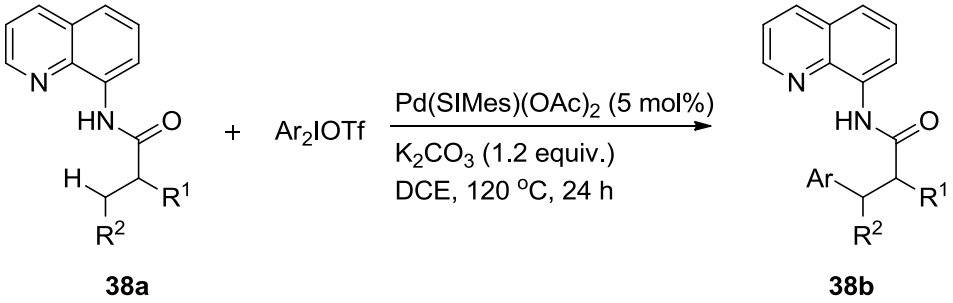
Scheme 28 2-Methoxyiminoacetyl directed arylation of γ-C-(sp^3)-H bonds.

Chen and co-workers[12h]reported8-AQ directed C-H activation of amino acid derivatives and the synthesis of mono-arylated α-amino acids at room temperature. The arylation reaction of substrate **37a** with aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) and AgTFA (2 equiv.) in 1,1,2,2-tetrachloroethane (TCE)/H_2O at rtfor two days afforded the β-arylated aminoacid derivatives **37b**in good yield (Scheme 29).



Scheme 29 Pd-catalyzed trifluoroacetate-promotedβ-C-(sp^3)-H bond arylation.

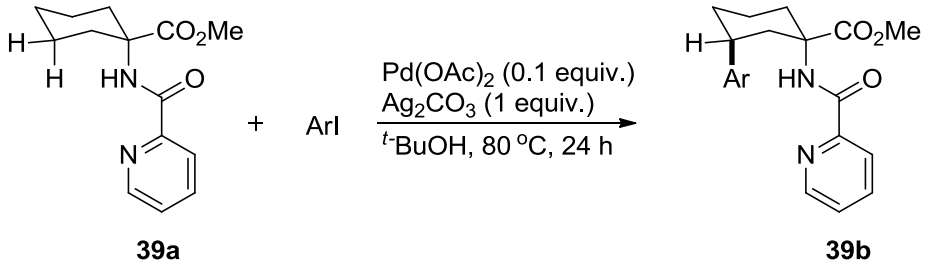
Shi and co-workers[13a]reported the Pd-catalyzed arylation of C-(sp^3)-Hbonds by using diarylhyperiodonium salts as the arylation sources. The reaction of **38a** with a variety ofdiarylhyperiodonium triflatesin the presence of $Pd(SIMes)(OAc)_2$ (5 mol%) and K_2CO_3(1.2 equiv.) in DCE at 120 ^oC afforded β-arylated carboxamides **38b** in good yields (Scheme 30).



Scheme 30 Pd-catalyzed C-(sp^3)-H arylation with diarylhyperiodonium salts.

Chen and co-workers[13b] reported a practical synthetic strategy based on the picolinamide directed Pd(II)-catalyzed arylation on cyclic and aliphatic amines. The reaction of **39a** with a

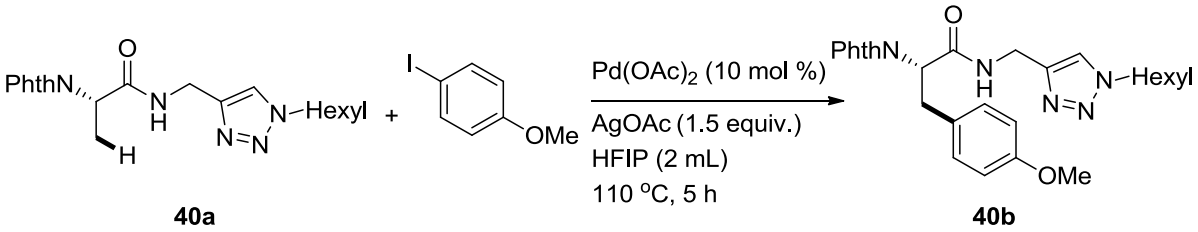
variety of aryl halides in the presence of $Pd(OAc)_2$ (0.1 equiv.) and Ag_2CO_3(1equiv.) in *tert*-BuOH at 80 ^oC for 24 h afforded γ-arylated product**39b** in good yields (Scheme 31).



39a **39b**

Scheme 31 Picolinamide directed Pd-catalyzed C-(sp^3)-H arylation.

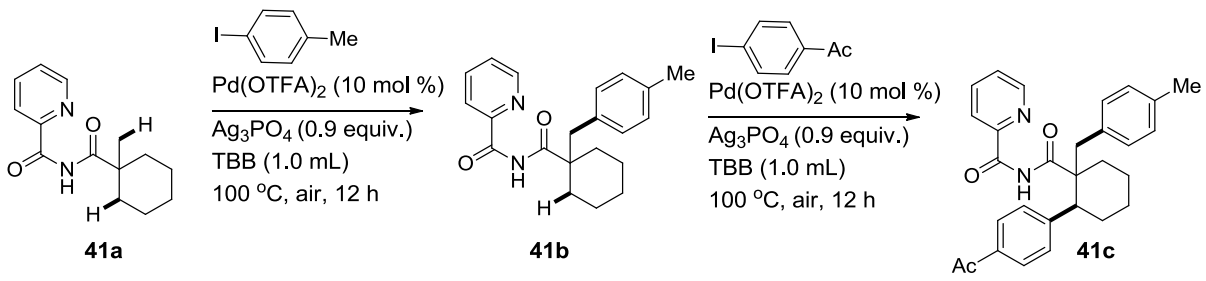
Ding and co-workers[13c] reported a new click chemistry based product triazoles as a removable directing group for C(sp^3)-H monoarylation of amino acid derivatives **40a**.The Pd(II)-catalyzed reaction of substrate **40a** with iodo anisole in the presence of 10 mol% $Pd(OAc)_2$ and 1.5 equiv. of AgOAc in HFIPat 110 °C for 5 h afforded the desired product **40b** in excellent yield (Scheme32).



40a **40b**

Scheme 32 Triazole directed arylation of**40a**.

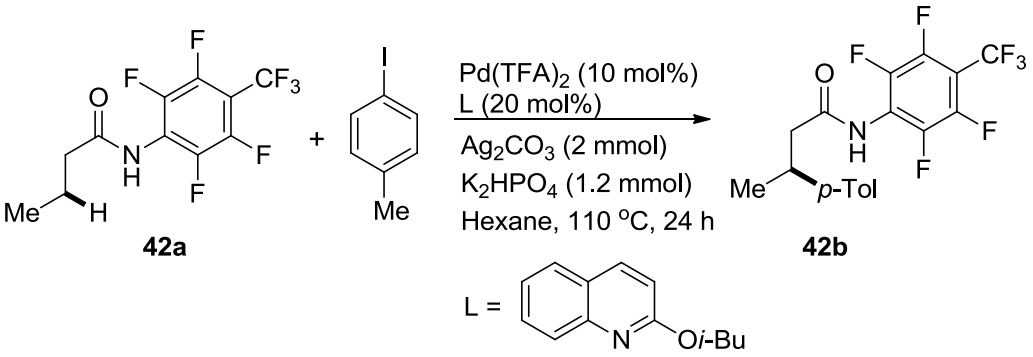
Shi and co-workers[13d]developed 2-picolinamideas a removable directing group for the Pd-catalyzedsequential double C-H activation of carboxamide derivatives. The arylation reaction of carboxamide **41a** with corresponding aryl iodide in the presence of $Pd(OTFA)_2$ (10 mol%),Ag_3PO_4(0.9 equiv.) under air in TBB solvent at 100^{o}Cfor 12 h afforded the primary β-arylated products **41b** in good yields (Scheme 33). Further, the second arylation of substrate **41b** with different aryl iodide under same reaction condition was repeated which result into the formation of secondary β-arylated products **41c** (Scheme 33).



41a **41b** **41c**

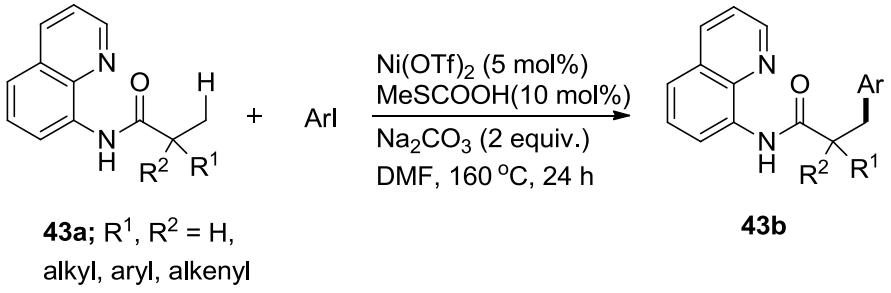
Scheme 33 Arylation of primary and secondary C(sp^3)-H bonds by using **41a.**

Yu and co-workers[13e] reported Pd-catalyzed *β*-arylation of *N*-arylamide derivatives. The Pd(II)-catalyzed reaction of substrate **42a** with 4-iodo toluene in the presence of $Pd(TFA)_2$ (10 mol%), ligand (20 mol%), Ag_2CO_3 (2 mmol) and K_2HPO_4 (1.2 mmol) in hexane at 110 ^oC for 24 h gave the arylated product **42b** in good yields (Scheme 34).



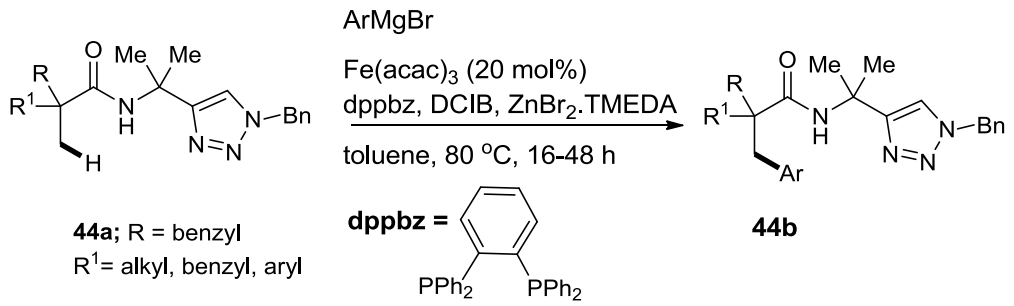
Scheme 34 *β*-arylation of methylene C-H bonds of substrate **42a**.

Chatani[13f] andco-workers and Chenand co-workers[13g]independently reported Ni(II)-catalyzed C(sp^3)-H arylation of unactivated C-H bonds of aliphatic carboxamides. The reaction proceeds with the probable participation of Ni(II)/Ni(IV) species. The Ni(II)-catalyzed arylation of primary *β*-C(sp^3)-H bonds of aliphatic carboxamide **43a** with wide range of aryl iodide sources in the presence of Ni(II)-catalyst, Na_2CO_3 (2 equiv.) and MeSCOOH (10 mol%) as additive in DMF at 160 ^oC for 24 h gave to the arylated product **43b** in good yield (Scheme 35).



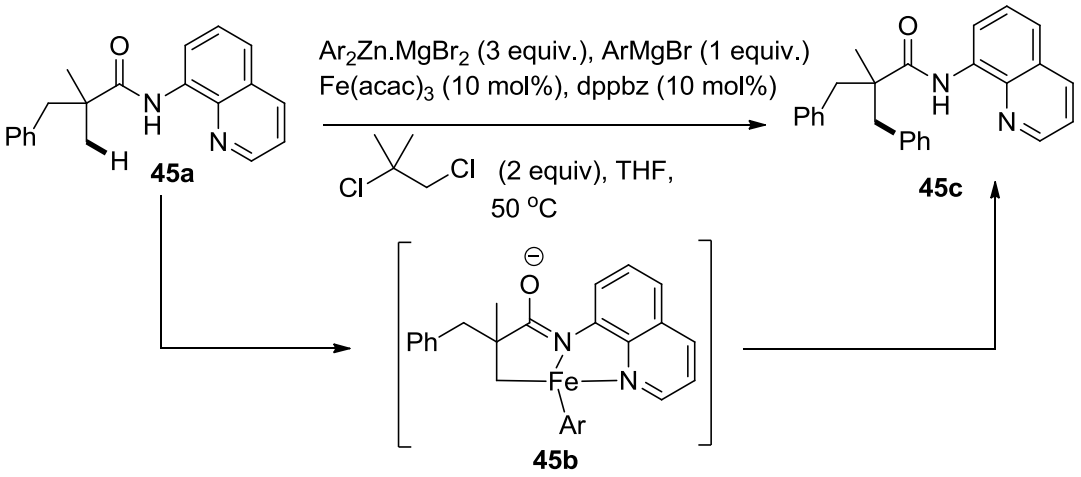
Scheme 35 Ni catalyzed arylation of C-(sp^3)-H bond of aliphatic carboxamide **43a**.

Ackermann and co-workers[13h, i] reported triazole directed, an iron-catalyzed direct C-H arylation of aliphatic carboxamides. The reaction of **44a** with ArMgBr in the presence of $Fe(acac)_3$ (20 mol%), 1,2-bis(diphenylphosphino)benzene (dppbz) (20 mol%), ($ZnBr_2$.TMEDA) (3 equiv.) and 1,2-dichloro-2-methylpropane (DCIB) (2 equiv.) in toluene at 80 ^oC for 16-48 h afforded the arylated product **44b** in good yields (Scheme 36).



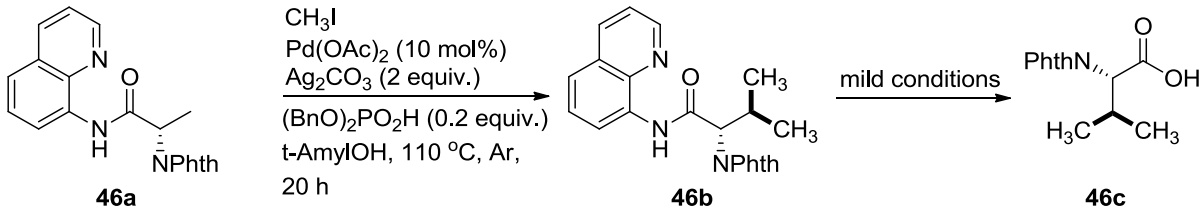
Scheme 36 Iron catalyzed direct C-H arylation of **44a.**

Nakamura and co-workers[13j]disclosediron-catalyzed arylation of 2,2-disubstituted propionamide system **45a**. The Fe-catalyzed reaction of substrate **45a** with Ar_2.Zn.MgBr (3 equiv.) as organic oxidant and bisphosphine ligand (dppbz) (10 mol%) in THF at 50 ^oC gave the selective monoarylated product **45c.** A higher reactivity of methyl group over the benzylic C-H bonds was observed, which is different from the palladium-catalyzed reactions (Scheme 37).



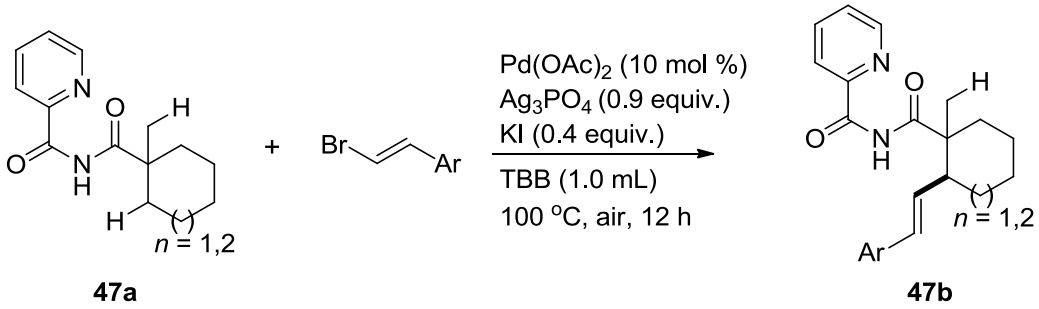
Scheme 37 Iron-catalyzed C-(sp^3)-H bond arylation of carboxamide **45a**.

Chan and co-workers[13k] reported Pd(II)-catalyzed alkylation of inactivated methylene bonds of aminoquinolyl aliphatic carboxamides. The Pd(II)-catalyzed reaction of substrate **46a** with Methyl iodide in the presence of 10 mol% $Pd(OAc)_2$,2 equiv. of Ag_2CO_3 and 0.2 equiv. of $(BnO)_2PO_2H$ in *tert*-AmylOH at 110 °C for 20 h afforded the desired product **46b** in excellent yield (Scheme40). Further, the cleavage of directing group under the mild reaction conditions gave the amino acid derivative **46c** in good yield (Scheme 38).



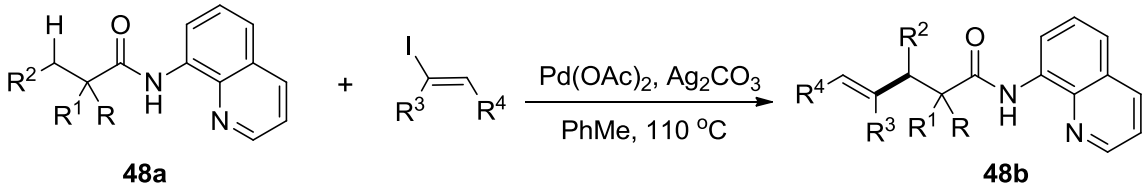
Scheme 38 Pd-catalyzed alkylation of inactivated methylene C-(sp^3)-H bonds.

Shi and co-workers[13d] reported the Pd(II)-catalyzed alkenylation of methylene C(sp^3)-H bond of substrate **47a**. The significance of this methodology was the alkenylation of methylene C-H bonds was achieved instead of primary C-H bonds. The reaction of substrate **47a** with alkenyl bromides in the presence of $Pd(OAc)_2$ (10 mol%), Ag_3PO_4 (0.9 equiv.) and KI (0.9 equiv.) in TBB at 100 ^oC for 12 h to give the alkenylated product **47b** in good yields (Scheme 39).



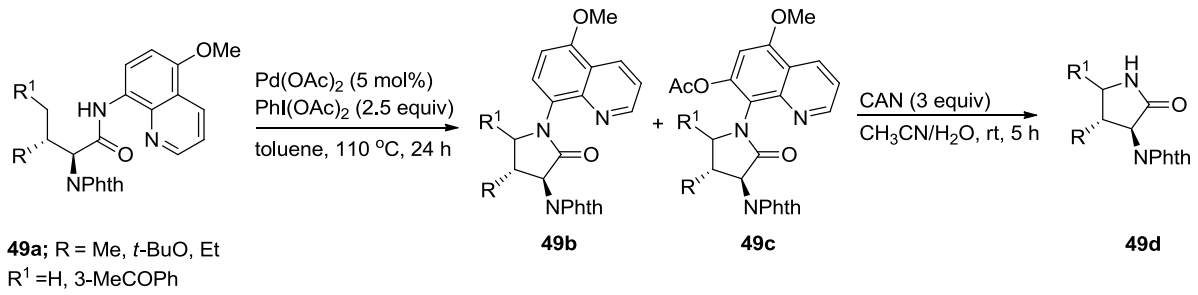
Scheme 39 Palladium(II)-catalyzed alkenylation of C(sp^3)-H bonds with vinyl bromides.

Rao and co-wokers[13l]reported palladium(II)-catalyzed alkenylation of acyclic aliphatic amides **48a** with alkenyl halides in the presence of $Pd(OAc)_2$, Ag_2CO_3 and toluene at 110 ^oC to obtain the **48b** in good yield (Scheme 40).



Scheme 40 Pd-catalyzed alkenylation of unactivated C(sp^3)-H bonds of **48a.**

Chen and co-workers[14a]reported pyrrolidones synthesis *via* the palladium-catalyzed intramolecular amination of unactivated γ-C(sp^3)-H bonds. The reaction of amide **49a** in the presence of $Pd(OAc)_2$ (5 mol%) and $PhI(OAc)_2$ (2.5 equiv.) in toluene at 110 ^oC for 24 h afforded the mixture of products **49b/49c**. Further, reaction with CAN in CH_3CN/H_2O provided the pyrrolidones **49d** (Scheme 41).

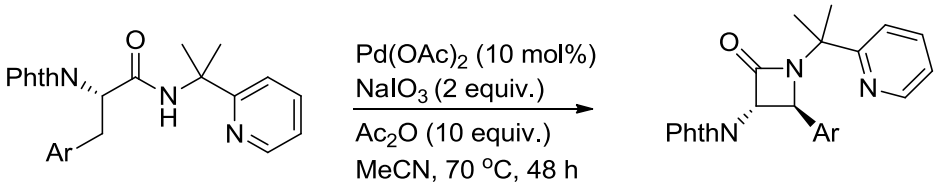


49a; R = Me, *t*-BuO, Et
R^1 =H, 3-MeCOPh

49b **49c** **49d**

Scheme 41 8-AQ- directed intramolecular amination of γ-C-(sp^3)-H bonds **49a.**

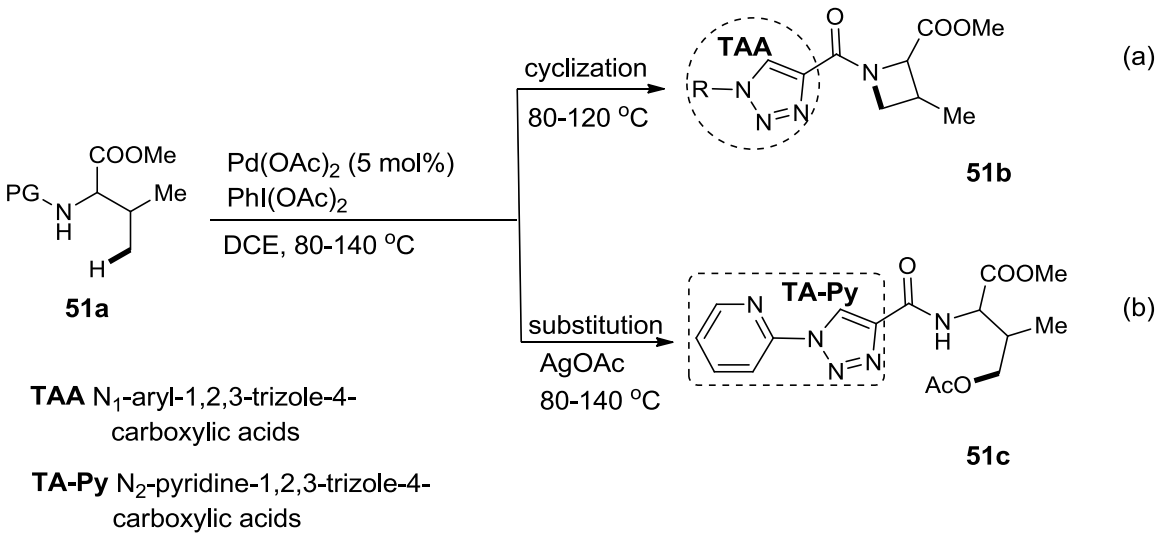
Shi and co-workers[14b] reported the PIP-directed stereoselective synthesis ofα-amino-β-lactam from the amino acid carboxamide derivatives. The intramolecular cyclization of **50a** in the presence of $Pd(OAc)_2$ (10 mol%), $NaIO_3$ (2 equiv.) and AC_2O (10 equiv.) in MeCN gave β-lactams **50b** in good yield (Scheme 42).



50a **50b**

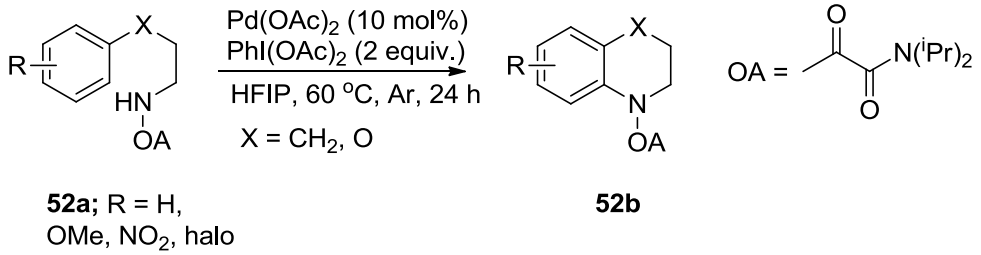
Scheme 42 Synthesis β-lactams through PIP directed C-(sp^3)-H functionalization**.**

Shi and co-workers[14c] reported the 1,2,3-triazoles as a versatile directing group for selective cyclization *vs.* substitution. The Pd-catalyzed C-(sp^3)-H activation of TAA-directinggroup enabled **51a** in the presence of $Pd(OAc)_2$ (5 mol%) and $PhI(OAc)_2$ in DCE at 80-120 ^oC afforded the cyclised product **51b** (Scheme 43a). On the other hand, the Pd-catalyzed reaction TA-Py-directing group enabled **51a** in the presence of $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ and AgOAc in DCE at 140 ^oC afforded the mono-acetoxylation product **51c** as a major product in good yields (Scheme 43b).



Scheme 43 Triazole directed selective cyclization *vs.* substitution of **51a.**

Zhao and co-workers[14d] reported easily accessible directing group for the Palladium-catalyzedintramolecular amination of C-(sp^2)-H and C-(sp^3)-H bonds of various carboxamides. The cyclization of substrate **52a** in the presence of $Pd(OAc)_2$ (10 mol%) and $PhI(OAc)_2$(2 equiv.) in HFIP at 60°Cfor 24 h afforded the cyclised product **52b** (Scheme 44).



Scheme 44 Pd-catalyzed intramolecular amination of substrate **52a.**

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Chapter 2

Remote functionalization of phenylacetamides and heterocyclic amides via Pd(II)-catalyzed bidentate directing group assisted γ-C-(sp^3/sp^2)-H bond arylation/ benzylation and acetoxylation.

Over the past decades, C-H activation/functionalization has emerged as a significant approach for the construction of C-C bond via a metal-catalyzed coupling reaction.[1] C-H activation is an atom economic method which converts inert and straightforward C-H bonds into the desired derivatizable functional groups and thereby allowing to express the assembly of organic compounds.[2] The functionalization of γ-C-(sp^3/sp^2)-H bond has been widely studied over the decades by employing various bidentate auxiliaries. Multiple reports dealing with the bidentate directing group assisted[3, 4] functionalization of γ-C-(sp^3/sp^2)-H bond and remoteδ-and ε-C-H bonds of amine and carboxylic system were well studied. After the report disclosed by Daugulis, many research group's attention has been shifted towards the remote C-H activation/functionalization. Accordingly, the **chapter 2** revealed some outstanding paperdealing with the directing group based functionalization/activation ofγ-C-(sp^3/sp^2)-H bond that are significant to this thesis work. Parallel to the literary works, a part of this thesis (Chapter 1) envisages investigating the Pd-(II)-catalyzed directing group assisted C-H functionalization of phenylacetamides and heterocyclic carboxamide system.

a) Importance of functionalized acetamides

Functionalized phenylacetamides are significant structural motifs in a cornucopia of bioactive compounds, drugs and crop protection agents. It also plays a crucial role as anessential synthetic intermediate in organic synthesis and medicinal chemistry. For occurrence, atenolol is a selective β_1-receptor antagonist primarily used for cardiovascular disease; β-blockers are useful for treating the physical effects of anxiety. In these instances, dosing is used as needed instead of regular daily dosing. While 1-naphthaleneacetamide serves as an auxin for rooting hormone.[5a, b]Due to theirvaluable importance, there is a continued high demand for general strategies that provide access to substituted phenylacetamides in a sustainable manner (Figure 1).

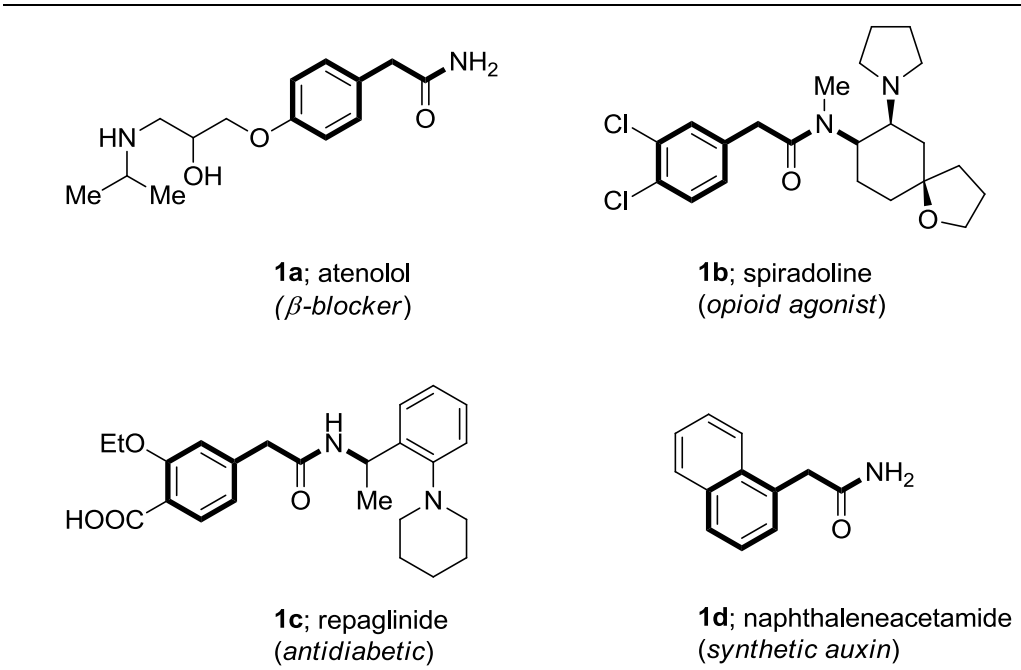


Figure1. Biologically active molecules featuring phenylacetamide cores (**1a-d**).

b) Importance of functionalized heteocryclic compounds

Heterocyclic compounds represent themselves as a fundamental division of organic chemistry, with its origin rooted in medicinal chemistry [5d]. Heterocycles are present in a wide range of drugs, most of the vitamins, many natural products, biomolecules and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal and insecticidal agents (Figure 2).[5c] Also, they have been frequently found as a critical structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit a significant solvatochromic, photochromic, and bioluminescence properties. The shape, and size of ring structures, together with the substituent groups of the core motifs, impact strongly on the physicochemical properties.For e.g., furan rings demonstrated excellent anticancer activity against all cell lines, benzofurans are regularly found in nature and are known for their antitumor activities (Figure 2). For instance, ticlipidine is selectively used for antiplatelet disease, while zileuton is frequently used as an enzyme inhibitor. As depicted in figure 2, the importance of heterocyclic compounds and their prevalence in various disciplines, the synthesis of heterocyclic compounds is always desirable.

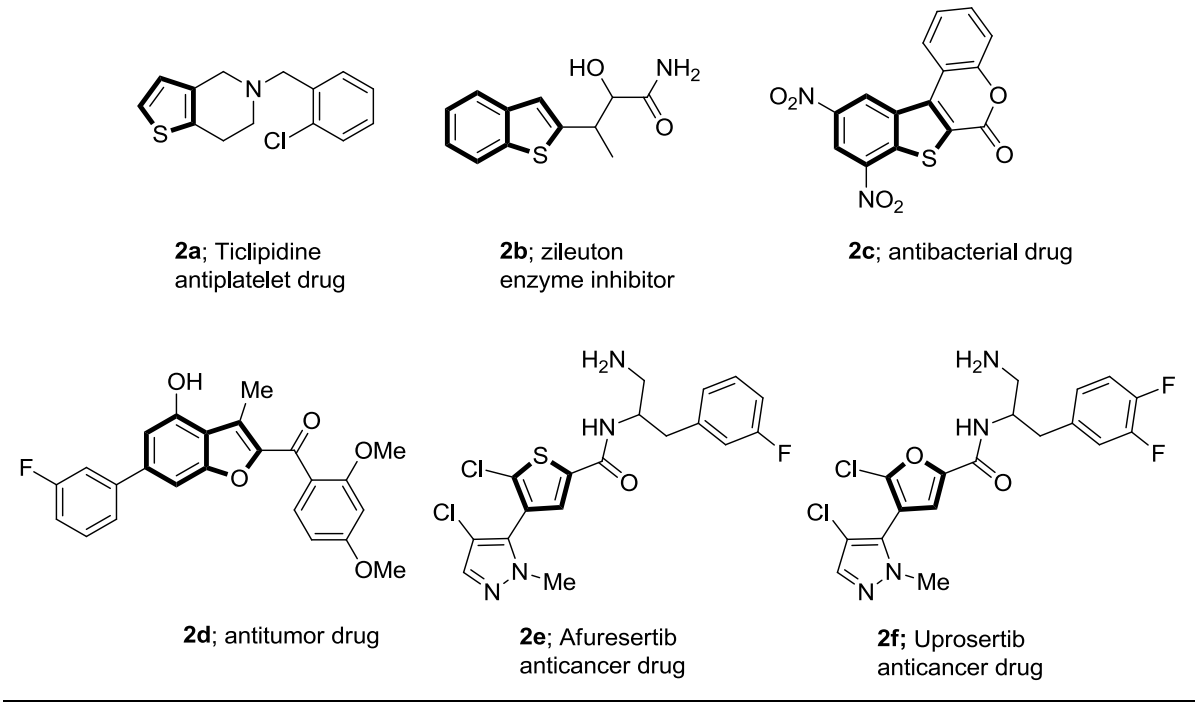
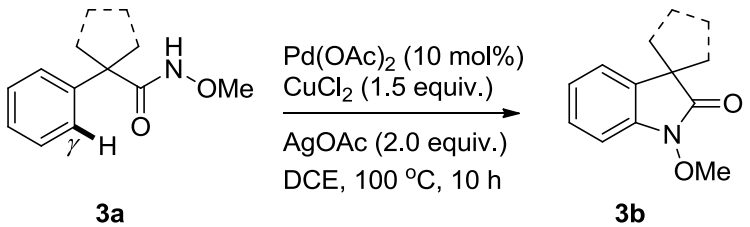


Figure 2. A biologically active molecule containing heterocyclic moiety (**2a**-**2d**)

Given the importance of phenylacetamide system and heterocyclic cores in essential disciplines such as pharmaceuticals and medicinal chemistry, we were interested in synthesizing these molecules via the step economical C-H activation strategy.

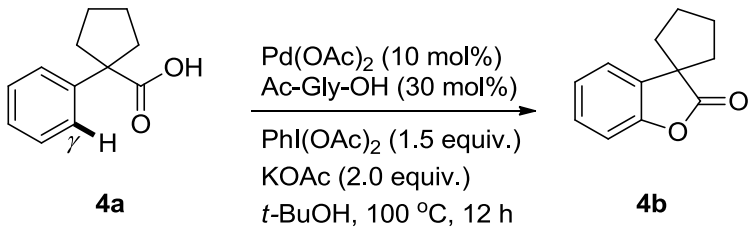
Representative reports dealing on the *γ*-C-(sp^2)-H bond of phenylacetamide and phenylacetic acid system which are related to this chapter.

Yu and co-workers[6a] reported weak amide directed *γ*-C-(sp^2)-H activation and the formation of a lactam or intramolecular cyclization of phenylacetamide systems **3a.** The reaction of *N*-methoxy-1-phenylcyclopentanecarboxamide**3a** in the presence of$Pd(OAc)_2$ (10 mol %) as catalyst and co-catalyst $CuCl_2$ (1.5 equiv.) with AgOAc (1.5 equiv.) as an additive in dichloroethane (DCE) at 100 °C for 10 h gave the *γ*-lactam **3b** (Scheme 1).



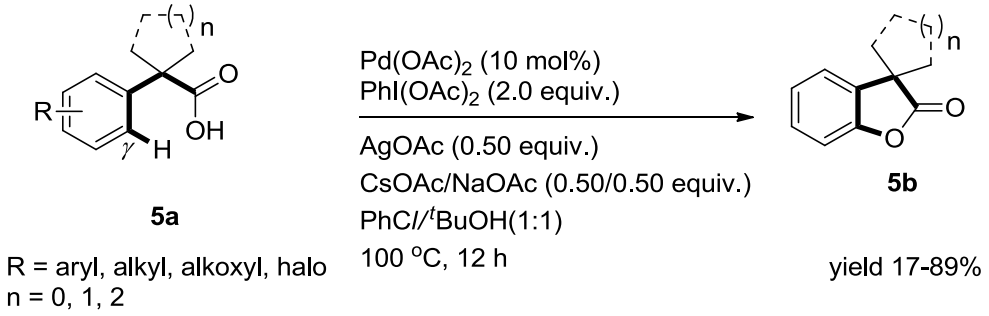
Scheme 1 $Pd(OAc)_2$-catalyzed synthesis of lactam **3b**.

In 2013, the same group reported the weak coordinating group,[6b] such as carboxylic acid directed γ-C-(sp^2)-H activation and the lactonization of 1-phenylcyclopentanecarboxylic acid **4a.** The reaction of 1-phenylcyclopentanecarboxylic acid **4a** with $Pd(OAc)_2$ (10 mol %) as catalyst, $PhI(OAc)_2$ (1.5 equiv.) as oxidant, and KOAc (2.0 equiv.) as additive with Ac-Gly-OH (30 mol%) as an external ligand in *tert*-BuOH at 100 °C for 12 h lead to the γ-lactones **4b** formation **,** which involves activation of the ortho C-H bonds (Scheme 2).



Scheme 2 $Pd(OAc)_2$-catalyzed synthesis of lactone **4b**.

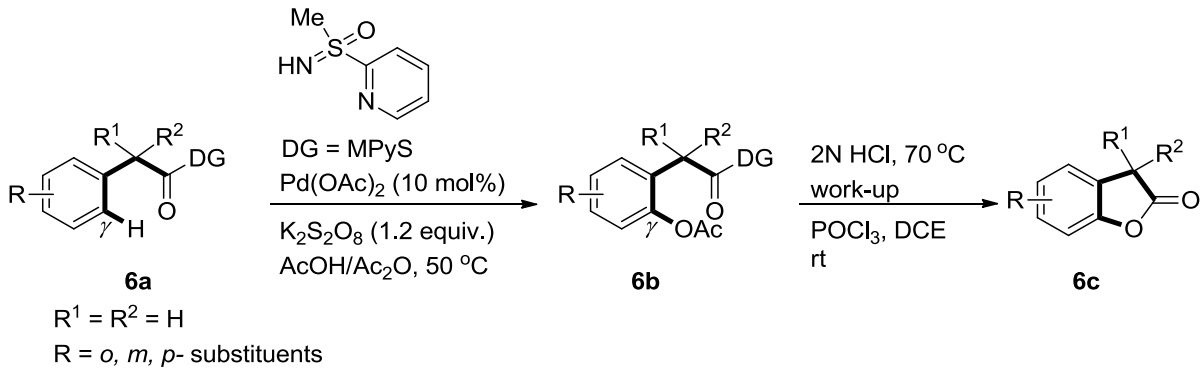
In 2013, Shi and co-workers[6c] reported the similar kind of work, *i.e.*, direct lactonization of phenylacetic acid system **5a**. Phenylacetic acid system **5a** in the presence of (10 mol %) $Pd(OAc)_2$ catalyst, $PhI(OAc)_2$ (2.0 equiv.) as an oxidant and AgOAc (0.50 equiv.) as an additive, with mixture of bases CsOAc/NaOAc (1/1 equiv.) and in presence of mixture of solvents PhCl/^{t}BuOH (1:1) at 100 °C for 12 h afforded the lactonized product **5b** (Scheme 3).



Scheme 3 Lactonization of phenylacetic acid system **5a.**

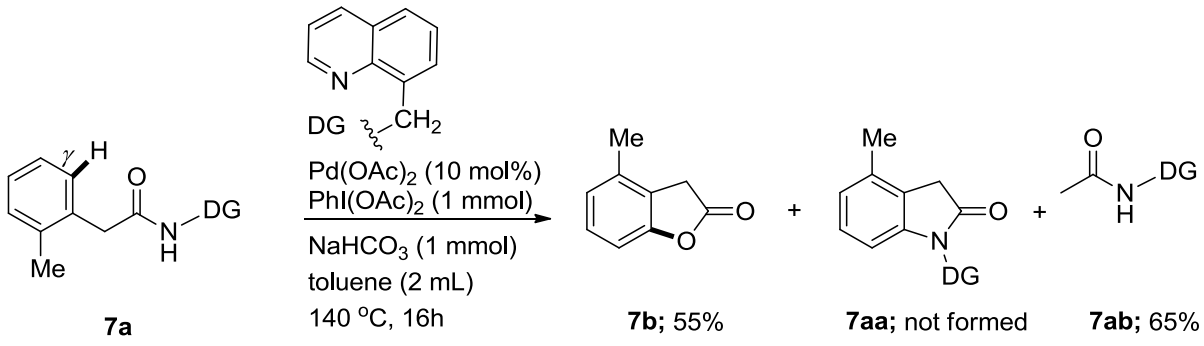
Sahoo and co-workers[6d] introduced the *S*-methyl-*S*-2-pyridyl sulfoximine (MPyS) as a directing group for C-O bond formation and reported the stepwise lactonization of arylacetamides system **6a**. The Pd-catalyzed, phenylacetic acid system **6a** reaction in the presence of $Pd(OAc)_2$ (10 mol %) catalyst, $K_2S_2O_8$ (1.2 equiv.) and a mixture of solvents Ac_2O/AcOH (1:1) at 50 °C offered an acetoxylated product **6b**. Further hydrolysis of the product **6b** with 2N HCl lead to the formation of *o*-hydroxyarylacetic acid intermediate,

which then underwent the lactonization in the presence of $POCl_3$ and DCE to afford cyclised product **6c** (Scheme 4).



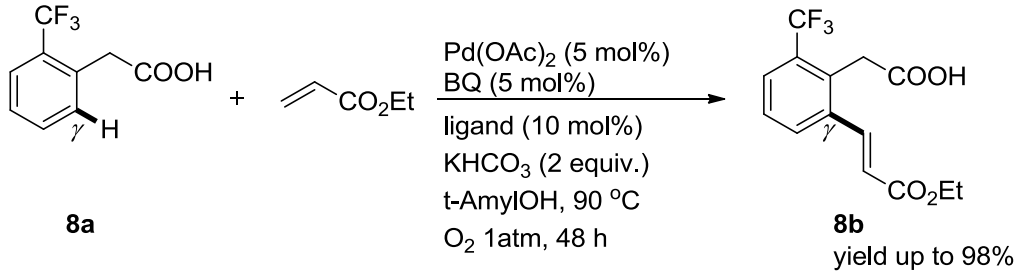
Scheme 4 Stepwise lactonization of phenylacetic acid system **6a** assisted by novel DG MPyS.

Chatani and co-workers[6e] reported quinoline-8-ylmethylamine directed γ-C-H lactonization of phenylacetamides **7a**. The reaction of quinoline-8-ylmethylamine**7a,**in the presence of $Pd(OAc)_2$ (10 mol %) as catalyst, $PhI(OAc)_2$ (1.0 mmol) as oxidant, and $NaHCO_3$ (1.0 mmol) as additive in toluene at 110 °C gave the γ-lactones **7b,** which involves activation of the ortho C-H bonds, with parallel cleavage of the directing group **7ab** (Scheme 5).



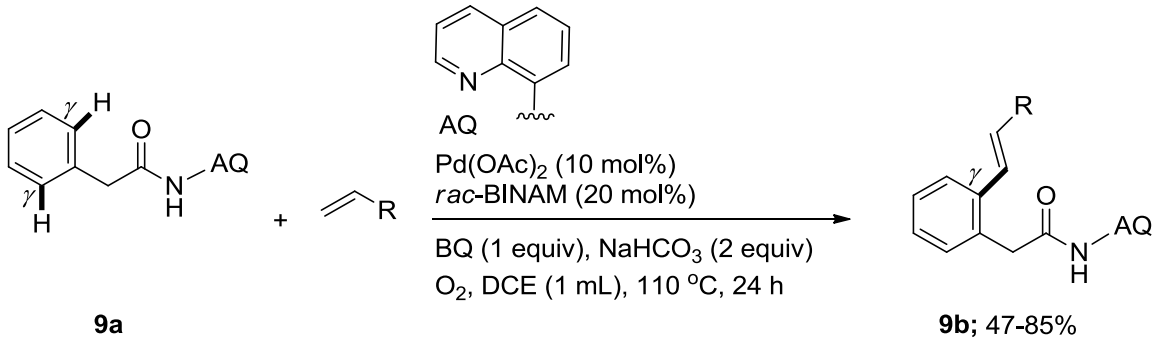
Scheme 5 Lactonization of phenylacetic acid system **7a**.

Yu and co-workers[7a] reported the Pd(II)-catalyzed ligand accelerated weak acid assisted C-H bond olefination of phenylacetic acid system **8a** in the presence of $Pd(OAc)_2$ (5 mol %) as catalyst, BQ (5 mol %) as oxidant and $KHCO_3$ (2.0 equiv.) as an additive, with an external ligand (10 mol%), ethyl acrylate as the coupling partner in*tert*-AmylOH as solvent at 90 °C for 48 h leads to the formation of product **8b** in excellent yield (Scheme 6).



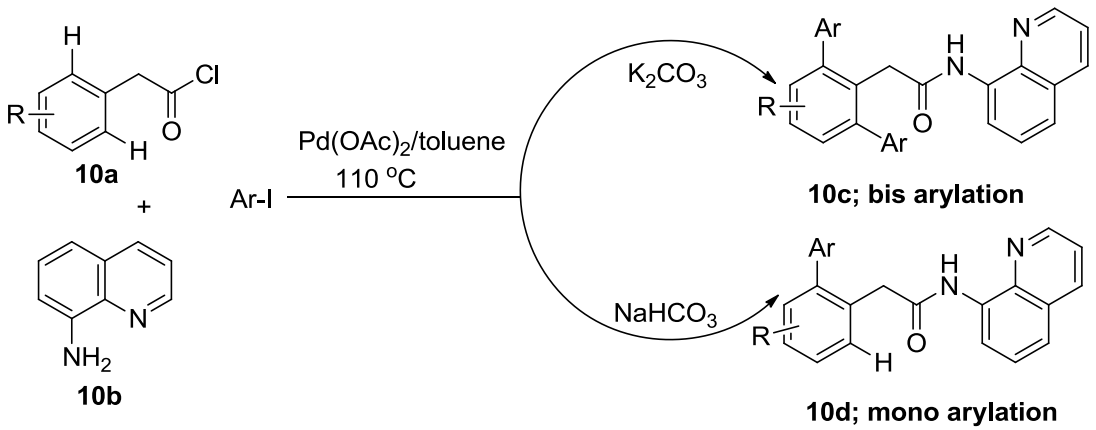
Scheme 6 Olefination of phenylacetic acid system **8a**.

Maiti and co-workers[7b] reported Pd(II)-catalyzed 8-aminoquinoline assisted C-H bond olefination of phenylacetic acid system **9a** in the presence of $Pd(OAc)_2$ (10 mol %) as catalyst, BQ (1.0 equiv.) as oxidant and $NaHCO_3$ (2.0 equiv.) as an additive with unactivated aliphatic alkenes in DCE at 110 °C for 24 h afforded the product **9b** in excellent yields having high regio/ stereoselectivity manner. The adaptability of this operationally simple method has been demonstrated through subsequent C-H olefination for synthesizing **9b** (Scheme 7).



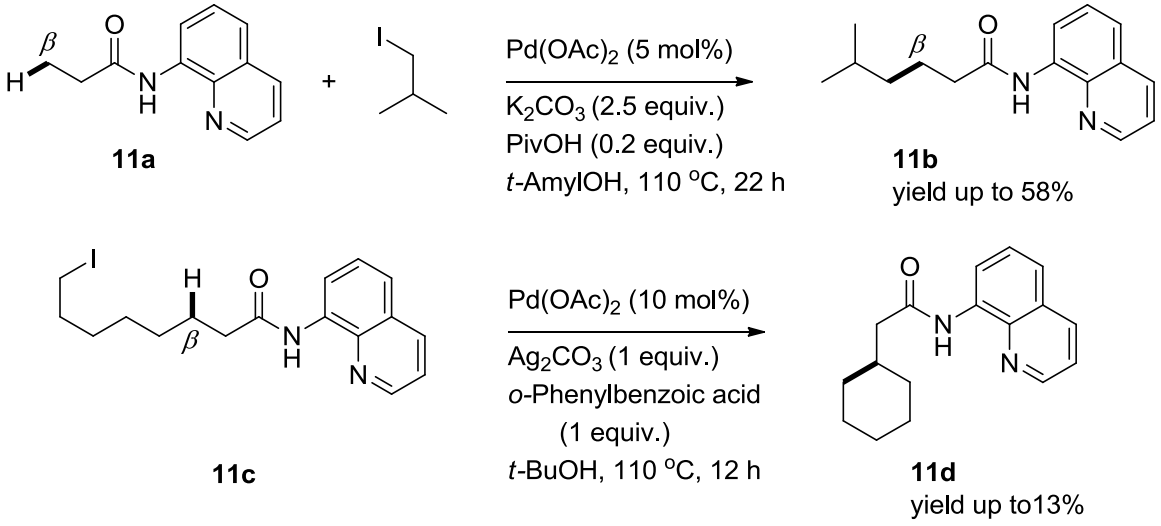
Scheme 7 Olefination of phenylacetamide system **9a**.

Wan and co-workers[7c] reported Pd(II)-catalyzed one pot remote γ-C(sp^2)-H bond arylation of **10a** with 8-aminoquinoline **10b** in the presence of Ar-I by using $Pd(OAc)_2$ (10 mol %), K_2CO_3 (2 equiv.) and $NaHCO_3$ (4 equiv.) in toluene solvent at 110 °C for 24 h offered the γ-arylated phenylacetamide derivatives bis **10c/** mono **10d** respectively (Scheme 8).



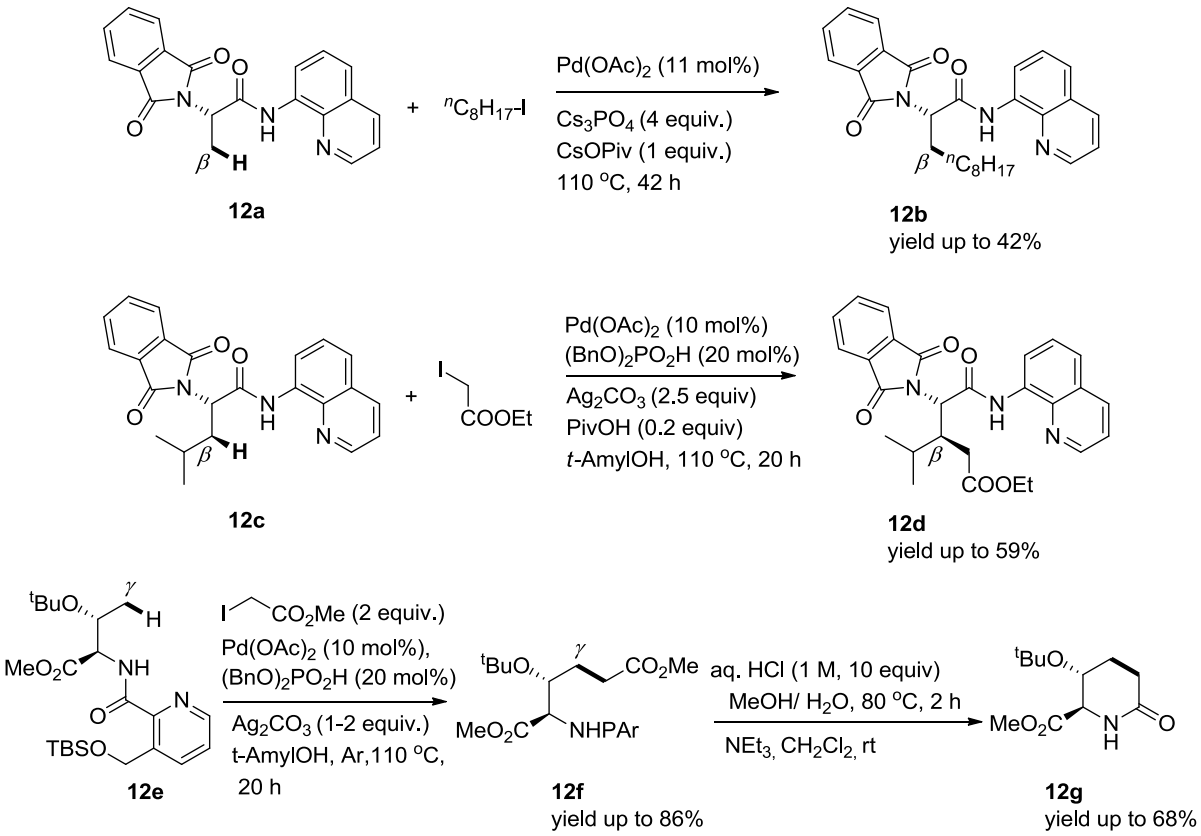
Scheme 8 Pd-catalyzed γ-C-(sp^2)-H arylation of the phenylacetamide system in one pot manner**.**

Daugulis and co-workers[8a] reported the Pd(II)-catalyzed 8-aminoquinoline directed primary β-C(sp^3)-H activation and the synthesis of β-alkylated carboxamide derivative **11b.** The reaction of *N*-(quinoline-8-yl) propionamide **11a** in the presence$Pd(OAc)_2$ (5 mol %) as catalyst with K_2CO_3 (2.5 equiv.) as oxidant/base and PivOH (0.2 equiv.) as an additive in*tert*-AmylOH solvent at 110 °C for 22 h gave the β-alkylated butane carboxamide derivative **11b** (scheme 9). Chen and co-workers[8b] developed a new route for the synthesis of benzo-rings by the intramolecular coupling of an aryl iodide and a methylene C-H bond of 8-iodo-*N*-(quinoline-8-yl)octanamide **11c** *via* Pd(II)-catalysis directed by the 8-aminoquinoline bidentate directing group. Unfortunately, meager yield was obtained for **11d** (Scheme 9).



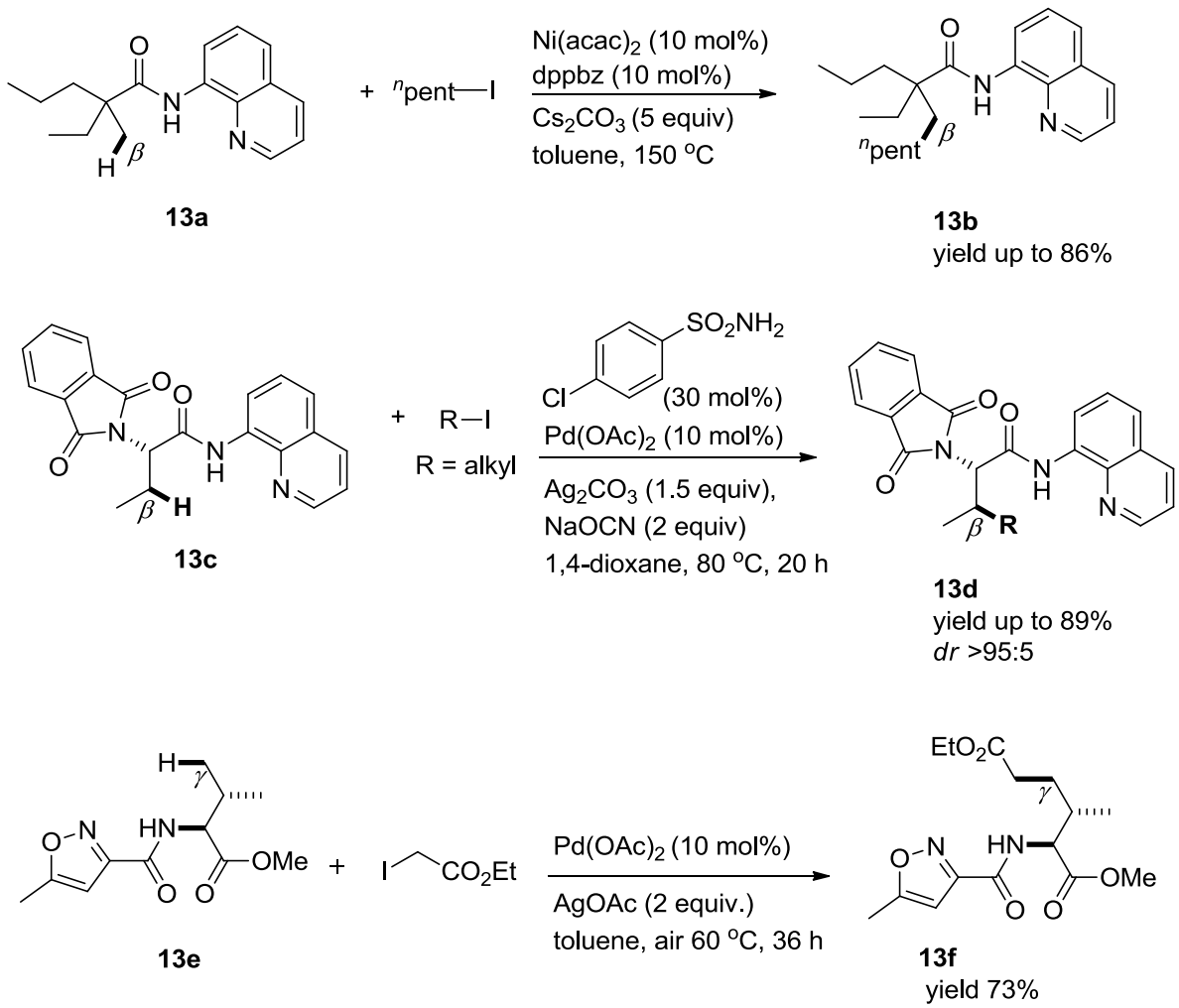
Scheme 9 Pd-catalyzed β-C(sp^3)-H alkylation and intramolecular cyclization of carboxamide system **11a** and **11c.**

Daugulis and co-workers[8c] reported the Pd(II)-catalyzed 8-aminoquinoline directed primary β-C(sp^3)-H activationof *N*-phthaloylalanine carboxamide system **12a** with 1-iodooctane by using 11 mol % of $Pd(OAc)_2$ as a catalyst along with the combination of bases Cs_3PO_4 (4 equiv.) and CsOPiv (1 equiv.) at 110 °C, under neat reaction conditions for 42 h, which led to the desired alkylated product **12b** in moderate yield (Scheme10). Chen and co-workers[8d] developed a new methodology for the stereoselective synthesis of β-alkylated α-amino acid carboxamide derivatives **12d** *via* Pd(II)-catalyzed alkylation of secondary β-C(sp^3)−H bonds of **12c** with α-iodoacetate in the presence of $Pd(OAc)_2$ (10 mol %) as a catalyst, Ag_2CO_3 (2.5 equiv.) as an oxidant/ base and the mixture of additives $(BnO)_2PO_2H$ (20 mol%) and PivOH (0.2 equiv.) in *tert*-AmylOH at 110 ^oC for 20 h which resulted in the formation of product **12d** in good yield (Scheme 10). In 2013, Chen and coworkers[8e] reported the easily removable Picolinamide (PA) as an auxiliary for the γ-C-(sp^3)-H alkylation of the aminoacid picolinamide system **12e** in the presence of $Pd(OAc)_2$ (10 mol%) and Ag_2CO_3 (1-2 equiv.) as an oxidant, $(BnO)_2PO_2H$ (20 mol%) as an additive in *tert*-AmylOH at 110 ^oC for 20 h which afforded the product **12f**. The auxiliary of **12f** was removed in the presence of HCl(aq)/MeOH solution at 80 ^oC for 2 h offering the free amine as an intermediate, which then underwent lactonization to form 5,6- disubstituted piperidinone**12g** in 68% yield (Scheme 10)



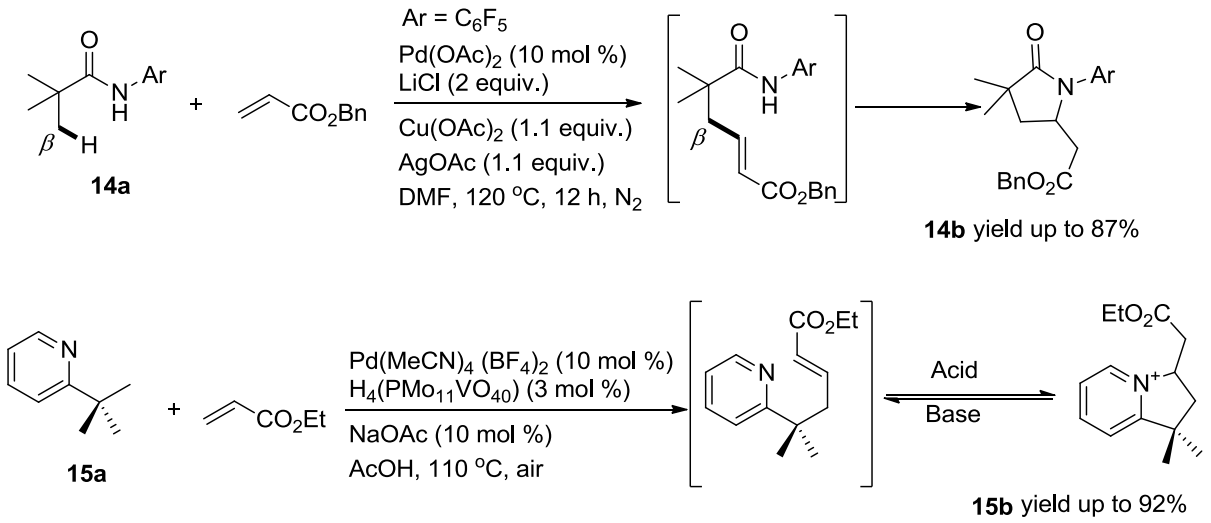
Scheme 10 Pd-catalyzed $1^o/2^o$ β-C-(sp^3)-H alkylation of aminoacid carboxamide system **12a, 12c** and **12e**.

Ge and co-workers[9a] reported the first nickel(II)-catalyzed 8-aminoquinoline directed β-alkylation of aliphatic carboxamides system **13a**. The alkylation of 8-AQ carboxamides 1**3a** with alkyl halide in the presence of [Ni(acac)$_2$] (10 mol%) with 1,2-bis(diphenylphosphino)benzene (dppbz) (10 mol%) as a ligand, Cs_2CO_3 (5 equiv.) as a mild base in toluene at 150 °C resulted in the formation of β-alkylation product **13b** in 86% yield (Scheme 11). Shi and co-workers[9b] reported sulfonamide-promoted alkylation of unactivated methylene β-C-(sp^3)-H bonds of α-amino acid carboxamide system **13c** by using alkyl iodides in the presence of (10 mol %) Pd(OAc)$_2$ followed by the the addition of NaOCN (2 equiv.) and p-Cl-$C_6H_4SO_2NH_2$ as a ligand (30 mol%), whichafforded unnatural β-disubstituted amino acid derivatives **13d** in good yields and excellent diastereoselectivity (Scheme 11). The Liu group[9c] reported the 3-methyl oxazolidine carboxamide directed γ-C(sp^3)-H bond alkylation of **13e** with ethyl iodoacetate in the presence of 10 mol % Pd(OAc)$_2$, and AgOAc (2 equiv.) in toluene at 60 °C for 36 h, which gave the product **13f** with 73% yield (Scheme 11).



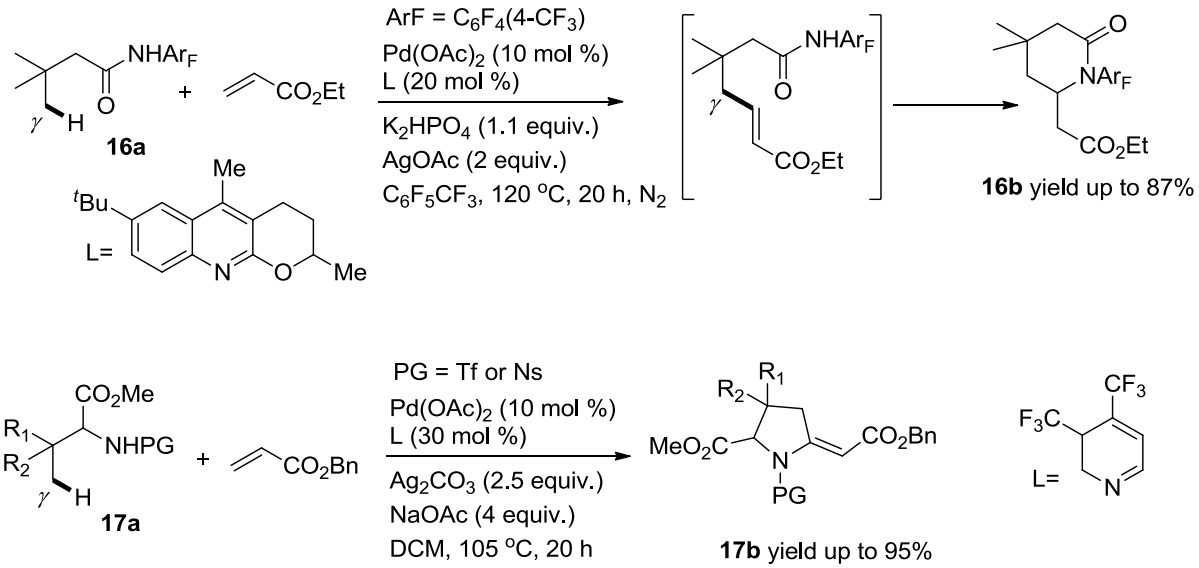
Scheme 11 Pd-catalyzed *β*-*γ*-C-(sp^3)-H alkylation of aminoacid carboxamide system **13a, 13c** and **13e.**

Yu and co-workers[9d] reported the Pd-catalyzed olefination of *β*-C-(sp^3)-H bond in *N*-arylpivalamide system **14a.** The reaction of **14a** with benzyl acrylate in the presence of 10 mol % of $Pd(OAc)_2$ with an additive of 2 equiv. LiCl, 1.1 equiv. of AgOAc and 1.1 equiv. of $Cu(OAc)_2$ as a terminal oxidant in DMF at 120 ^oC for 12 h afforded the desired product **14b** in good yield (Scheme 12). In 2011 Sanford and co-workers[9e] developed a conventional route for *γ*-C-(sp^3)-H olefination of the heterocyclic system such as 2-*tert*-butylpyridine (2-tbp) **15a.** The Pd catalyzed reaction of **15a** with ethyl acrylate led to the formation of product **15b** in good yield (Scheme 12).



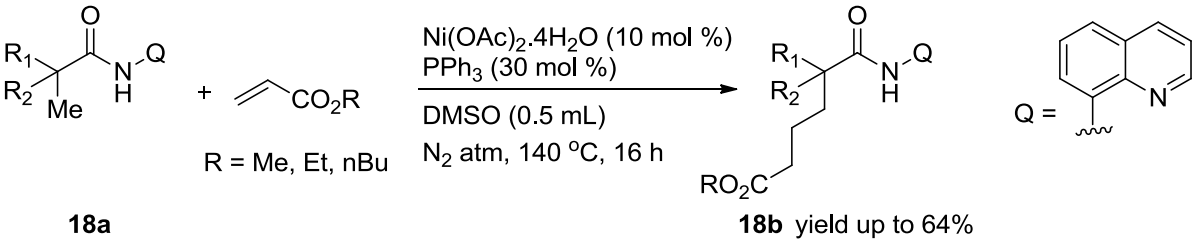
Scheme 12 Pd-catalyzed β-γ-C-(sp^3)-H olefination of aliphatic acid carboxamide system/ heterocyclic system **14a** and **15a.**

Yu and co-workers[10a] reported the Pd(II)-catalyzed ligand enabled γ-C(sp^3)-H bond activation of β–quaternary amides **16a** and the synthesis of γ-C-H olefinated and carbonylated quaternary amides. The olefination of **16a** in the presence of 10 mol % of $Pd(OAc)_2$, 20 mol % of Ligand, 2.0 equiv. of AgOAc, and 1.1 equiv. of K_2HPO_4 in $C_6F_5CF_3$ offered an intermediate which underwent intramolecular hetero-Michael addition reaction and thereby resulted into desired lactam product **16b** in 87% yield (Scheme 13). In 2016, again the same group[10b] reported the ligand enabled Pd-catalyzed γ-C(sp^3)-H bond of Tf and Ns-protected amine system **17a** and the synthesis of a cyclised product or pyrrolidine **17b**. For this reaction, they used 10 mol % of $Pd(OAc)_2$, 30 mol % of pyridine-based ligand, 2.5 equiv. of Ag_2CO_3 and 4.0 equiv. of NaOAc in DCM to afford pyrrolidine derivative **17b** in 95% yield. Initially C-(sp^3)-H olefination intermediate is formed which then underwent Pd-catalyzed intramolecular aza-wacker oxidative cyclization reaction leading to the final product pyrrolidine**17b**formation (Scheme 13).



Scheme 13 Pd-catalyzed ligand enabled γ-C-(sp^3)-H olefination and the synthesis of lactam and pyrrolidine**.**

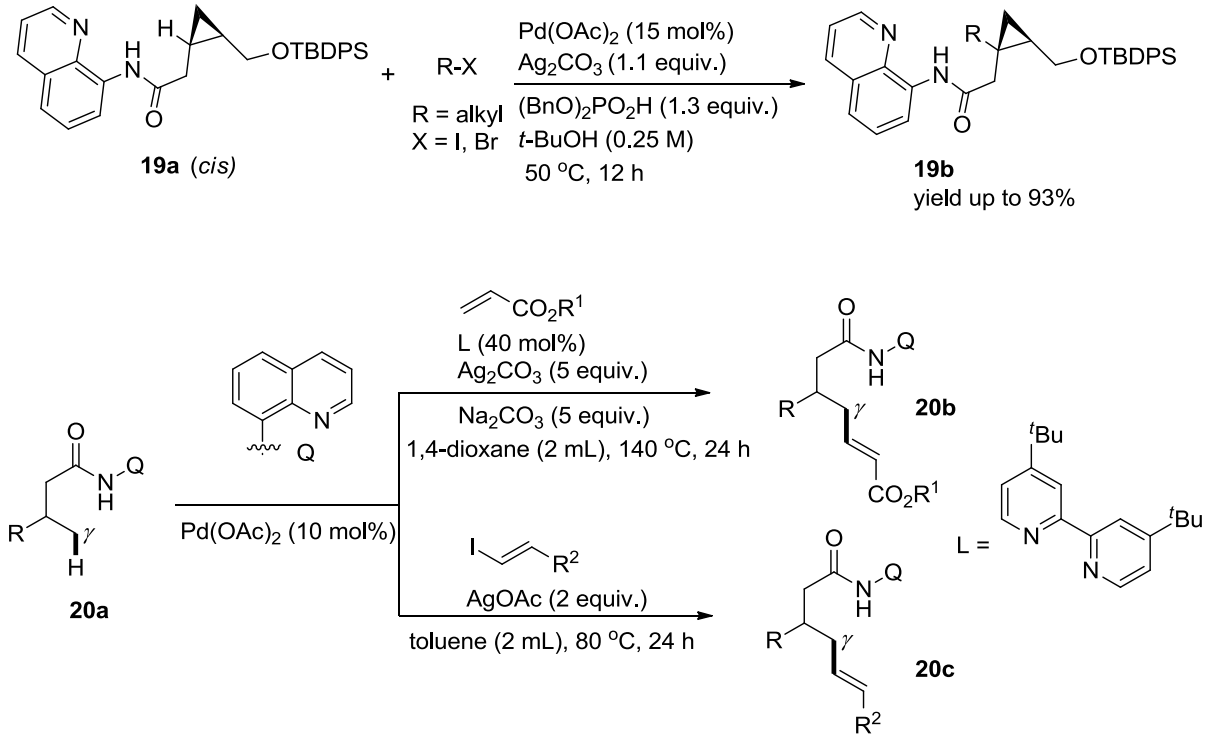
Maiti and co-workers[10c] reported the nickel catalyzed C-(sp^3)-H activation of the unactivated bond of quaternary amides **18a**. The Ni-catalyzed reaction of **18a,** with acrylate derivatives in the presence of 10 mol % $Ni(OAc)_2.4H_2O$, 30 mol % of PPh_3 in DMSO at 140 ^oC for 16 h offered **18b** in good yield (Scheme 14).



Scheme 14 Ni-catalyzed C-(sp^3)-H olefination of quaternary amides **18a.**

Shuto and co-workers[10d] reported the synthesis of chiral 1, 1, 2-trialkyl substituted cyclopropanes **19b** *via* the palladium-catalyzed, 8-AQ-assisted alkylation of tertiary C-(sp^3)-H bond of cyclopropanec arboxamide **19a**. The alkylation of *cis* cyclopropanes **19a** with R-X in the presence of (15 mol %) $Pd(OAc)_2$ as a catalyst, (1.1 equiv.) Ag_2CO_3 as a base and (1.3 equiv.) of $(BnO)_2PO_2H$ as an additive in ^{t}BuOH at 50 ^oC afforded alkylcyclopropanes **19b** in good yields (Scheme 15). Recently Maiti and co-workers[10e] reported 8-aminoquinoline assisted, unactivated distal γ-C-(sp^3)-H bond alkenylation of the aliphatic acid carboxamide system **20a**. The alkenylation of **20a** with ethyl acrylate in the presence of $Pd(OAc)_2$ (10

mol%)as a catalyst, a mixture of salts Ag_2CO_3 (5.0 equiv.)/ Na_2CO_3 (5.0 equiv.) with 40 mol% of 4,4'-di-tert-butyl-2,2'-bipyridine (DTBD) in 1,4-dioxane at 140 ^oC afforded distal γ-alkenylated product **20b** in good yields (Scheme 14). The alkenylation of **20a** with vinyl iodides in the presence of $Pd(OAc)_2$ (10 mol %) and the AgOAc (2.0 equiv.) in toluene at 80 ^oC afforded the distal γ-alkenylated product **20c** in good yields (Scheme 15).



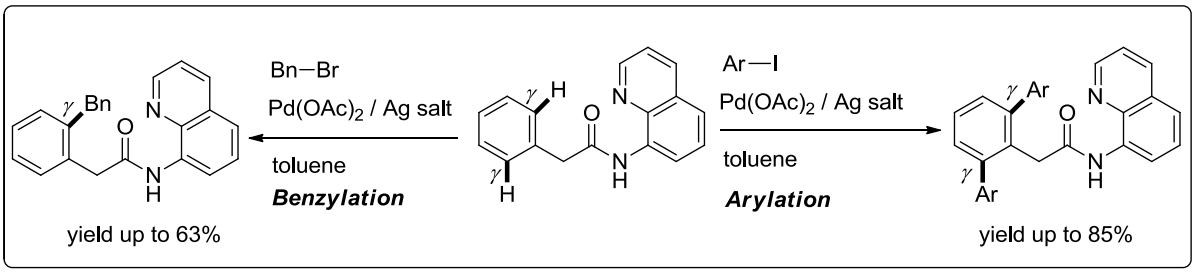
Scheme 15 Pd-catalyzed β-γ-C-(sp^3)-H alkylation/ alkenylation of aliphatic acid carboxamide system **19a** and **20a.**

Result and Discussion

Part 1: Synthesis of *ortho*-arylated/ benzylated phenylacetamide derivatives: Pd(II)-catalyzed, bidentate ligand enabled arylation/ benzylation of the γ-C(sp^3)-H bond of phenylacetamides

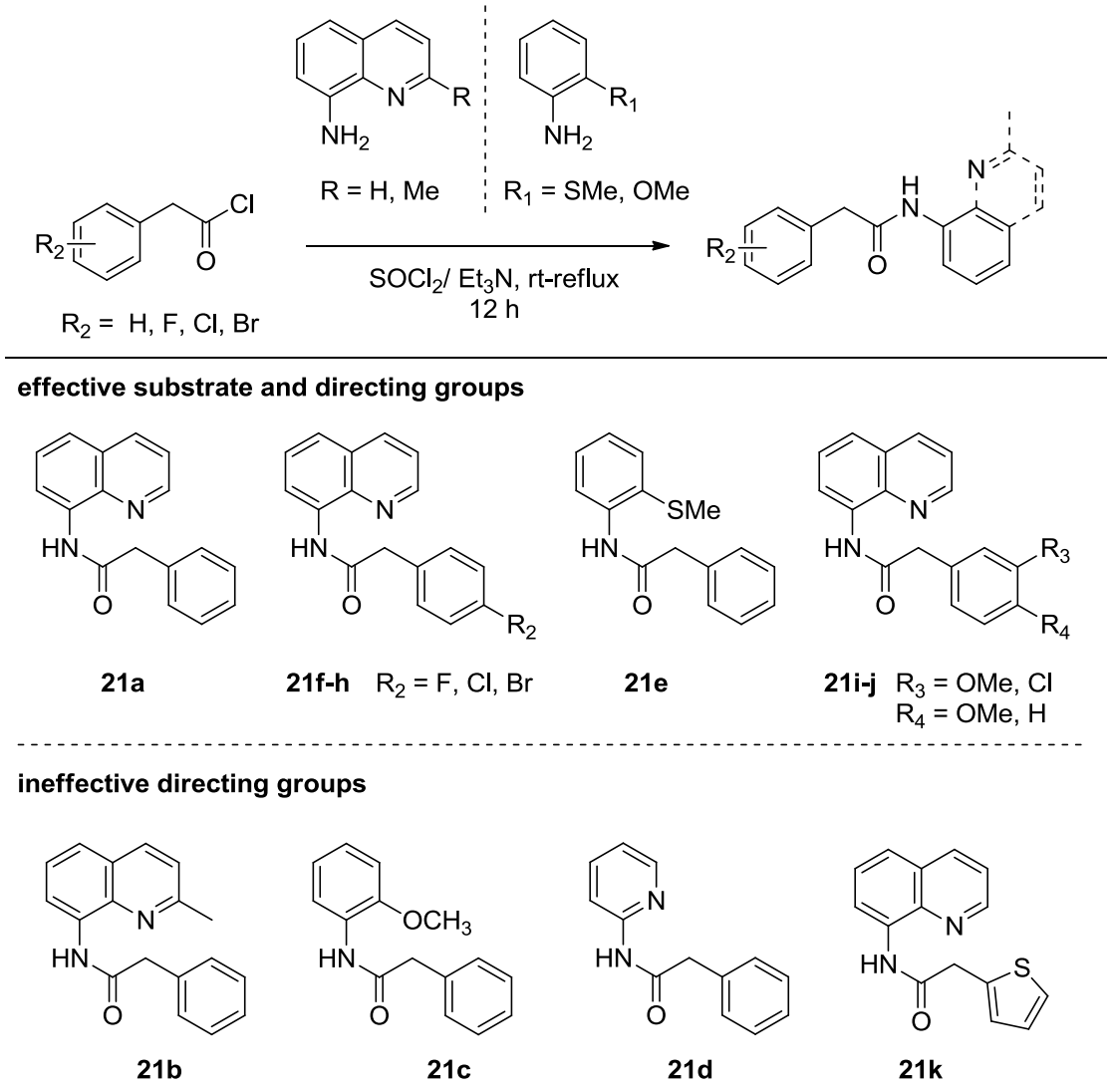
Phenylacetamide derivatives play a crucial role in organic synthesis as well as medicinal chemistry. In particular, various γ-C-H arylated arylacetamide derivatives were found to exhibit a wide range of biological activities. Phenylacetamide scaffolds are essentialstructural

units frequently found in analgesics and anti-inflammatory drugs like as ibuprofen, naproxen[10f]. A literature survey revealed that there are only limited reports available dealing with the synthesis of phenylacetamide systems. Notably, some of the literature reports were discussed in the introduction section. Motivated by their importance and limited reports for their synthesis, developing a new or alternative route for the competent synthetic methods involving a simple procedure for the construction of new kind of mono and bis phenylacetamides derivatives is always desirable. A part of this thesis work is envisaged to examine the Pd(II)-catalyzed bidentate ligand assisted γ-C-(sp^2)-H functionalization of phenylacetamides system and the synthesis of mono/ bis arylated and benzylated derivatives of arylacetamide system (Scheme 16).



Scheme 16 Title of this work: Directing group enabled synthesis of mono/bis arylated and benzylated phenylacetamide system.

By using the standard literature procedure, various arylacetamide systems were synthesized using the bidentate directing groups, such as 8-aminoquinoline, 2-(methylthio) aniline along with some other auxiliaries and their corresponding phenylacetyl system /carboxylic acid system. Various arylacetamide substrates **21a-k** were assembled for γ-C-(sp^2)-H activation (Scheme 17).



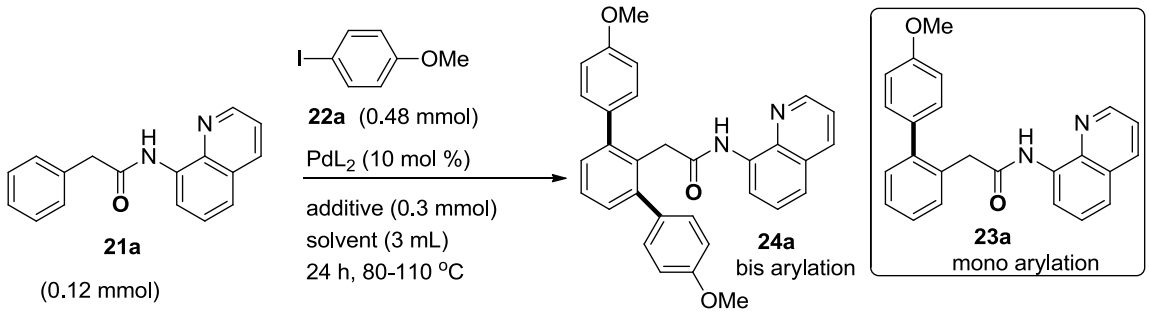
Scheme 17 Directing groups and substrates employed for performing the γ-C-(sp^2)-H arylation (Condition: Substrate (0.12 mmol), **22** or ArI (0.48 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), toluene (3 mL), 24 h and 110 ^oC (the arylation reaction using **24a-q** (bis arylation), **23o-r** (mono arylation) were successful as discussed in results and discussion part and the arylation with **21b-d** and **21k** were not successful).

Then, it was envisaged to find out the best reaction conditions for the synthesis of γ-C-(sp^2)-H bis/mono arylated derivatives of the phenylacetamides system using **21a**. Table 1 shows the optimized reaction conditions; we performed several reactions comprising the Pd(II)-catalyzed, 8-aminoquinoline directed γ-C-H arylation of the substrate **21a** (Table 1). The reaction of substrate **21a** with **22a** in the absence of any catalyst did not give any C-H

arylated products (entry 1, Table 1) and we also examined the reaction of **21a, 22a** and 10 mol % of $Pd(OAc)_2$ catalyst without any additive and this reaction did not give any γ-C-H arylated product. Then the reaction of **21a** (1 equiv.) with **22a** (4 equiv.) in the presence of the well-explored $Pd(OAc)_2$/AgOAc-catalytic system gave the expected bis γ-C-H arylated product **24a** in high yield (85% entry 2, Table 1).

To improve efficiency of the reaction process and yield of the product **24a** (Table 1), we further carried out the optimization reactions with **21a** and **22a** in the presence of additives such as Ag_2CO_3 or K_2CO_3, which resulted into product **24a** in 30 and 67% yields respectively (entries 3 and 4, Table 1). The arylation of **21a** with **22a** in the presence of additives such as KOAc or $PhI(OAc)_2$ did not give the product **24a** (entries 5 and 6 ,Table 1). The arylation of **21a** with **22a** in the presence of the palladium catalysts such as $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ gave the products **24a** in 25 and 46% yield respectively (entries 7 and 8, Table 1). The arylation of **21a** with **22a** in the presence of the palladium catalyst $Pd(TFA)_2$ and $Pd(PPh_3)_4$ did not give the product **24a** (entries 9 and 10, Table 1). The arylation of **21a** with **22a** in solvents, such as 1, 2-DCE or *tert*-butanol failed to give the product **24a** (entries 11 and 12, Table 1). However, the arylation of **21a** with **22a** in 1, 4-dioxane or *tert*-AmylOH gave the product **24a** in 53% yield (entries 13 and 14, Table 1). In these reactions, the formation of the monoarylated product **23a** was also expected. However, we did not get any characterizable amount of the product **23a** from column chromatographic purification of the respective crude reaction mixture of the reactions as shown in Table 1 (entries 1-14). Our previous experience and survey of the literature indicated that generally 3-4 equivalents of aryl iodide were used for obtaining the monoarylated products in high yields, under the palladium-catalyzed C-H arylation method. In the present case, it seems that the bis arylation of **21a** is a simple reaction and the arylation of **21a** with 4 equivalents of **22a** directly gave the bis arylated products **24a** in maximum yield of 85% (entry 2, Table 1).

Table 1 Optimization of reaction conditions. Pd(II)-catalyzed γ-C-H arylation of the phenylacetamide system **21a**

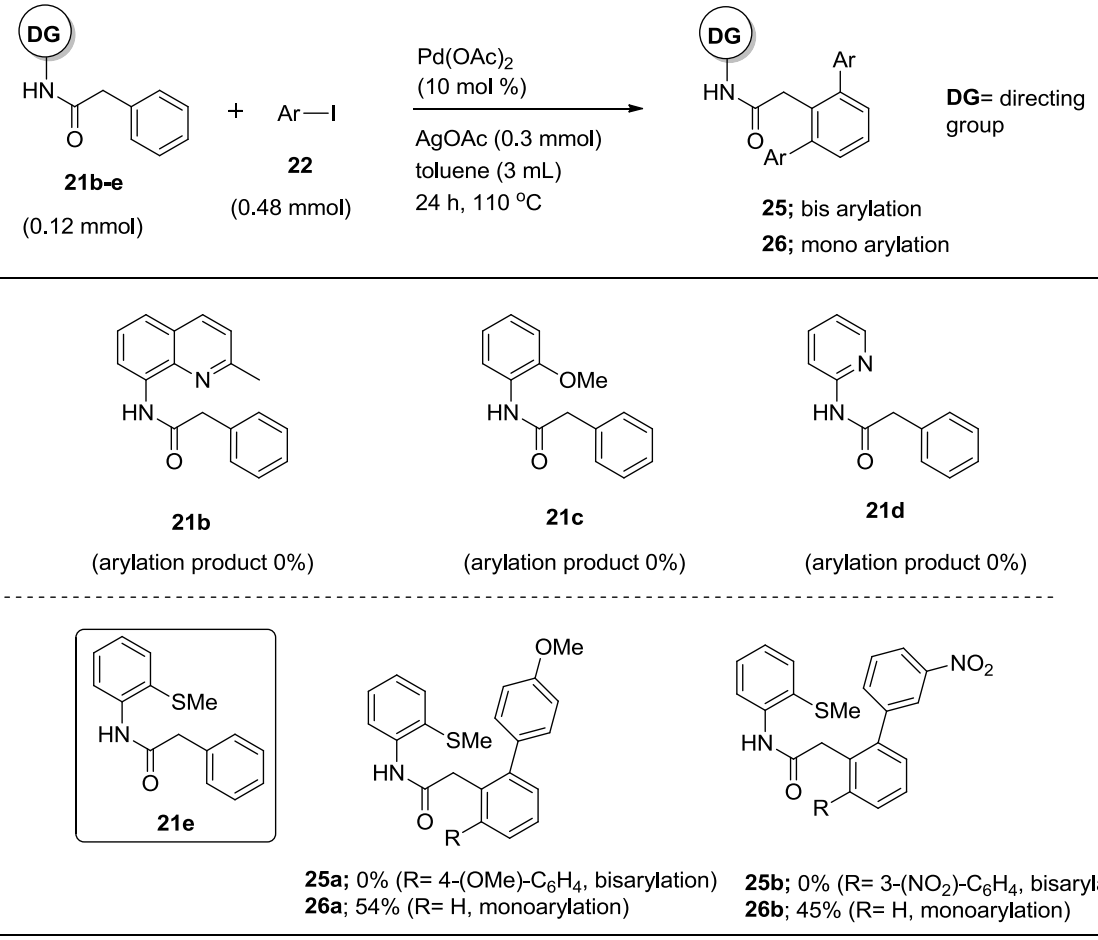


entry	PdL_2	additive	solvent (3 mL)	*t* (°C)	**24a**; yield (%)	**23a**; yield (%)
1	nil	AgOAc	toluene	110	0	-
2	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**85**	**-**
3	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	30	-
4	$Pd(OAc)_2$	K_2CO_3	toluene	110	67	-
5	$Pd(OAc)_2$	KOAc	toluene	110	0	-
6	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0	-
7	$PdCl_2$	AgOAc	toluene	110	25	-
8	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	46	-
9	$Pd(TFA)_2$	AgOAc	toluene	110	0	-
10	$Pd(PPh_3)_4$	AgOAc	toluene	110	0	-
11	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	0	-
12	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	0	-
13	$Pd(OAc)_2$	AgOAc	1,4-Dioxane	100	53	-
14	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	53	-
15[a]	$Pd(OAc)_2$	AgOAc	toluene	110	14	25
16[b]	$Pd(OAc)_2$	AgOAc	toluene	110	34	25
17[c]	$Pd(OAc)_2$	AgOAc	toluene	110	53	-
18[d]	$Pd(OAc)_2$	AgOAc	toluene	110	-	-
19[e]	$Pd(OAc)_2$	AgOAc	toluene	110	37	36

a= 1 equiv (0.12 mmol) of 2a; b= 2 equiv (0.24 mmol) of 2a; c= 3 equiv (0.36 mmol) of 2a
d= 0.1 equiv (0.012 mmol) of AgOAc; e= 1 equiv (0.12 mmol) of AgOAc

Then, we wished to check whether the arylation of **21a** with fewer equivalents of **22a**can give the mono arylation product **23a**. The arylation of **21a** with 1 equiv of **22a** gave the mono arylated products **23a** in 25% yield and bis arylated product **24a** in 14% yield (entry 15, Table 1). A similar trend was observed when the arylation of **21a** was carried out with 2 equiv. of **22a**and in this case, the compounds **24a** and **23a** were obtained in 34 and 25 % yields respectively (entry 16, Table 1). These two reactions indicated that the bis arylation of

21a is a facile reaction though fewer equivalents of **22a** were used. The arylation of **21a** with 3 equivalents of **22a** gave the bis arylated product **24a** in 53% yield (entry 17, Table 1). This reaction and the reaction of entry 2 (Table 1) revealed that the second arylation of the product **23a** is a facile reaction and 3-4 equivalents of **22a** are needed for obtaining the bis γ-C-H arylated product **24a** in high yield from the phenylacetamide system **21a**. Furthermore, we also did the arylation of **21a** with **22a** (4 equiv) in the presence of catalytic amounts of AgOAc and this reaction gave an inseparable crude reaction mixture containing the starting materials as the major compounds (entry 18, Table 1). The arylation of **21a** with **22a** (4 equiv.) in the presence of 1 equiv. of AgOAc instead of 2.5 equiv. of AgOAc (entry 2) gave the mono arylated product **23a** in 36% yield and the bis arylated product **24a** in 37% yield (entry 19, Table 1).

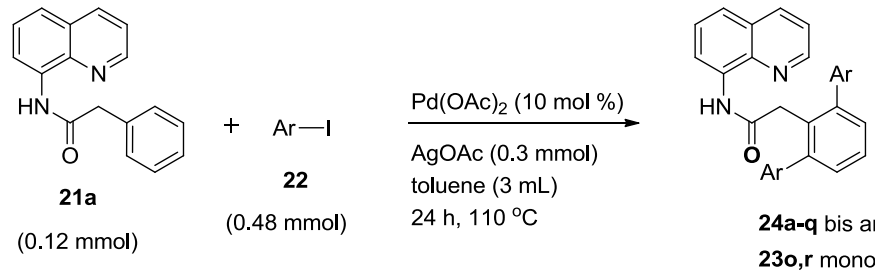


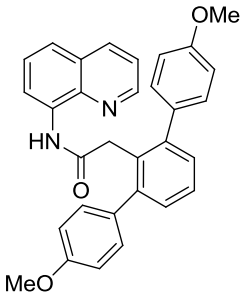
Scheme 18 Bidentate ligands explored for the γ-C-H arylation of the phenylacetamide system.

After obtaining good optimized reaction condition for the bis arylation of γ-C-H bond of the phenylacetamide system 2**1a** containing 8-aminoquinoline as the directing group; then we wished to establish some alternative suitable directing groups for γ-C-H arylation reaction instead of 8-aminoquinoline directing group. Respectively, we performed the C-H arylation of the substrates 2**1b-e** with various bidentate ligands. The arylation of the substrates **21b-d** failed to afford the corresponding γ-C-H arylated products (Scheme 18). However, the γ-C-H arylation of the substrate **21e** with **22a** successfully provided the monoarylated product **26a** in 54% yield (Scheme 18). Similarly, the mono arylated product **26b** was obtained in 45% yield from the γ-C-H arylation of the substrate **21e** with corresponding aryl iodide (scheme 18).

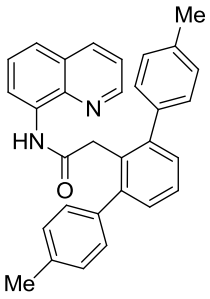
Once we obtained the optimized reaction conditions, it was envisaged to reveal the generality of this Pd(II)-catalyzed 8-aminoquinoline directed, γ-C-H arylation of phenylacetamides. Accordingly, the $Pd(OAc)_2$/ AgOAc-catalytic system based, bidentate auxiliary directed γ-C-H arylation of phenylacetamide **21a** with a wide range of aryl iodides afforded the products **24a-d** in 63-85% yields, respectively (Table 2). The bis γ-C-H arylation of **21a** with iodobenzene furnished the product **24e** in 81% yield (Table 2). Then, the bis γ-C-H arylation of **21a** with disubstituted aryl iodides provided the products **24f-i** in 45-73% yields, respectively (Table 2). Further, we performed the direct bis arylation of **21a** with aryl iodides containing an electron withdrawing group at the *para/meta* position, which afforded the products **24j-o** in 50-70% yields, respectively (Table 2). In one of the case, the monoarylated product **23o** (43%) was obtained along with the bis arylated product **24o** (56%).

Table 2 The Pd(II)-catalyzed synthesis of the ortho-arylated arylacetamide derivatives **24a-q**/ **23o, r**

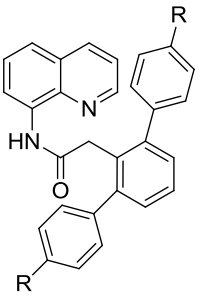




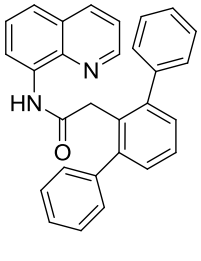
24a, 85%



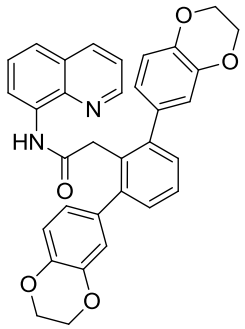
24b, 81%



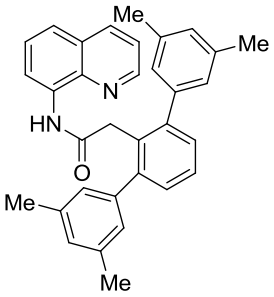
24c, R = Et; 80%
24d, R = ^{t}Bu; 63%



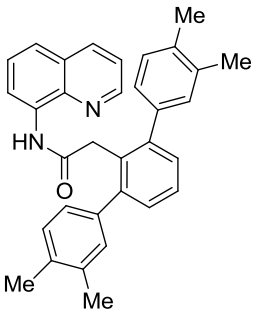
24e, 81%



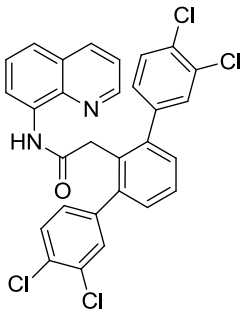
24f, 63%



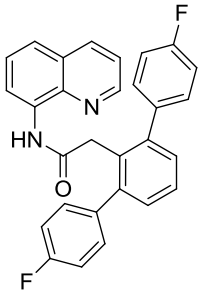
24g, 73%



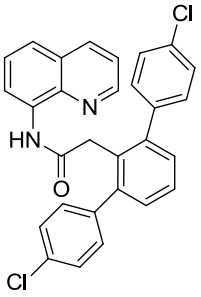
24h, 66%



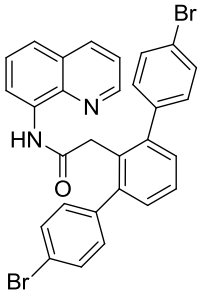
24i, 45%



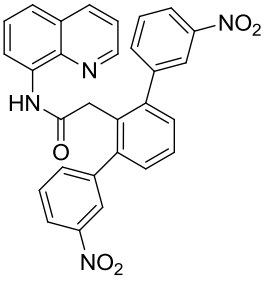
24j, 64%



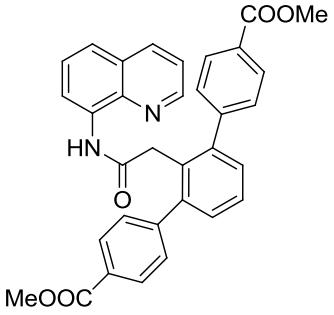
24k, 70%



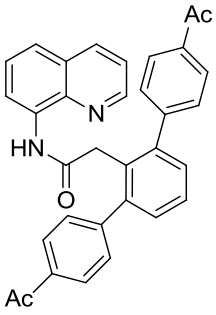
24l, 58%



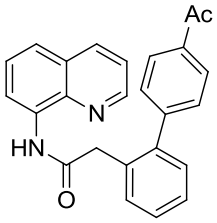
24m, 50%



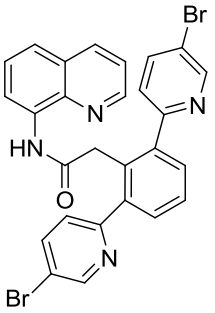
24n, 63%



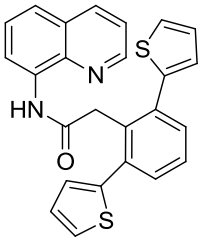
24o, 56%



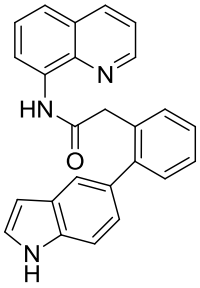
23o, 43%



24p, 44%



24q, 70%

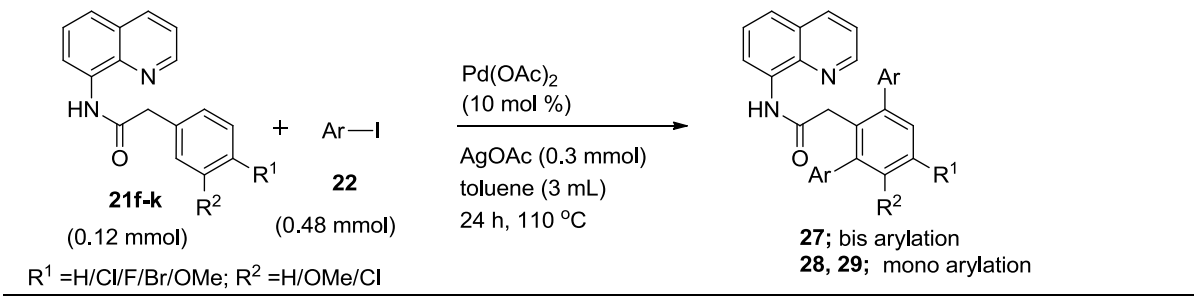


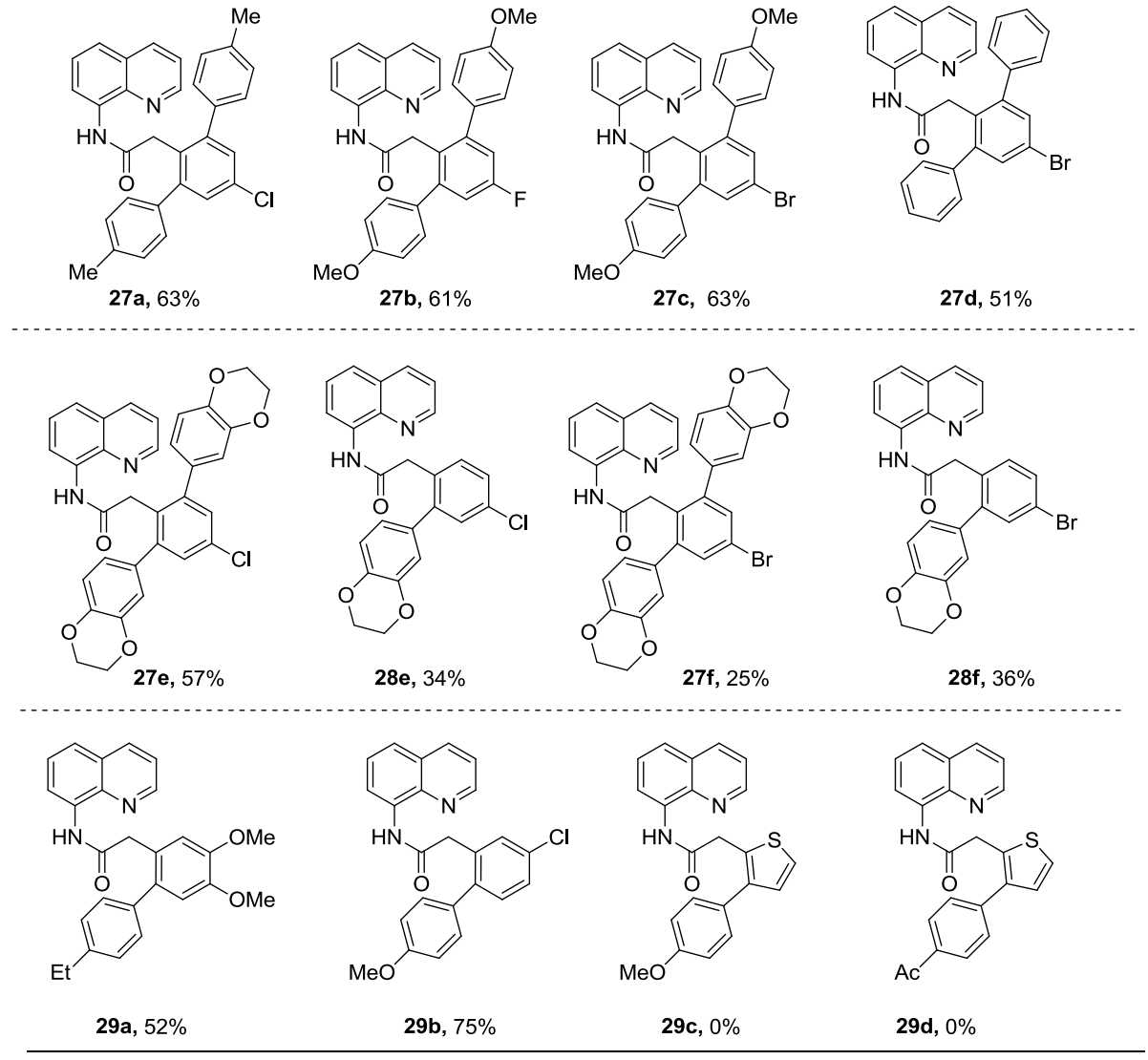
23r, 44%

Next, we kept the reaction of direct bis arylation of the γ-C-H bond of phenylacetamide system **21a** with hetero aryl iodides which also gave the corresponding bis arylated products **24p** (44%) and **24q** (70%). Another reaction comprising the γ-C-H arylation of the substrate **21a** with 5-iodoindole afforded only mono arylated product **23r** (44%) as the major isomer, and the corresponding bis arylated product was not obtained in any characterizable amounts from the column chromatographic purification of the crude reaction mixture. Presumably, since the indole unit is relatively bigger and installation of a second indole moiety in **23r** seems to be difficult due to steric crowding in the bis arylated compound. Hence, only monoarylated product **23r** was obtained as the major isomer (Table 2).

Successively to explore the reaction conditions, we performed the γ-C-H arylation of various phenylacetamides containing different substituents in the aryl ring. Accordingly, we synthesized the bis arylated products **27a-f** in 25-63% yields from their respective starting materials (Table 3). In some exceptional case, the mono arylated products such as **28e** (34%) and **28f** (36%) were also obtained along with their corresponding bis arylated products **27e** and **27f.** We also observed the mono arylated products **29a** and **29b** in 52% and 75% yields respectively (Table 3).

Table 3 The Pd(II)-catalyzed synthesis of the ortho-arylated arylacetamide derivatives **27/28/29**.

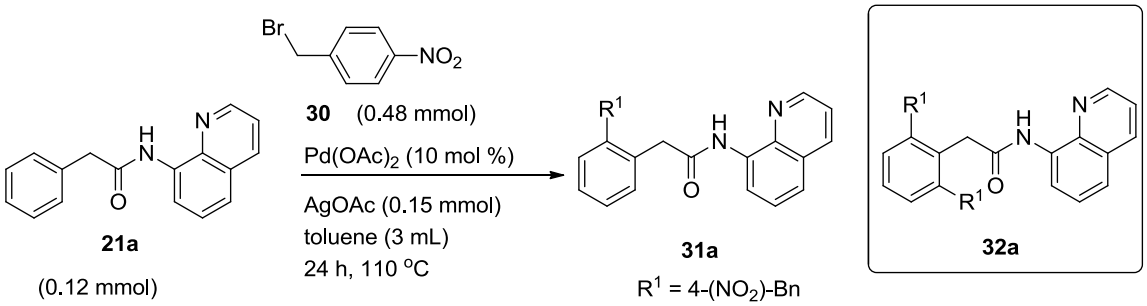




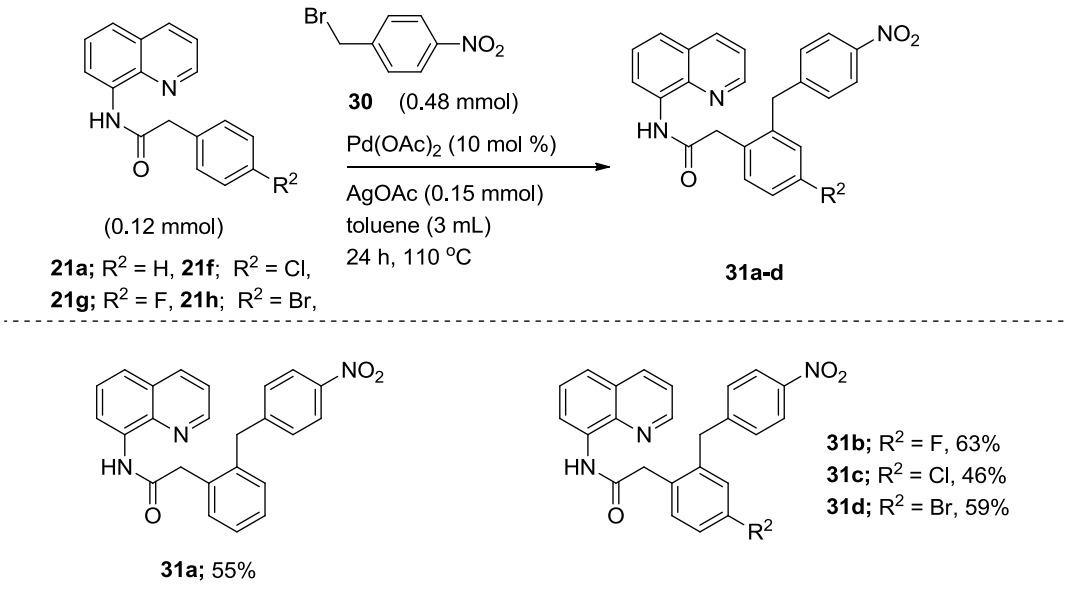
In further trials to extend the substrate scope, we did not get any arylated products **29c** and **29d** from the corresponding thiophenylacetamide starting material **21k**, which structurally resembles the phenylacetamide system **21a**. The reason for the failure of the arylation of thiophenylacetamide is not apparent at this stage.

Finally, we attempted benzylation of the γ-C-H bond of the phenylacetamide system (Table 4). Fortunately, in an initial trial, the benzylation of the γ-C-H bond of the phenylacetamide system **21a** afforded the mono benzylated product **31a** in 55% yield (Table 4). The column chromatographic purification of the crude reaction mixture gave only **31a** as the single product and the bis benzylated product **32a** was not observed. In order to improve the yield of **31a**, we have carried out the benzylation of **21a** by using different reaction conditions (entries 2-9, Table 4). However, we did not find any suitable reaction conditions for obtaining the product **31a** in better yield than the initial reaction condition (entry 1, Table 4). Similarly, the γ-C-H benzylation of the phenylacetamide system **21f-h** gave the mono benzylated products **31b-d** in 46-63% yields, respectively (Table 4). The reason for the formation of monobenzylated products **31a-d** is not apparent. Generally, the benzyl bromide reagent is highly reactive and hence, it is assumed that benzyl bromide reagent might be decomposed or converted into 4-nitrobenzyl acetate under the reaction condition and therefore, the second benzylation of the substrate **31a-d** did not give the bis benzylated products (e.g., **32a**)

Table 4: The Pd(II)-catalyzed synthesis of the ortho-benzylated arylacetamide derivatives **31a-d**

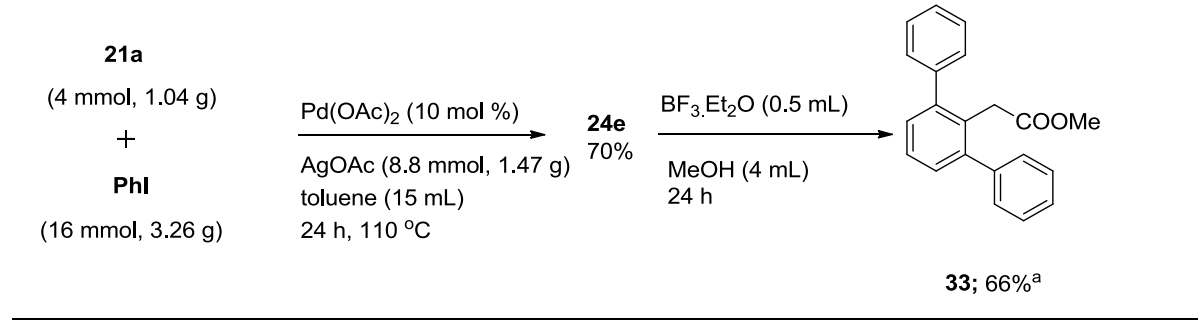


entry	PdL_2	additive	solvent (3 mL)	*t* (°C)	**31a**; yield (%)	**32a**; yield (%)
1[a]	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**55**	**-**
2	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	20	-
3	$Pd(OAc)_2$	KOAc	toluene	110	43	-
4	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0	-
5	$PdCl_2$	AgOAc	toluene	110	0	-
6	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	28	-
7	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	0	-
8	$Pd(OAc)_2$	AgOAc	1,2-DCE	110	0	-
9	$Pd(OAc)_2$	AgOAc	^{t}BuOH	110	0	-



[a] The reaction was performed using **21a** (0.12 mmol), **30** (0.48 mmol) and AgOAc (0.15 mmol).

We also performed double arylation on the γ-C-H bond of phenylacetamide system **21a** with iodobenzene in a gram scale and this reaction furnished the product **24e** in 70% yield (Scheme 19). Then, we wished to remove the bidentate ligand from the representative γ-C-H arylated arylacetamide system. Accordingly, we treated the bis arylated phenylacetamide system **24e** with $BF_3.OEt_2$ in MeOH, which successfully gave the methyl ester of ortho-diarylated phenylacetic acid **33,** in 66% yield (Scheme 19).



[a] The conversion of **24e** to **33** was performed by using 1.4 mmol of **24e**

Scheme 19: Gram scale reaction of the γ-C-H arylation of 2**1a** and removal of the bidentate ligand 8-aminoquinoline.

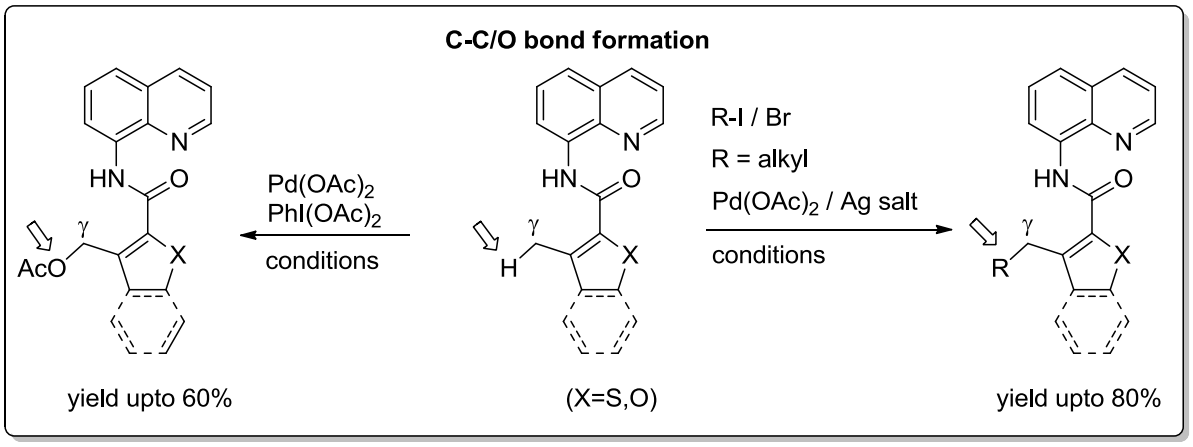
Overall, while the arylation and benzylation of arylacetamides were successful. Our various attempts on the 8-aminoquinoline directed alkylation, acetoxylation and hydroxylation of phenylacetamides was not successful. Apparently, it indicates that the bidentate ligand 8-aminoquinoline does not assist C-O bond formation in the arylacetamide system. However, Chatani's group[10a] was victorious in the construction of C-O bond in the phenylacetamide system by using less common bidentate ligand, quinoline-8-ylmethanamine (Scheme 5). Since we were unsuccessful in developing C-O bond formation, we focussed towards the development of arylation/benzylation of phenylacetamides. For this, different ligands were screened for performing the arylation/benzylation of phenylacetamide but 8-aminoquinoline was found to be the best ligand. Various aryl iodides containing electron donating or withdrawing groups and heteroaryl iodides along with some benzyl bromides were used to examine their reactivity pattern. In general, γ-C-H arylation of arylacetamide with aryl iodides containing electron donating groups gave ortho-diarylated arylacetamides as the major compound in high yields (Table 2). The γ-C-H arylation of arylacetamide with aryl iodides containing electron withdrawing groups gave ortho-diarylated arylacetamides as the

predominant compound in moderate yields (Table 2). Based on the substituents of aryl iodides and in some specific case, the mono ortho-arylated arylacetamides were obtained. The γ-C-H arylation of arylacetamides containing substituents at *meta* position in combination with aryl iodides gave only mono ortho-arylated arylacetamides as the potent compounds in moderate to good yields (Table 3). Presumably, the installation of a second aryl moiety may result in steric crowding in the bis arylated compoundand hence the arylation of phenylacetamides containing substituents at the *meta* position gave only the mono ortho-arylated arylacetamides. While the γ-C-H benzylation of arylacetamides gave only mono ortho-benzylated arylacetamides as the major compounds (Table 4). Our trails to obtain the bis γ-C-H benzylated compounds were not fruitful.

Part 2: Pd(II)-catalyzed alkylation/acetoxylation and benzylation of γ-C-(sp^3)-H bonds of heterocyclic amides

Given the importance of functionalization of the γ-C-(sp^3)-H bond of aliphatic chains, aliphatic cyclic system and heterocyclic system assisted by different bidentate directing groups such as 8-AQ, 2-picolinamide and 2-(methylthio) aniline) and some monodentate directing group like 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline, pyridine separately used for the Pd(II)-catalyzed functionalization/ activation of β-C(sp^3)-H bond of various amide system.

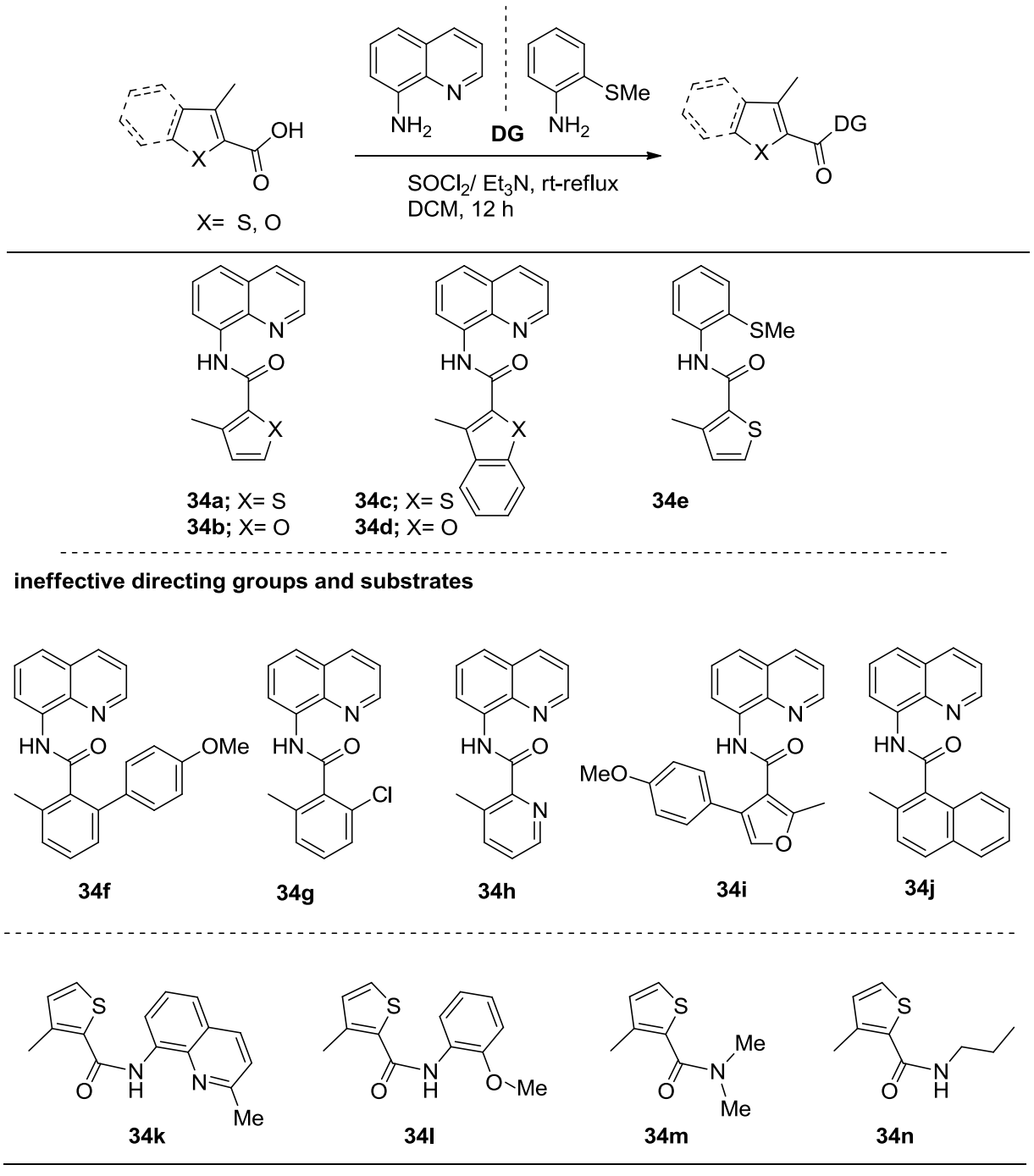
This work



Scheme 20 Title of this work: Construction of γ-alkylated, acetoxylated and benzylated heterocyclic system with the aid of 8-AQ.

There are numerous reports available with picolinamide enabled activation of γ-C-(sp^3)-H bond of various amine systems. Notably, that the 8-aminoquinoline type bidentate groups were very frequently used for the β-C-(sp^3)-H bonds of a differentkind of carboxylic system. However, there are very few reports on γ-C-(sp^3)-H bond of the carboxylic system enabled by 8-aminoquinoline. A part of this thesis work envisaged investigating the $Pd(OAc)_2$ catalyzed, functionalization of γ-C-(sp^3)-H bond of heterocyclic carboxamides, e.g., 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/benzothiophene-2-carboxamide system (Scheme 20).

To examine the activation on γ-C-(sp^3)-H bond of 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/benzothiophene-2-carboxamide system, we prepared the following carboxamides **34a-n** with their corresponding carboxylic acids/chlorides by using literature reports (Scheme 21).



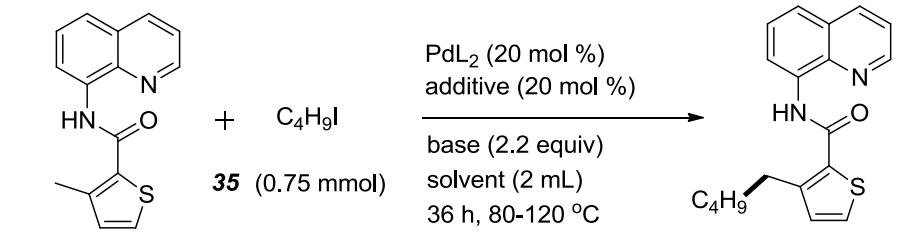
Scheme 21 3-Methylfuran/thiophene-2-carboxamide, 3-methylbenzofuran/benzothiophene-2-carboxamide, and related systems assembled for the investigation of the γ-C-(sp^3)-H alkylation, acetoxylation,and benzylation.

After preparation of the suitable starting materials, we started to optimize various reaction conditions to achieve the alkylheteromethane moiety **36b** via the Pd(II)-catalyzed, 8-aminoquinoline assisted γ-C-(sp^3)-H alkylation of thiophene-2-carboxamide system **34a** (Table 5). The reaction of γ-C-(sp^3)-H alkylation of thiophene-2-carboxamide system **34a** with 6 equiv. of alkyl iodide **35** in the presence of $Pd(OAc)_2$ catalyst, AgOAc and $(BnO)_2PO_2H$ in ^{t}AmylOH at 120 ^{o}C for 24 h was found to be the best developed condition, which gave the alkylheteromethane derivatives **36b** in a maximum of 80% yield.(entry 5, Table 5). First, the catalytic reaction was tested without a catalyst under a nitrogen atmosphere, which failed to afford any product (entry 1, Table 5). We also tested the reaction without any additive; no fruitful result was observed (entry 3, Table 5). Further, various bases were screened for the alkylation of heterocarboxamide, such as Ag_2CO_3, AgOAc, K_2CO_3, KOAc and these afforded good to moderate yields (entries 5, 7 and 11, 12, Table 5). The Pd-catalyzed C-H alkylation of heterocarboxamide **34a** with **35,** without base Ag_2CO_3 under nitrogen atmosphere failed to afford any product (entry 2, Table 5). This reaction indicated that Ag_2CO_3 generates Ag^+ ions that could play a crucial role to abstract the halide from alkyl halides which resulted in the formation of the desired product 36b (entry 5, Table 5). The C-H alkylation of heterocaboxamide **34a** with **35** in the presence of AgOAc instead of the Ag_2CO_3 base was found to be effective and gave **36b** in good yield 75% (entry 7, Table 5). The alkylation of **34a** with **35** in the presence of a base such as K_2CO_3 or KOAc did not give the product **36b** (entries 11 and 12, Table 5). The C-H alkylation of heterocaboxamide **34a** with **35** in the presence of $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ instead of $Pd(OAc)_2$ catalyst gave the product **36b** in 50 and 32% yields, respectively (entries 8 and 9, Table 5). The alkylation of **34a** with **35**in the presence of $Pd(PPh_3)_2Cl_2$ catalyst gave the product **36b** in <5% yields (entries 10, Table 5). Further, we tested the Pd-catalyzed alkylation of heterocarboxamide **34a** with **35** using different solvents such as toluene, 1,2-DCE, 1,4-dioxane and ^{t}BuOH leads to the formation of product **36b** in less to moderately 10-40% yields, respectively (entries 13-16, Table 5). The C-H alkylation of heterocarboxamide **34a** (0.125 mmol) with 35 (0.75 mmol) in presence of $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (0.25 mmol), and $(BnO)_2PO_2H$ (20 mol%) in ^{t}AmylOH at 120 ^{o}C for 24 h furnished the alkylheteromethane **36b** in 80% yield (entry 5, Table 5).

We next examined the role of additive in the present developed reaction condition. When we used PivOH as an additive in the reaction **34a** with **35** afforded the product **36b** in 67% yield (entry 4, Table 5). To improve the yield of product, we replaced PivOH with $(BnO)_2PO_2H$; then the desired product **36b** was obtained in excellent yield 80% (entry 5, Table 5). From this, we can clearly assume that the $(BnO)_2PO_2H$ is playing a key role in the present developed condition. $(BnO)_2PO_2H$ was apparently more effective than PivOH. May be $(BnO)_2PO_2H$ forms more homogenous mixture with base Ag_2CO_3 in the ^{t}AmylOH solvent, parallel it could act as a ligand for palladium during the C-H activation step such as oxidative addition and reductive elimination. We also suspect that $(BnO)_2PO_2H$ could help the protonolysis of the Pd-complexed alkylated intermediate, promoting the release of the product in the reaction mechanism.

For a clear understanding of catalyst loading needed to obtain a good result, we then tested the mol% of the catalyst loading. First, the Pd-catalyzed C-H alkylation of heterocarboxamide **34a** was performed by using 5 mol% of $Pd(OAc)_2$ gave only the alkylheteromethane as a product in 35% yield (entry 17, Table 1). Then we increased the loading of $Pd(OAc)_2$ in multiples of five like 10%, 15% and 20% which resulted into a gradual raise of the product yields to 47%, 61%, and 80% respectively (entry 18, 19, and 20, Table 5). To examine how many equivalents of alkyl iodide were required for producing the alkylheteromethane product **36b**, the Pd(II)-catalyzed C-H activation, alkylation of heterocarboxamide **34a** was performed by varying of the alkyl iodide **35** (Table 5). The Pd(II)-catalyzed C-H activation of heterocarboxamide **34a** with two equivalents of alkyl iodide **35** gave only the alkylheteromethane **36b** in very less yield 33% (entry 21, Table 5). Further, we increased the equivalent of alkyl iodide to 4%, 6% and 8%, which showed improvement of the product **36b** in 59%, 80%, and 83%, respectively (entry 22, 23, and 24 Table 5). After the optimization of loading of Pd(II)-catalyst and equivalent of alkyl iodide, we concluded that the 20 mol% of $Pd(OAc)_2$ and 6 equiv. of alkyl iodide were needed to get product **36b** in 80% yield (entry 5, Table 5).

Table 5 Optimization reactions.



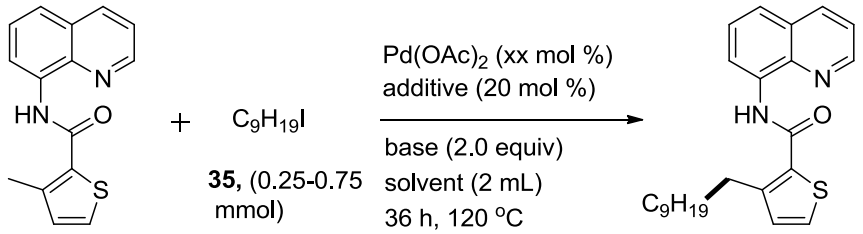
entry	PdL_2	additive	base	solvent	*t* (°C)	yield (***36b***%)[a]
1	nil	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	0
2	$Pd(OAc)_2$	$(BnO)_2PO_2H$	nil	^{t}AmylOH	120	0
3	$Pd(OAc)_2$	nil	Ag_2CO_3	^{t}AmylOH	120	0
4	$Pd(OAc)_2$	PivOH	Ag_2CO_3	^{t}AmylOH	120	67
5	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	80
6	$Pd(OAc)_2$	PivOH	AgOAc	^{t}AmylOH	120	59
7	$Pd(OAc)_2$	$(BnO)_2PO_2H$	AgOAc	^{t}AmylOH	120	74
8	$PdCl_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	110	50
9	$Pd(CH_3CN)_2Cl_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	32
10	$Pd(PPh_3)_2Cl_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	<5
11	$Pd(OAc)_2$	$(BnO)_2PO_2H$	K_2CO_3	^{t}AmylOH	120	36
12	$Pd(OAc)_2$	$(BnO)_2PO_2H$	KOAc	^{t}AmylOH	120	15
13	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	toluene	110	10
14	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	1,2-DCE	80	0
15	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	1,4-Dioxane	100	20
16	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}BuOH	85	45
17[b]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	35
18[c]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	47
19[d]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	61
20[e]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	80
21[f]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	33
22[g]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	59
23[h]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	80
24[i]	$Pd(OAc)_2$	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	83

[a] All the reactions were performed using 1-iodobutane (2a) under nitrogen atmosphere. [b] 5

mol%, [c] 10 mol% and [d] 15 mol% , [e] 20 mol% $Pd(OAc)_2$ was used.[f] 2 equiv. [g] 4 equiv and [h] 6 equiv, [i] 8 equiv alkyl iodide was used.

Then, we also examined the alkylation of **34a** with fewer equivalents of **35** and different mol % of catalyst loading, to check whether we can obtain the alkylation product **36g** in good yield. The alkylation of **34a** with 2 equiv. of **35** in the presence of 5 mol % of $Pd(OAc)_2$ gave the alkylated product **36g** in 20% yield (entry 1, Table 6). A similar trend was observed when the alkylation of **34a** was carried out with 2 equiv. of **35** in the presence of 10, 15 and 20 mol % of $Pd(OAc)_2$ gave the alkylated products **36g** in 28, 34 and 42% yield, respectively (entries 2-4, Table 6). Again, this reaction is carried out with 4 equiv. of **35** in the presence of 5, 10, 15 and 20 mol % of $Pd(OAc)_2$ resulting in the formation of alkylated products **36g** having the yield 44, 51, 53 and 60%, respectively (entries 5-8, Table 6).

Table 6 Optimization for catalyst loading and equivalent of alkyl iodide were used for alkylheteromethane.



34a, (0.125 mmol)

35, (0.25-0.75 mmol)

36g

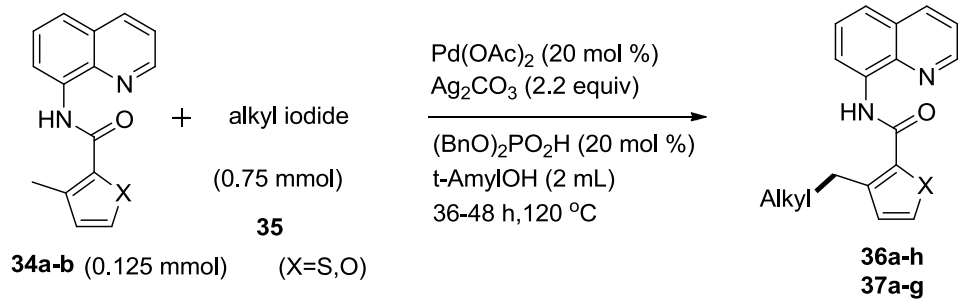
entry	$Pd(OAc)_2$	additive	base	solvent	*t* (°C)	**36g** yield (%)
1[a]	$Pd(OAc)_2$ (5 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	20
2[a]	$Pd(OAc)_2$ (10 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	28
3[a]	$Pd(OAc)_2$ (15 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	34
4[a]	$Pd(OAc)_2$ (20 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	42
5[b]	$Pd(OAc)_2$ (5 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	44
6[b]	$Pd(OAc)_2$ (10 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	51
7[b]	$Pd(OAc)_2$ (15 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	53
8[b]	$Pd(OAc)_2$ (20 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	60
9[c]	$Pd(OAc)_2$ (20 mol%)	$(BnO)_2PO_2H$	Ag_2CO_3	^{t}AmylOH	120	68
10[c]	$Pd(OAc)_2$ (20 mol%)	$(BnO)_2PO_2H$	AgOAc	^{t}AmylOH	120	64

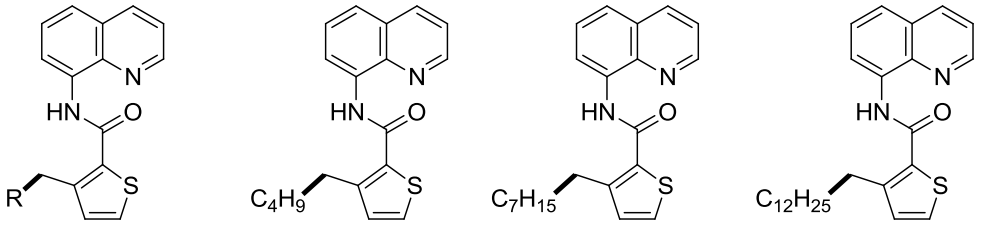
[a] 2 equiv., [b] 4 equiv., [c] 6 equiv. of alkyl iodide was used

The alkylation of **34a** with 6 equiv. of **35** in the presence of 20 mol % $Pd(OAc)_2$ and 2 equiv. of Ag_2CO_3 gave the alkylated product **36g** in 68% yield (entry 9, Table 6). Finally, a similar kind of yield was observed, when we used AgOAc Oxidant instead of Ag_2CO_3 in the present reaction condition (entry 10, Table 6). This reaction revealed that the alkylation is facile with 20 mol % of $Pd(OAc)_2$ and 6 equiv. of **35** to obtain the alkylated product **36g** in high yield from the heterocyclic carboxamide system **34a**.

Having developed reaction condition, it was envisaged to explore the generality and scope of the 8-aminoquinoline assisted Pd(II)-catalyzed C-H activation and alkylation of heterocarboxamides (Table 7). The Pd(II)-catalyzed alkylation of γ-C(sp^3)-H bond of 3-methylfuran/thiophene-2-carboxamide system **34a-b** with various alkyl halide containing shorter and longer chain lengths afforded the corresponding alkylated heterocarboxamides **36a-h** and **37a-g** in 40-80% yields.(Table 7)

Table 7 Synthesis of thiophene/furan basedalkylheteromethane **36a-h and 37a-g**.



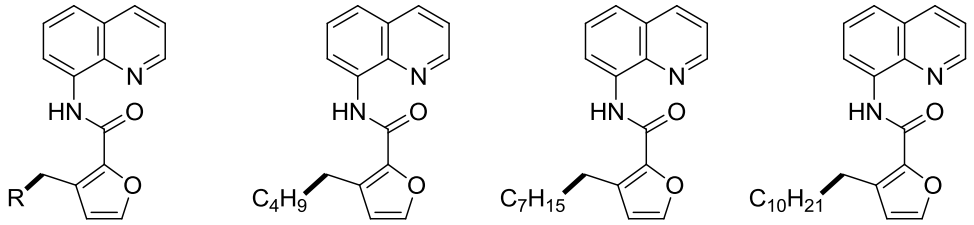


36a; R = C_3H_7; 70%
36c; R = C_5H_{11}; 70%
36e; R = C_8H_{17}; 50%
36f; R = C_9H_{19}; 67%
36g; R = $C_{10}H_{21}$;55%

36b; 80%

36d; 55%

36h; 50%



37a; R = C_3H_7; 42%
37c; R = C_5H_{11};52%
37e; R = C_8H_{17}; 53%
37f; R = C_9H_{19}; 50%

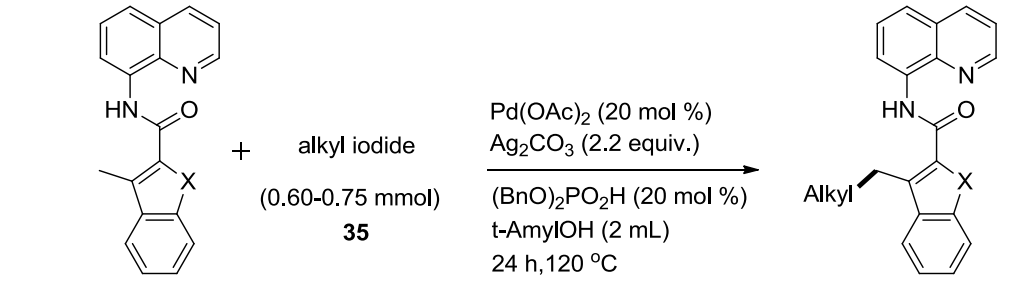
37b; 65%

37d; 59%

37g; 50%

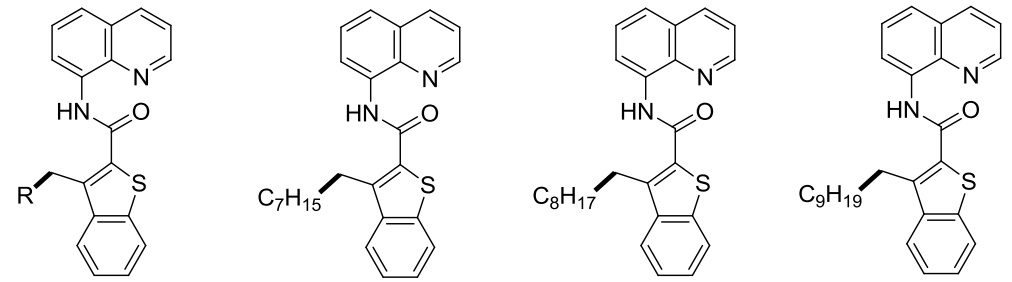
Accordingly, Table 8 revealed that the results of the Pd(II)-catalyzed 8-aminoquinoline assisted alkylation of γ-C-(sp^3)-H of substrate **34c** and **34d**. The $Pd(OAc)_2$-catalyzed, Ag_2CO_3 mediated γ-C-(sp^3)-H alkylation of the 3-methylbenzothiophene-2-carboxamide system **34c** with a wide range of alkyl iodides afforded the corresponding benzothiophene based alkyl heteromethane derivatives **38a-e** in 60-69% yields (Table 8). Similarly the Pd(II)-catalyzed, Ag_2CO_3 mediated γ-C-(sp^3)-H alkylation of 3-methylbenzofuran-2-carboxamide system **34d** with a wide range of alkyl iodides having longer and shorter chain length afforded the corresponding γ-C-(sp^3)-H alkylated akylheteromethane derivatives **39a-e** in 42-70% yields (Table 8).

Table 8 Synthesis of benzothiophene/benzofuran based alkylheteromethane **38/39a-e**.



34c-d (0.10-0.125 mmol) X= O, S

38/39a-e

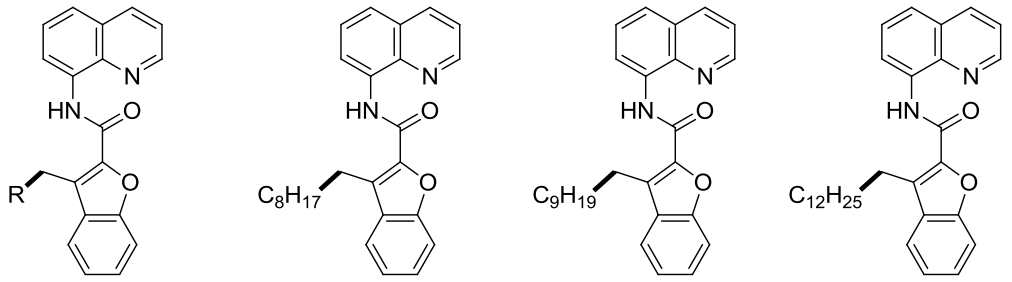


38a; R = C_4H_9; 62%
38b; R = C_5H_{11}; 60%

38c; 60%

38d; 69%

38e; 66%



39a; R = C_5H_{11}; 45%
39b; R = C_7H_{15}; 52%

39c; 42%

39d; 70%

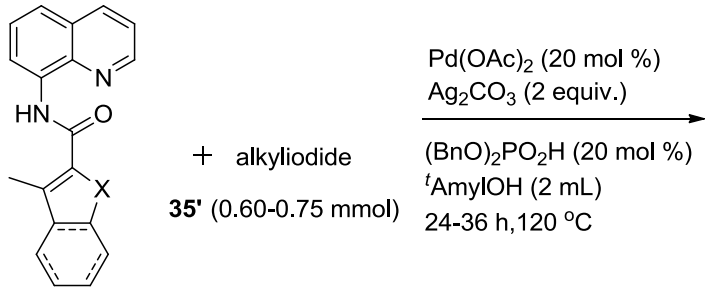
39e; 45%

Then, the scope of this method was further extended by using various alkyl iodides. We performed the $Pd(OAc)_2$-catalyzed, Ag_2CO_3 mediated γ-C-(sp^3)-H alkylation of 3-Methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/benzothiophene-2-carboxamide system **34a-d** in the presence of alkyl iodide having two different groups such as ester, acetate at both ends, which then offered the corresponding γ-C-(sp^3)-H alkylated, thiophene, furan and benzothiophene,benzofuran based alkylheteromethane **40a-g** in 40-65% yields (Table 9). Furthermore, Table 8 shows the $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C-(sp^3)-H benzylation of the substrate **34a-b** with 4-nitrobenzyl bromide and 2-methyl benzyl bromides **35'**, which gave the corresponding γ-C-(sp^3)-H benzylated thiophene-2-

carboxamide system **40i** and benzylated furan-2-carboxamide system **40h** in 43-50% yields (Table 9).

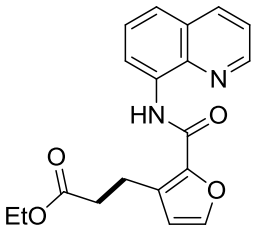
Subsequently, we also explored the remote acetoxylation on 3-Methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/benzothiophene-2-carboxamide system **34a-d** with literature well known developed condition where we used $PhI(OAc)_2$ as an oxidant in the presence of Pd-catalyzed 8-aminoquinoline directed γ-C-(sp^3)-H acetoxylation furnished the acetoxylated furan/thiophene-2-carboxamide and acetoxylated benzofuran/benzothiophene-2-carboxamide derivatives **41a-d** in 20-60% yields, respectively (Table 10). While doing the acetoxylation on 3-Methylbenzofuran-2-carboxamide, we also observed the bis acetoxylation on γ-C-(sp^3)-H bond to give diacetoxylated benzofuran-2-carboxamide derivatives **41d'** in 15% yield (Table 10). After exploring the acetoxylation on 3-Methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/benzothiophene-2-carboxamide system, we further interested in checking the acetoxylation on the secondaryγ-C-(sp^3)-H bond of 3-pentyl thiophene-2-carboxamide substrate **36b**. The substrate **36b** we got, as a result of Pd-catalyzed alkylation on the 3-Methyl thiophene-2-carboxamide **34a**, the Pd(II)-catalyzed, 8-aminoquinoline assisted secondary γ-C-(sp^3)-H bond acetoxylation of **36b** with $PhI(OAc)_2$ as an oxidant furnished the tertiary γ-C-(sp^3)-H acetoxylated thiophene-2-carboxamide derivative **41e** in 15 % yield (Table 10).

Table 9 Synthesis of different alkylated heteromethane by using various Alkyl halides **40a-i**.

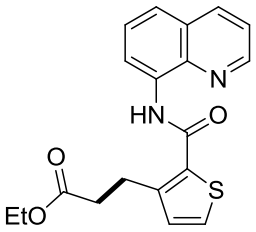


34a-d (0.10-0.125 mmol) X=O,S

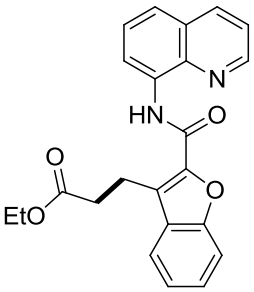
40a-i



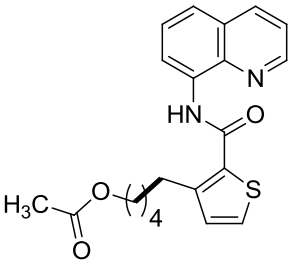
40a; 55%



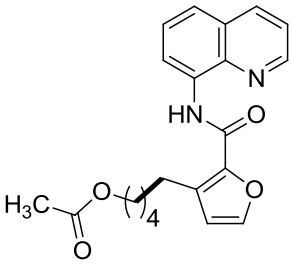
40b; 45%



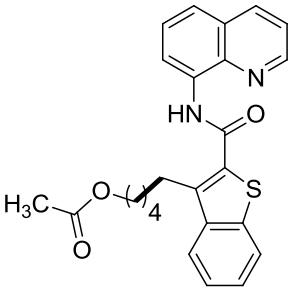
40c; 40%



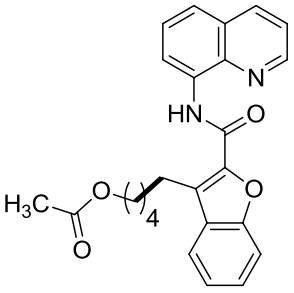
40d; 65%



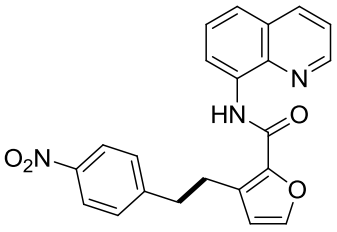
40e; 40%



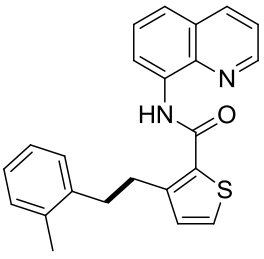
40f; 60%



40g; 55%



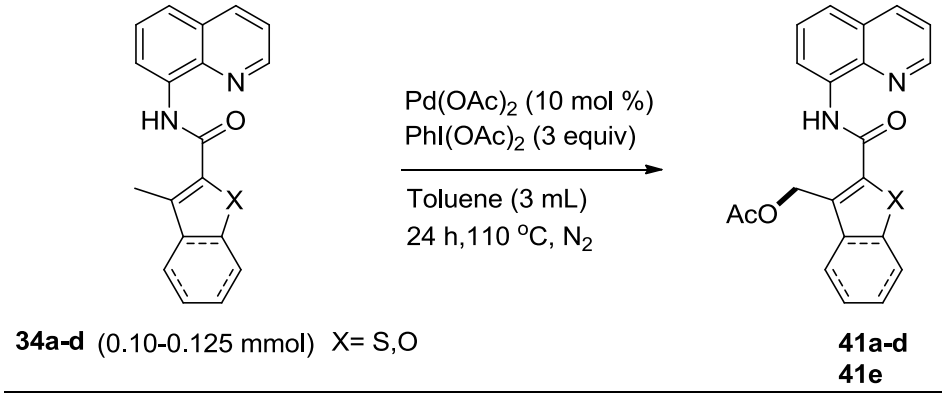
40h; (50%)[j]

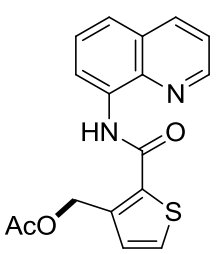


40i; (43%)[j]

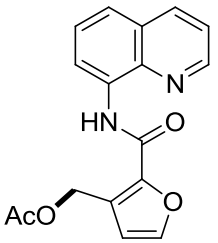
[j] substrate **34a-b** (0.10-0.125 mmol), *p*-nitrobenzyl bromide (0.40-0.50 mmol), $Pd(OAc)_2$ (10 mol %), toluene (2 mL), 24 h in 110 ^oC condition was used for benzylation.

Table 10 Synthesis of acetoxylated heteromethanes **41a-e**.

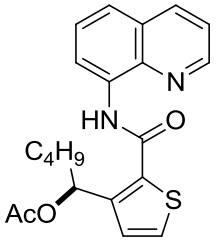




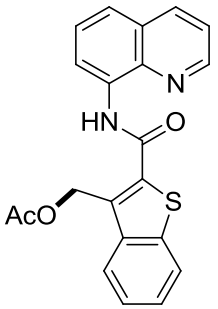
41a; 60%



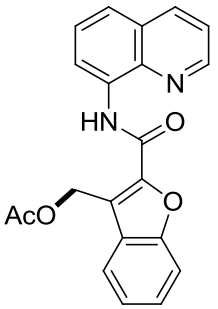
41b; 50%



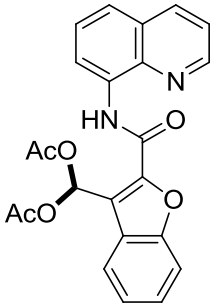
41e; 15%



41c; 30%

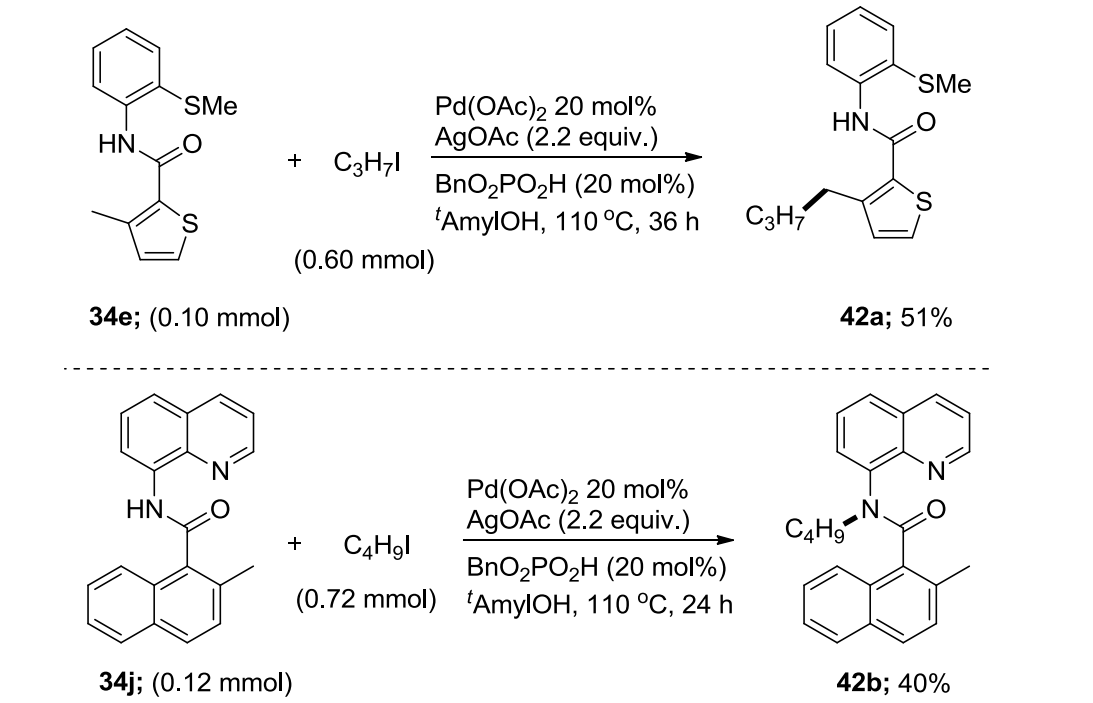


41d; 22%



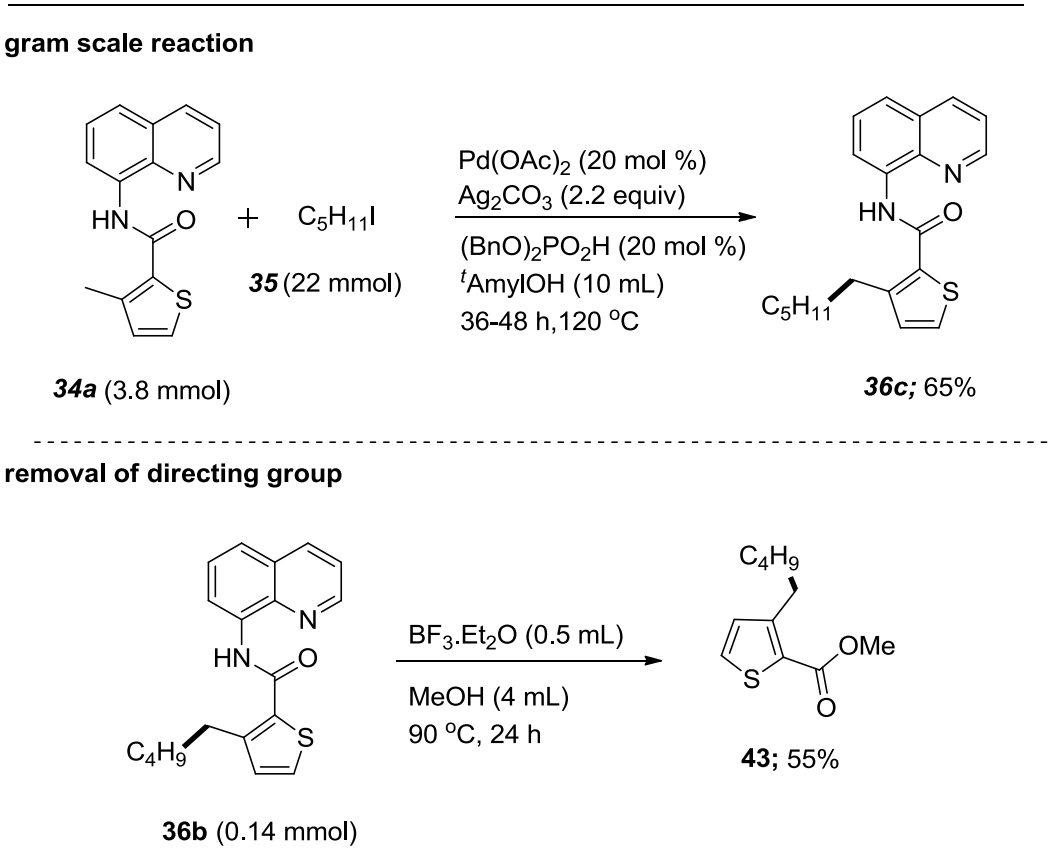
41d'; 15%

Subsequently, we also tried to explore the *γ*-alkylation on the 3-Methylthiophene-2-methylthiocarboxamide **34e** with a variety of alkyl halide **35** in the developed condition, unfortunately, in this case, only one derivative **42a** formed in pure form having the 51% of yield (Scheme 22). Then, we developed alkylation condition on substrate **34j** with iodobutane gave to the *N*-alkylated product **42b** in 40% of yield (Scheme 22).



Scheme 22 γ-C-(sp^3)-H bond alkylation on 3-Methylthiophene-2-methylthiocarboxamide **34e** substrate and substrate **34j** resulting into an unexpected product.

After successful completion of alkylation/ acetoxylation on 3-Methyl furan/thiophene-2-carboxamide and 3-Methyl benzofuran/benzothiophene-2-carboxamide derivatives, we also tested the alkylation of the γ-C-(sp^3)-H bond of the 3-Methyl thiophene-2-carboxamide system with iodopentane in a gram scale manner and this reaction afforded the product **36c** in 65% yield (Scheme 23).



Scheme 23 Gram scale reaction of γ-C-(sp^3)-H bond of 3-Methyl thiophene-2-carboxamide **34a** and removal of the bidentate ligand 8-aminoquinoline.

Finally, we wished to remove the bidentate ligand 8-aminoquinoline from the γ-C-(sp^3)-H alkylheteromethane carboxamide system.We treated the 3-pentyl thiophene-2-carboxamide substrate **36b** with $BF_3.OEt_2$ in MeOH, which successfully led to the methyl ester of methyl 3-pentylthiophene-2-carboxylic acid **43** in 55% yield (Scheme 23).

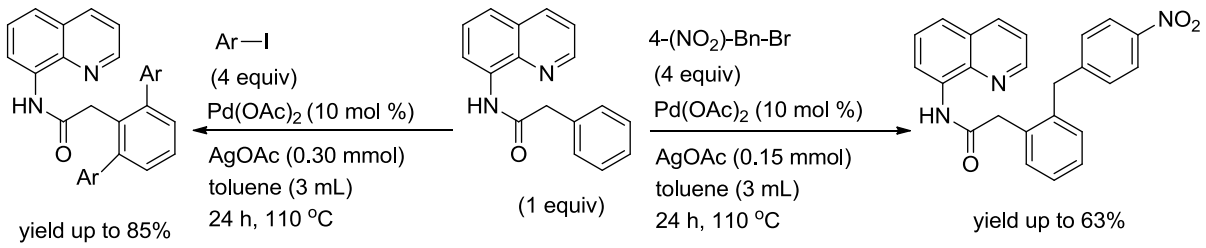
Overall, the alkylation, benzylation and acetoxylation of γ-C-(sp^3)-H bond of 3-Methyl furan/thiophene-2-carboxamide and 3-Methyl benzofuran/benzothiophene-2-carboxamides were successful. However, our attempts towards 8-aminoquinoline assisted hydroxylation and intramolecular amination were not successful. To improve the variety of derivatives, we also put our efforts towards the various kinds of alkyl iodide sources such as 1-iodo-2-nitrile ethane, allyl bromide, propargyl bromide cyclo pentyl methyl iodide, etc. Unfortunately, we could not get any desirable product. It indicates, depending on the substituents of alkyl iodides and only in specific cases, the alkylation of heteromethane carboxamides

wasobtained. The γ-C-(sp^3)-H alkylation of heterocarboxamide substituents such as 3-Methyl quinoline picolinamide, 2-Methyl quinoline naphthamide, etc., could not give any fruitful result.

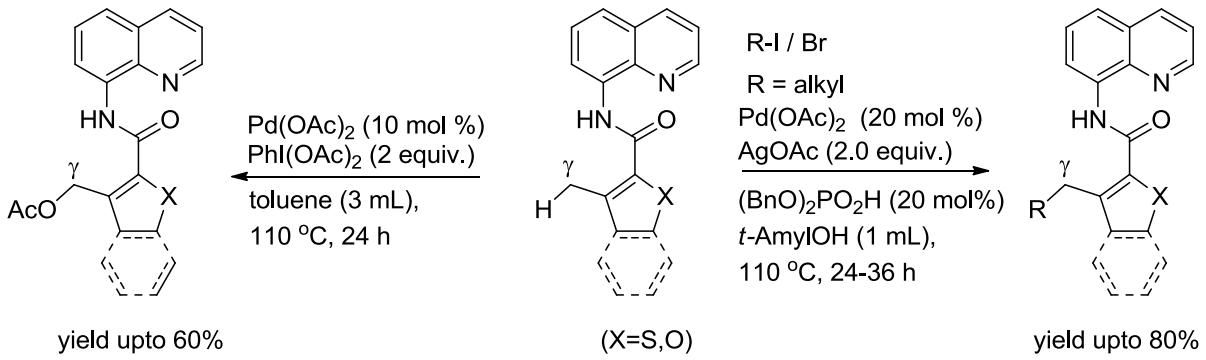
Conclusion

In summary, **Chapter 2** revealed our investigation on the Pd(II)-catalyzed, bidentate ligand-directed arylation and benzylation of γ-C-(sp^3/sp^2)-H bond of phenylacetamide and heterocarboxamide system.

The part 1 of **chapter 2** revealed the investigation on the $Pd(OAc)_2$-catalyzed γ-C-(sp^2)-H bond activation of the phenylacetamide system. Given the importance of the arylacetic acid derivatives in organic synthesis and medicinal chemistry, this method has provided access to assemble new *ortho*-substituted arylacetamides.



The part 2 of **chapter 2** revealed the Pd(II)-catalyzed alkylation, acetoxylation and benzylation of γ-C-(sp^3)-H bonds using 3-Methyl furan/thiophene-2-carboxamide and 3-Methyl benzofuran/benzothiophene-2-carboxamide system. The Pd(II)-catalyzed γ-C(sp^3)-H alkylation, acetoxylation,and benzylation led to the synthesis of a variety of thiophene/furan-based alkylheteromethane moiety and acetoxylated, diacetoxylated heteromethane scaffolds.



All the compounds included in **chapter 2** of this thesis were characterized by 1H and 13C NMR, IR and HRMS. The relevant characterization data of all compounds and complete experimental details are given in the experimental section.

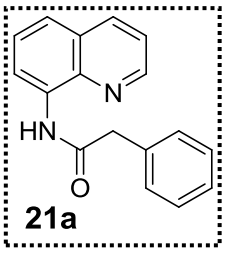
Experimental Section.

Part 1:

General. IR spectra were recorded as KBr pellets or thin films. ^{1}H / ^{13}C NMR spectra were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under a nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulfate. TLC investigation was carried out on silica gel,and the components were visualized by observation under iodine vapor. Isolated yields of all the compounds are reported, andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures.[7b, 11, 12] Characterization data of the arylated compound**s, 24a, 24b, 24e, 24g, 24k, 24l, 24o, 23o** and **27a** are reported in literature.[7c]

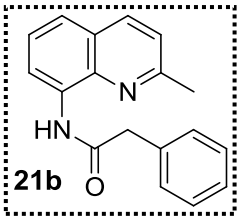
Procedure for the synthesis of phenylactamides 21a-e and 21k: A dry flask containing the corresponding amine (1 mmol) and Et_3N (121 mg, 1.2 mmol) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by drop-wise addition of the corresponding acid chloride. The resultant mixture was stirred overnight at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The composite organic layers were dried over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the raw reaction mixture by column chromatography (silica gel, 100–200 mesh, (EtOAc/hexanes = 20:80) furnished the corresponding products **21a-e** and **21k**.

2-Phenyl-*N*-(quinolin-8-yl)acetamide(21a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21a** as a dark brown color solid



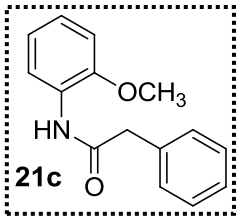
(449 mg, 68%); R_f (20% EtOAc/hexane) 0.5; mp: 91-93 ^oC; IR (KBr): 3345, 3055, 1681, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.94 (br. s, 1H), 8.79 (dd, 1H, J_1 = 7.3, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.4 Hz), 7.55-7.51 (m, 1H), 7.49 (dd, 1H, J_1 = 8.6, J_2 = 1.7 Hz), 7.46-7.40 (m, 5H), 7.38-7.33 (m, 1H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.5, 148.2, 138.4, 136.3, 134.7, 134.4, 129.6, 129.0, 127.9, 127.4, 121.6, 121.6, 116.4, 45.4; HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$ 263.1184 found 263.1177.

***N*-(2-Methylquinolin-8-yl)-2-phenylacetamide (21b):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21b** as a yellow color



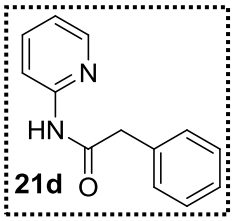
solid (480 mg, 86%); R_f (20% EtOAc/hexane) 0.5; mp: 86-88 ^oC; IR (KBr): 3307, 3055, 1679, 1532, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.97 (br. s, 1H), 8.73 (dd, 1H, J_1 = 6.9, J_2 = 2.0 Hz), 7.96 (d, 1H, J = 8.4 Hz), 7.48-7.44 (m, 4H), 7.44-7.40 (m, 3H), 7.23 (d, 1H, J = 8.4 Hz) 3.93 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.5, 157.1, 137.8, 136.2, 134.7, 133.7, 129.9, 129.2, 127.5, 126.3, 125.9, 122.3, 121.4, 116.0, 45.5, 25.0; HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1341 found 277.1333.

***N*-(2-Methoxyphenyl)-2-phenylacetamide (21c):**The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21c** as an orange color solid



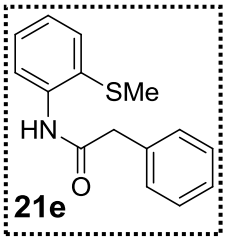
(210 mg, 72%); R_f (20% EtOAc/hexane) 0.4; mp: 85-87 ^oC; IR (KBr): 3385, 3056, 1683, 1530, 1263, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H8.42 (d, 1H, J = 6.8 Hz), 7.93 (br. s, 1H), 7.46-7.36 (m, 5H), 7.06 (td, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 6.98 (td, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 6.83 (d, 1H, J = 8.3 Hz), 3.81 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.4, 148.0, 134.6, 129.6, 129.5, 129.1, 128.6, 127.5, 127.2, 124.0, 121.1, 119.7, 110.1, 55.7, 45.1; HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181.found 242.1174.

2-Phenyl-*N*-(pyridin-2-yl)acetamide (21d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21d** as a pale yellow color solid



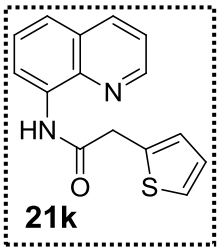
(150 mg, 89%); R_f (20% EtOAc/hexane) 0.3; mp: 115-117 ^oC; IR (KBr): 3233, 3053, 1650, 1578, 1291, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H8.25-8.22 (m, 2H), 8.12 (br. s, 1H), 7.70 (td, 1H, J_1 = 8.5, J_2 = 1.7 Hz), 7.42-7.34 (m, 5H), 7.04 (t, 1H, J = 7.6 Hz), 3.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 151.6, 147.7, 138.4, 133.9, 129.5, 129.3, 127.7, 120.0, 114.0, 45.0; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1028 found 213.1022.

***N*-(2-(methylthio)phenyl)-2-phenylacetamide (21e):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21e** as a colorless



solid (449 mg, 87%); R_f (20% EtOAc/hexane) 0.5; mp: 94-96 ^oC; IR (KBr): 3311, 3055, 1683, 1517, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H8.38 (d, 2H, J = 8.0 Hz), 7.46-7.35 (m, 6H), 7.30 (t, 1H, J = 7.1 Hz), 7.03 (t, 1H, J = 6.7 Hz), 3.82 (s, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.3, 138.5, 134.4, 133.6, 129.7, 129.3, 129.2, 127.8, 125.0, 124.3, 120.0, 45.4, 18.7;. HRMS (ESI) calcd for $C_{15}H_{16}NOS$ $[M+H]^+$ 258.0953 found 258.0946.

***N*-(Quinolin-8-yl)-2-(thiophen-2-yl)acetamide (21k):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21k** as a brown solid

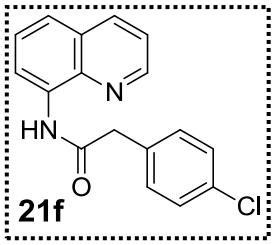


(449 mg, 68%); R_f (20% EtOAc/hexane) 0.4; mp: 70-72 ^oC; IR (KBr): 3339, 3054, 2308, 1527, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H10.0 (br. s, 1H), 8.79 (dd, 1H, J_1 = 7.1, J_2 = 1.8 Hz), 8.73 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.32 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.14 (d, 1H, J = 3.4 Hz), 7.08 (dd, 1H, J_1 = 5.2, J_2 = 3.5 Hz), 4.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.3, 148.3, 138.5, 136.3, 135.3, 134.2, 127.9, 127.5, 127.3, 125.6, 121.6, 116.4, 39.1;. HRMS (ESI) calcd for $C_{15}H_{13}N_2OS$ $[M+H]^+$ 269.0749 found 269.0742.

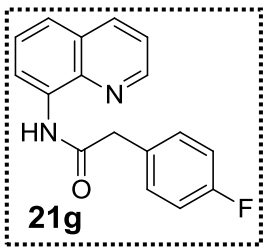
Procedure for the synthesis of phenylactamides 21f-j

A dry flask containing the corresponding carboxylic acid (1 mmol) and $SOCl_2$ (0.6 mL) was heated at 80 ^oC for 4 h under a nitrogen atmosphere. After the reaction duration, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (2 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (1 mmol), Et_3N (111 mg, 1.1 mmol) and DCM (4 mL) under a nitrogen atmosphere. The resultant mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The collective organic layers were dried over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. Purification of the impure reaction mixture by column chromatography {neutral alumina (EtOAc/hexanes = 25:75)} furnished the corresponding products **21f-j**.

2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)acetamide (21f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21f** as a yellow color solid (153 mg, 79%); R_f (20% EtOAc/hexane) 0.6; mp: 95-97 ^oC; IR (KBr): 3343, 3054, 1682, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.93 (br. s, 1H), 8.77-8.74 (m, 2H), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.56-7.50 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.39 (s, 4H), 3.88 (s, 2H) ;^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.9, 148.3, 138.4, 136.3, 134.2, 133.3, 133.2, 130.9, 129.1, 127.9, 127.3, 121.8, 121.6, 116.4, 44.5; HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O$ $[M+H]^+$ 297.0795 found 297.0788.

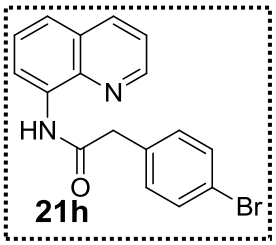


2-(4-Fluorophenyl)-*N*-(quinolin-8-yl)acetamide (21g): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21g** as a yellow color solid (197 mg, 23%); R_f (20% EtOAc/hexane) 0.5; mp: 88-90 ^oC; IR (KBr): 3345, 3054, 1682, 1529, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.93 (br. s, 1H), 8.78 (d, 1H, J = 7.2Hz), 8.72 (d, 1H, J = 4.2 Hz), 8.11 (d, 1H, J = 8.2 Hz), 7.53-7.47 (m, 2H), 7.42-7.39 (m, 3H), 7.10 (t, 2H, J = 8.6Hz), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.3, 162.2 (d, J_{C-F} = 243.6Hz), 148.2, 138.4, 136.3, 134.3, 131.2, (d, J_{C-F} =

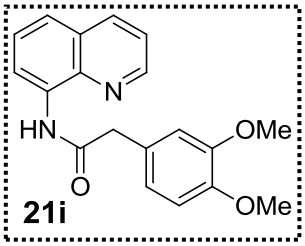


8.0Hz), 130.5 (d, J_{C-F} = 3.1Hz), 127.9, 127.3, 121.7, 121.6, 116.4, 115.8 (d, J_{C-F} = 21.2Hz), 44.3; HRMS (ESI) calcd for $C_{17}H_{14}FN_2O$ $[M+H]^+$ 281.1090found 281.1082.

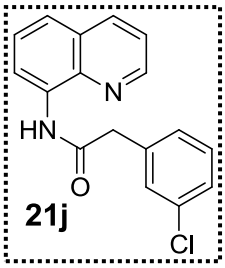
2-(4-Bromophenyl)-*N*-(quinolin-8-yl)acetamide (21h): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21h** as a brown color solid (624 mg, 52%); R_f (20% EtOAc/hexane) 0.6; mp: 104-106 ^oC; IR (KBr): 3342, 3054, 1682, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.93 (br. s, 1H), 8.76 (dd, 1H, J_1 = 7.0, J_2 = 2.0 Hz), 8.74 (dd, 1H, J_1 = 4.3, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.55-7.48 (m, 4H), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.32 (d, 2H, J = 8.4 Hz), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.8, 148.3, 138.3, 136.3, 134.2, 133.7, 132.0, 131.3, 127.9, 127.3, 121.8, 121.7, 121.4, 116.4, 44.5; HRMS (ESI) calcd for $C_{17}H_{14}BrN_2O$ $[M+H]^+$ 341.0290 found 341.0278.



2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)acetamide (21i):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21i** as a colorless solid (218 mg, 45%); R_f (20% EtOAc/hexane) 0.4; mp: 108-110 ^oC; IR (KBr): 3339, 3055, 1679, 1527, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.97 (br. s, 1H), 8.77 (dd, 1H, J_1 = 7.3, J_2 = 1.6 Hz), 8.70 (dd, 1H, J_1 = 4.2, J_2 = 1.5 Hz), 8.12 (d, 1H, J = 8.3 Hz), 7.54-7.47 (m, 2H), 7.40 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 6.99-6.97 (m, 2H), 6.91 (d, 1H, J = 8.6 Hz), 3.93 (s, 3H), 3.91 (s, 3H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.8, 149.3, 148.4, 148.2, 138.5, 136.3, 134.4, 127.9, 127.3, 127.1, 121.8, 121.6, 121.6, 116.3, 112.5, 111.5, 56.0, 55.9, 45.0;. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1396 found 323.1384.



2-(3-Chlorophenyl)-*N*-(quinolin-8-yl)acetamide (21j): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **21j** as an orange color solid (550 mg, 61%); R_f (20% EtOAc/hexane) 0.6; mp: 84-86 ^oC; IR (KBr): 3341, 3055, 1682, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.96 (br. s 1H,), 8.76 (dd, 1H, J_1 = 7.0, J_2 = 1.9 Hz), 8.74 (dd,

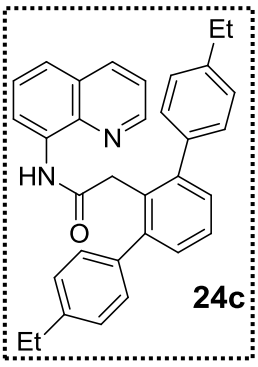


1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.54-7.46 (m, 3H), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.34-7.31 (m, 3H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.6, 148.3, 138.4, 136.6, 136.3, 134.7, 134.2, 130.2, 129.7, 127.9, 127.8, 127.5, 127.3, 121.8, 121.7, 116.4, 44.7;. HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O$ $[M+H]^+$ 297.0795 found 297.0786.

General procedure for the Pd(II)-catalyzed arylation of phenylacetamides and preparation of the compounds 24a-q / 27a-f (bis arylation products), 23o,r/ 26a,b/ 28e,f / 29a,d (mono arylation products).

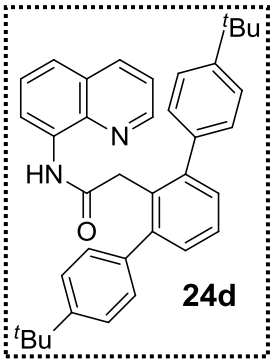
An appropriate phenylacetamide (0.12 mmol, 1equiv), an appropriate iodo compound (0.48 mmol, 4 equiv.), $Pd(OAc)_2$ (2.7 mg, 10 mol%), and AgOAc (50 mg, 0.3 mmol) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding arylated products **24a-q/27a-f** (bis arylation products), **23o,r/26a,b/28e,f/29a,d** (monoarylation products) (see corresponding Tables/Schemes for specific examples and reaction conditions).

2-(4,4''-Diethyl-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (24c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24c** as a yellow color semi-solid (45 mg, 80%); R_f (20% EtOAc/hexane) 0.7; IR (KBr): 3349, 3054, 2305, 1682, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (br. s, 1H), 8.68 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.65 (dd, 1H, J_1 = 7.1, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.49 (m, 2H), 7.47-7.45 (m, 1H), 7.44-7.40 (m, 2H), 7.38-7.34 (m, 1H), 7.35 (d, 4H, J = 8.1 Hz), 7.14 (d, 4H, J = 8.1 Hz), 3.83 (s, 2H), 2.54 (q, 4H, J = 7.6 Hz), 1.13 (t, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.2, 147.9, 143.8, 143.0, 138.9, 138.3, 136.2, 134.5, 130.7, 129.6, 129.2, 127.8, 127.7, 127.4, 127.0, 121.4, 121.2, 116.0, 40.5, 28.4, 15.3;. HRMS (ESI) calcd for $C_{33}H_{31}N_2O$ $[M+H]^+$ 471.2436 found 471.2424.

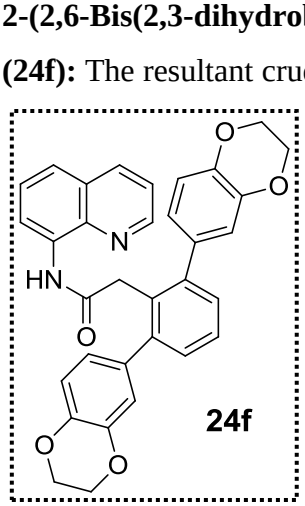


24c

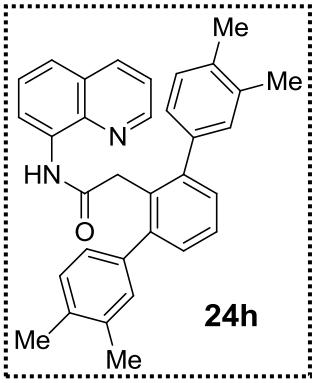
2-(4,4''-di-tert-butyl-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (24d):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24d** as a pale yellow solid (40 mg, 63%); R_f (20% EtOAc/hexane) 0.7; mp: 161-163 ^oC; IR (KBr): 3353, 3054, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ_H9.45 (br. s, 1H), 8.67-8.64 (m, 2H), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.46 (m, 3H), 7.44-7.40 (m, 1H), 7.39-7.37 (m, 6H), 7.32 (d, 4H, J = 8.5 Hz), 3.85 (s, 2H), 1.21 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.3, 149.8, 148.0, 143.8, 138.7, 136.2, 134.5, 130.8, 129.6, 128.9, 127.8, 127.4, 127.0, 125.1, 121.5, 121.2, 116.0, 40.6, 34.4, 31.2; HRMS (ESI) calcd for $C_{37}H_{39}N_2O$ $[M+H]^+$ 527.3062 found 527.3045.



2-(2,6-Bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (24f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24f** as a yellow color solid (40 mg, 63%); R_f (20% EtOAc/hexane) 0.3; mp: 98-100 ^oC; IR (KBr): 3343, 3054, 2986, 1680, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (br. s, 1H), 8.69 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.65 (dd, 1H, J_1 = 7.3, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.46 (m, 2H), 7.44-7.39 (m, 2H), 7.32 (d, 2H, J = 7.1 Hz), 6.94 (d, 2H, J = 2.0 Hz), 6.90 (dd, 2H, J_1 = 8.6, J_2 = 2.1 Hz), 6.79 (d, 2H, J = 8.2 Hz), 4.12 (s, 8H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.0, 148.0, 143.2, 143.1, 142.8, 138.3, 136.1, 135.0, 134.5, 131.0, 129.6, 127.8, 127.4, 126.9, 122.4, 121.4, 121.2, 118.3, 117.0, 116.1, 64.2, 64.2, 40.4; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_5$ $[M+H]^+$ 531.1920 found 531.1904.

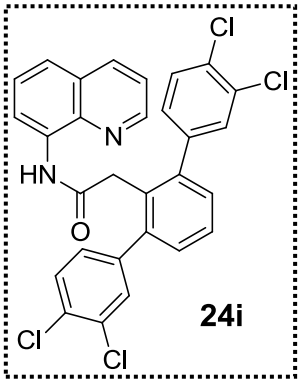


***N*-(Quinolin-8-yl)-2-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide (24h):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24h** as a colorless solid (37 mg, 66%); R_f (20% EtOAc/hexane) 0.7; mp: 99-101 ^oC; IR (KBr): 3349, 3054, 1681, 1525, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.38 (br. s, 1H), 8.71 (dd, 1H, J_1 = 4.1, J_2 = 1.3 Hz), 8.66 (dd, 1H, J_1 = 7.1, J_2 = 1.5 Hz), 8.15 (d, 1H, J = 8.0 Hz), 7.53-7.47 (m, 2H), 7.45-7.41 (m,

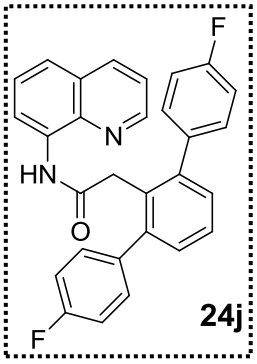


2H), 7.34 (d, 2H, *J* = 7.9 Hz), 7.20-7.18 (m, 4H), 7.07 (d, 2H, *J* = 8.1 Hz), 3.82 (s, 2H), 2.10 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.3, 147.8, 143.8, 139.2, 138.2, 136.3, 136.1, 135.4, 134.7, 130.8, 130.6, 129.5, 129.4, 127.8, 127.4, 126.8, 126.6, 121.4, 121.1, 116.0, 40.6, 19.6, 19.3; HRMS (ESI) calcd for $C_{33}H_{31}N_2O$ $[M+H]^+$ 471.2436 found 471.2422.

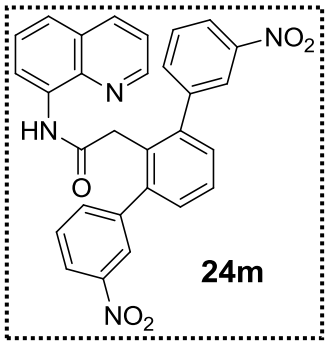
***N*-(Quinolin-8-yl)-2-(3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)acetamide (24i):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24i** as a yellow color solid (30 mg, 45%); R_f (20% EtOAc/hexane) 0.6; mp: 210-212 ^{o}C; IR (KBr): 3345, 3055, 2305, 1422, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H9.36 (br. s, 1H), 8.74 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.61 (t, 1H, *J* = 4.6 Hz), 8.17 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.54-7.51 (m, 4H), 7.48-7.42 (m, 2H), 7.36-7.29 (m, 6H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.2, 148.3, 141.5, 141.2, 138.1, 136.3, 134.0, 132.4, 131.8, 131.2, 130.7, 130.3, 130.0, 128.7, 127.9, 127.3, 127.3, 121.7, 121.6, 116.2, 40.2; HRMS (ESI) calcd for $C_{29}H_{19}Cl_4N_2O$ $[M+H]^+$ 551.0251found 551.0263.



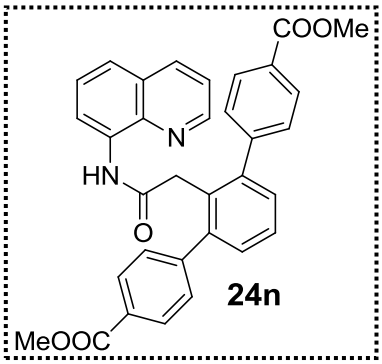
2-(4,4''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (24j): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24j** as a yellow color solid (35 mg, 64%); R_f (20% EtOAc/hexane) 0.5; mp: 116-118 ^{o}C; IR (KBr): 3345, 3055, 1681, 1525, 1262, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H9.42 (br. s, 1H), 8.69 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 5.8, J_2 = 3.2 Hz), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.52-7.50 (m, 2H), 7.46-7.39 (m, 6H), 7.34 (d, 2H, *J* = 7.4 Hz), 7.02-6.98 (m, 4H), 3.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.7, 162.2 (d, J_{C-F} = 244.6Hz), 148.1, 142.9, 138.2, 137.4 (d, J_{C-F} = 3.1Hz), 136.3, 134.2, 130.8 (d, J_{C-F} = 8.7Hz), 129.9, 127.9, 127.3, 127.1, 121.6, 121.5, 116.1, 115.3 (d, J_{C-F} = 21.2Hz), 40.3; HRMS (ESI) calcd for $C_{29}H_{21}F_2N_2O$ $[M+H]^+$ 451.1622 found 451.1607.



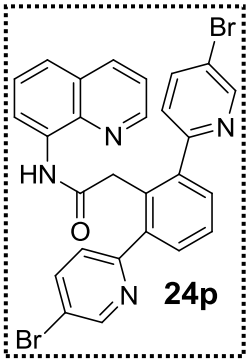
2-(3,3''-Dinitro-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (24m): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24m** as a brown color solid (30 mg, 50%); R_f (20% EtOAc/hexane) 0.3; mp: 97-99 ^oC; IR (KBr): 3340, 3054, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.32 (br. s, 1H), 8.67 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.56 (dd, 1H, J_1 = 5.6, J_2 = 3.3 Hz), 8.35 (t, 2H, J = 1.9 Hz), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 2.2, J_2 = 0.9 Hz), 8.08 (dd, 1H, J_1 = 2.1, J_2 = 0.8 Hz), 7.83 (d, 2H, J = 7.6 Hz), 7.56-7.54 (m, 1H), 7.51-7.49 (m, 3H), 7.47-7.44 (m, 2H), 7.42 (d, 2H, J = 7.6 Hz), 3.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7, 148.2, 148.1, 142.7, 141.6, 138.0, 136.4, 135.5, 133.7, 130.6, 130.4, 129.4, 127.8, 127.7, 127.3, 124.2, 122.5, 121.9, 121.7, 116.3, 40.1;. HRMS (ESI) calcd for $C_{29}H_{21}N_4O_5$ $[M+H]^+$ 505.1512 found 505.1495.



Dimethyl 2'-(2-oxo-2-(quinolin-8-ylamino)ethyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (24n): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24n** as a yellow color solid (40 mg, 63%); R_f (20% EtOAc/hexane) 0.3; mp: 144-146 ^oC; IR (KBr): 3343, 3055, 1721, 1422, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.33 (br. s, 1H), 8.65 (dd, 1H, J_1 = 4.1, J_2 = 1.6 Hz), 8.59 (dd, 1H, J_1 = 5.8, J_2 = 3.0 Hz), 8.14 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.98 (d, 4H, J = 8.2 Hz), 7.53 (d, 4H, J= 8.2 Hz), 7.51-7.49 (m, 3H), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.37 (d, 2H, J= 7.7 Hz), 3.85 (s, 6H), 3.75 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.3, 166.8, 148.0, 146.1, 143.0, 138.1, 136.2, 134.2, 130.2, 129.7, 129.6, 129.4, 129.4, 129.1, 127.8, 127.4, 127.3, 121.5, 121.4, 116.1, 52.1, 40.1; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_5$ $[M+H]^+$ 531.1920 found 531.1902.

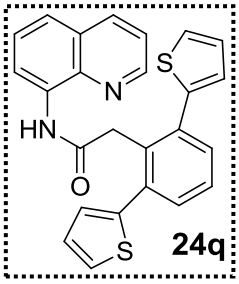


2-(2,6-Bis(5-bromopyridin-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (24p): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



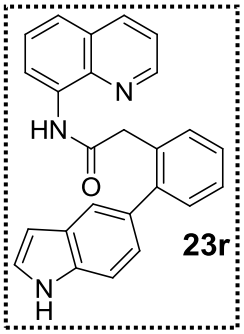
24p as a pale yellow color solid (30 mg, 44%); R_f (20% EtOAc/hexane) 0.4; mp: 209-211 ^oC; IR (KBr): 3375, 3055, 2987, 1422, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.82-8.79 (m, 3H), 8.59 (dd, 1H, J_1 = 5.8, J_2 = 3.3 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.88 (d, 1H, J = 2.4 Hz), 7.86 (d, 1H, J = 2.4 Hz), 7.52-7.48 (m, 7H), 7.45 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 4.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.7, 158.0, 150.2, 148.1, 141.1, 139.4, 136.2, 135.0, 131.5, 130.7, 128.0, 127.4, 127.3, 125.9, 121.5, 121.4, 119.6, 116.7, 39.3;. HRMS (ESI) calcd for $C_{27}H_{18}Br_2N_4NaO$ $[M+Na]^+$ 594.9745found 594.9766.

2-(2,6-Di(thiophen-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (24q): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **24q** as a



yellow color solid (36 mg, 70%); R_f (20% EtOAc/hexane) 0.2; mp: 144-146 ^oC; IR (KBr): 3338, 3055, 1681, 1525, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.73 (br. s, 1H), 8.76 (dd, 1H, J_1 = 7.3, J_2 = 1.6 Hz), 8.67 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.57-7.53 (m, 3H), 7.51 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.47-7.41 (m, 2H), 7.29 (dd, 2H, J_1 = 5.1, J_2 = 1.1 Hz), 7.15 (dd, 2H, J_1 = 3.5, J_2 = 1.1 Hz), 7.00-6.98 (m, 2H), 4.04 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.0, 148.1, 141.9, 138.4, 136.5, 136.2, 134.5, 132.6, 131.7, 127.9, 127.4, 127.3, 127.1, 126.0, 121.6, 121.5, 116.3, 41.0; HRMS (ESI) calcd for $C_{25}H_{19}N_2OS_2$ $[M+H]^+$ 427.0939 found 427.0924.

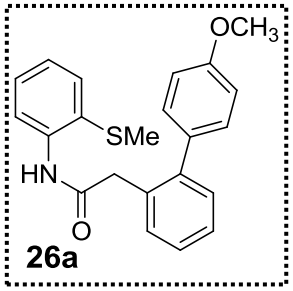
***2*-(2-(1H-Indol-5-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (23r):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **23r** as a



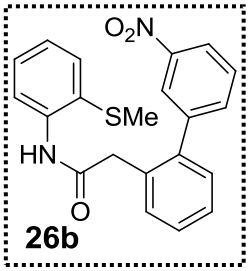
brown color solid (20 mg, 44%); R_f (20% EtOAc/hexane) 0.4; mp: 159-161 ^oC; IR (KBr): 3329, 3055, 1422, 1265, 896, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.75 (br. s, 1H), 8.74 (dd, 1H, J_1 = 7.8, J_2 = 0.8Hz), 8.65 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.23 (br. s, 1H), 8.13 (dd, 1H, J_1 = 8.3, J_2 = 1.6Hz), 7.67 (br. s, 1H), 7.58-7.56 (m, 1H), 7.53-7.49 (m, 2H), 7.46-7.38 (m, 4H), 7.25-7.22 (m, 2H), 6.51 (t, 1H, J = 2.1Hz), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.2, 148.0, 143.9, 138.4, 136.1, 135.0, 134.5, 132.8,

132.7, 131.1, 130.5, 127.9, 127.8, 127.5, 127.3, 127.2, 124.8, 123.6, 121.5, 121.4, 121.3, 116.3, 110.8, 102.8, 42.8; HRMS (ESI) calcd for $C_{25}H_{20}N_3O$ $[M+H]^+$ 378.1606 found 378.1594.

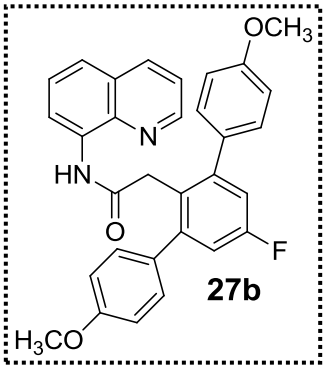
2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-*N*-(2-(methylthio)phenyl)acetamide (26a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford (**26a**) as a pale yellow color solid (25 mg, 54%); R_f (20% EtOAc/hexane) 0.5; mp: 108-110 ^oC; IR (KBr): 3309, 3055, 2305, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H8.62 (br. s, 1H), 8.47 (dd, 1H, J_1 = 8.2, J_2 = 1.0 Hz), 7.46 (dd, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 7.43-7.28 (m, 7H), 7.06 (td, 1H, J_1 = 7.6, J_2 = 1.2 Hz), 6.93 (d, 2H, J = 8.8 Hz), 5.15 (s, 1H), 3.82 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.7, 158.9, 139.4, 138.6, 133.7, 131.1, 130.2, 129.3, 129.0, 129.0, 127.5, 125.1, 124.4, 120.1, 114.4, 59.9, 55.4, 18.9; HRMS (ESI) calcd for $C_{29}H_{27}NNaO_3S$ $[M+Na]^+$ 386.1191 found 386.1190.



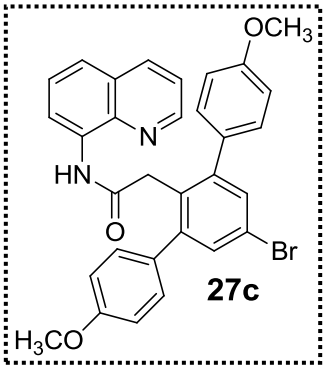
***N*-(2-(Methylthio)phenyl)-2-(3'-nitro-[1,1'-biphenyl]-2-yl)acetamide (26b):** The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **26b** as a pale yellow color solid (20 mg, 45%); R_f (20% EtOAc/hexane) 0.3; mp: 87-89 ^oC; IR (KBr): 3312, 3055, 1686, 1526, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H8.61 (br. s, 1H), 8.40 (dd, 1H, J_1 = 8.2, J_2 = 1.0 Hz), 8.27 (br. s, 1H), 8.19 (dd, 1H, J_1 = 7.5, J_2 = 1.3 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.57 (t, 1H, J = 8.0 Hz), 7.48-7.38 (m, 4H), 7.35-7.31 (m, 1H), 7.09 (td, 1H, J_1 = 1.2, J_2 = 7.6 Hz), 5.25 (s, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.9, 148.5, 141.1, 139.1, 137.7, 135.3, 133.5, 129.7, 129.5, 129.2, 129.0, 128.3, 125.4, 124.9, 124.2, 122.5, 120.3, 59.8, 18.9; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_3S$ $[M+H]^+$ 379.1116 found 379.1102.



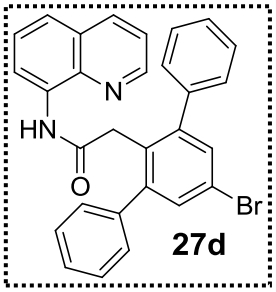
2-(5'-Fluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (27b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **27b** as a pale yellow color solid (30 mg, 61%); R_f (20% EtOAc/hexane) 0.4; mp: 145-147 ^oC; IR (KBr): 3345, 3055, 2305, 1514, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.43 (br. s, 1H), 8.71 (dd, 1H, J_1 = 4.1, J_2 = 1.9 Hz), 8.65 (dd, 1H, J_1 = 6.4, J_2 = 2.0 Hz), 8.15 (d, 1H, J = 8.2 Hz), 7.52-7.50 (m, 2H), 7.46-7.43 (m, 1H), 7.34 (d, 4H, J = 8.6 Hz), 7.07 (d, 2H, J = 9.1 Hz), 6.83 (d, 4H, J = 8.6 Hz), 3.75 (s, 2H), 3.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.0, 161.0 (d, J_{C-F} = 245.5Hz), 159.0, 148.1, 145.4 (d, J_{C-F} = 8.0Hz), 138.2, 136.2, 134.4, 133.1, 133.1, 130.1, 127.8, 127.4, 127.2 (d, J_{C-F} = 3.0Hz), 121.5, 121.3, 116.3 (d, J_{C-F} = 20.6Hz), 116.0, 113.7, 55.1, 39.8; HRMS (ESI) calcd for $C_{31}H_{26}FN_2O_3$ $[M+H]^+$ 493.1927 found 493.1931.



2-(5'-Bromo-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (27c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **27c** as an orange color solid (35 mg, 63%); R_f (20% EtOAc/hexane) 0.4; mp: 149-151 ^oC; IR (KBr): 3343, 3053, 2926, 1682, 1264, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H9.40 (br. s, 1H), 8.71 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.49 (m, 4H), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.33 (d, 4H, J = 8.7 Hz), 6.83 (d, 4H, J = 8.7 Hz), 3.74 (s, 2H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.6, 159.0, 148.1, 145.3, 138.2, 136.2, 134.4, 132.6, 132.3, 130.5, 130.2, 127.8, 127.4, 121.6, 121.4, 120.6, 116.0, 113.8, 51.1, 40.0; HRMS (ESI) calcd for $C_{31}H_{26}BrN_2O_3$ $[M+H]^+$ 553.1127 found 553.1105.

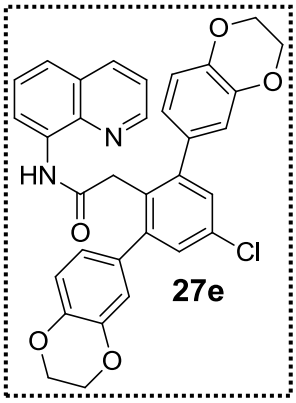


2-(5'-Bromo-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(quinolin-8-yl)acetamide (27d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **27d** as a pale red color solid (25 mg, 51%); R_f (20% EtOAc/hexane) 0.6; mp: 150-152 ^oC; IR (KBr): 3343, 3049, 1688, 1525, 1422, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (br. s, 1H), 8.70 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 6.3, J_2 = 2.6 Hz), 8.15 (dd,

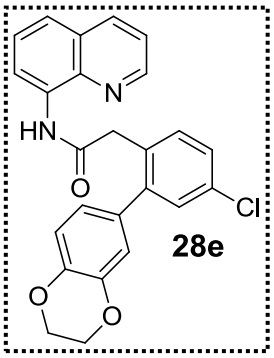


1H, J_1 = 8.3, J_2 = 1.5 Hz), 7.54 (s, 2H), 7.51-7.49 (m, 2H), 7.45-7.40 (m, 5H), 7.34-7.30 (m, 4H), 7.26 (t, 2H, J = 7.2 Hz), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.3, 148.1, 145.7, 140.2, 138.2, 136.2, 134.3, 132.3, 129.8, 129.0, 128.4, 127.8, 127.7, 127.4, 121.6, 121.4, 120.7, 116.1, 39.9; HRMS (ESI) calcd for $C_{29}H_{22}BrN_2O$ $[M+H]^+$ 493.0916 found 493.0899.

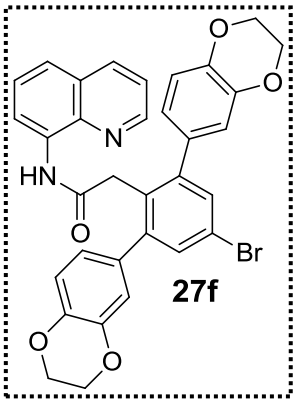
2-(4-Chloro-2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (27e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **27e** as a colorless solid (32 mg, 57%); R_f (20% EtOAc/hexane) 0.4; mp: 168-170 ^{o}C; IR (KBr): 3343, 3054, 1679, 1422, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (br. s, 1H), 8.73 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.63 (dd, 1H, J_1 = 7.0, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.47 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.3 Hz), 7.32 (s, 2H,), 6.91-6.86 (m, 4H), 6.79 (d, 2H, J = 8.2 Hz), 4.13-4.10 (m, 8H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.6, 148.1, 144.8, 143.2, 143.1, 138.2, 136.2, 134.4. 133.7, 132.3, 129.8, 129.4, 127.8, 127.5, 122.2, 121.5, 121.3, 118.1, 117.2, 116.2, 64.2, 64.2, 39.8; HRMS (ESI) calcd for $C_{33}H_{26}ClN_2O_5$ $[M+H]^+$ 565.1530 found 565.1553.



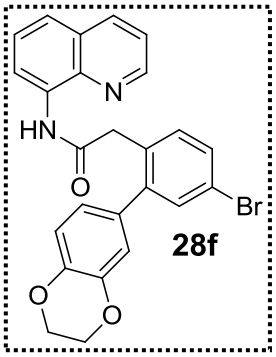
2-(4-Chloro-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (28e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **28e** as a pale yellow color solid (15 mg, 34%); R_f (20% EtOAc/hexane) 0.5; mp: 141-143 ^{o}C; IR (KBr): 3339, 3054, 2305, 1422, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H9.72 (br. s, 1H), 8.75 (dd, 1H, J_1 = 4.2, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.43 (m, 4H), 7.38-7.34 (m, 2H), 6.91-6.86 (m, 3H), 4.25-4.21 (m, 4H), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.3, 148.2, 148.2, 143.8, 143.4, 143.3, 138.3, 136.2, 134.3, 133.1, 132.9, 132.0, 131.1, 130.4, 130.4, 127.8, 127.8, 127.4, 122.3, 121.6, 118.1, 118.0, 117.4, 116.3, 64.4, 64.3, 42.0; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_3$ $[M+H]^+$ 431.1162 found 431.1156.



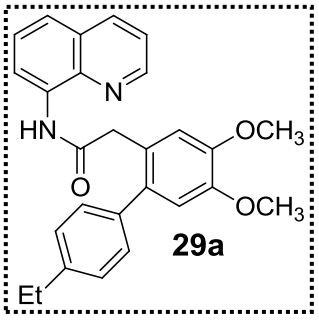
2-(4-Bromo-2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (27f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **27f** as a brown color solid (15 mg, 25%); R_f (20% EtOAc/hexane) 0.3; mp: 197-199 ^oC; IR (KBr): 3343, 3057, 1682, 1423, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (br. s, 1H), 8.73 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.63 (dd, 1H, J_1 = 7.0, J_2 = 1.9 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.47 (m, 4H), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 6.90-6.85 (m, 4H), 6.78 (d, 2H, J = 8.2 Hz), 4.13-4.10 (m, 8H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.5, 148.1, 145.0, 143.2, 143.1, 138.2, 136.2, 134.4, 133.5, 132.3, 130.3, 127.8, 127.5, 122.2, 121.5, 121.2, 120.6, 118.1, 117.2, 116.2, 64.2, 64.2, 39.9; HRMS (ESI) calcd for $C_{33}H_{26}BrN_2O_5$ $[M+H]^+$ 609.1025 found 609.1002.



2-(4-Bromo-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-*N*-(quinolin-8-yl)acetamide (28f): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **28f** as a brown color thick liquid (17 mg, 36%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): 3339, 3057, 2926, 1682, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (br. s, 1H), 8.76 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.71 (dd, 1H, J_1 = 6.6, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.53-7.50 (m, 4H), 7.45 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.40 (d, 1H, J = 8.0 Hz), 6.91-6.87 (m, 2H), 6.84 (dd, 1H, J_1 = 8.3, J_2 = 1.9 Hz), 4.25-4.21 (m, 4H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.2, 148.2, 144.1, 143.4, 143.3, 138.3, 136.3, 134.3, 133.3, 133.0, 132.2, 131.7, 130.7, 127.8, 127.3, 122.3, 121.6, 121.1, 118.1, 117.3, 116.3, 64.2, 64.3, 42.1; HRMS (ESI) calcd for $C_{25}H_{20}BrN_2O_3$ $[M+H]^+$ 475.0657 found 475.0640.

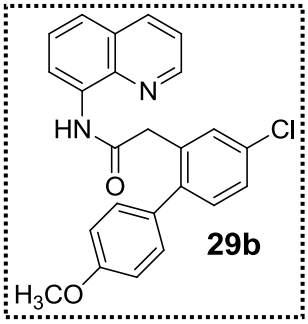


2-(4'-Ethyl-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (29a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **29a** as a yellow color solid (20 mg, 52%); R_f (20% EtOAc/hexane) 0.4; mp: 101-103 ^oC; IR (KBr): 3335, 3055, 2987, 1681, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (br. s,



1H), 8.75 (dd, 1H, J_1 = 7.1, J_2 = 1.8 Hz), 8.72 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.05 (s, 1H), 6.89 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.81 (s, 2H), 2.67 (q, 2H, J = 7.6 Hz), 1.26 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.2, 148.5, 148.1, 148.0, 143.1, 138.5, 138.3, 136.2, 135.3, 134.5, 129.4, 127.9, 127.4, 124.3, 121.6, 121.5, 116.3, 113.5, 113.2, 56.1, 56.0, 42.4, 28.5, 15.5;. HRMS (ESI) calcd for $C_{27}H_{27}N_2O_3$ $[M+H]^+$ 427.2022 found 427.2009.

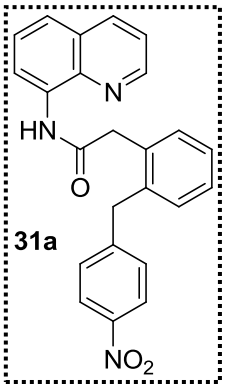
2-(4-Chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (29b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **29b** as an orange color solid (30 mg, 75%); R_f (20% EtOAc/hexane) 0.4; mp: 118-120 ^{o}C; IR (KBr): 3338, 3055, 2305, 1682, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (br. s, 1H), 8.75-8.71 (m, 2H), 8.16 (dd, 1H, J_1 = 8.2, J_2 = 1.2 Hz), 7.55-7.52 (m, 3H), 7.45 (dd, 1H, J_1 = 8.2, J_2 = 4.3 Hz), 7.36 (dd, 1H, J_1 = 8.2, J_2 = 2.0 Hz), 7.31-7.26 (m, 3H), 6.91 (d, 2H, J = 8.6 Hz), 3.83 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.0, 159.0, 148.2, 140.9, 138.4, 136.3, 134.4, 134.3, 133.3, 132.2, 131.8, 130.6, 130.3, 127.9, 127.5, 127.4, 121.7, 121.6, 116.4, 113.9, 55.2, 42.5; HRMS (ESI) calcd for $C_{24}H_{20}ClN_2O_2$ $[M+H]^+$ 403.1213 found 403.1198.



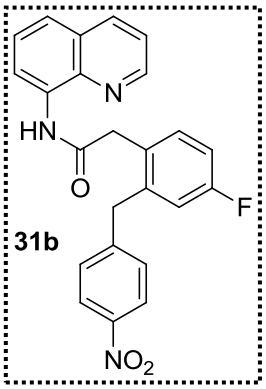
General procedure for the Pd(II)-catalyzed benzylation of phenylacetamides and preparation of the compounds 31a-d

An appropriate phenylacetamide (0.12 mmol, 1 equiv), $Pd(OAc)_2$ (2.7 mg, 10 mol%), 4-nitrobenzyl bromide (0.48 mmol, 1 equiv) AgOAc (25 mg, 0.15 mmol) in anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding benzylated compounds **31a-d** (see Tables/Schemes for specific examples).

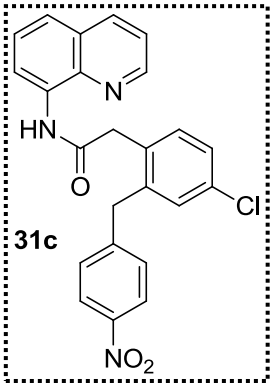
2-(2-(4-Nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (31a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **31a** as a brown color viscous liquid (26 mg, 55%); R_f (20% EtOAc/hexane) 0.3; IR (KBr): 3341, 3055, 2987, 1522, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.67 (br. s, 1H), 8.64 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.58 (t, 1H, J = 4.7 Hz), 8.14 (dd, 1H, J_1 = 8.2, J_2 = 1.6 Hz), 7.83 (d, 2H, J = 8.8 Hz), 7.49-7.46 (m, 3H), 7.44-7.40 (m, 4H), 7.24 (d, 2H, J = 8.8 Hz), 4.23 (s, 2H), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7, 148.1, 147.7, 138.2, 138.0, 136.3, 133.9, 133.5, 131.8, 131.3, 129.4, 128.3, 128.0, 127.8, 127.2, 123.6, 123.5, 121.8, 121.6, 116.2, 43.1, 39.2; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_3$ $[M+H]^+$ 398.1505 found 398.1491.



2-(4-Fluoro-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (31b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **31b** as a yellow color solid (26 mg, 63%); R_f (20% EtOAc/hexane) 0.2; mp: 94-96 ^oC; IR (KBr): 3353, 3055, 1738, 1519, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (br. s, 1H), 8.68 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.59 (dd, 1H, J_1 = 5.7, J_2 = 3.3 Hz), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.88 (d, 2H, J = 8.8 Hz), 7.49-7.42 (m, 4H), 7.25 (d, 2H, J = 8.8 Hz), 7.11 (td, 1H, J_1 = 8.3, J_2 = 2.3 Hz), 6.96 (dd, 1H, J_1 = 9.4, J_2 = 2.7 Hz), 4.20 (s, 2H,), 3.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.4 (d, J_{C-F} = 1.0Hz), 162.4 (d, J_{C-F} = 245.6Hz), 148.2, 146.7, 146.3, 140.4 (d, J_{C-F} = 7.3Hz), 138.2, 136.4, 133.8, 133.3 (d, J_{C-F} = 8.1Hz), 129.5, 129.3 (d, J_{C-F} = 3.5Hz), 127.8, 127.2, 123.6, 121.9, 121.6, 118.0 (d, J_{C-F} = 21.5Hz), 116.2, 114.7 (d, J_{C-F} = 21.0Hz), 42.3, 39.2, 39.1;. HRMS (ESI) calcd for $C_{24}H_{19}FN_3O_3$ $[M+H]^+$ 416.1410 found 416.1395.

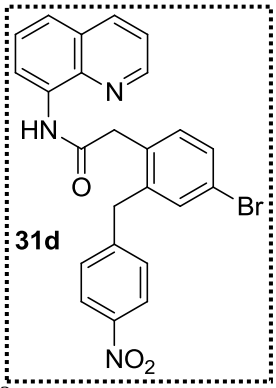


2-(4-Chloro-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (31c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



31c as a colorless solid (20 mg, 46%); R_f (20% EtOAc/hexane) 0.3; mp: 134-136 ^{o}C; IR (KBr): 3339, 3055, 1682, 1523, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (br. s, 1H), 8.69 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 8.57 (dd, 1H, J_1 = 6.1, J_2 = 2.9 Hz), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.7 Hz), 7.89 (d, 2H, J = 8.8 Hz), 7.49-7.44 (m, 3H), 7.41-7.40 (m, 2H), 7.26-7.24 (m, 3H), 4.20 (s, 2H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.1, 148.2, 146.7, 146.4, 139.9, 138.2, 136.4, 133.9, 133.8, 133.0, 132.1, 131.0, 129.4, 128.0, 127.8, 127.2, 123.7, 122.0, 121.7, 116.2, 42.4, 39.0; HRMS (ESI) calcd for $C_{24}H_{19}ClN_3O_3$ $[M+H]^+$ 432.1115 found 432.1099.

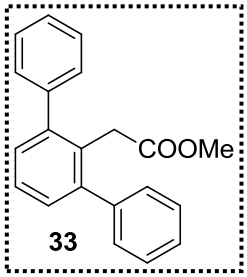
2-(4-Bromo-2-(4-nitrobenzyl)phenyl)-*N*-(quinolin-8-yl)acetamide (31d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



31d as a yellow color solid (25 mg, 59%); R_f (20% EtOAc/hexane) 0.2; mp: 139-141 ^{o}C; IR (KBr): 3339, 3054, 1681, 1523, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (br. s, 1H), 8.70 (dd, 1H, J_1 = 4.1, J_2 = 1.4 Hz), 8.57 (dd, 1H, J_1 = 6.2, J_2 = 2.7 Hz), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.4 Hz), 7.89 (d, 2H, J = 8.6 Hz), 7.55 (dd, 1H, J_1 = 8.0, J_2 = 1.8 Hz), 7.49-7.44 (m, 3H), 7.40 (d, 1H, J = 1.6 Hz), 7.35 (d, 1H, J = 8.1 Hz), 7.25 (d, 2H, J = 8.1 Hz), 4.20 (s, 2H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.0, 148.2, 146.7, 140.2, 138.1, 136.4, 133.9, 133.7, 133.3, 132.6, 131.0, 129.4, 127.8, 127.3, 123.7, 122.0, 122.0, 121.7, 116.2, 42.4, 39.0; HRMS (ESI) calcd for $C_{24}H_{19}BrN_3O_3$ $[M+H]^+$ 476.0610 found 476.0595.

Procedure for the hydrolysis of the carboxamide 24b and preparation of the compound 33: To dry flask was added the compound **24b** (1.4 mmol) dissolved in MeOH (4 mL), and then, $BF_3.Et_2O$ (0.5 mL) was added slowly, and the reaction mixture was heated at 90 °C for 24 h. After this stage, the reaction mixture was neutralized with NEt_3, and the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the compound **33**.

Methyl 2-([1,1':3',1''-terphenyl]-2'-yl)acetate (33): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford (**33**) as a viscous liquid (28 mg, 66%); R_f (20% EtOAc/hexane) 0.8; IR (KBr): 3412, 3053, 2926, 1740, 1523, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45-7.34 (m, 11H), 7.30 (d, 2H, J = 7.4 Hz), 3.53 (s, 2H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.6, 143.4, 141.6, 130.0, 129.3, 129.2, 128.2, 127.2, 126.8, 51.7, 36.9; HRMS (ESI) calcd for $C_{21}H_{19}O_2$ $[M+H]^+$ 303.1385 found 303.1374**.**

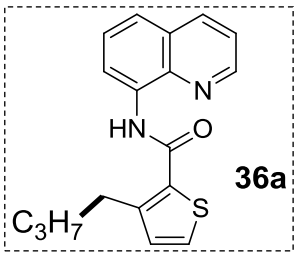


33

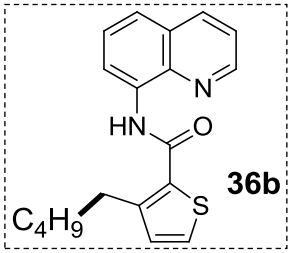
Part2: General IR spectra were recorded as KBr pellets or thin films. ^1H / ^{13}C NMR spectra were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under a nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulphate. TLC analysis was carried out on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported, andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures. Characterization data of the carboxamide starting materials, **34a-n** are reported in the literature.[13a]

General Procedure for the Pd(II)-Catalyzed alkylation of Carboxamides 34a-n and Preparation of the Compounds 36a-h, 37a-g, 38/39a-e, 40a-g and 42a. An appropriate carboxamide (0.125 mmol, 1 equiv.), an appropriate alkyl iodide (0.75 mmol, 6 equiv), $Pd(OAc)_2$ (5.6 mg, 20 mol%) and AgOAc (46 mg, 0.27 mmol, 2.2 equiv) or Ag_2CO_3 (68 mg, 0.25 mmol, 2.0 equiv) with $(BnO)_2PO_2H$ (8 mg, 20 mol%) in *tert*-AmylOH (2 mL) was heated at 110-150 ^oC for 24-48 h under a nitrogen atm. After the reaction time, 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 alkylheteroarylmethanes **36a-h, 37a-g, 38/39a-e, 40a-g** and **42a.** (see the corresponding Tables/Schemes for specific examples).

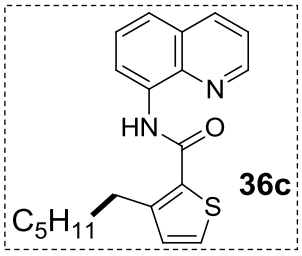
3-Butyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide*(nb 907 36a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36a** as a dirty white color solid (26 mg, 70%); R_f (20% EtOAc/hexane) 0.7; mp: 98-100 ^oC; IR (KBr): 3054, 2305, 1524, 1265, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (d, 1H, J = 7.4 Hz), 8.85 (d, 1H, J = 4.2 Hz), 8.20 (d, 1H, J = 8.3 Hz), 7.62-7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.43 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 3.16 (t, 2H, J = 8.1 Hz), 1.79 (quint., 2H, J = 7.8 Hz), 1.55-1.46 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.4, 138.6, 136.4, 134.8, 132.5, 131.1, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 33.1, 29.8, 22.8, 14.0; HRMS (ESI) calcd for $C_{18}H_{19}N_2OS$ $[M+H]^+$ 311.1218 found 311.1203.



3-Pentyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide *(nb 1342,893,888 36b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36b** as a brown color solid (30 mg, 80%); R_f (20% EtOAc/hexane) 0.65; mp: 110-112^oC; IR (KBr): 3054, 2858, 1651, 1265, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.46 (br. s, 1H), 8.88 (d, 1H, J = 7.4 Hz), 8.83-8.82 (m, 1H), 8.17 (d, 1H, J = 8.2 Hz), 7.60-7.52 (m, 2H), 7.46 (dd, 1 H, J_1 = 8.2, J_2 = 4.2Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.03 (d, 1H, J = 5.0 Hz), 3.14 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.4 Hz), 1.50-1.35 (m, 4H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.6, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 31.8, 30.6, 30.0, 22.6, 14.1; HRMS (ESI) calcd for $C_{19}H_{21}N_2OS$ $[M+H]^+$ 325.1375 found 325.1359

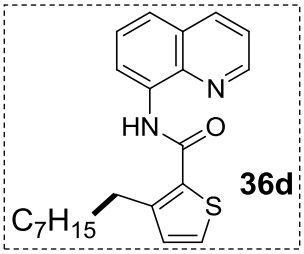


3-Hexyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide*(nb 899,896 36c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36c** as a brown color solid (28 mg, 70%); R_f (20% EtOAc/hexane) 0.7; mp: 108-110 ^oC; IR (KBr): 3054, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.47 (br. s, 1H), 8.90-8.84 (m, 2H), 8.19 (d, 1H, J = 8.2 Hz), 7.61-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 3.15 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.8 Hz), 1.48 (quint., 2H, J = 7.0 Hz), 1.38-1.31 (m,



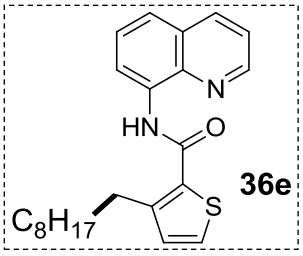
4H), 0.89 (t, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.6, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 31.7, 30.9, 30.0, 29.4, 22.7, 14.1; HRMS (ESI) calcd for $C_{20}H_{23}N_2OS$ $[M+H]^+$ 339.1531 found 339.1514.

3-Octyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide*(nb 908 36d):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36d** as a



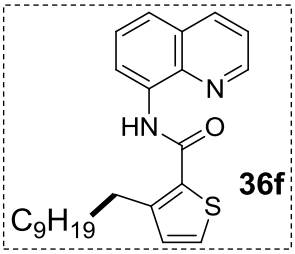
dirty white color solid (24 mg, 55%); R_f (20% EtOAc/hexane) 0.7; mp: 78-80 ^{o}C; IR (KBr): 3054,2925, 1525, 1265, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (d, 1H, J = 7.4 Hz), 8.85-8.84 (m, 1H), 8.20 (d, 1H, J = 8.2 Hz), 7.61-7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 3.15 (t, 2H, J = 8.1 Hz), 1.80 (quint., 2H, J = 7.9 Hz), 1.47 (quint., 2H, J = 7.3 Hz), 1.37-1.27 (m, 8H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.6, 136.4, 134.8, 132.5, 131.2, 128.0, 127.9, 127.5, 121.7, 121.6, 116.6, 31.9, 30.9, 30.0, 29.8, 29.5, 29.3, 22.8, 14.1; HRMS (ESI) calcd for $C_{22}H_{27}N_2OS$ $[M+H]^+$ 367.1844 found 367.1827.

3-Nonyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide*(nb 914rep 36e):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36e** as a



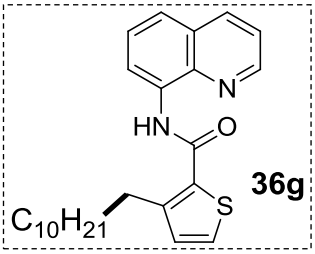
dirty white color solid (23 mg, 50%); R_f (20% EtOAc/hexane) 0.6; mp: 93-95 ^{o}C; IR (KBr): 3054, 2926, 1525, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (dd, 1H, J_1 = 7.4, J_2 = 1.5Hz), 8.85 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.21 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 7.62-7.58 (m, 1H), 7.55 (dd, 1H, J_1 = 8.3, J_2 = 1.5Hz), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 7.43 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.1 Hz), 3.15 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.9 Hz), 1.47 (qui., 2H, J = 7.3 Hz), 1.39-1.34 (m, 2H), 1.32-1.26 (m, 8H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.7, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 31.9, 30.9, 30.1, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1; HRMS (ESI) calcd for $C_{23}H_{29}N_2OS$ $[M+H]^+$ 381.2001 found 381.2019.

3-Decyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide*(nb 1106a 36f):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36f** as a



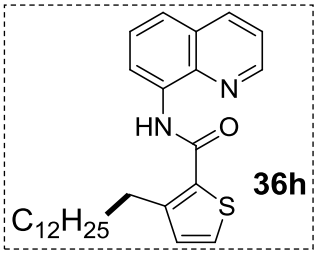
dirty white color solid (32 mg, 67%); R_f (20% EtOAc/hexane) 0.7; mp: 134-136 ^{o}C; IR (KBr): 3054, 2987, 1525, 1265, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (d, 1H, J = 7.3Hz), 8.84 (d, 1H, J = 3.3Hz), 8.20 (d, 1H, J = 7.8Hz), 7.62-7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 3.15 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.8 Hz), 1.47 (quint., 2H, J = 7.4 Hz), 1.37-1.25 (m, 12H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.7, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 31.9, 30.9, 30.0, 29.7, 29.6, 29.6, 29.5, 29.3, 22.7, 14.1; HRMS (ESI) calcd for $C_{24}H_{31}N_2OS$ $[M+H]^+$ 395.2157 found 395.2140.

N*-(Quinolin-8-yl)-3-undecylthiophene-2-carboxamide*(nb 951a 36g): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36g** as a



dirty white color solid (27 mg, 55%); R_f (20% EtOAc/hexane) 0.6; mp: 84-86 ^{o}C; IR (KBr): 3054, 2987, 1525, 1265, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (dd, 1H, J_1 = 7.4, J_2 = 1.4Hz), 8.84 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.20 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 7.62-7.58 (m, 1H), 7.55 (dd, 1H, J_1 = 8.2, J_2 = 1.5Hz), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.43 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.1 Hz), 3.15 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.9 Hz), 1.47 (quint., 2H, J = 7.3 Hz), 1.37-1.25 (m, 14H), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.6, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 31.9, 30.9, 30.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 22.7, 14.2; HRMS (ESI) calcd for $C_{25}H_{33}N_2OS$ $[M+H]^+$ 409.2314 found 409.2321.

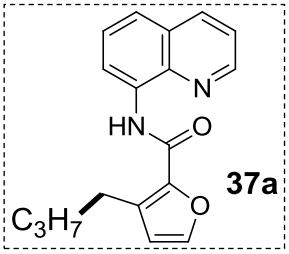
N*-(Quinolin-8-yl)-3-tridecylthiophene-2-carboxamide*(nb 988a 36h): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **36h** as a



dirty brown color solid (24 mg, 50%); R_f (20% EtOAc/hexane) 0.7; mp: 77-79 ^{o}C; IR (KBr): 2924, 1655, 1525, 1263, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.89 (dd, 1H, J_1 = 7.4, J_2 = 1.3Hz), 8.84 (dd, 1H, J_1 = 4.2, J_2 = 1.4Hz), 8.20 (dd, 1H,J_1

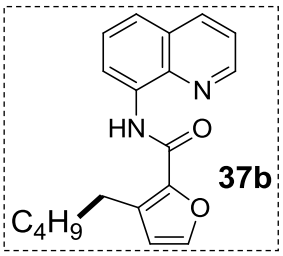
= 8.2, J_2 = 1.3Hz), 7.62-7.58 (m, 1H), 7.55 (dd, 1H, J_1 = 8.2, J_2 = 1.2Hz), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 3.15 (t, 2H, J = 8.0 Hz), 1.80 (quint., 2H, J = 7.9 Hz), 1.47 (quint., 2H, J = 7.2 Hz), 1.37-1.25 (m, 18H), 0.80 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.3, 148.2, 146.5, 138.7, 136.4, 134.8, 132.5, 131.2, 128.0, 127.8, 127.5, 121.7, 121.6, 116.6, 32.0, 31.0, 30.9, 30.6, 30.0, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 22.7, 14.2; HRMS (ESI) calcd for $C_{27}H_{37}N_2OS$ $[M+H]^+$ 437.2627 found 437.2608.

3-Butyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 1018,995a 37a):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37a** as a



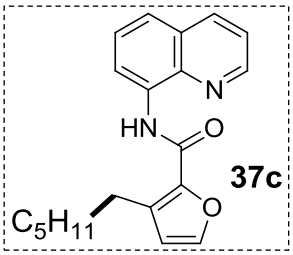
faint yellow color solid (42 mg, 42%); R_f (20% EtOAc/hexane) 0.7; mp: 141-143 ^{o}C; IR (KBr): 3054, 2925, 1531, 1265, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.77 (br. s, 1H), 8.91 (d, 1H, J = 1.3 Hz), 8.90 (t, 1H, J = 2.1 Hz), 8.20 (dd, 1H, J_1 = 8.3, J_2 = 1.6Hz), 7.60-7.56 (m, 1H), 7.54 (dd, 2H, J_1 = 10.3, J_2 = 1.7Hz), 7.50 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 6.49 (d, 1H, J = 1.7 Hz), 3.01 (t, 2H, J = 7.8 Hz), 1.68 (quint., 2H, J = 7.3 Hz), 1.50-1.41 (m, 2H), 0.98 (t, 3H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.4, 143.0, 142.2, 138.8, 136.4, 134.5, 134.0, 128.1, 127.4, 121.7, 121.5, 116.4, 114.4, 32.0, 25.2, 22.6., 14.0; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1447 found 295.1433.

3-Pentyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 927,938,959 37b):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37b** as a

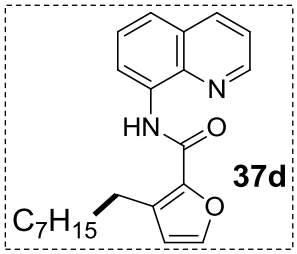


brown color solid (24 mg, 65%); R_f (20% EtOAc/hexane) 0.7; mp: 99-101 ^{o}C; IR (KBr): 3054, 2987, 1530, 1265, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.90 (d, 2H, J = 5.5 Hz), 8.21-8.19 (m, 1H), 7.60-7.53(m, 3H), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 6.49 (br. s, 1H), 3.00 (t, 2H, J = 7.6 Hz), 1.69 (quint., 2H, J = 7.6 Hz), 1.43-1.36 (m, 4H), 0.92 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.3, 143.0, 142.2, 138.8, 136.3, 134.6, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 31.6, 29.6, 25.4, 22.6., 14.1; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1603 found 309.1618.

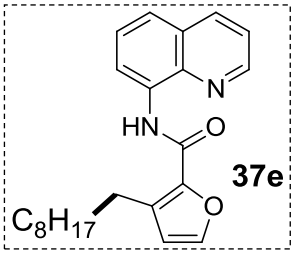
3-Hexyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 960 37c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37c** as a brown solid (231 mg, 52%); R_f (20% EtOAc/hexane) 0.7; mp: 114-116 ^oC; IR (KBr): 3054, 2956, 1672, 1265, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.91 (dd, 1H, J_1 = 2.9, J_2 = 1.5Hz), 8.89 (br. s, 1H), 8.19 (d, 1H, J = 8.2 Hz), 7.60-7.55 (m, 1H), 7.53 (d, 2H, J = 9.7Hz), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 6.49 (br. s, 1H), 3.00 (t, 2H, J = 7.9 Hz), 1.73-1.67 (m, 2H), 1.47-1.43 (m, 2H), 1.36-1.33 (m, 4H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.3, 143.0, 142.2, 138.7, 136.3, 134.5, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 31.8, 29.9, 29.2, 25.5, 22.7., 14.1; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1760 found 323.1744.



3-Octyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 996 37d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37d** as a black color solid (25 mg, 59%); R_f (20% EtOAc/hexane) 0.7; mp: 77-79 ^oC; IR (KBr): 3054, 1673, 1530, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.91-8.89 (m, 2H), 8.19 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.60-7.56 (m, 1H), 7.54 (dd, 2H, J_1 = 10.1, J_2 = 1.5 Hz), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 6.49 (d, 1H, J = 1.5 Hz), 3.00 (t, 2H, J = 7.7 Hz), 1.68 (quint., 2H, J = 7.9 Hz), 1.46-1.28 (m, 10H), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.3, 143.0, 142.2, 138.7, 136.3, 134.5, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 31.9, 29.9, 29.7, 29.5, 29.3, 25.5, 22.7., 14.1; HRMS (ESI) calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2073 found 351.2066.

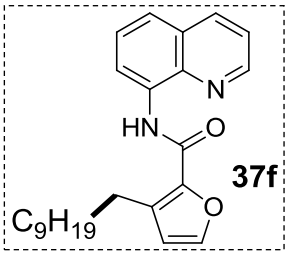


3-Nonyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 970a 37e):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37e** as a dirty brown solid (23 mg, 53%); R_f (20% EtOAc/hexane) 0.6; mp: 90-92 ^oC; IR (KBr): 3054, 2987, 1530, 1265, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.91 (dd, 1H, J_1 = 3.4, J_2 = 1.6Hz), 8.89 (d, 1H, J = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.2, J_2 = 1.5Hz), 7.60-7.56 (m, 1H), 7.53 (dd, 2H, J_1 = 9.9, J_2 = 1.6 Hz), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 6.49 (d, 1H, J = 1.6 Hz), 3.00 (t, 2H, J = 7.7 Hz), 1.68 (quint., 2H, J = 7.8 Hz), 1.44-1.28 (m, 12H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7,

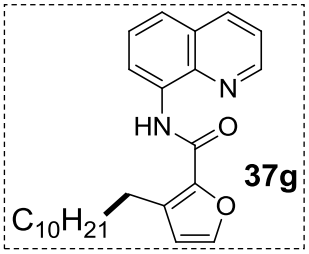


148.3, 143.0, 142.2, 138.7, 136.3, 134.5, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 31.9, 29.9, 29.6, 29.6, 29.5, 29.4, 25.5, 22.7., 14.2; HRMS (ESI) calcd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2229 found 365.2212.

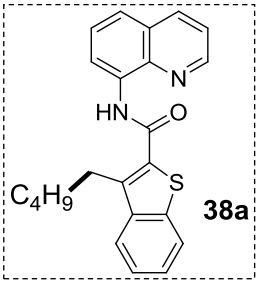
3-Decyl-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 1004a 37f):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37f** as a brown color solid (19 mg, 50%); R_f (20% EtOAc/hexane) 0.6; mp: 86-88 ^oC; IR (KBr): 3054, 2987, 1422, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.92-8.89 (m, 2H), 8.19 (dd, 1H, J_1 = 8.2, J_2 = 1.3Hz), 7.60-7.56 (m, 1H), 7.54 (dd, 2H, J_1 = 10.0, J_2 = 1.2 Hz), 7.49 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 6.49 (d, 1H, J = 1.3 Hz), 3.00 (t, 2H, J = 7.7 Hz), 1.68 (quint., 2H, J = 7.8 Hz), 1.46-1.27 (m, 14H), 0.89 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.3, 143.0, 142.2, 138.7, 136.3, 134.6, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 31.9, 29.9, 29.7, 29.6, 29.5, 29.5, 29.4, 25.5, 22.7., 14.2; HRMS (ESI) calcd for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2386 found 379.2369.



N*-(Quinolin-8-yl)-3-undecylfuran-2-carboxamide*(nb 1005a 37g): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **37g** as a black color solid (20 mg, 50%); R_f (20% EtOAc/hexane) 0.7; mp: 183-185 ^oC; IR (KBr): 3054, 2925, 1531, 1265, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.90 (d, 2H, J = 5.7 Hz), 8.20 (dd, 1H, J_1 = 8.2, J_2 = 1.3Hz), 7.60-7.56 (m, 1H), 7.54 (dd, 2H, J_1 = 10.6, J_2 = 1.3 Hz), 7.50 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 6.49 (d, 1H, J = 1.3 Hz), 3.00 (t, 2H, J = 7.7 Hz), 1.70-1.66 (m, 2H), 1.44-1.27 (m, 16H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.7, 148.3, 143.0, 142.2, 138.7, 136.3, 134.6, 134.0, 128.1, 127.4, 121.6, 121.5, 116.4, 114.4, 37.9, 29.9, 29.7, 29.7, 29.7, 29.5, 29.5, 29.4, 25.5, 22.7, 14.2; HRMS (ESI) calcd for $C_{25}H_{33}N_2O_2$ $[M+H]^+$ 393.2542 found 393.2524.

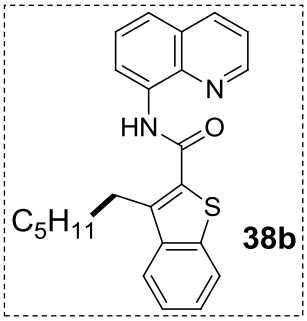


3-Pentyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide*(nb 928a,939,958 38a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **38a** as a dirty white color solid (23 mg, 62%); R_f (20% EtOAc/hexane) 0.6; mp: 140-142 ^oC; IR (KBr): 3054, 2987, 1526, 1265, 7.48 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.61 (br. s, 1H), 8.94 (d, 1H, J = 7.3Hz), 8.87 (dd, 1H, J_1 = 4.2, J_2 = 1.3Hz), 8.21 (dd,



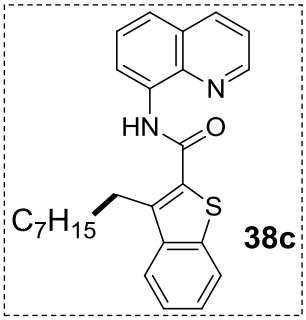
1H, J_1 = 8.2, J_2 = 1.2Hz), 7.92-7.88 (m, 2H), 7.64-7.57 (m, 2H), 7.52-7.47 (m, 3H), 3.38 (t, 2H, J = 8.2 Hz), 1.93-1.85 (m, 2H), 1.60-1.53 (m, 2H), 1.44 (sext., 2H, J = 7.6 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.7, 148.3, 141.3, 140.2, 139.4, 138.6, 136.4, 134.6, 131.9, 128.0, 127.5, 126.5, 124.6, 123.5, 122.8, 121.9, 121.8, 116.8, 32.2, 30.4, 27.8, 22.7, 14.1; HRMS (ESI) calcd for $C_{23}H_{23}N_2OS$ $[M+H]^+$ 375.1531 found 375.1514.

3-Hexyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide*(nb 967 38b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



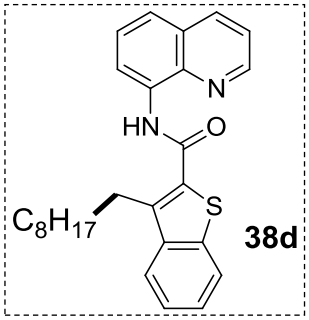
38b as a brown color solid (24 mg, 60%); R_f (20% EtOAc/hexane) 0.7; IR (KBr): 3054, 2928, 1526, 1264, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.61 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.2, J_2 = 1.6Hz), 8.87 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.22 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 7.92-7.88 (m, 2H), 7.64-7.60 (m, 1H), 7.58 (dd, 1H, J_1 = 8.3, J_2 = 1.7Hz), 7.53-7.46 (m, 3H), 3.38 (t, 2H, J = 8.1 Hz), 1.91-1.84 (m, 2H), 1.61-1.54 (m, 2H), 1.44-1.33 (m, 4H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.7, 148.3, 141.3, 140.2, 139.5, 138.7, 136.4, 134.6, 131.9, 128.0, 127.5, 126.5, 124.6, 123.5, 122.8, 121.9, 121.8, 116.8, 31.8, 30.7, 29.8, 27.8, 22.7, 14.2; HRMS (ESI) calcd for $C_{24}H_{25}N_2OS$ $[M+H]^+$ 389.1688 found 389.1671.

3-Octyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide*(nb 965 38c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



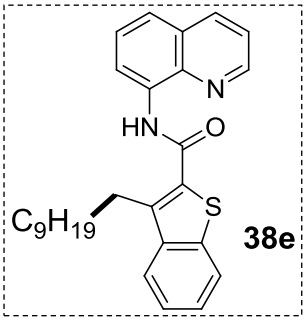
38c as a yellow color solid (25 mg, 60%); R_f (20% EtOAc/hexane) 0.6; IR (KBr): 2926, 1661, 1525, 1264, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.61 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.3, J_2 = 1.6Hz), 8.87 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.22 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 7.92-7.88 (m, 2H), 7.64-7.60 (m, 1H), 7.58 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 7.52-7.46 (m, 3H), 3.38 (t, 2H, J = 8.2 Hz), 1.87 (quint., 2H, J = 8.0 Hz), 1.57 (quint., 2H, J = 7.6 Hz), 1.43-1.26 (m, 8H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.7, 148.3, 141.3, 140.2, 139.5, 138.7, 136.4, 134.6, 132.0, 128.0, 127.5, 126.5, 124.6, 123.5, 122.8, 121.9, 121.8, 116.8, 31.9, 30.7, 30.1, 29.6, 29.4, 27.8, 22.7, 14.1; HRMS (ESI) calcd for $C_{26}H_{29}N_2OS$ $[M+H]^+$ 417.2001 found 417.1982.

3-Nonyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide*(nb 993 38d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



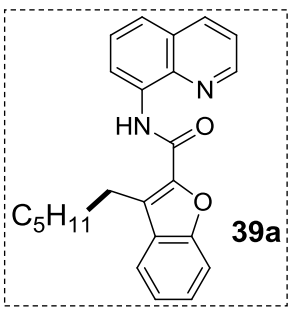
38d as a yellow viscous (30 mg, 69%); R_f (20% EtOAc/hexane) 0.6; IR (KBr): 3054, 2987, 1421, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.61 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.2, J_2 = 1.4Hz), 8.87 (dd, 1H, J_1 = 4.1, J_2 = 1.4Hz), 8.22 (dd, 1H, J_1 = 8.2, J_2 = 1.2Hz), 7.92-7.88 (m, 2H), 7.64-7.60 (m, 1H), 7.58 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.52-7.46 (m, 3H), 3.38 (t, 2H, J = 8.2 Hz), 1.87 (quint., 2H, J = 8.2 Hz), 1.59-1.53 (m, 2H), 1.45-1.36 (m, 2H), 1.30-1.25 (m, 8H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.7, 148.3, 141.3, 140.2, 139.5, 138.7, 136.4, 134.6, 132.0, 128.0, 127.5, 126.5, 124.6, 123.5, 122.8, 121.9, 121.8, 116.8, 31.9, 30.7, 30.1, 29.8, 29.7, 29.6, 29.4, 27.8, 22.7, 14.1; HRMS (ESI) calcd for $C_{27}H_{31}N_2OS$ $[M+H]^+$ 431.2157 found 431.2174.

3-Decyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide*(nb 994 38e):* The resultant



crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **38e** as a yellow color semisolid (28 mg, 66%); R_f (20% EtOAc/hexane) 0.6; IR (KBr): 3054, 2925, 1526, 1265, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.61 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.2, J_2 = 1.6Hz), 8.87 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.22 (dd, 1H, J_1 = 8.3, J_2 = 1.5Hz), 7.92-7.88 (m, 2H), 7.64-7.60 (m, 1H), 7.58 (dd, 1H, J_1 = 8.3, J_2 = 1.6Hz), 7.53-7.46 (m, 3H), 3.38 (t, 2H, J = 8.2 Hz), 1.92-1.83 (m, 2H), 1.59-1.53 (m, 2H), 1.44-1.36 (m, 2H) 1.30-1.25 (m, 10H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.7, 148.3, 141.3, 140.2, 139.5, 138.7, 136.4, 134.6, 132.0, 128.0, 127.5, 126.5, 124.6, 123.5, 122.8, 121.9, 121.8, 116.8, 31.9, 30.7, 30.1, 29.8, 29.7, 29.6, 29.3, 27.8, 22.7, 14.2; HRMS (ESI) calcd for $C_{28}H_{33}N_2OS$ $[M+H]^+$ 445.2314 found 445.2333.

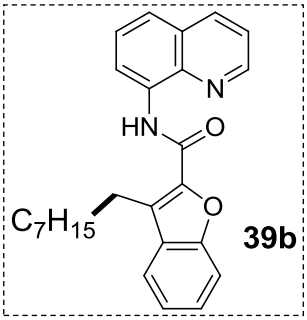
3-Hexyl-*N*-(quinolin-8-yl)benzofuran-2-carboxamide*(nb 992,1205 39a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



39a as a faint yellow color solid (17 mg, 45%); R_f (20% EtOAc/hexane) 0.7; mp: 113-115 ^oC; IR (KBr): 3054, 1672, 1530, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.04 (br. s, 1H), 8.97 (d, 2H, J = 4.8 Hz), 8.22 (d, 1H, J = 8.2 Hz), 7.73-7.68 (m,

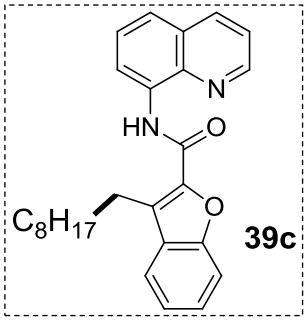
2H), 7.63-7.57 (m, 2H), 7.54-7.48 (m, 2H), 7.35 (t, 1H, *J* = 7.5 Hz), 3.28 (t, 2H, *J* = 7.6 Hz), 1.84-1.78 (m, 2H), 1.54-1.47 (m, 2H), 1.41-1.31 (m, 4H), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C158.3, 153.6, 148.5, 142.9, 138.8, 136.4, 134.4, 129.5, 128.5, 128.1, 127.4, 127.2, 123.1, 121.9, 121.7, 121.3, 116.8, 112.1, 31.8, 30.0, 29.5, 24.1, 22.7, 14.1; HRMS (ESI) calcd for $C_{24}H_{25}N_2O_2$ $[M+H]^+$ 373.1916 found 373.1900.

3-Octyl-*N*-(quinolin-8-yl)benzofuran-2-carboxamide*(nb 997 39b):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **39b** as a



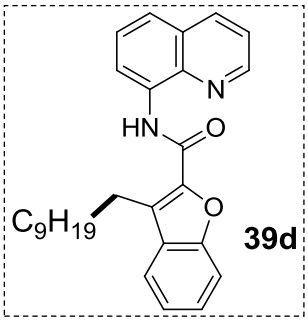
dirty yellow color solid (21 mg, 52%); R_f (20% EtOAc/hexane) 0.6; IR (KBr): 3054, 2306, 1423, 1265, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.05 (br. s, 1H), 8.98-8.96 (m, 2H), 8.22 (dd, 1H, J_1 = 8.3, J_1 = 1.6 Hz), 7.72 (d, 1H, *J* = 7.8 Hz), 7.69 (d, 1H, *J* = 8.3 Hz), 7.63-7.57 (m, 2H), 7.55-7.48 (m, 2H), 7.35 (t, 1H, *J* = 7.0 Hz), 3.27 (t, 2H, *J* = 7.7 Hz), 1.85-1.78 (m, 2H), 1.52-1.45 (m, 2H), 1.41-1.25 (m, 8H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C158.3, 153.6, 148.5, 142.8, 138.8, 136.4, 134.4, 129.5, 128.5, 128.1, 127.4, 127.2, 123.1, 121.9, 121.8, 121.3, 116.8, 112.1, 31.9, 30.0, 29.8, 29.6, 29.3, 24.1, 22.7, 14.1; HRMS (ESI) calcd for $C_{26}H_{29}N_2O_2$ $[M+H]^+$ 401.2229 found 401.2213.

3-Nonyl-*N*-(quinolin-8-yl)benzofuran-2-carboxamide*(nb 998 39c):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **39c** as a



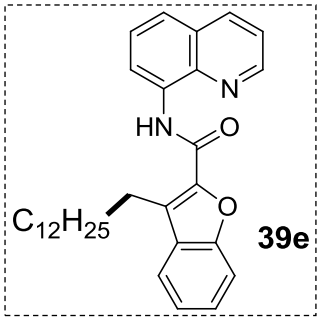
dirty brown color solid (18 mg, 42%); R_f (20% EtOAc/hexane) 0.6; mp: 95-97 ^{o}C; IR (KBr): 3054, 2927, 1673, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.05 (br. s, 1H), 8.98-8.96 (m, 2H), 8.22 (dd, 1H, J_1 = 8.3, J_1 = 1.6 Hz), 7.72 (d, 1H, *J* = 7.7 Hz), 7.69 (d, 1H, *J* = 8.3 Hz), 7.63-7.57 (m, 2H), 7.55-7.48 (m, 2H), 7.35 (t, 1H, *J* = 7.1 Hz), 3.27 (t, 2H, *J* = 7.7 Hz), 1.81 (quint., 2H, *J* = 7.5 Hz), 1.52-1.45 (m, 2H), 1.39-1.34 (m, 2H), 1.31-1.27 (m, 8H), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C158.3, 153.6, 148.5, 142.8, 138.8, 136.4, 134.4, 129.5, 128.5, 128.1, 127.4, 127.2, 123.1, 121.9, 121.7, 121.3, 116.8, 112.1, 31.9, 30.0, 29.8, 29.7, 29.6, 29.4, 24.1, 22.7, 14.1; HRMS (ESI) calcd for $C_{27}H_{31}N_2O_2$ $[M+H]^+$ 415.2386 found 415.2367.

3-Decyl-*N*-(quinolin-8-yl)benzofuran-2-carboxamide*(nb 1206 39d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **39d** as a



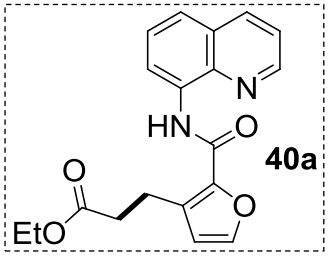
yellow color solid (30 mg, 70%); R_f (20% EtOAc/hexane) 0.7; mp: 99-101 ^oC; IR (KBr): 3054, 2987, 1531, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.05 (br. s, 1H), 8.97 (d, 2H, J = 5.1 Hz), 8.22 (d, 1H, J = 8.2 Hz), 7.73-7.68 (m, 2H), 7.63-7.57 (m, 2H), 7.54-7.48 (m, 2H), 7.35 (t, 1H, J = 7.5 Hz), 3.28 (t, 2H, J = 7.5 Hz), 1.82 (quint., 2H, J = 7.9 Hz), 1.53-1.44 (m, 2H), 1.39-1.27 (m, 12H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C158.3, 153.6, 148.5, 142.9, 138.8, 136.4, 134.4, 129.5, 128.5, 128.1, 127.4, 127.2, 123.1, 121.9, 121.7, 121.3, 116.8, 112.1, 31.9, 30.0, 29.8, 29.6, 29.6, 29.4, 25.2, 24.1, 22.7, 14.1; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_2$ $[M+H]^+$ 429.2542 found 429.2561.

N*-(Quinolin-8-yl)-3-tridecylbenzofuran-2-carboxamide*(nb 1016 39e): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **39e** as a



dirty white color solid (22 mg, 45%); R_f (20% EtOAc/hexane) 0.6; IR (KBr): 3054, 2987, 2853, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.05 (br. s, 1H), 8.98-8.96 (m, 2H), 8.22 (dd, 1H, J_1 = 8.3, J_1 = 1.6 Hz), 7.72 (d, 1H, J = 7.6 Hz), 7.69 (d, 1H, J = 8.3 Hz), 7.63-7.57 (m, 2H), 7.55-7.48 (m, 2H), 7.35 (t, 2H, J = 7.2 Hz), 3.27 (t, 2H, J = 7.7 Hz), 1.81 (quint., 2H, J = 7.7 Hz), 1.52-1.45 (m, 2H), 1.40-1.26 (m, 16H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C158.3, 153.6, 148.5, 142.8, 138.8, 136.4, 134.4, 129.5, 128.5, 128.1, 127.4, 127.2, 123.1, 121.9, 121.7, 121.3, 116.8, 112.1, 31.9, 30.0, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 24.1, 22.7, 14.2; HRMS (ESI) calcd for $C_{31}H_{38}N_2O_2$ $[M+H]^+$ 471.3012 found 471.3030.

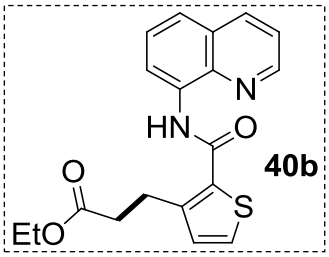
Ethyl 3-(2-(quinolin-8-ylcarbamoyl)furan-3-yl)propanoate*(nb 1130 40a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



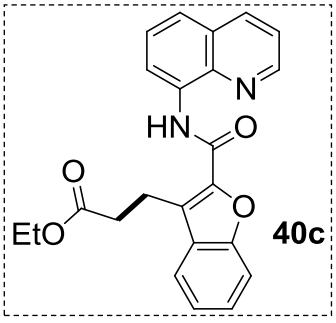
40a as a reddish brown color semisolid (17 mg, 55%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): 3055, 1731, 1533, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.77 (br. s, 1H), 8.91-8.87 (m, 2H), 8.20 (dd, 1H, J_1 = 8.2, J_1 = 1.5 Hz), 7.60-7.53 (m, 2H), 7.52

(d, 1H, J = 1.6 Hz), 7.50 (dd, 1H, J_1 = 8.3, J_2 = 4.2 Hz), 6.52 (d, 1H, J = 1.6 Hz), 4.16 (q, 2H, J = 7.1 Hz), 3.30 (t, 2H, J = 7.4 Hz), 2.75 (t, 2H, J = 7.4 Hz), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C173.0, 157.4, 148.4, 143.1, 142.5, 138.7, 136.4, 134.4, 131.9, 128.1, 127.4, 121.7, 121.7, 116.4, 114.7, 60.5, 34.3, 21.1, 14.3; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1345 found 339.1329.

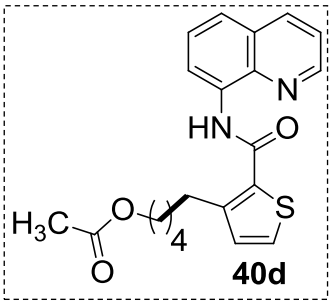
Ethyl 3-(2-(quinolin-8-ylcarbamoyl)thiophen-3-yl)propanoate*(nb 1114b 40b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **40b** as a brown color solid (17 mg, 45%); R_f (20% EtOAc/hexane) 0.5; mp: 139-141 ^{o}C; IR (KBr): 3054, 1731, 1529, 1264, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.48 (br. s, 1H), 8.86 (d, 1H, J = 1.3 Hz), 8.85-8.84 (m, 1H), 8.20 (dd, 1H, J_1 = 8.2, J_2 = 1.1 Hz), 7.62-7.55 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2, J_1 = 4.2 Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.08 (d, 1H, J = 5.0 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.46 (t, 2H, J = 7.6 Hz), 2.83 (t, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C172.9, 160.9, 148.4, 145.3, 138.6, 136.4, 134.6, 132.3, 131.4, 128.0, 127.5, 127.4, 127.4, 121.7, 116.5, 60.5, 35.0, 25.0, 14.3; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3S$ $[M+H]^+$ 355.1116 found 355.1133.



Ethyl 3-(2-(quinolin-8-ylcarbamoyl)benzofuran-3-yl)propanoate*(nb 1132 40c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **40c** as a orange color solid (15 mg, 40%); R_f (20% EtOAc/hexane) 0.4; mp: 140-142 ^{o}C; IR (KBr): 3055, 1732, 1531, 1265, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.05 (br. s, 1H), 8.97-8.94 (m, 2H), 8.22 (d, 1H, J = 7.4 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.69 (d, 1H, J = 8.2 Hz), 7.63-7.58 (m, 2H), 7.54-7.48 (m, 2H), 7.36 (t, 1H, J = 7.6 Hz), 4.12 (q, 2H, J = 7.2 Hz), 3.55 (t, 2H, J = 7.6 Hz), 2.88 (t, 2H, J = 7.6 Hz), 1.21 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C173.0, 158.0, 153.6, 148.5, 143.3, 138.8, 136.4, 134.2, 129.0, 128.1, 127.4, 127.3, 126.5, 123.4, 122.1, 121.8, 121.2, 116.8, 112.1, 60.5, 34.2, 19.5, 14.2; HRMS (ESI) calcd for $C_{23}H_{21}N_2O_4$ $[M+H]^+$ 389.1501 found 389.1518.

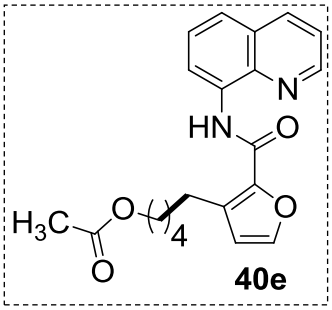


5-(2-(Quinolin-8-ylcarbamoyl)thiophen-3-yl)pentyl acetate*(nb 1188 40d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



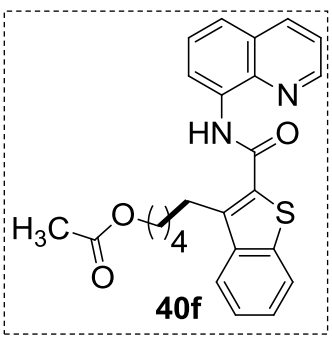
40d as a brown color solid (22 mg, 65%); R_f (20% EtOAc/hexane) 0.3; mp: 147-149 ^oC; IR (KBr): 3054, 1734, 1527, 1263, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.46 (br. s, 1H), 8.88-8.85 (m, 1H), 8.21 (d, 1H, J = 8.2 Hz), 7.62-7.55 (m, 2H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.43 (d, 1H, J = 5.0 Hz), 7.04 (d, 1H, J = 5.0 Hz), 4.08 (t, 2H, J = 6.8 Hz), 3.16 (t, 2H, J = 7.8 Hz), 2.04 (s, 3H), 1.83 (quint., 2H, J = 7.9 Hz), 1.75-1.69 (m, 2H), 1.54 (quint., 2H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C171.3, 161.2, 148.3, 146.4, 138.6, 136.4, 134.7, 132.3, 131.1, 128.0, 127.7, 127.5, 121.7, 121.7, 116.6, 64.5, 30.5, 29.8, 28.5, 26.0, 21.0; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_3S$ $[M+H]^+$ 383.1429 found 383.1413.

5-(2-(Quinolin-8-ylcarbamoyl)furan-3-yl)pentyl acetate*(nb 1189 40e):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **40e** as a



dirty brown color semisolid (13 mg, 40%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): 2937, 1734, 1528, 1262, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.76 (br. s, 1H), 8.89 (d, 2H, J = 6.4 Hz), 8.19 (d, 1H, J = 8.2 Hz), 7.60-7.53 (m, 3H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 6.48 (br. s, 1H), 4.08 (t, 2H, J = 6.6 Hz), 3.02 (t, 2H, J = 7.6 Hz), 2.06 (s, 3H), 1.76-1.69 (m, 4H), 1.49 (quint., 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C171.3, 157.7, 148.4, 143.1, 142.3, 138.7, 136.4, 134.5, 133.5, 128.1, 127.4, 121.7, 121.6, 116.4, 114.3, 64.6, 29.5, 28.4, 25.7, 25.3, 21.1; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_4$ $[M+H]^+$ 367.1658 found 367.1642.

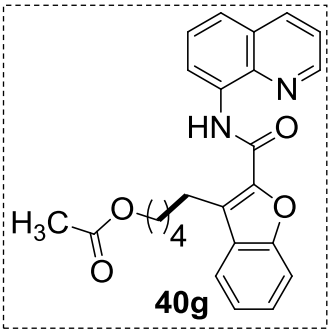
5-(2-(Quinolin-8-ylcarbamoyl)benzo[*b*]thiophen-3-yl)pentyl acetate *(nb 1190 40f):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to



afford **40f** as a black color solid (24 mg, 60%); R_f (20% EtOAc/hexane) 0.5; mp: 94-96 ^oC; IR (KBr): 3055, 2942, 1732, 1262, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.60 (br. s, 1H), 8.92 (d, 1H, J = 7.2 Hz), 8.88 (dd, 1H, J_1 = 4.0, J_2 = 1.3 Hz), 8.22 (d, 1H, J = 8.2 Hz), 7.93-7.87 (m, 2H), 7.64-7.57 (m, 2H), 7.53-

7.46 (m, 3H), 4.09 (t, 2H, J = 6.5 Hz), 3.39 (t, 2H, J = 8.0 Hz), 2.04 (s, 3H), 1.90 (quint., 2H, J = 8.0 Hz), 1.78-1.71 (m, 2H), 1.67-1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C171.3, 161.6, 148.4, 141.2, 140.1, 139.3, 138.6, 136.4, 134.5, 131.7, 128.0, 127.5, 126.6, 124.7, 123.4, 122.8, 122.0, 121.8, 116.8, 64.6, 30.3, 28.6, 27.6, 26.3, 21.0; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_3$ $[M+H]^+$ 433.1586 found 433.1568.

5-(2-(Quinolin-8-ylcarbamoyl)benzofuran-3-yl)pentyl acetate*(nb 1194,40g):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford

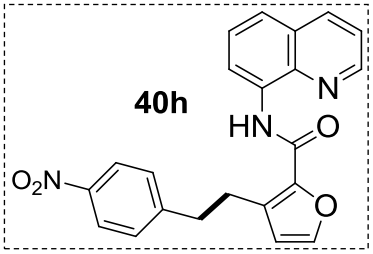


40g as a yellow color semisolid (20 mg, 55%); R_f (20% EtOAc/hexane) 0.5; IR (KBr): 2924, 1736, 1671, 1239, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.06 (br. s, 1H), 8.98-8.95 (m, 2H), 8.23 (dd, 1H, J_1 = 8.2, J_2 = 1.4 Hz), 7.71-7.68 (m, 2H), 7.63-7.58 (m, 2H), 7.55-7.49 (m, 2H), 7.36 (t, 1H, J = 7.8 Hz), 4.08 (t, 2H, J = 6.6 Hz), 3.30 (t, 2H, J = 7.6 Hz), 2.04 (s, 3H), 1.86 (quint., 2H, J = 7.8 Hz), 1.73 (quint., 2H, J = 6.9 Hz), 1.58-1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C171.3, 161.6, 148.4, 141.2, 140.1, 139.3, 138.6, 136.4, 134.5, 131.7, 128.0, 127.5, 126.6, 124.7, 123.4, 122.8, 122.0, 121.8, 116.8, 64.6, 30.3, 28.6, 27.6, 26.3, 21.0; HRMS (ESI) calcd for $C_{25}H_{24}NaN_2O_4$ $[M+Na]^+$ 439.1634 found 439.1630.

General procedure for the Pd(II)-catalyzed benzylation of Carboxamide 1b and preparation of the compounds 40h-i

An appropriate carboxamide 1b (0.125 mmol, 1 equiv.), $Pd(OAc)_2$ (3.0 mg, 10 mol%), 4-nitrobenzyl bromide (108 mg, 0.50 mmol, 4 equiv.) AgOAc (25 mg, 0.15 mmol) in anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding benzylated compounds **40h-i** (see Tables/Schemes for specific examples).

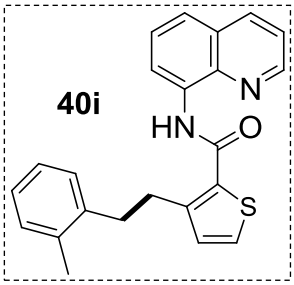
3-(4-Nitrophenethyl)-*N*-(quinolin-8-yl)furan-2-carboxamide*(nb 1135,40h):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford



40h as a faint yellow color solid (18 mg, 50%); R_f (20% EtOAc/hexane) 0.2; mp: 183-185 ^{o}C; IR (KBr): 3056, 1529, 1340, 1264, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.78 (br. s, 1H), 8.91 (d, 1H, J = 3.9 Hz), 8.88 (dd, 1H, J_1 = 7.0, J_2 =

1.5 Hz), 8.21 (d, 1H, *J* = 8.2 Hz), 8.16 (d, 2H, *J* = 8.5 Hz), 7.62-7.56 (m, 2H), 7.53-7.50 (m, 2H), 7.44 (d, 2H, *J* = 8.5 Hz), 6.36 (d, 1H, *J* = 0.9 Hz), 3.35 (t, 2H, *J* = 8.2 Hz), 3.14 (t, 2H, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C157.4, 149.4, 148.4, 146.5, 143.2, 142.7, 138.7, 136.4, 134.3, 131.7, 129.5, 128.1, 127.4, 123.6, 121.8, 121.8, 116.4, 114.4, 35.9, 26.9; HRMS (ESI) calcd for $C_{22}H_{18}N_3O_4$ $[M+H]^+$ 388.1297 found 388.1281.

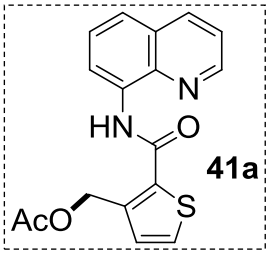
3-(2-Methylphenethyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide *(nb 1137,40i):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **40i** as a brick color solid (18 mg, 43%); R_f (20% EtOAc/hexane) 0.45; mp: 190-192 ^{o}C; IR (KBr): 3345, 3055, 1681, 1527, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.30 (d, 1H, *J* = 5.0 Hz), 8.92 (d, 1H, *J* = 7.9 Hz), 8.40 (d, 1H, *J* = 8.2 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.51 (dd, 1H, J_1 = 8.1, J_2 = 5.2 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.35 (q, 2H, *J* = 5.1), 7.04 (t, 1H, *J* = 7.9 Hz), 6.98 (d, 1H, *J* = 7.2 Hz), 6.75 (d, 1H, *J* = 7.4 Hz), 6.51 (t, 1H, *J* = 7.3 Hz), 3.35 (t, 2H, *J* = 7.4 Hz), 2.97 (t, 2H, *J* = 7.4 Hz), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 150.6, 147.1, 146.5, 144.7, 140.5, 139.7, 138.7, 138.3, 136.2, 130.6, 130.1, 129.9, 129.1, 127.3, 126.2, 126.0, 123.0, 121.5, 120.5, 33.5, 28.2, 19.2; HRMS (ESI) calcd for $C_{23}H_{21}N_2OS$ $[M+H]^+$ 373.1375 found 373.1371.



General procedure for the Pd(II)-catalyzed acetoxylation of Carboxamide 1a-d and 3b preparation of the compounds 41a-d and 41e.

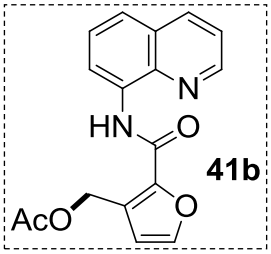
An appropriate carboxamide (0.10-0.125 mmol, 1 equiv.), $Pd(OAc)_2$ (2.4-3.0 mg, 10 mol%), $PhI(OAc)_2$ (64-80 mg, 0.20-0.25 mmol, 2 equiv.) in anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the corresponding acetoxylated compounds **41a-d** and **41e** (see Tables/Schemes for specific examples).

(2-(Quinolin-8-ylcarbamoyl)thiophen-3-yl)methyl acetate*(nb 1193 41a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41a** as a dirty brown color solid (20 mg, 60%); R_f (20% EtOAc/hexane) 0.4; mp: 121-123 ^{o}C; IR (KBr): 3096, 1737, 1531, 1253, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.51 (br. s, 1H), 8.87-8.83 (m, 2H), 8.20 (dd, 1H, J_1 = 8.2, J_2 = 1.1Hz), 7.62-7.56 (m,

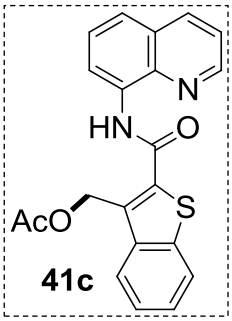


2H), 7.51-7.48 (m, 2H), 7.21 (d, 1H, J = 5.0 Hz), 5.58 (s, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.8, 160.3, 148.4, 139.7, 138.7, 136.4, 135.3, 134.5, 130.4, 128.2, 128.0, 127.4, 122.1, 121.8, 117.0, 60.7, 21.1; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3S$ $[M+H]^+$ 327.0803 found 327.0819.

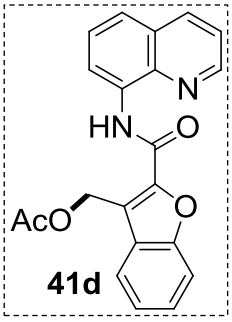
(2-(Quinolin-8-ylcarbamoyl)furan-3-yl)methyl acetate*(nb 1195 41b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41b** as a brown color solid (15 mg, 50%); R_f (20% EtOAc/hexane) 0.3; mp: 149-151 ^{o}C; IR (KBr): 3054, 1727, 1534, 1263, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.81 (br. s, 1H), 8.91-8.87 (m, 2H), 8.20 (d, 1H, J = 8.2 Hz), 7.61-7.55 (m, 3H), 7.50 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 6.65 (d, 1H, J = 1.2 Hz), 5.58 (s, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.8, 160.3, 148.4, 139.7, 138.7, 136.4, 135.3, 134.5, 130.4, 128.2, 128.0, 127.4, 122.1, 121.8, 117.0, 60.7, 21.1; HRMS (ESI) calcd for $C_{17}H_{14}NaN_2O_4$ $[M+Na]^+$ 333.0851 found 333.0835.



(2-(Quinolin-8-ylcarbamoyl)benzo[*b*]thiophen-3-yl)methyl acetate*(nb 1200b 41c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41c** as a faint yellow color solid (12 mg, 30%); R_f (20% EtOAc/hexane) 0.4; mp: 128-130 ^{o}C; IR (KBr): 3056, 1739, 1531, 1227, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.69 (br. s, 1H), 8.93 (d, 1H, J = 6.3 Hz), 8.86 (d, 1H, J = 3.8 Hz), 8.23 (d, 1H, J = 8.2 Hz), 8.02-7.93 (m, 1H), 7.66-7.61 (m, 2H), 7.54-7.50 (m, 3H), 5.82 (s, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.9, 157.4, 153.8, 148.6, 144.6, 138.8, 136.4, 134.0, 128.1, 127.9, 127.6, 127.4, 123.9, 122.4, 122.0, 121.9, 121.6, 117.1, 112.3, 56.8, 21.0; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_3S$ $[M+H]^+$ 377.0960 found 377.0942.

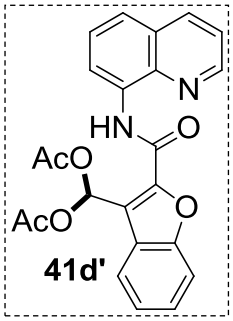


(2-(Quinolin-8-ylcarbamoyl)benzofuran-3-yl)methyl acetate*(nb 1204a 41d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41d** as a brown color solid (9 mg, 22%); R_f (20% EtOAc/hexane) 0.4; mp: 158-160 ^{o}C; IR (KBr): 3055, 1740, 1532, 1264, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.11 (br. s, 1H), 8.98-8.95 (m, 2H), 8.23 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.85 (d, 1H, J = 7.8 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.64-7.60 (m, 2H), 7.56-7.52 (m, 2H), 7.39 (t, 1H, J = 7.5 Hz), 5.90

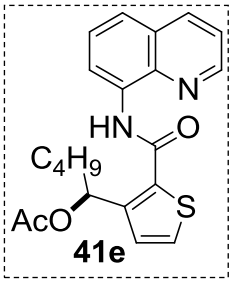


(s, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.9, 157.4, 153.6, 148.6, 144.6, 138.8, 136.4, 134.0, 128.1, 127.9, 127.6, 127.4, 123.9, 122.4, 122.0, 121.9, 121.6, 117.0, 112.3, 56.8, 21.0; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_4$ $[M+H]^+$ 361.1188 found 361.1206.

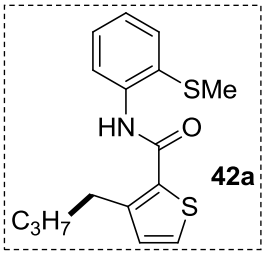
(2-(Quinolin-8-ylcarbamoyl)benzofuran-3-yl)methylene diacetate*(nb 1204b 41d'):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41d'** as a brown color solid (6 mg, 15%); R_f (20% EtOAc/hexane) 0.3; mp: 230-232 ^{o}C; IR (KBr): 3054, 1764, 1532, 1264, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.10 (br. s, 1H), 9.01 (t, 1H, J = 4.4 Hz), 8.96 (d, 1H, J = 4.0 Hz), 8.88 (br. s, 1H), 8.23 (d, 1H, J = 8.2 Hz), 8.01 (d, 1H, J = 7.8 Hz), 7.75 (d, 1H, J = 8.4 Hz), 7.61 (d, 2H, J = 4.5 Hz), 7.57-7.52 (m, 2H), 7.42 (t, 1H, J = 7.6 Hz), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.3, 156.5, 153.8, 148.6, 144.9, 138.7, 136.4, 133.7, 128.0, 127.6, 127.4, 126.1, 124.2, 122.8, 122.5, 121.8, 120.8, 117.5, 112.4, 85.3, 20.9; HRMS (ESI) calcd for $C_{23}H_{18}NaN_2O_6$ $[M+Na]^+$ 441.1063 found 441.1086.



1-(2-(Quinolin-8-ylcarbamoyl)thiophen-3-yl)pentyl acetate*(nb 1165 41e):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **41e** as a yellow color solid (10 mg, 15%); R_f (20% EtOAc/hexane) 0.4; mp: 114-116 ^{o}C; IR (KBr): 2930, 1661, 1529, 1263, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.54 (br. s, 1H), 8.86 (d, 2H, J = 6.2 Hz), 8.20 (dd, 1H, J_1 = 8.2, J_2 = 0.4Hz), 7.62-7.54 (m, 3H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 4.2Hz), 7.43 (d, 1H, J = 5.1 Hz), 7.40-7.36 (m, 1H), 7.20 (d, 1H, J = 5.1 Hz), 6.62 (t, 1H, J = 6.6 Hz), 2.11 (s, 3H), 2.01-1.96 (m, 2H), 1.43-1.35 (m, 4H), 0.90 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.3, 160.4, 48.3, 140.1, 138.8, 136.3, 134.6, 132.6, 128.0, 128.0, 127.6, 127.4, 121.9, 121.7, 117.0, 71.5, 35.7, 27.6, 22.5, 21.2, 14.0; HRMS (ESI) calcd for $C_{21}H_{22}NaN_2O_3S$ $[M+Na]^+$ 405.1249 found 405.1231.



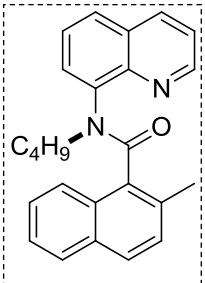
3-Butyl-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide*(nb 1238a 42a):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **42a** as a dirty white color solid (16 mg, 51%); R_f (10% EtOAc/hexane) 0.7; mp: 129-131^{o}C; IR (KBr): 3345, 3055, 1681, 1527, 1265, 745 cm$^-$



[1]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.16 (br. s, 1H), 8.54 (d, 1H, *J* = 8.3 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.39-7.36 (m, 2H), 7.08 (t, 1H, *J* = 7.5 Hz), 6.98 (d, 1H, *J* = 4.9 Hz), 2.78 (t, 2H, *J* = 7.4 Hz), 2.67 (s, 3H), 1.57 (quint., 2H, *J* = 7.3 Hz), 1.41 (sext., 2H, *J* = 7.1 Hz), 0.88 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.0, 142.1, 139.9, 135.4, 132.5, 131.7, 129.7, 127.5, 124.0, 123.1, 120.0, 36.3, 31.6, 21.8, 16.1, 13.6; HRMS (ESI) calcd for $C_{16}H_{20}NOS_2$ $[M+H]^+$ 306.0986 found 306.1001.

General Procedure for the Pd(II)-Catalyzed N-alkylation of Carboxamides 34j and Preparation of the Compound 42b. An appropriate carboxamide (0.12 mmol, 1 equiv), an appropriate alkyl iodide (0.72 mmol, 6 equiv.), $Pd(OAc)_2$ (5.6 mg, 20 mol%) and AgOAc (46 mg, 0.27 mmol, 2.2 equiv.) with $(BnO)_2PO_2H$ (8 mg, 20 mol%) in *tert*-AmylOH (2 mL) was heated at 110-150 ^{o}C for 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 N-alkylated carboxamide **42b** (see the corresponding Tables/Schemes for specific examples).

N*-Butyl-2-methyl-*N*-(quinolin-8-yl)-1-naphthamide*(nb 1087a 42b):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **42b** as a

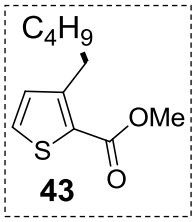


42b

dirty white color solid (15 mg, 40%); R_f (20% EtOAc/hexane) 0.6; mp: 123-125^{o}C; IR (KBr): 3345, 3055, 1681, 1527, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.94 (dd, 1H, J_1 = 4.1, J_2 = 1.6Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 7.96 (dd, 1H, J_1 = 8.0, J_2 = 0.7Hz), 7.66 (d, 1H, *J* = 7.9 Hz), 7.60 (d, 1H, *J* = 8.4 Hz), 7.39-7.31 (m, 3H), 7.25 (d, 1H, *J* = 8.1 Hz), 7.13 (d, 1H, *J* = 8.4 Hz), 7.01 (t, 1H, *J* = 7.6 Hz), 6.76 (d, 1H, *J* = 7.2 Hz), 4.79 (t, 2H, *J* = 6.3 Hz), 2.41 (s, 3H), 1.93 (quint., 2H, *J* = 7.5 Hz), 1.58 (sext., 2H, *J* = 10.2 Hz), 1.03 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C160.6, 149.2, 145.0, 142.3, 135.8, 134.0, 131.3, 131.0, 130.0, 128.7, 128.7, 128.0, 127.7, 126.3, 126.2, 125.9, 125.1, 122.7, 120.9, 118.9, 67.2, 31.0, 20.5, 19.5, 14.0; HRMS (ESI) calcd for $C_{25}H_{25}N_2O$ $[M+H]^+$ 369.1967 found 369.1957.

General procedure for thehydrolysis of carboxamide 36b and Preparation of the carboxylate derivative 43. To a solution of 3-(4-methoxybenzyl)-*N*-(quinoline-8-yl)thiophene-2-carboxamide **36b** (50-60 mg, 0.12-0.14 mmol, 1 equiv.) in dry methanol (3 mL), $BF_3.Et_2O$ (0.5 mL) was added dropwise. Then, the resulting mixture was stirred at 90 °C for 24 h. The reaction mixture was neutralized with NEt_3,and the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the crude reaction mixture by column chromatography furnished the compound **43.**

Methyl 3-pentylthiophene-2-carboxylate*(nb 1212 43):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **43** as a yellow color semisolid (16 mg, 55%); R_f (20% EtOAc/hexane) 0.7; IR (KBr): 3053, 2928, 1657, 1527, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H, 7.41 (d, 1H, *J* = 5.0 Hz), 6.98 (d, 1H, *J* = 5.0 Hz), 3.88 (s, 3H), 3.02 (t, 2H, *J* = 7.6 Hz), 1.64 (quint., 2H, *J* = 7.3 Hz), 1.37-1.34 (m, 4H), 0.91 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.1, 151.7, 130.7, 130.1, 126.1, 51.7, 31.7, 30.2, 29.6, 22.5, 14.1; HRMS (ESI) calcd for $C_{11}H_{17}O_2S$ $[M+H]^+$ 213.0949 found 213.0950.



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(2) For selected reviews of remote functionalizations see (a) Dey, A.; Maity, S.; Maiti, D. *Chem. Commun*., **2016**, *52*, 12398. (b) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.*,**2013**, *135*, 5877. (c) Tobisu, M.; Chatani, N., *Science*, **2014**, *343*, 850. (d) Topczewski, J. J.; Sanford, M. S. *Chem. Sci*.**2015**, *6*, 70.

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Chapter 3

4-amino-2,1,3-benzothiadiazole (ABTD) assisted Pd(II)-catalyzed: β-γ-C-(sp^2)-H bond arylation/benzylation/Acetoxylaton and amination of aryl carboxamide

A new bidentate auxiliary 4-amino-2,1,3-benzothiadiazole (ABTD) discloses a new method for direct arylation, benzylation, acetoxylation/ intramolecular cyclization or amination of β-γ-C-(sp^2)-H bonds in various types of carboxamide system. Understandably, the immense potential of C-H activation for organic and medicinal transformations using metal catalysts realized in powerful and proficient methods for C-C, C-O and C-N bond formation over the years.[1] Several bidentate directing groups were known in the literature for Pd-catalyzed direct C-C, C-O and C-N coupling.[2-7] However, functionalized by a bidentate auxiliary or directing groups in the agreement of organometallic catalysts powerful tool to achieve important transformations, which provides a convenient route in these fields.[9-16] Given the importance of the C-H activation/functionalization strategy in organic synthesis and the availability of other bidentate directing groups are still emerging, and their limitation or scope scrutinized. Henceforth, given the significance and the development of C-H activation/functionalization approaches in the organic synthesis, leading the research area pertaining to the bidentate directing groups enabled C-H activation/functionalization by a new bidentate directing group, 4-amino-2,1,3-benzothiadiazole (ABTD)[16], to achieve a powerful Pd metallacycle transition state and the availability of commercially available with the scope and limitation of bidentate directing groups for site-selective β-γ-C-(sp^2)-H activation and arylation of aromatic and aliphatic carboxamides and various suitable substrates.

a) Application of functionalized benzothiadizoles

Benzothiadiazole is a nitrogen-sulphur containing heteroarene moiety possessing a range of unique bioactive molecules and bioisostatic replacement properties showing outstanding characteristics of functional groups. The benzothiadiazole-thiophene motif derivative is based on a donor-acceptor assembly developed for high-performance optoelectronic materials.[17]However, the atom economical C–C cross-coupling reactions are attractive and sustainable approaches towards the synthesis of functionalization of molecules.Benzothiadiazolecore containing molecules are most commonly used in medicinal applications such as timolol, useful for the treatment of glaucoma and tizanidine, which is

sometimes used to treat multiple sclerosis and also used as a muscle relaxant. Benzothiadiazolehas also been incorporated into a wide variety of biologically activecompounds including cephalosporinand oxazolidinonebased antibacterial agents, thiadiazole thione derivatives agrochemical fungicideshave been patented as novel bleach catalysts for fabric detergents.[17] Various substituted benzothiadiazole have been approved as antimicrobial agents in particular for marine microorganisms(Figure 1). Benzothiadiazole structurally resembles 8-aminoquinoline, due to which it is developed as an important bidentate directing group or ligand auxiliary in the area of C-H activation.

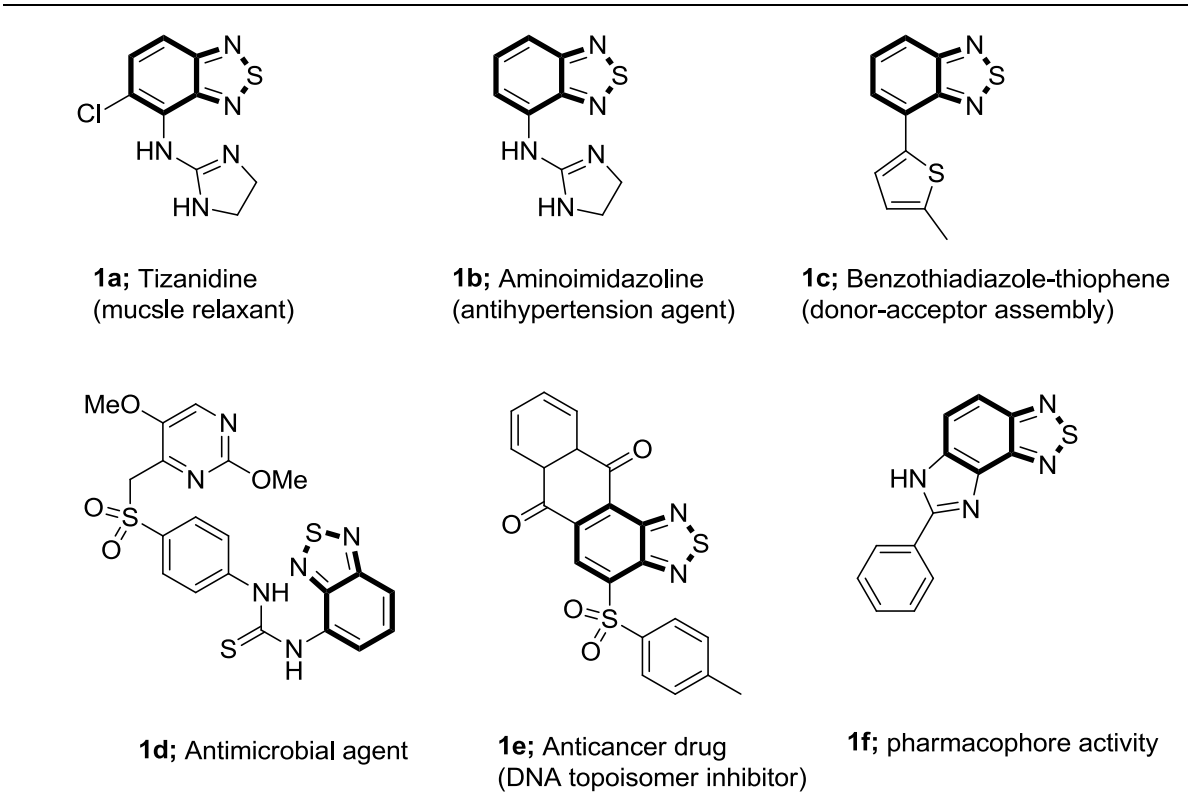


Figure 1 The biologically active molecule is featuring benzothiadiazole motif (**1a-1f**).

b) Application of functionalized benzamides

Benzamides and their substituents such as mono,bis-aryls and oxygenated molecules are essential scaff olds that are present in a variety of pharmaceutical, dyes, organic materials, and agrochemically significant compounds.[18] Thus, significant interest has been paid towards the synthesis of these motifs for more than a century.[19]Benzamides are the essential core units found in various natural products and biologically active molecules.[21] For example these molecule constitute the core of some of the valuable compounds such as a)

benzamideriboside (antineoplastic agent) b) tazematostat (EZH2 inhibitors) as neurotrophin activity enhancers. Aspirin is used in treating the physical effects of anxiety and nitazoxamides, antiractamare generally used as an antiviral/ neurotransmitter inhibitor activity. Despite these significant advances, there is always a demand for the development of a new methodology toward the synthesis of mono/ bis-aryl benzamide molecules under newly developed reaction conditions in sustainable manner (Figure 2).

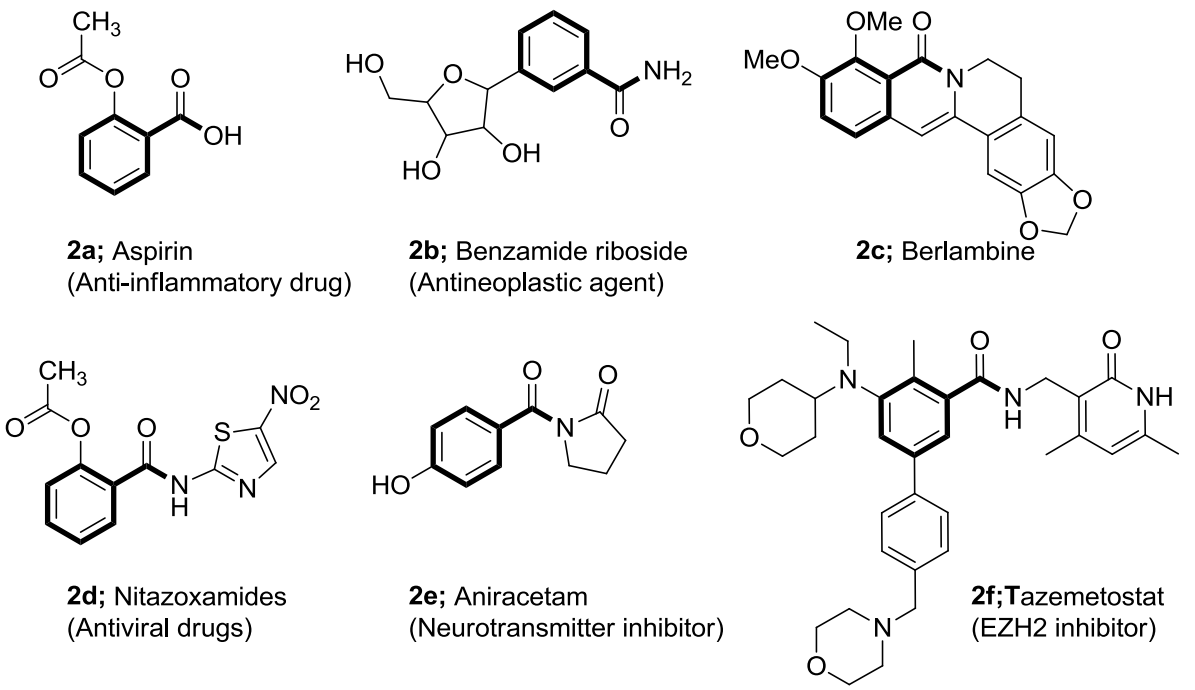


Figure 2 A biologically active molecule is containing benzamides (**2a-2f**).

c) Application of functionalized indolinones

The indolinone framework is a privileged heterocyclic scaffold that occurs in a large number of biologically active, natural products such as alkaloids and medicinally active compounds[21], which act as anticonvulsant agents, an antimicrobial agent, antimalarial agent, and pharmacophore agent (Figure 3). Indolinone and their derivatives are the groundwork of a large area of chemistry, owing to their fruitful synthetic applications towards targets significant to natural product chemistry and medicine.[21]

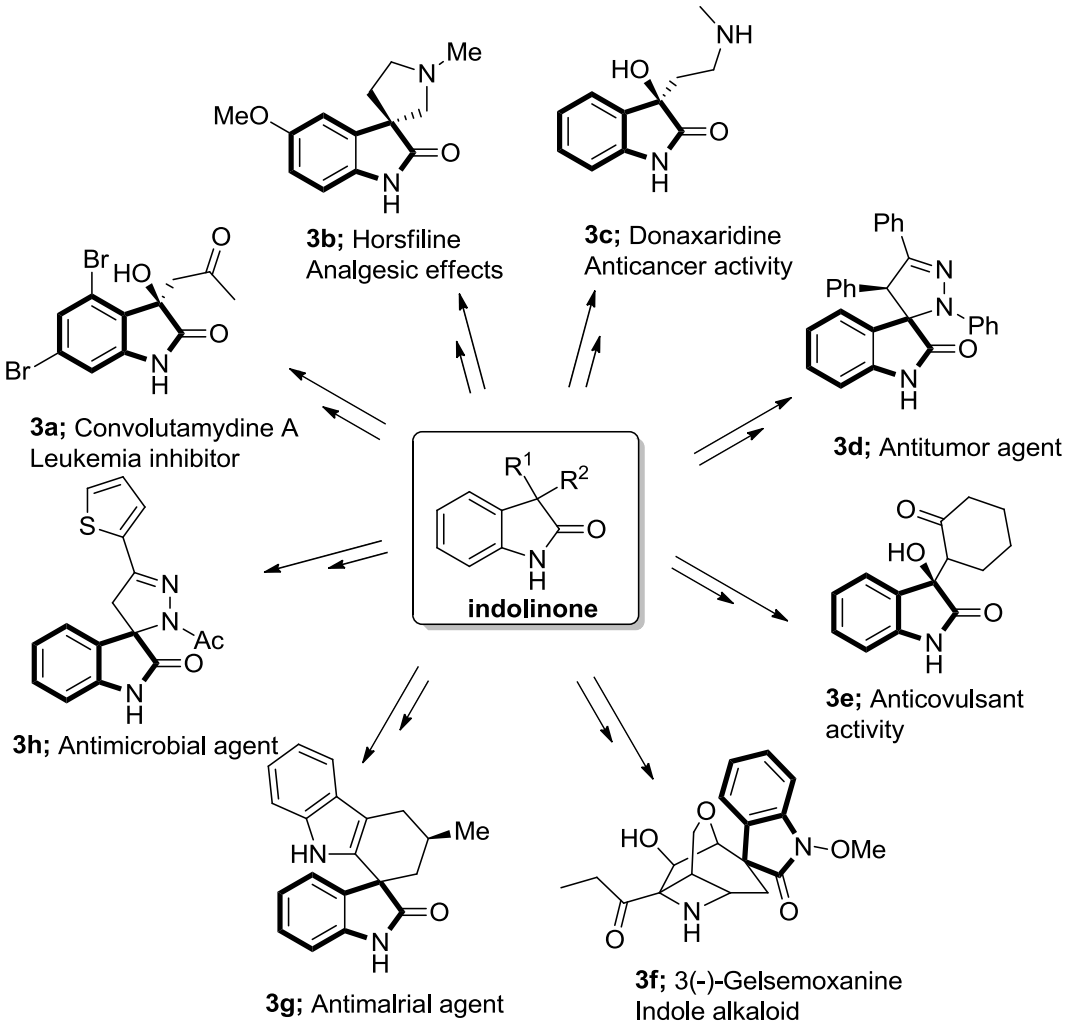
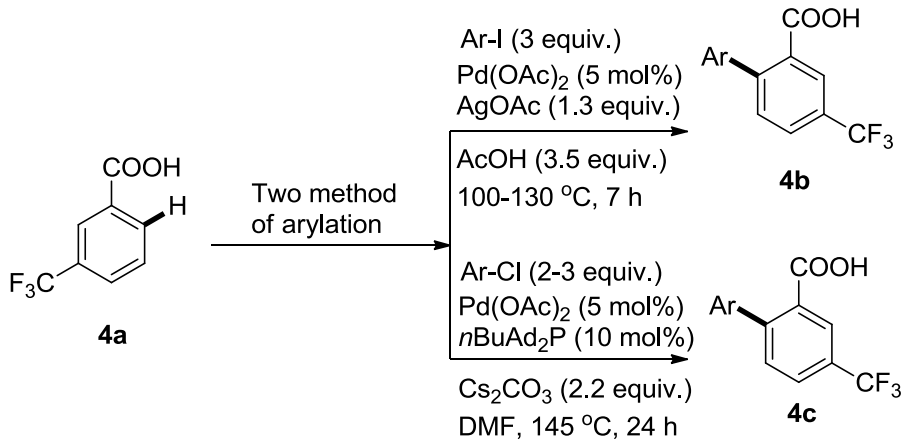


Figure 3 Natural product and biologically active molecules containing indolinone core (**3a-3h**).

Even though the indolinone core is having structural similarities with the isatin molecule, still a direct and an integrated synthetic platform for making these motifs remains difficult.Thus, the development of efficient approaches for the synthesis of the indolinone framework is a continuing interest in organic synthesis. Generally, they are prepared by standard procedures such as reduction of isatins[21], oxidation of the indoles.[21]All these procedure involves the synthesis of isatin molecule, which is classically achieved by traditional methods employing harsh conditions. DevelopmentofaPd-catalyzed cyclization by C-H activation was found to be a famous landmark in this area, as it provides a robust alternative route to parent indolinone.

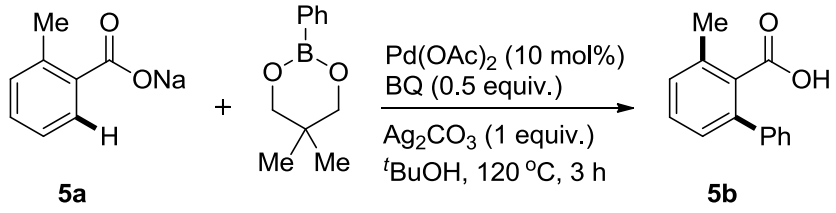
Representative reports dealing with different mono/bidentate directing groups of β-γ-C-(sp^2)-H bond functionalization of benzamide and phenylacetamide system, which are related to the result of this work.

Daugulis and co-workers[22a] developed two new methods of C-H activation by using benzoic acid as a model substrate for direct ortho-arylation. The first method involves the use of a catalytic amount of palladium acetate (5 mol%), 1.3 equiv.of silver acetate, and an aryl iodide coupling partner in 3.5 equiv. of acetic acid at 100-130 ^{o}C for 7 h, which lead to the product **4b** (Scheme 1). This method is also useful for chloro and bromo substitution and most likely proceeds through a Pd-(II)-Pd(IV) coupling cycle. The second method involves the use of $Pd(OAc)_2$ (5 mol%) in combination with *n*-butyl-di-1-adamantylphosphine (10 mol%) as a ligand, 2.2 equiv. of cesium carbonate as a base, and an aryl chloride coupling partner in DMF at 145 ^{o}C for 24 h. The reaction requires the presence of molecular sieves and offered the product **4c** in good yield (Scheme 1)



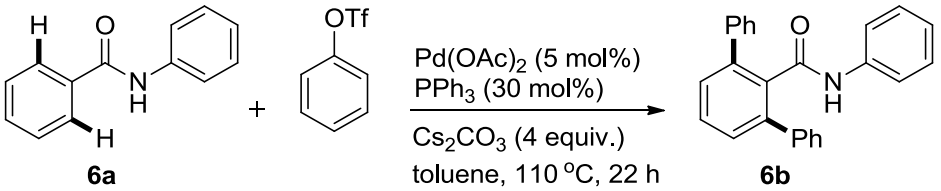
Scheme 1 Development of a new method for C-H arylation of **4a.**

Yu and co-workers[22b] reported the Pd-catalyzed C-H functionalization/ activation processes assisted by carboxyl groups. Thus, the Pd(II)-catalyzed C-H activation of stirring sodium toluate **5a** with 10 mol % of $Pd(OAc)_2$, 0.5 equiv. of benzoquinone (BQ), 1 equiv. of Ag_2CO_3, and 1 equiv. of phenylboronate in *tert*-BuOH at 120 °C for 3 h afforded ortho arylated product **5b** in moderate yield (Scheme 2).



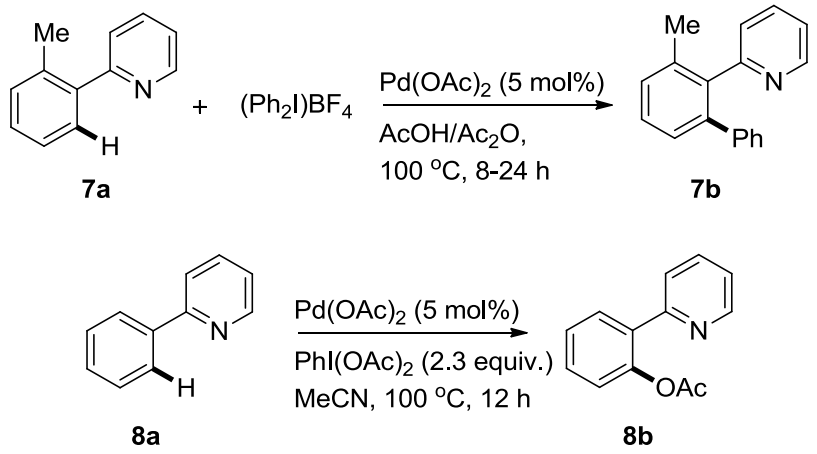
Scheme 2 Carboxylic acid assisted arylation of sodium toluate **5a.**

Nomura and co-workers[22c] reported amide-directed β-C-(sp^2)-H bond activation of benzamide system **6a.** The reaction of *N*-phenylbenzamide **6a** with phenyl triflatein the presence of $Pd(OAc)_2$ (5 mol %) as catalyst and PPh_3 (30 mol %.) as an external ligand with Cs_2CO_3 (4 equiv.) oxidant/ additive in toluene at 110 °C for 22 h gave the β-bis arylated product **6b** (Scheme 3).



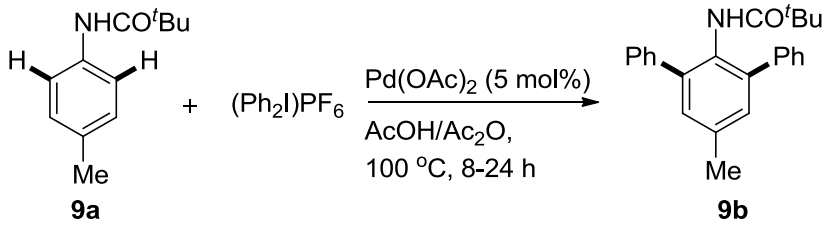
Scheme 3 $Pd(OAc)_2$-catalyzed bisarylation of benzamide **6b**.

For the first time Melanie and co-workers[22d,e] introduced the pyridine as a monodentate directing group in the field of C-H activation. The method descibes 2-tolyl pyridine system **7a** reacted with an iodonium regent (phenyl source) in the presence of $Pd(OAc)_2$ (5 mol%) in AcOH and Ac_2O (1:1) at 100 ^oC for 8-24 h there by offering phenylated product **7b** (Scheme 4). The same group[22b] also reported a new and straight forward Pd-catalyzed reaction for the oxygenation and functionalization of β-C-(sp^2)-H bond of 2-phenyl pyridine **8a**.The reaction of **8a** in the presence of $Pd(OAc)_2$ (5 mol%) and 2.3 equiv. of $PhI(OAc)_2$ (oxygenation source) in MeCN at 100 ^oC for 12 h led to the product **8b** in good yield. Further, various functional groups were screened including pyridine, pyrazole, imine, azobenzene, and their derivatives for the direct phenyl C-H bond acetoxylation(Scheme 4). Wang *et. al*[22f] and Z. J Shi groups[22g] also reported the similar kind of work by using aryl boronic acid and benzene/ silyl benzene as a coupling partner.



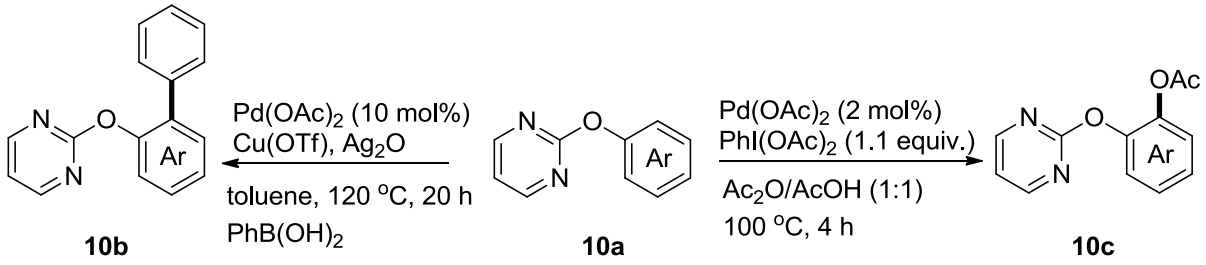
Scheme 4 $Pd(OAc)_2$-catalyzed arylation and oxygenation of system **7a** and **8a**.

Daugulis and co-workers[22h, i] reported the aliphatic amide as a directing group. The Pd-catalyzed *ortho*-arylation of aliphatic carboxamides, and the synthesis of 2,6-bis-arylcarboxamides product **9b**. The reaction of *tert*-butyl carboxamide system **9a** in the presence of $Pd(OAc)_2$ (5 mol%) and commercially available PhI or $(Ph_2I)PF_6$ as aryl source in acetic acid and TFA at 100-130 ^oC for 8-24 h allowed the formation of the diphenylated product in good yield (Scheme 5).



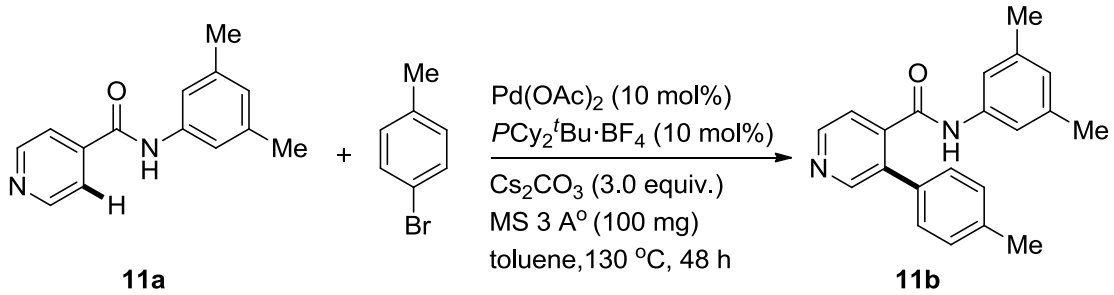
Scheme 5 $Pd(OAc)_2$-catalyzed aliphatic carboxamide directed arylation of system **9a**.

Chen and co-workers[23a] reported 2-phenoxypyrimidine as a temporary directing group for the direct arylation and acetoxylation of phenols via a six-membered palladacycle intermediate. Phenol can be transformed merely to 2-phenoxypyrimidine by copper-catalyzed C-O coupling reaction with 2-halopyrimidine. The reaction of 2-phenoxypyrimidine system **10a** with phenylboronic acid in the presence of $Pd(OAc)_2$ (15 mol%), 3.0 equiv. of $Cu(OTf)_2$, 3.0 equiv. of Ag_2O in toluene at 120 ^oC for 20 h gave the arylated product **10b**. For acetoxylation reaction, they used the same starting material **9a**, 2 mol% of $Pd(OAc)_2$ and 3.0 equiv. of $PhI(OAc)_2$ in the mixture of AcOH and Ac_2O at 100 ^oC for 4 h offered the desired product **10c** (Scheme 6).



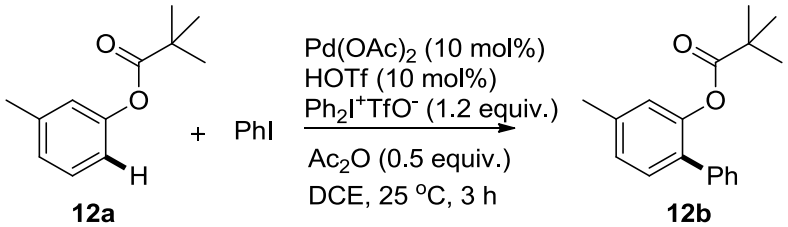
Scheme 6 2-phenoxypyrimidineas a temporary directing group for acetoxylation and arylation **10c**/**10b**.

Yu and co-workers[23b] reported the *N*-Phenyl amide as a directing group in the C-H activation process. They reported the first example of the activation of pyridine ring using *N*-Phenyl amide as a directing group. They described the synthesis of **11b** via Pd(0) catalyzed C-H activation of system **11a** in combination of $Pd(OAc)_2/PCy_2{}^tBu{\cdot}BF_4$ with 3.0 equiv. of Cs_2CO_3 in toluene at 130 °C for 48 h (Scheme 7).



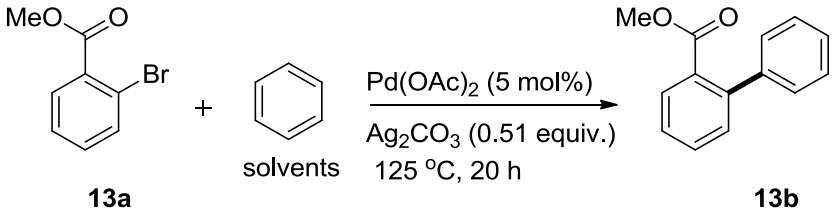
Scheme 7 *N*-Phenyl amide as a directing group for arylation of system **11a**.

Liu and co-workers[23c] reported the acyloxy group directed C-H activation of the aromatic system. The C-H activation of stirring solution of Phenol esters **12a** in the presence of $Pd(OAc)_2$ (10 mol %), 0.5 equiv. of Ac_2O, 1.2 equiv. of $Ph_2I^+OTf^-$ and 10 mol % HOTf in DCE at room temperature for 3 h under open atmosphere afforded the *ortho*-phenylated products **12b** in good yield (Scheme 8)



Scheme 8 Phenolic esteras a directing group for arylation of system **12a**.

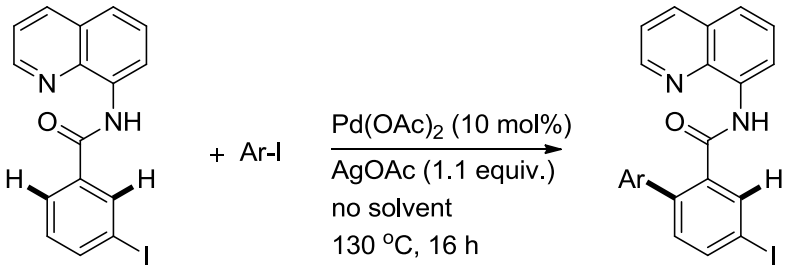
Charette and co-workers[23d]reported the umpolung version of the directing group such as aryl halides containing an α-directing group for an unactivated arene system. The reaction of **13a** with 5 mol% of $Pd(OAc)_2$, 0.51 equiv. of Ag_2CO_3 in 125 ^oC for 20 h offered the monoarylated product exclusively **13b**, indicating the role of the directing group (Scheme 9).



13a 13b

Scheme 9 Umpolung directing group for arylation of system **13a**.

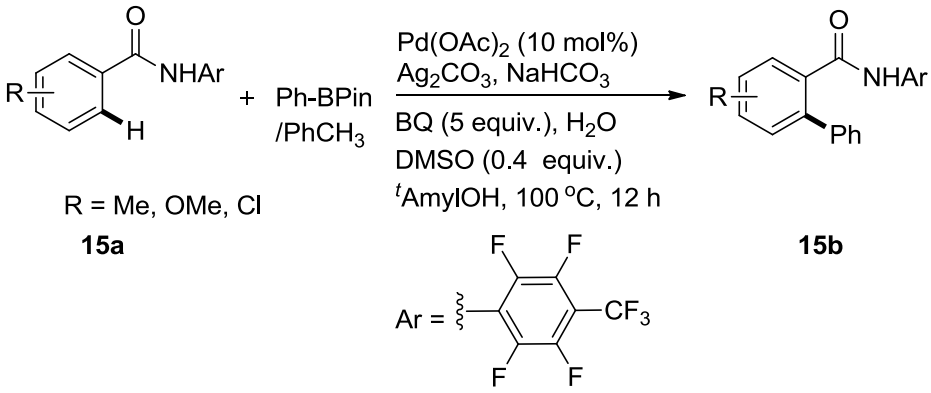
For the first time Daugulis and co-workers[22i] reported the *ortho*-arylation of carboxamide by using 8-Aminoquinoline as a bidentate directing group in C-H activation field. The reaction of carboxamide **14a** with aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) and 1.1 equiv. of AgOAc as an oxidant/additive without any solvent at 130^oC for 16 h offered the monoarylated product **14b** in good yield (Scheme 10).



14a 14b

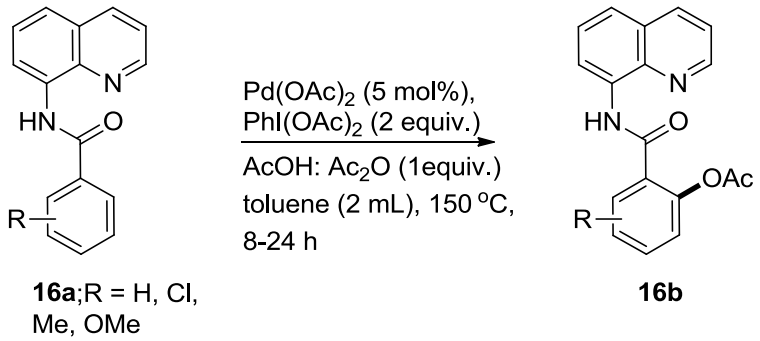
Scheme 10 $Pd(OAc)_2$-catalyzed bidentate directed arylation of system**14a.**

Yu and co-workers[23e, f] reported the 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline as a directing group for the C-(sp^2)-H bond of *N*-arylamide system. The reaction of *N*-arylamide substrate **15a** and nontoxic, abundant phenylboronic acid pinacolester (PhBPin) as the coupling partner in the presence of $Pd(OAc)_2$ (10 mol%) as the catalyst, Ag_2CO_3 as the terminal oxidant, and $NaHCO_3$ as the base with 5 equiv. of benzoquinone, 0.4 equiv.of DMSO in ^{t}AmylOH at 100 ^oC for 12 h lead to the cross-coupling product **15b** (Scheme 11).



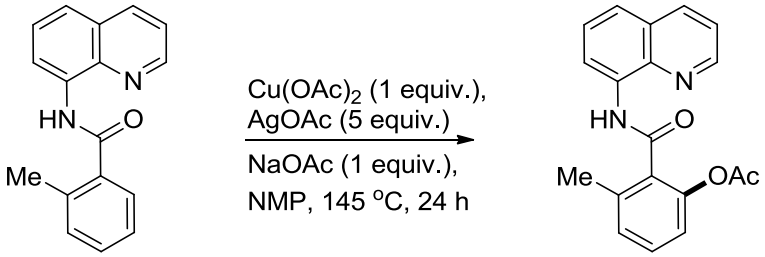
Scheme 114-trifluoromethyl-2,3,5,6-tetrafluoroaniline as directing groupfor arylation of system **15a**.

Liang and co-workers[24a] reported 8-Aminoquinoline directed oxygenation of C-(sp^2)-H bond of carboxamide substrate. The C-H oxygenation of substrate **16a** is carried in the presence of catalyst $Pd(OAc)_2$(5 mol%), 2equiv. of $PhI(OAc)_2$ in a mixture of $AcOH/Ac_2O$ solvent at 150 ^oC for 8-24 h offered the **16b** in good yield (Scheme 12).



Scheme 12 Oxygenation of **16a** by using 8-AQ as a directing group.

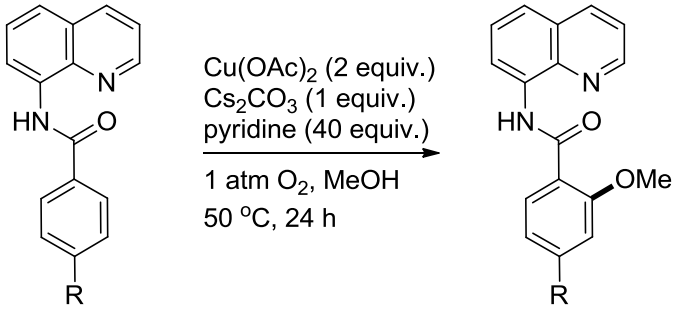
Kuninobu and Kanaico-workers[24b] reported 8-Aminoquinoline directed copper catalyzed oxygenation of C-(sp^2)-H bond of carboxamide substrate. The C-H oxygenation of substrate **17a** in the presence of catalyst $Cu(OAc)_2$ (5 mol%), 5equiv. of AgOAc and 1equiv. of NaOAc in NMP solvent at 140 ^oC for 24 h offered the **17b** in average yield (Scheme 13).



17a **17b**

Scheme 13 Cu(II)-catalyzed acetoxylation of **17a** substrate.

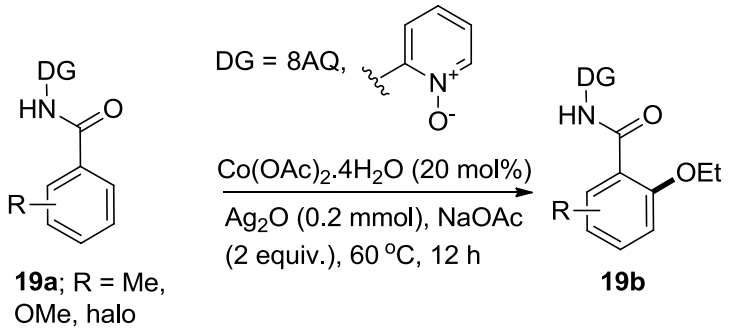
Ertem co-workers[24c] reported 8-Aminoquinoline directed copper catalyzed oxygenation of C-(sp^2)-H bond of carboxamide substrate. The C-H oxygenation of substrate **18a** in the presence of catalyst $Cu(OAc)_2$(2 equiv.), 1equiv. of Cs_2CO_3 and 40 equiv. of pyridine in MeOH solvent under 1 atm oxygen atmosphere at 50 ^oC for 24 h offered the **18b** in moderate yield (Scheme 14).



18a; R = H, Me, Cl, OMe **18b**

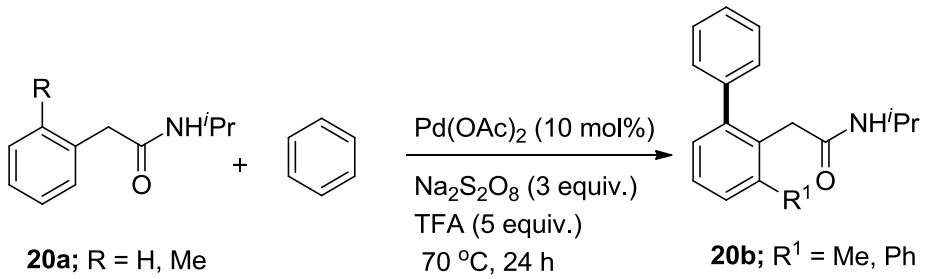
Scheme 14 Cu(II)-catalyzed oxygenation of **18a** substrate.

Song and co-workers[24d] reported pyridine *N*-oxide(PyO) and 8-Aminoquinoline directed copper catalyzed oxygenation of C-(sp^2)-H bond of carboxamide substrate. The C-H oxygenation of substrate **19a** in the presence of catalyst $Cu(OAc)_2H_2O$ (20 mol%), Ag_2O (0.2 mmol) and 2equiv. of NaOAc under air atmosphere at 60 ^oC for 12 h offered the **19b** in good yield (Scheme 15).



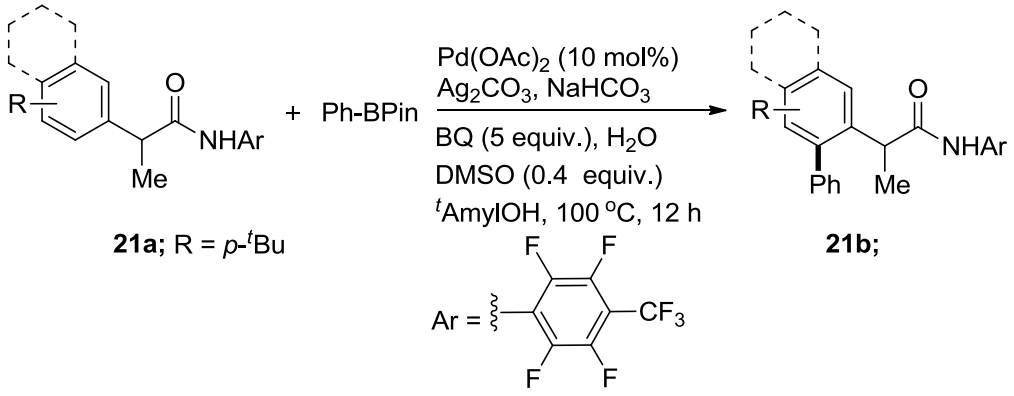
Scheme 15 Cu(II)-catalyzed oxygenation of substrate **19a**.

Dong and co-workers[25a] reported amide as a directing group for the γ-C-(sp^2)-H activation of phenylacetamides by the green strategy. The Pd-catalyzed C-H activation of the *N*-isopropyl-2-o-substituted acetamide **20a** in the presence of $Pd(OAc)_2$(10 mol%), with a range of simple arenes using sodium persulfate $Na_2S_2O_8$, 5 equiv. of trifluoroacetic acid (TFA) as an oxidant, at 70 °C for 24 h gave the desired product **20b** in good yield (Scheme 16).



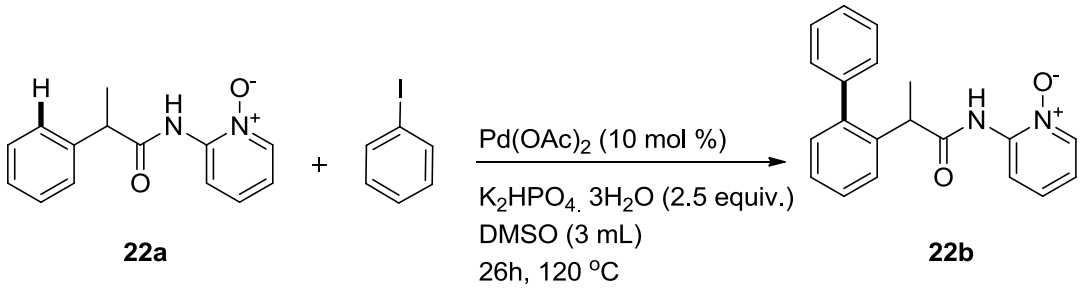
Scheme 16 Amide as the directing group for phenylacetamide system **20a.**

Yu and co-workers[25b] reported the 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline as a directing group for the γ-C-(sp^2)-H bond of *N*-arylamide system. The arylation of *N*-arylamide substrate **21a** with phenylboronic acid pinacolester (PhBPin) as the coupling partner is carried out in the presence of catalyst 10 mol% of $Pd(OAc)_2$, Ag_2CO_3(terminal oxidant), and $NaHCO_3$(base) 5 equiv. of benzoquinone and 0.4 equiv.of DMSO in ^{t}AmylOH at 100 °C for 12 h offered the cross-coupling product **21b**(Scheme 17).



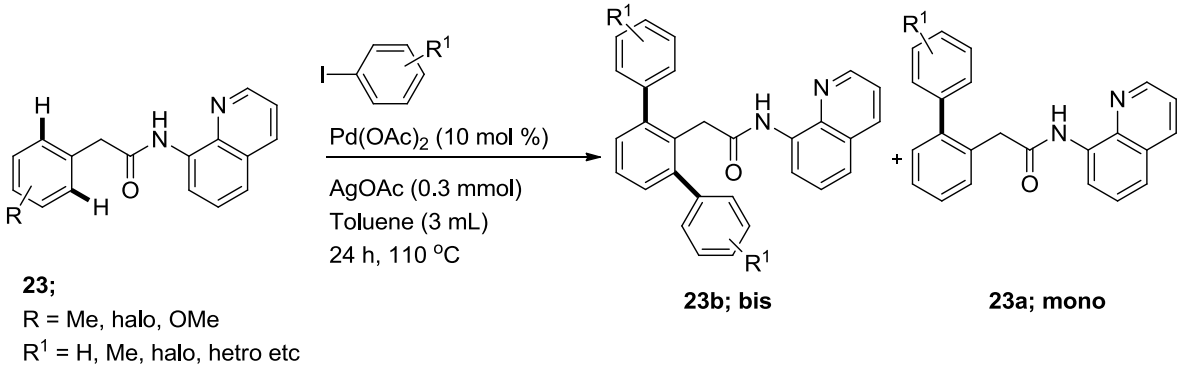
Scheme 17 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline as the directing groupfor arylation of system **21a.**

Song and co-workers[25c] developed *N*-Oxide as the directing group for γ-C-(sp^2)-H activation of aromatic carboxamide. Carboxamide system **22a** is treated with the source of aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%), 2.5 equiv. of hydrated potassium hydrogen phosphate in DMSO at 120 ^oC for 26 h to afford desired product **22b** in moderate yield (Scheme 18).



Scheme 18 *N*-oxide as a directing group for arylation of system **22a.**

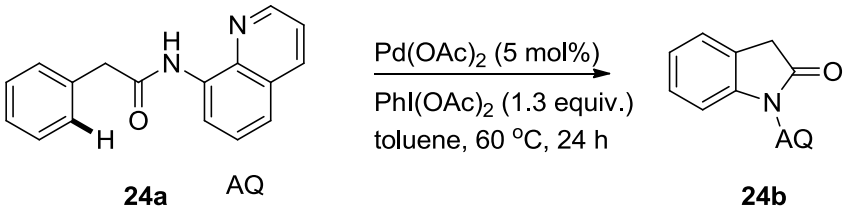
Babu and co-workers[26d] also reported 8-aminoquinoline directed γ-C(sp^2)-H activation of remote position in the phenylacetamide system. The Pd-catalyzed reaction of system **23** reacted with a wide range of iodide sources in the presence of $Pd(OAc)_2$ (10 mol%), 2.2 equiv. of AgOAc in toluene at 110 ^oC for 24 h leading to the synthesis of γ-arylated arylacetamide mono and bis derivatives **23a** and **23b** respectively in good yield (Scheme 19).



Scheme 19 8-Aminoquinoline as directing group for arylation of system **23.**

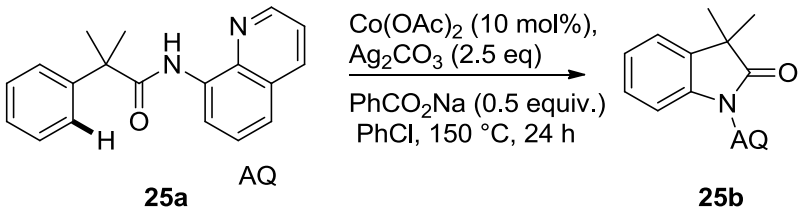
Chen and co-workers[25e] reported the 8-Aminoquinoline directed γ-C-(sp^2)-H activation of phenylacetamide systems **24a** leading to the formation of indolinone via intramolecular cyclization. The reaction of phenylacetamide **24a** in presence $Pd(OAc)_2$ (5 mol %) as a

catalyst with $PhI(OAc)_2$ (1.3 equiv.) as an oxidant/ additive in toluene at 100 °C for 10 h gave the indolinone **24b** (Scheme 20).



Scheme 20 $Pd(OAc)_2$-catalyzed synthesis of indolinone from **24a.**

Ge and co-workers[25f] reported 8-aminoquinoline directed cobalt catalyzedγ-C-(sp^2)-H activation and the formation of indolinoneas a result of intramolecular cyclization of phenylacetamide systems **25a.** The reaction of phenylacetamide **25a** in the presence of $Co(OAc)_2$ (10 mol %) as a catalyst with Ag_2CO_3 (2.5 equiv.) as the oxidant, sodium benzoate (0.5 equiv.) as an additive in chlorobenzene at 150 °C for 24 h offered the indolinone **25b** (Scheme 21).



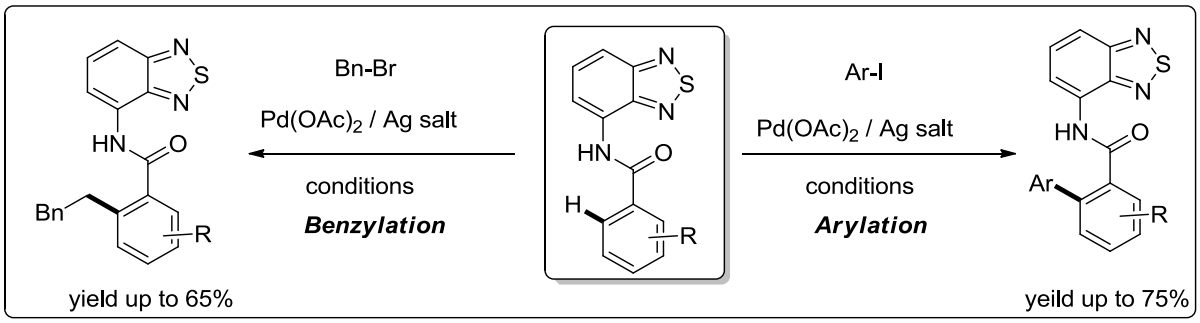
Scheme 21 $Co(OAc)_2$-catalyzed synthesis of indolinone by using 8-aminoquinoline as directing group **25b.**

Result and Discussion

Part 1: 4-Amino-2,1,3-Benzothiadiazole(ABTD) as a Removable Bidentate Directing Group for the Pd(II)-Catalyzed Arylation/Oxygenation of sp^2 C–H Bonds of Carboxamides

Aiming towards the importance of heterocycle and benzamide derivatives in the organic synthesis and medicinal chemistry research, developing an efficient synthetic method involving a simple procedure for constructing bis arylated benzamide moiety will be highly useful to enrich the library of carboxamide scaffolds. A literature survey revealed that various bidentate directing group were found to be helpful for the β-C-H bond functionalization of carboxylic acid and amine system. Although, scientists kept on working towards the

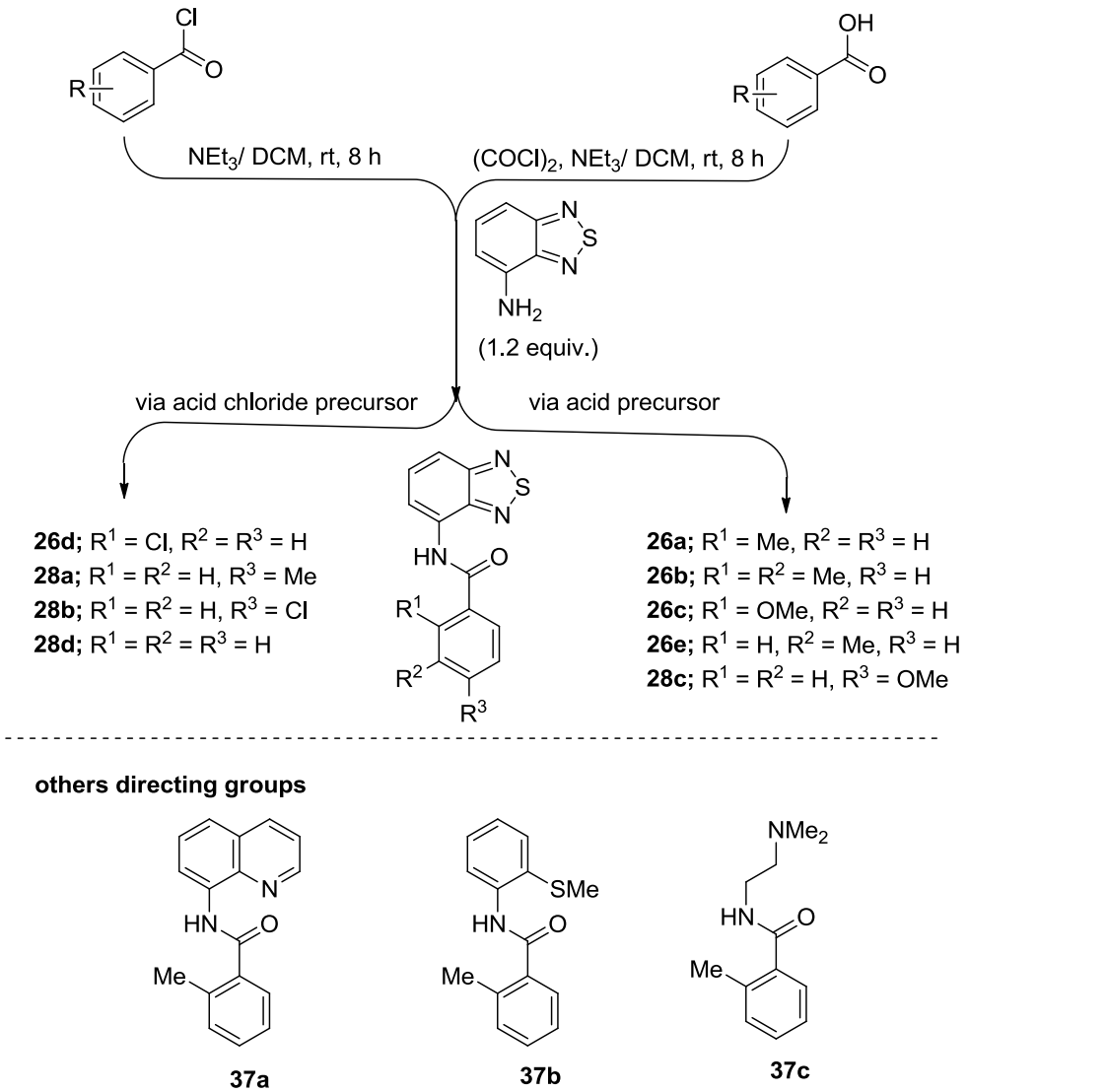
development of the new bidentate directing group to pronounce the availability of another possible route in the field of C-H activation/functionalization. Several research groups showed the interest towards the functionalization of sp^2/sp^3 C-H bonds of carboxylic acid derivatives using highly efficient and less active directing groups[1-8]. We also wish to introduce a new directing group 4-amino-2,1,3-benzothiadiazole (ABTD) for the Pd(II)-catalyzed, sp^2 C–H activation/functionalization of aromatic carboxamide systems (Scheme 22)



Scheme 22 Title of this work: ABTD enabled synthesis of mono/bis arylated and benzylated benzamides system.

Among the heterocycles, thiazoles and benzothiazoles occupy a prominent position. They possess a broad range of biological activities and found in many potent biologically active molecules and drugs such as vitamin thiamine, sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (an antifungal drug) and tiazofurin (antineoplastic drug). The thiazole moiety is abundantly found in natural products, while benzothiazole moiety is rare. 2,1,3-Benzothiadiazole (BTD) is one of the essential nuclei used in the chemistry of photoluminescent compounds and many others, attention has been focused on BTD π-extended derivatives with potential use in this exciting area.

By using the standard literature procedure, various benzamides were synthesized using the bidentate directing groups, such as 4-amino-2,1,3-benzothiadiazole (ABTD),8-aminoquinoline, 2-(methylthio)aniline other groups and their corresponding benzoyl system /carboxylic acid system. Various benzamide substrates **26a-e** and **28a-d** were assembled for β-C(sp^2)-H activation (Scheme 23).

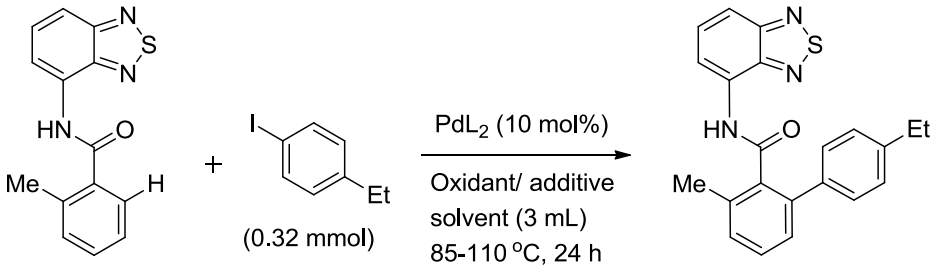


Scheme 23 New directing groups and substrates employed for performing the*β*-C(sp^2)-H arylation (Condition: Substrate (0.12 mmol), ArI (0.48 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), toluene (3 mL), 24 h, and 110 ^{O}C (the arylations reaction using **26a-e**/ **28a-d** and **37a** were successful as discussed in results and discussion part and the arylation with **37b-c** were not successful).

To begin the investigations on the Pd(II)-catalyzed 4-amino-2,1,3-benzothiadiazole (ABTD) directed sp^2 C-H functionalization of benzamides **26a-e** and **28a-d**, initially, various reactionswere carried out to find the optimized reaction conditions. Table 1 & Table 3 shows the Pd-catalyzed arylation of **26a** and **28a** the result of ABTD-directed monoarylation of ortho C(sp^2)-H bond of benzamide **26a** and bis arylation of *ortho* C(sp^2)-H bonds of benzamide **28a** in the presence of various palladium catalysts and additives in different solvents. The arylation reaction of *ortho* C(sp^2)-H bond of benzamide **26a** with 1-ethyl-4-

iodobenzene in the presence of 10 mol% of the $Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 110 ^oC afforded the mono C-H arylated benzamide **27a** in a maximum yield of 70% (entry 2, Table 1). Apart from these reactions, the other optimization reactions comprising the mono arylation of *ortho* $C(sp^2)$-H bonds of the corresponding benzamides **26a** in the presence of other palladium catalysts or additives or solvents were not fruitful (entries 3-11, Table 1). Next, to examine the generality of this work, we planned to perform thearylation of *ortho* $C(sp^2)$–H bonds of various 2/3-substituted-benzamides **26a-e**, which were prepared using ABTD directing group (Table 2). Using the optimized reaction conditions (entry 2, Table 1), we attempted the $Pd(OAc)_2$/AgOAc-catalytic system-based, ABTD-directed arylation of *ortho* $C(sp^2)$–H bonds of 2/3-substituted-benzamides **26a-d** with different aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para/meta* position of the aryl ring. These reactions afforded a wide range of the corresponding mono C-H arylated benzamides **27a-n** in 50-77% yields (Table 2). The arylation of the *meta*-substituted benzamide **26e** with 1-iodo-4-methoxybenzene afforded the corresponding mono and bis arylated benzamides **27o** and **27o′** in 44 and <10% yields. Further, the arylation of **26e** with 1-iodo-3-nitrobenzene furnished the corresponding mono and bis arylated benzamides **27p** (<10%) and **27p′** (<20%) in low yields (Table 2).

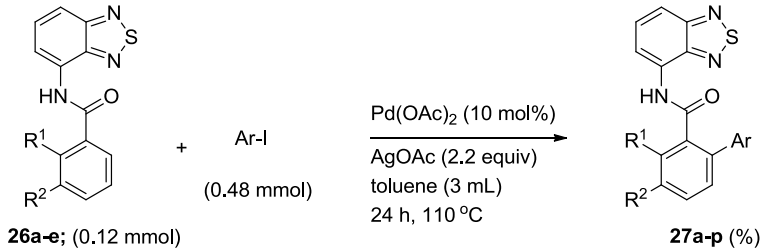
Table 1 Optimization reactions. Pd(II)-catalyzed, ABTD-directed arylation of *ortho*C-(sp^2)-H bonds of benzamides **26a.**



26a; (0.08 mmol) **27a; mono-arylation**

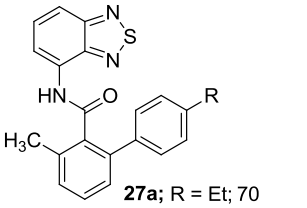
entry	PdL_2 (10 mol%)	solvent (3 mL)	additive/ oxidant	*t* (°C)	**27a** (yield %)
1	nil	toluene	AgOAc	110	0
2	**$Pd(OAc)_2$**	**toluene**	**AgOAc**	**110**	**70**
3	$PdCl_2$	toluene	AgOAc	110	24
4	$Pd(PPh_3)_4$	toluene	AgOAc	110	<5
5	$Pd(TFA)_2$	toluene	AgOAc	110	<5
6	$Pd(OAc)_2$	toluene	Ag_2CO_3	110	0
7	$Pd(OAc)_2$	toluene	$PhI(OAc)_2$	110	0
8	$Pd(OAc)_2$	toluene	KOAc	110	<5
9	$Pd(OAc)_2$	1,4 dioxane	AgOAc	100	30
10	$Pd(OAc)_2$	^{t}Amyl-OH	AgOAc	110	0
11	$Pd(OAc)_2$	^{t}BuOH	AgOAc	85	0

Table 2 Substrate scope and generality of the Pd(II)-catalyzed, ABTD-directed arylation of *ortho* C(sp^2)-H bond of benzamides **26a-e.**

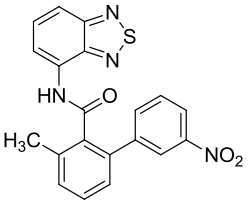


26a-e; (0.12 mmol)

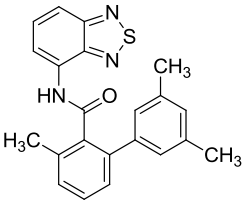
27a-p (%)



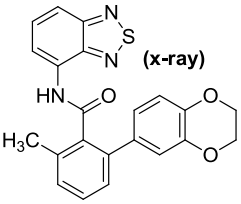
27a; R = Et; 70
27b; R = OCH_3; 58
27c; R = H; 55



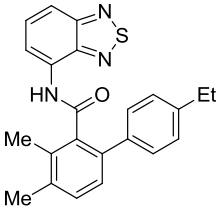
27d; 65



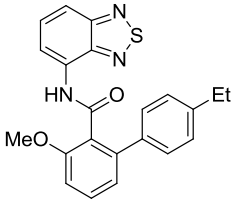
27e; 58



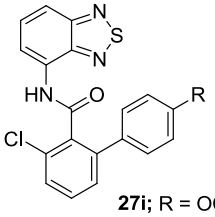
27f; 77



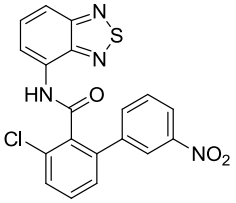
27g; 58



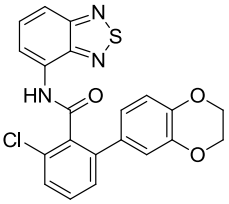
27h; 50



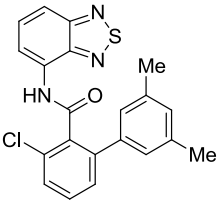
27i; R = OCH_3; 70
27k; R = Et; 65
27l; R = H; 60



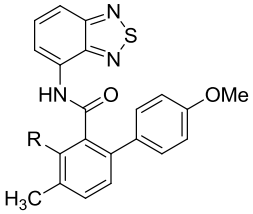
27j; 53



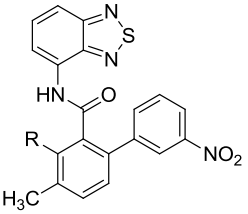
27m; 59



27n; 75



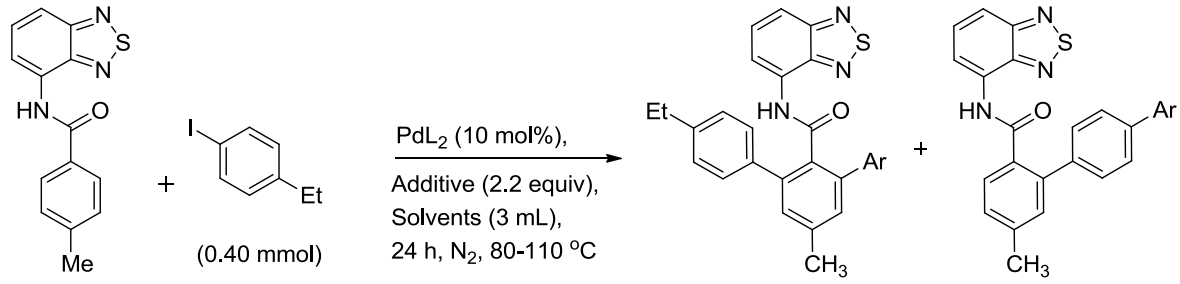
27o; R = H; 44
27o'; R = C_6H_4(*p*)-OMe;<10



27p; R = H; <10
27p';R = C_6H_4(*m*)-NO_2; <20

Similarly, the Pd(II)-catalyzed arylation of *ortho* C(sp^2)-H bonds of benzamide **28a** with 1-ethyl-4-iodobenzene afforded the bis C-H arylated benzamide **29a** in maximum yield of 75% (entry 2, Table 3). Apart from these reactions, the other optimization reactions comprising the mono and bis arylation of *ortho* C(sp^2)-H bonds of the benzamides **28a** in the presence of other palladium catalysts or additives or solvents were not fruitful (entries 3-11, Table 3). Then we planned to extend the substrate scope by examining the bis arylation of *ortho* C(sp^2)-H bonds of benzamides **28a-d**.

Table 3 Optimization Reactions. Pd(II)-Catalyzed, ABTD-Directed Arylation of *Ortho*C(sp^2)-H Bonds of Benzamides **28a**[a-c]



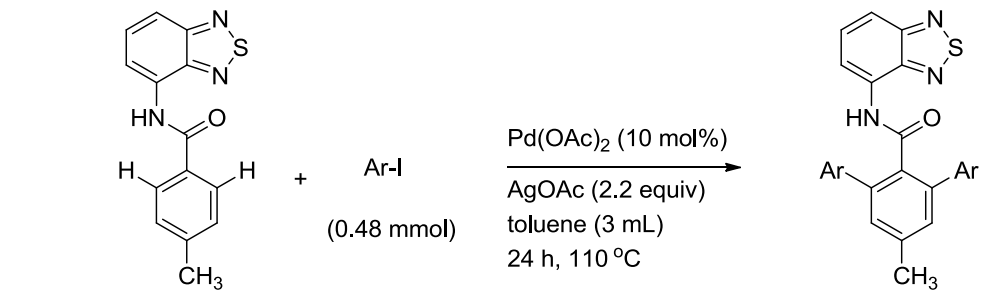
28a; (0.10 mmol) **29a** **30a**

entry	PdL_2 (10 mol%)	solvent (3 mL)	additives/ oxidants (2.2 equiv)	*t* (°C)	**29a** (% yield)[a]
1	nil	toluene	AgOAc	110	0
2	$Pd(OAc)_2$	toluene	AgOAc	110	75
3	$PdCl_2$	toluene	AgOAc	110	50
4	$Pd(PPh_3)$	toluene	AgOAc	110	<5
5	Pd(TFA)	toluene	AgOAc	110	<5
6	$Pd(OAc)_2$	toluene	Ag_2CO_3	110	0
7	$Pd(OAc)_2$	toluene	$PhI(OAc)_2$	110	0
8	$Pd(OAc)_2$	toluene	KOAc	110	<5
9	$Pd(OAc)_2$	1,4 dioxane	AgOAc	100	<5
10	$Pd(OAc)_2$	^{t}Amyl-OH	AgOAc	110	0
11	$Pd(OAc)_2$	^{t}Bu-OH	AgOAc	85	0

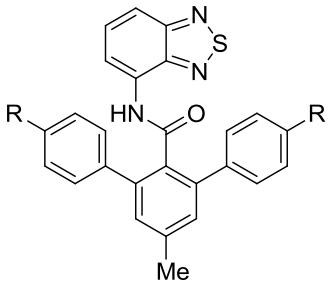
[a] The product **30a** was not observed in the reactions involving the substrate **28a**.

We attempted the $Pd(OAc)_2$/AgOAc-catalytic system-based, ABTD-directed arylation of *ortho* C(sp^2)-H bonds of benzamides **28a-d** with several aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para/meta* position of the aryl ring. These reactions furnished a wide range of bis C-H arylated benzamides **29a-m** in 42-75% yields, respectively. (Table 4)

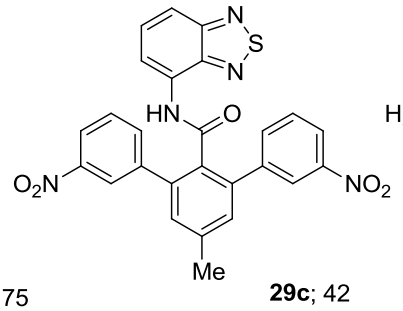
Table4 Substrate scope of the Pd(II)-catalyzed, ABTD-directed arylation of *ortho* C(sp^2)-H bond of benzamides **28a-d.**



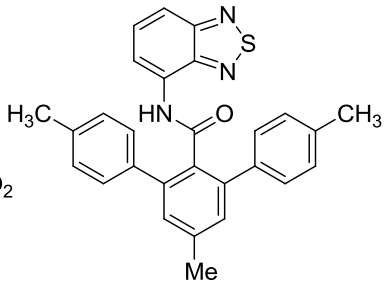
28a-d (0.12 mmol) **29a-m** %



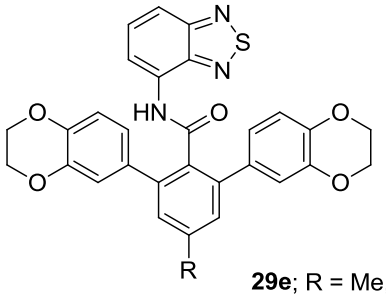
29a; R = Et; 75
29b; R = OMe; 65



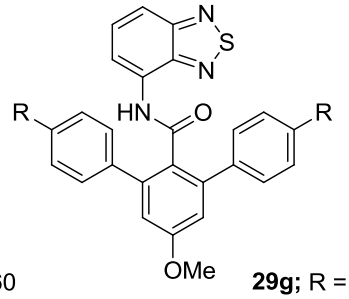
29c; 42



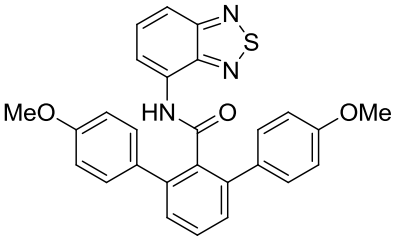
29d; 70



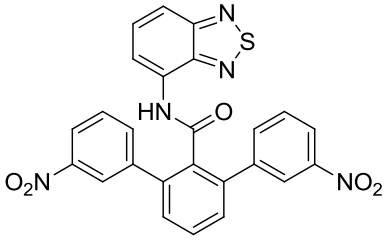
29e; R = Me, 60
29f; R = H; 50



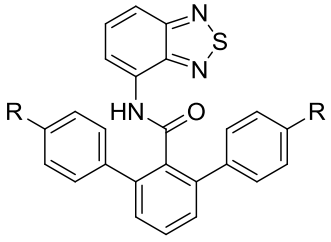
29g; R = OMe; 60
29h; R = Et; 61



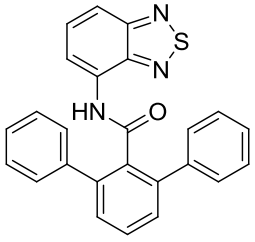
29i; 60



29j; 50



29k; R = Me; 75
29l; R = Et; 74

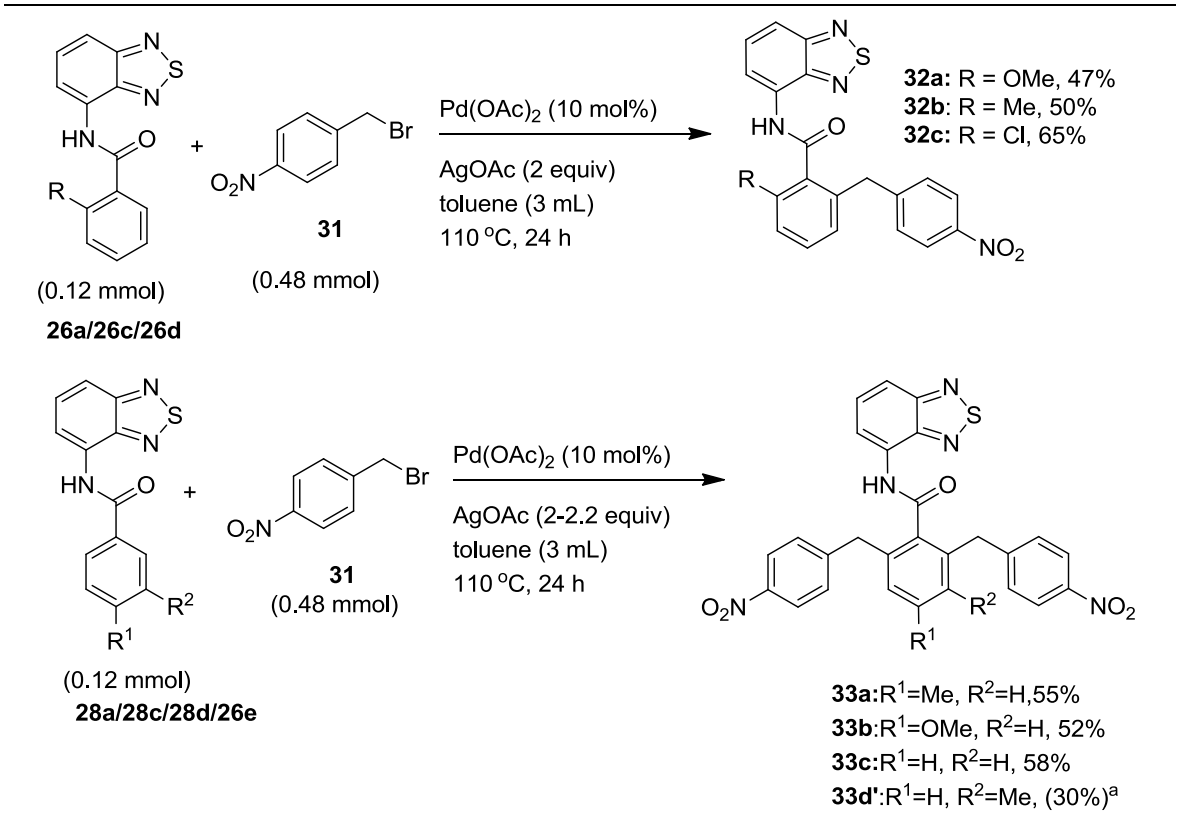


29m; 50

Next, we focused our attention on exploring the Pd(II)-catalyzed direct benzylation of *ortho*-C(sp^2)-H bonds of benzamides with the help of the ABTD bidentate directing group. In this regard, initially, we carried out the $Pd(OAc)_2$/AgOAc-catalytic system-based, ABTD-directed

ortho-C-H benzylation of **26a**/**26c**/**26d** with 1-(bromomethyl)-4-nitrobenzene (**31**).These reactions afforded the corresponding *ortho*-C-H benzylated benzamides **32a-c** in 47-65% yields respectively (Scheme 24). Having done the Pd(II)-catalyzed mono benzylation of *ortho*-C(sp^2)-H bond of **26a**/**26c**/**26d**, we then performed the Pd(II)-catalyzed, ABTD-directed bis benzylation of *ortho*-C(sp^2)-H bonds of benzamides **28a**/**28c**/**28d**/**26e** with **31**. These reactions furnished the corresponding bis *ortho*-C–H benzylated benzamides **33a-c** and**33d′** in 30-58% yields, respectively (Scheme 24).

Scheme 24 The Pd(II)-catalyzed, ABTD-directed mono and bis benzylation of *ortho*-C(sp^2)-H bonds of benzamides **26** and **28**.[a]

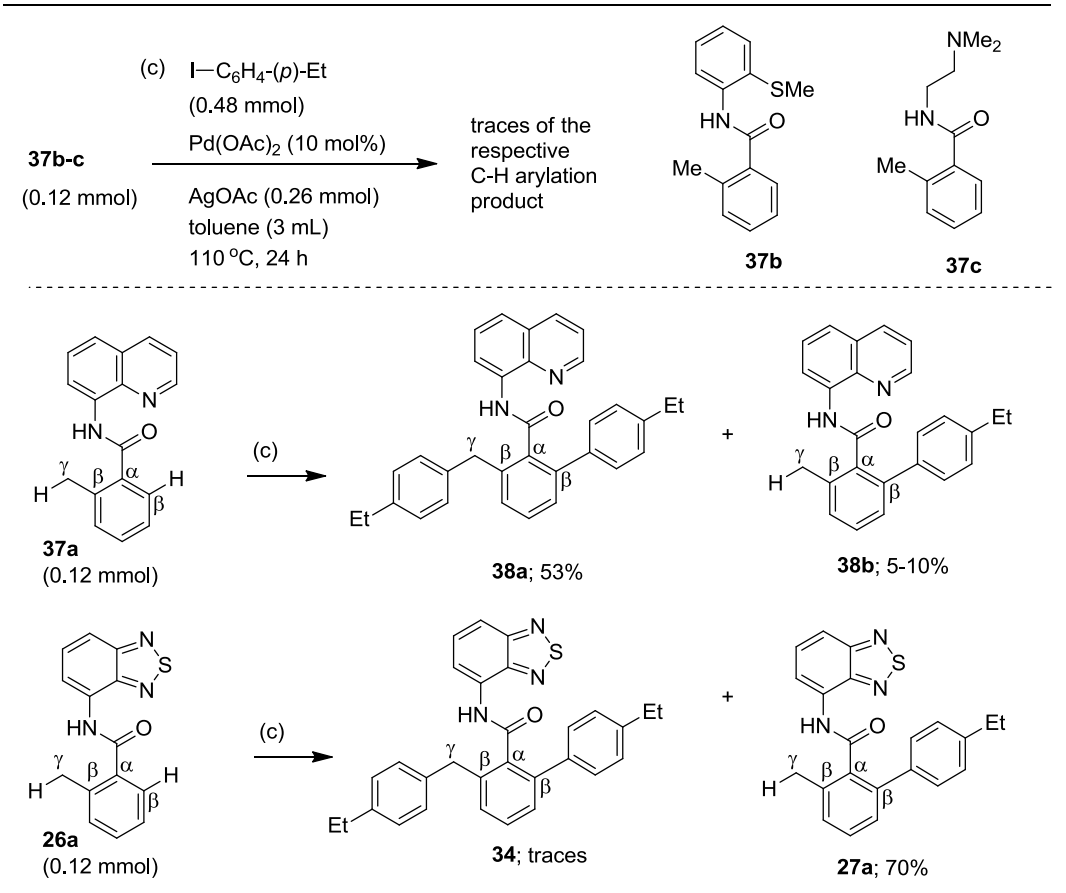


[a]The benzylation of **26e** afforded the bis benzylated product **33d'** along with the corresponding mono benzylated product **33d** in <10% yield in impure form.

The C-H arylated/benzylated compounds **27a-p**, **29a-m**, **32a-c**, **33a-c**and **33d′** obtained from the Pd(II)-catalyzed, ABTD-directed arylation/benzylation of *ortho* C–H bonds of the corresponding substrates **26a-e** and **28a-d** were characterized based on their NMR spectra

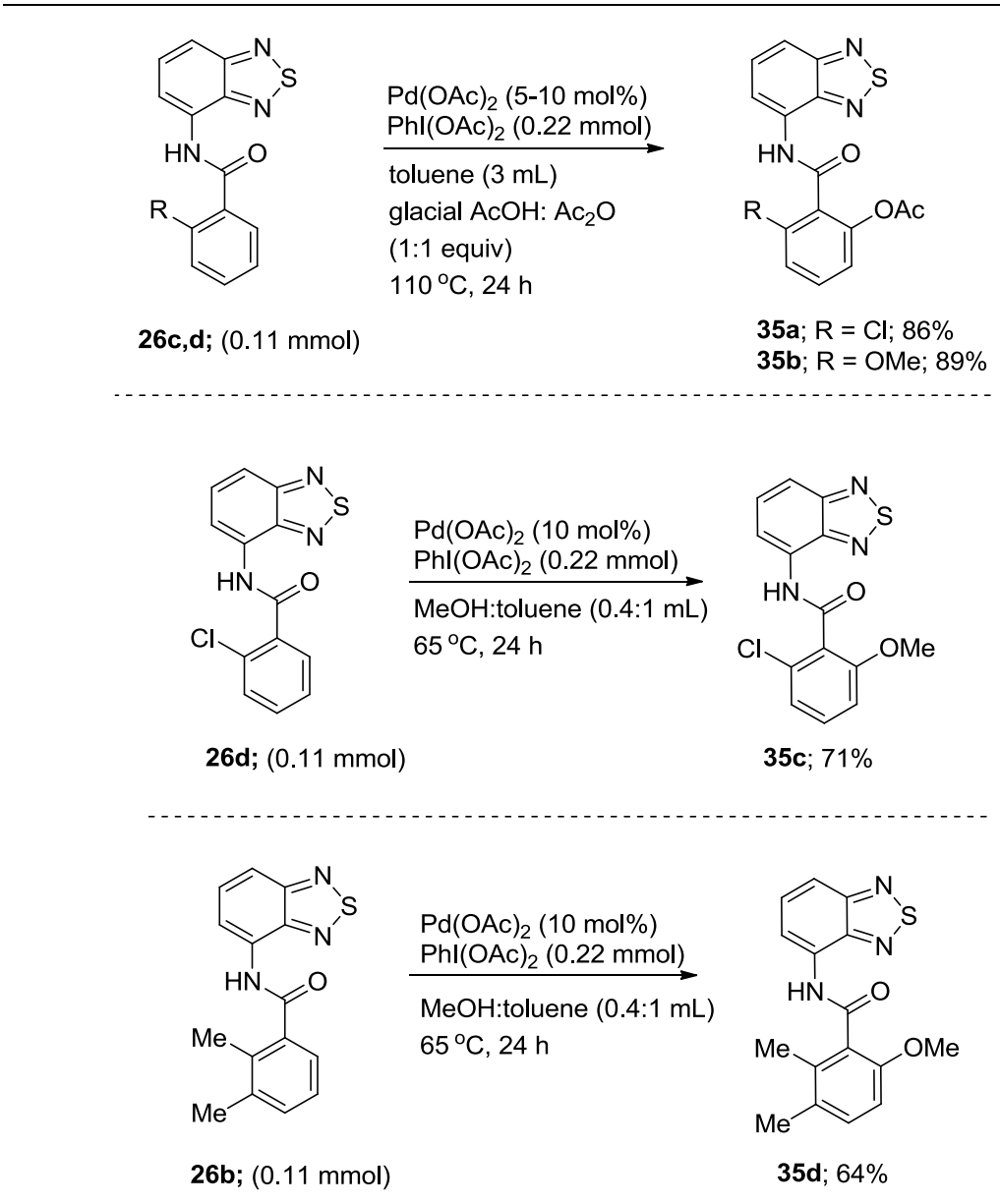
and HRMS analyses data. For example, a comparison of the ^{1}H NMR spectra of substrate **26b** and carboxamide **27g** was performed. The corresponding distinct doublet peaks of the *meta* and *para* protons of *ortho* C-H arylated carboxamide **27g** revealed that the arylation occurred at the *ortho* C–H bond of the 2,3-dimethylbenzamide system **26b**. Similarly, a comparison of the ^{1}H NMR spectra of substrate **28a** and carboxamides **29d**/**33a** was performed. The corresponding distinct singlet peak of the *meta* protons of the bis *ortho* C-H arylated/benzylated 4-methylbenzamide systems **29d**/**33a** revealed that the arylation/benzylation occurred at both the *ortho* C-H bonds of the 4-methylbenzamide system **28a**. Additionally, the observed regioselectivity in the reactions comprising the Pd(II)-catalyzed, ABTD-directed *ortho*-C(sp^2)-H arylation/benzylation of benzamides **26a-e** and **28a-d** was unambiguously confirmed from the X-ray structure of a representative *ortho*-C-H arylated benzamide **27f** (see the Supporting Information for the X-ray structure of **27f**).

Scheme 25 A typical comparison of ABTD with the other pivotal directing groups used for the C-H arylation carboxamides.



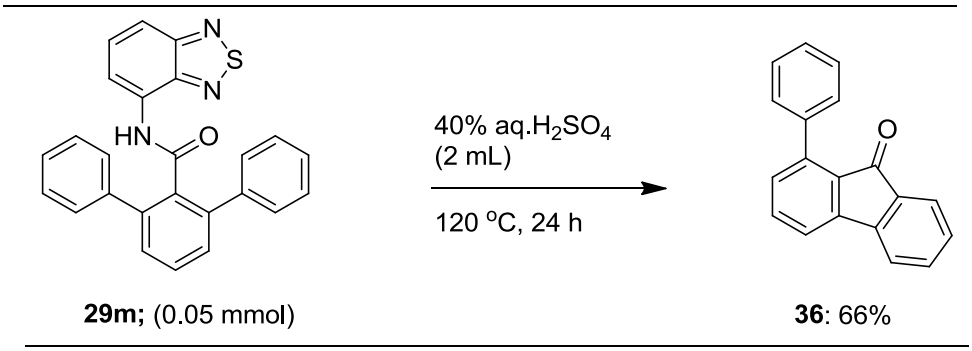
The Pd(II)-catalyzed C-H arylation of ABTD-directed C-H arylation of **26a** selectively afforded the monoarylation product **27a** in 70% yield (Scheme 25). On the other hand, the 8-aminoquinoline-directed C-H arylation of **37a** provided the bis arylated product **38a** in 53% yield along with the compound **38b** in 5-10% yield (Scheme 25).

Additionally, we performed the Pd(II)-catalyzed, ABTD-directed *β*-C-H acetoxylation of substrates **26c,d**, which afforded the corresponding C-H acetoxylated **35a,b** in 86-89% yields, respectively (Scheme 26). Similarly, the Pd(II)-catalyzed, ABTD-directed*β*-C-H methoxylation of **26b,d** afforded the corresponding C-H methoxylated products **35c,d** in 64-71% yields, respectively.



Scheme 26 ABTD-directed C-H Acetoxylation/Alkoxylation of Carboxamides.

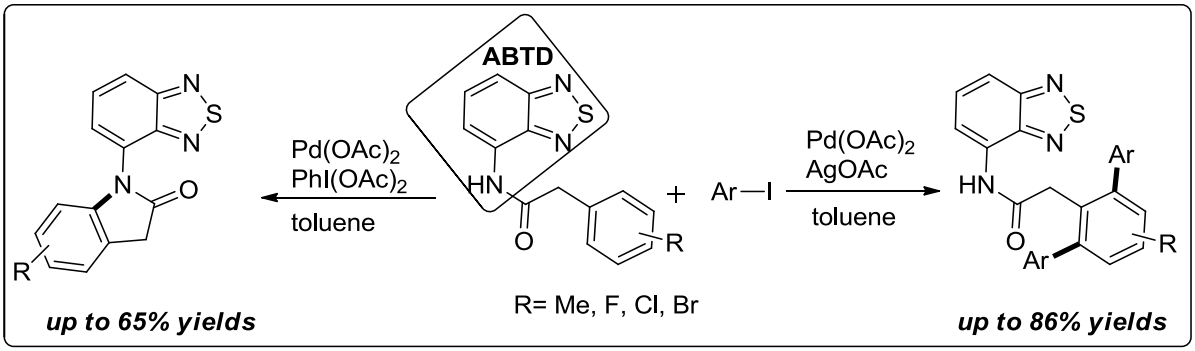
Finally, we also attempted the removal of the ABTD bidentate directing group after the C-H arylation of reactions using representative C-H arylated carboxamides (Scheme 27). Initially, we tried the amide hydrolysis reaction of **29m** with aq. H_2SO_4, which afforded the 9-fluorenone derivative **36** (Scheme 27). In this reaction, the corresponding carboxylic acid was not obtained in characterizable amount. After the removal of the directing group, the corresponding carboxylic acid has undergone an intramolecular Friedel-Crafts acylation thereby affording the compound **36** under the experimental condition.



Scheme 27 Removal of the ABTD directing group for *β*-C-H arylated of carboxamides.

Part 2: Synthesis of ortho-substituted arylacetamide and indolinone derivatives via Pd(II) Catalyzed ABTD as a directing group assisted *γ*-C(sp^2)-H Bonds of phenylacetamides.

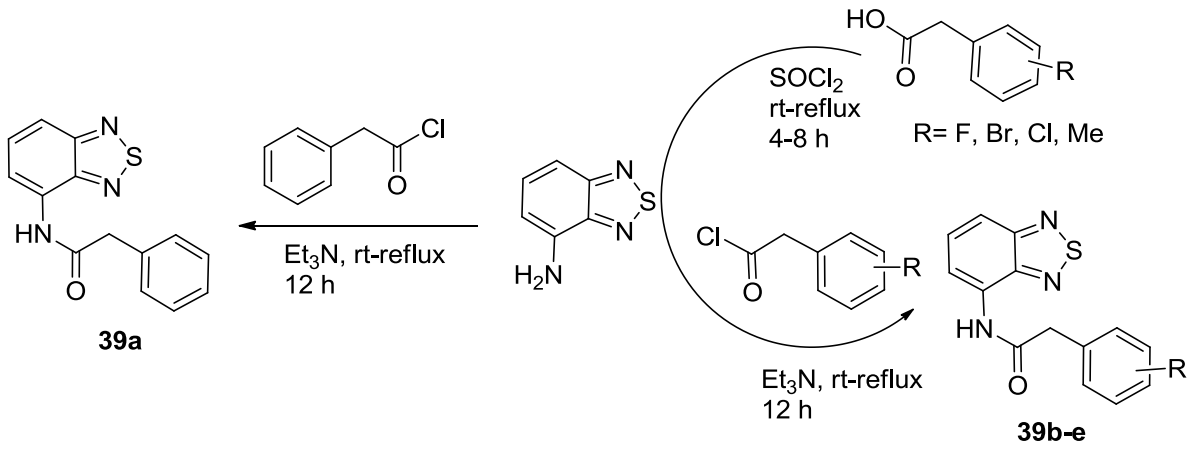
This work



Scheme 28 Title of this work. ABTD enabled construction of Indolinone and bis-substitutedphenylacetamides.

Aiming the importance of directing group development and playing a crucial role in the C-H activation fields, we also introduced a very low reactive and highly selective ABTD as a directing group to developed, the arylacetamide and indolinone derivatives in organic synthesis and medicinal chemistry research, promoting the efficient synthetic methods involving the well-known procedure for synthesizing new phenylacetamides. Mono and bis arylacetamides moiety will be highly fluorescent and pharmaceutical useful to enrich the library of indolinone scaffolds. A literature survey revealed that there are minimal reports[26] dealing with the synthesis of mono/bis arylation and cyclization, phenylacetamide frameworks. Notably, some of the literature reports discussed in the introduction section of this chapter appeared during or after the investigation of this work. A part of this thesis work envisaged investigating the $Pd(OAc)_2$catalyzed new bidentate directing group enabled $C(sp^2)$-H functionalization of phenylacetamide and synthesis of fluorophore and pharmaceutical active compounds having the indolinone as a core moiety (Scheme 28).

Following the literature procedures, various phenylacetamides were prepared using the ABTD as a directing group (Scheme 29). The reaction of amines with corresponding acid chloride and triethylamine in DCM gave the desired amides.

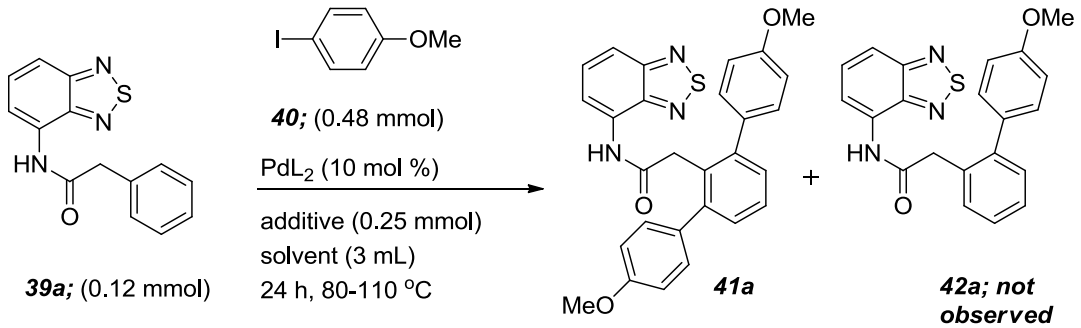


Scheme 29 Preparation of phenylacetamide starting materials **39a-e.**

We initiated our studies to optimize the reaction condition on the Pd(II)-catalyzed directing group assisted $C(sp^2)$-H functionalization of phenylacetamides **39a**. Initially, various additives, solvents,and oxidants were examined in the reaction of phenylacetamide **39a** with 1-iodo-4-methoxybenzene **40** in the presence of $Pd(OAc)_2$ (10 mol%) at 110 ^oC for 24 h. First, the catalytic reaction was tested without additive, and various additives such as

Ag_2CO_3, K_2CO_3, KOAc, $PhI(OAc)_2$ which were not fruitful (entries 4-7, Table 5). The Pd-catalyzed C-H arylation of arylacetamide **39a** with **40** without AgOAc additive under a nitrogen atmosphere failed to afford any product (entry 2, Table 5). This reaction indicated that AgOAc is very important to regenerate the catalyst via ligand exchange step via producing AgI and $Pd(OAc)_2$. The C-H arylation of arylacetamide **39a** with **40** in the presence of Ag_2CO_3 instead of AgOAc additives was not effective (entry 4, Table 5). The reaction of **39a** with **40** in the presence of K_2CO_3 gave the bisarylated product **41a** in less than 5% conversion of starting material (entry 5, Table 5).The arylation of **39a** with **40** in the presence of additives such as KOAc or $PhI(OAc)_2$ did not give the product **41a** (entries 6 and 7, Table 5). The C-H functionalization reaction of **39a** and **40** without any palladium catalyst failed to achieved any products (entry 1, Table 5) The C-H arylation of arylacetamide **39a** with **40** in presence of $PdCl_2$ and $Pd(TFA)_2$ instead of $Pd(OAc)_2$ catalyst gave the product **41a** in 50 and 44% yields, respectively (entries 8 and 9, Table 5). When the arylation of **39a** with **40** in the presence of the $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$ catalyst gave the product **41a** in 46 and 38% yields, respectively (entries 10 and 11, Table 5). The Pd-catalyzed arylation of arylacetamide **39a** with **40** using different solvents such as 1,2-DCE, 1,4-dioxane and ^{t}BuOH failed to give the product **41a** (entries 12-14, Table 5). The C-H arylation of **39a** with **40** in the presence of ^{t}AmylOH afforded the bisarylated product **41a** in 10% yield (entry 15, Table 5). The C-H arylation of phenylacetamide **39a** (0.12 mmol) with **40** (0.48 mmol) in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (0.25 mmol) in toluene at 110 ^{o}C furnished the arylated phenylacetamide **41a** in 86% yield (entry 3, Table 5).

Table 5 Optimization reactions.



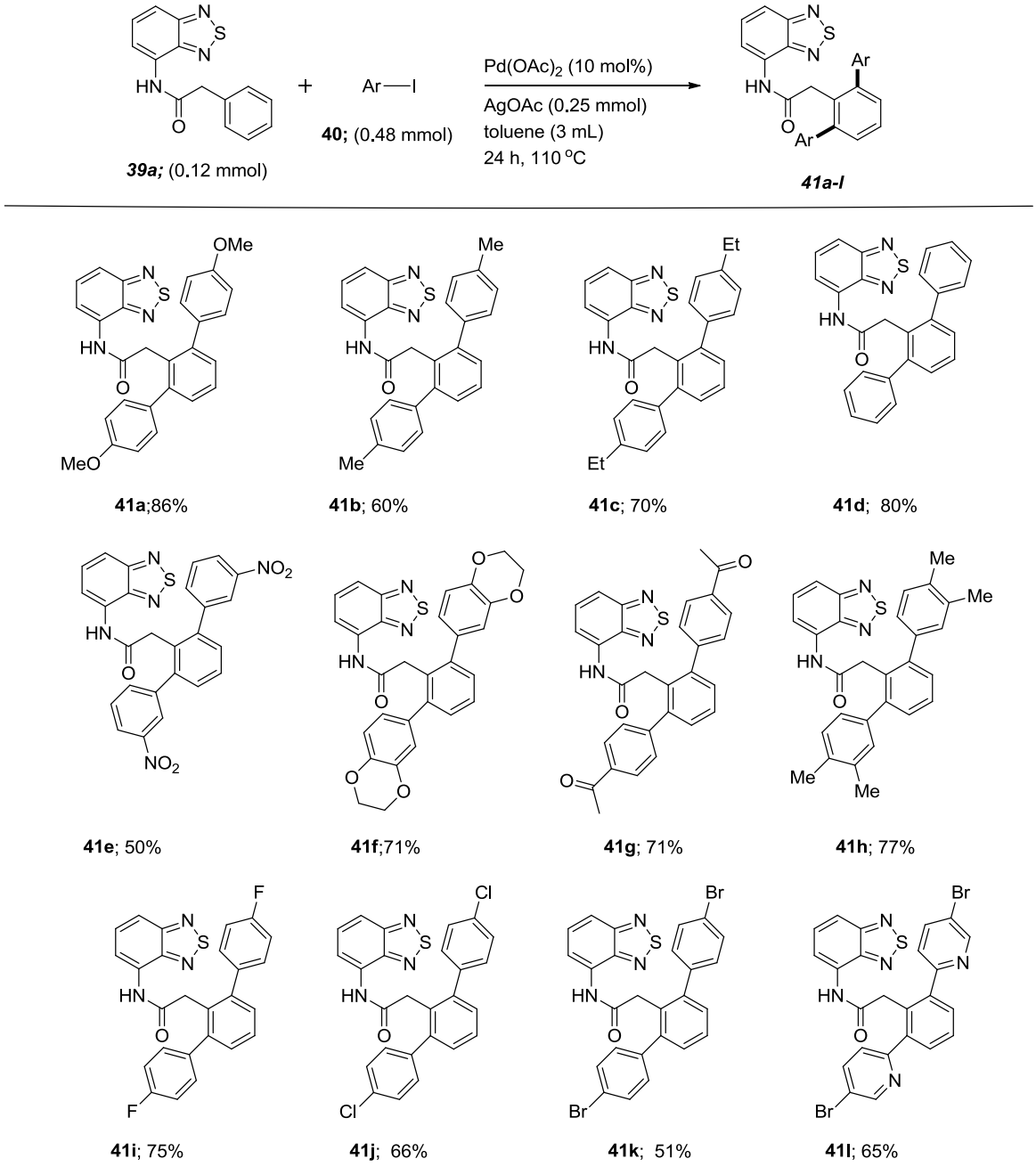
entry	PdL_2	additive	solvent (3 mL)	*t* (°C)	yield (***41a***)[a]
1	nil	AgOAc	toluene	110	0
2	$Pd(OAc)_2$	nil	toluene	110	0
3	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**86**
4	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	32
5	$Pd(OAc)_2$	K_2CO_3	toluene	110	5
6	$Pd(OAc)_2$	KOAc	toluene	110	15
7	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0
8	$PdCl_2$	AgOAc	toluene	110	50
9	$Pd(TFA)_2$	AgOAc	toluene	110	44
10	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	46
11	$Pd(PPh_3)_4$	AgOAc	toluene	110	38
12	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	0
13	$Pd(OAc)_2$	AgOAc	1,4-Dioxane	100	53
14	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	18
15	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	10

[a] All the reactions were performed using 1-iodo-4-methoxybenzene (**40**) under a nitrogen atmosphere.

Having the best optimization reaction conditions, we explore the scope of this ABTD directing group assisted Pd-catalyzed direct arylation of C(sp^2)-H bond of the phenylacetamide system using various electron donating and electron withdrawing group containing aryl iodides (Table 6). The Pd(II)-catalyzed arylation of C-H bond of phenylacetamide **39a** with iodobenzene and various electron donating group containing aryl iodides (e.g., OMe, Me, Et) gave the corresponding arylated phenylacetamide **41a-d** in 60-

86% yields. The arylation of C-H bond of **39a** with 1-iodo-3-nitrobenzene and 6-iodo-1,4-benzodioxane gave the arylated arylacetamide **41e** and **41f** in 50 and 71% yields respectively (Table 6).

Table 6 Bisarylated phenylacetamide C-H arylation of **39a**.

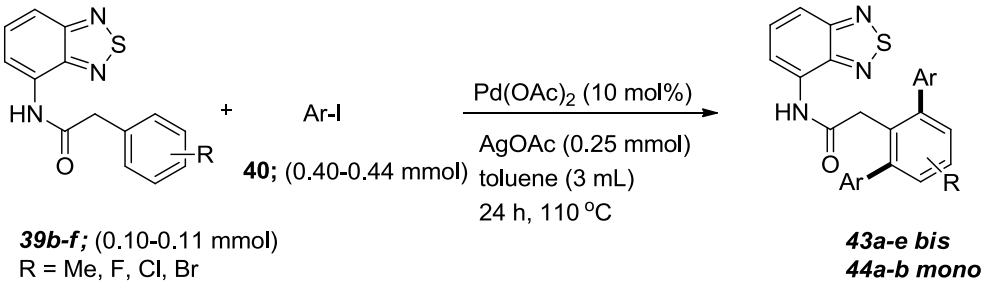


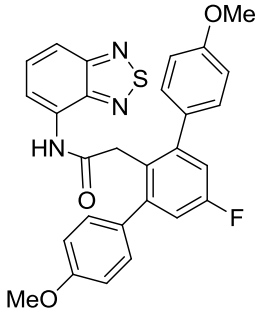
The Pd-catalyzed arylation of phenylacetamide **39a** with disubstituted aryl iodides such as dimethyl group afforded the bis phenylacetamide **41h** in 77% yield. The Pd-catalyzed

arylation of phenylacetamide **39a** with 4-iodoacetophenone and aryl iodide containing different halides gave the similar arylated phenylacetamide products **41g** and **41i-k** in 71 and 51-75% yields respectively (Table 6). After performing the reaction with aryl iodides, we further used the heterocyclic aryl halides such as 5-bromo-2-iodopyridine with **39a** afforded the heterocycle arylacetamides products **41l** with 65% yield.

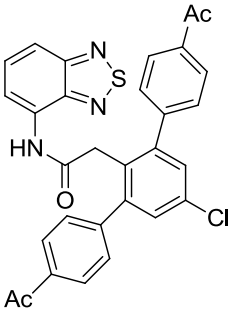
Then, the scope of this method further extended by using various substrate scope, we performed the γ-C-H arylation of multiple phenylacetamides containing different substituents in the phenyl ring. Accordingly, we synthesized the bis arylated products **43a-e** in 47-71% yields from their respective starting materials (Table 7). Then, we attempted the Pd(II) catalyzed ABTD-directed arylation of *ortho* C(sp^2)-H bonds of 2/3-substituted-benzamides **39b-f** with different aryl iodides that possessed electron donating groups at the *para/meta* position of the aryl ring in the corresponding aryl iodides and heterocyclic aryl iodide. These reactions afforded mono C-H arylated phenylacetamide **44a-b** in 50-65% yields (Table 7).

Table 7 Bis arylated phenylacetamide C-H arylation of substituted phenylacetamides **39b-f**.

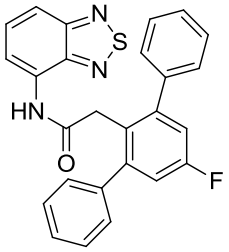




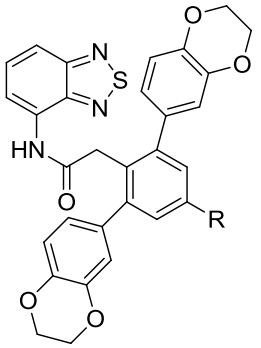
43a; 53%



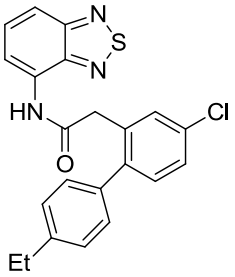
43b; 47%



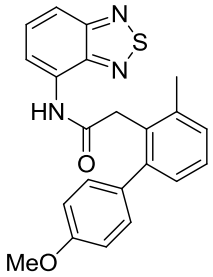
43c; 65%



43d; R= F; 52%
43e; R= Cl; 71%



44a; 51%

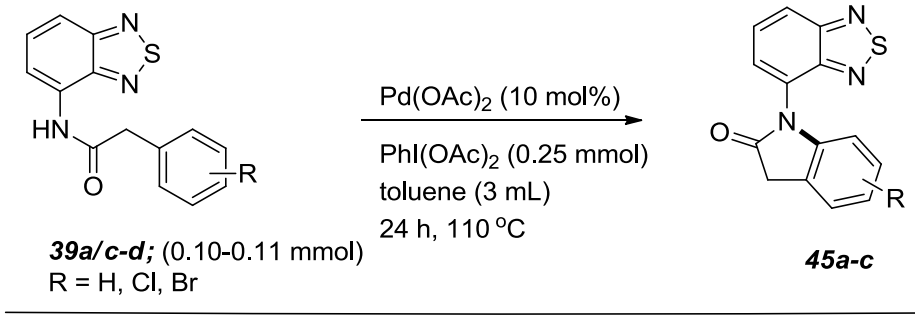


44b; 65%

Having done the development of Pd(II)-catalyzed bis/ monoarylated phenylacetamide by using various substituted/ nonsubstituted phenylacetamide system, finally we focus, on the cyclization of the γ-C-H bond of the phenylacetamide systems because, after the cyclization it will give very attractive biological active core moiety such as indolinone, The indolinone nucleus is an essential element of many natural and synthetic molecules with significant biological activity. Keeping the importance of indolinone in mind, we synthesis various indolinone derivatives by using different substrate with literature well-known condition[28]. Fortunately, in an initial trial, the cyclization of the γ-C-H bond of the phenylacetamide

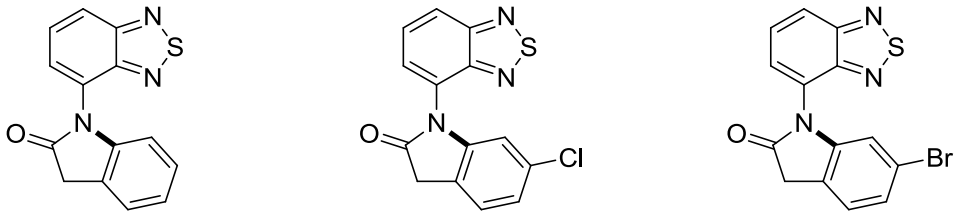
system **39a** (0.10-0.12 mmol) in the presence of $Pd(OAc)_2$ in 10 mol% and $PhI(OAc)_2$ in (2 equiv.) successfully afforded the cyclized phenylacetamide system or indolinone **45a** in 65% yield (Table 8). To improvethe substrate scope we carried out the cyclization of **39c-d** by using substituted phenylacetamides with standard cyclization condition & we afforded the indolinone derivatives **45b-c** in 45-50 % yields respectively (Table 8).

Table 8 Synthesis of indolinone moiety by the intramolecular cyclization of **39a/c-d**.



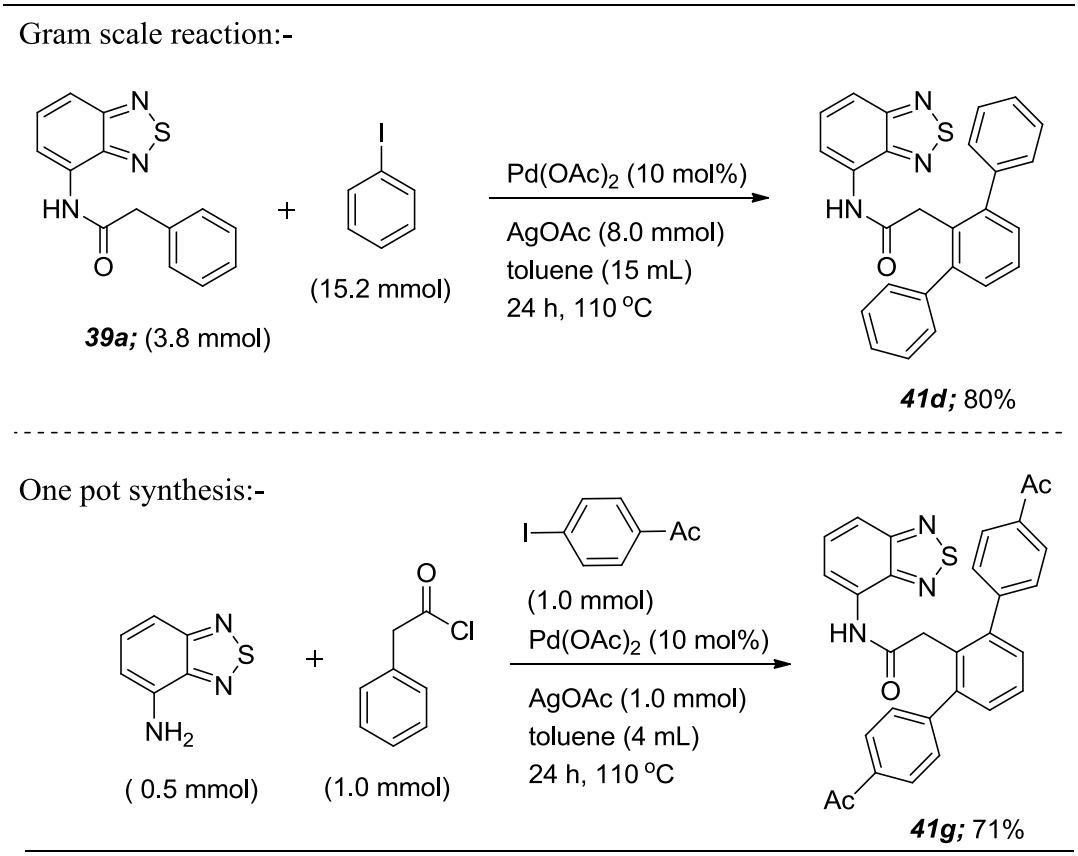
39a/c-d; (0.10-0.11 mmol)
R = H, Cl, Br

45a-c



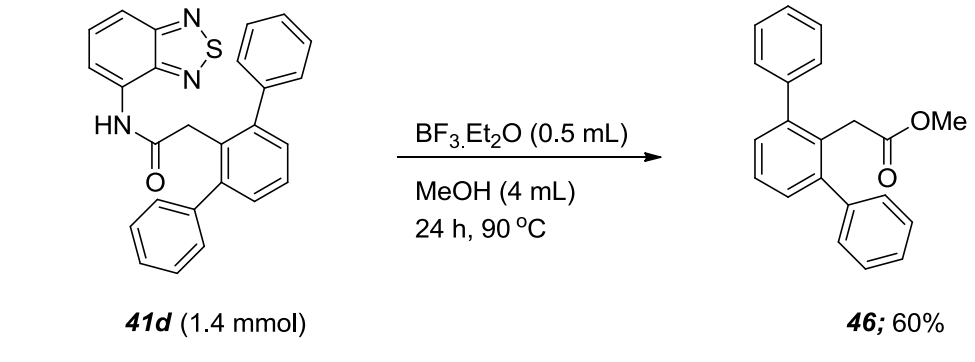
45a; 65% **45b;** 50% **45c;** 45%

After the successful development of indolinone derivatives, we also tested the double arylation of the γ-C-H bond of the arylacetamide system with iodobenzene in a gram scale manner and this reaction afforded the product **41d** in 80% yield (Scheme 30). We also put our efforts to the developed efficient synthesis of the bis-arylacetamide derivative in one pot manner of the γ-C-H bond. We envisioned that a one-pot reaction was also happend in our case with the use of phenylacetyl chloride and 4-Amino-2,1,3-Benzothiadiazole (ABTD) precursor directly in one pot manner. This method could be able to enhance the synthetic efficiency of C-H activation by merging the extra step and installation of the DGs. The Pd(II)-catalyzed γ-C-H activation of phenylacetamide in the presence of ABTD, by means of one pot reactions by directly using phenylacetyl chloride (1 mmol), ABTD (0.5 mmol) and 4-iodoacetophenone (2 mmol) as an aryl iodide source, furnished the product **41g** in 71% yield (Scheme 30).



Scheme 30 Gram scale reaction of phenylacetamide **39a** and one-pot synthesis.

Then, we wished to remove the bidentate ligand (ABTD) from the γ-C-H arylated phenylacetamide system.We treated the bis arylated arylacetamidesystem **41d** with $BF_3.OEt_2$ in MeOH, which successfully lead to the methyl ester of ortho-diarylated phenylacetic acid **46** after the removal of the bidentate ligand 4-Amino-2,1,3-Benzothiadiazole (ABTD) in 60% yield (Scheme 31).



Scheme 31 Removal of the bidentate ligand 4-Amino-2,1,3-Benzothiadiazole (ABTD).

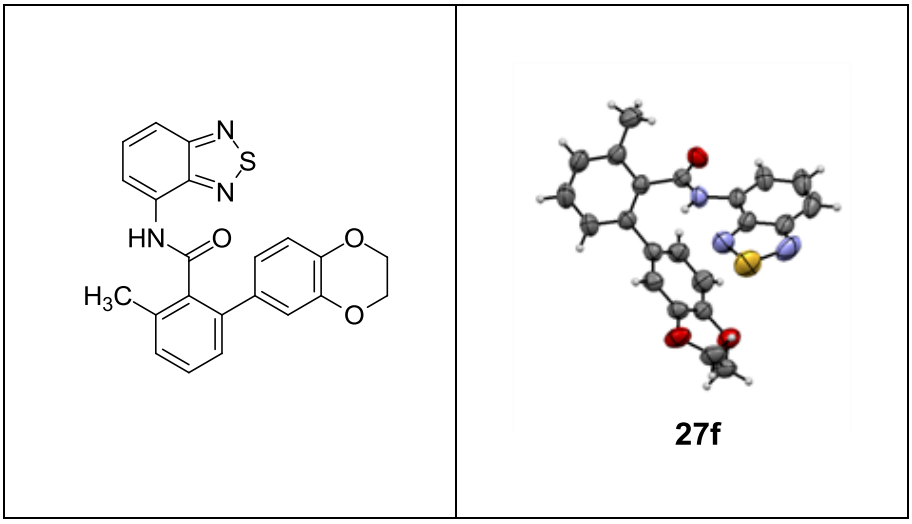
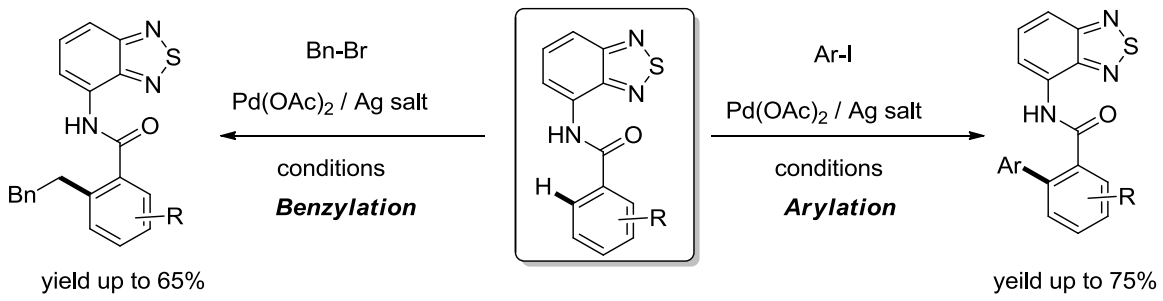


Figure 4 X-ray (ORTEP diagram) structure of the compound **27f**.

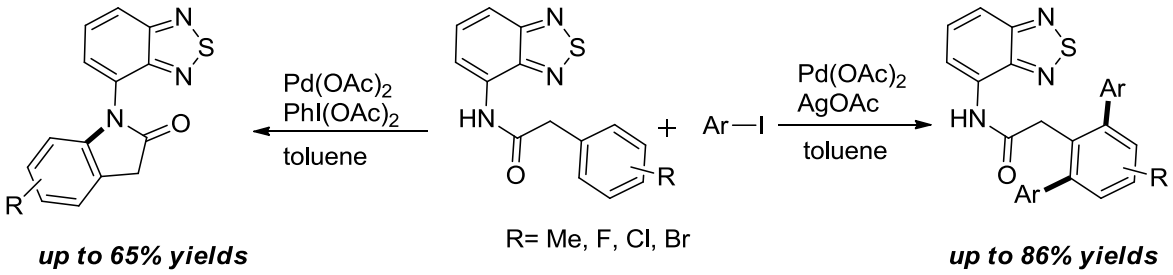
Conclusion

In summary, **Chapter 3** revealed that 4-amino-2,1,3-benzothiadiazole (ABTD) as a new bidentate directing group for the $Pd(OAc)_2$/AgOAc catalytic system-based β–γ-C(sp^2)-H activation/functionalization and C-C/C-O bond formation.

The part 1 of **chapter 3** revealed the investigation on the $Pd(OAc)_2$-catalyzed β-C(sp^2)-H bond of benzamide system. Given the importance of the benzamide and heterocyclic derivatives in organic synthesis and medicinal chemistry, this method has provided access to assemble new ortho-substituted benzamides.



The part 2 of **chapter 3** revealed the Pd(II)-catalyzed arylation and intramolecular cyclization of γ-C(sp^2)-H bonds using the substituted phenylacetamide system. Various example made up of the γ-C-H activation of phenylacetamide was synthesized in moderate to good yield. Further, the Pd(II)-catalyzed, ABTD-directed cyclization *via*γ-C-H activation of various phenylacetamides afforded the cyclised products such as indolinone in good yield, this route has provided anew path of synthesis of indolinone core from various phenylacetamide.



Hence, we believe that ABTD might serve as an optional directing group when the site-selective C-H activation/functionalization of suitable carboxylic acid substrates is explored.

All the compounds included in chapter 3 of the thesis are characterized by ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data of all compounds and complete experimental details are given in the experimental section.

Experimental Section.

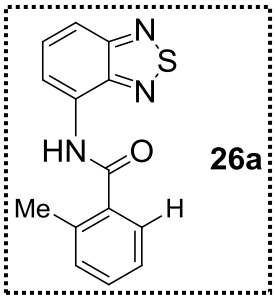
Part 1:

General. IR spectra were recorded as KBr pellets or thin films. ^{1}H / ^{13}C NMR spectrawere recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulfate. TLC analysis was performed on silica gel, and the components were visualized by observation under iodine vapor. Isolated yields of all the compounds are reported, and yields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures. Compound **37a-c** reported in the literature[4,5,6].

General procedure for the synthesis of benzamides/carboxamides 26d, 28a, 28b, and 28d. A dry flask containing 4-amino-2,1,3-benzothiadiazole (1 mmol, 151 mg), Et_3N (1.1 mmol, 115 mg) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by dropwise addition of an appropriate acid chloride (1 mmol). The resulting mixture allowed to stir at rt for 12 h. After this duration, the reaction mixture was diluted with dichloromethane and washed with water and twice with a saturated aqueous $NaHCO_3$ solution. The combined organic layers were dehydrated over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture was done by column chromatography (silica gel, 100-200 mesh, EtOAc/hexanes = 1:4) furnished the corresponding benzamides **26d, 28a, 28b,** and **28d**.

General procedure for the synthesis of benzamides 26a-c, 26e and 28c. The corresponding carboxylic acid (3 mmol) was dissolved in dry DCM (15 mL) by adding 2 to 3 drops of dry DMF, to this reaction mixture oxalyl chloride (1.5 equiv, 190 mg) was added at 0 ^oC and then, the reaction mixture was stirred and allowed to attain rt over the period of 6-8 h under a nitrogen atm. After this period, the reaction mixture was concentrated in vacuum to remove excess oxalyl chloride and solvent. The resultant acid chloride was dissolved in DCM (15 mL). Then, this DCM solution was added to a separate flask containing 4-amino-2,1,3-benzothiadiazole (2 mmol, 302 mg) and Et_3N (1.5 equiv., 303 mg) in DCM (3 mL) at 0 ^oC. After this, the resultant reaction mixture was stirred and allowed to attain rt over the period of 6-8 h under a nitrogen atm. After this time period, the reaction mixture was diluted with dichloromethane and then washed with water followed by a saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried up over anhydrous Na_2SO_4 and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, EtOAc/hexanes = 20:80) furnished benzamides **26a-c, 26e,** and **28c**.

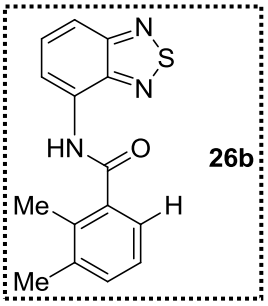
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-methylbenzamide (26a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **26a** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.68; Yield: 60% (326 mg); mp: 147−149 °C; IR (DCM): 3054, 2305, 1265, 895, 743, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.88 (br. s, 1H), 8.68 (d, 1H, *J*= 7.2 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 7.70-7.66 (m, 2H), 7.46 (t, 1H, *J*= 7.1



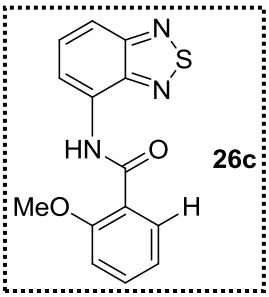
26a

Hz), 7.37-7.34 (m, 2H), 2.61.(s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 154.8, 147.9, 136.9, 135.6, 131.6, 131.2, 130.9, 130.1, 127.1, 126.2, 116.0, 115.0, 20.2; HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M+H]^+$ 270.0701 found 270.0708.

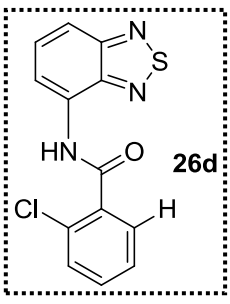
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2,3-dimethylbenzamide (26b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **26b** as a yellow color solid; R_f (20% EtOAc/Hexanes) 0.70; Yield: 35% (100 mg); mp: 147−149 °C; IR (DCM): 3054, 2986, 1421, 895, 739, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.83 (br. s, 1H), 8.79 (d, 1H, *J*= 7.3 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2= 0.8 Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2= 7.3 Hz), 7.45 (d, 1H, *J*= 7.4 Hz), 7.33 (d, 1H, *J*= 7.4 Hz), 7.24 (t, 1H, *J*= 7.6 Hz), 2.46 (s, 3H), 2.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.0, 154.8, 147.9, 138.5, 136.6, 134.8, 132.1, 131.2, 130.1, 125.9, 124.6, 116.0, 115.1, 204, 16.5; HRMS (ESI) calcd for $C_{15}H_{14}N_3OS$ $[M+H]^+$ 284.0858 found 284.0862.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-methoxybenzamide (26c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **26c** as a yellow colour solid; R_f (20% EtOAc/Hexanes) 0.54; Yield: 25% (100 mg); mp: 144−146 °C; IR (DCM): 3054, 2986, 1550, 895, 747, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.50 (br. s, 1H), 8.71 (dd, 1H, J_1 = 7.1, J_2= 1.2 Hz), 8.35 (dd, 1H, J_1 = 7.8, J_2= 1.8 Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2= 1.2 Hz), 7.66-7.62 (m, 1H), 7.57-7.53 (m, 1H), 7.19-7.15 (m, 1H), 7.10 (d, 1H, *J*= 8.3 Hz), 4.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 157.7, 154.9, 148.5, 133.7, 132.5, 131.4, 130.9, 121.6, 121.2, 115.4, 115.3, 111.7, 56.3; HRMS (ESI) calcd for $C_{14}H_{12}N_3O_2S$ $[M+H]^+$ 286.0650 found 286.0659.

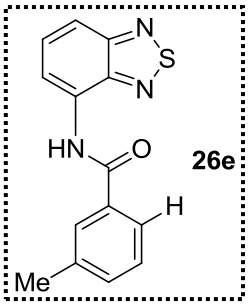


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-chlorobenzamide (26d)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **26d** as a yellow color solid; R_f (20% EtOAc/Hexanes) 0.60; Yield: 86% (250 mg); mp: 141-143 °C**;** IR (DCM); 3053, 1699, 1456, 895, 747, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (br. s, 1H), 8.69 (d, 1H, *J*= 7.3 Hz), 7.90 (dd, 1H, J_1 = 7.4 J_2= 1.9 Hz), 7.76 (dd, 1H, J_1 = 8.8 J_2= 0.8 Hz), 7.70-7.66 (m, 1H),

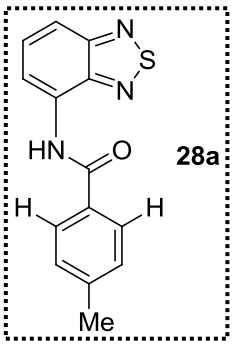


7.55-7.43 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 154.8, 147.9, 134.4, 132.2, 131.1, 131.0, 130.7, 130.7, 129.8, 127.4, 116.4, 115.5; HRMS (ESI) calcd for $C_{13}H_9ClN_3OS$ $[M+H]^+$ 290.0155 found 290.0150.

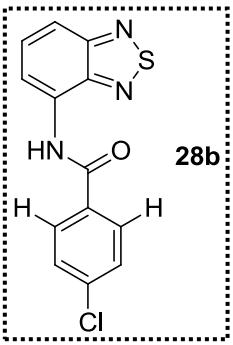
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methylbenzamide(26e)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane = 20:80) to afford **26e** as a pale yellow solid; Yield: 51% (274 mg); R_f (20% EtOAc/Hexanes) 0.68; mp: 145−147 °C; IR (DCM): 3054, 1653, 1411, 1265,746, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (br. s, 1H), 8.67 (d, 1H, *J*= 7.2 Hz), 7.84 (br. s, 1H), 7.82 (d, 1H, *J*= 6.7, Hz), 7.74 (d, 1H, *J*= 8.8, Hz), 7.70-7.66 (m, 1H), 7.48-7.49 (m, 2H), 2.50 (s, 3H) $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.8, 154.8, 148.1, 139.0, 134.2, 133.2, 131.2, 130.1, 128.9, 127.9, 124.2, 115.9, 115.0, 21.5, HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M+H]^+$ 270.0701 found 270.0689.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-methylbenzamide (28a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **28a** as a pale yellow color solid; R_f (20% EtOAc/Hexanes) 0.68; Yield: 94% (255 mg); mp: 118−120 °C; IR (DCM): 3053, 2986, 1548, 895, 741, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (br. s, 1H), 8.67 (dd, 1H, J_1 = 7.2, J_2 = 1.0 Hz), 7.94 (d, 2H, *J* = 8.2 Hz), 7.74 (dd, 1H, J_1 = 8.8, J_2 = 1.1 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.38 (d, 2H, *J* = 7.9 Hz), 2.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 154.8, 148.1, 143.1, 131.3, 130.2, 129.7, 129.2, 127.2, 115.8, 115.0, 21.6; HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M+H]^+$ 270.0701 found 270.0711.

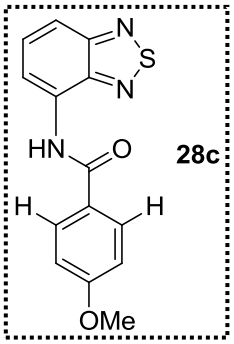


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-chlorobenzamide (28b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **28b** as a pale yellow color solid; R_f (20% EtOAc/Hexanes) 0.60; Yield: 60% (174 mg); mp: 151−153 °C**;** IR (DCM): 3054, 2986, 1548, 1265, 741, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (br. s, 1H), 8.64 (dd, 1H, J_1= 7.3, J_2= 0.8 Hz), 7.97 (d, 2H, *J*= 8.7 Hz), 7.75 (dd, 1H, J_1= 8.8, J_2= 1.0 Hz), 7.68 (dd, 1H,

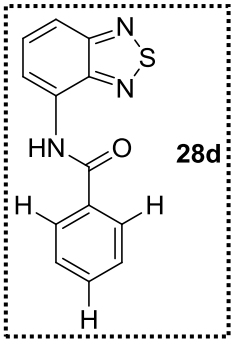


J_1 = 8.8, J_2 = 7.3 Hz), 7.55 (d, 2H, J= 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 154.8, 148.0, 138.8, 132.5, 131.2, 129.8, 129.3, 128.6, 116.2, 115.2; HRMS (ESI) calcd for $C_{13}H_9ClN_3OS$ $[M+H]^+$ 290.0155 found 290.0161.

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-methoxybenzamide (28c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **28c** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.54; Yield: 35% (100 mg); mp: 150−152 °C**;** IR (DCM): 3054, 2986, 2305, 895, 741, cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (br. s, 1H), 8.65 (dd, 1H, J_1 = 7.2, J_2= 1.0 Hz), 8.01 (d, 2H, J= 8.8 Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2= 1.1 Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.06 (d, 2H, J= 8.8 Hz), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 162.9, 154.8, 148.1, 131.3, 129.2, 126.4, 115.7, 114.8, 114.2, 55.6; HRMS (ESI) calcd for $C_{14}H_{12}N_3O_2S$ $[M+H]^+$ 286.0650 found 286.0644.



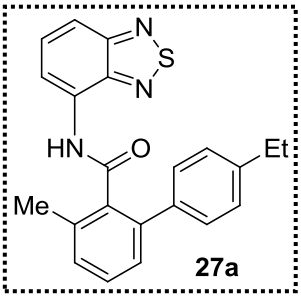
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)benzamide (28d)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **28d** as a pale yellow color solid; R_f (20% EtOAc/Hexanes) 0.70; Yield: 70% (177 mg); mp: 124−126 °C; IR (DCM): 3054, 2986, 1681, 895, 747, cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 9.27 (br. s, 1H), 8.66 (dd, 1H, J_1= 7.2, J_2= 0.6 Hz), 8.03 (d, 2H, J= 7.0 Hz), 7.73 (dd, 1H, J_1= 8.8, J_2= 0.9 Hz), 7.67 (dd, 1H, J_1= 8.8, J_2= 7.3 Hz), 7.62 (d, 1H, J= 7.2 Hz), 7.57 (t, 1H, J= 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 154.8, 148.0, 134.2, 132.4, 131.2, 130.0, 129.0, 127.2, 116.0, 115.1; HRMS (ESI) calcd for $C_{13}H_{10}N_3OS$ $[M+H]^+$ 256.0545 found 256.0547.



General procedure for the Pd(II)-catalyzed, ABTD-directed *ortho*-C(sp^2)-H arylation and benzylation of benzamides 26a-e and 28a-d. An appropriate benzamide **26/28** (0.12 mmol, 1 equiv.), $Pd(OAc)_2$ (10 mol%, 2.7 mg), an appropriate aryl iodide or 1-(bromomethyl)-4-nitrobenzene (0.36 mmol-0.48 mmol, 4 equiv.) and AgOAc (0.24-0.264 mmol, 2-2.2 equiv., 40-43.8 mg,) in anhydrous toluene (3 mL) was heated at 110 ^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

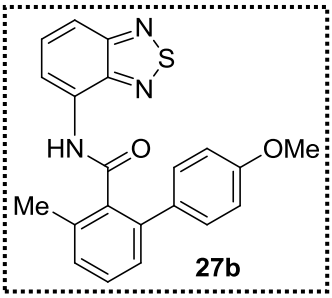
furnished the corresponding *ortho*C(sp^2)-H arylated/benzylatedbenzamides **27**/**29**/**32**/**33**(see the corresponding Tables/Schemes for specific examples).

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-ethyl-3-methyl-[1,1'-biphenyl]-2-carboxamide (27a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27a** as a pale yellow semi-solid; R_f (20% EtOAc/Hexanes) 0.72; Yield: 70% (21 mg); IR (DCM): 3054, 2986, 1421, 1265, 895 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, 1H, J_1= 7.2, J_2 = 0.8 Hz), 8.26 (br. s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 0.9 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.41 (d, 2H, J = 8.3 Hz), 7.32 (t, J = 2H, 7.5 Hz), 7.06 (d, 2H, J = 8.0 Hz), 2.55 (s, 3H), 2.46 (q, 2H, J = 7.6 Hz), 0.98 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.6, 154.6, 147.6, 143.6, 139.8, 137.4, 136.2, 135.7, 131.0, 129.9, 129.7, 129.5, 128.5, 127.9, 127.6, 115.8, 114.8, 28.3, 19.8, 15.3; HRMS (ESI) calcd for $C_{22}H_{20}N_3OS$ $[M+H]^+$ 374.1327 found : 374.1319.



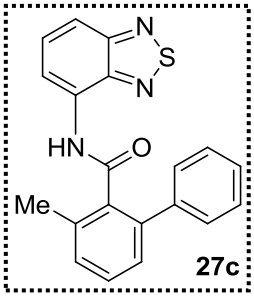
27a

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (27b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27b** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.46; Yield: 58% (25 mg); mp: 112−114 °C; IR (DCM): 3054, 2987, 2305, 1683, 740 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H J = 7.3 Hz), 8.30 (br. s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H J_1 = 8.8, J_2 = 7.3 Hz), 7.45 (d, 2H, J = 8.6 Hz), 7.46-7.42 (m, 1H), 7.31 (d, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 7.6 Hz), 6.80 (d, 2H, J = 8.6 Hz), 3.68 (s, 3H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.7, 159.1, 154.6, 147.6, 139.3, 136.1, 135.8, 132.5, 131.0, 129.8, 129.7, 129.3, 127.6, 115.9, 114.9, 113.9, 55.1, 19.8; HRMS (ESI) calcd for $C_{21}H_{18}N_3O_2S$ $[M+H]^+$ 376.1120 found 376.1130.

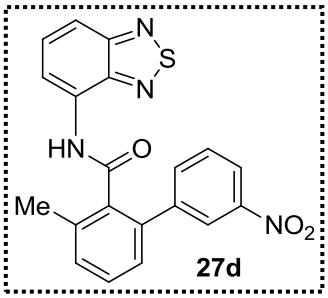


27b

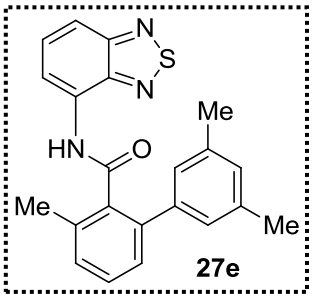
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (27c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27c** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.52; Yield: 55% (22 mg); mp: 154−156 °C**;** IR (DCM): 2987, 2306, 1422, 1265, 743 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 7.5 Hz), 8.31 (d, 1H, *J* = 8.2 Hz), 8.22 (d, 1H, *J* = 8.9 Hz), 7.85 (dd, 1H, J_1 = 8.8, J_2 = 7.0 Hz), 7.72-7.69 (m, 2H), 7.44 (d, 1H, *J* = 7.4 Hz), 7.30-7.21 (m, 3H), 6.49 (d, 1H, *J* = 8.1 Hz), 2.92 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.5, 156.3, 152.1, 143.3, 138.6, 135.9, 132.3, 132.0, 131.0, 130.5, 129.6, 129.2, 123.8, 122.8, 122.6, 120.3, 119.5, 115.9, 24.5; HRMS (ESI) calcd for $C_{20}H_{16}N_3OS$ $[M+H]^+$ 346.1014 found 346.1015. The NH proton was detected in the ^{1}H NMR spectrum.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methyl-3'-nitro-[1,1'-biphenyl]-2-carboxamide (27d)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27d** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.40; Yield: 65% (30 mg); mp: 133−135 °C**;** IR (DCM): 3055, 2987, 2305, 1422, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, *J* = 7.4 Hz), 8.42 (br. s, 1H), 8.34 (br. s, 1H), 8.03 (dd, 1H, J_1 = 8.2, J_2 = 0.9 Hz), 7.85 (d, 1H, *J* = 7.7 Hz), 7.69 (d, 1H, *J* = 8.9 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.43 (t, 2H, *J* = 7.8 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 2.57 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.7, 154.6, 148.2, 147.5, 141.7, 137.1, 136.4, 135.9, 134.6, 130.9, 130.8, 130.1, 129.4, 129.2, 127.5, 123.6, 122.5, 116.5, 115.4, 19.7; HRMS (ESI) calcd for $C_{20}H_{15}N_4O_3S$ $[M+H]^+$ 391.0865 found 391.0857.

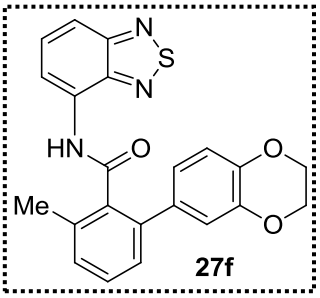


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3,3',5'-trimethyl-[1,1'-biphenyl]-2-carboxamide (27e)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27e** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.64; Yield: 58% (26 mg); mp: 118−120 °C**;** IR (DCM): 3055, 2987, 2305, 1422, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, 1H, J_1 = 7.2, J_2 = 0.9



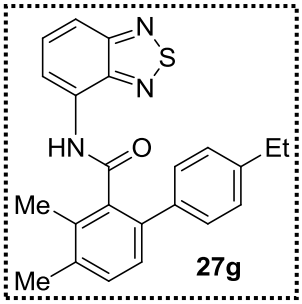
Hz), 8.26 (br. s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 1.1 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.32 (d, 1H, J = 7.7 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.10 (br. s, 2H), 6.69 (br. s, 1H), 2.55 (s, 3H), 2.15 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.6, 154.6, 147.6, 140.1, 140.0, 137.9, 136.2, 135.7, 131.0, 130.0, 129.7, 129.5, 129.0, 127.5, 126.4, 115.7, 114.6, 21.1, 19.9; HRMS (ESI) calcd for $C_{22}H_{20}N_3OS$ $[M+H]^+$ 374.1327 found 374.1322.

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-methylbenzamide (27f).** Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27f** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.45; Yield: 77% (37 mg); mp: 159−161 °C**;** IR (DCM): 3055, 2987, 2305, 1422, 749 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 1H, J_1 = 7.2, J_2 = 0.8 Hz), 8.32 (br. s, 1H), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 1.0 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.42 (dd, 1H, J_1 = 8.0, J_2 = 7.8 Hz), 7.29 (d, 2H, J = 7.0 Hz), 7.04 (d, 1H, J = 2.2 Hz), 6.97 (dd, 1H, J_1 = 8.4, J_2 = 2.2 Hz), 6.71 (d, 1H, J = 8.3 Hz), 4.13-4.10 (m, 4H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.5, 154.7, 147.7, 143.4, 139.1, 136.1, 135.7, 133.5, 131.1, 129.9, 129.7, 129.4, 127.6, 121.8, 117.5, 117.2, 115.9, 115.0, 64.3, 64.2, 19.8; HRMS (ESI) calcd for $C_{22}H_{18}N_3O_3S$ $[M+H]^+$ 404.1069 found 404.1065.



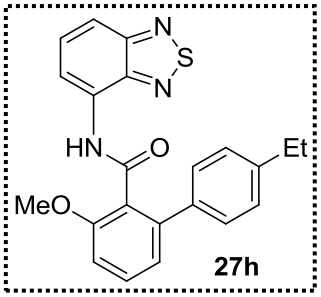
27f

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-ethyl-3,4-dimethyl-[1,1'-biphenyl]-2-carboxamide (27g)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27g** as a pale yellow colour semi-solid; R_f (20% EtOAc/Hexanes) 0.65; Yield: 58% (27 mg); IR (DCM): 3054, 2987, 2686, 1547, 748 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, 1H, J_1 = 7.2, J_2 = 1.0 Hz), 8.31 (br. s, 1H), 7.65 (dd, 1H, J_1= 8.9, J_2 = 1.0 Hz), 7.59 (dd, 1H, J_1= 8.8, J_2 = 7.2 Hz), 7.40 (d, 2H, J = 8.2 Hz), 7.34 (d, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 7.8 Hz), 7.05 (d, 2H, J = 8.2 Hz), 2.46 (q, 2H, J = 7.6 Hz), 2.43 (s, 3H), 2.40 (s, 3H), 0.99 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 154.6, 147.6, 143.3, 137.5, 137.4, 136.6, 136.2, 134.2, 131.1, 131.0, 129.9, 128.5, 127.8, 127.4, 115.8, 114.9, 28.3, 20.2, 16.7, 15.3; HRMS (ESI) calcd for $C_{23}H_{22}N_3OS$ $[M+H]^+$ 388.1484 found 388.1484.

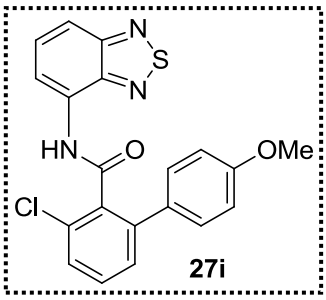


27g

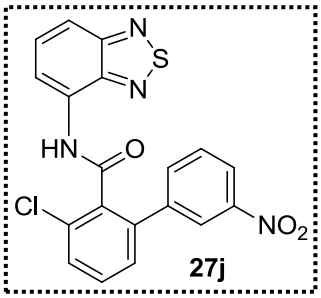
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-ethyl-3-methoxy-[1,1'-biphenyl]-2-carboxamide (27h)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27h** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.64; Yield: 50% (21 mg); mp: 152−154 °C; IR (DCM): 3054, 2986, 1421, 895, 742 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (br. s, 1H), 8.53 (d, 1H, *J*= 7.3Hz), 7.66 (d, 1H, *J*= 8.8Hz), 7.59 (dd, 1H, J_1 = 8.6, J_2 = 7.6 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 7.9 Hz), 7.13-7.08 (m, 3H), 7.03 (d, 1H, *J* = 8.4 Hz), 3.93 (s, 3H), 2.54 (q, 2H, *J* = 7.6 Hz), 1.10 (t, 3H, *J* = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.2, 156.8, 154.7, 147.7, 143.7, 141.9, 137.0, 131.2, 130.9, 130.1, 128.4, 127.9, 125.2, 122.7, 115.6, 115.0, 109.9, 56.1, 28.4, 15.3; HRMS (ESI) calcd for $C_{22}H_{19}N_3NaO_2S$ $[M+Na]^+$ 412.1096 found 412.1087.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide (27i)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27i** as a green colour semi-solid; R_f (20% EtOAc/Hexanes) 0.48; Yield: 70% (33 mg); IR (DCM): 3054, 2987, 1689, 1422, 751 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J* = 7.3, Hz), 8.45 (br. s, 1H), 7.70 (d, 1H, *J* = 8.8 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.50-7.44 (m, 4H), 7.38 (dd, 1H, J_1 = 6.0, J_2 = 6.0 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 159.5, 154.7, 147.6, 141.5, 135.1, 131.8, 131.1, 131.0, 130.7, 129.7, 129.5, 128.7, 128.4, 116.3, 115.4, 114.0, 55.2; HRMS (ESI) calcd for $C_{20}H_{15}ClN_3O_2S$ $[M+H]^+$ 396.0574 found 396.0554.

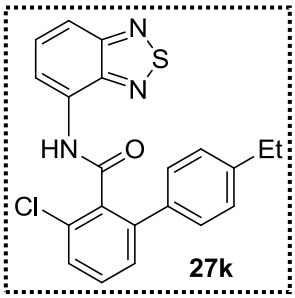


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-chloro-3'-nitro-[1,1'-biphenyl]-2-carboxamide (27j)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27j** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.39; Yield: 53% (26 mg); mp: 198−200 °C**;** IR (DCM): 3055, 2987, 1422, 1265, 741 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (br. s,

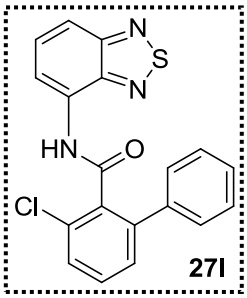


1H), 8.44 (d, 1H *J* = 7.4 Hz), 8.41 (br. s, 1H), 8.12 (d, 1H, *J* = 8.2 Hz), 7.87 (d, 1H, *J* = 7.6 Hz), 7.71 (d, 1H, *J* = 8.8 Hz), 7.61-7.54 (m, 3H,), 7.49 (t, 1H, *J* = 8.0Hz), 7.43 (d, 1H, *J* = 7.4 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 154.6, 148.2, 147.5, 140.4, 139.4, 135.3, 134.6, 132.1, 131.2, 130.9, 130.0, 129.6, 129.0, 128.6, 123.6, 123.1, 116.8, 115.8; HRMS (ESI) calcd for $C_{19}H_{12}ClN_4O_3S$ $[M+H]^+$ 411.0319 found 411.0311.

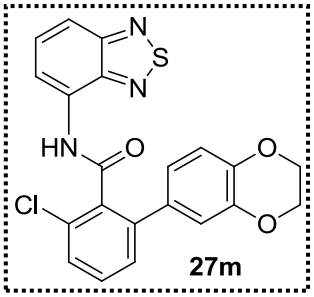
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-chloro-4'-ethyl-[1,1'-biphenyl]-2-carboxamide (27k)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27k** as a greenish yellow colour semi-solid; R_f (20% EtOAc/Hexanes) 0.64; Yield: 65% (30 mg); IR (DCM): 3054, 2305, 1422, 896, 741 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, 1H, *J* = 7.3 Hz), 8.44 (br. s, 1H), 7.68 (d, 1H, *J* = 8.8 Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.50-7.46 (m, 2H), 7.43 (d, 2H, *J* = 8.1 Hz), 7.41-7.39 (m, 1H), 7.12 (d, 2H, *J* = 8.1 Hz), 2.53 (q, 2H, *J* = 7.6Hz), 1.07 (t, 3H, *J* = 7.6Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 154.6, 147.6, 144.3, 141.9, 136.1, 135.1, 131.8, 131.0, 130.7, 129.5, 128.7, 128.6, 128.4, 128.1, 116.2, 115.3, 28.4, 15.2; HRMS (ESI) calcd for $C_{21}H_{17}ClN_3OS$ $[M+H]^+$ 394.0781 found 394.0783.



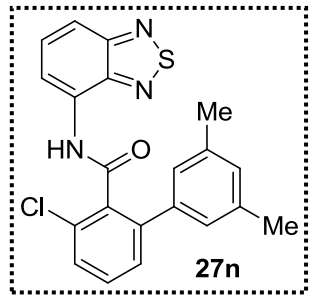
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-chloro-[1,1'-biphenyl]-2-carboxamide (27l)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27l** as a pale yellow colour semi-solid; R_f (20% EtOAc/Hexanes) 0.59; Yield: 60% (26 mg); IR (DCM): 3384, 2923, 1688, 1547, 784 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.45 (br. s, 1H), 7.69 (dd, 1H, J_1 = 8.9, J_2 = 0.9 Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.54-7.48 (m, 4H), 7.41 (dd, 1H, J_1 = 6.9, J_2 = 6.9 Hz), 7.31 (t, 2H, *J* = 7.4 Hz), 7.25-7.20 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.2, 154.6, 147.6, 141.9, 138.8, 135.2, 131.8, 131.0, 130.8, 129.4, 128.8, 128.7, 128.6, 128.5, 128.1, 116.3, 115.3; HRMS (ESI) calcd for $C_{19}H_{13}ClN_3OS$ $[M+H]^+$ 366.0468 found 366.0454.



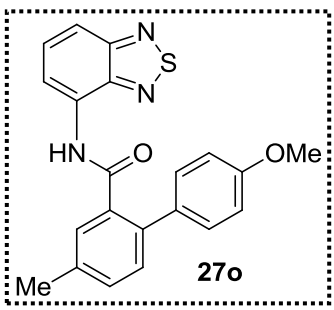
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-chloro-6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)benzamide (27m)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27m** as a greenish yellow colour semi-solid; R_f (20% EtOAc/Hexanes) 0.48; Yield: 59% (30 mg); mp: 98−100 °C**;** IR (DCM): 2987, 2305, 1422, 896, 740 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, J = 7.3 Hz), 8.48 (br. s, 1H), 7.70 (d, 1H, J = 8.8 Hz), 7.62 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.49-7.44 (m, 2H), 7.36 (dd, 1H, J_1 = 6.8, J_2 = 6.8 Hz), 7.03 (d, 1H, J = 2.0 Hz), 6.99 (dd, 1H, J_1 = 8.3, J_2 = 2.0 Hz), 6.76 (d, 1H, J = 8.3 Hz), 4.16 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 154.7, 147.7, 143.6, 143.5, 141.3, 135.0, 132.1, 131.8, 131.1, 130.7, 129.6, 128.6, 128.5, 121.7, 117.6, 117.4, 116.2, 115.4, 64.3, 64.2; HRMS (ESI) calcd for $C_{21}H_{15}ClN_3O_3S$ $[M+H]^+$ 424.0523 found 424.0529.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxamide (27n)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **27n** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.65; Yield: 75% (35 mg); mp: 116−118 °C**;** IR (DCM): 3054, 2986, 1421, 895, 740 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, 1H, J_1= 7.3, J_2 = 0.6 Hz), 8.43 (br. s, 1H), 7.69 (dd, 1H, J_1 = 8.9, J_2 = 0.9 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.51-7.45 (m, 2H), 7.39 (dd, 1H, J_1= 7.1, J_2= 7.1 Hz), 7.11 (s, 2H), 6.80 (s, 1H), 2.19 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3, 154.6, 147.6, 142.2, 138.7, 138.1, 135.1, 131.8, 131.0, 130.7, 129.7, 129.6, 128.6, 128.6, 126.3, 116.1, 115.2, 21.2; HRMS (ESI) calcd for $C_{21}H_{17}ClN_3OS$ $[M+H]^+$ 394.0781 found 394.0770.

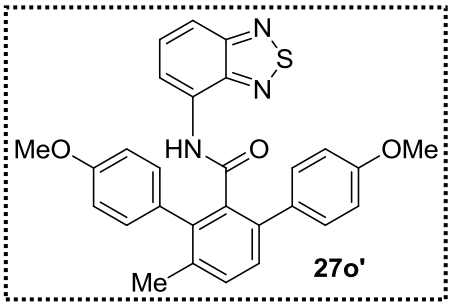


***N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-methoxy-4-methyl-[1,1'-biphenyl]-2-carboxamide(27o)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **27o** as a pale yellow viscous liquid; Yield: 44% (20 mg); R_f (20% EtOAc/Hexanes) 0.52; IR (DCM): 3385, 3057, 1545, 1265, 744, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, J= 7.1 Hz), 8.43 (br. s, 1H), 7.72 (br. s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2= 1.0, Hz), 7.60 (dd, 1H, J_1 = 8.8,

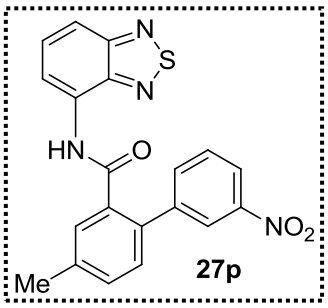


J_2= 7.2, Hz), 7.42 (d, 2H, *J*= 8.6, Hz), 7.39-7.36 (m, 2H), 6.85 (d, 2H, *J*= 8.6, Hz), 3.71 (s, 3H) 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.2, 159.5, 154.6, 147.5, 137.4, 137.0, 134.6, 131.9, 131.8, 131.1, 130.6, 130.1, 130.0, 115.7, 114.5, 114.3, 55.2, 21.0; HRMS (ESI) calcd for $C_{21}H_{18}N_3O_2S$ $[M+H]^+$ 376.1120 found 376.1106.

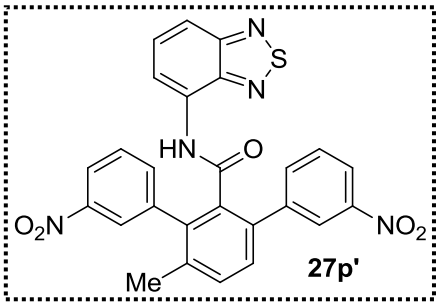
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4''-dimethoxy-4'-methyl-[1,1':3',1''-terphenyl]-2'-carboxamide (27o′)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **27o′**as a pale yellow viscous liquid; Yield: <10% (6 mg); R_f (20% EtOAc/Hexanes) 0.45; IR (DCM): 3385, 3057, 1545, 1265, 744, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (br. s, 1H), 8.17 (d, 1H, *J*= 7.4 Hz), 7.58 (d, 1H, *J*= 8.8, Hz), 7.47-7.43 (m, 4H), 7.36 (d, 1H, *J*= 7.8 Hz), 7.26 (d, 2H, *J*= 7.4 Hz), 6.81 (d, 4H, *J*= 8.6, Hz), 3.71 (s, 3H), 3.70 (s, 3H), 2.21 (s, 3H); HRMS (ESI) calcd for $C_{28}H_{24}N_3O_3S$ $[M+H]^+$ 482.1538 found 482.1521. This compound contains residual grease impurity and purity of this compound is about 90-95% and for this compound only a representable proton NMR was recorded.



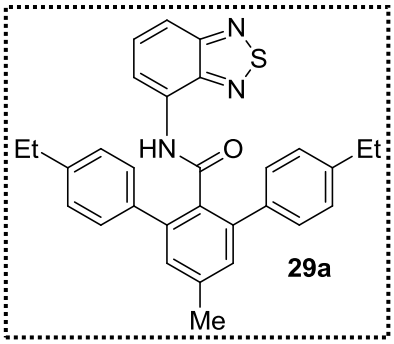
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-methyl-3'-nitro-[1,1'-biphenyl]-2-carboxamide (27p)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **27p** as a pale yellow solid; Yield: <10% (6 mg); R_f (20% EtOAc/Hexanes) 0.42; mp: 161−163 °C; IR (DCM): 3054, 2987, 1526, 1265, 747, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (br. s, 1H), 8.48 (d, 1H, *J*= 6.9, Hz), 8.42 (br. s, 1H), 8.10 (d, 1H, *J*= 8.7, Hz), 7.77 (d, 1H, *J*= 8.6, Hz), 7.72 (br. s, 1H), 7.68 (d, 1H, *J*= 8.8, Hz), 7.60 (dd, 1H, J_1 = 7.8, J_2= 7.6, Hz), 7.49-7.42 (m, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.2, 154.6, 148.5, 147.5, 141.6, 139.2, 135.1, 135.0, 132.1, 131.0, 130.7, 129.6, 129.5, 129.5, 123.6, 122.5, 116.2, 115.0, 21.2; HRMS (ESI) calcd for $C_{20}H_{15}N_4O_3S$ $[M+H]^+$ 391.0865 found 391.0852. This compound contains residual grease impurity and purity of this compound is about 95%.



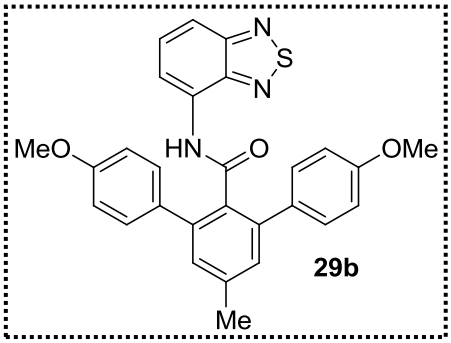
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4'-methyl-3,3''-dinitro-[1,1':3',1''-terphenyl]-2'-carboxamide (27p′)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **27p′**as a pale yellow solid; Yield: <20% (13 mg); R_f (20% EtOAc/Hexanes) 0.36; mp: 159−161 °C; IR (DCM): 3054, 2987, 1526, 1265, 747, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br. s, 1H), 8.32 (br. s, 1H), 8.24 (br. s, 1H), 8.09 (d, 2H, *J*= 8.1, Hz), 8.00 (d, 1H, *J*= 7.4, Hz), 7.86 (d, 1H, *J*= 7.8, Hz), 7.71 (d, 1H, *J*= 7.6, Hz), 7.62-7.58 (m, 2H), 7.53-7.49 (m, 2H), 7.46 (d, 1H, *J*= 7.5, Hz), 7.42 (d, 1H, *J*= 8.6, Hz), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.3, 154.4, 148.3, 148.1, 147.2, 141.2, 139.9, 137.7, 137.3, 136.2, 135.4, 134.6, 132.2, 130.7, 130.1, 129.6, 129.5, 128.6, 124.3, 123.6, 122.8, 122.7, 116.6 115.3, 20.7 HRMS (ESI) calcd for $C_{26}H_{18}N_5O_5S$ $[M+H]^+$ 512.1029 found 512.1015. This compound contains residual grease impurity and purity of this compound is about 90-95%.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4''-diethyl-5'-methyl-[1,1':3',1''-terphenyl]-2'-carboxamide (29a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29a** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.75; Yield: 75% (33 mg); mp: 145−147 °C; IR (DCM): 3055, 2987, 2306, 1265, 742 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (br. s, 1H), 8.27 (br. s, 1H), 7.58 (d, 1H, *J* = 8.4Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.43 (d, 4H, *J* = 8.0 Hz), 7.29 (s, 2H), 7.11 (d, 4H, *J* = 8.0 Hz), 2.53 (q, 4H, *J* = 7.6Hz), 2.50 (s, 3H), 1.07 (t, 6H, *J* = 7.6Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 154.5, 147.5, 143.5, 140.8, 139.8, 137.6, 132.5, 131.1, 130.0, 130.0, 128.5, 127.9, 115.4, 114.4, 28.4, 21.4, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3OS$ $[M+H]^+$ 478.1953 found 478.1944.

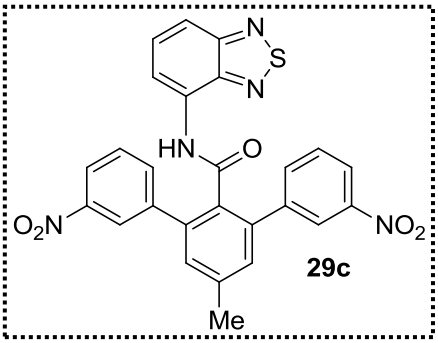


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4''-dimethoxy-5'-methyl-[1,1':3',1''-terphenyl]-2'-carboxamide (29b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29b** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.48; Yield: 65% (39 mg); mp: 145−147 °C; IR (DCM): 3054, 2987, 1609, 1422, 744 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (br. s, 1H), 8.31 (d, 1H, *J* = 6.7 Hz), 7.60 (d, 1H, *J* = 8.8Hz), 7.51 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (d, 4H, *J* = 8.7 Hz), 7.26 (s, 2H), 6.83(d, 4H, *J* = 8.7 Hz), 3.72 (s, 6H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 159.0, 154.6, 147.5, 140.3, 139.7, 132.7, 132.5, 131.1, 129.9, 129.7, 115.6, 114.6, 113.8, 55.2, 21.4; HRMS (ESI) calcd for $C_{28}H_{23}N_3NaO_3S$ $[M+Na]^+$ 504.1358 found 504.1370.



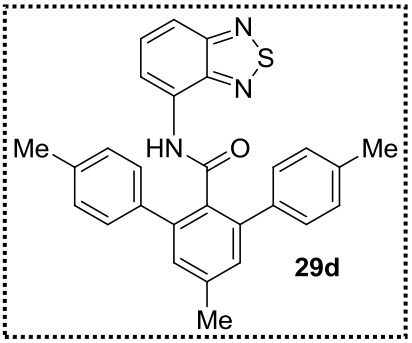
29b

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-5'-methyl-3,3''-dinitro-[1,1':3',1''-terphenyl]-2'-carboxamide (29c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29c** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.35; Yield: 42% (25 mg); mp: 225−227 °C**;** IR (DCM): 2918, 1647, 1529, 1351, 805 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br. s, 2H), 8.28 (br. s, 1H), 8.15 (d, 1H, *J* = 7.4 Hz), 8.10 (dd, 2H, J_1 = 8.2, J_2 = 1.2 Hz), 7.85 (d, 2H, *J* = 7.7 Hz), 7.63 (d, 1H, *J* = 8.8 Hz), 7.50-7.45 (m, 3H), 7.41 (s, 2H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.5, 154.5, 148.2, 147.3, 141.4, 141.0, 138.5, 134.7, 132.7, 131.0, 130.7, 129.4, 128.8, 123.7, 122.7, 116.6, 115.4, 21.47; HRMS (ESI) calcd for $C_{26}H_{18}N_5O_5S$ $[M+H]^+$ 512.1029 found 512.1008.

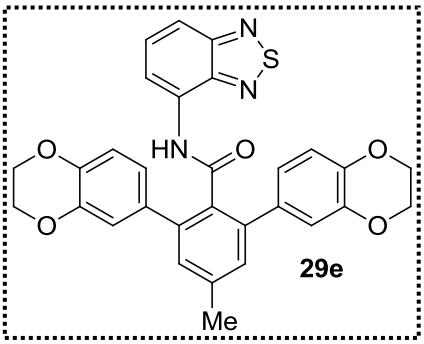


29c

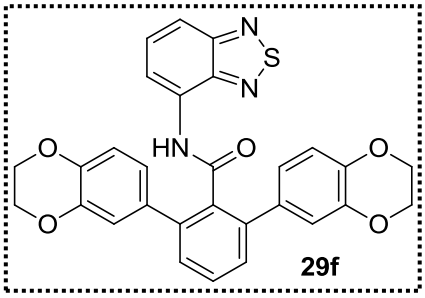
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4'',5'-trimethyl-[1,1':3',1''-terphenyl]-2'-carboxamide (29d)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29d** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.72; Yield: 70% (37 mg); mp: 139−141 °C; IR (DCM): 3055, 2987, 2306, 1422, 750 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br. s, 1H), 8.29 (d, 1H, J = 7.5 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.41 (d, 4H, J = 8.0 Hz), 7.27 (s, 2H), 7.09 (d, 4H, J = 8.0 Hz), 2.50 (s, 3H), 2.24 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 154.6, 147.5, 140.8, 139.7, 137.4, 137.2, 132.5, 131.1, 130.0, 129.9, 129.1, 128.4, 115.5, 114.6, 21.4, 21.1; HRMS (ESI) calcd for $C_{28}H_{24}N_3OS$ $[M+H]^+$ 450.1640 found 450.1644.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-methylbenzamide (29e)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29e** as a yellow colour semi-solid; R_f (20% EtOAc/Hexanes) 0.43; Yield: 60% (40 mg); IR (DCM): 2986, 2305, 1421, 895, 742 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br. s, 1H), 8.31 (br. s, 1H), 7.62 (d, 1H, J = 8.7 Hz), 7.53 (dd, 1H, J_1 = 8.7, J_2 = 7.3 Hz), 7.23 (s, 2H), 7.04 (d, 2H, J = 2.0 Hz), 6.96 (dd, 2H, J_1 = 8.3, J_2 = 2.1 Hz), 6.73 (d, 2H, J = 8.3 Hz), 4.16 (s, 8H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.9, 148.2, 144.8, 143.8, 141.0, 138.2, 136.3, 134.4, 131.7, 131.1, 130.3, 130.0, 129.7, 129.4, 128.1, 127.8, 127.3, 127.2, 126.2, 122.9, 122.2, 121.6, 116.5, 58.9, 53.9, 45.0, 30.1, 22.3; HRMS (ESI) calcd for $C_{30}H_{23}N_3NaO_5S$ $[M+Na]^+$ 560.1256 found 560.1276.

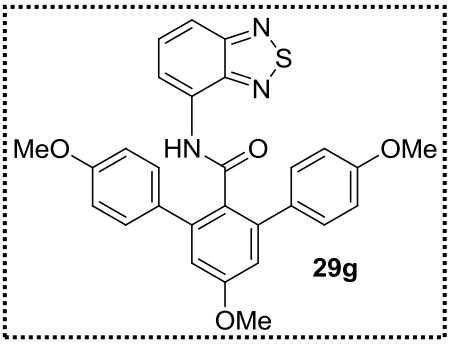


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)benzamide (29f)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29f** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.45; Yield: 50%

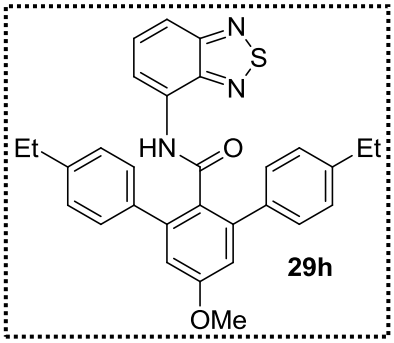


(31 mg); mp: 178−180 °C; IR (DCM): 3054, 2986, 2305, 1687,730 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br. s, 1H), 8.32 (d, 1H, J = 7.3 Hz), 7.63 (dd, 1H, J_1 = 8.8, J_2 = 0.7 Hz), 7.56-7.51 (m, 2H), 7.42 (d, 2H, J = 7.6 Hz), 7.05 (d, 2H, J = 2.1 Hz), 6.98 (dd, 2H, J_1 = 8.4, J_2 = 2.2 Hz), 6.74 (d, 2H, J = 8.3 Hz), 4.16 (s, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.8, 154.6, 147.6, 143.3, 143.2, 140.1, 134.9, 133.5, 131.1, 129.9, 129.7, 129.2, 121.8, 117.6, 117.2, 115.6, 114.8, 64.3, 64.2; HRMS (ESI) calcd for $C_{29}H_{22}N_3O_5S$ $[M+H]^+$ 524.1280 found 524.1282.

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-carboxamide (29g)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29g** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.38; Yield: 60% (35 mg); mp: 68−70 °C; IR (DCM): 2987, 2686, 2305, 896, 739 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br. s, 1H), 8.28 (br. s, 1H), 7.60 (d, 1H, J= 8.8 Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (d, 4H, J = 8.7 Hz), 6.94 (s, 2H), 6.83 (d, 4H, J = 8.7 Hz), 3.93 (s, 3H), 3.71 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.0, 159.9, 159.2, 154.6, 147.5, 142.2, 132.6, 131.1, 129.9, 129.6, 128.2, 115.5, 114.5, 113.8, 55.6, 55.2; HRMS (ESI) calcd for $C_{28}H_{24}N_3O_4S$ $[M+H]^+$ 498.1488 found 498.1497.

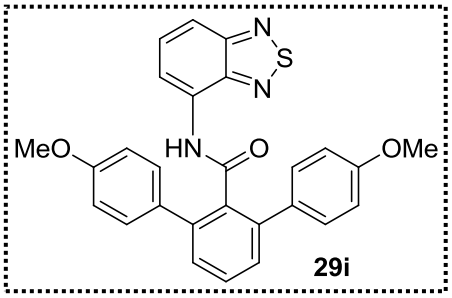


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4''-diethyl-5'-methoxy-[1,1':3',1''-terphenyl]-2'-carboxamide (29h)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29h** as a yellow colour solid; R_f (20% EtOAc/Hexanes) 0.52; Yield: 61% (36 mg); mp: 105−107 °C**;** IR (DCM): 2987, 2411, 2306, 1422,748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, J_1 = 7.3 Hz), 8.24 (br. s, 1H), 7.58 (d, 1H, J= 8.6 Hz), 7.49 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.44 (d, 4H, J = 8.0 Hz), 7.11 (d, 4H, J = 8.0 Hz), 6.99 (s, 2H), 3.93 (s, 3H), 2.53 (q, 4H, J = 7.6 Hz), 1.06 (t, 6H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.9, 159.9, 154.5, 147.4, 143.8, 142.7, 137.6, 131.1,



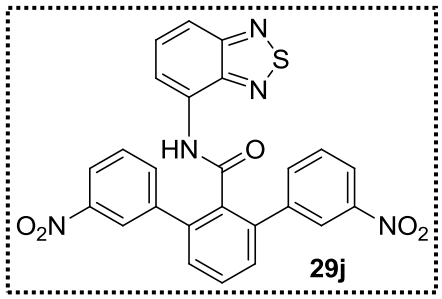
130.1, 128.4, 128.2, 127.9, 115.3, 114.7, 114.3, 55.6, 28.4, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_2S$ $[M+H]^+$ 494.1902 found 494.1890.

***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-carboxamide (29i)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29i** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.41; Yield: 60% (33 mg); mp: 148−150 °C; IR (DCM): 3055, 2987, 2306, 1547, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br. s, 1H), 8.31 (d, 1H J = 7.5 Hz), 7.61 (d, 1H, J = 8.8 Hz), 7.59-7.49 (m, 2H), 7.46 (d, 4H J = 8.8Hz), 7.45-7.43 (m, 2H), 6.84 (d, 4H, J = 8.8 Hz), 3.72 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.0, 159.1, 154.6, 147.5, 140.2, 135.1, 132.5, 131.0, 129.8, 129.8, 129.7, 129.2, 115.7, 114.8, 113.9, 55.2; HRMS (ESI) calcd for $C_{27}H_{22}N_3O_3S$ $[M+H]^+$ 468.1382 found 468.1370.



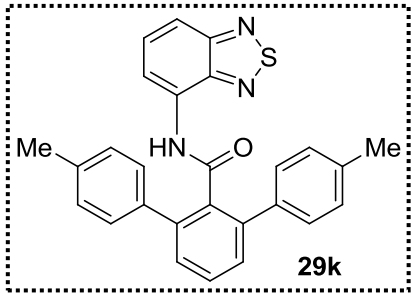
29i

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3,3''-dinitro-[1,1':3',1''-terphenyl]-2'-carboxamide (29j)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29j** as a pale yellow colour solid R_f (20% EtOAc/Hexanes) 0.33; Yield: 50% (30 mg); mp: 227−229 °C; IR (DCM): 3055, 2308, 1422, 1265, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (br. s, 2H), 8.32 (br. s, 1H), 8.15-8.11 (m, 3H), 7.87 (d, 2H, J = 7.7 Hz), 7.75 (t, 1H, J = 7.7 Hz), 7.65-7.60 (m, 3H), 7.51-7.47 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.2, 154.5, 148.3, 147.3, 141.2, 138.5, 135.3, 134.7, 130.7, 130.7, 130.4, 129.5, 128.7, 123.7, 122.9, 116.7, 115.5; HRMS (ESI) calcd for $C_{25}H_{16}N_5O_5S$ $[M+H]^+$ 498.0872 found 498.0855.



29j

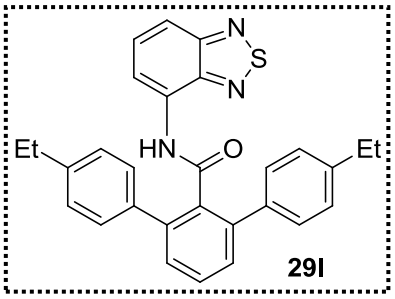
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-carboxamide (29k)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29k** as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.68; Yield: 75% (39 mg); mp: 189−191



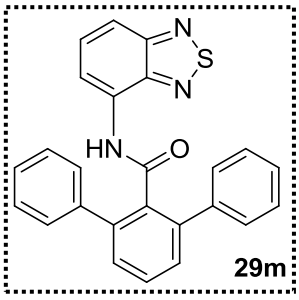
29k

°C**;** IR (DCM): 3055, 2987, 2306, 1422,748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br. s, 1H), 8.18 (dd, 1H, J_1 = 7.4, J_2 = 0.7 Hz), 7.51-7.45 (m, 2H), 7.40 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.35 (d, 2H, J = 7.4 Hz), 7.31 (d, 4H, J = 8.0 Hz), 7.00 (d, 4H, J = 8.0 Hz), 2.14 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.9, 154.6, 147.5, 140.6, 137.3, 137.2, 135.1, 131.1, 129.8, 129.7, 129.4, 129.1, 128.5, 115.6, 114.8, 21.1; HRMS (ESI) calcd for $C_{27}H_{22}N_3OS$ $[M+H]^+$ 436.1484 found 436.1506.

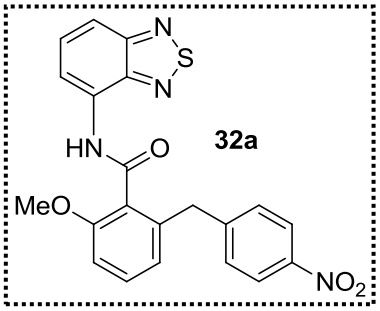
***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-carboxamide (29l)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29l** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.69; Yield: 74% (41 mg); mp: 152−154 °C**;** IR (DCM): 3055, 2987, 2305, 1546, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (br. s, 1H), 8.26 (br. s, 1H), 7.61-7.57 (m, 2H), 7.52-7.46 (m, 3H), 7.44 (d, 4H, J = 8.0 Hz), 7.11 (d, 4H, J = 8.0 Hz), 2.53 (q, 4H, J = 7.6 Hz), 1.07 (t, 6H, J = 7.6Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.0, 154.5, 147.5, 143.6, 140.7, 137.5, 135.1, 131.1, 129.9, 129.8, 129.3, 128.6, 127.9, 115.5, 114.6, 28.4, 15.3; HRMS (ESI) calcd for $C_{29}H_{26}N_3OS$ $[M+H]^+$ 464.1797 found 464.1784.



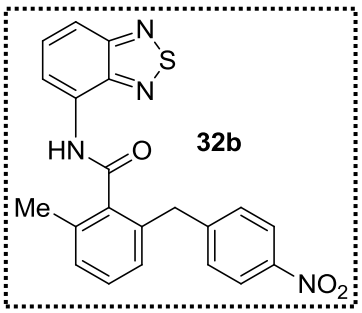
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (29m)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **29m** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.61; Yield: 50% (24 mg); mp: 175−177 °C**;** IR (DCM): 3054, 2685, 2305, 895, 749 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br. s, 1H), 8.26 (dd, 1H, J_1 = 7.4, J_2 = 0.4 Hz), 7.64-7.58 (m, 2H), 7.55-7.47 (m, 7H), 7.31 (t, 4H, J= 7.3 Hz), 7.24-7.20 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.6, 154.5, 147.4, 140.7, 140.1, 135.2, 131.0, 129.8, 129.6, 129.5, 128.6, 128.4, 127.6, 115.7, 114.7; HRMS (ESI) calcd for $C_{25}H_{18}N_3OS$ $[M+H]^+$ 408.1171 found 408.1166.



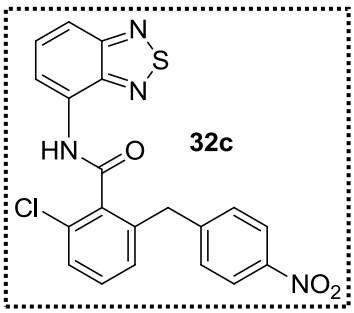
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-methoxy-6-(4-nitrobenzyl)benzamide (32a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **32a** as a yellow colour solid; R_f (20% EtOAc/Hexanes) 0.38; Yield: 47% (23 mg); mp: 157−159 °C; IR (DCM): 3054, 2986, 2305, 895, 740 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (br. s, 1H), 8.61 (d, 1H, *J* = 7.3 Hz), 7.98 (d, 2H, *J* = 8.6 Hz), 7.73 (d, 1H, *J* = 8.8 Hz), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.42 (t, 1H, *J* = 8.0 Hz), 7.36 (d, 2H, *J* = 8.6 Hz), 6.98 (d, 1H, *J* = 8.4 Hz), 6.91 (d, 1H, *J* = 7.7 Hz), 4.29 (s, 2H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 156.8, 154.8, 148.3, 147.7, 146.3, 139.7, 131.4, 131.1, 129.8, 129.8, 125.4, 123.6, 123.3, 116.1, 115.1, 110.0, 56.0, 39.2; HRMS (ESI) calcd for $C_{21}H_{17}N_4O_4S$ $[M+H]^+$ 421.0971 found 421.0963.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-methyl-6-(4-nitrobenzyl)benzamide (32b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **32b** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.35; Yield: 50% (24 mg); mp: 179−181 °C; IR (DCM): 2987, 2306, 1422, 1265, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, *J* = 7.3 Hz), 8.37 (br. s, 1H), 7.94 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.37 (t, 1H *J* = 7.6Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 1H *J* = 7.6 Hz), 7.15 (d, 1H *J* = 7.6 Hz), 4.19 (s, 2H); 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.3, 154.7, 148.0., 147.4, 146.4, 137.1, 136.1, 135.2, 130.9, 130.0, 129.6, 129.3 128.0, 123.6, 116.6, 115.3, 39.3, 19.5; HRMS (ESI) calcd for $C_{21}H_{17}N_4O_3S$ $[M+H]^+$ 405.1021 found 405.1019.

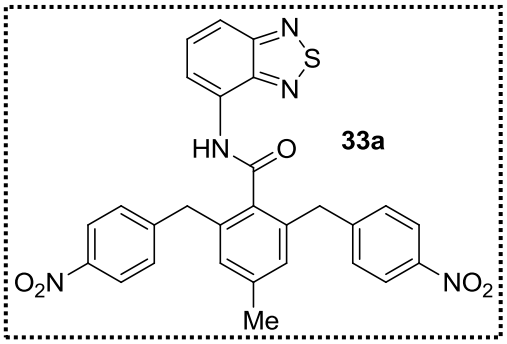


***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-chloro-6-(4-nitrobenzyl)benzamide (32c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **32c** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.38; Yield: 65% (33 mg); mp: 172−174 °C; IR (DCM): 3055, 2987, 2307,

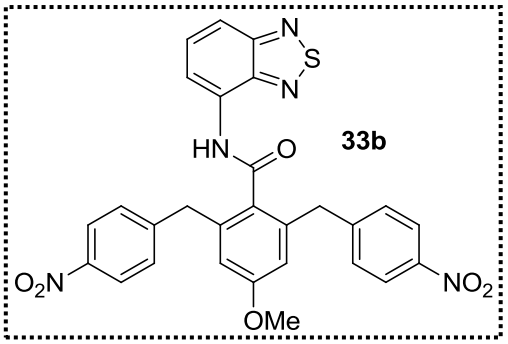


896, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.45 (br. s, 1H), 7.96 (d, 2H, J = 8.8 Hz), 7.78 (dd, 1H, J_1= 8.9, J_2 = 0.9 Hz), 7.68 (dd, 1H, J_1= 8.8, J_2 = 7.4 Hz), 7.45-7.39 (m, 2H), 7.33 (d, 2H, J = 8.8 Hz), 7.23 (dd, 1H, J_1 = 6.8, J_2 = 2.0 Hz), 4.22 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 154.7, 147.4, 147.0, 146.5, 139.1, 136.1, 131.5, 131.1, 130.9, 129.8, 129.1, 129.0, 128.5, 123.7, 116.8, 115.6, 39.2; HRMS (ESI) calcd for $C_{20}H_{14}ClN_4O_3S$ $[M+H]^+$ 425.0475 found 425.0471.

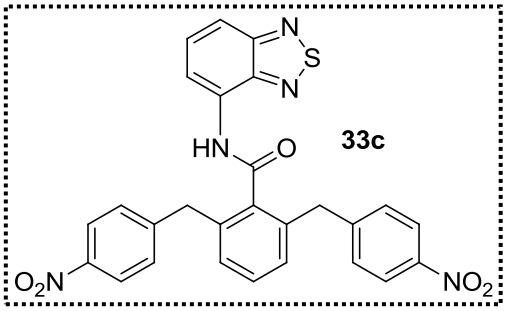
***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methyl-2,6-bis(4-nitrobenzyl)benzamide (33a)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **33a** as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.31; Yield: 55% (35 mg); mp: 165−167 °C; IR (DCM): 3055, 2987, 1422, 1265, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, J = 7.4 Hz), 8.13 (br. s, 1H), 7.97 (d, 4H, J= 8.5 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.65 (dd, 1H, J_1= 8.8, J_2 = 7.4 Hz), 7.30 (d, 4H, J = 8.5 Hz), 7.03 (s, 2H), 4.16 (s, 4H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.9, 154.6, 147.6, 147.1, 146.5, 140.6, 136.7, 134.6, 130.8, 129.9, 129.6, 129.0, 123.7, 116.8, 115.2, 39.5, 21.4; HRMS (ESI) calcd for $C_{28}H_{20}N_5O_5S$ $[M-H]^-$ 538.1185 found 538.1163.



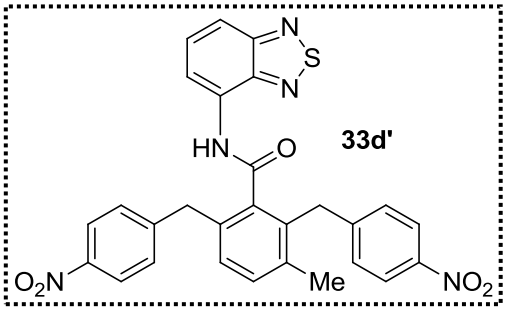
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-4-methoxy-2,6-bis(4-nitrobenzyl)benzamide (33b)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **33b** as a pale yellow colour solid R_f (20% EtOAc/Hexanes) 0.30; Yield: 52% (24 mg); mp: 240−242 °C; IR (DCM): 3054, 2987, 1422, 896, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.14 (br. s, 1H), 7.98 (d, 4H, J= 8.8 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.31 (d, 4H, J = 8.7 Hz), 6.72 (s, 2H), 4.18 (s, 4H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.7, 160.6, 154.5, 147.3, 146.5, 138.6, 130.8, 130.1, 129.6, 129.0, 123.8, 116.7, 115.1, 114.6, 55.5, 39.5; HRMS (ESI) calcd for $C_{28}H_{22}N_5O_6S$ $[M+H]^+$ 556.1291 found 556.1298.



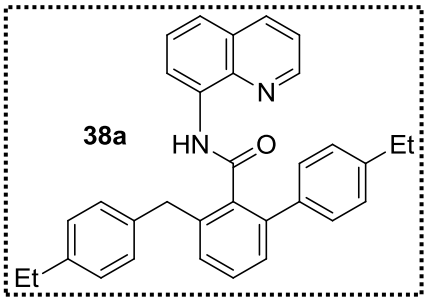
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2,6-bis(4-nitrobenzyl)benzamide (33c)**. Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to afford **33c** as a yellow colour solid; R_f (20% EtOAc/Hexanes) 0.33; Yield: 58% (36 mg); mp: 188−190 °C; IR (DCM): 3055, 2306, 1348, 1265, 896 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H *J* = 7.3 Hz), 8.15 (br. s, 1H), 7.96 (d, 4H, *J* = 8.6 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (t, 1H, *J* = 7.7Hz), 7.30 (d, 4H, *J* = 8.6 Hz), 7.24 (d, 2H, *J* = 7.7 Hz), 4.20 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.6, 154.5, 147.5, 147.1, 146.5, 137.2, 136.7, 130.8, 130.4, 129.6, 129.3, 128.9, 123.8, 116.9, 115.3, 39.2; HRMS (ESI) calcd for $C_{27}H_{20}N_5O_5S$ $[M+H]^+$ 526.1185 found 526.1197.



***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methyl-2,6-bis(4-nitrobenzyl)benzamide (33d′)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **33d′** as a pale yellow solid; Yield: 30% (19 mg); R_f (20% EtOAc/Hexanes) 0.33; mp: 144−146 °C; IR (DCM): 3054, 2987, 1421, 1265,747, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J*= 7.4 Hz), 8.16 (br. s, 1H), 8.01 (d, 2H, *J*= 8.6 Hz), 7.96 (d, 2H, *J*= 8.6, Hz), 7.72 (d, 1H, *J*= 8.8, Hz), 7.61 (dd, 1H, J_1 = 8.7, J_2 = 7.6, Hz), 7.35 (d, 1H, *J*= 7.9 Hz), 7.32 (d, 2H, *J*= 8.6, Hz), 7.23 (d, 2H, *J*= 8.6, Hz), 7.19 (d, 1H, *J*= 7.8, Hz), 4.19 (s, 4H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 154.5, 147.8, 147.1, 147.1, 146.4, 138.2, 136.9, 134.1, 134.1, 132.4, 130.8, 129.6, 129.5, 128.9, 128.9, 123.8, 123.7, 116.8, 115.2, 39.1, 36.4, 19.9 HRMS (ESI) calcd for $C_{28}H_{22}N_5O_5S$ $[M+H]^+$ 540.1342 found 540.1360.



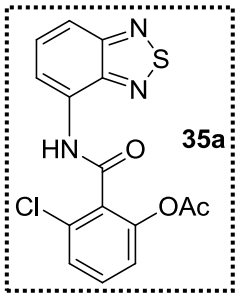
4'-Ethyl-3-(4-ethylbenzyl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (38a): The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **38a** as a colourless solid; R_f (20% EtOAc/Hexanes) 0.53; Yield: 53% (30 mg); mp 138-140 ^{o}C; IR (DCM): 3054, 2928, 1422, 1265, 747 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (br. s, 1H), 8.77 (d, 1H, *J*= 7.6 Hz), 8.55



(d, 1H, *J*= 4.1 Hz), 8.07 (d, 1H, *J*= 8.4 Hz), 7.54-7.41 (m, 5H), 7.35 (d, 2H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 7.5 Hz), 7.05 (d, 2H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 7.5 Hz), 4.22 (s, 2H), 2.44 (q, 4H, *J* = 7.6 Hz), 1.07 (t, 3H, *J* = 7.6 Hz), 0.99 (t, 3H, *J* = 7.6 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 147.8, 143.2, 141.8, 139.8, 139.5, 137.6, 136.7, 135.9, 134.4, 129.3, 129.1, 129.0, 128.6, 128.6, 128.1, 127.8, 127.7, 127.7, 127.2, 121.5, 121.3, 116.5, 38.8, 28.3, 28.3, 15.5, 15.2; HRMS (ESI) calcd for $C_{33}H_{31}N_2O$ $[M+H]^+$ 471.2436 found 471.2422

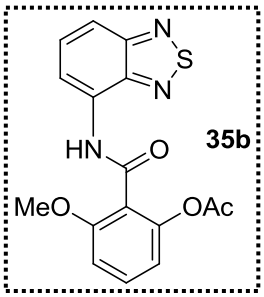
Typical procedure for the β-acetoxylation of 26c,d: An appropriate amide **26c** or **26d** (0.11 mmol, 30 mg), $Pd(OAc)_2$ (10 mol%, 2.3 mg), $PhI(OAc)_2$ (0.22 mmol, 70 mg), glacial AcOH (7 mg) and Ac_2O (13 mg) in anhydrous toluene (3 mL) was heated at 110 ^oC for 24 h under a nitrogen atmosphere. After the reaction duration, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture through column chromatography furnished the corresponding acetoxylated amides **35a**,**b**.

2-(Benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)-3-chlorophenyl acetate(35a): The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **35a**



as a pale yellow solid R_f (20% EtOAc/Hexanes) 0.50; Yield: 86% (33 mg); mp: 129−131 °C**;** IR (DCM): 3314, 1771, 1692, 1548 and 751 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (br. s, 1H), 8.64 (d, 1H, *J* = 7.3 Hz), 7.77 (d, 1H, *J* = 8.8 Hz), 7.67 (dd, 1H, J_1 = 8.7, J_2 = 7.4 Hz), 7.46 (t, 1H, *J* = 7.3 Hz), 7.41 (dd, 1H, J_1 = 8.1, J_2 = 1.0 Hz), 7.17 (dd, 1H, J_1 = 8.0, J_2 = 1.1 Hz), 2.21 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.4, 162.0, 154.8, 148.5, 147.7, 132.1, 131.4, 130.9, 129.8, 129.3, 127.7, 121.9, 116.7, 115.8, 20.8; HRMS (ESI) calcd for $C_{15}H_{10}ClNaN_3O_3S$ $[M+Na]^+$ 370.0029 found 370.0014.

2-(Benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)-3-methoxyphenyl acetate (35b): The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to

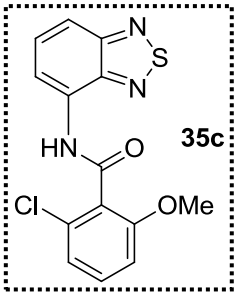


afford **35b** as a yellow solid; R_f (20% EtOAc/Hexanes) 0.52; Yield: 89% (33 mg); mp: 130−132 °C; IR (DCM): 3055, 2987, 1679, 1266 and 744 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (br. s, 1H), 8.64 (d, 1H, *J* = 7.2 Hz), 7.72 (d, 1H, *J* = 8.7 Hz), 7.65 (dd, 1H, J_1 = 8.7, J_2 = 7.4 Hz), 7.49 (t, 1H, *J* = 8.3 Hz), 6.97 (d, 1H, *J* = 8.5 Hz), 6.84 (d, 1H,

J = 8.2 Hz), 4.01 (s, 3H), 2.31 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 162.2, 157.6, 154.8, 150.4, 148.0, 132.0, 131.2, 130.2, 117.9, 116.3, 115.9, 115.3, 109.3, 56.5, 21.1; HRMS (ESI) calcd for $C_{16}H_{13}N_3NaO_4S$ $[M+Na]^+$ 366.0524 found 366.0511.

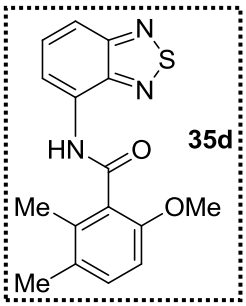
Typical procedure for the *β*-alkoxylation of 26d,b. An appropriate amide **26b** or **26d** (0.11 mmol, 30 mg), $Pd(OAc)_2$ (10 mol%, 2.3 mg), $PhI(OAc)_2$ (0.22 mmol, 70 mg) and MeOH (0.4 mL) and anhydrous toluene (1 mL) was heated at 65 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction duration, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture through column chromatography furnished the corresponding alkoxylated amides**35c**,**d**.

***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-chloro-6-methoxybenzamide(35c)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford **35c**



as a yellow solid R_f (20% EtOAc/Hexanes) 0.44; Yield: 71% (25 mg); mp: 173−175 °C; IR (DCM): 3054, 2987, 1689, 1574 and 744 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (br. s, 1H), 8.73 (d, 1H, *J* = 6.9 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.35 (t, 1H, *J* = 8.3 Hz), 7.08 (dd, 1H, J_1 = 8.0, J_2 = 0.5 Hz), 6.90 (d, 1H, *J* = 8.4 Hz), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5, 157.5, 154.8, 147.8, 132.4, 131.4, 131.2, 129.9, 125.6, 122.0, 116.2, 115.5, 109.7, 56.2; HRMS (ESI) calcd for $C_{14}H_{11}ClN_3O_2S$ $[M+H]^+$ 320.0261 found 320.0249.

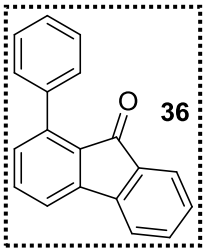
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-6-methoxy-2,3-dimethylbenzamide(35d)**: The resultant crude mixture was purified by column chromatography (EtOAc/hexane, 20:80) to afford



(35d) as a yellow viscous liquid; R_f (20% EtOAc/Hexanes) 0.45; Yield: 64% (22 mg); IR (DCM): 2965, 1651, 1587, 1462 and 736 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br. s, 1H), 8.74 (dd, 1H, J_1 = 7.2, J_2 = 0.8 Hz), 7.73 (dd, 1H, J_1 = 8.8, J_2 = 1.0 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.2 Hz), 7.20 (d, 1H, *J* = 8.4 Hz), 6.76 (d, 1H, *J* = 8.4 Hz), 3.83 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.2, 154.9, 154.5, 147.9, 135.6, 131.6, 131.3, 130.2, 129.7, 126.4, 115.8, 115.1, 108.4, 55.9, 19.4, 16.7; HRMS (ESI) calcd for $C_{16}H_{16}N_3O_2S$ $[M+H]^+$ 314.0963 found 314.0951.

Procedure for the synthesis of the compound 36. The bis-arylated benzamide **29m** (0.05 mmol, 20 mg) and 40% aq. H_2SO_4 (2 mL) was heated at 120 °C for 24 h. After this duration, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL), the combined organic layers were dried up over Na_2SO_4, and then, the solvent was removed under vacuum. Purification of the crude reaction mixture by silica gel column chromatography furnished the corresponding compound **36**.

***1*-Phenyl-9*H*-fluoren-9-one (36)**.[20a] Following the general procedure described above, the resultant crude mixture was purified by column chromatography (EtOAc:Hexanes = 20:80) to



afford **36** as a greenish-black colour semi-solid; R_f (20% EtOAc/Hexanes) 0.80; Yield: 66% (8 mg); IR (DCM): 3054, 1711, 1608, 916, 737 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 7.62-7.59 (m, 2H), 7.57-7.49 (m, 6H), 7.47 (d, 2H, J = 7.5 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.23 (dd, 1H, J_1= 7.0, J_2 = 1.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.1, 145.5, 143.6, 142.3, 137.4, 134.5, 134.2, 131.6, 129.7, 129.2, 129.2, 129.0, 128.2, 127.9, 127.2, 124.1, 120.0, 119.2; HRMS (ESI) calcd for $C_{19}H_{13}O$ $[M+H]^+$ 257.0966 found 257.0956.

Part 2

General. IR spectra were recorded as KBr pellets or thin films. ^1H / ^{13}C NMR spectra of were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under a nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulfate. TLC analysis was performed on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported,andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures. Compound **46** known in the literature[25h].

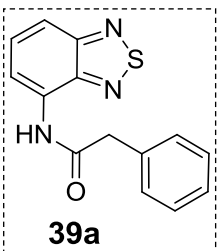
Procedure for the synthesis of ABTD phenylacetamide 39a.

A dry flask the corresponding containing amine (3 mmol) and Et_3N (363 mg, 3.6 mmol) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (7 mL) was added followed by drop-wise addition of the corresponding acid chloride. The resulting mixture allowed to stir overnight at rt for 12 h. After this time, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude reaction mixture. The crude reaction mixture purified by column chromatography on silica gel (100–200 mesh, EtOAc/hexanes = 20:80) furnished the corresponding products **39a.**

Procedure for synthesis ABTD phenylacetamide39b-e.

A dry flask was having the corresponding carboxylic acid (3 mmol) and $SOCl_2$ (1.8 mL) at room temperature for 24 h under a nitrogen atmosphere. After the reaction time, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (4 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (2.8 mmol), Et_3N (333 mg, 3.3 mmol) and DCM (7 mL) under a nitrogen atmosphere. The resulting mixture allowed to stir at rt for 12 h. After this duration, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. The crude reaction mixture Purified by column chromatography (neutral alumina (EtOAc/hexanes = 25:75) furnished the corresponding products **39b-e.**

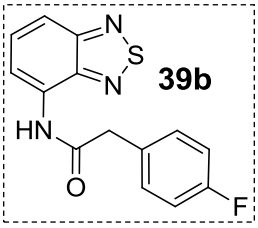
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-phenylacetamide*(nb 224/1298 39a): Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford ***39*a** as a dirty white color solid (231 mg, 72%); R_f (10% EtOAc/hexane) 0.45; mp: 123-125^{o}C; IR (KBr): 3310, 3055, 1675, 1548, 1266, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (br. s, 1H), 8.49 (d, 1H, *J* = 7.3 Hz), 7.66 (d, 1H, *J* = 8.6Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 7.48-



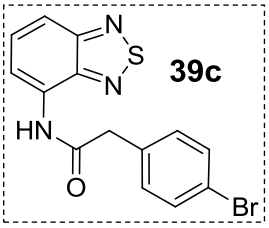
39a

7.39 (m, 5H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 154.7, 147.7, 134.0, 131.0, 129.7, 129.5, 129.3, 127.8, 115.9, 114.8, 45.0; HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M+H]^+$ 270.0701 found 270.0707.

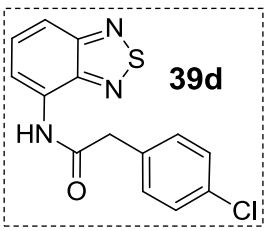
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4-fluorophenyl)acetamide*(nb 430 /1038 39b):Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford ***39*b** as a dirty white color solid (240 mg, 42%); R_f (10% EtOAc/hexane) 0.45; mp: 152-154 ^{o}C; IR (KBr): 3309, 3055, 1670, 1548, 1265, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (br. s, 1H), 8.49 (d, 1H, J = 7.4 Hz), 7.68 (dd, 1H, J_1 = 8.9, J_2 = 0.9Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.43-7.38 (m, 2H), 7.16-7.12 (m, 2H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.4, 162.3 (d, $J_{C\text{-}F}$ = 245.2 Hz), 154.7, 147.7, 131.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 131.0, 129.7, 129.6, 116.2 (d, $J_{C\text{-}F}$ = 21.3 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.2 Hz), 115.0, 44.0; HRMS (ESI) calcd for $C_{14}H_{11}FN_3OS$ $[M+H]^+$ 288.0607 found 288.0596.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4-bromophenyl)acetamide*(nb 438/1370 39c):Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford ***39*c** as a faint yellow solid (360 mg, 34%); R_f (10% EtOAc/hexane) 0.5; mp: 191-193 ^{o}C; IR (KBr): 3055, 2986, 2685, 1423, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.51 (br. s, 1H), 8.47 (d, 1H, J = 7.4 Hz), 7.68 (d, 1H, J = 8.8 Hz), 7.60 (d, 1H, J = 7.8Hz), 7.57 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.8, 154.7, 147.6, 132.9, 132.3, 131.2, 131.0, 129.6, 121.8, 116.1, 115.0, 44.3; HRMS (ESI) calcd for $C_{14}H_{11}BrN_3OS$ $[M+H]^+$ 347.9806 found 347.9795.

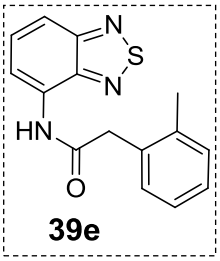


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4-chlorophenyl)acetamide*(nb 1037 39d):Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford ***39*d** as a dirty white color solid (181 mg, 30%); R_f (20% EtOAc/hexane) 0.45; mp: 178-180 ^{o}C; IR (KBr): 3305, 3055, 1664, 1422, 1265, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (br. s, 1H), 8.47 (d, 1H, J = 7.4 Hz), 7.68 (d, 1H, J = 8.6 Hz), 7.59 (dd, 1H, J_1 = 8.7, J_2 = 7.4Hz), 7.43-7.35 (m, 4H), 3.85 (s, 2H);



^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.9, 154.7, 147.8, 133.8, 132.4, 131.0, 130.8, 129.6, 129.4, 116.1, 115.0, 44.2; HRMS (ESI) calcd for $C_{14}H_{11}ClN_3OS$ $[M+H]^+$ 304.0311 found 304.0296.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(o-tolyl)acetamide*(nb 1369 39e): Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford ***39e*** as a Faint yellow color solid (665 mg, 94%); R_f (10% EtOAc/hexane) 0.5; mp: 187-189 ^{o}C; IR (KBr): 3372, 3055, 1680, 1546, 1269, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.49 (d, 1H, J = 7.3 Hz), 8.45 (br. s, 1H), 7.66 (d, 1H, J = 8.8Hz), 7.60-7.56 (m, 1H), 7.38-7.32 (m, 4H), 3.91 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.4, 154.7, 147.7, 137.3, 132.5, 131.1, 130.6, 129.7, 128.3, 127.0, 115.9, 114.8, 43.1, 19.7; HRMS (ESI) calcd for $C_{15}H_{14}N_3OS$ $[M+H]^+$ 284.0858 found 284.0844

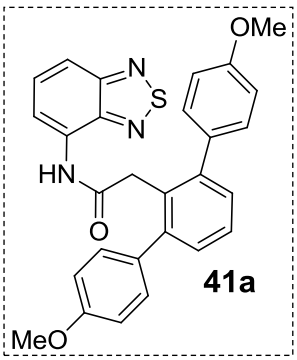


39e

General procedure for the Pd(II)-catalyzed ABTD assisted arylation of phenylacetamide and preparation of the compounds 41a-l, 43a-e (bis arylation products), 44a-b (monoarylation products).

An appropriate natural/unnatural carboxamide (0.10-0.12 mmol, 1equiv), an appropriate iodo compound (0.40-0.48 mmol, 4equiv), $Pd(OAc)_2$ (2.5-2.7 mg, 10 mol%), and AgOAc (48-50 mg, 2.2 equiv.) in anhydrous toluene (3 mL) was heated at 110 ^{o}C, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was concentrated in vacuum and purification of the resulting crude reaction mixture by silica gel column chromatography furnished the corresponding arylated products **41a-l, 43a-e**(bis-arylation products), **44a-b** (mono-arylation products) (see corresponding Tables/Schemes for specific examples and reaction conditions).

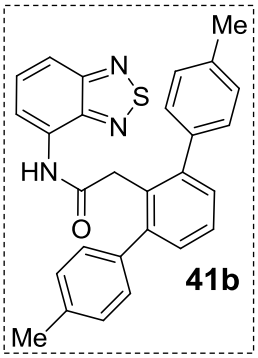
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)acetamide(nb 233a 41a):** The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41a** as a yellow color solid (28 mg, 86%); R_f (10% EtOAc/hexane) 0.4; mp: 172-174 ^{o}C; IR (KBr): 3055, 2987, 1265, 896, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, 1H, J = 7.3 Hz), 8.04 (br. s, 1H), 7.65 (d, 1H, J



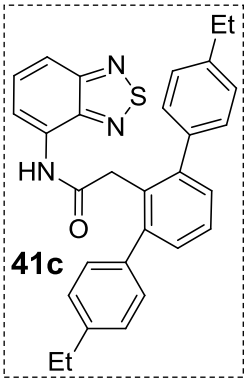
41a

= 8.8 Hz), 7.58-7.54 (m, 1H), 7.44 (dd, 1H, J_1 = 8.1, J_2 = 7.1Hz), 7.35-7.33 (m, 6H), 6.85 (d, 4H, J = 8.6 Hz), 3.81 (s, 2H), 3.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.2, 158.8, 154.6, 147.5, 143.4, 133.8, 131.1, 130.6, 130.3, 129.9, 129.8, 127.3, 115.5, 114.4, 113.7, 55.1, 40.2; HRMS (ESI) calcd for $C_{28}H_{25}N_3O_3S$ $[M+H]^+$ 482.1538 found 482.1547.

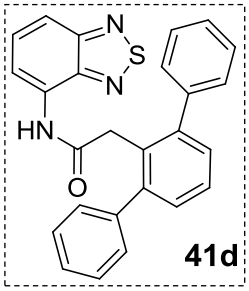
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 242a/1521a* 41*b): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41b** as a yellow color solid (21 mg, 60%); R_f (10% EtOAc/hexane) 0.6; mp: 195-197 ^{o}C; IR (KBr): 3055, 2686, 1423, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, 1H, J = 7.3 Hz), 8.09 (br. s, 1H), 7.66 (d, 1H, J = 8.7 Hz), 7.56 (dd, 1H, J_1 = 8.6, J_2 = 7.4Hz), 7.47 (dd, 1H, J_1 = 8.2, J_2 = 7.0Hz), 7.37 (d, 2H, J = 7.4 Hz), 7.32 (d, 4H, J = 8.0 Hz), 7.15 (d, 4H, J = 7.8 Hz), 3.82 (s, 2H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.2, 158.8, 154.6, 147.5, 143.4, 133.8, 131.1, 130.6, 130.3, 129.9, 129.8, 127.3, 115.5, 114.4, 113.7, 55.1, 40.2; HRMS (ESI) calcd for $C_{28}H_{24}N_3OS$ $[M+H]^+$ 450.1640 found 450.1629.



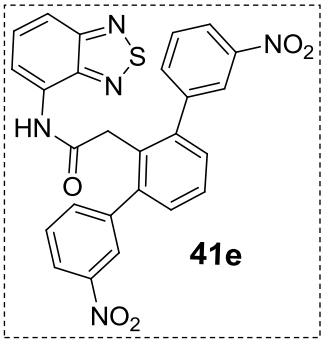
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 469a* 41*c): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41c** as a yellow color solid (24 mg, 70%); R_f (10% EtOAc/hexane) 0.7; mp: 196-198 ^{o}C; IR (KBr): 3330, 3055, 2967, 1548, 1267, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, 1H, J = 7.2 Hz), 8.07 (br. s, 1H), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 0.9Hz), 7.56 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.47 (dd, 1H, J_1 = 8.3, J_2 = 6.8Hz), 7.38 (d, 2H, J = 7.2 Hz), 7.34 (d, 4H, J = 8.1 Hz), 7.17 (d, 4H, J = 8.2 Hz), 3.83 (s, 2H), 2.57 (q, 4H, J = 7.6 Hz), 1.16 (t, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.2, 154.7, 147.5, 143.7, 143.3, 138.7, 131.2, 130.1, 129.9, 129.8, 129.1, 127.8, 127.4, 115.5, 114.4, 40.2, 28.5, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3OS$ $[M+H]^+$ 478.1953 found 478.1933.



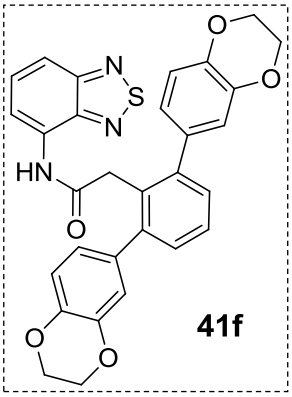
2-([1,1':3',1''-terphenyl]-2'-yl)-*N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)acetamide *(nb 1065a/837/261* 41*d):* The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41d** as a faint yellow color solid (26 mg, 80%); R_f (10% EtOAc/hexane) 0.6; mp: 168-170 ^oC; IR (KBr): 3055, 2987, 1422, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, 1H, J = 7.4 Hz), 8.06 (br. s, 1H), 7.65 (d, 1H, J = 8.8Hz), 7.57-7.53 (m, 1H), 7.51-7.48 (m, 1H), 7.43-7.38 (m, 6H), 7.36-7.32 (m, 4H), 7.29-7.25 (m, 2H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.9, 154.7, 147.5, 143.8, 141.3, 131.1, 129.8, 129.8, 129.2, 129.0, 128.4, 127.4, 127.4, 115.6, 114.5, 40.5; HRMS (ESI) calcd for $C_{26}H_{20}N_3OS$ $[M+H]^+$ 422.1327 found 422.1317.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(3,3''-dinitro-[1,1':3',1''-terphenyl]-2'-yl)acetamide *(nb 259* 41*e): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41e** as a faint yellow color solid (17 mg, 50%); R_f (10% EtOAc/hexane) 0.3; mp: 230-232 ^oC; IR (KBr): 3055, 2987, 1526, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (t, 2H, J = 1.9 Hz), 8.29 (d, 1H, J = 7.4 Hz), 8.16 (dd, 1H, J_1 = 2.2, J_2 = 1.0Hz), 8.14 (dd, 1H, J_1 = 2.2, J_2 = 1.0Hz), 7.95 (br. s, 1H), 7.81 (dt, 2H, J_1 = 7.8, J_2 = 1.2Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 0.7Hz), 7.59-7.53 (m, 4H), 7.44 (d, 2H, J = 7.6 Hz), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.7, 154.6, 148.2, 147.3, 142.5, 141.6, 135.4, 130.9, 130.5, 129.9, 129.5, 129.1, 128.1, 124.2, 122.7, 116.3, 115.1, 39.8; HRMS (ESI) calcd for $C_{26}H_{18}N_5O_5S$ $[M+H]^+$ 512.1029 found 512.1008.

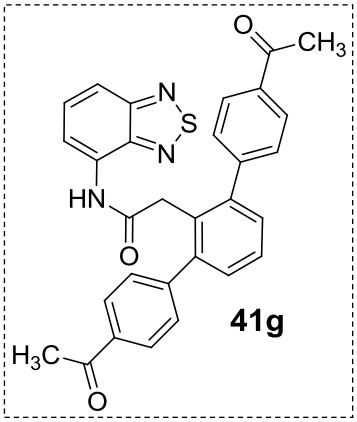


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)acetamide*(nb 255* 41*f): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41f** as a brown color solid (44 mg, 71%); R_f (10% EtOAc/hexane) 0.3; mp: 110-112 ^oC; IR (KBr): 3055, 2987, 1423, 1265, 740 cm^{-1};; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.36 (d, 1H, J = 7.3 Hz), 8.08 (br. s, 1H), 7.65 (d, 1H, J_1 = 8.8 Hz), 7.56 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.42

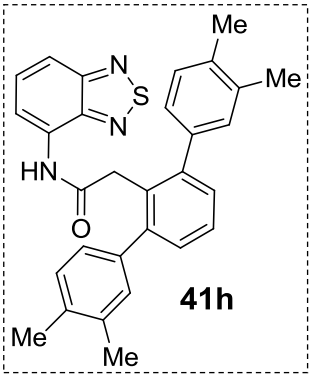


(dd, 1H, J_1 = 8.3, J_2 = 6.8Hz), 7.32 (d, 2H, J = 7.3 Hz), 6.92 (d, 2H, J = 2.0 Hz), 6.88 (dd, 2H, J_1 = 8.2, J_2 = 2.0Hz), 6.81 (d, 2H, J = 8.2 Hz), 4.17-4.14 (m, 8H), 3.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.0, 154.7, 147.5, 143.2, 143.1, 142.9, 134.7, 131.2, 130.4. 129.9, 129.8, 127.3, 122.3, 118.2, 117.1, 115.4, 114.6, 64.3, 40.1; HRMS (ESI) calcd for $C_{30}H_{24}N_3O_5S$ $[M+H]^+$ 538.1437 found 538.1462.

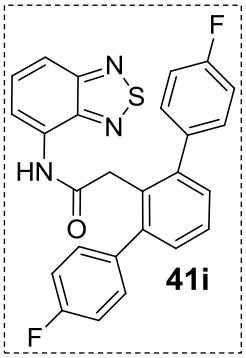
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 271* 41*g): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41g** as a light brown color solid (24.5 mg, 71%); R_f (10% EtOAc/hexane) 0.4; mp: 208-210 ^{o}C; IR (KBr): 3055, 2987, 1423, 1265, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, 1H, J = 7.4 Hz), 7.96 (br. s, 1H), 7.94 (d, 4H, J = 8.4Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.57 (d, 1H, J = 7.4 Hz), 7.54 (d, 4H, J = 8.4 Hz), 7.51 (d, 1H, J = 7.2 Hz), 7.39 (d, 2H, J = 7.6 Hz), 3.73 (s, 2H), 2.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.5, 169.3, 154.6, 147.3, 146.0, 142.8, 136.1, 131.0, 129.9, 129.5, 129.5, 128.5, 127.7, 115.9, 114.6, 112.0, 39.9, 26.6; HRMS (ESI) calcd for $C_{30}H_{23}N_3NaO_3S$ $[M+Na]^+$ 528.1358 found 528.1365



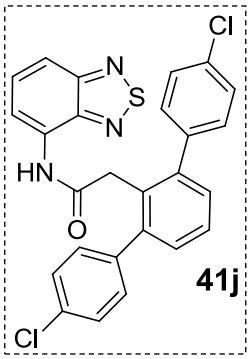
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 303a* 41*h): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41h** as a pale yellow color solid (44 mg, 77%); R_f (10% EtOAc/hexane) 0.7; mp: 169-171 ^{o}C; IR (KBr): 3383, 3055, 2986, 1700, 1418, 1265, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40-8.36 (m, 1H), 8.06 (d, 1 H, J = 9.2Hz), 7.70-7.65 (m, 1H), 7.62-7.55 (m, 1H), 7.48-7.44 (m, 1H), 7.40-7.35(m, 2H), 7.22-7.18 (m, 4H), 7.15-7.10 (m, 2H), 3.85-3.83 (m, 2H), 2.17 (s, 6H), 2.15 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.3, 154.7, 147.5, 143.8, 139.0, 136.5, 135.6, 131.2, 130.6, 130.2, 130.2, 130.0, 129.6, 127.3, 126.5, 115.4, 114.4, 40.3, 19.7, 19.4; HRMS (ESI) calcd for $C_{30}H_{28}N_3OS$ $[M+H]^+$ 478.1953 found 478.1931.



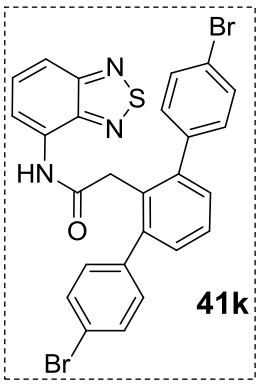
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 264a* 41*i): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41i** as a yellow color solid (24 mg, 75%); R_f (10% EtOAc/hexane) 0.6; mp: 170-172 ^oC; IR (KBr): 3055, 2986, 1510, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (d, 1 H, J = 7.4 Hz), 7.97 (br. s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.54 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.44 (dd, 1H, J_1 = 8.2, J_2 = 7.0Hz), 7.38-7.34 (m, 4H), 7.32 (d, 2H, J = 7.5 Hz), 7.02-6.98 (m, 4H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 162.2 (d, J_{C-F}= 245.5 Hz), 154.6, 147.4, 142.8, 137.1 (d, J_{C-F}= 3.2 Hz), 131.0, 130.8 (d, J_{C-F}= 7.9 Hz), 130.2, 130.0, 129.5, 127.4, 115.8, 115.3 (d, J_{C-F}= 21.4 Hz), 114.6, 40.0; HRMS (ESI) calcd for $C_{26}H_{18}F_2N_3OS$ $[M+H]^+$ 458.1139 found 458.1129.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)acetamide *(nb 246a* 41*j): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41j** as a yellow color solid (21.5 mg, 66%); R_f (10% EtOAc/hexane) 0.6; mp: 214-216 ^oC; IR (KBr): 3055, 2987, 1420, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, 1H, J = 7.4 Hz), 7.97 (br. s, 1H), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 0.6Hz), 7.56 (dd, 1H, J_1 = 8.8, J_2 = 7.5Hz), 7.46 (dd, 1H, J_1 = 8.0, J_2 = 7.3Hz), 7.38-7.34 (m, 5H), 7.32-7.29 (m, 5H), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 154.6, 147.4, 142.6, 139.6, 133.6, 131.0, 130.6, 130.0, 129.9, 129.6, 128.6, 127.5, 115.9, 114.5, 39.9; HRMS (ESI) calcd for $C_{26}H_{18}Cl_2N_3OS$ $[M+H]^+$ 490.0548 found 490.0560.

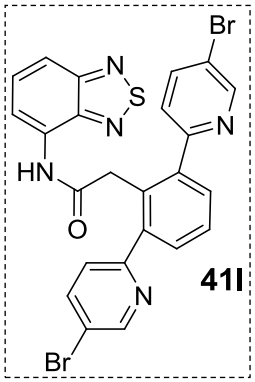


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 470a* 41*k): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41k** as a pale yellow color solid (32 mg, 51%); R_f (10% EtOAc/hexane) 0.6; mp: 244-246 ^oC; IR (KBr): 3055, 2987, 2686, 1423, 1265, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, 1H, J = 7.3 Hz), 7.95 (br. s, 1H), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.57 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.48-7.44 (m, 5H), 7.33 (d, 2H, J = 7.6 Hz), 7.30 (d, 4H, J = 8.4 Hz), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):

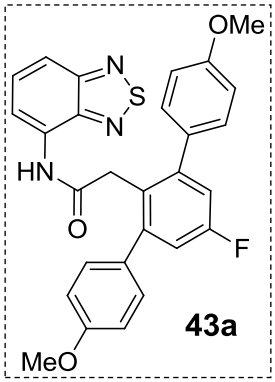


δ_C169.6, 154.6, 147.3, 142.6, 140.1, 131.5, 131.0, 130.9, 129.9, 129.8, 129.6, 127.5, 121.8, 115.9, 114.5, 39.9; HRMS (ESI) calcd for $C_{26}H_{18}Br_2N_3OS$ $[M+H]^+$ 577.9537 found 577.9512.

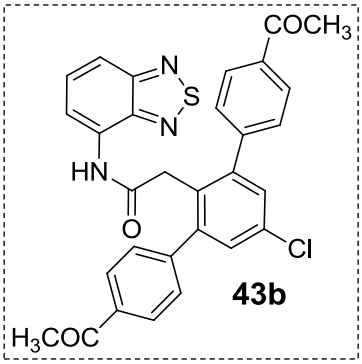
***N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(2,6-bis(5-bromopyridin-2-yl)phenyl)acetamide*(nb 471a/458a* **41*l*):**The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **41l** as a dirty yellow color solid (41 mg, 65%); R_f (10% EtOAc/hexane) 0.4; mp: 226-228 ^oC; IR (KBr): 3337, 3055, 1681, 1526, 1264, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.61 (br. s, 1H), 8.96 (d, 2H, J = 2.0 Hz), 8.32 (d, 1H, J = 7.5Hz), 8.01 (dd, 2H, J_1 = 8.3, J_2 = 2.4Hz), 7.63 (dd, 1H, J_1 = 8.8, J_2 = 0.9Hz), 7.55 (dd, 1H, J_1 = 8.7, J_2 = 7.4Hz), 7.48 (br. s, 3H), 7.45 (d, 2H, J = 8.2 Hz), 4.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 157.8, 155.1, 150.1, 148.1, 140.9, 139.9, 131.5, 131.3, 131.1, 131.0, 127.5, 125.9, 119.9, 115.3, 115.2, 39.3; HRMS (ESI) calcd for $C_{24}H_{16}Br_2N_5OS$ $[M+H]^+$ 579.9442 found 579.9452.



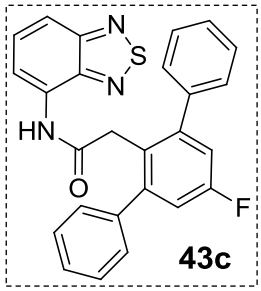
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(5'-fluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)acetamide *(nb 434a* 43*a):The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane =10:90) to afford **43a** as a faint yellow color solid (17 mg, 53%); R_f (10% EtOAc/hexane) 0.6; mp: 197-199 ^oC; IR (KBr): 3055, 2986, 1513, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.34 (d, 1H, J = 7.2 Hz), 8.00 (br. s, 1H), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 0.9Hz), 7.56 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.32 (d, 4H, J = 8.8 Hz), 7.06 (d, 2H, J = 9.0Hz), 6.85 (d, 4H, J = 8.8 Hz), 3.73 (s, 2H), 3.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.0, 160.7 (d, $J_{C\text{-}F}$ = 246.6 Hz), 159.1, 154.1, 147.4, 145.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 132.8, 131.1, 130.1, 129.8, 126.7, 116.4 (d, $J_{C\text{-}F}$ = 20.8 Hz), 115.6, 114.2 (d, $J_{C\text{-}F}$ = 34.0 Hz), 113.9, 55.2, 39.5; HRMS (ESI) calcd for $C_{28}H_{23}FN_3O_3S$ $[M+H]^+$ 500.1444 found 500.1433



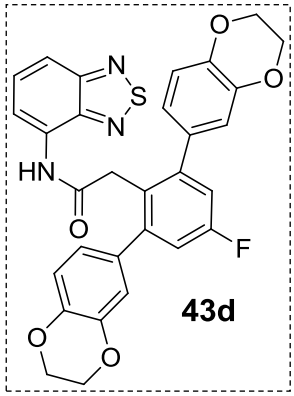
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4,4''-diacetyl-5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)acetamide *(nb 1062b* 43*b):The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **43b** as a faint yellow color solid (25 mg, 47%); R_f (10% EtOAc/hexane) 0.35; mp: 250-252 ^oC; IR (KBr): 3055, 2987, 1676, 1422, 1266, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.31 (d, 1H, *J* = 7.2 Hz), 7.94 (d, 4H, *J* = 8.1 Hz), 7.89 (br. s, 1H), 7.69 (d, 1H, *J* = 8.8 Hz), 7.60-7.56 (m, 1H), 7.53 (d, 4H, *J* = 8.2 Hz), 7.38 (br. s, 2H), 3.66 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.4, 168.9, 154.6, 147.3, 144.7, 144.4, 142.5, 136.4, 133.2, 131.0, 129.6, 129.4, 128.6, 128.4, 116.1, 114.7, 39.4, 26.6; HRMS (ESI) calcd for $C_{30}H_{23}ClN_3O_3S$ $[M+H]^+$ 540.1149 found 540.1169



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(5'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)acetamide*(nb 1063a /465* 43*c):The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **43c** as a fainy yellow color solid (28 mg, 65%); R_f (10% EtOAc/hexane) 0.8; mp: 200-202 ^oC; IR (KBr): 3055, 2987, 1680, 1526, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, 1H, *J* = 7.4 Hz), 8.02 (br. s, 1H), 7.66 (d, 1 H, *J* = 8.8 Hz), 7.58-7.54 (m, 1H), 7.40 (d, 4H, *J* = 7.1 Hz), 7.37-7.27 (m, 6H), 7.11 (d, 2H, *J* = 8.9 Hz), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.7, 161.1 (d, $J_{C\text{-}F}$ = 246.7 Hz), 154.7, 147.8, 145.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 140.4 (d, $J_{C\text{-}F}$ = 1.7 Hz), 131.1, 129.7, 128.9, 128.5, 127.8, 126.0, 116.5 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.7, 114.6, 39.4; HRMS (ESI) calcd for $C_{26}H_{19}FN_3OS$ $[M+H]^+$ 440.1233 found 440.1219

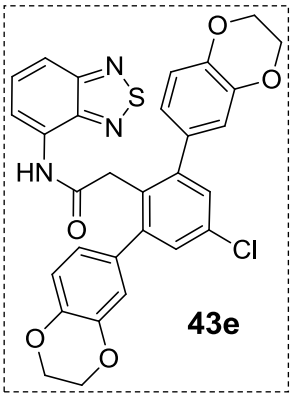


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-fluorophenyl)acetamide *(nb 1068b* 43*d):The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **43d** as a dirty white color solid (29 mg, 52%); R_f (10% EtOAc/hexane) 0.3; mp: 235-237 ^oC; IR (KBr): 3055, 2986, 1580, 1416, 1266, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, 1H, *J* = 7.4 Hz), 8.04 (br. s, 1H), 7.66 (d, 1H, *J* = 8.8 Hz), 7.59-7.55 (m, 1H), 7.05 (d, 2H, *J* = 9.0 Hz), 6.90

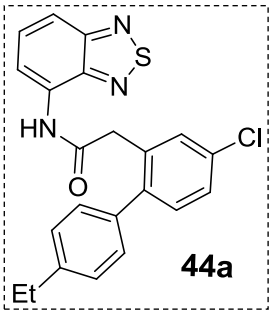


(br. s, 2H), 6.86 (d, 2H, *J* = 8.4 Hz), 6.81 (d, 2H, *J* = 8.2 Hz), 4.17-4.13 (m, 8H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.9, 161.1 (d, $J_{C\text{-}F}$ = 246.1 Hz), 154.6, 147.5, 145.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 143.3, 143.2, 133.7, 131.2, 129.8, 126.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 122.1, 122.1, 118.0, 117.3, 116.5 (d, $J_{C\text{-}F}$ = 21.6 Hz), 115.5, 114.6, 64.3, 64.2, 39.4; HRMS (ESI) calcd for $C_{30}H_{23}FN_3O_5S$ $[M+H]^+$ 556.1342 found 556.1365.

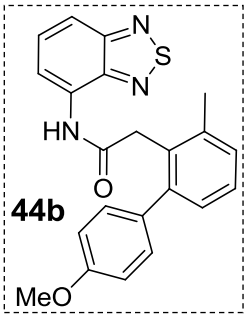
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4-chloro-2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)acetamide*(nb 1044a 43e): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford **43e** as a dirty white color solid (38 mg, 71%); R_f (10% EtOAc/hexane) 0.3; mp: 251-253 ^{o}C; IR (KBr): 3055, 2987, 1548, 1423, 1265, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, 1H, *J* = 8.0 Hz), 8.02 (br. s, 1H), 7.66 (d, 1 H, *J* = 8.8 Hz), 7.59-7.55 (m, 1H), 7.32 (br. s, 2H), 6.90 (br. s, 2H), 6.86 (d, 2H, *J* = 8.3 Hz), 6.80 (d, 2H, *J* = 8.2Hz) 4.16-4.13 (m, 8H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.6, 154.6, 147.5, 144.7, 143.3, 143.2, 133.5, 132.8, 131.2, 129.7, 129.5, 129.2, 122.1, 118.1, 117.3, 115.5, 114.7, 64.3, 64.2, 39.6; HRMS (ESI) calcd for $C_{30}H_{21}ClN_3O_5S$ $[M-H]^-$ Exact Mass: 570.0890 found 570.0915.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4-chloro-4'-ethyl-[1,1'-biphenyl]-2-yl)acetamide*(nb 499a 44a): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford ***44*a** as a faint yellow color solid (23 mg, 51%); R_f (10% EtOAc/hexane) 0.4; mp: 158-160 ^{o}C; IR (KBr): 3330, 3054, 1689, 1550, 1269, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (d, 1H, *J* = 7.3 Hz), 8.30 (br. s, 1H), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 0.9Hz), 7.58 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.51 (d, 1H, *J* = 2.2 Hz), 7.39 (dd, 1H, J_1 = 8.2, J_2 = 2.2Hz), 7.31-7.21 (m, 5H), 3.82 (s, 2H), 2.65 (q, 2H, *J* = 7.6 Hz), 1.23 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.0, 154.7, 147.6, 143.8, 141.2, 137.0, 133.6, 133.6, 131.9, 131.0, 130.5, 129.6, 129.0, 128.2, 127.9, 115.9, 114.9, 42.2, 28.5, 15.4; HRMS (ESI) calcd for $C_{22}H_{19}ClN_3OS$ $[M+H]^+$ 408.0937 found 408.0920.



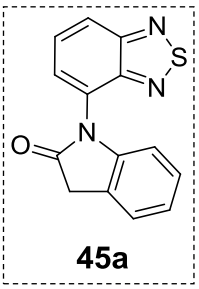
N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(4'-methoxy-3-methyl-[1,1'-biphenyl]-2-yl)acetamide*(nb 1370a 44b): The resultant crude mixture was purified by silica gel column chromatography (EtOAc:hexane = 10:90) to afford ***44*b** as a Faint yellow color solid (49 mg, 65%); R_f (10% EtOAc/hexane) 0.5; mp: 187-189 ^oC; IR (KBr): 3055, 1681, 1527, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (d, 1H, J = 7.3 Hz), 8.38 (br. s, 1H), 7.66 (d, 1H, J = 8.8Hz), 7.60-7.56 (m, 1H), 7.37-7.30 (m, 4H), 7.26 (d, 1H, J = 7.3Hz), 6.91 (d, 2H, J = 8.4Hz), 3.89 (s, 2H), 3.80 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.7, 158.9, 154.7, 147.7, 143.3, 138.0, 133.8, 131.0, 130.6, 130.2, 130.0, 129.8, 128.8, 127.7, 115.8, 114.8, 113.9, 55.3, 39.8, 20.5; HRMS (ESI) calcd for $C_{22}H_{20}N_3O_2S$ $[M+H]^+$ 390.1276 found 390.1275.



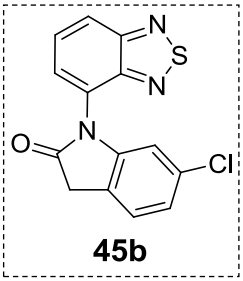
General procedure for the Pd(II)-catalyzed ABTD assisted cyclization of phenylacetamide and preparation of the compounds 45a-c (indolinone)

An appropriate phenylacetamide (0.10-0.12 mmol, 1equiv), $Pd(OAc)_2$ (2.5-2.7 mg, 10 mol%), and $PhI(OAc)_2$ (97-100 mg, 2.5-3 equiv.) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel furnished the corresponding cyclized products **45a-c** (see corresponding Tables/Schemes for specific examples and reaction conditions).

1-(Benzo[*c*][1,2,5]thiadiazol-4-yl)indolin-2-one*(nb 285* 45*a):* Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford **45a** as a dark brown color solid (21 mg, 65%); R_f (10% EtOAc/hexane) 0.4; mp: 143-145 ^oC; IR (KBr): 3055, 2986, 1729, 1370, 1266, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.15 (dd, 1H, J_1 = 8.7, J_2 = 1.1Hz), 7.78 (dd, 1H, J_1 = 8.7, J_2 = 7.1Hz), 7.72 (dd, 1H, J_1 = 7.2, J_2 = 1.2Hz), 7.39 (dd, 1H, J_1 = 7.1, J_2 = 0.6Hz), 7.20 (tt, 1H, J_1 = 7.7, J_2 = 0.5Hz), 7.13 (td, 1H, J_1 = 7.5, J_2 = 1.1Hz), 6.52 (dd, 1H, J_1 = 7.7, J_2 = 0.3Hz), 3.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C174.5, 156.1, 151.0, 144.8, 129.3, 128.7, 127.8, 126.9, 124.8, 124.3, 123.2, 122.3, 109.8, 36.1; HRMS (ESI) calcd for $C_{14}H_{10}N_3OS$ $[M+H]^+$ 268.0545 found 268.0553.

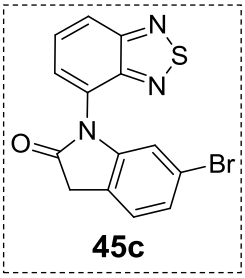


1-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-6-chloroindolin-2-one*(nb 1046* 45*b):* Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford **45b** as a dark brown color solid (14.5 mg, 50%); R_f (10% EtOAc/hexane) 0.4; mp: 161-163 ^oC; IR (KBr): 3055, 2986, 1728, 1424, 1265, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.17 (d, 1H, J = 8.8Hz), 7.81-7.77 (m, 1H), 7.70 (d, 1H, J = 7.0Hz), 7.30 (d, 1H, J = 8.0Hz), 7.11 (dd, 1H, J_1 = 7.8, J_2 = 0.6Hz), 6.50 (br. s, 1H), 3.93-3.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C174.5, 156.1, 150.8, 145.9, 133.7, 129.3, 128.8, 126.3, 125.7, 123.1, 122.7, 122.5, 110.4, 35.7; HRMS (ESI) calcd for $C_{14}H_9ClN_3OS$ $[M+H]^+$ 302.0155 found 302.0140.



45b

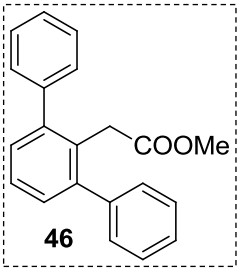
1-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-6-bromoindolin-2-one*(nb 535* 45*c):* Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford **45c** as a dark brown color solid (16 mg, 45%); R_f (10% EtOAc/hexane) 0.4; mp: 177-179 ^oC; IR (KBr): 3055, 2987, 1729, 1423, 1265, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.17 (dd, 1H, J_1 = 8.8, J_2 = 1.0Hz), 7.79 (dd, 1H, J_1 = 8.8, J_2 = 7.1Hz), 7.70 (dd, 1H, J_1 = 7.1, J_2 = 1.0Hz), 7.26 (d, 2H, J = 1.5Hz), 6.65 (br. s, 1H), 3.90-3.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C174.3, 156.1, 150.8, 146.0, 129.3, 128.8, 126.3, 126.1, 126.0, 123.1, 122.7, 121.4, 113.1, 35.7; HRMS (ESI) calcd for $C_{14}H_9BrN_3OS$ $[M+H]^+$ 345.9650 found 345.9654.



45c

Typical Procedure for the hydrolysis of carboxamide 41d and preparation of the carboxylate derivative 46. To a solution of carboxamide **41d** (47 mg, 0.125 mmol, 1equiv.) in dry methanol (3 mL) was added $BF_3.Et_2O$ (0.5 mL) added dropwise. Then, the resulting mixture was allowed to stir at 80 °C for 36 h. Then, the reaction mixture was allowed to attain the rt. Next, neutralize the crude mixture by Et_3N (304 mg, 3 mmol) was added dropwise with stirring. After this, the solvent was evaporated in vacuum to afford the carboxylate derivative **46**.

Methyl 2-([1,1':3',1''-terphenyl]-2'-yl)acetate (nb 839, 46): Purification ofthe resultant crude mixture by column chromatography on silica gel (EtOAc:hexane = 10:90) to afford **46** as a viscous liquid (25 mg, 60%); R_f (10% EtOAc/hexane) 0.8; IR (KBr): 3412, 3053, 2926, 1740, 1523, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H7.44-7.34 (m, 11H), 7.30 (d, 2H, J = 7.4 Hz), 3.53 (s, 2H),



46

3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.6, 143.4, 141.6, 130.0, 129.3, 129.2, 128.2, 127.2, 126.8, 51.7, 36.9; HRMS (ESI) calcd for $C_{21}H_{19}O_2$ $[M+H]^+$ 303.1385 found 303.1374.

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Chapter 4

Pd(II)-catalyzed4-amino-2,1,3-benzothiadiazole (ABTD) assisted β-γ-C-(sp^3)-H functionalization of natural/unnatural amino acid derivatives and heterocarboxamides system

Functionalization of β-γ-C(sp^3)-H bonds of amino acid and heterocyclic system offers new systematic approaches for the synthesis of useful molecular entities.[1] The amino acid is building blocks molecule of protein. Focusing towards the necessity of such kind of molecules, their synthesis and development is still a challenging task for the scientists. Recently, transition-metal-catalyzed C-H activation/ functionalization has emerged as a promising strategy for broadening the diversity of amino acid and heterocycle containing compounds.[2] Given the importance of these molecules scientists try to develop various directing groups for C-H functionalization reaction. The beginning of a directing group that coordinates to the palladium catalyst and facilitates the cleavage of a nearest β-γ-C-H bond has become one of the most successful methodologies to achieve such kind of biological and medicinal important molecules. A variety of directing groups (e.g. 8-aminoquinoline, 2-thiomethylaniline, ester, carbamate, 2-(pyridine-2-yl) isopropyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline) were used for accomplishing the diastereoselective β-sp^3 C–H functionalization/activation. Our group has recently achieved the β-monoarylation of natural/unnatural amino acid and the homo bisarylation of alanine using our newly developed 4-amino-2,1,3-benzothiadiazole (ABTD) directing group.

a) Importance of functionalized amino acid

One of the most considerable challenges in modern medicinal chemistry is developing drugs which are highly effective against a target, with minimal toxicity and side-effects to the patient. An amino acid is a monomer unit of proteins. Amino acid are the building blocks of proteins andas drug candidates have attracted important consideration in pharmaceuticals andbiochemistry.[3] On numerous occasions, unnatural peptides have been found to show enhanced biological activities and improved pharmacokinetic properties when compared to their natural counterparts.[3c,d] Such properties are directly correlated to the constitution of the target site. Preferably, the drug should have a shape that is entirely complementary to a disease-causing target, so that it binds it with high specificity. For occurrence phenylalanine and its derivativesare used for a skin disease called vitiligo, depression, attention deficit-

hyperactivity disorder (ADHD), Parkinson's disease, multiple sclerosis, pain, acupuncture anesthesia, osteoarthritis, rheumatoid arthritis, weight loss, and alcohol withdrawal symptoms. Cetrotide is an artificial decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity.It is used in assisted reproduction to inhibit premature Luteinizing hormone surges and found to lower both testosterone and Luteinizing hormone levels more extended than the carbon analog. Leucine and its derivative help in the regulation of blood-sugar levels and prevent disease like phenylketonuria and maple syrup urine disease (Figure 1)

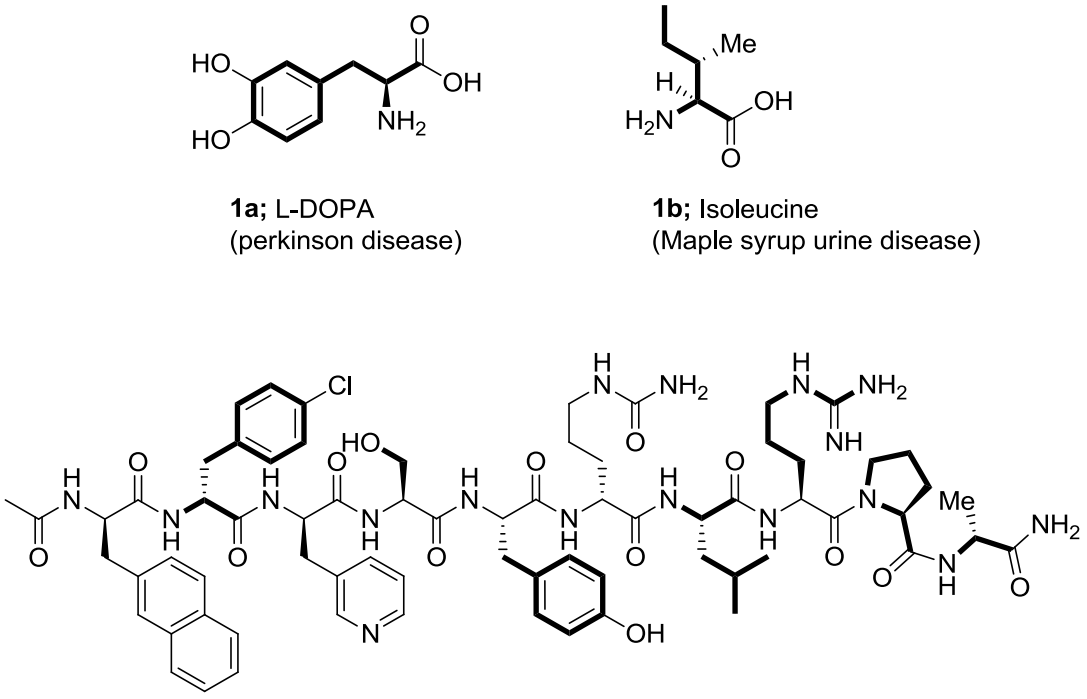


Figure 1 Medicinally important core molecule featuring various amino acids (**1a-1c**).

b) Importance of functionalized heterocycle system

Heterocyclic compounds have a vast range of applications but are of particular interest in the medicinal and biological field due to its activity in multiple illnesses. Organic molecules such as DNA, RNA, chlorophyll, hemoglobin, vitamins and many more molecule contain the heterocyclic ring in the main skeleton. There is a bundle of heterocyclic compounds which have been used in many regular diseases such as; triazine-based molecule used as antimicrobial herbicides, urinary antiseptics, and anti-inflammatory agents. Benzimidazole derivatives have been reported to possess a wide range of biological activities such as antibacterial, antifungal, antiviral and anthelmintic. In another way, it is essential to be

significant about the seminal role of heterocyclic based molecules and their derivative (unsymmetrical diarylmethane) scaffolds in organic synthesis. Firstly, functionalized furans/thiophenes and benzo-furans/benzo-thiophenes considered essential building blocks in organic synthesis, pharmaceutical and medicinal chemistry research.[4] For the example benzofuran occurs in a range of plant and microbial-derived natural products, ranging in complexity from 5-methoxybenzofuran, through the orange 'aurones', a group of plant pigments isomeric with co-occurring flavones to griseofulvin, from Penicilliumgriseofulvum, used in medicine as an antifungal agent. Then, arylheteroarylmethane (unsymmetrical diarylmethane) scaffolds are a subclass of diarylmethanes, which occupy an essential place in medicinal chemistry due to their broad range of pharmacological activities[5]. Additionally, these compounds are also found as subunits in supramolecular assemblies. Representative examples of bio-active furan/thiophene-based molecules and arylheteroarylmethane[6] are given below (Figure 2).

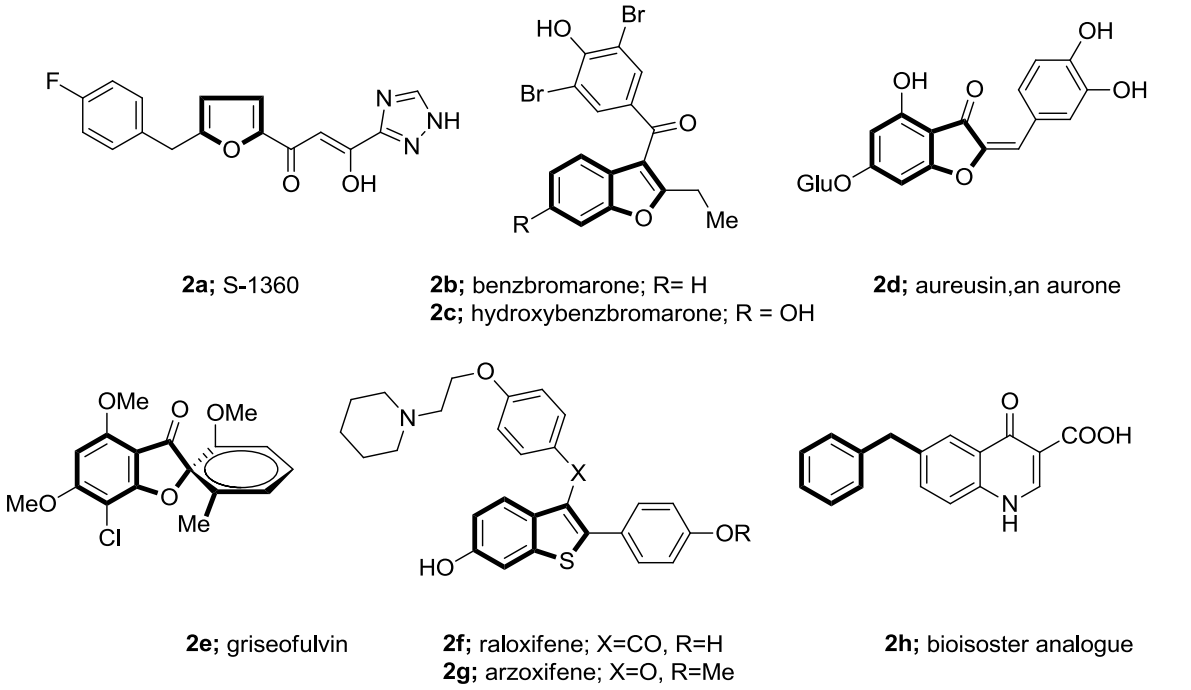
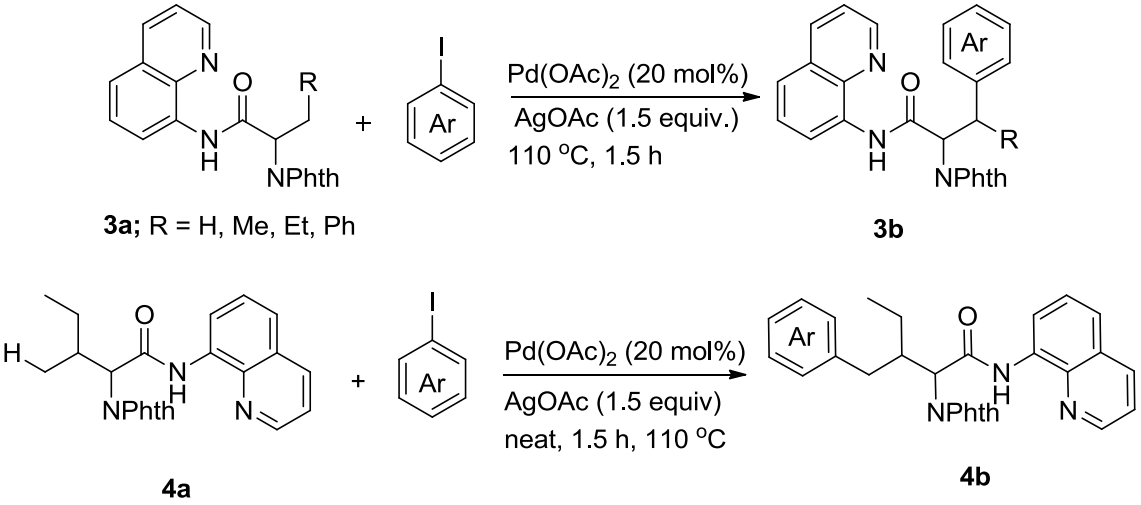


Figure 2 Biological active core molecule featuring various heterocyclic molecules (**2a-2h**).

Our group has developed an alternative route for the construction of the substituted heteroarylmethane and its derivative with the help of 4-amino-2,1,3-benzothiadiazole (ABTD) as a bidentate directing group in the Pd(II)-catalyzed functionalization of the β-γ-C(sp^3)-H bond of natural/unnatural amino acid and 3-methyl thiophene-2-carboxamide system.

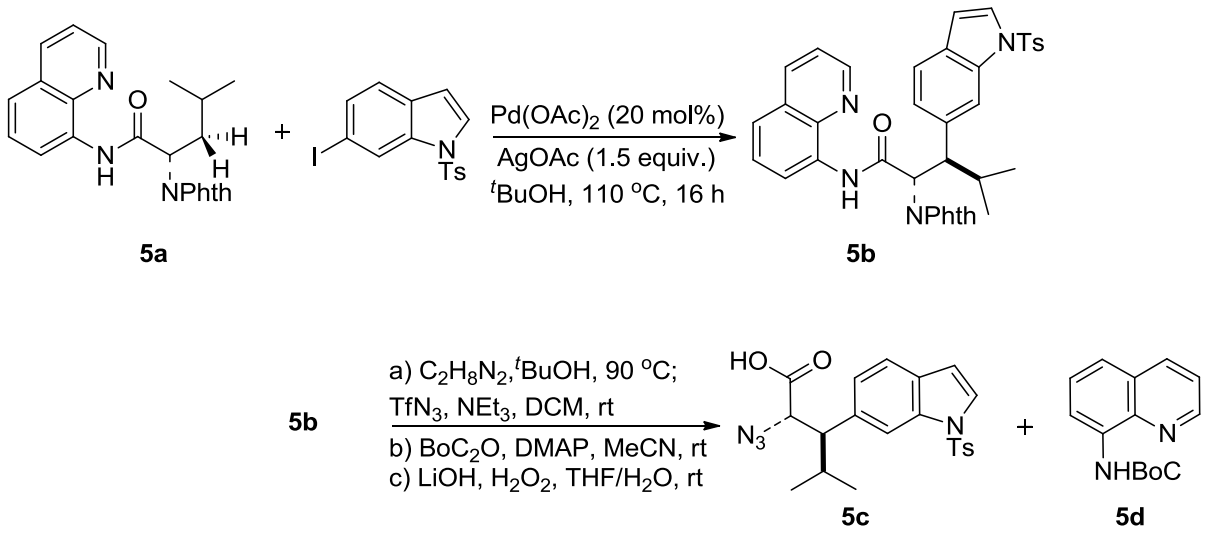
Representative reports dealing on the β-γ-C-(sp^3)-H bond of natural/unnatural carboxamide and heterocyclic carboxamides: the synthesis of functionalized heterocyclic and amino acid moieties *via* C–H activation.

Corey and co-workers[7a] reported 8-aminoquinoline directed β-γ-C-(sp^3)-H activation of amino acid carboxamides **3a**/**4a**. The reaction of **3a**/**4a** with 4 equiv. of iodobenzene in the presence of $Pd(OAc)_2$ (20 mol %) as a catalyst, 1.5 equiv. of AgOAc as oxidant/ base, neat reaction condition at 110 °C in 1.5 h under an atmosphere of nitrogen gave the mono/ bis arylated product **3b**/**4b** in excellent yield (Scheme 1).



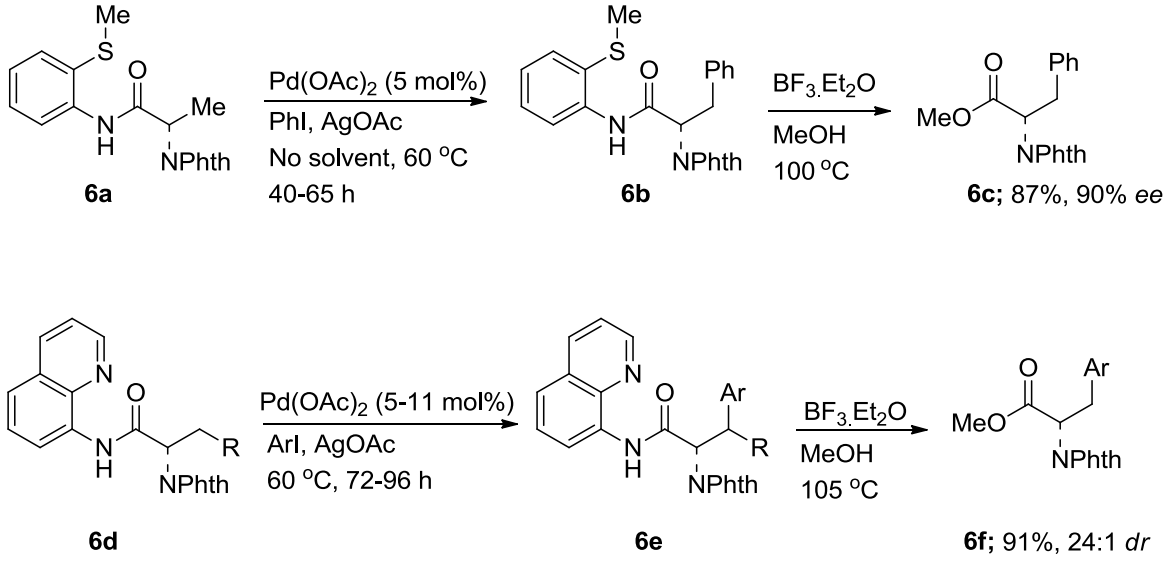
Scheme 1 Synthesis of the modified amino acid derivative by using 8-aminoquinoline as a directing group.

Chan and co-workers[7b] reported 8-aminoquinoline directed total synthesis of Celogentin-C by using C-H activation/ functionalization process. The Pd(II)-catalyzed C-H activation of leucine carboxamide **5a** with tryptophan iodide in the presence of $Pd(OAc)_2$ (20 mol%), 1.5 equiv. of AgOAc in ^{t}BuOH at 110 ^{o}C for 16 h offered the product **5b** in good yield (Scheme 2). The cleavage of the amide linkage group with Evans hydrolytic condition at room temperature, give the desired azido acid product **5c** with complete chiral integrity (Scheme 2).



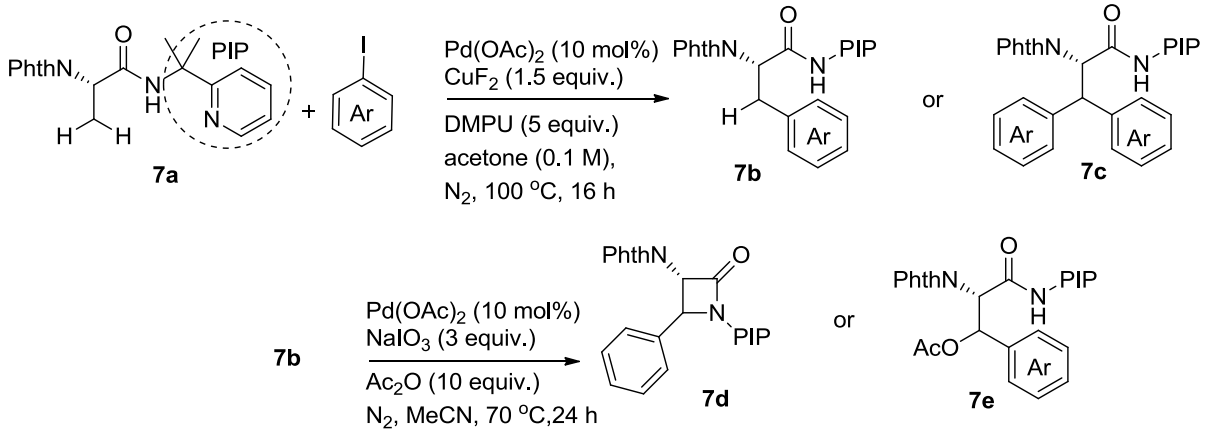
Scheme 2 Synthesis of Celogentin-C by using chiral leucine carboxamide.

Daugulis and co-workers[7c] reported 2-thiomethylaniline/8-aminoquinoline directed β-C-(sp^3)-H activation of unnatural amino acid carboxamides **6a** and **6d**. The reaction of **6a** and **6d** with iodobenzene in presence of $Pd(OAc)_2$ (5-11 mol %) as a catalyst, AgOAc as an oxidant/ base, neat reaction condition at 60 °C for 40-96 h under an atmosphere of nitrogen gave the mono/ bis arylated product **6b** and **6e** which involves activation of the β C-(sp^3)-H bonds. The cleavage of the directing group offered the desired product **6c** & **6f**, respectively in highly enantioselective and diastereoselective manner (Scheme 3).



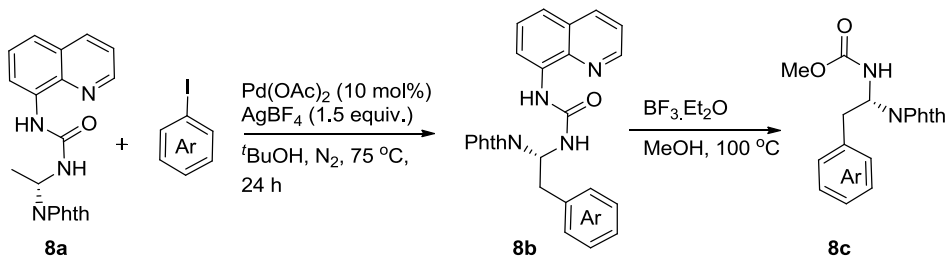
Scheme 3 Synthesis of the modified phenylalanine derivative by using 2-thiomethylaniline and 8-aminoquinoline as directing groups.

Shi and co-workers[7d] reported 2-pyridine-2-yl-isopropylamine (PIP) directed β-C-(sp^3)-H bond activation of amino acid carboxamides **7a**. The Pd (II)-catalyzed β-C-(sp^3)-H activation of carboxamide **7a** with a wide range of aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 1.5 equiv. of CuF_2 as an additive in the mixture of solvent DMPU and acetone at 100 ^oC for 16 h offered mono and bis product **7b/ 7c** in the ratio of 30:1 (Scheme 4). Then, the further use of monoarylated product **7b** for the intramolecular cyclization or amination through 10 mol% of $Pd(OAc)_2$ with 3 equiv. of $NaIO_3$. 10 equiv. of Ac_2O in MeCN at 70 ^oC for 24 h offered β-lactam as a major **7d** and acetoxylation as a minor product **7e** (Scheme 4).



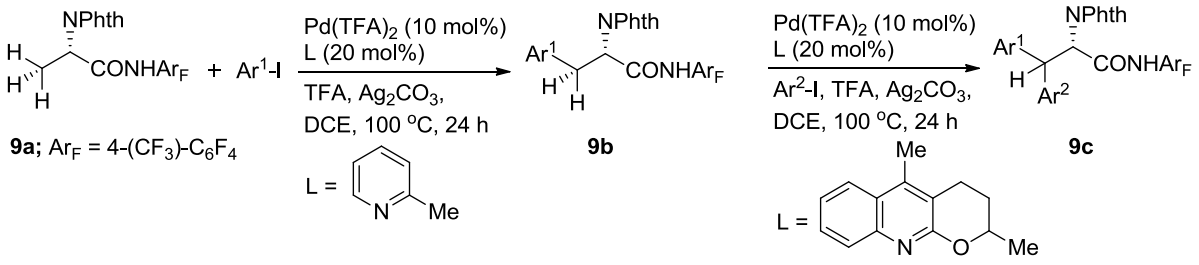
Scheme 4 Synthesis of Chiral α-Amino-β-Lactams through Sequential Monoarylation/Amidation of PIP directed amino acid carboxamide **7a**.

Shi and co-workers[7e] reported 8-aminoquinoline (8-AQ) directed monoarylation of β-C-(sp^3)-H bond activation of amino acid carboxamides **8a.** The Pd (II)-catalyzed β-C-(sp^3)-H activation of carboxamide **8a** with 1.2 equiv. of substituted aryl iodide sources in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 1.5 equiv. of $AgBF_4$ as an additive in the *tert*-BuOH solvent at 75 ^oC for 16 h offered exclusively monoarylated product **8b** in good yield. Finally removal of the directing group gave the ester of substituted amino acid product **8c** (Scheme 5).



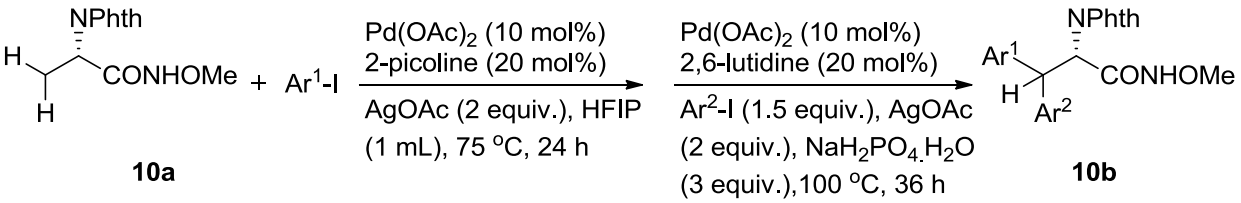
Scheme 5 Synthesis of selective monoarylation of amino acid carboxamide **8a**.

Yu and co-workers[7f]reported 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline assisted ligand controlled β-C-(sp^3)-H bond activation of amino acid carboxamides **9a.** The Pd (II)-catalyzed reaction of carboxamide **9a** with substituted aryl iodide sources in the presence of $Pd(TFA)_2$ (10 mol%) as catalyst, 20 mol% of TFA, Ag_2CO_3 as additive in the DCE solvent at 100 ^oC for 20 h by using 20 mol% pyridine as a ligand lead to absolutely monoarylated product **9b** in good yield (Scheme 6). The same condition further applies on the monoarylated product **9b** by tuning the 20 mol% of quinoline as ligand instead of pyridine offered the chiral product in good yield, an excellent enantioselective manner (Scheme 6).



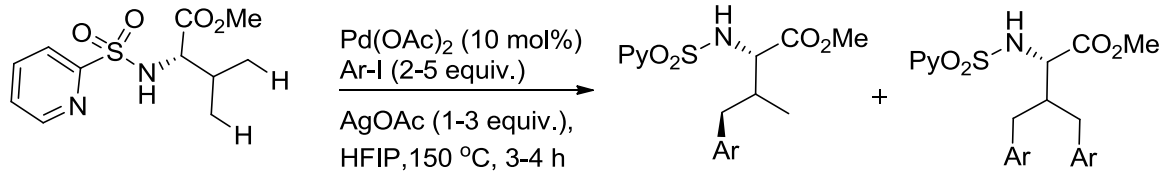
Scheme 6 Synthesis of ligand controlled chiral unnatural amino acid **9**.

Yu and co-workers[7g] developed a very simple and practical auxiliary *N*-methoxyamide aided ligand controlled β-C-(sp^3)-H activation of amino acid carboxamides **10a.** The Pd (II)-catalyzed reaction of carboxamide **10a** treated with 1.2 equiv. of substituted aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 20 mol% of 2-picoline as a ligand, 2 equiv. of AgOAc as an additive in 1 mL of HFIP solvent at 75 ^oC for 24 h lead to the absolutely monoarylated product in good yield (Scheme 7). The monoarylated product treated with 1.5 equiv. of substituted aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 20 mol% of 2,6-lutidine as a ligand, 2 equiv. of AgOAc as an additive, 3 equiv of $NaH_2PO_4.H_2O$ in 1 mL of HFIP solvent at 100 ^oC for 36 h offered the hetero bis arylated product in good yield with a diastereoselective ratio >20:1 manner **10b** (Scheme 7).



Scheme 7 Synthesis of heterobisarylated amino acid by using *N*-methoxyamide as a directing group of system **10a.**

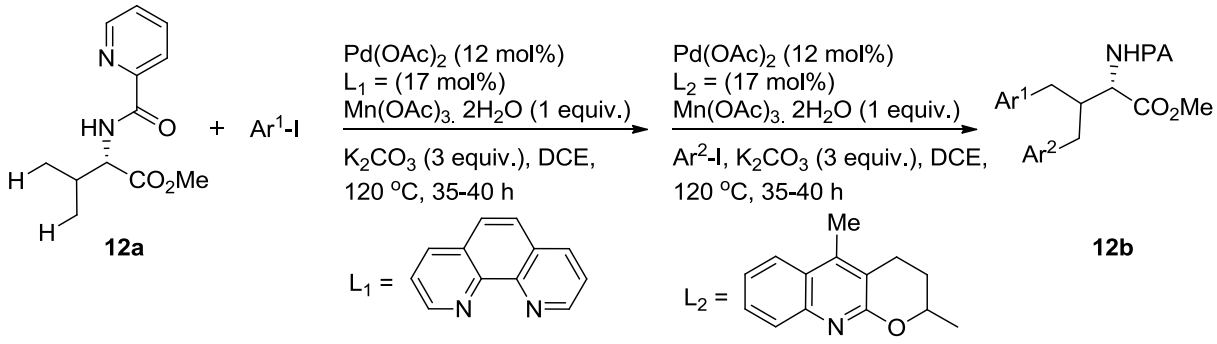
Carretero andco-workers[7h] reported *N*-(2-pyridyl)sulfonyl-directed γ-C-(sp3)-H arylation of amino acid system **11a**. The reaction of **13a** with 2-5 equiv. of aryl iodide source in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 1-3 equiv. of AgOAc as oxidant in 1 M HFIP solvent at 150 ^oC for 3-4 h offered **11b** in dr > 20:1 and **11c** in ee > 99% (Scheme 8).



11a **11b** **11c**

Scheme 8 Diastereoselective/enantioselective arylation of amino acid by using *N*-(2-pyridyl) sulfonyl as directing a group of system **11a.**

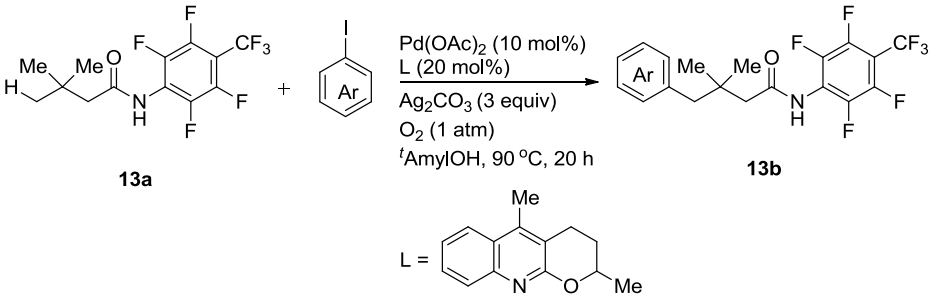
Jana and co-workers[7i] reported the picolinamide directed monoarylation of amino acid carboxamides **12a**. The Pd(II)-catalyzed γ-C-(sp^3)-H activation of amino acid in the presence of ligand and replacement of toxic silver acetate with natural abundant manganese acetate. Amino acid carboxamide **12a** reacted with a wide range of aryl iodides in the presence of 1,10-phenanthroline as an inexpensive ligand and 12 mol% of $Pd(OAc)_2$, 1 equiv. of $Mn(OAc)_2.2H_2O$, 3 equiv. of K_2CO_3 in DCE at 120 ^oC for 35-40 h lead to monoarylation of system **12a**, further the reaction of monoarylated product in the presence of similar condition and just changing the ligand give to hetero bis product **12b** (Scheme 9).



12a **12b**

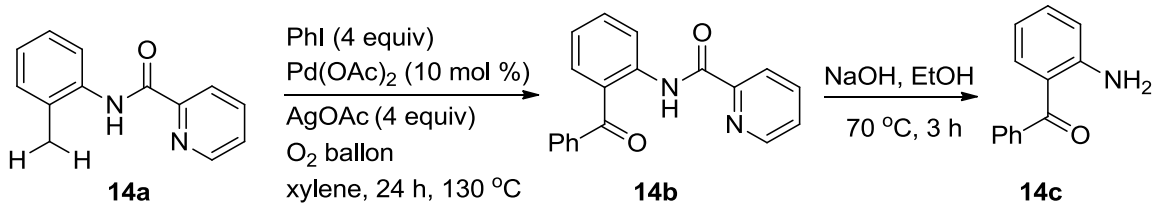
Scheme 9 Ligand controlled picolinamide directed arylation of amino acid system **12a**.

Yu and co-workers[7j] reported 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline assisted γ-C(sp^3)-H arylation of **13a**. The reaction of **13a** in the presence of $Pd(OAc)_2$ (10 mol%) as a catalyst, 20 mol% of ligand and 3 equiv. of Ag_2CO_3 in ^{t}AmylOH at 90 °C under an atmosphere of oxygen offered the arylated product in good yield **13b** (Scheme 10).



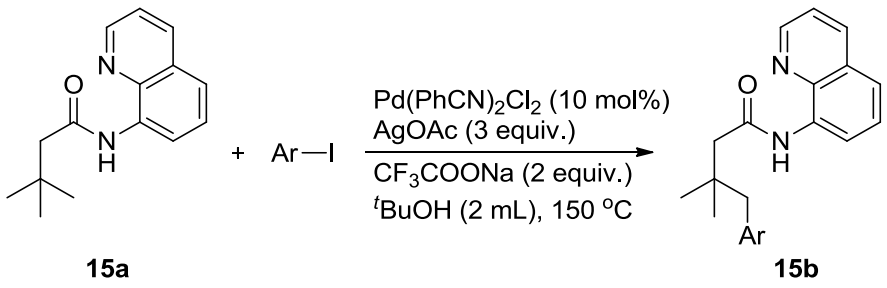
Scheme 10 Ligand-enabled γ-C(sp^3)-H arylation of carboxamide **13a**

Zhang and co-workers[8a, b] reported a Pd(II)-catalyzed benzylic *γ*-C(sp^3)-H arylation/oxidation of carboxamide system **14a.** The carboxamide **14a** react with 4 equiv. of aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%),4 equiv of AgOAc under an oxygen atmosphere in xylene at 130 ^oCfo 24 h gave the product **14b** in excellent yield (Scheme 11). Further, they attempt the removable of directing group from the product **14b** under basic hydrolysis conditions to afford 2-aminobenzophenone as product **14c** (Scheme 11).



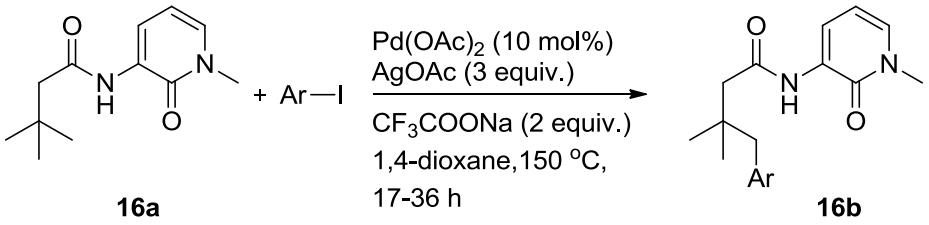
Scheme 11 Palladium-catalyzed arylation/oxidation of a benzylic C-H bond.

Maiti and co-workers[8c] reported 8-aminoquinoline directed *γ*-C-(sp^3)-H bond of aliphatic carboxamide system **15a**. The reaction of **15a** with a variety of aryl iodides in the presence of $Pd(PhCN)_2Cl_2$ (10 mol%), AgOAc (3 equiv.) and 2 equiv. sodium salt of trifluoroacetic acid in *tert*-BuOH solvent at 150 ^oC gave the desired product **15b** (Scheme 12).



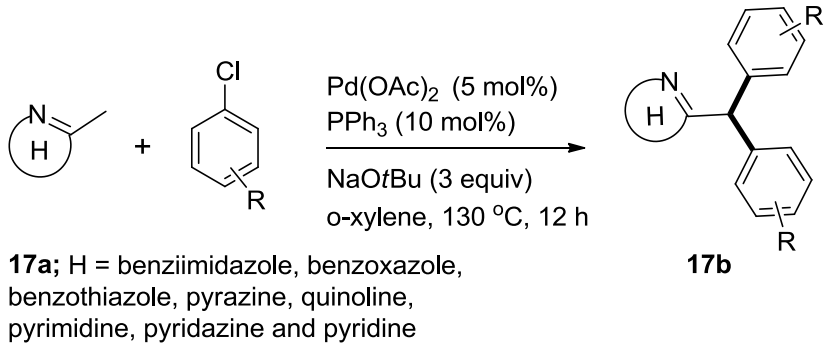
Scheme 12 8-Aminoquinoline directed arylation of *γ*-C-(sp^3)-H bond of aliphatic carboxamide **15a**.

Maiti and co-workers[8d] reported 3-Amino-1-methyl 1 H pyridine-2-one directed γ-C-(sp^3)-H bond of aliphatic carboxamide system **16a**. The reaction of **16a** with a variety of aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (3 equiv.) and 2 equiv. sodium salt of trifluoroacetic acid in 1, 4-dioxane solvent at 150 ^oC for 17-36 h lead to the product **16b** (Scheme 13).



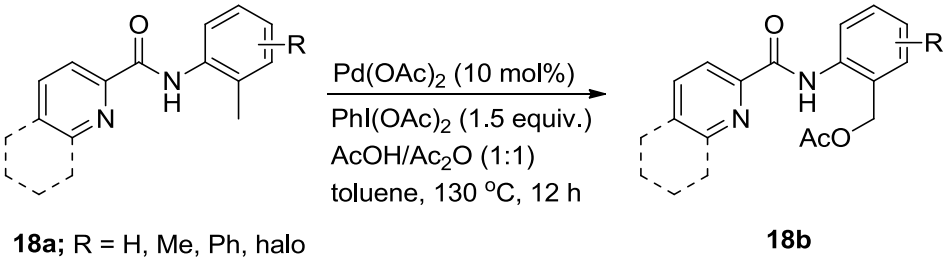
Scheme13 3-Amino-1-methyl 1 H pyridine-2-one directed arylation of γ-C-(sp^3)-H bond of aliphatic carboxamide **16a**.

Li and co-workers[8e] developed Pd(II)-catalyzed cross-coupling of (2-azaryl)-methanes **17a.** The Pd(II)-catalyzed reaction of **17a** with aryl chlorides in the presence of $Pd(OAc)_2$ (5 mol%), 10 mol% of PPh_3 as ligand and 3 equiv. of NaO^tBu as a base in *o*-xylene as solvent at 130 ^oC for 12 h offered the diarylated compound **17b** (Scheme 14).



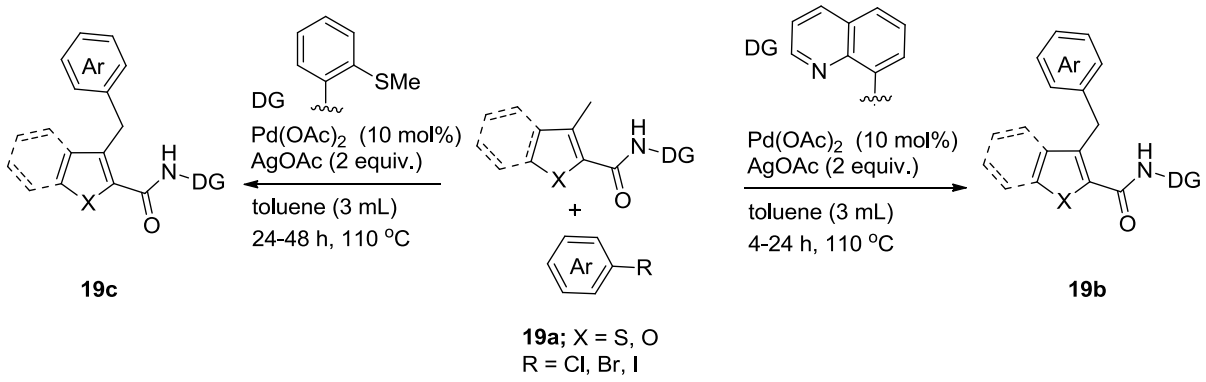
Scheme 14 Pd-Catalyzed diarylation of (2-azaryl) methanes **17a.**

Zhang and co-workers[8q] reported picolinamide assisted acetoxylation on benzylic C-H bond. The Pd-catalyzed benzylic sp^3C-H activation of carboxamide system **18a** in the presence of $Pd(OAc)_2$ (10 mo%), 1.5 equiv. of $PhI(OAc)_2$ and mixture of $AcOH/Ac_2O$ (1:1) in toluene at 130 ^oC for 12 h lead to acetoxylation product **18b** (Scheme 15).



Scheme 15 Pd-Catalyzed acetoxylation of the benzylic C-H bond of carboxamide **18a**.

Babu and co-worekers[8g] reported 8-aminoquinoline and 2-(methylthio)aniline directed benzylic C-H bond activation of the heterocyclic system. The Pd-catalyzed benzylic sp^3C-H activation of heterocarboxamide **19a** with a wide range of substituted aryl halides in the presence of $Pd(OAc)_2$ (10 mo%), AgOAc (2 equiv.) in toluene at 110 °C for 24-48 h lead to heteroarylmethane product **19b**/**19c** (Scheme 16).

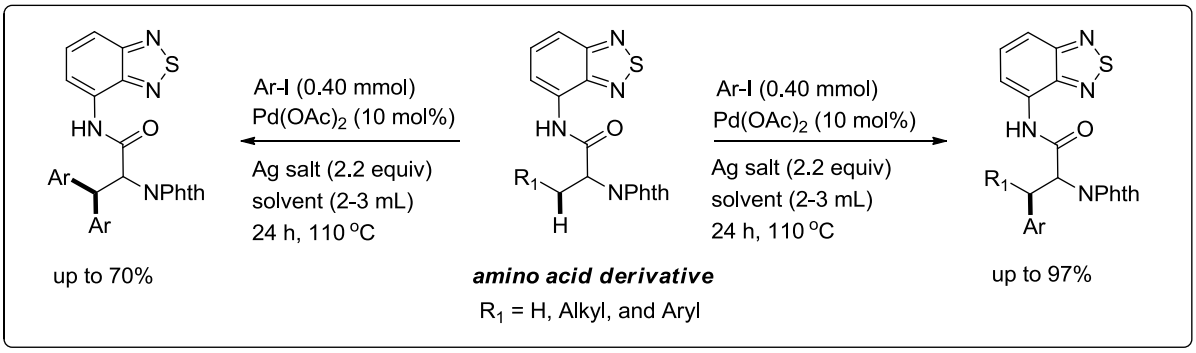


Scheme 16 Synthesis of heteroarylmethane product **19b/19c.**

Result and Discussion

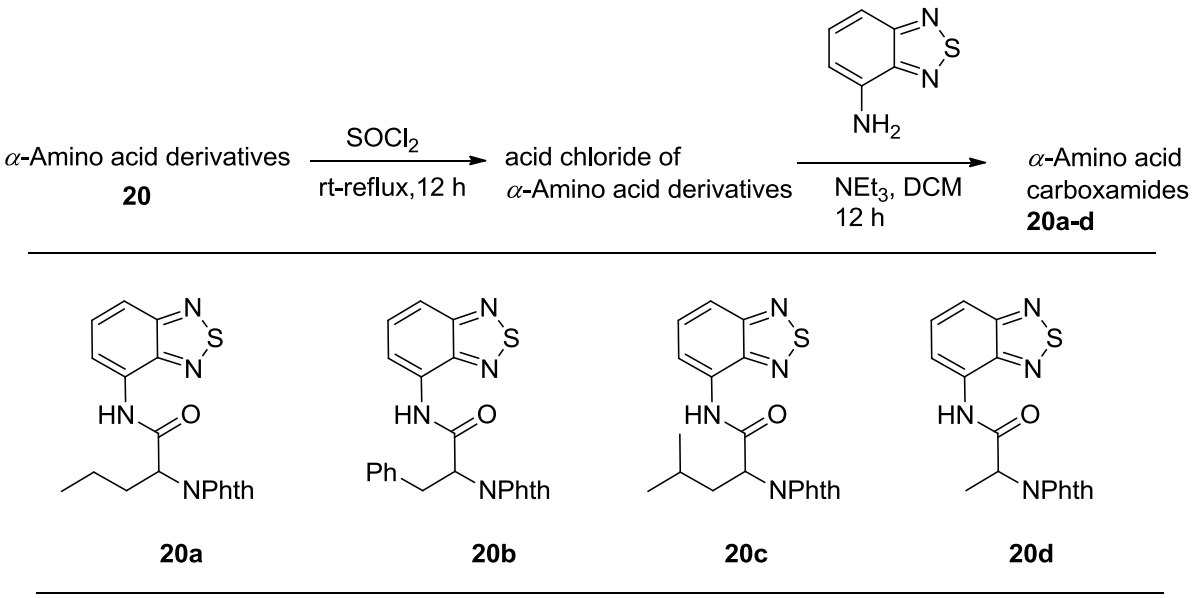
Part 1:- 4-Amino-2,1,3-Benzothiadiazole (ABTD) assisted Pd(II)-catalyzed C-(sp^3)-H arylation reaction on natural/unnatural amino acid derivatives.

This work



Scheme 17 ABTD enabled synthesis of natural/ unnatural amino acid from natural amino acid derivatives.

Aiming towards the massive potential of C-H bond activation for an organic compound using various metal catalysts has been successfully completed a different construction method for C-C and C-X bond formation.[9] The seminal work of Daugulis and Chen on the palladium-catalyzed arylation of primary/secondary C-(sp^3)-H bonds with an 8-aminoquinoline-derived *N,N*-bidentate directing group has inspired several C-H activation research groups to use this type of auxiliary to develop a diverse collection of novel C-(sp^3)-H functionalization reactions[10] Encouraged by their studies, we recently developed a commercially available 4-Amino-2,1,3-Benzothiadiazole (ABTD) as a new bidentate directing group. This directing group exhibited less reactivity and high selectivity in the activation of primary/secondary C-(sp^3)-H bonds. For e.g., 4-Amino-2,1,3-Benzothiadiazole (ABTD) directing group was involved in the development of a Pd(II)-catalyzed primary/secondary C-(sp^3)-H arylation. Mainly, we were focusing towards the idea of using the new bidentate ligand ABTD reaction for the synthesis of various bis/mono-arylated α-amino acid derivatives. As part of this chapter, our efforts towards the development of biologically relevant organic molecules by direct C-(sp^3)-H activation, and the development of β-aryl-α-amino acids could be accessed by the arylation of various α-amino acid derivatives. Accordingly, the test of this hypothesis on the synthesis of C-(sp^3)-H arylated α-amino carboxamides via the Pd(II)-catalyzed ABTD assisted C-(sp^3)-H arylation (Scheme 17).

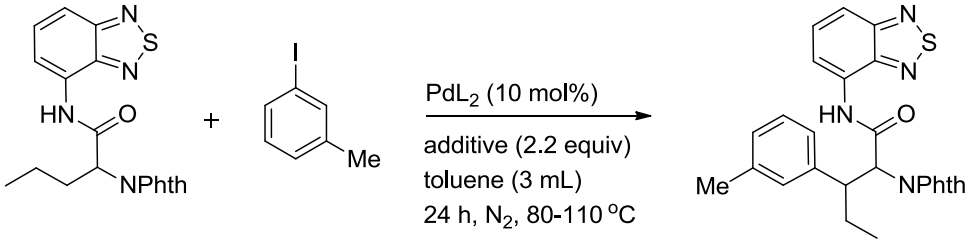


Scheme 18 Preparation of α-amino acid carboxamides.

Following the literature procedure, various α-amino acids carboxamides system **20a-d** prepared from many α-amino acids (Scheme 18). Then to initiate our investigation on the arylation of amino acid carboxamides, different optimization reactions were performed for getting the arylation on norvaline carboxamide system **20a** (Table 1).

The C-H activation reaction on norvaline carboxamide system **20a** with 3-iodo toluene **21** in the absence of Pd(II)-catalyst with AgOAc did not give the desired product **22a** (entry 1, Table 1). The C-(sp^3)-H arylation on norvaline carboxamide system **20a** not offered any product **22a** in the absence of additive (entry 2, Table 1). The reaction of norvaline carboxamide system **20a**, aryl iodide **21** and AgOAc in the presence of a catalyst, such as $Pd(CH_3CN)_2Cl_2$ catalyst failed to give satisfactory products **22a** (entry 3, Table 1). However, the Pd(II)-catalyzed C-H arylation on norvaline carboxamide **20a** with **21** in the presence of $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ leads to the C-H arylated norvaline carboxamide system **22a** in 40 and 32% yields respectively (entry 4 and 5, Table 1).

Table 1 Optimization reaction conditions.



20a; (0.10 mmol) ***21;*** (0.40 mmol) ***22a***

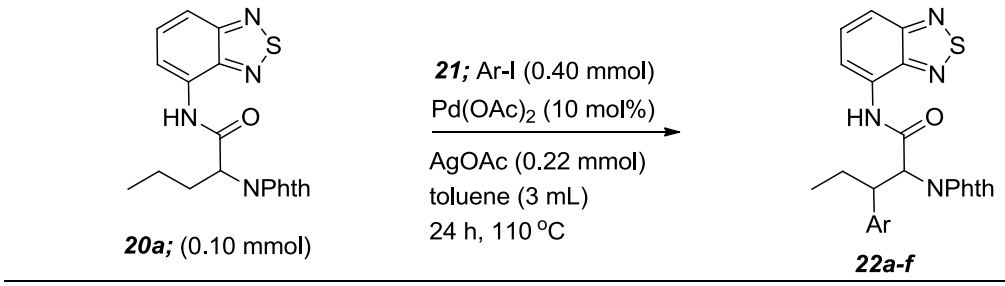
entry	PdL_2	additive	solvent	*t* (°C)	yield (***22a* %**)
1	nil	AgOAc	toluene	110	0
2	$Pd(OAc)_2$	nil	toluene	110	0
3	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	0
4	$PdCl_2$	AgOAc	toluene	110	40
5	$Pd(PPh_3)_2Cl_2$	AgOAc	toluene	110	32
6	$Pd(TFA)_2$	AgOAc	toluene	110	<5
7	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**97**
8	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	46
9	$Pd(OAc)_2$	Ag_2O	toluene	110	<5
10	$Pd(OAc)_2$	K_2CO_3	toluene	110	36
11	$Pd(OAc)_2$	KOAc	toluene	110	-
12	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	10
13	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	0
14	$Pd(OAc)_2$	AgOAc	1,4-Dioxane	100	20
15	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	45
16	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	100	50

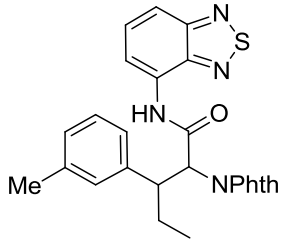
The C-H bond activation on norvaline carboxamide system **20a,** aryl iodide **21** and AgOAc in the presence of catalyst $Pd(TFA)_2$ catalyst does not give a satisfactory yield of products **22a** in less than 5% conversion (entry 6, Table 1). The reaction of norvaline carboxamide system **20a** (0.10 mmol) with aryl iodide **21** (0.40 mmol) in presence of additive AgOAc (0.22 mmol) and 10 mol% of the $Pd(OAc)_2$ as a catalyst afforded the arylated product **22a** in 97% yield (entry 7, Table 1). The Pd(II)-catalyzed C-H activation arylation of the norvaline carboxamides system **20a** with **21** in the presence of Ag_2CO_3 as an additive instead of

AgOAc afforded the C-(sp^3)-H arylated norvaline carboxamide system **22a** in 46 % yield (entry 8, Table 1). The Pd(II)-catalyzed C-H activation arylation of the norvaline carboxamides system **20a** with **21** in the presence of additives, such as Ag_2O, KOAc and $PhI(OAc)_2$ does not leads to desired products **22a** (entry 9 and 11-12, Table 1). However, the Pd(II)-catalyzed C-H bond arylation of the norvaline carboxamides system **20a** with **21** in the presence of K_2CO_3 afforded the **22a** product in 36% yields (entry 10, Table 1). After optimized the catalyst and additive, we moved further to optimize the various solvents having polar and nonpolar in nature, in the course of reaction solvent will play a crucial role to get a good yield. The Pd(II)-catalyzed C-H bond arylation of the norvaline carboxamides system **20a** with **21** in solvents, such as 1, 2-DCE were not that much fruitful with desired product (entry 13, Table 1). The Pd(II)-catalyzed C-H activation arylation of the norvaline carboxamides system **20a** with **21** in 1, 4-dioxane and *tert*-BuOH afforded the C-(sp^3)-H arylated norvaline carboxamide system **22a** in 20% and 45% yields respectively (entry 14 and 15, Table 1). The Pd(II)-catalyzed C-H activation arylation of the norvaline carboxamides system **20a** with **21** in *tert*-amylOH afforded the C-(sp^3)-H arylated norvaline carboxamide system **22a** in 50% yields (entry 16, Table 1).

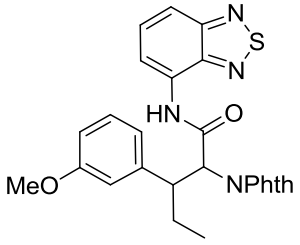
After having the developed reaction conditions, we decided the generality of this methodology, the Pd(II)-catalyzed new bidentate auxiliary ABTD assisted direct arylation of C-(sp^3)-H bond of the norvaline carboxamides system **20a** by using various aryl iodide sources. Accordingly, the arylation of norvaline carboxamide **20a** with aryl iodide containing a substituent at *meta* or *para* positions such as Me, OMe and NO_2 afforded the corresponding arylated norvaline carboxamide **22a-d** in 70-97% yields (Table 2). Then the Pd(II)-catalyzed C-(sp^3)-H activation arylation of the norvaline carboxamides system **20a** with 6-iodo-1,4-dioxanebenzene afforded the corresponding arylated norvaline carboxamide **22e** in 86% yield (Table 2). The Pd(II)-catalyzed C-(sp^3)-H activation arylation of the norvaline carboxamides system **20a** with heterocyclic aryl iodide such as 2-iodo thiophene lead to the corresponding arylated norvaline carboxamide **22f** in 60% yield (Table 2).

Table 2 Synthesis of arylated norvaline carboxamide derivatives **22a-f**.

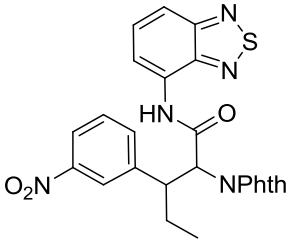




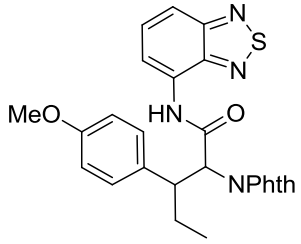
22a; 97%



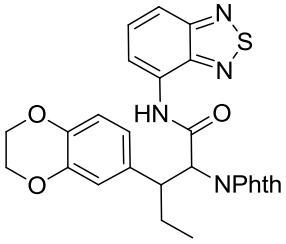
22b; 94%



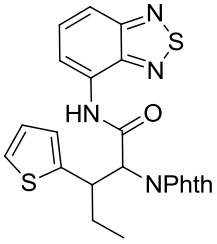
22c; 88%



22d; 70%



22e; 86%

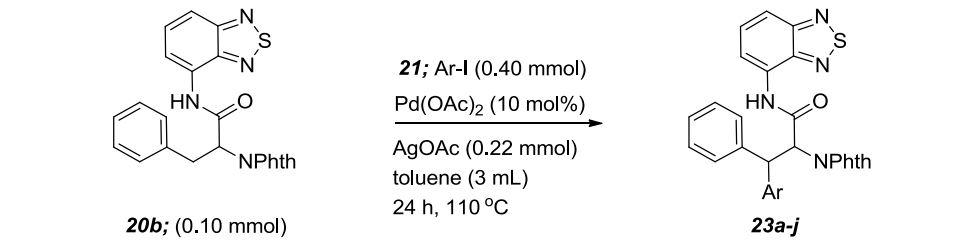


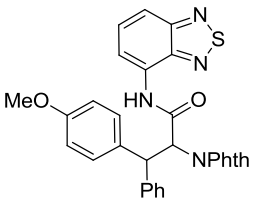
22f; 60%

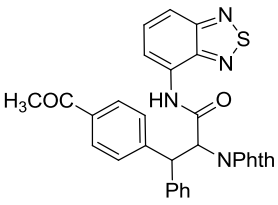
Next, to further examined the generality of this advanced method it was envisioned to conduct the Pd(II)-catalyzed, ABTD directed direct C(sp^3)-H arylation of the phenylalanine carboxamide system **20b** (Table 3). Then, the C-H arylation of C-(sp^3)-H bond of phenylalanine carboxamide system **20b** with a variety of aryl iodides in the present developed condition. The Pd(II)-catalyzed C-(sp^3)-H bond arylation of the phenylalanine carboxamides system **20b** with 4-iodo anisole in the presence of AgOAc (0.22 mmol) as an additive and 10 mol% of the $Pd(OAc)_2$ catalyst were used and gave the arylated phenylalanine carboxamides system **23a** in 60 % yield (Table 3). The Pd(II)-catalyzed C-(sp^3)-H activation arylation of the phenylalanine carboxamides system **20b** with aryl iodide (**21**) containing other electron donating group at *meta* position in the phenyl ring, e.g. *m*-OMe and *m*-Me afforded the arylated phenylalanine carboxamides system **23e-f** in 60-80 % yield respectively (Table 3). The Pd(II)-catalyzed C-(sp^3)-H activation arylation of the phenylalanine carboxamides system **20b** with aryl iodide (**21**) containing other electron

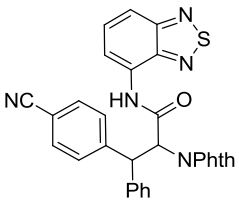
withdrawing group at *meta/para* position in the phenyl ring, e.g.*m*-NO_2 and *p*-Cl/CN afforded the arylated phenylalanine carboxamides system **23g** and **23c-d** in 50-56 % yields respectively (Table 3). The Pd(II)-catalyzed C-(sp^3)-H activation arylation of the phenylalanine carboxamides system **20b** with 4-iodo acetophenone and 4-iodomethylbenzoate leads to the arylated phenylalanine carboxamides system **23b** and **23j** in 50-55 % yields respectively (Table 3). The Pd(II)-catalyzed C-H activation arylation of the phenylalanine carboxamides system **20b** with 6-1odo-1,4-benzodioxane and disubstituted aryl halides such as 3,5-dichloroiodobenzene leads to the arylated phenylalanine carboxamides system **23i** and **23h** in 50-52 % yields respectively (Table 3).

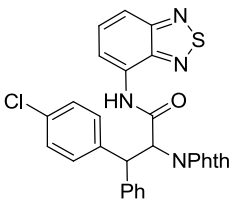
Table 3 Synthesis of arylated phenylalanine carboxamide derivative **23a-j**.

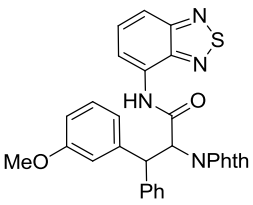


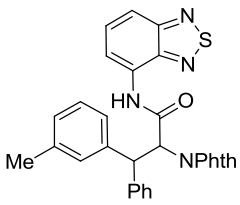

23a; 60%

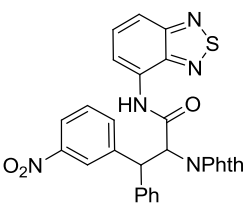

23b; 50%

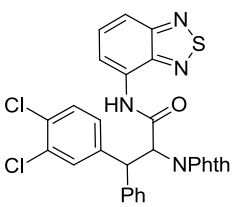

23c; 50%

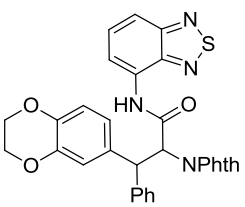

23d; 52%

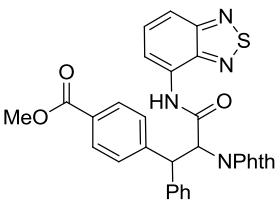

23e; 60%


23f; 80%

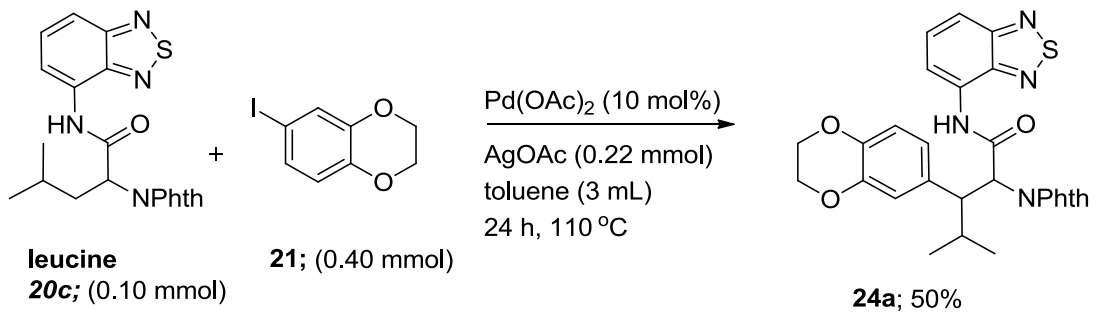

23g; 56%


23h; 52%


23i; 50%


23j; 55%

Subsequently, this method envisaged to explore the Pd(II)-catalyzed ABTD enabled C-H arylation of the C-(sp^3)-H bond of leucine carboxamide system **20c** with 6-iodo-1,4-benzodioxane afforded the arylated leucine carboxamide product **24a** in 50% yield (Scheme 19).

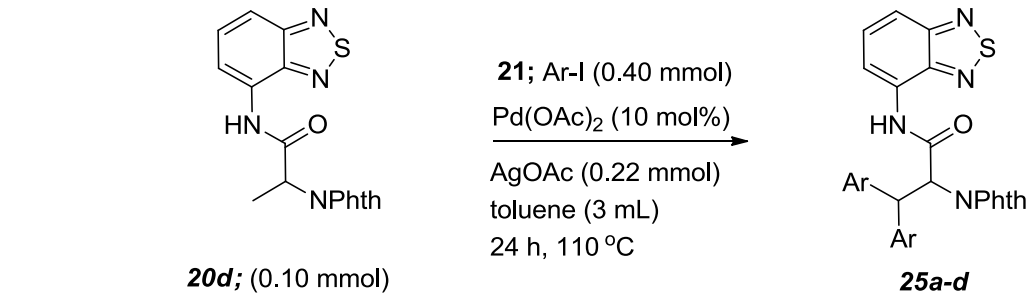


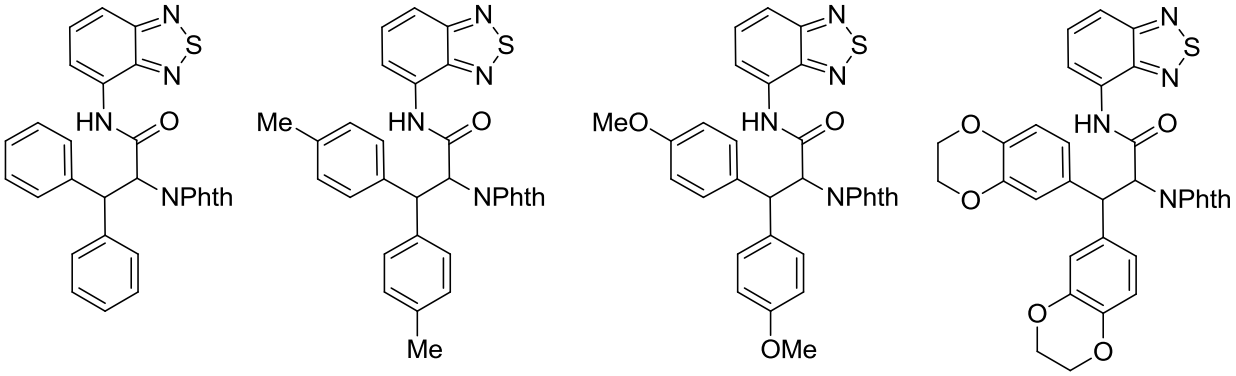
Scheme 19 Synthesis of arylated leucine carboxamide derivative **24a**.

After successful secondary C-(sp^3)-H arylation, we explored our protocol for primary C-(sp^3)-H arylation and, the alanine carboxamide system **20d** was chosen to be the next substrate (Table 4). The Pd(II)-catalyzed primary C-(sp^3)-H activation offered to arylated alanine carboxamides derivatives **25a-d** were obtained using various iodides in moderate to good yield 60-70%. The Pd(II)-catalyzed primary C-(sp^3)-H activation arylation of the alanine carboxamides system **20d** with aryl iodide containing neutral and electron donating group at *para* position in the phenyl ring, e.g.,*p*-Me and *p*-OMe afforded the arylated alanine carboxamides system **25a-c** in 60-70 % yield (Table 4). The Pd(II)-catalyzed primary C-(sp^3)-H activation arylation of the alanine carboxamides system **20d** with 6-iodo-1,4-benzodioxane lead to the arylated alanine carboxamides system **25d** in 65 % yield (Table 4).

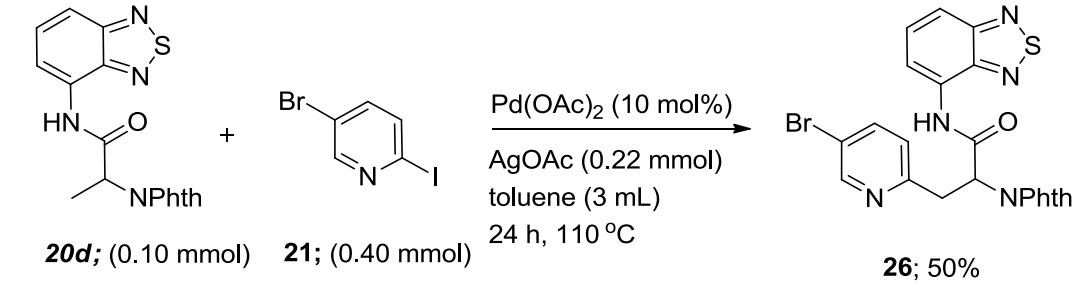
The Pd(II)-catalyzed primary C-(sp^3)-H activation arylation of substrate **20d** with 5-bromo-2-iodo pyridine gave monoarylated product **26** due to decidedly less reactive in nature (Scheme 20).

Table 4 Synthesis of arylated alanine carboxamide derivatives **25a-d**.





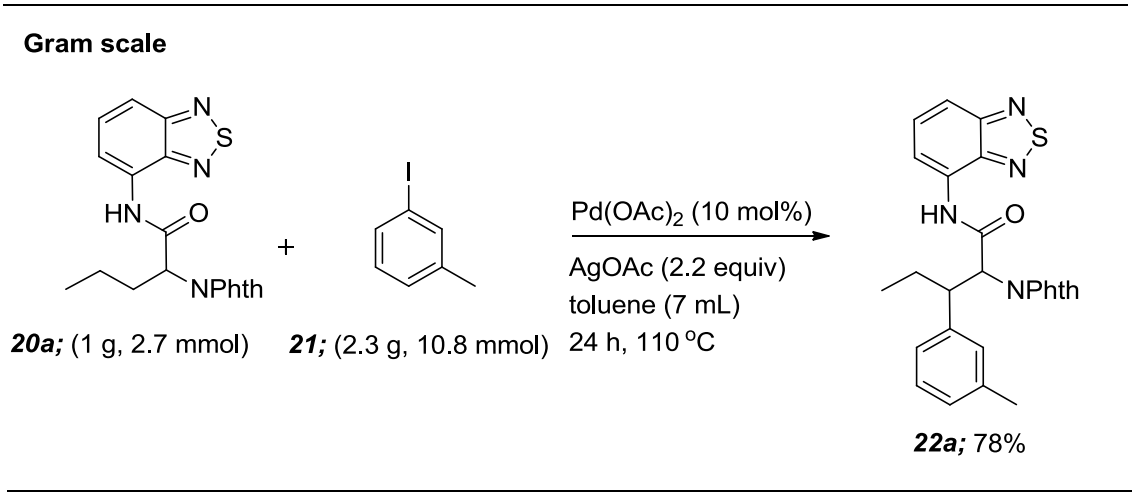
Although, this is one kind of assumption the actual reason of why are we getting the monoarylated product still not known and the yield of the monoarylated compound **26** is 50% (Scheme 20).



Scheme 20 Synthesis of monoarylated alanine carboxamide derivative **26**.

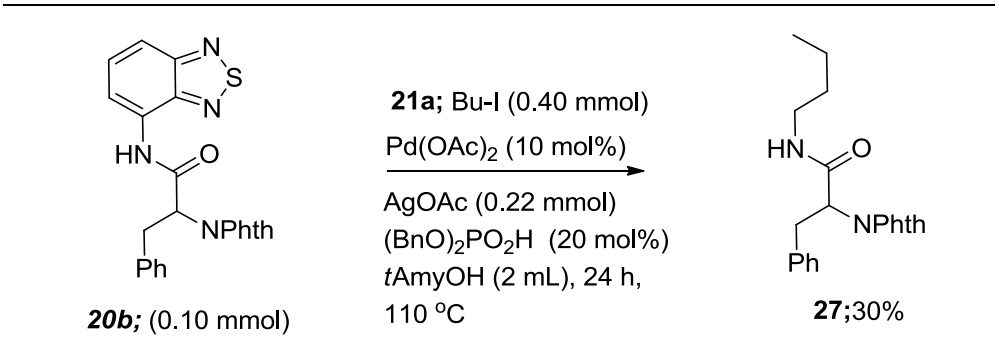
To show the efficiency of the protocol, the Pd(II)-catalyzed secondary C-(sp^3)-H bond of the norvaline carboxamide system **20a** with 3-iodo toluene (**21**) was carried out in a gram scale manner, which afforded the arylated norvaline carboxamide **22a** in 78% yield (Scheme 21). Then, we wished to attempt the removal of the new bidentate directing group ABTD from the

arylated norvaline carboxamide system. Unluckily, hydrolyzed product NMR is impure. It was confirmed by HRMS and ^{1}H NMR.



Scheme 21 Pd(II)-catalyzed C-H arylation in a gram scale manner.

After successfully achieved the arylation on primary/secondary C-(sp^3)-H bond on natural/unnatural aminoacid carboxamide system, we put our efforts towards alkylation on natural/unnatural aminoacid carboxamide system but unluckily we could not able to get desired product, instead of that we got an alkylation along with removal of directing group (Scheme 22).



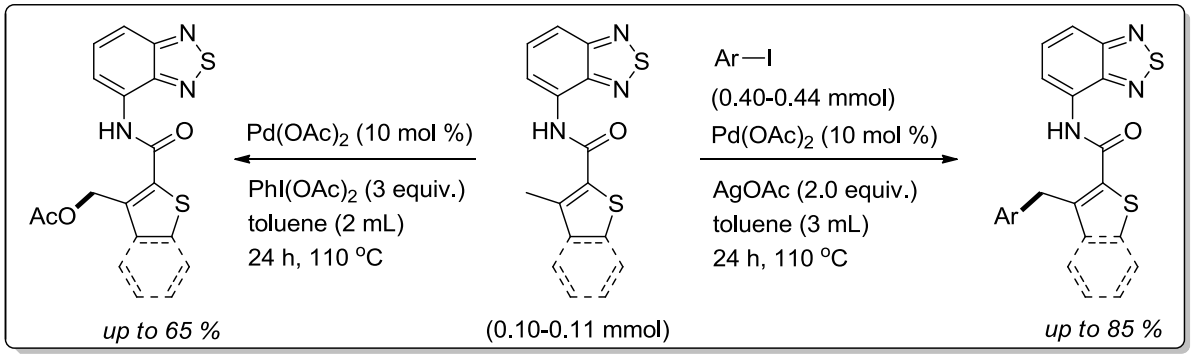
Scheme 22 Pd(II)-catalyzed secondary C-(sp^3)-H alkylation on phenylalanine system.

Overall, while the arylation on primary/secondary C-(sp^3)-H bond on natural/unnatural aminoacid carboxamide was successful, our various attempts on the ABTD directed alkylation, acetoxylation and intramolecular amination of aminoacid carboxamide were not successful. Apparently, the bidentate ligand ABTD seems to be not assisting the C-N bond formation in the aminoacid carboxamide system. Notably, bidentate directing groups such as

8-aminoquinoline,(pyridine-2-yl) isopropyl and Methyl-2-pyridylsufoximine etc. directing group was victorious in the constructing the C-O/C-N in the aminoacid carboxamide system. Various alkyl iodides and aminoacid carboxamide starting material were used to examine their reactivity pattern. Unfortunately, we were not able to get any alkylated product.

Part 2: Pd(II)-catalyzed ABTD enabled arylation of γ-C(sp^3)-H bonds: Synthesis of arylheteromethanes from the heterocarboxamide systems.

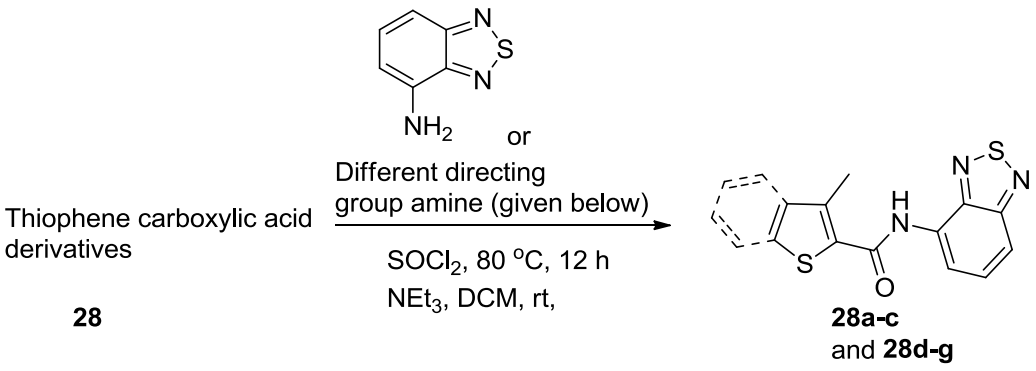
This work

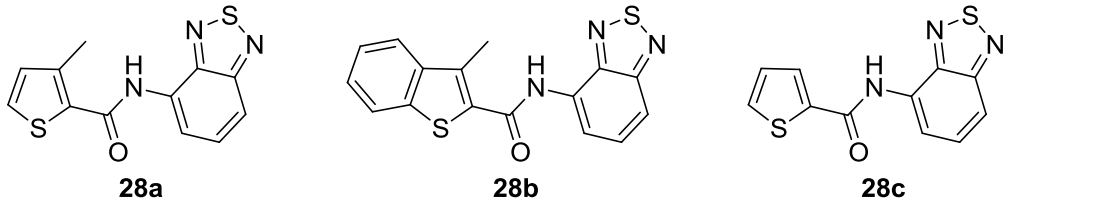


Scheme 23ABTD enabled construction of heteroarylmethane and acetoxylation from the heterocarboxamide systems.

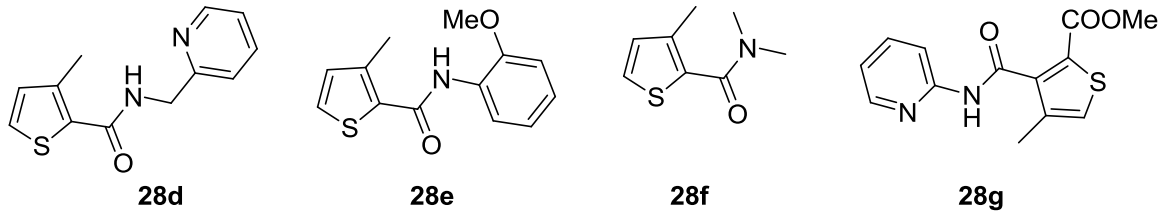
The importance of directing groups in C-H activation, especially cause to go towards the development of new directing group in this fields, which had some fascinating feature such as cost-effective, and fluorescent etc, by keeping this goal in mind our groups also invented a new directing group 4-Amino-2,1,3-Benzothiadiazole (ABTD). It is highly selective and fluorescent, ABTD contains thiadiazoline core moiety due to this, it's essential to medicinal and fluorescent chemistry. In the C-H activation field, various bidentate directing groups were commonly used for the functionalization of the β-C-H bonds of carboxylic acid systems.[11-15] But there are very few reports dealing with the γ-C(sp^3)-H bond of carboxylic acid systems.[16-18] Our group focused on this point and provide an alternative pathway to activate the γ-C-(sp^3)-H bond of the heterocarboxamide with the help of a new auxiliary 4-Amino-2,1,3-Benzothiadiazole (ABTD). Functionalization of the heterocyclic system such as thiophenes and benzothiophenes including heteroarylmethane are an important class of molecules in organic synthesis and medicinal chemistry. In this chapter, we mainly focusing

on the development of a new method for synthesizing thiophenes and benzothiophenes based heteroarylmethane. Accordingly, a part of this chapter reports the synthesis of heteroarylmethanes from thiophene derivatives via the Pd(II)-catalyzed arylation of γ-C(sp^3)-H bonds (Scheme 23).





ineffective substrates / directing groups



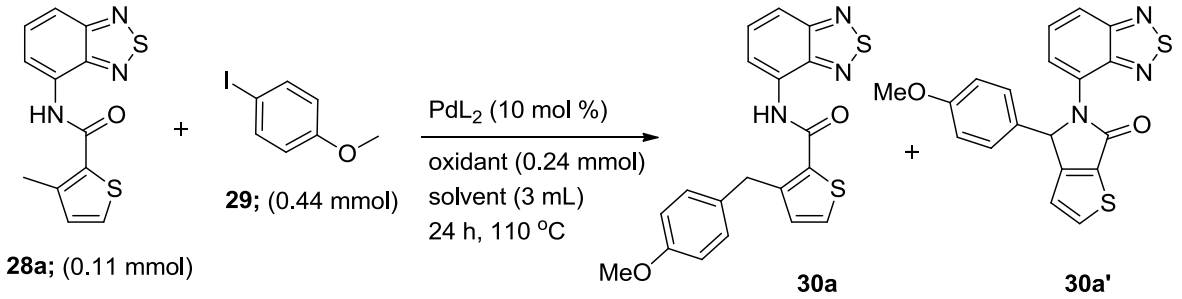
Scheme 24 3-Methylthiophene/benzothiophene-2-carboxamide, thiophene-2-carboxamide and related systems made for examine the γ-C-(sp^3)-H arylation.

(General reaction conditions: Substrate (0.11 mmol), **29** or ArI (0.40-0.44 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.20 mmol), toluene (2-3 mL), 24 h, and 110 °C. The arylations of substrates **28a-c** were successful and the arylation of substrates **28d-g** were not fruitful).

To initiate our work on the γ-C-(sp^3)-H bond containing system, we prepared various starting materials having the γ-C-(sp^3)-H bond such as 3-methyl thiophene-2-carboxylic acid and 3-methyl benzothiophene-2-carboxylic acid/chlorides with directing group ABTD, having literature known condition, successfully formed appropriate starting material carboxamide derivatives **28a-g** (Scheme 24).

After preparation of the suitable starting materials, we initiated our studies for optimization. Various reaction conditions were attempted to achieve the arylheteroarylmethane moiety **30a** via the Pd(II)-catalyzed, ABTD-assisted γ-C-(sp^3)-H arylation of thiophene-2-carboxamide system **28a** (Table 5). The reaction leading the γ-C-(sp^3)-H arylation of thiophene-2-carboxamide system **28a** with 4 equiv. of **29** in the presence of the $Pd(OAc)_2$ as a catalyst and AgOAc as an additive in toluene at 110 ^oC for 24 h was found to be the best reaction condition, which afforded the arylheteroarylmethane derivative **30a** in a maximum of 85% yield (entry 7 Table 5). Initially, various additives, solvents, andoxidants were examined in the reaction of 3-Methylthiophene-2-carboxamide **28a** with 4-ethyl iodobenzene **29** in the presence of $Pd(OAc)_2$ (10 mol %) at 110 ^oC for 24 h. First, the catalytic reaction was tested without catalyst and additive, reaction does not lead to the desired products (entry 1 and 2, Table 5). It means for the reaction catalyst, and additives are essential. After that various catalyst were screened such as $Pd(CH_3CN)_2Cl_2$, $PdCl_2$,$Pd(PPh_3)_2Cl_2$ and $Pd(TFA)_2$. The γ-C-(sp^3)-H arylation of heterocarboxamide **28a** with **29** in the presence of $Pd(CH_3CN)_2Cl_2$ and $PdCl_2$ instead of $Pd(OAc)_2$ catalyst gave the product **30a** in less than 5% and 25% yields, respectively (entries 3 and 4, Table 5). When the γ-C-(sp^3)-H arylation of **28a** with **29** in the presence of the $Pd(PPh_3)_2Cl_2$ and $Pd(TFA)_2$ catalyst, it afforded the product **30a** in 10 and 30% yields, respectively (entries 5 and 6, Table 5).The γ-C-(sp^3)-H arylation of **28a** with **29** in the presence of the additives such as Ag_2CO_3 and K_2CO_3 afforded the moderate yields 60 and 45%, respectively (entries 8 and 9, Table 5). The arylation of **28a** with **29** in the presence of additives, such as KOAc or $PhI(OAc)_2$ did not give the product **30a** in amount (entries 10 and 11, Table 5). At finally we optimized the solvents some are polar, neutral and nonpolar in nature. The C-H activation reaction also depends on the solvent and its solubility nature with reagents, more soluble solvent provide a homogenous platform to both reagents and leads to good yields. The Pd-catalyzed γ-C-(sp^3)-H arylation of heterocarboxamide **28a** with **29** using different solvents such as 1,2-DCE, and 1,4-dioxane offered to give the product **30a** in very less or negligible yield. (entries 12 and 13, Table 5). The Pd-catalyzed γ-C-(sp^3)-H arylation of heterocarboxamide **28a** with **29** using solvents tBuOH and tAmylOH, leads to the product in moderately yields, 30-36%, respectively (entries 14 and 15, Table 5). The γ-C-(sp^3)-H arylation of heterocarboxamide **28a** (0.11 mmol) with **29** (0.44 mmol) in the presence of 10 mol% $Pd(OAc)_2$ and AgOAc (0.20 mmol) in toluene at 110 ^oC furnished the arylheteromethane **30a** in 85% yield (entry 7, Table 5).

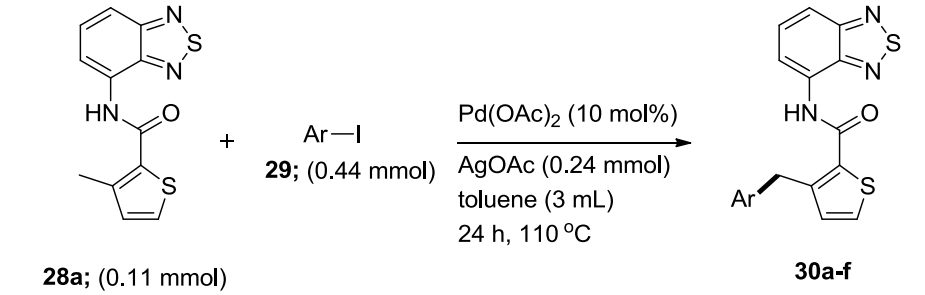
Table 5 Optimization reaction conditions.

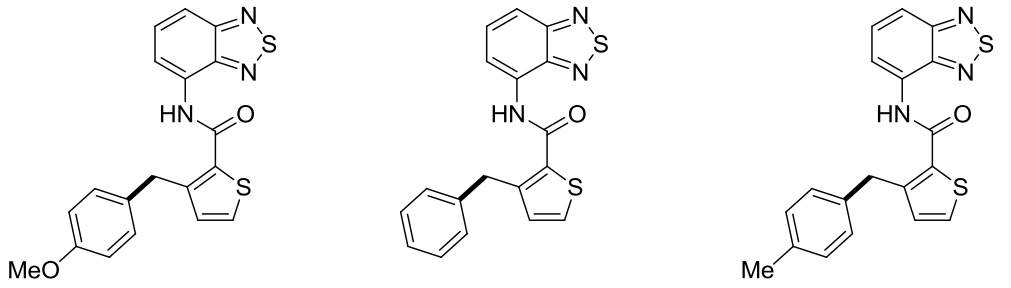


entry	PdL_2	additive	solvent	t °C	yield (%) **30a**	yield (%) **30a'**
1	nil	AgOAc	toluene	110	-	-
2	$Pd(OAc)_2$	nil	toluene	110	-	-
3	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	<5	-
4	$PdCl_2$	AgOAc	toluene	110	25	-
5	$Pd(PPh_3)_2Cl_2$	AgOAc	toluene	110	10	-
6	$Pd(TFA)_2$	AgOAc	toluene	110	30	-
7	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**85**	**-**
8	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	60	-
9	$Pd(OAc)_2$	K_2CO_3	toluene	110	45	-
10	$Pd(OAc)_2$	KOAc	toluene	110	<5	-
11	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	-	-
12	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	-	-
13	$Pd(OAc)_2$	AgOAc	1,4-Dioxane	100	10	-
14	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	30	-
15	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	100	36	-

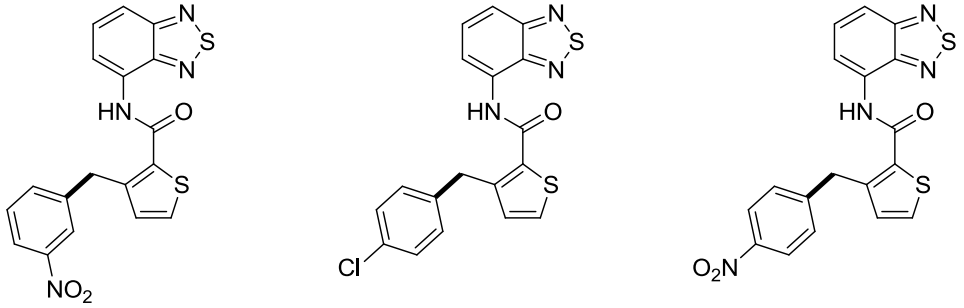
To show the role of our directing group Amino-2,1,3-Benzothiadiazole (ABTD), and find out the other working bidentate directing groups various arylation reactions were performed by using the substrates **28d-g** under the developed reaction condition (entry 7, Table 5). Unluckily, the Pd(II)-catalyzed γ-C-(sp^3)-H arylation of the heterocarboxamides **28d-g** did not lead to the desired products and these reactions indicated that the corresponding directing groups/amides did not provide the assistance for the arylation of γ-C-(sp^3)-H bond of the related substrates **28d-g** (Scheme 24).

Table 6 Synthesis of arylheteromethane from γ-C-(sp^3)-H arylation of **28a**.





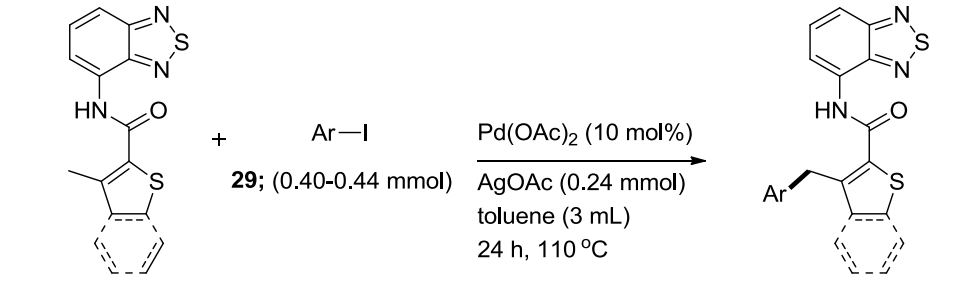
30a; 85% **30b**; 70% **30c**; 70%

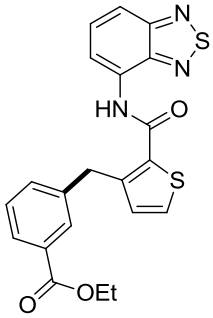


30d; 48% **30e**; 42% **30f**; 50%

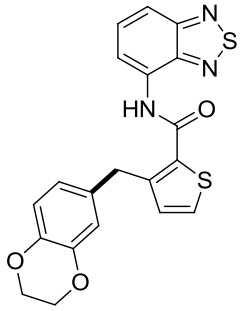
Having the best-developed reaction condition in our hand, then we examined the scope/generality of this ABTD directing group assisted Pd-catalyzed direct arylation of γ-C(sp^3)-H bond of the heterocarboxamide system using various electron donating and electron withdrawing group containing aryl iodides (Table 6). The Pd(II)-catalyzed arylation of γ-C-(sp^3)-H bond of 3-methyl thiophene-2-carboxamide **28a** with iodobenzene and various electron donating group containing aryl iodides (e.g., OMe, Me, H) gave the corresponding arylheteromethane **30a-c** in 70-85% yields (Table 6)

Table 7 Synthesis of arylheteromethane from γ-C-(sp^3)-H arylation of **28a** & **28b**.

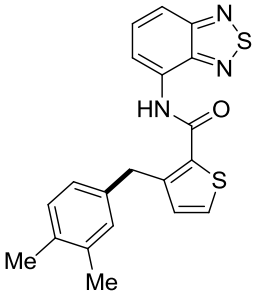




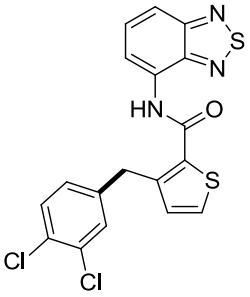
30g; 55%



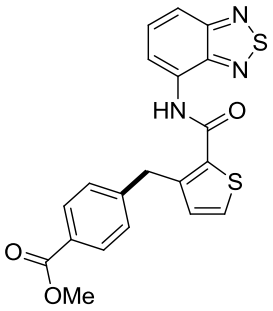
30h; 60%



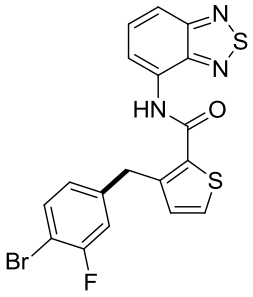
30i; 68%



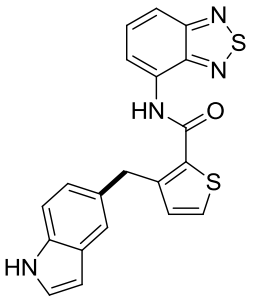
30j; 65%



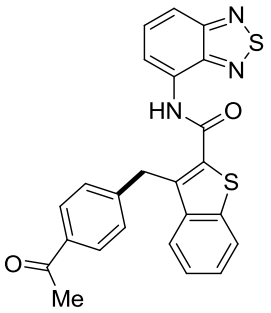
30k; 52%



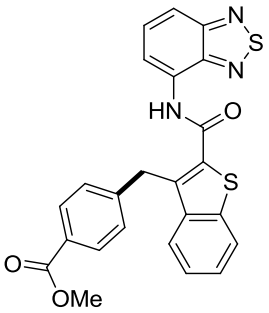
30l; 42%



30m; 40%



31a; 50%



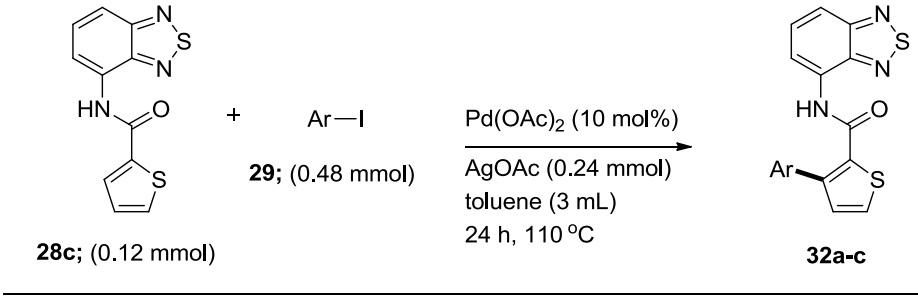
31b; 44%

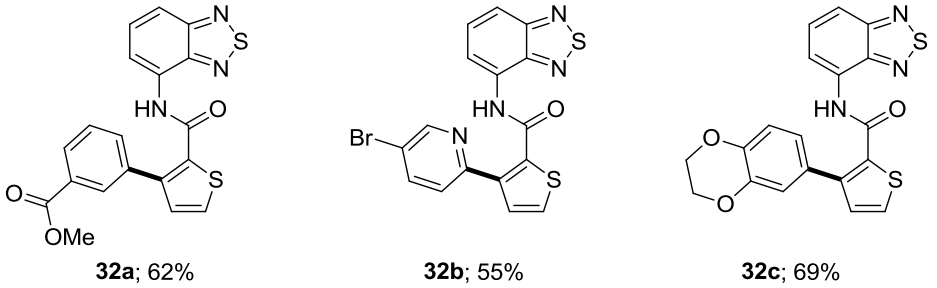
The arylation of γ-C-(sp^3)-H bond of **28a** with 1-iodo-3-nitrobenzene and 1-iodo-4-nitrobenzene gave the arylated arylheteromethane **30d** and **30f** in 48-50% yields, respectively (Table 6). The Pd(II)-catalyzed arylation of γ-C-(sp^3)-H bond of **28a** with *p*-

chloroiodobenzene offered aryheteromethane **30e** in 42% yield (Table 6). The Pd(II)-catalyzed arylation of γ-C-(sp^3)-H bond of **28a** with aryl halides such as 3-iodo-ethyl benzoate and 6-iodobenzenedioxane offered aryheteromethane **30g** and **30h** in 55% and 60% yields, respectively (Table 7). Then we further used the aryl iodide having disubstituted groups like 3,5-dimethyl iodobenzene, 3,5-dichloro iodobenzene and 4-bromo-3-fluoroiodobenzene with **28a** leads to the desire products **30i-j** and **30l** in 65-68% and 42% yields, respectively (Table 7). The Pd(II)-catalyzed arylation of γ-C-(sp^3)-H bond of **28a** with methyl iodobenzoate and heterocyclic compound 5-iodo indole offered to the products **30k** and **30m** in moderately yields 40-52% (Table 7).

To show the scope and advantage of ABTD, by using various substrate scopes. We also performed the developed reaction condition by using **28b** as starting materials with 4-iodoacetophenone,and 4-iodo methyl benzoate gave the desired product **31a** and **31b** in 44-50% yields (Table 7).

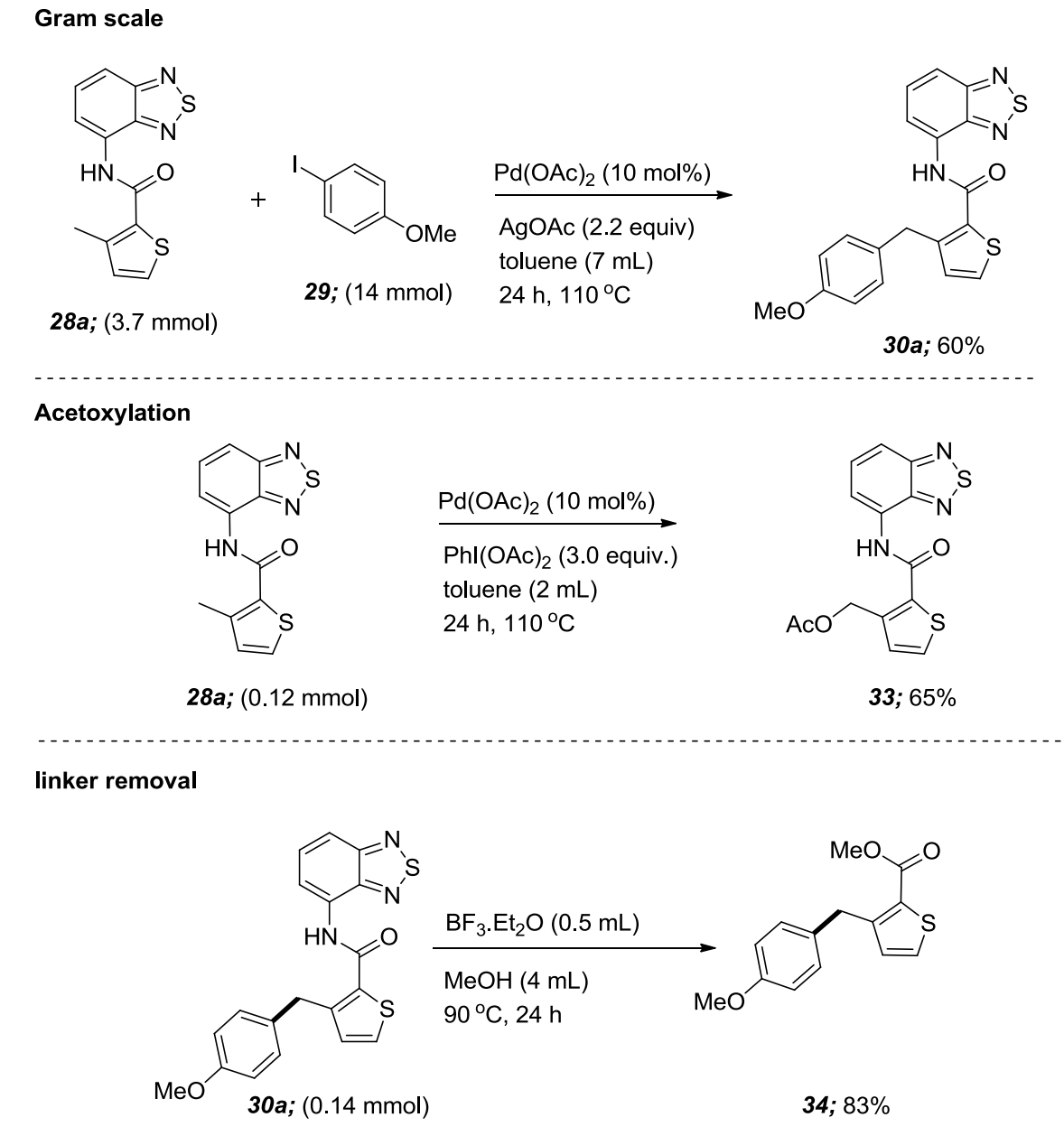
Table 8 Synthesis of arylheterocarboxamide from β-C-(sp^2)-H arylation of **28c**.





Further, we examine the same reaction condition with thiophene-2-carboxamide **28c** with different aryl iodide source having electron donating, withdrawing as well as some heteroaryl iodides. The Pd(II)-catalyzed arylation of β-C(sp^2)-H bond of **28c** with 6-iodo-1,4-dioxanebenzene offered arylated product **32c** in 69% yield (Table 8).

The Pd(II)-catalyzed arylation of β-C(sp^2)-H bond of **28c** with methyl iodobenzoate and 5-bromo-2-iodo pyridine leads to the arylated products **32a** and **32b** in 62% and 55% yields, respectively (Table 8).



Scheme 25 Gram scale reaction and acetoxylation of **28a** and ABTD removal.

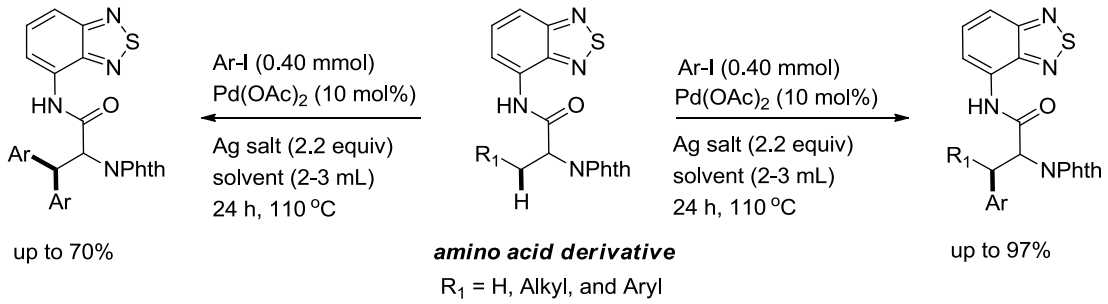
Furthermore, Scheme 25 shows the $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C-(sp^3)-H arylation in gram scale manner by using **28a** (3.7 mmol) with **29** (14 mmol) in presence of 10 mol % of $Pd(OAc)_2$ as a catalyst and AgOAc (8.1 mmol) in toluene (7 mL) at 110 ^oC furnished the arylheteromethane **30a** in 60% yield (Scheme 25). Subsequently, the Pd(II)-

catalyzed, 4-Amino-2,1,3-Benzothiadiazole (ABTD) directed γ-C-(sp^3)-H acetoxylation of **28a** with $PhI(OAc)_2$ as an oxidant leads to the γ-C-(sp^3)-H acetoxylated thiophene-2-carboxamide derivative **33** in 65% yield (Scheme 25).

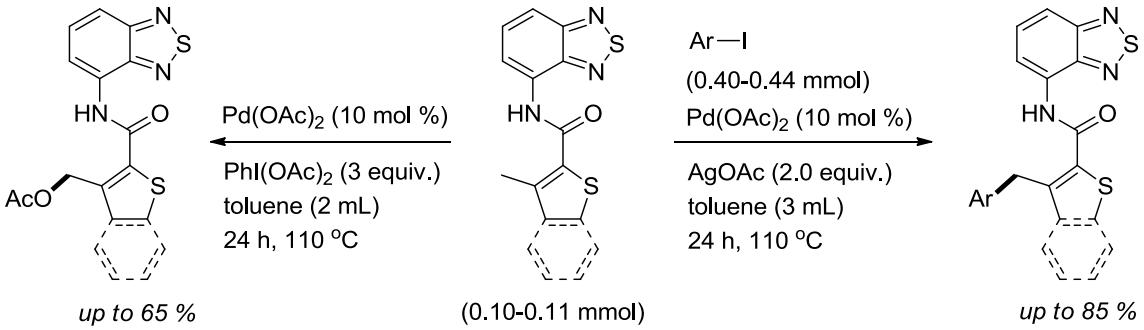
Then, at finally we desired to attempt the removal of the bidentate ligand (ABTD) from the γ-C-(sp^3)-H arylated arylheteromethanecarboxamide **30a**. We treated the aryheteromethanecarboxamide **30a** with $BF_3.OEt_2$ (0.5 mL) in (4 mL) MeOH, which successfully offered to the methyl 3-(4-methoxybenzyl)thiophene-2-carboxylate **34** after the removal of the bidentate auxiliary 4-Amino-2,1,3-Benzothiadiazole (ABTD) in 83% yield (Scheme 25).

Summary and conclusion:

In conclusion, we report a new ABTD directing group for primary/secondary C-(sp^3)-H bond activation on natural/unnatural aminoacid carboxamide system. The scope and generality of this methodology giving the evidence by successive arylation of several types of primary/secondary C(sp^3)-H bond at the β-position of the natural/unnatural aminoacid carboxamide system.



We also demonstrated the Pd(II)-catalyzed arylation of γ-C-(sp^3)-H bond of 3-methyl thiophene/benzothiophene-2-carboxamides and β-C-(sp^2)-H of thiophene-2-carboxamides with aryl iodide. These reactions are highly selective and versatile having the broad substrate scope. ABTD assisted γ-C-(sp^3)-H / β-C-(sp^2)-H activation reactions show the first fluorescent development and applicable methods for the catalytic arylation of heterocyclic carboxamides.



These reactions enable a new strategy for the synthesis of various heteroarylmethane compounds, starting from very cheap and readily market available starting materials. The γ-C-(sp^3)-H and β-C-(sp^2)-H bond arylation methodology in the synthesis of heteroarylmetahane and arylated heterocarboxamides via new directing group ABTD provides an alternative pathway in the C-H activation fields.

All the compounds included in chapter 4 of the thesis were characterized by ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data of all compounds and complete experimental details are given in the experimental section.

Experimental Section.

Part 1

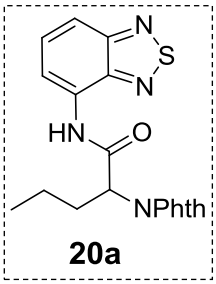
General IR spectra were recorded as KBr pellets or thin films. ^{1}H / ^{13}C NMR spectra of samples were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under nitrogen atm. Organic layers, after the workup procedure were dried using anhydrous sodium sulphate. TLC inspection was carried out on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported, andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures.[9h, 10b, 18]

Procedure for the synthesis of amino acid carboxamide 20a-d

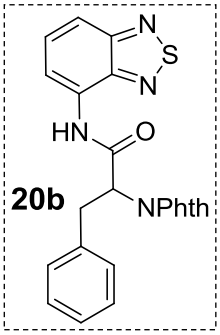
A dry RBF having the corresponding carboxylic acid (3 mmol) and $SOCl_2$ (1.8 mL) at room temperature was stirred for 24 h under N_2 atmosphere. After the reaction course, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (3 mL). The DCM

solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (1 mmol), Et_3N (333 mg, 3.3 mmol) and DCM (7 mL) under a nitrogen atmosphere. The resulting combination was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. Purification of the raw reaction mixture by column chromatography (neutral alumina (EtOAc/hexanes = 25:75) furnished the corresponding products **20a-d**.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)pentanamide*(nb 1161 sm 20a): The compound **20a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (950 mg, 83%); R_f (20% EtOAc/hexane) 0.6; mp: 176-178 ^oC; IR (KBr): 3055, 1716, 1383, 1266, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.41 (br. s, 1H), 8.48 (d, 1H, J = 6.9 Hz), 7.94 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.79 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 5.13 (dd, 1H, J_1 = 10.6, J_2 = 5.8Hz), 2.58-2.48 (m, 1H), 2.36-2.28 (m, 1H), 1.50-1.40 (m, 2H), 1.02 (t, 3H, J = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.3, 167.6, 154.7, 147.8, 134.5, 131.6, 131.0, 129.6, 123.9, 116.2, 115.5, 55.7, 30.9, 19.7, 13.5; HRMS (ESI) calcd for $C_{19}H_{17}N_4O_3S$ $[M+H]^+$ 381.1021 found 381.1004.

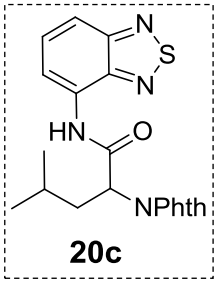


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide*(nb 1140 sm 20b): The compound **20b** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (900 mg, 70%); R_f (20% EtOAc/hexane) 0.5; mp: 181-183 ^oC; IR (KBr): 3055, 2986, 1714, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.37 (br. s, 1H), 8.50 (d, 1H, J = 7.4Hz), 7.86 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.74 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.70 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.29-7.27 (m, 2H), 7.23 (t, 2H, J = 7.0Hz), 7.17 (d, 1H, J = 7.1Hz), 5.43 (t, 1H, J = 8.4Hz), 3.76 (d, 2H, J = 8.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.1, 167.0, 154.7, 147.8, 136.1, 134.5, 131.3, 130.9, 129.5, 129.0, 128.8, 127.2,



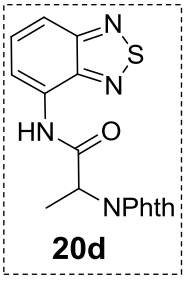
123.8, 116.3, 115.6, 57.0, 34.9; HRMS (ESI) calcd for $C_{23}H_{17}N_4O_3S$ $[M+H]^+$ 429.1021 found 429.1002.

N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanamide *(nb 1162 sm* 20*c):The compound **20c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (650 mg, 55%); R_f (20% EtOAc/hexane) 0.6; mp: 185-187 ^oC; IR (KBr): 3055, 1715, 1382, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.39 (br. s, 1H), 8.45 (d, 1H, J = 7.3Hz), 7.93-7.92 (m, 2H), 7.79-7.77 (m, 2H), 7.67 (d, 1H, J = 8.8Hz), 7.57 (t, 1H, J = 8.6Hz), 5.22 (dd, 1H, J_1 = 10.8, J_2 = 5.0Hz), 2.62-2.55 (m, 1H), 2.12-2.05 (m, 1H), 1.63-1.60 (m, 1H), 1.02 (d, 6H, J = 6.5Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.3, 167.9, 154.7, 147.8, 134.5, 131.6, 130.9, 129.6, 123.9, 116.2, 115.4, 54.4, 37.6, 25.4, 23.1, 21.4; HRMS (ESI) calcd for $C_{20}H_{19}N_4O_3S$ $[M+H]^+$ 395.1178 found 395.1160.



20c

N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)propanamide*(nb 216/1381 sm* 20*d):The compound **20d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (850 mg, 80%); R_f (20% EtOAc/hexane) 0.5; mp: 183-185 ^oC; IR (KBr): 3055, 1716, 1384, 1266, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.15 (br. s, 1H), 8.47 (d, 1H, J = 7.4 Hz), 7.93 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.79 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 5.25 (q, 1H, J = 7.4Hz), 1.95 (d, 3H, J = 7.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C167.9, 167.7, 154.6, 147.7, 134.5, 131.7, 130.9, 129.4, 123.7, 116.2, 115.4, 50.5, 15.4; HRMS (ESI) calcd for $C_{17}H_{13}N_4O_3S$ $[M+H]^+$ 353.0708 found 353.0725.



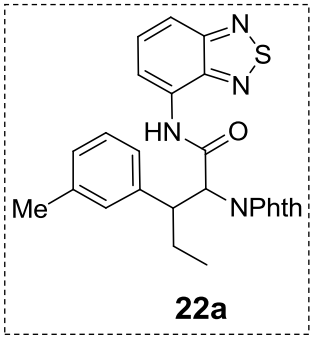
20d

General procedure for the Pd(II)-catalyzed arylation of natural/unnatural amino acid and preparation of the compounds 25a-d (bis arylation products), 22a-f/ 23a-j/ 24a/ 26 (mono arylation products).

An appropriate natural/unnatural carboxamide (0.10-0.12 mmol, 1equiv), an appropriate iodo compound (0.40-0.48 mmol, 4equiv), $Pd(OAc)_2$ (2.5-2.7 mg, 10 mol%), and AgOAc (48-50 mg, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24 h under a nitrogen

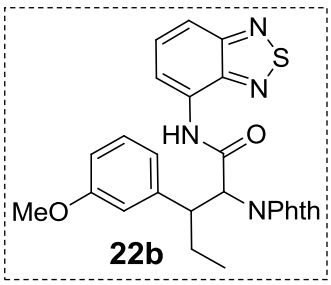
atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the raw reaction mixture by column chromatography furnished the corresponding arylated products **25a-d** (bis arylation products), **22a-f/ 23a-j/ 24a/ 26** (mono arylation products) (see corresponding Tables/Schemes for specific examples and reaction conditions).

N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(m-tolyl)pentanamide** ***(nb 1172 a 22a):The compound ***22*a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color semisolid (55 mg, 97%); R_f (20% EtOAc/hexane) 0.5; IR (KBr): 3341, 1716, 1550, 1383, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.22 (br. s, 1H), 8.25 (d, 1H, J = 7.4Hz), 7.96 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.80 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.61 (d, 1H, J = 8.8Hz), 7.47 (t, 1H, J = 7.9Hz), 7.28-7.20 (m, 3H), 7.04 (d, 1H, J = 6.6Hz), 5.31 (d, 1H, J = 11.8Hz), 3.99 (td, 1H, J_1 = 11.4, J_2 = 3.5Hz), 2.31 (s, 3H), 1.76-1.71 (m, 1H), 1.66-1.58 ((m, 1H), 0.72 (t, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.5, 166.4, 154.6, 147.7, 139.3, 138.9, 134.5, 131.6, 130.9, 129.5, 129.2, 129.1, 128.5, 125.6, 123.9, 115.9, 115.3, 61.4, 45.9, 26.2, 21.5, 11.3; HRMS (ESI) calcd for $C_{26}H_{23}N_4O_3S$ $[M+H]^+$ 471.1491 found 471.1471.



22a

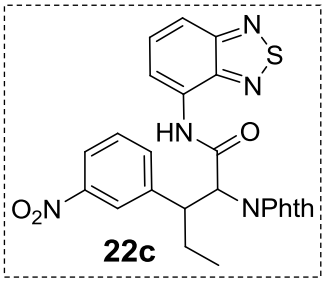
N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(3-methoxyphenyl)pentanamide** ***(nb 1168 a 22b):The compound ***22*b** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (45 mg, 93%); R_f (20% EtOAc/hexane) 0.4; mp: 175-177 ^oC; IR (KBr): 3338, 1715, 1549, 1267, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.24 (br. s, 1H), 8.27 (d, 1H, J = 7.4Hz), 7.97 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.80 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.62 (d, 1H, J = 8.8Hz), 7.47 (t, 1H, J = 8.0Hz), 7.29-7.25 (m, 1H), 7.05 (d, 1H, J = 7.6Hz), 6.99 (br. s, 1H), 6.78 (dd, 1H, J_1 = 8.1, J_2 = 1.7Hz), 5.31 (d, 1H, J = 11.9Hz), 4.00 (td, 1H, J_1 = 11.4, J_2 = 3.5Hz), 3.76 (s, 3H), 1.75-1.70 (m, 1H), 1.66-1.58 (m, 1H), 0.74 (t, 3H, J = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.5, 166.3, 160.2, 154.6, 147.7, 141.1, 134.5, 131.6, 130.9,



22b

130.4, 129.5, 123.9, 120.5, 116.0, 115.3, 114.5, 113.1, 61.3, 55.2, 46.1, 26.2, 11.2; HRMS (ESI) calcd for $C_{26}H_{23}N_4O_4S$ $[M+H]^+$ 487.1440 found 487.1421.

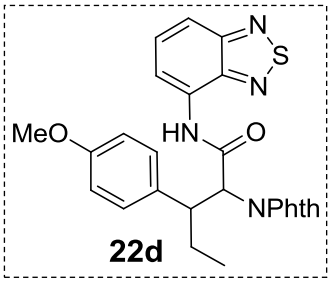
N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(3-nitrophenyl)pentanamide *(nb 1173 a 22c):The compound ***22*c** was obtained after



22c

purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (43 mg, 86%); R_f (20% EtOAc/hexane) 0.3; mp: 175-177 ^oC; IR (KBr): 2967, 1716, 1531, 1352, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (br. s, 1H), 8.33 (br. s, 1H), 8.17 (d, 1H, J = 7.4Hz), 8.10 (d, 1H, J = 8.1Hz), 7.98 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.83 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.78 (d, 1H, J = 7.7Hz), 7.63 (d, 1H, J = 8.8Hz), 7.51 (t, 1H, J = 7.9Hz), 7.45 (t, 1H, J = 7.9 Hz), 5.29 (d, 1H, J = 11.8 Hz), 4.24 (td, 1H, J_1 = 11.3, J_2 = 3.4Hz), 1.81-1.67 (m, 2H), 0.75 (t, 3H, J = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.3, 165.5, 154.6, 148.6, 147.6, 141.9, 135.0, 134.9, 131.3, 130.7, 129.9, 129.1, 124.1, 123.4, 122.8, 116.4, 115.6, 61.2, 45.7, 25.6, 11.2 ; HRMS (ESI) calcd for $C_{25}H_{20}N_5O_5S$ $[M+H]^+$ 502.1185 found 502.1163.

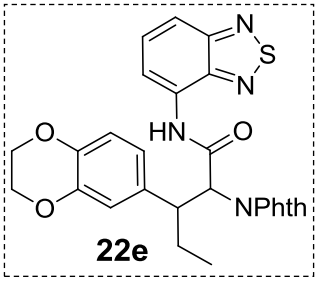
N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)pentanamide*(nb 1163 a 22d):The compound ***22*d** was obtained after



22d

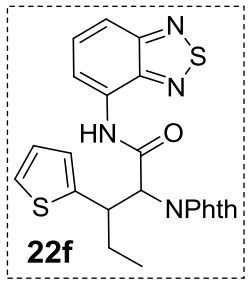
purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a pale yellow color solid (34 mg, 70%); R_f (20% EtOAc/hexane) 0.4; mp: 153-155 ^oC; IR (KBr): 2963, 1715, 1550, 1254, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.32 (br. s, 1H), 8.26 (d, 1H, J = 7.4Hz), 7.96 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.80 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.62 (d, 1H, J = 8.8Hz), 7.47 (t, 1H, J = 7.8Hz), 7.35 (d, 2H, J = 8.5Hz), 6.87 (d, 2H, J = 8.5 Hz), 5.25 (d, 1H, J = 12.0 Hz), 3.99 (td, 1H, J_1 = 11.4, J_2 = 3.4Hz), 3.76 (s, 3H), 1.75-1.69 (m,1 H), 1.62-1.54 (m, 1H), 0.72 (t, 3H, J = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.5, 166.4, 159.0, 154.6, 147.7, 134.6, 131.6, 131.1, 130.9, 129.5, 129.5, 123.9, 116.0, 115.3, 114.6, 61.8, 55.2, 45.2, 26.1, 11.2; HRMS (ESI) calcd for $C_{26}H_{23}N_4O_4S$ $[M+H]^+$ 487.1440 found 487.1418.

N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(1,3-dioxoisoindolin-2-yl)pentanamide *(nb 1169 a 22e):The compound ***22*e** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (44 mg, 86%); R_f (20% EtOAc/hexane) 0.4; mp: 139-141 ^oC; IR (KBr): 3335, 2986, 1715, 1286, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.18 (br. s, 1H), 8.29 (d, 1H, J = 7.4Hz), 7.95 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.79 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.62 (d, 1H, J = 8.7Hz), 7.48 (t, 1H, J = 7.9Hz), 6.97 (br. s, 1H), 6.93 (d, 1H, J = 8.4Hz), 6.83 (d, 1H, J = 8.2Hz), 5.24 (d, 1H, J = 11.9 Hz), 4.27-4.18 (m, 4H), 3.91 (td, 1H, J_1 = 11.4, J_2 = 3.3Hz), 1.68-1.65 (m, 1H), 1.60-1.48 (m, 1H), 0.73 (t, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.5, 166.4, 154.6, 147.7, 144.1, 143.1, 134.5, 132.6, 131.6, 130.9, 129.6, 123.9, 121.4, 118.1, 115.9, 115.3, 64.3, 61.3, 45.3, 26.3, 11.2; HRMS (ESI) calcd for $C_{27}H_{23}N_4O_5S$ $[M+H]^+$ 515.1389 found 515.1373.



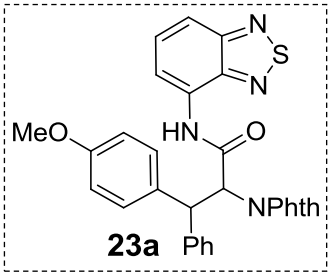
22e

N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(thiophen-2-yl)pentanamide*(nb 1174 a 22f):The compound ***22*f** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (28 mg, 60%); R_f (20% EtOAc/hexane) 0.5; mp: 168-170 ^oC; IR (KBr): 3055, 1716, 1325, 1266, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.36 (d, 1H, J = 8.9Hz), 8.20 (dd, 1H, J_1 = 10.1, J_2 = 7.5Hz), 8.02-7.97 (m, 2H), 7.86-7.81 (m, 2H), 7.69 (d, 1H, J = 11.2Hz), 7.66 (d, 1H, J = 8.1Hz), 7.51-7.47 (m, 2H), 7.30 (br. s, 1H), 5.31-5.26 (m, 1H), 4.21-4.13 (m, 1H), 1.81-1.69 (m, 2H), 0.77-0.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.4, 165.8, 154.7, 147.7, 140.5, 134.8, 131.8, 131.4, 130.8, 129.6, 129.2, 125.6, 124.1, 116.3, 115.5, 61.4, 45.9, 25.7, 11.2; HRMS (ESI) calcd for $C_{23}H_{19}N_4O_3S_2$ $[M+H]^+$ 463.0899 found 463.0900.



22f

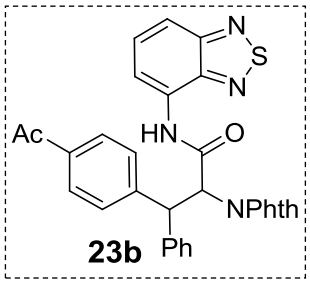
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-3-phenylpropanamide*(nb 509a 23a):T The compound **23a** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a brown color solid (32 mg, 60%); R_f (20% EtOAc/hexane) 0.4; mp: 226-228 ^oC; IR (KBr): 3055, 1714, 1423, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (br. s, 1H), 8.35 (d, 1H, J =



23a

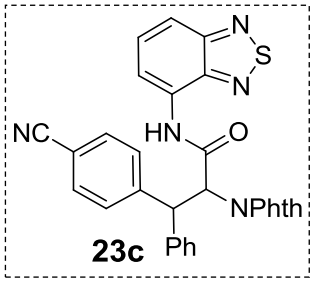
7.4Hz), 7.79 (dd, 2H, J_1 = 5.5, J_2 = 3.0Hz), 7.68-767 (m, 2H), 7.65 (d, 1H, J = 6.6Hz), 7.53-7.49 (m, 3H), 7.36 (d, 2H, J = 7.4Hz), 7.19 (t, 2H, J = 7.5Hz), 7.07 (t, 1H, J = 7.4 Hz), 6.85 (d, 2H, J = 8.7 Hz), 5.88 (d, 1H, J = 12.6 Hz), 5.52 (d, 1H, J = 12.6 Hz), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.2, 159.0, 154.7, 147.7, 140.3, 134.3, 131.8, 131.2, 130.9, 129.5, 129.1, 128.8, 127.5, 127.1, 123.7, 116.5, 116.2, 115.5, 114.7, 59.8, 53.2, 49.8; HRMS (ESI) calcd for $C_{30}H_{23}N_4O_4S$ $[M+H]^+$ 535.1440 found 535.1418

3-(4-Acetylphenyl)-*N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide *(nb 510a,1152 23b):* The compound ***23*b** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (26 mg, 47%); R_f (20% EtOAc/hexane) 0.4; mp: 180-182 ^{o}C; IR (KBr): 3055, 1681, 1604, 1265, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (br. s, 1H), 8.32 (d, 1H, J = 7.4 Hz), 7.91 (d, 2H, J = 8.4Hz), 7.81 (dd, 2H, J_1 = 5.5, J_2 = 3.0Hz), 7.70-7.68 (m, 4H), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 0.6Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.6Hz), 7.37 (d, 2H, J = 7.2Hz), 7.20 (t, 2H, J = 7.4Hz), 7.09 (t, 1H, J = 7.4 Hz), 5.96 (d, 1H, J = 12.6 Hz), 5.67 (d, 1H, J = 12.6 Hz), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.5, 168.1, 165.7, 154.6, 147.7, 145.2, 139.0, 136.2, 134.5, 131.0, 130.8, 129.3, 129.3, 129.0, 128.3, 127.8, 127.6, 123.8, 116.4, 115.6, 59.3, 50.3, 26.6; HRMS (ESI) calcd for $C_{31}H_{23}N_4O_4S$ $[M+H]^+$ 547.1440 found 547.1460.



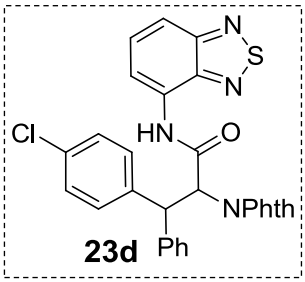
23b

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-cyanophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide*(nb 511a 23c): The compound ***23*c** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (27 mg, 51%); R_f (20% EtOAc/hexane) 0.55; mp: 178-180 ^{o}C; IR (KBr): 3055, 2987, 1714, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (br. s, 1H), 8.31 (d, 1H, J = 7.4 Hz), 7.85 (dd, 2H, J_1 = 7.2, J_2 = 1.2Hz), 7.81 (dd, 2H, J_1 = 5.5, J_2 = 3.1Hz), 7.71-7.69 (m, 2H), 7.68 (d, 1H, J = 4.4Hz), 7.55-7.49 (m, 2H), 7.43 (t, 1H, J = 8.3Hz), 7.35 (d, 2H, J = 7.2Hz), 7.22 (t, 2H, J = 7.4Hz), 7.12 (t, 1H, J = 7.4Hz),), 5.89 (d, 1 H, J = 12.5 Hz), 5.65 (d, 1 H, J = 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.0, 165.4, 154.7, 147.7, 141.6, 138.5, 134.6, 132.5, 131.9, 131.2, 130.9, 130.8, 129.9, 129.2, 127.7, 123.9, 118.5, 116.6, 115.8, 113.2, 59.1, 49.9; HRMS (ESI) calcd for $C_{30}H_{20}N_5O_3S$ $[M+H]^+$ 530.1287 found 530.1263.

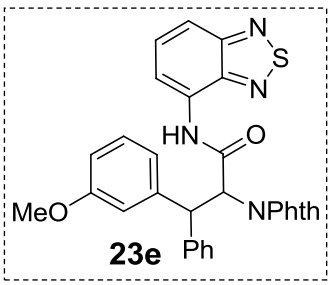


23c

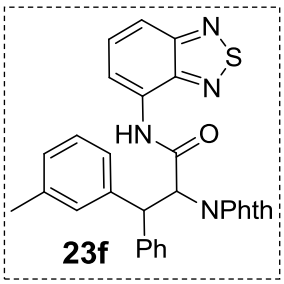
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-chlorophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide*(nb 666a 23d): The compound ***23*d** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (28 mg, 52%); R_f (20% EtOAc/hexane) 0.6; mp: 235-237^{o}C; IR (KBr): 3055, 1713, 1421, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.53 (br. s, 1H), 8.34 (d, 1H, J = 7.4 Hz), 7.80 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.69-7.68 (m, 2H), 7.66 (d, 1H, J = 4.9 Hz), 7.55-7.50 (m, 3H), 7.35 (d, 2H, J = 7.3Hz), 7.29 (d, 2H, J = 7.3Hz), 7.20 (t, 2H, J = 7.8Hz), 7.09 (t, 1H, J = 7.3Hz), 5.88 (d, 1H, J = 12.6 Hz), 5.57 (d, 1H, J = 12.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.1, 165.7, 154.6, 147.7, 139.5, 138.4, 134.5, 133.6, 131.1, 130.8, 129.5, 129.4, 129.4, 128.9, 127.6, 127.4, 123.8, 116.4 115.6, 59.5, 49.9; HRMS (ESI) calcd for $C_{29}H_{20}ClN_4O_3S$ $[M+H]^+$ 539.0945 found 539.0920.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(3-methoxyphenyl)-3-phenylpropanamide*(nb 673a 23e): The compound ***23*e** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (32 mg, 60%); R_f (20% EtOAc/hexane) 0.4; mp: 197-199 ^{o}C; IR (KBr): 3056, 1713, 1549, 1266, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.46 (br. s, 1H), 8.35 (d, 1H, J = 7.4Hz), 7.79 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.69-7.63 (m, 3H), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.5Hz), 7.38 (d, 2H, J = 7.3Hz), 7.27-7.23 (m, 2H), 7.18 (t, 2H, J = 7.8Hz), 7.13 (br. s, 1H), 7.07 (t, 1H, J = 7.3Hz), 6.76-7.73 (m, 1H), 5.94 (d, 1H, J = 12.6 Hz), 5.54 (d, 1H, J = 12.6 Hz), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.1, 166.0, 160.2, 154.6, 147.7, 141.4, 139.9, 134.3, 131.2, 130.9, 130.5, 129.5, 128.8, 127.7, 127.2, 123.7, 120.1, 116.2, 115.5, 114.2, 113.0, 59.3, 55.2, 50.6; HRMS (ESI) calcd for $C_{30}H_{23}N_4O_4S$ $[M+H]^+$ 535.1440 found 535.1416.

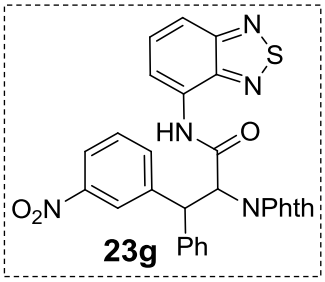


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-3-(m-tolyl)propanamide*(nb 1577a 23f): The compound ***23*f** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a brown color solid (41 mg, 79%); R_f (20% EtOAc/hexane) 0.5; mp: 201-203 ^{o}C; IR (KBr): 3059, 1716, 1381, 1269, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.43 (br. s, 1H), 8.34 (d, 1H, J = 7.1Hz), 7.79 (dd, 2H, J_1 = 5.5, J_2 = 3.0Hz), 7.67-7.63 (m, 3H), 7.50 (dd, 1H, J_1 =



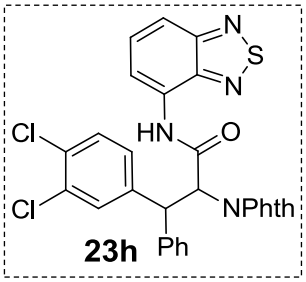
8.8, J_2 = 7.5Hz), 7.43-7.38 (m, 4H), 7.23-7.16 (m, 3H), 7.06 (t, 1H, J = 7.4 Hz), 7.01 (d, 1H, J = 7.4 Hz), 5.95 (d, 1H, J = 12.6 Hz), 5.52 (d, 1H, J = 12.6 Hz), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.1, 166.1, 154.6, 147.7, 140.2, 139.7, 139.1, 134.3, 131.2, 130.9, 129.5, 129.3, 128.9, 128.8, 128.6, 127.7, 127.1, 124.9, 123.6, 116.1, 115.5, 59.3, 50.6, 21.5; HRMS (ESI) calcd for $C_{30}H_{23}N_4O_3S$ $[M+H]^+$ 519.1491 found 519.1500.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-(3-nitrophenyl)-3-phenylpropanamide*(nb 545a 23g): The compound ***23*g** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (29 mg, 53%); R_f (20% EtOAc/hexane) 0.4; mp: 244-246 ^{o}C; IR (KBr): 3055, 1715, 1527, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.64 (br. s, 1H), 8.45 (t, 1H, J = 1.8Hz), 8.29 (d, 1H, J = 7.7Hz), 8.07 (dd, 1H, J_1 = 8.2, J_2 = 2.0,Hz), 7.95 (d, 1H, J = 7.7Hz), 7.81 (dd, 2H, J_1 = 5.5, J_2 = 3.1 Hz), 7.70 (dd, 2H, J_1 = 5.5, J_2 = 3.1Hz), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 0.6Hz), 7.54-7.48 (m, 2H), 7.39 (d, 2H, J = 7.3Hz), 7.23 (t, 2H, J = 7.5Hz), 7.12 (t, 1H, J = 7.3 Hz), 5.95 (d, 1H, J = 12.5 Hz), 5.75 (d, 1H, J = 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.0, 165.4, 154.6, 148.6, 147.7, 142.2, 138.4, 134.6, 134.3, 130.9, 130.7, 130.1, 129.2, 129.2, 127.9, 127.8, 123.9, 123.2, 122.6, 116.6, 115.8, 59.1, 50.0; HRMS (ESI) calcd for $C_{29}H_{20}N_5O_5S$ $[M+H]^+$ 550.1185 found 550.1164.



23g

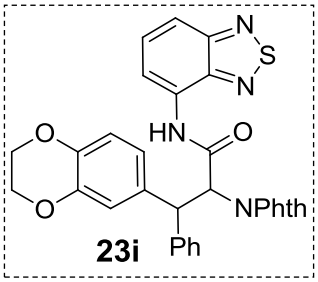
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(3,4-dichlorophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide*(nb 647a 23h): The compound ***23*h** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (30 mg, 52%); R_f (20% EtOAc/hexane) 0.6; mp: 239-241 ^{o}C; IR (KBr): 3329, 1708, 1376, 1265, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.44 (br. s, 1H), 8.34 (d, 1H, J = 7.5 Hz), 7.80 (dd, 2H, J_1 = 5.5, J_2 = 3.0 Hz), 7.69-7.66 (m, 4H), 7.53 (dd, 1H, J_1 =8.8, J_2 = 7.5 Hz), 7.46 (dd, 1H, J_1 = 8.4, J_2 = 2.2Hz), 7.38 (d, 1H, J = 8.3Hz), 7.34 (d, 2H, J = 7.2Hz), 7.21 (t, 2H, J = 7.4Hz), 7.11(t, 1H, J = 7.3Hz), 5.86 (d, 1H, J = 12.5 Hz), 5.56 (d, 1H, J = 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.0, 165.5, 154.6, 147.6, 140.3, 138.9, 134.5, 133.3, 131.9, 131.2, 131.0, 130.8, 130.3, 129.2, 129.1,



23h

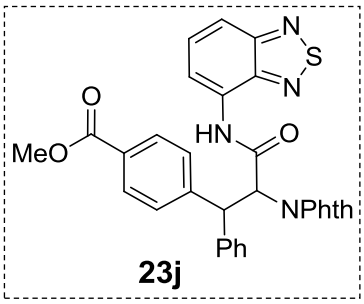
127.7, 127.6, 127.3, 123.8, 116.5, 115.7, 59.0, 49.6; HRMS (ESI) calcd for $C_{29}H_{19}Cl_2N_4O_3S$ $[M+H]^+$ 573.0555 found 573.0531.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide** ***(nb 419,663a 23i):The compound ***23*i** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (27 mg, 48%); R_f (20% EtOAc/hexane) 0.3; mp: 248-250 ^oC; IR (KBr): 3333, 1713, 1549, 1286, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (br. s, 1H), 8.38 (d, 1H, J = 7.4 Hz), 7.78 (dd, 2H, J_1 = 5.6, J_2 = 3.2 Hz), 7.67-7.64 (m, 3H), 7.52 (dd, 1H, J_1 = 8.8, J_2 = 7.6 Hz), 7.36 (d, 2H, J = 7.3Hz), 7.18 (t, 2H, J = 7.5Hz), 7.12-7.04 (m, 3H), 6.81 (d, 1H, J = 8.2 Hz), 5.87 (d, 1H, J = 12.6 Hz), 5.44 (d, 1H, J = 12.6 Hz), 4.23-4.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.1, 154.7, 147.7, 144.1, 143.2, 140.3, 134.3, 133.1, 131.2, 131.0, 129.6, 128.8, 127.5, 127.1, 123.6, 120.9, 118.3, 116.9, 116.1, 115.5, 64.3, 59.3, 50.0; HRMS (ESI) calcd for $C_{31}H_{23}N_4O_5S$ $[M+H]^+$ 563.1389 found 563.1364.



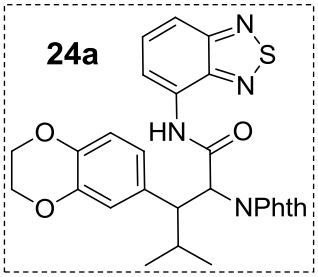
23i

Methyl 4-(3-(benzo[*c*][1,2,5]thiadiazol-4-ylamino)-2-(1,3-dioxoisoindolin-2-yl)-3-oxo-1-phenylpropyl)benzoate*(nb 665a 23j):*The compound ***23*j** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (36 mg, 64%); R_f (20% EtOAc/hexane) 0.3; IR (KBr): 3055, 1658, 1409, 1269, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.55 (br. s, 1H), 8.31 (d, 1H, J = 7.3Hz), 7.98 (d, 2H, J = 8.4Hz), 7.80 (dd, 2H, J_1 = 5.5, J_2 = 3.1 Hz), 7.70-7.64 (m, 5H), 7.49 (dd, 1H, J_1 =8.7, J_2 = 7.5 Hz), 7.37 (d, 2H, J = 7.4Hz), 7.20 (t, 2H, J = 7.4Hz), 7.09 (t, 1H, J = 7.4 Hz), 5.95 (d, 1H, J = 12.6 Hz), 5.66 (d, 1H, J = 12.6 Hz), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.0, 166.6, 165.6, 154.6, 147.7, 145.0, 139.1, 134.5, 131.1, 130.8, 130.5, 129.4, 129.3, 129.0, 128.1, 127.8, 127.5, 123.8, 116.4, 115.6, 59.4, 52.1, 50.4; HRMS (ESI) calcd for $C_{31}H_{23}N_4O_5S$ $[M+H]^+$ 563.1389 found 563.1393.



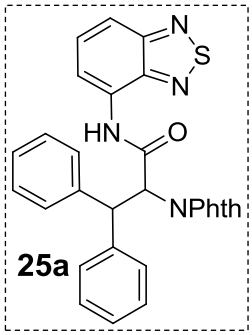
23j

N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanamide *(nb 1328 24a):The compound ***24*a** was



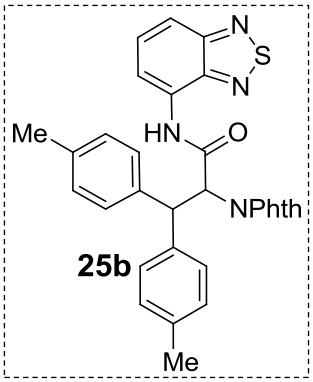
obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (26 mg, 50%); R_f (20% EtOAc/hexane) 0.4; mp: 154-156 ^oC; IR (KBr): 3055, 2985, 1493, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.20 (br. s, 1H), 8.28 (d, 1H, J = 7.4Hz), 7.96 (dd, 2H, J_1 = 5.5, J_2 = 3.1 Hz), 7.79 (dd, 2H, J_1 = 5.5, J_2 = 3.1 Hz), 7.61 (d, 1H, J = 8.8Hz), 7.46 (dd, 1H, J_1 = 8.6, J_2 = 7.6 Hz), 6.99 (d, 1H, J = 1.5Hz), 6.94 (d, 1H, J = 8.3Hz), 6.87 (d, 1H, J = 8.3 Hz), 5.54 (d, 1H, J = 12.5 Hz), 4.29-4.24 (m, 4H), 4.08 (dd, 1H, J_1 = 12.5, J_2 = 3.5 Hz), 1.98-1.91 (m, 1H), 0.86 (d, 3H, J = 6.8 Hz), 0.81(d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.6, 166.7, 154.6, 147.8, 143.7, 143.3, 134.5, 131.7, 130.9, 129.7, 129.1, 123.9, 117.6, 115.9, 115.3, 64.3, 58.2, 48.2, 29.7, 29.1, 21.6, 16.3; HRMS (ESI) calcd for $C_{28}H_{25}N_4O_5S$ $[M+H]^+$ 529.1546 found 529.1540.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3,3-diphenylpropanamide*(nb 1170a 25a):The compound **25a** was obtained after purification by

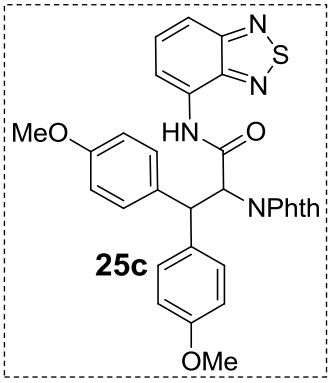


column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (30 mg, 60%); R_f (20% EtOAc/hexane) 0.7; mp: 222-224 ^oC; IR (KBr): 3338, 1714, 1549 1381, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (br. s, 1H), 8.33 (d, 1H, J = 7.4Hz), 7.79 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.66 (dd, 2H, J_1 = 5.2, J_2 = 3.1Hz), 7.63-7.60 (m, 3H), 7.49 (t, 1H, J = 8.2Hz), 7.39 (d, 2H, J = 7.6Hz), 7.32 (t, 2H, J = 7.6Hz), 7.22-7.17 (m, 3H), 7.07 (t, 1H, J = 7.2Hz), 5.96 (d, 1H, J = 12.6Hz), 5.58 (d, 1H, J = 12.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.0, 154.6, 147.7, 140.0, 139.8, 134.4, 131.2, 130.9, 129.5, 129.3, 128.8, 128.1, 127.7, 127.7, 127.2, 123.7, 116.2, 115.5, 59.6, 50.6; HRMS (ESI) calcd for $C_{29}H_{21}N_4O_3S$ $[M+H]^+$ 505.1334 found 505.1320.

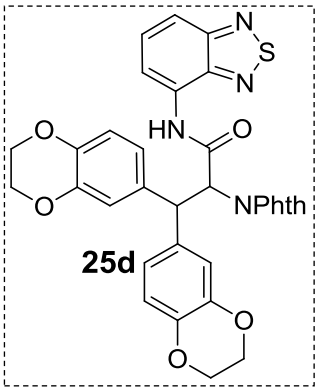
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3,3-di-*p*-tolylpropanamide*(nb 258a* 25*b):The compound **25b** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (37 mg, 70%); R_f (20% EtOAc/hexane) 0.56; mp: 269-271 ^oC; IR (KBr): 3328, 1773, 1703, 1269, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.53 (br. s, 1H), 8.34 (d, 1H, J = 7.4Hz), 7.80 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.68 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.64 (d, 1H, J = 8.8 Hz), 7.50 (dd, 1H, J_1 = 8.7, J_2 = 7.6Hz), 7.46 (d, 2H, J = 8.0Hz), 7.25 (d, 2H, J = 8.0Hz), 7.11 (d, 2H, J = 7.9Hz), 6.98 (d, 2H, J = 7.9Hz), 5.90 (d, 1H, J = 12.7Hz), 5.49 (d, 1H, J = 12.7Hz), 2.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.2, 154.7, 147.7, 146.8, 137.2, 137.2, 137.1, 136.6, 134.3, 131.3, 130.9, 130.1, 129.6, 129.5, 127.8, 127.4, 123.7, 116.1, 115.4, 59.7, 49.8, 21.1, 20.9; HRMS (ESI) calcd for $C_{31}H_{25}N_4O_3S$ $[M+H]^+$ 533.1647 found 533.1622.



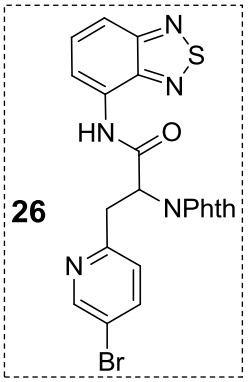
N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-(1,3-dioxoisoindolin-2-yl)-3,3-bis(4-methoxyphenyl)propanamide*(nb 234a* 25*c):The compound **25c** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a brown color solid (34 mg, 60%); R_f (20% EtOAc/hexane) 0.4; mp: 215-217 ^oC; IR (KBr): 3333, 1714, 1611, 1253, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (br. s, 1H), 8.34 (d, 1H, J = 7.5Hz), 7.80 (dd, 2H, J_1 = 5.5, J_2 = 3.0Hz), 7.67 (dd, 2H, J_1 = 5.5, J_2 = 3.0Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 0.7Hz), 7.52-748 (m, 3H), 7.28 (d, 2H, J = 8.7Hz), 6.84 (d, 2H, J = 8.7Hz), 6.72 (d, 2H, J = 8.7Hz), 5.84 (d, 1H, J = 12.7Hz), 5.47 (d, 1H, J = 12.7Hz), 3.72 (s, H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.2, 166.3, 158.9, 158.4, 154.6, 147.7, 134.4, 132.5, 132.2, 131.2, 130.9, 129.6, 129.0, 128.6, 123.7, 116.1, 115.4, 114.7, 114.2, 60.0, 55.2, 55.1, 49.0; HRMS (ESI) calcd for $C_{31}H_{25}N_4O_5S$ $[M+H]^+$ 565.1546 found 565.1525.



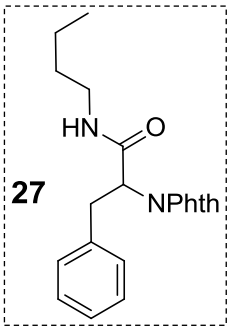
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3,3-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(1,3-dioxoisoindolin-2-yl)propanamide*(nb 253a* 25*d): The compound **25d** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color solid (41 mg, 66%); R_f (20% EtOAc/hexane) 0.3; mp: 249-251 ^oC; IR (KBr): 3055, 1714, 1378, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.38 (br. s, 1H), 8.35 (d, 1H, J = 7.4Hz), 7.81 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.68 (dd, 2H, J_1 = 5.4, J_2 = 3.0Hz), 7.63 (d, 1H, J = 8.8Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.6Hz), 7.08 (d, 1H, J = 2.0Hz), 7.05 (dd, 1H, J_1 = 8.3, J_2 = 2.2Hz), 6.86-6.81 (m, 2H), 6.80 (d, 1H, J = 8.4Hz), 6.65 (d, 1H, J = 8.3Hz), 5.79 (d, 1H, J = 12.6Hz), 5.33 (d, 1H, J = 12.6Hz), 4.22-4.10 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.1,166.1, 154.6, 147.7, 144.0, 143.5, 143.1, 142.5, 134.2, 133.6, 133.3, 131.4, 130.9, 129.6, 123.7, 120.8, 120.2, 118.2, 117.4, 116.8, 116.5, 116.1, 115.4, 64.3, 64.1, 59.3, 49.2; HRMS (ESI) calcd for $C_{33}H_{25}N_4O_7S$ $[M+H]^+$ 621.1444 found 621.1419.



N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(5-bromopyridin-2-yl)-2-(1,3-dioxoisoindolin-2-yl)propanamide*(nb 1574a 26): The compound **26** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a faint yellow color solid (25 mg, 49%); R_f (20% EtOAc/hexane) 0.4; mp: 168-170 ^oC; IR (KBr): 3055, 2987, 1714, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.63 (br. s, 1H), 8.94 (d, 1H, J = 2.1Hz), 8.50 (dd, 1H, J_1 = 7.4, J_2 = 0.6Hz), 7.93 (dd, 2H, J_1 = 5.5, J_2 = 3.1Hz), 7.83 (dd, 1H, J_1 = 8.2, J_2 = 2.4Hz), 7.78 (dd, 2H, J_1 = 5.5, J_2 = 3.1Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.57 (dd, 1H, J_1 = 8.8, J_2 = 7.5Hz), 7.21 (d, 1H, J = 8.2Hz), 5.68 (dd, 1H, J_1 = 8.7, J_2 = 3.8 Hz), 4.23 (dd, 1H, J_1 = 16.4, J_2 = 8.7Hz), 3.61 (dd, 1H, J_1 = 16.4, J_2 = 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.2, 167.3, 156.1, 154.9, 150.6, 148.1, 140.0, 134.4, 131.9, 131.0, 130.3, 125.0, 123.7, 119.3, 116.0, 115.8, 53.2, 37.6; HRMS (ESI) calcd for $C_{22}H_{15}BrN_5O_3S$ $[M+H]^+$ 508.0079 found 508.0060.



N*-butyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide*(nb 1157a 27): The compound **27** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color semisolid (5 mg, 20%); R_f (20% EtOAc/hexane) 0.7; IR (KBr): 2961, 1718, 1388, 1264, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.70 (dd, 2H, J_1 = 5.4, J_2 = 3.1Hz), 7.23-7.13 (m, 5H), 517 (dd, 1H, J_1 = 11.2, J_2 = 5.4Hz), 4.21 (t, 2H, J = 6.3Hz), 3.65-3.52 (m, 2H), 1.65-1.59 (m, 2H), 1.38-1.30 (m, 2H), 0.90 (t, 3H, J = 7.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C168.9, 167.5, 136.8, 134.1, 131.6, 128.9, 128.6, 126.8, 123.5, 65.9, 53.5, 34.7, 30.5, 19.0, 13.6; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1709 found 351.1703.



Part 2

General IR spectra were recorded as KBr pellets or thin films. ^1H / ^{13}C NMR spectra of were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under a nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulphate. TLC inspection was carried out on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported, andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures.[9h, 10b, 18]

Procedure for the synthesis of heterocarboxamide 28a-b and 28d-g.

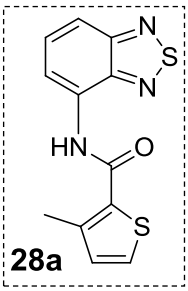
A dry RB flask is having the corresponding carboxylic acid (3 mmol) and $SOCl_2$ (1.8 mL) at rt for 24 h under a nitrogen atmosphere. After the reaction duration, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (3 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (1 mmol), Et_3N (333 mg, 3.3 mmol) and DCM (7 mL) under a nitrogen atmosphere. The resulting crude mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated

aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. Purification of the raw reaction mixture by column chromatography on silica gel (EtOAc/hexanes = 20:80) furnished the corresponding products **28a-b**. Compound **28d-g** known in literature.[8r]

Procedure for the synthesis of heterocarboxamide 28c.

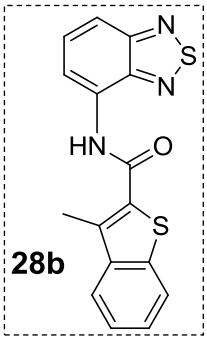
A dry flask the corresponding containing amine (3 mmol) and Et_3N (363 mg, 3.6 mmol) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by drop-wise addition of the corresponding acid chloride. The crude reaction mixture was stirred overnight at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dried out over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the reaction mixture by column chromatography (silica gel, 100-200 mesh, (EtOAc/hexanes = 20:80) furnished the corresponding products **28c.**

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methylthiophene-2-carboxamide*(nb 612 sm 28a): The compound ***28*a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (590 mg, 71%); R_f (20% EtOAc/hexane) 0.55; mp: 158-160 ^oC; IR (KBr): 3412, 1658, 1409, 1269, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.04 (br. s, 1H), 8.58 (dd, 1H, J_1 = 7.3, J_2 = 0.9Hz), 7.71 (dd, 1H, J_1 = 8.8, J_2 = 1.0Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.3Hz), 7.45 (d, 1H, J = 5.0Hz), 7.01 (d, 1H, J = 5.0Hz), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.1, 154.7, 148.0, 141.8, 132.6, 131.5, 131.2, 130.0, 128.4, 115.8, 114.8, 16.2; HRMS (ESI) calcd for $C_{12}H_{10}N_3OS_2$ $[M+H]^+$ 276.0265 found 276.0252.

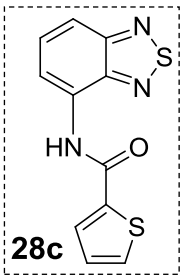


28a

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-methylbenzo[b]thiophene-2-carboxamide*(nb 1546/743 sm 28b):The compound ***28*b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (549 mg, 56%); R_f (20% EtOAc/hexane) 0. 5; mp: 174-176 ^oC; IR (KBr): 3412, 1647, 1527, 1268, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.16 (br. s, 1H), 8.64 (d, 1H, *J* = 7.3Hz), 7.90 (d, 2H, *J* = 7.0Hz), 7.75 (d, 1H, *J* = 8.8Hz), 7.71-7.66 (m, 1H), 7.53-7.50 (m, 2H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C154.8, 147.9, 140.6, 139.0, 137.5, 135.8, 131.2, 130.4, 129.9, 127.1, 125.0, 123.6, 122.7, 116.1, 115.1, 13.4; HRMS (ESI) calcd for $C_{16}H_{12}N_3OS_2$ $[M+H]^+$ 326.0422 found 326.0409.



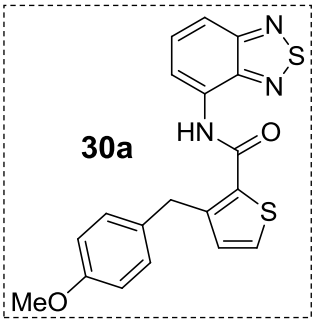
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)thiophene-2-carboxamide*(nb 636 sm 28c):The compound ***28*c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brownish yellow color solid (475 mg,60%); R_f (20% EtOAc/hexane) 0.5; mp: 155-157 ^oC; IR (KBr): 3055, 1544, 1416, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.10 (br. s, 1H), 8.57 (d, 1H, *J* = 7.3Hz), 7.80 (dd, 1H, J_1 = 3.8, J_2 = 1.0Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.67-7.63 (m, 2H), 7.21 (dd, 1H, J_1 = 4.9, J_2 = 3.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C159.9, 154.7, 147.8, 138.8, 131.7, 131.2, 129.8, 128.9, 128.1, 115.9, 115.0; HRMS (ESI) calcd for $C_{11}H_8N_3OS_2$ $[M+H]^+$ 262.0109 found 262.0110.



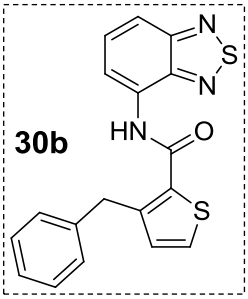
General procedure for the Pd(II)-catalyzed arylation of heterocarboxamide and preparation of arylated compounds 30a-m, 31a-b, 32a-c.

An appropriate natural/unnatural carboxamide (0.10-0.12 mmol, 1equiv), an appropriate iodo compound (0.40-0.48 mmol, 4equiv), $Pd(OAc)_2$ (2.5-2.7 mg, 10 mol%), and AgOAc (48-50 mg, 2.2 equiv.) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the raw reaction mixture by column chromatography furnished the corresponding arylated products **30a-m, 31a-b, 32a-c** (see corresponding Tables/Schemes for specific examples and reaction conditions).

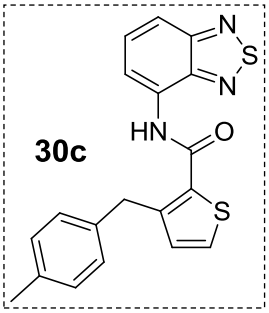
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-methoxybenzyl)thiophene-2-carboxamide*(nb 637 a* 30*a):The compound **30a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a dark yellow color solid (35 mg, 85%); R_f (20% EtOAc/hexane) 0.4; mp: 142-144 ^oC; IR (KBr): 3054, 1512, 1414, 1265, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.99 (br. s, 1H), 8.58 (dd, 1H, J_1 = 7.3, J_2 = 0.7Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 0.9Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.3Hz), 7.42 (d, 1H, J = 5.0Hz), 7.23 (d, 2H, J = 8.7 Hz), 6.93 (d, 1H, J = 5.0 Hz), 6.86 (d, 2H, J = 8.7Hz), 4.43 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.0, 158.3, 154.7, 147.9, 146.6, 131.9, 131.7, 131.1, 130.8, 130.0, 129.9, 128.0, 115.9, 115.1, 114.1, 55.3, 34.5, HRMS (ESI) calcd for $C_{19}H_{16}N_3O_2S_2$ $[M+H]^+$ 382.0684 found 382.0665.



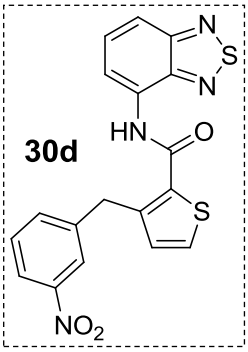
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-benzylthiophene-2-carboxamide*(nb 683 a* 30*b):The compound **30b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (27 mg, 70%); R_f (20% EtOAc/hexane) 0.6; mp: 135-137 ^oC; IR (KBr): 3055, 2987, 1421, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.00 (br. s, 1H), 8.58 (dd, 1H, J_1 = 7.3, J_2 = 0.7Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 1.0Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.3Hz), 7.42 (d, 1H, J = 5.1Hz), 7.36-7.23 (m, 5H), 6.93 (d, 1H, J = 5.1Hz), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.0, 154.7, 147.9, 146.2, 139.7, 132.0, 131.1, 130.8, 130.0, 128.9, 128.7, 127.9, 126.5, 115.9, 115.1, 35.4, HRMS (ESI) calcd for $C_{18}H_{14}N_3OS_2$ $[M+H]^+$ 352.0578 found 352.0560.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-methylbenzyl)thiophene-2-carboxamide*(nb 684 a* 30*c):The compound **30c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (28 mg, 70%); R_f (20% EtOAc/hexane) 0.6; mp: 114-116 ^oC; IR (KBr): 3055, 1544, 1416, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.00 (br. s, 1H), 8.58 (d, 1H, J = 7.3 Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 0.7Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.41 (d, 1H, J = 5.0Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 6.93 (d, 1H, J = 5.0Hz), 4.46 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.0, 154.7, 147.9, 146.4, 136.6, 136.0, 132.0, 131.1, 130.8, 130.0, 129.4, 128.8, 127.9, 115.9, 115.1, 35.0, 21.1, HRMS (ESI) calcd for $C_{19}H_{16}N_3OS_2$ $[M+H]^+$ 366.0735 found 366.0719.

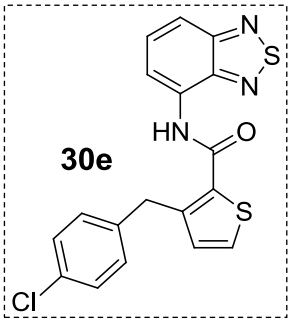


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(3-nitrobenzyl)thiophene-2-carboxamide*(nb 634 a 30d): The compound ***30*d** was obtained after purification by column chromatography on silica



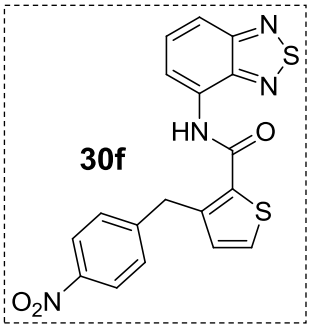
gel (EtOAc:hexane = 20:80) as a yellow color solid (21 mg, 48%); R_f (20% EtOAc/hexane) 0.3; mp: 149-151 ^oC; IR (KBr): 3054, 1665, 1419, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (br. s, 1 H), 8.55 (d, 1H, J = 7.4 Hz), 8.17 (d, 2H, J = 8.7 Hz), 7.74 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.49 (br., s, 1H), 7.47 (d, 2H, J = 2.8Hz), 6.98 (d, 1H, J = 5.0 Hz), 4.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C160.6, 154.7, 147.8, 147.7, 146.6, 145.2, 131.7, 131.0, 130.6, 129.8, 129.7, 129.6, 128.1, 126.7, 124.6, 123.9, 116.2, 115.1, 35.0; HRMS (ESI) calcd for $C_{18}H_{13}N_4O_3S_2$ $[M+H]^+$ 397.0429 found 397.0446.

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-chlorobenzyl)thiophene-2-carboxamide*(nb 655 a 30e): The compound ***30*e** was obtained after purification by column chromatography on silica



gel (EtOAc:hexane = 20:80) as a yellow color solid (18 mg, 42%); R_f (20% EtOAc/hexane) 0.5; mp: 122-124 ^oC; IR (KBr): 3055, 1542, 1414, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.96 (br. s, 1H), 8.56 (d, 1H, J = 7.4 Hz), 7.73 (d, 1H, J = 8.8 Hz), 7.67-7.63 (m, 1H), 7.44 (d, 1H, J = 5.0Hz), 7.29-7.23 (m, 4H), 6.93 (d, 1H, J = 5.0Hz), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C160.9, 154.7, 147.9, 146.0, 138.3, 132.3, 131.8, 131.1, 130.7, 130.2, 129.9, 128.8, 127.9, 116.0, 115.1, 34.7; HRMS (ESI) calcd for $C_{18}H_{13}ClN_3OS_2$ $[M+H]^+$ 386.0189 found 386.0170.

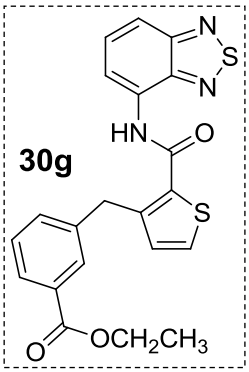
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-nitrobenzyl)thiophene-2-carboxamide*(nb 686 a 30f): The compound ***30*f** was obtained after purification by column chromatography on silica



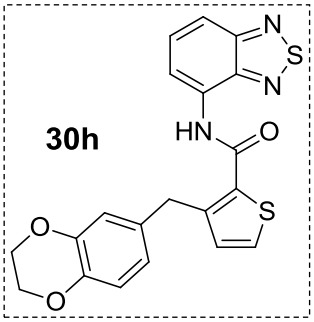
gel (EtOAc:hexane = 20:80) as a orange color solid (21 mg, 50%); R_f (20% EtOAc/hexane) 0.3; mp: 181-183 ^oC; IR (KBr): 3054,1665, 1419, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (br. s, 1H), 8.55 (d, 1H, J = 7.4 Hz), 8.17 (d, 2H, J = 8.7 Hz), 7.74 (dd, 1H, J_1 = 8.8, J_2 = 0.8Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.49 (br. s, 1H), 7.47 (d, 2H, J = 2.8Hz), 6.98 (d, 1H, J = 5.0 Hz), 4.60

(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C160.6, 154.7, 147.8, 147.7, 146.6, 145.2, 131.7, 131.1, 130.6, 129.8, 129.6, 128.1, 123.9, 116.2, 115.1, 35.0; HRMS (ESI) calcd for $C_{18}H_{13}N_4O_3S_2$ $[M+H]^+$ 397.0429 found 397.0439.

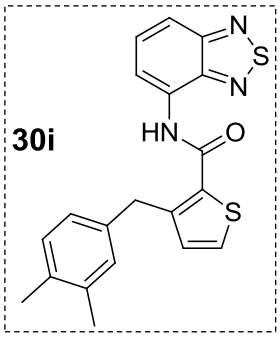
Ethyl 3-((2-(benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)thiophen-3-yl)methyl)benzoate*(nb 745 a 30g):* The compound ***30*g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (26 mg, 55%); R_f (20% EtOAc/hexane) 0.3; mp: 125-127 ^{o}C; IR (KBr): 3054, 1544, 1420, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (br. s, 1H), 8.58 (d, 1H, *J* = 7.3 Hz), 8.01 (br. s, 1H), 7.92 (d, 1H, *J* = 7.6 Hz), 7.72 (d, 1H, *J* = 8.8 Hz), 7.67-7.63 (m, 1H), 7.50 (d, 1H, *J* = 7.6 Hz), 7.44 (d, 1H, *J* = 5.0Hz), 7.39 (t, 1H, *J* = 7.7Hz), 6.93 (d, 1H, *J* = 5.0 Hz), 4.55 (s, 2H), 4.37 (q, 2H, *J* = 7.1Hz), 1.38 (t, 3H, *J* = 7.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.6, 160.9, 154.7, 147.9, 145.8, 140.1, 133.4, 131.8, 131.1, 130.8, 130.8, 130.0, 129.9, 128.7, 128.0, 127.7, 116.0, 115.1, 61.0, 35.1, 14.3; HRMS (ESI) calcd for $C_{21}H_{17}N_3NaO_3S_2$ $[M+Na]^+$ 446.0409 found 446.0419.



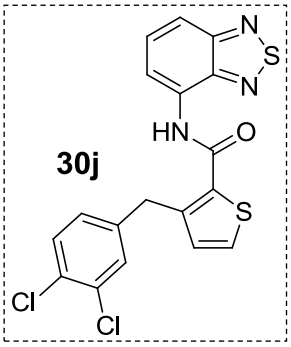
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)thiophene-2-carboxamide*(nb 682 a 30h): The compound ***30*h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (26 mg, 60%); R_f (20% EtOAc/hexane) 0.4; mp: 132-134 ^{o}C; IR (KBr): 3055, 1506, 1419, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (br. s, 1H), 8.57 (dd, 1H, J_1 = 7.3, J_2 = 0.7Hz), 7.71 (dd, 1H, J_1 = 8.9, J_2 = 0.9Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.43 (d, 1H, *J* = 5.0 Hz), 6.96 (d, 1H, *J* = 5.0Hz), 6.83-6.76 (m, 3H), 4.38 (s, 2H), 4.25 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.0, 154.7, 147.9, 146.1, 143.5, 142.2, 132.9, 132.0, 131.1, 130.0, 128.0, 121.8, 119.8, 117.6, 117.4, 115.9, 115.1, 64.4, 64.3, 34.6; HRMS (ESI) calcd for $C_{20}H_{16}N_3O_3S_2$ $[M+H]^+$ 410.0633 found 410.0613.



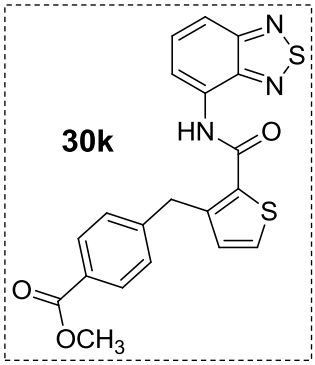
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(3,4-dimethylbenzyl)thiophene-2-carboxamide*(nb 694 a 30i): The compound ***30*i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a greenish yellow color solid (28 mg, 68%); R_f (20% EtOAc/hexane) 0.7; mp: 129-131 ^oC; IR (KBr): 3055, 2987, 1668, 1264, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.00 (br. s, 1H), 8.58 (dd, 1H, J_1 = 7.3, J_2 = 0.7Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 1.0Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.42 (d, 1H, J = 5.0 Hz), 7.09-7.08 (m, 2H), 7.03 (d, 1H, J = 9.4Hz), 6.94 (d, 1H, J = 5.1Hz), 4.43 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.1, 154.7, 147.9, 146.3, 137.0, 136.8, 134.7, 132.0, 131.2, 130.9, 130.2, 130.0, 129.9, 128.0, 126.2, 115.9, 115.1, 35.0, 19.8, 19.4; HRMS (ESI) calcd for $C_{20}H_{18}N_3OS_2$ $[M+H]^+$ 380.0891 found 380.0904.



N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(3,4-dichlorobenzyl)thiophene-2-carboxamide*(nb 649 a 30j): The compound ***30*j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a dark yellow color solid (29 mg, 65%); R_f (20% EtOAc/hexane) 0.6; mp: 152-154 ^oC; IR (KBr): 3055, 1670, 1418, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.94 (br. s, 1H), 8.55 (d, 1H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.8 Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.46 (d, 1H, J = 5.0 Hz), 7.40 (d, 1H, J = 2.0 Hz), 7.37 (d, 1H, J = 8.2Hz), 7.15 (dd, 1H, J_1 = 8.2, J_2 = 2.0Hz), 6.95 (d, 1H, J = 5.1Hz), 4.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 160.7, 154.7, 147.8, 145.3, 140.1, 132.5, 131.7, 131.1, 130.8, 130.7, 130.5, 130.5, 129.8, 128.3, 128.1, 116.1, 115.1, 34.3; HRMS (ESI) calcd for $C_{18}H_{12}Cl_2N_3OS_2$ $[M+H]^+$ 419.9799 found 419.9779.

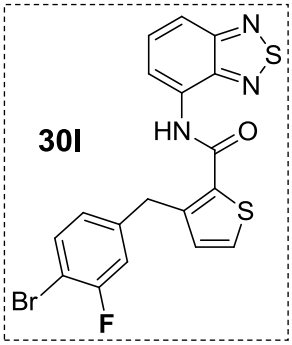


Methyl 4-((2-(benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)thiophen-3-yl)methyl)benzoate*(nb 628 a 30k):* The compound ***30*k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a faint yellow color solid (22 mg, 52%); R_f (20% EtOAc/hexane) 0.4; mp: 161-163 ^oC; IR (KBr): 3055, 1718, 1418, 1266, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.97 (br. s, 1H), 8.57 (dd, 1H, J_1 = 7.4, J_2 = 0.6Hz), 7.99 (d, 2H, J = 8.4 Hz), 7.73 (dd, 1H, J_1 = 8.9, J_2 = 0.9Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4Hz), 7.44 (d, 1H, J = 5.0

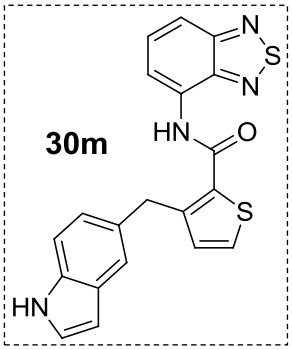


Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 6.93 (d, 1H, *J* = 5.1Hz), 4.55 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 160.8, 154.7, 147.9, 145.6, 145.2, 131.8, 131.1, 130.7, 130.0, 129.9, 128.9, 128.4, 127.9, 116.1, 115.1, 52.1, 35.3; HRMS (ESI) calcd for $C_{20}H_{16}N_3O_3S_2$ $[M+H]^+$ 410.0633 found 410.0650.

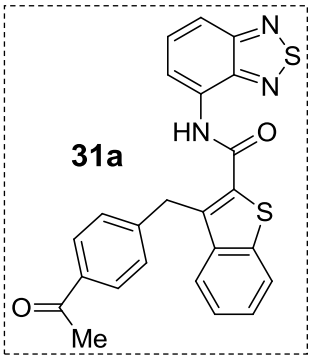
N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(4-bromo-3-fluorobenzyl)thiophene-2-carboxamide*(nb 746 a 30l): The compound ***30*l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (21 mg, 42%); R_f (20% EtOAc/hexane) 0.7; mp: 150-152 ^{o}C; IR (KBr): 3055, 1542, 1416, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.95 (br. s, 1H), 8.56 (d, 1H, *J* = 7.1 Hz), 7.73 (d, 1H, *J* = 8.2 Hz), 7.65 (dd, 1H, J_1 = 8.7, J_2 = 7.4Hz), 7.49-7.45 (m, 2H), 7.13-7.07 (m, 1H), 6.99 (dd, 1H, J_1 = 8.2, J_2 = 1.6Hz), 6.96 (d, 1H, *J* = 5.0 Hz), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 160.7, 159.1 (d, J_{C-F} = 245.7 Hz), 154.7, 146.5 (d, J_{C-F} = 250.0 Hz), 141.6 (d, J_{C-F} = 6.7 Hz),, 133.5, 131.7, 131.1, 130.7, 129.8, 128.0, 125.7 (d, J_{C-F} = 3.3 Hz), 117.0 (d, J_{C-F} = 22.3 Hz), 116.3, 116.1, 115.1, 106.7 (d, J_{C-F} = 20.9 Hz), 34.5; HRMS (ESI) calcd for $C_{18}H_{12}BrFN_3OS_2$ $[M+H]^+$ 447.9589 found 447.9579.



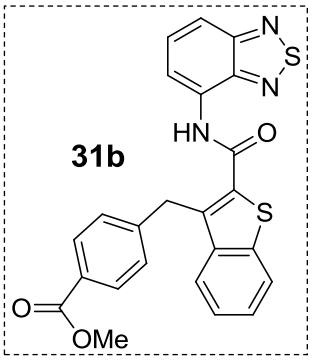
3-((1H-indol-5-yl)methyl)-*N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)thiophene-2-carboxamide*(nb 640 a 30m):* The compound ***30*m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a mud color solid (18 mg, 40%); R_f (20% EtOAc/hexane) 0.4; mp: 139-141 ^{o}C; IR (KBr): 3055, 2303, 1422, 1265, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.05 (br. s, 1H), 8.59 (dd, 1H, J_1 = 7.3, J_2 = 0.8Hz), 8.17 (br. s, 1H), 7.70 (dd, 1H, J_1 = 8.8, J_2 = 1.0Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.3Hz), 7.55 (br. s, 1H), 7.42 (d, 1H, *J* = 5.1 Hz), 7.36 (d,1H, *J* = 8.3 Hz), 7.22 (t, 1H, *J* = 2.8Hz),7.15 (dd, 1H, J_1 = 8.2, J_2 = 1.5Hz) 6.96 (d, 1H, *J* = 5.1Hz), 6.51-6.50 (m, 1H), 4.59 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.2, 154.7, 147.9, 146.6, 134.7, 132.2, 131.2, 131.1, 130.9, 130.1, 128.3, 128.1, 124.6, 123.3, 120.6, 115.8, 115.1, 111.3, 102.6, 35.5; HRMS (ESI) calcd for $C_{20}H_{15}N_4OS_2$ $[M+H]^+$ 391.0687 found 391.0672.



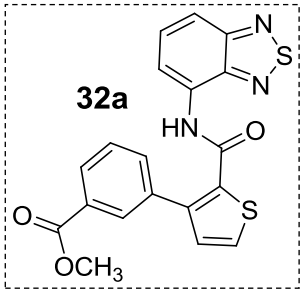
3-(4-Acetylbenzyl)-*N*-(benzo[*c*][1,2,5]thiadiazol-4-yl)benzo[b]thiophene-2-carboxamide ***(nb 750 a 31a):***The compound **31a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a faint yellow color solid (22 mg, 50%); R_f (20% EtOAc/hexane) 0.4; mp: 206-208 ^oC; IR (KBr): 3055, 2987, 1422, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.14 (br. s, 1H), 8.61 (d, 1H, J = 7.3 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.88 (d, 2H, J = 8.3 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.6Hz), 7.66 (dd, 1H, J_1 = 8.7, J_2 = 7.4Hz), 7.52 (t, 1H, J = 7.1Hz), 7.44 (d, 1H, J = 7.4 Hz), 7.42 (d, 2H, J = 8.4Hz), 4.83 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 197.8, 161.2, 154.7, 147.8, 144.8, 139.8, 139.6, 138.8, 135.4, 131.0, 129.7, 128.8, 128.7, 128.6, 127.4, 125.4, 124.0, 122.9, 116.4, 115.3, 32.9, 26.6; HRMS (ESI) calcd for $C_{24}H_{18}N_3O_2S_2$ $[M+H]^+$ 444.0840 found 444.0852.



Methyl 4-((2-(benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)benzo[*b*]thiophen-3-yl) methyl) benzoate ***(nb 755 a* 31*b):***The compound **31b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a faint yellow color solid (20 mg, 44%); R_f (20% EtOAc/hexane) 0.3; mp: 167-169 ^oC; IR (KBr): 3055, 2987, 1530, 1266, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.13 (br. s, 1H), 8.61 (d, 1H, J = 7.2 Hz), 7.96-7.92 (m, 3H), 7.78 (d, 1H, J = 8.0Hz), 7.75 (d, 1H, J = 8.9Hz), 7.66 (dd, 1H, J_1 = 8.7, J_2 = 7.4Hz), 7.52 (t, 1H, J = 7.0Hz), 7.43 (d, 1H, J = 7.2Hz), 7.39 (d, 2H, J = 8.3Hz), 4.83 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 161.3, 154.7, 147.8, 144.5, 139.9, 139.8, 139.6, 138.8, 131.1, 131.0, 130.0, 129.7, 128.5, 127.3, 125.3, 124.0, 122.9, 116.4, 115.3, 52.1, 33.0; HRMS (ESI) calcd for $C_{24}H_{18}N_3O_3S_2$ $[M+H]^+$ 460.0790 found 460.0801.

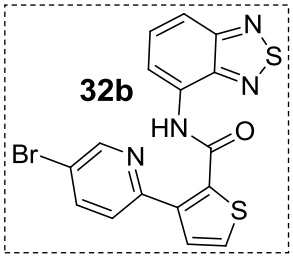


Methyl 3-(2-(benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)thiophen-3-yl)benzoate*(nb 652 a 32a):*The compound ***32*a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a faint yellow color solid (29 mg, 62%); R_f (20% EtOAc/hexane) 0.4; mp: 120-122 ^oC; IR (KBr): 3055, 1659, 1417, 1265, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.28 (dd, 1H, J_1 = 8.8, J_2 = 0.6Hz), 8.16 (d, 1H, J = 8.3 Hz), 7.97 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.95 (d, 1H, J = 5.3 Hz), 7.90 (br. s,

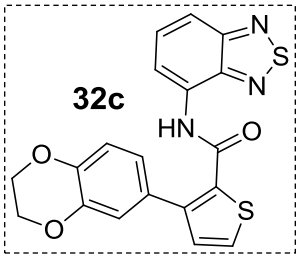


1H), 7.89-7.86 (m, 1H), 7.75 (d, 1H, *J* = 7.0 Hz), 7.35 (d, 1H, *J* = 1.3 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 157.9, 156.2, 151.9, 142.2, 139.1, 134.6, 132.2, 130.8, 130.2, 129.5, 129.3, 124.6, 123.8, 123.3, 122.9, 121.7, 117.8, 52.4; HRMS (ESI) calcd for $C_{19}H_{14}N_3O_3S_2$ $[M+H]^+$ 396.0477 found 396.0497. (NH peak not coming)

N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(5-bromopyridin-2-yl)thiophene-2-carboxamide*(nb 653 a 32b): The compound ***32*b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (27 mg, 55%); R_f (20% EtOAc/hexane) 0.3; mp: 218-220 ^{o}C; IR (KBr): 3055, 2987, 1422, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 14.46 (br. s, 1H), 9.26 (d, 1H, *J* = 2.3 Hz), 8.76 (d, 1H, *J* = 7.4 Hz), 8.02(dd, 1H, J_1 = 8.5, J_2 = 2.4Hz), 7.74 (d, 1H, *J* = 8.6 Hz), 7.67 (d, 2H, *J* = 8.9 Hz), 7.63 (d, 1H, *J* = 5.3 Hz), 7.45 (d, 1H, *J* = 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 161.0, 155.3, 151.9, 150.2, 148.5, 141.5, 140.7, 136.6, 131.4, 131.2, 130.5, 130.2, 125.0, 119.7, 117.0, 116.0; HRMS (ESI) calcd for $C_{16}H_{10}BrN_4OS_2$ $[M+H]^+$ 416.9479 found 416.9475.

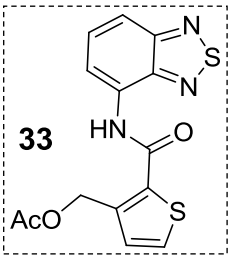


N*-(Benzo[*c*][1,2,5]thiadiazol-4-yl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)thiophene-2-carboxamide*(nb 716 a 32c): The compound ***32*c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (33 mg, 69%); R_f (20% EtOAc/hexane) 0.4; mp: 157-159 ^{o}C; IR (KBr): 3055, 1544, 1421, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.03 (br. s, 1H), 8.54 (dd, 1H, J_1 = 7.1, J_2 = 1.0 Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 1.1Hz), 7.61-757 (m, 2H), 7.10 (d, 1H, *J* = 5.0 Hz), 7.07 (d, 1H, *J* = 0.7 Hz), 7.01 (d, 2H, *J* = 1.6 Hz), 4.39-4.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 160.6, 154.6, 147.7, 144.6, 144.3, 143.0, 134.5, 131.5, 131.3, 130.2, 130.0, 127.8, 122.4, 118.6, 118.2, 115.6, 114.8, 64.6, 64.5; HRMS (ESI) calcd for $C_{19}H_{14}N_3O_3S_2$ $[M+H]^+$ 396.0477 found 396.0497.



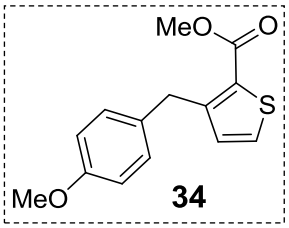
Typical procedure for the *γ*-acetoxylation of 28a: An appropriate amide **28a** (0.12 mmol, 30 mg), $Pd(OAc)_2$ (10 mol%, 2.5 mg), $PhI(OAc)_2$ (0.24 mmol, 77 mg) in anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction duration, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture through column chromatography furnished the corresponding acetoxylated amides **33.**

(2-(Benzo[*c*][1,2,5]thiadiazol-4-ylcarbamoyl)thiophen-3-yl)methyl acetate*(nb 701 a 33):*The compound **33** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color solid (23 mg, 65%); R_f (20% EtOAc/hexane) 0.4; mp: 141-143 ^oC; IR (KBr): 3055, 1665, 1418, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.49 (br. s, 1 H), 8.60 (d, 1 H, *J* = 7.3Hz), 7.76 (d, 1 H, *J* = 8.8Hz), 7.69-7.65 (m, 1 H), 7.54 (d, 1 H, *J* = 5.0Hz), 7.23 (d, 1 H, *J* = 5.0Hz), 5.50 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.7, 160.3, 154.9, 148.0, 139.2, 135.4, 131.1, 130.7, 130.0, 129.1, 116.3, 115.8, 60.3, 21.2; HRMS (ESI) calcd for $C_{14}H_{11}N_3NaO_3S_2$ $[M+Na]^+$ 356.0140 found 356.0124.



Typical Procedure for the hydrolysis of carboxamide 30a and preparation of the carboxylate derivative 34. To a solution of carboxamide **30a** (47 mg, 0.125 mmol, 1 equiv.) in dry methanol (3 mL) was added $BF_3.Et_2O$ (0.5 mL) added dropwise. Further, the resulting mixture was stirred at 80 °C for 36 h. Then, the reaction mixture was allowed to attain the rt. Next, neutralize the crude mixture by Et_3N (304 mg, 3 mmol) was added dropwise with stirring. After this, the solvent was evaporated in vacuum to afford the carboxylate derivative **34**.

Methyl 3-(4-methoxybenzyl)thiophene-2-carboxylate (34): The compound **34** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless liquid (27 mg, 83%); R_f (20% EtOAc/hexane) 0.50; IR (DCM): 1709, 1610, 1511, 1413, 1074 cm-1; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (d, 1 H, *J* = 5.1 Hz), 7.17 (d, 2 H, *J*= 8.6 Hz), 6.86-6.84 (m, 3 H), 4.35 (s, 2 H), 3.90 (s, 3 H), 3.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 163.1, 158.0, 149.7, 132.3, 131.0, 130.4, 129.8, 126.4, 113.9, 55.3, 51.9, 34.4; HRMS (ESI) calcd for $C_{14}H_{15}O_3S$ $[M+H]^+$ 263.0742; found 263.0736.



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Chapter 5

Pd-(II)-catalyzed arylation of *ortho*-C-(sp^2)-H bonds of chiral and nonchiral methyl/ ethyl benzylamine picolinamides

Inactivated C-H bonds are among the simplest and most common structural motifs in the naturally occurring organic molecules, and they are the ideal target for expansion of new chemical transformations based on catalytic activation and functionalization. The inactivated C-H bonds have the potential to simplify the synthesis of complex molecules significantly. Transition metal catalysis has emerged as a powerful tool to convert these unreactive bonds into carbon-carbon and carbon-heteroatom bonds.[1-2] Currently, most of the example involving sp^2/sp^3 β- and γ-C-H bond functionalization are present in literature, using various transition metals such as, Pd, Ru, Rh, Co, Ni and Fe etc.[3-6] Accordingly, diverse directing group have been developed for the synthesis of C-C and C-X bonds via the transition metal catalyzed C-H activation/ functionalization. Some of the remarkable directing groups used in this field such as pyridine, 8-aminoquinoline, pyridine *N*-oxides, pyrazole, oxime, amide, carbamate, acid are successfully applied for sp^2 C-H bond functionalization. These directing group initially synchronize with transition metal bring the coordinating metal species to the close propinquity to the C-H bond, resulting the enrichment of selectivity.[1,7] Accordingly, the chapter 5 revealed some outstanding paper dealing with the directing group based functionalization/activation γ-C-(sp^2)-H that are significant to this thesis work. Parallel to the literary works, a part of this thesis (Chapter 5) envisages exploring the Pd-(II)-catalyzed directing group assisted C-H functionalization of chiral/ nonchiral methyl benzylaminepicolinamide system.

a) Importance of benzylamine derivatives.

Benzylamine is found in Moringa oleifera, a plant used to treat diabetes in traditional medicine, derivatives are also equally important class of biologicallyand medicinal active compound which serve as synthetic building blocks in organic synthesis. Chiral amines have been established to be potent pharmacophores for defining new pharmaceutical drugs or alkaloids; for occurrence, Rivastigmine is selectively used for Alzheimer's disease, *R*-etomidate and repaglinide are generally used asanaesthetic and antidiabetic respectively. Cinacalcet and sertraline are used explicitly for the hyperparathyroidism and antidepressant agent, etc (Figure 1). Next, both the enantiomers of γ-methyl-benzylamine or 1-

phenylethylamine remain as attractive chirality sources in various asymmetric transformations (Figure 1).[8,9,10a,b] This Chiral auxiliary use as resolving agent's chiral ligands in catalytic processes and synthetic chiral auxiliaries in stereo differentiating reactions of the prochiral substrate. It is worth to mention that benzylamine and their chiral derivatives play a crucial role in the organic synthesis and asymmetric transformations. In this chapter, some of the recent development that occurred to regioselective and stereoselective arylation of *γ*-methyl-benzylamine and the construction of chiral derivatives are described.

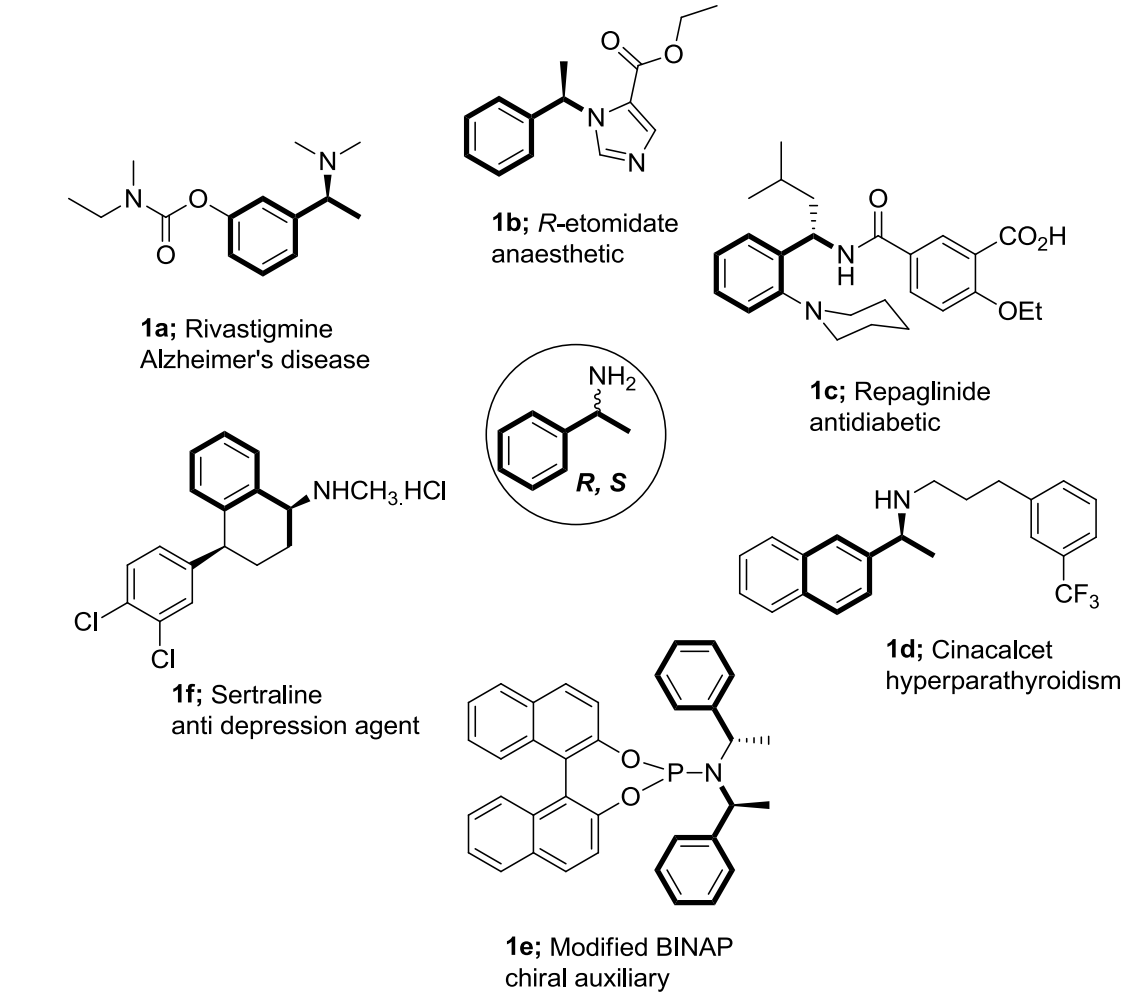
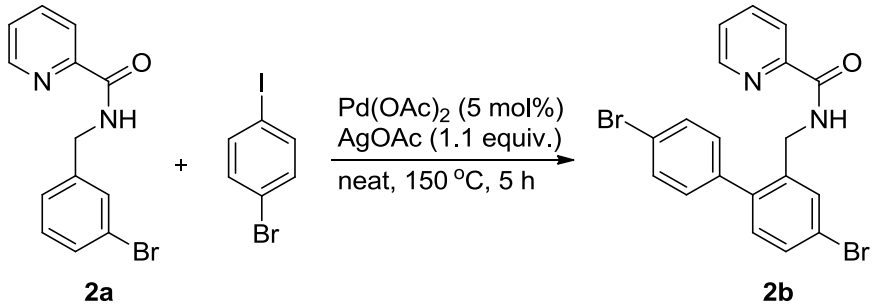


Figure 1 Biologically active molecule containing chiral methyl benzylamine moiety (**1a-f**).

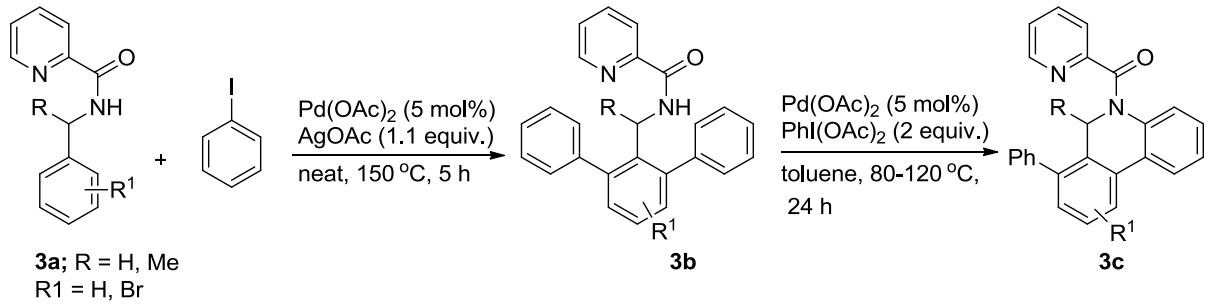
Representative reports dealing on the γ-C-(sp^2)-H bond of chiral/nonchiral benzylamine/ methyl benzylamine system which is related to the result of this work.

Daugulis and co-workers[10c] reported picolinamide directed γ-C-(sp^2)-H activation of the benzylamine derivatives via five-membered palladacycles. The palladium (II)-catalyzed direct γ-C-(sp^2)-H arylation of benzylamine derivative **2a** with disubstituted halide benzene in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst and 1.1 equiv. of AgOAc as an oxidant/additives in neat reaction condition at 150 ^oC for 5 h offered arylated product **2b** in excellent yield (Scheme 1).



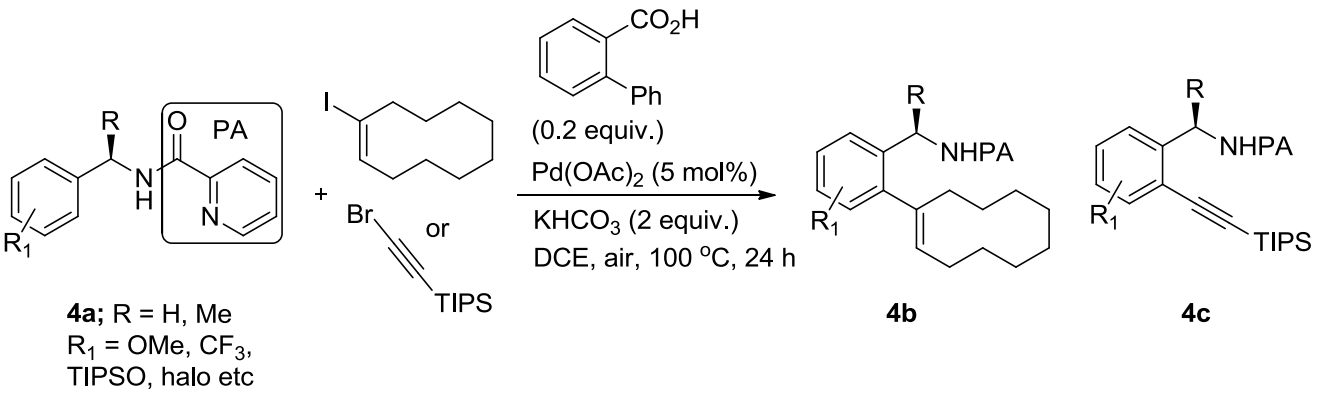
Scheme 1 Picolinamide directed γ-C-(sp^2)-H arylation of amine derivative **2a.**

Daugulis and co-workers[10d] reported picolinamide directed cyclization of arylated γ-C-(sp^2)-H of the benzylamine derivatives **3b**. The Pd-(II)-catalyzed cyclization of arylated benzylamine derivative **3b** in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst and 2 equiv. of $PhI(OAc)_2$ as an oxidant/additives in toluene at 80-120 ^oC for 24 h offered cyclized product **3b** in excellent yield (Scheme 2).



Scheme 2 Picolinamide directed cyclization of amine derivative **3b.**

Chan and co-workers[10e] reported picolinamide directed alkenylation and alkynylation of γ-C-(sp^2)-H bond of monosubstituted benzylamine system **4a**. The reaction of substituted benzylpicolinamide system **4a** reacts with a wide range of alkenylating agent (derivatives of vinyl halide) or alkynylating agent (bromo derivatives of acetylene) in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst, $KHCO_3$ (2 equiv.) as a base and 0.2 equiv. of ortho-phenyl benzoic acid as carboxylate promoter in DCE solvent under an air atmosphere at 100 ^oC for 24 h offered alkenylated and alkynylated product **4b**/**4c** in good yield (Scheme 3)

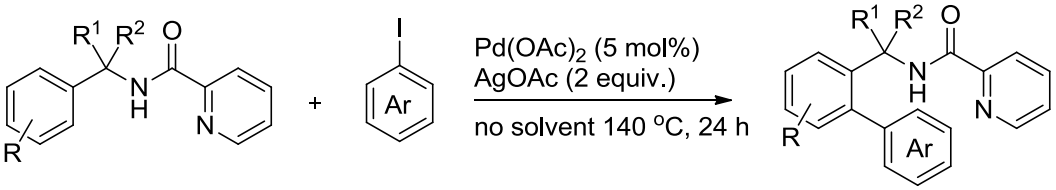


4a; R = H, Me
R_1 = OMe, CF_3,
TIPSO, halo etc

4b **4c**

Scheme 3 Picolinamide directed alkenylation/ alkynylation of benzylamine derivative **4a.**

Daugulis and co-workers[10f] reported auxiliary assisted Pd(II)-catalyzed arylation of γ-C-(sp^2)-H bond of benzylamine system **5a**. The Pd(II)-catalyzed reaction of benzylamine derivative **5a** with a large variety of aryl iodide sources in the presence of $Pd(OAc)_2$ (5 mol%), 2 equiv. of AgOAc in neat reaction condition at 140 ^oC for 24 h offered desired product **5b** in excellent yield (Scheme 4).



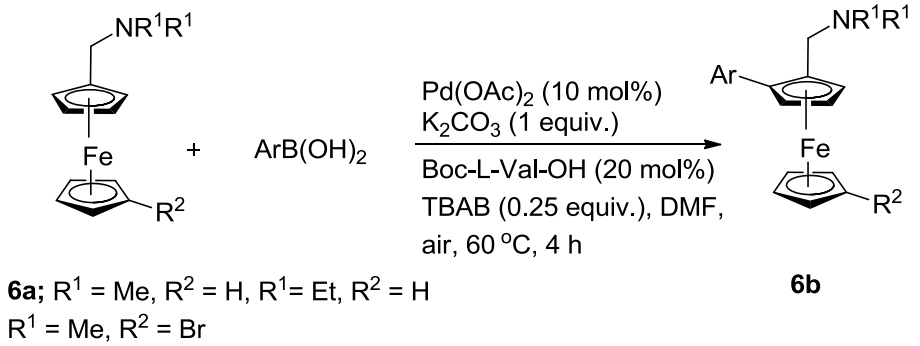
5a; R^1 = R^2 = H or Me
R = H, OMe,

5b

Scheme 4 Picolinamide directed arylation of benzylamine derivative **5a.**

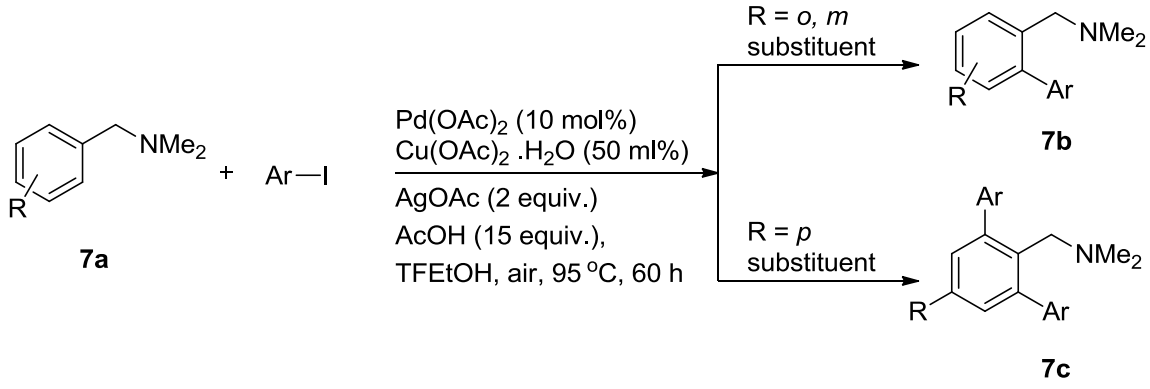
You and co-workers[10g] reported the enantioselective synthesis of chiral ferrocene via Pd(II)-catalyzed arylation of γ-C-(sp^2)-H bond of ferrocene amines system **6a.** The Pd(II)-catalyzed

reaction of ferrocene amines system **6a** with aryl boronic acid as an aryl source in the presence of $Pd(OAc)_2$ (10 mol%), 1 equiv. of K_2CO_3, by using 20 mol% Boc-L-Val-OH as chiral auxiliary and 0.25 equiv. of TBAB in DMF solvent under an air atmosphere at 60 ^oC for 4 h offered the desired product **6b** in an excellent enantioselective manner ee>98% (Scheme 5).



Scheme 5 Enantioselective arylation of ferrocene amine system **6a**.

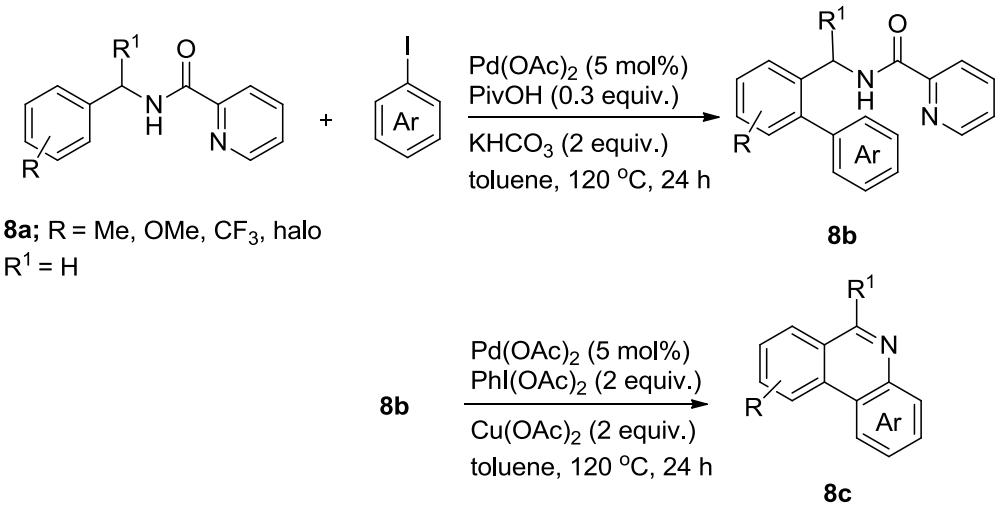
Zhang and co-workers[10h] reported Pd(II)-catalyzed arylation of γ-C-(sp^2)-H bond of *N*,*N*-dimethylbenzylamine system **7a**. The **7a** reacts with a wide range of aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) and 50 mol% of $Cu(OAc)_2.H_2O$, 2 equiv. of AgOAc, 15 equiv. of AcOH in TFEtOH solvent under air atmosphere at 95 ^oC for 65 h afford to mono and bis arylated product **7b** and **7c** (Scheme 6).



Scheme 6 Arylation of *N*, *N*-dimethylbenzylamine system **7a.**

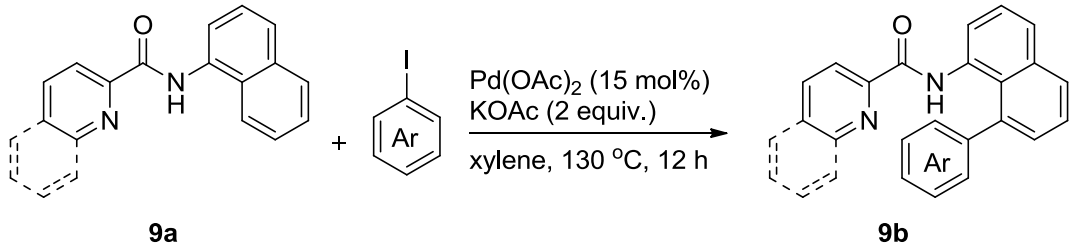
Chan and co-workers[10i] reported the picolinamide assisted direct *ortho* arylation of γ-C-(sp^2)-H bond of benzylamine system **8a**. The **8a** reacts with a wide range of aryl iodide in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst, and instead of silver salt, they employed 0.3 equiv. of PivOH as an additive, 2 equiv. of $KHCO_3$ as a base in toluene solvent under a

nitrogen atmosphere at 120 ^{o}C for 24 h lead to mono and bis arylated product **8b** (Scheme 6). Further, synthesis of phenanthridines derivative, the reaction of derivative **8b** with 5 mol% of $Pd(OAc)_2$ andthe mixture of an oxidant/ additive, 2 equiv. of $PhI(OAc)_2$ and 2 equiv. of $Cu(OAc)_2$ in toluene at 120 ^{o}C for 24 h lead to the cyclized product **8c** in good yield (Scheme 7)



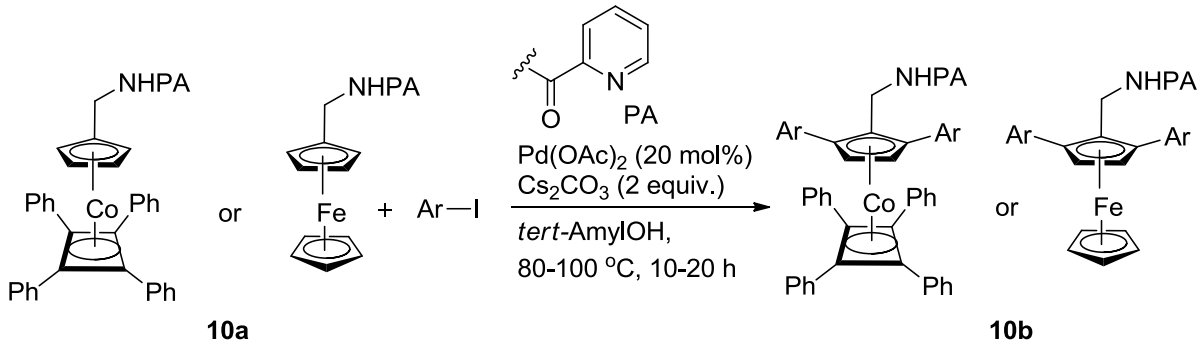
Scheme 7 Synthesis of phenanthridine derivative from **8a** to **8c** via **8b.**

Qi and co-workers[10j] reported the quinolinamide bidentate directing group for the regioselective arylation of γ-C-(sp^2)-H bond of naphthylamides system **9a**. The Pd(II)-catalyzed reaction of **9a** with aryl iodide in the presence of Pd-catalyst by using KOAc instead of Ag salt in xylene solvent at 130 ^{o}Cfor 12 h offered arylated product **9b** in high regioselective manner (Scheme 8).



Scheme 8 Quinolinamide directed regioselective arylation of system **9a**.

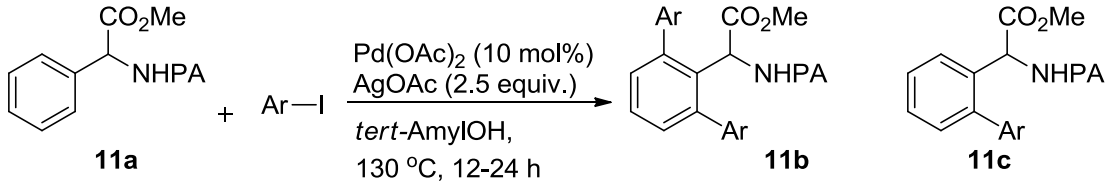
Elias and co-workers[10k] reported picolinamide directed γ-C-(sp^2)-H bond arylation of sandwich compound **10a**. The reaction of sandwich compound **10a** with aryl iodide sources in the presence of $Pd(OAc)_2$ (20 mol%), 2 equiv. of Cs_2CO_3 in *tert*-AmylOH at 80-100 ^{o}C for 10-20 h lead to bis-arylation of sandwich compound **10a** (Scheme 9).



10a **10b**

Scheme 9. Picolinamide directed arylation of sandwich compound **10a**.

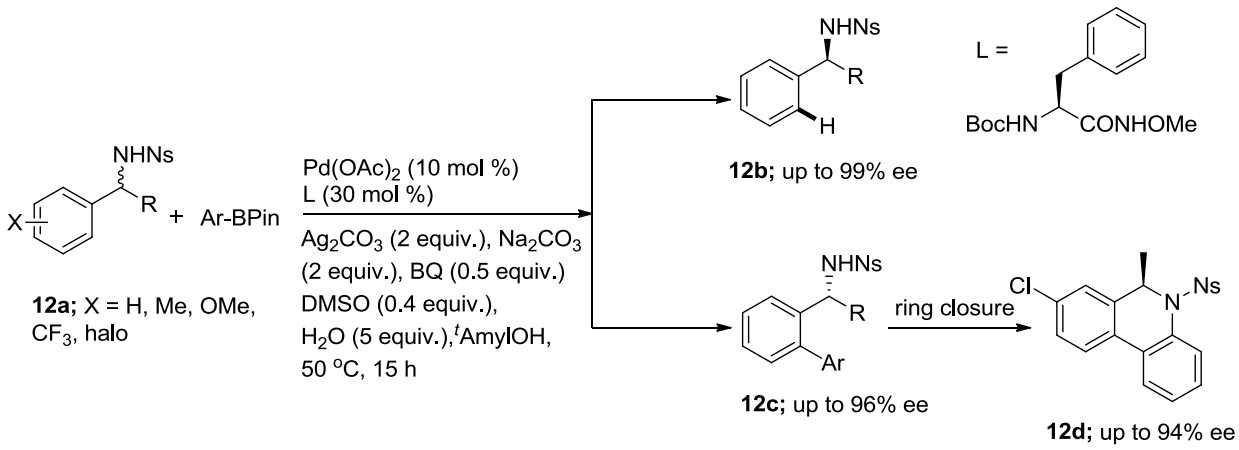
Jiang and co-workers[10l] recently reported the picolinamide directed arylation γ-C-(sp^2)-H bond of unnatural α-aminoacid **11a**. The Pd(II)-catalyzed C-H activation of α-aminoacid system **11a** with the variety of aryl iodide sources in the presence of $Pd(OAc)_2$ (10 mol%), 2.5 equiv. of AgOAc in *tert*-AmylOH at 130 ^oC for 12-24 h lead to homo bisarylationas major product and mono arylation as minor product of α-aminoacid system **11a** (Scheme 10).



11a **11b** **11c**

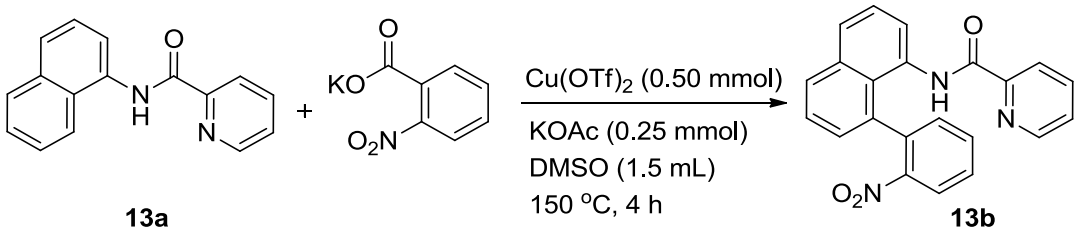
Scheme 10 Picolinamide directed arylation of unnatural α-aminoacid system **11a**.

Yu and co-workers[10m] reported readily removable Nosyl (Ns) protected amino group as the directing group for Pd(II)-catalyzed enantioselective kinetic resolution of benzylamines has been achieved by using chiral mono-*N*-protected α-amino-*o*-methylhydroxamic acid (MPAHA) ligands via C-H cross-coupling reaction. In this reaction, both chiral benzylamines and ortho-arylated benzylamines are obtained in high enantiomeric purity. The reaction of protected amine **12a** with a wide range of aryl boric ester derivatives in the presence of $Pd(OAc)_2$ (10 mol %), 30 mol % of ligand, 2 equiv. of Ag_2CO_3, 2 equiv. of Na_2CO_3 and 0.5 equiv. of BQ in DMSO/H_2O and *tert*-AmylOH at 50 ^oC for 15 h offered **12b** and **12c** in highly enantioselective (ee > 99) manner (Scheme 11). Then **12c** could be further transformed into chiral 6-substituted 5,6-dihydrophenanthridines as significant structural motifs in natural products and bioactive molecules (Scheme 11).



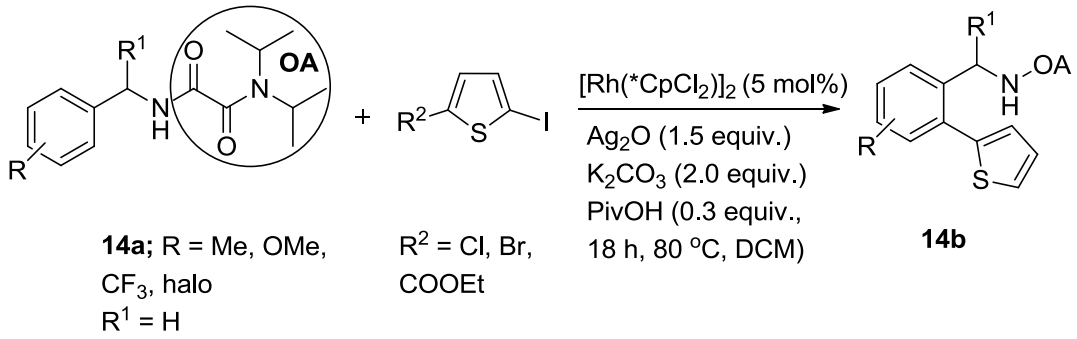
Scheme 11 Nosyl directed kinetic resolution of benzylamines **12a**.

Miura and co-workers[10n,f] reported picolinamide directed Cu-catalyzed decarboxylative coupling of *ortho*nitrobenzoic acid. The Cu-catalyzed decarboxylative coupling of system **13a** with *ortho*nitrobenzoic acid in the presence of $Cu(OTf)_2$ (0.50 mmol) as a catalyst, 0.25 mmol of KOAc as a base in DMSO solvent at 150 ^oC for 4 h offered the product **13b** in moderate yield (Scheme 12).



Scheme 12 Picolinamide directed decarboxylative arylation of system **13a**.

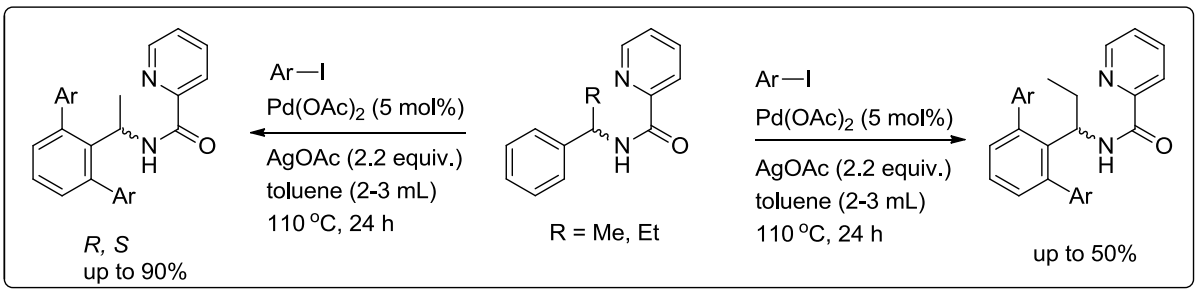
Zhao and co-workers[10o] reported the oxylylamide directed Rh-catalyzed heteroarene coupling of 2-iodo thiophene substituents. The substrate **14a** react with a variety of 2-iodo thiophene substituents in the presence of $[Rh(*CpCl_2)]_2$ (5 mol%) and 1.5 equiv. of Ag_2O , 2.0 equiv. of K_2CO_3, 0.3 equiv. of PivOH in DCM solvent at 80 ^oC for 18 h offered the desired product **14b** in good yield (Scheme 13).



Scheme 13 Oxylylamide directed heteroarene coupling of system **14a**.

Given the importance of aryl-substituted arylation are often utilized as medical potent in medicinal chemistry achiral/chiral methyl-benzylamine is a necessary functionality present in natural products, biological molecules, metabolic intermediate and pharmaceuticals. Increase in demand for chiral/ achiral methyl-benzylamine derivative has resulted in the need for simple, easy to use, cheap, and reliable methods for the determination of achiral compounds. In this chapter of the thesis work, we are intended to develop metal catalyzed stereoselective C-H functionalization of achiral/chiral 1-phenylethylpicolinamide*via* palladium-catalyzed direct arylation to prepare bis-substituted optically active 1-phenylethylpicolinamide derivatives (Scheme 14).

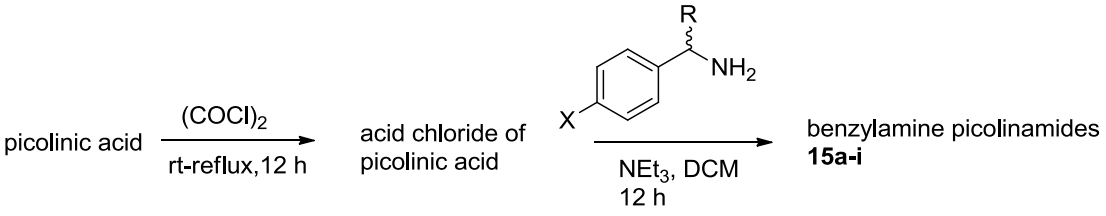
This work

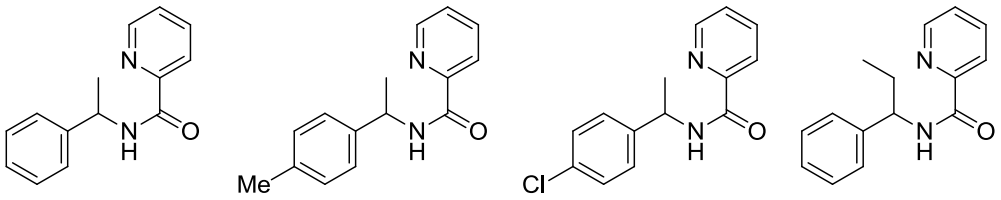


Scheme 14 Picolinamide assisted synthesis of bis arylated methyl-benzylamines chiral/ achiral derivatives.

Result & discussion

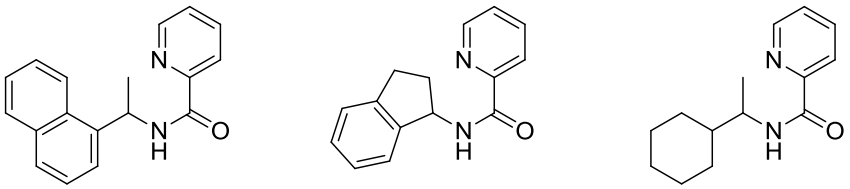
To start our study, the development of bis arylated optically active and inactive methyl-benzylamines, following the known literature procedure, achiral/chiral 1-phenylethylpicolinamide **15a-i** system prepared from various chiral/achiral methyl-benzylamine and ethyl-benzylamine with the bidentate directing group as picolinic acid chloride system (Scheme 15). Simultaneously, we also prepared picolinamide having different substrate **16a-c** such as methyl naphthylamine, methylcycolohexylamines,etc. Along with that, to check the directing group effect on reaction condition, we prepared methyl-benzylamine carboxamides system **17a-c** by using a variety of directing groups such as pyrazinamide, oxylylamide,andquinolinamide,etc (Scheme 15).





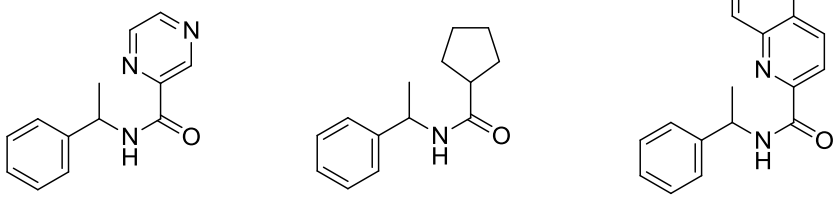
15a; RS **15b**; R **15c**; S **15d**; RS **15e**; R **15f**; S **15g**; R **15h**; S **15i**; RS

ineffective substrate



16a; 0% **16b**; 0% **16c**; 0%

ineffectve DG



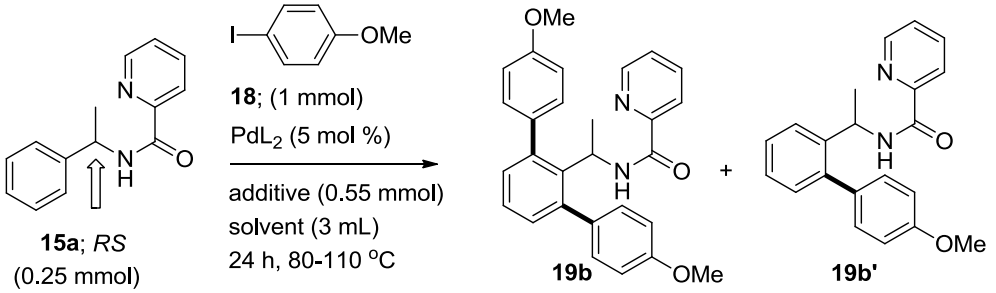
17a; <30% **17b**; 0% **17c**; 0%

Scheme 15 Preparation of various picolinamide system: substrates employed for investigating the γ-C(sp^2)-H arylation (Conditions: Substrate (0.25 mmol), **18** or ArI (1 mmol), $Pd(OAc)_2$ (5 mol%), AgOAc (0.55 mmol), toluene (2-3 mL), 24h, and 110 °C (the arylations reactions using **15a-i** and **17a** were successful as discussed in the results and discussion part and the arylations with **16a-c** and **17b-c** were not successful).

To evaluate the feasibility of this methodology, 1-phenylethylpicolinamide **15a** was chosen as a examine substrate treated with iodoanisole **18** under various palladium catalyzed conditions. we performed several reactions conditions (Table 1). The C-H functionalization reaction of **15a** with 1-iodo-4-methoxybenzene **18** in the absence of a palladium catalyst did not afford any product under toluene condition (entry 1, Table 1). The Cγ-C(sp^2)-H arylation on 1-phenylethylpicolinamide system **15a** not offered any product **18** in the absence of additive (entry 2, Table 1). It means additive is necessary for the reaction by two reasons, first to activate the aryl iodide by abstracting the halide, and forms reactive species in the reaction. And second, to helps the conversion of Pd-catalyst from Pd(II) to Pd(IV) in the oxidative addition step. The reaction of 1-phenylethylpicolinamide **15a** (0.25 mmol) with aryl iodide **18** (1.0 mmol) in presence of an additive AgOAc (0.55 mmol) and 5 mol% of the $Pd(OAc)_2$ catalyst afforded the *bis* arylated 1-phenylethylpicolinamide **19b** in 90% yield (entry 3, Table 1). Then, we examine the various additive for the Pd-catalyzed C-(sp^2)-H arylation reaction such as Ag_2CO_3, K_2CO_3, KOAc and $PhI(OAc)_2$, etc. The Pd-catalyzed C-(sp^2)-H arylation of 1-phenylethylpicolinamide **15a** with **18** in the presence of Ag_2CO_3 and $PhI(OAc)_2$ did not give the desired product **19b** (entry 4 and 7, Table 1). The Pd(II)-catalyzed C-(sp^2)-H arylation of 1-phenylethylpicolinamide **15a** with aryl iodide **18** in the presence of K_2CO_3 and KOAc afforded very less product **19b** in less than 5% and 22% respectively (entry 5 and 6, Table 1). Further, we moved to check the role of various Pd-catalyst in the reaction such as $PdCl_2$, $Pd(TFA)_2$, $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$, etc. The Pd(II)-catalyzed C-(sp^2)-H arylation of 1-phenylethylpicolinamide **15a** with aryl iodide **18** in the presence of $PdCl_2$ and $Pd(TFA)_2$ instead of $Pd(OAc)_2$ leads to the very less amount of product **19b** in 21-33% respectively (entry 8 and 9, Table 1). However, the C-(sp^2)-H arylation of 1-phenylethylpicolinamide **15a** with aryl iodide **18** in the presence of $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ furnished to the product **19b** in 20 and 0% yields respectively (entry 10 and 11, Table 1). As we know the solvent play a crucial role in the C-H activation reaction condition, so that, we optimized the feasibility of various solvents such as 1,2-DCE, 1,4-dioxane, ^{t}BuOH and ^{t}AmylOH. The Pd-catalyzed C-(sp^2)-H arylation of 1-

phenylethylpicolinamide **15a** with **18** using solvent 1,2-DCE, 1,4-dioxane afforded the desired product **19b** in 20 and 0 % yields (entry 12-13, Table 1). However, the Pd-catalyzed C-(sp^2)-H arylation of 1-phenylethylpicolinamide **15a** with **18** in ^{t}BuOH, and ^{t}AmylOH gave the product **19b** in 0 and 10 % yields respectively (entry 14 and 15, Table 1).

Table 1 Optimization reaction conditions.



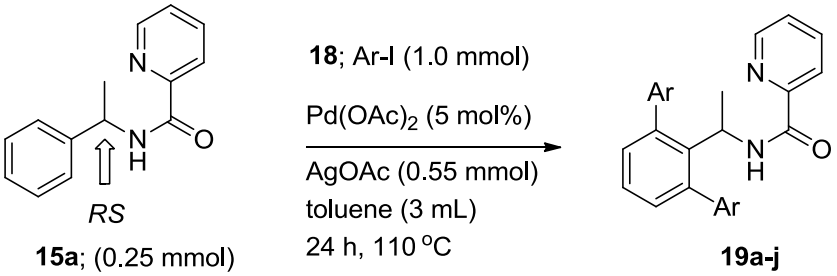
entry	PdL_2	additive	solvent	*t* (°C)	**19b** yield (%)[a]	**19b'**
1	nil	AgOAc	toluene	110	0	-
2	$Pd(OAc)_2$	nil	toluene	110	0	-
3	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**90** (<40)[b]	-
4	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	0	-
5	$Pd(OAc)_2$	K_2CO_3	toluene	110	<5	-
6	$Pd(OAc)_2$	KOAc	toluene	110	20	-
7	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0	-
8	$PdCl_2$	AgOAc	toluene	110	33	-
9	$Pd(TFA)_2$	AgOAc	toluene	110	21	-
10	$Pd(CH_3CN)_2Cl_2$	AgOAc	toluene	110	20	-
11	$Pd(PPh_3)_4$	AgOAc	toluene	110	0	-
12	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	20	-
13	$Pd(OAc)_2$	AgOAc	1,4-Dioxane	100	0	-
14	$Pd(OAc)_2$	AgOAc	^{t}BuOH	85	10	-
15	$Pd(OAc)_2$	AgOAc	^{t}AmylOH	110	35	-
16[c]	$Pd(OAc)_2$	AgOAc	toluene	110	15	-
17[d]	$Pd(OAc)_2$	AgOAc	toluene	110	36	-
18[e]	$Pd(OAc)_2$	AgOAc	toluene	110	60	-
19[f]	$Pd(OAc)_2$	AgOAc	toluene	110	90	-

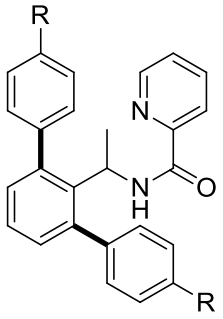
a= yield of the isolated product; b= 1 equiv (0.25 mmol) of AgOAc was used; c= 1 equiv (0.25 mmol) of 2; d= 2 equiv (0.50 mmol) of 2; e= 3 equiv (0.75 mmol) of 2; f= 4 equiv (1.0 mmol) of 2.

Further, we wished to check the effects of the amount of aryl iodide source in the reaction condition for getting the mono and *bis*-arylated 1-phenylethylpicolinamide product. So we start to optimize it whether the arylation of **15a** with fewer equivalents of **18** will give the *mono*-arylation products **19b'**. The arylation of **15a** with 1 equiv. of **18** did not provide the monoarylated products **19b'** but still finish up with *bis*-arylated product **19b** in 15% yield (entry 16, Table 1). A similar trend was experienced when the arylation of **15a** was carried out with 2 equiv. of **18** and in this case, the compounds **19b** and 1**9b'** were obtained in 36 and 0 % yields, respectively (entry 17, Table 1). These two reactions indicated that the *bis*-arylation of **15a** is a facile reaction though fewer equivalents of **18** were used. The arylation of **15a** with 3 equivalents of **18** gave the *bis*-arylated product **19b** in 60% yield (entry 18, Table 1). This reaction revealed that the second arylation of the product **19b** is a facile reaction and 3-4 equivalents of **18** are needed for obtaining the *bis* γ-C-(sp^2)-H arylated products **19b** in high yield (entry 18, Table 1). Furthermore, we also examine the arylation of **15a** (0.25 mmol) with **18** aryl iodide (4 equiv.) in the presence of 1 equiv. of AgOAc instead of 2.2 equiv. of AgOAc gave only the *bis*-arylated product **19b** in 36% yield (entry 3, Table 1).

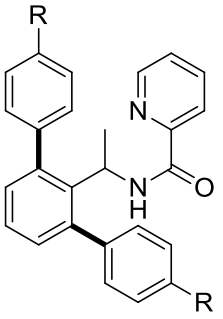
Under the best optimal conditions for the *bis*-arylation of the γ-C-(sp^2)-H bond of optically inactive 1-phenylethylpicolinamide **15a** with various aryl iodide sources. The Pd(II)-catalyzed picolinamide assisted γ-C-(sp^2)-H bond of achiral substrate **15a** with aryl iodide having the electron releasing group such as Me, Et, and OMe furnished the corresponding *bis*-arylated achiral 1-phenylethylpicolinamide product **19a-d** in 65-83% respectively (Table 2). The Pd(II)-catalyzed picolinamide assisted γ-C-(sp^2)-H bond of achiral substrate **15a** with aryl iodide having the electron deficient group such as F, Cl, and $COCH_3$ offered the corresponding *bis*-arylated achiral 1-phenylethylpicolinamide product **19e-g** in 53-65% respectively (Table 2). Then, the Pd(II)-catalyzed C-H arylation of the achiral 1-phenylethylpicolinamide **15a** using the 6-iodo-1,4-benzodioxane aryl iodide afforded the corresponding *bis*-arylated product **19h** in 76% yield. The Pd(II)-catalyzed C-H activation on the substrate **15a** with multi substituted aryl iodide such as dimethyl iodobenzene and dichloro iodobenzene also afforded the corresponding arylated product **19i-j** in 68-84% yield respectively, (Table 2)

Table 2 Synthesis of *bis*-arylated achiral 1-phenylethylpicolinamide derivative **19a-j**.

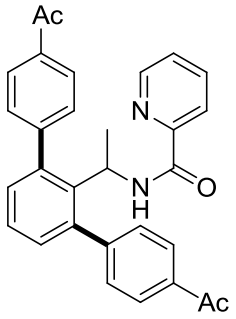




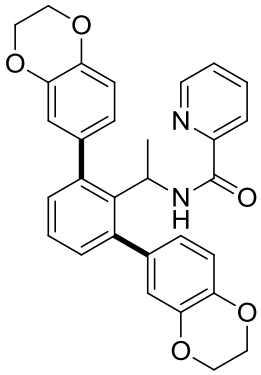
19a; R = H; 66%
19b; R = OMe; 83%
19c; R = Me; 65%
19d; R = Et; 67%



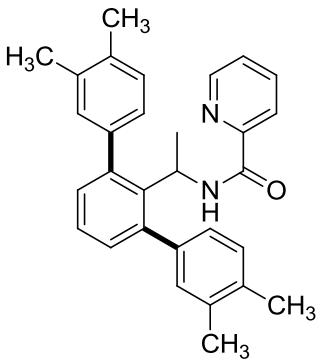
19e; R = F; 65%
19f; R = Cl; 53%



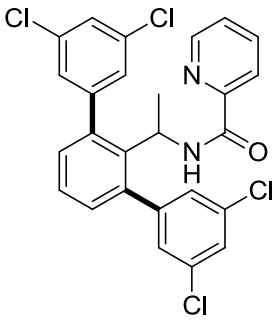
19g; 61%



19h; 76%



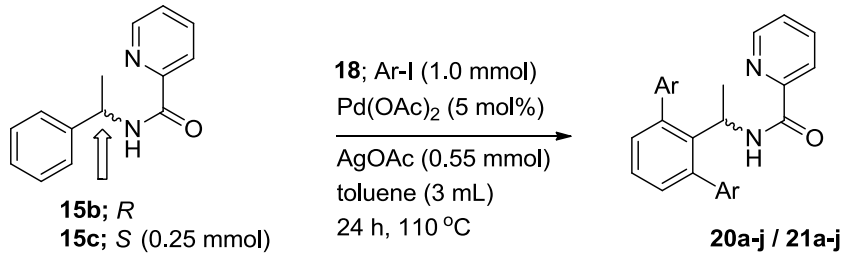
19i; 84%



19j; 68%

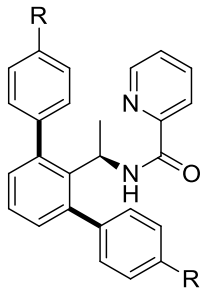
Subsequently, this methodology also applied to the Pd(II)-catalyzed C-H arylation of the γ-C-(sp^2)-H bond of the optically pure 1-phenylethylpicolinamide system and synthesize enantiomerically pure arylated 1-phenylethylpicolinamide derivatives. In this regard, the enantiomerically pure 1-phenylethylpicolinamide system **15b** (*R*-isomer) and **15c** (*S*-isomer) were prepared from their respective methyl benzylamine and picolinamide acid chloride (Scheme 15).

Table 3 Synthesis of bis arylated optically pure 1-phenylethylpicolinamide derivative **20a-j**/ **21a-j**.

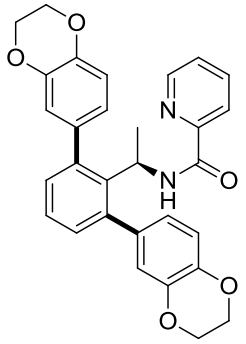


15b; *R*
15c; *S* (0.25 mmol)

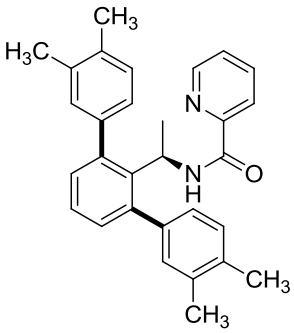
20a-j / 21a-j



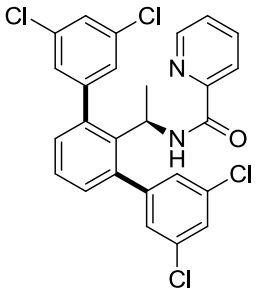
20a; R = H; 75%
20b; R = OMe; 90%
20c; R = Me; 66%
20d; R = Et; 51%
20e; R = F; 69%
20f; R = Cl; 55% (*ee* >99%)
20g; R = $COCH_3$; 85%



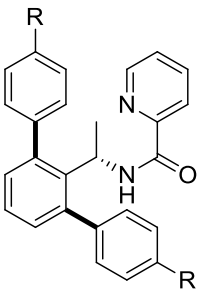
20h; 85%



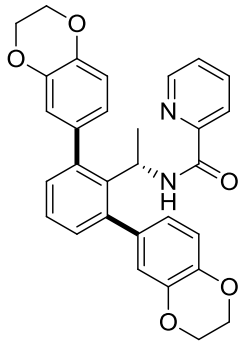
20i; 70%



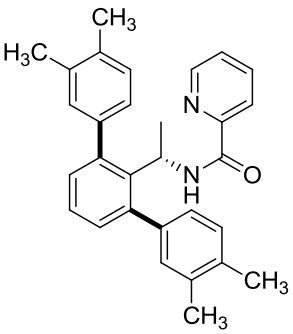
20j; 62%



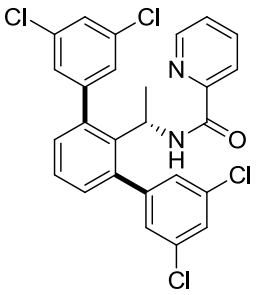
21a; R = H; 60%
21b; R = OMe; 67%
21c; R = Me; 82%
21d; R = Et; 55%
21e; R = F; 65%
21f; R = Cl; 40% (*ee* >99%)
21g; R = $COCH_3$; 45%



21h; 72%



21i; 71%



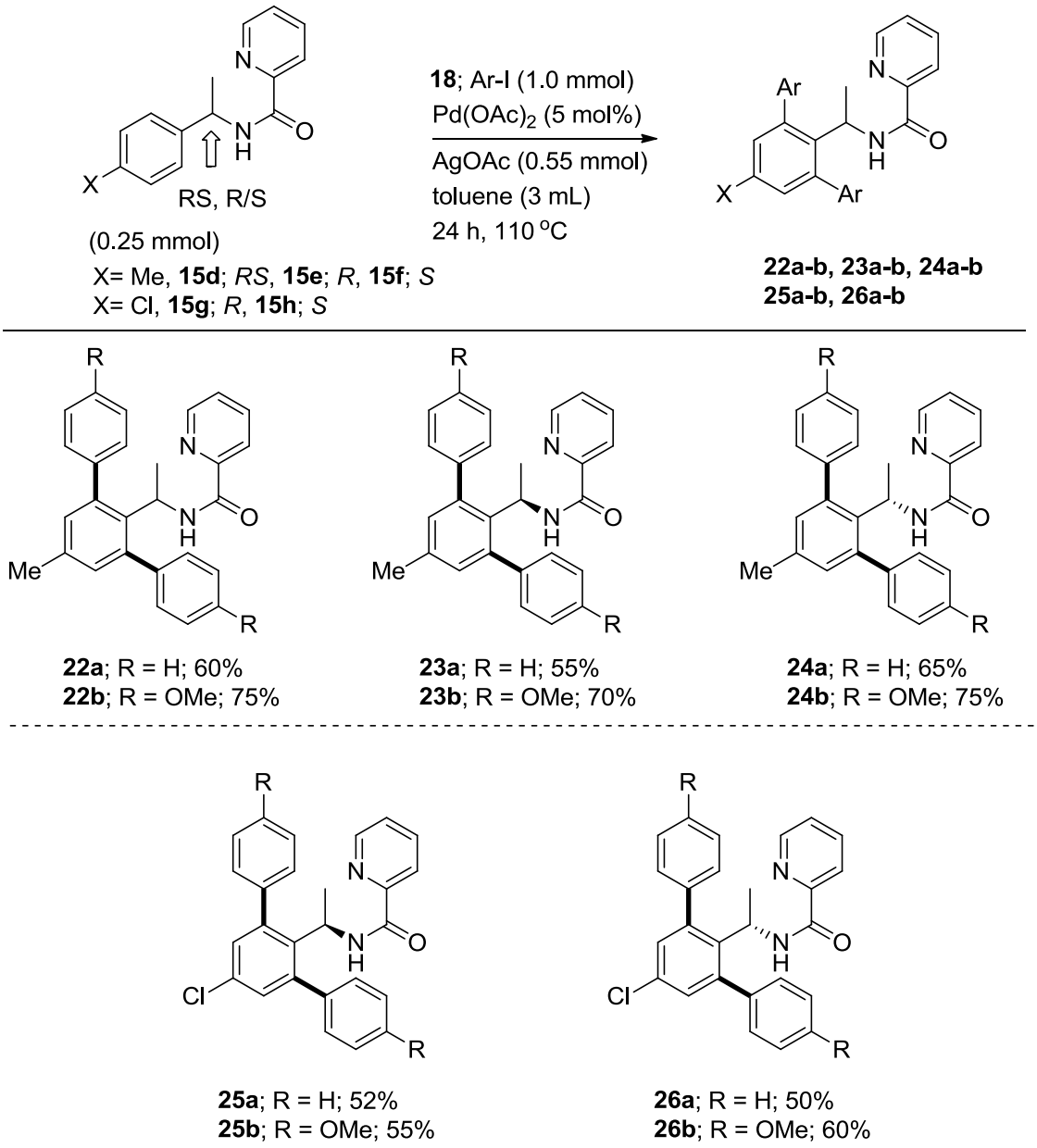
21j; 61%

The Pd(II)-catalyzed γ-C-(sp^2)-H arylation of optically pure 1-phenylethylpicolinamide system **15b** and **15c** with various aryl iodide having a different substituent in the phenyl ring such as OMe, Me, Et, halo, and Ac was performed. These reactions of the corresponding

optically pure substrate 1-phenylethylpicolinamide **15b** (*R*-isomer) and **15c** (*S*-isomer) offered to the product **20a-g** and **21a-g** in 60-90 % and 60-80% yield, respectively (Table 3) Then, the Pd(II)-catalyzed C-H arylation of the optically pure 1-phenylethylpicolinamide **15b/15c** using the 6-iodo-1,4-benzodioxane aryl iodide afforded the corresponding bis arylated product **20h/21h** in 72-85% yield. The Pd(II)-catalyzed C-H activation on the substrate **15b/15c** with multi substituted aryl iodide such as dimethyl iodobenzene and dichloro iodobenzene also lead to the corresponding arylated product **20i-j** and **21i-j** in 62-70% and 61-71% yield respectively, (Table 3).

Successively, to explore the generality and scope of the reaction condition we performed the γ-C-(sp^2)-H arylation of various chiral and achiral substrate containing different substituents in the aryl ring like Me and Cl. Accordingly, we synthesized the achiral bis arylated products **22a-b** by using phenyl iodide and iodo anisole in 60-75% yields from their respective starting material 1-*p*-tolylethylpicolinamide **15d** (Table 4). The Pd(II)-catalyzed γ-C-(sp^2)-H arylation of optically active substrate **15e** and **15f** treated with phenyl iodide and iodo anisole offered to *bis*-arylated enantiomerically pure product **23a-b** and **24a-b** in 50-75% yield respectively (Table 4). The Pd(II)-catalyzed γ-C-(sp^2)-H arylation of optically pure substrate **15g** and **15h** reacted with phenyl iodide, andiodo anisole furnished to bis-arylated optically active product **25a-b** and **26a-b** in 50-60% yield respectively (Table 4).

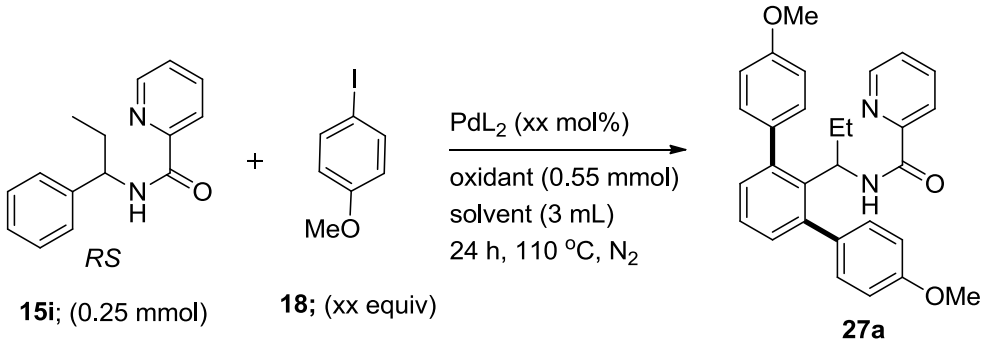
Table 4 Synthesis of *bis*-arylated optically pure substituted 1-phenylethylpicolinamide derivative **22-26(a-b).**



Further, we wished to extend the substrate scope of reaction condition, we performed the γ-C-(sp^2)-H arylation on 1-phenylpropylpicolinamide (0.25 mmol) **15i** with 4-iodoanisole (1.0 mmol) **18** in the presence of AgOAc additive (2 equiv.) and 5 mol% of $Pd(OAc)_2$ catalyst, which leads to the mixture of product as final result **27a**. Its indicate that the reacting substrate 1-phenylpropylpicolinamide (**15i**) having two active position γ-C-(sp^2)-H and γ-C-

(sp^3)-H for arylation because of that the Pd(II)-catalyst slightly confusing between two active position and resultant the mixture of the product as an outcome. So, the get rid of this situation we start a short optimization reaction by controlling mol% of Pd catalyst and the equivalent of iodo anisole will give the pure γ-C-(sp^2)-H arylated products **27a**. The arylation of **15i** with 1 equiv. of **18** in the presence of $Pd(OAc)_2$ (5 mol %) did not give the products **27a** (entry 1, Table 5). A similar trend was experienced when the arylation of **15i** was carried out with 2 equiv. of **18,** and in the presence of $Pd(OAc)_2$ (5 mol %), so many spots were obtained on (TLC) thin layer chromatography (entry 2, Table 5). The arylation of **15i** with 3 equivalents of **18** gave the *bis*-arylated product **27a** in 22% yield (entry 3, Table 5). The arylation of **15i** with 4 equivalents of **18** gave a mixture of product again **27a** (entry 4, Table 5). The Pd(II)-catalyzed arylation of **15i** with 3 equivalents of **18** in the presence of 10 mol % $Pd(OAc)_2$, offered pure bis product **27a** in 30% yield (entry 4, Table 5). This reaction revealed that the arylation of the product **27a** is a facile reaction and 3 equivalents of **18** and 10 mol% of $Pd(OAc)_2$ are needed for obtaining the *bis*γ-C(sp^2)-H arylated products **27a** in moderate yield (entry 5, Table 5).

Table 5 Optimization reaction conditions for **27a**

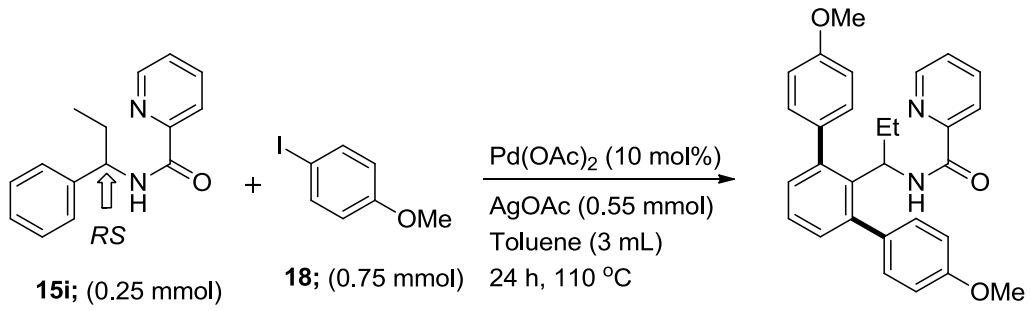


entry	PdL_2 (mol %)	oxidant	solvent (3 mL)	*t* (°C)	**27a** yield (%)
1[a]	$Pd(OAc)_2$ (5)	AgOAc	toluene	110	-
2[b]	$Pd(OAc)_2$ (5)	AgOAc	toluene	110	-
3[c]	$Pd(OAc)_2$ (5)	AgOAc	toluene	110	22
4[d]	$Pd(OAc)_2$ (5)	AgOAc	toluene	110	-
5[c]	$Pd(OAc)_2$ (10)	AgOAc	toluene	110	30

a = 1 equiv; b = 2 equiv; c = 3 equiv; d = 4 equiv of aryl iodide was used.

Next, the Pd(II)-catalyzed C-H activation on the substrate **15i** with 4-iodoanisole in the presence of AgOAc additive (3 equiv.) and 10 mol% of $Pd(OAc)_2$ catalyst was performed,

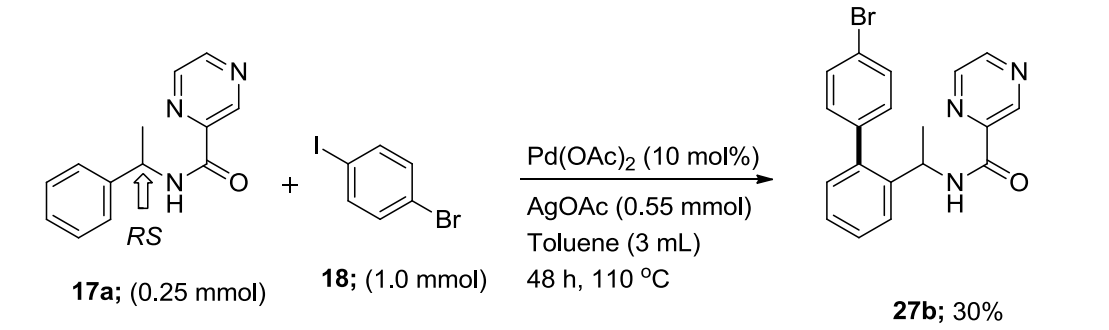
which lead to the bis-arylated 1-phenylpropylpicolinamide **27a** in 30% yield (Scheme 16). Unfortunately, we were not able to explore the derivative of this substrate 1-phenylpropylpicolinamide **15i**; various trails reaction was kept by using a variety of aryl iodide, e.g. 3-iodo toluene, 4-iodo acetophenone as well as 4-iodo methyl benzoate, etc, we could not be able to get any *bis*-product in pure form.



Scheme 16 Preparation of *bis*-1-phenylpropylpicolinamide system **27a**.

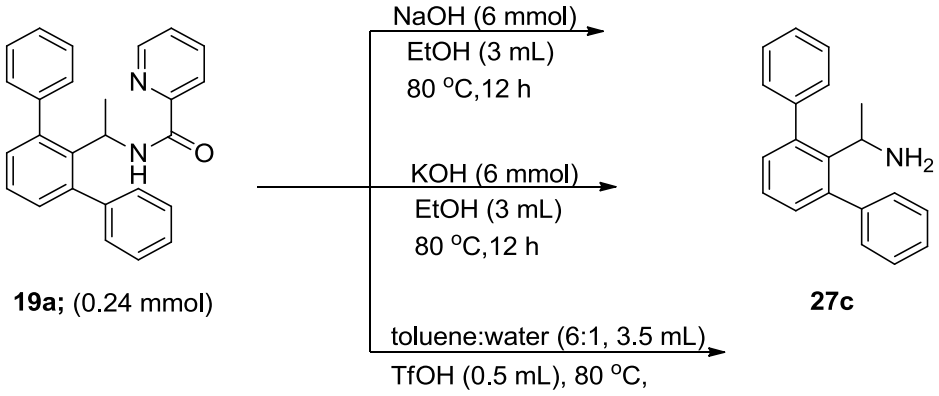
To examine the developed methodology and trails to extend the substrate scope, we did not get the arylated products from the corresponding starting material **16a-d**, which structurally resembles the 1-phenylethylpicolinamide system **15a**. To check the role of the directing group we assembled the various directing groups instead of picolinamide **17a-c** from their respective starting materials. The substrate **17a** where pyrazine serve as a directing group gave the only C-H activation product in very less yield. Rest of directing group is **17b-c** found to be ineffective (Scheme 15).

The Pd(II)-catalyzed C-H activation on the substrate 1-phenylethylpyrazine-2-carboxamide system **17a** with 4-Bromoiodobenzene **18** in the presence of AgOAc additive (4 equiv.) and 10 mol% of $Pd(OAc)_2$ catalyst lead to the *mono*-arylated 1-phenylethylpyrazine-2-carboxamide system **27b** in 30% yield (Scheme 17). The reasons for obtaining monoarylated product, is the number of heteroatom more in pyrazine directing group. So they can confuse the Pd-catalyst hence the reactivity of this directing group slow down. Similarly, For the arylation reaction, we need to more catalyst loading and extend the time from 24 h to 48 h.



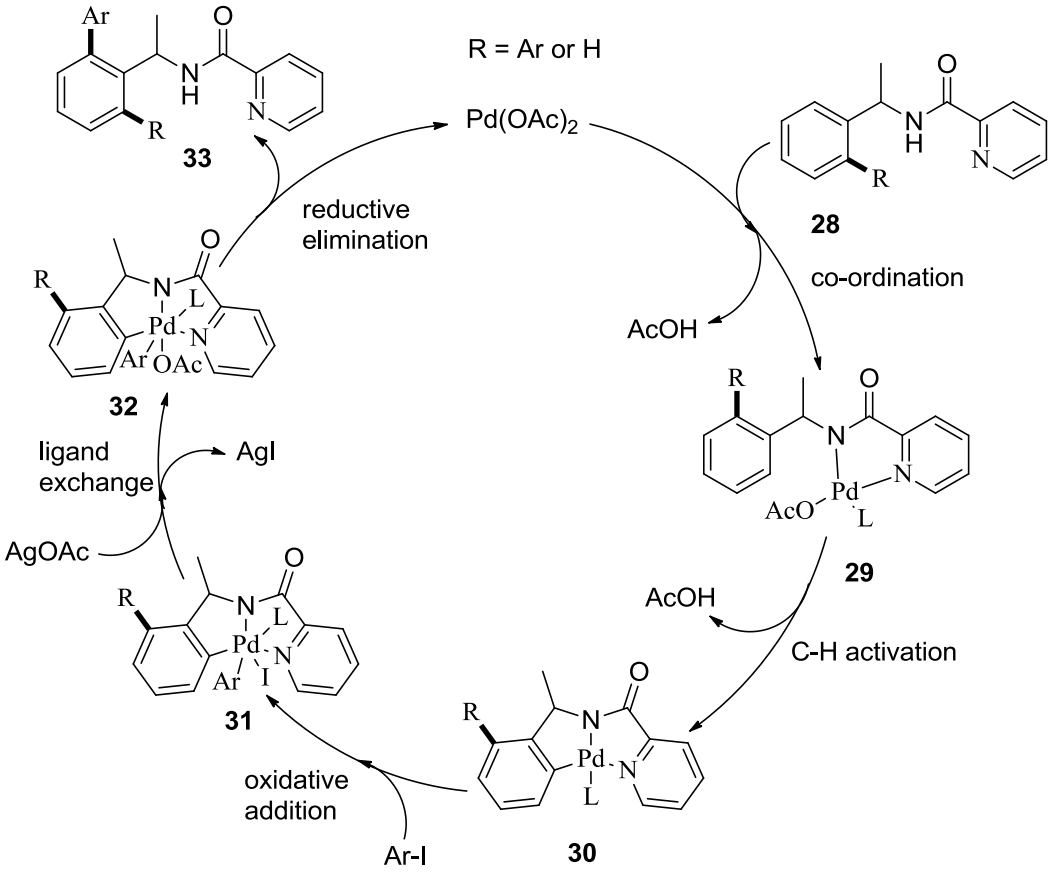
Scheme 17 Preparation of *bis*-arylated from the substrate **17a**.

Finally, we wished to remove the bidentate ligand picolinamide from the γ-C-(sp^2)-H *bis*-arylated achiral 1-phenylethylpicolinamide product **19a**. We treated the *bis*-arylated achiral 1-phenylethylpicolinamide substrate **19a** with various reaction conditions such as NaOH in EtOH, KOH in EtOH and TfOH in ratio of toluene: water; unfortunately we could not get desired product **27c** (Scheme 18).



Scheme 18 Trails towards the removal of directing from the substrate **19a**.

In concurrence with the mechanistic pathway studies by Chen[10e], a proposed mechanism for the directing group assisted $Pd(OAc)_2$-catalyzed AgOAc-promoted double C-H activation and direct γ-C(sp^2)-H arylation of methyl benzylamine furnished bis C-H arylation of methyl 1-phenylethylpicolinamide is depicted in the scheme 19.



Scheme 19 Plausible mechanism for the Pd(II)-catalyzed double C-H arylation of 1-phenylethylpicolinamide.

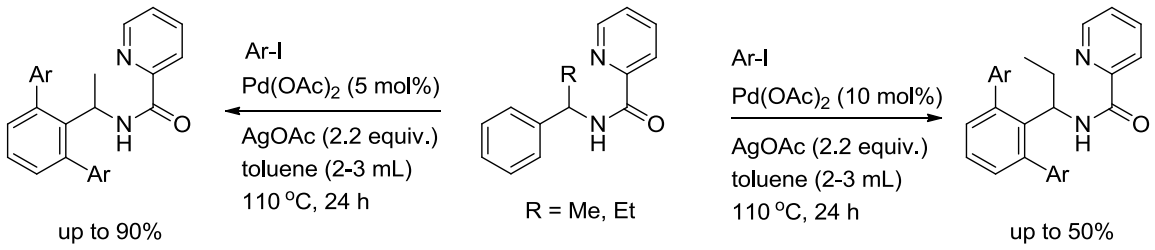
The polarimetry experiment of all *bis*-arylated compound **20a-j** and **21a-j** shows that all the compound are optically active in the present reaction condition. To check the purity of optical active compound, we also performed the HPLC analysis of the corresponding enantiomerically pure *bis*-arylated compound **20f/ 21f** revealed that the Pd(II)-catalyzed C-H arylation of the enantiomerically pure methyl benzylamine picolinamide system **15b/15c** resulted in the optically pure *bis*-arylated **20f/21f** with *ee*>99% under the experimental conditions.

Overall, while the γ-C-(sp^2)-H arylation on optically pure and achiral substrate **15a-I** were successful, our various attempts on the picolinamide directed alkylation, acetoxylation and intramolecular amination of the achiral substrate were not successful. In fact, the bidentate ligand picolinamide seems to be not assisting the C-N bond formation in the 1-

phenylethylpicolinamide system **15a**. Various aryl iodides with **16a-c** and **17a-c** starting material were used to examine their reactivity pattern. Unluckily, we were not able to get any arylated product. The C-(sp^2)-H activation on achiral and the optically pure substrate with aryl iodides containing electron withdrawing / electron releasing groups gave the *bis*-arylated optically pure product as the predominant compound in excellent yields (Table 3).

Summary and conclusion:

In conclusion, the chapter 5 revealed that the picolinamide serve as a directing group for C-(sp^2)-H bond activation on optically active benzylamine system. The scope and generality of this methodology giving the evidence by successive arylation of C-(sp^2)-H bond at the γ-position of the optically active benzylamine system. The picolinamide assisted γ-C-H activation method provides us to an alternative route to synthesize highly biologically active, medicinally potential optically active pure derivatives, which will find the remarkable application in the medicinal and natural science and their applied branches.



Experimental Section:

General: IR spectra were recorded as KBr pellets or thin films. ^1H / ^{13}C NMR spectra of sample were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from the QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under nitrogen atm. After the workup procedure organic layers were dried over anhydrous sodium sulphate. TLC analysis was performed on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are

reported, andyields of all the reactions were not optimized. Carboxamide starting materials were prepared by using the literature procedures.

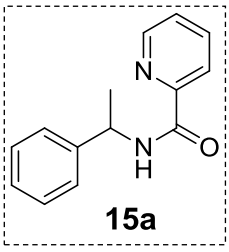
Procedure for the synthesis of carboxamides 15a-i, 16a-c 17a, and 17c.

An oven-dried RB flask was charged with an appropriate carboxylic acid (3 mmol, 1 equiv.) and anhydrous DCM (7-8 mL) and two-three drops (catalytic amount) of DMF. To this solution oxalyl chloride (3.6 mmol, 1.2 equiv.) was added dropwise at 0 °C. After this, the reaction mixture was stirred at rt for 12 h, and then, the solvent was removed under vacuum and diluted with DCM (5 mL the resulting acid chloride solution was instantly used in the next step without purification). Another oven-dried RB flask was charged with an appropriate amine or benzylamine derivatives (3 mmol, 1.0 equiv.), Et_3N (3.6 mmol, 1.2 equiv.), DMAP (0.1 mmol, 0.1 equiv.). To this solution, the acid chloride solution (obtained in the previous step) was added dropwise at 0 °C, and after the addition, the reaction mixture was warmed to rt and allowed to stirrer for overnight. Then, the crude reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (10-15 mL) and the organic layer were dried over anhydrous Na_2SO_4, evaporated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluant: EtOAc:Hexanes = 20:80) to afford the corresponding picolinamides **15a-i, 16a-c, 17a, and 17c.**

Procedure for the synthesis of carboxamide 17b:

An oven-dried RB flask containing 1-phenylethylamine (1 mmol) and Et_3N (1.2 mmol, 1.2 equiv.) was stirred for 5-10 min under nitrogen atmosphere. Then, to the reaction, RB flask anhydrous DCM (5 mL) was added followed by drop-wise addition of cyclopentane carbonyl chloride and the mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and twice with a saturated aqueous $NaHCO_3$ solution. The combined organic layer was dehydrated over Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh, EtOAc/hexanes = 20:80) furnished the corresponding product as white crystalline solid **17b**.

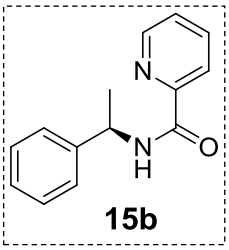
N*-(1-phenylethyl)picolinamide*(nb 91/98 sm 15a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15a** as a dirty white solid (650 mg, 98%); R_f (20% EtOAc/hexane) 0.5; mp: 134-136 ^oC; $[\alpha]^{25}_D = 0$ (c = 0.10, DCM); IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (m, 1H), 8.36 (d, 1H, J = 6.7 Hz), 8.22 (dt,



15a

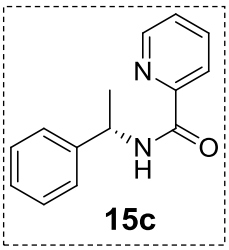
1H, J_1 = 7.8, J_2 = 0.8Hz), 7.88-7.83 (m, 1H), 7.45-7.42 (m, 3H), 7.39-7.35 (m, 2H), 7.31-7.26 (m, 1H), 5.38-5.31 (m, 1H), 1.65 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.4, 149.9, 148.0, 143.3, 137.4, 128.7, 127.3, 126.3, 126.2, 122.3, 48.8, 22.1; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO$ $[M+Na]^+$ 249.1004 found 249.1015.

(*R*)-*N*-(1-phenylethyl)picolinamide*(nb 95 sm 15b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15b** as a dirty white solid (600 mg, 88%); R_f (20% EtOAc/hexane) 0.5; mp: 134-136 ^{o}C; $[\alpha]^{25}_D$ = -7.12 (c = 0.10, DCM); IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (m, 1H), 8.36 (d, 1H, J = 6.7 Hz), 8.22 (dt, 1H, J_1 = 7.8, J_2 = 0.8Hz), 7.88-7.83 (m, 1H), 7.45-7.42 (m, 3H), 7.39-7.35 (m, 2H), 7.31-7.26 (m, 1H), 5.38-5.31 (m, 1H), 1.65 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.4, 149.8, 148.0, 143.3, 137.3, 128.7, 127.3, 126.2, 122.2, 48.8, 22.1; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO$ $[M+Na]^+$ 249.1004 found 249.1015.



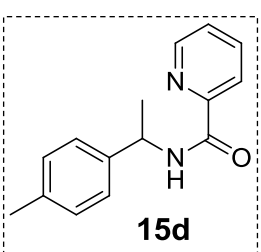
15b

(*S*)-*N*-(1-phenylethyl)picolinamide*(nb 118 sm 15c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15c** as a dirty white solid (540 mg, 80%); R_f (20% EtOAc/hexane) 0.5; mp: 134-136 ^{o}C; $[\alpha]^{25}_D$ = 8.17 (c = 0.10, DCM); IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (m, 1H), 8.36 (d, 1H, J = 6.7 Hz), 8.22 (dt, 1H, J_1 = 7.8, J_2 = 0.8Hz), 7.88-7.83 (m, 1H), 7.45-7.42 (m, 3H), 7.39-7.35 (m, 2H), 7.31-7.26 (m, 1H), 5.38-5.31 (m, 1H), 1.65 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.4, 149.8, 148.0, 143.3, 137.3, 128.7, 127.3, 126.2, 122.2, 48.8, 22.1; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO$ $[M+Na]^+$ 249.1004 found 249.1015.



15c

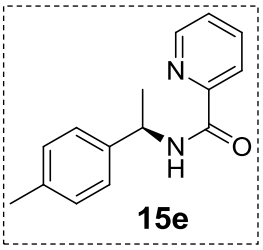
N*-(1-(*p*-tolyl)ethyl)picolinamide*(nb 339 sm 15d): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15d** as a faint orange solid (570 mg, 80%); R_f (20% EtOAc/hexane) 0.6; mp: 90-92 ^{o}C; $[\alpha]^{25}_D$ = 0.0 (c = 0.10, DCM); IR (KBr): 3055, 1673, 1515, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (d, 1H, J = 8.3Hz), 8.21 (d, 1H, J = 4.0 Hz), 7.99 (d, 1H, J = 7.8Hz), 7.45-7.41 (m, 1H), 7.09 (d, 2H, J =



15d

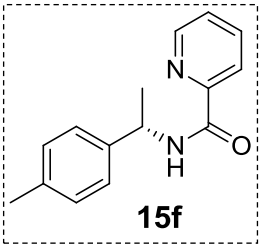
8.0Hz), 7.03-7.00 (m, 1H), 6.88 (d, 2H, *J* = 7.9Hz), 5.20-5.14 (m, 1H), 2.04 (s, 3H), 1.37 (d, 3H, *J* = 6.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.1, 149.9, 147.9, 140.4, 137.1, 136.5, 129.1, 126.0, 126.0, 122.0, 48.4, 21.8, 20.8; HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$ 263.1160 found 263.1162.

(*R*)-*N*-(1-(p-tolyl)ethyl)picolinamide*(nb 532 sm 15e):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15e** as a dirty white solid (550 mg, 75%); R_f (20% EtOAc/hexane) 0.6; mp: 90-92 ^oC; $[\alpha]^{25}_D$ = -6.13 (c = 0.10, DCM); IR (KBr): 3055, 1673, 1515, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (dd, 1H, J_1 = 4.7, J_2 = 0.6 Hz), 8.34 (br. s, 1H), 8.21 (d, 1H, *J* = 7.8Hz), 7.84 (m, 1H), 7.44-7.41 (m, 1H), 7.33 (d, 2H, *J* = 8.0Hz), 7.18 (d, 2H, *J* = 8.0Hz), 5.95-5.27 (m, 1H), 2.35 (s, 3H), 1.63 (d, 3H, *J* = 6.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.4, 150.0, 148.0, 140.3, 137.4, 137.0, 129.4, 126.2, 126.2, 122.3, 48.6, 22.1, 21.1; HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$ 263.1160 found 263.1162.



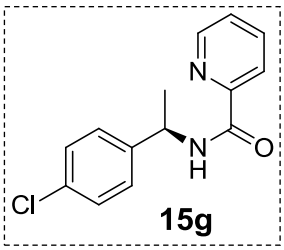
15e

(*S*)-*N*-(1-(p-tolyl)ethyl)picolinamide*(nb 534 sm 15f):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15f** as a dirty white solid (477 mg, 65%); R_f (20% EtOAc/hexane) 0.6; mp: 90-92 ^oC; $[\alpha]^{25}_D$ = 9.11 (c = 0.10, DCM); IR (KBr): 3055, 1673, 1515, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (dd, 1H, J_1 = 4.7, J_2 = 0.6 Hz), 8.34 (br. s, 1H), 8.21 (d, 1H, *J* = 7.8Hz), 7.84 (m, 1H), 7.44-7.41 (m, 1H), 7.33 (d, 2H, *J* = 8.0Hz), 7.18 (d, 2H, *J* = 8.0Hz), 5.95-5.27 (m, 1H), 2.35 (s, 3H), 1.63 (d, 3H, *J* = 6.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.4, 150.0, 148.0, 140.4, 137.4, 137.0, 129.4, 126.2, 126.2, 122.3, 48.6, 22.1, 21.1; HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$ 263.1160 found 263.1162.



15f

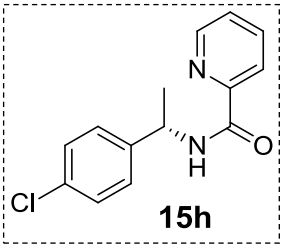
(*R*)-*N*-(1-(4-chlorophenyl)ethyl)picolinamide*(nb 422 sm 15g):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15g** as a white color solid (490 mg, 60%); R_f (20% EtOAc/hexane) 0.6; mp: 116-118 ^oC; $[\alpha]^{25}_D$ = -10.12 (c = 0.10, DCM); IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (d, 1H, *J* = 4.4Hz), 8.32 (d, 1H, *J* = 7.0Hz), 8.20 (dt, 1H, J_1 = 7.8, J_2 = 0.9Hz),



15g

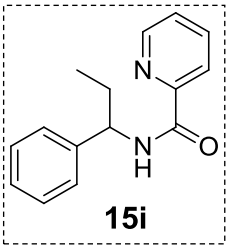
7.88-7.84 (m, 1H), 7.46-7.43 (m, 1H), 7.37-7.31 (m, 4H), 5.33-5.26 (m, 1H), 1.62 (d, 3H, *J* = 7.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.5, 149.7, 148.1, 142.0, 137.4, 133.0, 128.8, 127.6, 126.3, 122.3, 48.3, 22.1; HRMS (ESI) calcd for $C_{14}H_{13}ClN_2NaO$ $[M+Na]^+$ 283.0614 found 283.0627.

(*S*)-*N*-(1-(4-chlorophenyl)ethyl)picolinamide*(nb 423 sm 15h):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15h** as a white solid (510 mg, 65%); R_f (20% EtOAc/hexane) 0.6; mp: 116-118 ^oC; $[\alpha]^{25}_D$ = 15.12 (c = 0.10, DCM); IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (d, 1H, *J* = 4.4Hz), 8.32 (d, 1H, *J* = 7.0Hz), 8.20 (dt, 1H, J_1 = 7.8, J_2 = 0.9Hz), 7.88-7.84 (m, 1H), 7.46-7.43 (m, 1H), 7.37-7.31 (m, 4H), 5.33-5.26 (m, 1H), 1.62 (d, 3H, *J* = 7.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.5, 149.7, 148.1, 142.0, 137.4, 133.0, 128.8, 127.6, 126.3, 122.3, 48.3, 22.1; HRMS (ESI) calcd for $C_{14}H_{13}ClN_2NaO$ $[M+Na]^+$ 283.0614 found 283.0627.



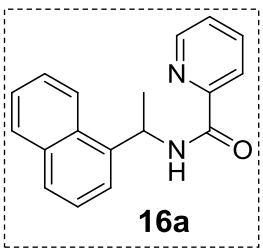
15h

N*-(1-phenylpropyl)picolinamide*(nb 164/1093 sm 15i): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15i** as a dirty white solid (688 mg, 95%); R_f (20% EtOAc/hexane) 0.6; mp: 119-121 ^oC; $[\alpha]^{25}_D$ = 0.0 (c = 0.10, DCM); IR (KBr): 3055, 2987, 1710, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (d, 1H, *J* = 4.7 Hz), 8.39 (d, 1H, *J* = 7.8Hz), 8.20 (d, 1H, *J* = 7.8Hz), 7.84 (t, 1H, *J* = 7.7 Hz), 7.44-7.40 (m, 3H), 7.38-7.34 (m, 2H), 7.29-7.25 (m, 1H), 5.10 (q, 1H, *J* = 7.4Hz), 2.03-1.95 (m, 2H), 0.99 (t, 3H, *J* = 7.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.6, 150.0, 148.0, 142.3, 137.4, 128.6, 127.3, 126.7, 126.1, 122.3, 55.0, 29.5, 10.9; HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$ 263.1160 found 263.1149.



15i

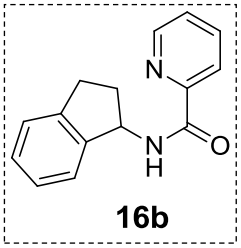
N*-(1-(naphthalen-1-yl)ethyl)picolinamide*(nb 138 sm 16a): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **16a** as a yellow color semisolid (580 mg, 70%); R_f (20% EtOAc/hexane) 0.5; IR (KBr): 3055, 1709, 1528, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (d, 1H, *J* = 8.6Hz), 8.33 (d, 1H, *J* = 4.3Hz), 8.26 (d, 1H, *J* = 8.5Hz), 8.23 (d, 1H, *J* = 7.8Hz), 7.82 (d, 1H, *J* = 8.1Hz), 7.75 (d, 1H, *J* = 8.2Hz), 7.64 (t, 1H, *J* = 7.7Hz), 7.59 (d, 1H, *J* = 7.2Hz), 7.52 (t,



16a

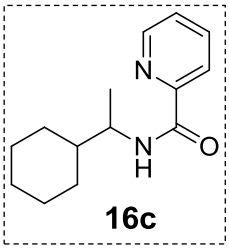
1H, *J* = 7.0Hz), 7.46-7.39 (m, 2H), 7.19-7.16 (m, 1H), 6.25-6.18 (m, 1H), 1.76 (d, 3H, *J* = 6.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.3, 149.8, 148.0, 138.6, 137.3, 134.0, 131.2, 128.9, 128.3, 126.5, 126.2, 125.8, 125.4, 123.4, 122.7, 122.3, 44.8, 21.3; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO$ $[M+Na]^+$ 299.1160 found 299.1153.

N*-(2,3-dihydro-1H-inden-1-yl)picolinamide*(nb 153 sm 16b):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **16b** as a crystallian white color solid (550 mg, 75%); R_f (20% EtOAc/hexane) 0.5; mp: 117-119 ^{o}C; IR (KBr): 3347, 3056, 1771, 1266, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53-8.51 (m, 1H), 8.34 (d, 1H, *J* = 8.2Hz), 8.28 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.90-7.86 (m, 1H), 7.45-7.41 (m, 1H), 7.37 (d, 1H, *J* = 7.2Hz), 7.31-7.21 (m, 3H), 5.72 (q, 1H, *J* = 7.8Hz), 3.11-3.04 (m, 1H), 2.99-2.91 (m, 1H), 2.75-2.67 (m, 1H), 2.05-1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C164.2, 149.9, 148.1, 143.5, 143.2, 137.4, 128.0, 126.8, 126.2, 124.8, 124.3, 122.4, 54.6, 34.1, 30.4; HRMS (ESI) calcd for $C_{15}H_{14}N_2NaO$ $[M+Na]^+$ 261.1004 found 261.1008.



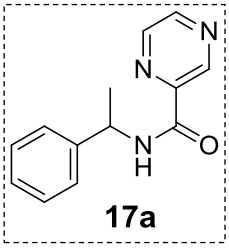
16b

N*-(1-cyclohexylethyl)picolinamide*(nb 119 sm 16c):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **16c** as a dirty white color solid (428 mg, 60%); R_f (20% EtOAc/hexane) 0.7; mp: 116-118 ^{o}C; IR (KBr): 3346, 2937, 1394, 1266, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (d, 1H, *J* = 4.2Hz), 8.21 (d, 1H, *J* = 7.8Hz), 7.97 (d, 1H, *J* = 6.8Hz), 7.87-7.83 (m, 1H), 7.43-7.41 (m, 1H), 4.08-4.03 (m, 1H), 1.92-1.64 (m, 6H), 1.51-1.43 (m, 1H), 1.26-1.15 (m, 5H), 1.12-1.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.5, 150.2, 148.0, 137.4, 126.0, 122.3, 49.5, 43.3, 29.2, 26.4, 26.2, 18.0; HRMS (ESI) calcd for $C_{14}H_{21}N_2O$ $[M+H]^+$ 233.1654 found 233.1665.



16c

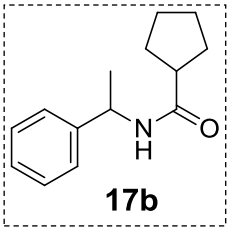
N*-(1-phenylethyl)pyrazine-2-carboxamide*(nb 600/585sm 17a):The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **17a** as a dirty white color solid (375 mg, 55%); R_f (20% EtOAc/hexane) 0.4; mp: 145-147 ^{o}C; IR (KBr): 3055, 2936, 1721, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (d, 1H, *J* = 1.4Hz), 8.76 (d, 1H, *J* = 2.5Hz), 8.53 (dd, 1H, J_1 = 2.4, J_2 = 1.5Hz), 8.08 (d, 1H, *J* = 10.0Hz), 7.44-7.42 (m, 4H), 7.38-7.30 (m, 3H), 5.39-5.32 (m, 1H), 1.66 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100



17a

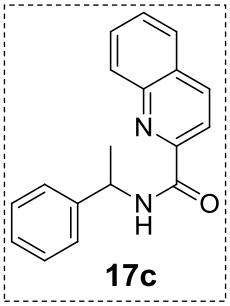
MHz, $CDCl_3$): δ_C162.1, 147.3, 144.5, 144.5, 142.8, 142.5, 128.8, 127.6, 126.2, 49.0, 22.0; HRMS (ESI) calcd for $C_{19}H_{17}N_4O_3S$ $[M+H]^+$ 228.1137 found 228.1149.

N*-(1-phenylethyl)cyclopentanecarboxamide*(nb 570 sm 17b): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **17b** as a dirty white color solid (450 mg, 70%); R_f (20% EtOAc/hexane) 0.6; mp: 102-104 ^oC; IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.37-7.31 (m, 4H), 7.29-7.25 (m, 1H), 5.78 (d, 1 H, J = 6.5Hz), 5.18-5.11 (m, 1H), 2.57-2.49 (m, 1H), 1.90-1.81 (m, 3H), 1.79-1.70 (m, 3H), 1.61-1.53 (m, 2H), 1.49 (d, 3H, J = 6.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C175.3, 143.5, 128.6, 127.2, 126.1, 48.5, 45.9, 30.4, 26.0, 21.8; HRMS (ESI) calcd for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1545 found 218.1553.



17b

N*-(1-phenylethyl)quinoline-2-carboxamide*(nb 130 sm 17c): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **17c** as a faint orange color solid (500 mg, 60%); R_f (20% EtOAc/hexane) 0.5; mp: 104-106 ^oC; IR (KBr): 3055, 1709, 1424, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.66 (d, 1H, J = 8.2Hz), 8.33 (d, 1H, J = 8.4Hz), 8.20 (br. s, 1H), 8.10 (d, 1H, J = 8.1Hz), 7.77 (d, 1H, J = 7.4Hz), 7.68 (d, 1H, J = 6.6Hz), 7.53 (d, 1H, J = 6.8Hz), 7.45 (d, 2H, J = 6.6Hz), 7.35-7.32 (m, 2H), 7.26 (d, 1H, J = 6.2Hz), 5.43 (qui, 1H, J = 7.0Hz), 1.65 (d, 3H, J = 5.5Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.6, 149.8, 146.5, 143.4, 137.5, 130.1, 129.7, 129.3, 128.7, 127.9, 127.8, 127.4, 126.3, 118.9, 49.0, 22.0; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO$ $[M+Na]^+$ 299.1160 found 299.1157.



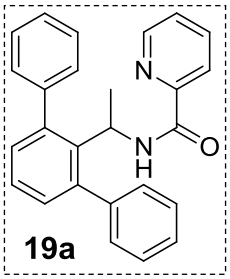
17c

General procedure for the Pd (II)-catalyzed arylation of substituted benzylamine picolinamides and preparation of the *bis*-arylation products 19, 20, 21 (a-j)/22, 23, 24 (a-b)/25, 26 (a-b) and 27a-b.

An appropriate benzylamine picolinamide (0.25 mmol, 1 equiv) with a wide range ofiodo compound (1.00 mmol, 4 equiv.), $Pd(OAc)_2$ (2.8 mg, 5 mol%), and AgOAc (91 mg, 2.2 equiv.) in anhydrous toluene (3 mL) was heated at 110 ^oC, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. Purification of the resulting reaction mixture by column chromatography on

silica gel furnished the corresponding bisarylated products**19, 20, 21 (a-j)/22, 23, 24 (a-b)/25, 26 (a-b) and 27a-b** (see relevant Tables/Schemes for specific examples and reaction conditions).

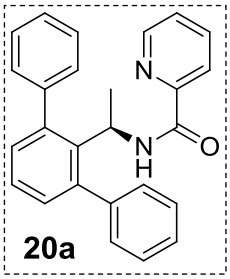
N*-(1-([1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 102a, 19a): The resultant compound **19a** was obtained after purification by column chromatography on silica gel



19a

(EtOAc:hexane = 20:80) as a yellow color semisolid (62 mg, 66%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_{D}$ = 0.12 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1514, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.38 (m, 1H), 8.07 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.75 (m, 1H), 7.72 (d, 1H, J = 8.7Hz), 7.55-7.33 (m, 10H), 7.30-7.27 (m, 2H), 7.16 (d, 2H, J = 7.3Hz), 5.54-5.47 (m, 1H), 1.38 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.8, 147.6, 142.3, 141.9, 138.6, 137.0, 130.6, 129.6, 128.0, 127.0, 125.8, 125.7, 121.9, 46.6, 23.4; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO$ $[M+Na]^+$ 401.1630 found 401.1628.

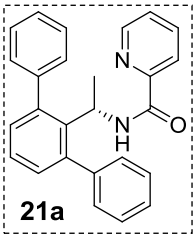
(*R*)-*N*-(1-([1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 113a, 20a):* The resultant compound **20a** was obtained after purification by column chromatography on silica gel



20a

(EtOAc:hexane = 20:80) as a yellow color semisolid (70 mg, 75%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_{D}$ = -30.6 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1513, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.38 (m, 1H), 8.07 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.75 (m, 1H), 7.72 (d, 1H, J = 8.7Hz), 7.55-7.33 (m, 10H), 7.30-7.27 (m, 2H), 7.16 (d, 2H, J = 7.3Hz), 5.54-5.47 (m, 1H), 1.38 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.8, 147.6, 142.3, 141.9, 138.6, 137.0, 130.6, 129.6, 128.0, 127.0, 125.8, 125.7, 121.9, 46.6, 23.4; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO$ $[M+Na]^+$ 401.1630 found 401.1628.

(*S*)-*N*-(1-([1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 132a, 21a):* The resultant compound **21a** was obtained after purification by column chromatography on silica gel

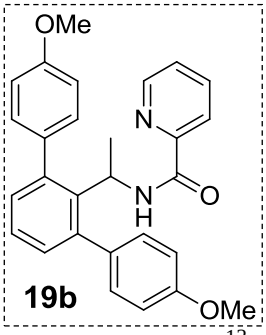


21a

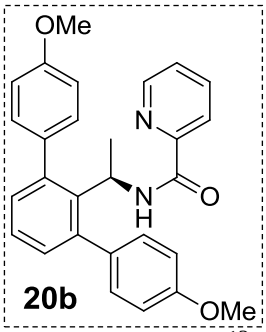
(EtOAc:hexane = 20:80) as a yellow color semisolid (58 mg, 60%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_{D}$ = 30.6 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1513, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.38 (m, 1H), 8.07 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.75 (m, 1H), 7.72

(d, 1H, *J* = 8.7Hz), 7.55-7.33 (m, 10H), 7.30-7.27 (m, 2H), 7.16 (d, 2H, *J* = 7.3Hz), 5.54-5.47 (m, 1H), 1.38 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.8, 147.6, 142.3, 141.9, 138.6, 137.0, 130.6, 129.6, 128.0, 127.0, 125.8, 125.7, 121.9, 46.6, 23.4; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO$ $[M+Na]^+$ 401.1630 found 401.1628.

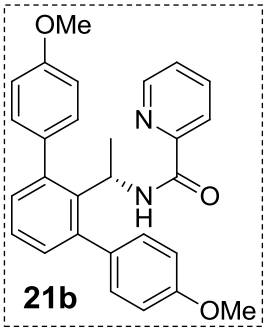
N*-(1-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 109,93a, 19b):The resultant compound **19b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a dirty white color solid (91 mg, 83%); R_f (20% EtOAc/hexane) 0.4; mp: 107-109 ^{o}C; $[\alpha]^{25}_D$ = 1.2 (c = 0.10, DCM); IR (KBr): 3056, 1674, 1512, 1265, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.08-8.06 (m, 1H), 7.80-7.76 (m, 2H), 7.39-7.35 (m, 4H), 7.28-7.23 (m, 2H), 7.14 (d, 2H, *J* = 7.4Hz), 6.93 (br. s, 4H), 5.58-5.50 (m, 1H), 3.87 (s, 6H), 1.38 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 149.9, 147.5, 141.6, 139.2, 137.0, 134.7, 130.8, 130.6, 125.8, 121.9, 113.4, 55.3, 46.6, 23.4; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO_3$ $[M+Na]^+$ 461.1841 found 461.1849.



(R)-N*-(1-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 97a, 20b):The resultant compound **20b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a dirty white color solid (99 mg, 90%); R_f (20% EtOAc/hexane) 0.4; mp: 107-109 ^{o}C; $[\alpha]^{25}_D$ = -10.2 (c = 0.10, DCM); IR (KBr): 3055, 1674, 1513, 1263, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.08-8.06 (m, 1H), 7.80-7.76 (m, 2H), 7.39-7.35 (m, 4H), 7.28-7.23 (m, 2H), 7.14 (d, 2H, *J* = 7.4Hz), 6.93 (br. s, 4H), 5.58-5.50 (m, 1H), 3.87 (s, 6H), 1.38 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 149.9, 147.5, 141.6, 139.2, 137.0, 134.7, 130.8, 130.6, 125.8, 121.9, 113.4, 55.3, 46.6, 23.4; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO_3$ $[M+Na]^+$ 461.1841 found 461.1849.

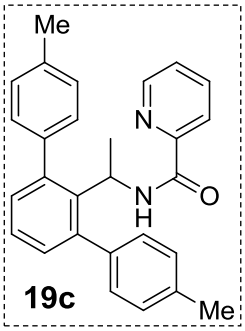


(S)-N*-(1-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 120a, 21b):The resultant compound **21b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a dirty white color solid (74 mg, 67%); R_f (20% EtOAc/hexane) 0.4; mp: 107-109 ^{o}C; $[\alpha]^{25}_D$ = 16.8 (c = 0.10, DCM); IR (KBr): 3055, 1674, 1513, 1263, 740 cm^{-1}; ^{1}H

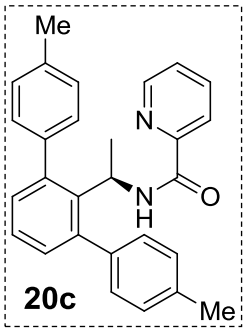


NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.08-8.06 (m, 1H), 7.80-7.76 (m, 2H), 7.39-7.35 (m, 4H), 7.28-7.23 (m, 2H), 7.14 (d, 2H, *J* = 7.4Hz), 6.93 (br. s, 4H), 5.58-5.50 (m, 1H), 3.87 (s, 6H), 1.38 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 149.9, 147.5, 141.6, 139.2, 137.0, 134.7, 130.8, 130.6, 125.8, 121.9, 113.4, 55.3, 46.6, 23.5; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO_3$ $[M+Na]^+$ 461.1841 found 461.1849.

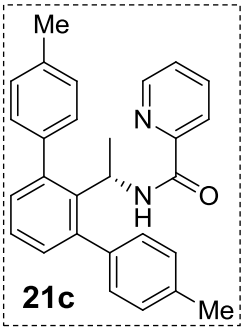
N*-(1-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 115a, 19c): The resultant compound **19c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color viscous solid (68 mg, 65%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_D$ = 0.80 (c = 0.10, DCM); IR (KBr): 3053, 1675, 1513, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.19-8.08 (m, 1H), 7.81-7.77 (m, 2H), 7.54-7.33 (m, 4H), 7.30-7.20 (m, 5H), 7.17 (d, 2H, *J* = 7.2Hz), 7.13-7.01 (m, 1H), 5.59-5.51 (m, 1H), 2.45 (s, 6H), 1.40 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 149.9, 147.5, 141.9, 139.4, 138.9, 137.0, 136.6, 130.6, 129.4, 128.8, 125.8, 125.7, 122.0, 46.6, 23.5, 21.3; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO$ $[M+Na]^+$ 429.1943 found 429.1950.



(R)-N*-(1-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 117a, 20c): The resultant compound **20c** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 20:80) as a yellow color viscous solid (66 mg, 66%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_D$ = -56.99 (c = 0.10, DCM); IR (KBr): 3054, 1675, 1513, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.19-8.08 (m, 1H), 7.81-7.77 (m, 2H), 7.54-7.33 (m, 4H), 7.30-7.20 (m, 5H), 7.17 (d, 2H, *J* = 7.2Hz), 7.13-7.01 (m, 1H), 5.59-5.51 (m, 1H), 2.45 (s, 6H), 1.40 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 149.9, 147.5, 141.9, 139.4, 138.9, 137.0, 136.6, 130.6, 129.4, 128.8, 125.8, 125.7, 122.0, 46.6, 23.5, 21.3; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO$ $[M+Na]^+$ 429.1943 found 429.1950.

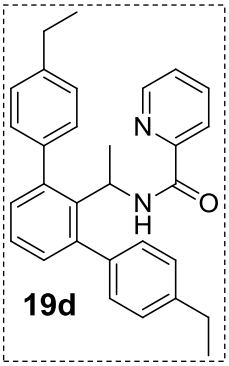


(S)-N*-(1-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 133a, 21c): The resultant compound **21c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color viscous solid (83 mg, 82%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_D$ = 59.79 (c = 0.10, DCM); IR (KBr): 3054, 1675, 1513, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.19-8.08 (m, 1H), 7.81-7.77 (m, 2H), 7.54-7.33 (m, 4H), 7.30-7.20 (m, 5H), 7.17 (d, 2H, *J* = 7.2Hz), 7.13-7.01 (m, 1H), 5.59-5.51 (m, 1H), 2.45 (s, 6H), 1.40 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 149.9, 147.5, 141.9, 139.4, 138.9, 137.0, 136.6, 130.6, 129.4, 128.8, 125.8, 125.7, 122.0, 46.6, 23.5, 21.3; HRMS (ESI) calcd for $C_{28}H_{26}N_2NaO$ $[M+Na]^+$ 429.1943 found 429.1950.



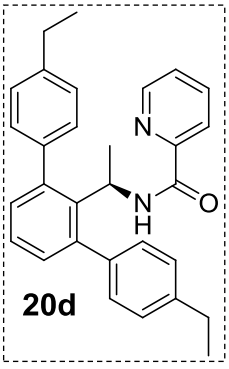
21c

N*-(1-(4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 160a, 19d): The resultant compound **19d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color semisolid (72 mg, 67%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = 4.20 (c = 0.10, DCM); IR (KBr): 2967, 1675, 1513, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.37 (m, 1H), 8.08 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.76 (m, 1H), 7.72 (d, 1H, *J* = 8.8Hz), 7.44-7.30 (m, 4H), 7.28-7.18 (m, 5H), 7.16 (d, 2H, *J* = 7.3Hz), 7.13-7.01 (m, 1H), 5.57-5.49 (m, 1H), 2.74 (q, 4H, *J* = 7.6Hz), 1.40 (d, 3H, *J* = 7.2Hz), 1.33 (t, 6H, *J* = 7.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 150.0, 147.5, 142.8, 141.9, 139.6, 138.9, 137.0, 130.6, 129.5, 127.5, 125.7, 125.7, 121.9, 46.7, 28.6, 23.5, 15.5; HRMS (ESI) calcd for $C_{30}H_{31}N_2O$ $[M+H]^+$ 435.2436 found 435.2439.



19d

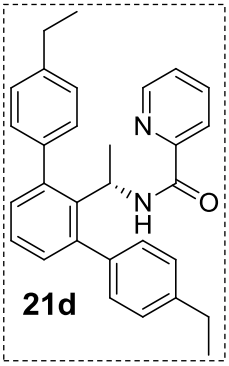
(R)-N*-(1-(4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 161a, 20d): The resultant compound **20d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color semisolid (55 mg, 51%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = -53.26 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1512, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.37 (m, 1H), 8.08 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.76 (m, 1H), 7.72 (d, 1H, *J* = 8.8Hz), 7.44-7.30 (m, 4H), 7.28-7.18 (m, 5H), 7.16 (d, 2H, *J*=



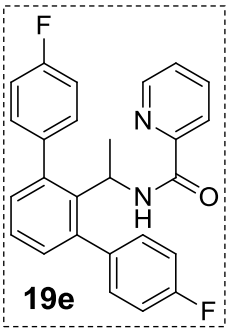
20d

7.3Hz), 7.13-7.01 (m, 1H), 5.57-5.49 (m, 1H), 2.74 (q, 4H, *J* = 7.6Hz), 1.40 (d, 3H, *J* = 7.2Hz), 1.33 (t, 6H, *J* = 7.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.9, 147.5, 142.8, 141.9, 139.6, 138.8, 137.0, 130.7, 129.5, 127.5, 125.7, 125.7, 122.0, 46.7, 28.6, 23.5, 15.5; HRMS (ESI) calcd for $C_{30}H_{31}N_2O$ $[M+H]^+$ 435.2436 found 435.2439.

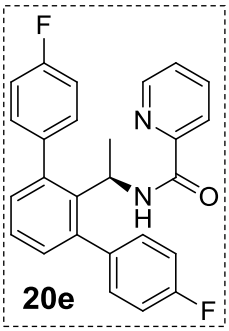
(S)-N*-(1-(4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide ***(nb 162a, 21d):*** The resultant compound **21d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color stickysolid (58 mg, 55%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = 60.26 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1512, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.37 (m, 1H), 8.08 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.80-7.76 (m, 1H), 7.72 (d, 1H, *J* = 8.8Hz), 7.44-7.30 (m, 4H), 7.28-7.18 (m, 5H), 7.16 (d, 2H, *J* = 7.3Hz), 7.13-7.01 (m, 1H), 5.57-5.49 (m, 1H), 2.74 (q, 4H, *J* = 7.6Hz), 1.40 (d, 3H, *J* = 7.2Hz), 1.33 (t, 6H, *J* = 7.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.9, 147.5, 142.8, 141.9, 139.6, 138.8, 137.0, 130.6, 129.5, 127.5, 125.7, 125.7, 122.0, 46.7, 28.6, 23.5, 15.5; HRMS (ESI) calcd for $C_{30}H_{31}N_2O$ $[M+H]^+$ 435.2436 found 435.2439.



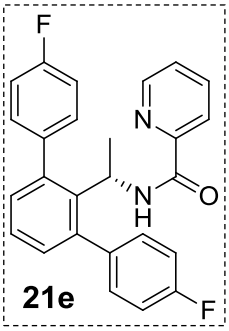
N*-(1-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide ***(nb 136a, 19e):*** The resultant compound **19e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color viscous (67 mg, 65%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3055, 1673, 1511, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.43-8.41 (m, 1H), 8.08-8.05 (m, 1H), 7.79 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.68 (d, 1H, *J* = 8.4Hz), 7.41-7.38 (m, 3H), 7.29-7.25 (m, 4H), 7.14 (d, 2H, *J* = 7.5Hz), 7.08-6.88 (m, 3H), 5.49-5.41 (m, 1H), 1.37 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 162.0 (d, J_{C-F}= 244.0Hz), 149.5, 147.7, 140.9, 139.0, 138.1 (d, J_{C-F}= 3.5Hz), 137.1, 131.1, 131.1, 131.0, 126.0 (d, J_{C-F}= 7.6Hz), 121.9, 114.9 (d, J_{C-F}= 21.2Hz), 46.6, 23.3; HRMS (ESI) calcd for $C_{26}H_{21}F_2N_2O$ $[M+H]^+$ 415.1622 found 415.1630.



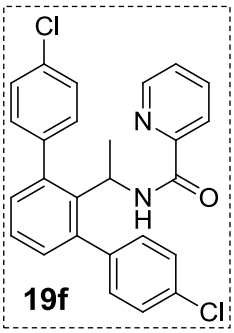
***(R)-N*-(1-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 150a, 20e):**The resultant compound **20e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color viscous (72 mg, 69%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = -54.12 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1511, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43-8.41 (m, 1H), 8.08-8.05 (m, 1H), 7.79 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.68 (d, 1H, J = 8.4Hz), 7.41-7.38 (m, 3H), 7.29-7.25 (m, 4H), 7.14 (d, 2H, J = 7.5Hz), 7.08-6.88 (m, 3H), 5.49-5.41 (m, 1H), 1.37 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 162.0 (d, J_{C-F}= 244.0Hz), 149.5, 147.7, 140.9, 139.0, 138.1 (d, J_{C-F}= 3.5Hz), 137.1, 131.1, 131.1, 131.0, 126.0 (d, J_{C-F}= 7.6Hz), 121.9, 114.9 (d, J_{C-F}= 21.2Hz), 46.6, 23.3; HRMS (ESI) calcd for $C_{26}H_{21}F_2N_2O$ $[M+H]^+$ 415.1622 found 415.1630.



***(S)-N*-(1-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 163a, 21e):**The resultant compound **21e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow color viscous (67 mg, 65%); R_f (20% EtOAc/hexane) 0.7; $[\alpha]^{25}_D$ = 65.10 (c = 0.10, DCM); IR (KBr): 3055, 1674, 1512, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43-8.41 (m, 1H), 8.08-8.05 (m, 1H), 7.79 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.68 (d, 1H, J = 8.4Hz), 7.41-7.38 (m, 3H), 7.29-7.25 (m, 4H), 7.14 (d, 2H, J = 7.5Hz), 7.08-6.88 (m, 3H), 5.49-5.41 (m, 1H), 1.37 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 162.0 (d, J_{C-F}= 244.0Hz), 149.5, 147.7, 140.9, 139.0, 138.1 (d, J_{C-F}= 3.5Hz), 137.1, 131.1, 131.1, 131.0, 126.0 (d, J_{C-F}= 7.6Hz), 121.9, 114.9 (d, J_{C-F}= 21.2Hz), 46.6, 23.3; HRMS (ESI) calcd for $C_{26}H_{21}F_2N_2O$ $[M+H]^+$ 415.1622 found 415.1630.

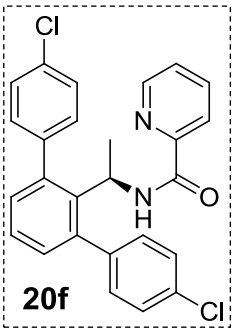


***N*-(1-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 101a, 19f):**The resultant compound **19f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a faint white color solid (59 mg, 53%); R_f (20% EtOAc/hexane) 0.7; mp: 165-167 ^oC; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1513, 1267, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45-8.44 (m, 1H), 8.05 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.82-7.77 (m, 1H), 7.63 (d, 1H, J = 8.4Hz), 7.42-7.39 (m, 4H), 7.36-7.26



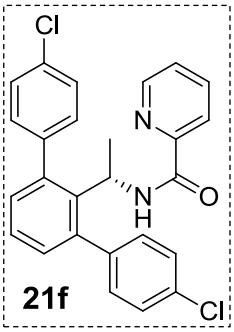
(m, 6H), 7.12 (d, 2H, *J* = 7.6Hz), 5.46-5.39 (m, 1H), 1.37 (d, 3H, *J* = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.4, 147.8, 140.6, 140.6, 138.8, 137.1, 133.1, 130.8, 130.8, 128.3, 126.0, 121.7, 46.6, 23.5; HRMS (ESI) calcd for $C_{26}H_{21}Cl_2N_2O$ $[M+H]^+$ 447.1031 found 447.1030.

(R)-N*-(1-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide ***(nb 112a, 20f):*** The resultant compound **20f** was obtained after purification by column chromatography on silica



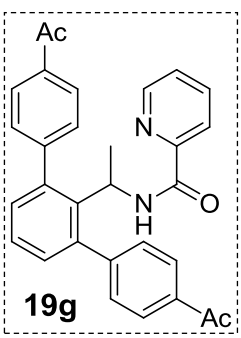
(EtOAc:hexane = 20:80) as a faint white color solid (60 mg, 55%); R_f (20% EtOAc/hexane) 0.7; mp: 165-167 ^oC; $[\alpha]^{25}_D$ = -9.97 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1513, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.45-8.44 (m, 1H), 8.05 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.82-7.77 (m, 1H), 7.63 (d, 1H, *J* = 8.4Hz), 7.42-7.39 (m, 4H), 7.36-7.26 (m, 6H), 7.12 (d, 2H, *J* = 7.6Hz), 5.46-5.39 (m, 1H), 1.37 (d, 3H, *J* = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.4, 147.8, 140.6, 140.6, 138.8, 137.1, 133.1, 130.8, 130.8, 128.3, 126.0, 121.7, 46.6, 23.5; HRMS (ESI) calcd for $C_{26}H_{21}Cl_2N_2O$ $[M+H]^+$ 447.1031 found 447.1030.

(S)-N*-(1-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide ***(nb 127a, 21f):*** The resultant compound **21f** was obtained after purification by column chromatography on silica



(EtOAc:hexane = 20:80) as a faint white color solid (45.5 mg, 40%); R_f (20% EtOAc/hexane) 0.7; mp: 165-167 ^oC; $[\alpha]^{25}_D$ = 15.23 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1513, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.45-8.44 (m, 1H), 8.05 (dt, 1H, J_1 = 7.8, J_2 = 1.0Hz), 7.82-7.77 (m, 1H), 7.63 (d, 1H, *J* = 8.4Hz), 7.42-7.39 (m, 4H), 7.36-7.26 (m, 6H), 7.12 (d, 2H, *J* = 7.6Hz), 5.46-5.39 (m, 1H), 1.37 (d, 3H, *J* = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.4, 147.8, 140.6, 140.6, 138.8, 137.1, 133.1, 130.8, 130.8, 128.3, 126.0, 121.7, 46.6, 23.5; HRMS (ESI) calcd for $C_{26}H_{21}Cl_2N_2O$ $[M+H]^+$ 447.1031 found 447.1030.

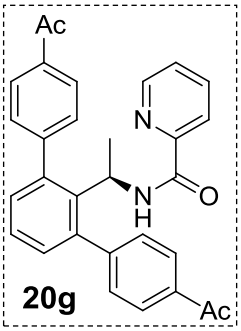
N*-(1-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide** ***(nb 100a, 19g): The resultant compound **19g** was obtained after purification by column chromatography on silica



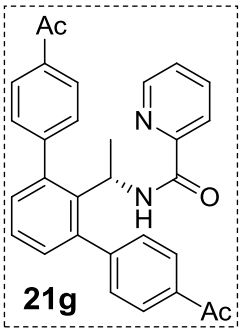
(EtOAc:hexane = 20:80) as a yellow color viscous (71 mg, 61%); R_f (20% EtOAc/hexane) 0.3; $[\alpha]^{25}_D$ = 1.60 (c = 0.10, DCM); IR (KBr):

3055, 1679, 1514, 1266, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27 -8.25 (m, 1H), 8.05-8.03 (m, 2H), 7.99-7.82 (m, 3H), 7.80-7.76 (m, 1H), 7.70-7.40 (m, 4H), 7.38-7.35 (m, 1H), 7.33-7.26 (m, 2H), 7.14 (d, 2H, *J* = 7.6Hz), 5.41-5.34 (m, 1H), 2.65 (s, 6H), 1.37 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.8, 162.7, 149.3, 147.6, 147.3, 140.8, 138.3, 137.2, 135.8, 130.6, 129.8, 128.2, 126.1, 126.1, 121.8, 46.7, 26.7, 23.4; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_3$ $[M+Na]^+$ 485.1841 found 485.1834.

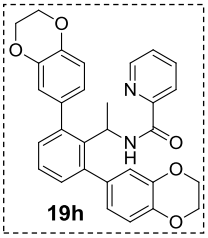
(R)-N*-(1-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 111a, 20g): The resultant compound **20g** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (99.5 mg, 85%); R_f (20% EtOAc/hexane) 0.3; $[\alpha]^{25}_D$ = -186.96 (c = 0.10, DCM); IR (KBr): 3055, 1679, 1513, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27 -8.25 (m, 1H), 8.05-8.03 (m, 2H), 7.99-7.82 (m, 3H), 7.80-7.76 (m, 1H), 7.70-7.40 (m, 4H), 7.38-7.35 (m, 1H), 7.33-7.26 (m, 2H), 7.14 (d, 2H, *J* = 7.6Hz), 5.41-5.34 (m, 1H), 2.65 (s, 6H), 1.37 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.8, 162.7, 149.3, 147.6, 147.3, 140.8, 138.3, 137.2, 135.8, 130.6, 129.8, 128.2, 126.1, 126.1, 121.8, 46.7, 26.7, 23.4; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_3$ $[M+Na]^+$ 485.1841 found 485.1834.



(S)-N*-(1-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 122a, 21g): The resultant compound **21g** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (71 mg, 45%); R_f (20% EtOAc/hexane) 0.35; $[\alpha]^{25}_D$ = 150.37 (c = 0.10, DCM); IR (KBr): 3055, 1679, 1513, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27 -8.25 (m, 1H), 8.05-8.03 (m, 2H), 7.99-7.82 (m, 3H), 7.80-7.76 (m, 1H), 7.70-7.40 (m, 4H), 7.38-7.35 (m, 1H), 7.33-7.26 (m, 2H), 7.14 (d, 2H, *J* = 7.6Hz), 5.41-5.34 (m, 1H), 2.65 (s, 6H), 1.37 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C197.8, 162.7, 149.3, 147.6, 147.3, 140.8, 138.3, 137.2, 135.8, 130.6, 129.8, 128.2, 126.1, 126.1, 121.8, 46.7, 26.7, 23.4; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_3$ $[M+Na]^+$ 485.1841 found 485.1834.

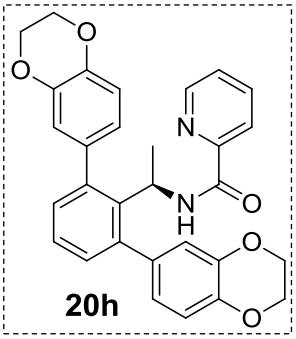


N*-(1-(2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)ethyl)picolinamide *(nb 165a, 19h): The resultant compound **19h** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a orange color solid (93 mg, 76%);

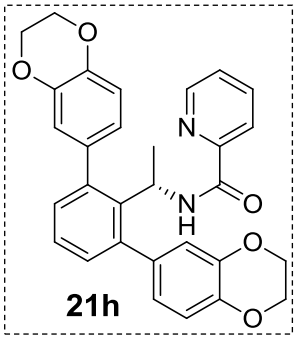


R_f (20% EtOAc/hexane) 0.4; mp: 95-97 ^oC; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3055, 1672, 1509, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (d, 1H, *J* = 4.4Hz), 8.08 (d, 1H, *J* = 7.8Hz), 7.92 (d, 1H, *J* = 8.8Hz), 7.77 (td, 1H, J_1 = 7.6, J_2 = 1.7 Hz), 7.37-7.34 (m, 1H), 7.22 (dd, 1H, J_1 = 8.2, J_2 = 6.8 Hz), 7.13 (d, 2H, *J* = 7.2Hz), 7.06-6.76 (m, 6H), 5.63-5.55 (m, 1H), 4.30 (s, 8H), 1.44 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 150.0, 147.6, 142.9, 142.7, 141.2, 139.0, 137.0, 135.6, 130.8, 125.7, 125.6, 122.8, 122.0, 118.5, 116.8, 64.4, 46.6, 23.6; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_5$ $[M+Na]^+$ 517.1739 found 517.1740.

(R)*-N-(1-(2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)ethyl)picolinamide *(nb 166a, 20h): The resultant compound **20h** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a orange color solid (104 mg, 85%); R_f (20% EtOAc/hexane) 0.4; mp: 95-97 ^oC; $[\alpha]^{25}_D$ = -195.20 (c = 0.10, DCM); IR (KBr): 3055, 1673, 1508, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (d, 1H, *J* = 4.4Hz), 8.08 (d, 1H, *J* = 7.8Hz), 7.92 (d, 1H, *J* = 8.8Hz), 7.77 (td, 1H, J_1 = 7.6, J_2 = 1.7 Hz), 7.37-7.34 (m, 1H), 7.22 (dd, 1H, J_1 = 8.2, J_2 = 6.8 Hz), 7.13 (d, 2H, *J* = 7.2Hz), 7.06-6.76 (m, 6H), 5.63-5.55 (m, 1H), 4.30 (s, 8H), 1.44 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 150.0, 147.6, 142.9, 142.7, 141.2, 139.0, 137.0, 135.6, 130.8, 125.7, 125.6, 122.8, 122.0, 118.5, 116.8, 64.4, 46.6, 23.6; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_5$ $[M+Na]^+$ 517.1739 found 517.1740.

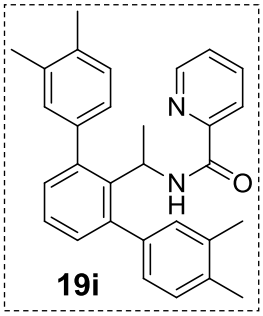


(S)-N*-(1-(2,6-bis (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)ethyl)picolinamide *(nb 176a, 21h): The resultant compound **21h** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a orange color solid (89 mg, 72%); R_f (20% EtOAc/hexane) 0.35; mp: 95-97 ^oC; $[\alpha]^{25}_D$ = 196.01 (c = 0.10, DCM); IR (KBr): 3055, 1672, 1510, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (d, 1H, *J* = 4.4Hz), 8.08 (d, 1H, *J* = 7.8Hz), 7.92 (d, 1H, *J* = 8.8Hz), 7.77 (td, 1H, J_1 = 7.6, J_2 = 1.7 Hz), 7.37-7.34 (m, 1H), 7.22 (dd, 1H, J_1 = 8.2, J_2 = 6.8 Hz), 7.13 (d, 2H, *J* = 7.2Hz), 7.06-6.76 (m, 6H), 5.63-5.55 (m, 1H), 4.30 (s, 8H), 1.44 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 150.0, 147.6, 142.9, 142.7, 141.2, 139.0, 137.0, 135.6, 130.8, 125.7, 125.6, 122.8, 122.0,

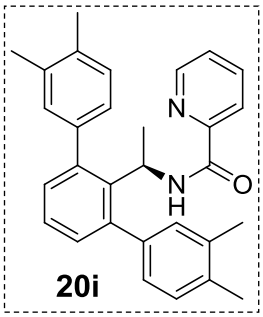


118.5, 116.8, 64.4, 46.6, 23.6; HRMS (ESI) calcd for $C_{30}H_{26}N_2NaO_5$ $[M+Na]^+$ 517.1739 found 517.1740.

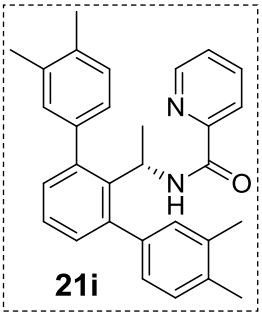
N*-(1-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl) ethyl)picolinamide *(nb 173a, 19i):The resultant compound **19i** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a brown color solid (96 mg, 84%); R_f (20% EtOAc/hexane) 0.65; mp: 98-100 ^oC; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3054, 1675, 1512, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.11 (d, 1H, J = 7.8Hz), 7.79 (td, 2H, J_1 = 7.7, J_2 = 1.7 Hz), 7.39-7.36 (m, 1H), 7.34-7.19 (m, 5H), 7.17-6.98 (m, 4H), 5.60-5.52 (m, 1H), 2.35 (s, 12H), 1.41 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 150.1, 147.6, 142.0, 140.0, 138.6, 137.0, 136.1, 135.2, 130.8, 130.5, 129.2, 127.0, 125.6, 122.1, 46.8, 23.5, 19.8, 19.6; HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO$ $[M+Na]^+$ 457.2256 found 457.2264.



(R)*-N-(1-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide *(nb 174a, 20i):The resultant compound **20i** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a brown color solid (80 mg, 70%); R_f (20% EtOAc/hexane) 0.65; mp: 98-100 ^oC; $[\alpha]^{25}_D$ = -49.09 (c = 0.10, DCM); IR (KBr): 3055, 1674, 1511, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.11 (d, 1H, J = 7.8Hz), 7.79 (td, 2H, J_1 = 7.7, J_2 = 1.7 Hz), 7.39-7.36 (m, 1H), 7.34-7.19 (m, 5H), 7.17-6.98 (m, 4H), 5.60-5.52 (m, 1H), 2.35 (s, 12H), 1.41 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 150.1, 147.6, 142.0, 140.0, 138.6, 137.0, 136.1, 135.2, 130.8, 130.5, 129.2, 127.0, 125.6, 122.1, 46.8, 23.5, 19.8, 19.6; HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO$ $[M+Na]^+$ 457.2256 found 457.2264.

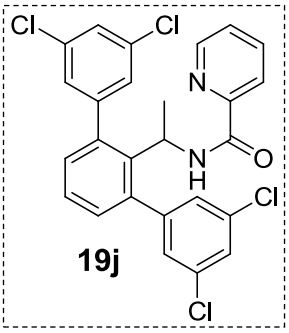


(S)*-N-(1-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 175a, 21i):The resultant compound **21i** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a brown color solid (96 mg, 71%); R_f (20% EtOAc/hexane) 0.65; mp: 98-100^oC; $[\alpha]^{25}_D$ = 52.20 (c = 0.10, DCM); IR (KBr): 3055, 1675, 1511, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.11 (d, 1H, J = 7.8Hz),

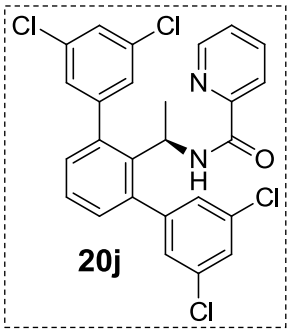


7.79 (td, 2H, J_1 = 7.7, J_2 = 1.7 Hz), 7.39-7.36 (m, 1H), 7.34-7.19 (m, 5H), 7.17-6.98 (m, 4H), 5.60-5.52 (m, 1H), 2.35 (s, 12H), 1.41 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 150.1, 147.6, 142.0, 140.0, 138.6, 137.0, 136.1, 135.2, 130.8, 130.5, 129.2, 127.0, 125.6, 122.1, 46.8, 23.5, 19.8, 19.6; HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO$ $[M+Na]^+$ 457.2256 found 457.2264.

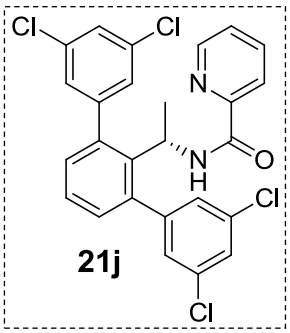
N*-(1-(3,3'',5,5''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl) picolinamide*(nb 178a, 19j):The resultant compound **19j** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a dirty white color semisolid (88 mg, 68%); R_f (20% EtOAc/hexane) 0.75; $[\alpha]^{25}_D$= 0.00 (c = 0.10, DCM); IR (KBr): 3056, 1675, 1510, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48-8.46 (m, 1H), 8.10 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.82-7.78 (m, 1H), 7.70 (d, 1H, J = 7.8Hz), 7.61-7.47 (m, 2H), 7.41-7.39 (m, 1H), 7.37 (t, 2H, J = 1.9Hz), 7.30-7.26 (m, 1H,), 7.12 (d, 4H, J = 7.6Hz), 5.39-5.31 (m, 1H), 1.43 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.9, 149.2, 148.2, 144.8, 139.2, 138.6, 137.2, 134.7, 131.0, 128.1, 127.4, 126.3, 126.1, 122.0, 46.6, 23.2; HRMS (ESI) calcd for $C_{26}H_{19}Cl_4N_2O$ $[M+H]^+$ 515.0251 found 515.0259.



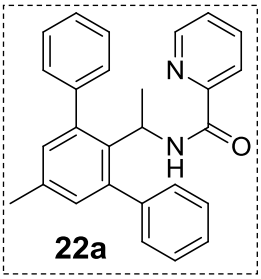
(R)-N*-(1-(3,3'',5,5''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 179a, 20j):The resultant compound **20j** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a dirty white color semisolid (80 mg, 62%); R_f (20% EtOAc/hexane) 0.75; $[\alpha]^{25}_D$ = -22.25 (c = 0.10, DCM); IR (KBr): 3056, 1676, 1509, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48-8.46 (m, 1H), 8.10 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.82-7.78 (m, 1H), 7.70 (d, 1H, J = 7.8Hz), 7.61-7.47 (m, 2H), 7.41-7.39 (m, 1H), 7.37 (t, 2H, J = 1.9Hz), 7.30-7.26 (m, 1H,), 7.12 (d, 4H, J = 7.6Hz), 5.39-5.31 (m, 1H), 1.43 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.9, 149.2, 148.2, 144.8, 139.2, 138.6, 137.2, 134.7, 131.0, 128.1, 127.4, 126.3, 126.1, 122.0, 46.6, 23.2; HRMS (ESI) calcd for $C_{26}H_{19}Cl_4N_2O$ $[M+H]^+$ 515.0251 found 515.0259.



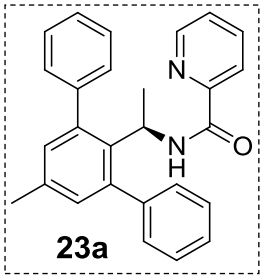
(S)-N*-(1-(3,3'',5,5''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 180a, 21j): The resultant compound **21j** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a dirty white color semisolid (78 mg, 61%); R_f (20% EtOAc/hexane) 0.75; $[\alpha]^{25}_D$ = 25.25 (c = 0.10, DCM); IR (KBr): 3056, 1677, 1509, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.48-8.46 (m, 1H), 8.10 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.82-7.78 (m, 1H), 7.70 (d, 1H, J = 7.8Hz), 7.61-7.47 (m, 2H), 7.41-7.39 (m, 1H), 7.37 (t, 2H, J = 1.9Hz), 7.30-7.26 (m, 1H,), 7.12 (d, 4 H, J = 7.6Hz), 5.39-5.31 (m, 1H), 1.43 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.9, 149.2, 148.2, 144.8, 139.2, 138.6, 137.2, 134.7, 131.0, 128.1, 127.4, 126.3, 126.1, 122.0, 46.6, 23.2; HRMS (ESI) calcd for $C_{26}H_{19}Cl_4N_2O$ $[M+H]^+$ 515.0251 found 515.0259.



N*-(1-(5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 351a, 22a): The resultant compound **22a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (58 mg, 60%); R_f (20% EtOAc/hexane) 0.5; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3055, 2987, 1424, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (d, 1H, J = 4.6Hz), 8.09 (d, 1H, J = 7.8Hz), 7.80-7.74 (m, 2H), 7.50-7.25 (m, 11H), 7.02 (s, 2H), 5.52-5.45 (m, 1H), 2.36 (s, 3H), 1.39 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.9, 147.6, 142.4, 141.8, 137.0, 135.7, 135.3, 131.4, 129.6, 128.0, 127.0, 125.7, 121.9, 46.4, 23.4, 20.8; HRMS (ESI) calcd for $C_{27}H_{24}N_2NaO$ $[M+Na]^+$ 415.1786 found 415.1802.

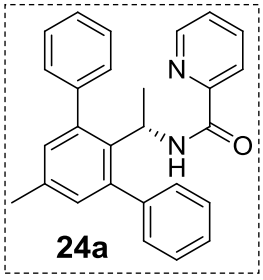


(R)-N*-(1-(5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 537a, 23a): The resultant compound **23a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (53 mg, 55%); R_f (20% EtOAc/hexane) 0.5; $[\alpha]^{25}_D$ = -45.05 (c = 0.10, DCM); IR (KBr): 3055, 2987, 1424, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (d, 1H, J = 4.6Hz), 8.09 (d, 1H, J = 7.8Hz), 7.80-7.74 (m, 2H), 7.50-7.25 (m, 11H), 7.02 (s, 2H), 5.52-5.45 (m, 1H), 2.36 (s, 3H), 1.39 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.9, 147.6, 142.4, 141.8, 137.0,

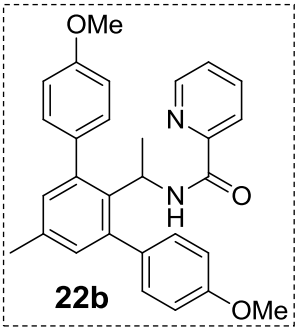


135.7, 135.3, 131.4, 129.6, 128.0, 127.0, 125.7, 121.9, 46.4, 23.4, 20.8; HRMS (ESI) calcd for $C_{27}H_{24}N_2NaO$ $[M+Na]^+$ 415.1786 found 415.1802.

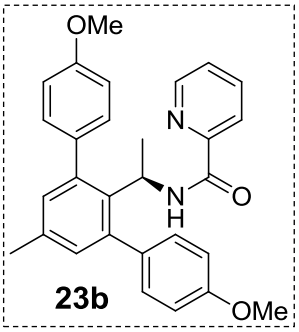
(S)-N*-(1-(5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide ***(nb 539a, 24a):*** The resultant compound **24a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (64 mg, 65%); R_f (20% EtOAc/hexane) 0.5; $[\alpha]^{25}_D$ = 50.50 (c = 0.10, DCM); IR (KBr): 3055, 2987, 1424, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (d, 1H, *J* = 4.6Hz), 8.09 (d, 1H, *J* = 7.8Hz), 7.80-7.74 (m, 2H), 7.50-7.25 (m, 11H), 7.02 (s, 2H), 5.52-5.45 (m, 1H), 2.36 (s, 3H), 1.39 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 149.9, 147.6, 142.4, 141.8, 137.0, 135.7, 135.3, 131.4, 129.6, 128.0, 127.0, 125.7, 121.9, 46.4, 23.4, 20.8; HRMS (ESI) calcd for $C_{27}H_{24}N_2NaO$ $[M+Na]^+$ 415.1786 found 415.1802.



N*-(1-(4,4''-dimethoxy-5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide** ***(nb 340a, 22b): The resultant compound **22b** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (85 mg,75%); R_f (20% EtOAc/hexane) 0.4; $[\alpha]^{25}_D$ = 0.00 (c = 0.10, DCM); IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.09-8.06 (m, 1H), 7.81-7.75 (m, 2H), 7.38-7.35 (m, 5H), 6.98-6.93 (m, 6H), 5.54-5.47 (m, 1H), 3.87 (s, 6H), 2.33 (s, 3H), 1.37 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 150.0, 147.5, 141.5, 137.0, 136.3, 135.2, 134.8, 131.6, 130.6, 125.7, 121.9, 113.4, 55.3, 46.4, 23.5, 20.7; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178 found 453.2163.

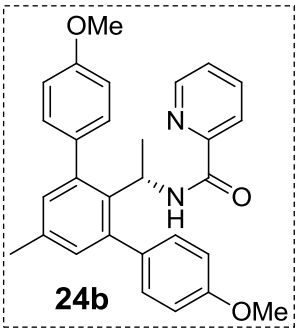


(R)-N*-(1-(4,4''-dimethoxy-5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide** ***(nb 536a, 23b): The resultant compound **23b** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) to afford **23b** as a yellow color semisolid (79 mg,70%); R_f (20% EtOAc/hexane) 0.4; $[\alpha]^{25}_D$ = -60.35 (c = 0.10, DCM); IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.09-8.06 (m, 1H), 7.81-7.75 (m, 2H), 7.38-7.35 (m, 5H), 7.07-6.93 (m,



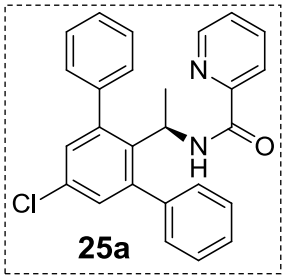
6H), 5.54-5.47 (m, 1H), 3.87 (s, 6H), 2.33 (s, 3H), 1.37 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 150.0, 147.5, 141.5, 137.0, 136.3, 135.2, 134.8, 131.6, 130.6, 125.7, 121.9, 113.4, 55.3, 46.4, 23.5, 20.7; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178 found 453.2163.

(S)-N*-(1-(4,4''-dimethoxy-5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 538a, 24b):The resultant compound **24b** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color semisolid (85 mg,75%); R_f (20% EtOAc/hexane) 0.4; $[\alpha]^{25}_D$ = 80.20 (c = 0.10, DCM); IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42-8.40 (m, 1H), 8.09-8.06 (m, 1H), 7.81-7.75 (m, 2H), 7.38-7.35 (m, 5H), 7.07-6.93 (m, 6H), 5.54-5.47 (m, 1H), 3.87 (s, 6H), 2.33 (s, 3H), 1.37 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.6, 158.6, 150.0, 147.5, 141.5, 137.0, 136.3, 135.2, 134.8, 131.6, 130.6, 125.7, 121.9, 113.4, 55.3, 46.4, 23.5, 20.7; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178 found 453.2163.



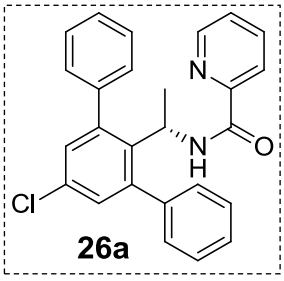
24b

(R)-N*-(1-(5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 425a, 25a):The resultant compound **25a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color liquid (54 mg, 52%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_D$ = -8.19 (c = 0.10, DCM); IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38-8.36 (m, 1H), 8.08-8.06 (m, 1H), 7.80-7.76 (m, 1H), 7.64 (d, 1H, J = 8.2Hz), 7.55-7.21 (m, 11H), 7.17 (s, 2H), 5.46-5.38 (m, 1H), 1.36 (d, 3H, J = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.8, 149.6, 147.6, 143.6, 141.0, 137.5, 137.0, 131.2, 130.3, 129.4, 128.2, 127.4, 125.9, 121.9, 46.3, 23.2; HRMS (ESI) calcd for $C_{26}H_{22}ClN_2O$ $[M+H]^+$ 413.1421 found 413.1402.



25a

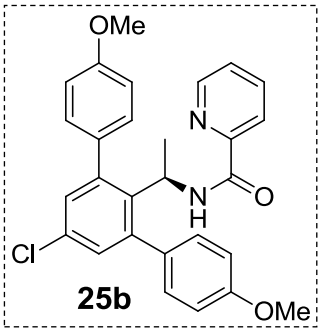
(S)-N*-(1-(5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 427a, 26a):The resultant compound **26a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color liquid (59 mg, 50%); R_f (20% EtOAc/hexane) 0.6; $[\alpha]^{25}_D$ = 10.80 (c = 0.10, DCM); IR (KBr): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38-8.36 (m, 1H), 8.08-8.06 (m, 1H), 7.80-7.76 (m, 1H), 7.64 (d, 1H,



26a

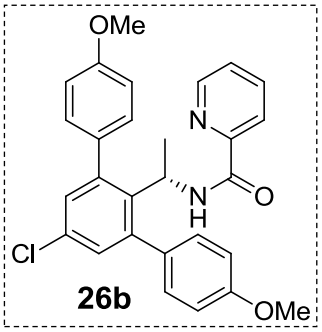
J = 8.2Hz), 7.55-7.21 (m, 11H), 7.17 (s, 2H), 5.46-5.38 (m, 1H), 1.36 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.8, 149.6, 147.6, 143.6, 141.0, 137.5, 137.0, 131.2, 130.3, 129.4, 128.2, 127.4, 125.9, 121.9, 46.3, 23.2; HRMS (ESI) calcd for $C_{26}H_{22}ClN_2O$ $[M+H]^+$ 413.1421 found 413.1402.

(R)-N*-(1-(5'-chloro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide *(nb 424a, 25b):The resultant compound **25b** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color liquid (65 mg, 55%); R_f (20% EtOAc/hexane) 0.4; $[\alpha]^{25}_D$ = -53.20 (c = 0.10, DCM); IR (KBr): 3351, 2933, 1531, 1265, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40-8.39 (m, 1H), 8.07 (d, 1H, *J* = 7.8Hz), 7.81-7.77 (m, 1H), 7.71 (d, 1H, *J* = 8.5Hz), 7.48-7.28 (m, 5H), 7.14 (s, 2H), 6.92 (br. s, 4H), 5.49-5.28 (m, 1H), 3.87 (s, 6H), 1.35 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 158.9, 149.7, 147.6, 143.2, 138.1, 137.1, 133.3, 131.1, 130.5, 130.4, 125.8, 121.9, 113.5, 55.3, 46.2, 23.2; HRMS (ESI) calcd for $C_{28}H_{26}ClN_2O_3$ $[M+H]^+$ 473.1632 found 473.1630.



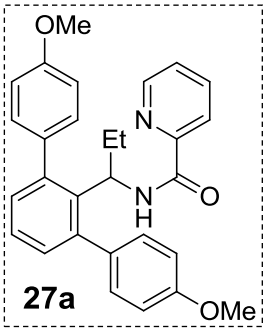
25b

(S)-N*-(1-(5'-chloro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)ethyl)picolinamide*(nb 426a, 26b):The resultant compound **26b** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a yellow color liquid (70 mg, 60%); R_f (20% EtOAc/hexane) 0.4; $[\alpha]^{25}_D$ = 65.30 (c = 0.10, DCM); IR (KBr): 3351, 2933, 1531, 1265, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40-8.39 (m, 1H), 8.07 (d, 1H, *J* = 7.8Hz), 7.81-7.77 (m, 1H), 7.71 (d, 1H, *J* = 8.5Hz), 7.48-7.28 (m, 5H), 7.14 (s, 2H), 6.92 (br. s, 4H), 5.49-5.28 (m, 1H), 3.87 (s, 6H), 1.35 (d, 3H, *J* = 7.2Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C162.7, 158.9, 149.7, 147.6, 143.2, 138.1, 137.1, 133.3, 131.1, 130.5, 130.4, 125.8, 121.9, 113.5, 55.3, 46.2, 23.2; HRMS (ESI) calcd for $C_{28}H_{26}ClN_2O_3$ $[M+H]^+$ 473.1632 found 473.1630.



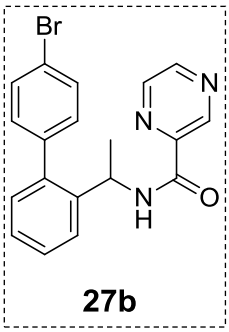
26b

N*-(1-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)propyl)picolinamide *(nb 1080b, 27a):The resultant compound **27a** was obtained after purification by column chromatography on silica (EtOAc:hexane = 20:80) as a black color liquid (35 mg, 30%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): 3346, 2937, 1394, 1265, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (d, 1H, *J* = 4.6Hz), 8.09 (d, 1H, *J* = 7.8Hz), 7.80-7.75 (m, 1H), 7.39-7.36 (m, 4H), 7.27 (d, 1H, *J* = 7.0 Hz), 7.24 (d, 1H, *J* = 7.5Hz), 7.14 (d, 2H, *J* = 7.5Hz), 6.95 (br. s, 4H), 5.36-5.30 (m, 1H), 3.89 (s, 6H), 1.73 (qui., 2H, *J* = 7.3Hz), 0.66 (t, 3H, *J* = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C163.1, 158.6, 149.9, 147.5, 141.8, 138.5, 137.0, 134.7, 130.8, 130.7, 125.7, 125.7, 122.0, 113.4, 55.3, 52.7, 30.8, 11.6; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178 found 453.2158.



27a

N*-(1-(4'-bromo-[1,1'-biphenyl]-2-yl)ethyl)pyrazine-2-carboxamide*(nb 603, 27b):The resultant crude mixture was purified on silica gel by column chromatography (EtOAc:hexane = 20:80) to afford **27b** as a dirty white color solid (25 mg, 30%); R_f (20% EtOAc/hexane) 0.7; mp: 131-133 ^oC; IR (KBr): 3055, 1721, 1428, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.30 (d, 1H, *J* = 1.4Hz), 8.71 (d, 1H, *J* = 2.4Hz), 8.44 (br. s, 1H), 7.53-7.50 (m, 3H), 7.41 (d, 2H, *J* = 8.2Hz), 7.31-7.27 (m, 1H), 7.14 (d, 2H, *J* = 7.6Hz), 5.45-5.38 (m, 1H), 1.41 (d, 3H, *J* = 7.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C161.5, 147.1, 144.1, 144.1, 144.0, 142.6, 140.2, 138.1, 132.1, 130.9, 130.3, 129.7, 128.1, 126.2, 122.4, 46.7, 23.4; HRMS (ESI) calcd for $C_{19}H_{17}BrN_3O$ $[M+H]^+$ 382.0555 found 382.0567.



27b

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Chapter 6

Thiophene directed Pd-catalyzed regioselective activation / functionalization of the aromatic system: a new approach to synthesize multiple-substituted phenylacetyl.

For, last few years, oxidative C-H activation of heteroarenes and arenes have fascinated much more attention towards providing a simple route for furnishing various bis-hetero aryls from heteroarenes.[1, 2] For example, the regioselective thiophenation of arenes via C-H activation/functionalization process, assisted by directing groups such as pyridines, quinoline, pyrimidines, thiazole, oxime, ethers, amides and carboxylic acids has been separately developed by the groups of Kambe, You, Glorius, Zhao, and Miura.[3] These discoveries have significantly enriched the approaches towards the synthesis of bis-heteroaryl. Nevertheless, to the best of our knowledge, there is still no example of oxidative C-H activation of phenyl acetyl system, and heteroarenes is available in the literature. Very few research papers are available by using thiophene and sulphur as directing group with different-different transition metal catalyst. Zhang and co-workers[4a] in 2012 first time reported the Pd-catalyzed the olefination of the arene system using thioether as co-ordinating group. This result concluded that a sulphur atom could serve as a coordinating group for the site-selective C-H activation. In the line later Shi and co-workers[4b] reported rhodium catalyzed thioether directed ortho-olefination of benzyl thioethers. In 2014, Zhang and co-workers[4c] reported a sulfoxide assisted *ortho* selective olefination reaction by using palladium as a catalyst. It is revealed that only transition metal-catalyzed C-H activation is one of the dominant approaches for the construction of such kind of molecule by using pre-functionalized phenyl acetyl system with thiophenes. But still, there has been a lack of structural diversity in terms of thiophene substituted phenyl acetyl system, which has significantly explored to the bioactivities of these compounds.

a) Bioactive molecules containing thiophene core

Thiophenyl scaffold containing arenes are the significant class of building blocks in various natural products and medicinally active molecules. For example, a variety of renowned drugs such as zileuton, raloxifene, suprofen, canagliflozin, and tiaprofenic acid contain thiophene moiety as important functional group. Thiophene scaffold is usually essential structure of various useful materials[5] (Figure 8). Thus, the use of thiophene derivatives as starting

materials to construct thiophenyl-containing arenes is a simple way and is in huge demand. This part of the thesis work is aimed to study the Pd-catalyzed regioselective thiophene directed C-H activation and the construction of multiple substituted phenyl acetyl molecules.

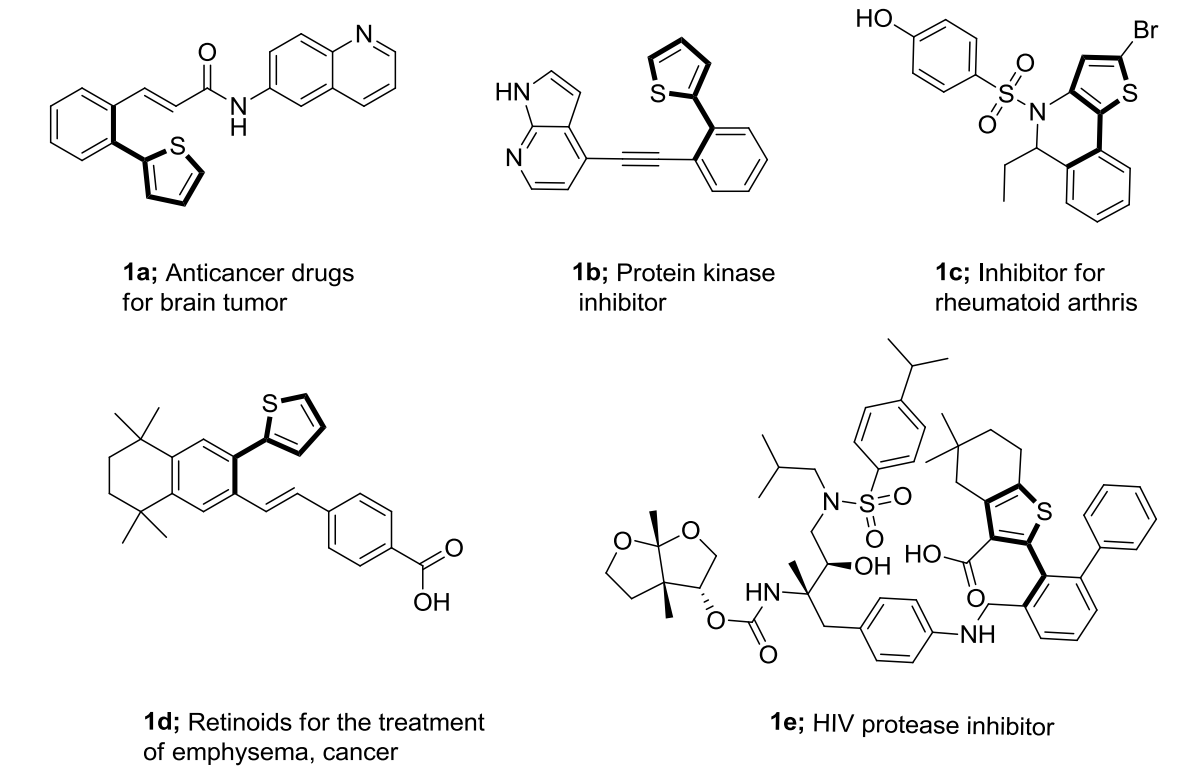


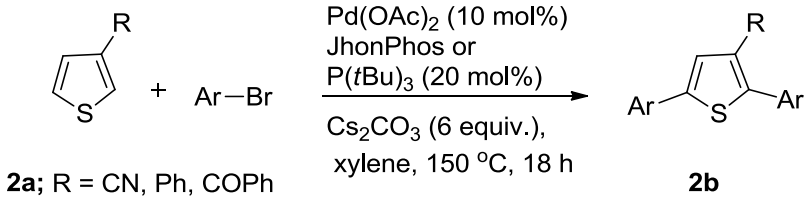
Figure 1 Representative example of the significant biological active molecule containing thiophenes

It is worth to mention here that variety of substituted thiophene compound has been prepared starting from phenylacetamide, after installation of thiophene its serves as a directing group for the second C-H activation. In this chapter, some of the recent reports, dealing with thiophene and sulphur as coordinating group for olefination and synthesis of multiple substituted phenyl acetyl were described.

Representative literature work dealing on the C-H functionalization reaction of thiophene and sulphur substrates

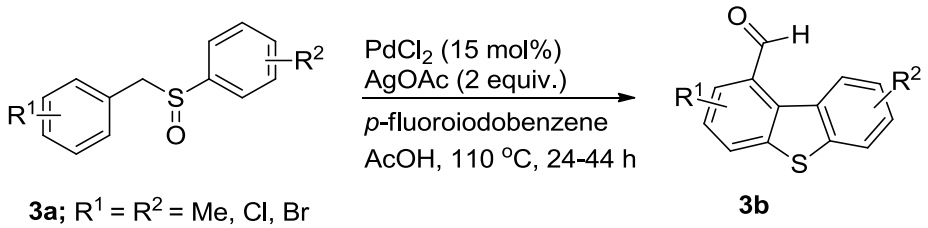
Miura and co-workers[6a] reported Pd(II)-catalyzed multiple arylations of thiophenes. The Pd-catalyzed hetero-aryl coupling reaction in the presence of $Pd(OAc)_2$ (10 mol%) and 20 mol%

of external ligand, 6 equiv. of Cs_2CO_3 in xylene at 150 ^oC for 18 h offered **2b** in excellent yield (Scheme 1).



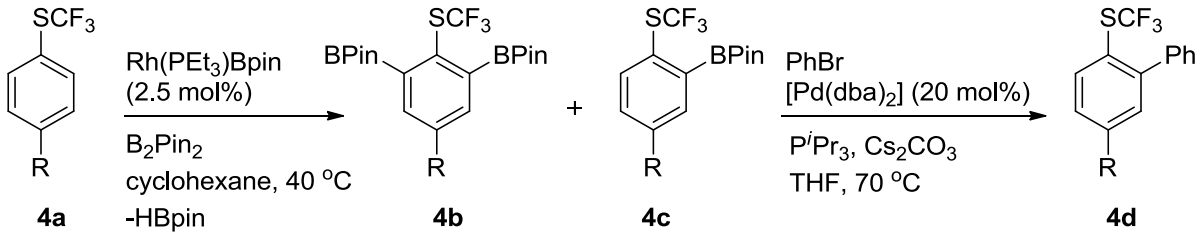
Scheme 1 Synthesis of multiply substituted thiophenes.

Antonchick and co-workers[6b] reported Sulfoxide as a new traceless directing group for the Pd-catalyzed double C-H activation of **3a.**The reaction of substrate **3a** and their various derivatives in the presence of $PdCl_2$ (15 mol%) as a catalyst, AgOAc (2 equiv.) as an oxidant/additive in AcOH at 110 ^oC for 24-44 h offered to the highly regioselective synthesis of polysubstituted dibenzothiophenes **3b** in good yield via relay reaction (Scheme 2).



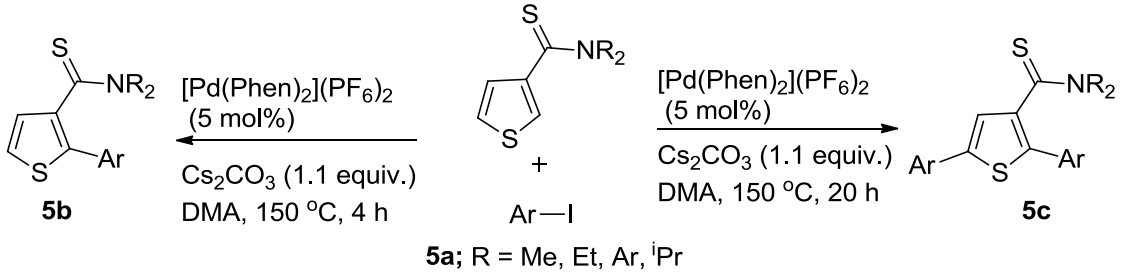
Scheme 2 Synthesis of polysubstituted dibenzothiophenes via double C-H activation.

Braun and co-workers[6c] reported SCF_3 to serve as a directing group for the Rh-catalyzed regioselective arylation of system **4a**. The reaction of **4a** in the presence of substituted Rh-boryl complexes as a catalyst 2.5 (mol%) and B_2Pin_2 in cyclohexane at 40 ^oC leads to the mono and bis product **4b/4c** in excellent yield (Scheme 3). Further, the Pd-catalyzed reaction of **4c** in the presence of Suzuki-Miyaura condition gave the product **4d** (Scheme 3).



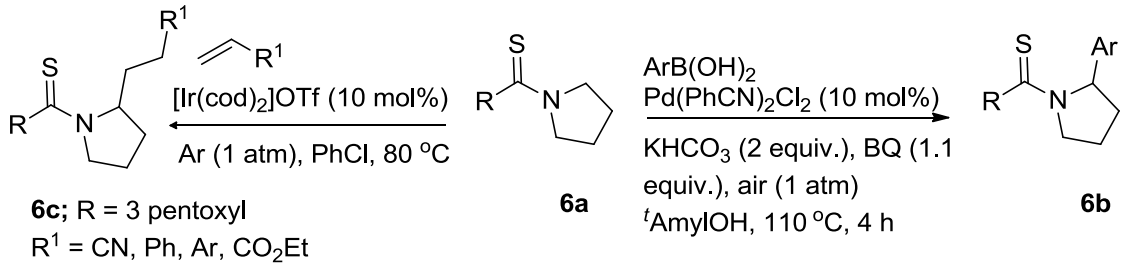
Scheme 3 SCF_3 as directing group for the arylation of **4d** via **4c**.

Murai and co-workers[6d] reported thiethyl thioamides $[Pd(phen)_2](PF_6)_2$catalyzed C-H bond arylation of substrate **5a**. The reaction of substrate **5a** in the presence of $[Pd(phen)_2](PF_6)_2$ (5 mol%) and 1.1 equiv. of Cs_2CO_3 in DMA as solvent at 150 ^oC for 20 h gave the bis arylated product **5c** in good yield. While controlling the reaction time from 20 h to 4 h with same reaction condition offered monoarylated product **5b** in good yield (Scheme 4)



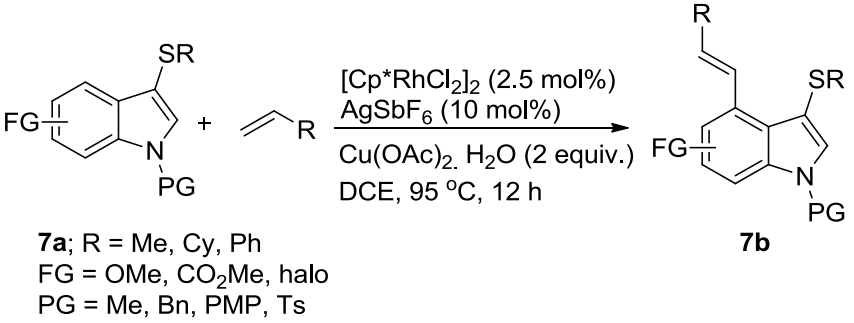
Scheme 4 Time controlling mono and bis product of substrate **5a**.

Yu and co-workers[6e, f] reported *N*-thioamide directed Pd(II)-catalyzed α-C-(sp^3)-H arylation of heterocyclic systems **6a** and their derivatives such as pyrrolidines, piperidines, azepanes, and *N*-methylamines. The Pd-catalyzed reaction of **6a** with a wide range of aryl boronic acid in the presence of $Pd(PhCN)_2Cl_2$ (10 mol%) as a catalyst, $KHCO_3$ (2 equiv.) as a base and 1.1 equiv. of BQ as an oxidant under 1 atm an air atmosphere in *tert*-AmylOH at 110 ^oC for 4h gave arylated product **6b** in excellent yield (Scheme 5). In 2017, same group Yu and co-workers[6g] reported Iridium catalyzed alkylation on the substrate **6a**. The Ir-catalyzed reaction of **6a** with a variety of alkylating agents in the presence of $[Ir(cod)_2]OTf$ (10 mol%) under 1 atm an argon atmosphere in chlorobenzene at 80 ^oC offered **6c** in good yield (Scheme 5)



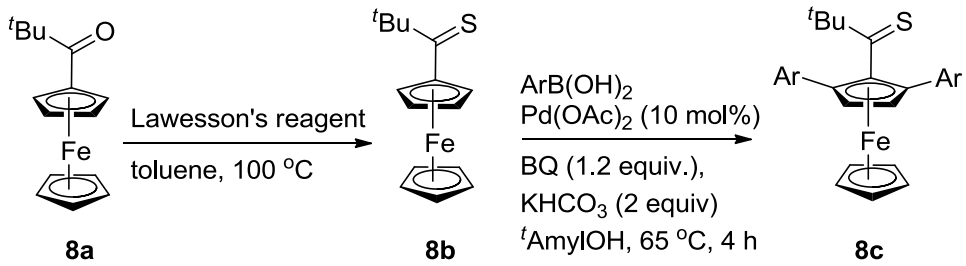
Scheme 5 Pd and Ir catalyzed arylation and alkylation of substrate **6a**.

Miura and co-workers[7a] reported thioether directed Rh(III)-catalyzed C-H alkenylation of substituted indole and their derivatives. The Rh-catalyzed reaction of substrate **7a** with the variety of alkenylating agents in the presence of $[Cp^*RhCl_2]_2$ (2.5 mo%), 10 mol% of $AgSbF_6$ and 2 equiv. of $Cu(OAc)_2.H_2O$ in DCE at 95 °C for 12 h proceed through five member metalacycle to offer product **7b** in excellent yield (Scheme 6).



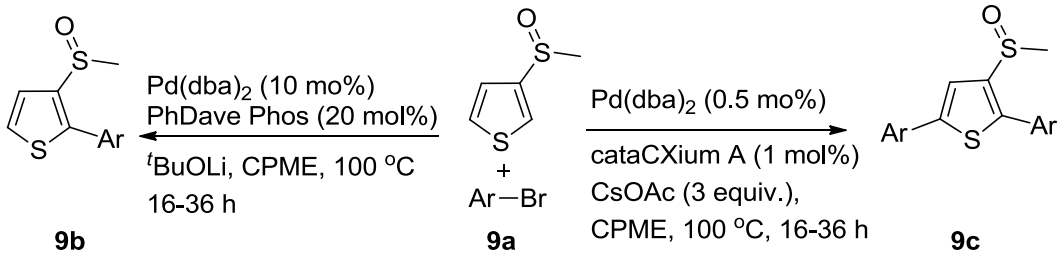
Scheme 6 Rh catalyzed arylation of substituted indole derivative **7a**.

You and co-workers[7b] reported thioketone directed Pd(II)-catalyzed C-H arylation of ferrocenes. For the preparation of the starting material, reaction of substrate **8a** with lawesson's regent in toluene at 100 °C gave the product **8b**. The reaction of **8b** with aryl boronic acids in the presence of $Pd(OAc)_2$ and 1.2 equiv. of BQ, 2 equiv. of $KHCO_3$ in *tert*-AmylOH at 100 °C for 4 h lead to the bis arylated product **8c** in good yield (Scheme 7)



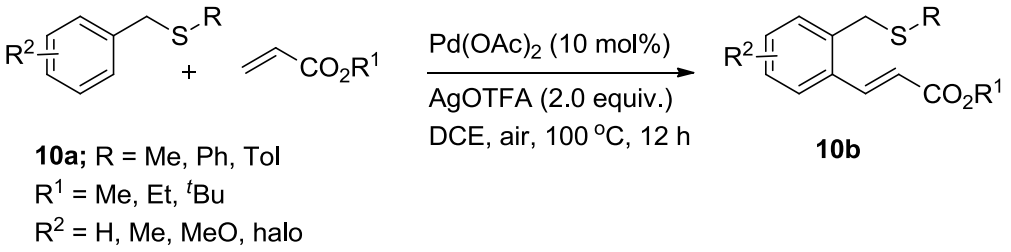
Scheme 7 Thioketone directed Pd catalyzed arylation of ferrocene derivatives **8b**.

Walsh and co-workers[7c] reported Pd-catalyzed direct arylation of (3-thiophene)SOMe substrate **9a**. The Pd-catalyzed reaction of substrate **9a** with a wide range of aryl bromide in the presence of $Pd(dba)_2$ (10 mo%) and an external ligand PhDave Phos (20 mol%), 2 equiv. of ^{t}BuOLi as a base, CPME (cyclopentyl methyl ether) as solvent at 100 ^{o}C for 16-36 h lead to the monoarylated product **9b** in excellent yield (Scheme 8). Again the same reaction was performed of substrate **9a** with a variety of aryl bromide in the presence of $Pd(dba)_2$ (0.5 mo%) and external ligand cataCXium A (1 mol%), 3 equiv. of CsOAc as a base, CPME (cyclopentyl methyl ether) at 100 ^{o}C for 16-36 h gave the bisarylated product **9c** in good yield (Scheme 8).



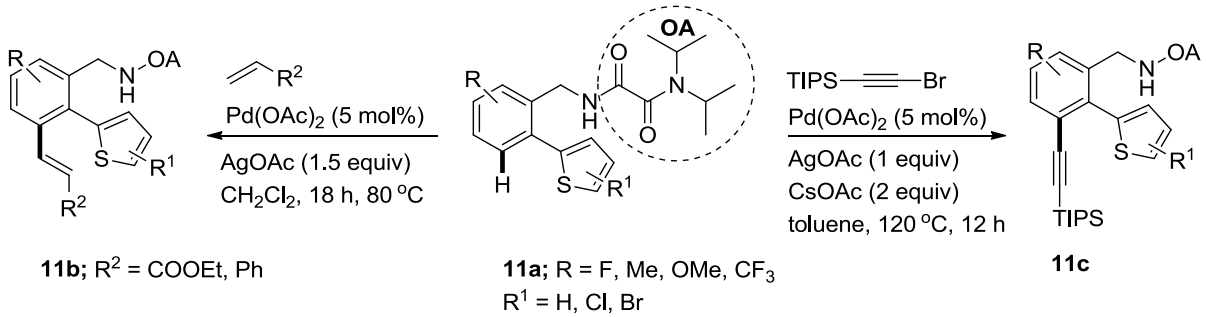
Scheme 8 Ligand controlled Pd catalyzed arylation of (3-thiophene)SOMe substrate **9a**.

Zhang and co-workers[7d] reported thioether as a directing group for Pd(II)-catalyzed C-H activation of aryl system. The Pd-catalyzed C-H activation via dinuclear cyclopalladation intermediate of substrate **10a** with a large variety of acrylate derivatives in the presence of $Pd(OAc)_2$ (10 mol%) and 2 equiv. of AgOTFA under an open atmosphere in DCE at 100 ^{o}C for 12 h offered **10b** product in excellent yield (Scheme 9).



Scheme 9 Thioether as a directing group for arylation of arenes **10a**.

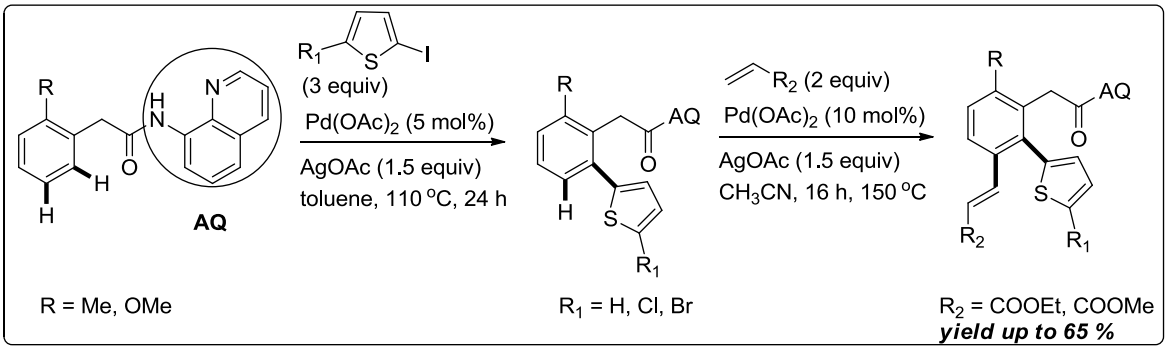
Zhao and co-workers[7e] reported thiophene directed Pd(II)-catalyzed regioselective C-H activation of benzylamines system. The substrate **11a** treated with ethyl acrylate in the presence of $Pd(OAc)_2$ (5 mol%) and AgOAc (1.5 equiv.) in DCM at 80 ^oC for 18 h gave the product **11b** in good yield (Scheme 10). Further, they explored the reaction condition for alkynylation of the benzylamines substrate **11a**. The reaction of **11a** with acetylenic bromide (TipsccBr) in the presence of $Pd(OAc)_2$ (5 mol%) and AgOAc (1 equiv.), 2 equiv. of CsOAc in toluene at 120 ^oC for 12 h offered **11c** product in good yield (Scheme 10).



Scheme 10 Thiophene directed arylation on benzylamines substrate **11a**.

Given the importance of multiple-substituted phenyl acetyl system, are essential synthetic units in organic synthesis and biologically active molecules of pharmaceuticals and medicinal chemistry research area, developing a new route for synthesizing new multiple substituted phenyl acetyl cores will enrich the library of thiophene containing multiple substituted phenyl acetyl scaffolds. However, only a few methods for constructing multiply substituted thiophene-containing phenyl acetyl system have been disclosed. The general approaches are the transition-metal catalyzed cross-coupling with pre-functionalized phenyl acetyl derivatives. Thus, the development of highly regioselective C-H functionalization to synthesize multiple-substituted thiophene-containing phenyl acetyl derivatives is still challenging. Therefore, the use of thiophene-containing phenyl acetyl derivatives as starting materials to construct thiophene-containing phenyl acetyl arenes is a straight forward route and is in high demand. A literature survey revealed that there exist only limited reports dealing on the synthesis of multiple substituted benzylamines and arenes. Accordingly, a part of this thesis reports the construction of new multiple substituted phenyl acetyl derivatives, via 8-Aminoquinoline, directed Pd(II)-catalyzed AgOAc promoted double C-H activation of the phenylacetamide system using 2-iodo thiophene and acrylate as the coupling partners.

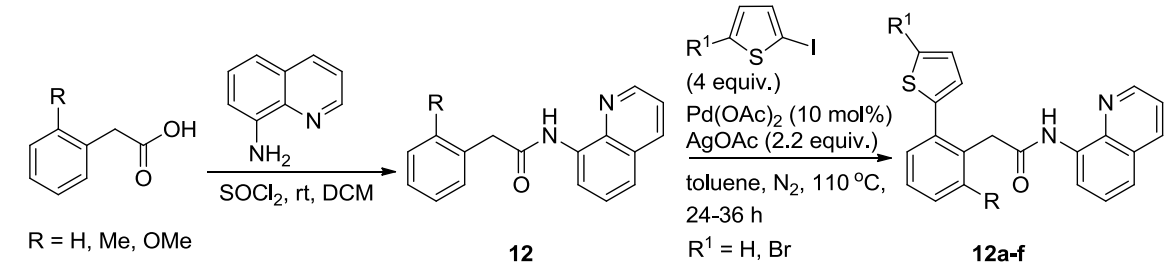
This work

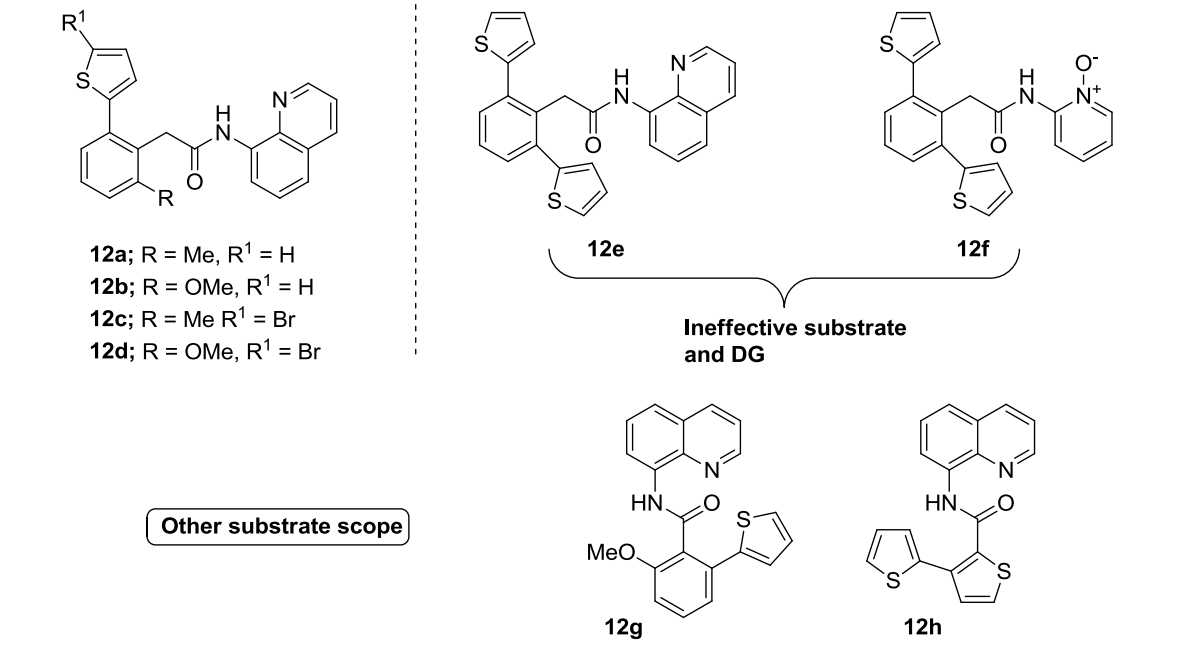


Scheme 11 Title of this work: Thiophene directed Pd-catalyzed regioselective arylation of the phenylacetamide system.

Result and discussion

To start the synthesis of multiple substituted phenyl acetyl system, initially, the substitute phenylacetamide substrate **12a-f** were assembled from their corresponding phenyl acetyl system and directing groups using the known literature procedure (Scheme 12).



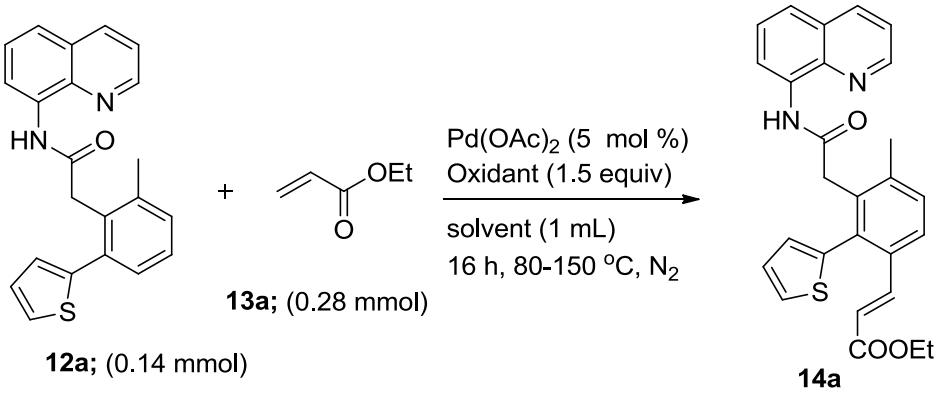


Scheme 12 Directing group and substrate employed for the investigating the thiophene directed alkenylation (conditions: Substrate (0.14 mmol), **13a** or acrylate derivatives (0.28 mmol or 2 equiv.), $Pd(OAc)_2$ (20 mol%), AgOAc (0.21 mmol or 1.5 equiv.), CH_3CN or DCM (1 mL), 16-24 h and 120-150 ^oC (the alkenylation reactions using **12a-d** and **12g-h** were successful as discussed in results and discussion part and the alkenylation with **12e-f** were not successful).

After preparation of the required phenylacetamide substrates **12a-h**, we initially attempted the synthesis of multiple substituted phenyl acetyl system **14a** via the $Pd(OAc)_2$/AgOAc catalytic system-based, weak co-ordinating group, thiophene directed and chelation-assisted C-(sp^2)-H alkenylation of phenyl acetyl substituted system **12a**. Table 1 shows the optimization of the reaction conditions of thiophene assisted C-(sp^2)-H bond alkenylation of phenyl acetylsubstituted system **12a** with **13a** in the presence of $Pd(OAc)_2$ as catalyst and variety of additives/ oxidant and various solvents.

The thiophene directed C-H bond alkenylation of substituted phenylacetamide substrate **12a** with ethyl acrylate **13a** (2 equiv.) in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst and AgOAc (additives, 1.5 equiv.) in CH_3CN at 150 ^oC found to be the best reaction conditions, which afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in 60% yield (entry 7, Table 1). Further, we wished to check the yield of the product **14a** can be improved using various solvent and oxidants. The Pd(II)-catalyzed reaction of **12a** with **13a** in toluene and HFIP solvents were not fruitful (entries 1 and 4, Table 1). The Pd(II)-catalyzed reaction of **12a** with **13a** in ^{t}AmylOH afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in only traces amount (entry 2, Table 1).

Table 1 Optimization of reaction conditions.



12a; (0.14 mmol)

13a; (0.28 mmol)

14a

entry	oxidant	solvent	t (°C)	**14a** yield (%)
1	AgOAc	Toluene	150	-
2	AgOAc	^{t}AmylOH	120	traces
3	AgOAc	DCM	80	50
4	AgOAc	HFIP	100	-
5	Ag_2CO_3	CH_3CN	80	<5
6	Ag_2O	CH_3CN	80	-
7	**AgOAc**	**CH_3CN**	**150**	**60**
8	$Cu(OAc)_2$	CH_3CN	80	-
9	BQ	CH_3CN	80	traces
10	$K_2S_2O_8$	CH_3CN	80	traces
11[a]	AgOAc	CH_3CN	150	62
12[b]	AgOAc	CH_3CN	150	65
13[c]	AgOAc	CH_3CN	150	70

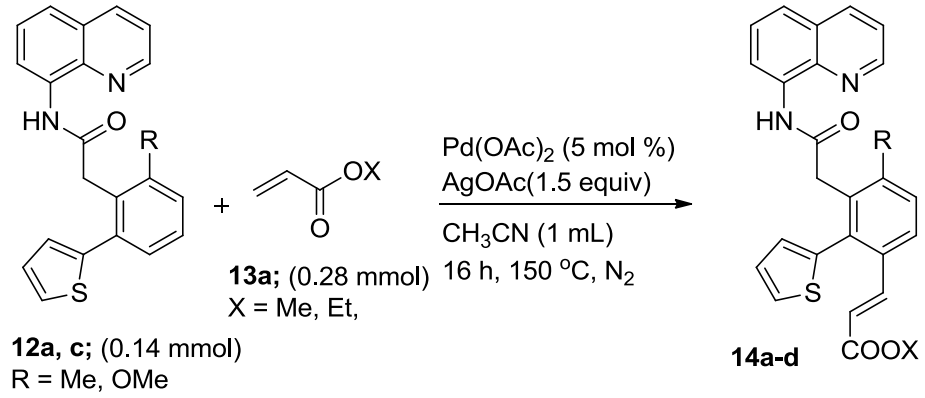
[a] 10 mol%; [b] 15 mol%; [c] 20 mol% $Pd(OAc)_2$ were used.

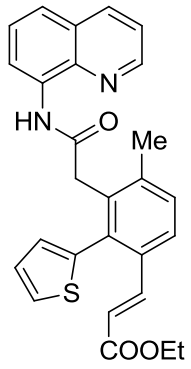
The Pd(II)-catalyzed reaction of **12a** with **13a** in DCM afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in 50% yield (entry 3, Table 1). To improve the yield we also performed the reaction by using different additives/oxidants. The $Pd(OAc)_2$ catalyzed C-(sp^2)-H alkenylation of **12a** with **13a** in the presence of Ag_2CO_3 as an additive instead of AgOAc afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in less than 5% yield (entry 5, Table 1).

The Pd(II)-catalyzed C-(sp^2)-H alkenylation of substituted phenylacetamide substrate **12a** with ethyl acrylate **13a** in the presence of Ag_2O or $Cu(OAc)_2$ as an additive instead of AgOAc failed to afford alkenylated phenyl acetyl derivatives **14a** (entries 6 and 8, Table 1). The Pd(II)-catalyzed C-(sp^2)-H alkenylation of substituted phenylacetamide substrate **12a** with **13a** in the presence of 1, 4-benzoquinone or $K_2S_2O_8$ as an additive instead of AgOAc afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in only traces (entries 9 and 10, Table 1). In order to improve the yield of **14a**, we also screened the Pd(II)-catalyzed arylation of substituted phenylacetamide substrate **12a** using different mol% of $Pd(OAc)_2$ catalyst. Accordingly, the Pd(II)-catalyzed C-H alkenylation reaction of substituted phenylacetamide substrate **12a** with 2equiv. of ethyl acrylate **13a** in the presence of $Pd(OAc)_2$ (10 mol%) afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in 62% yield (entry 11, Table 1). The Pd(II)-catalyzed C-H alkenylation reaction of **12a** with 2 equiv. of **13a** in the presence of $Pd(OAc)_2$ (15 mol%) afforded the C(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in 65% yield (entries 12, Table 1). The Pd(II)-catalyzed C-H alkenylation reaction of **12a** with 2 equiv. of **13a** in the presence of $Pd(OAc)_2$ (15-20 mol%) afforded the C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a** in 70% yield (entries 13, Table 1).

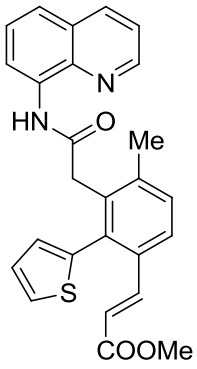
After completion of the optimization reactions, we next wished to explore the generality and substrate scope of this developed condition comprising the Pd(II)-catalyzed, weak directing group thiophene directed C-(sp^2)-H alkenylation of substituted phenyl acetyl system. Accordingly, Scheme 13 shows the $Pd(OAc)_2$-catalyzed, AgOAc-mediated thiophene assisted C-(sp^2)-H alkenylation of **12a** with a wide range of acrylate under the optimized reaction conditions (entry 7, Table 1). The $Pd(OAc)_2$/AgOAc-catalytic system based, thiophene directed C-(sp^2)-H alkenylation of **12a** with substituted acrylate containing a substituent such as ethyl and methyl acrylate afforded the corresponding C-(sp^2)-H alkenylated phenyl acetyl derivatives **14a-b** (multiply substituted phenyl acetyl) in 55-60% yields, respectively (Scheme 13). The $Pd(OAc)_2$/AgOAc-catalytic system based, thiophene directed C-(sp^2)-H alkenylation of **12b** with substituted acrylate such as methyl and ethyl acrylate afforded the corresponding C-(sp^2)-H alkenylated phenyl acetyl derivatives **14c** and **14d** (multiply substituted phenyl acetyl) in 50-62% yields (Scheme 13). The $Pd(OAc)_2$/AgOAc-catalytic system based, thiophene directed C-(sp^2)-H alkenylation of **12c-d** with substituted acrylate such as methyl and ethyl acrylate afforded the corresponding C-(sp^2)-H alkenylated phenyl acetyl derivatives is in impure forms.

Scheme 13 Thiophene directed, weak co-ordinate assisted construction of multiply substituted phenyl acetyls.

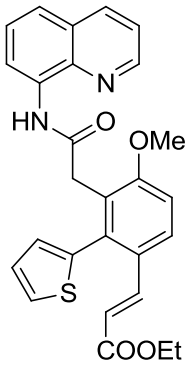




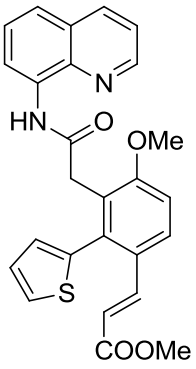
14a; 60%



14b; 55%



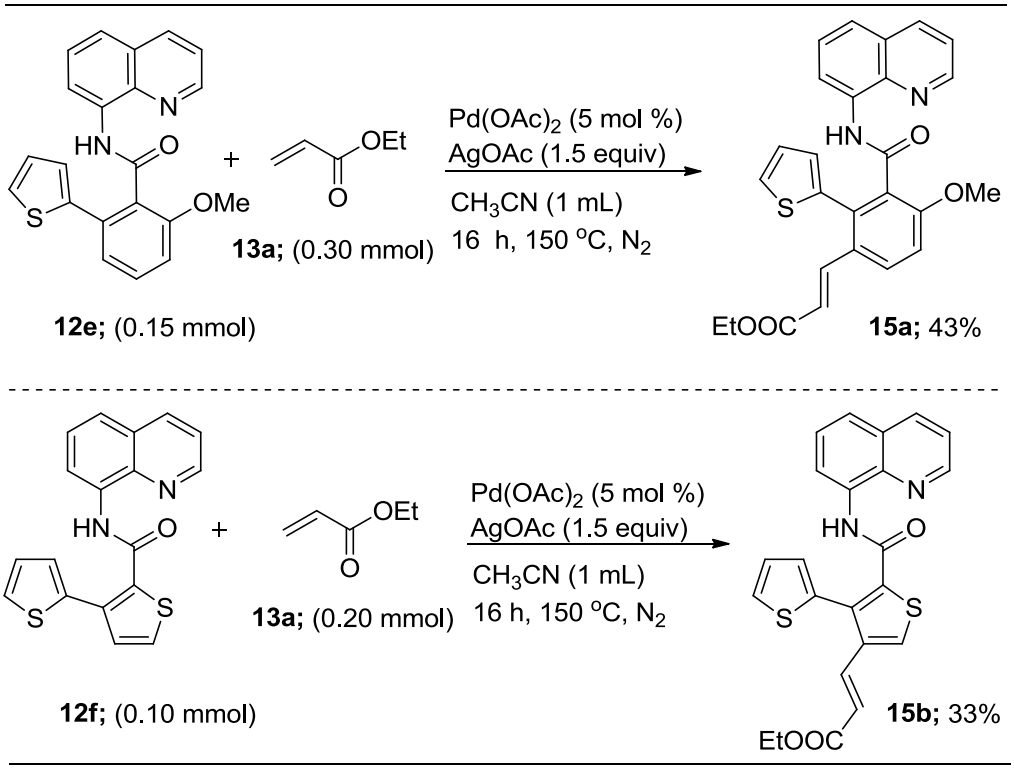
14c; 62%



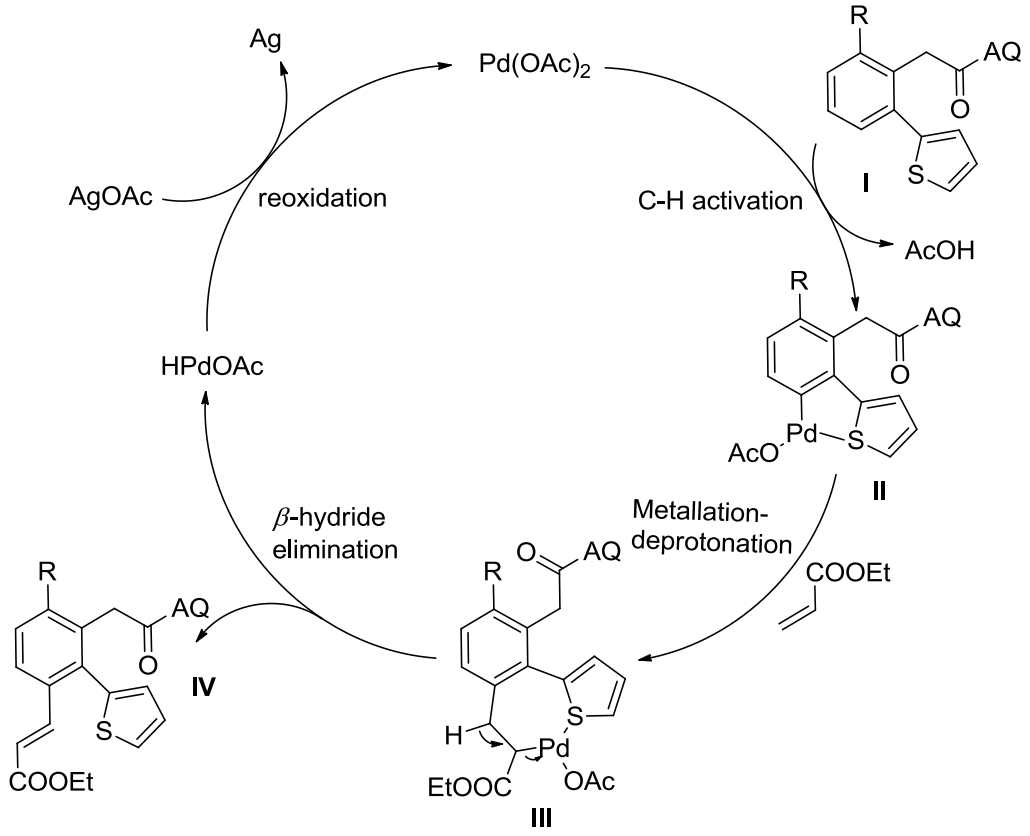
14d; 50%

Next, to elaborate our investigation on the $Pd(OAc)_2$/AgOAc-catalytic system based C-(sp^2)-H alkenylation of arene and heteroarenes system, we performed the Pd(II)-catalyzed reaction of thiophene directed substituted benzamide system **12e** with **13a** and this reaction afforded the C-(sp^2)-H alkenylated substituted benzamide derivative **15a** in 43% yield (Scheme 14). Then, the Pd(II)-catalyzed reaction of heterocyclic carboxamide system **12f** (derived from 2-thiophene carboxylic acid and 8-Aminoquinoline) with **13a** afforded the C(sp^2)-H alkenylated substituted heterocyclic carboxamide derivative **15b** in only 33% yield (Scheme 14).

Scheme 14 Thiophene directed, the weak directing group assisted construction of multiply substituted arene and heteroarene system.



The Pd(II)-catalyzed alkenylation of the weak directing group thiophene derivatives **12a-b** and **12e-f** afforded the corresponding C-(sp^2)-H alkenylated product **14** and **15** as the most compelling product (Scheme 13-14). Based on these significant consideration and agreement with the generally accepted Pd^{II}-Pd^{IV} catalytic pathway comprising the $Pd(OAc)_2$/AgOAc catalytic cycle based, thiophene directed C-(sp^2)-H alkenylation of phenyl acetyl system, a proposed mechanism for the C-(sp^2)-H alkenylation of the substrates **12a-b** and **12e-f** was depicted in scheme 15.

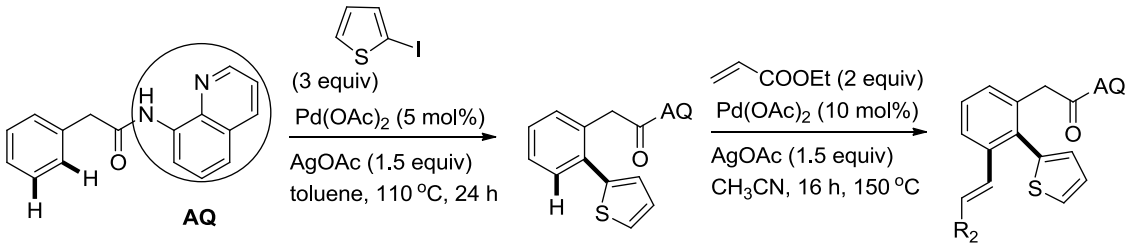


Scheme 15 Plausible mechanism for the alkenylation of **12a-d** and **12g-h.**

Finally, the alkenylation of phenyl acetyl system was successful. Our various effort on the weak co-ordinating thiophene directed alkynylation were not successful. The different directing group was screened for performing the alkenylation of substituted phenyl acetyl system. Only substituted phenyl acetyl and thiophene were found to be the best weak directing group for alkenylation. Further, various alkenylating agents such as Phenyl, acetylene and hydroxyl functional groups containing starting material were used to examine their reactivity pattern. Unfortunately, none of the alkenylating agents work for us. In the case of starting materials **12c-d** there was a lot of reaction tried, but in allevidence, a mixture of the productwere formed. In general, C-(sp^2)-H alkenylation of substituted phenyl acetyl with ethyl or methyl acrylate gave multiply substituted phenyl acetyl as the primary product in high yield (Scheme 13). Presumably, the installation of an acrylate moiety may result in a double C-H activation of phenyl acetyl system directed by thiophene. Our other trials to get the C-(sp^2)-H alkenylated product were not successful at this stage.

Conclusion

In summary, the chapter 6 revealed the Pd(II)-catalyzed alkenylation of C-(sp^2)-H bonds using thiophene substituted carboxamides such as thiophene substituted phenyl acetyl carboxamide, thiophene substituted benzamide and heterocarboxamide system. The Pd(II)-catalyzed C-(sp^2)-H bond alkenylation afforded the synthesis of multiply substituted phenyl acetyl, benzamide and heterocarboxamide molecules.



Experimental section

General. IR spectra of the samples were recorded as KBr pellets or thin films. ^{1}H / ^{13}C NMR spectra were recorded on 400 and 100 MHz spectrometers, respectively. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under nitrogen atm. Organic layers after the workup procedure were dried using anhydrous sodium sulphate. TLC analysis was performed on silica gel,and the components were visualized by observation under iodine vapour. Isolated yields of all the compounds are reported, andyields of all the reactions were not optimized.

Procedure for the synthesis of thiophene substituted phenylacetamide 12a-f and 12g.

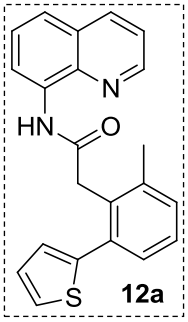
A dry RBF containing the corresponding carboxylic acid (1 mmol) and $SOCl_2$ (0.6 mL) was heated at 80 ^{o}C for 4 h under a nitrogen atmosphere. After the reaction time period, the reaction mixture was concentrated under reduced pressure to remove the volatiles and then, the resultant crude reaction mixture was diluted with anhydrous DCM (2 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the corresponding amine (1 mmol), Et_3N (111 mg, 1.1 mmol) and DCM (4 mL) under a nitrogen atmosphere. The resulting mixture was allowed to stir at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. The crude reaction was purified by column chromatography (neutral alumina (EtOAc/hexanes = 25:75) furnished the phenylacetamide system. Further, an appropriatephenylacetamide (0.12 mmol, 1equiv), an appropriate 2-iodo thiophene (0.48 mmol, 4equiv), $Pd(OAc)_2$ (2.7 mg, 10 mol%), and AgOAc (50 mg, 0.3 mmol) in anhydrous toluene (3 mL) was heated at 110 ^{o}C, for 24 h under a nitrogen atmosphere. After the reaction period, the solvent was evaporated in vacuo to afford a crude reaction mixture. The crude reaction was purified by column chromatography (silica gel (EtOAc/hexanes = 10:90)

furnished the corresponding arylated products **12a-f** and **12g** (see corresponding Tables/Schemes for specific examples and reaction conditions) **12e** known in literature.[1i]

Procedure for the synthesis of thiophene substituted phenylacetamide 12h.

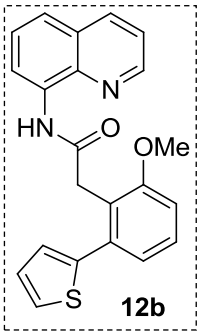
A dry RB flask containing the corresponding amine (1 mmol), Et_3N (111 mg, 1.1 mmol) and DCM (4 mL) was stirred for 10 min under a nitrogen atmosphere. Then corresponding acid chloride was added drop-wise. The resulting mixture allowed to stir at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and saturated aqueous $NaHCO_3$ solution (twice). The combined organic layers were dehydrated over anhydrous Na_2SO_4, and then, the solvent was evaporated in vacuo to afford a crude mixture. The crude reaction was purified by column chromatography (silica gel (EtOAc/hexanes = 25:75) furnished the heterocyclic-carboxamide system. Further, an appropriate heterocyclic-carboxamide (1 mmol, 1equiv), an appropriate 2-iodo thiophene (4 mmol, 4equiv), $Pd(OAc)_2$ (11 mg, 5 mol%), and AgOAc (332 mg, 2 mmol) in anhydrous toluene (5 mL) was heated at 110 ^oC, for 24 h under a nitrogen atmosphere. After the reaction duration, the solvent was evaporated in vacuo to afford a crude reaction mixture. The crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes = 10:90) furnished the corresponding thiophenated products **12h** (see corresponding Tables/Schemes for specific examples and reaction conditions).

2-(2-Methyl-6-(thiophen-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide*(nb 1489/ 1371 sm 12a):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12a** as a yellow colour solid (200 mg, 50%); R_f (20% EtOAc/hexane) 0.5; mp: 112-114 ^oC; IR (KBr): 3055, 2986, 1423, 1265, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.87 (br. s, 1H), 8.78 (d, 1H, J = 7.3Hz), 8.66 (d, 1H, J = 4.2Hz), 8.13 (d, 1H, J = 8.3 Hz), 7.56-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.36-7.31 (m, 3H), 7.14 (d, 1H, J = 3.2 Hz), 7.03 (t, 1H, J = 4.2 Hz), 4.03 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.5,

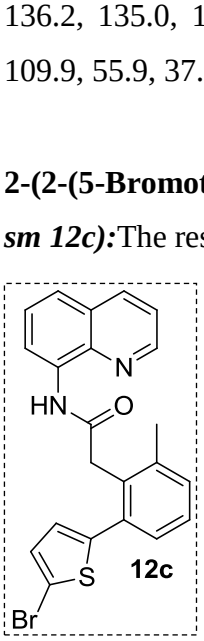


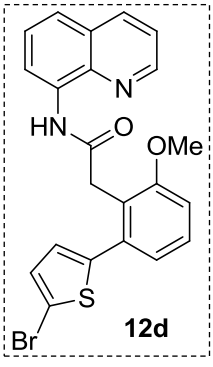
148.2, 142.5, 138.5, 138.5, 136.2, 135.8, 134.4, 132.1, 130.7, 129.5, 127.8, 127.4, 127.4, 127.3, 127.2, 127.1, 125.7, 121.6, 116.3, 40.3, 20.6; HRMS (ESI) calcd for $C_{22}H_{19}N_2OS$ $[M+H]^+$ 359.1218 found 359.1212.

2-(2-Methoxy-6-(thiophen-2-yl)phenyl)-*N*-(quinolin-8-yl)acetamide*(nb 1600/1587sm 12b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12b** as a faint yellow colour solid (119 mg, 72%); R_f (20% EtOAc/hexane) 0.5; mp: 127-129 ^oC; IR (KBr): 3055, 2987, 1424, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.40 (br. s, 1H), 8.82 (d, 1H, J = 7.5Hz), 8.79-8.75 (m, 1H), 8.14 (d, 1H, J = 8.2 Hz), 7.56-7.52 (m, 1H), 7.48 (d, 1H, J = 7.9 Hz), 7.46-7.40 (m, 2H), 7.36-7.29 (m, 2H), 7.18 (d, 1H, J = 7.8 Hz), 7.14-7.11 (m, 1H), 7.01-6.96 (m, 1H), 4.02 (s, 2H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.1, 157.9, 148.0, 141.7, 138.6, 136.7, 136.2, 135.0, 128.0, 128.0, 127.9, 127.5, 127.4, 126.8, 123.8, 122.3, 121.5, 121.3, 116.5, 109.9, 55.9, 37.3; HRMS (ESI) calcd for $C_{22}H_{19}N_2O_2S$ $[M+H]^+$ 375.1167 found 375.1183.



2-(2-(5-Bromothiophen-2-yl)-6-methylphenyl)-*N*-(quinolin-8-yl)acetamide*(nb 1488/1597 sm 12c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12c** as a yellow colour solid (120 mg, 55%); R_f (20% EtOAc/hexane) 0.6; mp: 134-136 ^oC; IR (KBr): 3055, 2986, 1424, 1265, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (br. s, 1H), 8.76 (dd, 1H, J_1 = 7.1, J_2 = 1.7Hz), 8.68 (dd, 1H, J_1 = 4.2, J_2 = 1.6Hz), 8.14 (dd, 1H, J_1 = 8.3, J_2 = 1.6Hz), 7.57-7.53 (m, 1H), 7.51 (dd, 1H, J_1 = 8.4, J_2 = 1.9Hz), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 7.36-7.31 (m, 3H), 6.97 (d, 1H, J = 3.8 Hz), 6.89 (d, 1H, J = 3.7 Hz), 4.03 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.2, 148.2, 144.2, 138.7, 138.5, 136.2, 134.9, 134.3, 132.2, 131.1, 130.2, 129.4, 127.9, 127.6, 127.4, 127.3, 121.7, 121.6, 116.4, 112.1, 40.1, 20.6; HRMS (ESI) calcd for $C_{22}H_{18}BrN_2OS$ $[M+H]^+$ 437.0323 found 437.0339.

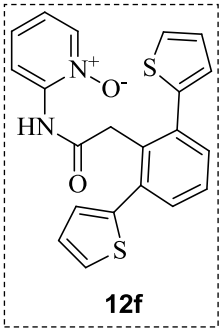




2-(2-(5-Bromothiophen-2-yl)-6-methoxyphenyl)-*N*-(quinolin-8-yl)acetamide*(nb1596 sm 12d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12d** as a

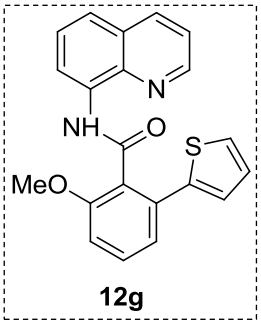
yellow colour solid (90 mg, 79%); R_f (20% EtOAc/hexane) 0.5; mp: 151-153 ^oC; IR (KBr): 3298, 2924, 1677, 1530, 1266, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.43 (br. s, 1H), 8.81-8.77 (m, 2H), 8.15 (dd, 1H, J_1 = 8.2, J_2 = 1.5Hz), 7.56-7.52 (m, 1H), 7.49 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.44 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 7.35-7.31 (m, 1H), 7.23 (d, 1H, J = 3.8 Hz), 7.10 (d, 1H, J = 7.2 Hz), 7.07 (d, 1H, J = 3.8 Hz), 7.00 (d, 1H, J = 8.2 Hz), 4.02 (s, 3H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.9, 157.9, 148.0, 143.3, 138.6, 136.3, 135.7, 134.9, 130.5, 128.6, 128.2, 128.0, 127.4, 123.5, 122.3, 121.5, 121.4, 116.5, 112.2, 110.3, 56.0, 37.2; HRMS (ESI) calcd for $C_{22}H_{18}BrN_2O_2S$ $[M+H]^+$ 453.0272 found 453.0294.

2-(2-(2,6-Di(thiophen-2-yl)phenyl)acetamido)pyridine-1-oxide*(nb 107 sm 12f):*The afford **12f** as a greenish yellow colour solid (221 mg, 56%); R_f (50% MeOH/EtOAc) 0.6; mp: 243-245 ^oC; IR (KBr): 3106, 1699, 1505, 1267, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.83 (br. s, 1H), 8.40 (dd, 1H, J_1 = 8.5, J_2 = 1.8Hz), 8.20 (dd, 1H, J_1 = 6.5, J_2 = 1.4Hz), 7.52-7.50 (m, 2H), 7.42 (dd, 1H, J_1 = 8.4, J_2 = 6.8Hz), 7.35-7.31 (m, 3H), 7.07 (dd, 2H, J_1 = 3.5, J_2 = 1.2Hz), 7.05 (d, 1H, J = 3.5Hz), 7.03 (d, 1H, J = 3.5Hz), 7.00-6.96 (m, 1H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.3, 144.1, 141.6, 137.0, 136.4, 131.7, 131.7, 128.2, 127.5, 127.4, 127.3, 126.2, 118.5, 114.6, 40.6; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_2S_2$ $[M+H]^+$ 393.0731 found 393.0738.



12f

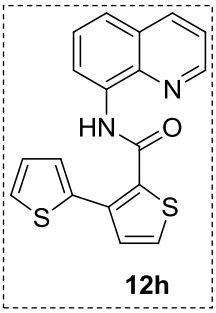
2-Methyl-*N*-(quinolin-8-yl)-6-(thiophen-2-yl)benzamide*(nb 1598 sm 12g):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12g** as a dirty white solid (248 mg, 68%); R_f (20% EtOAc/hexane) 0.4; mp: 142-144 ^oC; IR (KBr): 3054, 2985, 1691, 1264, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.98 (br. s, 1H), 8.95 (dd, 1H, J_1 = 7.4, J_2 = 1.0Hz), 8.70 (dd, 1H, J_1 = 4.1, J_2 = 1.5Hz), 8.13 (dd, 1H, J_1 = 8.2, J_2 = 1.4Hz), 7.60-7.56 (m, 1H), 7.52 (dd, 1H, J_1 = 8.2, J_2 = 1.1Hz), 7.45 (d, 1H, J = 8.1 Hz), 7.40 (dd, 1H, J_1 = 8.2, J_2 = 4.0Hz), 7.33 (dd, 1H, J_1 = 3.5, J_2 = 0.8Hz), 7.23-7.19 (m, 2H), 6.99 (d, 1H, J = 8.3 Hz), 6.90 (dd, 1H, J_1 = 5.0, J_2 = 3.4Hz), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.1, 156.9, 148.1, 141.0, 138.4, 136.2, 134.7, 133.5, 130.4, 127.9, 127.6, 127.4, 126.6, 126.1, 126.0,



12g

122.3, 121.8, 121.5, 116.8, 110.4, 56.1; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_2S$ $[M+H]^+$ 361.1011 found 361.1027.

N*-(Quinolin-8-yl)-[2,3'-bithiophene]-2'-carboxamide*(nb 1599 sm 12h): The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **12h** as a turmeric colour solid (177 mg, 69%); R_f (20% EtOAc/hexane) 0.5; mp: 113-115 ^oC; IR (KBr): 3054, 1653, 1424, 1266, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.49 (br. s, 1H), 8.87 (d, 1H, J = 7.5Hz), 8.51 (d, 1H, J = 4.1Hz), 8.10 (d, 1H, J = 8.2 Hz), 7.57-7.53 (m, 2H), 7.50-7.48 (m, 2H), 7.38-7.35 (m, 2H), 7.19 (d, 1H, J = 5.0 Hz), 7.15-7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C160.3, 147.8, 138.6, 136.5, 136.0, 135.3, 134.7, 134.5, 132.0, 129.0, 129.0, 127.9, 127.8, 127.4, 127.1, 121.7, 121.5, 116.7; HRMS (ESI) calcd for $C_{18}H_{13}N_2OS_2$ $[M+H]^+$ 337.0469 found 337.0485.

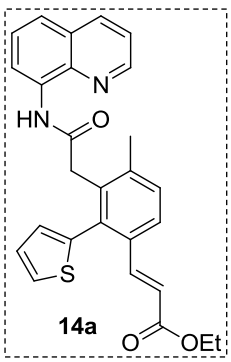


12h

Procedure for the synthesis of multiply substituted phenylacetamide 14 and 15.

A dry RBF containing mixture of product **12** (0.14 mmol, 1.0 equiv), ethyl acrylate **13a** (0.28 mmol, 2.0 equiv), $Pd(OAc)_2$ (3.0 mg, 5 mol%), AgOAc (34.8 mg, 1.5 equiv) in a DCM (0.8 mL) was heated at 110 ^oC for 16-24 hours. The reaction mixture was cooled to rt, filtered and washed with 5-10 mL of DCM then concentrated in vacuo. Purification of the crude reaction mixture by column chromatography furnished the corresponding alkenylated products **14** and **15** (see corresponding Tables/Schemes for specific examples and reaction conditions).

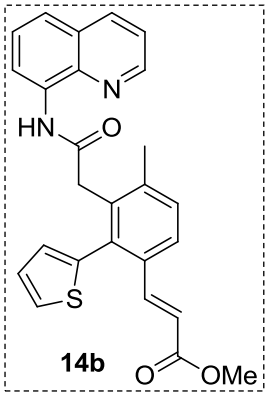
(*E*)-Ethyl 3-(4-methyl-3-(2-oxo-2-(quinolin-8-ylamino)ethyl)-2-(thiophen-2-yl) phenyl) acrylate *(nb 1487b/1413 14a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **14a** as a greenish colour semisolid (27 mg, 60%); R_f (20% EtOAc/hexane) 0.5; IR (KBr): 3055, 2986, 1423, 1265, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.86 (br. s, 1H), 8.76 (dd, 1H, J_1 = 7.1, J_2 = 1.8Hz), 8.66 (dd, 1H, J_1 = 4.2, J_2 =



14a

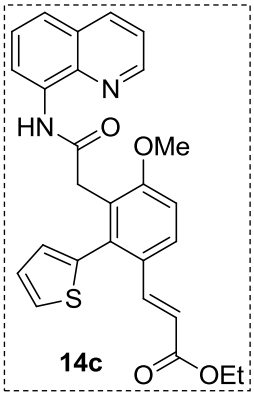
1.6Hz), 8.14 (dd, 1H, J_1 = 8.3, J_2 = 1.6Hz), 7.71 (d, 1H, J = 15.6 Hz), 7.57-7.53 (m, 1H), 7.51 (dd, 1H, J_1 = 8.4, J_2 = 2.0Hz), 7.42 (dd, 1H, J_1 = 8.3, J_2 = 4.2Hz), 7.38 (dd, 1H, J_1 = 5.6, J_2 = 3.5 Hz), 7.36-7.33 (m, 2H), 7.16 (d, 1H, J = 3.4 Hz), 7.07 (d, 1H, J = 3.7 Hz), 6.15 (d, 1H, J = 15.7 Hz), 4.25 (q, 2H, J = 7.1 Hz), 4.04 (s, 2H), 2.47 (s, 3H), 1.33 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.1, 166.9, 148.2, 145.8, 139.8, 138.8, 138.4, 137.0, 136.2, 135.1, 134.3, 132.0, 131.4, 131.2, 129.2, 128.3, 127.9, 127.4, 127.4, 121.7, 121.6, 116.7, 116.4, 60.5, 40.1, 20.6, 14.3; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_3S$ $[M+H]^+$ 457.1586 found 457.1568.

(*E*)-Methyl 3-(4-methyl-3-(2-oxo-2-(quinolin-8-ylamino)ethyl)-2-(thiophen-2-yl)phenyl)acrylate*(nb 1592b/1585 14b):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **14b** as a pale yellow colour solid compound (25 mg, 55%); R_f (20% EtOAc/hexane) 0.5; mp: 101-103 ^oC; IR (KBr): 3055, 2986, 1527, 1265, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (br. s, 1 H), 8.76 (d, 1H, J = 7.0 Hz), 8.66 (d, 1H, J = 3.2 Hz), 8.14 (d, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 15.7 Hz), 7.56-7.50 (m, 2H), 7.42 (dd, 1H, J_1 = 8.1, J_2 = 4.1Hz), 7.39-7.34 (m, 3H), 7.16 (d, 1H, J = 3.4 Hz), 7.07 (d, 1H, J = 3.5 Hz), 6.15 (d, 1H, J = 15.7 Hz), 4.03 (s, 2H), 3.79 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.1, 167.3, 148.2, 145.9, 139.7, 138.8, 138.4, 137.3, 136.2, 135.0, 134.3, 132.0, 131.5, 131.3, 129.2, 128.3, 127.9, 127.4, 127.4, 121.7, 121.6, 116.4, 116.3, 51.8, 40.1, 20.6; HRMS (ESI) calcd for $C_{26}H_{23}N_2O_3S$ $[M+H]^+$ 443.1429 found 443.1446.



14b

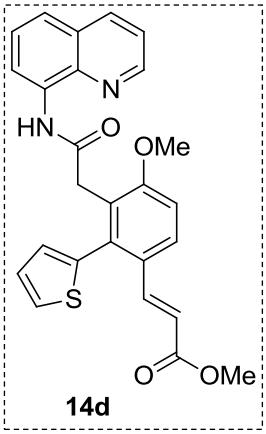
(*E*)-Ethyl 3-(4-methoxy-3-(2-oxo-2-(quinolin-8-ylamino)ethyl)-2-(thiophen-2-yl)phenyl)acrylate*(nb 1594a 14c):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **14c** as a faint yellow viscous (32 mg, 62%); R_f (20% EtOAc/hexane) 0.4; IR (KBr): 3055, 2986, 1424, 1266, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.44 (br. s, 1H), 8.81-8.77 (m, 2H), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.5 Hz), 7.76 (d, 1H, J = 15.7 Hz), 7.56-7.52 (m, 1H), 7.50 (dd, 1H, J_1 = 8.2, J_2 = 1.4 Hz), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 1H), 7.26 (d, 1H, J = 3.7 Hz),



14c

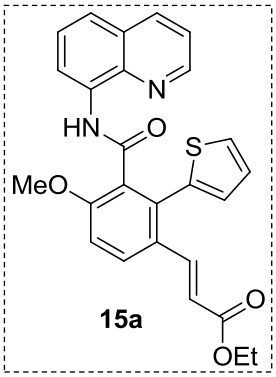
7.15 (d, 1H, *J* = 7.6 Hz), 7.02 (d, 1H, *J* = 8.2 Hz), 6.22 (d, 1H, *J* = 15.6 Hz), 4.26 (q, 2H, *J* = 7.1 Hz), 4.03 (s, 3H), 4.01 (s, 2H), 1.34 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.8, 166.9, 158.0, 148.0, 144.9, 139.8, 138.6, 137.1, 136.3, 135.9, 134.9, 131.7, 129.3, 128.2, 128.0, 127.4, 123.4, 122.3, 121.5, 121.3, 116.8, 116.6, 110.5, 60.5, 56.0, 37.2, 14.4; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_4S$ $[M+H]^+$ 473.1535 found 473.1552.

(*E*)-Methyl 3-(4-methoxy-3-(2-oxo-2-(quinolin-8-ylamino)ethyl)-2-(thiophen-2-yl)phenyl)acrylate *(nb 1595a 14d):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **14d** as a turmeric colour semisolid (23 mg, 50%); R_f (20% EtOAc/hexane) 0.3; IR (KBr): 3055, 1678, 1531, 1266, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.44 (br. s, 1H), 8.81-8.76 (m, 2H), 8.16 (dd, 1H, J_1 = 8.3, J_2 = 1.5Hz), 7.75 (d, 1H, *J* = 15.6 Hz), 7.56-7.52 (m, 1H), 7.50 (dd, 1H, J_1 = 8.2, J_2 = 1.5Hz), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 1H), 7.26 (d, 1H, *J* = 3.7 Hz), 7.15 (d, 1H, *J* = 7.2 Hz), 7.02 (d, 1H, *J* = 8.2 Hz), 6.22 (d, 1H, *J* = 15.7 Hz), 4.03 (s, 3H), 4.01 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C169.9, 167.4, 158.0, 148.0, 145.1, 139.7, 138.6, 137.4, 136.3, 135.8, 134.9, 131.8, 129.3, 128.3, 128.0, 127.5, 123.4, 122.3, 121.5, 121.4, 116.6, 116.2, 110.5, 56.0, 51.7, 37.2; HRMS (ESI) calcd for $C_{26}H_{23}N_2O_4S$ $[M+H]^+$ 459.1379 found 459.1396.



14d

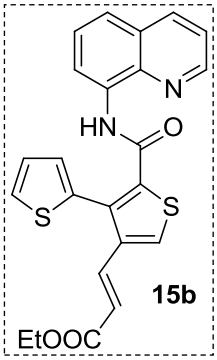
(*E*)-Ethyl 3-(4-methoxy-3-(quinolin-8-ylcarbamoyl)-2-(thiophen-2-yl)phenyl)acrylate *(nb 1604a 15a):* The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford **15a** as a faint brown colour solid (40 mg, 43%); R_f (20% EtOAc/hexane) 0.7; mp: 167-169 ^{o}C; IR (KBr): 3340, 3055, 1703, 1265, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.10 (br. s, 1H), 8.75 (dd, 1H, J_1 = 6.3, J_2 = 2.6 Hz), 8.71 (dd, 1H, J_1 = 4.1, J_2 = 1.4 Hz), 8.12 (dd, 1H, J_1 = 8.2, J_2 = 1.4 Hz), 7.63 (d, 1H, *J* = 15.8Hz), 7.52-7.47 (m, 3H), 7.41 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.17 (s, 2H), 7.11 (d, 1H, *J* = 8.4 Hz), 7.03 (d, 1H, *J* = 7.6 Hz), 6.17 (d, 1H, *J* = 15.9 Hz), 4.08 (q, 2H, *J* = 7.1 Hz), 3.94 (s, 3H), 1.22 (t, 3H, *J* = 7.1 Hz);



15a

^{13}C NMR (100 MHz, $CDCl_3$): δ_C167.2, 164.5, 156.8, 148.0, 143.1, 138.4, 137.1, 136.1, 134.7, 134.6, 132.4, 130.5, 128.0, 127.8, 127.4, 126.0, 125.0, 124.4, 121.6, 121.5, 118.3, 116.6, 111.9, 60.2, 56.1, 14.3; HRMS (ESI) calcd for $C_{26}H_{23}N_2O_4S$ $[M+H]^+$ 459.1379 found 459.1359.

(*E*)-Ethyl 3-(2'-(quinolin-8-ylcarbamoyl)-[2,3'-bithiophen]-4'-yl)acrylate*(nb 1474 b 15b):*The resultant crude mixture was purified by column chromatography (EtOAc:hexane = 20:80) to afford**15b** as a black colour solid (22 mg, 33%); R_f (20% EtOAc/hexane) 0.4; mp: 181-183^{o}C; IR (KBr): 3055, 1706, 1646, 1265, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.23 (br. s, 1H), 8.81 (d, 1H, *J* = 7.4Hz), 8.48 (d, 1H, *J* = 3.7Hz), 8.09 (d, 1H, *J* = 8.2 Hz), 7.63 (d, 1H, *J* = 5.0Hz), 7.55-7.46 (m, 5H), 7.36 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.12 (d, 1H, *J* = 5.0 Hz), 6.21 (d, 1H, *J* = 15.8 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C166.9, 159.5, 147.6, 139.6, 138.5, 136.8, 136.7, 136.1, 136.0, 134.3, 132.2, 131.9, 129.8, 127.7, 127.5, 127.4, 125.7, 121.7, 121.4, 119.5, 116.6, 60.5, 14.3; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_3S_2$ $[M+H]^+$ 435.0837 found 435.0858



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