Studies on Stereo- and Regioselective Synthesis of Functionalized Carbocycles, Heterocycles and Olefins through the Pd(II)-Catalyzed C-H Activation

A Thesis

Submitted for the Degree of

Doctor of Philosophy

in the Faculty of Science

By

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July, 2017

DEDICATED to

MY BELOVED PARENTS

Lakshmaiah and seshamma

GRAND MOTHER

Samrajyam

BROTHER

Surendra Babu

SISTER

Bhulakshmi

Declaration

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

Ramarao Parella

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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

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Date:

Place:

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List of publications from the thesis work

1) **Parella, R.**; Naveen; Babu, S. A.* *Catal. Comm*. **2012**, *29*, 118-121.

Title: Magnetic nano Fe_3O_4 and $CuFe_2O_4$ as heterogeneous catalysts: A green method for the stereo- and regioselective reactions of epoxides with indoles/pyrroles.

2) **Parella, R.**; Naveen; Kumar, A.; Babu, S. A.* *Tetrahedron Lett*. **2013**, *54*, 1738-1742.

Title: Catalytic Friedel–Crafts acylation: magnetic nanopowder $CuFe_2O_4$ as an efficient and magnetically separable catalyst.

3) **Parella, R.**; Gopalakrishnan, B.; Babu, S. A.* *Org. Lett.* **2013**, *15*, 3238-3241

Title: Auxiliary-enabled Pd-catalyzed direct arylation of methylene C(sp^3)-H bond of cyclopropanes: Highly diastereoselective assembling of di- and trisubstituted cyclopropanecarboxamides.

4) **Parella, R.**; Gopalakrishnan, B.; Babu, S. A.* *J. Org. Chem.* **2013**, *78*, 11911-11934.

Title: Direct bis-arylation of cyclobutanecarboxamide via double C−H activation: An auxiliary-aided diastereoselective Pd-catalyzed access to trisubstituted cyclobutane scaffolds having three contiguous stereocenters and an all-cis stereochemistry.

5) **Parella, R.**; Babu, S. A.* *Synlett* **2014***,* 1395-1402.

Title: Palladium-catalyzed double activation and arylation of 2° and 3° C(sp^3)–H bonds of the norbornane system: Formation of a C–C bond at the bridgehead carbon and bridgehead quaternary stereocenter.

6) **Parella, R.**; Babu, S. A.* *J. Org. Chem.* **2015**, *80*, 2339−2355.

Title: Regio- and stereoselective Pd-catalyzed direct arylation of unactivated sp^3 C(3)-H bonds of tetrahydrofuran and 1,4-benzodioxane systems.

7) **Parella, R.**; Babu, S. A.* *J. Org. Chem.* **2015**, *80*, 12379−12396.

Title: $Pd(OAc)_2$-Catalyzed, AgOAc-promoted Z selective directed β-arylation of acrylamide systems and stereoselective construction of Z-cinnamamide Scaffolds.

8) **Parella, R.**; Babu, S. A.* *Manuscript accepted in J. Org. Chem* ***(DOI: 10.1021/acs.joc.7b00535)***.

Title: Pd(II)-Catalyzed picolinamide-directed *Z* selective *γ*-C-H arylation of allylamine systems and regio- and stereoselective construction of cinnamylamine derivatives.

9) **Parella, R.**; Babu, S. A.* *Manuscript accepted in J. Org. Chem* ***(DOI: 10.1021/acs.joc.7b00582)***.

Title: Pd(II)-Catalyzed arylation and intramolecular amination of γ-C(sp^3)-H bonds: En route To arylheteroarylmethanes and pyrrolidone-ring annulated furan/thiophene and benzo-furan/thiophene motifs.

10) Reddy, C.;[+] Bisht, N.;[+] **Parella, R.;**[+] Babu, S. A.* *J. Org. Chem.* **2016***, 81,* 12143-12168.

([+]*authors contributed equally*).

Title: 4-Amino-2,1,3-benzothiadiazole as a removable bidentate directing group for the Pd(II)-catalyzed arylation/oxygenation of sp^2/sp^3 β-C-H bonds of carboxamides.

List of publications as a co-author

1) Naveen; **Parella, R.**; Babu, S. A.* *Tetrahedron Lett.* **2013**, *54*, 2255-2260.

Title: RCM strategy-based entry into new crown ether/polyether macrocyclic systems derived from hydroxy benzaldehydes.

2) Kumar, A.; **Parella, R.**; Babu, S. A.* *Synlett* **2014***,* 0835-0842.

Title: Magnetic nano Fe_3O_4 catalyzed solvent-free stereo- and regioselective aminolysis of epoxides by amines; A green method for the synthesis of β-amino alcohols.

3) Padmavathi, R; Sankar, R; Gopalakrishnan, B; **Parella, R.**; Babu, S. A.* *Eur. J. Org. Chem.* **2015**, 3727-3742.

Title: $Pd(OAc)_2$/AgOAc Catalytic system based bidentate ligand directed regiocontrolled C–H arylation and alkylation of the C-3 position of thiophene- and furan-2-carboxamides.

4) Gopalakrishnan, B; Mohan, S.; **Parella, R.**; Babu, S. A.* *J. Org. Chem.* ***2016****, 81,* 8988−9005.

Title: Diastereoselective Pd(II)-catalyzed sp^3 C–H arylation followed by ring opening of cyclopropanecarboxamides: construction of anti β-acyloxy carboxamide derivatives.

Patent application filed

Inventors: Srinivasarao Arulananda Babu, **Ramarao Parella** and Bojan Gopalakrishnan. Indian Patent Application No. 1240/DEL/2013 “entitled Process for the preparation of novel di- and trisubstituted cyclopropanecarboxamide compounds”.

Conferences/Symposia

1) Oral presentation entitled "$Pd(OAc)_2$/AgOAc catalytic system-based Z selective arylation of acrylamide and Amides-derived from allyl amines" **Parella, R.**; S. A. Babu at the *11th Junior National Organic Symposium (J-NOST)* held at the National Institute of Science Education and Research (NISER) Bhubaneswar, India (14-17 December, 2015).

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).

3) Participated in the *7th Junior National Organic Symposium (J-NOST)* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (14-17 December, 2011).

Preamble.

Over the past decades, the transition-metal-catalyzed cross-coupling reactions have led construction of various small and complex organic molecules. From the past few years, the transition metal-catalyzed functionalization of C–H bonds of organic compounds is emerging as one of key strategies that provide alternative environmentally friendly and efficient ways for the construction of functionalized small and complex organic molecules. The C-H functionalization/activation method considered complimentary to the conventional cross-coupling reactions. The C-H activation strategy does not require the pre-functionalized materials, thus access to a wide range of substrates for C-H functionalization broadens the synthetic utility of this methodology.

This thesis work aimed to obtain functionalized carbocycles, heterocycles and olefins through the Pd-catalyzed directing group-aided diastereoselective $C(sp^3)$-H and $C(sp^2)$-H functionalization/arylation strategy.

Accordingly, this thesis entitled "*Studies on Stereo- and Regioselective Synthesis of Functionalized Carbocycles, Heterocycles and Olefins through the Pd(II)-Catalyzed C-H Activation*" consists of the following **five chapters** along with objectives of the thesis work. Individual chapters contain the sub-sections, such as, introduction, results and discussion and conclusions, experimental section and references.

Chapter 1: Introduction to C-H bond activation/ functionalization, this chapter provides a brief outlook on the evolution of directing group assisted C-H functionalization. The synthetic potential of the bidentate ligand directed C-H activation/functionalization has been highlighted with representative literature works

Chapter 2: Regio- and stereoselective construction of functionalized cyclopropanes/cyclobutanes/norbornanes and saturated heterocycles *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation.

Chapter 3: Pd(II)-catalyzed, directing group-aided *Z* selective β-arylation of acrylamide systems and stereoselective construction of *Z* cinnamamides.

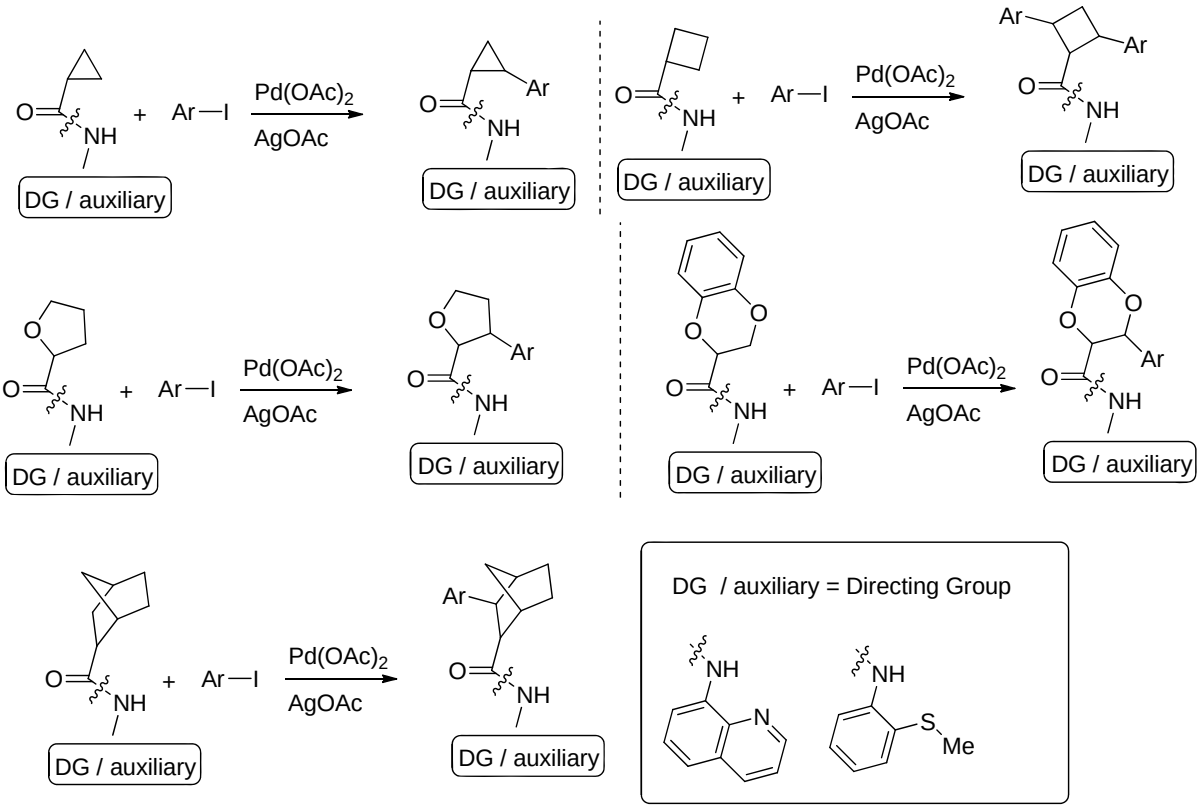
Chapter 4: Regio- and stereoselective Pd(II)-catalyzed picolinamide-directed Z selective γ-C-H arylation of allylamine systems and construction of cinnamylamines.

Chapter 5: Pd(II)-catalyzed arylation and intramolecular amination of *γ*-C(sp^3)-H bonds: Synthesis of arylheteroarylmethanes and pyrrolidone-ring annulated furan/thiophene derivatives.

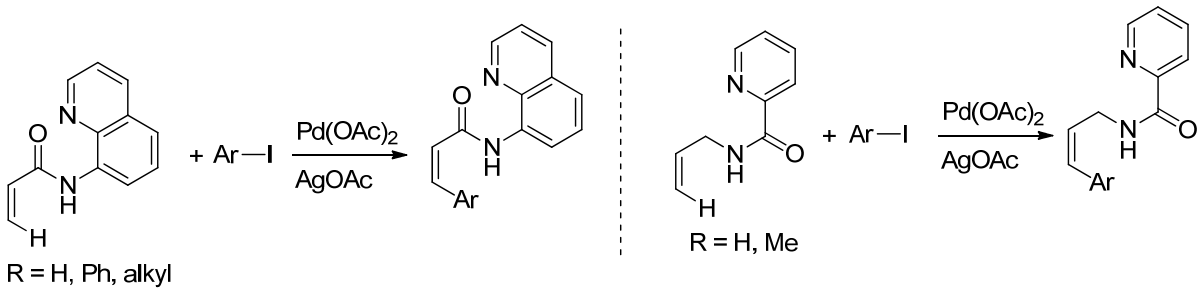
Objectives of this thesis work.

The main objectives of this thesis work are given below.

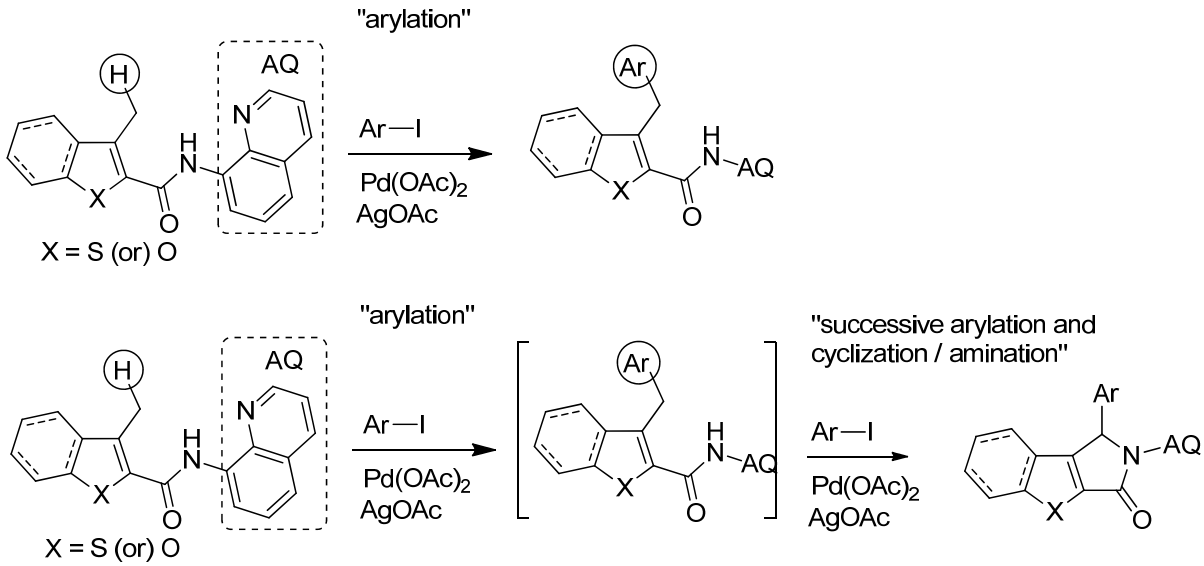
1. Inspired by the significance of the functionalized cyclopropane, cyclobutane, norbornane, tetrahydrofuran and 1,4-benzodioxane molecules; a part of this thesis work envisages to investigate the Pd-catalyzed directing group-aided diastereoselective C-H functionalization/arylation of cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems to obtain C-H arylated/functionalized cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems (**Chapter 2**).



2. Given the importance of various acrylamides, allylamine systems in medicinal chemistry research; a part of this thesis work envisages to investigate the Pd-catalyzed directing group-aided regio- and stereoselective C-H functionalization/arylation of acrylamides and allylamines to obtain C-H arylated/functionalized acrylamides, allylamines systems having Z configuration (**Chapters 3 and 4**).



3. Given the importance of the 3-aryl isoindolinones and diarylmethane molecules in organic synthesis and medicinal chemistry research; a part of this thesis work envisages the synthesis of a variety of substituted arylheteroarylmethanes and pyrrolidone-ring annulated furan/thiophene and benzo-furan/thiophene motifs via the Pd(II)-catalyzed directing group-aided C-H arylation and intramolecular C-H amination of γ-C(sp^3)-H bonds (**Chapter 5**).



Chapter 1: Introduction on the C-H Bond Activation.

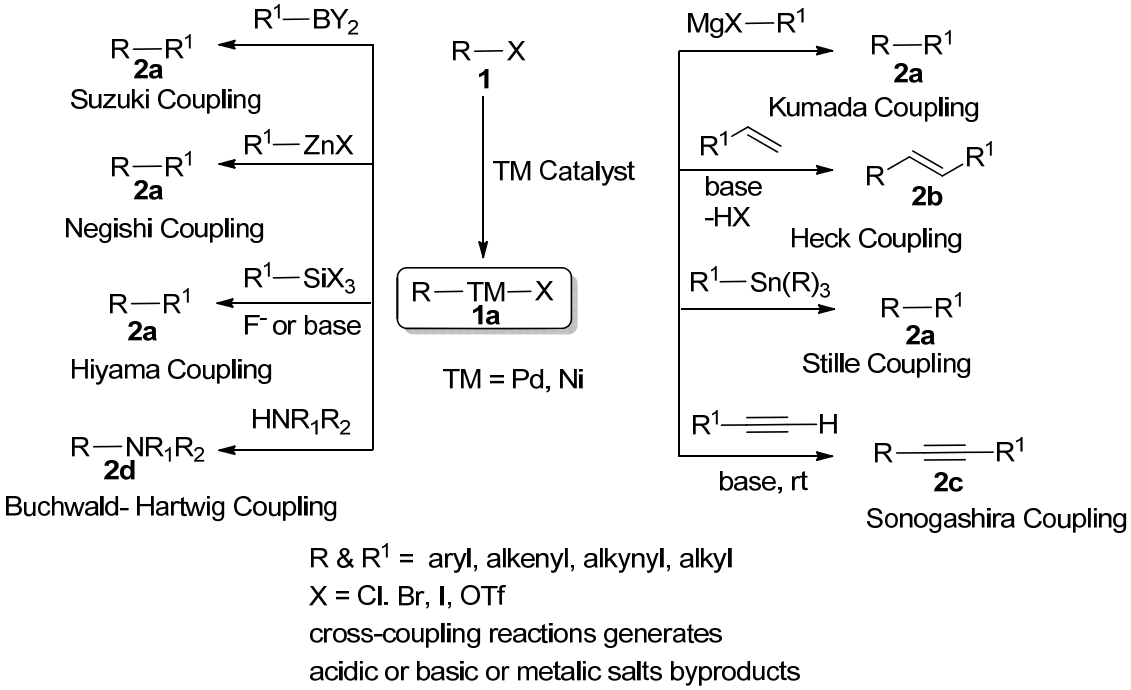
From the past few years, the transition metal-catalyzed functionalization of C–H bonds of organic compounds is emerging as one of key strategies that provide alternative environmentally friendly and efficient ways for the construction of C–C and C–X bonds (X = C, N, O, P, etc.).[1-4] The C-H functionalization/activation method considered complimentary to the cross-couplings and the well-established C-heteroatom bond forming processes. The C-H activation strategy does not require the pre-functionalized materials, thus access to a wide range of substrates for C-H functionalization broadens the synthetic utility of this methodology. In general, C–H functionalization process mainly focuses on addressing the following two issues: (i) reaction efficiency and (ii) site selectivity.

Given that organic molecules that contain a wide range of C-H bonds, regioselectivity is an important issue while attempting the transition metal-catalyzed C-H functionalization. The use of a directing group helps to overcome the issue of regiocontrol by allowing the catalyst to be in proximity of the targeted C-H bonds. A wide variety of functional groups have been evaluated as directing groups for the functionalization C-H bonds.[5] In the last two decades, the transition metal-catalyzed, C-H functionalization of $C(sp^2)$–H bonds of arenes, heteroarenes and olefins have been extensively investigated.[3,4] In contrast, the direct activation and functionalization of 'inert' $C(sp^3)$-H bonds of alkyl groups is relatively less explored. High bond dissociation energy (BDE), the 'inert' nature of sp^3 C-H bond and the lack of π-assistance when compared to sp^2 C-H bond and the difficulties in the reductive elimination are the specific challenges that prevent the effective functionalization of unactivated sp^3 C-H bonds.[5a] The directing group-aided strategy provides solutions to the challenges connected with the $C(sp^3)$-H bond activation. For example, the directing group promotes reactivity by enhancing the catalyst concentration as well as selectivity.[2,6] Amongst the transition-metal catalysts used in the C-H activation, the Pd(II)-catalyst showed outstanding reactivity and controllable selectivity in $C(sp^3)$-H activation.

The Cross-Coupling Reactions

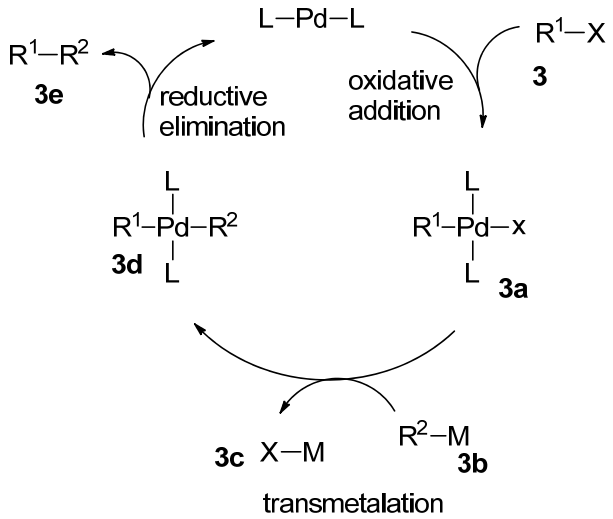
The transition metal-catalyzed cross-coupling reactions were proved to be highly valuable in the history of organic synthesis. Especially, several biological/pharmaceutically active molecules, agrochemicals and organic materials have been synthesized via the Pd-catalyzed cross-coupling reactions.[7-9] In general, the cross-coupling reactions require halides or pseudo halides **1** and organometallic nucleophilic reagents (Scheme 1). Given the impact of these

reactions in chemical sciences, Heck, Negishi, and Suzuki have been awarded with the Nobel Prize in 2010 for discovery of respective cross-coupling reactions.



Scheme 1. Representative examples of cross-coupling reactions.

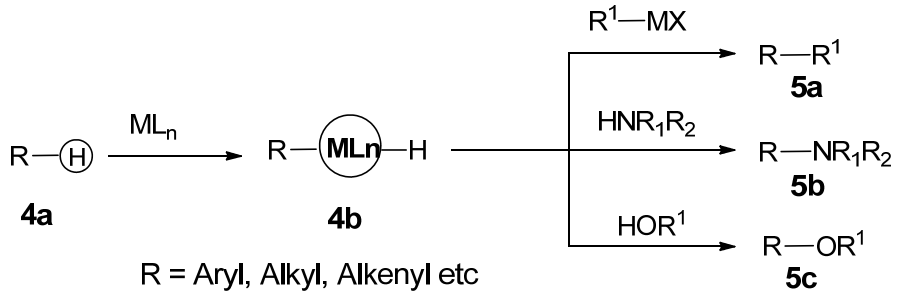
A general mechanism for the Pd(0)-catalyzed cross-coupling is shown in Scheme 2.[7-9]The reaction begins with the oxidative addition of an organic electrophile **3** with the metal to give intermediate **3a**. Next, the transmetalation of organometallic reagent **3b** with **3a** affords the intermediate **3d**. Finally, the reductive elimination of step involving **2d** affords the desired aryl-carbon and aryl-heteroatom coupled product **3e** along with the regeneration of the catalyst.



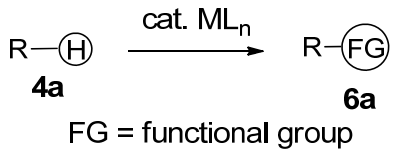
Scheme 2. General mechanism of palladium catalyzed cross-coupling reactions.

In spite of the important developments, the cross-coupling reactions suffer with some limitations, i.e. 1) pre-functionalized starting materials are required, 2) often bulky and costly ligands are used, and 3) stoichiometric amount of hazardous acidic or basic or metal salts are produced as the byproducts. Therefore, development of an alternate and environmentally benign method is desirable. The formation of C-C and C-heteroatom bond through the functionalization/activation of C-H bonds considered as an alternative and effective method. The C-H activation protocol avoids the use of pre-functionalized precursors. Despite the ready accessibility, the C-H bonds possess high bond dissociation energy (85-120 Kcal/mol), and is non-polarized in nature (pKa> 35). Due to the high bond dissociation energies, the C-H bonds are thermodynamically stable and relatively less reactive. Thus, the direct utilization of C-H bonds for the construction of C-C and C-X bonds is a challenging task.[10,11]

In general, the C-H activation can be defined as catalytic or stoichiometric reactions of transition metal complexes with the unreactive C-H bonds of organic molecules **4a** to form a more reactive new metal-carbon bond **4b** (Scheme 3).The newly formedmetal-carbon bond intermediate **4b** is relatively more reactive than corresponding C-H bond and it readily undergoreactions with electrophiles or nucleophiles to afford C-C, C-O, and C-Nbonds (Scheme 3).[4] Broadly the transformation of C-H bond **4a** to C-FG **6a** (FG= Functional Group) is termed as C-H bond functionalization (Scheme 4). Accordingly, the Friedel-Crafts alkylation reactions or aromaticsubstitution reactions are considered as C-H functionalization rather C-H activation reactions.

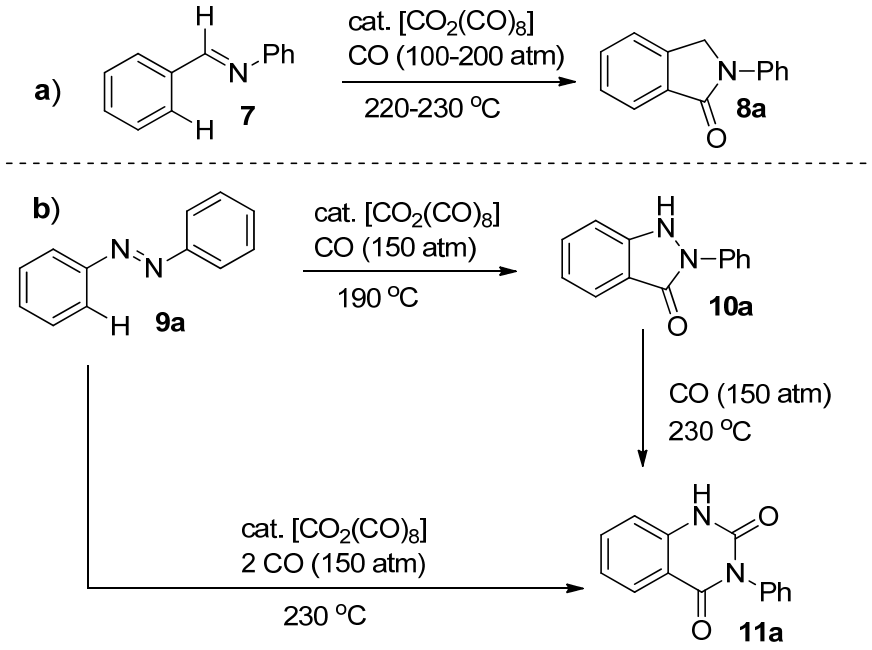


Scheme 3. General representation of C-H activation.



Scheme 4. General representation of C-H bond functionalization.

Notably, the earliest examples of transition-metal-catalyzed, regioselective functionalization of C-H bonds were reported in the mid-1950s (Scheme 5). Murahashi[12a] showed that the reaction of an aldimine **7** in the presence of $[Co_2(CO)_8]$ under carbon monoxide atm at high temperature led to the insertion of CO into the *ortho*-C(sp^2)-H bond of **7**, thereby affording an isoindolinone derivative **8a** (Scheme 5). The reaction of azobenzene **9a** in the presence of $[Co_2(CO)_8]$ led to the insertion of one or two molecules of carbon monoxide, depending on the reaction conditions used, thereby affording the products **10a** and **11a**.[12b]



Scheme 5. Cobalt-catalyzed *ortho*-carbonylation of C-H bonds.

Different Methods of C-H Functionalization

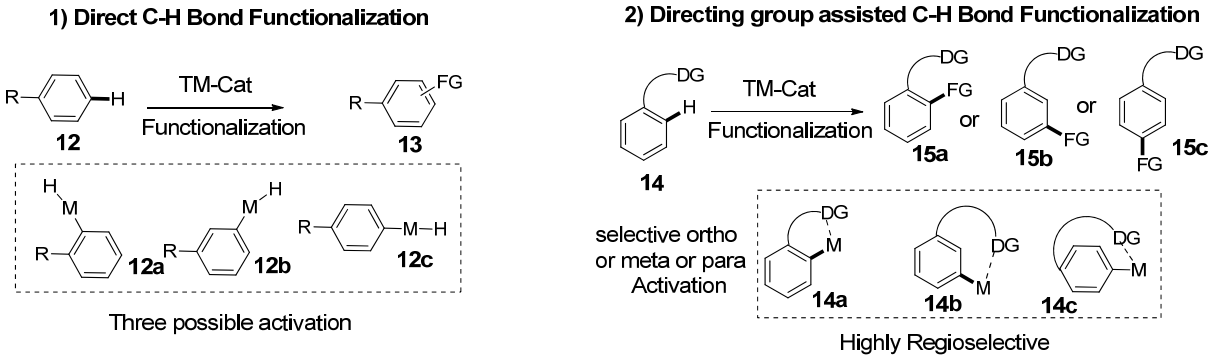
Generally, the C-H functionalizations of organic molecules are carried out in two ways as shown in Scheme 6.

1) The direct functionalization of inert C-H bond without using any directing group[13]

2) The chelation-assisted C-H functionalization using suitable directing group.[10h]

The first approach involves the direct insertion of electrophilic metal to the inert C-H bonds. However, a large number of C-H bonds in the molecule get equal opportunity for activation, making this process non-regioselective. Whereas the chelation assisted C-H bond functionalization operates through the coordination of heteroatom to the metal catalyst and

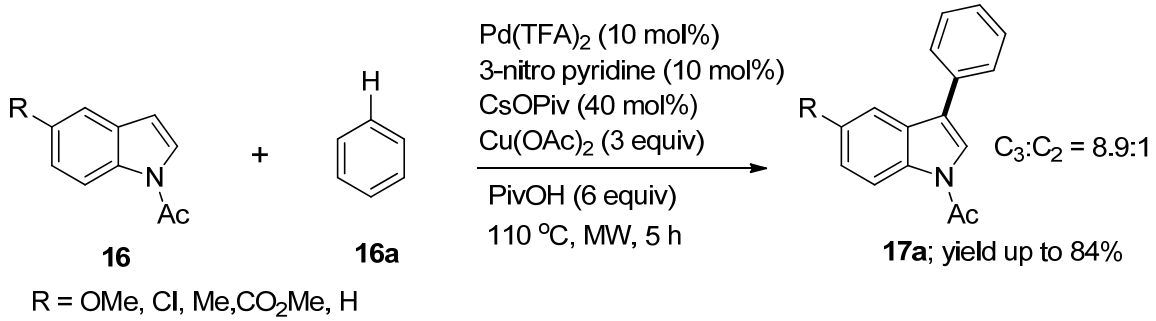
this process selectively activates the C-H bond in the proximity by leaving the other C-H bonds that are not in the proximity.



Scheme 6. C-H activation methods.

Direct C-H Bond Functionalization

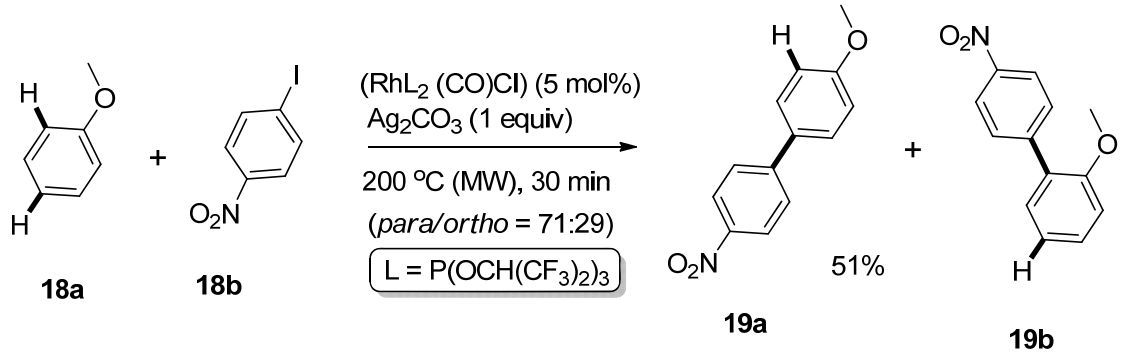
Representative examples involving the direct C-H bond functionalization are discussed here. In 2007, Fagnou and coworkers[14a] demonstrated an interesting regioselective cross dehydrogenative arylation of *N*-protected indoles **16** with arenes **16a** in the presence of $Pd(TFA)_2$ catalyst, terminal oxidant $Cu(OAc)_2$ in PivOH, which afforded the C3-arylation product **17a** (Scheme 7). The high selectivity was accountable due to the nucleophilicity at C3 position of indole and notably, no homocoupling product among indoles or arenes were observed.



Scheme 7. Pd-Catalyzed direct arylation of *N*-protected indole with arenes.

Itami and co-workers[14b,c] reported the rhodium-catalyzed direct arylation of anisoles **18a** with *para* nitrophenyl iodide **18b** in the presence of Ag_2CO_3 under microwave heating conditions. Unfortunately, the reaction afforded a mixture of *para /ortho substituted* products **19a&19b** (Scheme 8). These reports suggested that the selectivity largely depends on acidity of C-H bond of the heterocyclic compounds or arenes and a mixture of regioisomeric products is

observed through the competitive activation of *ortho*, *meta* and *para* C-H bonds of arenes as discussed in Schemes 7 and 8.



Scheme 8. Rh-Catalyzed direct arylation of anisoles with *p*-nitro iodobenzene.

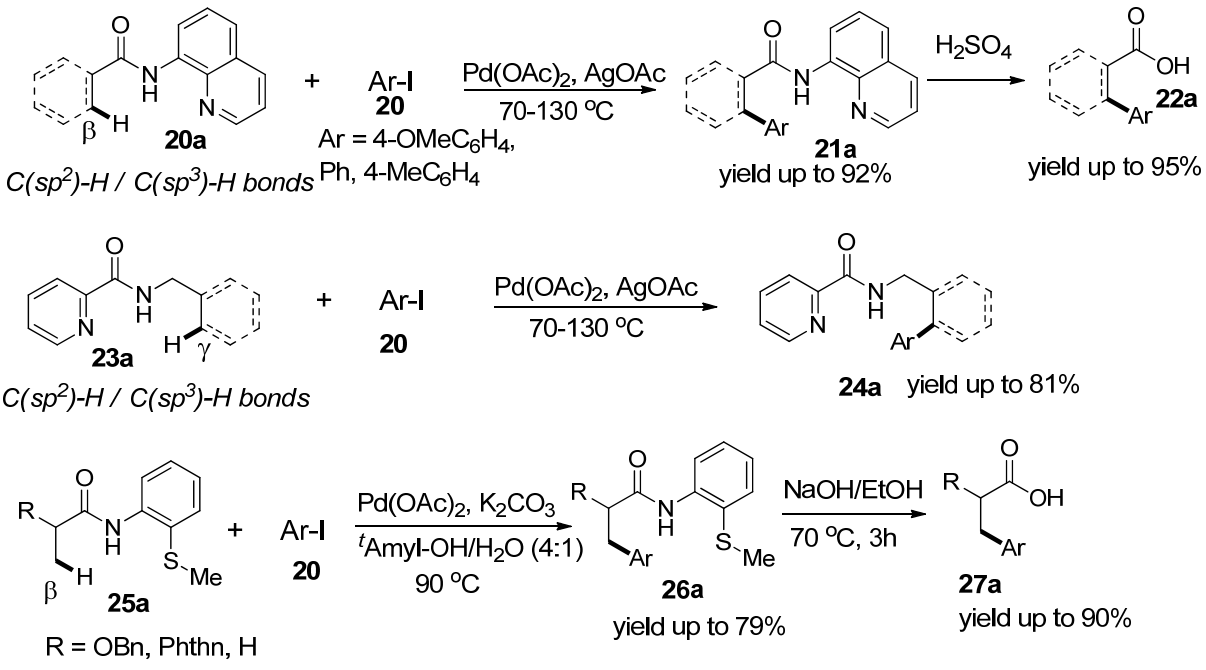
Representative Literature Works Dealing With the Directing Group (Chelation)-Assisted C-H Bond Activation/Functionalization. Construction of C–C and C–X bonds (X = C, N, O, P, S, Si, B, etc).

Given that a large number of C-H bonds in a given organic molecule get an equal opportunity for activation makes this process non-regioselective and hence, it is believed that the introduction of a heteroatom chelating group in the substrate would direct or control the C-H activation process. Directing group initially co-ordinates to the transition metal and brings the coordinating metal species to the close proximity to the C-H bond, resulting a substantial enhancement of reactivity as well as selectivity.[10,6b] Accordingly, various types of directing groups have been developed and deployed for the construction of C-C and C-X bonds via the transition metal catalyzed C-H activation/functionalization. Some of the notable directing groups used for C-H functionalization are; pyridine, pyridine *N*-oxides, pyrazole, pyrimidine, acetanilide, oxime, ester, carbamate, imine, amide, etc.

A survey of the literature[10,11] revealed that the transition metal-catalyzed C–H activation/functionalization strategy was well exploited for functionalization of sp^2 C–H bonds of arenes, heteroarenes and olefins etc. However, until the report by the Daugulis[15] group in 2005, the transition metal-catalyzed C–H activation/functionalization strategy was relatively less exploited for the functionalization of inert sp^3 C–H bonds of alkyl chains. After the report by Daugulis,[15] various research groups have revealed that the sp^3 C–H activation/functionalization is an attainable task with the help of directing groups.

Accordingly, some outstanding papers dealing with the directing group-based activation/functionalizationsp^3 C–H bonds that are relevant to this thesis work are described in the following sections.

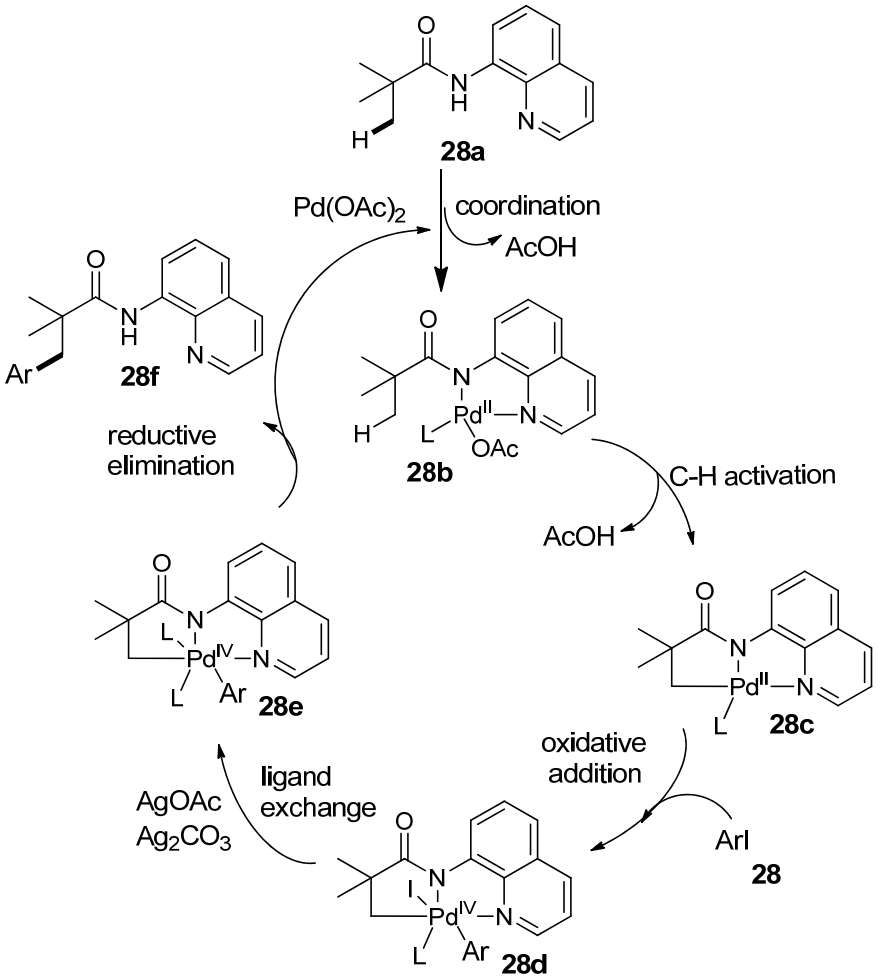
In 2005, Daugulis group reported[15] the first paper dealing with the arylation of the sp^3 C–H bonds of aliphatic carboxamides using 8-aminoquinoline (AQ), picolinamides (PA) as the bidentate directing groups. Later, the same group reported the arylation of the sp^3 C–H bonds of aliphatic carboxamides using 2-methylthioaniline as the bidentate directing group. The Pd(II)-catalyzed 8-aminoquinoline (8-AQ) directed C-H arylation of C(sp^2)-H/C(sp^3)-H bond of carboxamides **20a** with aryl iodides **20** afforded the β-arylated carboxamide **21a** (Scheme 9). Similarly the Pd(II)-catalyzed picolinamide (PA) directed C-H arylation of C(sp^2)-H/ C(sp^3)-H bond of carboxamides **23a** with arylating agents **20** gave the γ-arylated carboxamide **24a** (Scheme 9). The mono arylation reaction of 2-methylthioaniline-derived carboxamides **25a** with aryl iodide **20** and K_2CO_3 in *t*-amyl alcohol gave the β-monoarylated carboxamide **26a** (Scheme 9). Daugulis also showed that the directing groups were readily removed from the final product under the standard amide hydrolysis reaction conditions.



Scheme 9. Daugulis's work on the Pd(II)-catalyzed bidentate directing group-directed C-H arylation of **20a, 23a** and **25a**.

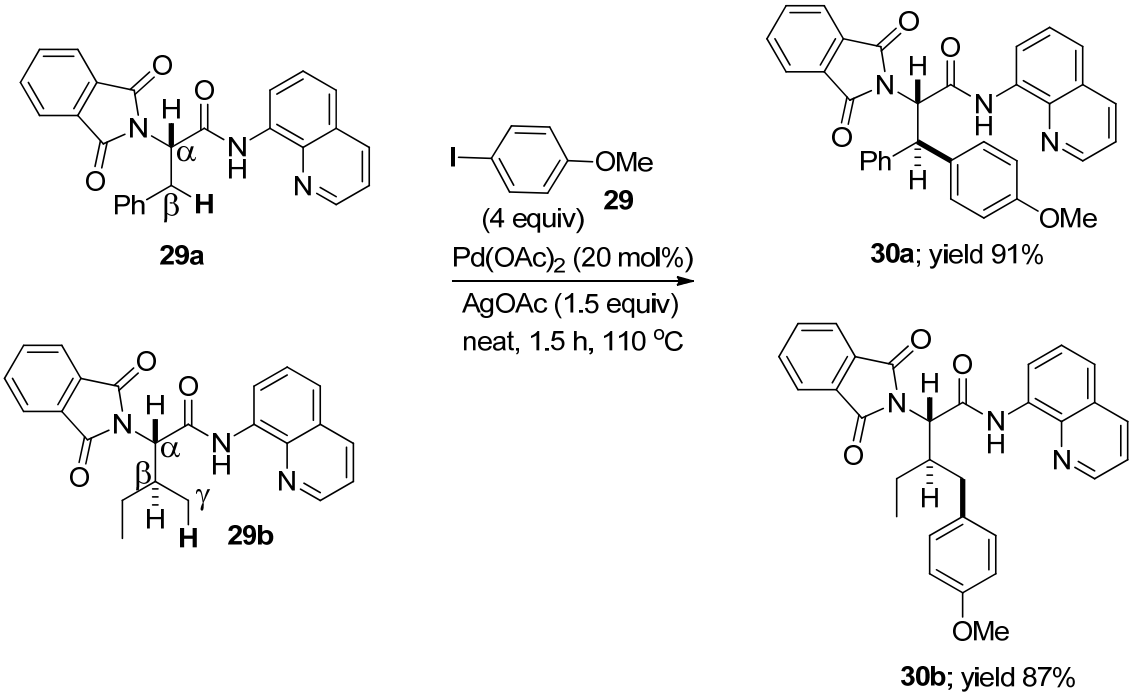
A plausible mechanism for the observed regioselectivity in the Pd(II)-catalyzed 8-aminoquinoline (8-AQ) directed C-H arylation was explained based as shown in Scheme 10. The coordination of carboxamide **28a** to the Pd(II) catalyst followed by a ligand exchange

process generates the palladium complex **28b**. Next the activation of the β-C-H bond of complex **28b** generates the five-membered palladacycle intermediate **28c** (Scheme 10). Then, the oxidative addition of intermediate **28c** with an aryl iodide **28** generates the palladium complex **28d**, followed by ligand exchange and reductive elimination generates the desired product **28f** and the catalyst is regenerated for the next cycle (Scheme 10).[15]



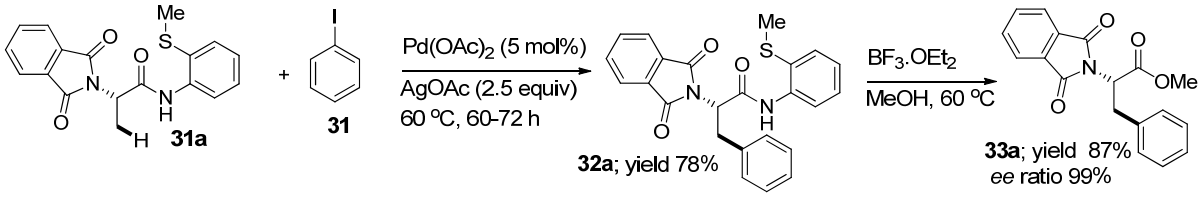
Scheme 10. Proposed mechanism for the Pd(II)-catalyzed 8-aminoquinoline (8-AQ) directed β-C-H arylation.

After the initial paper reported by Daugulis, Corey et al.[16a] reported the Pd(II)-catalyzed β- and γ-C(sp^3)-H arylation of α-amino acid derivatives. Arylation of *N*-phthaloylated phenylalanine amide **29a** with *p*-iodoanisole **29** gave the β-arylated compound **30a** (Scheme 11). An interesting outcome was observed in the reaction of isoleucine **29b** with *p*-iodoanisole **29** under similar reaction conditions gave the γ-C-H arylated product **30b** (Scheme 11).



Scheme 11. Pd(II)-catalyzed β- and γ-C(sp^3)-H arylation of amino acid derivatives **29a**and**29b**.

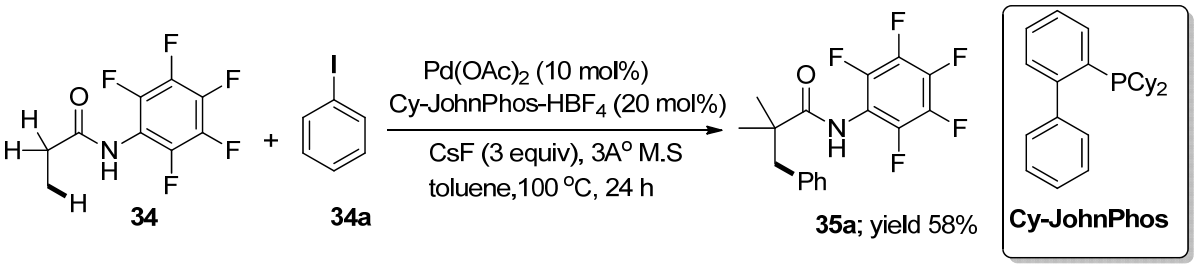
Daugulis et al.[16b] reported the Pd(II)-catalyzed selective mono β-arylation using 2-thiomethylaniline directing group derived carboxamide **31a**. The arylation ofalanine carboxamides **31a** in the presence of $Pd(OAc)_2$ (5 mol%) and AgOAc in toluene at 60 °C produced enantiopure phenylalanine derivatives **32a** (Scheme 12). Further hydrolysis of compounds **32a** in the presence of $BF_3{\cdot}Et_2O$ in methanol at 100 °C resulted the ester derivative **33a** (Scheme 12).



Scheme 12. β-C(sp^3)-H arylation of amino acid derivatives **31a**.

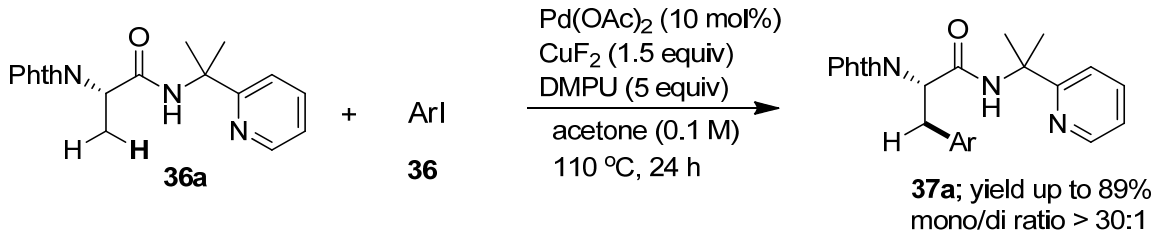
During the period in which the Pd(II)-catalyzed 8-aminoquinoline (8-AQ) directed C-H arylation was reported by Daugulis, Yu and co-workers also was actively involved in developing the functionalization of C(sp^3)-H bonds of aliphatic chains. Yu reported[16c] the

Pd(II)-catalyzed arylation of *N*-arylamide **34** derived from pentafluoroaniline with iodobenzene **34a** in the presence of $Pd(OAc)_2$ (10 mol%), Cy-JohnPhos-HBF_4 (20 mol%), CsF (3 equiv) in toluene at 110 ^oC for 24 h to give the β-arylated **35a** (Scheme 13)



Scheme 13. Yu's work on the β-C-H arylation using *N*-arylamide as the directing group **34**.

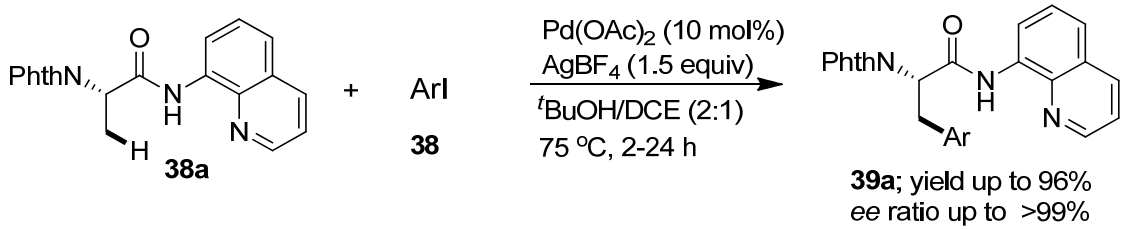
Shi et al.[16d]reported the β-C-H arylation of amide **36a** using 2-(pyridin-2-yl)isopropyl (PIP) as directing group. The monoarylation of amino acid derivatives **36a** with PhI **36** in the presence of $Pd(OAc)_2$ (10 mol%), CuF_2 (1.5 equiv), DMPU (5 equiv) in acetone (0.1 M) at 100 ^oC for 24 h gave the mono-arylated product **37a** (Scheme 14).



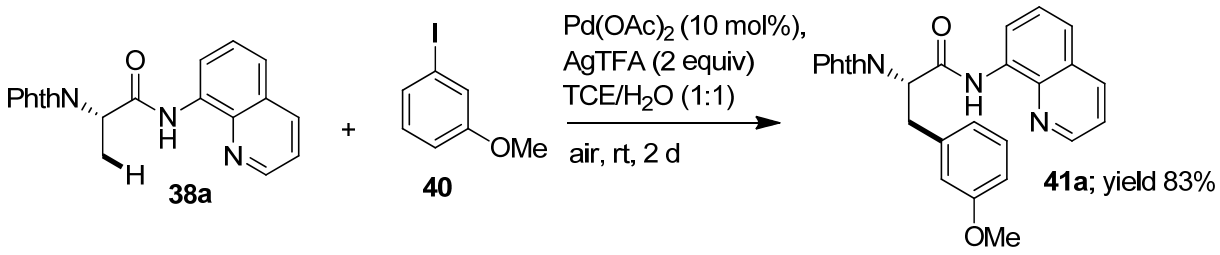
Scheme 14. PIP-directed β-C(sp^3)-H arylation of amino acid derivatives **36a**.

Shi and co-workers[16e] also reported the Pd(II)-catalyzed selective monoarylation of the methyl C(sp^3)–H bond of amino acid derivatives **38a** under mild reaction conditions. The reaction of 8-AQ-derived amino acid derivatives **38a** with ArI **38**, $Pd(OAc)_2$, $AgBF_4$ in *t*-BuOH/DCE at 75 ^oC afforded the β-C-H arylated α-amino acid derivatives **39a** (Scheme 15). Chen and co-workers[16f] reported the synthesis of mono β-C-H arylated α-amino acids at room temperature. The arylation reaction of *N*-quinolylcarboxamides **38a** with 3-iodo anisole **40** in the presence of $Pd(OAc)_2$ (10 mol%) and AgTFA (2 equiv) in 1,1,2,2-tetrachloroethane (TCE) at rt afforded the β-C-H arylated alanine derivatives **41a** (Scheme 16). Yu and co-workers[17a] reported the Pd(II)-catalyzed sequential arylation of *N*-arylamide **42a** with ArI **42** in the presence of afforded the mono C-H arylated product **43**, which was further subjected to

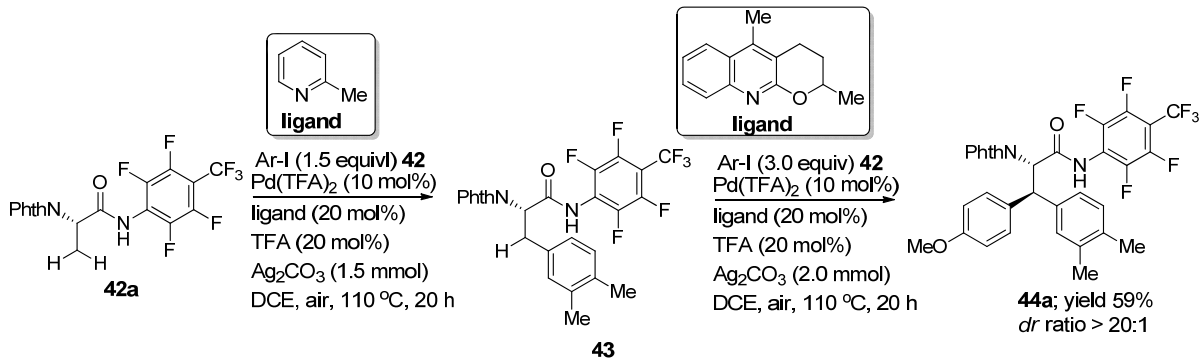
a second arylation in the presence another ArI **42**, to give the β,β,-diarylated amino acid derivatives **44a** (Scheme 17).



Scheme 15. Pd(II)-catalyzed mono arylation of amino acid derivatives **38a**.

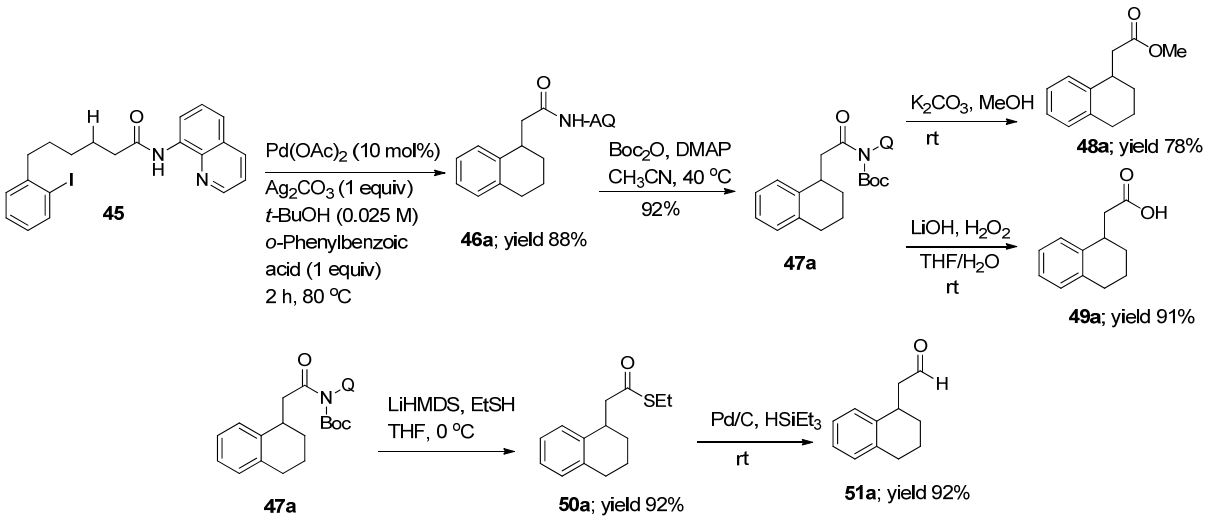


Scheme 16. Pd(II)-catalyzed β-C(sp^3)-H arylation of amino acid derivatives at rt.



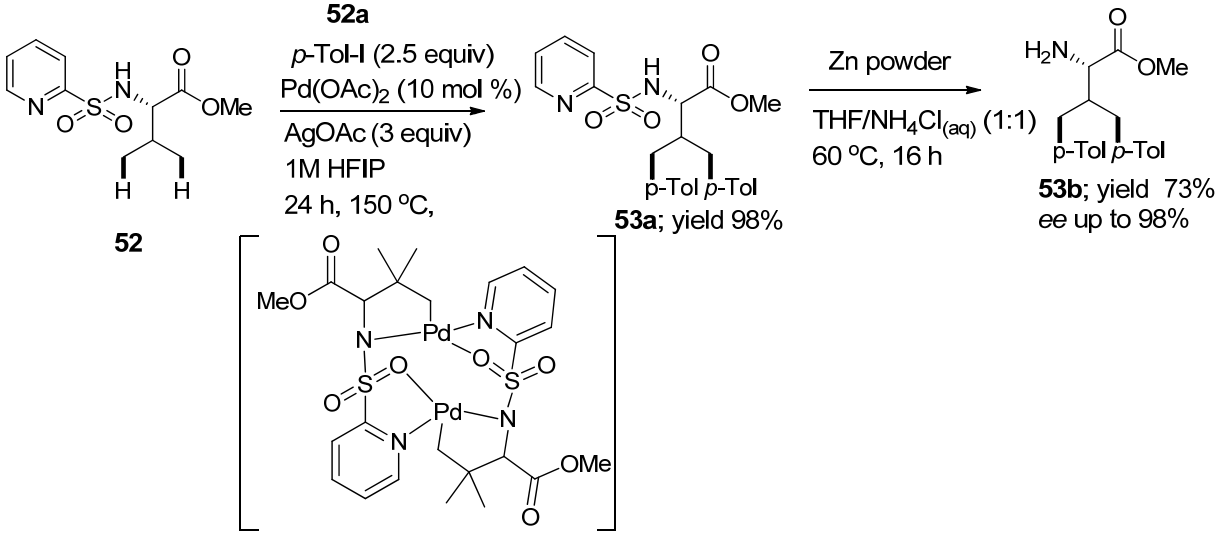
Scheme 17. Pd(II)-catalyzed β-C(sp^3)-H arylation of amino acid derivatives.

Chen's group reported[17b] an intramolecular β-C-H arylation of amide **45** for the construction of different benzannulated products **46a** (Scheme 18). Boc protection of the cyclic product **46a** gave **47a**, which was subjected to hydrolysis reaction conditions to afford the corresponding ester **48a**, free acid **49a**, and *S*-ester **50a** in excellent yields under mild conditions (Scheme 18). Furthermore, the *S*-ester was converted into the corresponding aldehyde **51a** (scheme 18).



Scheme 18. Pd(II)-catalyzed intramolecular β-C(sp^3)-H arylation.

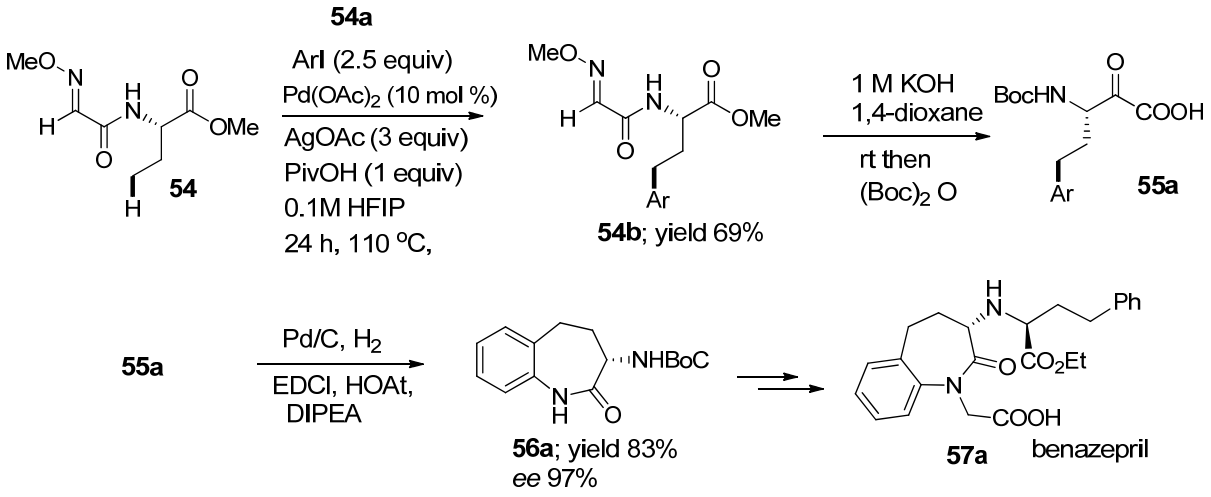
The Carretero has used[17c] 2-pyridylsulfonyl moiety as the directing group in the Pd(II)-catalyzed bis-arylation of **52**. The selective mono C-H arylation of methyl group of **52** with 4-iodotoluene **52a** led to formation of bis-arylation product **53a** in 98% yield (Scheme 19). The reductive elimination of the sulfonyl moiety took place with less than 2% of racemization to give the product **53b** (Scheme 19).



Scheme 19. Pd(II)-catalyzed γ-arylation of C(sp^3)-H bonds of **52**.

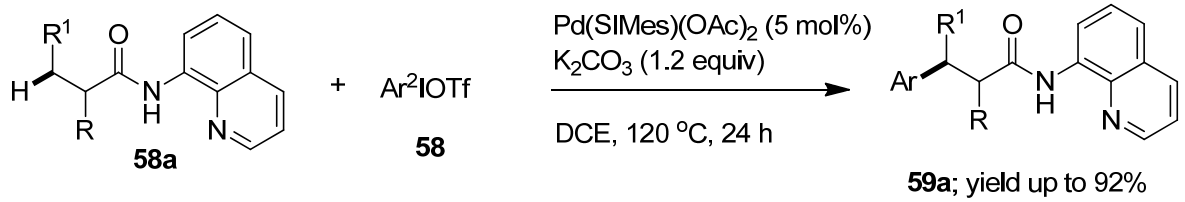
Ma reported[17d]MIA (2-Methoxyiminoacetyl) directed Pd(II)-catalyzed arylation of **54** with aryl iodide **54a** to give the product **54b** (Scheme 20). Further, KOH mediated cleavage of

directing group led to the formation of amino acids **55a**, which were treated with $(Boc)_2O$ to afford **56a** with good yields and excellent enantiopurity. The **55a** was used for the preparation of lactam **56a**, which can a promising intermediate for the synthesis of antihypertensive drug benazepril **57a** (Scheme 20).



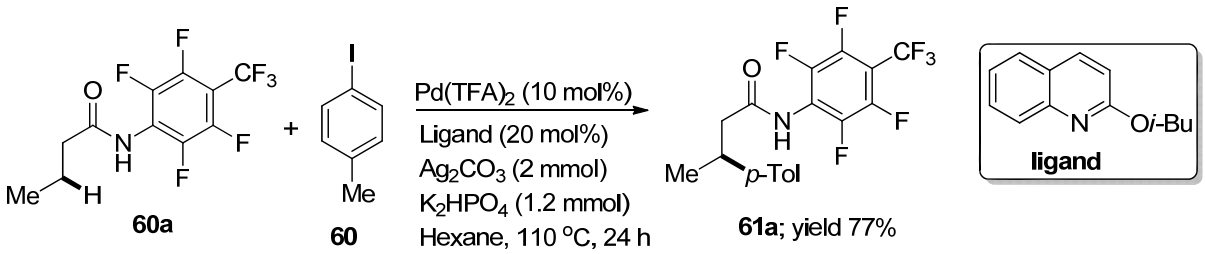
Scheme 20. MIA directed γ-C-H arylation of **54** and formal synthesis of benazepril.

Shi and co-workers[17e] reported the Pd(II)-catalyzed arylation of sp^3 C-H bonds by using diarylhyperiodonium salts **58** as the arylation reagents. The reaction of **58a** with different diarylhyperiodonium triflates **58** in the presence of $Pd(SIMes)(OAc)_2$ (5 mol%) and K_2CO_3 (1.2 equiv) in DCE at 120 °C afforded a variety of β-C-H arylated aliphatic carboxamides **59a** in good yields (Scheme 21).



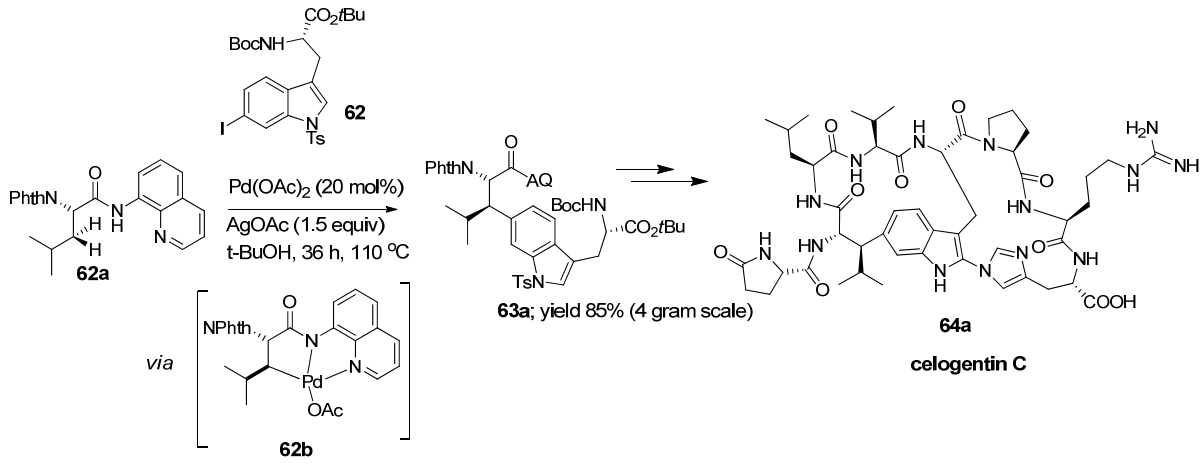
Scheme 21. Pd(II)-catalyzed sp^3 C-H bonds arylation with diarylhyperiodonium salts.

Yu and co-workers reported[17f] thePd(II)-catalyzed β-C-H arylation of *N*-arylamide **60a** with 4-iodotoluene **60** in the presence of $Pd(TFA)_2$ (10 mol%), ligand (20 mol%), Ag_2CO_3 (2 mmol), K_2HPO_4 (1.2 mmol) in hexane at 110 °C for 24 h to give the arylated product **61a** (Scheme 22).



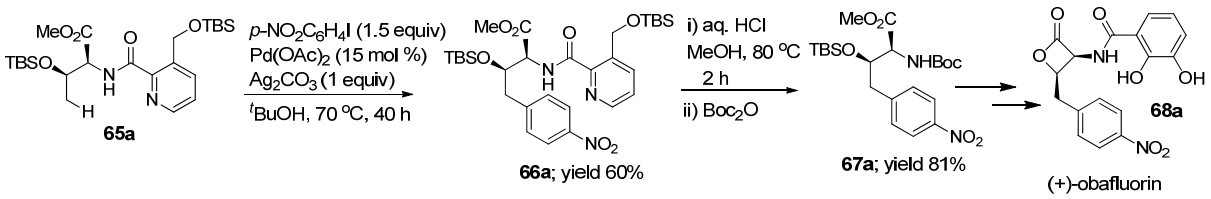
Scheme 22. β-C-H arylation of methylene C-H bonds of **60a**.

Chen and co-workers[18a] reported the total synthesis of bicyclic peptide celogentin C **62a** via the transition-metal-catalyzed stereoselective direct β-C-H functionalization strategy (Scheme 23) The Pd(II)-catalyzed sp^3 C-H arylation enabled construction of C-C bond between **62a** and **62** gave the 6-indolylation product **63a** in high yield and diastereoselectivity. The Total synthesis of celogentin C (**64a)** involves 23 steps from simple amino acid building blocks. Whereas the synthesis of **63a** was possible in gram scale via the direct C-H arylation step, which formed a key step for the synthesis of celogentin C **64a** (Scheme 23).



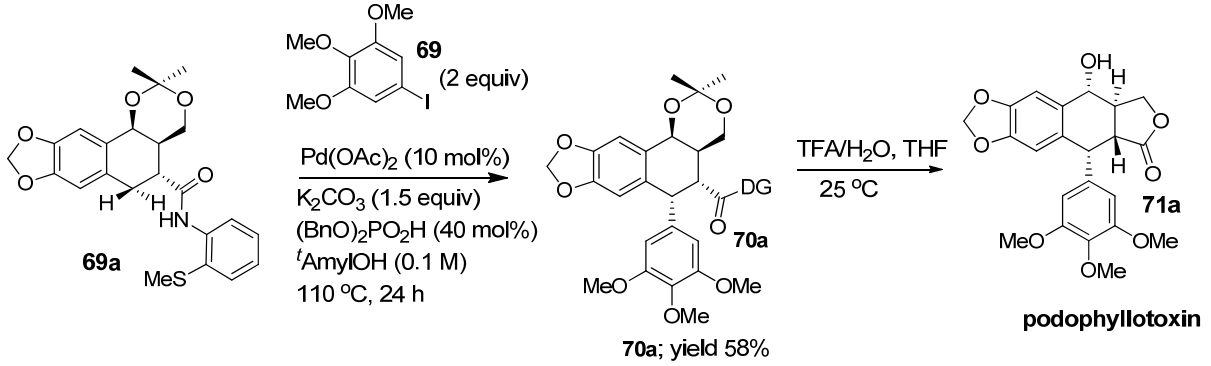
Scheme 23. Synthesis of celogentin C *via* β-C-H arylation of **62a**.

Chen group[18b] reported the formal synthesis of (+)-obafluorin **68a** from a readily accessible threonine derivative **67a**. The Pd(II)-catalyzed C-H bond activation and arylation of **65a** afforded **66a** The removal of the directing group under milder conditions gave the product **67a**, which was used in the synthesis of (+)-obafluorin **68a** (Scheme 24).



Scheme 24. Formal synthesis of (+)-obafluorin *via* C(sp^3)-H arylation of picolinamide **65a**.

Recently, Maimone and co-workers[18c] reported the synthesis of aryltetralin lignan podophyllotoxin **71a** in two steps *via* the chelation assisted/directing group-enabled Pd(II)-catalyzed β-C(sp^3)-H arylation. The selective arylation of the **69a** with 3,4,5-trimethoxyiodobenzene **69** led to formation of β-C-H arylated structures **70a**, which was used to complete the synthesis of **71a** (Scheme 25).

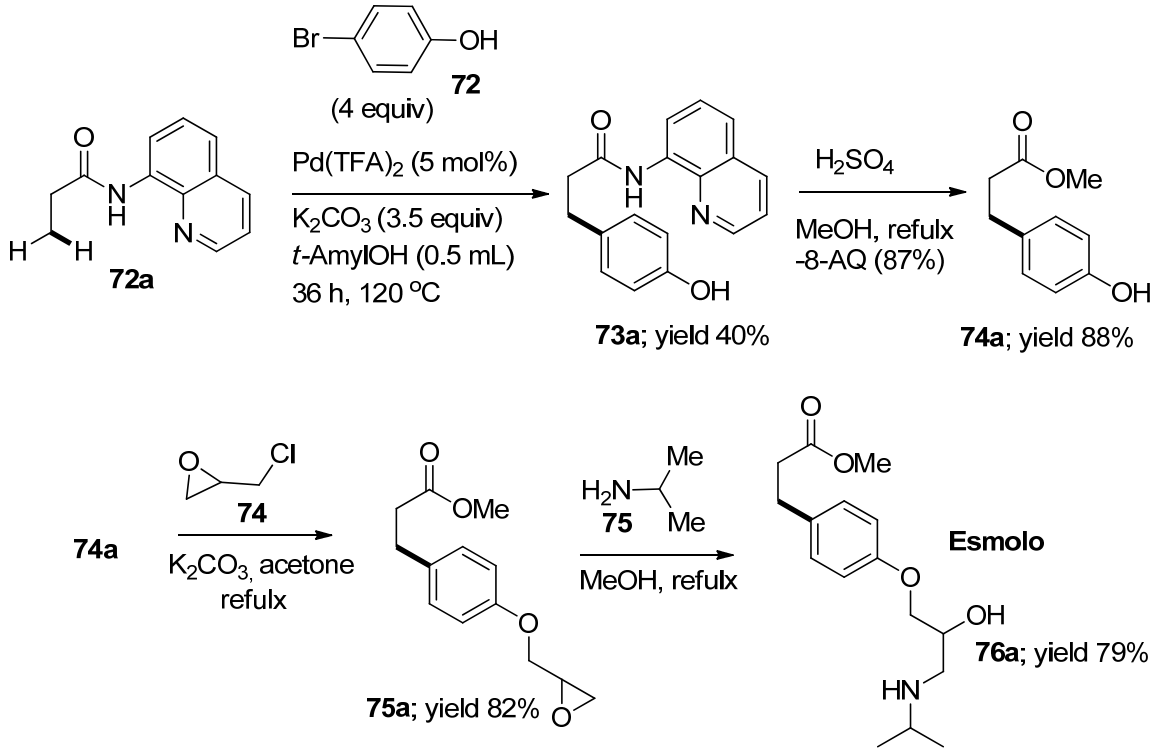


Scheme 25. Synthesis of podophyllotoxin *via* β-C-H arylation **69a**.

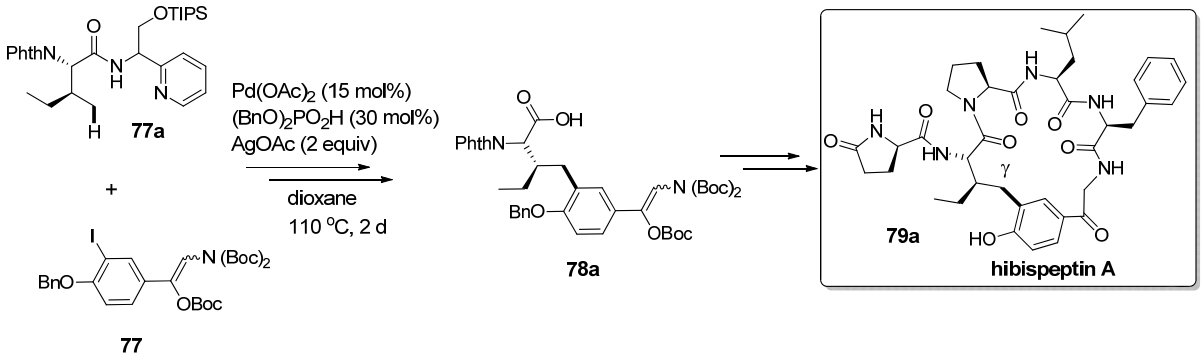
Zeng group reported[18d] 8-aminoquinoline assisted Pd(II)-catalyzed C(sp^3)-H functionalization of **72a** with less reactive aryl bromides **72** as arylating agents, which afforded the product **73a**. Potassium carbonate as a base and pivalic acid as an additive was shown to be important for obtaining high efficiency. The utility of this method was realized with a concise synthesis of cardioselective β-blocker drug esmolol **76a** (Scheme 26).

Chen group reported[18e] a new pyridyl unit based bidentate carboxamide as the directing group for the Pd(II)-catalyzed arylation of the γ-C-H bond of methyl group. The remote C-H

arylation of isoleucinederivative **77a** withmore sterically hindered *ortho* substituted aryl iodide **77** gave the product **78a**.The formation**78a** is the key step for the synthesis ofhibispeptin A **79a** (Scheme 27).



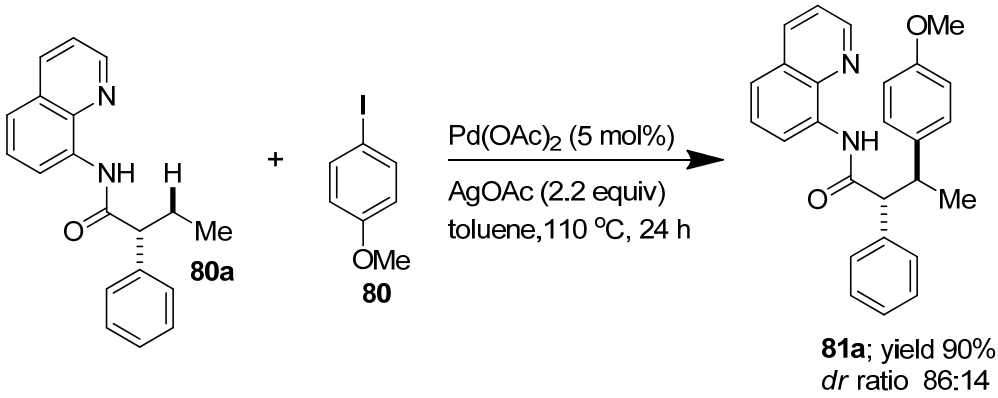
Scheme 26. β-C(sp^3)-H arylation of amide **72a** using aryl bromides.



Scheme 27. Pd-catalyzed γ-C(sp^3)-H arylation of **77a** and the total synthesis ofhibispeptin A **79a**.

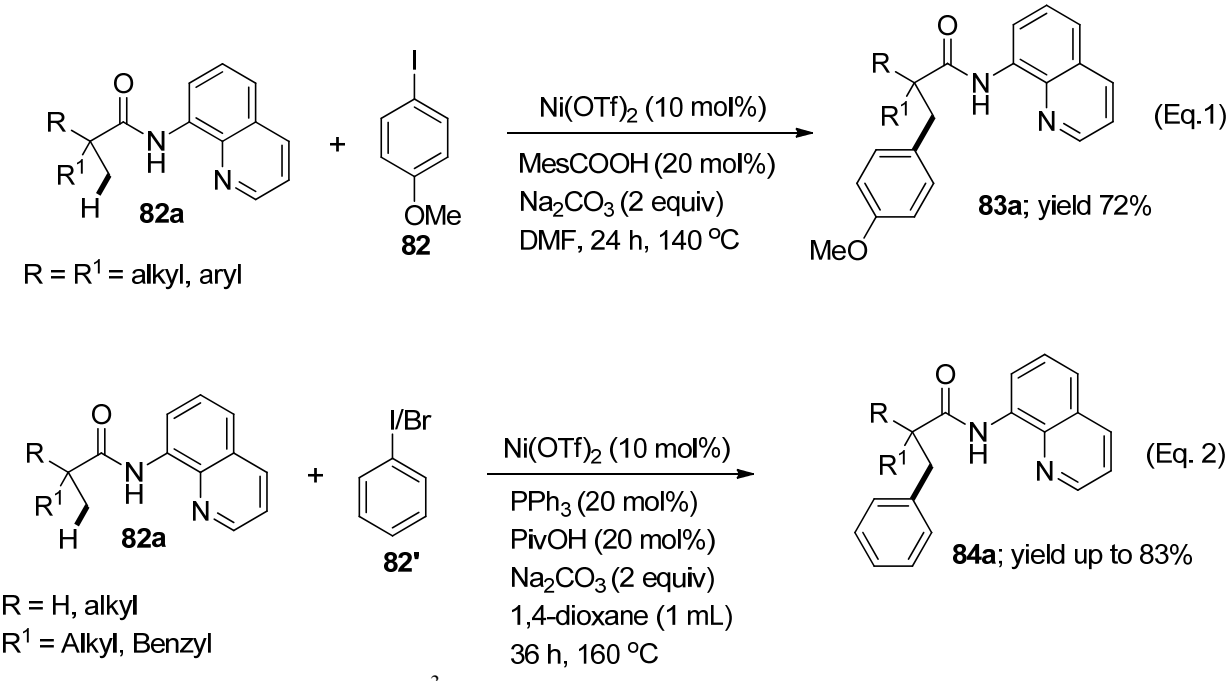
Our group[18f] reported the Pd(II)-catalyzed diastereoselective β-arylation of the prochiral secondary sp^3 C-H bonds of 2-phenylbutanamides (Scheme 28). The arylation of **80a** with 1-

iodo-4-methoxybenzene **80** in the prescence of 5 mol % of $Pd(OAc)_2$, 2.2 equiv of AgOAc in toluene at 110 ^oC for 24 h gave to the β-C-H arylated product **81a** in good yield and diastereoselectivity.



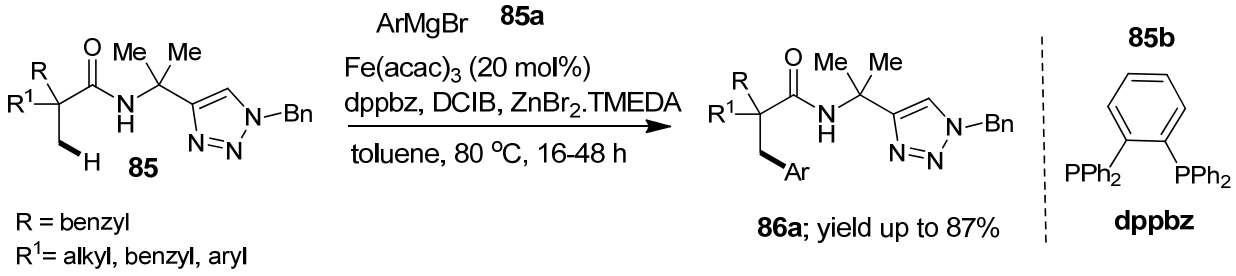
Scheme 28. Diastereoselective β-arylation of the C(sp^3)-H bonds of **80a**.

While the C(sp^3)-H arylation was commonly studied using palladium catalysts, Chatani and co-workers[18g] reported C(sp^3)-H arylation of unactivated C-H bonds using commercially cheap Ni(II) catalysts. Arylation of primary β-C(sp^3)-H bonds of aliphatic amide **82a** with aryl iodide **82** in the presence of Ni(II)-catalyst gave the arylated product **83a** (Scheme 29). The reaction proceeds with the probable involvement of Ni(II)/Ni(IV) species. Recently, You and co-workers[18h] also reported a similar work for the synthesis β-arylated carboxamides **84a** *via* the Ni-catalyzed arylation strategy (Scheme 29).



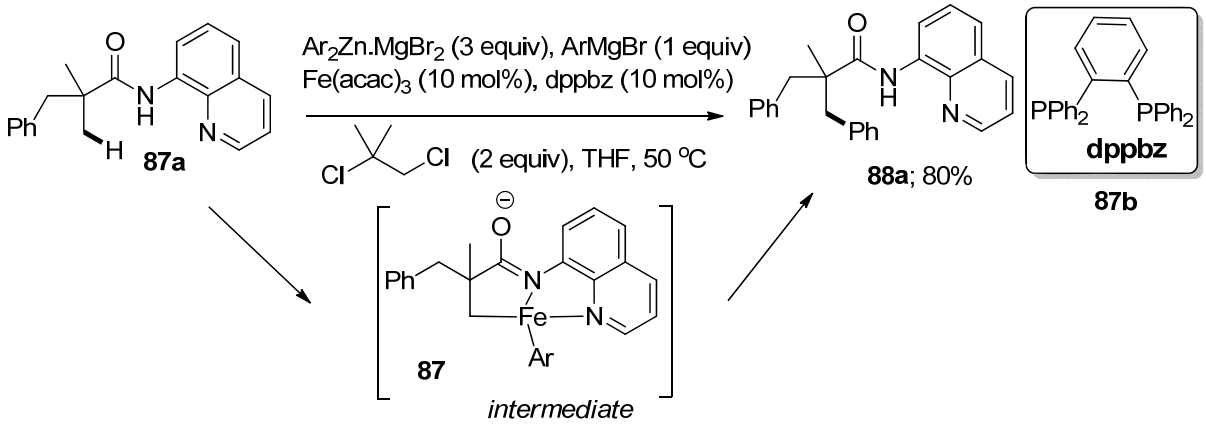
Scheme 29. Ni(II) catalyzed C(sp^3)-H arylation of aliphatic carboxamide **82a.**

Ackermann and co-workers [19a] reported the Fe-catalyzed direct C–H arylation of **85** using a triazole-based bidentate directing group. The reaction of amide **85** with ArMgBr **85a** in the presence of $Fe(acac)_3$ (20 mol%), $ZnBr_2$.TMEDA (3 equiv), (1,2-bis(diphenylphosphino)benzene (dppbz, **85b**) (20 mol%), (1,2-dichloro-2-methylpropane (DCIB)) (2 equiv) in toluene afforded the β-C-H arylated products **86a** in good yields (Scheme 30).



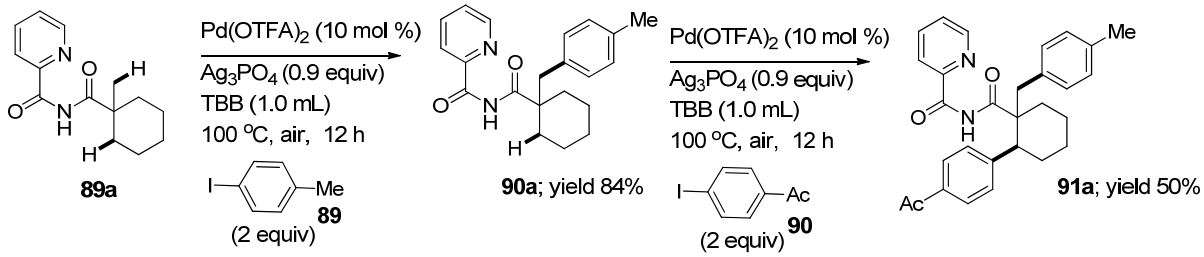
Scheme 30. Iron-catalyzed direct C–H arylation of **85.**

Nakamura's group[19b] also disclosed the Fe-catalyzed β-C-H arylation of 2,2-disubstituted propionamide **87a** with an organozinc reagent in the presence of an organic oxidant and a bisphosphine ligand **87b** to give the product **88a** (Scheme 31). A high selectivity for methyl group over benzylic C-H bonds was observed without 'over arylation' of methyl groups, which is distinct from the palladium-catalyzed reactions.



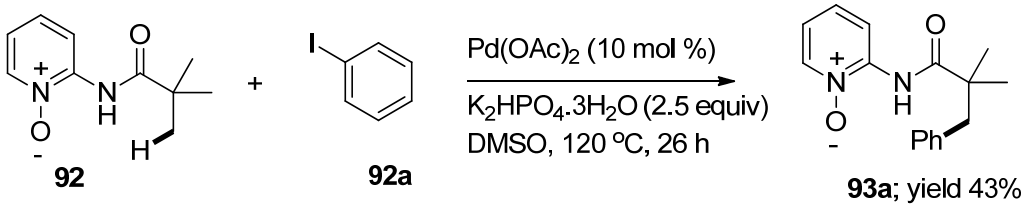
Scheme 31. β-C-H arylation of carboxamides *via* Fe-catalyzed C(sp^3)–H bond activation.

Shi and co-workers[19c] reported 2-picolinamide directing group-directed Pd(II)-catalyzed sequential double C-H arylation of **89a**. The arylation reaction of carboxamide **89a** with $Pd(OTFA)_2$, Ag_3PO_4 in TBB solvent at 100 ^oC afforded the primary β-C-H arylated products **90a** in good yields (Scheme 32). Further, a second arylation of **90a** with aryl iodide gave the secondary β-C-H arylated products **91a** (Scheme 32)



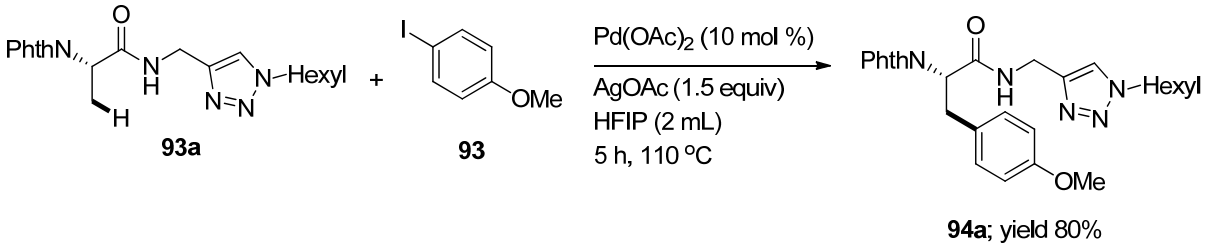
Scheme 32. Arylation of primary and secondary $C(sp^3)$-H bonds of **89a.**

Song and co-workers[19d] designed a new removable 2-aminopyridine-1-oxide moiety (PyO) for the Pd(II)-catalyzed β-C-H arylation of **92**. The arylation 3-propionamidopyridine 1-oxide **92** with PhI **92a**, 10 mol % $Pd(OAc)_2$ in DMSO at 120 °C for 26 h gave the desired mono-arylated product **93a** (scheme 33).



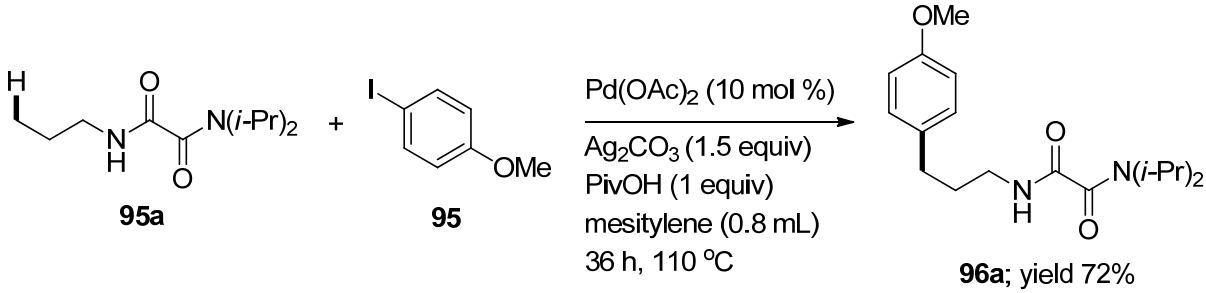
Scheme 33. 2-Aminopyridine-1-oxide moiety assisted arylation of **92**.

Ding and co-workers[19e] reported click-triazoles as a removable directing group for the $C(sp^3)$-H mono arylation of amino acid derivatives **94a**. The reaction of **93a** with 10 mol% $Pd(OAc)_2$, AgOAc (1.5 equiv.) and 1-iodo-4-methoxybenzene (**93**, 1.2 equiv.) at 100 °C in HFIP afforded the desired product **94a** in 80% yield (Scheme 34).



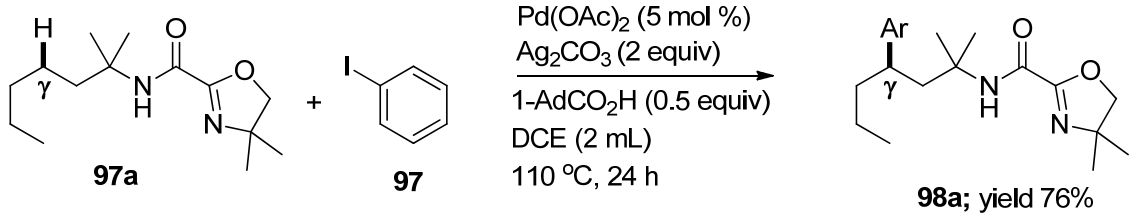
Scheme 34. Pd(II)-catalyzed arylation of **93a** with aryl iodides.

Zhao and co-workers[19f] reported oxalyl amide-directed γ-C-H arylation of aliphatic amine-derived oxalylamide **95a**. The treatment of oxalyl amide **95a** with 4-iodoanisole **95** in the presence of $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.5 equiv), and pivalic acid (1.0 equiv) in mesitylene at 110 °C in a sealed vial gave the product **96a** (Scheme 35).

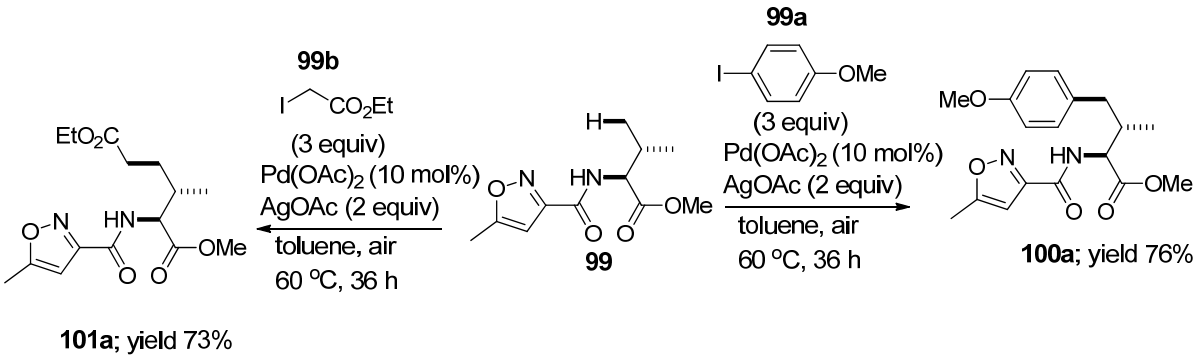


Scheme 35. Oxalyl amide directed γ-C-H arylation of aliphatic amine **95a**.

Shi and co-workers[19g] reported oxazoline-carboxylate directing group for the arylation of unactivated γ-methylene C(sp^3)-H bonds of **97a**. The reaction of amide **97a** with PhI **97** in the presence of 5 mol% $Pd(OAc)_2$, 2 equiv of Ag_2CO_3 in 1, 2-DCE solvent at 100 °C for 24 h gave the product **98a** (Scheme 36).



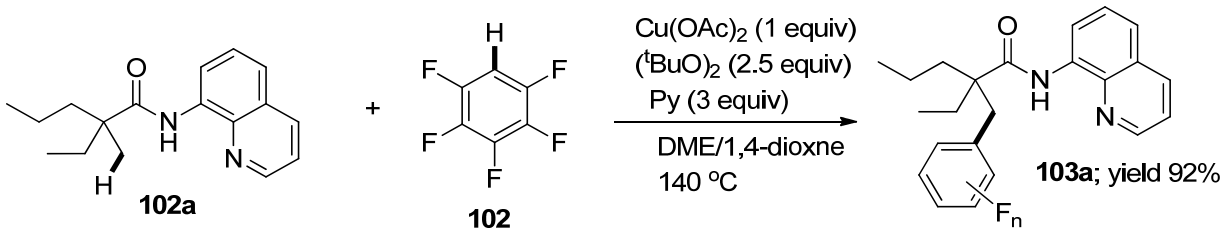
Scheme 36. Pd(II)-catalyzed arylation of γ-methylene C(sp^3)-H bonds of **97a**.



Scheme 37. 5-methylisoxazole-3-carboxamide directed γ -C-H functionalization of **99.**

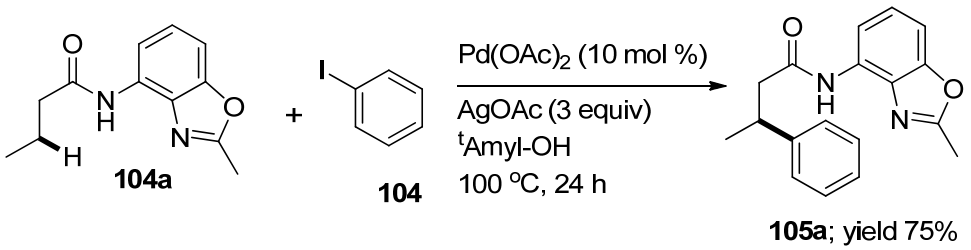
The Liu group[20a] reported the arylation of **99** with 4-iodoanisole **99a** (3 equiv), 10 mol % of $Pd(OAc)_2$, and AgOAc (2 equiv) in toluene at 60 °C for 36 h gave the product **100a** in good yield and selectivity (Scheme 37). Similarly the alkylation of **99** with ethyl iodoacetate **99b** provided the C-H alkylated product **101a** (Scheme 37).

Ge[20b] reported the copper-promoted dehydrogenative coupling of 2-ethyl-2-methyl-*N*-(quinolin-8-yl)pentanamide **102a** and pentafuorobenzene **102** in 1,4-dioxane with stoichiometric amounts of $Cu(OAc)_2$ under atmospheric oxygen to give the mono coupling product **103a** (Scheme 38).



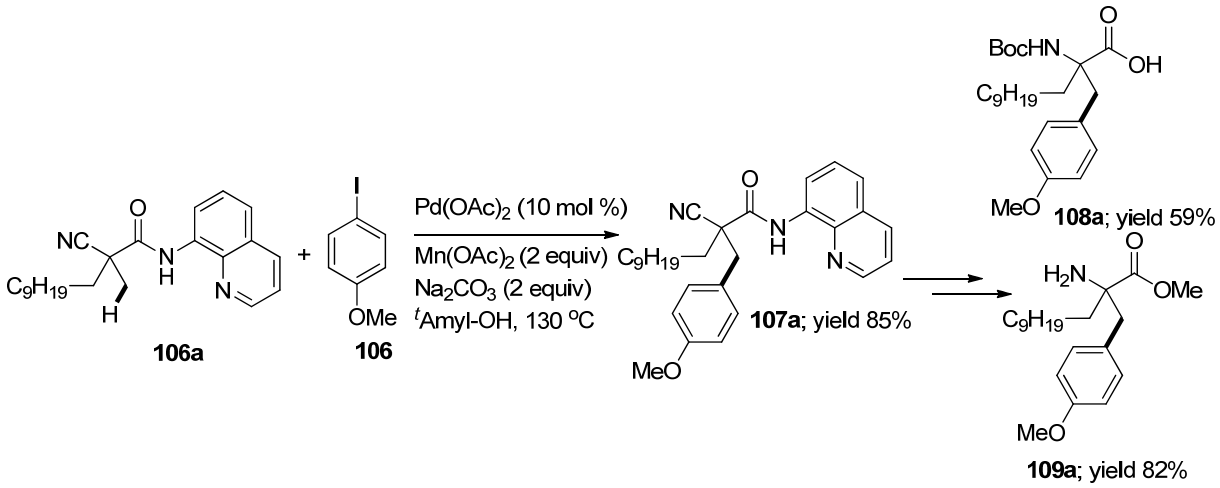
Scheme 38. Copper-promoted cross dehydrogenative coupling (CDC) reaction.

Li, Zhoua group[20c] reported the palladium(II)-catalyzed β-C-H arylation of $C(sp^3)$-H bond of **104a** with iodobenzene **104** in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in *t*-amyl-OH at 100 °C to give the desired product **105a** in good yield (Scheme 39).



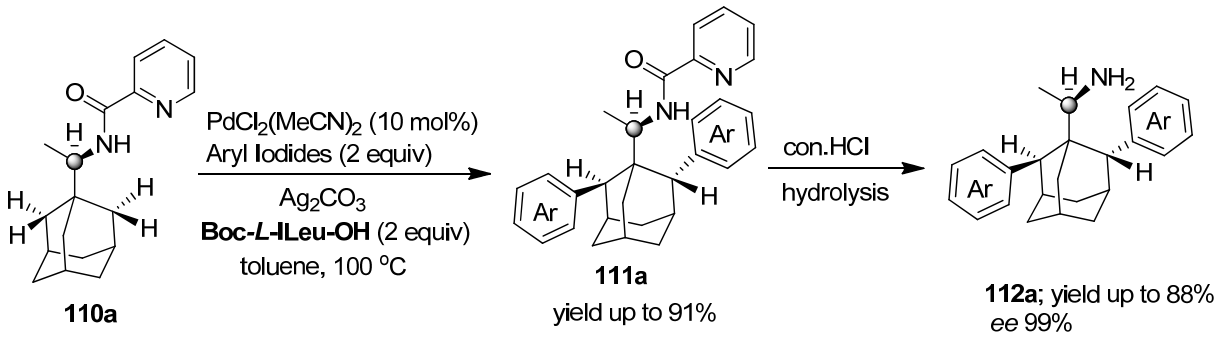
Scheme 39. C(sp^3)-H arylation of aliphatic amide **104a**.

Watkins group[20d] reported Pd-catalyzed arylation of α-cyano amide **106a** with 4-iodo anisole **106** in the prescence of 10 mol % of $Pd(OAc)_2$, $Mn(OAc)_2$ (2 equiv) and Na_2CO_3 (2 equiv) in *t*-amylOH at 130 °C for 30 h to give the product **107a** in good yield (Scheme 40). Furthermore, the synthetic utility of the products has been demonstrated through the synthesis of medicinally important amino acid derivatives **108a** and **109a**(Scheme 40).



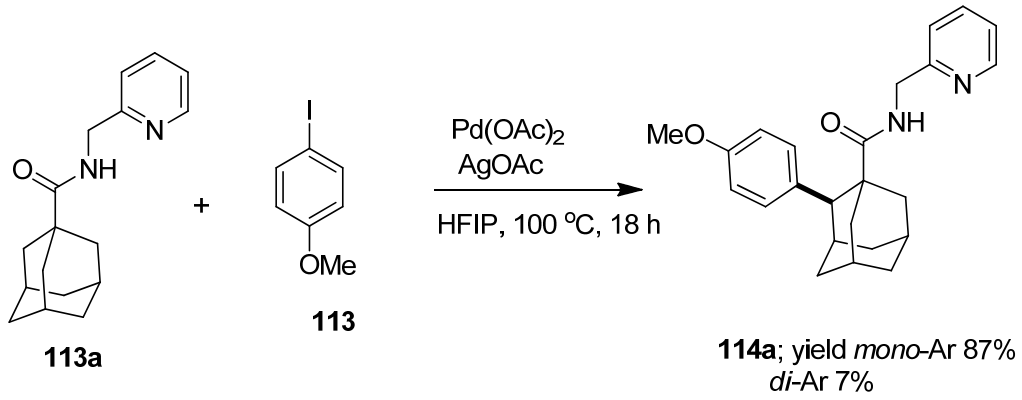
Scheme 40. C(sp^3)-H Arylation of α-cyano aliphatic amides.

Zhang group[20e] reported the C-H arylation of chiral-*N*-(pyridinyl-2-ylcarbonyl)rimantadine **110a** bearing the 2-picolinic acid moiety as the directing group (Scheme 41). The arylation of **110a** with $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant, mono-*N*-protected amino acid (MPAA) as a ligand in toluene at 100 °C for 15 h gave the diarylated product **111a** (Scheme 41).



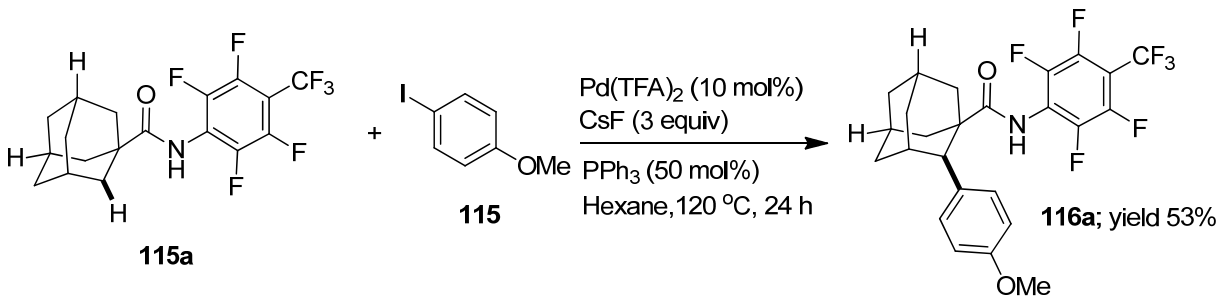
Scheme 41.C(sp^3)-H Arylation of rimantadinyl amide.

Hrdinaa and Becker [20f] reported the selective mono-arylation of the adamantane framework **113a** by using picolylamide as the directing group (Scheme 42). The selective arylation of **113a** with 4-iodo anisole **113** in the presence of $Pd(OAc)_2$ as the catalyst and AgOAc as the additive in HFIPat 110 °C for 18 h gave the monoarylated product **114a** (Scheme 42).

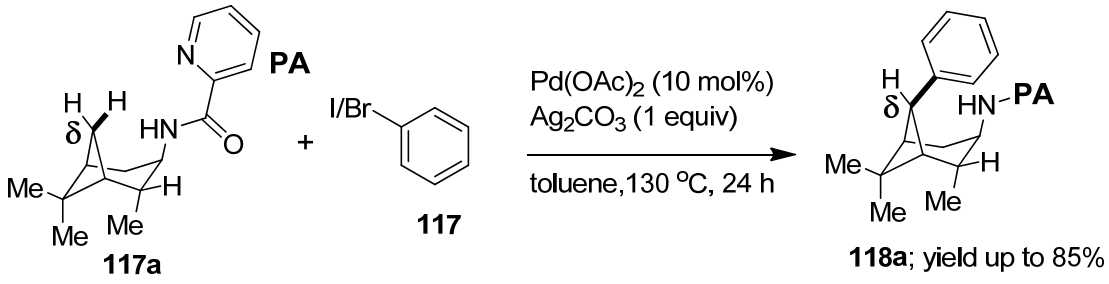


Scheme 42. $Pd(OAc)_2$-catalyzed arylation of adamantane system **113a**.

Wang group reported[20g] methylene C(sp^3)-H arylation of the adamantyl scaffold with the assistance of an arylamide group. The Pd-catalyzed sp^3 C–H activation of **115a** with4-iodo anisole **115** in the presence of $Pd(TFA)_2$ (10 mol%), PPh_3 (50 mol%), CsF (3 equiv) in hexaneat 120 °C for 24 h gave the monoarylated product **116a** (Scheme 43).



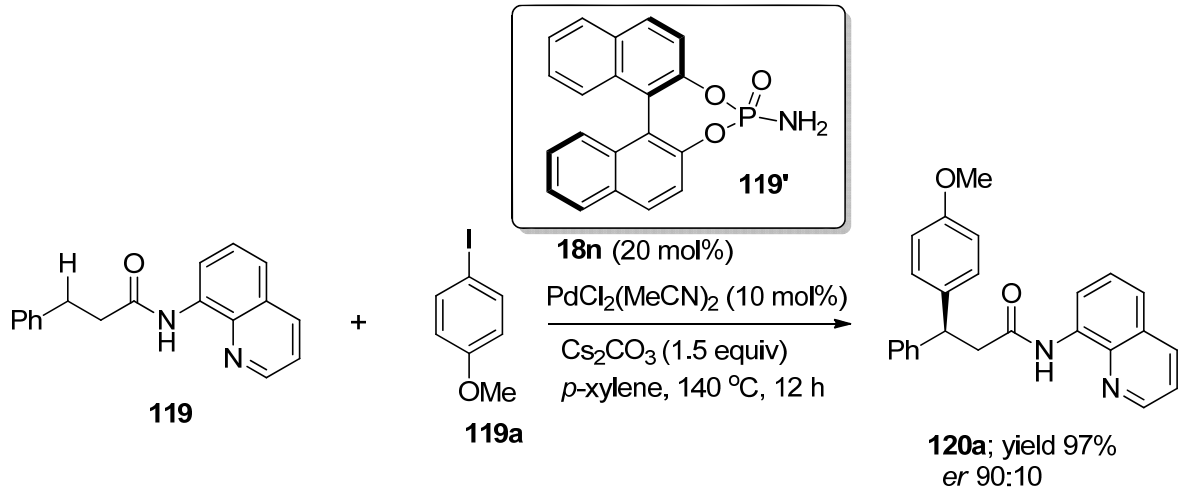
Scheme 43. Pd(II)-catalyzed C(sp^3)-H arylation of *N*-arylamide **115a**.



Scheme 44. Picolinamide-directed C(sp^3)-H arylation of 3-pinanamine **117a.**

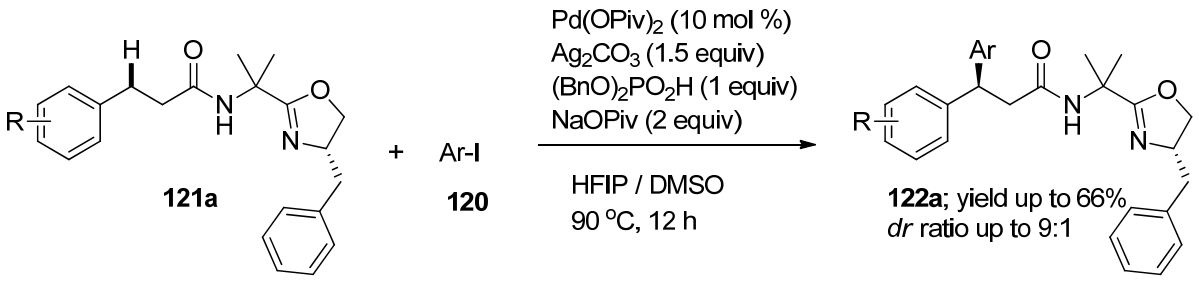
Wang and co-workers[21a] reported the Pd(II)-catalyzed C(sp^3)−H arylation of 3-pinanamine system **117a**. The picolinamide directed arylation of pinanamine **117a** with ArX **117** in the presence of $Pd(OAc)_2$ (10 mol%) and Ag_2CO_3 (1 equiv) in toluene at 130 °C gave the remote δ-C-H arylated products **118a** (Scheme 44).

Duan group[21b] reported asymmetric arylation of C(sp^3)-H bonds of aliphatic amides **119** with 4-iodo anisole **119a** using chiral phosphoric amide ligand **119'** to achieve the β-C-H arylation product **120a** in good yield and selectivity (Scheme 45).



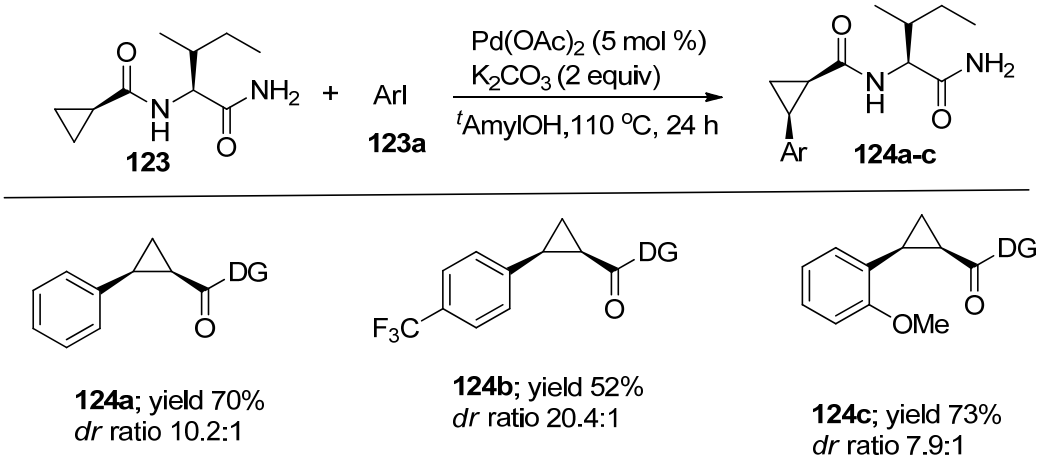
Scheme 45. Enantioselective arylation of carboxylic amide **119.**

Shi and co-workers [21c] reported a modifiable amino oxazoline directing group for asymmetric C(sp^3)-H arylation of **121a** (Scheme 46).The reaction of amide **121a** with PhI **120** in the presence of 10 mol% $Pd(OPiv)_2$ as the catalyst, 2 equivalents of NaOPiv in HFIP/DMSO solvent at 90 ^oC for 14 h gave the product **122a** in good yield and selectivity (Scheme 46).



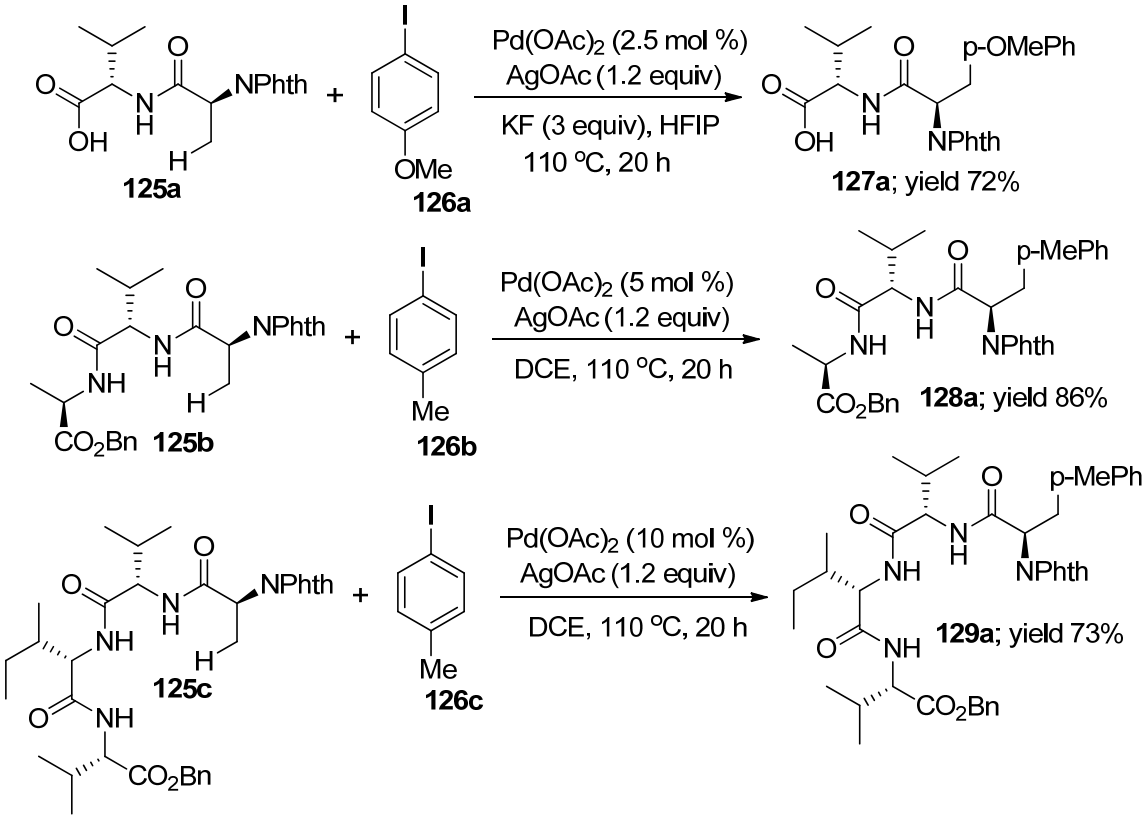
Scheme 46. Asymmetric C(sp^3)-H arylation of modifiable amino oxazoline DG **121a.**

Hong group [21d] reported the Pd(II)-catalyzed asymmetric C-H arylation of cyclopropanes using an isoleucine-NH_2 bidentate directing group (Scheme 47).The reaction of **123** with different aryliodides **123a** in the presence of $PdOAc)_2$ (10 mol%) and K_2CO_3 in *t*-amylOH at 100 ^oC afforded a variety of β-arylated carboxamides **124a-124c** with *cis* stereochemistry (Scheme 47).



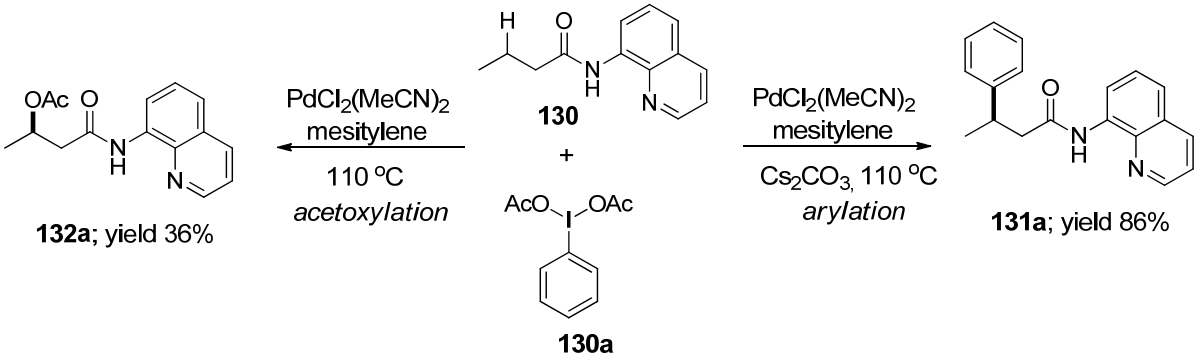
Scheme 47. Pd(II)-catalyzed asymmetric C-H arylation of cyclopropanes **123**.

Yu and co-workers[21e] reported the palladium-catalyzed arylation of *N*-phthaloyl protected peptides **125a**, **125b** and **125c** with aryl iodides **126a**, **126b** and **126c** to give the corresponding β-C-H arylated dipeptides **127a**, tripeptides **128a** and tetrapeptides **129a** (Scheme 48).



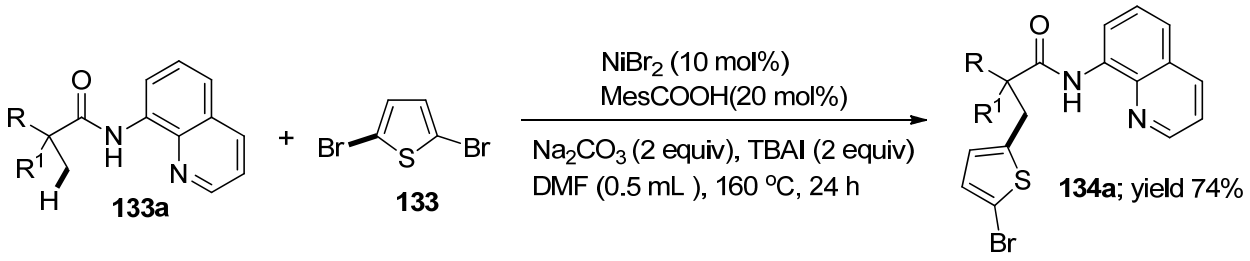
Scheme 48. Pd-catalysed C-H arylation of di-, tri-, and tetrapeptides **125a**, **125b** and **125c**.

Qin group[21f] reported the selective arylation and acetoxylation of C(sp^3)-H bonds of aliphatic amides (Scheme 49).The arylation of amide **130** with (diacetoxyiodo)arenes **130a** in the presence of $PdCl_2(CH_3CN)_2$, Cs_2CO_3 gave the arylated product **131a** and notably, under the similar experimental conditions without Cs_2CO_3, the reaction of **130** with **130a** afforded the acetoxylation product **132a** in low yields (Scheme 49).



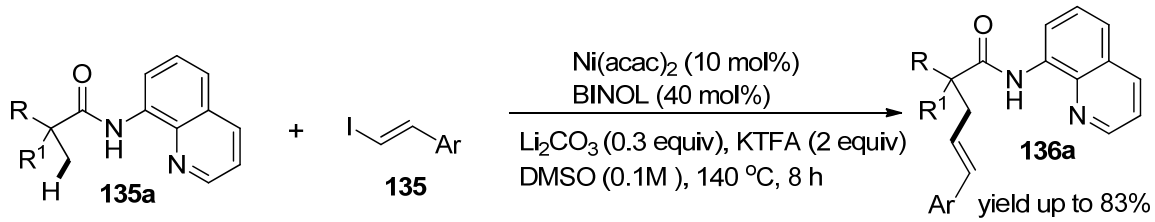
Scheme 49. Arylation of unactivated C(sp^3)-H bonds using (diacetoxyiodo)arenes **130.**

Qui and co-workers[21g] reported the Ni-catalyzed C (sp^3)-H arylation of aliphatic amides **133a** with2,5-dibromothiophene **133** in the presence ofcatalytic amounts of $NiBr_2$ and MesCOOH using excess Na_2CO_3 in DMF gave the monoheteroarylated product **134a** (Scheme 50).



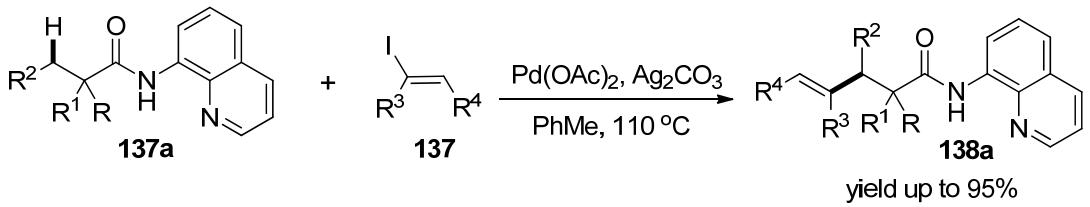
Scheme 50. Ni-catalyzed C (sp^3)-H arylation of aliphatic amides **133a**.

Shi group[22a] reported Ni(II)-catalyzed reaction of **135a** with **135** in the presence of 10 mol% $Ni(acac)_2$, BINOL (40 mol%), Li_2CO_3 (2.0 equiv), and KTFA (2.0 equiv) in DMSO to give the C-H alkenylated product **136a** (Scheme 51).



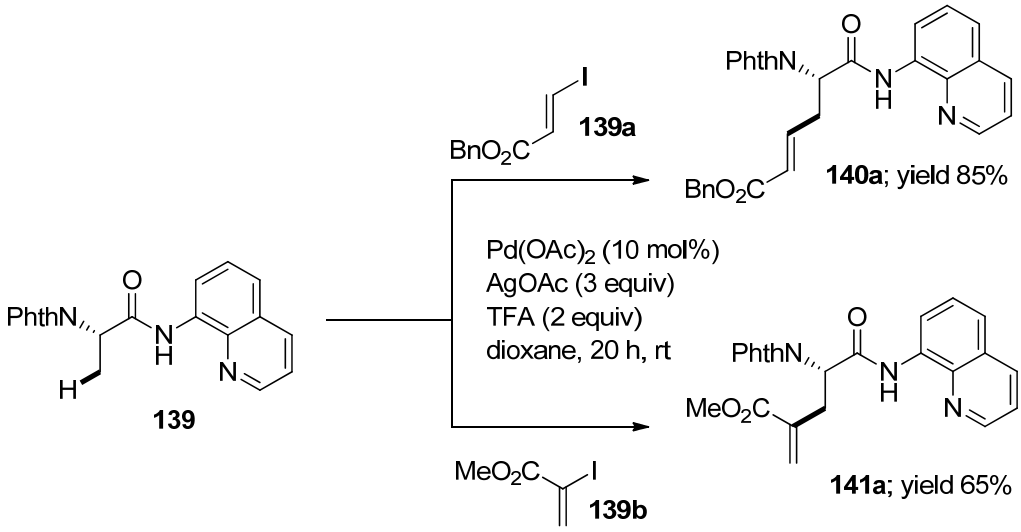
Scheme 51. Ni(II)/BINOL-catalyzed alkenylation of unactivated C(sp^3)-H bonds of **135a**.

Rao group[22b] reported the palladium(II)-catalyzed alkenylation of acyclic aliphatic amides **137a** with alkenyl halides **137** in the presence of $Pd(OAc)_2$, Ag_2CO_3 in toluene afforded the C-H alkenylated product **138a** in good yield (Scheme 52).



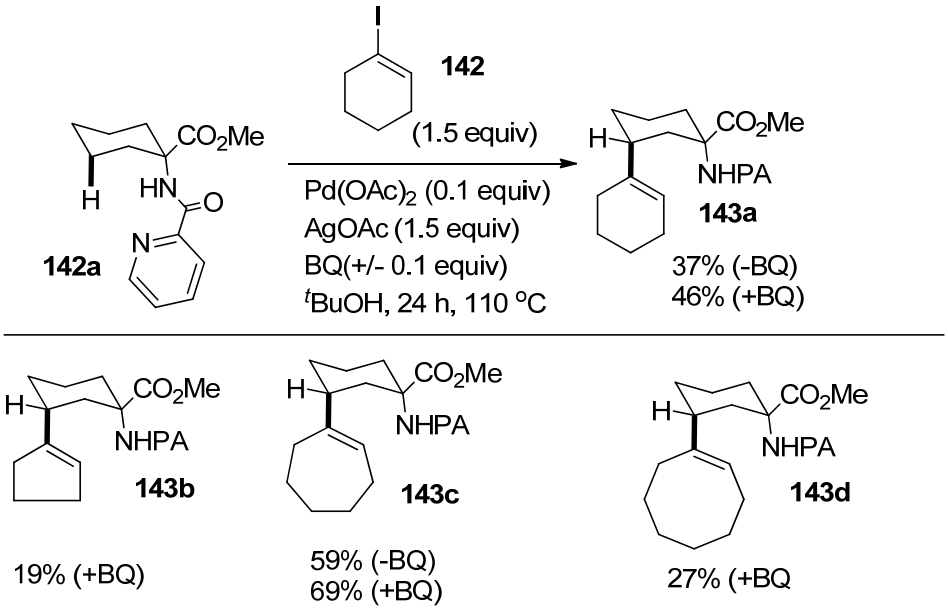
Scheme 52. Pd(II)-catalyzed alkenylation of C(sp^3)-H bond of amides **137a**.

Chen co-worker reported[22c] the Pd(II)-catalyzed olefination of unactivated C(sp^3)-H bonds of **139** with vinyl iodides **139a** and**139b** at room temperature to give the corresponding β-C-H olefinated α-amino acid **140a** and **140b** derivatives (Scheme 53).



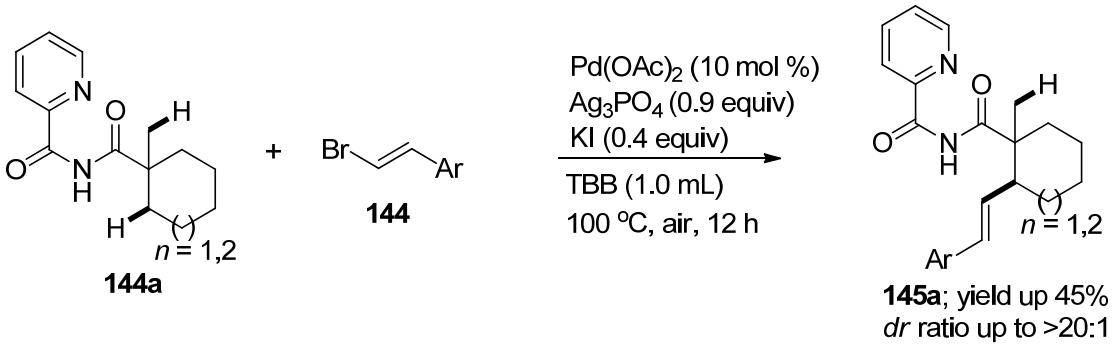
Scheme 53. :AQ-directed β C(sp^3)-H olefination of **139.**

Chen group reported[22d] picolinamide directed alkenylation of **142a** with cyclic vinyl iodides **142** provided the desired alkenylated product **143a-d** in moderate yields in the presence of $Pd(OAc)_2$ (0.1 equiv), and AgOAc (1.5 equiv) in *t*BuOH at 110 °C (Scheme 54).



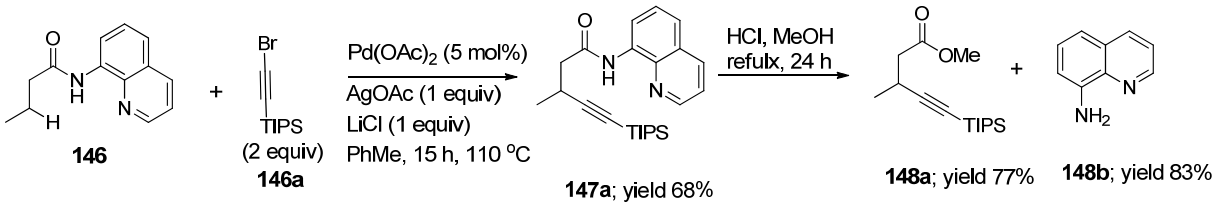
Scheme 54. Picolinamide-directed C(sp^3)-H alkenylation using cyclic vinyl iodides.

Shi and co-workers [19c] reported the Pd(II)-catalyzed alkenylation of β-methylene C(sp^3)-H bond using alkenyl bromides **144** (Scheme 55). Alkenylation of **144a** with vinyl bromides **144** provided the desired alkenylated product **145a**. Main importance of this method was the alkenylation of methylene C-H bonds was achieved instead of primary C-H bonds in moderate yield (Scheme 55).



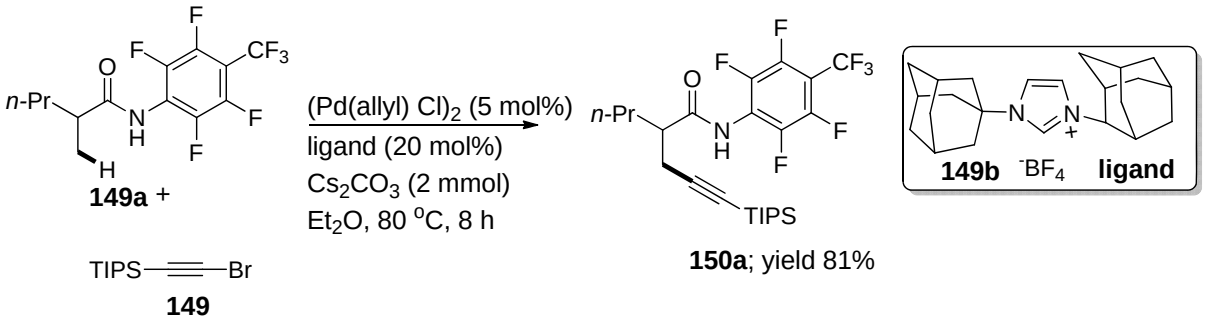
Scheme 55. Palladium(II)-catalyzed alkenylation of C(sp^3)-H bonds with vinyl bromides.

Chatani group reported[23a] the β-C-H alkynylation of unactivated C(sp^3)-H bonds of carboxylic derivatives **146** (Scheme 56). In the absence of a C(sp^3)-H hydrogen at the β-position, the C-H alkynylation occurred at the γ-C-H position. The β-C-H alkynylation of **146** with **146a** under the Pd(OAc)/AgOAc catalytic system gave the product **147a** (Scheme 56). Notably, the directing group was readily removed from the C-H alkynylated products under acid hydrolysis (HCl/MeOH) condition to give the product **148a** (Scheme 56).

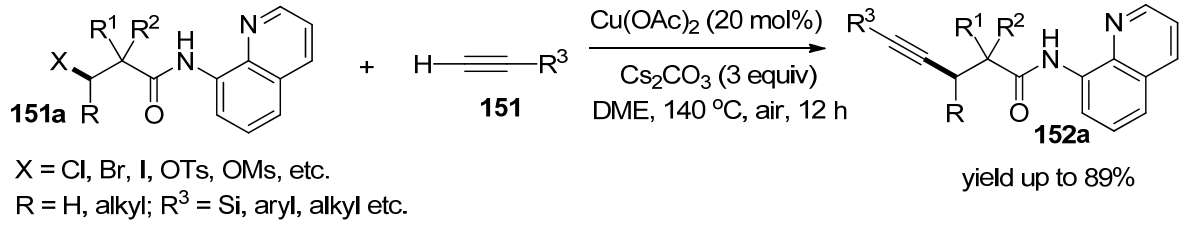


Scheme 56. Direct alkynylation of C(sp^3)-H bonds using 8-aminoquinoline directing group.

Yu group reported[23b] Pd-catalyzed β-C(sp^3)-H alkynylation of *N*-arylamide **149a** with bromoalkyne **149** in the presence of $(Pd(allyl)Cl)_2$ (5 mol%) and Cs_2CO_3 in Et_2O, which afforded the alkynylated product **150a** (Scheme 57). Shi and co-workers[23c] reported the copper-catalyzed direct alkynylation of aliphatic organohalides **151a** with terminal alkynes **151** afforded the desire product **152a** (Scheme 58).

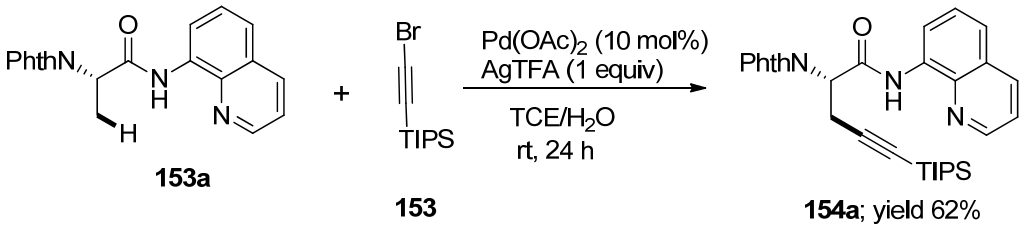


Scheme 57. *N*-arylamide directed β-alkynylation of **149a**.

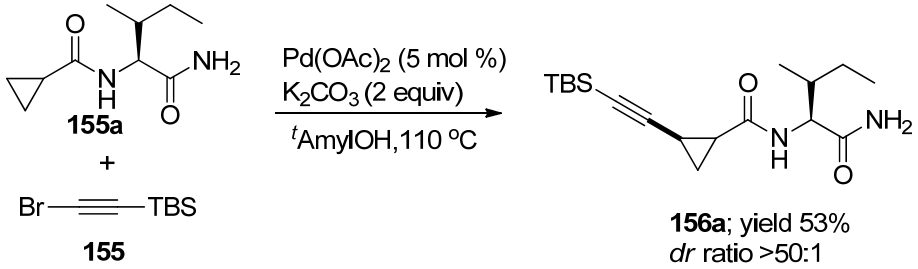


Scheme 58. Cu-Catalyzed alkynylation of unactivated C(sp^3)-X bonds of **151a**.

Chen group[22c] reported the synthesis of alkyne containing amino acid derivative **154a** through the Pd(II)-catalyzed methyl C(sp^3)-H activation at room temperature using amide **153a** and TIPS protected acetylene **153** (Scheme 59).Hong group[21d] reported Pd(II)-catalyzed diastereoselective C-H alkynylation of amide **155a** with bromoalkyne **155** in the presence of $Pd(OAc)_2$ (10 mol%) and K_2CO_3 in *t*-amylOH gave the single diastereomer **156a** (Scheme 60).

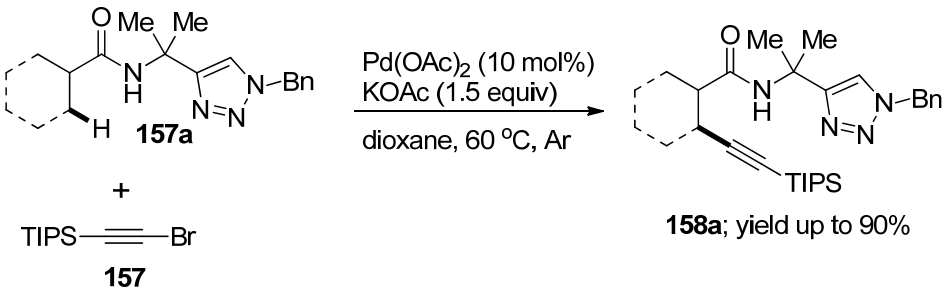


Scheme 59. AQ-directed β C(sp^3)-H alkynylation of **153a**.

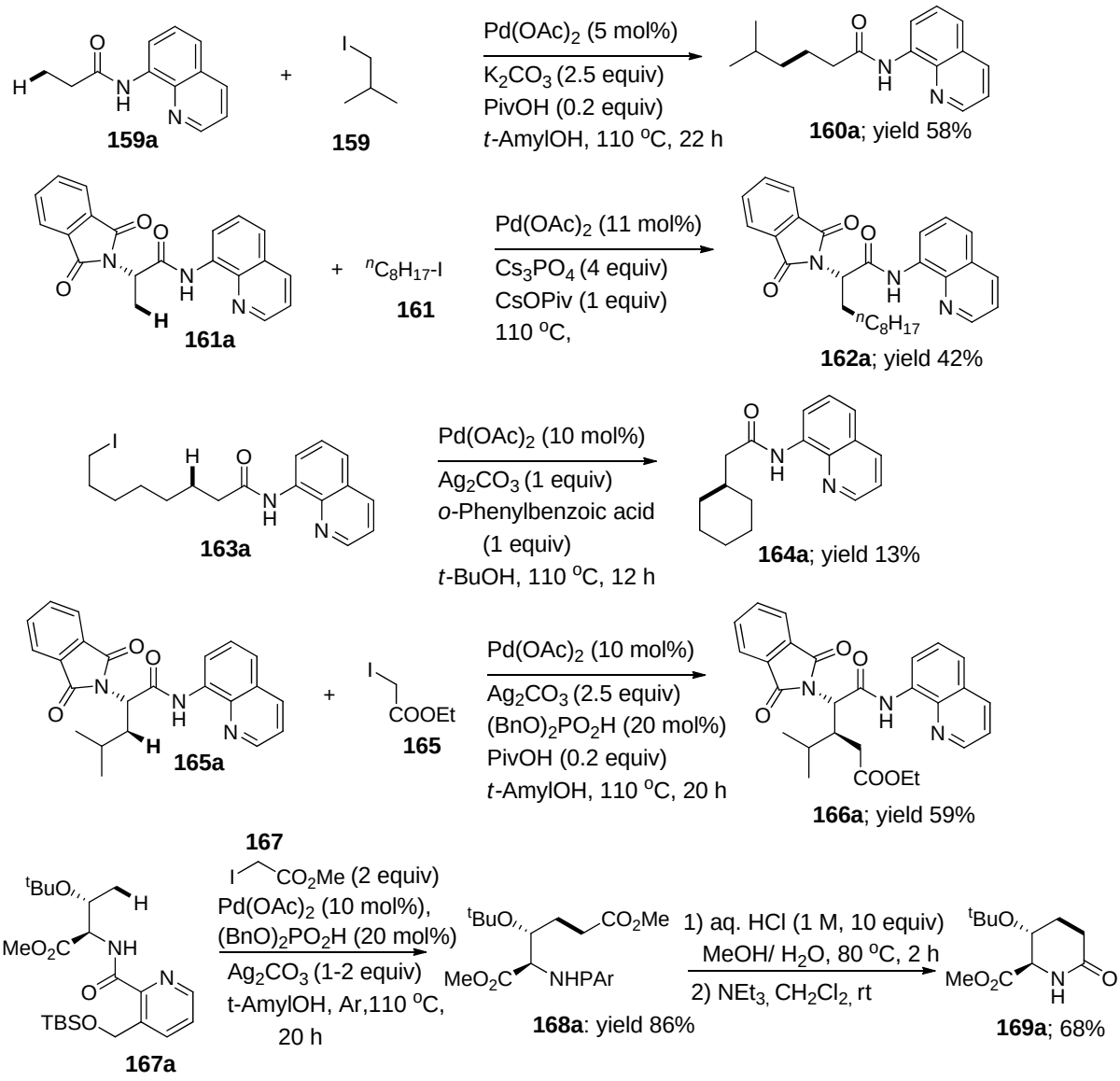


Scheme 60. Pd(II)-catalyzed alkynylation of unactivated C(sp^3)-H bonds of **155a**.

Recently, Shi group [23d] reported 1,2,3-triazole amine (TAM) as the directing group for the selective C-H alkynylation. The β-C-Halkynylation of **157a** with **157** under $Pd(OAc)_2$/KOAc catalytic system in 1,4-dioxane gave the product **158a** (Scheme 61).



Scheme 61. 1,2,3-Triazole amine directed sp^3 C-H alkynylation of **157a.**



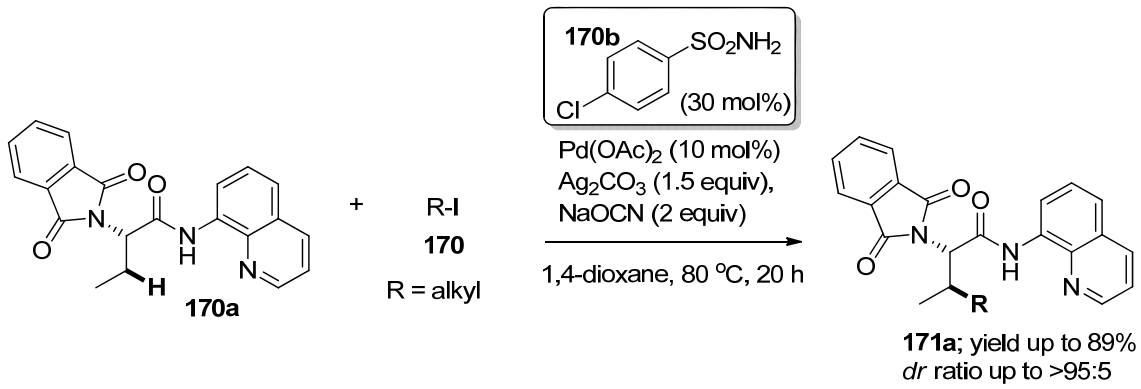
Scheme 62. Pd(II)-catalyzed alkylation of C(sp^3)-H bonds of **159a**,**161a**,**163a**,**165a** and **167a**.

Daugulis *et al.*[24a] reported the synthesis of β-C-H alkylated butane carboxamide derivative **160a** *via* the directing group-enabled Pd(II)-catalyzed alkylation of unactivated 1° C(sp^3)−H bonds of **159a** with alkyl halides **159** (Scheme 62). Daugulis's group[24b] also reported the reaction of *N*-phthaloylalanine derived system **161a** with 1-iodooctane **161** in the presence of 11 mol % of $Pd(OAc)_2$, Cs_3PO_4 and CsOPiv bases at 110 °C afforded the desired alkylated product **162a** in moderate yield (Scheme 62).

Chen and co-workers[24c] reported the intramolecular coupling of an aryl iodide and a methylene C-H bond **163a** *via* Pd(II)-catalysis(Scheme 62). Chen and co-workers[24d] developed an efficient method for the stereoselective construction of β-C-H alkylated α-

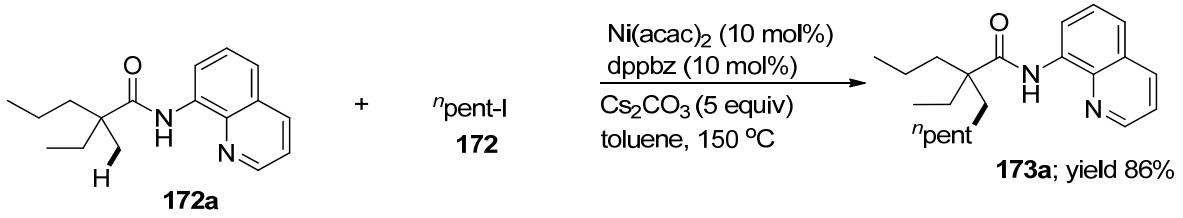
amino acid derivatives **166a** *via* the Pd(II)-catalyzed alkylation of 2° C(sp^3)−H bonds of **165a** with α-iodoacetates **165** (Scheme 62). Chen[24e] reported picolinamide as the removable directing group for the C−H alkylation, and the treatment of **167a** with **167** gave the C-H alkylated product **168a** (Scheme 62).The picolinamide directing group of **168a** was removed in the presence of HCl(aq)/MeOH solution to give the corresponding free amine intermediate, which underwent further lactonization to form 5,6- disubstituted piperidinone **169a** in 68% yield (Scheme 62).

Recently, Shi [24f] reported sulfonamide-promoted alkylation of unactivated methylene C(sp^3)-H bonds of α-amino acid derivatives **170a** by using alkyl iodides **170** (Scheme 63). The addition of NaOCN and 4-Cl-$C_6H_4SO_2NH_2$ ligand **170b** was crucial for the synthesis unnatural β-disubstituted amino acid derivatives **171a** in good yields and diastereoselectivity (Scheme 63).



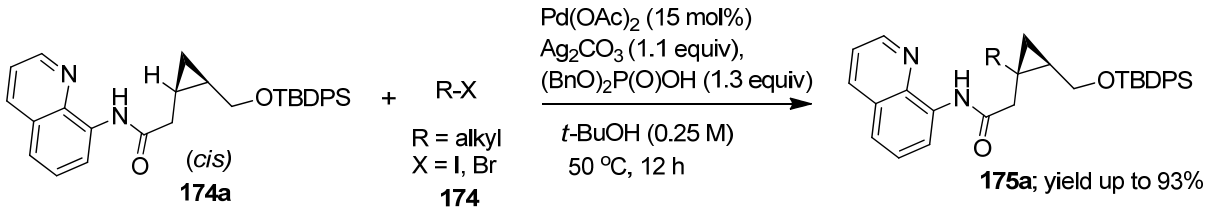
Scheme 63. Sulfonamide-promoted β-alkylation of C(sp^3)−H bonds of carboxamides **170a**.

Ge group reported[24g] on the nickel(II)-catalyzed β-C-H alkylation of aliphatic amides with the assistance of an 8-aminoquinoline directing group. The alkylation of AQ-embedded carboxamides **172a** with alkyl halide **172** in the presence of [Ni(acac)$_2$] (10 mol%) with 1,2-bis(diphenylphosphino)benzene (dppbz) (10 mol%) as the ligand, Cs_2CO_3 (5 equiv) in toluene at 150 °C gave the β-alkylation product **173a** (Scheme 64).

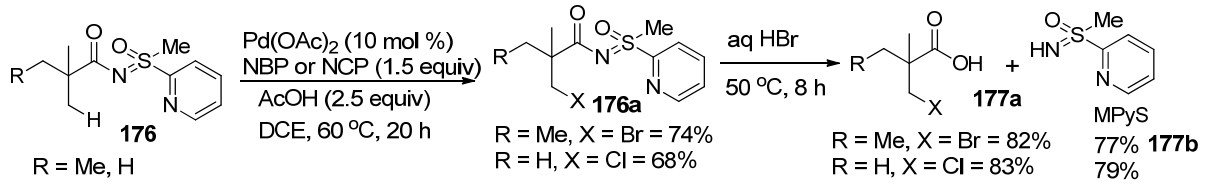


Scheme 64. Ni(II)catalyzed β-C(sp^3)-H alkylation of aliphatic amides **172a.**

Recently, Shuto and co-workers[24h] reported the synthesis of chiral 1,1,2-trialkyl substituted cyclopropanes **175a** *via* the palladium-catalyzed AQ-enabled alkylation of tertiary C(sp^3)-H bond of cyclopropanes **174a**. The alkylation of *cis* cyclopropanes **174a** with RX **174** in the presence of $Pd(OAc)_2$, Ag_2CO_3, $(BnO)_2P(O)OH$ in ^tBuOH at 50 ^oC provided the alkylcyclopropanes **175a** in good yields (Scheme 65).



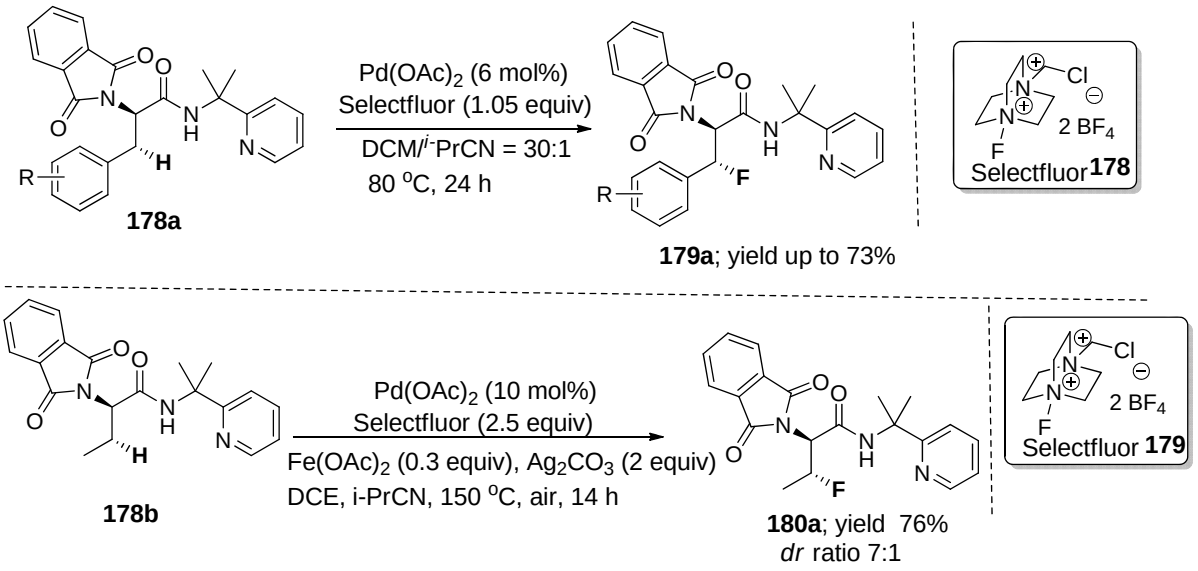
Scheme 65. Pd(II)-catalyzed alkylation of cyclopropanes **174a**.



Scheme 66. Pd(II)-catalyzed β-halogenation of amide with the aid of MPyS-DG **176**.

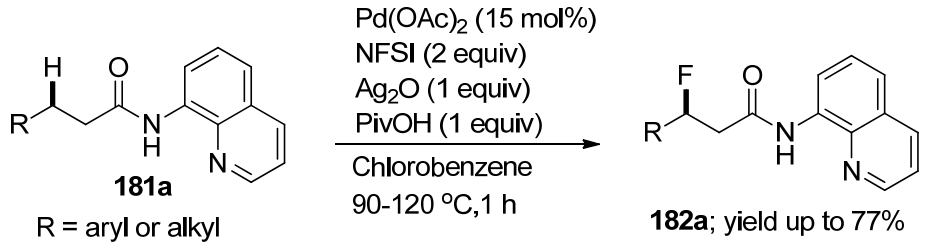
Sahoo [25a] reported methyl-2-pyridylsulfoximine **176** (MPyS) as the bidentate directing group for the bromination and chlorination of 1^o-β-C(sp^3)-H bond using *N*-Br/Cl-phthalimides in the presence of Pd(II)-catalyst to give the product **176a** (Scheme 66). Acid hydrolysis of **176a** produced the β-halo carboxylic acids **177a** and MPyS-DG **177b** was also recovered (Scheme 66).

Shi[25b] reported the Pd(II)-catalyzed fluorination of unactivated methylene C(sp^3)-H bonds of α-amino acid derivatives **178a** by using $Pd(OAc)_2$, selectflour in mixture of DCM and *i*-PrCN (v/v = 30:1), which afforded the *β*-fluorinated α-amino acid derivatives **179a** (Scheme 67). Recently, Ge and co-workers[25c] also reported the synthesis of *β*-fluorinated α-amino acid derivatives **180a** (Scheme 67).

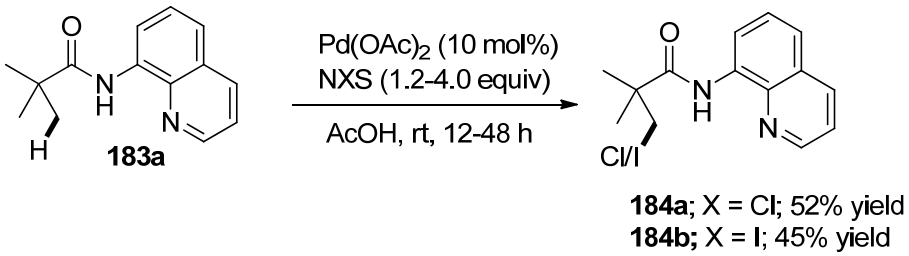


Scheme 67. Pd(II)-catalyzed fluorination of C(sp^3)-H bonds of **178a** and **178b**.

Xu group[25d] reported the 8-aminoquinoline-directed, Pd(II)-catalyzed C-H fluorination of β-position of carboxamides **181a**,which gave β-fluorinated carboxylic acid derivatives **182a** (Scheme 68). Rao group[25e] reported the Pd(II)-catalyzed C-H chlorination/iodination at the β-position of carboxamides **183a** under room temperature, which gave the corresponding chlorinated/iodinated carboxamides **184a** and **184b** (Scheme 69).

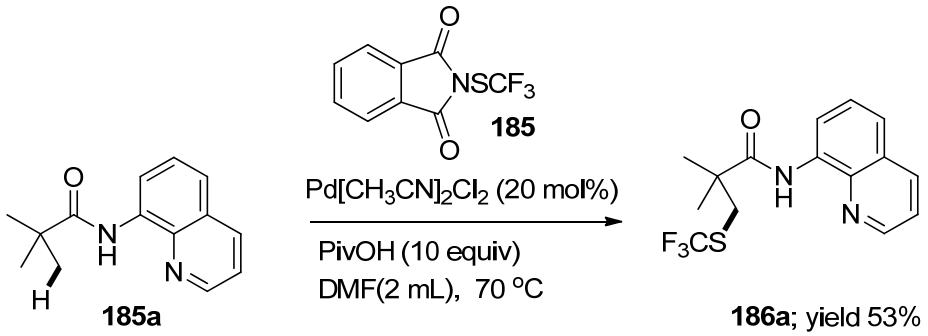


Scheme 68. AQ-assisted fluorination of aliphatic C(sp^3)-H bond of **181a**.

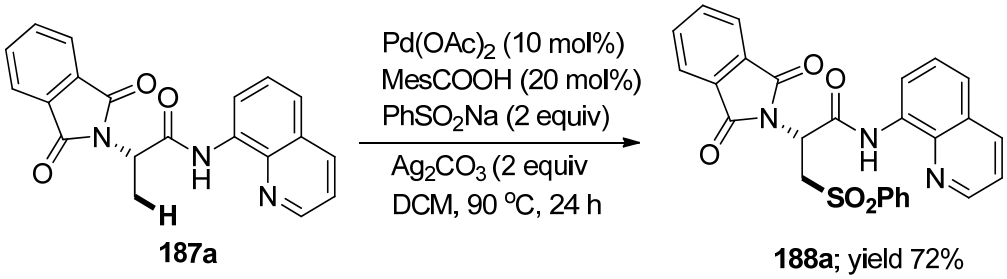


Scheme 69. Halogenation of unactivated C(sp^3)-H bonds at room temperature.

Besset group[26a] reported Pd(II)-catalyzed trifluoromethylthiolation of **185a** with the *N*-SCF_3-phthalimide **185** in the presence of $Pd(OAc)_2$ as a catalyst, in DMF, which afforded the product **186a** in moderate good yield (Scheme 70). Shi group[26b] reported example of Pd(II)-catalyzed sulfonylation of an unactivated C(sp^3)-H bond of **187a** with sodium sulfinates, which gave sulfonylated product **188a** in good yield and selectivity (Scheme 71).

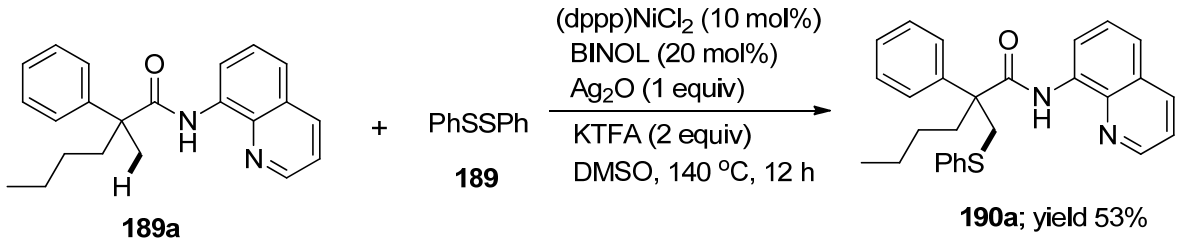


Scheme 70. Pd(II)-catalyzed trifluoromethylthiolation of C(sp^3)-H bonds **185a**.



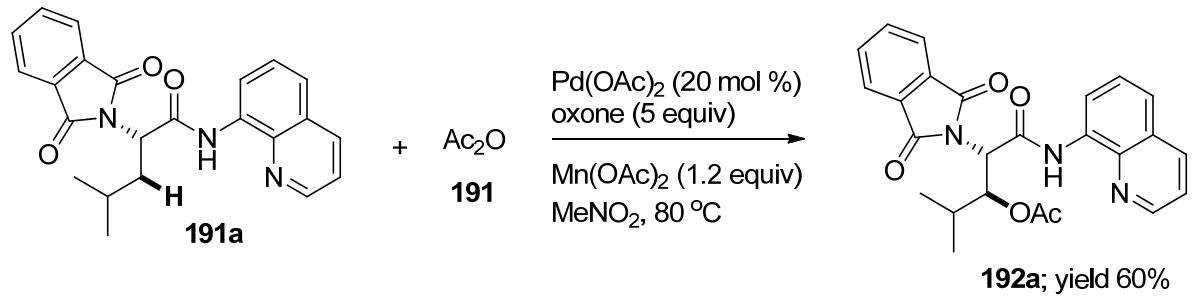
Scheme 71: Pd(II)-Catalyzed sulfonylation of C(sp^3)-H bonds of **187a**.

Shi group[26c] reported example of nickel-catalyzed thiolation of unactivated C(sp^3)-H bonds **189a** with disulfides **189**. This transformation was carried in the presence of $(dppp)NiCl_2$ as a catalyst and BINOL as a ligand to obtain the β-C-H thiolation product **190a**(scheme 72).



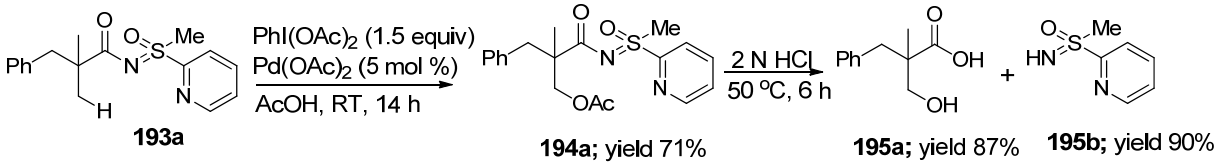
Scheme 72. Nickel-catalyzed direct thiolation of unactivated C(sp^3)-H bonds of **189a**.

Corey and co-workers[27a] reported the Pd(II)-catalyzed β-acetoxylation of unactivated C(sp^3)-H bond of *N*-phthaloyl-α-amino acid amides. The acetoxylation of amide **191a** with acetic anhydride **191** in the presence of $Pd(OAc)_2$ (20 mol%), oxone, manganese(II) acetate in nitromethane at 80 °C, which gave the β-C-H acetoxylated amino acid derivatives **192a** (Scheme 73).

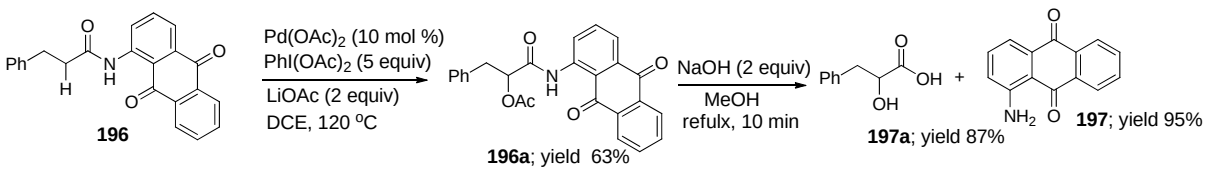


Scheme 73. β-C-H acetoxylation of C(sp^3)-H bond of the carboxamides **191a**.

Sahoo[27b] reported methyl-2-pyridylsulfoximine (MPyS) as the bidentate directing group for the C-H oxidation of aliphatic C-H bonds. Pd-catalyzed regioselective 1°-β-C(sp^3)-H acetoxylation of amide derivatives **193a** was achieved at room temperature (Scheme 74). acid hydrolysis of the product **194a** produced the β-hydroxycarboxylic acid **195a** with recovery of MPyS-DG **195b** (Scheme 74).



Scheme 74. MPyS-directed β-C-H acetoxylation of amide **193a**.

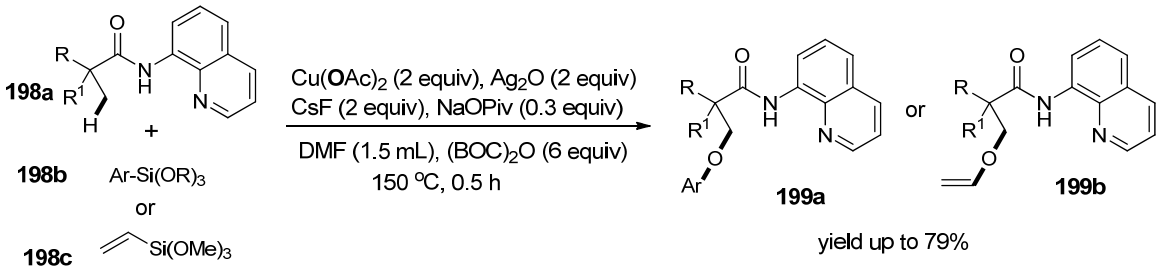


Scheme 75. AAQ directed acetoxylation of amide **196**.

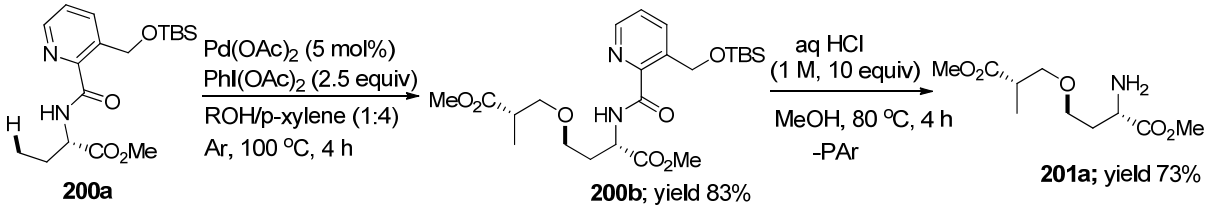
Recently, Zhang group[27c] accomplished α-selective methylene C(sp^3)-H acetoxylation of carboxamide **196** using 1-aminoanthraquinone (AAQ) directing group in the presence of Pd-

catalyst, which gave the product **196a** (Scheme 75). Amide hydrolysis of **196a** afforded the acid **197a** and directing group **197** in 95% yield.

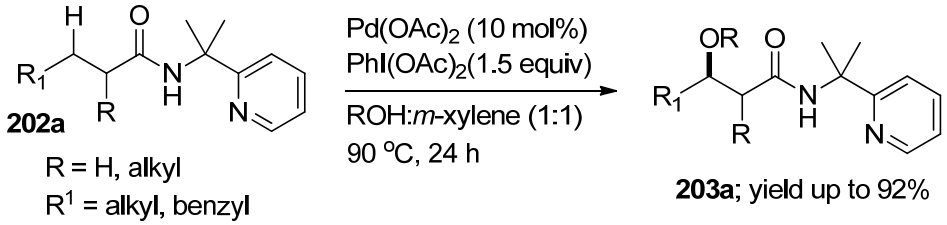
Zhang group[27d] reported copper-mediated aryloxylation and vinyloxylation of β-C(sp^3)-H bond of propionamides using organosilanes (Scheme 76). The reaction of amide **198a** with **198b** or **198c** in the presenc of $Cu(OAc)_2$ in DMF gave the corresponding products **199a** and **199b** in good yields (Scheme 76). Chen group[27e] demonstrated the Pd(II)-catalyzed alkoxylation of primary β-C(sp^3)-H bond of amide **200a**. Acid hydrolysis of product **200b**gave α-amino ester **201a** and (Scheme 77). Shi[27f] reported palladium-catalyzed alkoxylation of unactivated methylene C(sp^3)-H bonds of amide **202a** with ROH in the presence of $Pd(OAc)_2$/$PhI(OAc)_2$ to give mono-alkoxylated product **203a** (Scheme 78).



Scheme 76. Copper-mediated aryloxylation and vinyloxylation of aliphatic amides **198a**.

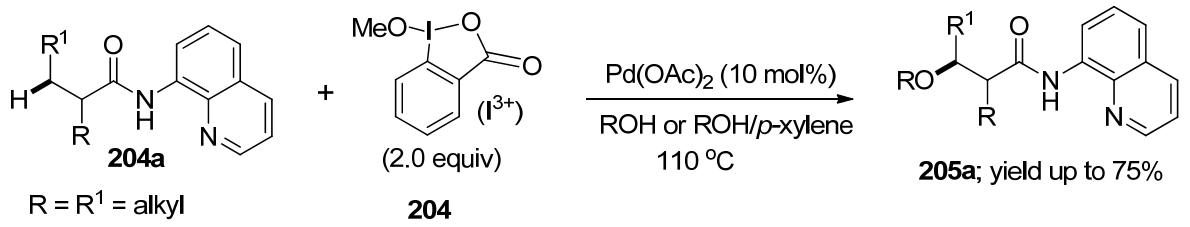


Scheme 77. β-Alkoxylation of amide with the aid of PAr directing group.

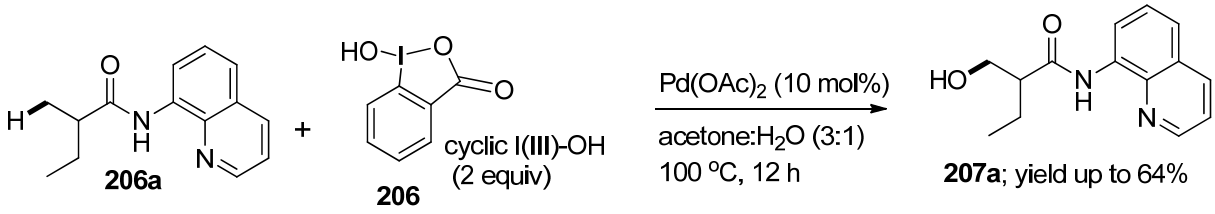


Scheme 78. Pd-catalyzed alkoxylation of C(sp^3)-H bonds of **202a**.

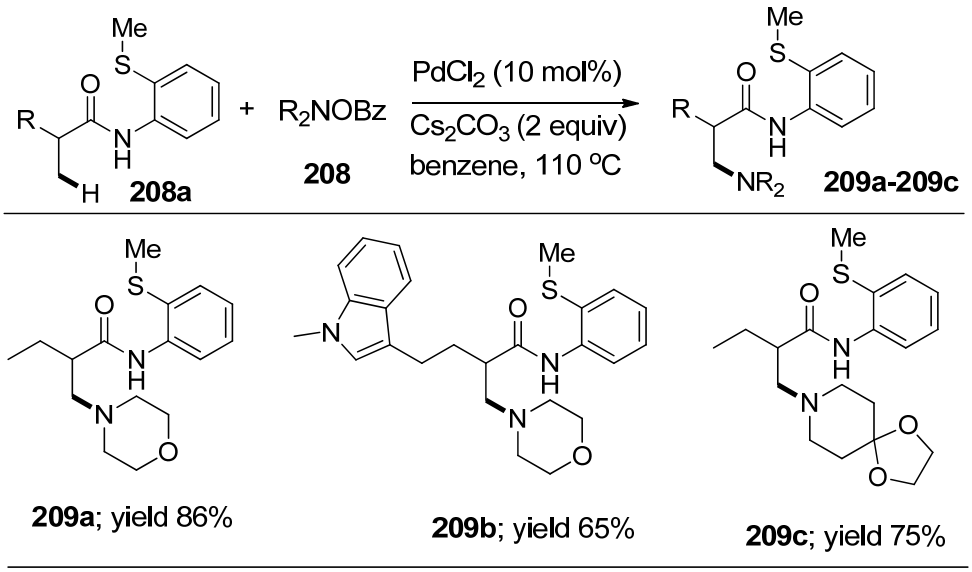
Rao et al.[27g] reported Pd-catalyzed alkoxylation of **204a** with hypervalent iodine oxidant **204** in the prescence of $Pd(OAc)_2$ in alcoholicsolvent to give the alkoxylated product **205a** (Scheme 79). Rao et al.[27h] alsoreported the Pd(II)-catalyzed hydroxylation of $C(sp^3)$-H bonds **206a** in water as the hydroxyl group source (Scheme 80).The reaction of AQ protected 2-methylbutyric acid **206a** with I^{3+} reagent **206** in water and acetone as co-solvent gave the C–H hydroxylated products **207a** (Scheme 80).



Scheme 79. $C(sp^3)$-H alkoxylation of **204a**with cyclic hypervalent Iodine (I^{3+}) oxidant.

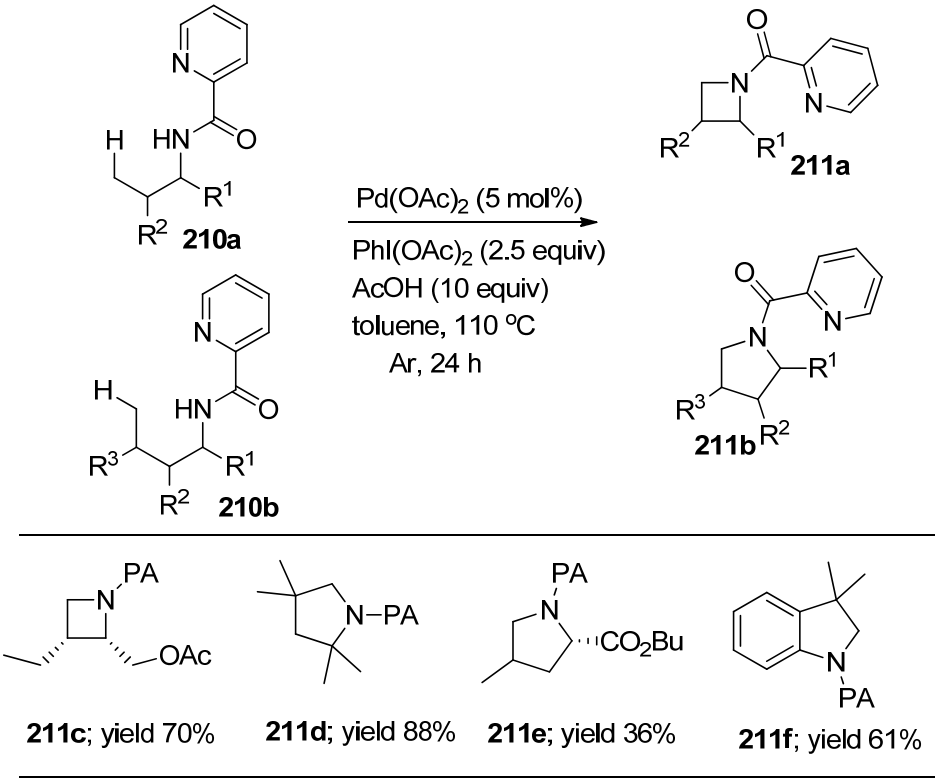


Scheme 80. Pd-catalyzed $C(sp^3)$-H hydroxylation using H_2O as the oxygen source.



Scheme 81. Intermolecular amination of unactivated $C(sp^3)$-H bonds of **208a**.

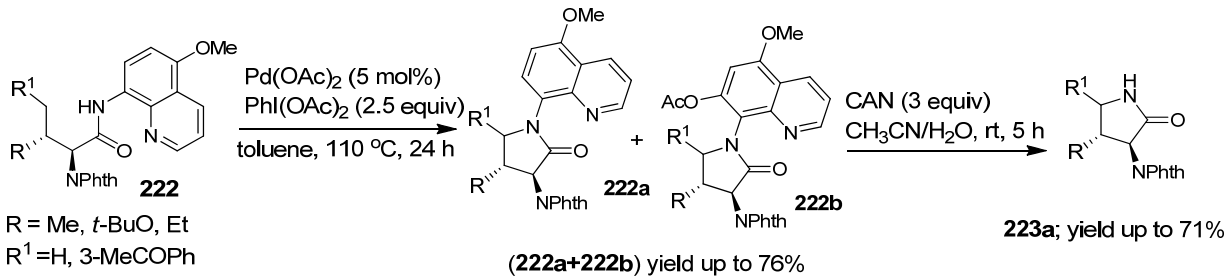
Qin[28a] reported the Pd(II)-catalyzed intermolecular amination of unactivated C(sp^3)-H bonds using bidentate directing group (Scheme 81). The reaction of **208a** with RNOBz **208** as aminating reagents gave the β-amino acid derivatives **209a-209c** (Scheme 81).



Scheme 82. Pd(II)-catalyzed intramolecular amination C(sp^3)-H bonds.

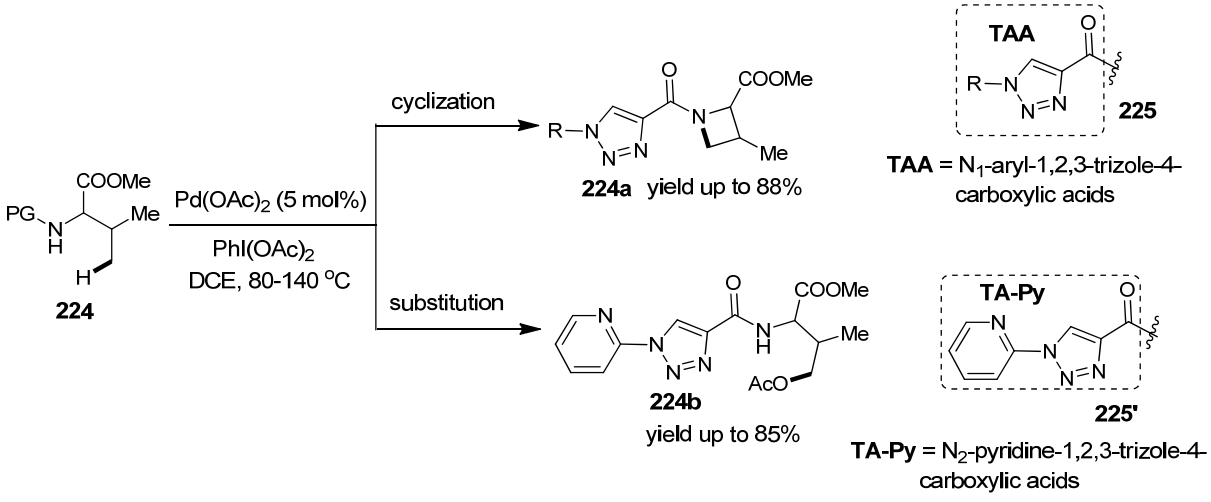
Chen group [28b] reported the Pd(II)-catalyzed picolinamide directed intramolecular C-N bond formation reaction (Scheme 82). In this reaction, γ- and δ-C(sp^3)-H bonds of **210a** and **210b** of was activated followed by the formation of C-N bond afforded the corresponding four- and five-membered heterocycles **211a-f**. Concurrently, the Daugulis group[28c] also reported Pd(II)-catalyzed intermolecular C-N bond formation (Scheme 82).

Chen and co-workers[28d] reported the synthesis pyrrolidones *via* the palladium-catalyzed intramolecular amination of unactivated γ-C(sp^3)-H bonds (Scheme 83) The reaction of amide **222** with $PhI(OAc)_2$ in toluene at 110 ^oC afforded the mixture of products **222a**/**222b**, which on further reaction with CAN in CH_3CN/H_2O afforded the pyrrolidones **223a** (Scheme 83).

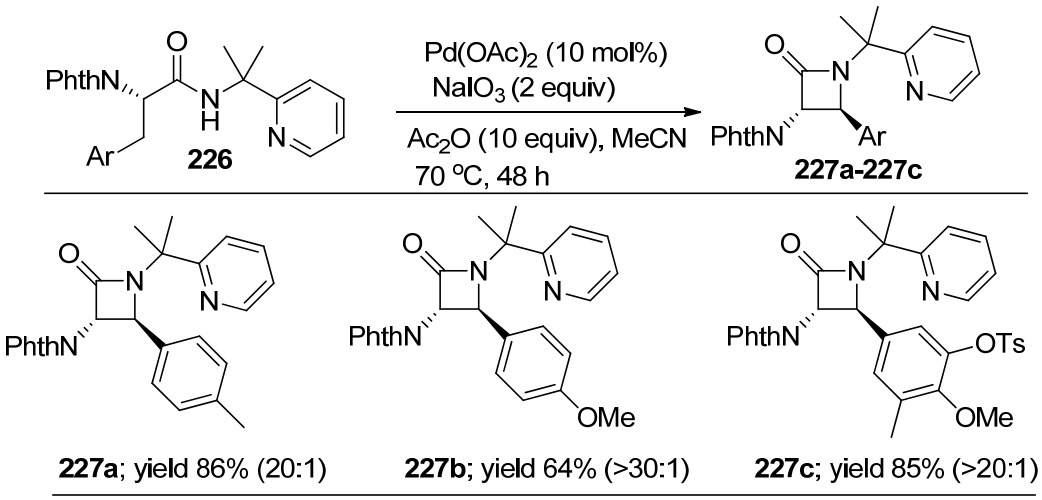


Scheme 83 AQ- directed intramolecular amination of γ-C(sp^3)-H bonds **222.**

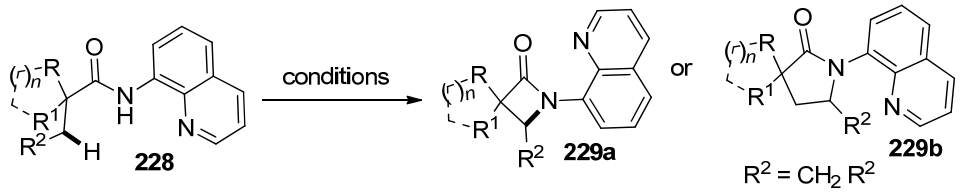
Shi [28e] reported 1,2,3-triazoles as versatile directing group for the selective cyclization *vs* substitution. The Pd-catalyzed sp^2 and sp^3 C–H activation of **224**enabled by TAA directing group in the presence of $PhI(OAc)_2$ in DCE at 80-120 °C afforded the cyclised product **224a** (Scheme 84). On the other hand, the Pd-catalyzed reaction **224** enabled by TA-Py directing group with $PhI(OAc)_2$ and AgOAc in DCE at 140 °C afforded the mono-acetoxylation product **224b** in good yields (Scheme 84). Shi and co-workers[28f] reported the stereoselective synthesis of α-amino-β-lactam **226** through PIP-directed cyclization (Scheme 85). The intramolecular amidation of **226** in the presence of $Pd(OAc)_2$ (10 mol%), $NaIO_3$ (2 equiv), Ac_2O (10 equiv) in MeCN gave the β-lactams **227a-c** (Scheme 85). Direct intramolecular C–H/N–H coupling of amide **228** was reported by Kuninobu.[28g] Ge, [28h-j] Yang and You [28k] also reported the synthesis of *N*-heterocycles **229a** and **229b** (Scheme 86).



Scheme 84: Triazole directed selective cyclization *vs* substitution of **224**.



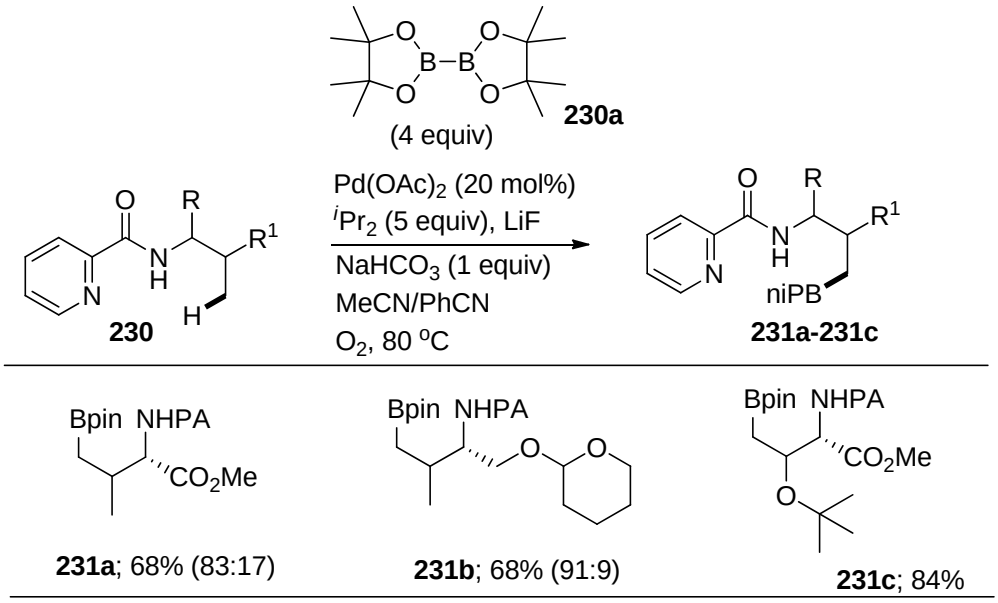
Scheme 85. Synthesis β-lactams through PIP directed C(sp^3)-H functionalization **226**.



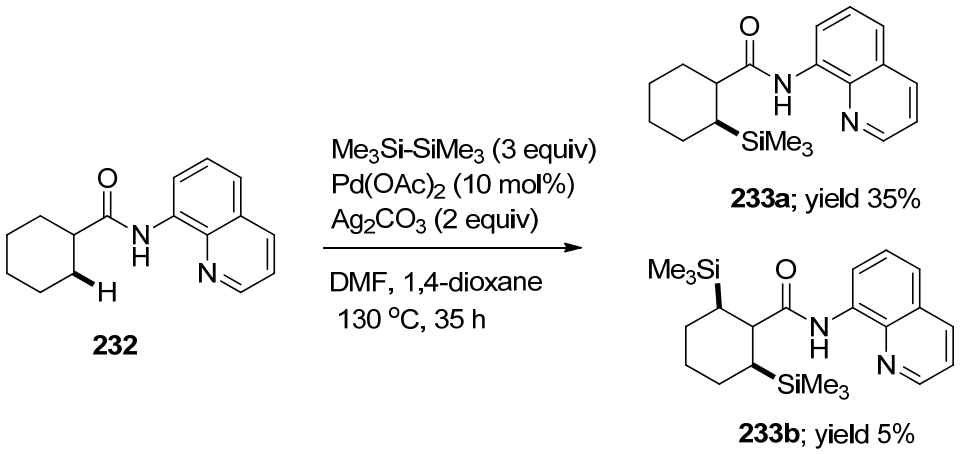
Ref. 28g. **Kanai et al**: $Cu(OAc)_2$ (20 mol%), Ag_2CO_3 (3 equiv), DCE, 140 °C,
Ref. 28h. **Ge et al**: CuCl (20 mol%), duroquinine (1.2 equiv), $PhCO_2Na$ (1.5 equiv), *o*-xylene, 160 °C, air
Ref. 28i. **Ge et al**: $Ni(DME)_2I_2$ (10 mol%), TEMPO (3 equiv), K_2HPO_4 (2 equiv), TBAI (0.1 equiv), *n*PrCN/PhCN, 150 °C
Ref. 28j. **Ge et al**: $Co(OAc)_2$ (10 mol%), Ag_2CO_3 (2.5 equiv), $PhCO_2Na$ (0.5 equiv), PhCl, 150 °C
Ref. 28k. **Yang and You et al**: CuI (20 mol%), O_2 (1 atm), Na_2CO_3 (2 equiv), PhCN/*o*-xylene, 140 °C

Scheme 86: Lactam synthesis *via* direct intramolecular C-H amination using.

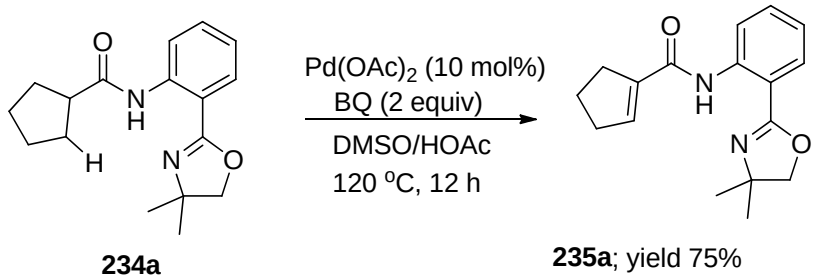
Shi and co-workers [29a] reported the borylation of C(sp^3)-H bonds of amine **230**with B_2pin_2 **230a** in the prescence of *i*Pr_2, $NaHCO_3$ in MeCN/PhCN at 80 °C to give γ-C-H borylated derivatives **231a-231c**(Scheme 87). The palladium-catalyzed 8-aminoquinoline directed C(sp^3)-H bond silylation was reported by the Kanai group[29b] (Scheme 88).The silylation of aliphatic C(sp^3)-H bonds **232** with hexamethyldisilane gave the mono **233a** and bis **233b** silylated carboxamide (Scheme 88). Yu and co-workers[29c] reported the palladium-catalyzed dehydrogenation of cyclopentylcarboxamides **234a** containing an oxazoline moiety in the presence of $Pd(OAc)_2$ (10 mol%), BQ (2 equiv) in DMSO/HOAc at 120 °C, for 12 h, which gave the dehydrogenated product **235a** (Scheme 89).



Scheme 87. Pd(II)-catalyzed C(sp^3)-H bond borylation of amine derivatives **230**.



Scheme 88. Pd-catalyzed 8-aminoquinoline directed C(sp^3)-H bond silylation **232**.



Scheme 89. Dehydrogenation of an unactivated C(sp^3)-H bond of **234a**.

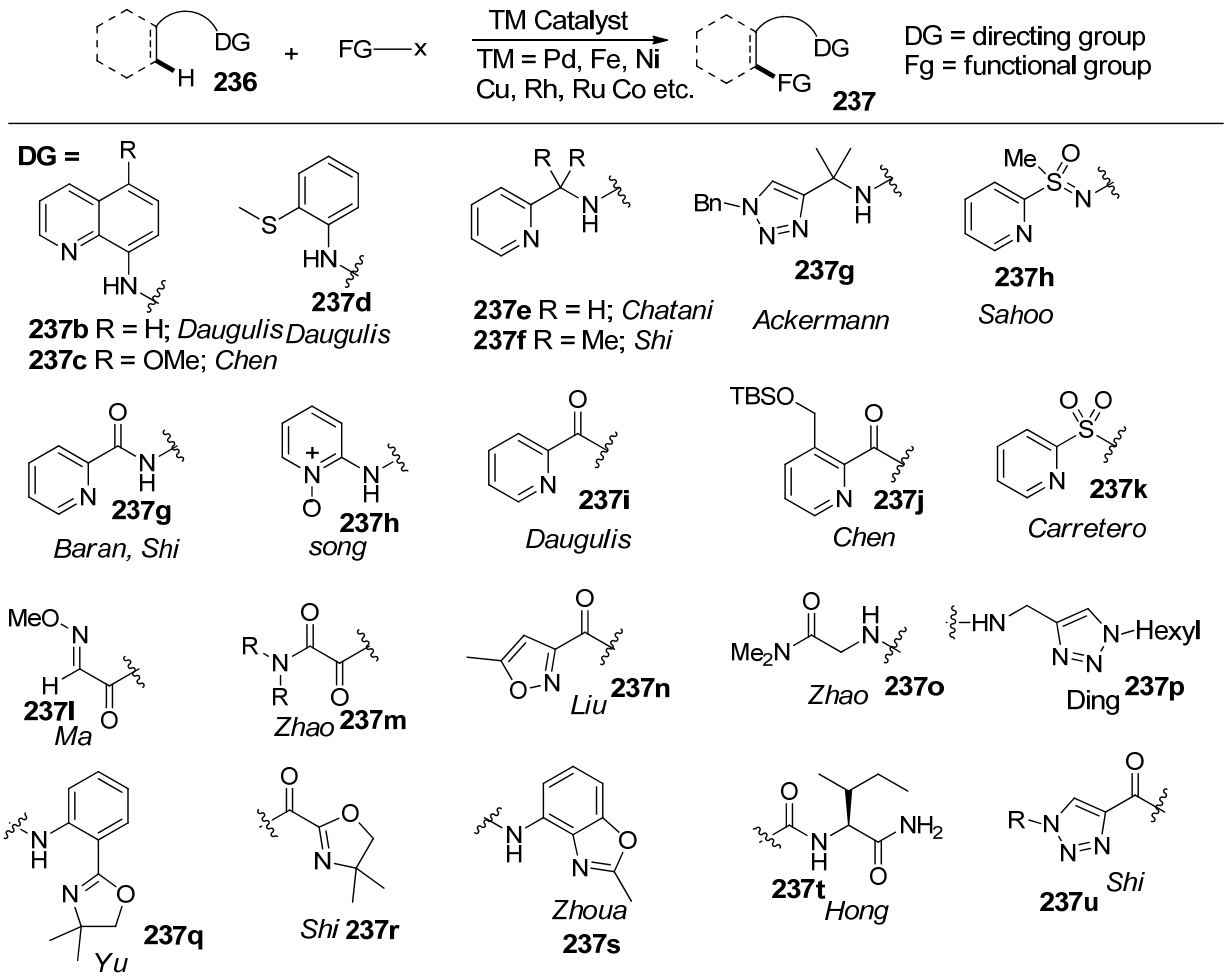


Figure 1. Bidentate ligand systems **237b-237u** reported for the sp^3 C–H activation.

Some of the notable reactions pertaining to the sp^3 C–H activation enabled by various bidentate directing groups have been presented in the above discussion. It is worth mentioning that a literature survey revealed that after the discovery of 8-aminoquinoline and 2-picolinic acid as the bidentate directing groups for the sp^3 C–H activation/functionalization, various other bidentate directing groups have also been identified for performing the sp^3 C–H activation/functionalization of different carboxamide substrates with proficiency. The list of bidentate auxiliaries used in the literature for the sp^3 C–H activation/functionalization of different carboxamide substrates are (Figure 1); 8-aminoquinoline **237bc**,[15a, 28d] 2-methylthioaniline **237d**,[15b] pyridine methyl amines (**237ef**)[30a, 16d] triazole- methyl amine **237g**,[19a]2-pyridyl-sulfoximine **237h**, [25a] picolinamide **237g**,[30b, 9c] 2-aminopyridine-1-oxide **237h**,[19d] picolinicacid **237ij**,[15a, 18b]*N*-(2-pyridyl)sulfonamide **237k**,[17c] 2-methoxyiminoacetyl **237l**,[17d] oxalylamide **237m**,[19f] 5-methylisoxazole **237n**,[20a] glycine dimethylamide**237o**,[30c]

triazole- methyl amine **237p**,[19e] oxazoline amide **237q**,[29c] oxazoline-carboxylate **237r**,[19g]7-aminobenzoxazole **237s**,[20c] isoleucine-NH_2**237t**,[21d] and triazole-acid **237u** (Figure 1).[28e]

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Chapter 2. **Regio- and stereoselective construction of functionalizedcyclopropanes/cyclobutanes/norbornanes and saturated heterocycles *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation.**

A survey of the literature revealed that the transition metal-catalyzed C–H activation/functionalization strategy was well exploited for the functionalization of sp^2 C–H bonds of arenes, heteroarenes and olefins etc. On the other hand, until the report by the Daugulisgroup in 2005, the transition metal-catalyzed sp^3 C–H activation/functionalization of alkyl chains was relatively less studied. After the report by Daugulis, various research groups have revealed that the sp^3 C–H activation/functionalization is an attainable task with the help of directing groups. Accordingly, the Chapter 1 revealed some outstanding papers dealing with the directing group-based activation/functionalizationsp^3 C–H bonds that are relevant to this thesis work. Concurrent to the literature works, a part of this thesis (**Chapter 2)** envisages to investigate the Pd(II)-catalyzeddirecting group-aideddiastereoselectiveC-H functionalization/arylation of cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems to obtain C-H arylated/functionalized cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems.

Functionalized cyclopropanes

Cyclopropane is one of the privileged, smallest carbocyclic motifs present as a core unit in various natural products, biologically active and drug molecules. Cyclopropane derivatives also served as valuable synthetic intermediates in organic synthesis.[1-2] Incorporation of cyclopropanes in the molecular frameworks is an important molecular tool to constrain the conformation.[3] Various arylated cyclopropane carboxylic acid derivatives found to exhibit potential biological activities.[3] Carbene or carbenoid intermediates-based synthetic methods were used for the production of substituted cyclopropanes (Figure 1).

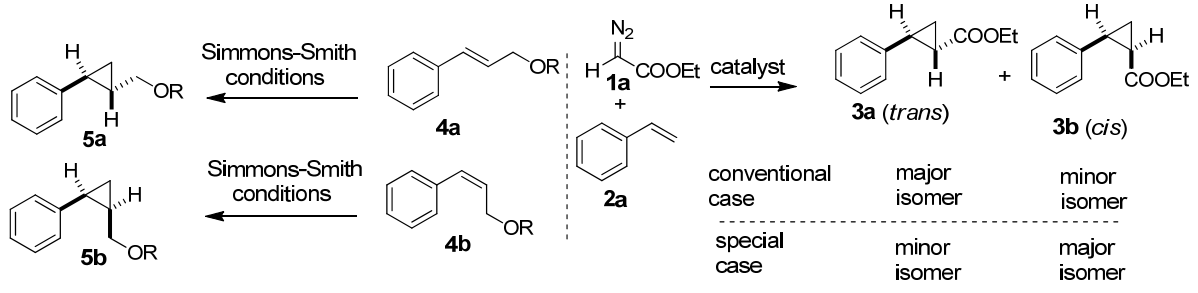


Figure 1. Popular ways of assembling substituted cyclopropanes.

For example, the metal-catalyzed reaction of a diazo compound **1a**with styrene **2a** results in the cyclopropane **3a** with *trans* stereochemistry as the major isomer (Figure 1).[1b,c] The *cis*/*trans* substituted cyclopropanes **5a**/**5b** can also be obtained under the Simmons-Smith reaction conditions.[5a-c] Representative important biological active molecules[4](**6a-6c)** possessing aryl cyclopropane ring are shown in Figure 2. A simple and an alternative route for the production of the *cis* substituted cyclopropanes would be the direct metal-catalyzed functionalization of the C(sp^3)-H bond of cyclopropanes.[1,2]

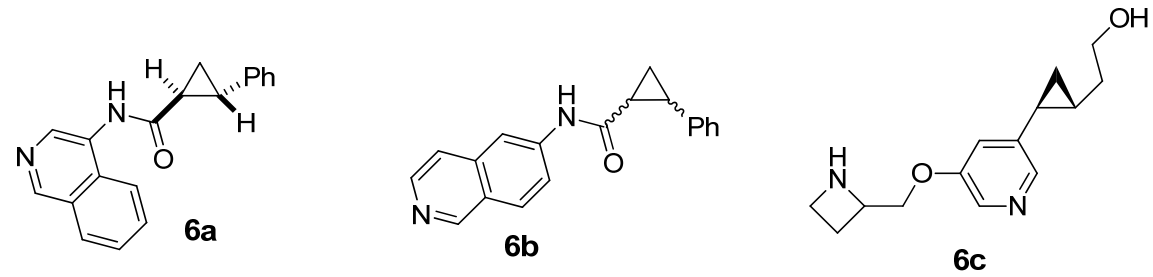


Figure 2. Biologically active molecules containing aryl cyclopropane ring (**6a-6c**).

Functionalized cyclobutanes

Cyclobutane is the second smallest, strained four-membered carbocyclic ring and present as a core unit of various natural products, bioactive- and synthetic compounds (Figure 3).[7-9] Various cyclobutane natural products, especially, mono arylated and bis arylated cyclobutanecarboxamides found to exhibit biologically activities and medicinal properties.[7-9, 27c,d] For example, incarvillateine has been traditionally used in treating rheumatism and relieving pain.[10] Biyouyanagin[11] found exhibiting activity against HIV and inhibiting cytokine production. Littoralisone[12] is an active agent for increased NGF-induced neurite outgrowth in PC12D cells. Cyclobutanes isolated from *Piper nigram and Piper chaba* exhibit broad pharmacological activities.[13,14] Given the importance of cyclobutane systems, the total synthesis of various cyclobutane-based natural products were reported.[27c,d]stereoisomers.[17]

Accordingly, a probable route for the construction of stereodefined, arylated cyclobutanecarboxamides would be the direct metal-catalyzed C-H arylation of the C(sp^3)-H bond of cyclobutanes.

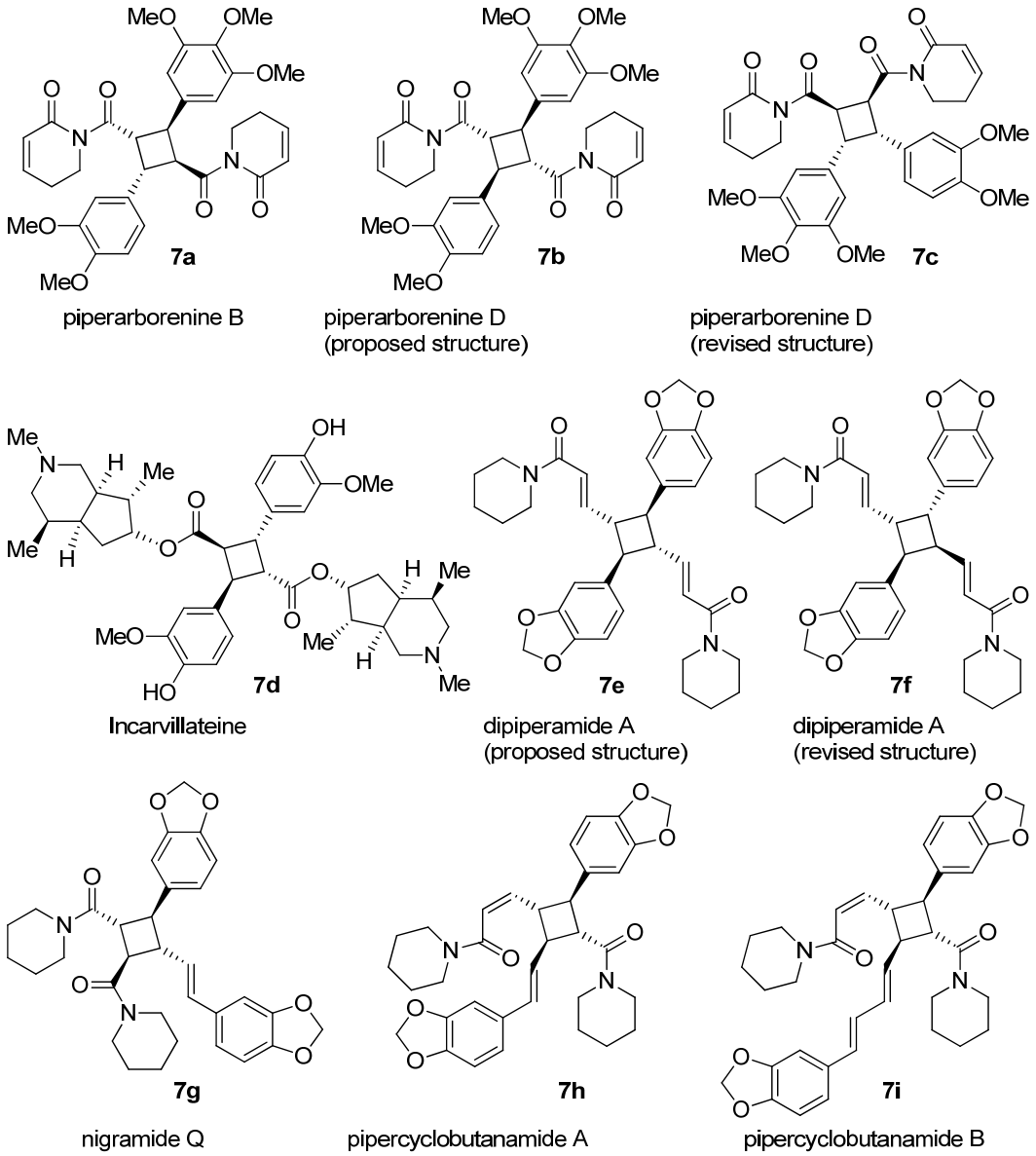


Figure 3. Representative cyclobutane natural products.

Cyclobutane natural products are constructed *via* the direct coupling of the parent monomeric olefins with high degree of stereo- and regiocontrol. The [2+2] photocycloaddition involving two similar olefins or heterodimerizations of two different olefins have been the desirable routes for assembling cyclobutane compounds (Figure 4).[15,16] It is worth to note that the synthetic method has limitations, e.g., head-to-head or head-to tail type cycloadditions, homodimerization and *E/Z* isomerization of olefins under the experimental conditions, there by affording uncontrolled production of a complex mixture of products.

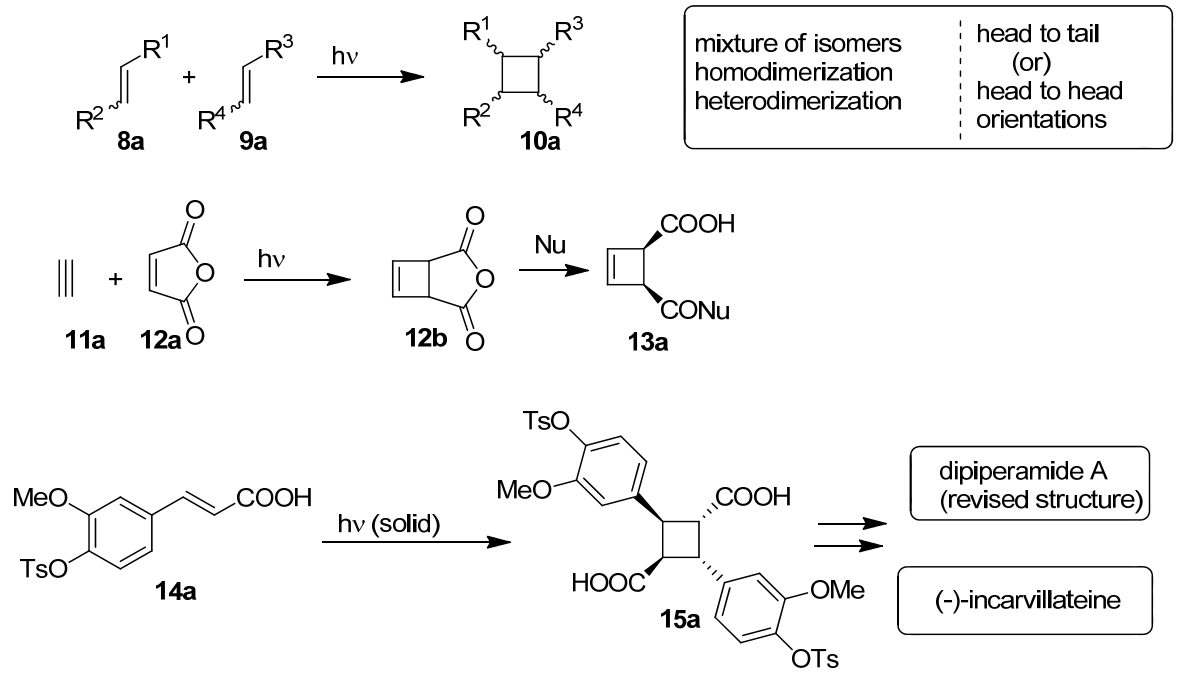


Figure 4. Methods for assembling substituted cyclobutane derivatives.

Functionalized norbornanes

The chemistry of bridgehead-substituted bicyclic frameworks, e.g. norbornanes is an interesting topic in the history of organic synthesis.[18,19] Especially, functional group transformation at a bridged center of a bicyclic framework such as norbornane system and the generation of an quaternary bridgehead carbon-based bridged bicyclic compounds is one of the interesting topic of research.

Apart from the celebrated substitution reactions at the bridgehead carbon of bicyclic compounds, there exist versatile routes,[18,19] e.g., enolate chemistry[18i,j] and Diels–Alder reaction[18a–h] that can be used to assemble bridgehead carbon-substituted bicyclic frameworks. While the type 1 reaction involving diene and dienophile can be used to generate functionalized fused bicyclic ring system **18a** and the type 2 reaction involving diene and dienophile can be used to generate functionalized bicyclic ring system **20a** (type 2, Figure 6). It would be interesting to investigate the production of functionalized norbornane frameworks via the C-H activation route.

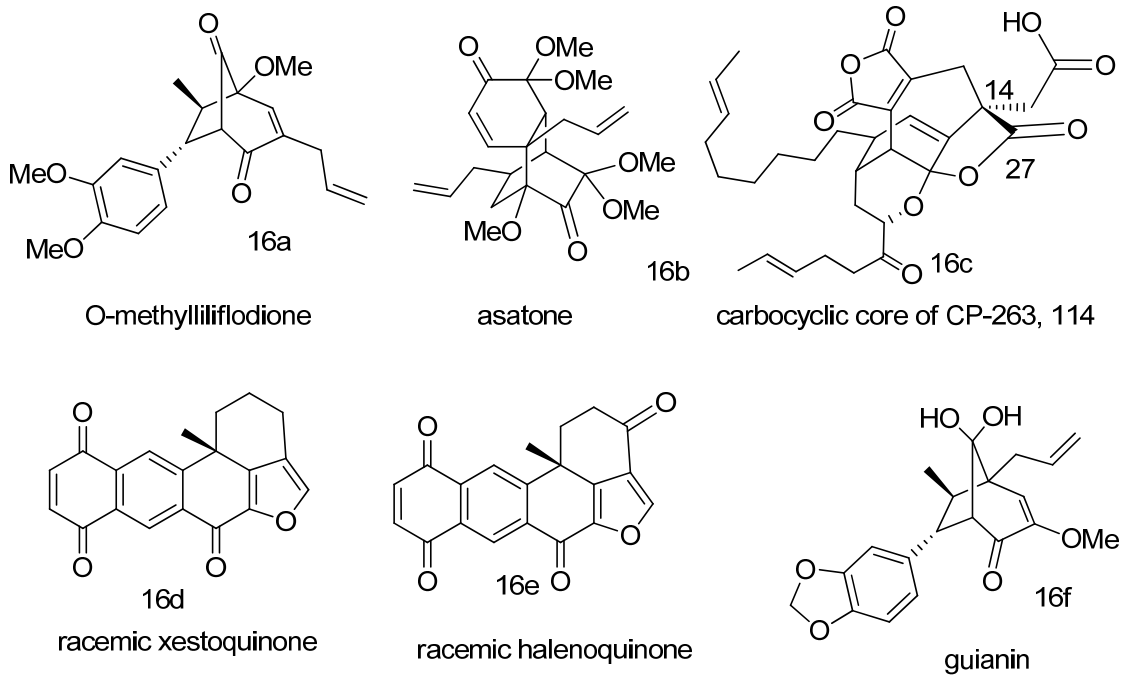


Figure 5. Representative examples of bridge-head substituted bicyclic systems.[20]

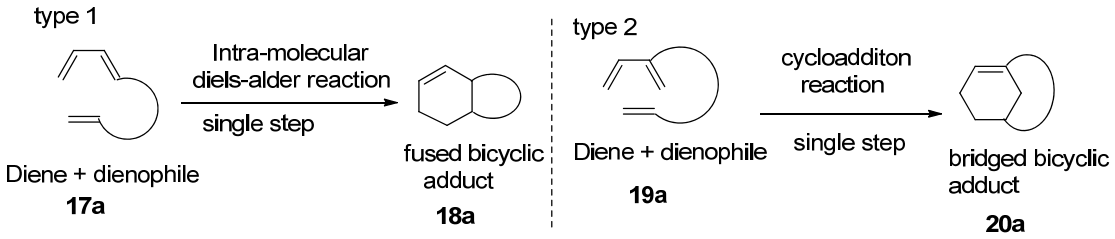


Figure 6. General methods for the construction bicyclic systems.

Functionalized tetrahydrofuran and 1,4-benzodioxane systems

Saturated oxygen heterocycles, such as tetrahydrofuran (THF) and benzodioxane based motifs are recurrently encountered in natural products (e.g., lignans, annonaceous acetogenins, polyether ionophores/antibiotics, macrodiolides) and bioactive- and synthetic compounds.[21,22] Substituted THF and benzodioxane-based synthetic molecules and various lignan-, neolignan- and norlignan natural products were found to exhibit various biological activities, e.g., anticancer, antioxidant, antimicrobial, anti-inflammatory and immunosuppressive activities.[21-24]

Especially, THF-norlignan and benzodioxane-neolignan motifs possessing an aryl group at the C3-position were found to exhibit various biological activities (Figure 7).[21,22] Recently, a

family of THF-norlignan systems, such as metasequirins A, B, E, F, G and H were identified[22a-c] and metasequirins E and F were evaluated for their cytotoxicity.[22a]Benzodioxane-neolignan systems, such as isoamericanol A, americanol A, isoamericanin A and americanin A were found to exhibit neurotropic and acetylcholine enhancing activities.[22d,e]

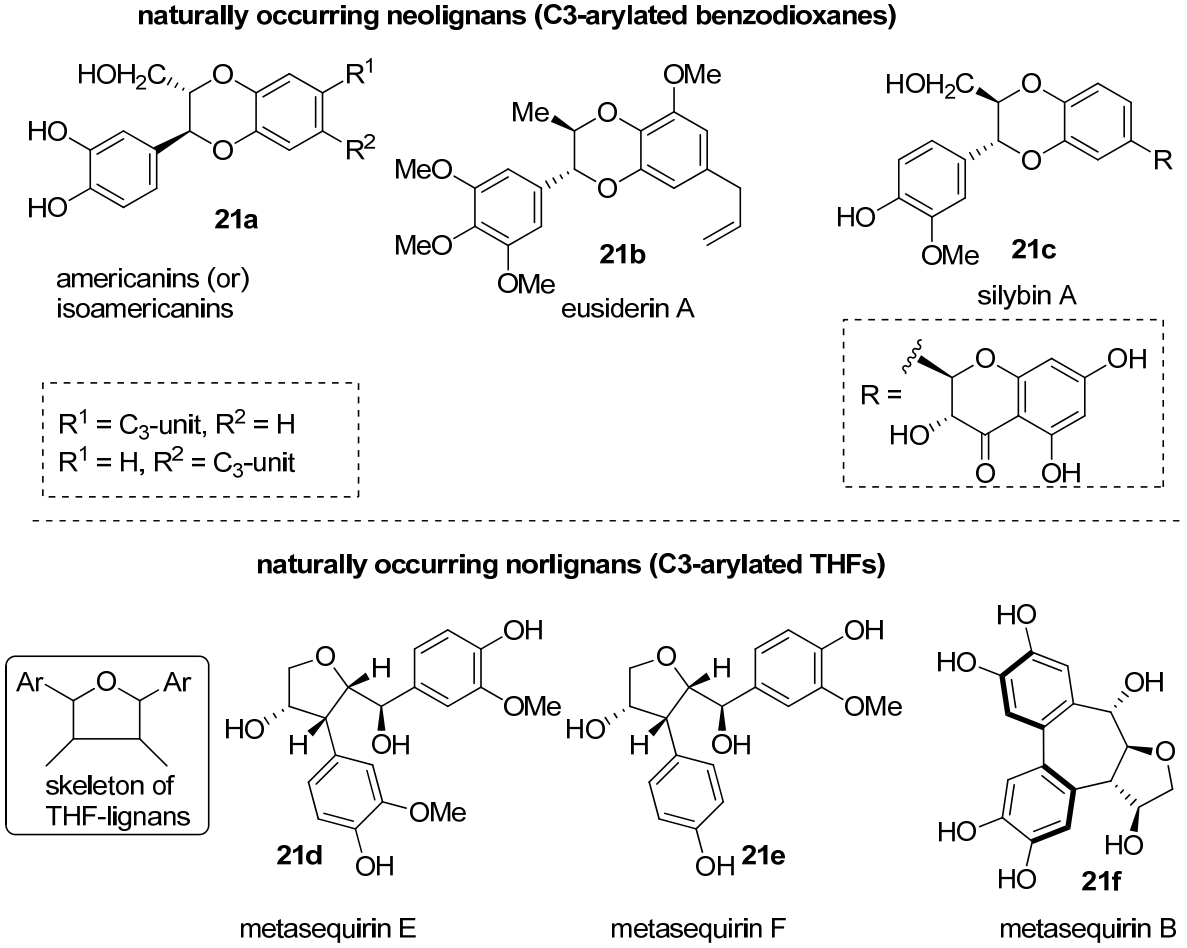


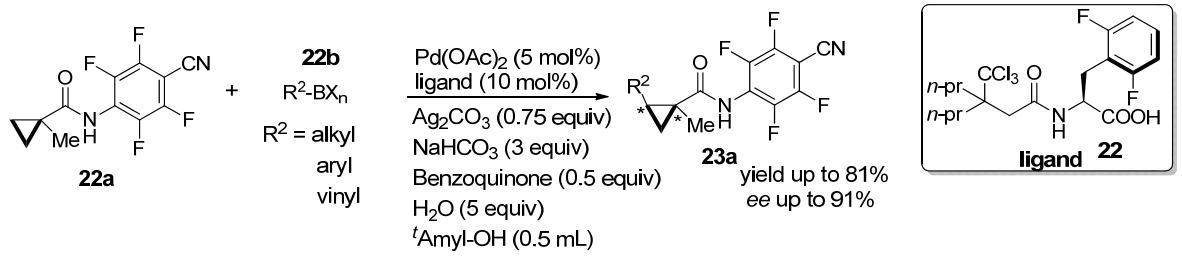
Figure 7. Representative examples of lignan natural products.

Given their important biological activities and ability as building blocks, numerous stereoselective synthetic methods[21-24]including the α-C-H functionalization methods[25] have been reported for synthesizing functionalized tetrahydrofuran and benzodioxane derivatives. It would be useful to broaden the C-H activation route for the production of functionalized tetrahydrofuran and benzodioxane derivatives.

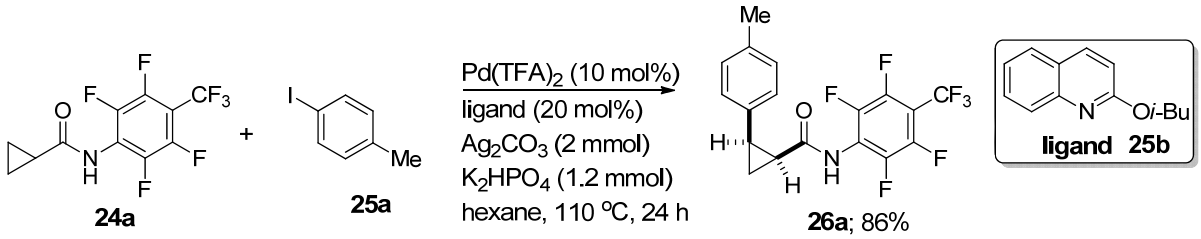
In line with the objective of this thesis, in the following sections some of the available reports or the developments during this thesis work with regard to the stereoselective C-H arylation

of alicyclic (cyclopropanes, cyclobutanes) and heterocyclic systems (tetrahydrofuran (THF) and benzodioxane) affording alicyclic and heterocyclic functionalized compounds are described.

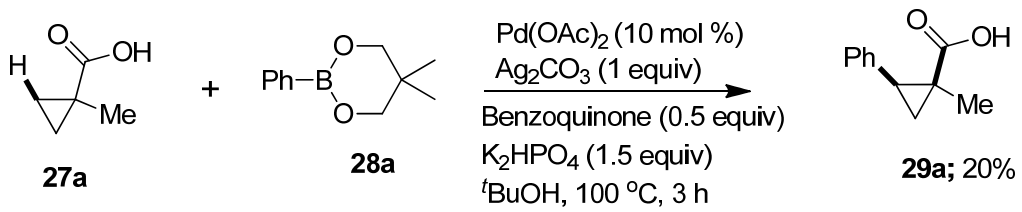
Representative reports dealing on the C-H functionalization reactions of cyclopropanes. Yu and co-workers[26a] reported the Pd(II)-Catalyzed enantioselective C-H activation of cyclopropanes **22a** using phenylboronic acid pinacol ester and alkyl trifluoroborate salts (R2-BXn) **22b** and mono *N*-protected amino acid ligand **22**, to construct enantioenriched *cis*-substituted cyclopropanecarboxylic acids **23a** (Scheme 1). Yu [26b] reported the ligand-enabled methylene C(sp^3)-H bond activation of cyclopropane **24a** with 4-iodotoluene **25a** using the electron rich quinoline ligand **25b**, which afforded the monoarylated cyclopropane derivative **26a** (Scheme 2). Yu[26c] reported the Pd-catalyzed arylation of 1-methyl cyclopropanecarboxylic acid **27a** using an arylboronic acid **28a** as the coupling partner, which afforded the arylated product **29a** in 20% yield (Scheme 3).



Scheme 1. Enantioselective C-H arylation of cyclopropanes **22a**.

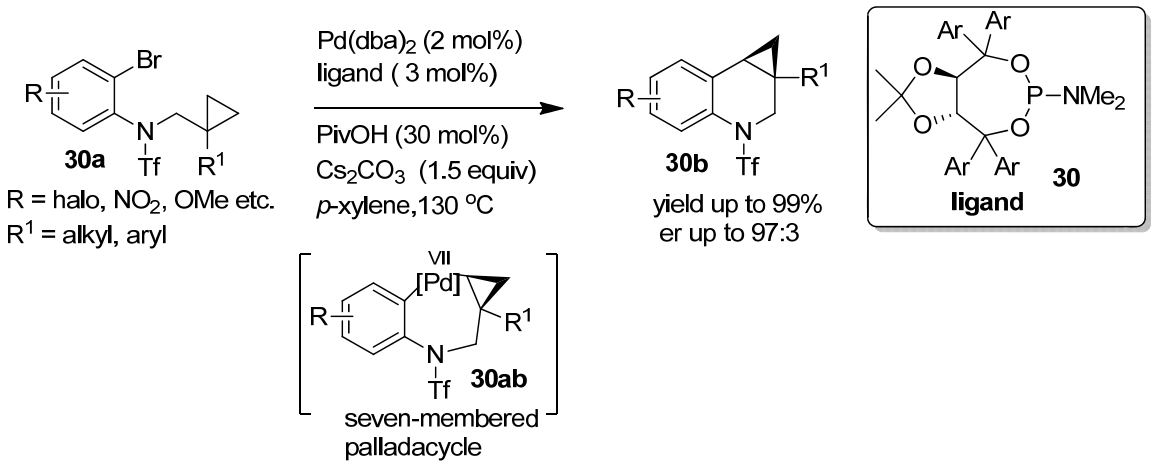


Scheme 2. Arylation of cyclopropane methylene C(sp^3)-H bonds of **24a**.

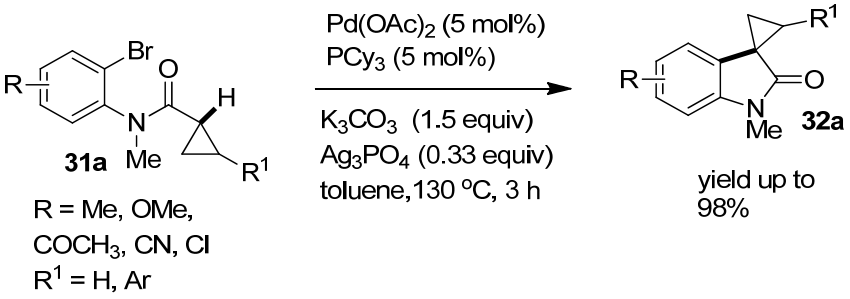


Scheme 3. β-Arylation of 1-methyl cyclopropanecarboxylic acid with Ph-B(OR)$_2$.

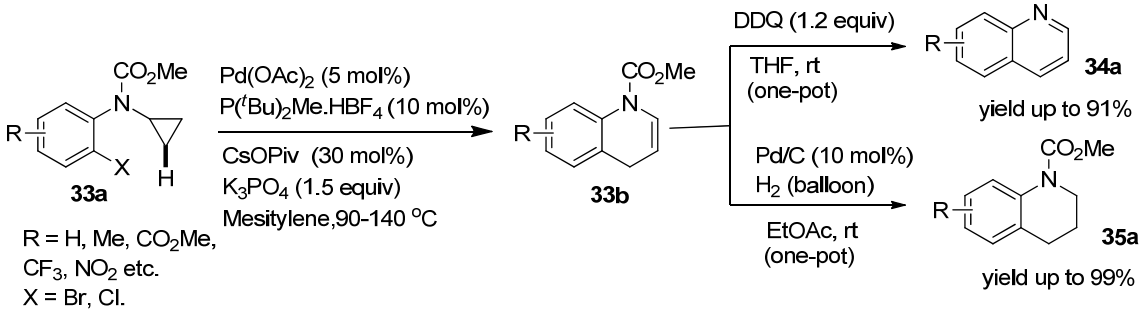
Cramer and co-workers[26d] reported the palladium(0)-catalyzed enantioselective direct C-H arylation of cyclopropanes **30a** in the presence Pd(dba)$_2$ and ligand **30**, which afforded access tetrahydroquinoline scaffold **30b**. The enantioselective concerted metalation–deprotonation (CMD) mechanism step occurs *via* a rare seven-membered palladacycle **30ab** (Scheme 4). Charette and co-workers[26e] reported the silver-promoted, palladium-catalyzed direct arylation of cyclopropanes **31a**, which afforded spiro 3,3'-cyclopropyl oxindoles **32a**in excellent yields (Scheme 5). Rousseaux and co-workers[26f] reported the palladium(0)-catalyzed cyclopropane C–H bond functionalization of **33a**, which directly gave the quinoline **34a** and tetrahydroquinoline derivatives **35a** (Scheme 6).



Scheme 4. Enantioselective synthesis of tetrahydroquinolines from **30a**.

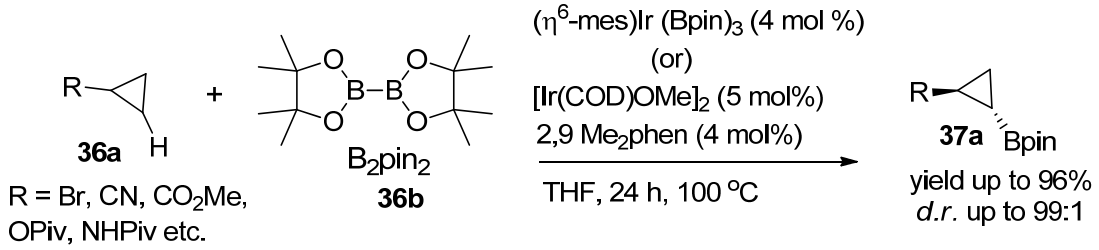


Scheme 5. Synthesis of cyclopropyl oxindoles *via* intramolecular arylation.

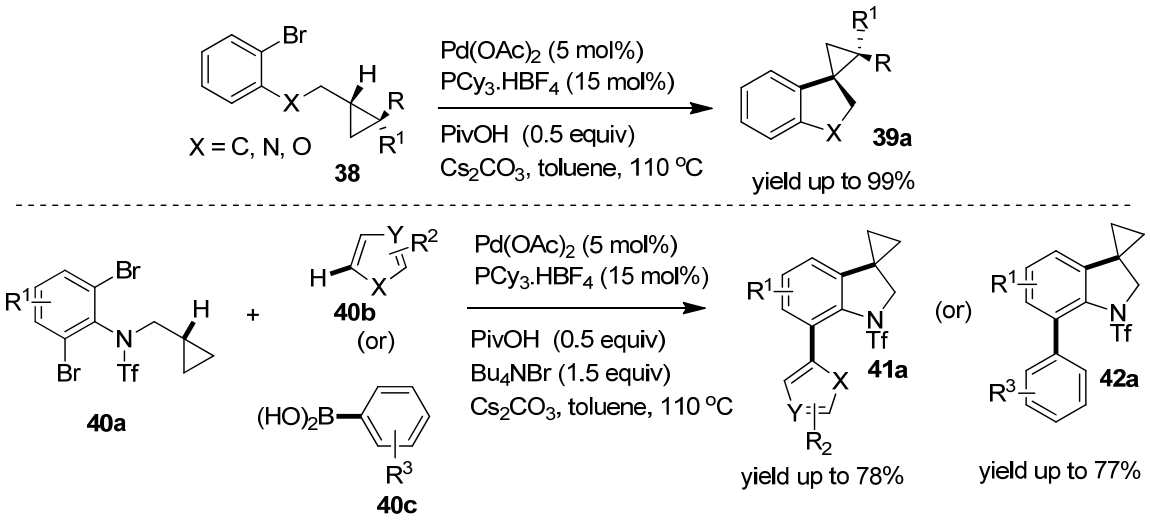


Scheme 6. Synthesis of quinolines and tetrahydroquinolines *via* the sp^3 C–H bond activation.

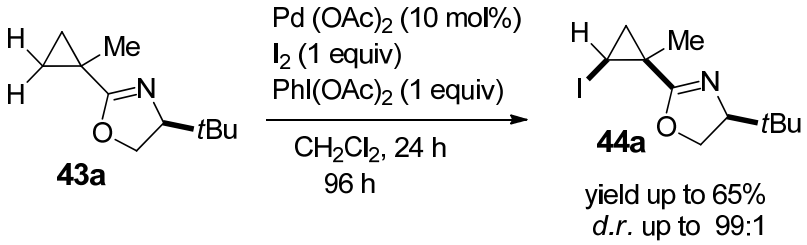
Hartwig and co-workers[26g] reported the iridium-catalyzed C−H borylation of cyclopropanes **36a** with **36b** in the presence of (η^6-mes)IrBpin$_3$ or [Ir(COD)-OMe]$_2$ and a phenanthroline ligand. These reactions occur in good yields with good diastereoselectivity affording the *trans* isomer **37a** as the major compound (Scheme 7).



Scheme 7. C-H Borylation of cyclopropanes **36a**.



Scheme 8. C-H arylation of **38**and **40a**.



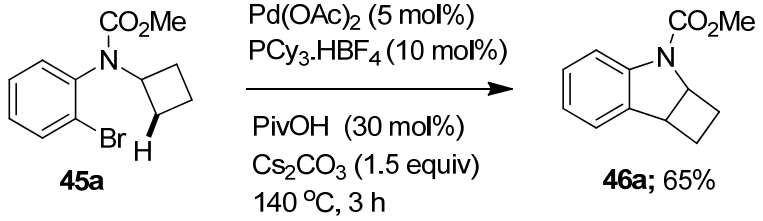
Scheme 9. $Pd(OAc)_2$ catalyzed monoiodination of **43a**.

Cramer and co-workers[26h] reported the intramolecular palladium(0)-catalyzed C-H functionalization of cyclopropane **38** which afforded functionalized cyclopropyl

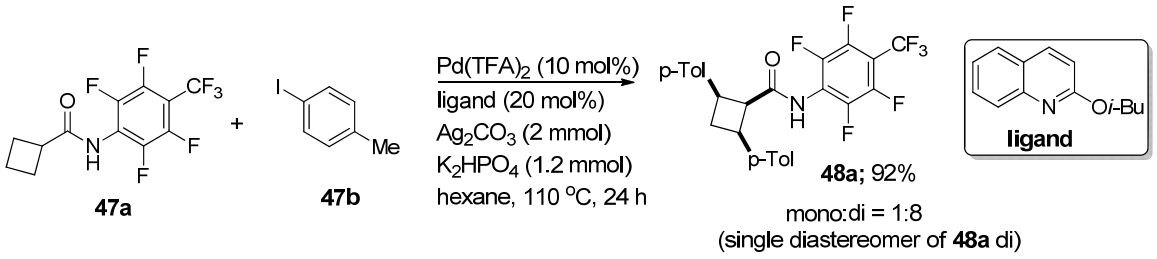
spiroindolines **39a**.The reaction conditions were well suited for consecutive Suzuki coupling and intermolecular C-H arylations for obtaining functionalized indoline scaffolds **41a**and**42a**(Scheme 8). Yu[26i] reported monoiodination of cyclopropane substrate **43a** as shown in Scheme 9. The reaction of **43a** with $Pd(OAc)_2$, $PhI(OAc)_2$ and I_2 (1 equiv) in CH_2Cl_2 for 24 h afforded iodinated product **44a** as a single isomer in 65% yield. The *cis* geometry of **44a** was established by NOE experiments.

Representative reports dealing on the C-H functionalization reactions of cyclobutanes.

Rousseaux and co-workers[27a] reported the palladium(0)-catalyzed cyclobutane C–H bond functionalization of **45a**, which afforded cyclobutyl indoline derivatives **46a** (Scheme 10). Yu and co-workers[27b] reported an example of ligand-enabled methylene C(sp^3)-H bond activation of cyclobutane **47a** using a 1-iodo-4-methylbenzene **47b**, which afforded bis-arylated cyclobutane derivative **48a**(Scheme 11).



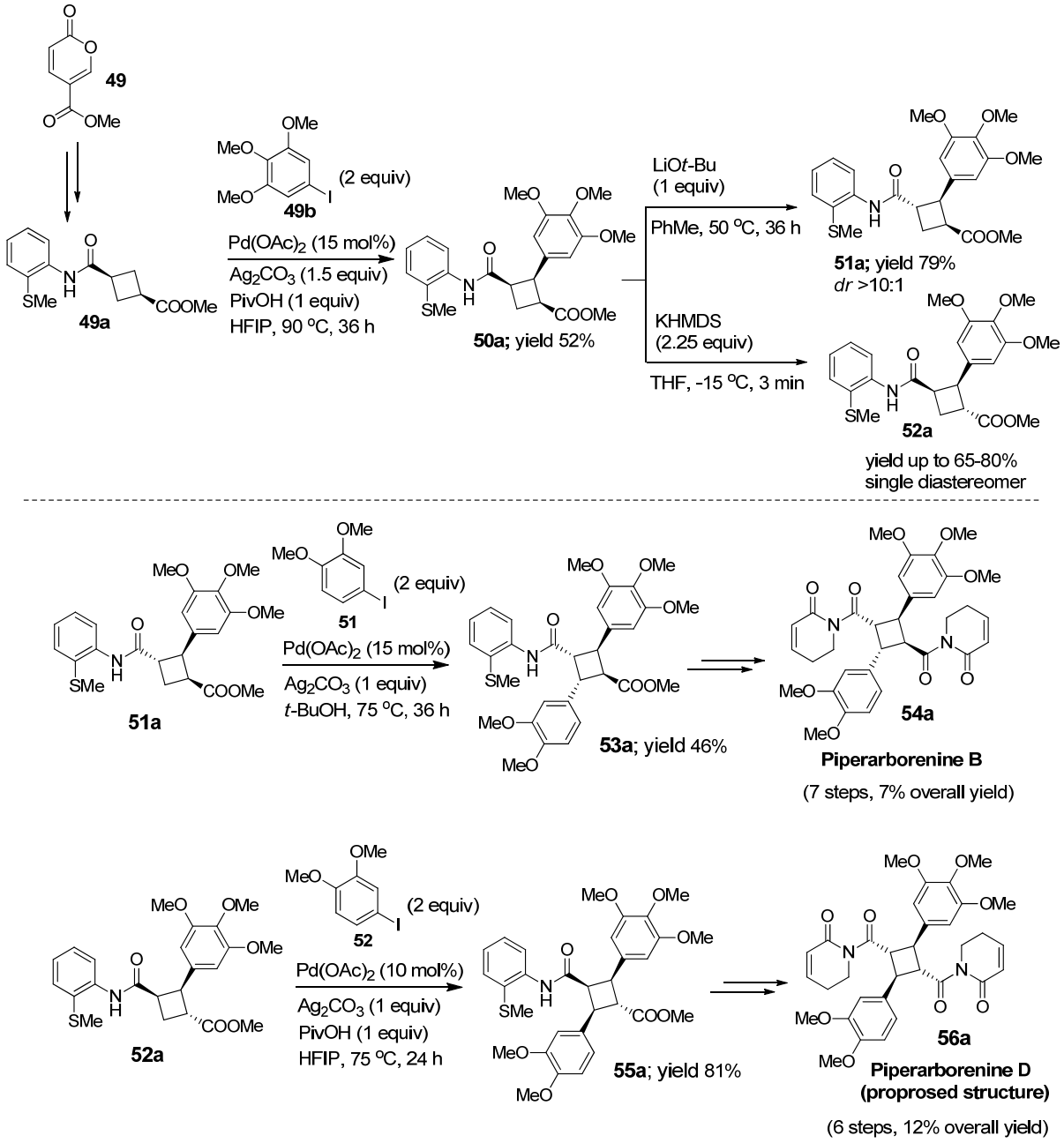
Scheme 10. Synthesis of cyclobutyl indoline *via* intra-molecular arylation of **45a**.



Scheme 11. Arylation of cyclobutane methylene C(sp^3)-H bonds of **47a**.

Baran and co-workers[27c] reported a new strategy for the construction of unsymmetrical cyclobutanes *via* the β-C-H functionalization and completed the synthesis of piperarborenine B **54a** and piperarborenine D **56a** (Scheme 12).The stereoselective C-H arylation of **49a** with 3,4,5 trimethoxyiodobenzene **49b** afforded mono arylation product **50a**. Epimerization conditions afforded diastereomers **51a** and **52a** (Scheme 12). Then, the C-H arylation of the **51a** or **52a** with 3,4-dimethoxyiodobenzene **51** afforded the corresponding tetra-substituted

cyclobutane cores **53a** and **55a**. Further modifications of **53a** and **55a** led to piperarborenine B **54a** and **56a**, respectively (Scheme 12).

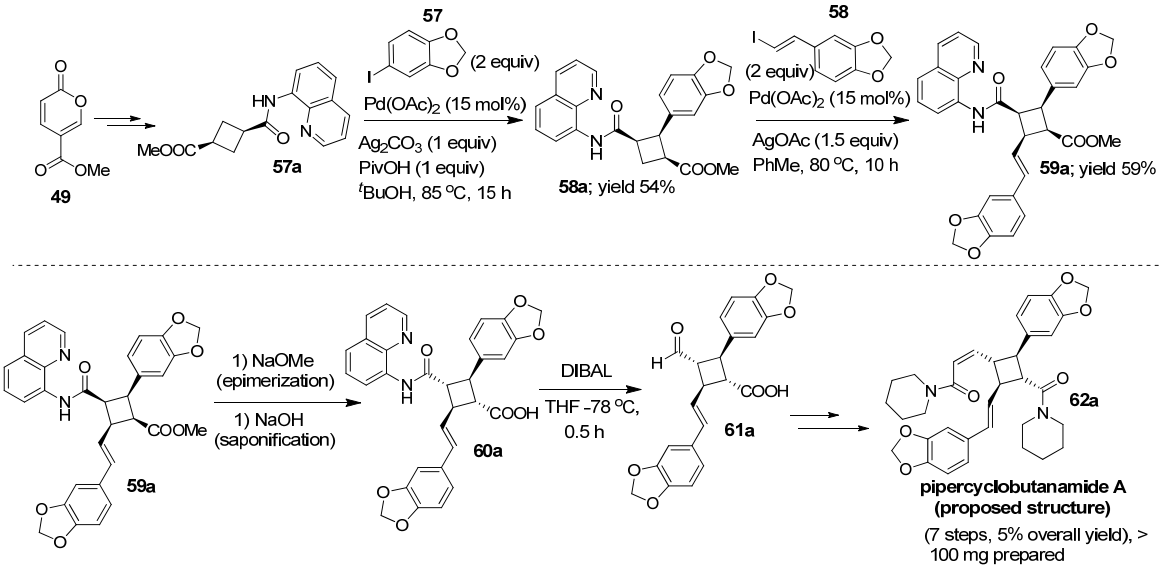


Scheme 12. Synthesis of piperarborenine B and D *via* sequential β-C-Harylation.

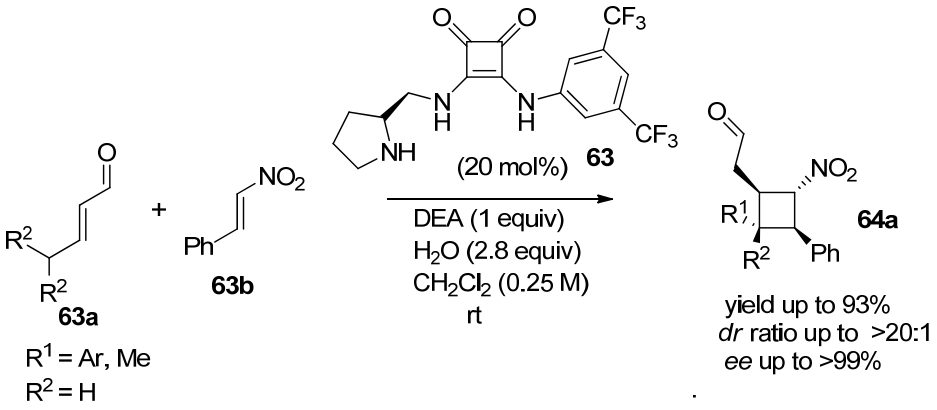
Further, Baran and co-workers[27d] reported the total synthesis of pipercyclobutanamide A **62a***via* the Pd-catalyzed sequential arylation/vinylation of the C(sp^3)-H bonds of cyclobutane ring **57a** (Scheme 13).

Jørgensen and co-workers[27e] demonstrated organocatalysis based [2+2]-cycloaddition, which afforded substituted cyclobutanes **64a** having quaternary stereocenter with excellent

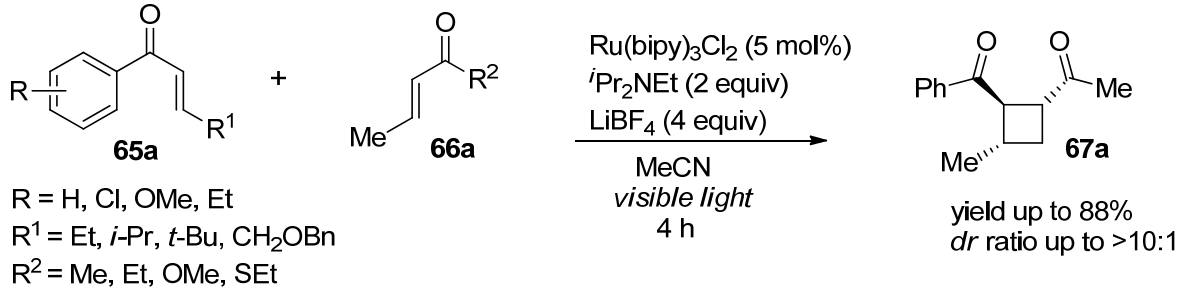
diastereo- and enantioselectivities (Scheme 14). Yoon and co-workers[27f] demonstrated an efficient [2+2] cycloadditions of acyclic enones **65a** and **66a** promoted by visible light, which afforded functionalized cyclobutanes **67a** with excellent diastereo- and enantioselectivities (Scheme 15).



Scheme 13. Synthesis of pipercyclobutanamide A *via* β-arylation/olefination of **57a**.



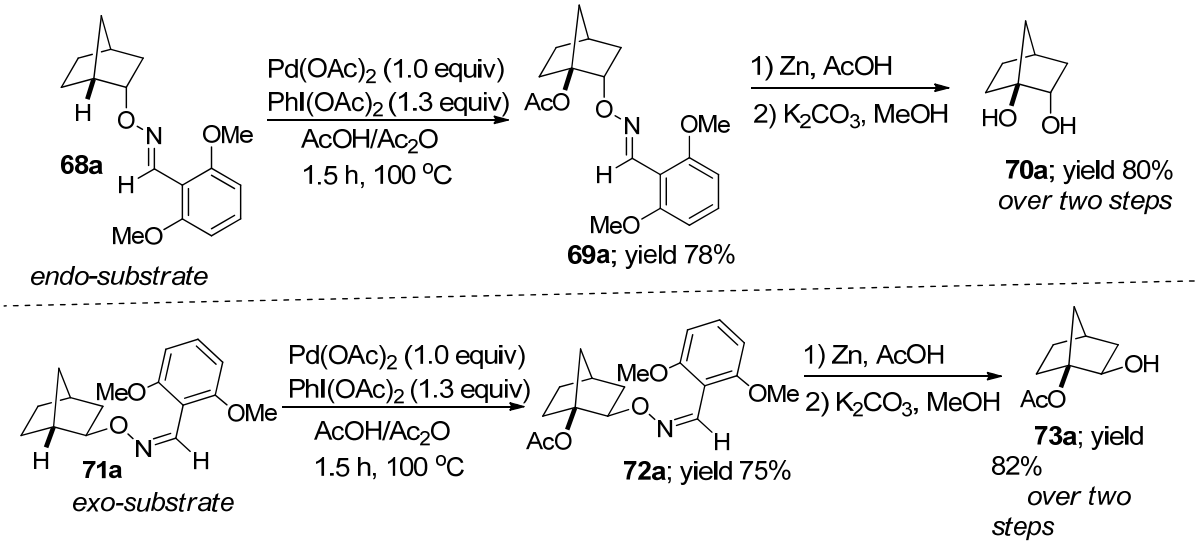
Scheme 14. Organocatalytic formal [2 + 2]-cycloaddition of **63a** with a nitroolefin.



Scheme 15. Intermolecular [2+2] cycloaddition of **65a** with **66a**.

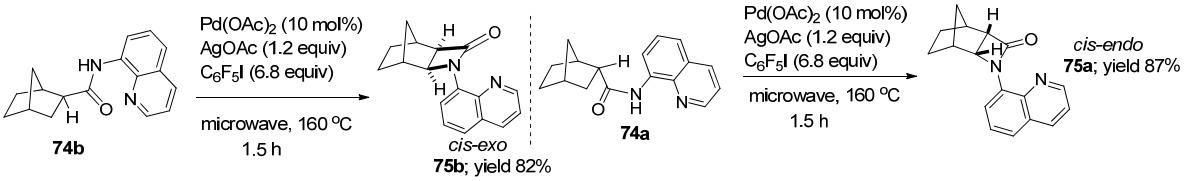
Representative reports dealing on the C-H functionalization reactions of norbornanesubstrates.

Dong group[28a] reported the Pd-catalyzed oxime moiety-directed site-selective acetoxylation of bridge-head C-H bond of **68a** and **71a** which afforded chemically differentiated 1,2-diols **70a** and **73a** from their respective mono alcohol derivatives **69a** and **72a** (Scheme 16).



Scheme 16. Oxime-directed site-selective C-H functionalization of norbornanes **68a**and**71a**.

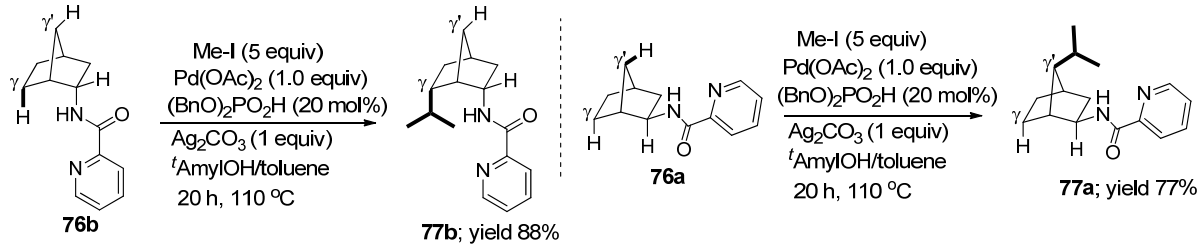
Wu group[28b] reported an efficient method to synthesize β-lactams *via* Pd-catalyzed C(sp^3)-H bond activation and intramolecular amination (Scheme 17). The Pd-catalyzed C(sp^3)-H bond activation and intramolecular amination *endo*-**74a** and *exo*-**74b** afforded the corresponding *cis*-fused products, such as *cis-endo*-**75a** and *cis-exo*-**75b** in 87% and 82% yields (Scheme 17).



Scheme 17. Production of *cis* fused β-lactams *via* intramolecular amination of endo **74a**.

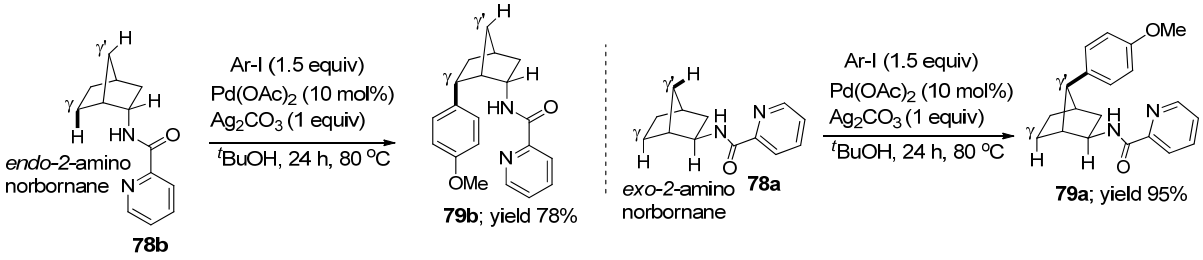
Chen and co-workers[28c] reported the palladium-catalyzed multiple C(sp^3)-H methylation of *exo*-2-aminonorbornane substrate **76a**, *endo* 2-aminonorbornane substrate **76b**. The reactions of *exo*-2-aminonorbornane **76a**, *endo* 2-aminonorbornane **76b** with 5 equiv of MeI afforded

the isopropyl group-substituted **77a** in 77% yield and **77b** in 88% yield, respectively (Scheme 18).



Scheme 18. Sequential C(sp^3)-H methylation of *exo* and *endo*-norbornene system.

Chen and co-workers[28d] reported the palladium-catalyzed γ-C(sp^3)-H arylation of *exo*-2-aminonorbornane substrate **78a**, *endo* 2-aminonorbornanesubstrate**78b** (Scheme 19). The arylation of *exo*-2-aminonorbornane **78a** gave the product **79a** exclusively. Whereas the arylationof *endo*-2-aminonorbornane **78b** gave the product **79b** exclusively. This methodology shows that that regio-, and stereoselectivity of the reactions were dependent on the relative conformation of the C-H bond with respective to the directing group present in the respective substrates.

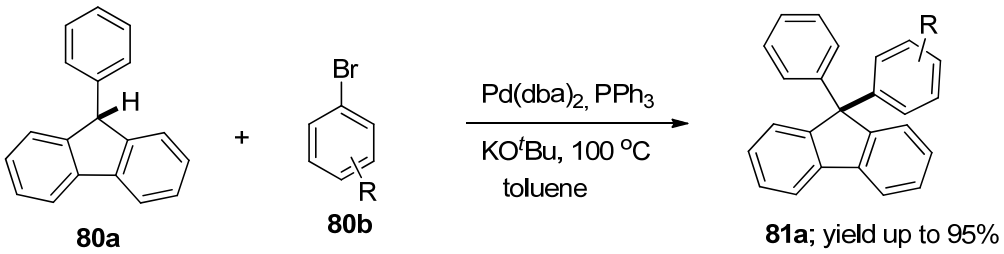


Scheme 19. Palladium-catalyzed C(sp^3)-H arylation *of* **78b** and **78a.**

Representative reports dealing on the construction of quaternary carbon center *via* the sp^3 C-H bond arylation.

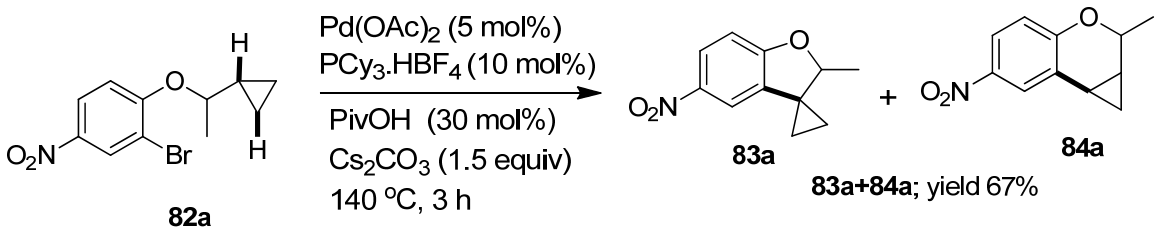
Huang and co-workers[28e] reported an efficient Pd-catalyzed cross-coupling of triarylmethyl C-H bonds **80a** with aryl halides **80b** and the synthesis of unsymmetric diarylfluorenes **81a** (Scheme 20). In this methodology quaternary carbon center was easily built. A series of diarylfluorenes were smoothly obtained. Rousseaux and co-workers[28f] reported palladium (0)-catalyzed intramolecular arylation of **82a** gave an inseparable mixture of dihydrobenzofuran **83a** and chroman **84a** in 67% yield (3:1 ratio, Scheme 21).

Shuto and co-workers[28g] reported Pd-catalyzed arylation of cyclopropanes **85a***via* the directing group-aided C(sp^3)-H bond activation, which afforded quaternary carbon center based cyclopropanes **86a** (Scheme 22).



80a **80b** **81a**; yield up to 95%

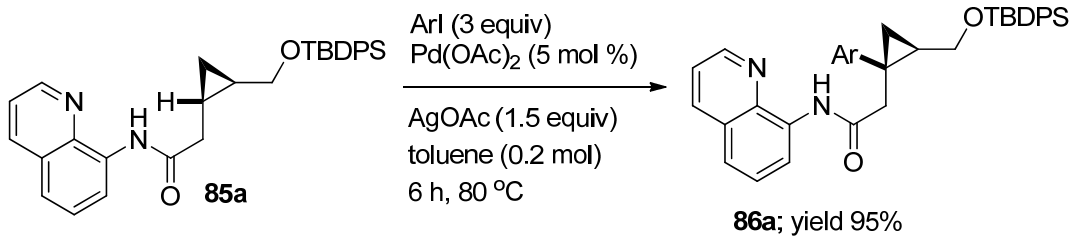
Scheme 20. Arylation of monoarylfluorene and construction of quaternary carbon center.



82a **83a** **84a**

83a+84a; yield 67%

Scheme 21.Pd-catalyzed dihydrobenzofuran synthesis and construction of quaternary carbon center containing derivative **83a**.



85a

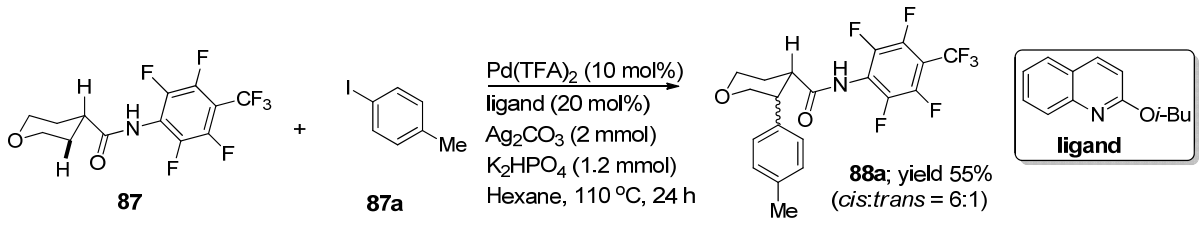
86a; yield 95%

Scheme 22 Pd(II)-catalyzed C(sp^3)-H arylation and construction carbon center based cyclopropanes **86a**.

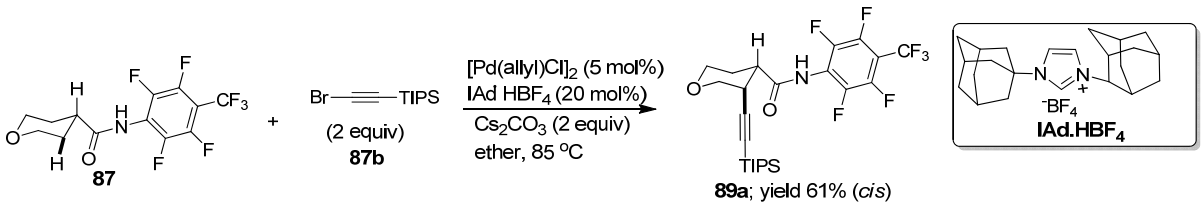
Representative reports dealing on the C-H functionalization reactions of saturated heterocycles.

Yu group[29a] reported an example of the palladium-catalyzed arylation of tetrahydro-2*H*-pyran-4-carboxamide **87** with 1-iodo-4-methylbenzene **87a**, which afforded a mixture of *cis* and *trans* arylated products **88a** in 55% yield with 6:1 ratio (Scheme 23).

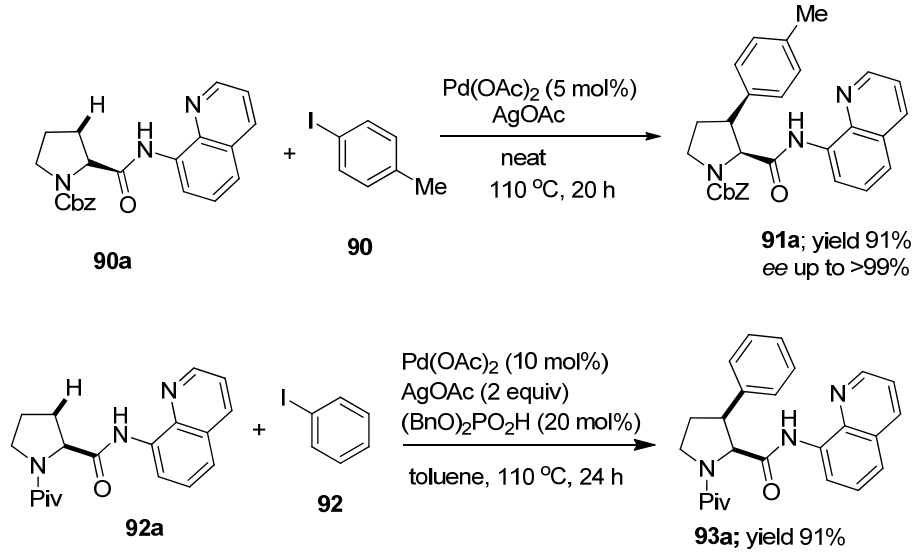
Further, Yu and co-workers[29b] reported an example of the palladium-catalyzed alkynylation of tetrahydropyran carboxamide **87** with bromo alkyne **87b**, which provided the *cis* mono alkynylated product **89a** without further dialkynylation (Scheme 24).



Scheme 23. Arylation of methylene C(sp^3)-H bonds of tetrahydropyran substrate **87**.



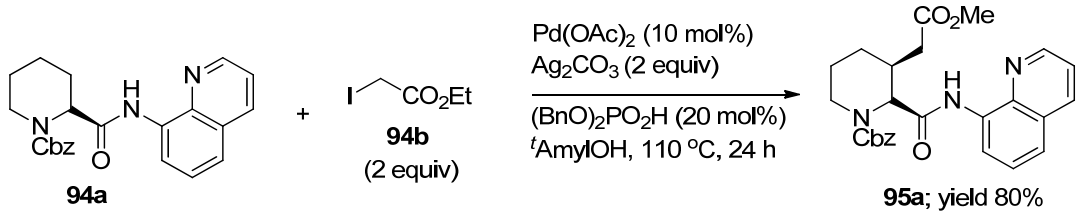
Scheme 24. β-Alkynylation of C(sp^3)−H bonds of tetrahydropyran substrates **87**.



Scheme 25. Pd-catalyzed C(sp^3)–H arylation of **90a** and **92a**.

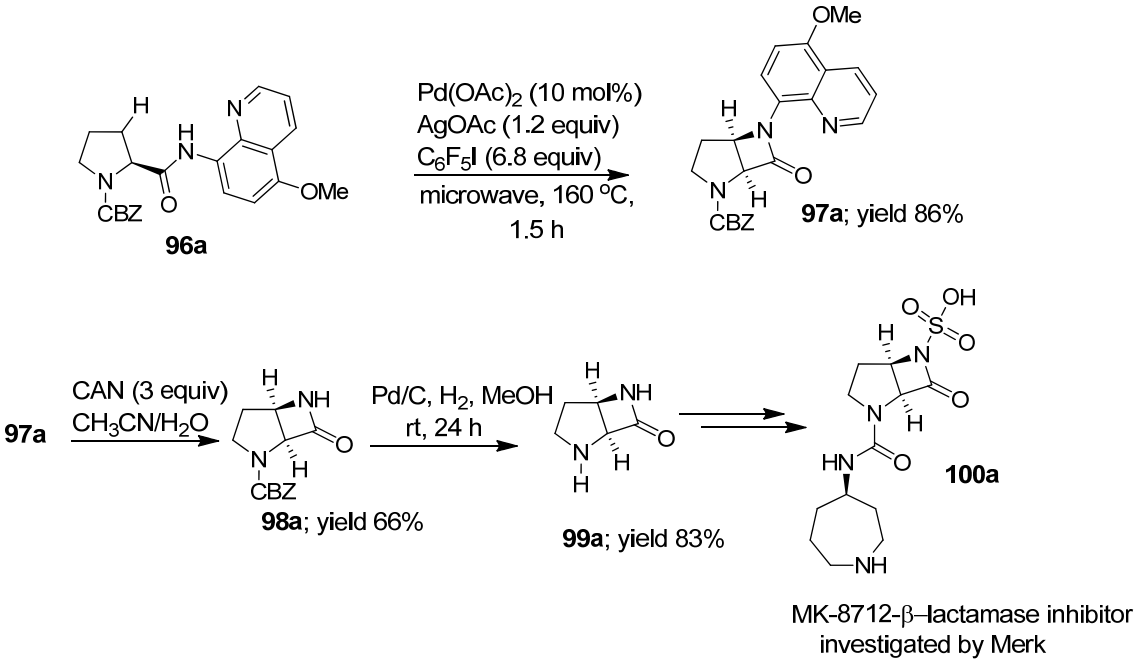
Bull and co-workers[29c] reported the arylation C(3)-H bond of proline derivatives **90a***via* the Pd(II)-catalyzed C(sp^3)-H arylation affording pyrrolidine-2-carboxamides **91a** under solvent-free conditions at 110 °C. Zhang and co-workers[29d] also reported a similar work comprising the synthesis of C(3)-arylated proline derivatives **93a***via* the Pd(II)-catalyzed arylation of pyrrolidine-2-carboxamides **92a**with PhI **92** in the presence of $(BnO)_2PO_2H$ (20 mol%),

$Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in toluene at 110 ^oC (Scheme 14). Chen and co-workers[29e] reported an example of alkylation of β-methylene $C(sp^3)$−H bond of six-membered cyclic alkane carboxamide **94a** affording alkylated compound **95a** in excellent yield and diastereoselectivity (Scheme 26).



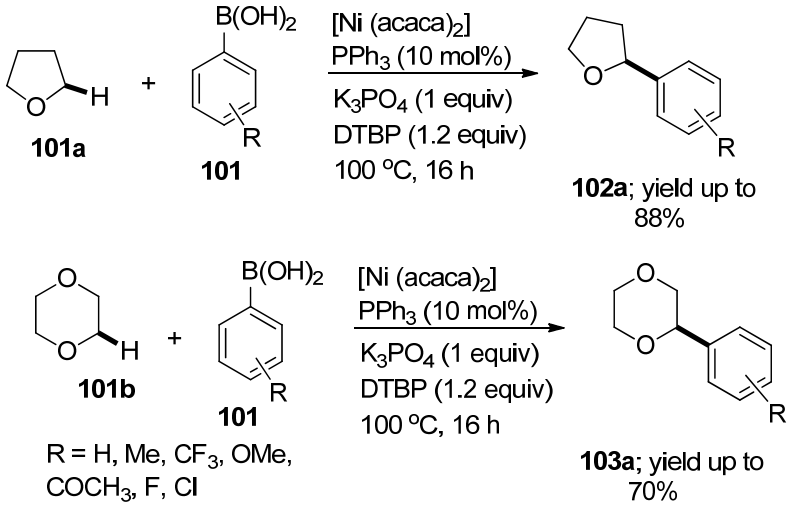
Scheme 26. $C(sp^3)$-H alkylation of carboxamide substrates **94a**.

Wu group[29f] reported intermolecular amination of **96a** with C_6F_5I gave the cyclized product **97a**(Scheme 27). Treatment of **97a** with CAN followed by hydrogenation gave **99a**. The compound **99a** is a key starting material for the synthesis β-lactamase inhibitor MK-8712 **100a** (Scheme 27).



Scheme 27. Pd(II)-catalyzed β-$C(sp^3)$-H amination of carboxylic acid derivatives **96a**.

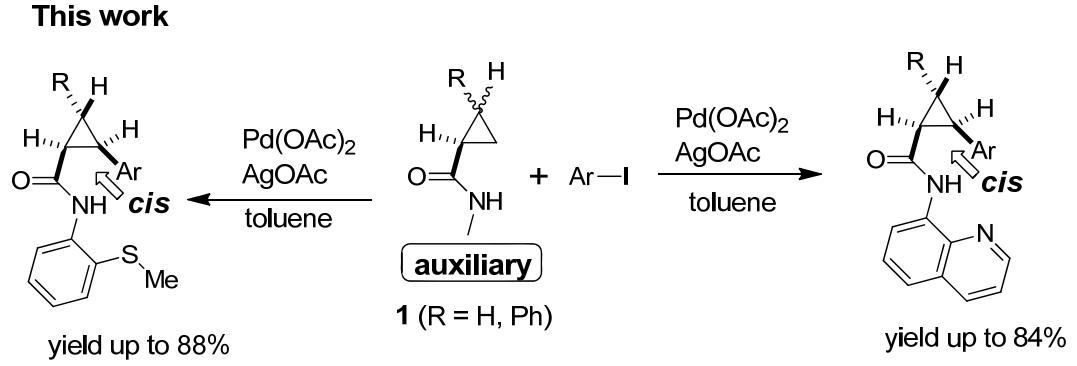
Lei and co-workers[29g] reported the nickel-catalyzed oxidative arylation of $C(sp^3)$-H bonds of THF **101a** and 1,4-dioxane **101b** with arylboronic acids, which afforded the correspondingα-arylated ethers **102a** and **103a** (Scheme 28). Preliminary mechanistic studies suggested that this reaction likely to proceeded through a radical pathway.



Scheme 28. Ni-catalyzed oxidative arylation of THF and 1,4-dioxane with arylboronic acids.

Results and Discussion

Part 1: Regio- and stereoselective construction of functionalizedcyclopropanes*via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation.

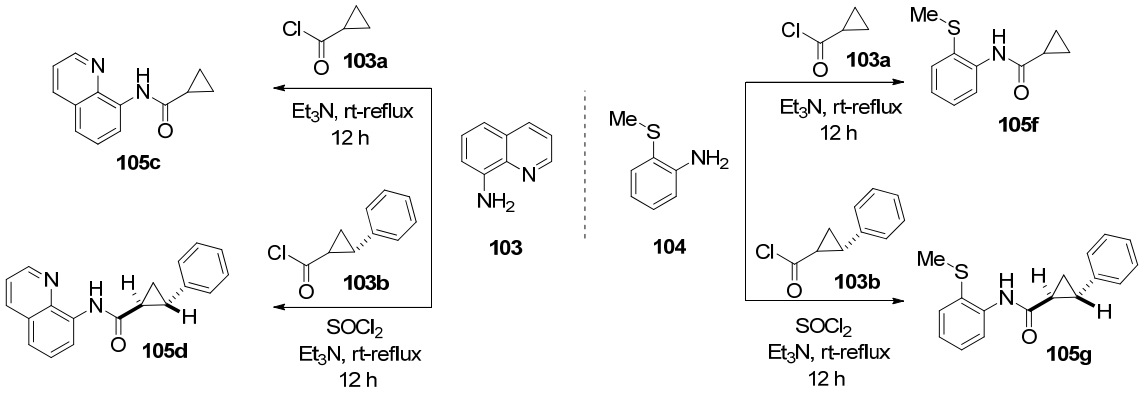


Scheme 29. Topic of this work. Directing group-enabled construction of novel di- and trisubstituted cyclopropanes having *cis* stereochemistry.

Given the importance of arylcyclopropane derivatives in organic synthesis and medicinal chemistry research, developing the efficient synthetic methods involving simple procedures for synthesizing new *cis* substituted cyclopropanes and mono and bis arylatedcyclopropane scaffolds will be highly useful to enrich the library of cyclopropane scaffolds. A literature survey revealed that there exist only limited reports dealing with the synthesis of *cis* arylated cyclopropanes frameworks. It is to be noted that some of the literature reports discussed in the introduction section of this chapter appeared during or after the investigation of the

current wok. A part of this thesis work envisaged to investigate the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization of cyclopropanecarboxamides and synthesis of novel arylated cyclopropanecarboxamide frameworks having *cis* stereochemistry (Scheme 29).

Following the standard literature procedures, various cyclopropanecarboxamides were prepared using the directing groups, such as 8-aminoquinoline **103**, 2-(methylthio)aniline **104** (Scheme 30). The reaction of amines **103**or **104** with acid chloride **103a** or **103b** and triethylamine in DCM gave the corresponding amides **105c**, **105d**, **105f** and **105g**.



Scheme 30. Preparation of cyclopropanecarboxamide starting materials **105c**, **105d**, **105f** and **105g**.

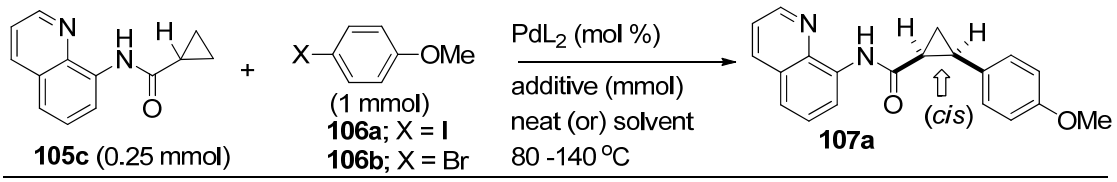
To begin the investigations on the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization of cyclopropanecarboxamides **105c**, **105d**, **105f** and **105g**, initially, various reactions were carried out to find out the optimized reaction conditions. Table 1 shows the Pd-catalyzed arylation of *N*-(quinolin-8-yl)cyclopropane-carboxamide (**105c**), prepared from cyclopropanecarbonyl chloride and 8-aminoquinoline. The C-H functionalization reaction of *N*-(quinolin-8-yl)cyclopropanecarboxamide (**105c**) with 1-iodo-4-methoxybenzene (**106a**) without any palladium catalyst failed to afford any product (entry 1, Table 1). The C-H arylated cyclopropanecarboxamide **107a** was obtained in 28% yield when the arylation was performed in the presence of $Pd(OAc)_2$ catalyst without any additive under neat condition (entry 2, Table 1). The C-H arylation of cyclopropanecarboxamide **105c** with aryl iodide **106a** in the presence of 5 mol% $Pd(OAc)_2$ and AgOAc under neat condition gave the arylated cyclopropanecarboxamide **107a** in only 35% yield (entry 3, Table 1). The Pd-catalyzed arylation of cyclopropanecarboxamide **105c** using different solvents such as

1,2-DCE, 1,4-dioxane, MeCN, DMF and AcOH afforded the product**107a**in 10-32% (entries 4-8, Table 1). The C-H arylation of cyclopropanecarboxamide **105c** (0.25 mmol) with **107a** (1 mmol) in the presence of 5 mol% $Pd(OAc)_2$ and AgOAc (0.55mmol) in toluene at 110 ^oC furnished the arylated cyclopropanecarboxamide **107a** having *cis* stereochemistry in 71% yield as a single diastereomer (entry 9, Table 1). Employing other palladium salts, such as $PdCl_2$, $Pd(PPh_3)_4$, $Pd(TFA)_2$, $Pd(acac)_2$, $Pd(CH_3CN)_2Cl$ and $Ni(acac)_2$ catalysts gave the product **107a**in 10-37%(entries 10-15, Table 1).

The Pd-catalyzed C-H arylation of cyclopropanecarboxamide **105c** with **106a** under an open atmosphere gave the arylated cyclopropanecarboxamide **107a** in 50%(entry 16, Table 1). The C-H arylation of cyclopropanecarboxamide **105c** with **106a** in the presence a variety of additives, such as $PhI(OAc)_2$, KOAc, $Cu(OAc)_2$, benzophenone, oxone were not fruitful (entries 17-21, Table 1). The Pd-catalyzed C-H arylation of cyclopropanecarboxamide **105c** with **106a** without AgOAc additive under an open atmosphere gave the arylated cyclopropanecarboxamide **107a** in 10% yield (entry 22, Table 1). This reaction indicated that perhaps AgOAc helps to regenerate the catalyst via the ligand exchange process, producing AgI and $Pd(OAc)_2$.[9] The C-H arylation of cyclopropanecarboxamide **105c** with **106a** in the presence of K_2CO_3 instead of AgOAc additive was not effective (entry 23, Table 1). The C-H arylation of cyclopropanecarboxamide **105c** with 1-bromo-4-methoxybenzene(**106b**) or chlorobenzene (**106c**) instead of **106a** was not effective (entries 24 and 25, Table 1). The C-H arylation of cyclopropanecarboxamide **105c** with 0.26 mmol of **106a** instead of 1 mmol in toluene or xylene gave the arylated cyclopropanecarboxamide **107a** only in 37% yield (entry 26 and 27, Table 1).

Having done the optimization reactions, then we tested the scope of this directing group-enabled Pd-catalyzed direct arylation of methylene $C(sp^3)$-H bond of cyclopropanecarboxamide using various electron-withdrawing and donating group containing aryl iodides (Table 2). The Pd(II)-catalyzed arylation of methylene C-H bond of cyclopropanecarboxamide **105c** with 1-iodo-3-nitrobenzene gave the arylated cyclopropanecarboxamide **107b** in 28% yield. The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105c** with iodobenzene and various electron donating group containing aryl iodides (e.g. Me, Et) gave the corresponding arylated cyclopropanecarboxamides **107c-107e** in 67-69% yields.

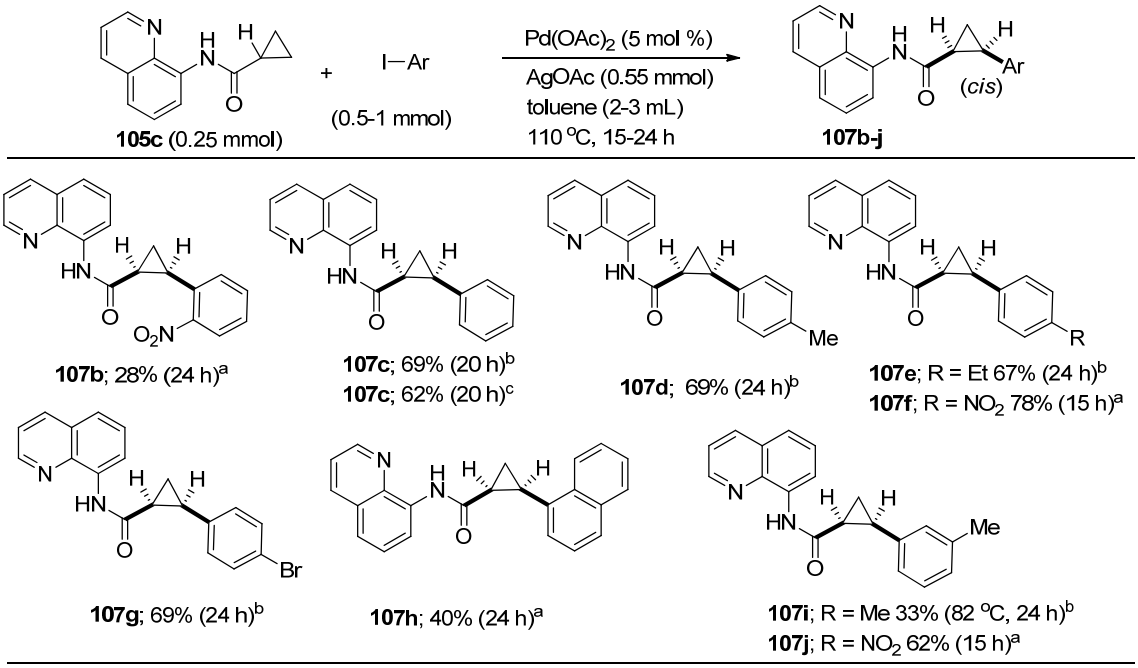
Table 1. Optimization reactions. C-H arylation reaction of **105c** with **106a**.



entry	catalyst (mol %)	additive (mmol)	solvent (mL)	*t* (°C)	time (h)	**107a**: yield (%)[a]
1	**nil**	AgOAc (1.5)	neat	110	36	0
2[b]	$Pd(OAc)_2$ (5)	**nil**	neat	110	36	28
3	$Pd(OAc)_2$ (5)	AgOAc (0.27)	neat	110	10	35
4	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,2-DCE	80	20	32
5	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,4-Dioxane	100	20	15
6	$Pd(OAc)_2$ (5)	AgOAc (0.55)	CH_3CN	80	20	5
7	$Pd(OAc)_2$ (5)	AgOAc (0.55)	DMF	130	20	0
8	$Pd(OAc)_2$ (5)	AgOAc (0.55)	AcOH	110	20	10
9	**$Pd(OAc)_2$ (5)**	**AgOAc (0.55)**	**toluene**	**110**	**20**	**71** (39)[c] (51)[d]
10	$PdCl_2$ (5)	AgOAc (0.55)	toluene	110	20	37
11	$Pd(PPh_3)_4$ (5)	AgOAc (0.55)	toluene	110	20	0
12	$Pd(TFA)_2$ (5)	AgOAc (0.55)	toluene	110	20	10
13	$Pd(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	20	26
14	$Pd(CH_3CN)_2Cl_2$ (5)	AgOAc (0.55)	toluene	110	20	33
15	$Ni(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	20	0
16[e]	$Pd(OAc)_2$(5)	AgOAc (0.55)	toluene	110	20	50
17	$Pd(OAc)_2$(5)	$PhI(OAc)_2$ (0.55)	toluene	110	20	0
18	$Pd(OAc)_2$(5)	KOAc (0.55)	toluene	110	20	6
19	$Pd(OAc)_2$(5)	$Cu(OAc)_2$ (0.55)	toluene	110	20	6
20	$Pd(OAc)_2$(5)	Benzophenone	toluene	110	20	15
21	$Pd(OAc)_2$(5)	Oxone (0.55)	toluene	110	20	0
22	$Pd(OAc)_2$(5)	O_2 (air)	toluene	110	20	10
23	$Pd(OAc)_2$ (5)	K_2CO_3 (0.55)	toluene	110	20	0
24[f]	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	24	0
25[g]	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	24	0
26[h]	$Pd(OAc)_2$ (10)	AgOAc (2.2)	toluene	110	36	37
27[h]	$Pd(OAc)_2$ (10)	AgOAc (2.2)	xylene	140	36	48

[a] All the reactions were performed using 1-iodo-4-methoxybenzene (**106a**) under nitrogen atmosphere. [b] 1.2 mmol of **106a** was used. [c] In this case, 0.5 mmol of **106a** was used. [d] In this case, 0.75 mmol of **106a** was used. [e] The reaction was performed under an open atmosphere. [f] In this case, 1-bromo-4-methoxybenzene (**106b**) was used instead of **106a**. [g] In this case, 1-chlorobenzene (**106c)** was used instead of **106a**. [h] In this case, 0.26 mmol of **106a**was used.

Table 2. Diastereoselective mono C-H arylation of **105c**.



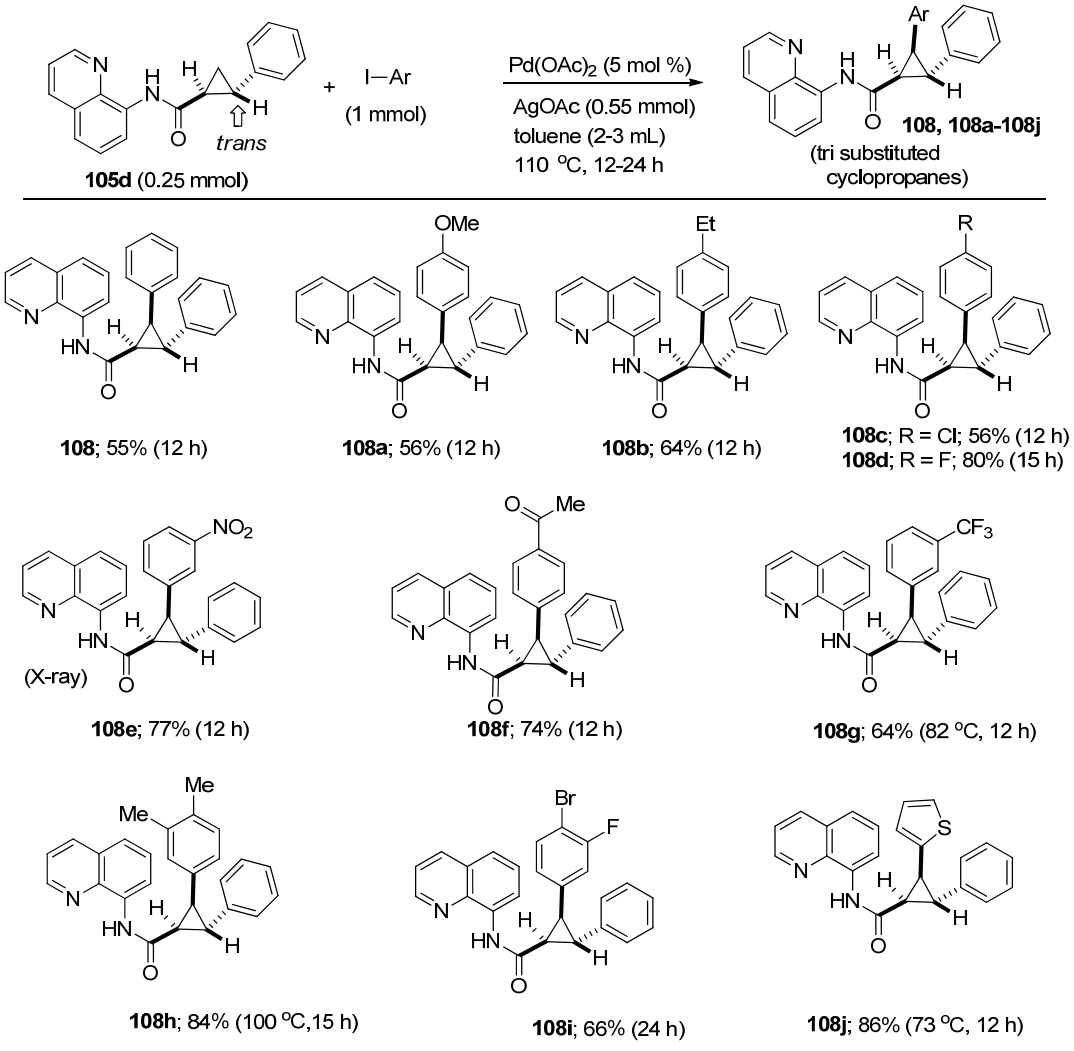
[a] In this case, 1 mmol of ArI was used. [b] In this case, 0.5 mmol of ArI was used. [c] The reaction was performed using **105c** (1.06 g, 5 mmol), ArI (1.02 g, 10 mmol), AgOAc (1.83 g, 11 mmol) and toluene 15 mL.

The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105c** with different electron withdrawing group containing aryl iodides afforded the arylated cyclopropanecarboxamides **107f-107g** in 69-78% yields. The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105c** with 1-iodonaphthalene and 1-iodo-3-methylbenzene gave the corresponding arylated cyclopropanecarboxamides **107h** and **107i** in only 40 and 33% yields. The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105c** with 1-iodo-3-nitrobenzene gave the arylated cyclopropanecarboxamides **107j** in 62% yield. All these reactions were highly stereoselective and gave arylated cyclopropanecarboxamideshaving *cis* stereochemistry as the major isomers.The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105c** with iodobenzene in a gram scale also furnished the arylated cyclopropanecarboxamides**107j** in 62% yield .

Then, the scope of this method was extended by synthesizing various trisubstituted cyclopropane carboxamides *via* the Pd(II)-catalyzed arylation of the C-H bond of (*1S*,2S**)-2-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (**105d**, Table 3).[10b] The Pd(II)-catalyzed arylation of cyclopropanecarboxamide (**105d**) with PhI and various aryl iodides having electron-donating (e.g. OMe, Et) or electron-withdrawing groups (e.g. Cl, F) at the

para-position afforded the corresponding trisubstituted cyclopropanecarboxamides **108**, **108a-108d** as single diastereomers in 55-80% yields. Similarly, the Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105d** with various aryl iodides having different electron-withdrawing substituents (e.g. NO_2, Ac and CF_3) in the aromatic ring gave the corresponding trisubstituted cyclopropanecarboxamides **108e** (77%), **108f** (74%) and **108g** (64%).

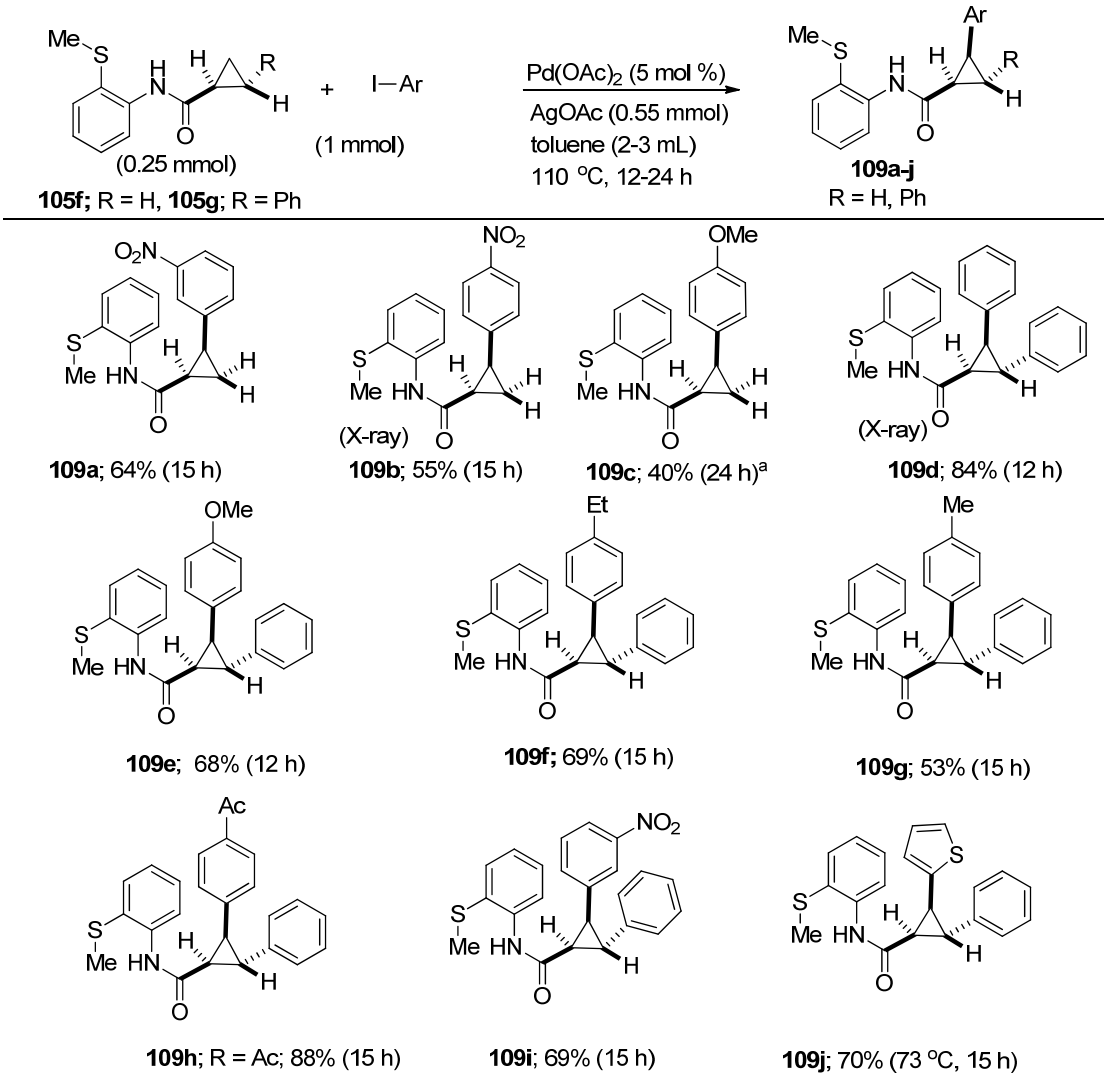
Table 3. Stereoselective C-H arylation of **105d**. Synthesis trisubstituted cyclopropanes.



Further, the Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105d** with di-substituted aryl iodides (e.g. Me, halide) also gave the corresponding arylated cyclopropanecarboxamide **108h** (84%) and **108i** (66%) (Table 3). The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105d** with 2-iodothiophene successfully gave the arylated cyclopropanecarboxamide **108j** (86%). The results shown in Table 3, revealed the successful

synthesis of novel trisubstituted cyclopropane-carboxamides **108, 108a-108j** having contiguous stereocenters as the single diastereomers with high diastereoselectivity.

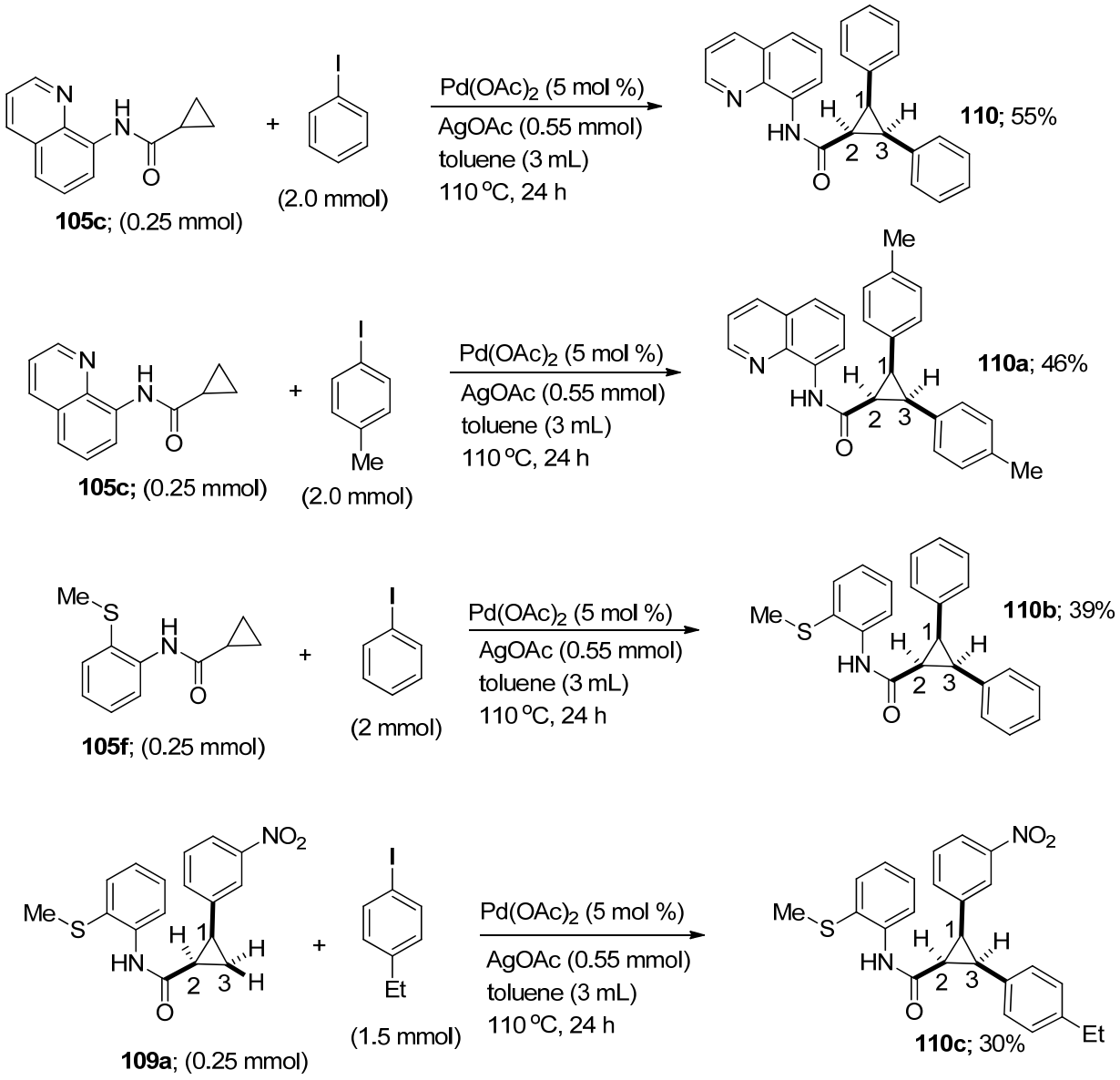
Table 4. Diastereoselective C-H arylation of cyclopropanecarboxamides **105f**,**105g**.



[a] In this case, 0.5 mmol of aryl iodide was used.

Having done the Pd(II)-catalyzed arylation of cyclopropane systems **105c** and **105d** using 8-aminoquinoline as the directing group, then the scope of this Pd(II)-catalyzed arylation of cyclopropane systems was tested by using other auxiliaries. Accordingly, the Pd(II)-catalyzed C-H arylation of *N*-(2-(methylthio)phenyl)-cyclopropanecarboxamides**105f**, **105g**, with various aryl iodides were studied (Table 4). The Pd(II)-catalyzed arylation of cyclopropanecarboxamide **105f** with various aryl iodides having different substituents (e.g.

NO_2, OMe) in the aromatic ring afforded the corresponding arylated cyclopropanecarboxamides **109ac** in 64, 55 and 40% yields as single diastereomers (Table 4).

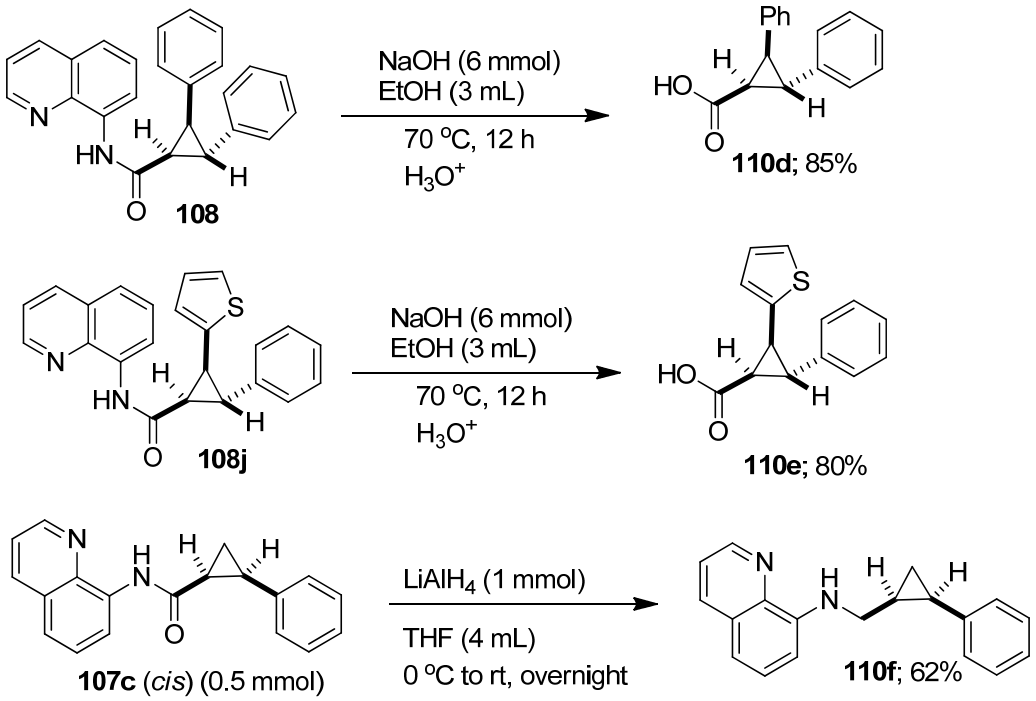


Scheme 31. Synthesis of di- and trisubstituted cyclopropanecarboxamides **110**, **110a-c**.

Next, the production of trisubstituted cyclopropanecarboxamides was attempted via the Pd(II)-catalyzed C-H arylation of (*1S*,2S**)-*N*-(2-(methylthio)phenyl)-2-phenylcyclopropanecarboxamide (**105g**) with different aryl iodides. The Pd(II)-catalyzed C-H arylation of **105g** with iodobenzene and other aryl iodides having electron-donating groups (e.g. OMe, Me, Et) at the *para*-position gave the corresponding trisubstituted cyclopropanecarboxamides **109d-109j** as single diastereomers in 53-84% yields (Table 4).

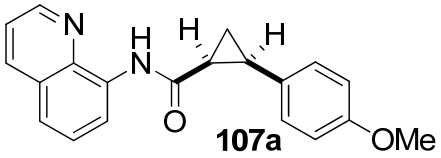
The Pd(II)-catalyzed C-H arylation of **105g** with aryl iodides having electron-withdrawing groups (e.g. Ac, NO_2) gave the trisubstituted cyclopropanecarboxamides **109h**, **109i** as single diastereomers in 88% and 69% yields. The Pd(II)-catalyzed C-H arylation of **109g** with 2-iodothiophene successfully gave the trisubstituted cyclopropanecarboxamide **109j** (70%). The results shown in Table 4, revealed the successful synthesis of novel di- and trisubstituted cyclopropanecarboxamides **109a-109j** having contiguous stereocenters as the single diastereomers with high diastereoselectivity.

Additionally, the Pd(II)-catalyzed C-H arylation of *N*-(quinolin-8-yl)cyclopropanecarboxamide (**105c**), with excess iodobenzene or 1-iodo-4-methylbenzene (8 equiv) furnished the corresponding di-arylated cyclopropanecarboxamides **110**, **110a** having the 1,2-*cis*/2,3-*cis*/1,3-*cis* stereochemistry(Scheme 31). Then, the Pd(II)-catalyzed C-H arylation of *N*-(2-(methylthio)phenyl)-cyclopropanecarboxamides (**105f**) with excess iodobenzene furnished the di-arylated cyclopropanecarboxamide **110b** (Scheme 31). Likewise, the Pd(II)-catalyzed C-H arylation of cyclopropanecarboxamide **109a** having the 1,2-*cis* stereochemistry with 1-iodo-4-ethylbenzene (6 equiv) furnished the trisubstituted cyclopropanecarboxamide **110c** having the 1,2-*cis*/2,3-*cis*/1,3-*cis* stereochemistry (Scheme 31).

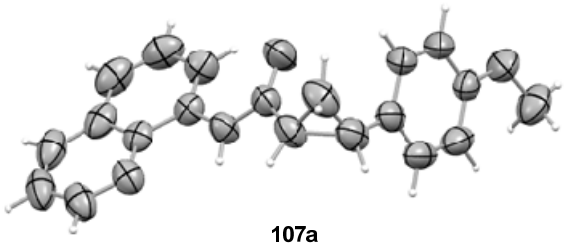


Scheme 32. Synthetic transformations. Synthesis of functionalized carboxylic acids/ amines.

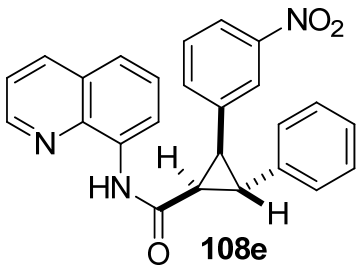
Finally, to show that the directing groups can be removed after the C-H arylation reactions as well as the utility of this protocol, the amide hydrolysis of the trisubstituted cyclopropanes **108,108j** were performed, which gave the corresponding substituted cyclopropanecarboxylic acids **110d,110e**. Further, the $LiAlH_4$-mediated reduction of the amide group of a representative compound **107c** afforded *N*-(((*1S*,2R**)-2-phenylcyclopropyl)methyl)quinolin-8-amine (**110f**) (Scheme 32).



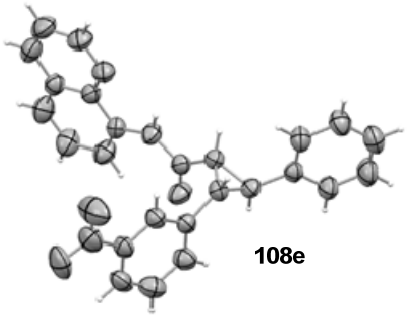
107a



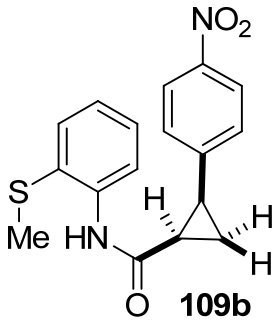
107a



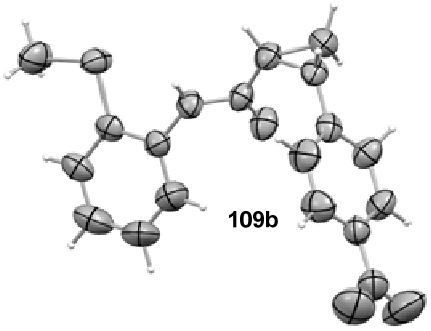
108e



108e



109b



109b

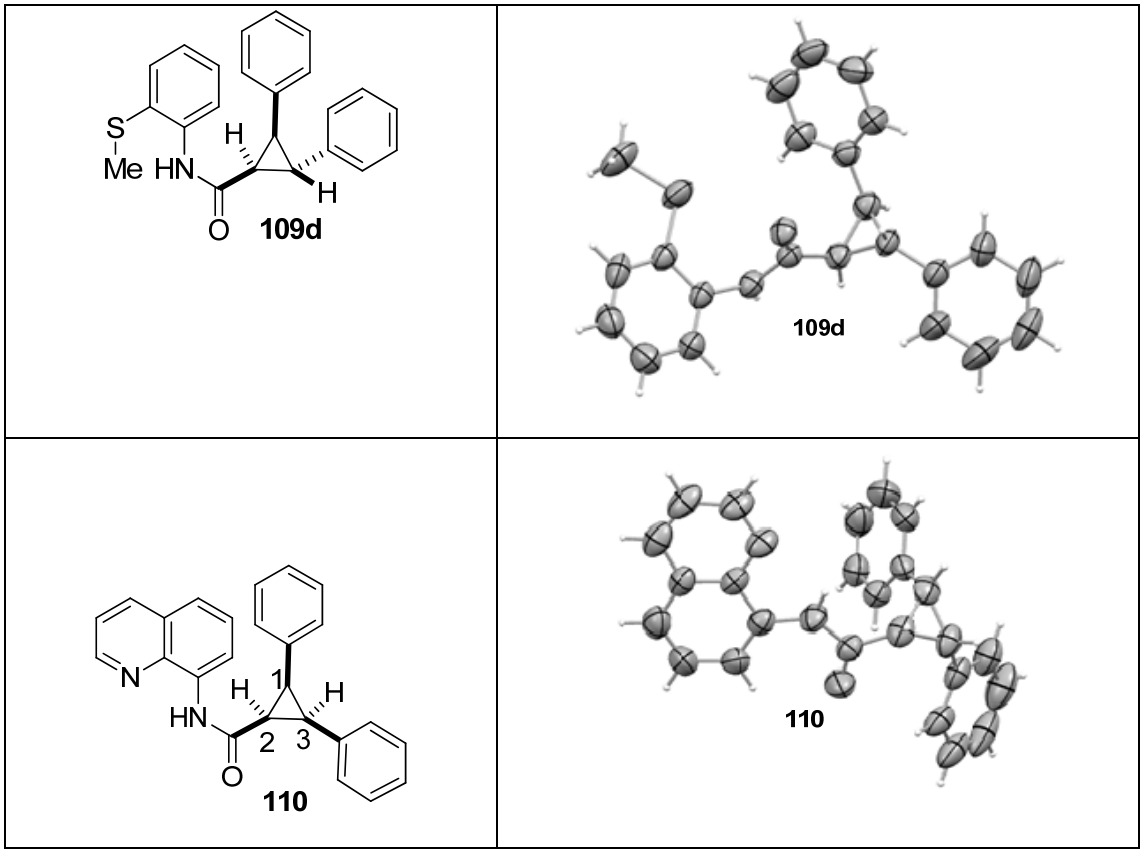
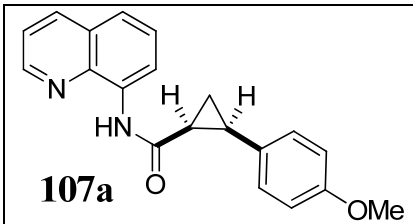
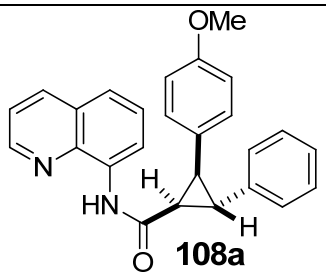
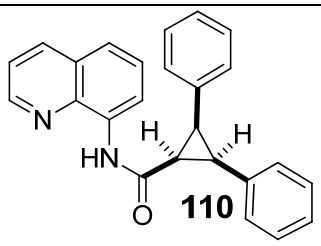


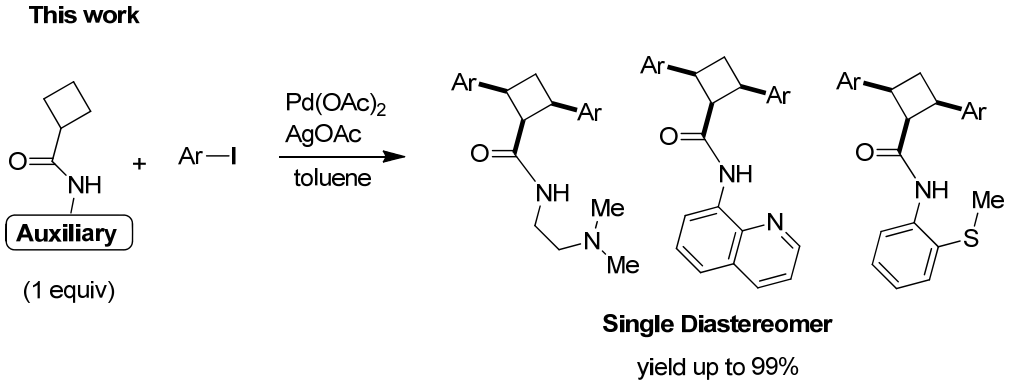
Figure 8. X-ray (ORTEP diagram) structures of the compounds **107a**, **108e, 109b, 109d**and **110**.

^{1}H Coupling constant values for cyclopropyl ring:

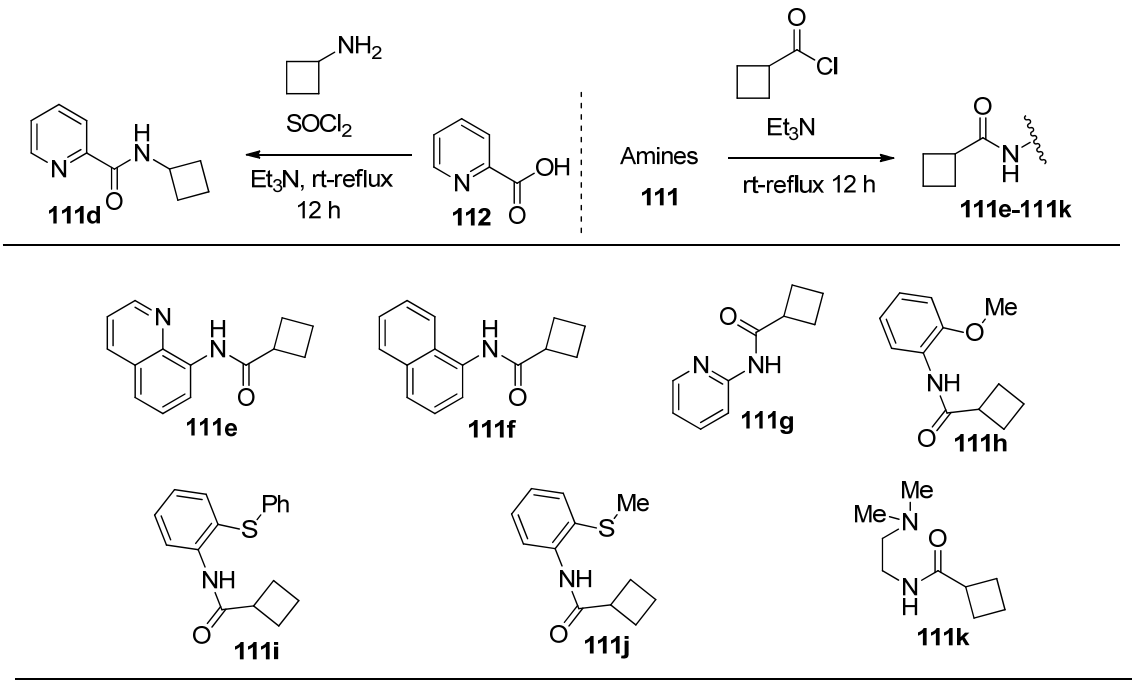
 **107a**	 **108a**	 **110**
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (dd, 1H, J_1 = 17.2 Hz, J_2 = 9.1 Hz) 2.33-2.27 (m, 1H), 1.90-1.86 (m, 1H), 1.46-1.44 (m, 1H);	^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, 1H, J_1 = 7.2 Hz, J_2 = 5.2 Hz), 3.03 (dd, 1H, J_1 = 9.4 Hz, J_2 = 7.2 Hz), 2.60 (dd, 1H, J_1 = 9.4 Hz, J_2 = 5.2 Hz);	^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (d, 2H, J = 9.1 Hz), 2.79 (t, 1H, J = 9.1 Hz);

Part 2: Regio- and stereoselective construction of functionalizedtrisubstituted cyclobutane scaffolds having three contiguous stereocenters and an all-*cis* stereochemistry *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation.

Given the importance of arylcyclobutane derivatives in organic synthesis and medicinal chemistry research, developing the efficient synthetic methods involving simple procedures for synthesizing new *cis* substituted cyclobutanes and mono and bis arylatedcyclobutane scaffolds will be highly useful to enrich the library of cyclobutane scaffolds. A literature survey revealed that there exist only limited reports dealing with the synthesis of *cis* arylated cyclobutane frameworks with high degree of stereo- and regiocontrol involving simple methods. Accordingly, in continuation of the investigations on the construction of functionalizedcyclopropanecarboxamides*via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation, a part of this thesis work envisaged to investigate the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization of cyclobutanecarboxamides and synthesis of novel mono and bis arylatedcyclobutanecarboxamide frameworks having *cis* stereochemistry (Scheme 33).



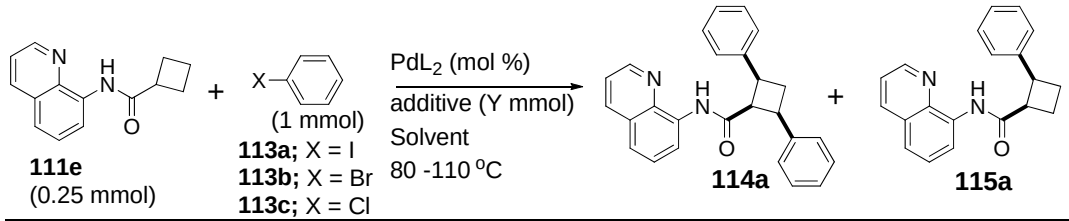
Scheme 33. Topic of this work. Directing group-enabled construction of novel di- and trisubstituted cyclobutanes having *cis* stereochemistry.



Scheme 34. Preparation of cyclobutanecarboxamides.

Following the standard literature procedures, various cyclobutanecarboxamide systems **111d-111k** linked with the directing groups were prepared from directing groups/amines/carboxylic acid **111**or **112** (Scheme 34). Then, to investigate the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization of cyclobutanecarboxamides, initially optimization reactions were performed. Table 5 reveals optimization reactions using **111e**. The Pd(II)-catalyzed C-H arylation of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**111e**) with iodobenzene (**113a**) in the presence of AgOAc additive and in the absence of a Pd(II) catalyst failed to afford any C-H arylated product (entry 1, Table 5). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamides **111e** in the presence of $Pd(OAc)_2$ catalyst and AgOAc additive in 1,2-DCE afforded the bis C-H arylated cyclobutanecarboxamide **114a** in 68% yield (entry 2, Table 1).

Table 5. Optimization of the reaction conditions. The C-H arylation of **111e**.



entry	catalyst (mol %)	additive (Y mmol)	solvent (mL)	temp (°C)	time (h)	**114a**: yield (%)[a]	**115a**: yield (%)
1	nil	AgOAc (1.0)	toluene	110	24	0	N. D.
2	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,2-DCE	80	15	68	N. D.
3	$Pd(OAc)_2$ (5)	AgOAc (0.55)	1,4-Dioxane	100	15	63	N. D.
4	$Pd(OAc)_2$ (5)	AgOAc (0.55)	CH_3CN	80	15	37	N. D.
5	$Pd(OAc)_2$(5)	AgOAc (0.55)	toluene	110	20	94	N. D.
6	$Pd(PPh_3)_4$ (5)	AgOAc (0.55)	toluene	110	15	0	N. D.
7	$PdCl_2$ (5)	AgOAc (0.55)	toluene	110	15	73	N. D.
8	$Pd(TFA)_2$ (5)	AgOAc (0.55)	toluene	110	15	70	N. D.
9	$Pd(AcAc)_2$ (5)	AgOAc (0.55)	toluene	110	15	69	N. D.
10	$Pd(CH_3CN)_2Cl_2$ (5)	AgOAc (0.55)	toluene	110	15	72	N. D.
11	$Pd(OAc)_2$(5)	$PhI(OAc)_2$ (0.55)	toluene	110	24	5	N. D.
12	$Pd(OAc)_2$(5)	KOAc (0.55)	toluene	110	20	20	N. D.
13	$Pd(OAc)_2$(5)	$Cu(OAc)_2$ (0.55)	toluene	110	24	0	N. D.
14	$Pd(OAc)_2$(5)	Ag_2CO_3 (0.55)	toluene	110	24	68	N. D.
15[b]	$Pd(OAc)_2$(5)	Ag_2CO_3 (0.55)	toluene	110	24	0	N. D.

[a] All the reactions were performed using PhI (**113a**) and solvent (3 mL) under a nitrogen atm. The yields were calculated based on the starting compound **111e**. [b] In this case, bromobenzene (**113b**) or chlorobenzene (**113c**) was used instead of iodobenzene (**113a**).

The Pd(II)-catalyzed C-H arylation of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**111e**) with iodobenzene (**113a**) in solvents, such as 1,4-dioxane or MeCN did not improve the yield of the bis C-H arylated cyclobutanecarboxamide **114a** (entries 3 and 4, Table 5). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** in the presence of $Pd(OAc)_2$ and AgOAc in toluene at 110 °C afforded the bis-arylated cyclobutanecarboxamide **114a** in 94% yield as a single diastereomer (entry 5, Table 5). Employing $Pd(PPh_3)_4$ as a catalyst instead of $Pd(OAc)_2$ did not give the bis-arylated cyclobutanecarboxamide **114a** (entry 6, Table 5) andtheC-H arylation of cyclobutanecarboxamide **111e** using other Pd catalysts instead of $Pd(OAc)_2$ afforded the bis-arylated cyclobutanecarboxamide **114a** in 69-73% yields(entries 7-10, Table 5).

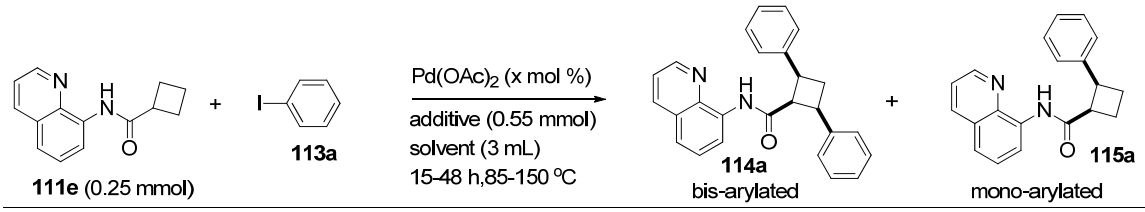
The Pd(II)-catalyzed C-H arylation reaction of cyclobutanecarboxamide **111e** with **113a** in the presence of other additives, such as $PhI(OAc)_2$, KOAc and $Cu(OAc)_2$ afforded the bis-arylated cyclobutanecarboxamide **114a** in low yields or traces (entries 11-13, Table 5). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** with **113a** in the presence of

Ag_2CO_3 additive instead of AgOAc additive gave the bis-arylated cyclobutanecarboxamide **114a** in 68% yield (entry 14, Table 5). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** with bromobenzene (**113b**) or chlorobenzene (**113c**) instead of iodobenzene (**113a**) did not afford the bis-arylated cyclobutanecarboxamide **113a** (entry 15, Table 5).

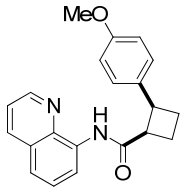
For gaining an insight regarding how many equivalents of phenyl iodide are required for producing the mono arylated cyclobutanecarboxamide**115a**or the bis arylated cyclobutanecarboxamide **114a**, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** was performedby varying the amounts of the aryl iodide **113a** (Table 6). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** with one equivalent or more than one equivalent of iodobenzene (**113a)** gave only the bis-arylated cyclobutanecarboxamide **114a**(entries 1-5, Table 6). The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** with 0.75 equivalent of iodobenzene (**113a**) afforded both the bis arylated cyclobutanecarboxamide **114a** (11%) and the mono arylated cyclobutanecarboxamide **115a** (33%) (entry 6, Table 6). The Pd(II)-catalyzed C-H arylation reaction of cyclobutanecarboxamide **111e** with only 0.5 equivalent of iodobenzene (**113a**) in toluene selectively afforded the mono arylated cyclobutanecarboxamide **115a** in 20% yield (entry 7, Table 6). Increasing the reaction period from 15 h to 48 h did not improve the yield of the arylated cyclobutanecarboxamide(entry 8, Table 6). Next, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** with 0.5 equivalent of iodobenzene using 15 mol% of $Pd(OAc)_2$ loading also afforded the mono arylated cyclobutanecarboxamide **115a** in 35% yield (entry 9, Table 6).

Furthermore, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111e** was performed by changing the reaction conditions and however, attempts to get the mono-arylated cyclobutanecarboxamide **115a** in good yields were not successful (entries 10-13. Table 6). Finally, using the best reaction conditions (entries 8 and 9) described in Table 6, the few other mono arylated cyclobutanecarboxamide**s 115b**, **115c** and **115d** were synthesized (Table 6).

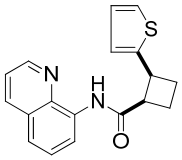
Table 6. Mono- or bis C-H arylation of **111e**.[a]



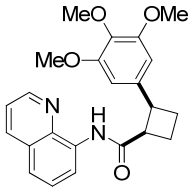
entry	phenyl iodide **113a** (mmol)	ratio of **111e** : **113a**	$Pd(OAc)_2$ (x mol %)	additive	solvent	temp (°C)	time (h)	**114a**: yield (%)[a]	**115a**: yield (%)[a]
1	1.5	1 : 6	5	AgOAc	toluene	110	15	98	0
2	1.0	1 : 4	5	AgOAc	toluene	110	15	94	0
3	0.75	1 : 3	5	AgOAc	toluene	110	15	78	0
4	0.5	1 : 2	5	AgOAc	toluene	110	15	63	0
5	0.25	1 : 1	5	AgOAc	toluene	110	15	49	traces
6	0.187	1 : 0.75	5	AgOAc	toluene	110	15	11	33
7	0.125	1 : 0.5	5	AgOAc	toluene	110	15	traces	20
8	0.125	1 : 0.5	5	AgOAc	toluene	110	48	0	22
9	0.125	1 : 0.5	15	AgOAc	toluene	110	48	0	35
10	0.125	1 : 0.5	15	AgOAc	*p*-xylene	140	48	0	18
11	0.125	1 : 0.5	15	AgOAc	mesitylene	150	48	0	20
12	0.125	1 : 0.5	15	Ag_2CO_3	toluene	110	48	0	19
13	0.125	1 : 0.5	15	Ag_2CO_3	^{t}BuOH	85	48	0	10



115b; (42%)[c]
115b; (30%)[b]



115c; (42%)[b]

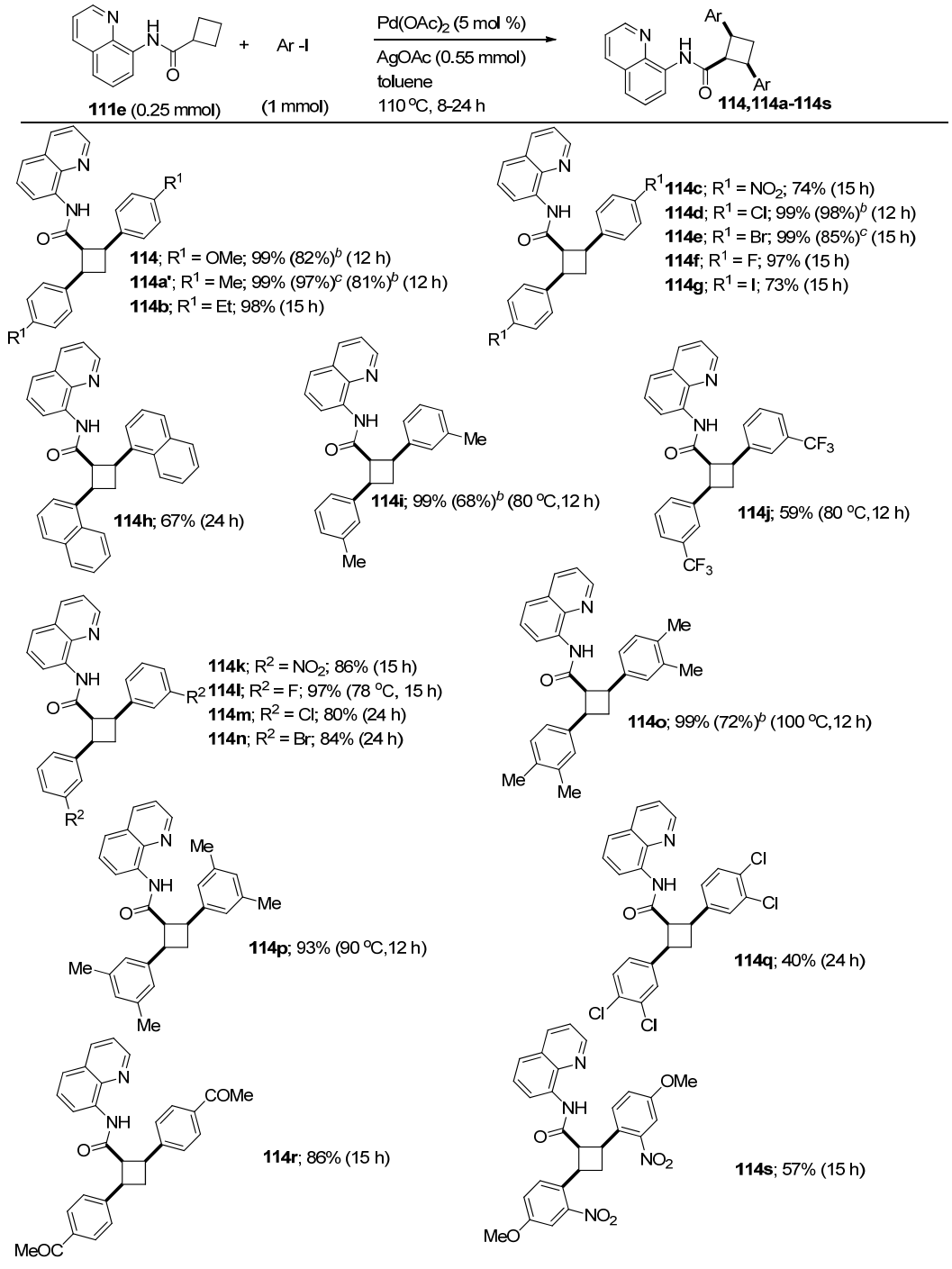


115d; (32%)[c]

[a]All the reactions were performed under a nitrogen atm.[b] The reaction was performed using 5 mol% of catalyst (entry 8).[c] The reaction was performed using 15 mol% of catalyst (entry 9).

Having done the optimization reactions, it was envisaged to explore the generality and scope of this directing group-aided Pd(II)-catalyzed double C-H activation and bis arylation of cyclobutanecarboxamides (Table 7). The Pd(II)-catalyzed arylation of methylene C-H bonds of cyclobutanecarboxamides **111e** with *para*-substituted aryl iodides containing electron-withdrawing and donating groups afforded the corresponding arylated cyclobutanecarboxamides **114, 114a'-114g** in 73-99% yields.

Table 7. Pd(II)-catalyzed double C-H arylation of **111e** and stereoselective synthesis of trisubstituted cyclobutanes[a]



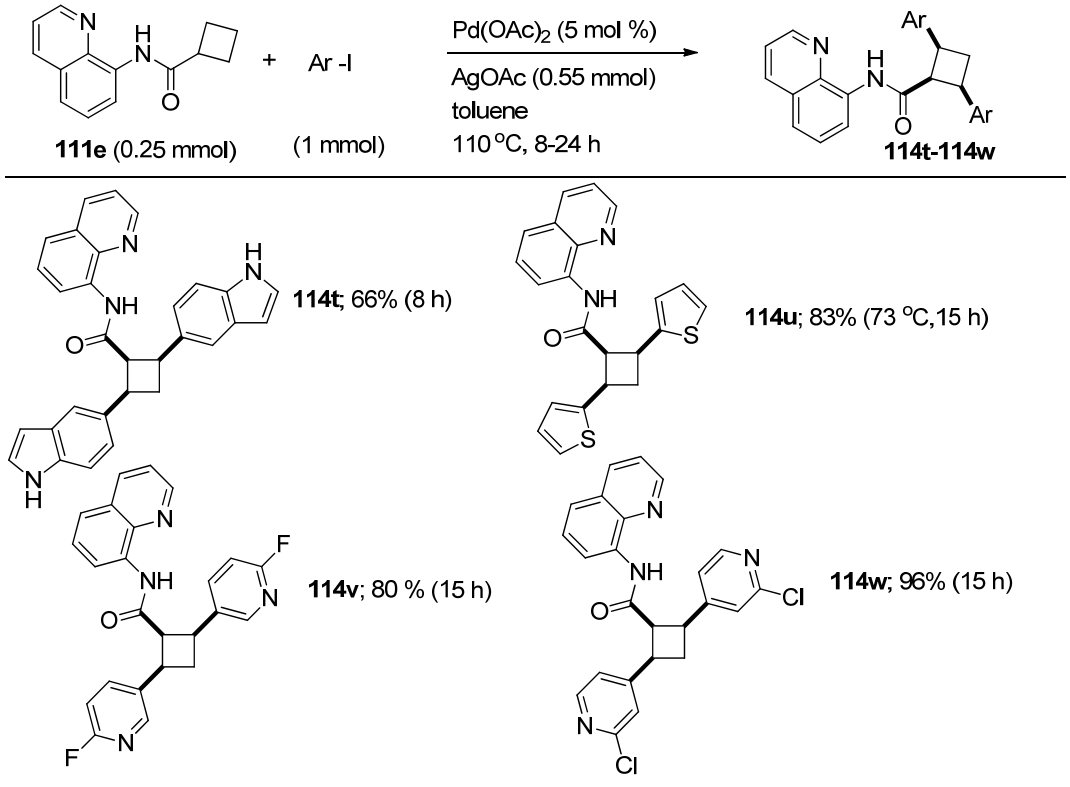
[a] All the reactions were performed under a nitrogen atm. The yields were calculated based on **111e**. [b] The reaction was performed using 1.7 mol% of $Pd(OAc)_2$. [c] The reaction was performed using 3 mol% of $Pd(OAc)_2$.

Next, the Pd(II)-catalyzed arylation of cyclobutanecarboxamide **111e** with aryl iodides, such as 1-iodonaphthalene, 1-iodo-3-methylbenzene and 1-iodo-3-(trifluoromethyl)benzene afforded the corresponding arylated cyclobutanecarboxamides **114h-114j** in 59-99% yields. Then, the Pd(II)-catalyzed arylation of cyclobutanecarboxamide of **111e** with *meta*-

substituted aryl iodides containing electron-withdrawing groups afforded the corresponding arylated cyclobutanecarboxamides **114k-114n** in 80-97% yields.

Next, the Pd(II)-catalyzed bis C-H arylation of the cyclobutanecarboxamide **111e** with various disubstituted aryl iodides and 1-(4-iodophenyl)ethanone afforded the arylated cyclobutanecarboxamides **114o-114s** (Table 7). In some cases, the C-H arylation reactions of cyclobutanecarboxamide **111e** were performed using 3 mol% of $Pd(OAc)_2$, which also afforded the corresponding bis-arylated cyclobutanecarboxamides **114a'**and **114e** in 97 and 85% yields (Table 7). The Pd(II)-catalyzed C-H arylation of **111e** in the presence of only 1.7 mol% of $Pd(OAc)_2$ also afforded the corresponding bis-arylated cyclobutanecarboxamides **114** (82%), **114a'** (81%), **114d** (98%), **114i** (68%),and **114o** (72%) in good yields (Table 7).

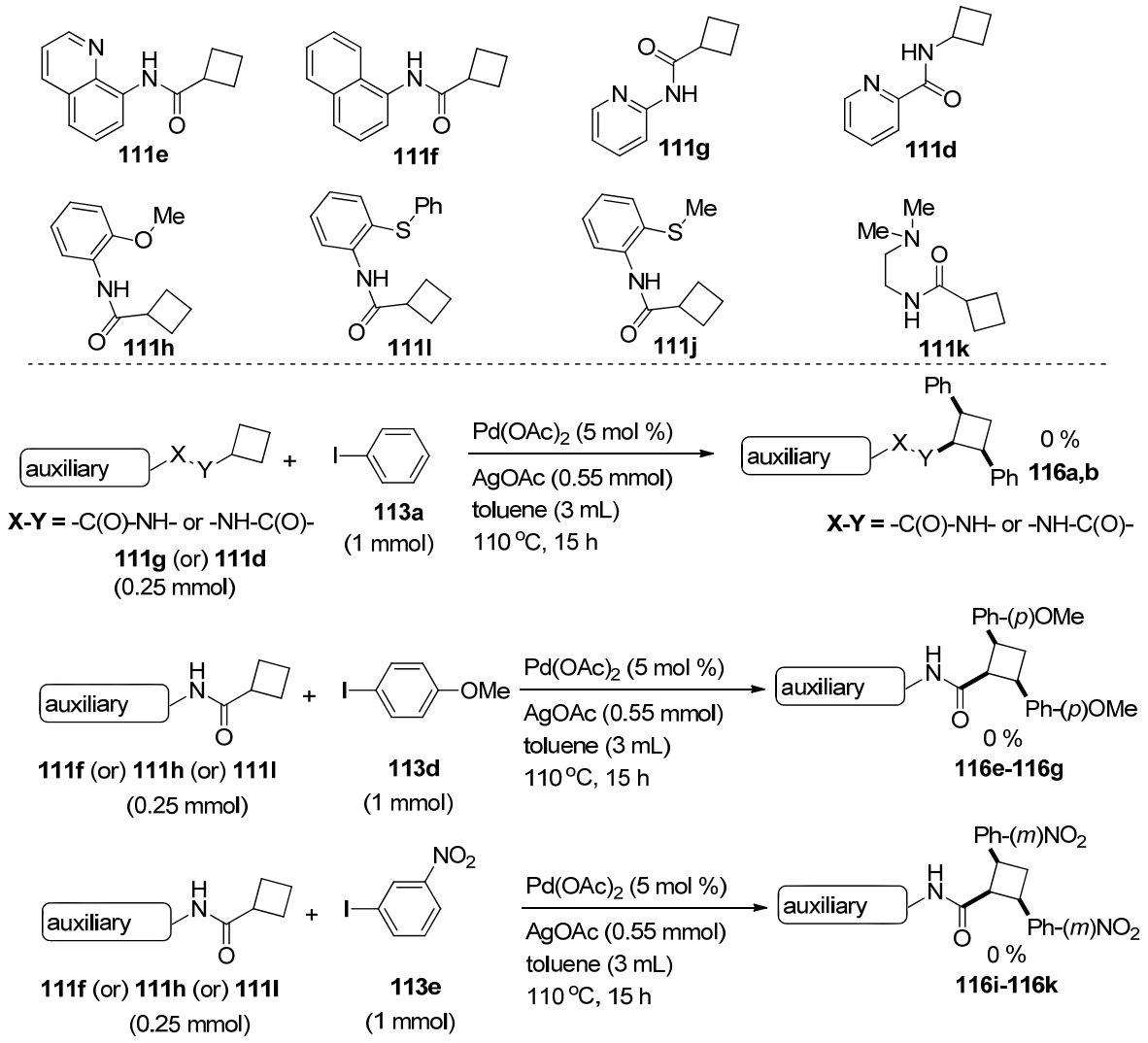
Table 8. Pd(II)-catalyzed double C-H arylation of **111e** and stereoselective synthesis of trisubstituted cyclobutanes.



[a] All the reaction were done under nitrogen atmosphere. The yields denoted here were calculated based on the starting compound **111e**.

Next, it was envisaged to perform the Pd(II)-catalyzed double C-H activation and bis-arylation of $C(sp^3)$-H bond of cyclobutanecarboxamides using heteroaryl iodides (Table 8). The Pd(II)-catalyzed double C-H arylation of cyclobutanecarboxamide **111e** with heteroaryl iodides afforded the trisubstituted cyclobutanecarboxamide scaffolds **114t-114w** in good to

excellent yields (66-96%) (Table 8). It is noteworthy to mention that all the Pd(II)-catalyzed double C-H activation and bis-arylation of C(sp^3)-H bond of cyclobutanecarboxamide with aryl iodides selectively gave the 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamides having three contiguous stereocenters with a high degree of stereo- and regiocontrol. The stereochemistry of the 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamides **114**, **114a'-114w** (Table 7 and 8) was assigned based on the X-ray structure analysis of the representative trisubstituted cyclobutanecarboxamides **114a'**, **114d**, **114e** and **114k**.

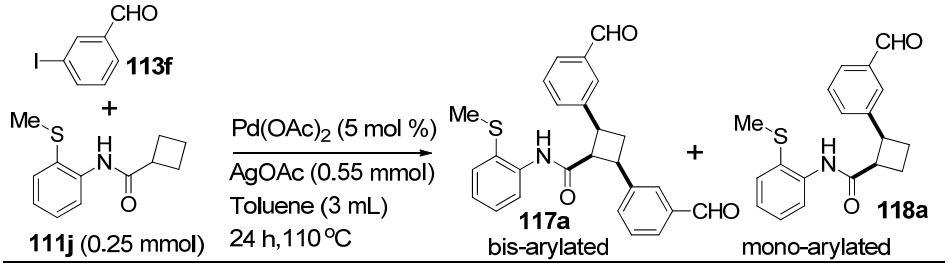


Scheme 35. screening of various auxiliaries for the C-H Activation of cyclobutane.

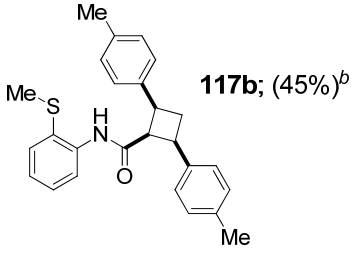
Having done the Pd(II)-catalyzed bis-arylation reactions of cyclobutanecarboxamide **111e** using 8-aminoquinoline as the directing group, next a variety of cyclobutanecarboxamides **111d-111k** were prepared by linking cyclobutanecarbonyl chloride with various other directing groups (Scheme 35). Then, the cyclobutanecarboxamides **111d-111k** were

subjected to the Pd(II)-catalyzed bis-arylation reactions. The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamides **111f-111l** did not afford the expected bis arylated cyclobutanecarboxamides. The reason for the failure of arylations of substrates **111f-111l** may be that the corresponding directing groups linked with the cyclobutanecarboxamides **111f-111l** have not aided the C-H functionalization of the cyclobutane ring. However, the Pd(II)-catalyzed C-H arylations of *N*-(2-(methylthio)phenyl)cyclobutanecarboxamide (**111j**), which was prepared from the directing group 2-(methylthio)aniline) with various aryl iodides were found to afford the arylated cyclobutanecarboxamides. In this regard, initially, the C-H arylation of **111j** was investigated by varying the equivalents of **113f** (Table 9).

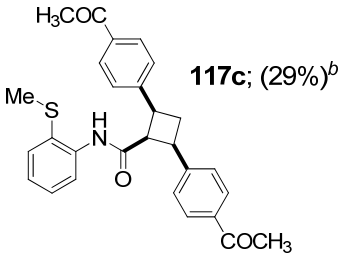
Table 9. Pd(II)-catalyzed C-H arylation **111j**.



entry	aryl iodide **113f** (mmol)	ratio of **111j** : **113f**	**117a**: yield (%)[a]	**118a**: yield (%)[a]
1	1.0	1 : 4	52	0
2	0.5	1 : 2	37	0
3	0.25	1 : 1	20	0
4	0.125	1 : 0.5	0	0



117b; (45%)[b]

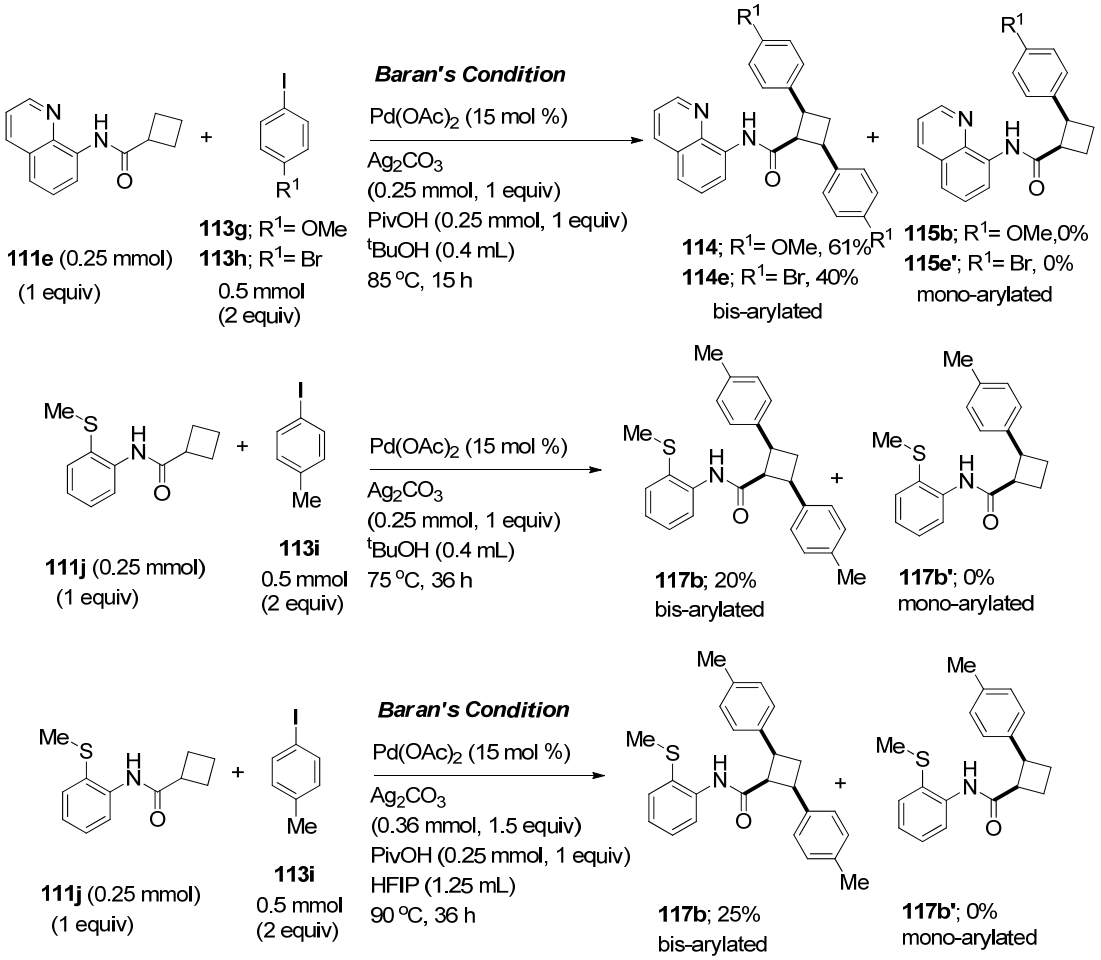


117c; (29%)[b]

[a] All the reactions were performed under a nitrogen atm. The yields were calculated based on the starting compound **111j**. [b] The reaction was performed using the reaction condition given for entry 1.

The Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111j** with one equivalent or more than one equivalent of 3-iodobenzaldehyde (**113f**) gave only the bis arylated product **117a**(entries 1-3, Table 9). Similarly, further examples of the bis-arylated cyclobutanecarboxamides **117b** and **117c**possessingthe1,2-*cis*, 1,3-*cis* and 2,3-*cis*

stereochemistry were synthesized (Table 9).[37] When compared to the cyclobutanecarboxamide **111e**, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111j** afforded relatively low yields of the bis C-H arylated cyclobutanecarboxamides **117a**, **117b-117c**. However, unlike the cyclobutanecarboxamide **111e**, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111j** with 0.5 equivalent of 3-iodobenzaldehyde (**113f**) failed to afford the mono C-H arylated cyclobutanecarboxamide **118a** (entry 4, Table 9). Under the experimental conditions of used in this work, the Pd(II)-catalyzed C-H arylation of the cyclobutanecarboxamides **111j** or **111e**with one equivalent of an aryl iodide afforded only the bis C-H arylated cyclobutanecarboxamidesas the major compounds.



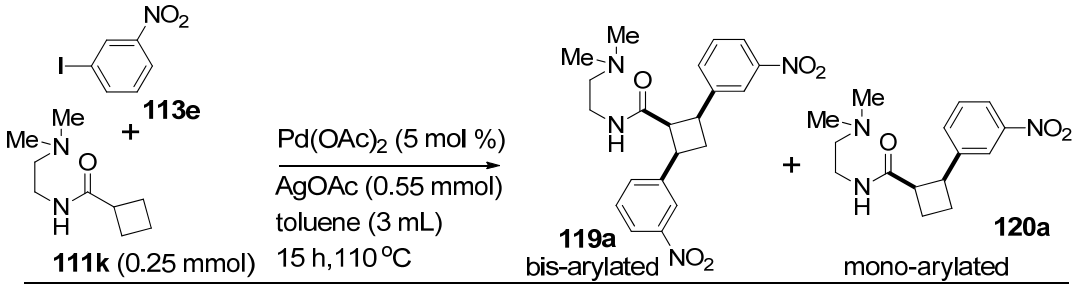
Scheme 36. Trials performed to obtain the mono arylation of **111e** and **111j** using the Baran's reaction conditions.

Consequently, it was envisaged to test the fate of cyclobutanecarboxamides **111j** and **111e** under the Baran's reaction conditions. Accordingly, the Pd(II)-catalyzed C-H arylation reactions of the cyclobutanecarboxamide **111e** and **111j** under the mono C-H arylation reaction conditionsreported by the Baran's group for the Pd(II)-catalyzed C-H arylation of

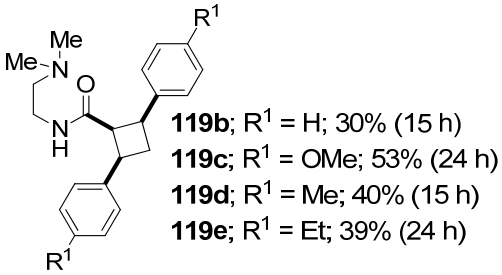
Baran's cyclobutanecarboxamide. However, our attempts afforded only the bis C-H arylated cyclobutanecarboxamides **114, 114e** and **115a** as the single isomers (Scheme 36) and the mono C-H arylated cyclobutanecarboxamides **115b**, **115e'** and **117b'** were not obtained (Scheme 36). The reason for formation of only the respective bis C-H arylated cyclobutanecarboxamides **114, 114e** and **117b**fromthecyclobutanecarboxamides **111e** and **111j** may be due to the substituent present on the cyclobutane ring. The Baran's cyclobutanecarboxamidehas a functional group (carboxylic acid ester group) in the third position of the cyclobutane ring and hence, the double C-H arylation reaction of cyclobutanecarboxamidemight be a less favoured due to the steric hindrance of aryl groups (if two aryl groups are introduced in the cyclobutane ring). However, the cyclobutanecarboxamidesinvestigated in this work, such as **111e**, **111j** and **111k** do not have any substituent or functional groups at the third position of the cycobutane ring when compared to the Baran's cyclobutanecarboxamide. Hence, the double C-H arylations of the cyclobutanecarboxamides **111e**, **111j** and **111k** have occurred in a facile manner.

Subsequently, it was envisaged to elaborate the scope of this Pd(II)-catalyzed C-H arylation protocol using *N*-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (**111k**), which was prepared from an aliphatic directing group, *N',N'*-dimethylethane-1,2-diamine and cyclobutanecarbonyl chloride. The Pd(II)-catalyzed C-H arylation of *N*-(2-(dimethylamino)ethyl)-cyclobutanecarboxamide (**111k**)using either one equivalent or more than one equivalent of 1-iodo-3-nitrobenzene (**113e**) selectively afforded the bis C-H arylated cyclobutanecarboxamide **119a** (entries 1-5, Table 10). It is to be noted that these reactions did not give any traces of the mono C-H arylated cyclobutanecarboxamide 1**20a** (entries 1-5, Table 10). However, unlike the cyclobutanecarboxamide **111e**, the Pd(II)-catalyzed C-H arylation of cyclobutanecarboxamide **111k** with 0.5 equivalent of iodo-3-nitrobenzene (**113e**) did not give the mono C-H arylated cyclobutanecarboxamide **120a** (entry 6, table 10). Then, the Pd(II)-catalyzed C-H arylations of C(sp^3)-H bonds of cyclobutanecarboxamide **111k** using different aryl iodides and heteroaryl iodides were performed, which afforded various 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamides **119a, 119b-119n** with a high degree of stereo- and regiocontrol (Table 10).

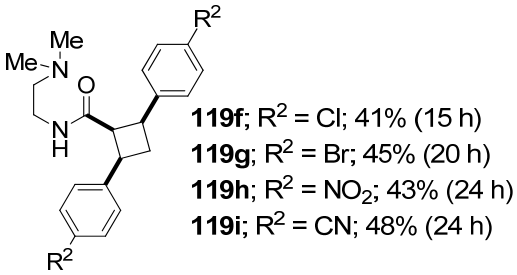
Table 10. Pd(II)-catalyzed C-H arylation of *N*-(2 (Dimethylamino)ethyl) cyclobutanecarboxamide.



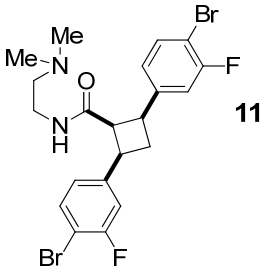
entry	aryl iodide **113e** (mmol)	ratio of **111k** : **113e**	**119a**: yield (%)[a]	**120a**: yield (%)[a]
1	1.5	1 : 6	56	0
2	1.0	1 : 4	45	0
3	0.75	1 : 3	34	0
4	0.5	1 : 2	24	0
5	0.25	1 : 1	10	0
6	0.125	1 : 0.5	0	0



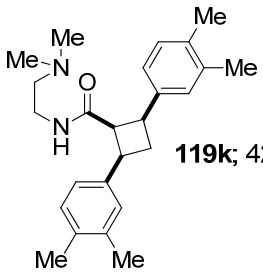
119b; R^1 = H; 30% (15 h)
119c; R^1 = OMe; 53% (24 h)
119d; R^1 = Me; 40% (15 h)
119e; R^1 = Et; 39% (24 h)



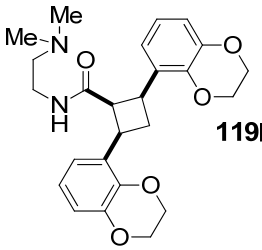
119f; R^2 = Cl; 41% (15 h)
119g; R^2 = Br; 45% (20 h)
119h; R^2 = NO_2; 43% (24 h)
119i; R^2 = CN; 48% (24 h)



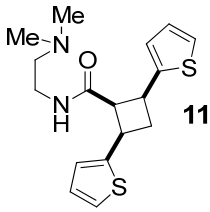
119j; 53% (24 h)



119k; 42% (100 °C, 24 h)



119l; 41 % (24 h)



119m; 30% (73 °C, 24 h)

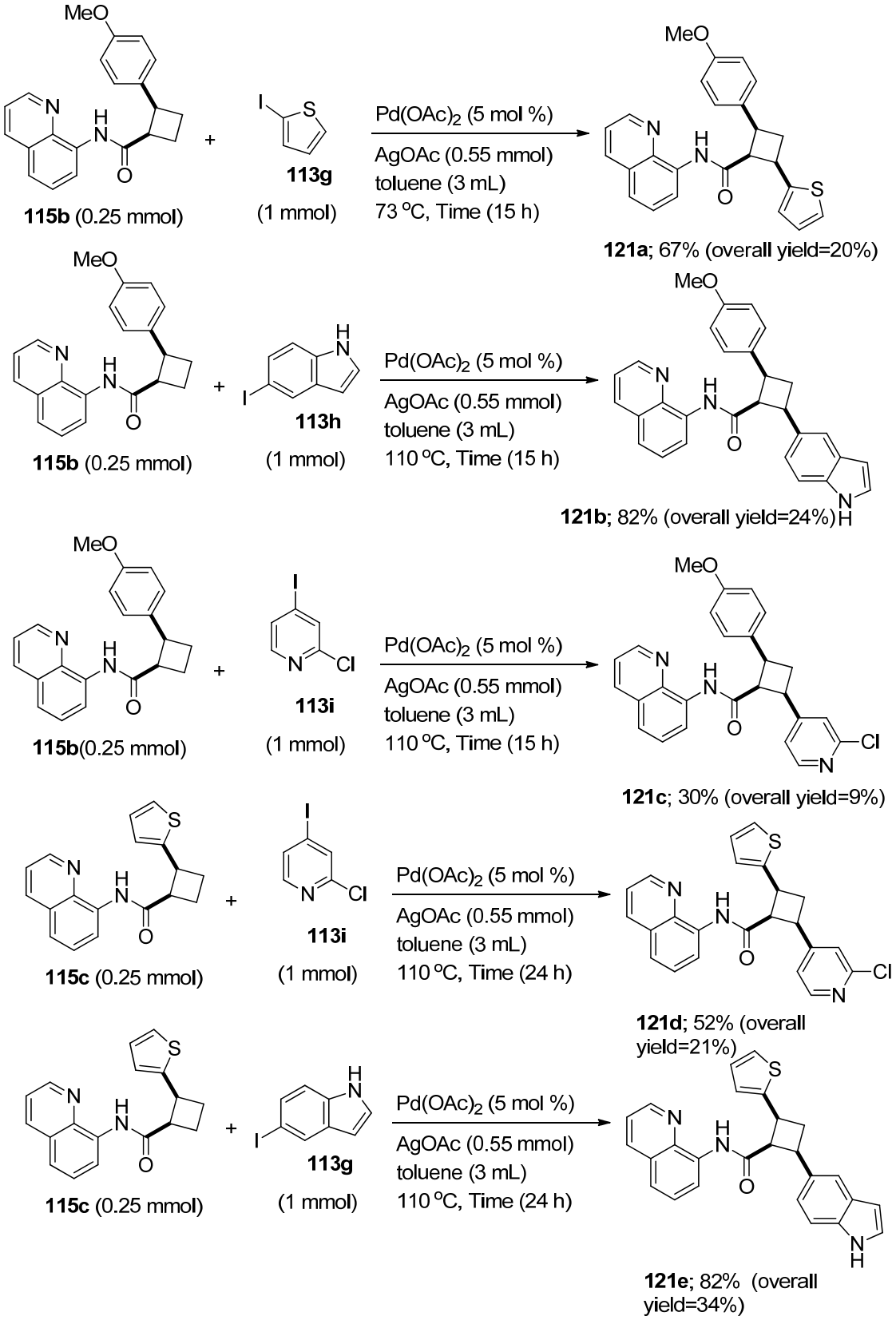
[a] All the reactions were performed under a nitrogen atm. The yields were calculated based on the **111k**. [b] The preparation of the compounds **119b-119m** was carried out using the reaction conditions given for 'entry 2'.

Noticeably, the Pd(II)-catalyzed double C-H activation and bis-arylation of C(sp^3)-H bond of cyclobutanecarboxamide with aryl iodides selectively gave the 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamides having three contiguous stereocenters with a high

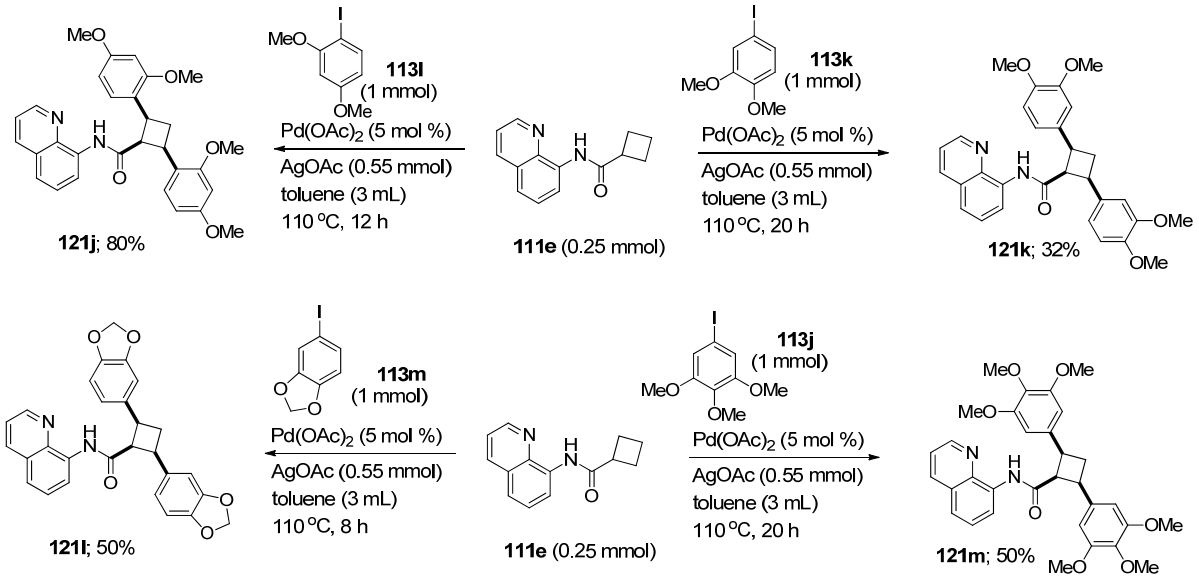
degree of stereo- and regiocontrol. The stereochemistry of the cyclobutanecarboxamides **119a, 119b-119n** (Table 10) was assigned based on the X-ray structure analysis of the representative arylated cyclobutanecarboxamides **119a** and **119f**.

Next, it was envisaged to attempt the Pd(II)-catalyzed C-H second arylation of the mono arylated cyclobutanecarboxamides **115b** and **115c**with heteroaryl iodides **113g**, **113h** and **113i**. Accordingly, the Pd(II)-catalyzed C-H second arylation of the mono arylated cyclobutanecarboxamides **115b** and **115c**with heteroaryl iodides **113g**, **113h** and **113i**.in the presence of $Pd(OAc)_2$ catalyst and AgOAc afforded the corresponding trisubstituted cyclobutanecarboxamides 1**21a-121e** having two different aryl groups in30-82% yields. The stereochemistry of the arylated cyclobutanecarboxamides 1**21a-121e** (Scheme 37) was assigned based on the X-ray structure analysis of the representative arylated cyclobutanecarboxamides **114a'**, **114d**, **114e** and **114k** and the similarity in their ^{1}H NMR spectral pattern. Additionally, it was envisaged to construct trisubstituted cyclobutanecarboxamide frameworks analogous to the naturally occurring cyclobutanecarboxamides shown in Figure 3 (Scheme 38). In this line, initially, the Pd(II)-catalyzed C-H arylation of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**111e**) with aryl iodides **113i-k, 113m** selectively afforded the corresponding bis C-H arylated cyclobutanecarboxamide frameworks**121j**, 1**21k**, 1**21l** and 1**21m** having an all *cis*-stereochemistry (Scheme 38).

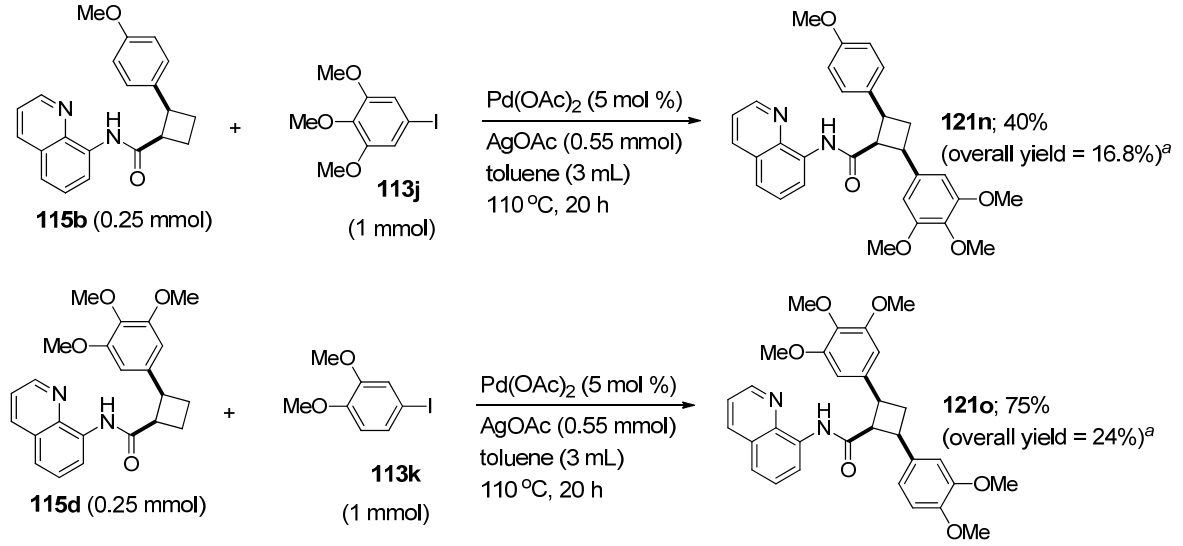
Along this line, the C-H arylation of the mono C-H arylated cyclobutanecarboxamides **115b** and **115d**with aryl iodides **113j** and **113k** in the presence of the catalyst $Pd(OAc)_2$ and AgOAc additive afforded the corresponding trisubstituted cyclobutanecarboxamides 1**21n** (40%) and 1**21o** (75%), which are structurally analogous to some of the naturally occurring cyclobutanecarboxamides with respect to the aryl groups (Scheme 39 and Figure 3). It was also envisaged to elaborate the scope of this Pd(II)-catalyzed C-H activation of cyclobutanecarboxamide **111e** using alkyl iodides as the coupling partners. Accordingly, the Pd(II)-catalyzed C-H functionalization of cyclobutanecarboxamide **111e** using different alkyl iodides **122a, 122b-d** were performed under various reaction conditions.
However, all the attempts failed to give the expected mono- or bis C-H alkylated cyclobutanecarboxamide, e.g., **123a**, **123b**, **123c** and **123d** (Scheme 40).



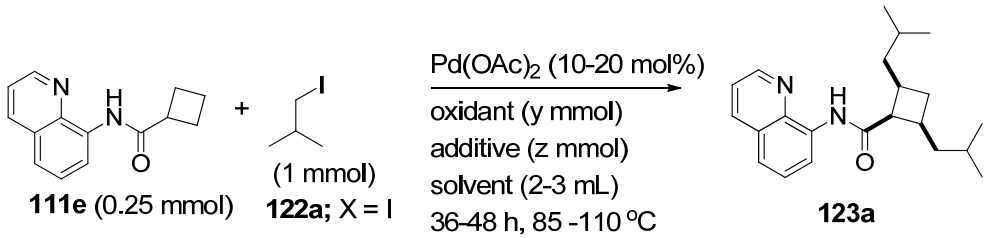
Scheme 37. Synthesis of cyclobutane derivatives analogous to cyclobutane natural products.(The overall yields were calculated for the reaction of the starting material **111e** converting in to the corresponding bis-arylated products).



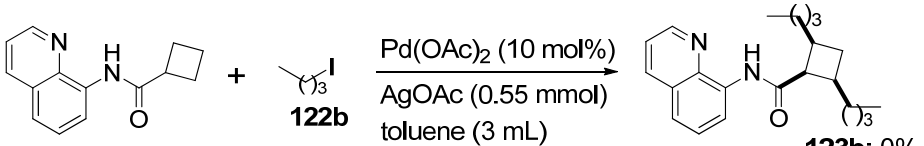
Scheme 38. Synthesis of cyclobutane derivatives analogous to cyclobutane natural products. (The overall yields were calculated for the reaction of **111e** converting into the corresponding bis-arylated products).

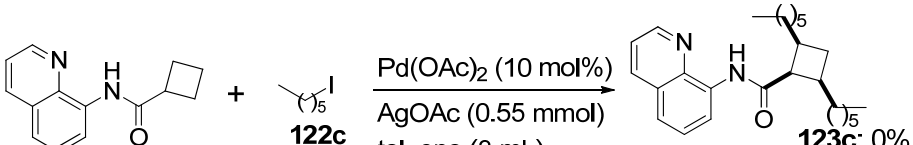


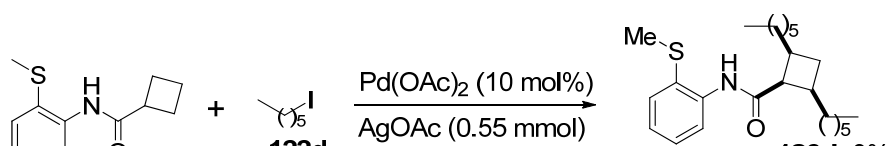
Scheme 39. Synthesis of cyclobutane derivatives analogous to cyclobutane natural products.(The overall yields were calculated for the reaction of the starting material **111e** converting in to the corresponding bis-arylated products).



entry	$Pd(OAc)_2$ (mol%)	oxidant (y mmol)	additive (z mmol)	solvent (mL)	temp (°C)	time (h)	**123a**:yield (%)[a]
1	$Pd(OAc)_2$ (10)	AgOAc (0.55)	none	toluene	110	48	0
2	$Pd(OAc)_2$ (15)	AgOAc (0.55)	none	toluene	110	36	0
3	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	none	toluene	110	36	0
4	$Pd(OAc)_2$ (15)	AgOAc (0.55)	PivOH (0.25)	toluene	110	36	0
5	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	traces
6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	PivOH (0.25)	t-BuOH	85	48	0
7	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	PivOH (0.25)	t-BuOH	85	48	0
8	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	Ag_3PO_4 (0.25)	t-BuOH	85	48	0
9	$Pd(OAc)_2$ (20)	Ag_2CO_3 (0.25)	Ag_3PO_4 (0.25)	toluene	110	48	0
10[b]	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	0
11[c]	$Pd(OAc)_2$ (15)	Ag_2CO_3 (0.25)	PivOH (0.25)	toluene	110	48	0

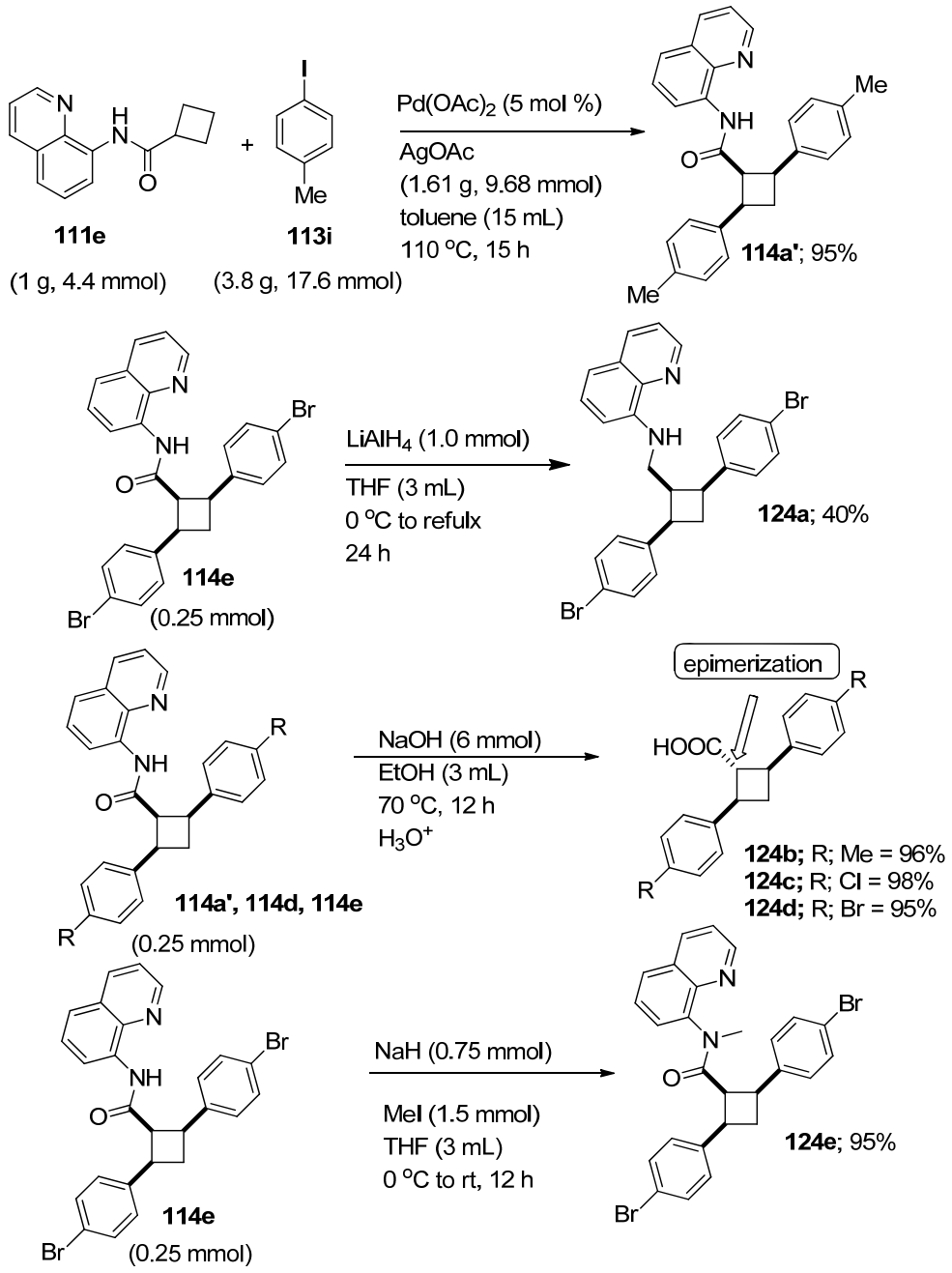






[a] All the reaction were done under nitrogen atmosphere. [b] In this case, 1.5 mmol of **122a** was used. [c] The reaction was carried out in the open atmosphere.

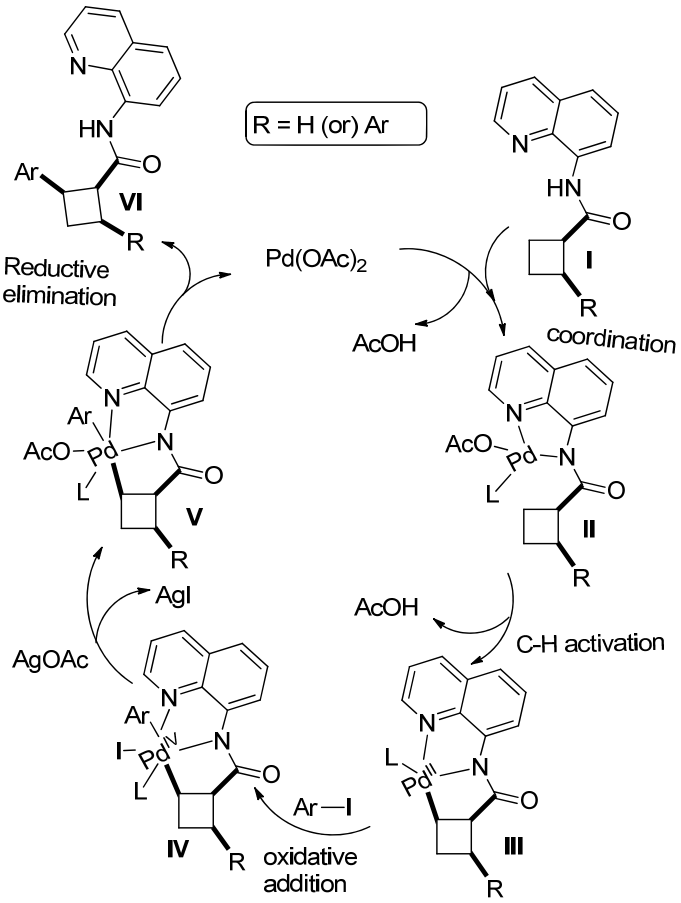
Scheme 40. Trials on the C-H alkylation of cyclobutanecarboxamide **111e**.



Scheme 41. Gram scale double C-H arylation of **111e** and synthetic transformations.

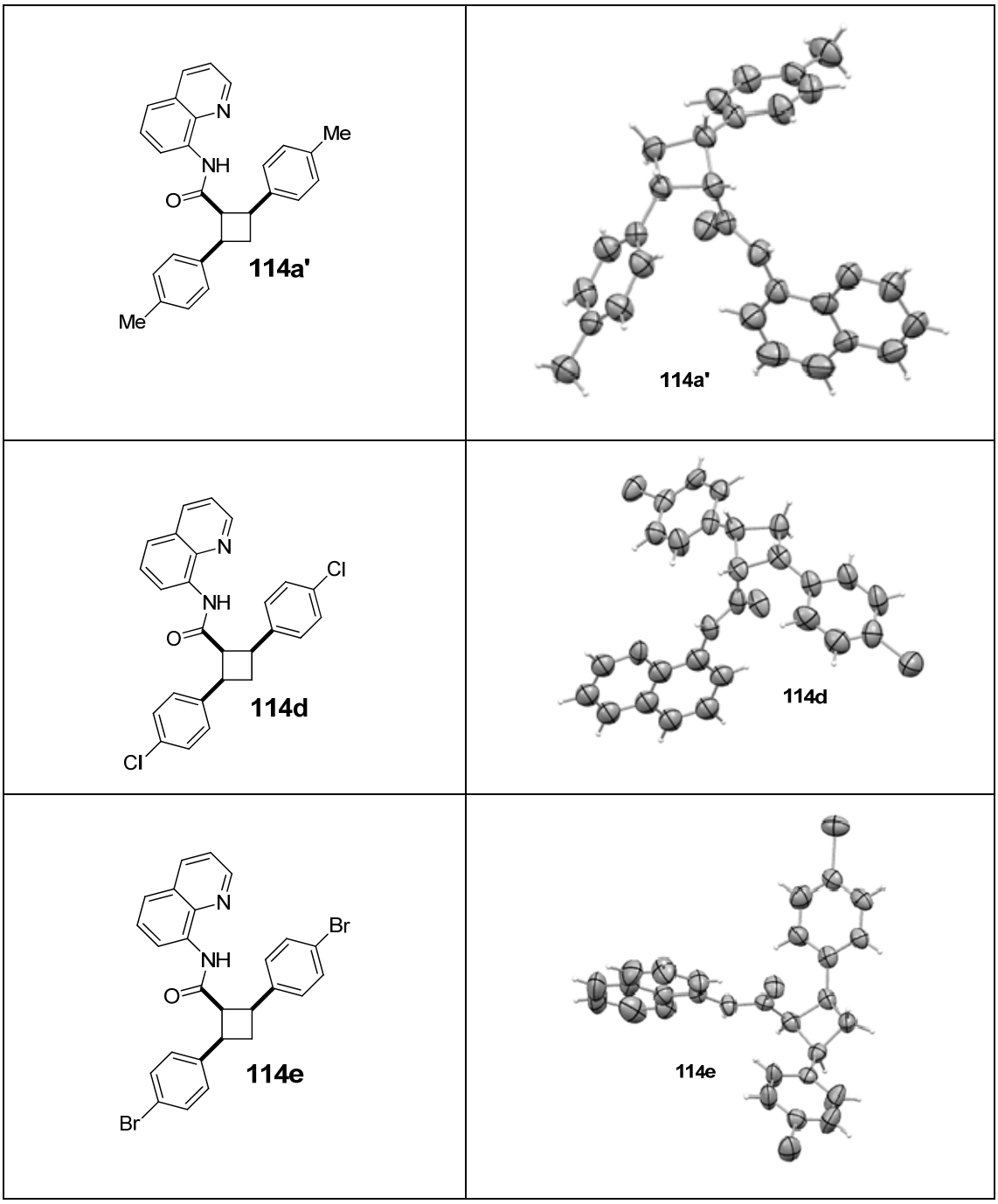
To divulge the synthetic utility of this method, the Pd(II)-catalyzed direct bis C-H arylation of the C-H bonds of the cyclobutanecarboxamide **111e** was performed in a gram scale, which gave the arylated cyclobutanecarboxamide **114a'** in an excellent yield (95%) (Scheme 38). Then, the $LiAlH_4$-mediated reduction of the amide group of a representative arylated cyclobutanecarboxamide **114e** was performed to afford *N*-(((*1s*,2R*,4S**)-2,4-bis(4-bromophenyl)cyclobutyl)methyl)quinolin-8-amine (**124a**). Finally, the base-mediated amide

hydrolysis of the representative arylated cyclobutanecarboxamides **114a'**, **114d** and **114e** afforded the corresponding substituted bis C-H arylated cyclobutanecarboxylic acids **124b-124d** (Scheme 41). The stereochemistry of the cyclobutanecarboxamides 1**24b-124d** was unambiguously established from on the X-ray structure analysis of a representative C-H arylated cyclobutanecarboxylic acid **124c**, which revealed the occurrence of complete epimerization at the carbonyl group containing stereocenter of the cyclobutane systems **114a'**, **114d** and **114e** during the formation of **124b-124d** from the base-mediated hydrolysis of the corresponding cyclobutanecarboxamides **114a', 114d and 114e**. Treatment of the cyclobutanecarboxamides **114e** with NaH followed by MeI afforded the *N*-methylated cyclobutanamide **124e** having an *cis*-sterochemistry similar to the starting material **111e** and we did not observe epimerization in this reaction (Scheme 41). The stereochemistry of the cyclobutanecarboxamide **124e** was unambiguously assigned from on the single crystal X-ray structure analysis.



Scheme 42. Plausible mechanism for the Pd(II)-catalyzed double C-H arylation of cyclobutanecarboxamide.

In concurrence with the studies carried out by Daugulis,[26j] Chen[28d] and a recent report by Charette,[26e] a plausible mechanism for the directing group-directed $Pd(OAc)_2$-catalyzed, AgOAc-promoted double C-H activation and direct C-H arylation of methylene $C(sp^3)$-H bonds of cyclobutanecarboxamides affording mono C-H arylated and bis C-H arylated cyclobutanecarboxamide is shown in the Scheme 42.



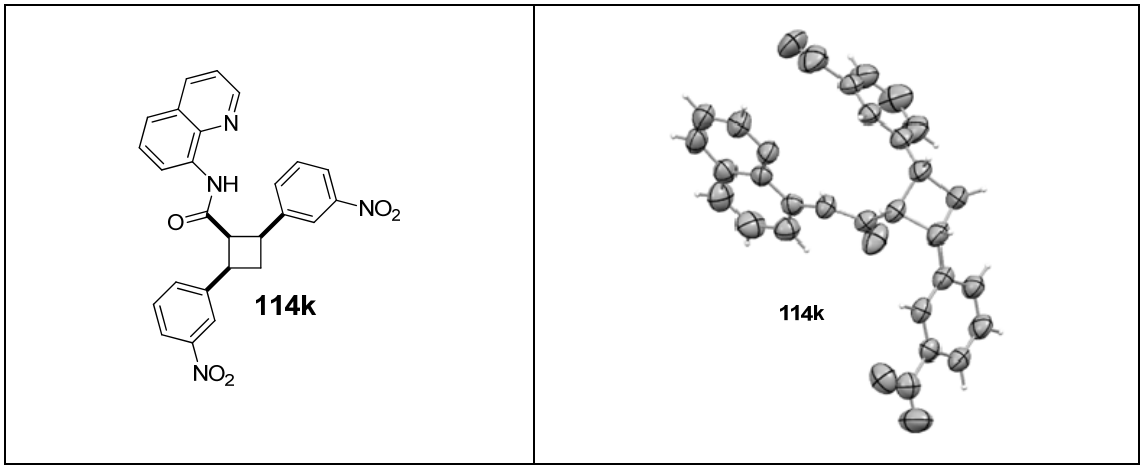
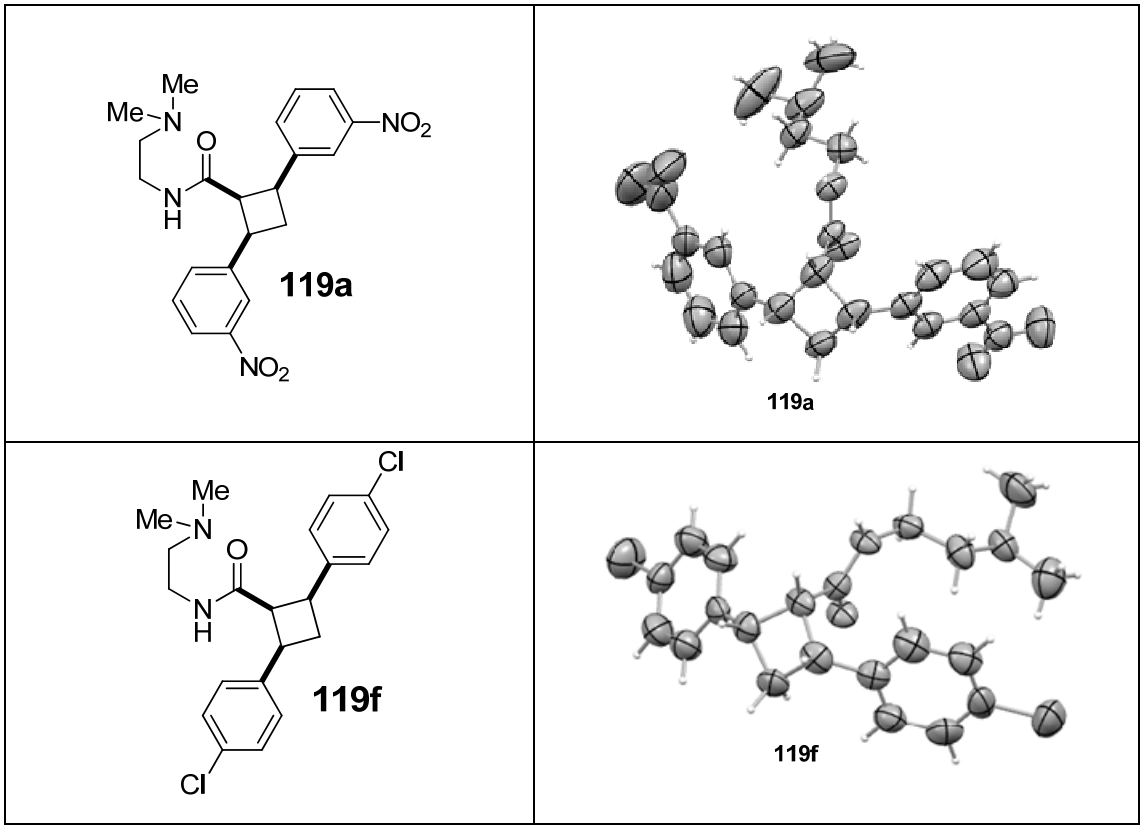


Figure 9. X-ray (ORTEP diagram) structures of the compounds **114a**, **114d, 114e, 114k,119a, 119f**, **124c** and **124e**.



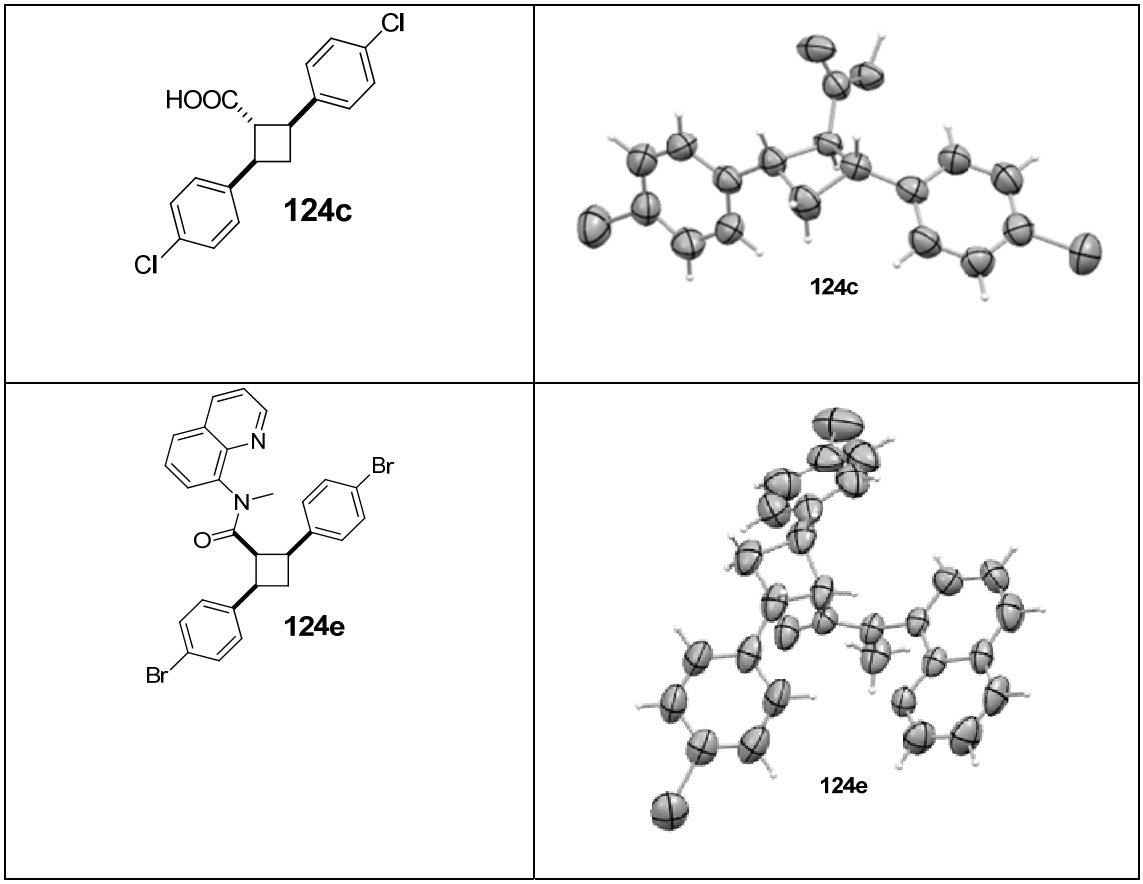
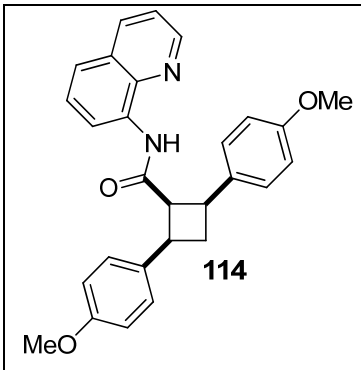
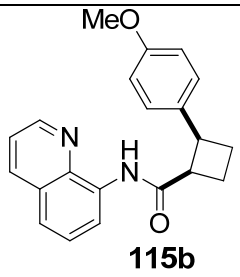
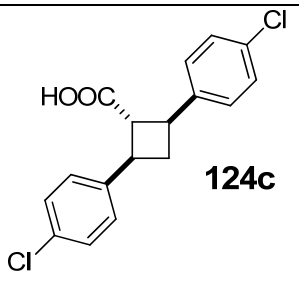


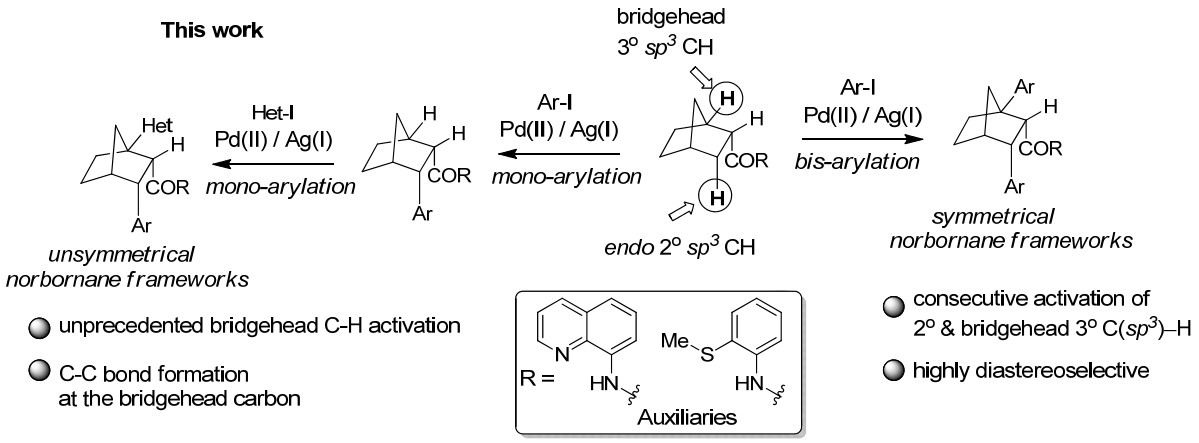
Figure 9. X-ray (ORTEP diagram) structures of the compounds **114a**, **114d, 114e, 114k,119a, 119f**, **124c** and **124e**.

^{1}H Coupling constant values for cyclobutyl ring:

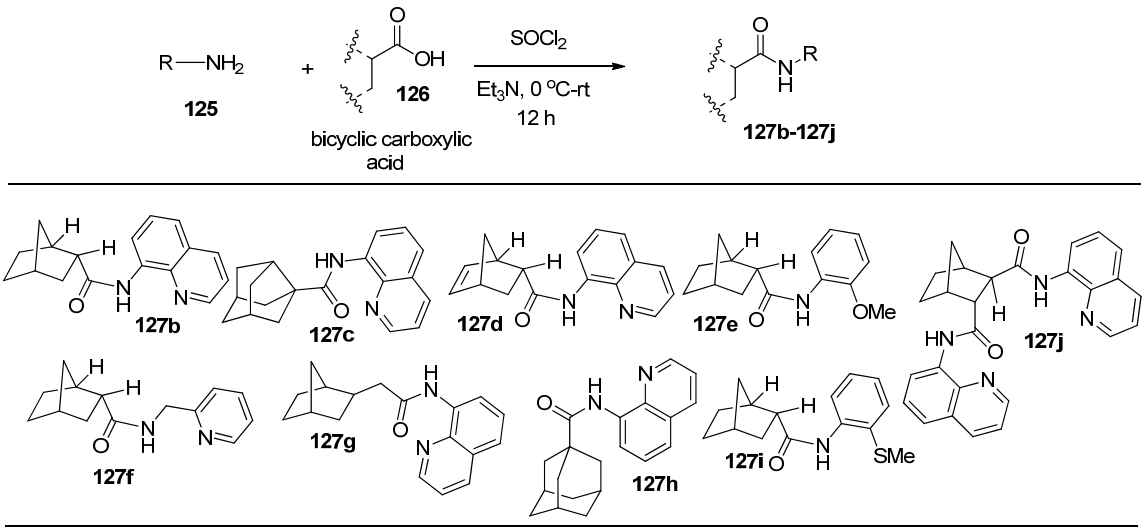
		
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03-3.97 (m, 1H), 3.95-3.90 (m, 2H), 3.43 (dd, 1H, J_1 = 21.5 Hz, J_2 = 11.0 Hz) 2.65-2.61 (m, 1H);	^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (dd, 1H, J_1= 17.8 Hz, J_2= 9.1 Hz), 3.79-3.71 (m, 1H), 3.57 (s, 3H), 2.70-2.63 (m, 2H), 2.43-2.35 (m, 2H);	^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (dd, 2H, J_1 = 18.3 Hz, J_2 = 10.0 Hz), 3.24 (t, 1H, J = 10.0 Hz), 2.84-2.78 (m, 1H), 2.27 (dd, 1H, J_1 = 21.0 Hz, J_2 = 10.0 Hz);

Part 3. Pd(II)-catalyzed double arylation of 2° and 3° C(sp^3)-H bonds of the norbornane systems and regio- and stereoselective construction of functionalizedC-H arylatednorbornane systems *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation.

In continuation of investigations on the construction of C-H arylated/functionalizedcyclopropanecarboxamides and cyclobutanecarboxamides *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation, a part of this thesis work envisaged to synthesize functionalized/arylated norbornane frameworks via the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization/arylation of 2^o and the bridgehead 3^o C(sp^3)-H bonds of norbornanecarboxamides (Scheme 43). A literature survey revealed that there exist only limited reports dealing on the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization/arylation of C(sp^3)-H bonds of norbornanecarboxamides.



Scheme 43. Topic of this work. Regio- and stereoselective C-H arylation of norbornane frameworks.



Scheme 44. Preparation of bicyclic carboxamides systems.

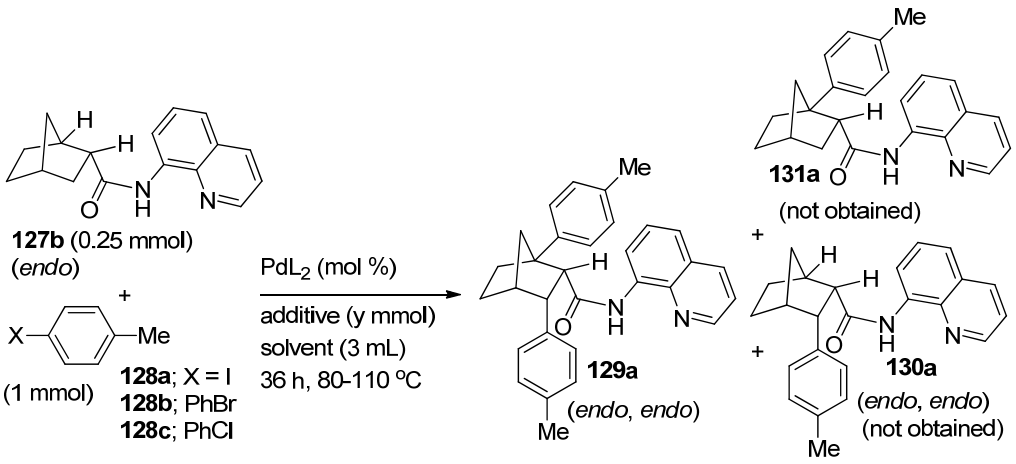
Following the standard literature procedures, initially, the norbornanecarboxamide **127b** (*endo N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide) was assembled from an *endo* bicyclo[2.2.1]heptane-2-carboxylic acid chloride and the directing group, e.g., 8-aminoquinoline. Then, by following the standard literature procedures, various bicyclic carboxamides systems **127c-127j** were also prepared from various directing groups/amines **125** (Scheme 44).To begin the investigation of C-H functionalization of 2° C(sp^3)-H bond and "the bridgehead substitution" via C-H activation and to arrive at the optimized reaction conditions various optimization reactions were performed. Accordingly, Table 11 demonstrates the reaction scheme, which comprised of the Pd(II)-catalyzed C-H arylation of the norbornanecarboxamide **127b** with 1-iodo-4-methylbenzene (**128a**). The reaction of a mixture of the norbornanecarboxamide **127b** (*endo*), aryl iodide **128a** and AgOAc additive with or without the $Pd(OAc)_2$ catalyst (10 mol%) in toluene at 110 °C failed to afford any C-H arylated product (entries 1 and 2, Table 11). Next, Pd(II)-catalyzed the C-H arylation of the norbornanecarboxamide **127b** with **128a** in the presence of Ag_2CO_3 as an additive instead of AgOAc additive in toluene at 110 °C was performed. This reaction afforded the product **129a** (65%, entry 3, Table 11) via the direct bis C-H arylation of both 2° C(sp^3)-H (*endo*) and the bridgehead 3° C(sp^3)-H bonds and it is to be noted that an unprecedented C-C bond formation occurred at the bridgehead carbon of the norbornane system **127b**.

The Pd(II)-catalyzed C-H functionalization of the norbornanecarboxamide **127b** with 1-iodo-4-methylbenzene (**128a**) in the presence of Ag_2CO_3 and the $Pd(OAc)_2$ catalyst (10 mol%) in

tert-butanol afforded the C-H arylated norbornanecarboxamide **129a** with improved yield (70%, entry 4, Table 11). When C-H functionalization of the norbornanecarboxamide **127b** was performed using only 5 mol % of the $Pd(OAc)_2$ catalyst, the product **129a** was obtained in 60% yield (entry 5, Table 11). The Pd(II)-catalyzed C-H arylations of norbornanecarboxamide **127b** with **128a** in the presence of various other additives, such as K_2CO_3, Na_2CO_3, KOAc and $PhI(OAc)_2$ afforded the -H arylated norbornanecarboxamide **129a** in 24-30% yields (entries 6-9, Table 11). The C-H arylations of norbornanecarboxamide **127b** with **128a** using palladium catalysts, such as $PdCl_2$, $Pd(TFA)_2$, $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$ were ineffective (entries 10-13). The C-H arylations of norbornanecarboxamide **127b** with **128a** in the presence of Ag_2CO_3 and the $Pd(OAc)_2$ catalyst (10 mol%) in solvents, such as MeCN, 1,2-DCE, 1,4-dioxane, EtOH, AcOH and *tert*-amyl alcohol were not fruitful (entries 14-19, Table 11). The Pd(II)-catalyzed C-H arylations of the norbornanecarboxamide **127b** with bromobenzene (**128b**) or chlorobenzene (**128c**) were not fruitful (entries 20 and 21, Table 11).

Notably, under the optimized reaction conditions (entries 3 and 4, Table 11), the Pd(II)-catalyzed C-H arylation of norbornanecarboxamide **127b** (1 equiv) with 4 equiv of 1-iodo-4-methylbenzene (**127a**) afforded the arylated norbornanecarboxamide **129a** via the direct bis arylation of both 2^o $C(sp^3)$-H (*endo*) and the bridgehead 3^o $C(sp^3)$-H bonds of norbornanecarboxamide **127b**. It is to be noted that under the experimental conditions, the formation of both the mono- and bis C-H arylated norbornanecarboxamides **130a** or **131a** and **129a**, respectively (Table 11) is expected. However, mono C-H arylated norbornanecarboxamides **130a** or **131a** were not observed under the reaction conditions shown in Table 11.

Table 11. Optimization of reaction conditions. Pd(II)-catalyzed arylation of **127b**.



entry	PdL_2 (mol %)	additive (y mmol)	solvent (3 mL)	*t* (°C)	**129a** yield (%)
1	nil	AgOAc (0.55)	toluene	110	0
2	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	5
3	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	toluene	110	65
4	**$Pd(OAc)_2$ (10)**	**Ag_2CO_3 (0.25)**	**^{t}BuOH**	**85**	**70**
5	$Pd(OAc)_2$ (5)	Ag_2CO_3 (0.25)	^{t}BuOH	85	60
6	$Pd(OAc)_2$ (10)	K_2CO_3 (0.25)	^{t}BuOH	85	0
7	$Pd(OAc)_2$ (10)	Na_2CO_3 (0.25)	^{t}BuOH	85	0
8	$Pd(OAc)_2$ (10)	KOAc (0.25)	^{t}BuOH	85	24
9	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (0.25)	^{t}BuOH	85	30
10	$PdCl_2$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	25
11	$Pd(TFA)_2$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	26
12	$Pd(CH_3CN)_2Cl_2$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	0
13	$Pd(PPh_3)_4$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	0
14	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	CH_3CN	80	11
15	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	1,2-DCE	80	9
16	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	1,4-Dioxane	100	15
17	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	EtOH	80	54
18	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	AcOH	110	0
19	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	^{t}AmylOH	100	40
20[a]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	0
21[b]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	^{t}BuOH	85	0

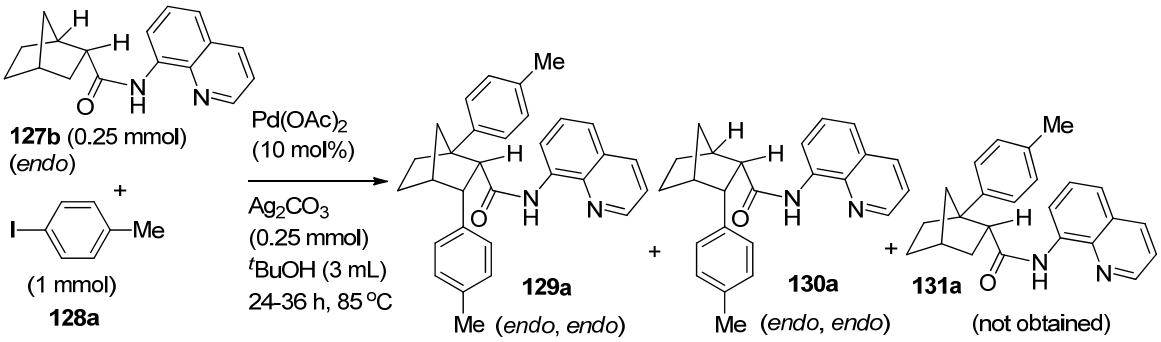
[a] 1-Bromobenzene (**128b**) was used instead of **128a**; the corresponding product was not obtained. [b] 1-Chlorobenzene (**128c**) was used instead of **128a**; the corresponding product was not obtained.

Then, it was decided to further scrutinize the reaction conditions and examine to find out how many equivalents of aryl iodide are required for obtaining only the mono C-H arylated norbornanecarboxamide **130a** or **131a** (Table 12). The Pd(II)-catalyzed C-H functionalization of norbornanecarboxamide**127b** with 2-4 equivalents of 1-iodo-4-methylbenzene (**128a**)

furnished only the bis C-H arylated norbornanecarboxamide**129a** (entries 1-3, Table 12). Then, the Pd(II)-catalyzed C-H functionalization of norbornanecarboxamide **127b** with 1.5 equivalent of aryl iodide (**128a**) afforded the bis C-H arylated norbornanecarboxamide **129a** (6%) and mono C-H arylated norbornanecarboxamide **130a** (40%, entry 4, Table 12). The Pd(II)-catalyzed C-H functionalization of norbornanecarboxamide **127b** with 1 or 0.5 equivalent of 1-iodo-4-methylbenzene (**127a**) in *tert*-butanol selectively gave the mono C-H arylated norbornanecarboxamide system **130a** in 57 and 32% yields, respectively (entries 5 and 6, Table 12). In these reactions, the formation of other expected norbornanecarboxamide **131a** was not observed, which indicated that perhaps the Pd(II)-catalyzed arylation of 2^o C(sp^3)-H bond is relatively easier than the bridgehead 3^o C(sp^3)-H bond of norbornanecarboxamide.

Next, it was envisaged to extend the scope of this protocol to obtain the mono C-H arylated norbornanecarboxamide **130a** (entry 5, Table 12). Accordingly, under the optimized reaction condition (Table 11), the Pd(II)-catalyzed C-H arylations of 2^o C(sp^3)-H (*endo*) bond of the norbornanecarboxamide system **127b** with a variety of aryl iodides afforded the corresponding mono C-H arylated norbornanecarboxamide frameworks **130a-130f** in 49-73% yields (Table 12) with high degree of stereoselectivity. Additionally, under the optimized reaction conditions, the Pd(II)-catalyzed C–H arylations of other norbornanecarboxamide substrates **127c**–**h** and **127j**, which were prepared using various substrates and directing groups were ineffective (Scheme 44). The reason for this may be that the respective directing groups attached to the norbornanecarboxamide system did not direct the Pd(II)-catalyzed C–H arylation of the corresponding norbornane rings of **127c**–**h** and **127j**. In line with the attempts to find out some other working directing groups attached to the norbornanecarboxamide framework, next the Pd(II)-catalyzed arylations of the norbornanecarboxamide **127i** (*endoN*-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide, which was prepared from the directing group, e.g., 2-(methylthio)aniline)) with various aryl iodides were carried out. Under the optimized reaction conditions, the Pd(II)-catalyzed C-H activation and arylation of an *endo* 2^o C(sp^3)-H bond of the norbornanecarboxamide **127i** afforded the mono C-H arylated norbornanecarboxamide systems **132a-c** in 32-36% yields with high stereoselectivity (Table 13).

Table 12. Pd(II)-catalyzed mono- and bis- C-H functionalization of **127b**.



entry	**127b** (mmol)	**128a** (mmol)	ratio **127b** : **128a**	**129a** yield (%)	**130a** yield (%)
1	0.25	1.0	1 : 4	70	0
2	0.25	0.75	1 : 3	50	0
3	0.25	0.5	1 : 2	36	0
4	0.25	0.375	1 : 1.5	6	40
5	0.25	0.25	1 : 1	0	57
6	0.25	0.125	1 : 0.5	0	32

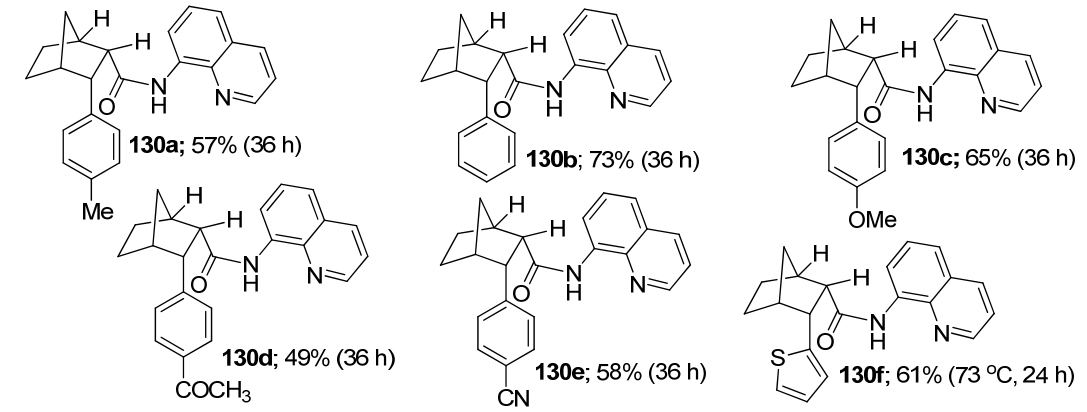
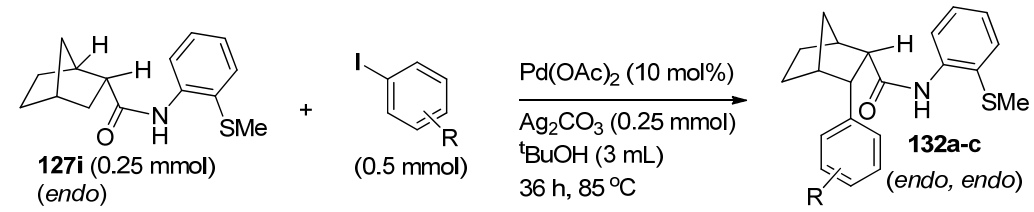
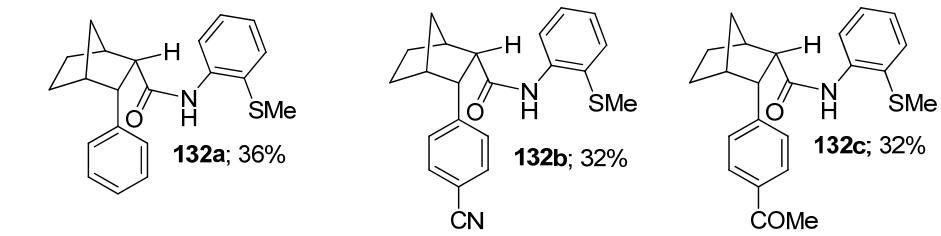


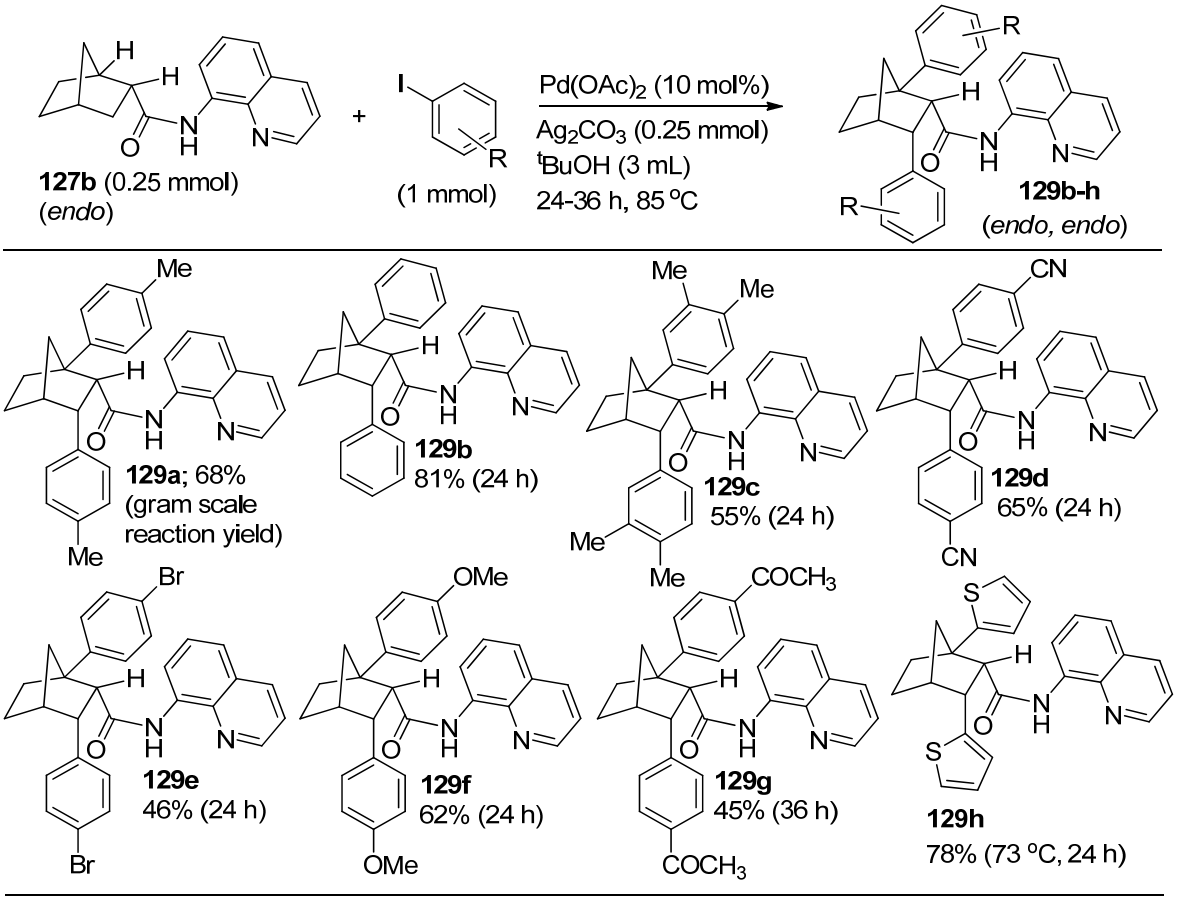
Table 13. Pd(II)-catalyzed C-H activation and arylation of **23i**.





The yields of the C-H arylated norbornanecarboxamides **132a-c** were relatively lower than the C-H arylated norbornanecarboxamides **130a-c**. This is perhaps due to the difference in the abilities or efficiencies of the respective directing groups (which are attached with the norbornanecarboxamides **127i** and **127b**) in assisting the Pd-catalyzed C-H activation reactions.

Table 14. Pd(II)-catalyzed arylation of 2° and bridgehead 3° C-H bonds of **127b**.



Further it was decided to elaborate the generality of this method comprising Pd(II)-catalyzed, direct arylation of 2° and the bridgehead 3° C(sp^3)-H bonds of norbornanecarboxamides (Table 14). Accordingly, to reveal the synthetic utility, the Pd(II)-catalyzed bis C-H arylation of norbornanecarboxamide system **127b** was carried out in a gram scale, which afforded the C-H arylated norbornanecarboxamide system **129a** in an excellent yield (68%) (Table 14). Then, under the optimized reaction conditions, a wide range bis C-H arylated norbornanecarboxamide frameworks **129b-129h** (45-81%) were obtained from the direct arylation of 2° C(sp^3)-H (*endo*) and the bridgehead 3° C(sp^3)-H bonds of the norbornanecarboxamide substrate **127b** using employing various aryl iodides containing

electron-withdrawing and donating groups (Table 14). The arylation of 2° C(sp^3)-H (*endo*) and the bridgehead 3° C(sp^3)-H bonds of the norbornanecarboxamide substrate **127b** using 2-iodothiophene afforded the norbornanecarboxamide **129h** (78%, Table 14). Similarly, the $Pd(OAc)_2$-catalyzed, Ag_2CO_3-mediated arylation of the C-H bonds of the norbornane system **127i** with various aryl iodides containing a substituent at the *para* or *meta* position (e.g., alkyl, OMe, CN, $COCH_3$ and NO_2) also afforded the wide range of bis C-H arylated norbornanecarboxamide frameworks **133a-g** (23-50%, Table 15). All the corresponding arylations of 2° C(sp^3)-H (*endo*) and the bridgehead 3° C(sp^3)-H bonds of the norbornanecarboxamide substrates furnished the arylated norbornanecarboxamides **129a,129b-129h** and **133a-133g** as single diastereomers via the selective incorporation of corresponding aryl groups at the *endo* 2° C(sp^3)-H and bridgehead 3° C(sp^3)-H positions of the corresponding norbornanecarboxamide systems.

Table 15. Arylation of 2° and bridgehead 3° C-H bonds of **127i**.

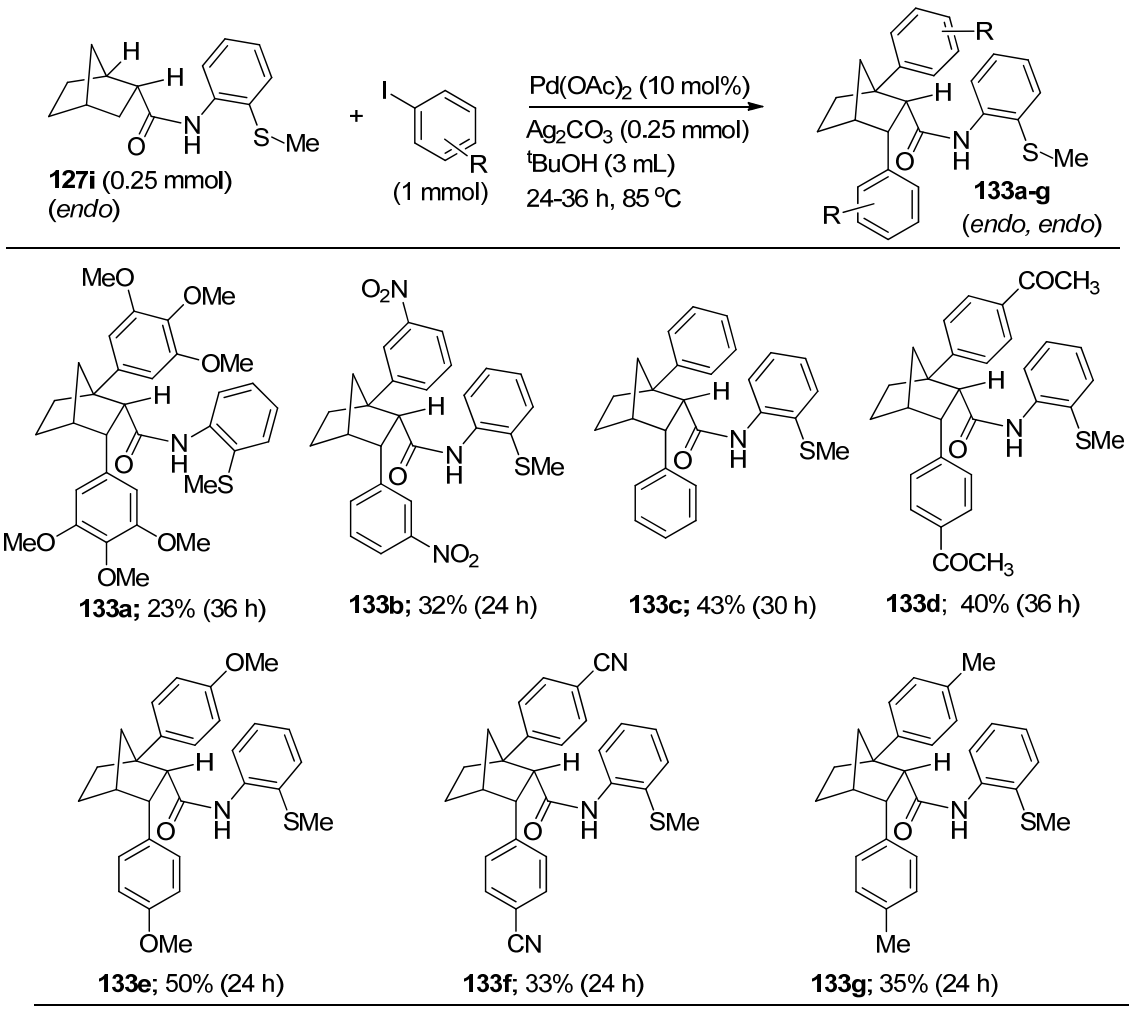
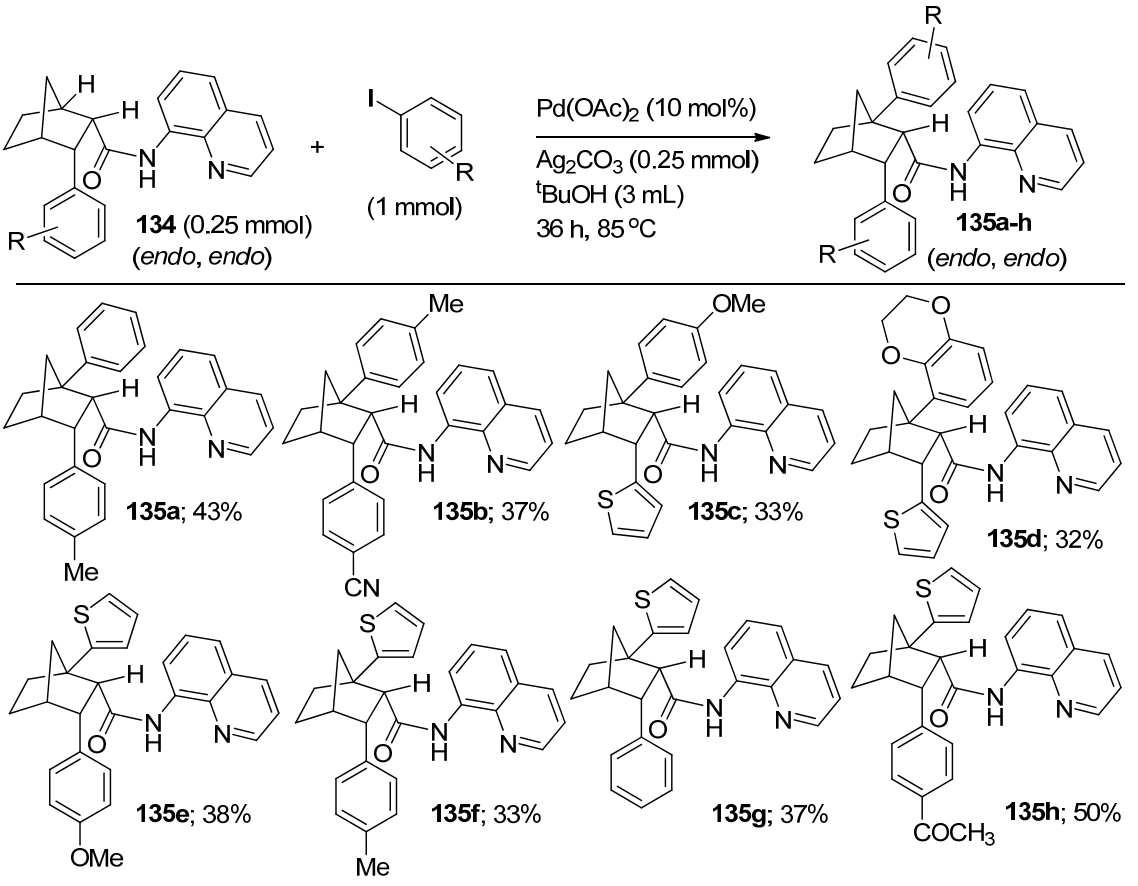


Table 16. Pd(II)-catalyzed C-H arylation of bridgehead 3° C-H bonds.



Further it was envisaged to study the scope of this "bridgehead carbon substitution" via C-H activation. Given that the Pd(II)-catalyzed C-H arylation of **127b** or **127i** provided the 2° and the bridgehead 3° C(sp^3)-H arylated norbornanecarboxamides having similar kind of aryl groups introduced at the 2° and bridgehead 3° C(sp^3)-H, it was envisaged to introduce a different aryl group at the 2° and bridgehead 3° C(sp^3)-H bonds (Table 16).[7b] Accordingly, some of the mono C-H arylated *endo* substituted norbornanecarboxamides systems obtained from Table 12 were treated with generilised substrate **(134)** with a variety of aryl iodides and heteroaryl iodide in the presence of $Pd(OAc)_2$ catalyst under the optimized reaction conditions (Table 16). Similarly, the $Pd(OAc)_2$-catalyzed, Ag_2CO_3-mediated arylation of the C-H bonds of the norbornane system **134** with various aryl iodides containing a substituent at diffirent position afforded the corresponding norbornanecarboxamides **135a-h** (32-50%) via the C-H activation of the bridgehead 3° C(sp^3)-H bond. The products **135a-h** were obtained in low to moderate yields, which indicated that perhaps the Pd(II)-catalyzed C-H arylation of the bridgehead 3° C(sp^3)-H bond is relatively a difficult reaction.

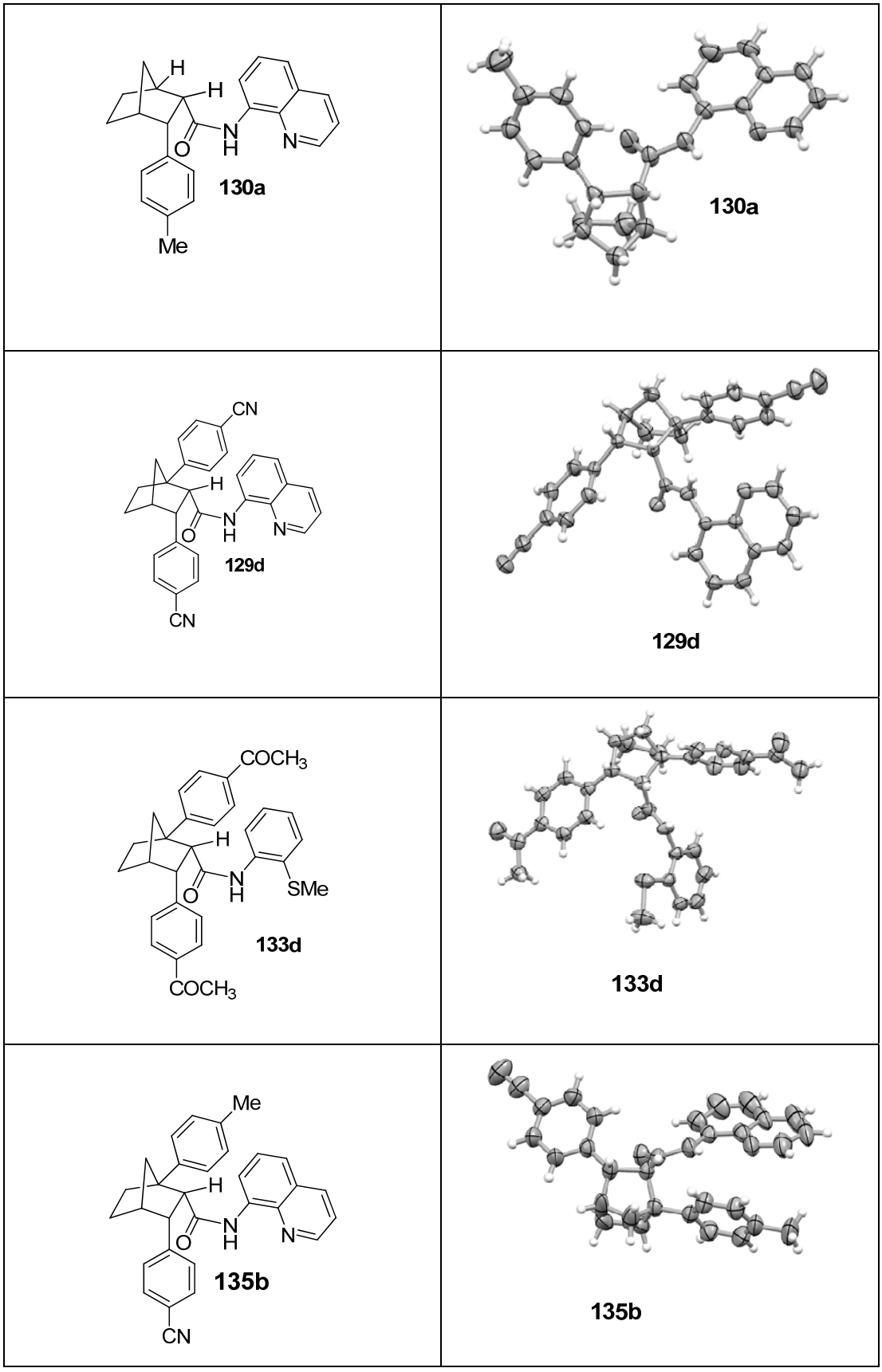
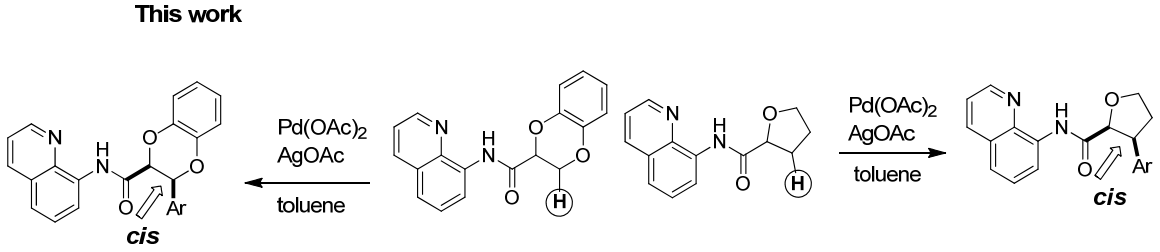


Figure 10. X-ray (ORTEP diagram) structures of the compounds **130a**, **129d, 133d,** and **135d**.

Part 4. Regio- and stereoselective Pd-catalyzed, directing group-aided direct arylation of sp^3 C(3)-H of THF and 1,4-benzodioxane systems and the construction of *cis* 2,3-disubstituted THF-norlignan and benzodioxane-neolignan motifs.

Given the importance of saturated oxygen heterocycle derivatives in organic synthesis and medicinal chemistry research area as described in the introduction part, developing efficient synthetic methods for synthesizing *cis*-substituted tetrahydrofuran (THF), benzodioxane will enrich the library of saturated oxygen heterocycle scaffolds. Accordingly, in continuation of the investigations on the construction of C-H arylated/functionalizedcyclopropanecarboxamides, cyclobutanecarboxamides and norbornanecarboxamides *via* the Pd(II)-catalyzed directing group-aided C(sp^3)-H arylation, a part of this thesis work envisaged to synthesize the construction of *cis* 2,3-disubstituted THF-norlignan and benzodioxane-neolignan motifs via the Pd(II)-catalyzed bidentate directing group-directed C(sp^3)-H functionalization/arylation of sp^3 C(3)-H of THF and 1,4-benzodioxane systems (Scheme 45).

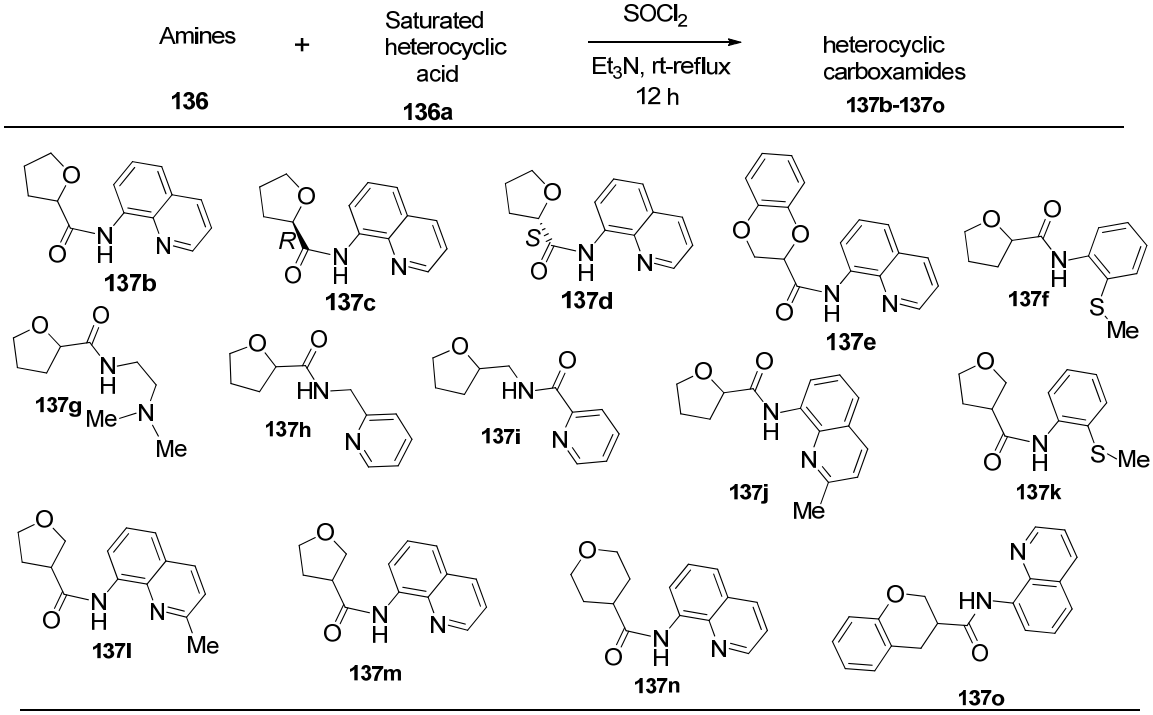


Scheme 45. Topic of this work. sp^3 C-H activation and direct C(3)-H arylation of THF and benzodioxane systems.

Following the literature procedures, various tetrahydrofuran-type and related carboxamide systems **137b-o** prepared from various directing groups/amines **136** (Scheme 46). Then, to begin the investigation on the arylation of methylene C(sp^3)-H bond of tetrahydrofuran system, initially, various optimization reactions were performed for achieving the C(3)-H arylation of THF carboxamide system **137b** as shown in Table 17.

The C-H functionalization reaction THF carboxamide system **137b** with 1-iodo-4-methoxybenzene (**138a**) in the presence of AgOAc additive without any catalyst palladium catalyst failed to afford any product (entry 1, Table 17). The C-H arylated THF carboxamide system **139a** was obtained in <15% yield in the presence of $Pd(OAc)_2$ catalyst without any additive (entry 2).The reaction of THF carboxamide system **137b**, aryl iodide **138a** and

AgOAc (additive) in the presence 5 or 10 mol% of the $Pd(OAc)_2$ catalyst afforded the C3-arylated product, *cis* 2,3-disubstituted tetrahydrofurancarboxamide**139a** (norlignan analogue) in 70 and 81% yields, respectively (entries 3 and 4, Table 17). The Pd(II)-catalyzed C-H arylation of the THF carboxamide system **137b** with **138a** in the presence of Ag_2CO_3 as an additive instead of AgOAc afforded the C-H arylated THF carboxamide system **139a** in 69% yield (entry 5, Table 17).

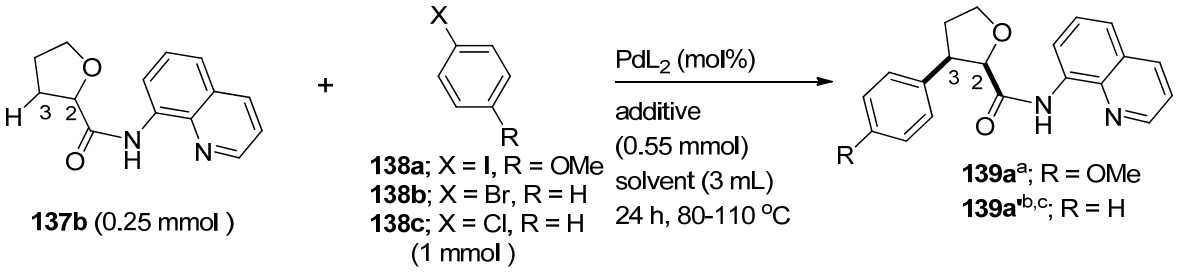


Scheme 46. Preparation of heterocycle carboxamides.

The Pd(II)-catalyzed C(3)-H arylations of THF carboxamide system **137b** with **138a** in the presence of additives, such as K_2CO_3 or KOAc or $PhI(OAc)_2$ were not fruitful (entries 6-8, Table 17). The Pd(II)-catalyzed C-H arylation of THF carboxamide system **137b** in the presence of catalysts, such as $PdCl_2$ or $Pd(TFA)_2$ failed to give satisfactory yields (entries 9 and 10, Table 17). However, the Pd(II)-catalyzed C-H arylation of THF carboxamide system **137b** in the presence of the catalysts, such as $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$ afforded the C-H arylated THF carboxamide system **139a** in 69 and 30% yields, respectively (entries 11 and 12, Table 17). The Pd(II)-catalyzed C-H arylation of THF carboxamide system **137b** with **138a** in solvents, such as MeCN or 1,2-DCE or *tert*-butyl alcohol were not fruitful (entries 13-15, Table 17). The Pd(II)-catalyzed C-H arylation of THF carboxamide system **137b** with

138a in 1,4-dioxane or *tert*-amyl alcohol afforded the C-H arylated THF carboxamide system **139a'** in 46 and 57% yields, respectively (entries 16 and 17, Table 17).

Table 17. Optimization of reaction conditions. Pd(II)-catalyzed C-H arylation of THF carboxamide system.



137b (0.25 mmol)

138a; X = **I**, R = OMe
138b; X = Br, R = H
138c; X = Cl, R = H
(1 mmol)

139a[a]; R = OMe
139a'[b,c]; R = H

entry	PdL_2 (mol%)	additive (mmol)	solvent (3 mL)	T (°C)	**139a**; yield (%)[a]
1	nil	AgOAc (0.55)	toluene	110	0
2	$Pd(OAc)_2$ (10)	nil	toluene	110	<15
3	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	70
4	**$Pd(OAc)_2$ (10)**	**AgOAc (0.55)**	**toluene**	**110**	**81**
5	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.55)	toluene	110	69
6	$Pd(OAc)_2$ (10)	K_2CO_3 (0.55)	toluene	110	0
7	$Pd(OAc)_2$ (10)	KOAc (0.55)	toluene	110	traces
8	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (0.55)	toluene	110	0
9	$PdCl_2$ (10)	AgOAc (0.55)	toluene	110	<10
10	$Pd(TFA)_2$ (10)	AgOAc (0.55)	toluene	110	0
11	$Pd(CH_3CN)_2Cl_2$ (10)	AgOAc (0.55)	toluene	110	69
12	$Pd(PPh_3)_4$ (10)	AgOAc (0.55)	toluene	110	30
13	$Pd(OAc)_2$ (10)	AgOAc (0.55)	CH_3CN	80	0
14	$Pd(OAc)_2$ (10)	AgOAc (0.55)	1,2-DCE	80	0
15	$Pd(OAc)_2$ (10)	AgOAc (0.55)	^{t}BuOH	85	0
16	$Pd(OAc)_2$ (10)	AgOAc (0.55)	1,4-Dioxane	100	46
17	$Pd(OAc)_2$ (10)	AgOAc (0.55)	^{t}AmylOH	110	57
18	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	0[b,c]
19[d]	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	35
20[e]	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	59
21[f]	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	68

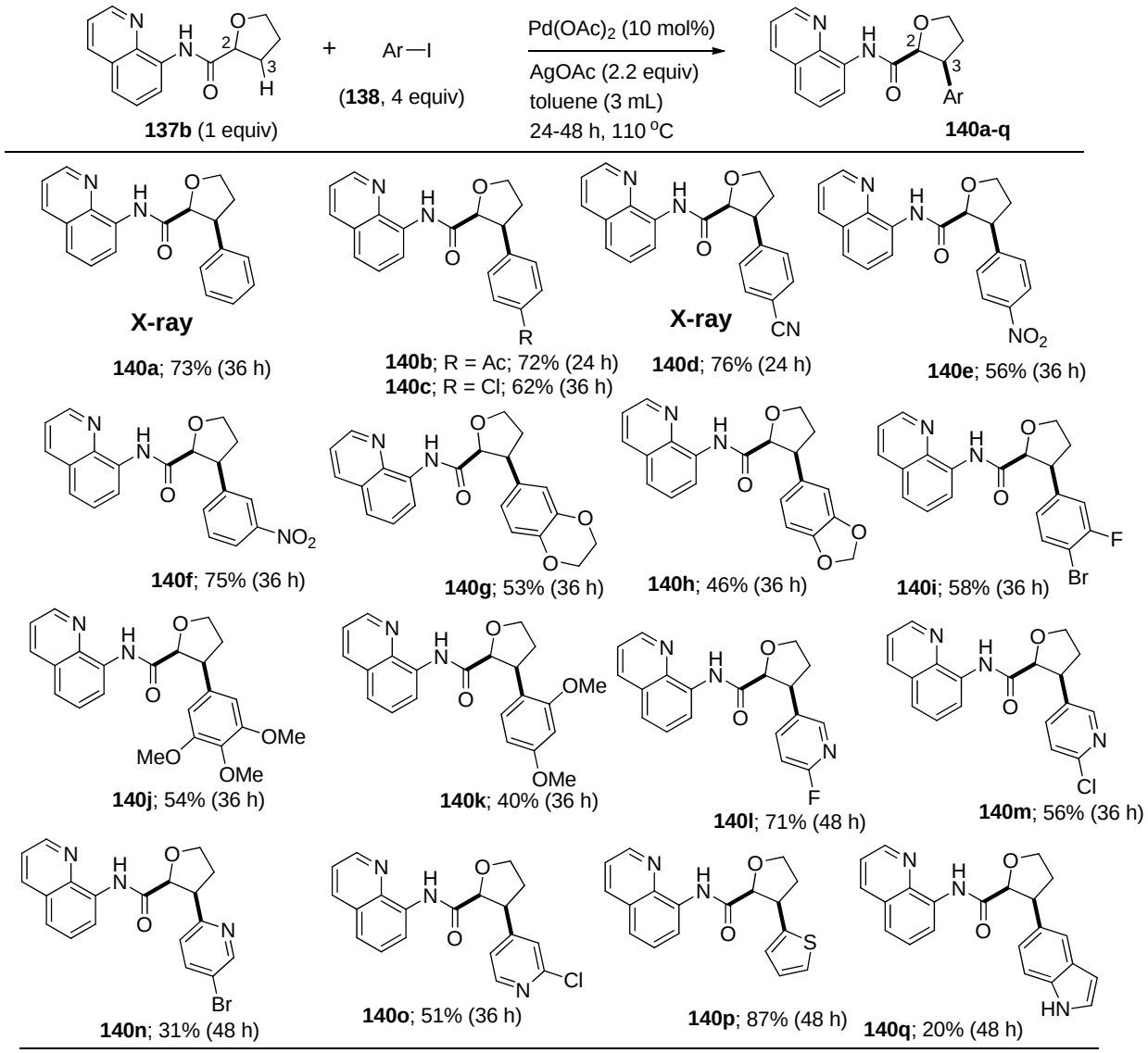
[a] The yield corresponds to the reaction of **137b** with **138a**. [b] The yield corresponds to the reaction of **137b** with **138b**. [c] The yield corresponds to the reaction of **137b** with **138c**. [d] 1 Equivof**130a** was used. [e] 2 Equivof**130a** was used. [f] 3 Equivof**130a** was used.

The Pd(II)-catalyzed C-H arylations of THF carboxamide system **137b** using coupling partners **138b** or **138c** instead of **130a** were not fruitful (entry 18, Table 17). Additionally, to find out how many equivalents of aryl iodide **138a** are required for obtaining the C3-H arylated THF carboxamide system **139a**in good yield, the THF carboxamide system **137b**was treatedwith different equivalents of **138a** (Table 17). The Pd(II)-catalyzed C-H arylation of THF carboxamide **137b** with one equivalent of **138a** afforded the C3-H arylated THF carboxamide system **139a** 35% yield(entry 19, Table 17). The Pd(II)-catalyzed C-H arylation of THF carboxamide system **137b** with two or three equivalents of **138a** afforded the C3-H arylated THF carboxamide system **139a** in 59% and 68% yields, respectively (entries 20 and 21, Table 17).

After finding suitable reaction conditions, it was decided to establish the generality of this , Pd(II)-catalyzed bidentate directing group-aided direct arylation of C(3)-H bond of the THF carboxamide system **137b**using a variety of aryl iodides (Table 18). Accordingly, the direct arylation of the methylene sp^3 C(3)-H bond of the THF carboxamide system **137b** with aryl iodides containing a substituent at the *para* or *meta* position (e.g., Ac, Cl and NO_2) afforded the corresponding *cis* 2,3-disubstituted tetrahydrofuran carboxamides **140a-140f** in 56-76% yields. Then, the Pd(II)-catalyzed C-H arylation of the THF carboxamide system **137b** using the benzodioxane- or benzodioxole-based aryl iodides afforded the corresponding C3-arylated THF carboxamides **140g** and **140h**. The Pd(II)-catalyzed C-H arylation of the THF carboxamide system **137b** with multi substituted aryl iodides also afforded the corresponding C3-arylated THF carboxamides**140i-k** in 40-58% yields. Next, the Pd(II)-catalyzed direct arylation of the C(3)-position of the THF carboxamide **137b**with various heteroaryl iodides, furnished the corresponding C3-arylated THF carboxamides**140l-140q** in 20-87% yields. The coupling constants (*J*) of the doublet peaks of the C2 proton of all the compounds **140a-q** were calculated from their respective ^{1}H NMR spectra and they was found to be in the range of 6.6-8.2 Hz (except the compound **140p** having a thiophene moiety at the C3-position,C2H, doublet,*J* = 6.3 Hz). The stereochemistry of C3-arylated THF carboxamides**140a-q** were assigned as *cis* on the basis of the X-ray structure analyses of the C3-arylated THF carboxamides**140a** and **140d** coupled with the similarity in the NMR spectral pattern of the compounds **140a-q**. After investigating the Pd(II)-catalyzed bidentate directing group-aided direct arylation of C(3)-H bond of the THF carboxamide system **137b**, then it was envisaged, to investigate the Pd(II)-catalyzed C−H arylation of THF carboxamide systems, such as **137f-**

o (Scheme 46). However, the Pd(II)-catalyzed C−H arylation reactions of THF carboxamide systems **137f-o** with ArI were not successful.

Table 18. Pd(II)-catalyzed arylation of sp^3 C(3)-H bond of **137b**: Construction of norlignan-THF scaffolds.



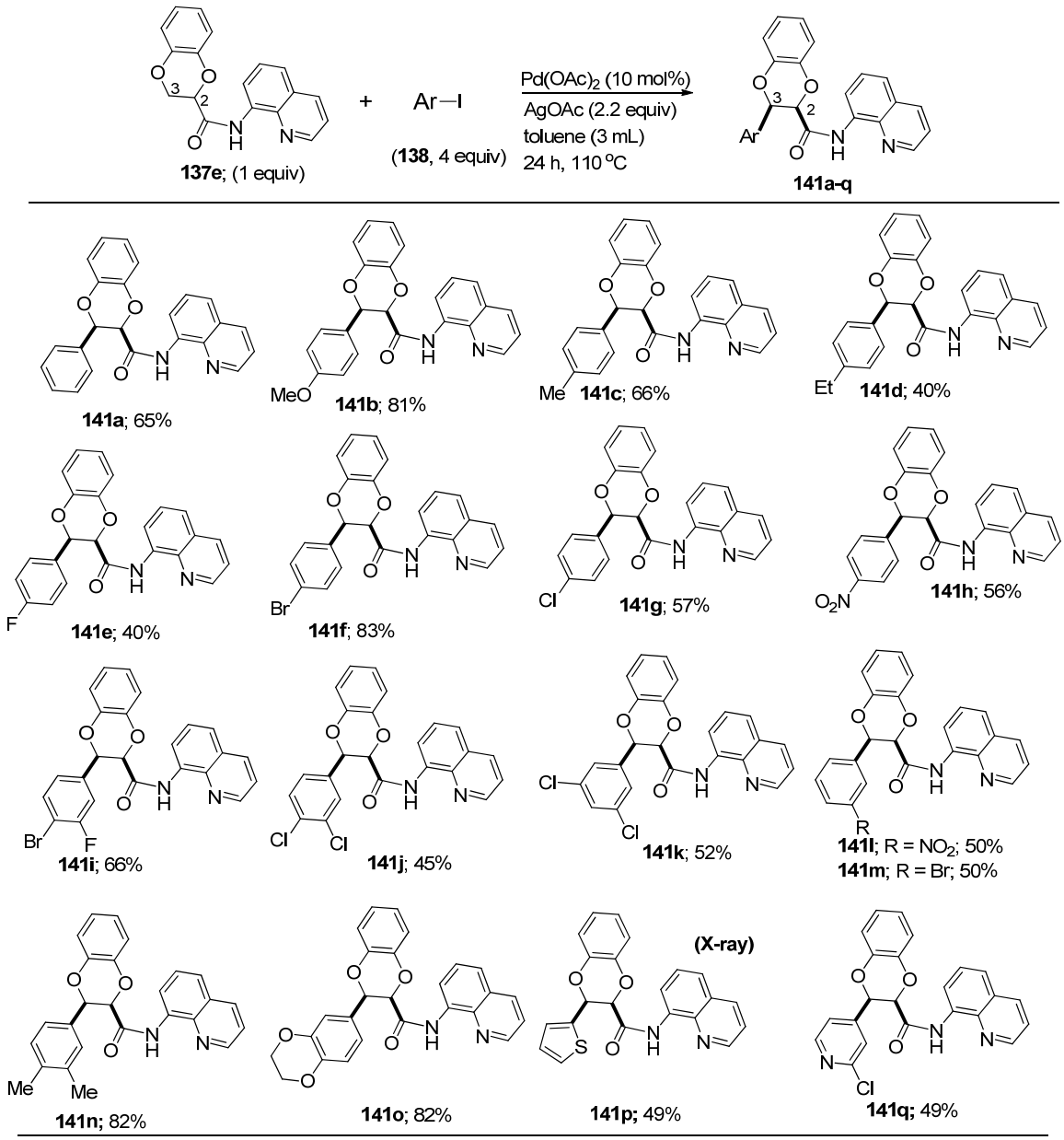
Next, to further extend the generality of this method it was envisaged to investigate the Pd(II)-catalyzed, directing-group-aided direct C-H arylation of the methylene C(sp^3)-H bond of 1,4-benzodioxane carboxamide system **137e** (Table 19). Then, the C-H arylation of the methylene C(sp^3)-H bond of 1,4-benzodioxane carboxamide system **137e**with phenyl iodide in the presence of AgOAc additive (2.2 equiv) and 10 mol% of the $Pd(OAc)_2$ catalyst was performed, which afforded the C3-H arylated *cis* 2,3-disubstituted 1,4-benzodioxane

carboxamide system **141aa** (neolignan analogue) in 65% yield (Table 19).The Pd(II)-catalyzed C-H arylation of the methylene C(sp^3)-H bond of 1,4-benzodioxane carboxamide system **137e** with aryl iodides containing electron donating groups at the *para* position in the aryl ring (e.g. OMe, Me, Et) afforded the corresponding C3-H arylated *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141b-141d** in 40-81% yields.

The Pd(II)-catalyzed C-H arylation of the methylene C(sp^3)-H bond of 1,4-benzodioxane carboxamide system **137e** with aryl iodides containing electron withdrawing groups at the *para* position in the aryl ring (e.g. halide, NO_2) afforded the corresponding C3-H arylated *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141e-141h** in 40-83% yields. The Pd(II)-catalyzed C-H arylation of the methylene C(sp^3)-H bond of 1,4-benzodioxane carboxamide system **137e** with disubstituted aryl iodides and aryl iodides containing electron withdrawing groups at the *meta* position in the aryl ring (e.g. NO_2, Br) afforded the corresponding C3-H arylated *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141i-141o** in 45-82% yields. The Pd(II)-catalyzed direct arylation of the methylene sp^3 C(3)-H bond of 1,4-benzodioxane system**137e** using heteroaryl iodides also afforded the corresponding C3-H arylated *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141p** and**141q** in 49% yields (Table 19).

Characteristically, the C2 and C3 protons in all the *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems (**141a-q**) appeared as doublets and the coupling constants (*J*) of the doublet peaks of C2 and C3 protons of all the *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141a-q** were calculated from their respective ^{1}H NMR spectra and they were found to be in the range of 2.8-3.1 Hz. Accordingly, the stereochemistry of the 2,3-disubstituted 1,4-benzodioxane carboxamides **141a-q**was assigned as *cis* on the basis of the X-ray structure analysis of the *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide system**141p** coupled with the similarity in their NMR spectral pattern and the characteristic coupling constant values of the doublet peaks of the C2 protons and C3 protons of all the *cis* 2,3-disubstituted 1,4-benzodioxane carboxamide systems**141a-q**.

Table 19. Arylation of sp^3 C(3)-H Bond of benzodioxane motifs **137e.**

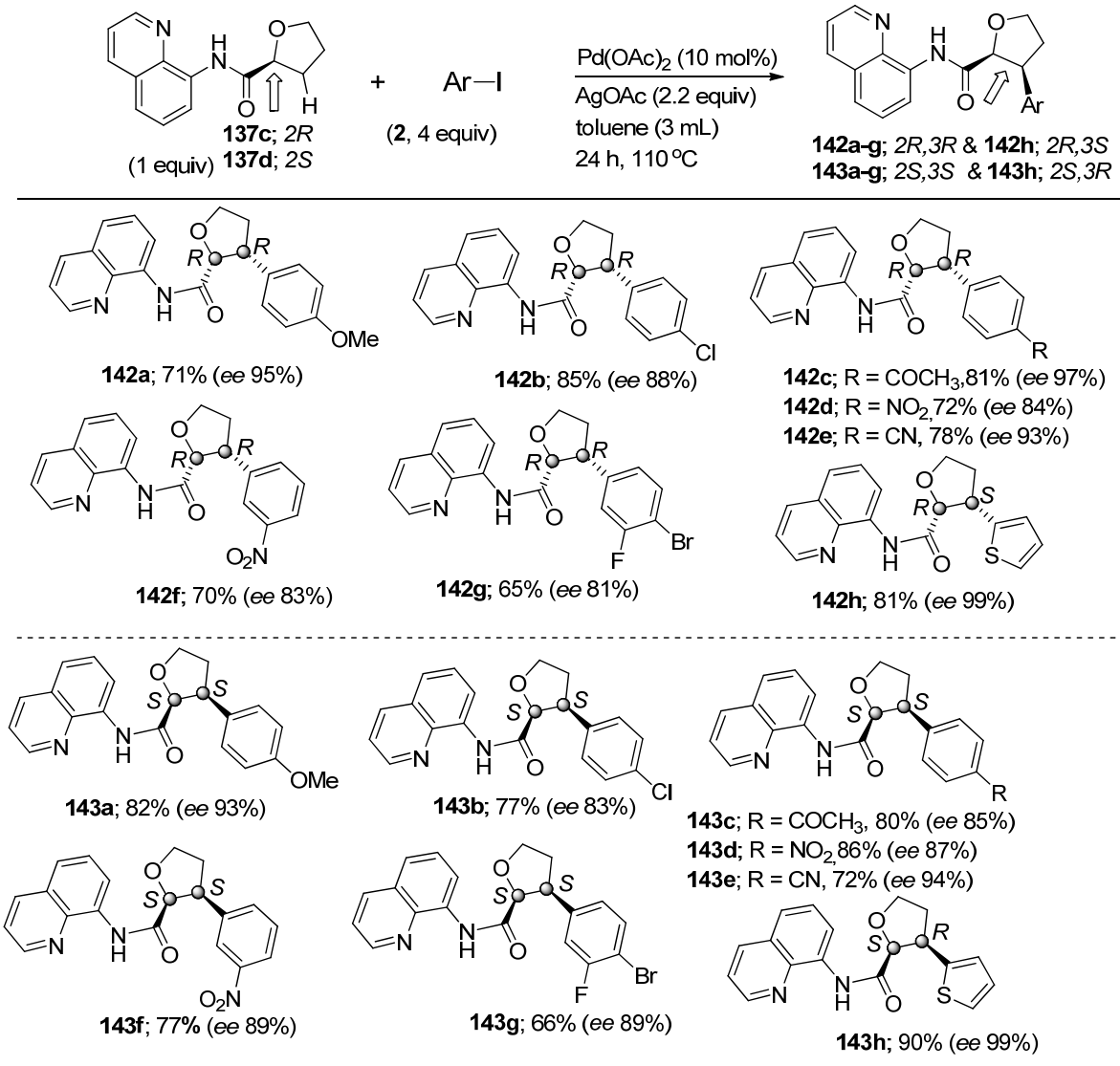


Subsequently, it was envisaged to explore the Pd(II)-catalyzed C-H arylation of the sp^3 C(3)-H bond of optically pure tetrahydrofuran-2-carboxamide systems and synthesize optically pure C3-arylated tetrahydrofuran-2-carboxamide derivatives. In this regard, the optically pure tetrahydrofuran-2-carboxamide systems **137c** (*R*-isomer) and **137d** (*S*-isomer Table 20) were assembled from their respective carboxylic acids and the directing group, such as 8-aminoquinoline.

The Pd(II)-catalyzed C(sp^3)-H arylations of optically pure THF carboxamide systems**137c** and **137d** with various aryl iodides containing different substituents in the aryl ring (e.g., OMe, Cl, Ac, NO_2 and CN) were performed. These reactions afforded the corresponding

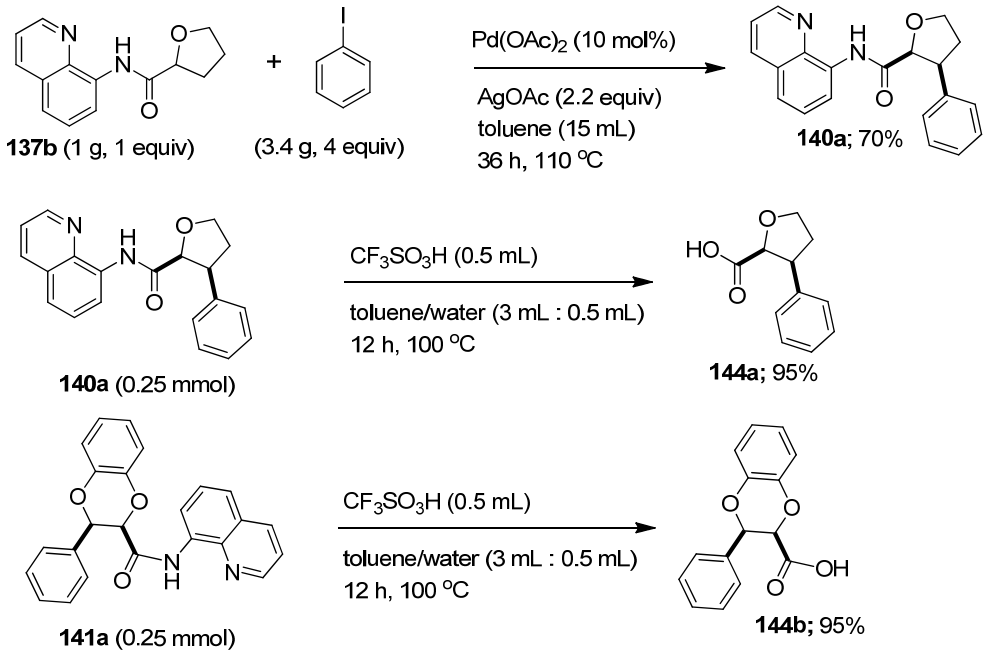
optically pure 2,3-disubstituted tetrahydrofuran carboxamides **142a-g** (*2R,3R*, major isomer) and **143a-g** (*2S,3S*, major isomer) in 70-86% yields. Similarly, the Pd(II)-catalyzed C(sp^3)-H arylations of optically pure THF carboxamide systems**137c** and **137d** with 2-iodothiophene afforded the corresponding optically pure 2,3-disubstituted tetrahydrofuran carboxamides**142h**(*2R,3S*, major isomer) and **143h**(*2S,3R*, major isomer) in 81 and 90% yields, respectively (Table 20).

Table 20. Arylation of sp^3 C(3)-H bond of 1h,i and construction of norlignan-THF scaffolds.



The HPLC analyses of the corresponding optically pure 2,3-disubstituted tetrahydrofuran carboxamides**142a-h** and **143a-h**revealed that the Pd(II)-catalyzed C-H arylation of the optically pure tetrahydrofuran carboxamides**137c** and**137d** resulted the optically pure 2,3-disubstituted tetrahydrofuran carboxamides**142a-h** with *ee* 81 to >99% and **143a-h** with *ee* 83 to >99% and partial racemizations were also observed in most of the reactions under the

experimental conditions. The Pd(II)-catalyzed C-H arylation of the optically pure tetrahydrofuran carboxamides**137c** and**137d** occurred only at the C3-position and selectively gave the optically pure 2,3-disubstituted tetrahydrofuran carboxamides**142a-h** and **143a-h**with *cis* stereochemistry (C2 and C3 stereocenters). The tetrahydrofuran carboxamides**142a-h** and **143a-h**were isolated in pure form as single diastereomers and characterized by NMR spectral data, mass and HPLC analyses. The stereochemistry all the tetrahydrofuran carboxamides**142a-h** and **143a-h** (*cis* isomers) were assigned on the basis of the X-ray structure analyses of tetrahydrofuran carboxamides**140a** and **140d** and discussions given for assigning the stereochemistry of the racemic tetrahydrofuran carboxamides**140a-q**.



Scheme 47. Pd(II)-catalyzed C-H arylation in a gram scale and removal of the directing group.

To show the utility of the protocol, the Pd(II)-catalyzed direct arylation of C(3)-H bond of the tetrahydrofuran carboxamide**137b** with iodobenzene was carried out in a gram scale, which afforded the C3-arylated tetrahydrofuran carboxamide**140a** in 70% yield (Scheme 47). Then, it was envisaged to attempt the removal of the bidentate directing group (8-aminoquinoline) from the C3-arylated *cis* 2,3-disubstituted THF carboxamideand benzodioxane carboxamide systems.Accordingly,the hydrolysis of carboxamide derivatives **140a** and **141a** in the presence of triflic acid (TfOH) afforded the corresponding carboxylic acids **144a** and **144b** (Scheme 47).

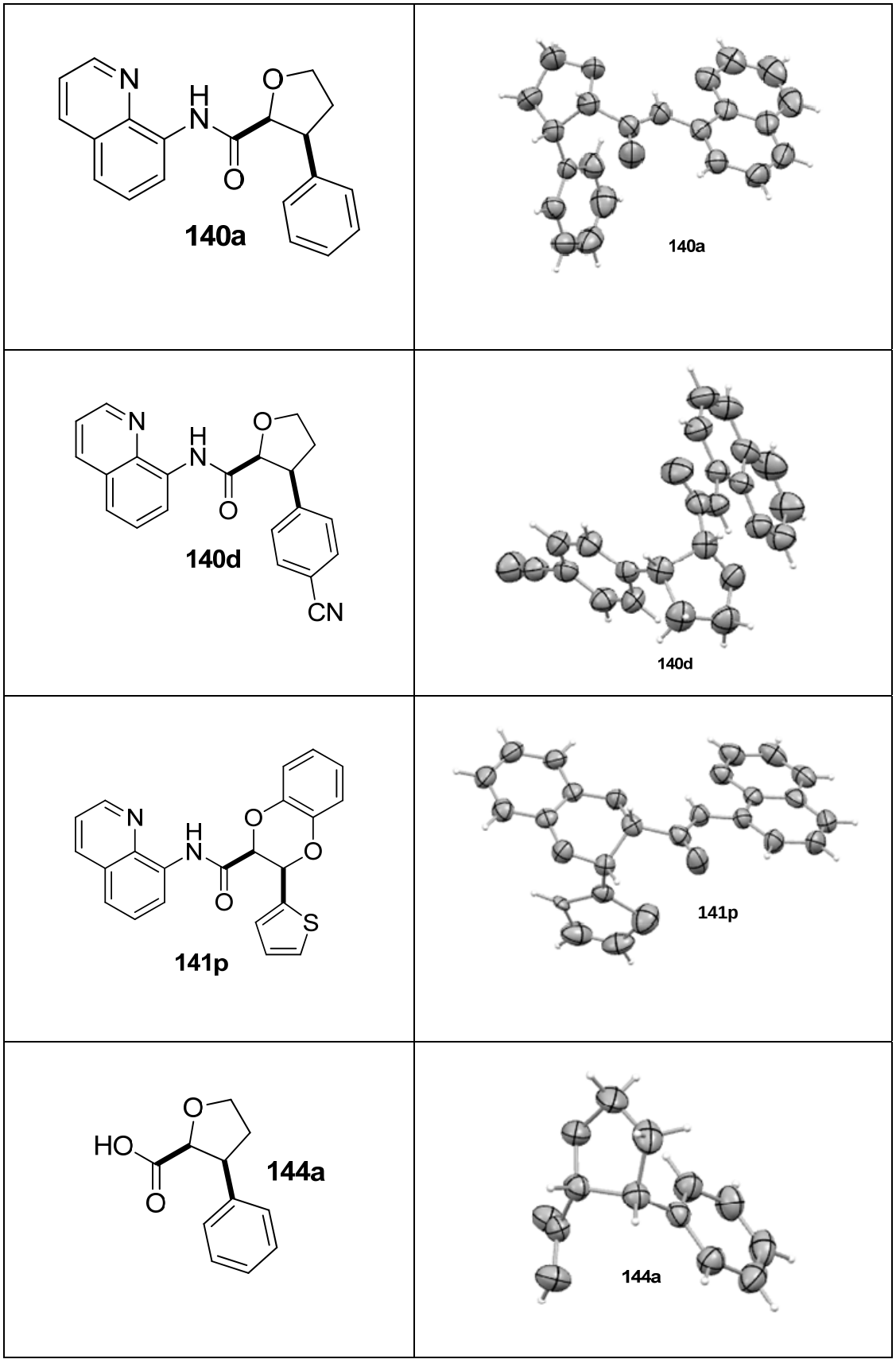
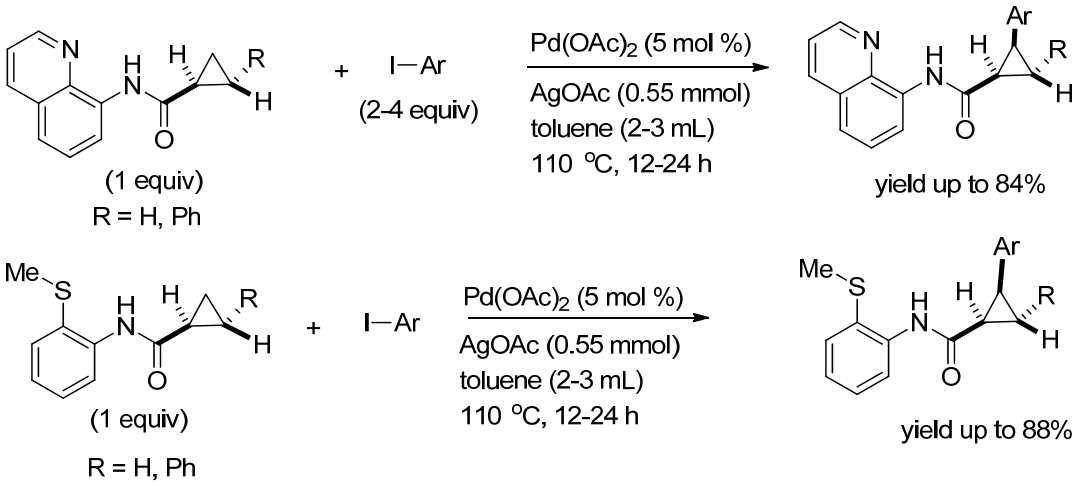


Figure 11. X-ray (ORTEP diagram) structures of the compounds **140a**, **140d, 141p,** and **144a**.

The stereochemistry of the compound **144a** (C2-C3 stereocenters) was found to be *cis*(see X-ray structure of **144a**) and no epimerization was observed under the experimental condition employed for hydrolyzing the carboxamide derivative **26a**. The C2 proton in the carboxylic acid **144a** appeared as a doublet (δ = 4.65 ppm) due to its coupling with the C3 proton similar to its parent carboxamide derivative **140a** (C2H, doublet, δ = 4.78, *J* = 7.0 Hz). The coupling constant (*J*) of the doublet peak of the C2 proton of the carboxylic acid**144a** (*cis* isomer) was found to be 7.7 Hz similar to its parent carboxamide derivative **140a** (*cis* isomer). Likewise, the stereochemistry of the C2-C3 stereocenters of the carboxylic acid **144b** was assigned as *cis* based on the coupling constant (*J* = 3.2 Hz) of the doublet peaks of the C2/C3 protons, which was found to be in agreement with the literature and its parent carboxamide derivative **141a** (*cis* isomer), in which the coupling constant (*J*) of the doublet peaks of the C2/C3 protons was 3.1 Hz.

Conclusion.

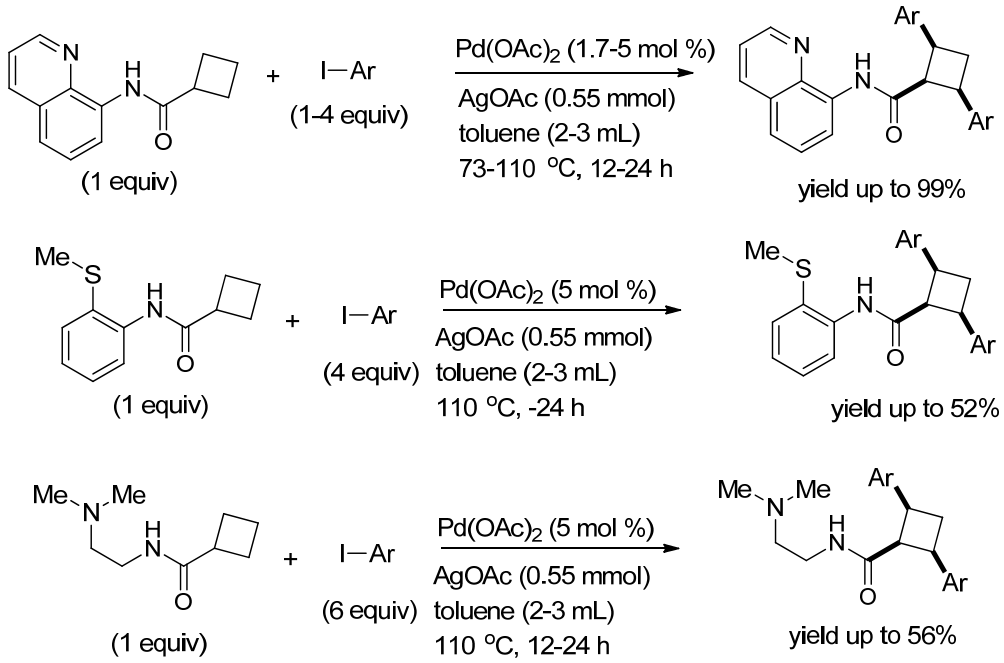
In general, the Chapter 2 revealed the investigations on the Pd(II)-catalyzed,directing group-aideddiastereoselectiveC-H functionalization/arylation of cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems to obtain C-H arylated/functionalized cyclopropanes, cyclobutanes, norbornanes, tetrahydrofurans and 1,4-benzodioxane systems.



The Part 1 of the Chapter 2 revealed the investigations on the $Pd(OAc)_2$-catalyzed highly diastereoselective direct arylation of the methylene $C(sp^3)$-H bond of cyclopropanecarboxamides and a facile access to various di and trisubstituted

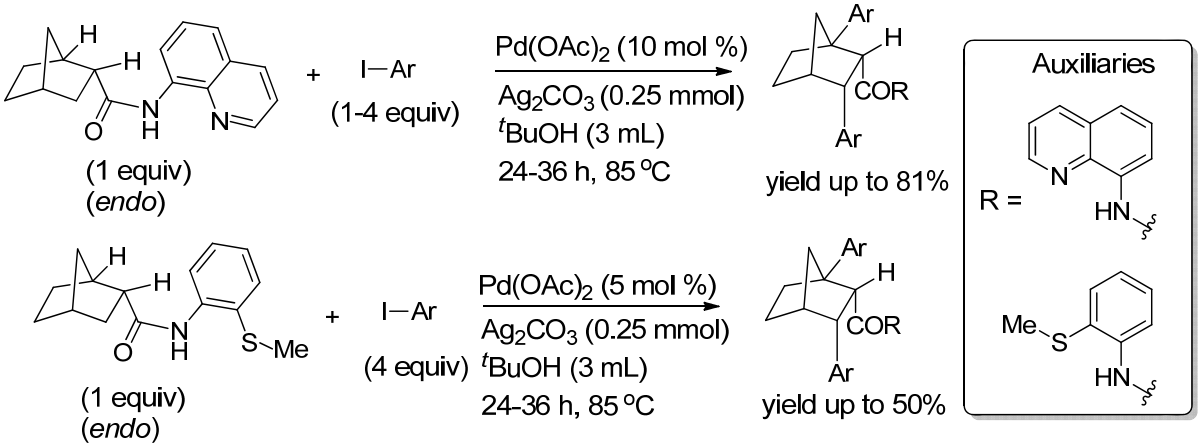
cyclopropanecarboxamides. Synthesis of several mono- and di- aryl-*N*-(quinolin-8-yl)cyclopropanecarboxamide scaffolds and mono- and di- aryl-*N*-(2-(methylthio)phenyl)-cyclopropanecarboxamide scaffolds having contiguous stereocenters was achieved with high degree of stereocontrol.

The Part 2 of the Chapter 2 revealed the investigations on the Pd(II)-catalyzed highly diastereoselective, double C-H activation and direct bis C-H arylation of methylene C(sp^3)-H bonds of cyclobutanecarboxamides. Extensive screening of several directing groups and reaction conditions were performed to find out the reaction conditions required for effecting the mono- or double C-H arylation of cyclobutanecarboxamides with high degree of stereocontrol. The direct double C-H activation of cyclobutanecarboxamide led to the installation of two aryl groups on cyclobutanecarboxamide systems and a facile synthesis of several 1,2-*cis*, 1,3-*cis* and 2,3-*cis* trisubstituted cyclobutanecarboxamide frameworks having three contiguous stereocenters with high degree of stereocontrol.

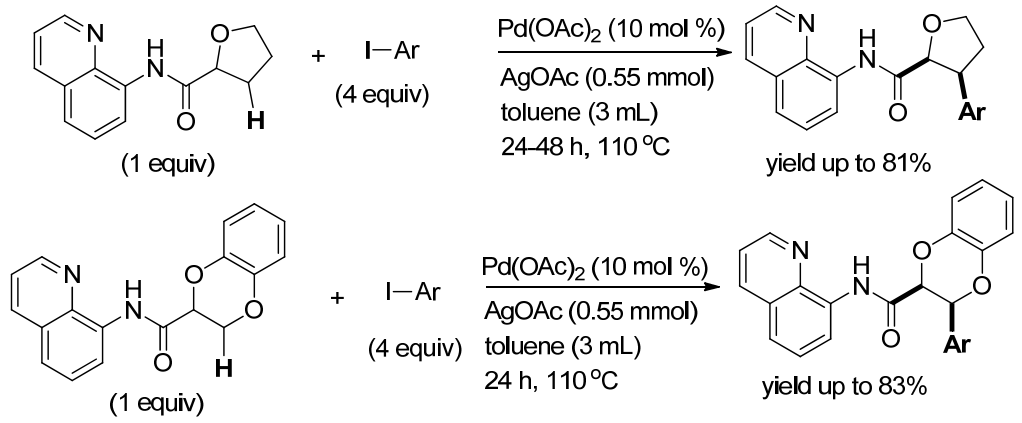


The Part 3 of the Chapter 2 revealedthe investigations on the Pd(II)-catalyzed arylation of 2° and the bridgehead 3° C(sp^3)-H bonds of norbornanecarboxamides. Extensive screening of several directing groups and reaction conditions were performed to find out the reaction conditions required for effecting the Pd(II)-catalyzed arylation of 2° and the bridgehead 3° C(sp^3)-H bonds of norbornanecarboxamides with high degree of stereocontrol. Regio- and stereoselective construction of various functionalizedC-H arylatednorbornane systemshaving

contiguous stereocenters andan unprecedented “formation of C-C bond at the bridgehead carbon and bridgehead quaternary stereocenter via the C-H activation route” were shown.



The Part 4 of the Chapter 2 revealed the investigations on the Pd(II)-catalyzed, bidentate directing group-aided highly regio- and stereoselective sp^3 C-H activation and direct arylation of the C(3)-H position of tetrahydrofuran and 1,4-benzodioxane carboxamides. The direct C-H arylation occurred only at the C3 position of racemic tetrahydrofuran-2-carboxamides and gave the corresponding racemic C3-arylated tetrahydrofuran-2-carboxamides with excellent regio- and diastereoselectivities. Further, the Pd(II)-catalyzed C-H arylation of optically pure (*R*)- or (*S*)- tetrahydrofuran-2-carboxamides afforded the corresponding chiral (*2R,3R*) and (*2S,3S*) C3-arylated tetrahydrofuran-2-carboxamides having *cis* stereochemistry with excellent regio- and diastereoselectivitiesand *ee*. Synthesis of a wide range of *cis* 2,3-disubstituted- THF-norlignan and benzodioxane-neolignan derivatives was shown.



All the compounds included in the **Chapter 2** of this thesis are characterized by various characterization techniques including ^1H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The structure and observed diastereoselectivity of representative major products were

established from the single crystal X-ray structure analyses of representative compounds. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental section.

General. IR spectra were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of compoounds were recorded on 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Column chromatography of the crude reaction mixtures was carried out on silica gel (100-200 mesh). Reactions were carried out in anhydrous solvent under a nitrogen atm. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography was performed on silica gel or alumina plates and components were visualized by observation under iodine vapour. Isolated yields of all the products were reported (yields were not optimized). In all the reactions, the colulmn chromatographic purification of the reaction mixture afforded only the major diastereomer in pure form.

Procedure for the synthesis of 105c: A dry flask containing8-aminoquinoline (1 mmol) and Et_3N (1.1 mmol) was stirred for 5-10 min under nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by drop-wise addition of cyclopropane carbonylchloride. The resulting mixture was stirred for overnight at rt, then the reaction mixture refluxed for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and twice with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh, EtOAc/hexanes = 15:85) furnished the corresponding product **105c**.

Procedure for synthesis of 105d: *(1S*,2S*)*-2-Phenylcyclopropanecarboxylic acid (racemic, 1.5 mmol) was dissolved in $SOCl_2$ (6 mmol) and stirred for 24 h at rt under nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum to afford (*1S*,2S**)-2-phenylcyclopropanecarbonyl chloride as a crude product, which was diluted with anhydrous DCM (3 ml) under nitrogen atmosphere. Then, the DCM solution containing (*1S*,2S**)-2-phenylcyclopropanecarbonyl chloride was added to an another flask containing 8-aminoquinoline (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt for 10 min. Next, the reaction mixture was refluxed for 12 h. Then,

the reaction mixture was further diluted with dichloromethane (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes = 20:80) furnished the corresponding product **105d.**

Procedure for the synthesis of 105f: A dry flask containing2-aminothioanisole (1 mmol) and Et_3N (1.1 mmol) was stirred for 5-10 min under nitrogen atmosphere. Then, to the reaction flask anhydrous DCM (4 mL) was added followed by drop-wise addition of cyclopropane carbonylchloride. The resulting mixture was stirred for overnight at rt, then the reaction mixture refluxed for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed with water and twice with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh, EtOAc/hexanes = 15:85) furnished the corresponding product **105f**.

Procedure for synthesis of 105g: *(1S*,2S*)*-2-Phenylcyclopropanecarboxylic acid (racemic, 1.5 mmol) was dissolved in $SOCl_2$ (6 mmol) and stirred for 24 h at rt under nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum to afford (*1S*,2S**)-2-phenylcyclopropanecarbonyl chloride as a crude product, which was diluted with anhydrous DCM (3 ml) under nitrogen atmosphere. Then, the DCM solution containing (*1S*,2S**)-2-phenylcyclopropanecarbonyl chloride was added to an another flask containing 2-aminothioanisole (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt for 10 min. Next, the reaction mixture was refluxed for 12 h. Then, the reaction mixture was further diluted with dichloromethane (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes = 20:80) furnished the corresponding product **105g**.

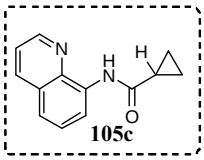
General procedure for arylation of cyclopropanecarboxamides 105c-105d and 105f-105g: A solution of N-(Quinolin-8-yl)cyclopropanecarboxamide (53 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol = 5 mol %), iodo compound (2-4 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (2-3 mL) was heated at an appropriate temperature (60-110 ^oC, see Tables/Schemes for specific examples)for 12-24 h under nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum

and purification of the resulting reaction mixture by column chromatography silica gel furnished the corresponding arylated cyclopropanecarboxamides(see the corresponding Tables/Schemes for specific examples.

Procedure for the hydrolysis of amide (108/108j): The compound **108/108j** (0.25 mmol) and NaOH (6 mmol) were heated in ethanol (3 mL) for overnight at 80 °C. After this period, the reaction mixture was diluted with water and extracted with ether (10 mL x 2). Then, acidified with 1 N HCl to get pH~2. Extraction with ether (10 mL x 2) and drying of the combined organic layers over Na_2SO_4 and evaporation in vacuum gave the corresponding carboxylic acid (**110d/110e**).

Procedure for the reduction of 107c: To dry flask was added anhydrous THF (4 mL) and (*1S*,2R**)-2-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide(**107c**) (0.5 mmol) and the reaction flask was cooled to 0 ^oC under a nitrogen atmosphere. To this solution was added $LiAlH_4$ (1 mmol) in portions and allowed to stir overnight at rt. Then EtOAc (3 mL) and water (1-2 mL) were added sequentially. The resulting solution was extracted with EtOAc (2x15 mL) and dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation and product was purified by column chromatography on silica gel (EtOAc/Hexane 10:90), which afforded the product **110f**.

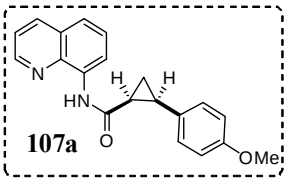
***N*-(Quinolin-8-yl)cyclopropanecarboxamide (105c):**Following the general procedure described above, **105c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as light yellow colour solid; Yield: 95%; mp 80-82^oC; IR (KBr): 3351, 1677, 1525, 11487, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (br s, 1H), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.71 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.49-7.37 (m, 3H), 1.79-1.74 (m, 1H), 1.15-1.11 (m, 2H), 0.89-0.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 148.1, 138.2, 136.3, 134.7, 127.9, 127.4, 121.6, 121.2, 116.3, 16.3, 8.2. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{12}ON_2Na$: 235.0847; found 235.0841.



105c

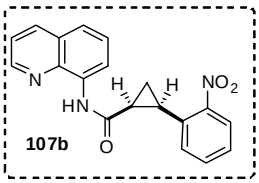
(*1S*,2R)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide (107a):**Following the general procedure described above, **107a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light yellow colour solid; Yield: 71%; mp 126-128^oC; IR (KBr): 3350, 1525, 1485, 1249, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.8 Hz), 8.59

(t, 1H, J = 4.6 Hz), 8.13 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.46-7.43 (m, 3H), 7.30 (d, 2H, J= 8.4), 6.80 (dt, 2H, J_1 = 8.4 Hz, J_2 = 3.1 Hz), 3.74 (s, 3H), 2.62 (dd, 1H, J_1 = 17.2 Hz, J_2 = 9.1 Hz) 2.33-2.27 (m, 1H), 1.90-1.86 (m, 1H), 1.46-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 158.2, 148.0, 138.1, 136.3, 134.7, 130.2, 128.7, 127.9, 127.4, 121.5, 121.0, 116.2, 113.5, 55.1, 25.3, 25.0, 11.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}O_2N_2$: 319.1447; found 319.1445.



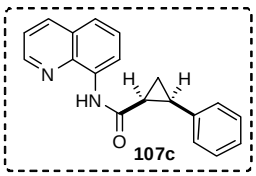
107a

(*1S*,2R)-2-(2-Nitrophenyl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide (107b):** Following the general procedure described above, **107b**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 28%; mp 128-130 ^oC; IR (KBr): 3435, 1679, 1525, 1324, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (br s, 1H), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.43 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.90 (d, 1H, J = 8.2 Hz), 7.59 (d, 2H, J = 4.2 Hz), 7.47-7.35 (m, 4H), 2.98 (dd, 1H, J_1 = 16.9 Hz, J_2 = 8.5 Hz), 2.57-2.51 (m, 1H), 1.96-1.91 (m, 1H), 1.61-1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 150.2, 148.2, 138.2, 136.2, 134.5, 132.8, 132.7, 132.2, 127.8, 127.7, 127.2, 124.4, 121.6, 121.3, 116.3, 25.1, 24.3, 12.0.



107b

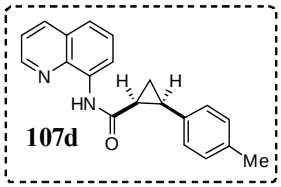
(*1S*,2R)-2-Phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide(107c):** Following the general procedure described above, **107c**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as whit colour solid; Yield: 69%; mp 92-94^oC; IR (KBr): 3353, 1683, 1525, 1324, 790 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.59 (t, 1H, J = 4.2 Hz), 8.11 (d, 1H, J = 8.2 Hz), 7.45-7.39 (m, 5H), 7.28 (t, 2H, J = 7.4 Hz), 7.19 (t, 1H, J = 7.4 Hz), 2.68 (dd, 1H, J_1 = 16.9 Hz, J_2 = 8.5 Hz), 2.38-2.32 (m, 1H), 1.98-1.94 (m, 1H), 1.49-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.0, 138.1, 136.7, 136.3, 134.6, 129.2, 128.0, 127.8, 127.4, 126.6, 121.5, 121.0, 116.3, 26.0, 25.2, 11.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1341; found 289.1347.



107c

(*1S*,2R)-*N*-(Quinolin-8-yl)-2-p-tolylcyclopropanecarboxamide (107d)**:Following the general procedure described above, **107d**was obtained after purification by column

chromatography on silica gel (EtOAc:Hexanes = 30:70) as white colour solid; Yield: 69%; mp 172-174^{o}C; IR (DCM): 3335, 1685, 1524, 1485, 791 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ

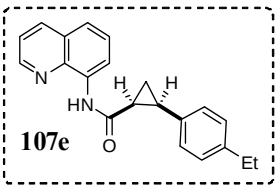


107d

9.95 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.60 (t, 1H, J = 4.2 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.46-7.43 (m, 3H), 7.27 (d, 2H, J = 8.0 Hz), 7.07 (d, 2H, J = 8.0 Hz), 2.64 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.35-2.29 (m, 1H), 2.28 (s, 3H), 1.94-1.89 (m, 1H), 1.47-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 138.1, 136.3, 136.0, 134.7, 133.6, 129.1, 128.8, 127.9, 127.4, 121.5, 121.0, 116.3, 25.7, 25.1, 21.1, 11.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_2O$: 303.1497; found 303.1495.

(*1S*,2R)-2-(4-Ethylphenyl)-*N*-(quinolin-8yl)cyclopropanecarboxamide**

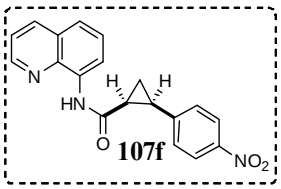
(107e): Following the general procedure described above, **107e**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light yellow colour



107e

liquid; Yield: 67%; IR (DCM): 3352, 1665, 1485, 1324, 825 cm^{-1};^{1}HNMR (400 MHz, $CDCl_3$): δ 9.94 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.4 Hz, J_2 = 1.8 Hz), 8.60 (t, 1H, J = 4.4), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.46-7.43 (m, 3H), 7.30 (d, 2H, J = 8.3 Hz), 7.09 (d, 2H, J = 8.3 Hz), 2.67-2.56 (m, 3H), 2.35-2.29 (m, 1H), 1.94-1.90 (m, 1H), 1.47-1.42 (m, 1H), 1.19 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 142.3, 138.1, 136.3, 134.7, 133.9, 129.1, 127.8, 127.6, 127.3, 121.5, 121.0, 116.2, 28.5, 25.8, 25.2, 15.5, 11.1; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}ON_2$: 317.1654; found 317.1636.

(*1S*,2R)-2-(4-Nitrophenyl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide (107f):** Following the general procedure described above, **107f**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 78%; mp 169-171^{o}C; IR (KBr): 2923, 1598, 1450, 1120, 890 cm^{-1};^{1}H NMR (400 MHz,

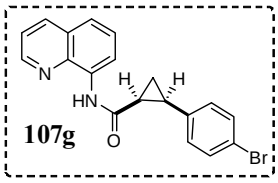


107f

$CDCl_3$): δ 10.03 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.51 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.14 (dt, 2H, J_1 = 6.9 Hz, J_2 = 2.4 Hz), 7.53-7.40 (m, 5H), 2.70 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.6 Hz), 2.48-2.43 (m, 1H), 2.01-1.97 (m, 1H), 1.59-1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 148.1, 146.5, 145.0, 138.0, 136.4, 134.2, 130.0, 127.9, 127.3, 123.1, 121.6, 121.5, 116.3, 25.8, 25.6, 11.6; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}O_3N_3$: 334.1192; found 334.1178.

(*1S*,2R)-2-(4-Bromophenyl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide**

(107g): Following the general procedure described above, **107g**was obtained after purification

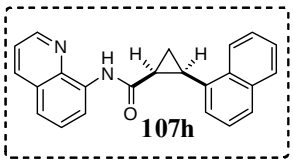


107g

by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as white colour solid; Yield: 69%; mp 168-170^{o}C; IR (KBr): 3349, 1684, 1525, 1324, 790 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.51 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.4 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.42-7.37 (m, 3H), 7.33-7.30 (m, 2H), 7.23-7.17 (m, 2H), 2.53 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.32-2.26 (m, 1H), 1.86-1.81 (m, 1H), 1.44-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 148.0, 138.1, 136.4, 135.8, 134.5, 131.1, 131.0, 127.9, 127.4, 121.5, 121.2, 120.4, 116.3, 25.4, 25.1, 11.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}ON_2Br$: 367.0446; found 367.0435.

(*1S*,2R)-2-(Naphthalen-1-yl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide**

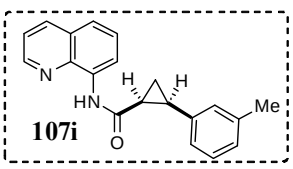
(107h): Following the general procedure described above, **107h**was obtained after purification



107h

by column chromatography on silica gel (EtOAc:Hexanes = 40:70) as brown colour solid; Yield: 40%; mp 82-84^{o}C; IR (KBr): 3351, 1681, 1525, 1324, 791 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (br s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.37 (d, 1H, J = 8.3 Hz), 8.32 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.6 Hz), 8.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.76 (d, 1H, J= 7.7 Hz), 7.71 (d, 1H, J= 8.3 Hz), 7.56 (d, 1H, J = 7.1 Hz), 7.47-7.25 (m, 6H), 2.98 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.4 Hz), 2.60-2.55 (m, 1H), 2.09-2.05 (m, 1H), 1.65-1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 147.8, 138.0, 136.2, 134.4, 133.4, 133.3, 132.8, 128.5, 127.7, 127.4, 127.2, 126.9, 125.8, 125.4, 125.3, 123.9, 121.4, 120.8, 116.2, 24.7, 24.0, 11.3; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ON_2$: 339.1497; found 339.1491.

(*1S*,2R)-*N*-(Quinolin-8-yl)-2-m-tolylcyclopropanecarboxamide (107i):** Following the general procedure described above, **107i**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light yellow colour liquid; Yield:

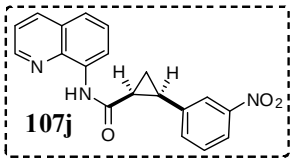


107i

33%; IR (DCM): 3352, 1685, 1523, 1324, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.55 (t, 1H, J = 4.2 Hz), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.41-7.37 (m, 3H), 7.17-7.08 (m, 3H), 6.94 (d, 1H, J = 7.0 Hz), 2.60 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.6 Hz), 2.31-2.26 (m, 1H), 2.24 (s, 3H), 1.90-1.85 (m, 1H), 1.43-1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 148.0, 138.1, 137.4, 136.6, 136.3,

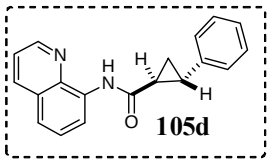
134.7, 130.2, 127.9, 127.8, 127.4, 126.1, 121.5, 121.0, 116.4, 116.3, 25.9, 25.1, 21.4, 11.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}ON_2$: 303.1497; found 303.14916.

(*1S*,2R)-2-(3-Nitrophenyl)-*N*-(quinolin-8-yl)cyclopropanecarboxamide (107j):**Following the general procedure described above, **107j**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as red colour solid; Yield: 62%; mp 148-150^oC; IR (KBr): 3341, 1684, 1526, 1348, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.46 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.23 (t, 1H, J = 1.8 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.00 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.8 Hz), 7.67-7.64 (m, 1H), 7.45-7.35 (m, 4H), 2.69 (dd, 1H, J_1 = 16.6 Hz, J_2= 8.6 Hz), 2.43-2.35 (m, 1H), 1.98-1.94 (m, 1H), 1.56-1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 148.1, 148.0, 139.0, 138.0, 136.4, 135.3, 134.3, 128.7, 127.9, 127.3, 124.6, 121.7, 121.6, 121.4, 116.3, 25.3, 25.2, 11.4; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}N_3O_3$: 334.1192; found 334.1180.



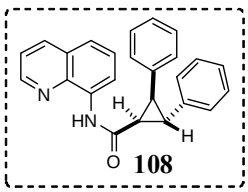
107j

(*1S*,2S)-2-Phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (105d):** Following the general procedure described above, **105d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour solid; Yield: 94%; mp 84-86 ^oC; IR (DCM): 3331, 1648, 1528, 1190, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.1 (br s, 1H), 8.84-8.79 (m, 2H), 8.16 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.9 Hz), 7.58-7.50 (m, 2H), 7.46 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.2 Hz), 7.35 (td, 2H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.28-7.23 (m, 1H), 7.21-7.19 (m, 2H), 2.74-2.70 (m, 1H), 2.11-2.07 (m, 1H), 1.87-1.82 (m, 1H), 1.49-1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.1, 140.6, 138.2, 136.3, 134.6, 128.5, 128.0, 127.4, 126.4, 126.1, 121.4, 116.4, 28.2, 26.1, 16.6; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}ON_2$: 289.1341; found 289.1332.



105d

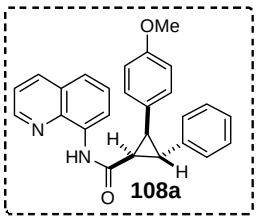
(*2S*,3S)-2,3-Diphenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108):**Following the general procedure described above, **108**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 55%; IR (DCM): 3337, 1670, 1578, 1294, 753 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (t, 1H, J = 4.9 Hz), 8.15 (dd, 1H, J_1= 8.3 Hz, J_2 = 1.6 Hz),



108

7.50-7.23 (m, 13H), 3.48 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.09 (dd, 1H, J_1 = 9.3 Hz, J_2 = 7.0 Hz), 2.65 (dd, 1H, J_1 = 9.3 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 148.0, 140.1, 138.1, 136.3, 136.2, 134.5, 129.2, 128.6, 128.4, 128.2, 127.9, 127.4, 126.8, 126.7, 126.6, 121.5, 121.2, 116.4, 34.9, 34.8, 29.2; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}ON_2$: 365.1654; found 365.1648.

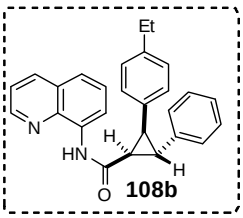
(*1R*,2S*,3S)-2-(4-Methoxyphenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108a):** Following the general procedure described above,



108a

108a was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as red colour liquid; Yield: 56%; IR (DCM): 3350, 1684, 1524, 1248, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (t, 1H, J = 4.5 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48-7.44 (m, 3H), 7.41-7.34 (m, 6H), 7.31-7.27 (m, 1H), 6.85 (d, 2H, J= 6.7 Hz), 3.78 (s, 3H), 3.41 (dd, 1H, J_1 = 7.2 Hz, J_2 = 5.2 Hz), 3.03 (dd, 1H, J_1 = 9.4 Hz, J_2 = 7.2 Hz), 2.60 (dd, 1H, J_1 = 9.4 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 158.4, 148.0, 140.2, 138.1, 136.3, 134.6, 130.1, 128.6, 128.2, 127.9, 127.4, 126.7, 126.6, 121.5, 121.2, 116.3, 113.7, 55.1, 34.8, 34.2, 29.3; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{130a2}N_2$: 395.1760; found 395.1754.

(*1R*,2S*,3S)-2-(4-Ethylphenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108b):** Following the general procedure described above, **108b** was obtained after

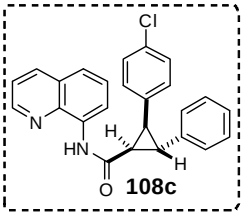


108b

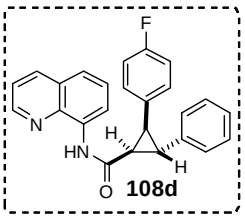
purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as green colour liquid; Yield: 64%; IR (DCM): 3350, 1595, 1524, 1324, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.66 (t, 1H, J = 4.5 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47-7.44 (m, 3H), 7.41-7.36 (m, 6H), 7.31-7.27 (m, 1H), 7.15 (d, 2H, J = 8.0 Hz), 3.45 (dd, 1H, J_1 = 7.2 Hz, J_2 = 5.2 Hz), 3.05 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.2 Hz), 2.66-2.60 (m, 3H), 1.23 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 148.0, 142.6, 140.3, 136.3, 134.5, 133.3, 129.1, 128.6, 127.9, 127.7, 127.4, 126.8, 126.6, 126.1, 121.5, 121.2, 116.4, 34.9, 34.6, 29.3, 28.5, 15.4; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}ON_2$: 393.1967; found 393.1954.

(*1R*,2S*,3S)-2-(4-Chlorophenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108c):**Following the general procedure described above, **108c** was obtained after

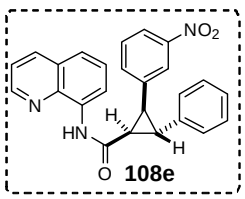
purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light green colour liquid; Yield: 56%; IR (DCM): 3349, 1684, 1555, 1324, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.49-7.28 (m, 12H), 3.42 (dd, 1H, J_1 = 7.2 Hz, J_2 = 5.2 Hz), 3.01 (dd, 1H, J_1 = 9.2 Hz, J_2 = 7.2 Hz), 2.63 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 148.1, 140.6, 139.7, 138.1, 134.8, 134.4, 132.5, 130.5, 128.7, 128.5, 128.0, 128.0, 126.8, 126.8, 126.1, 121.6, 116.4, 34.8, 34.0, 29.4; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}ON_2Cl$: 399.1264; found 399.1251.



(*1R*,2S*,3S)-2-(4-Fluorophenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108d):** Following the general procedure described above, **108d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light green colour liquid; Yield: 80%; IR (DM): 3345, 1597, 1523, 1342, 891 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.63 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.50-7.27 (m, 10H), 7.0 (td, 2H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 3.41 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.03 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz), 2.62 (dd, 1H, J_1 = 9.0 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 162.0 (d, J_{C-F}= 244 Hz), 148.1, 139.8, 138.1, 136.4, 134.5, 131.9 (d, J_{C-F}= 2.0 Hz), 130.7 (d, J_{C-F}= 8.0 Hz), 128.5, 127.9, 127.4, 126.7, 126.7, 121.6, 121.3, 116.4, 115.1 (d, J_{C-F}= 21.0 Hz), 34.7, 33.9, 29.4. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{19}ON_2FNa$: 405.1379; found 405.1367.

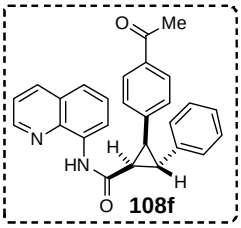


(*1R*,2S*,3S)-2-(3-Nitrophenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108e):**Following the general procedure described above, **108e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as red colour solid; Yield: 77%; mp 173-175°C; IR (KBr): 3335, 1662, 1525, 1348, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.34 (s, 1H), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.78 (d, 1H, J = 7.7 Hz), 7.50-7.28 (m, 9H), 3.50 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.10 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz), 2.70 (dd, 1H, J_1 = 9.0 Hz, J_2 = 5.2 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 148.2, 148.1, 139.0, 138.5, 138.1, 136.4, 135.3, 134.2, 128.9,



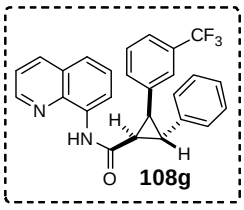
128.8, 127.9, 127.3, 127.0, 126.7, 124.4, 122.0, 121.7, 121.6, 116.4, 34.8, 33.8, 29.6; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}O_3N_3$: 410.1505; found 410.1498.

(*1R*,2S*,3S)-2-(4-Acetylphenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108f):**Following the general procedure described above, **108f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid;



Yield: 74%; mp 138-140^{o}C; IR (KBr): 3344, 1679, 1525, 1267, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.09 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.4 Hz, J_2 = 1.8 Hz), 8.60 (dd, 1H, J_1 = 7.1 Hz, J_2 = 2.4 Hz), 8.16 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.90 (d, 2H, J= 8.2 Hz), 7.55 (d, 2H, J= 8.2 Hz), 7.50-7.33 (m, 8H), 3.50 (dd, 1H, J_1 = 7.3 Hz, J_2 = 5.2 Hz), 3.08 (dd, 1H, J_1 = 9.5 Hz, J_2 = 7.3 Hz), 2.70 (dd, 1H, J_1 = 9.5 Hz, J_2 = 5.2 Hz), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 166.6, 148.1, 142.1, 139.5, 138.1, 136.4, 135.6, 134.3, 129.4, 128.7, 128.3, 127.9, 127.4, 126.9, 126.7, 121.7, 121.5, 116.4, 35.1, 34.5, 29.4, 26.6; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{130a2}N_2$: 407.1760; found 407.1743.

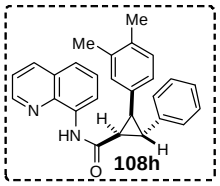
(*1R*,2S*,3S)-2-(3-(Trifluoromethyl)phenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108g):**Following the general procedure described above,



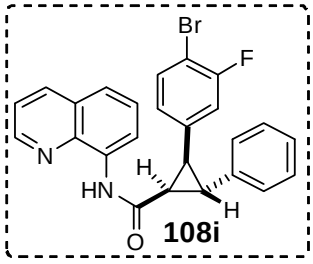
108g was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 64%; IR (DCM): 2923, 1620, 1524, 1162, 787 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.59 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.72 (s, 1H), 7.64 (d, 1H, J = 7.7 Hz), 7.50-7.28 (m, 10H), 3.47 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.08 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.0 Hz), 2.68 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 148.1, 139.4, 138.1, 137.3, 136.4, 134.3, 132.3, 130.4 (q, J_{C-F}= 31Hz), 128.7, 128.5, 127.9, 127.4, 126.9 (q, J_{C-F}= 270 Hz), 126.8, 126.7, 126.3 (q, J_{C-F}= 12.5 Hz),123.7 (q, J_{C-F}= 3.4 Hz), 121.6, 121.4, 116.4, 34.8, 34.1, 29.4; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}ON_2F_3$: 433.1528; found 433.1506.

(*1R*,2S*,3S)-2-(3,4-Dimethylphenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108h):**Following the general procedure described above, **108h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; IR (DCM): 3351, 291, 1685, 1485, 756

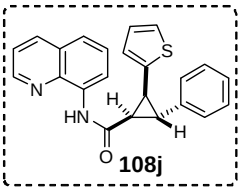
cm^{-1};Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.68 (t, 1H, J = 4.2 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.48-7.18 (m, 10H), 7.07 (d, 1H, J = 8.0 Hz), 3.43 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.02 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.0 Hz), 2.61 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.2 Hz), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 148.0, 140.4, 138.1, 136.3, 136.2, 135.0, 134.6, 133.6, 130.6, 129.5, 128.6, 127.4, 126.8, 126.5, 126.4, 126.3, 126.1,121.5, 121.2, 116.4, 34.8, 34.6, 29.3, 19.9, 19.5; HRMS(ESI): *m/z* [M + H]$^+$ calcd for $C_{27}H_{25}ON_2$: 393.1967; found 393.1955.



(*1R*,2S*,3S)-2-(3-Bromo-5-fluorophenyl)-3-phenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (108i):**Following the general procedure described above, **108i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as black colour liquid; Yield: 66%; IR (DCM): 3345, 1577, 1485, 1324, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51-7.28 (m, 9H), 7.24 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.6 Hz), 7.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 3.40 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 2.98 (dd, 1H, J_1 = 9.2 Hz, J_2 = 7.0 Hz), 2.64 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 158.5(d, $J_{C\text{-}F}$= 246 Hz), 148.1, 139.3, 138.2(d, $J_{C\text{-}F}$= 7.0 Hz), 138.1 136.4, 134.3, 133.0, 128.7, 127.9, 127.4, 126.9, 126.6, 126.1 (d, $J_{C\text{-}F}$= 2.0 Hz), 121.6 (d, $J_{C\text{-}F}$= 52.0 Hz) 117.4 (d, $J_{C\text{-}F}$= 92.0 Hz), 116.5, 107.2 (d, $J_{C\text{-}F}$= 21.0 Hz), 34.8, 33.8, 29.5; HRMS(ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{19}ON_2BrF$: 461.0665; found 461.0653.

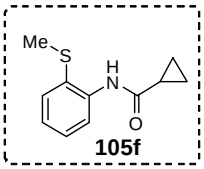


(*1R*,2R*,3S)-2-Phenyl-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)cyclopropanecarboxamide (108j):**Following the general procedure described above, **108j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 86%;IR (DCM): 3349, 1685, 1524, 1324, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 5.3 Hz, J_2 = 3.8 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.50-7.45 (m, 3H), 7.41-7.28 (m, 5H), 7.16 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz), 7.10 (dt, 1H, J_1 = 3.52 Hz, J_2 = 1.1 Hz), 6.96 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 3.47 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.4 Hz), 3.12-3.07 (m, 1H), 2.67 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 148.0, 139.5, 139.4, 138.2, 136.4, 134.5,

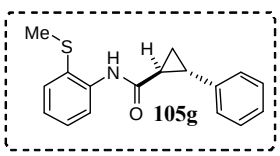


128.6,127.9, 127.4, 126.8, 126.7, 126.3, 126.1, 124.3, 121.6, 121.3, 116.5, 35.3, 30.9, 29.2; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ON_2S$: 371.1218; found 371.1207.

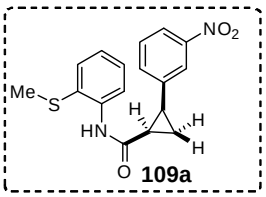
***N*-(2-(Methylthio)phenyl)cyclopropanecarboxamide (105f):**Following the general procedure described above, **105f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as white colour solid; Yield: 93%; mp 81-83 ^oC; IR (KBr): 3350, 1596, 1415, 1121, 791 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.34 (d, 1H, J = 6.3 Hz), 7.50 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.32-7.28 (m, 1H), 7.07 (t, 1H, J = 7.2 Hz), 2.42 (s, 3H), 1.65-1.60 (m, 1H), 1.15-1.11 (m, 2H), 0.92-0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 132.8, 128.7, 125.0, 124.1, 120.7, 18.9, 16.0, 8.15. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{13}NOSNa$: 230.0616; found 230.0614.



(*1S*,2S)-*N*-(2-(Methylthio)phenyl)-2-phenylcyclopropanecarboxamide (105g):**Following the general procedure described above, **105g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as white colour solid; Yield: 78%; mp 121-1130aC; IR (KBr): 3331, 1648, 1528, 1190, 695 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (br s, 1H), 8.41 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.36-7.24 (m, 3H), 7.18 (d, 2H, J = 7.2 Hz), 7.10 (t, 1H, J = 7.2 Hz), 2.69-2.64 (m, 1H), 2.41 (s, 3H), 1.90-1.86 (m, 1H), 1.80-1.76 (m, 1H), 1.46-1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 140.5, 138.6, 133.2, 129.0, 128.6, 126.5, 126.1, 124.7, 124.2, 120.4, 27.9, 26.1, 19.2, 16.7; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}ONS$: 284.1109; found 284.1103.

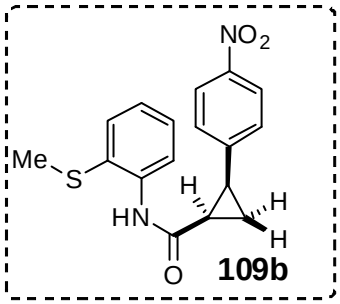


(*1S*,2R)-*N*-(2-(Methylthio)phenyl)-2-(3-nitrophenyl)cyclopropanecarboxamide (109a):**Following the general procedure described above, **109a**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 64%; mp 140-142^oC;IR (KBr): 2921, 1578, 1526, 1348, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 8.12 (s, 1H), 7.94 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.84 (d, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.34-7.29 (m, 2H), 7.06 (td, 1H, J_1 = 8.0 Hz, J_2 = 1.1 Hz), 6.92 (t, 1H, J = 7.2 Hz), 2.57 (dd, 1H, J_1 = 16.5 Hz, J_2 = 8.4 Hz), 2.26 (s, 3H), 2.17-2.11 (m, 1H), 1.86-1.81 (m, 1H), 1.43-1.39 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 147.9,



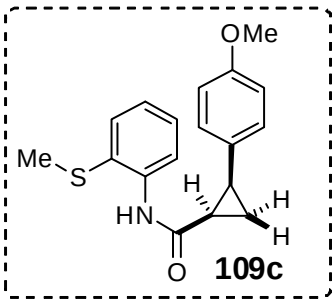
138.9, 137.8, 135.3, 132.3, 128.8, 128.5, 125.5, 124.5, 123.4, 121.7, 120.9, 25.2, 24.9, 18.7, 11.2; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}O_3N_2S$: 329.0960; found 329.0954.

(*1S*,2R)-*N*-(2-(methylthio)phenyl)-2-(4-nitrophenyl)cyclopropanecarboxamide (109b):** Following the general procedure described above, **109b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 55%; mp 108-110°C; IR (KBr): 3337, 1515, 1432, 1342, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.13 (d, 2H, *J* = 8.4 Hz), 8.00 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 7.3 Hz), 7.21 (td, 1H, J_1 = 8.0 Hz, J_2 = 1.4 Hz), 7.03 (t, 1H, *J* = 7.4 Hz), 2.67 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.4 Hz), 2.36 (s, 3H), 2.30-2.25 (m, 1H), 1.98-1.93 (m, 1H), 1.57-1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 146.6, 144.7, 137.9, 132.6, 129.9, 128.7, 125.0, 124.5, 123.2, 120.7, 25.6, 25.5, 18.8, 11.5; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}O_3N_2S$: 329.0960; found 329.0954.



109b

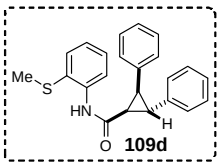
(*1S*,2R)-2-(4-Methoxyphenyl)-*N*-(2-(methylthio)phenyl)cyclopropanecarboxamide (109c):** Following the general procedure described above, **109c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as black colour liquid; Yield: 40%; IR(DCM): 3337, 1578, 1433, 1248, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 8.09 (d, 1H, *J* = 7.2 Hz), 7.44 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.26-7.18 (m, 3H), 7.01 (t, 1H, *J* = 7.5 Hz), 6.81 (dt, 2H, J_1 = 9.6 Hz, J_2 = 2.0 Hz), 3.77 (s, 3H), 2.58 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.6 Hz), 2.32 (s, 3H), 2.16-2.10 (m, 1H), 1.84-1.80 (m, 1H), 1.42-.1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 158.3, 138.6, 133.0, 130.0, 128.9, 128.4, 127.9, 123.9, 120.6, 113.5, 55.1, 25.1, 18.9, 10.8; HRMS(ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}O_2NSNa$: 336.1034; found 336.1028.



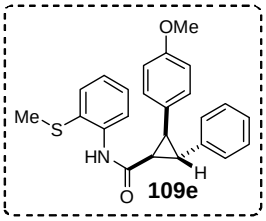
109c

(*2S*,3S)-*N*-(2-(Methylthio)phenyl)-2,3-diphenylcyclopropanecarboxamide (109d):** Following the general procedure described above, **109d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 84%; mp 100-102°C; IR (DCM): 3337, 1670, 1578, 1294, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.15 (d, 1H, *J* = 7.6 Hz), 7.47 (dd, 1H, J_1= 7.6 Hz, J_2= 1

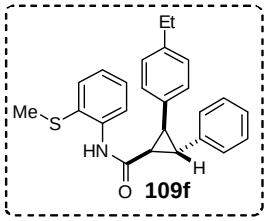
Hz), 7.43-7.28 (m, 9H), 7.26-7.21 (m, 2H), 7.04 (t, 1H, *J*= 7.1 Hz), 3.41 (dd, 1H, J_1= 7.0 Hz, J_2= 5.3 Hz), 3.03 (dd, 1H, J_1= 9.0 Hz, J_2= 7.0 Hz), 2.47 (dd, 1H, J_1= 9.0 Hz, J_2= 5.3 Hz), 2.33 (s, 3H); ^{13}C.NMR (100 MHz, $CDCl_3$): δ 166.6, 139.9, 138.5, 136.0, 133.1, 128.9, 128.6, 128.2, 126.9, 126.8, 126.7, 124.6, 124.1, 120.6, 34.8, 34.6, 28.9, 19.0; HRMS(ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{21}ONSNa$: 382.1242; found 382.12339.



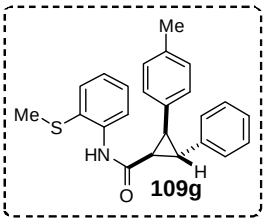
(*1R*,2S*,3S)-2-(4-Methoxyphenyl)-*N*-(2-(methylthio)phenyl)-3-phenylcyclopropanecarboxamide (109e):** Following the general procedure described above, **109e**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 68%; mp 115-117^{o}C; IR (DCM): 3338, 1578, 1508, 1247, 754 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.18 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.44-7.22 (m, 8H), 7.05 (t, 1H, *J* = 7.4 Hz), 6.89 (dt, 2H, J_1 = 8.7 Hz, J_2 = 1.9 Hz), 3.80 (s, 3H), 3.37 (dd, 1H, J_1 = 7.0 Hz, J_2 = 5.2 Hz), 3.0 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.0 Hz), 2.43.(dd, 1H, J_1 = 9.0 Hz, J_2 = 5.2 Hz), 2.35.(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 158.5, 140.0, 138.5, 133.0, 130.0, 128.9, 128.7, 128.6, 128.0,127.0, 126.7, 124.1, 120.7, 113.7, 55.2, 34.7, 34.0, 29.0, 19.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{130a2}NSNa$: 412.1347; found 412.13300.



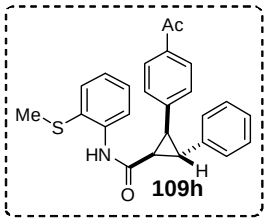
(*1R*,2S*,3S)-2-(4-Ethylphenyl)-*N*-(2-(methylthio)phenyl)-3-phenylcyclopropanecarboxamide (109f):** Following the general procedure described above, **109f**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 69%; mp 118-120 ^{o}C; IR (DCM): 3342, 1685, 1508, 1431, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.18 (d, 1H, *J* = 7.1 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.41-7.18 (m, 8H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 7.4 Hz), 3.39 (t, 1H, *J* = 6.0 Hz), 3.0 (t, 1H, *J* = 8.1 Hz), 2.64 (q, 2H, *J* = 7.6 Hz), 2.45 (dd, 1H, J_1 = 9.3 Hz, J_2 = 5.2 Hz), 2.32 (s, 3H), 1.24 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 142.7, 140.0, 138.5, 133.1, 128.9, 128.8, 128.6, 127.8, 126.7, 126.6, 126.2, 124.7, 124.1, 120.6, 34.8, 34.4, 29.1, 28.5, 19.0, 15.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{25}ONSNa$: 410.1555; found 410.1539.



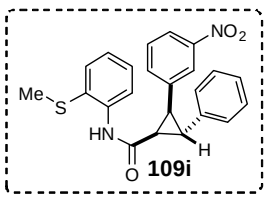
(*1R*,2S*,3S)-*N*-(2-(Methylthio)phenyl)-2-phenyl-3-p-tolylcyclopropanecarboxamide (109g):**Following the general procedure described above, **109g**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 53%; mp 105-107^{o}C; IR (DCM): 3335, 1578, 1435, 1295, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.18 (d, 1H, *J* = 8.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.40-7.29 (m, 7H), 7.23 (t, 1H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.04 (t, 1H, *J* = 7.3 Hz), 3.37 (t, 1H, *J* = 6.0 Hz), 3.0 (t, 1H, *J* = 8.0 Hz), 2.43 (dd, 1H, J_1= 9.3 Hz, J_2= 5.2 Hz), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 140.0, 138.5, 136.4, 133.1, 132.9, 129.0, 128.9, 128.8, 128.6, 126.7, 126.6, 124.6, 124.1, 120.6, 34.7, 34.3, 29.0, 21.1, 19.0; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}ONS$: 374.1579; found 374.1570.



(*1R*,2S*,3S)-2-(4-Acetylphenyl)-*N*-(2-(methylthio)phenyl)-3-phenylcyclopropanecarboxamide (109h)**: Following the general procedure described above, **109h**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 88%; mp 130-132^{o}C; IR (DCM): 3344, 1676, 1525, 1267, 751 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 8.10 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 2H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.47-7.30 (m, 6H), 7.23-7.20 (m, 1H), 7.05 (t, 1H, *J* = 7.4 Hz) 3.45 (dd, 1H, J_1= 6.8 Hz, J_2= 5.2 Hz), 3.05 (t, 1H, *J* = 7.5 Hz), 2.59 (s, 3H), 2.51 (dd, 1H, J_1= 9.4 Hz, J_2= 5.2 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 166.2, 141.8, 139.3, 138.1, 135.7, 132.9, 129.2, 128.8, 128.7, 128.3, 126.7, 126.6, 124.9, 124.4, 120.6, 35.0, 34.3, 29.1, 26.6, 19.0; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}O_2NS$: 402.1528; found 402.1517.

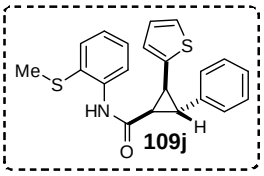


(*1R*,2S*,3S)-*N*-(2-(Methylthio)phenyl)-2-(3-nitrophenyl)-3-phenylcyclopropanecarboxamide (109i):**Following the general procedure described above, **109i**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 69%; mp 130-132^{o}C; IR (KBr): 3375, 1662, 1578, 1348, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.31 (br s, 1H), 8.10 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 7.75 (d, 1H, *J* = 7.6 Hz), 7.50-7.30 (m, 7H), 7.23-7.19 (m, 1H), 7.06 (t, 1H, *J* = 7.4 Hz), 3.46 (dd, 1H, J_1 = 6.8 Hz, J_2 = 5.2 Hz), 3.09 (t, 1H, *J* = 7.8 Hz), 2.51 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.2 Hz), 2.39 (s, 3H); ^{13}C NMR (100 MHz,

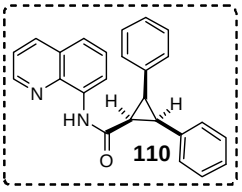


$CDCl_3$): δ 166.2, 148.1, 138.9, 138.3, 137.8, 135.2, 132.6, 129.0, 128.8, 128.7, 127.1, 126.6, 125.4, 124.6, 124.4, 122.0, 120.9, 34.6, 33.6, 29.3, 18.9; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}O_3N_2S$: 405.1273; found 405.1263.

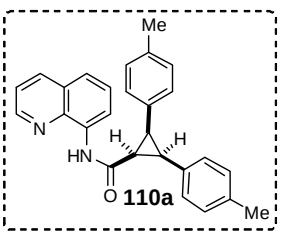
(*1R*,2R*,3S)-*N*-(2-(Methylthio)phenyl)-2-phenyl-3-(thiophen-2-yl)cyclopropanecarboxamide (109j)**: Following the general procedure described above, **109j**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 70%; IR (DCM): 3350, 1596, 1425, 1121, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.21 (d, 1H, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 7.6 Hz), 7.40-7.24 (m, 6H), 7.16 (dd, 1H, J_1= 5.1 Hz, J_2= 1.0 Hz), 7.05-7.04 (m, 2H), 6.95 (dd, 1H, J_1= 5.1 Hz, J_2= 3.6 Hz), 3.40 (t, 1H, *J* = 6.0 Hz), 3.06 (dd, 1H, J_1= 8.7 Hz, J_2= 7.0 Hz), 2.50-2.46 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 140.4, 139.2, 133.1, 129.0, 128.7, 128.5, 126.9, 126.7, 126.5, 126.2,126.1, 124.3, 124.2, 120.6, 35.2, 30.6, 29.0, 19.1; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}ONS_2$: 366.0986; found 366.0976.



(*2S*,3R)-2,3-Diphenyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (110):** Following the general procedure described above, **110**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as white colour solid; Yield: 55%; mp 164-166 ^oC; IR (DCM): 2929, 1563, 14552, 1158, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.69-8.67 (m, 2H), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 2H), 7.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30-7.28 (m, 4H), 7.22-7.15 (m, 6H), 3.08 (d, 2H, *J* = 9.1 Hz), 2.79 (t, 1H, *J* = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 147.8, 138.2, 136.2, 134.6, 134.4, 131.1, 127.8, 127.5, 127.3, 126.3, 121.4, 121.1, 116.4, 29.3, 29.1. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{20}ON_2Na$: 387.1473; found 387.1467.

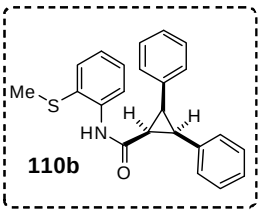


(*2S*,3R)-*N*-(Quinolin-8-yl)-2,3-di-*p*-tolylcyclopropanecarboxamide (110a):** Following the general procedure described above, **110a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 46%; IR (DCM): 3350, 1596, 1425, 1121, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.70-8.68 (m, 2H), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.45-7.40 (m, 3H),

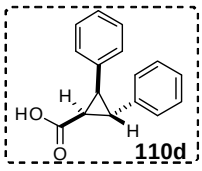


7.17 (d, 4H, *J* = 8.0 Hz), 7.02 (d, 4H, *J* = 8.0 Hz), 3.02 (d, 2H, *J* = 9.3 Hz), 2.72 (t, 1H, *J* = 9.3 Hz), 2.29 (6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 147.7, 138.2, 136.2, 135.7, 134.7, 131.3, 131.0, 128.2, 127.3, 121.4, 121.0, 116.5, 29.1, 28.8, 21.1. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{24}ON_2Na$: 415.1786; found 415.1776.

(*2S*,3R)-*N*-(2-(Methylthio)phenyl)-2,3diphenylcyclopropanecarboxamide (110b):** Following the general procedure described above, **110b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as Red colour liquid; Yield: 39%; IR (DCM): 3340, 1675, 1583, 1289, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 8.24 (d, 1H, *J* = 8.1 Hz), 7.40 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.3 Hz), 7.26-7.18 (m, 11H), 7.00 (t, 1H, *J* = 7.3 Hz), 3.02 (d, 2H, *J* = 9.4 Hz), 2.67 (t, 1H, *J* = 9.4 Hz), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 138.6, 134.3, 131.0, 128.8, 128.6, 128.2, 127.6, 126.7, 126.4, 124.0, 120.5, 29.4, 28.5, 18.9. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{21}ONSNa$: 382.1242; found 382.1238.



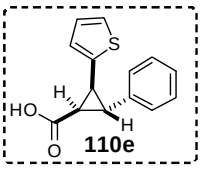
(*1S*,2S*,3R)-2-(4-Ethylphenyl)-*N*-(2-(methylthio)phenyl)-3-(3-nitrophenyl)cyclopropanecarboxamide (110c):** Following the general procedure described above, **110c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 30%; IR (KBr): 3335, 1520, 1415, 1365, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.22 (s, 1H), 8.16 (d, 1H, *J* = 8.0 Hz), 8.06-8.04 (m, 1H), 7.52 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 7.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 7.33 (t, 2H, *J* = 8.0 Hz), 7.24-7.19 (m, 1H), 7.08-7.02 (m, 4H), 3.10-3.01 (m, 2H), 2.68 (t, 1H, *J* = 9.3 Hz), 2.60 (q, 2H, *J* = 7.6 Hz), 2.17 (s, 3H), 1.20 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 147.5, 142.8, 138.1, 137.4, 136.5, 132.9, 130.5, 130.4, 128.8, 128.0, 126.5, 124.3, 121.4, 120.6, 116.9, 29.0, 28.6, 28.4, 28.1, 18.8, 15.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}O_3N_2S$: 433.1586; found 433.1580.



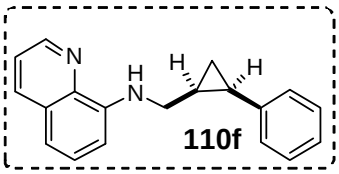
(*2S*,3S)-2,3-Diphenylcyclopropanecarboxylic acid (110d):** Following the general procedure described above, the compound **110d** was obtained as brown colour solid crude material was almost pure); Yield: 85%; mp 139-141 ^{o}C; IR (DCM): 3061, 1693, 1446, 1231, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.10 (m, 10H), 3.21 (dd, 1H, J_1 = 7.1 Hz, J_2 = 5.2 Hz), 2.96 (dd, 1H, J_1 = 9.6

Hz, J_2 = 7.1 Hz), 2.43 (dd, 1H, J_1 = 9.6 Hz, J_2 = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 139.5, 136.0, 129.2, 128.6, 128.0, 126.8, 126.7, 126.6, 34.7, 31.0, 29.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{14}O_2$: 238.0994 $[M]^+$; calcd for $C_{16}H_{13}O_2$: 237.0916 $[M - H]^-$; found 237.0917 $[M - H]^-$.

(*1R*,2R*,3S)-2-Phenyl-3-(thiophen-2-yl)cyclopropanecarboxylic acid (110e):** Following the general procedure described above, **110e** was obtained after concentrated in vacuum gave solid materialas brown colour solid (crude material was almost pure); Yield: 80%; mp 170-172 °C; IR (DCM): 2925, 1702, 1433, 1102, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 7.17-7.15 (m, 1H), 7.01- 6.93 (m, 2H), 3.20 (t, 1H, *J*= 6.4 Hz), 3.00-2.96 (m, 1H), 2.44 (dd, 1H, J_1 = 9.3 Hz, J_2 = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 138.8, 129.1, 128.6, 128.1, 127.0, 126.7, 126.6, 124.3, 31.7, 31.4, 29.0. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}O_2S$: 244.0558 $[M]^+$; calcd for $C_{14}H_{11}O_2S$: 243.0480 $[M - H]^-$; found 243.0478 $[M - H]^-$.



***N*-(((*1S*,2R**)-2-Phenylcyclopropyl)methyl)quinolin-8-amine (110f)**: Following the general procedure described above, **110f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as green colour liquid; Yield: 66%; IR (DCM): 3349, 1576, 1519, 1380, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.11 (dd, 1H, J_1= 8.3 Hz, J_2= 1.7 Hz), 7.47-7.10 (m, 9H), 6.75 (dd, 1H, J_1= 7.6 Hz, J_2= 0.8 Hz), 3.51 (dd, 1H, J_1= 12.7 Hz, J_2= 6.8 Hz), 3.34 (dd, 1H, J_1= 12.7 Hz, J_2= 6.8 Hz), 2.01-1.97 (m, 1H), 1.70-1.65 (m, 1H), 1.11 (t, 2H, *J*= 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 144.8, 142.8, 138.1, 136.1, 128.7, 128.4, 127.8, 125.8, 125.6, 121.4, 114.0, 104.7, 47.6, 22.7, 22.2, 15.0; HRMS (ESI): *m/z* [M + H]+ calcd for $C_{19}H_{19}N_2$: 275.1548; found 275.15359.



General procedure for the synthesis of cyclobutanecarboxamides 111e-111g and 111h-111k: A dry flask containing the corresponding amine (auxiliary) (1 mmol), Et_3N (1.1 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 cyclobutanecarbonyl chloride (1 mmol). The resulting mixture was stirred for 10 min at rt. Then, the reaction mixture was refluxed for 12 h. After this period, the reaction mixture was diluted with dichloromethane

and washed with water and twice with saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh, EtOAc/hexanes = 20:80) furnished the corresponding cyclobutanecarboxamides **111e-111g** and **111h-111k**.

Procedure for synthesis of cyclobutanecarboxamide 111d: 2-Picolinic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h at rt under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 ml) under nitrogen atmosphere. Then, the DCM solution containing 2-picolinoyl chloride was added to a separate flask containing cyclobutanamine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt for 10 min. Next, the reaction mixture was refluxed for 12 h. Then, the reaction mixture was further diluted with dichloromethane (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes = 20:80) furnished the cyclobutanecarboxamide **111d**.

General procedure for the preparation of bis-arylated cyclobutanecarboxamides 114,114-114w, 117a-117c/119a-119m/121a-121o: A solution of cyclobutanecarboxamide **111e** (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125mmol (5 mol %)), aryl iodide (1 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (2-3 mL) was heated at an appropriate temperature (73-110 ^oC, see the corresponding Tables/ Schemes for specific examples) for an appropriate time (8-24 h, see the corresponding Tables/ Schemes for specific examples) under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh) furnished the corresponding bis-arylated cyclobutanecarboxamides**114,114-114w, 117a-117c/119a-119m/121a-121o** (see the corresponding Tables/ Schemes for specific examples).

General procedure for the preparation of mono-arylated cyclobutanecarboxamides 115a-115d: A solution of *N*-(quinolin-8-yl)cyclobutanecarboxamide (**111e**, 56 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125mmol (5 mol %)), aryl iodide (0.125 mmol) AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (2-3 mL) was heated at an appropriate temperature (73-

110 ^{o}C, see the corresponding Tables/ Schemes for specific examples) for an appropriate time (15-24 h, see the corresponding Tables/ Schemes for specific examples) under nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel, 100–200 mesh) furnished the corresponding mono-arylated cyclobutanecarboxamides**115a-115d** (see the corresponding Tables/Schemes for specific examples).

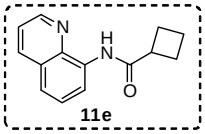
Procedure for the preparation 124a from 114e: To dry flask was added anhydrous THF (4 mL) and (*1s*,2R*,4S**)-2,4-bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (**114e**, 0.25 mmol) and the reaction flask was cooled to 0 ^{o}C under a nitrogen atmosphere. To this solution was added $LiAlH_4$ (1 mmol) in portions and refluxed overnight. Then EtOAc (3 mL) and water (1-2 mL) were added sequentially. The resulting solution was extracted with EtOAc (2 x 15 mL) and dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation and product was purified by column chromatography on silica gel (EtOAc/Hexane 10:90), which afforded the product **124a**.

Procedure for the hydrolysis of the bis-arylated cyclobutanecarboxamides 114a, 114d and **114e**: The corresponding bis-arylated cyclobutanecarboxamides **114a** or **114d** or **114e** (0.25 mmol) and NaOH (6 mmol) in ethanol (3 mL) were heated at 80 °C for overnight. After this period, the reaction mixture was diluted with water and extracted with ether (2 x 10 mL). Then, acidified with 1 N HCl to get a $p^H \sim 2$. Extraction with ether (2 x 10 mL) and drying of the combined organic layers over Na_2SO_4 followed by evaporation of the solvent in vacuum gave the corresponding carboxylic acids **124b-124d**.

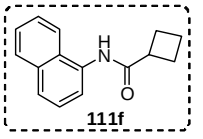
Procedure for *N*-Methylation of 114e. To a dry flask was added a suspension of NaH in oil (0.75 mmol) and washed with hexane (2 x 2 mL). Then, to this reaction flask, anhydrous THF (3 mL) and (*1s*,2R*,4S**)-2,4-bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (**114e**, 0.25 mmol) were added and the reaction flask was cooled to 0 ^{o}C and allowed to stir for 15 min under a nitrogen atmosphere. To this solution was added MeI (1.5 mmol) in drop wise and the reaction mixture was stirred at rt for 12 h. Then, EtOAc (3 mL) and water (1-2 mL) were added sequentially. The resulting solution was extracted with EtOAc (2 x 10 mL) and dried over anhydrous Na_2SO_4 and the solvent was removed by under vacuum and the

crude reaction mixture was purified by column chromatography on silica gel(EtOAc/Hexane 15:85), which afforded the product **124e**.

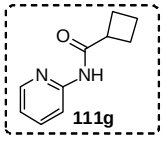
***N*-(Quinolin-8-yl)cyclobutanecarboxamide (111e)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown colour solid; 221 mg, 98% yield; mp 62-64 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 8.79 (d, 1H, J = 8.0 Hz), 8.70 (d, 1H, J = 4.0 Hz), 8.01 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.32 (dd, 1H, J_1= 8.0 Hz, J_2= 4.0 Hz), 3.37-3.29 (m, 1H), 2.50-2.41 (m, 2H), 2.30-2.22 (m, 2H), 2.02-1.87 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 148.0, 138.2, 136.2, 134.4, 127.8, 127.2, 121.5, 121.3, 116.2, 41.3, 25.4, 18.1; FT-IR (KBr): 2988, 1698, 1598, 1351, 778 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found 227.1189.



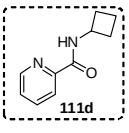
***N*-(Naphthalen-1-yl)cyclobutanecarboxamide (111f)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; red colour liquid; 164 mg, 73% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95-7.92 (m, 2H), 7.67-7.64 (m, 1H), 7.58-7.51 (m, 3H), 7.28 (dd, 1H, J_1= 7.2 Hz, J_2= 0.9 Hz), 3.55-3.48 (m, 2H), 2.44-2.30 (m, 2H), 2.11-2.02 (m, 1H), 1.91-1.78 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 134.8, 134.4, 131.0, 129.4, 128.7, 127.5, 127.2, 126.6, 125.4, 121.8, 41.5, 26.2, 25.0, 17.6 ; FT-IR (DCM): 2940, 1611, 1511, 1432, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}NO$: 226.1231; found 226.1226.



***N*-(Pyridin-2-yl)cyclobutanecarboxamide (111g)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white colour liquid; 132 mg, 75% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 9.68 (br s, 1H), 8.16-8.07 (m, 2H), 7.51 (dd, 1H, J_1= 8.2 Hz, J_2= 1.4 Hz), 6.86-6.83 (m, 1H), 3.08-3.02 (m, 1H), 2.26-2.16 (m, 2H), 1.94-1.92 (m 2H), 1.79-1.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 152.0, 147.0, 138.4, 119.3, 114.6, 40.4, 24.9, 18.0; FT-IR (DCM): 2850, 1601, 1530, 1421, 801 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1027; found 177.1029.

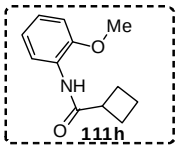


***N*-Cyclobutylpicolinamide (111d)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.60; red colour liquid; 140 mg, 81% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, J = 4.5 Hz), 8.21 (br s, 1H), 8.19 (d, 1H, J = 7.8 Hz), 7.84 (t, 1H, J = 7.8 Hz), 7.44-7.41 (m, 1H), 4.63-4.55 (m, 1H), 2.46-2.39 (m, 2H), 2.10-

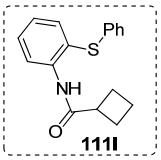


2.01 (m, 2H), 1.82-1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 149.8, 147.8, 137.5, 126.1, 122.3, 44.6, 31.2, 15.2; FT-IR (DCM): 2953, 1523, 1510, 1435, 798 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1027; found 177.1029.

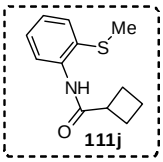
***N*-(2-Methoxyphenyl)cyclobutanecarboxamide (111h)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown colour liquid; 164 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dd, 1H, J_1= 7.9 Hz, J_2= 1.3 Hz), 7.74 (br s, 1H), 6.93 (dt, 1H, J_1= 7.8 Hz, J_2= 1.5 Hz), 6.85 (dt, 1H, J_1= 7.8 Hz, J_2= 1.2 Hz), 6.76 (dd, 1H, J_1= 8.0 Hz, J_2= 1.2 Hz), 3.74 (s, 3H), 3.16-3.08 (m, 1H), 2.37-2.27 (m, 2H), 2.18-2.10 (m, 2H), 1.95-1.82 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 147.8, 127.7, 123.4, 120.8, 119.6, 109.8, 55.5, 41.0, 25.2, 18.0; FT-IR (DCM): 2990, 1672, 1588, 1393, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$: 206.1181; found 206.1189.



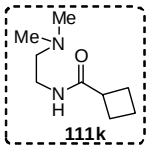
***N*-(2-(Phenylthio)phenyl)cyclobutanecarboxamide (111l)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow colour liquid; 240 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 8.0 Hz), 8.18 (br s, 1H), 7.61 (dd, 1H, J_1= 8.0 Hz, J_2= 1.5 Hz), 7.49-7.45 (m, 1H), 7.28-7.23 (m, 2H), 7.19-7.07 (m, 4H), 3.10-3.01 (m, 1H), 2.20-2.08 (m, 4H), 1.97-1.86 (m, 1H), 1.85-1.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 139.9, 136.9, 135.6, 131.1, 129.3, 126.9, 126.2, 124.1, 120.7, 119.5, 41.0, 25.1, 17.8; FT-IR (DCM): 2965, 1578, 1559, 1401, 815 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}NOS$: 284.1109; found 284.1104.



***N*-(2-Methylthio)phenyl)cyclobutanecarboxamide (111j).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; White colour solid; 194 mg, 88% yield; mp 66-68 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 1H, J = 7.2 Hz), 8.27 (br s, 1H), 7.45 (d, 1H, J = 7.2 Hz), 7.28 (dt, 1H, J_1= 8.0 Hz, J_2= 2.1 Hz), 7.04 (t, 1H, J = 8.0 Hz), 3.29-3.21 (m, 1H), 2.45-2.36 (m, 2H), 2.35 (s, 3H), 2.35-2.26 (m, 2H), 2.06-1.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 138.4, 132.9, 128.9, 125.1, 124.1, 120.4, 41.1, 25.4, 18.8, 18.2; FT-IR (KBr): 3322, 1621, 1532, 1413, 807cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NOS$: 222.0952; found 222.0943.

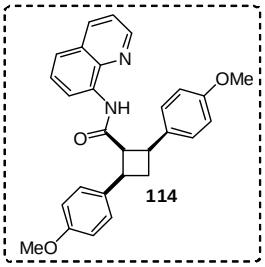


***N*-(2-(Dimethylamino)ethyl)cyclobutanecarboxamide (111k).** Analytical TLC on silica gel, 2.5:2.5 methanol/ethyl acetate R_f = 0.50; light yellow colour liquid; 136 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43-3.39 (m, 2H), 3.03-2.99 (m, 1H), 2.61 (t, 2H, J = 5.8



Hz), 2.36 (s, 6H), 2.30-2.23 (m, 2H), 2.16-2.09 (m, 2H), 1.98-1.83 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 57.7, 44.4, 39.8, 36.0, 25.3, 18.2; FT-IR (DCM): 3290, 1603, 1557, 1485, 861 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{19}N_2O$: 171.1497; found 171.1499.

(*1s*,2R*,4S)-2,4-Bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; yellow colour solid; 108 mg, 99% yield; mp 146-149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (br s, 1H), 8.64 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.30 (dd, 1H, J_1= 6.6 Hz, J_2= 2.5 Hz), 7.94 (dd, 1H, J_1= 8.3 Hz, J_2= 1.7 Hz), 7.27 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.24-7.20 (m, 6H), 6.71 (td, 4H, J_1= 8.7 Hz, J_2= 2.9 Hz), 4.03-3.97 (m, 1H), 3.95-3.90 (m, 2H), 3.61 (s, 6H), 3.43 (dd, 1H, J_1= 21.5 Hz, J_2= 11.0 Hz) 2.65-2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 157.9, 147.8, 138.2, 136.1, 134.3, 132.7, 128.2, 127.7, 127.2, 121.3, 120.9, 116.4, 113.5, 55.1, 54.8, 38.5, 30.5; FT-IR (KBr): 2936, 1689, 1612, 1519, 825 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_3$: 439.2021; found 439.2019.

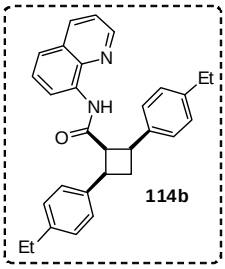


(*1s*,2R*,4S)-2,4-Diphenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114a)**.Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; brown colour solid; 89 mg, 94% yield; mp 145-147 ^{o}C; . ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 8.67 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.25 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 7.97 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.32-7.15 (m, 11H), 7.04 (t, 2H, J = 7.4 Hz), 4.14-4.10 (m, 1H), 4.06-3.99 (m, 2H), 3.52 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.8 Hz), 2.72-2.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 147.8, 140.6, 138.2, 136.1, 134.2, 128.1, 127.7, 127.2, 127.0, 126.1, 121.3, 120.9, 116.4, 54.6, 39.1, 29.9; FT-IR (KBr): 3342, 1669, 1521, 1484, 993 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{129a2}O$: 379.1810; found 379.1824.

(*1s*,2R*,4S)-*N*-(Quinolin-8-yl)-2,4-di-*p*-tolylcyclobutanecarboxamide(114a')**. Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; light yellow colour solid; 100 mg, 99% yield; mp 156-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (br s, 1H), 8.65 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.31 (dd, 1H, J_1= 6.2 Hz, J_2= 2.7 Hz), 7.93 (dd, 1H, J_1= 8.0 Hz, J_2= 1.7 Hz), 7.27 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.24-7.20

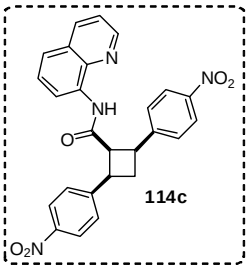
(m, 6H), 6.97 (d, 4H, J = 8.0 Hz), 4.09-4.04 (m, 1H), 4.0-3.93 (m, 2H), 3.47 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.67-2.64 (m, 1H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.5, 138.2, 137.5, 136.1, 135.4, 134.3, 128.9, 127.6, 127.3, 126.9, 121.2, 120.8, 116.4, 54.6, 38.9, 30.2, 21.0; FT-IR (KBr): 3359, 1689, 1595, 1484, 791 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O$: 407.2123; found 407.2117.

(*1s*,2R*,4S)-2,4-Bis(4-ethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114b).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.70; white colour solid; 106 mg, 98% yield; mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (br s, 1H), 8.68 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.30 (dd, 1H, J_1= 6.8 Hz, J_2= 2.2 Hz), 7.97 (dd, 1H, J_1= 8.3 Hz, J_2= 1.7 Hz), 7.31 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.27-7.22 (m, 6H), 7.02 (d, 4H, J = 8.0 Hz), 4.11-4.08 (m, 1H), 4.04-3.97 (m, 2H), 3.50 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.70-2.66 (m, 1H), 2.48 (q, 4H, J = 7.6 Hz), 1.06 (t, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 147.7, 141.8, 138.2, 137.8, 136.1, 134.3, 127.6, 127.5, 127.2, 127.0, 121.3, 120.8, 116.4, 54.7, 39.0, 30.2, 28.5, 15.5; FT-IR (KBr): 3358, 1519, 1462, 1378, 825 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2436; found 435.2436.



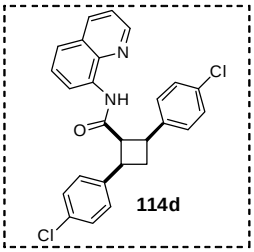
114b

(*1s*,2R*,4S)-2,4-Bis(4-nitrophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114c).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.50; brown colour solid; 86 mg, 74% yield; mp 182-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (br s, 1H), 8.73 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.18 (dd, 1H, J_1= 7.7 Hz, J_2= 1.1 Hz), 8.08-8.03 (m, 5H), 7.45 (d, 4H, J = 8.6 Hz), 7.41-7.36 (m, 2H), 7.27 (t, 1H, J = 8.0 Hz), 4.35-4.30 (m, 1H), 4.20-4.13 (m, 2H), 3.56 (dd, 1H, J_1= 21.6 Hz, J_2= 11.0 Hz), 2.89-2.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 148.2, 148.1, 146.4, 138.0, 136.5, 133.3, 127.8, 127.6, 127.1, 123.4, 121.9, 121.7, 116.4, 54.5, 38.6, 30.0; FT-IR (KBr): 3344, 1682, 1596, 1391, 840 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1511; found 469.1500.



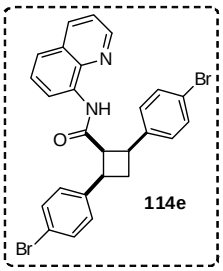
114c

(*1s*,2R*,4S)-2,4-Bis(4-chlorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114d).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; light yellow colour solid; 110 mg, 99% yield; mp 171-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 8.70 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.26 (dd, 1H, J_1= 7.6 Hz, J_2= 1.6 Hz), 8.06 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.39-7.27 (m, 3H), 7.22 (d, 4H, J = 8.5 Hz), 7.13 (td, 4H, J_1= 8.5 Hz,



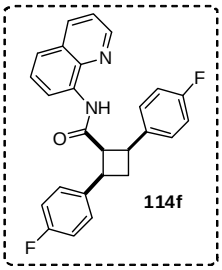
J_2= 1.9 Hz), 4.11-4.06 (m, 1H), 4.0-3.94 (m, 2H), 3.42 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.72-2.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 147.9, 138.9, 138.1, 136.3, 133.8, 131.9, 128.4, 128.2, 127.7, 127.2, 121.5, 121.4, 116.5, 54.3, 38.4, 30.1; FT-IR (KBr): 2988, 1698, 1598, 1351, 778 cm^{-1}; FT-IR (KBr): 3350, 1683, 1596, 1486, 790 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}Cl_2N_2O$: 447.1030; found 447.1010.

(*1s*,2R*,4S)-2,4-Bis(4-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114e).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; light yellow colour solid; 131 mg, 99% yield; mp 158-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (br s, 1H), 8.69 (dd,



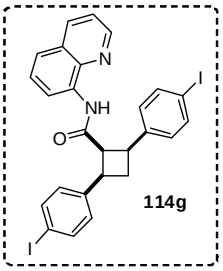
1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.26 (dd, 1H, J_1= 7.5 Hz, J_2= 1.2 Hz), 8.03 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.37-7.26 (m, 7H), 7.15 (d, 4H, J = 8.3 Hz), 4.10-4.05 (m, 1H), 3.96-3.90 (m, 2H), 3.40 (dd, 1H, J_1 = 21.7 Hz, J_2 = 11.0 Hz), 2.70-2.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 147.9, 139.5, 138.1, 136.3, 133.9, 131.1, 128.8, 127.7, 127.2, 121.5, 121.4, 120.1, 116.5, 54.2, 38.5, 30.1; FT-IR (KBr): 3349, 1687, 1524, 1323, 824 cm$^{-1;}$ HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}Br_2N_2O$: 535.0020; found 534.9999.

(*1s*,2R*,4S)-2,4-Bis(4-fluorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114f).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale yellow colour solid; 100 mg, 97% yield; mp 137-139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48



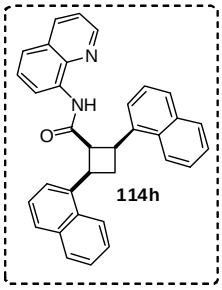
(br s, 1H), 8.69 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.27 (dd, 1H, J_1= 7.5 Hz, J_2= 1.4 Hz), 8.02 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.36-7.23 (m, 7H), 6.87 (tt, 4H, J_1= 8.4 Hz, J_2= 3.0 Hz), 4.10-4.05 (m, 1H), 4.01-3.94 (m, 2H), 3.44 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.72-2.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 161.5 (d, $J_{C\text{-}F}$= 242 Hz), 147.9, 138.2, 136.3, 136.2 (d, $J_{C\text{-}F}$= 3 Hz), 134.0, 128.5 (d, $J_{C\text{-}F}$= 8.0 Hz), 127.7, 127.2, 121.4, 121.3, 116.4, 115.1 (d, $J_{C\text{-}F}$= 21.1 Hz), 54.5, 38.3, 30.3; FT-IR (KBr): 3349, 1605, 1599, 1392, 737 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}F_2N_2O$: 415.1621; found 415.1611.

(*1s*,2R*,4S)-2,4-Bis(4-iodophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114g).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; brown colour solid; 114



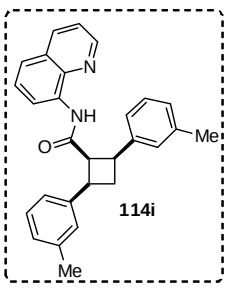
mg,73% yield; mp 169-171 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (br s, 1H), 8.70 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.27 (dd, 1H, J_1= 7.6 Hz, J_2= 1.3 Hz), 8.05 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.48 (dd, 4H, J_1= 8.3 Hz, J_2= 2.2 Hz), 7.39-7.28 (m, 3H), 7.03 (d, 4H, J = 8.0 Hz), 4.11-4.06 (m, 1H), 3.96-3.90 (m, 2H), 3.38 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.70-2.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 147.9, 140.2, 138.1, 137.1, 136.3, 133.9, 129.0, 127.7, 127.2, 121.5, 121.4, 116.5, 91.6, 54.2, 38.6, 29.9; FT-IR (KBr): 3346, 1681, 1520, 1485, 808 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}I_2N_2O$: 630.9743; found 630.9737.

(*1s*,2R*,4S)-2,4-Di(naphthalen-1-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114h).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; brown colour solid; 112



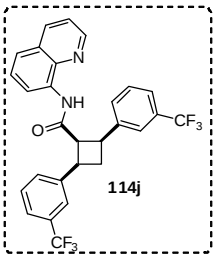
mg, 94% yield; mp 225-227 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (br s, 1H), 8.42 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.23 (d, 2H, J = 8.4 Hz), 7.84 (dd, 1H, J_1= 7.6 Hz, J_2= 1.3 Hz), 7.76 (dd, 1H, J_1= 8.4 Hz, J_2= 1.5 Hz), 7.69 (d, 2H, J = 7.0 Hz), 7.65 (d, 2H, J = 8.0 Hz), 7.58-7.51 (m, 4H), 7.42 (t, 2H, J = 8.0 Hz), 7.33 (t, 2H, J = 7.0 Hz), 7.16 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.03-6.94 (m, 2H), 4.78-4.72 (m, 3H), 4.07 (dd, 1H, J_1= 21.3 Hz, J_2= 10.0 Hz), 2.91-2.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 147.2, 137.7, 135.8, 135.7, 133.7, 133.5, 131.8, 128.8, 127.1, 126.9, 126.7, 126.0, 125.4, 125.2, 125.0, 123.5, 120.8, 120.4, 115.7, 56.6, 37.9, 28.1; FT-IR (KBr): 3351, 1683, 1523, 1485, 780 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{27}N_2O$: 479.2123; found 479.2115.

(*1s*,2R*,4S)-*N*-(Quinolin-8-yl)-2,4-di-*m*-tolylcyclobutanecarboxamide (114i)**: Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; light yellow colour solid;

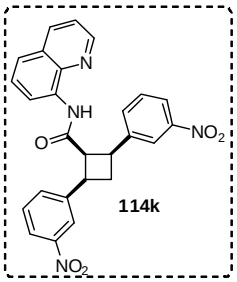


100 mg, 99% yield; mp 98-100 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 8.70 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.28 (dd, 1H, J_1= 7.2 Hz, J_2= 1.3 Hz), 8.0 (dd, 1H, J_1= 8.3 Hz, J_2= 1.5 Hz), 7.33 (dd, 1H, J_1= 8.3 Hz, J_2= 4.2 Hz), 7.30-7.23 (m, 2H), 7.13-7.04 (m, 6H), 6.85 (d, 2H, J = 8.0 Hz), 4.14-4.10 (m, 1H), 4.04-3.97 (m, 2H), 3.49 (dd, 1H, J_1= 21.6 Hz, J_2= 11.0 Hz), 2.71-2.67 (m, 1H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.8, 140.6, 138.2, 137.5, 136.2, 134.3, 127.9, 127.7, 127.5, 127.2, 126.8, 124.0, 121.3, 120.9, 116.4, 54.6, 39.1, 30.0, 21.4; FT-IR (KBr): 3400, 1596, 1389, 1360, 1047 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O$: 407.2123; found 407.2123.

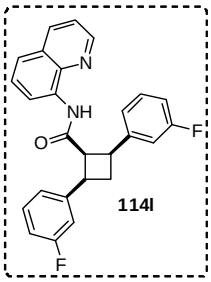
(***1s*,2R*,4S*)-N*-(Quinolin-8-yl)-2,4-bis(3-(trifluoromethyl)phenyl)cyclobutane-carboxamide (114j).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown colour solid; 75 mg, 59% yield; mp 114-116 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 8.65 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.14 (dd, 1H, J_1= 7.6 Hz, J_2= 1.3 Hz), 7.97 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.50 (s, 2H), 7.43 (d, 2H, J = 6.7 Hz), 7.32-7.18 (m, 7H), 4.17-4.12 (m, 1H), 4.06-3.99 (m, 2H), 3.48 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.77-2.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 148.0, 141.3, 138.0, 136.2, 133.6, 130.3 (q, J_{C-F} = 32 Hz) , 130.3, 128.5, 127.6, 127.1, 126.8 (q, J_{C-F} = 271 Hz), 123.7 (q, J_{C-F} = 4 Hz), 123.1 (q, J_{C-F} = 4 Hz), 121.4, 121.4, 116.3, 54.2, 38.7, 29.9; FT-IR (KBr): 3445, 1519, 1321, 1313, 989 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}F_6N_2O$: 515.1558; found 515.1536.



(*1s*,2R*,4S)-2,4-Bis(3-nitrophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114k).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.50; brown colour solid; 100 mg, 86% yield; mp 183-185 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.67 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.16 (s, 2H), 8.12 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.01 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.88 (dd, 2H, J_1= 8.0 Hz, J_2= 1.6 Hz), 7.63 (d, 2H, J = 8.0 Hz), 7.36-7.28 (m, 4H), 7.21 (t, 1H, J = 8.0 Hz), 4.29-4.24 (m, 1H), 4.17-4.10 (m, 2H), 3.57 (dd, 1H, J_1= 21.6 Hz, J_2= 11.0 Hz), 2.86-2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 148.2, 148.1, 142.4, 138.0, 136.3, 133.4, 133.1, 129.0, 127.7, 127.0, 122.0, 121.7, 121.6, 121.4, 116.3, 54.2, 38.3, 29.7; FT-IR (KBr): 3344, 1682, 1579, 1485, 792 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1511; found 469.1512.

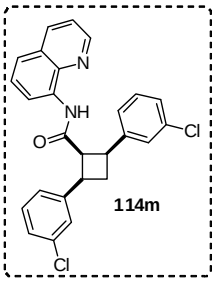


(*1s*,2R*,4S)-2,4-Bis(3-fluorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114l).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale yellow colour solid; 100 mg, 97% yield; mp 132-134 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.49 (br s, 1H), 8.68 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.24 (dd, 1H, J_1= 7.5 Hz, J_2= 1.3 Hz), 7.98 (dd, 1H, J_1= 8.2 Hz, J_2= 1.5 Hz), 7.33-7.20 (m, 3H), 7.12-6.98 (m, 6H), 6.73-6.69 (m, 2H), 4.12-4.07 (m, 1H), 4.01-3.94 (m, 2H), 3.42 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.71-2.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.0 (d, J_{C-F}= 244 Hz) 147.9, 143.1 (d, J_{C-F} = 8.0 Hz), 138.1, 136.2, 133.9, 129.5 (d, J_{C-F}= 9.0 Hz), 127.7, 127.2, 122.5 (d, J_{C-F}= 3

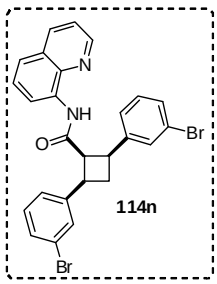


Hz), 121.4, 121.3, 116.4, 114.0 (d, $J_{C\text{-}F}$= 21.5 Hz), 113.1 (d, $J_{C\text{-}F}$= 20.9 Hz), 54.3, 38.6, 29.9; FT-IR (KBr): 3435, 1655, 1528, 1481, 793 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}F_2N_2O$: 415.1621; found 415.1609.

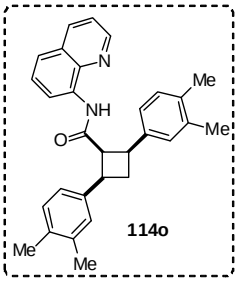
(*1s*,2R*,4S)-2,4-Bis(3-chlorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114m)** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white colour solid; 89 mg, 80% yield; mp 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 8.78 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.30 (dd, 1H, J_1= 7.5 Hz, J_2= 1.4 Hz), 8.09 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.44-7.31 (m, 5H), 7.21 (d, 2H, J = 7.6 Hz), 7.13 (t, 2H, J = 7.8 Hz), 7.07-7.04 (m, 2H), 4.19-4.14 (m, 1H), 4.06-4.0 (m, 2H), 3.48 (dd, 1H, J_1 = 21.5 Hz, J_2 = 11.0 Hz), 2.77-2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 142.5, 138.2, 136.2, 134.0, 133.8, 129.3, 127.7, 127.3, 127.2, 126.4, 125.1, 121.4, 121.3, 116.5, 54.3, 38.6, 29.9; FT-IR (KBr): 3434, 1601, 1525, 1323, 890 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}NCl_{22}O$: 447.1030; found 447.1018.



(*1s*,2R*,4S)-2,4-Bis(3-bromophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114n).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; yellow colour liquid; 106 mg, 80% yield^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.78 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.32 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 8.05 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.50 (s, 2H), 7.40-7.21 (m, 7H), 7.07 (t, 2H, J = 7.8 Hz), 4.17-4.12 (m, 1H), 4.05-3.98 (m, 2H), 3.47 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.76-2.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 142.8, 138.1, 136.2, 133.8, 130.1, 129.7, 129.3, 127.7, 127.2, 126.4, 125.6, 122.4, 121.4, 121.3, 116.5, 54.3, 38.5, 29.9; FT-IR (DCM): 3332, 1592, 1423, 1361, 889 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}Br_2N_2O$: 535.0020; found 535.0024.

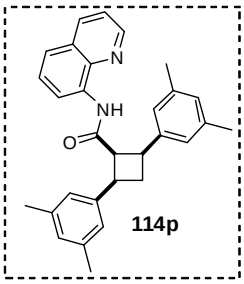


(*1s*,2R*,4S)-2,4-Bis(3,4-dimethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114o).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; light yellow colour solid; 107 mg, 99% yield; mp 99-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (br s, 1H), 8.64 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.32-8.30 (m, 1H), 7.92 (d, 1H, J =

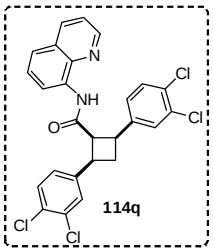


8.0 Hz), 7.26 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.23-7.17 (m, 2H), 7.07-7.03 (m, 4H), 6.91 (d, 2H, J = 8.0 Hz), 4.07-4.03 (m, 1H), 3.97-3.90 (m, 2H), 3.44 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.68-2.61 (m, 1H), 2.05 (s, 6H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.7, 138.2, 138.1, 136.1, 136.0, 134.4, 134.1, 129.4, 128.4, 127.6, 127.2, 124.5, 121.2, 120.8, 116.4, 54.7, 39.0, 30.3, 19.8, 19.4; FT-IR (KBr): 3435, 1575, 1365, 1291, 1047 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2423; found 435.2419.

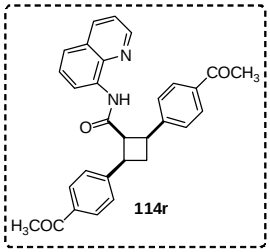
(*1s*,2R*,4S)-2,4-Bis(3,5-dimethylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114p).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; pale yellow colour liquid; 100 mg, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (br s, 1H), 8.68 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.28 (dd, 1H, J_1= 7.0 Hz, J_2= 2.0 Hz), 7.96 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.31 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.28-7.19 (m, 2H), 6.90 (s, 4H), 6.62 (s, 2H), 4.09-4.04 (m, 1H), 3.96-3.90 (m, 2H), 3.41 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.0 Hz), 2.65-2.62 (m, 1H), 2.09 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 147.7, 140.5, 138.3, 137.3, 136.1, 134.4, 127.8, 127.7, 127.2, 124.8, 121.2, 120.7, 116.4, 54.6, 39.0, 30.0, 21.3; FT-IR (DCM): 3358, 1690, 1520, 1387, 791 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2436; found 435.2423.



(*1s*,2R*,4S)-2,4-Bis(3,4-dichlorophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114q).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.60; white colour solid; 51 mg, 40% yield; mp 140-145^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (br s, 1H), 8.80 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.18 (dd, 1H, J_1= 7.6 Hz, J_2= 1.3 Hz), 8.07 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.44-7.36 (m, 4H), 7.30-7.18 (m, 5H), 4.58-4.53 (m, 1H), 4.19-4.12 (m, 2H), 3.57 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.66-2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 138.2, 136.3, 136.1, 134.0, 133.9, 132.6, 129.7, 128.8, 127.7, 127.1, 126.8, 121.4, 121.3, 116.2, 53.6, 37.4, 27.5; FT-IR (KBr): 3341, 1631, 1587, 1332, 804 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}Cl_4N_2O$: 515.0251; found 515.0249.

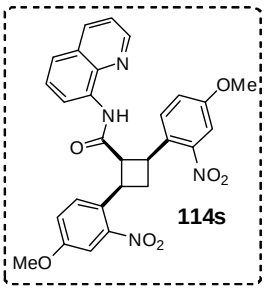


(*1s*,2R*,4S)-2,4-Bis(4-acetylphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114r).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow colour solid; 99 mg, 86% yield; mp181-183 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.24 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.06 (dd, 1H, J_1 = 8.2 Hz, J_2 =

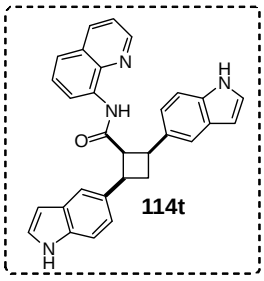


1.6 Hz), 7.80 (d, 4H, J = 8.3 Hz), 7.42-7.34 (m, 6H), 7.26 (t, 1H, J = 8.0 Hz), 4.30-4.25 (m, 1H), 4.16-4.09 (m, 2H), 3.57 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.84-2.78 (m, 1H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 168.4, 148.0, 146.3, 138.1, 136.3, 135.1, 133.8, 128.3, 127.7, 127.1, 127.0, 121.5, 121.4, 116.4, 54.4, 38.9, 29.8, 26.5; FT-IR (KBr): 3345, 1605, 1524, 1391, 793 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_3$: 463.2021; found 463.2012.

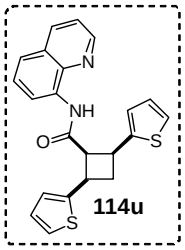
(*1s*,2R*,4S)-2,4-Bis(4-methoxy-2-nitrophenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114s)**. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow colour solid; 75 mg, 57% yield; mp145-147 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (br s, 1H), 8.74 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.12 (dd, 1H, J_1= 7.6 Hz, J_2= 1.2 Hz), 8.01 (dd, 1H, J_1= 8.0 Hz, J_2= 1.6 Hz), 7.57 (d, 2H, J = 8.7 Hz), 7.36 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.31 (d, 2H, J = 2.6 Hz), 7.32-7.29 (m, 1H), 7.22 (t, 1H, J = 7.6 Hz), 7.08 (dd, 2H, J_1= 8.7 Hz, J_2= 2.6 Hz), 4.68-4.63 (m, 1H), 4.34-4.27 (m, 2H), 3.70 (s, 6H), 3.53 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.64-2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 158.2, 148.9, 148.2, 138.2, 135.8, 133.9, 130.8, 127.5, 126.7, 121.4, 121.2, 119.5, 116.1, 109.3, 55.6, 55.2, 35.9, 28.1; FT-IR (KBr): 3430, 1555, 1521, 1493, 819 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_4O_7$: 529.1723; found 529.1728.



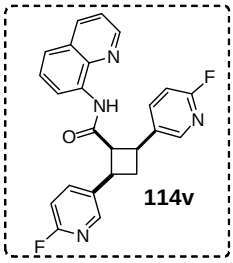
(*1s*,2R*,4S)-2,4-Di(*1H*-indol-5-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114t)**. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow colour semi solid; 75 mg, 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (br s, 1H), 8.95 (br s, 2H), 8.44 (d, 1H, J = 3.96 Hz), 8.12 (d, 1H, J = 7.6 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.59 (s, 2H), 7.23-6.98 (m, 9H), 6.32 (s, 2H), 4.15 (t, 3H, J = 6.5 Hz), 3.59-3.54 (m,1H), 2.80-2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 147.8, 138.1, 135.9, 134.6, 134.2, 131.5, 127.8, 127.5, 126.9, 124.3, 121.2, 120.7, 118.7, 116.2, 110.8, 101.8, 55.2, 39.7, 30.9; FT-IR (KBr): 3440, 1616, 1528, 1412, 710 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_4O$: 457.2028; found 457.2035.



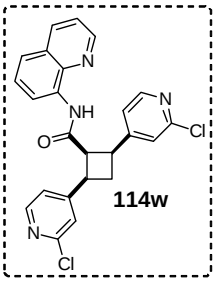
(*1s*,2R*,4S)-*N*-(Quinolin-8-yl)-2-(thiophen-2-yl)-4-(thiophen-3-yl)cyclobutane-carboxamide (114u).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow colour solid; 81 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (br s, 1H), 8.74 (dd, 1H, J_1 = 4.3. Hz, J_2 = 1.8 Hz), 8.58-8.53 (m, 1H), 8.06 (dd, 1H, J_1 = 8.2. Hz, J_2 = 1.6 Hz), 7.42-7.37 (m, 3H), 7.10-7.06 (m, 4H), 6.90 (dd, 2H, J_1 = 5.0. Hz, J_2 = 3.5 Hz), 4.22-4.16 (m, 2H), 4.06-4.01 (m, 1H), 3.56 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.2 Hz), 2.95-2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 147.9, 143.4, 138.2, 136.2, 134.3, 127.7, 127.3, 126.7, 125.2, 123.9, 121.4, 121.2, 116.6, 55.9, 35.7, 35.5; FT-IR (DCM): 3313, 1612, 1554, 1302, 801 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2OS_2$: 391.0938; found 391.0936.



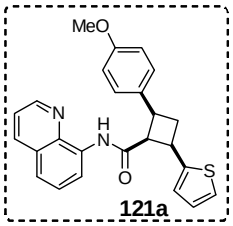
(*1s*,2R*,4S)-2,4-Bis(6-fluoropyridin-3-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114v).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow colour solid; 83 mg, 80% yield; mp187-189 ^{o}C; . ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 8.75 (dd, 1H, J_1 = 4.4 Hz, J_2 = 1.6 Hz), 8.23-8.17 (m, 4H), 7.83 (dt, 2H, J_1 = 8.1 Hz, J_2 = 2.5 Hz), 7.48-7.45 (m, 2H), 7.38 (t, 1H, J= 8.1 Hz), 6.80 (dd, 2H, J_1 = 8.5 Hz, J_2 = 2.8 Hz), 4.22-4.05 (m, 3H), 3.52 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.0 Hz), 2.80-2.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 162.4 (d, J_{C-F}= 236 Hz), 147.6, 146.2 (d, J_{C-F}= 14.5 Hz), 140.1 (d, J_{C-F}= 8 Hz), 137.8, 137.2, 133.1, 132.8, 128.0, 127.5, 122.3, 121.5, 118.2, 108.9 (d, J_{C-F}= 37.1 Hz), 54.1, 36.1, 30.0; FT-IR (KBr): 3430, 1624, 1554, 1341, 798 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}F_2N_4O$: 417.1526; found 417.1526.



(*1s*,2R*,4S)-2,4-Bis(2-chloropyridin-4-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (114w).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow colour liquid; 107 mg, 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (br s, 1H), 8.75 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.21 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 8.16 (d, 2H, J = 5.1 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.42-7.39 (m, 2H), 7.32 (t, 1H, J_1 = 7.8 Hz), 7.26 (s, 2H), 7.12 (d, 2H, J = 5.1 Hz), 4.28-4.23 (m, 1H), 4.03-3.96 (m, 2H), 3.42 (dd, 1H, J_1= 21.7 Hz, J_2= 11.0 Hz), 2.78-2.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.7, 151.5, 149.8, 148.3, 138.1, 136.5, 133.6, 127.8, 127.1, 122.7, 122.1, 121.7, 120.9, 116.7, 53.6, 37.7, 28.9; FT-IR (DCM): 3350, 1624, 1510, 1491, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}Cl_2N_4O$: 449.0935; found 449.0936.

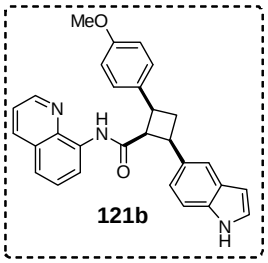


(*1S*,2S*,4R)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutane-carboxamide (121a).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow colour liquid; 69 mg, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.45 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.41-7.36 (m, 3H), 7.28 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.7 Hz), 7.07-7.03 (m, 2H), 6.87 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.6 Hz), 6.79 (td, 1H, J_1 = 8.7 Hz, J_2 = 3.0 Hz), 4.23-4.17 (m, 1H), 4.09-4.0 (m, 2H), 3.72 (s, 3H), 3.51 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.0 Hz), 2.83-2.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 157.9, 147.8, 143.8, 138.2, 136.2, 134.3, 132.4, 128.1, 127.7, 127.3, 126.6, 125.0, 123.8, 121.3, 121.0, 116.5, 113.5, 55.3, 55.1, 38.7, 35.2, 33.2; FT-IR (KBr): 3439, 1602, 1534, 1423, 990 cm^{-1}; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{129a2}O_2S$: 415.1480; found 415.1488.



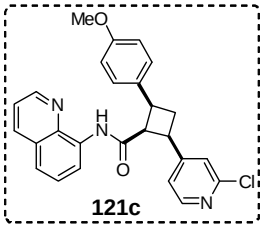
121a

(*1S*,2R*,4S)-2-(*1H*-Indol-5-yl)-4-(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutane-carboxamide (121b)**. Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; yellow colour liquid; 91 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.60 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.31 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.21 (br s, 1H), 7.95 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.67 (s, 1H), 7.32-7.13 (m, 6H), 7.06 (d, 1H, J= 8.4 Hz) 6.98 (t, 1H, J = 2.5 Hz), 6.77 (td, 2H, J_1 = 8.7 Hz, J_2 = 3.0 Hz), 6.41(t, 1H, J = 2.1 Hz), 4.20-4.13 (m, 2H), 4.08-4.04 (m, 1H), 3.68 (s, 3H), 3.58 (dd, 1H, J_1 = 21.1 Hz, J_2 = 11.0 Hz), 2.80-2.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 157.8, 147.7, 138.2, 136.0, 134.6, 134.2, 132.9, 131.6, 128.2, 127.8, 127.6, 127.1, 124.2, 121.3, 121.2, 120.9, 118.8, 116.4, 113.5, 110.8, 102.1, 55.1, 55.0, 39.3, 38.7, 30.7; FT-IR (KBr): 3430, 1623, 1515, 1421, 890 cm^{-1}; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{26}N_3O_2$: 448.2025; found 448.2034.



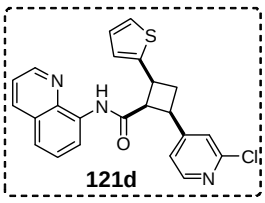
121b

(*1S*,2R*,4S)-2-(2-Chloropyridin-4-yl)-4-(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutane-carboxamide (121c).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; light yellow colour liquid; 33 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 8.70 (t, 1H, J = 4.0 Hz), 8.22-8.19 (m, 1H), 8.14 (t, 1H, J = 4.8 Hz), 8.06-



121c

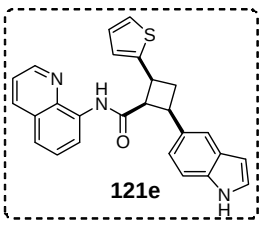
8.04 (m, 1H), 7.39-7.17 (m, 6H), 7.09 (t, 1H, J = 4.1 Hz), 6.65-6.62 (m, 2H), 4.24-3.87 (m, 3H), 3.59 (s, 3H), 3.41-3.34 (m, 1H), 2.70-2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.1, 154.2, 151.4, 149.0, 148.0, 147.9, 144.3, 138.1, 136.3, 133.7, 131.3, 128.2, 127.7, 127.1, 122.6, 121.5, 120.9, 116.5, 113.5, 55.1, 54.2, 39.0, 37.3, 31.9; FT-IR (KBr): 3423, 1566, 1513, 1448, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}ClN_3O_2$: 444.1478; found 444.1483.

***(1S*,2S*,4R*)*-2-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutane-carboxamide (121d).** 

121d

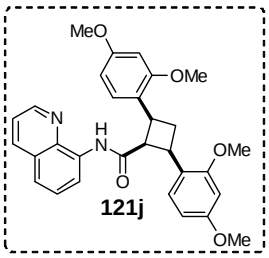
Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; yellow colour solid; 54 mg, 52% yield; mp 182-184 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (br s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.39 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.23 (d, 1H, J = 5.1 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.44-7.35 (m, 3H), 7.27 (s, 1H), 7.13 (d, 1H, J = 5.1 Hz), 7.03-7.02 (m, 2H), 6.82 (dd, 1H, J_1 = 4.8 Hz, J_2 = 3.7 Hz), 4.30-4.24 (m, 1H), 4.18-4.13 (m, 1H), 3.92-3.88 (m, 1H), 3.45 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.88-2.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 153.9, 151.5, 149.2, 148.0, 142.3, 138.2, 136.3, 133.8, 127.8, 127.3, 126.7, 125.4, 124.3, 122.5, 121.6, 121.5, 120.8, 116.6, 54.9, 37.5, 35.5, 32.5; FT-IR (KBr): 3530, 1654, 1529, 1409, 990 cm^{-1}; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClN_3OS$: 420.0937; found 420.0943.

(*1S*,2S*,4R)-2-(*1H*-Indol-5-yl)-*N*-(quinolin-8-yl)-4-(thiophen-2-yl)cyclobutane-carboxamide (121e)**: Analytical TLC on silica gel, 2.5:2.5 ethyl acetate/hexane R_f = 0.30; red colour liquid; 54 mg, 51% yield^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (br s, 1H), 8.60 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.40 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.16 (br s, 1H), 8.00 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.65 (s, 1H), 7.33-7.22 (m, 3H), 7.13 (s, 2H), 7.07-7.04 (m, 3H), 6.87 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.5 Hz), 6.44 (t, 1H, J = 2.5 Hz), 4.29-4.10 (m, 3H), 3.59 (dd, 1H, J_1 = 21.7 Hz, J_2 = 11.0 Hz), 2.93-2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.8, 144.0, 138.2, 136.0, 134.6, 134.3, 131.3, 127.9, 127.6, 127.2, 126.6, 125.0, 124.2, 123.8, 121.3, 121.2, 121.0, 118.7, 116.5, 110.8, 102.3, 55.6, 39.4, 35.5, 33.4; FT-IR (KBr): 3400, 1613, 1531, 1454, 910 cm^{-1}; HRMS(ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}N_3OS$: 424.1483; found 424.1492.



121e

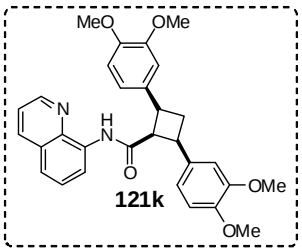
(*1s*,2R*,4S)-2,4-Bis(2,4-dimethoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide**



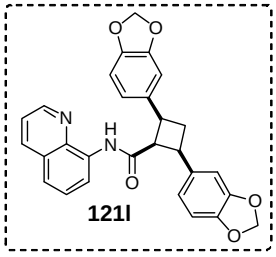
(121j). Analytical TLC on silica gel, 4:1 ethyl acetate /hexanes R_f = 0.60 red colour liquid; 100 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 8.79 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.35 (dd, 1H, J_1= 7.3 Hz, J_2= 1.6 Hz), 8.06 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.39 (dd, 1H, J_1= 8.2 Hz, J_2= 4.0 Hz), 7.31-7.24 (m, 4H), 6.47 (dd, 2H, J_1= 8.4 Hz, J_2= 2.4 Hz), 6.25 (d, 2H, J = 2.4 Hz), 4.27-4.24 (m, 1H), 4.09-4.02 (m, 2H), 3.75 (s, 6H), 3.71 (s, 6H), 3.38 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.2 Hz), 2.65-2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 159.1, 158.0, 147.6, 138.2, 136.2, 134.8, 128.1, 127.7, 127.4, 122.1, 121.2, 120.2, 115.9, 103.5, 97.5, 55.3, 55.2, 53.8, 35.4; FT-IR (DCM): 2881, 1643, 1511, 1423, 811 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2333; found 499.2227.

(*1s*,2R*,4S)-2,4-Bis(3,4-dimethoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide**

(121k). Analytical TLC on silica gel, 2.5:2.5 ethyl acetate /hexanes R_f = 0.30; pale yellow colour solid; 40 mg, 32% yield; mp 175-177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 8.72 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.42 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 8.09 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.42-7.32 (m, 3H), 6.90-6.87 (m, 4H), 6.75 (d, 2H, J = 8.7 Hz), 4.13-4.09 (m, 1H), 4.04-3.95 (m, 2H), 3.77 (s, 6H), 3.73 (s, 6H), 3.44 (dd, 1H, J_1 = 21.3 Hz, J_2 = 11.0 Hz), 2.78-2.74 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 148.5, 147.7, 147.2, 138.2, 136.3, 134.2, 133.3, 127.7, 127.3, 121.3, 121.1, 119.1, 116.4, 110.8, 110.1, 50.7, 55.6, 54.6, 38.8, 31.1; FT-IR (KBr): 2922, 1601, 1545, 1434, 821 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2233; found 499.2245.

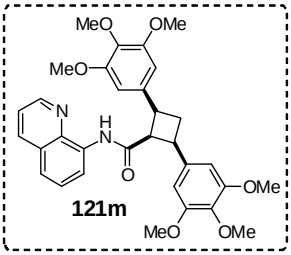


(*1s*,2R*,4S)-2,4-Bis(benzo-[*d*][1,3]-dioxol-5-yl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (121l).** Analytical TLC on silica gel, 4:1 ethyl acetate /hexanes R_f = 0.70 yellow colour liquid; 58 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51(br s, 1H), 8.75 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.40 (dd, 1H, J_1= 7.1 Hz, J_2= 1.8 Hz), 8.09 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.42-7.33 (m, 3H), 6.85-6.79 (m, 4H), 6.66 (d, 2H, J = 8.0 Hz), 5.81 (dd, 4H, J_1= 8.9 Hz, J_2= 1.6 Hz), 4.07-4.04 (m, 1H), 3.98-3.91 (m, 2H), 3.38 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.68-2.63 (m, 1H); ^{13}C NMR (100



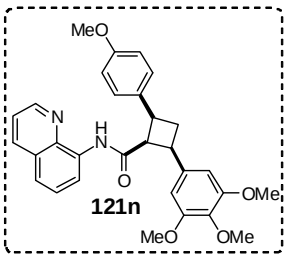
MHz, $CDCl_3$): δ 168.9, 147.8, 147.4, 145.8, 138.2, 136.2, 134.4, 134.2, 127.7, 127.7, 127.3, 121.3, 121.0, 120.0, 116.4, 107.9, 107.7, 100.7, 54.7, 38.8, 30.6; FT-IR (DCM): 3041, 1723, 1487, 1421, 991 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{129a2}O_5$: 467.1607; found 467.1608.

(*1s*,2R*,4S)-*N*-(Quinolin-8-yl)-2,4-bis(3,4,5-trimethoxyphenyl)cyclobutanecarboxamide (121m).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate /hexanes R_f= 0.30 light yellow colour liquid; 70 mg, 50% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (br s, 1H), 8.72 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.44 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 8.11 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.44-7.34 (m, 3H), 6.53 (s, 4H), 4.17-4.13 (m, 1H), 4.03-3.96 (m, 2H), 3.73 (s, 12H), 3.67 (s, 6H), 3.39 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.0 Hz), 2.80-2.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 152.9, 147.8, 138.1, 136.5, 136.3, 136.2, 134.2, 127.8, 127.3, 121.5, 121.3, 116.4, 103.7, 60.7, 55.9, 54.4, 39.2, 31.2; FT-IR (DCM): 3120, 1611, 1436, 1346, 771 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_7$: 559.2444; found 559.2455.



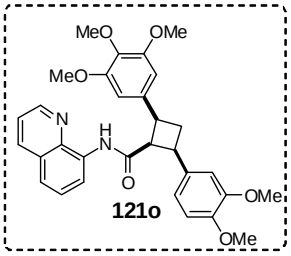
121m

(*1S*,2S*,4R)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-4-(3,4,5-trimethoxyphenyl)-cyclobutanecarboxamide (121n).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate /hexanes R_f = 0.40 red colour liquid; 50 mg, 40% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 8.72 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.41 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 8.09 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.42-7.32 (m, 3H), 7.26 (d, 2H, J = 8.1 Hz), 6.81 (td, 2H, J_1 = 8.7 Hz, J_2 = 3.0 Hz), 6.55 (s, 2H), 4.17-4.10 (m, 1H), 4.03-3.95 (m, 2H), 3.73 (s, 3H), 3.71 (s, 6H), 3.61 (s, 3H), 3.43 (dd, 1H, J_1 = 21.6 Hz, J_2 = 11.0 Hz), 2.77-2.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 157.8, 152.8, 147.8, 138.1, 136.4, 136.3, 136.2, 134.2, 132.7, 127.8, 127.7, 127.3, 121.4, 121.1116.4, 113.6, 103.8, 60.6, 55.8, 55.2, 54.6, 30.7, 38.1, 30.8; FT-IR (DCM): 2921, 1523, 1476, 1444, 749 cm^{-1};HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_5$: 499.2233; found 499.2234.



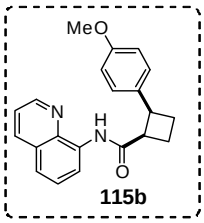
121n

(*1R*,2R*,4S)-2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)-4-(3,4,5-trimethoxyphenyl)-cyclobutanecarboxamide (121o).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate /hexanes R_f= 0.30 light brown colour liquid; 99 mg, 75% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.72 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.43 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6



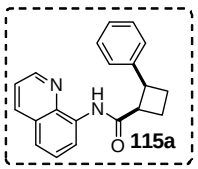
Hz), 8.09 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.41-7.32 (m, 3H), 6.90-6.88 (m, 2H), 6.76 (d, 1H, J = 8.7 Hz), 6.55 (s, 2H), 4.14-4.11 (m, 1H), 4.03-3.94 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.72 (s, 6H), 3.65 (s, 3H), 3.41 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.1 Hz), 2.80-2.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 152.9, 148.6, 147.8, 147.3, 138.1, 136.6, 136.3, 136.1, 134.2, 133.3, 127.7, 127.3, 121.4, 121.2, 119.0, 116.4, 110.8, 110.4, 103.8, 60.7, 55.9, 55.6, 54.5, 39.4, 38.6, 31.3; FT-IR (DCM): 2811, 1535, 1476, 1423, 981 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{33}N_2O_6$: 529.2338; found 529.2343.

(*1R*,2S)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)cyclobutanecarboxamide (115b)**.



Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown colour liquid; 25 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (br s, 1H), 8.72 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.56 (dd, 1H, J_1= 7.1 Hz, J_2= 1.7 Hz), 8.10 (dd, 1H, J_1= 8.3 Hz, J_2= 1.7 Hz), 7.47-7.39 (m, 3H), 7.24 (td, 2H, 1H, J_1= 8.7 Hz, J_2= 3.0 Hz), 6.64 (td, 2H, 1H, J_1= 8.7 Hz, J_2= 3.0 Hz), 4.07 (dd, 1H, J_1= 17.8 Hz, J_2= 9.1 Hz), 3.79-3.71 (m, 1H), 3.57 (s, 3H), 2.70-2.63 (m, 2H), 2.43-2.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 158.0, 147.8, 138.2, 136.1, 134.4, 132.8, 128.4, 127.7, 127.3, 121.3, 120.9, 116.1, 113.5, 55.0, 47.8, 42.8, 25.4, 20.4, ; FT-IR (DCM): 3231, 1610, 1494, 1321, 710 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2$: 333.1603; found 333.1599.

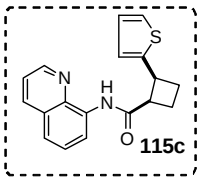
(*1R*,2S)-2-Phenyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (115a)**. Analytical TLC on



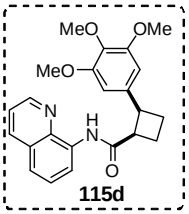
silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; brown colour liquid; 15 mg, 20% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (br s, 1H), 8.73 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.54 (dd, 1H, J_1= 6.6 Hz, J_2= 2.3 Hz), 8.10 (dd, 1H, J_1= 8.3 Hz, J_2= 1.6 Hz), 7.42-7.32 (m, 4H), 7.22 (t, 1H, J = 7.5 Hz), 7.13-7.09 (m, 2H), 6.98-6.94 (m, 1H), 4.16-4.09 (m, 1H), 3.82-3.76 (m, 1H), 2.77-2.61 (m, 2H), 2.45-2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 147.8, 140.7, 138.2, 136.1, 134.3, 128.0, 127.4, 127.3, 126.9, 126.3, 121.3, 121.1, 116.1, 47.7, 43.4, 25.1, 20.6; FT-IR (DCM): 3355, 1650, 1534, 1475, 890 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1504.

(*1R*,2S)-*N*-(Quinolin-8-yl)-2-(thiophen-2-yl)cyclobutanecarboxamide (115c).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow colour liquid; 32

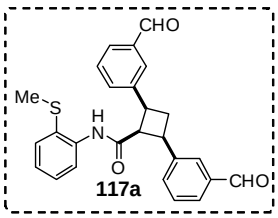
mg, 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (br s, 1H), 8.76 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.64 (dd, 1H, J_1= 7.3 Hz, J_2= 1.7 Hz), 8.11 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.49-7.38 (m, 3H), 6.98-6.93 (m, 2H), 6.75 (dd, 1H, J_1= 5.1 Hz, J_2= 3.5 Hz), 4.32 (dd, 1H, J_1= 16.2 Hz, J_2= 7.6 Hz), 3.79-3.73 (m, 1H), 2.73-2.51 (m, 3H), 2.36-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 147.9, 144.2, 138.3, 136.2, 134.4, 127.8, 127.4, 126.7, 124.7, 123.7, 121.4, 121.1, 116.2, 48.2, 38.7, 27.8, 20.6; FT-IR (KBr): 3335, 1641, 1510, 1431, 790 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2OS$: 309.1061; found 309.1071.



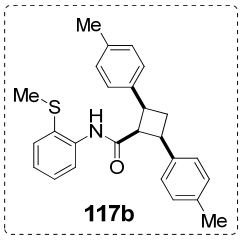
(*1R*,2S)-*N*-(Quinolin-8-yl)-2-(3,4,5-trimethoxyphenyl)-cyclobutane-carboxamide (115d).** Analytical TLC on silica gel, 2.5:2.5 ethyl acetate /hexanes R_f= 0.40; white solid 31 mg, 32% yield; mp 125-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (br s, 1H), 8.66 (dd, 1H, J_1= 4.2 Hz, J_2= 1.7 Hz), 8.63 (dd, 1H, J_1= 7.4 Hz, J_2= 1.6 Hz), 8.07 (dd, 1H, J_1= 8.2 Hz, J_2= 1.7 Hz), 7.46-7.36 (m, 3H), 6.50 (s, 2H), 4.09-4.03 (m, 1H), 3.76-3.71 (m, 1H), 3.67 (s, 6H), 3.30 (s, 3H), 2.72-2.57 (m, 2H), 2.40-2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 152.8, 147.7, 138.1, 136.4, 136.3, 136.2, 134.5, 127.8, 127.2, 121.4, 121.1, 115.8, 104.3, 60.3, 55.8, 48.2, 43.9, 25.5, 19.9; FT-IR (KBr): 2830, 1599, 1502, 1391, 881 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_4$: 393.1814; found 393.1808.



(*1s*,2R*,4S)-2,4-Bis(3-formylphenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-carboxamide (117a).** Analytical TLC on silica gel, 1.5:3.5 ethyl acetate/hexane R_f = 0.30; brown colour solid; 56 mg, 52% yield; mp 100-102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (s, 2H), 7.95 (br s, 1H), 7.84 (s, 2H), 7.69 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.0 Hz), 7.50-7.44 (m, 3H), 7.30-7.28 (m, 1H), 7.02-6.90 (m, 2H), 4.17-4.04 (m, 3H), 3.61 (dd, 1H, J_1= 21.6 Hz, J_2= 11.0 Hz), 2.82-2.79 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 168.0, 141.4, 137.1, 136.3, 133.1, 132.1, 128.9, 128.3, 125.6, 124.5, 121.0, 54.1, 38.5, 29.5, 18.5; FT- IR (KBr): 3351, 1668, 1582, 1398, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{24}NO_3S$: 430.1476; found 430.1482.



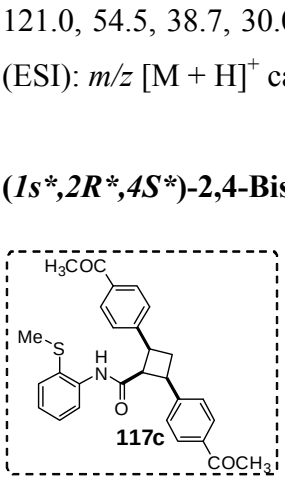
(*1s*,2R*,4S)-*N*-(2-(Methylthio)phenyl)-2,4-di-*p*-tolylcyclobutanecarboxamide (117b)**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; white colour solid; 45 mg, 45% yield; mp 98-100 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.74 (d, 1H, J =



117b

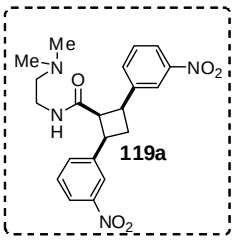
8.0 Hz), 7.34 (dd, 1H, J_1= 8.0 Hz, J_2= 1.6 Hz), 7.22 (d, 4H J = 8.0 Hz), 7.08-7.05 (m, 1H), 7.08 (d, 4H J = 8.0 Hz), 6.92 (t, 1H, J = 7.8 Hz), 4.03-3.91 (m, 3H), 3.44 (dd, 1H, J_1= 21.3 Hz, J_2= 10.4 Hz), 2.70-2.65 (m, 1H), 2.28 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 138.2, 137.3, 135.6, 132.8, 129.0, 128.9, 128.6, 126.8, 123.8, 121.0, 54.5, 38.7, 30.0, 21.1, 18.8; FT-IR (KBr): 3324, 1622, 1534, 1491, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{28}NOS$: 402.1891; found 402.1896.

(*1s*,2R*,4S)-2,4-Bis(4-acetylphenyl)-*N*-(2-(methylthio)phenyl)cyclobutane-carboxamide (117c)**. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.60; white colour solid; 33 mg, 29% yield; mp 189-191 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 1H), 7.88 (d, 4H, J = 8.2 Hz), 7.60 (dd, 1H J = 8.5 Hz), 7.39 (d, 4H, J = 8.2 Hz), 7.32 (dd, 1H, J_1= 7.8 Hz, J_2= 1.4 Hz), 7.05-7.0 (m, 1H), 6.93 (t, 1H, J = 7.6 Hz), 4.13-4.06 (m, 3H), 3.55 (dd, 1H, J_1 = 21.4 Hz, J_2 = 10.8 Hz), 2.80-2.78 (m, 1H), 2.56 (s, 6H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 168.0, 146.0, 137.3, 135.3, 134.9, 132.3, 128.5, 128.4, 128.3, 127.0, 125.3, 124.4, 120.9, 54.3, 38.9, 29.7, 26.6, 18.3; FT-IR (KBr): 3350, 1620, 1551, 1441, 710 cm^{-1}; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{27}NO_3SNa$: 480.1609; found 480.1604.



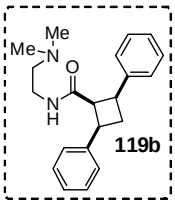
117c

(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(3-nitrophenyl)cyclobutane-carboxamide (119a).** Analytical TLC on silica gel, 2:3.methanol/ethyl acetate R_f = 0.40; black colour solid; 46 mg, 45% yield; mp 130-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 2H), 8.03 (dd, 2H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.60 (d, 2H, J = 8.0 Hz), 7.45 (t, 2H, J = 8.0 Hz), 6.34 (br s, 1H), 4.03-3.96 (m, 2H), 3.89-3.84 (m, 1H), 3.46 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.0 Hz), 2.83-2.74 (m, 3H), 2.01 (s, 6H), 1.95 (t, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 148.0, 143.0, 133.2, 129.0, 121.9, 121.3, 57.4, 52.5, 44.7, 37.9, 36.0, 29.7; FT-IR (KBr): 2876, 2325, 1618, 1532, 817 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{25}N_4O_5$: 413.1824; found 413.1813.



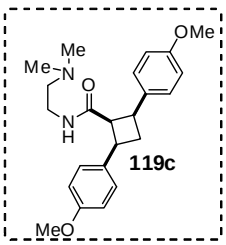
119a

(*1s*,2R*,4S*)-*N*-(2-(Dimethylamino)ethyl)-2,4-diphenylcyclobutanecarboxamide (119b). Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; red colour liquid; 24 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 8H), 7.22-7.17 (m, 2H), 5.78 (br s,

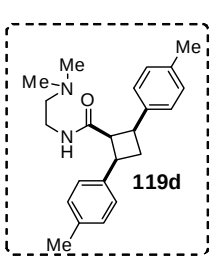


1H), 3.96-3.89 (m, 2H), 3.78-3.74 (m, 1H), 3.37 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.0 Hz), 2.81 (dd, 2H, J_1 = 11.0 Hz, J_2 = 6.0 Hz), 2.65-2.61 (m, 1H), 2.0 (s, 6H), 1.84 (t, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 140.9, 127.9, 127.1, 126.1, 57.4, 53.3, 44.8, 38.6, 35.9, 29.5; FT-IR (DCM): 2912, 2324, 1612, 1543, 809 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{27}N_2O$: 323.2123; found 323.2113.

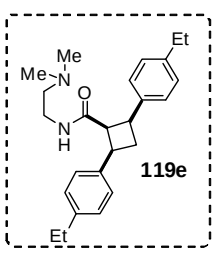
(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(4-methoxyphenyl)cyclobutane-carboxamide (119c).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; pale yellow colour liquid; 51mg, 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 4H, J = 8.5 Hz), 6.82 (d, 4H, J = 8.5 Hz), 5.67 (br s, 1H), 3.84-3.79 (m, 2H), 3.75 (s, 6H), 3.66-3.63 (m, 1H), 3.25 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.2 Hz), 2.81 (dd, 2H, J_1 = 11.2 Hz, J_2 = 6.0 Hz), 2.57-2.54 (m, 1H), 1.98 (s, 6H), 1.85 (t, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 157.9, 132.9, 128.2, 113.4, 57.6, 55.2, 53.5, 44.8, 38.0, 36.0, 30.1; FT-IR (DCM,): 2948, 2213, 1623, 1534, 812 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{31}N_2O_3$: 383.2335; found 383.2352.



(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-di-*p*-tolylcyclobutanecarboxamide (119d).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown colour liquid; 35 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 4H, J = 8.4 Hz), 7.12 (d, 4H, J = 8.4 Hz), 5.70 (br s, 1H), 3.91-3.84 (m, 2H), 3.73-3.70 (m, 1H), 3.31 (dd, 1H, J_1 = 22.6 Hz, J_2 = 11.2 Hz), 2.84 (dd, 2H, J_1 = 11.2 Hz, J_2 = 6.2 Hz), 2.60-2.57 (m, 1H), 2.33 (s, 6H), 2.01 (s, 6H), 1.84 (t, 2H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 137.8, 135.4, 128.6, 127.2, 57.5, 53.4, 44.8, 38.4, 36.0, 29.7, 21.1; FT-IR (DCM): 2900, 2316, 1627, 1553, 737 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{31}N_2O$: 351.2436; found 351.2429.

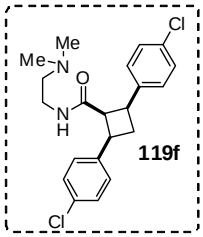


(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(4-ethylphenyl)cyclobutanecarboxamide (119e).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown colour solid; 37 mg, 39% yield; mp 185-188 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, 4H, J = 8.4 Hz), 7.13 (d, 4H, J = 8.4 Hz), 6.24 (br s, 1H), 3.90-3.84 (m, 2H),

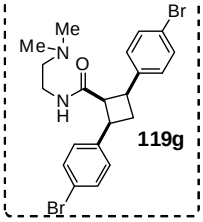


3.74-3.72 (m, 1H), 3.33 (dd, 1H, J_1 = 22.0 Hz, J_2 = 11.2 Hz), 2.91-2.87 (m, 2H), 2.61 (q, 4H, J = 7.7 Hz), 2.60-2.57 (m, 1H), 2.05 (s, 6H), 1.93 (t, 2H, J = 6.0 Hz), 1.22 (t, 6H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 141.8, 138.1, 127.4, 127.1, 57.4, 53.2, 44.1, 38.4, 35.6, 29.7, 28.5, 15.7; FT-IR (DCM): 3240, 1634, 1494, 1344, 710 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{35}N_2O$: 379.2749; found 3792746.

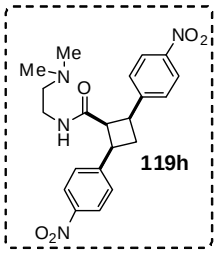
(*1s*,2R*,4S)-2,4-Bis(4-chlorophenyl)-*N*-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (119f).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; white colour solid; 40 mg, 41% yield; mp 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.18 (m, 8H), 5.71 (br s, 1H), 3.88-3.81 (m, 2H), 3.67 (dt, 1H, J_1 = 8.2 Hz, J_2 = 3.5 Hz), 3.32 (dd, 1H, J_1 = 21.7 Hz, J_2 = 11.2 Hz), 2.84 (dd, 2H, J_1 = 11.2 Hz, J_2 = 6.0 Hz), 2.62-2.55 (m, 1H), 2.01 (s, 6H), 1.89 (t, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 139.1, 131.9, 128.5, 128.1, 57.5, 53.2, 44.9, 38.1, 36.0, 29.7; FT-IR (KBr): 2912, 2323, 1618, 1512, 812 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{25}Cl_2N_2O$: 391.1343; found 391.1340.



(*1s*,2R*,4S)-2,4-Bis(4-bromophenyl)-*N*-(2-(dimethylamino)ethyl)cyclobutane-carboxamide (119g).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40; brown colour liquid; 54 mg, 45% yield^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 4H, J= 8.4 Hz), 7.13 (d, 4H, J = 8.4 Hz), 6.48 (br s, 1H), 3.83-3.77 (m, 2H), 3.70-3.65 (m, 1H), 3.31 (dd, 1H, J_1 = 21.5 Hz, J_2 = 11.0 Hz), 2.89 (dd, 2H, J_1 = 11.0 Hz, J_2 = 5.4 Hz), 2.59-2.52 (m, 1H), 2.09 (s, 6H), 1.99 (t, 2H, J = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 139.8, 130.9, 129.1, 119.9, 57.5, 52.9, 44.4, 38.1, 35.5, 29.5; FT-IR (KBr): 2912, 2316, 1637, 1544, 917 cm^{-1} HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{137b}r_2N_2O$: 479.0333; found 479.0316.

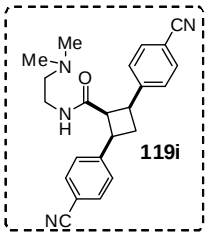


(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(4-nitrophenyl)cyclobutanecarboxamide (119h).** Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; yellow colour liquid; 44 mg, 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.08 (d, 4H, J = 8.0 Hz), 7.35 (d, 4H, J = 8.0 Hz), 6.56 (br s, 1H), 3.97-3.91 (m, 2H), 3.87-3.83 (m, 1H), 3.42 (dd, 1H, J_1 = 21.4 Hz, J_2 = 11.0 Hz), 2.79 (dd, 2H, J_1 = 11.0 Hz, J_2 = 5.6 Hz), 2.69-2.66 (m, 1H), 2.0 (s, 6H), 1.90 (t, 2H, J = 5.6 Hz); ^{13}C NMR (100

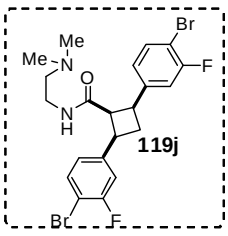


MHz, $CDCl_3$ and DMSO-d_6): δ 169.0, 148.8, 146.3, 127.7, 123.2, 57.6, 53.0, 44.7, 38.2, 35.9, 29.5; FT-IR (KBr): 3243, 1632, 1521, 1494, 810 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{25}N_4O_5$: 413.1824; found 4131823.

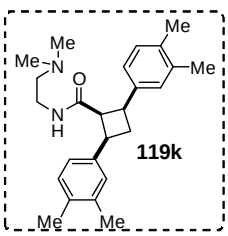
(*1s*,2R*,4S)-2,4-Bis(4-cyanophenyl)-*N*-(2-(dimethylamino)ethyl)cyclobutanecarboxamide (119i).** Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; black colour solid; 45 mg, 48% yield; mp 159-161 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 4H, *J*= 8.2 Hz), 7.34 (d, 4H, *J*= 8.2 Hz), 6.13 (br s, 1H), 3.97-3.90 (m, 2H), 3.81-3.77 (m, 1H), 3.41 (dd, 1H, J_1 = 21.5 Hz, J_2 = 11.0 Hz), 2.81 (dd, 2H, J_1 = 11.0 Hz, J_2 = 6.0 Hz), 2.66-2.63 (m, 1H), 2.03 (s, 6H), 1.93 (t, 2H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 146.4, 131.8, 127.8, 119.1, 109.8, 57.5, 53.0, 45.1, 44.8, 38.4, 35.9, 29.2; FT- IR (KBr): 2945, 2226, 1607, 1506, 827 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_4O$: 373.2028; found 373.2026.



(*1s*,2R*,4S)-2,4-Bis(4-bromo-3-fluorophenyl)-*N*-(2-(dimethylamino)ethyl)cyclobutane-carboxamide (119j).** Analytical TLC on silica gel, 2.5:2.5. methanol/ethyl acetate R_f = 0.40; red colour liquid; 68 mg, 53% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, 2H, *J* = 7.5 Hz), 7.01 (dd, 2H, J_1= 9.8 Hz, J_2= 1.8 Hz), 6.92 (dd, 2H, J_1= 8.2 Hz, J_2= 1.8 Hz), 6.27 (br s, 1H), 3.82-3.77 (m, 2H), 3.71-3.68 (m, 1H), 3.28 (dd, 1H, J_1 = 21.3 Hz, J_2 = 11.0 Hz), 2.91 (dd, 2H, J_1 = 11.0 Hz, J_2 = 5.4 Hz), 2.61-2.58 (m, 1H), 2.10 (s, 6H), 2.03 (t, 2H, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 160.1, 157.5 (d, J_{C-F}= 246 Hz), 142.6 (d, J_{C-F}= 7.0 Hz), 132.9, 123.9 (d, J_{C-F}= 3.0 Hz), 115.2 (d, J_{C-F}= 22.0 Hz), 106.3 (d, J_{C-F}= 20.0 Hz), 57.6, 52.8, 44.8, 37.8, 36.0, 29.7; FT-IR (DCM): 3252, 1601, 1511, 1468, 710 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{127b}r_2F_2N_2O$: 515.0145; found 517.0101.

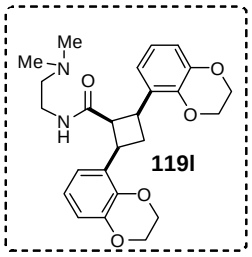


(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-bis(3,4-dimethylphenyl)cyclobutane-carboxamide (119k).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 black colour solid; 40 mg, 42% yield; mp 220-222 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08-7.01 (m, 6H), 6.08 (t, 1H, *J* = 5.4 Hz), 3.87-3.81 (m, 2H), 3.72-3.70 (m, 1H), 3.30 (dd, 1H, J_1 = 22.0 Hz, J_2 = 11.0 Hz), 2.90 (dd, 2H, J_1 = 11.0 Hz, J_2 = 6.0 Hz), 2.60-2.55 (m, 1H), 2.27 (s, 6H),



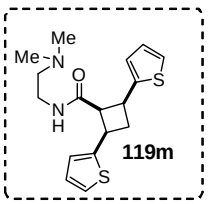
2.24 (s, 6H), 2.04 (s, 6H), 1.91 (t, 2H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 138.3, 135.9, 134.0, 129.3, 128.4, 124.5, 57.5, 53.2, 44.5, 38.4, 35.8, 29.7, 19.9, 19.4; FT-IR (KBr): 2937, 2316, 1567, 1516, 918 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{35}N_2O$: 379.2749; found 379.2748.

(*1s*,2R*,4S)-2,4-Bis(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-*N*-(2-(dimethylamino)ethyl)-cyclobutanecarboxamide (119l).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 brown colour solid; 45 mg, 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78-6.70 (m, 6H), 6.11 (t, 1H, J = 5.5 Hz), 4.20 (s, 8H), 3.77-3.70 (m, 2H), 3.63-3.58 (m, 1H), 3.15 (dd, 1H, J_1 = 22.0 Hz, J_2 = 11.4 Hz), 2.92 (dd, 2H, J_1 = 11.4 Hz, J_2 = 6.0 Hz), 2.52-2.49 (m, 1H), 2.08 (s, 6H), 2.00 (t, 2H, J = 6.0 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 143.0, 141.8, 134.3, 120.0, 116.7, 115.9, 64.3, 57.6, 52.9, 44.8, 44.7, 37.8, 35.9, 30.0; FT-IR (DCM): 3303, 1651, 1588, 1425, 890 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_5$: 439.2223; found 439.2233.



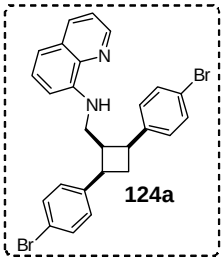
119l

(*1s*,2R*,4S)-*N*-(2-(Dimethylamino)ethyl)-2,4-di(thiophen-2-yl)cyclobutanecarboxamide (119m).** Analytical TLC on silica gel, 2:3. methanol/ethyl acetate R_f = 0.40 black colour liquid; 25 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, 2H, J_1 = 5.0 Hz, J_2 = 1.2 Hz), 6.99-6.94 (m, 4H), 6.03 (br s, 1H), 4.03-3.98 (m, 2H), 3.63-3.58 (m, 1H), 3.36 (dd, 1H, J_1 = 21.8 Hz, J_2 = 11.0 Hz), 3.00 (dd, 2H, J_1 = 11.0 Hz, J_2 = 5.4 Hz), 2.81-2.76 (m, 1H), 2.07 (s, 6H), 2.04 (t, 2H, J = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 143.7, 126.7, 125.1, 123.8, 57.6, 54.7, 48.1, 36.1, 35.4, 35.0; FT-IR (DCM): 2800, 2312, 1621, 1512, 800 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{129a2}OS_2$: 335.1251; found 335.1245.



119m

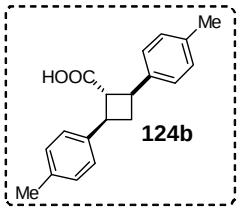
***N*-(((*1s*,2R*,4S**)-2,4-Bis(4-bromophenyl)cyclobutyl)methyl)quinolin-8-amine (124a).** Analytical TLC on silica gel, 1:4 ethyl acetate /hexanes R_f = 0.70 brown colour liquid; 51 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.07-8.04 (m, 1H), 7.50-7.17 (m, 11H), 7.07-7.04 (m, 1H), 6.60 (t, 1H, J = 6.5 Hz), 3.59 (d, 2H, J = 5.6 Hz), 3.40-3.26 (m, 2H), 2.93-2.72 (m, 2H), 2.22-2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 142.6, 138.1, 135.9, 131.5, 131.4, 128.5, 127.6, 127.5, 126.9, 120.1, 114.0,



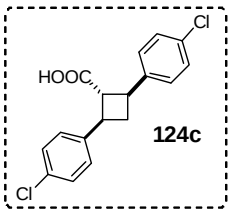
124a

104.7, 51.0, 46.8, 40.3, 34.0; FT-IR (DCM): 3234, 1644, 1412, 1382, 819 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{127b}r_2N_2$: 521.0228; found 521.0229.

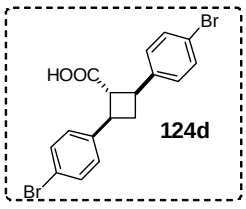
(*1r*,2R*,4S)-2,4-Di-*p*-tolylcyclobutanecarboxylic acid (124b).** Following the general procedure described above, **124b**was obtained as a brown colour liquid (crude material was almost pure); 67 mg, 96% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 4H, *J* = 8.0 Hz), 7.17 (d, 4H, *J* = 8.0 Hz), 3.76 (dd, 2H, J_1= 18.6 Hz, J_2= 10.0 Hz), 3.28 (t, 1H, *J* = 10.0 Hz), 2.80-2.74 (m, 1H), 2.38 (s, 6H), 2.31 (dd, 1H, J_1= 20.1 Hz, J_2= 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 139.7, 136.3, 129.2, 126.5, 52.6, 39.2, 32.9, 21.1; FT-IR (DCM): 2833, 1515, 1485, 1354, 806 cm^{-1}; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{19}H_{19}O_2$: 279.1385; found 279.1389.



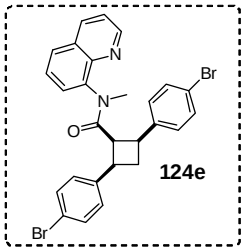
(*1r*,2R*,4S)-2,4-Bis(4-chlorophenyl)cyclobutanecarboxylic acid (124c).** Following the general procedure described above, **124c** was obtained as a white colour liquid (crude material was almost pure); 78 mg, 98% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, 4H, *J* = 8.5 Hz), 7.26 (d, 4H, *J* = 8.5 Hz), 3.78 (dd, 2H, J_1= 18.3 Hz, J_2= 10.0 Hz), 3.24 (t, 1H, *J* = 10.0 Hz), 2.84-2.78 (m, 1H), 2.27 (dd, 1H, J_1= 21.0 Hz, J_2= 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 140.8, 132.6, 128.6, 128.0, 52.3, 38.8, 32.5; FT-IR (DCM): 2966, 1565, 1432, 1331, 800 cm^{-1}; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{17}H_{13}Cl_2O_2$: 319.0292; found 319.0298.



(*1r*,2R*,4S)-2,4-Bis(4-bromophenyl)cyclobutanecarboxylic acid (124d).** Following the general procedure described above, **124d** was obtained as a brown colour solid (crude material was almost pure); 97 mg, 95% yield; mp131-133 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 4H, *J* = 8.4 Hz), 7.20 (d, 4H, *J* = 8.4 Hz), 3.76 (dd, 2H, J_1= 18.5 Hz, J_2= 10.0 Hz), 3.24 (t, 1H, *J* = 10.6 Hz), 2.84-2.77 (m, 1H), 2.26 (dd, 1H, J_1= 21.0 Hz, J_2= 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 141.3, 131.6, 128.3, 120.6, 52.2, 38.8, 32.3; FT-IR (KBr): 2922, 1698, 1516, 1425, 806 cm^{-1}; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{14}Br_2O_2Na$: 430.9258; found 430.9281.



(*1s*,2R*,4S)-2,4-Bis(4-bromophenyl)-*N*-methyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (124e).** Analytical TLC on silica gel, 1:4 ethyl acetate /hexanes



R_f = 0.70 light yellow colour liquid; 130 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.9 Hz), 8.24 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.9 Hz), 7.84 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.54-7.46 (m, 6H), 7.26-7.23 (m, 4H), 6.72 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 3.56-3.33 (m, 4H), 2.98 (s, 3H), 2.49-2.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 151.0, 144.2, 141.4, 141.3, 139.2, 136.3, 131.0, 130.8, 130.4, 129.4, 128.8, 128.9, 128.1, 126.4, 122.1, 120.8, 119.2, 50.0, 39.7, 37.7, 37.1; FT-IR (DCM): 2941, 1613, 1523, 1468, 791 cm^{-1}; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{127b}r_2N_2O$: 549.0177; found 549.0175.

General procedure for synthesis of bicycliccarboxamides 127b-i and 127j

Carboxylic acid (1.5 mmol) was dissolved in $SOCl_2$ (4mmol) and stirred for 24 h at rt under a nitrogen atmosphere.After this period, the reaction mixture was concentrated invacuum and diluted with anhydrous DCM (3 mL) undera nitrogen atmosphere. Then, the DCM solution containing acid chloride was added to a separate flask containingamine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). The reaction mixture was stirred at rt for 10 min andnext, the reaction mixture was refluxed for 12 h. Then, the reaction mixture was further diluted with dichloromethane (5mL) and washed with water followed by saturated aqueous$NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes =20:80) furnished the bridged bicycliccarboxamides **127b-i** and**127j.**

General procedure for direct C-H arylation of norbornane systems and the preparation of 129a−129h/133a-133g/135a−135h

A solution of bridged bicyclic framework**127b**or**126i** or**134**(0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol (10 mol %), aryl iodide (1mmol) Ag_2CO_3 (68.9 mg, 0.25 mmol) in anhydrous ^{t}BuOH (3mL) was heated at an appropriate temperature (73−85 °C, see the corresponding Tables/Schemes for specific examples) for an appropriate time (24-36 h, see the corresponding Tables/ Schemes for specific examples) under a nitrogen atmosphere.After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel,100−200 mesh) furnished the corresponding bis-arylated bicyclo[2.2.1]heptane-2-

carboxamides **129a−129h/133a-133g/135a−135h.** (see the corresponding Tables/Schemes for specific examples).

The same procedure was adopted to carry out the C-H arylation reactions using the bridged bicyclic frameworks **127c-127h** and**127j** with different aryl iodides. However, these substrates did not furnish any of the corresponding C-H arylated products (scheme 44).

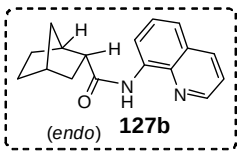
General procedure for mono C-H arylation 127b and the preparation of 130a-130f.

A solution of substrate **127b**(*endo*) (66.0 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol (10 mol %), aryl iodide (0.25mmol) and Ag_2CO_3 (68.9 mg, 0.25 mmol) in anhydrous ^{t}BuOH (3mL) was heated at an appropriate temperature (73−85 °C, see the corresponding Tables/Schemes for specific examples) for an appropriate time (24-36 h, see the corresponding Tables/ Schemes for specific examples) under a nitrogen atmosphere.After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel,100−200 mesh) furnished the corresponding mono-arylated norbornane systems **130a-130f**. (see the corresponding Tables/Schemes for specific examples).

General procedure for mono C-H arylation 127i and the preparation of 132a-c.

A solution of substrate **127i** (*endo*) (65.0 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol (10 mol %), aryl iodide (0.5mmol) Ag_2CO_3 (68.9 mg, 0.25 mmol) in anhydrous ^{t}BuOH (3mL) was heated at an appropriate temperature (85 °C, see the corresponding Tables/Schemes for specific examples) for an appropriate time (24-36 h, see the corresponding Tables/ Schemes for specific examples) under a nitrogen atmosphere.After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (silica gel,100−200 mesh) furnished the corresponding mono-arylated norbornane systems **132a-c**. (see the corresponding Tables/Schemes for specific examples).

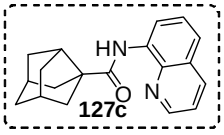
(*1S*,2R*,4R)-*N*-(Quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (127b):** Following the general procedure described above, **127b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour solid; Yield: 90%; mp 80-82 ^{o}C; IR (KBr): 3358, 1595, 1525, 1484, 790 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.83-8.78 (m, 2H), 8.17 (d, 1H, *J*= 8.2 Hz), 7.57-7.44 (m, 3H), 3.10-3.04 (m, 1H), 2.74-2.73 (m,



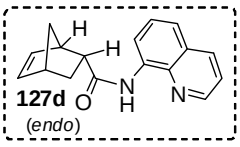
(*endo*) **127b**

1H), 2.38-2.36 (m, 1H), 1.94-1.89 (m, 1H), 1.82-1.75 (m, 1H), 1.65-1.53 (m, 3H), 1.48-1.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 148.1, 138.4, 136.3, 134.8, 127.9, 128.0, 121.5, 121.1, 116.1, 48.9, 41.4, 40.7, 37.2, 31.4, 29.3, 24.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O$: 267.1497; found 267.1498.

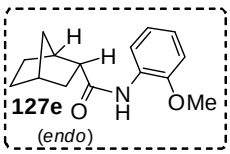
(2R*,3as*,5S*,6as*)-*N*-(Quinolin-8-yl)octahydro-2,5-methanopentalene-3a-carboxamide (127c):Following the general procedure described above, **127c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 85%; IR (DCM): 3340, 1688, 1578, 1297, 802 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (br s, 1H), 8.85-8.82 (m, 2H), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.58-7.45 (m, 3H), 2.92 (t, 1H, *J*= 6.8 Hz), 2.45-2.44 (m, 2H), 2.31-2.27 (m, 2H), 2.07-1.96 (m, 4H), 1.77-1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 148.2, 138.7, 136.3, 134.8, 127.9, 127.5, 121.5, 121.1, 116.1, 56.8, 47.7, 44.0, 43.8, 37.7, 34.7.



(*1R*,2R*,4R)-*N*-(Quinolin-8-yl)bicyclo[2.2.1]hept-5-ene-2-carboxamide (127d):** Following the general procedure described above, **127d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as black colour liquid; Yield: 95%; IR (DCM): 3355, 1525, 1484, 1325, 791 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.55-7.45 (m, 3H), 6.35 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.0 Hz), 6.12 (dd, 1H, J_1 = 5.6 Hz, J_2 = 2.8 Hz), 3.44-3.43 (m, 1H), 3.29-3.24 (m, 1H), 3.03-3.02 (m, 1H), 2.14-2.08 (m, 1H), 1.68-1.64 (m, 1H), 1.58-1.54 (m, 1H), 1.46-1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 148.2, 138.4, 138.0, 136.3, 134.7, 132.2, 127.9, 127.5, 121.5, 121.1, 116.2, 50.1, 46.6, 46.5, 42.9, 29.8;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O$: 265.1340; found 265.1342.

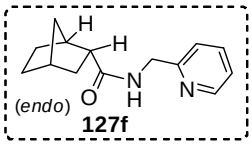


(*1S*,2R*,4R)-*N*-(2-Methoxyphenyl)bicyclo[2.2.1]heptane-2-carboxamide (127e):** Following the general procedure described above, **127e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 95%; IR (DCM): 3330, 2924, 1632, 1227, 791 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, 1H, *J*= 7.9 Hz), 7.83 (br s, 1H), 7.03-6.92 (m, 2H), 6.86 (d, 1H, *J*= 7.9 Hz), 3.87 (s, 3H), 2.87-2.82 (m, 1H), 2.55 (br s, 1H), 2.30 (br s, 1H), 1.82-1.62 (m, 2H), 1.56-1.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

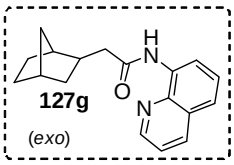


172.3, 147.6, 128.0, 123.2, 121.0, 119.5, 109.8, 55.7, 48.6, 41.4, 40.7, 37.1, 31.4, 29.2, 24.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1494; found 246.1494.

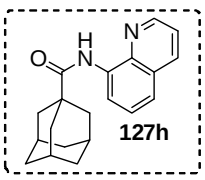
(*1S*,2R*,4R)-*N*-(Pyridin-2-ylmethyl)bicyclo[2.2.1]heptane-2-carboxamide (127f):** Following the general procedure described above, **127f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as black colour solid; Yield: 97%; mp 100-102 ^oC; IR (KBr): 3300, 1650, 1543, 1436, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 7.69-7.65 (m, 1H), 7.29-7.21 (m, 1H), 7.22-7.18 (m, 1H), 6.75 (br s, 1H), 4.60-4.56 (m, 2H), 2.77-2.72 (m, 1H), 2.50 (br s, 1H), 2.28 (br s, 1H), 1.76-1.66 (m, 2H), 1.56-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 156.9, 149.0, 136.7, 122.3, 122.2, 47.2, 44.5, 41.0, 40.5, 37.0, 31.5, 29.3, 24.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$: 231.1497; found 231.1506.



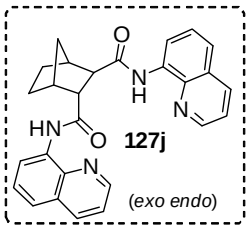
2-((*1S*,4R)-bicyclo[2.2.1]heptan-2-yl)-*N*-(quinolin-8-yl)acetamide (127g):** Following the general procedure described above, **127g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as yellow colour liquid; Yield: 92%;IR (DCM): 3355, 1712, 1688, 1525, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.83 (br s, 1H), 8.83-8.80 (m, 2H), 8.17-8.15 (m, 1H), 7.57-7.44 (m, 3H), 2.55 (dd, 1H, J_1 = 14.7 Hz, J_2 = 7.9 Hz), 2.43-2.38 (dd, 1H, J_1 = 14.6 Hz, J_2 = 7.6 Hz), 2.30-2.26 (m, 1H), 2.15-2.11 (m, 2H), 1.67-1.61 (m, 1H), 1.57-1.42 (m, 3H), 1.33-1.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 148.1, 138.3, 136.4, 134.6, 127.9, 127.4, 121.6, 121.3, 116.4, 45.2, 41.2, 39.0, 37.9, 36.8, 35.4, 29.9, 28.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O$: 281.1653; found 281.1662.



(3r*,5r*,7r*)-*N*-(Quinolin-8-yl)adamantane-1-carboxamide (127h) : Following the general procedure described above, **127h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as white colour liquid; Yield: 98%; IR (DCM): 3360, 1673, 1526, 1423, 824 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 10.3 (br s, 1H), 8.86-8.84 (m, 2H), 8.17 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.57-7.45 (m, 3H), 2.17-2.13 (m, 9H), 1.83 (t, 6H, J = 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 148.2, 138.9, 136.3, 134.7, 127.9, 127.5, 121.5, 121.2, 116.3, 42.3, 39.3, 36.5, 28.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{129a2}O$: 307.1810; found 307.1815.

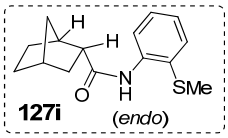


(*1R*,2R*,4S)-N2,*N3*-Di(quinolin-8-yl)bicyclo[2.2.1]heptane-2,3-dicarboxamide (127j):**

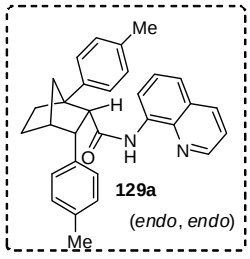


Following the general procedure described above, **127j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour solid; Yield: 99%; mp 181-183 ^{o}C; IR (KBr): 3450, 1611, 1543, 1322, 980 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (br s, 1H), 10.0 (br s, 1H), 8.83-8.77 (m, 4H), 8.12 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.4 Hz), 7.56-7.41 (m, 6H), 3.75-3.72 (m, 1H), 3.34-3.32 (m, 1H), 2.91 (br s, 1H), 2.78 (d, 1H, J = 3.7 Hz), 2.07-2.05 (m, 1H), 1.75-1.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.5, 148.2, 138.5, 138.3, 136.3, 136.2, 134.8, 134.6, 127.9, 127.3, 127.2, 121.6, 121.5, 121.4, 121.3, 116.3, 116.2, 52.4, 50.7, 42.7, 41.0, 38.9, 29.5, 24.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_4O_2$: 437.1978; found 437.1966.

(*1S*,2R*,4R)-*N*-(2-(Methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (127i) :** Following the general procedure described above, **127i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90)as white colour solid; Yield: 70%; mp 112-114 ^{o}C; IR (KBr): 3411, 1714, 1636, 1218, 902 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 8.38 (d, 1H, J = 8.2 Hz), 7.51 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.34-7.29 (m, 1H), 7.09-7.04 (m, 1H), 2.95-2.89 (m, 1H), 2.63 (br s, 1H), 2.39 (s, 3H), 2.34 (t, 1H, J = 3.8 Hz), 1.86-1.74 (m, 2H), 1.62-1.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 138.7, 133.2, 129.1, 124.6, 123.9, 120.3, 48.7, 41.2, 40.6, 37.1, 31.3, 29.2, 24.5, 19.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NOS$: 262.1265; found 262.1286.

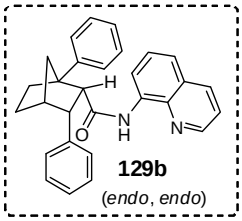


(*1R*,2R*,3R*,4R*)-*N*-(Quinolin-8-yl)-1,3-di-p-tolylbicyclo[2.2.1]heptane-2-carboxamide (129a): Following the general procedure described above, **129a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 70%; mp 172-174 ^{o}C; IR (KBr): 3401, 1629, 1521, 1322, 667 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 8.63 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.07 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.47-7.34 (m, 5H), 7.18 (d, 2H, J= 8.0 Hz), 7.09 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 3.88 (dd, 1H, J_1 = 11.0 Hz, J_2 = 2.8Hz), 3.57 (dd, 1H, J_1 = 11.0 Hz, J_2 = 1.3 Hz), 2.90-2.85 (m, 1H), 2.80 (br s, 1H), 2.32 (s, 3H), 2.30-2.26 (m, 2H), 2.23 (s, 3H), 1.93 (dd, 1H, J_1 = 9.5 Hz, J_2 = 1.6Hz),



1.83-1.77 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ170.3, 147.6, 141.2, 138.2, 137.6, 136.0, 135.7, 134.9, 134.6, 129.0, 128.6, 128.2, 127.7, 127.3, 127.1, 121.3, 120.9, 116.2, 58.0, 56.2, 49.2, 46.5, 41.6, 29.6, 23.9, 21.1, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{31}N_2O$: 447.2436; found 447.2444.

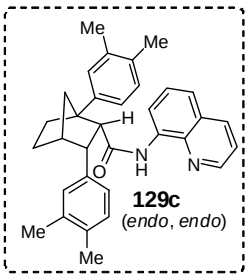
(*1R*,2R*,3R*,4R)-1,3-Diphenyl-*N*-(Quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide**



129b
(*endo*, *endo*)

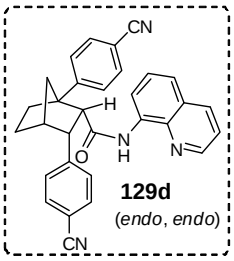
(129b) : Following the general procedure described above, **129b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as white colour solid; Yield: 81%; mp 135-137 ^oC; IR (KBr): 3300, 1668, 1587, 1321, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (br s, 1H), 8.63 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.9 Hz), 8.56-8.55 (m, 1H), 8.06 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.52-7.49 (m, 1H), 7.46-7.07 (m, 12H), 3.92 (dd, 1H, J_1 = 13.6 Hz, J_2 = 1.4Hz), 3.63 (dd, 1H, J_1 = 13.6 Hz, J_2 = 1.4Hz), 2.92-2.86 (m, 2H), 2.36-2.31 (m, 2H), 1.96 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.6 Hz), 1.86-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 147.7, 144.1, 140.7, 138.2, 136.0, 134.5, 128.3, 128.1, 127.8, 127.7, 127.3, 127.2, 126.3, 125.6, 121.3, 120.9, 116.1, 58.0, 56.5, 49.5, 46.4, 41.4, 29.6, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O$: 419.2123; found 419.2123.

(*1R*,2R*,3R*,4R)-1,3-Bis(3,4-dimethylphenyl)-N-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (129c) :** Following the general procedure described above, **129c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as white colourliquid; Yield: 55%; IR (KBr): 3400, 1629, 1464, 1345, 792 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (br s, 1H), 8.64 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 8.56 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48-7.41 (m, 2H), 7.37 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.28-7.24 (m, 2H), 7.09-7.03 (m, 3H), 6.96 (d, 1H, J = 7.8 Hz), 3.87, (dd, 1H, J_1 = 11.9 Hz, J_2 = 2.7Hz), 3.58 (dd, 1H, J_1 = 11.9 Hz, J_2 = 1.1Hz), 2.90-2.81 (m, 2H), 2.31(d, 2H, J = 9.8 Hz), 2.24 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.93 (dd, 1H, J_1 = 9.3 Hz, J_2 = 1.4Hz), 1.83-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 147.5, 141.7, 138.3, 138.0, 136.2, 135.9, 135.7, 134.6, 134.4, 133.5, 129.7, 129.5, 129.1, 128.5, 127.7, 127.3, 125.7, 124.6, 121.2, 120.8, 116.2, 58.0, 56.1, 49.2, 46.5, 41.5, 29.6, 23.9, 19.8, 19.7, 19.4, 19.3.

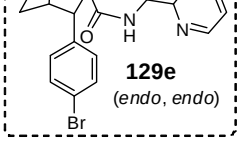


129c
(*endo*, *endo*)

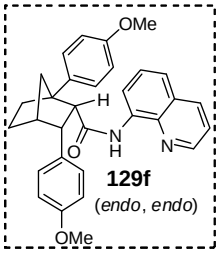
(*1R*,2R*,3R*,4R)-1,3-Bis(4-cyanophenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (129d) :** Following the general procedure described above, **129d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 65%; mp 213-215 ^{o}C; IR (KBr): 3335, 1606, 1523, 1384, 1096 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 8.54-8.48 (m, 2H), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.54-7.33 (m, 11H), 3.90 (d, 1H, J = 11.4 Hz), 3.62 (dd, 1H, J_1 = 11.6 Hz, J_2 = 1.8Hz), 2.92 (dd, 1H, J_1 = 4.4 Hz, J_2 = 1.0 Hz), 2.68-2.67 (m, 1H), 2.35 (d, 1H, J = 8.7 Hz), 2.25-2.17 (m, 1H), 1.98 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.7Hz), 1.93-1.86 (m, 1H), 1.80-1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 149.1, 147.9, 146.4, 137.9, 136.3, 133.6, 132.3, 131.7, 128.8, 128.1, 127.8, 127.2, 121.8, 121.7, 119.2, 119.0, 116.2, 110.4, 109.4, 58.2, 56.2, 49.2, 45.8, 40.8, 29.3, 23.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}N_4O$: 469.2028; found 469.2033.



(*1R*,2R*,3R*,4R)-1,3-Bis(4-bromophenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (129e):** Following the general procedure described above, **129e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as red colour solid; Yield: 46%; mp 137-139 ^{o}C; IR (KBr): 3400, 1594, 1484, 1322, 791 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (br s, 1H), 8.59 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.53 (dd, 1H, J_1 = 9.0 Hz, J_2 = 4.5 Hz), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.46-7.27 (m, 9H), 7.12 (d, 2H, J= 8.0 Hz), 3.80 (d, 1H, J= 11.5 Hz), 3.55 (dd, 1H, 11.6 Hz, J_2 = 1.8 Hz), 2.81 (dd, 1H, J_1 = 4.4 Hz, J_2 = 1.0 Hz), 2.73-2.68 (m, 1H), 2.28 (d, 1H, J= 9.5 Hz), 2.20-2.16 (m, 1H) 1.91-1.81 (m, 1H),1.83-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 147.9, 142.9, 139.6, 138.1, 136.1, 134.1, 131.4, 131.0, 130.9, 129.9, 129.0, 127.7, 127.2, 121.5, 121.3, 120.3, 119.5, 116.2, 58.0, 56.2, 48.7, 46.1, 41.1, 29.4, 23.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{137b}r_2N_2O$: 575.0333; found 575.0332.

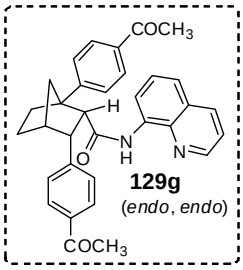


(*1R*,2R*,3R*,4R)-1,3-Bis(4-methoxyphenyl)-N-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (129f):** Following the general procedure described above, **129f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as red colour solid; Yield: 62%; mp 143-145 ^{o}C; IR (KBr): 2924, 1591, 1384, 1123, 607 cm^{-1}; ^{1}H NMR (400 MHz,

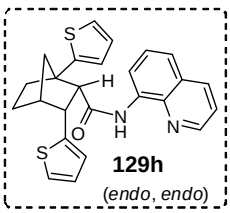


$CDCl_3$): δ 9.24 (br s, 1H), 8.61-8.56 (m, 2H), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.46-7.34 (m, 5H), 7.19 (d, 2H, *J*= 8.4 Hz), 6.83 (d, 2H, *J*= 9.2 Hz), 6.73 (d, 2H, *J*= 9.1 Hz), 3.85 (dd, 1H, J_1 = 11.9 Hz, J_2 = 2.4 Hz), 3.75 (s, 3H), 3.69 (s, 3H), 3.54 (dd, 1H, J_1 = 11.9 Hz, J_2 = 1.3 Hz), 2.87-2.84 (m, 1H), 2.76-2.75(m, 1H), 2.28-2.22 (m, 2H), 1.90 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.9Hz), 1.79-1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 157.9, 157.4, 147.6, 138.2, 136.4, 136.0, 134.5, 132.6, 129.3, 128.2, 127.7, 127.3, 121.2, 120.9, 116.1, 113.6, 113.3, 58.0, 55.8, 55.2, 55.1, 48.7, 46.5, 41.8, 29.6, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2334; found 479.2343.

(*1R*,2R*,3R*,4R)-1,3-Bis(4-acetylphenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (129g):** Following the general procedure described above, **129g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as white colour solid; Yield: 45%; mp 177-179 ^oC; IR (KBr): 3400, 1630, 1523, 1346, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 8.54 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.7 Hz), 8.45 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.06 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6Hz), 7.84 (d, 2H, *J*= 8.4 Hz), 7.83 (d, 2H, *J*= 8.4 Hz), 7.54 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.43-7.40 (m, 2H), 7.38-7.31 (m, 3H), 3.91 (d, 1H, *J*= 11.7 Hz), 3.66 (dd, 1H, 8.3 Hz, J_2 = 1.8 Hz), 2.92-2.90 (m, 1H), 2.76-2.73 (m, 1H), 2.52 (s, 3H), 2.49 (s, 3H), 2.35 (d, 1H, *J*= 8.9 Hz), 2.26-2.25 (m, 1H), 1.97 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.5Hz), 1.88-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 169.1, 149.4, 147.7, 146.7, 138.0, 136.1, 135.4, 134.6, 134.0, 128.5, 128.3, 128.0, 127.7, 127.5, 127.2, 121.4, 116.2, 58.2, 56.7, 49.3, 46.1, 41.0, 29.4, 26.6, 26.5, 23.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{31}N_2O_3$: 503.2334; found 503.2329.



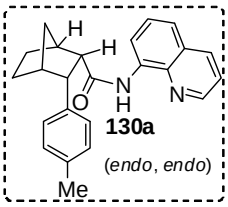
(*1R*,2R*,3R*,4R)-*N*-(Quinolin-8-yl)-1,3-di(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (129h) :** Following the general procedure described above, **129h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as light green colour solid; Yield: 78%; mp 135-137 ^oC; IR (KBr): 3400, 1611, 1423, 1387, 802 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.69-8.66 (m, 2H), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48-7.37 (m, 3H), 7.16 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.1 Hz), 7.03-7.01 (m, 3H), 6.91 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.4 Hz), 6.82 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.4 Hz), 4.13 (dd, 1H, J_1 = 12.3 Hz, J_2 = 3.6 Hz), 3.62 (dd, 1H, J_1 = 11.7 Hz, J_2 = 2.0Hz),



3.17-3.14 (m, 1H), 2.76 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.5 Hz), 2.39-2.36 (m, 1H), 2.19-2.16 (m, 1H), 2.04 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.0Hz), 1.92-1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 148.1, 147.8, 142.9, 138.2, 136.1, 134.4, 127.7, 127.3, 126.8, 126.6, 125.1, 123.9, 123.2, 123.1, 121.4, 121.1, 116.3, 57.9, 53.5, 49.1, 45.2, 44.2, 30.9, 24.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{129a2}OS_2$: 431.1252; found 431.1248.

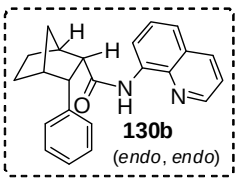
(*1S*,2S*,3R*,4R)-*N*-(Quinolin-8-yl)-3-(p-tolyl)bicyclo[2.2.1]heptane-2-carboxamide**

(130a) : Following the general procedure described above, **130a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as colourless solid; Yield: 57%; mp 121-123 ^oC; IR (KBr): 3360, 1591, 1523, 1384, 1051 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (br s, 1H), 8.68 (dd, 1H, J_1= 7.5 Hz, J_2= 1.4 Hz), 8.60 (dd, 1H, J_1= 4.2 Hz, J_2= 1.6 Hz), 8.08 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.50-7.41 (m, 2H), 7.38 (dd, 1H, J_1= 8.2 Hz, J_2= 4.2 Hz), 7.10 (d, 2H, J = 8.0 Hz), 6.95 (d, 2H, J = 7.9 Hz), 3.71 (dd, 1H, J_1= 12.0 Hz, J_2= 3.3Hz), 3.49.-3.44 (m, 1H), 2.86-2.85 (m, 1H), 2.59-2.58 (m, 1H), 2.23-2.20 (m, 1H), 2.14 (s, 3H), 1.89-1.82 (m, 1H), 1.75-1.73 (m, 1H), 1.69-1.60 (m, 2H), 1.52-1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 147.6, 138.3, 136.7, 136.0, 135.1, 134.6, 128.9, 128.4, 127.7, 127.3, 121.2, 120.8, 116.1, 51.1, 47.5, 43.2, 41.3, 40.6, 24.3, 23.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O$: 357.1966; found 357.1971.

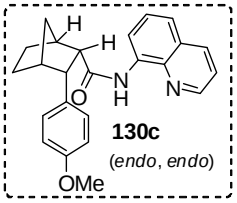


(*1S*,2S*,3R*,4R)-3-Phenyl-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide**

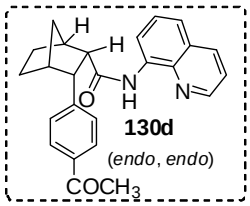
(130b): Following the general procedure described above, **130b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 73%; IR (DCM): 3400, 1566, 11404, 1324, 998 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (br s, 1H), 8.67 (dd, 1H, J_1= 7.4 Hz, J_2= 1.4 Hz), 8.60 (dd, 1H, J_1= 3.9 Hz, J_2= 1.6 Hz), 8.08 (dd, 1H, J_1= 8.2 Hz, J_2= 1.6 Hz), 7.49-7.35 (m, 4H), 7.29-7.20 (m, 2H), 7.18-7.13 (m, 1H), 7.02-6.96 (m, 1H), 3.75 (dd, 1H, J_1= 12.0 Hz, J_2= 3.8Hz), 3.52-3.48 (m, 1H), 2.86-2.85 (m, 1H), 2.62-2.61(m, 1H), 2.23-2.19 (m, 1H), 1.86-1.83 (m, 1H), 1.71-1.61 (m, 3H), 1.53-1.47 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 147.7, 139.9, 138.2, 136.0, 134.5, 128.9, 128.3, 127.8, 127.7, 127.6, 127.3, 125.8, 121.3, 120.9, 116.0, 51.0, 47.9, 43.1, 41.3, 40.6, 24.3, 23.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{129a2}O$: 343.1810; found 343.1816.



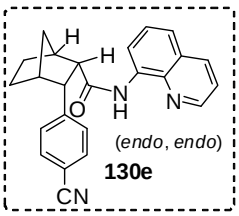
(*1S*,2S*,3R*,4R)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (130c):** Following the general procedure described above, **130c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 65%; IR (DCM): 3359, 1611, 1521, 1423, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (br s, 1H), 8.67 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.60 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.50-7.40 (m, 2H), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.13 (dd, 2H, J_1 = 6.8 Hz, J_2 = 1.7 Hz), 6.69 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 3.68 (dd, 1H, J_1 = 12.1 Hz, J_2 = 3.0 Hz), 3.61 (s, 3H), 3.45-3.43 (m, 1H), 2.84-2.83 (m, 1H), 2.57-2.56 (m, 1H), 2.35-2.15 (m, 1H), 1.85-1.78 (m, 1H), 1.74-1.62 (m, 3H), 1.50-1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 157.7, 147.6, 138.3, 136.0, 134.6, 131.8, 130.0, 127.7, 127.3, 121.3, 120.9, 116.0, 113.2, 55.0, 51.1, 47.1, 43.4, 41.1, 40.5, 24.2, 23.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_2$: 373.1916; found 373.1916.



(*1S*,2S*,3R*,4R)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (130d):** Following the general procedure described above, **130d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour liquid; Yield: 49%; IR (DCM): 3348, 1676, 1523, 1484, 1094 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 8.65-8.62 (m, 2H), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.76 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.7 Hz), 7.49-7.43 (m, 2H),7.39(dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, J = 8.3 Hz), 3.70 (dd, 1H, J_1 = 11.7 Hz, J_2 = 3.2 Hz), 3.57-3.53 (m, 1H), 2.87-2.86 (m, 1H), 2.68-2.67 (m 1H), 2.46 (s, 3H), 2.20-2.15 (m, 1H), 1.84-1.76 (m, 2H), 1.70-1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 170.9, 147.9, 146.5, 138.2, 136.2, 134.6, 134.4, 128.9, 127.8, 127.7, 127.4, 121.4, 121.5, 116.2, 51.0, 48.1, 42.3, 41.5, 40.7, 26.5, 24.5, 22.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2$: 385.1916; found 385.1924.

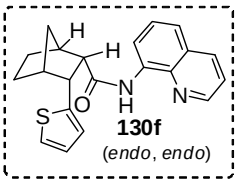


(*1S*,2S*,3R*,4R)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (130e):** Following the general procedure described above, **130e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour liquid; Yield: 58%; mp 212-214 ^oC; IR (DCM): 3340, 1633, 1403, 1389, 604 cm^{-1};^1H NMR (400

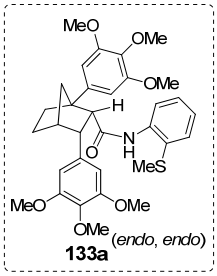


MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.60 (t, 1H, J= 4.5 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.49-7.41 (m, 5H), 7.29 (d, 2H, J= 8.0 Hz), 3.67 (dd, 1H, J_1 = 11.7 Hz, J_2 = 3.3Hz), 3.56-3.53 (m, 1H), 2.86-2.85 (m, 1H), 2.67-2.66 (m, 1H), 2.11-2.06 (m, 1H), 1.82-1.75 (m, 2H), 1.70-1.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 147.9, 146.7, 138.2, 136.3, 134.2, 131.4, 129.4, 127.8, 127.3, 121.5, 121.4, 119.2, 116.2, 109.2, 50.8, 48.1, 41.9, 41.6, 40.7, 24.6, 22.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}N_3O$: 368.1762; found 368.1767.

(*1S*,2S*,3R*,4R)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (130f)**: Following the general procedure described above, **130f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as green colour liquid; Yield: 61%; IR (DCM): 3398, 1601, 1598, 1221, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (br s, 1H), 8.70-8.68 (m, 2H), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6Hz), 7.50-7.42 (m, 2H), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.4 Hz), 6.99 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 6.89-6.88 (m, 1H), 6.78 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 3.94 (dd, 1H, J_1 = 12.0 Hz, J_2 = 3.8 Hz), 3.43-3.38 (m, 1H), 2.83-2.82 (m, 1H), 2.61-2.60 (m, 1H), 2.41-2.34 (m, 1H), 2.07-2.0 (m, 1H), 1.74-1.70 (m, 1H), 1.66-1.63 (m, 2H), 1.55-1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 147.8, 142.9, 138.3, 136.1, 134.6, 127.8, 127.4, 126.5, 125.4, 123.1, 121.4, 120.1, 116.1, 51.6, 44.2, 43.4, 41.4, 40.5, 23.8, 23.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2OS$: 349.1374; found 349.1374.

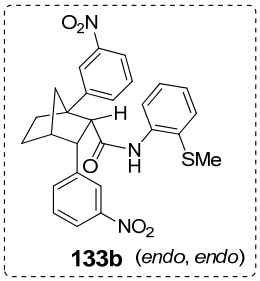


(*1R*,2R*,3R*,4R)-*N*-(2-(Methylthio)phenyl)-1,3-bis(3,4,5-trimethoxyphenyl)bicyclo[2.2.1]heptane-2-carboxamide (133a):** Following the general procedure described above, **133a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 23%; IR (DCM): 3420, 1661, 1414, 1134, 1112 cm^{-1}; ^{1}H NMR$^{\#}$ (400 MHz, $CDCl_3$): δ 8.23 (d, 1H, J = 8.1 Hz), 7.97 (br s, 1H), 7.37 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.20-7.16 (m, 1H), 6.70-6.95 (m, 1H), 6.67 (s, 2H), 6.49 (s, 2H), 3.84 (s, 3H), 3.80 (s, 6H), 3.79 (s, 3H), 3.73 (s, 6H), 3.31 (dd, 1H, J_1 = 12.0 Hz, J_2 = 1.1Hz), 2.94-2.90 (m, 1H), 2.76-2.75 (m, 1H), 2.27-2.17 (m, 2H), 2.00 (s, 3H), 1.94 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.4Hz), 1.82-1.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 152.9, 152.7, 139.8, 138.3, 136.6, 136.1, 136.0, 133.0, 128.7, 124.5, 124.0, 119.7, 105.5, 104.2, 60.8, 57.9, 56.8,



56.1, 56.0, 49.7, 46.3, 41.9, 35.2, 29.4, 23.9, 18.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{40}NO_7S$: 594.2525; found 594.2504.[#]One proton will be less in the counting and this proton got merged inside the OMe protons.

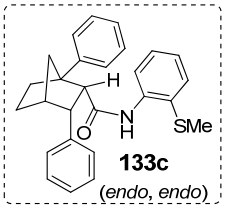
(*1R*,2R*,3R*,4R)-*N*-(2-(Methylthio)phenyl)-1,3-bis(3-nitrophenyl)bicyclo[2.2.1]heptane-2-carboxamide (133b):**



133b (*endo, endo*)

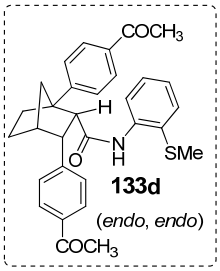
Following the general procedure described above, **133b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 32%; mp 198-200 ^oC; IR (KBr): 3333, 1578, 1525, 1346, 739 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (t, 1H, *J* = 3.8 Hz), 8.16-8.13 (m, 2H), 8.07-8.04 (m, 1H), 7.99 (d, 1H, *J*= 8.0 Hz), 7.79-7.75 (m, 2H), 7.57-7.50 (m, 2H), 7.44 (t, 1H, *J*= 8 Hz), 7.31 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 7.18-7.14 (m, 1H), 7.03-6.99 (m, 1H), 3.94 (d, 1H, *J*= 11.2 Hz), 3.48 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4Hz), 2.95-2.94 (m, 1H), 2.83-2.78 (m, 1H), 2.39 (d, 1H, *J* = 9.3 Hz), 2.26-2.16 (m, 1H), 2.05 (s, 3H), 2.02-.1.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.4, 148.1, 145.6, 142.4, 137.1, 134.3, 133.9, 132.1, 129.6, 128.8, 128.4, 125.4, 124.7, 123.1, 122.1, 121.9, 121.2, 120.4, 57.9, 56.3, 48.8, 46.2, 41.1, 29.2, 23.3, 18.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}N_3O_5S$: 504.1593; found 504.1586.

(*1R*,2R*,3R*,4R)-*N*-(2-(Methylthio)phenyl)-1,3-diphenylbicyclo[2.2.1]heptane-2-carboxamide (133c):** Following the general procedure described above, **133c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as red colour solid; Yield: 43%; mp 118-120 ^oC; IR (KBr): 3345, 1668, 1533, 1421, 878 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J* = 8.1 Hz), 7.93 (br s, 1H), 7.49-7.46 (m, 2H), 7.39-7.33 (m, 3H), 7.30-7.15(m, 7H), 6.99-6.95 (m, 1H), 3.88 (dd, 1H, J_1 = 11.8 Hz, J_2 = 3.0Hz), 3.43 (dd, 1H, J_1 = 11.8 Hz, J_2 = 1.4Hz), 2.85-2.82 (m, 2H), 2.31-2.24 (m, 1H), 1.92 (d, 1H, *J*= 11.8 Hz), 1.89 (s, 3H), 1.83-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 144.1, 140.5, 138.7, 133.4, 129.0, 128.4, 128.2, 128.0, 127.2, 126.5, 125.8, 124.4, 123.7, 120.0, 58.2, 56.5, 49.3, 46.5, 41.4, 29.2, 23.6, 18.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{28}NOS$: 414.1891; found 414.1901.[#]One proton will be less in the counting and this proton got merged inside the SMe protons.



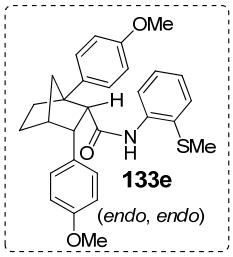
133c
(*endo, endo*)

(*1R*,2R*,3R*,4R)-1,3-Bis(4-acetylphenyl)-*N*-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (133d):**



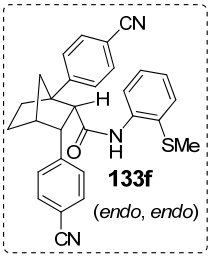
Following the general procedure described above, **133d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour solid; Yield: 40%; mp 170-172 ^{o}C; IR (KBr): 3334, 1688, 1509, 1126, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 1H, J = 8.2 Hz), 7.94 (dd, 2H, J_1 = 6.8 Hz, J_2 = 1.8 Hz), 7.87 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.82 (br s, 1H), 7.55 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 7.35-7.32 (m, 3H), 7.20-7.15 (m, 1H), 7.01-6.97 (m, 1H), 3.88 (d, 1H, J = 11.3 Hz), 3.46 (dd, 1H, J_1 = 11.7 Hz, J_2 = 1.4Hz), 2.91-2.90 (m, 1H), 2.78-2.72 (m, 1H), 2.60 (s, 3H), 2.57 (s, 3H), 2.32 (d, 1H, J = 8.8 Hz), 2.23-2.19 (m, 1H), 1.95 (s, 3H), 1.94-1.93 (m, 1H), 1.83-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 197.8, 168.7, 149.3, 146.4, 137.9, 135.6, 134.7, 132.8, 128.7, 128.6, 128.2, 128.1, 127.5, 124.8, 124.2, 120.1, 58.3, 56.7, 49.3, 46.2, 41.1, 29.2, 26.6, 23.4, 18.7; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{31}H_{32}NO_3S$: 498.2102; found 498.2094.

(*1R*,2R*,3R*,4R)-1,3-Bis(4-methoxyphenyl)-N-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (133e)**:



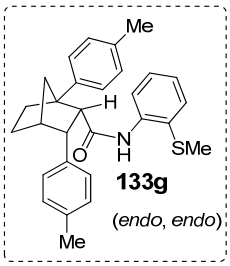
Following the general procedure described above, **133e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour solid; Yield: 50%; mp 141-143 ^{o}C; IR (KBr): 3350, 1611, 1578, 1429, 825 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 1H, J = 8.1 Hz), 7.90 (br s, 1H), 7.41-7.36 (m, 3H), 7.22-7.16 (m, 3H), 6.99-6.95 (m, 1H), 6.88 (dd, 2H, J_1 = 5.1 Hz, J_2 = 3.1Hz), 6.84 (dd, 2H, J_1 = 6.7 Hz, J_2 = 2.1Hz), 3.80 (s, 3H), 3.77 (s, 3H), 3.32 (dd, 1H, J_1 = 12.0 Hz, J_2 = 1.1 Hz), 2.84 (d, 1H, J = 11.4 Hz), 2.74-2.73 (m, 1H), 2.25-2.18 (m, 2H), 1.94 (s, 3H), 1.85 (dd, 1H, J_1 = 9.5 Hz, J_2 = 1.6 Hz), 1.78-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 158.1, 157.6, 138.7, 136.3, 133.4, 132.5, 129.2, 128.9, 128.2, 123.7, 120.0, 113.7, 113.4, 58.2, 55.8, 55.3, 55.2, 48.7, 46.7, 41.8, 29.3, 23.6, 18.8; HRMS (ESI): *m/z* [M + H]$^{+}$calcd for $C_{29}H_{32}NO_3S$: 474.2102; found 474.2104.$^{\#}$ One proton will be less in the counting and this proton got merged inside the SMe protons.

(*1R*,2R*,3R*,4R)-1,3-Bis(4-cyanophenyl)-*N*-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (133f)**: Following the general

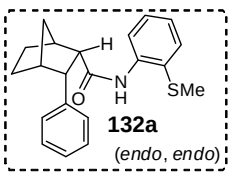


procedure described above, **133f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 33%; mp 218-220 ^{o}C; IR (KBr): 3339, 1606, 1431, 1272, 1094 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 8.0 Hz), 7.76 (br s, 1H), 7.64 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.7Hz), 7.57-7.54 (m, 4H), 7.36-7.32 (m, 3H), 7.21-7.17 (m, 1H), 7.06-7.02 (m, 1H), 3.85 (d, 1H, J = 11.4 Hz), 3.38 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.2Hz), 2.92-2.88 (m, 1H), 2.72-2.69 (m, 1H), 2.31-2.29 (m, 1H), 2.20-2.13 (m, 1H), 2.07 (s, 3H), 1.96 (dd, 1H, J_1 = 9.8 Hz, J_2 = 1.9Hz), 1.86-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 149.1, 146.1, 137.3, 132.4, 132.3, 131.8, 128.8, 128.6, 128.1, 125.1, 124.6, 120.1, 119.1, 118.8, 110.6, 109.7, 58.1, 56.7, 49.2, 46.0, 40.9, 29.1, 23.2, 18.6; HRMS (ESI): *m/z* [M + H]$^{+}$calcd for $C_{29}H_{26}N_3OS$: 464.1796; found 464.1803.

(*1R*,2R*,3R*,4R)-*N*-(2-(Methylthio)phenyl)-1,3-di-p-tolylbicyclo[2.2.1]heptane-2-carboxamide (133g) :** Following the general procedure described above, **133g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour solid; Yield: 35%; mp 140-142 ^{o}C; IR (KBr): 3401, 1636, 1384, 1292, 753 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 8.1 Hz), 7.93 (br s, 1H), 7.40-7.36 (m, 3H), 7.23-7.19 (m, 1H), 7.15 (d, 4H, J = 7.9 Hz), 7.08 (d, 2H, J = 8.0 Hz), 6.99-6.95 (m, 1H), 3.82 (dd, 1H, J_1 = 11.8 Hz, J_2 = 2.4 Hz), 3.37 (d, 1H, J= 11.9 Hz), 2.81-2.78 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.27-2.22 (m, 2H), 1.89 (s, 3H), 1.87 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.4 Hz), 1.79-1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 141.1, 138.9, 137.4, 135.9, 135.1, 133.5, 129.4, 129.1, 129.0, 128.7, 128.0, 127.1, 127.0, 123.6, 120.0, 58.3, 56.2, 49.1, 46.6, 41.5, 37.4, 29.2, 23.6, 21.0, 18.8; HRMS (ESI): *m/z* [M + H]$^{+}$calcd for $C_{29}H_{32}NOS$: 442.2204; found 442.2229.

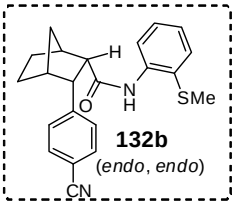


(*1S*,2S*,3R*,4R)-*N*-(2-(Methylthio)phenyl)-3-phenylbicyclo[2.2.1]heptane-2-carboxamide (132a) :** Following the general procedure described above, **132a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 36%; IR (DCM): 3422, 1637, 1520, 1050, 698 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H, J = 8.0 Hz), 7.96 (br s, 1H), 7.37 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.26-7.10 (m, 6H), 7.0-6.95 (m, 1H), 3.71 (dd, 1H, J_1 = 11.9 Hz, J_2 = 3.8Hz), 3.32-3.37 (m, 1H), 2.78-2.77 (m, 1H), 2.53-2.51 (m, 1H), 2.29-2.25 (m, 1H), 1.99 (s, 3H), 1.73-



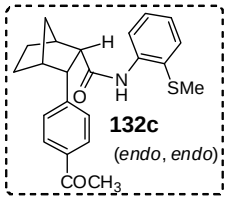
1.61 (m, 4H), 1.43-1.38 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ171.5, 139.7, 138.7, 133.3, 129.0, 128.9, 128.0, 126.1, 124.4, 123.6, 119.8, 50.8, 47.6, 44.1, 40.8, 40.4, 23.8, 23.1, 19.1; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{21}H_{24}NOS$: 338.1578; found 338.1577.

(*1S*,2S*,3R*,4R)-3-(4-Cyanophenyl)-*N*-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (132b)**: Following the general procedure described above, **132b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as



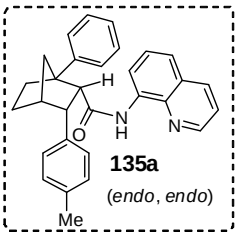
yellow colour solid; Yield: 32%; mp 182-184 ^oC; IR (KBr): 3271, 1649, 1504, 1045, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 1H, J = 8.2 Hz), 8.10 (br s, 1H), 7.53 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 7.41 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.29-7.21 (m, 3H), 7.06-7.02 (m, 1H), 3.63 (dd, 1H, J_1 = 11.6 Hz, J_2 = 2.4Hz), 3.38-3.34 (m, 1H), 2.78-2.77 (m, 1H), 2.61-2.60 (m, 1H), 2.23 (s, 3H), 2.10-2.05 (m, 1H), 1.75-1.56 (s, 5H), 1.54-1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 146.4, 138.0, 132.7, 131.6, 129.4, 128.8, 124.8, 124.2, 120.2, 119.2, 109.5, 50.6, 48.0, 42.4, 41.3, 40.6, 24.4, 22.7, 18.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{22}H_{129a2}OS$: 363.1531; found 363.1543.

(*1S*,2S*,3R*,4R)-3-(4-Acetylphenyl)-*N*-(2-(methylthio)phenyl)bicyclo[2.2.1]heptane-2-carboxamide (132c) :** Following the general procedure described above, **132c** was obtained



after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as yellow colour solid; Yield: 32%; mp 137-139 ^oC; IR (KBr): 3400, 1671, 1544, 1344, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 8.1 Hz), 8.01 (br s, 1H), 7.84 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.7 Hz), 7.39 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4Hz), 7.28-7.21 (m, 3H), 7.03-6.99 (m, 1H), 3.67 (dd, 1H, J_1 = 11.7 Hz, J_2 = 2.7 Hz), 3.37-3.30 (m, 1H), 2.78-2.77 (m, 1H), 2.62-2.60(m, 1H), 2.55 (s, 3H), 2.14 (s, 3H), 1.75-1.47 (m, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 170.7, 146.3, 138.3, 134.9, 133.0, 128.9, 128.8, 128.0, 124.6, 124.0, 120.1, 50.7, 47.9, 43.0, 41.2, 40.6, 26.6, 24.2, 22.9, 19.0; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{23}H_{26}NO_2S$: 380.1684; found 380.1678.

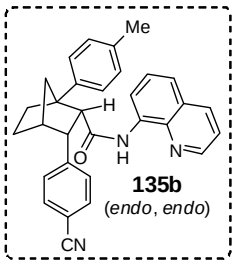
(*1R*,2R*,3R*,4R)-1-Phenyl-*N*-(quinolin-8-yl)-3-(p-tolyl)bicyclo[2.2.1]heptane-2-carboxamide (135a) :** Following the general procedure described above, **135a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as white colour solid; Yield: 43%; mp 164-166 ^oC; IR (KBr): 3340, 1604, 1430, 1272, 1051 cm^{-1}; ^{1}H



135a
(*endo*, *endo*)

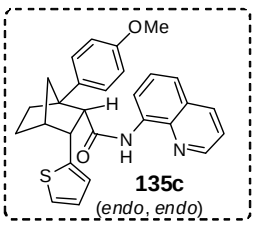
NMR (400 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 8.61 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.07 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48-7.40 (m, 4H), 7.35 (dd, 1H, J_1 = 11.8 Hz, J_2 = 1.4 Hz), 7.28-7.24 (m, 2H), 7.21-7.15 (m, 3H), 7.00 (d, 2H, J_1 = 7.9 Hz), 3.89 (dd, 1H, J_1 = 11.9 Hz, J_2 = 2.6 Hz), 3.60 (dd, 1H, J_1 = 11.8 Hz, J_2 = 1.4 Hz), 2.88-2.80 (m, 2H), 2.32-2.25 (m, 2H), 2.21 (s, 3H), 1.94 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.7 Hz), 1.82-1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 147.6, 144.2, 138.2, 137.5, 135.9, 134.9, 134.5, 128.6, 128.2, 128.1, 127.7, 127.3, 127.2, 126.3, 121.2, 120.9, 116.2, 57.9, 56.5, 49.1, 46.3, 41.5, 29.5, 23.7, 20.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{30}H_{29}N_2O$: 433.2279; found 433.2276.

(*1R*,2R*,3R*,4R)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)-1-(p-tolyl)bicyclo[2.2.1]heptane-2-carboxamide (135b):** Following the general procedure described above, **135b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:80) as yellow colour solid; Yield: 37%; mp 191-193 ^oC; IR (KBr): 3300, 1581, 1304, 1224, 1065 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 8.55-8.51 (m, 2H), 8.11 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 7.51 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.6 Hz), 7.46-7.30 (m, 7H), 7.07 (d, 2H, J = 7.9 Hz), 3.85 (d, 1H, J= 11.5 Hz), 3.65 (dd, 1H, J_1 = 11.8 Hz, J_2 = 1.4 Hz), 2.88-2.86 (m, 1H), 2.62-2.57 (m, 1H), 2.33-2.32 (m, 1H), 2.31 (s, 3H), 2.23-2.17 (m, 1H), 1.95 (dd, 1H, J_1 = 11.4Hz, J_2 = 1.4 Hz), 1.89-1.80 (m, 1H), .1.79-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 147.6, 147.2, 140.3, 138.1, 136.1, 136.0, 134.1, 131.6, 129.1, 128.7, 127.7, 127.3, 127.0, 121.4, 121.3, 119.3, 116.2, 109.1, 58.3, 56.4, 49.4, 46.2, 40.4, 29.7, 23.5, 21.0; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{31}H_{28}N_3O$: 458.2232; found 458.2233.



135b
(*endo*, *endo*)

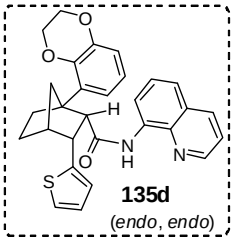
(*1R*,2R*,3R*,4R)-1-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (135c):** Following the general procedure described above, **135c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 33%; ^oC; IR (DCM): 3332, 1673, 1541, 1332, 876 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (br s, 1H), 8.66-8.64 (m, 2H), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6Hz), 7.47-7.36 (m, 5H), 7.02 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.98-6.96 (m, 1H), 6.83-6.79 (m, 3H), 4.09-4.05 (m, 1H), 3.75 (s, 3H), 3.43 (dd, 1H,



135c
(*endo*, *endo*)

J_1 = 12.7 Hz, J_2 = 1.8 Hz), 3.11-3.07 (m, 1H), 2.76-2.74 (m, 1H), 2.39-2.35 (m, 1H), 2.24 (dd, 1H, J_1 = 11.8 Hz, J_2 = 1.2 Hz), 1.91 (dd, 1H, J_1 = 9.6 Hz, J_2 = 1.6 Hz), 1.81-1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 158.0, 147.7, 143.4, 138.2, 136.1, 136.0, 134.5, 128.1, 127.7, 127.3, 126.5, 125.0, 124.1, 123.0, 121.3, 121.0, 116.2, 113.6, 58.1, 56.0, 55.2, 46.4, 45.5, 43.5, 29.4, 24.2; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{28}H_{27}N_2O_2S$: 455.1793; found 455.1795.

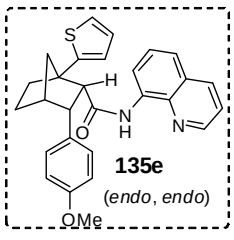
(*1R*,2R*,3R*,4R)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (135d):**



135d
(*endo*, *endo*)

Following the general procedure described above, **135d**was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 32%; ^{o}C; IR (DCM): 3400, 1632, 1413, 1286, 998 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (br s, 1H), 8.65-8.63 (m, 2H), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48-7.37 (m, 3H), 7.02 (dd, 1H, J_1 = 5.8 Hz, J_2 = 1.0 Hz), 6.97-6.94 (m, 3H), 6.83 (dd, 1H, J_1 = 5.8 Hz, J_2 = 1.5 Hz), 6.76 (d, 1H, *J*= 8.0 Hz), 4.23-4.04 (m, 5H), 3.41 (dd, 1H, J_1 = 12.0 Hz, J_2 = 4.0 Hz), 3.09-3.03 (m, 1H), 2.74-2.72 (m, 1H), 2.42-2.31 (m, 1H), 2.21-2.18 (m, 1H), 1.90-1.71 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 147.7, 143.4, 143.0, 142.0, 138.2, 137.4, 136.1, 134.5, 127.7, 127.3, 126.5, 125.0, 122.9, 121.3, 121.0, 120.2, 117.0, 116.3, 115.9, 64.3, 58.0, 56.1, 46.5, 45.4, 43.5, 29.3, 24.2; HRMS (ESI): *m/z* [M + H]$^+$calcd for $C_{28}H_{27}N_2O_3S$: 483.1742; found 483.1754.

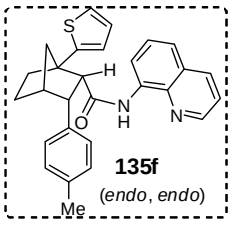
(*1R*,2R*,3R*,4R)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-1-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (135e)**: Following the general procedure described above, **135e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 38%; IR (DCM): 3280, 1608, 1566, 1321, 888 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (br s, 1H), 8.63-8.60 (m, 2H), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.46-7.36 (m, 3H), 7.20-7.15 (m, 3H), 7.03 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.2 Hz), 6.92 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 6.74-6.50 (m, 2H), 3.92 (dd, 1H, J_1 = 12.0 Hz, J_2 = 2.3 Hz), 3.70 (dd, 1H, J_1 = 11.9 Hz, J_2 = 2.0 Hz), 3.62 (s, 3H), 2.95-2.90 (m, 1H), 2.74-2.72 (m, 1H), 2.20-2.16 (m, 2H), 2.04 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.5 Hz), 1.93-1.89 (m, 1H), 1.82-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 157.5, 148.5, 147.7, 136.0, 134.4, 132.2, 129.3, 127.7, 127.3, 126.8, 124.0, 123.1, 121.3, 121.0, 116.2, 113.3,



135e
(*endo*, *endo*)

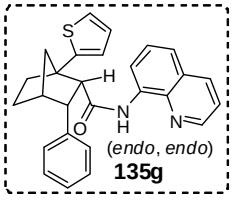
113.2, 57.8, 55.1, 53.4, 49.4, 48.6, 42.8, 31.0, 23.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{28}H_{27}N_2O_2S$: 455.1793; found 455.1795.

(*1R*,2R*,3R*,4R)-*N*-(Quinolin-8-yl)-1-(thiophen-2-yl)-3-(p-tolyl)bicyclo[2.2.1]heptane-2-carboxamide (135f):** Following the general procedure described above, **135f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as green colour liquid; Yield: 33%; IR (DCM): 3410, 1676, 1522, 1322, 825 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (br s, 1H), 8.64-8.61 (m, 2H), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.46-7.36 (m, 2H), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.17-7.14 (m, 3H), 7.02-7.0 (m, 3H), 6.91 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 3.90 (d, 1H, J= 12.0 Hz), 3.72 (dd, 1H, J_1 = 11.9 Hz, J_2 = 1.9 Hz), 2.90-2.85 (m, 1H), 2.78-2.76 (m, 1H), 2.24 (s, 3H), 2.23-2.19 (m, 2H), 2.04 (dd, 1H, J_1 = 9.4 Hz, J_2 = 3.6 Hz), 1.95-1.87 (m, 1H), 1.84-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 148.5, 147.7, 138.2, 137.1, 136.0, 135.0, 134.5, 128.6, 128.1, 127.7, 127.3, 126.8, 124.0, 123.1, 121.3, 120.9, 116.2, 57.9, 53.4, 49.4, 49.0, 42.4, 31.2, 23.9, 20.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{28}H_{27}N_2OS$: 439.1844; found 439.1840.



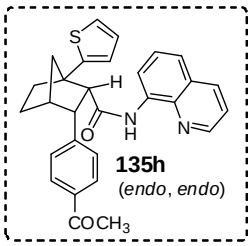
135f
(*endo*, *endo*)

(*1R*,2R*,3R*,4R)-3-Phenyl-*N*-(quinolin-8-yl)-1-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (135g):** Following the general procedure described above, **135g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as brown colour liquid; Yield: 37%; ^{o}C; IR (DCM): 3353, 1594, 1423, 1323, 825 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 8.63-8.59 (m, 2H), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.45-7.40 (m, 2H), 7.39 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.27 (d, 2H, J = 7.5Hz), 7.21-7.16 (m, 3H), 7.08-7.05 (m, 1H), 7.02 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.3 Hz), 6.92 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.5 Hz), 3.93 (d, 1H, J_1 = 11.8 Hz), 3.75 (dd, 1H, J_1 = 11.9 Hz, J_2 = 1.9 Hz), 2.86-2.79 (m, 2H), 2.26-2.20 (m, 2H), 2.06 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.6 Hz), 1.94-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 148.4, 147.7, 140.3, 138.2, 136.0, 134.4, 128.3, 127.8, 127.7, 127.3, 126.8, 125.7, 124.1, 123.1, 121.3, 120.9, 116.2, 58.0, 53.4, 49.4, 49.3, 42.3, 31.2, 23.9; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{27}H_{25}N_2OS$: 425.1687; found 425.1692.



(*endo*, *endo*)
135g

(*1R*,2R*,3R*,4R*)*-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)-1-(thiophen-2-yl)bicyclo[2.2.1]heptane-2-carboxamide (135h): Following the general procedure described above, **135h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 50%; ^{o}C; IR (DCM): 3340, 1679, 1510, 1122, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (br s, 1H), 8.62 (dd, 1H, J_1 = 4.2. Hz, J_2 = 2.5 Hz), 8.57 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 16 Hz), 7.81 (dd, 2H, J_1 = 6.7 Hz, J_2 = 1.6 Hz), 7.44-7.30 (m, 5H), 7.19 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 6.98 (dd, 1H, J_1 = 3.4 Hz, J_2 = 1.6 Hz), 6.91 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.4 Hz), 3.92 (dd, 1H, J_1 = 11.6 Hz, J_2 = 2.6 Hz), 3.78 (dd, 1H, J_1 = 11.6 Hz, J_2 = 1.2 Hz), 2.87-2.86 (m, 1H), 2.70-2.65 (m, 1H), 2.52 (s, 3H), 2.24-2.20 (m, 2H), 2.07 (dd, 1H, J_1 = 9.7 Hz, J_2 = 1.6 Hz), 1.93-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 169.1, 147.9, 147.8, 146.8, 138.2, 136.1, 134.5, 134.2, 128.2, 128.0, 127.7, 127.3, 126.9, 124.3, 123.3, 121.4, 121.2, 116.3, 58.3, 53.6, 49.3, 49.2, 41.6, 31.4, 26.5, 23.7; HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{29}H_{27}N_2O_2S$: 467.1793; found 467.1805.



Procedure for the synthesis of the carboxamides 137b-137o

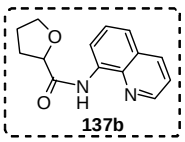
The corresponding carboxylic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h at rt under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atmosphere. Then, the corresponding acid chloride in DCM was added to a separate round botttomed flask containing amine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at rt for 10 min and then, the reaction mixture was refluxed for 12 h under a nitrogen atmosphere. After this period, the reaction mixture was diluted with DCM (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes = 30:70) furnished the corresponding cyclic ether carboxamides **137b-137o**

General procedure for the Pd-catalyzed C-H arylation of the carboxamides 137b-137oand preparation of 139a, 140a-140q, 141a-141q, 142a-142h and**143a-143h.** A mixture of the correspondingcyclic ether carboxamide **1** (0.25 mmol, 1 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol%), ArI (1.0 mmol, 4 equiv) and AgOAc (91.8 mg, 0.55 mmol, 2.2 equiv) in

anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24-48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding C-H arylated cyclic ether carboxamides **139a, 139a, 140a-140q, 141a-141q, 142a-142h** and**143a-143h.** (see Tables/Schemes for specific examples).

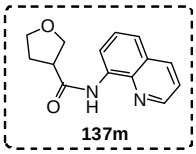
Procedure for the hydrolysis of the amides 140a and**141a**. To a RB flask (capacity 25 mL) molded with a Liebig condenser (length = 15 cm) sealed at the top and having a J Young air inlet valve at the side of the round botttomed flask was sequentially added the corresponding carboxamide **140a**or **141a** (0.25 mmol) dissolved in a mixture of toluene (3 mL) and water (0.5 mL) and CF_3SO_3H (0.5 mL) using syringes. The air inlet was closed and the reaction mixture was heated at 100 °C and chilled water was circulated in the outer glass tube of the condenser. After 12 h, the reaction mixture was transferred from the round botttomed flask into a separating funnel using a syringe, diluted with EtOAc and extracted with saturated aqueous Na_2CO_3 solution (20 mL x 2). Then, the combined aqueous layers were acidified with 1 N HCl (15 mL x 2) to get pH~2. Then, the aqueous layers were extracted using EtOAc (10 mL x 2), drying of the combined organic layers over anhydrous Na_2SO_4 and evaporation in vacuum gave the corresponding carboxylic acid **144a** or**144b**.

***N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (137b):** Following the general procedure, **137b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 95% (230 mg); mp 85-87 ^{o}C; IR (KBr): 3441, 1653, 1554, 1260, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.82 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58-7.53 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.28-4.23 (m, 1H), 4.08 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.48-2.39 (m, 1H), 2.32-2.25 (m, 1H), 2.04-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1154.



137b

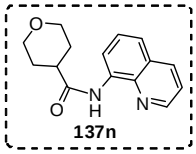
***N*-(Quinolin-8-yl)tetrahydrofuran-3-carboxamide (137m):** Following the general procedure, **137m** was obtained after purification by column chromatography on silica gel



137m

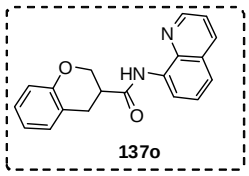
(EtOAc:Hexanes = 30:70) as red colour solid; Yield: 90% (218 mg); mp 80-82 ^{o}C; IR (KBr): 3440, 1676, 1527, 1385, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br s, 1H), 8.72 (d, 1H, J_1 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 3.1 Hz, J_2 = 1.7 Hz), 8.03 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.45-7.38 (m, 2H), 7.34 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.06 (d, 2H, J = 6.9 Hz), 4.02-3.97 (m, 1H), 3.87-3.81 (m, 1H), 3.27-3.19 (m, 1H), 2.34-2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.2, 138.2, 136.3, 134.3, 127.8, 127.2, 121.7, 121.6, 116.5, 71.0, 68.4, 46.9, 30.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1158.

***N*-(Quinolin-8-yl)tetrahydro-2*H*-pyran-4-carboxamide(137n):** Following the general procedure, **137n** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 40:60) as brown colour solid. Yield: 88% (225 mg); mp 141-143^{o}C; IR (KBr): 3352, 1682, 1528, 1280, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.80 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.19 (d, 1H, J= 8.3 Hz), 7.58-7.51 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.14 (t, 1H, J= 3.0 Hz), 4.11 (t, 1H, J= 3.0 Hz), 3.55 (dt, 2H, J_1 = 11.0 Hz, J_2 = 3.5 Hz), 2.80-2.72 (m, 1H), 2.09-1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 148.2, 138.4, 136.5, 134.3. 128.0, 127.4, 121.7, 121.6, 116.5, 67.3, 43.6, 29.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1290.



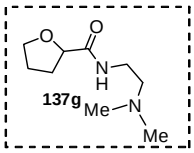
137n

***N*-(Quinolin-8-yl)chroman-3-carboxamide(137o):** Following the general procedure, **137o** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as yellow colour liquid. Yield: 85% (258 mg); IR (DCM): 3343, 1682, 1528, 1228, 1068, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.17 (br s, 1H), 8.82-8.79 (m, 2H), 8.19 (d, 1H, J = 8.2 Hz), 7.59-7.54 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.17 (t, 2H, J = 8.0 Hz), 6.93 (dd, 2H, J_1 = 12.2 Hz, J_2 = 8.0 Hz), 4.66-4.62 (m, 1H), 4.30 (t, 1H, J = 10.4 Hz), 3.37 (m, dd, 1H, J_1 = 15.3 Hz, J_2 = 10.0 Hz), 3.27-3.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 154.0, 148.3, 138.4, 136.4, 134.1, 129.9, 127.9, 127.6, 127.4, 121.9, 121.7, 120.8, 120.5, 116.8, 116.7, 67.4, 41.3, 28.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1290; found 305.1290.



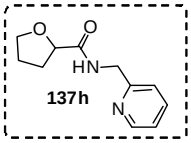
137o

***N*-(2-(Dimethylamino)ethyl)tetrahydrofuran-2-carboxamide (137g):** Following the general procedure, **137g** was obtained after purification by column chromatography on silica



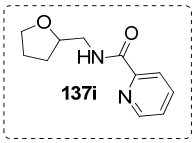
gel (MeOH: EtOAc = 10:90) as dark brown colour liquid; Yield: 40% (75 mg); IR (DCM): 3433, 1637, 1528, 1260, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.07 (br s, 1H), 4.36 (dd, 1H, J_1 = 8.3 Hz, J_2 = 5.8 Hz), 3.99-3.86 (m, 2H), 3.41-3.29 (m, 2H), 2.41 (dt, 2H, J_1 = 6.3 Hz, J_2 = 1.5 Hz), 2.33-2.26 (m, 1H), 2.24 (s, 6H), 2.10-2.02 (m, 1H), 1.95-1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 78.5, 69.4, 58.1, 45.3, 36.4, 30.2, 25.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{19}N_2O_2$: 187.1447; found 187.1459.

***N*-(Pyridin-2-ylmethyl)tetrahydrofuran-2-carboxamide (137h):** Following the general procedure, **137h** was obtained after purification by column chromatography on silica gel



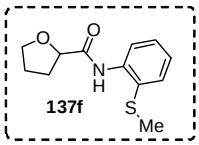
(EtOAc:Hexanes = 60:40) as dark brown colour liquid; Yield: 71% (146 mg); IR (DCM): 3396, 1650, 1530, 1075, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, *J* = 4.5 Hz), 7.67 (br s, 1H), 7.58 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 7.6 Hz), 7.12 (t, 1H, *J* = 5.9 Hz), 4.56-4.40 (m, 2H), 4.35 (dd, 1H, J_1 = 8.3 Hz, J_2 = 6.1 Hz), 3.95-3.90 (m, 1H), 3.85-3.79 (m, 1H), 2.27-2.18 (m, 1H), 2.06-1.96 (m, 1H), 1.88-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 156.7, 149.1, 136.7, 122.3, 121.8, 78.5, 69.4, 43.9, 30.2, 25.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.1133; found 207.1132.

***N*-((Tetrahydrofuran-2-yl)methyl)picolinamide (137i):** Following the general procedure



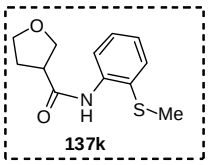
described above, **137i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as dark brown colour liquid; Yield: 80% (165 mg); IR (DCM): 3480, 1668, 1590, 1077, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.36 (br s, 1H), 8.19 (d, 1H, *J* = 7.8 Hz), 7.84 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.40 (m, 1H), 4.13-4.07 (m, 1H), 3.95-3.90 (m, 1H), 3.82-3.71 (m, 2H), 3.47-3.41 (m, 1H), 2.07-1.99 (m, 1H), 1.95-1.87 (m, 2H), 1.68-1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 149.8, 148.1, 137.3, 126.1, 122.2, 77.8, 68.3, 43.2, 28.8, 25.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.1134; found 207.1157.

***N*-(2-(Methylthio)phenyl)tetrahydrofuran-2-carboxamide (137f):** Following the general procedure, **137f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 81% (192 mg); IR (DCM): 3441, 1685, 1523, 1275, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.36 (dd, 1H, J_1

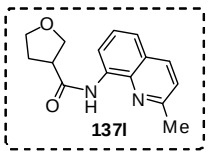


= 8.2 Hz, J_2 = 1.3 Hz), 7.47 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.32-7.28 (m, 1H), 7.09 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 4.54 (dd, 1H, J_1 = 8.5 Hz, J_2 = 5.4 Hz), 4.17-4.12 (m, 1H), 4.01 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.41 (s, 3H), 2.39-2.33 (m, 1H), 2.26-2.18 (m, 1H), 2.02-1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 137.5, 132.4, 128.6, 126.0, 124.5, 120.3, 79.0, 69.8, 30.4, 25.6, 18.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{15}NNaO_2S$: 260.0721; found 260.0734.

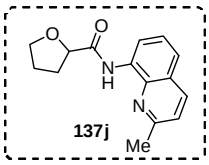
***N*-(2-(Methylthio)phenyl)tetrahydrofuran-3-carboxamide (137k):** Following the general procedure, **137k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless solid. Yield: 70% (65 mg); mp 64-66 ^oC; IR (KBr): 3437, 1661, 1471, 1554, 1261, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.26 (d, 1H, *J*= 8.2 Hz), 7.46 (d, 1H, *J*= 7.2 Hz), 7.28 (t, 1H, *J*= 8.2 Hz), 7.08 (t, 1H, *J*= 7.2 Hz), 4.09-3.97 (m, 3H), 3.87 (dd, 1H, J_1 = 15.4 Hz, J_2 = 7.5 Hz), 3.17-3.11 (m, 1H), 2.39 (s, 3H), 2.29 (dd, 2H, J_1 = 14.0 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 137.9, 132.4, 128.6, 125.8, 124.6, 121.0, 70.9, 68.2, 46.8, 30.5, 18.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0902; found 238.0908.



***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-2-carboxamide (137l):** Following the general procedure, **137l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 85% (217 mg); mp 83-85 ^oC; IR (KBr): 3440, 1603, 1573, 1260, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (br s, 1H), 8.76 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.4 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 7.48-7.47 (m, 2H), 7.32 (d, 1H, *J* = 8.4 Hz), 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.3 Hz), 4.29-4.24 (m, 1H), 4.12-4.07 (m, 1H), 2.77 (s, 3H), 2.44-2.37 (m, 1H), 2.33-2.25 (m, 1H), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 157.4, 138.3, 136.2, 133.3, 126.2, 126.1, 122.4, 121.7, 116.4, 79.2, 69.7, 30.5, 25.5, 25.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1298.

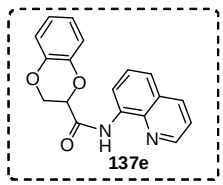


***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-3-carboxamide (137j):** Following the general procedure, **137j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour liquid. Yield: 90% (230 mg); IR (DCM): 3342, 1683, 1530, 1384, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 8.75-8.71 (m,

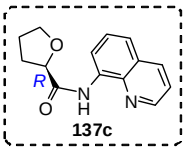


1H), 8.01 (d, 1H, *J*= 8.4 Hz), 7.45 (d, 2H, *J*= 4.2 Hz), 7.31 (d, 1H, *J*= 8.4 Hz), 4.17-4.05 (m, 3H), 3.93 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.7 Hz), 3.41-3.27 (m, 1H), 2.75 (s, 3H), 2.43-2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 157.3, 137.7, 136.4, 133.7, 126.3, 126.0, 122.5, 121.5, 116.5, 71.1, 68.5, 47.0, 30.7, 25.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1281.

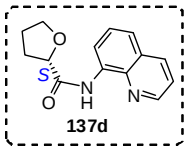
***N*-(Quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (137e):** Following the general procedure, **137e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 84% (257 mg); mp 121-123 ^oC; IR (KBr): 3440, 1682, 1491, 1274, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.81 (t, 1H, *J*= 4.4 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.57 (d, 2H, *J*= 4.3 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27-7.24 (m, 1H), 7.01-6.92 (m, 3H), 4.97 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.7 Hz), 4.69 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.7 Hz), 4.44 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 148.7, 143.4, 141.8, 138.7, 136.2, 133.5, 127.9, 127.1, 122.5, 122.5, 122.0, 121.8, 117.7, 117.7, 116.9, 73.8, 65.3 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_3$: 307.1083; found 307.1094.



(*R*)-*N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (137c): Following the general procedure, **137c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as dark brown colour liquid; Yield: 90% (218 mg); *ee* 99%; $([\alpha]^{25}D$ = -101.1 (*c* 0.05, DCM); IR (DCM): 3377, 2964, 1276, 1263, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.93 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.81 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.3 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56-7.50 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz) 4.63 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.26-4.21 (m, 1H), 4.06 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.44-2.37 (m, 1H), 2.31-2.23 (m, 1H), 2.02-1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1138.

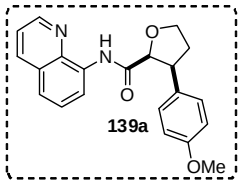


(*S*)-*N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (137d): Following the general procedure, **137d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as dark brown colour liquid; Yield: 88% (213 mg); *ee* 99%;



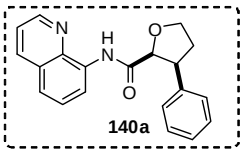
([α]^{25}D = +111.1 (*c* 0.05, DCM); IR (DCM): 3334, 1683, 1578, 1530, 1067, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.93 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.81 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58-7.53 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz) 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.28-4.22 (m, 1H), 4.08 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.48-2.38 (m, 1H), 2.32-2.24 (m, 1H), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 122.0, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1130.

(*2R*,3R)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**



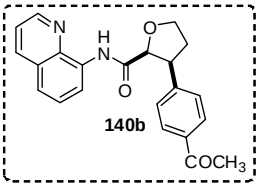
(139a): Following the general procedure, **139a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour viscous liquid; Yield: 81% (71 mg); IR (DCM): 3341, 1683, 1489, 1326, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.48 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47-7.40 (m, 3H), 7.21 (d, 2H, *J* = 8.8 Hz), 6.68 (d, 2H, *J* = 8.8 Hz), 4.74 (d, 1H, *J* = 7.0 Hz), 4.63-4.57 (m, 1H), 4.21-4.15 (m, 1H), 3.90-3.85 (m, 1H), 3.62 (s, 3H), 2.58-2.53 (m, 1H), 2.31-2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1563.

(*2R*,3R)-3-Phenyl-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140a):** Following



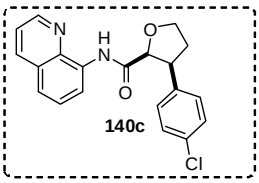
the general procedure, **140a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 73% (58 mg); mp 102-104 ^{o}C; IR (DCM): 3441, 1642, 1527, 1275, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47-7.39 (m, 3H), 7.31-7.29 (m, 2H), 7.15 (t, 2H, *J* = 7.3 Hz), 7.05 (t, 1H, *J* = 7.3 Hz), 4.78 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.94-3.89 (m, 1H), 2.64-2.55 (m, 1H), 2.37-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.5, 140.5, 138.8, 136.1, 133.6, 128.2, 127.9, 127.9, 127.1, 126.7, 121.7, 121.5, 116.6, 83.9, 68.7, 48.0, 33.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1447; found 319.1460.

(*2R*,3R)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140b):**

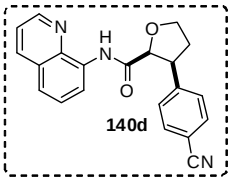


Following the general procedure, **140b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 72% (65 mg); mp 117-119 ^{o}C; IR (KBr): 3424, 1678, 1528, 1274, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (d, 2H, J = 8.3 Hz), 7.47-7.39 (m, 3H), 7.38 (d, 2H, J = 8.3 Hz), 4.79 (d, 1H, J = 7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.65-2.57 (m, 1H), 2.42 (s, 3H), 2.34-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1568.

(*2R*,3R)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140c):** Following the general procedure, **140c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 62% (55 mg); mp 143-145 ^{o}C; IR (DCM): 3339, 1682, 1528, 1057, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.49-7.41 (m, 3H), 7.22 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.62-2.53 (m, 1H), 2.29-2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.2, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1070.



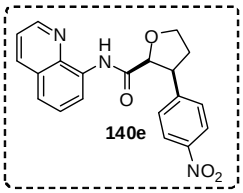
(*2R*,3R)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140d):**



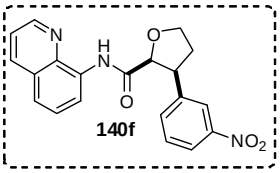
Following the general procedure, **140d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 76% (65 mg); mp 200-202 ^{o}C; IR (KBr): 3431, 1636, 1531, 1275, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.52-7.49 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.44-

7.7.38 (m, 5H), 4.78 (d, 1H, *J* = 7.0 Hz), 4.64-4.58 (m, 1H), 4.25-4.19 (m, 1H), 3.97-3.92 (m, 1H), 2.68-2.59 (m, 1H), 2.32-2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.6, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1408.

(*2R*,3R)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140e):**



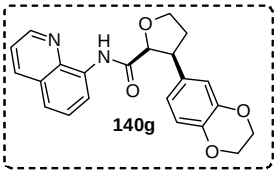
Following the general procedure, **140e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 56% (51 mg); mp 160-162 ^{o}C; IR (KBr): 3396, 1664, 1596, 1076, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 7.49-7.39 (m, 3H), 7.45 (d, 2H, *J* = 8.8 Hz), 4.80 (d, 1H, *J* = 7.0 Hz), 4.65-4.60 (m, 1H), 4.25-4.19 (m, 1H), 4.03-3.98 (m, 1H), 2.69-2.60 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1309.



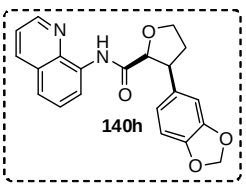
(*2R*,3R)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140f):** Following the general procedure, **140f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 75% (68 mg); mp 109-111 ^{o}C; IR (KBr): 3441, 1684, 1528, 1259, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.17 (t, 1H, *J*= 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.87-7.84 (m, 1H), 7.60 (d, 1H, *J*= 7.7 Hz), 7.47-7.42 (m, 2H), 7.38 (t, 1H, *J*= 8.0 Hz), 7.26 (t, 1H, *J*= 8.0 Hz), 4.78 (d, 1H, *J* = 6.8 Hz), 4.70-4.64 (m, 1H), 4.26-4.20 (m, 1H), 4.03-3.98 (m, 1H), 2.70-2.61 (m, 1H), 2.36-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0, 127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1310.

(*2R*,3R)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140g):** Following the general procedure, **140g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless liquid;

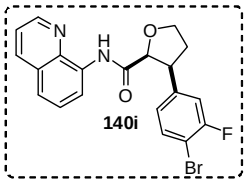
Yield: 53% (50 mg); IR (DCM): 3440, 1677, 1528, 1282, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.55 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.52 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.46-7.42 (m, 3H), 6.80 (d, 1H, J = 2.0 Hz), 6.75 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 6.60 (d, 1H, J = 8.3 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.60-4.55 (m, 1H), 4.20-4.14 (m, 1H), 4.09-3.94 (m, 4H), 3.82-3.78 (m, 1H), 2.58-2.49 (m, 1H), 2.30-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 148.5, 143.0, 142.2, 138.8, 136.0, 133.7, 127.9, 127.1, 121.6, 121.4, 120.9, 116.9, 116.8, 116.6, 83.8, 68.6, 64.1, 47.3, 33.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_4$: 377.1501; found 377.1508.



(*2R*,3R)-3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140h):** Following the general procedure, **140h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour liquid; Yield: 46% (42 mg); IR (DCM): 3432, 1637, 1528, 1269, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.51 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47-7.42 (m, 3H), 6.79 (d, 1H, J = 1.7 Hz), 6.75 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.7 Hz), 6.57 (d, 1H, J = 8.0 Hz), 5.76 (d, 1H, J = 1.5 Hz), 5.66 (d, 1H, J = 1.5 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.61-4.55 (m, 1H), 4.21-4.15 (m, 1H), 3.86-3.81 (m, 1H), 2.60-2.51 (m, 1H), 2.30-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.5, 147.4, 146.1, 138.8, 136.1, 134.3, 133.6, 127.9, 127.1, 121.7, 121.5, 121.1, 116.6, 108.4, 108.0, 100.7, 83.8, 68.5, 47.7, 33.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_4$: 363.1345; found 363.1352.

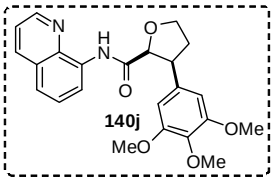


(*2R*,3R)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140i):** Following the general procedure, **140i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 58% (60 mg); mp 99-101 ^oC; IR (KBr): 3339, 1686, 1530, 1325, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50-7.42 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.1 Hz), 6.95 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.60-4.54 (m, 1H), 4.22-4.15 (m, 1H), 3.88-3.84 (m, 1H), 2.63-2.54 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.6 Hz), 148.6, 142.6



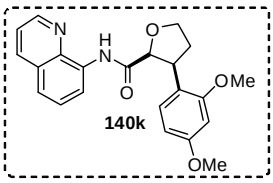
(d, $J_{C\text{-}F}$ = 6.4 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 122.1, 121.6, 116.7, 116.0 (d, $J_{C\text{-}F}$ = 22.2 Hz), 107.0 (d, $J_{C\text{-}F}$ = 20.7 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0465.

(*2R*,3R)-*N*-(Quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-carboxamide**



(140j): Following the general procedure, **140j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as brown colour solid; Yield: 54% (55 mg); mp 89-91 ^oC; IR (DCM): 3441, 1681, 1590, 1127, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.53 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.55 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.47-7.40 (m, 3H), 6.49 (s, 2H), 4.73 (d, 1H, J = 6.6 Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.85-3.81 (m, 1H), 3.63 (s, 6H), 3.44 (s, 3H), 2.62-2.53 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 152.8, 148.3, 138.6, 136.5, 136.4, 136.2, 133.6, 127.9, 127.2, 121.7, 121.5, 116.4, 104.8, 84.0, 68.6, 60.4, 55.7, 48.2, 33.8;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_5$: 409.1763; found 409.1768.

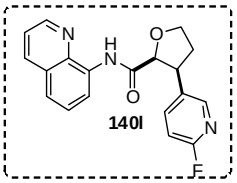
(*2R*,3R)-3-(2,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**



(140k): Following the general procedure, **140k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 40% (38 mg); mp 105-107 ^oC; IR (KBr): 3424, 1614, 1529, 1260, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.53 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.48-7.41 (m, 3H), 7.07 (d, 1H, J = 8.4 Hz), 6.39 (d, 1H, J = 2.4 Hz), 6.26 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.5 Hz), 4.91 (d, 1H, J = 8.2 Hz), 4.62-4.57 (m, 1H), 4.20-4.12 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H), 2.47-2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 159.5, 158.3, 148.3, 138.7, 136.1, 134.0, 127.9, 127.9, 127.2, 121.5, 121.4, 119.8, 116.4, 103.9, 98.4, 81.8, 68.7, 55.5, 55.1, 41.5, 30.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{129a2}O_4$: 379.1658; found 379.1672.

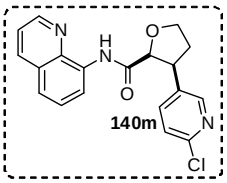
(*2R*,3R)-3-(6-Fluoropyridin-3-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**

(140l): Following the general procedure, **140l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 71% (60 mg); mp 117-119 ^oC; IR (KBr): 3441, 1679, 1528, 1259, 750 cm^{-1}; ^1H NMR (400 MHz,

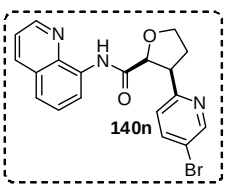


$CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.44 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.6 Hz), 8.14-8.11 (m, 2H), 7.70 (dt, 1H, J_1 = 8.0 Hz, J_2 = 2.6 Hz), 7.49-7.40 (m, 3H), 6.68 (dd, 1H, J_1 = 8.5 Hz, J_2 = 3.0 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.61-4.55 (m, 1H), 4.23-4.17 (m, 1H), 3.94-3.89 (m, 1H), 2.65-2.56 (m, 1H), 2.27-2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 162.6 (d, J_{C-F} = 236.5 Hz), 148.6, 146.8 (d, J_{C-F} = 14.6 Hz), 140.6 (d, J_{C-F} = 7.8 Hz), 138.7, 136.2, 133.9 (d, J_{C-F} = 4.6 Hz), 133.2, 127.9, 127.1, 122.2, 121.6, 116.6, 108.9 (d, J_{C-F} = 37.4 Hz), 83.4, 68.5, 44.5, 33.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}FN_3O_2$: 338.1305; found 338.1315.

(*2R*,3R)-3-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140m):** Following the general procedure, **140m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as colourless solid; Yield: 56% (50 mg); mp 127-129 ^oC; IR (DCM): 3435, 1579, 1459, 1325, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.7 Hz), 8.32 (d, 1H, J = 2.5 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.6 Hz), 7.50-7.41 (m, 3H), 7.08 (d, 1H, J = 8.3 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.60-4.54 (m, 1H), 4.23-4.17 (m, 1H), 3.92-3.87 (m, 1H), 2.66-2.57 (m, 1H), 2.25-2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 149.8, 149.1, 148.7, 138.7, 138.2, 136.2, 135.3, 133.2, 127.9, 127.1, 123.8, 122.2, 121.6, 116.7, 83.3, 68.5, 44.6, 33.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009; found 354.1023.

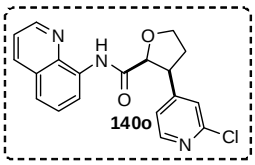


(*2R*,3R)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140n):** Following the general procedure, **140n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as brown colour liquid; Yield: 31% (31 mg); IR (DCM): 3436, 1638, 1530, 1275, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.40-8.39 (m, 1H), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.51-7.43 (m, 3H), 7.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.4 Hz), 4.87 (d, 1H, J = 7.6 Hz), 4.70 (dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.21 (dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.04 (dd, 1H, J_1 = 13.9 Hz, J_2 = 6.9 Hz), 2.49 (dd, 2H, J_1 = 13.9 Hz, J_2 = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 158.5, 150.1, 148.6, 138.8, 138.5, 136.1, 133.6, 127.9, 127.1, 124.7, 121.8, 121.5,



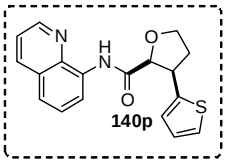
118.7, 116.5, 83.3, 69.5, 48.9, 32.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}BrN_3O_2$: 398.0504; found 398.0512.

(*2R*,3R)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**

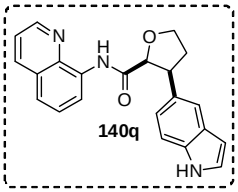


(140o): Following the general procedure, **140o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as brown colour solid; Yield: 51% (45 mg); mp 98-100 ^oC; IR (DCM): 3416, 1704, 1667, 1363, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.43 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.11 (d, 1H, J = 5.2 Hz), 7.51-7.41 (m, 3H), 7.26 (d, 1H, J = 1.4 Hz), 7.13 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.6 Hz), 4.77 (d, 1H, J = 6.7 Hz), 4.61-4.55 (m, 1H), 4.24-4.18 (m, 1H), 3.87-3.83 (m, 1H), 2.66-2.57 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 153.3, 151.5, 149.4, 148.7, 138.7, 136.2, 133.0, 127.9, 127.1, 123.7, 122.3, 122.0, 121.6, 116.8, 83.4, 68.5, 46.9, 33.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009; found 354.1025.

(*2R*,3S)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (140p):** Following the general procedure, **140p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 87% (71 mg); mp 134-136 ^oC; IR (DCM): 3424, 1643, 1275, 1094, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.49-7.43 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, J = 6.3 Hz), 4.62 (dd, 1H, J_1 = 16.1 Hz, J_2 = 7.5 Hz), 4.28-4.22 (m, 2H), 2.66-2.57 (m, 1H), 2.37-2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.1029.



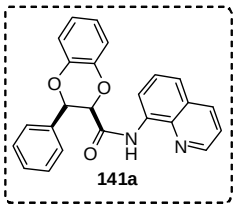
(*2R*,3R)-3-(1H-Indol-5-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (140q):** Following the general procedure, **140q** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as dark brown colour liquid; Yield: 20% (18 mg); IR (DCM): 3339, 1731, 1672, 1325, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.40 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7



140q

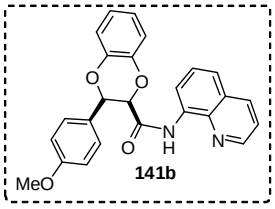
Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.03 (br s, 1H), 7.55 (s, 1H), 7.45-7.39 (m, 2H), 7.33 (t, 1H, J= 8.0 Hz), 7.11-7.05 (m, 2H), 7.00 (t, 1H, J= 3.0 Hz), 6.32 (t, 1H, J = 2.2 Hz), 4.81 (d, 1H, J = 7.2 Hz), 4.69-4.64 (m, 1H), 4.24-4.18 (m, 1H), 4.04-3.99 (m, 1H), 2.64-2.55 (m, 1H), 2.42-2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 148.4, 138.8, 136.0, 134.8, 133.7, 131.5, 127.8, 127.1, 124.1, 122.3, 121.5, 121.4, 119.7, 116.6, 110.8, 102.4, 84.1, 68.8, 48.3, 34.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_2$: 358.1556; found 358.1565.

(*2R*,3R)-3-Phenyl-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141a):** Following the general procedure, **141a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 65% (62 mg); mp 168-170 ^oC; IR (KBr): 3423, 1643, 1533, 1260, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (t, 1H, J = 4.2 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53-7.52 (m, 2H), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (d, 2H, J = 7.1 Hz), 7.28-7.26 (m, 1H), 7.22-7.00 (m, 6H), 5.95 (d, 1H, J = 3.1 Hz), 5.14 (d, 1H, J = 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.3, 142.1, 138.7, 136.1, 135.8, 133.4, 128.4, 127.9, 127.1, 123.3, 122.4, 121.7, 121.5, 117.8, 117.4, 116.9, 76.4, 76.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3$: 383.1396; found 383.1413.



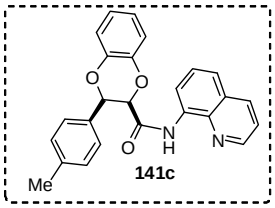
141a

(*2R*,3R)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141b):** Following the general procedure, **141b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 81% (84 mg); mp 119-121 ^oC; IR (KBr): 3431, 1634, 1531, 1259, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.72 (dd, 1H, J_1 = 5.9 Hz, J_2 = 3.0 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.53-7.52 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.28-7.26 (m,1H), 7.08-6.99 (m, 3H), 6.71 (d, 2H, J = 8.8 Hz), 5.88 (d, 1H, J = 3.1 Hz), 5.12 (d, 1H, J = 3.1 Hz), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 159.5, 148.6, 143.2, 142.0, 138.7, 136.1, 133.4, 128.5, 128.0, 127.9, 127.1, 123.3, 122.4, 121.7, 121.4, 117.7, 117.5, 116.9, 113.8, 76.4, 75.6, 55.0;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_4$: 413.1501; found 413.1515.

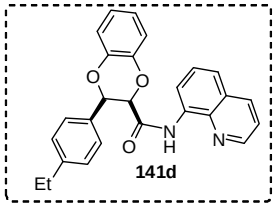


141b

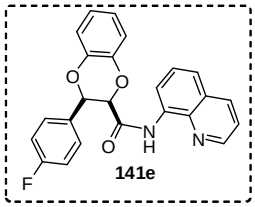
(*2R*,3R)-*N*-(Quinolin-8-yl)-3-(*p*-tolyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141c):** Following the general procedure, **141c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 66% (65 mg); IR (DCM): 3431, 1636, 1534, 1363, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.74 (t, 1H, J = 4.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53-7.52 (m, 2H), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.28-7.26 (m, 3H), 7.10-6.98 (m, 5H), 5.91 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 3.0 Hz), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 148.5, 143.3, 142.1, 138.7, 138.1, 136.1, 133.4, 132.8, 129.1, 127.9, 127.1, 127.0, 123.2, 122.4, 121.7, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1552; found 397.1562.



(*2R*,3R)-3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141d):** Following the general procedure, **141d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 40% (41 mg); mp 95-97 ^oC; IR (DCM): 3333, 1687, 1533, 1255, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.5 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.54-7.53 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.28-7.25 (m, 3H), 7.09-7.02 (m, 3H), 7.00 (d, 2H, = 8.0 Hz), 5.91 (d, 1H, J = 3.1 Hz), 5.12 (d, 1H, J = 3.1 Hz), 2.45 (q, 2H, J = 7.6 Hz), 1.01 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 148.5, 144.3, 143.3, 142.1, 138.7, 136.1, 133.4, 133.0, 127.9, 127.8, 127.1, 127.0, 123.2, 122.3, 121.6, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 28.4, 15.2;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{129a2}O_3$: 411.1708; found 411.1697.

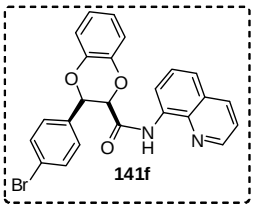


(*2R*,3R)-3-(4-Fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141e):** Following the general procedure, **141e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless solid; Yield: 40% (40 mg); mp 96-98 ^oC; IR (DCM): 3433, 1637, 1275, 1260, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57-7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.35 (dd, 2H, J_1 = 8.7 Hz, J_2 = 5.3 Hz), 7.28-7.26 (m, 1H), 7.10-7.00



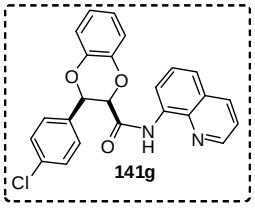
(m, 3H), 6.87 (t, 2H, J = 8.7 Hz), 5.91 (d, 1H, J = 3.1 Hz), 5.11 (d, 1H, J = 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 162.6 (d, J_{C-F} = 245.7 Hz), 148.6, 143.0, 141.9, 138.7, 136.2, 133.2, 131.7 (d, J_{C-F} = 3.1 Hz), 129.0 (d, J_{C-F} = 8.4 Hz), 127.9, 127.1, 123.4, 122.6, 121.7, 121.6, 117.8, 117.4, 116.9, 115.4 (d, J_{C-F} = 21.2 Hz), 76.2, 75.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{18}FN_2O_3$: 401.1301; found 401.1314.

(*2R*,3R)-3-(4-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141f):** Following the general procedure, **141f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 83% (96 mg); mp 146-148 ^{o}C; IR (KBr): 3424, 1684, 1490, 1257, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58-7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33-7.22 (m, 5H), 7.10-7.02 (m, 3H), 5.90 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.1, 134.9, 133.2, 131.5, 128.8, 127.9, 127.1, 123.5, 122.6, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{18}BrN_2O_3$: 461.0501; found 461.0506.



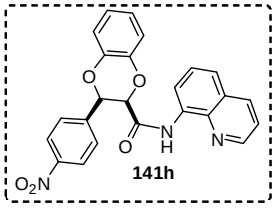
141f

(*2R*,3R)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141g):** Following the general procedure, **141g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 57% (59 mg); mp 148-149 ^{o}C; IR (KBr): 3431, 1785, 1635, 1533, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57-7.51 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, J = 8.6 Hz), 7.28-7.26 (m, 1H), 7.15 (d, 2H, J = 8.6 Hz), 7.11-7.01 (m, 3H), 5.92 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.2, 134.4, 134.3, 133.2, 128.6, 128.5, 127.9, 127.1, 123.5, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{18}ClN_2O_3$: 417.1006; found 417.0993.



141g

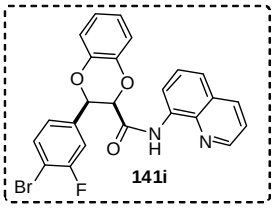
(*2R*,3R)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141h):** Following the general procedure, **141h** was obtained after purification



141h

by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as red colour solid; Yield: 56% (60 mg); mp 153-155^{o}C; IR (KBr): 3424, 1637, 1528, 1290, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.69 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.04 (d, 2H, J = 8.6 Hz), 7.58-7.52 (m, 4H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29-7.27 (m, 1H), 7.14-7.04 (m, 3H), 6.03 (d, 1H, J = 3.0 Hz), 5.17 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 148.7, 147.7, 143.1, 142.8, 141.8, 138.6, 136.2, 133.0, 128.0, 127.9, 127.0, 123.8, 123.5, 122.9, 122.1, 121.8, 118.0, 117.4, 116.9, 76.1, 75.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_5$: 428.1246; found 428.1241.

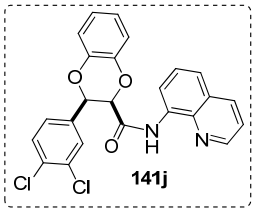
(*2R*,3R)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141i):** Following the general procedure, **141i**



141i

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 66% (79 mg); mp 117-119 ^{o}C; IR (KBr): 3329, 1685, 1490, 1256, 871 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59-7.52 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.34 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.1 Hz), 7.28-7.26 (m, 1H), 7.15 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.0 Hz), 7.11-7.03 (m, 4H), 5.90 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 158.9 (d, $J_{C\text{-}F}$ = 246.0 Hz), 148.7, 142.7, 141.8, 138.7, 137.6 (d, $J_{C\text{-}F}$ = 6.5 Hz), 136.2, 133.4, 133.1, 127.9, 127.1, 124.0 (d, $J_{C\text{-}F}$ = 3.5 Hz), 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 115.4 (d, $J_{C\text{-}F}$ = 23.4 Hz), 109.1 (d, $J_{C\text{-}F}$ = 20.6 Hz), 76.0, 74.9 (d, $J_{C\text{-}F}$ = 1.2 Hz);HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}BrFN_2O_3$: 479.0407; found 479.0403.

(*2R*,3R)-3-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141j):** Following the general procedure, **141j** was obtained after purification

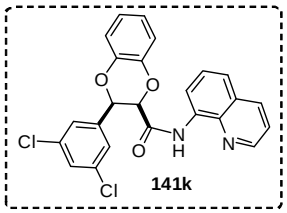


141j

by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as colourless solid; Yield: 45% (51 mg); mp 170-172 ^{o}C; IR (KBr): 3328, 1597, 1491, 1254, 1031, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58-7.52 (m, 2H), 7.49-7.45 (m, 2H), 7.28-7.18 (m, 3H), 7.10-7.01 (m, 3H), 5.87 (d, 1H, J = 3.0 Hz), 5.11 (d, 1H, J = 3.0

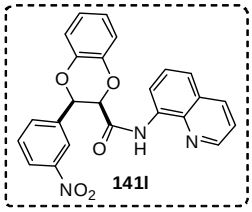
Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 148.7, 142.7, 141.8, 138.7, 136.2, 136.1, 133.1, 132.6, 132.5, 130.4, 129.2, 127.9, 127.0, 126.4, 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 76.1, 74.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O_3$: 451.0616; found 451.0599.

(*2R*,3R)-3-(3,5-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141k):** Following the general procedure, **141k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as colourless solid; Yield: 52% (59 mg); mp 213-215 ^oC; IR (KBr): 3393, 1597, 1393, 1194, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.3 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 1H), 7.58-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29-7.26 (m, 1H), 7.25 (dd, 2H, J_1 = 1.8 Hz, J_2 = 0.5 Hz), 7.13 (t, 1H, *J*= 1.9 Hz), 7.11- 7.08 (m, 1H), 7.07-7.04 (m, 2H), 5.84 (d, 1H, *J* = 3.0 Hz), 5.11 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 148.7, 142.7, 141.7, 139.2, 138.7, 136.2, 134.9, 133.0, 128.6, 127.9, 127.1, 125.6, 123.7, 122.7, 122.0, 121.8, 118.0, 117.4, 117.1, 76.0, 75.0;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O_3$: 451.0616; found 451.0600.



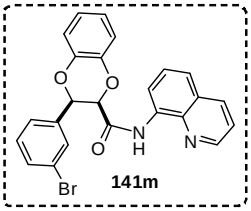
141k

(*2R*,3R)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141l):** Following the general procedure, **141l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 50% (54 mg); mp 205-207 ^oC; IR (KBr): 3417, 1683, 1531, 1256, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (br s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.69 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.27 (t, 1H, *J*= 2.1 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.02 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.3 Hz), 7.71 (d, 1H, *J*= 7.7 Hz), 7.58-7.51 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 7.30-7.28 (m, 1H), 7.14-7.04 (m, 3H), 6.02 (d, 1H, *J* = 3.0 Hz), 5.19 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 148.7, 148.1, 142.7, 141.7, 138.6, 138.0, 136.2, 133.1, 133.0, 129.4, 127.9, 127.1, 123.8, 123.3, 122.8, 122.3, 122.1, 121.8, 118.0, 117.5, 117.0, 76.1, 75.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_5$: 428.1246; found 428.1257.

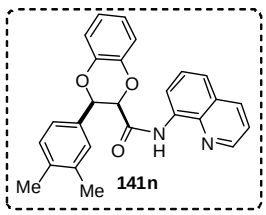


141l

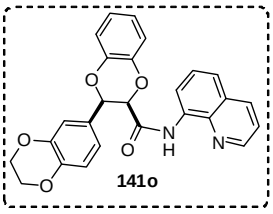
(*2R*,3R)-3-(3-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141m):** Following the general procedure, **141m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 50% (58 mg); IR (DCM): 3440, 1682, 1531, 1255, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.9 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.55-7.51 (m, 3H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.31-7.25 (m, 3H), 7.10-7.06 (m, 4H), 5.89 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.6, 143.0, 141.9, 138.7, 138.1, 136.1, 133.2, 131.5, 130.2, 129.9, 127.9, 127.1, 125.6, 123.5, 122.6, 122.5, 121.8, 121.7, 117.9, 117.4, 117.0, 76.2, 75.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}BrN_2O_3$: 461.0501; found 461.0503.



(*2R*,3R)-3-(3,4-Dimethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141n):** Following the general procedure, **141n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless liquid; Yield: 82% (84 mg); IR (DCM): 3440, 1641, 1533, 1275, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (t, 1H, J = 4.2 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53-7.52 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27-7.25 (m, 1H), 7.13-6.98 (m, 5H), 6.93 (d, 1H, J = 7.8 Hz), 5.86 (d, 1H, J = 3.1 Hz), 5.13 (d, 1H, J = 3.1 Hz), 2.04 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 148.5, 143.3, 142.1, 138.7, 136.8, 136.5, 136.1, 133.5, 133.1, 129.7, 128.5, 127.8, 127.1, 124.3, 123.2, 122.3, 121.6, 121.4, 117.7, 117.5, 116.9, 76.6, 75.8, 19.7, 19.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{129a2}O_3$: 411.1709; found 411.1694.

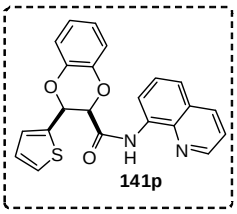


(*2R*,3R)-*N*-(Quinolin-8-yl)-2,2',3,3'-tetrahydro-[2,6'-bibenzo[*b*][1,4]dioxine]-3-carboxamide (141o):** Following the general procedure, **141o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless liquid; Yield: 82% (90 mg); IR (DCM): 3334, 1595, 1533, 1253, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.73 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.4 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-52 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27-7.24 (m, 1H), 7.07-6.97 (m, 3H), 6.90-6.86 (m, 2H), 6.67

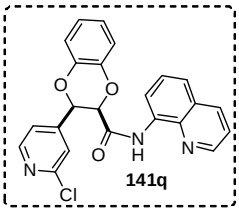


(d, 1H, J = 8.2 Hz), 5.82 (d, 1H, J = 3.1 Hz), 5.09 (d, 1H, J = 3.1 Hz), 4.07 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.6, 143.2, 143.1, 142.0, 138.7, 136.1, 133.4, 129.1, 127.9, 127.1, 123.3, 122.3, 121.7, 121.4, 120.5, 117.8, 117.4, 117.1, 116.9, 116.3, 76.4, 75.4, 64.2, 64.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_5$: 441.1450; found 441.1467.

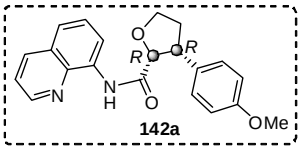
(*2R*,3S)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141p):** Following the general procedure, **141p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 49% (48 mg); mp 184-186 ^oC; IR (DCM): 3439, 1682, 1533, 1490, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.91 (br s, 1H), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.74 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59-7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33-7.29 (m, 1H), 7.16-7.15 (m, 1H), 7.12 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz), 7.05-7.02 (m, 3H), 6.82 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 6.24 (d, 1H, J = 2.8 Hz), 5.15 (d, 1H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.8, 141.7, 141.7, 138.8, 136.2, 136.2, 133.4, 127.9, 127.7, 127.1, 126.6, 126.4, 123.4, 122.5, 121.9, 121.8, 118.1, 117.7, 116.9, 75.7, 71.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3$ S: 389.0960; found 389.0970.



(*2R*,3R)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (141q):** Following the general procedure, **141q** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless liquid; Yield: 49% (51 mg); IR (DCM): 3439, 1682, 1533, 1490, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.20-8.16 (m, 2H), 7.60-7.54 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30-7.26 (m, 2H), 7.19 (dd, 1H, J_1 = 5.3 Hz, J_2 = 1.1 Hz), 7.14-7.05 (m, 3H), 5.92 (d, 1H, J = 3.0 Hz), 5.15 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 151.8, 149.7, 148.8, 148.0, 142.5, 141.7, 138.7, 136.2, 132.9, 127.9, 127.0, 123.8, 122.9, 122.5, 122.3, 121.9, 120.4, 118.1, 117.3, 117.1, 75.7, 74.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}ClN_3O_3$: 418.0958; found 418.0957.

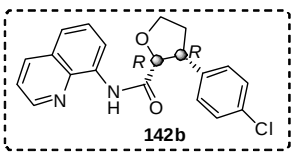


(*2R,3R*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142a): Following the general procedure, **142a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 71% (60 mg); *ee* 95%; $([\alpha]^{25}D$ = -243.5 (*c* 0.10, DCM); mp 90-92 ^{o}C; IR (DCM): 3340, 1682, 1530, 1255, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.48 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.48-7.41 (m, 3H), 7.21 (d, 2H, *J* = 8.8 Hz), 6.68 (d, 2H, *J* = 8.8 Hz), 4.74 (d, 1H, *J* = 7.0 Hz), 4.63-4.58 (m, 1H), 4.22-4.16 (m, 1H), 3.90-3.85 (m, 1H), 3.62 (s, 3H), 2.60-2.52 (m, 1H), 2.33-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1553.



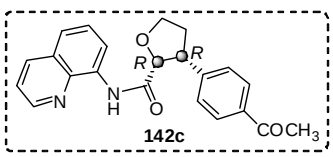
142a

(*2R,3R*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142b): Following the general procedure, **142b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as colourless solid; Yield: 85% (75 mg); *ee* 88%; $([\alpha]^{25}D$ = -216.8 (*c* 0.10, DCM); mp 130-132 ^{o}C; IR (KBr): 3336, 1682, 1528, 1325, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.49-7.41 (m, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 7.11 (d, 2H, *J* = 8.6 Hz), 4.75 (d, 1H, *J* = 7.0 Hz), 4.61-4.56 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.62-2.53 (m, 1H), 2.29-2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.6, 83.7, 68.6, 47.3, 33.7;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1051.



142b

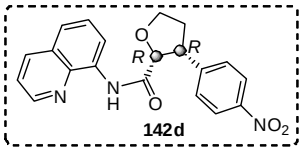
(*2R,3R*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142c): Following the general procedure, **142c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 81% (73 mg); *ee* 97%; $([\alpha]^{25}D$ = -239.6 (*c* 0.10, DCM); mp 148-150 ^{o}C; IR (KBr): 3441, 1607, 1528, 1267, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47-7.39 (m, 3H), 7.37 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* =



142c

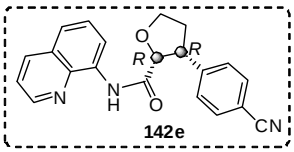
7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.63-2.58 (m, 1H), 2.42 (s, 3H), 2.32-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1545.

(*2R,3R*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142d): Following the general procedure, **142d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as red colour solid; Yield: 72% (65 mg); *ee* 84%; $([\alpha]^{25}D$ = -229.2 (*c* 0.10, DCM); mp 139-141 ^oC; IR (KBr): 3439, 1682, 1523, 1344, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 7.50-7.39 (m, 5H), 4.80 (d, 1H, *J* = 7.0 Hz), 4.66-4.61 (m, 1H), 4.26-4.20 (m, 1H), 4.03-3.99 (m, 1H), 2.70-2.61 (m, 1H), 2.33-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1298.



142d

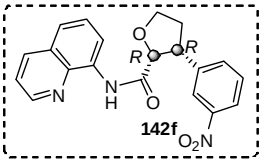
(*2R,3R*)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142e): Following the general procedure, **142e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 78% (67 mg); *ee* 93%; $([\alpha]^{25}D$ = -223.4 (*c* 0.10, DCM); mp 182-184 ^oC; IR (KBr): 3424, 1677, 1528, 1260, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.40 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51-7.48 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.42-7.37 (m, 5H), 4.77 (d, 1H, *J* = 7.0 Hz), 4.63-4.57 (m, 1H), 4.23-4.17 (m, 1H), 3.96-3.92 (m, 1H), 2.67-2.58 (m, 1H), 2.30-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1395.



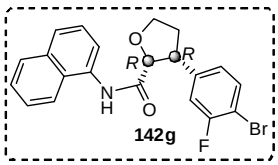
142e

(*2R,3R*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142f): Following the general procedure, **142f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 70%

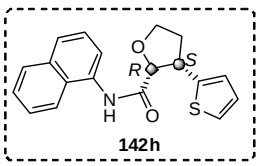
(64 mg); *ee* 83%; $([\alpha]^{25}D$ = -219.2 (*c* 0.10, DCM); mp 103-105 °C; IR (DCM): 3441, 1637, 1260, 1093, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.17 (t, 1H, *J*= 2.0 Hz,), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.87-7.85 (m, 1H), 7.62-7.59 (m, 1H), 7.47-7.43 (m, 2H), 7.39 (t, 1H, *J*= 8.0 Hz), 7.27 (t, 1H, *J*= 8.0 Hz), 4.78 (d, 1H, *J* = 6.8 Hz), 4.71-4.65 (m, 1H), 4.27-4.21 (m, 1H), 4.04-3.99 (m, 1H), 2.71-2.62 (m, 1H), 2.37-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.5, 133.1, 129.0, 127.8, 127.0, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1290.



(*2R,3R*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (142g): Following the general procedure, **142g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 65% (68 mg); *ee* 81%; $([\alpha]^{25}D$ = -153.6 (*c* 0.10, DCM); mp 100-102 °C; IR (KBr): 3425, 1682, 1485, 1530, 1092, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51-7.43 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.0 Hz), 6.95 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 4.74 (d, 1H, *J* = 6.8 Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.89-3.84 (m, 1H), 2.64-2.55 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.3 Hz), 148.6, 142.6 (d, J_{C-F} = 6.5 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, J_{C-F} = 3.2 Hz), 122.1, 121.6, 116.7, 116.0 (d, J_{C-F} = 22.3 Hz), 107.1 (d, J_{C-F} = 20.0 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0434.

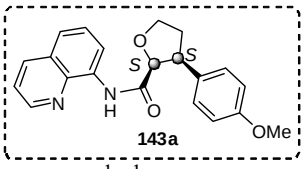


(*2R,3S*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (142h): Following the general procedure, **142h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 81% (66 mg); *ee* 99%; $([\alpha]^{25}D$ = -134.2 (*c* 0.10, DCM); mp 100-102 °C; IR (DCM): 3436, 1637, 1557, 1275, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50-7.43 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd,



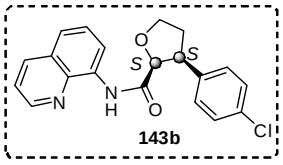
1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, J = 6.3 Hz), 4.61 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 4.28-4.22 (m, 2H), 2.66-2.57 (m, 1H), 2.37-2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.6, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.1003.

(*2S,3S*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143a): Following the general procedure, **143a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 82% (71 mg); *ee* 93%; ($[\alpha]^{25}$D = +218.4 (*c* 0.10, DCM); mp 100-102 ^{o}C; IR (KBr): 3432, 1636, 1528, 1260, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.49 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47-7.40 (m, 3H), 7.21 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.8 Hz), 4.74 (d, 1H, J = 7.0 Hz), 4.63-4.57 (m, 1H), 4.21-4.15 (m, 1H), 3.90-3.85 (m, 1H), 3.61 (s, 3H), 2.58-2.51 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1566.



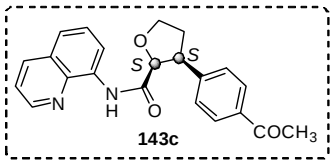
143a

(*2S,3S*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143b): Following the general procedure, **143b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 77% (68 mg); *ee* 83%; ($[\alpha]^{25}$D = +147.6 (*c* 0.10, DCM); mp 138-140 ^{o}C; IR (DCM): 3437, 1637, 1486, 1252, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50-7.42 (m, 3H), 7.22 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.62-4.56 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.63-2.54 (m, 1H), 2.29-2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.6, 139.2, 138.8, 136.2, 133.4, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.6, 116.6, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1039.



143b

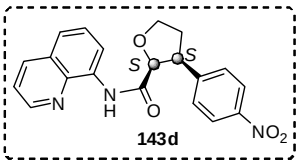
(*2S,3S*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143c): Following the general procedure, **143c** was obtained after purification by column



143c

chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 80% (72 mg); *ee* 85%; ($[\alpha]^{25}$D = +264.3 (*c* 0.10, DCM); mp 142-144 ^{o}C; IR (KBr): 3437, 1638, 1528, 1092, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47-7.39 (m, 3H), 7.38 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.66-2.57 (m, 1H), 2.42 (s, 3H), 2.34-2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1544.

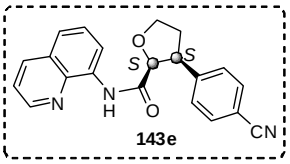
(*2S,3S*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143d):



143d

Following the general procedure, **143d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 86% (78 mg); *ee* 87%; ($[\alpha]^{25}$D = +280.3 (*c* 0.10, DCM); mp 134-136 ^{o}C; IR (DCM): 3336, 1598, 1486, 1344, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 7.49-7.38 (m, 5H), 4.80 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.25-4.19 (m, 1H), 4.02-3.98 (m, 1H), 2.67-2.60 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1281.

(*2S,3S*)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143e):

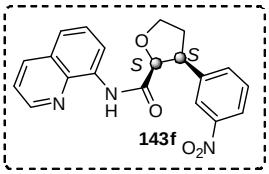


143e

Following the general procedure, **143e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 72% (62 mg); *ee* 94%; ($[\alpha]^{25}$D = +218.8 (*c* 0.10, DCM); mp 176-178 ^{o}C; IR (KBr): 3425, 1712, 1530, 1266, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.52-7.49 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.44-7.38 (m, 5H), 4.78 (d, 1H, = 6.9 Hz), 4.63-4.58 (m, 1H), 4.24-4.18 (m, 1H), 3.97-3.92 (m, 1H), 2.67-

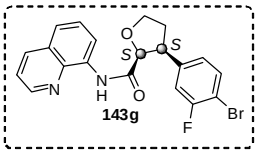
2.58 (m, 1H), 2.31-2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 34.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1412.

(*2S,3S*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (143f):



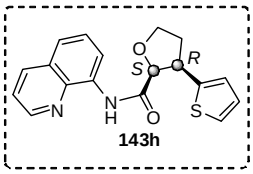
Following the general procedure, **143f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 77% (70 mg); *ee* 89%; ($[\alpha]^{25}$D = +235.9 (*c* 0.10, DCM); mp 114-116 ^oC; IR (DCM): 3335, 1683, 1528, 125, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 8.16 (t, 1H, *J*= 2.0 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.86-7.83 (m, 1H), 7.61-7.59 (m, 1H), 7.46-7.42 (m, 2H), 7.38 (t, 1H, *J*= 8.0 Hz), 7.26 (t, 1H, *J*= 8.0 Hz), 4.78 (d, 1H, *J* = 6.8 Hz), 4.70-4.64 (m, 1H), 4.26-4.19 (m, 1H), 4.03-3.98 (m, 1H), 2.70-2.61 (m, 1H), 2.37-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0, 127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.6, 68.6, 47.5, 33.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1304.

(*2S,3S*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide



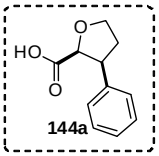
(143g): Following the general procedure, **143g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:70) as brown colour solid; Yield: 66% (69 mg); *ee* 89%; ($[\alpha]^{25}$D = +149.8 (*c* 0.10, DCM); mp 110-112 ^oC; IR (KBr): 3440, 1638, 1530, 1275, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51-7.43 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.0 Hz), 6.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 4.74 (d, 1H, *J* = 6.8 Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.89-3.84 (m, 1H), 2.64-2.55 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.4 Hz), 148.6, 142.6 (d, J_{C-F} = 6.5 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, J_{C-F} = 3.2 Hz), 122.1, 121.6, 116.7, 116.0 (d, J_{C-F} = 22.3 Hz), 107.1 (d, J_{C-F} = 20.0 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0443

(*2S,3R*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (143h): Following the general procedure, **143h** was obtained after purification by column



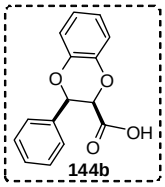
143h

chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 90% (73 mg); *ee* 99%; ($[\alpha]^{25}$D = +169.4 (*c* 0.10, DCM); mp 98-100 ^{o}C; IR (KBr): 3436, 1680, 1531, 1325, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.58 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.48-7.41 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, *J* = 6.3 Hz), 4.61 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 4.28-4.21 (m, 2H), 2.65-2.56 (m, 1H), 2.36-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.3, 43.3, 34.6;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.0998.



144a

(*2R*,3R)-3-Phenyltetrahydrofuran-2-carboxylic acid (144a)**: Following the general procedure, **144a** was obtained after concentrated in vacuum gave as brown colour solid (crude material was almost pure); Yield: 95% (46 mg); mp 216-218 ^{o}C; IR (KBr): 3432, 1637, 1275, 1260, 764, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.19 (m, 5H), 5.03 (br s, 1H), 4.65 (d, 1H, *J* = 7.7 Hz), 4.43-4.37 (m, 1H), 4.06 (dd, 1H, J_1 = 15.0 Hz, J_2 = 7.5 Hz), 3.76 (dd, 1H, J_1 = 15.0 Hz, J_2 = 7.5 Hz), 2.48-2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 138.6, 128.5, 127.8, 127.3, 81.4, 68.9, 48.0, 32.2; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{11}H_{11}O_3$: 191.0708; found 191.0700.



144b

(*2R*,3R)-3-Phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (144b):** Following the general procedure, **144b** was obtained after concentrated in vacuum gave solid material as brown colour liquid (crude material was almost pure). Yield: 95% (59 mg); IR (DCM): 3456, 1723, 1598, 1257, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.35 (m, 5H), 7.08-6.95 (m, 4H), 6.43 (br s, 1H), 5.51 (d, 1H, *J* = 3.2 Hz), 5.04 (d, 1H, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 143.0, 141.8, 134.8, 128.9, 128.6, 126.5, 122.5, 122.2, 117.4, 117.2, 75.1, 75.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}O_4$: 257.0814; found 257.0821.

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Chapter 3. **Pd(II)-catalyzed, directing group-aided *Z* selective β-arylation of acrylamide systems and stereoselective construction of *Z* cinnamates.**

Introduction

Transition metal-catalyzed functionalization of sp^2 C–H bonds is currently an attractive and efficient method for the construction of C–C and C–hetero bonds.[1] The transition metal-catalyzed, C-H functionalization of C(sp^2)–H bonds of arenes, heteroarenes and olefins have been extensively investigated.Especially, the directing group-aided transition metal-catalyzed C–H activation/functionalization strategy was well exploited for functionalization of sp^2 C–H bonds of arenes, heteroarenes and olefins etc. A variety of directing groups (e.g. pyridine, oxazole, pyrimidine, acetanilide, ester, carbamate, imines, amide, sulfoxide) were used for accomplishing the regioselective sp^2 C–H functionalization.

Cinnamamide derivatives are important class of agrochemicals and several cinnamamide derivatives show a wide range of biological activities and serve as synthetic building blocks in organic synthesis.[2-5] Generally, cinnamamide derivatives (β-arylated acrylamides) were prepared using the traditional methods or Mizoroki-Heck reaction.[6] Apart from the tradition methods, the β-arylated acrylic acid derivatives have also been prepared *via* the oxidative Heck-type arylation. It is to be noted that in these reactions, generally the corresponding β-arylated acrylic acid derivatives with the *E* geometry were obtained as the major isomers. Hence, the synthesis of β-arylated acrylic acid derivatives including cinnamamide derivatives with the *Z* geometry is seldom explored. The production of the Z arylated acrylamides can be easily accomplished via the transition metal-catalyzed functionalization of the C(sp^2)-H bond of acrylamide system.

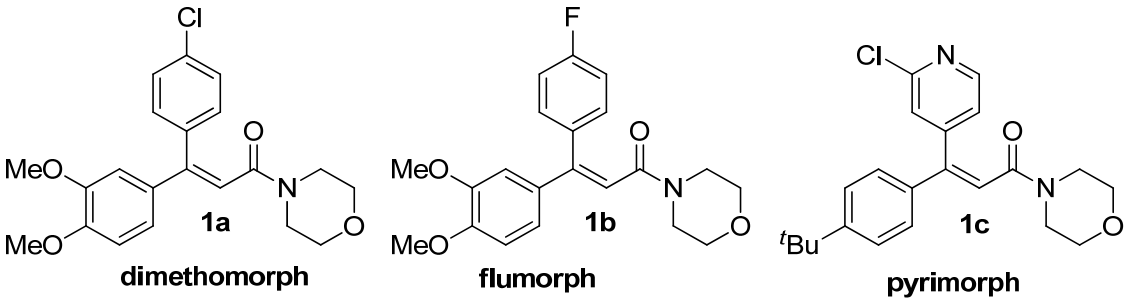
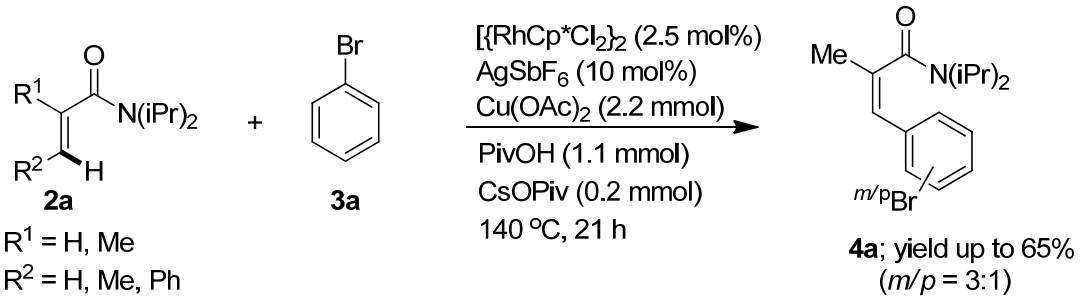


Figure 1. Representative examples of cinnamamide-based agrochemicals.

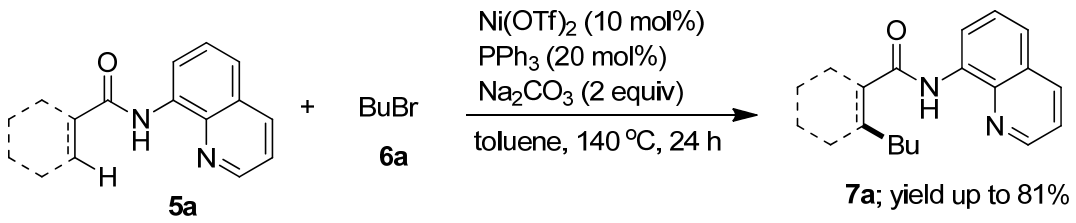
Several cinnamamide derivatives (e.g., dimethomorph (**1a**), flumorph (**1b**) and pyrimorph (**1c**), Figure 1) found to show herbicidal and fungicidal activities[2a] and biological activities, such as, anticonvulsant, analgesic,antituberculosis, antidepressant, antifungal and antiestrogenic agents and function as mPTP inhibitors,[5] KCNQ2 potassium channel openers and vanilloid receptor-1 antagonists. It is worth to mention that various heterocyclic compounds, e.g. quinolones have been prepared starting from cinnamamide derivatives.
In the following section some of the recent developments that occurred with regard to the stereoselective arylation of acrylamides systems and the construction of acrylamides are described.

Representative literature work dealing on the C-H functionalization reactions of acrylamide substrates.

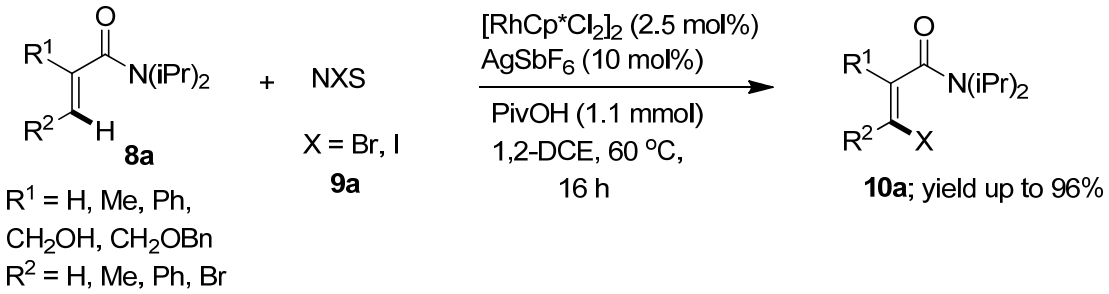
Glorius and co-workers[6a] reported [$Rh^{III}Cp^*$]-catalyzed cross-coupling reaction between bromoarenes **3a** and vinylic substrates **2a** bearing a directing group. The dehydrogenative alkene–arene coupling pathway afforded various *Z* olefins **4a** (Scheme 1). Chatani and co-workers[6b] reported the nickel-catalyzed alkylation reaction of α,β-unsaturated amides **5a** with alkyl bromides **6a,** which gave the corresponding products **7a** in good yields (Scheme 2). Glorius and co-workers[6c] reported the Rh(III)-catalyzed iodination/bromination of vinylic C-H bonds of **8a** with NXS **9a** in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH (1.1 mmol) in 1,2-DCE at 60 ^oC, which gave the *Z* olefins **10a** (Scheme 3). Ackermann and co-workers[6d] reported an example of Fe-catalyzed C-H arylation of acrylamide **11a** with phenyl magnesium bromide **12a** afforded the *Z*-olefin **13a** as the sole product (Scheme 4).



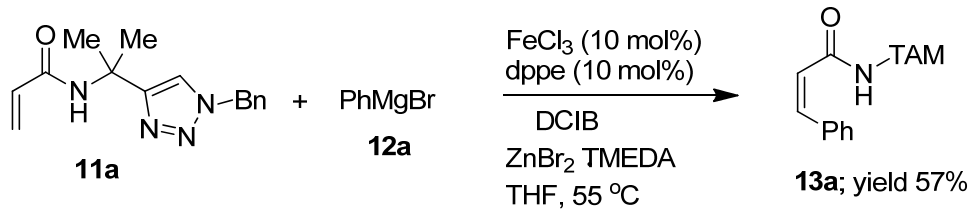
Scheme 1. The reaction of **2a** with bromobenzene **3a**.



Scheme 2. Butylation of C−H bonds of **5a.**

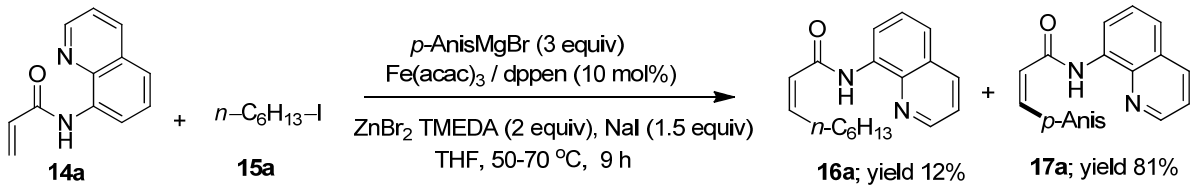


Scheme 3. Rh(III)-catalyzed halogenation of vinylic C-H bonds of **8a**.

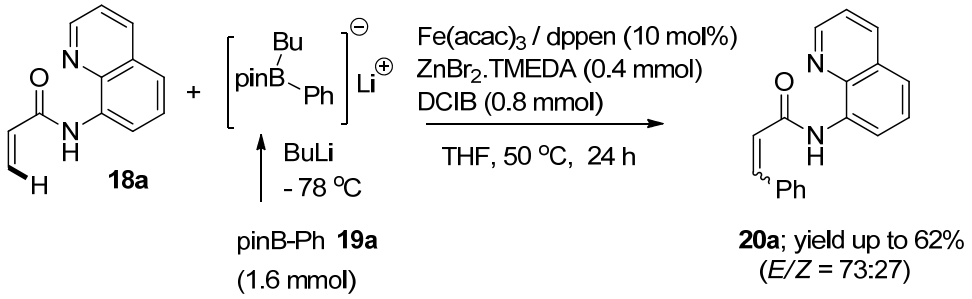


Scheme 4. Iron-catalyzed C-H arylation of acrylamide using triazole directing group **11a.**

Nakamura and co-workers[6e] reported the Fe-catalyzed C-H arylation of acrylamide **14a** with **15a**in the presence of Fe(acac)$_3$/diphosphine and ArZnBr as a base, which gave the olefin **16a**in 12% yield and β-arylated acrylamide **17a** in 81% yield (Scheme 5). Further, Nakamura and co-workers[6f] reported the Fe-catalyzed β-arylation of **18a** with **19a** in the presence of the iron and zinc catalysts, which afforded the corresponding β-arylated acrylamides **20a** in 62% yield (*E/Z* = 73:27) (Scheme 6).

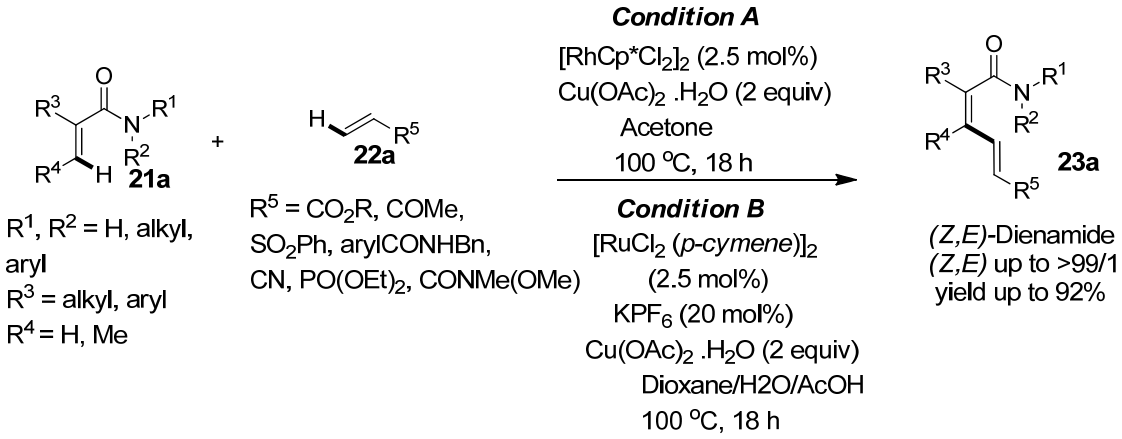


Scheme 5. Iron-catalyzed reaction of alkene carboxamides **14a** with **15a**.

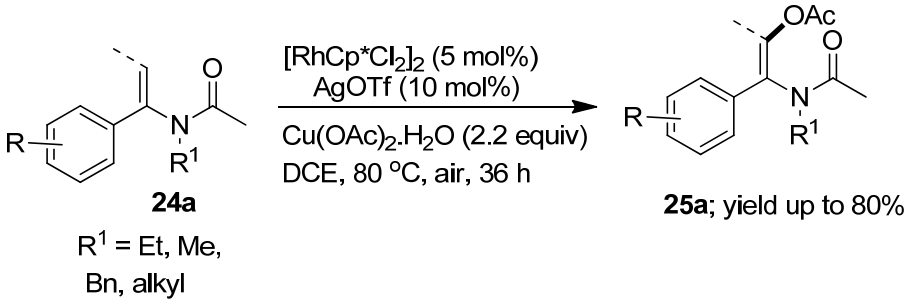


Scheme 6. Iron-catalyzed reaction of alkene carboxamides with aryl boronates.

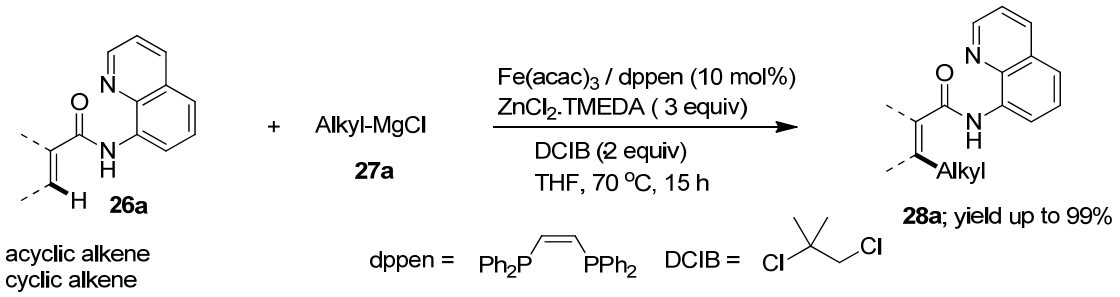
Loh and co-workers[6g] reported ruthenium- and rhodium-catalyzed cross-coupling reactions of various acrylamides **21a** with different alkenes **22a**, which provided *Z,E*-dienamides **23a** in excellent yields with good stereoselectivity (Scheme 7). Zhang and co-workers[6h] reported the rhodium-catalyzed acetoxylation of an olefinic C-H bonds of **24a,** whichgave the *Z*-configuration product **25a** (Scheme 8). Nakamura and co-workers[6i] reported the reaction of alkenes **26a** with alkyl magnesium chloride **27a** in the presence $Fe(acac)_3$ / dppen (10 mol%), $ZnCl_2$.TMEDA (3 equiv), DCIB (2 equiv) in THF at 70 °C for 15 h, which afforded the *Z* acrylamides **28a** (Scheme 9).



Scheme 7. The reaction of acrylamides **21a** with alkenes **22a**.

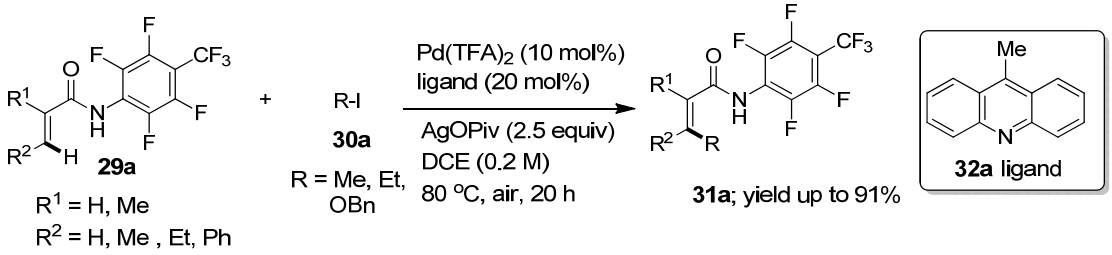


Scheme 8. Acetoxylation of enamides **24a**.

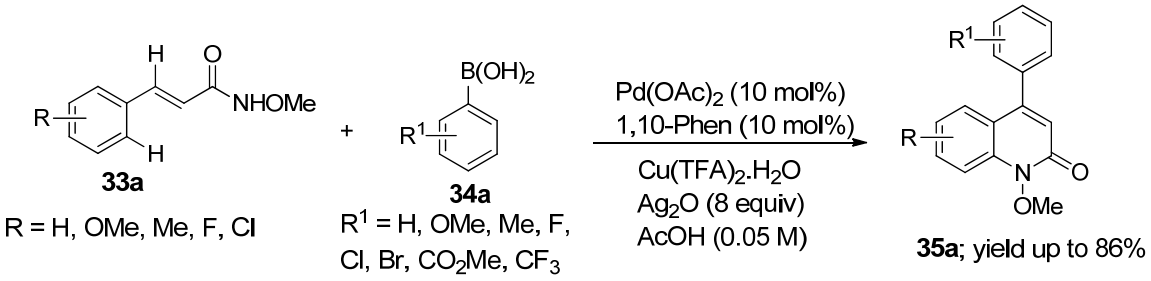


Scheme 9. Iron-catalyzed reaction of alkeneamides with alkyl magnesium chloride.

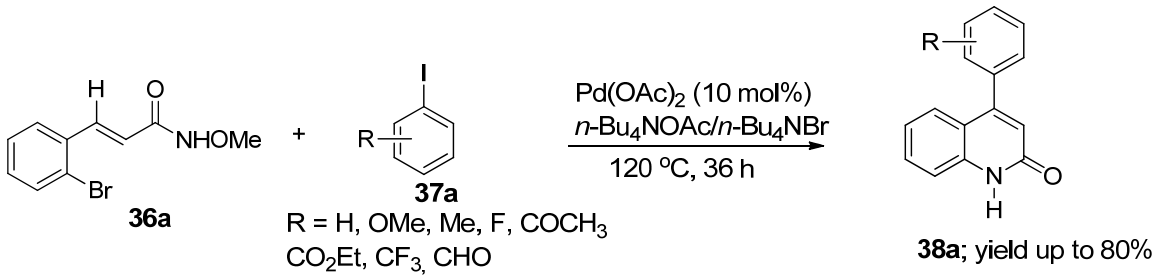
Yu and co-workers[6j] reported the alkylation of different vinyl C(sp^2)-H bonds **29a** with various alkyl iodides **30a** using a weakly coordinating amide directing group, which afforded the β- alkylated products **31a**with retention of stereochemistry (Scheme 10). Inamoto and co-workers[6k] reported the Pd(II)-catalyzed, oxidative Heck reaction/intramolecular C–H amidation of **33a** with boronic acids **34a** affording 4-aryl-2-quinolinone scaffolds **35a** (Scheme 11). Cacchi, Fabrizi and co-workers[6l] reportedsynthesis of **38a** through a pseudo-domino Heck/Buchwald-Hartwig reaction from acrylamide derivative **36a** (Scheme 12).



Scheme 10. Pd-catalyzed alkylation of vinylic C(sp^2)-H of **29a**.

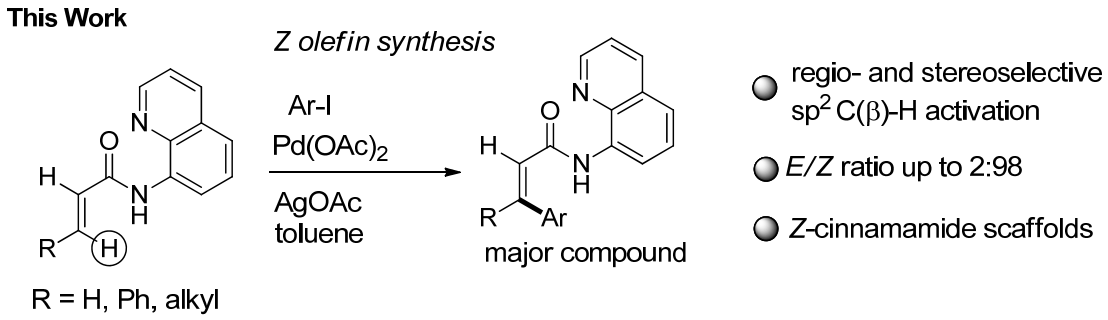


Scheme 11. Pd(II)-catalyzed reaction of acrylamide derivative **33a** with **34a**.



Scheme 12.Synthesis of 2-quinolones **38a** via the domino Heck/Buchwald-Hartwig reaction.

Given the importance of acrylamide derivatives in organic synthesis and medicinal chemistry research area, developing new methods for synthesizing new cinnamamides, especially, *Z* cinnamamide scaffolds will enrich the library of cinnamamide scaffolds. A literature survey revealed that there exist only limited reports dealing on the synthesis of *Z* acrylamide frameworks (Z cinnamamides). Accordingly, a part of this thesis reports the synthesis of new arylated acrylamide frameworks, especially, *Z* acrylamide frameworks (Z cinnamamides) via the $Pd(OAc)_2$-catalyzed, AgOAc-promoted β-arylation of acrylamide systems using aryl iodides as the coupling partners.



Scheme 13. Topic of this work. $Pd(OAc)_2$-catalyzed, AgOAc-promoted *Z* selective β-arylation of acrylamide systems.

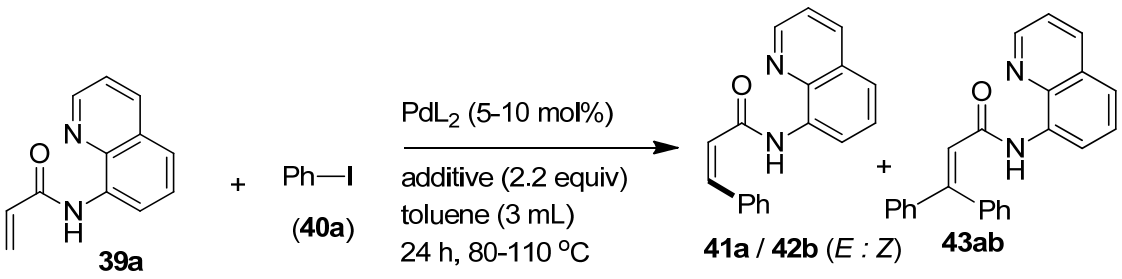
Results and Discussion

To begin with the investigations on the $Pd(OAc)_2$-catalyzed, AgOAc-promoted *Z* selective β-arylation of acrylamide systems, initially the acrylamide substrate **39a** was derived from acryloyl chloride and 8-aminoquinoline). Then several reactions optimization reactions were performed to find out the best reaction conditions for the $Pd(OAc)_2$-catalyzed 8-aminoquinoline-directed C-H activation and β-arylation of the acrylamide substrate **39a**

(Table 1). The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** (1 equiv), iodobenzene (**40a**, 4 equiv), $Pd(OAc)_2$ (5 mol%) and AgOAc (2.2 equiv) afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** (*E/Z* isomers) in 73% yield with an *E/Z* ratio of 9:91 (entry 1, Table 1). It is to be noted that the Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** afforded the β-C-H arylated acrylamide **42b** with the *Z* stereochemistry as the major isomer. The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** in the presence of 10 mol% of the $Pd(OAc)_2$ afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** (*E/Z* isomers) in 87% yield with an *E*/*Z* ratio of 11:89 (entry 2, Table 1). The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** (1 equiv) with **40a** in the presence of Ag_2CO_3 as an additive instead of AgOAc additive afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** in 36% yield (entry 3, Table 1).

The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** (1 equiv) with **40a** in the presence of additives, such as, K_2CO_3 or KOAc afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** (*E*/*Z* isomers) in poor *E*/*Z* selectivity and yields (entries 4 and 5, Table 1). The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** using palladium catalysts, such as, $PdCl_2$, $Pd(TFA)_2$ and $Pd(CH_3CN)_2Cl_2$ afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** (*E*/*Z* isomers) in 32-58% yields with an *E*/*Z* ratio up to 10:90 (entries 6-8, Table 1). The Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** with iodobenzene (**40a**) in solvents, such as, 1,2-DCE or *tert*-butanol or *tert*-amyl alcohol afforded the mono β-C-H arylated acrylamide derivatives **41b**/**42b** in 44% **(***E*/*Z* ratio = 2:98, entry 9, Table 1) and 36% (*E*/*Z* ratio = 17:83, entry 10, Table 1) and 63% yields (*E*/*Z* ratio = 12:88, entry 11, Table 1), respectively. When compared to the Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** with 4 equiv of iodobenzene (**40a**, entry 2), the yield of the mono β-C-H arylated acrylamide derivatives **41b**/**42b** (*E*/*Z* isomers) proportionately decreased in the Pd(II)-catalyzed C-H arylation of the acrylamide substrate **39a** with 3 or 2 or 1 equiv of iodobenzene (**40a**, entries 12-14, Table 1). The Pd(II)-catalyzed C-H arylations of the acrylamide substrate **39a** with the coupling partners other than iodobenzene (**9**), such as, bromobenzene (**40aa**) or chlorobenzene (**40ab**) were not fruitful (entries 15 and 16, Table 1).

Table 1. Optimization of Reaction Conditions. The Pd(II)-catalyzed C-H arylation of the acrylamide substrate**39a**.



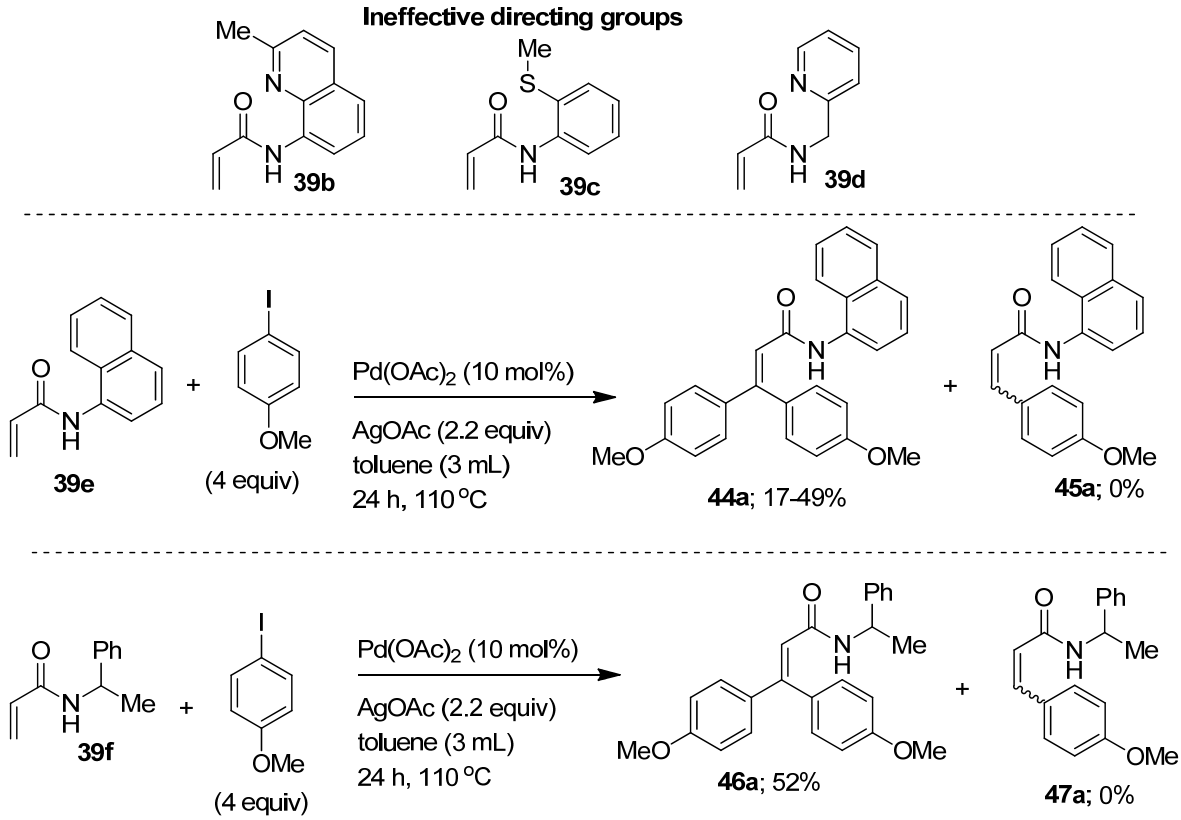
entry	PdL_2 (mol%)	additive	*T* (°C)	yield (%)[a] **41b** /**42b**	**41b** / **42b** *E : Z*
1	$Pd(OAc)_2$ (5)	AgOAc	110	73	9 : 91
2	**$Pd(OAc)_2$ (10)**	**AgOAc**	**110**	**87**	**11 : 89**
3	$Pd(OAc)_2$ (10)	Ag_2CO_3	110	36	12 : 88
4	$Pd(OAc)_2$ (10)	K_2CO_3	110	29	59 : 41
5	$Pd(OAc)_2$ (10)	KOAc	110	57	35 : 65
6	$PdCl_2$ (10)	AgOAc	110	58	10 : 90
7	$Pd(TFA)_2$ (10)	AgOAc	110	58	17 : 83
8	$Pd(CH_3CN)_2Cl_2$ (10)	AgOAc	110	32	28 : 72
9[b]	$Pd(OAc)_2$ (10)	AgOAc	80	44	2 : 98
10[c]	$Pd(OAc)_2$ (10)	AgOAc	85	36	17 : 83
11[d]	$Pd(OAc)_2$ (10)	AgOAc	105	63	12 : 88
12[e]	$Pd(OAc)_2$ (10)	AgOAc	110	73	10 : 90
13[f]	$Pd(OAc)_2$ (10)	AgOAc	110	55	11 : 89
14[g]	$Pd(OAc)_2$ (10)	AgOAc	110	37	10 : 90
15[h]	$Pd(OAc)_2$ (10)	AgOAc	110	0	-
16[i]	$Pd(OAc)_2$ (10)	AgOAc	110	0	-

[a] The reactions were performed using substrate **39a** (0.25 mmol), **40a** (4 equiv) and in these reactions, the product **43ab** was not obtained in the column purification, however, traces of the product **43ab** were seen in the crude NMR of some reactions. The *E*/*Z* ratios of diastereomers were determined from the NMR spectra of the crude reaction mixtures. [b] The reaction was carried out in 1,2-DCE. [c] The reaction was carried out in *tert*-butanol. [d] The reaction was carried out in *tert*-amyl alcohol. [e] 3 Equivof**40a** was used. [f] 2 Equivof**40a** was used. [g] 1 Equivof**40a** was used. [h] In this reaction, bromobenzene (**40aa**) was used instead of **40a**. [i] In this reaction, chlorobenzene (**40ab**) was used instead of **40a**.

After performing the optimization reactions using the directing group 8-aminoquinoline-derived substrate **39a** it was envisaged to find out other working directing groups. Accordingly, the arylation of the acrylamide substrates **39b-39f** (which were derived from their corresponding bidentate directing groups, Scheme 14) with aryl iodide using the $Pd(OAc)_2$/AgOAc-catalytic system were carried out. However, under the optimized reaction conditions used for the substrate **39a** (entry 2, Table 1), the Pd(II)-catalyzed acrylamide substrates **39b-39f** failed to afford the β-C-H arylated acrylamide derivatives (Scheme 14). Then, the Pd(II)-catalyzed β-arylation of acrylamide systems **39e** and **39f** which were derived from the corresponding amines, 1-naphthylamine and α-methylbenzylamine were performed. In contrast to the acrylamide systems **39a**, the $Pd(OAc)_2$/AgOAc-catalytic system-based arylation of the acrylamide systems **39e**and **39f** directly afforded the corresponding bis arylated acrylamide systems **44a** and **46a** instead of any of the corresponding mono β-arylated acrylamide systems (**45a** or **47a**,Scheme 14).

The Pd(II)-catalyzed C-H arylation of the acrylamide systems **39e**with 2 or 4 equiv of 4-iodoanisole afforded the bis C-H arylated acrylamide system **44a** in 17 and 49% yields (Scheme 14). Similarly, the Pd(II)-catalyzed C-H arylation of the acrylamide system **39f**with 4 equiv of 4-iodoanisole afforded the bis C-H arylated acrylamide system **46a** in 52% yield (Scheme 14).

It is to be noted that in an optimization reaction (entry 4, Table 1) comprising the Pd(II)-catalyzed C-H arylation of the acrylamide system **39a** with iodobenzene (**40a**) in the presence of K_2CO_3 as an additive afforded the C-H arylated acrylamide systems **41b**/**42b** (*E*/*Z* isomers) with an *E*/*Z* ratio of 59:41. It was envisaged to alter the *E*/*Z* ratio and the reaction of the Pd(II)-catalyzed C-H arylation of the acrylamide system **39a** with iodobenzene (**40a**) in the presence of K_2CO_3 in *tert*-amyl alcohol was performed, which afforded the C-H arylated acrylamide system **41b** as the major isomer having *E* stereochemistry in 80% yield (**41b**/**42b** = *E*/*Z* = 92:8, Scheme 15). Further, the Pd(II)-catalyzed C-H arylation of the acrylamide system **39a** with various aryl iodides in the presence of K_2CO_3 as an additive in *tert*-amyl alcohol afforded the corresponding C-H arylated acrylamide systems**41a**, **41c-g** and **48** as the major isomers having the *E* stereochemistry (Scheme 15).



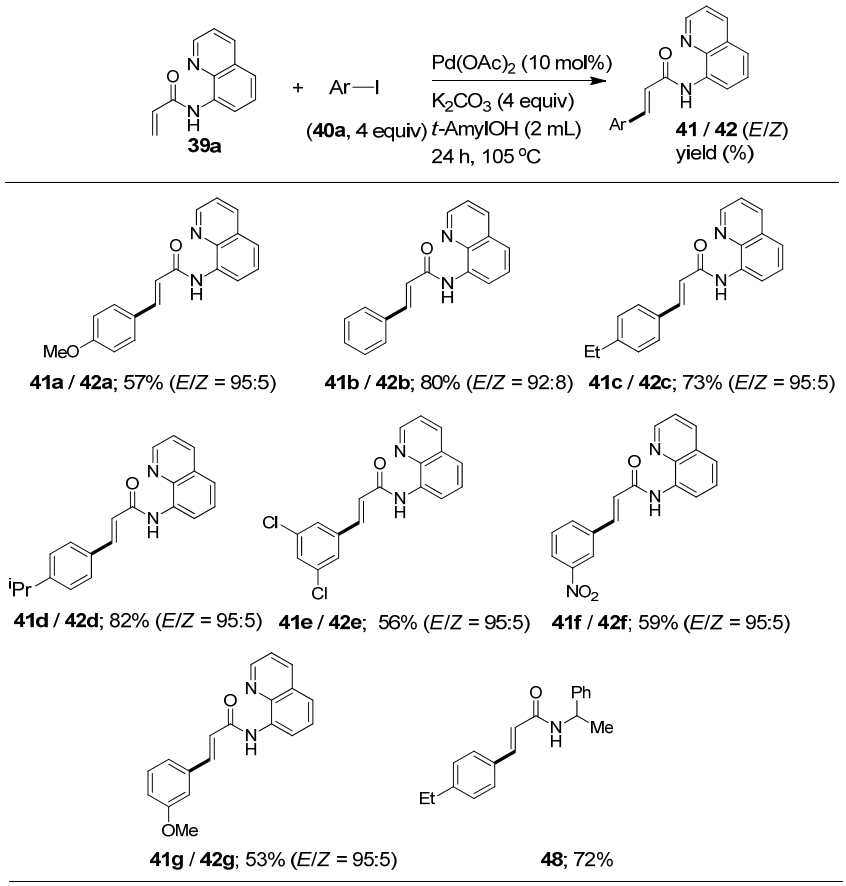
[a] All the reactions were carried out using 0.25 mmol of **39e** or **39f**.

Scheme 14. Screening of directing groups and reaction conditions for the β-C-H arylation of the **39b-39f.**

Then, it was envisaged to elaborate the scope and generality of this method comprising the *Z* selective β-arylation of *N*-(quinolin-8-yl)acrylamide (**39a**) using a variety of aryl iodides (Table 2). Accordingly, the $Pd(OAc)_2$/AgOAc-catalytic system-based direct β-C-H arylation of **39a** with various aryl iodides containing a substituent at the *para* or *meta* position in the aryl ring (e.g., alkyl, OMe, F, Cl and NO_2) furnished the corresponding mono β-arylated acrylamide systems **41a-f/42a-f** and **41h-q/42h-q** in good yields 32-88% and *E/Z* ratio up to 2:98. Then, the Pd(II)-catalyzed β-C-H arylation of acrylamide substrate **39a** with heteroaryl iodides afforded the corresponding mono β-arylated acrylamide systems **41r-t/42r-t** (*E/Z* isomers) in 59-73% yields and *E/Z* ratio up to 20:80. It is to be noted that in general, the Pd(II)-catalyzed β-C-H arylation of acrylamide substrate **39a** afforded β-C-H arylated acrylamides **41/42** (*E/Z* isomers) in good and *E/Z* ratios. Some reaction affordedthe β-C-H arylated acrylamides in low or moderate yield of and specifically, the *E/Z* ratiosof the β-C-H arylated acrylamides **41o/42o**, **41s/42s** and **41t/42t** (*E/Z* isomers) may be related to the reactivity of the corresponding aryl iodides. While, an exact reason is not clear for this,

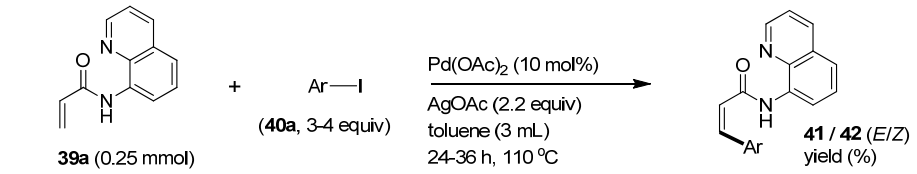
however, it is proposed that the corresponding aryl iodides have strong coordinating moieties (e.g. 1-idodo-2,4-dimethoxybenzene contains an *ortho* methoxy group and 2-fluoro-5-iodopyridine and 5-bromo-2-iodopyridine are pyridine based aryl iodides), and these coordinating moieties might be disturbing the Pd(II)-catalyzed C-H reaction. The *E* stereochemistry of the β-arylated acrylamide minor isomers **41** and the *Z* stereochemistry of the β-arylated acrylamide major isomers **42** (Scheme 15 and Table 2) were assigned based on the coupling constant values of the corresponding doublet peaks of the olefinic protons of the corresponding compounds (J = ~12.5 Hz for the *Z* isomer (**42a-f** and **42h-t**) and J = ~15.5 Hz for the *E* isomer (**41a-t**)). Additionally, the stereochemistry of a representative compound **42s** was confirmed from the X-ray structure.

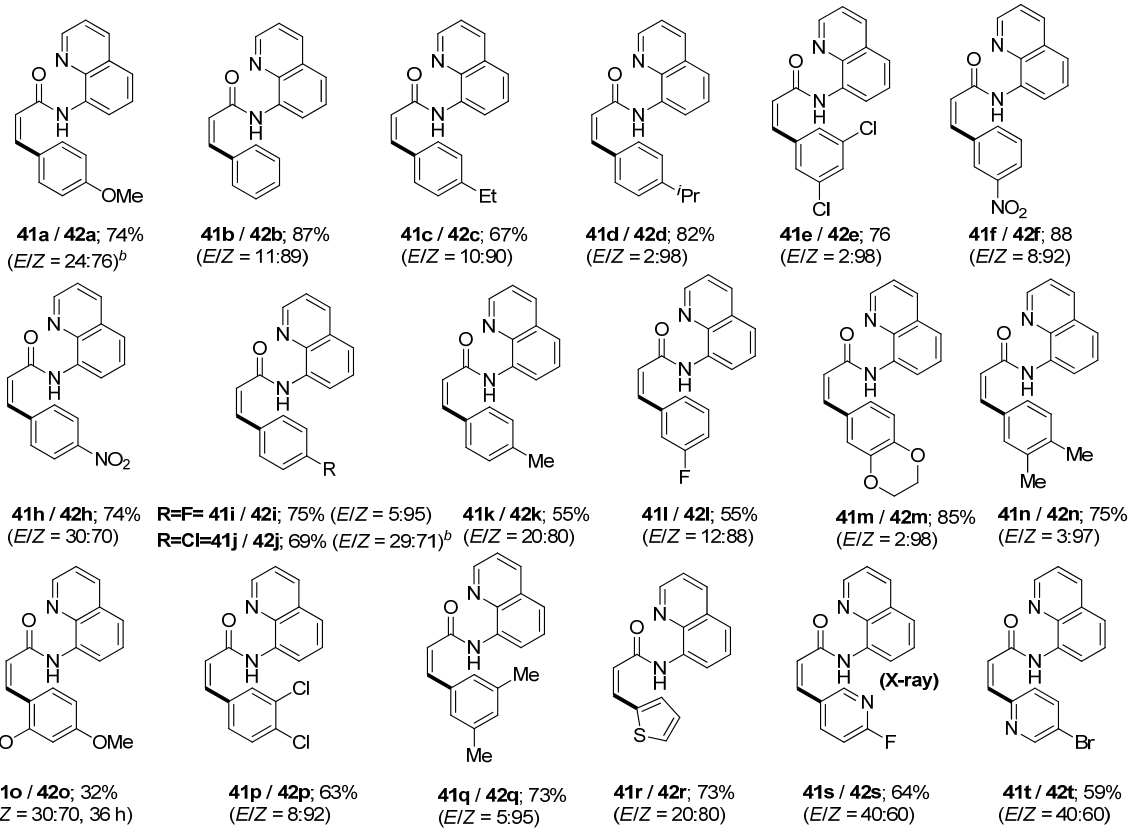
Scheme 15. Pd(II)-catalyzed β-arylation of **39a** and **39f** in the presence of K_2CO_3.[a,b]



[a] The *E*/*Z* ratios of diastereomers were determined from the NMR spectra of the corresponding crude reaction mixtures. All the reactions were carried out using 0.25 mmol of **39a**or **39f**. [b] In some case, the crude NMR revealed the presence of traces of the corresponding *Z* isomers and the bis C-H arylated compounds.

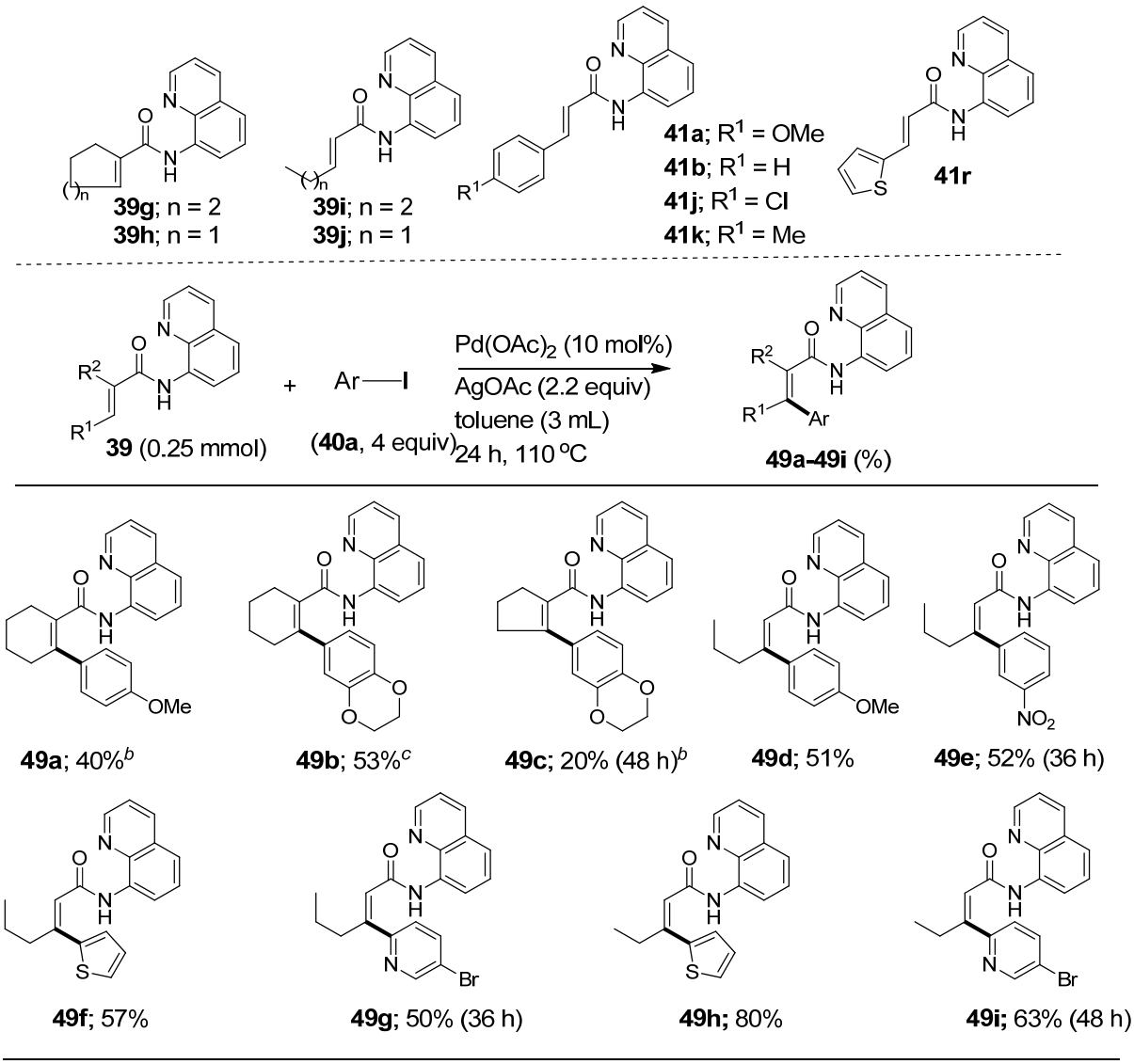
Table 2. Pd(II)-catalyzed *Z* selective mono βC-H arylation of **39a**.[a]





[a] The *E*/*Z* ratios of diastereomers were determined from the NMR spectra of the crude reaction mixtures. [b] In this case, 3 equiv of aryl iodide was used.

Table 3. Construction of the β-C-H arylated carboxamides **49a-i**.[a]



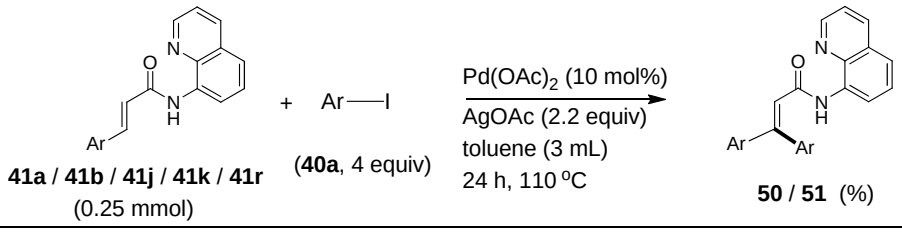
[a] The compounds **49a** and **49b** were obtained from the substrate **39g**. The Compound **49c** was obtained from the substrate **39h**. The compounds **49d-49g** were obtained from the substrate **39i**. The compounds **49h,i** were obtained from the substrate **39j**. [b] In this case, 2 equiv of the corresponding aryl iodide was used. [c] In this case, 4 equiv of the corresponding aryl iodide was used.

Subsequently, it was envisaged to extend the substrate scope of this method comprising the *Z* selective β-arylation of acrylamide systems using various acrylamide substrates, such as, cyclic carboxamides **39g**, **39h**, β-alkylated compounds **39i**, **39j** having the *E* stereochemistry

(Table 3).In this regard, initially the Pd(II)-catalyzed β-C-H arylations of thecyclic carboxamides **39g** and **39h** were performed, which afforded the corresponding C-H arylated cyclic carboxamides **49a-49c** in 20-53% yields (Table 3). Next, the Pd(II)-catalyzed β-C-H arylation of the β-alkylated compound **39i**having the *E* stereochemistry with various aryl iodides afforded the corresponding β-alkylated β′-C-H arylated acrylamide systems **49d-g** in 50-57% yields. Then, the Pd(II)-catalyzed β-C-H arylation of the β-alkylated compound **39h** having the *E* stereochemistry also afforded the corresponding β-alkylated β′-C-H arylated acrylamide systems **49h** and **49i** in 80 and 63% yields (Table 3). Successively, it was decided to extend the scope of this method by performing the $Pd(OAc)_2$-catalyzed second arylation of the C(β)-H bond of the mono β-arylated acrylamide derivatives **41a**, **41b**, **41j**, **41k** and **41r** having the *E* stereochemistry (Table 4). Accordingly, the $Pd(OAc)_2$-catalyzed, AgOAc-mediated and bidentate ligand 8-aminoquinoline-directed*Z* selective C(β)-H arylation of the mono β-arylated acrylamide **41b** having the *E* stereochemistry with several aryl- and heteroaryl iodides afforded the corresponding β,β′-C-H arylated acrylamide derivatives **43ab** and **50b-50k** in 40-81% yields (Table 4).

Next, the Pd(II)-catalyzed *Z* selective C-H arylation of other mono β-arylated acrylamide systems **41a**, **41j**, **41k** and **41r** (having the *E* stereochemistry) with various aryl- and heteroaryl iodides were performed. These reactions afforded the corresponding β,β′-C-H arylated acrylamide systems **50l-o** in 51-61% yields (Table 4). Additionally, it was envisaged to perform the $Pd(OAc)_2$-catalyzed benzylation of **41b**. Accordingly, the $Pd(OAc)_2$-catalyzed benzylation of **41b** with benzyl bromides afforded the corresponding C-H benzylated acrylamide systems **51a-c** in 54-79% yields (Table 4). The stereochemistry of the acrylamide systems **50b-50k** and **51a-c** were assigned based on the X-ray structure of the representative acrylamide system **50h**. The X-ray structure of the representative acrylamide system **50h** revealed that the Pd(II)-catalyzed, directing group-aided, C-H arylation of the acrylamide system **41b** having the *E* stereochemistry was stereoselective. Further, the stereochemistry of the phenyl group in the product **50h** was found to be unchanged with respect to the carboxamide moiety of the mono β-C-H arylated acrylamide system **41b**.

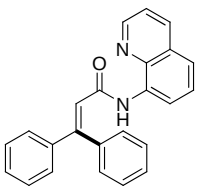
Table 4. Construction of acrylamide derivatives **50** and **51**.[a]



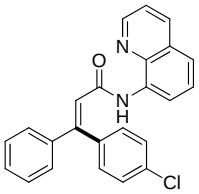
41a / **41b** / **41j** / **41k** / **41r** (0.25 mmol)

(**40a**, 4 equiv)

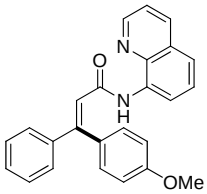
50 / **51** (%)



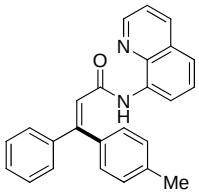
43ab; 65%



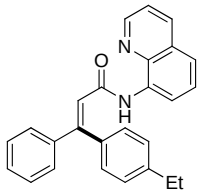
50b; 53%



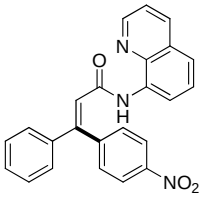
50c; 64%



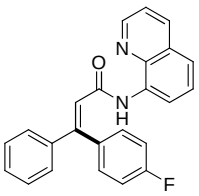
50d; 60%



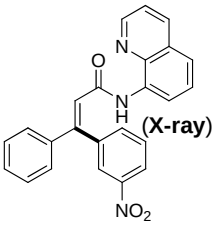
50e; 47%



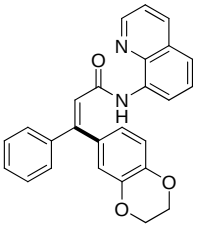
50f; 50%



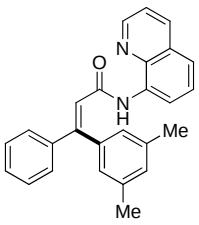
50g; 40%



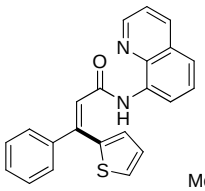
50h; 60% (**X-ray**)



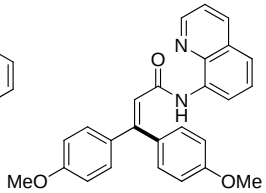
50i; 70%



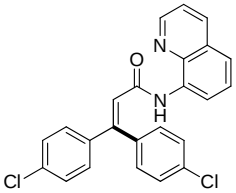
50j; 59%



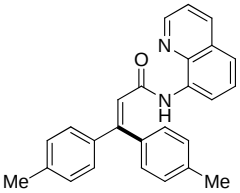
50k; 81%



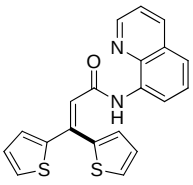
50l; 61% (36 h)



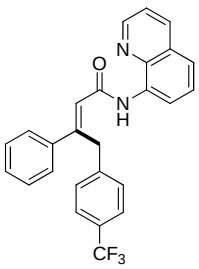
50m; 51% (48 h)



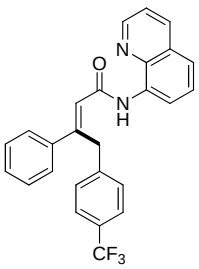
50n; 55%



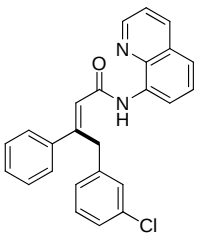
50o; 55% (36 h)



51a; 79%



51b; 54%



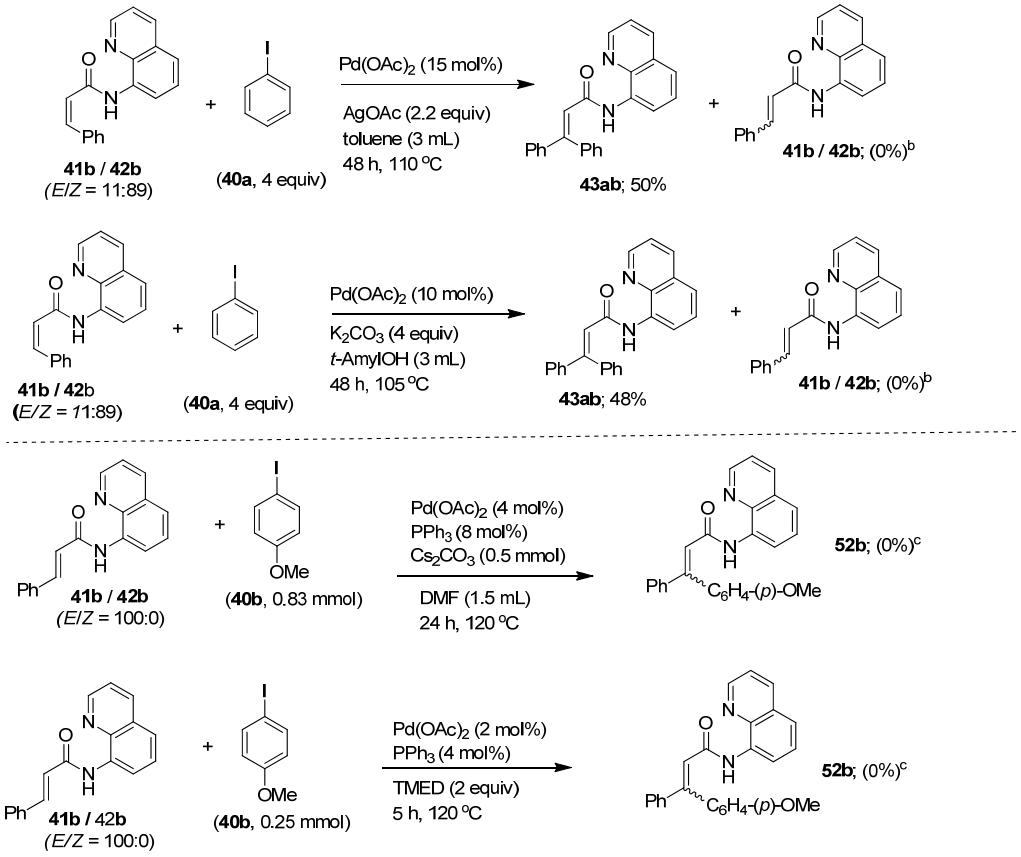
51c; 56%[d]

[a] The compounds **50a-k** were obtained from **41b**.Thecompounds **50l**,**50m**,**50n** and **50o** were obtained from the corresponding starting compounds **41a**, **41j**, **41k**, and **41r**. The compounds **51a-c** were obtained from the reaction of **41b** with the corresponding benzyl bromides.

Subsequently, it was envisaged to attempt the Pd(II)-catalyzed second β-C-H arylation of the mono β-C-H arylated acrylamide mixture **41b**/**42b** (*E*/*Z* isomers, *E*/*Z* ratio 11:89) obtained from the optimization reactions, in which the *Z* isomer is the major compound. Accordingly, the Pd(II)-catalyzed second β-C-H arylation of the mono β-C-H arylated acrylamide mixture **41b**/**42b** (*E*/*Z* isomers, *E*/*Z* ratio 11:89) with iodobenzene (**40a**) afforded the β,β′-C-H arylated acrylamide derivative **43ab** in 50% yield (Scheme 16). Similarly, the β-C-H arylation of **41b** / **42b** (*E*/*Z* isomers, *E*/*Z* ratio 11:89) with iodobenzene (**40a**) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 as an additive alsoafforded the β,β′-C-H arylated acrylamide derivative **43ab** in 48% yield. It was expected that these reactions either will not proceed or give **43ab** in low yield with recovery the *E* isomer **41b**. However, the β,β′-C-H arylated acrylamide derivative **43ab** was obtained in 48-50% yield (Scheme 16). This observation suggested that the occurrence of *E*/*Z* isomerization under the experimental conditions cannot be ignored at this stage. When compared to the results shown in Table 4, the directing group-aided β-C-H arylation of the mono β-arylated acrylamide system **41b** (having the *E* geometry)under the Mizoroki-Heck reaction conditions did not afford the corresponding β,β′-C-H arylated acrylamide derivative **52b** (Scheme 16).

The observed *Z* selective β-arylation of *N*-(quinolin-8-yl)acrylamide systems **39a** and **41b** linked with the bidentate ligand 8-aminoquinoline via the Pd(II)-catalyzed second β-C-H arylation reaction can be explicated *via* with the generally proposed Pd(II/IV) catalytic cycle involved chelation-based mechanism pertaining to the bidentate directing group-aided $Pd(OAc)_2$/AgOAc-catalytic system-based C-H activation/arylation of carboxamide derivatives as shown in Scheme 17. The plausible mechanism for bidentate directing group-aided $Pd(OAc)_2$/AgOAc-catalytic system-based C-H activation/arylation of carboxamide derivatives involves the following steps; (a) an initial coordination of the directing group to the $Pd(OAc)_2$ followed by the activation of the C(β)-H bond of carboxamide system generates the Pd(II) complex **53b**, (b) next, in the oxidative addition step, the oxidation of the Pd(II) complex **53b** generated the Pd(IV) complex **53c** in presence of an aryl iodide, (c) next, AgOAc additive helps to generate the Pd(IV) species **53d**, and finally, the reductive elimination of the Pd(IV) complex **53e** affords the C-H arylated product **42**/**50** along with the regeneration of the Pd(II) catalyst.

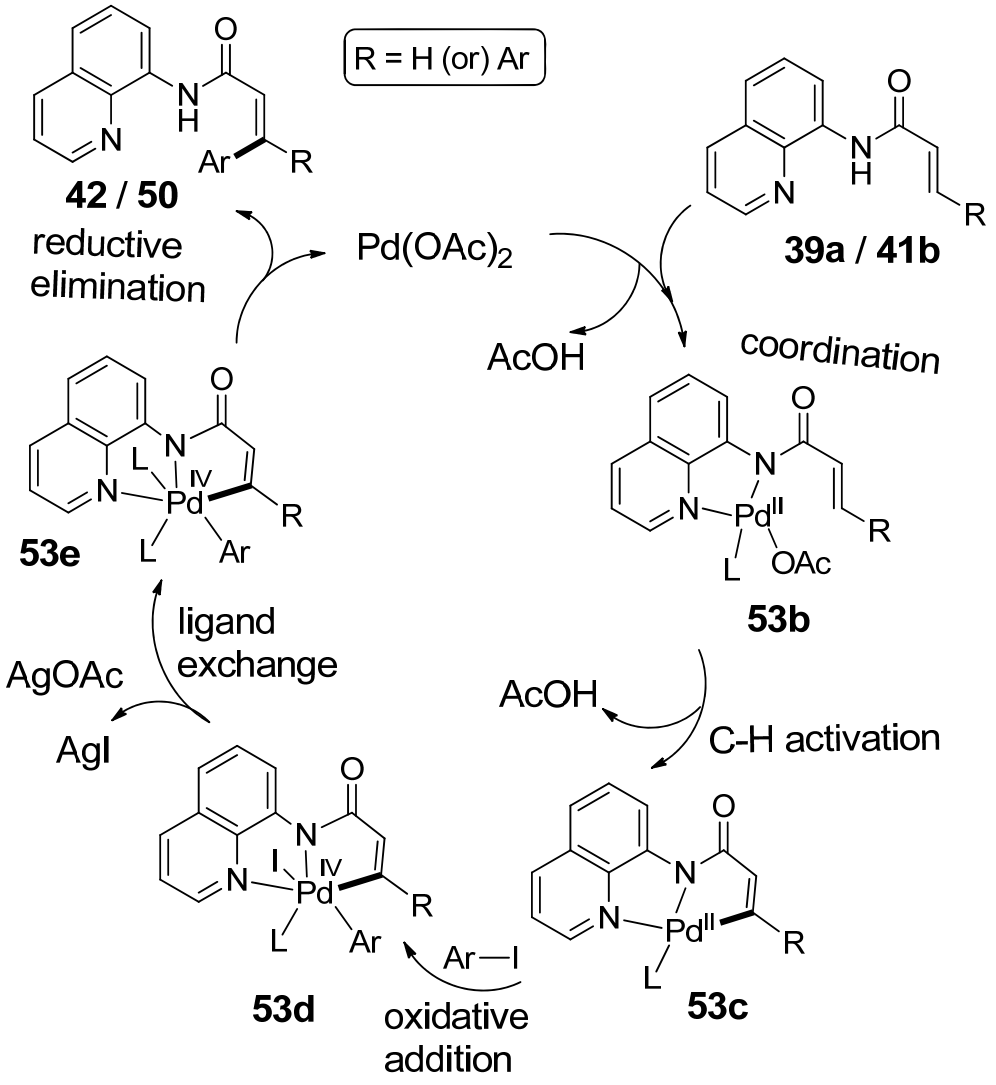
Scheme 16. Pd(II)-catalyzed β-arylation of **41b** / **42b** and some control experiments. [a]



[a] All the reactions were performed using 0.25 mmol of **41b** / **42b** (*E/Z* isomers, *E*/*Z* ratio 11:89). [b] The crude NMR spectra revealed the presence of only traces of compounds **41b** / **42b** apart from the product**43ab**. [c] The crude NMR spectra revealed the recovery of **41b** and the Heck product **52b** was not detected.

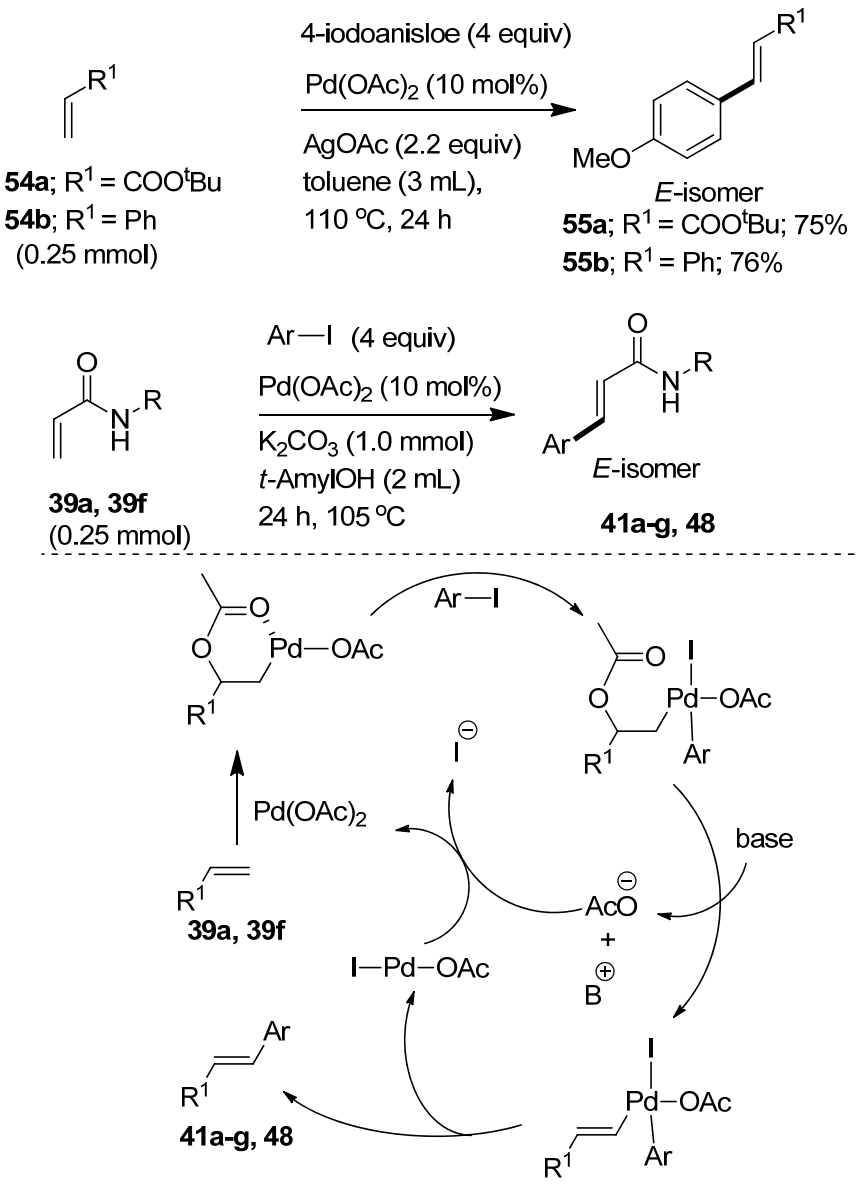
The Pd-catalyzed C-H arylation of olefins **54a** and **54b** underoptimized reaction conditions (used for the substrate 8) in the presence of the $Pd(OAc)_2$/AgOAc-catalytic system afforded the corresponding mono β-C-H arylated acrylamide derivatives **55a** and **55b** having the *E*-stereochemistry as the major isomers (Scheme 18) and these reactions plausibly proceeded *via* the ligand-free Mizoroki-Heck reaction pathway.[10] Additionally, The Pd(II)-catalyzed C-H arylation of acrylamide systems **39a** and **39f** in the presence of K_2CO_3 as an additive instead of AgOAc in *tert*-amyl alcohol [11] afforded the corresponding β-C-H arylated acrylamide derivatives **41a-g** and **48** having the *E*-stereochemistry as the major isomers, and these reactions plausibly proceeded *via* the ligand-free Mizoroki-Heck reaction pathway suggested by Yao[12] (Scheme 18).

Scheme 17. Plausible mechanism for the Z selective C-H arylation of **39a** and **41b**.



To reveal the synthetic utility of this Pd(II)-catalyzed β-C-H arylation of acrylamide systems, the Pd(II)-catalyzed β-C-H arylation of acrylamide system **39a** with iodobenzene (**40a**) was performed in a gram scale to afford the β-C-H arylated of acrylamides **41b** /**42b** in 62% yield (*E/Z* ratio 20:80, Scheme 19).

Scheme 18. Mizoroki-Heck-Type β-Arylation of **54a,b** and **39a,39f.**



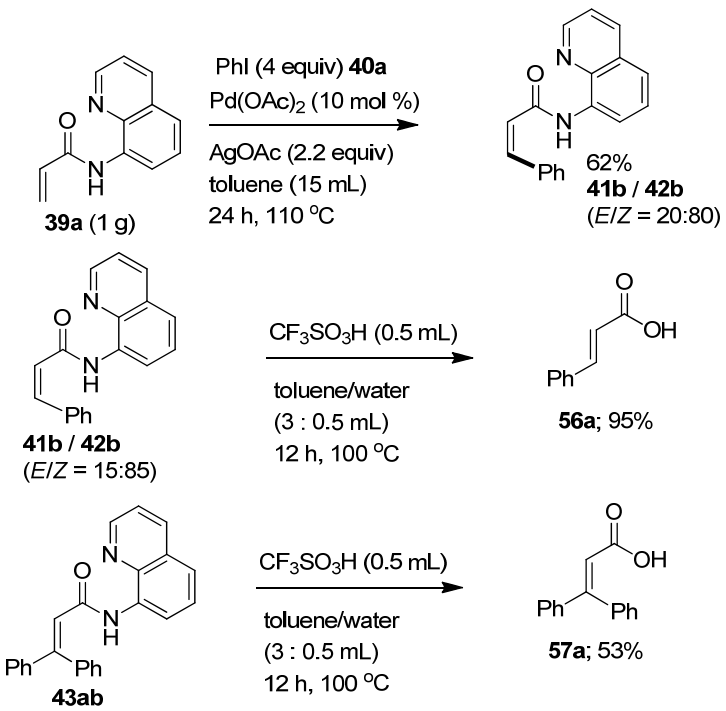
adapted from Yao's ligand-free Heck reaction mechanism

Next, removal of bidentate directing group from the representative β-C-H arylated acrylamide systems **41b** /**42b** (*E/Z* isomers, *E*/*Z* ratio 11:89) and **43ab** was attempted under various amide hydrolysis conditions. The TfOH-mediated hydrolysisof the representative C-H arylated acrylamide systems **41b** /**42b** (*E/Z* isomers, *E*/*Z* ratio 11:89) at 100 ^{o}C afforded the thermodynamically preferred *E*-cinnamic acid **56a** as the major compound under the experimental condition. Additionally, the TfOH-mediated hydrolysis of **43ab** also afforded the carboxylic acid **57a** in 53% yield (Scheme 19). On the basis of the literature reports dealing on the *cis-trans* isomerization of cinnamic acid under thermal conditions[12] and

considering the reaction conditions used (Scheme 19) to remove the bidentate directing group, 8-aminoquinoline, the *cis-trans* isomerization was unavoidable in the present work comprising the acid-mediated hydrolysis of substrates **41b** /**42b** / **43ab**.

The *E*/*Z* ratios of olefins were calculated from the NMR spectra of the corresponding crude reaction mixtures. In the cases of the Tables 1 and 2 and Schemes 15 and 18 the total isolated yields of *E*/*Z* isomers were reported. In general, the *E*/*Z* isomers are separable and the following points are with regard to Tables 1 and 2 and Scheme 15; after the Pd(II)-catalyzed mono C-H arylation of the corresponding acrylamide systems, the purification of the crude reaction mixture afforded the respective *E*/*Z* isomers as a mixture since the corresponding *E*/*Z* isomers had similar R_f values. Then, the respective *E*/*Z* isomers were again purified to get the pure major and minor isomers. In general, the purification of the corresponding crude reaction mixtures obtained after the C-H arylation reactions afforded only the major isomers in pure form and the corresponding minor isomers could not be completely separated from their respective major isomers. Additionally, except the reactions that gave very high *E*/*Z* ratio, the isolation of the corresponding major isomers also was not possible and only a few fractions of thecorresponding major isomers were obtained, which were used to characterize the corresponding major isomers.

Scheme 19. Gram scale reaction and removal of the directing group.



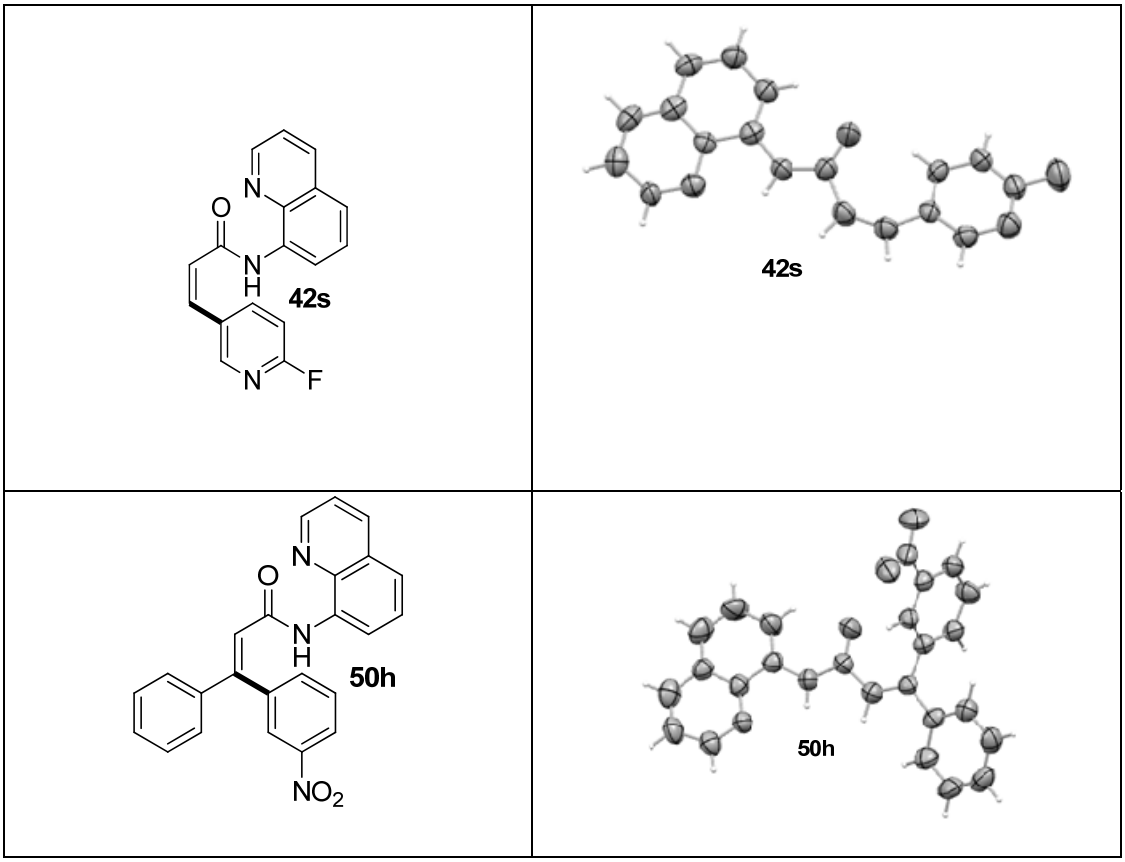
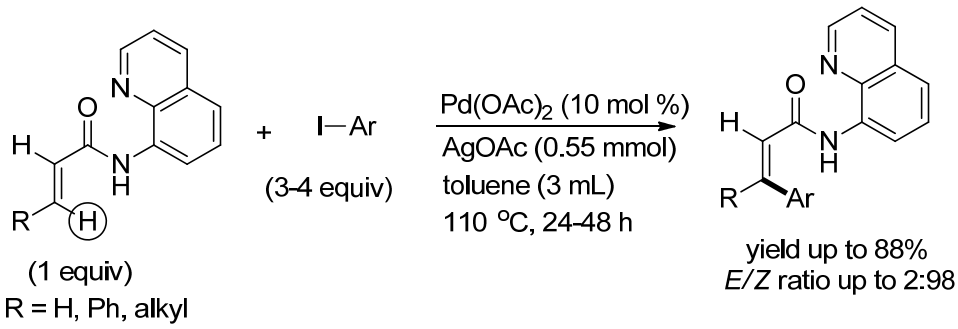


Figure 2. X-ray (ORTEP diagram) structures of the compounds **42s**, **50h**.

Conclusion

In summary, the **Chapter 3** revealed a contemporary cross-coupling method comprising the $Pd(OAc)_2$/AgOAc-catalytic system-based bidentate directing group-directed *Z* selective C-H arylation of C(β)-H bond of acrylamide systems using various aryl- and heteroaryl iodides. This $Pd(OAc)_2$/AgOAc-catalytic system-based bidentate directing group-directed *Z* selective C-H arylation method provided an easy access to several functionalized *Z* cinnamamide derivatives and β, β-C-H arylated acrylamide derivatives. The observed *Z* selective β-arylation of acrylamide systems was explained *via* the chelation-based C-H activation reaction pathway.



Experimental section.

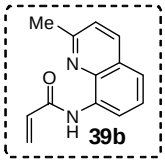
General. IR spectra of compounds were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of compounds were recorded on 400 MHz and 100 MHz spectrometers (using TMS as an internal standard) respectively. All the HRMS measurements reported here were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography purification of crude reaction mixtures was carried out using silica gel 100-200 mesh. All the reactions were performed in anhydrous solvent under a nitrogen atm. Yields were not optimized. All the amides starting materials used in this work were prepared from their corresponding acid chlorides and amines using the standard literature procedures.

General procedure for the β-arylation of acrylamides and preparation of 41a-f / 41h-t / 42a-f/42h-t/ 43ab, 50b-o 44a / 46a / 49k-s / 51a-c / 55a,b using the $Pd(OAc)_2$ and AgOAc catalytic system. An appropriate acrylamide (1.0 equiv, 0.25 mmol), $Pd(OAc)_2$ (5-15 mol%, 2.8-8.4 mg, 0.0125-0.0375 mmol), an appropriate aryl iodide (4.0 equiv, 1.0 mmol) and AgOAc (91.8 mg, 0.55 mmol) in anhydrous toluene (3 mL) was heated at 110 ^{o}C for 24-48 h under nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture through column chromatography furnished the corresponding arylated acrylamides**41a-f / 41h-t / 42a-f/42h-t/ 43ab, 50b-o 44a / 46a / 49k-s / 51a-c / 55a,b** (see the respective Tables/Schemes for specific examples).

General procedure for the preparation of 41a-g / 42a-g / 43ab / 48 using the $Pd(OAc)_2$ and K_2CO_3 catalytic system. An appropriateacrylamide (1.0 equiv, 0.25 mmol), $Pd(OAc)_2$ (10 mol%, 5.6 mg, 0.025 mmol), an appropriate aryl iodide (4.0 equiv, 1.0 mmol) K_2CO_3 (4.0 equiv, 138.2 mg, 1 mmol) in anhydrous *t*-AmylOH (2 mL) was heated at 105 ^{o}C, for 24 h under nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography

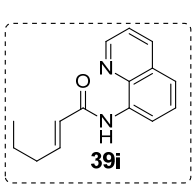
furnished the corresponding arylated acrylamides**41a-g / 42a-g / 43ab / 48**(see the respective Tables/Schemes for specific examples).

***N*-(2-Methylquinolin-8-yl)acrylamide (39b):** Compound **39b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; Yield: 75% (159 mg); IR (DCM): 3338, 1713, 1529, 1222, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.78 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 7.87 (d, 1H, *J*= 8.4 Hz), 7.40-7.32 (m, 2H), 7.17 (d, 1H, *J*= 8.4 Hz), 6.52-6.41 (m, 2H), 5.77 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.9 Hz), 2.64 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5, 157.2, 137.6, 136.3, 133.6, 131.9, 127.2, 126.1, 125.9, 122.4, 121.6, 116.6, 25.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1028; found 213.1025.



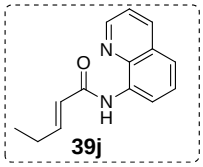
39b

(*E*)-*N*-(Quinolin-8-yl)hex-2-enamide (39i): Compound **39i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colour liquid; Yield: 54% (130 mg); IR (DCM): 3351, 1682, 1530, 1486, 1385, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (br. s, 1H), 8.87 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56 (t, 1H, *J*= 8.2 Hz), 7.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.5 Hz), 7.08 (td, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 6.19 (td, 1H, J_1 = 15.2 Hz, J_2 = 1.5 Hz), 2.28 (dq, 2H, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 1.60-1.52 (m, 2H), 0.99 (t, 3H, *J*= 7.3 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 148.1, 146.2, 138.4, 136.4, 134.7, 127.9, 127.5, 124.7, 121.6, 121.5, 116.7, 34.2, 21.5, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1341; found 241.1334.



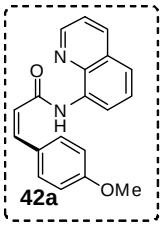
39i

(*E*)-*N*-(Quinolin-8-yl)pent-2-enamide (39j): Compound **39j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a yellow colour liquid; Yield: 57% (130 mg); IR (DCM): 3350, 1684, 1527, 1485, 1327, 971 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.55 (t, 1H, *J*= 8.1 Hz), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.13 (td, 1H, J_1 = 15.2 Hz, J_2 = 6.4 Hz), 6.19 (td, 1H, J_1 = 15.2 Hz, J_2 = 1.7 Hz), 2.36-2.29 (m, 2H), 1.50 (t, 3H, *J*= 7.4 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 148.1, 147.6, 138.4, 136.4, 134.7, 127.9, 127.5, 123.7, 121.6, 121.4, 116.7, 25.3, 12.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found 227.1180.



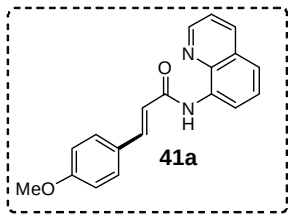
39j

(*Z*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (42a): Compound **42a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 27:73) as a brown colour liquid; Yield: 74% (56 mg), (*E:Z* = 24:76); IR (DCM): 3412, 1713, 1362, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.69 (d, 2H, *J*= 8.9 Hz), 7.57 (t, 1H, *J*= 8.2 Hz), 7.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.43 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.2 Hz), 6.90 (d, 1H, *J*= 12.5 Hz) 6.87 (d, 2H, *J*= 8.9 Hz), 6.18 (d, 1H, *J*= 12.5 Hz), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.2, 160.2, 148.0, 139.3, 138.4, 136.2, 134.6, 131.6, 127.9, 127.5, 127.4, 122.3, 121.5, 121.5, 116.6, 113.7, 55.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1290; found 305.1280.



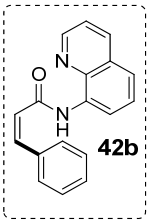
42a

(*E*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (41a): Compound **41a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 57% (44 mg), (*E:Z* = 95:5); mp 116-118 ^oC; IR (KBr): 2922, 1602, 1525, 1381, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.93 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.80 (d, 1H, *J*= 15.5 Hz), 7.62-7.58 (m, 3H), 7.54 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.95 (d, 2H, *J*= 8.3 Hz), 6.70 (d, 1H, *J*= 15.5 Hz), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 161.1, 148.1, 141.8, 138.5, 136.5, 134.8, 129.7, 128.0, 127.5, 121.7, 121.5, 119.1, 116.8, 114.3, 55.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1290; found 305.1277.



41a

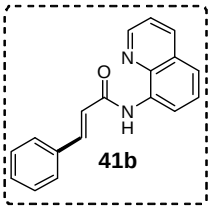
(*Z*)-3-Phenyl-*N*-(quinolin-8-yl)acrylamide (42b): Compound **42b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as a brown colour liquid; Yield: 87% (59 mg), (*E:Z* = 11:89); IR (DCM): 3342, 176, 1523, 1484, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.62 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.14 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 7.64-7.62 (m, 2H), 7.56 (t, 1H, *J*= 8.1 Hz), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.35-7.28 (m, 3H), 7.01 (d, 1H, *J*= 12.5 Hz), 6.30 (d, 1H, *J*= 12.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 148.0, 139.0, 138.4, 136.2, 135.0, 134.4, 129.4,



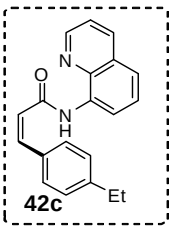
42b

128.7, 128.3, 127.9, 127.4, 124.7, 121.6, 121.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$: 275.1184; found 275.1171.

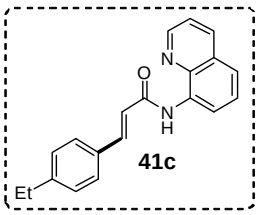
***N*-(Quinolin-8-yl)cinnamamide (41b):** Compound **41b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 80% (55 mg), (*E:Z* = 92:8); mp 117-119 ^oC; IR (KBr): 3346, 1629, 1526, 1259, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.04 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.85 (d, 1H, *J*= 15.5 Hz), 7.65-7.63 (m, 2H), 7.59 (t, 1H, *J*= 7.6 Hz), 7.55 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.46-7.41 (m, 3H), 6.83 (d, 1H, *J*= 15.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 148.2, 142.1, 138.5, 136.5, 134.8, 134.6, 129.9, 128.9, 128.1, 128.0, 127.5, 121.7, 121.5, 116.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$: 275.1184; found 275.1170.



(*Z*)-3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)acrylamide (42c): Compound **42c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; Yield: 67% (50 mg), (*E:Z* = 10:90); IR (DCM): 3344, 1713, 1363, 1270, 530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.96 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.59 (d, 2H, *J*= 8.1 Hz), 7.55 (d, 1H, *J*= 7.7 Hz), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.16 (d, 2H, *J*= 8.1 Hz), 6.96 (d, 1H, *J*= 12.5 Hz), 6.25 (d, 1H, *J*= 12.5 Hz), 2.63 (q, 2H, *J*= 7.2 Hz), 1.20 (t, 3H, *J*= 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 147.9, 145.2, 139.3, 138.4, 136.2, 134.5, 132.3, 129.7, 127.9, 127.8, 127.4, 123.7, 121.6, 121.5, 116.6, 28.7, 15.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1488.

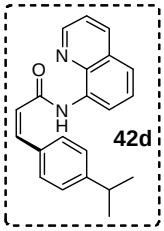


(*E*)-3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)acrylamide (41c): Compound **41c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 73% (55 mg), (*E:Z* = 85:15); mp 125-127 ^oC; IR (KBr): 3348, 1675, 1526, 1485, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.84 (d, 1H, *J*= 15.6 Hz), 7.62-7.53 (m, 4H), 7.49 (dd, 1H,



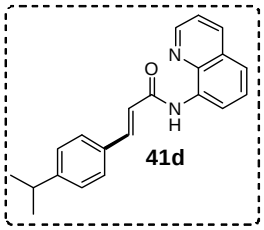
J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27 (d, 2H, *J*= 8.1 Hz), 6.80 (d, 1H, *J*= 15.6 Hz), 2.71 (q, 2H, *J*= 7.6 Hz), 1.29 (t, 3H, *J*= 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 148.1, 146.6, 142.1, 138.5, 136.5, 134.7, 132.3, 128.4, 128.2, 128.0, 127.5, 121.7, 121.6, 120.5, 116.8, 28.8, 15.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1488.

(*Z*)-3-(4-Isopropylphenyl)-*N*-(quinolin-8-yl)acrylamide (42d): Compound **42d** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as



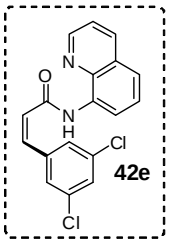
colourless liquid; Yield: 82% (65 mg), (*E/Z* = 2:98); IR (DCM): 3345, 1675, 1524, 1484, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.87 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.96 Hz), 8.63 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (d, 2H, *J*= 8.2 Hz), 7.55 (d, 1H, *J*= 7.7 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.19 (d, 2H, *J*= 8.2 Hz), 6.96 (d, 1H, *J*= 12.5 Hz), 6.24 (d, 1H, *J*= 12.5 Hz), 2.91-2.84 (m, 1H), 1.21 (d, 6H, *J*= 6.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 149.8, 147.9, 139.2, 138.4, 136.2, 134.5, 132.4, 129.7, 127.9, 127.4, 126.4, 123.7, 121.5, 121.5, 116.5, 34.0, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O$: 317.1654; found 317.1657.

(*E*)-3-(4-Isopropylphenyl)-*N*-(quinolin-8-yl)acrylamide (41d): Compound **41d** was



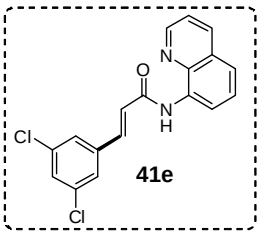
obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 82% (65 mg), (*E/Z* = 95:5); mp 136-138 °C; IR (KBr): 3278, 1655, 1618, 1544, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (br. s, 1H), 8.95 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.84 (d, 1H, *J*= 15.5 Hz), 7.61-7.56 (m, 3H), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, *J*= 8.3 Hz), 6.79 (d, 1H, *J*= 15.5 Hz), 3.0-2.93 (m, 1H), 1.30 (d, 6H, *J*= 6.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 151.2, 148.1, 142.2, 138.4, 136.5, 134.7, 132.4, 128.2, 128.0, 127.5, 127.0, 121.7, 121.6, 120.5, 116.8, 34.1, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O$: 317.1654; found 317.1662.

(*Z*)-3-(3,5-Dichlorophenyl)-*N*-(quinolin-8-yl)acrylamide (42e): Compound **42e** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 76% (65 mg), (*E/Z* = 2:98); mp 67-69 °C; IR (KBr): 3340, 1676, 1558, 1485, 1329, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (br. s, 1H), 8.79 (dd,



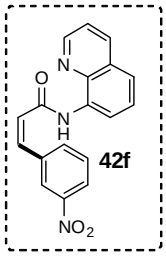
1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56-7.50 (m, 4H), 7.41 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26-7.25 (m, 1H), 6.83 (d, 1H, J= 12.5 Hz), 6.35 (d, 1H, J= 12.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 148.1, 138.3, 137.9, 136.5, 136.3, 134.8, 134.1, 128.5, 127.9, 127.7, 127.4, 126.9, 122.0, 121.7, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{13}Cl_2N_2O$: 343.0405; found 343.0403.

(*E*)-3-(3,5-Dichlorophenyl)-*N*-(quinolin-8-yl)acrylamide (41e): Compound **41e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 56% (48 mg), (*E:Z* = 95:5); mp 148-150 ^oC; IR (KBr):



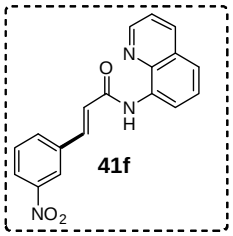
2922, 1738, 1357, 1217, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.08 (br. s, 1H), 8.90 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.8 Hz), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.70 (d, 1H, J= 15.5 Hz), 7.62-7.55 (m, 2H), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.48 (d, 2H, J= 1.8 Hz), 7.38 (t, 1H, J = 1.8 Hz), 6.83 (d, 1H, J= 15.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 148.3, 139.2, 138.4, 137.8, 136.5, 135.5, 134.3, 129.5, 128.0, 127.5, 126.2, 124.2, 122.1, 121.8, 117.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{13}Cl_2N_2O$: 343.0405; found 343.0394**.**

(*Z*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)acrylamide (42f): Compound **42f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a



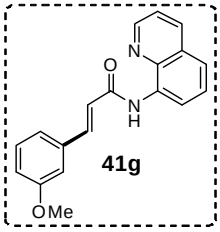
yellow colour solid; Yield: 88% (70 mg), (*E:Z* = 8:92); mp 150-152 ^oC; IR (KBr): 3410, 1713, 1363, 1222, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.82 (dd, 1H, J_1 = 6.1 Hz, J_2 = 2.9 Hz), 8.70 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.50 (br. s, 1H), 8.17 (dd, 2H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 8.02 (d, 1H, J= 7.8 Hz), 7.58-7.53 (m, 2H), 7.50 (t, 1H, J= 8.0 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.02 (d, 1H, J= 12.4 Hz), 6.46 (d, 1H, J= 12.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5, 148.2, 148.1, 138.3, 137.3, 136.6, 136.4, 135.4, 134.0, 129.1, 127.9, 127.4, 126.8, 124.5, 123.3, 122.1, 121.7, 116.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}N_3O_3$: 320.1035; found 320.1020.

(*E*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)acrylamide (41f): Compound **41f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 59% (47 mg), (*E:Z* = 95:5); mp 199-201 ^oC; IR (KBr): 2922, 1677, 1526, 1485, 1350, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (br. s, 1H), 8.91

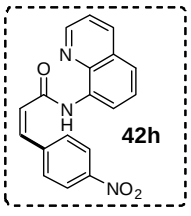


(dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.50 (t, 1H, J= 1.8 Hz), 8.26-8.24 (m, 1H), 8.22 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.91 (s, 1H), 7.87 (d, 1H, J= 15.5 Hz), 7.64-7.57 (m, 3H), 7.52 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.96 (d, 1H, J= 15.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 148.7, 148.3, 139.3, 138.4, 136.6, 136.5, 134.3, 134.1, 130.0, 128.0, 127.5, 124.6, 124.2, 122.1, 122.0, 121.8, 117.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}N_3O_3$: 320.1035; found 320.1020.

(*E*)-3-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (41g): Compound **41g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colour solid; Yield: 53% (41 mg), (*E:Z* = 95:5); mp 113-115 ^oC; IR (KBr): 2922, 1703, 1604, 1513, 1254, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.04 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.21 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.82 (d, 1H, J= 15.5 Hz), 7.61 (t, 1H, J= 8.2 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.36 (t, 1H, J= 7.8 Hz), 7.24 (d, 1H, J= 7.6 Hz), 7.16 (t, 1H, J= 2.2 Hz), 6.98-6.96 (m, 1H), 6.82 (d, 1H, J= 15.5 Hz), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 159.9, 148.2, 142.1, 138.5, 136.5, 136.2, 134.6, 129.9, 128.0, 127.5, 121.8, 121.7, 121.7, 120.8, 116.9, 115.8, 112.9, 55.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1290; found 305.1283.

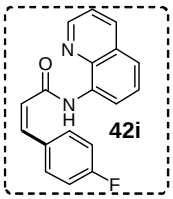


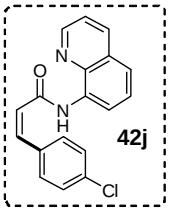
(*Z*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)acrylamide (42h): Compound **42h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour solid; Yield: 74% (59 mg), (*E:Z* = 30:70); mp 154-156 ^oC; IR (KBr): 3411, 113, 1421, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.80 (dd, 1H, J_1 = 5.3 Hz, J_2 = 3.7 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.18 (d, 2H, J= 8.6 Hz), 8.17 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 7.77 (d, 2H, J= 8.6 Hz), 7.56-7.55 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.03 (d, 1H, J= 12.5 Hz), 6.49 (d, 1H, J= 12.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 148.2, 147.5, 141.7, 138.3, 137.2, 136.4, 134.0, 130.2, 127.9, 127.5, 127.4, 123.5, 122.2, 121.8, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}N_3O_3$: 320.1035; found 320.1040.



(*Z*)-3-(4-Fluorophenyl)-*N*-(quinolin-8-yl)acrylamide (42i): Compound **42i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a

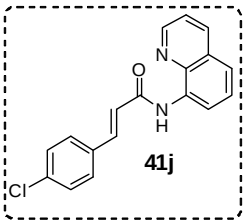
yellow colour solid; Yield: 75% (55 mg), (*E:Z* = 5:95); mp 101-103 ^{o}C; IR (KBr): 3344, 1673, 1484, 1159, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.67 (dd, 2H, J_1 = 8.6 Hz, J_2 = 5.5 Hz), 7.56 (t, 1H, *J*= 8.2 Hz), 7.53 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.7 Hz), 7.42 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.02 (t, 2H, *J*= 8.6 Hz), 6.93 (d, 1H, *J*= 12.5 Hz), 6.27 (d, 1H, *J*= 12.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.6, 163.0 (d, J_{C-F} = 247.7 Hz), 148.1, 138.3, 136.3, 134.4, 131.7 (d, J_{C-F} = 8.5 Hz), 131.0 (d, J_{C-F} = 3.2 Hz), 127.9, 127.4, 124.3, 121.8, 121.6, 116.6, 115.3 (d, J_{C-F} = 21.5 Hz); HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{14}FN_2O$: 293.1090; found 293.1075.



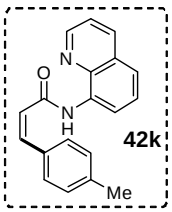


(*Z*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (42j): Compound **42j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 29:71) as a brown colour liquid; Yield: 69% (53 mg), (*E:Z* = 29:71); IR (DCM): 3441, 1713, 1524, 1363, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.83 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59 (d, 2H, *J*= 8.5 Hz), 7.56-7.52 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, *J*= 8.5 Hz), 6.94 (d, 1H, *J*= 12.5 Hz), 6.31 (d, 1H, *J*= 12.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.5, 148.1, 138.3, 138.0, 136.3, 134.7, 134.3, 133.4, 130.9, 128.5, 127.9, 127.4, 125.1, 121.8, 121.6, 116.7; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{14}ClN_2O$: 309.0795; found 309.0779.

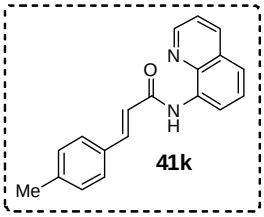
(*E*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (41j): Compound **41j** was obtained (from the reaction of 8-aminoquinoline and 4-chlorocinnamoyl chloride) after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 58% (180 mg); mp 172-174 ^{o}C; IR (KBr): 3342, 1675, 1528, 1485, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (br. s, 1H), 8.92 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.1 Hz), 8.85 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.78 (d, 1H, *J*= 15.5 Hz), 7.62-7.59 (m, 1H), 7.58-7.53 (m, 3H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.39 (d, 2H, *J*= 8.8 Hz), 6.79 (d, 1H, *J*= 15.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.8, 148.2, 140.7, 138.4, 136.5, 135.7, 134.5, 133.3, 129.2, 129.1, 128.0, 127.5, 122.1, 121.8, 121.7, 116.9; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{14}ClN_2O$: 309.0795; found 309.0787.



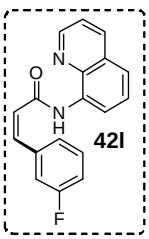
(*Z*)-*N*-(Quinolin-8-yl)-3-(*p*-tolyl)acrylamide (42k): Compound **42k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; Yield: 55% (40 mg), (*E:Z* = 20:80); IR (DCM): 3411, 1714, 1420, 1363, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.93 (br. s, 1H), 8.87 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58-7.52 (m, 1 H), 7.55 (d, 2H, *J*= 7.8 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.41 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.14 (d, 2H, *J*= 8.0 Hz), 6.96 (d, 1H, *J*= 12.5 Hz), 6.24 (d, 1H, *J*= 12.5 Hz), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 147.9, 139.2, 138.9, 138.4, 136.2, 134.5, 132.1, 129.5, 129.0, 127.9, 127.4, 123.7, 121.6, 121.5, 116.6, 21.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1341; found 289.1331.



(*E*)-*N*-(Quinolin-8-yl)-3-(*p*-tolyl)acrylamide (41k): Compound **41k** was obtained (from the reaction of 8-aminoquinoline and 4-methylcinnamoyl chloride) after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 55% (160 mg); mp 157-159 ^oC; IR (KBr): 3343, 1628, 1528, 1485, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.82 (d, 1H, *J*= 15.5 Hz), 7.58 (t, 1H, *J*= 8.1 Hz), 7.53-7.51 (m, 1H), 7.52 (d, 2H, *J*= 7.8 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.22 (d, 2H, *J*= 7.8 Hz), 6.77 (d, 1H, *J*= 15.5 Hz), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 148.1, 142.1, 140.3, 138.4, 136.4, 134.7, 132.0, 129.6, 128.1, 127.9, 127.5, 121.7, 121.6, 120.4, 116.8, 21.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1341; found 289.1334.

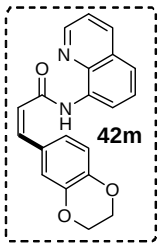


(*Z*)-3-(3-Fluorophenyl)-*N*-(quinolin-8-yl)acrylamide (42l): Compound **42l** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 55% (40 mg), (*E/Z* = 12:88); mp 59-61 ^oC; IR (KBr): 3340, 1675, 1524, 1485, 877 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.84 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.58-7.51 (m, 2H), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.40-7.37 (m, 2H), 7.31-7.25 (m, 1H), 7.03-6.98 (m, 1H), 6.95 (d, 1H, *J*= 12.5 Hz), 6.34 (d, 1H, *J*= 12.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 162.6 (d, J_{C-F} = 244.2 Hz) 148.1, 138.4, 137.7, 137.7, 137.1 (d, J_{C-F} = 8.0 Hz), 136.3, 134.3, 129.8 (d, J_{C-F} = 8.5 Hz), 127.9, 127.4, 125.7, 125.3 (d, J_{C-F} = 2.9 Hz),

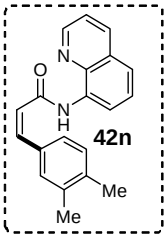


121.8, 121.6, 116.7, 116.2 (d, $J_{C\text{-}F}$ = 22.1 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.0 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{14}FN_2O$: 293.1090; found 293.1091.

(*Z*)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)acrylamide (42m): Compound **42m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 85% (70 mg), (*E:Z* = 2:98); IR (DCM): 3411, 1748, 1420, 1364, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 8.71 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.56 (t, 1H, *J* = 8.2 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29 (s, 1H), 7.20 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.1 Hz), 6.84 (d, 1H, *J*= 12.6 Hz), 6.82 (d, 1H, *J*= 8.4 Hz), 6.18 (d, 1H, *J*= 12.6 Hz), 4.26-4.19 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.0, 147.9, 144.4, 143.1, 138.9, 138.4, 136.3, 134.6, 128.4, 127.9, 127.4, 123.6, 123.0, 121.5, 121.5, 118.8, 117.1, 116.6, 64.5, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_3$: 333.1239; found 333.1227.

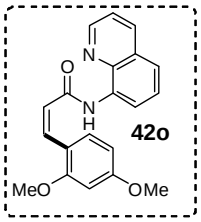


(*Z*)-3-(3,4-Dimethylphenyl)-*N*-(quinolin-8-yl)acrylamide (42n): Compound **42n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a green colour liquid; Yield: 75% (57 mg), (*E:Z* = 3:97); IR (DCM): 3410, 1713, 1363, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.87 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.61 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.56 (t, 1H, *J*= 8.2 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.42-7.39 (m, 2H), 7.37 (br. s, 1H), 7.09 (d, 1H, *J*= 7.8 Hz), 6.95 (d, 1H, *J*= 12.5 Hz), 6.23 (d, 1H, *J*= 12.5 Hz), 2.23 (s, 3H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 147.9, 139.2, 138.4, 137.5, 136.4, 136.2, 134.6, 132.5, 130.7, 129.6, 127.9, 127.4, 126.9, 123.7, 121.5, 121.5, 116.6, 19.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1488.

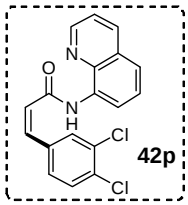


(*Z*)-3-(2,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (42o): Compound **42o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; Yield: 32% (27 mg), (*E:Z* = 30:70); IR (DCM): 3411, 1714, 1363, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.8 Hz), 8.62 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.66

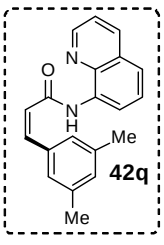
(d, 1H, *J*= 8.5 Hz), 7.54 (t, 1H, *J*= 8.1 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.14 (d, 1H, *J*= 12.4 Hz), 6.46 (d, 1H, *J*= 2.4 Hz), 6.41 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 6.20 (d, 1H, *J*= 12.4 Hz), 3.84 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 161.8, 158.7, 147.8, 138.4, 136.1, 134.8, 134.7, 131.8, 127.9, 127.4, 123.1, 121.4, 121.3, 116.8, 116.4, 104.4, 98.2, 55.6, 55.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found 335.1383.



(*Z*)-3-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)acrylamide (42p): Compound **42p** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 63% (54 mg), (*E/Z* = 8:92); mp 101-103 ^oC; IR (KBr): 3337, 1675, 1525, 1485, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.82 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.9 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.74 (d, 1H, *J*= 1.7 Hz), 7.58-7.53 (m, 2H), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.37 (d, 1H, *J*= 8.4 Hz), 6.87 (d, 1H, *J*= 12.5 Hz), 6.35 (d, 1H, *J*= 12.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9, 148.1, 138.3, 136.9, 136.3, 135.0, 134.2, 132.7, 132.4, 131.4, 130.2, 128.8, 127.9, 127.3, 126.1, 122.0, 121.7, 116.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{13}Cl_2N_2O$: 343.0405; found 343.0415.

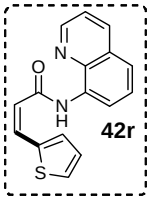


(*Z*)-3-(3,5-Dimethylphenyl)-*N*-(quinolin-8-yl)acrylamide (42q): Compound **42q** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a green colour liquid; Yield: 73% (55 mg), (*E:Z* = 5:95); IR (DCM): 3411, 1713, 1421, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.89 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.7 Hz), 8.58 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56 (t, 1H, *J*= 8.2 Hz), 7.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.21 (br. s, 2H), 6.96 (d, 1H, *J*= 12.5 Hz), 6.93 (br. s, 1H), 6.25 (d, 1H, *J*= 12.5 Hz), 2.22 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.2, 147.8, 139.0, 138.4, 137.8, 136.1, 134.8, 134.6, 130.4, 127.9, 127.4, 127.0, 124.7, 121.5, 121.5, 116.6, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1488.

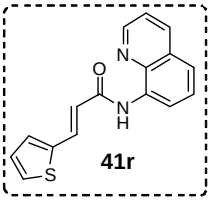


(*Z*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)acrylamide (42r): Compound **42r** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a green colour liquid; Yield: 73% (51 mg), (*E:Z* = 20:80); IR (DCM): 3410, 1713, 1363, 1222,

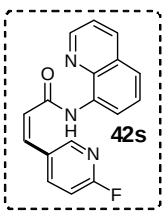
737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.96 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58 (t, 1H, J= 8.1 Hz), 7.54-7.51 (m, 2H), 7.47-7.44 (m, 2H), 7.11 (d, 1H, J= 12.3 Hz), 7.08 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.7 Hz), 6.07 (d, 1H, J= 12.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 148.1, 138.4, 137.8, 136.4, 135.2, 134.6, 134.3, 131.8, 128.0, 127.5, 126.5, 121.6, 121.6, 117.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}N_2OS$: 281.0749; found 281.0737.



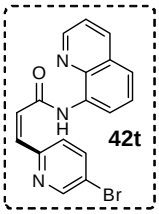
(*E*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)acrylamide (41r): Compound **41r** was obtained (from the reaction of 8-aminoquinoline and 2-thiophenecarbonyl chloride) after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow colour solid; Yield: 53% (150 mg); mp 158-160 ^oC; IR (KBr): 2922, 1617, 1526, 1484, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.91 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.94 (d, 1H, J= 15.2 Hz), 7.56 (t, 1H, J= 8.2 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.37 (d, 1H, J= 5.0 Hz), 7.29 (d, 1H, J= 3.6 Hz), 7.07 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.6 Hz), 6.60 (d, 1H, J= 15.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9, 148.2, 140.0, 138.4, 136.4, 134.8, 134.6, 130.7, 128.1, 128.0, 127.9, 127.8, 127.5, 121.7, 120.3, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}N_2OS$: 281.0749; found 281.0742.



(*Z*)-3-(6-Fluoropyridin-3-yl)-*N*-(quinolin-8-yl)acrylamide (42s): Compound **42s** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a yellow colour solid; Yield: 64% (47 mg), (*E:Z* = 40:60); mp 140-142 ^oC; IR (KBr): 3351, 1713, 1486, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.82 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.9 Hz), 8.75 (d, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.44-8.40 (td, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 8.38 (d, 1H, J = 2.0 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.58-7.53 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.93-6.90 (m, 1H), 6.91 (d, 1H, J= 12.5 Hz), 6.41 (d, 1H, J= 12.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 163.3 (d, $J_{C\text{-}F}$ = 240.5 Hz), 149.2 (d, $J_{C\text{-}F}$ = 14.9 Hz), 148.2, 142.4 (d, $J_{C\text{-}F}$ = 8.1 Hz), 138.3, 136.4, 135.2, 134.1, 128.9 (d, $J_{C\text{-}F}$ = 4.8 Hz), 127.9, 127.3, 125.9, 122.1, 121.8, 116.8, 109.0 (d, $J_{C\text{-}F}$ = 37.1 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{13}FN_3O$: 294.1043; found 294.1032.

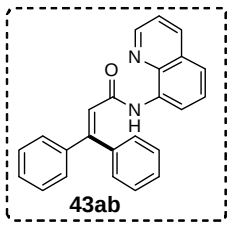


(*Z*)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)acrylamide (42t): Compound **42t** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a yellow colour solid; Yield: 59% (52 mg), (*E:Z* = 40:60); mp 123-125 ^{o}C; IR (KBr): 3411, 1715, 1420, 1364, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.7 (br. s, 1H), 8.97 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 8.89 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.88 (d, 1H, *J*= 2.3 Hz), 8.20 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.87 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.61-7.55 (m, 2H), 7.55-7.49 (m, 2H), 6.84 (d, 1H, *J*= 13.4 Hz), 6.44 (d, 1H, *J*= 13.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.4, 152.1, 150.3, 148.3, 139.5, 139.3, 136.4, 135.4, 134.2, 130.5, 128.2, 127.4, 126.7, 122.2, 121.5, 120.3, 118.1; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{17}H_{13}BrN_3O$: 354.0242; found 354.0233.



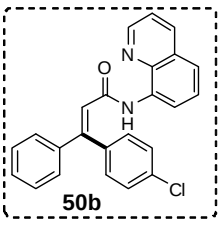
42t

3,3-Diphenyl-*N*-(quinolin-8-yl)acrylamide (43ab): Compound **43ab** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 65% (57 mg); mp 123-125 ^{o}C; IR (KBr): 3440, 1652, 1522, 1325, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.59 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.07 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.50 (t, 1H, J_1 = 8.2 Hz), 7.46-7.40 (m, 11H), 7.36 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.3 Hz), 6.70 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.6, 152.2, 147.7, 141.4, 138.4, 138.4, 136.1, 134.6, 129.8, 129.2, 128.6, 128.5, 128.5, 128.4, 127.8, 127.4, 122.8, 121.5, 121.4, 116.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{19}N_2O$: 351.1497; found 351.1501.



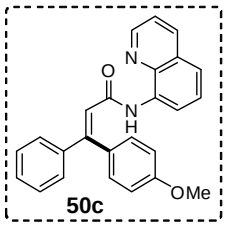
43ab

(*Z*)-3-(4-Chlorophenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50b): Compound **50b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 53% (51 mg); mp 137-139 ^{o}C; IR (KBr): 3058, 1714, 1420, 1222, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (br. s, 1H), 8.79 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-7.47 (m, 2H), 7.43 (t, 1H, *J*= 4.2 Hz), 7.41-7.33 (m, 9H), 6.66 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.2, 151.2, 147.9, 141.0, 138.3, 136.8, 136.2, 134.6, 134.4, 131.2, 129.4, 128.8, 128.5, 128.3, 127.8, 127.4, 122.9, 121.6, 116.5; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{18}ClN_2O$: 385.1108; found 385.1100.



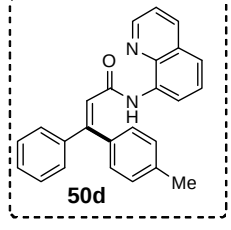
50b

(*Z*)-3-(4-Methoxyphenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50c): Compound **50c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; Yield: 64% (61 mg); IR (DCM): 3414, 1713, 1647, 1269, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (br. s, 1H), 8.83 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52 (t, 1H, J= 7.6 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.41-7.37 (m, 6H), 7.34 (d, 2H, J= 8.8 Hz), 6.92 (d, 2H, J= 8.8 Hz), 6.58 (s, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 160.1, 152.0, 147.6, 141.9, 138.4, 136.1, 134.7, 131.4, 130.4, 129.1, 128.5, 128.4, 127.8, 127.4, 122.3, 121.4, 121.2, 116.4, 113.9, 55.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_2$: 381.1603; found 381.1569.



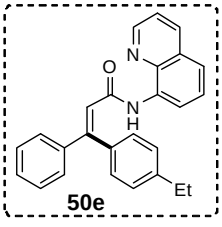
50c

(*Z*)-3-Phenyl-*N*-(quinolin-8-yl)-3-(*p*-tolyl)acrylamide (50d): Compound **50d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as a yellow colour solid; Yield: 60% (55 mg); mp 146-148 ^oC; IR (KBr): 3004, 1713, 1422, 1363, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (br. s, 1H), 8.82 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51 (t, 1H, J= 8.2 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.41-7.39 (m, 6H), 7.29 (d, 2H, J= 7.9 Hz), 7.20 (d, 2H, J= 7.9 Hz), 6.62 (s, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.8, 152.4, 147.6, 141.7, 138.4, 138.4, 136.1, 135.4, 134.7, 129.8, 129.2, 129.1, 128.4, 128.4, 127.8, 127.4, 122.4, 121.4, 121.3, 116.5, 21.4 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O$: 365.1654; found 365.1658.



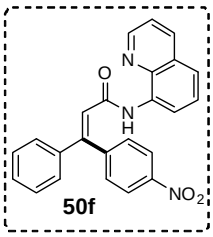
50d

(*Z*)-3-(4-Ethylphenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50e): Compound **50e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; Yield: 47% (44 mg); IR (DCM): 3410, 1713, 1522, 1363, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.51 (t, 1H, J= 8.2 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.40-7.36 (m, 6H), 7.31 (d, 2H, J= 8.3 Hz), 7.20 (d, 2H, J= 8.3 Hz), 6.60 (s, 1H), 2.63 (q, 2H, J= 7.6 Hz), 1.16 (t, 3H, J= 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 152.3, 147.6, 144.7, 141.7, 138.4, 136.1, 135.5, 134.6, 129.9, 129.0, 128.5, 128.4, 127.9, 127.7, 127.4, 122.6, 121.3, 121.2, 116.3, 28.6, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found 379.1803.

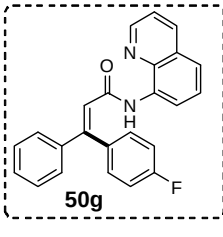


50e

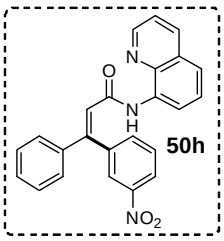
(*Z*)-3-(4-Nitrophenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50f): Compound **50f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; Yield: 50% (49 mg); IR (DCM): 3441, 1713, 1522, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.90 (br. s, 1H), 8.72 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.70 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.28 (d, 2H, J= 8.8 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55 (d, 2H, J= 8.8 Hz), 7.51-7.50 (m, 2H), 7.46-7.39 (m, 4H), 7.35-7.28 (m, 2H), 6.79 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.3, 151.1, 148.0, 147.7, 146.0, 139.9. 138.3, 136.4, 134.2, 130.5, 129.8, 128.8, 128.1, 127.9, 127.4, 123.6, 123.1, 121.9, 121.7, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_3$: 396.1348; found 396.1335.



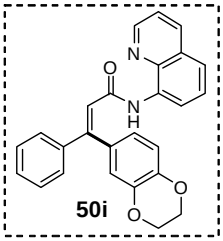
(*Z*)-3-(4-Fluorophenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50g): Compound **50g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; Yield: 40% (37 mg); IR (DCM): 3331, 1713, 1523, 1325, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (br. s, 1H), 8.80 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.63 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.52-7.47 (m, 2H), 7.44-7.35 (m, 8H), 7.09 (t, 2H, J= 8.8 Hz), 6.65 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 163.1 (d, J_{C-F} = 246.2 Hz), 151.3, 147.8, 141.2, 138.3, 136.2, 134.4, 134.3 (d, J_{C-F} = 3.1 Hz), 131.7 (d, J_{C-F} = 8.2 Hz), 129.3, 128.5, 128.3, 127.8, 127.4, 122.9, 121.5, 121.5, 116.5, 115.6 (d, J_{C-F} = 21.3 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}FN_2O$: 369.1403; found 369.1407.



(*Z*)-3-(3-Nitrophenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50h): Compound **50h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour solid; Yield: 60% (59 mg); mp 161-162 ^oC; IR (KBr): 3437, 1673, 1524, 1484, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s, 1H), 8.71 (dd, 1H, J_1 = 6.8 Hz, J_2 = 3.4 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.25-8.23 (m, 2H), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.74 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.59-7.54 (m, 1H), 7.50 (s, 1H), 7.49 (d, 1H, J= 2.3 Hz), 7.47-7.39 (m, 4H), 7.35 (dd, 2H, J_1 = 7.9 Hz, J_2 = 1.5 Hz), 6.78 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.3, 150.7, 148.2, 148.0, 140.5, 140.1, 138.3, 136.4, 135.8, 134.2, 129.8, 129.2, 128.8, 128.2, 127.9, 127.4, 124.5, 123.2, 121.8, 121.7, 116.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_3$: 396.1348; found 396.1350.

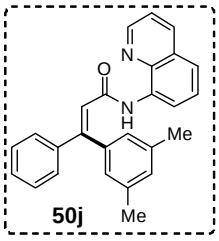


(*Z*)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50i):



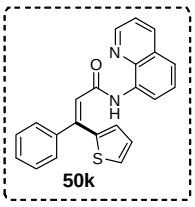
Compound **50i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 70% (71 mg); mp 117-119 ^{o}C; IR (KBr): 3411, 1714, 1420, 1270, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (br. s, 1H), 8.83 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52 (t, 1H, J= 7.8 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.41-7.36 (m, 6H), 6.93-6.90 (m, 3H), 6.57 (s, 1H), 4.21-4.15 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 151.5, 147.7, 144.2, 143.6, 141.5, 138.4, 136.1, 134.7, 131.4, 129.1, 128.4, 128.4, 127.8, 127.4, 123.3, 122.6, 121.4, 121.3, 118.9, 117.4, 116.4, 64.4, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_3$: 409.1552; found 409.1533.

(*Z*)-3-(3,5-Dimethylphenyl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (50j): Compound **50j**



was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a green colour solid; Yield: 59% (56 mg); mp 198-200 ^{o}C; IR (KBr): 3410, 1713, 1363, 1222, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.51 (t, 1H, J= 8.1 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.41-7.37 (m, 6H), 7.01 (br. s, 2H), 6.99 (br. s, 1H), 6.62 (s, 1H), 2.26 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.9, 152.1, 147.6, 141.4, 138.5, 138.1, 138.1, 136.0, 134.7, 130.2, 129.0, 128.4, 128.3, 127.8, 127.4, 127.3, 122.8, 121.4, 121.3, 116.4, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found 379.1803.

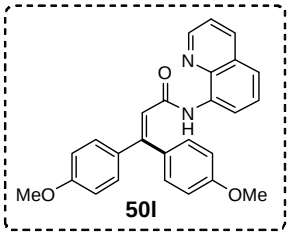
(*Z*)-3-Phenyl-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)acrylamide (50k): Compound **50k** was



obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a green colour liquid; Yield: 81% (72 mg); IR (DCM): 3343, 1522, 1483, 1160, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.1 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54 (t, 1H, J= 7.6 Hz), 7.51-7.38 (m, 8H), 7.27 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.2 Hz), 7.03 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 6.53 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.4, 147.9, 144.5, 141.8, 139.1, 138.4, 136.2, 134.6, 130.6, 129.3, 128.5, 128.4, 128.3, 127.9, 127.4, 127.1, 123.6,

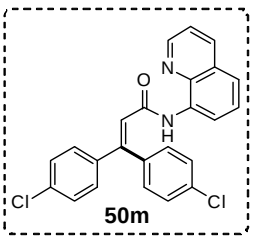
121.5, 121.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2OS$: 357.1062; found 357.1053.

3,3-Bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (50l): Compound **50l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 61% (63 mg); mp 153-155 ^oC; IR (KBr): 3316, 1603, 1522, 1484, 1385, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.79 (br. s, 1H), 8.82 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.50 (t, 1H, *J*= 8.1 Hz), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.32 (d, 2H, *J*= 8.8 Hz), 7.30 (d, 2H, *J*= 8.8 Hz), 6.92 (d, 2H, *J*= 8.8 Hz), 6.90 (d, 2H, *J*= 8.8 Hz), 6.52 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 160.5, 160.1, 151.7, 147.6, 138.4, 136.1, 134.8, 134.2, 131.4, 130.6, 129.9, 127.8, 127.4, 121.4, 121.1, 120.5, 116.3, 113.9, 113.7, 55.4, 55.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3$: 411.1709; found 411.1728.



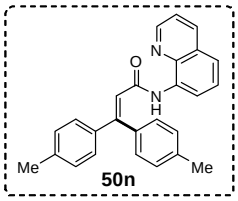
50l

3,3-Bis(4-chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (50m): Compound **50m** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 51% (54 mg); mp 156-158 ^oC; IR (KBr): 3331, 1657, 1524, 1486, 1091, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (br. s, 1H), 8.77 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.54-7.49 (m, 2H), 7.43 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.40-7.35 (m, 4H), 7.32-7.27 (m, 4H), 6.63 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9, 149.9, 147.9, 139.4, 138.3, 136.4, 136.2, 135.5, 134.9, 134.3, 131.1, 129.6, 128.9, 128.8, 127.8, 127.4, 123.2, 121.7, 121.6, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O$: 419.0718; found 419.0720.



50m

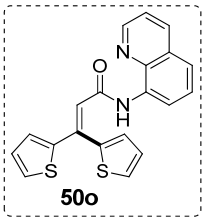
***N*-(Quinolin-8-yl)-3,3-di-*p*-tolylacrylamide (50n):** Compound **50n** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 55% (52 mg); mp 175-177 ^oC; IR (KBr): 2923, 1656, 1521, 1484, 1326, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.1 Hz), 8.57 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.50 (t, 1H, *J*= 8.2 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.39 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2



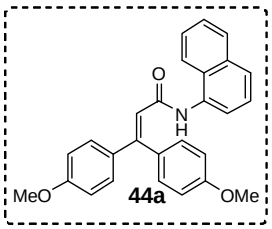
50n

Hz), 7.28 (d, 2H, *J*= 8.0 Hz), 7.27 (d, 2H, *J*= 8.0 Hz), 7.19 (d, 2H, *J*= 8.0 Hz), 7.18 (d, 2H, *J*= 8.0 Hz), 6.59 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 152.4, 147.5, 139.2, 138.8, 138.4, 138.3, 136.1, 135.5, 134.7, 129.8, 129.1, 129.1, 128.3, 127.8, 127.4, 121.6, 121.3, 121.2, 116.4, 21.4, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found 379.1801.

***N*-(Quinolin-8-yl)-3,3-di(thiophen-2-yl)acrylamide (50o):** Compound **50o** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow colour liquid; Yield: 55% (50 mg); IR (DCM): 3339, 1523, 1423, 1326, 1133, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-7.49 (m, 2H), 7.46 (dd, 1H, J_1 = 5.2 Hz, J_2 = 4.4 Hz), 7.43-7.40 (m, 2H), 7.33 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.2 Hz), 7.13 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.2 Hz), 7.10 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 7.06 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.7 Hz), 6.71 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 147.8, 145.1, 138.4, 137.7, 137.4, 136.2, 134.6, 129.7, 129.2, 127.9, 127.8, 127.8, 127.4, 127.1, 122.0, 121.5, 121.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}N_2OS_2$: 363.0626; found 363.0620.

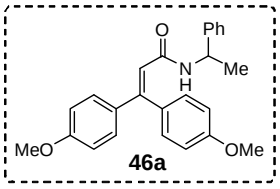


3,3-Bis(4-methoxyphenyl)-*N*-(naphthalen-1-yl)acrylamide (44a): Compound **44a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 49% (50 mg); IR (DCM): 3441, 1748, 1420, 1363, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 1H, *J*= 7.4 Hz), 7.80 (d, 1H, *J*= 8.2 Hz), 7.70 (br. s, 1H), 7.61 (d, 1H, *J*= 8.1 Hz), 7.47-7.39 (m, 4H), 7.30-7.24 (m, 3H), 7.02 (d, 2H, *J*= 8.4 Hz), 6.90 (d, 2H, *J*= 8.6 Hz), 6.65 (d, 1H, *J*= 8.4 Hz), 6.54 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 160.6, 149.6, 133.9, 133.6, 132.4, 131.4, 130.4, 129.7, 128.6, 125.9, 125.7, 125.5, 124.7, 121.3, 120.0, 118.8, 114.7, 113.8, 55.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}NO_3$: 410.1756; found 410.1749.



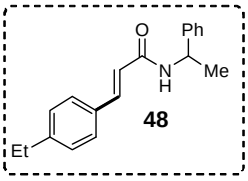
3,3-Bis(4-methoxyphenyl)-*N*-(1-phenylethyl)acrylamide (46a): Compound **46a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 52% (50 mg); mp 130-132 ^{o}C; IR (KBr): 3415, 1713, 1511, 1248, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 3H), 7.21 (d, 2H, *J*= 8.8 Hz),

7.18 (d, 2H, *J*= 8.7 Hz), 7.03 (dd, 2H, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 6.89 (d, 2H, *J*= 8.7 Hz), 6.84 (d, 2H, *J*= 8.8 Hz), 6.31 (s, 1H), 5.53 (d, 1H, *J*= 7.9 Hz), 5.04 (q, 1H, *J*= 6.8 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 1.26 (d, 3H, *J*= 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 160.3, 159.9, 148.8, 143.0, 133.4, 130.8, 130.6, 129.4, 128.5, 127.2, 126.1, 120.8, 114.1, 113.7, 55.3, 55.3, 48.6, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}NO_3$: 388.1913; found 388.1913.



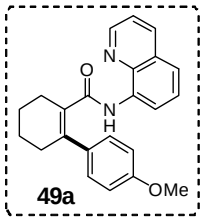
46a

(*E*)-3-(4-Ethylphenyl)-*N*-(1-phenylethyl)acrylamide (48): Compound **48** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 72% (50 mg); mp 117-119 ^oC; IR (KBr): 3292, 1619, 1542, 1224, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 1H, *J*= 15.6 Hz), 7.41 (d, 2H, *J*= 8.1 Hz), 7.39-7.33 (m, 3H), 7.30-7.26 (m, 2H), 7.18 (d, 2H, *J*= 8.1 Hz), 6.45 (d, 1H, *J*= 15.6 Hz), 6.34 (d, 1H, *J*= 7.8 Hz), 5.32-5.28 (m, 1H), 2.66 (q, 2H, *J*= 7.6 Hz), 1.57 (d, 3H, *J*= 6.9 Hz), 1.26 (t, 3H, *J*= 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 146.2, 143.3, 141.2, 132.3, 128.7, 128.3, 127.9, 127.4, 126.3, 119.8, 48.9, 28.8, 21.8, 15.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}NO$: 280.1701; found 280.1696.



48

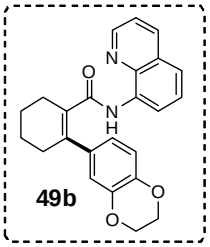
4'-Methoxy-*N*-(quinolin-8-yl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxamide (49a): Compound **49a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid; Yield: 40% (36 mg); IR (DCM): 3344, 1520, 1483, 1248, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.40 (br. s, 1H), 8.72 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.9 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.05 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.48 (t, 1H, *J*= 8.1 Hz), 7.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.9 Hz), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, *J*= 8.6 Hz), 6.70 (d, 2H, *J*= 8.6 Hz), 3.57 (s, 3H), 2.64-2.63 (m, 2H), 2.50-2.48 (m, 2H), 1.84-1.80 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 159.0, 147.5, 140.2, 138.4, 135.9, 134.7, 132.6, 128.8, 127.7, 127.3, 121.2, 121.0, 116.0, 113.7, 55.1, 32.0, 27.2, 22.8, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_2$: 359.1760; found 359.1762.



49a

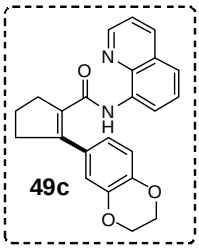
2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)cyclohex-1-enecarboxamide (49b): Compound **49b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 53% (51 mg); mp 131-133

^{o}C; IR (KBr): 3334, 1661, 1523, 1423, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (br. s, 1H), 8.72 (d, 1H, *J*= 7.5 Hz), 8.62 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.07 (d, 1H, *J*= 8.2 Hz),



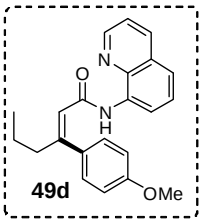
7.49 (t, 1H, *J*= 8.0 Hz), 7.41 (d, 1H, *J*= 8.1 Hz), 7.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.1 Hz), 6.91 (d, 1H, *J*= 1.8 Hz), 6.81 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 6.61 (d, 1H, *J*= 8.3 Hz), 4.06-4.00 (m, 4H), 2.62-2.60 (m, 2H), 2.48-2.46 (m, 2H), 1.85-1.79 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.7, 147.5, 143.4, 142.9, 140.2, 138.5, 136.0, 135.3, 134.8, 132.8, 127.7, 127.4, 121.2, 121.0, 121.0, 117.0, 116.5, 116.0, 64.2, 64.1, 32.0, 27.1, 22.8, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.1709; found 387.1705.

2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)cyclopent-1-enecarboxamide (49c): Compound **49c** was obtained after purification by column chromatography on neutral



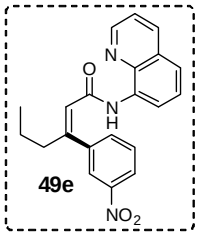
alumina (EtOAc:Hexanes = 25:75) as a colourless semisolid; Yield: 20% (19 mg) ; IR (KBr): 3354, 1667, 1527, 1485, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s, 1H), 8.83 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 8.54 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.53 (t, 1H, *J*= 8.1 Hz), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.37 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.97-6.94 (m, 2H), 6.83 (d, 1H, *J*= 8.8 Hz), 4.22-4.19 (m, 2H), 4.18-4.14 (m, 2H), 3.06-3.01 (m, 2H), 2.95-2.90 (m, 2H), 2.11-2.04 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 147.5, 147.3, 143.7, 143.5, 138.5, 136.0, 134.8, 133.5, 129.9, 127.8, 127.4, 121.3, 121.2, 121.0, 117.4, 117.0, 116.2, 64.4, 64.2, 40.3, 35.6, 21.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_3$: 373.1552; found 373.1548.

(*Z*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)hex-2-enamide (49d): Compound **49d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes =

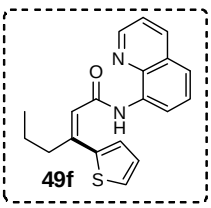


20:80) as a brown colour solid; Yield: 51% (44 mg); mp 93-95 ^{o}C; IR (KBr): 3343, 1606, 1523, 1484, 1380, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (br. s, 1H), 8.77 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.53 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.48 (t, 1H, *J*= 8.1 Hz), 7.43 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.37 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, *J*= 8.7 Hz), 6.89 (d, 2H, *J*= 8.7 Hz), 6.14 (s, 1H), 3.75 (s, 3H), 2.52 (dt, 2H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 1.51-1.45 (m, 2H), 0.97 (t, 3H, *J*= 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.2, 159.6, 153.7, 147.5, 138.4, 136.0, 134.7, 131.3, 129.2, 127.7, 127.4, 122.3, 121.3, 121.0, 116.2, 114.0, 55.2, 42.4, 20.8, 13.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_2$: 347.1760; found 347.1773.

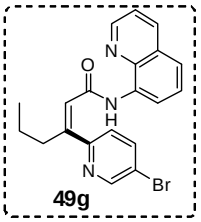
(*Z*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)hex-2-enamide (49e): Compound **49e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 52% (47 mg); mp 176-178 ^{o}C; IR (KBr): 3342, 1677, 1524, 1484, 1348, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (br. s, 1H), 8.67-8.63 (m, 2H), 8.23 (br. s, 1H), 8.18-8.11 (m, 2H), 7.63 (d, 1H, *J*= 7.6 Hz), 7.52-7.46 (m, 3H), 7.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.30 (s, 1H), 2.56 (t, 2H, *J*= 7.5 Hz), 1.56-1.47 (m, 2H), 1.01 (t, 3H, *J*= 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.6, 152.7, 148.2, 147.9, 141.6, 138.2, 136.3, 134.2, 134.2, 129.2, 127.8, 127.3, 123.2, 122.7, 122.4, 121.6, 116.5, 42.1, 20.6, 13.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_3$: 362.1505; found 362.1514.



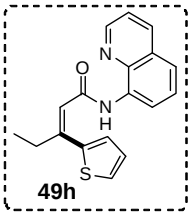
(*Z*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)hex-2-enamide (49f): Compound **49f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid; Yield: 57% (46 mg); IR (DCM): 2923, 1663, 1523, 1483, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 8.65 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.53 (t, 1H, *J*= 8.2 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.33 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 7.26 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.1 Hz), 6.96 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 6.18 (s, 1H), 2.57 (dt, 2H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 1.64-1.54 (m, 2H), 1.0 (t, 3H, *J*= 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.0, 147.8, 144.9, 139.8, 138.4, 136.1, 134.6, 127.9, 127.8, 127.4, 127.2, 126.7, 122.9, 121.4, 121.3, 116.4, 42.9, 21.4, 13.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2OS$: 323.1218; found 323.1206.



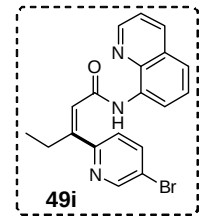
(*Z*)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)hex-2-enamide (49g): Compound **49g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colour liquid; Yield: 50% (50 mg); IR (DCM): 2922, 1672, 1525, 1485, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (br. s, 1H), 8.76-8.75 (m, 1H), 8.73-8.72 (m, 1H), 8.69 (t, 1H, *J*= 4.5 Hz), 8.13 (d, 1H, *J*= 8.2 Hz), 7.70 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.5 Hz), 7.48-7.47 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27 (d, 1H, *J*= 8.5 Hz), 6.31 (br. s, 1H), 2.63 (t, 2H, *J*= 7.5 Hz), 1.53-1.46 (m, 2H), 0.99 (t, 3H, *J*= 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1, 156.6, 152.7, 150.4, 148.0, 138.6, 138.3, 136.3, 134.4, 127.9, 127.3, 125.1, 123.3, 121.6, 121.6, 119.7, 116.7, 40.3, 20.7, 13.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{18}BrN_3NaO$: 418.0531; found 418.0539.



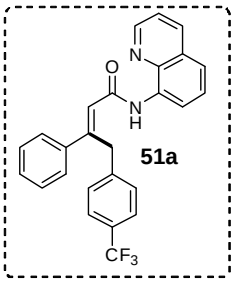
(*Z*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)pent-2-enamide (49h): Compound **49h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown colour liquid; Yield: 80% (62 mg); IR (DCM): 3347, 1664, 1522, 1483, 1262, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.86 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53 (t, 1H, J= 8.2 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.32 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 7.27 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.1 Hz), 6.96 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 6.18 (t, 1H, J= 1.2 Hz), 2.62 (dq, 2H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 1.21 (t, 3H, J= 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 147.8, 146.2, 139.9, 138.4, 136.1, 134.6, 127.8, 127.8, 127.4, 127.2, 126.6, 121.8, 121.5, 121.4, 116.4, 33.7, 12.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2OS$: 309.1062; found 309.1058.



(*Z*)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)pent-2-enamide (49i): Compound **49i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid; Yield: 63% (60 mg); IR (DCM): 3339, 1677, 1524, 1325, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (br. s, 1H), 8.75-8.73 (m, 2H), 8.69 (t, 1H, J= 4.6 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.71 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.49 (s, 1H), 7.48 (dd, 1H, J_1 = 4.9 Hz, J_2 = 0.8 Hz), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.26 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.4 Hz), 6.30 (t, 1H, J= 1.4 Hz), 2.67 (dq, 2H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 1.16 (t, 3H, J= 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 156.8, 154.0, 150.4, 148.0, 138.6, 138.2, 136.3, 134.4, 127.9, 127.3, 124.9, 122.3, 121.6, 121.6, 119.7, 116.7, 31.2, 12.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{17}BrN_3O$: 382.0555; found 382.0560.

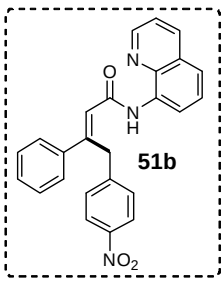


(*E*)-3-Phenyl-*N*-(quinolin-8-yl)-4-(4-(trifluoromethyl)phenyl)but-2-enamide (51a): Compound **51a** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a colourless liquid; Yield: 79% (85 mg); IR (DCM): 3057, 1713, 1524, 1424, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.09 (br. s, 1H), 8.92 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.22 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60-7.53 (m, 2H), 7.51-7.43 (m, 7H), 7.40-7.36 (m, 3H), 6.61 (s, 1H), 4.77 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 154.0, 148.2, 143.3, 140.9, 138.4, 136.5, 134.6, 129.2, 129.0, 128.4 (q, J_{C-F} = 32.0 Hz), 128.0, 127.5,

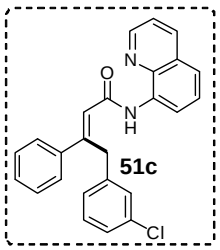


126.9, 125.3 (q, J_{C-F} = 3.6 Hz), 124.4 (q, J_{C-F} = 270.3 Hz), 122.5, 121.8, 121.7, 116.6, 36.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}F_3N_2O$: 433.1528; found 433.1546.

(*E*)-4-(4-Nitrophenyl)-3-phenyl-*N*-(quinolin-8-yl)but-2-enamide (51b): Compound **51b** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a pale yellow colour liquid; Yield: 54% (55 mg); IR (KBr): 3345, 1670, 1522, 1343, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.09 (br. s, 1H), 8.88 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.08 (d, 2H, *J*= 8.8 Hz), 7.58-7.57 (m, 2H), 7.51-7.46 (m, 5H), 7.39-7.37 (m, 3H), 6.62 (s, 1H), 4.81 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 153.5, 148.2, 147.1, 146.4, 140.6, 138.4, 136.5, 134.5, 129.6, 129.2, 128.8, 128.0, 127.4, 126.9, 123.6, 122.8, 121.9, 121.8, 116.7, 36.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}N_3O_3$: 410.1505; found 410.1487.



(*E*)-4-(3-Chlorophenyl)-3-phenyl-*N*-(quinolin-8-yl)but-2-enamide (51c): Compound **51c** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 25:75) as a pale yellow colour liquid; Yield: 56% (56 mg); IR (DCM): 3412, 1713, 1363, 1222, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (br. s, 1H), 8.92 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60-7.53 (m, 2H), 7.50-7.47 (m, 3H), 7.41-7.36 (m, 3H), 7.33-7.31 (m, 1H), 7.20-7.11 (m, 3H), 6.59 (s, 1H), 4.69 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 154.1, 148.2, 141.1, 141.0, 138.4, 136.4, 134.7, 129.6, 128.9, 128.8, 128.6, 128.0, 127.5, 127.0, 126.9, 126.2, 122.5, 121.7, 116.6, 35.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$: 399.1264; found 399.1275.



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Chapter 4. **Regio- and stereoselective Pd(II)-catalyzed picolinamide-directed Z selective γ-C-H arylation of allylamine systems and construction of cinnamylamines.**

Introduction

Allylamine derivatives are important class of nitrogen containing compounds and in medicinally chemistry research and pharmaceuticals and in particular, various *γ*-arylated allylamine derivatives (cinnamylamines) were found to exhibit a wide range of biological activities, e.g., naftifine (**1a**), flunarizine (**1b**), flunarizine (**1b**), cinnarizine (**1c**) and CP-724,714 (**1e**) (Figure 1).[1,2] Various methods were developed for the synthesis of allylamine derivatives including cinnamylamines (*γ*-arylated allylamine derivatives). Especially, the Mizoroki-Heck-type reaction was well exploited for the synthesis of cinnamylamines (*γ*-arylated allylamine derivatives). The Mizoroki-Heck-type reaction usually afforded the corresponding cinnamylamines (*γ*-arylated allylamine derivatives) having the *E* geometry as the major isomer and accordingly, the synthesis of *Z* cinnamylamines (*γ*-arylated allylamine derivatives) as the major isomers is not well explored.[3] Additionally, a literature survey revealed that some of the Mizoroki-Heck-type arylations of simple allylamines afforded both the regioisomers, such as *γ*- and *β*-arylated allylamines.

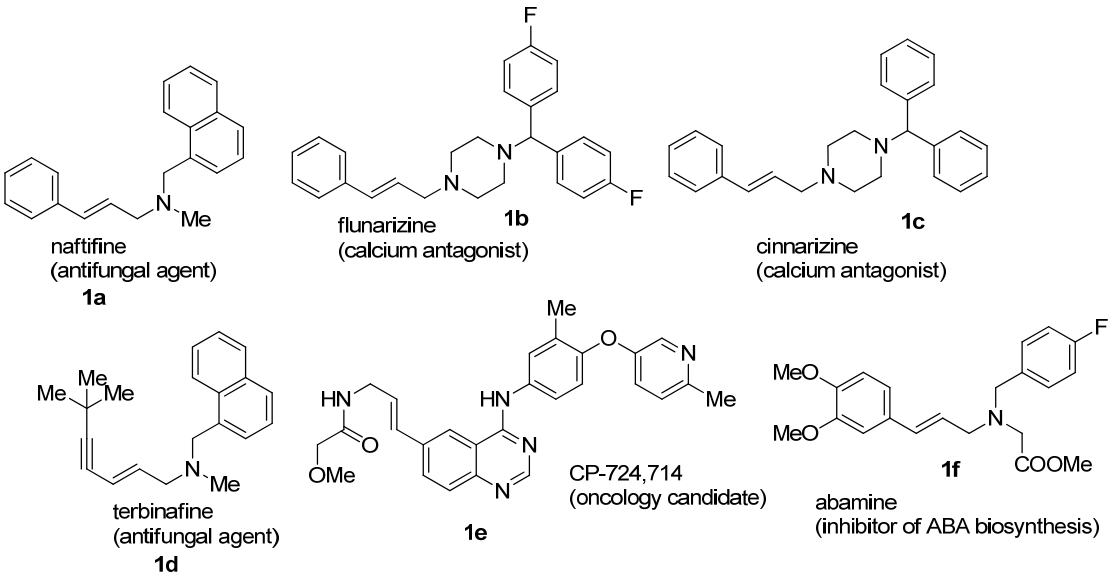
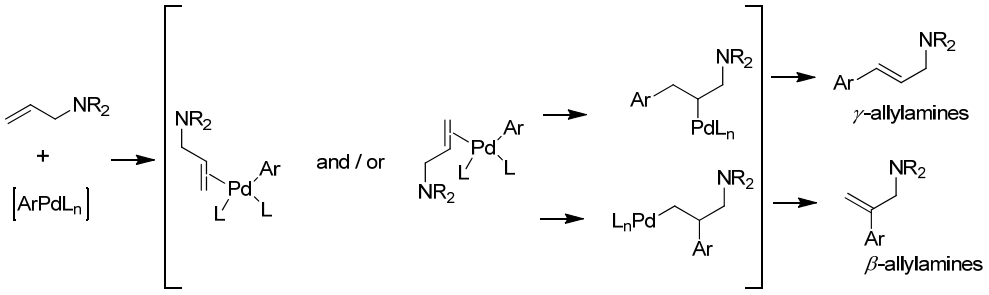


Figure 1. Representative examples of bio-acive allylamines/cinnamylamines (*γ*-arylated allylamine derivatives).

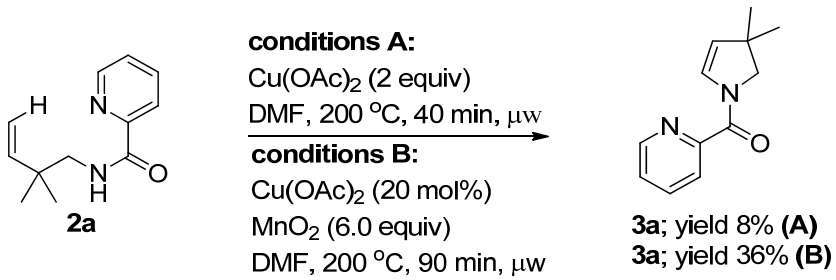
In the following section reveal some of the representative reports dealing with the stereoselective arylation of allylamine systems affording of *γ*- and *β*-arylated allylamines are described.



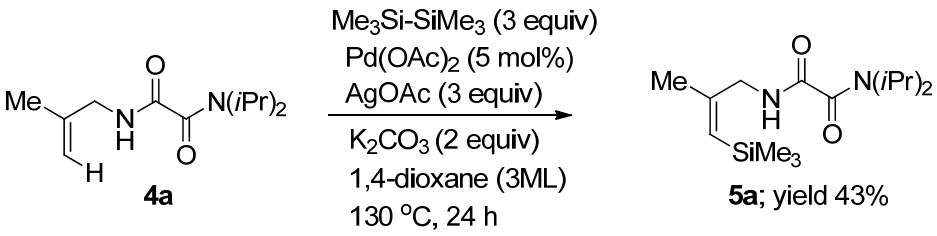
Scheme 2. The Mizoroki-Heck reaction and the formation of γ- and β-arylated allylamines.

Representative reports dealing with the stereoselective arylation of allylamine systems affording of γ- and β-arylated allylamines.

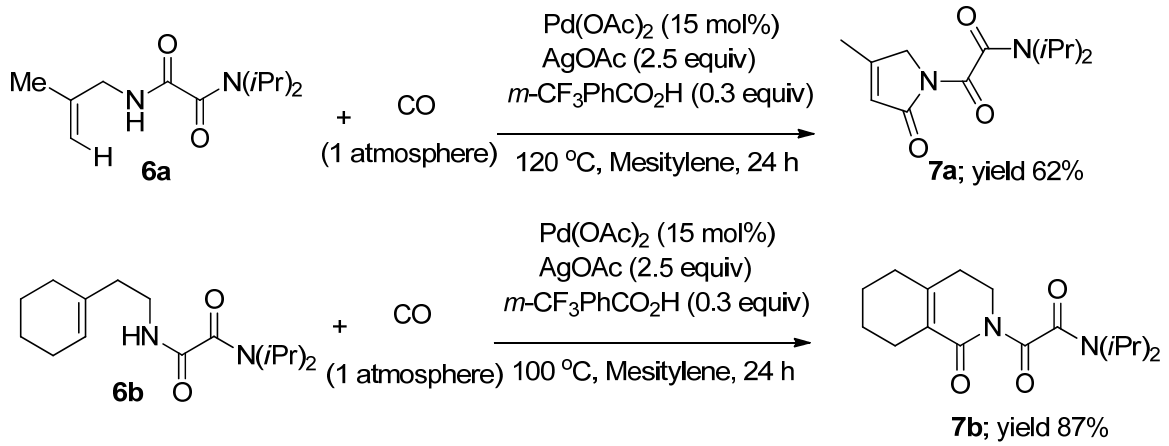
Miura and co-workers [4a] reported the Cu-catalyzed C-H amination of allylamine sytem **2a** in the presence of $Cu(OAc)_2$, MnO_2, in DMF, which afforded the dihydropyrrole **3a** in a moderate yield (Scheme 3). Zhao and co-workers[4b] reported the Pd-catalyzed silylation of allylamine substrate **4a** with $Me_3Si\text{-}SiMe_3$ (3 equiv) in the presence of $Pd(OAc)_2$ (5 mol%), AgOAc (3 equiv), K_2CO_3 (2 equiv) in 1,4-dioxane at 130 ^oC, which afforded the γ-silylated product **5a** (Scheme 4). Zhao group [4c] reported the Pd(II)-catalyzed regioselective γ-carbonylation of oxalylamide protected allylamine **6a** and **6b** under carbon monoxide atm, which afforded the products **7a** and **7b** (Scheme 5).



Scheme 3. Copper-catalyzed intramolecular C-H amination of **2a**.

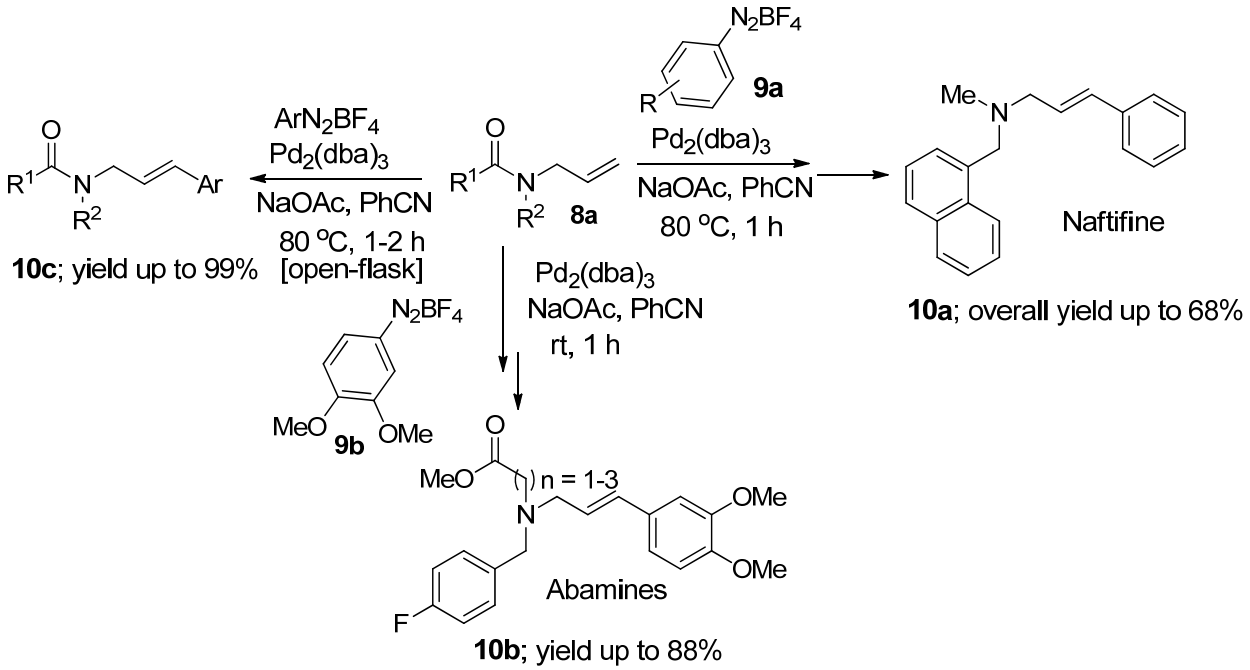


Scheme 4. Pd(II)-catalyzed silylation of allylamine substrate **4a**.

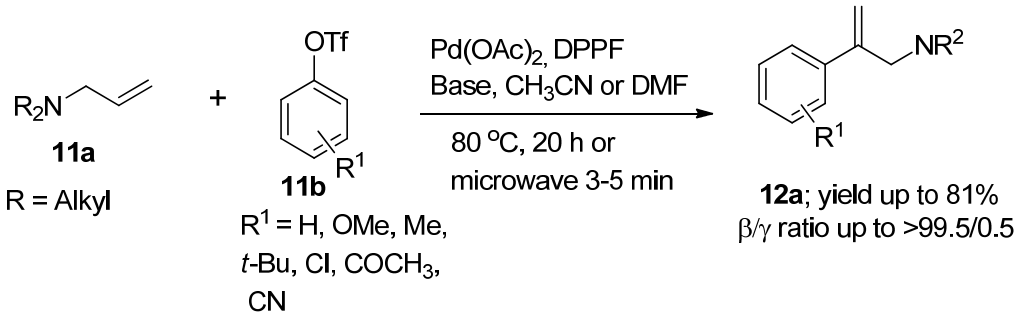


Scheme 5. Pd(II)-catalyzed carbonylation of γ-C(sp^2)-H bonds of **6a** and **6b**.

Correia and co-workers[4d] reported the Pd(II)-catalyzed Heck-Matsuda reaction of allylamine derivatives **8a** with arenediazonium salts **9a**,**9b**, which served as a simple route for the synthesis of bioactive compounds naftifine **10a**, abamines **10b** (Scheme **6**). Hallberg co-worker[4e] reported the Pd(II)-catalyzed regioselective β-arylation of *N,N*-dialkylallylamines **11a** with aryl triflates **11b**, which afforded **12a** under thermal heating or microwave irradiation (Scheme **7**).

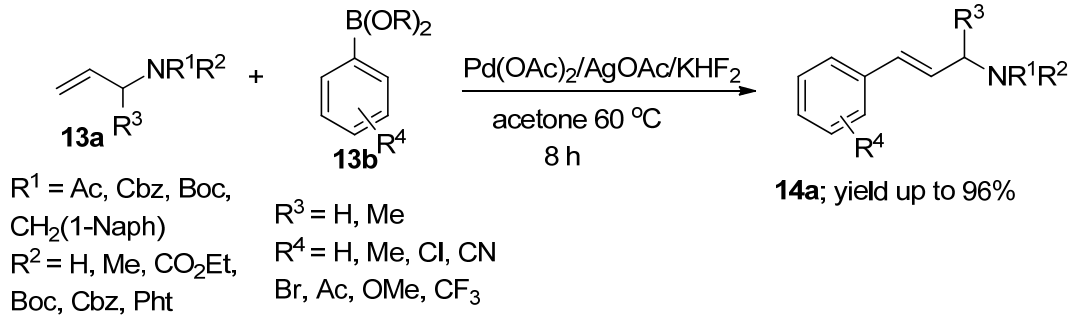


Scheme 6. Arylation of allylamines **8a**: synthesis the biologically active compounds.



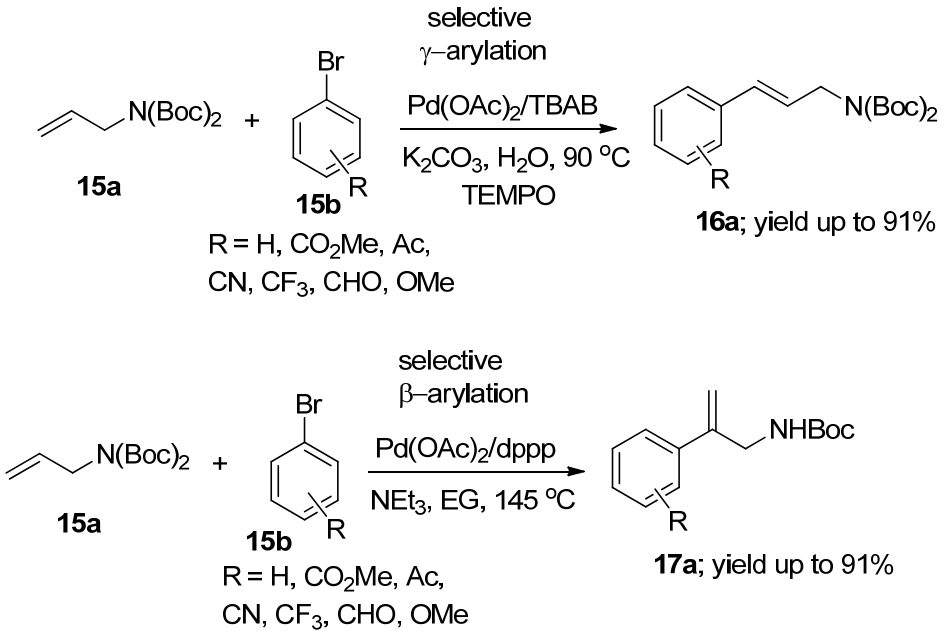
Scheme 7. Pd(II)-catalyzed arylation of allylamine **11a**.

Xu co-workers[4f]reported the oxidative Heck-type reactions of both *N*-protected and *N,N*-diprotected allylic amine derivatives **13a** using arylboronic acids **13b** in the presence of $Pd(OAc)_2$, AgOAc and KHF_2, which afforded γ-C-H arylated allylicamines **14a** (Scheme 8). Xu co-workers[4g] reported the Pd(II)-catalyzed Heck cross-coupling reaction of aryl bromides with electron-rich allylamines **15a**, which afforded the γ-C-H arylated allylamines **16a** and β-arylated allylamines **17a** (Scheme 9).

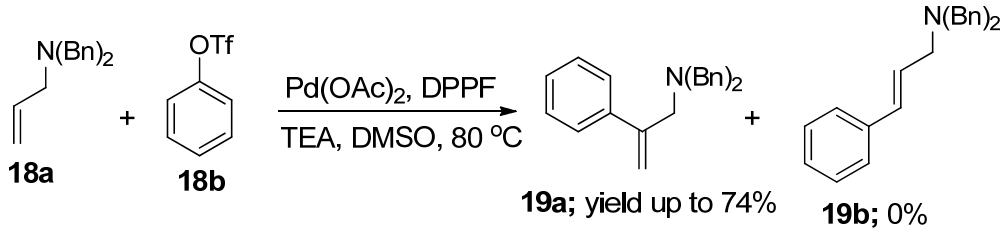


Scheme 8. Oxidative Heck arylation of protected allylic amines **13a** with **13b**.

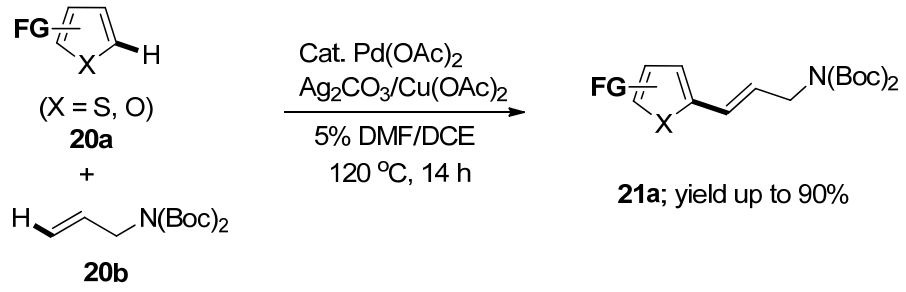
Wu co-workers[4h] reported the Pd(II)-catalyzed intermolecular Heck arylation of *N,N*-disubstituted allylamines **18a** with phenyl triflate **18b** using 4 mol% $Pd(OAc)_2$ and 6 mol% DPPF in DMSO, which afforded the products **19a** in good to excellent yields (Scheme 10). Xu co-workers[4i] reported the direct coupling of hetero arenes **20a** with allylamines **20b** in the presence of catalytic amounts of $Pd(OAc)_2$ and appropriate oxidant, which afforded γ-C-H arylated (*E*)-allylamines **21a** (Scheme 11).



Scheme 9. Regioselective Heck arylation of allylic amines **15a** with aryl bromides **15b**.



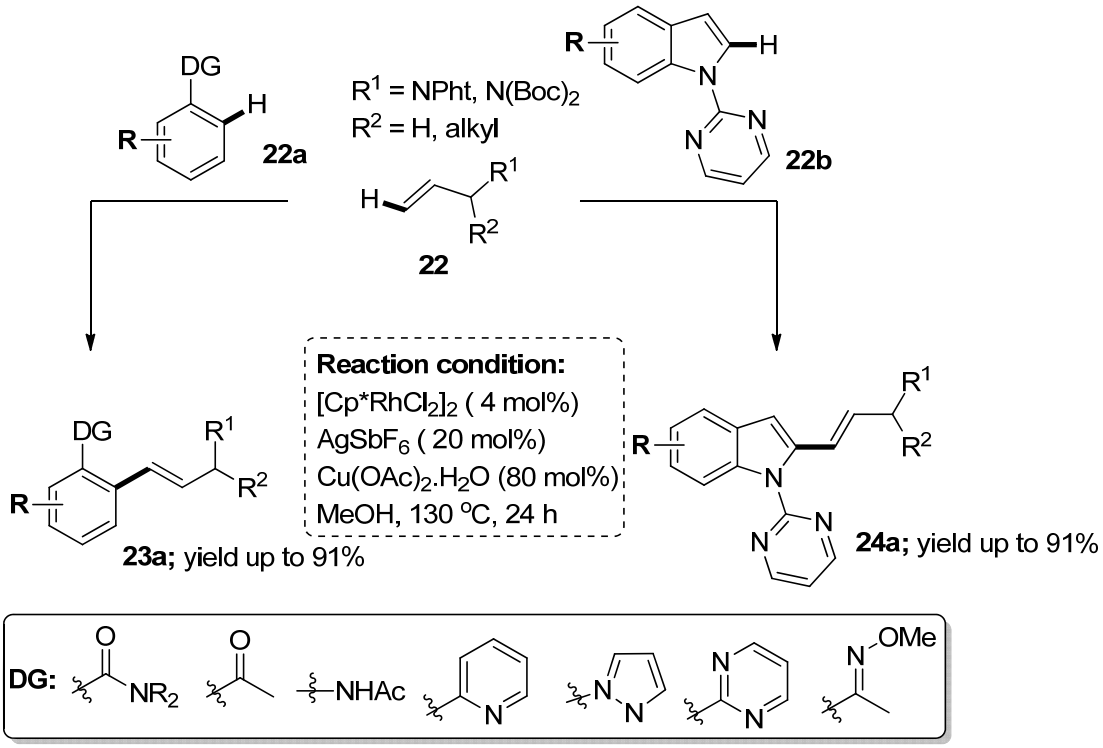
Scheme 10. β-Regioselective Heck arylation of allylic amines of 1**8a.**



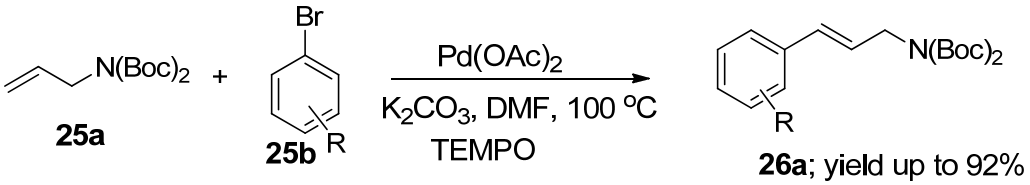
Scheme 11. Regioselective arylation of allylamines **20b** with thiophenes and furans **20a**.

Zhang and Xu's group[5a] reported the coupling of arenes **22a, 22b** with aliphatic olefins **22**in the presence of $[Cp^*RhCl_2]_2$ (4 mol%), $Cu(OAc)_2 \cdot H_2O$ (80 mol%) and $AgSbF_6$ (20m

mol%), which afforded *E*-allylamine products **23a, 24a** (scheme 12). Xiao group[5b] reported the palladium-catalyzed regioselective and stereoselective arylation of electron-rich allylamines **25a** with aryl bromides **25b**in the presence of $Pd(OAc)_2$ and K_2CO_3 DMF solvent at 100 ^oC, which afforded (*E*)-allylamine product **26a** (Scheme 13).



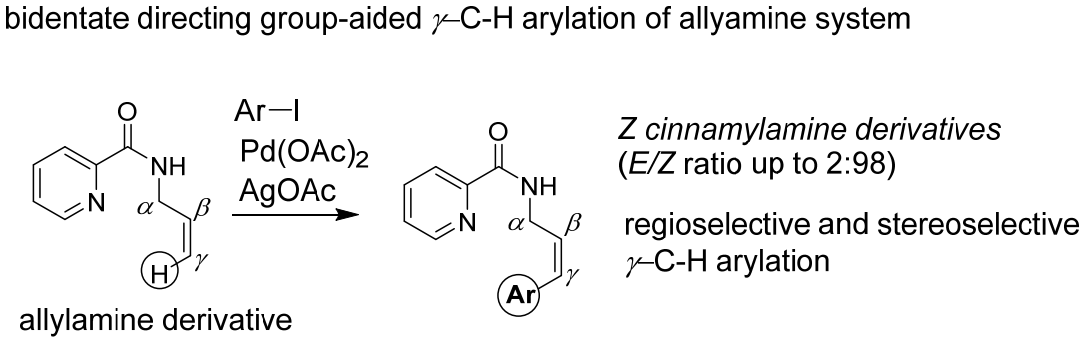
Scheme 12. Rhodium(III)-catalyzed direct C-H olefination of arenes **22a, 22b.**



Scheme 13. palladium-catalyzed of allylic amines **25a** with aryl bromides **25b**.

Given the importance of *γ*-arylated allylamine derivatives (cinnamylamines) in organic synthesis and medicinal chemistry research area, developing new methods for synthesizing new *γ*-arylated allylamine derivatives (cinnamylamines) will enrich the library of cinnamamide scaffolds. A literature survey revealed that there exist only limited reports dealing on the synthesis of *Z* cinnamylamines (*γ*-arylated allylamine derivatives). Accordingly, a part of this thesis reports the synthesis of new *γ*-arylated allylamine

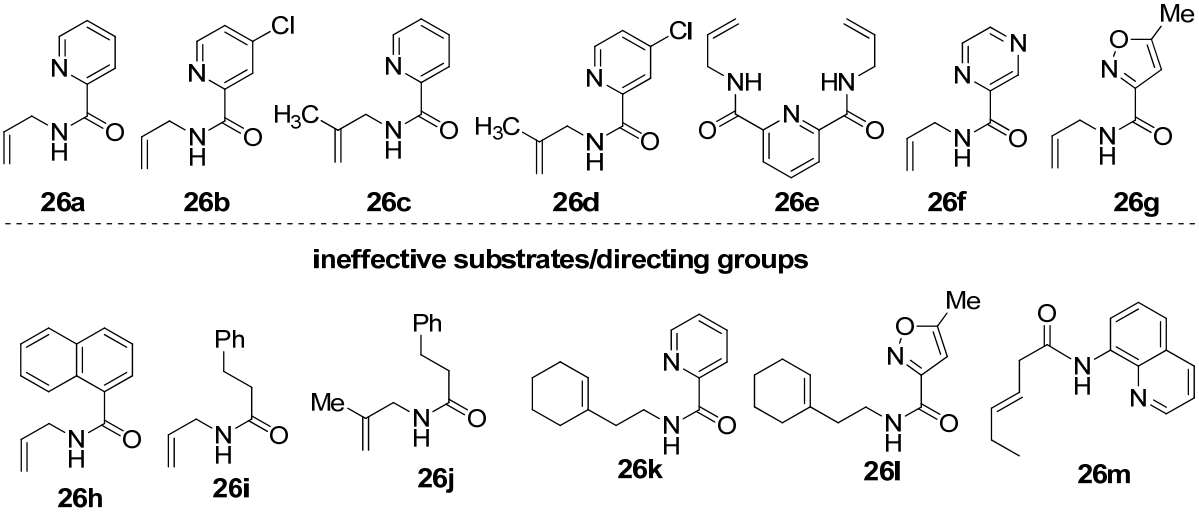
derivatives, especially, *Z* cinnamylamines via the $Pd(OAc)_2$-catalyzed, AgOAc-promoted γ-arylation of allylamine derivatives using aryl iodides as the coupling partners.



Scheme 14. Topic of this work. Z selective γ-C-H arylation of allylamine systems.

Results and Discussion

To begin with the synthesis of *Z* cinnamylamines (γ-arylated allylamine derivatives), initially, the *N*-allylcarboxamide substrates **26a-m** were assembled from their corresponding allylamine systems and directing groups/carboxylic acid derivatives using the standard literature procedures (Scheme 15).

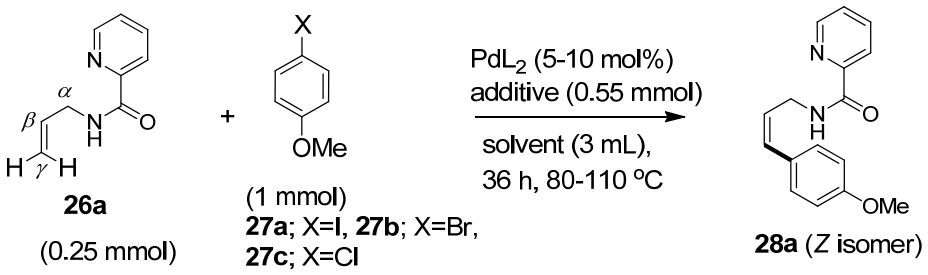


Scheme 15. Directing groups and substrates employed for investigating the γ-C(sp^2)-H arylation (Conditions: Substrate (0.25 mmol), **27a** or ArI (1 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.55 mmol), toluene (3 mL), 24h, and 110 °C (the arylations reactions using **26a-g** were successful as discussed in the results and discussion part and the arylations with **26h-m** were not successful).

Then, it was envisaged to find out the best reaction conditions for performing the synthesis of *Z* cinnamylamine (*γ*-arylated allylamine derivative) using *N*-allylpicolinamide system **26a**. Table 1 shows the optimization of the reaction of picolinamide-directed *γ*-C(sp^2)-H arylation of *N*-allylpicolinamide system **26a** with aryl halides **27a-c**. The C-H arylation reaction of *N*-allylpicolinamide system **26a** (1 equiv) with 1-iodo-4-methoxybenzene (**27a**, 4 equiv) in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (additive, 2.2 equiv) in toluene at 110 ^oC found to be the best reaction conditions, which afforded the *γ*-C(sp^2)-H arylated allylamine derivatives **28a′/28a** (*E/Z* isomers) in 64% yield with an *E/Z* ratio of 11:89 (entry 2, Table 1).

Then, we wished to check whether the yield and *E/Z* ratio of **28a′/28a** can be further improved using various palladium catalysts, additives and solvents. The Pd(II)-catalyzed *γ*-C(sp^2)-H arylation of **26a** with **27a** in the presence of Ag_2CO_3 as an additive instead of AgOAc afforded the *γ*-C(sp^2)-H arylated cinnamalyamine derivatives **28a′/27a** (*E/Z* isomers) in only 36% yield with a *E/Z* ratio of 8:92 (entry 3, Table 1). The Pd(II)-catalyzed *γ*-C(sp^2)-H arylation of **26a** with **27a** in the presence of $PhI(OAc)_2$ or KOAc as an additive instead of AgOAc failed to afford cinnamalyamine derivatives **28a′/27a** (entries 4 and 5, Table 1). The Pd(II)-catalyzed *γ*-C(sp^2)-H arylation of **26a** with **27a** in the presence of K_2CO_3 as an additive instead of AgOAc afforded the *γ*-C(sp^2)-H arylated cinnamalyamine derivatives **28a′/27a** (*E/Z* isomers) in only 29% yield with a *E/Z* ratio of 70:30 (entry 6, Table 1). Notably, this reaction afforded the *γ*-C-H arylated allylamine derivative **28a′** (*E* cinnamylamine derivative) having the *E* stereochemistry as the major isomer and this result indicated the involvement of a conventional Heck-type reaction mechanism in this reaction. Next, we attempted the *γ*-C(sp^2)-H arylation of **26a** with **27a** using$PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ as the catalysts insteadof $Pd(OAc)_2$. The reaction of **26a** with **27a** in the presence of $PdCl_2$ or $Pd(CH_3CN)_2Cl_2$ (10 mol%) and AgOAc (additive, 2.2 equiv) afforded the *γ*-C(sp^2)-H arylated allylamine derivatives **28a′/27a** in only 31-37% yields with a *E/Z* ratio of 11:89 (entries 7 and 8, Table 1). We also performed the *γ*-C(sp^2)-H arylation of **26a** with **27a** in different solvents, e.g. 1,2-DCE, *t*-BuOH and *t*-AmylOH.The Pd(II)-catalyzed reaction of **26a** with **27a** in 1,2-DCE and *t*-BuOH solvents were not fruitful (entries 9 and 10, Table 1). The Pd(II)-catalyzed reaction of **26a** with **27a** in *t*-AmylOH afforded the *γ*-C(sp^2)-H arylated allylamine derivatives **28a′/27a** in only 37% yields with a *E/Z* ratio of 12:88 (entry 11, Table 1).

Table 1. Optimization of reaction conditions. Pd(II)-catalyzed picolinamide-directed, *Z* selective arylation of allylamine **26a**.



entry	PdL_2 (10 mol%)	additive	solvent	*T* (°C)	**28a**: (%)	yield *E*:*Z* ratio (**28a′**:**28a**)
1[a]	$Pd(OAc)_2$	AgOAc	toluene	110	51	21:79
2	**$Pd(OAc)_2$**	**AgOAc**	**toluene**	**110**	**64**	**11:89**
3	$Pd(OAc)_2$	Ag_2CO_3	toluene	110	36	8:92
4	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	110	0	-
5	$Pd(OAc)_2$	K_2CO_3	toluene	110	29	70:30
6	$Pd(OAc)_2$	KOAc	toluene	110	<5	-
7	$PdCl_2$	AgOAc	toluene	110	37	11:89
8	$Pd(MeCN)_2Cl_2$	AgOAc	toluene	110	31	11:89
9	$Pd(OAc)_2$	AgOAc	1,2-DCE	80	19	21:79
10	$Pd(OAc)_2$	AgOAc	*t*-BuOH	85	18	16:84
11	$Pd(OAc)_2$	AgOAc	*t*-AmlOH	105	37	12:88
12[b]	$Pd(OAc)_2$	AgOAc	toluene	110	69	4:96
13[c]	$Pd(OAc)_2$	AgOAc	toluene	110	48	16:84
14[d]	$Pd(OAc)_2$	AgOAc	toluene	110	25	18:82
15[e]	$Pd(OAc)_2$	AgOAc	toluene	110	0	-

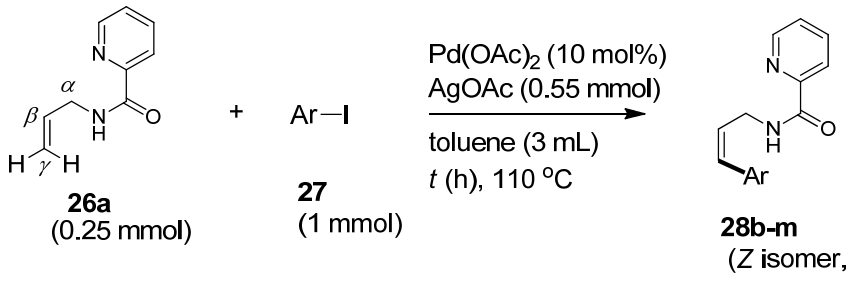
16[f]	$Pd(OAc)_2$	AgOAc	toluene	110	0	-

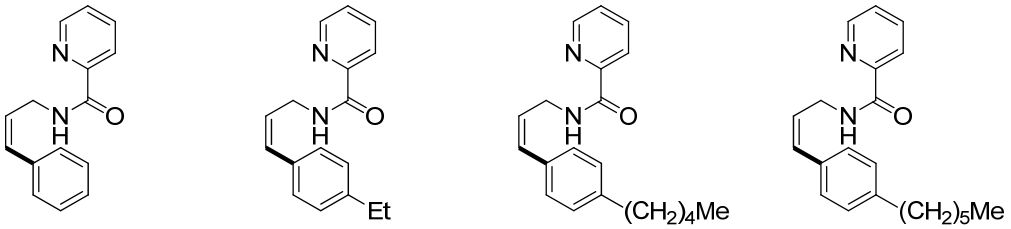
[a] 5 mol% of $Pd(OAc)_2$ was used. [b] 6 Equiv (1.5 mmol) of **27a** was used. [c] 3 Equiv (0.75 mmol) of **27a** was used.[d] 2 Equiv (0.5 mmol) of **6a** was used. [e] The reaction was performed using **27b** instead of **27a**.[f] The reaction was performed using **27c** instead of **27a**. The *E*/*Z* ratios of diastereomers were determined from the NMR spectra of the corresponding crude reaction mixtures.

In order to improve the yield and *E/Z* ratio of **28a′/27a** , we screened the Pd(II)-catalyzed arylation of **26a** using different equiv of **27a**. Accordingly, The Pd(II)-catalyzed C-H arylation reaction of a mixture of **26a** (1 equiv) with 6 equiv of **27a**, afforded the γ-C(sp^2)-H arylated allylamine derivatives **28a′/27a** in better yield (69%) with a *E/Z* ratio of 5:95 (entry 12, Table 1). On the other hand, the Pd(II)-catalyzed C-H arylation reaction of a mixture of **26a** (1 equiv) with 2-3 equiv of **27a**, afforded the γ-C(sp^2)-H arylated allylamine derivatives **28a′/27a** in low yields (25-48%) with slightly decreased *E/Z* ratio (*E/Z* ratio up to 16:84, entries 13 and 14, Table 1). The Pd(II)-catalyzed arylation of **26a** with the coupling partners 1-bromo-4-methoxybenzene (**27b**) and 1-chloro-4-methoxybenzene (**27c**) instead of **27a** did not afford the γ-C(sp^2)-H arylated allylamine derivatives **28a′/27a** (entries 15 and 16, Table 1).

After finding the optimized reaction conditions, it was envisaged to reveal the generality of this Pd(II)-catalyzed picolinamide-directed, *Z* selective arylation of allylamine. Accordingly, the $Pd(OAc)_2$/AgOAc-catalytic system based, picolinamide-directed *Z* selective γ-C(sp^2)-H arylation of allylamine **26a** with a wide range of aryl iodides afforded the cinnamylamine **28b-m** in 40-69% yields with satisfactory to good *E/Z* ratios (*E/Z* up to 2:98, Scheme 16). The Pd(II)-catalyzed γ-C-H arylation of allylamine **26a** was directed by the picolinamide unit and then it was envisaged test the $Pd(OAc)_2$/AgOAc-catalytic system based, *Z* selective γ-C(sp^2)-H arylation of allylamine usingother directing groups. In this regard, it was envisaged to perform the $Pd(OAc)_2$/AgOAc-catalytic system based *Z* selective γ-C(sp^2)-H arylation of **26b** using4-chloropicolinamide unit as the directing group.The $Pd(OAc)_2$/AgOAc-catalytic system based, 4-chloropicolinamide-directed γ-C(sp^2)-H arylation of allylamine **26b** with a wide range of aryl iodides also furnished the cinnamylamine derivatives **29a-n** in 41-63% yields with satisfactory to good *E/Z* ratios (*E/Z* up to 12:88, Scheme 17).

Scheme 16. Picolinamide-directed, construction of *Z* cinnamylamines.



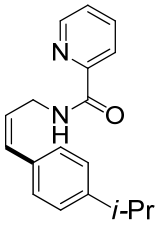


28b; 57%
E:*Z* = 26:74 (36 h)

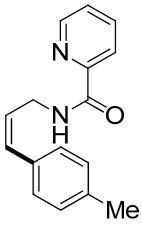
28c; 66%
E:*Z* = 28:72 (36 h)

28d; 69%
E:*Z* = 9:91 (48 h)[b]

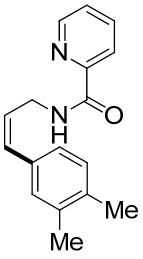
28e; 64%
E:*Z* = 14:86 (48 h)[b]



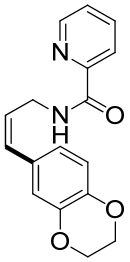
28f; 50%
E:*Z* = 20:80 (36 h)



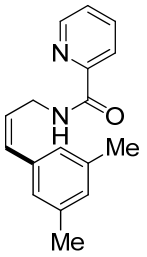
28g' = 11% (*E*)
28g = 71% (*Z*)
E:*Z* = 29:71 (36 h)[c]



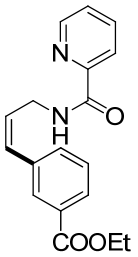
28h; 40%
E:*Z* = 29:71 (36 h)



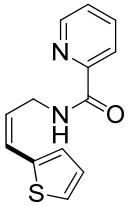
28i; 59%
E:Z = 27:73 (48 h)



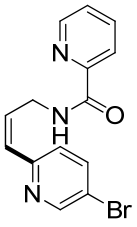
28j; 51%
E:*Z* = 38:62 (48 h)[d]



28k; 54%
E:*Z* = 22:78 (36 h)



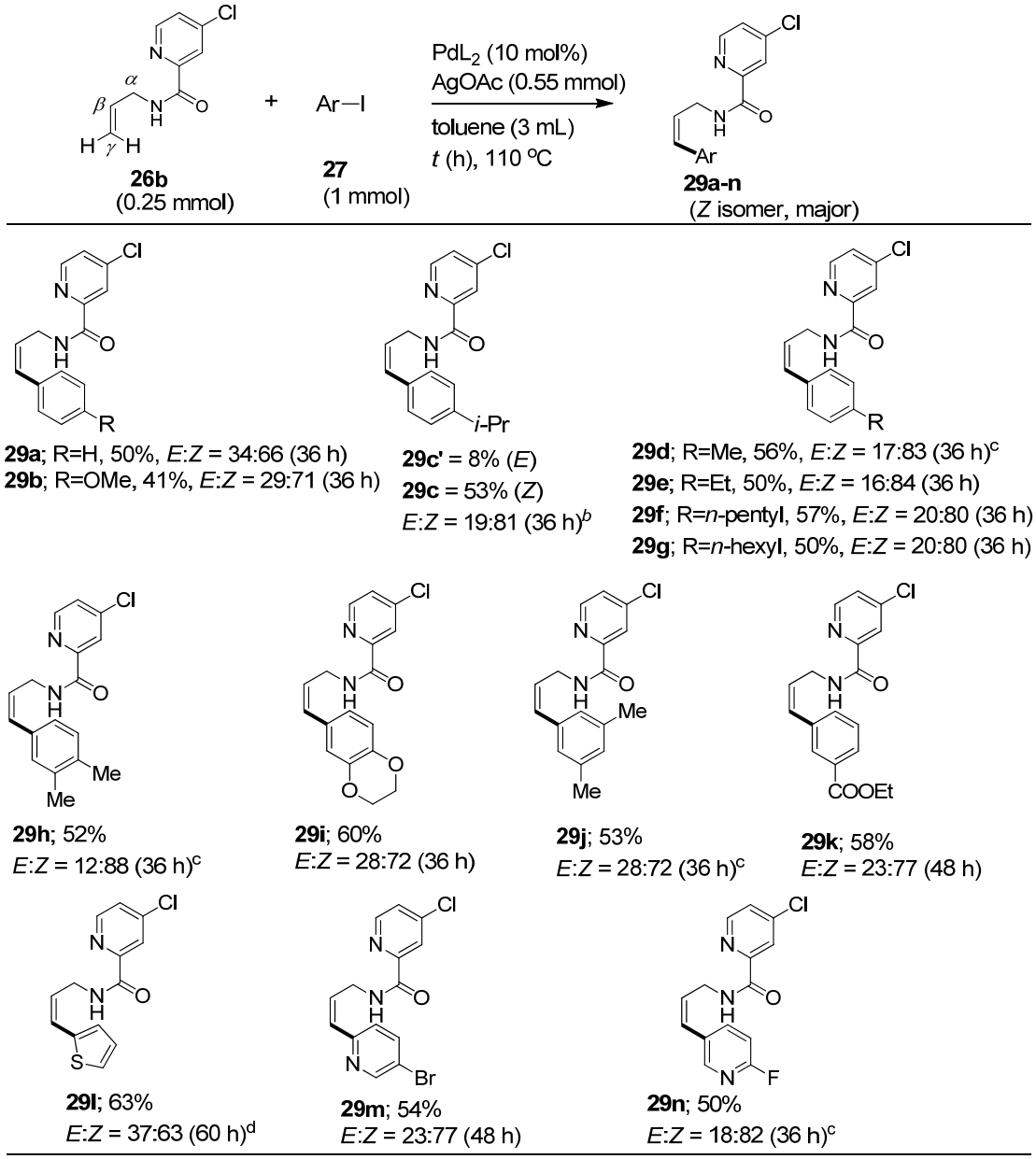
28l; 69%
E:*Z* = 10:90 (48 h)[e]



28m; 50%
E:Z = 2:98 (48 h)

[a] The *E*/*Z* ratios were determined from the NMR spectra of the corresponding crude reaction mixtures.[b]2 mmol of ArI was used. [c]In this case, **28g′** (*E*) and **28g** (*Z*) isomers were isolated in pure form. [d]2 mmol of ArI and 15 mol% of $Pd(OAc)_2$ were used. [e]5 mol% of $Pd(OAc)_2$ was used.

Scheme 17. 4-Chloro picolinamide-directed, construction of *Z* cinnamylamines.

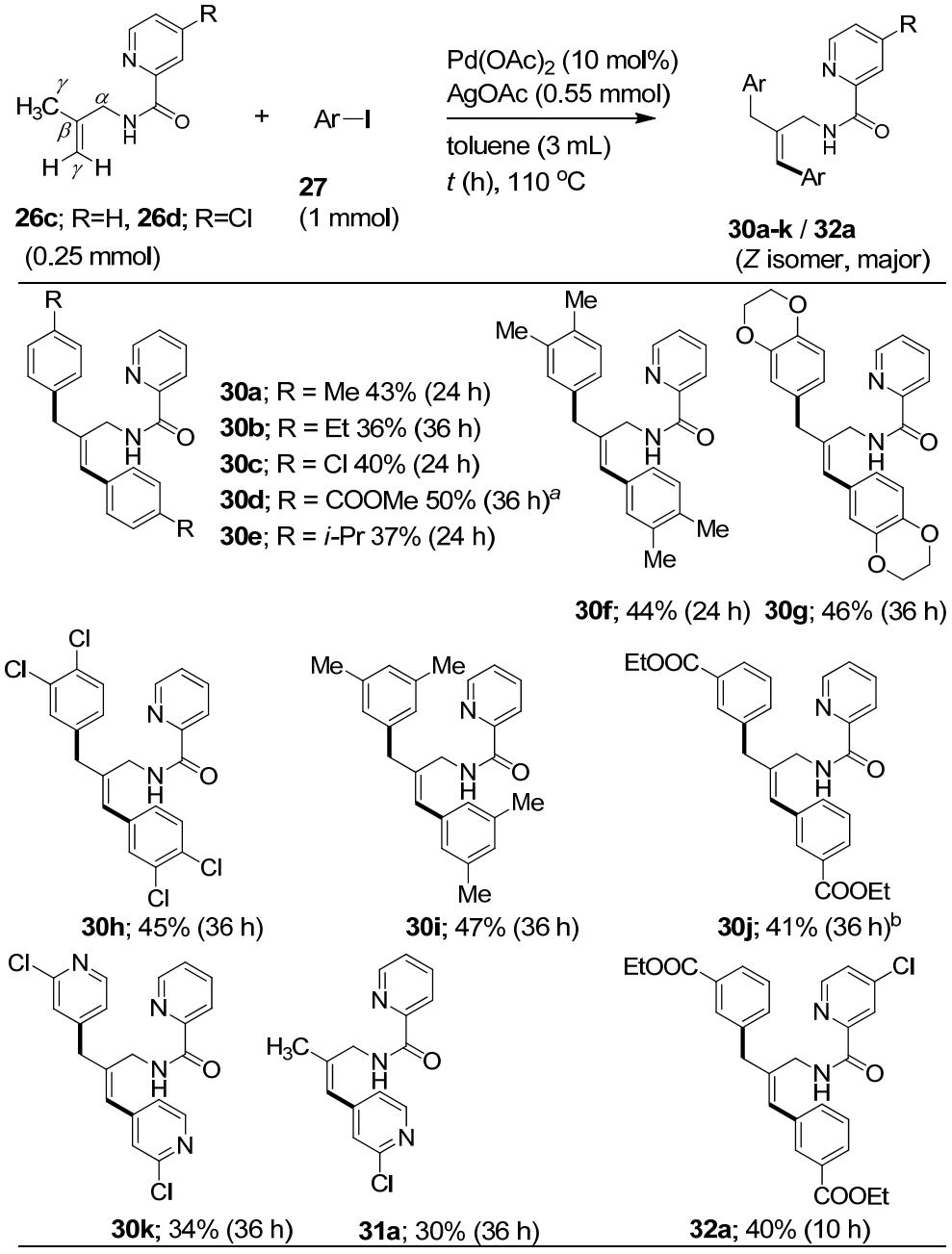


[a] The *E*/*Z* ratios were determined from the NMR spectra of the corresponding crude reaction mixtures and in most of the cases, the corresponding major isomer (*Z*) was isolated in pure form. [b]In this case, **29c′** (*E*) and **29c** (*Z*) isomers were isolated in pure form.
[c]15 mol% of $Pd(OAc)_2$ was used. [d]2 mmol of ArI was used.

Next it was envisaged perform the *Z* selective γ-C(sp^2)-H arylation of *N*-(2-methylallyl)picolinamide systems **26c** and **26d** and it is to be noted that the allylamine systems **26c** and **26d** contain both γ-C(sp^3)-H and γ-C(sp^2)-H bonds which can give the

corresponding γ-C(sp^3)-H and γ-C(sp^2)-H arylated products . The $Pd(OAc)_2$/AgOAc-catalytic system based γ-C-H arylation of **26c**/**26d** with various aryl iodides afforded the corresponding γ-C(sp^2)-H and γ-C(sp^3)-H arylated allylamine derivatives **30a-j** in 36-50% yields (Scheme 18).

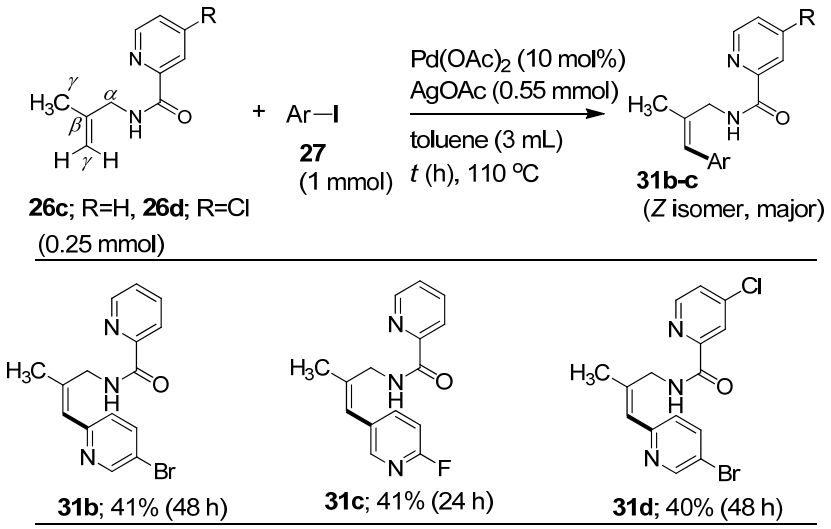
Scheme 18. Picolinamide-directed, sp^2 and $sp^3\gamma$-C-H arylation and construction of *Z* cinnamylamines.



[a]15 mol% of $Pd(OAc)_2$ was used. [b]20 mol% of $Pd(OAc)_2$ was used.

It is to be noted that the arylation reaction involving **26c** with2-chloro-4-iodopyridine afforded the γ-C(sp^2)-H arylated product **31a** as well as the expected γ-C(sp^2)-H and γ-C(sp^3)-H arylated allylamine derivative **30k**. Specifically, the arylation of **26c** with2-chloro-4-iodopyridine might be a slower reaction than the other arylation reactions. Then, the Pd(II)-catalyzed arylation of **26c** withvariousiodopyridines were performed to obtain additional examples similar to the product **31a**. Accordingly, γ-C(sp^2)-H arylated products **31b-d** in 40-41% yields were obtained from their respective Pd(II)-catalyzed arylations of **26c** (Scheme 19).

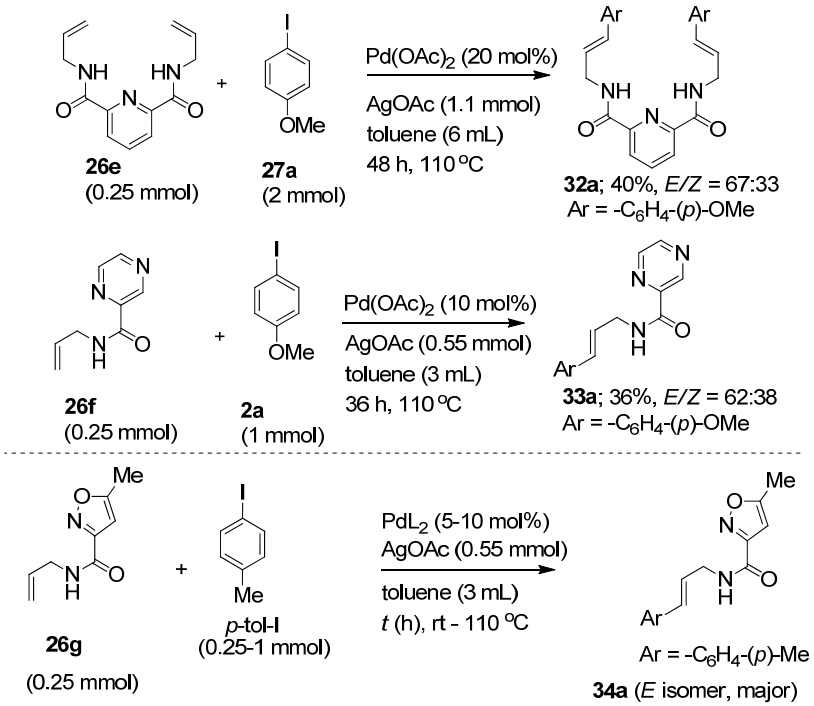
Scheme 19. Picolinamide-directed, chelation-assisted chemoselective sp^2 γ-C-H arylation and construction of *Z* cinnamylamine motifs **31b-c**.



Subsequently, the Pd(II)-catalyzed bis arylation of picolinamide system **26e** with **27a** was attempted and this reaction afforded the bis γ-C-H arylated allylamine system **32a** in 40% yield with an *E/Z* ratio of 62:38 (Scheme 20). Next, the Pd(II)-catalyzed, pyrazine-2-carboxamide-directed arylation of allylamine substrate **26f** with **27a** was attempted, which afforded the γ-C-H arylated allylamine derivative **33a** in 36% yield with an *E/Z* ratio of 67:33 (Scheme 20). Then, it was envisaged to attempt the arylation using isoxazole-3-carboxamide as the directing group. Accordingly, the arylation of **26g** was carried out using different reaction conditions (Scheme 20). The reaction of **26g** (1 equiv) with *p*-tolyl iodide (1 equiv) in the presence of 5 or 10 mol% of $Pd(OAc)_2$ in toluene afforded the compound **34a** in 33-48% yield and *E* isomer was obtained as the major isomer in these cases (entries 1 and 2,

Scheme 20). The reaction of **26g** (1 equiv) with *p*-tolyl iodide (1 equiv) at and 50 °C afforded the **34a** in78% yield with an *E/Z* ratio of 98:2 (entry 3, Scheme 20).

Scheme 20. $Pd(OAc)_2$/AgOAc-Catalytic system based *E* selective *γ*-C-H arylation of allylamine substrates **26e,f and g**.

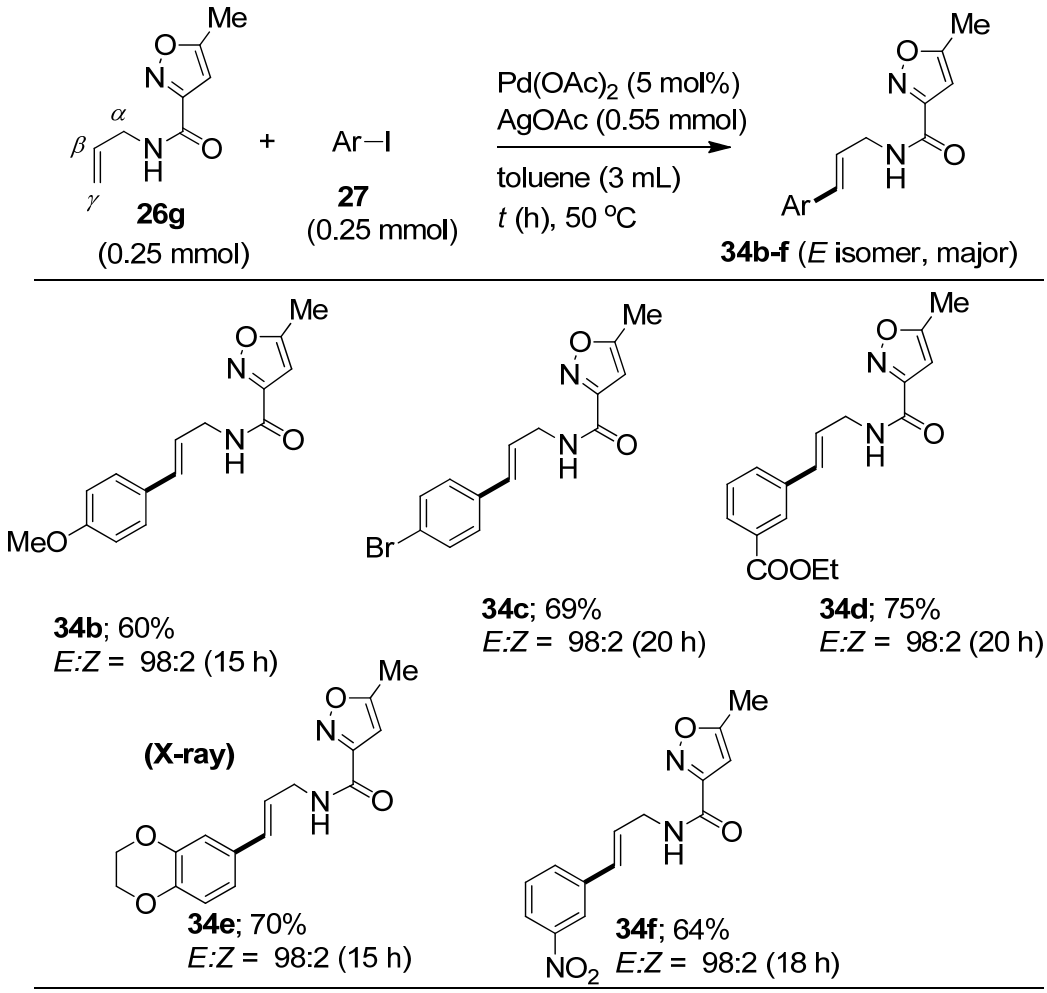


entry	PdL_2 (mol%)	*p*-tol-I (mmol)	*T* (°C)	*t* (h)	**34a** yield (%)	*E*:*Z* ratio
1	$Pd(OAc)_2$ (10)	0.25	110	0.5	48	98:2
2	$Pd(OAc)_2$ (5)	0.25	rt	60	33	89:11
3	$Pd(OAc)_2$ (5)	0.25	50	24	78	98:2
4[b]	$Pd(OAc)_2$ (5)	1	rt	24	-	-
5[b]	$Pd(OAc)_2$ (5)	1	50	24	-	-
6[b]	$Pd(OAc)_2$ (10)	0.5	110	48	-	-
7[b]	$Pd(OAc)_2$ (10)	1	110	48	-	-

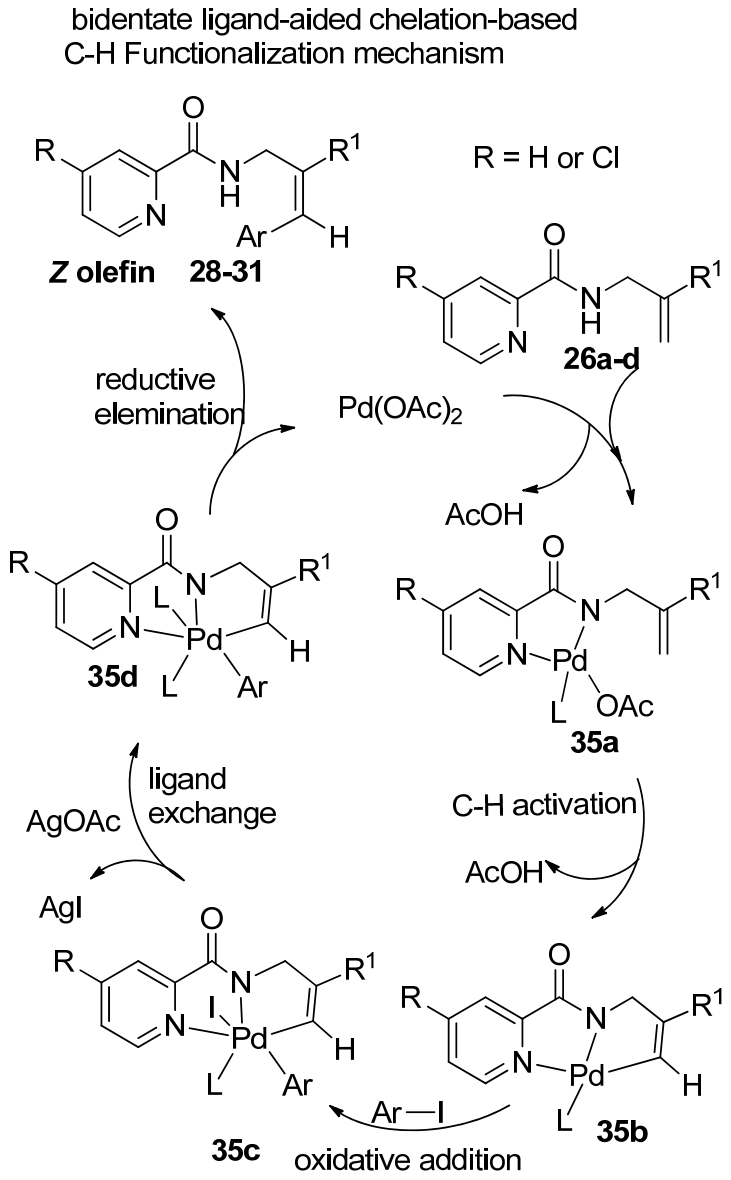
[a] The *E*/*Z* ratios of diastereomers were determined from the NMR spectra of the corresponding crude reaction mixtures. [b] A complex mixture was obtained and purification of the crude reaction mixture did not afford the corresponding cinnamylamine in pure form.

Other trials to obtain the *Z* isomer from the arylation of **26g** were not fruitful (entries 4-7, Scheme 20). The formation of the compounds **32a**, **33a** and **34a** having the *E* stereochemistry as the major isomers in the corresponding reactions, suggested that the arylation reactions of the corresponding substrates **26e-g** might occurred via the Heck-type reaction mechanism and without the assistance of corresponding directing groups (Scheme 20). Additionally, treatment of **26g** with various aryl iodides in the presence of $Pd(OAc)_2$ (5 mol%) in toluene at 50 ^oC furnished various γ-C-H arylated allylamine derivatives **34b-f** having the *E* stereochemistry in 60-75% yields (Scheme 21).

Scheme 21. Isoxazole-3-carboxamide-directed, *E* selective arylation of allylamine system 26g.



Scheme 23. Plausible mechanism for the *Z* selective γ-C-H arylation of **26a-d**.



The Pd(II)-catalyzed arylations of the picolinamide derivatives **26a-d** afforded the corresponding *γ*-C(sp^2)-H arylated products **28-31** with *Z* stereochemistry as the major isomers (Table 1, Schemes 16-19). It is to be noted that in the Pd-catalyzed Mizoroki-Heck reactions of olefins, [6-8] including allylamine systems generally afforded the arylated olefins with *E* stereochemistry as the major isomers. Notably, the $Pd(OAc)_2$-catalyzed, AgOAc-promoted picolinamide-directed arylations of **30a-d** furnished the corresponding *γ*-C-H arylated products **28-31** with *Z* stereochemistry as the major isomers (Table 1, Schemes 16-19). Based on the previous works[9] and the generally accepted Pd^{II-IV} catalytic cycle mechanism comprising the $Pd(OAc)_2$/AgOAc-catalytic system-based, directing group-

assisted C-H functionalization[9] the observed*Z* selective *γ*-C-H arylations of **26a-d** can be explained *via* the directing group-aided and chelation-based C-H activation mechanism (Scheme 23).

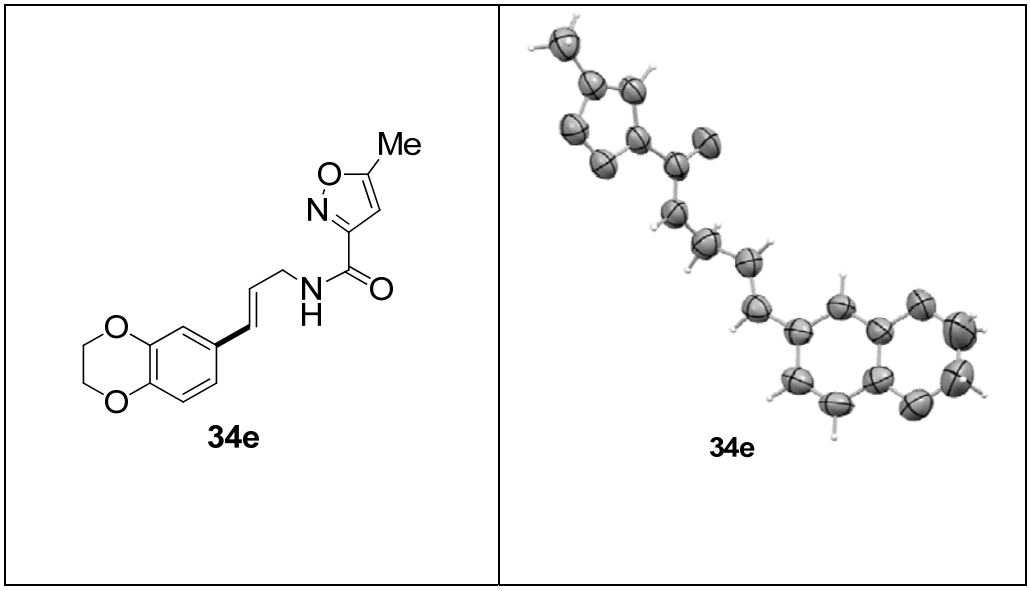
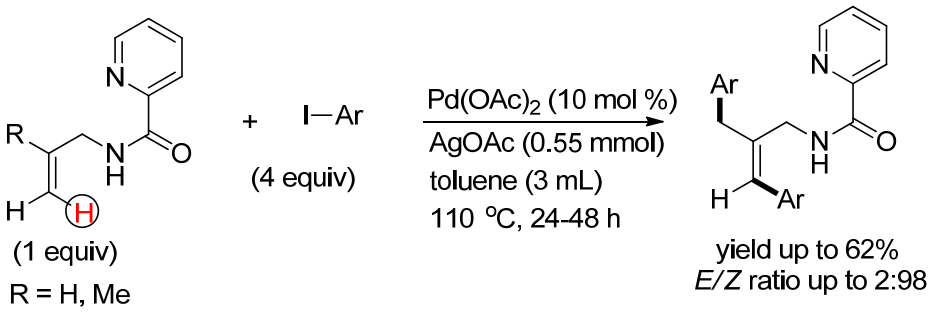


Figure 2. X-ray (ORTEP diagram) structure of the compound **34e**.

Conclusion

In summary, the **Chapter 4** revealed a directing group-aided *Z* selective C-H arylation of the *γ*-C(sp^2)-H bond of *N*-allylpicolinamide derivatives with various aryl- and heteroaryl iodides. This method provided a simple route to obtain various *Z*cinnamylamines derivatives. The observed *Z* selective *γ*-C(sp^2)-H arylation of *N*-allylpicolinamide systems was explained via the directing group-aided and chelation-based C-H activation mechanism.



Experimental section.

General. IR spectra were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively (using TMS as an internal standard). HRMS data reported in this work were obtained from QTOF mass analyzer using electrospray ionization method (ESI). Column chromatography was carried out using silica gel (100-200 mesh) or neutral alumina. Isolated yields of all the compounds were reported and yields were not optimized. TLC analysis was performed on silica gel or alumina plates and the components were visualized by observation under iodine vapour. Amides starting materials used in the Pd(II)-catalyzed C-H arylation reactions were prepared by using the standard literature procedures.

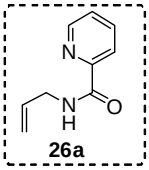
Procedure for Synthesis of *N*-Allylamide 26a-f, 26h-k and 26m: An oven-dried round bottomed flask (25 mL capacity) was charged with an appropriate carboxylic acid (1.2 mmol, 1 equiv) and anhydrous DCM (4-6 mL) and two-three drops of DMF. To this solution oxalyl chloride (1.5 mmol, 1.5 equiv, 190 mg) was added dropwise at 0 °C. The mixture was stirred at rt for 12 h and then, the solvent was removed in vacuum and then dissolved in DCM (4-6 mL, the resulting acid chloride solution was immediately used in the next step without further purification). Another oven-dried round bottomed flask (25 mL capacity) was charged with an appropriate allylamine (1.0 mmol, 1 equiv), Et_3N (1.5 mmol, 1.5 equiv, 152 mg), DMAP (0.1 mmol, 0.1 equiv, 12 mg). To this solution, the acid chloride solution (obtained in the previous step) was added dropwise at 0 °C and after the addition the solution was warmed to rt and allowed to for overnight. Then, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10-15 mL) and the organic layer was separated, dried over anhydrous MgSO4 and evaporated in vacuum. The crude reaction mixture was purified by column chromatography on silica gel (eluent: EtOAc:Hexanes = 30:70) to afford the corresponding carboxamides **26a-f, 26h-k** and **26m.**

Procedure for Synthesis of carboxamides 26g and 26l: An oven-dried round bottomed flask (25 mL capacity) was charged with 5-methylisoxazole-3-carboxylic acid (1 mmol, 1 equiv) and DCM (6 mL) under a nitrogen atm. Then, EDCI (1.1 mmol, 1.1 equiv, 172 mg) and HOBt•H_2O (1.1 mmol, 1.1 equiv, 168 mg) were added dropwise at 0 °C and the reaction mixture was stirred for 15 min. Then, to the reaction mixture an appropriate allylamine (1 mmol, 1.1 equiv) was added dropwise at 0 °C. Then, the solution was warmed to room temperature and the stirring was continued for 12 h. After this period, water (4-7 mL) was

added and extracted with DCM (4-7 mL, 2-3 times). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuum. The crude reaction mixture was purified by column chromatography on silica gel (eluent: EtOAc:Hexanes = 35:65) to afford the corresponding products **26g** and **26l**.

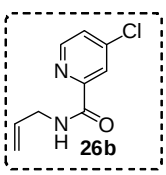
General procedure for the Pd(II)-catalyzed arylation of *N*-allylamide derivatives 26a-m and the preparation of 28a-28m/29a-29n/30a-30k/31a-31d, 31a and**34a-34f** An oven-dried round bottomed flask (10 mL capacity) was charged with an appropriate *N*-allylamide derivative (0.25 mmol, 1 equiv), an appropriate aryl iodide (1.0 mmol, 4.0 equiv), $Pd(OAc)_2$ (10 mol%, 5.6 mg,), AgOAc (0.55 mmol, 2.2 equiv, 91.8 mg) and toluene (3 mL). This reaction mixture was heated at 110 ^oC for 24-48 h under a nitrogen atm. After this period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel furnished the corresponding γ-C-H arylated allylamine derivatives **28a-28m/29a-29n/30a-30k/31a-31d, 31a** and**34a-34f** (see the corresponding Tables/Schemes for specific examples).

***N*-Allylpicolinamide(26a):**The compound **26a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; R_f = 0.51 (EtOAc/hexane = 1:4); Yield: 77% (126 mg); IR (DCM): 3446, 2064, 1642, 1529, 1465 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (dd, 1H, J_1 = 4.8 Hz, J_2 = 0.8 Hz), 8.21 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.17 (br. s, 1H), 7.85 (t, 1H, *J*= 7.7 Hz), 7.45-7.41(m, 1H), 5.99-5.89 (m, 1H), 5.30-5.16 (m, 2H), 4.13-4.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.7, 148.0, 137.3, 134.0, 126.2, 122.2, 116.3, 41.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O$: 163.0871; found 163.0875.



26a

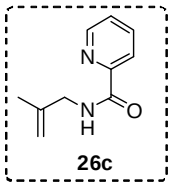
***N*-Allyl-4-chloropicolinamide(26b):** The compound **26b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 67% (133 mg); IR (DCM): 3441, 2063, 1643, 1524, 1290 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 1H, *J*= 5.2 Hz), 8.17 (d, 1H, *J*= 2.0 Hz), 8.10 (br. s, 1H), 7.41 (td,



26b

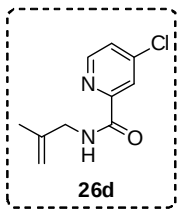
1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 5.95-5.85 (m, 1H), 5.26-5.13 (m, 2H), 4.09-4.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.8, 133.8, 126.3, 122.9, 116.6, 41.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{10}ClN_2O$: 197.0482; found 197.0484.

***N*-(2-Methylallyl)picolinamide (26c):** The compound **26c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.52 (EtOAc/hexane = 1:4); Yield: 69% (123 mg); IR (DCM): 3389, 1675, 1527, 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.31 (m, 1H), 8.17 (br. s, 1H), 8.00 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.61 (td, 1H, *J*= 7.7 Hz, *J*= 1.8 Hz), 7.21-7.19 (m, 1H), 4.69-4.63 (m, 2H), 3.82 (d, 2H, *J*= 6.4 Hz), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 149.6, 147.9, 141.6, 137.2, 126.1, 122.1, 110.8, 44.7, 20.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1028; found 177.1023.



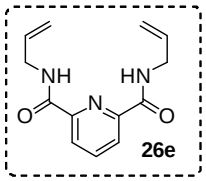
26c

4-Chloro-*N*-(2-methylallyl)picolinamide (26d): The compound **26d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 157% (74 mg); IR (DCM): 3391, 1677, 1527, 1292 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, *J*= 5.2 Hz), 8.21 (d, 1H, *J*= 1.4 Hz), 8.14 (br. s, 1H), 7.44-7.42 (m, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 4.01 (d, 2H, *J*= 6.2 Hz), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 151.3, 149.0, 145.9, 141.6, 126.3, 123.0, 111.2, 45.1, 20.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{12}ClN_2O$: 211.0638; found 211.0629.

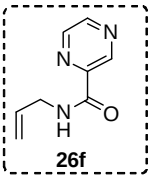


26d

***N*$_2$,*N*$_6$-Diallylpyridine-2,6-dicarboxamide (26e):** The compound **26e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.52 (EtOAc/Hexanes = 1:4); Yield: 65% (161 mg); IR (DCM): 3287, 1667, 1537, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (t, 2H, *J*= 6.0 Hz), 8.28 (d, 2H, *J*= 7.8 Hz), 7.95 (t, 1H, *J*= 7.8 Hz), 5.69-5.59 (m, 2H), 4.96-4.91 (m, 2H), 4.83-4.81 (m, 2H), 3.86 (t, 4H, *J*= 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 148.8, 138.9, 133.8, 124.9, 116.1, 42.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{15}N_3NaO_2$: 268.1062; found 268.1068.

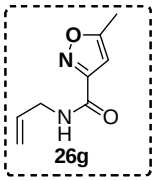


26e

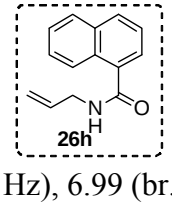


***N*-Allylpyrazine-2-carboxamide (26f):** The compound **26f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 70% (115 mg); IR (DCM): 3397, 1667, 1532, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (dd, 1H, J_1 = 3.4 Hz, J_2 = 1.3 Hz), 8.74 (dd, 1H, J_1 = 5.1 Hz, J_2 = 2.5 Hz), 8.53 (br. s, 1H), 7.95 (br. s, 1H), 5.97-5.88 (m, 1H), 5.30-5.16 (m, 2H), 4.13-4.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 147.3, 144.4, 144.4, 142.6, 133.6, 116.8, 41.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{10}N_3O$: 164.0824; found 164.0822.

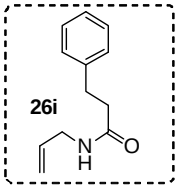
***N*-Allyl-5-methylisoxazole-3-carboxamide(26g):** The compound **26g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 50% (83 mg); IR (DCM): 3332, 1673, 1599, 1458, 1280 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 7.07 (br. s, 1H), 6.43 (s, 1H), 5.92-5.83 (m, 1H), 5.26-5.14 (m, 2H), 4.04 (t, 2H, *J*= 5.8 Hz), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 159.0, 158.7, 133.4, 116.8, 101.4, 41.7, 12.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{11}N_2O_2$: 167.0821; found 167.0815.



***N*-Allyl-1-naphthamide (26h):** The compound **26h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.52 (EtOAc/Hexanes = 1:4); Yield: 65% (138 mg); IR (KBr): 3284, 1640, 1536, 1422 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 1H, *J*= 8.1 Hz), 7.77-7.73 (m, 2H), 7.45-7.37 (m, 2H), 7.32 (d, 1H, *J*= 7.0 Hz), 7.18 (t, 1H, *J*= 7.9 Hz), 6.99 (br. s, 1H), 5.80-5.71 (m, 1H), 5.12-5.01 (m, 2H), 3.84 (t, 2H, *J*= 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 139.1, 134.1, 133.5, 130.3, 130.1, 128.2, 126.8, 126.2, 125.5, 125.0, 124.6, 116.1, 42.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}NO$: 212.1075; found 212.1082.

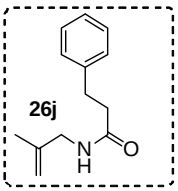


***N*-Allyl-3-phenylpropanamide(26i):**The compound **26i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 72% (137 mg); IR (DCM): 3293, 1643, 1551, 1454, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.22-7.19 (m, 3H), 6.28 (br. s, 1H), 5.82-5.72 (m, 1H), 5.10-5.06 (m, 2H), 3.83 (t, 2H, *J*= 5.6 Hz), 2.97 (t, 2H, *J*= 7.5 Hz), 2.52 (t, 2H, *J*= 7.5 Hz);

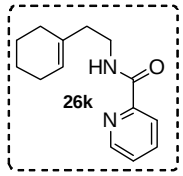


^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 140.9, 134.2, 128.5, 128.3, 126.2, 116.1, 41.9, 38.3, 31.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}NO$: 190.1232; found 190.1228.

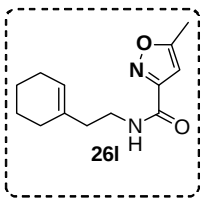
***N*-(2-Methylallyl)-3-phenylpropanamide(26j):**The compound **26j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 74% (152 mg); IR (DCM): 3294, 1648, 1553, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2H), 7.22-7.20 (m, 3H), 6.00 (br. s, 1H), 4.78 (s, 1H), 4.70 (s, 1H), 3.77 (d, 2H, *J*= 5.9 Hz), 2.99 (t, 2H, *J*= 7.9 Hz), 2.54 (t, 2H, *J*= 7.9 Hz), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 141.9, 140.9, 128.5, 128.4, 126.2, 110.8, 45.0, 38.4, 31.8, 20.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO$: 204.1388; found 204.1379.



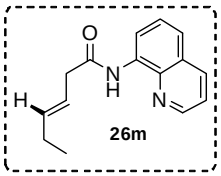
***N*-(2-(Cyclohex-1-en-1-yl)ethyl)picolinamide(26k):**The compound **26k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 80% (184 mg); IR (DCM): 3392, 1665, 1590, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, 1H, J_1 = 4.7 Hz, J_1 = 0.5 Hz), 8.14 (d, 1H, *J*= 7.8 Hz), 8.05 (br. s, 1H), 7.77 (td, 1H, *J*= 7.7 Hz, *J*= 1.7 Hz), 7.37-7.33 (m, 1H), 5.47 (s, 1H), 3.52-3.47 (m, 2H), 2.22-2.19 (m, 2H), 1.94-1.92 (m, 4H), 1.60-1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 150.0, 148.0, 137.2, 134.5, 125.9, 123.4, 122.0, 37.7, 37.5, 28.0, 25.2, 22.8, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$: 231.1497; found 231.1491.



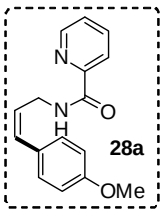
***N*-(2-(Cyclohex-1-en-1-yl)ethyl)-5-methylisoxazole-3-carboxamide(26l):** The compound **26l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.52 (EtOAc/Hexanes = 1:4); Yield: 65% (153 mg); IR (DCM): 3365, 1660, 1601, 1545, 1270 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (br. s, 1H), 6.42 (s, 1H), 5.51 (s, 1H), 3.52-3.47 (m, 2H), 2.47 (s, 3H), 2.22 (t, 2H, *J*= 6.8 Hz), 1.99-1.95 (m, 4H), 1.65-1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 159.0, 158.9, 134.2, 123.9, 101.4, 37.4, 37.3, 27.9, 25.2, 22.8, 22.3, 12.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.



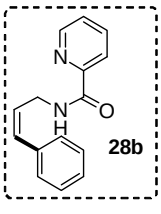
(*E*)-*N*-(quinolin-8-yl)hex-3-enamide (26m): The compound **26m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a brown colour liquid; R_f = 0.51 (EtOAc/Hexane = 1:4); Yield: 70% (168 mg); IR (DCM): 3054, 2305, 1422, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.10 (br. s, 1H), 8.80-8.77 (m, 2H), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 5.92-5.72 (m, 2H), 3.28 (d, 2H, J= 7.1 Hz), 2.24-2.16 (m, 2H), 1.14 (t, 3H, J= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 148.1, 138.7, 138.5, 136.3, 134.5, 127.9, 127.4, 121.6, 121.5, 121.4, 116.3, 42.1, 25.8, 13.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1341; found 241.1330.



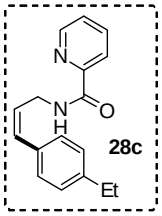
(*Z*)-*N*-(3-(4-Methoxyphenyl)allyl)picolinamide (28a): The compound **28a** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as a brown colour liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 64% (43 mg, *E:Z* = 11:89); IR (DCM): 3441, 1667, 1511, 1251, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.24-8.22 (m, 1H), 8.16 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.26 (d, 2H, J= 8.6 Hz), 6.92 (d, 2H, J= 8.8 Hz), 6.59 (d, 1H, J= 11.5 Hz), 5.71 (dt, 1H, J_1 = 11.5 Hz, J_2= 6.7 Hz), 4.41 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 158.8, 149.8, 148.1, 137.4, 131.3, 130.1, 129.0, 126.2, 122.3, 113.8, 55.3, 37.9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO_2$: 291.1109; found 291.1099.



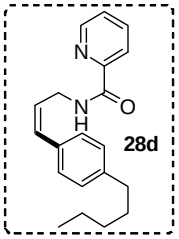
(*Z*)-*N*-(3-Phenylallyl)picolinamide (28b): The compound **28b** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/hexane = 1:4); Yield: 57% (34 mg, *E:Z* = 25:75); IR (DCM): 3441, 1659, 1524, 1383, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.25-8.22 (m, 1H), 8.17 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.41-7.37 (m, 2H), 7.33-7.28 (m, 3H), 6.67 (d, 1H, J= 11.6 Hz), 5.81 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.41 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.87 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.8, 148.1, 137.4, 136.4, 131.8, 128.8, 128.4, 127.9, 127.3, 126.2, 122.3, 37.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{14}N_2NaO$: 261.1004; found 261.0995.



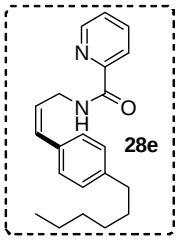
(*Z*)-*N*-(3-(4-Ethylphenyl)allyl)picolinamide (28c): The compound **28c** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 66% (44 mg, *E:Z* = 25:75); IR (DCM): 3441, 1735, 1623, 1383, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.25-8.22 (m, 1H), 8.16 (br. s, 1H), 7.88 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (m, 1H), 7.26-7.20 (m, 4H), 6.63 (d, 1H, *J*= 11.6 Hz), 5.76 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 2.67 (q, 2H, *J*= 7.6 Hz), 1.26 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.8, 148.1, 143.5, 137.4, 133.7, 131.8, 128.8, 127.9, 127.1, 126.2, 122.3, 37.9, 28.6, 15.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}N_2NaO$: 289.1317; found 289.1309.



(*Z*)-*N*-(3-(4-Pentylphenyl)allyl)picolinamide (28d): The compound **28d** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 69% (53 mg, *E:Z* = 9:91); IR (DCM): 3442, 2921, 1643, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, *J*= 4.7 Hz), 8.23 (d, 1H, *J*= 7.8 Hz), 8.15 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.23 (d, 2H, *J*= 8.2 Hz), 7.20 (d, 2H, *J*= 8.2 Hz), 6.63 (d, 1H, *J*= 11.6 Hz), 5.76 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.7 Hz), 2.62 (t, 2H, *J*= 7.6 Hz), 1.67-1.60 (m, 2H), 1.36-1.27 (m, 4H), 0.92 (t, 3H, *J*= 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.1, 142.2, 137.4, 133.7, 131.8, 128.8, 128.4, 127.1, 126.2, 122.3, 37.9, 35.7, 31.5, 31.2, 22.6, 14.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}N_2NaO$: 331.1786; found 331.1776.

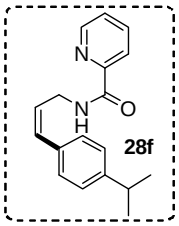


(*Z*)-*N*-(3-(4-Hexylphenyl)allyl)picolinamide (28e): The compound **28e** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 64% (52 mg, *E:Z* = 14:86); IR (DCM): 2928, 1678, 1523, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.23 (d, 1H, *J*= 7.8 Hz), 8.15 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.23 (d, 2H, *J*= 8.2 Hz), 7.20 (d, 2H, *J*= 8.2 Hz), 6.64 (d, 1H, *J*= 11.6 Hz), 5.76 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.7 Hz), 2.62 (t, 2H, *J*= 7.6 Hz), 1.68-1.59 (m, 2H), 1.38-1.27 (m, 6H), 0.91 (t, 3H, *J*= 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):

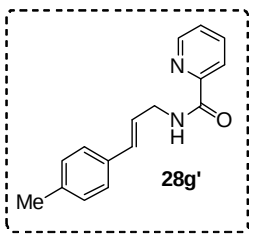


δ 164.2, 149.9, 148.1, 142.2, 137.4, 133.7, 131.8, 128.8, 128.4, 127.1, 126.2, 122.3, 37.9, 35.7, 31.8, 31.4, 29.0, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{27}N_2O$: 323.2123; found 323.2111.

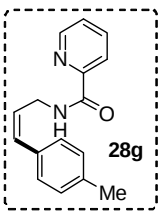
(*Z*)-*N*-(3-(4-Isopropylphenyl)allyl)picolinamide (28f): The compound **28f** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 50% (35 mg, *E:Z* = 20:80); IR (DCM): 3390, 1672, 1523, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.23 (d, 1H, *J*= 7.8 Hz), 8.15 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.25 (s, 4H), 6.63 (d, 1H, *J*= 11.6 Hz), 5.76 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.8 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 2.97-2.90 (m, 1H), 1.27 (d, 6H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.1, 137.4, 133.9, 131.8, 128.8, 127.1, 126.4, 126.2, 122.3, 37.9, 33.9, 24.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{20}N_2NaO$: 303.1473; found 303.1462.



(*E*)-*N*-(3-(*p*-Tolyl)allyl)picolinamide (28g'): The compound **28g'** ((*E*)minor isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/hexane = 1:4); Yield: 11% (7 mg, *E:Z* = 29:71); IR (DCM): 3442, 1738, 1642, 1365, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59-8.57 (m, 1H), 8.26-8.24 (m, 1H), 8.21 (br. s, 1H), 7.88 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (m, 1H), 7.30 (d, 2H, *J*= 8.8 Hz), 7.13 (d, 2H, *J*= 8.8 Hz), 6.61 (d, 1H, *J*= 15.8 Hz), 6.27 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.3 Hz), 4.28 (td, 2H, J_1 = 6.3 Hz, J_2 = 1.4 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.1, 137.5, 137.4, 133.8, 132.2, 129.3, 126.3, 126.2, 124.3, 122.3, 41.5, 21.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO$: 275.1160; found 275.1147.

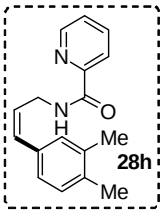


(*Z*)-*N*-(3-(*p*-Tolyl)allyl)picolinamide (28g): The compound **28g** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 71% (45 mg, *E:Z* = 29:71); IR (DCM): 3386, 1668, 1525, 1463, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.25-8.22 (m, 1H), 8.16 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.23-7.12 (m, 4H), 6.63 (d, 1H, *J*= 11.5 Hz), 5.75 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.41 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8

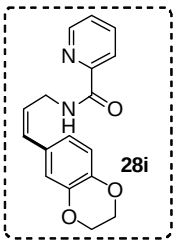


Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.8, 148.1, 137.4, 137.1, 133.5, 131.7, 129.1, 128.8, 127.2, 126.2, 122.3, 37.9, 21.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO$: 275.1160; found 275.1148.

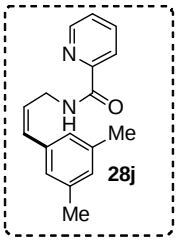
(*Z*)-*N*-(3-(3,4-Dimethylphenyl)allyl)picolinamide (28h): The compound **28h** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 40% (27 mg, *E:Z* = 29:71); IR (DCM): 3441, 1643, 1367, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.25-8.22 (m, 1H), 8.15 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.15 (d, 1H, *J*= 7.6 Hz), 7.08-7.05 (m, 2H), 6.60 (d, 1H, *J*= 11.6 Hz), 5.74 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.1, 137.4, 136.5, 135.8, 134.0, 131.8, 130.1, 129.6, 127.0, 126.3, 126.2, 122.3, 37.9, 19.9, 19.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}N_2NaO$: 289.1317; found 289.1308.



(*Z*)-*N*-(3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)allyl)picolinamide (28i): The compound **28i** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 59% (44 mg, *E:Z* = 27:73); IR (DCM): 3442, 1671, 1506, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.55 (m, 1H), 8.23 (d, 1H, *J*= 7.8 Hz), 8.16 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 6.87 (d, 1H, *J*= 8.3 Hz), 6.83 (d, 1H, *J*= 2.0 Hz), 6.80 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 6.53 (d, 1H, *J*= 11.5 Hz), 5.70 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.40 (td, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 4.29 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.8, 148.1, 143.2, 142.9, 137.4, 131.1, 130.0, 126.8, 126.2, 122.3, 122.2, 117.6, 117.1, 64.4, 64.3, 37.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1239; found 297.1248.

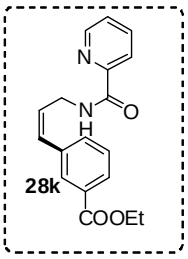


(*Z*)-*N*-(3-(3,5-Dimethylphenyl)allyl)picolinamide (28j): The compound **28j** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 51% (34 mg, *E:Z* = 38:62); IR (DCM): 1717, 1679, 1521, 1203 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.25-8.22 (m, 1H), 8.15 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2



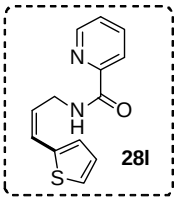
= 1.7 Hz), 7.46-7.43 (m, 1H), 6.94-6.93 (m, 3H), 6.60 (d, 1H, *J*= 11.6 Hz), 5.76 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.9 Hz), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.1, 137.9, 137.4, 136.3, 132.0, 129.0, 127.6, 126.6, 126.2, 122.3, 37.9, 21.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}N_2NaO$: 289.1317; found 289.1317.

(*Z*)-Ethyl 3-(3-(picolinamido)prop-1-en-1-yl)benzoate (28k): The compound **28k** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel



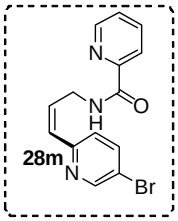
(EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 54% (42 mg, *E:Z* = 21:79); IR (DCM): 3380, 1717, 1523, 1282 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.55 (m, 1H), 8.22 (d, 1H, *J*= 7.8 Hz), 8.19 (br. s, 1H), 7.97 (dd, 2H, J_1 = 6.4 Hz, J_2 = 1.4 Hz), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.53-7.42 (m, 3H), 6.68 (d, 1H, *J*= 11.6 Hz), 5.87 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.43-4.36 (m, 4H), 1.41 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 164.2, 149.7, 148.1, 137.4, 136.6, 133.0, 130.9, 130.6, 129.8, 129.2, 128.5, 128.4, 126.3, 122.3, 61.1, 37.7, 14.3 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1396; found 311.1410.

(*Z*)-*N*-(3-(Thiophen-2-yl)allyl)picolinamide (28l): The compound **28l** ((*Z*)major isomer)was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as pale yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 69% (42 mg, *E:Z* =



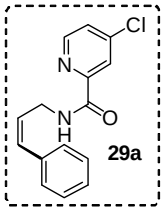
10:90); IR (DCM): 3442, 1662, 1532, 1386 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.24 (d, 1H, *J*= 7.8 Hz), 8.24 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (m, 1H), 7.34 (t, 1H, *J*= 3.0 Hz), 7.06 (t, 2H, *J*= 3.5 Hz), 6.70 (d, 1H, *J*= 11.6 Hz), 5.71 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.51 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8, 148.1, 139.3, 137.4, 128.1, 127.2, 126.2, 126.1, 126.1, 124.0, 122.3, 38.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2OS$: 245.0749; found 245.0749.

(*Z*)-*N*-(3-(5-Bromopyridin-2-yl)allyl)picolinamide (28m): The compound **28m** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour liquid; R_f = 0.45 (EtOAc/Hexanes = 1:4); Yield: 50% (40 mg, *E:Z* = 2:98); IR (DCM): 3337, 1651, 1521 cm^{-1}; ^{1}H NMR (400 MHz,

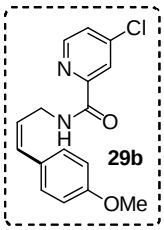


$CDCl_3$): δ 8.73 (d, 1H, *J*= 2.2 Hz), 8.67 (br. s, 1H), 8.58-8.56 (m, 1H), 8.22 (d, 1H, *J*= 7.8 Hz), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.80 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.45-7.41 (m, 1H), 7.15 (d, 1H, *J*= 8.3 Hz), 6.50 (d, 1H, *J*= 11.7 Hz), 6.09 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.66 (td, 2H, J_1 = 6.5 Hz, J_2 = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 154.1, 150.4, 150.1, 148.1, 138.9, 137.3, 133.7, 129.0, 126.1, 125.5, 122.3, 118.7, 37.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{13}BrN_3O$: 318.0242; found 318.0244.

(*Z*)-4-Chloro-*N*-(3-phenylallyl)picolinamide (29a): The compound **29a** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 50% (34 mg, *E:Z* = 34:66); IR (DCM): 3382, 1674, 1525, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 1.9 Hz), 8.08 (br. s, 1H), 7.46 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.41-7.37 (m, 2H), 7.32-7.30 (m, 3H), 6.68 (d, 1H, *J*= 11.6 Hz), 5.79 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.8 Hz), 4.41 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 136.3, 132.1, 128.8, 128.4, 127.5, 127.4, 126.4, 122.9, 37.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}ClN_2O$: 273.0795; found 273.0782.

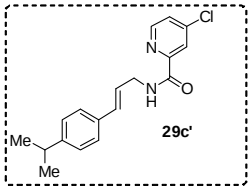


(*Z*)-4-Chloro-*N*-(3-(4-methoxyphenyl)allyl)picolinamide (29b): The compound **29b** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 41% (31 mg, *E:Z* = 29:71); IR (DCM): 3442, 1670, 1511, 1383 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 2.0 Hz), 8.07 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.25 (d, 2H, *J*= 8.6 Hz), 6.92 (d, 2H, *J*= 8.8 Hz), 6.60 (d, 1H, *J*= 11.5 Hz), 5.69 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.40 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 158.8, 151.3, 149.0, 145.9, 131.6, 130.1, 128.9, 126.4, 125.8, 122.9, 113.8, 55.3, 38.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}ClN_2O_2$: 303.0900; found 303.0889.

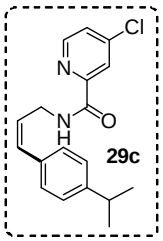


(*E*)-4-Chloro-*N*-(3-(4-isopropylphenyl)allyl)picolinamide (29c'): The compound **29c'** ((*E*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4);

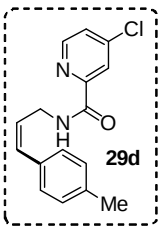
Yield: 8% (7 mg, *E:Z* = 19:81); IR (DCM): 3412, 1670, 1520, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, 1H, *J*= 5.2 Hz), 8.25 (d, 1H, *J*= 2.0 Hz), 8.12 (d, 1H, *J*= 0.5 Hz), 7.46 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.33 (d, 2H, *J*= 8.2 Hz), 7.19 (d, 2H, *J*= 8.2 Hz), 6.61 (d, 1H, *J*= 15.8 Hz), 6.25 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.27 (td, 2H, J_1 = 6.4 Hz, J_2 = 1.4 Hz,), 2.94-2.87 (m, 1H), 1.25 (d, 6H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.4, 149.0, 148.7, 145.9, 134.1, 132.4, 126.7, 126.4, 126.4, 124.1, 123.0, 41.6, 33.9, 23.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}ClN_2O$: 315.1264; found 315.1266.



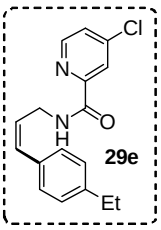
(*Z*)-4-Chloro-*N*-(3-(4-isopropylphenyl)allyl)picolinamide (29c): The compound **29c** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 53% (42 mg, *E:Z* = 19:81); IR (DCM): 3385, 1673, 1532, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (s, 1H), 8.06 (br. s, 1H), 7.45 (d, 1H, *J*= 5.2 Hz), 7.25 (s, 4H), 6.64 (d, 1H, *J*= 11.6 Hz), 5.74 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 4.42 (t, 2H, *J*= 6.4 Hz), 2.97-2.90 (m, 1H), 1.28 (d, 6H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 148.2, 145.9, 133.8, 132.0, 128.8, 126.7, 126.5, 126.3, 122.9, 38.0, 33.9, 23.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}ClN_2O$: 315.1264; found 315.1252.



(*Z*)-4-Chloro-*N*-(3-(*p*-tolyl)allyl)picolinamide (29d): The compound **29d** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 56% (40 mg, *E:Z* = 17:83); IR (DCM): 2926, 1677, 1525, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.23 (d, 1H, *J*= 2.0 Hz), 8.07 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.20 (s, 4H), 6.63 (d, 1H, *J*= 11.5 Hz), 5.73 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.41(td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 137.2, 133.4, 132.0, 129.1, 128.7, 126.8, 126.4, 122.9, 38.0, 21.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{15}ClN_2NaO$: 309.0771; found 309.0772.

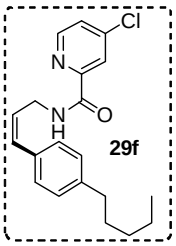


(*Z*)-4-Chloro-*N*-(3-(4-ethylphenyl)allyl)picolinamide (29e): The compound **29e** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield:



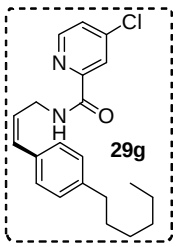
50% (38 mg, *E:Z* = 16:84); IR (DCM): 2964, 1675, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 2.0 Hz), 8.07 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.25 (s, 4H), 6.65 (d, 1H, *J*= 11.5 Hz), 5.74 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.41(td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 2.67 (q, 2H, *J*= 7.6 Hz), 1.26 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 143.6, 133.6, 132.0, 128.8, 127.9, 126.8, 126.4, 122.9, 38.0, 28.6, 15.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}ClN_2O$: 301.1108; found 301.1100.

(*Z*)-4-Chloro-*N*-(3-(4-pentylphenyl)allyl)picolinamide (29f): The compound **29f** ((*Z*)major isomer) was obtained after purification by column chromatography on neutral alumina

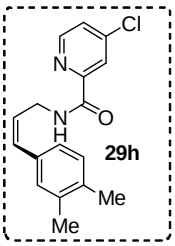


(EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 57% (49 mg, *E:Z* = 20:80); IR (DCM): 2928, 1679, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 2.0 Hz), 8.07 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.23 (d, 2H, *J*= 8.5 Hz), 7.20 (d, 1H, *J*= 8.5 Hz), 6.64 (d, 1H, *J*= 11.6 Hz), 5.74 (dt, 1H, *J*= 11.6 Hz, *J*= 6.7 Hz), 4.41 (td, 2H, *J*= 1.8 Hz, *J*= 6.7 Hz), 2.62 (t, 2H, *J*= 7.6 Hz), 1.67-1.60 (m, 2H), 1.39-1.32 (m, 4H), 0.92 (t, 3H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 142.3, 137.2, 133.6, 132.0, 130.6, 128.7, 128.5, 126.7, 126.3, 122.9, 38.0, 35.7, 31.5, 31.1, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}ClN_2O$: 343.1577; found 343.1562.

(*Z*)-4-Chloro-*N*-(3-(4-hexylphenyl)allyl)picolinamide (29g): The compound **29g** ((*Z*)major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield:

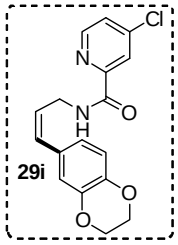


50% (45 mg, *E:Z* = 20:80); IR (DCM): 2929, 1674, 1508, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 1.9 Hz), 8.07 (br. s, 1H), 7.44 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.9 Hz), 7.22 (d, 2H, *J*= 8.4 Hz), 7.20 (d, 1H, *J*= 8.4 Hz), 6.63 (d, 1H, *J*= 11.5 Hz), 5.73 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.41 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.5 Hz), 2.62 (t, 2H, *J*= 7.6 Hz), 1.65-1.59 (m, 2H), 1.38-1.28 (m, 6H), 0.91 (t, 3H, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 142.3, 133.6, 132.0, 128.7, 128.4, 126.7, 126.3, 122.9, 38.0, 35.7, 31.7, 31.4, 29.0, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}ClN_2O$: 357.1734; found 357.1718.

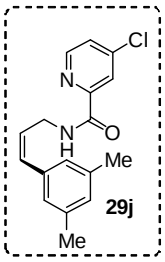


(*Z*)-4-Chloro-*N*-(3-(3,4-dimethylphenyl)allyl)picolinamide (29h): The compound **29h** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 52% (39 mg, *E:Z* = 12:88); IR (DCM): 1717, 1522, 1281, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 2.0 Hz), 8.07 (br. s, 1H), 7.44 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.15 (d, 1H, *J*= 7.6 Hz), 7.07-7.04 (m, 2H), 6.61 (d, 1H, *J*= 11.6 Hz), 5.72 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.6 Hz), 4.41 (td, 2H, J_1 = 6.6 Hz, J_2 = 1.4 Hz), 2.29 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 136.6, 135.9, 133.9, 132.0, 130.1, 129.6, 126.6, 126.3, 126.2, 122.9, 38.0, 19.9, 19.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}ClN_2O$: 301.1108; found 301.1100.

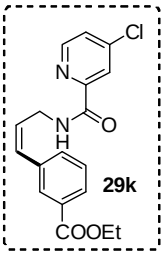
(*Z*)-4-Chloro-*N*-(3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)allyl)picolinamide (29i): The compound **29i** ((*Z*)major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 60% (50 mg, *E:Z* = 28:72); IR (DCM): 3377, 1674, 1580, 1293 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.3 Hz), 8.23 (d, 1H, *J*= 2.1 Hz), 8.07 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 6.87 (d, 1H, *J*= 8.2 Hz), 6.83-6.77 (m, 2H), 6.53 (d, 1H, *J*= 11.5 Hz), 5.67 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.39 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz), 4.28 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 143.2, 143.0, 131.4, 129.8, 126.4, 126.3, 122.9, 122.2, 117.6, 117.2, 64.4, 64.3, 38.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}ClN_2O_3$: 331.0849; found 331.0839.



(*Z*)-4-Chloro-*N*-(3-(3,5-dimethylphenyl)allyl)picolinamide (29j): The compound **29j** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.51 (EtOAc/Hexanes = 1:4); Yield: 53% (40 mg, *E:Z* = 28:72); IR (DCM): 3391, 1675, 1523, 1289 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.24 (d, 1H, *J*= 1.8 Hz), 8.06 (br. s, 1H), 7.44 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 6.94-6.92 (m, 3H), 6.61 (d, 1H, *J*= 11.6 Hz), 5.73 (dt, 1H, J_1 = 11.6 Hz, J_2 = 6.6 Hz), 4.41

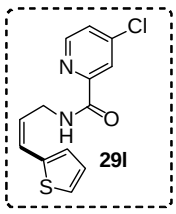


(td, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.3, 149.0, 145.9, 137.9, 136.2, 132.2, 129.0, 127.2, 126.6, 126.3, 122.9, 38.0, 21.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{17}ClN_2NaO$: 323.0927; found 323.0923.

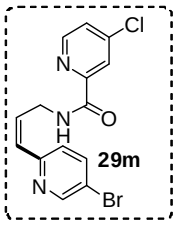


(*Z*)-Ethyl 3-(3-(4-chloropicolinamido)prop-1-en-1-yl)benzoate (29k): The compound **29k** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 58% (50 mg, *E:Z* = 23:77); IR (DCM): 3319, 1718, 1531, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J*= 5.2 Hz), 8.23 (d, 1H, *J*= 2.0 Hz), 8.10 (br. s, 1H), 7.99-7.97 (m, 2H), 7.51-7.42 (m, 3H), 6.69 (d, 1H, *J*= 11.5 Hz), 5.86 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.43-4.37 (m, 4H), 1.42 (t, 3H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 163.1, 151.2, 149.0, 145.9, 136.5, 132.9, 131.1, 130.7, 129.8, 128.8, 128.5, 128.4, 126.4, 122.9, 61.1, 37.8, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{18}ClN_2O_3$: 345.1006; found 345.0994.

(*Z*)-4-Chloro-*N*-(3-(thiophen-2-yl)allyl)picolinamide (29l): The compound **29l** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 63% (44 mg, *E:Z* = 37:63); IR (DCM): 3369, 1674, 1526, 1287 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, *J*= 5.0 Hz), 8.24 (d, 1H, *J*= 1.8 Hz), 8.17 (br. s, 1H), 7.45 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.36-7.34 (m, 1H), 7.08-7.06 (m, 2H), 6.71 (d, 1H, *J*= 11.5 Hz), 5.69 (dt, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 4.49 (td, 2H, J_1 = 6.7 Hz, J_2 = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 151.2, 149.0, 145.9, 139.2, 128.2, 127.2, 126.4, 126.2, 125.7, 124.2, 122.9, 38.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{12}ClN_2OS$: 279.0359; found 279.0348.

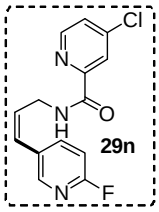


(*Z*)-*N*-(3-(5-Bromopyridin-2-yl)allyl)-4-chloropicolinamide (29m): The compound **29m** ((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a pale yellow colour liquid; R_f = 0.45 (EtOAc/Hexanes = 1:4); Yield: 54% (48 mg, *E:Z* = 23:77); IR (DCM): 3386, 1663, 1524, 1217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, 1H, *J*= 2.2 Hz), 8.69 (br. s, 1H), 8.47 (dd, 1H, J_1 = 5.2 Hz, J_2 = 0.4 Hz), 8.23 (dd, 1H, J_1 = 2.0 Hz, J_2 = 0.4 Hz), 7.81 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.44 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.0 Hz), 7.15 (d, 1H, *J*= 8.3 Hz), 6.52 (d, 1H, *J*= 11.6 Hz), 6.10 (dt, 1H, J_1 =



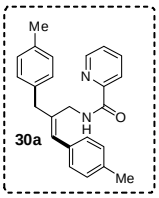
11.6 Hz, J_2 = 6.8 Hz), 4.64 (td, 2H, J_1 = 6.8 Hz, J_2 = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 154.0, 151.7, 150.4, 149.1, 145.8, 139.0, 133.3, 129.3, 126.2, 125.6, 123.0, 118.0, 37.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}BrClN_3O$: 351.9852; found 351.9844.

(*Z*)-4-Chloro-*N*-(3-(6-fluoropyridin-3-yl)allyl)picolinamide (29n): The compound **29n**



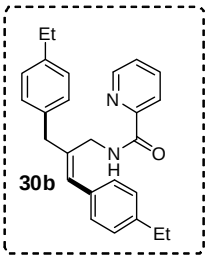
((*Z*)major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.45 (EtOAc/Hexanes = 1:4); Yield: 50% (37 mg, *E:Z* = 18:82); IR (DCM): 3381, 1717, 1678, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47-8.45 (m, 1H), 8.22 (br. s, 1H), 8.16 (br. s, 1H), 8.13 (br. s, 1H), 7.78 (t, 1H, *J*= 8.0 Hz), 7.47-7.46 (m, 1H), 6.98 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.8 Hz), 6.58 (d, 1H, *J*= 11.6 Hz), 5.95-5.90 (m, 1H), 4.35-4.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 162.6 (d, J_{C-F} = 238.6 Hz), 151.0, 149.0, 147.6 (d, J_{C-F} = 14.6 Hz), 146.0, 141.1 (d, J_{C-F} = 7.8 Hz), 130.1, 130.0 (d, J_{C-F} = 4.7 Hz), 127.0, 126.5, 123.0, 109.3 (d, J_{C-F} = 37.2 Hz), 37.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}ClFN_3O$: 292.0653; found 292.0644.

(*Z*)-*N*-(2-(4-Methylbenzyl)-3-(*p*-tolyl)allyl)picolinamide (30a): The compound **30a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70)



as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 43% (39 mg); IR (DCM): 3442, 1675, 1521, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.21 (d, 1H, *J*= 7.8 Hz), 7.99 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (m, 1H), 7.21-7.19 (m, 4H), 8.16 (d, 2H, *J*= 7.8 Hz), 7.11 (d, 2H, *J*= 7.8 Hz), 6.56 (s,1H), 4.26 (d, 2H, *J*= 5.8 Hz), 3.55 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8, 148.0, 137.4, 137.3, 136.6, 136.1, 135.8, 134.0, 130.4, 129.2, 129.0, 129.0, 128.7, 126.1, 122.2, 42.1, 39.3, 21.2, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O$: 357.1967; found 357.1982.

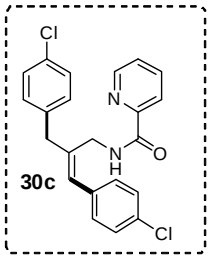
(*Z*)-*N*-(2-(4-Ethylbenzyl)-3-(4-ethylphenyl)allyl)picolinamide (30b): The compound **30b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes =



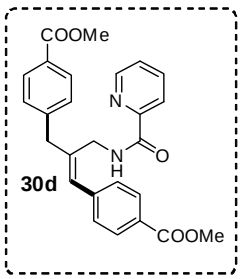
30:70) as a colourless liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 36% (29 mg); IR (DCM): 3389, 1679, 1512, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.21 (d, 1H, *J*= 7.8 Hz), 7.99 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 7.25-7.18 (m, 6H), 7.14 (d, 2H, *J*= 8.1 Hz), 6.59 (s, 1H), 4.27 (d, 2H, *J*= 5.8 Hz), 3.56 (s, 2H), 2.69-2.60 (m, 4H), 1.27-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8,

148.0, 143.0, 142.2, 137.4, 137.3, 136.3, 134.3, 130.5, 129.0, 128.8, 128.0, 127.9, 126.1, 122.2, 42.2, 39.3, 28.6, 28.5, 15.6, 15.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O$: 385.2280; found 385.2290.

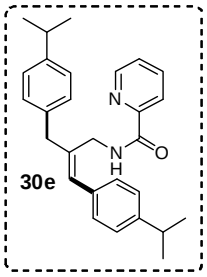
(*Z*)-*N*-(2-(4-chlorobenzyl)-3-(4-chlorophenyl)allyl)picolinamide (30c): The compound **30c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 40% (40 mg); IR (DCM): 3443, 1637, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.18 (d, 1H, *J*= 7.8 Hz), 7.96 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.44 (m, 1H), 7.33 (d, 2H, *J*= 8.5 Hz), 7.27-7.21 (m, 6H), 6.50 (s, 1H), 4.23 (d, 2H, *J*= 6.0 Hz), 3.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.5, 148.1, 138.4, 137.4, 137.4, 135.1, 132.9, 132.3, 130.4, 130.1, 129.6, 128.7, 128.6, 126.3, 122.2, 41.8, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}Cl_2N_2O$: 397.0874; found 397.0865.



(*Z*)-Dimethyl 4,4'-(2-(picolinamidomethyl)prop-1-ene-1,3-diyl)dibenzoate (30d): The compound **30d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 50% (56 mg); IR (DCM): 3377, 1718, 1678, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51-8.49 (m, 1H), 8.17 (d, 1H, *J*= 7.8 Hz), 8.03 (d, 2H, *J*= 8.3 Hz), 7.99 (br. s, 1H), 7.97 (d, 2H, *J*= 8.3 Hz), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.38 (m, 1H), 7.37 (d, 4H, *J*= 8.2 Hz), 6.56 (s, 1H), 4.27 (d, 2H, *J*= 5.9 Hz), 3.92 (s, 3H), 3.91 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 166.8, 164.3, 149.4, 148.0, 144.3, 141.4, 139.5, 137.4, 130.1, 129.9, 129.7, 129.1, 128.8, 128.6, 128.4, 126.3, 122.2, 52.1, 52.1, 42.3, 39.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_5$: 445.1763; found 445.1748.

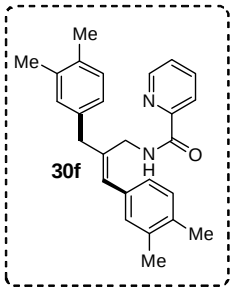


(*Z*)-*N*-(2-(4-Isopropylbenzyl)-3-(4-isopropylphenyl)allyl)picolinamide (30e): The compound **30e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 37% (39 mg), IR (DCM): 3390, 1680, 1518, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.21 (d, 1H, *J*= 7.8 Hz), 7.99 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 7.28-7.19 (m, 6H), 7.16 (d, 2H, *J*= 8.1 Hz), 6.59 (s, 1H), 4.28 (d, 2H, *J*=

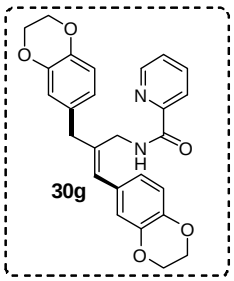


5.7 Hz), 3.56 (s, 1H), 2.98-2.85 (m, 2H), 1.26 (d, 6H, *J*= 6.9 Hz), 1.24 (d, 6H, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8, 148.0, 147.6, 146.8, 137.3, 137.3, 136.4, 134.4, 130.6, 128.9, 128.7, 126.5, 126.4, 126.1, 122.2, 42.3, 39.3, 33.8, 33.7, 24.1, 24.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{33}N_2O$: 413.2593; found 413.2594.

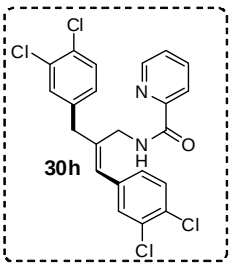
(*Z*)-*N*-(2-(3,4-Dimethylbenzyl)-3-(3,4-dimethylphenyl)allyl)picolinamide (30f): The compound **30f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a yellow colour liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 44% (43 mg); IR (DCM): 3396, 1678, 1520, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 8.20 (d, 1H, *J*= 7.8 Hz), 7.97 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 7.13-7.03 (m, 6H), 6.55 (s, 1H), 4.28 (d, 2H, *J*= 5.7 Hz), 3.52 (s, 2H), 2.27 (s, 6H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.0, 137.2, 136.6, 136.6, 136.4, 135.3, 134.5, 134.4, 130.4, 130.4, 130.1, 129.7, 129.6, 126.4, 126.1, 126.0, 122.1, 42.3, 39.4, 19.8, 19.8, 19.5, 19.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O$: 385.2280; found 385.2292.



(*Z*)-*N*-(3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)allyl)picolinamide (30g): The compound **30g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 46% (52 mg); IR (DCM): 3441, 1637, 1505, 1284, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (m, 1H), 8.20 (d, 1H, *J*= 7.8 Hz), 7.98 (br. s, 1H), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 6.85-6.83 (m, 2H), 6.81-6.78 (m, 3H), 6.75 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 6.47 (s, 1H), 4.30-4.22 (m, 10H), 3.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.8, 148.0, 143.4, 143.2, 142.6, 142.1, 137.3, 136.9, 132.4, 130.4, 129.9, 126.1, 122.2, 122.1, 122.0, 117.6, 117.6, 117.2, 117.1, 64.5, 64.4, 64.3, 64.3, 41.8, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_5$: 445.1763; found 445.1775.

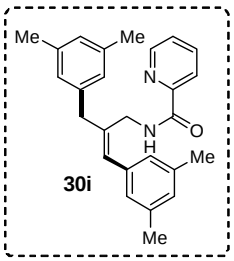


(*Z*)-*N*-(2-(3,4-Dichlorobenzyl)-3-(3,4-dichlorophenyl)allyl)picolinamide (30h): The compound **30h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield:

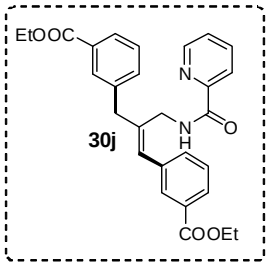


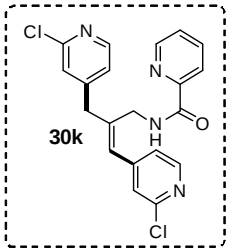
45% (53 mg); IR (DCM): 3384, 1738, 1676, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 8.17 (d, 1H, *J*= 7.8 Hz), 7.96 (br. s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.45 (m, 1H), 7.44 (d, 1H, *J*= 8.2 Hz), 7.40 (d, 1H, *J*= 1.7 Hz), 7.35 (d, 2H, *J*= 8.3 Hz), 7.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 7.12 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.0 Hz), 6.45 (s, 1H), 4.24 (dd, 2H, J_1 = 6.1 Hz, J_2 = 0.7 Hz), 3.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.3, 148.1, 139.2, 139.0, 137.4, 136.5, 132.6, 132.5, 131.2, 130.9, 130.7, 130.6, 130.5, 130.4, 128.7, 128.4, 128.1, 126.4, 122.2, 41.5, 39.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}Cl_4N_2O$: 465.0095; found 465.0081.

(*Z*)-*N*-(2-(3,5-Dimethylbenzyl)-3-(3,5-dimethylphenyl)allyl)picolinamide (30i): The compound **30i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 47% (46 mg); IR (DCM): 3388, 1679, 1520, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.21 (d, 1H, *J*= 7.8 Hz), 7.97 (br. s, 1H), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 6.94-6.91 (m, 5H), 6.83 (s, 1H), 6.54 (s, 1H), 4.30 (d, 2H, *J*= 5.8 Hz), 3.51 (s, 2H), 2.33 (s, 6H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 147.9, 139.1, 137.9, 137.8, 137.6, 137.2, 136.9, 130.6, 128.5, 127.9, 126.9, 126.6, 126.0, 122.1, 42.5, 39.5, 21.3, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O$: 385.2280; found 385.2289.



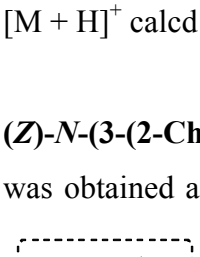
(*Z*)-Diethyl 3,3'-(2-(picolinamidomethyl)prop-1-ene-1,3-diyl)dibenzoate (30j): The compound **30j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 41% (49 mg); IR (DCM): 1716, 1680, 1521, 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52-8.50 (m, 1H), 8.18 (d, 1H, *J*= 7.8 Hz), 8.02 (br. s, 1H), 7.97-7.91 (m, 3H,), 7.89-7.83 (m, 2H), 7.51 (d, 2H, *J*= 7.7 Hz), 7.45-7.37 (m, 3H), 6.56 (s, 1H), 4.39 (q, 2H, *J*= 7.1 Hz), 4.37 (q, 2H, *J*= 7.1 Hz), 4.27 (d, 2H, *J*= 5.9 Hz), 3.66 (s, 2H), 1.41 (t, 3H, *J*= 7.1 Hz), 1.38 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 166.5, 164.3, 149.5, 148.0, 139.1, 138.9, 137.3, 137.0, 133.7, 133.0, 130.8, 130.6, 130.2, 130.0, 129.9, 128.6, 128.5, 128.1, 127.8, 126.2, 122.2, 61.1, 61.0, 41.9, 39.3, 14.4, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5$: 473.2076; found 473.2093.



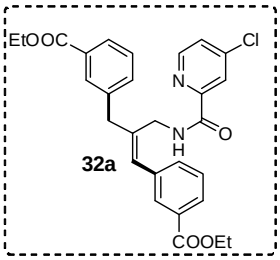


(*Z*)-*N*-(3-(2-Chloropyridin-4-yl)-2-((2-chloropyridin-4-yl)methyl)allyl)picolinamide (30k): The compound **30k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.45 (EtOAc/Hexanes = 1:4); Yield: 34% (34 mg); IR (DCM): 3371, 1672, 1527, 1465, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52-8.51 (m, 1H), 8.39 (d, 1H, *J*= 5.1 Hz), 8.27 (d, 1H, *J*= 5.1 Hz), 8.16 (d, 1H, *J*= 7.8 Hz), 8.03 (br. s, 1H), 7.88 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.49-7.45 (m, 1H), 7.29 (br. s, 1H), 7.23 (br. s, 1H), 7.21 (dd, 1H, J_1 = 5.1 Hz, J_2 = 0.9 Hz), 7.14 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.4 Hz), 6.42 (s, 1H), 4.27 (d, 2H, *J*= 5.6 Hz), 3.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 152.0, 150.8, 149.8, 148.9, 148.2, 147.1, 141.3, 137.6, 127.8, 126.6, 124.6, 124.0, 122.9, 122.3, 122.2, 41.1, 39.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}Cl_2N_4O$: 399.0779; found 399.0765.

(*Z*)-*N*-(3-(2-Chloropyridin-4-yl)-2-methylallyl)picolinamide (31a): The compound **31a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.48 (EtOAc/Hexanes = 1:4); Yield: 30% (22 mg); IR (DCM): 2925, 1713, 1423, 1364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.35 (d, 1H, *J*= 5.1 Hz), 8.22 (d, 1H, *J*= 7.8 Hz), 8.16 (br. s, 1H), 7.89 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.49-7.45 (m, 1H), 7.25 (br. s, 1H), 7.18 (dd, 1H, J_1 = 5.1 Hz, J_2 = 0.9 Hz), 6.38 (s, 1H), 4.30 (d, 2H, *J*= 6.1 Hz), 2.01 (d, 3H, *J*= 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 151.8, 149.6, 149.4, 148.1, 148.0, 140.6, 137.5, 126.4, 124.9, 123.9, 122.3, 40.6, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}ClN_3O$: 288.0904; found 288.0895.

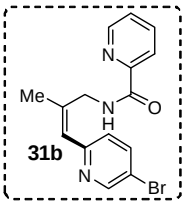


(*Z*)-Diethyl 3,3'-(2-((4-chloropicolinamido)methyl)prop-1-ene-1,3-diyl)dibenzoate (32a): The compound **32a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 40% (51 mg); IR (DCM): 1716, 1679, 1521, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, 1H, *J*= 4.4 Hz), 8.17 (d, 1H, *J*= 1.9 Hz), 7.95-7.94 (m, 3H), 7.91-7.89 (m, 2H,), 7.50 (dd, 2H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.46-7.36 (m, 3H), 6.58 (s,1H), 4.39 (q, 4H, *J*= 7.1 Hz), 4.27 (d, 2H, *J*= 6.0 Hz), 3.65 (s, 2H), 1.40 (t, 6H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 166.4, 163.1, 151.0, 148.9,

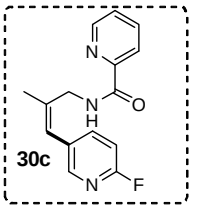


145.8, 139.1, 138.5, 136.9, 133.5, 133.0, 130.8, 130.6, 130.2, 130.1, 129.8, 128.6, 128.5, 128.2, 127.8, 126.3, 122.8, 61.1, 61.0, 42.0, 39.4, 14.4, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{28}ClN_2O_5$: 507.1687; found 507.1669.

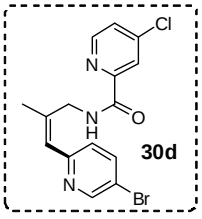
(*Z*)-*N*-(3-(5-Bromopyridin-2-yl)-2-methylallyl)picolinamide (31b): The compound **31b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.43 (EtOAc/Hexanes = 1:4); Yield: 41% (34 mg); IR (DCM): 2929, 1716, 1674, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.91 (br. s, 1H), 8.72 (d, 1H, *J*= 2.3 Hz), 8.56 (d, 1H, *J*= 4.8 Hz), 8.22 (d, 1H, *J*= 7.8 Hz), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.77 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.43-7.40 (m, 1H), 7.10 (d, 1H, *J*= 8.4 Hz), 6.39 (s, 1H), 4.49 (d, 2H, *J*= 6.6 Hz), 2.08 (d, 3H, *J*= 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 154.5, 150.3, 150.2, 148.2, 142.5, 138.9, 137.2, 126.1, 126.0, 125.2, 122.3, 118.0, 40.6, 24.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}BrN_3O$: 332.0398; found 332.0388.



(*Z*)-*N*-(3-(6-Fluoropyridin-3-yl)-2-methylallyl)picolinamide (30c): The compound **30c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.43 (EtOAc/Hexanes = 1:4); Yield: 41% (28 mg); IR (DCM): 2927, 1672, 1526, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 8.22 (d, 1H, *J*= 7.8 Hz), 8.12 (d, 1H, *J*= 1.8 Hz), 8.12 (br. s, 1H), 7.89 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.78 (td, 1H, J_1 = 8.1 Hz, J_2 = 2.4 Hz), 7.48-7.45 (m, 1H), 6.93 (dd, 1H, J_1 = 8.4 Hz, J_2 = 3.0 Hz), 6.43 (s, 1H), 4.24 (d, 2H, *J*= 6.0 Hz), 2.01 (d, 3H, *J*= 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 162.3 (d, J_{C-F} = 237.8 Hz), 149.5, 148.1, 147.4 (d, J_{C-F} = 14.5 Hz), 141.2 (d, J_{C-F} = 7.8 Hz), 137.8, 137.5, 130.8 (d, J_{C-F} = 4.6 Hz), 126.4, 123.7, 122.3, 109.1 (d, J_{C-F} = 37.1 Hz), 40.5, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}FN_3O$: 272.1199; found 272.1188.

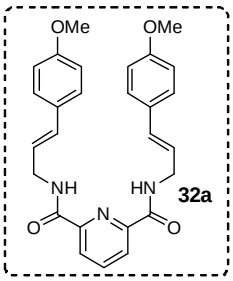


(*Z*)-*N*-(3-(5-Bromopyridin-2-yl)-2-methylallyl)-4-chloropicolinamide (30d): The compound **30d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.40 (EtOAc/Hexanes = 1:4); Yield: 40% (37 mg); IR (DCM): 3384, 1675, 1515, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (br. s, 1H), 8.72 (d, 1H, *J*=

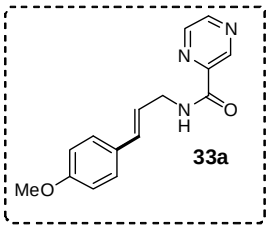


2.3 Hz), 8.46 (d, 1H, *J*= 5.2 Hz), 8.23 (d, 1H, *J*= 2.0 Hz), 7.78 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.43 (dd, 1H, J_1 = 5.2 Hz, J_2 = 2.1 Hz), 7.09 (d, 1H, *J*= 8.2 Hz), 6.39 (s, 1H), 4.48 (d, 2H, *J*= 6.7 Hz), 2.08 (d, 3H, *J*= 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 154.4, 151.8, 150.2, 149.1, 145.7, 142.3, 139.0, 126.2, 126.1, 125.2, 123.0, 118.1, 40.7, 24.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}BrClN_3O$: 366.0009; found 366.0021.

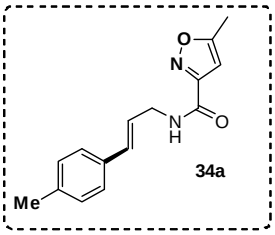
N_2,N_6-Bis((*E*)-3-(4-methoxyphenyl)allyl)pyridine-2,6-dicarboxamide (32a): The compound **32a** ((*E*) major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 40% (46 mg, *E:Z* = 67:33); IR (DCM): 3441, 1643, 1524, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 2H, *J*= 7.8 Hz), 8.05 (t, 1H, *J*= 7.8 Hz), 8.00 (t, 1H, *J*= 6.1 Hz), 7.26 (d, 4H, *J*= 8.8 Hz), 6.82 (d, 4H, *J*= 8.8 Hz), 6.52 (d, 2H, *J*= 15.8 Hz), 6.13 (dt, 2H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.27 (td, 4H, J_1 = 6.3 Hz, J_2 = 1.2 Hz), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 159.3, 148.8, 139.0, 132.0, 129.0, 127.6, 125.3, 122.8, 114.0, 55.3, 41.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{27}N_3NaO_4$: 480.1899; found 480.1916.



(*E*)-*N*-(3-(4-Methoxyphenyl)allyl)pyrazine-2-carboxamide (33a): The compound **33a** ((*E*) major isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 35% (24 mg, *E:Z* = 62:38); IR (DCM): 3447, 1637, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (d, 1H, *J*= 1.5 Hz), 8.78 (d, 1H, *J*= 2.5 Hz), 8.55 (dd, 1H, J_1 = 2.5 Hz, J_2 = 1.5 Hz), 7.96 (br. s, 1H), 7.33 (d, 2H, *J*= 8.8 Hz), 6.87 (d, 2H, *J*= 8.8 Hz), 6.59 (d, 1H, *J*= 15.8 Hz), 6.17 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.28 (td, 2H, J_1 = 6.4 Hz, J_2 = 1.4 Hz), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 159.4, 147.3, 144.5, 142.6, 132.3, 129.2, 127.6, 122.5, 114.2, 55.3, 41.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{15}N_3NaO_2$: 292.1062; found 292.1051.

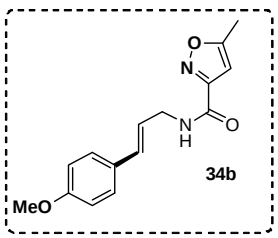


(*E*)-5-Methyl-*N*-(3-(*p*-tolyl)allyl)isoxazole-3-carboxamide (34a): The compound **34a** ((*E*) major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.50 (EtOAc/Hexane = 1:4); Yield: 78% (50 mg, *E:Z* = 98:2); IR (DCM): 3294, 1660, 1558, 1304 cm^{-1};^{1}H NMR (400 MHz,

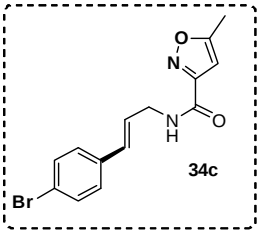


$CDCl_3$): δ 7.28 (d, 2H, *J*= 8.0 Hz), 7.14 (d, 2H, *J*= 8.0 Hz), 7.02 (br. s, 1H), 6.58 (d, 1H, *J*= 15.8 Hz), 6.48 (d, 1H, *J*= 0.7 Hz), 6.20 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.22 (td, 2H, J_1 = 6.4 Hz, J_2 = 1.4 Hz), 2.49 (d, 3H, *J*= 0.7 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 159.0, 158.7, 137.7, 133.6, 132.6, 129.3, 126.3, 123.5, 101.5, 41.5, 21.2, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1281.

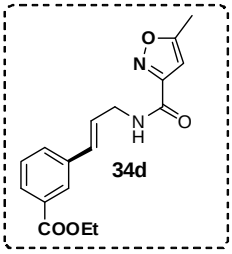
(*E*)-*N*-(3-(4-Methoxyphenyl)allyl)-5-methylisoxazole-3-carboxamide (34b): The compound **34b** ((*E*) major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as colourless liquid; R_f = 0.50 (EtOAc/hexane = 1:4); Yield: 60% (41 mg, *E:Z* = 98:2); IR (DCM): 3290, 1659, 1553, 1455 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 2H, *J*= 8.7 Hz), 6.96 (br. s, 1H), 6.87 (d, 2H, *J*= 8.7 Hz), 6.56 (d, 1H, *J*= 15.8 Hz), 6.48 (br. s, 1H), 6.12 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.21 (td, 2H, J_1 = 6.2 Hz, J_2 = 1.4 Hz), 3.83 (s, 3H) 2.50 (d, 3H, *J*= 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 159.4, 159.0, 158.7, 132.3, 129.1, 127.6, 122.2, 114.0, 101.5, 55.3, 41.5, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{16}N_2NaO_3$: 295.1059; found 295.1048.



(*E*)-*N*-(3-(4-Bromophenyl)allyl)-5-methylisoxazole-3-carboxamide (34c): The compound **34c** ((*E*) major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 69% (56 mg, *E:Z* = 98:2); IR (DCM): 3288, 1656, 1552, 1453, cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J*= 8.5 Hz), 7.24 (d, 2H, *J*= 8.5 Hz), 7.05 (br. s, 1H), 6.54 (d, 1H, *J*= 15.8 Hz), 6.48 (d, 1H, *J*= 0.9 Hz), 6.25 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.2 Hz), 4.22 (td, 2H, J_1 = 6.1 Hz, J_2 = 1.5 Hz), 2.49 (d, 3H, *J*= 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 159.0, 158.6, 135.3, 131.7, 131.3, 128.0, 125.5, 121.6, 101.5, 41.2, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}BrN_2O_2$: 321.0239; found 321.0227.

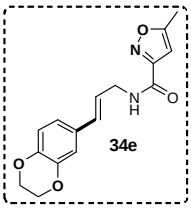


(*E*)-Ethyl 3-(3-(5-methylisoxazole-3-carboxamido)prop-1-en-1-yl)benzoate (34d): The compound **34d** ((*E*) major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.50



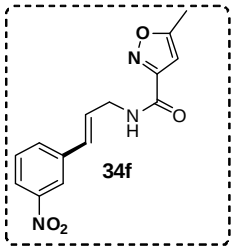
(EtOAc/Hexanes = 1:4); Yield: 75% (59 mg, *E:Z* = 98:2); IR (DCM): 3335, 1716, 1681, 1546 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.93 (d, 1H, *J*= 7.8 Hz), 7.55 (d, 1H, *J*= 7.8 Hz), 7.40 (t, 1H, *J*= 7.7 Hz), 7.06 (br. s, 1H), 6.64 (d, 1H, *J*= 15.9 Hz), 6.48 (d, 1H, *J*= 0.7 Hz), 6.34 (dt, 1H, J_1 = 15.9 Hz, J_2 = 6.1 Hz), 4.39 (q, 2H, *J*= 7.1 Hz) 4.25 (td, 2H, J_1 = 6.1 Hz, J_2 = 1.4 Hz), 2.50 (s, 3H), 1.41 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 166.4, 159.1, 158.7, 136.7, 131.5, 130.9, 130.6, 128.8, 128.6, 127.5, 126.0, 101.5, 61.1, 41.2, 14.4, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}N_2NaO_4$: 337.1164; found 337.1152.

(*E*)-*N*-(3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)allyl)-5-methylisoxazole-3-carboxamide (34e): The compound **34e** ((*E*) major isomer) was obtained after purification by column



chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless solid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 70% (53 mg, *E:Z* = 98:2); mp 115-117 ^{o}C; IR (DCM): 3434, 1673, 1508, 1308 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (br. s, 1H), 6.90-6.85 (m 2H), 6.81 (d, 1H, *J*= 8.3 Hz), 6.48 (d, 1H, *J*= 15.8 Hz), 6.47 (s, 1H), 6.09 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 4.27-4.24 (m, 4H), 4.19 (td, 2H, J_1 = 6.2 Hz, J_2 = 1.4 Hz), 2.50 (d, 3H, *J*= 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 158.9, 158.7, 143.5, 143.4, 132.1, 130.2, 122.9, 119.9, 117.3, 115.0, 101.5, 64.4, 64.3, 41.4, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_4$: 301.1188; found 301.1176.

(*E*)-5-Methyl-*N*-(3-(3-nitrophenyl)allyl)isoxazole-3-carboxamide (34f): The compound



34f ((*E*) major isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 35:65) as a colourless liquid; R_f = 0.50 (EtOAc/Hexanes = 1:4); Yield: 64% (46 mg, *E:Z* = 98:2); IR (DCM): 3325, 1674, 1529, 1457 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.10 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.7 Hz), 7.68 (d, 1H, *J*= 7.7 Hz), 7.50 (t, 1H, *J*= 8.0 Hz), 7.11 (br. s, 1H), 6.66 (d, 1H, *J*= 15.9 Hz), 6.49 (s, 1H), 6.42 (dt, 1H, J_1 = 15.9 Hz, J_2 = 5.9 Hz), 4.29-4.27 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 159.1, 158.6, 148.6, 138.2, 132.2, 129.9, 129.5, 128.3, 122.4, 121.1, 101.5, 41.0, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_4$: 288.0984; found 288.0971.

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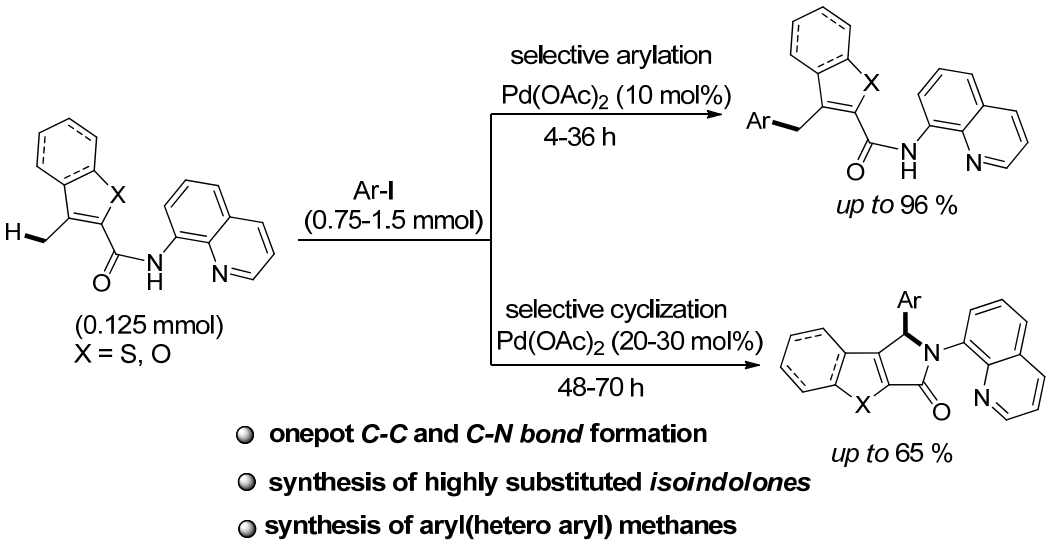
Chapter 5. **Pd(II)-catalyzed arylation and intramolecular amination of γ-C(sp^3)-H bonds: Synthesis of arylheteroarylmethanes and pyrrolidone-ring annulated furan/thiophene derivatives.**

Introduction

The functionalization of the C(sp^3)-H bonds of alkyl chains and cyclic compounds, etc has gained attention after the papers by Daugulis [1] and Yu [2] in which they independently showed the Pd(II)-catalyzed functionalization of *β*-C(sp^3)-H bonds of carboxamidesusing bidentate directing groups (e.g. 2-picolinamide, 8-aminoquinoline and 2-(methylthio)aniline) and the monodentate directing group 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline. Sarpong and coworkers shown recent advances in intramolecular C(sp^3)-H amination.[9]

There exist numerous reports dealing with the picolinamide-aided[3,4] functionalization of the *γ*-C-H bonds of amine systems and functionalization of the remote *δ*- and *ε*-C-H bonds of amine systems were also studied. It is to be noted that the 8-aminoquinoline-type bidentate directing groups and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline monodentate directing group werecommonly studied for the functionalization of the *β*-C-H bonds of carboxylic acid systems. However, there exist only exceptional reportson the 8-aminoquinoline-aided functionalization of *γ*-C-H bonds of carboxylic acid systems.



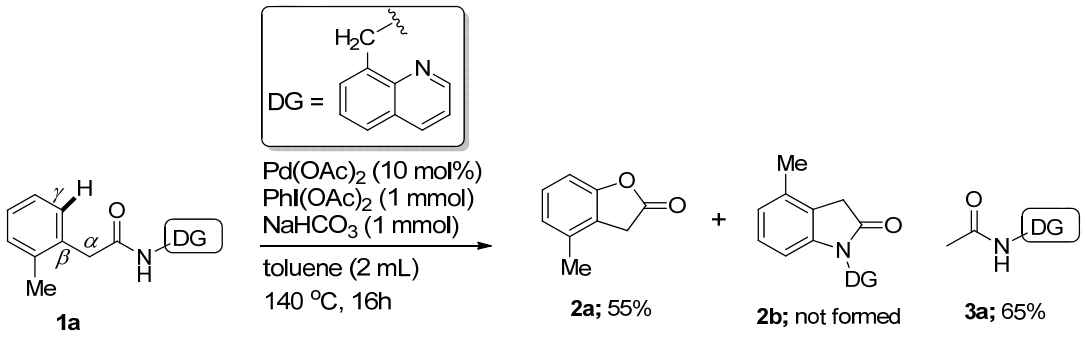
A part of this thesis envisages the functionalization of the *γ*-C(sp^3)-H bonds using newcarboxamide systems, e.g., 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/thiophene-2-carboxamide systems Accordingly, if the *γ*-C(sp^3)-H bonds of these substrates are subjected to the Pd(II)-catalyzed arylation or successive arylation and

intramolecular amination,thenthe synthesis of furan/thiophene-based arylheteroarylmethane scaffolds and pyrrolidone-ring annulated furan/thiophene-based novel heterocycles can be accomplished.

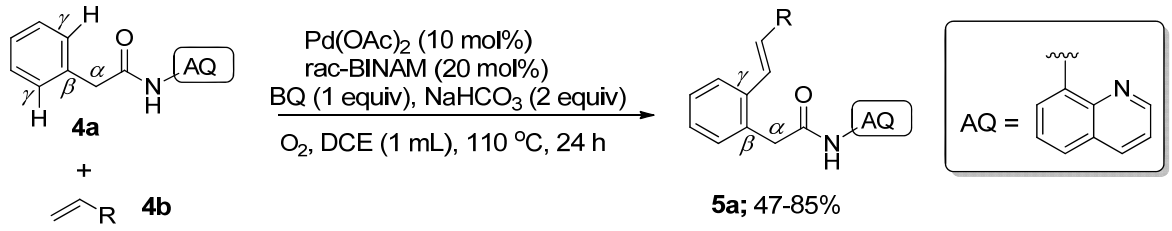
Functionalized furans/thiophenes and benzo-furans/thiophenes including arylheteroarylmethane (unsymmetrical diarylmethanes) are important class of molecules in organic synthesis and medicinal chemistry. In the following section, representative reports dealing with the Pd(II)-catalyzed functionalization of the *γ*-, *δ*- and *ε*-C-H bonds of appropriate carboxamides, intramolecular amination process and the importance of isoindolin-1-one heterocycles which are relevant to the results of this part of the thesis are discussed.

Representative reports dealing with the functionalization of the *γ*-, *δ*- and *ε*-C-H bonds of appropriate carboxamides, intramolecular amination process and the importance of isoindolin-1-one heterocycles which are relevant to the results of this part of the thesis.

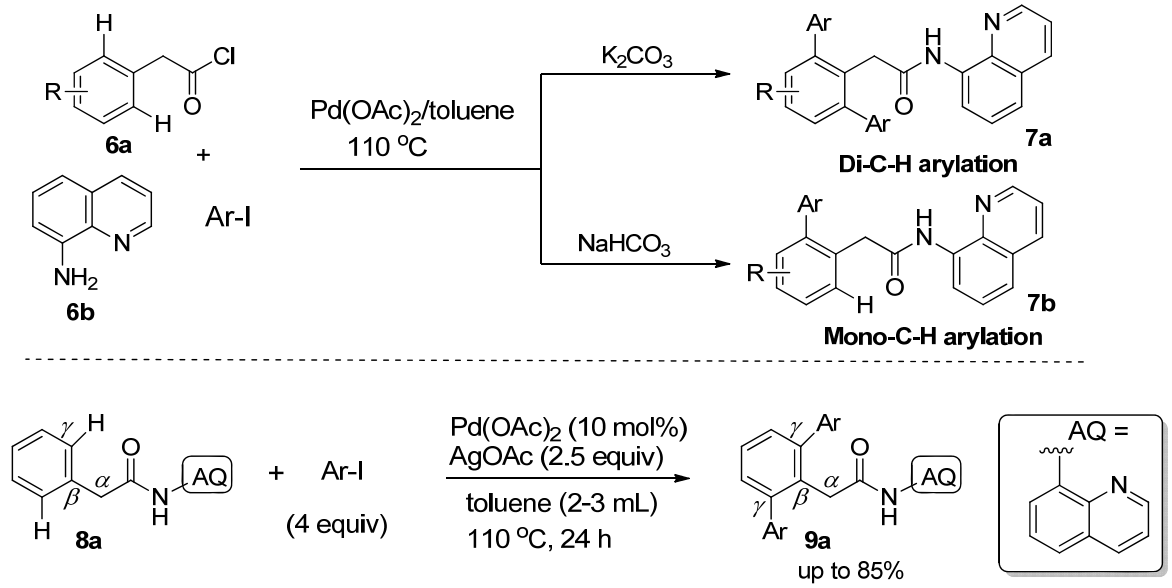
Chatani and co-workers[5a]reported quinolin-8-ylmethylamine directed γC-H activation/ lactonization of arylacetamides**1a**. Treatment of quinolin-8-ylmethylamine **1a** with $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.0 mmol) and $NaHCO_3$ (1.0 mmol) in toluene afforded the γ-lactones **2a** (Scheme 3). Maiti and co-workers[5b] reportedthe Pd-catalyzed *ortho* C-H bond olefination **4a** with unactivated aliphatic alkenes **4b**, whichafforded the product **5a** (Scheme4). Wan[5c] reported the Pd(II)-catalyzed C(sp^2)-H bond one-pot arylation reaction involving **6a**, **6b** andAr-I K_2CO_3 and $NaHCO_3$, which afforded the corresponding products **7a** and **7b** (Scheme 5). Concurrently, our group[5d] also reported a similar work for the synthesis of γ-arylated arylacetamide derivatives **9a** (Scheme 5).



Scheme 3. $Pd(OAc)_2$-catalyzed synthesis of lactone of **1a**



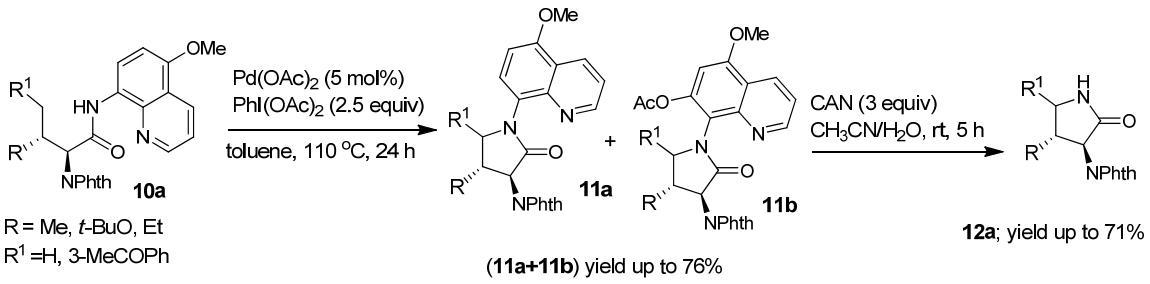
Scheme 4. Pd-catalyzed γ-C(sp^2)-H olefination of arylacetamides **4a**.



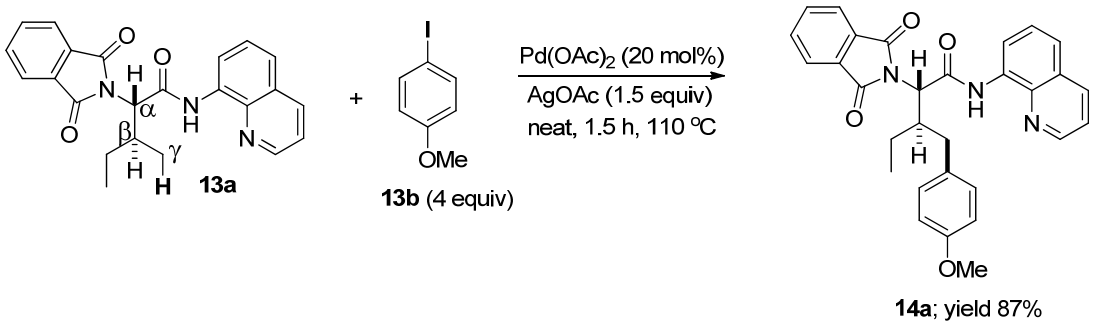
Scheme 5. Pd(II)-catalyzed γ-C(sp^2)-H arylation of arylacetamides**.**

Chen and co-workers[6a] reported the synthesis pyrrolidones *via* the Pd-catalyzed intramolecular amination of unactivated γ-C(sp^3)-H bonds (Scheme 6).The reaction of amide **10a** with $PhI(OAc)_2$ in toluene at 110 °C afforded the mixture of products **11a**/**11b**, which on further reaction with CAN in CH_3CN/H_2O afforded the pyrrolidones **12a** (Scheme 6).

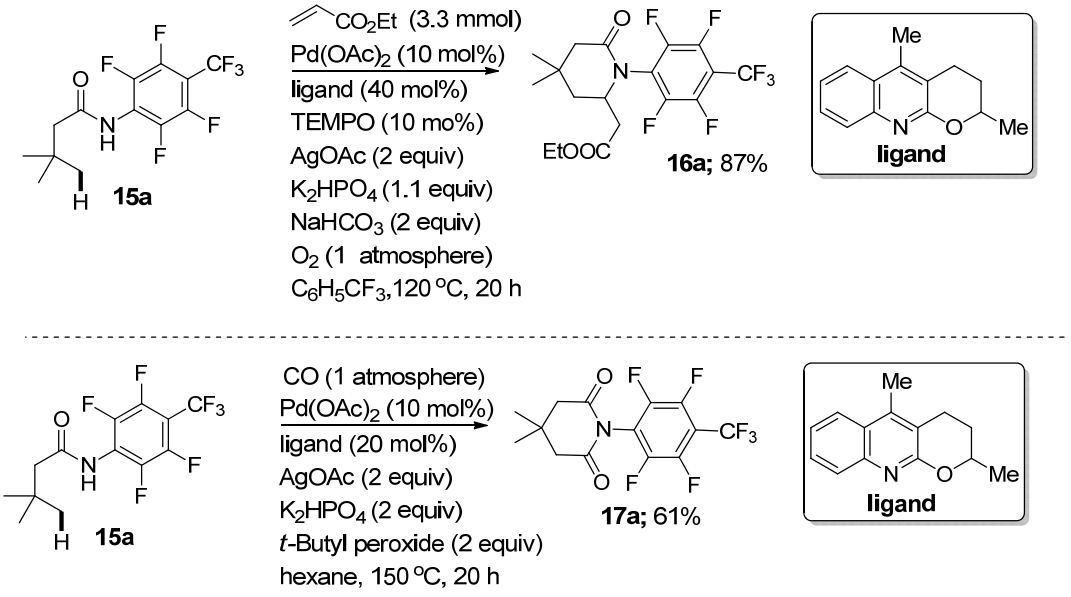
Corey [6b] reportedthe Pd(II)-catalyzed γ-C(sp^3)-H arylation of α-amino acid derivatives. The arylation of amide **13a**with *p*-iodoanisole**13b** afforded theγ-C-H arylated derivative **14a** (Scheme 7). Yu[6c]reported examples of γ-C(sp^3)-H carbonylation/olefination of **15a**, which provided the pyrrolidone-rings **16a** and **17a** (Scheme 8).



Scheme 6. Intramolecular amination of γ-C(sp^3)-H bonds**10a**.



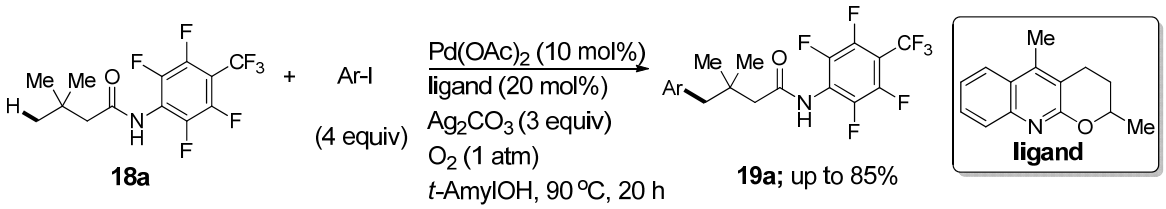
Scheme 7. Pd-catalyzed γ-C(sp^3)-H arylation of amino acid derivatives **13a**.



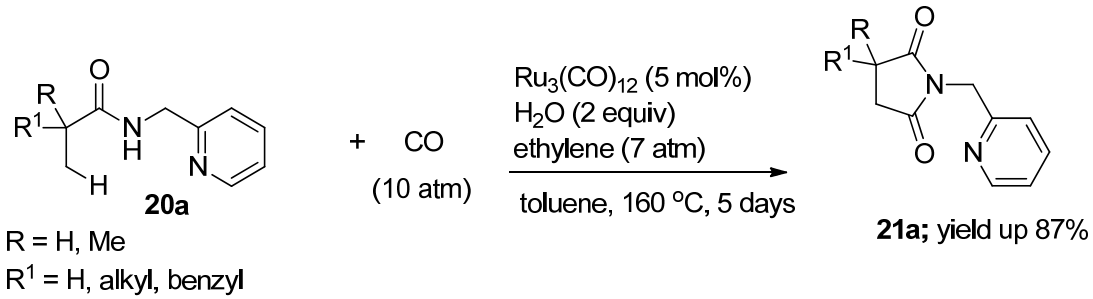
Scheme 8.Ligand-enabled γ-C(sp^3)-H olefination and carbonylation of **15a**.

Yu [7a] reportedγ-C(sp^3)-H arylationof **18a** in the presence of $Pd(OAc)_2$ (10 mol %), ligand (20 mol%), and Ag_2CO_3 (3equiv) in *t*-amylOH at 90 °C under an oxygenatm, which gave the γ-C-H arylated aliphatic acids **19a** (Scheme 9). Chatani group [7b] published a ruthenium-catalyzed β-C-H carbonylation reaction, directed by the 2-pyridylmethylamine auxiliary **20a**

(Scheme 10).The carbonylation of amide **20a** with $Ru_3(CO)_{12}$ as a catalyst in the presence CO/ethylene atmosphere in toluene at 160 ^oC afforded the functionalized cyclic lactams **21a** (Scheme 10).

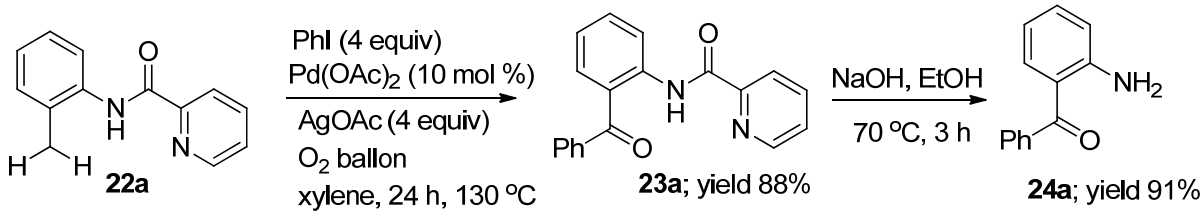


Scheme 9.Ligand-enabled γ-C(sp^3)-H arylationof carboxamide **18a.**

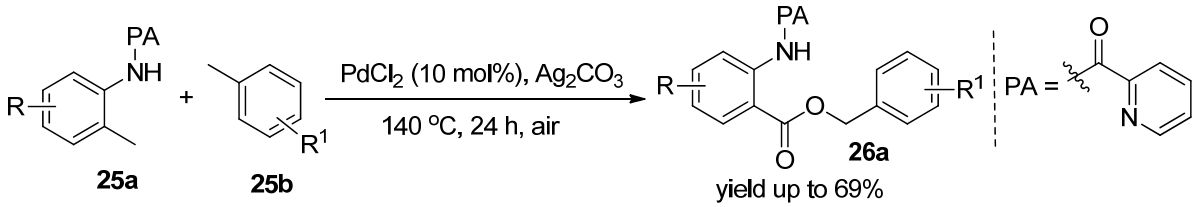


Scheme 10. Ruthenium-catalyzed synthesis of succinimides *via*β-carbonylation of **20a.**

Zhang andco-workers[7c] reported the palladium-catalyzed benzylicC-H arylation/oxidation of **22a** with aryl iodide, which afforded product **23a** in 88% yield (Scheme 11).Further, removal of the directing group from the product **23a** under basic hydrolysis conditions afforded 2-aminobenzophenone derivatives **24a** in 91% yield. Zhang[7d] reported picolinamide-directed Pd-catalyzed benzylic C(sp^3)-H activation of alkylbenzene **25a**,which afforded benzyl esters **26a** *via* multiple C-H bond functionalization(Scheme 12).

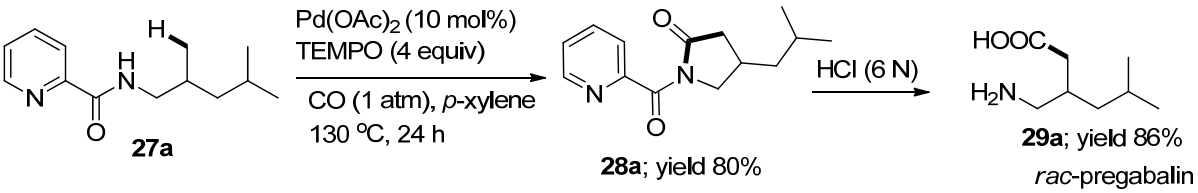


Scheme 11. Pd-catalyzed arylation/oxidation of a benzylic C-Hbond.

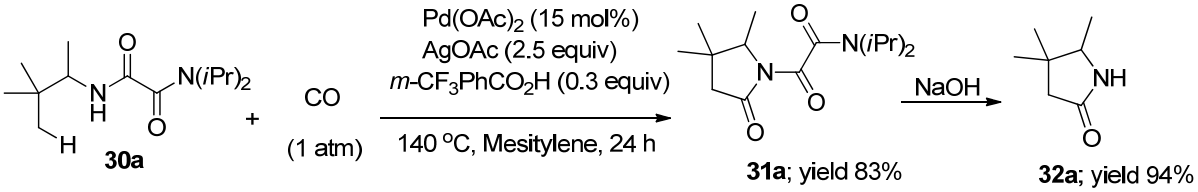


Scheme 12. Pd-catalyzed one pot arylation/oxidation of **25a**.

Wang group[7e] reported picolinamide-directed Pd-catalyzed C(sp^3)-H carbonylationof alkylamines **27a** and the synthesis of γ-lactams **28a** and γ-amino acidderivatives **29a**(Scheme 13).Zhao group[7f] reported the Pd-catalyzed regioselective γ-C-H carbonylation of oxalylamide **30a** with carbon monoxide and the synthesis of pyrrolidones **31a**, which were subjected to hydrolysis reaction to give **32a** (Scheme 14).



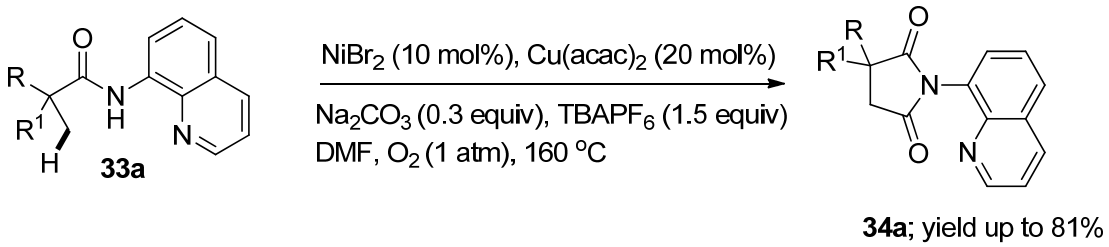
Scheme 13. Pd(II)-catalyzed C(sp^3)-H carbonylation of **27a**.



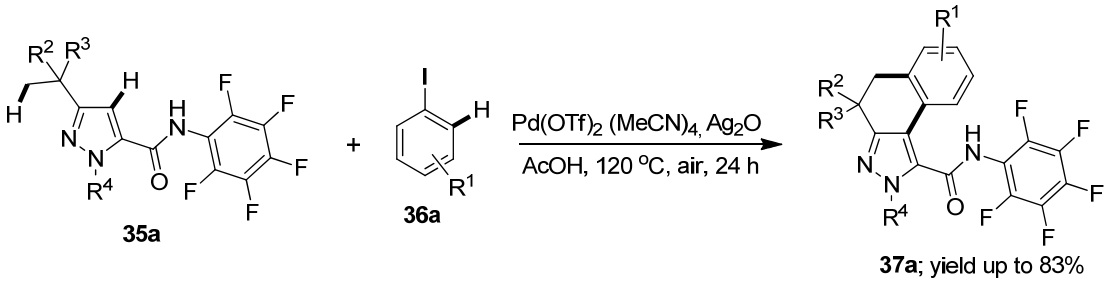
Scheme 14. Palladium-catalyzed carbonylation of γ-C(sp^3)-H bonds**30a**.

Ge group[7g] reported the direct carbonylation of aliphatic amides**33a**with nickel/coppersynergistic catalysis under atmospheric oxygen with DMF as the carbon source of carbonyl group, which afforded the product **34a** (Scheme 15).

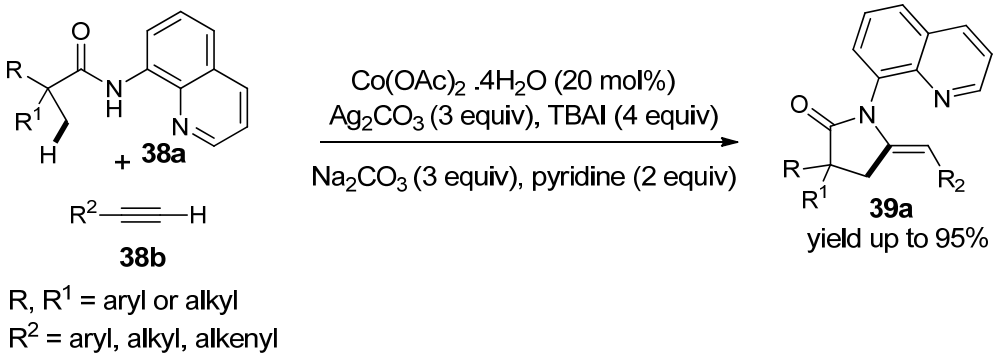
Yu group[7h] developed the Pd(II)-catalyzed pyrazole-directed C(sp^3)-H arylation of amide **35a** with aryl iodide **36a** followed by an intramolecular C-H activation/cyclization, which affordedthe dihydro benzo[*e*]indazole derivatives **37a** (Scheme 16). Zhang and co-workers[7i]reported the cobalt-catalyzed synthesis of pyrrolidinones **39a** from aliphatic amides **38a** and terminal alkynes **38b** (Scheme 17).



Scheme 15. Aerobic carbonylation of C(sp^3)-H bonds via nickel/copper catalysis.



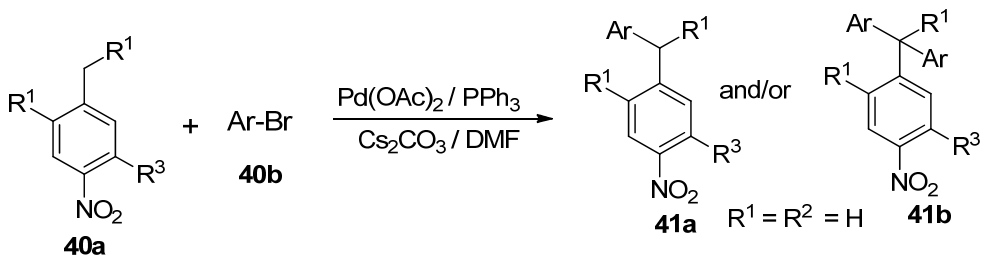
Scheme 16. Synthesis ofpyrazole derivatives**37a**.



Scheme 17. Cobalt-catalyzed synthesis of **39a.**

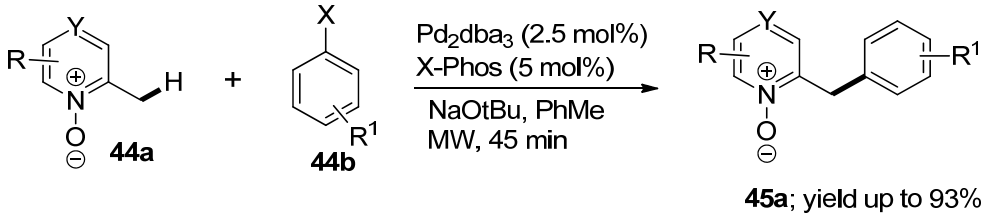
Representative reports dealing on the C-H functionalization reactions of benzylic substrates and the synthesis functionalized diarylmethanemoieties *via*benzylicsp^3 C-H bond activation.

Miura and co-workers [8a] reported the Pd-catalyzed coupling of4-alkylnitrobenzenes **40a** with aryl bromides **40b**, which afforded mono- and/or di-arylated products **41a** and **41b** in good yields (Scheme 18). Charettegroup[8b] reported Pd-catalyzed benzylic C-H arylation of *N*-iminopyridinium ylides **42a** with aryl chloride **42b,** whichgave 2-substituted *N*-iminopyridinium ylides **43a** (Scheme 19). Fagnouand co-workers[8c-d]developed the site-selectiveC(sp^3)-H arylation of azine *N*-oxides **44a** with aryl halides **44b,** whichgave the benzylated compounds **45a** (Scheme 20).



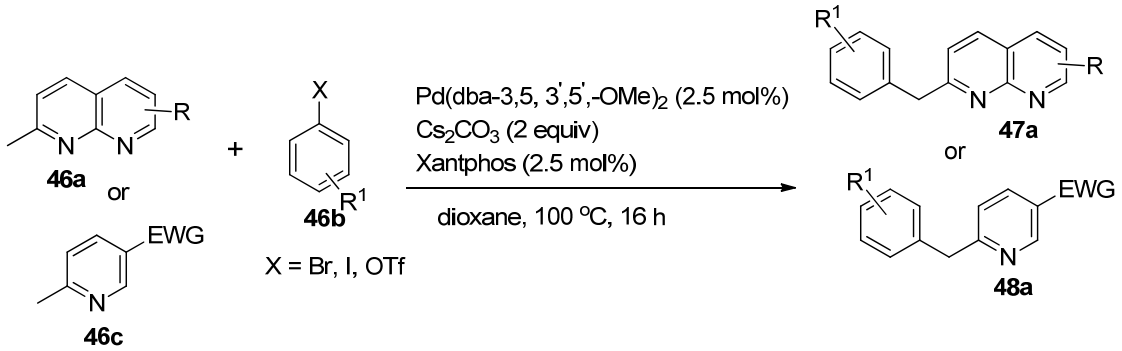
Scheme 18. Pd-catalyzed coupling reaction of 4-alkylbenzenes **40a** with aryl bromides **40b**.

Scheme 19. Pd-catalyzed arylation of *N*-iminopyridinium ylide**42a** with aryl chloride **42b**.



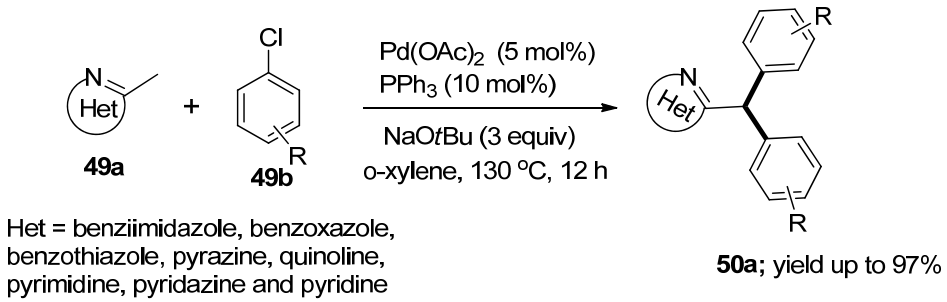
Scheme 20. Pd-catalyzed sp^{3}arylation of picoline *N*-oxide.

Morrisgroup[8e] reported the palladium-catalyzed direct arylation of benzylic sp^{3}C-H bonds adjacent to electron-deficient heteroaromatics **46a, 46c** with aryl halides **46b** under mild conditions, which gave **6n** and **6o** (Scheme 21).



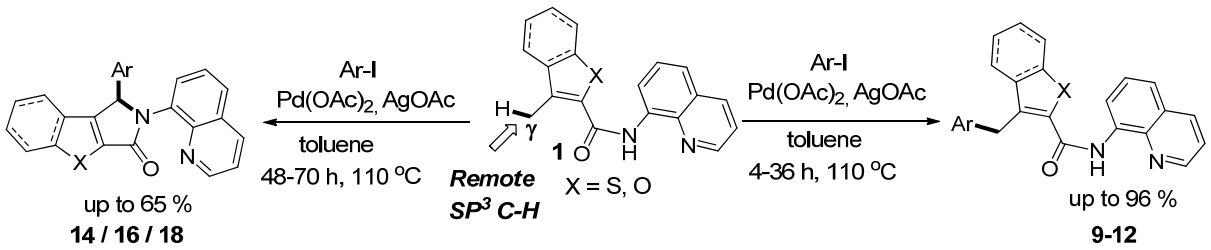
Scheme 21. Pd-Catalyzed sp^3 C-H arylation of electron-deficient heterocycles **46a** and **46c.**

Li group[8f] developed the Pd-catalyzed cross-coupling of (2-azaaryl)-methanes**47a** with aryl chlorides **48a,** whichgavethe diarylation products **50a** (Scheme 22).



Scheme 22. Pd-Catalyzed diarylation of (2-azaaryl) methanes **49a**.

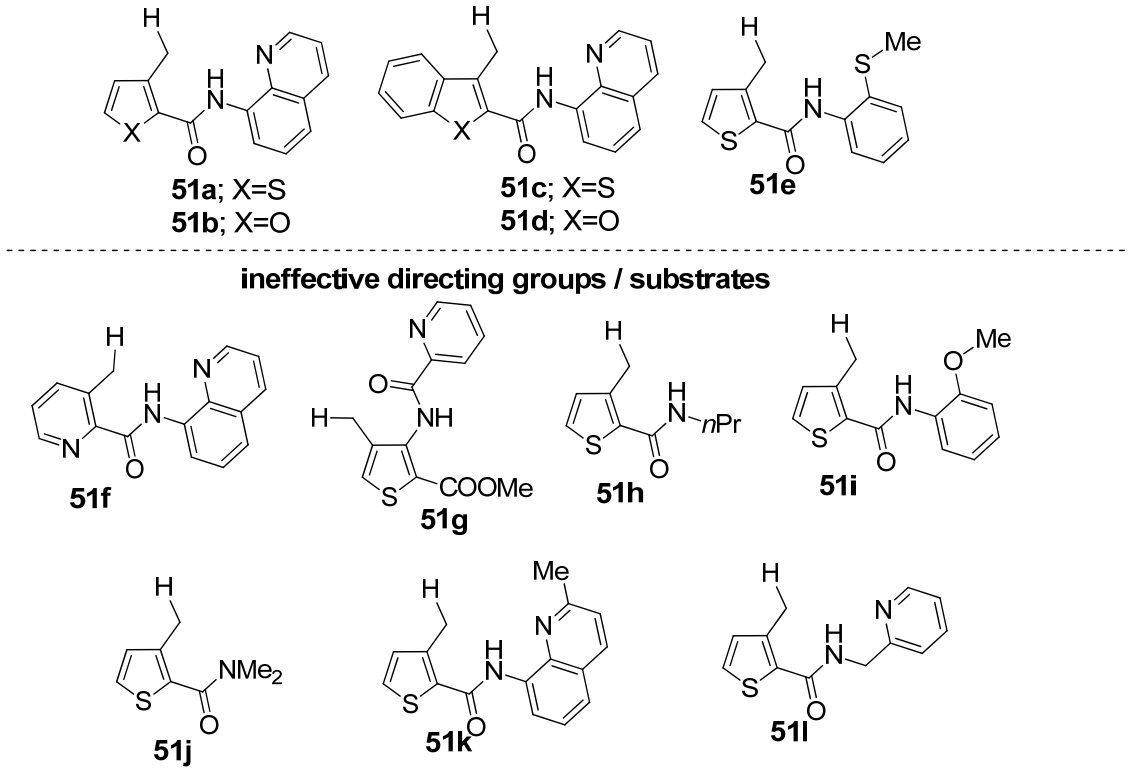
While the the 8-aminoquinoline-type bidentate directing groups and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline monodentate directing group werecommonly used for the functionalization of the *β*-C-H bonds of carboxylic acid systems. However, a literature survey revealed that there exist only exceptional reportson the 8-aminoquinoline-aided functionalization of *γ*-C-H bonds of carboxylic acid systems. Accordingly, a part of this thesis envisages the functionalization of the *γ*-C(sp^3)-H bonds using newcarboxamide systems, e.g., 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/thiophene-2-carboxamide systems.Accordingly, if the *γ*-C(sp^3)-H bonds of these substrates are subjected to the Pd(II)-catalyzed arylation or successive arylation and intramolecular amination,thenthe synthesis of furan/thiophene-based arylheteroarylmethane scaffolds and pyrrolidone-ring annulated furan/thiophene-based novel heterocycles can be accomplished.



Scheme 23. Topic of this work. Pd(II)-catalyzed γ-C-H arylation/cyclization and synthesis of functionalized furan/thiophene derivatives.

Considering functionalized furans/thiophenes and benzo-furans/thiophenes including arylheteroarylmethane (unsymmetrical diarylmethanes) are important class of molecules in organic synthesis and medicinal chemistry, developing new method for synthesizing furans/thiophenes and benzo-furans/thiophenes will be a useful contribution to their library. Accordingly, a part of this thesis reports the synthesis of arylheteroarylmethanes and pyrrolidone-ring annulated furan/thiophene derivatives via the Pd(II)-catalyzed arylation and intramolecular amination of γ-C(sp^3)-H bonds (Scheme 23).

Results and Discussion



Scheme 24. 3-Methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/thiophene-2-carboxamide and related systems assembled for investigating the γ-C(sp^3)-H arylation. (General reaction conditions: Substrate (0.125 mmol), **52a** or ArI (0.75-1 mmol), $Pd(OAc)_2$ (10-20 mol %), AgOAc (0.27 mmol), toluene (3 mL), 24-48 h, and 110 °C. The arylations of substrates **51a-e** were successful and the arylations of substrates **51f-l** were not fruitful).

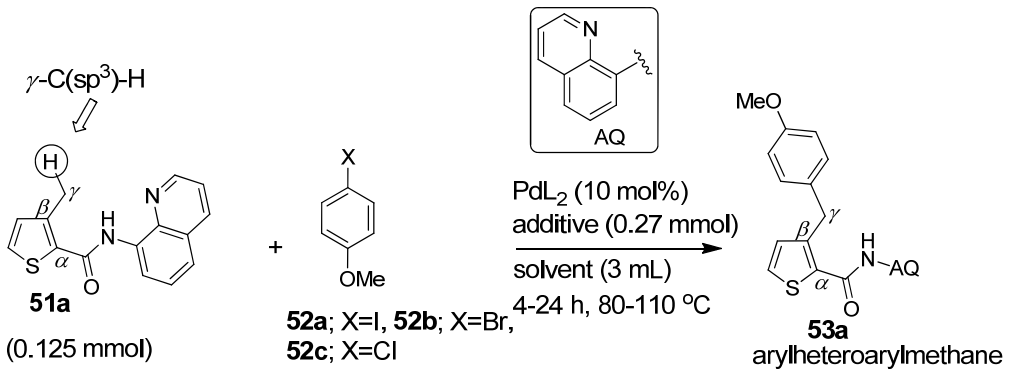
To examine the functionalization of the γ-C(sp^3)-H bond of 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/thiophene-2-carboxamide systems, appropriate starting

materials, e.g., 3-methylthiophene/furan-2-carboxamide and 3-methylbenzothiophene/furan-2-carboxamide derivatives **51a-l** were prepared using the corresponding carboxylic acids/chlorides and directing groups, 8-aminoquinoline and 2-(methylthio)aniline (Scheme 24).

Having prepared the suitable starting materials, initially various optimization reactions were attempted to assemble arylheteroarylmethane scaffold **53a** via the Pd(II)-catalyzed, 8-aminoquinoline-aided γ-C(sp^3)-H arylationof thiophene-2-carboxamide system **51a**(Table 1). The reaction comprising γ-C(sp^3)-H arylationof thiophene-2-carboxamide system **51a** with 6 equiv of**52a**in the presence of the $Pd(OAc)_2$ catalyst and AgOAc additivein toluene at 110 ^oC for 4 h was found to be the best reaction conditions, which afforded the arylheteroarylmethanederivative **53a** in a maximum of 72% yield (entry 5Table 1). Further trials to improve the yield of the product γ-C(sp^3)-H arylated product **53a** were not fruitful (Table 1). To show the role of the directing group 8-aminoquinoline and to find out the other working directing groups, various arylation reactions were attempted using the substrates **51g-l** under thetheoptimized reaction conditions (entry 5, Table 1).

Unfortunately, the Pd(II)-catalylzed γ-C(sp^3)-H arylation of the substrates **51g-l** failed toafford the corresponding arylheteroarylmethane derivatives (Scheme 24) 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 corresponding substrates **51g-l** (Scheme 24). Additionally, it is a limitation that the Pd(II)-catalyzed γ-C(sp^3)-arylationof substrate **51f** also did not afford the corresponding arylheteroarylmethane derivative and an exact reaction for the failure of arylation of **51f** is not clear to us at this stage. Presumably, the presence of multiple coordinating heteroatoms might be hindering the C-H activation reaction process.

Table 1. Optimization of reaction conditions. γ-C(sp^3)-H arylation of substrate **51a.**[a]

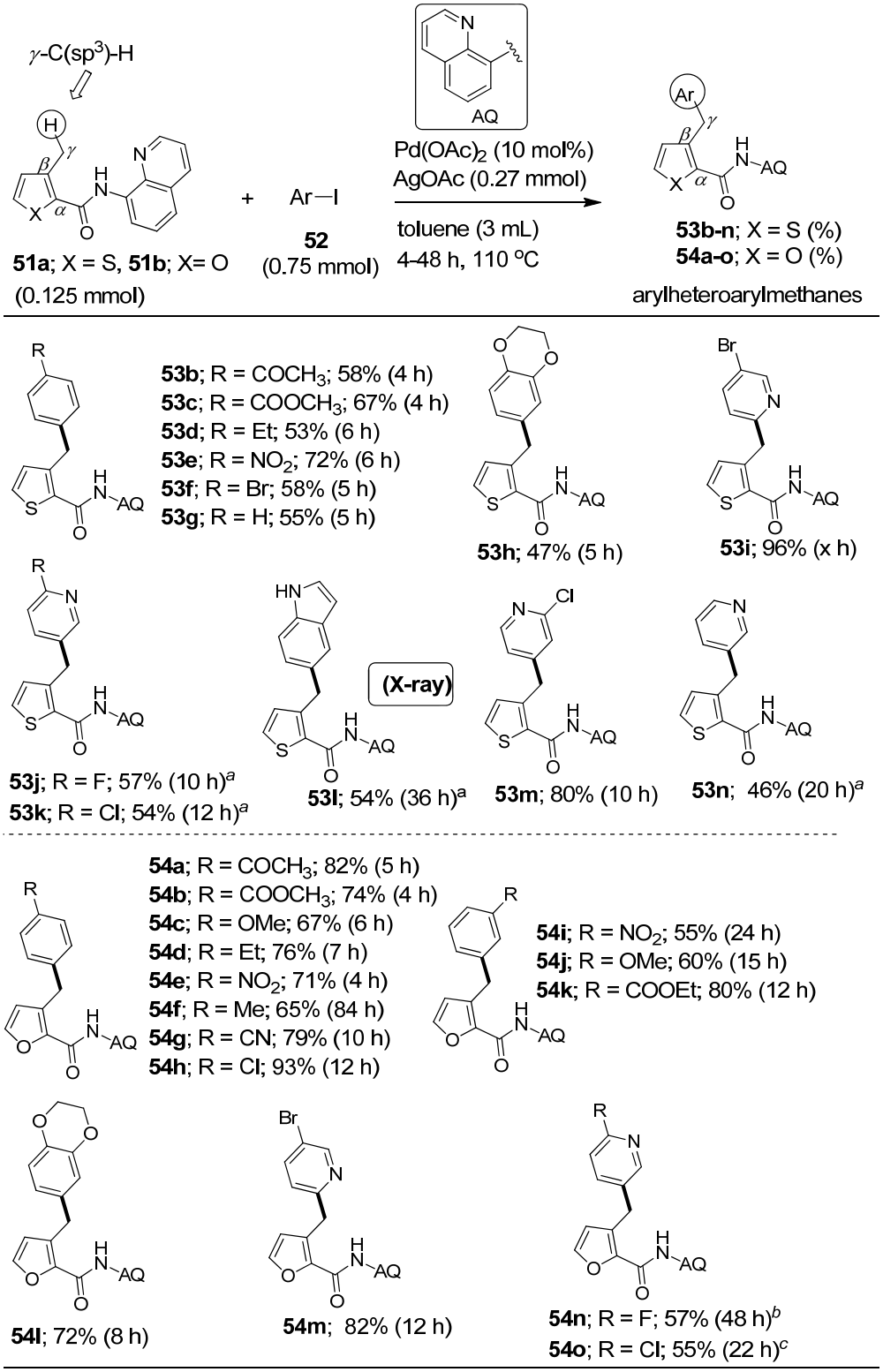


entry	PdL_2(10 mol%)	**52a** (mmol)	additive	solvent	*T* (°C)	*t* (h)	**53a**: yield (%)
1	$Pd(OAc)_2$	0.5	-	toluene	110	24	14
2	-	0.5	AgOAc	toluene	110	24	0
3	$Pd(OAc)_2$	0.25	AgOAc	toluene	110	4	32
4	$Pd(OAc)_2$	0.5	AgOAc	toluene	110	4	45
5	**$Pd(OAc)_2$**	**0.75**	**AgOAc**	**toluene**	**110**	**4**	**72**
6	$PdCl_2$	0.75	AgOAc	toluene	110	4	41
7	$Pd(MeCN)_2Cl_2$	0.75	AgOAc	toluene	110	4	43
8	$Pd(TFA)_2$	0.75	AgOAc	toluene	110	4	42
9	$Pd(OAc)_2$	0.75	KOAc	toluene	110	4	9
10	$Pd(OAc)_2$	0.75	K_2CO_3	toluene	110	4	5
11	$Pd(OAc)_2$	0.75	Ag_2CO_3	toluene	110	4	41
12	$Pd(OAc)_2$	0.75	Cs_2CO_3	toluene	110	4	6
13	$Pd(OAc)_2$	0.75	AgOAc	1,2-DCE	80	4	15
14	$Pd(OAc)_2$	0.75	AgOAc	1,4-dioxane	100	4	49
15	$Pd(OAc)_2$	0.75	AgOAc	*t*AmylOH	110	4	45
16	$Pd(OAc)_2$	0.75	AgOAc	*t*BuOH	85	4	6
17[b]	$Pd(OAc)_2$	0.75	AgOAc	toluene	110	4	0
18[c]	$Pd(OAc)_2$	0.75	AgOAc	toluene	110	4	0

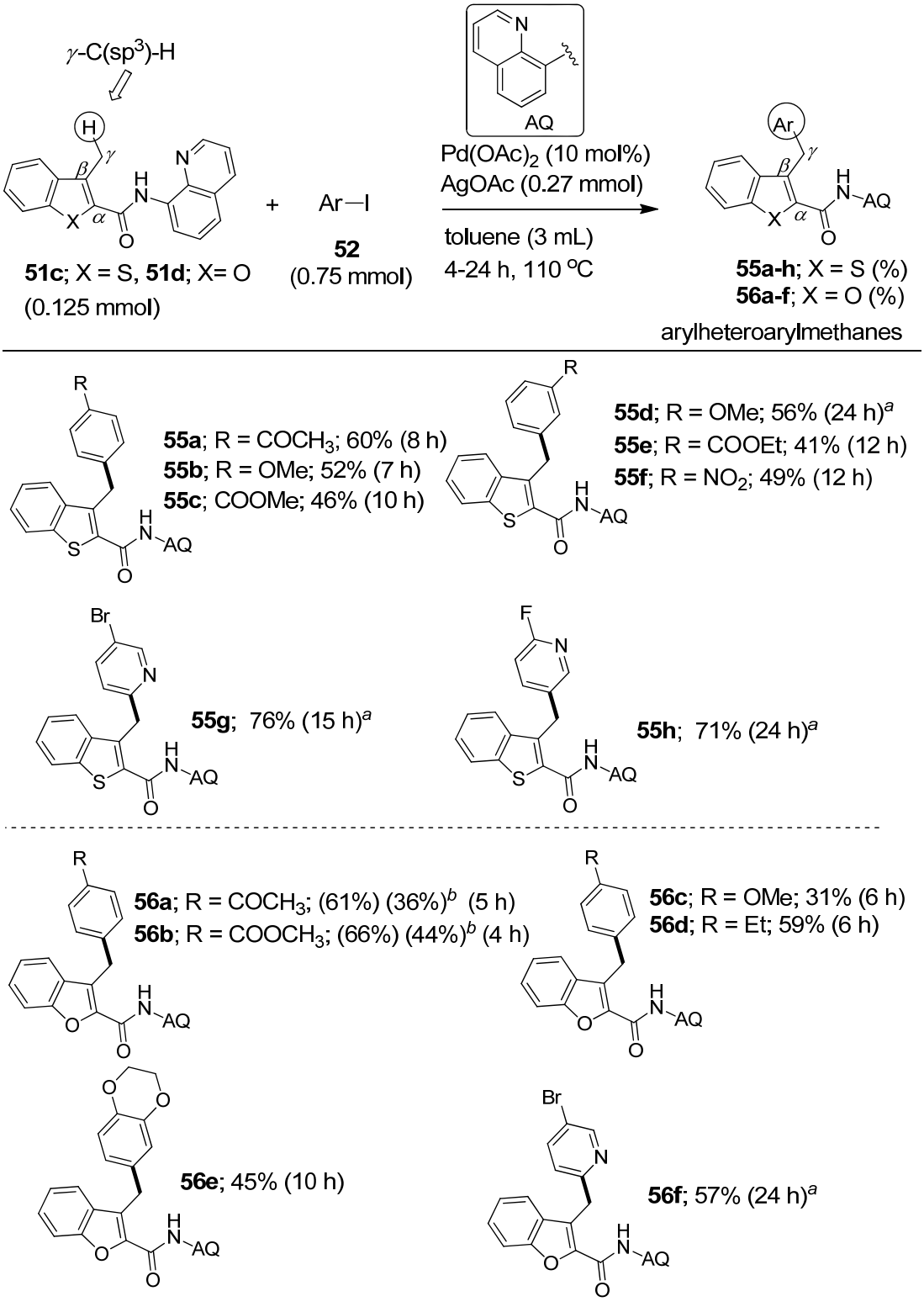
[a] All the reactions were performed using **52a**. [b]**52b** was used instead of **52a**. [c]**52c** was used instead of **52a**.

After performing the optimization reactions as shown in Table 1, it was envisaged to reveal the generality/scope of this Pd(II)-catalyzed, 8-aminoquinoline-directed γ-C(sp^3)-H arylationmethod affording arylheteroarylmethane. In this regard, Scheme 25 reveals the Pd(II)-catalyzed 8-aminoquinoline-directed γ-C(sp^3)-H arylationof thiophene-2-carboxamide system **51a**andfuran-2-carboxamide system **51b**. The $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C(sp^3)-H arylation of thiophene-2-carboxamide system **51a**witha wide range of aryl iodides afforded the corresponding γ-C(sp^3)-H arylated arylheteroarylmethanederivatives **53b-n** in 46-96% yields (Scheme 25). Similarly, the $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C(sp^3)-H arylation of furan-2-carboxamide system **51b** witha wide range of aryl iodides afforded the corresponding γ-C(sp^3)-H arylated arylheteroarylmethanederivatives **54a-o** in 55-93% yields (Scheme 25).

Next it was envisaged to extend the generality/scope of this Pd(II)-catalyzed, 8-aminoquinoline-directed γ-C(sp^3)-H arylationmethod affording arylheteroarylmethanes by performing the γ-C(sp^3)-H arylation of 3-methylbenzothiophene-2-carboxamide system **51c** and 3-methylbenzofuran-2-carboxamide system **51d** (Scheme 26). Accordingly, Scheme 26 reveals the results of the Pd(II)-catalyzed 8-aminoquinoline-directed γ-C(sp^3)-H arylationof substrates **51c** and **51d**. The $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C(sp^3)-H arylation of 3-methylbenzothiophene-2-carboxamide system **51c** witha wide range of aryl iodides afforded the corresponding benzothiophene-based arylheteroarylmethanederivatives **55a-h** in 41-76% yields (Scheme 26).

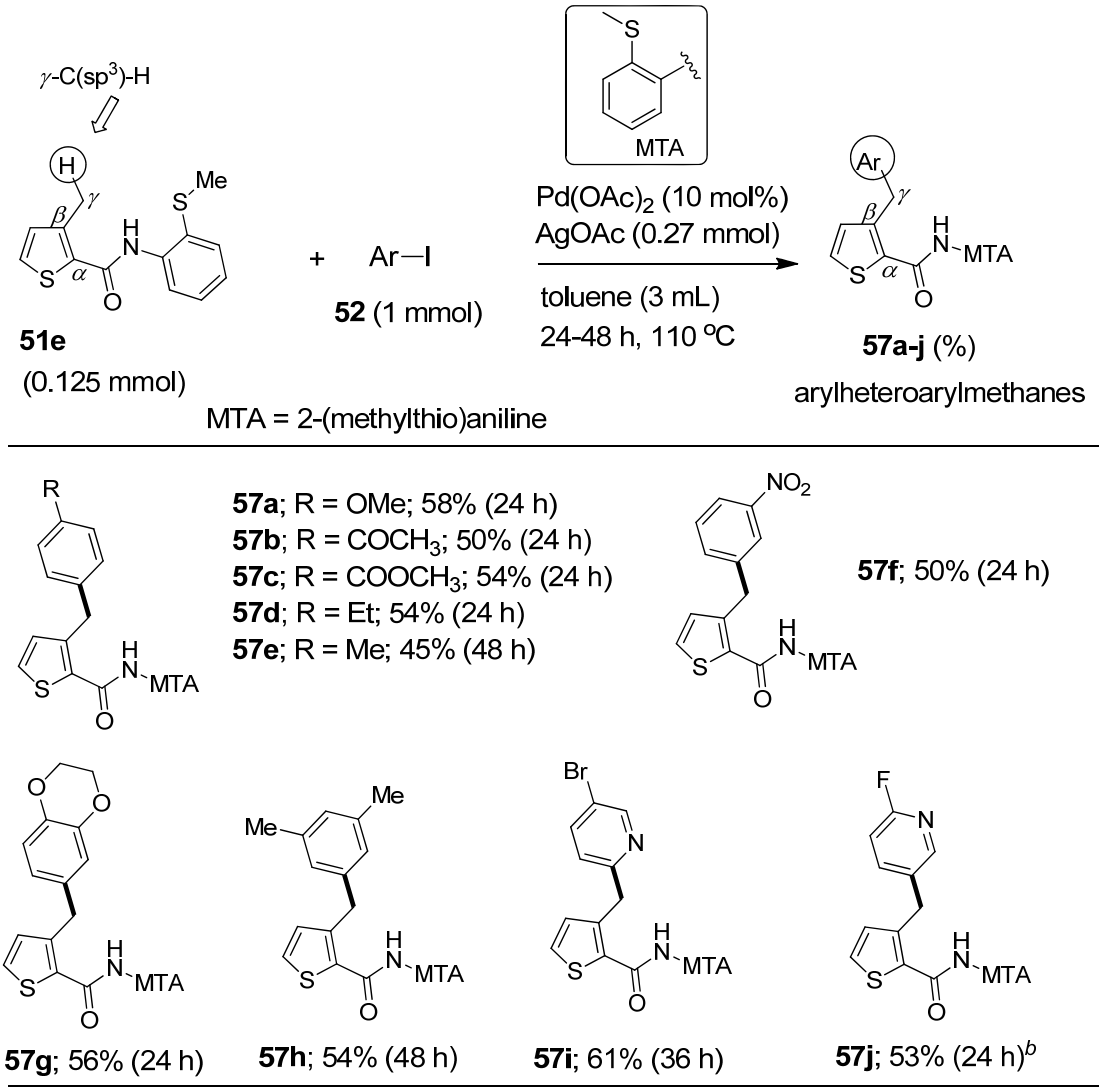


Scheme 25. γ-C(sp^3)-H arylation of thiophene-2-carboxamide system **51a**andfuran-2-carboxamide system **51b**. Construction of thiophene/furan-based arylheteroarylmethanes**53**/**54** ([a] 1.0 mmol of the corresponding aryl iodide was used.[b] 20 mol% catalyst was used. [c]1.0 mmol of the corresponding aryl iodide was used).



Scheme 26. γ-C(sp^3)-H Arylation ofsubstrates **51c,d**.Construction of benzo-thiophene/furan-based arylheteroarylmethanes **55/56** ([a] 1.0 mmol of the corresponding aryl iodide was used. 0.5 mmol of the corresponding aryl iodide was used).

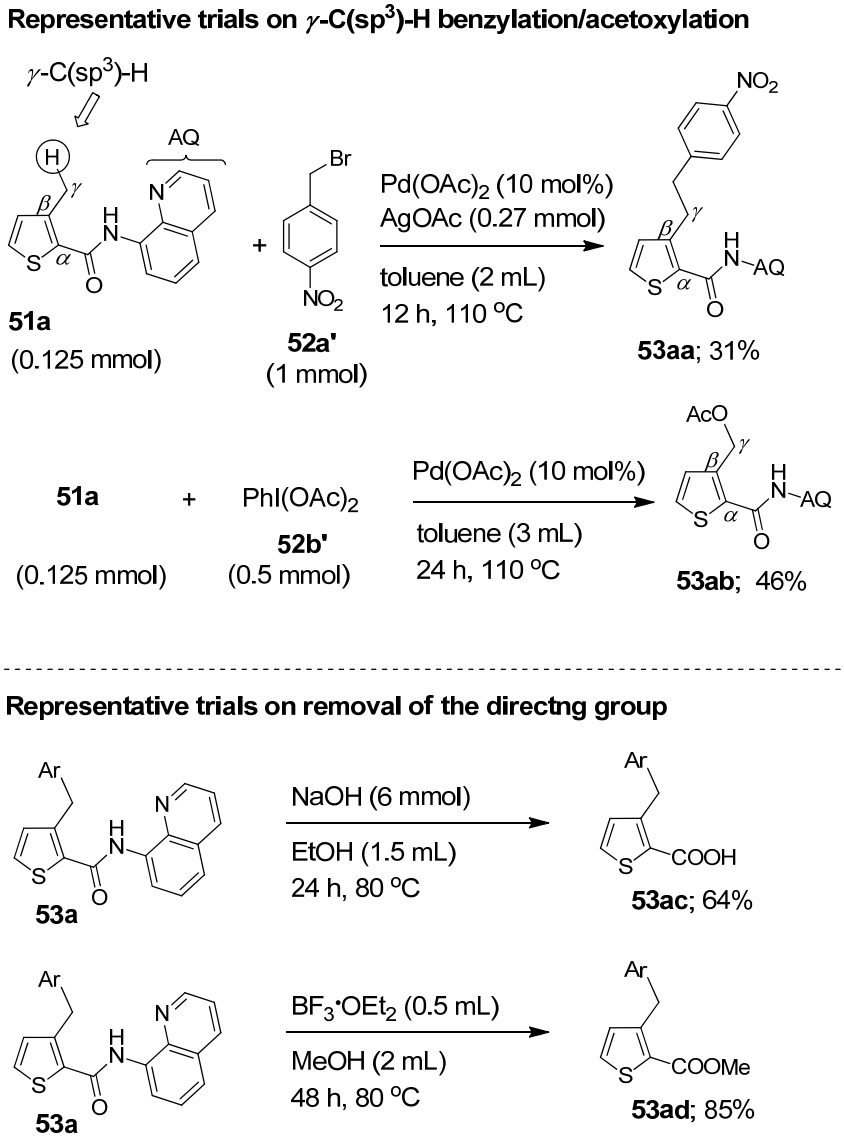
Similarly, the $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C(sp^3)-H arylation of 3-methylbenzofuran-2-carboxamide system **51d** witha wide range of aryl iodides afforded the corresponding γ-C(sp^3)-H arylated arylheteroarylmethanederivatives **56a-f** in 31-66% yields (Scheme 26).



Scheme 27. Pd(II)-catalyzed, γ-C(sp^3)-H arylationusing 2-(methylthio)aniline as the directing group. Construction of thiophene -based arylheteroarylmethane**s** **57** (^{b}0.75 mmol of the corresponding aryl iodide was used).

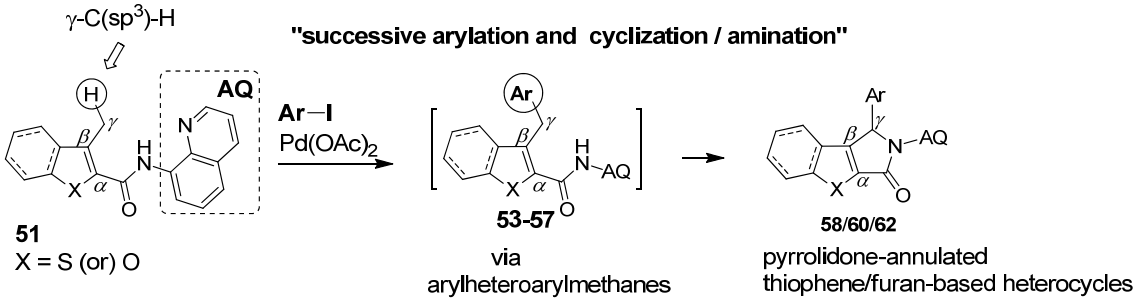
After investigating the generality/substrate scope of this Pd(II)-catalyzed, γ-C(sp^3)-H arylationof the substrates **51a-d**, which were prepared from the directing group 8-aminoquinoline, it was envisaged to investigate the Pd(II)-catalyzed, γ-C(sp^3)-H arylationusing 2-(methylthio)aniline as the directing group. In this regard, Scheme 27 reveals the results of the $Pd(OAc)_2$-catalyzed, AgOAc-mediated, 2-(methylthio)aniline-directed γ-C(sp^3)-H arylation of thiophene-2-carboxamide system **51e** with a wide range of aryl

iodides, which afforded the corresponding γ-C(sp^3)-H arylated, thiophene-based arylheteroarylmethanes **57a-j** in 45-61% yields (Scheme 27). Furthermore, Scheme 28 shows the $Pd(OAc)_2$-catalyzed, AgOAc-mediated γ-C(sp^3)-H benzylationof the substrate **51a** with benzyl bromide **52a′**, which gave the corresponding γ-C(sp^3)-H benzylated thiopene-2-carboxamide system **53aa** in 31% (Scheme 28). Subsequently, the Pd(II)-catalyzed, 8-aminoquinoline-directed γ-C(sp^3)-H acetoxylation of **51a** with $PhI(OAc)_2$ as an oxidant furnished the γ-C(sp^3)-H acetoxylated thiophene-2-carboxamide derivative **53ab** in 46% yield.



Scheme 28. γ-C(sp^3)-H benzylation and acetoxylation of **7a** and removal of the directing group.

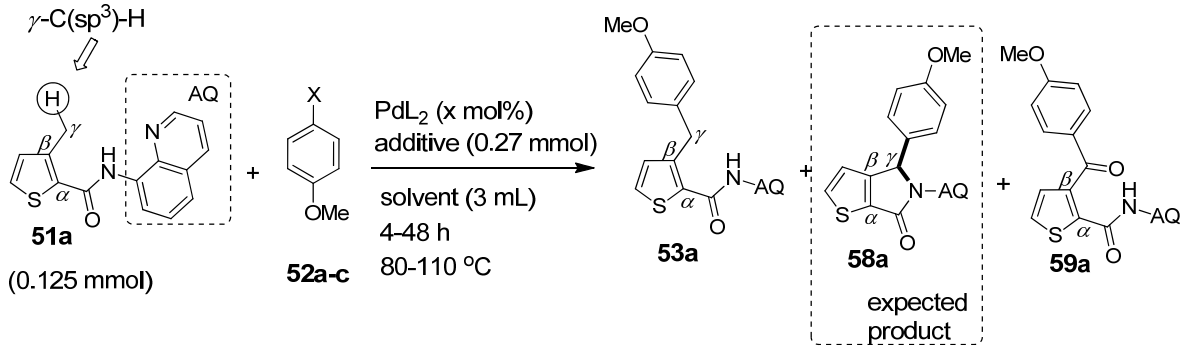
It is to be noted that the γ-C-H arylations of the methyl group in the corresponding carboxamides **51a-e** afforded the corresponding arylheteroarylmethane derivatives **53-57**, which possessthemethylene γ-C-H bonds. It is to be noted that it is also possible to accomplish the intramolecular C-H amination at the methylene γ-C-H bonds present in the corresponding arylheteroarylmethane derivatives **53-57**. Accordingly, it was envisaged to examine the possibility of successive γ-C(sp^3)-H arylation and intramolecular amination of using the substates **51a-e**. If the successive γ-C(sp^3)-H arylation and intramolecular amination of using the substates **51a-e** are successful then, these processes are expected toafford pyrrolidone-ring annulated furan/thiophene and benzo-furan/thiophene heterocycles **58**/**60**/**62** (Scheme 29).



Scheme 29. Successive γ-C(sp^3)-H arylation and intramolecular amination.

To realize the successive γ-C(sp^3)-H arylation and intramolecular amination of using the substates **51a-e** , initially various optimization reactions were performed using the thiophene-2-carboxamide system **51a**. Accordingly, Table 2 shows the optimization of the reaction conditions comprising the directing group 8-aminoquinoline-directed the successive γ-C(sp^3)-H arylation and intramolecular amination of **51a** in the presence of various palladium catalysts, additives/solvents. The reaction of substrate **51a**(1 equiv), aryl iodide **52a** (4-10 equiv)in toluene at 110 ^oC for 24 h in the presence of 10-20 mol% of the $Pd(OAc)_2$ catalyst affordedthe expected successive γ-C(sp^3)-H arylation and intramolecular amination product, pyrrolidone-ring annulated thiophene system **58a** in 59-71% (entries 3-5, Table 2). The pyrrolidone-ring annulated thiophene system **58a** was obtained in a maximum of 71% yield (entry 6, Table 2). Other trials to improve the yield of the pyrrolidone-ring annulated thiophene system **58a** were not fruitful (Table 2).

Table 2. Optimization of reaction conditions. Successive γ-C(sp^3)-H arylation and intramolecular amination ofsubstrate **51a**[a]



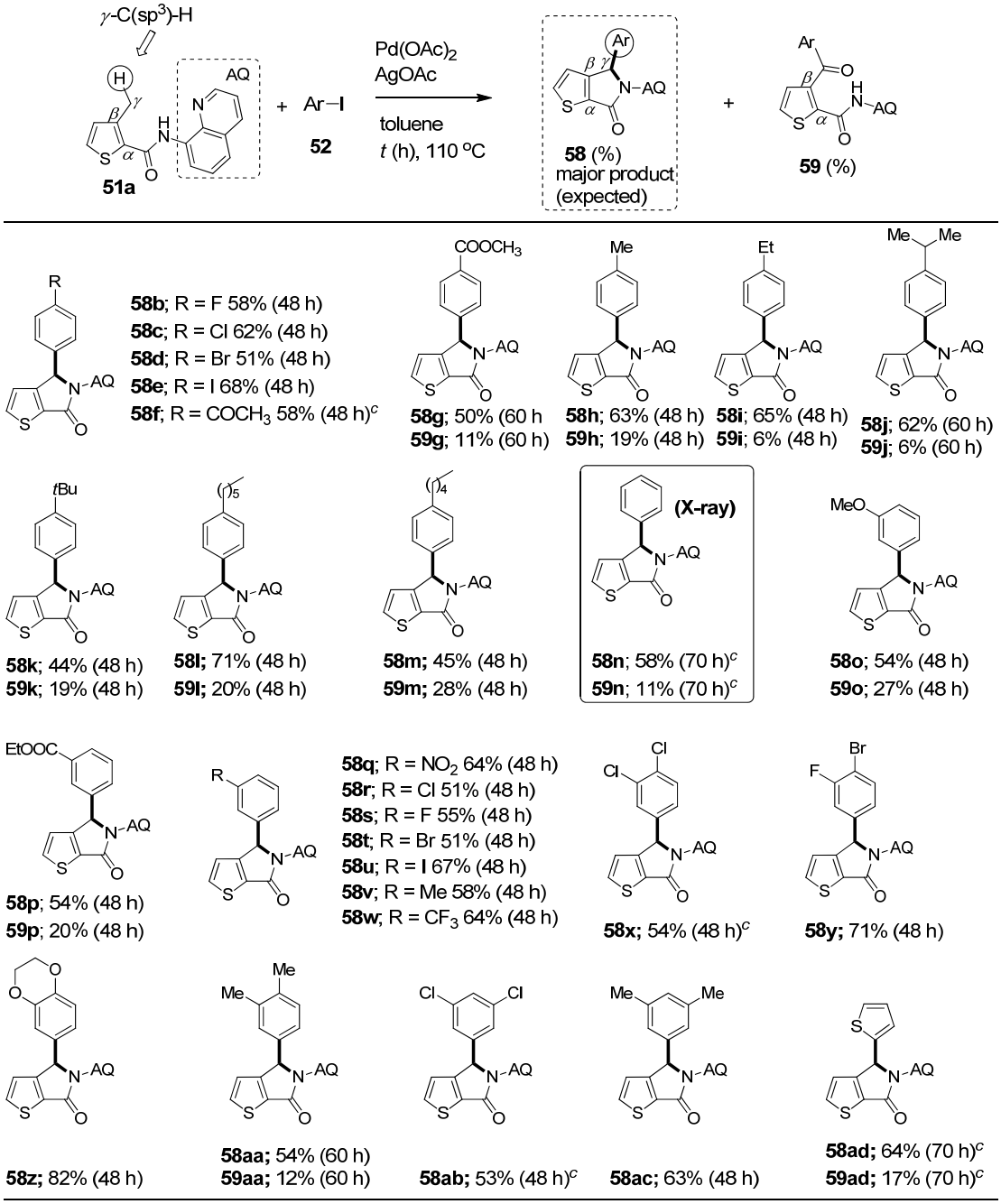
entry	PdL_2 (x mol%)	**52a** (mmol)	additive	solvent	*T* (°C)	*t* (h)	yield (%)		
							53a	**58a**	**59a**
1[b]	$Pd(OAc)_2$ (10)	0.75	AgOAc	toluene	110	4	72	-	-
2	$Pd(OAc)_2$ (10)	0.5	AgOAc	toluene	110	24	40	20	2
3	$Pd(OAc)_2$ (10)	1	AgOAc	toluene	110	48	<5	59	12
4	$Pd(OAc)_2$ (20)	1	AgOAc	toluene	110	48	<5	64	10
5	**$Pd(OAc)_2$ (20)**	**1.25**	**AgOAc**	**toluene**	**110**	**48**	**<5**	**71**	**12**
6	$PdCl_2$ (20)	1.25	AgOAc	toluene	110	48	49	39	4
7	$Pd(MeCN)_2Cl_2$ (20)	1.25	AgOAc	toluene	110	48	32	45	4
8	$Pd(TFA)_2$ (20)	1.25	AgOAc	toluene	110	48	36	21	16
9	$Pd(OAc)_2$ (20)	1.25	KOAc	toluene	110	48	64	<5	<5
10	$Pd(OAc)_2$ (20)	1.25	K_2CO_3	toluene	110	48	49	0	0
11	$Pd(OAc)_2$ (20)	1.25	Ag_2CO_3	toluene	110	48	0	43	6
12	$Pd(OAc)_2$ (20)	1.25	Cs_2CO_3	toluene	110	48	43	0	0
13	$Pd(OAc)_2$ (20)	1.25	AgOAc	1,2-DCE	80	48	30	9	4
14	$Pd(OAc)_2$ (20)	1.25	AgOAc	1,4-dioxane	100	48	34	21	2

15	$Pd(OAc)_2$ (20)	1.25	AgOAc	*t*AmylOH	110	48	17	15	2
16	$Pd(OAc)_2$ (20)	1.25	AgOAc	*t*BuOH	85	48	58	<5	<5
17[c]	$Pd(OAc)_2$ (20)	1.25	AgOAc	toluene	110	48	0	0	0
18[d]	$Pd(OAc)_2$ (20)	1.25	AgOAc	toluene	110	48	0	0	0

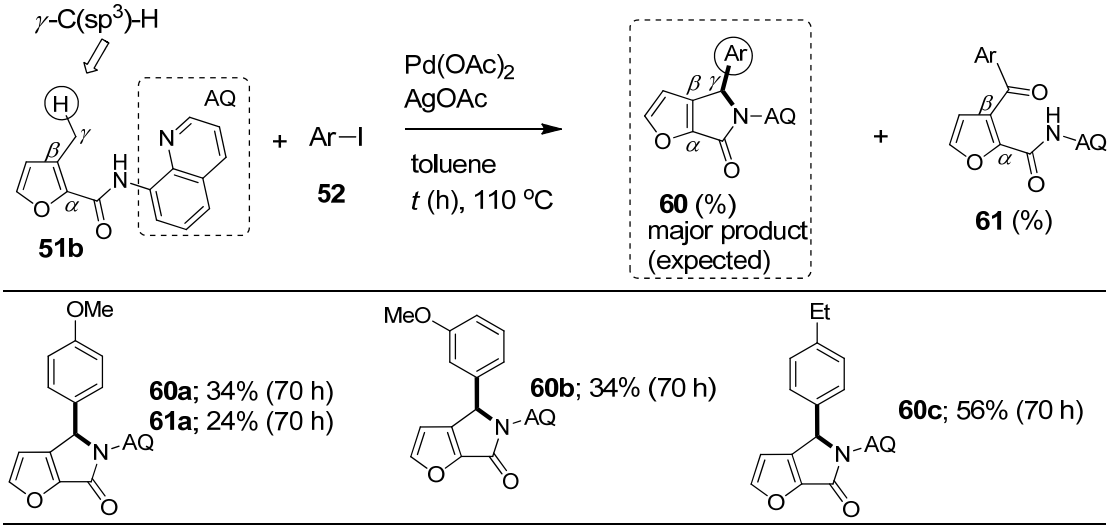
[a] All the reactions were performed using **52a**. [b]Result of entry 5, Table 1.[c]**52b** was used instead of **52a**. [d]**52c** was used instead of **52a**.

After finding an optimized reaction condition affording the expected successive γ-C(sp^3)-H arylation and intramolecular amination product, pyrrolidone-ring annulated thiophene system **58a**, next, it was envisaged to explore the generality/substrate scope of this method using the substrates **58a-c**. Scheme 30 shows the results of the Pd(II)-catalyzed γ-C(sp^3)-H arylation and intramolecular amination of the substrate **51a**with a wide range of aryl iodides, which afforded the corresponding pyrrolidone-ring annulated thiophene-based heterocyclic scaffolds **58b-z** and **58aa-ad** in 44-82% yields (Scheme 30).

In some cases the corresponding arylheteroarylketone systems **59g-p** and **59aa** and **59ad** were also obtained as the by-products in 6-28% yields.Successively, it was envisaged to extend the generality/substrate scope of this method comprising the Pd(II)-catalyzed, successive γ-C(sp^3)-H arylation and intramolecular amination process using the substrate **51b**.Scheme 31 shows the results of the Pd(II)-catalyzed, successive γ-C(sp^3)-H arylation and intramolecular amination of the substrate **51b** with various aryl iodides, which afforded the corresponding pyrrolidone-ring annulated furan-based heterocycles **60a-c** in 34-56% yields (Scheme 31). In one of the reaction, the corresponding arylheteroarylketone system **61a** was also obtained as the by-product in 24% yield. Additionally, Scheme 32 also shows the results of the Pd(II)-catalyzed, successive γ-C(sp^3)-H arylation and intramolecular amination of the substrate **60c** with various aryl iodides, which afforded the corresponding pyrrolidone-ring annulated benzothiophene-based heterocycles **62a-f** in 37-53% yields (Scheme 32).

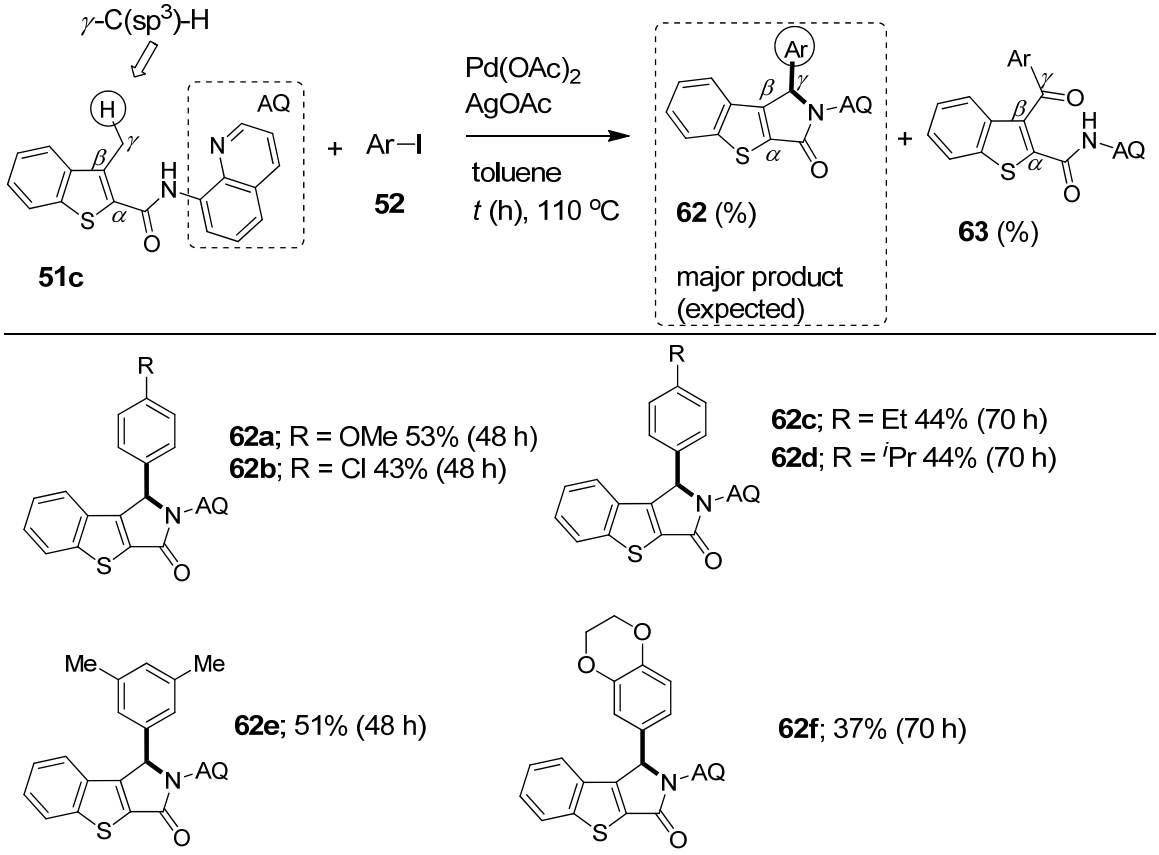


Scheme 30. Generality/substrate scope of successive arylation and intramolecular amination of γ-C(sp^3)-H bond of **51a**. Synthesis of pyrrolidone-ring annulated thiophene systems**58b-z** and **58aa-ad** ([a]All reactions were peformed using **51a** (0.125 mmol), ArI (1.25 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (0.27 mmol) in toluene (2-3 mL) for 48-70 h. [b]The corresponding ketone products **59g-p**, **59aa** and **59ad** (minor products) were isolated in pure form. In rest of the cases, the correspondingketone products **59** (minor products) were obtained in <5% yields and could not be obtained in characterizable amounts. [c]1.5 mmol of ArI was used)



Scheme 31. Successive γ-C(sp^3)-H arylation and intramolecular amination of **51b**. Synthesis of pyrrolidone-ring annulated furan derivatives **60a-c** and **61a** (*[a]*All reactions were peformed using **51b** (0.125 mmol), ArI (1.5 mmol), $Pd(OAc)_2$ (20-30 mol%), AgOAc (0.27 mmol) in toluene (2-3 mL) for 70 h. [b]The corresponding ketone products **61a** (minor products) was isolated in pure form. In rest of the cases, the correspondingketone products **61** (minor products) were obtained in <5% yields and could not be obtained in characterizable amounts).

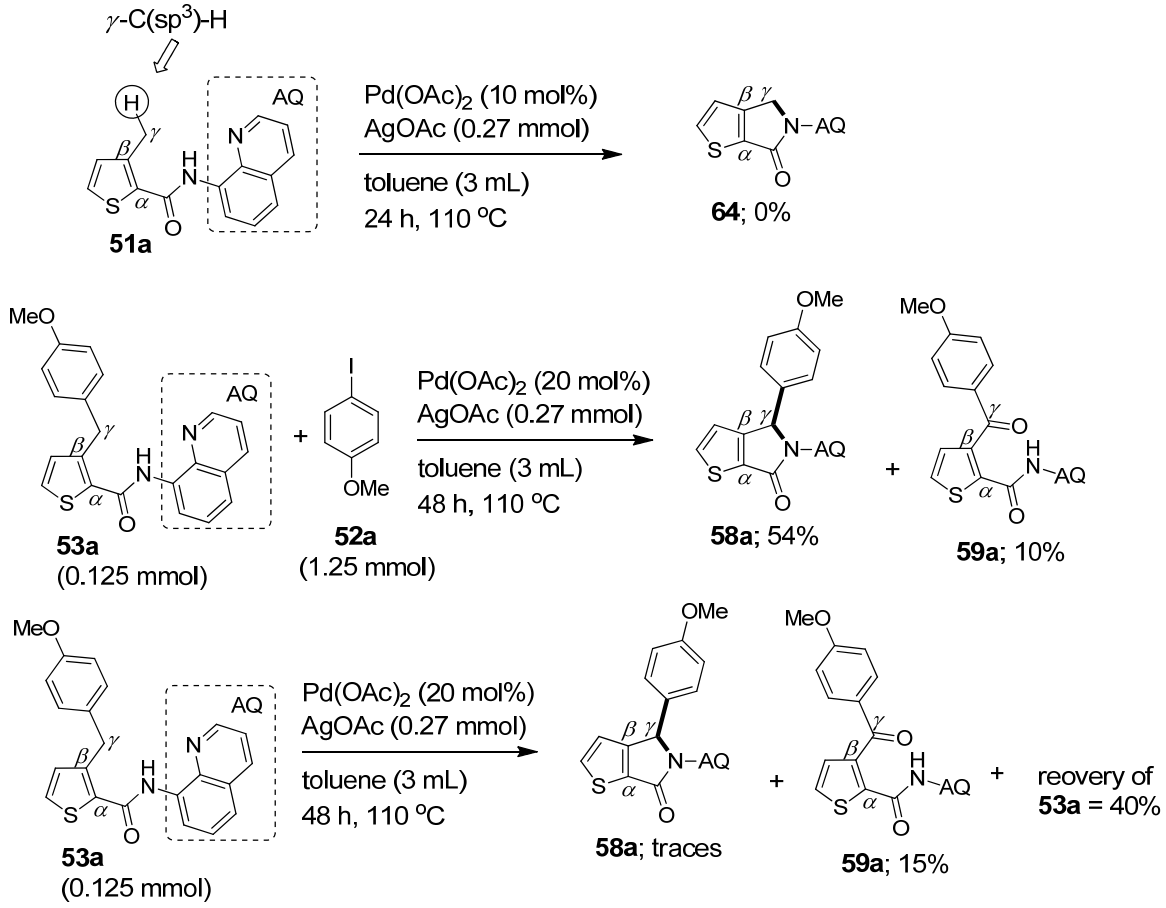
Scheme 33 shows the results of some control experiments performed to proposea plausible mechanism for the formation of the corresponding heterocyclic systems **58a-z/58aa-ad**, **60a-c**and **62a-f** from the Pd(II)-catalyzed, directing group-aided successive γ-C(sp^3)-H arylation and intramolecular amination of the corresponding starting materials **51a-c**. The Pd(II)-catalyzed reaction of **51a** in the absence of any aryl iodide failed to afford the expected the product **64**. The Pd(II)-catalyzed reaction of arylheteroarylmethane derivative **53a** with **52a** afforded the expected pyrrolidone-ring annulated heterocyclic scaffold **58a** along with the arylheteroaryl ketone **59a** (Table 2).



Scheme 32. Successive γ-C(sp^3)-H arylation and intramolecular amination of **51c**. Synthesis of pyrrolidone-ring annulated benzothiophene heterocycles **62a-f** (*[a]*All reactions were peformed using **51c** (0.125 mmol), ArI (1.5 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (0.27 mmol) in toluene (2-3 mL) for 48-70 h. [b]The corresponding ketone products **63** (minor products) were obtained in <5% yields and could not be obtained in characterizable amounts).

The Pd(II)-catalyzed reaction of **53a** without any aryl iodide (e.g. **52a**) failed to afford the expected the product **58a** and the starting material **59a** was recovered (40% recovery). This reaction afforded the arylheteroaryl ketone derivative **59a**in 15% yield. Presumably, the ketone product **59a** was formed from the Pd-catalyzed oxidation of methylene group of **53a** under the experimental condition. These control reactions suggested the following points; (1) the formation of the corresponding pyrrolidone-ring annulated heterocyclic scaffold (e.g., **58a-z/58aa-ad**, **60a-c** and **62aa-f**) involves two step-based reactions, i.e. arylation and intramolecular amination, (2) the pyrrolidone-ring annulated heterocyclic scaffolds were formed only after the formation of the corresponding γ-C(sp^3)-H arylated products, such as arylheteroarylmethanes/diheteroarylmethanes **53-57**, and (c) presumably, aryl iodide plays is an important role in the intramolecular amination step, which helps to afford the corresponding pyrrolidone-ring annulated heterocyclic scaffolds from the corresponding γ-

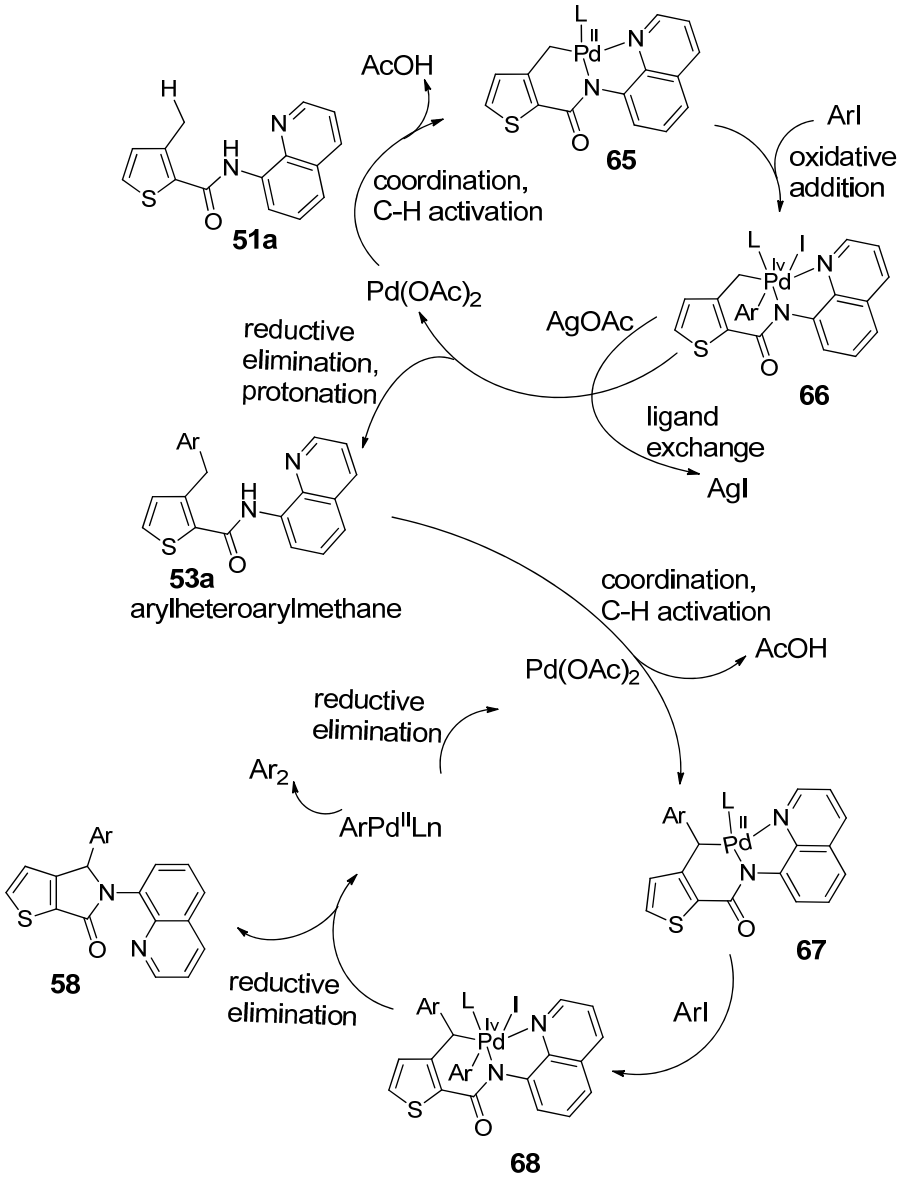
$C(sp^3)$-H arylated products **53-57**. Based on these deliberations, and in concurrence with the generally accepted Pd^{II}-Pd^{IV}catalytic cycle mechanismcomprising the $Pd(OAc)_2$/AgOAc catalytic system-based, bidentate directing group-enabled C-H arylation of carboxamides, a plausible mechanism for the γ-$C(sp^3)$-H arylation and intramolecular amination of the substrates **51a-e** was proposed in Scheme 34.



Scheme 33. Control experiments to explain the proposed mechanism of successive arylation and intramolecular amination.

In all the cases, after the Pd(II)-catalyzed arylation and arylation/amination reactions, the respective crude reaction mixtures were subjected to column chromatographic purification. Then, the fractions were collected according to the TLC and in all the cases we focused to isolate the corresponding γ-$C(sp^3)$-H arylation products **53-57** and heterocyclic motifs **58**/**60**/**62**. In the reactions involving the γ-$C(sp^3)$-H arylation and intramolecular amination of **51a-c**, in some cases, we isolated the corresponding ketone products **59**/**61** (minor products) as the by-products. The products **59a**, **59g-p**,**59aa**, **59ad** and**61a** were isolated in pure form. In other cases, the corresponding ketone products **59**/**61** were obtained in <5% yields and could not be obtained in characterizable amounts. Arylheteroarylmethane and

diheteroarylmethane scaffolds **53-57** and benzylated/acetoxylated thiophene compounds **53aa**/**53ab** were characterized based on their NMR and HRMS data. Further, a representative diheteroarylmethane compound **51l** was also characterized based on the X-ray structure analysis The pyrrolidone-ring annulated heterocyclic scaffolds **58a-z/58aa-ad**,**60a-c**,and **62a-f** were characterized based on their NMR and HRMS data and a representative pyrrolidone-ring annulated thiophene-based compound **52n** was also characterized based on the X-ray structure analysis (Figure 1). The by-products, arylheteroarylketone systems **59g-p**, **59aa**, **59ad** and**61a** were also characterized based on their NMR and HRMS data.



Scheme 34. Proposed mechanism for the Pd(II)-catalyzed γ-C(sp^3)-H Arylation of **51a-d** and Successive arylation and intramolecular amination of **51a-c**.[1, 4e,6a,b]

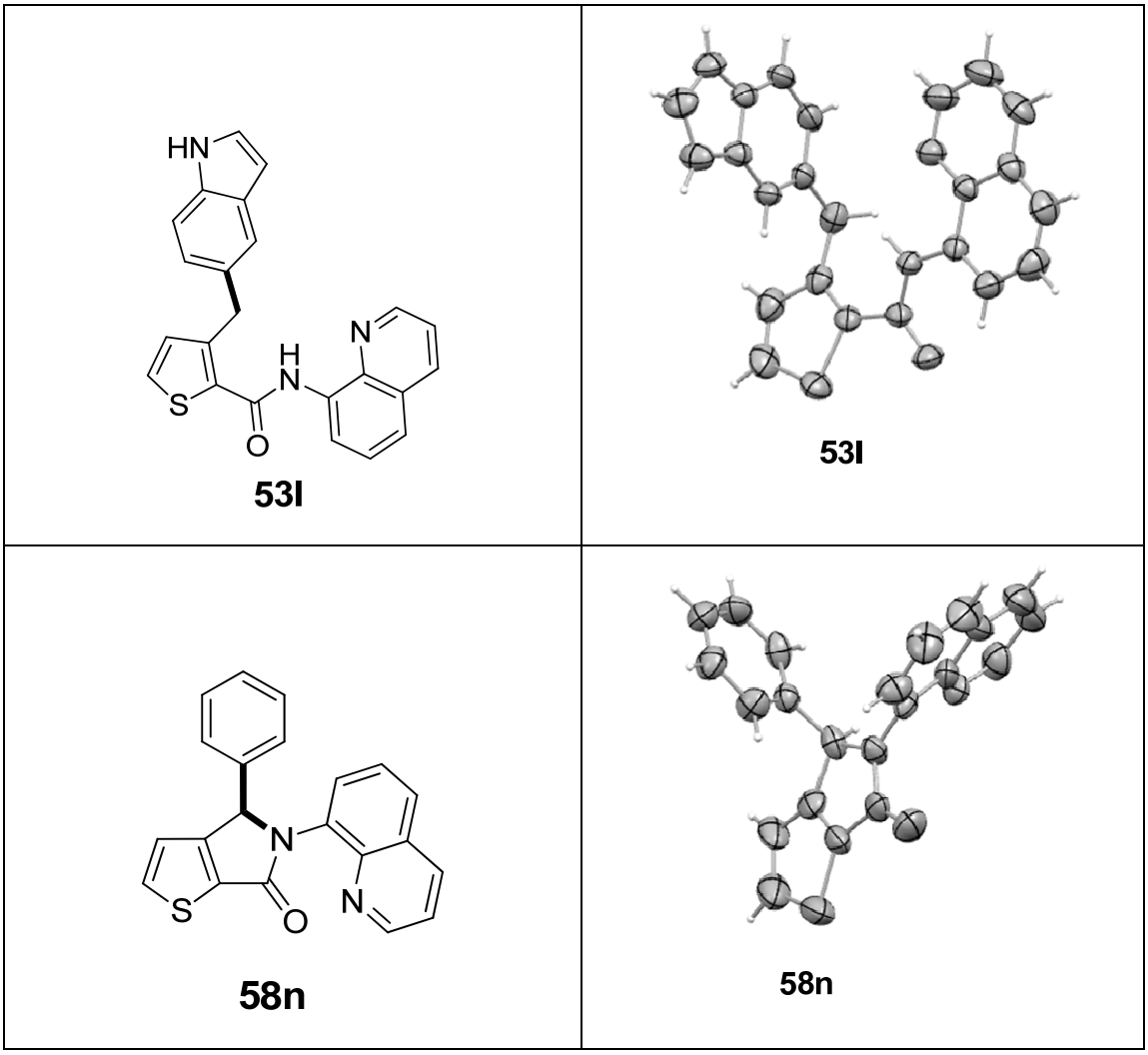
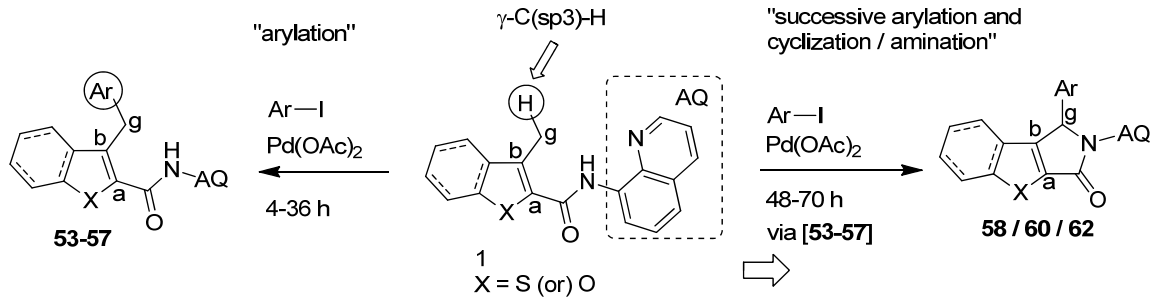


Figure 1. X-ray (ORTEP diagram) structures of the compounds **53l** and**58n**.

Conclusion

In summary, the **Chapter 5** revealed the Pd(II)-catalyzed arylation and intramolecular amination of γ-C(sp^3)-H bonds using carboxamide systems, e.g., 3-methylfuran/thiophene-2-carboxamide and 3-methylbenzofuran/thiophene-2-carboxamide systems. The Pd(II)-catalyzed γ-C(sp^3)-H arylation or successive arylation and intramolecular amination have led to the synthesis of a wide range of furan/thiophene-based arylheteroarylmethane scaffolds and pyrrolidone-ring annulated furan/thiophene-based novel heterocycles.



Experimental section.

General. IR spectra of samples were recorded as KBr pellets or thin films or neat. Proton and Carbon NMR spectra of all compounds were recorded using TMS as an internal standard in 400 and 100 MHz spectrometers, respectively. The HRMS measurements of all the compounds were obtained from QTOF mass analyzer using electrospray ionization (ESI) technique. Column chromatography purification of crude reaction mixtures were carried out on silica gel (100–200 mesh) or neutral alumina. TLC analysis was performed on silica/alumina plates and components were visualized by observation under iodine vapour. Reactions were conducted in anhydrous solvents under a nitrogen or argon atmosphere wherever required and organic layers obtained after work up procedure were dried using anhydrous Na_2SO_4. Isolated yields of all the products are reported and yields of the reactions/products were not optimized..

General Procedure for Synthesis of Carboxamides 51a-l. An appropriate carboxylic acid (1-1.2 mmol, 1 equiv) in $SOCl_2$ (3-4 mmol, 3-4 equiv) was heated at 80 ^oC, for 15 h under a nitrogen atm. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atm. Then, the DCM solution containing the corresponding acid chloride was added to a separate flask containing an appropriate amine (directing group, 1 mmol, 1 equiv) and Et_3N (112-123 mg, 1.1-1.2 mmol, 1.1-1.2 equiv) in anhydrous DCM (2 mL). After this, the reaction mixture was stirred at rt for 10 min and the reaction mixture was refluxed for 12 h. After this period, the reaction mixture was diluted with DCM (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purification of the resulting reaction mixture by column chromatography (EtOAc:Hexanes = 30:70) furnished the corresponding carboxamides **51a-l**.

General Procedure for the Pd(II)-Catalyzed Arylation of Carboxamides 51a-l and Preparation of the Compounds 53a-n, 54a-o, 55a-h, 56a-f and 57a-j. An appropriate carboxamide (0.125 mmol, 1 equiv), an appropriate aryl iodide (0.75-1.0 mmol, 6-8 equiv), $Pd(OAc)_2$ (2.8 mg, 10 mol%) and AgOAc (46 mg, 0.27 mmol, 2.2 equiv) in anhydrous toluene (2-3 mL) was heated at 110 ^oC for 4-48 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 arylheteroarylmethanes **53a-n, 54a-o, 55a-h, 56a-f and 57a-j** (see the corresponding Tables/Schemes for specific examples).

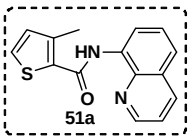
General Procedure for the Pd(II)-Catalyzed Arylation and Intramolecular Amination of Carboxamides 51a-c and Preparation of 58a-z, 58aa-ad 60a-c and 62a-f. An appropriate carboxamide (0.125 mmol, 1 equiv), an appropriate aryl iodide (1.25 mmol, 10 equiv) $Pd(OAc)_2$ (5.6 mg, 20 mol%), AgOAc (45.9 mg, 0.27 mmol, 2.2 equiv) in anhydrous toluene (2-3 mL) was heated at 110 ^oC for 48-60 h under a nitrogen atm. After this 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 pyrrolidone-ring annulated motifs **58a-z, 58aa-ad 60a-c and 62a-f** (see the corresponding Tables/Schemes for specific examples).

Typical Procedure for the Hydrolysis of Carboxamide 9a. Preparation of the Carboxylic Acid 53ac. A solution of 3-(4-methoxybenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (**53a**, 47 mg, 0.125 mmol, 1 equiv) and NaOH (240 mg, 6 mmol) in ethanol (1.5 mL) was heated at 80 °C for 24 h. After this period, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL). The aqueous layer was acidified with 1 N HCl and extracted with ether (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and then the solvent was evaporated in vacuum to afford the carboxylic acid **53ac**.

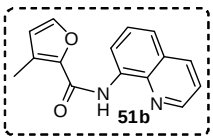
Typical Procedure for thehydrolysis of carboxamide 53a and Preparation of the Carboxylate Derivative 53ad. To a solution of 3-(4-methoxybenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide **53a** (47 mg, 0.125 mmol, 1 equiv) in dry methanol (3 mL) was added $BF_3{\cdot}Et_2O$ (0.5 mL) added dropwise. Then, the resulting mixture was stirred at 80 °C for 48 h. Then, the reaction mixture was allowed to attain the rt. Next, Et_3N (304 mg, 3

mmol) was added dropwise to the reaction mixture with stirring. After this, the solvent was evaporated in vacuum to afford the carboxylate derivative **53ad**.

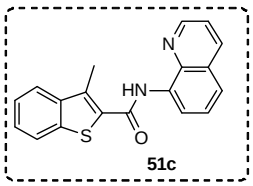
3-Methyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide(51a): The compound **51a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 70% (188 mg); R_f = 0.55 (EtOAc:Hexanes = 1:4); mp 104-106 ^oC; IR (KBr): 3355, 1649, 1526, 1485, 1384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.3 Hz), 7.43 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.40 (d, 1H, J= 5.0 Hz), 6.97 (d, 1H, J= 5.0 Hz), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 148.3, 141.0, 138.6, 136.3, 134.7, 132.9, 132.4, 127.9, 127.8, 127.4, 121.7, 121.6, 116.5, 16.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2OS$: 269.0749; found 269.0742.



3-Methyl-*N*-(quinolin-8-yl)furan-2-carboxamide (51b): The compound **51b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 71% (179 mg); R_f = 0.52 (EtOAc:Hexanes = 1:4); mp 118-120 ^oC; IR (KBr): 3345, 1669, 1529, 1484, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.75 (br. s, 1H), 8.91-8.88 (m, 2H), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.57 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.52 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.50 (d, 1H, J= 1.6 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.43 (d, 1H, J= 1.6 Hz), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 148.3, 142.9, 142.6, 138.7, 136.3, 134.5, 128.8, 128.0, 127.4, 121.6, 121.5, 116.3, 115.8, 11.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_2$: 253.0977; found 253.0985.

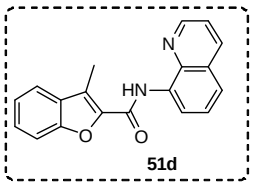


3-Methyl-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide(51c): The compound **51c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 85% (270 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); mp 133-135 ^oC; IR (KBr): 3303, 1649, 1526, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br. s, 1H), 8.92 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.91-7.87 (m, 2H), 7.61 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.51-7.46 (m, 3H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 148.5, 140.7, 139.1, 138.6, 136.4, 136.3,

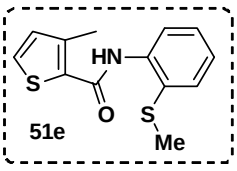


134.5, 132.0, 128.0, 127.4, 126.7, 124.7, 123.4, 122.7, 121.9, 121.8, 116.6, 13.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{15}N_2OS$: 319.0905; found 319.0909.

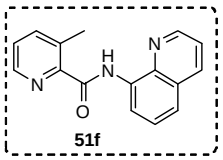
3-Methyl-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (51d): The compound **51d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 50% (151 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 178-180 ^oC; IR (KBr): 1648, 1527, 1486, 1354 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.99 (br. s, 1H), 8.96 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.66-7.63 (m, 2H), 7.58 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.50-7.46 (m, 2H), 7.33 (t, 1H, *J*= 7.9 Hz), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 153.5, 148.5, 143.0, 138.7, 136.3, 134.3, 129.9, 128.0, 127.3, 127.3, 123.6, 123.2, 121.9, 121.7, 120.9, 116.6, 112.0, 9.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{15}N_2O_2$: 303.1134; found 303.1129.



3-Methyl-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide(51e): The compound **51e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 70% (184 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 82-84 ^oC; IR (KBr): 1526, 1486, 1423, 1384, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (br. s, 1H), 8.49 (d, 1H, *J*= 8.2 Hz), 7.55 (d, 1H, *J*= 7.7 Hz), 7.38 (d, 1H, *J*= 5.0 Hz), 7.35 (t, 1H, *J*= 7.6 Hz), 7.11 (t, 1H, *J*= 7.6 Hz), 6.97 (d, 1H, *J*= 5.0 Hz), 2.68 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 141.9, 138.8, 133.5, 132.5, 131.8, 129.2, 127.6, 125.2, 124.4, 120.4, 19.3, 16.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}NOS_2$: 264.0517; found 264.0520.

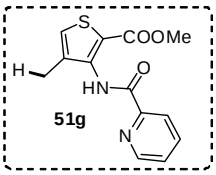


3-Methyl-*N*-(quinolin-8-yl)picolinamide (51f): The compound **51f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 59% (157 mg); R_f = 0.35 (EtOAc:Hexanes = 1:4); mp 170-172 ^oC; IR (KBr): 1679, 1578, 1523, 1485, 1325, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.34 (br, s, 1H), 9.01 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.0 Hz) 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.66 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.7 Hz), 7.63-7.59 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz),



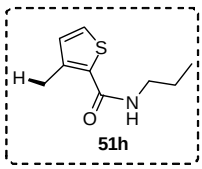
7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.39 (dd, 1H, J_1 = 7.7 Hz, J_2 = 4.6 Hz), 2.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 148.6, 147.7, 146.0, 141.1, 139.4, 136.2, 135.9, 134.9, 128.2, 127.3, 125.9, 121.7, 121.6, 116.4, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$: 264.1137; found 264.1130.

Methyl 4-methyl-3-(picolinamido)thiophene-2-carboxylate(51g): The compound **51g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 70% (193 mg); R_f = 0.62 (EtOAc:Hexanes = 1:4); IR (DCM): 3333, 1693, 1564, 1495, 1274 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0 (br, s, 1H), 8.73 (d, 1H, *J*= 4.4 Hz), 8.28 (d, 1H, *J*= 7.8 Hz), 7.91 (t, 1H, *J*= 7.7 Hz), 7.51 (t, 1H, *J*= 6.2 Hz), 7.22 (s, 1H), 3.88 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 162.1, 149.6, 148.6, 142.0, 137.4, 136.2, 127.6, 126.6, 122.7, 118.5, 52.0, 15.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_3S$: 277.0647; found 277.0636.



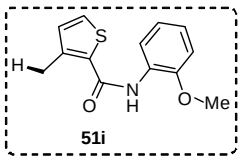
51g

3-Methyl-*N*-propylthiophene-2-carboxamide (51h): The compound **51h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless liquid; Yield: 89% (164 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); IR (DCM): 3369, 1717, 1636, 1521, 1281, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 1H, *J*= 5.0 Hz), 6.78 (d, 1H, *J*= 5.0 Hz), 6.23 (br. s, 1H), 3.30-3.25 (m, 2H), 2.42 (s, 3H), 1.59-1.50 (m, 2H), 0.89 (t, 3H, *J*= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 140.3, 131.7, 131.4, 126.2, 41.6, 22.9, 15.6, 11.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{14}NOS$: 184.0796; found 184.0790.



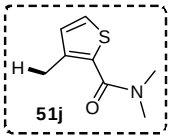
51h

***N*-(2-Methoxyphenyl)-3-methylthiophene-2-carboxamide (51i):** The compound **51i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless liquid; Yield: 64% (160 mg); R_f = 0.43 (EtOAc:Hexanes = 1:4); IR (DCM): 2927, 1656, 1522, 1460, 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 8.37 (br. s, 1H), 7.37 (d, 1H, *J*= 5.0 Hz), 7.10 (td, 1H, *J*= 1.7 Hz, J_2 = 7.7 Hz), 7.03 (td, 1H, *J*= 1.4 Hz, J_2 = 7.8 Hz), 6.96-6.92 (m, 2H), 3.94 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 148.0, 140.7, 132.6, 132.3, 127.7, 127.4, 123.8, 121.2, 119.7, 109.9, 55.9, 15.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}NO_2S$: 248.0745; found 248.0738.

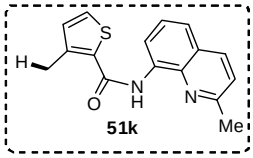


51i

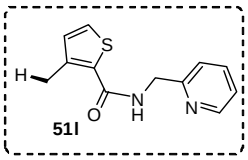
***N,N*,3-Trimethylthiophene-2-carboxamide (51j):** The compound **51j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless liquid; Yield: 79% (135 mg); R_f = 0.65 (EtOAc:Hexanes = 1:4); IR (DCM): 2927, 1622, 1547, 1392, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 1H), 6.79-6.77 (m, 1H), 3.01 (m, 6H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 137.0, 130.7, 129.6, 125.7, 14.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{12}NOS$: 170.0640; found 170.0634. The *N*-methyl signals of amide group did not appear in the ^{13}C NMR spectrum.



3-Methyl-*N*-(2-methylquinolin-8-yl)thiophene-2-carboxamide(51k): The compound **51k** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless liquid; Yield: 67% (191 mg); R_f = 0.51 (EtOAc:Hexanes = 1:4); IR (DCM): 3350, 1716, 1530, 1384, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.47 (br, s, 1H), 8.78 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 7.92 (d, 1H, *J*= 8.4 Hz), 7.44 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.7 Hz) 7.39-7.37 (m, 2H), 7.22 (d, 1H, *J*= 8.4 Hz), 6.94 (d, 1H, *J*= 5.0 Hz), 2.73 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 157.1, 140.1, 137.8, 136.3, 134.0, 133.7, 132.4, 128.1, 126.3, 125.9, 122.4, 121.3, 116.3, 25.2, 16.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}N_2OS$: 283.0905; found 283.0898.

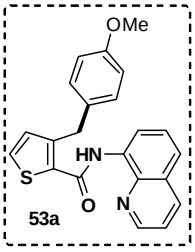


3-Methyl-*N*-(pyridin-2-ylmethyl)thiophene-2-carboxamide (51l): The compound **51l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid; Yield: 67% (156 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); IR (DCM): 3394, 1632, 1511, 1414, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.66-7.63 (m, 1H), 7.40 (br, s, 1H), 7.30-7.25 (m, 2H), 7.19-7.18 (m, 1H), 6.87-6.86 (m, 1H), 4.70 (m, 2H), 2.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 156.2, 149.0, 140.7, 136.8, 132.0, 131.5, 126.8, 122.4, 122.0, 44.7, 15.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0749; found 233.0742.

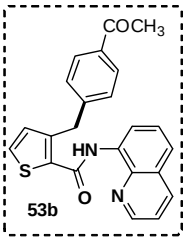


3-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53a): The compound **53a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 72% (34 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); IR (DCM): 3308, 1651, 1523, 1483, 1244, 1029 cm^{-1}; ^1H NMR (400

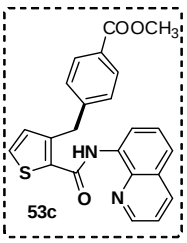
MHz, $CDCl_3$): δ 10.48 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.39 (d, 1H, J= 5.1 Hz), 7.25 (d, 2H, J= 8.7 Hz), 6.90 (d, 1H, J= 5.1 Hz), 6.87 (d, 2H, J= 8.7 Hz),), 4.48 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 158.1, 148.3, 145.6, 138.6, 136.3, 134.7, 132.2, 132.1, 131.6, 129.9, 128.0, 127.5, 127.4, 121.7, 116.6, 113.9, 55.3, 34.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2S$: 375.1167; found 375.1180.



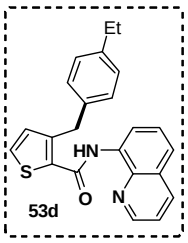
3-(4-Acetylbenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53b): The compound **53b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 58% (28 mg); R_f = 0.35 (EtOAc:Hexanes = 1:4); mp 126-128 ^oC; IR (KBr):1653, 1525, 1485, 1384, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.92 (d, 2H, J= 8.2 Hz), 7.62-7.55 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.43-7.42 (m, 3H), 6.92 (d, 1H, J= 5.0 Hz), 4.60 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 160.9, 148.3, 145.9, 144.3, 138.6, 136.4, 135.3, 134.5, 132.2, 131.4, 129.1, 128.7, 128.0, 127.6, 127.4, 121.8, 121.8, 116.6, 35.2, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2S$: 387.1167; found 387.1179.



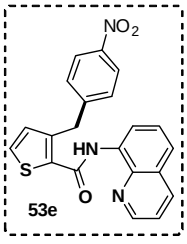
Methyl 4-((2-(quinolin-8-ylcarbamoyl)thiophen-3-yl)methyl)benzoate (53c): The compound **53c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a brown colour solid; Yield: 67% (34 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); mp 134-136 ^oC; IR (KBr): 3303, 1656, 1525, 1485, 1327, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.99 (d, 2H, J= 8.3 Hz), 7.59 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.9 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.42-7.39 (m, 3H), 6.90 (d, 1H, J= 5.1 Hz), 4.59 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 161.0, 148.3, 145.6, 144.4, 138.6, 136.4, 134.5, 132.2, 131.4, 129.9, 128.9, 128.2, 128.0, 127.6, 127.4, 121.8, 121.7, 116.6, 52.0, 35.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3S$: 403.1116; found 403.1101.



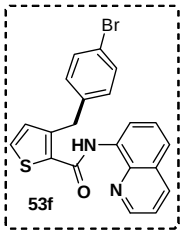
3-(4-Ethylbenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53d): The compound **53d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 53% (25 mg); R_f = 0.51 (EtOAc:Hexanes = 1:4); IR (DCM): 2962, 1660, 1524, 1484, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.49 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.76 Hz), 7.55 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.39 (d, 1H, *J*= 5.1 Hz), 7.25 (d, 2H, *J*= 8.1 Hz), 7.16 (d, 2H, *J*= 8.1 Hz), 6.91 (d, 1H, *J*= 5.1 Hz), 4.51 (s, 2H), 2.64 (q, 2H, *J*= 7.6 Hz), 1.24 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 148.3, 145.4, 142.1, 138.6, 137.3, 136.3, 134.7, 132.1, 131.7, 128.9, 128.0, 128.0, 127.4, 121.7, 116.6, 35.0, 28.5, 15.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2OS$: 373.1375; found 373.1367.



3-(4-Nitrobenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53e): The compound **53e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 72% (35 mg); R_f = 0.43 (EtOAc:Hexanes = 1:4); mp 153-155 ^oC; IR (KBr): 1648, 1529, 1484, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.48 (br. s, 1H), 8.84-8.82 (m, 2H), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.16 (d, 2H, *J*= 8.8 Hz), 7.62-7.56 (m, 2H), 7.52-7.49 (m, 3H), 7.45 (d, 1H, *J*= 5.0 Hz), 6.94 (d, 1H, *J*= 5.0 Hz), 4.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 148.4, 148.1, 146.5, 143.8, 138.5, 136.5, 134.4, 132.2, 131.3, 129.6, 128.0, 127.7, 127.4, 123.8, 122.0, 121.8, 116.6, 35.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}N_3O_3S$: 390.0912; found 390.0917.

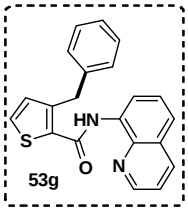


3-(4-Bromobenzyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53f): The compound **53f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 58% (31 mg); R_f = 0.41 (EtOAc:Hexanes = 1:4); mp 112-114 ^oC; IR (KBr): 1660, 1525, 1485, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.43 (d, 2H, *J*= 8.4 Hz), 7.41 (d, 1H, *J*= 5.1 Hz), 7.21 (d, 2H, *J*= 8.4 Hz), 6.90 (d, 1H, *J*= 5.1 Hz), 4.48 (s, 2H); ^{13}C

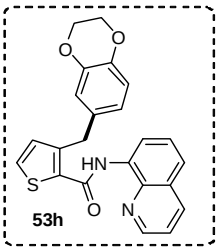


NMR (100 MHz, $CDCl_3$): δ 161.0, 148.3, 144.7, 139.2, 138.6, 136.4, 134.5, 132.1, 131.6, 131.4, 130.7, 127.9, 127.5, 127.4, 121.8, 121.8, 120.1, 116.6, 34.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{16}BrN_2OS$: 423.0167; found 423.0164.

3-Benzyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53g): The compound **53g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 55% (24 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); mp 138-140 ^oC; IR (KBr): 1661, 1525, 1485, 1328 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.49 (br. s, 1H), 8.88 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.39 (d, 1H, J= 5.1 Hz), 7.34-7.30 (m, 4H), 7.26-7.22 (m, 1H), 6.91 (d, 1H, J= 5.1 Hz), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 148.3, 145.1, 140.1, 138.6, 136.3, 134.6, 132.2, 131.6, 128.9, 128.5, 128.0, 127.5, 127.4, 126.3, 121.7, 116.6, 35.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2OS$: 345.1062; found 345.1048.

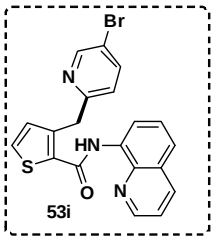


3-((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53h): The compound **53h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a brown colour solid; Yield: 47% (24 mg); R_f = 0.48 (EtOAc:Hexanes = 1:4); mp 209-211 ^oC; IR (KBr): 3339, 1658, 1525, 1429, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.87 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.59 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.39 (d, 1H, J= 5.1 Hz), 6.93 (d, 1H, J= 5.0 Hz), 6.84 (s, 1H), 6.82-6.81 (m, 2H), 4.43 (s, 2H), 4.24 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 148.3, 145.3, 143.4, 142.0, 138.6, 136.3, 134.7, 133.4, 132.1, 131.6, 128.0, 127.5, 127.4, 121.9, 121.7, 117.6, 117.2, 116.6, 64.4, 64.3, 34.6; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3S$: 403.1116; found 403.1104.

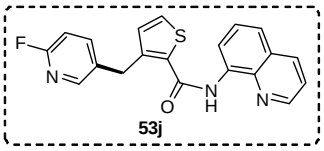


3-((5-Bromopyridin-2-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53i): The compound **53i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a brown colour solid; Yield: 96% (51 mg); R_f = 0.35

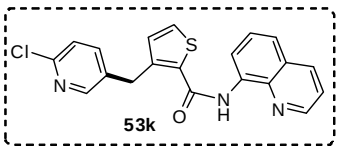
(EtOAc:Hexanes = 1:4); mp 150-152 ^{o}C; IR (KBr): 1654, 1524, 1485, 1382 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (br. s, 1H), 8.84 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (d, 1H, J = 2.3 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.61-7.54 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.42 (d, 1H, J= 5.1 Hz), 7.30 (d, 1H, J= 8.6 Hz), 7.04 (d, 1H, J= 5.1 Hz), 4.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.5, 150.3, 148.3, 142.7, 139.3, 138.8, 136.3, 134.7, 132.9, 131.4, 128.0, 127.6, 127.3, 124.7, 121.9, 121.7, 118.4, 117.1, 37.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}BrN_3OS$: 424.0119; found 424.0114.



3-((6-Fluoropyridin-3-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53j): The compound **53j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a pale yellow colour solid; Yield: 57% (26 mg); R_f = 0.32 (EtOAc:Hexanes = 1:4); mp 124-126 ^{o}C; IR (KBr): 1659, 1526, 1484, 1328, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.83 (d, 2H, J= 7.2 Hz), 8.19 (d, 2H, J= 8.6 Hz), 7.80-7.76 (m, 1H), 7.61-7.55 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.43 (d, 1H, J= 5.0 Hz), 6.93 (d, 1H, J= 8.3 Hz), 6.86 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.5 Hz), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (d, J_{C-F} = 236.2 Hz), 160.8, 148.4, 147.3 (d, J_{C-F} = 14.4 Hz), 144.3, 141.7 (d, J_{C-F} = 7.6 Hz), 138.5, 136.4, 134.4, 133.5 (d, J_{C-F} = 4.4 Hz), 132.0, 131.2, 128.0, 127.7, 127.4, 121.9, 121.8, 116.6, 109.3 (d, J_{C-F} = 37.2 Hz), 31.5 (d, J_{C-F} = 1.1 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}FN_3OS$: 364.0920; found 364.0913.

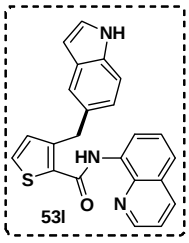


3-((6-Chloropyridin-3-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53k): The compound **53k** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 54% (26 mg); R_f = 0.34 (EtOAc:Hexanes = 1:4); mp 122-124 ^{o}C; IR (KBr): 1657, 1585, 1385, 1244, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.84-8.82 (m, 2H), 8.39 (d, 1H, J= 2.1 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.65 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.5 Hz), 7.62-7.56 (m, 2H), 7.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.44 (d, 1H, J= 5.1 Hz), 7.26 (d, 1H, J= 8.2 Hz), 6.94 (d, 1H, J= 5.1 Hz), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 149.8, 149.4, 148.4, 144.0, 139.4, 138.5, 136.4, 134.8, 134.4, 132.1, 131.2, 128.0,



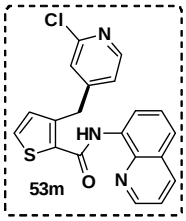
127.8, 127.4, 124.1, 122.0, 121.8, 116.6, 31.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}ClN_3OS$: 380.0624; found 380.0611.

3-((1*H*-Indol-5-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53l): The compound **53l** was obtained after purification by column chromatography on neutral alumina



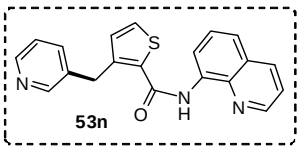
(EtOAc:Hexanes = 60:40) as a colourless liquid; Yield: 54% (26 mg); R_f = 0.22 (EtOAc:Hexanes = 1:4); IR (DCM): 3319, 1707, 1651, 1526, 1484, 1384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.48 (br. s, 1H), 8.96 (br. s, 1H), 8.84 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 8.67 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.57-7.49 (m, 3H), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.32-7.30 (m, 2H), 7.16-7.11 (m, 2H), 6.87 (d, 1H, *J*= 5.1 Hz), 6.44-6.43 (m, 1H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 161.3, 148.3, 146.1, 138.6, 136.2, 134.7, 134.7, 132.1, 131.9, 131.0, 128.2, 127.9, 127.4, 127.3, 124.6, 123.2, 121.7, 121.7, 120.4, 116.6, 111.2, 111.0, 35.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3OS$: 384.1171; found 384.1159.

3-((2-Chloropyridin-4-yl)methyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53m): The compound **53m** was obtained after purification by column chromatography on neutral



alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 80% (38 mg); R_f = 0.35 (EtOAc:Hexanes = 1:4); IR (DCM): 1657, 1591, 1526, 1485, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (br. s, 1H), 8.83-8.81 (m, 2H), 8.29 (d, 1H, *J*= 5.1 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.61-7.56 (m, 2H), 7.51-7.47 (m, 2H), 7.28 (s, 1H), 7.20-7.18 (m, 1H), 6.95 (d, 1H, J_1 = 5.1 Hz), 4.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 152.6, 151.7, 149.6, 148.4, 142.6, 138.5, 136.4, 134.3, 132.6, 131.3, 128.0, 127.8, 127.4, 124.4, 123.0, 122.0, 121.9, 121.8, 116.6, 34.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}ClN_3OS$: 380.0624; found 380.0626.

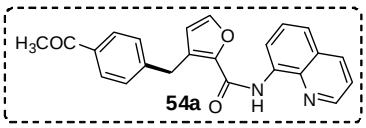
3-(Pyridin-3-ylmethyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (53n): The compound **53n** was obtained after purification by column chromatography on neutral alumina



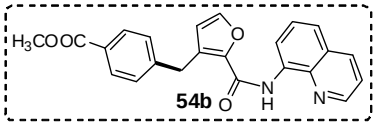
(EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 46% (20 mg); R_f = 0.39 (EtOAc:Hexanes = 1:4); IR (DCM): 1656, 1525, 1484, 1385, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.48 (br. s, 1H), 8.85 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.63 (d, 1H, *J*= 1.6 Hz), 8.48 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.1 Hz), 8.20 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.65 (d, 1H, *J* = 7.8 Hz), 7.62-7.55 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.43

(d, 1H, *J*= 5.1 Hz), 7.23 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.8 Hz), 6.93 (d, 1H, *J*= 5.1 Hz), 4.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 150.2, 148.4, 147.7, 144.3, 138.5, 136.4, 135.8, 134.5, 132.2, 131.4, 128.0, 127.7, 127.4, 123.5, 121.9, 121.9, 116.6, 32.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{16}N_3OS$: 346.1014; found 346.1001.

3-(4-Acetylbenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54a): The compound **54a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 82% (38 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 143-145 ^{o}C; IR (KBr): 3302, 1671, 1529, 1484, 1328 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.81 (br. s, 1H), 8.89 (d, 1H, *J*= 1.8 Hz), 8.87 (dd, 1H, J_1 = 2.9 Hz, J_2 = 1.7 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.90 (d, 2H, *J*= 8.4 Hz), 7.59-7.53 (m, 2H), 7.51 (d, 1H, *J*= 8.3 Hz), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.42 (d, 2H, *J*= 8.4 Hz), 6.35 (d, 1H, *J*= 1.8 Hz), 4.44 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 157.5, 148.4, 145.7, 143.4, 142.6, 138.7, 136.4, 135.4, 134.3, 131.0, 129.1, 128.7, 128.1, 127.4, 121.8, 121.7, 116.5, 114.5, 31.5, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1396; found 371.1389.

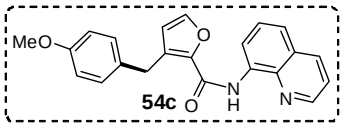


Methyl 4-((2-(quinolin-8-ylcarbamoyl)furan-3-yl)methyl)benzoate (54b): The compound **54b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a brown colour solid; Yield: 74% (36 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 158-160 ^{o}C; IR (KBr): 3436, 1648, 1529, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (br. s, 1H), 8.92-8.89 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.99 (d, 2H, *J*= 8.4 Hz), 7.61-7.54 (m, 2H), 7.52-7.48 (m, 2H), 7.42 (d, 2H, *J*= 8.4 Hz), 6.35 (d, 1H, *J*= 1.8 Hz), 4.46 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 157.5, 148.4, 145.4, 143.4, 142.5, 138.7, 136.4, 134.3, 131.1, 129.9, 128.9, 128.3, 128.1, 127.4, 121.8, 121.7, 116.5, 114.5, 52.0, 31.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_4$: 387.1345; found 387.1337.

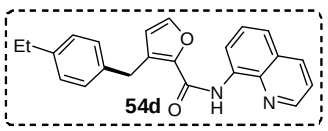


3-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54c): The compound **54c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a brown colour solid; Yield: 67% (30 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 125-127 ^{o}C; IR (KBr): 3341, 1668, 1530, 1484, 1245 cm^{-1}; ^{1}H

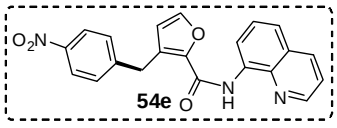
NMR (400 MHz, $CDCl_3$): δ 10.82 (br. s, 1H), 8.94-8.90 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52-7.49 (m, 2H), 7.28 (d, 2H, *J*= 8.7 Hz), 6.87 (d, 2H, *J*= 8.7 Hz), 6.36 (d, 1H, *J*= 1.7 Hz), 4.34 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 157.7, 148.4, 143.2, 142.1, 138.7, 136.4, 134.4, 132.7, 132.1, 129.8, 128.1, 127.4, 121.7, 121.6, 116.5, 114.6, 113.9, 55.3, 30.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1396; found 359.1405.



3-(4-Ethylbenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54d): The compound **54d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 76% (34 mg); R_f = 0.43 (EtOAc:Hexanes = 1:4); IR (DCM): 3341, 1670, 1529, 1484, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (br. s, 1H), 8.94 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.51-7.48 (m, 2H), 7.29 (d, 2H, *J*= 8.1 Hz), 7.17 (d, 2H, *J*= 8.1 Hz), 6.38 (d, 1H, *J*= 1.8 Hz), 4.38 (s, 2H), 2.65 (q, 2H, *J*= 7.6 Hz), 1.25 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 148.4, 143.2, 142.2, 142.2, 138.7, 137.2, 136.4, 134.5, 132.5, 128.8, 128.1, 128.0, 127.4, 121.7, 121.6, 116.5, 114.7, 31.1, 28.5, 15.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_2$: 357.1603; found 357.1597.

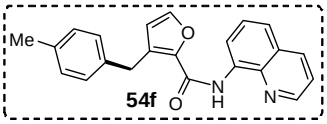


3-(4-Nitrobenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54e): The compound **54e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 71% (33 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); IR (DCM): 1655, 1525, 1485, 1327 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.85 (br. s, 1H), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.87 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.17 (d, 2H, *J*= 8.8 Hz), 7.61-7.55 (m, 3H), 7.52-7.50 (m, 3H), 6.39 (d, 1H, *J*= 1.8 Hz), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 148.5, 147.7, 146.6, 143.6, 142.8, 138.7, 136.4, 134.2, 130.1, 129.6, 128.1, 127.3, 123.8, 121.9, 121.8, 116.6, 114.4, 31.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}N_3O_4$: 374.1141; found 374.1149.

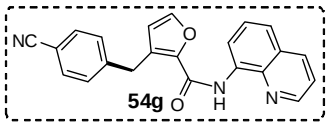


3-(4-Methylbenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54f): The compound **54f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes =

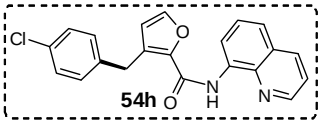
30:70) as a colourless solid; Yield: 65% (28 mg); R_f = 0.42 (EtOAc:Hexanes = 1:4); mp 118-120 ^{o}C; IR (KBr): 1665, 1596, 1384, 1247, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (br. s, 1H), 8.93 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.52-7.49 (m, 2H), 7.26 (d, 2H, J= 7.8 Hz), 7.14 (d, 2H, J= 7.8 Hz), 6.35 (d, 1H, J= 1.7 Hz), 4.37 (s, 2H), 2.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 148.4, 143.2, 142.2, 138.7, 136.9, 136.4, 135.8, 134.5, 132.6, 129.2, 128.8, 128.1, 127.4, 121.7, 121.6, 116.5, 114.6, 31.1, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2$: 343.1447; found 343.1434.



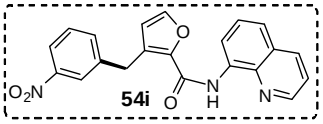
3-(4-Cyanobenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54g): The compound **54g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 79% (35 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); mp 163-165 ^{o}C; IR (KBr): 1657, 1533, 1484, 1385, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (br. s, 1H), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.88 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.62-7.53 (m, 5H), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.46 (d, 2H, J= 8.4 Hz), 6.37 (d, 1H, J= 1.7 Hz), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 148.5, 145.6, 143.6, 142.8, 138.7, 136.4, 134.2, 132.4, 130.2, 129.6, 128.1, 127.3, 121.9, 121.8, 119.1, 116.5, 114.4, 110.2, 31.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_2$: 354.1243; found 354.1231.



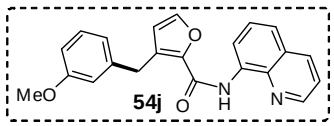
3-(4-Chlorobenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54h): The compound **54h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 93% (42 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); mp 108-110 ^{o}C; IR (KBr): 1593, 1502, 1384, 1122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (br. s, 1H), 8.91-8.90 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.62-7.55 (m, 2H), 7.52-7.49 (m, 2H), 7.29 (s, 4H), 6.35 (d, 1H, J= 1.7 Hz), 4.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 148.4, 143.3, 142.4, 138.7, 138.5, 136.4, 134.3, 132.1, 131.6, 130.2, 128.6, 128.1, 127.4, 121.8, 121.7, 116.5, 114.5, 30.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}ClN_2O_2$: 363.0900; found 363.0887.



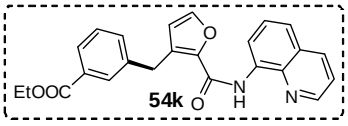
3-(3-Nitrobenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54i): The compound **54i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 55% (26 mg); R_f = 0.41 (EtOAc:Hexanes = 1:4); mp 157-159 ^oC; IR (KBr): 1666, 1598, 1483, 1350, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.85 (br. s, 1H), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.89 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.2 Hz), 8.22-8.20 (m, 2H), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.72 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.3 Hz), 7.62-7.56 (m, 3H), 7.53-7.46 (m, 2H), 6.41 (d, 1H, J= 1.8 Hz), 4.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 148.5, 143.6, 142.8, 142.0, 138.7, 136.4, 135.2, 134.2, 130.2, 129.4, 128.1, 127.4, 123.5, 121.9, 121.8, 121.5, 116.6, 114.4, 31.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}N_3O_4$: 374.1141; found 374.1127.



3-(3-Methoxybenzyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54j): The compound **54j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 60% (27 mg); R_f = 0.48 (EtOAc:Hexanes = 1:4); IR (DCM): 1668, 1530, 1384, 1260, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.82 (br. s, 1H), 8.94-8.90 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.52-7.49 (m, 2H), 7.25 (t, 1H, J= 7.8 Hz), 6.95 (d, 1H, J= 7.6 Hz), 6.91 (br. s, 1H), 6.79 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.4 Hz), 6.37 (d, 1H, J= 1.7 Hz), 4.39 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 157.7, 148.4, 143.2, 142.3, 141.5, 138.7, 136.4, 134.4, 132.1, 129.5, 128.1, 127.4, 121.7, 121.7, 121.3, 116.5, 114.7, 114.6, 111.7, 55.2, 31.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1396; found 359.1384.

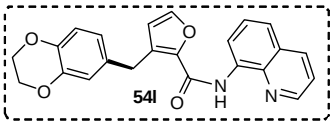


Ethyl 3-((2-(quinolin-8-ylcarbamoyl)furan-3-yl)methyl)benzoate (54k): The compound **54k** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 80% (40 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); IR (DCM): 1714, 1668, 1578, 1484, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.83 (br. s, 1H), 8.93-8.90 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.02 (br. s, 1H), 7.93 (d, 1H, J= 7.8 Hz), 7.61-7.54 (m, 3H), 7.52-7.48 (m, 2H), 7.39 (t, 1H, J= 7.7 Hz), 6.35 (d, 1H, J= 1.7 Hz), 4.46 (s, 2H), 4.38 (q, 2H, J= 7.1 Hz), 1.40 (t, 3H, J= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 157.6, 148.4, 143.4, 142.4, 140.3, 138.7, 136.4, 134.4,

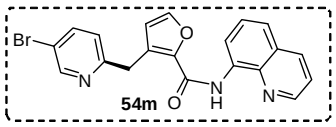


133.5, 131.5, 130.7, 129.8, 128.6, 127.6, 127.4, 121.7, 116.5, 114.5, 61.0, 31.3, 14.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_4$: 401.1501; found 401.1486.

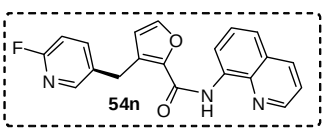
3-((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)-N-(quinolin-8-yl)furan-2-carboxamide (54l): The compound **54l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 72% (35 mg); R_f = 0.49 (EtOAc:Hexanes = 1:4); mp 100-102 ^oC; IR (KBr): 3345, 1668, 1532, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.81 (br. s, 1H), 8.91-8.90 (m, 2H), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 7.52-7.50 (m, 2H), 6.86-6.82 (m, 3H), 6.38 (d, 1H, *J*= 1.8 Hz), 4.29 (s, 2H), 4.26-4.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 148.4, 143.4, 143.2, 142.2, 142.0, 138.7, 136.4, 134.4, 133.3, 132.4, 128.1, 127.4, 121.8, 121.7, 121.6, 117.5, 117.2, 116.5, 114.6, 64.4, 64.3, 30.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_4$: 387.1345; found 387.1340.



3-((5-Bromopyridin-2-yl)methyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54m): The compound **54m** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 82% (42 mg); R_f = 0.35 (EtOAc:Hexanes = 1:4); mp 146-148 ^oC; IR (KBr): 3339, 1666, 1598, 1531, 1425, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.83 (br. s, 1H), 8.91-8.88 (m, 2H), 8.62 (d, 1H, *J*= 2.2 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.61-7.53 (m, 3H), 7.49 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.33 (d, 1H, *J*= 8.3 Hz), 6.53 (d, 1H, *J*= 1.7 Hz), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 157.5, 150.2, 148.4, 143.4, 143.4, 142.6, 139.3, 138.7, 136.4, 134.3, 129.9, 128.1, 127.3, 124.8, 121.8, 118.5, 116.5, 114.8, 33.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}BrN_3O_2$: 408.0348; found 408.0334.

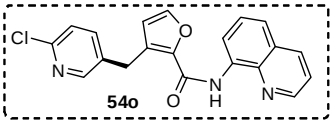


3-((6-Fluoropyridin-3-yl)methyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54n): The compound **54n** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 57% (25 mg); R_f = 0.30 (EtOAc:Hexanes = 1:4); mp 129-131 ^oC; IR (KBr): 1667, 1598, 1532, 1483, 1385, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.84 (br. s, 1H), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.88 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.22-8.20 (m, 2H), 7.81 (td, 1H, J_1 = 2.5 Hz, J_2 = 8.2 Hz), 7.62-7.55 (m,

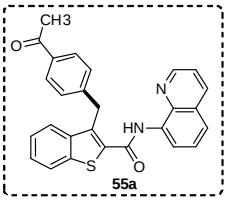


3H), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.88 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 6.38 (d, 1H, J= 1.7 Hz), 4.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, J_{C-F} = 236.0 Hz), 157.4, 148.5, 147.2 (d, J_{C-F} = 13.9 Hz), 143.6, 142.6, 141.7 (d, J_{C-F} = 7.8 Hz), 138.7, 136.4, 134.2, 133.2 (d, J_{C-F} = 4.4 Hz), 130.7, 128.1, 127.4, 121.9, 121.8, 116.5, 114.3, 109.4 (d, J_{C-F} = 37.5 Hz), 27.8 (d, J_{C-F} = 1.2 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}FN_3O_2$: 348.1148; found 348.1135.

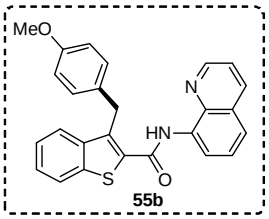
3-((6-Chloropyridin-3-yl)methyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (54o): The compound **54o** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 55% (25 mg); R_f = 0.30 (EtOAc:Hexanes = 1:4); mp 148-150 ^{o}C; IR (KBr): 1666, 1597, 1531, 1459, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (br. s, 1H), 8.91 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.87 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.2 Hz), 8.39 (d, 1H, J= 2.2 Hz), 8.21 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.67 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.4 Hz), 7.62-7.55 (m, 3H), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27 (d, 1H, J= 8.2 Hz), 6.37 (d, 1H, J= 1.6 Hz), 4.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 149.7, 149.5, 148.5, 143.6, 142.7, 139.4, 138.7, 136.4, 134.5, 134.2, 130.3, 128.1, 127.3, 124.2, 121.9, 121.8, 116.5, 114.3, 28.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}ClN_3O_2$: 364.0853; found 364.0840.



3-(4-Acetylbenzyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55a): The compound **55a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as pale yellow colour solid; Yield: 60% (33 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 157-159 ^{o}C; IR (KBr): 1655, 1526, 1485, 1384, 1265, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br. s, 1H), 8.89 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.5 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.93 (d, 1H, J= 8.0 Hz), 7.88 (d, 2H, J= 8.4 Hz), 7.74 (d, 1H, J= 8.0 Hz), 7.62-7.56 (m, 2H), 7.51-7.47 (m, 2H), 7.44 (d, 2H, J= 8.4 Hz), 7.42-7.38 (m, 1H), 4.87 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 161.3, 148.4, 145.1, 139.9, 139.0, 138.5, 138.1, 136.4, 135.3, 134.4, 132.9, 128.7, 128.7, 128.0, 127.3, 126.9, 125.1, 123.8, 122.8, 122.1, 121.8, 116.8, 33.0, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_2S$: 437.1324; found 437.1329.

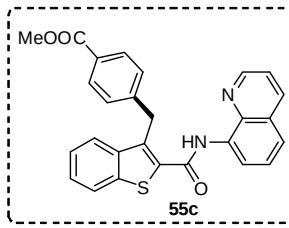


3-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55b): The compound **55b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 52% (28 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); IR (DCM): 3311, 1657, 1522, 1482, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br. s, 1H), 8.91 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.92 (d, 1H, *J*= 8.0 Hz), 7.81 (d, 1H, *J*= 8.0 Hz), 7.62-7.56 (m, 2H), 7.49-7.45 (m, 2H), 7.42-7.38 (m, 1H), 7.27 (d, 2H, *J*= 8.7 Hz), 6.82 (d, 2H, *J*= 8.7 Hz), 4.74 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 158.0, 148.4, 140.2, 139.2, 139.0, 138.6, 136.3, 134.5, 132.8, 131.3, 129.4, 127.9, 127.4, 126.6, 124.8, 124.1, 122.7, 122.0, 121.7, 116.8, 113.9, 55.2, 32.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_2S$: 425.1324; found 425.1330.



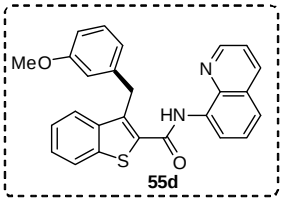
55b

Methyl 4-((2-(quinolin-8-ylcarbamoyl)benzo[*b*]thiophen-3-yl)methyl)benzoate (55c): The compound **55c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 46% (26 mg); R_f = 0.43 (EtOAc:Hexanes = 1:4); mp 208-210 ^oC; IR (DCM): 1720, 1661, 1529, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br. s, 1H), 8.89 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.75 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.20 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.97-7.92 (m, 3H), 7.74 (d, 1H, *J*= 8.1 Hz), 7.62-7.57 (m, 2H), 7.54-7.47 (m, 2H), 7.43-7.35 (m, 3H), 4.87 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 161.3, 148.4, 144.8, 139.9, 139.1, 138.6, 138.0, 136.4, 134.4, 133.0, 129.9, 128.5, 128.2, 128.0, 127.4, 126.9, 125.0, 123.8, 122.8, 122.1, 121.8, 116.8, 52.0, 33.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_3S$: 453.1273; found 453.1276.



55c

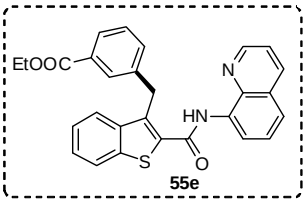
3-(3-Methoxybenzyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55d): The compound **55d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 56% (30 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 133-134 ^oC; IR (KBr): 3422, 1656, 1527, 1484, 1385, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br. s, 1H), 8.92 (d, 1H, *J*= 7.1 Hz), 8.73 (d, 1H, *J*= 4.1 Hz), 8.18 (d, 1H, *J*= 8.2 Hz), 7.92 (d, 1H, *J*= 8.0 Hz), 7.82 (d, 1H, *J*= 8.0 Hz), 7.62-7.55 (m, 2H), 7.49-7.45 (m, 2H), 7.40 (t, 1H, *J*= 7.8 Hz), 7.21 (t, 1H, *J*= 7.8 Hz), 6.95-6.93 (m, 2H), 6.75 (d, 1H, *J*= 8.7 Hz), 4.80 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz,



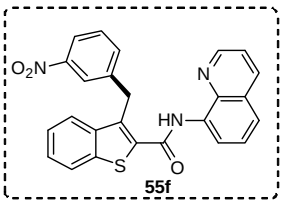
55d

$CDCl_3$): δ 161.5, 159.7, 148.4, 140.9, 140.2, 139.1, 138.6, 138.4, 136.3, 134.5, 133.0, 129.5, 127.9, 127.4, 126.7, 124.9, 124.1, 122.7, 122.0, 121.7, 120.9, 116.8, 114.4, 111.4, 55.1, 32.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_2S$: 425.1324; found 425.1308.

3-(3-Methoxybenzyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55e): The compound **55e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 41% (24 mg); R_f = 0.46 (EtOAc:Hexanes = 1:4); IR (DCM): 3324, 1715, 1656, 1484, 1328, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br. s, 1H), 8.90 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.8 Hz), 8.76 (d, 1H, *J*= 3.6 Hz), 8.19 (d, 1H, *J*= 8.2 Hz), 8.11 (br. s, 1H), 7.93 (d, 1H, *J*= 8.0 Hz), 7.89 (d, 1H, *J*= 7.7 Hz), 7.77 (d, 1H, *J*= 8.1 Hz), 7.62-7.57 (m, 2H), 7.50-7.46 (m, 3H), 7.40 (t, 1H, *J*= 7.8 Hz), 7.33 (t, 1H, *J*= 7.7 Hz), 4.86 (s, 2H), 4.35 (q, 2H, *J*= 7.1 Hz), 1.36 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 161.4, 148.4, 140.0, 139.6, 139.1, 138.6, 138.3, 136.3, 134.4, 133.0, 132.9, 130.6, 129.6, 128.6, 128.0, 127.5, 127.4, 126.8, 125.0, 123.9, 122.8, 122.1, 121.8, 116.8, 60.9, 32.8, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_2O_3S$: 467.1429; found 467.1413.

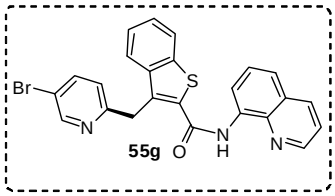


3-(3-Nitrobenzyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55f): The compound **55f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 49% (27 mg); mp 220-222 ^oC; R_f = 0.41 (EtOAc:Hexanes = 1:4); IR (KBr): 3302, 1649, 1527, 1485, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.65 (br. s, 1H), 8.88 (dd, 1H, J_1 = 5.7 Hz, J_2 = 3.3 Hz), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.27 (br. s, 1H), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.06 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.96 (d, 1H, *J*= 8.0 Hz), 7.75 (d, 1H, *J*= 8.0 Hz), 7.69 (d, 1H, *J*= 7.2 Hz), 7.61-7.58 (m, 2H), 7.54-7.50 (m, 2H), 7.44 (t, 2H, *J*= 8.0 Hz), 4.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 148.5, 141.5, 139.7, 139.0, 138.6, 137.8, 136.4, 134.8, 134.3, 132.9, 129.4, 128.0, 127.3, 127.1, 125.3, 123.5, 123.4, 123.0, 122.2, 121.9, 121.5, 116.8, 32.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_3S$: 440.1069; found 440.1069.

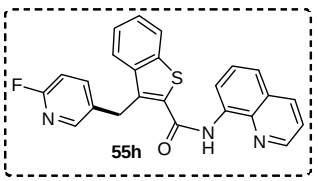


3-((5-Bromopyridin-2-yl)methyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55g): The compound **55g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 76% (45 mg);

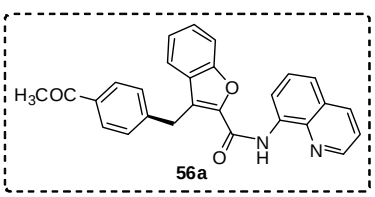
R_f = 0.39 (EtOAc:Hexanes = 1:4); mp 178-180 ^oC; IR (KBr): 1650, 1594, 1385, 1261, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.06 (br. s, 1H), 8.89 (dd, 1H, J_1 = 6.7 Hz, J_2 = 1.9 Hz), 8.78 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.1 Hz), 8.67 (d, 1H, J= 2.2 Hz), 8.20 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.92 (t, 2H, J= 8.9 Hz), 7.70 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 7.64-7.58 (m, 2H), 7.50-7.40 (m, 3H), 7.36 (d, 1H, J= 8.4 Hz), 4.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 157.8, 150.2, 148.4, 139.8, 139.3, 139.1, 138.9, 136.7, 136.3, 134.6, 133.6, 128.1, 127.3, 126.7, 125.0, 124.5, 124.0, 122.7, 122.3, 121.8, 118.5, 117.5, 35.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}BrN_3OS$: 474.0276; found 474.0259.



3-((6-Fluoropyridin-3-yl)methyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (55h): The compound **55h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) asa colourless solid; Yield: 71% (37 mg); R_f = 0.33 (EtOAc:Hexanes = 1:4); mp 169-171 ^oC; IR (KBr): 1655, 1595, 1531, 1385, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br. s, 1H), 8.89 (dd, 1H, J_1 = 6.1 Hz, J_2 = 2.7 Hz), 8.84 (d, 1H, J= 4.2 Hz), 8.30 (br. s, 1H), 8.21 (d, 1H, J= 4.2 Hz), 7.94 (d, 1H, J= 8.0 Hz), 7.79 (d, 2H, J= 8.1 Hz), 7.63-7.58 (m, 2H), 7.53-7.49 (m, 2H), 7.44 (t, 1H, J= 7.9 Hz), 6.82 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.7 Hz), 4.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (d, J_{C-F} = 236.0 Hz), 161.1, 148.5, 147.1 (d, J_{C-F} = 14.5 Hz), 141.4 (d, J_{C-F} = 7.6 Hz), 139.5, 139.0, 138.5, 138.1, 136.4, 134.3, 132.7, 132.6, (d, J_{C-F} = 10.9 Hz), 128.0, 127.3, 127.1, 125.2, 123.5, 123.0, 122.3, 121.9, 116.8, 109.4 (d, J_{C-F} = 37.2 Hz), 29.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}FN_3OS$: 414.1076; found 414.1060.

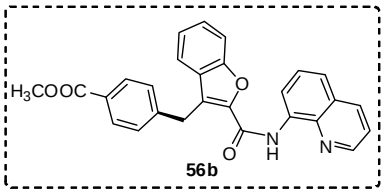


3-(4-Acetylbenzyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (56a): The compound **56a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 61% (32 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 189-191 ^oC; IR (KBr): 1649, 1529, 1487, 1327, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.13 (br. s, 1H), 8.98-8.95 (m, 2H), 8.23 (d, 1H, J = 8.2 Hz), 7.89 (d, 2H, J= 8.1 Hz), 7.70 (d, 1H, J= 8.4 Hz), 7.65-7.59 (m, 2H), 7.56-7.52 (m, 4H), 7.52-7.47 (m, 1H), 7.29 (t, 1H, J= 7.7 Hz), 4.77 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 158.1, 153.8, 148.6, 145.1, 143.5, 138.8, 136.4, 135.4, 134.2, 128.9, 128.8, 128.7, 128.1, 127.5, 127.3, 125.2, 123.5, 122.2, 121.8, 121.3, 116.9,



112.3, 30.0, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_3$: 421.1552; found 421.1558.

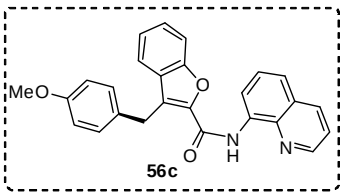
Methyl 4-((2-(quinolin-8-ylcarbamoyl)benzofuran-3-yl)methyl)benzoate (56b): The



56b

compound **56b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a brown colour solid; Yield: 66% (36 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 213-215 ^oC; IR (KBr): 1527, 1486, 1423, 1384, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.13 (br. s, 1H), 8.99-8.95 (m, 2H), 8.23 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.97 (d, 2H, *J*= 8.4 Hz), 7.70 (d, 1H, *J*= 8.3 Hz), 7.65-7.59 (m, 2H), 7.54 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.52-7.50 (m, 3H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.30-7.26 (m, 1H), 4.77 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 158.2, 153.8, 148.6, 144.8, 143.5, 138.8, 136.4, 134.2, 129.9, 128.8, 128.8, 128.2, 128.1, 127.5, 127.4, 125.2, 123.5, 122.2, 121.8, 121.4, 116.9, 112.2, 52.0, 30.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_4$: 437.1501; found 437.1494.

3-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (56c): The compound

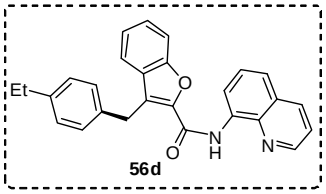


56c

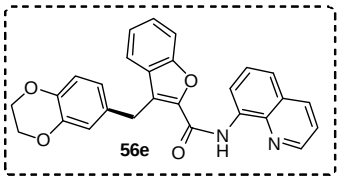
56c was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a colourless solid; Yield: 31% (16 mg); R_f = 0.46 (EtOAc:Hexanes = 1:4); mp 208-210 ^oC; IR (KBr): 1668, 1528, 1486, 1423, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.11 (br. s, 1H), 9.00-8.97 (m, 2H), 8.23 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.68 (d, 1H, *J*= 8.3 Hz), 7.65-7.52 (m, 4H), 7.46 (td, 1H, *J*= 7.2 Hz, *J*= 1.2 Hz), 7.38 (d, 2H, *J*= 8.7 Hz), 7.29-7.25 (m, 1H), 6.83 (d, 2H, *J*= 8.7 Hz), 4.64 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 158.1, 153.8, 148.6, 143.1, 138.8, 136.4, 134.3, 131.5, 129.7, 129.0, 128.1, 127.4, 127.3, 126.7, 123.3, 122.0, 121.8, 121.7, 116.9, 113.9, 112.1, 55.2, 29.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_3$: 409.1552; found 409.1557.

3-(4-Ethylbenzyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (56d): The compound **56d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 59% (30 mg); R_f = 0.46 (EtOAc:Hexanes = 1:4); mp 150-152 ^oC; IR (KBr): 2961, 1668, 1529, 1487, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.11 (br. s, 1H), 9.01-8.97 (m, 2H), 8.22 (dd, 1H, J_1 = 8.3 Hz, J_2

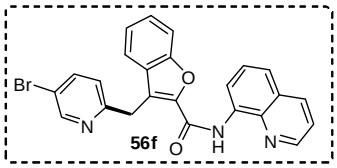
= 1.6 Hz), 7.68-7.58 (m, 4H), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.47 (td, 1H, *J*= 1.2 Hz, *J*= 7.2 Hz), 7.38 (d, 2H, *J*= 8.1 Hz), 7.28 (td, 1H, *J*= 7.3 Hz, *J*= 0.9 Hz), 7.13 (d, 2H, *J*= 8.1 Hz), 4.68 (s, 2H), 2.61 (q, 2H, *J*= 7.6 Hz) 1.22 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 153.7, 148.5, 143.2, 142.1, 138.8, 136.6, 136.4, 134.3, 129.1, 128.7, 128.1, 128.0, 127.4, 127.2, 126.5, 123.3, 122.0, 121.8, 121.7, 116.9, 112.1, 29.6, 28.5, 15.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2O_2$: 407.1760; found 407.1749.



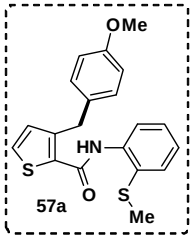
3-((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (56e): The compound **56e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 45% (25 mg); mp 216-218 ^oC; R_f = 0.44 (EtOAc:Hexanes = 1:4); IR (KBr): 1668, 1525, 1486, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.1 (br. s, 1H), 8.99-8.97 (m, 2H), 8.23 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.68 (d, 1H, *J*= 8.3 Hz), 7.64-7.59 (m, 3H), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.47 (td, 1H, *J*= 7.2 Hz, *J*= 1.2 Hz), 7.31-7.27 (m, 1H), 6.96-6.93 (m, 2H), 6.79 (d, 1H, *J*= 8.8 Hz), 4.60 (s, 2H), 4.22 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 153.7, 148.5, 143.3, 143.2, 142.0, 138.8, 136.4, 134.3, 132.7, 129.0, 128.1, 127.4, 127.3, 126.4, 123.4, 122.0, 121.8, 121.7, 117.4, 117.2, 116.9, 112.1, 64.3, 64.3, 29.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_4$: 437.1501; found 437.1498.



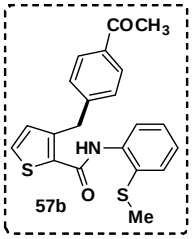
3-((5-Bromopyridin-2-yl)methyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (56f): The compound **56f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 57% (33 mg); R_f = 0.38 (EtOAc:Hexanes = 1:4); mp 209-211 ^oC; IR (KBr): 3333, 1657, 1596, 1385, 1266, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.13 (br. s, 1H), 8.97-8.95 (m, 2H), 8.62 (d, 1H, *J*= 2.0 Hz), 8.22 (d, 1H, *J*= 8.2 Hz), 7.73-7.67 (m, 3H), 7.64-7.59 (m, 2H), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.50-7.46 (m, 1H), 7.38 (d, 1H, *J*= 8.4 Hz), 7.31 (d, 1H, *J*= 7.5 Hz), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 158.1, 153.7, 150.1, 148.6, 143.4, 139.2, 138.8, 136.4, 134.2, 128.9, 128.1, 127.5, 127.3, 124.7, 124.5, 123.5, 122.2; 122.0, 121.8, 118.6, 116.9, 112.1, 32.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}BrN_3O_2$: 458.0504; found 458.0489.



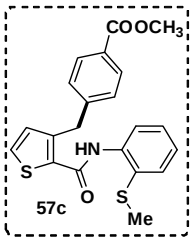
3-(4-Methoxybenzyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57a): The compound **57a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pale yellow colour solid; Yield: 58% (27 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); mp 104-106 ^oC; IR (KBr): 3312, 1578, 1510, 1433, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (br. s, 1H), 8.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.39-7.37 (m, 1H), 7.35 (d, 1H, *J*= 5.1 Hz), 7.22 (d, 2H, *J*= 8.7 Hz), 7.12 (td, 1H, *J*= 7.6 Hz, *J*= 1.3 Hz), 6.90 (d, 1H, *J*= 5.1 Hz), 6.86 (d, 2H, *J*= 8.6 Hz), 4.41 (s, 2H), 3.80 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 158.1, 146.1, 138.7, 133.4, 132.2, 131.8, 131.1, 129.9, 129.1, 127.3, 125.5, 124.5, 120.6, 114.0, 55.3, 34.4, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_2S_2$: 392.0755; found 392.0756.



3-(4-Acetylbenzyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57b): The compound **57b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 50% (24 mg); R_f = 0.51 (EtOAc:Hexanes = 1:4); mp 97-99 ^oC; IR (KBr): 3342, 1678, 1511, 1432, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (br. s, 1H), 8.43 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.91 (d, 2H, *J*= 7.8 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.41-7.34 (m, 4H), 7.12 (td, 1H, *J*= 7.6 Hz, *J*= 1.4 Hz), 6.91 (d, 1H, *J*= 5.1 Hz), 4.53 (s, 2H), 2.59 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 160.7, 145.9, 145.4, 138.5, 135.3, 133.4, 131.6, 131.1, 129.1, 129.1, 128.7, 127.3, 125.6, 124.6, 120.6, 35.2, 26.6, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO_2S_2$: 404.0755; found 404.0746.

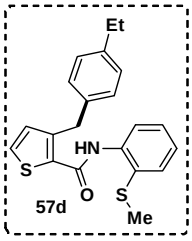


Methyl 4-((2-((2-(methylthio)phenyl)carbamoyl)thiophen-3-yl)methyl)benzoate (57c): The compound **57c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 54% (27 mg); R_f = 0.52 (EtOAc:Hexanes = 1:4); IR (DCM): 1719, 1667, 1610, 1578, 1279, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (br. s, 1H), 8.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.3 Hz), 7.98 (d, 2H, *J*= 8.4 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.38-7.34 (m, 4H), 7.12 (td, 1H, *J*= 7.6 Hz, *J*= 1.4 Hz), 6.89 (d, 1H, *J*= 5.1 Hz), 4.53 (s, 2H), 3.91 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz,

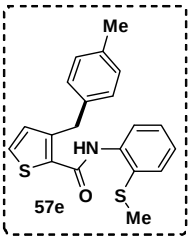


$CDCl_3$): δ 167.1, 160.7, 145.6, 145.4, 138.5, 133.4, 131.6, 131.1, 129.9, 129.2, 128.9, 128.2, 127.3, 125.5, 124.6, 120.6, 52.0, 35.2, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO_3S_2$: 420.0704; found 420.0701.

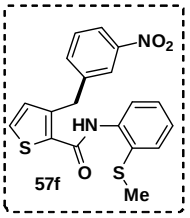
3-(4-Ethylbenzyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57d): The compound **57d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 54% (25 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); IR (DCM): 3312, 1667, 1578, 1511, 1432, 1304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (br. s, 1H), 8.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.9 Hz), 7.51 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.35-7.31 (m, 2H), 7.18 (d, 2H, *J*= 8.0 Hz), 7.12 (d, 2H, *J*= 8.0 Hz), 7.08 (td, 1H, *J*= 7.6 Hz, *J*= 1.3 Hz), 6.87 (d, 1H, *J*= 5.1 Hz), 4.41 (s, 2H), 2.60 (q, 2H, *J*= 7.6 Hz), 2.33 (s, 3H), 1.21 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 146.2, 142.2, 138.7, 137.2, 133.4, 131.8, 131.2, 129.2, 128.2, 128.1, 127.3, 125.5, 124.5, 120.7, 34.9, 28.5, 19.2, 15.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{21}NNaOS_2$: 390.0962; found 390.0955.



3-(4-Methylbenzyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57e): The compound **57e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 45% (20 mg); R_f = 0.52 (EtOAc:Hexanes = 1:4); IR (DCM): 1665, 1578, 1525, 1487, 1383, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (br. s, 1H), 8.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.55 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.37 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.7 Hz), 7.35 (d, 1H, *J*= 5.0 Hz), 7.19 (d, 2H, *J*= 8.0 Hz), 7.14-7.10 (m, 3H), 6.89 (d, 1H, *J*= 5.0 Hz), 4.43 (s, 2H), 2.38 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 146.3, 138.7, 137.0, 135.8, 133.4, 131.8, 131.2, 129.3, 129.2, 128.8, 127.3, 125.5, 124.5, 120.6, 34.9, 21.1, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{19}NNaOS_2$: 376.0806; found 376.0814.

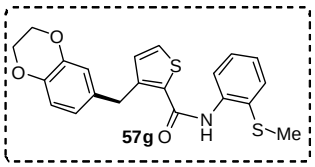


***N*-(2-(Methylthio)phenyl)-3-(3-nitrobenzyl)thiophene-2-carboxamide (57f):** The compound **57f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 50% (24 mg); mp 130-132 ^oC; R_f = 0.51 (EtOAc:Hexanes = 1:4); IR (KBr): 3304, 1665, 1578, 1525, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (br. s, 1H), 8.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 8.16 (br. s, 1H), 8.10-8.07 (m, 1H), 7.68 (dd,

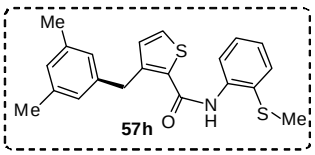


1H, J_1 = 7.6 Hz, J_2 = 0.5 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.47 (t, 1H, J= 8.0 Hz), 7.42 (d, 1H, J= 5.0 Hz), 7.36 (td, 1H, J= 7.6 Hz, J= 1.4 Hz), 7.13 (td, 1H, J= 7.6 Hz, J= 1.4 Hz), 6.95 (d, 1H, J= 5.0 Hz), 4.58 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 148.4, 145.0, 142.3, 138.4, 135.2, 133.3, 131.5, 131.2, 129.4, 129.1, 127.6, 125.7, 124.7, 123.6, 121.5, 120.6, 34.7, 19.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3S_2$: 385.0681; found 385.0684.

3-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57g): The compound **57g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 25:75) as a brown colour solid; Yield: 56% (28 mg); R_f = 0.51 (EtOAc:Hexanes = 1:4); mp 101-103 ^oC; IR (KBr): 3312, 1665, 1506, 1432, 1304, 1285 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (br. s, 1H), 8.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.51 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.35-7.31 (m, 2H), 7.08 (td, 1H, J= 7.6 Hz, J= 1.3 Hz), 6.88 (d, 1H, J= 5.1 Hz), 6.79-6.73 (m, 3H), 4.33 (s, 2H), 4.21 (s, 4H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 146.2, 143.4, 142.0, 138.7, 133.4, 133.3, 131.8, 131.2, 129.1, 127.3, 125.5, 124.5, 121.8, 120.7, 117.5, 117.3, 64.4, 64.3, 34.5, 19.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}NO_3S_2$: 398.0885; found 398.0876.

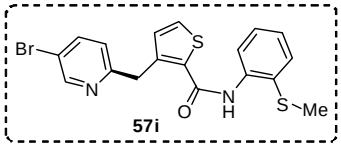


3-(3,5-Dimethylbenzyl)-*N*-(2-(Methylthio)phenyl)thiophene-2-carboxamide (57h): The compound **57h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 54% (25 mg); R_f = 0.53 (EtOAc:Hexanes = 1:4); IR (DCM): 3313, 1666, 1578, 1510, 1430, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (br. s, 1H), 8.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.55 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.38 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.35 (d, 1H, J= 5.1 Hz), 7.12 (td, 1H, J= 7.6 Hz, J_2 = 1.4 Hz), 6.91-6.90 (m, 3H), 6.88 (br. s, 1H), 4.40 (s, 2H), 2.38 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 146.0, 139.9, 138.7, 138.1, 133.4, 131.8, 131.3, 129.1, 128.0, 127.3, 126.7, 125.5, 124.5, 120.7, 35.1, 21.3, 19.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{21}NNaOS_2$: 390.0962; found 390.0959.



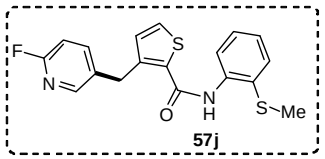
3-((5-Bromopyridin-2-yl)methyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57i): The compound **57i** was obtained after purification by column chromatography on

neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 61% (32 mg); R_f = 0.40 (EtOAc:Hexanes = 1:4); IR (DCM): 1652, 1527, 1486, 1384, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.28 (br. s, 1H), 8.63 (dd, 1H, J_1 = 2.4 Hz, J_2 = 0.4 Hz), 8.07 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.3 Hz), 7.77 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.46 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.39 (d, 1H, J= 5.1 Hz), 7.33 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.30 (s, 1H), 7.18 (td, 1H, J= 7.6 Hz, J= 1.4 Hz), 6.98 (d, 1H, J= 5.0 Hz), 4.51 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 158.2, 150.4, 141.3, 139.7, 137.3, 134.1, 130.8, 130.7, 129.1, 128.1, 127.7, 125.5, 124.6, 123.6, 118.6, 37.1, 17.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}BrN_2OS_2$: 418.9887; found 418.9883.



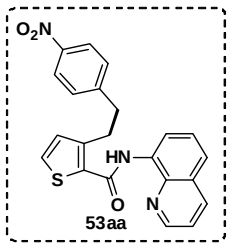
57i

3-((6-Fluoropyridin-3-yl)methyl)-*N*-(2-(methylthio)phenyl)thiophene-2-carboxamide (57j): The compound **57j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a brown colour solid; Yield: 53% (24 mg); R_f = 0.45 (EtOAc:Hexanes = 1:4); mp 146-148 ^oC; IR (KBr): 3306, 1663, 1523, 1483, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (br. s, 1H), 8.41 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 8.17-817 (m, 1H), 7.78 (td, 1H, J = 8.2 Hz, J= 2.5 Hz), 7.56 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.40 (d, 1H, J= 5.1 Hz), 7.39-7.35 (m, 1H), 7.14 (td, 1H, J = 7.6 Hz, J= 1.3 Hz), 6.93 (d, 1H, J= 5.0 Hz), 6.86 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 4.45 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (d, $J_{C\text{-}F}$ = 236.2 Hz), 160.6, 147.2 (d, $J_{C\text{-}F}$ = 14.4 Hz), 145.5, 141.8 (d, $J_{C\text{-}F}$ = 7.6 Hz), 138.4, 133.5 (d, $J_{C\text{-}F}$ = 4.7 Hz), 133.4, 131.4, 130.9, 129.2, 127.5, 125.6, 124.7, 120.5, 109.3 (d, $J_{C\text{-}F}$ = 37.1 Hz), 31.4 (d, $J_{C\text{-}F}$ = 1.1 Hz), 19.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}FN_2OS_2$: 359.0688; found 359.0692.



57j

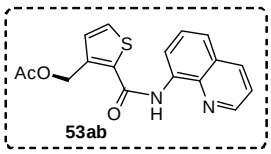
3-(4-Nitrophenethyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide(53aa): Following the general procedure described above, **53aa** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes =25:75) as colourless solid; Yield: 31% (16 mg);mp 185-187 ^oC; IR (KBr):1649, 1527, 1486, 1327, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.38 (br s, 1H), 8.84-8.80 (m, 2H), 8.22 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 8.08 (d, 2H, J= 8.7 Hz), 7.63-7.56 (m, 2H), 7.50 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.41 (d, 1H, J= 5.0 Hz), 7.37 (d, 2H, J= 8.7 Hz), 6.93 (d, 1H, J= 5.0 Hz), 3.51-3.47 (m, 2H), 3.20-3.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 149.3, 148.4, 146.4, 145.5, 138.5,



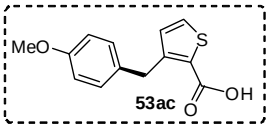
53aa

136.5, 134.5, 132.0, 131.1, 129.5, 128.0, 127.4, 123.5, 121.9, 121.8, 116.5, 36.8, 30.9;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}N_3O_3S$: 404.1069; found 404.1072.

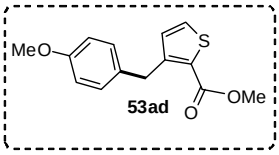
(2-(Quinolin-8-ylcarbamoyl)thiophen-3-yl)methyl acetate(53ab): Following the general procedure described above, **53ab** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) ascolourless liquid; Yield: 46% (19 mg); IR (DCM): 3317, 1741, 1658, 1527, 1486, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.51 (br, s, 1H), 8.86 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.21 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz) 7.63-7.57 (m, 2H), 7.52-7.48 (m, 2H), 7.22 (d, 1H, *J*= 5.1 Hz), 5.58 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 160.3, 148.2, 139.7, 138.7, 136.4, 135.3, 134.5, 130.4, 128.2, 128.0, 127.4, 122.1, 121.8, 117.0, 60.6, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_3S$: 327.0803; found 327.0791.



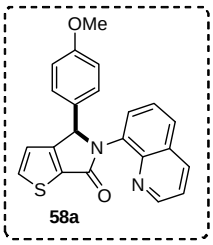
3-(4-Methoxybenzyl)thiophene-2-carboxylic acid(53ac): Following the general procedure, the compound **53ac** was obtained as brown colour viscous liquid (the crude material was almost pure); Yield: 64% (20 mg); IR (DCM): 2922, 1665, 1533, 1427, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.48 (m, 1H), 7.18 (d, 2H, *J*= 8.5 Hz), 6.89-6.85 (m, 3H), 4.37 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.1, 151.3, 132.1, 132.0, 131.4, 129.9, 126.1, 113.9, 55.3, 34.6;HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_3S$: 249.0585; found 249.0585.



Methyl 3-(4-methoxybenzyl)thiophene-2-carboxylate (53ad): The compound **53ad** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid; Yield: 85% (28 mg); R_f = 0.50 (EtOAc:Hexanes = 1:4); IR (DCM): 1709, 1610, 1511, 1413, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, 1H, *J*= 5.1 Hz), 7.18 (d, 2H, *J*= 8.6 Hz), 6.86-6.84 (m, 3H), 4.36 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 158.0, 149.7, 132.3, 131.0, 130.4, 129.8, 126.4, 113.8, 55.2, 51.9, 34.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}O_3S$: 263.0742; found 263.0736.



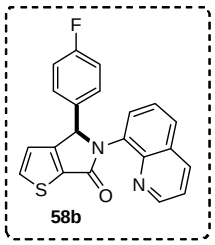
4-(4-Methoxyphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58a): The compound **58a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a brown colour liquid; Yield: 71% (33 mg); R_f = 0.24 (EtOAc:Hexanes = 2:3); IR (DCM): 1692, 1527, 1486, 1384, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz),



58a

7.74-7.72 (m, 1H), 7.70 (d, 1H, *J*= 4.8 Hz), 7.59 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49-7.43 (m, 2H), 6.96-6.93 (m, 4H), 6.68 (d, 2H, *J*= 8.7 Hz), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 159.4, 157.4, 150.0, 144.6, 136.4, 135.4, 134.9, 134.0, 130.3, 129.3, 128.9, 128.7, 127.5, 126.3, 121.3, 121.2, 113.9, 65.8, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_2S$: 373.1011; found 373.1017.

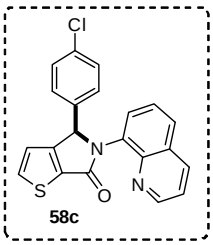
4-(4-Fluorophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58b): The compound **58b** was obtained after purification by column chromatography on neutral alumina



58b

(EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 57% (26 mg); R_f = 0.24 (EtOAc:Hexanes = 2:3); IR (DCM): 3451, 1694, 1508, 1389 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75-7.72 (m, 2H), 7.61 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51-7.44 (m, 2H), 7.04 (s, 1H), 7.03-7.00 (m, 2H), 6.93 (d, 1H, *J*= 4.8 Hz,) 6.86-6.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.5 (d, J_{C-F} = 245.6 Hz), 156.9, 150.0, 144.5, 136.5, 135.7, 135.0, 133.8, 132.6 (d, J_{C-F} = 3.3 Hz), 130.2, 129.4, 129.4 (d, J_{C-F} = 13.5 Hz), 127.6, 126.3, 121.4, 121.1, 115.6 (d, J_{C-F} = 21.6 Hz), 65.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}FN_2OS$: 361.0811; found 361.0819.

4-(4-Chlorophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58c): The

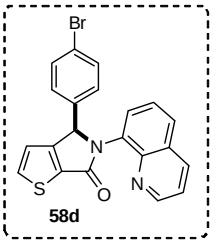


58c

compound **58c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 61% (29 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 3353, 1694, 1490, 1389, 1221 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75-7.73 (m, 2H), 7.64 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51-7.43 (m, 2H), 7.13 (d, 2H, *J*= 8.5 Hz), 7.06 (s, 1H), 7.00 (d, 2H, *J*= 8.5 Hz) 6.93 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 156.7, 150.0, 144.4, 136.5, 135.8, 135.4, 135.0, 134.1, 133.7, 130.1, 129.3, 129.0, 128.9, 127.6, 126.3, 121.4, 121.0, 65.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}ClN_2OS$: 377.0515; found 377.0519.

4-(4-Bromophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58d): The compound **58d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 51% (27 mg); R_f = 0.32 (EtOAc:Hexanes = 2:3); IR (DCM): 3418, 1694, 1500, 1472, 1220 cm^{-1}; ^{1}H NMR (400 MHz,

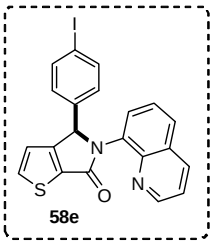
$CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz),



58d

7.75-7.71 (m, 2H), 7.64 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51-7.43 (m, 2H), 7.29 (d, 2H, *J*= 8.4 Hz), 7.06 (s, 1H), 6.94 (d, 2H, *J*= 8.5 Hz), 6.93 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 156.7, 150.0, 144.4, 136.5, 136.0, 135.8, 135.0, 133.7, 131.9, 130.1, 129.3, 127.6, 126.4, 122.3, 121.4, 121.0, 65.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}BrN_2OS$: 421.0010; found 421.0000.

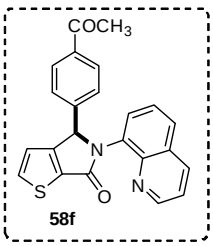
4-(4-Iodophenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58e): The compound **58e** was obtained after purification by column chromatography on neutral alumina



58e

(EtOAc:Hexanes = 90:10) as a brown colour liquid; Yield: 68% (40 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 1692, 1500, 1389, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75-7.71 (m, 2H), 7.65 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 7.52-7.48 (m, 3H), 7.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.04 (s, 1H), 6.92 (d, 1H, *J*= 4.8 Hz) 6.82 (d, 2H, *J*= 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 156.6, 150.0, 144.4, 137.8, 136.7, 136.5, 135.8, 134.9, 133.7, 130.1, 129.5, 129.3, 127.6, 126.4, 121.4, 121.0, 94.1, 65.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}IN_2OS$: 468.9872; found 468.9857.

4-(4-Acetylphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58f): The

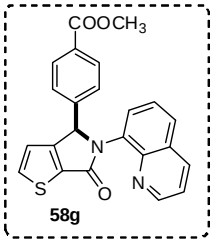


58f

compound **58f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a pale yellow colour liquid; Yield: 58% (28 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 2924, 1683, 1526, 1487, 1387 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.18 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 7.77-7.72 (m, 4H), 7.68 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51-7.44 (m, 2H), 7.19 (d, 2H, *J*= 8.4 Hz), 7.18 (s, 1H), 6.93 (d, 1H, *J*= 4.8 Hz), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 164.6, 156.4, 150.0, 144.3, 142.3, 137.0, 136.5, 136.0, 135.0, 133.7, 130.1, 129.3, 128.8, 127.8, 127.6, 126.3, 121.4, 121.0, 65.7, 26.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_2S$: 385.1011; found 385.1008.

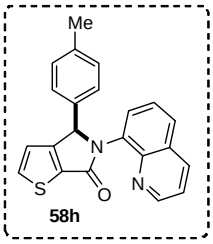
Methyl 4-(6-oxo-5-(quinolin-8-yl)-5,6-dihydro-4*H*-thieno[2,3-*c*]pyrrol-4-yl)benzoate (58g): The compound **58g** was obtained after purification by column chromatography on

neutral alumina (EtOAc:Hexanes = 90:10) as a colourless solid; Yield: 50% (25 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); mp 162-164 ^oC; IR (KBr): 1721, 1698, 1282, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.83 (d, 2H, J= 8.4 Hz), 7.74-7.13 (m, 2H), 7.65 (dd, 1H, J_1 = 6.0 Hz, J_2 = 1.4 Hz), 7.49-7.44 (m, 2H), 7.16 (d, 2H, J= 8.4 Hz), 7.14 (s, 1H), 6.93 (d, 1H, J= 4.8 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 164.6, 156.5, 150.0, 144.4, 142.0, 136.5, 135.9, 135.0, 133.7, 130.1, 130.1, 130.0, 129.3, 127.7, 126.3, 121.4, 121.0, 65.7, 52.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_3S$: 401.0960;found 401.0949.



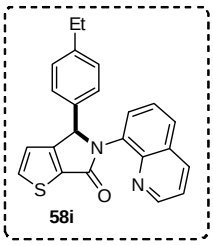
58g

5-(Quinolin-8-yl)-4-(*p*-tolyl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58h): The compound **58h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless solid; Yield: 63% (28 mg); R_f = 0.34 (EtOAc:Hexanes = 2:3); mp 126-128 ^oC; IR (KBr): 2923, 1693, 1526, 1472, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.72 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.69 (d, 1H, J= 4.8 Hz), 7.62 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49-7.42 (m, 2H), 6.99-6.93 (m, 6H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.4, 149.9, 144.6, 138.0, 136.4, 135.4, 134.8, 134.0, 133.8, 130.3, 129.3, 129.3, 127.5, 127.5, 126.3, 121.3, 121.2, 66.1, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2OS$: 357.1062; found 357.1069.



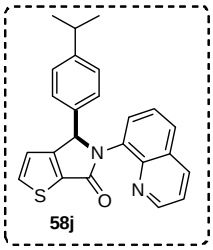
58h

4-(4-Ethylphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58i): The compound **58i** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 65% (30 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 2963, 1693, 1526, 1485, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.5 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.72 (d, 1H, J= 8.2 Hz), 7.69 (d, 1H, J= 4.8 Hz), 7.63 (d, 1H, J= 7.3 Hz), 7.49-7.42 (m, 2H), 7.00-6.93 (m, 6H), 2.53 (q, 2H, J= 7.6 Hz), 1.42 (t, 3H, J= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.5, 149.9, 144.7, 144.2, 136.4, 135.4, 134.8, 134.1, 134.0, 130.4, 129.3, 128.1, 127.5, 127.5, 126.3, 121.3, 121.3, 66.1, 28.4, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS$: 371.1218; found 371.1220.



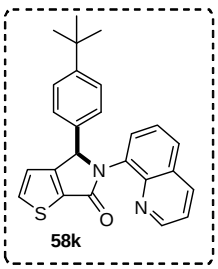
58i

4-(4-Isopropylphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-c]pyrrol-6(*5H*)-one(58j): The compound **58j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 62% (30 mg); R_f = 0.34 (EtOAc:Hexanes = 2:3); IR (DCM): 2959, 1694, 1527, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.72 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.68 (d, 1H, *J*= 4.8 Hz), 7.62 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49-7.41 (m, 2H), 7.03-6.97 (m, 5H), 6.95 (d, 1H, *J*= 4.8 Hz), 2.82-2.75 (m, 1H), 1.15 (d, 3H, *J*= 2.8 Hz), 1.14 (d, 3H, *J*= 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 157.5, 150.0, 148.8, 144.7, 136.4, 135.4, 134.7, 134.1, 130.4, 129.3, 127.5, 127.5, 126.7, 126.3, 121.3, 121.3, 66.1, 33.7, 23.8, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2OS$: 385.1375; found 385.1384.



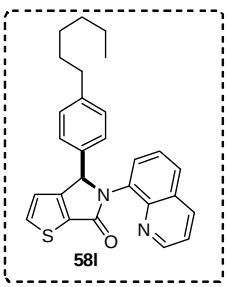
58j

4-(4-(*Tert*-butyl)phenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58k): The compound **58k** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 85:15) as a colourless liquid; Yield: 44% (22 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 1692, 1594, 1385, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.73 (d, 1H, *J*= 7.8 Hz), 7.68 (d, 1H, *J*= 4.8 Hz), 7.64 (d, 1H, *J*= 7.3 Hz), 7.50-7.42 (m, 2H), 7.18 (d, 2H, *J*= 8.3 Hz), 7.01 (s, 1H), 6.99 (d, 2H, *J*= 8.3 Hz), 6.95 (d, 1H, *J*= 4.8 Hz), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 157.5, 151.1, 150.0, 144.7, 136.4, 135.3, 134.1, 133.7, 130.5, 129.3, 127.5, 127.1, 126.3, 125.5, 121.3, 121.3, 66.0, 34.5, 31.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2OS$: 399.1531; found 399.1516.



58k

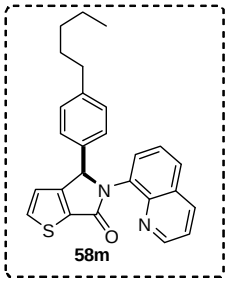
4-(4-Hexylphenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58l): The compound **58l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a colourless liquid; Yield: 71% (38 mg); R_f = 0.32 (EtOAc:Hexanes = 2:3); IR (DCM): 1693, 1594, 1385, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, 1H, *J*= 3.9 Hz), 8.16 (d, 1H, *J*= 8.2 Hz), 7.71 (d, 1H, *J*= 8.2 Hz), 7.69 (d, 1H, *J*= 4.8 Hz), 7.61 (d, 1H, *J*= 7.3 Hz), 7.48-7.41 (m, 2H), 6.98-6.94 (m, 6H), 2.48 (t, 2H, *J*= 7.6 Hz), 1.52-1.46 (m, 2H), 1.30-1.25 (m, 6H), 0.86 (t, 3H, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.4, 150.0, 144.7, 143.1, 136.4, 135.4, 134.8, 134.1,



58l

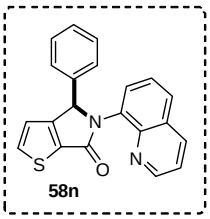
133.9, 130.4, 129.3, 128.6, 127.5, 126.3, 121.3, 66.1, 35.6, 31.6, 31.1, 28.9, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2OS$: 427.1844; found 427.1828.

4-(4-Pentylphenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58m): The compound **58m** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a colourless liquid; Yield: 44% (23 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 3385, 1595, 1385, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (d, 1H, *J*= 4.0 Hz), 8.17 (d, 1H, *J*= 8.2 Hz), 7.72 (d, 1H, *J*= 8.2 Hz), 7.69 (d, 1H, *J*= 4.8 Hz), 7.61 (d, 1H, *J*= 7.4 Hz), 7.49-7.42 (m, 2H), 6.98-6.93 (m, 6H), 2.47 (t, 2H, *J*= 7.7 Hz), 1.53-1.47 (m, 2H), 1.31-1.21 (m, 4H), 0.86 (t, 3H, *J*= 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.4, 150.0, 144.7, 143.1, 136.4, 135.4, 134.8, 134.1, 133.9, 130.4, 129.3, 128.6, 127.5, 126.3, 121.3, 66.1, 35.5, 31.5, 30.9, 22.5, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2OS$: 413.1688; found 413.1673.



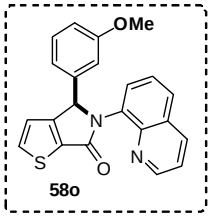
58m

4-Phenyl-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58n): The compound **58n** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 85:15) as a brown colour solid; Yield: 58% (25 mg); mp 218-220 ^oC; R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (KBr): 1694, 1500, 1390, 1351 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.73-7.70 (m, 2H), 7.62 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49-7.43 (m, 2H), 7.18-7.15 (m, 3H), 7.07-7.05 (m, 2H), 7.03 (s, 1H), 6.94 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.2, 150.0, 144.6, 136.8, 136.4, 135.5, 134.9, 134.0, 130.3, 129.3, 128.6, 128.3, 127.6, 127.5, 126.3, 121.3, 121.2, 66.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2OS$: 343.0905; found 343.0891.



58n

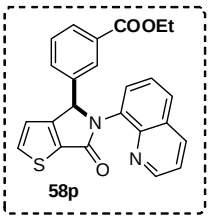
4-(3-Methoxyphenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58o): The compound **58o** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 53% (25 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 1694, 1598, 1472, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.70 (d, 1H, *J*= 4.8 Hz), 7.67 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50-7.42



58o

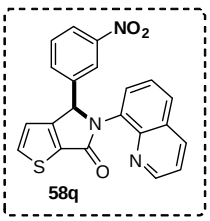
(m, 2H), 7.09 (t, 1H, *J*= 7.9 Hz), 7.00 (s, 1H), 6.95 (d, 1H, *J*= 4.8 Hz), 6.72-6.67 (m, 2H), 6.62 (t, 1H, *J*= 1.8 Hz), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 159.7, 157.2, 150.0, 144.6, 138.4, 136.4, 135.6, 134.7, 134.0, 130.2, 129.7, 129.3, 127.5, 126.3, 121.3, 121.2, 119.9, 113.6, 113.1, 66.2, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_2S$: 373.1011;found 373.1002.

Ethyl 3-(6-oxo-5-(quinolin-8-yl)-5,6-dihydro-4*H*-thieno[2,3-*c*]pyrrol-4-yl)benzoate (58p): The compound **58p** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 54% (28 mg); R_f = 0.32 (EtOAc:Hexanes = 2:3); IR (DCM): 2982, 1701, 1500, 1283 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.85 (d, 1H, *J*= 7.2 Hz), 7.78 (s, 1H), 7.73-7.71 (m, 2H), 7.67 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50-7.43 (m, 2H), 7.31-7.24 (m, 2H), 7.12 (s, 1H), 6.92 (d, 1H, *J*= 4.8 Hz), 4.32 (q, 2H, *J*= 7.2 Hz), 1.34 (t, 3H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 164.7, 156.8, 150.1, 144.5, 137.4, 136.5, 135.9, 134.9, 133.7, 131.8, 131.0, 130.2, 129.5, 129.3, 128.8, 128.8, 127.7, 126.3, 121.4, 121.0, 65.8, 61.1, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3S$: 415.1116; found 415.1110.



58p

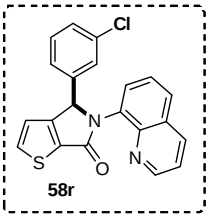
4-(3-Nitrophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58q): The compound **58q** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a brown colour liquid; Yield: 64% (31 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 3453, 1698, 1530, 1438, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.04-7.99 (m, 2H), 7.77-7.72 (m, 3H), 7.52-7.44 (m, 3H), 7.39-7.33 (m, 1H), 7.27 (s, 1H), 6.95 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 155.9, 150.1, 148.3, 144.2, 139.4, 136.6, 136.4, 135.2, 133.6, 133.4, 129.9, 129.8, 129.4, 127.8, 126.4, 123.4, 122.7, 121.6, 120.8, 65.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}N_3O_3S$: 388.0756; found 388.0764.



58q

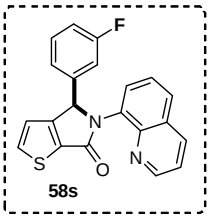
4-(3-Chlorophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58r): The compound **58r** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless solid; Yield: 51% (24 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); mp 180-182 ^{o}C; IR (KBr): 3302, 1695, 1472, 1388 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.76-7.72 (m, 2H), 7.66 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.16-7.08 (m, 3H), 7.04 (s, 1H), 6.96 (dt, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 6.94 (d, 1H, J= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 156.6, 150.0, 144.4, 139.0, 136.5, 135.9, 134.9, 134.5, 133.7, 130.2, 130.0, 129.4, 128.5, 127.7, 127.7, 126.3, 125.8, 121.4, 121.1, 65.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}ClN_2OS$: 377.0515; found 377.0523.



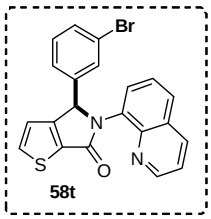
58r

4-(3-Fluorophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58s): The compound **58s** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 55% (25 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 1696, 1500, 1472, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75-7.72 (m, 2H), 7.67 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51-7.44 (m, 2H), 7.16-7.11 (m, 1H), 7.08 (s, 1H), 6.94 (d, 1H, J= 4.8 Hz), 6.89-6.84 (m, 2H), 6.81-6.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 162.8 (d, J_{C-F} = 245.6 Hz), 156.6, 150.0, 144.4, 139.5 (d, J_{C-F} = 6.7 Hz), 136.5, 135.8, 134.9, 133.7, 130.3, 130.2, 129.3, 127.6, 126.3, 123.3 (d, J_{C-F} = 2.8 Hz), 121.4, 121.1, 115.3 (d, J_{C-F} = 21.5 Hz), 114.5 (d, J_{C-F} = 21.8 Hz), 65.6 (d, J_{C-F} = 1.6 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}FN_2OS$: 361.0811; found 361.0812.



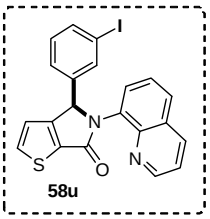
58s

4-(3-Bromophenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58t): The compound **58t** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 51% (27 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 1694, 1527, 1486, 1327 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.72 (d, 1H, J= 4.8 Hz), 7.66 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.8 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.31-7.29 (m, 1H), 7.25 (br. s, 1H), 7.07-7.01 (m, 3H), 6.94 (d, 1H, J= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 156.6, 150.0, 144.3, 139.3, 136.6, 135.9, 134.9, 133.6, 131.5, 130.6, 130.3, 130.2, 129.4, 127.7, 126.4, 126.3, 122.7, 121.4, 121.1, 65.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}BrN_2OS$: 421.0010; found 421.0001.



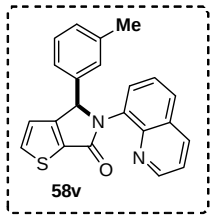
58t

4-(3-Iodophenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58u): The compound **58u** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a brown colour liquid; Yield: 66% (39 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 1692, 1592, 1471, 1388, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.72 (d, 1H, *J*= 4.8 Hz), 7.66 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.3 Hz), 7.53-7.43 (m, 4H), 7.06 (d, 1H, *J*= 7.8 Hz), 6.97 (s, 1H), 6.94 (d, 1H, *J*= 4.8 Hz) 6.91 (t, 1H, *J*= 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 156.6, 150.1, 144.4, 139.3, 137.4, 136.5, 136.5, 135.9, 134.9, 133.7, 130.4, 130.2, 129.4, 127.8, 126.9, 126.3, 121.4, 121.1, 94.4, 65.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{14}IN_2OS$: 468.9872; found 468.9855.



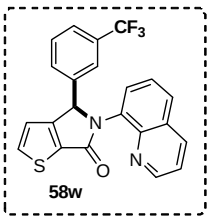
58u

5-(Quinolin-8-yl)-4-(*m*-tolyl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58v): The compound **58v** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 58% (26 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 1694, 1501, 1472, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.70 (d, 1H, *J*= 4.8 Hz), 7.63 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50-7.42 (m, 2H), 7.06 (t, 1H, *J*= 7.4 Hz), 6.98-6.94 (m, 3H), 6.87 (d, 2H, *J*= 8.7 Hz), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 157.4, 150.0, 144.6, 138.4, 136.7, 136.4, 135.5, 134.7, 134.1, 130.3, 129.3, 128.5, 128.1, 127.5, 126.3, 124.7, 121.3, 121.2, 66.3, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2OS$: 357.1062; found 357.1046.



58v

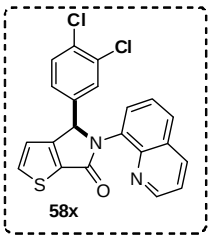
5-(Quinolin-8-yl)-4-(3-(trifluoromethyl)phenyl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58w): The compound **58w** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a brown colour solid; Yield: 64% (33 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); mp 175-177 ^oC; IR (KBr): 1698, 1501, 1390, 1331, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.75-7.73 (m, 2H), 7.65 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50 (d, 1H, *J*= 8.0 Hz), 7.47-7.41 (m, 2H), 7.35 (br. s, 1H), 7.33-7.28 (m, 2H), 7.13 (s, 1H), 6.94 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 156.4, 150.1, 144.4, 138.1, 136.5, 136.1, 135.0, 133.6, 131.0 (q, *JC-F* = 32.2 Hz), 130.9, 129.4, 129.2, 126.4 (q, *JC-F* = 271.5 Hz),



58w

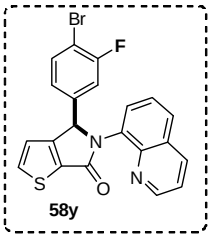
126.3, 125.2 (q, *JC-F* = 3.4 Hz), 124.5 (q, *JC-F* = 3.7 Hz), 121.5, 121.0, 65.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{14}F_3N_2OS$: 411.0779; found 411.0773.

4-(3,4-Dichlorophenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58x): The compound **58x** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a colourless solid; Yield: 54% (28 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); mp 218-220 ^oC; IR (KBr): 1697, 1472, 1391, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.77-74 (m, 2H), 7.68 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.53 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.24 (d, 1H, J= 8.3 Hz), 7.19 (d, 1H, J= 2.1 Hz), 7.07 (s, 1H), 6.95-6.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 156.2, 150.0, 144.3, 137.3, 136.5, 136.1, 135.0, 133.5, 132.8, 132.4, 130.7, 130.0, 129.6, 129.4, 127.8, 126.9, 126.4, 121.5, 120.9, 64.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{13}Cl_2N_2OS$: 411.0126; found 411.0114.



58x

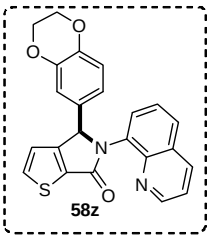
4-(4-Bromo-3-fluorophenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58y): The compound **58y** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a brown colour solid; Yield: 71% (39 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); mp 150-152 ^oC; IR (KBr): 1697, 1472, 1424, 1345, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.77-7.74 (m, 2H), 7.68 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.52 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.7 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.36-7.32 (m, 1H), 7.10 (s, 1H), 6.93 (d, 1H, J= 4.8 Hz), 6.87 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 6.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 159.0 (d, J_{C-F} = 247.0 Hz), 156.1, 150.0, 144.3, 138.8 (d, J_{C-F} = 6.0 Hz), 136.6, 136.1, 135.0, 133.8, 133.4, 130.0, 129.4, 127.7, 126.4, 124.5 (d, J_{C-F} = 3.5 Hz), 121.5, 120.9, 115.7 (d, J_{C-F} = 22.7 Hz), 108.9 (d, J_{C-F} = 21.0 Hz), 65.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{13}BrFN_2OS$: 438.9916;found 438.9921.



58y

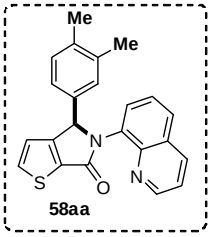
4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-c]pyrrol-6(5*H*)-one (58z): The compound **58z** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 82% (41 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 1693, 1506, 1472, 1285, 1011 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$): δ 8.94 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.72 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.68 (d, 1H, *J*= 4.8 Hz), 7.65 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.7 Hz), 7.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 6.95-6.94 (m, 2H), 6.63 (d, 1H, *J*= 4.8 Hz), 6.56 (d, 1H, *J*= 2.0 Hz), 6.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz), 4.17-4.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 157.4, 150.0, 144.6, 143.5, 143.4, 136.4, 135.5, 134.7, 133.9, 130.4, 129.9, 129.3, 127.5, 126.4, 121.3, 121.2, 120.7, 117.4, 116.4, 65.7, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_3S$: 401.0960;found 401.0952.



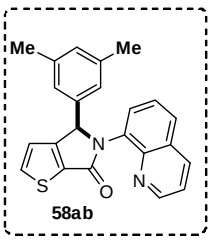
58z

4-(3,4-Dimethylphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58aa): The compound **58aa** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 54% (25 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 3396, 1693, 1504, 1391, 1137, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.72 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.69 (d, 1H, *J*= 4.8 Hz), 7.63 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.49-7.42 (m, 2H), 6.94-6.91 (m, 3H), 6.83 (br. s, 1H), 6.79 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 2.13 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 157.6, 150.0, 144.7, 136.9, 136.7, 136.4, 135.4, 134.6, 134.1, 130.4, 129.8, 129.3, 128.6, 127.5, 126.3, 125.1, 121.3, 121.3, 66.2, 19.7, 19.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS$: 371.1218; found 371.1206.



58aa

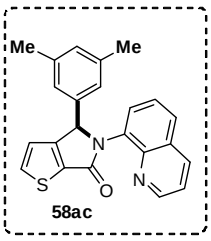
4-(3,5-Dichlorophenyl)-5-(quinolin-8-yl)-4*H*-thieno[2,3-*c*]pyrrol-6(5*H*)-one (58ab): The compound **58ab** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a brown colour solid ; Yield: 52% (27 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); mp 229-231 ^oC; IR (KBr): 1703, 1571, 1472, 1390 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.75 (d, 1H, *J*= 4.8 Hz), 7.70 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.55 (dd, 1H, J_1 = 8.2 Hz, J_2 = 7.6 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.16 (t, 1H, *J*= 1.9 Hz), 7.04 (s, 1H), 7.01 (d, 2H, *J*= 1.9 Hz), 6.95 (d, 1H, *J*= 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 155.9, 150.1, 144.3, 140.6, 136.6, 136.2, 135.2,



58ab

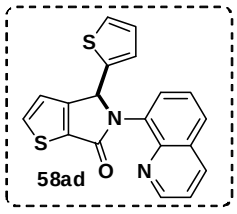
135.0, 133.4, 130.1, 129.4, 128.6, 127.9, 126.4, 126.0, 121.5, 120.9, 65.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{13}Cl_2N_2OS$: 411.0126; found 411.0109.

4-(3,5-Dimethylphenyl)-5-(quinolin-8-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one(58ac): The compound **58ac** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 62% (29 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 3406, 1694, 1597, 1439, 1349, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.8 Hz), 7.73 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.68 (d, 1H, J= 4.8 Hz), 7.63 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50-7.42 (m, 2H), 6.93 (d, 1H, J= 4.8 Hz), 6.88 (s, 1H), 6.79 (br. s, 1H), 6.70 (br. s, 1H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 157.6, 150.0, 144.7, 138.1, 136.7, 136.4, 135.4, 134.6, 134.2, 130.3, 129.9, 129.3, 127.5, 126.3, 125.3, 121.3, 121.3, 66.4, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS$: 371.1218; found 371.1229.



58ac

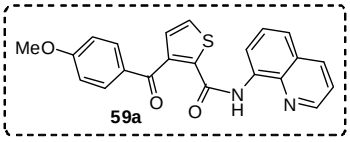
5-(Quinolin-8-yl)-4-(thiophen-2-yl)-*4H*-thieno[2,3-*c*]pyrrol-6(*5H*)-one (58ad): The compound **58ad** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 64% (28 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 1693, 1527, 1486, 1384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.21 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.75 (d, 1H, J= 4.8 Hz), 7.68 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.53 (dd, 1H, J_1 = 8.0 Hz, J_2 = 7.7 Hz), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.42 (s, 1H), 7.12 (dd, 1H, J_1 = 5.1 Hz, J_2 = 0.8 Hz), 7.08 (d, 1H, J= 4.8 Hz), 6.75 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 6.68 (dd, 1H, J_1 = 3.5 Hz, J_2 = 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 156.2, 150.0, 144.6, 139.8, 136.5, 135.6, 135.3, 133.6, 130.4, 129.3, 127.6, 127.1, 126.5, 126.4, 126.1, 121.4, 61.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{13}N_2OS_2$: 349.0469; found 349.0474.



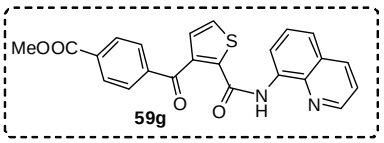
58ad

3-(4-Methoxybenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59a): The compound **59a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 16% (8 mg); R_f = 0.45 (EtOAc:Hexanes = 2:3); IR (DCM): 3306, 1653, 1531, 1261, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.38 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.77 (dd, 1H, J_1 = 6.1 Hz,

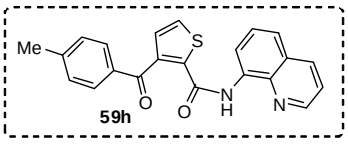
J_2 = 2.9 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.92 (d, 2H, J= 9.0 Hz), 7.57 (d, 1H, J= 5.2 Hz), 7.54-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.25 (d, 1H, J= 5.2 Hz), 6.93 (d, 2H, J= 9.0 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 164.0, 159.7, 148.6, 142.3, 140.2, 139.2, 136.1, 134.6, 132.7, 130.5, 130.4, 128.5, 128.0, 127.1, 122.4, 121.6, 117.9, 113.7, 55.6; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_3S$: 389.0960; found 389.0948.



Methyl 4-(2-(quinolin-8-ylcarbamoyl)thiophene-3-carbonyl)benzoate (59g): The compound **59g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 11% (6 mg); R_f = 0.46 (EtOAc:Hexanes = 2:3); IR (DCM): 1722, 1661, 1531, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.40 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.8 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.10 (d, 2H, J= 8.6 Hz), 7.95 (d, 2H, J= 8.6 Hz), 7.59 (d, 1H, J= 5.2 Hz), 7.58-7.49 (m, 3H), 7.27 (d, 1H, J= 5.2 Hz), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 166.2, 159.3, 148.7, 143.4, 141.1, 139.5, 139.1, 136.3, 134.4, 133.9, 130.5, 129.7, 129.6, 128.7, 128.0, 127.2, 122.5, 121.7, 117.8, 52.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{17}N_2O_4S$: 417.0909; found 417.0906.

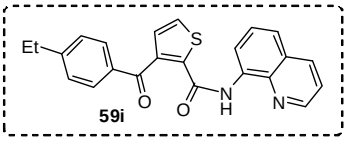


3-(4-Methylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59h): The compound **59h** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 19% (9 mg); R_f = 0.47 (EtOAc:Hexanes = 2:3); IR (DCM): 3302, 1651, 1530, 1485, 1274 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.44 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.77 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.82 (d, 2H, J= 8.2 Hz), 7.57-7.53 (m, 3H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.26-7.24 (m, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 159.7, 148.6, 144.5, 142.8, 140.0, 139.2, 136.1, 135.1, 134.6, 130.6, 130.3, 129.2, 128.4, 128.0, 127.1, 122.4, 121.6, 117.9, 21.7; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_2S$: 373.1011; found 373.1023.

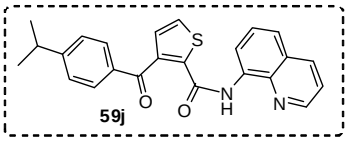


3-(4-Ethylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59i): The compound **59i** was obtained after purification by column chromatography on neutral alumina

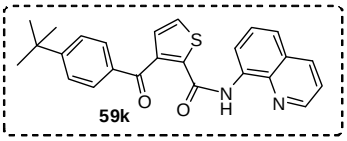
(EtOAc:Hexanes = 50:50) as a colourless liquid; Yield: 6% (3 mg); R_f = 0.46 (EtOAc:Hexanes = 2:3); IR (DCM): 1655, 1528, 1486, 1327, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.45 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.84 (d, 2H, J= 8.3 Hz), 7.56 (d, 1H, J= 5.2 Hz), 7.54-7.46 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.28-7.26 (m, 3H), 2.69 (q, 2H, J= 7.6 Hz), 1.23 (d, 3H, J= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 159.7, 150.7, 148.6, 142.9, 140.0, 139.2, 136.1, 135.3, 134.6, 130.6, 130.4, 128.4, 128.0, 128.0, 127.1, 122.4, 121.6, 117.9, 29.0, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2S$: 387.1167; found 387.1163.



3-(4-Isopropylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59j): The compound **59j** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 6% (3 mg); R_f = 0.46 (EtOAc:Hexanes = 2:3); IR (DCM): 3435, 1650, 1528, 1486, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.44 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.5 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.85 (d, 2H, J= 8.4 Hz), 7.56 (d, 1H, J= 5.2 Hz), 7.54-7.52 (m, 1H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30-7.27 (m, 3H), 2.98-2.91 (m, 1H), 1.24 (d, 6H, J= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 159.7, 155.2, 148.6, 142.9, 140.0, 139.2, 136.1, 135.4, 134.6, 130.6, 130.4, 128.4, 128.0, 127.1, 126.6, 122.4, 121.6, 117.9, 34.3, 23.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_2S$: 401.1324; found 401.1316.

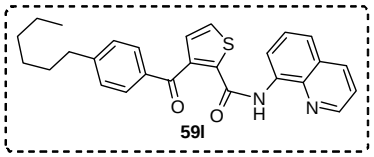


3-(4-(*Tert*-butyl)benzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59k): The compound **59k** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 19% (10 mg); R_f = 0.47 (EtOAc:Hexanes = 2:3); IR (DCM): 1655, 1596, 1384, 1273, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.42 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.75 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.4 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.85 (d, 2H, J= 8.4 Hz), 7.56 (d, 1H, J= 5.1 Hz), 7.54-7.52 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.44 (d, 2H, J= 8.4 Hz), 7.29 (d, 1H, J= 5.1 Hz), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 159.7, 157.4, 148.6, 143.0, 140.0, 139.2, 136.1, 135.0, 134.6, 130.7, 130.1, 128.4, 128.0, 127.1, 125.4, 122.4,

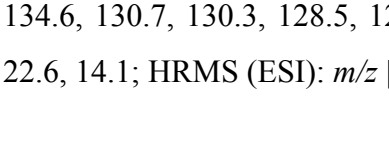


121.6, 117.9, 35.2, 31.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_2S$: 415.1480; found 415.1465.

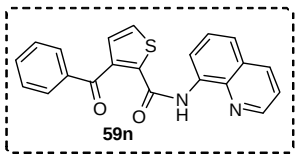
3-(4-Hexylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59l): The compound **59l** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 20% (11 mg); R_f = 0.44 (EtOAc:Hexanes = 2:3); IR (DCM): 1654, 1533, 1422, 1384, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.44 (br. s, 1H), 8.94 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.1 Hz), 8.76 (d, 1H, *J*= 6.2 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.83 (d, 2H, *J*= 8.1 Hz), 7.57 (d, 1H, *J*= 5.2 Hz), 7.54-7.53 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27-7.23 (m, 3H), 2.64 (t, 2H, *J*= 7.6 Hz), 1.64-1.57 (m, 2H), 1.29-1.29 (m, 6H), 0.89 (t, 3H, *J*= 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 159.7, 149.5, 148.6, 142.9, 140.0, 139.2, 136.1, 135.3, 134.6, 130.7, 130.3, 128.5, 128.4, 128.0, 127.1, 122.4, 121.6, 117.9, 36.1, 31.6, 31.0, 28.9, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_2S$: 443.1793; found 443.1777.



3-(4-Pentylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59m): The compound **59m** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 28% (15 mg); R_f = 0.45 (EtOAc:Hexanes = 2:3); IR (DCM): 1658, 1603, 1532, 1119, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.44 (br. s, 1H), 8.93 (d, 1H, *J*= 4.0 Hz), 8.76 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.6 Hz), 8.17 (d, 1H, *J*= 8.3 Hz), 7.84 (d, 2H, *J*= 8.0 Hz), 7.56 (d, 1H, *J*= 5.2 Hz), 7.54-7.52 (m, 2H), 7.47 (dd, 1H, J_1 = 8.5 Hz, J_2 = 4.4 Hz), 7.26-7.23 (m, 3H), 2.64 (t, 2H, *J*= 7.6 Hz), 1.63-1.56 (m, 2H), 1.34-1.28 (m, 4H), 0.89 (t, 3H, *J*= 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 159.7, 149.5, 148.6, 142.9, 140.0, 139.2, 136.1, 135.3, 134.6, 130.6, 130.3, 128.5, 128.4, 128.0, 127.1, 122.4, 121.6, 117.9, 36.0, 31.4, 30.8, 22.5, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_2S$: 429.1637; found 429.1621.

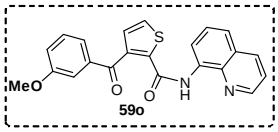


3-Benzoyl-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59n): The compound **59n** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 50:50) as a brown colour solid; Yield: 11% (5 mg); R_f = 0.43 (EtOAc:Hexanes = 2:3); mp 138-140 ^oC; IR (DCM): 3311, 1659, 1532, 1425, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.47 (br. s,



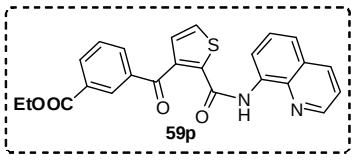
1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.92-7.90 (m, 2H), 7.59-7.43 (m, 7H), 7.27 (d, J= 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 159.6, 148.7, 143.2, 139.7, 139.2, 137.7, 136.2, 134.6, 133.5, 130.7, 130.1, 128.4, 128.0, 127.1, 122.4, 121.6, 117.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}N_2O_2S$: 359.0854; found 359.0852.

3-(3-Methoxybenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59o): The compound **59o** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 27% (13 mg); R_f = 0.44 (EtOAc:Hexanes = 2:3); mp 136-138 ^{o}C; IR (KBr): 3312, 1658, 1532, 1275 cm^{-1}; ^{1}H NMR



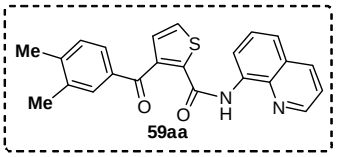
(400 MHz, $CDCl_3$): δ 11.40 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57 (d, 1H, J= 5.2 Hz), 7.55-7.53 (m, 2H), 7.51-7.47 (m, 2H), 7.41 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.34 (t, 1H, J= 8.0 Hz), 7.28 (d, 1H, J= 5.2 Hz), 7.12-7.09 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 159.6, 159.6, 148.6, 143.0, 139.9, 139.1, 139.0, 136.2, 134.5, 130.6, 129.4, 128.4, 128.0, 127.2, 123.1, 122.4, 121.6, 120.2, 117.9, 113.7, 55.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3S$: 389.0960; found 389.0962.

Ethyl 3-(2-(quinolin-8-ylcarbamoyl)thiophene-3-carbonyl)benzoate (59p): The compound **59p** was obtained after purification by column chromatography on neutral alumina



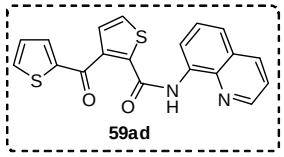
(EtOAc:Hexanes = 50:50) as a colourless solid; Yield: 20% (11 mg); R_f = 0.40 (EtOAc:Hexanes = 2:3); mp 113-115 ^{o}C; IR (KBr): 2985, 1719, 1660, 1532, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.40 (br. s, 1H), 8.94 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.9 Hz), 8.56 (br. s, 1H), 8.23 (d, 1H, J= 7.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.08 (d, 1H, J= 7.8 Hz), 7.60 (d, 1H, J= 5.2 Hz), 7.57-7.53 (m, 3H), 7.49 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.28 (d, 1H, J= 5.2 Hz), 4.38 (q, 2H, J= 7.1 Hz), 1.39 (t, 3H, J= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 165.6, 159.4, 148.7, 143.3, 139.5, 139.1, 138.0, 136.2, 134,4, 134.1, 133.9, 130.9, 130.9, 130.5, 128.7, 128.7, 128.0, 127.2, 122.5, 121.7, 117.8, 61.4, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_4S$: 431.1066; found 431.1058.

3-(3,4-Dimethylbenzoyl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (59aa): The compound **59aa** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 12% (6 mg); R_f = 0.40 (EtOAc:Hexanes = 2:3); IR (DCM): 3317, 1654, 1529, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.45 (br. s, 1H), 8.94 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.71 (br. s, 1H), 7.61 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.56 (d, 1H, J= 5.1 Hz), 7.55-7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26 (d, 1H, J= 5.1 Hz), 7.19 (d, 1H, J= 7.9 Hz), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 159.8, 148.7, 143.3, 142.9, 140.1, 139.2, 136.9, 136.1, 135.5, 134.6, 131.1, 130.7, 129.5, 128.3, 128.1, 128.0, 127.1, 122.4, 121.6, 117.9, 20.1, 19.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2S$: 387.1167; found 387.1152.



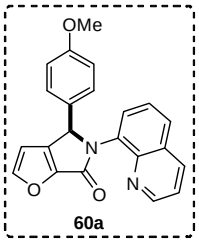
59aa

***N*-(Quinolin-8-yl)-3-(thiophene-2-carbonyl)thiophene-2-carboxamide (59ad):** The compound **59ad** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 17% (8 mg); R_f = 0.40 (EtOAc:Hexanes = 2:3); IR (DCM): 3310, 1643, 1530, 1484, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.37 (br. s, 1H), 8.93 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.78 (dd, 1H, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.74 (dd, 1H, J_1 = 4.9 Hz, J_2 = 1.1 Hz), 7.65 (dd, 1H, J_1 = 3.8 Hz, J_2 = 1.1 Hz), 7.59 (d, 1H, J= 5.2 Hz), 7.57-7.52 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.42 (d, 1H, J= 5.2 Hz), 7.14 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.5, 159.5, 148.7, 144.3, 142.7, 139.2, 139.1, 136.1, 135.8, 135.6, 134.6, 130.1, 128.8, 128.3, 128.0, 127.1, 122.5, 121.7, 117.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{13}N_2O_2S_2$: 365.0418; found 365.0430.



59ad

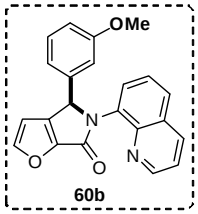
4-(4-Methoxyphenyl)-5-(quinolin-8-yl)-4*H*-furo[2,3-*c*]pyrrol-6(5*H*)-one (60a): The compound **60a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 33% (15 mg); R_f = 0.35 (EtOAc:Hexanes = 2:3); IR (DCM): 1595, 1385, 1258, 1093, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.18 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.74-7.71 (m, 2H), 7.51 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.47-7.43 (m, 2H), 6.93 (d, 2H, J= 8.7 Hz), 6.83 (s, 1H), 6.68 (d, 2H, J= 8.7 Hz), 6.50 (d, 1H, J= 1.7 Hz), 3.71 (s, 3H); ^{13}C NMR (100 MHz,



60a

$CDCl_3$): δ 159.5, 150.2, 150.2, 150.0, 144.7, 141.4, 136.5, 133.8, 130.4, 129.3, 129.0, 127.8, 127.6, 126.3, 121.3, 113.9, 107.4, 62.3, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3$: 357.1239; found 357.1227.

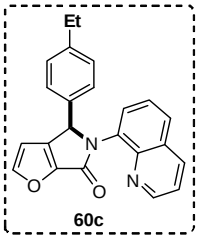
4-(3-Methoxyphenyl)-5-(quinolin-8-yl)-4*H*-furo[2,3-*c*]pyrrol-6(5*H*)-one (60b): The compound **60b** was obtained after purification by column chromatography on neutral alumina



60b

(EtOAc:Hexanes = 80:20) as a colourless liquid; Yield: 33% (15 mg); R_f = 0.34 (EtOAc:Hexanes = 2:3); IR (DCM): 1702, 1597, 1471, 1386, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.74-7.72 (m, 2H), 7.58 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.8 Hz), 7.48 (d, 1H, *J*= 7.9 Hz), 7.45 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.6 Hz), 7.09 (t, 1H, *J*= 7.9 Hz), 6.87 (s, 1H), 6.71 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.1 Hz), 6.65 (d, 1H, *J*= 7.6 Hz), 6.59 (t, 1H, *J*= 1.9 Hz), 6.51 (d, 1H, *J*= 1.7 Hz), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 159.3, 150.3, 150.1, 150.0, 144.6, 141.4, 137.6, 136.5, 133.8, 130.3, 129.6, 129.3, 127.6, 126.3, 121.4, 120.0, 113.9, 113.0, 107.4, 62.7, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3$: 357.1239; found 357.1226.

4-(4-Ethylphenyl)-5-(quinolin-8-yl)-4*H*-furo[2,3-*c*]pyrrol-6(5*H*)-one (60c): The

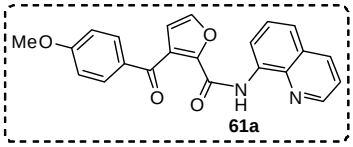


60c

compound **60c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless solid; Yield: 56% (25 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); mp 186-188 ^oC; IR (KBr): 3301, 1711, 1648, 1529, 1388 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73-7.71 (m, 2H), 7.53 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 7.47-7.43 (m, 2H), 6.99 (d, 2H, *J*= 8.2 Hz), 6.94 (d, 2H, *J*= 8.2 Hz), 6.87 (s, 1H), 6.50 (d, 1H, *J*= 1.8 Hz), 2.54 (q, 2H, *J*= 7.6 Hz), 1.15 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 150.2, 150.1, 150.0, 144.7, 144.3, 141.5, 136.4, 133.9, 133.2, 130.4, 129.3, 128.1, 127.6, 127.6, 126.3, 121.3, 107.4, 62.6, 28.4, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2$: 355.1447; found 355.1443.

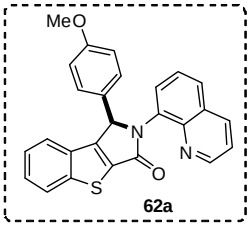
3-(4-Methoxybenzoyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (61a): The compound **61a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid; Yield: 23% (11 mg); R_f = 0.45 (EtOAc:Hexanes = 2:3); IR (DCM): 1597, 1482, 1385, 1215, 1094 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ 11.23 (br. s, 1H), 8.95 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.81 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 8.19 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.98 (d, 2H, *J*= 8.8 Hz), 7.71 (d, 1H, *J*= 1.6 Hz), 7.57-7.50 (m, 3H), 6.97 (d, 2H, *J* = 8.8 Hz), 6.75 (d, 1H, *J*= 1.6 Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 164.1, 155.5, 12+48.6, 146.0, 143.7, 138.9, 136.3, 134.1, 132.3, 130.1, 128.5, 128.0, 127.3, 122.3, 121.7, 117.5, 113.9, 113.6, 55.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_4$: 373.1188; found 373.1175.



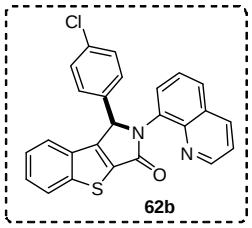
61a

1-(4-Methoxyphenyl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62a): The compound **62a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 85:15) as a colourless liquid; Yield: 53% (28 mg); R_f = 0.30 (EtOAc:Hexanes = 2:3); IR (DCM): 3452, 1694, 1512, 1472, 1388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.98 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.9 Hz), 7.63 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50 (d, 1H, *J*= 7.6 Hz), 7.48-7.41 (m, 3H), 7.32 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 7.18 (s, 1H), 7.02 (d, 2H, *J*= 8.7 Hz), 6.69 (d, 2H, *J*= 8.7 Hz), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 159.5, 151.8, 150.0, 146.6, 144.6, 136.4, 135.4, 133.8, 132.6, 130.3, 129.3, 129.1, 127.9, 127.6, 126.4, 126.4, 125.0, 124.3, 122.8, 121.4, 114.1, 65.9, 55.1; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{26}H_{19}N_2O_2S$: 423.1167; found 423.1175.



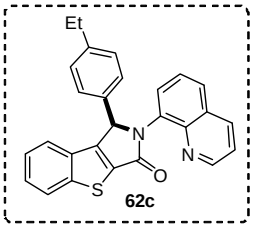
62a

1-(4-Chlorophenyl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62b): The compound **62b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a colourless liquid; Yield: 43% (23 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 3406, 1698, 1529, 1472, 1388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.20 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.7 Hz), 8.00 (d, 1H, *J*= 8.2 Hz), 7.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.66 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.52 (d, 1H, *J*= 8.0 Hz), 7.49-7.42 (m, 3H), 7.34 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 7.27 (s, 1H), 7.15 (d, 2H, *J*= 8.5 Hz), 7.07 (d, 2H, *J*= 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 151.1, 150.0, 146.6, 144.4, 136.5, 135.6, 134.7, 134.3, 133.4, 132.3, 130.1, 129.3, 129.3, 129.1, 127.7, 126.6, 126.4, 125.1, 124.4, 122.6, 121.5, 65.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{16}ClN_2OS$: 427.0672; found 427.0676.



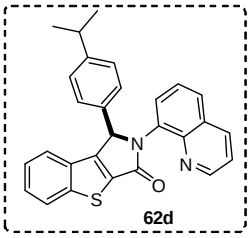
62b

1-(4-Ethylphenyl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62c): The compound **62c** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as colourless liquid; Yield: 44% (23 mg); R_f = 0.32 (EtOAc:Hexanes = 2:3); IR (DCM): 1698, 1501, 1389, 1346, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.97 (d, 1H, *J*= 8.2 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.65 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.52-7.41 (m, 4H), 7.32 (td, 1H, J_1 = 7.4 Hz, J_2 = 1.0 Hz), 7.21 (s, 1H), 7.05 (d, 2H, *J*= 8.2 Hz), 7.00 (d, 2H, *J*= 8.2 Hz), 2.53 (q, 2H, *J*= 7.6 Hz), 1.14 (t, 3H, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 151.9, 150.0, 146.6, 144.4, 136.4, 135.3, 133.8, 133.1, 132.6, 130.4, 129.3, 128.2, 127.7, 127.6, 126.4, 126.4, 125.0, 124.3, 122.8, 121.4, 66.3, 28.4, 15.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2OS$: 421.1375; found 421.1371.



62c

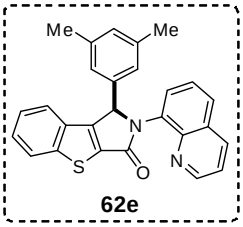
1-(4-Isopropylphenyl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62d): The compound **62d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 90:10) as a colourless liquid; Yield: 44% (24 mg); R_f = 0.33 (EtOAc:Hexanes = 2:3); IR (DCM): 1698, 1501, 1389, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.98 (d, 1H, *J*= 8.2 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.66 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.52-7.41 (m, 4H), 7.33 (td, 1H, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.21 (s, 1H), 7.06 (d, 2H, *J*= 8.3 Hz), 7.02 (d, 2H, *J*= 8.3 Hz), 2.82-2.75 (m, 1H), 1.15 (d, 3H, *J*= 7.0 Hz), 1.14 (d, 3H, *J*= 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 151.9, 150.0, 149.0, 146.6, 144.7, 136.4, 135.3, 133.8, 133.2, 132.6, 130.4, 129.3, 127.7, 127.6, 126.8, 126.4, 126.3, 125.0, 124.2, 122.9, 121.4, 66.3, 33.7, 23.8, 23.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_2OS$: 435.1531; found 435.1534.



62d

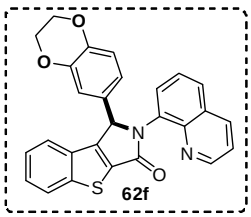
1-(3,5-Dimethylphenyl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62e): The compound **62e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 85:15) as a pale green colour solid; Yield: 51% (27 mg); R_f = 0.32 (EtOAc:Hexanes = 2:3); mp 249-251 ^oC; IR (KBr): 3436, 1646, 1527, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3

Hz, J_2 = 1.7 Hz), 7.98 (d, 1H, J= 8.2 Hz), 7.75 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.64 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.50-7.41 (m, 4H), 7.33 (td, 1H, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.07 (s, 1H), 6.80 (br. s, 1H), 6.77 (br.s s, 2H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 151.9, 150.0, 146.6, 144.7, 138.2, 136.4, 135.8, 135.2, 133.9, 132.6, 130.4, 130.2, 129.3, 127.7, 126.4, 126.3, 125.5, 125.0, 124.2, 122.8, 121.4, 66.6, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2OS$: 421.1375; found 421.1387.



62e

1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(quinolin-8-yl)-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3(2*H*)-one (62f): The compound **62f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 80:20) as a colourless liquid; Yield: 37% (21 mg); R_f = 0.31 (EtOAc:Hexanes = 2:3); IR (DCM): 1694, 1506, 1390, 1285 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.97 (d, 1H, J= 8.2 Hz), 7.76 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.68 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.54-7.50 (m, 2H), 7.47-7.42 (m, 2H), 7.34 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.0 Hz), 7.15 (s, 1H), 6.66-6.60 (m, 3H), 4.19-4.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 151.7, 150.0, 146.6, 144.6, 143.6, 143.6, 136.5, 135.3, 133.7, 132.6, 130.3, 129.3, 1291.1, 127.6, 126.5, 126.4, 125.0, 124.3, 122.9, 121.4, 121.0, 117.5, 116.6, 65.8, 64.1, 64.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{19}N_2O_3S$: 451.1116; found 451.1121.



62f

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(1) For selected articles on BDG-directed C-H functionalization, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2005**, 127, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(2) For selected articles, see: (a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

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