Studies on Stereoselective Synthesis of Functionalized Aliphatic Chains Containing Stereogenic Centers through the Pd(II)-Catalyzed C-H Activation

A Thesis

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By

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Dedicated to

MY BELOVED PARENTS AND BROTHERS

GOD IS GREAT AND LOVE IS GOD

Declaration

I hereby declare that the matter embodied in this thesis "*Studies on Stereoselective Synthesis of Functionalized Aliphatic Chains Containing Stereogenic Centers 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 have 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 judgement is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.

Gopalakrishnan B

Date:

Place:

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

Dr. S. Arulananda Babu

Associate Professor
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Date:

Place:

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List of Publications from thesis work

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

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

- **Gopalakrishnan, B.**; Sruthi, M.; Parella, R.; Babu, S. A.* *J. Org. Chem.* **2016**, *81*, 8988.

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

- **Gopalakrishnan, B.**; Babu, S. A.* Bidentate directing group-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides: construction of functionalized 2-arylpropionamides (unpublished work).

List of Publication as co-author

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

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

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

  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.

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

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

- Sruthi, M.; **Gopalakrishnan, B.**; Babu, S. A. * *Tetrahedron* **2016**, *72*, 5853.

  Title: Multicomponent reaction comprising one-pot installation of bidentate directing group and Pd(II)-catalyzed direct β-arylation of $C(sp^3)$-H bond of aliphatic and alicyclic carboxamides.

- Naveen; Rajkumar, V.; Babu, S. A.;* **Gopalakrishnan, B.** *J. Org. Chem.* **2016**, *81*, 12197.

  Title: Pd(II)-Catalyzed bidentate directing group-aided chemoselective acetoxylation of remote ε-$C(sp^2)$−H Bonds in heteroaryl−aryl-based biaryl systems.

- Akshey, S.; **Gopalakrishnan, B.**; Babu, S. A.*

  Title: $Pd(OAc)_2$ catalysed Heck coupling of morpholine derived acrylamides and cinnamides (unpublished work).

Conferences

- Participated in the *National Seminar on Crystalography 43A* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30 March, 2014).
- Poster presentation entitled "$Pd(OAc)_2$/AgOAc-Catalytic System-Based Construction of Aliphatic Carboxamides Possessing Vicinal Stereocenters" **Gopalakrishnan, B.**; Babu, S. A.;* Padmavathi, R. at the *11^{th} J-NOST conference* held at NIISER Bhubaneswar, Orissa, India (December 14-17, 2015).
- Oral Presentation entitled "Pd(II)-Catalyzed sp^3 C-H Arylation Followed by Ring-Opening of Cyclopropanecarboxamides" **Gopalakrishnan, B.**; Sruthi, M.; Parella, R.; Babu, S. A. * at Inter-IISER chemistry meet-2017 held at IISER Bhopal, Bhopal, India (January 20-22, 2017).

Contents

Preamble

Organic chemistry is a vibrant scientific discipline which deals with reactions/transformations among chemicals to achieve target molecules such as natural products, medicinally and synthetically useful compounds.[1-6] To attain the best transformations, chemists have searched for processes which will lead to products with high yield and selectivity. Accordingly, a wide range of disciplines comprising rearrangements, pericyclic/concerted, photochemical/thermal metal-catalyzed, organocatalyzed, organometallic reagents-based reactions etc have been discovered.

Among the available vast transformations, the transition-metal catalyzed transformations have received significant attention with regard to the construction of C-C bond formation.[1-7] Along this line, the transition metal-catalyzed C(sp^3)-H and C(sp^2)-H functionalization is emerging as one of the important synthetic transformations and efficient method for the construction of C–C and C–X bonds (X = C, N, O, P, etc.).

This thesis work aimed to obtain functionalized aliphatic chains containing stereogenic centers through the Pd-catalyzed directing group-aided diastereoselective C(sp^3)-H functionalization/arylation strategy.

Accordingly, this thesis entitled "*Studies on Stereoselective Synthesis of Functionalized Aliphatic Chains Containing Stereogenic Centers 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 the references pertaining to the chapters have been included at the end of the chapters.

Chapter 1: Introduction to the transition metal-catalyzed C-H functionalization, this chapter provides a brief perspective on the directing group assisted C-H functionalization. In particular, the existing developments on the bidentate ligand directed C-H activation/functionalization have been shown with representative literature works.

Chapter 2: Bidentate directing group 8-aminoquinoline-aided Pd(II)-catalyzed diastereoselective β-arylation of the prochiral secondary sp^3 C-H bonds of 2-phenylbutanamides and related aliphatic carboxamides.

Chapter 3: Diastereoselective Pd(II)-Catalyzed sp^3 C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamides: Construction of *anti* β-Acyloxy Carboxamide Derivatives.

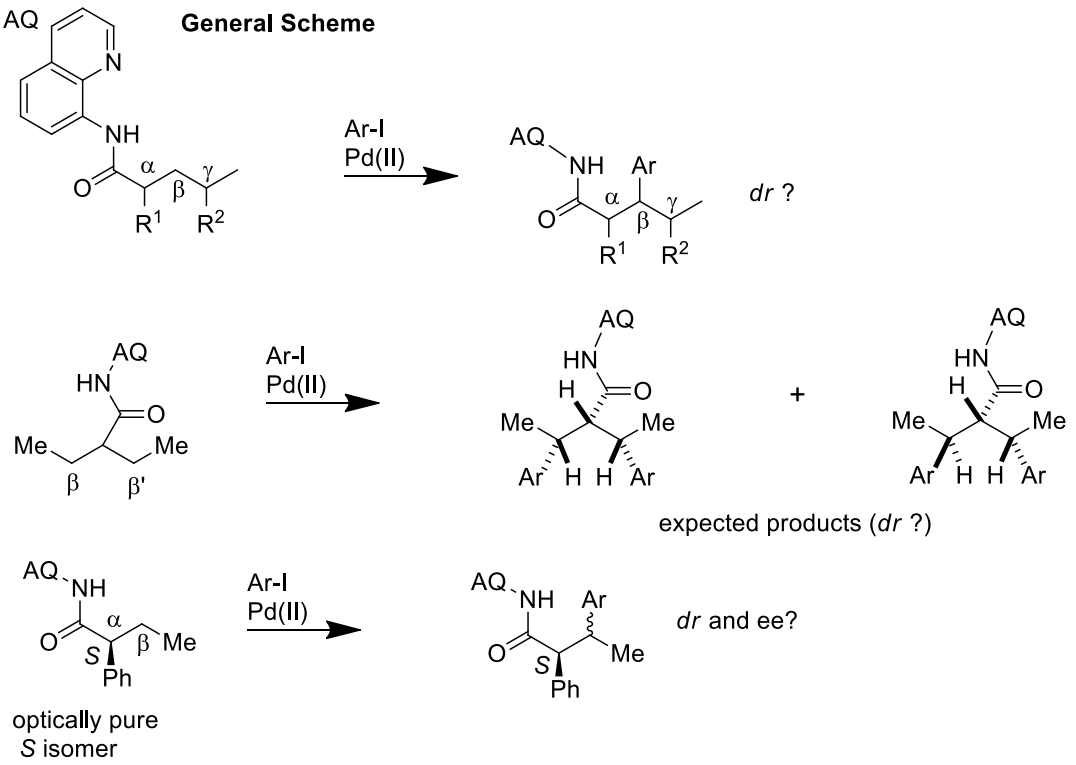
Chapter 4: Bidentate directing group-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides: construction of functionalized 2-arylpropionamides.

Chapter 5: Desymmetrization of symmetrical dicarboxylic acid systems via bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds: construction of functionalized dicarboxylic acid derivatives.

Objectives of this thesis work.

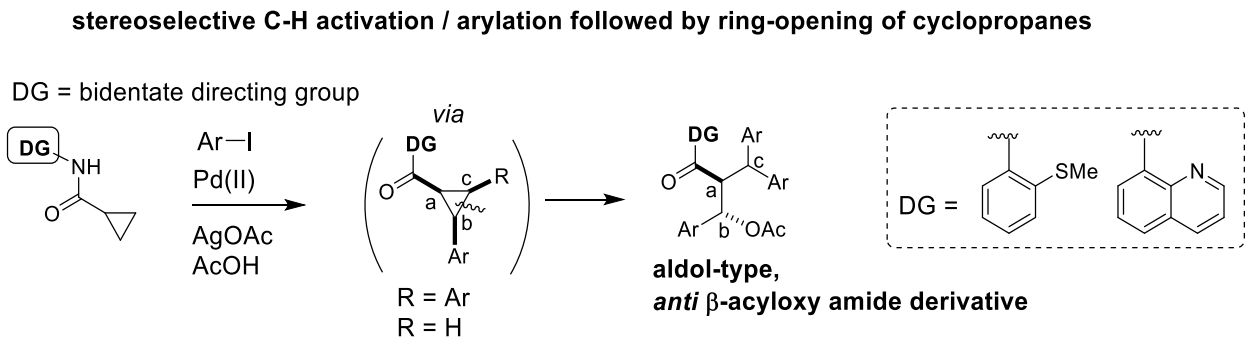
The main objectives of this thesis work are given below.

1. In recent years the transition metal-catalyzed directing group-aided β-C-H activation/functionalization of carboxamides has received significant attention. A part of this thesis work envisages to investigate the bidentate directing group 8-aminoquinoline-directed $Pd(OAc)_2$-catalyzed diastereoselective β-C-H arylation of aliphatic carboxamides having substituents at the α- or γ-positions and the construction of functionalized aliphatic carboxamides possessing two vicinal stereocenters.

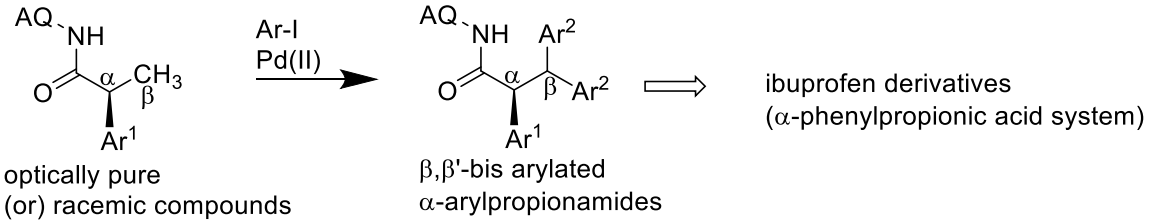


2. Inspired by the transition metal-catalyzed ring opening of cyclopropanes including the C-H/C-C bond activation strategy, a part of this thesis work envisioned a one-pot method comprising Pd(II)-catalyzed, bidentate directing group-directed β-C-H arylation followed by ring opening of cyclopropanecarboxamide derivatives. Accordingly, the results from the investigations including

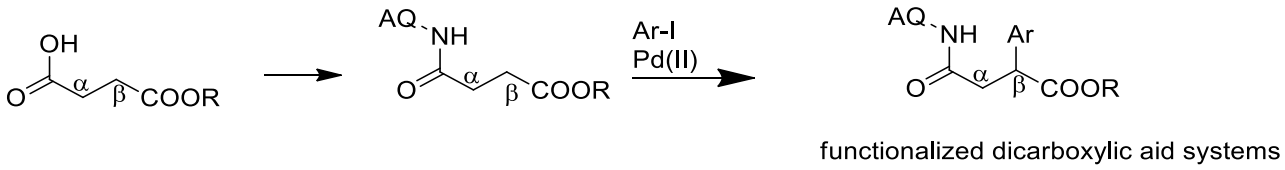
the formation of the open-chain carboxamide derivatives from the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides are discussed.



3. Given the importance of ibuprofen derivatives (α-phenylpropionic acid system) in medicinal chemistry research area, a part of this thesis work envisages to synthesize a variety of β,β'-bis arylated α-arylpropionamides via the bidentate directing group-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides.



4. To elaborate the utility of the directing group-aided β-C-H activation/functionalization tool, a part of this thesis envisages to investigate the desymmetrization of symmetrical dicarboxylic acid systems via the Pd(II)-catalyzed bidentate directing group-aided β-C-H arylation of methylene sp^3 C-H bonds of symmetrical dicarboxylic acid systems.



functionalized dicarboxylic aid systems

Chapter 1: General introduction

The traditional cross coupling methods have largely administrated the research area pertaining to the C-C bond formation. In recent years, the construction of C-C bonds via the direct functionalization/activation of C-H bonds of organic molecules considered as an effective method (Figure 1).[8-25]

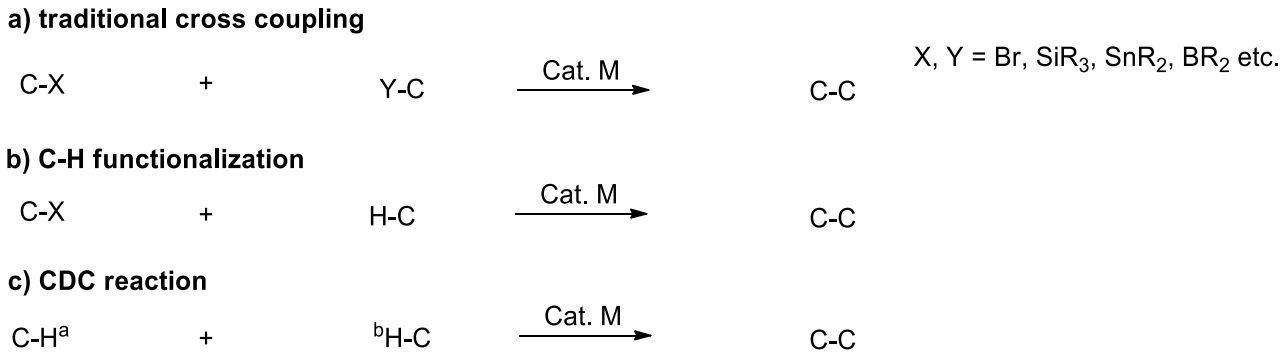


Figure 1: Various cross coupling methods leading to C-C bond construction.

In general, the functionalization/activation of C-H bonds of organic molecules has been carried out using different approaches. Approach (a) is comprised of the direct functionalization/activation of C-H bonds without using any directing group and this approach involves the direct insertion of an electrophilic metal in to a C-H bond. However, this approach is non-regioselective as a large number of C-H bonds in the molecule get equal opportunity for C-H activation. Notably, the non-directed C-H functionalization of the C-H bond nearer to heteroatom in electron-rich heterocycles has been thoroughly investigated and that can be predictably and regioselectively arylated.[11]

Approach (b) is comprised of the chelation-assisted functionalization/activation of C-H bonds using suitable directing group. This approach operates through the coordination of the heteroatom present in the directing group to the metal catalyst and thereby selectively activates

the C-H bond in the proximity of the directing group by leaving all the other C-H bonds that are not in the proximity of the directing group. For example, Sanford reported the mechanistic details for the chelation-assisted functionalization/activation of C-H bonds comprising the C-H acetoxylation of 2-phenylpyridine moieties (Figure 2).[8i-j]

Approach (c) is comprised of the C-H coupling process in the absence of functionalized coupling partners by a method known as cross dehydrogenative coupling (CDC).[12-14] CDC reactions function well in the presence of variety of metal catalyst such as Cu, Fe, and Pd which serve to activate the C-H bonds.

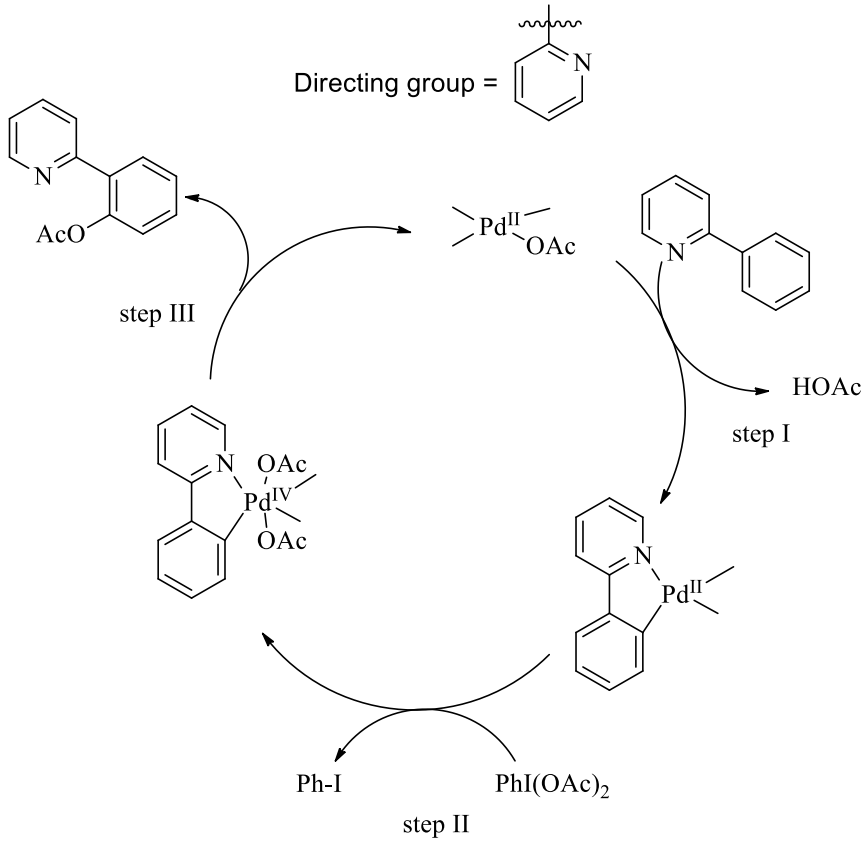
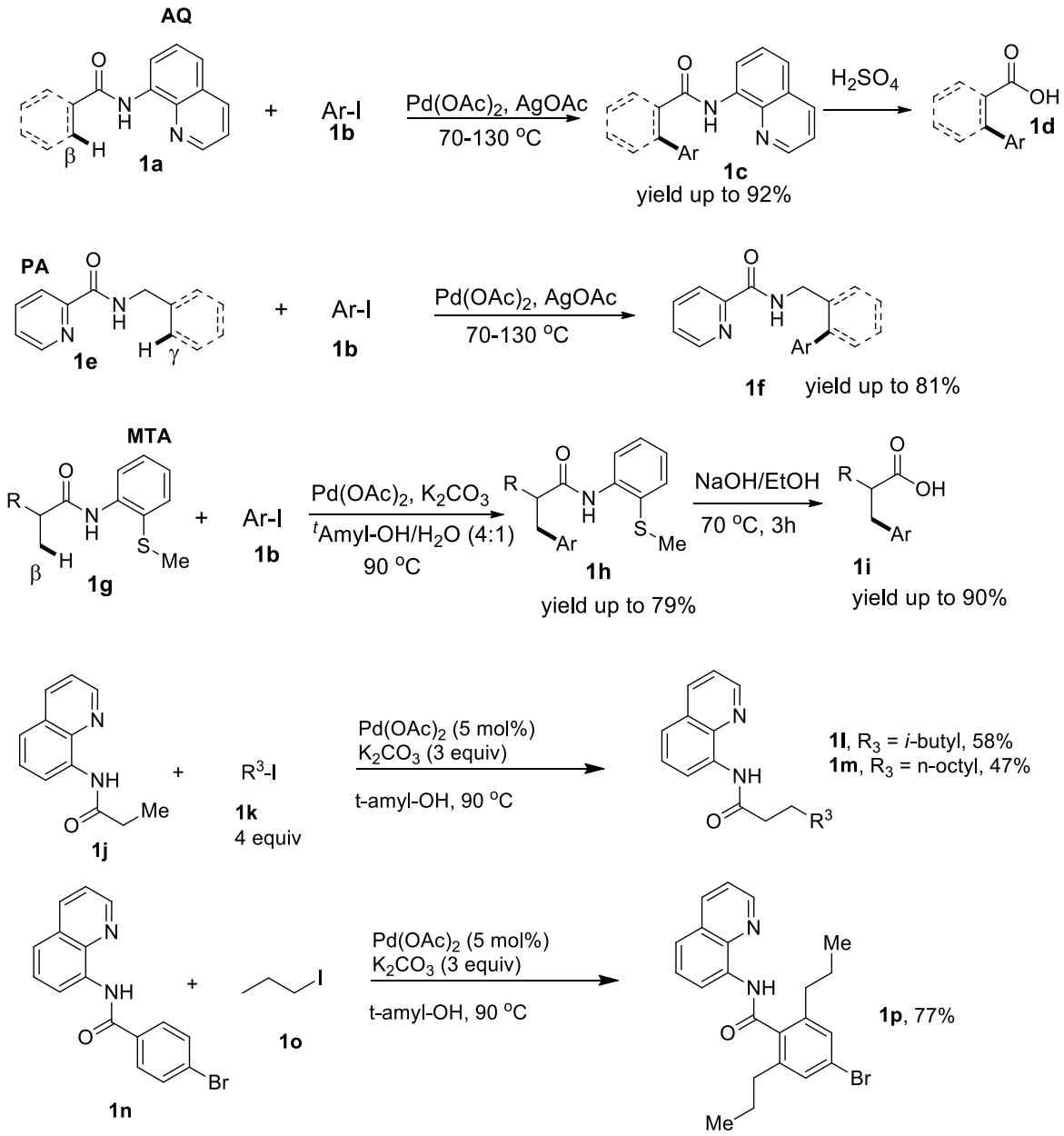


Figure 2: A general schematic diagram for directing group/chelation-aided C-H functionalization. Step I: Metal inserts into C-H bond (oxidative addition), AcOH is released. Step II: Oxidant oxidizes Pd(II) to Pd(IV), Ph-I is released. Step III: C-O bond formation by reductive elimination, Pd(IV) is reduced to Pd(II).

The transition metals catalysts used in the catalytic cycle comprising chelation or non-chelation-based C-H activation strategy are usually the precious metals Pd, Rh, Ru, Pt and reports on usage of inexpensive metals such as Fe, Co and Ni are also known for the C-H alkylation and arylation reactions. Particularly, the versatile Pd(II)/Pd(IV) catalytic cycle, generated by Pd organometallic complex in situ, has been applied to functionalize the sp^2 and sp^3 C-H bonds of vast number of molecules using a directing group or without using any directing group.[8-25]

Functionalization of sp^3 C-H bond of organic compounds. Representative literature works dealing with the directing group (chelation)-assisted C-H bond activation/Functionalization of carboxamides

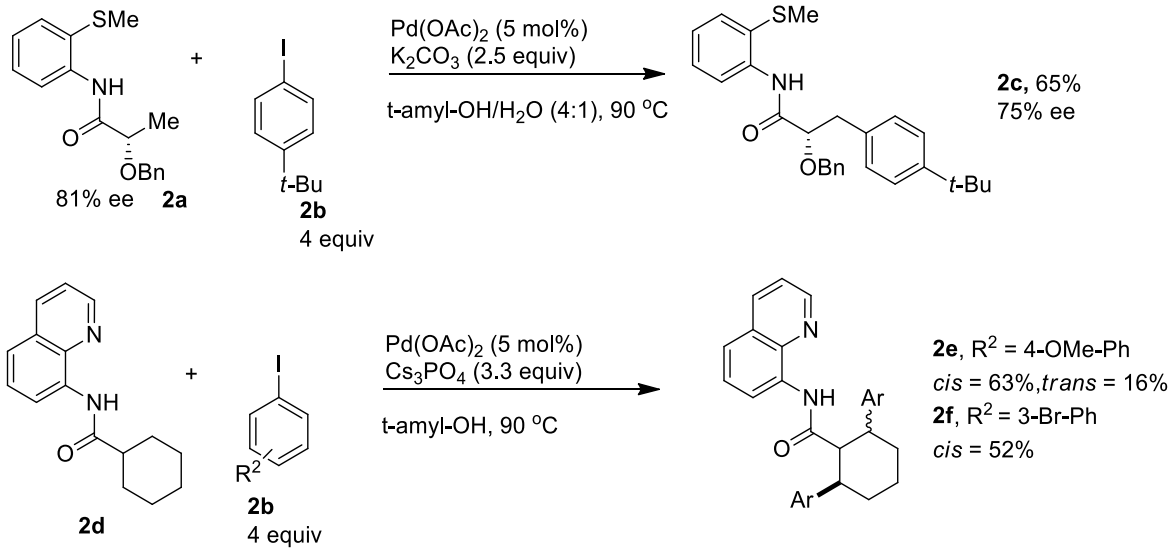
A survey of the literature[8-25] revealed that the transition metal-catalyzed C–H activation/functionalization of sp^2 C–H bonds of a wide range of arenes, heteroarenes and olefins etc have been well explored. On the other hand, until the paper published by Daugulis in 2005, the transition metal-catalyzed C–H activation/functionalization of sp^3 C–H bonds of alkyl chains was relatively less explored. Accordingly, Daugulis reported the sp^3 C–H arylation of aliphatic carboxamides using bidentate directing groups, 8-aminoquinoline (AQ), picolinamides (PA) and 2-methylthioaniline (MTA). After the seminal report by Daugulis, other research groups have reported the sp^3 C–H activation/functionalization of various aliphatic chains or cyclic. The Pd(II)-catalyzed 8-aminoquinoline (8-AQ)-aided arylation of β-C-H bond of carboxamides **1a** with aryl iodides **1b** gave the β-C-H arylated carboxamide **1c** (Scheme 1). The Pd(II)-catalyzed picolinamide (PA)-directed arylation of γ-C-H bond of carboxamides **1e** with aryl iodides **1b** gave the γ-C-H arylated carboxamides **1f** (Scheme 1). The arylation reaction of 2-methylthioaniline-aided arylation of β-C-H bond of carboxamides **1g** with aryl iodides **1b** gave the β-C-H arylated carboxamides **1h** (Scheme 1). Notably, the directing groups were readily removed after the C-H arylation under the standard amide hydrolysis reaction conditions (Scheme 1). Further, the alkylations of sp^2 and sp^3 C-H bonds of carboxamides **1j,n** were also achieved using the Pd(II)-catalyzed 8-aminoquinoline (8-AQ)-directed C-H activation strategy (Scheme 1).



Scheme 1. Pd(II)-catalyzed bidentate directing group-directed C-H arylation of **1a**, **1e**, **1g** and **1j,n**.

The preparation of functionalized aliphatic carboxamides containing stereogenic centers were also explored by various research groups. Accordingly, enantio- and diastereoselective sp^3 C–H arylation of aliphatic carboxamides were achieved using the Pd(II)-catalyzed 8-aminoquinoline (8-AQ)-directed C-H activation strategy.

The Pd(II)-catalyzed, MTA-directed sp^3 C-H arylation of optically active carboxamide **2a** (81% ee) afforded the arylated product **2c** (75% ee) (Scheme 2). The diastereoselective sp^3 C–H arylation of cyclic carboxamide **2d** was achieved using the Pd(II)-catalyzed 8-aminoquinoline (8-AQ)-directed C-H activation strategy (Scheme 2).

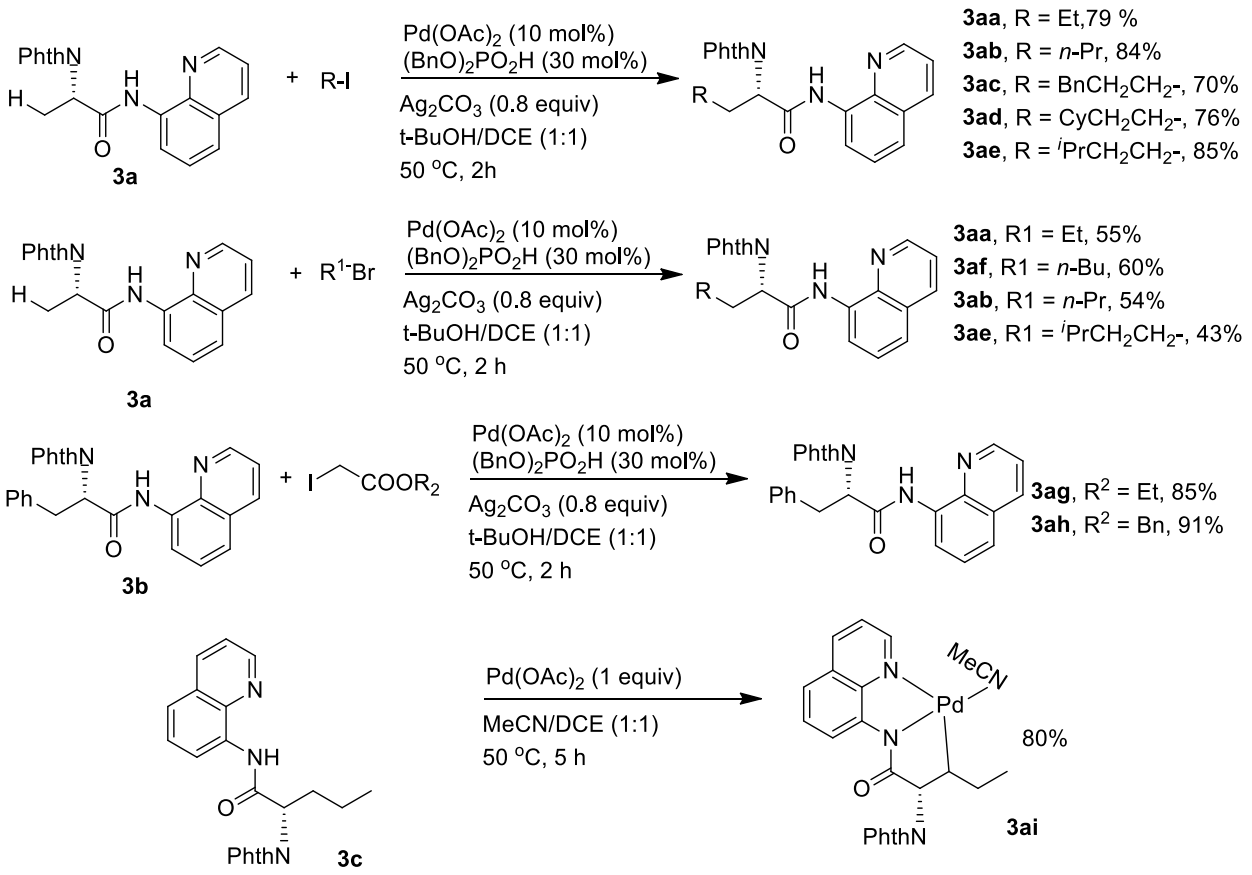


Scheme 2: Pd(II)-catalyzed bidentate directing group-directed stereoselective C-H arylation of **2a** and **2d**.

Unnatural amino acids are present in the core structure of peptides, peptidomimetics and pharmaceutical compounds[17c] and play a key role in asymmetric catalysis and synthesis of complex organic compounds. Shi et al.[17b] demonstrated alkylation of methylene sp^3 C-H bond of *N*-protected α-amino acid based carboxamides to obtain unnatural amino acids under mild reaction conditions. Pd-catalyzed sp^3 C-H alkylation of organic compounds remained as a difficult task in the past decades, however, in recent years efforts were put to alkylate unactivated sp^3 C-H bond. Yu group used alkylboronic acids and methylboroxine as alkylating reagents to alkylate unactivated sp^3 C-H bonds.[17d-e]

Shi's group discovered mild alkylation condition that neglects high temperature and prolonged reaction time to form various unnatural α-amino acids (α-AAs) with retention of configuration.

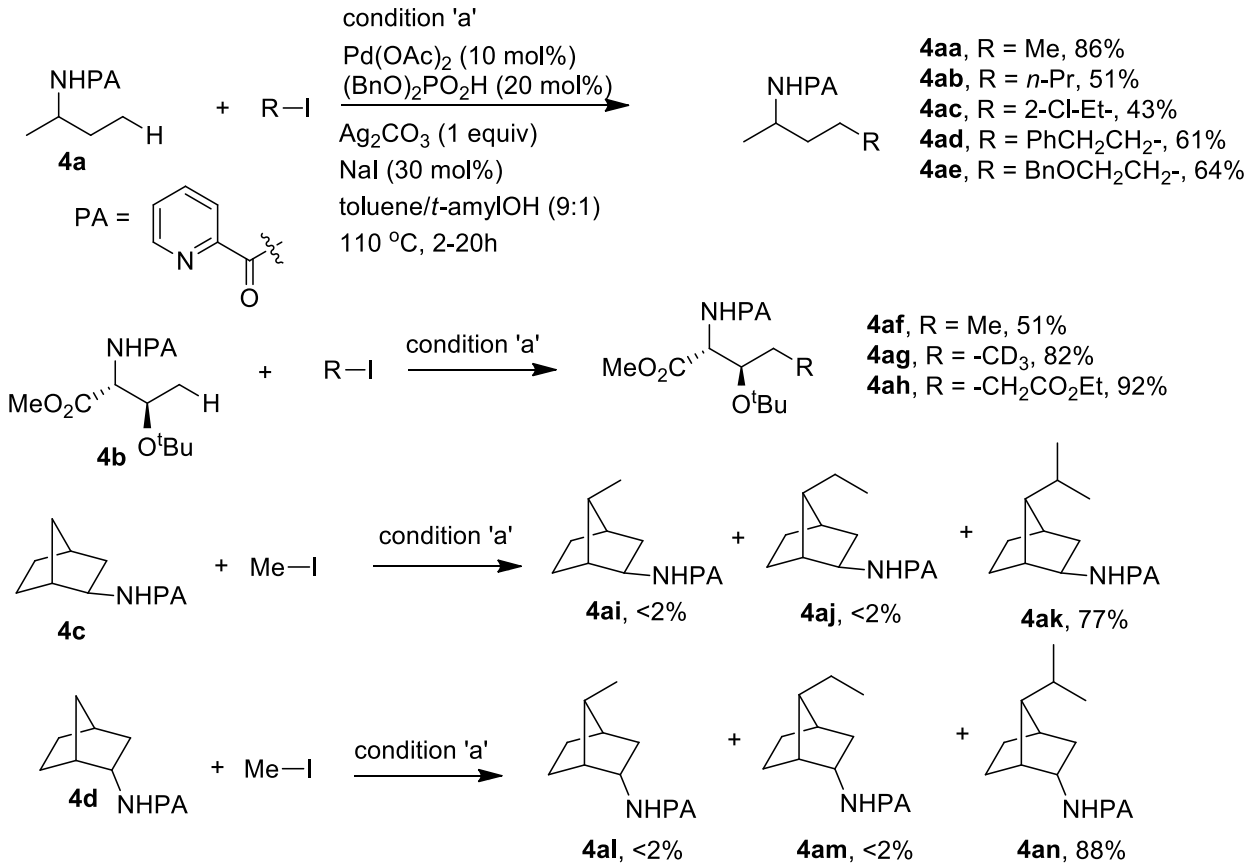
α-Amino acids coupled with the bidentate directing group 8-aminoquinoline **3a,b** were subjected to the Pd(II)-catalyzed alkylation conditions. The alkylation of **3a** using the combination of 10 mol% $Pd(OAc)_2$, 30 mol% $(BnO)_2PO_2H$, 0.8 equiv of Ag_2CO_3 and 1.5 equiv of different alkyl iodides or alkyl bromides in DCE/*t*-BuOH afforded the alkylation products **3aa-ah** (Scheme 3). The intermediate **3ai** (palladacycle) involved in the activation of β-C-H *trans* to amino group has been isolated by treating norvaline with 1.0 equiv. of $Pd(OAc)_2$ in DCE/MeCN at 50 ^oC.



Scheme 3: Synthesis of unnatural amino acids via alkylation of carboxamides derived from α-amino acids.

Chen et al. [18a,b] developed $Pd(OAc)_2$-catalyzed alkylation conditions for the functionalization of unactivated primary sp^3 γ-C-H bond of aliphatic amines **4a** using picolinamide (PA) as the bidentate directing group (Scheme 4). The alkylation of **4a** using the combination of 10 mol% $Pd(OAc)_2$, 20 mol% $(BnO)_2PO_2H$, 1 equiv of Ag_2CO_3 and 30 mol% of NaI using different alkyl iodides in toluene/*t*-amylOH afforded the γ-C-H alkylation products **4aa-ae** (Scheme 4). The

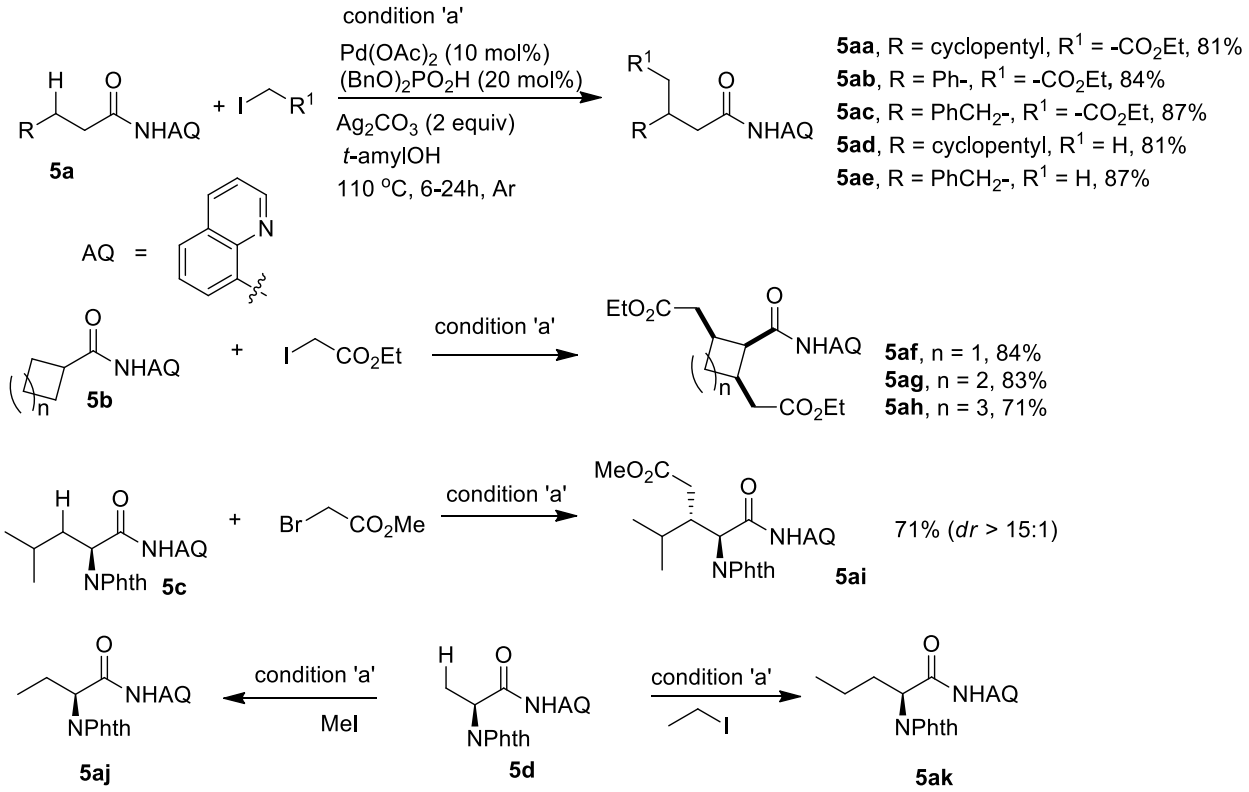
alkylation of amino acid derived substrate **4b** using the combination of 10 mol% $Pd(OAc)_2$, 20 mol% $(BnO)_2PO_2H$, 1 equiv of Ag_2CO_3 and 30 mol% of NaI with different alkyl iodides in toluene/*t*-amylOH afforded the γ-C-H alkylation products **4af-ah** (Scheme 4).[18] The Pd(II)-catalyzed alkylation of both *exo*- and *endo*-norbornene systems (**4c,d**) with 5 equivalents of MeI afforded the corresponding γ-C-H methylated norbornene systems (Scheme 4).



Scheme 4: Pd(II)-catalyzed, picolinamide-directed alkylation of carboxamides.

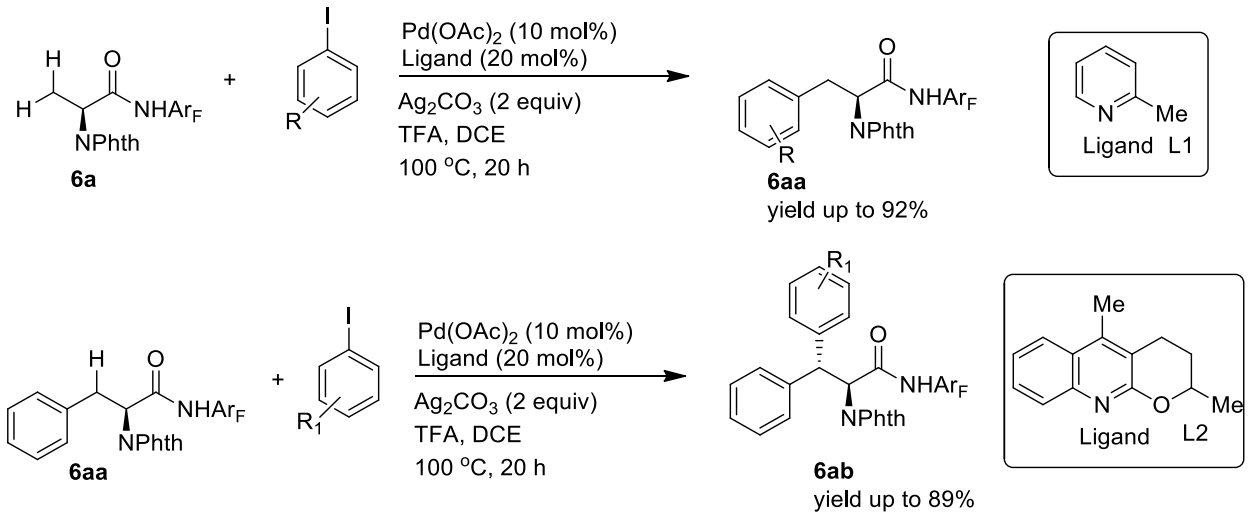
Chen et al.[19a-c] reported an expedient 8-aminoquinoline directed β-C(sp^3)-H alkylation of carboxamides of both simple aliphatic carboxylic acids and amino acids. Corey[19d] and Daugulis [19e] have elegantly demonstrated β-C(sp^3)-H functionalization of *N*-protected α-amino acid carboxamide using 8-aminoquinoline auxiliary. The Pd(II)-catalyzed β-C(sp^3)-H alkylation of simple aliphatic and cyclic carboxamides **5a,b** with different alkyl iodides afforded the corresponding products **5aa-ah** (Scheme 5).

The treatment of luecine amino acid derived substrate **5c** with ethyl bromoacetate provided the β-C(sp^3)-H alkylation product **5ai** with high diastereoselectivity (Scheme 5). Similarly, the treatment of alanine derived substrate **5d** with MeI or EtI provided the β-C(sp^3)-H alkylation products **5aj** (valine derivative) and **5ak** (norvaline derivative) (Scheme 5). Thus, varying the sequence of β-C-H alkylation a series of amino acids can be synthesized by this protocol.



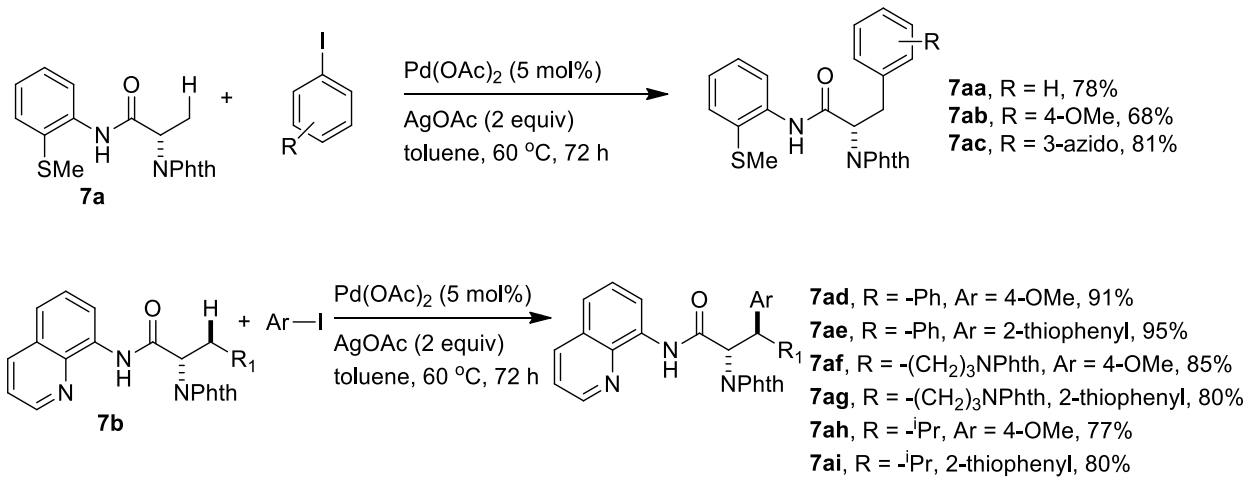
Scheme 5: Pd(II)-catalyzed, 8-aminoquinoline-directed alkylation of carboxamides.

Yu et al.[20a] disclosed a versatile method for exclusive transformation of alanine amides to β-Ar-β-Ar'-α amino acids via the Pd-catalyzed sequential β-C-H arylation of alanine derivative **6a** with two different aryl halides. Screening of ligands to selectively form mono arylated alanine derivative **6aa** (phenylalanine derivatives) showed that pyridine based ligand **L1** can efficiently promote mono arylation of alanine-derived amide **6a**. Then, the second arylation of less reactive secondary C(sp^3)-H bond of phenylalanine-derived substrate **6aa** has been explored with the help of ligand **L2**, which afforded the β-Ar-β-Ar'-α amino acids **6ab** (Scheme 6).



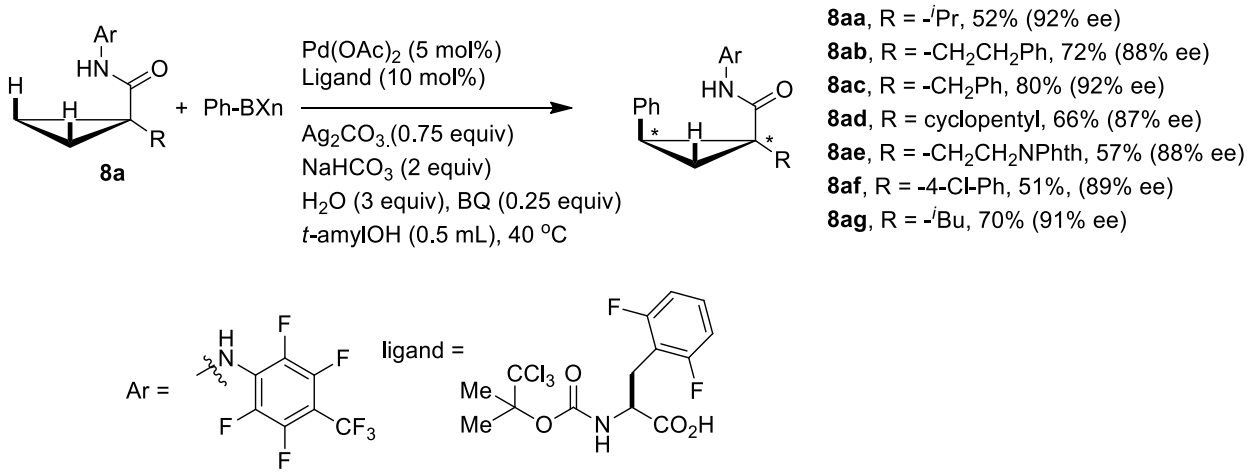
Scheme 6: Pd(II)-catalyzed, 8-aminoquinoline-directed arylation and synthesis of β-Ar-β-Ar'-α amino acids.

Daugulis et al.[20b] reported directing group controlled synthesis of unnatural amino acids by applying the $Pd(OAc)_2$ catalyzed C-H functionalization tactic. 2-Methylthioaniline has been chosen as the directing group for the mono arylation of methyl group of alanine system **7a** which afforded the β-C-H arylated compounds **7aa-ac** (Scheme 7). The Pd(II)-catalyzed C-H arylation of methylene C(sp^3)-H bonds of phenylalanine, lysine and leucine-derived carboxamides **7b** afforded the β-C-H arylated compounds **7ad-ai** with high yields and diastreoselectivity (Scheme 7).



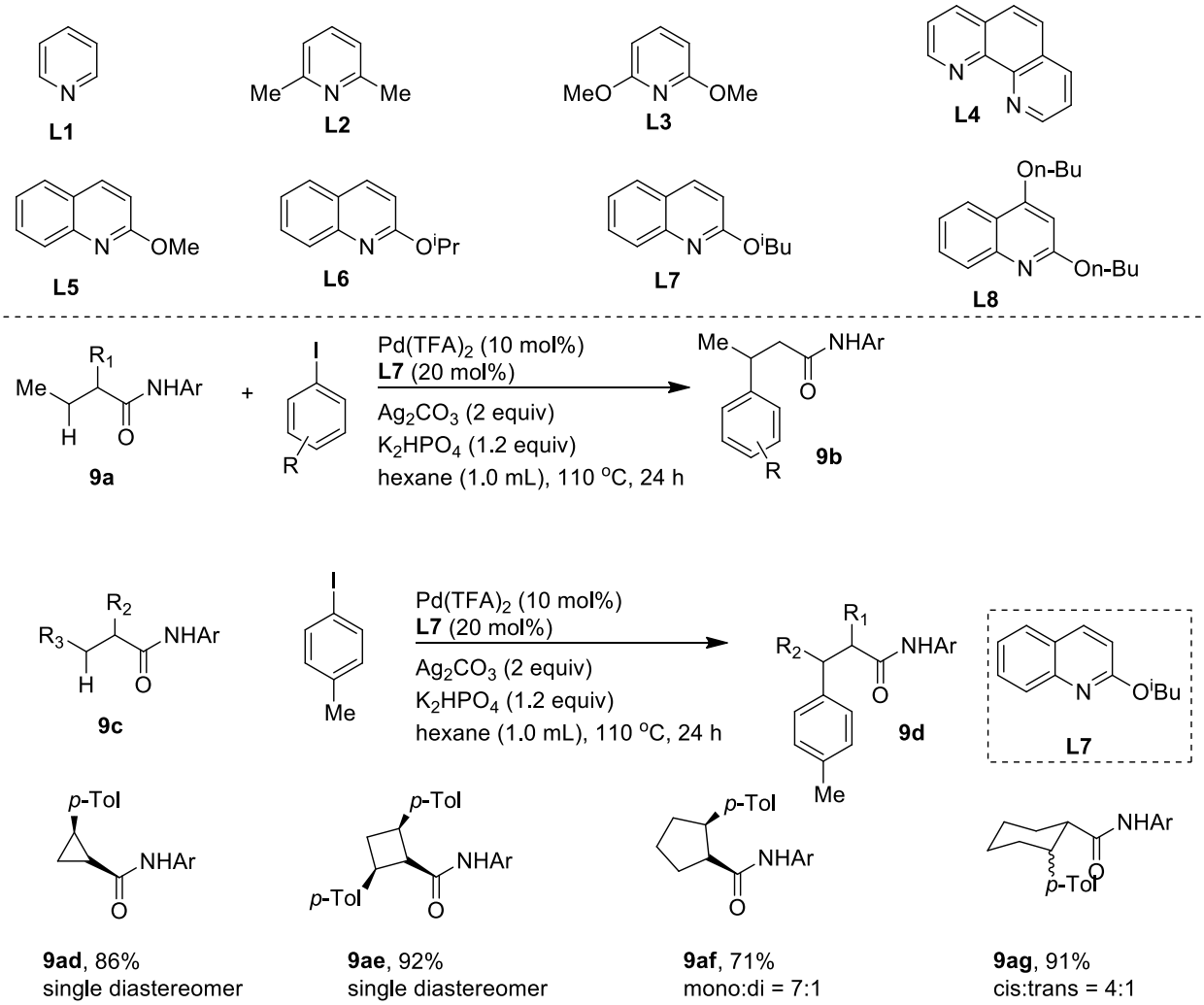
Scheme 7: Pd(II)-catalyzed, directing group-aided C-H arylation and synthesis of unnatural amino acids.

Enantiopure cyclopropane ring is prominent in natural products and pharmaceutical compounds and many transformations have been developed for their synthesis.[21b-d] Yu et al.[21a] disclosed *N*-monoprotected amino acid ligand enabled, Pd(II)-catalyzed enantioselective arylation of prochiral β-C(sp^3)-H bond of cyclopropane carboxamides **8a** afforded a wide range of β-C-H arylated cyclopropane carboxamides **8aa-ag** under mild reaction condition (Scheme 8).



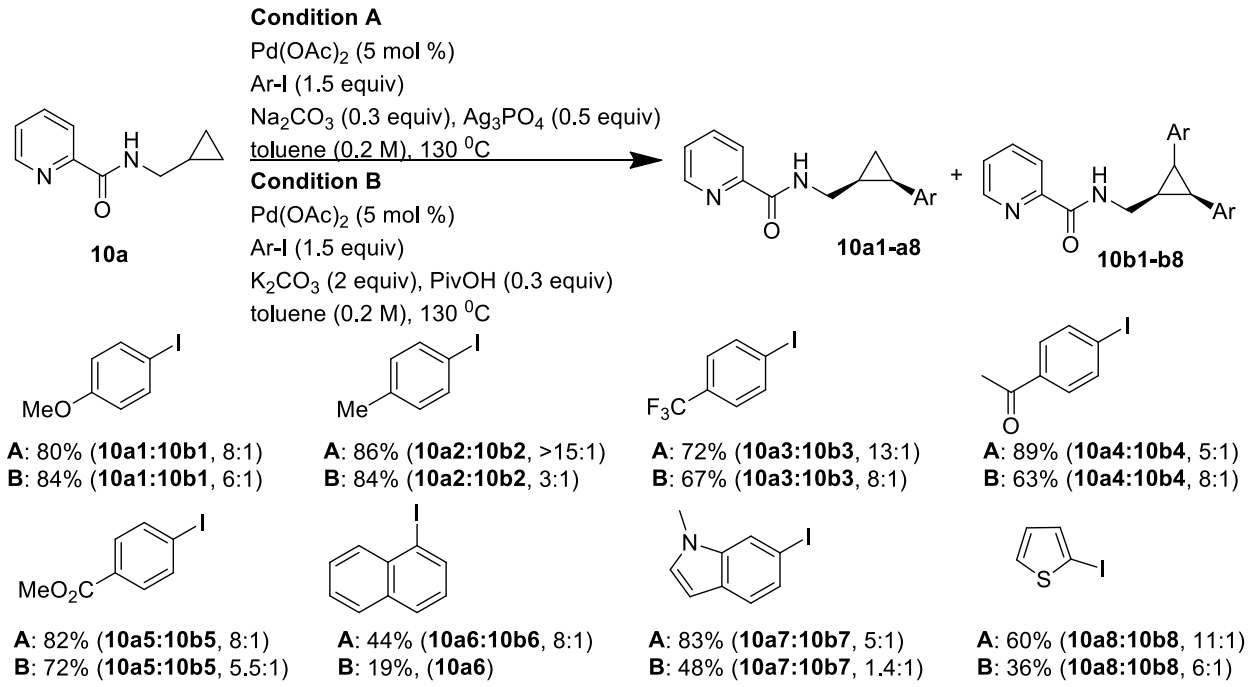
Scheme 8: Ligand-enabled enantioselective arylation of β-C(sp^3)-H of cyclopropane carboxamides.

Yu et al.[22a-e] developed pyridine-type ligand promoted, weakly coordinating *N*-aryl amide auxiliary directed methylene C(sp^3)-H bond functionalization of various cyclic and acyclic *N*-aryl carboxamides. A variety of pyridine ligands were screened for effecting the Pd(II)-catalyzed methylene C-H arylation of acyclic *N*-aryl carboxamides **9a** and cyclic *N*-aryl carboxamides **9c** to obtain high yield and diastereoselectivity (Scheme 9).

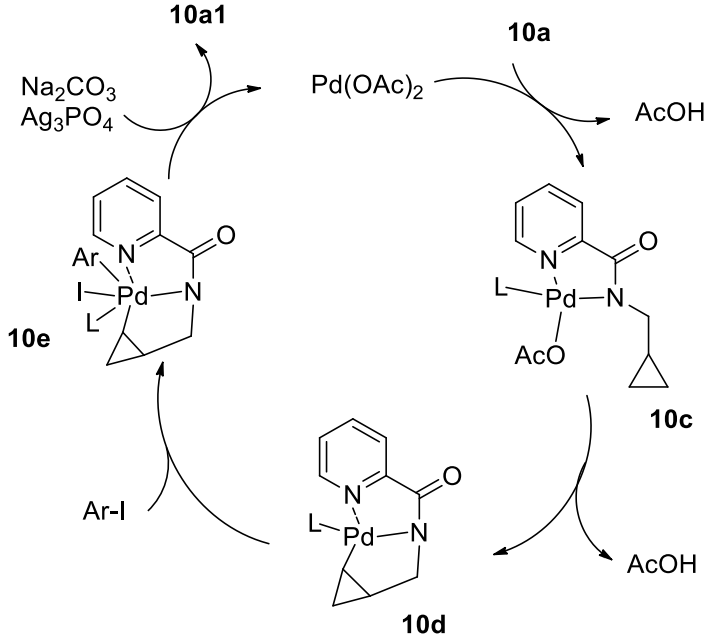


Scheme 9: Ligand-enabled methylene C-H arylation of acyclic *N*-aryl carboxamides **9a** and cyclic *N*-aryl carboxamides **9c**.

Charette et al.[23a] developed a robust and efficient method for the diastereoselective γ-C-H arylation of cyclopropylmethanamine derived carboxamide **10a** using picolinamide as the directing group (Scheme 10a).[21a, 23b-f] In general, condition A (Scheme 10) provided better yields and ratios between mono arylated and bis arylated cyclopropanes. Selected examples of mono and bis arylated cyclopropylmethanamine derived carboxamide are given in Scheme 10. In concurrence with the Daugulis's report,[8f] Charette proposed a plausible mechanism for the stereoselective γ-C-H arylation of cyclopropylmethanamine derived carboxamide **10a** using picolinamide as the directing group (Scheme 10b).



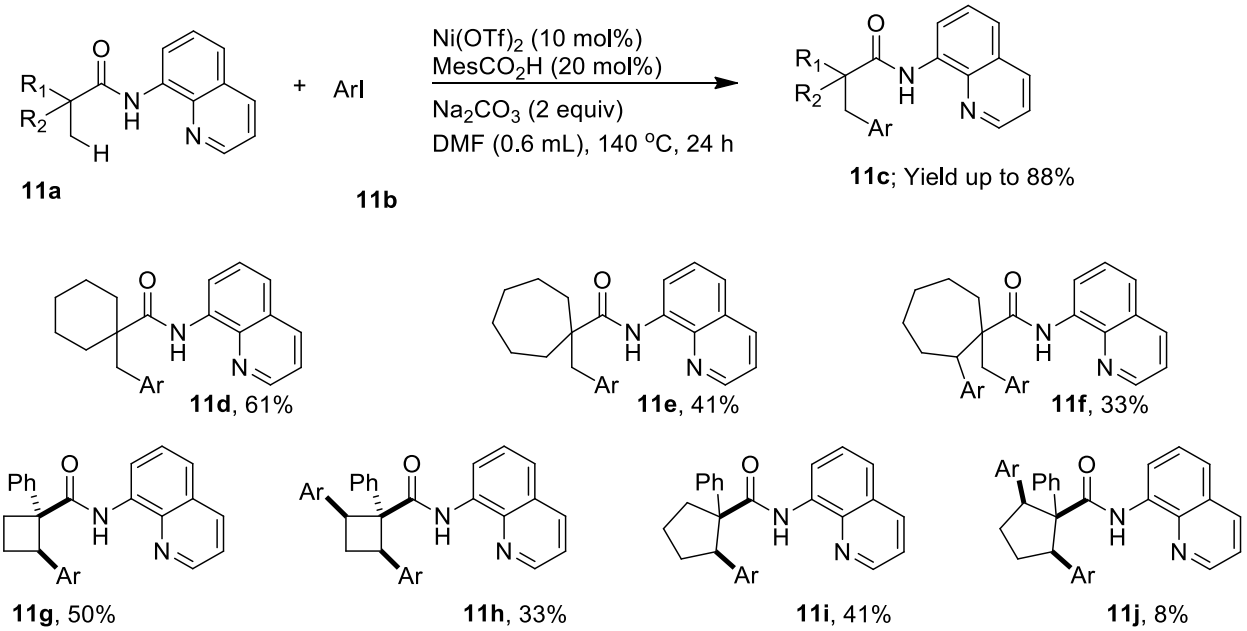
Scheme 10a: Picolinamide-enabled C-H functionalization of cyclopropylmethanamine derived carboxamide.



Scheme 10b: Mechanism of $Pd(OAc)_2$-catalyzed, picolinamide-directed C-H functionalization of cyclopropyl methylamine carboxamides.

Most of the catalytic C-H transformation reactions involve use of palladium complexes for functionalization. The reactions utilizing transition metals other than palladium catalyst to functionalize C(sp^3)-H bond are limited.[24a-d] Efforts have been focused to replace palladium catalysts by reactive and less expensive catalysts. Currently, both Ni^0 and Ni^{II} catalyzed C-H functionalization process have attracted the attention of the synthetic chemists.

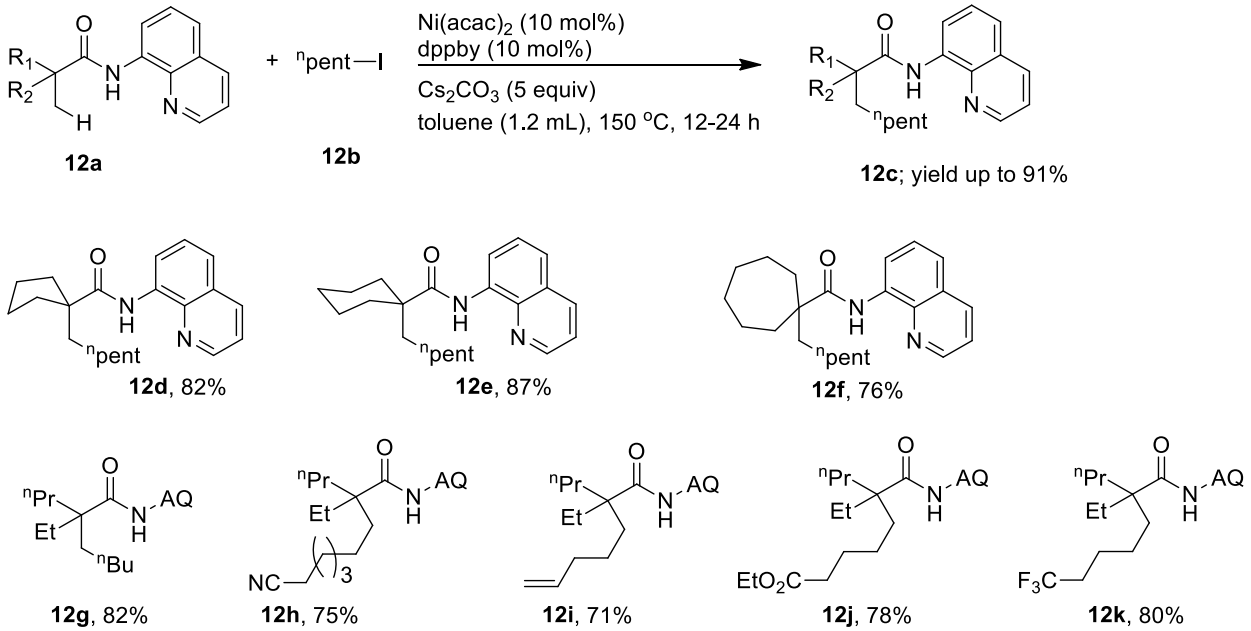
Chatani et al.[24e] reported an efficient and scalable nickel-catalyzed bidendate auxiliary directed C(sp^3)-H functionalization of aliphatic carboxamides with aryl iodides. The reaction of amide **11a** with ArI in presence of $Ni(OTf)_2$ (10 mol%) and Na_2CO_3 (2 equiv) afforded β-C(sp^3)-H arylated compounds (**11c**, Scheme 11). The addition of sterically bulk benzoic acids such as 2,4,6-trimethylbenzoic acid or 2,6-diphenylbenzoic acid improved the arylated product yield. Various 8-aminoqunoline-derived aliphatic acyclic carboxamides (**11a-e**) were treated with aryl halides under standard condition to afford several β-arylated products (**11d-j**).



Scheme 11: Nickel-catalyzed 8-aminoquinoline directed C-H arylation.

Ge et al. [25a] reported Ni(II) catalyzed highly regioselective alkylation of unactivated β-C(sp^3)-H bond of 2,2-disubstituted propane carboxamides with the aid of bidentate directing group (AQ). The amide **12a** and alkyl iodide are treated with catalytic amount of $Ni(acac)_2$ and dppby ligand

to afford β-alkylated amide (**12c**). A range of 2,2-disubstituted propane carboxamides bearing both linear and cyclic chains are treated with 1-iodopentane under standard condition to afford β-alkylated amides (**12d-k**) in good to excellent yield (Scheme 12).



Scheme 12: Nickel-catalyzed 8-aminoquinoline directed C-H alkylation of 2,2-disubstituted aliphatic carboxamides.

Plausible mechanism was proposed for the nickel-catalyzed 8-aminoquinoline directed C-H alkylation of 2,2-disubstituted aliphatic carboxamides as shown in Figure 3.[25b-d] Coordination of amide **12a** to Ni(II) complex followed by ligand exchange process generates intermediate **A**. Oxidative addition of intermediate **C** with alkyl iodide followed by reductive elimination forms intermediate **D**, which produces the alkylated product upon protonation and generates Ni(II) species. Alternatively, the oxidative addition of alkyl radical to intermediate **B** generates Ni(III) complex [25e-g] which further undergoes reductive elimination to form alkylated product with the generation of Ni(I) species. In another experiment, it is shown that treatment of Ni(I) species with alkyl halide produces alkyl radical and Ni(II) species. Moreover, the reaction fails to give alkylated products upon addition of excess amount of TEMPO and forms 2,2,6,6-tetramethyl-1-(pentyloxy)piperidine along with desired product. This suggested that a free radical mechanism might have involved in the alkylation process.

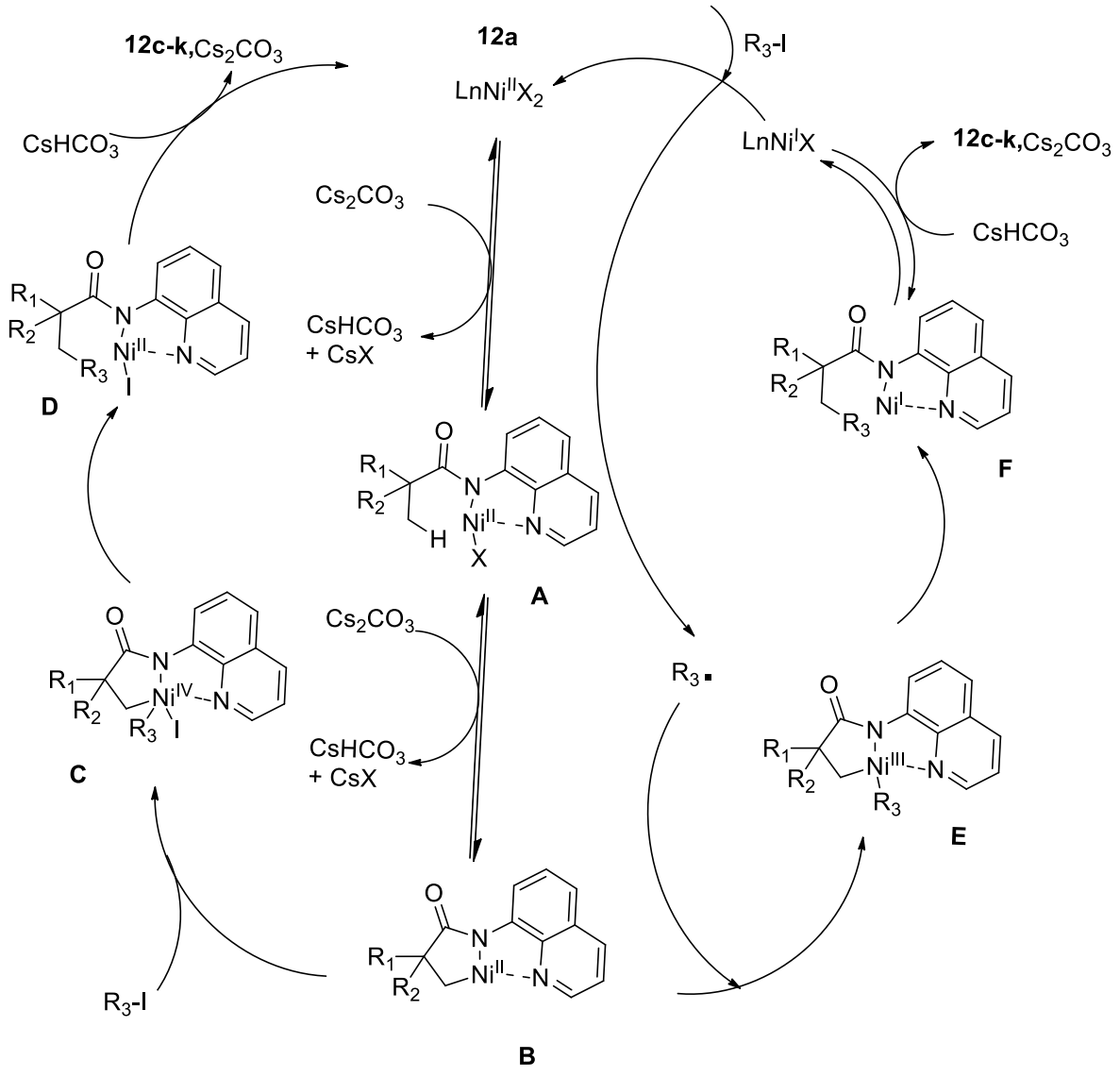
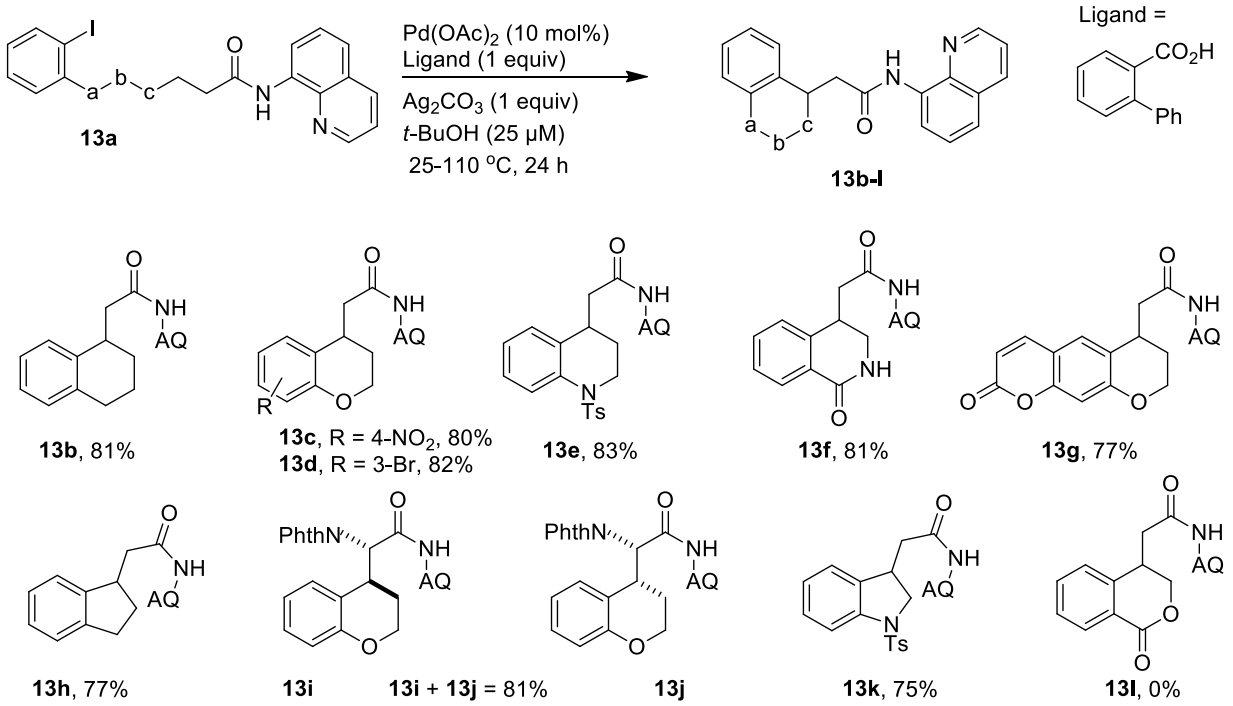


Figure 3: Plausible mechanism for nickel catalyzed 8-aminoquinoline directed C-H alkylation of 2,2-disubstituted aliphatic carboxamides.

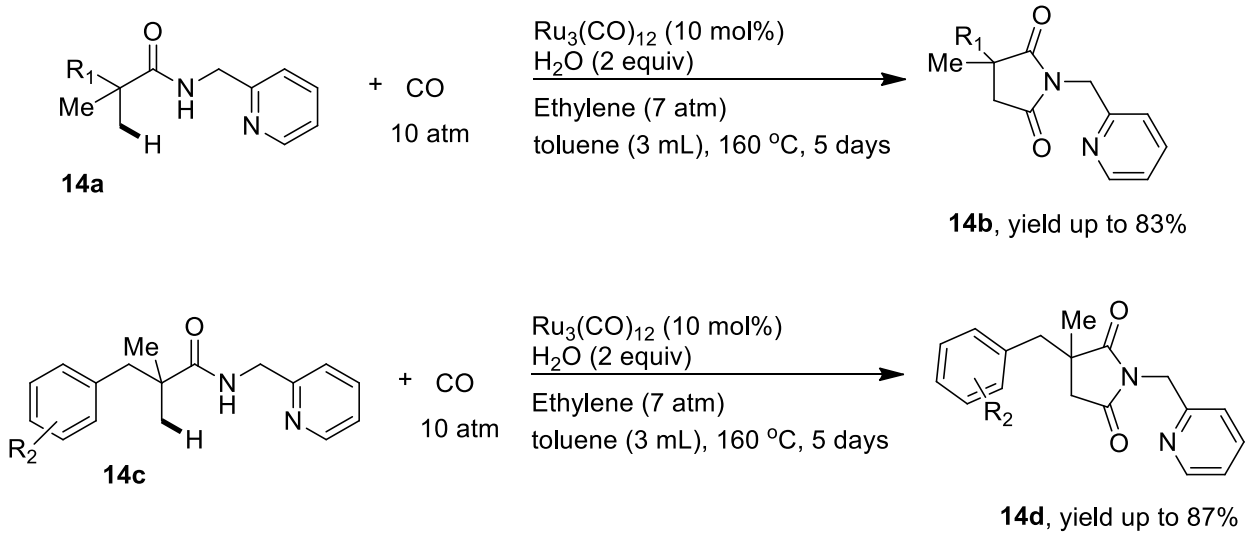
Chen et al.[26a] developed 8-aminoquinoline directed $Pd(OAc)_2$-catalyzed intramolecular C-H arylation process under mild condition. Where the starting amide substrate bearing aryl iodide substituent on the backbone of carboxylic acid undergoes transition metal catalyzed coupling and creates C-C bond at β-position.[26b-f] Selected examples of cyclized carboxamides obtained from

8-aminoquinoline directed $Pd(OAc)_2$-catalyzed intramolecular C-H arylation process are given in Scheme 13.



Scheme 13: 8-Aminoquinoline directed $Pd(OAc)_2$-catalyzed intramolecular C-H arylation.

Notably, low valent late-transition metal catalyzed C-H functionalization reactions involving C-H activation of unactivated sp^3 C-H bond have attracted synthetic chemists.[27a-h] Chatani et al. [27g] demonstrated carbonylation of unactivated sp^3 C-H bond of α,α-disubstituted propane carboxamides with the aid of 2-pyridinylmethylamino bidentate auxiliary using $Ru_3(CO)_{12}$. The representative examples of C-H carbonylated compounds are given in Scheme 14. The amide substrate having more than one methyl substituent proceeds C-H carbonylation to provide succinimide derivatives **14b,d** indicating that five-membered ring closure is preferred over the formation of six-membered ring. Notably, C-H carbonylation of amide **14a** was demonstrated to provide a derivative of succinimide anticonvulsant ethosuximide, which is used mainly in the treatment of absence seizures. The C-H activation of methyl C-H bond preferentially takes place over methylene C-H even when the methylene carbon is activated by the presence of phenyl ring.



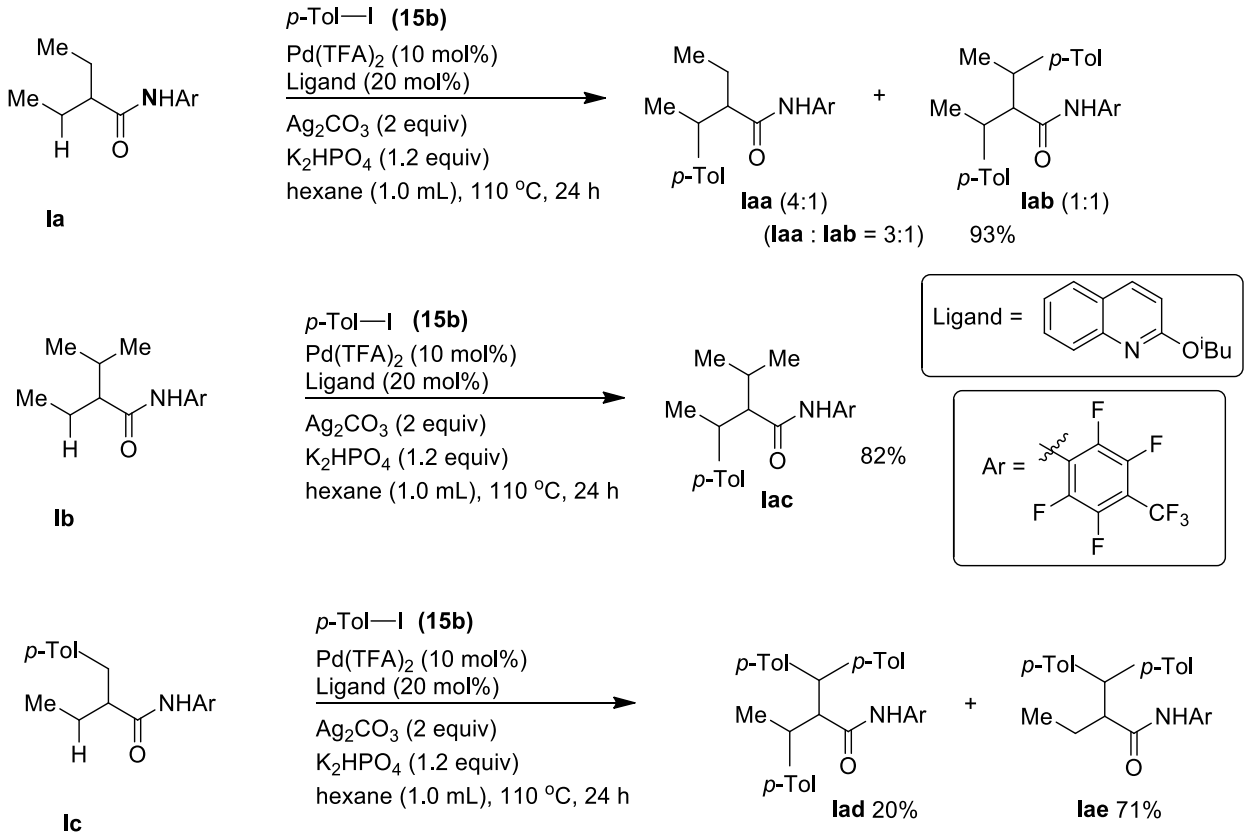
Scheme 14: Synthesis of succinimide derivatives via 2-pyridinylmethylamine directed C-H corbonylation of α,α-disubstituted aliphatic carboxamides.

Chapter 2: Bidentate directing group 8-aminoquinoline-aided Pd(II)-catalyzed diastereoselective β-arylation of the prochiral secondary sp^3 C-H bonds of 2-phenylbutanamides and related aliphatic carboxamides.

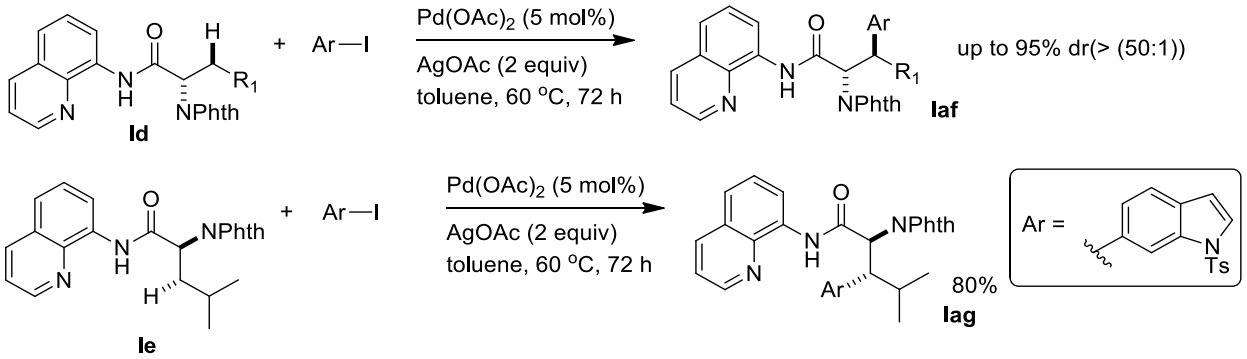
Some of the notable reactions pertaining to the sp^3 C–H activation enabled by various bidentate directing groups have been presented in the Chapter 1.[8-37] Notably, bidentate directing group directed Pd-catalyzed arylation of sp^3 C-H bond were demonstrated using a variety of aliphatic carboxamide, amino acid carboxamides, carbocyclic system and saturated heterocyclic system. It is to be noted that the Pd-catalyzed C-H functionalization of cyclic carboxamides can create two or three stereocenters on a carboxylic acid back bone. Accordingly, the diastereoselective C-H functionalization have also been successfully demonstrated on carbocyclic systems such as cyclopropane,[35a,b] cyclobutane,[35c,d,e,f] medium-sized rings,[33c, 8g] norbornane-frame work,[35g] saturated heterocyclic systems (tetrahydropyran,[36b] tetrahydrofuran,[36e] proline,[36c,d] 1,4-benzodioxane[36e]) Daugulis,[37f] Chen,[37a] and Corey[37e] have elegantly demonstrated the diastereoselective C-H arylation reactions on various amino acid systems (Scheme 1). Yu et al. [37a] reported ligand controlled auxiliary directed diastereoselective C-H arylation of aliphatic carboxamides with 4-iodotoluene using $Pd(TFA)_2$ catalyst (Scheme 1). Where weekly coordinating auxiliary (assembled from the respective carboxylic acid and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline) with external ligand (2-isobutoxyquinoline) and notably, the stereochemistry of the products obtained were unknown.

In continuation of our lab's interest on the Pd-catalyzed diastereoselective C-H functionalization reactions, a part of this thesis envisaged to examine the diastereoselective β-arylation of the prochiral 2^o sp^3 C-H bonds of various aliphatic carboxamides having substituents at α- or γ-positions using the bidentate ligand 8-aminoquinoline-directed C-H activation and the

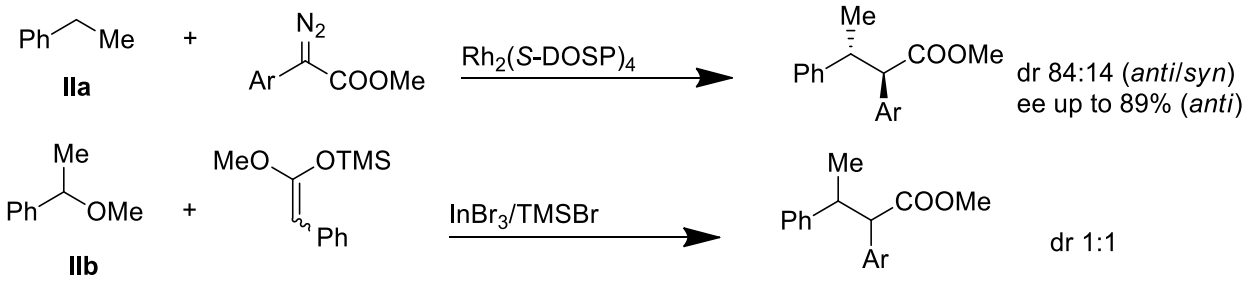
construction of β-C-H arylated aliphatic carboxamides possessing vicinal stereocenters (Scheme 2). It is to be noted that the construction of β-aryl 2-phenylbutyric acids possessing two vicinal stereocenters have also been reported using classical pathways.[38b,c] Davis's group reported Rh-catalyzed intermolecular C-H insertion method and Baba's group showed $InCl_3$ catalyzed enolate addition to methyl ether of styrallyl alcohol for the construction of β-aryl 2-phenylbutyric acid derivatives (Scheme 3). Complementary to these existing methods, the present method reveals that synthesis of β-C-H arylated aliphatic carboxamides possessing vicinal stereocenters via the diastereoselective β-arylation of the prochiral 2^o sp^3 C-H bonds of various aliphatic carboxamides (Scheme 2).



Scheme 1: Selected available examples of diastereoselective β-arylation of prochiral 2^o sp^3 C-H bond of aliphatic carboxamides.



Scheme 2: Theme of this work. 8-Aminoquinoline aided β-arylation of prochiral 2° sp^3 C-H bonds of aliphatic carboxamides.



Scheme 3: Representative literature methods dealing with the construction of β-aryl 2-phenylbutyric acid derivatives.

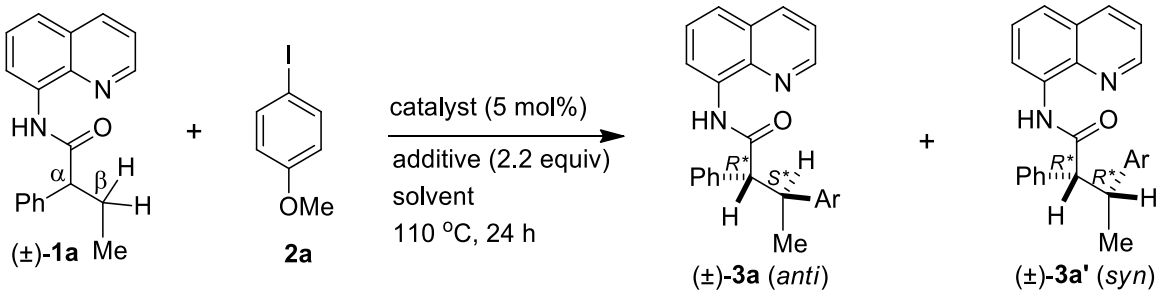
Results and Discussion

To examine the diastereoselective β-arylation of the prochiral 2° sp^3 C-H bonds of various aliphatic carboxamides having substituents at α- or γ-positions using the bidentate ligand 8-aminoquinoline-directed C-H activation, initially we prepared the racemic compound **1a** by linking 2-phenylbutanoyl chloride with the bidentate directing group 8-aminoquinoline. Then, to find out the suitable and best reaction conditions, we carried out the optimization reactions as shown in Table 1. A reaction mixture containing aliphatic carboxamide **1a**, 1-iodo-4-methoxybenzene (**2a**) and an additive AgOAc, 5 mol% of $Pd(OAc)_2$ catalyst was heated at 110 °C for 24 h. This reaction afforded the β-C-H arylated product **3a**/**3a′** (racemic compounds) having two vicinal stereocenters in 82% yield with good diastereoselectivity. The diastereomeric ratio was found to be 78:22, **3a** (*anti*) / **3a′** (*syn*) (entry 1, Table 1). Next, the Pd(II)-catalyzed β-C-H arylation of aliphatic carboxamide **1a** in toluene at 110 °C for 24 h gave the β-C-H arylated

product **3a**/**3a′** with an improved yield (89%) with good diastereoselectivity. The diastereomeric ratio was found to be 86:14 (entry 2, Table 1). When the C-H arylation of aliphatic carboxamide **1a** was carried out with 2 or 3 equivalents of ArI **2a**, the corresponding products **3a**/**3a′** were obtained in moderate yields (66 and 71%, dr 75:25, entries 3 and 4, Table 1). The C-H arylation of aliphatic carboxamide **1a** with ArI **2a** using other palladium catalysts, such as $Pd(MeCN)_2Cl_2$, $Pd(acac)_2$, $PdCl_2$ and $Pd(TFA)_2$ also afforded the products **3a**/**3a′** in 57-85% yields (dr up to 75:25, entries 5-8, Table 1). Then, the Pd(II)-catalyzed C-H arylation of aliphatic carboxamide **1a** with ArI **2a** in other solvents, such as DMF, 1,4-dioxane and DMSO furnished the products **3a**/**3a′** in moderate yields (44-64%, dr up to 80:20, entries 9-11, Table 1). Then, the Pd-catalyzed C-H arylation of substrate **1a** with **2a** using other silver salts or additives instead of AgOAc were performed and these reactions were found to be ineffective (entries 12-15, Table 1).

Having done the optimization reactions, then, it was envisaged to examine the generality and scope of 8-aminoquinoline-aided, Pd(II)-catalyzed diastereoselective β-C-H arylation of the prochiral 2^o sp^3 C-H bond of carboxamide substrate (±)-**1a** (Table 2). The β-C-H arylation of carboxamide substrate (±)-**1a** with a variety of aryl iodides bearing electron-donating group or electron-withdrawing group at the *para* or meta position of the aryl ring were performed under the optimized reaction conditions (entry 2, Table 1). Accordingly, a variety of β-C-H arylated 2-phenyl-butanamides (±)-**3b-h** (*anti* isomers) having two vicinal stereocenters were acquired in 62-91% yields (dr up to 81:19, Table 2). Then, the Pd(II)-catalyzed β-C-H arylation of carboxamide substrate (±)-**1a** with disubstituted aryl iodides gave the corresponding β-C-H arylated 2-phenyl-butanamides (±)-**3i-k** (*anti* isomers) in 65-93% yields with moderate to very good diastereoselectivities (dr up to 80:20, Table 2). Next, the Pd(II)-catalyzed β-C-H arylation of the prochiral sp^3 C-H bond of carboxamide substrate (±)-**1a** with a hetero aryl iodide (e.g., 2-iodothiophene) also gave the C-H arylated product (±)-**3l** (*anti* isomer) in 90% yield with good diastereoselectivity (dr 77:23, Table 2).

Table 1. Optimization reactions. Diastereoselective β-C-H arylation of the prochiral 2° sp^3 C-H bonds of aliphatic carboxamide (±)-**1a**[a]



entry	catalyst	solvent	additive	yield (%)	dr = *anti* / *syn*
1	$Pd(OAc)_2$	neat	AgOAc	82	78:22
2	**$Pd(OAc)_2$**	**Toluene**	**AgOAc**	**89**	**86:14**
3[b]	$Pd(OAc)_2$	Toluene	AgOAc	66	75:25
4[c]	$Pd(OAc)_2$	Toluene	AgOAc	71	75:25
5	$Pd(MeCN)_2Cl_2$	Toluene	AgOAc	85	75:25
6	$Pd(acac)_2$	Toluene	AgOAc	67	70:30
7	$PdCl_2$	Toluene	AgOAc	61	66:34
8	$Pd(TFA)_2$	Toluene	AgOAc	57	75:25
9	$Pd(OAc)_2$	DMF	AgOAc	64	80:20
10	$Pd(OAc)_2$	dioxane	AgOAc	55	77:23
11	$Pd(OAc)_2$	DMSO	AgOAc	44	75:25
12	$Pd(OAc)_2$	Toluene	Ag_2CO_3	0	–
13	$Pd(OAc)_2$	Toluene	Ag_2O	0	–
14	$Pd(OAc)_2$	Toluene	Oxone	0	–
15	$Pd(OAc)_2$	Toluene	$K_2S_2O_8$	7	67:33

[a] All the reactions were carried out using (±)-**1a** (0.25 mmol) and **2a** (1 mmol, 4 equiv) in a solvent (3 mL). [b] In this case, 0.5 mmol (2 equiv) of 1-iodo-4-methoxybenzene (**2a**) was used. [c] In this case, 0.75 mmol (3 equiv) of 1-iodo-4-methoxybenzene (**2a**) was used. The total yield of both the diastereomers is reported. The ratios of diastereomers were determined from the NMR spectra of the crude reaction mixtures.

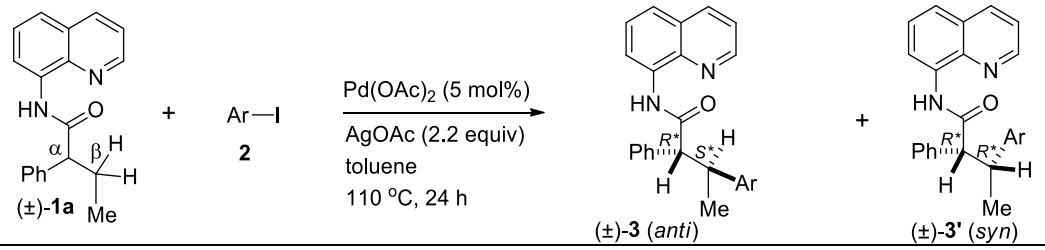
Next, the β-C-H arylation of carboxamide substrate (±)-**1a** with aryl bromides instead of aryl iodides (Scheme 4a) were also attempted. Accordingly, the Pd(II)-catalyzed β-C-H arylation of carboxamide substrate (±)-**1a** with 1-bromo-4-methoxybenzene (**2aA**) also gave the β-C-H arylated product (±)-**3a** in 68% yield and the diastereoselectivity was found to be 75:25 (Scheme 4a). Similarly, the Pd(II)-catalyzed β-C-H arylation of carboxamide (±)-**1a** with 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (**2kA**) gave the β-C-H arylated product (±)-**3k** in only 33% yield with moderate diastereoselectivity and the diastereomeric ratio was found to be dr 70:30 (Scheme 4a). The stereochemistry of all the major isomers (±)-**3a-l** was assigned on the basis of the following discussion.

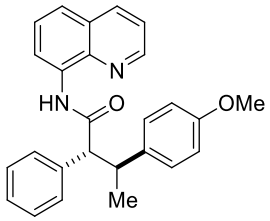
In all the reactions, attempts were made to isolate both major and minor isomers in pure form from the column chromatography purification. In most of the attempts, the major diastereomers were successfully isolated in pure form. Representatively, the major isomers (±)-**3b,c,e,l** were recrystallized to obtain the single crystals, which were then subjected to the X-ray structure analyses. The X-ray structure analyses of the major isomers (±)-**3b,c,e,l** unambiguously revealed that the major diastereomers formed in the β-C-H arylation of carboxamide substrate (±)-**1a** were having the *anti* stereochemistry (Figure 1). Furthermore, upon analyzing the ^{1}H NMR spectra, a typical pattern was found in the chemical shift values for the doublet peaks of the methyl protons present in the products (±)-**3**. Characteristically, the methyl protons of the major diastereomers (±)-**3a-l** (*anti* isomers) appeared as doublet at δ 1.10-1.25 ppm. On the other hand, the methyl protons of the minor isomers (±)-**3a′-3l′** (*syn* isomers) appeared as doublet at δ 1.51-1.64 ppm. Accordingly, the stereochemistry of all the major isomers (±)-**3a-l** (*anti* isomers) and minor isomers (±)-**3a′-3l′** (*syn* isomers) were assigned on the basis of the X-ray structures of the compounds (±)-**3b,c,e,l** coupled with the similarity in their NMR spectral pattern.

Next, to find out the other working bidentate directing groups for the diastereoselective β-C-H arylation of carboxamides, we assembled a series of 2-phenyl-butanamides (±)-**1b-e** by linking 2-phenylbutanoyl chloride with various bidentate directing groups, such as 2-picolyl amine, 2-aminopyridine, *N*,*N*-dimethylethylene diamine and 2-(methylthio)aniline (Scheme 4b). Then, we performed the $Pd(OAc)_2$–catalyzed C-H arylation reactions of substrates (±)-**1b-e** with aryl

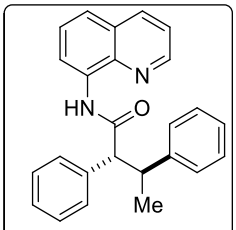
iodides in toluene at 110 ^{o}C for 24 h. Unfortunately, in these reactions we did not get any of the corresponding β-arylated 2-phenyl-butanamides **4/5**.

Table 2. Synthesis of β-arylated-2-phenylbutanamides (±)-**3a-l** from the diastereoselective C-H-arylation of (±)-**1a**[a]

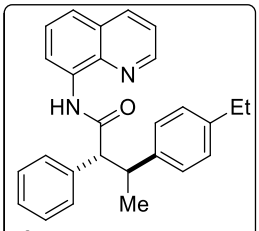




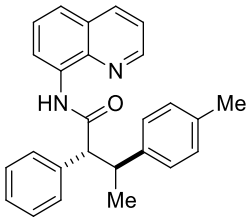
3a; 90% (86:14)



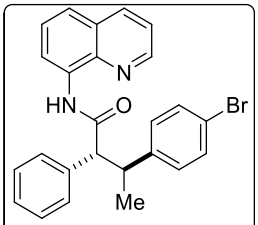
3b; 91% (80:20)
X-ray (major)



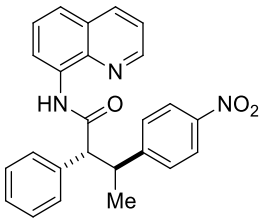
3c; 90% (80:20)
X-ray (major)



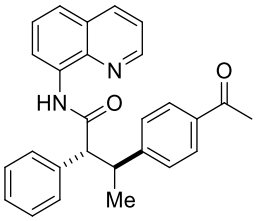
3d; 89% (75:25)



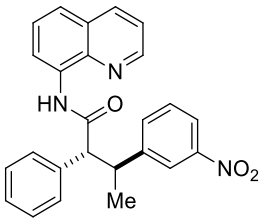
3e; 77% (77:23)
X-ray (major)



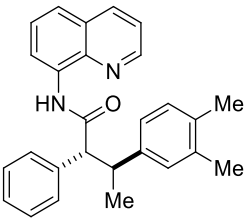
3f; 80% (78:22)



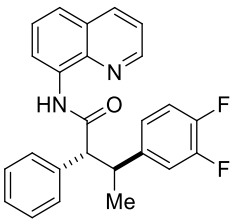
3g; 89% (78:22)



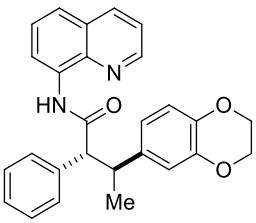
3h; 62% (81:19)



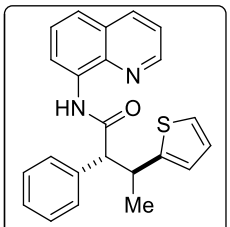
3i; 76% (80:20)



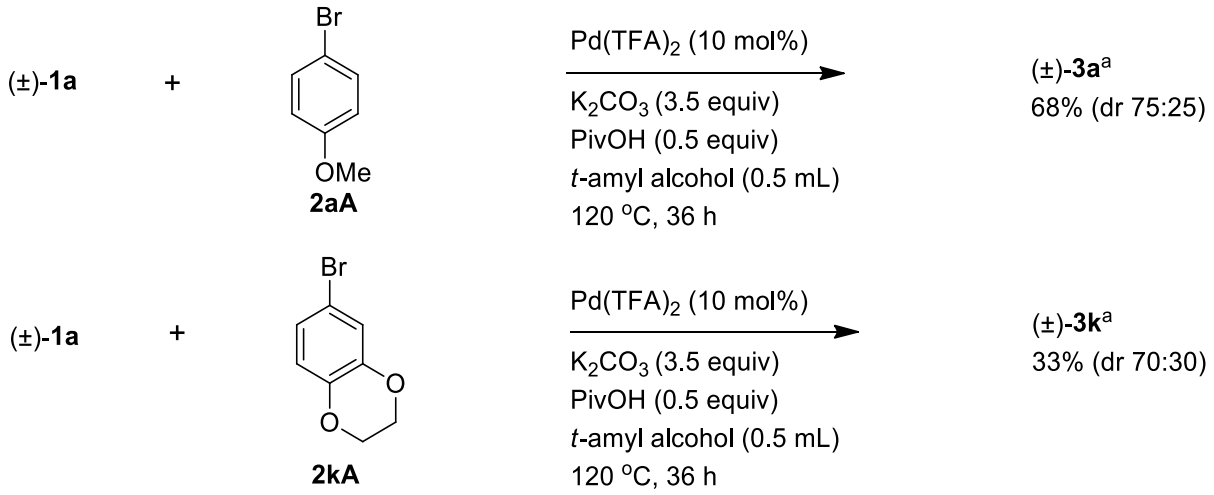
3j; 93% (80:20)



3k; 65% (70:30)



3l; 90% (77:23)
X-ray (major)



[a] The reaction was carried out using (±)-**1a** (0.25 mmol) and aryl halide (1 mmol, 4 equiv).

Scheme 4a. The Pd-catalyzed β-arylation of substrate (±)-**1a** with aryl bromides.

ineffective auxiliaries

Scheme 4b. The Pd-catalyzed β-arylation of substrates **1b-e** and ineffective directing groups

Furthermore, it was envisaged to explore the bidentate directing group-directed Pd(II)-catalyzed diastereoselective β-C-H arylation of the prochiral 2° sp^3 C-H bonds of various aliphatic carboxamides possessing a substituent at the γ-position (Scheme 5). In this regard, we

prepared the carboxamide substrates (±)-**1f** and (±)-**1g** from the corresponding acid chlorides and the 8-aminoquinoline. Then, we attempted the Pd(II)-catalyzed β-C-H arylation of carboxamide substrate (±)-**1f** with aryl iodides, such as 2-iodothiphene and 1-bromo-4-iodobenzene, which furnished the corresponding β-C-H arylated products (±)-**4a** (84%, dr 52:48) and (±)-**4b** (40%, dr 67:33) with poor diastereoselectivities. Likewise, the Pd(II)-catalyzed β-C-H arylation of carboxamide substrate (±)-**1f** with 1-chloro-4-iodobenzene and 1,2-dichloro-4-iodobenzene

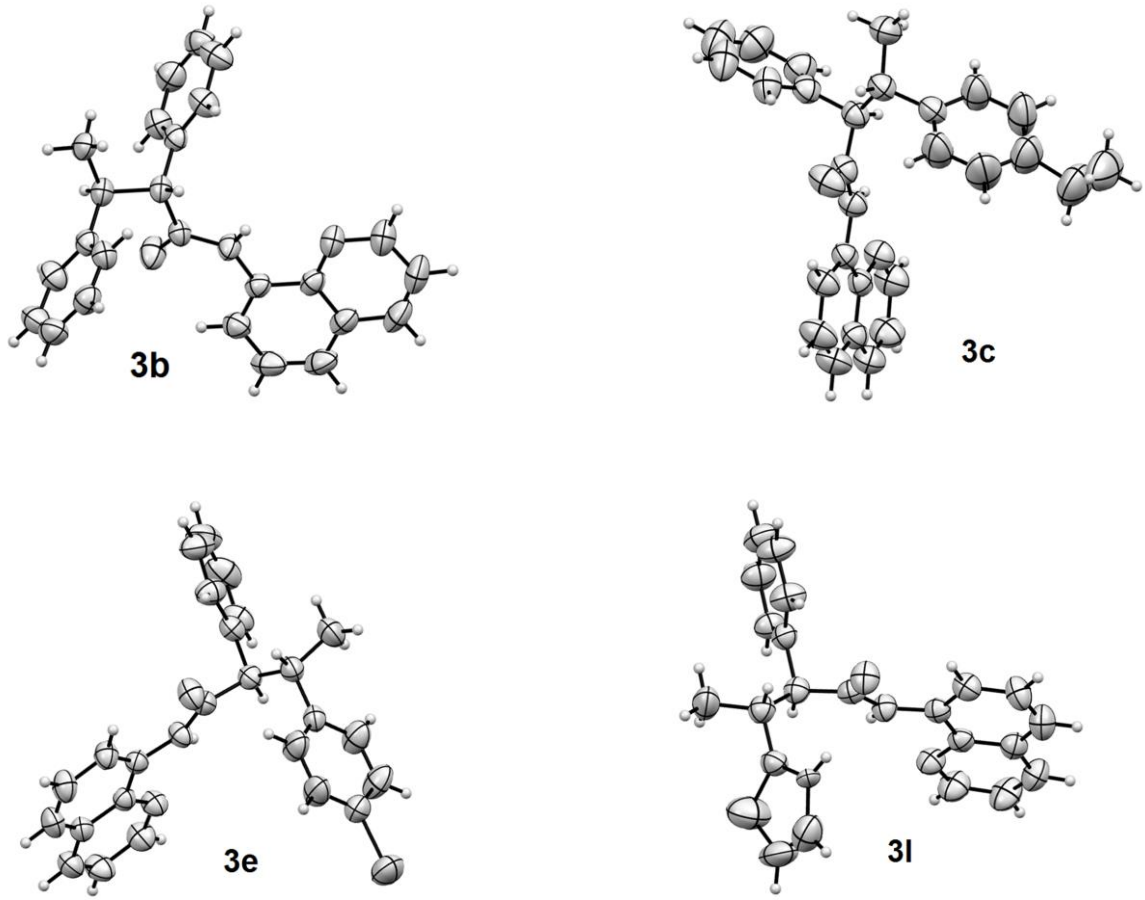
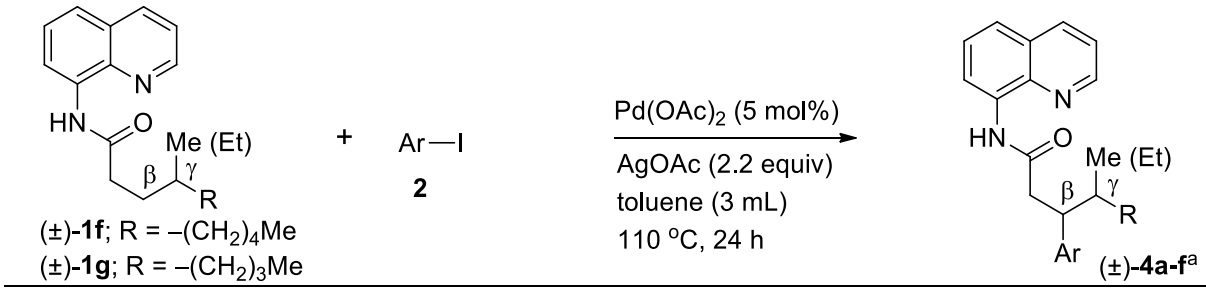
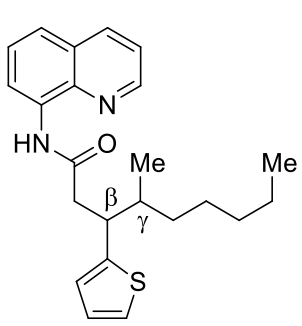


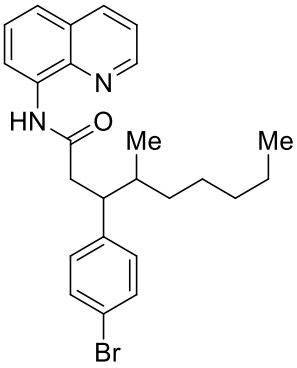
Figure 1. X-ray structures of the major diastereomers (±)-**3b**,**c**,**e**,**l** (*anti* isomers)

afforded the corresponding β-C-H arylated products (±)-**4c** (53%, dr 70:30) and (±)-**4d** (68%, dr 54:46) with poor diastereoselectivities. The Pd-catalyzed β-C-H arylation of carboxamide substrate (±)-**1g** with aryl iodides, such as 1-bromo-4-iodobenzene and 1-iodo-4-methoxybenzene also gave the corresponding β-C-H arylated products (±)-**4e** (50% dr 77:23) and (±)-**4f** (57%, dr 65:35, Scheme 5).

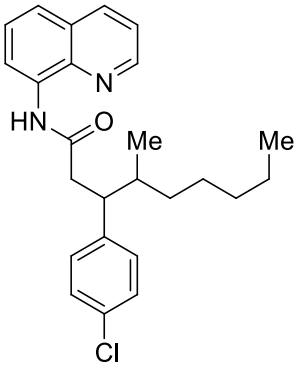




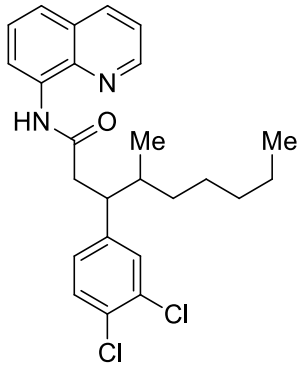
4a; 84% (52:48)



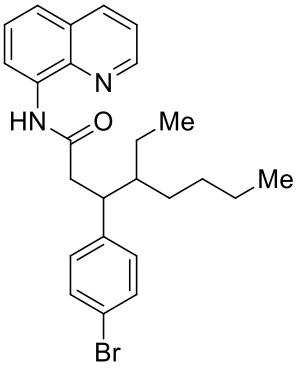
4b; 40% (67:33)



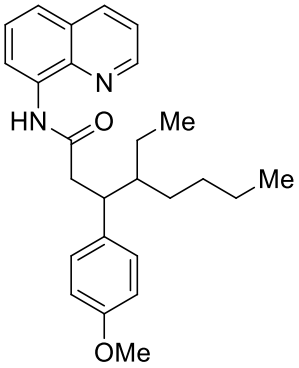
4c; 53% (70:30)



4d; 68% (54:46)



4e; 50% (77:23)

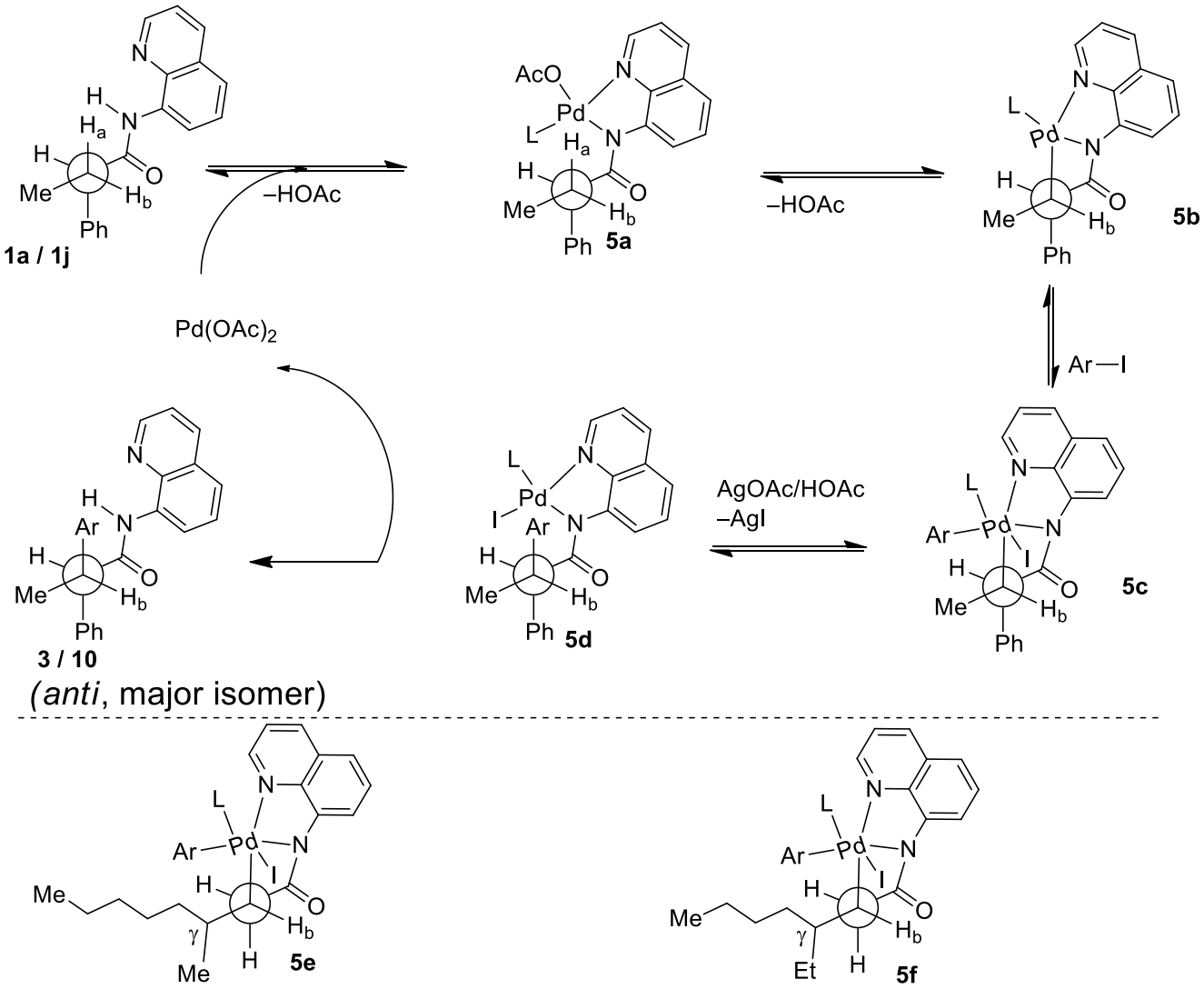


4f; 57% (65:35)

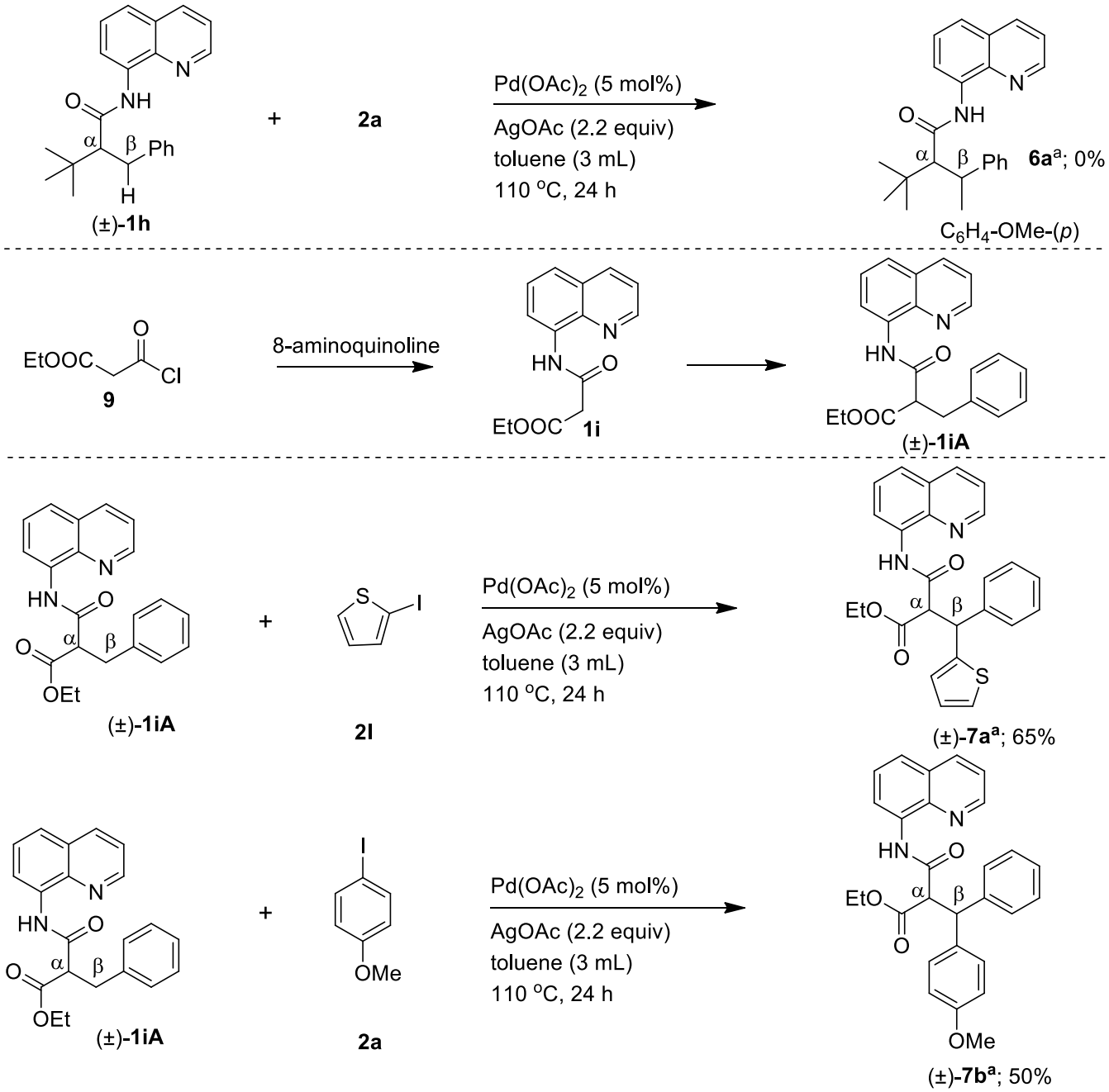
[a] The reaction was carried out using (±)-1f or (±)-1g (0.25 mmol) and aryl halide (1 mmol, 4 equiv). [b] The total yield of both the diastereomers is reported. The ratio of diastereomers was determined from the NMR spectra of the crude reaction mixture. [c] In these cases, the products (±)-4a-f were isolated as mixture of diastereomers and our efforts to separate the major and minor isomer in pure form were not fruitful, hence we could not predict the stereochemistry of the products (±)-4a-f.

Scheme 5. The bidentate ligand-aided Pd-catalyzed β-arylation of aliphatic carboxamides (±)-**1f** and (±)-**1g**.

The observed *anti* stereochemistry of the isomers (±)-**3a-l** can be realized *via* the plausible reaction pathway shown in Scheme 6 in concurrence with the mechanism proposed in the literature pertaining to the bidentate ligand-aided Pd(II)-catalyzed sp^3 C-H activation of aliphatic carboxamides. Accordingly, in the present work, the C-H activation of one of the diastereotopic protons of **5a** (produced from **1a**) generates the metallocycle TS **5b**. Upon the reaction of **5b** with an aryl iodide generates the TS **5c**, from which the C-H arylated TS **5d** is generated. Subsequently, the product **3** with *anti* stereochemistry and the catalyst is regenerated from **5d**. On the other hand, the formation of the products (±)-**4a-f** with poor diastereoselectivities is not a surprising point and it is to be noted that characteristically, only the β-C-H bond of the aliphatic carboxamide is activated. In the present study, when compared to the substrate (±)-**1a**, which has a substituent at the α-position, the substrates (±)-**1f,g** are having a substituent at the γ-position. Further, the aliphatic carboxamide chains in the substrates (±)-**1f,g** are highly flexible due to the free rotation. Based on these discussions, the observed poor diastereoselectivities of the products (±)-**4a-f** may be realized based on the following points; (a) the substituent at the γ-position in **1f,g** has not helped and provided the rigidity to the TS (see the plausible TS **5e** and **5f**, Scheme 6), and (b) the aliphatic chain after the γ-carbon and the γ-substituent are not part of the ring of the metallocycle TS **5e,f**.



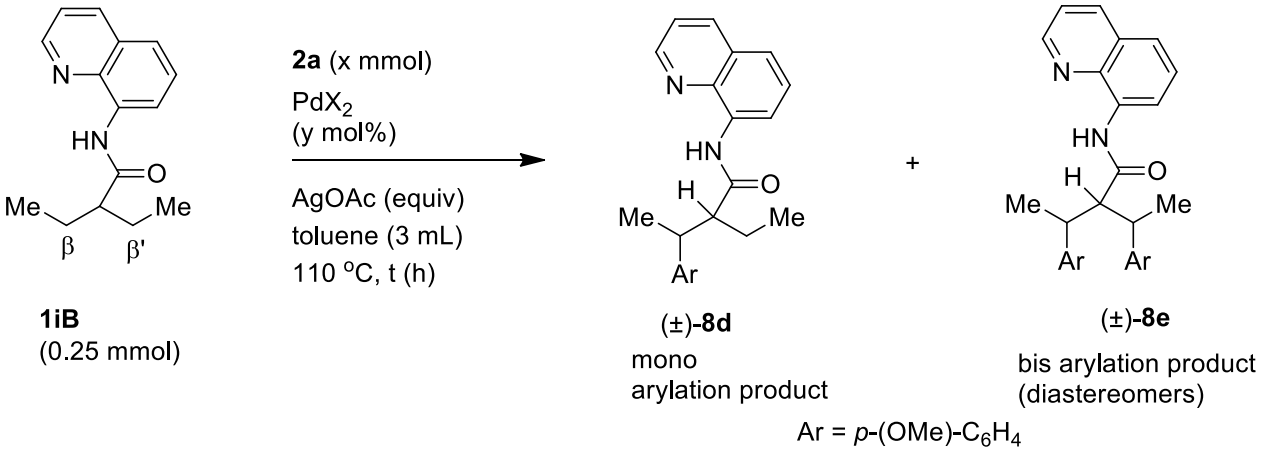
Scheme 6. Proposed reaction pathway in concurrence with the literature reports and plausible TS for the observed stereoselectivity (the structure of one of the plausible conformers **1a,j, 3/10** and **5a-d** is drawn just for understanding the observed *anti* stereochemistry of (±)-**3a-l**. However, considering the free C-C bond rotation, there will be more than one conformers of **1a,j, 3/10** and **5a-e**).



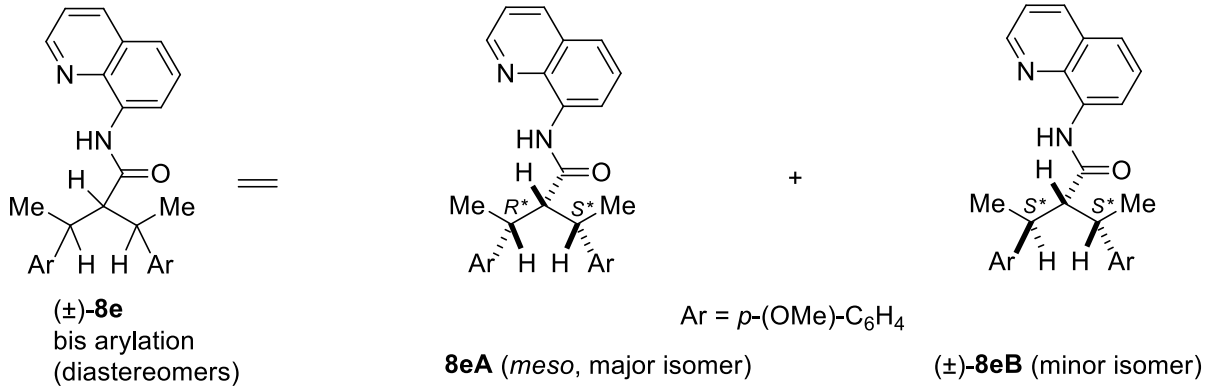
[a] The reaction was carried out using (±)-**1h** or (±)-**1iA** (0.25 mmol) and aryl halide (1 mmol, 4 equiv). The total yield of both the diastereomers is reported. The ratio of diastereomers was determined from the NMR spectra of the crude reaction mixture. The respective products (±)-**7a** and (±)-**7b** were obtained as diastereomers (dr 1:1).

Scheme 7. Bidentate ligand-directed Pd-catalyzed β-arylation of aliphatic carboxamides (±)-**1h** and (±)-**1iA**.

Table 3. Bidentate ligand-aided Pd-catalyzed double β-arylation of the prochiral 2^o sp^3 C-H bonds of aliphatic carboxamide **1iB**.

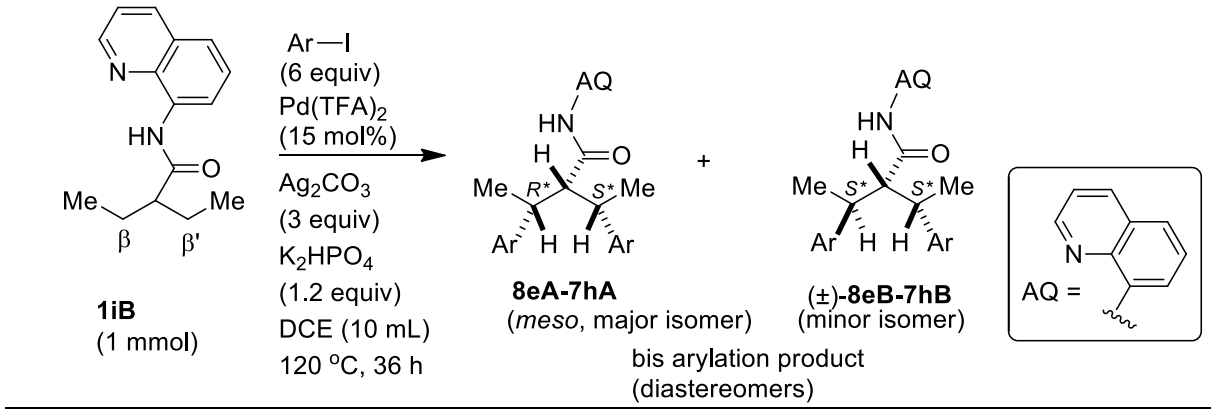


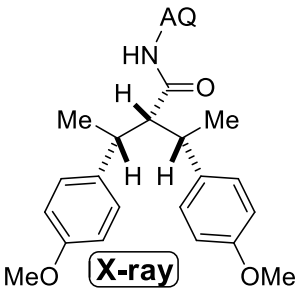
entry	**2a** (x mmol)	PdX_2 (y mol%)	AgOAc (equiv / mmol)	*t* (h)	yield (%) (±)-**8d**	yield (%) (±)-**8e** (dr)
1	1	$Pd(OAc)_2$ (5)	2.2 / 0.55	36	traces	8 (65:35)
2	1	$Pd(OAc)_2$ (10)	2.2 / 0.55	24	traces	19 (62:38)
3	1	$Pd(OAc)_2$ (10)	3.2 / 0.8	36	traces	16 (-)[b]
4	1.5	$Pd(OAc)_2$ (10)	3.2 / 0.8	36	traces	19 (-)[b]
5	6	$Pd(TFA)_2$ (15)	3 / 3[a]	36	traces	62 (70:30)



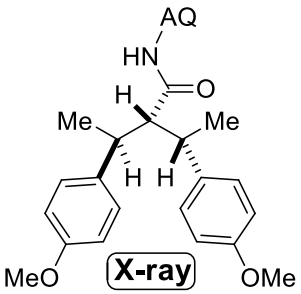
[a] This reaction was performed using (±)-**1iB** (1 mmol), $Pd(TFA)_2$ (15 mol%), Ag_2CO_3 (3 mmol, 3 equiv), K_2HPO_4 (1.2 mmol, 1.2 equiv) in DCE (10 mL) at 120 ^oC for 36 h. The total yield of both the diastereomers is reported. The ratios of diastereomers were determined from the NMR spectra of the crude reaction mixtures. [b] The dr was not determined in this case.

Table 4. Investigation on the Pd-catalyzed 8-aminoquinoline-aided diastereoselective double β-arylation of the sp^3 C-H bonds of aliphatic carboxamide (±)-1iB[a].



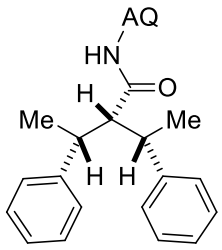


8eA; 40%

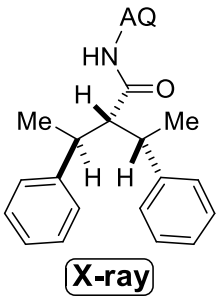


8eB; 22%

dr = **8eA**:**8eB** = 70:30

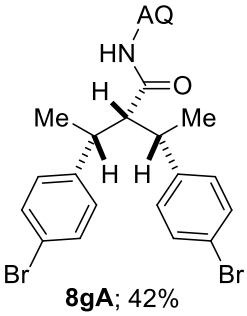


8fA; 50%

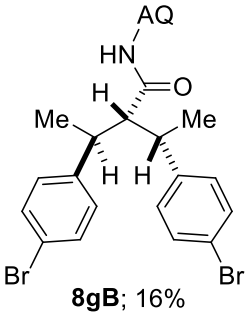


8fB; 21%

dr = **8fA**:**8fB** = 67:33

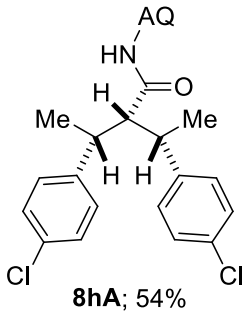


8gA; 42%

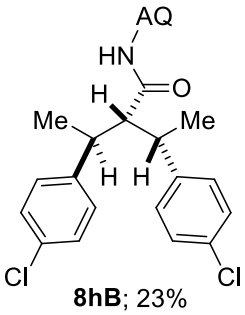


8gB; 16%

dr = **8gA**:**8gB** = 75:25



8hA; 54%



8hB; 23%

dr = **8hA**:**8hB** = 74:26

Successively, it was intended to explore the Pd(II)-catalyzed 8-aminoquinoline-enabled diastereoselective sp^3 C-H arylation of aliphatic carboxamides having bulky substituents at both the α- and β-positions as shown in Scheme 7. In this regard, initially the C-H arylation reaction of substrate (±)-**1h** with **2a** was performed and this reaction failed to give the corresponding β-C-

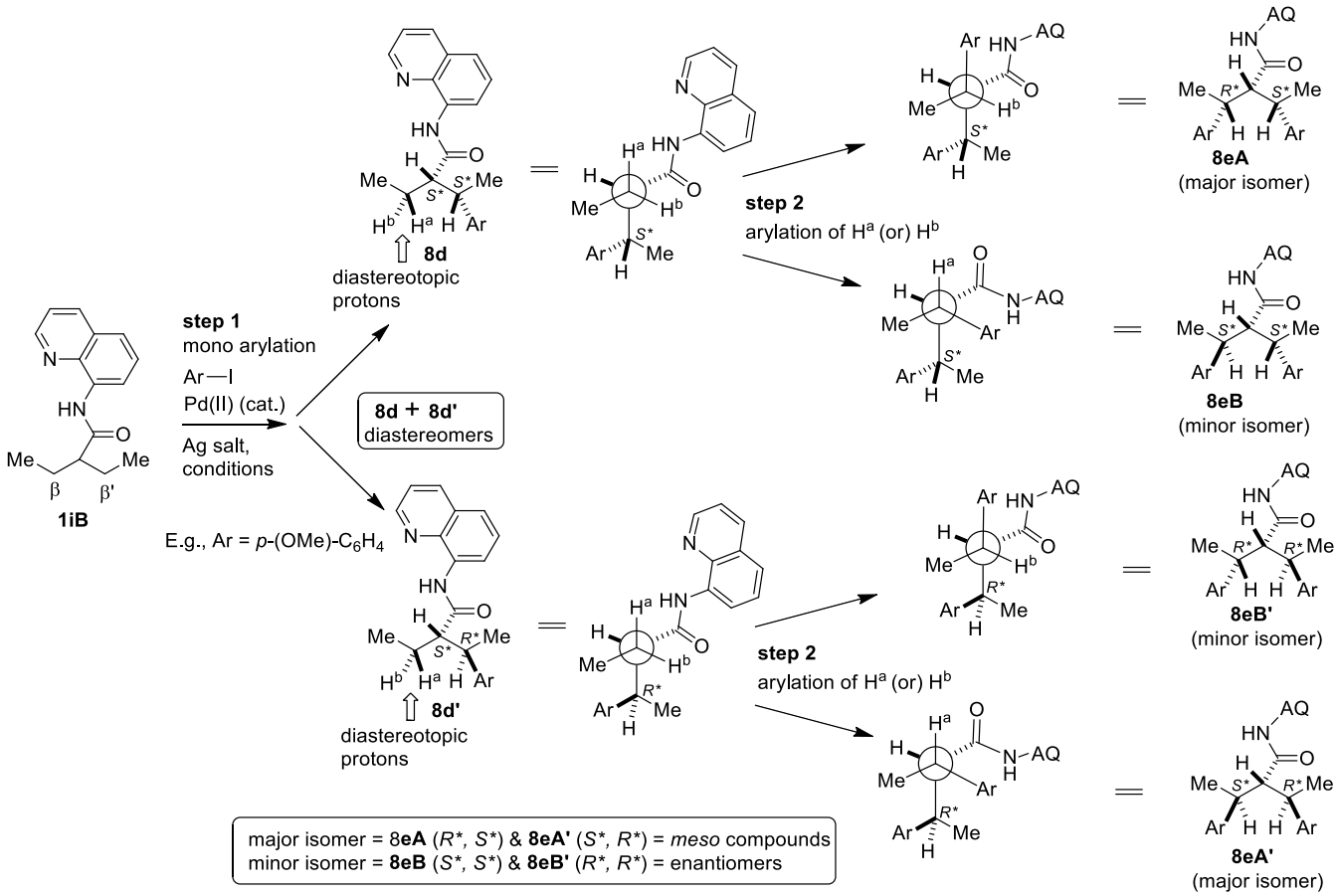
H arylated product (±)-**6a**. Presumably, the presence of the bulky *tertiary* butyl group at the α-position might have hindered the β-C-H arylation. Then, the substrate (±)-**1iA** having an ester group (COOEt) at the α-position was assembled. The Pd(II)-catalyzed β-C-H arylation of the compound (±)-**1iA** with aryl iodides, such as 2-iodothiphene and 1-iodo-4-methoxybenzene, afforded the corresponding products (±)-**7a** and (±)-**7b** in 65 and 50% yields (Scheme 7). Unlike in the substrate (±)-**1h**, the presence of COOEt moiety at the α-position of substrate (±)-**1iA** did not hinder the β-C-H arylation of the prochiral 2^o sp^3 C-H bond of the substrate (±)-**1iA**. Notably, the corresponding products (±)-**7a** and (±)-**7b** were obtained as diastereomers and the diastereomeric ratio was found to be 1:1. Perhaps, this could be because of the following reasons; (a) there is only a slight difference between the two structurally similar aryl groups present at the β-carbon, and (b) the compounds **7c,b** contain an acidic proton at the α-carbon, which may be not configurationally stable under the experimental condition.

Successively, it was planned to explore the Pd(II)-catalyzed 8-aminoquinoline-enabled double C-H arylation of a suitable substrate containing two sp^3 prochiral centers. Accordingly, substrate **1iB** was prepared from 2-ethylbutanoyl chloride and the bidentate directing group 8-aminoquinoline. Then, to find out the best reaction conditions to obtain the double C-H arylated product from the compound **1iB**, the optimization reactions were performed as shown in Table 3, which comprises of the Pd(II)-catalyzed C-H arylation of substrate **1iB** with **2a**.

The reaction of a mixture of **1iB**, **2a** and AgOAc in the presence of $Pd(OAc)_2$ catalyst furnished the double C-H arylated product **8eA** (*meso*) and (±)-**8eB** in 8% yield and the diastereoselectivity was found to be 65:35 (entry 1, Table 3). To improve the yield, the double C-H arylation of substrate **1iB** was performed by using different reaction conditions. However, attempts were not fruitful and the diastereomers **8eA** (*meso*) and (±)-**8eB** were obtained without any further improvement in the overall yield (entries 2-4, Table 3). Then, the double C-H arylation of substrate **1iB** with **2a** (6 mmol) was performed by using Ag_2CO_3 as an additive and $Pd(TFA)_2$ catalyst in DCE at 120 ^oC for 36 h. This reaction afforded the double C-H arylated products *meso*-**8eA** (40%, major isomer) and (±)-**8eB** (22%, minor isomer) in good yields (total yield = 62%, dr 70:30, entry 5, Table 3). Subsequently, by using this reaction condition, the double C-H arylation reaction of substrate **1iB** was performed with different aryl iodides. These

reactions commendably afforded the corresponding products **8fA-hA** (*meso*) and (±)-**8fB-hB** in good yields (Table 4). The diastereomers **8fA-hA** (*meso*) and (±)-**8fB-hB** were isolated in pure form and characterized by NMR and HRMS analyses. The stereochemistry of the compounds *meso*-**8eA-hA** (major isomers) and (±)-**8eB-hB** (minor isomers) was assigned based on the single crystal X-ray structures (Figure 2) of **8eA** (*meso*, major isomer), (±)-**8eB** (minor isomer) and (±)-**8fB** (minor isomer) and the similarity in their NMR spectral pattern. In addition to the unambiguous assignment of the stereochemistry of the corresponding diastereomers *meso*-**8eA-hA** (major isomers) and (±)-**8eB-hB** (minor isomers) based on the single crystal X-ray structure analysis (Figure 2) of the diastereomers *meso*-**8eA** (major isomer), (±)-**8eB** (minor isomer) and (±)-**8fB** (minor isomer); the NMR spectral pattern of the respective series of the major diastereomers *meso*-**8eA-hA** and minor diastereomers (±)-**8eB-hB** were compared. Typically, since the major diastereomers **8eA-hA** have a molecular symmetry (absolute configuration, *3S*,2R**), only half of the required ^{13}C NMR signals were present in the ^{13}C NMR spectra of the corresponding major diastereomers *meso*-**8eA-hA**. On the other hand, the minor diastereomers (±)-**8eB-hB** (absolute configuration, *3S*,2S**) are structurally unsymmetrical and do not have a molecular symmetry. Hence, all the required ^{13}C NMR signals were present in the ^{13}C NMR spectra of the corresponding minor diastereomers (±)-**8eB-hB**.

Characteristically, the formation of two diastereomers *meso*-**8eA-hA** and (±)-**8eB-hB** can be rationalized based on the proposed reaction pathway as shown in Scheme 8. The substrate **1iB** has two chemically equivalent 2^{o} prochiral centers. The C-H arylation of these centers could have occurred stepwise and perhaps not simultaneously. Efforts to isolate the mono arylated product (±)-**8d** (structure of one of the diastereomers) was not fruitful as only traces of (±)-**8d** was present in the crude reaction mixture. Further, in all the reactions which were performed to optimize the reaction conditions, only the double C-H arylated products *meso*-**8eA** and (±)-**8eB** were isolated in pure forms (Table 3). It is believed that the direct double C-H arylation reaction seems to be a facile reaction and even by reducing the concentration of the aryl iodide **2a**, the mono arylated product (±)-**8d** was not obtained.



Scheme 8. The structure of one of the plausible conformers is drawn just for understanding the observed stereocontrol and the stereochemistry of *meso*-**8eA** (major isomer), (±)-**8eB** (minor isomer). However, considering the free C-C bond rotation, there will be more than one conformers. **Scheme 8.** Formation of diastereomers *meso*-**8eA** (major isomer (*R**, *S**)) and (±)-**8eB** (minor isomer (*S**, *S**)).

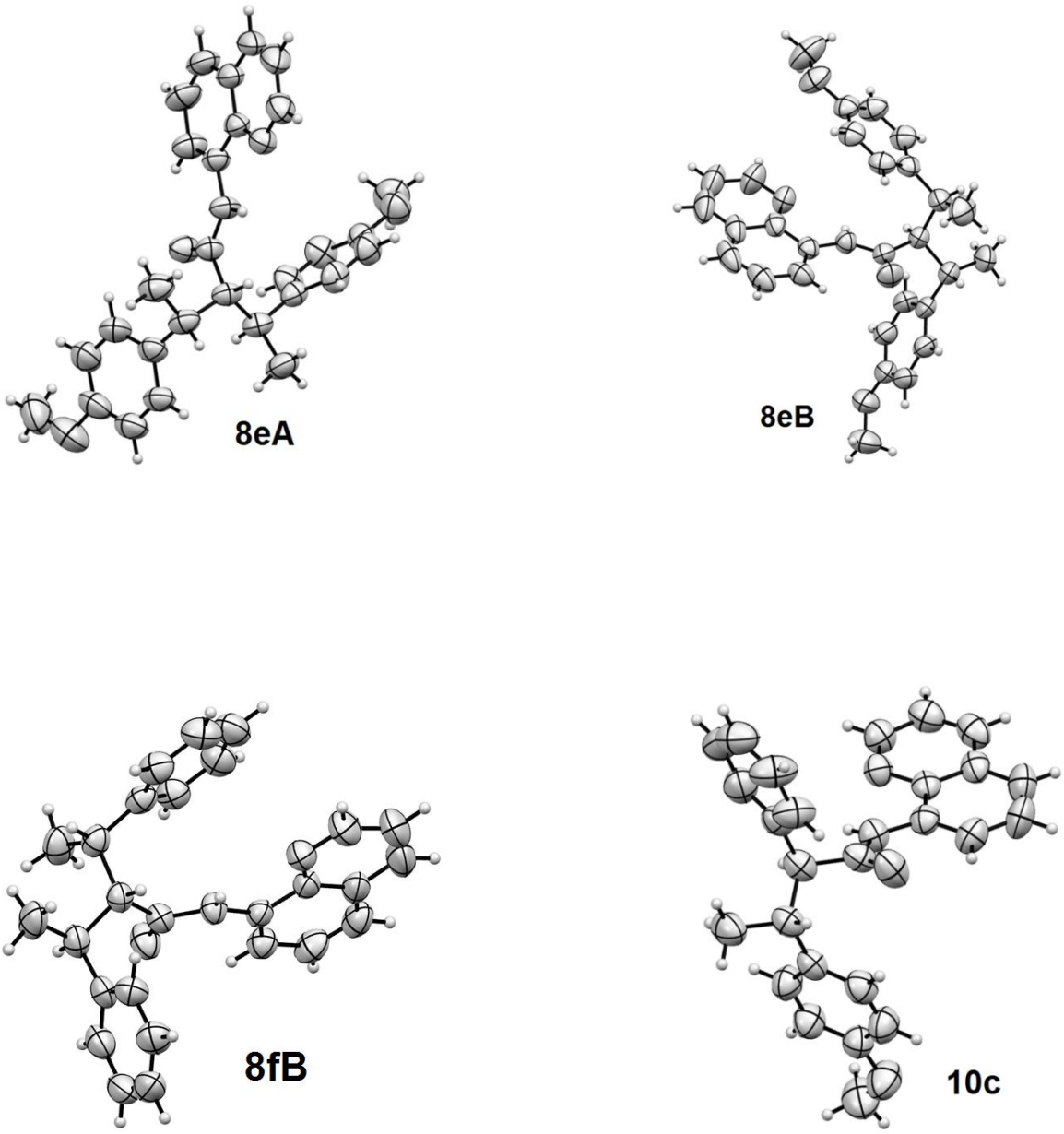


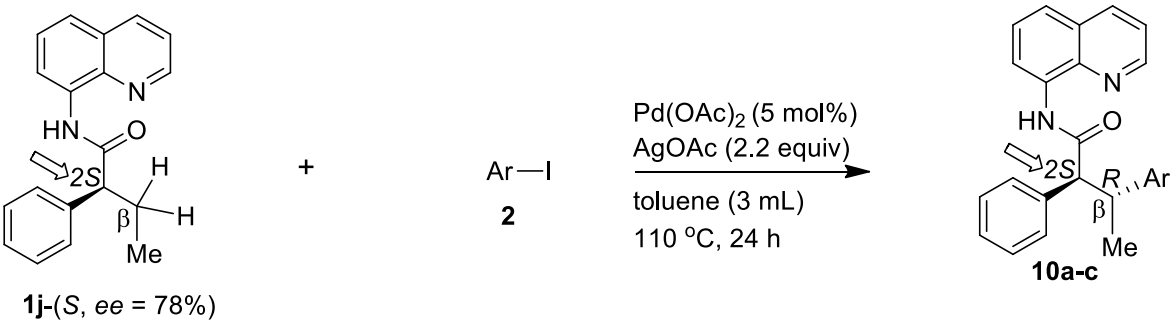
Figure 2. X-ray structures of *meso*-**8eA** (major isomer), (±)-**8eB** (minor isomer), (±)-**8fB** (minor isomer) and **10c** (enantiomerically enriched, major isomer).

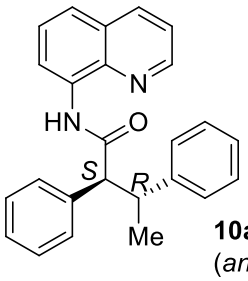
The mono C-H arylated product (±)-**8d** contains two diastereotopic C(β)-H^a and C(β)-H^b bonds and as a result, the second C-H arylation of these diastereotopic C(β)-H^a and C(β)-H^b bonds led to the formation of the corresponding diastereomers *meso*-**8eA** (*R**, *S**) and (±)-**8eB** (*S**, *S**). These deliberation accounts for the formation of two diastereomers *meso*-**8eA** (*R**, *S**) and (±)-

8eB (*S**, *S**) from the second C-H arylation of the mono arylated compound (±)-**8d**. One cannot ignore the instance that at first, the mono arylated product also could have formed as the diastereomers (±)-**8d** and (±)-**8d′** from the starting material **1iB** (Scheme 8). Hence, by considering this instance, it is proposed that the respective diastereomers (±)-**8d** and (±)-**8d′** independently underwent the subsequent second C-H arylation and gave the corresponding pair of diastereomers (Scheme 8). Accordingly, the diastereomers **8eA** (*R**, *S**) and **8eB** (*S**, *S**) were formed from the second C-H arylation of an intermediate substrate (±)-**8d** and the diastereomers **8eA′** (*S**, *R**) and **8eB′** (*R**, *R**) were formed from the second arylation of an intermediate substrate (±)-**8d′**. Basically, **8eA** (*R, S*) and **8eA′** (*S, R*) are *meso* compounds and **8eB** (*S, S*) and **8eB′** (*R, R*) are a pair of enantiomers. Since the diastereomers (±)-**8d** and (±)-**8d′** are not enantiomerically enriched compounds, eventually, the Pd-catalyzed second C-H arylation of the two diastereomers (±)-**8d** and (±)-**8d′** afforded the corresponding *meso* compound **8eA/8eA′** and racemic compound **8eB/8eB′** (Scheme 8).

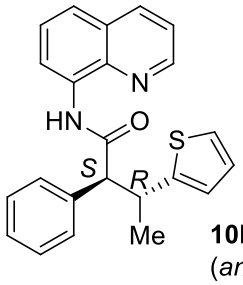
Then, it was envisaged to expand the scope of this protocol by synthesizing enantiomerically enriched β-arylated 2-phenyl-*N*-(quinolin-8-yl)butanamides through the Pd(II)-catalyzed C-H arylation strategy. Accordingly, at first the enantiomerically enriched substrate (*S*)-**1j** (Table 5) was prepared from enantiomerically enriched 2-phenylbutanoyl chloride and 8-aminoquinoline. Then, the $Pd(OAc)_2$-catalyzed β-arylation of enantiomerically enriched substrate (*S*)-**1j** (with ee 78%) with different aryl iodides were performed. These reactions furnished the corresponding C-H arylated products **10a-c** (*anti*, major diastereomers) in 68-93% yields with good diastereoselectivities and ee up to 78% for the *anti* diastereomers (Table 5). In all these reactions, attempts were made to obtain the major and minor isomers in pure form. However, only the major diastereomers (*anti* isomers) were isolated in pure form and the minor isomers could not be isolated in pure form. The *anti* stereochemistry of the major compounds **10a-c** (*2S,3R, anti* isomer) were assigned on the basis of the X-ray structures of the major isomers **3b,c,e,l** (racemic compounds) and the major isomer **10c** (enantiomerically enriched compound) coupled with the similarity in their NMR pattern.

Table 5. Synthesis of enantiomerically enriched β-arylated **10a-c** from the Pd-catalyzed β-arylation of (*S*)-**1j**[a].

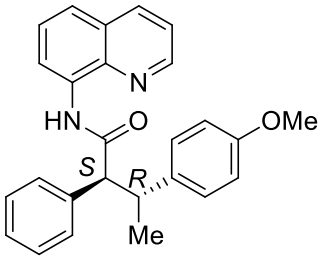




10a; 68%
(*anti/syn* = 80:20)
(anti: ee = 78%)



10b; 86%
(*anti/syn* = 77:23)
(anti: ee = 75%)



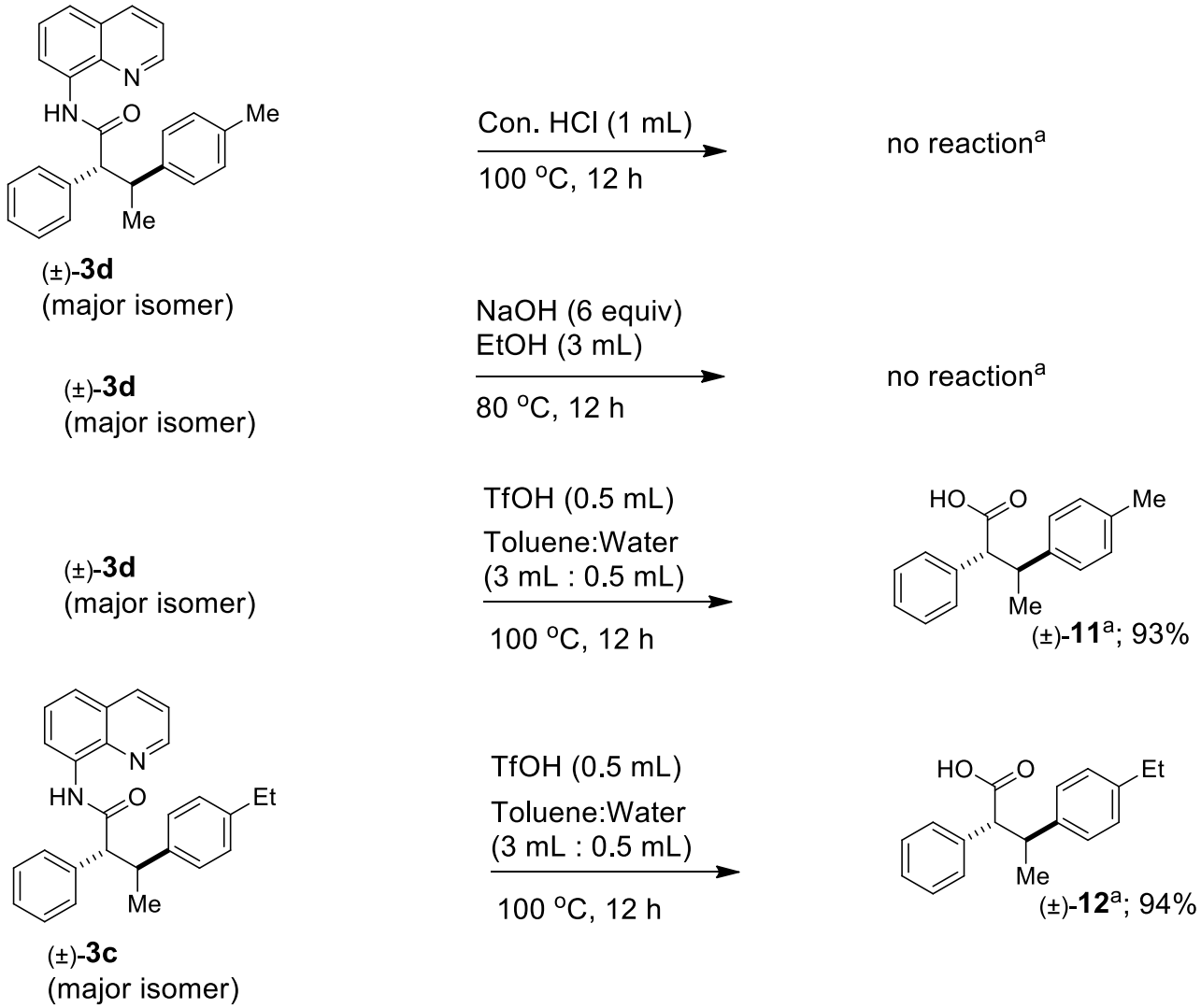
10c; 93%
(*anti/syn* = 78:22)
(anti: ee = 73%)

10c; *anti*
X-ray

[a] The reaction was carried out using (*S*)-**1j** (0.25 mmol) and aryl halide (1 mmol, 4 equiv). The total yield of both the diastereomers is reported. The ratios of diastereomers were determined from the NMR spectra of crude reaction mixtures and ee was determined from the HPLC analysis.

Furthermore, it was envisaged to perform the amide hydrolysis reactions to remove the 8-aminoquinoline by using the representative major isomers (±)-**3d** and (±)-**3c** (diastereomers with *anti* stereochemistry). Accordingly, the hydrolysis of the major isomer (±)-**3d** (diastereomers with *anti* stereochemistry) was attempted and the hydrolysis of (±)-**3d** under the well-known

amide hydrolysis reaction conditions involving the standard reagents, such as HCl or NaOH failed to afford the corresponding carboxylic acid (±)-**11** (Scheme 9). With further trials, it was found that the hydrolysis of the major isomer (±)-**3d** underwent in the presence of triflic acid (TfOH) gave the carboxylic acid (±)-**11**. Similarly, the amide hydrolysis of the major isomer (±)-**3c** in the presence of triflic acid (TfOH) also gave the corresponding carboxylic acid (±)-**12**.



[a] The reaction was carried out using 0.25 mmol of **(±)-3d** or **(±)-3c**.

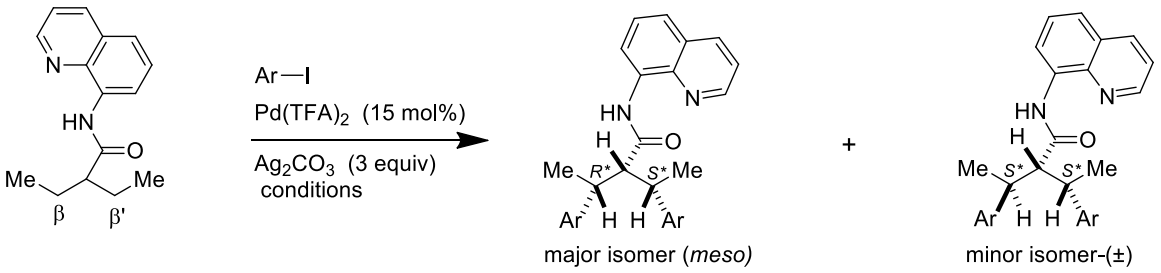
Scheme 9. Removal of the 8-aminoquinoline ligand and synthesis of carboxylic acids **11** and **12.**

Summary

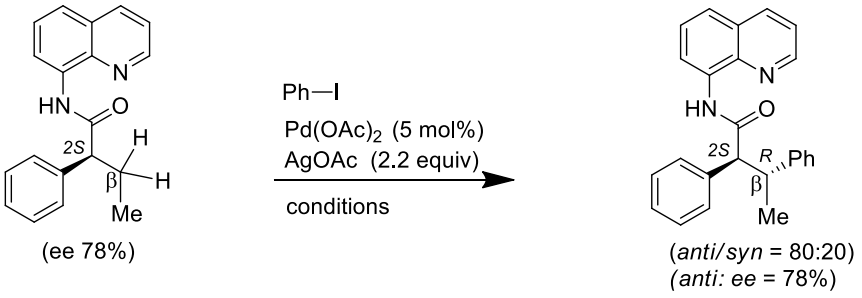
In summary, in this Chapter studies on the Pd(II)-catalyzed 8-aminoquinoline-aided diastereoselective β-C-H arylation of the prochiral 2^o sp^3 C-H bonds of various racemic aliphatic carboxamides are shown. The Pd(II)-catalyzed β-C-H arylation of racemic 2-phenylbutanamide substrate with aryl iodides gave several β-C-H arylated products possessing two vicinal stereocenters (dr up to 86:14).

It is a limitation that the β-C-H arylation of the prochiral 2^o sp^3 C-H bonds of aliphatic carboxamides having a substituent at the γ-position gave the β-C-H arylated products with poor diastereoselectivities. The β-C-H arylation of the prochiral 2^o sp^3 C-H bonds of an aliphatic carboxamide having a bulky *tertiary* butyl substituent at the α-position did not give any products. On the other hand, the β-C-H arylation of the prochiral 2^o sp^3 C-H bond of an aliphatic carboxamide having COOEt as a substituent at the α-position also afforded the corresponding product with poor diastereoselectivities.

Notably, the Pd(II)-catalyzed 8-aminoquinoline-aided double C-H arylation of 2-ethyl-*N*-(quinolin-8-yl)butanamide possessing two chemically equivalent 2^o sp^3 prochiral centers gave the corresponding double C-H arylated products as diastereomers.



The Pd(II)-catalyzed β-C-H arylation of enantiomerically enriched (*S*)-2-phenylbutanamide with different aryl iodides gave the corresponding enantiomerically enriched β-C-H arylated 2-phenylbutanamides.



Overall, the present work revealed a contemporary method for the stereoselective synthesis of several β-C-H arylated aliphatic carboxamides *via* the β-C-H activation method. The stereochemistry of the representative diastereomers was unambiguously established and the outcome of the stereocontrol and limitations in the Pd-catalyzed C-H activation process involving aliphatic carboxamides were also demonstrated.

Experimental Section

General.[39-42] All the reactions were performed using anhydrous solvents under nitrogen. Organic layers after the work up procedure were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis (TLC) was performed on silica gel plates and components were visualized by observation under iodine vapour. In the cases of the Tables 1-3,5 and Schemes 4,5,7 the total isolated yields of diastereomers were reported. In the case of Table 4, the isolated yields of individual diastereomers were reported. Yields of all the reactions were not optimized. The diastereomeric ratios were obtained from the integration of the ^{1}H NMR signal corresponding to the same proton of the major and minor isomers in ^{1}H NMR spectra of the respective crude reaction mixtures. After the Pd-catalyzed C-H arylation reaction, the purification of the crude reaction mixture gave the corresponding diastereomers as a mixture since the corresponding diastereomers had the same R_f values (at this stage, the total isolated yield of the corresponding diastereomers was calculated). Then, the corresponding diastereomers were again subjected to the column chromatographic purification to obtain the major and minor isomers in pure forms. In majority of the cases, the column chromatographic purification of the crude reaction mixtures gave only the corresponding major diastereomers in pure forms and the corresponding minor isomers could not be separated from the corresponding major isomers.

Additionally, in none of the case (except Table 4 compounds), the complete isolation of the corresponding major isomer also was possible and only a few fractions of the corresponding major isomers were obtained, which were used to characterize the respective major isomer. In some cases, the products were isolated as a mixture of inseparable diastereomers. The HPLC analyses were performed using AD-H (0.46 cm IDR, 25 cm length) as a chiral column.

General procedure for the synthesis of the carboxamides (±)**-1a-1h, 1iB and 1j-**(*S*).

The corresponding carboxylic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h at rt under nitrogen. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under nitrogen. Then, the DCM solution of acid chloride was added to another RB flask containing the corresponding auxiliary (amine, 1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL) at 0 ^oC. Then, reaction mixture was stirred at rt for 10 min and then, 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 = 15:85) furnished the corresponding carboxamides (±)**-1a-1h, 1iB** and **1j-**(*S*).

(±)-2-Phenyl-*N*-(quinolin-8-yl)butanamide (1a): Following the general procedure, **1a** (203 mg, 70%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.48; mp 99-101 ^oC; IR (KBr) ν_{max} 3343, 2964, 2630, 1678, 1532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.98 (1 H , br. s), 8.87 (1 H, dd, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 8.62 (dd, 1H, J_1 = 4.2, J_2 = 1.6 Hz), 7.85 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.55 (2 H, d, J = 7.2 Hz), 7.43-7.37 (3 H, m), 7.30-7.26 (2 H m), 7.18 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 3.66 (1 H, t, J = 7.6 Hz), 2.46-2.35 (1 H m), 2.07-1.96 (1 H m), 1.02 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.1, 148.1, 140.0, 138.2, 136.1, 134.5, 128.9, 128.1, 127.7, 127.4, 127.2, 121.5, 121.5, 116.3, 56.7, 26.8, 12.5; HRMS: *m/z* $[M + H]^+$, found 291.1494, $C_{19}H_{19}N_2O$ requires 291.1497.

(±)-2-Phenyl-*N*-(pyridin-2-ylmethyl)butanamide (1b): Following the general procedure, **1b** (107 mg, 42%) was obtained after purification by column chromatography on neutral alumina as a brown color liquid; R_f (20% EtOAc/Hexanes) 0.1; IR (thin film) ν_{max} 3278, 2960, 2929, 1658, 1528, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (1 H, dd, J_1 = 5.8, J_2 = 1.7 Hz), 7.60 (1 H, td, J_1 = 7.7, J_2 = 1.8 Hz), 7.36-7.23 (5 H, m), 7.16-7.13 (2 H, m), 6.95 (1 H, br. s), 4.55 (1 H, dd, J_1 = 16.2, J_2 = 5.3 Hz), 4.45 (1 H, dd, J_1 = 16.3, J_2 = 5.1 Hz), 3.36 (1 H, t, J = 7.6 Hz), 2.26-2.15 (1 H , m), 1.89-1.78 (1 H, m), 0.89 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.7, 156.7, 148.9, 140.0, 136.8, 128.7, 128.0, 127.1, 122.3, 122.0, 55.1, 44.5, 26.5, 12.4; HRMS: *m/z* $[M + H]^+$, found 255.1509, $C_{16}H_{19}N_2O$ requires 255.1497.

(±)-2-Phenyl-*N*-(pyridin-2-yl)butanamide (1c): Following the general procedure, **1c** (150 mg, 63%) was obtained after purification by column chromatography on alumina gel as colourless liquid; R_f (20% EtOAc/Hexanes) 0.1; IR (thin film) ν_{max} 3299, 2965, 2874, 1693, 1523, 1433, 1296 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.61 (1 H, br. s), 8.27 (1 H, d, J = 8.4 Hz), 8.23 (1 H, dd, J_1 = 4.9, J_2 = 1.0 Hz) 7.72-7.68 (1 H, m), 7.35-7.25 (5 H m), 7.04-7.00 (1 H, m), 3.41 (1 H, t, J = 7.5 Hz), 2.31-2.20 (1 H, m), 1.92-1.81 (1 H, m), 0.92 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.3, 151.6, 147.6, 139.2, 138.5, 128.9, 127.9, 127.5, 119.8, 114.3, 56.1, 26.4, 12.3; HRMS: *m/z* $[M + H]^+$, found 241.1350, $C_{15}H_{17}N_2O$ requires 241.1341.

(±)-*N*-(2-(Dimethylamino)ethyl)-2-phenylbutanamide (1d): Following the general procedure, **1d** (59 mg, 25%) was obtained after purification by column chromatography on neutral alumina as a brown colour liquid; R_f (10% EtOAc/Hexanes) 0.1; IR (thin film) ν_{max} 3292, 3063, 1809, 1658, 1649, 1552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.22 (5 H, m), 6.44 (1 H, br. s), 3.39-3.31 (1 H, m), 3.27-3.20 (2 H, m), 2.43-2.32 (2 H, m), 2.18 (6 H, s), 2.14-2.11 (1 H , m), 1.84-1.73 (1 H, m), 0.88 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.8, 140.3, 128.6, 127.9, 127.0, 57.8, 55.1, 44.9, 36.7, 26.5, 12.3; HRMS: *m/z* $[M + H]^+$, found 235.1803, $C_{14}H_{23}N_2O$ requires 235.1810.

(±)-*N*-(2-(Methylthio)phenyl)-2-phenylbutanamide (1e): Following the general procedure, **1e** (214 mg, 75%) was obtained after purification by column chromatography on Alumina as a colourless solid; R_f (10% EtOAc/Hexanes) 0.60; mp 60-62 ^oC; IR (KBr) ν_{max} 3278, 2960, 2929,

1658, 1528, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.41 (1 H, br. s), 8.38 (1 H, d, J = 8.3 Hz), 7.46-7.38 (5 H, m), 7.34-7.28 (2 H, m), 7.02 (1 H, td, J_1 = 7.6, J_2 = 1.2 Hz), 3.53 (1 H, dd, J_1 = 8.3, J_2 = 7.0 Hz), 2.40-2.32 (1 H , m), 2.03 (3 H, s), 2.02-1.92 (1 H, m), 0.99 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.9, 139.4, 138.8, 133.7, 129.3, 129.1, 128.2, 127.6, 124.9, 124.1, 120.2, 56.5, 25.7, 18.8, 12.4; HRMS: *m/z* $[M + H]^+$, found 286.1259, $C_{17}H_{20}NOS$ requires 286.1266.

(±)-4-Methyl-*N*-(quinolin-8-yl)nonanamide (1f): Following the general procedure, **1f** (235 mg, 79%) was obtained after purification by column chromatography on silica gel as a colourless liquid; R_f (15% EtOAc/Hexanes) 0.55; IR (thin film) ν_{max} 3356, 2925, 2859, 1688, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.84 (1 H , br. s), 8.84-8.80 (2 H, m), 8.18 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.58-7.49 (2 H, m), 7.47 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 2.66-2.52 (2 H, m), 1.93-1.85 (1 H, m), 1.70-1.54 (2 H, m), 1.41-1.17 (8 H, m), 0.97 (3 H, d, J = 6.6 Hz), 0.90 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2, 148.1, 138.3, 136.4, 134.6, 127.9, 127.5, 121.6, 121.3, 116.4, 36.8, 36.0, 32.6, 32.6, 32.2, 26.7, 22.7, 19.5, 14.1; HRMS: *m/z* $[M + H]^+$, found 299.2131, $C_{19}H_{27}N_2O$ requires 299.2123.

(±)-4-Ethyl-*N*-(quinolin-8-yl)octanamide (1g): Following the general procedure, **1g** (247 mg, 83%) was obtained after purification by column chromatography on silica gel as a colourless liquid; R_f (15% EtOAc/Hexanes) 0.53; IR (thin film) ν_{max} 3356, 2956, 2863, 1688, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.83 (1 H, br. s), 8.82-8.80 (2 H, m), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.56-7.44 (3 H, m), 2.58-2.54 (2 H, m), 1.84-1.78 (2 H, m), 1.41-1.31 (9 H, m), 0.92 (6 H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2, 148.1, 138.3, 136.4, 134.6, 127.9, 127.5, 121.6, 121.3, 116.4, 38.5, 35.6, 32.6, 28.9, 28.9, 25.7, 23.1, 14.2, 10.8; HRMS: *m/z* $[M + H]^+$, found 299.2128, $C_{19}H_{27}N_2O$ requires 299.2123.

(±)-2-Benzyl-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (1h): Following the general procedure, **1h** (315 mg, 95%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (15% EtOAc/Hexanes) 0.47; mp 104-106 ^oC; IR (KBr) ν_{max} 3364, 2961, 2896, 1677, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.56 (1 H, br. s), 8.81 (1 H, dd, J_1 = 7.6, J_2 = 1.3 Hz), 8.71 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.07 (1 H, dd, J_1 = 8.2, J_2 = 1.6

Hz), 7.51 (1 H, t, J = 8.2 Hz), 7.44 (1 H, dd, J_1 = 8.2, J_2 = 1.3 Hz), 7.36 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.30 (2 H, d, J = 7.1 Hz), 7.21 (2H, t, J = 7.4 Hz), 7.09 (1 H, t, J = 7.4 Hz), 3.25 (1 H, dd, J_1 = 13.3, J_2 = 11.6 Hz), 2.96 (1 H, dd, J_1 = 13.3, J_2 = 2.4 Hz), 2.53 (1 H, dd, J_1 = 11.5, J_2 = 2.6 Hz), 1.22 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.8, 148.0, 140.9, 138.3, 136.2, 134.3, 128.8, 128.4, 127.8, 127.3, 126.0, 121.4, 121.3, 116.4, 62.1, 34.4, 33.8, 28.2; HRMS: *m/z* $[M + H]^+$, found 333.1966, $C_{22}H_{25}N_2O$ requires 333.1970.

(*S*)-2-Phenyl-*N*-(quinolin-8-yl)butanamide (1j): Following the general procedure, **1j** (ee 78%) (168 mg, 58%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.51; mp 82-84 ^{o}C; IR (KBr) ν_{max} 3349, 2964, 2871, 1693, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.95 (1H, br. s), 8.81 (1 H, dd, J_1 = 7.4, J_2 = 1.4 Hz), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.12 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.54-7.46 (4 H, m), 7.44-7.38 (3 H, m), 7.30 (1 H, t, J = 7.3 Hz), 3.66 (1 H, t, J = 7.6 Hz), 2.43-2.32 (1 H, m), 2.06-1.95 (1 H, m), 1.03 (3 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2, 148.1, 139.9, 138.4, 136.2, 134.5, 128.9, 128.1, 127.8, 127.3, 127.3, 121.5, 121.5, 116.3, 56.8, 26.7, 12.5; HRMS: *m/z* $[M + H]^+$, found 291.1497, $C_{19}H_{19}N_2O$ requires 291.1497.

2-Ethyl-*N*-(quinolin-8-yl)butanamide (1iB): Following the general procedure, **1iB** (208 mg, 86%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (15% EtOAc/Hexanes) 0.58; mp 58-60 ^{o}C; IR (KBr) ν_{max} 3356, 2962, 2631, 1687, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.88 (1 H, br. s), 8.87 (1 H, dd, J_1 = 7.5, J_2 = 1.3 Hz), 8.80 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.11 (1 H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.54-7.45 (2 H, m), 7.41 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 2.35-2.29 (1 H, m), 1.88-1.79 (2 H, m), 1.70-1.60 (2 H, m), 1.01 (6 H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.8, 148.2, 138.4, 136.3, 134.5, 127.9, 127.4, 121.6, 121.4, 116.4, 52.6, 25.9, 12.1; HRMS: *m/z* $[M + H]^+$, found 243.1466, $C_{15}H_{19}N_2O$ requires 243.1497.

Procedures for the preparation of 1iA

Procedure for the preparation of ethyl 3-oxo-3-(quinolin-8-ylamino)propanoate 1i: Ethylmalonyl chloride (1 mmol)) was added dropwise to the mixture of 8-aminoquinoline (1

mmol) and Et_3N (1.1 mmol) dissolved in anhydrous DCM (5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 10 min and then, refluxed for 20 h. After the reaction period, the reaction mixture was extracted with DCM and washed with water followed by saturated $NaHCO_3$ solution. The collected organic layers were dried over anhydrous Na_2SO_4, concentrated under vacuum and purification of the crude reaction mixture by column chromatography (EtOAc/Hexanes = 20:80) furnished the product **1i**.

Ethyl 3-oxo-3-(quinolin-8-ylamino)propanoate (1i): Following the general procedure, **1i** (183 mg, 71%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.50; mp 98-100 ^oC; IR (KBr) ν_{max} 3312, 2984, 2938, 1739, 1486, 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.75 (1 H, br. s), 8.69 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.66 (1 H, dd, J_1 = 6.6, J_2 = 2.4 Hz), 7.95 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.37-7.31 (2 H, m), 7.26 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 4.18 (2 H, q, J = 7.2 Hz), 3.59 (2 H, s), 1.21 (3 H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.4, 163.5, 148.4, 138.4, 136.1, 134.2, 127.8, 127.0, 122.0, 121.5, 116.7, 61.7, 43.6, 14.0; HRMS: *m/z* $[M + H]^+$, found 259.1095, $C_{14}H_{15}N_2O_3$ requires 259.1083.

Procedure for the preparation of ethyl 2-benzyl-3-oxo-3-(quinolin-8-ylamino)propanoate (±)-1iA from 1i: Benzyl bromide (1.2 mmol) was added to a solution of ethyl 3-oxo-3-(quinolin-8-ylamino)propanoate (**1i**, 1 mmol) dissolved in dry THF (5 mL). Next, to this reaction mixture K_2CO_3 (3 mmol) was added under nitrogen at rt and then, the reaction mixture was refluxed for 20 h. After the reaction period, the reaction mixture was filtered to decant the inorganic salts, and then, the organic layers were concentrated under vacuum, purification of the crude reaction mixture by column chromatography (EtOAc/Hexanes = 30:70) furnished the product (±)-**1iA**.

(±)-Ethyl 2-benzyl-3-oxo-3-(quinolin-8-ylamino)propanoate (1iA): Following the general procedure, **1iA** (174 mg, 50%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.45; mp 73-75 ^oC; IR (KBr) ν_{max} 3323, 2963, 2913, 1731, 1672, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.59 (1 H, br. s), 8.86 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.79 (1 H, dd, J_1 = 5.9, J_2 = 3.1 Hz), 8.18 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.58-7.53 (2 H, m), 7.48 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.33-7.21 (5 H, m), 4.23 (2

H, q, J = 7.2 Hz), 3.88 (1 H, dd, J_1 = 8.8, J_2 = 6.6 Hz), 3.50-3.38 (2 H, m), 1.24 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.3, 166.0, 148.4, 138.6, 138.1, 136.3, 134.3, 129.0, 128.6, 127.9, 127.3, 126.8, 122.0, 121.7, 116.8, 61.8, 56.7, 35.9, 14.0; HRMS: *m/z* $[M + H]^+$, found 349.1556, $C_{21}H_{21}N_2O_3$ requires 349.1552.

General procedure for the β-arylation of aliphatic carboxamides and the preparation of the racemic compounds 3a-l, 4a-c, 5a, 6a-f, 8a-c, 8eA-hA, 8eB-hB and enantiomerically enriched 10a-c.

A mixture of the corresponding carboxamide ((±)-**1a-h** or (±)-**1iA** or **1iB** or **1j**-(*S*)) (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 5 mol%), aryl iodide (1.0 mmol, 4 equiv) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 ^oC for 24-70 h (see the respective Tables/Schemes for the reaction time for the specific examples) under nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding β-C-H arylated racemic compounds **3a-l**, **4a-c**, **5a**, **6a-f**, **8a-c**, **8eA-hA**, **8eB-hB** and enantiomerically enriched **10a-c** (see Tables/Schemes for the reaction conditions for the specific examples).

(*2R*,3S)-3-(4-Methoxyphenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3a):** Following the general procedure, **3a** (89 mg, 90%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.44; mp 96-98 ^oC; IR (KBr) ν_{max} 3328, 2959, 2927, 1683, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.61 (1 H, dd, J_1 = 6.9, J_2 = 2.2 Hz), 8.05 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.65 (2 H, d, J = 7.1 Hz), 7.43-7.36 (7 H, m), 7.33-7.29 (1 H, m), 6.80 (2 H, d, J = 8.7 Hz), 3.82 (1 H, d, J = 10.9 Hz), 3.77-3.71 (1 H, m), 3.68 (3 H, s), 1.13 (3 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.0, 158.0, 148.0, 138.8, 138.2, 137.3, 136.2, 134.4, 128.7, 128.6, 128.3, 127.7, 127.4, 127.2, 121.4, 121.2, 116.3, 113.8, 63.1, 55.1, 42.1, 20.3; HRMS: *m/z* $[M + H]^+$, found 397.1913, $C_{26}H_{25}N_2O_2$ requires 397.1916.

(*2R*,3S)-2,3-Diphenyl-*N*-(quinolin-8-yl)butanamide (3b):** Following the general procedure, **3b** (83 mg, 91%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (10% EtOAc/Hexanes) 0.46; mp 149-151 ^oC; IR (KBr) ν_{max} 3339, 2968, 2924, 1680, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.59 (1 H, dd, J_1 = 6.6, J_2 = 2.4 Hz), 8.05 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.66 (2 H, d, J = 7.1 Hz), 7.47 (2 H, d, J = 7.1 Hz), 7.43-7.25 (8 H, m), 7.13-7.08 (1H, m), 3.89 (1 H, d, J = 10.9 Hz), 3.83-3.73 (1 H, m), 1.15 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9, 148.0, 145.2, 138.7, 138.2, 136.2, 134.3, 128.8, 128.6, 128.5, 127.7, 127.5, 127.4, 127.2, 126.4, 121.4, 121.3, 116.3, 62.7, 43.0, 20.3; HRMS : *m/z* $[M + H]^+$, found 367.1821, $C_{25}H_{23}N_2O$ requires 367.1810. The NMR spectra of this compound contain traces of the corresponding minor isomer.

(*2R*,3S)-3-(4-Ethylphenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3c):** Following the general procedure, **3c** (88 mg, 90%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (10% EtOAc/Hexanes) 0.45; mp 122-124 ^oC; IR (KBr) ν_{max} 3338, 2966, 2925, 1676, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.67 (1H, br. s), 8.74 (1 H, dd, J_1 = 4.3, J_2 = 1.7 Hz), 8.60 (1 H, dd, J_1 = 7.2, J_2 = 1.8 Hz), 8.03 (1 H, dd, J_1 = 8.2, J_2 = 1.7 Hz), 7.66 (2 H, d, J = 7.1 Hz), 7.44-7.29 (8 H, m), 7.09 (2 H, d, J = 8.1 Hz), 3.87 (1 H, d, J = 10.9 Hz), 3.79-3.71 (1 H, m), 2.50 (2 H, q, J = 7.6 Hz), 1.14 (3 H, d, J = 6.9 Hz), 1.08 (3 H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.0, 147.9, 142.4, 142.1, 138.8, 138.2, 136.1, 134.4, 128.7, 128.6, 128.0, 127.7, 127.4, 127.2, 127.2, 121.4, 121.2, 116.2, 62.9, 42.6, 28.3, 20.3, 15.3; HRMS: *m/z* $[M + H]^+$, found 395.2123, $C_{27}H_{27}N_2O$ requires 395.2123.

(*2R*,3S)-2-Phenyl-*N*-(quinolin-8-yl)-3-(*p*-tolyl)butanamide (3d):** Following the general procedure, **3d** (85 mg, 89%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.44; mp 179-181 ^oC; IR (KBr) ν_{max} 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.60 (1 H, dd, J_1 = 6.2, J_2 = 2.8 Hz), 8.08 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.64 (2 H, d, J = 7.1 Hz), 7.44-7.38 (5H, m), 7.33 (2 H, d, J = 8.1 Hz), 7.31-7.29 (1 H, m), 7.06 (2 H, d, J = 7.8 Hz), 3.85 (1 H, d, J = 10.9 Hz), 3.76-3.68 (1 H, m), 2.20 (3 H, s), 1.12 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9, 147.9, 142.2, 138.8, 138.2, 136.2, 135.8, 134.4,

129.2, 128.7, 128.6, 127.7, 127.4, 127.2, 127.2, 121.4, 121.2, 116.3, 62.8, 42.5, 21.0, 20.4; HRMS: *m/z* $[M + H]^+$, found 381.1967, $C_{26}H_{25}N_2O$ requires 381.1967.

(*2R*,3S)-3-(4-Bromophenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3e):** Following the general procedure, **3e** (85 mg, 77%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; R_f (20% EtOAc/Hexanes) 0.67; mp 172-174 ^oC; IR (KBr) ν_{max} 3341, 2971, 2927, 1676, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.68 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.3, J_2 = 1.7 Hz), 8.58 (1 H, t, J = 4.6 Hz), 8.10 (1 H, dd, J_1 = 8.2, J_2 = 1.7 Hz), 7.62 (2 H, d, J = 7.1 Hz), 7.43-7.29 (10 H, m), 3.81 (1 H, d, J = 10.9 Hz), 3.77-3.68 (1 H, m), 1.11 (3 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.6, 148.1, 144.3, 138.3, 138.2, 136.3, 134.2, 131.6, 129.2, 128.8, 128.5, 127.8, 127.6, 127.2, 121.5, 121.4, 120.1, 116.3, 62.5, 42.4, 20.1; HRMS: *m/z* $[M + H]^+$, found 445.0917, $C_{25}H_{22}BrN_2O$ requires 445.0915. The NMR spectra of this compound contain traces of the corresponding minor isomer.

(*2R*,3S)-3-(4-Nitrophenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3f):** Following the general procedure, **3f** (82 mg, 80%) was obtained as a mixture of diastereomers after purification by column chromatography on silica gel as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.20; mp 142-144 ^oC; IR (KBr) ν_{max} 3333, 2968, 2929, 1679, 1526, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1 H , br. s), 8.73 (1 H, dd, J_1 = 4.3, J_2 = 1.6 Hz), 8.54 (1 H, dd, J_1 = 5.5, J_2 = 3.6 Hz), 8.12 (2 H, d, J = 8.8 Hz), 8.08 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.65-7.11 (10 H, m), 3.90-3.82 (2 H, m), 1.16 (3 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.6, 170.1, 153.2, 152.0, 148.3, 148.1, 146.6, 146.3, 138.3, 138.1, 137.8, 137.6, 136.4, 136.3, 134.3, 134.0, 129.0, 128.7, 128.6, 128.4, 128.4, 128.2, 127.9, 127.9, 127.8, 127.4, 127.3, 127.2, 123.8, 123.4, 121.9, 121.7, 121.7, 121.6, 116.6, 116.4, 62.1, 61.9, 43.7, 43.0, 20.9, 19.8; HRMS: *m/z* $[M + H]^+$, found 412.1641, $C_{25}H_{22}N_3O_3$ requires 412.1661. The compound **3f** was isolated as a mixture of diastereomers and the ^1H NMR data given here for the major isomer and the ^{13}C NMR values are given for both the diastereomers.

(*2R*,3S)-3-(4-Acetylphenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3g)**: Following the general procedure, **3g** (91 mg, 89%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; R_f (20% EtOAc/Hexanes) 0.18; mp

145-147 ^{o}C; IR (KBr) ν_{max} 3339, 2963, 2924, 1677, 1603, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1 H, br. s), 8.73 (1 H, dd, J_1 = 4.3, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 5.4, J_2 = 3.6 Hz), 8.05 (1 H, dd, J_1 = 8.2, J_2 = 1.7 Hz), 7.86 (2 H, d, J = 8.4 Hz), 7.65 (2 H, d, J = 7.1 Hz), 7.55 (2 H, d, J = 8.4 Hz), 7.44-7.29 (6 H, m) 3.91 (1 H, d, J = 10.9 Hz), 3.86-3.78 (1 H, m), 2.48 (3 H, s), 1.15 (3 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 197.9, 170.5, 151.1, 148.0, 138.2, 138.1, 136.2, 135.4, 134.1, 128.9, 128.7, 128.5, 127.7, 127.7, 127.7, 127.2, 121.5, 121.4, 116.3, 62.2, 43.0, 26.5, 20.0 ; HRMS: *m/z* $[M + H]^+$, found 409.1916, $C_{27}H_{25}N_2O_2$ requires 409.1916. The NMR spectra of this compound contain traces of the corresponding minor isomer.

(*2R*,3S)-3-(3-Nitrophenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3h):** Following the general procedure, **3h** (64 mg, 62%) was obtained as a mixture of diastereomers after purification by column chromatography on silica gel as a yellow solid; R_f (20% EtOAc/Hexanes) 0.20; mp 157-159 ^{o}C; IR (KBr) ν_{max} 3332, 2968, 2870, 1680, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1 H, br. s), 8.72 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.52 (1 H, dd, J_1 = 5.0, J_2 = 4.2 Hz), 8.36 (1 H, t, J = 1.9 Hz), 8.07 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.97-7.93 (1 H, m), 7.79-7.77 (1 H, m), 7.65 (2 H, d, J = 7.1 Hz), 7.57-7.10 (7 H, m), 3.93-3.83 (2 H, m), 1.18 (3 H, d, J = 6.4 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ_C 170.6, 170.1, 148.4, 148.3, 148.1, 147.4, 146.3, 138.3, 138.1, 137.8, 137.7, 136.4, 136.2, 134.6, 134.6, 134.3, 134.0, 129.3, 129.0, 128.9, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 122.4, 121.9, 121.8, 121.7, 121.7, 121.6, 121.6, 121.4, 116.6, 116.3, 62.3, 62.1, 43.5, 42.8, 21.0, 19.9; HRMS: *m/z* $[M + H]^+$, found 412.1646, $C_{25}H_{22}N_3O_3$ requires 412.1661. The compound **3h** was isolated as a mixture of diastereomers and the ^{1}H NMR data given here for the major isomer and the ^{13}C NMR values are given for both the diastereomers.

(*2R*,3S)-3-(3,4-Dimethylphenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3i):** Following the general procedure, **3i** (75 mg, 76%) was obtained after purification by column chromatography on silica gel as a brown colour solid; R_f (20% EtOAc/Hexanes) 0.43; mp 143-145 ^{o}C; IR (KBr) ν_{max} 3347, 2964, 2923, 1683, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.68 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.60 (1 H, dd, J_1 = 7.1, J_2 = 1.9 Hz), 8.05 (1 H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.66 (2 H, d, J = 7.4 Hz), 7.43-7.29 (6 H, m), 7.22-7.18 (2 H, m), 7.00 (1 H, d, J = 7.7 Hz), 3.87 (1 H, d, J = 10.9 Hz), 3.73-3.66 (1 H , m), 2.17 (3 H, s), 2.08 (3 H, s), 1.12 (3 H, d, J = 7.0

Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.1, 147.9, 142.6, 138.9, 138.2, 136.4, 136.1, 134.5, 134.4, 129.7, 128.7, 128.7, 128.6, 127.7, 127.4, 127.2, 124.5, 121.4, 121.1, 116.3, 62.7, 42.6, 20.5, 19.8, 19.3; HRMS (ESI): *m/z* $[M + H]^+$, found 395.2108, $C_{27}H_{27}N_2O$ requires 395.2123. The NMR spectra of this compound contain traces of the corresponding minor isomer.

(*2R*,3S)-3-(3,4-Difluorophenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3j):** Following the general procedure, **3j** (94 mg, 93%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colourless solid; R_f (10% EtOAc/Hexanes) 0.67; mp 182-184 ^{o}C; IR (KBr) ν_{max} 3339, 2970, 2924, 1674, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.58 (1 H, dd, J_1 = 5.5, J_2 = 3.5 Hz), 8.08 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.63 (2 H, d, J = 7.3 Hz), 7.46-7.25 (7 H, m), 7.18-7.14 (1 H, m), 7.05-6.98 (1 H, m), 3.78 (1 H, d, J = 10.8 Hz), 3.75-3.69 (1 H, m), 1.11 (3 H, d, J = 6.5 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ_C 170.4, 151.5 (d, $J_{C\text{-}F}$ = 12.7 Hz), 150.3 (dd, $J_{1C\text{-}F}$ = 246.0, $J_{2C\text{-}F}$ = 12.7 Hz), 149.0 (dd, $J_{1C\text{-}F}$ = 245.0, $J_{2C\text{-}F}$ = 12.7 Hz), 148.1, 142.3 (t, $J_{C\text{-}F}$ = 4.1 Hz), 138.2, 138.1, 136.3, 134.1, 128.9, 128.5, 127.8, 127.7, 127.2, 123.5 (dd, $J_{1C\text{-}F}$ = 5.9, $J_{2C\text{-}F}$ = 3.5 Hz), 121.5, 117.1 (d, $J_{C\text{-}F}$ = 16.8 Hz), 116.4, 116.1 (d, $J_{C\text{-}F}$ = 16.9 Hz), 62.7, 42.3, 20.0; HRMS: *m/z* $[M + H]^+$, found 403.1629, $C_{25}H_{21}F_2N_2O$ requires 403.1622.

(*2R*,3S)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (3k):** Following the general procedure, **3k** (69 mg, 65%) was obtained after purification by column chromatography on silica gel as a pale yellow colour solid; R_f (20% EtOAc/Hexanes) 0.21; mp 161-163 ^{o}C; IR (KBr) ν_{max} 3323, 2960, 2924, 1688, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.62 (1 H, dd, J_1 = 7.1, J_2 = 1.9 Hz), 8.06 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.63 (2 H, d, J = 7.1 Hz), 7.44-7.37 (5 H, m), 7.33-7.29 (1 H, m), 6.96-6.92 (2 H, m), 6.74 (1 H, d, J = 8.2 Hz), 4.16-4.09 (4 H, m), 3.79 (1 H, d, J = 10.9 Hz), 3.70-3.62 (1 H, m), 1.09 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9, 148.0, 143.3, 141.9, 138.7, 138.7, 138.2, 136.2, 134.4, 128.7, 128.6, 127.7, 127.4, 127.2, 121.4, 121.2, 120.5, 117.1, 116.3, 115.9, 64.3, 64.2, 62.9, 42.2, 20.4; HRMS: *m/z* $[M + H]^+$, found 425.1868, $C_{27}H_{25}N_2O_3$ requires 425.1865.

(*2R*,3S)-2-Phenyl-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)butanamide (3l):** Following the general procedure, **3l** (83 mg, 90%) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (15% EtOAc/Hexanes) 0.45; mp 161-163 ^oC; IR (KBr) ν_{max} 3347, 2970, 2925, 1679, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.69 (1 H, dd, J_1 = 7.2, J_2 = 1.7 Hz), 8.09 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.61 (2 H, d, J = 7.7 Hz), 7.48-7.37 (5 H, m), 7.34-7.30 (1 H, m), 7.08 (1 H, d, J = 5.1 Hz), 7.05 (1 H, d, J = 3.4 Hz), 6.85 (1 H, dd, J_1 = 5.0, J_2 = 3.5 Hz), 4.18-4.10 (1 H, m), 3.82 (1 H, d, J = 10.6 Hz), 1.22 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.8, 148.9, 148.0, 138.2, 138.2, 136.2, 134.4, 128.8, 128.5, 127.8, 127.6, 127.3, 126.6, 124.3, 123.0, 121.5, 121.4, 116.4, 63.8, 38.2, 21.1; HRMS: *m/z* $[M + H]^+$, found 373.1377, $C_{23}H_{21}N_2OS$ requires 373.1375.

4-Methyl-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)nonanamide (4a): Following the general procedure, **6a** (80 mg, 84%) was obtained as a mixture of diastereomers after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless semi solid; R_f (20% EtOAc/Hexanes) 0.47; IR (KBr) ν_{max} 3352, 2924, 2857, 1686, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (1 H, br. s), 8.80 (1 H, dd, J_1 = 4.2, J_2 = 1.8 Hz), 8.73 (1 H, dd, J_1 = 6.9, J_2 = 2.2 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.54-7.49 (2 H, m), 7.46 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.12 (1 H, dd, J_1 = 5.1, J_2 = 1.2 Hz), 6.93-6.91 (1 H, m), 6.89 (1 H, dd, J_1 = 5.0, J_2 = 3.5 Hz), 3.68-3.63 (1 H, m), 3.02 (1 H, dd, J_1 = 14.8, J_2 = 5 Hz), 2.86 (1 H, dd, J_1 = 14.7, J_2 = 9.7 Hz), 1.90-1.83 (1 H, m), 1.53-1.13 (8 H, m), 1.02 (3 H, d, J = 6.8 Hz), 0.92-0.85 (3 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.3, 148.0, 146.8, 138.3, 136.3, 134.4, 127.9, 127.4, 126.4, 124.9, 123.1, 121.5, 121.4, 116.4, 43.1, 42.4, 38.9, 33.8, 32.0, 27.0, 22.7, 17.1, 14.1; HRMS: *m/z* $[M + H]^+$, found 381.1992, $C_{23}H_{29}N_2OS$ requires 381.2000. The compound **6a** was isolated as a mixture of diastereomers and the NMR data given here for the major.

3-(4-Bromophenyl)-4-methyl-*N*-(quinolin-8-yl)nonanamide (4b): Following the general procedure, **6b** (45 mg, 40%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a pale yellow liquid; R_f (20% EtOAc/Hexanes) 0.44; IR (thin film) ν_{max} 3351, 2926, 1686, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1 H, br. s), 8.78 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.66 (1 H, dd, J_1 = 6.0, J_2 = 3.0 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.52-7.48 (2 H, m), 7.46 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.39 (2 H, d, J = 8.4 Hz),

7.17 (2 H, d, J = 8.4 Hz), 3.25-3.19 (1 H, m), 3.02 (1 H, dd, J_1 = 14.8, J_2 = 4.8 Hz), 2.82 (1 H, dd, J_1 = 14.8, J_2 = 10.2 Hz), 1.83-1.77 (1 H, m), 1.39-1.14 (8 H, m), 0.99 (3 H, d, J = 6.7 Hz), 0.86 (3 H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4, 148.0, 142.4, 138.2, 136.3, 134.3, 131.4, 130.0, 127.9, 127.3, 121.6, 121.4, 120.0, 116.4, 47.3, 41.2, 38.1, 33.9, 32.0, 26.8, 22.6, 17.0, 14.1; HRMS: *m/z* $[M + H]^+$, found 453.1541, $C_{25}H_{30}BrN_2O$ requires 453.1542. The characterization data corresponds to the major isomer and the ^{1}H NMR spectrum of this compound showed the presence of traces of the corresponding minor isomer.

3-(4-Chlorophenyl)-4-methyl-*N*-(quinolin-8-yl)nonanamide (4c): Following the general procedure, **6c** (54 mg, 53%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a pale yellow liquid; R_f (20% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 3352, 2926, 2857, 1687, 1526, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1 H, br. s), 8.78 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.66 (1 H, dd, J_1 = 6.1, J_2 = 2.9 Hz), 8.15 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.51-7.48 (2 H, m), 7.45 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.26-7.21 (4 H, m), 3.26-3.21 (1 H, m), 3.02 (1 H, dd, J_1 = 14.8, J_2 = 4.8 Hz), 2.82 (1 H, dd, J_1 = 14.8, J_2 = 10.2 Hz), 1.83-1.76 (1 H, m), 1.39-1.15 (8 H, m), 1.00 (3 H, d, J = 6.7 Hz), 0.86 (3 H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5, 148.0, 141.8, 138.2, 136.3, 134.3, 131.9, 129.6, 128.4, 127.9, 127.3, 121.6, 121.4, 116.4, 47.2, 41.3, 38.2, 33.9, 32.0, 26.8, 22.6, 17.0, 14.1; HRMS: *m/z* $[M + H]^+$, found 409.2066, $C_{25}H_{30}ClN_2O$ requires 409.2047. The characterization data corresponds to the major isomer.

3-(3,4-Dichlorophenyl)-4-methyl-*N*-(quinolin-8-yl)nonanamide (4d): Following the general procedure, **6d** (75 mg, 68%) was obtained after purification by column chromatography on silica gel as a pale yellow liquid; R_f (20% EtOAc/Hexanes) 0.40; IR (thin film) ν_{max} 3349, 2927, 2857, 1687, 1526, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1 H, br. s), 8.79 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.65 (1 H, dd, J_1 = 5.8, J_2 = 3.2 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.52-7.48 (2 H, m), 7.46 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.40 (1 H, d, J = 2.0 Hz), 7.31 (1 H, d, J = 8.3 Hz), 7.12 (1 H, dd, J_1 = 8.3, J_2 = 2.1 Hz), 3.25-3.19 (1 H, m), 3.02 (1 H, dd, J_1 = 14.9, J_2 = 4.7 Hz), 2.80 (1 H, dd, J_1 = 14.9, J_2 = 10.3 Hz), 1.84-1.75 (1 H, m), 1.38-1.16 (8 H, m), 1.00 (3 H, d, J = 6.7 Hz), 0.86 (3 H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.1, 148.1, 143.9, 138.2, 136.3, 134.2, 132.3, 130.2, 130.1, 130.1, 127.9, 127.3, 121.6, 121.5, 116.4, 47.1, 41.0, 38.9, 34.0,

32.0, 26.7, 22.6, 16.9, 14.1; HRMS: *m/z* $[M + H]^+$, found 443.1676, $C_{25}H_{29}Cl_2N_2O$ requires 443.1657. The characterization data corresponds to the major isomer.

3-(4-Bromophenyl)-4-ethyl-*N*-(quinolin-8-yl)octanamide (4e): Following the general procedure, **6e** (56 mg, 50%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a pale yellow liquid; R_f (20% EtOAc/Hexanes) 0.43; IR (thin film) ν_{max} 3352, 2928, 1686, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1 H, br. s), 8.78 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.66 (1 H, dd, J_1 = 6.1, J_2 = 2.9 Hz), 8.15 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.48 (2 H, m), 7.46 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.39 (2 H, d, J = 8.4 Hz), 7.18 (2 H, d, J = 8.4 Hz), 3.42-3.35 (1 H, m), 3.04-2.97 (1 H, m), 2.86-2.79 (1 H, m), 1.61-1.57 (1 H, m) 1.47-1.08 (8 H, m), 0.96 (3 H, t, J = 7.4 Hz), 0.92-0.84 (3 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4, 148.0, 142.2, 138.2, 136.3, 134.3, 131.4, 130.1, 127.9, 127.3, 121.5, 121.4, 120.0, 116.4, 44.3, 43.8, 41.4, 29.8, 29.2, 23.0, 22.7, 14.1, 11.1; HRMS: *m/z* $[M + H]^+$, found 453.1555, $C_{25}H_{30}BrN_2O$ requires 453.1542. The characterization data corresponds to the major isomer.

4-Ethyl-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)octanamide (4f): Following the general procedure, **6f** (57 mg, 57%) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless liquid; R_f (20% EtOAc/Hexanes) 0.44; IR (thin film) ν_{max} 3355, 2927, 1686, 1523, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.68 (1 H, dd, J_1 = 6.9, J_2 = 2.0 Hz), 8.13 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.51-7.47 (2 H, m), 7.44 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.21 (2 H, d, J = 8.6 Hz), 6.81 (2 H, d, J = 8.6 Hz), 3.73 (3 H, s), 3.40-3.32 (1 H, m), 3.03-2.96 (1 H, m), 2.87-2.80 (1 H, m), 1.60-1.55 (1 H, m), 1.46-1.08 (8 H, m), 0.91 (3 H, t, J = 6.8 Hz), 0.88 (3 H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.0, 157.9, 147.9, 138.3, 136.2, 135.1, 134.5, 129.2, 127.8, 127.4, 121.5, 121.2, 116.3, 113.6, 55.1, 44.5, 43.7, 42.1, 29.5, 29.3, 29.0, 23.1, 23.1, 14.1, 11.3; HRMS: *m/z* $[M + H]^+$, found 405.2541, $C_{26}H_{33}N_2O_2$ requires 405.2542. This compound was isolated as a mixture of diastereomers. The NMR spectra of this compound correspond to mixture of diastereomers and the ^{13}C NMR data given here corresponds to the major isomer.

Ethyl 3-oxo-2-(phenyl(thiophen-2-yl)methyl)-3-(quinolin-8-ylamino)propanoate (7a): Following the general procedure, **7a** (70 mg, 65%) was obtained as a mixture of diastereomers after purification by column chromatography on silica gel as a colourless solid; R_f (25% EtOAc/Hexanes) 0.23; mp 103-105 ^oC; IR (KBr) ν_{max} 3328, 2979, 1729, 1684, 1529, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.45 (1 H, br. s), 10.36 (1 H, br.s)* , 8.90-8.88 (1 H, 1 H*, m), 8.70 (1 H, dd, J_1 = 6.2, J_2 = 2.8 Hz), 8.54 (1 H, dd, J_1 = 7.4, J_2 = 1.6 Hz)* , 8.16 (1 H, 1 H*, td, J_1 = 8.2, J_2 = 1.7 Hz), 7.53-7.43 (5 H, 5 H*, m) , 7.38-7.34 (1 H, 1 H*, m), 7.29-7.19 (2 H, 2 H*, m), 7.09-7.02 (2 H, 2 H*, m), 6.95 (1 H, dd, J_1 = 5.1, J_2 = 3.5 Hz), 6.82 (1 H, dd, J_1 = 5.1, J_2 = 3.5 Hz)*, 5.25 (1 H, d, J = 11.9 Hz), 5.24 (1 H, d, J = 11.9 Hz)*, 4.45 (1 H, d, J = 11.9 Hz), 4.43 (1 H, 1 H*, d, J = 12.0 Hz), 4.21-4.15 (2 H*, m), 4.05-3.99 (2 H, q, J = 7.1 Hz), 1.17 (3 H, t, J = 7.1 Hz)*, 1.00 (3 H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.0, 168.5, 164.4, 164.0, 148.5, 148.4, 145.0, 144.7, 141.0, 140.6, 138.5, 138.4, 136.3, 136.3, 134.1, 133.9, 128.7, 128.7, 128.0, 127.8, 127.8, 127.4, 127.3, 127.2, 126.8, 126.6, 125.1, 124.7, 124.7, 124.6, 122.0, 122.0, 121.7, 121.7, 116.8, 116.7, 62.3, 62.2, 62.0, 61.8, 47.6, 47.5, 13.9, 13.7; HRMS: *m/z* $[M + H]^+$, found 431.1435, $C_{25}H_{23}N_2O_3S$ requires 431.1429. This compound was isolated as a mixture of diastereomers. * Represents the ^1H NMR data of the corresponding other diastereomer. The ^{13}C NMR data given here for both the diastereomers.

Ethyl 3-(4-methoxyphenyl)-3-phenyl-2-(quinolin-8-ylcarbamoyl)propanoate (7b): Following the general procedure, **7b** (56 mg, 50%) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (20% EtOAc/Hexanes) 0.18; mp 73-75 ^oC; IR (KBr) ν_{max} 3326 2981, 2930, 1733, 1690, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.43 (1 H, br. s), 8.89 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.60 (1 H, dd, J_1 = 7.0, J_2 = 2.0 Hz), 8.16 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.50-7.47 (3 H, m), 7.42 (2 H, d, J = 7.2 Hz), 7.34-7.29 (4 H, m), 7.23-7.22 (1 H, m), 6.74 (2 H, d, J = 8.8 Hz), 4.91 (1 H, d, J = 12.2 Hz), 4.46 (1 H, d, J = 12.2 Hz), 4.06 (2 H, q, J = 7.2 Hz), 3.66 (3 H, s), 1.04 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.4, 164.8, 158.3, 148.4, 141.8, 138.5, 136.2, 134.1, 133.2, 128.9, 128.6, 127.8, 127.2, 126.8, 123.4, 121.8, 121.6, 116.7, 114.1, 61.7, 61.1, 55.1, 51.7, 13.8; HRMS: *m/z* $[M + H]^+$, found 455.1965, $C_{28}H_{27}N_2O_4$ requires 455.1971.

(*2r, *3S**)-3-(4-Methoxyphenyl)-2-((*R**)-1-(4-methoxyphenyl)-ethyl)-*N*-(quinolin-8-yl)butanamide (8eA):** Following the general procedure, **8eA** (181 mg, 40% *meso* (major) isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.10; mp 143-145 ^oC; IR (KBr) ν_{max} 3357, 2962, 2932, 1684, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.37 (1 H, br. s), 8.70 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.55 (1 H, dd, J_1 = 6.8, J_2 = 1.8 Hz), 8.07 (1 H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.44-7.37 (3 H, m), 7.28 (4 H, d, J = 8.6 Hz), 6.74 (4 H, d, J = 8.6 Hz), 3.66 (6 H, s), 3.33-3.26 (2 H, m), 3.01 (1 H, t, J = 7.8 Hz), 1.55 (6 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.2, 158.0, 147.8, 138.2, 136.1, 136.1, 134.2, 129.0, 127.7, 127.3, 121.4, 120.9, 116.0, 113.5, 62.7, 55.0, 39.0, 21.7; HRMS: *m/z* $[M + H]^+$, found 455.2345, $C_{29}H_{31}N_2O_3$ requires 455.2335.

(*S)-3-(4-Methoxyphenyl)-2-((*S**)-1-(4-methoxyphenyl)ethyl)-*N*-(quinolin-8-yl)butanamide (8eB):** Following the general procedure, **8eB** (100 mg, 22%, minor isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (15% EtOAc/Hexanes) 0.11; mp 157-159 ^oC; IR (KBr) ν_{max} 3355, 2963, 2834, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.14 (1 H, br. s), 8.66-8.63 (2 H, m), 8.09 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.50-7.42 (2 H, m), 7.38 (1 H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.22 (2 H, d, J = 8.7 Hz), 7.16 (2 H, d, J = 8.7 Hz), 6.77 (2 H, d, J = 8.7 Hz), 6.72 (2 H, d, J = 8.7 Hz), 3.66 (3 H, s), 3.66 (3 H, s), 3.33-3.25 (2 H, m), 2.92 (1 H, t, J = 7.8 Hz), 1.44 (3 H, d, J = 7.0 Hz), 1.43 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.5, 158.1, 157.9, 147.7, 138.2, 137.3, 136.5, 136.0, 134.3, 128.9, 128.5, 128.0, 127.3, 121.3, 121.1, 116.2, 113.9, 113.4, 62.6, 55.1, 55.0, 39.4, 38.9, 20.4, 17.7; HRMS: *m/z* $[M + H]^+$, found 455.2343, $C_{29}H_{31}N_2O_3$ requires 455.2335.

(*2r*,3S)-3-Phenyl-2-((*R**)-1-phenylethyl)-*N*-(quinolin-8-yl)butanamide (8fA):** Following the general procedure, **8fA** (197 mg, 50%, *meso* (major) isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colourless liquid; R_f (10% EtOAc/Hexanes) 0.12; IR (thin film) ν_{max} 3357, 3027, 2965, 1687, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.41 (1 H, br. s), 8.71 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.52-8.50 (1 H, m), 8.09 (1 H, dd, J_1 = 8.3, J_2 = 1.0 Hz), 7.42-7.35 (5 H, m), 7.32-7.26 (1 H, m), 7.24-7.15 (5 H, m), 7.10 (2 H, t, J = 7.6 Hz), 3.37-3.31 (2 H, m), 3.09 (1 H, t, J = 7.8 Hz), 1.57 (6 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.0, 147.8, 144.2, 138.3, 136.1, 134.1, 128.2, 128.1, 127.7,

127.3, 126.3, 121.4, 120.9, 116.0, 62.2, 39.9, 21.0; HRMS: *m/z* $[M + H]^+$, found 395.2127, $C_{27}H_{27}N_2O$ requires 395.2123.

(*S)-3-Phenyl-2-((*S**)-1-phenylethyl)-*N*-(quinolin-8-yl)butanamide (8fB):** Following the general procedure, **8fB** (82 mg, 21%, minor isomer) was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 10:90) as a colourless solid; R_f (10% EtOAc/Hexanes) 0.10; mp 142-144 ^oC; IR (KBr) ν_{max} 3356, 3059, 3027, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.20 (1 H, br. s), 8.66-8.64 (2 H, m), 8.08 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.50-7.42 (2 H, m), 7.38 (1 H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.33-7.23 (6 H, m), 7.18 (2 H, t, J = 7.4 Hz), 7.13 (1 H, t, J = 7.3 Hz), 7.07 (1 H, t, J = 7.2 Hz), 3.40-3.30 (2 H, m), 3.03 (1 H, t, J = 7.8 Hz), 1.48 (3 H, d, J = 7.0 Hz), 1.46 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.3, 147.8, 145.3, 144.4, 138.2, 136.0, 134.2, 128.6, 128.1, 128.0, 127.7, 127.7, 127.3, 126.4, 126.3, 121.3, 121.1, 116.2, 62.1, 40.3, 40.0, 20.3, 17.8; HRMS: *m/z* $[M + H]^+$, found 395.2126, $C_{27}H_{27}N_2O$ requires 395.2123.

(*2r*,3S)-3-(4-Bromophenyl)-2-((*R**)-1-(4-bromophenyl)ethyl)-*N*-(quinolin-8-yl)butanamide (8gA):** Following the general procedure, **8gA** (231 mg, 42%, *meso* (major) isomer) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (10% EtOAc/Hexanes) 0.70; mp 152-154 ^oC; IR (KBr) ν_{max} 3350, 2967, 2931, 1686, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.41 (1 H, br. s), 8.74 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.49 (1 H, dd, J_1 = 5.6, J_2 = 3.4 Hz), 8.11 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.45-7.42 (3 H, m), 7.31 (4 H, d, J = 8.5 Hz), 7.22 (4 H, d, J = 8.5 Hz), 3.30-3.23 (2 H, m), 3.00 (1 H, t, J = 7.9 Hz), 1.52 (6 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4, 148.1, 142.9, 138.2, 136.2, 133.8, 131.3, 129.9, 127.8, 127.3, 121.6, 121.4, 120.3, 116.2, 61.8, 39.4, 20.9; HRMS: *m/z* $[M + H]^+$, found 551.0311, $C_{27}H_{25}Br_2N_2O$ requires 551.0334.

(*S)-3-(4-Bromophenyl)-2-((*S**)-1-(4-bromophenyl)ethyl)-*N*-(quinolin-8-yl)butanamide (8gB):** Following the general procedure, **8gB** (88 mg, 16%, minor isomer) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (10% EtOAc/Hexanes) 0.80; mp 148-150 ^oC; IR (KBr) ν_{max} 3347, 2967, 2917, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.09 (1 H, br. s), 8.66 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.57 (1 H, dd,

J_1 = 6.0, J_2 = 2.9 Hz), 8.11 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.49-7.45 (2 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.19-7.15 (8 H, m), 3.34-3.27 (2 H, m), 2.90 (1 H, dd, J_1 = 8.5, J_2 = 7.1 Hz), 1.43 (3 H, d, J = 7.0 Hz), 1.42 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5, 148.0, 143.4, 142.9, 138.0, 136.1, 133.8, 132.1, 132.0, 129.3, 128.9, 128.7, 128.2, 127.7,127.2, 121.5, 121.4, 116.3, 61.9, 39.5, 39.2, 20.1, 16.9; HRMS: *m/z* $[M + H]^+$, found 551.0313, $C_{27}H_{25}Br_2N_2O$ requires 551.0334.

(*2r*,3S)-3-(4-Chlorophenyl)-2-((*R**)-1-(4-chlorophenyl)ethyl)-*N*-(quinolin-8-yl)butanamide (8hA):** Following the general procedure, **8hA** (250 mg, 54%, *meso* (major) isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.70; mp 108-110 ^{o}C; IR (KBr) ν_{max} 3350, 2967, 2931, 1685, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.39 (1 H, br. s), 8.73 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.48 (1 H, dd, J_1 = 6.0, J_2 = 2.9 Hz), 8.12 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.45-7.42 (3 H, m), 7.27 (4 H, d, J = 8.5 Hz), 7.15 (4 H, d, J = 8.5 Hz), 3.31-3.23 (2 H, m), 2.99 (1 H, t, J = 7.9 Hz), 1.52 (6 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4, 148.0, 142.3, 138.2, 136.2, 133.8, 132.1, 129.5, 128.3, 127.8, 127.3, 121.5, 121.3, 116.1, 62.0, 39.3, 20.9; HRMS: *m/z* $[M + H]^+$, found 463.1341, $C_{27}H_{25}Cl_2N_2O$ requires 463.1344.

(*S)-3-(4-Chlorophenyl)-2-((*S**)-1-(4-chlorophenyl)ethyl)-*N*-(quinolin-8-yl)butanamide (8hB):** Following the general procedure, **8hB** (106 mg, 23%, minor isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.60; mp 165-167 ^{o}C; IR (KBr) ν_{max} 3347, 2977, 1683, 1524, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.09 (1 H, br. s), 8.66 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.57 (1 H, dd, J_1 = 6.1, J_2 = 2.9 Hz), 8.12 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.48-7.46 (2 H, m), 7.42 (1 H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.19-7.15 (8 H, m), 3.36-3.28 (2 H, m), 2.90 (1 H, dd, J_1 = 8.5, J_2 = 7.1 Hz), 1.43 (3 H, d, J = 7.0 Hz), 1.42 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5, 148.0, 143.4, 142.9, 138.0, 136.1, 133.8, 132.1, 132.0, 129.3, 128.9, 128.7, 128.2, 127.7, 127.1, 121.5, 121.5, 116.3, 61.9, 39.5, 39.2, 20.1, 16.9; HRMS: *m/z* $[M + H]^+$, found 463.1340, $C_{27}H_{25}Cl_2N_2O$ requires 463.1344.

(*2S,3R*)-2,3-Diphenyl-*N*-(quinolin-8-yl)butanamide (10a): Following the general procedure, **10a** (62 mg, 68%, ee 78% for the *anti* (major) isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.48; mp 153-155 ^{o}C; IR (KBr) ν_{max} 3343, 2965, 2925, 1680, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1 H, br. s), 8.75 (1 H, dd, J_1 = 4.3, J_2 = 1.7 Hz), 8.59 (1 H, dd, J_1 = 6.4, J_2 = 2.6 Hz), 8.06 (1 H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.66 (2 H, d, J = 7.1 Hz), 7.47 (2 H, d, J = 7.0 Hz), 7.43-7.37 (5 H, m), 7.34-7.25 (3 H, m), 7.13-7.09 (1 H, m), 3.88 (1 H, d, J = 10.9 Hz), 3.81-3.73 (1 H, m), 1.15 (3 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9, 148.0, 145.2, 138.7, 138.2, 136.2, 134.3, 128.8, 128.6, 128.5, 127.7, 127.5, 127.4, 127.2, 126.4, 121.4, 121.2, 116.3, 62.7, 43.0, 20.3; HRMS: *m/z* $[M + H]^+$, found 367.1813, $C_{25}H_{23}N_2O$ requires 367.1810. The characterization data corresponds the *anti* (major) isomer.

(*2S,3R*)-2-Phenyl-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)butanamide (10b): Following the general procedure, **10b** (80 mg, 86%, ee 75% for the *anti* (major) isomer) was obtained after purification by column chromatography on silica gel as a pale yellow solid; R_f (15% EtOAc/Hexanes) 0.46; mp 130-132 ^{o}C; IR (KBr) ν_{max} 3345, 2966, 2923, 1682, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (1 H, br. s), 8.76 (1 H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.70 (1 H, dd, J_1 = 7.0, J_2 = 2.0 Hz), 8.09 (1 H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.61 (2 H, d, J = 7.0 Hz), 7.48-7.38 (5 H, m), 7.34-7.29 (1 H, m), 7.08 (1 H, dd, J_1 = 5.1, J_2 = 1.1 Hz), 7.04-7.03 (1 H, m), 6.84 (1 H, dd, J_1 = 5.1, J_2 = 3.5 Hz), 4.18-4.10 (1 H, m), 3.81 (1 H, d, J = 10.6 Hz), 1.22 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.8, 148.9, 148.0, 138.3, 138.2, 136.2, 134.4, 128.8, 128.5, 127.8, 127.6, 127.3, 126.6, 124.3, 123.1, 121.5, 121.4, 116.4, 63.8, 38.2, 21.1; HRMS: *m/z* $[M + H]^+$, found 373.1369 $C_{23}H_{21}N_2OS$ requires 373.1375. The characterization data corresponds the *anti* (major) isomer.

(*2S,3R*)-3-(4-Methoxyphenyl)-2-phenyl-*N*-(quinolin-8-yl)butanamide (10c): Following the general procedure, **10c** (92 mg, 93%, ee 73% for the *anti* (major) isomer) was obtained after purification by column chromatography on silica gel as a colourless solid; R_f (10% EtOAc/Hexanes) 0.45; mp 153-155 ^{o}C; IR (KBr) ν_{max} 3351, 2961, 2927, 1685, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.67 (1 H, br. s), 8.74 (1 H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.61 (1 H, dd, J_1 = 6.1, J_2 = 3.0 Hz), 8.08 (1 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.63 (2 H, d, J = 7.2 Hz), 7.43-7.29 (8

H, m), 6.78 (2 H, d, J = 8.7 Hz), 3.81 (1 H, d, J = 10.9 Hz), 3.74-3.69 (1 H, m), 3.68 (3 H, s), 1.12 (3 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.1, 158.0, 147.8, 138.8, 137.9, 137.3, 136.4, 134.3, 128.7, 128.6, 128.3, 127.8, 127.4, 127.3, 121.4, 121.3, 116.5, 113.9, 63.0, 55.1, 42.2, 20.3; HRMS: *m/z* $[M + H]^+$, found 397.1924, $C_{26}H_{25}N_2O_2$ requires 397.1916. The characterization data corresponds the *anti* (major) isomer.

General procedure for the hydrolysis of carboxamides (±)-3c and (±)-3d and the preparation of carboxylic acids (±)**-11 and** (±)**-12**

To a round bottom flask (with a capacity of 25 mL) molded with a Liebig condenser (approximate length = 15 cm) sealed at the top portion and having a J Young air inlet valve at the side of the round bottom flask, was sequentially added a solution of carboxamide (±)-**3c** or (±)-**3d** (0.25 mmol) dissolved in a mixture of toluene (3 mL) and water (0.5 mL) and CF_3SO_3H (0.5 mL) with the help of syringes. Next, 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. The reaction mixture was heated for 12 h, then, the reaction mixture was transferred into a separating funnel with the help of a syringe. The reaction mixture was diluted with ethyl acetate 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 ethyl acetate (10 mL x 2) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporation in vacuum afforded the corresponding carboxylic acid (±)-**11** or (±)-**12**.

(*2R*,3S)-2-Phenyl-3-(*p*-tolyl)butanoic acid (11):** Following the general procedure, **11** (59 mg, 93%) was obtained after the work up procedure (the crude material was almost pure; purity of the compound >95%) as a colourless solid; mp 172-174 ^oC; IR (KBr) ν_{max} 3418, 1714, 1661, 1025, 999 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ_H 7.43 (2 H, d, J = 7.1 Hz), 7.31-7.18 (5 H, m), 7.05 (2 H, d, J = 7.8 Hz), 3.64 (1 H, d, J = 11.3 Hz), 3.41-3.33 (1 H, m), 2.26 (3 H, s) 0.94 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ_C 175.0, 142.3, 138.1, 135.7, 129.0, 128.6, 128.5, 127.4, 127.3, 59.4, 42.7, 21.0, 20.4; HRMS: *m/z* $[M - H]^+$, found 253.1211, $C_{17}H_{17}O_2$ requires 253.1229.

(2*R,3*S**)-3-(4-Ethylphenyl)-2-phenylbutanoic acid (12):** Following the general procedure, the compound **12** (62 mg, 93%) was obtained after the work up procedure (the crude material was almost pure; purity of the compound >95%) as a colourless solid; mp 99-101 ^{o}C; IR (KBr) ν_{max} 3418, 1714, 1661, 1025, 999 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ_H 7.50 (2 H, d, J = 7.0 Hz), 7.38 (2 H, t, J = 7.5 Hz), 7.33-7.30 (1 H, m), 7.27 (2 H, d, J = 8.1 Hz), 7.15 (2 H, d, J = 8.2 Hz), 3.76 (1 H, d, J = 11.5 Hz), 3.45-3.37 (1 H, m), 2.62 (2 H, q, J = 7.6 Hz), 1.23 (3 H, t, J = 7.6 Hz), 0.97 (3 H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ_C 175.5, 142.4, 142.2, 138.3, 128.3, 128.3, 127.4, 127.2, 127.1, 59.4, 42.7, 28.1, 19.4, 14.9; MS: *m/z* 268 ($[M]^+$, 1), 266 ($[M^+ - H_2]^+$, 8), 265 ($[M^+ - H_3]^+$, 88%).

Chapter 3: Diastereoselective Pd(II)-Catalyzed sp^3 C−H Arylation Followed by Ring Opening of Cyclopropanecarboxamides: Construction of *anti* β-Acyloxy Carboxamide Derivatives

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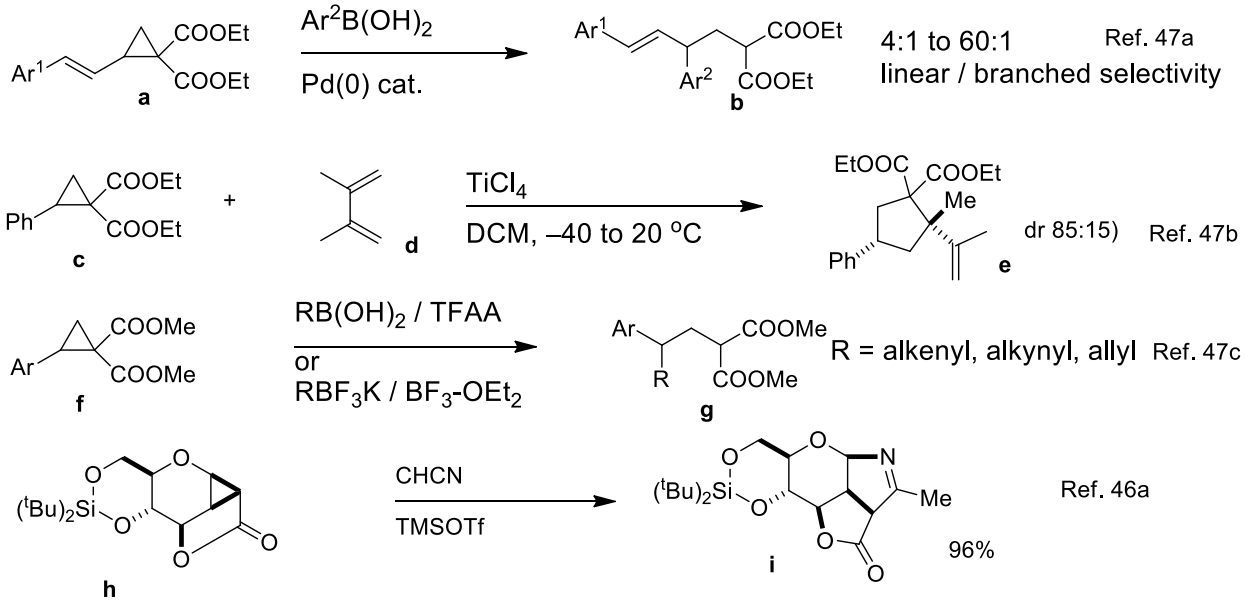
Among the cycloalkane family, the chemistry of cyclopropane unit is fascinating as it discloses an array of interesting synthetic transformations.[43-46] Particularly, the electronic and chemical properties of cyclopropane ring have attracted experimental and theoretical chemists to study the importance of cyclopropane unit. It is to be noted that the angular strain and torsional strain make the cyclopropane moiety more reactive. [43-46] The inherent ring strain and sp^2-like character of methylene C-H bond of cyclopropane have led to functionalization or ring cleavage in presence of various chemical reagents.[43-54] Thus, the reactivity of C-C bond of cyclopropane moiety resembles that of C-C double bond. The relief of strain energy associated with ring-cleavage facilitate cyclopropane scaffolds to react with different chemical species, such as electrophiles, nucleophiles and C-C multiple bonds. The ring-cleavage can occur when cyclopropane moiety is activated by the presence of suitable substituents. The electron withdrawing substituents make cyclopropane ring as homo-Michael acceptor and electron donating substituents afford cationic equivalents in presence of electrophilic species.[47-51] When both electron-acceptor and electron-donor groups are present cyclopropane moiety undergo ring-cleavage in the presence of Lewis's acid by synergistic electron 'push-pull' mechanism. Some of ring-cleavage reactions of donor-acceptor cyclopropane systems are given in Scheme 1.

The three-membered carbocycles such as cyclopropenes, [48a] methylenecyclopropanes, [49] alkyledienecyclopropanes [49] and cyclopropanones [51a,b] are the most important classes of compounds belonging to cyclopropane family. In general, the chemistry of regularly encountered cyclopropane systems prompted many researchers to develop wide range of chemical transformations.[44, 46] The transition metal-catalyzed/promoted different modes of cleavage of

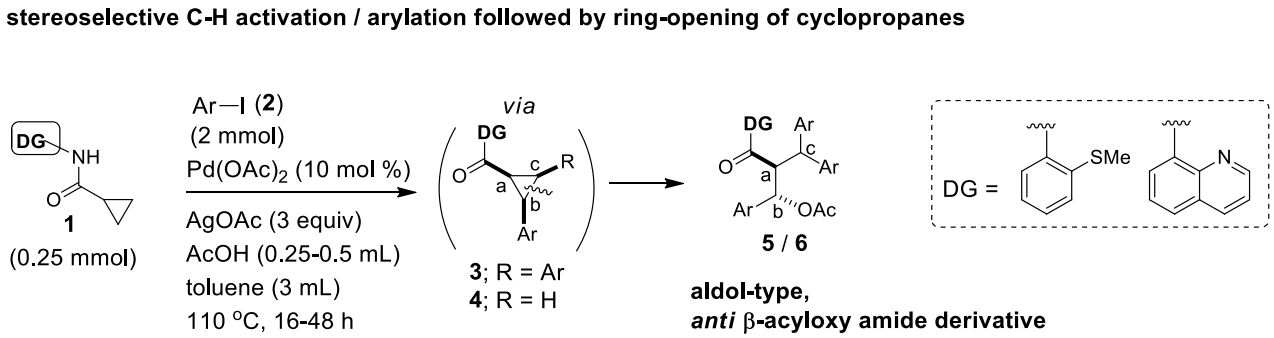
substituted cyclopropanes, cyclopropenes, vinylcyclopropanes, methylenecyclopropanes, alkyledienecyclopropanes system has been thoroughly reviewed by Cramer, [50c] Rubin/Gevorgyan, [48a] Pellissier, [49a,b] Brandi, [49c] Shi [49d,e] and Marek. [49f]



Scheme 1: Selected ring-opening reactions of cyclopropane systems

In general, the transition metal-catalyzed bidentate directing group-directed C-H activation/functionalization reactions have received significant attention (Chapter 1).[8,53] Among the transition metal catalysts, the Pd(II) catalysts are frequently employed to perform sp^2 and sp^3 C-H activation/functionalization reactions. Although the directing group-assisted or directing group-free sp^2 C-H activation/functionalization reactions have been extensively studied, the sp^3 C–H activation/functionalization reactions have received much attention after the seminal reports by Daugulis, Yu and other research groups.[21-23,33] Although sp^3 C–H activation/functionalization was investigated using a variety of aliphatic/alicyclic substrates, it is important to note that cyclopropane, which is the smallest carbocyclic ring, was also successfully subjected to the Pd(II)-catalyzed C–H activation/functionalization.[54,35b] In this regard, our group recently reported the diastereoselective Pd(II)-catalyzed, bidentate ligand-directed β-C-H arylation of cyclopropanecarboxamide derivatives.[54,35b]

Inspired by the transition metal-catalyzed ring opening of cyclopropanes including the C-H/C-C bond activation strategy as well as our previous work,[48-50,54,35b] we envisioned a one-pot method involving Pd(II)-catalyzed, bidentate directing group-aided β-C-H arylation followed by ring opening of cyclopropanecarboxamide derivatives. Accordingly, the reaction of unsubstituted cyclopropanecarboxamide **1** with excess amounts of aryl iodide **2** in the presence of $Pd(OAc)_2$ as a catalyst, AgOAc and AcOH as the additive afforded the open-chain carboxamide derivatives **5**/**6** with a high degree of stereocontrol (Scheme 2). Herein, the results from our investigations including a plausible mechanism for the formation of the open-chain carboxamide derivatives **5**/**6** from the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides **1** are reported.



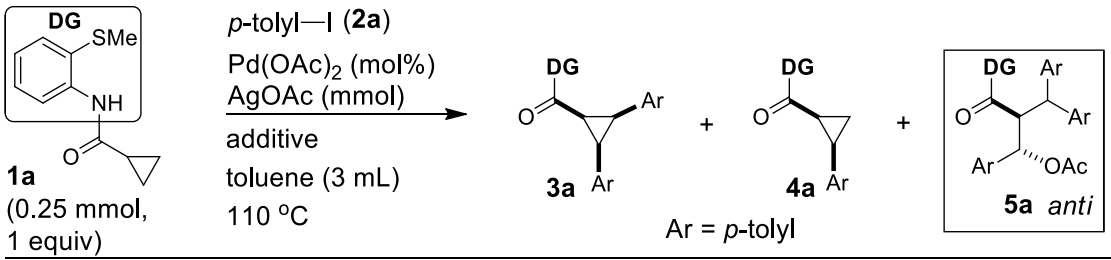
Scheme 2. Diastereoselective Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamides 1.

Results and Discussion

To initially explore the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides, we performed optimization reactions using unsubstituted cyclopropanecarboxamide **1a**, which was prepared from the 2-aminothioanisole bidentate ligand. Table 1 shows the results for the $Pd(OAc)_2$–catalyzed reaction of **1a** with excess amounts of *p*-tolyl iodide in the presence of various additives. Upon treatment of cyclopropanecarboxamide **1a** with excess amounts of *p*-tolyl iodide in the presence of the $Pd(OAc)_2$ catalyst and AgOAc, we expected that compound **1a** would undergo mono/bis C-H arylation followed by ring opening to afford the corresponding open-chain carboxamide derivatives. Accordingly, the reaction of **1a** (0.25 mmol) with excess amounts of *p*-tolyl iodide (0.38-2.0 mmol) in the presence of the

$Pd(OAc)_2$ catalyst and AgOAc afforded bis-arylated cyclopropanecarboxamide **3a** (yields up to 37%) and mono-arylated cyclopropanecarboxamide **4a** (yields up to 40%) along with anticipated ring-opened product **5a** (yields up to 20%, entries 1-7, Table 1).

Table 1. Optimization Reactions. Pd(II)-Catalyzed C-H Arylation/Ring Opening of Cyclopropanecarboxamide 1a.



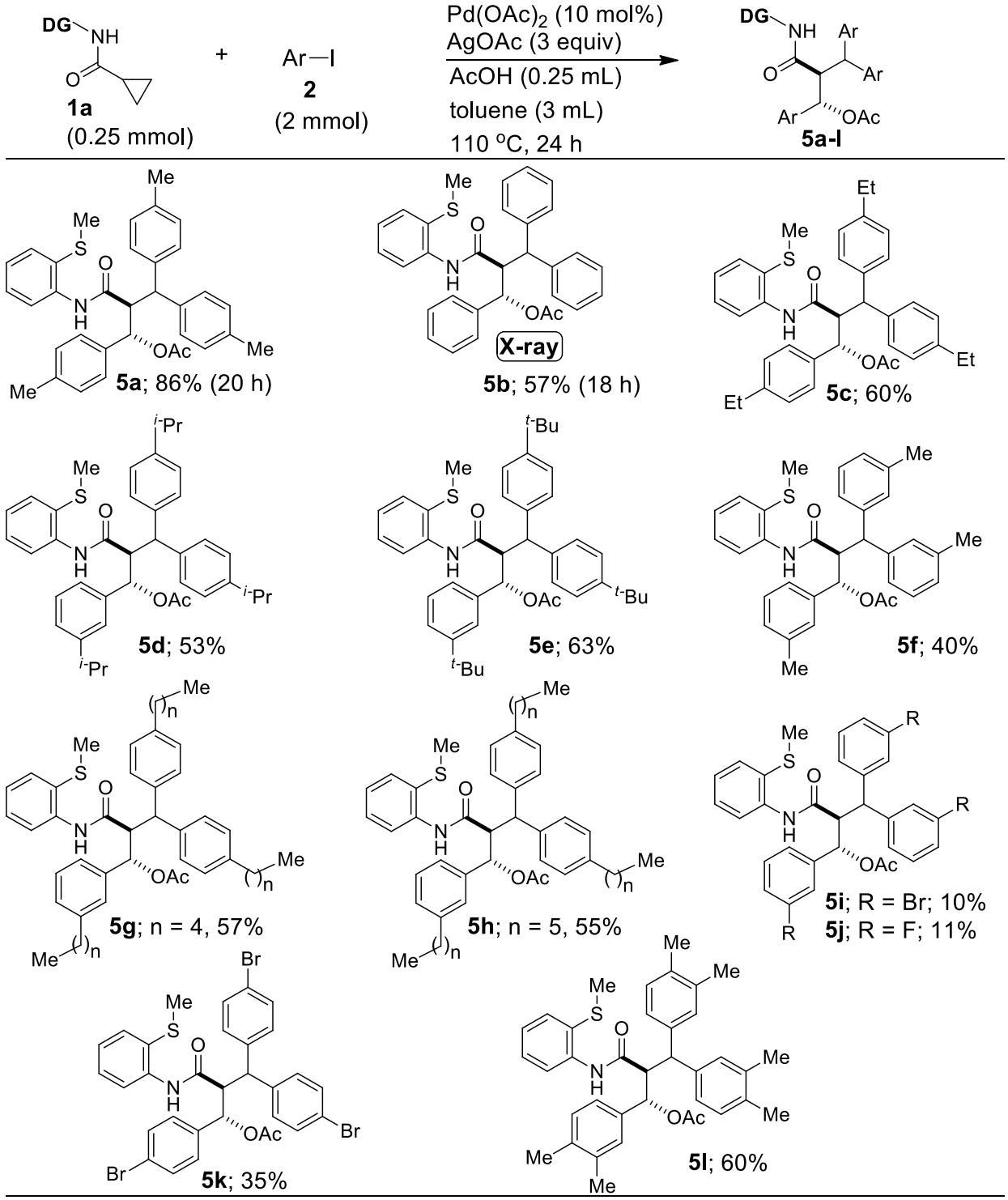
entry	**2a** (mmol)	AgOAc (mmol)	$Pd(OAc)_2$ (mol%)	additive (equiv) / mL	*t* (h)	yield (%) **3a**	**4a**	**5a**
1	1.5	0.55	5	nil	24	0	15	7
2	2	0.55	5	nil	16	37	40	7
3	1.5	0.55	10	nil	16	8	35	11
4	1.5	0.55	10	nil	7	29	38	7
5	1.5	0.55	5	nil	15	23	13	7
6	1.5	0.55	20	nil	15	0	13	15
7	1.5	0.75	5	nil	19	12	13	20
8	1.5	0.38	10	Na_2SO_4 (0.5)	12	12	12	7
9	1.5	0.38	5	NaOAc (0.5)	19	5	38	28
10	1.5	0.25	10	NaOAc (2.5)	16	5	47	0
11	1.5	0.25	10	KOAc (2.5)	16	7	30	0
12	1.5	0.55	30	KOAc (2.5)	16	6	30	20
13	1.5	0.55	10	PivOH (2)	16	0	19	5
14	1.5	0.55	10	TfOH (0.5 mL)	16	0	0	0
15	1.5	0.55	10	AcOH (0.5 mL)	16	0	0	47
16	2	0.75	10	AcOH (0.5 mL)	24	0	0	62
17	2.5	1.0	10	AcOH (0.5 mL)	24	0	0	60
18	2	0.75	10	AcOH (0.5 mL)	20	0	0	64
19	2	0.75	10	AcOH (0.25 mL)	20	0	0	86

To obtain ring-opened product **5a** as the major compound in satisfactory yield, we performed the Pd(II)-catalyzed reaction of **1a** with **2a** in the presence of additional additives (e.g., Na_2SO_4, NaOAc and KOAc). These reactions also afforded the corresponding three products (**3a**, **4a** and **5a**) without much selectivity (entries 8-12, Table 1). Next, we performed the Pd(II)-catalyzed reaction of **1a** with **2a** in the presence of PivOH or TfOH, which was also ineffective (entries 13 and 14, Table 1). Fortunately, the $Pd(OAc)_2$/AgOAc catalytic system-based reaction of **1a** with excess amounts of aryl iodide **2a** in the presence of AcOH directly afforded multiple β-C-H arylated open-chain carboxamide (*anti* β-acyloxy amide) **5a** in 47-86% yields (entries 15-19, Table 1). It is important to note that this process consists of the $Pd(OAc)_2$/AgOAc-catalytic system-based reaction of **1a** with excess amounts of aryl iodide **2a** in the presence of AcOH, has led to the construction of *anti* β-acyloxy amide **5a**, possessing vicinal stereocenters with a high degree of stereocontrol with the formation of a new C-O bond and three new C-C bonds.

After determining the suitable reaction conditions for obtaining multiple β-C-H arylated open-chain carboxamide **5a** from **1a**, we investigated the generality of this protocol and performed the diastereoselective C-H arylation followed by ring opening of substrate **1a** using various aryl iodides (Table 2). Using the optimized reaction conditions (entry 19, Table 1), we performed the $Pd(OAc)_2$/AgOAc catalytic system-based diastereoselective C-H arylation followed by ring opening of substrate **1a** with different aryl iodides, which furnished the corresponding multiple β-C-H arylated open-chain carboxamides (*anti* β-acyloxy amides) **5a-l** in 10-86% yields (Table 2). We observed that the C-H arylation followed by ring opening of substrate **1a** proceeded smoothly and afforded products **5a-h** and **5l** when the Pd(II)-catalyzed reaction of substrate **1a** was performed with aryl iodides that possessed electron-donating alkyl groups (e.g., Me, Et and ^{i}Pr) at the *para* or *meta* position of the aryl ring in the aryl iodides. However, we experienced some difficulty when the Pd(II)-catalyzed C-H arylation reaction of substrate **1a** was performed with aryl iodides that possessed electron-withdrawing groups (i.e., Br, F) at the *para* or *meta* position of the aryl ring in the aryl iodides. Therefore, the $Pd(OAc)_2$/AgOAc catalytic system-based reaction of substrate **1a** with aryl iodides possessing electron-withdrawing groups afforded corresponding products **5i-k** in low yields. Although a clear reason is not known at this stage, we assume that the aryl iodides that possess electron-

withdrawing groups may be less reactive than aryl iodides containing alkyl groups under our experimental conditions.

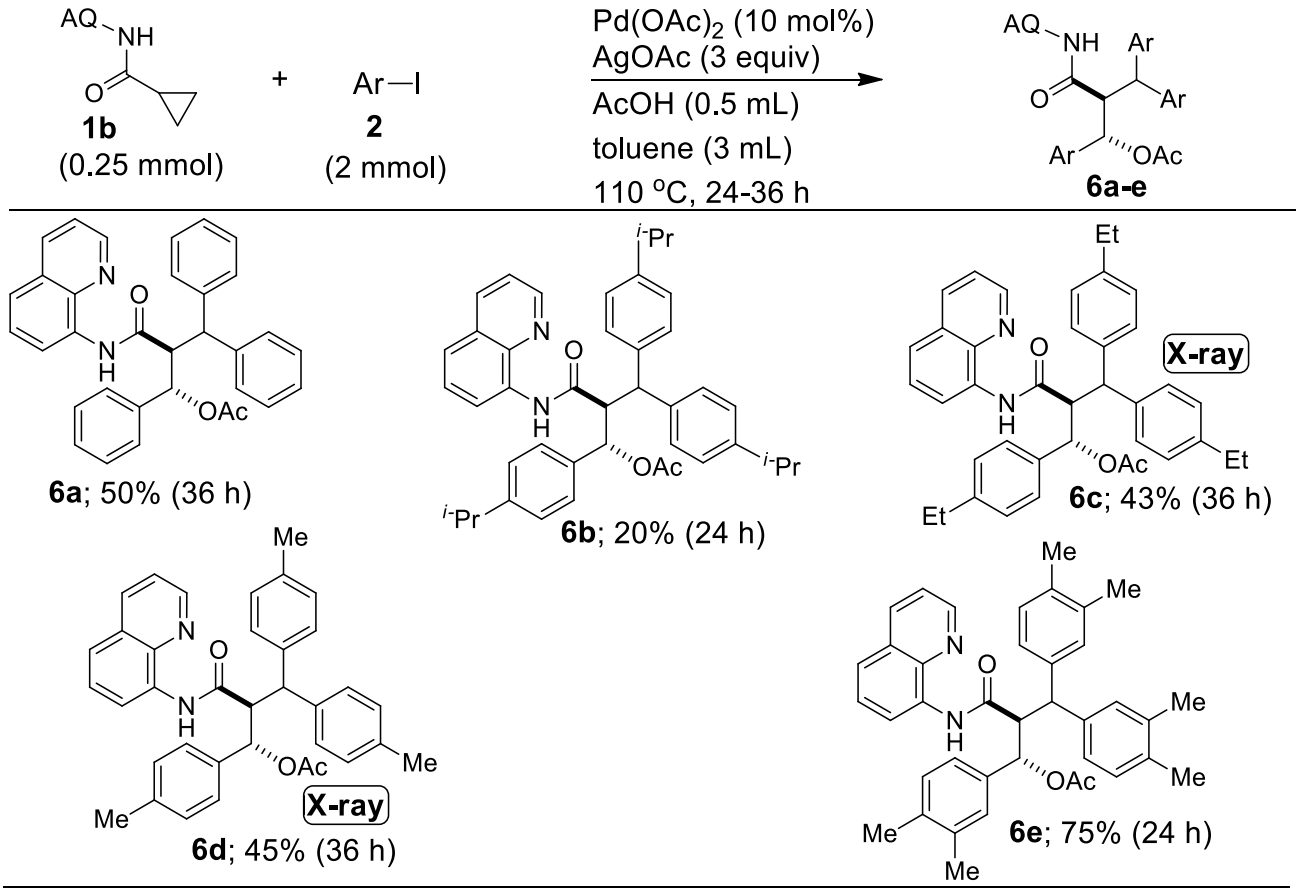
Table 2. Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamide 1a.

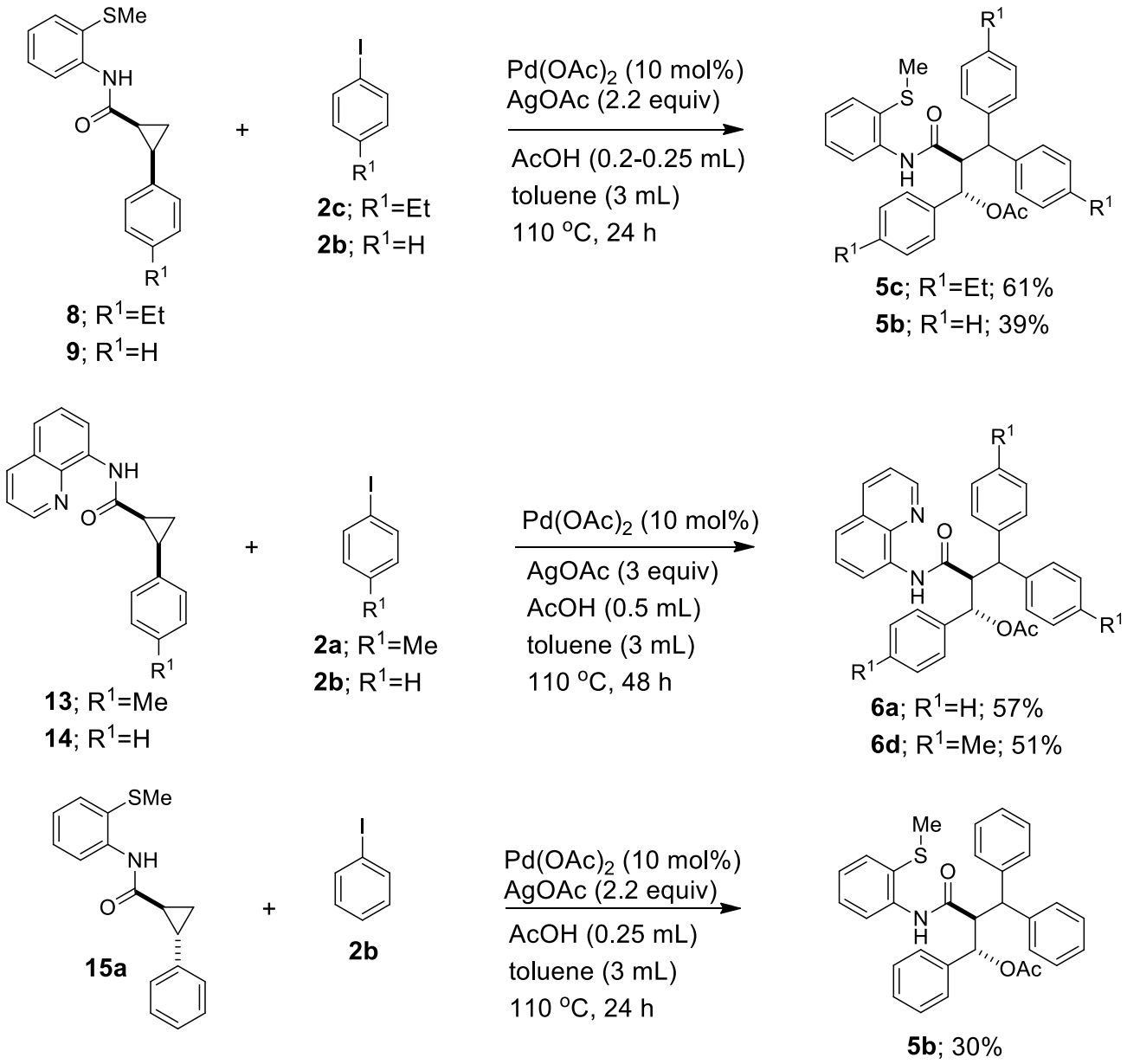


Next, we investigated diastereoselective C-H arylation followed by ring opening of cyclopropanecarboxamide using cyclopropanecarboxamide **1b**, which was assembled from 8-aminoquinoline bidentate ligand (Table 3). The $Pd(OAc)_2$/AgOAc catalytic system-based

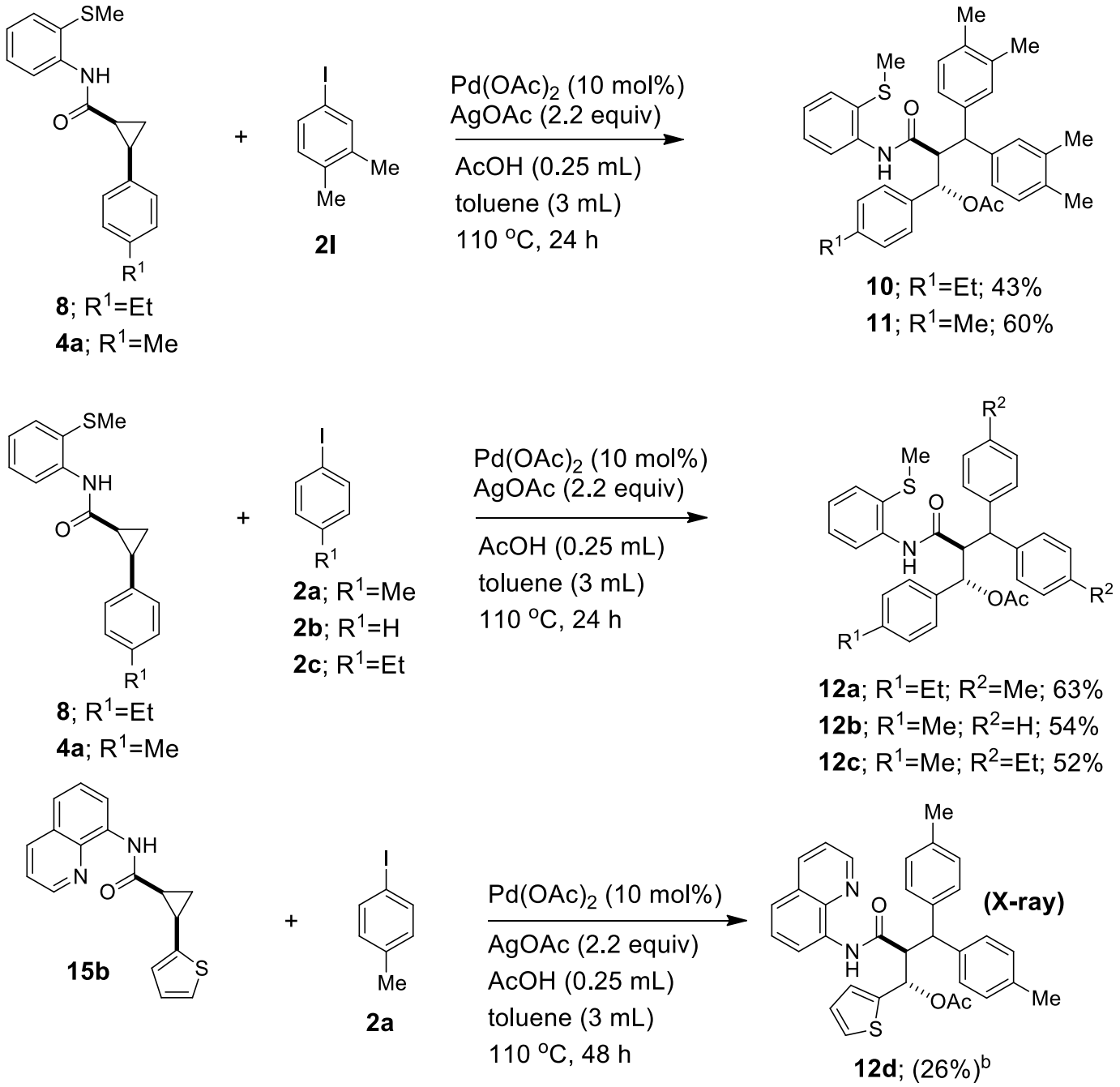
diastereoselective C-H arylation followed by ring opening of cyclopropanecarboxamide **1b** with different aryl iodides in AcOH afforded the corresponding multiple β-C-H arylated open-chain carboxamides **6a-e** (*anti* β-acyloxy amides possessing vicinal stereocenters) in 20-75% yields (Table 3). In these studies, we have revealed the concept of Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides using unsubstituted cyclopropanecarboxamides **1a** and **1b** as the substrates. Next, we examined the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides using various mono-arylated cyclopropanecarboxamides **4a**/**8**/**9**/**13**/**14**/**15b** (*cis* isomers) and **15a** (*trans* isomer) as the substrates (Scheme 2).

Table 3. Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamide 1b.





Scheme 3. Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamides 4a, 8, 9, 13, 14 and 15a,b.[a]

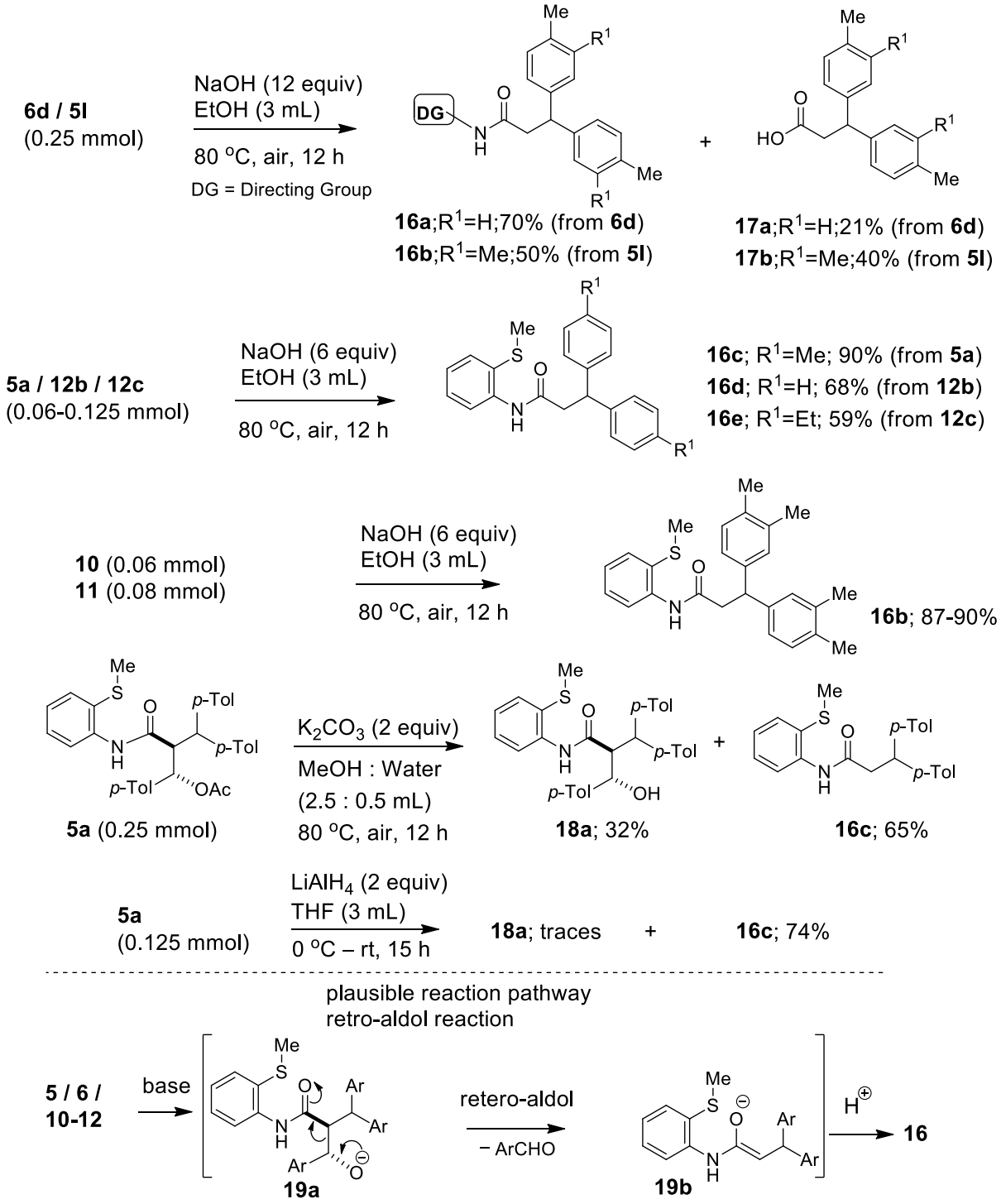


[a] The reactions were performed using the corresponding carboxamide (0.25 mmol) and ArI (1.2 mmol). [b] This reaction was performed using carboxamide **15b** (0.25 mmol) and ArI (2 mmol).

Scheme 3 (continued). Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamides 4a, **8**, **9**, **13, 14 and 15a,b.**[a]

The Pd(II)-catalyzed C-H arylation followed by ring opening of *cis* cyclopropanecarboxamides **8** and **9** with aryl iodides **2c**/**2b** furnished the corresponding multiple β-C-H arylated open-chain carboxamides **5c** (61%) and **5b** (39%, Scheme 3). It is important to note that the substituents present at the *para* positions of the respective aryl iodides (**2c**/**2b**) and the substituents present at the *para* positions of the aryl rings of the respective substrates (**8**/**9**) were identical. Therefore, the Pd(II)-catalyzed C-H arylation followed by ring opening of **8**/**9** with **2c**/**2b** furnished corresponding products **5c** and **5b**, in which the corresponding aryl rings had identical substituents at the *para* positions. Similar to the reactions involving substrates **8** and **9**, the Pd(II)-catalyzed C-H arylation followed by ring opening of the *cis* cyclopropanecarboxamides **13** and **14** with *para*-substituted aryl iodides **2a** and **2b** afforded the corresponding multiple β-C-H arylated open-chain carboxamides **6d** (51%) and **6a** (57%, Scheme 3). Additionally, the Pd(II)-catalyzed C-H arylation followed by ring opening of the *trans* cyclopropanecarboxamide **15a** with iodobenzene also furnished multiple β-C-H arylated open-chain carboxamides **5b** in 30% yield (Scheme 3).

The Pd(II)-catalyzed C-H arylation followed by ring opening of *cis* cyclopropanecarboxamides **4a** and **8** with the corresponding aryl iodides **2a-c** and **2l** furnished the respective multiple β-C-H arylated open-chain carboxamides **10**,**11** (43-60%) and **12a-c** (52-63%, Scheme 3).[57] It is important to note that the substituents present at the *para/meta* positions of the respective aryl iodides **2a-c** and **2l** and the substituents present at the *para* positions of the aryl rings of the respective substrates **4a** and **8** were not identical. Therefore, the Pd(II)-catalyzed C-H arylation followed by ring opening of **4a** and **8** with **2a-c** and **2l** furnished corresponding products **10**,**11** and **12a-c**, in which the corresponding aryl rings did not contain identical substituents at the *para* positions.[57] Along this line, the Pd(II)-catalyzed C-H arylation followed by ring opening of *cis* cyclopropanecarboxamide **15b** with **2a** furnished the respective multiple β-C-H arylated open-chain carboxamide **12d** in 26% yield (Scheme 3). The structure and stereochemistry of compound **12d** were unambiguously established based on X-ray structure analysis.



Scheme 4. Representative Synthetic Transformations.

We also performed synthetic transformations to remove the directing groups from the representative multiple β-C-H arylated open-chain carboxamides that were obtained from the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamide. Initially, we attempted the amide hydrolysis reaction of *anti* β-acyloxy amide **6d** with 12 equiv of NaOH in EtOH, and this reaction afforded carboxamide **16a**, which contain the directing group, and carboxylic acid **17a** (formed from carboxamide **16a**, Scheme 4). Similarly, the amide hydrolysis reaction of *anti* β-acyloxy amide **5l** with 12 equiv of NaOH in EtOH afforded carboxamide **16b** and carboxylic acid **17b** (formed from carboxamide **16b**, Scheme 4). Then, the treatment of *anti* β-acyloxy amide **5a** with less NaOH (6 equiv) in EtOH only furnished carboxamide **16c**, and in this case, the corresponding carboxylic acid was not detected. In addition, we reacted carboxamides **10**, **11** and **12b**,**c** possessing different aryl groups at the 1,3-positions with less NaOH (6 equiv) to afford corresponding carboxamides **16b,d**,**e** (Scheme 4).

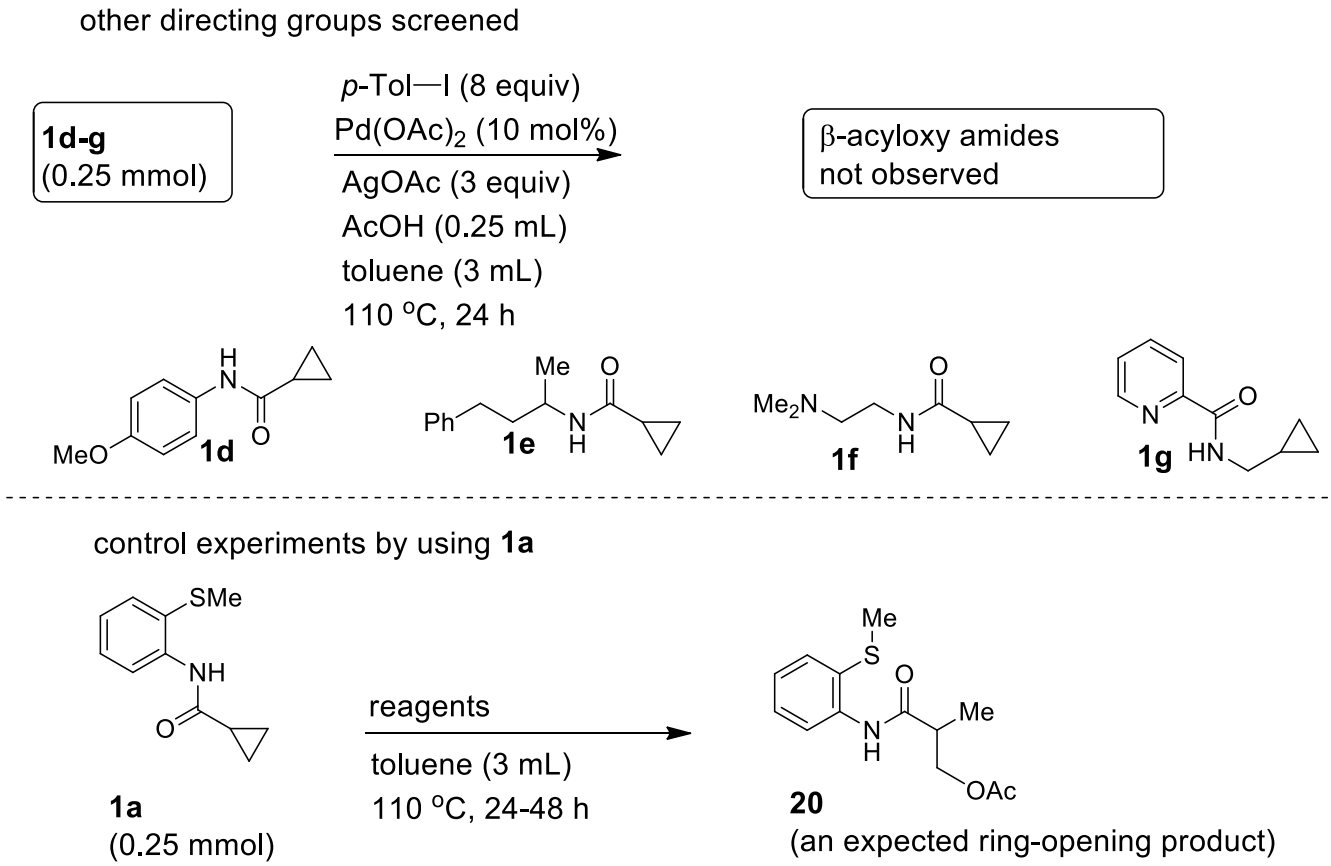
Next, the amide hydrolysis reaction was investigated under mild reaction conditions. We performed the amide hydrolysis of *anti* β-acyloxy amide **5a** in the presence of K_2CO_3 in MeOH, and this reaction afforded β-hydroxy amide **18a** and carboxamide **16c** (to support the proposed mechanism, we have recorded the crude NMR for the reaction mixture of the experiment involving amide hydrolysis of **5a** in the presence of K_2CO_3, which revealed the formation of *p*-tolualdehyde *via* the retro-aldol reaction). In addition, the reaction of *anti* β-acyloxy amide **5a** in the presence of $LiAlH_4$ afforded carboxamide **16c**. We also attempted the amide hydrolysis and removal of the directing groups (i.e., 8-aminoquinoline and 2-(methylthio)aniline) under acidic conditions. However, these trials were not fruitful at this stage. In the base-mediated amide hydrolysis reactions of the substrates investigated in Scheme 4, we expected the removal of the directing groups (i.e., 8-aminoquinoline and 2-(methylthio)aniline) as well as the deprotection of the OAc group present in the corresponding substrates. However, because the products (**5**/**6**/**10**-**12**) obtained from the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides were aldol-type derivatives, these compounds readily underwent retro-aldol type reactions[56b,c] even under mild or strongly basic conditions and furnished corresponding products **16** under the experimental conditions.[56e]

Because the Pd-catalyzed reaction of cyclopropanecarboxamides with aryl iodides in AcOH affords the corresponding open-chain carboxamides **5**/**6**/**10-12**, control experiments were performed to determine a plausible mechanism for the formation of products **5**/**6**/**10-12** from their corresponding cyclopropanecarboxamide substrates shown in Tables 1-3 and Scheme 3. Initially, we attempted the Pd(II)-catalyzed C-H arylation followed by ring opening of cyclopropanecarboxamides **1d** and **1e**, which contain no directing groups, and cyclopropanecarboxamides **1f** and **1g**, which were prepared using other bidentate ligands. The Pd(II)-catalyzed C-H arylation followed by ring opening of substrates **1d-g** failed to yield the corresponding β-acyloxy amides (Scheme 5). These reactions revealed that 8-aminoquinoline and 2-(methylthio)aniline were efficient bidentate ligands and essential for accomplishing the Pd(II)-catalyzed C-H arylation followed by ring opening of the respective cyclopropanecarboxamides shown in Tables 1-3 and Scheme 3.

Then, we performed control experiments to understand at what stage the C-C cleavage of the corresponding cyclopropanecarboxamides occurs and how the open-chain carboxamides **5**/**6**/**10-12** are formed with a high degree of stereocontrol. Initially, we performed the control experiments using unsubstituted cyclopropanecarboxamide **1a**. The reaction of **1a** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH did not yield β-acyloxy amide **20** (i.e., the expected open-chain compound, entry 1, Scheme 5). The treatment of **1a** with only AgOAc and AcOH did not yield compound **20** (entry 2, Scheme 4). In addition, the reaction of **1a** with only AcOH did not yield expected compound **20** (entry 3, Scheme 5).

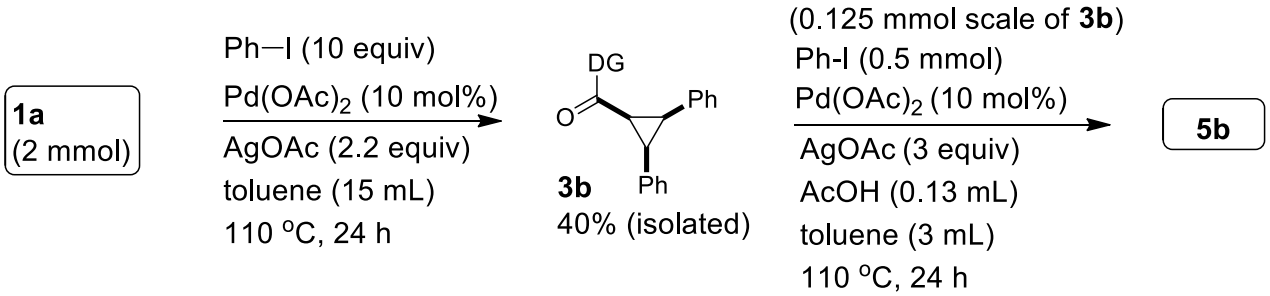
Next, we performed control experiments using bis-arylated cyclopropanecarboxamide **3b**. We assembled compound **3b**, which was subjected to a Pd(II)-catalyzed C-H arylation reaction with iodobenzene in the presence of AcOH (Scheme 6). This reaction resulted in the formation of product **5b**, which was directly obtained from **1a** (entry 19, Table 2). The reaction of **3b** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH afforded expected open-chain compound **21**, which was isolated in 25% yield and characterized (entry 1, Scheme 6). The treatment of **3b** with only AgOAc and AcOH did not yield compound **21** (entry 2, Scheme 6). Similarly, the reaction of **3b** with only AgOAc or AcOH also did not yield compound **21** (entries 3 and 4, Scheme 6). Next, we performed a control experiment involving the C-H arylation reaction of **21** with PhI in

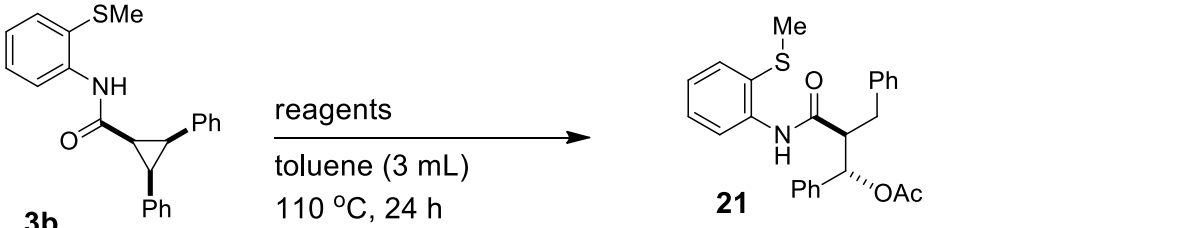
the presence of the $Pd(OAc)_2$ catalyst and AgOAc, which resulted in the formation of **5b** (Scheme 6).



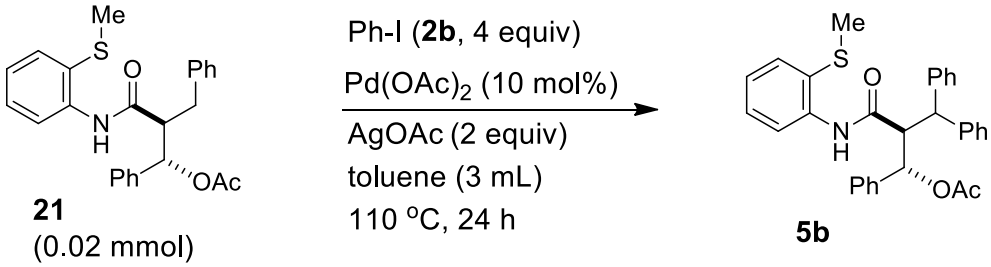
entry	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (0.75 mmol)	AcOH (1 mL)	observation
1	×	✓	✓	✓	no ring-opening product
2	×	×	✓	✓	no ring-opening product
3	×	×	×	✓	no ring-opening product

Scheme 5. Screening of Other Ligands and Control Experiments Performed using Substrate 1a.[a]



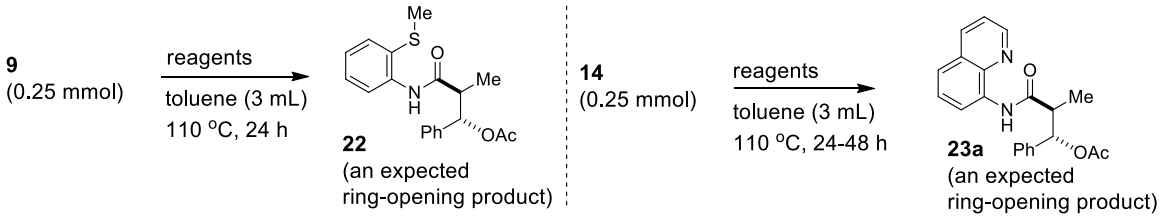


entry	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (3 equiv)	AcOH (0.1-1 mL)	observation
1[a]	×	✓	✓	✓	**21**; yield = 25%
2[b]	×	×	✓	✓	no ring-opening product
3[c]	×	×	✓	×	no ring-opening product
4[d]	×	×	×	✓	no ring-opening product

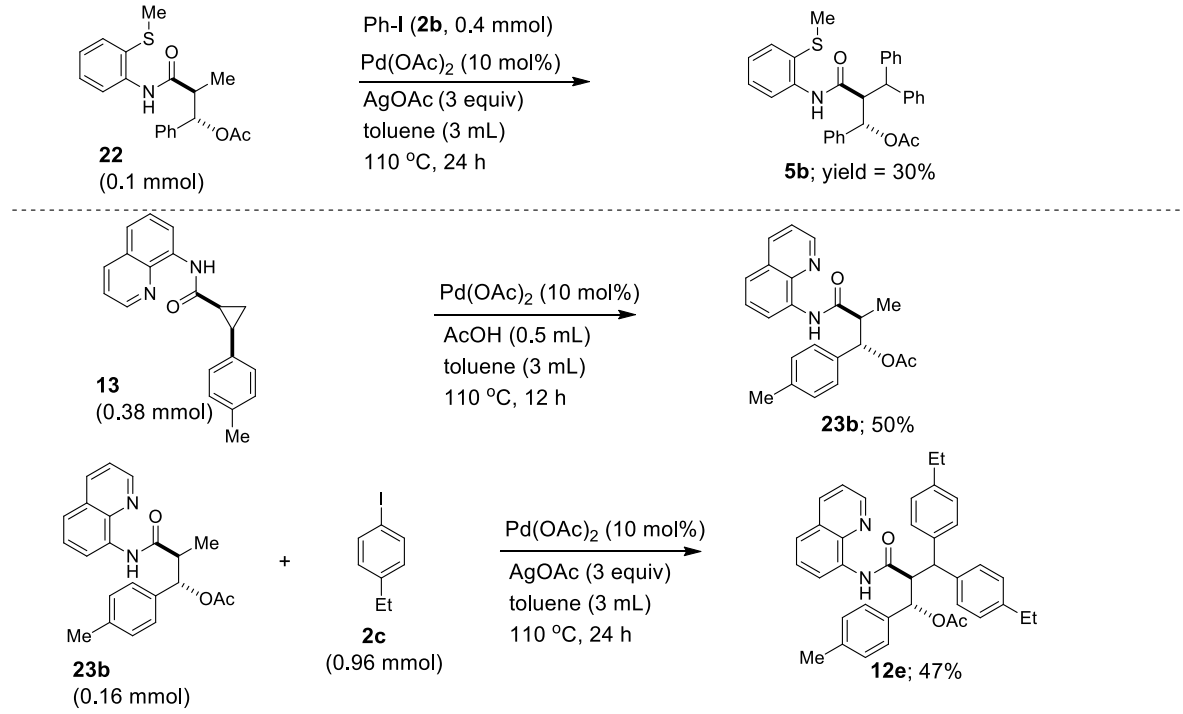


[a] 0.17 mmol of **3b** and 0.2 mL of AcOH were used. [b] 0.08 mmol of **3b**, 0.1 mL of AcOH and 2 mL of toluene were used. [c] 0.04 mmol of **3b** were used. [d] 0.125 mmol of **3b** and 1 mL of AcOH were used.

Scheme 6. Control Experiments Performed using Substrates 3b and 21 to Elucidate the Proposed Mechanism.



entry	substrate	ArI	$Pd(OAc)_2$ (10 mol%)	AgOAc (0.75 mmol)	AcOH (0.5 mL)	observation
1	**9**	×	✓	✓	✓	**22**; yield = 33%
2	**14**[a]	×	✓	✓	✓	**23a**; yield = 43%
3	**9** (or) **14**[a]	×	×	✓	✓	no ring-opening product
4	**9** (or) **14**	×	×	✓	×	no ring-opening product
5	**9**	×	×	×	✓	no ring-opening product
6[b]	**4a**	×	×	×	✓	no ring-opening product
7	**9** (or) **14**	×	✓	✓	×	no ring-opening product
8	**14**[a]	×	✓	×	✓	**23a**; yield = 47%



Scheme 7. Control Experiments Performed using Substrates 9, 13, 14 and 22 to Elucidate the Proposed Mechanism.[a]

[a] The reaction time was 48 h. [b] This reaction was performed using **4a** (0.125 mmol) rather than **9** and 1 mL of AcOH.

Although we performed the control reactions using unsubstituted cyclopropanecarboxamide **1a** and bis-arylated cyclopropanecarboxamide **3b**, based on the results shown in Scheme 3, we envisioned that the ring opening can also occur after the mono-arylation of **1a** (or before the bis-arylation of **1a**). To validate this hypothesis, control experiments were performed using mono-arylated cyclopropanecarboxamides **9** and **14** (Scheme 7). The reaction of substrates **9** and **14** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH yielded the corresponding open-chain compounds (i.e., **22** (33%) and **23a** (43%)), which were isolated and characterized (entries 1 and 2, Scheme 7). Then, a control experiment involving the C-H arylation reaction of **22** with PhI in the presence of the $Pd(OAc)_2$ catalyst and AgOAc resulted in the formation of **5b**, which was obtained directly from **1a** (entry 19, Table 2). Then, additional control experiments were performed using substrates **9**/**14** by varying the control reagents (entries 3-7, Scheme 7). However, none of these reactions afforded the corresponding compounds **22** and **23a**. A control experiment involving the reaction of **14** with only the $Pd(OAc)_2$ catalyst and AcOH afforded open-chain compound **23a** (entry 8, Scheme 7). In addition, the reaction of **13** with only the $Pd(OAc)_2$ catalyst and AcOH afforded open-chain compound **23b** (Scheme 7). Then, the C-H arylation reaction of **23b** with **2c** in the presence of the $Pd(OAc)_2$ catalyst and AgOAc afforded compound **12e** (47%, Scheme 6). It is important to note that the substituent present at the *para* position of **2c** and the substituent present at the *para* position of the aryl ring of **23b** were not identical.

The formation of compounds **22**/**23a** from the reactions of respective substrates **9**/**14** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH indicated that mono-arylated cyclopropanecarboxamides **9**/**14** and ring-opened carboxamides **22**/**23a** were possible intermediates in the reaction of **1a**/**1b** with PhI in the presence of the $Pd(OAc)_2$ catalyst, AgOAc and AcOH. This hypothesis was further validated from the $Pd(OAc)_2$-catalyzed double C-H arylation reaction of the methyl group of **22** with PhI, which yielded compound **5b**. Based on the results from the control reactions (Schemes 5-7) as well as observed products **5**/**6**/**10-12** (*anti* β-acyloxy amides), we propose a plausible mechanism for the diastereoselective Pd(II)-catalyzed

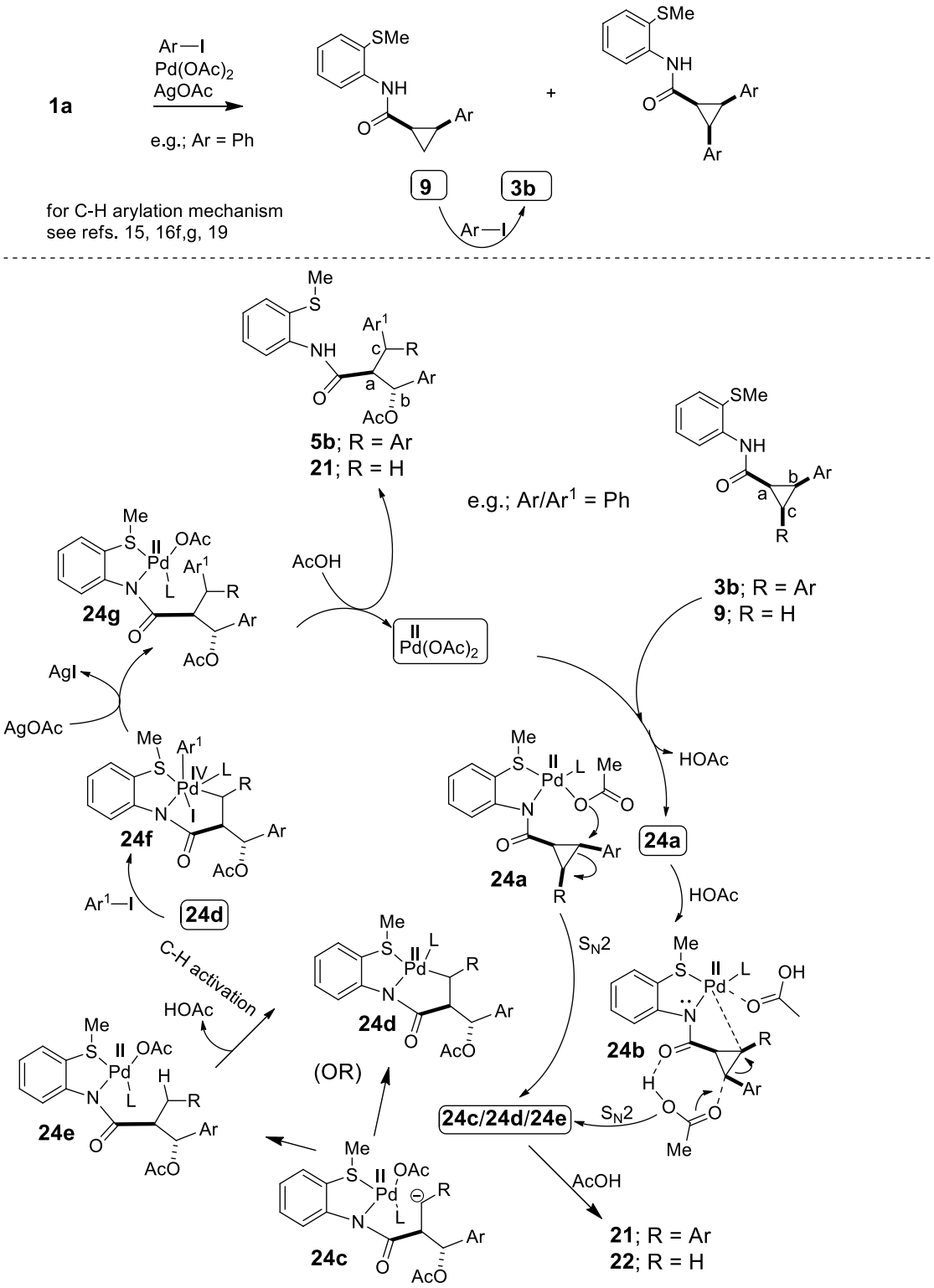
C-H arylation followed by ring opening of cyclopropanecarboxamides in Scheme 8. The mechanism is proposed on the basis of the generally accepted Pd(II/IV) catalytic cycle mechanism involving bidentate ligand-aided C-H arylation. Based on the control experiments (Schemes 5-7), we have elucidated a possible mechanism for the formation of *anti* β-acyloxy amide **5b** from the Pd(II)-catalyzed reaction of **1a** with PhI in the presence of AgOAc and AcOH. The C-C cleavage of the cyclopropane ring is predicted to only occur after the formation of mono-arylation product **9** as well as bis-arylation product **3b**. For the C-C bond cleavage process, both the $Pd(OAc)_2$ catalyst and AcOH are essential. However, AgOAc is not essential for the C-C bond cleavage process, and AgOAc simply helps to regenerate the $Pd(OAc)_2$ catalyst in the C-H arylation process involved in the Pd(II/IV) catalytic cycle mechanism.[36a, 37f, 58]

Under the current experimental conditions, compound **3b** or **9** is also expected to be present as **24a**. Then, due to the ring strain, the mono or bis C-H arylated cyclopropanecarboxamide system **24a** undergoes C-C cleavage through (a) a S_N2 type internal attack by the OAc group of the Pd(II) species **24a** or (b) an AcOH-influenced Pd-based C-C activation/C-C bond cleavage[23f] involving a S_N2 type attack by the OAc group of AcOH (as shown in species **24b**). Both of these possibilities could form any one of the plausible intermediates **24c**/**24d**/**24e** with a high degree of stereocontrol. It is important to note that the stereochemistry of the OAc and CONH groups were determined to be *anti* in the X-ray structures (e.g., **5b**, **6c** and **6d**). Notably, the C-H arylation of cyclopropanecarboxamides has been reported to be a stereoselective process,[35b, 36a, 37f, 58] and in the current study, the ring opening of the cyclopropanecarboxamides was determined to be a stereoselective process.

The formation of compounds **21** (entry 1, Scheme 6) and **22** (entry 1, Scheme 7) from **3b** or **9** confirmed the involvement of the plausible ring-opened intermediates **24c/24d/24e** in the proposed mechanism. If intermediates **24c-e** were not quenched by AcOH, a further C-H arylation of intermediates **24c/24d/24e** (R = H/Ph) affords product **5b**.[36a, 37f, 58, 59] However, starting from **9** (R = H), if compound **22** was formed after the ring opening and before any further C-H arylation due to the AcOH-mediated quenching of **24c/24d/24e** (when R = H), the double C-H arylation of the methyl group of **22** would afford compound **5b** (based on the control reaction shown in Scheme 6). Similarly, starting from **3b** (R = Ph), if compound **21** was formed

after the ring opening and before any further C-H arylation due to the AcOH-mediated quenching of **24c**/**24d**/**24e** (when R = Ph), the C-H arylation of the methylene group of **21** would afford compound **5b** (based on the control reaction shown in Scheme 6). Moreover, the second arylation of **9** may be a slow reaction due to the formation of the corresponding sterically crowded trisubstituted cyclopropanecarboxamide **3b**. Therefore, the ring opening of **9** may occur before the C-H arylation to afford **5b** *via* **24a-e** (based on the control reaction shown in Scheme 7). Furthermore, starting from **1a**, product **5b** may have been directly formed from **9** rather than **3b**.

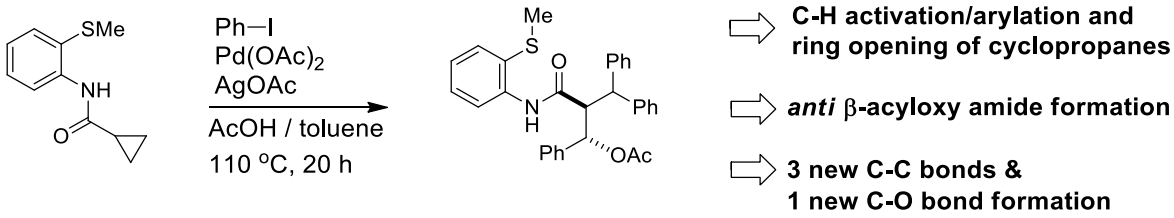
Finally, based on these discussions and the formation of ring-opened carboxamide **23b** from the reaction of **13** with only the $Pd(OAc)_2$ catalyst, AgOAc and AcOH (Scheme 7) as well as the subsequent formation of **12e** from the $Pd(OAc)_2$-catalyzed double C-H arylation of the methyl group of **23b** with **2c** indicated the following conclusions. First, the proposed structures of compounds **10**, **11**, **12a-d** (Scheme 3) have been confirmed. Second, the arylation of **8**/**4a**/**15b** with the respective aryl iodides **2a-c,l** may involve the corresponding ring-opened product similar to **23b** as the potential predominantly formed intermediates. In addition, because the second arylation of **8**/**4a**/**15b** may be a slow reaction due to the formation of the corresponding sterically crowded trisubstituted cyclopropanecarboxamide (e.g., compound type **3b**), we believe that the ring opening of **8**/**4a**/**15b** may occur prior to the C-H arylation of **8**/**4a**/**15b**. Therefore, although the respective reactions of **8**/**4a**/**15b** with **2a-c** and **2l** are expected to afford more than one isomer, the respective arylation reactions of **8**/**4a**/**15b** with **2a-c** and **2l** yielded the respective compounds **10-12** (Scheme 3) as the predominant compounds.



Scheme 8. Plausible Mechanism for the Diastereoselective Pd(II)-Catalyzed C-H Arylation Followed by Ring Opening of Cyclopropanecarboxamides. [36a, 37f, 58]

Summary

The Chapter 3 demonstrated $Pd(OAc)_2$-catalyzed, bidentate ligand-directed sp^3 C-H activation/arylation followed by ring opening of cyclopropanecarboxamides. The treatment of various cyclopropanecarboxamides with excess amounts of aryl iodides in the presence of the $Pd(OAc)_2$ catalyst, AgOAc and AcOH directly afforded the corresponding multiple β-C-H arylated open-chain carboxamides (*anti* β-acyloxy amides).



This method has led to the construction of several *anti* β-acyloxy amides that possess vicinal stereocenters with a high degree of stereocontrol with the formation of a new C-O bond and three new C-C bonds. Based on various control experiments, a plausible mechanism has been proposed for the formation of multiple β-C-H arylated open-chain carboxamides from the diastereoselective Pd-catalyzed, bidentate ligand-directed β-C-H arylation and ring opening of cyclopropanecarboxamides.

The observed diastereoselectivity and *anti* stereochemistry of the obtained products were confirmed by X-ray structure analysis of representative β-acyloxy amides.

Experimental Section

General.[56-61] The melting points of the compounds were uncorrected, and the IR spectra of the products were recorded as thin films or KBr pellets. The ^1H and $^{13}C\{^1H\}$ NMR spectra of all of the compounds were recorded on 400 MHz and 100 MHz spectrometers, respectively, using TMS as an internal standard. The HRMS measurements of the samples were obtained from QTOF mass analyzer using the electrospray ionization (ESI) method. Column chromatography

was performed using neutral alumina (in some cases, silica gel 100-200 mesh was used). The cyclopropanecarboxamides that were employed in the Pd(II)-catalyzed C-H arylation reactions were prepared from their corresponding acid chlorides and amines using standard literature procedures. The reactions were performed in anhydrous solvents, which were prepared using standard procedures, under a nitrogen atmosphere. The isolated yields of all of the compounds are reported, and the yields were not optimized. In most cases, the purification of the crude reaction mixtures yielded only the major diastereomer in pure form and did not afford any other characterizable compounds.

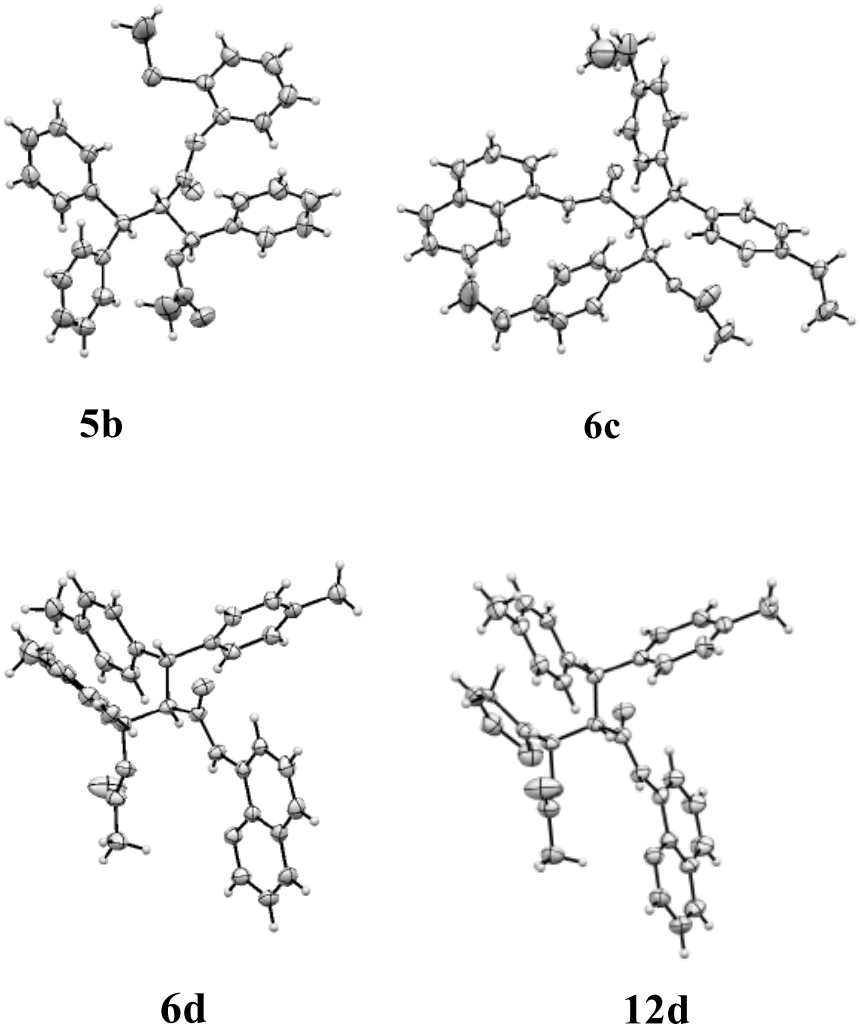


Figure 1: X-ray structures of compounds **5b**, **6c**, **6d** and **12d**.

General procedure for the preparation of 1a,b/1d-g/15a: To a dry round bottom (RB) flask, an appropriate ligand/amine (1 mmol), triethyl amine (1.1 mmol) and DCM (6 mL) were added under a nitrogen atmosphere. To this solution, the corresponding acid chloride (1 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 20 h. After the reaction period, the mixture was diluted with DCM (2 x 10 mL) and transferred to a separatory funnel, and the DCM solution was washed with water followed by an aq. $NaHCO_3$ solution (2-5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum, and purification of the crude reaction mixture by column chromatography (EtOAc/hexane) furnished products **1a,b/1d-g/15a**.

General procedure for the Pd(II)-catalyzed C-H arylation/ring opening of 1a/1b and the preparation of 5a-l/6a-e: To an oven dried RB flask, an appropriate cyclopropanecarboxamide (0.25 mmol, 1 equiv), the corresponding aryl iodide (2 mmol, 8 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol%, 0.1 equiv), AgOAc (125 mg, 0.75 mmol, 3 equiv), AcOH (0.25 mL) and anhydrous toluene (2-3 mL) were added, and the reaction mixture was refluxed at 110 °C for 16-36 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (15-20 mL), transferred to a separatory funnel and washed with a dilute aq. $NaHCO_3$ solution (2-5 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum, and purification of the reaction crude mixture by column chromatography on neutral alumina furnished the corresponding multiple C-H arylated aliphatic carboxamides **5a-l/6a-e** (β-acyloxy amide derivatives) (see the corresponding Tables/Schemes for specific examples).

General procedure for the Pd(II)-catalyzed mono C-H arylation of 1a/1b and the preparation of 4a/8/9/13/14/15b: To an oven dried RB flask, an appropriate cyclopropanecarboxamide (1.0 mmol, 1 equiv), the corresponding aryl iodide (4 mmol, 4 equiv), $Pd(OAc)_2$ (11.2 mg, 5 mol%, 0.05 equiv), AgOAc (367 mg, 2.2 mmol, 2.2 equiv) and anhydrous toluene (6-8 mL) were added, and the reaction mixture was refluxed at 110 °C for 15 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated under vacuum, and purification of the resulting reaction mixture by column chromatography on neutral alumina furnished the corresponding carboxamides **4a/8/9/13/14/15b**.

General procedure for the Pd(II)-catalyzed bis C-H arylation of 1a and the preparation of 3b: To an oven dried RB flask, cyclopropanecarboxamide **1a** (1.0 mmol, 1 equiv), iodobenzene (10 mmol, 10 equiv), $Pd(OAc)_2$ (22.4 mg, 10 mol%, 0.1 equiv), AgOAc (367 mg, 2.2 mmol, 2.2 equiv) and anhydrous toluene (6-8 mL) were added, and the reaction mixture was refluxed at 120 °C for 20 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated under vacuum, and purification of the resulting reaction mixture by column chromatography on neutral alumina furnished the corresponding carboxamide **3b** (careful repetitive purification was performed to obtain the pure compound **3b**).

General procedure for the Pd(II)-catalyzed C-H arylation/ring-opening of 4a/8/9/13-15 and the preparation of 5c,b/6a,d/10/11/12a-d: To an oven dried RB flask, an appropriate cyclopropanecarboxamide (0.25 mmol, 1 equiv), the corresponding aryl iodide (1.5 mmol, 6 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol%, 0.1 equiv), AgOAc (92 mg, 0.55 mmol, 2.2 equiv), AcOH (0.25 mL) and anhydrous toluene (2-3 mL) were added, and the reaction mixture was refluxed at 110 °C for 24-48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (15-20 mL), transferred to a separatory funnel and washed with a dilute aq. $NaHCO_3$ solution (2-5 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum, and purification of the reaction crude mixture by column chromatography on neutral alumina furnished the corresponding multiple C-H arylated aliphatic carboxamides **5c,b/6a,d/10/11/12a-d** (β-acyloxy amide derivatives).

General procedure for the K_2CO_3–mediated hydrolysis carboxamide 5a and the preparation of 18a/16c: To a RB flask (with a capacity of 25 mL) fitted with a condenser, a solution of carboxamide **5a** (0.25 mmol) dissolved in a mixture of methanol (2.5 mL), water (0.5 mL) and K_2CO_3 (69 mg, 2 equiv) were sequentially added. The reaction mixture was heated at 80 °C for 12 h in an open atmosphere. Then, the reaction mixture was transferred to a separatory funnel with the aid of a syringe. The reaction mixture was diluted with ethyl acetate and washed with a dilute aq. Na_2CO_3 solution (5-10 mL). The combined organic layers were separated and concentrated under vacuum, and purification of the reaction mixture on neutral alumina furnished products **18a/16c**.

General procedure for the $LiAlH_4$–mediated reduction of carboxamide 5a and the preparation of 16c: To a dry RB flask containing carboxamide **5a** (0.125 mmol, 1 equiv) in THF (3 mL), $LiAlH_4$ (10 mg, 0.25 mmol, 2 equiv) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for a total period of 15 h. After this period, the THF was evaporated, and the reaction mixture was diluted with EtOAc and water. Then, the reaction mixture was transferred to a separatory funnel, and the layers were separated. The organic layer was concentrated under vacuum, and purification of the reaction mixture on neutral alumina furnished products **16c**.

General procedure for the NaOH–mediated hydrolysis of carboxamides 5a,l/6d/10/11/12b,c: To a RB flask (with a capacity of 25 mL) fitted with a condenser, a solution of an appropriate carboxamide (0.25 mmol) dissolved in ethanol (3 mL) and NaOH (6 or 12 equiv) were sequentially added. The reaction mixture was heated at 80 °C for 12 h in an open atmosphere. Then, EtOH was removed under vacuum, and the reaction mixture was diluted with ethyl acetate (10-15 mL) and washed with aq. 1 N NaOH (5 mL x 2). The organic layer was concentrated under vacuum, and purification of the reaction mixture on a neutral alumina column furnished the corresponding products **16a-e**. Then, the combined aqueous layers were acidified with 1 N HCl (15 mL x 2) to achieve a pH of ~2. The aqueous layers were extracted using ethyl acetate (10 mL x 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporation under vacuum to afford the corresponding carboxylic acids **17a,b**.

***N*-(2-(Methylthio)phenyl)cyclopropanecarboxamide (1a):** Following the general procedure, **1a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a colourless solid; mp 69-71 °C; Yield: 45% (93 mg); IR (KBr): 3264, 3005, 2916, 1651, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (br. s,1H), 8.27 (d, 1H, J = 6.0 Hz), 7.44 (d, 1H, J = 7.7 Hz), 7.26-7.21 (m, 1H), 7.03 (t, 1H, J = 7.4 Hz), 2.36 (s, 3H), 1.63-1.58 (m, 1H), 1.10-1.06 (m, 2H), 0.87-0.82 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 132.7, 128.7, 125.2, 125.2, 124.2, 120.8, 18.9, 16.0, 8.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{14}NOS$: 208.0796; found 208.0793.

***N*-(Quinolin-8-yl)cyclopropanecarboxamide (1b):** Following the general procedure, **1b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colourless solid; mp 81-83 °C; Yield: 83% (176 mg); IR (KBr): 3242, 3351, 1676, 1525, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.05 (br. s,1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56-7.49 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 1.87-1.81 (m, 1H), 1.20-1.16 (m, 2H), 0.96-0.91 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.3, 148.1, 138.2, 136.4, 134.7, 128.0, 127.5, 121.6, 121.2, 116.4, 16.3, 8.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1028; found 213.1035.

(*1S*,2S)-*N*-(2-(Methylthio)phenyl)-2-phenylcyclopropanecarboxamide (15a):** Following the general procedure, **15a** (*trans* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 10:90) as a colourless solid; mp 119-121 °C; Yield: 78% (220 mg); IR (KBr): 3434, 3242, 3098, 1649, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (br. s, 1H), 8.41 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 7.6 Hz), 7.36-7.24 (m, 4H), 7.19 (d, 2H, J = 7.3 Hz), 7.10 (t, 1H, J = 7.3 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 140.5, 138.6, 133.2, 129.1, 128.6, 126.5, 126.2, 124.7, 124.2, 120.4, 28.0, 26.1, 19.2, 16.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}NOS$: 284.1109; found 284.1090.

***N*-(4-Methoxyphenyl)cyclopropanecarboxamide (1d):** Following the general procedure, **1d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a pink coloured solid; mp 134-136 °C; Yield: 68% (130 mg); IR (KBr): 3283, 3095, 2822, 1648, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (br. s, 1H), 7.41 (d, 2H, J = 8.9 Hz), 6.83 (d, 2H, J = 8.9 Hz), 3.79 (s, 3H), 1.53-1.49 (m, 1H), 1.07-1.03 (m, 2H), 0.82-0.77 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 156.2, 131.4, 121.8, 114.0, 55.5, 15.4, 7.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$: 192.1025; found 192.1020.

***N*-(4-Phenylbutan-2-yl)cyclopropanecarboxamide (1e):** Following the general procedure, **1e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colourless solid; mp 109-111 °C; Yield: 92% (199 mg); IR (KBr): 3270, 3094,

2967, 1638, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.21-7.18 (m, 3H), 6.01 (br. s, 1H), 4.13- 4.05 (m, 1H), 2.67 (t, 2H, *J* = 8.4 Hz), 1.84-1.73 (m, 2H), 1.38-1.34 (m, 1H), 1.19 (d, 3H, *J* = 6.6 Hz), 0.99-0.94 (m, 2H), 0.74-0.69 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 141.9, 128.4, 128.4, 125.9, 45.2, 38.8, 32.6, 21.1, 14.8, 7.0, 6.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO$: 218.1545; found 218.1538.

***N*-(2-(Dimethylamino)ethyl)cyclopropanecarboxamide (1f):** Following the general procedure, **1f** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as a colourless liquid ; Yield: 8% (13 mg); IR (KBr): 3241, 3189, 3096, 1592, 1561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.34 (dd, 1H, J_1 = 11.5 Hz, J_2 = 5.6 Hz), 2.85 (br. s, 1H), 2.41 (t, 1H, *J* = 6.0), 2.23 (s, 6H), 1.42-1.35 (m, 1H), 0.96-0.91 (m, 2H), 0.73-0.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 58.0, 45.1, 36.9, 14.6, 7.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{17}N_2O$: 157.1341; found 157.1338.

***N*-(Cyclopropylmethyl)picolinamide (1g):** Following the general procedure, **1g** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless liquid ; Yield: 63% (111 mg); IR (KBr): 3241, 3186, 3092, 1667, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.56 (m, 1H), 8.21 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.16 (br. s, 1H), 7.85 (dt, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 7.44-7.41 (m, 1H,), 3.34 (dd, 2H, J_1 = 7.0 Hz, J_2 = 6.0 Hz), 1.13-1.08 (m, 1H), 0.58-0.54 (m, 2H), 0.32-0.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 150.1, 148.0, 137.3, 126.1, 122.2, 44.2, 10.8, 3.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$: 177.1028; found 177.1024.

(*1S*,2R*,3S)-*N*-(2-(Methylthio)phenyl)-2,3-di-*p*-tolylcyclopropanecarboxamide (3a):** Following the general procedure, **3a** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 2:98) as a colourless semi-solid; Yield: 35% (28 mg); IR (KBr): 3241, 3094, 1692, 1578, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (br. s, 1H), 8.26 (d, 1H, *J* = 8.0 Hz), 7.40 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.23-7.19 (m, 1H), 7.14 (d, 4H, *J* = 8.1 Hz), 7.02 (d, 4H, *J* = 8.1 Hz), 7.03-6.98 (m, 1H), 2.96 (d, 2H, *J* = 9.4 Hz), 2.60 (t, 1H, *J* = 9.4 Hz), 2.30 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 138.6, 135.9, 133.1, 131.2,

130.9, 128.8, 128.8, 123.9, 120.6, 29.7, 29.2, 28.2, 21.1, 18.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}NNaOS$: 410.1555; found 410.1540.

(*1R*,2S)-*N*-(2-(Methylthio)phenyl)-2-(*p*-tolyl)cyclopropanecarboxamide (4a):** Following the general procedure, **4a** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 77-79 °C; Yield: 56% (166 mg); IR (KBr): 3234, 3014, 2919, 1681, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (br. s,1H), 8.10 (d, 1H, J = 7.4 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.23-7.21 (m, 3H), 7.08 (d, 2H, J = 7.9 Hz), 7.01 (t, 1H, J = 7.4 Hz), 2.60 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.31 (s, 3H), 2.30 (s, 3H), 2.18-2.13 (m, 1H), 1.87-1.83 (m, 1H), 1.43-1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 138.6, 138.6, 136.1, 133.4, 133.1, 133.0, 128.9, 124.6, 123.9, 120.6, 25.4, 25.1, 21.1, 18.9, 10.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}NNaOS$: 320.1085; found 320.1105.

(*1S*,2R*,3S)-*N*-(2-(Methylthio)phenyl)-2,3-diphenylcyclopropanecarboxamide (3b):** Following the general procedure, **3b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 2:98) as a colourless solid; mp 92-94 °C; Yield: 40% (144 mg); IR (KBr): 3337, 3091, 1692, 1578, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (br. s,1H), 8.23 (d, 1H, J = 8.0 Hz), 7.40 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.25-7.16 (m, 11H), 7.0 (t, 1H, J = 7.5 Hz), 3.02 (d, 2H, J = 9.4 Hz), 2.67 (t, 1H, J = 9.4 Hz), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.7, 138.5, 134.3, 133.1, 131.0, 128.8, 127.6, 126.4, 124.9, 124.0, 120.5, 29.4, 28.5, 19.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}NOS$: 360.1422; found 360.1404.

(*1S*,2S)-2-(Di-*p*-tolylmethyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(*p*-tolyl)propyl acetate (5a):** Following the general procedure, **5a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colourless solid; mp 123-125 °C; Yield: 86% (115 mg); IR (KBr): 3241, 3264, 2921, 1739, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (br. s, 1H), 7.95 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.43-7.39 (m, 3H), 7.27 (d, 2H, J = 8.1 Hz), 7.22-7.15 (m, 5H), 7.09 (d, 2H, J = 8.1 Hz), 7.04-6.98 (m, 3H), 6.12 (d, 1H, J = 6.3 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.94 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.3 Hz), 2.36 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.3, 140.0, 139.1, 138.1, 138.0, 136.2, 135.9, 134.0, 132.7, 129.6, 129.3, 128.8, 128.7, 128.1,

127.5, 125.0, 124.2, 120.6, 76.0, 57.4, 51.3, 21.3, 21.1, 21.0, 20.9, 19.0; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{34}H_{35}NNaO_3S$: 560.2235; found 560.2249.

(*1S*,2S)-2-Benzhydryl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (5b):** Following the general procedure, **5b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 170-172 °C; Yield: 57% (71 mg); IR (KBr): 3228, 3025, 2920, 1735, 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (br. s, 1H), 7.80 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.51 (d, 2H, J = 7.3 Hz), 7.40-7.35 (m, 5H), 7.26-7.11 (m, 9H), 7.05 (t, 1H, J = 7.4 Hz), 6.98 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 6.16 (d, 1H, J = 7.0 Hz), 4.40 (d, 1H, J = 11.5 Hz), 3.93 (dd, 1H, J_1 = 11.5 Hz, J_2 = 7.0 Hz), 2.19 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.8, 168.2, 142.6, 141.9, 137.6, 137.3, 132.5, 128.9, 128.6, 128.6, 128.5, 128.3, 128.2, 127.8, 127.5, 126.8, 126.6, 125.1, 124.4, 120.6, 76.1, 57.6, 52.6, 20.8, 19.0; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{31}H_{29}NNaO_3S$: 518.1766; found 518.1779.

(*1S*,2S)-2-(Bis(4-ethylphenyl)methyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5c):** Following the general procedure, **5c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 68-70 °C; Yield: 60% (87 mg); IR (DCM): 3542, 3427, 3024, 2918, 1708, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br. s, 1H), 7.80 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.41 (d, 2H, J = 8.1 Hz), 7.36 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.22-7.18 (m, 4H), 7.14 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.09 (d, 2H, J = 8.2 Hz), 7.01-6.96 (m, 3H), 6.12 (d, 1H, J = 6.9 Hz), 4.33 (d, 1H, J = 11.5 Hz), 3.90 (dd, 1H, J_1 = 6.9 Hz, J_2 = 11.5 Hz), 2.64 (q, 2H, J = 7.6 Hz), 2.58 (q, 2H, J = 7.6 Hz), 2.47 (q, 2H, J = 7.6 Hz), 2.17 (s, 3H), 1.75 (s, 3H), 1.24 (t, 3H, J = 7.6 Hz), 1.16 (t, 3H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.8, 168.5, 144.3, 142.4, 142.2, 140.2, 139.4, 137.9, 134.6, 132.6, 128.6, 128.3, 128.2, 128.1, 127.6, 127.5, 125.1, 124.2, 120.6, 76.1, 57.8, 51.8, 28.5, 28.4, 28.3, 20.8, 18.9, 15.5, 15.3, 15.3; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{37}H_{41}NNaO_3S$: 602.2705; found 602.2721.

(*1S*,2S)-2-(Bis(4-isopropylphenyl)methyl)-1-(4-isopropylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5d):** Following the general procedure, **5d** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 109-111 °C; Yield: 53% (82 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (br. s, 1H), 7.63 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 2H, *J* = 8.1 Hz), 7.33-7.29 (m, 4H), 7.21 (d, 4H, *J* = 8.2 Hz), 7.11-7.07 (m, 2H), 7.01 (d, 2H, *J* = 8.1 Hz), 6.94 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 6.14 (d, 1H, *J* = 7.6 Hz), 4.37 (d, 1H, *J* = 11.4 Hz), 3.84 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.6 Hz), 2.95-2.87 (m, 1H), 2.85-2.77 (m, 1H), 2.74-2.66 (m, 1H), 2.11 (s, 3H), 1.63 (s, 3H), 1.25 (d, 3H, *J* = 6.9 Hz), 1.25 (d, 3H, *J* = 6.9 Hz), 1.15 (d, 6H, *J* = 6.9 Hz), 1.07 (d, 6H, *J* = 6.9 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.7, 148.8, 146.9, 146.8, 140.2, 139.6, 137.7, 135.1, 132.4, 128.5, 128.2, 127.7, 127.4, 126.8, 126.6, 126.3, 125.3, 124.2, 120.7, 76.3, 58.3, 52.4, 33.8, 33.7, 33.5, 24.0, 23.9, 23.8, 23.8, 23.8, 20.7, 18.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{40}H_{47}NNaO_3S$: 644.3174; found 644.3190.

(*1S*,2S)-2-(Bis(4-(*tert*-butyl)phenyl)methyl)-1-(4-(*tert*-butyl)phenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5e):** Following the general procedure, **5e** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 227-229 °C; Yield: 63% (104 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br. s, 1H), 7.56 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.4 Hz), 7.34-7.26 (m, 7H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.07 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 6.94 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 6.17 (d, 1H, *J* = 7.8 Hz), 4.41 (d, 1H, *J* = 11.3 Hz), 3.84 (dd, 1H, J_1 = 11.3 Hz, J_2 = 7.8 Hz), 2.09 (s, 3H), 1.58 (s, 3H), 1.32 (s, 9H), 1.22 (s, 9H), 1.15 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.8, 151.0, 149.1, 149.0, 139.8, 139.2, 137.6, 134.9, 132.3, 128.4, 128.0, 127.5, 127.2, 125.6, 125.5, 125.4, 125.2, 124.3, 120.8, 76.3, 58.5, 52.4, 34.5, 34.4, 34.2, 31.4, 31.2, 31.2, 20.6, 18.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{43}H_{53}NNaO_3S$: 686.3644; found 686.3635.

(*1S*,2S)-2-(Di-*m*-tolylmethyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(*m*-tolyl)propyl acetate (5f):** Following the general procedure, **5f** (*anti* isomer) was obtained after purification by

column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 105-107 °C; Yield: 40% (54 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (br. s, 1H), 7.90 (dd,1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.38 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.34-7.26 (m, 4H) 7.21-6.97 (m, 9H), 6.86 (d, 1H, J = 7.5 Hz), 6.10 (d, 1H, J = 6.7 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.92 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.7 Hz), 2.40 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.3, 142.7, 141.9, 138.3, 138.0, 137.9, 137.6, 137.2, 132.7, 129.3, 129.2, 128.7, 128.7, 128.5, 128.3, 128.0, 127.5, 127.4, 125.3, 124.9, 124.5, 124.5, 124.2, 120.4, 76.1, 57.6, 52.3, 21.6, 21.5, 21.4, 20.9, 18.9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{34}H_{35}NNaO_3S$: 560.2235; found 560.2247.

(*1S*,2S)-2-(Bis(4-pentylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(4-pentylphenyl)propyl acetate (5g):** Following the general procedure, **5g** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a pale yellow solid; mp 60-62 °C; Yield: 57% (100 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (br. s, 1H), 7.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.35 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.29-7.18 (m, 4H), 7.13 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.07 (d, 2H, J = 8.2 Hz), 6.99-6.95 (m, 3H), 6.15 (d, 1H, J = 7.2 Hz), 4.34 (d, 1H, J = 11.4 Hz), 3.88 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.2 Hz), 2.59 (t, 2H, J = 7.9 Hz), 2.52 (t, 2H, J = 7.9 Hz), 2.42 (t, 2H, J = 7.9 Hz), 2.16 (s, 3H), 1.72 (s, 3H), 1.66-1.15 (m, 18H), 0.92 (t, 3H, J = 7.0 Hz), 0.87 (t, 3H, J = 7.0 Hz), 0.83 (t, 3H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.6, 143.0, 141.1, 140.9, 140.1, 139.4, 137.8, 134.7, 132.6, 128.8, 128.6, 128.6, 128.2, 128.2, 127.7, 127.5, 125.1, 124.2, 120.6, 76.2, 58.0, 52.1, 35.6, 35.5, 35.4, 31.6, 31.5, 31.4, 31.2, 31.0, 30.9, 22.6, 22.5, 22.5, 20.8, 18.9, 14.1, 14.0, 14.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{46}H_{59}NNaO_3S$: 728.4113; found 728.4096.

(*1S*,2S)-2-(Bis(4-hexylphenyl)methyl)-1-(4-hexylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5h):** Following the general procedure, **5h** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as pale yellow solid; mp 68-70 °C; Yield: 55% (102 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (br. s, 1H), 7.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.39 (d, 2H, J = 8.1 Hz), 7.35 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.20-7.17 (m,

4H), 7.12 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.06 (d, 2H, J = 8.2 Hz), 6.98-6.95 (m, 3H), 6.14 (d, 1H, J = 7.2 Hz), 4.34 (d, 1H, J = 11.4 Hz), 3.86 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.2 Hz), 2.59 (t, 2H, J = 7.9 Hz), 2.52 (t, 2H, J = 7.9 Hz), 2.41 (t, 2H, J = 7.9 Hz), 2.16 (s, 3H), 1.71 (s, 3H), 1.65-1.19 (m, 24H), 0.91 (t, 3H, J = 6.9 Hz), 0.91 (t, 3H, J = 6.9 Hz) 0.85 (t, 3H, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.6, 143.1, 141.1, 140.9, 140.1, 139.4, 137.8, 134.7, 132.6, 128.8, 128.6, 128.6, 128.2, 128.2, 127.6, 127.5, 125.1, 124.2, 120.6, 76.2, 58.0, 52.0, 35.7, 35.6, 35.4, 31.8, 31.7, 31.7, 31.5, 31.3, 31.2, 29.1, 29.0, 28.9, 22.6, 22.6, 22.5, 20.8, 18.9, 14.1, 14.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{49}H_{65}NNaO_3S$: 770.4583; found 770.4565.

(*1S*,2S)-2-(Bis(3-bromophenyl)methyl)-1-(3-bromophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5i):** Following the general procedure, **5i** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown coloured solid; mp 161-163 °C; Yield: 10% (73 mg); IR (DCM): 3322, 3064, 2925, 1744, 1676, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (br. s, 1H), 7.78 (d, 1H, J = 8.1 Hz), 7.60 (s, 1H), 7.50 (s, 1H), 7.43-7.38 (m, 5H), 7.31-7.02 (m, 8H), 6.04 (d, 1H, J = 7.0 Hz), 4.33 (d, 1H, J = 11.4 Hz), 3.78 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz), 2.27 (s, 3H), 1.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 167.3, 143.9, 143.2, 139.2, 137.0, 132.2, 131.8, 131.4, 130.7, 130.6, 130.4, 130.4, 130.2, 129.9, 128.6, 127.0, 126.6, 126.3, 125.8, 124.9, 123.1, 122.8, 122.4, 120.8, 75.1, 57.2, 51.8, 20.7, 18.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}Br_3NO_3S$: 729.9262; found 729.9246.

(*1S*,2S)-2-(Bis(3-fluorophenyl)methyl)-1-(3-fluorophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5j):** Following the general procedure, **5j** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown solid; mp 176-178 °C; Yield: 11% (15 mg); IR (KBr): 3314 3067, 2930, 1743, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (br. s, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.41-7.35 (m, 2H), 7.28-6.94 (m, 12H), 6.79 (t, 1H, J = 7.2 Hz), 6.10 (d, 1H, J = 6.9 Hz), 4.42 (d, 1H, J = 11.4 Hz), 3.81 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz), 2.25 (s, 3H), 1.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 167.4, 163.1 (d, $J_{C\text{-}F}$ = 245 Hz), 162.8 (d, $J_{C\text{-}F}$ = 245 Hz), 162.6 (d, $J_{C\text{-}F}$ = 245 Hz), 144.3 (d, $J_{C\text{-}F}$ = 6.9 Hz), 143.7 (d, $J_{C\text{-}F}$ = 6.9 Hz), 139.5 (d, $J_{C\text{-}F}$ = 6.9 Hz), 137.1, 132.3, 130.6 (d, $J_{C\text{-}F}$ = 8.4 Hz), 130.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.3

Hz), 128.6, 125.6, 124.8, 124.0 (d, J_{C-F} = 2.8 Hz), 123.6 (d, J_{C-F} = 2.5 Hz), 123.2 (d, J_{C-F} = 2.8 Hz), 120.7, 115.6 (d, J_{C-F} = 20.8 Hz), 115.2 (d, J_{C-F} = 21.5 Hz), 114.7 (d, J_{C-F} = 21.7 Hz), 114.3 (d, J_{C-F} = 22.3 Hz), 114.1 (d, J_{C-F} = 20.8 Hz), 114.0 (d, J_{C-F} = 21.0 Hz). 75.2 (d, J_{C-F} = 1.5 Hz), 57.3, 51.8, 20.7, 18.8; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{31}H_{25}F_3NO_3S$: 548.1507; found 548.1522.

(*1S*,2S)-2-(Bis(4-bromophenyl)methyl)-1-(4-bromophenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5k):** Following the general procedure, **5k** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 187-189 °C; Yield: 35% (64 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.0 (br. s, 1H), 7.77 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.42-7.38 (m, 3H), 7.32 (d, 4H, J = 8.3 Hz), 7.21-7.16 (m, 3H), 7.09-7.04 (m, 3H), 6.03 (d, 1H, J = 6.6 Hz), 4.23 (d, 1H, J = 11.5 Hz), 3.80 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.6 Hz), 2.27 (s, 3H), 1.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.6, 167.4, 140.8, 140.0, 136.9, 135.6, 132.2, 132.0, 131.9, 131.4, 129.9, 129.4, 129.3, 128.5, 125.7, 125.0, 122.9, 121.1, 120.9, 120.8, 75.1, 56.7, 51.0, 20.9, 18.7; HRMS (ESI): *m/z* [M - H] calcd for $C_{31}H_{25}Br_3NO_3S$: 727.9105; found 727.9108.

(*1S*,2S)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(3,4-dimethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (5l):** Following the general procedure, **5l** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a brown coloured semi-solid; Yield: 60% (87 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (br. s, 1H), 8.03 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.43 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.28-7.12 (m, 6H), 7.06-6.93 (m, 5H), 6.04 (d, 1H, J = 6.0 Hz), 4.19 (d, 1H, J = 11.6 Hz), 3.94 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.0 Hz), 2.32 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.5, 140.6, 139.6, 138.3, 136.9, 136.7, 136.5, 136.0, 134.8, 134.5, 134.4, 132.9, 130.1, 129.8, 129.7, 129.4, 129.1, 128.8, 128.8, 125.5, 124.8, 124.7, 124.5, 124.0, 120.4, 75.9, 57.3, 51.1, 21.1, 20.0, 19.9, 19.8, 19.6, 19.4, 19.3, 19.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{37}H_{41}NO_3SNa$: 602.2705; found 602.2708.

(*1S*,2S)-2-Benzhydryl-3-oxo-1-phenyl-3-(quinolin-8-ylamino)propyl acetate (6a):** Following the general procedure, **6a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 171-173 °C; Yield: 50% (63 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s,1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.48 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.54 (d, 2H, J = 7.4 Hz), 7.48-7.38 (m, 7H), 7.27-7.14 (m, 6H), 7.13 (t, 2H, J = 7.7 Hz), 6.99 (t, 1H, J = 7.4 Hz), 6.16 (d, 1H, J = 5.8 Hz), 4.39 (d, 1H, J = 11.7 Hz), 4.22 (dd, 1H, J_1 = 11.7 Hz, J_2 = 5.8 Hz), 1.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 168.0, 147.9, 143.1, 142.0, 138.3, 136.6, 136.3, 134.1, 129.0, 128.5, 128.4, 128.0, 127.8, 127.6, 127.6, 127.4, 126.8, 126.3, 121.6, 121.3 116.4, 75.8, 56.8, 51.6, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{28}N_2O_3$: 501.2178; found 501.2172.

(*1S*,2S)-2-(Bis(4-isopropylphenyl)methyl)-1-(4-isopropylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate (6b):** Following the general procedure, **6b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 201-203 °C; Yield: 20% (31 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.44 (dd, 1H, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.46-7.41 (m, 5H), 7.31 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.2 Hz), 7.15 (d, 2H, J = 8.2 Hz), 7.01 (d, 2H, J = 8.2 Hz), 6.94 (dd, 2H, J = 8.2 Hz), 6.15 (d, 1H, J = 6.6 Hz), 4.36 (d, 1H, J = 11.6 Hz), 4.11 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.6 Hz), 2.93-2.87 (m, 1H), 2.76-2.59 (m, 2H), 1.80 (s, 3H), 1.26 (d, 3H, J = 6.9 Hz), 1.25 (d, 3H, J = 6.9 Hz), 1.06 (d, 3H, J = 6.9 Hz), 1.05 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.97 (d, 3H, J = 6.9 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 168.6, 148.6, 147.8, 146.8, 146.3, 140.6, 139.7, 138.2, 136.2, 134.5, 134.2, 128.3, 127.8, 127.4, 127.4, 127.3, 126.8, 126.5, 126.1, 121.4, 121.1, 116.2, 76.1, 57.5, 51.4, 33.7, 33.7, 33.4, 24.0, 23.7, 23.7, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{42}H_{47}N_2O_3$: 627.3587; found 627.3610.

(*1S*,2S)-2-(Bis(4-ethylphenyl)methyl)-1-(4-ethylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate (6c):** Following the general procedure, **6c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 160-162 °C; Yield: 43% (63 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.50 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.6 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.48-7.41 (m, 5H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 6.93 (d, 2H, *J* = 8.0 Hz), 6.12 (d, 1H, *J* = 5.8 Hz), 4.32 (d, 1H, *J* = 11.7 Hz), 4.16 (dd, 1H, J_1 = 11.8 Hz, J_2 = 6.0 Hz), 2.65 (q, 2H, *J* = 7.6 Hz), 2.51 (q, 2H, *J* = 7.6 Hz), 2.40 (q, 2H, *J* = 7.6 Hz), 1.91 (s, 3H), 1.25 (t, 3H, *J* = 7.6 Hz), 1.08 (t, 3H, *J* = 7.6 Hz), 1.0 (t, 3H, *J* = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 168.4, 147.9, 144.2, 142.4, 141.8, 140.6, 139.5, 138.2, 136.2, 134.3, 134.0, 128.4, 128.3, 128.0, 127.8, 127.5, 127.5, 127.4, 127.4, 121.5, 121.2, 116.3, 75.9, 57.0, 50.8, 28.5, 28.4, 28.2, 21.1, 15.5, 15.2, 15.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{41}N_2O_3$: 585.3117; found 585.3134.

(*1S*,2S)-2-(Di-*p*-tolylmethyl)-3-oxo-3-(quinolin-8-ylamino)-1-(*p*-tolyl)propyl acetate (6d):** Following the general procedure, **6d** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 174-176 °C; Yield: 45% (61 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s,1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.55 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.49-7.43 (m, 3H), 7.41 (d, 2H, *J* = 7.9 Hz), 7.27 (d, 2H, *J* = 8.7 Hz), 7.21 (d, 2H, *J* = 7.9 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 6.93 (d, 2H, *J* = 8.0 Hz), 6.10 (d, 1H, *J* = 5.2 Hz), 4.27 (d, 1H, *J* = 11.8 Hz), 4.19 (dd, 1H, J_1 = 11.8 Hz, J_2 = 5.2 Hz), 2.35 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 168.2, 147.9, 140.5, 139.2, 138.3, 138.1, 136.3, 136.2, 135.5, 134.4, 133.5, 129.7, 129.2, 128.7, 128.2, 127.8, 127.5, 127.5, 127.3, 121.5, 121.2, 116.4, 75.7, 56.6, 50.4, 21.2, 21.2, 21.1, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{35}N_2O_3$: 543.2648; found 543.2659.

(*1S*,2S)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(3,4-dimethylphenyl)-3-oxo-3-(quinolin-8-ylamino)propyl acetate (6e):** Following the general procedure, **6e** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 134-136 °C; Yield: 75% (109 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s,1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.59 (t, 1H, *J* = 4.5 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.49-7.46 (m, 3H), 7.31-7.28 (m, 2H),

7.20-7.17 (m, 3H), 6.99-6.90 (m, 4H), 6.09 (d, 1H, 1H, J = 4.5 Hz), 4.23-4.21 (m, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.10 (s, 6H), 2.03 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 168.5, 147.9, 141.0, 139.8, 138.3, 136.9, 136.6, 136.4, 136.3, 135.9, 134.8, 134.5, 134.2, 134.0, 130.2, 129.8, 129.8, 129.3, 129.1, 129.0, 127.8, 127.5, 125.6, 124.9, 124.3, 121.5, 121.2, 116.4, 75.8, 56.7, 50.4, 21.2, 20.0, 19.9, 19.7, 19.5, 19.4, 19.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{41}N_2O_3$: 585.3117; found 585.3105.

(*1R*,2S)-2-(4-Ethylphenyl)-*N*-(2-(methylthio)phenyl)cyclopropanecarboxamide (8):** Following the general procedure, **8** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as pale brown color solid; mp 95-97 °C; Yield: 51% (159 mg); IR (KBr): 3252, 2999, 2961, 2919, 1659, 1585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (br. s, 1H), 8.09 (d, 1H, J = 4.8 Hz), 7.45 (d, 1H, J = 7.6 Hz), 7.28-7.19 (m, 3H), 7.11 (d, 1H, J = 7.6 Hz), 7.03-6.99 (m, 1H), 2.60 (dd, 1H, J_1 = 15.4 Hz, J_2 = 7.6 Hz), 2.60 (q, 2H, J = 7.6 Hz), 2.29 (s, 3H), 2.19-2.13 (m, 1H), 1.87-1.83 (m, 1H), 1.43-1.38 (m, 1H), 1.21 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 142.5, 138.6, 133.7, 133.1, 128.9, 127.7, 124.6, 124.6, 124.0, 120.6, 28.5, 25.5, 25.2, 18.9, 15.5, 10.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}NNaOS$: 334.1242; found 334.1243.

(*1R*,2S)-*N*-(2-(Methylthio)phenyl)-2-phenylcyclopropanecarboxamide (9):** Following the general procedure, **9** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 112-114 °C; Yield: 62% (176 mg); IR (KBr): 3231, 3019, 2917, 1652, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (br. s, 1H), 8.07 (d, 1H, J = 7.5 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.34 (d, 2H, J = 7.2 Hz), 7.30-7.25 (m, 2H), 7.22-7.17 (m, 2H), 7.01 (t, 1H, J = 7.3 Hz), 2.63 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.31 (s, 3H), 2.21-2.16 (m, 1H), 1.90-1.86 (m, 1H), 1.45-1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 138.5, 136.5, 133.0, 129.0, 128.1, 126.7, 124.7, 124.6, 124.0, 120.7, 25.7, 25.2, 18.9, 10.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{17}NNaOS$: 306.0929; found 306.0925.

(*1S*,2S)-2-(Bis(3,4-dimethylphenyl)methyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (10):** Following the general procedure, **10** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina

(EtOAc:Hexanes = 20:80) as a colourless solid; mp 118-120 °C; Yield: 43% (62 mg); IR (KBr): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (br. s, 1H), 7.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.41 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.26-7.09 (m, 10H), 7.0 (dt, 1H, J_1 = 7.3 Hz, J_2 = 1.3 Hz), 6.94 (d, 1H, J = 8.3 Hz), 6.10 (d, 1H, J = 6.2 Hz), 4.22 (d, 1H, J = 11.7 Hz), 3.93 (dd, 1H, J_1 = 11.7 Hz, J_2 = 6.2 Hz), 2.60 (q, 2H, J = 7.6 Hz), 2.31 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.85 (s, 3H), 1.19 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.5, 144.3, 140.5, 139.6, 138.1, 136.8, 136.5, 134.8, 134.5, 134.3, 132.8, 130.1, 129.8, 129.6, 129.1, 128.7, 127.6, 127.5, 125.5, 124.9, 124.6, 124.1, 120.5, 76.0, 57.4, 51.3, 28.6, 20.9, 20.0, 19.9, 19.4, 19.3, 19.0, 15.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{37}H_{41}NNaO_3S$: 602.2705; found 602.2706.

(*1S*,2S)-2-(Bis(3,4-dimethylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(*p*-tolyl)propyl acetate (11):** Following the general procedure, **11** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 121-123 °C; Yield: 60% (85 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (br. s, 1H), 7.98 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.28-7.07 (m, 10H), 7.01 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 6.93 (d, 1H, J = 8.3 Hz), 6.09 (d, 1H, J = 6.1 Hz), 4.20 (d, 1H, J = 11.7 Hz), 3.94 (dd, 1H, J_1 = 11.7 Hz, J_2 = 6.1 Hz), 2.31 (s, 6H), 2.25 (s, 6H), 2.13 (s, 3H), 2.08 (s, 3H), 1.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 168.4, 140.5, 139.5, 138.1, 138.1, 136.9, 136.5, 134.8, 134.5, 134.0, 132.7, 130.1, 129.8, 129.6, 129.6, 129.1, 128.7, 127.5, 125.5, 124.9, 124.6, 124.1, 120.5, 75.9, 57.3, 51.1, 21.2, 21.0, 20.0, 19.9, 19.4, 19.3, 19.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{36}H_{39}NNaO_3S$: 588.2548; found 588.2553.

(*1S*,2S)-2-(Di-*p*-tolylmethyl)-1-(4-ethylphenyl)-3-((2-(methylthio)phenyl)amino)-3-oxopropyl acetate (12a):** Following the general procedure, **12a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 99-101 °C; Yield: 63% (89 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (br. s, 1H), 7.90 (d, 1H, J = 7.8 Hz), 7.40-7.37 (m, 3H), 7.25 (d, 2H, J = 8.0 Hz), 7.19-7.14 (m, 5H), 7.09 (d, 1H, J = 7.9 Hz), 7.01-6.97 (m, 3H), 6.10 (d, 1H, J = 6.4 Hz), 4.29 (d, 1H, J = 11.6 Hz), 3.91 (dd, 1H, J_1 = 11.6 Hz, J_2 = 6.5 Hz), 2.59

(q, 2H, *J* = 7.6 Hz), 2.34 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.83 (s, 3H), 1.17 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.4, 144.3, 140.0, 139.2, 138.0, 136.2, 135.9, 134.3, 132.7, 129.6, 129.3, 128.7, 128.1, 127.6, 127.5, 127.5, 125.0, 124.2, 120.5, 76.0, 57.5, 51.4, 28.5, 21.0, 20.9, 20.9, 19.0, 15.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{37}NNaO_3S$: 574.2392; found 574.2392.

(*1S*,2S)-2-Benzhydryl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(*p*-tolyl)propyl acetate (12b):** Following the general procedure, **12b** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 146-148 °C; Yield: 54% (69 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (br. s, 1H), 7.84 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.51 (d, 2H, *J* = 7.4 Hz), 7.41-7.37 (m, 5H), 7.25 (t, 1H, *J* = 7.4 Hz), 7.19-7.13 (m, 5H), 7.09-7.03 (m, 3H), 6.99 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 6.12 (d, 1H, *J* = 6.8 Hz), 4.37 (d, 1H, *J* = 11.5 Hz), 3.94 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.8 Hz), 2.29 (s, 3H), 2.20 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.2, 142.7, 141.9, 138.2, 137.7, 134.1, 132.5, 128.9, 128.7, 128.6, 128.4, 127.8, 127.5, 126.8, 126.5, 125.1, 124.3, 120.6, 76.0, 57.5, 52.4, 21.2, 20.9, 18.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{31}NNaO_3S$: 532.1922; found 532.1940.

(*1S*,2S)-2-(Bis(4-ethylphenyl)methyl)-3-((2-(methylthio)phenyl)amino)-3-oxo-1-(*p*-tolyl)propyl acetate (12c):** Following the general procedure, **12c** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 20:80) as a colourless solid; mp 79-81 °C; Yield: 52% (73 mg); IR (DCM): 3350, 2970, 2922, 1677, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br. s, 1H), 7.83 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.41 (d, 2H, *J* = 8.1 Hz), 7.38 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.28 (d, 2H, *J* = 7.2 Hz), 7.21 (d, 2H, *J* = 8.1 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.16-7.13 (m, 1H), 7.07 (d, 2H, *J* = 8.0 Hz), 7.01-6.97 (m, 3H), 6.11 (d, 1H, *J* = 6.7 Hz), 4.31 (d, 1H, *J* = 11.5 Hz), 3.90 (dd, 1H, J_1 = 11.5 Hz, J_2 = 6.7 Hz), 2.64 (q, 2H, *J* = 7.6 Hz), 2.24 (q, 2H, *J* = 7.6 Hz), 2.29 (s, 3H), 2.19 (s, 3H), 1.78 (s, 3H), 1.24 (t, 3H, *J* = 7.6 Hz), 1.07 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.4, 142.4, 142.1, 140.1, 139.3, 138.1, 137.9, 134.3, 132.6, 128.8, 128.6, 128.3, 128.2, 128.0, 127.6, 127.5, 125.1, 124.2, 120.7, 76.1, 57.7, 51.7, 28.4, 28.3, 21.2, 20.9, 18.9, 15.5, 15.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{36}H_{39}NNaO_3S$: 588.2548; found 588.2549.

(*1S*,2S)-2-(Di-*p*-tolylmethyl)-3-oxo-3-(quinolin-8-ylamino)-1-(thiophen-2-yl)propyl acetate (12d):** Following the general procedure, the compound **12d** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a pale yellow color solid; mp 114-116 °C; Yield: 26% (35 mg); IR (KBr): 3240, 3094, 1687, 1591, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.59 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.49-7.46 (m, 3H), 7.35 (d, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.20 (d, 1H, J = 5.0 Hz), 7.17 (d, 2H, J = 7.8 Hz), 6.95-6.93 (m, 3H), 6.87 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.8 Hz), 6.39 (d, 1H, J = 5.6 Hz), 4.40 (d, 1H, J = 11.7 Hz), 4.16 (dd, 1H, J_1 = 11.7 Hz, J_2 = 5.7 Hz), 2.33 (s, 3H), 2.11 (s, 3H), 2.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 168.2, 147.9, 140.2, 138.8, 138.6, 138.3, 136.3, 135.7, 134.3, 129.6, 129.3, 128.2, 127.8, 127.5, 127.4, 127.3, 126.3, 126.0, 121.5, 121.3, 116.6, 116.4, 71.9, 56.5, 50.6, 21.1, 21.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{31}N_2O_3S$: 535.2055; found 535.2035.

(*1S,*2S)-2-(Bis(4-ethylphenyl)methyl)-3-oxo-3-(quinolin-8-ylamino)-1-(*p*-tolyl)propyl acetate (12e):** Following the general procedure, **12e** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; Yield: 47% (43 mg); IR (KBr): 3241, 2963, 1741, 1690, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.51 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.49-7.42 (m, 5H), 7.29 (d, 2H, J = 7.3 Hz), 7.22 (d, 2H, J = 7.9 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.12 (d, 1H, J = 5.6 Hz), 4.30 (d, 1H, J = 11.8 Hz), 4.17 (dd, 1H, J_1 = 11.8 Hz, J_2 = 5.6 Hz), 2.65 (q, 2H, J = 7.6 Hz), 2.40 (q, 2H, J = 7.6 Hz), 2.24 (s, 3H), 1.95 (s, 3H), 1.25 (2.65 (t, 3H, J = 7.6 Hz), 0.99 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 168.3, 147.9, 142.4, 141.8, 140.6, 139.5, 138.3, 138.0, 136.3, 134.3, 133.7, 128.7, 128.4, 128.3, 128.0, 127.8, 127.5, 127.4, 127.4, 121.5, 121.2, 116.4, 75.8, 56.9, 50.7, 28.4, 28.2, 21.2, 21.1, 15.5, 15.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{39}N_2O_3$: 571.2961; found 571.2943.

(*1S*,2R)-*N*-(Quinolin-8-yl)-2-(thiophen-2-yl)cyclopropanecarboxamide (15b):** Following the general procedure, **15b** was obtained after purification by column chromatography on alumina (EtOAc:Hexanes = 2:98) as a brown color liquid; Yield: 41% (121 mg); IR (KBr): 3241,

3191, 3095, 1684, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65-8.61 (m, 1H), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.50-7.45 (m, 3H), 7.09 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 6.99-6.98 (m, 1H), 6.89 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 2.72 (dd, 1H, J_1 = 16.6 Hz, J_2 = 8.3 Hz), 2.39-2.33 (m, 1H), 1.96-1.92 (m, 1H), 1.57-1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 148.0, 140.4, 138.2, 136.4, 134.6, 127.9, 127.5, 126.7, 126.3, 124.1, 121.6, 121.2, 116.4, 25.9, 20.2, 12.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2OS$: 295.0905; found 295.0893.

***N*-(Quinolin-8-yl)-3,3-di-*p*-tolylpropanamide (16a):** Following the general procedure, **16a** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as an orange coloured solid; mp 110-112 °C; Yield: 70% (67 mg); IR (KBr): 3353, 3242, 1685, 1524, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53-7.46 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.26 (d, 4H, J = 8.0 Hz), 7.12 (d, 4H, J = 8.0 Hz), 4.75 (t, 1H, J = 7.8 Hz), 3.32 (d, 2H, J = 7.8 Hz), 2.30 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 148.0, 141.0, 138.3, 136.3, 135.9, 134.4, 129.3, 127.9, 127.6, 127.4, 121.5, 121.4, 116.5, 46.4, 44.6, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O$: 381.1967; found 381.1983.

3,3-Bis(3,4-dimethylphenyl)-*N*-(2-(methylthio)phenyl)propanamide (16b): Following the general procedure, **16b** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a pale yellow solid; mp 111-113 °C; Yield: 50% (50 mg); IR (KBr): 3242, 2919, 1676, 1578, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 1H, J = 8.2 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, J = 7.0 Hz), 7.30-7.26 (m, 1H), 7.09-7.02 (m, 7H), 4.57 (t, 1H, J = 7.8 Hz), 3.15 (d, 2H, J = 7.8 Hz), 2.23 (s, 6H), 2.21 (s, 6H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 141.3, 138.5, 136.8, 134.7, 133.3, 129.9, 129.0, 124.9, 124.8, 124.2, 120.6, 116.4, 46.8, 44.8, 19.9, 19.4, 18.9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{29}NNaOS$: 426.1868; found 426.1856.

***N*-(2-(Methylthio)phenyl)-3,3-di-*p*-tolylpropanamide (16c):** Following the general procedure, **16c** was obtained after purification by column chromatography on neutral alumina

(EtOAc:Hexanes = 5:95) as yellow solid; mp 89-91 °C; Yield: 65% (61 mg); IR (KBr): 3330, 2918, 1665, 1577, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, 1H, *J* = 8.3 Hz), 8.26 (br. s, 1H), 7.46 (d, 1H, *J* = 7.7 Hz), 7.30-7.26 (m, 1H), 7.21 (d, 4H, *J* = 8.0 Hz), 7.11 (d, 4H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 4.64 (t, 1H, *J* = 7.8 Hz), 3.15 (d, 2H, *J* = 7.8 Hz), 2.31 (s, 6H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.6, 140.8, 138.4, 136.1, 133.3, 129.4, 129.0, 127.5, 125.0, 124.3, 120.6, 46.7, 44.8, 21.0, 19.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{25}NNaOS$: 398.1555; found 398.1565.

***N*-(2-(Methylthio)phenyl)-3,3-diphenylpropanamide (16d):**[19b] Following the general procedure, **16d** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as yellow solid; mp 87-89 °C; Yield: 68% (14 mg); IR (KBr): 3242, 3098, 1639, 1594, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, *J* = 8.4 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, *J* = 7.4 Hz), 7.32-7.23 (m, 9H), 7.32-7.23 (m, 2H), 7.05 (t, 1H, *J* = 7.5 Hz), 4.72 (t, 1H, *J* = 7.8 Hz), 3.19 (d, 2H, *J* = 7.8 Hz), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.4, 143.5, 138.3, 133.3, 129.0, 128.7, 127.8, 126.7, 125.0, 124.4, 120.6, 47.4, 44.6, 19.0; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{21}NNaOS$: 370.1242; found 370.1230.

3,3-Bis(4-ethylphenyl)-*N*-(2-(methylthio)phenyl)propanamide (16e): Following the general procedure, **16e** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 5:95) as a yellow solid; mp 67-69 °C; Yield: 59% (14 mg); IR (KBr): 3243, 3099, 1594, 1115, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, *J* = 8.3 Hz), 8.25 (br. s, 1H), 7.45 (d, 1H, *J* = 7.7 Hz), 7.27-7.20 (m, 1H), 7.23 (d, 4H, *J* = 8.1 Hz), 7.13 (d, 4H, *J* = 8.1 Hz), 7.04 (t, 1H, *J* = 7.4 Hz), 4.65 (t, 1H, *J* = 7.8 Hz), 3.16 (d, 2H, *J* = 7.8 Hz), 2.60 (q, 4H, *J* = 7.6 Hz), 2.16 (s, 3H), 1.21 (t, 6H, *J* = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.6, 142.4, 141.0, 133.4, 129.4, 129.1, 128.2, 127.6, 124.9, 124.2, 120.6, 46.7, 44.8, 28.4, 19.0, 15.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{29}NNaOS$: 426.1868; found 426.1855.

3,3-Di-*p*-tolylpropanoic acid (17a): Following the general procedure, **17a** was obtained after the work up as a pale brown semi-solid (purity ~95%); Yield: 21% (13 mg); IR (KBr): 3242, 2923, 1704, 1261, 1114 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 7.21 (d, 4H, *J* = 8.0 Hz), 7.09 (d, 4H, *J* = 8.0 Hz), 4.46 (t, 1H, *J* = 7.9 Hz), 3.05 (d, 2H, *J* = 7.9 Hz), 2.26 (s, 6H); $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$): δ 172.1, 141.5, 135.5, 129.0, 127.5, 46.3, 39.8, 20.1; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{17}H_{17}O_2$: 253.1229; found 253.1220.

3,3-Bis(3,4-dimethylphenyl)propanoic acid (17b): Following the general procedure, **17b** was obtained after the work up as pale brown solid; mp 96-98 °C; Yield: 40% (28 mg); IR (KBr): 3242, 3098, 11702, 1593, 1445 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 7.09 (br. S, 2H), 7.06-7.03 (m, 4H), 4.39 (t, 1H, *J* = 8.0 Hz), 3.04 (d, 2H, *J* = 8.0 Hz), 2.20 (s, 6H), 2.18 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 142.0, 136.1, 134.1, 129.5, 128.9,124.8, 46.3, 39.8, 19.0, 18.4; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{19}H_{21}O_2$: 281.1542; found 281.1529. The carboxylic acid OH signal could not be detected in the ^1H NMR spectrum.

(*2S*,3S)-2-(Di-*p*-tolylmethyl)-3-hydroxy-*N*-(2-(methylthio)phenyl)-3-(*p*-tolyl)propanamide (18a):** Following the general procedure, **18a** (*anti* isomer) was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 15:85) as a colorless solid; mp 140-142 °C; Yield: 32% (40 mg); IR (KBr): 3341, 2920, 1677, 1578,1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (br. s, 1H), 8.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.43 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 7.20 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.15 (d, 2H, *J* = 7.8 Hz), 7.11 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 8.2 Hz), 7.02-6.99 (m, 3H), 5.01 (t, 1H, *J* = 3.5 Hz), 4.25 (d, 1H, *J* = 11.7 Hz), 3.91 (dd, 1H, J_1 = 11.7 Hz, J_2 = 4.5 Hz), 2.79 (d, 1H, *J* = 3.2 Hz), 2.33 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 140.3, 139.5, 138.3, 137.6, 137.5, 136.3, 135.8, 133.0, 129.8, 129.4, 128.8, 128.8, 128.0, 127.3, 126.6, 125.2, 124.1, 120.6, 74.2, 59.0, 50.0, 21.2, 21.0, 20.9, 19.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{34}NO_2S$: 496.2310; found 496.2305.

(*1S*,2S)-2-Benzyl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (21):** Treatment of **3b** (0.17 mmol) with $Pd(OAc)_2$ (3.8 mg, 10 mol%), AgOAc (84 mg, 3 equiv) and AcOH (0.2 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **21** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless semi-solid; Yield: 25% (17 mg); IR (KBr): 3240, 3091, 1742, 1686, 1581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, 1H, J_1 = 8.2 Hz, J_2 = 0.7 Hz), 7.74 (br. s, 1H), 7.44 (d, 2H, *J* = 7.2 Hz), 7.34-7.15 (m, 10H), 6.98 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 6.09 (d, 1H, *J* =

8.8 Hz), 3.22-3.11 (m, 2H), 3.08-3.02 (m, 1H), 2.17 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.3, 138.8, 138.5, 137.7, 133.0, 128.9, 128.8, 128.7, 128.6, 128.4, 126.9, 126.6, 125.3, 124.5, 120.7, 76.7, 57.9, 35.7, 21.3, 18.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{25}NNaO_3S$: 442.1453; found: 442.1435.

(*1S*,2S)-2-Methyl-3-((2-(methylthio)phenyl)amino)-3-oxo-1-phenylpropyl acetate (22):** Treatment of **9** (0.25 mmol) with $Pd(OAc)_2$ (5.6 mg, 10 mol%), AgOAc (124 mg, 3 equiv) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **22** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 10:90) as a colorless solid; mp 117-119 °C; Yield: 33% (28 mg); IR (KBr): 3236, 3183, 3091, 1738, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (br. s, 1H), 8.22 (d, 1H, J = 8.2 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.39-7.24 (m, 6H), 7.06 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 6.04 (d, 1H, J = 7.4 Hz), 2.99-2.92 (m, 1H), 2.22 (s, 3H), 2.16 (s, 3H), 1.39 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 169.8, 138.6, 138.0, 133.0, 129.0, 128.6, 128.3, 126.6, 125.1, 124.5, 120.6, 77.0, 49.1, 21.2, 18.9, 13.9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_3S$: 366.1140; found 366.1125.

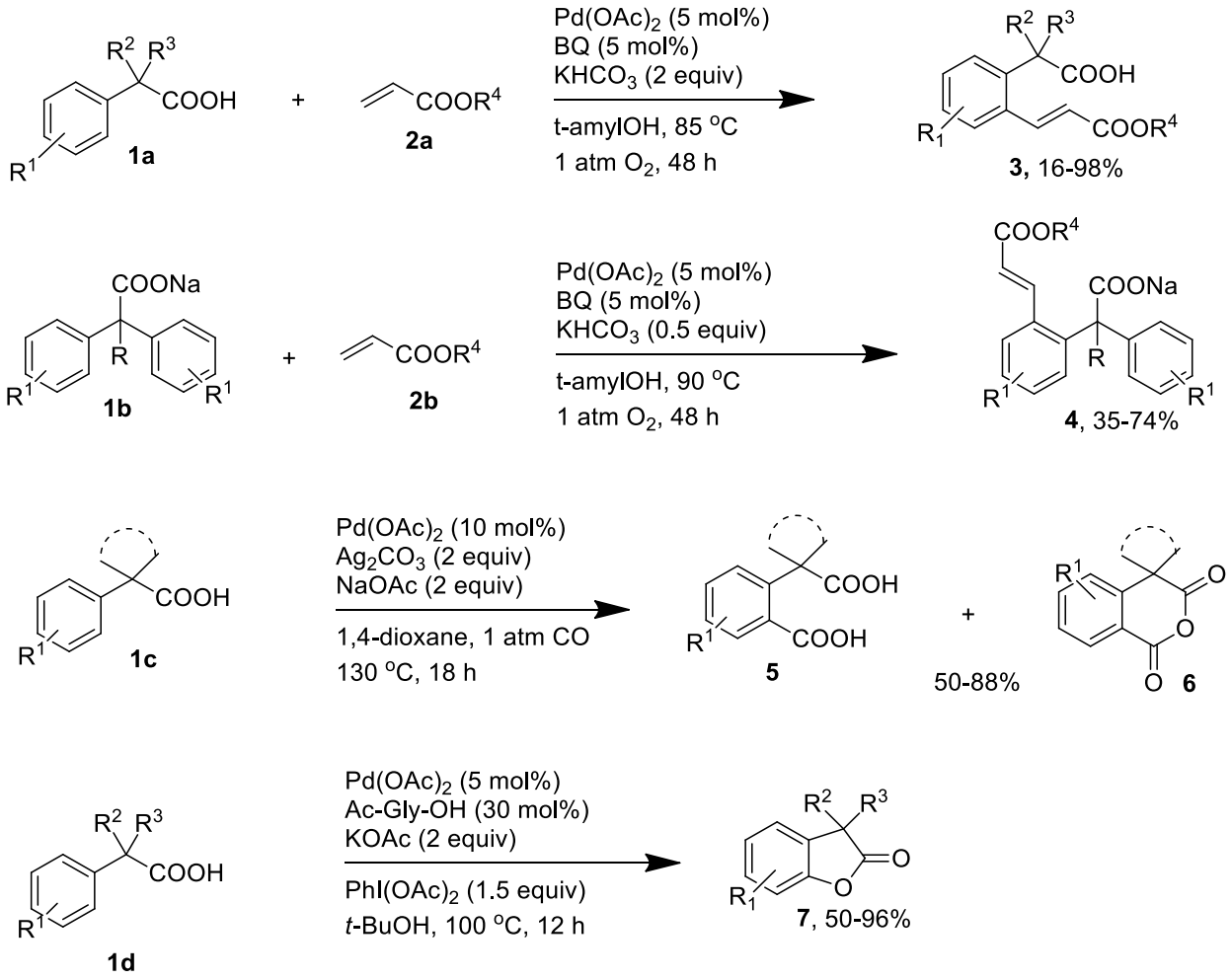
(*1S*,2S)-2-Methyl-3-oxo-1-phenyl-3-(quinolin-8-ylamino)propyl acetate (23a):** Treatment of **14** (0.25 mmol) with $Pd(OAc)_2$ (5.6 mg, 10 mol%), AgOAc (124 mg, 3 equiv) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 24 h afforded the compound **23a** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; 43% (37 mg); IR (KBr): 3240, 3093, 1741, 1684, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.72 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55-7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.39 (d, 2H, J = 7.2 Hz), 7.31-7.27 (m, 2H), 7.22 (t, 1H, J = 7.3 Hz), 6.13 (d, 1H, J = 6.4 Hz), 3.20-3.13 (m, 1H), 2.23 (s, 3H), 1.42 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 169.9, 148.1, 138.4, 138.3, 136.4, 128.4, 128.2, 127.9, 127.4, 126.7, 121.6, 121.6, 116.6, 76.9, 48.5, 21.2, 13.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1536.

(*1S,*2S)-2-Methyl-3-oxo-3-(quinolin-8-ylamino)-1-(*p*-tolyl)propyl acetate (23b):** Treatment of **13** (0.38 mmol) with $Pd(OAc)_2$ (8.5 mg, 10 mol%) and AcOH (0.5 mL) in toluene (3 mL) at 110 °C for 12 h afforded the compound **23b** after purification of the crude reaction mixture by column chromatography on alumina (EtOAc:Hexanes = 15:85) as a colorless liquid; Yield: 50% (68 mg); IR (KBr): 3241, 3094, 1742, 1687, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.80-8.79 (m, 1H), 8.73 (d, 1H, J = 6.6 Hz), 8.17 (d, 1H, J = 8.2 Hz), 7.53-7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.09 (d, 2H, J = 7.7 Hz), 6.09 (d, 1H, J = 6.4 Hz), 3.19-3.12 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.41 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 169.9, 148.0, 138.4, 137.9, 136.4, 135.2, 134.4, 129.1, 127.9, 127.5, 126.6, 121.6, 121.5, 116.6, 76.9, 48.4, 21.3, 21.1, 13.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_3$: 363.1709; found 363.1695.

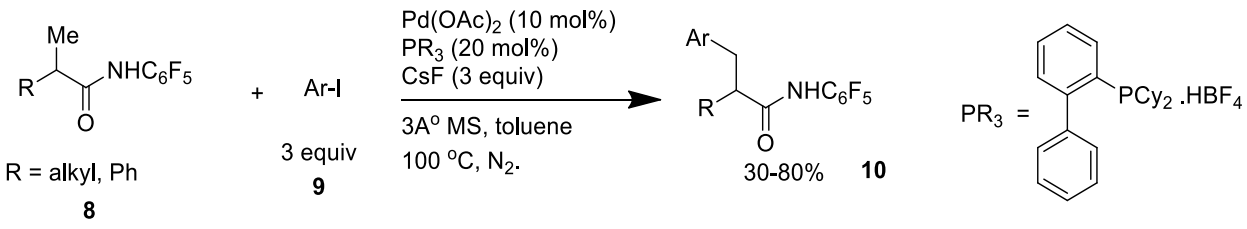
Chapter 4: Bidentate directing group-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides: construction of functionalized 2-arylpropionamides

The existing developments on the Pd(II)-catalyzed bidentate ligand-directed C-H activation/functionalization reactions of carboxylic acids have been shown with representative literature works in Chapter 1. Furthermore, part of this thesis work reported in the Chapters 2 and 3 have also revealed the Pd(II)-catalyzed β-arylation of the prochiral secondary sp^3 C-H bonds of 2-phenylbutanamides and C−H arylation followed by ring opening of cyclopropanecarboxamides. These reactions have led to the diastereoselective construction of functionalized 2-arylated carboxamide derivatives. In line with the above works, this chapter reports bidentate directing group-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides and the construction of functionalized 2-arylpropionamides.

2-Phenylacetic acids and their derivatives[62-67] are versatile compounds in organic synthesis and medicinal chemistry research and they are also building blocks of agrochemicals and commodity chemicals. Functionalization of 2-phenylacetic acid renders valuable products.[68] Representative examples involving the C-H activation/functionalization reactions of 2-phenylacetic acids have been shown in Scheme 1. Yu et al. reported examples of sp^2 C-H functionalization of 2-arylcarboxylic acids and enantioselective olefination of α,α-diaryl carboxylic acids (Scheme 1).[62, 67] The $Pd(OAc)_2$ catalyzed ligand enabled arylation of 2-phenylcarboxamide **8** led to the monoarylation of sp^3 C-H bond of methyl group of carboxamide **8** (Scheme 2). Variety of carboxamides including ibuprofen, fenoprofen, ketoprofen, gemfibrozil, flurbiprofen derived carboxamides have been subjected to the monoarylation of sp^3 C-H bond of methyl group.



Scheme 1: Inter- and intramolecular C-H functionalization of 2-phenylacetic acid derivatives.



Scheme 2: Monoarylation of sp^3 C-H bond of methyl group of carboxamide **8**.

Non-steroidal anti-inflammatory drugs (NSADs) including ibuprofen, naproxen, ketoprofen, flurbiprofen etc. are used as prodrugs that reduce side effects and irritation because of over dose of Non-steroidal anti-inflammatory drugs (NSADs).[69] The carboxylic acid group of these compounds can be linked with amino acids or steroids or other biochemicals to form prodrugs.

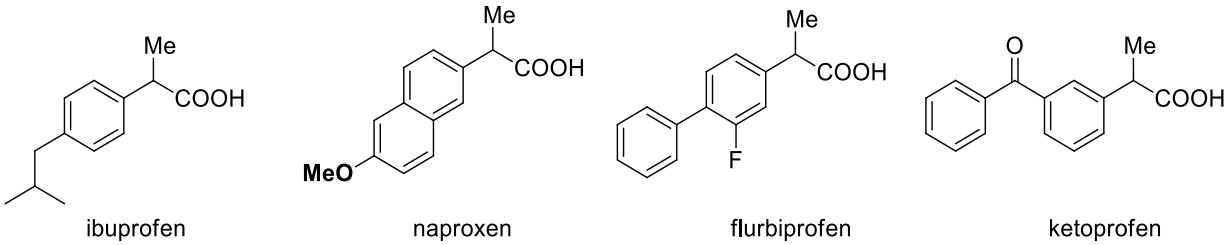
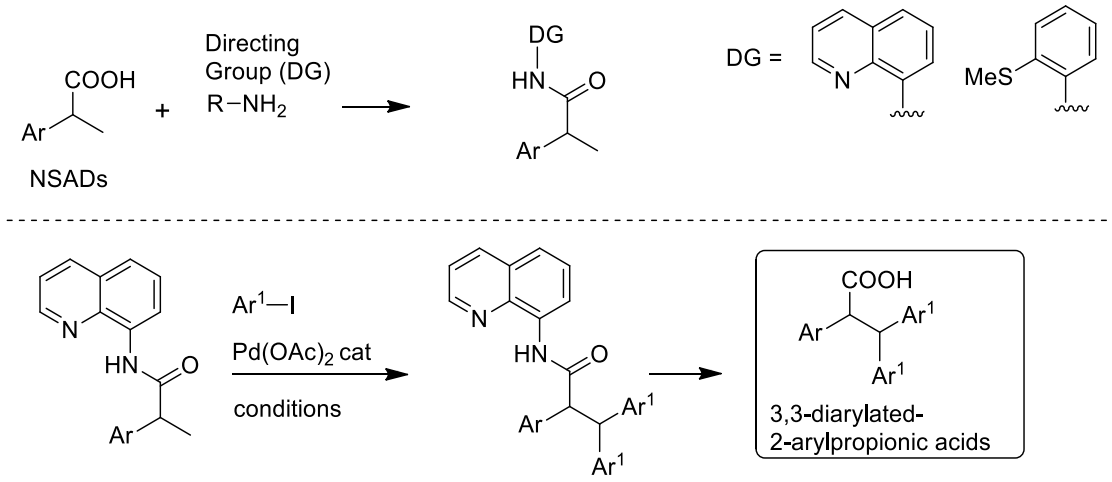


Figure 1: Structures of some Non-steroidal anti-inflammatory drugs (NSADs).

In general, the anti-inflammatory drugs (NSADs) including ibuprofen, naproxen, ketoprofen, flurbiprofen etc belong to the family of 2-arylpropanecarboxylic acid derivatives. Notably, functionalization of sp^2 or sp^3 C-H bonds of 2-arylpropanecarboxylic acid derivatives via the Pd(II)-catalyzed C-H functionalization can provide a library of new 2-arylpropanecarboxylic acid derivatives and can be tested for their medicinal activities. Accordingly, this chapter reports the bidentate directing group 8-aminoquinoline-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides and the construction of functionalized 2-arylpropionamides. The Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of the anti-inflammatory drugs (NSADs) including ibuprofen, naproxen, flurbiprofen carboxamides and also other 2-arylpropanecarboxamides have been examined.

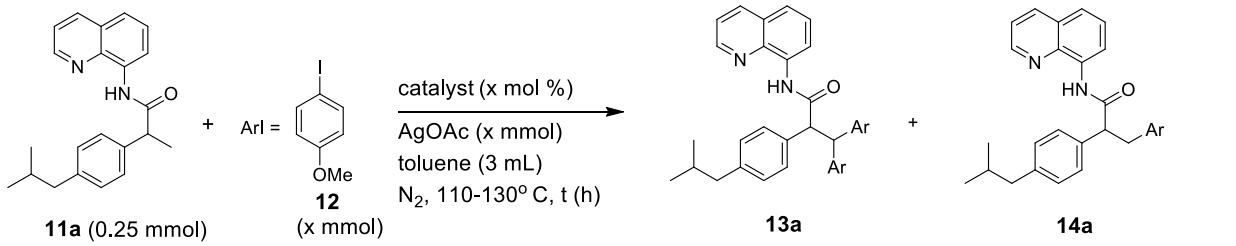


Scheme 3: $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of 2-arylpropanecarboxamides toward the synthesis of 3,3-diarylated-2-aryl propionic acids.

Results and Discussion

At the outset, the substrate **11a** was subjected to the Pd(II)-catalyzed sp^3 C-H activation and arylation reaction under different reaction conditions (Table 1). The sp^3 C-H arylation reaction of substrate **11a** (0.25 mmol) with 0.125 mmol of 4-iodoanisole **12a** in presence of $Pd(OAc)_2$ and AgOAc afforded traces of bis-arylated compound and monoarylated compound in 22% yield (entry 1, Table 1). The sp^3 C-H arylation of the substrate **11a** (0.25 mmol) with 0.25 mmol of **12a** afforded the bis-arylated compound **13a** in yields 35-37% and monoarylated compound in **14a** 10% yield (entries 2-4, Table 1). The bis-arylated compound **13a** was produced in 50-59% yields and traces of **14a** when 0.5-1 mmol of **12a** was used (entries 5-7, Table 1). Further increase of **12a** concentration gave the bis-arylated product **13a** in good yield 80% (entry 8, Table 1).

Table 1: Optimization reactions: Pd(II)-catalyzed arylation of ibuprofen-derived carboxamide **11a**.



11a (0.25 mmol) **13a** **14a**

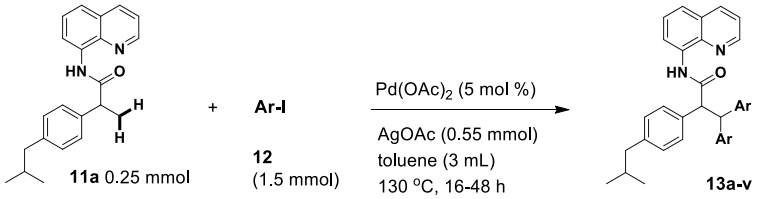
entry	Ar-**I** (mmol)	catalyst (x mol %)	AgOAc (mmol)	time (h)	yield (%) mono (**14a**)	yield (%) di (**13a**)
1	0.125	$Pd(OAc)_2$ (5)	0.55	24	22	traces
2	0.25	$Pd(OAc)_2$ (5)	0.55	36	10	37
3	0.25	$Pd(OAc)_2$ (5)	0.55	24	10	15
4	0.25	$Pd(OAc)_2$ (10)	0.55	24	traces	32
5	0.5	$Pd(OAc)_2$ (5)	0.55	18	traces	50
6	1	$Pd(OAc)_2$ (5)	0.55	36	traces	59
7	1	$Pd(OAc)_2$ (5)	075	24	7	54
8	**1.5**	**$Pd(OAc)_2$ (5)**	**0.55**	**24**	**traces**	**80**

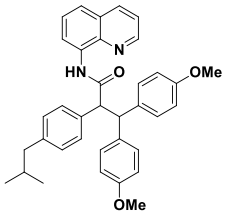
The scope of this sp^3 C-H activation and bis-arylation reaction was explored by treating the ibuprofen carboxamide **11a** with various aryl iodides in presence of $Pd(OAc)_2$ and AgOAc (Table 2). The reaction of **11a** with aryl iodides bearing electron donating substituents such as OMe, isopropyl, ethyl and methyl gave the corresponding bis-arylated carboxamides **13a-f** in 61-85% yield (Table 2). The arylation of carboxamide **11a** with PhI afforded bis-arylated product **13g** in 99% yield. Aryl iodides carrying halide substituents such as -Br, -Cl at *meta* and/or *para* positions gave the corresponding bis-arylated compounds **13h-13l** also in 76-93% yield (Table 2). The aryl iodide possessing electron withdrawing substituents such as keto and ester group provided the respective products **13m-n** in 76-85% (Table 2). The bis-arylation of **11a** with 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine smoothly underwent to afford the product **13o** in 83% yield (Table 2). The $Pd(OAc)_2$-catalyzed arylation of carboxamide **11a** with different fluorine substituted aryl iodides also provided the corresponding bis-arylated products **13p-r** in moderate to good yields (66-76%, Table 2). It was observed that the arylation reaction of **11a** with

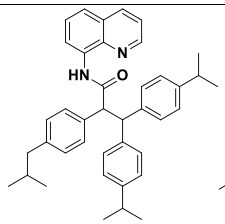
heteroaryl iodides was not compatible under the present reaction conditions. The reaction of **11a** with 2-fluoro-4-iodopyridine provided the arylated product **13s** only in 23% yield (Table 2). Notably, the treatment of **11a** with 5-iodo-1*H*-indole gave only monoarylated product **13t** in 27% yield (Table 2).

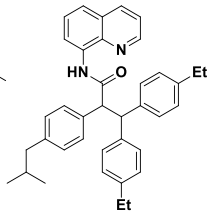
Subsequently, the sp^3 C-H activation and bis-arylation reaction was examined using carboxamides **11b** and **11c**, which were prepared using the corresponding bidentate directing groups. The carboxamides **11b** and **11c** were obtained from the amide coupling of ibuprofen with 2-(methylthio)aniline and benzo[*c*][1,2,5]thiadiazol-4-amine under the standard reaction conditions. Then, the carboxamide 1**1b** was reacted with 1-iodo-4-methylbenzene to afford the arylated compounds **15a** in 52% yield (Table 3). Unexpectedly, the treatment of carboxamide **11c** with 1-(4-iodophenyl)ethanone and 1-iodo-4-methoxybenzene gave the corresponding arylated products **16a,b** in 38-42% yields (Table 3). Where the second arylation takes place at C-3 position of aryl ring incorporated by the first C-H activation.

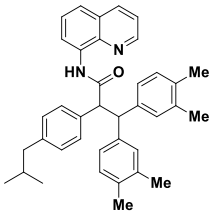
Table 2: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of ibuprofen carboxamide **11a** with different aryl iodides.

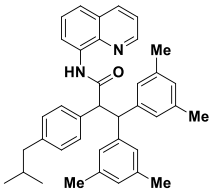


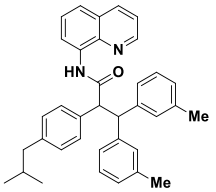

13a, 80% (24 h)

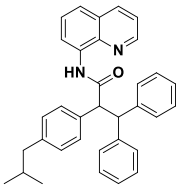

13b, 61% (20 h)

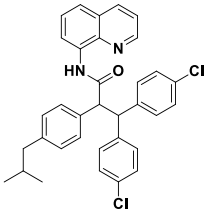

13c, 85% (16 h)

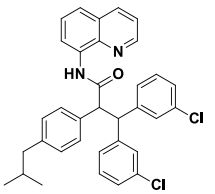

13d, 81% (24 h)

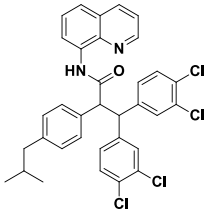

13e, 67% (20 h)

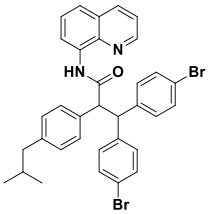

13f, 70% (24 h)

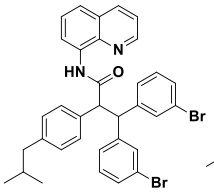

13g, 99% (23 h)

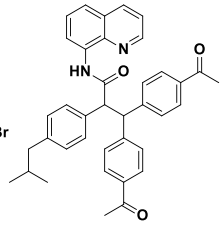

13h, 76% (24 h)

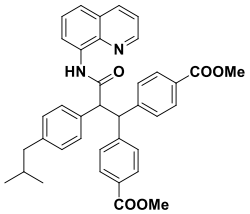

13i, 77% (20 h)

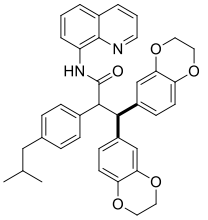

13j, 93% (24 h)

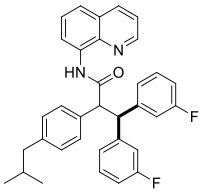

13k, 78% (16 h)

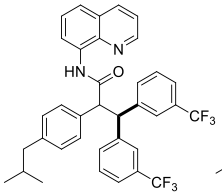

13l, 77% (24 h)

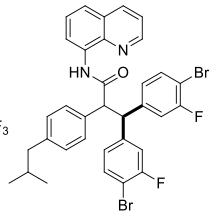

13m, 76% (48 h)

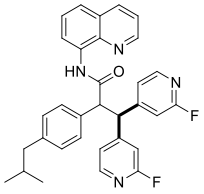

13n, 85% (24 h)


13o, 83% (20 h)


13p, 73% (38 h)


13q, 66% (36 h)


13r, 76% (36 h)


13s, 23% (48 h)

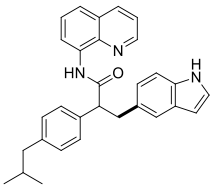
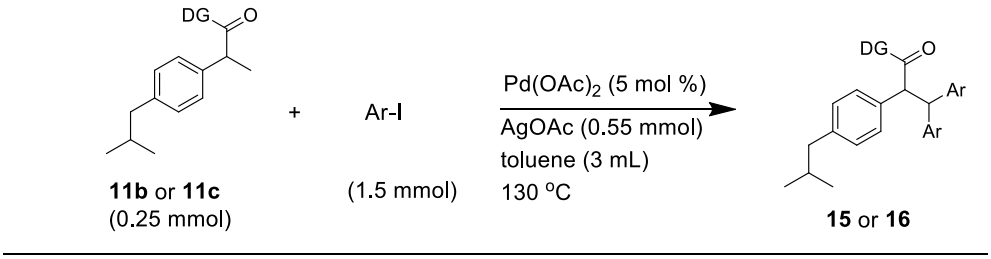
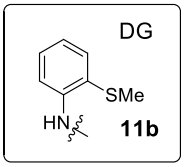
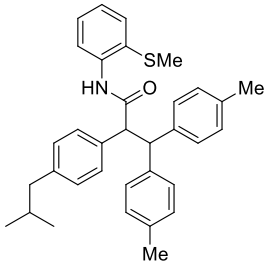

13t, 27% (48 h)

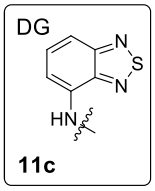
Table 3: The sp^3 C-H activation and bis-arylation of ibuprofen carboxamide **11b,c** using different directing groups.

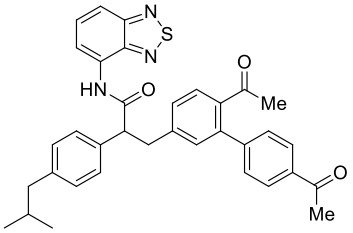


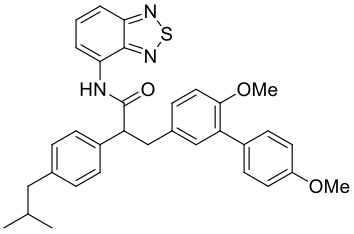




15a, 52% (20 h)





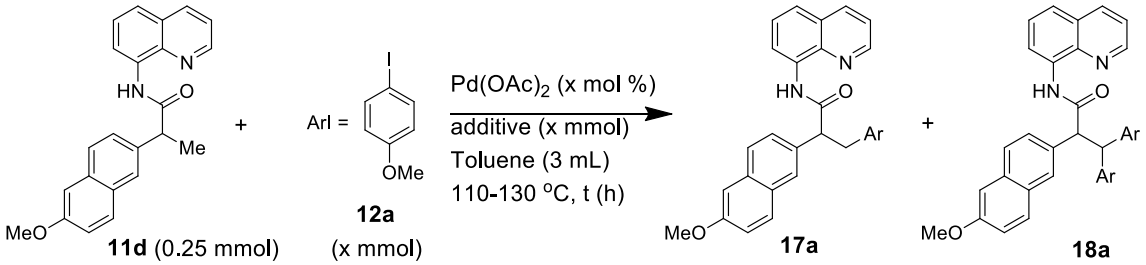


16a, 38% (40 h) **16b**, 42% (36 h)

Next, it was envisaged to subject the naproxen carboxamide **11d** to the Pd(II)-catalyzed sp^3 C-H activation and bis-arylation to afford the corresponding bis-arylated compounds. The reaction of **11d** (0.25 mmol) with 1 mmol of 1-iodo-4-methoxybenzene in presence of $Pd(OAc)_2$ and AgOAc provided the bis-arylated compound **18a** in 30% yield and traces of monoarylated product **17a** (entry 1, Table 4). Enhancing the temperature did not afford the compound **18a** but the monoarylated product was obtained in 17% (entry 2, Table 4). The reaction of **11d** (0.25 mmol) with 1.5 mmol of 1-iodo-4-methoxybenzene afforded the bis-arylated product in 53% (entry 3, Table 4). Then, the reaction period was increased to improve the yield of **18a** and the bis-arylated product was obtained in 64% (entry 4, Table 4). When the reaction was performed at 130 ^oC for 22 h the product **18a** was formed in 46% (entry 5, Table 4). The product **18a** was

obtained in 72% when the reaction was performed using 10 mol% of $Pd(OAc)_2$ catalyst (entry 6, Table 4). Moreover, no improvement in product yield **18a** was noted with increasing the amount of oxidant (3.3 equiv. of AgOAc, entry 7, Table 14). The Pd(II)-catalyzed arylation of **11d** failed when silver salts such as Ag_2CO_3 and AgOTf were employed (entries 8 and 9, Table 4).

Table 4: Optimization reactions: The reaction of naproxen carboxamide **11d** with **12a** to form bis-arylated compound **18a**.



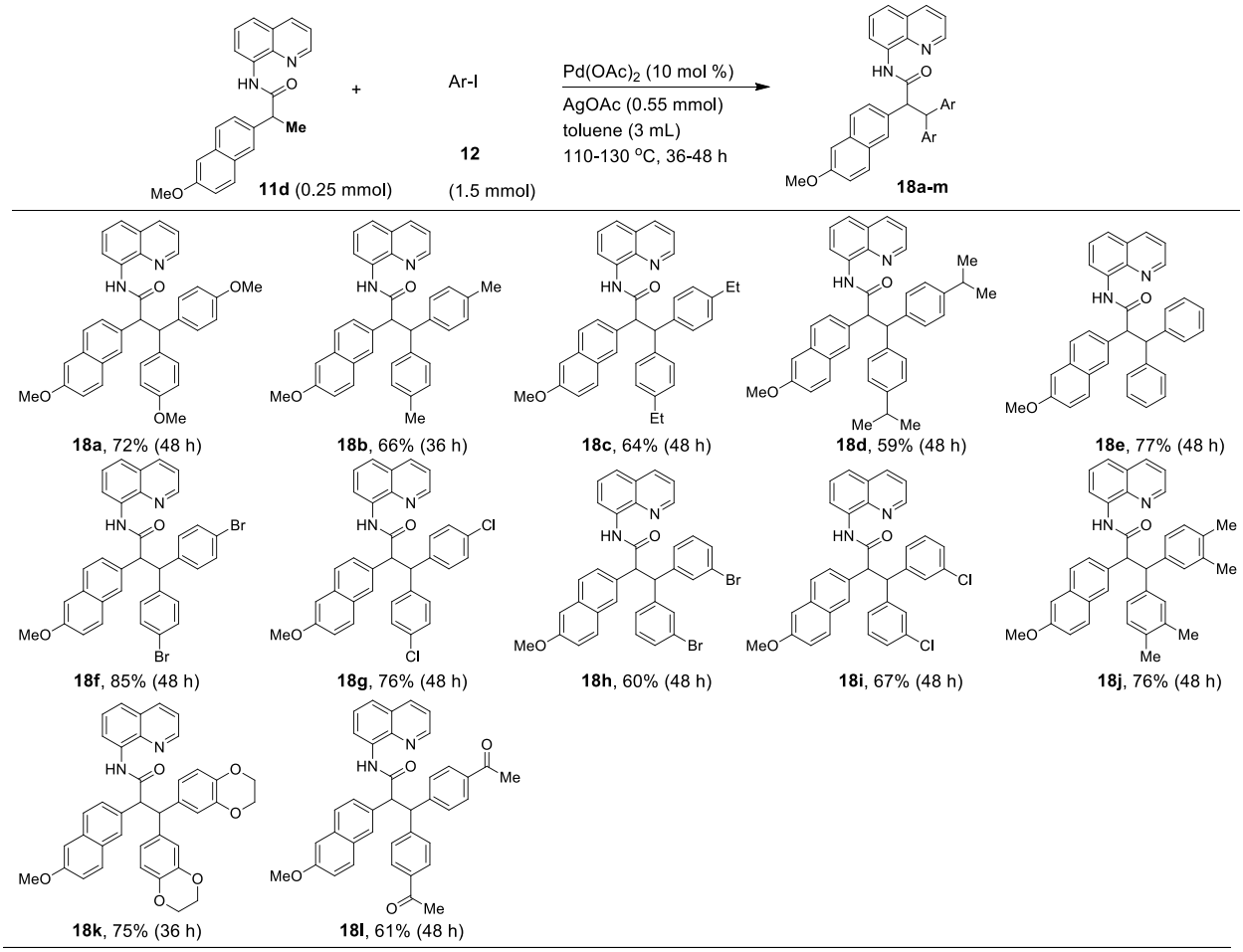
11d (0.25 mmol) **12a** (x mmol) **17a** **18a**

entry	Ar-I (mmol)	catalyst (mol %)	additive (mmol)	time (h)	T (°C)	yield (%) mono(**17a**)	yield (%) di(**18a**)
1	1	$Pd(OAc)_2$ (5)	AgOAc (0.55)	48	110	traces	30
2	1	$Pd(OAc)_2$ (5)	AgOAc (0.55)	36	130	17	-
3	1.5	$Pd(OAc)_2$ (5)	AgOAc (0.55)	36	110	-	53
4	1.5	$Pd(OAc)_2$ (5)	AgOAc (0.55)	48	110	traces	64
5	1.5	$Pd(OAc)_2$ (5)	AgOAc (0.55)	22	130	traces	46
6	**1.5**	**$Pd(OAc)_2$ (10)**	**AgOAc (0.55)**	**40**	**130**	**-**	**72**
7	1.5	$Pd(OAc)_2$ (10)	AgOAc (0.83)	40	130	-	68
8	1.5	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.55)	24	130	-	-
9	1.5	$Pd(OAc)_2$ (10)	AgOTf (0.55)	24	130	-	-

Then, it was envisaged to obtain various bis-arylated naproxen derivatives by extending the scope of the bis-arylation of naproxen carboxamide **11d** (Table 5). The Pd(II)-catalyzed arylation of **11d** with aryl iodides bearing electron donating functional groups such as OMe, Et, Me, ^{i}Pr, at *para* position gave the respective bis-arylated compounds **18a-d** in 59-72% yield (Table 5). The Pd(II)-catalyzed arylation of **11d** with PhI afforded the arylated compound **18e** in 77% yield (Table 5). The arylation of carboxamide **11d** with aryl iodides possessing halide substituents such as Cl, Br at *para* position gave the corresponding compounds **18f-g** in 55-75% yield (Table

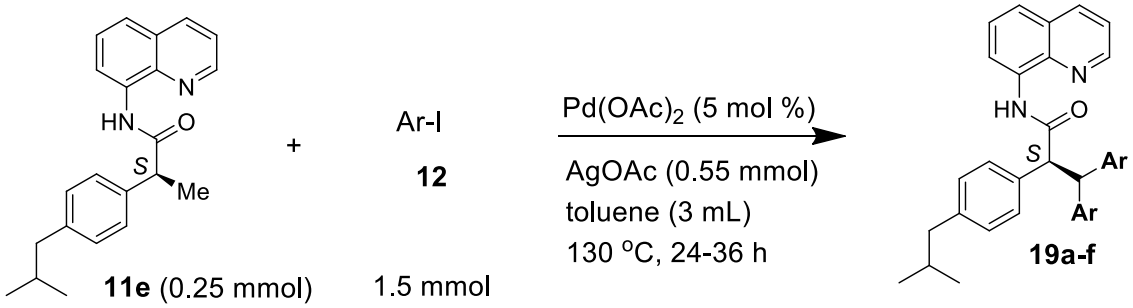
5). Similarly, the arylation of carboxamide **11d** with aryl iodides bearing -Cl or -Br substituents at *meta* position afforded the respective arylated products **18h-i** in 60-67% yield. The arylation of naproxen carboxamide **11d** with disubstituted aryl iodides such as 4-iodo-1,2-dimethylbenzene and 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine furnished the respective arylated compounds **18j-k** in 76-75% yield (Table 5). The arylation of naproxen carboxamide **11d** with aryl iodide bearing electron withdrawing group e.g., COMe at *para* position provided the arylated compound **18l** in 61% yield (Table 5).

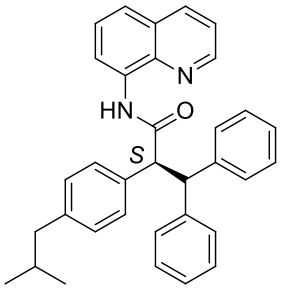
Table 5: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of naproxen carboxamide **11d** with different aryl iodides.



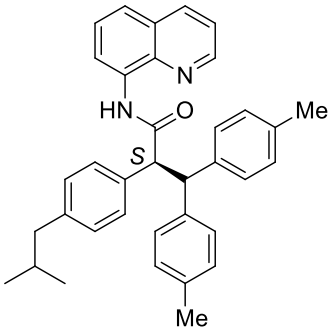
To extend the scope and usefulness of Pd(II)-catalyzed sp^3 C-H activation of ibuprofen and naproxen carboxamides, their corresponding enantiomerically enriched substrates (*S*)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide **11e** and (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide **11f** were subjected to the bis-arylation (Table 6). The $Pd(OAc)_2$-catalyzed bis-arylation of enantiomerically enriched substrate **11e** with PhI and aryl iodide containing electron donating methyl group at *para* position gave the corresponding arylated compounds **19a,b** in 69-86% yields (Table 6). Next, the arylation of **11e** with aryl iodides bearing substituents such as Br, Cl and disubstituted aryl iodide afforded corresponding bis-arylated compound **19c-f** in 58-77% yields (Table 6). Similar to the reactions of carboxamide **11e**, the arylation of enantiomerically enriched substrate **11f** with PhI and aryl iodides bearing electron donating alky substituents such as Et and Me groups provided the respective arylated compounds **20a-c** in 68-86% yield (Table 7). The treatment of compound **11f** with 1,2-dichloro-4-iodobenzene under the standard condition resulted the arylated product **20d** in 80% yield (Table 7). The arylation of **11f** with aryl iodides bearing *p*-bromo and *m*-bromo substituents also furnished the corresponding bis-arylated products **20e,f** in 81-89% yields (Table 7).

Table 6: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of enantiomerically enriched ibuprofen carboxamide **11e**.

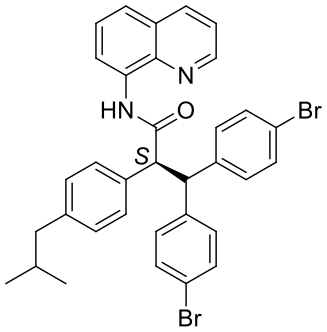




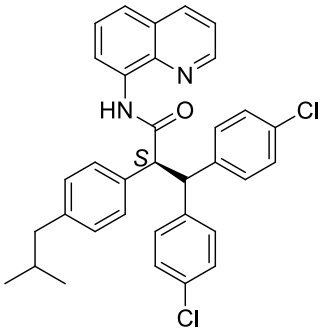
19a, 69% (36 h)



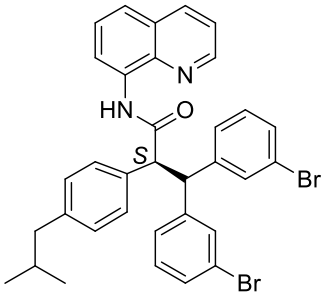
19b, 86% (24 h)



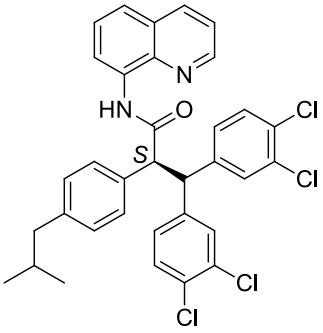
19c, 58% (36 h)



19d, 68% (24 h)

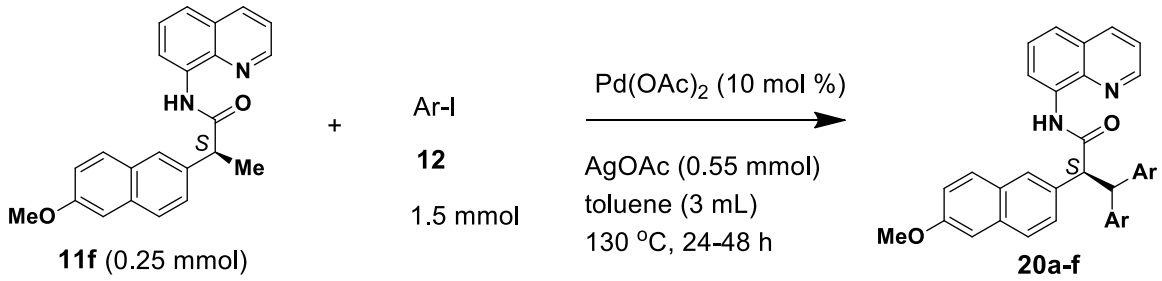


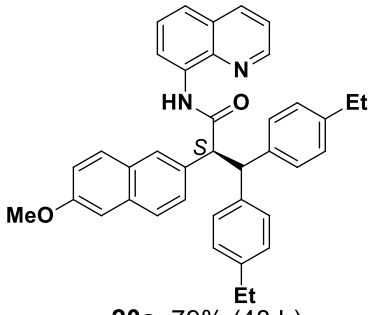
19e, 69% (24 h)



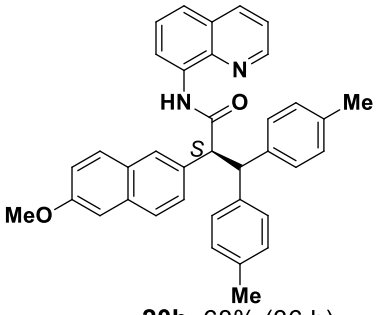
19f, 77% (24 h)

Table 7: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of enantiomerically enriched naproxen carboxamide **11f**.

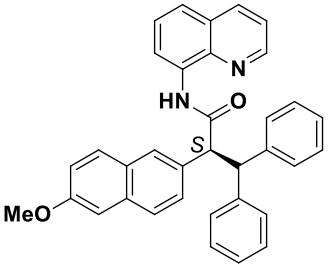




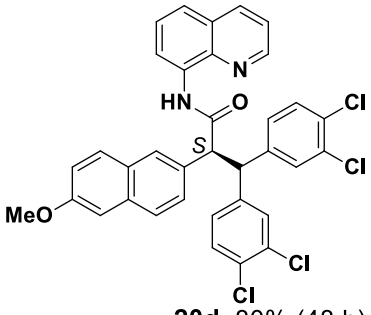
20a, 79% (48 h)



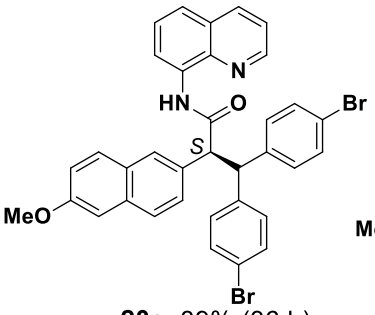
20b, 68% (36 h)



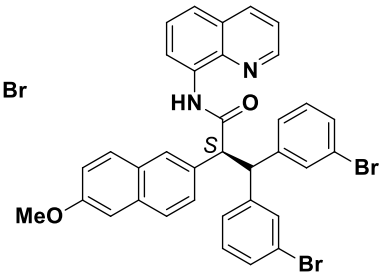
20c, 86% (36 h)



20d, 80% (48 h)



20e, 89% (36 h)



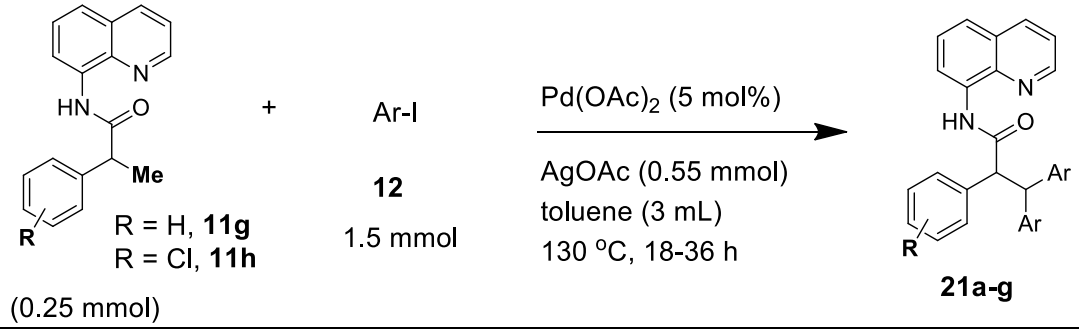
20f, 81% (24 h)

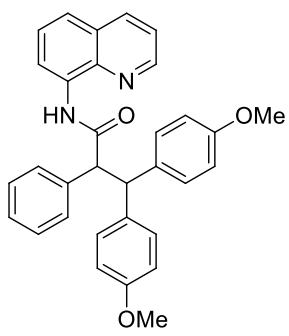
Having done the sp^3 C-H activation and bis-arylation of ibuprofen and naproxen carboxamides, it was envisaged to further extend the generality of this work by investigating the arylation of carboxamides analogous to ibuprofen carboxamide **11a**. Accordingly, (±)-2-phenyl-*N*-(quinolin-8-yl)propanamide **11g** and (±)-2-(4-chlorophenyl)-*N*-(quinolin-8-yl)propanamide **11h** were assembled. The arylation of **11g** with PhI and aryl iodides possessing electron donating OMe, Me groups afforded the respective bis-arylated products **21a-c** in 44-96% yields (Table 8). The arylation of **11g** with aryl iodides possessing *p*-bromo and *m*-bromo substituents afforded the corresponding arylated compounds **21d,e** in 75-79% yields (Table 8). Similarly, the C-H

arylation of carboxamide **11h** with 1-ethyl-4-iodobenzene and 1-bromo-4-iodobenzene provided the corresponding arylated compounds **21f,g** in 82% and 71% yields (Table 8). Finally, (±)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)propanamide **11i** was prepared from the acid chloride of flurbiprofen with 8-aminoquinoline under the standard condition. The $Pd(OAc)_2$ catalyzed C-H arylation of carboxamide **11i** with a variety of aryl iodides possessing Me, OMe, Br groups provided the corresponding bis-arylated compounds **22a-c** in 69-81% yields (Table 9).

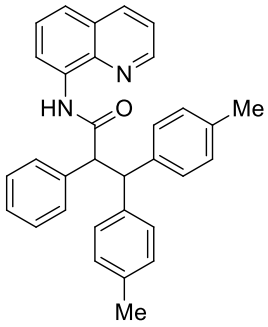
To show utility of this Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of the carboxamides of anti-inflammatory drugs (NSADs) including ibuprofen, naproxen, flurbiprofen, it was envisaged to synthesize 3,3-diarylated-2-aryl propionic acids from the representative bis-arylated derivatives of carboxamides derived from NSADs. Accordingly, the removal of the 8-aminoquinoline directing group was attempted. The amide hydrolysis of **13c,g** under standard NaOH or KOH or HCl mediated hydrolysis conditions were not fruitful. Notably, the amide hydrolysis of **13c,g** in presence of triflic acid at 100 ^oC in toluene afforded the bis-arylated ibuprofen derivatives **23** and **24** (Scheme 4).

Table 8: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of 2-arylpropanecarboxamides **11g,h**.

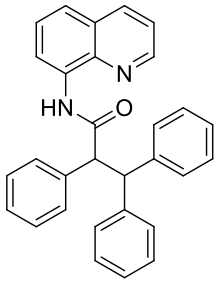




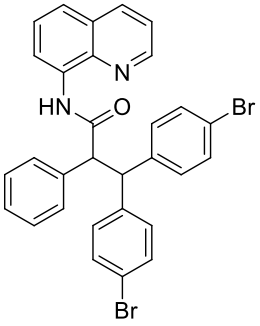
21a, 75%, 18 h



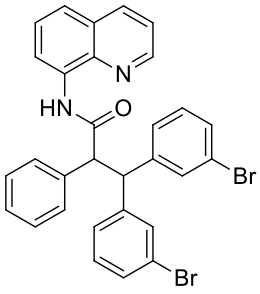
21b, 96%, 24 h



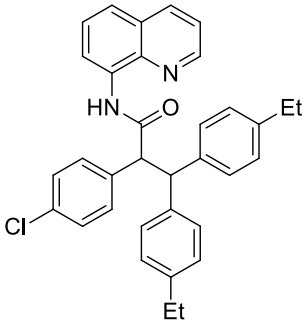
21c, 44%, 36 h



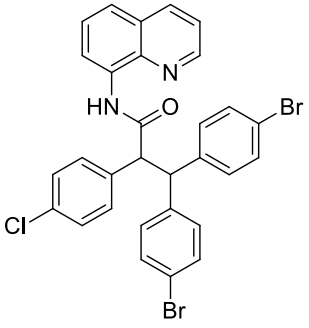
21d, 79%, 24 h



21e, 75%, 24 h

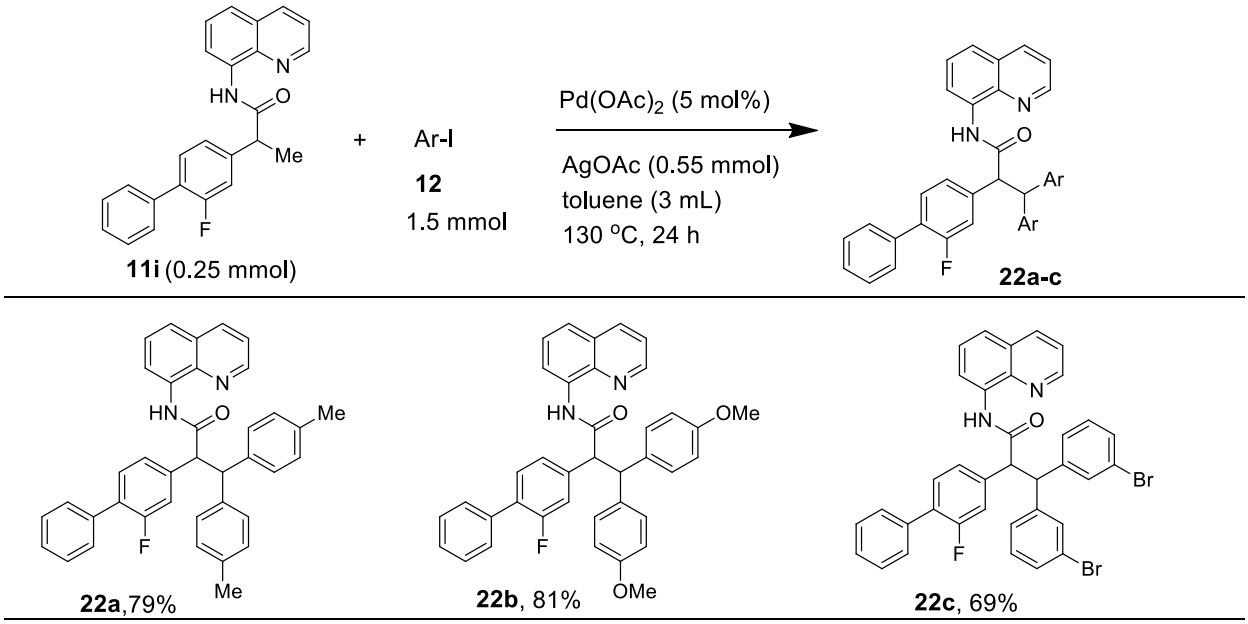


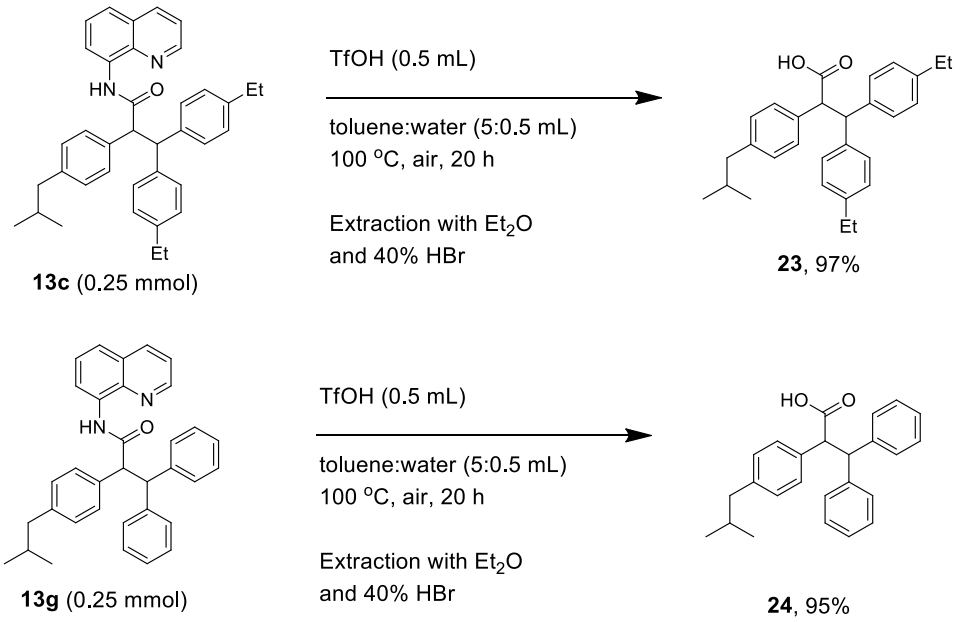
21f, 82%, 24 h



21g, 71%, 24 h

Table 9: The $Pd(OAc)_2$ catalyzed 8-aminoquinoline-directed sp^3 C-H activation and bis-arylation of **11i**.



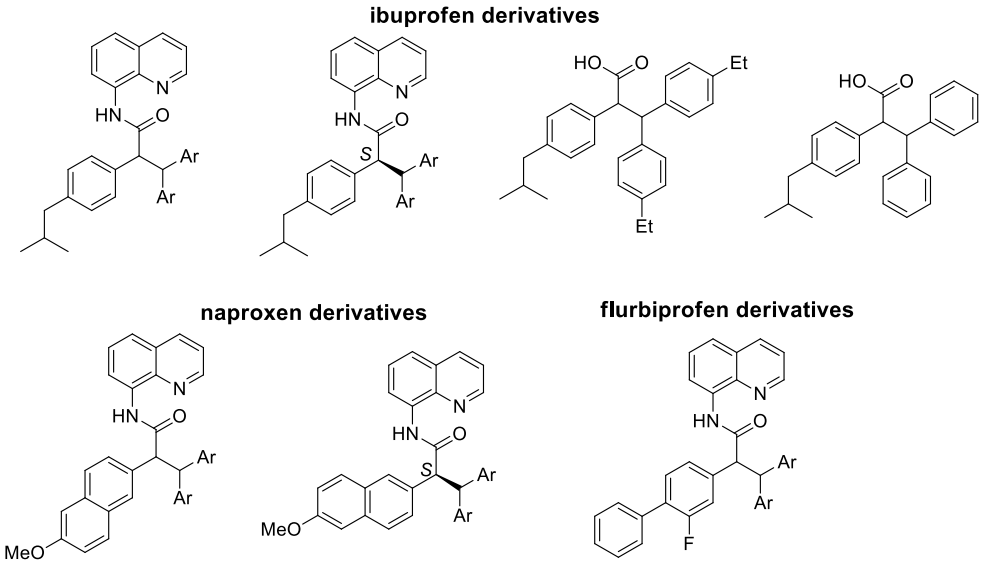


Scheme 4: Synthesis of 3,3-diarylated-2-aryl propionic acids (ibuprofen derivatives) **23** and **24** from the presentative bis-arylated ibuprofen carboxamide **13c,g**.

Summary

In summary, this Chapter 3 reported the bidentate directing group 8-aminoquinoline-aided Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of racemic and optically pure 2-arylpropionamides and the construction of functionalized 2-arylpropionamides.

Especially, the Pd(II)-catalyzed bis-arylation of methyl sp^3 C-H bonds of the carboxamides derived from anti-inflammatory drugs (NSADs) including ibuprofen, naproxen, flurbiprofen and other 2-arylpropanecarboxamides have led to the synthesis of a library of new 2-arylpropanecarboxylic acid derivatives and bis arylated carboxamides.



Experimental Section

General Considerations. Melting points are uncorrected. IR spectra of all the compounds were recorded as KBr pellets or thin films. ^{1}H and ^{13}C NMR spectra of all the compounds were recorded on 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Column chromatography was carried out using silica gel 100-200 mesh. All the reactions were performed using anhydrous solvents under a nitrogen atmosphere. Organic layers after the work up procedure were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis (TLC) was performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized.

General procedure for synthesis of carboxamides 11a-i.

The corresponding carboxylic acid (1.1 mmol) was dissolved in 5 mL of dry DCM and stirred for 0.5 h at 0 ^{o}C under a nitrogen atmosphere. To this reaction mixture, 2 equivalents of $(COCl)_2$ was added in drops and allowed to stir at 0 ^{o}C for overnight. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atmosphere. Then, the resulting acid chloride was added to another RB flask containing the corresponding auxiliary (amine, 1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt 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 = 15:85) furnished the corresponding carboxamides **11a-i**.

General procedure for di-arylation of 2-arylpropane carboxamides for the preparation of 13a-t/15a/16a-b/18a-l/19a-f/20a-f/21a-g/22a-c. A mixture of the corresponding carboxamide (**11a-i**) (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 5 mol%), aryl iodide (1.5 mmol, 6 equiv) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 130 ^{o}C for 16-48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with

EtOAc (3-4 mL) and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding bis-arylated aliphatic carboxamides **13a-t/15a/16a-b/18a-l/19a-f/20a-f/21a-g/22a-c** (see Tables/Schemes for specific examples, chapter 3).

General procedure for β-C-H di-arylation of 2-arylpropane carboxamides for the preparation of 21a-g. A mixture of the corresponding carboxamide (**11g/11h**) (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol%), aryl iodide (1.5 mmol, 6 equiv) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 130 ^oC for 36-48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (3-4 mL) and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding β-C-H bis-arylated aliphatic carboxamides **21a-g** (see Tables/Schemes for specific examples, chapter 3).

General procedure for the hydrolysis of carboxamides 13c and 13g: To a RB flask (capacity 25 mL) containing the corresponding carboxamide **13c** or **13g** (0.25 mmol) was sequentially added toluene (3 mL), water (0.5 mL) and CF_3SO_3H (0.5 mL). Then, RB flask was fitted with a condenser having a J Young air inlet valve molded at the top. 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 this period, the reaction mixture was diluted with EtOAc and extracted with saturated aqueous Na_2CO_3 solution (20 mL x 2). Then, aqueous layer was acidified with 1 N HCl (15 mL x 2) to get pH~2. Extraction of the aqueous layer with EtOAc (10 mL x 2) and drying of the combined organic layers over Na_2SO_4 and evaporation in vacuum gave the corresponding carboxylic acid **23** or **24**.

2-(4-Isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (11a) : Following the general procedure, **11a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 77-79 ^oC; R_f = 0.56 (20% EtOAc/Hexane); Yield: 51% (168 mg); IR (KBr): 3349, 2955, 1688, 1525, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.81 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz), 8.68 (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), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.42-7.38 (m, 3H), 7.19 (d, 2H, J =

8.0 Hz), 3.93 (q, 1H, *J* = 7.1 Hz), 2.50 (d, 2H, *J* = 7.2 Hz), 1.94-1.84 (m, 1H), 1.71 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 148.1, 140.8, 138.5, 138.2, 136.2, 134.6, 129.7, 127.9, 127.5, 127.4, 121.5, 121.4, 116.2, 48.3, 45.1, 30.3, 22.4, 18.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O$: 333.1967; found 333.1983.

2-(4-Isobutylphenyl)-*N*-(2-(methylthio)phenyl)propanamide (11b) : Following the general procedure, **11b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless liquid; R_f = 0.68 (20% EtOAc/Hexane); Yield: 82% (268 mg); IR (thin film): 3320, 2954, 1690, 1579, 1509, 1432 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, 1H, *J* = 8.3 Hz);), 8.38 (br. s, 1H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 1H, *J* = 7.4 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 7.01 (d, 1H, *J* = 7.5 Hz), 3.81 (q, 1H, *J* = 7.2 Hz), 2.50 (d, 2H, *J* = 7.2 Hz), 2.0 (s, 3H), 1.93-1.85 (m, 1H), 1.67 (d, 3H, *J* = 7.2 Hz), 0.94 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 141.2, 138.8, 137.9, 133.6, 129.9, 129.2, 127.6, 124.8, 124.0, 119.9, 48.1, 45.0, 30.3, 22.4, 18.8, 18.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{26}NOS$: 328.1735; found 328.1655.

***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-(4-isobutylphenyl)propenamide (11c) :** Following the general procedure, **11c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 77-79 ^oC; R_f = 0.67 (20% EtOAc/Hexane); Yield: 48% (164 mg); IR (KBr): 3372, 2954, 1691, 1545, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, *J* = 7.4 Hz), 8.47 (br. s, 1H), 7.62 (d, 1H, *J* = 8.7 Hz), 7.58-7.54 (m, 1H), 7.36 (d, 2H, *J* = 7.8 Hz), 7.21 (d, 2H, *J* = 7.8 Hz), 3.90 (q, 1H, *J* = 7.1 Hz), 2.51 (d, 2H, *J* = 7.2 Hz), 1.95-1.85 (m, 1H), 1.70 (d, 3H, *J* = 7.2 Hz), 0.94 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 154.6, 147.7, 141.3, 137.5, 131.1, 130.0, 130.0, 127.5, 115.6, 114.5, 48.0, 45.0, 30.3, 22.4, 18.2; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{19}H_{20}N_3OS$: 338.1327; found 338.0135.

2-(6-Methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (11d) : Following the general procedure, **11d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 135-137 ^oC; R_f = 0.38 (20% EtOAc/Hexane); Yield: 48% (168 mg); IR (KBr): 3338, 2936, 1682, 1604, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.80 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 8.63 (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), 7.89 (s, 1H), 7.79 (d, 1H, J = 4.1 Hz), 7.77 (d, 1H, J = 3.7 Hz), 7.59 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.53 (t, 1H, J = 8.2 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.18 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.5 Hz), 7.14 (d, 1H, J = 2.2 Hz), 4.09 (q, 1H, J = 7.1 Hz), 3.94 (s, 3H), 1.79 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 157.6, 148.1, 138.4, 136.3, 136.2, 134.5, 133.8, 129.4, 129.1, 127.8, 127.6, 127.3, 126.3, 126.2, 121.5, 121.4, 119.0, 116.2, 105.2, 55.3, 48.6, 18.7; HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{23}H_{20}N_2O_2$: 356.1525; found 356.9287.

(*S*)-2-(4-Isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (11e) : Following the general procedure, **11e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; mp 64-66 ^oC; R_f = 0.67 (20% EtOAc/Hexane); Yield: 99% (328 mg); IR (KBr): 3348, 2954, 1687, 1525, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (br. s, 1H), 8.80 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 8.68 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.52 (t, 1H, J = 8.2 Hz), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.43-7.40 (m, 3H), 7.19 (d, 2H, J = 8.1 Hz), 3.93 (q, 1H, J = 7.1 Hz), 2.49 (d, 2H, J = 7.2 Hz), 1.92-1.85 (m, 1H), 1.70 (d, 3H, J = 7.2 Hz), 0.93 (d, 6H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 148.1, 140.8, 138.5, 138.2, 136.2, 134.6, 129.7, 127.9, 127.5, 127.4, 121.5, 121.4, 116.2, 48.3, 45.1, 30.3, 22.4, 18.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O$: 333.1967; found 333.1942.

(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (11f) : Following the general procedure, **11f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 102-104 ^oC; R_f = 0.53 (20% EtOAc/Hexane); Yield: 66% (235 mg); IR (KBr): 3344, 2932, 1684, 1604, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.80 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.1 Hz), 8.63 (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), 7.89 (s, 1H), 7.79 (d, 1H, J = 4.1 Hz), 7.77 (d, 1H, J = 3.7 Hz), 7.59 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.53 (t, 1H, J = 8.1 Hz), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.18 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.5 Hz), 7.14 (d, 1H, J = 2.3 Hz), 4.09 (q, 1H, J = 7.1 Hz), 3.94 (s, 3H), 1.79 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 157.6, 148.1, 138.4, 136.3, 136.2, 134.5, 133.8, 129.4, 129.1,

127.8, 127.6, 127.3, 126.3, 126.2, 121.5, 121.4, 119.0, 116.2, 105.6, 55.3, 48.6, 18.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_2$: 357.1603; found 357.1596.

2-Phenyl-*N*-(quinolin-8-yl)propanamide (11g) : Following the general procedure, **11g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 107-109 ^oC; R_f = 0.49 (20% EtOAc/Hexane); Yield: 49% (136 mg); IR (KBr): 3347, 2932, 1687, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.79 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.1 Hz), 8.73 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 7.55-7.47 (m, 4H), 7.44-7.39 (m, 3H), 7.32 (t, 1H, *J* = 7.2 Hz), 3.96 (q, 1H, *J* = 7.1 Hz), 1.71 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 148.1, 141.1, 138.5, 136.2, 134.5, 129.0, 127.9, 127.7, 127.4, 127.3, 121.5, 121.4, 116.3, 48.7, 18.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1341; found 277.1353.

2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)propanamide (11h) : Following the general procedure, **11h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow liquid; R_f = 0.53 (20% EtOAc/Hexane); Yield: 58% (180 mg); IR (thin film): 3344, 2975, 1687, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.78-8.75 (m, 2H), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.46-7.43 (m, 3H), 7.37 (d, 2H, *J* = 8.5 Hz), 3.93 (q, 1H, *J* = 7.1 Hz), 1.69 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 148.2, 139.2, 138.4, 136.3, 134.3, 133.1, 129.0, 129.0, 127.9, 127.4, 121.6, 121.6, 116.3, 48.0, 18.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}ClN_2O$: 311.0951; found 311.0967.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)propenamide (11i) : Following the general procedure, **11i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow solid; mp 132-134 ^oC; R_f = 0.50 (20% EtOAc/Hexane); Yield: 56% (207 mg); IR (KBr): 3342, 2978, 1679, 1624, 1524, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.80 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.8 Hz), 8.77 (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), 7.56-7.44 (m, 8H), 7.41-7.32 (m, 3H), 3.99 (q, 1H, *J* = 7.1 Hz), 1.75 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 160.0 (d, J_{C-F} = 246.8 Hz), 148.2, 142.5 (d, J_{C-F} = 7.4 Hz), 138.5, 136.3, 135.5, 134.4 (d, J_{C-F} = 4.2 Hz), 131.1 (d,

$J_{C\text{-}F}$ = 4.1 Hz), 128.9 (d, $J_{C\text{-}F}$ = 2.7 Hz), 128.5, 128.1, 127.9, 127.9, 127.7, 127.4, 123.7 (d, $J_{C\text{-}F}$ = 3.3 Hz), 121.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 116.4, 115.5, 115.3, 48.1, 18.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}FN_2O$: 371.1560; found 371.1573.

2-(4-Isobutylphenyl)-3,3-bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)propanamide (13a) : Following the general procedure, **13a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 121-123 ^oC; Yield: 80% (109 mg); R_f = 0.42 (20% EtOAc/Hexane); IR (KBr): 3353, 2961, 1687, 1511, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.66-8.64 (m, 1H), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.45-7.41 (m, 5H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.0 (d, 2H, *J* = 8.7 Hz), 6.98 (d, 2H, *J* = 8.2 Hz), 6.76 (d, 2H, *J* = 8.6 Hz), 6.64 (d, 2H, *J* = 8.6 Hz), 4.88 (d, 1H, *J* = 11.8 Hz), 4.44 (d, 1H, *J* = 11.8 Hz), 3.69 (s, 3H), 3.67 (s, 3H), 2.36 (d, 2H, *J* = 7.2 Hz), 1.82-1.72 (m, 1H), 0.83 (d, 3H, *J* = 0.8 Hz), 0.81 (d, 3H, *J* = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 157.9, 157.5, 148.0, 140.4, 138.3, 136.3, 135.8, 135.5, 134.9, 134.9, 129.5, 129.2, 128.6, 128.2, 127.8, 127.3, 121.5, 121.3, 116.4, 114.0, 113.4, 59.9, 55.1, 52.8, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{37}N_2O_3$: 545.2804; found 545.2828.

2-(4-Isobutylphenyl)-3,3-bis(4-isopropylphenyl)-*N*-(quinolin-8-yl)propanamide (13b) : Following the general procedure, **13b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 164-166 ^oC; R_f = 0.72 (20% EtOAc/Hexane); Yield: 61% (87 mg); IR (KBr): 3350, 2958, 1688, 1524, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 8.04 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.48 (d, 1H, *J* = 8.2 Hz), 7.44-7.35 (m, 5H), 7.10 (d, 1H, *J* = 8.2 Hz), 7.07 (d, 1H, *J* = 8.3 Hz), 6.97-6.95 (m, 4H), 4.94 (d, 1H, *J* = 11.8 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 2.81-2.70 (m, 2H), 2.38 (d, 1H, *J* = 2.9 Hz), 2.36 (d, 1H, *J* = 2.8 Hz), 1.81-1.74 (m, 1H), 1.15 (d, 6H, *J* = 6.9 Hz), 1.10 (d, 3H, *J* = 1.2 Hz), 1.08 (d, 3H, *J* = 1.2 Hz), 0.84-0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 148.0, 146.5, 140.7, 140.3, 139.7, 138.2, 136.2, 135.6, 134.5, 129.1, 128.5, 128.3, 128.3, 127.7, 127.6, 127.3, 126.7, 126.0, 121.5, 121.2, 116.3, 59.7, 53.9, 45.0, 33.5, 33.5, 30.2, 24.0, 23.8, 238, 23.8, 22.3, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{40}H_{45}N_2O$: 569.3532; found 569.3510.

3,3-Bis(4-ethylphenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13c) : Following the general procedure, **13c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 187-189 ^{o}C; R_f = 0.65 (20% EtOAc/Hexane); Yield: 85% (115 mg); IR (KBr): 3343, 2955, 1687, 1524, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.45-7.40 (m, 5H), 7.35 (d, 2H, J = 8.1 Hz), 7.06 (d, 2H, J = 4.9 Hz), 7.04 (d, 2H, J = 4.9 Hz), 6.98 (d, 2H, J = 8.0 Hz), 6.92 (d, 2H, J = 8.0 Hz), 4.93 (d, 1H, J = 11.8 Hz), 4.54 (d, 1H, J = 11.8 Hz), 2.52-2.46 (m, 4H), 2.37-2.35 (m, 2H), 1.80-1.71 (m, 1H), 1.12 (t, 3H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz), 0.82 (d, 3H, J = 3.6 Hz), 0.81 (d, 3H, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 148.0, 141.9, 141.6, 140.7, 140.3, 139.6, 138.2, 136.3, 135.6, 134.5, 129.1, 128.5, 128.3, 128.1, 127.8, 127.6, 127.5, 127.3, 121.4, 121.2, 116.5, 59.6, 53.8, 45.0, 30.1, 28.3, 22.3, 22.2, 15.4, 15.2; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{38}H_{41}N_2O$: 541.3219; found 541.3235.

3,3-Bis(3,4-dimethylphenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13d) : Following the general procedure, **13d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 174-176 ^{o}C; R_f = 0.58 (20% EtOAc/Hexane); Yield: 81% (110 mg); IR (KBr): 3352, 2953, 2920, 1688, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.65 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.4 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.45-7.37 (m, 5H), 7.30-7.27 (m, 2H), 7.01-6.97 (m, 3H), 6.89-6.87 (m 3H), 4.84 (d, 1H, J = 11.8 Hz), 4.53 (d, 1H, J = 11.9 Hz), 2.37 (d, 2H, J = 7.2 Hz), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 1.83-1.73 (m, 1H), 0.84 (d, 3H, J = 2.0 Hz), 0.83 (d, 3H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 148.0, 141.0, 140.3, 139.9, 138.3, 136.5, 136.2, 135.9, 135.7, 134.6, 134.3, 133.8, 130.1, 129.8, 129.4, 129.3, 129.1, 128.3, 127.8, 127.3, 125.7, 124.5, 121.4, 121.2, 116.4, 59.5, 53.7, 45.0, 30.1, 22.3, 22.3, 19.9, 19.8, 19.3; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{38}H_{41}N_2O$: 541.3219; found 541.3198.

3,3-Bis(3,5-dimethylphenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13e) : Following the general procedure, **13e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 195-197 ^{o}C; R_f = 0.67 (20%

EtOAc/Hexane); Yield: 67% (91 mg); IR (KBr): 3353, 2953, 2918, 1689, 1524, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.45-7.40 (m, 3H), 7.36 (d, 2H, J = 8.2 Hz), 7.16 (s, 2H), 7.00 (d, 2H, J = 8.1 Hz), 6.73 (s, 2H), 6.68 (s, 1H), 6.66 (s, 1H), 4.79 (d, 1H, J = 11.8 Hz), 4.52 (d, 1H, J = 11.8 Hz), 2.37 (d, 2H, J = 7.2 Hz), 2.19 (s, 6H), 2.16 (s, 6H), 1.84-1.74 (m, 1H), 0.85 (d, 3H, J = 1.3 Hz), 0.83 (d, 3H, J = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 147.9, 143.1, 142.1, 140.3, 138.3, 137.7, 137.1, 136.2, 135.6, 134.5, 129.0, 128.3, 128.1, 127.8, 127.6, 127.3, 126.3, 125.6, 121.4, 121.2, 116.5, 59.5, 54.5, 45.0, 30.2, 22.3, 21.4, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{41}N_2O$: 541.3219; found 541.3198.

2-(4-Isobutylphenyl)-*N*-(quinolin-8-yl)-3,3-di-m-tolylpropanamide (13f) : Following the general procedure, **13f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 171-173 ^oC; R_f = 0.67 (20% EtOAc/Hexane);Yield: 70% (90 mg); IR (KBr): 3353, 2953, 1604, 1524, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.45-7.34 (m, 7H), 7.14 (t, 1H, J = 7.6 Hz), 7.03-6.89 (m, 6H), 6.85 (d, 1H, J = 7.2 Hz), 4.89 (d, 1H, J = 11.8 Hz), 4.55 (d, 1H, J = 11.8 Hz), 2.37 (d, 2H, J = 7.2 Hz), 2.25 (s, 3H), 2.20 (s, 3H), 1.83-1.74 (m, 1H), 0.84 (d, 3H, J = 1.4 Hz), 0.83 (d, 3H, J = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 148.0, 143.2, 142.2, 140.4, 138.3, 138.0, 137.4, 136.3, 135.5, 134.5, 129.6, 129.1, 129.0, 128.4, 128.3, 127.9, 127.8, 127.3, 127.2, 126.7, 125.6, 124.4, 121.5, 121.3, 116.4, 59.5, 54.5, 45.0, 30.1, 22.3, 22.3, 21.5, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{37}N_2O$: 513.2906; found 513.2900.

2-(4-Isobutylphenyl)-3,3-diphenyl-*N*-(quinolin-8-yl)propanamide (13g) : Following the general procedure, **13g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 176-178 ^oC; R_f = 0.63 (20% EtOAc/Hexane); Yield: 99% (120 mg); IR (KBr): 3455, 2957, 2925, 1686, 1524, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.55 (d, 2H, J = 7.2 Hz), 7.46-7.41 (m, 3H), 7.36 (d, 2H, J = 8.1 Hz), 7.26 (t, 2H, J = 7.6 Hz), 7.15-7.09 (m, 5H), 7.06-7.01 (m, 1H), 6.99 (d, 2H, J = 8.1 Hz), 4.99 (d, 1H, J = 11.8 Hz), 4.57 (d, 1H, J = 11.8 Hz), 2.36 (d, 2H, J = 7.2 Hz), 1.82-

1.72 (m, 1H), 0.83 (d, 3H, J = 1.8 Hz), 0.82 (d, 3H, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 148.1, 143.2, 142.2, 140.5, 138.2, 136.3, 135.3, 134.4, 129.2, 128.7, 128.6, 128.2, 128.1, 127.8, 127.8, 127.3, 126.4, 126.0, 121.5, 121.3, 116.4, 59.4, 54.6, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{33}N_2O$: 485.2593; found 485.2578.

3,3-Bis(4-chlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13h) : Following the general procedure, **13h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 187-189 ^oC; Yield: 85% (115 mg); IR (KBr): 3343, 2955, 1687, 1524, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64-8.62 (m, 1H), 8.12 (d, 1H, J = 8.2 Hz), 7.47-7.43 (m, 5H), 7.31 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.08 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 2.4 Hz), 6.99 (d, 2H, J = 1.9 Hz), 4.94 (d, 1H, J = 11.7 Hz), 4.44 (d, 1H, J = 11.8 Hz), 2.37 (d, 2H, J = 7.2 Hz), 1.83-1.73 (m, 1H), 0.83 (d, 6H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.1, 141.4, 141.0, 140.3, 138.2, 136.4, 134.7, 134.2, 132.4, 132.0, 129.9, 129.4, 129.1, 128.9, 128.3, 128.1, 127.8, 127.3, 121.6, 116.5, 59.2, 53.2, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Cl_2N_2O$: 553.1813; found 553.1821.

3,3-Bis(3-chlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13i) : Following the general procedure, **13i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 180-182 ^oC; R_f = 0.58 (20% EtOAc/Hexane); Yield: 77% (107 mg); IR (KBr): 3341, 2954, 1687, 1524, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.62 (dd, 1H, J_1 = 4.9 Hz, J_2 = 4.2 Hz), 8.09 (d, 1H, J = 8.3 Hz), 7.49-7.41 (m,5H) 7.33 (d, 2H, J = 8.0 Hz), 7.20 (t, 1H, J = 7.9 Hz), 7.12-6.58 (m, 7H), 4.93 (d, 1H, J = 11.8 Hz), 4.47 (d, 1H, J = 11.8 Hz), 2.37 (d, 2H, J = 7.2 Hz), 1.83-1.73 (m, 1H), 0.84 (d, 3H, J = 2.0 Hz), 0.82 (d, 3H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 148.1, 144.5, 143.5, 141.0, 138.2, 136.3, 134.5, 134.2, 133.9, 130.0, 129.4, 129.4, 128.8, 128.2, 128.1, 127.8, 127.2, 127.0, 126.9, 126.5, 125.8, 121.6, 121.6, 116.5, 58.9, 53.9, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Cl_2N_2O$: 553.1813; found 553.1800.

3,3-Bis(3,4-dichlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13j) : Following the general procedure, **13j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 153-155 ^{o}C; R_f = 0.65 (20% EtOAc/Hexane); Yield: 93% (145 mg); IR (KBr): 3337, 2955, 2924, 1686, 1525, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.61 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55 (d, 1H, J = 1.7 Hz), 7.48-7.43 (m, 3H), 7.37-7.34 (m, 2H), 7.31 (d, 2H, J = 8.2 Hz), 7.19 (d, 1H, J = 8.3 Hz), 7.14 (d, 1H, J = 1.8 Hz), 7.04 (d, 2H, J = 8.1 Hz), 6.89 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz), 4.90 (d, 1H, J = 11.7 Hz), 4.39 (d, 1H, J = 11.8 Hz), 2.38 (d, 2H, J = 7.2 Hz), 1.83-1.74 (m, 1H), 0.84 (d, 3H, J = 1.1 Hz), 0.82 (d, 3H, J = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 148.2, 142.4, 141.4, 138.2, 136.4, 134.1, 134.0, 132.9, 132.3, 131.0, 130.8, 130.6, 130.2, 129.9, 129.6,128.0, 128.0, 127.8, 127.2, 126.9, 121.8, 121.7, 116.6, 58.8, 52.8, 44.9, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{29}Cl_4N_2O$: 621.1034; found 621.1015.

3,3-Bis(4-bromophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13k) : Following the general procedure, **13k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 204-206 ^{o}C; R_f = 0.64 (20% EtOAc/Hexane); Yield: 78% (125 mg); IR (KBr): 3344, 2954, 1687, 1525, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64-8.62 (m, 1H), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.45-7.39 (m, 7H), 7.32 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.01 (d, 2H, J = 8.1 Hz), 6.96 (d, 2H, J = 8.4 Hz), 4.93 (d, 1H, J = 11.8 Hz), 4.44 (d, 1H, J = 11.8 Hz), 2.37 (d, 3H, J = 7.2 Hz), 1.81-1.73 (m, 1H), 0.84 (s, 3H), 0.82 (d, 3H, J = 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.2, 141.8, 141.0, 140.8, 138.2, 136.3, 134.6, 134.2, 131.9, 131.3,130.3, 129.5, 128.1, 127.9, 127.3, 121.1, 121.6, 120.6, 120.2, 116.5, 59.0, 53.3,45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Br_2N_2O$: 641.0803; found 641.0795.

3,3-Bis(3-bromophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13l) : Following the general procedure, **13l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 185-187 ^{o}C; R_f = 0.54 (20% EtOAc/Hexane); Yield: 77% (124 mg); IR (KBr): 3342, 2954, 2923, 1687, 1525, 1485 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.7 Hz), 8.63-8.61 (m, 1H), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.64 (t, 1H, J = 1.6 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.45-7.41 (m, 3H), 7.32 (d, 2H, J = 8.1 Hz), 7.27-7.23 (m, 2H), 7.19 (dt, 1H, J_1 = 6.0 Hz, J_2 = 1.6 Hz), 7.13 (t, 1H, J = 7.8 Hz), 7.03-6.96 (m, 4H), 4.90 (d, 1H, J = 11.8 Hz), 4.46 (d, 1H, J = 11.8 Hz), 2.37 (d, 2H, J = 7.2 Hz), 1.84-1.75 (m, 1H), 0.84 (d, 3H, J = 2.0 Hz), 0.82 (d, 3H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.2, 144.8, 143.8, 141.0, 138.2, 136.3, 134.5, 134.2, 131.7, 131.1, 130.3, 130.0, 129.7, 129.5, 128.1, 127.8, 127.3, 127.2, 126.2, 122.9, 122.2, 121.6, 121.6,116.5, 58.9, 53.9, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Br_2N_2O$: 641.0803; found 641.0778.

3,3-Bis(4-acetylphenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13m) : Following the general procedure, **13m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow solid; mp 180-182 ^oC; R_f = 0.67 (20% EtOAc/Hexane); Yield: 76% (108 mg); IR (KBr): 3340, 2955, 1682, 1602, 1524, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.61 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.87 (d, 2H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.46-7.41 (m, 3H), 7.34 (d, 2H, J = 8.1 Hz), 7.22 (d, 2H, J = 8.3 Hz), 6.99 (d, 2H, J = 8.1 Hz), 5.12 (d, 1H, J = 11.8 Hz), 4.60 (d, 1H, J = 11.8 Hz), 2.50 (s, 3H), 2.49 (s, 3H), 1.79-1.71 (m, 1H), 0.81 (d, 3H, J = 2.4 Hz), 0.80 (d, 3H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 197.6, 169.9, 148.2, 147.9, 146.9, 141.1, 138.2, 136.3, 135.6, 134.4, 134.2, 129.5, 129.0, 128.9, 128.4, 128.1, 128.0, 127.8, 127.2, 121.7, 121.6, 116.5, 58.7, 54.5, 44.9, 30.1, 26.5, 22.3, 22.2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{38}H_{36}N_2NaO_3$: 591.2624; found 591.2589.

Dimethyl 4,4'-(2-(4-isobutylphenyl)-3-oxo-3-(quinolin-8-ylamino)propane-1,1-diyl)dibenzoate (13n) : Following the general procedure, **13n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 242-244 ^oC; R_f = 0.28 (20% EtOAc/Hexane); Yield: 85% (128 mg); IR (KBr): 3443, 2953, 1720, 1634, 1524 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 = 1.7 Hz), 8.60 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.6 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.94 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.46-7.43 (m, 3H), 7.32 (d,

2H, *J* = 8.1 Hz), 7.19 (d, 2H, *J* = 8.4 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 5.10 (d, 1H, *J* = 11.8 Hz), 4.56 (d, 1H, *J* = 11.8 Hz), 3.86 (s, 3H), 3.83 (s, 3H), 2.35 (d, 2H, *J* = 7.2 Hz), 1.80-1.710 (m, 1H), 0.81 (d, 3H, *J* = 1.1 Hz), 0.79 (d, 3H, *J* = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.9, 166.8, 147.7, 146.7, 141.0, 138.2, 136.3, 134.4, 134.2, 130.2, 129.6, 129.5, 128.8, 128.6, 128.2, 128.1, 127.9, 127.8, 127.3, 121.6, 121.6, 116.5, 58.8, 54.5, 52.0, 52.0, 44.9, 30.1, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{37}N_2O_5$: 601.2702; found 601.2680.

3,3-Bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13o) : Following the general procedure, **13o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; mp 192-194 ^oC; R_f = 0.18 (20% EtOAc/Hexane); Yield: 83% (125 mg); IR (KBr): 3346, 2954, 2928, 1686, 1524, 1425 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.43-7.39 (m, 3H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.01-6.98 (m, 4H), 6.71 (d, 1H, *J* = 8.9 Hz), 6.63 (s, 1H), 6.58-6.59 (m, 2H), 4.75 (d, 1H, *J* = 11.8 Hz), 4.40 (d, 1H, *J* = 11.8 Hz), 4.14-4.09 (m, 8H), 2.36 (d, 2H, *J* = 7.2 Hz), 1.84-1.73 (m, 1H), 0.83 (d, 3H, *J* = 2.3 Hz), 0.82 (d, 3H, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 148.0, 143.4, 142.9, 142.0, 141.6, 140.4, 136.8, 136.3, 135.8, 135.4, 134.5, 129.2 128.2, 127.8, 127.3, 121.5, 121.3, 120.5, 117.3, 116.7, 116.4, 64.2, 64.2, 59.6, 53.0, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{37}N_2O_5$: 601.2702; found 601.2679.

3,3-Bis(3-fluorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13p) : Following the general procedure, **13p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 174-176 ^oC; R_f = 0.57 (20% EtOAc/Hexane); Yield: 73% (95 mg); IR (KBr): 3343, 2955, 2925, 1686, 1589, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64-8.63 (m, 1H), 8.12-8.09 (m, 1H), 7.44-7.41 (m, 3H), 7.35-7.32 (m, 3H), 7.26-7.20 (m, 2H), 7.10-7.04 (m, 1H), 7.01 (d, 2H, *J* = 8.0 Hz), 6.88 (d, 1H, *J* = 7.8 Hz), 6.85-6.80 (m, 2H), 6.78-6.73 (m, 1H), 4.98 (d, 1H, *J* = 11.8 Hz), 4.48 (d, 1H, *J* = 11.8 Hz), 2.37 (d, 2H, *J* = 7.2 Hz), 1.83-1.74 (m, 1H), 0.83 (d, 3H, *J* = 2.1 Hz), 0.81 (d, 3H, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 162.9 (d, J_{C-F} = 244.7 Hz), 162.6 (d, J_{C-F} = 244.1 Hz), 148.1, 145.2 (d, J_{C-F} = 6.8 Hz) , 144.2 (d,

J_{C-F} = 7.1 Hz), 140.9, 138.2, 136.4, 134.6, 134.2, 130.2 (d, J_{C-F} = 8.2 Hz), 129.6 (d, J_{C-F} = 8.2 Hz), 129.4, 128.1, 127.8, 127.3, 124.4 (d, J_{C-F} = 2.8 Hz), 123.3 (d, J_{C-F} = 2.5 Hz), 121.6, 116.5, 115.5 (d, J_{C-F} = 21.6 Hz), 114.8 (d, J_{C-F} = 21.6 Hz), 113.7 (d, J_{C-F} = 20.8 Hz), 113.2 (d, J_{C-F} = 20.8 Hz), 59.0, 53.9, 45.0, 30.1, 22.3, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}F_2N_2O$: 521.2404; found 521.2382.

2-(4-Isobutylphenyl)-*N*-(quinolin-8-yl)-3,3-bis(3-(trifluoromethyl)phenyl)propanamide (13q): Following the general procedure, **13q** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow solid; mp 121-123 ^oC; R_f = 0.58 (20% EtOAc/Hexane); Yield: 66% (102 mg); IR (KBr): 3346, 2957, 1681, 1524, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.8 Hz), 8.11 (d, 1H, *J* = 8.2 Hz), 7.78 (s, 1H), 7.75-7.73 (m, 1H), 7.45-7.40 (m, 5H), 7.33-7.23 (m, 6H), 7.01 (d, 2H, *J* = 8.1 Hz), 5.12 (d, 1H, *J* = 11.7 Hz), 4.52 (d, 1H, *J* = 11.7 Hz), 2.36 (d, 2H, *J* = 7.2 Hz), 1.78-1.71 (m, 1H), 0.82 (d, 3H, *J* = 3.0 Hz), 0.81 (d, 3H, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 148.2, 143.2, 142.3, 141.2, 138.2, 136.3, 134.2 (d, J_{C-F} = 17.1 Hz), 132.1,131.1, 131.0 (d, J_{C-F} = 32.0 Hz), 130.4 (d, J_{C-F} = 31.9 Hz), 129.5, 129.3, 128.7, 128.1, 127.8, 127.2, 125.5 (q, J_{C-F} = 3.5 Hz), 125.3 (d, J_{C-F} = 6.2 Hz), 124.7 (q, J_{C-F} = 4.2 Hz), 123.8 (q, J_{C-F} = 3.5 Hz), 123.3 (q, J_{C-F} = 4.6 Hz), 122.6 (d, J_{C-F} = 6.5 Hz), 121.6 (d, J_{C-F} = 10.0 Hz), 116.5, 59.1, 54.2, 44.9, 30.0, 22.2, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{31}F_6N_2O$: 621.2341; found 621.2316.

3,3-Bis(4-bromo-3-fluorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13r): Following the general procedure, **13r** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 214-216 ^oC; R_f = 0.72 (20% EtOAc/Hexane); Yield: 76% (129 mg); IR (KBr): 3340, 2955, 2924, 1685, 1525, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.61 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.47-7.41 (m, 4H), 7.31 (d, 2H, *J* = 8.3 Hz), 7.28-7.25 (m, 2H), 7.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 7.03 (d, 2H, *J* = 8.1 Hz), 6.85 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.0 Hz), 6.74 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.9 Hz), 4.93 (d, 1H, *J* = 11.7 Hz), 4.40 (d, 1H, *J* = 11.7 Hz), 2.38 (d, 2H, *J* = 7.2 Hz), 1.82-1.74 (m, 1H), 0.84 (d, 3H, *J* = 1.2 Hz), 0.82 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 160.2 (d, J_{C-F} = 40.3

Hz), 157.7 (d, $J_{C\text{-}F}$ = 39.8 Hz), 148.2, 144.0 (d, $J_{C\text{-}F}$ = 6.3 Hz), 143.0 (d, $J_{C\text{-}F}$ = 6.3 Hz), 141.3, 138.2, 136.4, 134.0 (d, $J_{C\text{-}F}$ = 2.3 Hz), 133.8, 133.2, 129.6, 128.0, 127.5 (d, $J_{C\text{-}F}$ = 60.7 Hz), 125.5, (d, $J_{C\text{-}F}$ = 3.4 Hz), 124.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 121.7 (d, $J_{C\text{-}F}$ = 15.0 Hz), 116.8, 116.6, 116.0 (d, $J_{C\text{-}F}$ = 22.4 Hz), 107.4 (d, $J_{C\text{-}F}$ = 20.6 Hz), 106.9 (d, $J_{C\text{-}F}$ = 20.7 Hz); HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{34}H_{29}Br_2F_2N_2O$: 677.0615; found 677.0645.

3,3-Bis(2-fluoropyridin-4-yl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13s): Following the general procedure, **13s** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 168-170 ^oC; R_f = 0.18 (20% EtOAc/Hexane); Yield: 23% (30 mg); IR (KBr): 3330, 2956, 1685, 1595, 1526, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.78 (d, 1H, *J* = 4.1 Hz), 8.61 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.1 Hz), 8.42 (s, 1H), 8.13 (d, 1H, *J* = 8.2 Hz), 7.94-7.88 (m, 2H), 7.52-7.43 (m, 4H), 7.32 (d, 2H, *J* = 7.9 Hz), 7.03 (d, 2H, *J* = 7.8 Hz), 6.87 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.8 Hz), 6.73 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.8 Hz), 5.07 (d, 1H, *J* = 11.7 Hz), 4.45 (d, 1H, *J* = 11.7 Hz), 2.37 (d, 2H, *J* = 7.2 Hz), 7.78-1.82 (m, 1H), 0.82 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 162.6 (d, $J_{C\text{-}F}$ = 238.0 Hz), 162.2 (d, $J_{C\text{-}F}$ = 237.8 Hz), 148.2, 147.5 (d, $J_{C\text{-}F}$ = 14.6 Hz) , 146.6 (d, $J_{C\text{-}F}$ = 14.7 Hz), 141.6, 141.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 140.8 (d, $J_{C\text{-}F}$ = 7.8 Hz), 138.2, 136.4, 135.3 (d, $J_{C\text{-}F}$ = 4.7 Hz), 134.3 (d, $J_{C\text{-}F}$ = 4.6 Hz), 133.9, 133.7, 129.8, 128.0, 127.8, 127.2, 122.0, 121.7, 116.6, 109.8 (d, $J_{C\text{-}F}$ = 37.3 Hz), 109.2 (d, $J_{C\text{-}F}$ = 37.2 Hz), 58.9,48.2, 44.9, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{32}H_{29}F_2N_4O$: 523.2309; found 523.2331.

3-(1H-Indol-5-yl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (13t) : Following the general procedure, **13t** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.38 (20% EtOAc/Hexane); Yield: 27% (30 mg); IR (thin film): 3336, 2957, 2921, 1674, 1525, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (br. s, 1H), 8.82 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.66 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.09 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52-7.44 (m, 5H), 7.41 (d, 2H, *J* = 8.0 Hz), 7.38 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.3 Hz), 7.24 (d, 1H, *J* = 8.4 Hz), 7.15-7.13 (m, 3H), 7.06 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 4.05 (t, 1H, *J* = 7.5 Hz), 3.81 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.9 Hz), 3.26 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.8 Hz), 2.46 (d, 2H, *J* = 7.2 Hz), 1.89-1.81 (m, 1H), 0.91 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.0, 140.7, 138.4, 137.1, 136.1, 134.6, 134.6, 131.1, 129.5,

128.0, 127.9, 127.8, 127.3, 124.2, 123.6, 121.4, 121.3, 120.8, 116.3, 110.7, 102.4, 57.4, 45.1, 39.9, 30.2, 22.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{30}N_3O$: 448.2389; found 448.2370.

2-(4-Isobutylphenyl)-*N*-(2-(methylthio)phenyl)-3,3-di-p-tolylpropanamide (15a) : Following the general procedure, **15a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 186-188 ^oC; R_f = 0.92 (20% EtOAc/Hexane); Yield: 52% (66 mg); IR (KBr): 3246, 2952, 2920, 1654, 1512, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (br. s, 1H), 8.13 (d, 1H, *J* = 7.8 Hz), 7.43 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.29-7.20 (m, 3H), 7.08 (d, 2H, *J* = 7.8 Hz), 6.99-6.96 (m, 5H), 6.89 (d, 2H, *J* = 7.9 Hz), 4.86 (d, 1H, *J* = 11.8 Hz), 4.33 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 140.6, 140.5, 139.2, 138.8, 135.3, 135.2, 133.8, 129.4, 129.3, 129.3, 128.8, 128.4, 128.1, 127.5, 124.7, 124.0, 120.6, 59.6, 53.0, 45.0, 30.1, 22.3, 22.3, 21.0, 20.9, 19.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{38}NOS$: 508.2674; found 508.2652.

***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4',6-diacetyl-[1,1'-biphenyl]-3-yl)-2-(4-isobutylphenyl)propanamide (16a) :** Following the general procedure, **16a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as yellow colour solid; mp 67-69 ^oC; R_f = 0.33 (20% EtOAc/Hexane); Yield: 38% (55 mg); IR (KBr): 3380, 2921, 1680, 1603, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, *J* = 7.3 Hz), 8.19 (br. s, 1H), 7.99 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 2H, *J* = 8.2 Hz), 7.68-7.64 (m, 2H), 7.57 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.4 Hz), 7.30-7.28 (m, 1H), 7.05 (d, 2H, *J* = 8.2 Hz), 6.99 (d, 2H, *J* = 1.6 Hz), 3.94 (dd, 1H, J_1 = 8.5 Hz, J_2 = 6.4 Hz), 3.64 (dd, 1H, J_1 = 13.5 Hz, J_2 = 6.4 Hz), 3.22 (dd, 1H, J_1 = 13.5 Hz, J_2 = 8.6 Hz), 2.69 (s, 3H), 2.58 (s, 3H), 2.51 (d, 2H, *J* = 7.2 Hz), 1.95-1.85 (m, 1H), 0.93 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 197.7, 171.2, 154.6, 147.6, 145.9, 144.8, 141.4, 141.3, 136.1, 135.4, 132.7, 131.0, 130.5, 129.9, 129.7, 129.5, 128.6, 128.4, 127.2, 115.9, 114.6, 50.9, 44.9, 39.1, 30.2, 26.7, 26.7, 22.4, 22.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{35}H_{34}N_3O_3SNa$: 598.2140; found 598.2311.

***N*-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4',6-dimethoxy-[1,1'-biphenyl]-3-yl)-2-(4-isobutylphenyl)propanamide (16b) :** Following the general procedure, **16b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as yellow colour

liquid; R_f = 0.67 (20% EtOAc/Hexane); Yield: 42% (59 mg); IR (thin film): 3379, 2951, 1695, 1609, 1544, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J* = 7.3 Hz), 8.17 (br. s, 1H), 7.64-7.53 (m, 3H), 7.21 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.01 (d, 1H, *J* = 1.6 Hz), 6.95-6.91 (m, 5H), 6.74 (d, 2H, *J* = 8.6 Hz), 4.01 (t, 1H, *J* = 7.4 Hz), 3.89 (s, 3H), 3.77 (s, 3H), 3.54 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.8 Hz), 3.09 (dd, 1H, J_1 = 13.7 Hz, J_2 = 8.0 Hz), 2.49 (d, 2H, *J* = 7.1 Hz), 1.92-1.84 (m, 1H), 0.93 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 158.8, 158.1, 154.6, 147.7, 142.0, 140.6, 133.9, 133.5, 131.5, 131.2, 131.1, 130.3, 130.2, 130.0, 129.0, 127.0, 115.4, 114.5, 113.9, 113.8, 113.6, 55.4, 55.2, 51.4, 45.0, 38.2, 30.2, 22.4, 22.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{34}N_3O_3S$: 552.2321; found 552.2342.

2-(6-Methoxynaphthalen-2-yl)-3,3-bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)propanamide (18a) : Following the general procedure, **18a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 197-199 ^oC; R_f = 0.17 (20% EtOAc/Hexane); Yield: 72% (102 mg); IR (KBr): 3355, 2934, 1682, 1633, 1605, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.99 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.3 Hz), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.88 (s, 1H), 7.69 (d, 1H, *J* = 9.0 Hz), 7.62 (s, 2H), 7.48 (d, 1H, *J* = 8.7 Hz), 7.42-7.38 (m, 3H), 7.12-7.08 (m, 3H), 7.02 (d, 1H, *J* = 2.4 Hz), 6.79 (d, 2H, *J* = 8.7 Hz), 6.62 (d, 2H, *J* = 8.7 Hz), 5.04 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.8 Hz), 3.86 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.9, 157.6, 157.5, 148.1, 138.2, 136.3, 135.9, 134.6, 134.4, 133.7, 133.6, 129.4, 129.4, 128.9, 128.7, 127.8, 127.5, 127.3, 127.0, 127.0, 121.5, 121.4, 118.7, 116.4, 114.1, 113.6, 105.4, 60.2, 55.3, 55.1, 55.0, 52.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{33}N_2O_4$: 569.2440; found 569.2416.

2-(6-Methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)-3,3-di-p-tolylpropanamide (18b): Following the general procedure, **18b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 153-155 ^oC; R_f = 0.45 (20% EtOAc/Hexane); Yield: 66% (89 mg); IR (KBr): 3351, 3048, 2921, 1686, 1523, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.01 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.0 Hz), 8.06 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.90 (s, 1H), 7.70 (d, 1H, *J* = 9.0 Hz), 7.64-7.63 (m, 2H), 7.47 (d, 2H, *J* = 8.1 Hz), 7.42-7.38 (m, 3H), 7.13-7.06 (m, 5H),

7.02 (d, 1H, *J* = 6.4 Hz), 6.89 (d, 2H, *J* = 7.9 Hz), 5.08 (d, 1H, *J* = 11.9 Hz), 4.75 (d, 1H, *J* = 11.9 Hz), 3.86 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.5, 148.0, 140.6, 139.3, 138.2, 136.2, 135.8, 135.4, 134.4, 133.7, 133.6, 129.4, 129.0, 128.9, 128.4, 127.8, 127.5, 127.5, 127.3, 127.0, 121.5, 121.3, 118.7, 116.4, 105.4, 59.8, 55.2, 53.5, 21.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{33}N_2O_2$: 537.2542; found 537.2529.

3,3-Bis(4-ethylphenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18c) : Following the general procedure, **18c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; mp 160-162 ^oC; R_f = 0.42 (20% EtOAc/Hexane); Yield: 64% (90 mg); IR (KBr): 3349, 2963, 2931, 1686, 1523, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.92 (s, 1H), 7.87 (s, 1H), 7.68 (d, 1H, *J* = 9.0 Hz), 7.63-7.62 (m, 2H), 7.49 (d, 1H, *J* = 8.1 Hz), 7.42-7.39 (m, 3H), 7.14 (d, 2H, *J* = 8.1 Hz), 7.10-7.06 (m, 3H), 7.02 (d, 1H, *J* = 2.4 Hz), 6.91 (d, 2H, *J* = 8.0 Hz), 5.07 (d, 1H, *J* = 11.9 Hz), 4.73 (d, 1H, *J* = 11.9 Hz), 3.86 (s, 3H), 2.51-2.43 (m, 4H), 1.11-1.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.4, 148.0, 142.0, 141.6, 140.8, 139.5, 138.2 , 136.2, 134.4, 133.7, 133.6, 129.4, 128.9, 128.4, 128.1, 127.7, 127.7, 127.6, 127.5, 127.3, 127.0, 127.0, 121.5, 121.3, 118.6, 116.4, 105.4, 59.9, 55.2, 53.6, 28.3, 28.2, 15.2, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{37}N_2O_2$: 565.2855; found 565.2832.

3,3-Bis(4-isopropylphenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18d) : Following the general procedure, **18d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 171-173 ^oC; R_f = 0.42 (20% EtOAc/Hexane); Yield: 59% (87 mg); IR (KBr): 3337, 2935, 1685, 1604, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.79 (d, 1H, *J* = 4.2 Hz), 8.64 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.4 Hz), 8.04 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.85 (s, 1H), 7.68-7.60 (m, 3H), 7.50 (d, 2H, *J* = 6.9 Hz), 7.43-7.36 (m, 3H), 7.15 (d, 2H, *J* = 7.0 Hz), 7.11-7.07 (m, 3H), 7.02 (d, 1H, *J* = 2.4 Hz), 6.95 (d, 2H, *J* = 7.8 Hz), 5.06 (d, 1H, *J* = 11.7 Hz), 4.73 (d, 2H, *J* = 11.8 Hz), 3.86 (s, 3H), 2.77-2.71 (m, 2H), 1.12 (d, 6H, *J* = 6.9 Hz), 1.08 (d, 6H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.4, 148.0, 146.5, 146.3, 140.8, 139.5, 138.2 , 136.2, 134.5, 133.7, 133.6, 129.4, 128.9, 128.4, 127.7, 127.6, 127.6, 127.2, 127.0, 126.9, 126.7, 126.2, 121.4,

121.2, 118.6, 116.3, 105.4, 60.0, 55.2, 53.7, 33.5, 33.4, 23.9, 23.8, 23.8, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{41}H_{41}N_2O_2$: 593.3168; found 593.3157.

2-(6-Methoxynaphthalen-2-yl)-3,3-diphenyl-*N*-(quinolin-8-yl)propanamide (18e) : Following the general procedure, **18e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 214-216 ^oC; R_f = 0.32 (20% EtOAc/Hexane); Yield: 77% (98 mg); IR (KBr): 3350, 3027, 1686, 1523, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.03 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.7 Hz), 8.65 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.06 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.89 (s, 1H), 7.69 (d, 1H, *J* = 9.0 Hz), 7..42-7.37 (m, 3H), 7.30-7.22 (m, 4H), 7.14-7.08 (m, 4H), 7.02-6.98 (m, 2H), 5.15 (d, 1H, *J* = 11.8 Hz), 4.78 (d, 1H, *J* = 11.8 Hz), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 157.5, 1 143.3, 142.1, 138.2, 136.3, 134.4, 133.7, 133.3, 129.4, 128.9, 128.7, 128.6, 128.2, 127.8, 127.5, 127.3, 127.1, 126.9, 126.5, 126.1, 121.5, 121.4, 118.7, 116.4, 105.5, 59.7, 55.3, 54.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_2$: 509.2229; found 509.2207.

3,3-Bis(4-bromophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18f) : Following the general procedure, **18f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 173-175 ^oC; R_f = 0.38 (20% EtOAc/Hexane); Yield: 85% (142 mg); IR (KBr): 3436, 1631, 1524, 1485, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.01 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.8 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.86 (s, 1H), 7.69 (d, 1H, *J* = 9.0 Hz), 7.64 (d, 1H, *J* = 8.6 Hz), 7.56 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.44-7.39 (m, 7H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.12 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.05-7.03 (m, 3H), 5.08 (d, 1H, *J* = 11.8 Hz), 4.65 (d, 1H, *J* = 11.8 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 157.7, 148.2, 141.9, 140.6, 138.2, 136.3, 134.1, 133.8, 132.6, 131.9, 131.4, 130.3, 129.5, 129.4, 128.9, 127.8, 127.4, 127.4, 127.2, 126.6, 121.7, 121.6, 120.7, 120.3, 119.1, 116.5, 105.5, 59.3, 55.3, 53.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Br_2N_2O_2$: 665.0439; found 665.0414.

3,3-Bis(4-chlorophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18g) : Following the general procedure, **18g** was obtained after purification by column

chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.34 (20% EtOAc/Hexane); Yield: 76% (110 mg); IR (thin film): 3350, 3027, 1686, 1604, 1523, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.63-8.61 (m, 1H), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.85 (s, 1H), 7.69 (d, 1H, J = 5.0 Hz), 7.63 (d, 1H, J = 8.6 Hz), 7.55 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.8 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.45-7.41 (m, 3H), 7.25 (d, 2H, J = 8.5 Hz), 7.13-7.03 (m, 6H), 5.85 (d, 1H, J = 11.8 Hz), 4.64 (d, 1H, J = 11.8 Hz), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 157.7, 148.2, 141.4, 140.2, 138.2, 136.4, 134.1, 133.8, 132.7, 132.5, 132.1, 129.9, 129.4, 129.1, 129.0, 128.8, 128.5, 127.8, 127.4, 127.3, 127.2, 126.6, 121.7, 121.6, 119.0, 116.5, 105.5, 59.4, 55.3, 53.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Cl_2N_2O_2$: 577.1450; found 577.1440.

3,3-Bis(3-bromophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18h) : Following the general procedure, **18h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 205-207 ^oC; R_f = 0.42 (20% EtOAc/Hexane); Yield: 60% (100 mg); IR (KBr): 3342, 1686, 1604, 1524, 1484, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.92 (s, 1H), 7.87 (s, 1H), 7.68 (d, 1H, J = 9.0 Hz), 7.63-7.62 (m, 2H), 7.49 (d, 1H, J = 8.1 Hz), 7.42-7.39 (m, 3H), 7.14 (d, 2H, J = 8.1 Hz), 7.10-7.06 (m, 3H), 7.02 (d, 1H, J = 2.4 Hz), 6.91 (d, 2H, J = 8.0 Hz), 5.07 (d, 1H, J = 11.9 Hz), 4.73 (d, 1H, J = 11.9 Hz), 3.86 (s, 3H), 2.51-2.43 (m, 4H), 1.11-1.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.4, 148.0, 142.0, 141.6, 140.8, 139.5, 138.2 , 136.2, 134.4, 133.7, 133.6, 129.4, 128.9, 128.4, 128.1, 127.7, 127.7, 127.6, 127.5, 127.3, 127.0, 127.0, 121.5, 121.3, 118.6, 116.4, 105.4, 59.9, 55.2, 53.6, 28.3, 28.2, 15.2, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Br_2N_2O_2$: 665.0439; found 665.0413.

3,3-Bis(3-chlorophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18i) : Following the general procedure, **18i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 208-210 ^oC; R_f = 0.38 (20% EtOAc/Hexane); Yield: 67% (97 mg); IR (KBr): 3445, 2975, 2941, 1739, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.05 (br. s, 1H), 8.76 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.9 Hz), 8.47 (d, 1H, J = 2.4 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz,

J_2 = 1.7 Hz), 8.01 (d, 1H, J = 2.4 Hz), 7.94 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.6 Hz) 7.84 (d, 1H, J = 1.3 Hz), 7.66 (d, 2H, J = 9.4 Hz), 7.59-7.53 (m, 2H), 7.46-7.40 (m, 3H), 7.12 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.5 Hz), 7.03 (d, 1H, J = 2.4 Hz), 6.89 (dd, 1H, J_1 = 8.5 Hz, J_2 = 3.0 Hz), 6.69 (dd, 1H, J_1 = 8.5 Hz, J_2 = 3.0 Hz), 5.21 (d, 1H, J = 11.8 Hz), 4.65 (d, 1H, J = 11.8 Hz), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 162.6, (d, J_{C-F} = 237.9 Hz), 162.2 (d, J_{C-F} = 238.2 Hz), 158.0, 148.2, 147.5 (d, J_{C-F} = 14.6 Hz), 146.7 (d, J_{C-F} = 22.4 Hz), 141.0 (d, J_{C-F} = 7.9 Hz), 140.8 (d, J_{C-F} = 7.8 Hz), 138.1, 136.4, 135.4 (d, J_{C-F} = 4.6 Hz), 134.1 (d, J_{C-F} = 4.6 Hz), 134.0, 133.8, 131.6, 129.3, 128.8, 127.9, 127.8, 127.4, 127.2, 126.0, 122.0, 121.7, 119.4, 116.6, 109.9 (d, J_{C-F} = 37.2 Hz), 109.5 (d, J_{C-F} = 37.3 Hz), 105.5, 59.1, 55.3, 48.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Cl_2N_2O_2$: 577.1450; found 577.1428.

3,3-Bis(3,4-dimethylphenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18j) : Following the general procedure, **18j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 141-143 ^oC; R_f = 0.42 (20% EtOAc/Hexane); Yield: 76% (107 mg); IR (KBr): 3353, 2919, 1743, 1685, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.64 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 8.03 (d, 2H, J = 8.2 Hz), 7.92 (s, 1H), 7.71-7.68 (m, 2H), 7.62 (d, 1H, J = 8.6 Hz), 7.43-7.34 (m, 5H), 7.09 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.02-7.00 (m, 4H), 6.85 (d, 1H, J = 8.2 Hz), 5.02 (d, 1H, J = 11.9 Hz), 4.77 (d, 1H, J = 11.9 Hz), 3.85 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0,157.4, 148.0, 141.1, 139.7, 138.3, 136.6, 136.2 , 136.1, 134.5, 134.4, 134.0, 133.8, 133.7, 129.9, 129.4, 129.4, 129.3, 128.9, 127.7, 127.6, 127.2, 127.1, 127.0, 125.7, 124.6, 121.4, 121.2, 118.6, 116.4, 105.5, 59.8, 55.2, 53.5, 19.9, 19.8, 19.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{37}N_2O_2$: 565.2855; found 565.2833.

3,3-Bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18k) : Following the general procedure, **18k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.07 (20% EtOAc/Hexane); Yield: 75% (117 mg); IR (thin film): 3346, 2933, 1685, 1589, 1524, 1506, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.64 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.05 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.7 Hz), 7.87 (s,

1H), 7.69 (d, 1H, J = 9.0 Hz), 7.62 (s, 2H), 7.41-7.37 (m, 3H), 7.10-7.01 (m, 4H), 6.75-6.73 (m, 2H), 6.68 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 6.56 (d, 1H, J = 8.3 Hz), 4.91 (d, 1H, J = 11.9 Hz), 4.61 (d, 1H, J = 11.9 Hz), 4.12-4.09 (m, 8H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 157.5, 148.1, 143.4, 143.1, 142.0, 141.7, 138.2, 136.9, 136.2, 135.6, 134.4, 133.7, 133.5, 129.4, 128.9, 127.7, 127.5, 127.3, 127.0, 127.0, 121.5, 121.4, 121.3, 120.6, 118.6, 117.3, 117.1, 116.9, 116.4, 116.4, 105.4, 64.2, 64.2, 64.2, 64.1, 59.8, 55.3, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{33}N_2O_6$: 625.2339; found 625.2316.

3,3-Bis(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (18l) : Following the general procedure, **18l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.05 (20% EtOAc/Hexane); Yield: 61% (90 mg); IR (thin film): 3340, 1681, 1602, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.89-7.87 (m, 3H), 7.70 (m, 7H), 7.45-7.42 (m, 3H), 7.29 (d, 2H, J = 7.9 Hz), 7.10 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.02 (d, 1H, J = 2.4 Hz), 5.26 (d, 1H, J = 11.8 Hz), 4.80 (d, 1H, J = 11.8 Hz), 3.87 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 169.8, 157.7, 148.1, 148.0, 146.7, 138.1, 136.5, 135.7, 135.3, 134.0, 133.9, 132.3, 129.4, 129.1, 128.8, 128.8, 128.6, 128.0, 127.8, 127.4, 127.2, 126.5, 121.8, 121.6, 119.1, 116.6, 105.4, 58.9, 55.3,54.3, 26.6, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{33}N_2O_4$: 593.2440; found 593.2416.

(*S*)-2-(4-Isobutylphenyl)-3,3-diphenyl-*N*-(quinolin-8-yl)propanamide (19a) : Following the general procedure, **19a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 175-177 ^oC; R_f = 0.60 (20% EtOAc/Hexane); Yield: 69% (84 mg); IR (KBr): 3351, 2954, 1688, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 8.07 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.57 (d, 2H, J = 7.2 Hz), 7.45-7.37 (m, 5H), 7.29-7.25 (m, 2H), 7.17-7.09 (m, 5H), 7.07-7.03 (m, 1H), 7.0 (d, 2H, J = 8.1 Hz), 2.37 (d, 2H, J = 7.2 Hz), 1.83-1.73 (m, 1H), 0.84 (d, 3H, J = 1.8 Hz), 0.83 (d, 3H, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 148.1, 143.3, 142.3, 140.6, 138.2, 136.3, 135.3, 134.4, 129.2, 128.7, 128.7, 128.3, 128.1, 127.8, 127.8, 127.8, 127.3, 126.4, 126.0, 121.5, 121.4, 116.4, 59.5, 54.6,

45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{33}N_2O$: 485.2593; found 485.2574.

(*S*)-2-(4-Isobutylphenyl)-*N*-(quinolin-8-yl)-3,3-di-p-tolylpropanamide (19b) : Following the general procedure, **19b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 170-172 ^oC; R_f = 0.62 (20% EtOAc/Hexane); Yield: 86% (110 mg); IR (KBr): 3352, 2953, 1688, 1524, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.5 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.45-7.37 (m, 7H), 7.05-6.99 (m, 6H), 6.91 (d, 2H, *J* = 7.9 Hz), 4.93 (d, 1H, *J* = 11.8 Hz), 4.53 (d, 1H, *J* = 11.8 Hz), 2.37 (d, 2H, *J* = 7.2 Hz), 2.20 (s, 3H), 2.19 (s, 3H), 1.83-1.73 (m, 1H), 0.84 (d, 3H, *J* = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 148.0, 140.5, 140.4, 139.5, 138.3, 136.2, 135.7, 135.5, 135.2, 134.5, 129.3, 129.2, 128.8, 128.4, 128.3, 127.8, 127.6, 127.3, 121.4, 121.2, 116.4, 59.5, 53.6, 45.0, 30.1, 22.3, 22.3, 21.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{37}N_2O$: 513.2906; found 513.2928.

(*S*)-3,3-Bis(4-bromophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (19c) : Following the general procedure, **19c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 185-187 ^oC; R_f = 0.8 (20% EtOAc/Hexane); Yield: 57% (91 mg); IR (KBr): 3437, 1629, 1526, 1486, 1388 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.65-8.63 (m, 1H), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.45-7.39 (m, 7H), 7.33 (d, 2H, *J* = 8.1 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 6.96 (d, 2H, *J* = 8.4 Hz), 2.38 (d, 2H, *J* = 7.2 Hz), 1.83-1.73 (m, 1H), 0.84 (d, 3H, *J* = 0.8 Hz), 0.82 (d, 3H, *J* = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.2, 141.8, 141.0, 140.8, 138.2, 136.3, 134.6, 134.2, 131.9, 131.3, 130.4, 129.5, 128.1, 127.8, 127.3, 121.6, 121.6, 120.6, 120.2, 116.5, 59.0, 53.4, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Br_2N_2O$: 641.0776; found 641.0803.

(*S*)-3,3-Bis(4-chlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (19d) : Following the general procedure, **19d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 181-183 ^oC; R_f = 0.58 (20% EtOAc/Hexane); Yield: 68% (94 mg); IR (KBr): 3343, 2955, 1687, 1524, 1486 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 5.4 Hz, J_2 = 3.6 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.46-7.40 (m, 5H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 7.10 (d, 2H, *J* = 8.5 Hz), 7.03 (d, 2H, *J* = 2.2 Hz), 7.01 (d, 2H, *J* = 1.7 Hz), 4.97 (d, 1H, *J* = 11.8 Hz), 4.46 (d, 1H, *J* = 11.8 Hz), 2.38 (d, 2H, *J* = 7.2 Hz), 1.84-1.73 (m, 1H), 0.84 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.2, 141.4, 141.0, 140.3, 138.2, 136.3, 134.7, 134.2, 132.0, 130.0, 129.4, 129.1, 128.9, 128.3, 128.2, 127.8, 127.3, 121.6, 121.6, 116.5, 59.2, 53.3, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Cl_2N_2O$: 553.1813; found 553.1826.

(*S*)-3,3-Bis(3-bromophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (19e) : Following the general procedure, **19e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 184-186 ^oC; Yield: 74% (118 mg); R_f = 0.73 (20% EtOAc/Hexane); IR (KBr): 3342, 2954, 1687, 1525, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.61 (dd, 1H, J_1 = 5.3 Hz, J_2 = 3.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.62 (s, 1H), 7.48-7.43 (m, 4H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.26-7.17 (m, 3H), 7.13 (t, 1H, *J* = 7.8 Hz), 7.01-6.95 (m, 4H), 4.88 (d, 1H, *J* = 11.8 Hz), 4.44 (d, 1H, *J* = 11.8 Hz), 2.36 (d, 2H, *J* = 7.2 Hz), 1.81-1.73 (m, 1H), 0.83 (d, 3H, *J* = 1.7 Hz), 0.82 (d, 3H, *J* = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.2, 144.8, 143.8, 141.0, 138.2, 136.3, 134.5, 134.2, 131.7, 131.1, 130.3, 130.0, 129.7, 129.4, 128.1, 127.8, 127.3, 127.2, 126.2, 122.9, 122.2, 121.6, 121.6, 116.5, 58.9, 53.9, 45.0, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{31}Br_2N_2O$: 641.0803; found 641.0787.

(*S*)-3,3-Bis(3,4-dichlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (19f) : Following the general procedure, **19f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 112-114 ^oC; R_f = 0.54 (20% EtOAc/Hexane); Yield: 90% (140 mg); IR (KBr): 3342, 2955, 1677, 1523, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55 (d, 1H, *J* = 1.6 Hz), 7.49-7.44 (m, 3H), 7.35-7.28 (m, 4H), 7.19 (d, 1H, *J* = 8.3 Hz), 7.13 (d, 1H, *J* = 2.1 Hz), 7.03 (d, 2H, *J* = 8.1 Hz), 6.89 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz), 4.89 (d, 1H, *J* = 11.7 Hz), 4.39 (d, 1H, *J* = 11.8 Hz), 2.38 (d, 2H, *J* = 7.2 Hz), 1.84-1.73 (m, 1H), 0.84 (d, 3H, *J* = 1.1 Hz), 0.82 (d, 3H, *J* =

1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 148.2, 142.4, 141.4, 141.3, 138.2, 136.4, 134.0, 132.9, 132.2, 131.0, 130.9, 130.8, 130.6, 130.2, 129.9, 129.6, 128.0, 128.0, 127.8, 127.3, 127.2, 126.9, 121.8, 121.7, 116.6, 58.7, 52.8, 44.9, 30.1, 22.3, 22.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{29}Cl_4N_2O$: 621.1034; found 621.1060.

(*S*)-3,3-Bis(4-ethylphenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (20a) : Following the general procedure, **20a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown solid; mp 145-147 ^oC; R_f = 0.37 (20% EtOAc/Hexane); Yield: 78% (111 mg); IR (KBr): 3346, 2961, 1683, 1603, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.5 Hz), 8.07 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.87 (s, 1H), 7.68 (d, 1H, *J* = 9.0 Hz), 7.63-7.62 (m, 2H), 7.48 (d, 2H, *J* = 8.1 Hz), 7.12-7.39 (m, 3H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.10-7.06 (m, 3H), 7.02 (d, 1H, *J* = 2.4 Hz), 6.90 (d, 2H, *J* = 8.0 Hz), 5.06 (d, 1H, *J* = 11.8 Hz), 4.73 (d, 1H, *J* = 11.9 Hz), 3.86 (s, 3H), 2.52-2.43 (m, 4H), 1.11-1.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.4, 148.0, 142.0, 141.6, 140.8, 139.4, 138.2, 136.2, 134.4, 133.6, 133.6, 129.4, 128.9, 128.4, 128.2, 127.8, 127.7, 127.6, 127.5, 127.3, 127.0, 127.0, 121.5, 121.3, 118.6, 116.4, 105.4, 59.9, 55.2, 53.6, 28.3, 28.2, 15.2, 15.2 ; ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{37}N_2O_2$: 565.2855; found 565.2837.

(*S*)-2-(6-Methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)-3,3-di-p-tolylpropanamide (20b) : Following the general procedure, **20b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as yellow colour solid; mp 150-152 ^oC; R_f = 0.33 (20% EtOAc/Hexane); Yield: 68% (91 mg); IR (KBr): 3351, 2921, 1687, 1523, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.8 Hz), 8.04 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.91 (s, 1H), 7.70 (d, 1H, *J* = 9.0 Hz), 7.68-7.62 (m, 2H), 7.49 (d, 2H, *J* = 8.1 Hz), 7.44-7.36 (m, 3H), 7.15-7.07 (m, 5H), 7.02 (d, 1H, *J* = 2.4 Hz), 6.90 (d, 2H, *J* = 7.9 Hz), 5.10 (d, 1H, *J* = 11.9 Hz), 4.77 (d, 1H, *J* = 11.9 Hz), 3.85 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 157.5, 148.0, 140.6, 139.3, 138.2,136.2, 135.8, 135.4, 134.4, 133.7, 133.6, 129.4, 129.4, 129.0, 128.9, 128.4, 127.7, 127.6, 127.5, 127.3, 127.1, 127.0, 121.5, 121.3, 118.7, 116.4, 105.4, 59.8, 55.2, 53.5, 21.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{33}N_2O_2$: 537.2542; found 537.2519.

(*S*)-2-(6-Methoxynaphthalen-2-yl)-3,3-diphenyl-*N*-(quinolin-8-yl)propanamide (20c) : Following the general procedure, **20c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 125-127 ^{o}C; R_f = 0.38 (20% EtOAc/Hexane); Yield: 86% (109 mg); IR (KBr): 3348, 1686, 1604, 1523, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.63 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.5 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.87 (s, 1H), 7.68 (d, 1H, J = 9.0 Hz), 7.61-7.58 (m, 4H), 7.43-7.40 (m, 3H), 7.29-7.25 (m, 2H), 7.20 (d, 2H, J = 7.2 Hz), 7.13-7.06 (m, 4H), 7.02-6.98 (m, 2H), 5.12 (d, 1H, J = 11.8 Hz), 4.76 (d, 1H, J = 11.9 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 157.5, 148.1, 143.3, 142.1, 138.2, 136.3, 134.4, 133.7, 133.3, 129.4, 128.9, 128.7, 128.6, 128.2, 127.8, 127.8, 127.5, 127.3, 127.0, 126.9, 126.5, 126.1, 121.5, 121.4, 118.7, 116.4, 105.5, 59.7, 55.3, 54.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{29}N_2O_2$: 509.2229; found 509.2280.

(*S*)-3,3-Bis(3,4-dichlorophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (20d) : Following the general procedure, **20d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown liquid; R_f = 0.38 (20% EtOAc/Hexane); Yield: 80% (129 mg); IR (thin film): 3337, 2935, 1685, 1524, 1485, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.5 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.86 (s, 1H), 7.69 (d, 1H, J = 9.0 Hz), 7.64 (d, 1H, J = 8.6 Hz), 7.57 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.8 Hz), 7.45-7.39 (m, 7H), 7.21 (d, 2H, J = 8.4 Hz), 7.12 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.05-7.03 (m, 3H), 5.08 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 157.7, 148.2, 141.9, 140.6, 138.2, 136.4, 134.1, 133.8, 132.6, 131.9, 131.4, 130.3, 129.5, 129.4, 128.9, 127.8, 127.4 127.4, 127.2, 126.6, 121.7, 121.6, 120.7, 120.3, 119.1, 116.6, 105.5, 59.2, 55.3, 53.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{25}Cl_4N_2O_2$: 645.0670; found 645.0684.

(*S*)-3,3-Bis(4-bromophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (20e): Following the general procedure, **20e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown liquid; R_f = 0.33 (20% EtOAc/Hexane); Yield: 89% (148 mg); IR (thin film): 3343, 3057, 1687, 1604, 1524 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 10.01 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.63 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.8 Hz), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.86 (s, 1H), 7.69 (d, 1H, J = 9.0 Hz), 7.64 (d, 1H, J = 8.6 Hz), 7.56 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.44-7.39 (m, 7H), 7.21 (d, 2H, J = 8.4 Hz), 7.12 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.05-7.03 (m, 3H), 5.08 (d, 1H, J = 11.8 Hz), 4.65 (d, 1H, J = 11.8 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 157.7, 148.2, 141.9, 140.6, 138.2, 136.3, 134.1, 133.8, 132.6, 131.9, 131.4, 130.3, 129.5, 129.4, 128.9, 127.8, 127.4, 127.4, 127.2, 126.6, 121.7, 121.6, 120.7, 120.3, 119.1, 116.5, 105.5, 59.3, 55.3, 53.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Br_2N_2O_2$: 665.0439; found 665.0428.

(*S*)-3,3-Bis(3-bromophenyl)-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (20f) : Following the general procedure, **20f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 182-184 ^oC; R_f = 0.38 (20% EtOAc/Hexane); Yield: 81% (135 mg); IR (KBr): 3342, 3056, 1686, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.62 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.06 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.87 (s, 1H), 7.71-7.63 (m, 3H), 7.59 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.53 (d, 2H, J = 7.8 Hz), 7.42-7.37 (m, 4H), 7.27-7.25 (m, 1H), 7.16-7.08 (m, 4H), 7.02 (d, 1H, J = 2.4 Hz), 6.93 (t, 1H, J = 7.8 Hz), 5.07 (d, 1H, J = 11.8 Hz), 4.68 (d, 1H, J = 11.8 Hz), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 157.7, 148.2, 144.9, 143.6, 138.2, 136.3, 134.1, 133.9, 132.4, 131.5, 131.1, 130.4, 130.0, 129.9, 129.6, 129.4, 128.9, 127.8, 127.5, 127.4, 127.3, 127.2, 126.6, 126.2, 122.9, 122.4, 121.7, 121.6, 119.0, 116.5, 105.5, 59.1, 55.3, 53.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{27}Br_2N_2O_2$: 665.0439; found 665.0415.

3,3-Bis(4-methoxyphenyl)-2-phenyl-*N*-(quinolin-8-yl)propanamide (21a) : Following the general procedure, **21a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 147-149 ^oC; R_f = 0.26 (20% EtOAc/Hexane); Yield: 75% (92 mg); IR (KBr): 3348, 2931, 1686, 1604, 1524, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 5.6 Hz, J_2 = 3.4 Hz), 8.09 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.49 (d, 2H, J = 7.2 Hz), 7.45-7.40 (m, 5H), 7.23 (t, 2H, J = 7.2 Hz), 7.15 (t, 2H, J = 7.4 Hz), 7.07 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 8.7 Hz), 6.67 (d, 2H, J = 8.7 Hz), 4.93 (d, 1H, J = 11.8 Hz), 4.52 (d, 1H, J = 11.9

Hz), 3.69 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 157.9, 157.6, 148.1, 138.3, 138.2, 136.3, 135.8, 134.6, 129.4, 128.6, 128.5, 127.8, 127.3, 127.1, 121.5, 121.4, 116.5, 114.0, 113.5, 60.3, 55.1, 52.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_3$: 489.2178; found 489.2164.

2-Phenyl-*N*-(quinolin-8-yl)-3,3-di-p-tolylpropanamide (21b) : Following the general procedure, **21b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale green colour solid; mp 162-164 ^oC; R_f = 0.45 (20% EtOAc/Hexane); Yield: 96% (110 mg); IR (KBr): 3350, 3048, 1687, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.66 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.5 Hz), 8.07 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53 (d, 2H, *J* = 7.2 Hz), 7.46-7.39 (m, 5H), 7.25 (t, 2H, *J* = 7.3 Hz), 7.16 (t, 2H, *J* = 7.4 Hz), 7.08 (t, 2H, *J* = 8.1 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 6.94 (d, 2H, *J* = 7.9 Hz), 4.98 (d, 1H, *J* = 11.9 Hz), 4.61 (d, 1H, *J* = 11.9 Hz), 2.21 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.1, 140.5, 139.3, 138.3, 138.2, 136.3, 135.8, 135.4, 134.4, 129.4, 128.9, 128.6, 128.5, 128.4, 127.8, 127.5, 127.3, 127.1, 121.5, 121.4, 116.4, 59.9, 53.6, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O$: 457.2280; found 457.2261.

2,3,3-Triphenyl-*N*-(quinolin-8-yl)propanamide (21c) : Following the general procedure, **21c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 184-186 ^oC; R_f = 0.43 (20% EtOAc/Hexane); Yield: 44% (47 mg); IR (KBr): 3349, 3027, 1686, 1524, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.64 (dd, 1H, J_1 = 5.3 Hz, J_2 = 3.7 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.57 (d, 2H, *J* = 7.3 Hz), 7.49 (d, 2H, *J* = 7.3 Hz), 7.29-7.09 (m, 10H), 7.05 (t, 1H, *J* = 7.2 Hz), 5.03 (d, 1H, *J* = 11.9 Hz), 4.62 (d, 1H, *J* = 11.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.1, 143.2, 142.1, 138.2, 136.3, 136.3, 134.3, 128.7, 128.7, 128.6, 128.5, 128.2, 127.8, 127.3, 127.3, 126.5, 126.1, 121.5, 121.4, 116.4, 59.8, 54.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O$: 429.1967; found 429.1948.1020.

3,3-Bis(4-bromophenyl)-2-phenyl-*N*-(quinolin-8-yl)propanamide (21d) : Following the general procedure, **21d** was obtained after purification by column chromatography on silica gel

(EtOAc:Hexanes = 15:85) as colourless solid; mp 228-230 ^{o}C; R_f = 0.45 (20% EtOAc/Hexane); Yield: 79% (116 mg); IR (KBr): 3343, 3041, 1682, 1523, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.61 (dd, 1H, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.45-7.38 (m, 9H), 7.29-7.23 (m, 4H), 7.17 (t, 1H, J = 7.3 Hz), 6.99 (d, 2H, J = 8.4 Hz), 4.96 (d, 1H, J = 11.8 Hz), 4.50 (d, 1H, J = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 148.2, 141.7, 140.6, 138.2, 137.4, 136.4, 134.1, 131.9, 131.4, 130.3, 129.4, 128.8, 128.4, 127.8, 127.6, 127.3, 121.7, 121.6, 120.6, 120.3, 116.5, 59.3, 53.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}Br_2N_2O$: 585.0177; found 585.0153.

3,3-Bis(3-bromophenyl)-2-phenyl-*N*-(quinolin-8-yl)propanamide (21e) : Following the general procedure, **21e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour solid; mp 101-103 ^{o}C; R_f = 0.67 (20% EtOAc/Hexane); Yield: 75% (110 mg); IR (KBr): 3440, 2970, 2922, 1691, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.62-8.60 (m, 1H), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.65 (t, 1H, J = 5.6 Hz), 7.50-7.41 (m, 6H), 7.13 (t, 1H, J = 7.8 Hz), 7.06 (d, 1H, J = 7.8 Hz), 6.99 (t, 1H, J = 7.8 Hz), 4.95 (d, 1H, J = 11.8 Hz), 4.52 (d, 1H, J = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 148.2, 144.7, 143.6, 138.2, 137.3, 136.3, 134.1, 131.6, 131.0, 130.4, 130.0, 129.9, 129.6, 128.8, 128.4, 127.8, 127.6, 127.3, 127.3, 126.2, 122.9, 122.4, 121.7, 121.6, 116.5, 59.2, 53.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}Br_2N_2O$: 585.0177; found 585.0155.

2-(4-Chlorophenyl)-3,3-bis(4-ethylphenyl)-*N*-(quinolin-8-yl)propanamide (21f) : Following the general procedure, **21f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 115-117 ^{o}C; R_f = 0.58 (20% EtOAc/Hexane); Yield: 83% (107 mg); IR (KBr): 3346, 2964, 1687, 1524, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.63 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.8 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.46-7.40 (m, 7H), 7.20 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.1 Hz), 7.06 (d, 2H, J = 8.1 Hz), 6.99 (d, 2H, J = 8.0 Hz), 4.92 (d, 1H, J = 11.9 Hz), 4.58 (d, 1H, J = 11.9 Hz), 2.54 (q, 2H, J = 7.6 Hz), 2.47 (q, 2H, J = 7.6 Hz), 1.16 (t, 3H, J = 7.6 Hz), 1.05 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 148.1, 142.2, 141.9, 140.3, 139.1, 138.2, 136.9, 136.3, 134.2, 129.9,128.6, 128.4, 128.2, 127.8, 127.8, 127.5,

127.3, 121.5, 121.5, 116.5, 59.3, 53.7, 28.3, 28.3, 15.3, 15.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{32}ClN_2O$: 519.2203; found 519.2181.

3,3-Bis(4-bromophenyl)-2-(4-chlorophenyl)-*N*-(quinolin-8-yl)propanamide (21g) : Following the general procedure, **21g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 251-253 ^oC; R_f = 0.53 (20% EtOAc/Hexane); Yield: 71% (110 mg); IR (KBr): 3341, 1688, 1525, 1486, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.92 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.3 Hz, J_2 = 1.6 Hz), 8.59 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 5H), 7.29-2.27 (m, 2H), 7.21 (d, 2H, *J* = 8.4 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 4.89 (d, 1H, *J* = 11.8 Hz), 4.47 (d, 1H, *J* = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 148.2, 141.4, 140.2, 138.2, 136.4, 136.0, 133.9, 133.4, 131.9, 131.6, 130.2, 129.7, 129.3, 128.9, 127.2, 121.9,121.7, 120.8, 120.5, 116.6, 58.7, 53.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{22}Br_2ClN_2O$: 618.9787; found 618.9760.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)-3,3-di-p-tolylpropanamide (22a) : Following the general procedure, **22a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown solid; mp 238-240 ^oC; R_f = 0.50 (20% EtOAc/Hexane); Yield: 85% (116 mg); IR (KBr): 3346, 3050, 2922, 1688, 1525, 1483, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.65-8.63 (m, 1H), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.49-7.29 (m, 13H), 7.11 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 7.9 Hz), 4.94 (d, 1H, *J* = 11.9 Hz), 4.61 (d, 1H, *J* = 11.9 Hz), 2.23 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 159.6 (d, J_{C-F} = 246.5 Hz), 148.1, 140.1, 139.7 (d, J_{C-F} = 7.8 Hz), 138.9, 138.3, 136.3, 135.9, 135.7, 135.5, 134.3, 130.5 (d, J_{C-F} = 3.8 Hz), 129.4, 129.1, 128.9 (d, J_{C-F} = 2.9 Hz), 128.4, 128.3, 128.3, 127.8, 127.7, 127.5, 127.5, 127.3, 124.7 (d, J_{C-F} = 3.0 Hz), 121.6, 116.6, 116.2 (d, J_{C-F} = 23.8 Hz), 59.3, 53.5, 21.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{32}FN_2O$: 551.2499; found 551.2476.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-3,3-bis(4-methoxyphenyl)-*N*-(quinolin-8-yl)propanamide (22b): Following the general procedure, **22b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow solid; mp 224-226 ^oC; R_f

= 0.26 (20% EtOAc/Hexane); Yield: 81% (118 mg); IR (KBr): 3346, 2835, 1687, 1524, 1511, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (br. s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.66-8.64 (m, 1H), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.49-7.29 (m, 13H), 7.13 (d, 2H, J = 8.6 Hz), 6.77 (d, 2H, J = 8.7 Hz), 6.72 (d, 2H, J = 8.6 Hz), 4.92 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 11.9 Hz), 3.72 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 159.6 (d, J_{C-F} = 247.0 Hz), 158.0, 157.8, 148.2, 139.7 (d, J_{C-F} = 7.7 Hz), 138.3, 136.3, 135.5, 135.3, 134.2 (d, J_{C-F} = 4.2 Hz), 130.6, 130.6, 129.4 (d, J_{C-F} = 2.5 Hz), 128.9 (d, J_{C-F} = 2.5 Hz), 128.6, 128.4, 127.8, 127.7, 127.5 (d, J_{C-F} = 4.6 Hz), 127.3. 124.7, 124.7, 121.6, 116.6, 116.3, 114.1 (d, J_{C-F} = 4.5 Hz), 113.7 (d, J_{C-F} = 3.9 Hz), 59.7, 55.1 (d, J_{C-F} = 4.5 Hz), 55.1 (d, J_{C-F} = 3.9 Hz), 52.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{38}H_{32}FN_2O_3$: 583.2397; found 583.2372.

3,3-Bis(3-bromophenyl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)propanamide (22c) : Following the general procedure, **22c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 184-186 ^oC; R_f = 0.37 (20% EtOAc/Hexane); Yield: 78% (133 mg); IR (KBr): 3445, 2922, 1742, 1686, 1525, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.98 (br. s, 1H), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.61 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.64 (s, 1H), 7.50-7.24 (m, 15H), 7.13 (t, 2H, J = 7.8 Hz), 7.06 (t, 1H, J = 7.8 Hz), 4.93 (d, 1H, J = 11.8 Hz), 4.53 (d, 1H, J = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 159.6 (d, J_{C-F} = 247.2 Hz), 148.3, 144.3, 143.2, 138.6, 138.2, 136.4, 135.3, 133.9, 131.6, 131.0, 130.9 (d, J_{C-F} = 3.7 Hz), 130.4, 130.2, 130.1, 129.9, 128.9 (d, J_{C-F} = 2.8 Hz), 128.4, 128.3, 128.2, 127.8, 127.7, 127.2 (d, J_{C-F} = 5.3 Hz), 126.2, 124.5 (d, J_{C-F} = 3.3 Hz), 123.0, 122.5, 121.9, 121.7, 116.7, 116.0 (d, J_{C-F} = 23.8 Hz), 58.7, 53.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{36}H_{26}Br_2FN_2O$: 679.0396; found 679.0377.

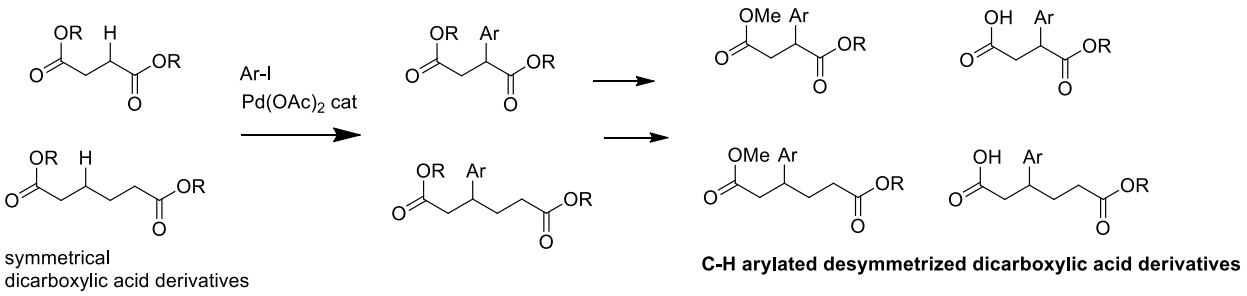
3,3-Bis(4-ethylphenyl)-2-(4-isobutylphenyl)propanoic acid (23) : Following the general procedure, **23** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; mp 144-146 ^oC; R_f = 0.73 (50% EtOAc/Hexane); Yield: 97% (101 mg); IR (KBr): 3425, 2962, 2930, 1707, 1511, 1462, 1418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.97 (br. s, 1H), 8.73 (d, 2H, J = 7.9 Hz), 8.61 (d, 2H, J = 7.8 Hz), 8.44-8.40 (m, 4H), 8.27 (d, 2H, J = 7.9 Hz), 8.18 (d, 2H, J = 7.9 Hz), 3.84 (q, 2H, J = 7.6

Hz), 3.70 (q, 2H, *J* = 7.6 Hz), 3.64 (d, 2H, *J* = 7.2 Hz), 3.09-2.99 (m, 1H), 2.44 (t, 3H, *J* = 7.6 Hz), 2.32 (t, 3H, *J* = 7.6 Hz), 2.10 (d, 3H, *J* = 2.9 Hz), 2.08 (d, 3H, *J* = 2.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 143.2, 142.7, 142.7, 141.4, 141.3, 136.7, 130.1, 129.9, 129.6, 129.1, 129.0, 128.7, 56.7, 55.2, 45.9, 31.3, 29.3, 29.2, 22.9, 22.9, 16.4, 16.3; HRMS (ESI): *m/z* [M – 2H, M - 3H]$^+$ calcd for $C_{29}H_{32}O_2$, $C_{29}H_{31}O_2$ (other oxidized fragment): 412.2402, 411.2324; found 412.2415, 411.2383.

2-(4-Isobutylphenyl)-3,3-diphenylpropanoic acid (24) : Following the general procedure, **24** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; mp 127-129 ^{o}C; R_f = 0.70 (50% EtOAc/Hexane); Yield: 95% (85 mg); IR (KBr): 3437, 2954, 2924, 1707, 1511, 1494, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, *J* = 7.8 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 7.9 Hz), 7.08 (t, 2H, *J* = 7.6 Hz), 7.0 (d, 2H, *J* = 8.2 Hz), 6.96 (d, 1H, *J* = 6.8 Hz), 4.79 (d, 1H, *J* = 12.4 Hz), 4.66 (d, 1H, *J* = 12.4 Hz), 2.37 (d, 2H, *J* = 7.2 Hz), 1.83-1.72 (m, 1H), 0.82 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 144.0, 142.6, 140.2, 135.3, 128.8, 128.6, 128.5, 128.3, 128.0, 127.9, 126.3, 125.9, 55.3, 54.7, 44.6, 30.0, 29.6, 29.4, 29.2, 29.0, 28.8, 28.6, 28.4, 21.7; HRMS (ESI): *m/z* [M - H]$^+$ calcd for $C_{25}H_{25}O_2$: 357.1855; found 357.1837.

Chapter 5: Desymmetrization of symmetrical dicarboxylic acid systems via bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds: construction of functionalized dicarboxylic acid derivatives

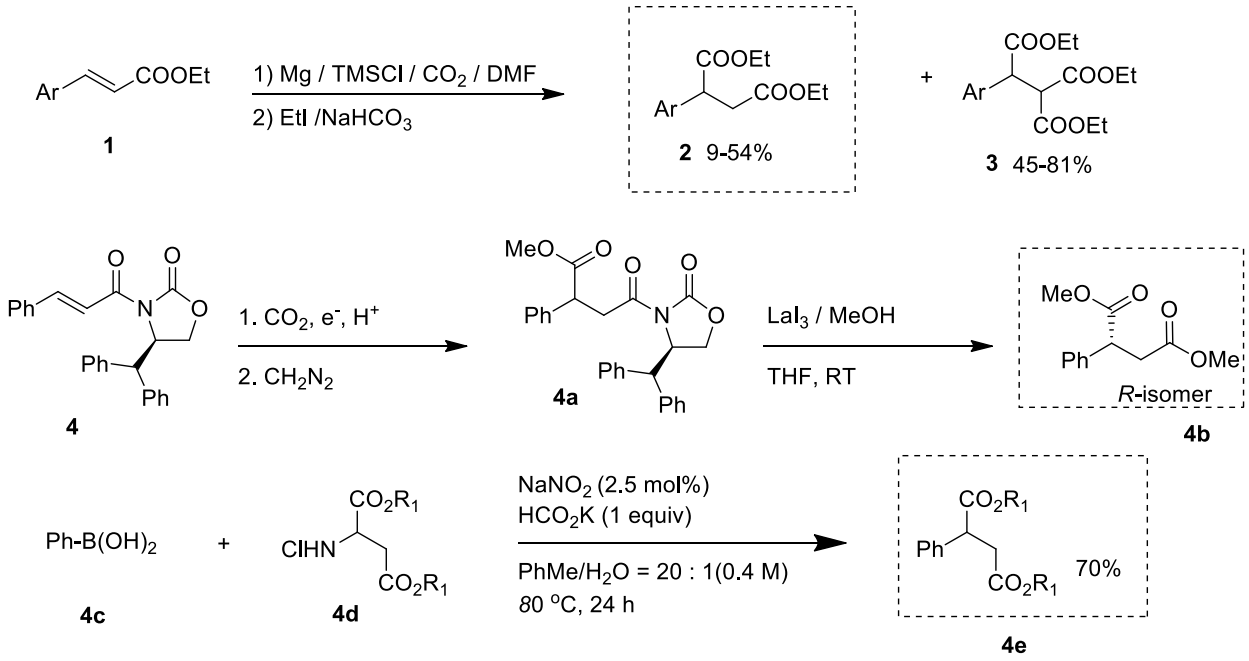
Chapter 1 revealed the existing developments on the Pd(II)-catalyzed bidentate ligand-directed C-H activation/functionalization reactions of carboxylic acids with representative literature works. It is to be noted that the Pd(II)-catalyzed bidentate ligand-directed C-H activation/functionalization strategy was also well explored to install one or more stereogenic centers in a given carboxylic acid system. Along this line, the research works reported in the Chapters 2-4 have also revealed the usefulness of the Pd(II)-catalyzed β-arylation of the prochiral secondary sp^3 C-H bonds of carboxylic acid derivatives, which have led construction of functionalized β-arylated carboxamide derivatives. In line with works reported in the Chapters 2-4, this chapter reports the desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds and the construction of functionalized dicarboxylic acid derivatives (Scheme 1).



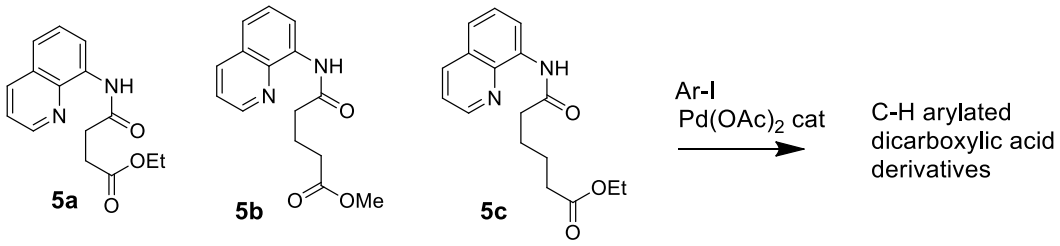
Scheme 1: Theme of this work. Desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds and the construction of functionalized dicarboxylic acid derivatives.

Desymmetrization is a process that eliminates the symmetry element precluding the chirality of a substrate of interest. Stereoselective and enantioselective desymmetrization reactions reported to afford only one isomer predominantly from the symmetrical substrate and the stereoselective and enantioselective desymmerization process have been well utilized in assembling

enantiomerically pure compounds pertaining to pharmaceutical, agricultural and food industries. Representative examples involving the construction of functionalized dicarboxylic acid derivatives, especially arylated dicarboxylic acid derivatives, have been shown in Scheme 2.



Scheme 2: Representative examples involving the construction of arylated dicarboxylic acid derivatives.



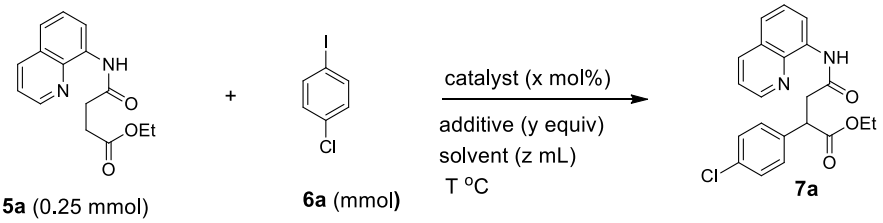
Scheme 3: Substrates used in the desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds.

Results and Discussion

At the outset, to commence the studies pertaining to the desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds, substrates **5a-c** were assembled from their corresponding dicarboxylic acid and 8-aminoquinoline. Heating a mixture of the substrate **5a** (0.25 mmol) with 4-chloro-1-iodobenzene (0.5 mmol) in presence of $Pd(OAc)_2$ (5 mol%) and AgOAc (2.2 equiv) in toluene at 130 ^oC afforded the arylated product **7a** in 34% (entry 1, Table 1). Increasing the aryl iodide concentration enhanced efficiency of formation of arylated compound **7a** (entries 2 and 3, Table 1).

Next, the $Pd(OAc)_2$ catalyst loading was increased to further improve the yield of arylated product. Accordingly, the C-H arylation of carboxamide **5a** (0.25 mmol) was performed using 10 mol% of $Pd(OAc)_2$ and 0.5 mmol of aryl iodide to afford the arylated product **7a** in 31% (entry 4, Table 1). Then, the reaction was performed using different equivalents of **6a** (0.75-1.5 mmol), and these reactions afforded the product **7a** in 52-74% yield (entries 5-7, Table 1). The C-H activation of **5a** with different palladium sources such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, $PdCl_2$ afforded the arylated compound **7a** in 17-54% yields (entries 8-12, Table 1). The effect of solvent for the arylation was examined by replacing toluene with 1,2-dichloroethane or 1,4-dioxane under the optimal condition and the arylated product was obtained in 25% and 71% yield (entries 13 and 14, Table 1). The Pd(II)-catalyzed arylation of **5a** using $K_2S_2O_8$ or oxone as additive instead of AgOAc were also found to afford the arylated product **7a** in yield 54-70% yield (entries 15 and 16, Table 1).

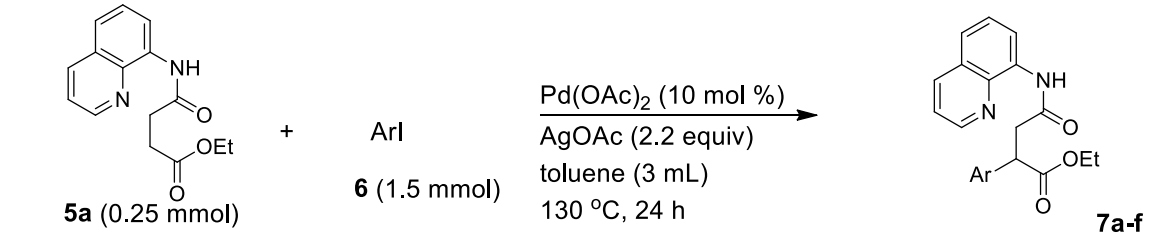
Table 1: Optimization reactions: Bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrate **5a**.

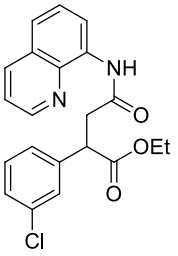


5a (0.25 mmol) **6a** (mmol) **7a**

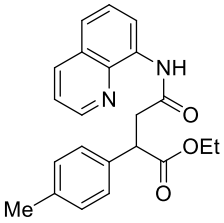
entry	catalyst (mol %)	Ar-**I** (mmol)	oxidant (equiv)	solvent (mL)	time (h)	T °C	yield (**7a**) (%)
1	$Pd(OAc)_2$ (5)	0.5	AgOAc (2.2)	toluene (3)	24	130	34
2	$Pd(OAc)_2$ (5)	1	AgOAc (2.2)	toluene (3)	24	130	38
3	$Pd(OAc)_2$ (5)	1.5	AgOAc (2.2)	toluene (3)	24	130	69
4	$Pd(OAc)_2$ (10)	0.5	AgOAc (2.2)	toluene (3)	24	130	31
5	$Pd(OAc)_2$ (10)	0.75	AgOAc (2.2)	toluene (3)	45	130	52
6	$Pd(OAc)_2$ (10)	1	AgOAc (2.2)	toluene (3)	24	130	32
7	**$Pd(OAc)_2$ (10)**	**1.5**	**AgOAc (2.2)**	**toluene (3)**	**36**	**130**	**74**
8	$PdCl_2(PPh_3)_2$ (5)	1	AgOAc (2.2)	toluene (3)	36	130	traces
9	$Pd(PPh_3)_4$ (5)	1	AgOAc (2.2)	toluene (3)	36	130	17
10	$Pd(MeCN)_2Cl_2$ (5)	1	AgOAc (2.2)	toluene (3)	24	130	42
11	$Pd(Cl)_2$ (5)	1	AgOAc (2.2)	toluene (3)	24	130	45
12	$Pd(TFA)_2$ (10)	1.5	AgOAc (2.2)	toluene (3)	45	130	54
13	$Pd(OAc)_2$ (10)	1.5	AgOAc (2.2)	DCE (3)	24	120	25
14	$Pd(OAc)_2$ (10)	1.5	AgOAc (2.2)	1,4-dioxane (3)	45	130	71
15	$Pd(OAc)_2$ (5)	1	$K_2S_2O_8$ (2)	toluene (3)	24	130	70
16	$Pd(OAc)_2$ (5)	1	oxone (2)	toluene (3)	24	130	54

Table 2: The Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrate **5a** with different aryl iodides.

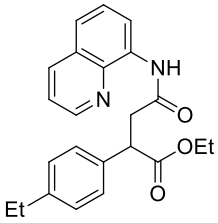




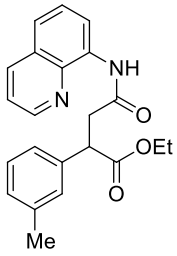
7a; 62%



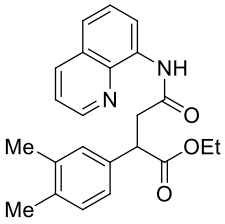
7b; 65%



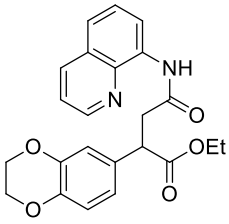
7c; 68%



7d; 53%



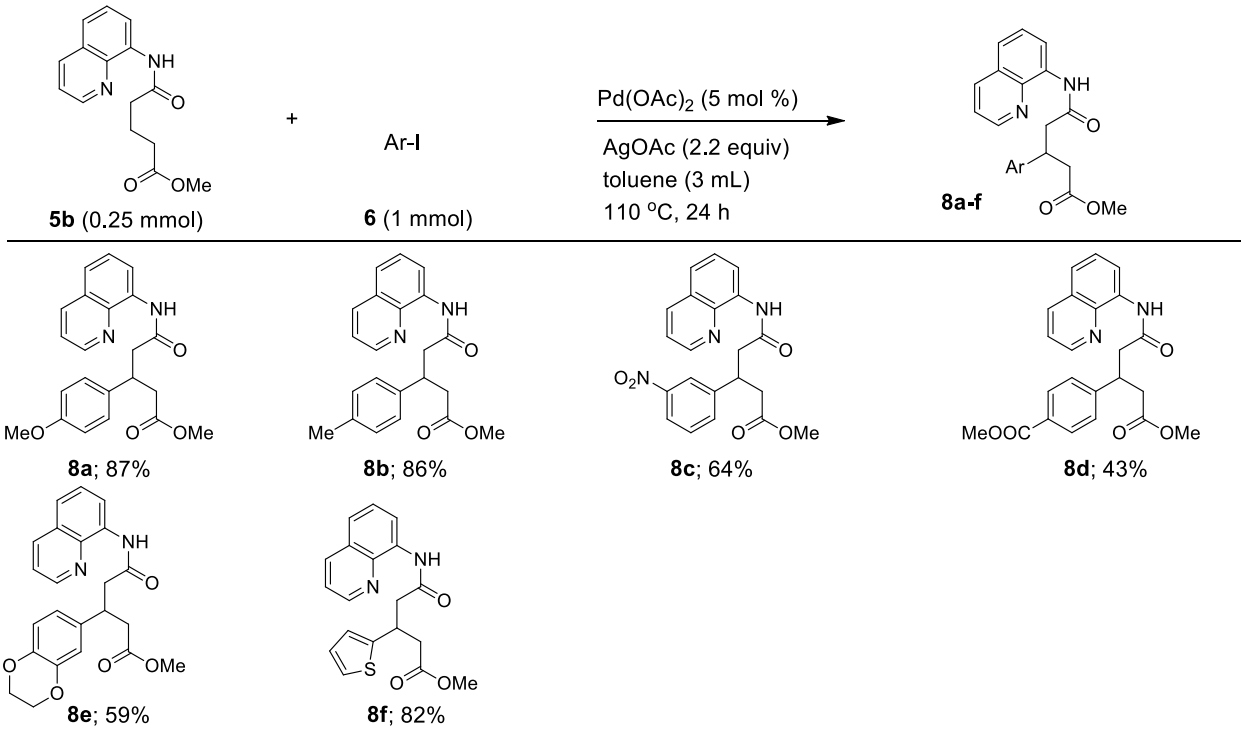
7e; 66%



7f; 62%

Having obtained the optimized reaction condition, next it was envisaged to examine the Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrate **5a** with different aryl iodides to synthesize a series of C-H arylated dicarbonyl compounds (Table 2). Accordingly, the C-H arylation of succinic acid derived carboxamide **5a** with aryl iodides bearing halogen substituents or alkyl groups underwent the arylation to afford the corresponding C-H arylated succinic acid derived carboxamides **7a-d** in 53-68% yields (Table 2). The C-H arylation of succinic acid derived carboxamide **5a** with disubstituted aryl iodides 4-iodo-1,2-dimethylbenzene and 6-iodo-2,3-dihydrobenzo[b][1,4]dioxine smoothly underwent the arylation to provide the corresponding C-H arylated succinic acid derived carboxamides **7e-f** in 62-66% yields (Table 2).

Table 3: The Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrate **5b** with different aryl iodides.

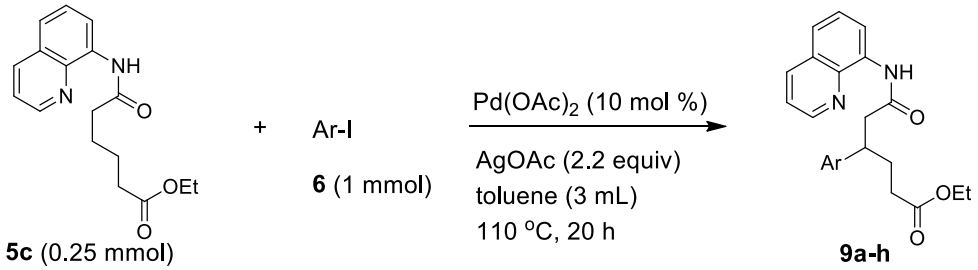


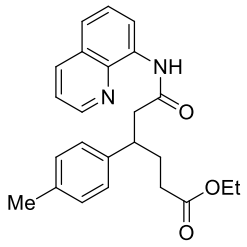
Next, to extend the scope of this work, it was envisaged to perform the Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of glutaric acid derived carboxamide **5b** (Table 3). Accordingly, the C-H arylation of glutaric acid derived carboxamide **5b** with aryl iodides bearing OMe, Me, NO_2 and COOMe groups underwent the arylation to afford the corresponding C-H arylated glutaric acid derived carboxamides **8a-d** in 43-87% yields (Table 3). Further the C-H arylation of glutaric acid derived carboxamide **5b** with disubstituted aryl iodide and heteroaryl iodide smoothly underwent the arylation to provide the corresponding C-H arylated glutaric acid derived carboxamides **8e** and **8f** in 59% and 82% yields respectively (Table 3).

Finally, it was envisaged to perform the Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of adipic acid derived carboxamide **5c** (Table 4). Accordingly, the C-H arylation of adipic acid derived carboxamide **5c** with aryl iodides bearing Me, isopropyl, F, Br and NO_2 groups underwent the arylation to afford the corresponding C-H arylated adipic acid derived

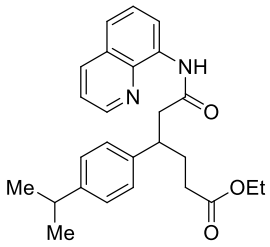
carboxamides **9a-e** in 51-79% yields (Table 4). Additionally, the C-H arylation of adipic acid derived carboxamide **5c** with disubstituted aryl iodide and heteroaryl iodide also underwent the arylation to afford the corresponding C-H arylated adipic acid derived carboxamides **9f-g** in 56-68% yields (Table 4).

Table 4: The Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrate **5c** with different aryl iodides.

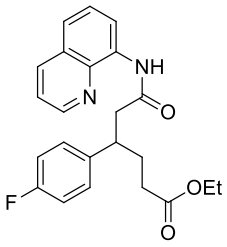




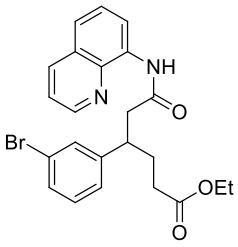
9a; 59 %



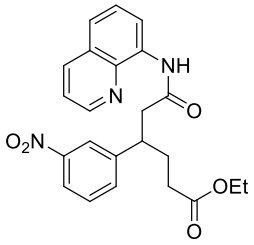
9b; 58 %



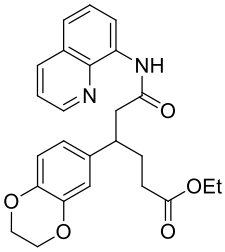
9c; 51%



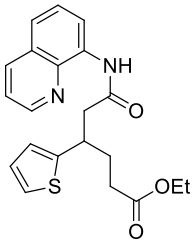
9d; 70%



9e; 79 %



9f; 56%

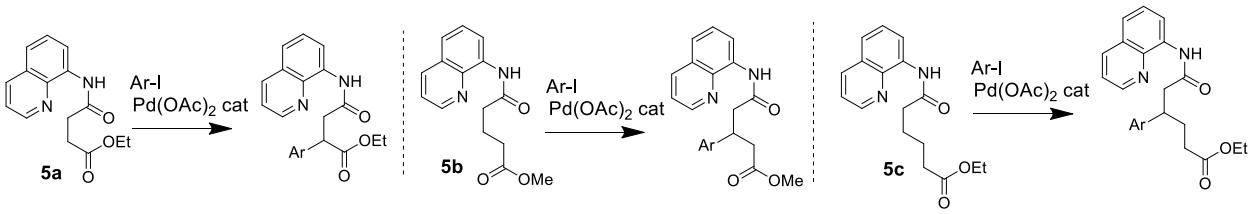


9g; 68%

Summary

In summary, Chapter 5 reported the desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds and the construction of functionalized dicarboxylic acid derivatives.

A variety of C-H arylated succinic-, glutaric- and adipic acid derived carboxamides were successfully obtained from the 8-aminoquinoline-directed Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of their corresponding carboxamides **5a-c**.



While this Chapter 5 reported the preliminary works related to the Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds of substrates **5a-c** with different aryl iodides, further works with regard to the desymmetrization of symmetrical dicarboxylic acid systems via the bidentate directing group-aided Pd(II)-catalyzed arylation of methylene sp^3 C-H bonds are in progress in our laboratory.

Experimental Section

General Considerations. Melting points are uncorrected. IR spectra of all the compounds were recorded as KBr pellets or thin films. ^1H and ^{13}C NMR spectra of all the compounds were recorded on 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Column chromatography was carried out using silica gel 100-200 mesh. All the reactions were performed using anhydrous solvents under a nitrogen atmosphere. Organic layers after the work up procedure were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis (TLC) was performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized.

General procedure for synthesis of carboxamide 5a.

The corresponding acid chloride (1 mmol) was dissolved in 5 mL of dry DCM and stirred for 0.5 h at 0 ^{o}C under a nitrogen atmosphere. To this reaction mixture, corresponding auxiliary (amine, 1 mmol) and Et_3N (1.1 mmol) were added. Then, reaction mixture was stirred at rt 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 = 15:85) furnished the corresponding carboxamides **5a**.

General procedure for synthesis of carboxamides 5b/5c.

The corresponding carboxylic acid (1 mmol) was dissolved in 5 mL of dry DCM and stirred for 0.5 h at 0 ^{o}C under a nitrogen atmosphere. To this reaction mixture, 2 equivalents of $(COCl)_2$ was added in drops and allowed to stir at 0 ^{o}C for overnight. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atmosphere. Then, the resulting acid chloride was added to another RB flask containing the corresponding auxiliary (amine, 1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL). Then, reaction mixture was stirred at rt 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 = 15:85) furnished the corresponding carboxamides **5b/5c**.

General procedure for β-C-H arylation of dicarbonyl compounds for the preparation of 7a-f. A mixture of the corresponding carboxamide (**5a**) (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol%), aryl iodide (1.5 mmol, 6 equiv) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 130 ^{o}C for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (3-4 mL) and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the

corresponding β-C-H arylated aliphatic carboxamides **7a-f** (see Tables/Schemes for specific examples, chapter 4).

General procedure for β-C-H arylation of dicarbonyl compounds for the preparation of 8a-f/9a-g. A mixture of the corresponding carboxamide (**5b/5c**) (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol%), aryl iodide (1 mmol, 4 equiv) and AgOAc (92 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 130 ^oC for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc (3-4 mL) and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding β-C-H arylated aliphatic carboxamides **8a-f/9a-g** (see Tables/Schemes for specific examples, chapter 4).

Ethyl 4-oxo-4-(quinolin-8-ylamino)butanoate (5a) : Following the general procedure, **5a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 98-100 ^oC; R_f = 0.24 (20% EtOAc/Hexane); Yield: 66% (179 mg); IR (KBr): 3328, 2990, 1727, 1679, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.91 (br. s, 1H), 8.83-8.82 (m, 1H), 8.77 (d, 1H, *J* = 6.9 Hz), 8.17 (d, 1H, *J* = 8.3 Hz), 7.56-7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 2.92 (t, 2H, *J* = 6.7 Hz), 2.83 (t, 2H, *J* = 6.9 Hz), 1.29 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 170.0, 148.2, 138.3, 136.4, 134.4, 127.9, 127.4, 121.6, 121.5, 116.5, 60.8, 32.5, 29.5, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1239; found 273.1227.

Methyl 5-oxo-5-(quinolin-8-ylamino)pentanoate (5b) : Following the general procedure, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 64-66 ^oC; R_f = 0.33 (20% EtOAc/Hexane); Yield: 56% (38 mg); IR (KBr): 3353, 2956, 1735, 1689, 1525, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (br. s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.79 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.19 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.58-7.51 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 3.72 (s, 3H), 2.67 (t, 2H, *J* = 7.3 Hz), 2.52 (t, 2H, *J* = 7.3 Hz), 2.21-2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 170.8, 148.2, 138.3, 136.4, 134.4, 127.9, 127.4, 121.6, 121.5, 116.4, 51.7, 36.9, 33.2, 20.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1239; found 273.1228.

Ethyl 6-oxo-6-(quinolin-8-ylamino)hexanoate (5c) : Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.33 (20% EtOAc/Hexane); Yield: 49% (38 mg); IR (thin film): 3355, 2938, 1731, 1689, 1525, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.79 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 4.14 (q, 2H, J = 7.1 Hz), 2.61 (t, 3H, J = 7.0 Hz), 2.40 (d, 2H, J = 7.4 Hz), 1.91-1.75 (m, 4H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 171.3, 148.1, 138.3, 136.4, 134.5, 127.9, 127.4, 121.6, 121.4, 116.4, 60.3, 37.8, 34.1, 25.1, 24.6, 14.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_3$: 301.1552; found 301.1567.

Ethyl 2-(3-chlorophenyl)-4-oxo-4-(quinolin-8-ylamino)butanoate (7a) : Following the general procedure, **7a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.45 (20% EtOAc/Hexane); Yield: 62% (59 mg); IR (thin film): 3345, 2981, 1727, 1689, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.5 Hz), 8.73 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.3 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.53-7.50 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.41 (s, 1H), 7.30-7.27 (m, 3H), 4.33-4.14 (m, 3H), 3.48 (dd, 1H, J_1 = 15.7 Hz, J_2 = 9.9 Hz), 2.93 (dd, 1H, J_1 = 15.7 Hz, J_2 = 9.9 Hz), 3.48 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.1 Hz), 2.93 (dd, 1H, J_1 = 15.7 Hz, J_2 = 5.1 Hz), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 168.8, 148.2, 140.2, 138.2, 136.3, 134.6, 134.2, 130.1, 128.0, 127.9, 127.8, 127.3, 126.2, 121.7, 121.6, 116.5, 61.4, 47.1, 41.1, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}ClN_2O_3$: 383.1162; found 383.1166.

3,3-Bis(4-chlorophenyl)-2-(4-isobutylphenyl)-*N*-(quinolin-8-yl)propanamide (7b) : Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 96-98 ^oC; R_f = 0.45 (20% EtOAc/Hexane); Yield: 70% (63 mg); IR (KBr): 3348, 2981, 1728, 1688, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56-7.50 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, J = 7.8 Hz), 7.17 (d, 2H, J = 7.9 Hz), 4.30 (dd, 1H, J_1 = 10.0 Hz, J_2 = 5.0 Hz), 4.23-4.12 (m, 2H), 3.48 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.1 Hz), 2.92 (dd, 1H, J_1 =

15.6 Hz, J_2 = 5.0 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 169.3, 148.2, 138.3, 137.2, 136.3, 135.3, 134.4, 129.6, 127.9, 127.7, 127.4, 121.6, 121.5, 116.5, 61.2, 47.1, 41.5, 21.1, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_3$: 363.1709; found 363.1725.

Ethyl 2-(4-ethylphenyl)-4-oxo-4-(quinolin-8-ylamino)butanoate (7c) : Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour semi-solid; R_f = 0.53 (20% EtOAc/Hexane); Yield: 68% (64 mg); IR (KBr): 3347, 2926, 1729, 1687, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56-7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.19 (d, 2H, J = 8.1 Hz), 4.30 (dd, 1H, J_1 = 10.1 Hz, J_2 = 4.9 Hz), 4.23-4.19 (m, 2H), 3.48 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.1 Hz), 2.92 (dd, 1H, J_1 = 15.6 Hz, J_2 = 4.9 Hz), 2.65 (q, 2H, J = 7.6 Hz), 1.26-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 169.4, 148.2, 143.5, 138.3, 136.3, 135.5, 134.4, 128.4, 127.9, 127.7, 127.4, 121.6, 121.5, 116.5, 61.2, 47.1, 41.5, 28.5, 15.5, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found 641.0795.

Ethyl 4-oxo-4-(quinolin-8-ylamino)-2-(m-tolyl)butanoate (7d) : Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 90-92 ^oC; R_f = 0.45 (20% EtOAc/Hexane); Yield: 53% (48 mg); IR (KBr): 3347, 2980, 1728, 1688, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.76 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.56-7.50 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.21-7.18 (m, 2H), 7.11 (d, 1H, J = 7.4 Hz), 4.29 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.8 Hz), 4.24-4.13 (m, 2H), 3.49 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.2 Hz), 2.92 (dd, 1H, J_1 = 15.6 Hz, J_2 = 4.8 Hz), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 169.3, 153.4, 148.1, 138.5, 138.2, 136.3, 134.4, 128.7, 128.5, 127.9, 127.4, 124.9, 121.6, 121.5, 116.5, 61.2, 47.4, 41.5, 21.4, 14.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{22}N_2O_3Na$: 385.1528; found 385.1517.

Ethyl 2-(3,4-dimethylphenyl)-4-oxo-4-(quinolin-8-ylamino)butanoate (7e) : Following the general procedure, **7e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 85-87 ^{o}C; R_f = 0.45 (20% EtOAc/Hexane); Yield: 67% (63 mg); IR (KBr): 3349, 2978, 1729, 1688, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.18 (s, 1H), 7.15-7.11 (m, 2H), 4.29-4.11 (m, 3H), 3.47 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.1 Hz), 2.91 (dd, 1H, J_1 = 15.6 Hz, J_2 = 4.9 Hz), 2.27 (s, 3H), 2.25 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 169.4, 148.1, 138.3, 137.1, 136.3, 135.9, 135.7, 134.4, 130.1, 129.0, 127.9, 127.4, 125.2, 121.6, 121.5, 116.5, 61.2, 47.1, 41.6, 19.9, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found 377.1870.

Ethyl 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxo-4-(quinolin-8-ylamino)butanoate (7f) : Following the general procedure, **7f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour semi-solid; R_f = 0.22 (20% EtOAc/Hexane); Yield: 62% (63 mg); IR (KBr): 3346, 2980, 1725, 1682, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (br. s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.92-6.83 (m, 3H), 4.25 (s, 4H), 4.23-4.12 (m, 3H), 3.43 (dd, 1H, J_1 = 15.6 Hz, J_2 = 10.0 Hz), 2.90 (dd, 1H, J_1 = 15.6 Hz, J_2 = 5.1 Hz), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 169.2, 148.1, 143.6, 143.0, 138.3, 136.3, 134.4, 131.4, 127.9, 127.4, 121.6, 121.5, 120.8, 117.5, 116.6, 116.5, 64.3, 61.2, 46.7, 41.5, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_5$: 407.1607; found 407.1626.

Methyl 3-(4-methoxyphenyl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (8a) : Following the general procedure, **8a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 99-101 ^{o}C; R_f = 0.18 (20% EtOAc/Hexane); Yield: 87% (82 mg); IR (KBr): 3348, 2951, 1734, 1683, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (br. s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53-7.47 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27 (d, 2H, J = 8.7 Hz), 6.84 (d, 2H, J = 8.7 Hz), 3.87-3.80 (m, 1H), 3.74 (s, 3H), 3.61

(s, 3H), 2.98 (dd, 1H, J_1 = 14.8 Hz, J_2 = 7.3 Hz), 2.92-2.85 (m, 2H), 2.74 (dd, 1H, J_1 = 15.4 Hz, J_2 = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 170.0, 158.4, 148.1, 138.2, 136.3, 134.7, 134.3, 128.3, 127.9, 127.3, 121.6, 121.5, 116.5, 114.1, 55.2, 51.7, 44.4, 40.7, 38.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_4$: 379.1658; found 379.1648.

Methyl 5-oxo-5-(quinolin-8-ylamino)-3-(*p*-tolyl)pentanoate (8b) : Following the general procedure, **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour solid; R_f = 0.22 (20% EtOAc/Hexane); Yield: 86% (78 mg); IR (KBr): 3351, 2950, 1735, 1687, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (br. s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-7.48 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 7.9 Hz), 3.89-3.82 (m, 1H), 3.61 (s, 1H), 2.99 (dd, 1H, J_1 = 14.8 Hz, J_2 = 11.4 Hz), 2.94-2.87 (m, 2H), 2.76 (dd, 1H, J_1 = 15.4 Hz, J_2 = 8.2 Hz), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 169.6, 148.1, 139.7, 138.2, 136.4, 136.3, 134.3, 129.4, 127.9, 127.4, 127.2, 121.6, 121.5, 116.5, 51.6, 44.3, 40.6, 38.3, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_3$: 363.1709; found 363.1701.

Methyl 3-(3-nitrophenyl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (8c) : Following the general procedure, **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 112-114 ^oC; R_f = 0.18 (20% EtOAc/Hexane); Yield: 64% (63 mg); IR (KBr): 3341, 2951, 1730, 1679, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (br. s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.69-8.67 (m, 1H), 8.25 (t, 1H, J = 2.0 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 8.08-8.06 (m, 1H), 7.72 (d, 2H, J = 7.7 Hz), 7.51-7.44 (m, 4H), 4.07-4.0 (m, 1H), 3.63 (s, 3H), 3.07 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 3.0-2.93 (m, 2H), 2.81 (dd, 1H, J_1 = 15.9 Hz, J_2 = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 168.5, 148.5, 148.2, 144.9, 138.1, 136.4, 134.4, 134.0, 129.6, 127.9, 127.3, 122.2, 122.1, 121.8, 121.7, 116.5, 51.9, 43.5, 40.0, 38.2 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_5$: 394.1403; found 394.1420.

Methyl 4-(1-methoxy-1,5-dioxo-5-(quinolin-8-ylamino)pentan-3-yl)benzoate (8d) : Following the general procedure, **8d** was obtained after purification by column chromatography

on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 108-110 ^{o}C; R_f = 0.16 (20% EtOAc/Hexane); Yield: 43% (44 mg); IR (KBr): 3449, 2951, 1720, 1685, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (br. s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.70 (dd, 1H, J_1 = 5.9 Hz, J_2 = 3.1 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.99 (d, 2H, J = sl8.4 Hz), 7.54-7.42 (m, 5H), 3.99-3.92 (m, 1H), 3.89 (s, 3H), 3.60 (s, 3H), 3.03 (dd, 1H, J_1 = 15.0 Hz, J_2 = 7.2 Hz), 2.97-2.91 (m, 2H), 2.79 (dd, 1H, J_1 = 15.6 Hz, J_2 = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.0, 166.9, 148.1, 148.1, 138.2, 136.4, 134.1, 130.1, 128.9, 127.9, 127.5, 127.3, 121.7, 121.6, 116.5, 52.1, 51.7, 43.8, 40.1, 38.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_5$: 407.1607; found 407.1620.

Methyl 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (8e): Following the general procedure, **8e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour liquid; R_f = 0.27 (20% EtOAc/Hexane); Yield: 59% (59 mg); IR (thin film): 3346, 2949, 1735, 1681, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.74 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.55-7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 3.81-3.74 (m, 1H), 3.63 (s, 3H), 2.97-2.83 (m, 3H), 2.75-2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.5, 148.1, 143.5, 142.4, 138.2, 136.3, 136.1, 134.3, 127.9, 127.4, 121.6, 121.5, 120.3, 117.4, 116.5, 115.9, 64.3, 64.3, 51.7, 44.3, 40.6, 38.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_5$: 407.1607; found 407.1619.

Methyl 5-oxo-5-(quinolin-8-ylamino)-3-(thiophen-2-yl)pentanoate (8f) : Following the general procedure, **8f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour liquid; R_f = 0.25 (20% EtOAc/Hexane); Yield: 82% (73 mg); IR (thin film): 3346, 2950, 1736, 1686, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (br. s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.77 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.3 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.56-7.50 (m, 1H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.16 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 6.99 (d, 2H, J = 3.4 Hz), 6.92 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.27-4.19 (m, 1H), 3.67 (s, 3H), 3.09-2.93 (m, 3H), 2.82 (dd, 1H, J_1 = 15.6 Hz, J_2 = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.0, 148.2, 146.2, 138.3, 136.4, 134.3, 127.9,

127.4, 126.8, 124.4, 123.7, 121.6, 116.5, 51.8, 44.841.3, 34.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_3S$: 355.1116; found 355.1124.

Ethyl 6-oxo-6-(quinolin-8-ylamino)-4-(*p*-tolyl)hexanoate (9a): Following the general procedure, **9a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour liquid; R_f = 0.36 (20% EtOAc/Hexane); Yield: 59% (57 mg); IR (thin film): 3353, 2927, 1729, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (br. s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-7.47 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.12 (d, 2H, *J* = 7.9 Hz), 4.07 (q, 2H, *J* = 7.2 Hz), 3.33-3.27 (m, 1H), 2.88 (d, 2H, *J* = 7.4 Hz), 2.30 (s, 3H), 2.26-2.14 (m, 3H), 2.07-1.96 (m, 1H), 1.21 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.0, 148.0, 139.8, 138.2, 136.3, 136.3, 134.4, 129.4, 127.9, 127.5, 127.4, 121.6, 121.4, 116.5, 60.3, 45.6, 41.6, 32.5, 31.2, 21.1, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found 391.2036.

Ethyl 4-(4-isopropylphenyl)-6-oxo-6-(quinolin-8-ylamino)hexanoate (9b) : Following the general procedure, **9b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale yellow colour liquid; R_f = 0.38 (20% EtOAc/Hexane); Yield: 58% (61 mg); IR (thin film): 3353, 2960, 1731, 1687, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (br. s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54-7.47 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.22 (d, 2H, *J* = 8.2 Hz), 7.16 (d, 2H, *J* = 8.1 Hz), 4.09-4.03 (m, 2H), 3.34-3.28 (m, 1H), 2.89-2.81 (m, 3H), 2.30-2.16 (m, 3H), 2.06-2.0 (m, 1H), 1.23-1.19 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 170.1, 148.0, 147.2, 140.2, 138.2, 136.3, 134.4, 127.9, 127.4, 127.4, 126.7, 121.6, 121.4, 116.4,60.3 45.6, 41.6,33.7, 32.5, 31.1, 24.0, 23.9, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{31}N_2O_3$: 419.2335; found 419.2344.

Ethyl 4-(4-fluorophenyl)-6-oxo-6-(quinolin-8-ylamino)hexanoate (9c) : Following the general procedure, **9c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 90-92 ^oC; R_f = 0.31 (20% EtOAc/Hexane); Yield: 51% (50 mg); IR (KBr): 3351, 2980, 1730, 1684, 1525 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ 9.68 (br. s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.71 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.54-7.49 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29-7.25 (m, 2H), 7.0 (t, 2H, J = 8.7 Hz), 4.08 (q, 2H, J = 7.2 Hz), 3.38-3.31 (m, 1H), 2.93-2.82 (m, 2H), 2.28-2.15 (m, 3H), 2.03-1.97 (m, 1H), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.6, 161.7 (d_{C-F}, J = 246.8 Hz), 148.1, 138.5 (d_{C-F}, J = 3.3 Hz), 138.2, 136.4, 134.2, 129.1 (d_{C-F}, J = 7.8 Hz), 127.9, 127.3, 121.6 (d_{C-F}, J = 6.3 Hz), 116.4, 115.7, 115.5, 60.4, 45.6, 41.3, 32.4, 31.2, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}FN_2O_3$: 395.1771; found 395.1761.

Ethyl 4-(3-bromophenyl)-6-oxo-6-(quinolin-8-ylamino)hexanoate (9d): Following the general procedure, **9d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as brown colour liquid; R_f = 0.25 (20% EtOAc/Hexane); Yield: 70% (79 mg); IR (thin film): 3347, 2931, 1729, 1686, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.71 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.54-7.44 (m, 4H), 7.35-7.32 (m, 1H), 7.24 (d, 1H, J = 7.8 Hz), 7.17 (t, 1H, J = 7.8 Hz), 4.08 (q, 2H, J = 7.2 Hz), 3.37-3.30 (m, 1H), 2.88 (d, 2H, J = 7.0 Hz), 2.29-2.15 (m, 3H), 2.06-1.96 (m, 1H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 169.3, 148.1, 145.5, 138.2, 136.3, 134.2, 130.5, 130.3, 130.0, 127.9, 127.3, 126.6, 122.9, 121.6, 121.6, 116.5, 60.5, 45.2, 41.7, 32.3, 31.0, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}BrN_2O_3$: 455.0970; found 455.0955.

Ethyl 4-(3-nitrophenyl)-6-oxo-6-(quinolin-8-ylamino)hexanoate (9e): Following the general procedure, **9e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour solid; mp 87-89 ^oC; R_f = 0.18 (20% EtOAc/Hexane); Yield: 79% (83 mg); IR (KBr): 3441, 1727, 1685, 1526, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (br. s, 1H), 8.77 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.0 Hz), 8.69-8.65 (m, 1H), 8.22 (s, 1H), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.51 (d, 1H, J = 4.6 Hz), 7.48-7.45 (m, 2H), 4.09 (dd, 1H, J_1 = 14.6 Hz, J_2 = 7.1 Hz), 3.56-3.49 (m, 1H), 3.03-2.89 (m, 2H), 2.32-2.03 (m, 4H), 1.24 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 168.8, 148.6, 148.2, 145.3, 138.2, 136.4, 134.5, 134.0, 129.7, 127.9, 127.3, 122.2, 122.1, 121.8,

121.7, 116.5, 60.6, 44.8, 41.6, 32.2, 31.0, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{24}N_3O_5$: 422.1716; found 422.1703.

Ethyl 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-oxo-6-(quinolin-8-ylamino)hexanoate (9f) : Following the general procedure, **9f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as pale brown colour liquid; R_f = 0.18 (20% EtOAc/Hexane); Yield: 56% (61 mg); IR (thin film): 3347, 2927, 1727, 1684, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.54-7.48 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 6.81-6.76 (m, 3H), 4.23-4.19 (m, 4H), 4.08 (q, 2H, J = 7.1 Hz), 3.26-3.19 (m, 1H), 2.84 (d, 2H, J = 7.4 Hz), 2.30-2.11 (m, 3H), 2.0-1.90 (m, 1H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 169.9, 148.1, 143.6, 142.3, 138.3, 136.3, 136.2, 134.4 127.9, 127.4, 121.6, 121.4, 120.6, 117.4, 116.5, 116.1, 64.3, 64.3, 60.3, 45.7, 41.4, 32.4, 31.3, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{27}N_2O_5$: 435.1920; found 435.1937.

Ethyl 6-oxo-6-(quinolin-8-ylamino)-4-(thiophen-2-yl)hexanoate (9g) : Following the general procedure, **9g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 15:85) as colourless solid; mp 85-87 ^oC; R_f = 0.31 (20% EtOAc/Hexane); Yield: 68% (65 mg); IR (KBr): 3347, 2931, 1729, 1684, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (br. s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55-7.49 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.17 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.0 Hz), 6.95-6.91 (m, 2H), 4.10 (q, 2H, J = 7.0 Hz), 3.76-3.69 (m, 1H), 2.93 (d, 2H, J = 7.3 Hz), 2.35-2.22 (m, 3H), 2.06-1.99 (m, 1H), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.4, 148.1, 146.7, 138.2, 136.3, 134.3, 127.9, 127.4, 126.8, 124.8, 123.7, 121.6, 121.6, 116.5, 60., 46.4, 37.4, 32.3, 32.2, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_3S$: 383.1429; found 383.1442.

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39. (a) The total yield of both the diastereomers is reported. The ratio of diastereomers was determined from the NMR spectra of the crude reaction mixture. [37a,e] (b) In these cases, the products **4a-f** were isolated as mixture of diastereomers and our efforts to separate the major and minor isomer in pure form were not fruitful, hence we could not predict the stereochemistry of the products **4a-f**. (c) In Scheme 6, the structure of one of the plausible conformers **1a,j**, and **5a-d** is drawn just for understanding the observed *anti* stereochemistry of (±)-**3a-l**. However, considering the free C-C bond rotation, there will be more than one conformers of **1a,j, 3/10** and **5a-e**. [8g,i] (d) The respective products (±)-**7** and (±)-**7b** were obtained as diastereomers (dr 1:1).
40. See the Supplementary data file for the HPLC profile.[37a,e]
41. CCDC-1061839 (for (±)-**3b**), 1061840 (for (±)-**3c**), 1061841 (for (±)-**3e**), 1061842 (for (±)-**3l**), 1061846 (for enantiomerically enriched compound **10c**), 1061843 (for meso-**8eA**), 1061844 (for (±)-**8eB**), and 1061845 (for (±)-**8fB**) contain the supplementary crystallographic data.
42. The reaction involving the C-H arylation of **1k** indicated that the ee values were not changed during the course of the reaction (as both starting material **1k** and product **10a** (anti, major diastereomer) have the ee value about 78%) and hence, the configuration at the stereocenter was conserved in the products **10a-c**. [37a,e]
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of the experiment involving amide hydrolysis of **1a** in the presence of K_2CO_3, which revealed the formation of *p*-tolualdehyde via the retro-aldol reaction (see the SI for the crude NMR). (d) On the basis of the literature reports regarding the ring opening reactions of cyclopropanes, during our revisiting of the C−H arylation of cyclopropanes, we attained the C−H arylation/ ring-opening of cyclopropanecarboxamides (e.g. 1a), which successfully underwent with excess of aryl iodide in the presence of AcOH. Perhaps, in our previous work, ref 35b, we have missed the ring-opened product which is forming only in negligible quantity based on the optimization reaction Table 8. (e) A literature survey revealed that in general, the removal of bidentate ligands, such as, 8-aminoquinoline and 2-(methylthio)aniline) was successful only under harsh reaction conditions (e.g., see refs 55 and 54d).

57. Stereochemistry of the compounds **5a−l**, **6a−e**, **10**, **11**, **12a-c**: (a) The *anti* stereochemistry of the compounds **5a−l**, **6a−e**, **10**, **11**, **12a-c** was assigned based on the X-ray structures of the compounds **5b**, **6c**, **6d** and **12d** and the similarity in their NMR spectral pattern. (b) The respective reactions of **4a**, **8**, **15b** with **2a−c** and **2l** are expected to give more than one isomer; however, the compounds **10**, **11**, **12a-d** were obtained as the predominant compounds from the column chromatography purification of the respective crude reaction mixtures and our trials to find out/obtain the formation of any other characterizable by-products were not fruitful. The structures of **10**, **11**, **12a-d** were assigned based on the retro-aldol reaction of **10**, **11**, **12a** and **12b** which afforded the corresponding compounds **16b,d,e** (Scheme 3). Further the assignment of stereochemistry and structures of the compounds **10**, **11**, **12a-c** and **12e** were supported by the single-crystal X-ray structure of the compound **12d**. Additionally, we have isolated the ring-opened carboxamide **23b** (Scheme 6) from **13**. Then, we have performed the $Pd(OAc)_2$-catalyzed double C−H arylation reaction of the methyl group of **23b** with **2c** to afford the compound **12e**. These sequences also supported the assigning of structures/stereochemistry of **10**, **11**, **12a-c**. (c) The reaction of **15a** with iodobenzene also gave the product **5b** (the NMR spectral pattern of **5b** obtained in this reaction was similar to the product **5b** obtained from **1a**).
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